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Research Article

Studies towards the Total Synthesis of (+)-Discodermolide: Desymmetrization Approach

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Abstract

A new synthetic strategy for the construction of C-1 to C-7 and C-8 to C-15 subunits of (+)-discodermolide, a highly potent anticancer natural product, is reported in which we have exploited desymmetrization approach to create six stereogenic centers at once and stigmatic elements of the successful methodology include elaboration of two advanced fragments from a common precursor.

Keywords: (+)-Discodermolide; Retrosynthesis; Fragment or sub-unit; Anti-cancer activity; Natural products.

Introduction

Cancer is a leading cause of death worldwide, accounting for nearly 10 million deaths in 2020, or nearly one in six deaths.[1] Cancer is among the most costly and deadly healthcare burdens globally, and the International Agency for Research on Cancer has estimated that by the year 2030, the number of existing cancer cases will increase to 21.7 million globally. The number of annual global cancer deaths is also projected to increase to 13 million by 2030 based on rates of population growth and aging. The investigation on natural anticancer agents is an important subject of current research all over the world.[2-4]

Natural products (NPs) and structural analogues have long been important in medicinal chemistry,[5-7] and divergent syntheses of complex natural products from a common intermediate have piqued the interest of the chemical community in recent years due to their potential to improve chemical synthesis efficiency.[8-12] Total synthesis of complex natural products will continue to be one of the most intriguing and dynamic fields of research in the future.[13]

In 1990, Gunasekara and colleagues at the Harbor Branch Oceanographic Institute discovered Discodermolide, a novel cytotoxic polyketide, from the extracts of the uncommon Caribbean deep-sea sponge *Discodermia dissolute*.[14] Discodermolide has substantial cytotoxic action against a wide range of human tumor cell lines, as well as significant anticancer efficacy in animals. The mechanism of action is similar to paclitaxel in that it binds to microtubules and stabilizes them, causing mitotic arrest and cell death.[15-16] Phase I clinical trials for discodermolide (**1**) are presently underway. Extensive spectroscopic analyses, including a combination of 1-D and 2-D NMR methods, were required for structure elucidation. X-ray crystallography was used to determine the relative stereochemistry.

However, until Schreiber and colleagues synthesized both antipodes, the absolute configuration remained unknown.[17]

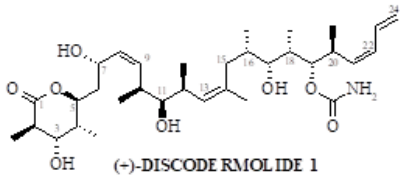
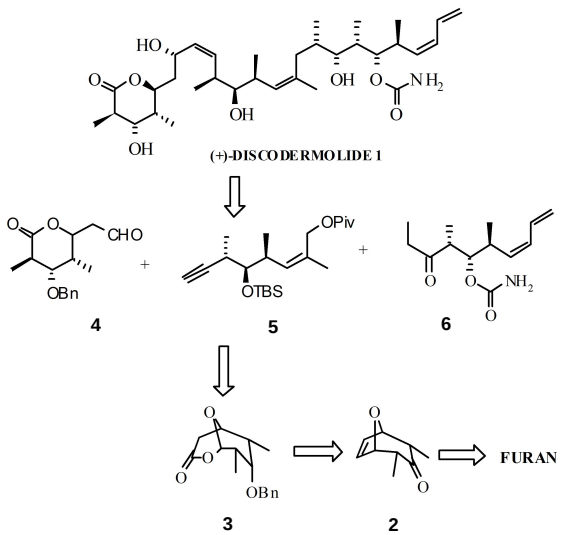


Figure 1. Stereochemistry of **1**

The molecule bears 13 stereogenic centers, a tetrasubstituted δ-lactone (C1-C5), one di- and one trisubstituted (Z)-double bond, a pendant carbamate moiety (C19), and a terminal (Z)-diene (C21-C24) (**Figure 1**). Unfortunately, **1** is in scarcity; the reported isolation yield is only 0.002 percent (w/w from frozen sponge), resulting in only 7 mg of natural product being extracted from 434 g of sponge. As a result, synthesis of (+)-discodermolide is an appealing, and as far as we know, the only cost-effective way of obtaining the quantities of **1** required for further biological study. Discodermolide **1** has gained the interest of synthetic chemists in recent decades due to its structural complexity, excellent biological activities, and natural scarcity. Several complete syntheses of discodermolide, its fragments, and analogues have been reported as a result.[18-22]



Scheme 1. Retrosynthetic strategy of (+)-Discodermalide

To start the synthesis, we looked into a highly convergent approach to (+)-discodermolide **1** that involved disconnecting the carbon backbone at C (7-8) and C (15-16) as shown in the retrosynthetic pathway (**Scheme 1**), which required the creation of three advanced subtargets **4**, **5**, and **6** from a common precursor **3** that possessed the stereogenicity triad that appears in each subtarget. We have synthesized the fragments from a common bicyclic precursor. We have exploited desymmetrization approach to create six stereogenic centers at once. Asymmetric hydroboration and epimerization are the key steps. Thus, we could synthesize the target fragments C-1 to C-7 and C-8 to C-15 towards the total synthesis of (+)-Discodermolide.

Experimental Section

2-((2*S*,3*S*,4*S*,5*S*)-4-(benzyloxy)-3,5-dimethyl-6-oxo-tetrahydro-2*H*-pyran-2-yl)acetaldehyde(19)

To a stirred clear solution of IBX (108 mg, 0.38 mmol) in DMSO (0.5 mL) at R.T was added drop wise a solution of alcohol **18** (90 mg, 0.32 mmol) in dry CH_2Cl_2. The reaction mixture was stirred for 2 h at R.T. After completion of reaction, the reaction mixture was diluted with ether, filtered through celite pad. The filtrate was washed with saturated aqueous $NaHCO_3$ solution, brine. The organic layer was dried over Na_2SO_4, concentrated *in vacuo*. Flash column chromatography on silica gel afforded the aldehyde **19** (79 mg, 89% yield) as a viscous liquid.

IR (Neat): 1740 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 9.83 (t, *J* = 1.57 Hz, CHO), 7.49-7.23 (m, 5H, Ar-H), 4.98 (ddd, *J* = 8.5 Hz, 4.96 Hz, 3.76 Hz, 1H, H-5), 4.60 (s, 2H, benzylic), 3.89(t, *J* = 4.96 Hz, 1H, H-3), 3.04 (ddd, *J* = 17.66 Hz, 1.57 Hz, 8.5 Hz, 1H, H-6), 2.80 (dq, *J* = 4.96 Hz, 7.16 Hz, 1H, H-2), 2.70 (ddd, *J*= 17.66, 1.57, 4.72 Hz, 1H, H-6), 2.47 (dd, *J* = 4.96 Hz, 3.76 Hz, 1H, H-4), 1.34 (d, *J* = 7.16 Hz, 3H), 0.99 (d, *J* = 7.16 Hz, 3H); Mass: *m/z* 276 (M^+).

(4*S*,5*R*,6*S*,*Z*)-5-(*tert*-butyldimethylsilyloxy)-2,4,6-trimethyloct-2-en-7-ynyl pivalate (5)

To a cooled (-78 °C) solution of dibromo olefin **36** (80 mg, 0.14 mmol) in anhydrous THF (5 mL) was added *n*-BuLi (0.11 mL, 0.17 mmol) and the reaction mixture was stirred at the same temperature for 30 min. After completion of reaction the suspension was quenched with saturated NH_4Cl solution (5 mL), diluted with EtOAc. The aqueous layer was re-extracted with EtOAc (3x5 mL). The combined organic extracts were dried (Na_2SO_4), and concentrated under vacuum. The crude product was purified by flash chromatography to give acetylenic compound **5** (45 mg, 82% yield) as colourless oil.

Optical rotation $[\alpha]_D$: (+) 7.38 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 5.24 (d, *J* = 10.5 Hz, 1H) 4.69 (d, *J* = 12.0 Hz, 1H), 4.56 (d, *J* = 12.0 Hz, 1H), 3.35 (dd, *J* = 3.0, 6.8 Hz, 1H), 2.79 (m, 1H), 2.62 (m, 1H), 2.03 (d, *J* = 2.3 Hz, 1H), 1.73 (d, *J* = 1.5 Hz, 3H), 1.21 (s, 9H), 1.16 (d, *J* = 7.5 Hz, 3H), 0.98 (d, *J*

= 6.8 Hz, 3H), 0.92 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H).; ^{13}C NMR ($CDCl_3$, 75 MHz) : δ178.5, 133.9, 129.5, 86.1, 78.5, 70.1, 63.4, 38.8, 36.9, 31.5, 27.1, 25.9, 21.5, 18.3, 17.7, 17.5, -3.6, -3.8; Mass: *m/z* 381 (M^+).

Results and Discussion

Synthesis of the C1-C7 fragment

Furan and 2,4-dibromopentanone were subjected to 4+2 cycloaddition to yield bicyclic ketone.[23] Bicyclic alcohol **8** is made from bicyclic ketone **2** in a three-step process that includes (-)-Ipc_2BH asymmetric hydroboration as a critical step. The best technique to open the bicyclic ketone is to make the matching ester and open it by hydrolysis, according to a clear observation. It was achieved by Baeyer-Villiger oxidation of ketone **9** using *m*-CPBA and $NaHCO_3$ in CH_2Cl_2 (**Scheme 2**).[23] The formation of lactone **3** was clearly indicated by the downfield shift of H-1 proton from δ 4.38 (compared with the parent ketone) to δ 5.44, which appeared as a doublet. The formation of the product also confirmed by the appearance of (M+1) peak at *m/z* 277 in the mass spectrum. The formation of the lactone was unreasonable because normally in Baeyer-Villiger reactions the oxygen goes to the more substituted carbon.

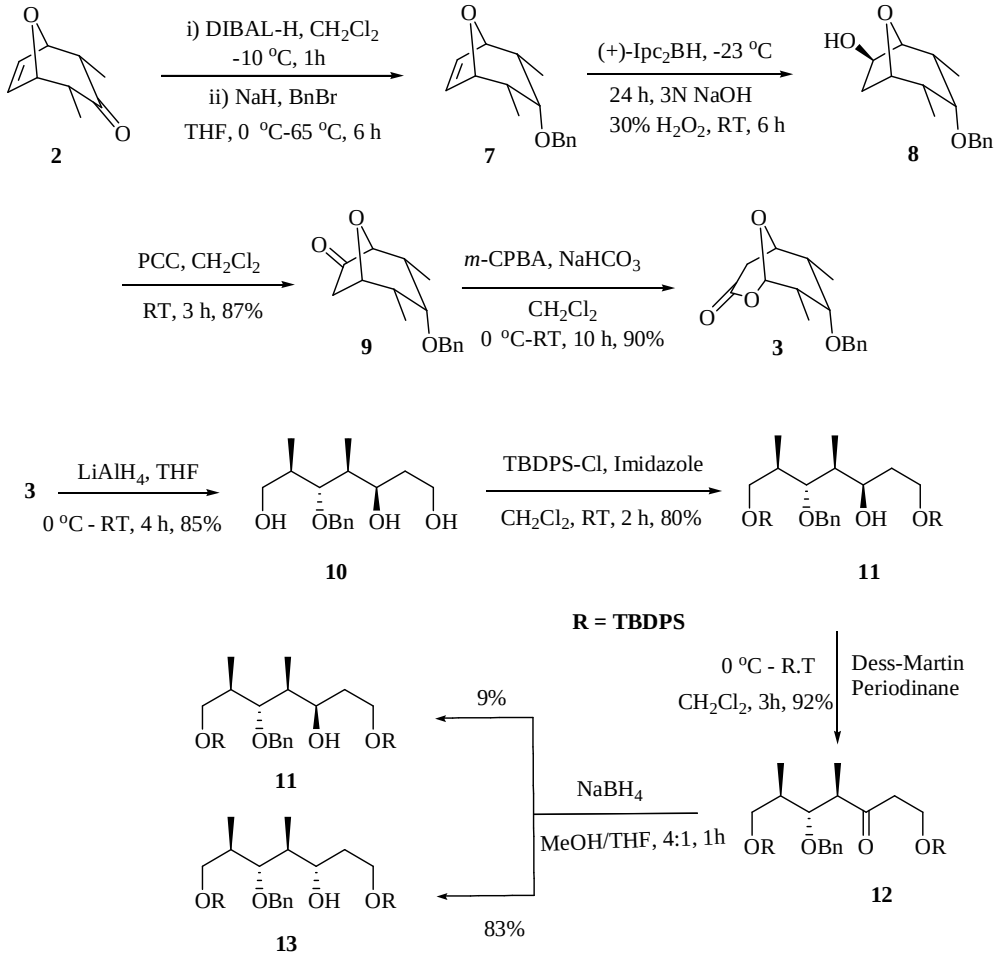
After obtaining the bicyclic lactone with all functions required for the creation of the C1-C7 fragment of **1**, the lactone ring was opened. Treatment of the bicyclic lactone **3** with $LiAlH_4$ in dry THF yielded a polar compound with 85% yield, which was identified as the predicted triol **10**. The triol was confirmed by its ^{1}H NMR spectrum in which two methyl doublets resonated at δ 1.00 (*J* = 6.5 Hz) and 1.10 (*J* = 6.5 Hz) respectively and two benzylic protons appeared as singlet at δ 4.70. The other protons of the structure appeared as multiplets. Mass spectrum showed a molecular ion peak at 283 *m/z* value.

The primary hydroxyl groups of compound**10** were selectively protected as TBDPS ether **11** using TBDPSCl and imidazole at 0 °C in 80% yield. The formation of product **11** was confirmed through ^{1}H NMR studies. The two tertiary butyl groups resonated at δ 1.01 and δ 1.04. Aromatic region integrated for 25 protons. It was decided to investigate the oxidation and reduction methodology after the Mitsunobu protocol[24] for the inversion at C-5 centre failed. The keto compound **12** was obtained in 92% yield by oxidizing compound **11** with Dess-Martin periodinane.[23] Formation of the keto compound was apparent by the disappearance of C-5 proton and also by the downfield shift of the C-4 and C-6 protons. The IR spectrum showed absorption at 1740 cm^{-1}. Molecular ion peak at *m/z* 779 (M+Na) further confirmed the product.

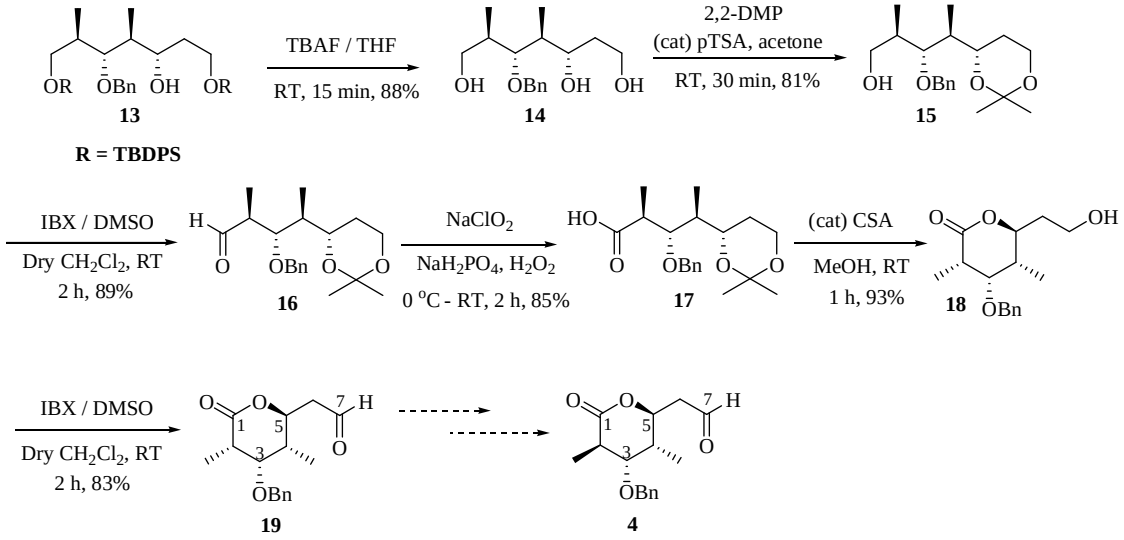
It was found that the reduction of keto compound **12** using $NaBH_4$ in MeOH:THF (4:1) afforded the required α-isomer **13** as the major product (**13**:**11** = 9:1). The structure of the compound **13** was confirmed by the comparative ^{1}H NMR studies of compound **13** with that of compound **11**. It was observed that the H-5 of compound **13** resonated upfield at δ 3.85 relative to H-5 compound **11**, which is resonated at δ 4.25 indicating an antirelationship between the CH_3 group at C-4 and -OH at C-5 in compound **13**. In the case of compound **13** the benzylic protons appeared as a singlet, where as for the compound **11** it appeared as an ABq. This is due to the fact that in compound **11** the magnetic environment of benzylic protons is different. Additionally, that the alcohol **13** was the C-5 epimer of alcohol **11** was unambiguously shown by oxidation of **13** to afford the keto compound **12**. Mass spectrum showed a molecular ion peak at *m/z* value 759 (M+1).

The deprotection of TBDPS group of compound **13** with TBAF afforded the triol **14** (**Scheme 3**). All signals in ^{1}H NMR spectrum resonated at expected chemical shifts. Molecular ion peak at *m/z* value 283 (M+1) further confirmed the product. The triol **14** was subjected to acetonation using dimethoxy propane and catalytic amount of PTSA in acetone to give monoacetonide**15** in 81% yield. The formation of compound **15** was identified from its ^{1}H NMR studies. The two methyl groups showed two sets of doublets at δ 0.96 and δ 1.00 and two singlets at δ 1.38 and δ 1.40 for the acetonide methyl protons. All the other protons resonated at the expected chemical shifts values. Compound **15** was also characterized by its mass spectral data, which showed molecular ion peak at *m/z* 345 (M+Na).

Oxidation of alcohol **15** using IBX in dry DMSO-CH_2Cl_2 system afforded the aldehyde **16** in 89% yield. ^{1}H NMR spectrum showed an aldehyde proton at δ 9.74 as a doublet. It was further confirmed by IR spectrum which is showing an absorption band at 1726 cm^{-1} (C=O stretching of aldehyde). Product was further confirmed by a molecular ion peak at *m/z* value 343 (M+Na). The aldehyde (**16**) was converted into acid **17** by treatment with NaH_2PO_4, $NaClO_2$ and H_2O_2. The product obtained by this method was used for next reaction without further purification. Thus treatment of crude acid with a catalytic amount of CSA in methanol afforded the δ-lactone **18** in 93% yield. The formation of the product was confirmed by its ^{1}H NMR spectrum. The C-2 and C-4 methyl resonated at δ 1.35 and δ 1.05 respectively. The C-5 proton appeared at δ 4.50 as dt. The free hydroxyl proton appeared as a broad singlet at δ 1.55.



Scheme 2. Synthesis of compound **13**



Scheme 3. Synthesis of compound **19**

The formation of the product was also confirmed by its IR and Mass spectral data. IR spectrum showed an absorption band at 3416 cm^{-1} and 1618 cm^{-1}, for -OH stretching, and (C=O) respectively while mass spectrum showed molecular ion peak at *m/z* 279 (M+1).

The oxidation of alcohol **18** to its aldehyde **19** was achieved by IBX. The structure of the compound **19** was well established from its ^{1}H NMR studies. The C-2 and C-4 methyl resonated at δ 1.34 and δ 0.99 respectively. The C-5 proton appeared as ddd at δ 4.95. The aldehydic proton appeared as triplet at δ 9.79. All the other protons resonated at the expected chemical shift values. The structure of compound **19** was further confirmed by its IR spectral studies. IR spectrum showed an absorption band at 1740 cm^{-1}. Subsequent modifications will be done to achieve fragment **4** during the coupling of fragments on the way to total synthesis of the title compound.

Synthesis of the C8-C15 fragment

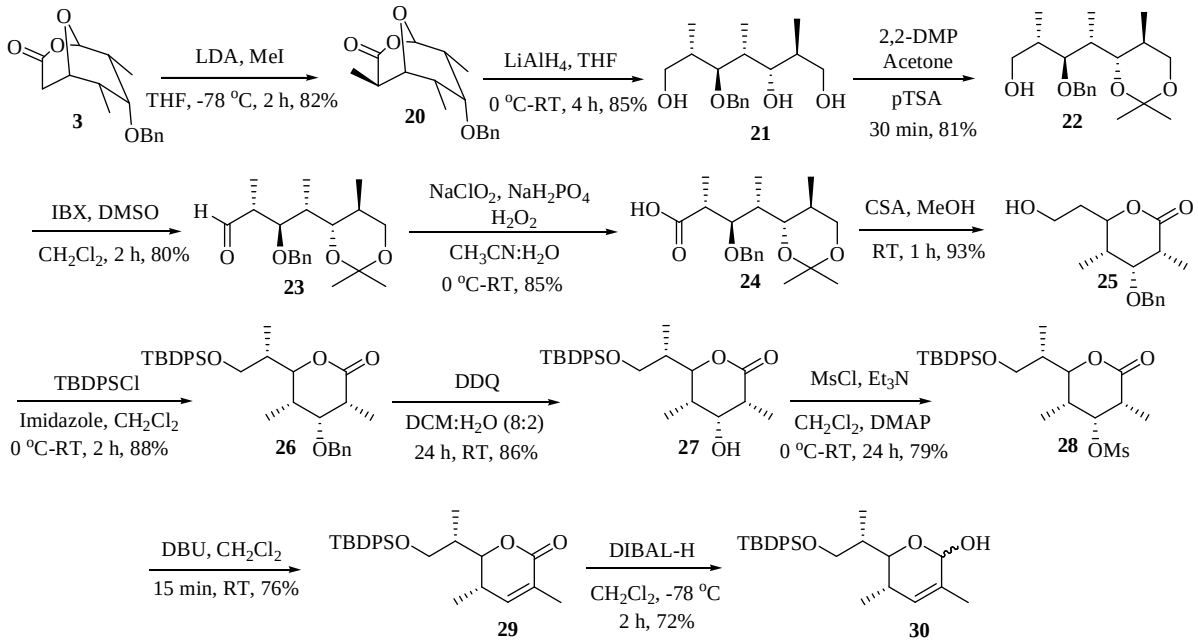
The methylated lactone **20** was created by combining the bicyclic lactone **3** with lithium diisopropylamide (LDA) and methyl iodide in dry THF at -78 ^oC in a three-step method that included (+)-IPC_2BH asymmetric hydroboration as a critical step. The lactone intermediate **3** was a common precursor for the synthesis of (+)-Discodermolide fragments **4** and **6** (**Scheme 4**). The structure of compound **20** was confirmed by its ^{1}H NMR spectrum, which revealed H-6 as a distinct quartet at δ 2.77, indicating that the H-6 proton had solely bonded with C-6 methyl protons. The equatorial quasi equatorial relationship caused the lack of coupling between H-5 and H-6. This indicates that the methyl group at C-6 was in exo-position. Furthermore, at δ 3.69 J = 4.30 Hz, a doublet for H-5 was discovered, showing that it solely connected with H-4 (equatorial axial coupling). The exo methyl group's resonance was observed at a significant down field position (δ 1.41). This also validates the methyl group's exo location. Hoffman et al.[25-26] made a similar observation, claiming that the downfield shift of the methyl proton is driven by a simple stereo-electronic effect in which the carbonyl system interacts preferentially with the axial C-CH_3 bond. The lactone carbonyl displayed absorption at 1753 cm^{-1} in the IR spectrum, which was corroborated by its mass data, which revealed (M+Na) peak at *m/z* 313. Having obtained the bicyclic lactone with all functionalities for elaboration of C-8 to C-15 fragment of **II**, attention was directed to the opening of the lactone ring.

Reductive opening of methylated lactone **20** with $LiAlH_4$ in dry THF gave a polar compound triol **21** in 90%. The triol was confirmed by its ^{1}H NMR spectrum in which three methyl doublets resonated at δ 1.12, δ 0.96, δ 0.73 corresponding to the three methyl groups and the two benzylic protons appeared as ABq at δ 4.68. The other protons of the structure appeared as multiplets. The triol **21** was also characterized by its mass spectral data, which showed (M+1) peat at *m/z* 297 and IR spectrum revealed the hydroxyl absorption at 3450 cm^{-1}.

The triol 21 was subjected to acetonation with 2,2-dimethoxy propane and catalytic amount of *p*-toluene sulfonic acid (PTSA) in dry acetone to give mono acetonide 22 (Scheme 4). The ^{1}H NMR spectrum of the 22 showed three sets of doublets at δ 1.22, δ 0.88 and δ 0.73 for three methyl groups and two singlets for the acetonide methyl protons at δ 1.36 and δ 1.35. Compound 22 was also characterized by its mass spectrum data, which showed (M+1) peak at *m/z* 337. The oxidation of alcohol using 1.1 equiv. of iodoxybenzoic acid afforded the corresponding aldehyde 23 in 89% of yield. The formation of the product was confirmed by the ^{1}H NMR spectrum, which showed an aldehydic proton resonated as doublet at δ 9.81. Mass spectrum showed molecular ion peak at *m/z* value 334 (M^+).

The aldehyde **23** was converted into the acid **24** by treatment with NaH_2PO_4, $NaClO_2$ and H_2O_2. The product obtained by this method was used for next reaction without further purification. Thus, treatment of crude acid **24** with catalytic amount of CSA in methanol gave the δ-lactone **25** in 93% yield. The formation of the product **25** was confirmed by its ^{1}H NMR spectrum. The C-2 and C-4 methyl resonated at δ 1.31 and δ 0.97 respectively. The C-2 proton appeared as pentet at δ 2.90, C-3 proton resonated as triplet at δ 3.97, C-4 proton resonated as pentet of doublet at δ 2.45, C-5 proton resonated as dd at δ 4.09. C-7, and C-7' protons appeared as dd at δ 3.82 and δ 3.68 respectively. The benzylic protons resonated as ABq at δ 4.55. The free hydroxyl proton appeared as broad singlet at δ1.87 and C-6 proton resonated as multiplet at δ 2.00. The formation of the product was also confirmed by its IR and Mass spectral data. IR spectrum showed an absorption band at 3418 cm^{-1} and 1731 cm^{-1}, for -OH stretching, and (C=O) respectively. Product was further confirmed by molecular ion peak at *m/z* 293 (M+1) in its mass spectrum.

The hydroxyl group of compound **25** was protected as its silyl ether using 1.1 equiv. of TBDPS-Cl and 1.2 equiv. of imidazole in anhydrous dichloromethane to afford **26** in 88% yield. In the ^{1}H NMR spectrum of compound **26** the tertiary butyl protons resonated at δ 1.05 as singlet.



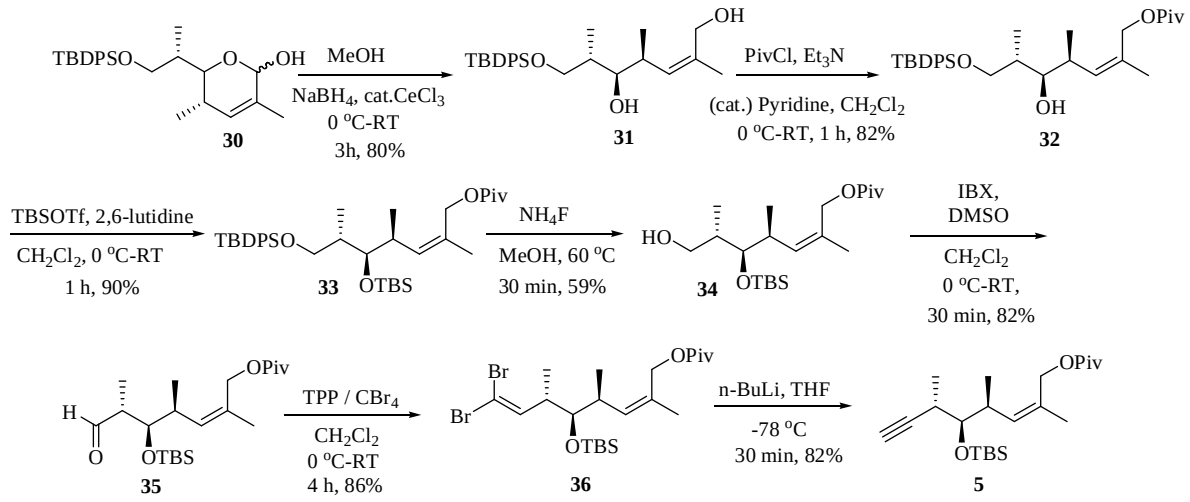
Scheme 4. Synthesis of compound **29**

Aromatic region integrated for 15 protons. Mass spectrum of compound **26** exhibited a molecular ion peak at *m/z* 548 ($M+NH_4^+$). Debenzylation of compound **26** to its alcohol **27** proved to be a difficult process. A large number of reducing agents were tested. All of these studies, however, yielded low yields or no reaction. With thehelp of DDQ, we were able to secure the desired product. On treatment with 5 equiv. of DDQ in 4:1 dichloromethane and water, benzyl ether was oxidatively cleaved to provide the corresponding alcohol **27** in 86% yield. The formation of the compound **27** was confirmed by its ^{1}H NMR, which showed the absence of benzylic protons at δ 4.54 and aromatic protons, which was also confirmed by its IR and Mass spectral data. IR spectrum showed an absorption band at 3418 cm^{-1}. The mass spectrum exhibited molecular ion peak at *m/z* 458 ($M+NH_4^+$).

The secondary hydroxyl group of compound **27** was mesylated using Et_3N and mesyl chloride to get the mesyl compound **28**. In the ^{1}H NMR spectrum of compound **28**, the newly generated sulfonyl methyl protons appeared as a singlet δ 3.05. The formation of compound **28** was also clearly indicated by the downfield shift of H-3 proton from δ 4.28 (compared with the parent alcohol) to δ 5.27. Treatment of mesyl compound **28** with DBU at room temperature afforded the α,β-unsaturated lactone **29**. In the PMR spectrum of compound **29** the newly generated olefinic proton appeared as a doublet at δ 6.67. It was further confirmed by a molecular ion peak at *m/z* value 440 ($M+NH_4^+$) in its mass spectrum. The conversion of compound **29** to the lactol**30** was carried out using 1.2 equiv. of DIBAL-H at -78 °C in anhydrous dichloromethane (**Scheme 5**). The structure of the lactol was confirmed by its ^{1}H NMR. The ^{1}H NMR spectrum showed the anomeric proton at δ 4.95.

The lactol **30** upon treatment with $NaBH_4$ and catalytic amount of $CeCl_3$ gave the allyl alcohol **31**. The formation of the compound was confirmed by its ^{1}H NMR spectrum. Mass spectrum showed a molecular ion peak at *m/z* value 427 (M+1). The primary hydroxyl group of the compound **31** was selectively protected as its pivaloyl ester **32** using pivaloyl chloride and triethylamine. The secondary hydroxyl group of the compound **32** was protected as its TBDMS ether using1.1 equiv. of TBDMSOTf and 1.1 equiv. of 2,6-lutidine in anhydrous dichloromethane at 0 °C to afford corresponding TBS ether **33** in 90% yield. The ^{1}H NMR spectrum of compound **33** showed additional tertiary butyl protons at δ 0.97 as singlet whilst the dimethyl protons attached to silicon atom corresponding TBDMS group resonated at δ 0.13 and δ 0.06 as singlets, mass spectrum of compound **33** showed a molecular ion peak at *m/z* value 647 (M+Na).

Selective desilylation of TBDPS group in compound **33** was achieved by stirring with 1 equiv. of ammonium fluoride in MeOH at 60 °C afforded the alcohol **34** in 70% yield. In its PMR spectrum compound **33** showed the absence of tertiary butyl



Scheme 5. Synthesis of subunit **5**

silyl and diphenylsilyl protons corresponding TBDPS group and presence of -OH functionality was confirmed by its IR spectrum, which showed an absorption band at 3440 cm^{-1}. It was further confirmed by molecular ion peak at *m/z* value 409 (M^++Na) in its mass spectrum. The hydroxyl group of compound**34** upon treatment with 1.1 equiv. of Dess-Martin periodinane afforded the aldehyde **35** in 90% yield. The formation of the product **35** was well established by its ^{1}H NMR spectrum, which showed the aldehydic proton at δ 9.67 as doublet and IR spectrum showed an absorption band at 1740 cm^{-1}. The formation of the product **35** was further confirmed by its mass spectrum which showed molecular ion peak *m/z* value at 407 (M+Na).

The aldehyde **35** was subjected to Corey-Fuchs homologation reaction using 4 equiv. of TPP, 2 equiv. of CBr_4 and 2 equiv. of 2,6-lutidine afforded the dibromo olefin **36** in 86% yield. The formation of product was identified from its ^{1}H NMR in which the newly generated olefinic proton appeared as a doublet at δ 6.41. All other protons resonated at the expected chemical shift values. The dibromo compound when treated with *n*-BuLi afforded the acetylene compound **5** in 82% yield. The formation of the compound was identified by its ^{1}H NMR spectrum which showed acetylenic proton at δ 2.03 which is further confirmed by its mass spectrum. FAB mass shows a molecular ion peak at *m/z* value 381 (M^+).

Conclusion

In summary, an efficient enantio and stereoselective synthetic pathway for the C1-C7 and C8-C15 fragments has been established. Further work is underway to synthesize the other fragment (C16-C24 unit) and also complete the total synthesis of discodermolide.

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Supporting Information

Available (IR, ^{1}H and ^{13}C NMR and Mass copies of significant compounds)

Conflict of Interests

The researchers have confirmed that there are no conflicting interests.

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