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SYNTHETIC EFFORTS DIRECTED TOWARDS THE TAXOL SKELETON. THE SATURATED C-RING APPROACH

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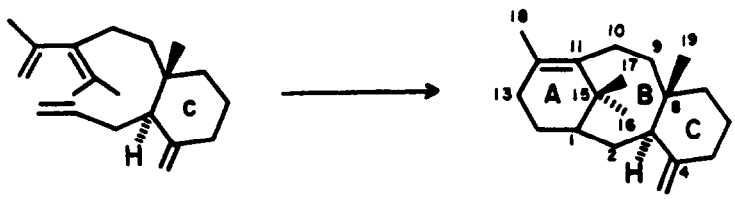
Summary: The type 2 intramolecular Diels-Alder reaction is utilized to assemble a taxol precursor.

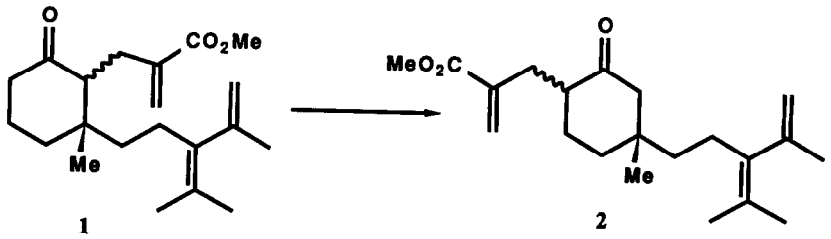
The Type 2 intramolecular Diels-Alder cycloaddition provides a direct entry into the tricyclo [9.3.1.$0^{3,8}$] pentadecane ring system (eq. 1), the key substructural unit of a number of biologically important naturally occurring molecules including taxol.[1] We recently reported examples of this strategy for the synthesis of C-aromatic derivatives of the ring system.[2,3] In the present communication we develop an approach that is useful for the synthesis of precursors to the saturated tricyclic skeleton[4] incorporating functionality at C-1, a strategic location for synthetic efforts directed towards taxol.



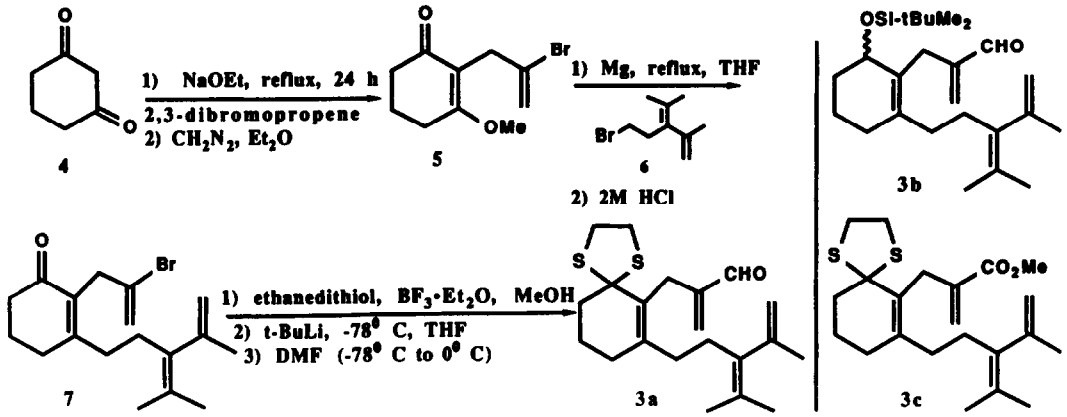
(1)

A direct approach, employing the C-ring at a cyclohexane oxidation level, was not successful under thermal conditions. Thus, Diels-Alder precursor 1[5] was recovered unchanged after heating at 200°C for 24h. Interestingly, at higher temperatures (220°C, 48h, xylene), cycloadduct could not be detected but rearrangement to 2 was observed.[6] The reaction presumably arises by a [3.3] sigmatropic rearrangement of an enol tautomer of 1.

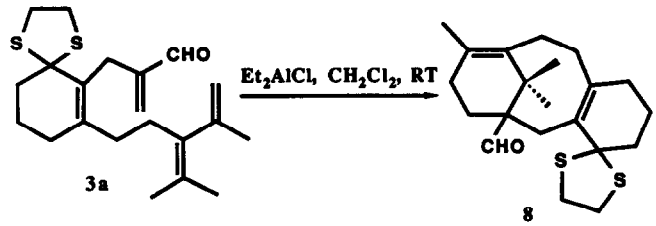
The low thermal reactivity of Diels-Alder precursor 1 is attributed, in part, to the conformational mobility of cyclohexane 1. Indeed, earlier studies on related cycloadditions revealed that when diene and dienophile are locked in a cis relationship, rate enhancements of up to 10^6 may be observed over conformationally mobile analogs.[2] A modified approach, therefore, utilizes a 1,2-disubstituted cyclohexene derivative 3a to set diene and dienophile in close proximate relationship.



Synthesis of 3a was achieved by treatment of 1,3-cyclohexadione with sodium ethoxide and 2,3-dibromopropene for 24h at reflux followed by isolation and esterification (CH_2N_2/Et_2O) to afford vinylogous ester 5 in a combined 52% yield.[7] The diene unit is introduced by reaction of 5 with the Grignard reagent derived from bromodiene 6[8] followed by hydrolytic work up in 2M HCl to give unsaturated bromoketone 7 (49%). Protection of the enone was eventually accomplished with ethandithiol, $BF_3 \cdot OEt_2$ for 22h in methanol[9] (77%). Dienophile activation proceeded upon metalation of the bromodithiane (t-BuLi, -78°C, ET_2O, 1h) followed by treatment with DMF (-78° → 0°C). After aqueous quench and chromatography (SiO_2) aldehyde 3a was isolated in 71% yield.[10]

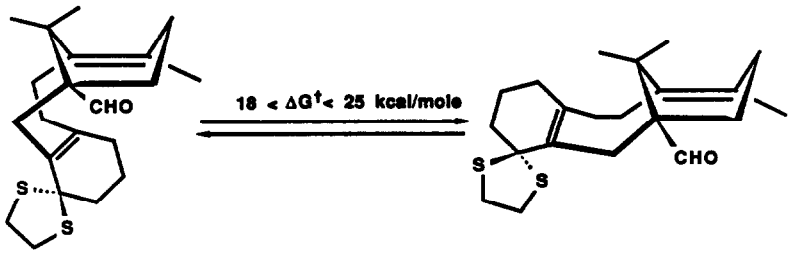


Despite the constraints imposed upon diene and dienophile, Diels-Alder reactivity of 3a is low. However, after 86h at 180°C (0.01M toluene) 12% of cycloadduct 8 is isolated.[11] This situation is improved somewhat by Lewis acid catalysis. Upon treatment of 3a with Et_2AlCl (4 eq., CH_2Cl_2 RT) cycloadduct 8 could be obtained in yields up to 30%.[12] Interestingly, Lewis acids such as Me_2AlCl, $SnCl_4$, $TiCl_4$, $BF_3 \cdot OEt_2$ and $ZnCl_2$ were not effective for the cycloaddition. Two modifications of the Diels-Alder precursor were also prepared (3b,c) but these did not prove to be as effective as 3a in the thermal or Lewis acid catalyzed cycloaddition reaction.



Based upon previous studies of the tricyclo [9.3.1.$0^{3,8}$] pentadecane ring system,[3,13] we anticipated the possibility of several discrete low energy conformations of this molecule.

Indeed, the NMR spectrum of cycloadduct 8 (prepared by Lewis acid catalysis) exhibits six methyl resonances and two aldehyde signals (10.0 and 9.69 ppm, $CDCl_3$). The ratio of intensities of the two aldehyde signals is 1:1. Since this ratio did not change upon heating at 130°C (p-xylene) we conclude that the two conformations are of equal energy. Variable temperature NMR spectroscopy reveals substantial peak broadening at 130°C but incomplete coalescence. This experiment permits an estimate of the barrier separating the two conformational isomers to be in excess of 18 kcal/mol. The failure to observe separation of the two conformational isomers by HPLC or column chromatography requires that the barrier for interconversion be less than 25 kcal/mol.[14]



ENDO - 8 EXO - 8

We believe this strategy provides an expeditious entry into taxane precursors. Of particular importance is the opportunity to incorporate bridgehead C-1 substituents and residual functionality that facilitates introduction of the methyl group at C-8, the remaining key carbon atom necessary for synthesis of the natural product skeleton. Efforts are presently underway to accomplish this goal.

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References and Footnotes

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2. Shea, K.J.; Davis, P.D. Angew. Chem. Int. Ed. Eng. 1983, 22, 419.
3. Shea, K.J.; Gilman, J.W.; Haffner, C.D.; Dougherty, T.K. J. Am. Chem. Soc. 1986, 108, 4953.
4. Several recent synthetic approaches to the taxane skeleton may be found in the following references. Brown, P.A.; Jenkins, P.R. J. Chem. Soc., Perkin Trans. 1 1986, 1303; Winkler, J.D.; Hey, J.P. J. Am. Chem. Soc. 1986, 108, 6425; Kende, A.S.; Johnson, S.; Sanfilippo, P.; Hodges, J.C.; Jungheim, L.N. J. Am. Chem. Soc. 1986, 108, 3513; Swindell, C.S.; Britcher, S.F. J. Org. Chem. 1986, 51, 793; Wender, P.A.; Snapper, M.L. Tetrahedron Lett. 1987, 2221. A more complete list of references regarding synthetic entries into the taxane natural products can be found in these references.
5. All new compounds gave spectral data consistent with the assigned structures.
6. Compound 2 (mixture of diastereomers) Diastereomer A: ^{1}H NMR (C_6D_6, 250 MHz) δ 6.46 (d, 1H, J = 1.7Hz, vinyl), 5.64 (d, 1H, J = 1.3 Hz, vinyl), 5.24 (m, 1H, vinyl), 4.93 (m, 1H, vinyl), 3.63 (s, 3H, -OMe), 3.42 (d of d, 1H, J = 13.1 Hz, J = 5.5 Hz), 2.68-2.65 (m, 1H), 2.43 (d of d, 1H, J = 7.7 Hz, J = 13.9 Hz), 2.30 (d, 1H, J = 12.4 Hz), 2.18-2.11 (m, 2H), 2.04-1.89 (m, 8H), 1.82 (s, 3H, -Me), 1.47-1.36 (m, 5H), 0.93 (s, 3H, -Me) ppm; ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 212.6, 168.2, 147.1, 138.9, 136.9, 127.8, 125.7, 113.8, 54.1, 52.6, 49.2, 43.7, 40.4, 36.7, 32.7, 29.7, 25.7, 23.4, 23.2, 22.4, 20.1 ppm; IR (film) 3075 w, (vinyl C-H), 2928 s, (aliphatic C-H), 1717 s, (C=O), 1631 m and 1439 s, (C=C) cm^{-1}; high resolution calculated for $C_{21}H_{32}O_3$: 332.2351, found: 332.2354. Diastereomer B: ^{1}H NMR (C_6D_6, 250 MHz) δ 6.43 (d, 1H, J = 1.7 Hz, vinyl), 5.60 (s(br), 1H, vinyl), 5.22 (m, 1H, vinyl), 4.92 (m, 1H, vinyl), 3.60 (s, 3H, -OMe), 3.38 (d of d, 1H, J = 5.6 Hz, J = 14.1 Hz), 2.70-2.65 (m, 1H), 2.47-2.28 (m, 3H), 2.15-2.09 (m, 1H), 2.00 (s, 3H, -Me), 1.95 (s, 3H, -Me), 1.89 (s, 3H, -Me), 2.00-1.89 (m, 2H), 1.65-1.46 (m, 5H), 0.97 (s, 3H, -Me) ppm; ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 212.3, 168.2, 147.0, 138.9, 136.8, 127.8, 125.8, 113.9, 54.6, 52.5, 48.8, 39.9, 36.5, 36.2, 32.7, 29.3, 28.3, 25.7, 23.4, 22.4, 20.1 ppm; IR (film) 3075 w, (vinyl C-H), 2928 s, (aliphatic C-H), 1717 s, (C=O), 1631 m and 1439 s, (C=C) cm^{-1}; high resolution calculated for $C_{21}H_{32}O_3$: 332.2351, found: 332.2337.
7. Compound 5: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.44 (m, 1H, vinyl), 5.30 (m, 1H, vinyl), 3.82 (s, 3H, -OMe), 3.41 (s, 2H, allylic), 2.60 (t, 2H, J = 6.1 Hz), 2.36 (t, 2H, J = 6.7 Hz), 2.01 (quint, 2H, J = 6.4 Hz) ppm; ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 197.2, 174.4, 132.4, 115.7, 55.9, 36.6, 34.2, 25.3, 21.1 ppm; IR (film) 2960 m, (aliphatic C-H), 1610 s, (C=O), 1240 s, (C-O) cm^{-1}; high resolution calculated for $C_{10}H_{13}BrO_2$: 247.0157 (^{81}Br), found: 247.0164 (^{81}Br).
8. Bromodiene 6 was prepared in three steps from 1,1-dibromo-2,2,3,3-tetramethylcyclopropane. Thermally induced dehydrohalogenative ring opening yields 3-bromo-2,4-dimethyl-1,3-pentadiene (84%). Metalation (t-buLi, -78°C) followed by an ethylene oxide quench gave a homoallylic alcohol (55%) which was converted to bromide 6 by tosylation followed by refluxing in acetone/NaBr (62%).
9. Williams, J.R.; Sarkisan, G.M.; Synthesis 1974, 32.
10. Compound 3a: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 9.63 (s, 1H, aldehyde), 6.10 (s(br), 1H, vinyl), 6.03 (s(br), 1H, vinyl), 4.87 (m, 1H, vinyl), 4.48 (m, 1H, vinyl), 3.26 (s, 4H, -S-CH_2-CH_2-S-), 2.12-2.05 (m, 4H), 1.85-1.81 (m, 4H), 1.72 (s, 3H, -Me), 1.63 (s, 3H, -Me), 1.62 (s, 3H, -Me) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 195.0, 150.5, 147.0, 141.1, 136.6, 134.2, 128.4, 126.1, 114.0, 72.5, 44.8, 40.7, 34.6, 29.9, 29.0, 23.3, 23.0, 22.3, 20.2 ppm; IR (melt) 3080 w, (vinyl C-H), 2930 s, (aliphatic C-H), 1690 s, (C=O), 1630 and 1430 s, (C=C) cm^{-1}; high resolution calculated for $C_{21}H_{30}OS_2$: 362.1738, found: 362.1722.
11. Compound 8: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 9.98 (s, 1H, aldehyde), 9.69 (s, 1H, aldehyde), 3.33-3.22 (m, 8H, -S-CH_2-CH_2-S-), 2.91-1.62 (m, 31H), 1.62 (m, 3H, -Me), 1.49 (s, 3H, -Me), 1.31 (s, 3H, -Me), 1.24 (s, 3H, -Me), 1.15 (s, 3H, -Me), 1.07 (s, 3H, -Me) ppm (the ^{1}H NMR spectra showed at ambient temperature an endo to exo ratio of ~1:1); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 208.6, 207.1, 143.0, 142.7, 141.3, 134.2, 132.9, 132.1, 127.1, 73.7, 72.6, 56.1, 56.0, 45.7, 45.0, 41.2, 40.7, 40.5, 40.0, 39.6, 38.8, 37.1, 34.9, 33.6, 33.2, 30.2, 28.9, 28.3, 28.2, 28.0, 27.9, 23.9, 23.5, 23.0, 22.5, 22.3, 21.9, 20.8 ppm (mixture of endo and exo); IR (film) 2961 s (C-H) aliphatic), 1717 s (C=O, aldehyde), 1652 m (C=C) cm^{-1}; high resolution mass spectra calculated for $C_{19}H_{28}OS_2$: 362.1738, found: 362.1739.
12. Yields for this reaction were somewhat erratic, possibly due to the long reaction time and large excess of Lewis acid needed.
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14. Oki, M. Top. Stereochem. 1983, 14, 1.

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