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A Convergent Carbohydrate Approach to the Synthesis of Taxol. Part 2. Ring C Subunit

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Abstract: The synthesis of an advanced C-ring subunit of taxol has been performed from D-glucose.

In the preceding Letter¹ we have disclosed some elements of the strategy and reported the synthesis of the A ring subunit of taxol. Following selective manipulations with its hydroxyl groups and Ferrier rearrangement, D-glucose was transformed first to cyclohexanone 1, then to enone 2, from which the A-ring subunit 3 was synthesized using a conjugate addition - α -functionalization sequence. Enone 2 was also considered to be a prospective intermediate towards the C-ring subunit 4 in a quite uniform pathway with the vinyl group as a precursor for the carboxyl function of 4 (Scheme 1).





Copper-mediated vinylmagnesium bromide addition to enone 2 in the presence of TMSCl in THF proceeded with the desired face selectivity to give a silyl enol ether 5 in almost quantitative yield² (Scheme 2). However, the latter was found to be of little value for the synthesis since attempts of its α -functionalization with appropriate C₁ electrophilic reagents failed³. Furthermore, the regeneration of the lithium enolate from 5 proved to be impractical, as it was accompanied by a significant silyl group migration and α 'enolization.



a. CH₂=CHMgBr, CuBr \cdot Me₂S, TMSCI/THF, -78°C; b. CH₂=CHMgBr, CuBr \cdot Me₂S - LiBr (2 eq)/THF-Me₂S-Et₂O (1:1:2), -78°C to 0°C; c. CH₂=CHCu(Me)(CN)Li₂/THF-Et₂O (1:3), -78°C to 0°C; d. MeLi/THF or BuLi/Et₂O, -78°C to rt; e. THF-AcOH-H₂O (8:1:1), rt; f. CH₂O/THF, -78°C; g. saturated K₂CO₃/MeOH - MeOH (1:4), rt, 4-5 h.

Scheme 2

No conjugate addition of vinylmagnesium bromide to enone 2, in the absence of TMSCl, took place in THF, and only 1,2-addition to the carbonyl group was found in ether; the latter result was attributed to the low rate of formation / solubility / stability of the vinylcopper reagent in this solvent. Eventually, the reagents generated in ether in the presence of added LiBr, or methyl sulfide as a co-solvent, or both, underwent the desired conjugate addition to give the magnesium enolate which afforded, on treatment with monomeric formaldehyde solution⁴, a mixture of aldols 6 and 7 in 60-70% yield⁵. The composition of the mixture was very close to equilibrium, as it was set up starting from the individual aldols 6 and 7 (6: 7 = 3: 7 at equilibrium), thus indicating a thermodynamic rather than a kinetic controlled reaction⁶. Indeed, "lithium" aldolate⁷, resulting from HO mixed cuprate⁸ addition followed by a formaldehyde trapping protocol, appeared configurationally more stable, and, after much experimentation, conditions were found to afford the desired adduct 6 in high yield⁹ (Scheme 3). After separation from the minor epimer 7, the aldol 6, possessing the correct taxol configuration at both newly introduced stereocentres, was protected at its primary hydroxyl as a MOM-ether and the ketone 8 thus obtained was subjected to Matteson's epoxide synthesis¹⁰ to give diastereometrically pure spiro-epoxide 9^{11} . Controlled ozonolysis of 9 followed by oxidation of the resulting aldehyde with KMnO₄ in buffered t-BuOH¹² afforded an acid, isolated, without purification of the intermediates, as its methyl ester 10 in good overall vield¹³.

With compound 10 in hand, elaboration of the protected epoxy alcohol moiety to allylic alcohol 14 was then addressed. To this end, 10 was desilylated to epoxy alcohol 11 and the latter was subjected to reductive isomerization with $[Cp_2TiCl]_2^{14}$ to give the desired 14 in only low (ca.15%) yield, the main product being the isomeric secondary allylic alcohol 13 of epoxide deoxygenation. This result was attributed to low reactivity of the axial hydroxyl group at C-5 vis-à-vis the bulky titanium reagent. Having in mind the alternative procedure via Pd-catalyzed allylic acetate isomerization¹⁵, the epoxy alcohol 11 was acetylated and acetate 12 was treated with the same reagent to give, quite unexpectedly, the desired allylic alcohol 14 *directly*, in one (instead of three) step.





Scheme 3

In contrast to what was found in acyclic series 1^4 , the reaction seems to proceed as a direct reductive oxirane fragmentation with the acetate group serving as an electron transmitting spacer, since neither secondary allylic alcohol 13 nor the acetates of 13 and 14 were found in the truncated reaction mixture.

The alcohol 14 was then silvlated to give 15 which represents the suitably protected C-ring subunit in the projected synthesis of taxol¹⁶. With minute variations, the epimeric subunit 16 has also been synthesized from aldol 7 following the same scheme 17. It should also be noted that the intermediate acetate 12 corresponds to the C-ring of baccatin I.

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References and Notes

- 1. The preceding Letter in this Issue.
- 2. For studies on related 4-alkoxy-3-methylcyclohexenones, lacking in silyloxy group α - to carbonyl, see Polla, M.; Frejd, T. Tetrahedron. 1991, 47, 5883-5894.
- 3. The following attempts were made: i. dimethoxymethylation: (a) Mukaiyama, T.; Hayashi, M. Chem. Lett. 1974, 15-16; (b) Suzuki, M.; Yanagisawa, A.; Noyori, R. Tetrahedron Lett. 1982, 23, 3595-3596; ii. hydroxymethylation: (a) Mukaiyama, T.; Banno, K.; Narasaka, K. J. Am. Chem. Soc. 1974, 96, 7503-7509; (b) Kobayashi, S. Chem. Lett. 1991, 2087-2090; iii. methoxycarbonylation: Crabtree, C. R.; Chu, W. L. A.; Mander, L. N. Synlet. 1990, 169-170. Schlosser, M.; Jenny, T.; Guggisberg, Y. Synlet. 1990, 704.
- 4.
- Given on the schemes are idealized conformations which fit NMR spectroscopy and reflect the selectivity 5. trends; see also Ref. 1.
- Magnesium and zinc aldolates are known to equilibrate fast even at low temperatures; Heathcock, C. H.; 6. Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. J. Org. Chem. 1980, 45, 1066-1081 and references cited therein.
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- 8. Behlin, J. R.; Babiak, K. A.; Ng, J. S.; Campbell, A. L.; Moretti, R.; Koerner, M.; Lipshutz, B. H. J. Am. Chem. Soc. 1988, 110, 2641-2643.
- 9. The combined yield of $\mathbf{6}$ and $\mathbf{7}$ is 87% with the selectivity ca. 10:1; the separation of the isomers is rather tedious and can be performed easily on several occasions later along the scheme. Yields given throughout this Letter correspond to chromotographically purified compounds.
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- A change of the cyclohexane ring conformation took place at that stage (cf. Ref. 1); the configuration of 11. the spiro-epoxide was established in a NOESY experiment.
- Abiko, A.; Roberts, J. C.; Takemasa, T.; Masamune, S. Tetrahedron Lett. 1986, 27, 4537-4540. 12.
- The main by-product of the transformation was the corresponding p-methoxybenzoate resulting from 13. benzylic oxidation at both ozonolysis and permanganate oxidation steps.
- 14. Yadav, J. S.; Shekharam, T.; Gadgil, V. R. J. Chem. Soc., Chem. Commun. 1990, 843-844.
- 15. Overman, L. E.; Kholl, F. M. Tetrahedron Lett. 1979, 321-324.
- 16. All new compounds were characterized by analytical and spectroscopic methods. Specific rotations were measured in CHCl₃ solutions. Selected $[\alpha]_D$ data are given below:

6: +16 (c 1.0); **7**: +28 (c 1.0); **8**: +30 (c 1.2); **9**: -6 (c 1.2); **10**: +22 (c 1.2); **11**: +26 (c 1.0); **12**: +15 (c 1.4); 14 : -8 (c 1.3).

15 : $[\alpha]_D$ +14 (c 1.1); ¹H NMR (300 MHz, CDCl₃), δ : 6.8 and 7.2 (2d, 4H, Ar), 5.65 (m, 1H, H-5), 4.52 and 4.49 (2d, 2H, Jgem=6.7 Hz, AB of O-CH2-O), 4.48 and 4.38 (2d, 2H, Jgem=11.5 Hz, AB of CH₂MP), 4.04 and 3.96 (2 br.d, 2H, J_{gem} =0.7 Hz, AB of O-CH₂-O), 4.48 and 4.36 (2d, 2H, J_{gem} =11.5 Hz, AB of CH₂MP), 4.04 and 3.96 (2 br.d, 2H, J_{gem} =13.6 Hz, 2xH-20), 3.88 (dd, 1H, $J_{6eg,7}$ =5.7 Hz, $J_{6ax,7}$ =10.2 Hz, H-7), 3.80 (s, 3H, C₆H₄OMe), 3.71 (dd, 1H, $J_{2,3}$ =5.3 Hz, J_{gem} =9.8 Hz, H-2), 3.65 (s, 3H, COOMe), 3.44 (t, 1H, $J_{2',3}$ = J_{gem} =9.8 Hz, H-2'), 3.21 (m, 1H, H-3), 2.41 (m, 1H, H-6eq), 1.95 (m, 1H, H-6ax), 1.15 (s, 3H, Me-19), 0.90 (s, 9H, t-BuSi), 0.06 (s, 6H, Me₂Si).

¹³C NMR (75 MHz, CDCl₃), δ: 177.4 (<u>C</u>OOMe), 159.2 (Ar), 135.8 (C-4), 131.1 (Ar), 129.1 (Ar), 120.5 (C-5), 113.8 (Ar), 96.7 (O-CH2-O), 79.3 (C-7), 71.2 (CH2MP), 65.8 (C-2), 65.0 (C-20), 55.7 (CH3OCH2O), 55.4 (CH3OC6H4), 51.8 (COOCH3), 49.3 (C-8), 44.7 (C-3), 28.0 (C-6), 26.1 (C(CH₃)₃), 18.3 (C(CH₃)₃), 9.8 (C-19), -5.1 and -5.2 (Me₂Si).

17. Will be published elsewhere.