Spirotetracycle Synthesis

Enantioselective Synthesis of the Spirotetracyclic Carbon Core of Mangicols by Using a Stereoselective Transannular Diels–Alder Strategy**

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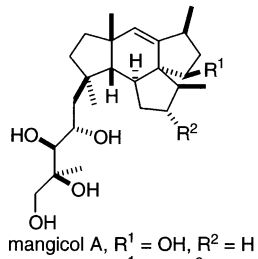
The synthesis of complex natural products has been investigated extensively by chemists, but the construction of architecturally novel carbon frameworks remains a challenging problem. Of particular importance is the effective synthesis of extremely complex carbocycles incorporating quaternary carbons and consecutive asymmetric centers.[1] Mangicols isolated from the marine fungus *Fusarium heterosporum* by Fenical and co-workers in 2000 are new sesterterpenoids with a novel carbon framework (Figure 1) that exhibit



1: mangicol A, R^1 = OH, R^2 = H
2: mangicol B, R^1 = H, R^2 = OH
3: mangicol C, R^1 = H, R^2 = H

Figure 1. Structure of the mangicols.

cytotoxic and antiinflammatory activities.[2] The highly complex spirotetracyclic skeleton of the mangicols was recognized as an attractive target for total synthesis, since its stereoselective construction, especially at the quaternary carbons, should be quite challenging.

We hypothesized that the stereoselective synthesis of the tetracyclic framework of mangicols, including the spiro carbon core, would be efficiently accomplished by employing a transannular Diels–Alder (TADA) reaction. TADA reactions are powerful tools for the construction of polycyclic frameworks and have often been used as the key step in the total synthesis of natural products.[3] The first report of a TADA reaction was that by Deslongchamps et al., who employed a 13-membered cyclic triene.[3b–d] Thereafter, this research group extensively investigated the TADA reactions of a 14-membered cyclic triene. Roush et al. investigated TADA reactions of 12-membered cyclic trienes for the

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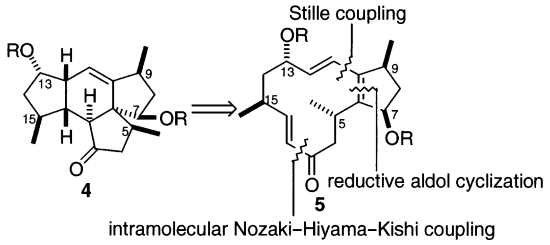
synthesis of spinosyn A;[3e] however, only poor stereoselectivity was achieved. The difficulties in controlling the stereochemistry of TADA reactions arise from the small differences in energy among the possible transition states. Thus, the careful design of the triene intermediate is essential for the stereoselective construction of the framework. As shown in Scheme 1, we chose trienone **5** as the key intermediate; the stereochemistry of the substituted positions—C5, C7, C9, C13, and C15—is such that trienone **5** would be in the desired conformation.

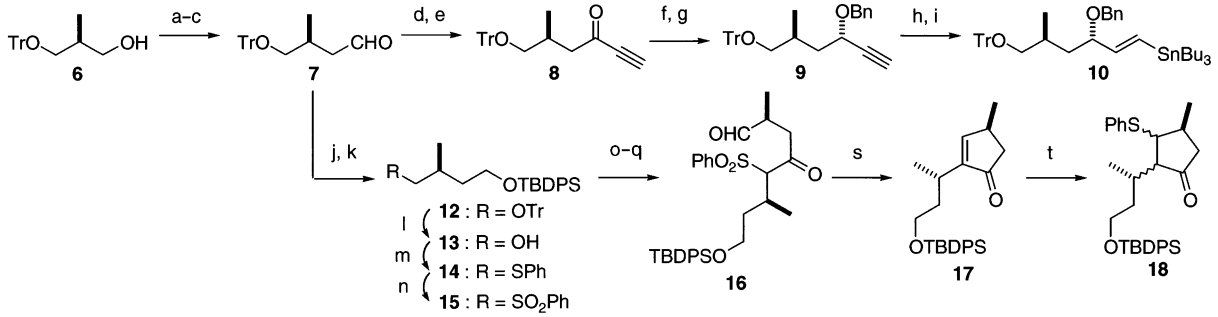


Scheme 1. Retrosynthetic analysis of tetracyclic compound **4**.

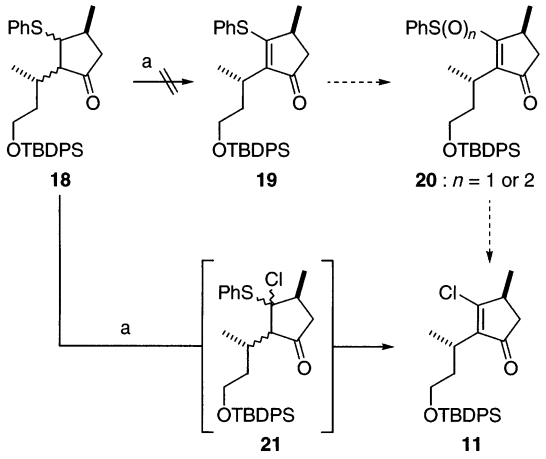
Our synthesis commenced with the tosylation of alcohol **6**,[4] derived from methyl (*R*)-3-hydroxy-2-methylpropionate in two steps (Scheme 2). Substitution of the tosylate with sodium cyanide gave the nitrile quantitatively. The resulting nitrile was reduced with DIBAL-H and the product then hydrolyzed to give the common intermediate aldehyde **7**. The addition of ethynylmagnesium bromide to aldehyde **7** afforded secondary alcohols in a diastereomeric mixture (1:1), which were then oxidized with MnO_2 to give ynone **8**. After the diastereoselective reduction of **8** was achieved by Corey's method,[5] protection with benzyl bromide gave benzyl ether **9**. Transformation of benzyl ether **9** to vinylstannane **10** was carried out in two steps: first, conversion to bromoalkyne by treatment of benzyl ether **9** with *N*-bromosuccinimide (NBS) and $AgNO_3$,[6] and then hydrostannation[7] of the bromoalkyne. β-Chlorocyclopentenone **11** was also derived from the common intermediate aldehyde **7**. Aldehyde **7** was reduced with $NaBH_4$, followed by formation of the TBDPS ether **12**. Subsequent acidic removal[8] of the Tr group gave alcohol **13**. Elaboration to the sulfide **14** was followed by oxidation of **14** with *m*CPBA to give sulfone **15**. The Julia coupling reaction[9] between the carbanion generated from sulfone **15** and the common intermediate aldehyde **7** gave a diastereomeric mixture of hydroxy sulfones. The Tr group was removed under acidic conditions, and the resulting diol was oxidized with Dess–Martin periodinane[10] to afford ketoaldehyde **16**. Several attempts at an intramolecular aldol cyclization reaction of **16** failed. However, a reductive aldol cyclization reaction with SmI_2 proceeded smoothly, and subsequent treatment with Al_2O_3 gave cyclopentenone **17**. The Michael addition of thiophenol to cyclopentenone **17** afforded β-thiophenylcyclopentanone **18** as a mixture of diastereomers (13:1).

The conversion of β-thiophenylcyclopentanone **18** into β-chlorocyclopentenone **11**, a Stille coupling precursor, was then examined (Scheme 3). We initially thought that this conversion would take several steps, namely, 1) conversion of β-thiophenylcyclopentanone **18** into vinylsulfide **19** by a published procedure,[11] 2) oxidation of vinylsulfide **19**, and 3) a Michael addition–elimination reaction with a chloride ion to the intermediate **20** to give β-chlorocyclopentenone **11**. We found, however, that β-chlorocyclopentenone **11** could be generated from β-thiophenylcyclopentanone **18** directly in a novel one-pot process through oxidative chlorination. When β-thiophenylcyclopentanone **18** was oxidized with trichloroisocyanuric acid, β-chlorocyclopentenone **11** was obtained in good yield. We considered the possibility that this type of oxidative chlorination proceeds via the Pummerer-type intermediate **21**. There are no published procedures for the direct β-halogenation of cyclopentenones, and thus this reaction was regarded as a promising strategy for the β-chlorination of enones.

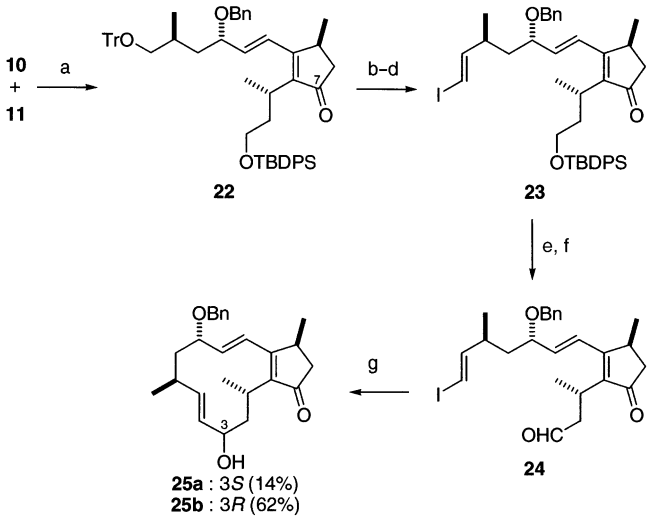
Stille coupling[12] between intermediates **10** and **11** was then examined (Scheme 4). The coupling reaction was con-



Scheme 2. Synthesis of **10** and **18**. a) TsCl, pyridine, RT, 20.5 h; b) NaCN, DMSO, 60 °C, 21 h; c) DIBAL-H, CH_2Cl_2, −78 °C, 30 min; then aq. NH_4Cl, 98% in 3 steps; d) ethynylmagnesium bromide, THF, 0 °C, 1 h; e) MnO_2, CH_2Cl_2, RT, 3 h, 64% in 2 steps; f) (*S*)-2-methyl-CBS-oxazaborolidine, $BH_3{\cdot}SMe_2$, toluene, −40 °C, 30 min, 95%, >98:2 d.r.; g) BnBr, NaH, DMF, 0 °C, 2 h, 100%; h) NBS, $AgNO_3$, acetone, RT, 1 h, 100%; i) Bu_3SnH, $[Pd(PPh_3)_4]$, THF, 0 °C, 30 min, 76%; j) $NaBH_4$, EtOH, 0 °C, 30 min; k) TBDPSCl, imidazole, DMF, RT, 1 h, 74% in 2 steps; l) TFAA, TFA, CH_2Cl_2, RT, 1 h; then MeOH, NEt_3, 0 °C, 1.5 h, 85%; m) PhSSPh, PBu_3, DMF, RT, 1.5 h; n) *m*CPBA, $NaHCO_3$, CH_2Cl_2, RT, 1.5 h, 89% in 2 steps; o) **15**, *n*BuLi, THF, −78 °C, 30 min; then **7**, THF, −78 °C, 1.5 h; p) HCOOH, Et_2O, RT, 5.5 h; q) aq. NH_3, MeOH, RT, 1.5 h, 75% in 3 steps; r) Dess–Martin periodinane, CH_2Cl_2, RT, 1 h, 67%; s) SmI_2, THF, RT, 1 h; then Al_2O_3, 73%; t) PhSH, NEt_3, THF, RT, 7 h, 71%. BnBr = benzyl bromide, CBS = Corey–Bakshi–Shibata, DIBAL-H = diisobutylaluminum hydride, DMF = dimethylformamide, DMSO = dimethyl sulfoxide, *m*CPBA = *m*-chloroperbenzoic acid, NBS = *N*-bromosuccinimide, RT = room temperature, TBDPSCl = *tert*-butyldiphenylsilyl chloride, TFA = trifluoroacetic acid, TFAA = trifluoroacetic anhydride, Tr = triphenylmethyl, TsCl = *p*-toluenesulfonyl chloride.



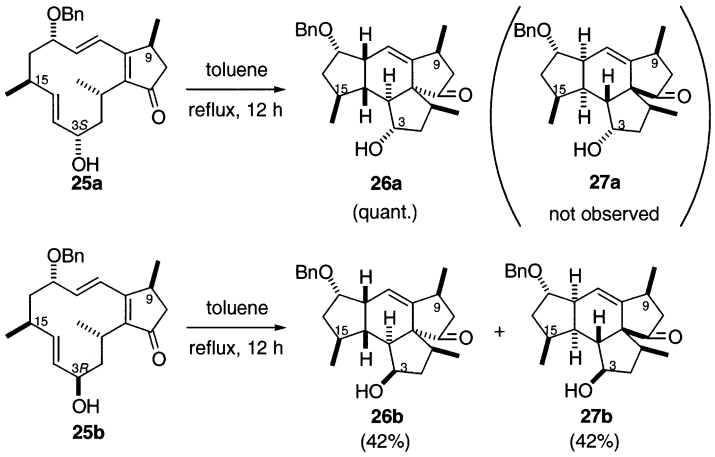
Scheme 3. Synthesis of **11**. a) Trichloroisocyanuric acid, benzene/Et_2O (2:1 v/v), 0 °C, 21 h, 79 %.



Scheme 4. Synthesis of **25**. a) $[Pd(PPh_3)_4]$, NMP, 100 °C, 22 h, 98 %; b) $ZnBr_2$, CH_2Cl_2, RT, 1.5 h, 94 %; c) Dess–Martin periodinane, CH_2Cl_2, RT, 1.5 h, 92 %; d) CHI_3, $CrCl_2$, THF, RT, 40 min, 90 %; e) TBAF, THF, RT, 6 h, 88 %; f) PDC, CH_2Cl_2, RT, 1 h, 86 %; g) $CrCl_2$, cat. $NiCl_2$, DMSO, 24 h, 50 °C. NMP = 1-methyl-2-pyrrolidinone, PDC = pyridinium dichromate, TBAF = tetrabutylammonium fluoride.

ducted with $[Pd(PPh_3)_4]$ as the catalyst and at a high temperature (100 °C) to afford dienone **22** in excellent yield. However, a subsequent Luche reduction of dienone **22** was low-yielding due to the instability of the reduced product. Thus, we avoided reducing C7s carbonyl group in order to stabilize the diene. After the Tr group of dienone **22** was removed with $ZnBr_2$,[13] subsequent oxidation of the primary alcohol gave an aldehyde, which was converted by a Takai reaction[14] into vinyliodide **23**. The TBDPS group of **23** was removed with TBAF to give an alcohol, which was oxidized to afford the aldehyde **24**. Because the 12-membered cyclic trienone was expected to be unstable, mild reaction conditions for the macrocyclization were thought necessary. Macrocyclization of **24** was accomplished by an intramolecular Nozaki–Hiyama–Kishi (NHK) coupling reaction.[15a] Although the intramolecular NHK coupling reactions reported to date have given poor yields,[15c] intramolecular cyclization of aldehyde **24** proceeded nicely to afford two diastereomers of the desired trienones **25a** (6 %) and **25b** (38 %), which were then easily separated by column chromatography. Moreover, when this coupling reaction was carried out at 50 °C, even higher yields of **25a** (14 %) and **25b** (62 %) resulted.

With the cyclic triene precursor in hand, we attempted TADA reactions of both **25a** and **25b** (Scheme 5). When either trienone was heated in toluene at reflux, the TADA



Scheme 5. Transannular Diels–Alder reactions of **25a** and **25b**.

reaction proceeded smoothly to give the desired tetracyclic compound. The stereochemistry of each tetracyclic compound was determined by NOE experiments and NOESY correlations in the ^1H NMR spectra. Surprisingly, we found that the stereoselectivity of the TADA reaction was primarily dependent on the stereochemistry of the hydroxy group at C3. The TADA reaction of trienone **25a** afforded predominantly the desired tetracyclic compound **26a**, whereas reaction of trienone **25b** gave both the desired isomer **26b** and the undesired isomer **27b** in a ratio of 1:1.

The diastereoselectivity of the TADA reaction can be accounted for by the energy differences for the possible conformations of the transition states (Figure 2). Obviously, products **26** and **27** are formed by an *exo* approach. The possibility of two *endo* approaches is excluded by severe ring strain in the transition states. Although transition state **A** shows allylic repulsion between the methyl group at C5 and the hydrogen atom at C12, transition state **B** has severe transannular interactions between the hydrogen atom at C11 and the methyl group at C15. As a result, transition state **A** is formed prior to transition state **B**, and **26a** is obtained as the sole product. However, in the transition state for the 3*R* alcohol **25b**, small difference in energy between transition state **C** and transition state **D** lead to dramatic changes in stereoselectivity. Unlike transition state **B**, transition state **D** does not have allylic repulsion between the hydrogen atom at C1 and the hydroxy group at C3. At the same time, transition state **C** has relatively higher energy due to the allylic interaction with the C3 alcohol. Consequently, the energy of

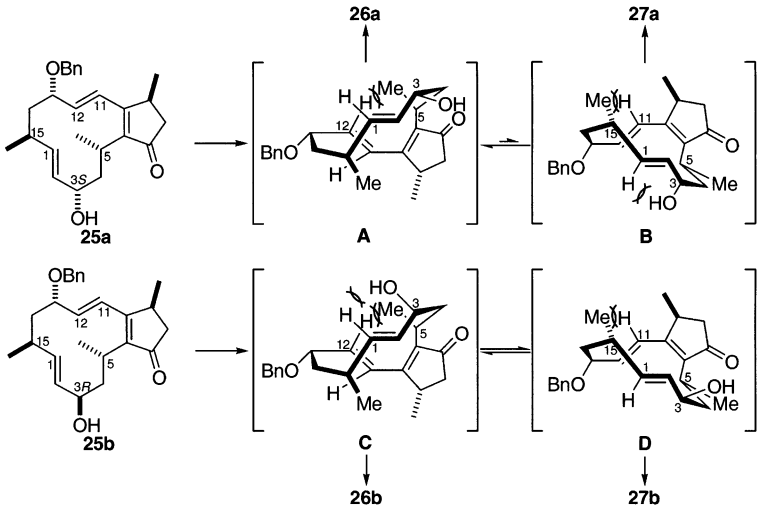


Figure 2. Transition states of the transannular Diels–Alder reactions of **25a** and **25b**.

transition state **C** is equal to that of transition state **D**, and thus **26b** and **27b** are produced in a ratio of 1:1.

In conclusion, we successfully completed the highly stereoselective synthesis of the spirotetracyclic carbon core of the mangicols. The present synthesis features a novel chlorination step, an intramolecular NHK coupling reaction, and the stereoselective construction of a tetracyclic compound through a TADA reaction. The steric repulsion of the hydroxy group of C3 was stereocontrolled in the TADA reaction to predominantly afford the desired tetracyclic compound. Compounds **26a** and **26b** are versatile intermediates for the synthesis of the mangicol family. Further studies on the total synthesis of mangicol A (**1**) are currently underway in our laboratory.

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Keywords: cycloaddition · diastereoselectivity · natural products · spiro compounds · synthesis design

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