Highly Enantioselective Construction of a Quaternary Carbon Centre by the Pummerer-type Reaction: A Total Synthesis of (−)-Sibirine

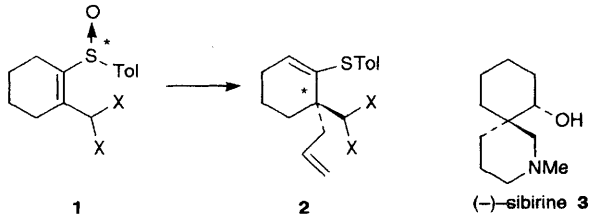
Takeshi Imanishi, Toshiki Kurumada, Naoyoshi Maezaki, Kenji Sugiyama and Chuzo Iwata*

Faculty of Pharmaceutical Sciences, Osaka University, 1-6 Yamadaoka, Suita, Osaka 565, Japan

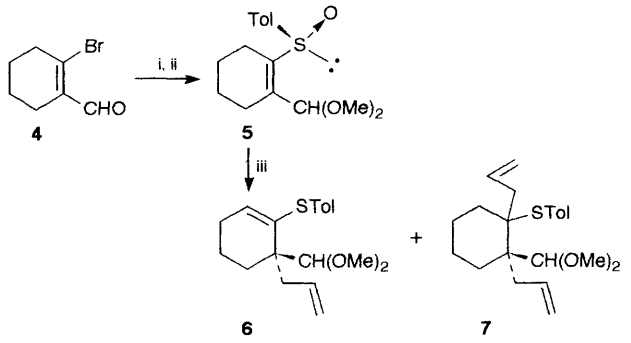
Highly enantioselective quaternary carbon formation (96% enantiomeric excess) is achieved by the Pummerer-type reaction of a chiral vinylic sulphoxide with allylmagnesium bromide; this method is applied to the synthesis of (−)-sibirine.

Creation of an asymmetric quaternary carbon centre is one of the most important features in the enantioselective synthesis of natural products.[1] In the preceding communication, we described a new method for carbon–carbon bond formation using a Pummerer-type reaction. The method involves the initial addition of allylmagnesium bromide to α,β-unsaturated sulphoxides followed by the Pummerer-type reaction or isomerization of the double bond.[2,3] The initial step would provide a potential tool for enantioselective C–C bond formation if optically active vinylic sulphoxides were used.[4] We turned our attention to the stereochemistry of this reaction and its application to the asymmetric synthesis of natural products. We considered that coordination of the Grignard reagent with the chiral auxiliary should make it possible to control the direction of nucleophilic attack on the β-position of a vinylic sulphoxide as illustrated in Scheme 1.

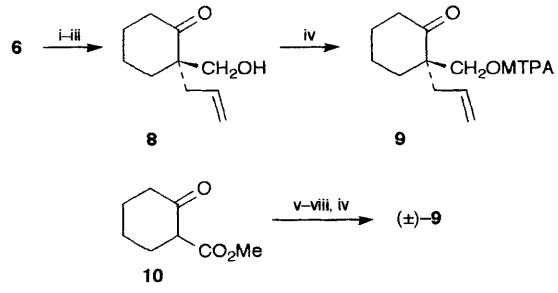
In this communication, we describe the application of the Pummerer-type reaction to asymmetric quaternary carbon formation and the synthesis of (−)-sibirine **3**, a compound isolated from *Nitraria sibirica* and possessing the unique 2-azaspiro[5.5]undecane skeleton. The alkaloid is attractive



Scheme 1 Tol = *p*-MeC_6H_4



Scheme 2 *Reagents and conditions*: i, $CH(OMe)_3$, *p*-$MeC_6H_4SO_3H$, room temp. (86%); ii, n-butyllithium, (−)-menthyl (*S*)-*p*-toluenesulphinate, tetrahydrofuran (THF), −78 °C (91%); iii, allylmagnesium bromide, THF, −78 °C to room temp. (**6**, 60%; **7**, 23%; diastereoisomer ratio of **7**, 3 : 1)



Scheme 3 *Reagents and conditions*: i, *p*-$MeC_6H_4SO_3H$, acetone, room temp. (92%); ii, $NaBH_4$, MeOH, 0 °C (83%); iii, 10% HCl, MeCN, reflux (62%); iv, (−)-MTPACl, 0 °C (93%); v, allyl bromide, NaH; vi, $CH(OMe)_3$; vii, $LiAlH_4$, THF; viii, HCl, acetone (63% of **7** from **10**)

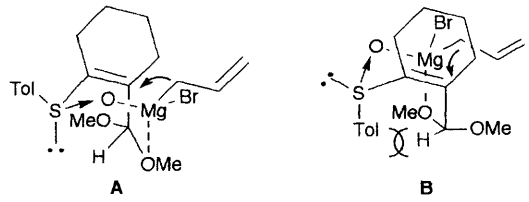
because of its structural similarity to histrionicotoxines, which possess the 1-azaspiro[5.5]undecan-8-ol unit and exhibit marked neurophysiological activities.

The chiral vinylic sulphoxide **5** was prepared from **4**[5] *via* dimethyl acetalization, lithiation, and then treatment with the (−)-menthyl (*S*)-*p*-tolylsulphinate.[6] The Pummerer-type reaction of the chiral vinylic sulphoxide **5** with allylmagnesium bromide afforded preferentially the vinylic sulphide **6** (60%) along with the diallyl compound **7** (23%).†

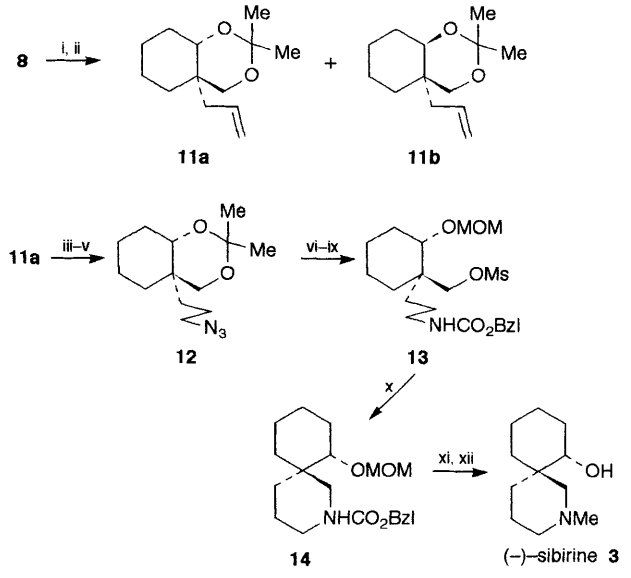
The optical purity of **6** was determined as follows. Deacetalization, reduction with sodium borohydride, and acid-catalysed hydrolysis of the vinylic sulphide moiety converted **6** to the ketol **8**, which was converted to the (−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) ester **9**. Compound **9** was confirmed as being formed with 96% enantiomeric excess (e.e.) by comparison of HPLC data with data for the MTPA ester synthesised from the racemic ketoester **10**[7] *via* five steps (Scheme 3).

The observed high stereoselectivity in the Pummerer-type reaction is explained as follows. Allylmagnesium bromide coordinates to both oxygens of the sulphoxide and the acetal as depicted in Scheme 4.[8] Transition state **A** seems to be more favourable than B owing to the $A^{(1,3)}$-strain between the tolyl

† Spectroscopic data for compound **6**: $[\alpha]_D^{25}$ −26.9° (*c* 0.94, $CHCl_3$); IR ($CHCl_3$): ν_{max}/cm^{-1} 1640 and 1070; ^1H NMR (90 MHz, $CDCl_3$): δ 1.02–2.55 (8H, m), 2.33 (3H, s), 3.43 (3H, s), 3.59 (3H, s), 4.44 (1H, s), 4.90–5.24 (2H, m), 5.62–6.10 (1H, m), 5.75 (1H, t, *J* 4 Hz), 7.11 (2H, d, *J* 8 Hz), 7.35 (2H, d, *J* 8 Hz); *m/z*: 318 (M^+, 100%), 286 (87%); *m/z*: 318.1675 (Calc. 318.1653). The minor product was a 5 : 2 mixture of diastereoisomers, which was separated by column chromatography, but the stereochemistry was not determined.



Scheme 4



Scheme 5 *Reagents and conditions*: i, $Zn(BH_4)_2$, diethyl ether–THF, −78 °C; ii, dimethoxypropane, *p*-$MeC_6H_4SO_3H$, room temp. (95% of **11** from **8**, **11a**: **11b** = 92 : 8); iii, BH_3·Me_2S, 0 °C; then H_2O_2, NaOH (75%); iv, $MeSO_2Cl$, pyridine, 0 °C (87%); v, NaN_3, tetra-n-butylammonium iodide, benzene, reflux (90%); vi, H_2, Pd–C; vii, $ClCO_2CH_2Ph$, K_2CO_3 (aq.), CH_2Cl_2, 0 °C to room temp.; viii, $MeSO_2Cl$, pyridine, 0 °C; ix, MOMCl, Pr^i_2NEt, CH_2Cl_2, room temp. (62% of **13** from **12**); x, KH, THF, 0 °C to room temp. (92%); xi, $LiAlH_4$, THF, 0 °C to room temp.; xii, 10% HCl, room temp. (70% of **3** from **14**) (MOM = $MeOCH_2$)

and acetal groups in B. Therefore, *si* face attack of allyl anion *via* the transition state **A** predominates and the newly created quaternary carbon should have the *S* configuration.

Next, we converted **8** into the known (−)-sibirine **3**.[9] Reduction of **8** with $Zn(BH_4)_2$ followed by acetalization afforded **11a** and **11b** in the ratio of 92 : 8.‡ The main product **11a** was converted to the azide **12** by hydroboration, mesylation and treatment with sodium azide. The azide moiety in **12** was reduced to amine by catalytic reduction and converted to the carbamate. Hydrolysis of the acetonide moiety in **12** occurred during the reduction.

The primary alcohol was selectively mesylated and the secondary alcohol protected as the MOM ether by treatment with MOMCl to give **13**. Treatment of **13** with KH afforded the azaspiro compound **14**. Compound **14** was converted to (−)-sibirine **3** with the natural configuration *via* three steps, and was identified by comparison of spectral data and specific

‡ Hydrogen bonding between the ketone and hydroxy group in **8** fixed the allyl group in a *quasi*-axial arrangement. As a result, nucleophilic attack on the ketone occurred from the opposite side of allyl group and afforded **11a** as the main product; **11a** had the required configuration at the carbon atom bearing the secondary hydroxy group, as confirmed by comparison of the *J* values for the methine proton in each diastereoisomer (major; *J* 11.3, 4.6 Hz, minor; $W_{1/2}$ 6 Hz).

rotation {$[\alpha]_D^{21}$ −23.4° (*c* 0.75, $CHCl_3$), lit.[9a] $[\alpha]_D^{20}$ −22.5° (c 0.81, $CHCl_3$)} with data for an authentic sample.§

We thank Professor A. G. Schultz (Rensselaer Polytechnic Institute) for an authentic data of sibirine and Yoshitomi Pharmaceutical Industry Ltd. for financial support.

Received, 1st July 1991; Com. 1/03272K

References

1 S. F. Martin, *Tetrahedron*, 1980, **36**, 419.
2 C. Iwata, N. Maezaki, T. Kurumada, H. Fukuyama, K. Sugiyama and T. Imanishi, *J. Chem. Soc., Chem. Commun.*, 1991, preceding communication.
3 Other examples of Pummerer-type reaction, see: D. Craig and K. Daniels, *Tetrahedron Lett.*, 1990, **44**, 6441, and references cited therein.
4 For other examples of asymmetric induction using a chiral sulphinyl group as a chiral auxiliary, see ref. 1 in the preceding communication.
5 Z. Arnord and A. Holy, *Collect. Czech. Chem. Commun.*, 1961, **26**, 3059.
6 M. Hulce, J. P. Mallamo, L. L. Frye, T. P. Kogan and G. H. Posner, *Org. Synth.*, 1986, **64**, 196.
7 M. Alderdice, F. W. Sum and L. Weiler, *Org. Synth.*, 1984, **62**, 14.
8 C. Iwata, M. Fujita, K. Hattori, S. Uchida and T. Imanishi, *Tetrahedron Lett.*, 1985, **26**, 2221; C. Iwata, M. Fujita, Y. Moritani, K. Hattori and T. Imanishi, *Tetrahedron Lett.*, 1987, **28**, 3135.
9 For the isolation and structure determination of *Nitraria* alkaloids, see: (*a*) Z. Osmanov, A. A. Ibragimov and S. Y. Yunusov, *Chem. Nat. Compd.* (*Engl. Trans.*), 1982, **18**, 206; (*b*) A. A. Ibragimov, Z. Osmanov, B. Tashkhozhaev, N. D. Abdullaev, M. R. Yagudaev and S. U. Yunusov, *Chem. Nat. Compd.* (*Engl. Trans.*), 1981, **17**, 458; B. Tashkhodzhaev, *Chem. Nat. Compd.* (*Engl. Trans.*), 1982, **18**, 70; for previous synthetic work on *Nitraria* alkaloids, see: P. J. McCloskey and A. G. Schultz, *Heterocycles*, 1987, **25**, 437; M. J. Wanner and G. J. Koomen, *Tetrahedron Lett.*, 1989, **30**, 2301; D. Tanner and H. M. He, *Tetrahedron*, 1989, **45**, 4309; D. Kim, H. S. Kim and J. Y. Yoo, *Tetrahedron Lett.*, 1991, **32**, 1577 and references cited therein.

§ Our synthetic sample of (−)-sibirine was identical on the basis of standard spectroscopic criteria with an authentic sample of (+)-sibirine provided by Professor A. G. Schultz.