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2-Azapinanes: Aza Analogues of the Enantiomeric Pinyl Carbocation Intermediates in Pinene Biosynthesis

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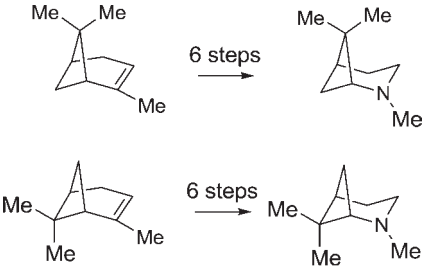
ABSTRACT



The enantiomeric 2-azapinanes, aza analogues of the pinyl carbocation intermediates in pinene biosynthesis, were synthesized from (−)- and (+)-*cis*-pinonic acids. The individual reactions in the 5-step sequence were Beckmann rearrangement of the pinonic acid oximes, cyclization to the *N*-acetyl lactams, hydrolysis to the NH-lactams, *N*-methylations, and $LiAlH_4$ reductions. The anti stereochemistry of the *N*-methyl groups in the salts with respect to the gem-dimethyl bridge was established by NOE measurements and by X-ray diffraction analysis.

α-Pinene and *β*-pinene are widespread monoterpene olefins based on the bicyclo[3.1.1]heptane nucleus[1] and major constituents of conifer oleo resin and its turpentine distillate.[2] Like many monoterpenes, the pinenes occur naturally in both enantiomeric forms, often even in the same plant.[1b,3] The availabilities of both enantiomers, together with the ring strain and steric bias imposed by the gem dimethyl bridge, have been exploited in the synthesis of enantio-pure organic compounds[4] and in the development of pinane-based chiral auxiliaries for asymmetric synthesis.[5]

Considerable evidence supports a catalytic mechanism for pinene biosynthesis in which the substrate geranyl diphosphate (**1**) first undergoes a stereospecific allylic rearrangement to the key enzyme-bound intermediates (*R*)- or (*S*)-linalyl diphosphate (**2**), thereby allowing the required 2,3-bond rotation essential for further progress toward the enzymatic bicyclic products (Scheme 1).[6] S_N'

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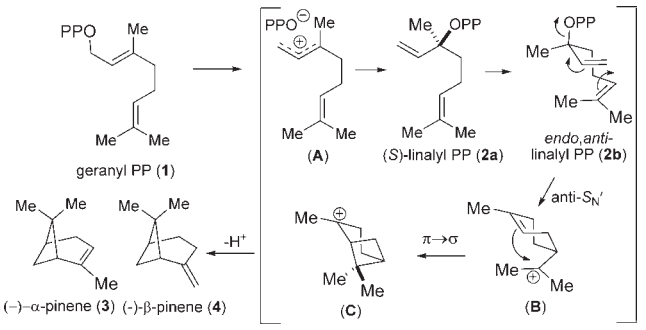
Scheme 1



cyclizations of the endo,anti conformations (e.g., **2b**) followed by π-cyclizations of the enantiomeric α-terpinyl carbocations generate the bicyclic pinyl ions (**C** and *ent*-**C**), which undergo proton eliminations to form the pinene isomers (Scheme 1 and Figure 1).

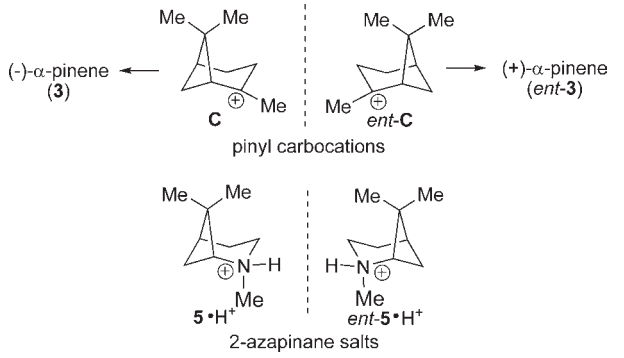
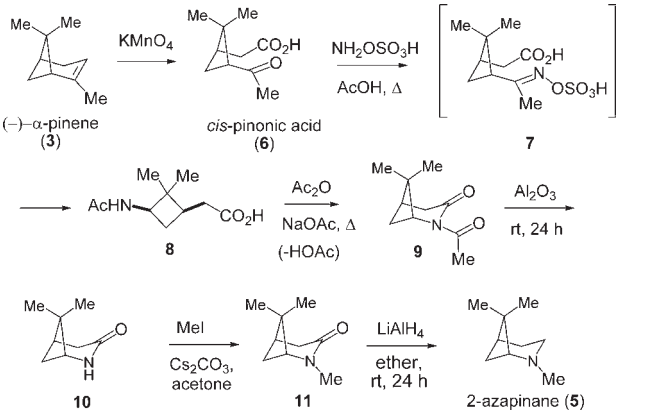


Figure 1. Enantiomeric 2-azapinane salts (**5**·H$^+$ and *ent*-**5**·H$^+$), aza analogues of the pinyl carbocation intermediates (**C** and *ent*-**C**) in pinene biosynthesis.

Terpene synthase inhibitors which bind tightly in the active sites of these enzymes afford mechanistic insights, and in some instances, serve as useful aids for crystallization of the proteins yielding valuable three-dimensional structural data by X-ray diffraction analysis.[7] Aza analogues of high-energy carbocation intermediates have found applications as mechanism-based inhibitors and active site probes for terpene synthases.[7,8] For the purpose of characterizing monoterpene synthases, we have carried out the synthesis, characterization, and applications of 3-aza-2,3-dihydrogeranyl diphosphate, the enantiomeric 7-aza-7,8-dihydrolimonenes, 2-azabornanes, 2-azacamphanes, and azatricyclenes.[9] In this paper we report the preparation and characterization of the enantiomeric 2-azapinanes (**5** and *ent*-**5**, Figure 1),[10] potential inhibitors and active site probes for the pinene synthases.

Scheme 2



The synthesis of [1*R*, 5*S*]-2-azapinane (**5**)[11] (Scheme 2) was accomplished in four steps (ca. 46−50% overall yield) starting from known acetamide **8**,[12] which was available via Beckmann rearrangement (H_2NOSO_3H, AcOH, reflux, 77−81%) of (−)-*cis*-pinonic acid (**6**)[12,13] ([α]$_D$ = −94.1° (*c* 0.63, $CHCl_3$) [lit.[13c] −93.7 (*c* 4.60, $CHCl_3$), lit.[14] −94.2 (c 5−10, $CHCl_3$)] obtained by $KMnO_4$ oxidation of (−)-α-pinene.[13] The optical purity of the starting (−)-*cis*-pinonic acid was estimated to be 99.0% assuming that the highest absolute value of specific rotation ([α]$_D$ = +95° ($CHCl_3$))[13b,15,16] reported for (+)- and (−)-*cis*-pinonic acids corresponds to 100% optically pure dextrorotatory enantiomer. An identical synthesis of the enantiomeric [1*S*, 5*R*]-2-azapinane (*ent*-**5**) was carried out in parallel

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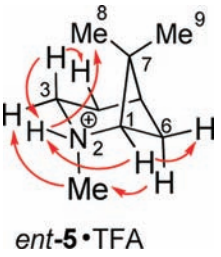
starting from (+)-α-pinene (**3**, $[\alpha]_D$ = +47.1° (neat), 91% ee) by the same reactions and procedures illustrated in Scheme 2.

Considerable effort was required to develop a satisfactory procedure for the initial cyclization step **8** → **9**. Thus, refluxing solutions of amide acid **8** in Ac_2O[17] for 1 h, led only to the corresponding mixed pinonic acetic anhydride as revealed by ^{13}C NMR analysis, δ_c 174.2 (NHCO), 169.7 (CH_2CO_2) and 168.2 ppm (CH_3CO_2). Although longer reaction time (17 h) effected partial cyclization to a 2:1 mixture of the mixed anhydride and *N*-acetyl lactam **9**, further progress toward the cyclized product was quite slow (2:3 mixture at 48 h). However addition of NaOAc and continuous removal of acetic acid during the reaction lead to increased conversion and satisfactory isolated yields of 77−80% after 72 h. Formation of the 6-membered ring in *N*-acetyl lactam **9** was accompanied by large downfield shifts of the bridgehead methine proton CH−N (4.03 → 4.80 ppm) and the *N*-acetyl CH_3 (1.95 → 2.57 ppm) in the ^1H NMR spectra which seem attributable to an altered conformation of the acetyl carbonyl group.

Other known procedures for dehydrative cyclizations were unsuccessful in the case of amide acid **8**. Exposure to P_2O_5 in refluxing toluene[18] led to the formation of pinonic anhydride as evidenced by the ^{13}C NMR carbonyl signals at 172.7 (NHCO), and 169.8 (O_2CO) ppm, without any evidence of cyclization. Similarly, no cyclization was observed when the corresponding methyl ester of **8**[19] was heated in refluxing xylenes. Experiments to effect cyclization of the related amino ester[20] through selective hydrolysis of the amide ester by means of amide *O*-alkylation[21] to the corresponding imidate with triethyl oxonium fluoroborate according to a literature procedure [$Et_3O^+BF_4^-$ (1 equiv)/CH_2Cl_2 followed by cold aq. $NaHCO_3$][22] led only to extensive decomposition to uncharacterized material.

The remaining steps in the 2-azapinane synthesis proceeded readily and in high yield without extensive experimentation. Thus, hydrolysis of the *N*-acetyl substituent was effected with alumina suspended in hexane−EtOAc[23] in yields up to 98%. The detachment of the exocyclic carbonyl group was accompanied now by an upfield shift of the bridgehead N−CH to 3.26 ppm (ddd) in the proton NMR spectrum. *N*-Methylation was brought about by reactions with dimethyl sulfate[24] or methyl iodide



ent-**5**•TFA

Figure 2. Key NOE correlations observed for [1*S*, 5*R*]-2-azapinane trifluoroacetate salt (*ent*-**5**·TFA): H1→NH, H1→H6-syn, H6-anti→NMe, NMe→H3-anti, NH→8Me, H3-syn→NH, H3-syn→H4-syn.

(Cs_2CO_3, acetone)[25] to give tertiary lactam **11** in 93−96% yield. Finally $LiAlH_4$ reduction of the lactam carbonyl afforded the highly volatile 2-azapinane (**5**) which was isolated and characterized as the trifluoroacetate salt **5**·TFA (80−84% yield over two steps) following a recently developed protocol for isolation of aziridine trifluoroacetate salts.[9e] Alternatively 2-azapinane was isolated as its hydrochloride salt **5**·HCl in 78% overall yield after recrystallization from dry THF. The enantiomeric 2-azapinane (*ent*-**5**) and its salts *ent*-**5**·TFA (Figure 2) and *ent*-**5**·HCl were obtained from (+)-α-pinene by the same reaction sequence.

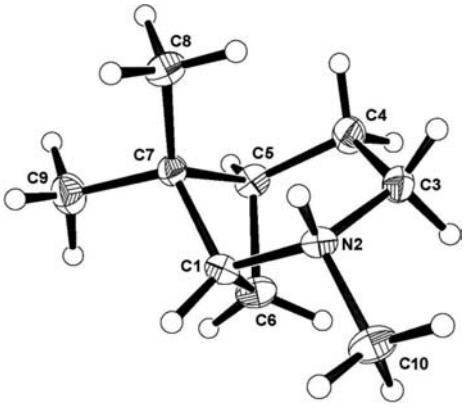


Figure 3. ORTEP diagram of [1*R*, 5*S*]-2-azapinane hydrochloride (**5**·HCl) from the X-ray crystal structure determination showing 40% probability with the chloride counterion omitted.

The structure of the 2-azapinane salts was confirmed and the anti configuration of the $N-CH_3$ group was established by 1-D, 2-D, and NOE NMR experiments with *ent*-**5** trifluoroacetate (Figure 2). The key proton resonances H3-anti (2.94 ppm), H3-syn (4.07), NH (9.21),

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H1 (3.53), H6-syn (1.82), 8-CH_3 (1.07) and 9-CH_3 (1.33) as well as the corresponding ^{13}C NMR signals were assigned by means of DEPT, HSQC, NOE, and analysis of coupling patterns. The NOE data in Figure 2 were critical in assigning the more stable anti position of the NCH_3 generated in the salt formation. This conclusion was verified by X-ray diffraction analysis of [1*R*, 5*S*]-2-azapinane hydrochloride salt (Figure 3) showing a bicyclic ring system with structural features very similar to those found in *N*-*tert*-butyloxycarbonyl-7-aza-4-oxatricyclo[4.3.1.$0^{2,6}$]decan-3-one.[26] Although protonation of 2-azapinane with TFA and HCl most likely occurs initially opposite to the germinal dimethyl bridge in accord with the stereochemistry of reactions with the pinenes and their derivatives,[1,5] equilibration through rapid proton transfers with the free amine evidently leads to the observed stable configuration of the isolated salts.

The 5-step synthetic schemes described provide efficient access to the [1*R*, 5*S*]- and [1*S*, 5*R*]-2-azapinanes (**5** and *ent*-**5**) in enantiomerically pure form. These novel aza analogues are now available for use as mechanism-based inhibitors of the pinene synthases, and as potential active site probes in the crystallography of these ubiquitous monoterpene cyclases. In addition, the enantiomerically pure bicyclic lactams [1*R*, 5*S*-]- and [1*S*. 5*R*]-**10** as well as the 2-azapinanes are suitable starting materials for synthesis of novel heterocycles related to the pinanes, such as the 2-azapinane analogue **13** of pinane-thromboxane A_2 (**12**)[27] (Figure 4). A proposed synthesis could follow synthetic procedures developed earlier for the synthesis of pinane-thromboxane A_2.[28]

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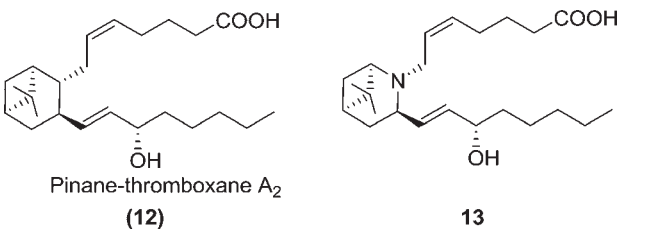

Pinane-thromboxane A_2 (**12**) **13**

Figure 4. Structures of pinane-thromboxane A_2 (**12**) and its 2-azapinane analogue (**13**).

Crystal Structure. The salt crystallizes in the chiral space group $P2_1$. Protonation occurs at the N2 position, with the chloride counterion also included in the crystal structure (see Supporting Information). The cyclobutyl ring C1−C6−C5−C7 displays the longest C−C bonds (in the 1.542(3)−1.560(3) range) and the most acute angles C−C−C angles (in the 85.24(16)−88.50(17) range).

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Supporting Information Available. General methods, materials, instrumentation, and experimental details for all compounds, ^1H and ^{13}C NMR spectra of all synthetic intermediates, 2-azapinane, and 2-azapinane salts; DEPT, HSQC, and NOE spectra of *ent*-**5**·TFA salt and X-ray crystallographic data for **5**·HCl. This material is available free of charge via the Internet at http://pubs.acs.org.

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