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SYNTHESIS AND STEREOCHEMISTRY OF A SATURATED TRICYCLIC TAXANE MODEL

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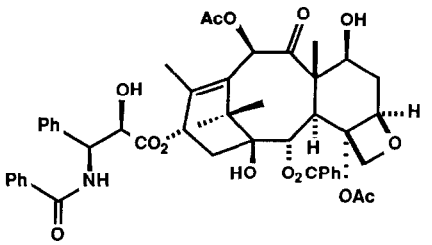
Summary: The construction through an A-ring annulation strategy of a fully B-ring methylated saturated tricyclic taxane model and the demonstration of its preference for *trans* BC ring junction stereochemistry are described.

Motivated in part by the anti-tumor and anti-leukemic activities of taxol[1] (**1**) which are expressed through a unique interaction with the cytoskeleton,[2] and by the challenge posed by taxol's complex structure, efforts toward the total synthesis[3-5] of the taxane diterpenes[6] are being reported with increasing frequency. We have regarded the construction of the carbon framework (**2**) with the full complement of sterically encumbering B-ring methyl groups and with proper relative stereochemistry at C-1, C-3, and C-8 as a critical preliminary test of any strategy for taxane synthesis. Only recently has such a structure been synthesized.[4] Since the A-ring bridgehead olefin appears to have a negligible effect on the total strain of the taxane ring system[7] and has been accommodated in several reported strategies, the construction of a saturated model possessing these characteristics remains an instructive exercise. Herein we summarize the synthesis of taxane model **9** through a route which illustrates the efficacy of an A-ring annulation strategy. In addition, we show unequivocally that the natural stereochemistry at C-3 relative to C-1 and C-8 in **9** is the thermodynamically preferred one, an observation which may be important for the proper introduction of these stereo-centers in synthetic taxanes.



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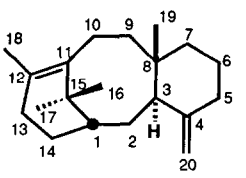

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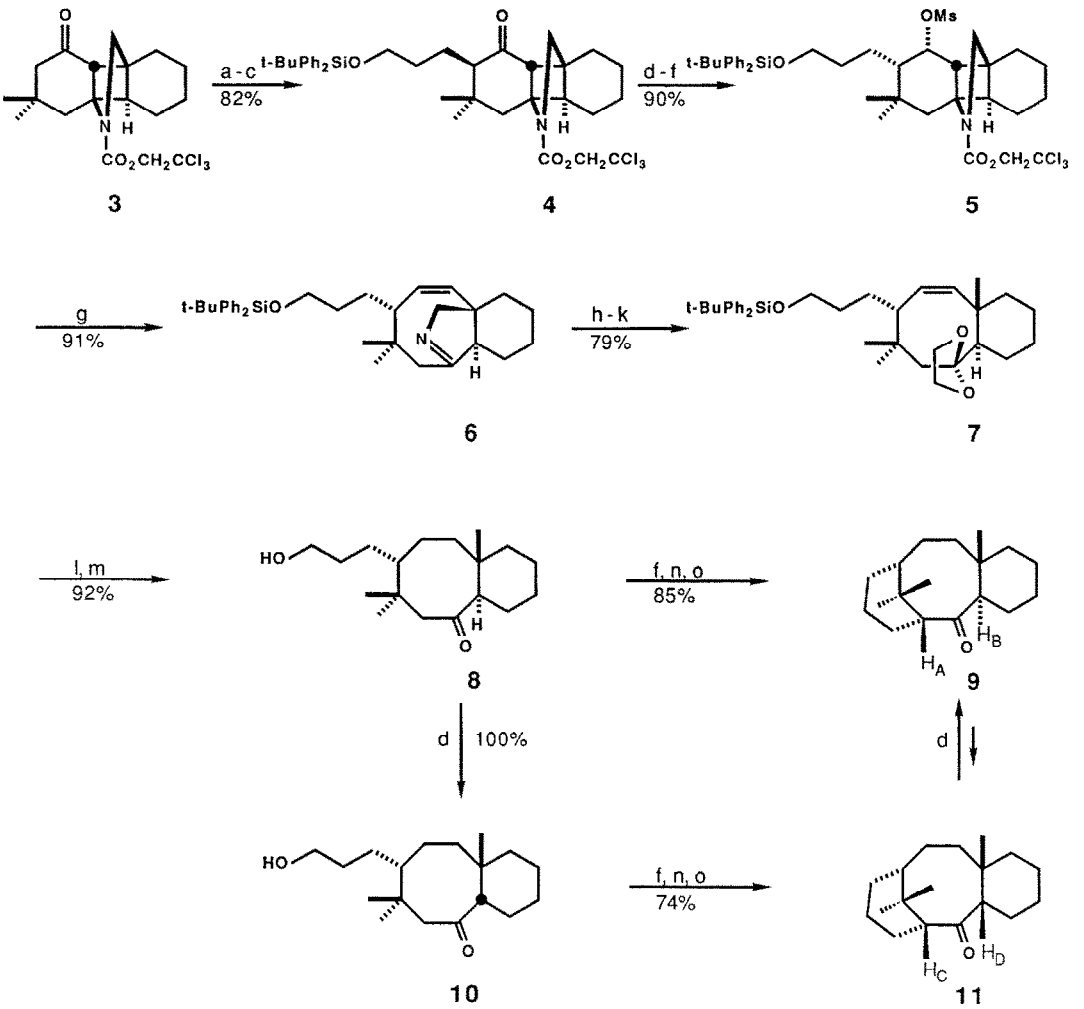
Our construction of **9** required the intended A-ring annulation to proceed in tandem with a fragmentation sequence to the BC sub-structure. Thus alkylation of **3**[5] with a three carbon unit destined to complete the A-ring was initiated through its conversion to the corresponding dimethylhydrazone (Scheme). Deprotonation and subsequent reaction with **12**[8] were followed by cleavage of the alkylated hydrazone to yield **4**. The stereochemistry of the sidechain follows from the known inclination of dimethylhydrazone anions to undergo axial alkylation[9] which in this case is reinforced by the hemispherical tetracyclic system. Adjustment of stereochemistry at C-11 through base-induced epimerization and transformation of the carbonyl into the α mesylate delivered an intermediate (**5**) appropriately set up for the B-ring forming fragmentation.[5] This was effected by trichloroethyl urethane cleavage[10] and led to bridgehead imine **6**. Hydrolytic liberation of the primary amine and its capture

Scheme



(a) $(CH_3)_2NNH_2$. (b) *i.* LDA; *ii.* *t*-$BuPh_2SiO(CH_2)_3I$ (**12**). (c) H_5IO_6. (d) CH_3ONa. (e) L-Selectride. (f) CH_3SO_2Cl, Et_3N. (g) Zn, 1 M K-PO_4 buffer (pH 4-5). (h) *i.* CH_3CO_2H, H_2O; *ii.* CH_3CO_2CHO, pyridine. (i) $(CH_2OH)_2$, H^+ (cat.). (j) CH_3SO_2Cl, pyridine. (k) Na, NH_3, NH_4Cl. (l) H_2, 10% Pd-C. (m) 15% aq. HF. (n) NaI. (o) LDA.

with aceticformic anhydride gave a formamide which led through ketalization, isocyanide formation, and dissolving metal reduction to **7**. Hydrogenation of the double bond and one-step deprotection of both the B-ring ketone and the sidechain hydroxyl delivered **8**. Taxane model **9**[11] followed in short order upon closure of the A-ring by intramolecular enolate alkylation.

To aid in the verification of the relative stereochemistry of **9** and to probe the thermodynamically preferred stereochemistry at C-3, we converted **8** to epimeric tricycle **11**.[12] The epimerization of **8** to **10** takes advantage of the frequent preference of bicyclo[6.4.0] structures for *cis* ring junction stereochem-

istry.[5] Tricycle **9** exhibited a ^{1}H NMR (270 MHz) methine signal[13] at 3.66 δ as an apparent triplet, suggesting its assignment as equatorial H_A. This was confirmed through its saturation which produced NOE's of two of the three methyl signals, those two which were themselves related through mutual NOE's and therefore are geminal. The H_B resonance for **9** was obscured by other signals. Tricycle **11**[13] indicated its equatorial H_C resonance as an apparent triplet at 3.48 δ, which was verified through NOE experiments similar to the above. An equatorial methine apparent triplet at 2.45 δ was evident in the spectrum of **11** and irradiation of it led to an NOE of the methyl resonance unaffected by irradiation of H_C. Therefore this signal is assigned to *cis* proton H_D and the *trans* and axial nature of H_B in **9** is confirmed indirectly.[14] Both **9** and **11** suffered equilibration in hot methanolic sodium methoxide to provide a 92/8 ratio of *trans* and *cis* tricycles, respectively. Thus in the saturated taxane skeleton, it is clear that the natural relative stereochemistry at C-1, C-3, and C-8 is the thermodynamic preference of the ring system.[15]

We can now be confident that the energetic and stereochemical issues characteristic of a general A-ring annulation approach to the taxanes are manageable. Although in constructing more heavily functionalized taxanes the appropriate annulations will differ in detail from the one employed here, it is worth noting that functionality sufficient for the introduction of B-ring oxygenation is encountered even in the described synthesis of **9.**

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References and Notes

1. Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325.

2. Schiff, P. B.; Fant, J.; Horwitz, S. B. *Nature* **1979**, *277*, 665. Manfredi, J. J.; Horwitz, S.B. *Pharmac. Ther.* **1984**, *25,* 83.

3. Taxane carbon skeleton: Kato, T.; Takayanagi, H.; Suzuki, T.; Uyehara, T. *Tetrahedron Lett.* **1978**, 1201. Kende, A. S.; Benechie, M.; Curran, D. P.; Fludzinski, P.; Swenson, W.; Clardy, J. *Ibid.* **1979**, 4513. Kitigawa, I.; Shibuya, H.; Fujioka, H.; Kejiwara, A.; Tsujii, S.; Yamamoto, Y.; Takagi, A. *Chemistry Lett.* **1980**, 1001. Inouye, Y.; Fukaya, C.; Kakisawa, H. *Bull. Chem. Soc. Jpn.* **1981**, *54,* 1117. Trost, B. M.; Hiemstra, H. *J. Am. Chem. Soc.* **1982**, *104,* 886. Martin, S. F.; White, J. B.; Wagner, R. *J. Org. Chem.* **1982**, *47,* 3190. Sakan, K.; Craven, B. M. *J. Am. Chem. Soc.* **1983**, *105,* 3732. Shea, K. J.; Davis, P. D. *Angew. Chem., Int. Ed.* **1983**, *22,* 419. Brown, P. A.; Jenkins, P. R.; Fawcett, J.; Russell, D. R. *J. Chem. Soc., Chem. Commun.* **1984**, 253. Ohtsuka, Y.; Oishi, T. *Heterocycles* **1984**, *21,* 371. Neh, H.; Blechert, S.; Schnick, W.; Jansen, M. *Angew. Chem., Int. Ed.* **1984**, *23*, 905. Clark, G. R.; Lin, J.; Nikaido, M. *Tetrahedron Lett.* **1984**, *25*, 2645. Swindell, C. S.; deSolms, S. J. *Ibid.* **1984**, *25*, 3801. Holton, R. A. *J. Am. Chem. Soc.* **1984**, *106,* 5731. Andriamialisoa, R. Z.; Fetizon, M.; Hanna, I.; Pascard, C.; Prange, T. *Tetrahedron* **1984**, *40,* 4285. Trost, B. M.; Fray, M. J. *Tetrahedron Lett.* **1984**, *25,* 4605. Nagaoka, H.; Ohsawa, K.; Takata, T.; Yamada, Y. *Ibid.* **1984**, *25,* 5389. Jackson, C. B.; Pattenden, G. *Ibid.* **1985**, *26,* 3393. Begley, M. J.; Jackson, C. B.; Pattenden, G. *Ibid.* **1985**, *26,* 3397. Kojima, T.; Inouye, Y.; Kakisawa, H. *Chemistry Lett.* **1985**, 323. Berkowitz, W. F.; Perumattam, J.; Amarasekara, A. *Tetrahedron Lett.* **1985**, *26,* 3665. Fetizon, M.; Hanna, I.; Zeghdoudi, R. *Synthetic Commun.* **1986**, *16,* 1. Ohtsuka, Y.; Oishi, T. *Tetrahedron Lett.* **1986**, *27,* 203. Trost, B. M.; Hiemstra, H. *Tetrahedron* **1986**, *42*, 3323. Shea, K. J.; Gilman, J. W.; Haffner, C. D.; Dougherty, T. K. *J. Am. Chem. Soc.* **1986**, *108*, 4953. Cervantes, H.; Do Khac, D.; Fetizon, M.; Guir, F.; Beloeil, J.-C.; Lallemand, J.-Y.; Prange, T. *Tetrahedron* **1986**, *42*, 3491. Brown, P. A.; Jenkins, P. R. *J. Chem. Soc., Perkin I* **1986**, 1303. Kaczmarek, R.; Blechert, S. *Tetrahedron Lett.* **1986**, *27*, 2845. Winkler, J. D.; Hey, J. P.; Williard, P.

G. *J. Am. Chem. Soc.* **1986**, *108,* 6425. Winkler, J. D.; Hey, J. P.; Darling, S. D. *Tetrahedron Lett.* **1986**, *27*, 5959. Benchikh-le-Hocine, M.; Do Khac, D.; Cervantes, H.; Fetizon, M. *Nouv. J. Chim.* **1986**, *10*, 715. Wender, P. A.; Snapper, M. L. *Tetrahedron Lett.* **1987**, *28*, 2221. Pettersson, L; Frejd, T.; Magnusson, G. *Ibid.* **1987**, *28*, 2753. C-ring features: Berkowitz, W. F.; Amarasekara, A. S. *Tetrahedron Lett.* **1985**, *26*, 3663. Swindell, C. S.; Britcher, S. F. *J. Org. Chem.* **1986**, *51*, 793. A-ring side-chain: Denis, J.-N.; Greene, A. E.; Serra, A. A.; Luche, M.-J. *J. Org. Chem.* **1986**, *51*, 46.

4. Kende, A. S.; Johnson, S.; Sanfilippo, P.; Hodges, J. C.; Jungheim, L. N. *J. Am. Chem. Soc.* **1986**, *108,* 3513.

5. Swindell, C. S.; Patel, B. P.; deSolms, S. J.; Springer, J. P. *J. Org. Chem.* **1987**, *52*, 2346.

6. Lythgoe, B. *The Alkaloids* **1968**, *10,* 597. Nakanishi, K.; et al. "Natural Products Chemistry"; Kodansha-Academic Press: Tokyo, **1974**; Vol. I, p. 281. Miller, R. W. *J. Nat. Prod.* **1980**, *43,* 425.

7. Swindell, C. S.; Isaacs, T. F.; Kanes, K. J. *Tetrahedron Lett.* **1985**, *26*, 289.

8. Prepared from 1,3-propanediol by sequential monosilylation, mesylation, and iodide displacement.

9. Corey, E. J.; Enders, D. *Chem. Ber.* **1978**, *111*, 1337. Corey, E. J.; Enders, D. *Ibid.* **1978**, *111*, 1362. Collum, D. B.; Kahne, D.; Gut, S. A.; DePue, R. T.; Mohamadi, F.; Wanat, R. A.; Clardy, J.; Van Duyne, G. *J. Am. Chem. Soc.* **1984**, *106*, 4865.

10. Just, G.; Grozinger, K. *Synthesis* **1976**, 457.

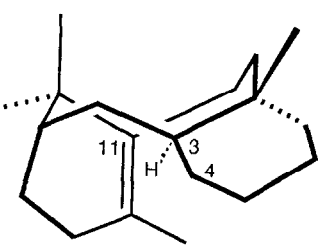
11. Data for **9**: ^{1}H NMR (270 MHz) δ 0.76 (3H, s, geminal CH_3), 1.04 (3H, s, geminal CH_3), 1.0-2.4 (19H, m, CH, CH_2), 1.27 (3H, s, CH_3), 2.68 (1H, dd, J = 9, 16, CH_2), 3.66 (1H, app t, J = 9, CHCO); ^{13}C NMR (67 MHz) δ 212.41, 43.10, 34.97 (quaternaries), 81.76, 51.05, 44.27 (CH), 41.02, 37.11, 37.01, 36.86, 30.54, 26.47, 25.36, 23.33, 20.79 (CH_2), 31.18, 22.61, 11.08 (CH_3); IR (CCl_4) 1730 cm^{-1}; mass spectrum *m/z* (relative intensity) 262 (M^+, 49), 247 (100); Anal. Calcd for $C_{18}H_{30}O$: C, 82.38; H, 11.52. Found: C, 82.53; H, 11.58.

12. Data for **11**: ^{1}H NMR (270 MHz) δ 0.67 (3H, s, geminal CH_3), 0.94 (3H, s, geminal CH_3), 1.0-2.2 (19H, m, CH, CH_2), 1.13 (3H, s, CH_3), 2.45 (1H, app t, J = 10, CHCO), 3.48 (1H, app t, J = 8, CHCO); ^{13}C NMR (67 MHz) δ 211.63, 68.71, 37.96 (quaternaries), 72.87, 41.61, 35.17 (CH), 38.10, 32.43, 32.28, 26.80, 26.14, 25.78, 24.71, 22.91, 22.53 (CH_2), 30.82, 26.73, 26.06 (CH_3); IR (CCl_4) 1730 cm^{-1}; mass spectrum *m/z* (relative intensity) 262 (M^+, 31), 247 (100); Anal. Calcd for $C_{18}H_{30}O$: C, 82.38; H, 11.52. Found: C, 82.43; H, 11.41.

13. Methine proton signals were located unambiguously through a combination of 1D and 2D DEPT experiments.

14. The conformation for **9** is predicted to be similar to that of a related hydrocarbon (see ref. 7).

15. Although as far as we know it has never been demonstrated, it is probably true that the same relative stereochemistry is the thermodynamic preference of the *unsaturated* skeleton as well. According to principles outlined by Still (Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37,* 3981), the eight-membered ring of the taxane skeleton (*i*) has an almost ideally substituted boat-chair conformation with the bridgehead olefin perfectly located so as to minimize the most severe transannular interaction involving substituents at C-3 and C-11. Reversal of stereochemistry at C-3 would force C-4 to interact strongly with C-11 and thus disrupt this energetically favorable situation.



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