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Total Synthesis of (−)-Crinipellin A

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Supporting Information

ABSTRACT: The first total synthesis of (−)-crinipellin A is described. The tetraquinane core skeleton of crinipellin A was assembled through the tandem [2 + 3] cycloaddition reaction of an allenyl diazo substrate containing a cyclopentane ring in a single operation. The absolute stereochemistry was confirmed through the total synthesis.

Crinipellins, first isolated in 1979 from basidiomycete *Crinipellis stipitaria* with antibacterial and anticancer activity, are the only tetraquinane natural products (Figure 1).[1,2] The structures of crinipellin A (**1**) and crinipellin B (**4**)

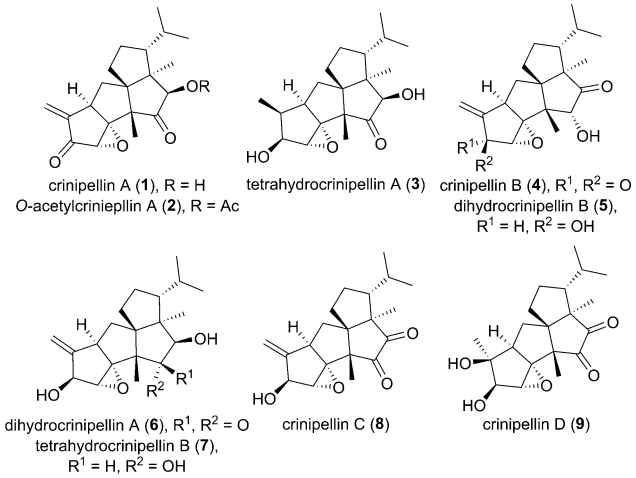


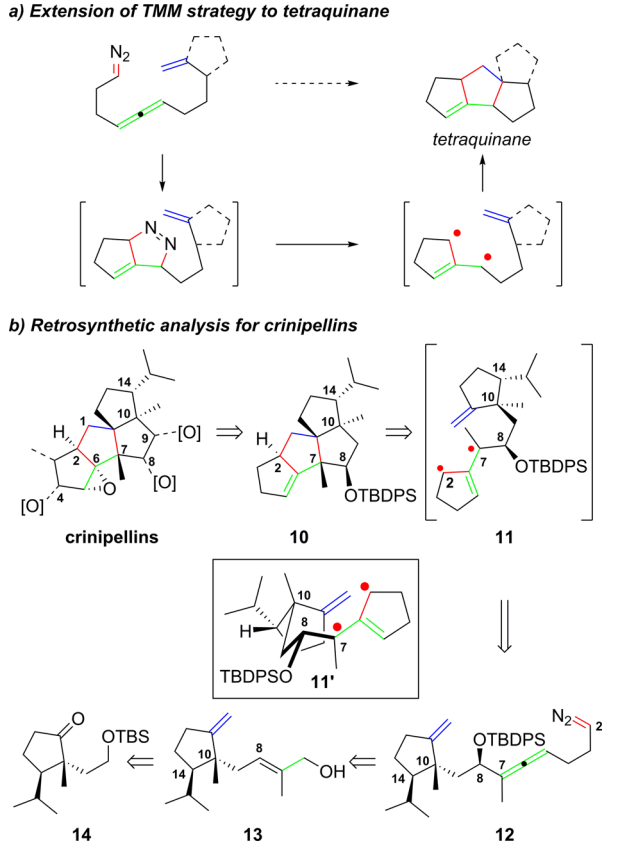
Figure 1. Members of crinipellins

along with their analogues (**2**, **3** and **5**) were deduced by NMR analysis and were confirmed by an X-ray structure determination of crinipellin B (**4**).[1b] Recently, structurally diverse crinipellins that do not possess the enone moiety (**6**–**9**) were isolated from a different fungal strain, *Crinipellis* sp. 113 and showed only moderate anticancer acitivity.[1c] The structural complexity in addition to the biological activities of crinipellins has drawn attention from the synthetic organic chemists. However, there have been only handful reports of synthetic efforts of the total synthesis of crinipellins,[3] and Piers' report of the total synthesis of crinipellin B[4] is the sole example of the total synthesis of crinipellin natural products.

The eight contiguous stereocenters in a congested tetraquinane skeleton poses still a formidable challenge to synthetic chemists and a test ground for synthetic strategies developed toward the ideal synthesis.[5]

Recently we reported a synthetic methodology for the synthesis of triquinanes from linear acyclic substrates through tandem cycloaddition reaction sequence via trimethylenemethane (TMM) diyl.[6] Application of the new synthetic methodology could be extended to the construction of tetraquinanes starting from cyclopentanes with proper appendages (Scheme 1a). A big challenge of the tetraquinane

Scheme 1. Synthetic Analysis of Crinipellins



synthesis via TMM diyl cycloaddition reaction is tolerance of the cycloaddition reaction against the added steric and electronic effect in the substrates.[7] Though challenging, high reactivity of TMM diyl and seemingly favorable conformational constraint in the tether prompted us to initiate the total synthesis of crinipellins.

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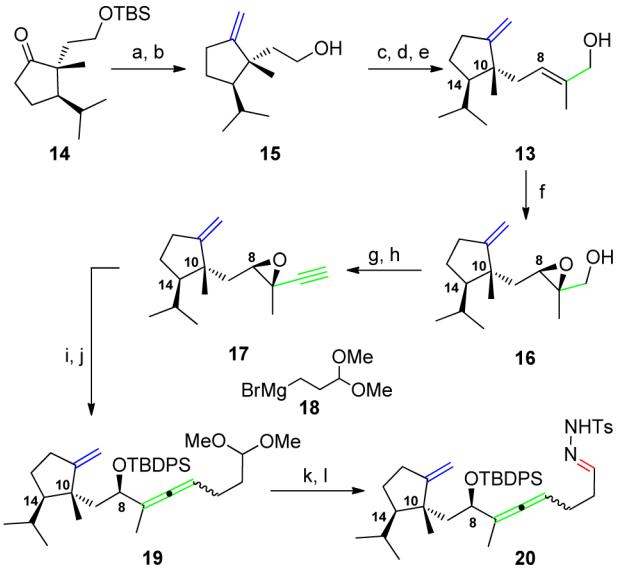
Synthetic analysis revealed that crinipellins could be synthesized from the tetraquinane **10** that could be obtained from **12** through the tandem cycloaddition reaction via TMM diyl **11** (Scheme 1b). The relative stereochemistry at the C-8, the C-10 and the C-14 stereocenters of **12** appears to be important as the OTBDPS group has to adopt pseudoequatorial position for the TMM diyl cycloaddition reaction. It was well-documented in the linear triquinane synthesis that the stereochemistry at that position controlled the relative stereochemistry of the cycloaddition product as it preferred the equatorial position in the transition state of the TMM cycloaddition reaction.[8] The substrate for **12** can be assembled from the intermediate **13** where the allylic alcohol can introduce the C-8 hydroxy group enantioselectively to control the relative stereochemistry of **12**. The allylic alcohol **13** can be prepared from a known compound **14** that was available in enantiomerically pure form.[9]

The total synthesis started with the known enantiomerically pure compound **14**[9] synthesized from 2-methyl-2-cyclopenten-1-one (Scheme 2). Wittig olefination of the ketone of **14** followed by deprotection of the TBS-ether produced **15**. The alcohol of **15** was oxidized to the corresponding aldehyde using Swern's protocol.[10] Stereoselective Wittig olefination of the aldehyde produced the allylic alcohol **13** after LAH reduction of the ester. Asymmetric Sharpless epoxidation reaction of **13** produced the epoxide **16** along with its diastereomeric product in 8:1 ratio, since the asymmetric epoxidation of such allylic alcohols is known to be less selective than other types of allylic alcohols.[11] The epoxyalcohol **16** was converted into the alkyne **17** with one carbon extension through oxidation of the alcohol of **16** to the corresponding aldehyde and subsequent treatment with Bestmann–Ohira reagent.[12] The epoxyalkyne moiety of **17** set the stage for the introduction of the remaining carbon atoms necessary for the tetracyclic core of crinipellins with formation of the allene functionality. The iron catalyzed S_N2'-type reaction[13] of the epoxyalkyne **17** with the Grignard reagent **18** produced allene compound **19** as an inseparable 1:1 mixture of diastereomers after protection of the alcohol of the product with the silyl protecting group. Finally, the acetal of **19** was removed by acidic hydrolysis[14] to unmask the aldehyde and the aldehyde was treated with *p*-toluenesulfonehydrazide to form the hydrazone **20**.

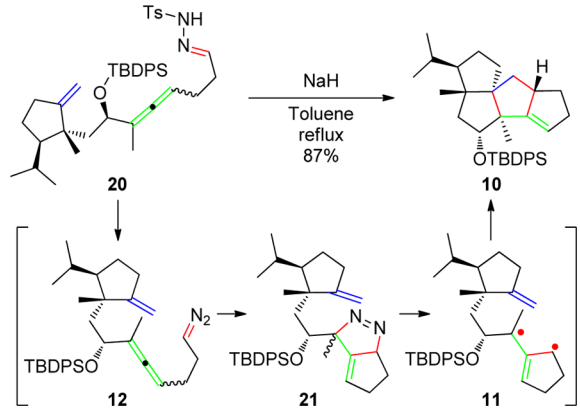
The key tandem cycloaddition reaction was initiated by generating the diazo functionality from **20** through the anion formation from the hydrazone of **20** under refluxing toluene solution.[15] To our delight, despite of seemingly high steric congestion during the TMM diyl cycloaddition reaction, successive cycloaddition reaction of the diazo intermediate via TMM diyl intermediate **11** produced the tetraquinane **10** in 87% yield with complete stereocontrol via the preferred conformer **11′** as anticipated in Scheme 1 (Scheme 3).

Scheme 2. Preparation of the Precursor for the TMM Diyl Cycloaddition Reaction[a]



[a](a) Ph_3PCH_3Br, ^{t}BuOK, ^{t}BuOH, Et_2O, r.t., 99%; (b) TBAF, THF, r.t., 99%; (c) $(COCl)_2$, DMSO, THF; TEA, −78 °C to r.t.; (d) Ph_3PCCH_3COOEt, THF, reflux, 91% for 2 steps; (e) LAH, Et_2O, 0 °C to r.t., 96%; (f) D-DET, TBHP, $Ti(O^iPr)_4$, CH_2Cl_2, −30 °C, 87%; (g) $(COCl)_2$, DMSO, CH_2Cl_2; TEA, −78 °C to r.t.; (h) K_2CO_3, Bestmann–Ohira reagent, MeOH, r.t., 87% for 2 steps; (i) $Fe(acac)_3$, **18**, THF, Toluene, −15 °C, 94%; (j) TBDPSCl, imidazole, DMAP, CH_2Cl_2, r.t., 96%; (k) *p*-TsOH·H_2O, HCHO, THF, H_2O, r.t., 93%; (l) H_2NNHTs, MeOH, r.t., 97%.

Scheme 3. Tandem Cycloaddition Reaction to Form Tetraquinane 10



With the complete carbon framework of crinipellins in hand, completion of the total synthesis of crinipellin A required introduction of various oxygen functionalities with stereocontrol. After deprotection of TBDPS group of **10**, PCC oxidation produced ketone **22**. *α*-Hydroxylation of **22** followed by PCC oxidation gave diketone **23**. Since *α*-hydroxylation of **22** using Davis' oxaziridine[16] gave the *β*-configuration of the hydroxyl group at the C-9 position that is the opposite streereochemistry of crinipellin A, the alcohol was oxidized to the diketone **23**. Since the reduction of the diketone of **23** reduced the C-8 ketone selectively,[4a,b] we devised an indirect way for introducing proper stereochemistry at the C-9 position. Treatment of the diketone **23** with sulfoximine anion produced **24** selectively.[17] In line with the chemo- and stereoselectivity for the reduction of the diketone **23**,[4b] sulfoximine anion attacked the C-8 ketone selectively from the back side to produce the tertiary alcohol with *β*-configuration. The stereochemistry of this alcohol of **24** was used for the introduction of the stereochemistry at the C-9 position of crinipellin A. Hydroxyl group directed reduction of the ketone of **24** using $NaBH(OAc)_3$[18] produced the diol **25** with complete stereocontrol. After protection of the alcohol at the C-9 of **25**, allylic oxidation of the olefin using PDC gave enone

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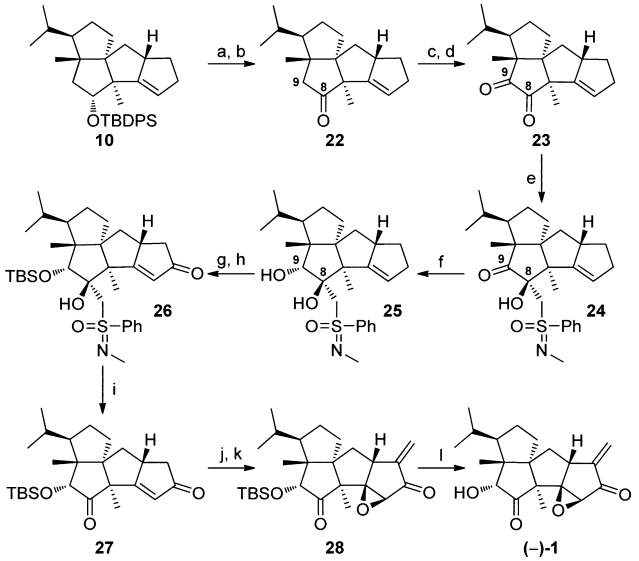
26.[19] At this stage, the sulfoximine group was removed easily to regenerate the ketone **27** by simply refluxing in toluene.[17] Treatment of **27** with hydrogen peroxide under basic condition followed by treatment with LDA and Eschenmoser's salt[20] introduced an epoxide and a methylene group to afford **28** that completed installation of all carbons and the proper functional groups of crinipellin A. The final deprotection reaction of TBS group was tested under various conditions.[21] Only TASF produced crinipellin A reproducibly with low conversion due to instability of **28** under basic condition. Nonetheless, desilylation of **28** using TASF produced natural (−)-crinipellin A (Scheme 4). All the physical and spectroscopic data for synthetic (−)-**1** were identical to the naturally occurring (−)-crinipellin A.

Scheme 4. Completion of the Synthesis[a]



[a](a) TBAF, THF, 60 °C; (b) PCC, CH_2Cl_2, r.t., 79% for 2 steps; (c) KHMDS, Davis' oxaziridine, THF, −78 °C; (d) DMP, pyr., CH_2Cl_2, r.t., 79% for 2 steps; (e) ^{n}BuLi, (+)-(*S*)-*N*,*S*-dimethyl-*S*-phenylsulfoximine, −78 °C, 80% (87% brsm); (f) $NaBH(OAc)_3$, CH_2Cl_2, r.t., 80% (90% brsm); (g) 2,6-lutidine, TBSOTf, CH_2Cl_2, r.t., 98%; (h) PDC, TBHP, PhH, r.t., 40%; (i) toluene, 125 °C, 69% (81% brsm); (j) H_2O_2, $NaHCO_3$, THF, H_2O, r.t., 90%; (k) LiHMDS, Eschenmoser's salt, THF, −78 °C to −70 °C, 58% (63% brsm); (l) TASF, DMF, r.t., 40% with 35% conversion.

In summary, we have succeeded in the first asymmetric total synthesis of crinipellin A from 2-methyl-2-cyclopenten-1-one. The unique tetraquinane structure was constructed efficiently via TMM diyl mediated tandem cycloaddition reaction. Absolute stereochemistry of (−)-crinipellin A was also confirmed through our asymmetric total synthesis.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedure and spectral data for compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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