Facile construction of the bicyclo[6.4.0]dodecane system by the intramolecular Michael addition of sulfonyl carbanion

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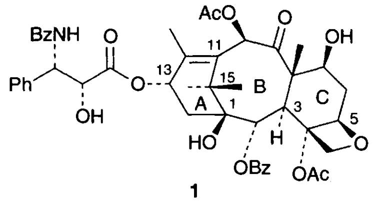
A bicyclo[6.4.0]dodecane system is synthesised *via* the intramolecular Michael addition of sulfonyl carbanion.

The potent antitumour agent taxol **1**, a diterpene isolated from the Pacific yew tree (*Taxus brevifolia*),[1] is an attractive synthetic target for organic chemists. Many synthetic approaches to taxol and its analogues have been reported,[2] and recently the total synthesis of taxol has been accomplished by three groups.[3] Nevertheless, an efficient method for the construction of the eight-membered ring (B-ring) has been a major problem. We report here a facile construction of the bicyclo[6.4.0]dodecane system *via* an intramolecular Michael addition of sulfonyl carbanion.

It is well known that the Michael addition of sulfonyl carbanion is a powerful method for carbon–carbon bond formation,[4] especially for the synthesis of cyclopropanecarboxylates.[5] However, its intramolecular version has not been reported. Therefore, we first examined the intramolecular Michael addition of the carbanion derived from sulfone **5** under various conditions.

The substrate **5** was prepared as follows (Scheme 1). Aldehyde **2**[6] was converted into **3** by the Wittig reaction using $Ph_3P^+CH_2(CH_2)_3CH_2OBnBr^-$† in the presence of BuLi, followed by reductive deprotection. Sulfenylation[7] of **3** and the subsequent oxidation[8] gave sulfone **4**. The cyclohexa-2,5-diene moiety of **4** was oxidized with a catalytic amount of tetrapropylammonium perruthenate (TPAP) and 4-methylmorphorine *N*-oxide (NMO)[9],‡ to give **5**.



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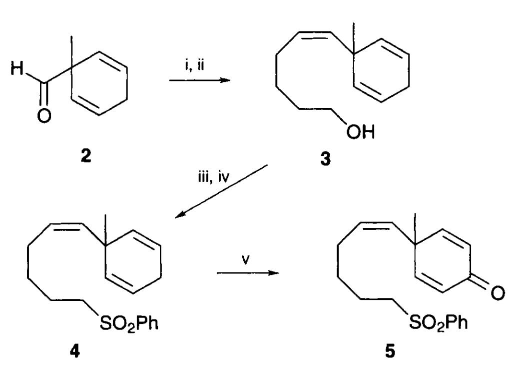
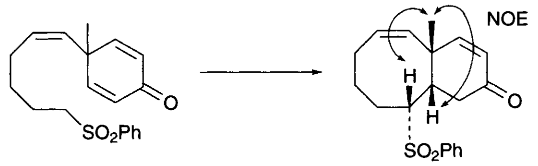


Scheme 1 *Reagents and conditions*: i, $Ph_3P^+CH_2(CH_2)_3CH_2OBnBr^-$, BuLi, THF, −78 → 0 °C; ii, Na, liq. NH_3, THF–Bu^{t}OH (10 : 1), −78 °C (27% for 2 steps); iii, $(PhS)_2$, Bu_3P, pyridine (100%); iv, OXONE®, THF–MeOH–H_2O (3 : 1 :) (95%); v, 10 mol% TPAP, NMO, 4 Å molecular sieves, MeCN (74% based on recovered starting material)

Results of the key reaction of **5** are summarized in Table 1. Treatment of **5** with LDA in the presence of HMPA gave a poor result (entry 1). When **5** was treated with $LiN(TMS)_2$ in the presence of HMPA, the bicyclic compound **6** was produced in

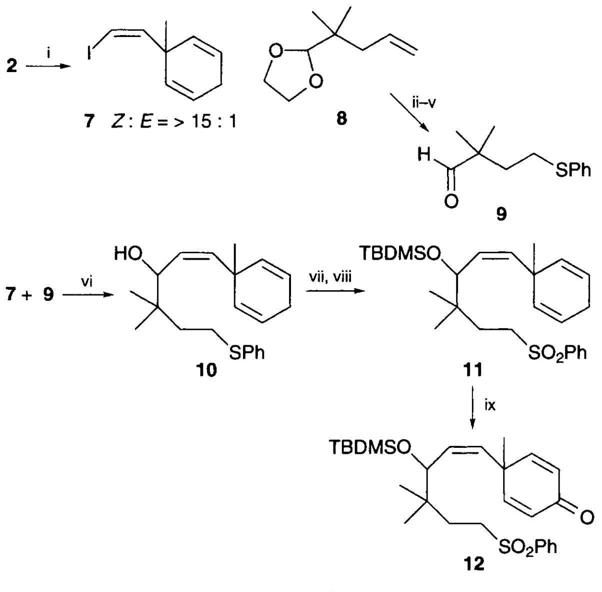
Table 1 Intramolecular Michael reaction of sulfone **5**[a]



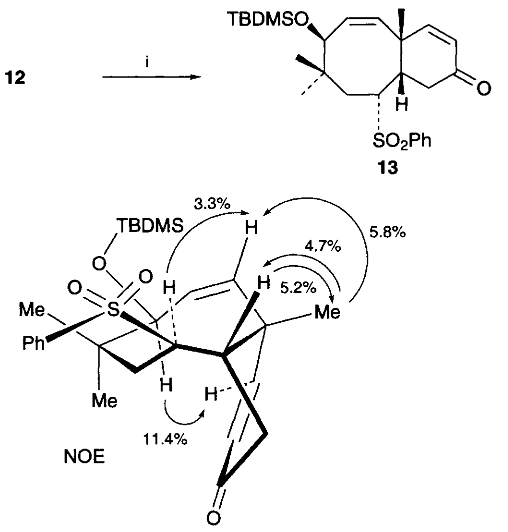
5 **6**

Entry	Base (equiv.)		Reaction conditions	Additive[e]	Yield (%)[f]
1[b]	LDA	(2.2)	THF, −50 → 20 °C	HMPA	12
2[b]	$LiN(TMS)_2$	(2.0)	THF, −78 → 20 °C	HMPA	48
3[b]	$LiN(TMS)_2$	(2.0)	THF, −78 → 20 °C	—	0
4[b]	$NaN(TMS)_2$	(2.0)	THF, −78 → 20 °C	—	68
5[b]	$KN(TMS)_2$	(2.0)	THF–toluene[d] −78 → −30 °C	—	72
6[c]	$KN(TMS)_2$	(1.2)	THF–toluene[d] 0 °C	—	91

[a] All reactions were quenched by sat. aq. NH_4Cl. [b] Sulfone was added to base. [c] Base was added to sulfone. [d] $KN(TMS)_2$–toluene was used. [e] 5 equiv. HMPA was used. [f] Isolated yield after purification by column chromatography on silica gel.



Scheme 2 *Reagents and conditions*: i, $ICH_2P^+Ph_3I^-$, $NaN(SiMe_3)_2$, THF, −78 → 20 °C (68%); ii, 5 mol% OsO_4, $NaIO_4$, Et_2O–H_2O (1 : 1); iii, $NaBH_4$, MeOH, 0 °C (66% for 2 steps); iv, $(PhS)_2$, Bu_3P, pyridine (84%); v, AcOH–H_2O (4 : 1), 50 °C (95%); vi, Bu^{t}Li, THF, −78 °C (81%); vii, OXONE®, Na_2HPO_4, MeOH–H_2O (2 : 1) (91%); viii, TBDMS = *tert*-butyldimethylsilyl trifluoromethanesulfonate, 2,6-lutidine, CH_2Cl_2 (92%); ix, 20 mol% TPAP, NMO, 4 Å molecular sieves, MeCN (73%)



Scheme 3 *Reagents and conditions*: i, $KN(SiMe_3)_2$, THF–toluene (4:1), 0 °C (100%)

48% yield as a single stereoisomer (the stereochemistry was determined by NOE measurements) (entry 2).§ However, in the absence of HMPA, the starting material was recovered (entry 3). On the other hand, $NaN(TMS)_2$ or $KN(TMS)_2$ was effective for the cyclization in the absence of HMPA (entries 4 and 5). The best result giving **6** in 91% yield was obtained by treatment with 1.2 equiv. of $KN(TMS)_2$ at 0 °C (entry 6).

Next, we tried the cyclization of sulfone **12** possessing the geminal dimethyl group and a hydroxy function at C-15 and C-11, respectively (taxane numbering). Sulfone **12** was prepared as described in Scheme 2. Vinyl iodide **7** was prepared from **2** by the Wittig reaction.[10] Acetal **8**[11] was converted into aldehyde **9** by the usual protocol (oxidative cleavage of alkene, reduction, sulfenylation[7] and deprotection). Coupling of the aldehyde **9** with iodide **7** was conducted in the presence of Bu^tLi to afford alcohol **10**. Oxidation of the sulfenyl group of **10**, followed by protection with *tert*-butyldimethylsilyl group, gave **11**. Oxidation of **11** with catalytic TPAP and NMO as above furnished **12**.

With sulfone **12** in hand, treatment of **12** with $KN(TMS)_2$ under ice cooling as above provided the bicyclic compound **13** as a single stereoisomer in quantitative yield.§ The stereochemistry was determined by NOE spectra as shown in Scheme 3.

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Footnotes

† This reagent was synthesized in 76% yield by treatment of 5-bromopentyl benzyl ether with Ph_3P.

‡ This is the first report for the oxidation of allylic position using TPAP and NMO.

§ *Selected physical and spectroscopic data* for **6**: mp 182.0–183.0 °C; ${}^1H$ NMR (500 MHz, C_6D_6) δ 7.88–7.78 (m, 2 H), 7.06–6.94 (m, 3 H), 6.03 (d, 1 H, *J* 9.8 Hz), 5.82 (d, 1 H, *J* 9.8 Hz), 5.31 (ddd, 1 H, *J* 11.6, 10.4, 7.9 Hz), 5.11 (d, 1 H, *J* 11.6 Hz), 3.43–3.37 (m, 1 H), 3.04 (dd, 1 H, *J* 16.5, 3.7 Hz), 2.89–2.83 (m, 1 H), 2.70 (dd, 1 H, *J* 16.5, 11.6 Hz), 2.27–2.19 (m, 1 H), 1.92–1.82 (m, 1 H), 1.81–1.73 (m, 1 H), 1.72–1.61 (m, 1 H), 1.29–1.11 (m, 2 H) and 0.95 (s, 3 H); ${}^{13}C$ NMR (75 MHz, $CDCl_3$) δ 198.5, 159.1, 138.2, 134.0, 133.6, 133.0, 129.5, 128.8, 126.0, 63.1, 42.3, 40.9, 36.4, 26.5, 25.6, 25.0 and 20.0; IR $\nu(CHCl_3)/cm^{-1}$ 1690, 1315 and 1160. For **13**: ${}^1H$ NMR (500 MHz, $CDCl_3$) δ 7.87–7.79 (m, 2 H), 7.64–7.58 (m, 1 H), 7.56–7.50 (m, 2 H), 6.62 (dd, 1 H, *J* 10.4, 1.2 Hz), 6.10 (d, 1 H, *J* 10.4 Hz), 5.51 (dd, 1 H, *J* 12.2, 7.3 Hz), 5.36 (dd, 1 H, *J* 12.2, 1.8 Hz), 4.28 (dd, 1H, *J* 7.3, 1.8 Hz), 3.62–3.55 (m, 1 H), 3.42 (br d, 1 H, *J* 18.3 Hz), 3.28–3.20 (m, 1 H), 2.80 (dd, 1 H, *J* 18.3, 7.3 Hz), 1.81–1.74 (m, 1 H), 1.71 (dd, 1 H, *J* 16.5, 6.1 Hz), 1.44 (s, 3 H), 0.81 (s, 9 H), 0.71 (s, 3 H), −0.01 (s, 3 H), −0.05 (s, 3 H) and −0.06 (s, 3 H); ${}^{13}C$ NMR (75 MHz, $CDCl_3$) δ 197.1, 156.4, 140.4, 138.3, 134.0, 133.2, 129.42, 129.39, 128.1, 73.5, 62.7, 42.0, 40.3, 39.2, 34.9, 34.3, 30.2, 29.2, 25.7, 17.9, 16.4, −4.1 and −4.9; IR $\nu\ (CHCl_3)/cm^{-1}$ 1680, 1300 and 1150.

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