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Stereoselective Synthesis of the C1–C13 Fragment of (+)-Discodermolide Using Asymmetric Allyltitanations

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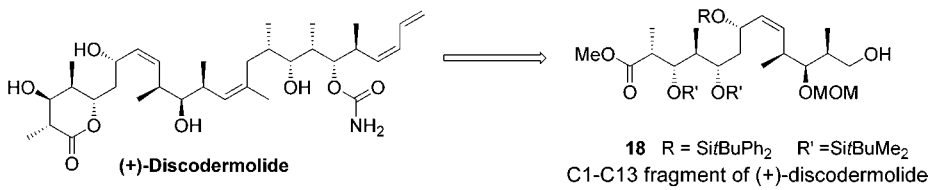
ABSTRACT



The synthesis of the C1–C13 fragment of (+)-discodermolide has been achieved. The configurations of the stereogenic centers have been controlled by enantioselective allyl- and crotyltitanations of aldehydes, and the *Z* configuration of the olefin at C8–C9 was controlled by a ring-closing metathesis.

Discodermolide was isolated by Gunasekera and co-workers at the Harbor Branch Oceanographic Institute in 1990 from the deep-water marine sponge *Discodermia dissoluta*.[1] This compound has a unique polyketide structure bearing 13 stereogenic centers, and the absolute configuration of these stereogenic centers was established by Schreiber et al. during their initial synthesis of both (+)- and (−)-discodermolide.

(+)-Discodermolide is both a potent immunosuppressive and anticancer agent as well as an antifungal agent.[2,3] It inhibits T-cell proliferation with an IC_{50} of 9 nM and graft-versus-host disease in transplanted mice.

Furthermore, startling cytotoxity causing cell cycle arrest in the G2/M phase in a variety of human and marine cell lines.[4] Discodermolide stabilizes microtubules and has been recognized as one of the most potent tubulin polymerizing agents. Due to the potential therapeutic applications and the extreme scarcity of (+)-discodermolide (0.002% w/w) from frozen marine sponge, there has been considerable synthetic effort toward discodermolide, culminating in several total syntheses[3,5] and numerous fragment syntheses.[6] Herein, we report the results of our synthetic studies concerning an approach toward the C1−C13 subunit **18** which sets the stage for a convergent synthesis of (+)-discodermolide (Scheme 1).

According to our retrosynthetic analysis, the C14−C15 bond could be formed by using a sp_2-sp_3-type palladium(0)-mediated cross-coupling reaction between a vinyl

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(6) References for synthetic approaches to discodermolide, see: Arefolov, A.; Panek J. S. *Org. Lett.* **2002**, *4*, 2397.

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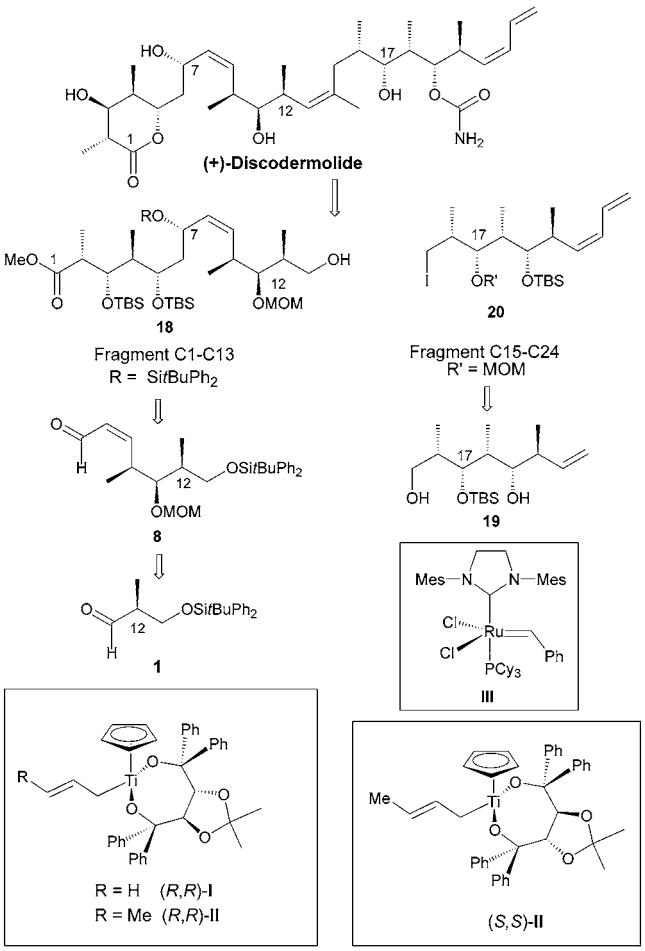
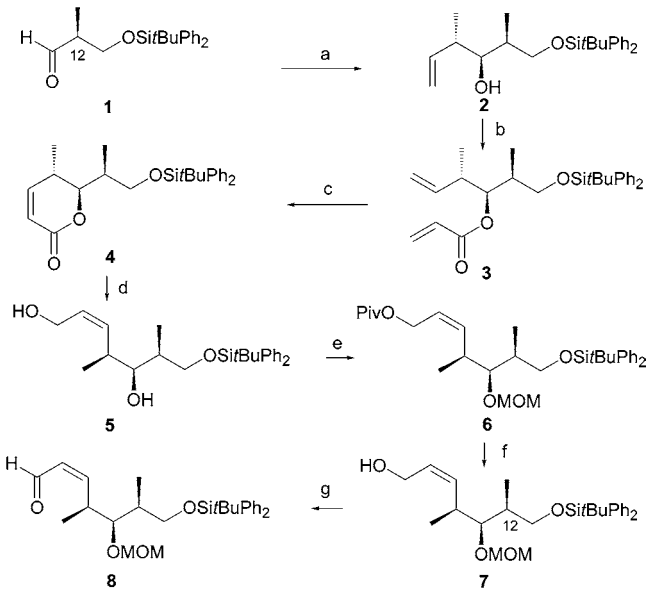
Scheme 1



iodide (C1−C14 fragment), which could be synthesized from compound **18** (C1−C13 fragment), and iodide **20** (C15−C24 fragment**)**, which could be obtained from stereopentad **19**.[7] Compound **18** could be synthesized from the unsaturated aldehyde **8**. We projected that the transformation of **8** to **18**, which implies the control of stereogenic centers C2, C4, C5, and C7, could be realized using the high face selective and stereoselective chiral allyltitanium complex (*R*,*R*)-**I** and the (*E*)-crotyltitanium complexes (*R*,*R*)-**II** and (*S*,*S*)-**II**.[8] Aldehyde **8** will be synthesized from the commercially available (*S*)-2-methyl-3-silyloxypropanal **1** using the (*E*)-crotyltitanium complex (*R*,*R*)-**II** to set the C10 and C11 stereogenic centers. A ring-closing metathesis (RCM) reaction will control the *Z* double bond present at C8−C9 (Scheme 1).

The synthesis of the C1−C13 fragment of (+)-discodermolide began with the addition of the cyclopentadienylalkoxycrotyltitanium complex (*R*,*R*)-**II** to (*S*)-2-methyl-3-silyloxypropanal **1**. This addition afforded a 96/4 mixture of two separable diastereomers from which compound **2** was isolated in 91% yield. By analogy with previous results, the (*S*)-configuration can be attributed to the C11 and C10 stereogenic centers.[9] To control the (*Z*) stereochemistry of the double bond at C8−C9, compound **2** was transformed to lactone **4** in two steps. Compound **2** was first converted to the unsaturated ester **3** in 89% yield by treatment with acryloyl chloride in the presence of *i*-Pr_2NEt (CH_2Cl_2, −78 °C). Subsequent ring-closing metathesis using Grubbs' catalyst **III**[10] in refluxing CH_2Cl_2 afforded lactone **4** (85% yield). This lactone was transformed to the allylic alcohol **5** in 72% yield by reduction with Dibal-H at −78 °C followed by reduction of the subsequent lactol by $NaBH_4$ in MeOH at 0 °C. It is worth noting that the ring-closing metathesis of an unsaturated ester followed by reduction of the lactone resulted in the exclusive formation of the (*Z*)-allylic alcohol **5**. Protection of this allylic alcohol as a pivaloyl ester (PivCl, pyridine, 25 °C) followed by protection of the secondary alcohol as a MOM ether (MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 25 °C) led to compound **6** in 81% yield. To transform **6** to aldehyde **8**, compound **6** was first reduced with Dibal-H (CH_2Cl_2, −78 °C) to the corresponding alcohol **7** and then transformed to aldehyde **8** with a Swern oxidation (90% yield) (Scheme 2).

Scheme 2 [a]



[a] Key: (a) (*R*,*R*-**II**, ether, −78 °C, 91%; (b) acryloyl chloride, *i*Pr_2NEt, CH_2Cl_2, −78 °C, 89%; (c) Grubbs' catalyst **III**, CH_2Cl_2, reflux, 85%; (d) (i) Dibal-H, CH_2Cl_2, −78 °C, (ii) $NaBH_4$, MeOH, 0 °C, 72%; (e) (i) PivCl, pyridine, 25 °C, (ii) MOMCl, *i*Pr_2NEt, CH_2Cl_2, 25 °C, 81%; (f) Dibal-H, CH_2Cl_2, −78 °C, 93%; (g) $(COCl)_2$, DMSO, −78 °C, Et_3N, CH_2Cl_2, 90%.

The elaboration of a suitable precursor to the C1−C13 fragment of (+)-discodermolide from **8** required the installation of the C7 stereogenic center with the (*S*)-configuration and, thus, the use of the allyltitanium complex (*R*,*R*)-**I** in ether at −78 °C. The homoallylic alcohol **9** was obtained in

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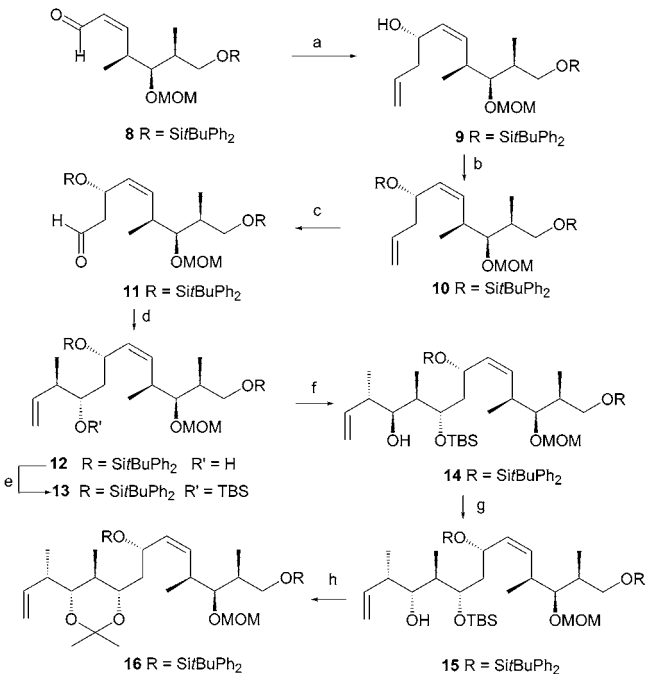
(9) The structure of **2** was determined by comparaison with the analytical data reported in the literature see: Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348.
(10) Grubbs, R. H.; Scholl, M.; Ding, S.; Lee, C. W. *Org. Lett.* **1999**, *1*, 953.

high diastereoselectivity (dr = 96/4) and in 90% yield by treatment of **8** with the (*R*,*R*)-**I** complex. The choice of a hindered protecting group for the hydroxy group is of significant importance for the progress of the synthesis because it will protect the disubstituted double bond at C8−C9 during the oxidation of the terminal olefin.[11] Thus, the homoallylic alcohol **9** was subjected to TBDPSCl (imidazole, CH_2Cl_2) and transformed to the silyl ether **10** in 93% yield. As anticipated, the oxidation of **10** with OsO_4/NMO/$NaIO_4$ (acetone/H_2O) was selective and gave exclusively aldehyde **11** in high yield (89%). Therefore, the presence of the aldehyde was appropriate for the introduction of the C4 and C5 stereogenic centers which were controlled by using the (*S*,*S*)-**II** complex at −78 °C. After treatment of **11** with the (*S*,*S*)-**II** complex, compound **12** was obtained in high diastereoselectivity (dr = 95/5) and in good yield (91%). Protection of the hydroxy group at C5 with TBSOTf (2,6-lutidine, −78 °C) afforded compound **13** in 85% yield. The last two stereogenic centers at C2 and C3 were introduced in a three-step sequence from compound **13** (Scheme 3). The

Scheme 3 [a]

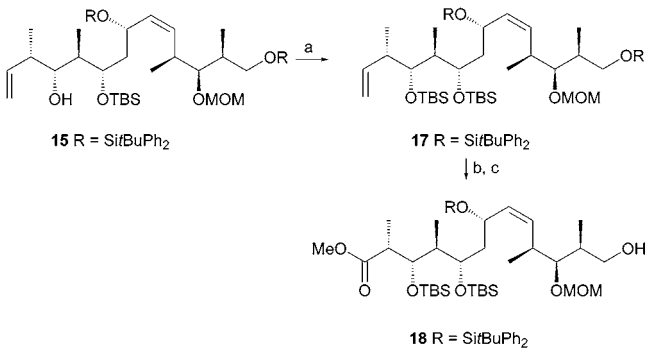


[a] Key: (a) (*R*,*R*)-**I**, ether, −78 °C, 90%; (b) ClSi*t*BuPh$_2$, imidazole, CH_2Cl_2, 93%; (c) OsO_4/NMO/$NaIO_4$, acetone/H_2O, 89%; (d) (*S*,*S*)-**II**, ether, −78 °C, 91%; (e) TBSOTf, 2,6-lutidine, −78 °C, 85%; (f) (i) OsO_4/NMO/$NaIO_4$, acetone/H_2O, (ii) (*R*,*R*)-**II**, ether, −78 °C, 78%; (g) (i) $(COCl)_2$, DMSO, −78 °C, Et_3N, CH_2Cl_2, (ii) Dibal-H, toluene, −80 °C, 81%; (h) (i) TBAF, THF, 25 °C, 24 h, (ii) ClSi-*t*-BuPh$_2$, imidazole, CH_2Cl_2, (iii) DMP, acetone, CSA, 25 °C, 60%.

terminal double bond present in **13** was selectively oxidized to the corresponding aldehyde (OsO_4/NMO/$NaIO_4$), which was then treated directly with the (*R*,*R*)-**II** complex (ether, −78 °C) to produce the homoallylic alcohol **14** in an overall yield of 78%, with the *anti* relative stereochemistry between the groups at C2 and C3. Inversion of the hydroxy group at C3 was achieved by using a Swern oxidation followed by a diastereoselective reduction of the obtained ketone by Dibal-H in toluene at −80 °C.[12] This two-step process led to compound **15** in an overall yield of 81% (*syn*/*anti* > 25/1) (Scheme 3).

To establish the relative stereochemistry at C3, C4, and C5, **15** was transformed to acetonide **16** in three steps. After removal of the three silyl protecting groups, the allylic alcohol at C7 was protected selectively with TBDPSCl (imidazole, CH_2Cl_2), and the obtained product was treated with dimethoxypropane in acetone in the presence of CSA to produce acetonide **16**[13] in 60% overall yield. The relative *syn* configuration of the hydroxy groups at C3 and C5 was confirmed by the analysis of the ^{13}C NMR (δ = 19.5, 30.0 for Me_2C) (Scheme 3). The transformation of **15** to ester **18**, which corresponds to the C1−C13 fragment of discodermolide, was achieved in five steps. The protection of the hydroxy group at C8 as a TBS ether led to **17** in 84% yield. After selective cleavage of the terminal double bond (OsO_4/NMO/$NaIO_4$), the aldehyde was oxidized to the carboxylic acid upon treatment with buffered $NaClO_2$. The methyl ester was produced by esterification of the acid ($TMSCHN_2$, MeOH, benzene, 65% yield) and selectively deprotected to give alcohol **18** in 82% yield upon treatment with NH_4F in refluxing MeOH (Scheme 4).

Scheme 4 [a]



[a] Key: (a) TBSOTf, 2,6-lutidine, −20 °C, 84%; (b) (i) OsO_4, NMO, $NaIO_4$, acetone/H_2O, 25 °C, (ii) $NaClO_2$, NaH_2PO_4, H_2O, *t*-BuOH/H_2O, (iii) $TMSCHN_2$, MeOH, benzene, 65%; (c) NH_4F, MeOH, 65 °C, 82%.

In conclusion, the synthesis of the fully elaborated C1−C13 fragment of (+)-discodermolide, compound **8**, was completed by using high face selective chiral allyl- and crotyltitanations. Progress toward the total synthesis of (+)-discodermolide continues and will be reported in due course.

Supporting Information Available: ^1H NMR and ^{13}C NMR spectra for compounds **5**, **10**, **16**, and **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Rychnovsky, S. D.; Rogers, B. N.; Richardson, R. I. *Acc. Chem. Res.* **1998**, *31*, 9.