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Synthesis of Enantiopure (Nor-)Azatropanes *via* *N*-Acylhydrazonium Ion Intermediates

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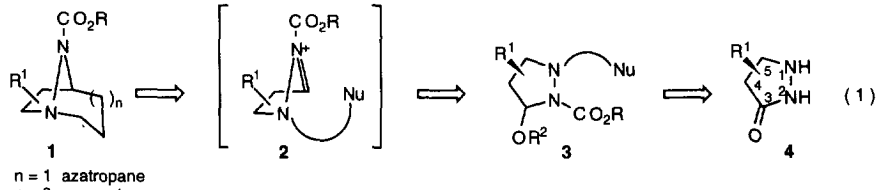
Abstract: The synthesis of a number of aza-analogues of (nor)tropanes is described. Key features of the synthesis include the efficient preparation of an enantiopure 5-substituted 3-pyrazolidinone and stereoselective cyclization of an *N*-acylhydrazonium ion intermediate.

The 3-pyrazolidinone moiety continues to be of interest to biologists and chemists.[1] Among the many known examples, only a fraction consists of enantiopure 3-pyrazolidinones[2] of which, to the best of our knowledge, only a few have been applied as building blocks for further synthetic applications.[3] In our search for optically active 3-pyrazolidinones that could be used in our previously developed route to azatropane derivatives starting from racemic 3-pyrazolidinone systems,[4] none of these known structures appeared suitable. In this article, we wish to present a short and efficient route to a novel enantiopure 3-pyrazolidinone, which is an appropriate starting material for the synthesis of a number of aza-analogues of (nor)tropanes **1**.

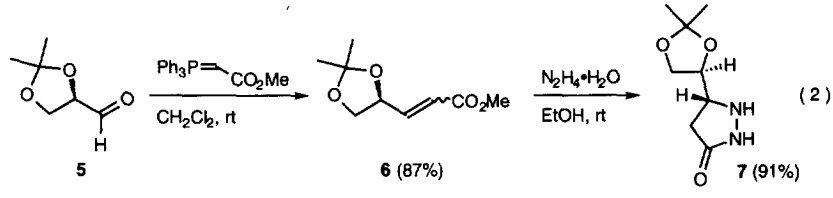


1 **2** **3** **4** (1)

n = 1 azatropane
n = 0 nor-azatropane

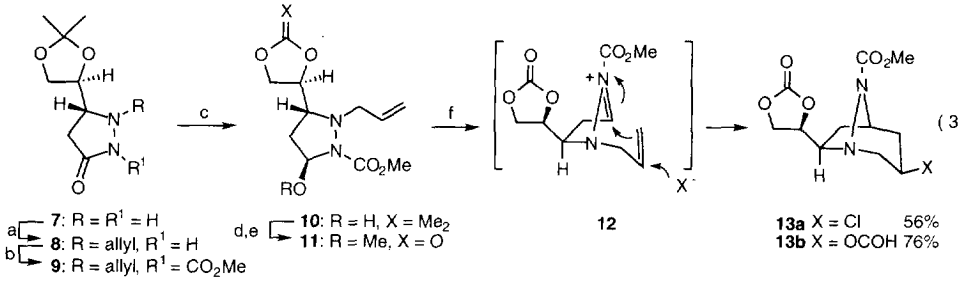
The strategy for the construction of such bicyclic hydrazines involves stereoselective ring closure of the *N*-acylhydrazonium ion intermediate **2** (eq 1).[5] A useful precursor for this reaction is the pyrazolidine **3**, in which a bulky substituent is present that determines the stereochemical outcome of the cyclization reaction. The cyclization precursor can be obtained starting from an enantiopure pyrazolidinone **4**.

After some unsuccessful attempts to prepare novel 4-substituted 3-pyrazolidinones, we decided to focus our efforts on 5-substituted ones. Modification of the results described by Liebscher *et al.*, where hydrazine reacts in a 1,4-fashion with chiral butenolides,[2a] led to a straightforward preparation of the pyrazolidinone **7**, as shown in eq 2.



5 **6** (87%) **7** (91%) (2)

The sequence began with a Horner-Wittig reaction of the readily available (*R*)-glyceraldehyde[6] to give the α,β-unsaturated ester **6** as a 1.2:1 mixture of E/Z-isomers.[7] Treatment of this mixture with hydrazine hydrate ($N_2H_4 \cdot H_2O$, EtOH, rt) afforded the pyrazolidinone **7** (*ca.* 9:1 ratio of diastereoisomers according to ^1H NMR) in high yield, which could be obtained in pure form by repeated recrystallization.[8]



Reagents and conditions: a) NaH (1 equiv), THF, rt, 30 min, then allyl bromide (2 equiv), 0 °C → rt, 4 h, 82%; b) NaH (1 equiv), THF, rt, 30 min, then $ClCO_2Me$ (3 equiv), 0 °C → rt, 4 h, 75%; c) $NaBH_4$ (4 equiv), EtOH, H_2SO_4 (cat), -25 °C, 4 h, 86%; d) HCl/MeOH, 0 °C, 1 h; e) $COCl_2$ (2 equiv), pyridine (2 equiv), CH_2Cl_2, 0 °C, 1 h, 82% (from **10**); f) $SnCl_4$ (4 equiv), CH_2Cl_2, -78 °C → rt, 4 h, 56% or HCOOH, rt, 18 h, 76%.

The route that led to the cyclization products **13a** and **b** is shown in eq 3 and started with alkylation of **7** at the amine nitrogen (N-1) with a nucleophile-containing side chain. Deprotonation and subsequent reaction with allyl bromide afforded **8** in 82% yield. Despite the fact that deprotonation took place at the amide nitrogen (N-2), alkylation occurred at N-1, which, surprisingly, appeared to be more nucleophilic under these conditions. Then, N-2 was methoxycarbonylated rendering the ring carbonyl function more electrophilic, so that smooth reduction to the pyrazolidinol **10** took place.[4] Remarkably, only the *trans*-isomer was found, which is probably a result of complexation of borohydride to the dioxolane function. At this point, conversion of the acid-labile isopropylidene function into the more stable carbonate was necessary to prevent loss of material in the cyclization step. Under the reaction conditions of the transprotection the hydrazonium ion was formed and trapped with MeOH to give the thermodynamically more stable *trans*-product. Conversion of the resulting diol into the cyclic carbonate **11**, followed by treatment with either $SnCl_4$ or formic acid resulted in the formation of the endocyclic *N*-acylhydrazonium ion **12** which then cleanly cyclized to **13a** and **b**, respectively. Only a single diastereomer, the one obtained by attack of the allyl group opposite to the carbonate fragment, could be detected in both cases. The X-substituent appeared to be equatorial which is in line with the expected chair like transition state conformation **12** and equatorial attack of the incoming nucleophile.[4] This stereochemistry was unequivocally proven by an X-ray crystallographic analysis of azatropane **13a** (Figure 1).[9]

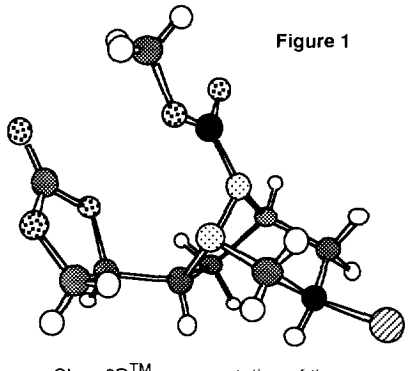


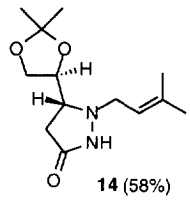
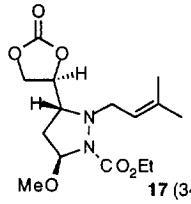
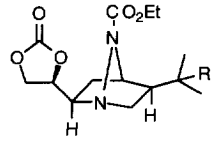
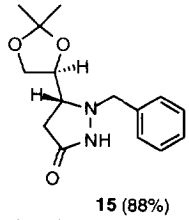
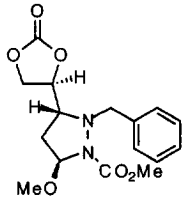
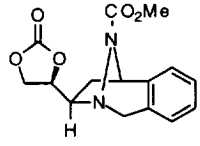
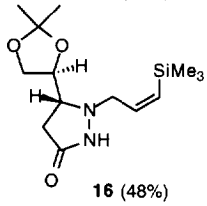
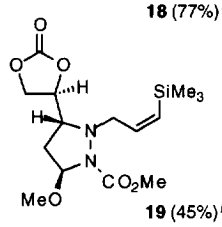
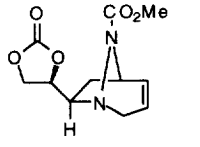
Figure 1

Chem3D™ representation of the crystal structure of **13a**.

Enantiopure 5,5- and 5,6-bicyclic hydrazines with diverse substitution patterns could be obtained by using different π-nucleophiles, of which a number of examples are shown in Table 1. The highest yields of alkylated products were obtained by applying different alkylation methods. The conditions used for allylation (method A) were also used to obtain the prenyl substituted pyrazolidinone **14** in 58% yield (entry 1). Unfortunately, application of this method for benzylation of N-1 resulted in a low yield (10-15%) so that an alternative procedure was used (entry 2). Condensation of **7** with benzaldehyde, followed by reduction of the resulting ylide ($NaBH_4$, MeOH, 0 °C; method B)[10] led to **15** in 88% overall yield. The alkylation method of choice for introducing the (*Z*)-vinylsilane moiety turned out to be reaction of **7** with the

corresponding bromide (2 equiv, $NaHCO_3$, LiI (cat), butanone, rt; method C) to give **16** in 48% (entry 3). The cyclization precursors **17-19** were prepared in high yields following the procedures described in eq 3.

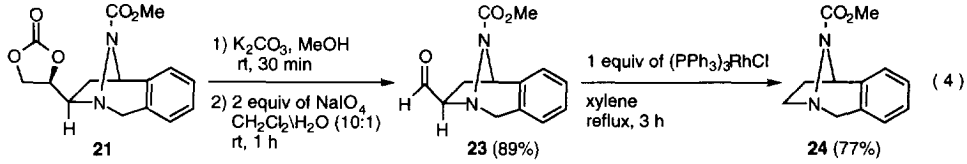
Table 1

entry	method	alkylation product (yield)	cyclization precursor (yield)	acid	product (yield)
1	A	 **14** (58%)	 **17** (34%)[a,b]	$SnCl_4$ HCOOH	 **20a** R = Cl (77%) **20b** R = OCOH (63%)
2	B	 **15** (88%)	 **18** (77%)[b]	$TiCl_4$	 **21** (87%)
3	C	 **16** (48%)	 **19** (45%)[b,c]	HCOOH	 **22** (73%)

[a]The ethyl ester was prepared using $(EtOCO)_2O$, Et_3N, DMAP and CH_2Cl_2. [b]Combined yield of the alkoxycarbonylation, reduction and transprotection. [c]The alkoxycarbonylated product was initially obtained as a mixture of *Z*/*E*-isomers in a ratio of 3:1 that could be separated by flash chromatography.

Pyrazolidine **17** cyclized under similar conditions as the allyl precursor **11** ($SnCl_4$ or formic acid) in a 5-exo fashion to produce the bicyclic hydrazines **20a** and **20b** in good yields (77% and 63%) as single isomers with the isopropyl substituent exclusively in the exo-position. This could be derived from the ^1H NMR spectrum in which the adjacent proton shows a doublet (4.66 ppm; J = 3.5 Hz).[11,4] Cyclization of the benzyl precursor **18** occurred only under strongly Lewis acidic conditions (4 equiv of $TiCl_4$, CH_2Cl_2, -78 °C → rt, 5 h) to afford the tricyclic hydrazine **21** in high yield. Treatment of the (*Z*)-vinylsilane precursor **19** with formic acid led to the bicyclic olefine **22** in a satisfactory 73% yield.

Finally, the benzyl cyclization product **21** was chosen to investigate removal of the cyclic carbonate moiety. Deprotection of the diol and oxidative cleavage gave aldehyde **23** (see eq 4).



21 **23** (89%) **24** (77%) (4)

Because Barton type radical decarboxylation of the corresponding carboxylic acid proved to be unsuccessful in this system, we focused our attention at decarbonylation methods using transition metal

complexes. After some optimization it was found that by using stoichiometric amounts of Wilkinson's catalyst[12] at elevated temperatures a clean conversion into azatropane **24** took place in 77% yield.[13]

In conclusion we have shown that the novel enantiopure pyrazolidinone **7**, which can be efficiently prepared in two steps from protected (*R*)-glyceraldehyde, is a suitable building block for preparing derivatives of enantiopure azatropane structures. Moreover, the 3-pyrazolidinone moiety is well-suited for attachment *via* the 5-substituent to a solid phase to allow for combinatorial production of tropane analogues.[14] While further applications of this methodology, including the synthesis of aza-analogues of several tropane (*e.g.* tropinone and atropine) and nor-tropane alkaloids (*e.g.* epibatidine), are currently under investigation and will be reported in due course, a preliminary account of studies towards aza-analogues of cocaine is presented in the following paper in this issue.

Acknowledgement:

We thank J. Fraanje and K. Goubitz of the AIMS' Laboratory of Crystallography for the X-ray crystal structure determination.

References and Notes:

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6. Jurczak, J.; Pikul, S.; Bauer, T. *Tetrahedron* **1986**, *42*, 447.
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8. Data for **7**: white crystals; mp 102-103 °C (EtOAc/hexanes); $[\alpha]^{22}_{D}$-12.4 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3432, 2991, 1697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (s, 1H, NHCO), 4.53 (br s, 1H, NH), 4.25 (m, 1H, CHO), 4.06 (dd, *J* = 8.4, 6.7 Hz, 1H, C*H*HO), 3.78 (dd, *J* = 8.4, 6.7 Hz, 1H, CH*H*O), 3.73 (m, 1H, H-5) 2.54 (dd, *J* = 16.4, 7.9 Hz, 1H, H-4), 2.43 (dd, *J* = 16.4, 7.9 Hz, 1H, H-4), 1.44 (s, 3H, CH_3), 1.36 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 109.8, 75.3, 65.9, 59.1, 34.1, 26.4, 25.0; anal. calc. for $C_8H_{14}N_2O$: C, 51.60; H, 7.58; N, 15.04, found: C, 51.72; H, 7.53; N, 15.14.
9. Experimental details of the X-ray structure determination, ORTEP representations and tables of fractional atomic coordinates, thermal parameters, interatomic distances and angles for **13a** were deposited by the editor at the Cambridge Crystallographic Data Centre.
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11. Davies, J.W.; Malpass, J.R. *Tetrahedron* **1985**, *37*, 4533.
12. Tsuji, J.; Ohno, K. *Synthesis* **1969**, 157.
13. Data for **24**: colorless oil; $[\alpha]^{22}_{D}$+21.3 (*c* 0.46, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3020, 2989, 1703, 1450 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.22-7.15 (m, 2H, Ar-H), 7.08 (d, *J* = 6.8 Hz, 1H, Ar-H), 7.02 (d, *J* = 6.8 Hz, 1H, Ar-H), 5.17 (d, *J* = 6.2 Hz, 1H, H-5), 4.67 (d, *J* = 16.9 Hz, 1H, H-2), 3.82 (d, *J* = 16.9 Hz, 1H, H-2), 3.77 (s, 3H, CO_2Me), 3.43 (td, *J* = 11.4, 3.5 Hz, 1H, H-7), 3.00-2.93 (m, 1H, H-7), 2.35-2.78 (m, 1H, H-6), 2.22-2.16 (m, 1H, H-6).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 139.1, 130.7, 127.5, 126.6, 126.5, 124.8, 60.4, 55.9, 54.1, 53.2, 38.4; HRMS calculated for $C_{12}H_{14}N_2O_2$ 218.1055, found 218.1067.
14. Koh, J.S.; Ellman, J.A. *J. Org. Chem.* **1996**, *61*, 4494.

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