Natural Product Synthesis

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Total Synthesis of (−)-atrop-Abyssomicin C**

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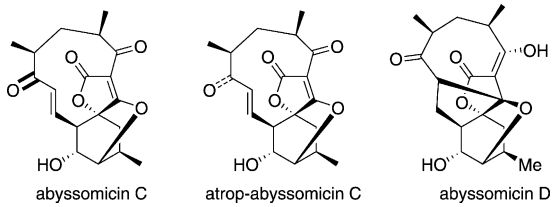
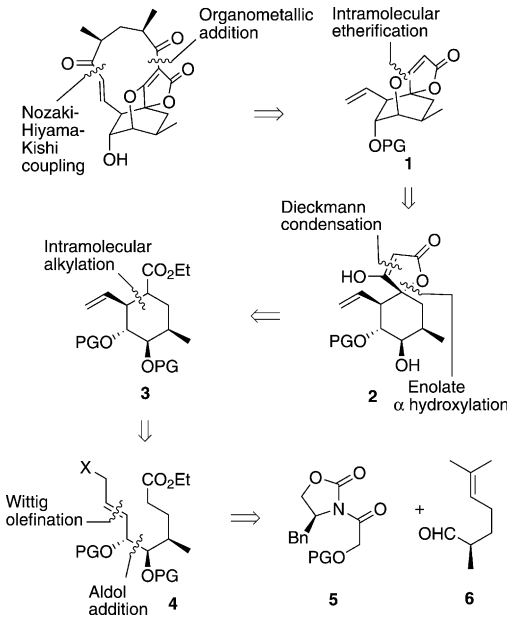
In 2004, Süssmuth and co-workers reported the isolation of abyssomicin C,[1] a naturally occurring antibiotic[2] of exotic origin and complex structure. The mechanism of antibiotic activity of abyssomicin C against Gram-positive bacteria, including methycillin- and vancomycin-resistant *Staphylococcus aureus* strains, was unprecedented: it inhibits tetrahydrofolate biosynthesis at an early stage.[3] In addition to abyssomicin C, several other congeners have been found in both marine and terrestrial *Streptomyces* strains (Scheme 1).[4] The combination of strong antibacterial activity



Scheme 1. Some members of the abyssomicin family.

and complex molecular architecture made abyssomicin C an attractive synthetic target.[5] Two total syntheses,[6,7] one formal synthesis[8] and several synthetic studies[9] have been reported. The common feature of all reported efforts is the recognition that the central cyclohexane core can be constructed through a Diels–Alder reaction. Another pivotal step, the formation of the oxygen bridge, has been invariably performed by an intramolecular epoxide ring opening reaction with a tetronate nucleophile, in a presumed biomimetic fashion. An interesting structural insight was disclosed by Nicolaou: the restricted rotation around one of the bonds in the eleven-membered ring gives rise to atropisomerism.[7] The compound named atrop-abyssomicin C turned out to be a genuine secondary metabolite and the most active bactericide among its congeners, whereas the initially described abyssomicin C derives from atrop-abyssomicin C.

We set out to develop an enantioselective synthesis of atrop-abyssomicin C based on an alternative strategy (Scheme 2) that would facilitate the synthesis of analogues not accessible through an intramolecular epoxide ring opening reaction. The eleven-membered ring could be disconnected by a combination of a Nozaki–Hiyama–Kishi coupling and an organometallic addition, to give the key tricyclic intermediate **1**. We planned to create **1** by the nucleophilic attack of a β-hydroxy group onto a tetronate motif, instead of the alternative route involving ring opening of an epoxide by the tetronate. We anticipated that this step would be challenging, perhaps requiring the development of some new chemistry. Retrosynthetic simplification of spirotetronate **2** based on a Dieckmann condensation and stereoselective oxidation of the enolate led to ester **3**, which is in turn obtainable by the cyclization of precursor **4**. The three contiguous stereocenters in this intermediate would be installed by an aldol reaction: whereas the absolute stereochemistry of the oxygen-bearing carbon atoms would be established in a reagent-controlled addition of Evans oxazolidinone **5**, the stereocenter bearing a methyl group would originate from (−)-(*R*)-norcitronellal (**6**).



Scheme 2. Retrosynthetic analysis of abyssomicin C. Bn = benzyl, PG = protecting group.

The synthesis encompasses three main stages: 1) formation of the cyclohexane core **3** with all stereocenters installed; 2) formation of the tricyclic core **1**; and 3) attachment of the side chain and completion of the synthesis. The realization of the first goal (Scheme 3) commenced with a boron enolate mediated enantioselective aldol addition of α-benzyloxy-

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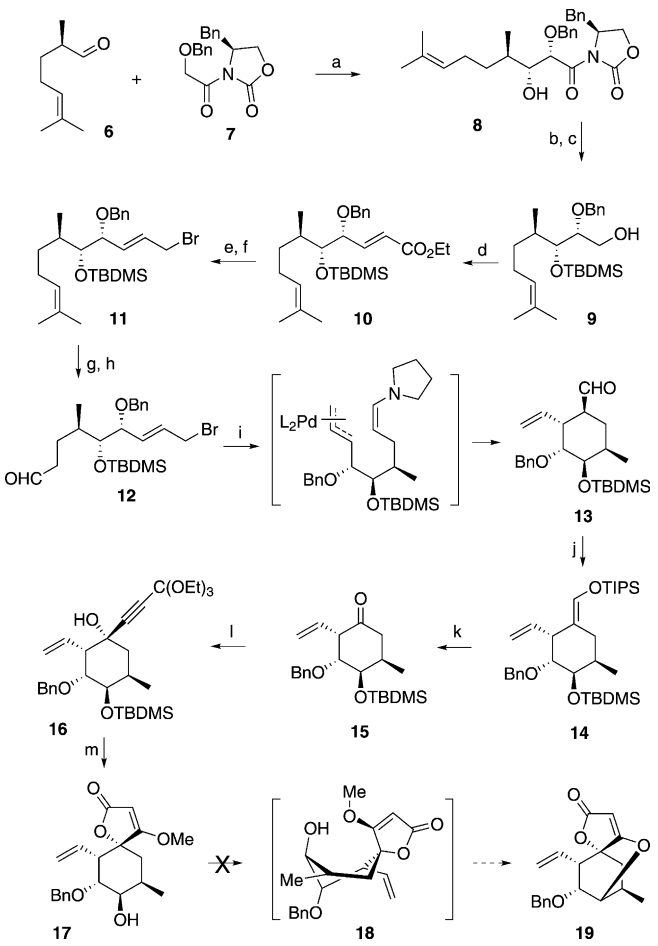
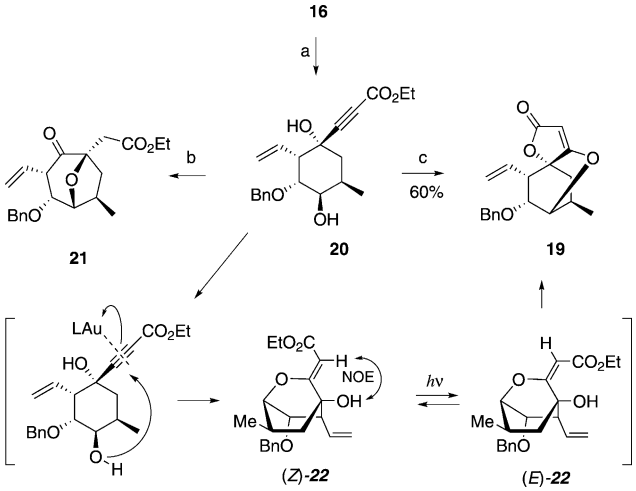


Scheme 3. Formation of the functionalized cyclohexane core: a) nBu$_2$BOTf, Et$_3$N, CH$_2$Cl$_2$, −78 °C; then H$_2$O$_2$, MeOH, phosphate buffer (77%; 90% based on the recovered starting material); b) TBDMSOTf, *sym*-collidine, CH$_2$Cl$_2$, 0 °C (99%); c) NaBH$_4$, THF, H$_2$O (86%); d) DMP, CH$_2$Cl$_2$, RT, then Ph$_3$P=CHCO$_2$Et (82%); e) DIBAL-H, Et$_2$O, −40 °C (85%); f) CBr$_4$, Ph$_3$P, CH$_2$Cl$_2$, 0 °C (95%); g) *m*CPBA, CH$_2$Cl$_2$, RT; h) H$_5$IO$_6$, Et$_2$O; i) [Pd(PPh$_3$)$_4$], pyrrolidine, THF, RT (83%, 3 steps, from **11**); j) TIPSOTf, Et$_3$N, CH$_2$Cl$_2$, reflux (99%); k) *m*CPBA, CH$_2$Cl$_2$; then H$_5$IO$_6$, Et$_2$O (87%); l) LDA, 3,3,3-triethoxyprop-1-yne, PhMe; then ketone **15** (88%); m) Nafion-Hg, MeOH, H$_2$O (92%); then: HF, MeCN, 60 °C (84%). DIBAL-H = diisobutylaluminum hydride, DMP = Dess–Martin periodinane, L = ligand, LDA = lithium diisopropylamide, *m*CPBA = *meta*-chloroperoxybenzoic acid, TBDMS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl, TIPS = triisopropylsilyl.

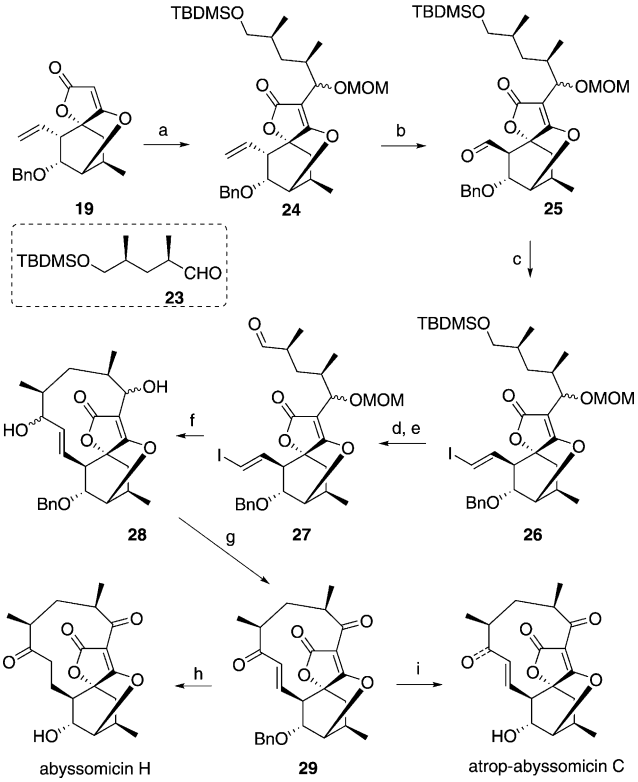
acetyloxazolidinone **7**[10] to (*R*)-norcitronellal (**6**),[11] which furnished the expected adduct **8** in 77% yield, as a single diastereoisomer. Silylation of the secondary hydroxy group,[12] followed by reductive removal of the oxazolidinone auxiliary with sodium borohydride afforded alcohol **9**, which upon homologation by a one-pot procedure involving DMP-mediated oxidation and Wittig olefination gave conjugated ester **10**.[13] To transform the conjugated ester into a leaving group, ester **10** was reduced with DIBAL, and the resulting alcohol converted into allylic bromide **11** with PPh$_3$/CBr$_4$ (81% over two steps). Selective oxidative cleavage of the isopropylidene group in **11** revealed the proenolate part of the cyclization precursor **12**. Initially, the cyclization was planned via an ester enolate but surprisingly, this reaction failed under a variety of reaction conditions, even after modification of the protecting groups in the molecule. Aldehyde **12** also did not cyclize under previously described reaction conditions.[14] Therefore, a new cyclization method was developed;[15] this method was based upon the concept of dual catalysis,[16] that is the combination of organotransition metal catalysis and organocatalysis.[17] Thus, when submitted to the conditions of the organocatalyzed Tsuji–Trost cyclization, that is when treated with catalytic amounts of [(Ph$_3$P)$_4$Pd] and pyrrolidine, aldehyde **12** was smoothly converted into cyclohexane carbaldehyde derivative **13** (83% over three steps). The assignment of the structure of **13** in our previous papers was ambiguous and therefore aldehyde **13** was converted into the corresponding methyl ester, the structure of which was unambiguously confirmed by a single crystal X-ray diffraction analysis (see Ref. [18]).

The planned elaboration of spirotetronate **2** via the α-hydroxyaldehyde derived from **13** had to be abandoned: α hydroxylation of **13** could not be performed stereoselectively, and the hydroxylated product was prone to side reactions.[18] Evidently, a modification of the approach was necessary: a three-carbon unit that would constitute the tetronate substructure had to be stereoselectively introduced by a nucleophilic addition to cyclohexanone **15**. To this end, **13** was first converted into silyl enolether **14**, which was converted into cyclohexanone derivative **15** using the aforementioned two-step procedure (87% overall yield). The best yield of propargylic derivative **16** was obtained by the addition of the lithium anion of ethyl orthopropiolate to a solution of **15** in toluene. Although **16** could undergo cyclization to give spirotetronate **17**, all attempts to convert **17** into tricyclic ether **19** failed. In retrospect, this failure was not surprising, given that an extremely unfavorable distorted conformation of the rigid spirobicycle is required in transition state **18** for the intramolecular hetero-Michael addition (i.e. to allow the approach of the hydroxy group to the alkene acceptor at a Bürgi–Dunitz angle of 105°). Therefore, a change in the order of the steps was required, namely the intramolecular etherification had to be performed on a conformationally more flexible alkyne derivative, prior to the spirotetronate formation.

For this purpose, we turned our attention to gold complexes,[19] which are known to be efficient promoters of nucleophilic additions to carbon–carbon multiple bonds. The treatment of alkyne **20** with AuCl$_3$, in the presence or absence of silver triflate, gave no reaction, and therefore we resorted to using the highly active Au^I catalyst that was described by Gagosz and co-workers.[20] The treatment of a solution of alkyne **20** in THF with Gagosz's gold catalyst resulted in no reaction, but when a dichloromethane solution of the mixture was heated to 120 °C bicyclic ether **21** was obtained (Scheme 4).[27] This result was encouraging, as the putative mechanism of formation of ether **21** might involve the initial formation of the desired bicyclic ether intermediate, and its subsequent rearrangement. After a screen of solvents and reaction conditions, we found that the intramolecular etherification could be effected by heating a solution of alkyne **20**



Scheme 4. Gold-catalyzed formation of the key intermediate **19**: a) HF, MeCN, 60 °C (85 %); b) $[(PPh_3)AuNTf_2]$ (10 mol %), CH_2Cl_2, 120 °C (68 %); c) $[(PPh_3)AuNTf_2]$ (10 mol %), *i*PrOH, 70 °C; then *hν* (254 nm), *i*PrONa (60 %).



Scheme 5. Attachment of the side chain and completion of the synthesis: a) *t*BuLi, THF, −78 °C; then aldehyde **23**, −78 °C to −40 °C; then MOMBr, −40 °C to −25 °C (44 %; 79 % based on recovered **19**); b) O_3, CH_2Cl_2, −78 °C; then Me_2S; then DBU (30 mol %) (81 %); c) $CrCl_2$, CHI_3, THF, RT to 50 °C (71 %); d) HCl, MeOH (94 %); e) DMP, CH_2Cl_2, RT (88 %); f) $CrCl_2$, $NiCl_2$, DMF, RT to 45 °C (90 %; 96 % based on recovered material); g) HCl_{aq}, MeOH, RT; then DMP, CH_2Cl_2 (78 %); h) H_2, Pd/C, EtOAc; i) BBr_3, CH_2Cl_2, RT (81 %). DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMF = dimethylformamide, MOM = methoxymethyl.

and a catalytic amount of $[(PPh_3)AuNTf_2]$ in isopropanol. However, the reaction produced the *Z* isomer of **22**, (*Z*)-**22**, while the *E* isomer of **22**, (*E*)-**22**, was required for the synthesis of spirotetronate **19**. Isomerization of (*Z*)-**22** could be effected by irradiation with UV light in a quartz vessel, and the *E* isomer cyclized to give spirotetronate when treated with sodium hydride. After further experimentation, we found that this three-step transformation could be accomplished much more efficiently as a one-pot sequence, which involved the initial heating of alkyne **20** in the presence of Gagosz's gold catalyst, followed by irradiation in the presence of a catalytic amount of sodium isopropoxide. In this way, although (*Z*)-**22** predominated in the photostationary state, it was converted via (*E*)-**22** into tetronate **19**, thus shifting the *Z*/*E* equilibrium and obviating the separation of isomers and recycling, and affording tricyclic tetronate **19** in a 60 % overall yield.

With the key intermediate **19** in hand, the stage was set for investigating the attachment of the side chain and completion of the synthesis (Scheme 5). Aldehyde **23** was obtained in optically pure form, from *cis*-2,4-dimethylglutaranhydride,[21] according to the literature procedure.[22] Treatment of **23** with lithiated **19**, followed by quenching the reaction with methoxymethyl bromide, gave protected allylic alcohol **24** as a mixture of diastereoisomers. The vinyl group was transformed into an aldehyde to give **25**; correction of the stereochemistry of the aldehyde-bearing stereocenter was accomplished through base-catalyzed epimerization. These two steps were best accomplished as a one-pot procedure, comprising ozonolysis, followed by the addition of a catalytic amount of DBU; this procedure provided the required aldehyde **25** as a single diastereoisomer in 81 % overall yield. Takai olefination of aldehyde **25**[23] gave vinyl iodide **26** and deprotection of the primary hydroxy group with a subsequent oxidation using DMP gave the precursor for macrocyclization, aldehyde **27**. The intramolecular Nozaki–Hiyama–Kishi reaction proceeded smoothly,[24] to afford tetracyclic intermediate **28** in 90 % yield (96 % calculated on the basis of recovered aldehyde **27**), as a mixture of four diastereoisomers.[25] Removal of the MOM ether in **28** was accomplished with methanolic hydrogen chloride. The crude diol was converted into diketone **29** in 78 % yield by treatment with freshly prepared DMP.[26] The NOESY spectrum of this compound showed correlations corresponding to the atrop-abyssomicin structure. An attempt to cleave the benzyl group in diketone **29** by hydrogenolysis resulted in concomitant reduction of the alkene and the formation of abyssomicin H. After some experimentation, the final deprotection step was accomplished by treatment of diketone **29** with boron tribromide at room temperature. This provided atrop-abyssomicin C identical to the natural product in all respects.

To summarize, an enantioselective synthesis of (−)-atrop-abyssomicin C was accomplished by a route that should allow us to prepare analogues for further structure–activity relationship (SAR) studies. The key features of the synthesis are the application of dual catalysis for the formation of the cyclohexane core (**12**→**13**), the gold-promoted reaction

cascade leading to the one-pot spirotetronate formation (**20**→**19**), and the remarkably efficient eleven-membered ring closure by the Nozaki–Hiyama–Kishi reaction (**27**→**28**).

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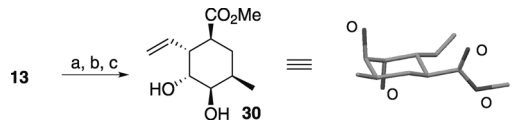
a) oxone, DMF; then CH_2N_2, Et_2O (65%); b) BBr_3, CH_2Cl_2, −78 °C (85%); c) HF (91%).



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