6.4 狄尔斯-阿尔德反应的发现

狄尔斯-阿尔德反应（Diels-Alder reaction）又叫双烯加成反应，1928 年德国化学家 Otto Paul Hermann Diels（1876—1954，图 24）及其学生 Kurt Alder（1902—1958，图 24）首次发现并报道了该反应[58]，他们也因此获得了 1950 年的诺贝尔化学奖。狄尔斯-阿尔德反应是现代有机合成特别是天然产物全合成常用的一个反应，被伍德沃德和 Nicolaou 等合成大师们青睐[59-62]。近 20 年，约有 400 余个天然的狄尔斯-阿尔德反应加成物被不断分离、鉴定[63]，探究植物中存在的狄尔斯-阿尔德反应合成酶也成为化学家和生物学家研究的热点[64-72]。

6.5 基于生物合成作用机制的药物发现——他汀（statins）

20 世纪 50 年代美国生化学家即 1964 年的诺贝尔生理学或医学奖获得者 Konrad Emil Bloch（1912—2000）阐明了胆固醇生物合成途径[73-74]（图 25）。当时胆固醇超标和心脏疾病之间具有一定联系的观点已经得到共识。1973 年，高尔斯坦和布朗教授成功建立了胆固醇合成速度分析技术，就是通过分析成纤维细胞 HMG-CoA 还原酶（HMGR）的活性，间接了解了细胞合成胆固醇的能力。然后利用这一简单技术，确定了血液中低密度脂蛋白是抑制胆固醇合成的关键因子。二人也因此获得了 1985 年诺贝尔医学奖[75-76]。

图 24 Otto Paul Hermann Diels (左) 和 Kurt Alder (右)

Fig. 24 Otto Paul Hermann Diels (left) and Kurt Alder (right)

受发现青霉素和链霉素的启发，日本科学家远藤章（Akira Endo，图 26）认为某种菌类可能会产生可以抑制胆固醇合成的物质。这些微生物代谢产物有可能抑制 HMGR。1972 年，远藤章在筛选了 3 800 种真菌后，终于发现了桔青酶 *Penicillium citrinum* 提取物能够有效地抑制胆固醇的合成，1 年后成功从桔青酶中提纯了活性物质，命名为 ML-236B，也就是世界上第一个调血脂的天然化合物——美伐他汀（mevastatin）。他汀又称为 HMG-CoA 还原酶抑制剂（HMG-CoA reductase inhibitors）。而 HMGR 正是胆固醇生物合成过程中的一个关键限速酶。他汀类药物的活性部位就是甲瓦龙酸相似的羟基戊酸部分。1979 年远藤章首次从红曲霉 *Monascus rubber* 中分离出具有 HMGR 抑制作用的化合物 monacolin K。几乎同一时间，默克公司的 Alfred Alberts 博士从土曲霉 *Aspergillus terreus* 中也分离出一个对于 HMGR 有抑制作用的化合物，命名为 mevinolin。后来证实 monacolin K 与 mevinolin 为同一物质，即洛伐他汀（lovastatin）。1987 年，洛伐他汀（商品名美降脂 Mevacor®）被

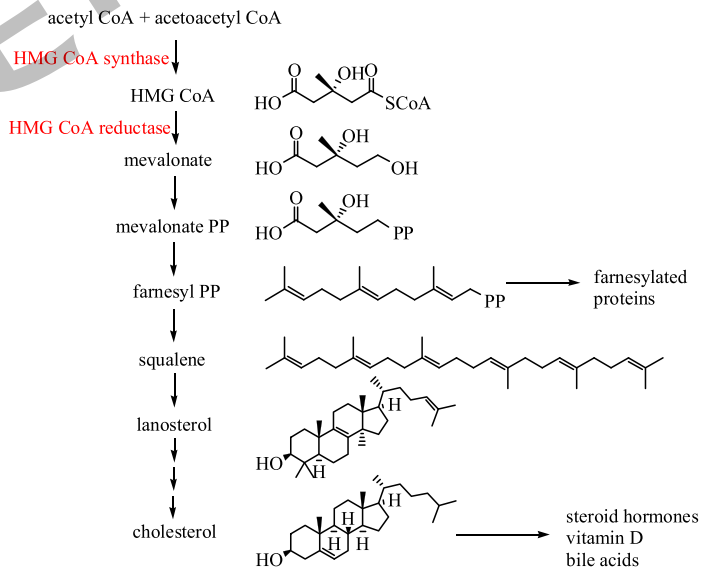


图 25 胆固醇的生物合成

Fig. 25 Biosynthesis of cholesterol

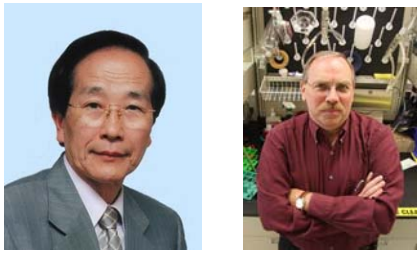
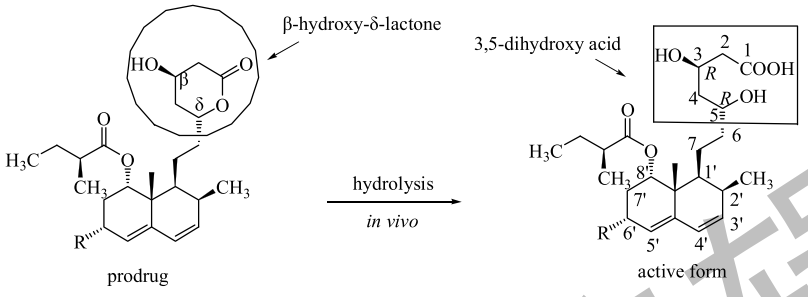


图 26 远藤章 (左) 和 Bruce D. Roth (右)

Fig. 26 Akira Endo (left) and Bruce D. Roth (right)

FDA 批准成为第一个上市的他汀药物（图 27）。受天然他汀类药物的活性部位的启发，1985 年 Warner-Lambert 公司的青年化学家 Bruce D. Roth（图 26）成功地研发出辉瑞（Pfizer Inc.）的第一个人工合成的他汀类药物——阿托伐他汀（atorvastatin）。1996 年底，美国食品药品监督管理局（FDA）批准了阿托伐他汀，商品名为立普妥，开始了一段药品发展史上的传奇。自 1996 年上市以来，立普妥连续保持



R = H; compactin = MLB-236B = mevastatin

R = CH_3; lovastatin = mevinolin = monacolin

图 27 美伐他汀、洛伐他汀的结构及体内活性形式

Fig. 27 Structures and *in vivo* active forms of mevastatin and lovastatin

销售冠军纪录达 10 年，且是第一个年销售额突破百亿大关的畅销药物，也是迄今药物史上销售额最大的药物，成了史上最成功的 me-best 药物。

7 结语

天然产物来源于自然界，其化学结构和功能是在自然界长期的进化过程中得以选择和优化的结果，它们所具有的独特结构特征赋予了天然产物与特定靶点专一性结合的能力并表现出良好的生物活性，是生物活性前体化合物和药物发现的重要源泉。自然界的天然产物已逾 10 万余种，结构千差万别。天然产物生物合成研究把这些包罗万象的结构从生源上进行系统分类，理清了这些天然产物内在的联系。天然药物化学的任务之一是阐明具有生物活性的天然产物的结构及进行全合成，生物合成的理论有助于天然产物合成的设计和结构的推导，如 Robinson 对吗啡结构的推导就是典型的案例之一。在生物体内，一次代谢形成的几百个化合物中只有几个是二次代谢产物的原料，由这些简单的原料进一步转化形成数目庞大、结构各异的天然化合物，如何对其形成的原理、涉及反应的类型及机制进行科学的分类引起了人们极大的兴趣。生物合成的反应很多也符合有机化学反应机制，甚至包括立体化学机制。通过生源合成途径研究，阐明一类化合物的生物合成的每个步骤，探索天然产物的形成规律，阐明天然化合物结构之间的联系及一次代谢和二次代谢产生的生源关系，解释复杂多变的天然药物化学成分之间的内在逻辑，为天然产物的全合成具有指导意义。天然产物化学和分子生物学的发展和融合为基础的化学生物学（chemical biology）和合成生物学（synthetic biology）的诞生将催生下一次生物技术革命[77-80]。

本文为《天然药物化学史话》系列文章之一。文中部分图片源自网络，在此向原作者表示衷心感谢。

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