α -Oxygenated Crotyltitanium and Dyotropic Rearrangement in the Total Synthesis of Discodermolide

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Scheme 2. Preparation of the *syn-anti* methyl-hydroxyl-methyl triad cores and subsequent use of the (*Z*)-*O*-enecarbamate function.

The crucial central subunit **3** possesses the C13-C14 (*Z*)-trisubstituted double bond and a terminal alkyne. The C8-C9 triple bond should be accessible by an *O*-enecarbamate rearrangement. For stereocontrolled building of the C13-C14 (*Z*)-trisubstituted functionalized double bond, we considered focusing on a dyotropic rearrangement of 5-lithiodihydrofuran, first examined by Fujisawa^[8] and developed by Kocienski^[9] and us.^[10] This attractive reaction should allow the construction of various (*Z*)- or (*E*)-trisubstituted double bonds, in good yields and with total control of their geometry.

The synthesis of subunit **3** began with commercially available bromo alcohol **8** (Scheme 3). A reaction sequence involving cyanide displacement of the bromide, partial reduction of the resulting hydroxy-nitrile compound^[11] and direct dehydration provided the optically pure (*S*)-3-methyl-2,3-dihydrofuran **9** in 64% overall yield for three steps. The stereochemical control of the C13-C14 (*Z*)-trisubstituted functionalized double bond was based on 1,2-cuprate transfer between the 5-lithio-**9** derivative and a cyano-Gilman dimethylcuprate, $\text{Me}_2\text{CuLi}\cdot\text{LiCN}$. The use of various additives, and in particular those containing sulphur, allowed us the efficient installation of a methyl group which remained the most difficult to introduce.^[12] After tri-*n*-butyltin chloride trapping, the unique (*Z*)-vinyl tin derivative **10** was obtained in an optimized yield of 68%.

A very large number of oxidation conditions were tested on alcohol **10**, but only the use of TEMPO/ $\text{PhI}(\text{OAc})_2$ led to the expected aldehyde **6b**.^[13] Subsequent allylation of **6b** with the (*R*)-crotyltitanium **5** delivered the pure adduct **7b** in 84% yield for two steps (no other isomers were detected by NMR analysis). A Fritsch-Buttenberg-Wiechell rearrangement allowed the transformation of the *O*-enecarbamate **7b** into the terminal alkyne by treatment with *t*BuLi.^[14] It is worthy to note that this α -elimination reaction, using two equivalents of *t*BuLi, was faster than the tin/lithium exchange. Subunit **3** was obtained in 26.4% overall yield for eight steps.

Scheme 3. Synthesis of the C8-C14 subunit (**3**). a) NaCN, DMSO, 60 °C, 24 h, 92%; b) DIBAL-H, CH_2Cl_2 , -78 °C, 2 h, 82%; c) *p*-TSA (0.2 mol%), quinoline, 160 → 210 °C, 30 min, 85%; d) *t*BuLi, $\text{Me}_2\text{CuLi}\cdot\text{LiCN}$, $\text{Et}_2\text{O}/\text{DMS}$ 4:1, 0 °C → RT, 18 h, then $n\text{Bu}_3\text{SnCl}$, -20 °C → RT, 4 h, 68%; e) TEMPO (10 mol%), $\text{PhI}(\text{OAc})_2$, CH_2Cl_2 , RT, 2 h; f) **5**, pentane/cyclohexane, -78 °C, 3 h, 84% (two steps); g) *t*BuLi, Et_2O , -40 → -20 °C, 20 min, 78%; h) MOMCl, TBAI, Hunig's base, CH_2Cl_2 , 18 h, 92%. *p*-TSA=*p*-toluenesulfonic acid, DMS=dimethyl sulfoxide, TEMPO=2,2,6,6-tetramethyl-1-piperidinyloxy, free radical, Hunig's base=diisopropylethylamine, MOM=methoxymethyl, TBAI=tetra-*n*-butylammonium iodide.

In order to elaborate subunit **2**, the optically pure aldehyde **6a** was needed (Scheme 4). This compound could be obtained by classical chemistry in three steps from commercially available (2*S*)-3-hydroxy-2-methylpropionic acid methyl ester **11** (Roche ester).^[15] The crotyltitanation reaction between aldehyde **6a** and (*R*)-crotyltitanium **5** furnished homoaldol compound **7a** in 66% yield for two steps with total diastereoselectivity. The *O*-enecarbamate function of **7a** has been deoxygenated under reducing conditions using *i*-propylmagnesium chloride and a nickel catalyst.^[16] To our surprise, all attempts to transform this terminal alkene into a α,β -unsaturated Weinreb amide function by cross-metathesis reaction using Grubbs II or Hoveyda catalyst^[17] failed and only the starting material was recovered.^[18] Therefore, we undertook an oxidation of *O*-enecarbamate **7a** with ozone; the resulting aldehyde was used in a Horner-Wadsworth-Emmons reaction with the commercially available diethyl (*N*-methoxy-*N*-methylcarbamoylmethyl) phosphonate to provide the expected α,β -unsaturated Weinreb amide **12** as a single stereomer. A hetero-Michael reaction, with benzaldehyde under anionic conditions, introduced the stereocenter in position C5 and simultaneously protected the C3 and C5 hydroxyl functions as a benzylidene group (diastereomeric ratio > 95:5).^[19] This sequence resulted in the effective formation of subunit **2**, in 35.2% overall yield for seven steps.

Scheme 4. Synthesis of the C1-C7 subunit (**2**). a) TBSCl, imid, DMF, 0 °C → RT, 18 h, 98%; b) DIBAL-H, CH₂Cl₂, -20 °C, 30 min, 92%; c) (COCl)₂, DMSO, Et₃N, CH₂Cl₂, -55 °C → RT, 1 h; d) **5**, pentane/cyclohexane, -78 °C, 3 h, 66% (two steps); e) O₃, sudan III, CH₂Cl₂, -78 °C, 1 h then PPh₃, -78 °C → RT, 3 h, 87%; f) (EtO)₂P(O)CH₂C(O)NMe(OMe), NaH, THF, 0 °C → RT, 45 min, 86%; g) PhCHO, KHMDS, THF, -20 °C, 45 min, 79%. TBS=*tert*-butyldimethylsilyl, imid=imidazole, DIBAL-H=diisobutylaluminium hydride, KHMDS=potassium bis(trimethylsilyl)amide.

The same Roche ester **11** was used for the preparation of the third subunit **4** (Scheme 5). This starting material was transformed into aldehyde **13** by successive protection, reduction and TEMPO/sodium chlorite oxidation.^[20] The C16-C18 *syn-syn* stereotriad was installed by a BF₃·OEt₂ catalyzed allylation reaction using achiral tri-*n*-butylcrotylstannane under simple asymmetric induction (diastereomeric ratio was optimized to 95:5).^[21] Protection of the C17 hydroxyl group allowed the isolation of the expected major isomer **14** (74% yield for two steps). An oxidative cleavage of this alkene then delivered the desired aldehyde **6c**.

In a single step, both the C18-C20 *syn-anti* stereotriad and the (Z)-C21-C22 double bond were set up by an allylation reaction of **6c** with (*R*)-crotyltitanium **5**. Therefore, carbamate **7c** was elaborated in 77% yield and total selectivity from alkene **14**. Protection of the C19 hydroxyl group and subsequent direct vinylation by a cross-coupling Ni(acac)₂ catalyzed reaction^[22] between the (Z)-*O*-enecarbamate moiety and commercially available vinylmagnesium bromide furnished the (Z)-diene **15** in 85% yield.^[23] After regeneration of the C15 primary hydroxyl group, the clean transformation into alkyl iodide **4** was realised under optimized Garegg conditions in a benzene/diethyl ether mixture under high dilution.^[24] In this way, the final subunit **4** bearing five stereocenters and the terminal diene was obtained in 16.5% overall yield for eleven steps.

Scheme 5. Synthesis of the C15-C24 subunit (**4**). a) 1. CCl₃C(N)OPMB, PPTS (5 mol%), CH₂Cl₂/cyclohexane, 20 °C, 40 h, 88%; b) LAH, THF, 0 °C → RT, 3 h, 95%; c) TEMPO (2 mol%), NaOCl, KBr, NaHCO₃, CH₂Cl₂/H₂O; d) Tri-*n*-butylcrotylstannane, BF₃·OEt₂, Et₂O, -100 °C, 2 h, 74% (two steps); e) TBSOTf, 2,6-lutidine, CH₂Cl₂, 0 °C → RT, 2 h, 92%; f) O₃, sudan III, CH₂Cl₂/MeOH, -78 °C, 2 h then Me₂S, -78 °C → RT, 16 h; g) **5**, pentane/cyclohexane, -78 °C, 3 h, 77% (two steps); h) TESOTf, 2,6-lutidine, CH₂Cl₂, 0 °C → RT, 1.5 h, 78%; i) vinylmagnesium bromide, Ni(acac)₂ (10 mol%), Et₂O, 0 °C, 16 h, 85%; j) DDQ, CH₂Cl₂/H₂O, 0 °C → RT, 40 min, 72%; k) I₂, PPh₃, imid, C₆H₆/Et₂O, 0 °C → RT, 2 h, 79%. PMB=*p*-methoxybenzyle, PPTS=pyridium *p*-toluenesulfonate, TEMPO=2,2,6,6-tetramethyl-1-piperidinyloxy, free radical, TBS=*tert*-butyldimethylsilyl, TES=triethylsilyl, acac=acetylacetonate, imid=imidazole.

The first coupling reaction of the subunits was achieved by nucleophilic addition of an organometallic species derived from **3** on Weinreb amide **2** (Scheme 6). Reaction of **2** with the lithio-**3** derivative, generated by metallation with *t*BuLi, afforded the ynone **16** in 80% yield. Reduction of **16**, employing the CBS reagent, allowed generation of the C7 chiral center (diastereomeric ratio > 95:5).^[25] After protection of the C7 hydroxyl group, regeneration of the primary alcohol at C1 and oxidation under TEMPO/PhI(OAc)₂ conditions, the crude aldehyde was treated with sodium chlorite^[26] to afford a carboxylic acid, readily converted into its methyl ester employing TMS-diazomethane.^[27] The partial reduction of the triple bond at C8-C9 was realised with PtO₂.^[28] Finally, iododestannylation gave the required vinyl iodide **18** in 30.6% overall yield for nine steps.

Scheme 6. Coupling reactions and total synthesis of (+)-discodermolide (**1**). a) **3**, *t*BuLi, Et₂O, -78 °C, 30 min, then **2**, 0 °C, 3h, 80%; b) (S)-(-)-2-Methyl-CBS-oxazaborolidine, BH₃.Me₂S, THF, -30 °C, 2 h, 95%; c) MOMCl, TBAI, Hunig's base, CH₂Cl₂, RT, 18 h, 86%; d) HF/py, py/THF, RT, 4 h, 96%; e) TEMPO (10 mol%), PhI(OAc)₂, CH₂Cl₂, RT, 3 h; f) NaClO₂, NaH₂PO₄, 2-methyl-but-2-ene, *t*BuOH/H₂O, RT, 1 h; g) TMSCHN₂, C₆H₆/MeOH, RT, 15 min, 66% (three steps); h) H₂, PtO₂ (30 mol%), AcOEt, RT, 12 h; i) I₂, CH₂Cl₂, 0 °C, 10 min, 71% (two steps); j) **4**, *t*BuLi, Et₂O, -78 °C, 5 min, *B*-methoxy-9-BBN, THF, -78 °C → RT, then **18**, CsCO₃, PdCl₂dppf, AsPh₃, DMF, H₂O, 18 h, 60%; k) *p*-TSA, MeOH, 0 °C, 1 h, 77%; l) Cl₃CC(O)NCO, CH₂Cl₂, RT, 15 min, then K₂CO₃, MeOH, RT, 1.5 h, 64%; m) HCl 4N, THF, RT, 72 h, 70%. CBS= Corey-Bakshi-Shibata, Hunig's base=diisopropylethylamine, MOM=methoxymethyl, TBAI=tetra-*n*-butylammonium iodide, py=pyridine, TMS=trimethylsilyl, BBN=borabicyclo[3,3,1]nonane, dppf=(diphenylphosphino)ferrocene, *p*-TSA=*p*-toluenesulfonic acid,

The σ-bond between the major fragment **18** and subunit **4** was formed by a *B*-alkyl Suzuki-Miyaura cross-coupling reaction.^[29] The reactive trialkyl boronate species, prepared from alkyl iodide **4** with *t*BuLi and *B*-methoxy-9-BBN, reacted with **18** under Pd(dppf)Cl₂ and AsPh₃ conditions,^[30] to give the fully elaborated discodermolide carbon skeleton **19** in 60% yield.

After cleavage of the C19 triethylsilyl group and installation of the carbamate moiety^[31] the final global deprotection of all protecting groups with concomitant lactonisation, was performed in a 4N HCl solution in THF. Purification of the crude product by flash chromatography (CH₂Cl₂/MeOH 80:20) afforded (+)-discodermolide **1** in 70% yield.

The spectroscopic data observed for our synthetic (+)-discodermolide (¹H NMR, ¹³C NMR and HRMS) were identical in all respects with those reported for the natural material or another synthetic discodermolide. The specific optical rotation, [α]_D²⁰ +16.2 (*c*=1.0, MeOH), was very close to previously reported values. In addition, in vitro cytotoxicity levels comparable to literature data^[1,2] were obtained.

In conclusion, total synthesis of discodermolide was achieved in twenty one linear steps with 1.6% overall yield from commercially available compounds (**8** or **11**).

We have shown homoallylic (*Z*)-*O*-enecarbamate alcohols to be powerful tools in the total synthesis of multi-functional compounds. Allylation reaction of α-(*S*)-methyl aldehydes **6a-c** with enantioenriched (*R*)-α-oxygenated crotyltitanium **5**, conveniently prepared in situ, ensured the stereocontrolled elaboration, for each subunit, of *syn-anti* methyl-hydroxyl-methyl triads connected to a (*Z*)-*O*-enecarbamate. This particular group allowed a direct and easy access to either triple bond or terminal (*Z*)-diene functions.

This efficient and versatile synthesis delivered the natural product and we are currently working to extend this methodology to the preparation of original unnatural discodermolide analogues.

Experimental Section

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Natural Product Synthesis

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α -Oxygenated Crotyltitanium and Dyotropic Rearrangement in Total Synthesis of Discodermolide

The total synthesis of **discodermolide** relied upon three particular points: elaboration of *syn-anti* stereotriads linked to a (*Z*)-O-enecarbamate group, direct

transformation into the terminal (*Z*)-diene and stereocontrolled generation of the (*Z*)-trisubstituted double bond by a dyotropic rearrangement.