Natural Product Synthesis

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Enantioselective Total Synthesis of the Diterpene (+)-Cubitene**

*Kristina Simon, Johannes Wefer, Elisabeth Schöttner, and Thomas Lindel**

Cubitanoids constitute a small group of diterpenoids that share a twelve-membered monocycle. The parent compound (+)-cubitene (**1**; Figure 1) was isolated by Prestwich, Clardy et al. from the front glands of soldiers of the East African termite *Cubitermes umbratus*.[1] (+)-Cubitene also occurs as a major component of defensive extracts of soldiers of *C. ugandensis*, *C. muneris*, *C. tenuiceps*, *C. sankurensis*, *C. fungifaber*, and in *Crenetermes mixtus*.[2] Look and Fenical isolated the oxygenated calyculones A–G (e.g. calyculone A (**2**)) from the gorgonian coral *Eunicea calyculata*.[3] Further natural products from the soft coral *Sinularia triangula* are closely related to **1**.[4]

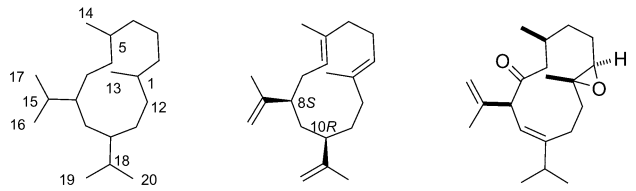
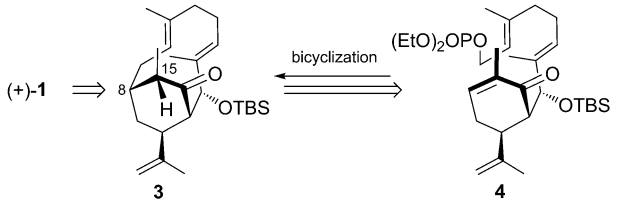


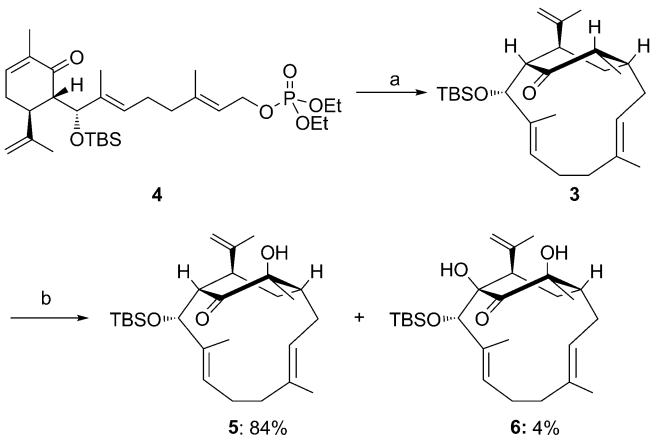
Figure 1. Cubitane skeleton, (+)-cubitene (**1**), and calyculone A (**2**).

The total synthesis of (+)-cubitene described herein utilizes the intramolecular SmI_2-mediated coupling reaction of an allylic phosphate and a carvone moiety. The route proceeds via bicyclic intermediates that are more functionalized and more compact than (+)-cubitene (Scheme 1).[5] In particular, the (8*S*,10*R*)-configuration of **1** is strictly controlled by placing the two isopropenyl side chains on the same side of the twelve-membered ring. There is only one enantioselective total synthesis of (+)-cubitene published to date by Kodama et al., which controls the relative configuration of the two isopropenyl-substituted carbons C8 and C10 on the level of open-chain precursors and requires separation of diastereomers at two occasions.[6]



Scheme 1. Retrosynthesis of monocyclic (+)-**1** via the bicyclic intermediate **3**. TBS = *tert*-butyldimethylsilyl.

The [8.2.2] bicycle **3** is accessible in high yields by treatment of allyl phosphate **4** (Scheme 2) with SmI_2 (5.5 equiv) in THF.[7,8] We could show that α-cleavage of the oxoethylene bridge of bicycle **3** is possible after intermediate hydroperoxylation at C15 and reduction to the diol,[7] but upscaling was difficult. Thus, a more robust conversion of bicyclic ketone **3** into an acyloin or to a diol had to be developed, followed by C–C cleavage. It was also unclear whether a possible acyloin could be cleaved directly, or if reduction to the diol would be required.



Scheme 2. Bicyclization and α-hydroxylation: a) Sm (5.5 equiv), $C_2H_4I_2$ (5.0 equiv), THF, RT, 3 h, then **4**, THF, 0 °C, 12 h, 73%; b) LHMDS (3.0 equiv), THF, −78 °C, 1 h; then $P(OEt)_3$ (4.0 equiv), O_2, −78 °C to −30 °C, 12 h, 84%. LHMDS = lithium hexamethyldisilazide.

Phosphate **4** was prepared in four steps from commercially available (*S*)-carvone.[7] Subsequent cyclization of **4** to bicycle **3**[7] benefitted from prolonged reaction times and slow overnight addition of phosphate **4** to the solution of SmI_2 in THF at 0 °C (Scheme 2). Undesired side reactions, such as dimerization, were suppressed, affording the bicycle **3** in 73% yield, because the concentration of the open-chain precursor was kept permanently low. Treatment of **3** with excess LHMDS at −78 °C led to deprotonation of the bridge

[*] Dr. K. Simon, M. Sc. J. Wefer, Dr. E. Schöttner, Prof. Dr. T. Lindel
Technische Universität Braunschweig
Institute of Organic Chemistry
Hagenring 30, 38106 Braunschweig (Germany)
E-mail: th.lindel@tu-braunschweig.de
Homepage: http://www.oc.tu-bs.de/lindel

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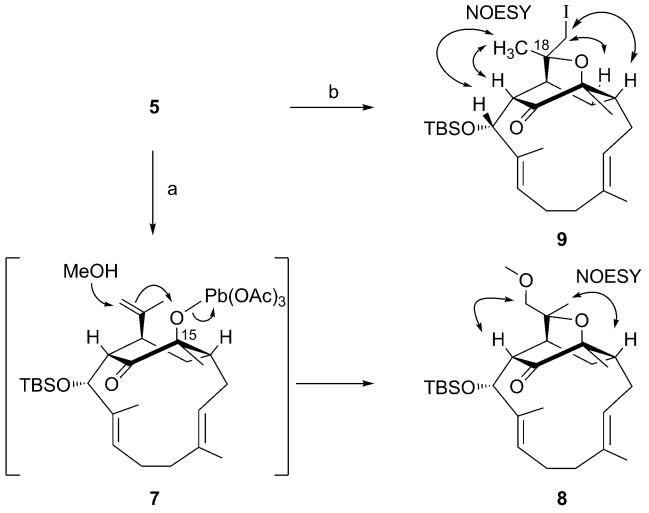
methine carbon C15 affording the enolate, which was quenched with oxygen at −30 °C. The hydroperoxide intermediate was reduced in situ with $P(OEt)_3$[9] affording acyloin **5** (84 %) together with traces of dihydroxyketone **6** (4 %), indicating that deprotonation at the bridge head carbon takes place at a slower rate than at the bridge carbon.

Attempts of direct cleavage of acyloin **5** by employing $Pb(OAc)_4$[10] did not afford the desired product. Instead, tricycle **8** was formed by dioxygenation of the isopropenyl double bond with incorporation of a methoxy group at the terminal carbon and bond formation between the central isopropenyl carbon and the α-oxygen (Scheme 3). According

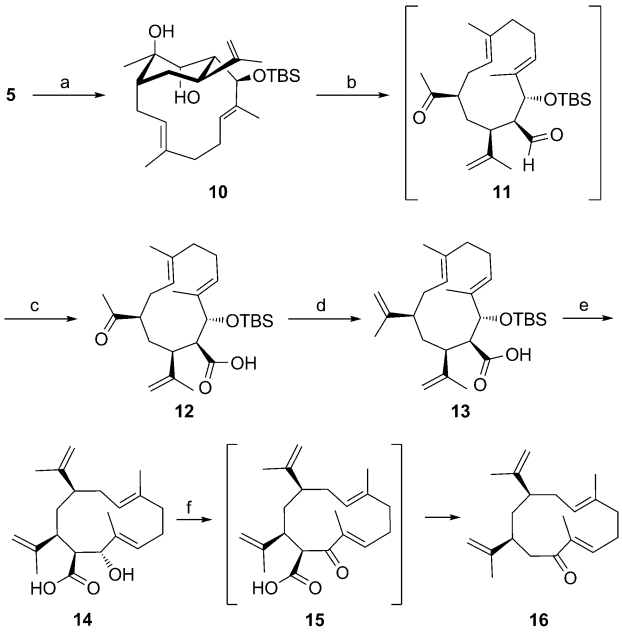


Scheme 3. Tricyclic products instead of acyloin cleavage: a) $Pb(OAc)_4$ (1.5 equiv), MeOH, RT, 10 min, 56 %; b) H_5IO_6 (1.1 equiv), EtOH, 7 d, RT, 64 %. Only relevant NOESY correlations are shown.

to NOESY analysis, the methoxy group is situated in proximity of the keto group. Possibly, in the first step, one of the acetate ligands of $Pb(OAc)_4$ is replaced by 15-OH, followed by nucleophilic attack of the isopropenyl group which simultaneously is attacked by the solvent MeOH (**7**, Scheme 3).

A similar product (**9**), differing from **8** by the presence of an iodo instead of a methoxy substituent and by its relative configuration, was obtained on treatment of **5** with H_5IO_6 in EtOH in a sluggish reaction (7 d) but in good yield (**9**, 64 %). Periodic acids form hypoiodic acid in the presence of reductants, leading to the formation of iodohydrins or iodomethylated cyclic ethers from alkenes.[11] In our case, no reducing agent was added. The solvent EtOH probably reduces H_5IO_6 slowly to hypoiodic acid over several days. H_5IO_6 itself did not react with substrate **5**.

As acyloin cleavage was not possible, acyloin **5** was reduced to *trans*-diol **10** by treatment with $LiAlH_4$ in THF at −30 °C (70 % over two steps starting from **3**, Scheme 4). Glycol cleavage was possible either by treatment of **10** with H_5IO_6 overnight or with $Pb(OAc)_4$ within 15 min, affording the monocyclic cyclododecadienyl carbaldehyde **11**, which was oxidized immediately to carboxylic acid **12** under Pinnick conditions ($NaClO_2$/2-methyl-2-butene, 54 % over 2 steps).



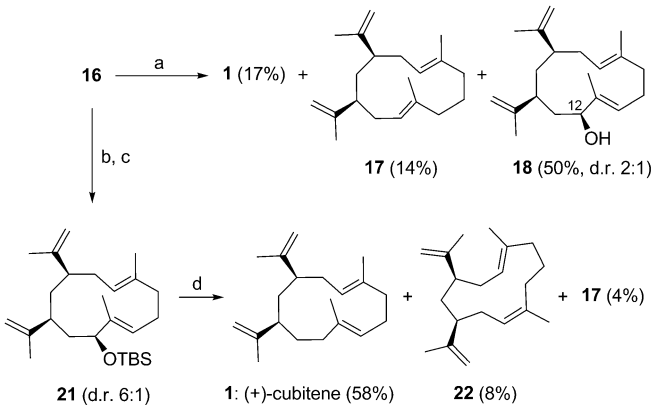
Scheme 4. Fragmentation of bicycle **10** and subsequent decarboxylation: a) $LiAlH_4$ (1.3 equiv), THF, −30 °C, 1 h, 83 %; b) H_5IO_6 (1.1 equiv), EtOH, RT, 20 h or $Pb(OAc)_4$ (1.1 equiv), MeOH, RT, 15 min; c) $NaClO_2$ (9 equiv), NaH_2PO_4 (10 equiv), 2-methyl-2-butene (90 equiv), H_2O, *t*BuOH, RT, 16 h, 54 % (2 steps); d) Ph_3PCH_3Br (5 equiv), *n*BuLi (5 equiv), THF, 0 °C, 1 h, then **12**, THF, 0 °C to RT, 16 h, 87 %; e) *p*-TsOH·H_2O (1.0 equiv), MeOH, RT, 20 h; f) Pyr·SO_3 (5.0 equiv), Et_3N (5.0 equiv), DMSO, RT, 30 min, then 1,4-dioxane, reflux, 30 min, 63 % (2 steps). Pyr = pyridine, *p*-Ts = *p*-toluenesulfonyl.

Subsequent Wittig reaction (Ph_3PCH_2, 5 equiv) afforded the C_{21} compound **13** in 87 % yield.

The challenging endgame of the total synthesis required decarboxylation of **13** and deoxygenation in the allylic position. It was not possible to convert the carboxy group into a Barton ester. Even the more advanced HOTT salt method failed.[12] Therefore, we modified the strategy. Fluoride-based desilylation of **13** with TBAF or HF·NEt_3 was very slow. Clean desilylation was possible using *p*-TsOH in MeOH, yielding β-hydroxycarboxylic acid **14** (Scheme 4). Oxidation of **14** under Parikh–Doering conditions (Pyr·SO_3, DMSO/NEt_3) afforded the β-ketocarboxylic acid **15**, which was decarboxylated immediately by refluxing in dioxane, forming ketone **16** ("cubitenone") in 63 % yield and in two steps from **13**.

Reductive deoxygenation of α,β-unsaturated ketone **16** failed even under modified Wolff–Kishner conditions employing $(TBSHN)_2$/$Sc(OTf)_3$ at 100 °C.[13] Direct deoxygenation of **16** was also attempted with $LiAlH_4$/$AlCl_3$,[14] which had allowed deoxygenation of α,β-unsaturated cyclopentenones and cyclohexenones without double-bond migration.[15]

In this case, a promising mixture of (+)-cubitene and the achiral isomer **17** ("isocubitene") was obtained in a 5:4 ratio in 31 % yield. The reduction of the carbonyl group took place and alcohol **18** was obtained in 50 % yield as a 2:1 mixture of diastereomers (Scheme 5).



Scheme 5. Deoxygenation of cubitenone (**16**): a) $AlCl_3$ (27 equiv)/$LiAlH_4$ (6 equiv), Et_2O, −20 °C, 2 h; b) $LiAlH_4$ (2 equiv), Et_2O, 0 °C, 15 min, 92%; c) TBSOTf (5 equiv), DIPEA (10 equiv), CH_2Cl_2, RT, 1 h, 91%; d) titration with Li/$EtNH_2$, THF, −78 °C. DIPEA = diisopropylethylamine, Tf = trifluoromethanesulfonyl.

With the aim of improving yield and selectivity, we turned to a three-step approach by deoxygenation of a protected allylic alcohol with Li/$EtNH_2$. Reduction of cubitenone **16** with $LiAlH_4$ afforded allylic alcohol **18** as a 6:1 mixture of diastereomers in 92% yield; the isomers could be separated by column chromatography. Stereochemical assignment was possible after trifluoroacetylation of the major diastereomer, affording compound **19**. Figure 2 shows the MM2-minimized conformation of **19**, which corresponds perfectly to the experimental NOESY correlations.

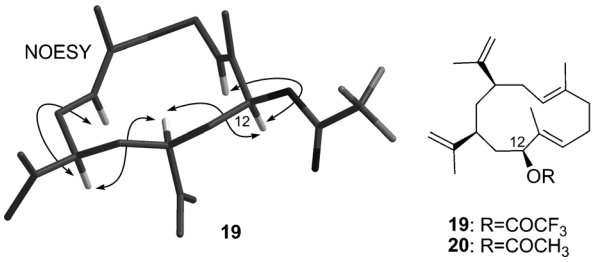


Figure 2. MM2 minimized model of trifluoroacetate **19** with decisive NOESY correlations.

Trifluoroacetate **19** was not suitable for deoxygenation with Li/$EtNH_2$, because immediate aminolysis occurred. When an acetyl group (in **20**) instead of a trifluoroacetyl group was used, careful titration with Li in $EtNH_2$ at −78 °C[16] (TLC monitoring to avoid overhydrogenation) afforded a mixture of (+)-cubitene, achiral regioisomer **17**, *Z*-isomer **22** (ratio 9:2:2, 52%), and alcohol **18** (27%).

Inspired by the work of Corey,[16] we then decided to replace the acetoxy by a silyloxy group (**21**), which would prevent formation of alcohol **18** (TBSOTf/Hünig's base). To our delight, reduction of **21** with Li/$EtNH_2$ afforded (+)-cubitene in the high yield of 58%, accompanied by isocubitene **17** (4%) and *Z*-isomer **22** (8%, Scheme 5). Overhydrogenation was only observed when excess of Li/$EtNH_2$ was added or if the reaction was run at elevated temperatures (confirmed by GC/MS).

Benefitting from the higher selectivity towards **1**, purification of (+)-cubitene now became possible by chromatography employing $AgNO_3$ (3%) loaded silica as stationary phase (pentane/Et_2O gradient). We obtained the natural product (+)-cubitene as a colorless solid with an optical rotation $[\alpha]_D^{23} = +90.8$ ($c = 0.25$, MeOH), which is in agreement with the value reported by Kodama et al. ($[\alpha]_D^{25} = +88$).[6d] However, the value is smaller than reported by Prestwich et al. for the isolated natural product ($[\alpha]_D^{25} = +128$), the relative configuration of which was confirmed by X-ray analysis.[1]

The ratio of products **1**, **17**, and **22** after reduction with Li/$EtNH_2$ was very similar for both diastereomeric silylallylethers **21**, thus suggesting an allylic anion intermediate.[17] Regioselective protonation of allylic anions has also been observed in other cases.[18]

In summary, we have completed an enantioselective total synthesis of (+)-cubitene (**1**) in an efficient linear 15-step sequence with an overall yield of 5.2%. Our approach is nine steps shorter than Kodama's synthesis of **1** from D-mannitol[6d] and proceeds via bicyclic intermediates, thus allowing strict control over the configuration of C8.

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