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

Masataka Ihara, Shuichi Suzuki, Yuji Tokunaga, Hiroshi Takeshita and Keiichiro Fukumoto*

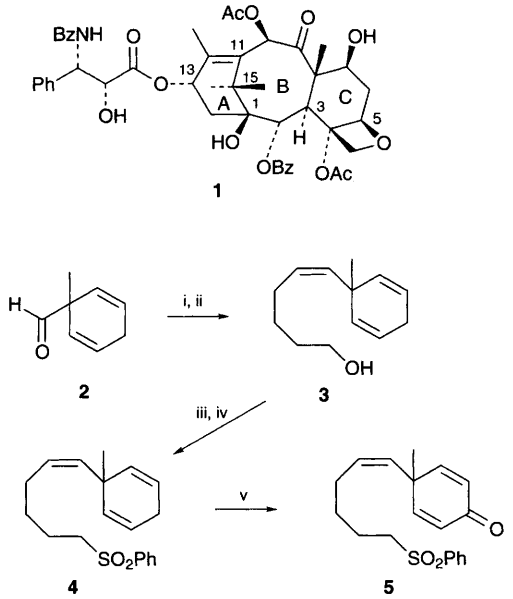
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980-77, Japan

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.

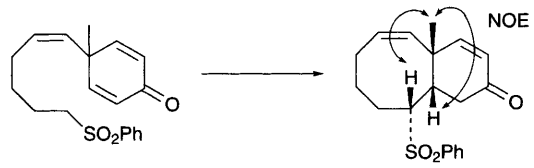
The substrate **5** was prepared as follows (Scheme 1). Aldehyde **2**[6] was converted into **3** by the Wittig reaction using $Ph_3P^+CH_2(CH_2)_3CH_2OBnBr^-$† in the presence of BuLi, followed by reductive deprotection. Sulfenylation[7] of **3** and the subsequent oxidation[8] gave sulfone **4**. 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**.



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)

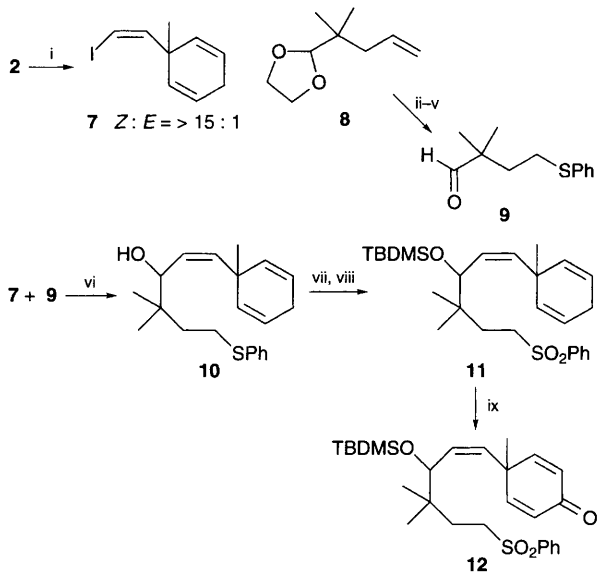
Results of the key reaction of **5** are summarized in Table 1. Treatment of **5** with LDA in the presence of HMPA gave a poor result (entry 1). When **5** was treated with $LiN(TMS)_2$ in the presence of HMPA, the bicyclic compound **6** was produced in

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

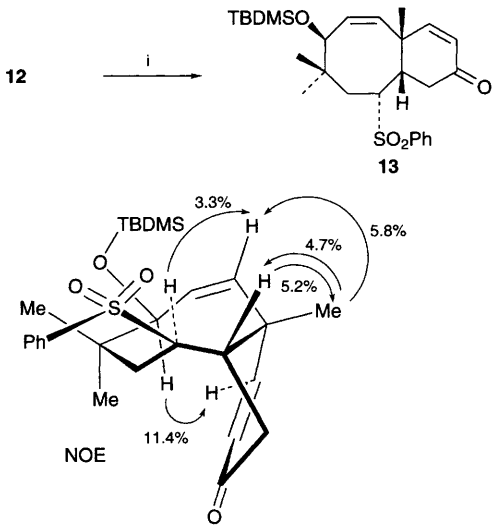


Entry	Base (equiv.)		Reaction conditions	Additive[e]	Yield (%)[f]
1[b]	LDA	(2.2)	THF, −50 → 20 °C	HMPA	12
2[b]	$LiN(TMS)_2$	(2.0)	THF, −78 → 20 °C	HMPA	48
3[b]	$LiN(TMS)_2$	(2.0)	THF, −78 → 20 °C	—	0
4[b]	$NaN(TMS)_2$	(2.0)	THF, −78 → 20 °C	—	68
5[b]	$KN(TMS)_2$	(2.0)	THF–toluene[d] −78 → −30 °C	—	72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

We gratefully acknowledge financial support from JSPS Research Fellowships for young scientists.

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 ν($CHCl_3$)/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 ν ($CHCl_3$)/cm^{-1} 1680, 1300 and 1150.

References

1 M. C. Wani, H. L. Taylor, M. E. Wall, P. Coggon and A. T. McPhail, *J. Am. Chem. Soc.*, 1971, **93**, 2325.
2 K. C. Nicolaou, W.-M. Dai and R. K. Guy, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 15; A. N. Boa, R. R. Jenkins and N. J. Lawrence, *Contemp. Org. Synth.*, 1994, **1**, 47.
3 R. A. Holton, H.-B. Kim, C. Somoza, F. Liang, R. J. Biediger, P. D. Boatman, M. Shindo, C. C. Smith, S. Kim, H. Nadizadeh, Y. Suzuki, C. Tao, P. Vu, S. Tang, P. Zhang, K. K. Murthi, L. N. Gentile and J. H. Liu, *J. Am. Chem. Soc.*, 1994, **116**, 1599; K. C. Nicolaou, Z. Yang, J.-J. Liu, H. Ueno, P. G. Nantermet, R. K. Guy, C. F. Claiborne, J. Renaud, E. A. Couladouros, K. Paulvannan and E. J. Sorensen, *Nature*, 1994, **367**, 630; J. J. Masters, J. T. Link, L. B. Snyder, W. B. Young and S. J. Danishefsky, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 1723.
4 N. S. Simpkins, *Sulphones in Organic Synthesis*, Pergamon Press, Oxford, 1993, p. 100.
5 J. Martel and C. Huynh, *Bull. Soc. Chim. Fr.*, 1967, 985; M. Julia and A. G-Rouault, *Bull. Soc. Chim. Fr.*, 1967, 1410; R. V. M. Campbell, L. Crombie, D. A. R. Findley, R. W. King, G. Pattenden and D. A. Whiting, *J. Chem. Soc., Perkin Trans. 1*, 1975, 897.
6 S. Arseniyadis, D. V. Yashunsky, M. M. Dorada, R. B. Alves, E. Toromanoff, L. Toupet and P. Potier, *Tetrahedron Lett.*, 1993, **34**, 4927.
7 I. Nakagawa and T. Hata, *Tetrahedron Lett.*, 1975, 1409; I. Nakagawa, K. Aki and T. Hata, *J. Chem. Soc., Perkin Trans. 1*, 1983, 1315.
8 B. M. Trost and D. P. Curran, *Tetrahedron Lett.*, 1981, **22**, 1287.
9 For review see: S. V. Ley, J. Norman,W. P. Griffith and S. P. Marsden, *Synthesis*, 1994, 639.
10 D. Seyferth, J. K. Heeren, G. Singh, S. O. Grim and W. B. Hughes, *J. Organomet. Chem.*, 1966, **5**, 267; G. Stork and K. Zhao, *Tetrahedron Lett.*, 1989, **30**, 2173.
11 M. Ihara, Y. Ishida, M. Abe, M. Toyota, K. Fukumoto and T. Kametani, *J. Chem. Soc., Perkin Trans. 1*, 1988, 1155.

Received, 8th May 1996; Com. 6/03226E