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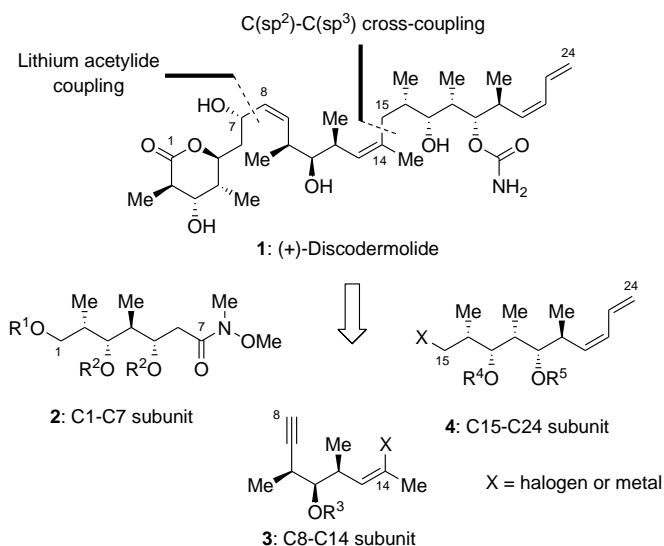
α -Oxygenated Crotyltitanium and Dyotropic Rearrangement in Total Synthesis of Discodermolide**

Elsa de Lemos, François-Hugues Porée, Alain Commerçon, Jean-François Betzer,* Ange Pancrazi, Janick Ardisson*

Discodermolide is a polyketide natural product that was first isolated in 1990 from extracts of the rare Caribbean marine sponge *Discodermia dissoluta* by Gunasekera.^[1] This compound has been shown to inhibit the proliferation of cells by arresting the G₂/M phase of the cell cycle.^[2] Discodermolide belongs to the class of antimetabolic agents known to act by microtubule stabilisation whose clinically used members are Taxol and Taxotere. This product is more potent in stabilizing microtubules, more water soluble than taxoid compounds and exhibits synergy with Taxol.^[3]

The marine sponge cannot provide the quantities of discodermolide needed for drug development. Therefore, efficient and highly convergent syntheses are needed, and work in the area is increasing.^[4]

In this paper, we report a new total synthesis of discodermolide which relies upon three particular points: elaboration of *syn-anti* stereotriads linked to an (*Z*)-*O*-enecarbamate group, direct transformation of this core into the terminal (*Z*)-diene, and stereocontrolled generation of the (*Z*)-trisubstituted double bond by dyotropic rearrangement. Our convergent synthetic strategy, outlined in Scheme 1, relies on the preparation of three subunits C1-C7 **2**, C8-C14 **3** and C15-C24 **4**.^[4h]



Scheme 1. Retrosynthetic analysis of discodermolide (**1**).

Each subunit, or their precursors, possesses a *syn-anti* methyl-hydroxyl-methyl triad (in C2-C4, C12-C10 and C18-C20 respectively for fragments **2**, **3** and **4**) with adjacent unsaturation (Scheme 2).

Therefore, we developed a convenient and scalable elaboration of this core motif. A crotyltitanation reaction, developed by Hoppe^[5] and widely used in total synthesis by us,^[6] was selected.

The enantioenriched (*R*)- α -(*N,N*-diisopropylcarbamoyloxy)-crotyltitanium **5** was easily prepared in situ from crotyl diisopropylcarbamate, an equimolar mixture of *n*-BuLi/(-)-sparteine and tetra(isopropoxy)titanium.^[7] Matched reactions between α -(*S*)-methyl aldehydes **6a-c** and (*R*)-crotyltitanium **5** should yield homoaldol adducts **7a-c** with high diastereoselectivities. These alcohols possess the three chiral centers in the correct absolute configurations linked to an (*Z*)-*O*-enecarbamate group.

Moreover, we wanted to take advantage of this (*Z*)-*O*-enecarbamate function to set up the required unsaturation. The alkyne function in C8-C9 of subunit **3** could result from a carbenoid rearrangement, the α,β -unsaturated Weinreb amide in C7 of subunit **2** from a cross-metathesis reaction, and the terminal (*Z*)-diene in C21-C24 of subunit **4** from a nickel-catalyzed cross-coupling reaction. For this strategy, we had to prepare suitable aldehydes for each subunit.

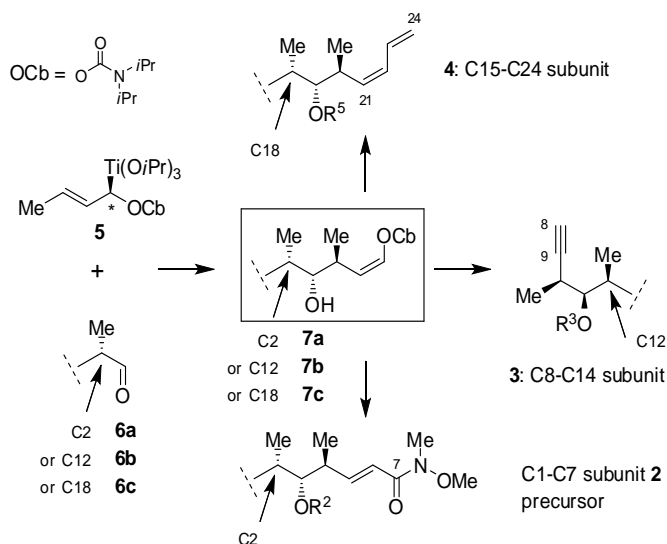
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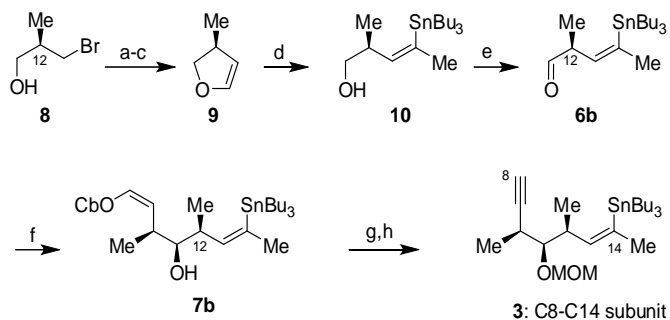


Scheme 2. Preparation of the *syn-anti* methyl-hydroxyl-methyl triad cores and subsequent use of the (*Z*)-*O*-enecarbamate function.

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.

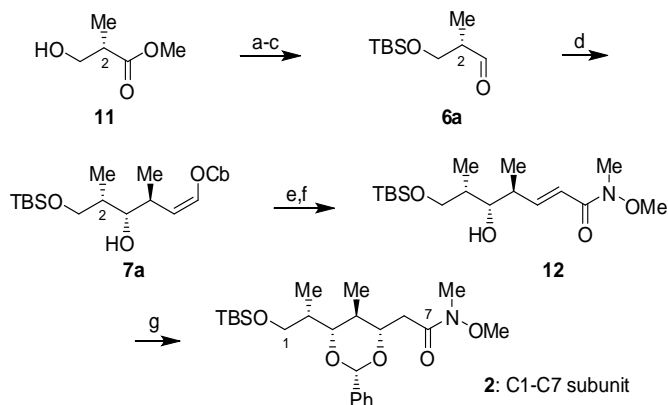
The synthesis of subunit **3** began with commercially available bromo alcohol **8** (Scheme 3). A reaction sequence involving cyanide displacement of the bromide, partial reduction of the resulting hydroxy-nitrile compound^[11] and direct dehydration provided the optically pure (*S*)-3-methyl-2,3-dihydrofuran **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, Me₂CuLi•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/PhI(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.

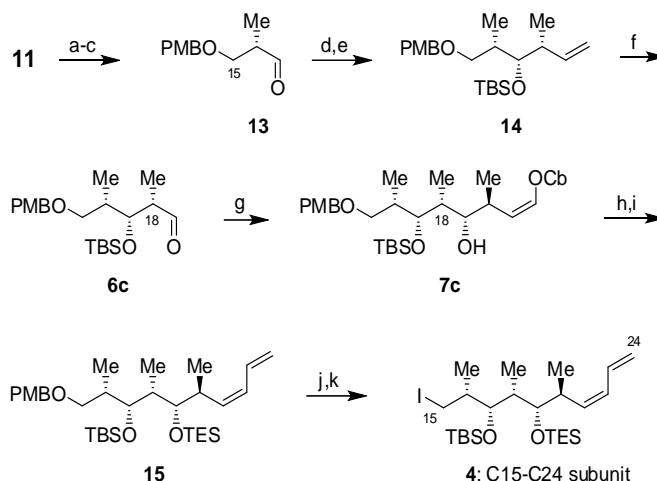


Scheme 3. Synthesis of the C8-C14 subunit (**3**). a) NaCN, DMSO, 60 °C, 24 h, 92%; b) DIBAL-H, CH₂Cl₂, -78 °C, 2 h, 82%; c) *p*-TSA (0.2 mol%), quinoline, 160 → 210 °C, 30 min, 85%; d) *t*BuLi, Me₂CuLi•LiCN, Et₂O/DMS 4:1, 0 °C → RT, 18 h, then *n*Bu₃SnCl, -20 °C → RT, 4 h, 68%; e) TEMPO (10 mol%), PhI(OAc)₂, CH₂Cl₂, RT, 2 h; f) **5**, pentane/cyclohexane, -78 °C, 3 h, 84% (two steps); g) *t*BuLi, Et₂O, -40 → -20 °C, 20 min, 78%; h) MOMCl, TBAI, Hunig's base, CH₂Cl₂, 18 h, 92%. *p*-TSA=*p*-toluenesulfonic acid, DMS=dimethyl sulfide, 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.

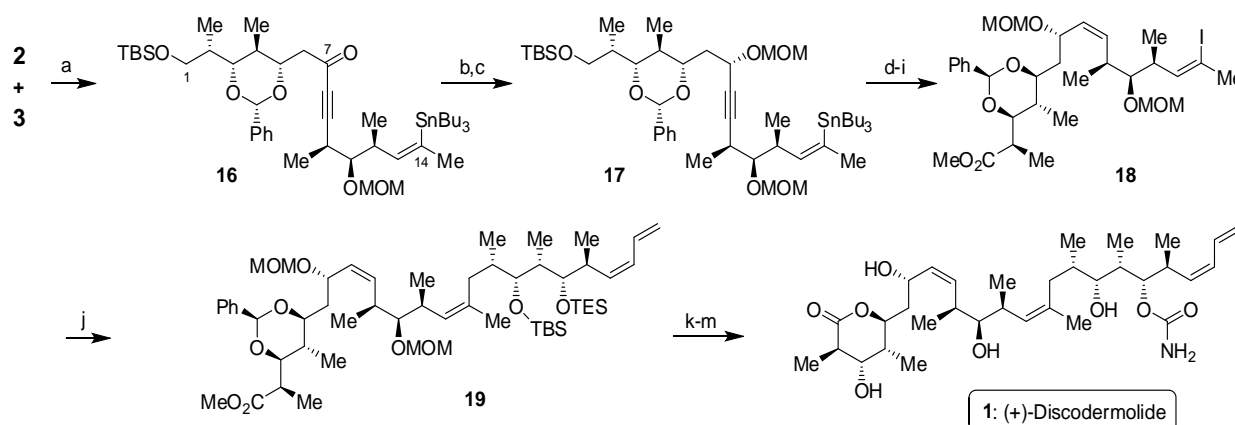


The same Roche ester **11** was used for the preparation of the third subunit **4** (Scheme 5). This starting material was transformed into aldehyde **13** by successive protection, reduction and TEMPO/sodium chlorite oxidation.^[20] The C16-C18 *syn-syn* stereotriad was installed by a BF₃•OEt₂ catalyzed 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

((Experimental Details))

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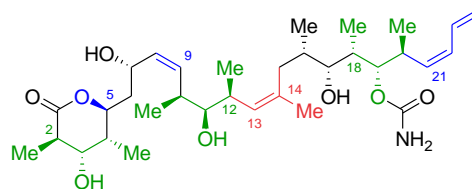
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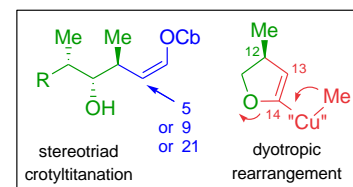
Natural Product Synthesis

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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.