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Mukaiyama-Type, Eight-Membered Ring Closure: Access to a Tricyclic System Related to Taxanes

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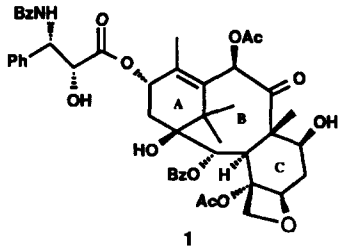
Abstract *: Addition of Me_2CuLi, with in situ trapping by TMSCl, to Hagemann's ester derivative* ***13****, furnished silyl enol ether* ***14****. Mukaiyama-type cyclization of the latter compound gave the tricyclic derivative* ***15****, structurally related to the taxane core.* © 1998 Elsevier Science Ltd. All rights reserved.

The synthesis of the members of the taxane family, exemplified by Taxol® **1**,[2] has become an area of intense research, because of the outstanding antitumor properties exhibited by some of these molecules.[3] From this standpoint, a large effort has been directed towards the challenging construction of the bridged eight-membered B ring of taxanes.[4] For our part, we have established that (*R*)-1-phenylethylamine-promoted annulation of keto-enoate **2** furnished predominantly the polycyclic derivative **3**,[5] structurally related to the taxane framework, a reaction in which the eight-membered ring was formed through an intramolecular asymmetric Michael addition. However, this methodology appeared not suited for the introduction of the bridgehead *gem*-dimethyl group of taxanes. In this paper, we report on the synthesis of the bridged tricyclic derivative **15**, bearing this *gem*-dimethyl group, based on the $TiCl_4$-induced cyclization of compound **14**. In this reaction, the eight-membered nucleus was now created through a Mukaiyama-type condensation involving the intramolecular conjugate addition of a silyl enol ether to an α,β-ethylenic ester.



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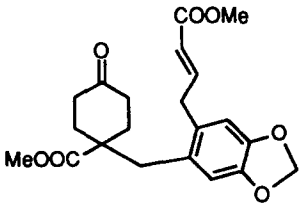

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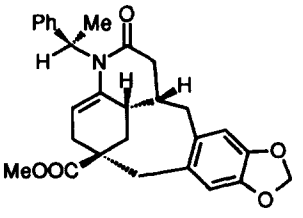

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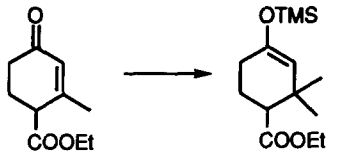
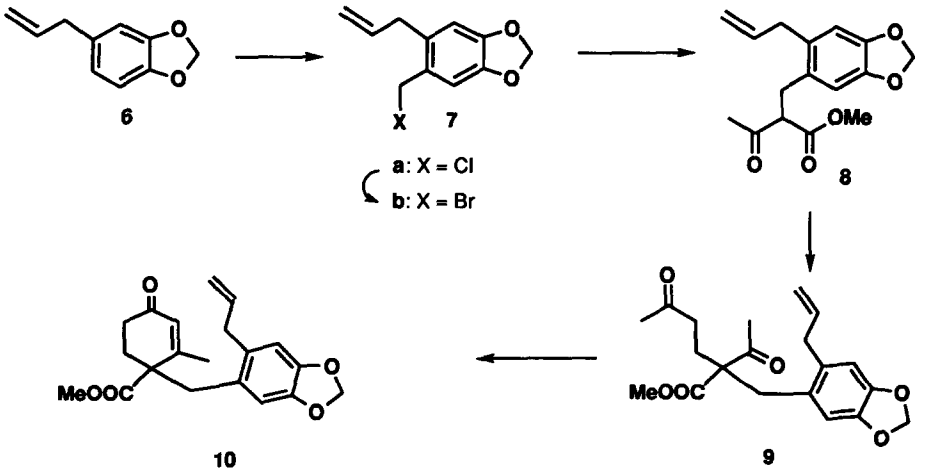
In our view, one particularly attractive entry to pivotal subgoals **12** or **14** involved the alkylation of ester **5** with appropriately substituted benzylic halides. The requisite starting compound **5**[6] was efficiently prepared by conjugate addition at -78 °C of Me_2CuLi to commercially available Hagemann's ester **4**, with *in situ* trapping by TMSCl (90 % yield). Unfortunately, all attempts at benzylation of ester **5**, by using LDA and BnBr, returned only starting material. As a matter of fact, formation of the enolate of **5** was thwarted by the steric hindrance of this ester; thus, in the sequential treatment of **5** with LDA (-40 °C) and D_2O, this compound was partially recovered, but without any incorporation of deuterium atom. An alternative benzylation reaction, by using the less bulky base KH at 0 °C, has not been successful so far: the silyl enol ether group of **5** was actually cleaved under these conditions.



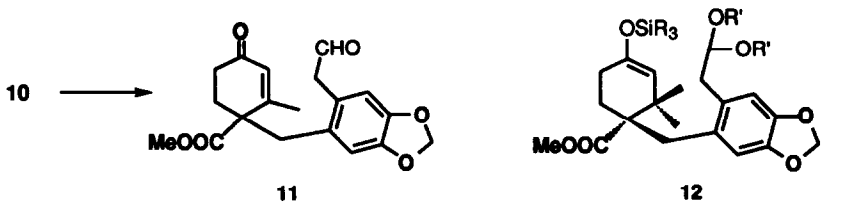
4 5

In view of these results, we decided to build the cyclohexene moiety of **12** or **14**, starting from an acyclic precursor carrying the requisite benzylic fragment. To attain this end, chloromethylsafrole **7a**, obtained by chloromethylation of commercially available safrole **6**, was first converted into the corresponding bromide **7b**[5] (NaBr, 2 h in refluxing acetone, 86 % yield). Condensation of methyl acetoacetate with **7b** (Cs_2CO_3, CH_2Cl_2, 24 h at 20 °C) then provided ketoester **8** [7] with a 80 % yield. Addition of **8** to methyl vinyl ketone (cat. MeONa, MeOH, 30 min at 0 °C) gave in a 70 % yield diketone **9**,[8] which was regioselectively annulated[9] into cyclohexenone **10** [10] (0.4 eq. of piperidine, 0.5 eq. of AcOH, 1 h at 100 °C, 83 % yield).

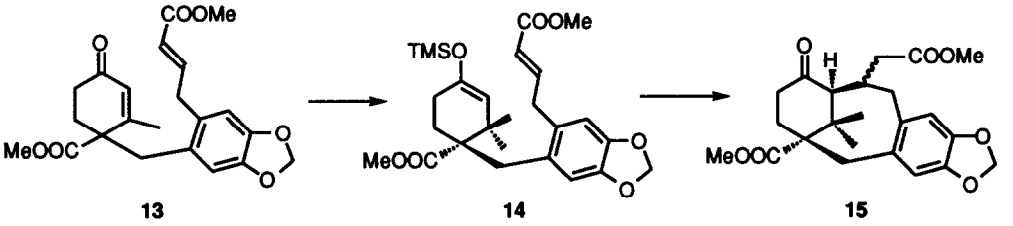


Chemoselective oxidation[10] of the methylene group of the Hagemann's ester derivative **10** next furnished aldehyde **11**[12] (cat. OsO_4, $NaIO_4$, Et_2O-H_2O, 1 h at 20 °C, 50 % yield). At this stage, it was our

original objective to convert **11** into silyl enol ether-acetals **12**; indeed these derivatives appeared to be good candidates for the crucial Lewis acid-induced (Mukaiyama-type) eight-membered annulation.[13] Unfortunately, all efforts to selectively acetalize the aldehyde function of **11** were invariably impeded by the competitive fragmentation of the cyclohexenone moiety of the molecule.



The next candidate for the eight-membered ring closure was keto-enoate (*E*)-**13**,[14] prepared through the Wittig condensation of aldehyde **11** (Ph_3P=CH-COOMe, CH_2Cl_2, 24 h at 20 °C, 75 % yield). Attempted "direct" annulation of **13**, based on the MIRC reaction (*inter*molecular chemoselective conjugate addition of Me_2CuLi to the enone moiety, followed by *intra*molecular capture of the resulting transient enolate by conjugate addition to the α,β-ethylenic ester) having failed,[15] this enolate was *inter*molecularly trapped with TMSCl, furnishing key silyl enol **14**[16] in good yield (*i*: Me_2CuLi, *ii*: TMSCl, *iii*: **13**; 5 min at - 78 °C in THF, 82 % yield). To our delight, Mukaiyama-type cyclization of **14** ($TiCl_4$, CH_2Cl_2, 1 h at 0 °C) finally afforded the expected tricyclic substrate **15**[17] in 61 % yield, as a 2/1 mixture of diastereomers. *Cis*-fused ring junction assignment in target **15** was fully consonant with MM2 results.[18]



An efficient access to the tricyclic derivative **15**, related to the taxane core, based on the Mukaiyama-type cyclization of **14**, has thus been achieved. New synthetic developments of this methodology are under investigation in our laboratory.

Notes and References

1 EC Postdoctoral Fellow, on leave from the Universitat Autonoma de Barcelona (Spain).

2 Taxol is a registered trademark for the substance also known under the generic name paclitaxel.

3 For a relatively recent review, see: Nicolaou, K. C.; Dai, W. M.; Guy, R. K. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 15-44. For the most recent synthesis of Taxol, and references to others, see: Wender, P. A.; Badham, N. F.; Conway, S. P.; Floreancig, P. E.; Glass, T. E.; Houze, J. B.; Krauss, N. E.; Lee, D.; Marquess, D. G.; Mc Grane, P. L.; Meng, W.; Natchus, M. G.; Shuker, A. J.; Sutton, J. C.; Taylor, R. E. *J. Am. Chem. Soc.* **1997**, *119*, 2757-2758.

4 For a recent eight-membered ring closure employing the protected cyanohydrin method, see: Stork, G.; Doi, T.; Liu, L. *Tetrahedron Lett.* **1997**, *38*, 7471-7474.

5 Cavé, C. Boggero, S.; Casas, R.; Dumas, F.; Mahuteau, J.; d'Angelo, J. *Tetrahedron: Asymmetry* **1995**, *6*, 2647-2650.

6 **5**: oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.4 (s, 1H), 3.95 (m, 2H), 2.10 (dd, J = 7.1, 13.8 Hz, 1H), 2.0-1.4 (m, 4H), 1.1 (t, J = 7.0 Hz, 3H), 0.95 (s, 3H), 0.75 (s, 3H), 0.0 (s, 9H).

7 **8**: oil; IR: 3060, 1747, 1719, 1640 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.63 (s, 1H), 6.61 (s, 1H), 5.89 (s, 2H), 5.89 (m, 1H), 5.08 (dt, J = 1.7, 10.2 Hz, 1H), 4.87 (dt, J = 1.7, 16.8 Hz, 1H), 3.70 (s, 3H), 3.70 (m, 1H), 3.31 (dt, J = 6.8, 3.3 Hz, 2H), 3.11 (dd, J = 2.0, 7.5 Hz, 1H), 3.08 (dd, J = 2.0, 3.4 Hz, 1H), 2.18 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 202.1 (C), 169.5 (C), 146.3 (C); 145.9 (C); 137.0 (CH), 130.9 (C), 129.0 (C), 115.7 (CH_2), 109.9 (CH), 109.5 (CH), 100.7 (CH_2), 60.2 (CH), 52.3 (CH_3), 36.6 (CH_2), 30.5 (CH_2), 29.6 (CH_3).

8 **9**: oil; IR: 3063, 1740, 1715 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.61 (s, 1H), 6.55 (s, 1H), 5.88 (s, 2H), 5.84 (m, 1H), 5.04 (dd, J = 1.7, 10.1 Hz, 1H), 4.94 (dd, J = 1.7, 17.1 Hz, 1H), 3.68 (s, 3H), 3.23 (d, J = 4.6 Hz, 2H), 3.18 (d, J = 14.8 Hz, 1H), 3.09 (d, J = 14.8 Hz, 1H), 2.35 (m, 2H), 2.15 (m, 2H), 2.09 (s, 3H), 2.06 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 206.8 (C), 205.4 (C), 172.4 (C), 146.5 (C), 145.9 (C), 136.9 (CH), 132.0 (C), 127.0 (C), 115.8 (CH_2), 109.9 (CH), 109.7 (CH), 100.9 (CH_2), 63.8 (C), 52.2 (CH_3), 38.4 (CH_2), 36.9 (CH_2), 34.4 (CH_2), 29.9 (CH_3), 27.9 (CH_3), 26.7 (CH_2).

9 Begbie, A. L.; Golding, B. T. *J. Chem. Soc. Perkin I* **1972**, 602-605. When cyclization of diketone **9** was performed in the presence of MeONa in MeOH, the regioselectivity of the six-membered annulation was inverted.

10 Ozonolysis of **10** was not chemoselective.

11 **10**: colorless solid; Mp: 102-105 °C (AcOEt); IR: 3062, 1735, 1722, 1673, 1640 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.64 (s. 1H), 6.56 (s, 1H), 5.99 (s, 1H), 5.90 (s, 2H), 5.85 (m, 1H), 5.05 (dd, J = 1.7, 10.1 Hz, 1H), 4.95 (dd, J = 1.7, 17.0 Hz, 1H), 3.76 (s, 3H), 3.46 (d, J = 14.7 Hz, 1H), 3.28 (m, 2H), 2.93 (d, J = 14.7 Hz, 1H), 2.46 (m, 1H), 2.26 (m , 2H), 2.08 (s, 3H), 1.98 (m, 1H); ^{13}C NMR (50 MHz. $CDCl_3$) δ 198.0 (C), 173.3 (C), 159.9 (C), 146.4 (C), 145.9 (C), 136.6 (CH), 132.0 (C), 129.6 (CH), 127.2 (C), 115.9 (CH_2), 109.9 (CH), 109.4 (CH), 100.8 (CH_2), 52.4 (CH_3), 51.6 (C), 37.1 (CH_2), 36.5 (CH_2), 34.0 (CH_2), 30.6 (CH_2), 21.7 (CH_3).

12 **11**: oil; IR: 2925, 1730, 1724, 1669 cm^{-1};^{1}H NMR (200 MHz, $CDCl_3$) δ 9.63 (t, J = 2.8 Hz), 6.62 (s, 2H), 5.99 (s, 1H), 5.94 (s, 2H), 3.75 (s, 3H), 3.65 (t, J = 2.8 Hz, 2H), 3.37 (d, J = 14.8 Hz, 1H), 2.90 (d, J = 14.8 Hz, 1H), 2.44 (m, 1H), 2.27 (m , 2H), 2.04 (s, 3H), 1.95 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 198.9 (CH), 197.9 (C), 173.4 (C), 159.8 (C), 147.3 (C), 147.1 (C), 130.0 (CH), 128.8 (C), 124.5 (C), 110.9 (CH), 110.3 (CH), 101.4 (CH_2), 52.7 (CH_3), 51.9 (C), 48.2 (CH_2), 36.9 (CH_2), 34.1 (CH_2), 30.9 (CH_2), 21.9 (CH_3).

13 Horiguchi,Y.; Furukawa, T.; Kuwajima, I. *J. Am. Chem. Soc.* **1989**, *111*, 8277-8279.

14 **13**: oil; IR: 1721, 1652 cm^{-1};^{1}H NMR (200 MHz, $CDCl_3$) δ 6.96 (dt, J = 6.0, 15.7 Hz, 1H), 6.55 (s, 2H), 5.95 (s, 1H), 5.88 (s, 2H), 5.62 (dt, J = 1.6, 15.6 Hz, 1H), 3.72 (s, 3H), 3.67 (s, 3H), 3.39 (m, 2H), 3.36 (d, J = 14.7 Hz, 1H), 2.86 (d, J = 14.7 Hz, 1H), 2.40 (m,1H), 2.24 (m , 2H), 2.04 (s, 3H), 1.95 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 197.5 (C), 173.1 (C), 166.3 (C), 159.7 (C), 147.1 (CH), 146.7 (C), 146.4 (C), 129.9 (C), 129.6 (CH), 127.6 (C), 121.8 (CH), 109.9 (CH), 109.7 (CH), 101.0 (CH_2), 52.4 (CH_3), 51.6 (C), 51.2 (CH_3), 36.5 (CH_2), 35.4 (CH_2), 33.9 (CH_2), 30.6 (CH_2), 21.6 (CH_3).

15 When an excess of Me_2CuLi was added to **13** at 0 °C, a double conjugate addition to the enone and enoate moieties was observed.

16 **14**: oil; IR: 1725 cm^{-1};^{1}H NMR (200 MHz, $CDCl_3$) δ 6.95 (dt, J = 6.0, 15.2 Hz, 1H), 6.55 (s, 1H), 6.49 (s, 1H), 5.82 (s, 2H), 5.61 (dt, J = 1.6, 15.6 Hz, 1H), 5.52 (s, 1H), 3.63 (s, 6H), 3.38 (m, 2H), 3.10 (d, J = 14.7 Hz, 1H), 2.86 (d, J = 14.7 Hz, 1H), 1.73 (m, 2H), 1.65 (s, 3H), 1.01 (s, 3H), 0.78 (m, 2H), 0.00 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 175.7 (C), 166.7 (C), 147.4 (CH), 146.2 (2C), 135.4 (CH), 133.4 (C), 129.8 (C), 129.3 (C), 121.7 (CH), 110.1 (CH), 109.7 (CH), 100.8 (CH_2), 71.1 (C), 51.9 (CH_3), 51.3 (CH_3), 51.2 (C), 35.7 (CH_2), 34.9 (CH_2), 29.7 (CH_3), 29.6 (CH_2), 29.1 (CH_2), 20.6 (CH_3), 2.3 ($3CH_3$).

17 **15**: oil; IR: 1735, 1725 cm^{-1};^{1}H NMR (200 MHz, $CDCl_3$), *major diastereomer* : δ 6.40 (s, 1H), 6.38 (s, 1H), 5.80 (m, 2H), 3.62 (s, 3H), 3.55 (s, 3H), 3.39 (d, J = 14.7 Hz, 1H), 2.80 (dd, J = 13.5, 2.0 Hz, 1H), 2.40 (dd, J = 13.5, 6.0 Hz, 1H), 2.40 (d, J = 14.7 Hz, 1H), 2.50-1.40 (m, 6H), 1.32 (s, 3H), 1.00 (s, 3H), 0.8 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$), *major diastereomer* : δ 203.1 (C), 177.7 (C), 174.7 (C), 147.0 (C), 146.8 (C), 131.2 (C), 129.9 (C), 108.3 (CH), 107.8 (CH), 100.6 (CH_2), 54.3 (CH_3), 51.4 (CH_3), 49.4 (CH), 46.1 (C), 44.4 (C), 41.5 (CH_2), 39.8 (CH), 38.2 (CH_2), 36.8 (CH_2), 28.0 (CH_2), 26.8 (CH_2), 25.2 (CH_3), 19.8 (CH_3).

18 Epimeric esters **15**, exhibiting a bridged *cis*-fused bicyclo[5.3.1] system, were found to be more stable by *ca* 14 kcal mol^{-1} than the corresponding *trans*-fused isomers by MM2 calculations.