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STEREOCONTROLLED SYNTHESIS OF A *TRANS-ANTI-TRANS* TRICYCLE *VIA* A TRANSANNULAR DIELS-ALDER STRATEGY

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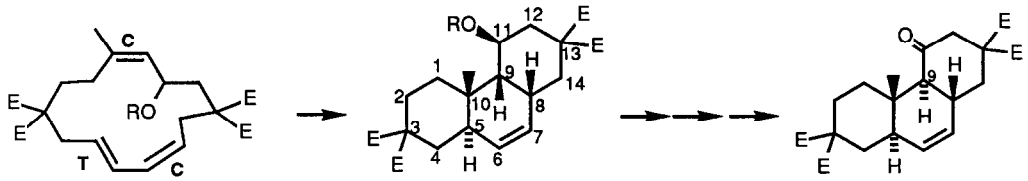
*ABSTRACT: Transannular Diels-Alder reaction of trans-cis-cis macrocyclic triene **20** yields trans-syn-cis tricycle **21** which is converted into trans-anti-trans tricycle **24** by epimerization at C_9 after appropriate functional group transformation.*

In earlier communications,[1,2,3] we have described the synthesis and transannular Diels-Alder reaction of three specific examples of 13-membered macrocyclic trienes, demonstrating a potentially powerful strategy for the construction of complex polycyclic molecules. More recently, Takahashi and co-workers[4] have reported the synthesis of a steroid using the above strategy. We have also reported a study[5,6] on the transannular Diels-Alder reaction of the eight possible geometric isomers of a 14-membered macrocyclic triene. In this general study, we have shown that direct construction of the *trans-anti-trans* (TAT) ring junction which corresponds to the configuration of most natural products is not possible by this synthetic approach.

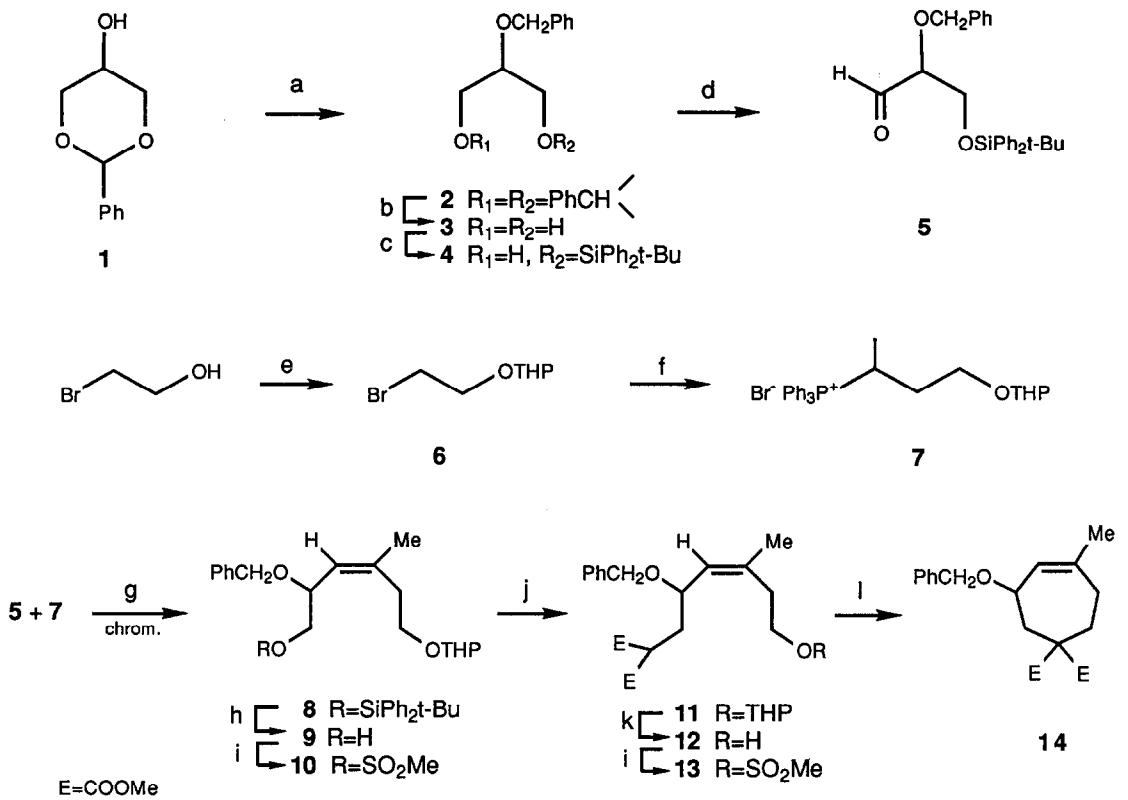
The *trans-cis-cis* (TCC) olefin geometry of macrocyclic triene **20** allows direct access, by transannular Diels-Alder reaction, to tricyclic adduct **21** having a *trans-syn-cis* (TSC) ring junction.[5] The protected alcohol of **21** can be transformed into a ketone, which allows subsequent epimerization at C_9 and thus entry to tricycle **24** having the TAT stereochemistry. We wish now to report this work which also constitutes a preliminary study for the synthesis of corticoids.



20 (TCC) E=CO_2Me, R=$CH_2C_6H_5$ **21**(TSC) **24**(TAT)

As previously described,[3,6] we chose a convergent approach for the synthesis of triene **20**. The preparation of the *cis* dienophile is summarized in Scheme I. The known alcohol **1**[7] was benzylated and then treated with dilute acid to give diol **3** (85% overall). After monosilylation [8] (51%), the resulting alcohol **4** was oxidized [9] to aldehyde **5**; subsequent condensation with the anion of phosphonium bromide **7**[10] provided a mixture [55:45] of *cis* and *trans* olefins (63% from **4**). Chromatographic separation gave pure *cis* olefin **8** which was desilylated[11] (**9**, 93%), mesylated (**10**) and alkylated with dimethyl malonate (84%) to give **11**. Methanolysis provided alcohol **12** which was then transformed into the mesylate ester **13**. Intramolecular cyclization of **13** (HMDSNa, DMF/THF 1:1, 80°C) gave the cycloheptene **14**, proving the *cis* geometry of the former.

The coupling between the dienophile **13** and the *trans-cis* diene **15**[6] was accomplished (NaH, THF/DMF 1:1) to give triene **16** in 84% yield (Scheme II). Alkylation of **16** with dimethyl malonate



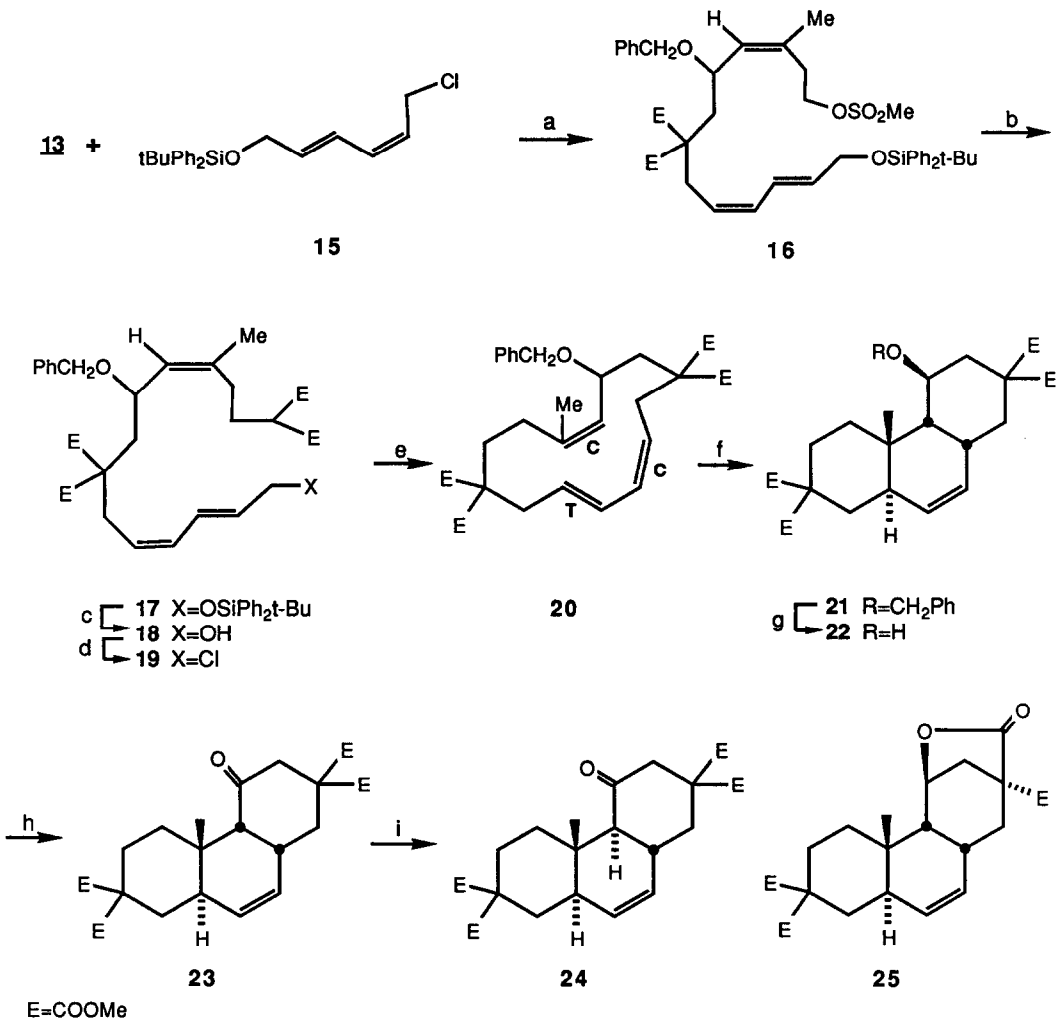
(a) $PhCH_2Br$, NaH, THF, 0°C to r.t. **(b)** HCl 10%, H_2O (85%) **(c)** t-$BuPh_2SiCl$, imidazole, THF, r.t. (51%) **(d)** $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78°C to r.t. **(e)** DHP, PPTS, CH_2Cl_2, r.t. (82%) **(f)** i) $Br^-Ph_3P^+CH_2CH_3$, HMDSK, toluene, THF, 0°C ii) **6**, THF, 48 h, r.t. (81%) **(g)** i) **7**, BuLi, hexane, THF, -78°C to 0°C ii) **5**, THF, chromatography (*cis* = 36%, *trans* = 27% from alcohol **4**) **(h)** n-Bu_4NF, THF, 0°C to r.t. (93%) **(i)** $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0°C **(j)** $CH_2(CO_2Me)_2$, NaH, THF/DMF 1:1, KI, 85°C (84%) **(k)** MeOH, PPTS, reflux (92%) **(l)** HMDSNa, THF/DMF 1:1, 80°C, 4.5×10^{-3} M (77%)

SCHEME I

provided **17** (80%) which was then desilylated[11] to give **18** (91%). Conversion of this allylic alcohol to the corresponding chloride[12] **19** was followed by macrocyclization (Cs_2CO_3, THF/DMF 1:1, 70°C, 10 h, 2.5×10^{-3} M, slow addition) to the 14-membered ring **20** (75% from alcohol **18**).

When heated at 270°C for 2.75 hours, macrocycle **20** underwent transannular Diels-Alder reaction to give, in 84% yield, the tricycle **21**[13] having five asymmetric centers. We can predict easily four of these five centers by analysis of molecular models;[5] with a *trans-cis* diene and a *cis* dienophile, the transannular Diels-Alder reaction is expected to give a tricycle having TSC relative stereochemistry.

The benzyl protective group was removed ($SnCl_4$, CH_2Cl_2)[14] and the β-orientation of the hydroxy group in the resulting alcohol **22** was established by NMR spectroscopy (4.02 ppm, doublet of doublet of doublet, 9.5 Hz, 9.5 Hz, 4.8 Hz). Then, oxidation (PCC, CH_2Cl_2)[15] gave ketone **23**.[16] The predicted TSC relative stereochemistry of this ketone was confirmed by single crystal X-ray diffraction analysis.[17] Treatment with sodium carbonate in methanol at 50°C over nine hours transformed **23** into another ketone **24**,[18] spectroscopically different from the former. This ketone **24** must therefore have the desired stereochemistry TAT by isomerization at position C_9.



(a) i) **13**, NaH, THF/DMF 1:1, 0°C to r.t. ii) **15**, THF/DMF 1:1, r.t. (84%) **(b)** i) $CH_2(CO_2Me)_2$, NaH, THF/DMF 1:1 ii) **16**, THF/DMF, 80°C (80%) **(c)** n-Bu_4NF, THF, 0°C to r.t. (91%) **(d)** $MeSO_2Cl$, s-collidine, LiCl, DMF, r.t. **(e)** Cs_2CO_3, DMF/THF 1:1, 2.5 x 10^{-3} M, 75°C, slow addition (75% from alcohol **18**) **(f)** sealed tube, toluene, 270°C, 2.75 h (84%) **(g)** $SnCl_4$, CH_2Cl_2, r.t. (80%)[20] **(h)** PCC, CH_2Cl_2, r.t. (80%)[20] **(i)** Na_2CO_3, MeOH, 50°C, 9h (60%)[20]

SCHEME II

The fact that only one diastereoisomer was obtained in the transannular Diels-Alder reaction shows a complete control of stereochemistry at position C_{11}. This indicates that it will be possible to realize a non-racemic synthesis of a given tricycle starting from an optically active precursor which has the appropriate absolute configuration for the C_{11} secondary benzyl ether.

In addition, we noted that acidic treatment of alcohol **22** (PTSA, benzene, 60°C) gave lactone **25**.[19] The two ester functions of the C_{13} malonate are thus easily differentiated and this type of

process could be useful in the synthesis of corticoids. For instance, the carbonyl carbon of the lactone moiety could represent the C_{18} hemi-acetal function of aldosterone.

In conclusion, this preliminary work demonstrates that a transannular Diels-Alder reaction followed by epimerization provides ready access to tricycles of TAT stereochemistry. In addition, this method appears very promising for the synthesis of optically active corticoids. Work in this direction is currently underway in our laboratory.

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(13) NMR **21**: δ (ppm): 0.92 (3H, s, -CH_3-C_{10}); 1.28-2.93 (13H, m, H-C_1, H-C_2, H-C_4, H-C_9, H-C_{12}, H-C_{14}, H-C_5 and H-C_8); 3.65 (3H, s, -$CO_2C\underline{H}_3$); 3.69 (6H, s, 2 -$CO_2C\underline{H}_3$) and 3.70 (3H, s, -$CO_2C\underline{H}_3$); 3.76 (1H, ddd, 9.9 Hz, 9.9 Hz, 4.2 Hz, H-C_{11}); 4.43 (1H, d, J_{AB} = 10.8 Hz, -O-$C\underline{H}_2$-Ph); 4.61 (1H, d, J_{AB} = 10.8 Hz, -O-$C\underline{H}_2$Ph); 5.27 (2H, s, H-C_6 and H-C_7); 7.24-7.39 (5H, m, -O-CH_2-$C_6\underline{H}_5$).
IR **21**: ν (cm^{-1}) ($CHCl_3$): 3020, 3030 and 2955 (aliphatic and aromatic C-H); 1730 (C=O); 1435 and 1455 (-CH_2-, -CH_3); 1220, 1250 and 1265 (C-O).
MS **21**: m/e 542 (M^+). Mol. Wt. (ms) calcd. for $C_{29}H_{35}O_8$ (M^+-OMe) = 511.2332; found = 511.2319.
Melting point **21**: 104-106°C.
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(16) NMR **23**: δ (ppm): 0.90 (3H, s, -CH_3-C_{10}); 1.13-2.55 and 3.05-3.17 (11H, m, H-C_1, H-C_2, H-C_4, H-C_5, H-C_8, H-C_9, H-C_{14}); 2.64 (1H, d, J_{AB} = 14.6 Hz, H-C_{12}); 2.86 (1H, dd, J_{AB} = 14.7 Hz, J_W = 1.0 Hz, H-C_{12}); 3.69, 3.70, 3.74 and 3.82 (12H, 4s, 4 -$CO_2C\underline{H}_3$); 5.33-5.47 (2H, m, H-C_6 and H-C_7).
IR **23**: ν (cm^{-1}) ($CHCl_3$): 3020, 2955 (aliphatic C-H); 1730 (C=O); 1435 (-CH_2-, -CH_3); 1260, 1220 (C-O).
MS **23**: m/e 450 (M^+). Mol. Wt. (ms) calcd. for $C_{23}H_{30}O_9$= 450.1890; found = 450.1884.
Melting point **23**: 150-151°C.
(17) A. Michel and G. Boulay. Unpublished results. Université de Sherbrooke, Sherbrooke, QC, Canada.
(18) NMR **24**: δ (ppm): 0.95 (3H, s, -CH_3-C_{10}); 1.05-2.61 (11H, m, H-C_1, H-C_2, H-C_4, H-C_5, H-C_8, H-C_9, H-C_{14}); 2.62 (1H, dd, J_{AB} = 14.0 Hz, J_W = 1.1 Hz, H-C_{12}); 2.91 (1H, dd, J_{AB} = 14.0 Hz, J_W = 2.2 Hz, H-C_{12}); 3.70, 3.73, 3.74 and 3.75 (12H, 4s, 4 -$CO_2C\underline{H}_3$); 5.37 (1H, dm, J_{AB} = 10.2 Hz, H-C_6 or H-C_7); 5.47 (1H, ddd, J_{AB} = 10.2 Hz, J_{BX} = 2.2 Hz, J_{BX} = 2.2 Hz, H-C_6 or H-C_7).
IR **24**: ν (cm^{-1}) ($CHCl_3$): 2955, 2920, 2850 (aliphatic C-H); 1730 (C=O); 1435, 1455, 1465 (-CH_2-, -CH_3); 1250, 1220 (C-O).
MS **24**: m/e 450 (M^+). Mol. Wt. (ms) calcd. for $C_{23}H_{30}O_9$ = 450.1890; found = 450.1884.
Melting point **24**: 114-115°C.
(19) NMR **25**: δ (ppm): 0.94 (3H, s, -CH_3-C_{10}); 1.28-2.81 (13H, m, H-C_1, H-C_2, H-C_4, H-C_5, H-C_8, H-C_9, H-C_{12}, H-C_{14}); 3.72, 3.77 and 3.78 (9H, 3s, 3 -$CO_2C\underline{H}_3$); 4.82 (1H, d, 4.3 Hz, H-C_{11}); 5.35 (1H, dm, J_{AB} = 9.8 Hz, H-C_6 or H-C_7); 5.58 (1H, ddd, J_{AB} = 9.8 Hz, J_{BX} = 2.3 Hz, J_{BX} = 2.3 Hz, H-C_6 or H-C_7).
IR **25**: ν (cm^{-1}) ($CHCl_3$): 3015, 2950, 2920 (aliphatic C-H); 1780 (C=O lactone); 1730 (C=O ester); 1450, 1435 (-CH_2-, -CH_3); 1255, 1220 (C-O).
MS **25**: m/e 420 (M^+). Mol. Wt. (ms) calcd. for $C_{22}H_{28}O_8$ = 420.1784; found = 420.1781.
Melting point **25**: 149-150°C.
(20) Not optimized yields, reactions made on scale of 5 mg.
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