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The First Chiral Version of Jackson *N*-Benzyl-*N*-tosylaminoacetal Cyclization. A New Enantioselective Total Synthesis of 1-S-(-)-Salsolidine

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Abstract The first chiral version of Jackson *N*-benzyl-*N*-tosylaminoacetal cyclization, enabling a new and efficient enantioselective total synthesis of 1-S-(-)-salsolidine, is reported. Chirality was introduced by oxazaborolidine-catalyzed reduction of an aralkyl ketone, coupled with a Mitsunobu-type amination of the resulting benzylic alcohol, resulting in complete configurational inversion of the latter.

The synthesis of optically pure 1-alkyltetrahydroisoquinolines has shown considerable interest over the years. Besides the development of chiral versions of the classical Bischler-Napieralski,[1a,1b] Pictet-Spengler[1c, 1d] and Bobbitt[1e, 1f] sequences, other strategies have been devised for that purpose and Seebach[2] has pointed out that all possible methods of preparing enantiomerically pure compounds have been applied in order to obtain this type of compounds.

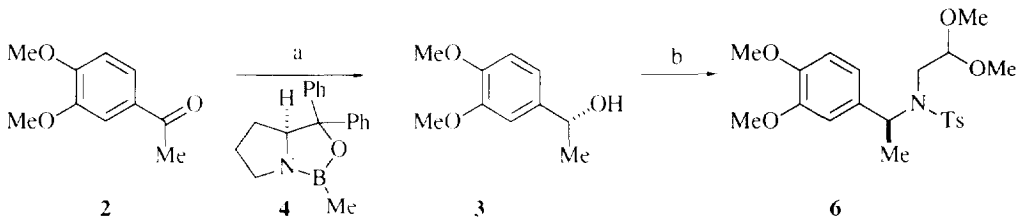
The synthesis of isoquinolines and 2-tosyl-1,2-dihydroisoquinolines by acid-catalyzed cyclization of toluene-*p*-sulfonamides of *N*-benzylaminoacetaldehyde acetals was first reported by Jackson and co-workers,[3] as an efficient modification of the Pomeranz-Fritsch process. The original strategy, which has been used as a synthetic tool in the preparation of a variety of isoquinoline systems,[4] was modified by Boger[5] and later by Castedo.[6] In addition, we have reported useful extentions of this cyclization for the elaboration of C-1 and C-3 substituted tetrahydroisoquinolines,[7] enhancing its synthetic power.

We now report the details of our investigation concerning the use of oxazaborolidine-catalyzed enantioselective reduction of aralkyl ketones (CBS process)[8] in tandem with the amination of benzylic alcohols under Mitsunobu[6] conditions for the elaboration of an optically active intermediate capable of undergoing Jackson cyclization, and the application of this method to the asymmetric synthesis of the naturally occurring 1-S-(-)-salsolidine (**1**).[9]

In our first approach (Scheme 1), commercially available ketone **2** was efficiently reduced to alcohol **3** in 88% enantiomeric excess (ee) as determined by ^{1}H NMR with (+)-Eu(hfc)$_3$ in C_6D_6, employing oxazaborolidine **4** and following the procedure of Mathre and co-workers.[8b] However, amination of **3** with toluene-*p*-sulfonamide **5** gave *N*-benzyl-*N*-tosylaminoacetal **6** in 50% yield and only 25% ee.

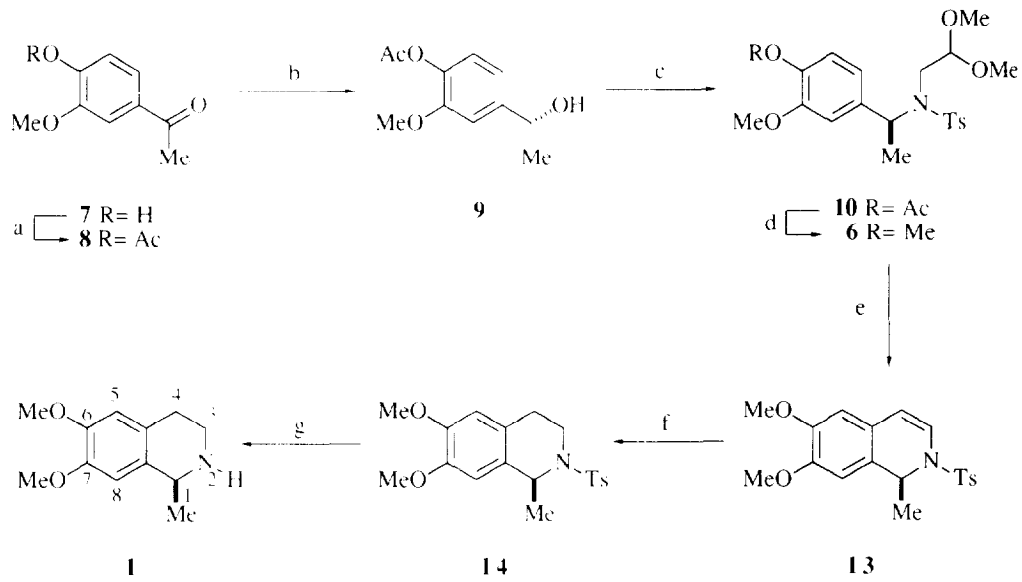
McCarthy[10] has recently reported that under Mitsunobu reaction conditions, *para*-methoxy benzylic alcohols unexpectedly gave racemic products *via* an S$_N$1 type reaction, probably resulting from a significant carbocation character of the intermediate phosphonium salt, favored by the electron donating capability of the

ether moiety. In contrast, replacement of the *para*-methyl ether with a less activating ester group furnished exclusively the product with inverted configuration at the benzylic centre.



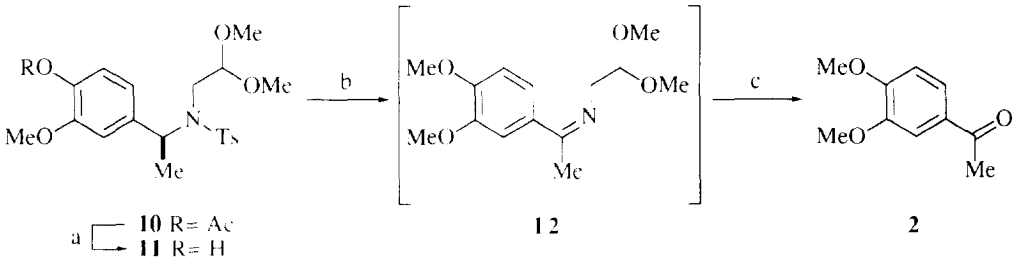
Scheme 1. *Reagents and conditions:* a) $BH_3.SMe_2$, THF, **4** (10 mol%), -20°C, 6 h (95%, 88% ee); b) $TsNHCH_2CH(OMe)_2$ (**5**), PPh_3, DEAD, THF, RT, 3h (50%, 25% ee).

Therefore, acetovanillone (**7**) was acetylated under standard conditions to give acetate **8**, which upon the oxazaborolidine-mediated reduction furnished alcohol **9** (> 95% ee). As depicted in Scheme 2, reaction of benzylic alcohol **9** with **5** employing the diethyl azodicarboxylate-triphenylphosphine couple in dry THF produced *N*-benzyl-*N*-tosylaminoacetal **10** in 60% yield and ee greater than 95%, together with 29% of the hydrazine derived from diethyl azodicarboxylate *N*-alkylation,[11] due to the low acidity of **5**.



Scheme 2. *Reagents and conditions:* a) Ac_2O, pyridine, CH_2Cl_2, RT (97%); b) $BH_3.SMe_2$, THF, **4** (10 mol%), -20°C, 6 h (95%, >95% ee); c) **5**, PPh_3, DEAD, THF, RT, 3h (60%); d) CH_2N_2, $EtOH/Et_2O$, piperidine, RT, 2 d (95%); e) 6N HCl, dioxane, reflux (80%); f) H_2 (4 atm), 10% Pd/C (cat.), 3:1 AcOEt-MeOH (97%); g) 1. Na-NH_3, 2. NH_4Cl (80%, >95% ee).

Replacement of the ester moiety with a methyl ether group was next approached. However, in spite that hydrolysis of the acetate was successful with potassium carbonate in anhydrous methanol at 0°C, without loss of optical purity, reaction of the resulting phenol **11** with methyl iodide at room temperature gave only decomposition products, among which ketone **2** was identified (Scheme 3). This was understood as being a consequence of base-promoted toluene-*p*-sulfinic acid elimination, followed by hydrolysis of the resulting imine **12** during work up, and suggested the need of using a milder method in order to circumvent this problem.



Scheme 3. *Reagents and conditions:* a) K_2CO_3 (excess), MeOH, 0°C (93%); b) MeI, RT; c) 1N HCl (work up).

Reaction of **10** with ethereal diazomethane and four equivalents of piperidine in absolute ethanol, as described by Nierenstein,[12] efficiently effected the desired ester to ether change, leading to a smooth production of **6** in 95% yield. This, in turn, rapidly afforded 1,2-dihydroisoquinoline **13** without signs of racemization after carefully controlled cyclization, following the Jackson protocol.[3]

Submission of dihydroisoquinoline **13**, dissolved in 3:1 ethyl acetate-methanol, to a palladium on carbon catalytic hydrogenation, cleanly gave tetrahydroisoquinoline **14** in 78% overall yield from **6** and, finally, reductive detosylation of **14** with sodium in liquid ammonia[7a] furnished **1** (80%, > 95% ee).[13]

A salient feature of the Jackson sequence is the possibility of synthesizing the relatively uncommon and difficult to obtain heterocycles carrying a 7,8-substitution pattern on the isocyclic ring. Research work on the course of the Mitsunobu amination of secondary benzylic alcohols carrying an *ortho*-methyl ether group and the enantioselective elaboration of 7,8-dialkoxy tetrahydroisoquinolines is underway.[14]

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References and Notes

1. For recent examples, see: (a) Kitamura, M.; Hsiao, Y.; Ohta, M.; Tsukamoto, M.; Ohta, T.; Takaya, H.; Noyori, R. *J. Org. Chem.* **1994**, 59, 297-310; (b) Czarnocki, Z. *J. Chem. Res. (S)* **1992**, 402-403; (c) Czarnocki, Z.; MacLean, D. B.; Szarek, W. A. *J. Chem. Soc., Chem. Commun.* **1985**, 1318-1319; (d) Comins, D. L.; Badawi, M. M. *Tetrahedron Lett.* **1991**, *26*, 2995-2996; (e) Hirsenkorn, R. *Tetrahedron Lett.* **1990**, 52, 7591-7594; (f) Hirsenkorn, R. *ibid.* **1991**, *53*, 1775-1778.

2. Huber, I. M. P.; Seebach, D. *Helv. Chim. Acta* **1987**, *70*, 1944-1954.
3. Birch, A.J.; Jackson, A.H.; Shannon, P.V.R. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2185-2189.
4. (a) Birch, A.J.; Jackson, A.H.; Shannon, P.V.R. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2190-2194; (b) Jackson, A. H.; Stewart, G. W. *J. Chem. Soc., Chem. Commun.* **1971**, 149-150; (c) Jackson, A.H.; Stewart, G.W.; Charnock, G.A.; Martin, J.A. *J. Chem. Soc., Perkin Trans 1* **1974**, 1911-1920.
5. Boger, D.L.; Brotherton, C.H.; Kelley, M.D. *Tetrahedron* **1981**, *37*, 3977-3980.
6. García, A.; Castedo, L.; Domínguez, D. *Synlett* **1993**, 271-272.
7. (a) Kaufman, T. S. *J. Chem. Soc., Perkin Trans. 1* **1993**, 403-404; (b) Ponzo, V. L.; Kaufman, T. S. *Can. J. Chem.* in the press.
8. (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551-5553; (b) Mathre, D. J.; Thompson, A. S.; Douglas, A. W.; Hoogsteen, K.; Carroll, J. D.; Corley, E. G.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 2880-2888.
9. (a) Menachery, M. D.; Lavanier, G. L.; Wetherly, M. L.; Guinaudeau, H.; Shamma, M. *J. Nat. Prod.* **1986**, *49*, 745-778, and references therein. (b) Battersby, A. R.; Edwards, T. P. *J. Chem. Soc.* **1960**, 1214-1221.
10. Brown, R. F. C.; Jackson, W. R.; McCarthy, T. D. *Tetrahedron* **1994**, *50*, 5469-5488.
11. Henry, J. R.; Marcin, L. R.; McIntosh, M. C.; Scola, P. M.; Davis Harris, G.; Weinreb, S. M. *Tetrahedron Lett.* **1989**, *30*, 5709-5712, and references therein.
12. Nierenstein, M. *J. Am. Chem. Soc.* **1930**, 52, 4012-4013.
13. All new compounds gave spectral and analytical data consistent with their structure. Data for selected compounds: **9**, $[\alpha]_D^{20}$: + 31 (c= 1.82, $CHCl_3$); ^1H NMR (200.13 MHz, $CDCl_3$): δ 1.48 (3 H, d, J= 6.4, Me), 2.02 (1 H, br s, OH), 2.31 (3 H, s, AcO), 3.84 (3 H, s, MeO), 4.87 (1 H, br q, J= 6.4, C*H*OH), 6.90 (1 H, dd, J= 1.7, 8.0, 6-H), 6.99 (1 H, d, J= 8.0, 5-H) and 7.03 (1 H, d, J= 1.7, 2-H); ^{13}C NMR (50.33 MHz, $CDCl_3$): δ 20.35, 24.90, 55.47, 69.54, 109.21, 117.21, 122.14, 138.30, 144.80, 150.61 and 169.07; **6**, $[\alpha]_D^{20}$: - 91 (c= 1.48, $CHCl_3$); ^1H NMR (200.13 MHz, $CDCl_3$): δ 1.50 (3 H, d, J= 7.0, Me), 2.43 (3 H, s, ArMe), 3.02 (1 H, dd, J= 6.2, 15.3, NCH_2), 3.14 (1 H, dd, J= 15.3, 4.1, NCH_2), 3.20 (3 H, s, MeO), 3.33 (3 H, s, MeO), 3.62 (3 H, s, MeO), 3.64 (3 H, s, MeO), 4.27 (1 H, dd, J= 4.1, 6.2, CH2C*H*), 5.03 (1 H, q, J= 7.0, ArC*H*Me), 6.43 (1 H, s, 2-H), 6.73 (1 H, s, 5-H), 6.74 (1 H, s, 6-H), 7.32 (2 H, d, J= 8.3, ArH of tosyl) and 7.80 (2 H, d, J= 8.3, ArH of tosyl); ^{13}C NMR (50.33 MHz, $CDCl_3$): δ 17.61, 21.24, 46.05, 54.16, 54.98, 55.31, 55.63, 55.87, 104.26, 110.24, 111.21, 119.28, 127.18 (2 x C), 129.43 (2 x C), 131.79, 137.84, 142.97, 148.34 and 148.53; **13**, mp: 126-127.5°C; $[\alpha]_D^{20}$: + 237 (c= 1.7, $CHCl_3$); ^1H NMR (200.13 MHz, $CDCl_3$): δ 1.32 (3 H, d, J= 6.7, Me), 2.33 (3 H, s, ArMe), 3.82 (3 H, s, MeO), 3.83 (3 H, s, MeO), 5.15 (1 H, q, J= 6.7, ArCH), 5.92 (1 H, d, J= 7.5, 4-H), 6.46 (1 H, s, 8-H), 6.50 (1 H, s, 5-H), 6.60 (1 H, d, J= 7.5, 3-H), 7.15 (2 H, d, J= 8.4, ArH of tosyl) and 7.61 (2 H, d, J= 8.4, ArH of tosyl); ^{13}C NMR (50.33 MHz, $CDCl_3$): δ 21.22, 22.63, 53.41, 55.68, 55.86, 107.97, 108.46, 111.22, 121.61, 121.93, 125.66, 126.22 (2 x C), 129.33 (2 x C), 136.83, 143.27, 147.96 and 148.27; **1.HCl** $[\alpha]_D^{20}$: -18 (c= 1.0, EtOH); [lit.:[9b] -17.5 (c= 2, EtOH)]; mp: 235-236°C (lit.:[9] 234-235°C); NMR data (D_2O) agreed with those reported in ref. 9.
14. Preliminary experiments indicate that obtention of 7,8-disubstituted compounds can be successfully achieved, even in fewer steps than their 6,7-dioxygenated counterparts.

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