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Progress towards an intramolecular Diels–Alder ring-expansion approach to taxinine: the interplay of Lewis acids and high pressure

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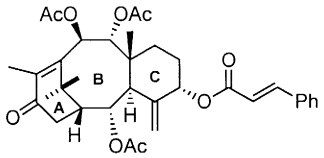
Abstract

A concise route to a bicyclo[4.2.1] ring system, based on an intramolecular Diels–Alder reaction, has been developed. Preliminary results on the interplay between Lewis acids and high pressure to facilitate the reaction are described. Products with isomerized double bonds were obtained with 1 equivalent of Lewis acid at 0°C. The stereochemistry of these compounds has been determined by X-ray crystallography. Double bond isomerization is suppressed by the use of excess Lewis acid at −78°C or high pressure. © 2000 Elsevier Science Ltd. All rights reserved.

The taxane class of natural products has generated a substantial amount of interest from the scientific community over the past decade.[1] This interest has been primarily driven by the clinical significance of the anti-cancer drugs paclitaxel and docetaxel. Several simpler taxanes also demonstrate interesting biological activity and we were attracted to taxinine (**1**) by its known ability to modulate multi-drug resistance in tumor cells.[2]



taxinine, **1**

Aside from those employed in the total syntheses,[1] a number of novel strategies have been explored as part of synthetic studies on the taxanes.[3] Shortly after their seminal paper[4] describing the type II intramolecular Diels–Alder (IMDA) reaction, the Shea group reported studies directed towards the taxanes based on an type II IMDA approach.[5] Although this approach has yet to result in a total synthesis, a number of groups have employed IMDA reactions as part of taxane synthetic studies. With these

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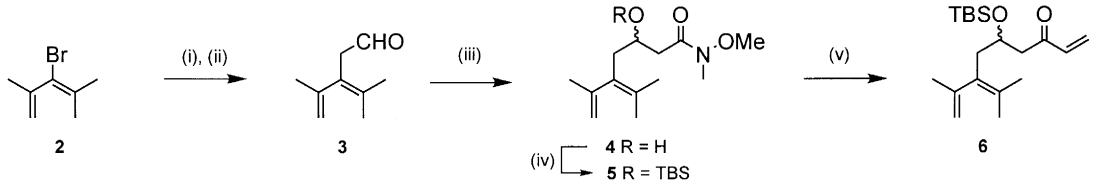
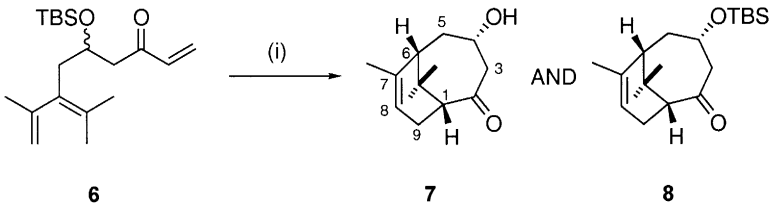
approaches, either the A or C ring is formed and the subsequent IMDA reaction is used to form the other two rings. In all cases the emphasis has been on forming the eight-membered ring directly. We were attracted to the possibility of using an IMDA reaction to assemble a bicyclo[4.2.1] ring system that would allow the exploration of a one-carbon ring expansion approach to the AB-ring system of taxinine.[6] It was felt that this approach would generate an appropriately functionalized AB-ring system to which the C-ring could be annealed in an efficient manner. In this paper we describe the preliminary results of this approach.

The synthesis of the IMDA substrate **6** is shown in Scheme 1.[7] The aldehyde **3**[8] is readily available in two steps from the bromodiene **2**.[9] The three step sequence [Scheme 1, steps (iii) to (v)] used to introduce the required enone functionality into the substrate utilizes enolate chemistry and the well known electrophilic properties of Weinreb amides. In the first step, an aldol reaction of **3** with the enolate obtained by treating *N*-methoxy-*N*-methylacetamide with lithium diisopropylamide at −78°C, gave adduct **4**. Reaction with *tert*-butyldimethylsilyl chloride then gave the protected aldol adduct **5** in a yield of 57% based on the aldehyde **3** after purification by flash chromatography. The final step involved addition of an excess of vinylmagnesium bromide to the Weinreb amide **5**, in THF at reflux, to afford the labile IMDA precursor **6** in 56% yield.



Scheme 1. Synthesis of the IMDA substrate. Reagents: (i) *t*-BuLi, THF, −78°C, 10 min then ethylene oxide, −78→0°C, quant.; (ii) DMSO, $(COCl)_2$, CH_2Cl_2, Et_3N, −78→25°C, 30 min; (iii) *N*-methyl-*N*-methoxyacetamide, LDA, THF, −78°C, 15 min, then **3**, −78°C, 30 min; (iv) TBSCl, DMF, imidazole, 25°C, 15 h, 57% for three steps; (v) CH_2=CHMgBr (2.5 equiv.), THF, reflux, 1 h, 56%

With compound **6** in hand, we set about studying the IMDA cyclization under a variety of conditions. Shea and Gilman have reported that similar IMDA reactions are slow when activated by heat, but can be dramatically accelerated using Lewis acids.[10] Disappointingly, exposure of **6** to either diethylaluminum chloride, or boron trifluoride diethyl etherate (one or two equivalents) in CH_2Cl_2 at −78°C proved ineffective at promoting the desired cycloaddition, with complex mixtures being isolated. However, treatment of the diene with one equivalent of boron trifluoride diethyl etherate in CH_2Cl_2 at 0°C for 30 min resulted in a cyclization with the formation of two new compounds, **7** and **8**, in 41% and 28% yield, respectively (Scheme 2).[7] From examination of the NMR spectra it was deduced that the only difference between **7** and **8** was the presence of the silyl group in **8**.[11] Surprisingly, these compounds were not the expected cycloadducts, but isomers where the double bond was at the $\Delta^{7,8}$ position[12] rather than the desired $\Delta^{6,7}$ position.



Scheme 2. Lewis acid promoted cyclization. Reagents: (i) $BF_3 \cdot OEt_2$ (1 equiv.), CH_2Cl_2, 0°C, 30 min, **7** (41%) and **8** (28%)

The gross structure and stereochemistry of these compounds was confirmed by conversion of **7** to the corresponding *p*-nitrobenzoate, which was subjected to a single crystal X-ray analysis (a perspective drawing with atomic labeling is shown in Fig. 1).[13] This analysis showed that the hydrogens at the ring-junction were *syn*, and the *p*-nitrobenzoate group was in an equatorial position. This stereochemistry is consistent with an *endo* cyclization via a chair conformation for the forming seven-membered ring.[14]

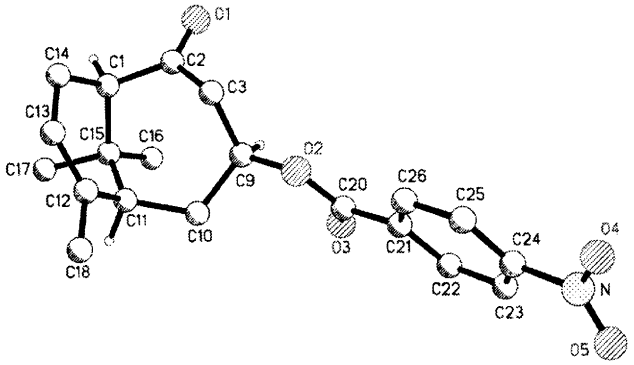
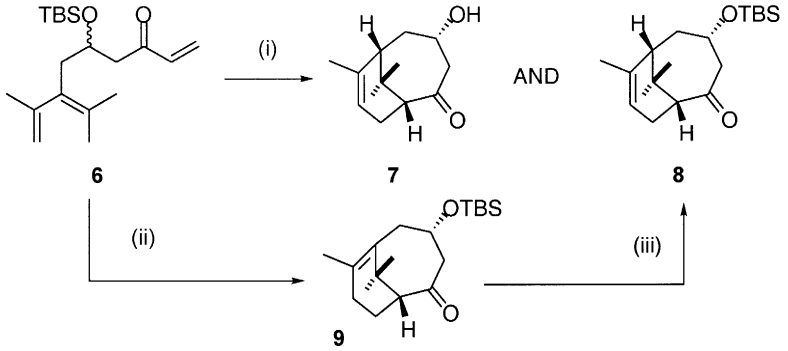


Fig. 1. An ORTEP representation of the *p*-nitrobenzoate of **7** showing the *syn* stereochemistry of the ring junction and the equatorial alcohol

Based on the expectation that the double-bond isomerization was occurring by a carbocation mechanism, we explored reactions of compound **6** at high pressure.[15] It was reasoned that the cycloaddition would be promoted under these conditions, whilst the isomerization should be retarded.[16] The results of preliminary experiments are summarized in Scheme 3. To our delight, the desired cyclization was realized at 25°C and 19 kbar to give Diels–Alder adduct **9**,[7] along with unreacted starting material in a ratio of 4:1[17] [see step (ii)]. The use of higher temperature at a lower pressure [see step (i)], in an effort to force the reaction to completion, resulted only in returned starting material and compounds **7** and **8** — the products of cyclization and double bond isomerization — in a ratio of 1:2:2.[17] The exact mechanisms of these processes and the reasons for the changes in product distribution at higher temperature remain unclear. To the best of our knowledge, the cyclization of **6** to give **7** under these conditions is the first example of a type II IMDA reaction at high pressure.[18]



Scheme 3. Lewis acid and high pressure promoted IMDA reaction. Reagents: (i) CH_2Cl_2, 55°C, 16 kbar, 64 h, 1:2:2 **6**:**7**:**8**: (by ^{1}H NMR)[17]; (ii) $BF_3 \cdot OEt_2$ (10 equiv.), CH_2Cl_2, −78°C, 1 h, (43% for two steps from **5**) or CH_2Cl_2, 25°C, 19 kbar, 24 h, 4:1 **9**:**6** (by ^{1}H NMR)[17]; (iii) $BF_3 \cdot OEt_2$ (2 equiv.), CH_2Cl_2, 0→25°C, 1 h

Concurrent with the work on the high pressure chemistry, it was discovered that exposure of **6** to a large excess of boron trifluoride diethyl etherate (10 equivalents) at −78°C also gave the desired product **9** (in 43% overall yield from **5**) (Scheme 3).[7] It is unclear why this reaction should proceed so well

when earlier experiments using only one or two equivalents of boron trifluoride diethyl etherate at −78°C afforded only complex mixtures. However, this result meant that a reliable method for forming the desired bicyclo[4.2.1] ring system was now available.

In summary, we have developed a concise route to a functionalized bicyclo[4.2.1] system via a type II IMDA reaction. The desired reaction can be promoted by either boron trifluoride diethyl etherate, or by the use of high pressure. Further studies on high pressure type II IMDA reactions, and progress towards taxinine will be reported in due course.

Acknowledgements

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7. Selected experimental data: IMDA substrate **6**: ^{1}H NMR δ −0.04 (s, 3H), 0.03 (s, 3H), 0.82 (s, 9H), 1.67 (s, 3H), 1.70 (s, 3H), 1.78 (bs, 3H), 2.26–2.42 (m, 2H), 2.57 (dd, 1H, *J*=3.4, 14.7 Hz), 2.72 (dd, 1H, *J*=8.3, 14.7 Hz), 4.20–4.28 (m, 1H), 4.59 (m, 1H), 4.99 (m, 1H), 5.81 (dd, 1H, *J*=1.5, 10.3 Hz), 6.19 (dd, 1H, *J*=1.5, 17.6 Hz), 6.33 (dd, 1H, *J*=10.7, 18.1 Hz). ^{13}C NMR δ −4.81, −4.49, 17.93, 20.34, 21.89, 22.61, 25.80, 29.69, 39.41, 46.41, 69.07, 114.18, 128.18, 133.08, 137.49, 145.90, 200.19. FTIR ($CDCl_3$, cm^{-1}) 1072.3, 1095.5, 1255.6, 1471.6, 1685.7, 2856.4, 2929.7, 2956.7. Isomerized Diels–Alder adducts **7** and **8***:* alcohol **7**: ^{1}H NMR δ 1.00 (s, 3H), 1.03 (s, 3H), 1.85 (bs, 1H), 1.87 (bd, 3H, *J*=2.4 Hz), 1.99–2.29 (m, 4H), 2.42–2.53 (m, 2H), 3.34 (dd, 1H, *J*=9.8, 12.2 Hz), 4.07 (m, 1H), 5.47 (bs, 1H). ^{13}C NMR δ 23.03, 26.26, 26.88, 29.59, 33.01, 33.25, 46.07, 49.59, 56.71, 67.29, 119.65, 138.58, 212.87. FTIR ($CDCl_3$, cm^{-1}) 1052.3, 1280.6, 1424.5, 1714.2, 2869.9, 3552.7. HRMS (EI) calcd for $C_{13}H_{20}O_2$: 208.14633; found: 208.14636. Selected data for silyl ether **8**: ^{1}H NMR δ 0.01 (s, 3H), 0.04 (s, 3H), 0.87 (s, 9H), 0.97 (s, 3H), 1.00 (s, 3H), 1.77 (s, 1H), 1.86 (bs, 3H), 1.88–2.32 (m, 4H), 3.36–2.62 (m, 2H), 3.39 (t, 1H, *J*=11.7 Hz), 4.09 (m, 1H), 5.42 (bs, 1H). HRMS (EI) calcd for $C_{15}H_{25}O_2Si$ [$M^+-C_4H_9$]: 265.16238; found: 265.16228. $BF_3\cdot OEt_2$ promoted IMDA to give **9***:* ^{1}H NMR δ 0.03 (s, 3H), 0.05 (s, 3H), 0.85 (s, 9H), 1.01 (s, 3H), 1.08 (s, 3H), 1.52–1.63 (m, 1H), 1.84 (s, 3H), 2.00–2.22 (m, 3H), 2.46–2.66 (m, 4H), 2.81–2.89 (m, 1H), 4.15 (m, 1H). ^{13}C NMR δ −4.93, −4.76, 17.91, 22.20, 22.49, 25.73, 25.98, 28.06, 28.99, 36.11, 38.85, 51.05, 62.61, 70.43, 133.79, 135.27, 213.53. FTIR ($CDCl_3$, cm^{-1}) 1057.6, 1273.6, 1421.7, 1719.9, 2869.2. HRMS (EI) calcd for $C_{19}H_{34}O_2Si$: 322.23281; found: 322.23323.
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9. Bromodiene **2** is readily prepared in large quantities from 2,3-dimethylbut-2-ene as described by Magnus, P.; Westwood, N.; Spyvee, M.; Frost, C.; Linnane, P.; Tavares, F.; Lynch, V. *Tetrahedron* **1999**, *55*, 6435 and references cited therein.
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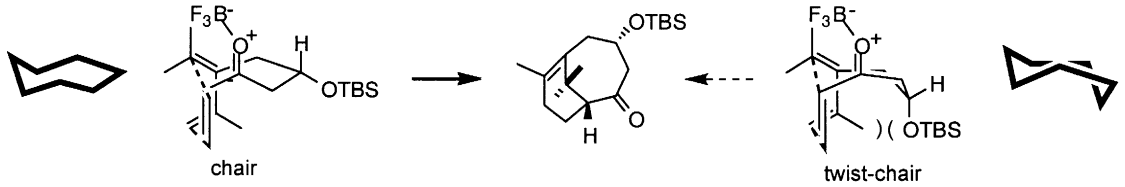
11. Rigorous purification of the boron trifluoride diethyl etherate, and all efforts to ensure complete exclusion of moisture failed to suppress desilylation.
12. The numbering system used is based on the system used for taxanes.
13. The *p*-nitrobenzoyl derivative was readily prepared by treatment with *p*-nitrobenzoyl chloride (Et_3N, DMAP, CH_2Cl_2, 0°C to 25°C, 12 h). ^{1}H NMR δ 1.06 (s, 3H), 1.11 (s, 3H), 1.84 (bs, 3H), 1.92 (bs, 1H), 2.16–2.24 (m, 2H), 2.33–2.58 (m, 3H),

2.73 (dd, 1H, *J*=4.4, 11.7 Hz) 3.44 (dd, 1H, *J*=9.8, 11.7 Hz), 5.37 (m, 1H), 5.50 (bs, 1H), 8.13 (d, 2H, *J*=8.8 Hz), 8.27 (d, 2H, *J*=8.8 Hz). ^{13}C NMR δ 23.05, 26.63, 27.04, 29.42, 30.42, 32.84, 45.31, 46.11, 56.64, 70.57, 119.63, 123.51, 130.64, 135.55, 137.00, 150.56, 163.65, 211.03. FTIR ($CDCl_3$, cm^{-1}) 1105.1, 1280.6, 1463.9, 1525.6, 1699.2, 1716.5, 2854.5, 2954.7. HRMS (EI) calcd for $C_{20}H_{23}NO_5$: 357.15762; found: 357.15793. Crystal data and structure refinement: $C_{18}H_{22}NO_5$. T=162(2) K. Wavelength 0.71073 Å. Triclinic. Space group=P-1. Unit cell dimensions *a*=7.011(2) Å, *a*=83.099(4)°; *b*=7.292(2) Å, *b*=83.957(4)°; *c*=18.357(6) Å, *g*=73.564(4)°. Volume=891.0(5) Å^3. *Z*=2. Density (calcd)=1.239 Mg/m^3. Absorption coefficient=0.090 mm^{-1}. F(000)=354. Crystal size=14×42×8 mm^3. Theta range for data collection 3.03 to 26.41°. Index ranges: −8<=h<=8, −3<=k<=8, −22<=l<=22. Reflections collected: 4223. Independent reflections: 3256 [R(int)=0.0284]. Completeness to theta=26.41° (89.0%). Absorption correction: none. Refinement method: full-matrix least-squares on F^2. Data/restraints/parameters: 3256/0/238. Goodness-of-fit on F^2=.888. Final R indices [I>2sigma(I)]: R1=0.0435, wR2=0.1016. R indices (all data): R1=0.0793, wR2=0.1116. Largest diff. peak and hole: 0.326 and −0.236 e.Å^{-3}.

14. It is conceivable that the cyclization could occur via either a chair or a twist chair conformation for the forming seven-membered ring. We favor the chair conformation because modeling indicated the twist-chair conformation has a potential unfavorable interaction between the silyl ether and the diene methyl group:



15. For a review of high pressure in synthesis, see: Matsumoto, K.; Sera, A.; Uchida, T. *Synthesis* **1985**, 1.
16. For a study of a type I IMDA reaction and discussion of the effect of pressure on competing processes, see: Diedrich, M. K.; Klarner, F. G. *J. Am. Chem. Soc.* **1998**, *120*, 6212.
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