DOI: 10.1002/ejoc.200901302

Quadrane Sesquiterpenes: Natural Sources, Biology, and Syntheses

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Keywords: Natural products / Sesquiterpenes / Quadrone / Terpenoids / Total synthesis / Structure–activity relationships

Quadranes, discovered with the isolation of (–)-quadrone in 1978, are biologically active naturally occurring sesquiterpenes featuring a distinctive set of bi- to tetracyclic ring systems. The available data for this family of natural products, including isolation data, biosynthetic considerations, a comprehensive compilation of the reported biological activities, and an exhaustive survey of the synthetic work in this area so far, are critically analyzed.

Introduction

Quadranes are a restricted family of naturally occurring sesquiterpenes belonging to the larger group of polyquinanes,[1] featuring a diquinane core fused with a bicyclo[3.2.1]octane system (Figure 1). They were discovered in 1978 with the isolation of (–)-quadrone (**1**, Figure 2),[2] which because of its challenging structure and highly potent biological activity has attracted considerable attention. In the past decade, new members of this family of natural products with enhanced biological activities have been isolated and have triggered renewed interest in these natural sesquiterpenes.

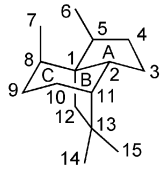

Figure 1. Quadrane sesquiterpene.

(–)-quadrone (**1**) (+)-terrecyclic acid A (**2**)

Figure 2. (–)-Quadrone (**1**) and (+)-terrecyclic acid A (**2**).

This microreview provides a critical analysis of the currently available data for quadranoids, including structural, biosynthetic, and biological considerations. The second part presents exhaustive coverage of the work directed towards the total synthesis of quadranoids up to October 2009.

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Structures, Biosynthesis, and Biology

Quadranoids exhibit distinctive, generally not highly oxidized, carbon frameworks based on bi- to tetracyclic cores, and some of them have shown highly potent biological activities against several panels of tumor cell lines.

Isolation and Structures

The story of quadrane sesquiterpenes, sometimes also referred to as suberosanes or terrecyclanes, started in 1978 with the isolation of (1*R*,2*R*,5*S*,8*R*,11*R*)-(–)-quadrone (**1**) by Calton and Ranieri.[2] (–)-Quadrone (**1**) was isolated from the fermentation broth of a strain of the fungus *Aspergillus terreus* collected in Australia, in a yield of 0.2 mg mL^{-1}. Structural analysis, including X-ray diffraction analysis, revealed the relative stereochemistry of the rigid tetracyclic structure, containing five stereogenic centers and three oxidized positions (Figure 2). Although another positional numbering generally consistent with IUPAC guidelines was later proposed,[3] for the reader's convenience the numbering of atoms and rings shown in Figure 1 is used for all quadranoids throughout the manuscript. After this pioneering work, Isogai and co-workers then reported in a series of papers the isolation and characterization of the closely related natural product (+)-terrecyclic acid A (**2**) from the broth of a sample of *Aspergillus terreus* collected in Japan with a fermentation yield of 1 mg mL^{-1} (Figure 2).[4] The structure of (+)-terrecyclic acid A (**2**) was established from spectroscopic evidence and, importantly, also by its chemical conversion (pyrolysis) into (–)-quadrone (**1**).[4b] It is noteworthy that the absolute stereochemistries of (–)-quadrone (**1**) and (+)-terrecyclic acid A (**2**) were determined in 1984 by Isoe and co-workers with the first

asymmetric total synthesis of (–)-terrecyclic acid A (**2**), and were confirmed by Smith III a few months later by an asymmetric synthesis of (+)-quadrone (**1**, vide infra).

Contemporaneously, Isogai and co-workers also reported the isolation of other quadranoids from a similar sample of *Aspergillus terreus*. Three of these new sesquiterpenes – namely (–)-8-hydroxyquadrone (**3**, Figure 3), (–)-isoquadrone (**4**), and (+)-6-hydroxyisoquadrone (**5**)[5] – have a tetracyclic framework comparable to that of (–)-quadrone (**1**), whereas terrecyclol (**6**)[6] is a reduced form of the tricyclic (+)-terrecyclic acid A (**2**). More recently, an investigation of a sample of *Aspergillus terreus* collected in the USA (Sonoran desert) revealed, in addition to the known compounds (–)-quadrone (**1**) and (+)-terrecyclic acid A (**2**), the two new quadranoids (+)-5(6)-dihydro-6-hydroxyterrecyclic acid (**7**, Figure 3) and (+)-5(6)-dihydro-6-methoxyterrecyclic acid (**8**)[7].

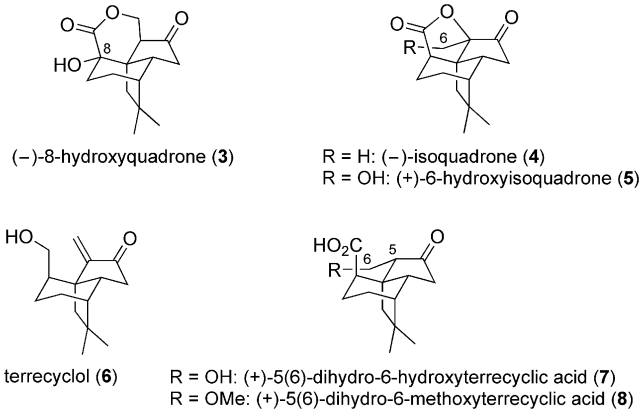


Figure 3. Other naturally occurring quadranes from fungal sources.

In 1996, Boyd and co-workers reported the isolation of (+)-suberosenone (**9**, Figure 4) from the organic extract of a sample of the gorgonian *Subergorgia suberosa*, available at the NCI.[8] It was the first time that a naturally occurring quadranoid had been isolated from a marine organism or any nonfungal source. (+)-Suberosenone (**9**) has the tricyclic core of (+)-terrecyclic acid A (**2**) with, remarkably, a completely reduced carbon atom at C-7 (methyl group), a feature later found in all naturally occurring quadranoids isolated from marine sources. The same group also reported the isolation of the dimeric natural product (+)-alertenone (**10**, Figure 4), together with (+)-suberosenone (**9**), from the gorgonian *Alertigorgia* sp.[9] Sheu and co-workers reported the isolation of (–)-suberosanone (**11**), (–)-suberosenol A (**12**), (–)-suberosenol B (**13**), (–)-suberosenol A acetate (**14**), and (–)-suberosenol B acetate (**15**) from a sample of the gorgonian *Isis hippuris* collected off the southeast coast of Taiwan in 1999 (Figure 4).[10] Additionally, a sample of the gorgonian *Subergorgia suberosa* collected in the South China Sea in 2003 also provided (–)-suberosenol A (**12**) and the novel quadranoid sesquiterpene alkaloid (+)-**16** (Figure 4).[11]

Marc Presset was born in Thonon-les-bains (France) in 1981. After completing his Master's degree in Chemistry in 2005 at the Université d'Avignon under the supervision of Prof. Bernard Pucci, he joined the Ecole Normale Supérieure de Cachan where he obtained the Agrégation de Sciences Physiques in 2007. He then moved to Marseille where he is currently a Ph.D. student under the supervision of the co-authors. His research focuses on the development of new synthetic methods and their applications in total synthesis.

Yoann Coquerel was born in Rouen (France) in 1975. After studying chemistry at the University Joseph Fourier in Grenoble (France), where he completed his Ph.D. in 2001 under the supervision of Prof. Jean-Pierre Deprés, he moved to Florida State University in Tallahassee (USA) to join the group of Prof. Robert A. Holton as a post-doctoral associate. Since 2003 he has been working as a CNRS researcher with Prof. Jean Rodriguez at the University Paul Cézanne in Marseille (France). His research interests include the development of eco-compatible synthetic organic chemistry (multiple bond-forming reactions and catalysis), and the total synthesis of natural products. In 2002 he was awarded the Fournier – French Chemical Society prize for his Ph.D. thesis dissertation, and in 2009 he completed his Habilitation at the University Paul Cézanne in Marseille.

Jean Rodriguez was born in Cieza (Spain) in 1958 and in 1959 his family emigrated to France. After studying chemistry at the University Paul Cézanne in Marseille (France), he completed his Ph.D. as a CNRS researcher with Prof. B. Waegell and Prof. P. Brun in 1987. He completed his Habilitation in 1992, also at Marseille, where he is currently Professor and Director of the UMR-CNRS-6263-iSm2. His research interests include the development of domino and multicomponent reactions and their application in stereoselective synthesis. In 1998 he was awarded the ACROS prize in Organic Chemistry, and in 2009 he was awarded the prize of the Division of Organic Chemistry from the French Chemical Society.

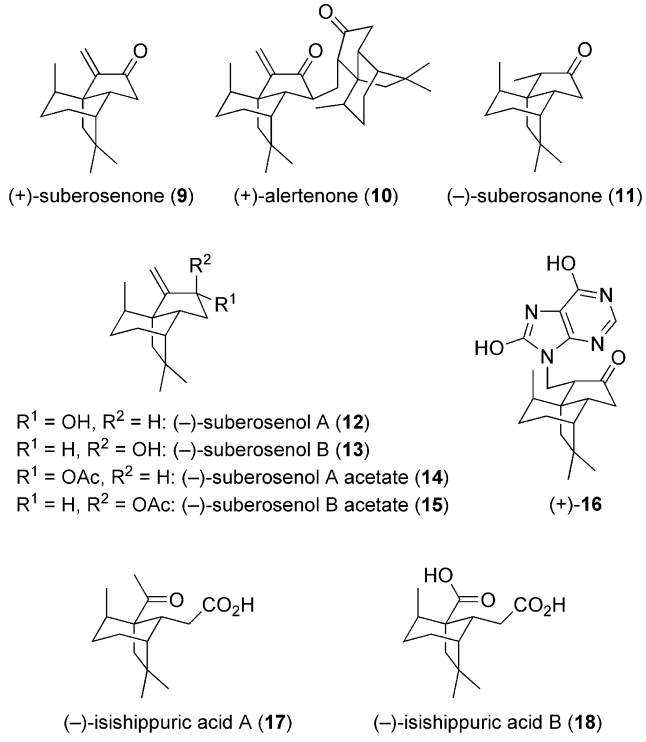


Figure 4. Naturally occurring quadranes from marine sources.

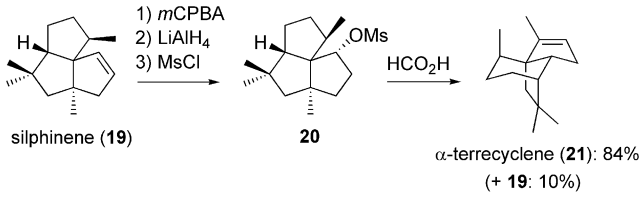
In 2004, Sheu and co-workers isolated the two first bicyclic quadranoids – namely the 4,5-secoquadrane (–)-isishippuric acid A (**17**) and the 4,5-seco-6-norquadrane (–)-isishippuric acid B (**18**) – from the same sample of the gorgonian *Isis hippuris* that allowed the isolation of suberosanone (**11**) and suberosenols **12**–**15** (Figure 4).[12]

It should be mentioned here that only the absolute configurations of (–)-quadrone (**1**), (+)-terrecyclic acid A (**2**), (–)-isishippuric acid A (**17**), and (–)-isishippuric acid B (**18**) have been established by chemical synthesis to be as depicted in Figures 2 and 4 (vide infra). However, some recent studies directed towards the determination of the absolute configurations of compounds **9**, **11**, and **14** through DFT calculations based on their $[\alpha]_D$ values indicate that their absolute configurations are likely to be as depicted in Figure 4.[13] Consequently, we can reasonably surmise that all of the compounds **1**–**18** in Figures 2, 3, and 4 are depicted here with their correct absolute configurations.

Biosynthesis

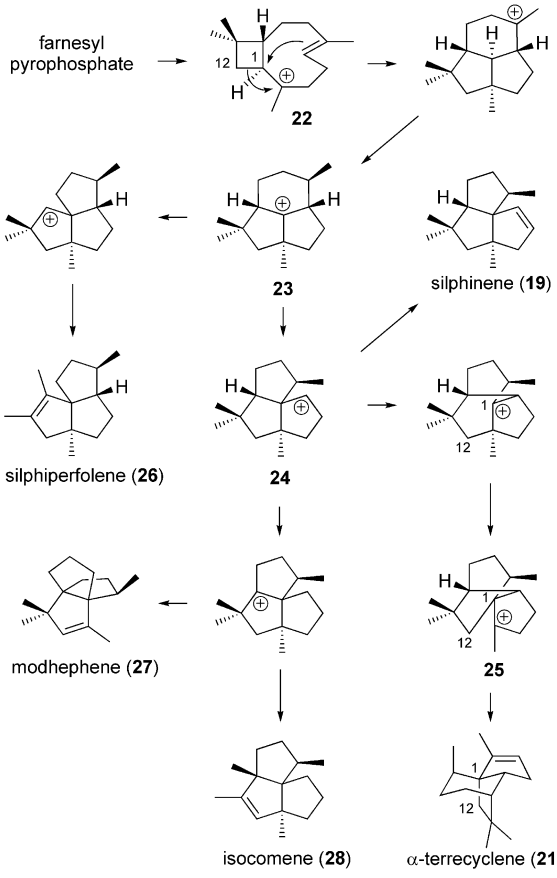
Early after the isolation of quadrone (**1**) and terrecyclic acid A (**2**), the groups of Isogai[14] and Cane[15] independently reported two very similar studies directed towards the identification of possible biosynthetic pathways for quadranoids. They incubated some fermentation broth of *Aspergillus terreus* with ^{13}C-labeled sodium acetate and both groups obtained the same labeling pattern of (+)-terrecyclic acid A (**2**). They concluded that quadranes were indeed sesquiterpenes biosynthetically derived from mevalonic acid, and also that cleavage of one or more carbon–carbon bonds took place in the biosynthetic route from farnesyl pyrophosphate. Rosazza and co-workers, who independently performed a comparable set of feeding experiments, confirmed these results a few months later.[16] Although the two groups of Isogai and Cane obtained the same experimental results, their proposals for the biosynthetic pathway were different. In a subsequent complementary study involving feeding experiments with deuterium-labeled sodium acetate, Isogai and co-workers actually ruled out Cane's group's proposal for the biogenesis of quadranes.[17] Subsequently, Cane and co-workers finally proposed a biosynthetic pathway very close to that originally proposed by Isogai.[18] Overall, according to these authors, their proposed biosynthetic routes to quadranes were speculative because the actual product of the farnesyl pyrophosphate cyclization could not be unambiguously identified.

In 1992, Coates and co-workers discovered the solvolytic rearrangement of the mesylate **20** (Scheme 1), derived from the triquinane sesquiterpene silphinene (**19**), into the previously unknown α-terrecyclene (**21**).[19] This observation led to the suggestion that the ABC ring system of quadranes might biosynthetically originate from a similar silphinyl (**24**) to terrecyclanyl (**25**) cation rearrangement (Scheme 2). Consistently with Bohlmann's hypothesis that the silphinyl cation (**24**) is biogenetically derived from ring reorganization of the caryophyllenyl cation (**22**),[20] Coates proposed that triquinanes **19** and **26**–**28** and quadranes such as **21** are all formally derivable from caryophyllene as shown in Scheme 2.[21] It should be noted here that a derivative of (+)-terrecyclic acid A (**2**) has been rearranged into a tetracyclic compound containing the carbon skeleton and complete absolute stereochemistry of siliphinene (**19**).[22] The proposed route for the rearrangement was very similar to the proposal of Coates in the backward sense (i.e. involving a cationic rearrangement closely related to **25** → **24**), but this result was judged "interesting" without further conclusion with regard to the biosynthetic origin of quadranes. More recently, the co-occurrence of the caryophyllane sesquiterpenes **29** and **30** with suberosenone (**9**)[8] and of the triquinanes **31** and **32** with the quadrane alkaloid (+)-**16** in different samples of *Subergorgia suberosa*,[11] as well as the co-occurrence of the triquinane **31** with quadranes **11**–**15** in *Isis hippuris*,[10] has provided some strong support for this hypothesis (Figure 5). Additional support for this hypothesis includes the fortuitous biomimetic total syntheses by Coates and co-workers during their studies of the later isolated (±)-suberosanone (**11**) and (±)-suberosenols **13** and **15**. The absolute configurations of silphinene (**19**) and qua-



Scheme 1. Coates's rearrangement of silphinene (**19**) into terrecyclene (**21**).

dranes are consistent with a common biogenetic origin, and the pioneering labeling experiments of Isogai and Cane mentioned above are also consistent with biogenesis of quadranes from the caryophyllenyl cation (**22**). As mentioned by Coates, it is amusing to note that the last of the four skeletal rearrangements reconnects the two carbon atoms that were disconnected in the initial ring-expansion step. From a retrospective point of view, the early remark of Isogai and co-workers[14] that "another route via the compound with a tricyclo[6.3.0.0^{1,5}]undecane carbon skeleton [e.g. **19**] was taken into consideration, but (...) does not seem to be reasonable" is quite ironic.



Scheme 2. Biogenetic relationship between triquinanes and quadranes.

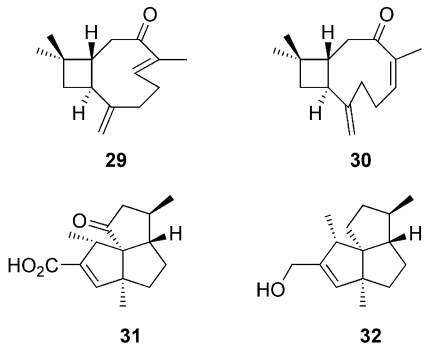


Figure 5. Natural sesquiterpenes co-occurring with quadranes.

Biology and Structure–Activity Relationship

The biological activities so far identified for natural quadrane sesquiterpenes, which are essentially in the antimicrobial and anticancer areas, are collected in Table 1. In the course of the isolation and structural determination studies of naturally occurring quadranes, several semisynthetic derivatives were prepared. These compounds obtained by derivatization of natural quadranes (hemisynthesis) are shown in Figure 6 and their biological activities are also reported in Table 1. Compounds **33** and **34** were prepared by reduction ($NaBH_4$) of **6** and **2**, respectively, and compound **35** by catalytic hydrogenation of **2**,[6,23] whereas its esterification led to **36**.[7] Of course, studies directed towards the total synthesis of quadranoids have produced a number of totally synthetic analogues (vide infra). When available, the biological activities of these compounds have been included in Table 1.

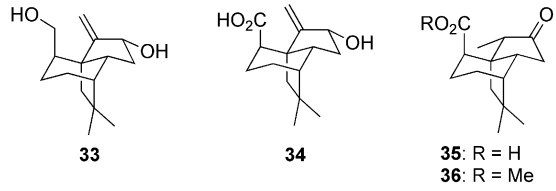


Figure 6. Hemisynthetic quadranes.

Cell cycle analysis of **1**, **2**, and **8** with use of the NCI-H460 cell line indicated that **2** is capable of disrupting the cell cycle through an apparent arrest of progression at the G_1 and G_2/M phases, which may underlie the cytotoxic activities observed for these compounds.[7] Suberosenone (**9**) demonstrated potent, differential cytotoxicity in the NCI human tumor-based primary screen: ovarian, renal, and melanoma lines were particularly sensitive to **9**, whereas leukemia lines were relatively insensitive.[8] In the same study, quadrone (**1**) showed only weak differential cytotoxicity in the NCI screen. However, alertenone (**10**) was surprisingly nontoxic against the same panel, giving relatively high IC_{50} values.[9] Whereas comparison of the antimicrobial activities of compounds **2** and **35** argues in favor of a crucial role for the α-methylene moiety in the antimicrobial activities of quadranes,[6] comparison of the data for compounds **9** and **11**, which both displayed potent anticancer activities, appears to indicate that the rigid molecular skeleton, not the enone, is an essential factor for the anticancer properties of quadranes.[8,10] Furthermore, compound **12**, which contains an α-hydroxy group, and not a ketone, at the allylic position exhibit potent cytotoxicity toward at least three cancer cells, whereas the corresponding acetyl derivative **14** is less active against the same cell lines.[10] It is interesting to note that the structurally simple compound isishippuric acid B (**18**) exhibited some of the most potent anti-cancer cytotoxic activity in the quadrane series of natural products.

Table 1. Known biological activities of quadrane sesquiterpenes.

Comp.	Activity[a]	Ref.
1	ED_{50} (KB cells) = 1.3 μg mL^{-1} LD_{50} (mouse) > 340 mg kg^{-1}[b] antifungal at 100 μg mL^{-1}: no antibacterial at 100 μg mL^{-1}: no	[2a]
1	IC_{50} (P-388) = 16 μg mL^{-1} antitumor (P-388) = no[b] LD_{50} (mouse) > 100 mg kg^{-1}[b] 10 MICs > 250 μg mL^{-1}	[5]
1	IC_{50} (NCI-H460) = 12.4 μM IC_{50} (MCF-7) = 14.3 μM IC_{50} (SF-268) = 16.9 μM	[7]
1	34 IC_{50} values (NCI in vitro anticancer drug screen) down to 17 μM (RXF-393)	[8]
1	IC_{50} (HeLa) = 2.3 μg mL^{-1}	[47]
1	IC_{50} (P-388) = 190 ng mL^{-1} IC_{50} (L-1210) = 650 ng mL^{-1} IC_{50} (3LL) = 390 ng mL^{-1} IC_{50} (LY) > 1000 ng mL^{-1}	[49b]
2	MIC (*Staphylococcus aureus*) = 25 μg mL^{-1} MIC (*Bacillus subtilis*) = 50 μg mL^{-1} MIC (*Micrococcus roseus*) = 25 μg mL^{-1} 7 MICs > 100 μg mL^{-1} antitumor (P-388) = yes[b] LD_{50} (mouse): 125 > LD_{50} > 63 mg kg^{-1}[b]	[4a]
2	IC_{50} (P-388) < 0.5 μg mL^{-1}	[5]
2	MIC (*Staphylococcus aureus*) = 25 μg mL^{-1} MIC (*Bacillus subtilis*) = 50 μg mL^{-1} MIC (*Micrococcus roseus*) = 25 μg mL^{-1} 7 MICs > 150 μg mL^{-1}	[6]
2	IC_{50} (NCI-H460) = 10.6 μM IC_{50} (MCF-7) = 24.1 μM IC_{50} (SF-268) = 14.7 μM	[7]
3	IC_{50} (P-388) = 125 μg mL^{-1} antitumor (P-388) = no[b] LD_{50} (mouse) > 100 mg kg^{-1}[b] 10 MICs > 500 μg mL^{-1}	[5]
4	IC_{50} (P-388) > 1000 μg mL^{-1} antitumor (P-388) = no[b] LD_{50} (mouse) > 100 mg kg^{-1}[b] MIC (*Staphylococcus aureus*) = 30 μg mL^{-1} 9 MICs > 500 μg mL^{-1}	[5]
4	IC_{50} (NCI-H460) > 10 μg mL^{-1} IC_{50} (MCF-7) > 10 μg mL^{-1} IC_{50} (SF-268) > 10 μg mL^{-1}	[7]
5	IC_{50} (P-388) = 500 μg mL^{-1} antitumor (P-388) = no[b] LD_{50} (mouse) > 100 mg kg^{-1}[b] 10 MICs > 500 μg mL^{-1}	[5]
6	MIC (*Staphylococcus aureus*) = 25 μg mL^{-1} MIC (*Bacillus subtilis*) = 12 μg mL^{-1} MIC (*Micrococcus roseus*) = 12 μg mL^{-1} MIC (*Penicillium chrysogenum*) = 25 μg mL^{-1} MIC (*Fusarium oxysporum*) = 25 μg mL^{-1} 5 MICs > 200 μg mL^{-1}	[6]
7	IC_{50} (NCI-H460) = 14.5 μM IC_{50} (MCF-7) = 16.5 μM IC_{50} (SF-268) = 7.8 μM	[7]
8	IC_{50} (NCI-H460) = 19.4 μM IC_{50} (MCF-7) = 20.6 μM IC_{50} (SF-268) = 21.4 μM	[7]
9	45 IC_{50} values (NCI in vitro anticancer drug screen) down to 0.13 μM (OVCAR-4)	[8,9]
9	antitumor lung (H-522) = yes[b] antitumor CNS (U-251) = yes[b]	[9]
10	10 IC_{50} values down to 35 μg mL^{-1}	[9]
11	ED_{50} (P-388) < 5.0×10^{-6} μg mL^{-1}[c] ED_{50} (A-549) = 3.6×10^{-2} μg mL^{-1}[c] ED_{50} (HT-29) < 5.0×10^{-6} μg mL^{-1}[c]	[10]
12	ED_{50} (P-388) < 5.0×10^{-6} μg mL^{-1}[c] ED_{50} (A-549) = 5.1×10^{-3} μg mL^{-1}[c] ED_{50} (HT-29) < 5.0×10^{-6} μg mL^{-1}[c]	[10]
13	ED_{50} (P-388) = 3.4 μg mL^{-1}[c] ED_{50} (A-549) = 0.2 μg mL^{-1}[c] ED_{50} (HT-29) = 2.1 μg mL^{-1}[c]	[10]
14	ED_{50} (P-388) = 7.6×10^{-3} μg mL^{-1}[c] ED_{50} (A-549) = 8.0×10^{-2} μg mL^{-1}[c] ED_{50} (HT-29) = 3.6×10^{-4} μg mL^{-1}[c]	[10]
15	ED_{50} (P-388) = 7.4×10^{-2} μg mL^{-1}[c] ED_{50} (A-549) = 3.6×10^{-1} μg mL^{-1}[c] ED_{50} (HT-29) = 5.0×10^{-3} μg mL^{-1}[c]	[10]
16	IC_{50} (MDA-MB-231) = 8.87 μg mL^{-1} cytotoxic (MCF) at 50 μM	[11]
18	ED_{50} (P-388) < 0.1 μg mL^{-1} ED_{50} (A-549) < 0.1 μg mL^{-1} ED_{50} (HT-29) < 0.1 μg mL^{-1}	[12]
33	10 MICs > 500 μg mL^{-1}	[6]
34	10 MICs > 500 μg mL^{-1}	[6]
35	10 MICs > 500 μg mL^{-1}	[6]
35	IC_{50} (NCI-H460) > 10 μg mL^{-1} IC_{50} (MCF-7) > 10 μg mL^{-1} IC_{50} (SF-268) > 10 μg mL^{-1}	[7]
36	IC_{50} (NCI-H460) = 9.4 μM IC_{50} (MCF-7) = 16.7 μM IC_{50} (SF-268) = 10.2 μM	[7]
129	IC_{50} (HeLa) = 4.0 μg mL^{-1}	[47]
129	IC_{50} (P-388) = 138 ng mL^{-1} IC_{50} (L-1210) = 64 ng mL^{-1}	[49c]
130	IC_{50} (P-388) = 94 ng mL^{-1} IC_{50} (L-1210) = 185 ng mL^{-1}	[49c]
131	IC_{50} (P-388) = 173 ng mL^{-1} IC_{50} (L-1211) = 106 ng mL^{-1} IC_{50} (3LL) = 80 ng mL^{-1} IC_{50} (LY) = 263 ng mL^{-1} MIC (*Staphylococcus aureus*) = 2.5–5 μg mL^{-1} MIC (*Candida albicans*) = 2.5–5 μg mL^{-1} MIC (*Trichophyton foetus*) = 2.5–5 μg mL^{-1}	[49b]
132	IC_{50} (P-388) = 416 ng mL^{-1} IC_{50} (L-1211) = 487 ng mL^{-1} IC_{50} (3LL) = 357 ng mL^{-1} IC_{50} (LY) > 1000 ng mL^{-1} MIC (*Staphylococcus aureus*) ≥ 20 μg mL^{-1} MIC (*Candida albicans*) ≥ 20 μg mL^{-1} MIC (*Trichophyton foetus*) ≥ 20 μg mL^{-1}	[49b]

[a] IC_{50}: concentration resulting in 50% inhibition of cell proliferation/survival; ED_{50}: effective dose required to inhibit cell growth by 50%; LD_{50}: median lethal dose; MIC: minimum inhibitory concentration. [b] In vivo experiments. [c] Experiments performed at various concentrations of pure test compound (not active if >4 μg mL^{-1}). It would be interesting to confirm the excellent activities of compounds **11** and **12**.

Interestingly, the totally synthetic nor- and trinor-quadrane analogues **129**–**132**, lacking the C^7 carbon atom, have been found to be biologically active (in their racemic forms). Cytotoxicities of analogues **131** and **132** against tumor cells of mice (in vitro) have been observed at almost the same level as **1**, and **131** exhibited better antimicrobial activity than **2**, whereas **1** has not been found to have anti-

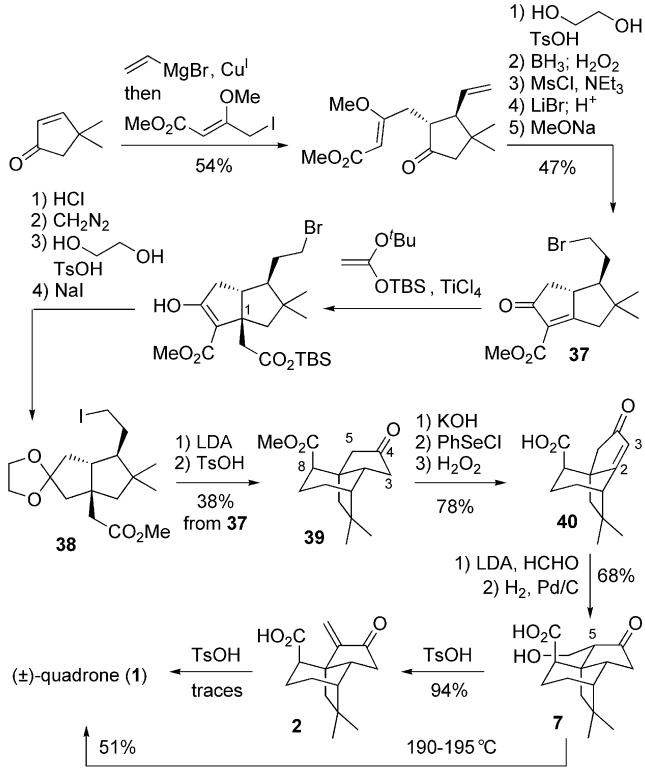
bacterial or antifungal activity.[49b] Additionally, analogues **129** and **130** exhibited higher cytotoxicities against tumor cells than **1**.[49c]

Total Syntheses of Natural Quadranes

Immediately after the report on the isolation of quadrone (**1**), many groups worldwide started research programs directed towards its total synthesis. A comprehensive overview of the work directed towards the total synthesis of naturally occurring quadranes is outlined below. This section is divided into four subsections according to the strategy employed for the construction of the ABC tricyclic core of these natural products (see Figure 1 for lettering). The focus throughout this section is on the challenging formation of the bicyclo[3.2.1] moiety (BC ring system).[24]

AB → ABC Strategy

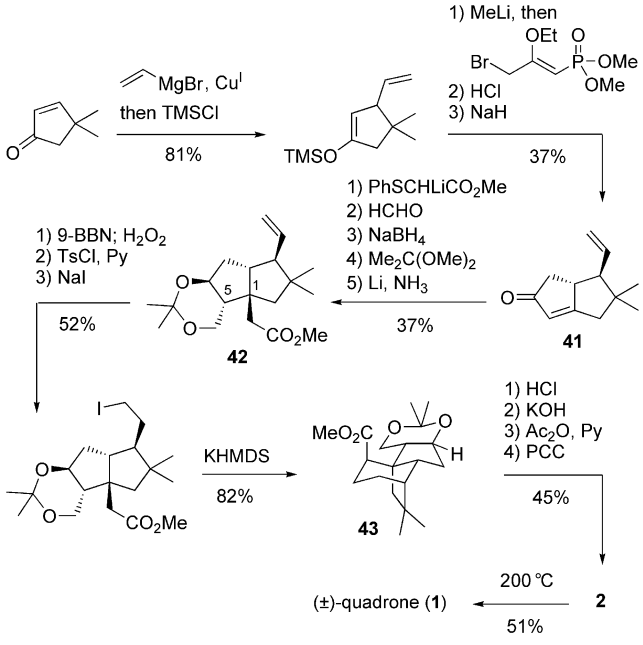
The first reported total synthesis of a naturally occurring quadrane was Danishefsky's total synthesis of (±)-quadrone (**1**) in 1980 (Scheme 3).[25] The ingenuity of this approach was the surmise that the construction of the D lactone ring in **1** could be achieved through an intramolecular oxa-Michael addition from the then unknown tricyclic unsaturated carboxylic acid **2**, which was actually isolated a few years later as terrecyclic acid A (**2**). Starting from 4,4-dimethylcyclopentenone as the B ring precursor, the AB bicyclo[3.3.0]octane ring system **37** was stereoselectively obtained in six steps including an initial copper(I)-catalyzed conjugated addition of vinyl Grignard reagent, followed by enolate trapping with a suitably functionalized alkyl iodide and a final addition/crotonization sequence of a pendant β-keto ester. A conjugated addition of a silylketene acetal to **37** installed the quaternary carbon atom C^1 with the correct relative configuration, and some subsequent functional group manipulations led to the intermediate **38**. The lithium enolate of the ester group in **38** was next cyclized to afford the expected ABC tricyclic framework **39** through substitution of the iodine atom and removal of the acetal protecting group. It is remarkable that this cyclization reaction, quite unexpectedly, directly afforded the correct configuration at carbon atom C^8. All attempts to generate the $\Delta_{4,5}$ enolate from ketone **39** led to the isomeric $\Delta_{3,4}$ enolate. This problem was circumvented by the temporary introduction of the $\Delta_{2,3}$ double bond in **40**, and the expected $\Delta_{4,5}$ regiomeric enolate could then be generated and used in an aldolization reaction with formaldehyde, which after diastereoselective hydrogenation led to the hydroxy acid intermediate **7**, which was isolated twenty-three years later as a natural product.[7] The stereochemistry at C^5 was attributed as depicted on Scheme 3 essentially on the basis that this compound did not undergo spontaneous lactonization to **1**. Treatment of **7** with *p*-toluenesulfonyl acid at 40–50 °C for 20 minutes afforded terrecyclic acid A (**2**). With a prolonged reaction time (1 h) in benzene at reflux, the same reaction mixture afforded essentially isoquadrone (**4**) and a minor amount of **1**. Alternatively, the pyrolysis of **7** afforded mainly **1** and minor amounts of **2**. Overall, this total synthesis of (±)-**1** was achieved in 19 steps and up to 3.1% yield. Here we should highlight the fact that after this work,[25] intermediate **40** became a popular synthetic target (vide infra). It is remarkable that this synthetic route to (±)-**1** also represents the first total syntheses, in the racemic series, of the later isolated compounds **2**, **4**, and probably **7**, provided that the stereochemical attribution of Danishefsky's synthetic intermediate **7** is correct (from the data available to us,[25b,7] this latter point remains unclear).



Scheme 3. Danishefsky's total synthesis of (±)-**1**.

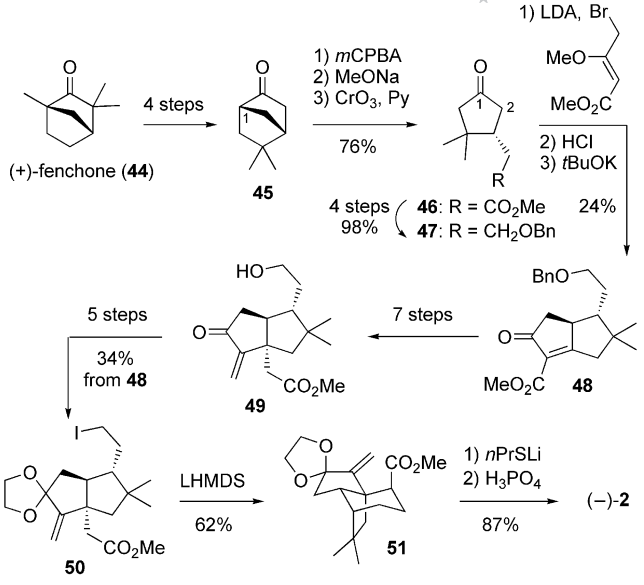
A year after the publication of Danishefsky's total synthesis of (±)-**1** (above), Helquist's group reported an alternative total synthesis of (±)-**1** by a similar strategy (Scheme 4).[26] Although, as recognized by Helquist himself, there are many strategy overlaps in the two syntheses, the early introduction of the hydroxymethyl group at C^5 in the latter synthesis largely facilitated the endgame work. Similarly to the previous work, Helquist's synthesis of **1** started with conjugated addition of vinyl Grignard reagent to 4,4-dimethylcyclopentenone, followed by stereoselective alkylation of the resulting enolate in a two-step protocol. Next, an intramolecular Horner–Wadsworth–Emmons reaction provided the bicyclic compound **41**, which underwent a conjugated addition of the enolate of methyl phenylmercaptoacetate to install the quaternary carbon atom at C^1. The resulting enolate was trapped with formaldehyde to introduce the hydroxymethyl group at C^5 early but with the wrong configuration, as previously observed by Danishefsky in a related transformation at a later stage of his

synthesis. The resulting β-hydroxy ketone was found to be unstable and so was transformed into the acetonide **42**. After regioselective introduction of an iodine atom, the key cyclization step was performed to give compound **43** with the same surprising diastereoselectively as observed by Danishefsky. From **43**, removal of the acetonide, saponification, selective acetylation of the primary alcohol, and oxidation of the resulting 1,3-hydroxyacetate to an enone provided the expected compound **2**, precursor of **1** by pyrolysis.



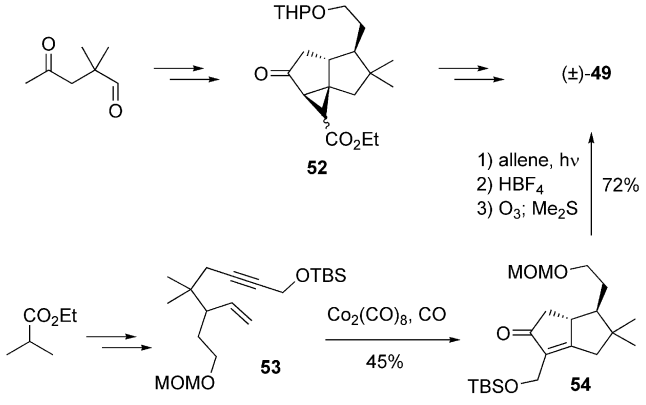
Scheme 4. Helquist's total synthesis of (±)-**1**.

The first non-racemic synthesis of (–)-terrecyclic acid A (**2**), the enantiomer of the natural product, was proposed by Isoe and co-workers in 1984 after a series of diastereoselective transformations of (+)-fenchone (**44**, terpene chiral pool).[27] A previously described four-step sequence starting from **44** afforded the bicyclo[2.2.1]heptanone **45**, which was converted into the expected cyclopentanone **46** through a sequence involving a regioselective Bayer–Villiger oxidation, methanolysis, and oxidation (Scheme 5). From the keto ester **46**, a four-step sequence furnished the corresponding benzyl ether **47**, which was regio- and stereoselectively alkylated at the 2-position with methyl 4-bromo-3-methoxycrotonate and, after deprotection, cyclized to the expected bicyclo[3.3.0]octane derivative **48**. The rest of the synthesis is very similar to the previously described syntheses of (±)-**2** from **37** and **41**, respectively (see Schemes 3 and 4). A series of functional group manipulations led to intermediate **50**, which underwent the key AB → ABC cyclization with a stereoselectivity consistent with previous work to give the advanced intermediate **51**, readily transformable into (–)-**2**. Because the sign of optical rotation of the synthetic compound was the opposite of that of the natural product, it was deduced that the absolute configurations of the two natural products (+)-**2** and (–)-**1** [synthetically derived from (+)-**2**; see above] are as depicted here.



Scheme 5. Isoe's total synthesis of (–)-**2** from the chiral pool.

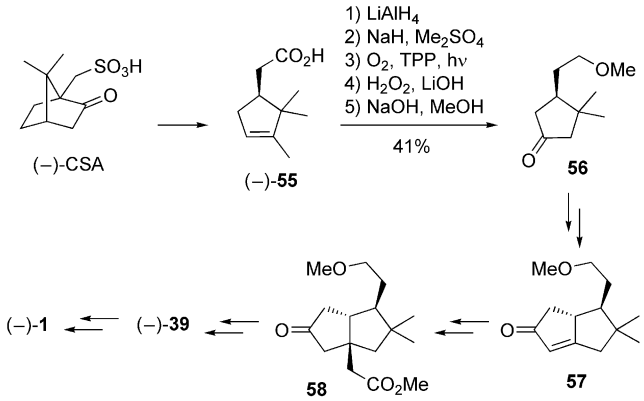
In 1985 Iwata and co-workers proposed a formal total synthesis of (±)-**2** and (±)-**1** based on Isoe's work, via the intermediate (±)-**49**, obtained in 20 steps and 3.8% overall yield from 2,2-dimethyl-4-oxopentanal, notably involving a stereoselective cyclopropanation to give **52**, and a regioselective opening of the three-membered ring followed by alkylation of the resulting enolate (Scheme 6).[28] In another related work, Magnus and co-workers used an intramolecular Pauson–Khand reaction of the enyne **53** to obtain the expected cyclopentenone **54**, which was converted into Isoe's intermediate (±)-**49** in three steps involving an allene [2+2] cycloaddition, removal of the ether protecting groups, and ozonolysis followed by reductive workup (Scheme 6).[29] In this latter work, Isoe's intermediate (±)-**49** was obtained in 15 steps and 6.5% overall yield from ethyl isobutyrate.



Scheme 6. Highlights of Iwata's and Magnus's formal syntheses of (±)-**2**.

In 1988 Liu reported the first total synthesis of the naturally occurring enantiomer of (–)-quadrone (**1**), from (–)-α-campholenic acid (**55**), obtained from (–)-camphorsulfonic

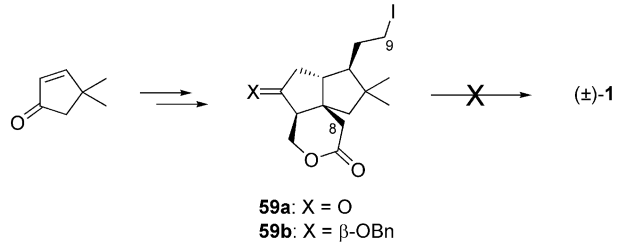
acid (terpene chiral pool), by an appropriate combination of the previously developed methods used to construct the key tricyclic Danishefsky's intermediate **39** (Scheme 7).[30] A series of straightforward transformations afforded the cyclopentanone **56** from (–)-**55**. Next, **56** was alkylated and cyclized to give the AB ring system **57** under conditions similar to those leading to the related compound **41** reported by Helquist. The allene [2+2] cycloaddition/ozonolysis sequence used by Magnus for the synthesis of **49** from **54** then stereoselectively gave the precursor **58** from **57**. After replacement of the methoxy group by an iodine atom and ketalization of the ketone carbonyl group in **58**, the expected optically active Danishefsky's intermediate (–)-**39** could be obtained and converted into (–)-**1** under the conditions developed earlier by Danishefsky. Overall, (–)-**1** was obtained from (–)-**55** in 21 steps and 1.0% yield.



Scheme 7. Liu's total synthesis of (–)-**1** from the chiral pool.

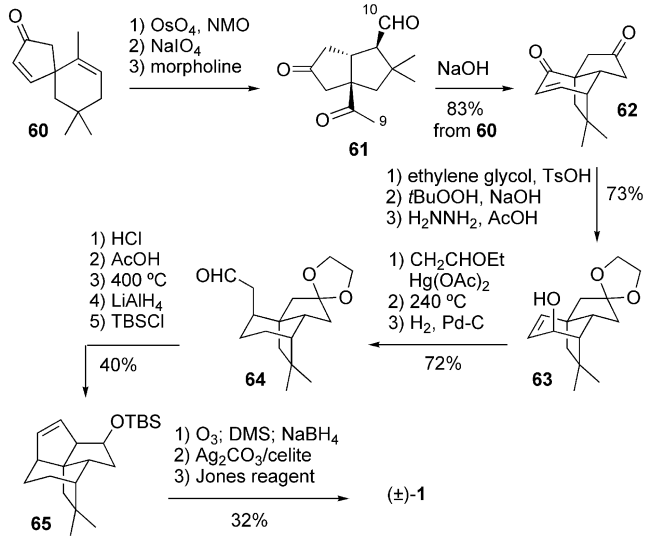
In an attempt to synthesize (±)-quadrone (**1**), the Paquette group proposed an alternative strategy for the construction of the ABCD tetracyclic core as early as 1982. They envisioned that the lactone D ring could be present prior to the formation of the six-membered C ring in the cyclization reaction presented above. Following a strategy they had developed for the total synthesis of the triquinane sesquiterpene pentalenolactone E methyl ester, they prepared the tricyclic iodolactones **59a** and **59b** from 4,4-dimethylcyclopentenone (Scheme 8).[31] Unfortunately, under none of the conditions tested was the expected cyclized product detected, although evidence of lactone enolate formation was obtained. At this stage, Paquette wisely noted that, in view of the existing total syntheses of **1** at the time,[25,26] a route involving cleavage of the lactone ring prior to C^8–C^9 carbon–carbon bond formation would have been workable.

In their total synthesis of (±)-**1**, Burke's group proposed a distinct annulation strategy involving the creation of the C^9–C^{10} carbon–carbon bond for the elaboration of the six-membered C ring (Scheme 9).[32] Starting with the spiro[4.5]decadienone **60**, they obtained the bicyclic precursor **61** by an oxidative cleavage followed by an intramolecular Michael addition. From the diketo aldehyde **61**, the key ring-forming aldolization/crotonization sequence gave the expected tricyclic keto enone **62**, which after chemoselective



Scheme 8. Paquette's proposed ABD → ABCD strategy.

ketalization was stereoselectively converted into the allylic alcohol **63**. Upon heating at 250 °C, the corresponding allyl vinyl ether underwent a Claisen rearrangement, and the resulting disubstituted olefin was hydrogenated to give the aldehyde **64**. In early work this was transformed in three steps (34%) into Danishefsky's intermediate **39**, thus securing the formal syntheses of **1** and **2**. An alternative route to **1** was then developed.[32b,32c] After deketalization, an intramolecular aldol/elimination sequence from **64**, followed by carbonyl reduction and protection of the resulting alcohol, afforded the cyclopentene **65**. Cleavage of the double bond with ozone followed by reductive workup afforded the corresponding diol, the oxidation of which furnished a separable 1:1 mixture of regioisomeric lactones. Final treatment of the correct silyl ether lactone isomer with the Jones reagent gave **1**.

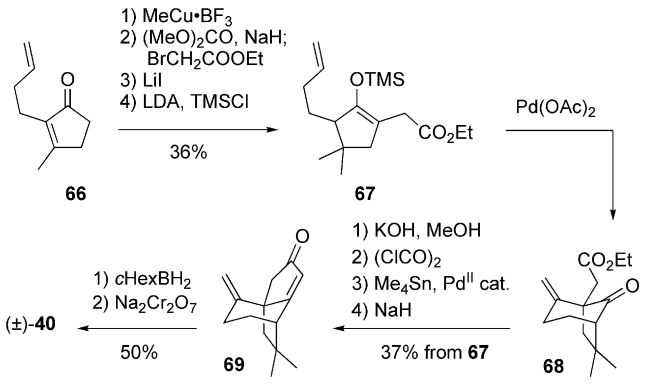


Scheme 9. Burke's total synthesis of (±)-**1**.

BC → ABC Strategy

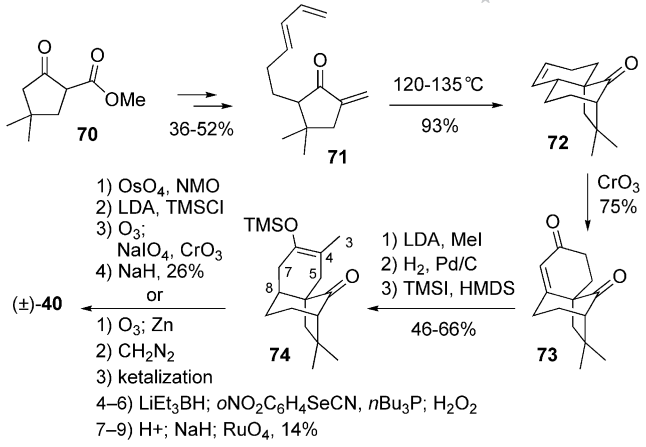
The alternative BC→ABC strategy for the construction of the functionalized quadrane backbone has also been keenly studied. The first report on this approach was from the Kende group, who proposed a formal synthesis of (±)-**1** via Danishefsky's intermediate **40** (Scheme 10).[33] Their synthesis began with the known compound **66**, which was readily transformed into the required silyl enol ether **67** for application of their palladium-mediated cycloalkenylation

reaction. Upon treatment with one equivalent of palladium acetate, **67** was selectively transformed into the expected bicyclo[3.2.1]octane derivative **68**, containing an *exo*-methylene group. The ethyl ester **68** was converted into the corresponding methyl ketone, which on treatment with sodium hydride underwent an aldolization/crotonization sequence to give the tricyclic compound **69**. Regioselective hydroboration of the *exo*-methylene group in **69** and oxidation gave Danishefsky's intermediate **40**.



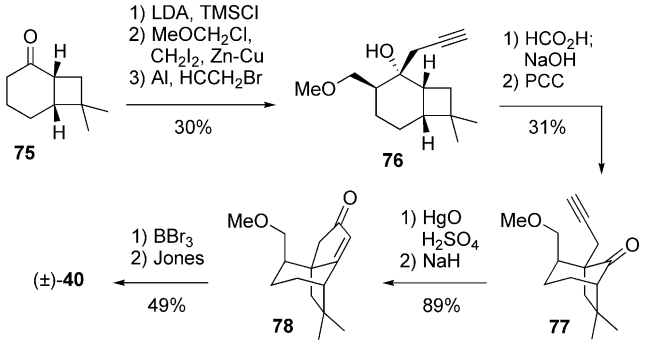
Scheme 10. Kende's formal synthesis of (±)-**1**.

The same intermediate **40** was also the target of Schlessinger's[34] formal synthesis of quadrone (Scheme 11). In this approach, an intramolecular Diels–Alder cycloaddition was used as the key step for the construction of the BC ring system, simultaneously creating elements of the A and D rings. The report from Schlessinger's group was followed within a few months by a very similar report from Vandewalle's group.[35] Both groups started with the β-keto ester **70**, which was rapidly converted into the Diels–Alder substrate **71**. Under thermal conditions, the *exo* adduct **72** containing a *trans*-decalin system was obtained in good yield and was converted into the enone **73** after allylic oxidation. Regioselective deprotonation/methylation at C^4 and subsequent stereoselective olefin hydrogenation and generation of the thermodynamic trimethylsilyl enol ether gave the *cis*-decalin system **74**. The two groups achieved the conversion of **74** into **40** in different ways. Schlessinger proposed an oxidation of the enol ether **74** to the corresponding hydroxyketone, and the regioisomeric trimethylsilyl enol ether was subjected to ozonolysis. Oxidative degradation of the resulting ozonide (fragmentation and expulsion of CO_2) gave the corresponding diketo acid, which was finally converted into **40** by aldolization/crotonization. Alternatively, Wandewalle proposed an ozonolytic cleavage of **74**, and the resulting ring-opened diketo acid was converted into the corresponding methyl ester. After ketalization of the newly created methyl ketone, the ester group was converted in three steps into a terminal olefin and the ketal protecting group was removed. At this stage, an aldolization/crotonization sequence installed the A ring as previously, and the axial vinyl group at C^8 was degraded under oxidative conditions to give the acid **40**.



Scheme 11. Schlessinger's and Vandewalle's formal syntheses of (±)-**1**.

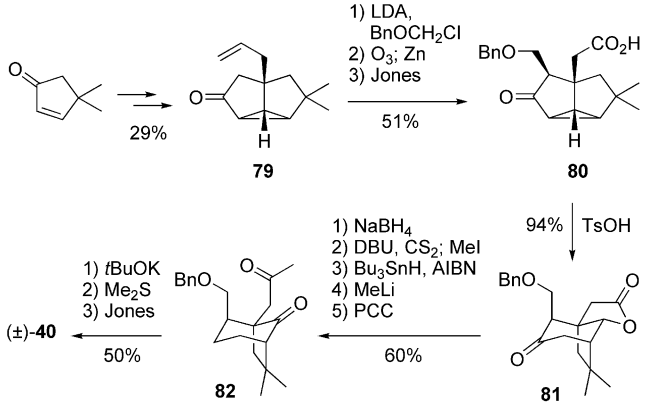
Compound **75**, obtained by [2+2] photocycloaddition between isobutene and cyclohex-2-enone, served as starting material in Yoshii's formal synthesis of (±)-**1** via Danishefsky's intermediate **40** (Scheme 12).[36] The intermediate **76** was obtained by regio- and stereoselective introduction of a (methoxy)methyl group, followed by nucleophilic addition of propargylaluminium bromide. On treatment with formic acid, **76** underwent a formolytic rearrangement to a bicyclo[3.2.1]octane derivative, which after hydrolysis and oxidation gave the ketone **77**. Hydration of the triple bond followed by the now classical aldolization/crotonization sequence afforded the expected tricyclic compound **78**, which was readily converted into **40**. Overall, this approach provides a relatively direct access to (±)-**1** from **75** (12 steps).



Scheme 12. Yoshii's formal synthesis of (±)-**1**.

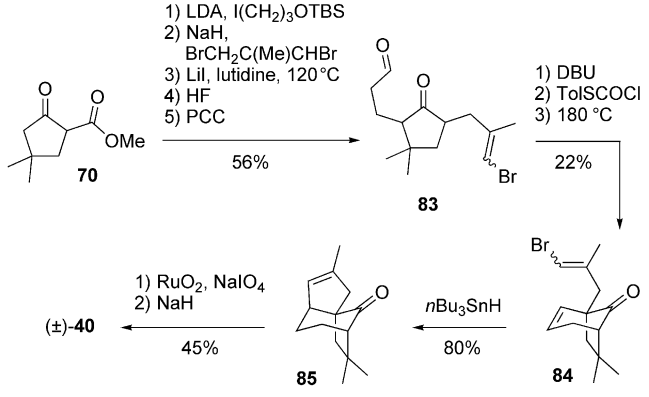
The anomalous fragmentation of tricyclo[3.3.0.$0^{2,8}$]octan-3-ones containing a *gem*-dimethyl group at C^7 (in the IUPAC recommended numbering, not the numbering for quadranes proposed here) into bicyclo[3.2.1]octanone products was exploited in Iwata's formal synthesis of (±)-**1** (Scheme 13).[37] The tricyclic product **79**, obtained in seven steps from 4,4-dimethylcyclopentenone, was alkylated with (benzyloxy)methyl chloride via its lithium enolate, and the terminal olefin was converted into the carboxylic acid on ozonization, reduction, and oxidation to give **80**. On treatment with *p*-toluenesulfonic acid, **80** afforded the γ-lactone **81** through the fragmentation described above. A three-step

complete reduction of the ketone carbonyl group in **81**, followed by lactone opening with methyllithium and oxidation of the resulting secondary alcohol, secured access to **82**, which was converted into Danishefsky's intermediate **40** in three steps.



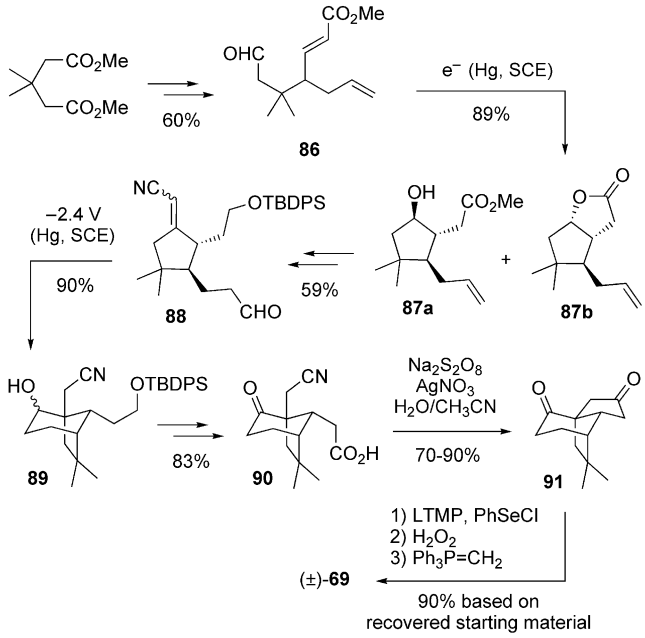
Scheme 13. Iwata's formal synthesis of (±)-**1**.

Parson and co-workers proposed another route to Danishefsky's intermediate (±)-**40** involving a radical cyclization (Scheme 14).[38] The readily available β-keto ester **70** was successively alkylated in both enolizable positions and decarboxylated, and the resulting silyl ether was converted into an aldehyde to give **83**. A base-promoted intramolecular aldolization provided the desired bicyclo[3.2.1]octanol as a diastereomeric mixture, which was dehydrated to give **84**. An intramolecular radical cyclization diastereoselectively furnished the cyclopentene **85**, which upon oxidative cleavage and the aldolization/crotonization sequence presented above gave the intermediate (±)-**40**.



Scheme 14. Parson's formal synthesis of (±)-**1**.

Little and co-workers proposed a formal synthesis of (±)-**1** involving a series of electrochemical reactions (Scheme 15).[39] Compound **86**, derived from dimethyl 3,3-dimethylglutarate in seven steps, was cyclized under electroreductive conditions to give the functionalized B ring precursors **87**. Through functional group manipulations these were transformed in six steps into intermediate **88**, which could undergo a second electroreductive cyclization to provide the BC ring system **89**. After yet another series of functional group manipulations compound **90** was obtained. Upon radical decarboxylation with sodium peroxydisulfate, **90** was transformed through an intramolecular cyclization to the nitrile group into the diketone **91** following hydrolysis of the intermediate imine. The diketone **91** was easily converted into Kende's intermediate **69**.

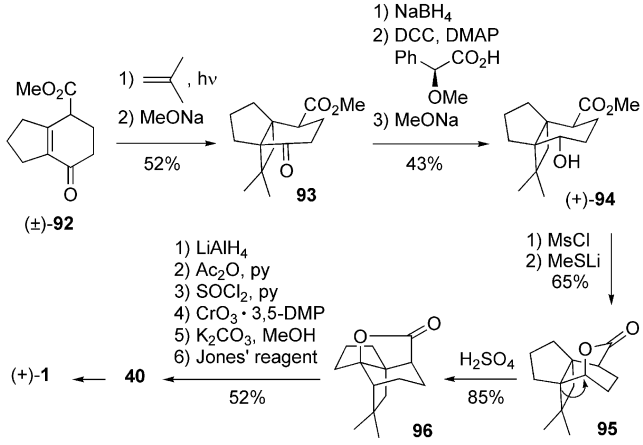


Scheme 15. Little's formal synthesis of (±)-**1**.

Rearrangement Strategies Directed Towards the ABC Tricyclic Core

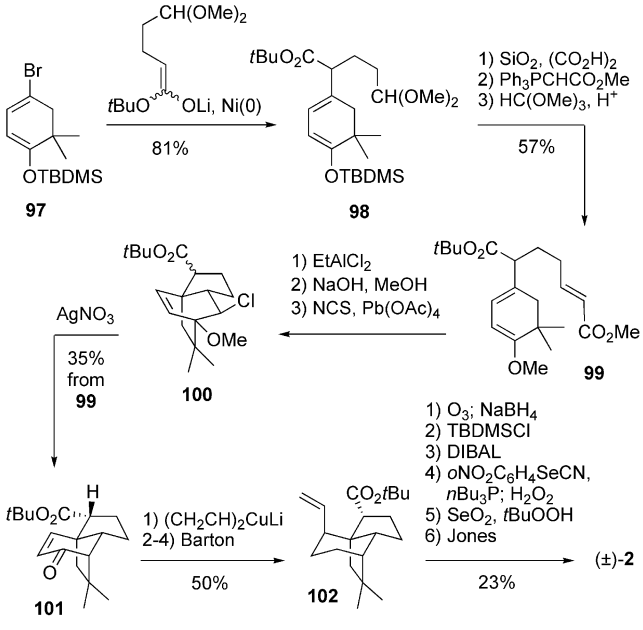
Contemporaneously with Isoe's determination of the absolute configuration of (+)-**2** and (–)-**1**, Smith III came to the same conclusion after his asymmetric total synthesis of (+)-**1** involving a kinetic resolution (Scheme 16).[40] The synthesis began with the photochemical [2+2] cycloaddition between isobutylene and the racemic bicyclic enone (±)-**92**, followed by epimerization of the carboxylate group to the equatorial position to give **93**. After stereoselective reduction of the ketone group, the resulting equatorial secondary alcohol was esterified with *(S)*-(+)-*O*-methylmandelic acid, the diastereomers (*dr* = 1.4:1) were separated, and the chiral auxiliary was removed to afford (+)-**94**. Intramolecular lactonization via the mesylate then afforded **95**, which was subjected to the key acid-promoted rearrangement to give the lactone **96**, containing the expected ABC tricyclic ring system. Six straightforward steps were then necessary to obtain Danishefsky's intermediate **40** in nonracemic form and in 52% overall yield. This was converted into unnatural (+)-**1** under the conditions previously developed by Danishefsky. By this sequence (–)-**94** was converted into naturally occurring (–)-**1**.

A key skeletal reorganization from a [2.2.2] bicyclic system to the crucial bicyclo[3.2.1]octane core is also the cornerstone of Wender's synthesis of (±)-**2** (Scheme 17).[41] From the vinylic bromide **97**, a nickel(0)-mediated coupling



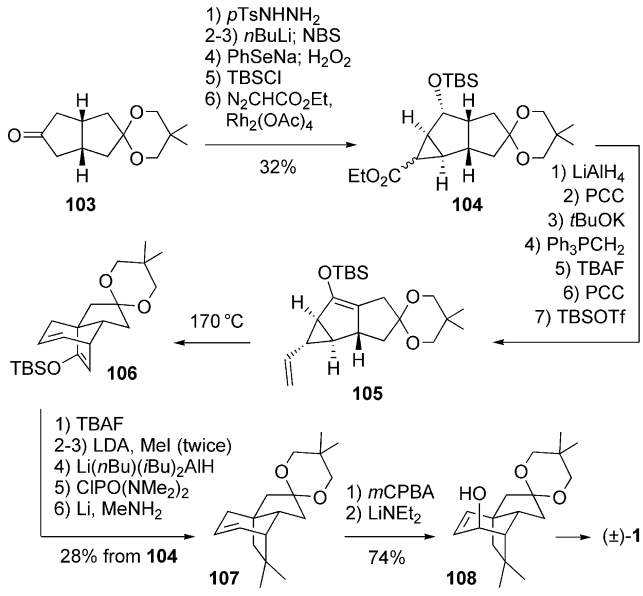
Scheme 16. Smith III's synthesis of (+)-**1**.

reaction afforded **98**, which was converted into the desired intramolecular Diels–Alder precursor **99**. Upon treatment with ethylaluminium dichloride, **99** cleanly underwent the expected cycloaddition, and the adduct was saponified and halodecarboxylated to give the chlorinated compound **100**. The key rearrangement of **100** was performed with silver nitrate to give **101**. A stereoselective conjugate addition of divinylcuprate and reduction of the ketone to a methylene group afforded **102**. The double bond in **102** was converted into a silyl ether by ozonolysis, reductive workup, and protection of the resulting primary alcohol. The ester was then converted into the corresponding exocyclic olefin, and a regiospecific allylic oxidation followed by a deprotection/oxidation sequence of the silyl ether with the Jones reagent finally gave (±)-**2**.



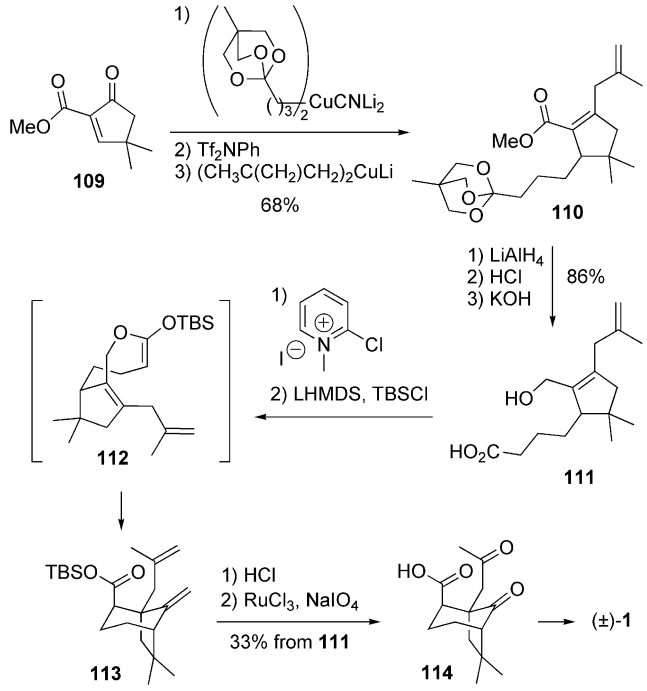
Scheme 17. Wender's synthesis of (±)-**2**.

Piers reported a formal synthesis of (±)-**1** involving a Cope rearrangement of a functionalized divinylcyclopropane derivative (Scheme 18).[42] The intermediate **104** was prepared by a rhodium-catalyzed stereoselective cyclopropanation of an olefin derived from the ketoketal **103**. The ethyl ester group in the diastereomeric mixture **104** was converted by a reduction/oxidation sequence into the corresponding aldehyde, which was equilibrated to the α-isomer and olefinated. Removal of the silyl ether, oxidation of the resulting secondary alcohol into a ketone, and silylation of the corresponding enol installed the second olefin to give the divinylcyclopropane derivative **105**. The key rearrangement step produced the expected tricyclic compound **106** with the quadrane ABC ring system. Installation of the *gem*-dimethyl system and reduction provided the intermediate **107**, which was readily converted into the allylic alcohol **108**. Compound **108** differs only in the nature of the ketal protecting group from the intermediate **63** employed by Burke and co-workers in their synthesis of (±)-**1** (Scheme 9), and the formal synthesis of **1** was completed by conversion of **108** into one of Burke's late intermediate (deprotected **64**) by a very similar sequence.



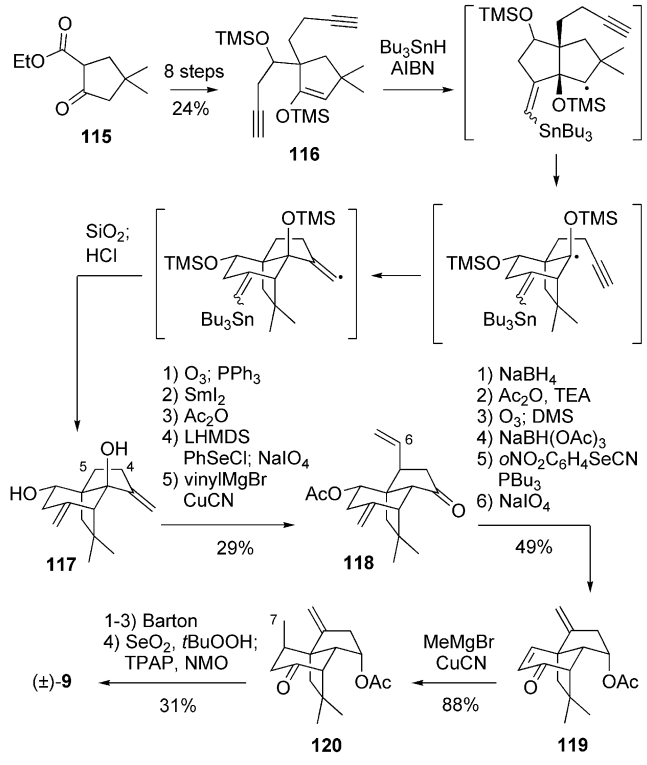
Scheme 18. Piers' formal synthesis of (±)-**1**.

A Claisen rearrangement is also in evidence in Funk's formal synthesis of (±)-**1** (Scheme 19).[43] The conjugated addition of a higher order cyanocuprate to the starting cyclopentenone **109**, followed by generation of a triflyl enol ether and subsequent treatment with methallyl cuprate, produced the β-substituted unsaturated ester **110**, which was readily transformed into the hydroxy acid **111**. Under macrolactonization conditions, the corresponding bicyclic lactone was obtained. When the required silylated lactone ketene ketal **112** was prepared, it was found to be surprisingly unstable and spontaneously underwent the expected Claisen rearrangement to give the bicyclic silyl ester **113**. This was hydrolyzed to the carboxylic acid, and a simultaneous oxidative cleavage of the two *exo* olefins gave the diketo acid **114**, which had previously been transformed into Danishefsky's intermediate **40** by Schlessinger (Scheme 11), thus completing a formal synthesis of **1**.



Scheme 19. Funk's formal synthesis of (±)-**1**.

A domino free radical cyclization/rearrangement sequence has been exploited by Lee's group to produce the tricyclic quadrane ring system and was successfully applied to the total synthesis of (±)-suberosenone (**9**, Scheme 20).[44] Compound **116**, the precursor for the free radical cascade reaction, was obtained from the β-keto ester **115**. Upon treatment with tin hydride, the enediyne **116** underwent a first cyclization to produce a bicyclo[3.3.0]octane radical intermediate, which rearranged to a bicyclo[3.2.1]octane radical, precursor of the tricyclic compound **117**, after C–Sn bond cleavage and removal of the silyl ether protecting groups. From **117**, the rest of the synthesis consists of the introduction of the two missing C^6 and C^7 carbon atoms by conjugated addition of Grignard reagents, together with intensive functional group manipulations in a total of sixteen steps to remove unwanted oxidized positions and to introduce the required conjugated enone at positions C^4 and C^5.



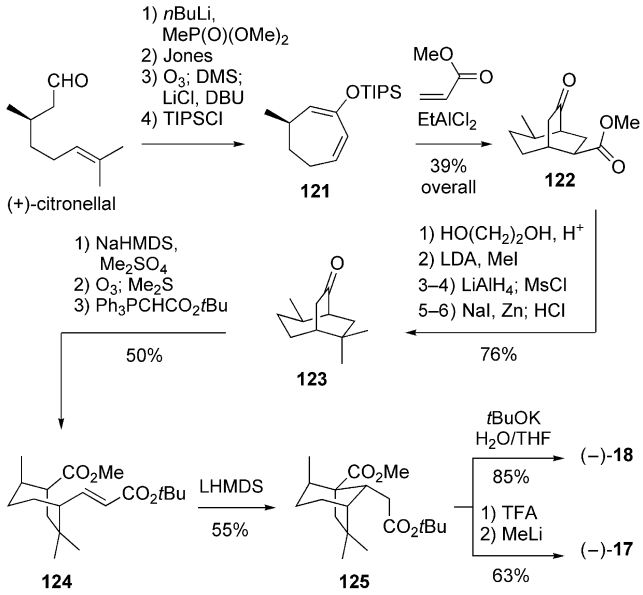
Scheme 20. Lee's total synthesis of (±)-**9**.

Miscellaneous Synthetic Work

In this section we briefly describe the total syntheses of the two naturally occurring bicyclic (BC ring system only) quadranes so far identified – the (–)-isishippuric acids A and B (**17** and **18**, respectively) – together with the synthetic work targeting some nonnatural biologically active quadrane derivatives and unfinished alternative routes to quadranes.

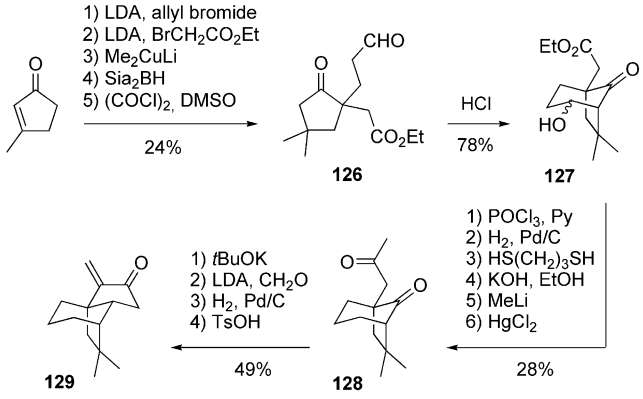
Recently, Kuwahara and co-workers reported the diastereoselective total synthesis of (–)-isishippuric acid B (**18**) from (+)-citronellal (Scheme 21).[45] The silyl cycloheptadienol ether **121** was obtained from (+)-citronellal in four steps including an intramolecular Horner–Wadsworth–Emmons reaction. A Diels–Alder cycloaddition with methyl acrylate then allowed the preparation of the bicyclic compound **122**, which was transformed into the *gem*-dimethyl compound **123** via its ketal-protected form by alkylation with iodomethane and reduction of the carboxylate. Next, the methyl enol ether derived from **123** was oxidatively cleaved, and the resulting ester aldehyde was engaged in a Horner–Emmons olefination to furnish **124**. An intramolecular Michael addition of **124** formed the desired bicyclic diester **125** with moderate diastereoselectivity (*dr* = 2.3:1), and this was saponified to the natural product (–)-**18**. In a subsequent report, the same group reported the synthesis of (–)-isishippuric acid A (**17**) by selective hydrolysis of the *tert*-butyl ester in 1**25** followed by treatment with methyllithium (Scheme 21).[46]

In an early synthetic study directed towards the total synthesis of quadrone, Smith and co-workers accomplished the synthesis of the quadrone analogue (±)-**129**, termed descarboxylquadrone (Scheme 22).[47] A successive double enolate alkylation sequence starting from 3-methylcyclopent-2-enone, followed by conjugated addition of a methyl group and conversion of the terminal olefin to an aldehyde, provided the cyclopentanone **126**. An acid-catalyzed aldol cyclization gave the desired BC ring system **127** as a mixture of isomers. After dehydration of the diastereomeric mixture and hydrogenation of the resulting olefin, the ethyl ester group was converted into an acetonyl unit in **128** via the corresponding thioketal. The key aldolization/crotonization step, later to be used in many syntheses of quadranes (vide supra), was accomplished with potassium *tert*-butoxide to give the



Scheme 21. Kuwahara's total syntheses of (–)-**18** and (–)-**17** from the chiral pool.

unsaturated tricyclic framework. Then, alkylation of the corresponding enolate with formaldehyde followed by stereoselective hydrogenation of the endocyclic double bond and dehydration produced the target compound **129**. (±)-Descarboxylquadrone (**129**) was found to display biological activity comparable to that of (–)-quadrone (**1**) (vide supra).[47]



Scheme 22. Smith's total synthesis of (±)-**129**.

Thanks to its potent biological activity and simplified structure, **129** became quite a popular target in the 1980s. Indeed, Yoshii and co-workers also proposed a synthesis of (±)-**129** by a route similar to the one they developed for the formal total synthesis of (±)-**1** (see Scheme 12).[36] Similarly, Iwata and co-workers applied their strategy for the synthesis of (±)-**1** (see Scheme 13) to (±)-**129**.[37a,48] In a related study, Kakiuchi and co-workers reported the syntheses of the nonnatural quadrane analogues (±)-**129** and (±)-**130**–**132** (Figure 7) by an approach involving a skeletal rearrangement comparable to the one used by Smith and co-workers in their total synthesis of (+)-**1** (see Scheme 16).[49] Monti and co-worker proposed an approach to (±)-quadrone (**1**) culminating in the synthesis of diketone **133** (Figure 7) involving a rearrangement of a bicyclo[2.2.2]octenone intermediate,[50] and a comparable strategy was used by Hua and co-workers for the preparation of compound **134** (Figure 7).[51] An unfinished carbohydrate-based synthetic approach to (–)-quadrone (**1**) was also reported.[52]

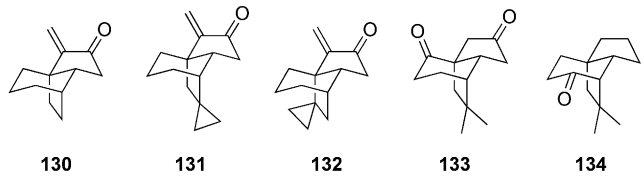


Figure 7. Kakiuchi's and Monti's nonnatural quadrane analogues.

Conclusions

Quadranes are a restricted class of naturally occurring sesquiterpenes that in the 1980s was the subject of considerable attention, due both to an original tricyclic carbon skeleton and to a potent biological profile. More recently, the isolation of new members of this family of natural products with enhanced anti-cancer cytotoxicities has triggered renewed interest. However, a systematic biological evaluation as well as an in depth structure–activity relationship study are still desirable. From the biosynthetic point of view, there are serious arguments in favor of a common origin of quadranes and triquinane sesquiterpenes. Quadrone (**1**), the first isolated and most famous quadrane, has been the subject of intense synthetic investigations, which have resulted in a number of total and formal syntheses. We can highlight the fact that Danishefsky's pioneering work in this field has been the cornerstone of many successful syntheses. Surprisingly, however, this bibliographic survey has revealed that, although a few asymmetric syntheses (from the chiral pool or by racemate resolution) have been reported, no enantioselective approach to naturally occurring quadranes is yet available. The considerable progress in the science of synthesis during the past few decades should now allow the total synthesis of these natural products by much more direct routes and, hopefully, in an enantiocontrolled manner.

Acknowledgments

M. P. thanks the ENS Cachan for a fellowship award. Financial support from the French Research Ministry, the Université Paul Cézanne, and the Centre National de la Recherche Scientifique (CNRS) (UMR 6263) is also gratefully acknowledged.

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Received: November 14, 2009
Published Online: March 1, 2010

