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STEREOCONTROLLED SYNTHESIS OF TROPANOL DERIVATIVES VIA PALLADIUM-CATALYZED REACTIONS

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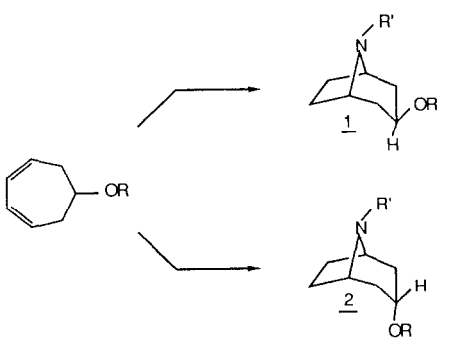
Summary: A general method for the transformation of 1,3-cycloheptadienes to tropane alkaloid derivatives was developed. The procedure was applied to the stereocontrolled synthesis of the exo- and endo-tropanol derivatives 1 and 2. The approach is based on a dual stereocontrol in the 1,4-functionalization of conjugated dienes.

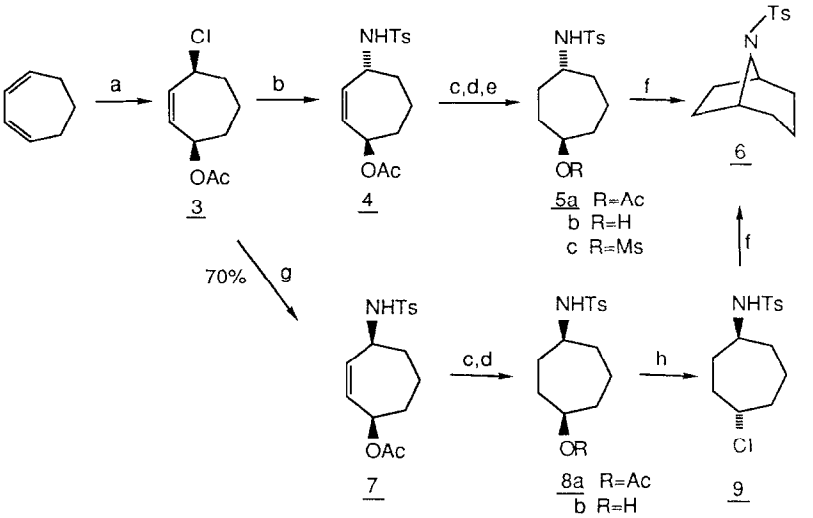
We have recently reported a methodology for 1,4-functionalizations of 1,3-dienes that allows a control of the 1,4-relative stereochemistry.[2-4] The approach is based on a palladium-catalyzed 1,4-chloroacetoxylation and subsequent allylic substitution of the chloro group with either retention or inversion. In some cases the functionalizations are diastereoselective towards an existing asymmetric centre in the diene. By using this methodology it should be possible to introduce a nitrogen to a 6-oxy-substituted 1,3-cycloheptadiene so that both the exo and endo isomers 1 and 2 of the tropane alkaloide derivatives[5] are obtained (cf pseudotropine (1b) and tropine (2b)). In this communication we report a stereocontrolled synthesis of derivatives 1 and 2 utilizing the chloroacetoxylation approach.



a R=PhCH$_2$, R'=Ts
b R=H, R'=Me
c R=R'=H

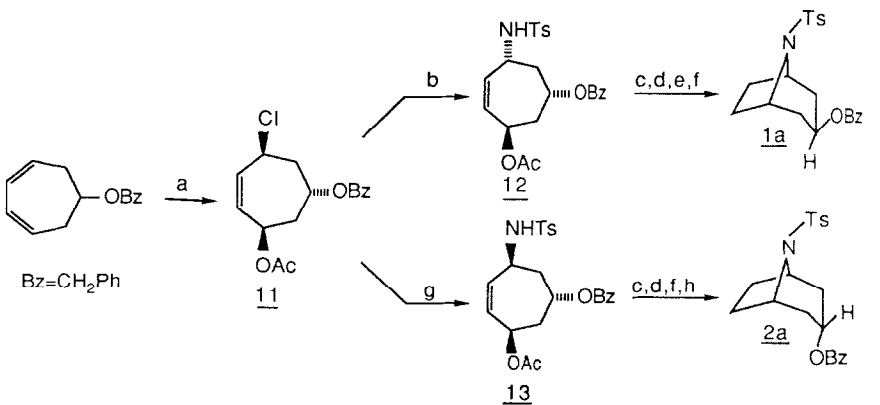
A number of synthetic strategies to tropane alkaloids have been investigated.[6,7] In the present approach we have utilized a 1,4-chloroacetoxylation of a 1,3-cycloheptadiene derivative with subsequent stereocontrolled substitution of the chloro group by an amide.[8] Cyclization of the amidoacetate would lead to an 8-aza[3.2.1]bicyclooctane system. We first studied the cyclization sequence on 1,3-cycloheptadiene. Chloroacetoxylation[2] of 1,3-cycloheptadiene and subsequent reaction of the chloroacetate 3 with sodium p-toluenesulfonamide (NaNHTs) either in CH_3CN-DMSO at 80 °C or palladium-catalyzed[8] in CH_3CN at 20 °C

Scheme 1



a. $Pd(OAc)_2$, (7%), LiCl, LiOAc, p-benzoquinone, HOAc (71%). b. NaNHTs, CH_3CN-DMSO, (1:1) 80°C, 3h (70%). c. H_2 (6 atm.), $RhCl(PPh_3)_3$, ethanol, 20°C, 20h, (94%, 85%). d. NaOH, MeOH-H_2O (97%, 100%). e. MsCl/Et_3N, THF (98%). f. K_2CO_3, MeOH (77%, 91%). g. NaNHTs, $Pd(PPh_3)_4$ (3%), CH_3CN, 20°C, 3h (80%). h. EtO_2C-N=N-CO_2Et, $ZnCl_2$, PBu_3, 20°C, 3h, (87%).

Scheme 2



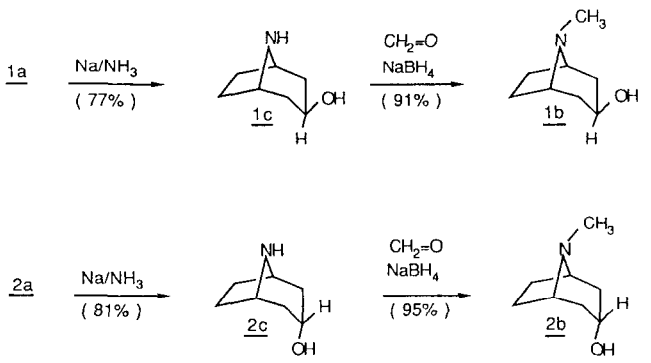
a. $Pd(OAc_2$ (7%), LiCl, LiOAc, p-benzoquinone, HOAc, (77%). b. NaNHTs, CH_3CN-DMSO (1:1), 80°C, 3h, (77%). c. H_2 (6 atm.), $RhCl(PPh_3)_3$, ethanol, 20°C, 15h, (98%, 95%). d. NaOH, MeOH-H_2O (99%, 95%). e. MsCl/Et_3N, THF, (100%). f. K_2CO_3, MeOH, 1h, 20°C (97%, 90%). g. NaNHTs, $Pd(PPh_3)_4$, (3%), CH_3CN-DMSO (1:1), 20°C, 12h, (64%). h. EtO_2C-N=N-CO_2Et, $ZnCl_2$, PBu_3, 20°C, 3h, (95%).

afforded 4 and 7 respectively (Scheme 1). Hydrogenation of 4 and 7 proceeded without epimerization to give 5a and 8a in 94 and 85% yield respectively, and subsequent hydrolysis afforded the corresponding alcohols (5b and 8b). Alcohol 5b was transformed to its mesylate which was cyclized to 6 in 77% yield by treatment with K_2CO_3 in methanol. The corresponding cis-alcohol 8b was transformed to the chloride 9 with complete inversion of configuration at carbon using a modification of the procedure described by Ho and Davies.[9,10] Cyclization of 9 to 6 in 91% yield was performed under the same conditions as for cyclization of 5b.

It would also be of great interest to cyclize the unsaturated substrate 7 by palladium-catalysis. For the 6-oxy-substituted case this would give an entry into scopolamin and related derivatives.[6] So far attempted palladium-catalyzed cyclization of 7 has only resulted in the formation of diene by elimination of acetic acid.

The two cyclizations shown in Scheme 1 were applied to 6-benzyloxy-1,3-cycloheptadiene, which leads to a complete stereocontrol of the 3-oxy substituent of the tropane derivative (Scheme 2). Chloroacetoxylation[2] of 6-benzyloxy-1,3-cycloheptadiene[11] was completely regio- and stereoselective and gave only one diastereoisomer (11) in 77% yield. Substitution of the chloride with tosylamide with either retention or inversion afforded amidoacetates 12 and 13 respectively having the two possible relative configurations between the nitrogen and benzyloxy substituents. By applying the sequences used in Scheme 1, 12 was transformed to 1a in 94% overall yield and 13 was transformed to 2a in 77% overall yield.

The protective groups on nitrogen and oxygen in 1a and 2a can readily be removed by standard methods.[12,13] This was demonstrated by the transformation of 1a to pseudonortropine 1c[14] and 2a to nortropine 2c.[14] By utilizing Na/NH_3 both protective groups were removed at the same time in each case. By utilizing other deprotection methods one of the protective groups can selectively be removed.[12] The pseudonortropine (1c) and nortropine (2c) obtained were further characterized by alkylation[15] to pseudotropine (1b) and tropine (2b) respectively.[16]



In a related approach to the one described here, tropane alkaloids were synthesized from 6-oxy-substituted 1,3-cycloheptadiene via a [4+2] nitroso cycloaddition. However, the latter approach does not allow a stereocontrol at the 3-oxy position and only the pseudotropine derivatives could be obtained. The present procedure allows a dual stereocontrol at the 3-position and furthermore it gives a much higher overall yield.

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10. The use of $SOCl_2/Et_3N$ gave lower yields of 9. Contrary to what was reported in ref 7 for an analogous compound there was a loss of stereospecificity using this reagent giving 9 with trans/cis ratios of 75/25.
11. Readily prepared from cycloheptatriene in three steps; cf. J.E. Bäckvall, S.E. Byström, and R.E. Nordberg, J. Org. Chem., 49, 4619 (1984).
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16. Nortropine (1b) gave identical ^1H and ^{13}C NMR spectra to those reported in ref. 7. The tropine (2b) obtained had identical spectral data with a commercial sample (Fluka AG).

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