Determination of the relative configuration of tropinone and granatanone aldols by using TBDMS ethers

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Abstract

The relative configurations of tert-butyldimethylsilyl (TBDMS) ethers of all four diastereomers of the aldols of tropinone (8-methyl-8-azabicyclo[3.2.1]octan-3-one), as well as of granatanone (9-methyl-9-azabicyclo[3.3.1]nonan-3-one), were determined from NMR data, and from the observed interconversion of the diastereomers (exo,anti to endo,anti and exo,syn to endo,anti). The exo forms invert to endo isomers in the presence of silica gel. The relative configuration of a new isomer of tropinone aldol accessible synthetically through the direct solventless reaction of tropinone and benzaldehyde in the presence of water was determined as exo,syn by comparison of NMR data of the aldol isomers, in particular vicinal coupling constants and shifts corresponding to the side-chain CH group, with data of related TBDMS derivatives and confirmed by single-crystal X-ray diffraction.

Introduction

Enantiomerically pure, and racemic, diastereomerically pure aldols of tropinone have been used as key intermediates in stereoselective syntheses of natural tropane alkaloids and their analogues [1], including the unnatural enantiomer of cocaine (ent-cocaine) [2], knightinol [3], alkaloid KD-B [3] and ferrugine [4,5]. Stereoselective syntheses of nortropinone aldols [6,7] and N-protected nortropinone aldols [5,8,9], which can open access to other N-substituted analogues, have also been described. The known diastereomERICALLY and enantiomerically pure aldols of tropinone (8-methyl-8-azabicyclo[3.2.1]octan-3-one) and granatanone (9-methyl-9-azabicyclo[3.3.1]nonan-3-one) (Figure 1) were synthesized by enantioselective deprotonation with lithium amide bases followed by diastereoselective aldol reaction with aldehydes [10,11]. In all the aldol reactions
promoted by achiral (LDA [5,12]) or by chiral lithium amides (e.g., lithium bis(1-phenylethyl)amide [4,5] or Koga’s amide [3]), including amides immobilized on a polymeric carrier [13,14], the major products had the exo,anti configuration (Scheme 1).

Configuration of the exo,anti-3 was assigned based on X-ray diffraction [15]. Granatanone aldols, including N-benzyl derivatives, obtained with lithium amides were identified as the exo,anti isomers based on X-ray crystallography [16,17]. Granatanone aldols with exo,syn configuration have been observed only as minor products [17]. Until recently other isomers and synthetic procedures for their preparation remained unknown. We succeeded in preparing other isomers through an unexpected direct reaction of the ketones with aromatic aldehydes in the presence of catalytic amounts of water (Scheme 1) [18-20]. In our preliminary synthetic report the major isomeric products accessible under these conditions were assigned the exo,syn configuration. DFT calculations suggest that selectivity in the solventless reaction results from equilibration and the higher stability of the O–H…N-hydrogen-bond-stabilized conformer of the exo,syn isomer [20,21].

Herein, we wish to report a method used for identification of the relative configuration of this new isomer of the tropinone aldol and closely related granatanone aldol. To the best of our knowledge, all diastereoisomers of tropinone and granatanone aldols synthesized to date have the exo configuration. The other possible isomers, i.e., the endo forms, have never been isolated or described. Their appearance in some experiments has been mentioned [22]. We have made an effort to devise a way to identify these elusive endo isomers.

In this paper, we propose a simple method for the fast identification of all of the diastereomers of tropinone and granatanone aldols, including the endo isomers, through their silyl ether derivatives.

Results and Discussion

The new aldol product of the solventless reaction of tropinone with benzaldehyde had relative stereochemistry different from the exo,anti configuration, as judged from its NMR spectra. In particular the chemical shift and coupling constant of the characteristic carbinol CH signal differed from the known exo,anti isomer. Coupling constants of both isomers (3.1 Hz for exo,anti and 2.6 Hz for the new product) were similar. Usually the vicinal coupling constants for syn and anti isomers differ enough to allow for configuration assignment [23] (e.g., aldols of cyclic ketones such as piperidone and cyclohexanone fall within the following typical ranges: syn: ca. 2–3 Hz, anti: ca. 7–9 Hz).

In principle the new product could have had any of the three remaining possible configurations. However, we suspected that the unknown isomer was likely the exo,syn-aldol (i.e., the other exo product formed by stereolectronically and sterically favored axial attack) [24] or the endo,syn isomer (resulting from the exo-endo inversion of the known exo,anti-3, Scheme 2).

The question of whether the exo isomer could invert to the endo form was answered by attempted isomerization (Scheme 2) under various conditions (basic, acidic, imidazole, silica gel in various solvents). The exo,anti aldols showed only decomposition to tropinone and benzaldehyde or elimination to benzylidene derivatives. The behavior of the new isomer under the same isomerization conditions was similar and gave no indications regarding its stereochemical form. It appeared that in this case (as it was for the exo,anti isomer [3]) attempts to convert the presumed exo isomers to the expectedly more thermodynamically stable endo isomers would be also fruitless, unless the hydroxy group was protected (e.g., by silyl ether). In light of
the sensitive nature of the aldols we reasoned that making a stable derivative was necessary.

The TBDMS ethers of aldols have been already used for exo–endo isomerization of tropinone aldols [3]. Blocking of the hydroxy group with an ether or ester group would make formation of internal hydrogen bonding to the amine nitrogen or the carbonyl oxygen H-bond acceptors impossible, thus changing significantly the structure of aldols in aprotic solvents used for NMR. N-Benzyl analogues of the granatanone [16] and tropinone [9] aldols as well as aldols of granatanone [17] showed in crystalline form an intramolecular hydrogen bonding involving the free hydroxy group. We expected that such a change, reflected in the chemical shift and couplings, could be useful for discerning relative configurations. The aldol of unknown configuration was converted into silyl ether by reaction with tert-butyldimethylsilyl chloride (TBDMSCl) in the presence of DMAP and triethylamine (Scheme 3).

Because TBDMS ethers with exo,anti and endo,syn configuration, as well as a method for their conversion, has been described [3], we expected that through comparison of $^1$H NMR
data we would be able to exclude or confirm the structure of the new aldol TBDMS ether as endo,syn. The TBDMS derivative was different from the known endo,syn-isomer 5. Thus the new aldol was either the exo,syn or the endo,anti isomer. Inducing isomerization of the unknown aldol TBDMS ether to the typically more stable endo form could be an indication pointing to the exo,syn configuration. From the tested methods for isomerization, the most suitable turned out to be the absorption on a silica column combined with separation. Although the silyl ether of the new isomer of tropinone aldol isomerized in the presence of silica, giving the last of the four isomeric TBDMS derivatives, in a similar way as described for the exo,anti-5, its conversion was noticeable faster than for the exo,anti-5. At this point it was clear that the new aldol isomer must have had the exo,syn configuration. Isomerization of its TBDMS derivative was so facile that its chromatographic purification was hardly possible. This agreed with expectations based on intuitive van der Waals radii and conformational analysis. Inspection of molecular models indicates that the pseudoaxial substituent of the syn isomer should experience more steric congestion on the tropinone bicyclic skeleton with equatorial N-methyl [9], than the same group of the anti configuration. It was interesting to see if one could obtain the free aldols in the endo forms by TBDMS deprotection. Under the typical desilylation conditions (1 M TBAF in THF) no formation of aldols, but rather products of their decomposition were detected in the resulting complex reaction mixtures. The presence of a relatively acidic pseudoaxial hydrogen atom at the a-carbon to carbonyl (C-2) is likely responsible for the facile elimination of a water molecule and formation of an isomeric mixture of condensation products ((E) and (Z)-2-benzylidene tropinones) in analogy to the known elimination of acetic acid from the acetyl derivative of the aldol [3].

More conclusive indication came from comparison of the characteristic signals (doublets) of the side-chain CH groups (side-chain β-carbon to the carbonyl group, Scheme 3). The fact that 1H NMR signals of exo,syn-5 differed markedly from the endo,syn-5 (as compared on the same NMR instrument) but were similar to the exo,anti-5 supported the tentative assignment further. Knowing that in tropinone the axial α-protons are deshielded versus the equatorial protons by ca. 0.5 ppm [12,25], we were also able to identify positively, within the pairs of interconverting isomeric TBDMS ethers, the isomer with exo and endo side chain (equatorial and axial α-CH, respectively). On the basis of the observed exo-endo isomerization, and trends in NMR data changes upon isomerization, we were fairly certain of the assigned stereochemistry of the new isomer as exo,syn-3. This procedure developed on tropinone aldols was reproduced on corresponding granatanone aldols, providing TBDMS ethers of all four possible diastereomers of 6 (Scheme 3) and identifying the major product of the solventless reaction of granatanone with benzaldehyde [20,21] as exo,syn-4.

The vicinal coupling constants characteristic for the aldols and the TBDMS ethers (Scheme 3) can provide some insight into the preferred conformations in solution. Using the familiar Karplus correlation of the vicinal J and the dihedral angle [26-28], we suggest the preferred conformations shown in Figure 2. The aldol conformations shown could likely be stabilized by formation of an internal H-bond to the amine nitrogen as observed in crystals.

![Figure 2: Approximate representations of likely conformations of tropinone aldols and their TBDMS ethers in solution, having dihedral H–αC–βC–H angles accounting for the observed vicinal couplings.](image-url)
The dihedral angle in the structure exo,anti-3 is estimated, based on $J = 3.1$ Hz, to be ca. 50° and for exo,syn-3 slightly more than 55° or 110°, based on $J = 2.6$ Hz. The alternative conformations, without a possible H-bond to nitrogen for exo,anti-3, and an angle of ca. 110–115° corresponding to $J = 3.1$ Hz would have significant steric strain. In both TBDMS derivatives exo,anti-5 and exo,syn-5 the estimated dihedral angle of 160–170° corresponds to reasonable conformations. In the endo forms 5 the angle determined as 18° or 135° for endo,syn-5 and 10° or 140° for endo,anti-5 can be found in two of the shown alternative arrangements. The analysis for tropinone aldols is representative also for the granatanone analogues 4 and 6.

After identifying the exo,syn configuration by the described procedure we succeeded in preparing the crystalline form of the new isomer of 3 suitable for single crystal diffraction. Meticulous purification by precipitation with hexane, followed by slow crystallization from ether gave suitable crystals of the isomer, configuration of which was unambiguously determined as exo,syn (Figure 3) by X-ray diffraction.

![Figure 3: X-ray structure of aldol exo,syn-3 synthesized by direct, solventless reaction of tropinone with benzaldehyde in the presence of catalytic amounts of water, showing an intramolecular H-bond. N1–O2 2.763(2) Å, N1–H 1.920(2) Å, N1–H2O–O2 151(2)°. Displacement ellipsoids are drawn at 30% probability level; atom numbering is arbitrary.](image)

Atoms H1 and H8 were found in syn relation to each other, while the 1'-hydroxybenzyl group at C1 is on the exo side of the bicyclic trope scaffold pointing towards the C4–N1–C7 bridge (pseudoaxial on the tropinone six-membered ring). The crystal structure is also characterized by internal hydrogen bonding between the nitrogen N1 and the oxygen O2 atom (N1–H2O–O2). The configuration of a related granatanone aldol ($p$-NO$_2$-PhCHO derived [20]) was also confirmed by X-ray analysis as exo,syn with analogous hydrogen bonding [17].

**Conclusion**

All four diastereomers of the aldols of tropinone and granatanone with benzaldehyde were characterized as TBDMS ethers. Assignment of the configuration was possible on the basis of comparison of the chemical shifts and coupling constants relevant to the side chain of the TBDMS ethers. The endo isomers could be prepared by equilibration combined with separation on a silica column. The major products of the direct solventless aldol reaction of tropinone and granatanone [20] were assigned the exo,syn configuration on the bases of their NMR data and NMR data of the corresponding TBDMS ethers. The assigned exo,syn configuration of the tropinone aldol was also confirmed by single-crystal diffraction. Derivatization of isomeric tropinone and granatanone aldols as TBDMS ethers combined with their isomerization in the presence of silica can be used for determination of the relative configurations of these types of compounds.

**Experimental**

Thin-layer chromatography (TLC) was performed on precoated plates (Merck, silica gel 60, $F_{254}$). The spots were detected by using UV light (254 nm) and with phosphomolybdic acid followed by charring. Magnetic resonance spectra (1H NMR and 13C NMR) were recorded on a Bruker AVANCE II 400 spectrometer in CDCl$_3$ at ambient temperature. Chemical shifts are reported in parts per million (ppm) downfield of tetramethylsilane. All reagents were purchased from Aldrich. Granatanone was sublimed; benzaldehyde was purified by standard techniques [29]. Dry triethylamine (Et$_3$N) and dichloromethane (DCM) were distilled from calcium hydride. All air-sensitive reactions were carried out under argon.

Crystallographic data were collected with a Bruker-Nonius Apex-X8 CCD-diffractometer with Cu Kα radiation ($λ = 1.54178$ Å) at 296 K. The structure was solved by direct methods and refined by using the SHELXS97 [30] and SHELXL97 [30] programs. All non-H atoms were refined anisotropically; all H atoms bonded to carbon atoms were placed on geometrically calculated positions and refined by using a riding model. The hydroxy H atom in the structure was located from Δρ maps and refined isotropically. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 887610, for compound exo,syn-3. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
exo\textit{,anti}-2-[\text{Hydroxy(phenyl)methyl}]\textit{-}8-methyl-8-azabicyclo[3.2.1]octan-3-one (exo\textit{,anti}-3) [3, 4, 12] Colorless solid; mp 118–121 °C (decomp.); \(^1\)H NMR \(\delta 7.32–7.25\) (m, 5H), 5.23 (d, \(J = 3.1\) Hz, 1H), 3.61–3.59 (m, 1H), 3.50–3.47 (m, 1H), 2.86 (ddd, \(J = 15.6\) Hz, 4.6 Hz, 1.5 Hz, 1H), 2.47 (s, 3H), 2.45–2.42 (m, 1H, eq-H at C-2), 2.33 (dt, \(J = 15.6\) Hz, 1.9 Hz, 1H), 2.21–2.12 (m, 1H), 1.69–1.53 (m, 1H); \(R_f\) 0.50 (10% MeOH/DCM).

exo\textit{,syn}-2-[\text{Hydroxy(phenyl)methyl}]\textit{-}8-methyl-8-azabicyclo[3.2.1]octan-3-one (exo\textit{,syn}-3) [20] Colorless solid; mp 81–83 °C (decomp.); \(^1\)H NMR \(\delta 7.47–7.22\) (m, 5H), 7.35 (br s, 1H), 5.01 (d, \(J = 2.6\) Hz, 1H), 3.51–3.43 (m, 1H), 3.25–3.18 (m, 1H), 2.98 (ddd, \(J = 17.0\) Hz, 5.2 Hz, 1.7 Hz, 1H), 2.43 (dt, \(J = 17.0\) Hz, 1.7 Hz, 1H), 2.39–2.37 (m, 1H, eq-H at C-2), 2.37 (s, 3H), 2.20–2.03 (m, 2H), 1.70–1.61 (m, 1H), 1.42–1.35 (m, 1H); \(^1\)C NMR \(\delta 210.7, 143.7, 128.3, 126.9, 125.5, 75.7, 63.1, 61.2, 50.3, 40.4, 26.8, 26.4;\) HRMS–ESI (m/z): [M + Na\(^+\)]\(^\circ\) caleed for C\(_{15}\)H\(_{19}\)NO\(_2\)Na, 268.1313; found, 268.1325; \(R_t\) 0.40 (10% MeOH/DCM, decomp.). The crystal structure has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 887610; unit-cell parameters: \(a = 6.1202(1), b = 16.9100(3), c = 12.6953(2)\) Å, \(\beta = 91.1250(10)\) space group P2\(_1\)/n.

\textit{exo, anti}-2-[(tert-Butyldimethylsiloxy)(phenyl)methyl]-8-methyl-8-azabicyclo[3.2.1]octan-3-one (\textit{exo, anti}-5) [3] The aldol \textit{exo, anti}-3 (0.982 g, 3.97 mmol) was dissolved in dry DCM (11 mL). DMAP (0.057 g, 0.46 mmol) and dry Et\(_3\)N (5.7 mL) were added, followed by the addition of TBDMSCl (1.193 g, 7.9 mmol). The resulting solution was allowed to stand at rt for 16 h. The reaction mixture was then diluted with DCM (5 mL), shaken with 20% aq \(K_2\)CO\(_3\) (10 mL) and extracted with DCM (3 × 10 mL). The combined organic extracts were dried (\(Na_2\)SO\(_4\)), the solvent was removed under vacuum, and the residue was subjected to flash chromatography in hexanes/AcOEt (1:9), which gave the pure product as a colorless oil (1.283 g, 89%). \(^1\)H NMR \(\delta 7.50–7.20\) (m, 5H), 5.28 (d, \(J = 9.6\) Hz, 1H), 3.39–3.37 (m, 1H), 2.87–2.82 (m, 1H, ax-H at C-4), 2.64–2.63 (m, 1H, \(H\)-CMe), 2.36–2.33 (m, 1H, eq-H at C-2), 2.22 (s, 3H), 2.05–1.88 (m, 3H), 1.62–1.53 (m, 1H), 1.40–1.32 (m, 1H), 0.78 (s, 3H), −0.06 (s, 3H), −0.31 (s, 3H); \(^1\)C NMR \(\delta 209.4, 142.5, 128.1, 127.7, 126.5, 74.1, 69.7, 63.3, 62.9, 50.7, 41.3, 18.1, 26.0, 25.8, 25.8, −4.51, −4.96;\) HRMS–ESI (m/z): [M + Na\(^+\)]\(^\circ\) caleed for C\(_{21}\)H\(_{32}\)NO\(_2\)SiNa, 382.2178; found, 382.2161; \(R_t\) 0.75 (40% AcOEt/hexanes).

\textit{exo, syn}-2-[(tert-Butyldimethylsiloxy)(phenyl)methyl]-8-methyl-8-azabicyclo[3.2.1]octan-3-one (\textit{exo, syn}-5) Product \textit{exo, syn}-5 was obtained as a yellow oil (0.390 g, 94%) in the same way as \textit{exo, anti}-5 by using \textit{exo, syn}-3 (0.283 g, 1.15 mmol), dry DCM (3.3 mL), DMAP (0.016 g, 0.13 mmol), dry Et\(_3\)N (1.6 mL), and TBDMSCl (0.344 g, 2.28 mmol).

Supporting Information
Supporting Information File 1
Experimental procedures for the preparation and characterization of the remaining compounds. [http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-216-S1.pdf]
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