Stereoselective Synthesis of the Taxane Ring System via the Tandem Diels−Alder Cycloaddition†

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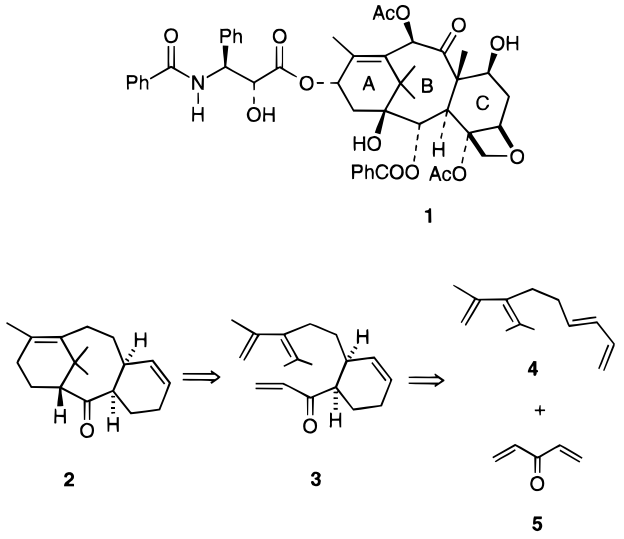
The application of the tandem Diels−Alder cycloaddition to the stereoselective synthesis of the tricyclic ring system of the taxane diterpenes is described. The exceedingly direct, *two-step* synthesis of the B/C cis-fused taxane nucleus in 50% overall yield from the reaction of two readily available acyclic precursors underscores the efficiency of this approach. A critical feature of the second, intramolecular Diels−Alder cyclcoaddition is the transmission of stereochemical information across the taxane framework, i.e., from the C ring to the A ring. The cycloaddition of both cis- and trans-disubstituted C ring constructs leads to the establishment of the requisite C-1/C-3 relative stereochemistry for the synthesis of taxanes. A computational model is presented to account for the high levels of asymmetric induction observed in these reactions.

Introduction

A notable feature of many of the published approaches to the synthesis of taxol is the application of the Diels−Alder reaction to prepare the A and C rings of taxol, respectively.[1,2] Nicolaou has disclosed the construction of both A and C ring synthons via intermolecular Diels−Alder cycloaddition,[1b] and several groups have examined either A or C ring formation via intramolecular Diels−Alder cycloaddition.[3] We have recently reported that the tandem Diels−Alder reaction leads to the preparation of polycyclic structures with excellent stereochemical control.[4,5] We describe herein the application of this methodology to the synthesis of the tricyclic taxane nucleus, in which both the A and C rings of the taxane ring system are prepared *via* Diels−Alder cycloaddition reactions.[6]

Scheme 1



The power of this tandem process is exemplified by the highly efficient construction of the taxane ring system **2** from the two simple acyclic precursors, **4** and **5**, as outlined in Scheme 1. We have probed the stereoselectivity of the second, intramolecular Diels−Alder cycloaddition reaction as a function of the C-3/C-8 relative stereochemistry. We report herein the highly stereoselective construction of the tricyclic ring system of the taxanes starting with both cis- and trans-disubstituted C-ring constructs, and we present a computational model to account for the high levels of asymmetric induction observed in these reactions.

† Dedicated to the memory of Professor Paul Dowd, a true gentleman and scholar who enriched the lives of all who knew him.

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(1) Total syntheses of taxol: (a) Holton, R. A.; Somoza, C.; Kim, H.-B.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1597. Holton, R. A.; Kim, H.-B.; Somoza, C.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1599. (b) Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Claiborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulvannan, K.; Sorensen, E. *Nature* **1994**, *367*, 630. Nicolaou, K. C.; Nantermet, P. G.; Ueno, H; Guy, R. K.; Couladouros, E. A.; Sorensen, E. J. *J. Am. Chem Soc.* **1995**, *117*, 624. Nicolaou, K. C.; Liu, J.-J.; Yang, Z.; Ueno, H.; Sorensen, E. J.; Claiborne, C. F.; Guy, R. K.; Hwang, C.-K.; Nakada, M.; Nantermet, P. G. *J. Am. Chem Soc.* **1995**, *117*, 634. Nicolaou, K. C.; Yang, Z.; Liu, J.-J.; Nantermet, P. G.; Claiborne, C. F.; Renaud, J.; Guy, R. K.; Shibayama, K. *J. Am. Chem Soc.* **1995**, *117*, 645. Nicolaou, K. C.; Ueno, H.; Liu, J.-J.; Nantermet, P. G.; Yang, Z.; Renaud, J.; Paulvannan, K.; Chadha, R. *J. Am. Chem Soc.* **1995**, *117*, 653. (c) Masters, J. J., Link, J. T., Snyder, L. B., Young, W. B., Danishefsky, S. J. *Angew. Chem., Intl. Ed. Engl.* **1995**, *34*, 1723. Danishefsky, S. J.; Masters, J. J.; Young, W. B.; Link, J. T.; Snyder, L. B.; Magee, T. V.; Jung, D. K.; Isaacs, R. C. A.; Bornmann, W. G.; Alaimo, C. A.; Coburn, C. A.; Di Grandi, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 2843.

(2) For excellent recent reviews on the synthesis of taxanes, see: (a) Swindell, C. S. *Org. Prep. Proc. Intl.* **1992**, *23*, 465. (b) Nicolaou, K. D.; Dai, W.; Guy, R. *Angew. Chem. Intl. Ed. Engl.* **1994**, *33*, 15. (c) Boa, A. N.; Jenkins, P. R.; Lawrence, N. J. *Contemp. Org. Synth.* **1994**, 47.

(3) For the application of Diels−Alder cycloaddition to the synthesis of taxanes, see the following. Intermolecular A ring: (a) Nicolaou, K.; Hwang, C.; Sorenson, E. J.; Clairborne, C. F. *J. Chem. Soc., Chem. Commun.* **1992** 1117. Intramolecular A ring: (b) Shea, K. J.; Wise, S. *J. Am. Chem. Soc.* **1978**, *100*, 6519. (c) Bonnert, R. V.; Jenkins, P. R. *J. Chem. Soc., Perkin Trans. 1* **1989**, 413. Intermolecular C ring: (d) Nicolaou, K. C.; Liu, J.-J.; Hwang, C. K.; Dai, W.M.; Guy, R. K. *J. Chem. Soc., Chem. Commun.* **1992**, 1118. Intramolecular C ring: (e) Sakan, K.; Smith, D. A.; Babirad, S. A.; Fronczek, F. R.; Houk, K. N. *J. Org. Chem.* **1991**, *56*, 2311 and references cited therein. (f) Lu, Y.-F.; Fallis, A. G. *Tetrahedron Lett.* **1993**, 3367.

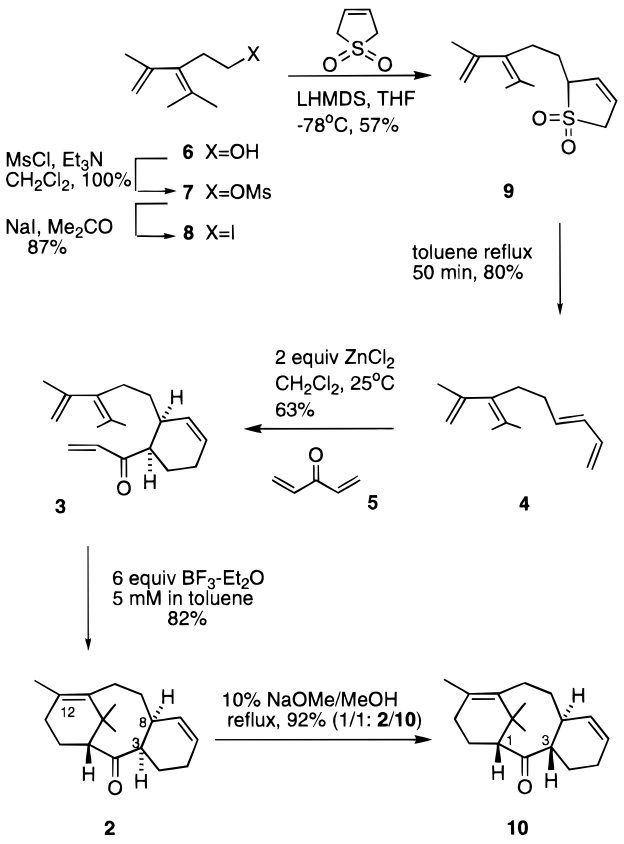
(4) Winkler, J. D.; Kim, S.; Condroski, K. R.; Asensio, A.; Houk, K. N. *J. Org. Chem.* **1994**, *59*, 6879.

(5) For a review on the use of the tandem Diels−Alder cycloaddition in organic synthesis, see: Winkler, J. D. *Chem. Rev.* **1996**, *96*, 167.

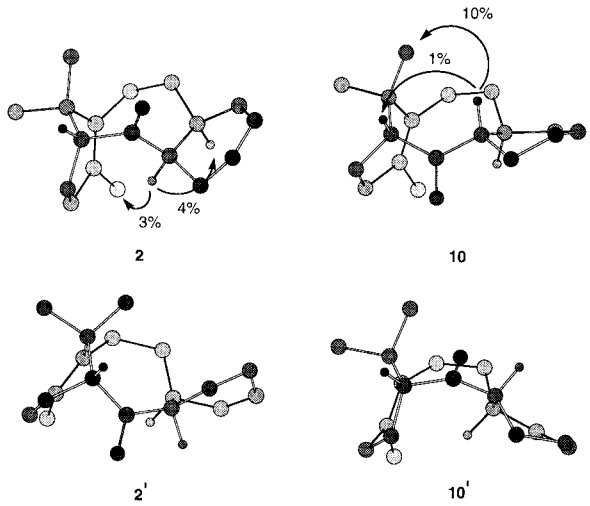
(6) For a preliminary account of some of this work, see: Winkler, J. D.; Kim, H. S.; Kim, S. *Tetrahedron Lett.* **1995**, *36*, 687.

S0022-3263(96)01620-9 CCC: $14.00

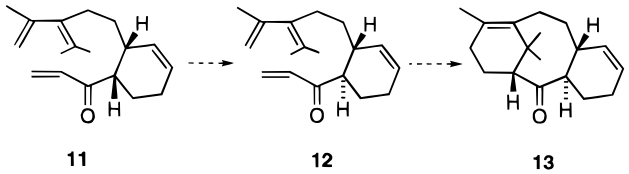
Scheme 2



Scheme 3



Scheme 4



Results and Discussion

The preparation of the requisite tetraene **4** is outlined in Scheme 2. The known diene alcohol **6**[7] was converted to the corresponding mesylate **7**, which on reaction with sodium iodide provided iodide **8**. Reaction of the monoanion of butadiene sulfone with **8** gave **9** in 57% yield (based on recovered starting material).[8] Extrusion of SO_2 from **9** resulted in the formation of **4**.

The intermolecular Diels–Alder reaction of **4** with **5** proceeded *via* $ZnCl_2$ catalysis to give cyclohexene **3** in 63% yield. In contrast to our preliminary study of the tandem Diels–Alder reaction,[6] we find here that the difference in reactivity of the mono- and tetrasubstituted diene units in **4** is sufficiently great that protection of the second diene moiety is not necessary for this highly regioselective cycloaddition to occur. The second, *intramolecular*, Diels–Alder cycloaddition occurs via BF_3·Et_2O catalysis to give the tricyclic ketone **2** as a single diastereomer in 82% yield. It is interesting to note that neither Lewis acid is capable of catalyzing both Diels–Alder reactions.

The stereochemistry of **2** could be unambiguously established by ^{1}H NOE experiments on **2** and on **10** (the C-3 epimer obtained on equilibration of **2** under basic reaction conditions).[9] As shown in Scheme 3, the cis relationship of the C-3 and C-8 hydrogens in **2**, as well as the proximity of the C-12 allylic methyl group to the C-3 hydrogen, could be established by 4% and 3% NOE's, respectively. In contrast, the equilibrated B/C trans-fused isomer **10** gave a 10% NOE from the C-3 hydrogen to one of the two C-15 quarternary methyl groups and a 1% NOE from the C-3 to the C-1 hydrogen. These experiments are consistent with the MM2-minimized conformations of **2** (cis) and **10** (trans), in which the conformation of **2** shown in Scheme 3 is ca. 7 kcal/mol more stable than the conformation in which the orientation of the carbonyl is as shown in **2′** (Scheme 3). Similarly, the conformation of **10** shown in Scheme 3 is ca. 4.5 kcal/mol more stable than that shown in **10′**. These results highlight the significance of the B/C ring fusion stereochemistry in controlling the conformation of the central B ring.[10]

A critical feature of the second, *intramolecular* Diels–Alder cycloaddition reaction, **3** → **2**, in this cascade is the transmission of stereochemical information across the taxane framework, i.e., from the C ring (C-3 and C-8) to the A ring (C-1). While the intramolecular Diels–Alder cycloaddition to form the A ring of the taxanes has been reported starting with aromatic C-ring substrates and trans-disubstituted saturated C-ring substrates, this is the first example of the intramolecular cycloaddition of a saturated cis-disubstituted C-ring substrate. It is noteworthy that this reaction leads to the exclusive establishment of the desired C-1/C-3 relative stereochemistry between the two six-membered rings of the taxane system. In an effort to understand the basis for the high level of stereochemical control in the cycloaddition of **3**, the cycloaddition of a trans-disubstituted intramolecular Diels–Alder substrate, **12**, was next examined.

We reasoned that the most efficient method for the preparation of the trans-disubstituted Diels–Alder substrate **12** (Scheme 4) would be to effect epimerization of the corresponding cis isomer, **11**.[11] In the event, however, exposure of **11** to either acidic or basic reaction conditions

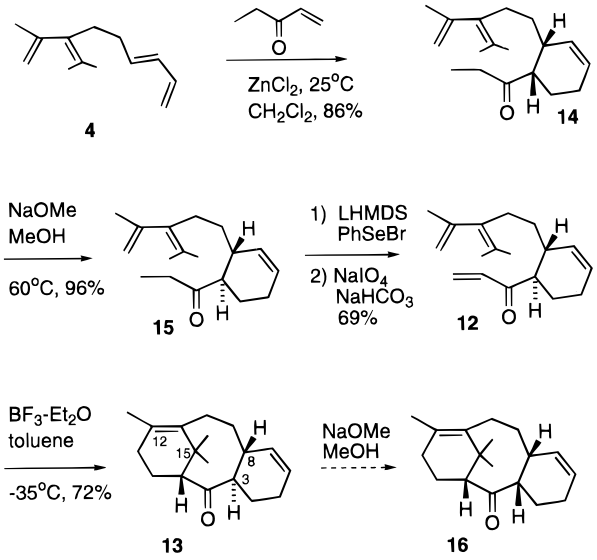
(7) We thank Professor Kenneth J. Shea (University of California, Irvine) for kindly supplying the experimental procedure for the preparation of **6**.

(8) (a) Chou, S.-S. P.; Lee, C. S.; Cheng, M. C.; Tai, H. P. *J. Org. Chem.* **1994**, *59*, 2010. (b) Chou, T. S.; Hung, S. C.; Tso, H.-H. *J. Org. Chem.* **1987**, *52*, 3394.

(9) Exposure of **2** to 10% methanolic sodium methoxide at reflux for 72 h led to a 1:1 mixture of **2** and its C-3 epimer **10**.

(10) For an insightful analysis of related conformational effects in the taxane ring system, see: Swindell, C. S.; Patel, B. P. *Tetrahedron Lett.* **1987**, *28*, 5275.

Scheme 5



resulted only in the decomposition of starting material. The sequence outlined in Scheme 5 was then developed for the synthesis of **12**. Intermolecular Diels−Alder cycloaddition of **4** with ethyl vinyl ketone led to the formation of the cis-disubstituted cyclohexene **14** in 86% yield. C-3 epimerization could then be efficiently achieved via exposure of **14** to refluxing sodium methoxide in methanol to give **15** in 96% yield (>94% trans). Introduction of the dienophilic alkene was then achieved via selenation and oxidation to give **12**. Exposure of **12** to $BF_3{\cdot}Et_2O$ led to the exclusive formation of **13** in 72% yield. Once again, the desired C-1/C-3 relative stereochemical relationship was established in the intramolecular cycloaddition reaction. The stereochemical assignments shown in **13** were unambiguously established by NOE experiments which revealed a 4.7% enhancement of the C-12 methyl group on irradiation of the C-3 proton, as well as a 3.7% enhancement of the C-15α methyl group on irradiation of the C-8 proton.

In contrast to the epimerization of the cis-B/C-fused cycloadduct **2**→**10** (Scheme 2), exposure of **13** to the epimerization conditions led to none of the cis isomer **16**, a result that is consistent with Swindell's observations in the B/C trans-fused C-8 angularly methylated series.[2a] The establishment of the desired C-1/C-3 relative stereochemistry (taxane numbering) in the cycloaddition of both the cis- and trans-disubstituted substrates **3** and **12** clearly indicates that the C-8 stereochemistry is not an important factor in the asymmetric induction observed in the cycloaddition.

In an effort to determine the factors governing the observed stereoselectivities, the transition state structures of the cycloadditions of **3** and **12** were analyzed by a systematic Monte Carlo conformational search and subsequent energy minimizations using the force field method described by one of us for internally activated Diels−Alder reactions.[12] The calculations show an energy difference of 1.7 kcal/mol between the lowest energy transition structures leading to **2** and **17** (epimeric with **2** at C-1), favoring the formation of **2**, as is experimentally observed. However, the lowest energy transition structures leading to **13** and **18** (epimeric with **13** at C-1) are equal in energy, whereas experimentally only **13** is observed. Because of the disagreement between the calculated and the experimental ratio in the intramolecular Diels−Alder reaction of **12**, we performed *ab initio* calculations on these intramolecular Diels−Alder reactions. At first, four transition structures for the reaction of the **3**−BH_3 complex were optimized with HF/3-21G calculations, using the GAUSSIAN94 program.[13] The BH_3 group was located on both sides of the carbonyl

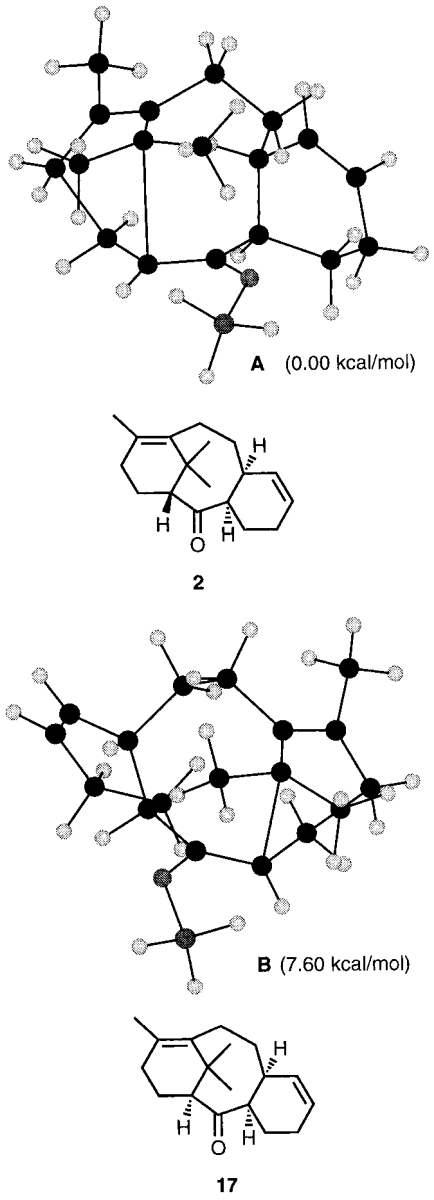
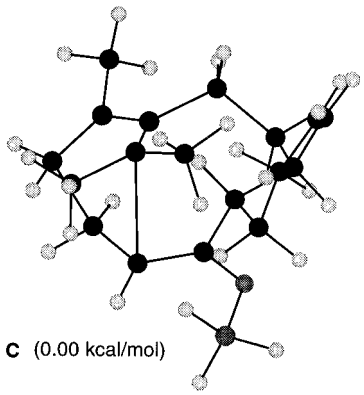


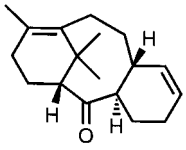
Figure 1. Transition structures of the Diels−Alder reaction of the **3**−BH_3 complex at RHF/3-21G.

(11) While **11** is the enantiomer of **3** (Scheme 2), all experiments were conducted in the racemic series. The different enantiomers are depicted to correlate with the requisite absolute C-3α hydrogen stereochemistry of the taxanes.

(12) Raimondi, L.; Brown, F. K.; Gonzalez, J.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 4796. The force field was implemented in MACROMODEL, Version 4.0 (Mohamadi, F., Richards, N. Guida, W., Liskamp, R., Caufield, C., Chang, G. Hendrickson, T. Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440) incorporating changes necessary for compatibility of these parameters with the MM2* force field.

(13) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. W.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox., D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A., Gaussian, Inc., Pittsburgh, PA, 1995.





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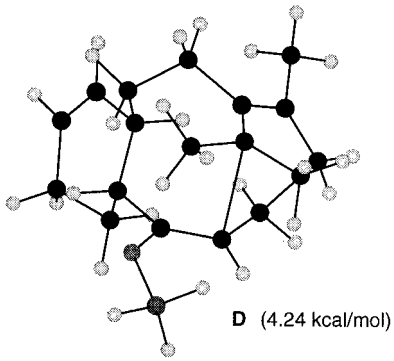

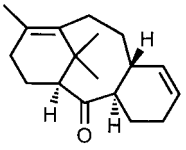

18

Figure 2. Transition structures of the Diels–Alder reaction of the **4**–BH_3 complex at RHF/3-21G.

oxygen and the structures having BH_3 in the syn position to the vinyl group turned out to be substantially more stable. The two lowest energy transition structures A and B, leading to **2** and **17**, respectively, are shown in Figure 1. Vibrational frequency calculations gave one imaginary frequency for all transition structures and confirmed that the structures are authentic transition structures. These transition structures are highly asynchronous, and the forming bond lengths are 1.89 and 3.23 Å in A and 1.88 and 3.21 Å in B. The transition structure B leading to unobserved **17** is less stable than A by 7.6 kcal/mol. Four transition structures for the reaction of the **12**–BH_3 complex were also located with RHF/3-21G calculations, and the two lowest energy transition state structures are shown in Figure 2. These two transition strucutres are also highly asynchronous, and forming bond lengths are 1.83 and 3.50 Å in C and 1.89 and 3.23 Å in D. The transition structure D leading to the undetected **18** is less stable than structure C by 4.2 kcal/mol.

As described in our earlier study,[4] the dienophiles adopt an *S*-trans conformation as a consequence of Lewis

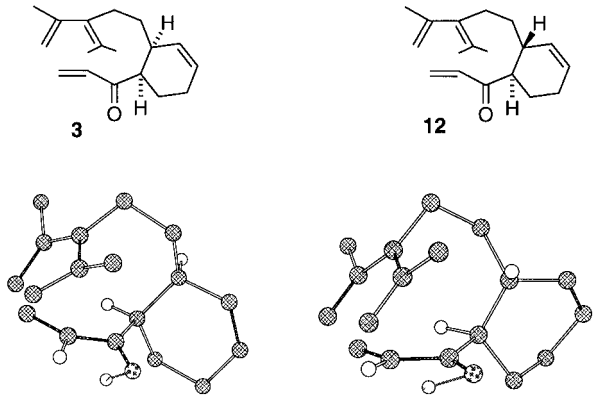

Figure 3.

acid coordination. Local conformation control therefore leads to the establishment of the C-1/C-3 anti stereochemical relationship, independent of the C-8 hydrogen stereochemistry as shown in Figure 3 for **3** and **12**.

Conclusion

We have demonstrated that the tandem Diels–Alder cycloaddition affords an effficient method for the stereoselective construction of the tricyclic ring system of the taxanes. The exceedingly direct, *two-step* synthesis of the B/C cis-fused taxane nucleus in 50% overall yield from the readily available acyclic precursors **4** and **5** underscores the efficiency of this approach. A critical feature of the second, *intramolecular* Diels–Alder cycloaddition reaction, **3** → **2** and **12** → **13**, in this cascade is the transmission of stereochemical information across the taxane framework, i.e., from the C ring (C-3 and C-8) to the A ring (C-1). This study establishes that the intramolecular Diels–Alder cycloaddition of both *cis*-**3** and *trans*-**12** leads to the establishment of the critical C-1/C-3 anti stereochemical relationship that is required for the synthesis of taxanes.

Experimental Section

Mesylate 7. To a stirred and cooled (0 °C) solution of alcohol **6** (2 g, 14.3 mmol) and triethylamine (6.0 mL, 43.1 mmol) in dry CH_2Cl_2 (50 mL) was added, dropwise, methanesulfonyl chloride (1.55 mL, 20.0 mmol). The resulting solution was stirred for 2 h at the same temperature, then poured into saturated aqueous $NaHCO_3$, and extracted with Et_2O (2 × 30 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give the desired mesylate **7** (3.60 g, 100% crude yield).

^{1}H NMR ($CDCl_3$, 250 MHz): δ 4.95 (bs, 1H), 4.55 (bs, 1H), 4.13 (t, J = 7.5 Hz, 2H), 2.95 (s, 3H), 2.53 (t, J = 7.5 Hz, 2H), 1.74 (bs, 3H), 1.68 (s, 3H), 1.65 (s, 3H). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 145.2, 130.2, 129.6, 114.3, 68.2, 37.3, 30.5, 22.3, 21.6, 19.7. FT-IR (film, cm^{-1}): 3076, 2967, 2914, 2859, 1632, 1446, 1356, 1175. HRMS calcd for $C_{10}H_{18}O_3S$ (M + NH_4) 236.1321, found 236.1317.

Iodide 8. The crude product from the previous reaction was dissolved in acetone (30 mL) and treated with NaI (6.42 g, 42.8 mmol), and the resulting mixture was heated to reflux for 4 h. The solvent was removed *in vacuo*, and the residue was dissolved in Et_2O (150 mL). The organic layer was washed with brine (3 × 20 mL), dried over magnesiun sulfate, filtered, and then concentrated under reduced pressure. Purification of the residue on silica gel (petroleum ether:ether = 10:1) affored the desired iodide (3.12 g, 87% from **6**) as a colorless oil.

^{1}H NMR ($CDCl_3$, 250 MHz): δ 4.95 (m, 1H), 4.60 (m, 1H), 3.09 (t, J = 8.0 Hz, 2H), 2.64 (t, J = 8.0 Hz, 2H), 1.73 (bs, 3H),

1.66 (s, 3H), 1.63 (s, 3H). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 144.8, 135.4, 128.2, 114.3, 35.3, 22.5, 21.8, 19.8, 4.6. FT-IR (film, cm^{-1}): 3073, 2963, 2924, 2855, 1632, 1442, 1372, 1243, 1166. HRMS: calcd for $C_9H_{15}I$ (M + NH_4) 268.0564, found 268.0573.

Sulfone 9. To a stirred and cooled (−78 °C) solution of iodide **8** (3.12 g, 12.5 mmol), HMPA (9.2 mL, 52.9 mmol), and butadiene sulfone (8.34 g, 70.6 mmol) in dry tetrahydrofuran (100 mL) was added dropwise lithium hexamethyldisilazide (1 M in toluene, 19.2 mL, 19.2 mmol) via syringe. The resulting reaction mixture was stirred for 2 h at the same temperature and then quenched with saturated aqueous $NaHCO_3$. The resulting mixture was partitioned between Et_2O (150 mL) and brine (20 mL). The separated organic layer was then washed with brine (5 × 20 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Purification of the residual oil on silica gel (hexane:ethyl acetate = 5:1) gave 1.01 g of recovered starting material and the desired alkylated sulfone (1.20 g, 40%; 57% based on recovered starting material).

^{1}H NMR ($CDCl_3$, 250 MHz): δ 5.91−6.06 (m, 2H), 4.94 (m, 1H), 4.54 (m, 1H), 3.52−3.83 (m, 3H), 2.28 (m, 2H), 1.52−2.04 (m, 2H), 1.73 (bs, 3H), 1.68 (s, 3H), 1.65 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 145.6, 134.5, 130.5, 127.2, 122.8, 114.0, 64.0, 55.6, 27.8, 27.3, 22.5, 21.8, 19.7. FT-IR (film, cm^{-1}): 3073, 2922, 1630, 1445, 1409, 1373, 1305, 1243, 1162, 1117. HRMS: calcd for $C_{13}H_{20}O_2S$ (M + 1) 241.1262, found 241.1274.

Tetraene 4. A mixture of alkylated sulfone (1.20 g, 4.99 mmol) and dry toluene (70 mL) was refluxed for 50 min. Toluene was removed under reduced pressure, and the residue was purified by flash column chromatography (hexane only) to afford bisdiene **4** (705 mg, 80%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.27 (dt, J = 17.0, 10.4 Hz, 1H), 6.04 (bdd, J = 15.2, 10.4 Hz, 1H), 5.69 (dt, J = 15.2, 6.8 Hz, 1H), 5.07 (bd, J = 17.0 Hz, 1H), 4.82−4.96 (m, 2H), 4.54 (m, 1H), 2.00−2.21 (m, 4H), 1.74 (bs, 3H), 1.53−1.64 (two singlets, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 146.4, 137.3, 135.9, 135.3, 130.8, 125.5, 114.6, 113.3, 31.5, 30.7, 22.7, 21.7, 19.6. FT-IR (film, cm^{-1}): 3073, 2933, 1632, 1444, 1372, 1112. HRMS: calcd for $C_{13}H_{20}$ (M + 1) 177.1643, found 177.1652.

Diels−Alder Monoadduct 3. To a stirred solution of bisdiene **4** (540 mg, 3.07 mmol) and divinyl ketone (0.46 mL, 4.60 mmol) in dry CH_2Cl_2 (26.4 mL) at 25 °C was rapidly added zinc chloride (1 M solution in Et_2O, 6.6 mL, 6.6 mmol). After being stirred for 12 h, the reaction mixture was poured into pH 7 phosphate buffer solution (100 mL). The aqueous layer was extracted with Et_2O (3 × 60 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Purification of the residue on silica gel (petroleum ether:ether = 15:1) afforded the endo Diels−Alder adduct **3** (540 mg, 68%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.44 (dd, J = 17.5, 10.6 Hz, 1H), 6.22 (dd, J = 17.5, 1.4 Hz, 1H), 5.10−5.83 (m, 2H), 5.69 (dd, J = 10.6, 1.4 Hz, 1H), 4.82 (m, 1H), 4.44 (m, 1H), 2.94 (pseudo ddd, J = 7.0, 6.8, 5.6 Hz, 1H), 2.46 (m, 1H), 1.87−2.13 (m, 4H), 1.68−1.76 (m, 2H), 1.66 (s, 3H), 1.59 (s, 3H), 1.57 (s, 3H), 1.10−1.29 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 202.3, 146.2, 136.3, 135.1, 129.6, 127.4, 126.9, 125.2, 113.2, 48.5, 36.3, 30.5, 28.8, 24.6, 22.6, 21.6, 19.5, 19.4. FT-IR (film, cm^{-1}): 3074, 3022, 2917, 1698, 1674, 1613, 1446, 1403, 1372, 1301, 1269, 1177, 1121. HRMS: calcd for $C_{18}H_{26}O$ (M + 1) 259.2062, found 259.2055.

Tricyclic Ketone 2. To a cooled (−70 °C), stirred solution of **3** (50 mg, 0.193 mmol) in dry toluene (40 mL) was added $BF_3{\cdot}Et_2O$ (0.14 mL, 1.10 mmol). The temperature of the solution was then slowly allowed to warm to 0 °C with stirring over 24 h. The resulting solution was quenched with saturated aqueous $NaHCO_3$ (10 mL), and 40 mL of Et_2O was then added to this mixture. After being stirred for 10 min at 25 °C, the separated organic layer was successively washed with distilled water (20 mL) and brine (20 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. Purification of the residue on silica gel (petroleum ether:ether = 15:1) gave a single isomer (41 mg, 82%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.73 (ddd, J = 10.2, 5.3, 2.7 Hz, 1H), 5.22 (dd, J = 10.2, 2.0 Hz, 1H), 3.08 (m, 1H), 2.67 (dt, J = 13.3, 6.2 Hz, 1H), 2.53 (m, 1H), 2.32−2.46 (m, 2H), 2.32 (d, J = 7.7 Hz, 1H), 2.11 (m, 1H), 2.07 (ddd, J = 18.4, 10.1, 2.4 Hz, 1H), 1.99 (dddd, J = 14.8, 11.0, 7.8, 2.5 Hz, 1H), 1.83 (m, 1H), 1.81 (dt, J = 10.2, 5.0 Hz, 1H), 1.75 (s, 3H), 1.42−1.61 (m, 4H), 1.19 (s, 3H), 1.08 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 219.0, 137.0, 131.0, 130.6, 126.7, 61.9, 41.3, 38.2, 36.5, 34.1, 29.0, 28.4, 27.1, 24.9, 24.61, 21.5, 21.5, 19.0. FT-IR (film, cm^{-1}): 3015, 2916, 1693, 1682. HRMS: calcd for $C_{18}H_{26}O$ (M + 1) 259.2062, found 259.2050.

Trans Ketone 10. A mixture of tricyclic ketone **2** (80 mg, 0.31 mmol) and 10% sodium methoxide in methanol (7.5 mL) was heated at reflux for 3 days. Evaporation of solvent *in vacuo* gave a residue which was dissolved in Et_2O (60 mL). This solution was successively washed with distilled water (20 mL) and brine (2 × 20 mL), then dried over magnesium sulfate, filtered, and concentrated under reduced pressure. Purification of the residue on silica gel (petroleum ether:diethyl ether = 15:1) afforded a new product (**10**) (35 mg, 44%) and recovered starting material (38 mg, 48%).

^{1}H NMR (C_6D_6, 500 MHz): δ 5.70 (m, 1H), 5.39 (bd, J = 10.0 Hz, 1H), 2.82 (ddd, J = 12.1, 8.5, 3.4 Hz, 1H), 2.60 (m, 1H), 2.39 (dt, J = 14.0, 9.9 Hz, 1H), 2.10−2.25 (m, 2H), 2.06 (d, J = 3.8 Hz, 1H), 1.92−2.05 (m, 3H), 1.61−1.79 (m, 5H), 1.51 (m, 1H), 1.46 (s, 3H), 1.39 (s, 3H), 0.96 (s, 3H). ^{13}C NMR (C_6D_6, 125 MHz): δ 212.2, 137.7 133.9, 132.2, 126.4, 60.1, 51.1, 39.5, 36.9, 36.7, 30.5, 29.6, 28.0, 27.8, 25.3, 24.3, 21.6, 20.3. FT-IR (film, cm^{-1}): 2914, 1682. HRMS: calcd for $C_{18}H_{26}O$ (M + 1) 259.2062, found 259.2067.

Cis Ketone 14. To a stirred solution of bisdiene **4** (163 mg, 0.926 mmol) and ethyl vinyl ketone (0.10 mL, 1.00 mmol) in dry CH_2Cl_2 (7 mL) at room temperature was rapidly added a 1 M solution of zinc chloride (in diethyl ether, 2.0 mL, 2.0 mmol). After the solution was stirred for 1 day at the same temperature, ethyl vinyl ketone (0.03 mL, 0.03 mmol) was added and the mixture was stirred for an additional 3 days and quenched by addition of saturated aqueous $NaHCO_3$ (5 mL). The resulting mixture was partitioned between diethyl ether (20 mL) and brine (20 mL), and the organic layer was separated. The aqueous layer was extracted with diethyl ether (20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, concentrated in vacuo, and purified by flash column chromatography (petroleum ether:ethyl acetate = 8:1) to give a mixture of the cis isomer **14** and the corresponding trans isomer (213 mg, 88%; ca. 17:1 as analyzed by proton NMR).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.80 (m, 1H), 5.68 (m, 1H), 4.87 (bs, 1H), 4.49 (bs, 1H), 2.69 (dt, J = 4.9, 10.2 Hz, 1H), 2.29−2.58 (m, 3H), 1.90−2.21 (m, 4H), 1.55−1.80 (m, 2H), 1.69 (d, J = 0.7 Hz, 3H), 1.62 (s, 3H), 1.61 (s, 3H), 1.05−1.31 (m, 2H), 1.02 (t, J = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 214.5, 146.3, 136.3, 129.7, 127.0, 125.3, 113.2, 50.5, 36.4, 34.2, 30.7, 28.7, 24.8, 22.6, 21.7, 19.6, 19.4, 7.7. FT-IR (film, cm^{-1}): 2937, 1711. HRMS: calcd 261.2218 for $C_{18}H_{28}O$ (M + 1), found 261.2213.

Trans Ketone by Epimerization of 15. A mixture of cis ketone **14** (204 mg, 0.783 mmol) and 2.3% sodium methoxide solution (in methanol, 44 mL) was stirred at 60−65 °C for 3 days. The reaction was monitored by proton NMR spectra. Methanol was removed in vacuo. The residue was partitioned between water (20 mL) and diethyl ether (20 mL). The organic layer was separated, and the aqueous layer was extracted with diethyl ether (20 mL × 2). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, evaporated in vacuo, and purified by flash column chromatography (petroleum ether:ethyl acetate = 8:1) to afford an equilibrated mixture (196 mg, 96%) as a mixture of the trans isomer **15** and the cis isomer **14** (ca. 11:1).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.57−5.72 (m, 2H), 4.86 (bs, 1H), 4.48 (bs, 1H), 2.31−2.61 (m, 3H), 1.92−2.14 (m, 3H), 1.50−1.83 (m, 4H), 1.71 (s, 3H), 1.62 (two singlets, 6H), 1.13−1.36 (m, 2H), 1.03 (t, J = 7.4 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 214.6, 146.4, 136.4, 130.3, 125.9, 125.0, 114.1, 51.9, 36.4, 35.0, 33.0, 27.9, 25.6, 24.8, 22.7, 21.7, 19.5, 7.79. FT-IR (film, cm^{-1}): 2978, 2925, 2849, 1712, 1672. HRMS: calcd 261.2218 for $C_{18}H_{28}O$ (M + 1), found 261.2226.

Trans Enone 12. To a stirred solution of trans ketone **15** (100 mg, 0.384 mmol) in dry THF(15 mL) at 0 °C was rapidly

added a THF solution of 1 M LHMDS (0.5 mL, 0.5 mmol). The resulting solution was stirred for an additional 30 min at the same temperature, followed by the addition of solid benzeneselenenyl bromide (100 mg, 0.424 mmol). After 10 min at 0 °C, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (20 mL) and was then extracted with diethyl ether (20 mL × 3). The organic extracts were dried over anhydrous $MgSO_4$, filtered, concentrated in vacuo, and purified by flash column chromatography (hexane:ethyl acetate = 35:1) to give the α-selenenyl ketone (153 mg) as a mixture of diastereomers (ca. 1:1).

The selenides were dissolved in methanol/water (6 mL/1 mL), followed by the succesive addition of solid sodium bicarbonate (48 mg, 0.571 mmol) and sodium metaperiodate (164 mg, 0.770 mmol). After the solution was stirred at room temperature for 1 h, the solvent was removed in vacuo, the residue was partitioned between diethyl ether (20 mL) and water (20 mL), and the organic layer was separated. The aqueous layer was extracted with diethyl ether (20 mL × 2). The combined extracts were dried over anhydrous $MgSO_4$, filtered, concentrated in vacuo, and purified by flash column chromatography (hexane:ethyl acetate = 15:1) to give a mixture of the trans enone **12** and the cis enone **3** (69 mg, 69% from **15**; trans:cis = 14:1).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.43 (dd, J = 17.5, 10.6 Hz, 1H), 6.24 (dd, J = 17.5, 1.4 Hz, 1H), 5.76 (dd, J = 10.6, 1.3 Hz, 1H), 5.62−5.72 (m, 2H), 4.84 (bs, 1H), 4.47 (bs, 1H), 2.74 (ddd, J = 11.7, 8.9, 3.0 Hz, 1H), 2.53 (bs,1H), 1.95−2.10 (m, 4H), 1.52−1.87 (m, 2H), 1.63 (bs, 3H), 1.60 (s, 3H), 1.59 (s, 3H), 1.18−1.31 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 203.4, 146.3, 136.4, 135.7, 130.4, 128.0, 125.9, 125.0, 113.1, 49.1, 36.3, 33.1, 28.1, 35.8, 24.7, 22.6, 21.66, 19.5. FT-IR (film, cm^{-1}): 2925, 1697, 1676, 1611. HRMS: calcd for $C_{18}H_{26}O$ (M + 1) 259.2062, found 259.2057.

Anti Trans Isomer 13. To a cooled (−35 °C), stirred solution of trans enone **12** (66 mg, 0.255 mmol) in dry toluene (26 mL) was added, dropwise, boron trifluoride etherate (94 mL, 0.742 mmol). After being stirred for 24 h at the same temperature, the reaction mixture was neutralized with saturated aqueous $NaHCO_3$ (10 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography (hexane:ethyl acetate = 100:1) gave pure anti trans isomer **13** (43.6 mg, 66%).

^{1}H NMR (C_6D_6, 500 MHz): δ 5.86 (m, 1H), 5.54 (m, 1H), 2.78 (d, J = 9.0 Hz, 1H), 2.69 (ddd, J = 12.7, 7.0, 4.5 Hz, 1H), 2.52 (m, 1H), 2.32−2.43 (m, 2H), 2.24 (qd, J = 12.8, 4.5 Hz, 1H), 2.15 (m, 1H), 1.76−1.96 (m, 4H), 1.70 (s, 3H), 1.63 (dddd, J = 17.0, 9.3, 7.6, 1.4 Hz, 1H), 1.44−1.54 (m, 3H), 1.19 (s, 3H), 1.10 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 218.9, 135.5, 133.2, 130.3, 126.1, 63.1, 48.1, 38.8, 37.7, 35.8, 29.0, 28.1, 28.0, 27.5, 25.9, 23.0, 21.3, 18.7. FT-IR (film, cm^{-1}): 3017, 2918, 2856, 1687. HRMS calcd for $C_{18}H_{26}O$ (M + NH_4) 276.2328, found 276.2325.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds synthesized (22 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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