Pergamon

Tetrahedron Letters 41 (2000) 7427–7432

TETRAHEDRON LETTERS

Radical cyclization strategies for the formation of ring constrained tricyclic tropane analogues

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Received 13 June 2000; accepted 30 June 2000

Abstract

A concise and efficient method for the construction of N,C3-constrained tropane derivatives has been developed. The key step of the reaction sequence involves either a 6- or a 7-*trig* radical cyclization.

It is well known that cocaine not only displays strong anesthetic effects, but that is also a strong reinforcing drug that leads to addiction. According to the dopamine theory of addiction, cocaine is believed to elicit its behavioral and pharmacological effects primarily by binding to the dopamine transporter (DAT), thereby elevating extracellular dopamine levels in some areas in the midbrain.[1,2] Cocaine also binds with high affinity to the serotonin (SERT) and norepinephrine transporters (NET).[3] We have postulated that drugs lacking the ability to inhibit transport at all three monoamine transporters may exhibit only partial cocaine-like properties, and thus possibly serve as medications.[4–6] Recently we demonstrated that it is possible to tune the selectivity of aryl-substituted tropanes for the SERT or the NET by introduction of a ring constraint between the nitrogen atom and carbon 3 of the tropane ring.[6] However, as we have shown, not only is the ring constraint an important feature for binding and selectivity, but additionally the phenyl substituent at the terminus of the alkylidene group contributes to the activity and selectivity as well. Thus compounds with high activity for either the SERT or the NET, or both have been obtained (Fig. 1).

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PII: S0040-4039(00)01288-0

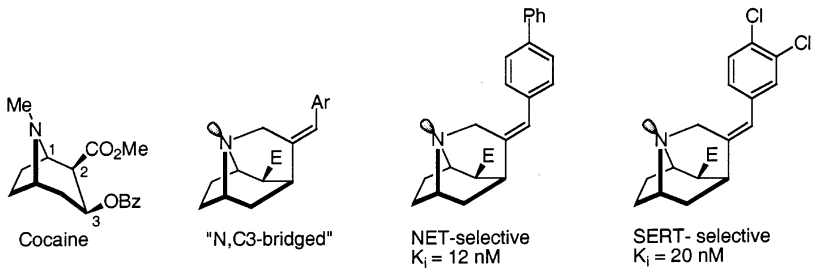
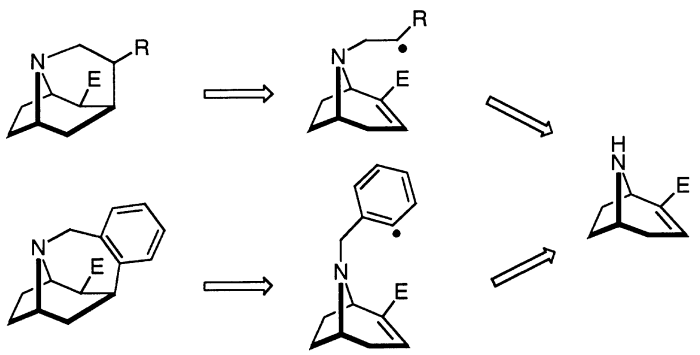


Figure 1.

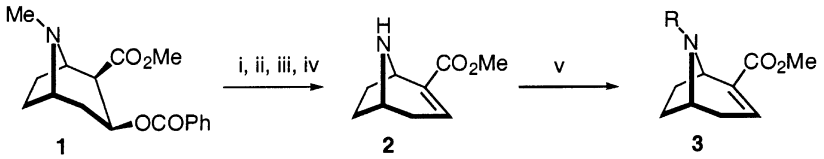
Our present aim was to further investigate the role of the additional carbon bridge and the influence of the phenyl substituent on binding activity and transporter selectivity. A compound lacking the phenyl substituent should substantiate the requirement for this structural feature, while compounds with either two phenyl substituents or one containing a phenyl ring constrained by incorporating it into the bridge would be useful in further elucidating the steric and geometric requirements for transporter binding and selectivity. In this letter we describe cyclization strategies that provide access to tropanes bearing these substituents or that have been rigidified through an aryl ring. This chemistry allows for a more comprehensive SAR, and hence provides further insights into the design of selective monoamine reuptake inhibitors.

Radical cyclization reactions have become a very powerful tool in organic synthesis, in particular in carbon–carbon bond forming reactions that lead to constrained compounds.[7,8] Thus we envisioned a synthesis strategy that involves a radical mediated ring closure as a key step. Our approach to the synthesis of the constrained tropanes is illustrated in Scheme 1. This chemistry is based on the 6- or 7-*trig* radical cyclization of an intermediate vinyl or aryl radical, generated by tri-*n*-butyltin hydride mediated carbon–halogen bond cleavage, followed by addition to the activated double bond in anhydroecgonine methyl ester.



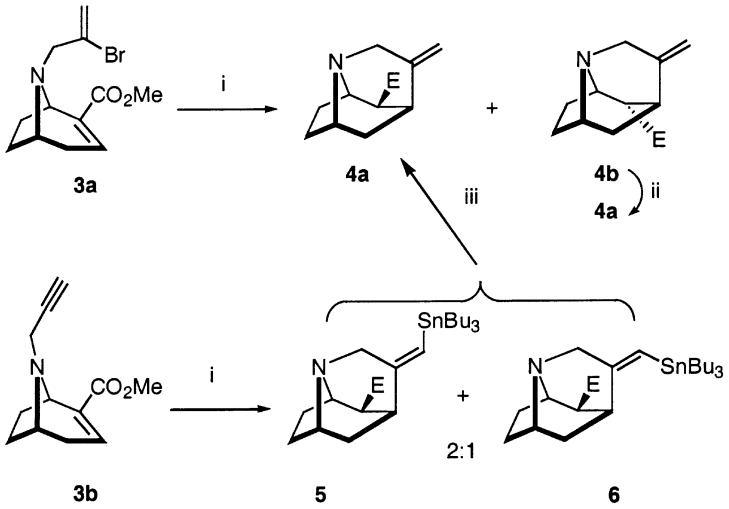
Scheme 1. E = COOMe

The synthetic pathway started with cocaine (**1**), which was converted to anhydroecgonine methyl ester by acid hydrolysis, dehydration, and reesterification.[9] Demethylation with α-chloroethyl chloroformate afforded noranhydroecgonine methyl ester (**2**).[10] The secondary amino group was in turn alkylated with a variety of substituents required for the radical cyclization step (Scheme 2).



Scheme 2. *Reagents and conditions*: (i) 1N HCl, reflux, 16 h; (ii) $POCl_3$, reflux, 4 h; (iii) MeOH, –40°C ~ rt, 20 min; (iv) $CH_3CH(Cl)OCOCl$, 1,2-dichloroethane, K_2CO_3; MeOH, 92%; (v) K_2CO_3, RBr, DMF, 77–85%; **a**, R = 2-bromopropenyl; **b**, R = 2-bromobenzyl; **c**, R = 2-bromo-1,1-diphenylprop-1-enyl; **d**, R = propargyl

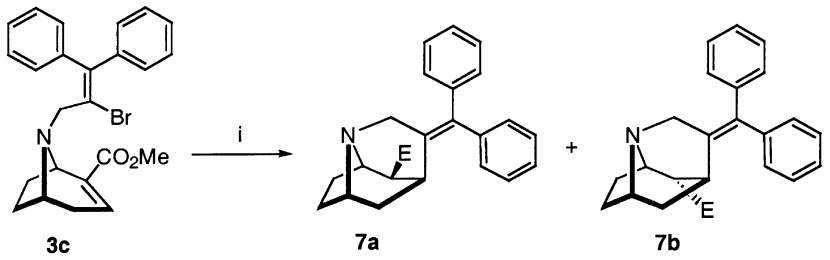
As our previously published series of compounds bears an aryl substituent at the terminus of the alkylidene group (Fig. 1),[6] we wished to probe the role of this aryl group by preparing compound **4a** which lacks this substituent as noted above. Thus, *N*-(2-bromopropenyl)noranhydroecgonine methyl ester (**3a**) was cyclized using tributyltin hydride and AIBN to afford a 1:1 mixture of diastereoisomers which we were unable to separate under various chromatographic conditions. However, one epimer could be enriched by basic epimerization in methanol (Scheme 3).



Scheme 3. *Reagents and conditions*: (i) *n*-Bu_3SnH, AIBN, benzene, reflux; (ii) NaOMe, MeOH, reflux; (iii) TFA, CH_2Cl_2

To confirm the structure of the major diastereoisomer, we prepared compound **4a** according to our previously published vinylstannane route.[6] This route utilizes the cyclization of a propargyl substituent which is converted into a stannylvinyl radical under the cyclization conditions. A *Z*/*E* mixture of the tricyclic vinylstannanes **5** and **6** with the ester group in the β-orientation was obtained in about 75% combined yield. Subsequent protodestannylation of this mixture was carried out to furnish diastereoisomerically pure **4a**. The reported procedure for protodestannylation that makes use of dry silica gel in dichloromethane proved to be inefficient.[11] However, the use of trifluoroacetic acid in dichloromethane led to the pure product in about 80% yield in 12 hours. Comparison of the NMR spectra and the optical rotation of the sample obtained in this way with that obtained using the epimerization protocol proved that the diastereoisomer **4a**, bearing the β-oriented ester, was the major diastereomer after epimerization.

With compound **4a** in hand and with the effect of compounds with one terminal aryl substituent already investigated, an interesting question was how a second phenyl substituent at the double bond terminus would influence the biological activity (Scheme 4).

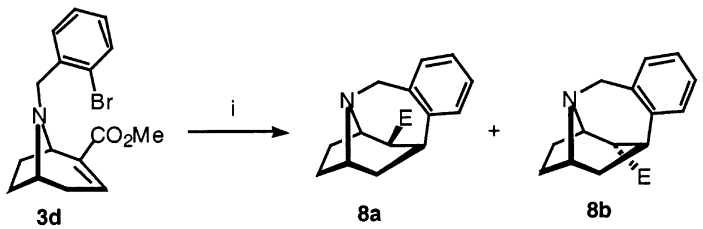


Scheme 4. *Reagents and conditions*: (i) n-Bu_3SnH, AIBN, benzene, reflux

The requisite starting material, *N*-(2-bromo-3,3-diphenylprop-2-enyl)anhydroecgonine methyl ester (**3c**) was obtained by alkylation of **2** with 2,3-dibromo-1,1-diphenylpropene which in turn was prepared following an established literature procedure.[12,13] Radical cyclization mediated by n-Bu_3SnH/AIBN furnished a variable mixture of diastereoisomers (β/α 4:1–6:1) in about 30% yield which we were unable to separate by standard chromatographic methods. The enhanced diastereoselectivity in comparison to the cyclization employing an unsubstituted vinyl radical is a consequence of the enhanced steric demand exerted by the voluminous substituent.

Finally, we reasoned that it would be of interest to investigate the activity of a benzoannelated tricyclic tropane system. In this system the phenyl ring is constrained by annelation with the newly formed bridge and adopts a position perpendicular to the basal plane of the tropane nucleus.

The orientation of this phenyl ring together with the strong restriction of conformational freedom was postulated to lead to enhanced selectivity at the monoamine reuptake sites. For the construction of the ring system we had to make use of a 7-*trig* radical cyclization. The formation of 7-membered rings through radical cyclization is usually difficult.[14] However, the radical stabilizing effect of the ester group in **3d** was anticipated to work in favor of the desired regiochemistry. In the event, simple refluxing of the reactants in benzene or toluene resulted only in the radical-mediated reduction of the aryl bromide. Only when tributyltin hydride and AIBN were added under kinetic conditions using a syringe pump, was the desired product obtained in 33% yield. Tris(trimethylsilyl)silane, a less reactive radical chain mediator, gave the same product but only in 4% yield (Scheme 5).



Scheme 5. *Reagents and conditions*: (i) n-Bu_3SnH, AIBN, benzene, reflux

By virtue of the bulky nature of the newly formed bridge, the final hydride delivery step leads predominantly to the product possessing a β-oriented ester group (β/α = 9:1). By crystallization with (–)-camphorsulfonic acid we were able to obtain crystals of the major diastereoisomer suitable for X-ray crystallography which confirmed the structure of this compound (Fig. 2).[15]

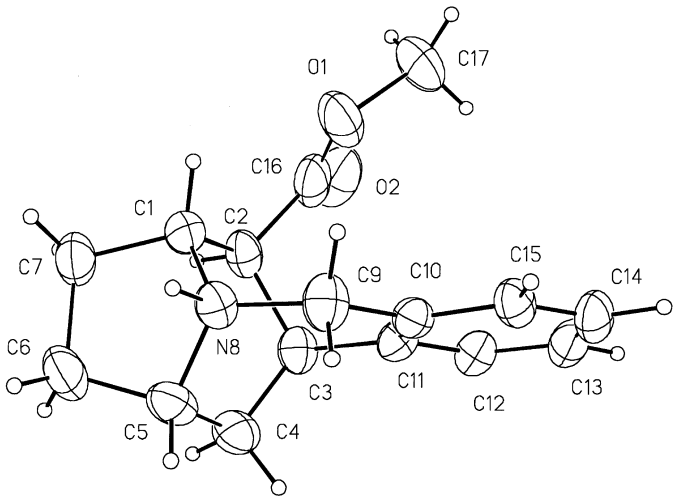


Figure 2. ORTEP drawing of the (–)-camphorsulfonate of **8a** (anion omitted). The figure is drawn from the experimentally determined coordinates with thermal parameters at the 20% probability level

In summary, we have developed a concise route to novel tricyclic tropanes based on radical cyclization technology.[16] The syntheses feature a 6-*trig* radical ring closure of a vinyl radical and a 7-*trig* ring closure of an aryl radical. The biological testing of the described compounds and the application of this method to the preparation of other modified tropanes with the aim of probing the SAR for the inhibition of monoamine reuptake are underway.

Acknowledgements

We are indebted to NIH/NIDA for support of this work (DA10458).

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15. Atomic coordinates for **8a** have been deposited with the Cambridge Crystallographic Data Base, 12 Union Road, Cambridge CB2 1EZ, UK (deposit@ccdc.cam.ac.uk).
16. Compound **4a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.46 (m, 3H), 1.99 (ddd, $J=2.7$, 9.6, 22.8 Hz, 1H), 2.13 (m, 2H), 2.34 (t, $J=3.3$ Hz, 1H), 2.62 (dd, $J=6.1$, 3.4 Hz, 1H), 3.26 (m, 1H), 3.28–3.66 (m, 2H), 3.66 (s, 3H), 4.68 (m, 1H), 4.72 (m, 1H). **7**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.46 (m, 3H), 2.18 (m, 3H), 2.26 (t, $J=2.7$ Hz, 1H), 2.93 (dd, $J=6.1$, 3.6 Hz, 1H), 3.18 (m, 1H, minor isomer) 3.27 (m, 1H), 3.44 (A part of ABq, $J=18.3$ Hz, 1H), 3.54 (s, 3H), 3.55 (s, 3H, minor isomer), 3.77 (m, 1H), 3.97 (B part of ABq, $J=18.3$ Hz, 1H), 7.0–7.4 (m, 10H). **8a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.53 (m, 2H), 1.86 (ddd, $J=14.2$, 7.1, 1.8 Hz, 1H), 2.13 (m, 2H), 2.42 (dd, $J=14.4$, 8.9 Hz, 1H), 2.78 (dd, $J=6.5$, 2.2 Hz, 1H) 3.09 (t, $J=6.6$ Hz, 1H), 3.38 (s, 3H), 3.61 (m, 1H), 4.12 (m, 1H), 4.48 and 4.69 (ABq, $J=18.1$ Hz, 2H), 6.9–7.1 (m, 4H).