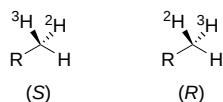


The Shortest Route to Chiral Ditosylmethylamine**

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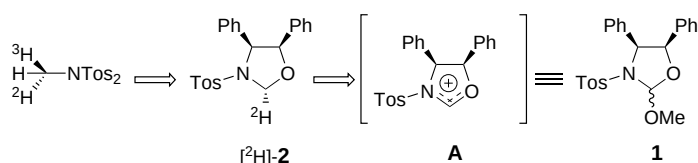
The chiral methyl group (Scheme 1) is an invaluable and unique tool in elucidating biological mechanisms, and has been used to clarify crucial biochemical transformations.^[1–2] Among the most powerful syntheses of the smallest asymmetric molecule,^[3–5] the most attractive deal with the preparation of chiral *N,N*-ditosylmethylamine. This synthon is of



Scheme 1. Chiral methyl group.

particular interest since it can be considered to be a bridgehead in obtaining numerous substrates that bear an enantiomerically enriched methyl group by means of a facile S_N2 reaction.^[6] Although very elegant, Floss's approach, in which chiral acetic acid is converted into the corresponding methylamine by means of a Schmidt degradation, suffers from problems of reproducibility, sometimes resulting in the marked loss of enantiomeric purity of the starting enantiomerically enriched acetic acid.^[7] Other drawbacks include low overall yield (about 5%) and the number of steps (seven) after the introduction of the radioactive label. Herein we report our preparation of chiral *N,N*-ditosylmethylamine.

We have designed a route based on the following retrosynthetic pathway, which involves two key steps (Scheme 2). The first step takes advantage of orthoamide **1** as a chiral formyl cation equivalent. We assumed that the postulated cationic intermediate **A**, which is obtained from the reaction of **1** with a suitable Lewis acid, could be reduced stereospecifically by a deuteride species to afford $[^2\text{H}]\text{-2}$. The second

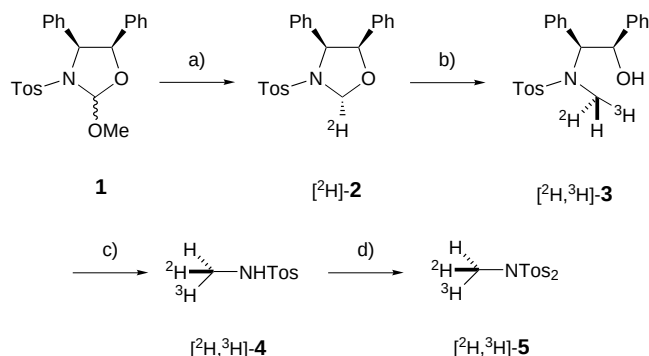


Scheme 2. Retrosynthetic pathway to chiral ditosylmethylamine. Tos = tosyl = *p*-toluenesulfonyl.

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[**] We thank Bruker for the loan of a lockswitch

key step involves the stereocontrolled opening of oxazolidine $[^2\text{H}]\text{-2}$ with a tritide to yield the chiral methyl group (Scheme 2).



Scheme 3. Synthesis of chiral ditosylmethyl amine. Reagents and conditions: a) $\text{Bu}_3\text{Sn}^2\text{H}$, $\text{BF}_3 \cdot \text{OEt}_2$; b) $\text{Et}_3\text{Si}^3\text{H}$, TiCl_4 ; c) HCO_2NH_4 , Pd/C (10%), 66%; d) NaH/TosCl , DMF, 80%. DMF = *N,N*-dimethylformamide.

Compound **1** was easily obtained as a mixture of epimeric C2 (d.r. 1:1) through the acid-catalyzed condensation of trimethyl orthoformate with (1*R*,2*S*)-*N*-tosyldiphenylethanamine (Scheme 3). We have already reported the conversion of **1** into enantiopure $[^2\text{H}]\text{-2}$ with a combination of $\text{Bu}_3\text{Sn}^2\text{H}$ and $\text{BF}_3 \cdot \text{OEt}_2$ to afford $[^2\text{H}]\text{-2}$ in 82% yield and with an isotopic enrichment higher than 95%.^[8] Addition of deuteride occurs on the *Re* face of postulated intermediate **A** (anti to the phenyl groups), thus giving (2*R*)- $[^2\text{H}]\text{-2}$ as the sole diastereomer, which was treated with $\text{Et}_3\text{Si}^3\text{H/TiCl}_4$ to give $[^2\text{H},^3\text{H}]\text{-3}$. $\text{Et}_3\text{Si}^3\text{H}$ was prepared from Et_3SiCl and LiAl^3H_4 to reach a specific activity of about $150 \text{ mCi mmol}^{-1}$.^[9] Hydrogenolysis of the chiral auxiliary under heterogeneous catalysis (ammonium formate/ Pd) afforded $[^2\text{H},^3\text{H}]\text{-4}$ in 66% yield. The *N*-tosylmethylamine was further protected with tosyl chloride to afford $[^2\text{H},^3\text{H}]\text{-5}$ in 80% yield. The enantiomeric purity of $[^2\text{H},^3\text{H}]\text{-5}$ was analyzed by using the Anet protocol.^[10] The product $[^2\text{H},^3\text{H}]\text{-5}$ was therefore submitted to S_N2 reaction with (*R*)-(-)-2-methylpiperidine^[11] to yield $[^2\text{H},^3\text{H}]\text{-6}$ (Figure 1), which can be used to determine the enantiomeric purity of the parent compound **5** by means of ^3H NMR. After dissolution of $[^2\text{H},^3\text{H}]\text{-6}$ (6 mCi) in CD_2Cl_2 , the 640-MHz ^3H NMR spectrum displayed two well-separated signals (Figure 1). A diastereomeric ratio of 83:17 in favor of (2*R*,7*S*)-**6** was determined by Lorentzian deconvolution and integration of the signals.^[12] Since the piperidine coupling occurs with inversion of configuration, $[^2\text{H},^3\text{H}]\text{-5}$ must have the *R* configuration. This major configuration may be attributed to a concerted mechanism during the conversion of **2** into **3** (S_N2 pathway). Unfortunately, the open transition state (*N*-tosyliminium intermediate) also leads to the same stereochemical outcome as assigned using molecular models. Therefore, we can not clearly establish which process governs the stereoselectivity of this reaction. Further experiments are currently in progress to assign the major mechanism of the opening reactions of *N*-tosyl oxazolidines.

In summary, we have described a new synthesis of an enantiomerically enriched methyl group by using only non-enzymatic transformations.^[13] This simple and reproducible

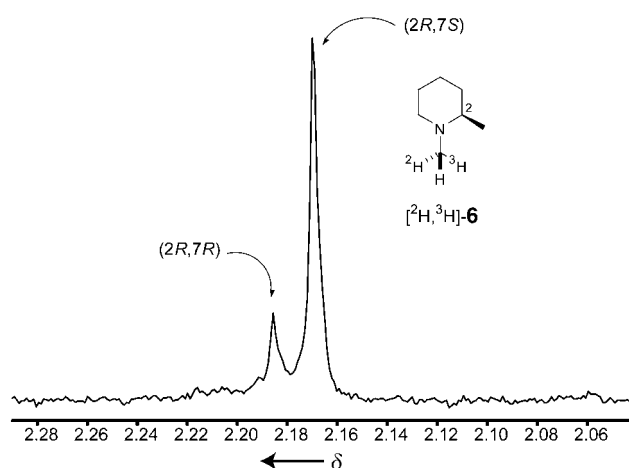


Figure 1. ^3H NMR spectrum of crude **6** (slow addition of TiCl_4) dissolved in CD_2Cl_2 acquired with simultaneous ^1H - and ^3H -decoupling (288 K, 640 MHz, 5-kHz spectral width, 2.8-s repetition time).

strategy for the synthesis of chiral *N,N*-ditosylmethylamine is an improvement on the Floss approach:^[7b] 5 steps compared to 7 in previous reports, and an overall yield of 30%, compared to < 5% in the Floss synthesis. Our strategy affords chiral ditosylmethylamine with 66% *ee* (62% for the Schmidt degradation) and can also be used to synthesize the opposite enantiomer starting from commercially available (1*R*,2*S*)-2-amino-1,2-diphenylethanol.

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- [1] a) J. Micklefield, K. J. Harris, S. Groger, U. Mocek, H. Hilbi, P. Dimroth, H. G. Floss, *J. Am. Chem. Soc.* **1995**, *117*, 1153–1154; b) A. M. Valentine, B. Wilkinson, K. E. Liu, S. Komar-Panicucci, N. D. Priestley, P. G. Williams, H. Morimoto, H. G. Floss, S. J. Lippard, *J. Am. Chem. Soc.* **1997**, *119*, 1818–1827; c) S. Lee, H. G. Floss, B. A. Gilbert, R. R. Rando, *J. Org. Chem.* **1998**, *63*, 898–899; d) B. Wilkinson, M. Zhu, N. D. Priestley, H.-H. T. Nguyen, H. Morimoto, P. G. Williams, S. I. Chan, H. G. Floss, *J. Am. Chem. Soc.* **1996**, *118*, 921–922; e) Y. Ahn, J. A. Krzycki, H. G. Floss, *J. Am. Chem. Soc.* **1991**, *113*, 4700–4701; f) L. J. Altman, C. Y. Han, A. Bertolino, G. Handy, D. Laungani, W. Muller, S. Schwart, D. Shanker, W. H. De Wolf, F. Yang, *J. Am. Chem. Soc.* **1978**, *100*, 3235–3237; g) N. D. Priestley, H. G. Floss, W. A. Froland, J. D. Lipscomb, P. G. Williams, H. Morimoto, *J. Am. Chem. Soc.* **1992**, *114*, 7561–7562; h) T. Frenzel, J. M. Beale, M. Kobayashi, M. H. Zenk, H. G. Floss, *J. Am. Chem. Soc.* **1988**, *110*, 7878–7880; i) Y.-F. Cheung, C. Walsh, *J. Am. Chem. Soc.* **1976**, *98*, 3397–3398.
- [2] R. M. Coates, S. Canan Koch, S. Hedge, *J. Am. Chem. Soc.* **1986**, *108*, 2762–2764.
- [3] a) H. G. Floss, S. Lee, *Acc. Chem. Res.* **1993**, *26*, 116–122; b) H. G. Floss in *Methods in Enzymology*, Vol. 87, Academic Press, San Diego, **1982**, pp. 126–159.
- [4] a) J. W. Cornforth, J. W. Redmond, H. Eggerer, W. Buckel, C. Gutschow, *Nature* **1969**, *221*, 1212–1213; b) J. Luthy, J. Retey, D. Arigoni, *Nature* **1969**, *221*, 1213–1215; c) J. W. Cornforth, J. W. Redmond, H. Eggerer, W. Buckel, C. Gutschow, *Eur. J. Biochem.* **1970**, *14*, 1–13; d) C. A. Townsend, T. Scholl, D. Arigoni, *J. Chem. Soc. Chem. Commun.* **1975**, 921–922; e) M. D. Fryzuk, B. Bosnich, *J. Am. Chem. Soc.* **1979**, *101*, 3043–3049.
- [5] a) J. D. Rozzell, Jr., S. A. Benner, *J. Org. Chem.* **1983**, *48*, 1190–1193; b) C. Dehnhardt, M. McDonald, S. Lee, H. G. Floss, J. Mulzer, *J. Am. Chem. Soc.* **1999**, *121*, 10848–10849; c) E. J. O'Connor, M. Kobayashi, H. G. Floss, J. A. Gladysz, *J. Am. Chem. Soc.* **1987**, *109*, 4837–4844; d) K. Kobayashi, P. K. Jadhav, T. M. Zydowsky, H. G. Floss, *J. Org. Chem.* **1983**, *48*, 3510–3512.
- [6] C. A. Townsend, A. B. Theis, *J. Org. Chem.* **1980**, *45*, 1697–1699.

- [7] a) R. W. Woodard, L. Mascaro, Jr., R. Horhammer, S. Eisenstein, H. G. Floss, *J. Am. Chem. Soc.* **1980**, *102*, 6314–6318; b) J. A. Bjorklund, T. Frenzel, M. Rueffer, M. Kobayashi, U. Mocek, C. Fox, J. M. Beale, S. Groger, M. H. Zenk, H. G. Floss, *J. Am. Chem. Soc.* **1995**, *117*, 1533–1545.
- [8] N. Faucher, J.-C. Cintrat, M. Nierlich, B. Rousseau, *Tetrahedron: Asymmetry* **2000**, *11*, 4001–4007.
- [9] G. Guillermin, F. Frappier, J.-C. Tabet, A. Marquet, *J. Org. Chem.* **1977**, *42*, 3776–3778.
- [10] a) F. A. L. Anet, M. Kopelevich, *J. Am. Chem. Soc.* **1989**, *111*, 3429–3431; b) F. A. L. Anet, D. J. O'leary, J. M. Beale, H. G. Floss, *J. Am. Chem. Soc.* **1989**, *111*, 8935–8936.
- [11] J. Cymerman Craig, A. R. Pinder, *J. Org. Chem.* **1971**, *36*, 3648–3649.
- [12] Keeping in mind that upon standing with TiCl_4 for a few hours, enantiopure $[\text{H}]\text{-2}$ is prone to epimerization at C2 through an open transition state (*N*-tosyliminium), a slow addition of TiCl_4 to the mixture of $[\text{H}]\text{-2}$ and Et_3SiH and careful control of the temperature is mandatory to avoid scrambling of the stereochemistry at the stereogenic methyl center.
- [13] T. M. Zydowsky, L. F. Courtney, V. Frasca, K. Kobayashi, H. Shimizu, L.-D. Yuen, R. G. Matthews, S. J. Benkovic, H. G. Floss, *J. Am. Chem. Soc.* **1986**, *108*, 3152–3153. The authors also describe a related approach starting from a chiral aminal, but with less success (*ee* 44%).

The Extended Borinium Cation: [$(\text{tBu}_3\text{PN})_2\text{B}$] $^{+**}$

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Much of the recent interest in main group metallocenes has arisen from applications as materials precursors for chemical vapor deposition and as activators or catalysts in olefin polymerization. Nonetheless, structure and bonding considerations continue to motivate researchers, as less is known about these main group systems than the transition metal analogues. In this regard, recent studies by Cowley and co-workers, who have described the first examples of decamethylgallocenium^[1] and decamethylborocenium cations,^[2] and by Schnöckel et al, who have reported the decamethylalumoocenium cation,^[3] have begun to redress the balance. Only the Al species displays the symmetric bis- η^5 -bonded structure analogous to ferrocene. The Ga species exhibits only marginal stability, while the boron compound is described as “tightly squeezed” presumably because of the high effective charge of the boron cation. It is noteworthy that the unsubstituted cyclopentadienyl (Cp) analogues of these cations are not known. In recent work, we employed bulky phosphinimide ligands as steric equivalents to cyclopentadienyl in the development of new active olefin polymerization catalysts.^[4, 5] Herein, we employ this concept in the formation of a steric

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