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ENANTIODIVERGENT TOTAL SYNTHESIS OF NATURALLY OCCURRING *trans*-2-BUTYL-5-PENTYLPYRROLIDINE

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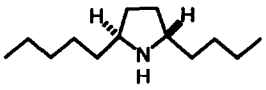
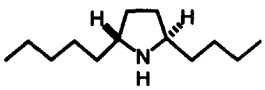
Abstract: The enantiodivergent total synthesis of (+)-(2*S*,5*S*)- and (–)-(2*R*,5*R*)-*trans*-2-butyl-5-pentylpyrrolidines was effected from the C_2 symmetric (*S*,*S*)- and (*R*,*R*)-diepoxides, respectively, both prepared from D-mannitol, by a sequence involving stereo-defined ring construction of the unsymmetrical *trans*-2,5-dialkylpyrrolidine via the cyclic sulfate as a key step.

Naturally occurring *trans*-2-butyl-5-pentylpyrrolidine (**1**) has been found as an ant venom alkaloidal component from *Solenopsis punctaticeps*,[1] *Monomorium pharaonis*,[2] and *M. latinode*.[3] Recently, this compound **1** has also been detected in a poison frog *Dendrobates histrionicus* from northwestern Colombia; it has been identified as one of a new class of dendrobates alkaloids and named pyrrolidine 197B.[4] In all these cases of the compound, however, the absolute configuration is unknown. In continuation of our work on the synthesis of dendrobates alkaloids,[5] we have now developed a new chiral approach for this alkaloid. In this paper we report the enantioselective preparation of both enantiomers of **1** based on a stereo-defined method utilizing as a C_2 symmetrical building block, the optically active diepoxide **4**, which is readily available in both enantiomeric forms from D-mannitol as a common chiral synthon. Our results represent the first example of the preparation of optically active **1**.[6]



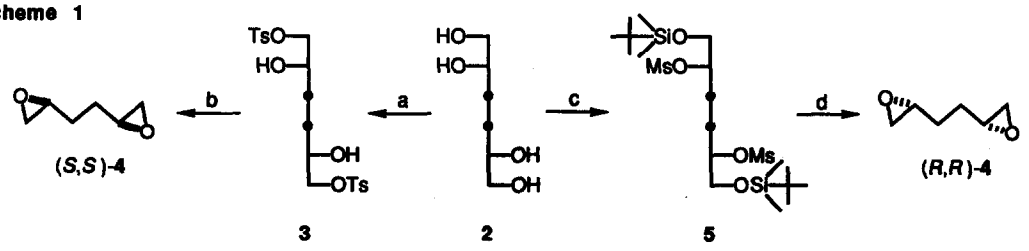
(+)-**1**



(–)-**1**

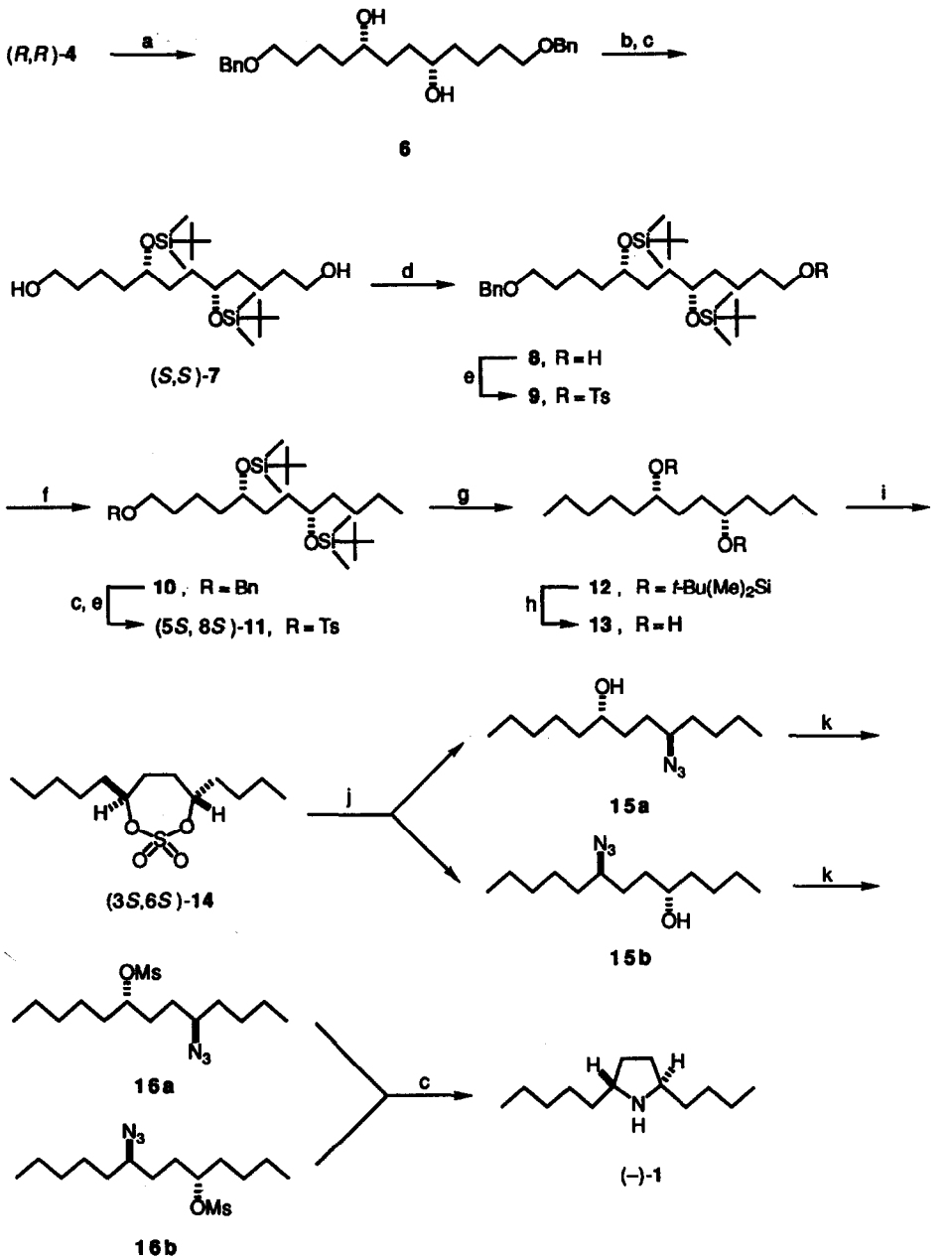
The (*S*,*S*)- and (*R*,*R*)-diepoxides **4** are both easily prepared in two and four steps, respectively, by utilizing (*S*,*S*)-1,2,5,6-hexanetetraol (**2**) as a single, common chiral synthon, available from D-mannitol[7] (Scheme 1). Thus, tosylation of the tetraol **2** followed by alkaline treatment provided (*S*,*S*)-**4**, $[\alpha]^{26}_{D}$ –15.8° (*c* 3.80, $CHCl_3$), as an oil in 58% overall yield from **2**. On the other hand, **2** was converted to the dimesylate **5** through

Scheme 1



(a) TsCl (2 equiv), Py; (b) 15% NaOH, THF; (c) *t*-Bu(Me)$_2$SiCl, imidazole, then MsCl, Et_3N, CH_2Cl_2; (d) conc. HCl–MeOH, then 20% KOH, THF.

Scheme 2



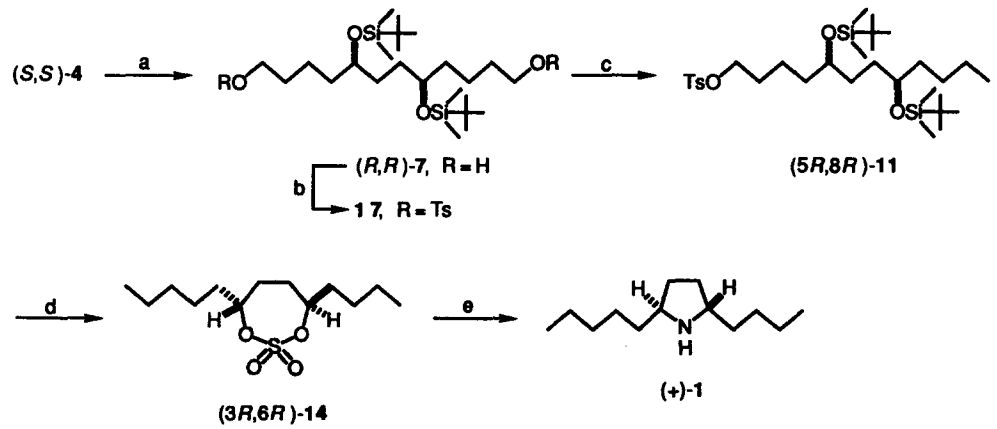
(a) $BnO(CH_2)_3MgBr$, cat. CuI, THF, –15 °C; (b) *t*-$Bu(Me)_2SiCl$, imidazole, DMF; (c) H_2, Pd–C, MeOH; (d) $PhCH_2Br$ (1 equiv), NaH, DMF; (e) TsCl, *N,N*-dimethylaminopyridine, CH_2Cl_2; (f) $LiAlH_4$, THF; (g) MeMgBr, cat. Li_2CuCl_4, THF, –78–0 °C; (h) conc. HCl–MeOH, 0 °C; (i) $SOCl_2$, Et_3N, CH_2Cl_2; then $NaIO_4$, cat. $RuCl_3$, $MeCN–H_2O$; (j) LiN_3, DMF, then cat. H_2SO_4, THF; (k) MsCl, Et_3N, CH_2Cl_2.

protection of the primary alcohol function followed by mesylation in 77% yield. Deprotection and alkaline treatment led to the (*R*,*R*)-diepoxide **4**, $[\alpha]^{26}_D$ +15.8° (*c* 2.22, $CHCl_3$), in 51% yield from **5**.

The (*R*,*R*)-diepoxides **4** thus obtained was treated with 2 equiv of 3-benzyloxypropylmagnesium bromide in the presence of a catalytic amount of cuprous ion (CuI, THF, –15 °C) to produce the dibenzyl compound **6** (62%); this was then converted to the diol (*S*,*S*)-**7** (91%) via silylation followed by debenzylation by hydrogenolysis (H_2, Pd–C). Monobenzylation of the diol (*S*,*S*)-**7** with C_2 symmetry was effected by treatment with 1 equiv of benzylbromide and NaH in DMF to give **8** (60%) with unsymmetrical structure, which was then converted to the tosylate **9** (100%) by a standard procedure (Scheme 2). After reduction with $LiAlH_4$, resulting **10** was subjected to debenzylation by hydrogenolysis (75% from **9**) and subsequent tosylation to give (5*S*,8*S*)-**11** (100%), which underwent coupling with methylmagnesium bromide in the presence of a catalyst (Li_2CuCl_4) to yield **12** (76%). When the diol **13**, obtained by deprotection of the disilyl ether **12**, was treated with thionyl chloride and triethylamine, followed by a catalytic amount of RuO_4 according to the Sharpless procedure,[8] the cyclic sulfate (3*S*,6*S*)-**14**, $[\alpha]^{26}_D$ +19.9° (*c* 1.36, $CHCl_3$), was produced in 77% overall yield from **13**. Nucleophilic ring opening of the cyclic sulfate by treatment with LiN_3, followed by hydrolysis of the resulting sulfate, afforded a 1:1 mixture (92% yield) of the two azides **15a** and **15b**, which was, without separation, converted to a mixture of the correponding mesylates **16a** and **16b** in 91% yield. These structural isomers **16a** and **16b** can be both convergently led to the same product by an intramolecular cyclization with inversion of the configurations of the carbons bearing the mesyloxy groups. Thus, the resultant 1:1 mixture of **16a** and **16b**, without separation, underwent hydrogenation over palladium on carbon, exclusively producing (2*R*,5*R*)-*trans*-2-butyl-5-pentylpyrrolidine [(–)-**1**],[9] oil; $[\alpha]^{27}_D$ –5.8° (*c* 0.61, $CHCl_3$),[10] in 91% yield.[11] Synthetic (–)-**1** exhibited the mass spectrum identical with that published for the natural alkaloid from both *S. punctaticeps*[1] and *D. histrionicus*.[4]

For the synthesis of the (+)-enantiomer of **1**, we employed a more convenient short route starting with the (*S*,*S*)-diepoxide **4**. (Scheme 3). Thus, (*S*,*S*)-**4** was converted to the C_2 symmetrical diol (*R*,*R*)-**7** in the same

Scheme 3



(a) 3 steps as in Scheme 2; (b) TsCl (2 equiv), *N*,*N*-dimethylaminopyridine, CH_2Cl_2; (c) $LiEt_3BH$ (1 equiv), THF, 0 °C; (d) 4 steps as in Scheme 2; (e) 4 steps as in Scheme 2.

manner as described above for (*S*,*S*)-**7**. After tosylation of (*R*,*R*)-**7**, the resulting ditosylate **17** was treated with 1 equiv of super hydride ($LiEt_3BH$) in THF at 0 °C. In this way, the monotosylate (5*R*,8*R*)-**11** was obtained in 60% yield (90% based on recovered **17**). This product was led to (+)-**1**, $[\alpha]^{27}_D$ +5.8° (*c* 0.79, $CHCl_3$), via the cyclic sulfate (3*R*,6*R*)-**14**, $[\alpha]^{22}_D$ −19.0° (*c* 1.00, $CHCl_3$), by the same procedure as that used for the preparation of (−)-**1** above.

Up to now, a total of seventeen 2,5-dialkylpyrrolidine analogs (including **1**) have been found in the secretions of thief ants and fire ants of the genera *Solenopsis* and *Monomorium*.[13,3] These naturally occurring pyrrolidines reportedly are all of the trans configuration although the absolute configuration of the chiral centers still remains unknown. The enantioselective preparation of the unsymmetrical *trans*-2,5-dialkylpyrrolidine in both enantiomeric forms described in this paper would provide a methodology efficiently applicable to the synthesis of these alkaloids, which are naturally produced only in trace amounts.

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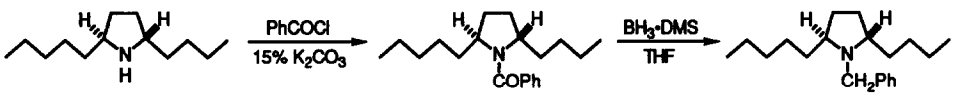
9. ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (3 H, t, *J* = 7.0 Hz), 0.89 (3 H, t, *J* = 7.0 Hz), 1.29–2.22 (18 H, m), 3.57–3.64 (2 H, unresolved); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 13.95, 14.00, 22.44, 22.55, 25.82, 26.33, 28.74, 29.63, 30.42, 30.45, 31.56, 32.39, 32.65, 59.57, 59.63.
10. No rotation data have been reported for the natural product.[1-4]
11. The trans stereochemistry of the product (+)-**1** was verified by the method of Hill and Chans[12] based on analysis of the benzyl methylene signal (δ 3.64 and 3.81, AB q, *J* = 13.9 Hz) in the ^1H NMR spectrum ($CDCl_3$) of the *N*-benzylpyrrolidine **ii** derived from (+)-**1** as follows.



(+)-**1** **I** **II**

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