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Natural Product Synthesis

Synthesis of Platensimycin

*Konrad Tiefenbacher and Johann Mulzer**

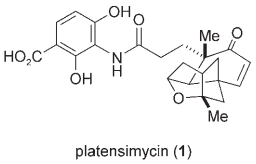
antibiotics · natural products · platensimycin · total synthesis

Dedicated to Professor Elias J. Corey on the occasion of his 80th birthday

In modern drug discovery, antibodies or libraries of simple synthetic organic compounds, mostly of heterocyclic origin, are favored. Natural products play an increasingly inferior role as they are considered structurally too complex, limited in quantity, and difficult to synthesize, manipulate, and derivatize. Thus it was a sensation when a Merck research group reported that classical screening of metabolites from Streptomyces platensis has unearthed a low-molecular-weight organic compound with remarkable antibiotic properties.

1. Introduction

The ever increasing multiresistance of bacteria is a serious and urgent problem, particularly in hospitals, where antibiotics are in permanent use and bacteria strains easily evolve that withstand multiple antibiotic classes. Especially worrying are infections by gram-positive pathogens, such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *enterococci* (VRE), and penicillin-resistant *Streptococcus pneumonia* (PRSP).[1] Newly discovered antibiotics usually address well-known targets just at new binding sites or through new binding modes. Finding a completely new structural class is a rare event. In this respect, the discovery of platensimycin (**1**; Scheme 1),[2] a metabolite of *Streptomyces platensis*, by Wang et al. who screened natural-product extracts for novel FabF/H inhibitors has been hailed as a true breakthrough in antibiotic research.



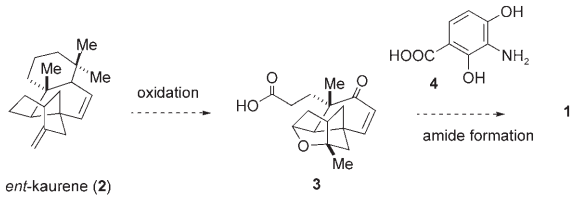
platensimycin (**1**)

Scheme 1. Structure of platensimycin.

Platensimycin acts by efficiently blocking bacterial fatty acid biosynthesis. The molecular target is the β-ketoacyl-(acyl-carrier-protein) synthase (FabF) which is one of the key enzymes in bacterial fatty acid biosynthesis. It was shown that platensimycin's benzoic acid moiety competes with the malonyl-acyl-carrier-protein for the malonyl binding site of FabF.[2]

Platensimycin has potent activity against gram-positive bacteria including multiresistant strains of *staphylococci* and *enterococci*. Owing to its unique mode of action no cross-resistances to existing drugs have been observed to date. In addition no toxic effects have been detected. However, the in vivo efficacy of **1** is low, owing to its limited metabolic stability, so that suitable derivatives of **1** will have to be investigated to find more promising drug candidates.[1]

Platensimycin has an intriguing structure which features a hydrophilic aromatic "western" unit and a lipophilic tetracyclic "eastern" unit both linked together by amide bond. With respect to the biosynthesis of **1**, it has been speculated that the unique tetracyclic unit could be derived from bacterial oxidation of *ent*-kaurene (**2**) or a related diterpene common in plants or fungi (Scheme 2).[1,2e]



ent-kaurene (**2**) **3**

Scheme 2. Speculation about the biosynthetic origin of platensimycin (**1**).

Retrosynthetically, **1** should arise from the amidation of carboxylic acid **3** with a suitably protected derivative of the aromatic amine **4**. Acid **3**, in turn could be prepared by a twofold alkylation of ketone **5** which thus is the key intermediate of the entire synthesis (Scheme 3). In fact, all

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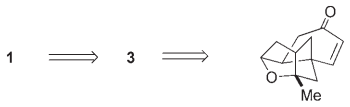


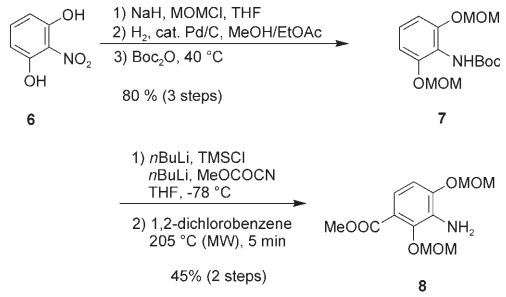
5

Scheme 3. Retrosyntheic analysis of platensimycin (**1**) by Nicolaou et al.[3b]

routes to date have followed this strategy.[3a] Only one synthesis[3b] has been carried through to **1**, the rest have formal character and terminate with the production of intermediate **5** in racemic or optically active form.

2. Synthesis of the Aromatic Unit

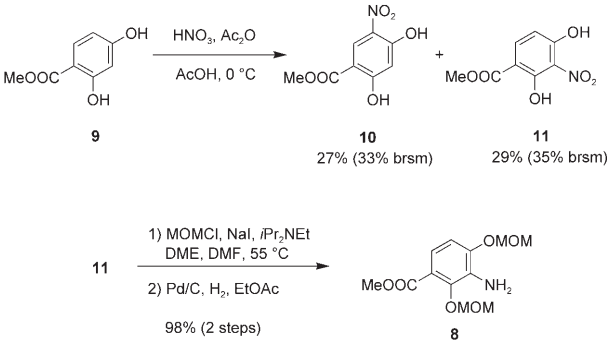
Two approaches to the aromatic part of platensimycin have been described. The synthesis by Nicolaou's group[3b] started from commercially available 2-nitroresorcinol (**6**) which is bis-MOM protected and reduced to the amine which was protected as the N-Boc derivative **7** (Scheme 4). The



Scheme 4. Synthesis of the aromatic part of **1** by Nicolaou et al.[3b] MOM = methoxymethyl, THF = tetrahydrofuran, Boc = *tert*-butoxycarbonyl, TMS = trimethylsilyl.

required carboxylic acid was introduced by *ortho*-metalation, after in situ silylation of the carbamte. Cleavage of the Boc protecting group gave amine **8** in moderate yield.

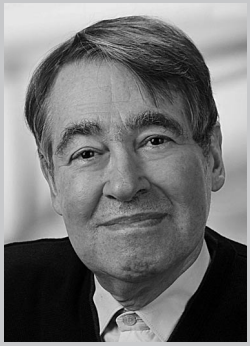
In an regio-unselective approach by Giannis et al.[4] commercially available methyl 2,4-dihydroxybenzoate (**9**) was nitrated to a 1:1 mixture of the two isomers **10** and **11** (Scheme 5). Since they are easily separable and just two more simple steps are required to complete the synthesis of **8** this synthetic sequence appears quite efficient.



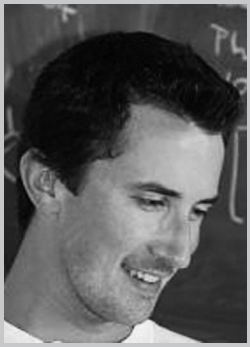
Scheme 5. Synthesis of the aromatic part of **1** by Giannis et al. [4]DME = dimethoxyethane, DMF = *N*,*N*-dimethylformamide. brsm = based on recovered starting material.

3. Total and Formal Synthesis of Platensimycin

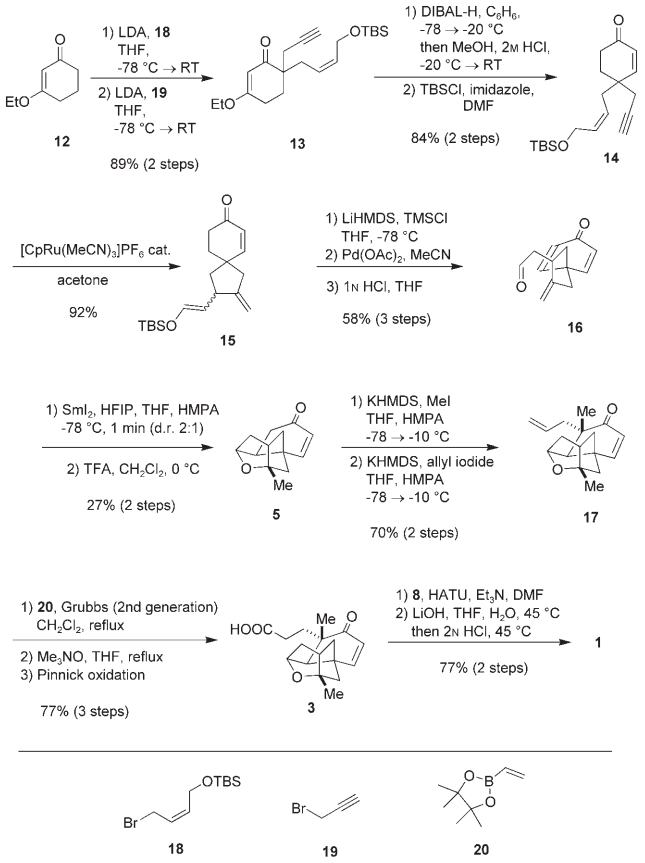
The first synthesis of racemic platensimycin was completed by the Nicolaou group about four months after the publication of the structure.[3] Their strategy first aimed for the core intermediate **5** which was then converted into **1** by attaching the appropriate appendages. For the preparation of **5**, a ruthenium-catalyzed cycloisomerization[5] of **14** was used to construct the spiro-cyclopentane derivative **15** from which the *cis* decalinoid system was formed by a ketyl radical cyclization (Scheme 6). The sequence started with the construction of the first quaternary center by double alkylation of ketone **12**. After allylic isomerization and reprotection of the primary alcohol the precursor for the cyclopentane formation was reached in excellent yields. Ruthenium-catalyzed cycloisomerization of **14** yielded **15** as an inconsequential 1:1 mixture of diastereomers which was converted into aldehyde **16** by Saegusa oxidation and hydrolysis of the silyl enolether. The following ketyl radical cyclization gave, even under carefully controlled conditions, a somehow disappointing 46% yield of a 2:1 mixture of diastereomeric secondary alcohols. Without separation this mixture was treated with trifluoroacetic acid, whereupon one of the diastereomers



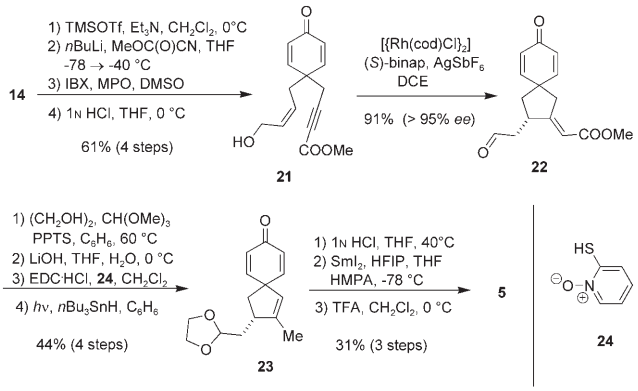
Johann Mulzer was born in 1944 in Prien, Germany. In 1974 he received his PhD degree under the supervision of Rolf Huisgen at the Ludwig-Maximilians University in Munich. Subsequently, he joined the group of E. J. Corey at Harvard as a postdoctoral fellow. From 1982 to1996 he held professorships at the University of Düsseldorf, the Free University of Berlin, and the Johann Wolfgang Goethe University in Frankfurt. Since 1996 he has been a full professor at the University of Vienna. His main research interests are focused on the total synthesis of structurally and physiologically interesting natural products.



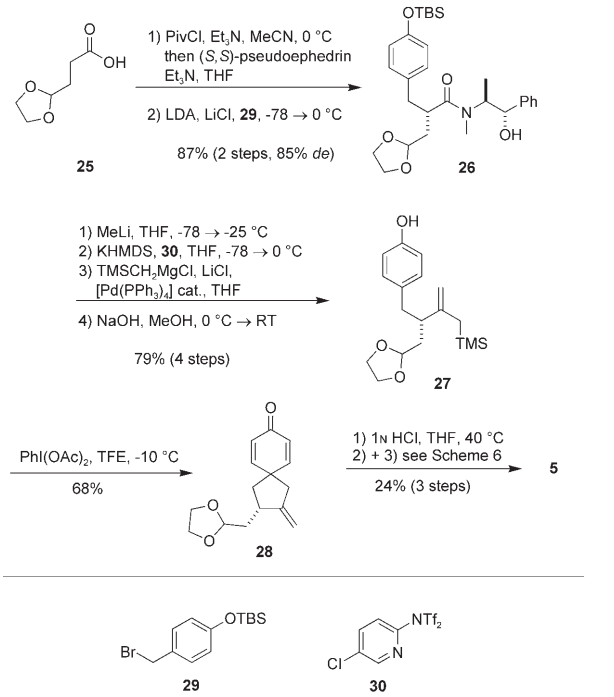
Konrad Tiefenbacher was born 1980 in Vienna, Austria. He studied chemistry at the Technical University of Vienna where he received his master degree in 2004 under the supervision of J. Fröhlich. Since joining the research group of J. Mulzer at the University of Vienna in 2005, he has been working on the total synthesis of the natural products ovalicin and platensimycin.



Scheme 6. Total synthesis of platensimycin by Nicolaou et al.[3b] LDA = lithium diisopropylamide, TBS = *tert*-butyldimethylsilyl, DIBAL-H = diisobutylaluminium hydride, Cp = cyclopentadienyl, HMDS = hexamethyldisilazide, HFIP = 1,1,1,3,3,3-hexafluoropropan-2-ol, TFA = trifluoroacetic acid, HMPA = hexamethylphosphoramide, HATU = O-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate.



Scheme 7. Synthesis of optically active **5** through enantioselective catalysis by Nicolaou et al.[6] IBX = *o*-iodoxybenzoic acid, MPO = 4-methoxypyridine-*N*-oxide, DMSO = dimethyl sulfoxide, cod = 1,5-cyclooctadiene, binap = 2,2′-bis(diphenylphosphino)-1,1′-binaphtalene, DCE = 1,2-dichloroethane, PPTS = pyridinium *p*-toluenesulfonate, EDC = *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide.



Scheme 8. Synthesis of optically active **5** through diastereoselective alkylation by Nicolaou et al.[6] Piv = pivaloyl, TFE = 2,2,2-trifluoroethanol.

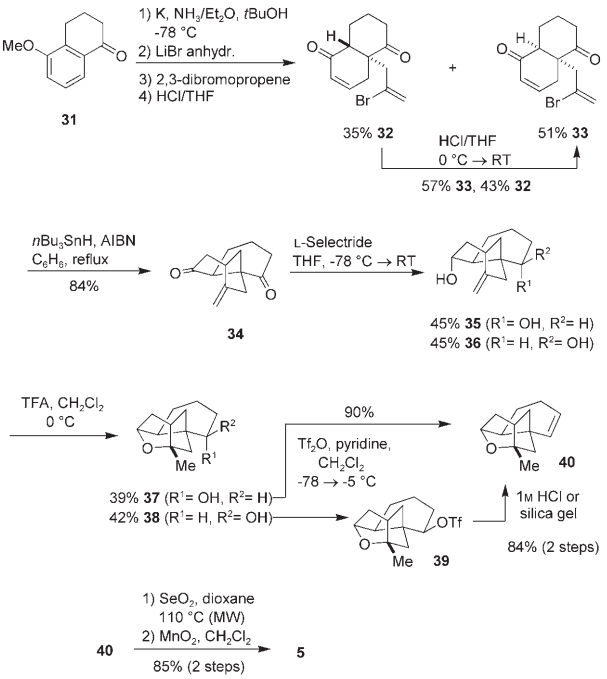
cyclized to the tetracyclic core system **5**. The synthesis was continued by stereoselective double alkylation to form the second quaternary carbon center of platensimycin. The further functionalization of the allylic side chain of **17** proved to be more troublesome than expected since routine hydroboration/oxidation failed to give reasonable yields. In the end, cross-metathesis with vinyl boronate **20**, followed by oxidation, produced the desired carboxylic acid **3** in good yields. The total synthesis was completed by standard peptide coupling of **3** and **8** followed by global deprotection.

This racemic synthesis was later upgraded to an asymmetric one either by an enantioselective cycloisomerization (Scheme 7) or diastereoselective alkylation (Scheme 8).[6] An attempt to apply enantioselective catalysis in the cycloisomerization step **14** to **15** of the racemic synthesis was never undertaken since, according to the Nicolaou group, it did not seem promising. Instead, they decided to achieve asymmetric induction with the chiral rhodium catalyst developed by Zhang et al.[7] Hence, intermediate **14** was converted into the symmetrical dienone **21** which gave spirocompound **22** in excellent yield and enantioselectivity. The drawback of this approach is the necessity to remove the undesired ester, which is done in three steps, and to protect the aldehyde functionalty (two additional steps). After removal of the acetal group in **23** the ketyl radical cyclization, under the same conditions as in the racemic synthesis, surprisingly gave the desired diastereomer selectively but still in low yields (39%). The high diastereoselectivity in this case must be attributed to the different position of the double bond (*endo* in **23**, *exo* in **16**). Finally cyclization under the same conditions as in the racemic series (Scheme 6) gave **5** in optically active form.

An auxiliary-based approach to optically active **5** was also investigated:[6] Oxidative cyclodearomatization of compound

27 provided an alternative access to spirocompound **28** which after deprotection was identical to intermediate **16** (Scheme 6). The required allyl silane **27** was prepared starting from carboxylic acid **25** (available in one step from commercially available material). Amide **26** was obtained after a Myers' asymmetric alkylation. Conversion into the methyl ketone, enol triflate formation, Kumada coupling with TMS-methyl magnesium chloride, and clevage of the TBS protecting group furnished the allylsilane **27**.

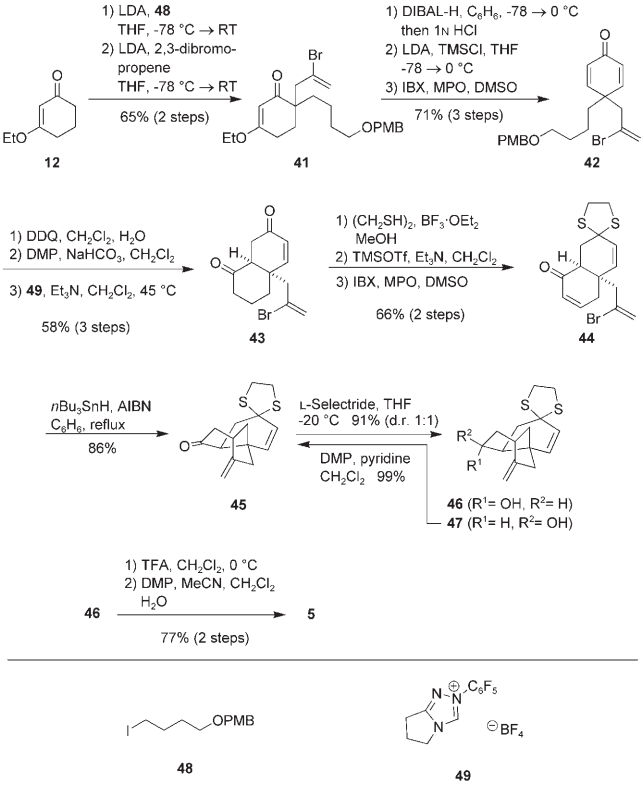
Soon after Nicolaou, Snider et al. reported a formal synthesis of racemic **5**.[8] Their approach is based on a known two step conversion of 5-methoxy-1-tetralone (**31**) into tricycle **34** by reductive alkylation with 2,3-dibromopropene followed by radical cyclization (Scheme 9).[9] Although this



Scheme 9. Synthesis of racemic **5** by Snider et al.[8] AIBN = 2,2′-Azo bisisobutyronitrile.

sequence was described the stereochemical outcome was not investigated. Snider et al. showed that the reductive alkylation step delivered the desired *cis*-bicylce **33** as the major product in 51 % yield along with 35 % of the undesired *trans*-bicycle **32**. Compound **32** could be equilibrated under acidic conditions to a 1.3:1 mixture of **33** and **32**, thereby increasing the yield of the desired product. Interestingly the tricycle **34**, obtained after radical cyclization gave upon basic equilibration a 1:4 mixture favoring the undesired *trans*-tricycle. These results were rationalized by molecular mechanics calculations which suggested the *cis*-triycyle to be 1.6 kcal mol^{-1} less stable than its epimer. With *cis*-tricycle **34** in hand the next objective was formation of the tetrahydrofuran ring. Reduction with an excess of L-Selectride afforded an inseparable 1:1 mixture of **35** and **36** which were cyclized to the separable tetracycles **37** and **38** in good yields. The axial alcohol **37** could directly be converted into alkene **40** by treatment with trifluoromethanesulfonic acid anhydride in pyridine. The equatorial isomer **38** did not undergo this elimination spontaneously but required treatment with 1M HCl or silica gel to form alkene **40**. Finally, allylic oxidation with three equivalents of selenium dioxide under microwave irradiation, followed by oxidation with manganese dioxide, gave Nicolaous key intermediate **5** in good yield.

A synthetic route relying on the same key step as in Snider's synthesis (Scheme 9) was published almost simultaneously by Nicolaou et al.[10] In contrast to Snider the Nicolaou group prepared the bicyclic precursor for the radical cyclization by a Stetter reaction (Scheme 10). Using the same

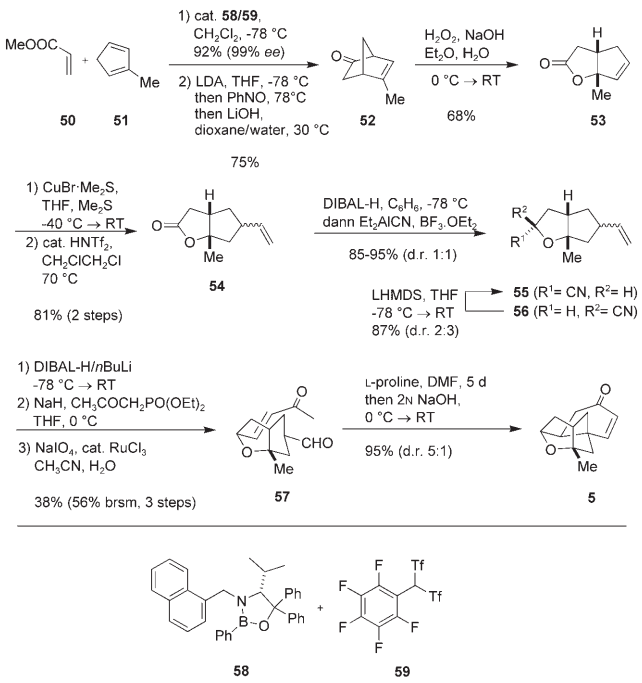


Scheme 10. Synthesis of racemic **5** by Nicolaou et al.[10] DDQ = 2,3-dichloro-5,6-dicyanobenzoquinone, DMP = Dess–Martin periodinane.

methodology as in their first synthesis (see Scheme 6) dienone **42** was reached in five steps. After clevage of the PMB protecting group and oxidation to the aldehyde, the Stetter reaction, using one equivalent of ylide precursor **49**,[11] yielded bicycle **43** in 64 % yield as a single diastereomer. After selective protection of the unsaturated ketone as dithioketal and introduction of the desired enone moiety the stage was set for the radical key step which succeeded under the same conditions and in comparable yield as in Sniders synthesis. A drawback of this approach by the Nicolaou group is the lack of selectivity in the following reduction which gave a 1:1 mixture of alcohols **46** and **47**. This result is in stark contrast to the diastereospecific reduction in Sniders synthesis (see Scheme 9) and could be explained by the steric shielding of the top face by the dithioketal. However, the undesired

isomer **47** could be recycled to **45** by Dess–Martin oxidation in excellent yield. Finally, formation of the tetrahydrofuran moiety and oxidative deprotection of the enone completed the racemic formal synthesis. The need of several protecting group operations makes this approach much longer than Snider's approach (15 steps instead of 7 steps).

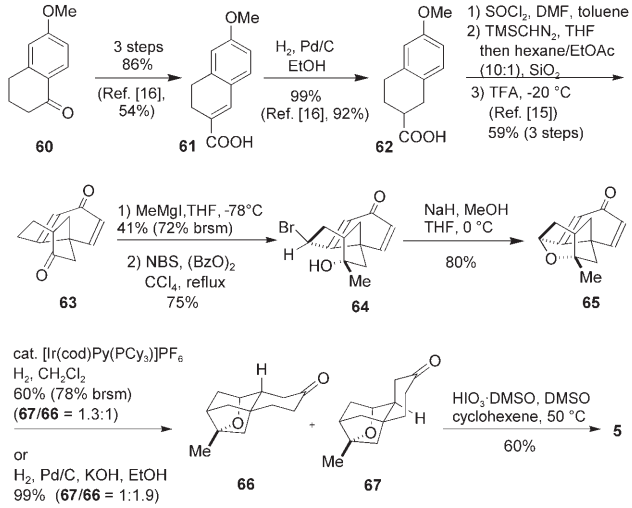
A very elegant enantioselective synthesis of **5** was published by Yamamoto et al.,[12] which is based on a diastereoselective Robinson annulation to construct the quaternary center and both six-membered rings in one step (Scheme 11, conversion of **57** to **5**). The synthesis started with



Scheme 11. Synthesis of optically active key intermediate **5** by Yamamoto et al.[12] Tf = trifluoromethanesulfonate.

a highly efficient (92% yield, 99% *ee*) Diels–Alder reaction of methyl acrylate (**50**) and methyl cyclopentadiene (**51**) using a Brœnsted acid assisted chiral Lewis acid (BLA) prepared in situ from **58** and **59**.[13] The product was converted into ketone **52** by nitrosoaldol reaction and oxidative decarboxylation using lithium hydroxide. Baeyer–Villiger oxidation of **52** gave lactone **53**, presumably by hydrolysis of the initially formed product followed by dehydrative lactonization. After addition of a vinyl cuprate reagent and acid-catalyzed lactonization, intermediate **54** was obtained as an inconsequential mixture of diastereomers (10:1). The next objective was the installation of the enone system for the Robinson annulation. This was done by reducing the lactone to the lactol, followed by Lewis acid mediated cyanation. This one-pot procedure delivered a separable 1:1 mixture of the desired compound **55** along with **56**. Side product **56** was equilibrated to a 2:3-diastereomeric mixture of **55** and **56**, thereby increasing the yield of the desired product. After conversion of the nitrile into the aldehyde, Horner–Wadsworth–Emmons reaction, and ruthenium-catalyzed oxidative cleavage of the terminal olefin the key intermediate **57** was obtained in moderate yields. Treatment of **57** with one equivalent of L-proline in DMF for five days furnished the Michael addition product which was converted into **5** by in situ addition of sodium hydroxide.

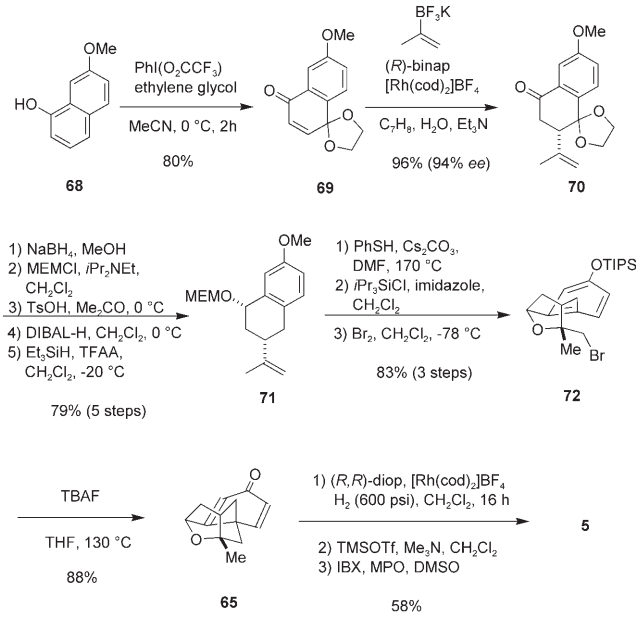
The synthesis of racemic **5** by our group[14] made use of an intermediate **63**, described by Mander et al. in 1974 which bears strong resemblance to the tetracyclic core system of platensimycin (Scheme 12).[15] This approach seemed attrac-



Scheme 12. Synthesis of racemic key intermediate **5** by Mulzer et al.[14] NBS = *N*-bromosuccinimide, Bz = benzoyl, Py = pyridine, Cy = cyclohexane.

tive since **63** can be obtained in 50% overall yield in seven steps from cheap methoxytetralone **60**.[15,16] Tricycle **63** was converted into a tertiary alcohol by regio- and stereoselective addition of methylmagnesium iodide to the more reactive (cyclopentanone) carbonyl group. The tertiary alcohol thus formed effectively shields the bottom face, thus enabling stereoselective bromination yielding compound **64** under standard conditions. After base-induced cyclization to the tetrahydrofuran moiety **65**, saturation of the dienone system was investigated under various conditions. Catalytic hydrogenation with Crabtree's catalyst furnished a separable 1.3:1 diastereomeric mixture of **67** and **66**, although only with moderate conversion. An alternative was the more cost-effective catalytic hydrogenation using palladium on charcoal under basic conditions, giving a 1:1.9 ratio of **67** and **66** in quantitative yield. Selective mono-oxidation of **67**, using an iodic acid dimethyl sulfoxide complex,[17] led to **5**. The undesired *trans*-decalin **66** was recycled to **65** by a more vigorous oxidation.

The enantioselective approach to **5** by Corey et al.[18] features a dearomatizing alkylation of **72** to give the known intermediate **65** (Scheme 13). The synthesis starts from compound **68** prepared in two steps from commercially available material. After oxidative ketalization, enantioselective cuprate addition of the isopropenyl group afforded compound **70** in 94% *ee* and high yield.[19] Stereoselective reduction of the ketone, protection of the alcohol group as

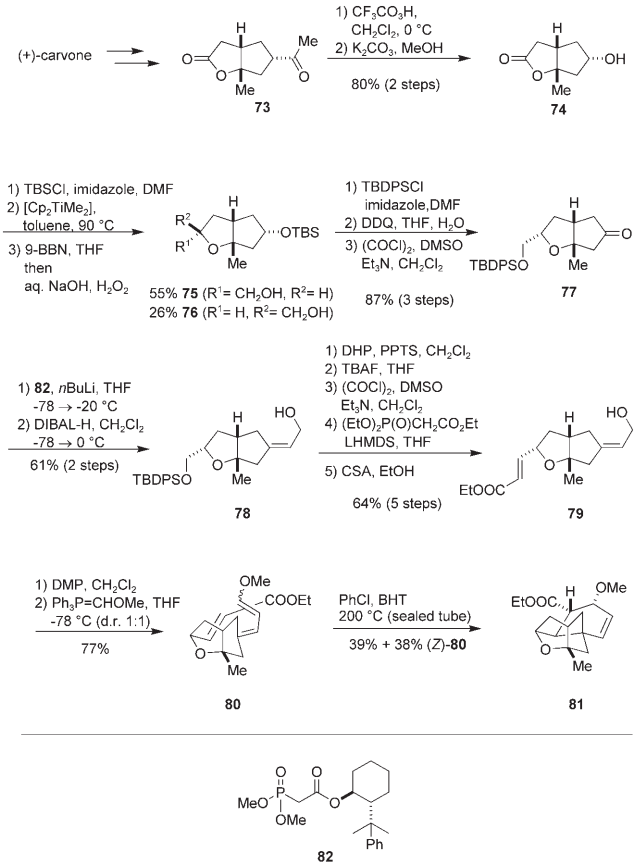


Scheme 13. Synthesis of optically active key intermediate **5** by Corey et al.[18] MEM = methoxyethoxymethyl, TFAA = trifluoroacetic anhydride, TBAF = tetra-*n*-butylammonium fluoride, DIOP = *O*-isopropylidine-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane.

MEM ether, removal of the ketal, and a two step reduction of the ensuing ketone furnished **71** in good yield. At this stage, a change in protecting groups had to be performed and therefore the phenolic methyl ether was replaced by a TIPS group. Reaction of this intermediate with bromine at −78 °C cleanly afforded bromoether **72** which was converted into the tetracyclic structure **65** (identical with Mulzer intermediate, Scheme 12) by treatment with TBAF in THF at 130 °C (sealed vessel). With optically active material in hand the problems concerning the selective reduction of **65** observed in the Mulzer synthesis, could be overcome by using an asymmetric hydrogenation catalyst. Finally the required enone system was reintroduced by the TMS enolether and IBX oxidation, delivering the key intermediate **5** in 16 linear steps in good yield.

4. An Unfinished Approach

The approach by Gosh et al.[20] focuses on a late intramolecular Diels–Alder reaction of compound **80** (Scheme 14). The product **81**, though closely related to Nicolaou's key intermediate **5**, does not constitute a formal synthesis yet. The sequence starts from known secondary alcohol **74** derived from commercially available (+)-carvone in five steps.[21] After TBS-protection the lactone was subjected to Petasis olefination conditions and the resulting enolether was converted into a separable mixture of the primary alcohols **75** and **76** (d.r. 2:1) by hydroboration/oxidation. Protecting group manipulations followed by Swern oxidation furnished ketone **77**, which was treated with chiral phosphonoacetate **82** to give a separable 3.2:1 mixture of *E*- and *Z*-ester (under standard Horner–Emmons olefination



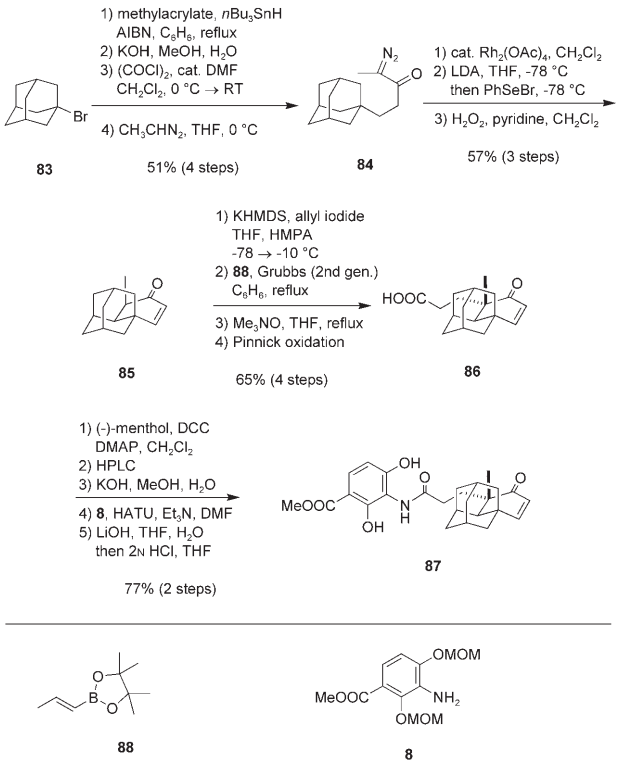
Scheme 14. Incomplete approach by Gosh et al.[20] 9-BBN = 9-Borabicyclo[3.3.1]nonane, TBDPS = *tert*-butyldiphenylsilyl, DHP = 3,4-dihydro-2*H*-pyran, CSA = campher sulfonic acid, BHT = 2,6-di-*tert*-butyl-4-methyl-phenol.

conditions a 1.5:1 mixture was obtained). After reduction alcohol **78** was obtained which, in a number steps, was prepared for the Diels–Alder reaction. First the enoate side chain was installed, followed by the diene moiety which was introduced as a inseparable 1:1 mixture of *E*/*Z* enol ethers. In this way precursor **80** was obtained which underwent a thermal Diels–Alder reaction to provide polycyclic adduct **81** as a single isomer along with recovered *Z*-diene.

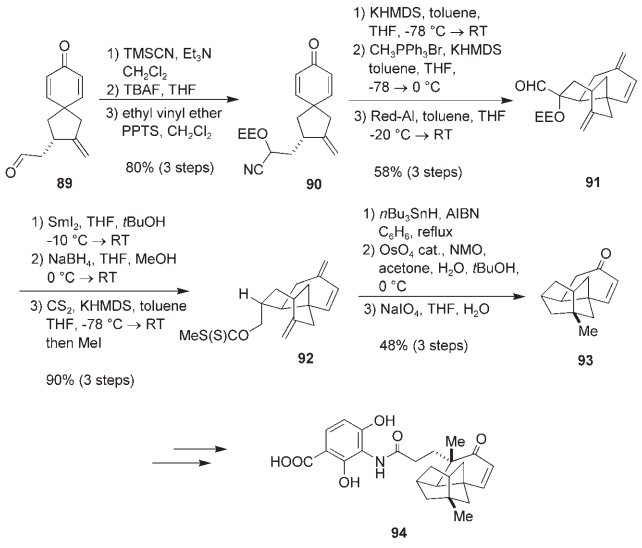
5. Analogues

To date, the Nicolaou group has prepared two analogues of platensimycin: adamantaplatensimycin (**87**, Scheme 15) and carbaplatensimycin (**94**, Scheme 16).

The idea behind adamantaplatensimycin[22] was to replace the synthetically challenging tetracyclic cage-like structure of **1** by a more readily accessible racemic adamantyl moiety **85**. The approach starts from bromoadamantane (**83**), which was added to to methyl acrylate through a radical 1,4-addition. The acid chloride, formed after saponification, was converted into diazoketone **84** in good yields. The CH-insertion of the rhodium carbene led to annulation of a cyclohexanone ring which was oxidized to enone **85**. This intermediate is closely related to the intermediate **5**, and it was elaborated in a



Scheme 15. Synthesis of optically active adamantaplatensimycin by Nicolaou et al.[22] DCC = dicyclohexylcarbodiimide, DMAP = 4-(dimethylamino)-pyridine.

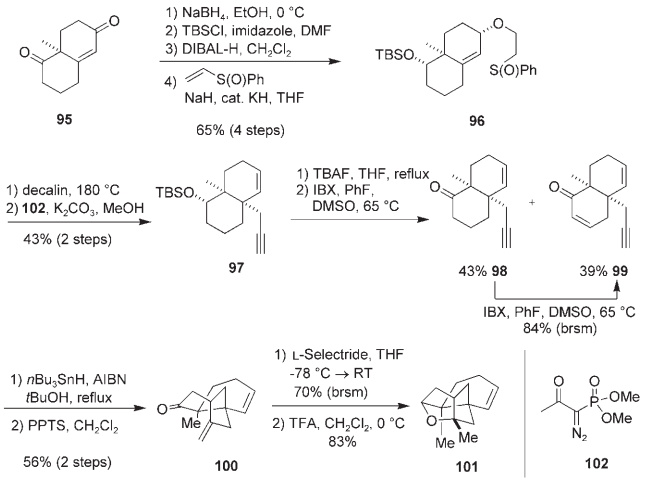


Scheme 16. Synthesis of optically active Carbaplatensimycin by Nicolaou et al.[23] NMO = *N*-methylmorpholine-*N*-oxide. EE = 1-ethoxyethyl.

similar manner. At the stage of carboxylic acid **86** optical resolution was achieved by esterification with (−)-menthol and HPLC separation of the diastereomers on a chiral phase.

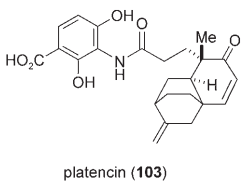
Carbaplatensimycin[23] was chosen to test the positive role of the ether oxygen for the biological acitivity of **1**. The synthesis began by transforming the known aldehyde **89**[6] into protected cyanohydrin **90** which was used in a base-induced conjugate addition to the enone. Wittig olefination and reduction of the nitrile led to aldehyde **91** in good yield. SmI_2-induced removal of the OEE group proceeded with inversion of configuration and after reduction of the aldehyde to the primary alcohol, xanthate **92** was prepared in excellent yield. The cage-like structure was assembled by a Barton–McCombie 5-*exo-trig* radical cascade reaction. Oxidative reintroduction of the ketone gave the carba-core system **93** which was converted into carbaplatensimycin (**94**) in the usual manner.

A methyl analogue of **40**, compound **101** was prepared by the Kaliappan group.[24] They used the readily available Wieland–Miescher ketone **95** as the starting material (Scheme 17). The required quaternary center was stereoselectively installed by a modified Claisen-rearrangement of sulfoxide **96**. After elongation of the aldehyde with the Bestmann–Ohira reagent **102** and oxidative introduction of the enone moiety, alkyne **99** was obtained. Radical cyclization, followed by destannylation with PPTS gave tricycle **100** which after reduction with L-Selectride and cyclization under standard conditions gave tetracycle **101**.



Scheme 17. Synthesis of an optically active platensimycin core system by Kaliappan et al.[24]

Recently platencin[25] (**103**, Scheme 18), an analogue of platensimycin, which also exhibits potent broad-spectrum antibiotic activity, was isolated from a strain of *Streptomyces platensis*. As with platensimycin (**1**), the Nicolaou group is the first to achieve a total synthesis for platencin (**103**).[26]



platencin (**103**)

Scheme 18. Structure of Platencin, isolated from a strain of *Streptomyces platensis*.[25]

6. Conclusion

The history of platensimycin to date bears much similarity to that of the anticancer drug epothilone.[27] Both have been isolated by screening microbial fermentation extracts and feature relatively simple molecular architectures. Both show considerable promise as drugs with potential block-buster capabilities. In consequence, the interest of synthetic groups has been immense from the very beginning, and preparative routes have poured out with immense speed and in broad methodological variety, thus demonstrating the power, creativity, and competitiveness of organic natural product synthesis.

Although various efficient routes to platensimycin have been developed, finding a promising drug candidate has still to be achieved.

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[1] a) D. Häbich, F. von Nussbaum, *ChemMedChem* **2006**, *1*, 951; b) U. Holzgrabe, T. Dingermann, I. Zündorf, *Pharm. Unserer Zeit* **2006**, *35*, 388.

[2] a) J. Wang, S. M. Soisson, K. Young, W. Shoop, S. Kodali, A. Galgoci, R. Painter, G. Parthasarathy, Y. S. Tang, R. Cummings, S. Ha, K. Dorso, M. Motyl, H. Jayasuriya, J. Ondeyka, K. Herath, C. Zhang, L. Hernandez, J. Allocco, A. Basilio, J. R. Tormo, O. Genilloud, F. Vicente, F. Pelaez, L. Colwell, S. H. Lee, B. Michael, T. Felcetto, C. Gill, L. L. Silver, J. D. Hermes, K. Bartizal, J. Barrett, D. Schmatz, J. W. Becker, D. Cully, S. B. Singh, *Nature* **2006**, *441*, 358; b) S. B. Singh, H. Jayasuriya, J. G. Ondeyka, K. B. Herath, C. Zhang, D. L. Zink, N. N. Tsou, R. G. Ball, A. Basilio, O. Genilloud, M. T. Diez, F. Vicente, F. Pelaez, K. Young, J. Wang, *J. Am. Chem. Soc.* **2006**, *128*, 11916; Addition/Correction: S. B. Singh, H. Jayasuriya, J. G. Ondeyka, K. B. Herath, C. Zhang, D. L. Zink, N. N. Tsou, R. G. Ball, A. Basilio, O. Genilloud, M. T. Diez, F. Vicente, F. Pelaez, K. Young, J. Wang, *J. Am. Chem. Soc.* **2006**, *128*, 15547; c) S. B. Singh, K. B. Herath, J. Wung, N. Tsou, R. G. Ball, *Tetrahedron Lett.* **2007**, *48*, 5429; d) S. B. Singh, J. Wang, A. Basilio, O. Genilloud, P. Hernandez, J. R. Tormo, WO 2005009391, **2005** (CAN 142:196607); e) K. B. Herath, A. B. Attygalle, S. B. Singh, *J. Am. Chem. Soc.* **2007**, *129*, 15422.

[3] a) A review on the synthesis of platensimycin: M. Rueping, *Nachr. Chem.* **2007**, *55*, 1212; b) K. C. Nicolaou, A. Li, D. J. Edmonds, *Angew. Chem.* **2006**, *118*, 7244; *Angew. Chem. Int. Ed.* **2006**, *45*, 7086.

[4] P. Heretsch, A. Giannis, *Synthesis* **2007**, 2614.

[5] Review: B. M. Trost, M. U. Frederiksen, M. T. Rudd, *Angew. Chem.* **2005**, *117*, 6788; *Angew. Chem. Int. Ed.* **2005**, *44*, 6630.

[6] K. C. Nicolaou, D. J. Edmonds, A. Li, G. S. Tria, *Angew. Chem.* **2007**, *119*, 4016; *Angew. Chem. Int. Ed.* **2007**, *46*, 3942.

[7] a) P. Cao, X. Zhang, *Angew. Chem.* **2000**, *112*, 4270; *Angew. Chem. Int. Ed.* **2000**, *39*, 4104; b) A. Lei, M. He, S. Wu, X. Zhang, *Angew. Chem.* **2002**, *114*, 3607; *Angew. Chem. Int. Ed.* **2002**, *41*, 3457; c) A. Lei, J. P. Waldkirch, M. He, X. Zhang, *Angew. Chem.* **2002**, *114*, 4708; *Angew. Chem. Int. Ed.* **2002**, *41*, 4526; A. Lei, M. He, X. Zhang, *J. Am. Chem. Soc.* **2002**, *124*, 8198.

[8] Y. Zou, C.-H. Chen, C. D. Taylor, B. M. Foxman, B. B. Snider, *Org. Lett.* **2007**, *9*, 1825.

[9] N. N. Marinovic, H. Ramanathan, *Tetrahedron Lett.* **1983**, *24*, 1871.

[10] K. C. Nicolaou, Y. Tang, J. Wang, *Chem. Commun.* **2007**, 1922.

[11] M. S. Kerr, J. Read de Alaniz, T. Rovis, *J. Org. Chem.* **2005**, *70*, 5725.

[12] P. Li, J. N. Payette, H. Yamamoto, *J. Am. Chem. Soc.* **2007**, *129*, 9534.

[13] J. N. Payette, H. Yamamoto, *J. Am. Chem. Soc.* **2007**, *129*, 9536.

[14] K. Tiefenbacher, J. Mulzer, *Angew. Chem.* **2007**, *119*, 8220; *Angew. Chem. Int. Ed.* **2007**, *46*, 8074.

[15] D. J. Beames, T. R. Klose, L. N. Mander, *Aust. J. Chem.* **1974**, *27*, 1269.

[16] P. Anantha Reddy, G. S. Krishna Rao, *Indian J. Chem. Sect. B* **1981**, *20*, 100.

[17] K. C. Nicolaou, T. Montagnon, P. S. Baran, *Angew. Chem.* **2002**, *114*, 1444; *Angew. Chem. Int. Ed.* **2002**, *41*, 1386.

[18] G. Lalic, E. J. Corey, *Org. Lett.* **2007**, *9*, 4921.

[19] a) T. Hayashi, K. Yamasaki, *Chem. Rev.* **2003**, *103*, 2829; b) M. Pucheault, S. Darses, J.-P. Genet, *Eur. J. Org. Chem.* **2002**, 3552; c) G. A. Molander, N. Ellis, *Acc. Chem. Res.* **2007**, *40*, 275.

[20] A. K. Ghosh, K. Xi, *Org. Lett.* **2007**, *9*, 4013.

[21] a) A. Srikrishna, P. Hemamalini, *J. Org. Chem.* **1990**, *55*, 4883; b) K. Weinges, H. Reichert, R. Braun, *Chem. Ber.* **1994**, *127*, 549.

[22] K. C. Nicolaou, T. Lister, R. M. Denton, A. Montero, D. J. Edmonds, *Angew. Chem.* **2007**, *119*, 4796; *Angew. Chem. Int. Ed.* **2007**, *46*, 4712.

[23] K. C. Nicolaou, Y. Tang, J. Wang, A. F. Stepan, A. Li, A. Montero, *J. Am. Chem. Soc.* **2007**, *129*, 14850.

[24] K. P. Kaliappan, V. Ravikumar, *Org. Lett.* **2007**, *9*, 2417.

[25] a) J. Wang, S. Kodali, S. H. Lee, A. Galgoci, R. Painter, K. Dorso, F. Racine, M. Motyl, L. Hernandez, E. Tinney, S. L. Colletti, K. Herath, R. Cummings, O. Salazar, I. González, A. Basilio, F. Vicente, O. Genilloud, F. Pelaez, H. Jayasuriya, K. Young, D. F. Cully, S. B. Singh, *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 7612; b) H. Jayasuriya, K. B. Herath, C. Zhang, D. L. Zink, A. Basilio, O. Genilloud, M. T. Diez, F. Vicente, I. Gonzalez, O. Salazar, F. Pelaez, R. Cummings, S. Ha, J. Wang, S. B. Singh, *Angew. Chem.* **2007**, *119*, 4768; *Angew. Chem. Int. Ed.* **2007**, *46*, 4684.

[26] K. C. Nicolaou, G. S. Tria, D. J. Edmonds, *Angew. Chem.* **2008**, *120*, 1804; *Angew. Chem. Int. Ed.* **2008**, *47*, 1780.

[27] K. H. Altmann, B. Pfeiffer, S. Arseniyadis, B. A. Pratt, K. C. Nicolaou, *ChemMedChem* **2007**, *2*, 396; E. B. Watkins, A. G. Chittiboyina, J.-C. Jung, M. A. Avery, *Curr. Pharm. Des.* **2005**, *11*, 1615; J. Mulzer, *Monatsh. Chem.* **2000**, *131*, 205.