An enantioselective synthesis of 2-alkyl-3-phenyltropanes by an asymmetric 1,3-dipolar cycloaddition reaction

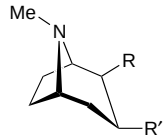
Gian Luca Araldi,[a] K. R. C. Prakash,[a] Clifford George[b] and Alan P. Kozikowski*[a]

[a] *Drug Discovery Laboratory, Georgetown University Medical Center, Institute for Cognitive and Computational Sciences, 3970 Reservoir Road NW, Washington, DC 20007-2197, USA*

[b] *Laboratory for the Structure of Matter, Code 6030, Naval Research Laboratory, 4555 Overlook Avenue SW, Washington, DC 20375-5000, USA*

A method for gaining access to 2-alkyl-3-phenyl-substituted tropanes using the chiral dipolarophile (*R*)-*p*-tolyl vinyl sulfoxide in the asymmetric 1,3-dipolar cycloaddition reaction with the oxidopyridinium betaine 4 is described.

(*R*)-Cocaine[1] **1** is a plant alkaloid purified from the leaves of *Erythroxylum coca*; its abuse is one of the greatest concerns of the American public today, and it is clear that immediate therapies are needed for the treatment of individuals who have become addicted to this powerful reinforcing drug.[2] In order to discover agents for use in the treatment of cocaine abuse, we believe that it will be valuable to identify molecules that can act as cocaine antagonists or partial agonists. Previously, we have shown that cocaine's C-2 ester group can be replaced by alkyl and alkenyl groups as in **3** with no loss in activity,[3] while other workers have shown that replacement of the C-3 benzoate by phenyl leads to compounds **2** of higher potency (these phenyl-bearing structures are often referred to as the WIN series compounds).[4] In order to more quickly identify those structural changes that may lead to altered functional activity, we required a chemical approach to diversely substituted 2-alkyl-3-phenyl-tropanes. We recently reported[5] a pyridinium betaine-based dipolar cycloaddition route to racemic tropane derivatives **3**.



1 R = CO_2Me, R′ = OBz
2 R = CO_2Me, R′ = Ph
3 R = alkyl or alkenyl, R′ = Ph

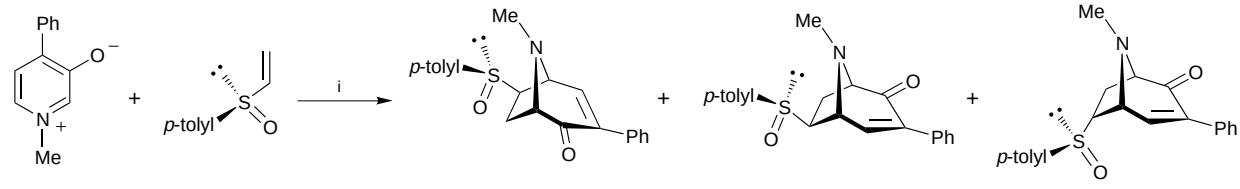
Asymmetric 1,3-dipolar cycloaddition reactions using chiral dipolarophiles are well documented.[6] Herein we report the cycloaddition reaction of the sulfoxide **5**[6a] and the oxidopyridinium betaine **4**[5] to afford the tropenone intermediates **6**–**8** with good diastereoselectivity and complete regioselectivity (Scheme 1). The reaction was performed in dioxane at reflux for 20 h to give a mixture of both *exo* and *endo* cycloadducts (70 : 30). Silica gel flash column chromatography of the crude mixture led to the separation of the *exo* products (4 : 1 mixture of the diastereomers **6** and **7**; 55% overall yield) from the *endo* product **8** (22% yield). The major *exo* diastereomer **6** was obtained by crystallization from EtOAc of the above 4 : 1 mixture and had $[\alpha]_D^{25}$ −51 (*c* 0.5, acetone), R_f 0.6 (EtOAc), and mp 166 °C. The *endo* product **8** had $[\alpha]_D^{25}$ +73 (*c* 0.5, acetone), R_f 0.3 (EtOAc), and mp 98–104 °C. The absolute configurations of **6** and **8** were determined by X-ray diffraction studies.†

The major *exo* product **6** was converted to the 2β-alkyl-3β-phenyltropane derivatives **11a** and **11b** as shown in Scheme 2. Thus, ketone **6** underwent exclusive 1,2-reduction using the Luche protocol[7] to provide the allylic alcohol intermediate as a mixture of the α- and β-stereoisomers. These alcohols were converted to their acetates followed by reduction of the sulfoxide with PCl_3 in DMF at 0 °C.[6b] The resulting sulfide **9** (3 : 1 mixture of the α- and β-acetates) underwent a CuCN-catalysed cross coupling reaction using RMgBr (R = Pr^n or Bu^n) as the nucleophile[8] to afford the alkene intermediates **10a** and **10b**. As previously reported,[5] this reaction is completely regioselective (only γ-alkylation products are observed), and the final stereochemistry of the alkyl-bearing centre is independent of that of the acetate intermediate (*i.e.* only β-diastereoisomers are observed).

The alkenes **10a** and **10b** were subjected in turn to a one-step desulfurization and hydrogenation reaction using Raney-nickel (W2) in EtOH to yield the 2β,3β-isomers **11a** and **11b** (12–13%) together with the 2β,3α-isomers **12a** and **12b** (40–43%) derived from β-face hydrogenation. These mixtures were separated by preparative TLC (hexane–EtOAc–Et_3N 9 : 0.8 : 0.2) on silica gel. The 2β-*n*-propyl-3β-phenyltropane **11a** had $[\alpha]_D^{25}$ −49 (*c* 0.25, CH_2Cl_2); the corresponding 2β,3α-isomer **12a** had $[\alpha]_D^{25}$ −50 (*c* 1.0, CH_2Cl_2). The *n*-butyl derivatives **11b** and **12b** had $[\alpha]_D^{25}$ −64 (*c* 0.2, CH_2Cl_2) and −43 (*c* 0.5, CH_2Cl_2), respectively.

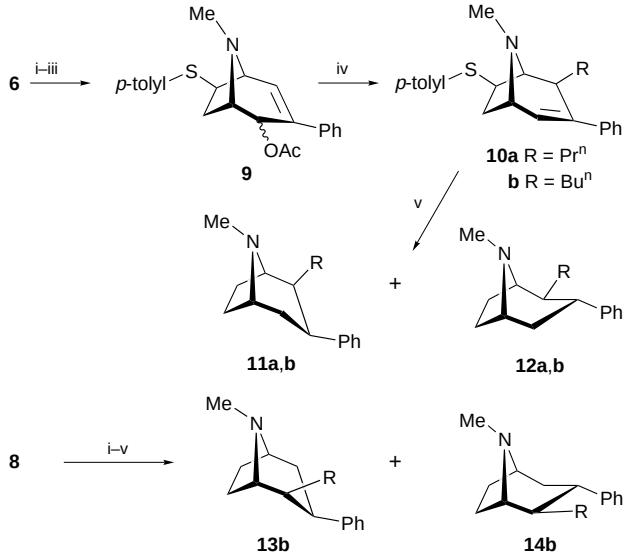
Compound **8** was subjected to the same sequence of reactions as presented in Scheme 2 for the intermediate **6** using Bu^nMgBr as Grignard reagent. Two products were obtained after complete reduction of the intermediate alkene: 2β-*n*-butyl-3β-phenyltropane **13b** with $[\alpha]_D^{25}$ +62 (*c* 0.2, CH_2Cl_2) and the corresponding 2β,3α isomer **14b** with $[\alpha]_D^{25}$ +41 (*c* 0.5, CH_2Cl_2).

The structures and stereochemical assignments for these compounds were determined using ^1H NMR, ^{13}C NMR,



4 **5** (1*S*, 5*S*, 6*R*, R_S)-**6** (44%) (1*R*, 5*R*, 6*S*, R_S)-**7** (11%) (1*R*, 5*R*, 6*R*, R_S)-**8** (22%)

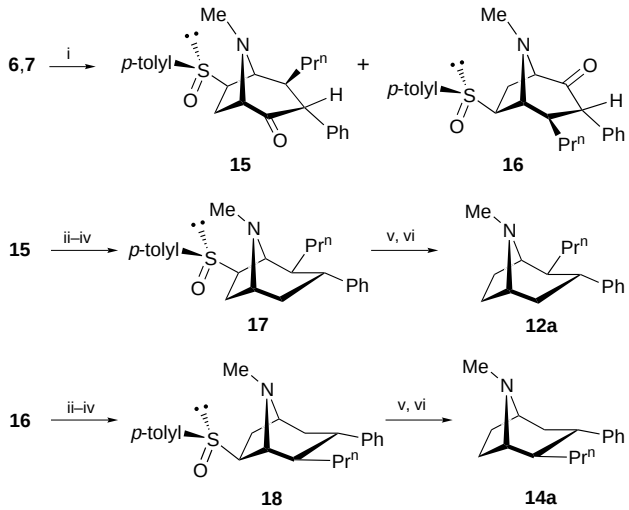
Scheme 1 *Reagents and conditions*: i, 1,4-dioxane, reflux, 24 h



Scheme 2 *Reagents and conditions*: i, $NaBH_4$, $CeCl_3$, MeOH, room temp.; ii, Ac_2O, pyridine, room temp.; iii, PCl_3, DMF, 0 °C, 88%; iv, RMgBr, CuCN, Et_2O, room temp., 77%; v, Raney-Ni (W2), EtOH, reflux

HETCOR and 2D COSY experiments. Because the stereochemical assignment of the final compounds **11** and **12** is problematic due to the complexity of their ^{1}H NMR spectra, we synthesized the chair-like compounds **11a**,**b** from natural (−)-cocaine by the procedure previously reported.[3] Our synthetic samples proved to be identical in all respects with the samples obtained from natural (−)-cocaine.

Additionally using the mixture of diastereoisomers **6** and **7**, we developed another route that would unequivocally afford only the 2β,3α-tropane derivatives **12a** and **14a** (Scheme 3). This mixture readily underwent the copper(I)-catalysed conjugate addition reaction of Pr^nMgBr in the presence of Me_3SiCl and HMPA[9] to afford the two alkylated derivatives **15** and **16**, which were separated by flash chromatography on silica gel. The relative stereochemistry of the C-3 and C-4 substituents in these two derivatives was assigned by the observation of $J_{3,4}$ = 8.1 and 7.5 Hz for compounds **15** and **16**, respectively. These coupling constants are comparable with those reported



Scheme 3 *Reagents and conditions*: i, Pr^nMgBr, CuBr.Me_2S, HMPA, Me_3SiCl, THF, −78 °C; ii, $LiAlH_4$, THF, room temp.; iii, LDA, ClC(S)OPh, THF, −78 °C; iv, Bu_3SnH, AlBN, toluene, 90 °C; v, PCl_3, DMF, 0 °C; vi, Raney-Ni, EtOH, reflux

earlier in the literature[5] wherein the stereochemistry of these compounds was confirmed by X-ray analysis.

The ketone **15** was reduced with $LiAlH_4$ to afford the 2α-alcohol in 56% yield as a single isomer. Next, this alcohol was treated with LDA followed by *O*-phenyl chlorothioformate in THF to provide the thiocarbonate intermediate, which was deoxygenated with Bu^n_3SnH and AIBN[10] to give the tropane **17** in an overall yield of 34%. Reduction of the sulfoxide with PCl_3 followed by desulfurization with Raney-nickel in EtOH at reflux yielded the tropane **12a**. The ^{1}H NMR spectrum and optical rotation of this sample were identical to those of the sample obtained by the methods of Scheme 2; this result accordingly further supports the assignment of the stereochemistry of compounds **11** and **12**.

Using the same methodology of Scheme 3, **16** was converted to the *trans* derivative **14a** that had $[\alpha]_D^{25}$ +53 (*c* 1.0, CH_2Cl_2).

In conclusion, the use of (*R*)-*p*-tolyl vinyl sulfoxide in the 1,3-dipolar cycloaddition reaction affords access to the non-racemic alkyltropanes **11** and **12**. This synthetic approach is particularly useful for the asymmetric synthesis of compounds of the general formula **3** bearing a substituent in position 6 of the tropane ring. The versatility of this method may be further enhanced through chemical modification of the *p*-tolyl sulfoxide moiety other than by reduction. Furthermore, using the method described in Scheme 3, we are able to selectively synthesize either enantiomer of the 2β,3α-tropane derivatives in optically pure form. These analogues are important since they are more selective for the dopamine transporter relative to the 5-HT transporter than the 2β,3β-isomers.[11]

We are indebted to NIH/NIDA (grant No. DA 10458) for support of this work.

Footnotes and References

* E-mail: kozikowa@GICCS.GEORGETOWN.EDU

† *Crystal data* for **6**: $C_{21}H_{21}NO_2S$, *M* = 351.45, orthorhombic, $P2_12_12_1$, *a* = 8.0505(6), *b* = 13.5650(11), *c* = 16.7466(9) Å, *V* = 1828.8(2) Å^3, *Z* = 4, *T* = 293(2) K, μ = 1.674, 1882 reflections, 1637 observed, *R* = 0.0376, *wR* = 0.0957. For **8**·0.4 EtOAc: $C_{21}H_{21}NO_2S$·0.4($C_4H_8O_2$), *M* = 386.69, monoclinic, $P2_1$, *a* = 12.9389(10), *b* = 6.1551(5), *c* = 14.340(2) Å, *V* = 1041.6(2) Å^3, *Z* = 2, *T* = 293(2) K, μ = 1.544, 1909 reflections, 1645 observed, *R* = 0.0486, *wR* = 0.1195. CCDC 182/581.

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Received in Corvallis, OR, USA, 16th June 1997; 7/04216G