An Enantioselective Construction of the ABC System of Taxol

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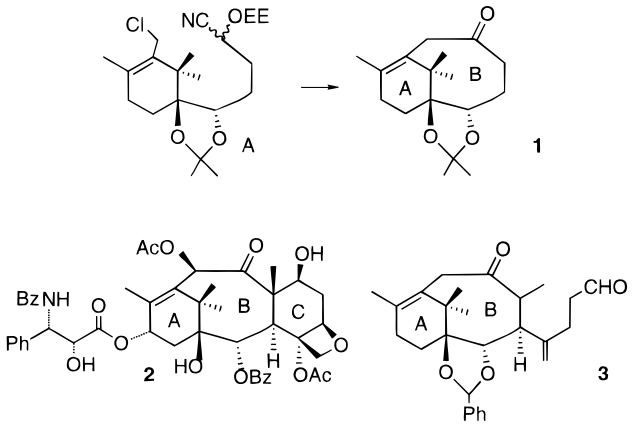
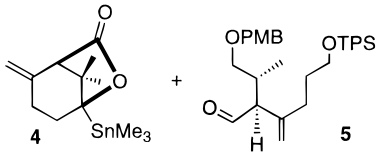
The successful use of protected cyanohydrin cyclization (cf. **A**) to form the A−B system **1**,[1] which includes the A/B framework of taxol [2] (**2**), suggested the possibility of extending the scheme to the construction of a substance such as **3** in which the 4-pentenal array would be expected to undergo facile aldol closure [3] with the formation of an A−B−C system in which only oxidation states would have to be adjusted to complete the construction of taxol.

Scheme 1

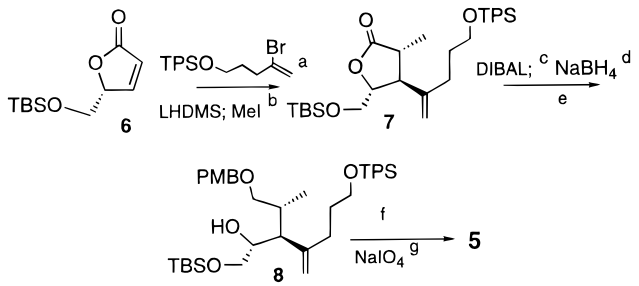


We assumed (incorrectly, as it developed) that either of the secondary methyl epimers in ring B would lead to the enolate required for the eventual aldol closure of ring C, and we initially selected aldehyde **5** as an acceptor for stannyl lactone **4**.



The enantiospecific synthesis of **5** is outlined below. As starting material we chose the known butenolide **6**,[4] available as the required enantiomer from (*R*)-glutamic acid. Conjugate addition of the protected 4-pentenol side chain,[5] followed by methylation, set up the required absolute stereochemistry of lactone **7**, which was then easily transformed into aldehyde **5**.

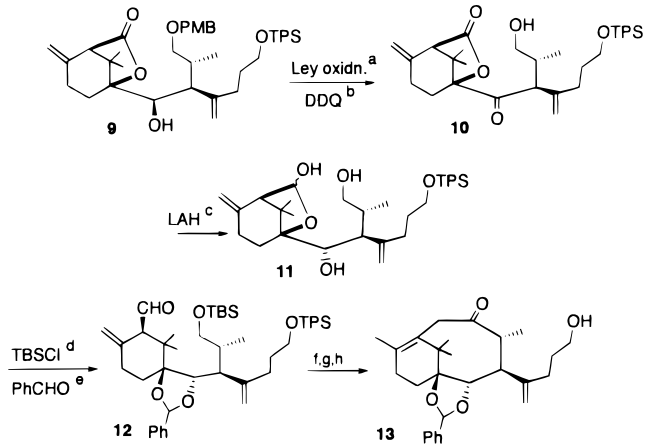
Scheme 2



[a] (i) *t*BuLi, ether, 78 °C, 1 h; (ii) 2-ThiophenylCu(CN)Li, 10 min; (iii) TMSCl, THF, −78 to 0 °C, 1 h; 81%. [b] (i) THF, −78 °C, 45 min; (ii) −78 to 0 °C, 50 min; >90%. [c] Toluene, −78 to −55 °C, 1.5 h. [d] Ethanol, overnight; 54% from 6. [e] 4-Methoxybenzyl trichloroacetimidate, catalyst TfOH, ether, 0 °C, 10 min; 36% (unoptimized) + bisbenzylated. [f] HOAc, H_2O, THF (6/2/3), 70 °C, 2.5 h; 88%. [g] SiO_2, CH_2Cl_2, 1 h; 92%.

As we had hoped, reaction of **5** with the lithium species derived from stannyl lactone **4** proceeded in high yield to give the C2 secondary alcohol **9**, which now had to be inverted to the required epimer. The assumption that this would best be achieved by intramolecular reduction of the C2 ketone via a hydride tethered to the primary alcohol shown in **10** proved correct: lithium aluminum hydride reduction of **10** gave mainly the correct alcohol epimer at C2, while simultaneously reducing the lactone, to produce **11**. The benzylidene derivative **12** thus became available in 49% overall yield from **10**. Further transformation of **12** to the bicyclic A−B ketone **13** confirmed the feasibility of extending the construction we had used for the simple A−B system **1** to

Scheme 3[a]



[a] TPAP, NMO, 4A molecular sieves, CH_3CN, 21 h; 70%. [b] CH_2Cl_2, H_2O, 11 h, 89%. [c] THF, 0 °C, 2 h; 75%. [d] Imidazole, CH_2Cl_2, room temperature, 12 h; 92%. [e] CSA, PhH, 1 h; 71%. [f] DBU, *t*-BuOH, PhH, 65 °C, 12 h; $NaBH_4$, EtOH, 0 °C, 1.5 h; Ac_2O, DMAP, CH_2Cl_2, 10 min; THF, HOAc, H_2O, 45 °C, 10 h; 64% overall. [g] Cyanohydrin closure: cf. ref 1. [h] TBAF.

the more complex system shown in **14,** which bears substituents formally capable of elaboration to the A−B−C system of taxol. It soon became clear, however, that an unforeseen difficulty lay within structure **14** because it resisted all our attempts to cyclize it.

A clue to the source of the difficulty came from deuterium exchange experiments (overnight refluxing of alcohol **13** with methoxide in deuteriomethanol). This showed no exchange of the hydrogen on the carbon bearing the secondary methyl group. Molecular modeling of systems such as **13** clearly showed that,

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(1) Stork, G.; Doi, T.; Liu, L. *Tetrahedron Lett.* **1997**, *38*, 7471.
(2) Taxol is the registered trademark for the substance known also as paclitaxel.
(3) (a) Chaudhary, A. G.; Rimoldi, J. M.; Kingston, G. I. *J. Org. Chem.* **1993**, *58*, 3798. (b) Miller, R. W.; Powell, R. G.; Smith, C. R., Jr.; Arnold, R.; Clardy, J. *J. Org. Chem.* **1981**, *46*, 1469.
(4) (a) *Org. Synth.* **1985**, *63*, 121. (b) *Tetrahedron* **1990**, *46*, 4503.
(5) (a) Lawler, D. M.; Simpkins, N. S. *Tetrahedron Lett.* **1988**, *29*, 1207. (b) Urban, E.; Knuhl, G.; Helmchen, G. *Tetrahedron* **1995**, *51*, 3031.

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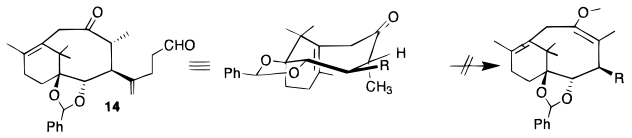
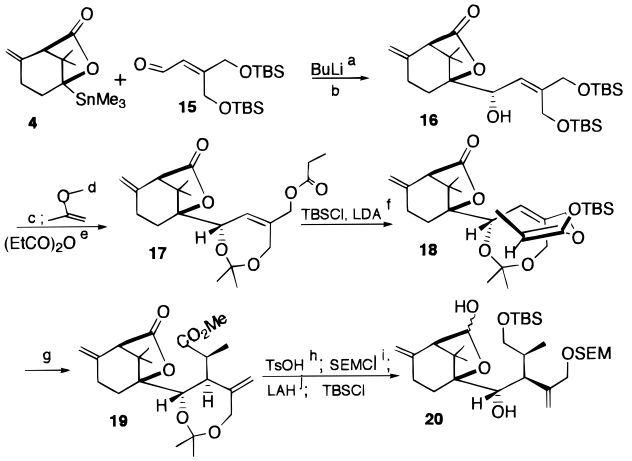
Scheme 4



in the lowest energy conformation, the hydrogen on the carbon bearing the α-methyl is held in the plane of the carbonyl, so that **14** is unable to form the enolate required for aldol cyclization. Models showed, however, that proper overlap should be obtained with the secondary methyl epimer of **14** which should, therefore, cyclize normally.[6] A stereoselective route to that epimer is now described.

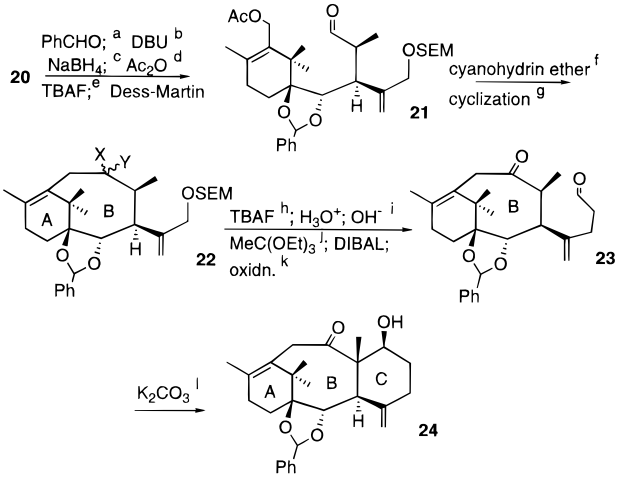
Scheme 5[a]



[a] THF, −90 to −100 °C, 15 min. (b) **15**, THF, −78 °C to room temperature 1.5 h; 40% **16**. [b] C_2 β epimer, recycled by (i) Dess Martin oxidation and (ii) $NaBH_4$-$CeCl_3$ reduction. [c] CSA, MeOH, 4 h. [d] DMF, 0 °C to room temperature THF−H_2O. [e] CH_2Cl_2, pyridine, catalyst DMAP, 0 °C to room temperature, 12 h. [f] (i) DMPU, THF, −78 °C, (ii) LDA, −78 °C, then to room temperature, 1.5 h. [g] (i) 110 °C, 12 h, (ii) CH_2Cl_2, CH_2N_2; 54% and recyclables. [h] CH_3CN−H_2O, 11 h. [i] $(iPr)_2NEt$, catalyst Bu_4NI, 7 h; 78% from **19**. [j] THF, −78 to 0 °C, 2 h; 57%.

Addition of the usual lithiolactone from **4** to the protected dihydroxyaldehyde **15**[7] gave a 1:1.4 mixture of the C2 alcohol epimers. Oxidation of the unwanted β-hydroxyl to the ketone, and reduction with borohydride, led to the predominant formation of the required secondary alcohol **16**. Desilylation was followed by conversion to the allylic propionate of the isopropylidene derivative shown in **17**, a structure designed to show a face differentiation which would permit use of a Claisen rearrangement to establish the correct streochemistry at C3. Importantly, a chair transition state for such a rearrangement (cf. **18**) should, in addition, lead to the required secondary methyl stereochemistry shown in **19**. In the event, application of the Ireland−Claisen conditions[8] to propionate **17** *did* produce the required structure and sterochemistry shown in **19**, as could be verified by X-ray structure determination of the γ-lactone [9] obtained by treatment of **19** with methanolic acid. Hydrolysis of the isopropylidene group of **19**, protection of the released allylic alcohol, LAH reduction, and silylation gave lactol **20**. Following standard transformations via **21**, the usual cyanohydrin sequence[1] was used for the closure of ring B. The resulting **22** (X, Y = 2-methoxyisopropyl, cyano; then, carbonyl) was converted, after Johnson−Claisen elongation of the pendant allyl alcohol, into **23**, the sought after secondary methyl epimer of **14**. The cyclization of **23** to the tricyclic aldol **24** (57%) now took place normally. The assigned stereochemistry was entirely consistent with nOe measurements.

Scheme 6[a]



[a] CSA, 60 °C, 2 h. [b] PhH, *t*-BuOH, 80 °C, 6 h. [c] $CeCl_3$, 2:1 THF−H_2O, 3 h. [d] Pyr., DMAP, overnight. [e] THF, 4A sieves; 40% from **22**. [f] TMSCN, H^+, 2-methoxypropene. [g] Cf. ref 1. [h] TBAF, HMPA, 4A molecular sieves, overnight. [i] THF−(aq)HCl, room temperature, 20 min; 1 N NaOH, 10 min. [j] $MeCH_2CO_2H$, PhMe, 120 °C, 12 h; 63%. [k] (i) PhMe, −78 °C, 40 min, (ii) Dess-Martin; 84%. [l] MeOH, 18-crown-6, reflux, 3 h; 55%.

It is worthy of note that the tricyclic system **24** differs from the tetracyclic system of taxol only in the oxidation state.[10]

Acknowledgment. We thank Professor Clark Still for his much appreciated help with modeling, especially of **14**, and the National Institutes of Health and the Kanagawa Academy of Science and Technology for support of this work.

Supporting Information Available: Spectral data for compounds **5**, **7**, **8**, **9**, **10**, **11**, **12**, and **13** and experimental and spectral data for compounds **4**, **16**, **17**, **19**, **20**, **21**, **22**, **23**, **24** and **i**, footnote 9 (37 pages). See any current masthead page for ordering information and Web access instructions.

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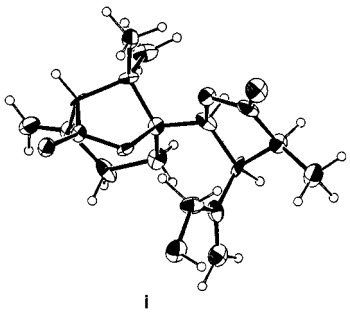
(6) Our observations related to the failure of **14** to undergo aldol cyclization, our rationalization of this result, and our corollary successful cyclization of **23** were first presented publicly in 1995. Related observations have been published recently, See: (a) Wender, P. A. et al. *J. Am. Chem. Soc.* **1997**, *119*, 2757. (b) Mukaiyama, T., et al. *Chem. Lett.* **1996**, 483.

(7) Made from dihydroxyacetone by silylation (Shao, X.; Dolder, M.; Tamm, C. *Helv. Chim. Acta* **1990**, *73*, 483), followed by condensation with dimethyl carbomethoxymethyl phosphonate, reduction (DIBAL), and oxidation (PCC).

(8) Inter alia: Ireland, R. E.; Wipf, P.; Armstrong, J. D. *J. Org. Chem.* **1991**, *56*, 352 and earlier papers.

(9) We thank Dr. John C. Huffman of the Indiana University Molecular Structure Center for this determination. The γ lactone (**i**) had mp 85−86 °C, $[\alpha]_D$ +183 (0.34, CHCl3), IR 1781 cm^{-1}



i

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(10) It is encouraging that silylation of **24** (triethyl silyl triflate) followed by SeO_2 oxidation (*tert*-butyl peroxide, hexane, catalyst acetic acid, reflux 1.5 h) appeared to result in the expected formation (~62%) of the desired 5α-hydroxy derivative.