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Carbocyclic Thromboxane A_2[1]

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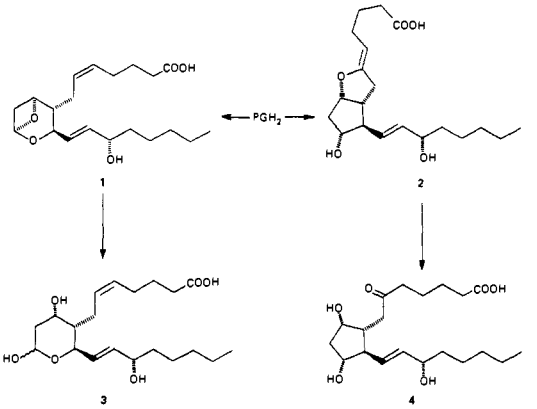
Abstract: The total synthesis of carbocyclic thromboxane A_2 (CTA_2) (**5**) and its hydroxy epimer (**5b**) has been achieved both in racemic and optically active forms. Bicyclo[3.1.1]heptan-2-one (**6**), synthesized by two alternative routes, was converted to the key intermediate **7**, which was efficiently transformed to the carbocyclic thromboxane A_2 skeleton by a cuprate 1,4 addition to introduce the lower side chain followed by homologation of the aldehyde function and Wittig reaction to complete the top chain. The resulting stable thromboxane A_2 analogues **5** and **5b** exhibited interesting and potent biological properties.

Introduction

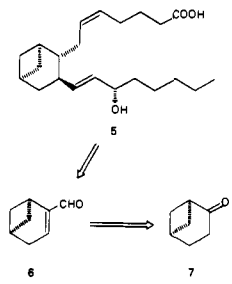
Thromboxane A_2 (TA_2) is an unstable substance with potent thrombotic and vasoconstricting properties generated by human blood platelets[3] from the prostaglandin endoperoxide H_2 (PGH_2). Samuelsson and his associates assigned structure **1** (Scheme I) to thromboxane A_2 on the basis of its origin and chemistry and deduced a physiological half-life of a few seconds ($t_{1/2}$ = 32 s in aqueous pH 7.4 solution at 37 °C)[3] for this important biomolecule. Although this compound has not yet been isolated in pure form, a vast body of biology surrounding it has already been created.[4] Its biological profile is opposite to that of prostacyclin (PGI_2)[5] (**2**, Scheme I), a compound also generated from PGH_2 which behaves as an antithrombotic and vasodilatory agent. Although both thromboxane A_2 and prostacyclin are biologically very potent, they exhibit relatively high chemical instability, degrading rapidly to their stable metabolites, thromboxane B_2 (**3**) and 6-keto-$PGF_{1\alpha}$ (**4**)

Scheme I. Thromboxane A_2, Prostacyclin, and Their Degradation Products

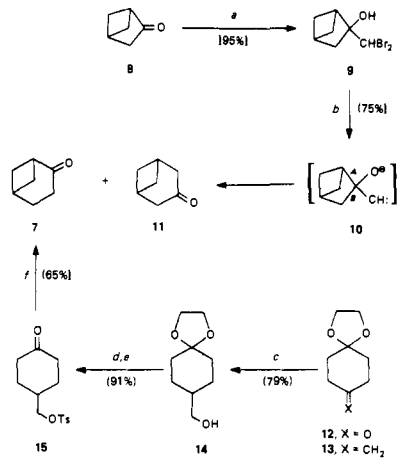


0002-7863/80/1502-1404$01.00/0

Scheme II. Retrosynthetic Analysis of Carbocyclic Thromboxane A_2 (CTA_2)



Scheme III. Synthesis of Bicyclo[3.1.1]heptan-2-one (7)



[a] LOA–CH_2Br_2/THF/−78°C. [b] *n*-BuLi–Et_2O/−76° C. [c] Diisoamylborane/NaOH/H_2O_2. [d] TsCl–pyr/−20° C. [e] AcOH–THF–H_2O (2:1:1)/75° C.

(Scheme I). Therefore, stable relatives of these chemically unusual and intriguing structures with agonistic or antagonistic properties would facilitate research in this area and may prove to be therapeutically useful. A large number of prostacyclins have already been reported.[6,7] In contrast to the prostacyclin area, however, thromboxane A_2 analogues have been rare and started to appear only recently[8] primarily owing to the unusual and difficult-to-synthesize structures involved. In this article we wish to report the total synthesis and properties of the parent carbon analogue of thromboxane A_2 (TA_2), namely, carbocyclic thromboxane A_2 (CTA_2), in which both ring oxygens have been replaced by methylene groups.[1]

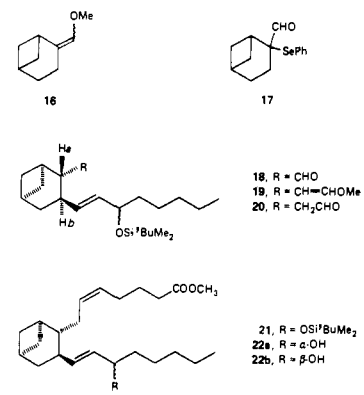
Synthesis of Carbocyclic Thromboxane A_2 (CTA_2) (5)

The most difficult task in the synthesis of thromboxane A_2-like compounds is undoubtedly the construction of the strained bicyclo[3.1.1]heptane nucleus. From this nucleus our strategy for completion of the synthesis is shown retrosynthetically in Scheme II, which represents a rather general route to this class of compounds.

The first key intermediate, bicyclo[3.1.1]heptan-2-one (**7**),[9] was efficiently synthesized by two alternative routes. In the first approach bicyclo[2.1.1]hexan-2-one (**8**)[10] was ring expanded via intermediate **9**,[11] which was prepared in 95% yield by addition of LDA (2.0 equiv) to a cold (−78 °C) solution of **8** in THF in the presence of dibromomethane (2.2 equiv). Treatment of the dibromo alcohol **9** with *n*-butyllithium (2.2 equiv) in ether at −78 °C generated the β-oxidocarbenoid **10**,[12] which suffered rearrangement of the ketone **7** (bond B migrates) contaminated with the regioisomer **11** (bond A migrates) in 75% total yield (ratio ca. 6:1 with **7** predominating). The two isomers were separated chromatographically (silica, 20% ether in petroleum ether, **7**, R_f 0.25; **11**, R_f 0.37) and identified by their previously reported spectral data. A more selective but slightly longer route to **7** was developed starting with 1,4-cyclohexanedione and proceeding (Scheme II) via intermediates **12** (1. excess $HOCH_2CH_2OH/H^+$ benzene/reflux; 2. AcOH–THF–H_2O, 3:2:2, 45 °C, 15 h, ca. 65% overall), **13** ($Ph_3P{=}CH_2/Me_2SO$/25 °C, 88%), **14** (diisoamylborane–NaOH–H_2O_2, 90%), **15** (1. TsCl/pyridine/−20 °C; 2. AcOH–THF–H_2O, 2:1:1, 75 °C, 2.5 h, 91% overall). The utilization of dimsylpotassium (KH–Me_2SO) (2.1 equiv) in dilute Me_2SO solution at 15–25 °C was crucial for the efficient conversion of **15** to **7** (65% yield).

With bicyclo[3.1.1]heptan-2-one (**7**) abundant we proceeded to construct the second key intermediate (**6**) along the route to carbocyclic thromboxane A_2. This was directly and most efficiently achieved utilizing recently developed selenium-based methodology[13] as follows. Treatment of **7** with methoxymethylenetriphenylphosphorane (2 equiv) in THF–toluene at 0 °C afforded the enol ether **16** (mixture of geometrical isomers), which was exposed to excess PhSeCl in CH_2Cl_2–toluene solution at −78 °C to produce after aqueous workup and chromatographic isolation directly the selenide **17** (62% overall from **7**).[13] Oxidation of **17** with *m*-CPBA (1.1 equiv) in CH_2Cl_2 at −78 °C followed by addition of diisopropylamine (2.2 equiv) and warming to 25 °C resulted in the rapid formation of the desired α,β-unsaturated aldehyde **6** (88%).

The lower side chain of the thromboxane molecule was then introduced by 1,4 addition of the cuprate reagent obtained from (±)-*trans*-1-lithio-1-octen-3-ol *tert*-butyldimethylsilyl ether and 1-pentynylcopper hexamethylphosphorous triamide complex to the aldehyde **6** (56% yield). The trans aldehyde **18** (J_{HaHb} = 10.8 Hz) was the major product of this reaction and was obtained exclusively as the thermodynamically more stable isomer (mixture of 15-epimers, PG numbering) after exposure to potassium carbonate in absolute methanol at 25 °C. The upper side chain was completed by (1) condensation of **18** with methoxymethylenetriphenylphosphorane (1.5 equiv) in toluene–THF solution at 0 °C furnishing the enol ether **19** in 81% yield as a mixture of geometrical isomers; (2) liberation of the aldehyde **20** (98%) by treatment with $Hg(OAc)_2$–KI in



aqueous THF at 25 °C; (3) Wittig reaction of **20** with the sodium salt of 4-carboxybutylidenetriphenylphosphorane in Me_2SO at 25 °C providing after diazomethane treatment the methyl ester **21** obtained as a mixture of diastereoisomers at the 15 position (PG numbering). After removal of the silyl ether (AcOH–THF–H_2O, 3:2:2, 45 °C, 12 h, 98% yield) the two diastereoisomers **22a** (assumed to be the 15α isomer on the basis of chromatographic mobility and biological activity) (R_f 0.25) and **22b** (R_f 0.28) were separated chromatographically on silica gel plates using ethyl acetate–petroleum ether mixtures (7.5:92.5) as solvent. Basic hydrolysis of the more polar compound (**22a**) with aqueous THF–LiOH solution at 25 °C led, in 95% yield, to the carbocyclic thromboxane A_2 (CTA_2) analogue **5**, whereas the less polar ester **22b** after similar treatment afforded the hydroxy epimer of **5** (**5b**) 97%).

Optically active (+)-CTA_2 and (−)-CTA_2 were prepared

by the above sequence using (+)-*trans*-1-iodo-1-octen-3-ol *tert*-butyldimethylsilyl ether,[14] which served as a resolving agent as well as a carrier of the lower side chain. Unlike thromboxane A_2 (TA_2), carbocyclic thromboxane A_2 (CTA_2) and its epimer are stable at ambient temperatures in solution or neat.

The biological profile[15,16] of CTA_2 appears to be unique among ecosanoids thus far synthesized. CTA_2 exhibited extremely potent vasoconstricting activity on the isolated cat coronary artery, mimicking thromboxane A_2 in this regard. However, it behaved as a potent thromboxane A_2 antagonist, rather than an agonist, on platelet aggregation induced by arachidonic acid and stable endoperoxide analogues. Furthermore, CTA_2 selectively inhibited the biosynthesis of thromboxanes without compromising PGI_2 production. A major and important difference of CTA_2 from pinane thromboxane A_2 (PTA_2), another stable thromboxane analogue recently reported from our laboratories,[8a] is the dissociation of vasoconstrictor and platelet aggregatory properties by CTA_2.

Conclusion

Despite the elegant experiments of the Karoniska group[3] regarding the structure of thromboxane A_2, this molecule still remains elusive to isolation and chemical synthesis. In view of the enormous difficulties in dealing with this compound, its structure still requires final proof and further support of this proposal is still being sought. In this article we described the total synthesis of the carbon analogue (**5**) of this unusual structure. Our synthetic scheme is general enough to allow the synthesis of a number of other analogues in this series. Unlike thromboxane A_2 (TA_2), CTA_2 is chemically stable and allows extensive investigations to be carried out. Its biology is rather exciting in that, although it mimics thromboxane A_2 in its action on the smooth muscle, it differs from it in its platelet aggregatory profile.[16]

Experimental Section

General. Melting points were recorded on a Thomas-Hoover Unimelt apparatus and are uncorrected. ^1H NMR spectra were recorded on a Varian A-60A MHz or a Bruker WH-360 MHz spectrophotometer in $CDCl_3$ unless otherwise stated and are reported in τ from Me_4Si. IR spectra were obtained with a Perkin-Elmer Model 237 or 281B infrared spectrophotometer and the IR figures reported are ν_{max} in cm^{-1}. Mass spectra were provided by the Mass Spectral Service of the Department of Chemistry, University of Pennsylvania, and are within acceptable limits unless otherwise stated. Microanalyses were performed by Galbraith Laboratories.

Thin layer chromatography (TLC) was carried out on 0.25-mm E. Merck precoated silica gel plates (60F-254) using UV light and/or 7% polyphosphomolybdic acid in ethanol–heat as developing agent. Preparative layer chromatography (PLC) was performed on 0.25, 0.5, 1 or 2 mm × 20 cm × 20 cm E. Merck silica gel plates (60F-254). For column chromatography E. Merck silica gel (60, particle size 0.063–0.200-mm) was used. Flash column chromatography was employed according to Still et al.[17] using E. Merck silica gel (60, particle size 0.040–0.063-mm).

All reactions were carried out under an argon atmosphere using dry, freshly distilled solvents under anhydrous conditions unless otherwise stated. Ethereal and hydrocarbon solvents were dried and distilled under argon from sodium–benzophenone ketyl. Methylene chloride was distilled under argon from calcium hydride. Dimethyl sulfoxide was distilled under argon from calcium hydride under aspirator pressure. Reaction temperatures were externally measured. NMR multiplicities are reported using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad; J = coupling constant (Hz). Only the strongest and/or structurally most important peaks are reported for the IR and mass spectra. The abbreviation Me_3Si is used for the trimethylsilyl group.

All yields refer to chromatographically and spectroscopically (^1H NMR) homogeneous materials.

Bicyclo[2.1.1]-2-dibromomethylhexan-2-ol (9). A dry flask equipped with a magnetic stirrer was charged with a solution of bicyclo[2.1.1]-hexan-2-one (**8**, 1.0 g, 10.4 mmol) in dry THF (20 mL) under argon. To this stirred and cold (−78 °C) solution was added sequentially dry dibromomethane (3.63 g, 20.8 mmol) and, after thermal equilibration, a solution of lithium diisopropylamide (LDA) (41.6 mL of 0.5 M THF solution prepared from *n*-BuLi and diisopropylamine, 20.8 mmol) in a dropwise fashion over 20 min. After 15 min when TLC indicated complete reaction the mixture was diluted with ice–water (100 mL) and ether (200 mL) and neutralized to pH 7 with 10% HCl solution. The ether layer was separated after shaking, combined with another ethereal extract (100 mL) of the aqueous phase, washed with brine (50 mL), and dried ($MgSO_4$). Removal of the solvents on the rotary evaporator followed by flash column chromatography[17] (silica, 20% ether in petroleum ether) afforded pure bicyclo[2.1.1]-2-dibromomethylhexane -2-ol (**9**, 2.75 g, 98%): oil; R_f 0.37 (silica, 20% ether in petroleum ether); IR (neat) ν_{max} 3546 (OH), 3448 (OH), 3049, 2985, 2967, 2890, 1718, 1477, 1445, 1333, 1285, 1250, 1209, 1199, 1188, 1176, 1126, 1101, 1081, 1060, 1032, 1022, 998, 935, 898, 867, 837, 829, 769, 735, 679 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) τ 4.03 (s, 1 H, $CHBr_2$), 7.40 (dt, J = 7.5, 3 Hz, 1 H), 7.45 (s, 1 H, OH), 7.47 (m, 1 H), 8.12 (m, 3 H), 8.83 (dd, J = 9.8, 7.5 Hz, 1 H); mass spectrum *m/e* (rel intensity) 253 ($M^+ - H_2O$, 0.2), 231 (13), 229 (26), 191 ($M^+ - {}^{79}Br$, 3), 189 ($M^+ - {}^{81}Br$, 3), 121 (16), 119 (14), 109 (21), 97 (base peak); exact mass 269.9073 (calcd for $(C_7H_{10}OBr_2)$, 269.9078). Anal. ($C_7H_{10}OBr_2$), C, H, Br.

Bicyclo[3.1.1]heptan-2-one (7). A. From Bicyclo[2.1.1]-2-dibromomethylhexan-2-ol (9). A solution of bicyclo[2.1.1]-2-dibromomethylhexan-2-ol (**9**, 1.0 g, 3.7 mmol) in anhydrous ether (37 mL) under argon was cooled to −78 °C. *n*-BuLi (4.8 mL, 1.7 M in hexane, 8.15 mmol) was added dropwise (syringe pump) over 20 min with stirring. The reaction was allowed to proceed at −78 °C with stirring until TLC analysis revealed completion (ca. 30 min) and then quenched with oxalic acid (8.15 mL, 1 N aqueous solution, 8.15 mmol) at −78 °C. The mixture was then diluted with ice–water (50 mL) and ether (100 mL) and after shaking the organic layer was separated and washed with water (25 mL) and brine (25 mL). Drying ($MgSO_4$) and evaporation of the solvent on the rotary evaporator (0 °C) gave an oily residue which was subjected to flash column chromatography (silica, 10% ether in pentane) to afford pure bicyclo[2.1.1]heptan-2-one (**7**, 236 mg, 58%, R_f 0.25 and a small amount of its regioisomer, bicyclo[2.1.1]heptan-3-one (**11**, 41 mg, 10%), R_f 0.37. The properties of **7** and **11** were in agreement with those previously reported.[9]

B. From Keto Tosylate 15. To a stirred solution of dimsylpotassium (KCH_2SOCH_3, 15 mL, 1 M in Me_2SO prepared from oil-free KH and anhydrous Me_2SO, 15 mmol) cooled in a 12 °C water bath was added over 1 h a solution of keto tosylate **15** (1.974, g, 7.0 mmol) in dry Me_2SO (55 mL). The cooling bath was removed and stirring was continued for an additional 1 h. The resulting red-orange mixture was quenched by pouring onto ice (100 g) and ether (150 mL). The organic phase was separated and the aqueous phase extracted with ether (3 × 100 mL). The combined ether layer was washed with (1) water (2 × 50 mL), (2) pH 7 phosphate buffer (50 mL), and (3) brine (50 mL). The dried ($MgSO_4$) solvent was removed on the rotary evaporator (0 °C) and the residue chromatographed on a flash column (silica, 10% ether in pentane) to afford pure bicyclo[2.1.1]heptan-2-one (**7**,[9a] 500 mg, 65%) as an oil: IR (CCl_4) ν_{max} 1720 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 360 MHz) τ 7.20 (m, 1 H), 7.40 (m, 3 H), 7.56 (m, 2 H), 8.00 (m, 2 H), 8.40 (m, 2 H).

4-Methylenecyclohexanone Ethylene Ketal (13). The monoketal of cyclohexane-1,4-dione (prepared by controlled deketalization of the corresponding diketal with AcOH–THF–H_2O, 3:2:2, 45 °C, 14 h), (18.8 g, 121 mmol) in dry benzene (40 mL) was added to methylenetriphenylphosphorane [192 mmol, prepared from 192 mmol of dimsyl sodium (2 M solution) and methyltriphenylphosphonium bromide (70.83 g, 200 mmol) in 300 mL of Me_2SO] in Me_2SO at 25 °C and allowed to react at that temperature for 2 h. The reaction mixture was poured into a separating funnel containing ether (300 mL) and ice (200 g). After shaking, the organic layer was separated and the aqueous phase was extracted with ether (3 × 300 mL). The combined ether layer was washed with water (3 × 200 mL) and brine (200 mL). Drying ($MgSO_4$) and evaporation of the solvent followed by flash chromatography (silica, 20% ether in petroleum ether) afforded pure olefin **12** (16.5 g, 88%) as a colorless oil: R_f 0.44; IR (neat) ν_{max} 3075 (=CH_2), 2940, 2880, 1650 (=CH_2), 1440, 1355, 1315, 1265, 1240, 1120, 1085, 1035, 1000, 940, 905, 755, 680 cm^{-1}; ^1H NMR ($CDCl_3$,

60 MHz) τ 5.33 (m, 2 H, CH_2=), 6.08 (s, 4 H, OCH_2CH_2O), 7.68 (m, 4 H, CH_2); 8.32 (m, 4 H, CH_2); mass spectrum *m/e* 154 (M^+). Anal. ($C_9H_{14}O_2$) C, H.

4-Hydroxymethylcyclohexanone Ethylene Ketal (14). To a magnetically stirred, cold (0 °C) solution of diisoamylborane (218 mmol, from 218 mL of 1 M solution of borane in THF and 46 mL of 2-methyl-2-butene) was added under argon a solution of the olefin **13** (15.62 g, 101 mmol) in THF (10 mL) at once. The cooling was removed and the stirring was continued for 3 h. The reaction mixture was cooled to −10 °C and treated dropwise with water (4.2 mL) before simultaneously adding with stirring solutions of 3 N NaOH (105 mL) and 30% H_2O_2 (105 mL) over a period of 30 min. The mixture was allowed to reach room temperature over 30 min while stirring, before being poured onto a saturated solution of sodium-potassium tartrate (100 mL). Extraction with ethyl acetate (3 × 500 mL) and washing of the combined organic layer with 10% $NaHSO_3$ solution (200 mL) and brine (200 mL) followed by drying ($MgSO_4$) and evaporation afforded crude hydroxy ketal **14**. Purification by flash column (silica, ethyl acetate–petroleum ether, 1:1) yielded pure **14**[9a] (15.62 g, 90%): R_f 0.40; IR (neat) ν_{max} 3420 cm^{-1} (OH); ^1H NMR ($CDCl_3$, 60 MHz) τ 6.14 (s, 4 H, OCH_2CH_2O), 6.60 (m, 2 H, CH_2O), 7.08 (bs, 1 H, OH), 8.00–8.84 (m, 9 H, CH, CH_2).

4-*p*-Toluenesulfonyloxymethylcyclohexanone (15). The tosylation of the hydroxy ketal **14** by the standard method proceeded according to Musso et al.[9a] and the product was converted without purification to the keto tosylate **15** as follows. Dissolution of the crude product (31 g, from 15.62 g (91 mmol) of **14**) in AcOH–THF–H_2O (2:1:1; 400 mL) and stirring at 75 °C under argon for 2.5 h (or 12 h at 25 °C + 15 min at 80 °C) resulted in complete deprotection of the ketone. The solution was cooled to 0 °C and carefully neutralized with solid $NaHCO_3$ (300 g). The resulting mixture was diluted with water (200 mL) and extracted with ether (3 × 400 mL). The combined ether extract was washed with 5% $NaHCO_3$ solution (300 mL) followed by washings with water (300 mL) and brine (150 mL). Drying ($MgSO_4$) and evaporation of the solvents gave a yellow residue which was recrystallized from ether–hexane to furnish **15**[9a] as a colorless, crystalline solid (23.3 g, 91% from **14**): mp 63–64 °C (lit.[9a] mp 64–65 °C); IR ($CHCl_3$) ν_{max} 1710 (C=O), 1360 (tosylate), 1170 cm^{-1} (tosylate); ^1H NMR ($CDCl_3$, 360 MHz) τ 2.13 (d, J = 7 Hz, 2 H, aromatic), 2.57 (d, J = 7 Hz, 2 H, aromatic), 6.05 (d, 2 H, J = 6 Hz, CH_2O), 7.53 (s, 3 H, CH_3), 7.68 (m, 4 H, CH_2CO), 7.83 (m, 1 H, CH), 7.95 (m, 2 H, CH_2), 8.58 (m, 2 H, CH_2).

2-Formyl-2-phenylselenenylbicyclo[3.1.1]heptane (17). To a stirred suspension of methoxymethyltriphenylphosphonium chloride (12.07 g, 35.2 mmol) in dry toluene (70 mL) at 0 °C was added under argon a solution of lithium diisopropylamide (LDA, 106 mL, 0.33 M in THF, 3.5 mmol) in a dropwise manner to generate a 0.2 M solution of the phosphorane. To the bright red methoxymethylenetriphenylphosphorane solution at 0 °C was added at once a solution of bicyclo[3.1.1]heptan-2-one (**7**, 800 mg, 7.3 mmol) in dry toluene (4 mL). After stirring for 5 h at 0 °C the reaction mixture was poured onto ice–water (100 mL) and pentane (200 mL). The organic layer was separated and the aqueous phase reextracted with pentane (300 mL). The combined organic layer was washed with (1) saturated $NaHCO_3$ (100 mL), (2) water (100 mL), and (3) brine (100 mL). The solution was dried ($MgSO_4$) and concentrated on the rotary evaporator below 0 °C to ca. 100 mL. This solution was flashed through a short column of silica gel with pentane to remove the triphenylphosphine oxide and reconcentrated below 0 °C to 100 mL containing crude enol ether **16**. Although the resulting enol ether **16** could be isolated by repetitive chromatographic procedures, R_f 0.71 (silica, CH_2Cl_2), and careful removal of the solvents, it was expedient to add PhSeCl to the above solution and isolate the resulting phenylseleno aldehyde. The above solution of the enol ether **16** was diluted with dry CH_2Cl_2 (20 mL), cooled to −78 °C, and treated successively with anhydrous K_2CO_3 (1.5 g) and PhSeCl (4.8 g, 25 mmol) under argon. The reaction mixture was stirred at that temperature for 2 h and then poured onto CH_2Cl_2 (50 mL) and saturated $NaHCO_3$ (50 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic solution was washed with 5% $NaHCO_3$ (100 mL) and water (3 × 100 mL) and dried ($MgSO_4$). Removal of the solvents followed by flash column chromatography (silica, 5% ether in petroleum ether) afforded the phenylseleno aldehyde **17** (1.26 g, 62% overall from **7**) as a pale yellow oil: R_f 0.10; IR (CCl_4) ν_{max} 3049, 2959, 2924, 2865, 2786, 2762, 2703 (CHO), 1724 (CHO), 1577, 1488, 1477, 1449, 1412, 1408, 1383, 1348, 1297, 1280, 1229, 1183, 1172, 1151, 1121, 1075, 1044, 1021, 952, 936, 909, 847 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) τ 0.47 (s, 1 H, CHO), 2.46 (m, 2 H, aromatic) 2.75 (m, 3 H, aromatic), 6.07 (m, 1 H), 7.60 (m, 2 H), 7.91 (m, 1 H), 8.06 (m, 1 H), 8.22 (m, 1 H), 8.37 (m, 2 H), 8.54 (m, 2 H); mass spectrum *m/e* (rel intensity) 280 ($^{80}Se - M^+$, 16), 279 ($M^+ - H$, 1), 251 ($M^+ - CHO$, 1.5), 158 ($PhSeH^+$, 11), 123 ($M^+ - PhSe$, 32.5), 95 (28), 81 (46), 67 (base peak); exact mass *m/e* 280.0366 (calcd for $C_{14}H_{16}O^{80}Se$, 280.0366).

2-Formylbicyclo[3.1.1]hept-2-ene (6). A magnetically stirred solution of the phenylselenide **17** (1.11 g, 3.98 mmol) in CH_2Cl_2 (10 mL) under argon was cooled to −78 °C and treated with *m*-chloroperbenzoic acid (24 mL of a 0.2 M solution of 85% *m*-CPBA in methylene chloride, 4.77 mmol). The reaction mixture was stirred at −78 °C for 30 min and then diisopropylamine (1.34 mL, 9.55 mmol) was added before the cooling bath was removed. By the time the reaction mixture reached room temperature the elimination was complete. The residue obtained after concentration was directly flash chromatographed (silica, 5% ether in petroleum ether) to afford the pure aldehyde **6** (427 mg, 88%) as a pale yellow oil: R_f 0.15; IR (CCl_4) ν_{max} 3030, 2985, 2950, 2899, 2880, 2817, 2717 (CHO), 1692 (CHO), 1631 (C=C), 1422, 1387, 1366, 1333, 1307, 1264, 1232, 1180, 1157, 1111, 1079, 1055, 971, 917, 901, 826 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) τ 0.60 (s, 1 H, CHO), 3.33 (m, 1 H, olefin), 6.83 (m, 1 H), 7.29 (m, 1 H), 7.35 (t, J = 3 Hz, 2 H), 7.73 (m, 2 H), 8.75 (m, 2 H); mass spectrum *m/e* (rel intensity) 122 (M^+, 9), 121 ($M^+ - H$, 15), 105 (32), 93 (25), 91 (37), 85 (24), 83 (41), 81 (50), 71 (65), 69 (64), 55 (base peak); exact mass *m/e* 122.0723 (calcd for $C_8H_{10}O$, 122.0732).

2-Formyl-3-(3α- and -β-*tert*-butyldimethylsilyloxyoct-1(*E*)-enyl)-bicyclo[3.1.1]heptane (18). A solution of (+)*trans*-1-iodo-3-*tert*-butyldimethylsilyl-1-octen-3-ol (4.74 g, 12.9 mmol) (pure (+) isomer[14] was used for the preparation of optically active CTA_2 and its epimer) in anhydrous ether (21.5 mL) was cooled to −78 °C under argon and treated dropwise while magnetically stirred with *tert*-butyllithium (21.5 mL, 1.2 M in pentane, 25.8 mmol). After 3 h of stirring at −78 °C an ethereal solution of copper 1-pentyne–HMPT complex prepared from copper 1-pentyne (1.73 g, 13.2 mmol) and HMPT (4.80 mL = 4.32 g, 26.5 mmol) in ether (3 mL) was added dropwise at −52.5 ± 2.5 °C, allowed to stir at that temperature for 15 min, and then cooled to −78 °C before the aldehyde **6** (400 mg, 3.23 mmol) in ether (3 mL) was added dropwise. Stirring at −78 °C was continued for 4 h (or until TLC indicated complete reaction) and then the reaction mixture was diluted with cold (0 °C) ether (250 mL) and quenched with saturated ammonium salfate solution (100 mL). The organic phase was washed successively with (1) saturated ammonium sulfate (75 mL), (2) water (100 mL), (3) 1% H_2SO_4 (3 × 75 mL), (4) water (100 mL), (5) saturated $NaHCO_3$ (100 mL), and (6) brine (100 mL). The organic layer was dried ($MgSO_4$) and evaporated to give an oily residue which was subjected to flash column chromatography (silica, 2.5% ether in petroleum ether) furnishing the aldehyde **18** (662 mg, 56%) as an oil, R_f 0.39 (silica, 5% ether in petroleum ether). The 360-MHz ^1H NMR spectrum of this material indicated the presence of some of the cis isomer of aldehyde **18** (τ − 0.17 (cis) and 0.04 (trans), ca. 1:2). Before proceeding, therefore, this material was completely epimerized to the desired trans aldehyde **18** by basic treatment as follows. The cis/trans mixture of aldehydes obtained as above (366 mg, 1 mmol) was dissolved in absolute methanol (20 mL) and treated under argon with anhydrous potassium carbonate (69 mg, 0.5 mmol) at room temperature for 12 h. The mixture was then diluted with ether (100 mL) and brine (25 mL) and neutralized with 1 N oxalic acid (1.0 mL). The organic layer was separated and the aqueous phase extracted with ether (2 × 50 mL). The combined ether extract was washed with brine (25 mL), dried ($MgSO_4$), and evaporated to afford essentially pure trans aldehyde **18** (mixture of hydroxy epimers) (348 mg, 95%): IR (CCl_4) ν_{max} 2994, 2959, 2915, 2833, 2801, 2688 (CHO), 1730 (CHO), 1661, 1464, 1458, 1379, 1366, 1357, 1256, 1136, 1075, 1006, 971, 938, 870, 840 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) τ 0.06 and 0.08 (doublets, J = 2 Hz, 1 H total, aldehyde), 4.37 (m, 2 H, olefin), 5.86 (m, 1 H, CHO), 6.91 (m, 1 H, $CHCH$=), 7.33 (m, 1 H), 7.42 (d, J = 10.8 Hz, collapsing on irradiation at τ 6.91, 0.4 H, $CHCHO$), 7.47 (d, J = 10.8 Hz, collapsing on irradiation at τ 6.91, 0.6 H, $CHCHO$), 7.58 (m, 1 H), 7.66 (m, 1 H), 7.81 (m, 1 H), 8.09 (m, 1 H), 8.40 (m, 3 H), 8.47 (m, 1 H), 8.56 (m, 1 H), 8.76 (m, 15 H), 8.82 (t, J = 8.5 Hz, 1 H), 9.09 (t, overlapping with *t*-Bu signal, 3 H each, $SiCH_3$), 9.09 (s, 9 H, $C(CH_3)_3$), 9.97, 9.99 (singlets, 3 H each, $SiCH_3$); mass spectrum *m/e*

(rel intensity) 349 ($M^+ - CH_3$, 1), 309 (2), 307 ($M^+ - t$-Bu, 42), 293 (11), 207 (18), 161 (13), 159 (10), 105 (23), 75 (base peak); exact mass *m/e* 307.2104 (calcd for $C_{22}H_{40}O_2Si$-*t*-Bu), 307.2094).

2α-((2*E*)- and (*Z*)-Methoxyvinyl)-3β-(3α- and β-*tert*-butyldimethylsilyloxyoct-(1*E*)-enyl)bicyclo[3.1.1]heptane (19). Methoxymethyltriphenylphosphonium chloride (1.41 g, 4.1 mmol) was suspended in dry toluene (7.0 mL) in a flame-dried flask equipped with a magnetic stirrer. To this cold (0 °C), stirred suspension was added dropwise, under argon, a solution of lithium diisopropylamide (LDA, 12.4 mL, 0.33 M, 4.1 mmol, prepared from *n*-BuLi in pentane and diisopropylamine in THF). The bright red solution was stirred at 0 °C for 15 min before the aldehyde **18** (500 mg, 1.4 mmol) in toluene (1 mL) was dropwise added at the same temperature. After 30 min TLC indicated complete reaction and the mixture was quenched with ice-water (30 mL) and ether (100 mL). The organic layer was separated and the aqueous phase reextracted with ether (50 mL). The combined organic solution was washed with brine (25 mL), dried ($MgSO_4$), and evaporated to afford an oily residue which was subjected to flash column chromatography (silica, 5% ether in petroleum ether) furnishing pure methoxyenol ether **19** (436 mg, 81%) as an oil: R_f 0.61 (geometrical isomers ca. 3:2 ratio); IR (CCl_4) ν_{max} 3030, 3003, 2941, 2915, 2833, 1661 (enol ether), 1645, 1466, 1460, 1447, 1433, 1383, 1355, 1258, 1215, 1209, 1145, 1111, 1089, 1006, 967, 935, 870, 836, 717, 693 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) τ 3.58 (m, 0.6 H, C*H*OCH_3), 4.03 (m, 0.4 H, C*H*OCH_3), 4.45 (m, 2 H, olefin), 5.20 (m, 0.6 H, C*H*=$CHOCH_3$), 5.60 (m, 0.4 H, C*H*=$CHOCH_3$), 5.87 (m, 1 H, CHO), 6.36, 6.38, 6.42, 6.44 (singlets, 3 H total, OCH_3), 7.25 (q, J = 9.7 Hz, 0.4 H), 7.57–8.80 (m, 18.6 H), 8.87 (t, J = 7.8 Hz, 0.4 H), 8.94 (t, J = 7.8 Hz, 0.6 H), 9.10 (m, 3 H, CH_3), 9.10 (s, 9 H, $C(CH_3)_3$), 9.93, 9.95 (singlets, 3 H each, $SiCH_3$); exact mass 392.3079 *m/e* (calcd for $C_{24}H_{44}O_2Si$, 392.3111). Anal. ($C_{24}H_{44}Si$) C, H.

2α-(6-Carbomethoxyhex-(2*Z*)-enyl)-3β-(3α- and β-*tert*-butyldimethylsilyloxyoct-(1*E*)-enyl)bicyclo[3.1.1]heptane (21). The enol ether **19** (197 mg, 0.5 mmol, mixture of cis/trans isomers) in THF (13.6 mL) and water (1.5 mL) stirred under argon at room temperature was treated with $Hg(OAc)_2$ (477 mg, 1.5 mmol). After 1 h stirring at 25 °C the yellow mixture was poured onto a 7% aqueous solution of potassium iodide (100 mL) and extracted with benzene (2 × 75 mL). The combined organic layer was washed with (1) 7% aqueous potassium iodide solution (40 mL) and (2) brine (25 mL), dried ($MgSO_4$), and evaporated to afford essentially pure aldehyde **20** (186 mg, 98%): R_f 0.29 (5% ether in petroleum ether); IR (neat) ν_{max} 2960, 2925, 2850, 2705 (CHO), 1725 (CHO), 1662, 1460, 1405, 1385, 1372, 1360, 1252, 1232, 1131, 1075, 1001, 970, 936, 908, 872, 805, 772, 735 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) τ 0.31 (m, 1 H, CHO), 4.58 (m, 2 H, olefin), 5.94 (m, 1 H, CHO), 7.58 (m, 2 H), 7.79 (m, 5 H), 7.96 (m, 1 H), 8.21 (m, 1 H), 8.46 (m, 2 H), 8.54 (m, 1 H), 8.66 (m, 1 H), 8.73 (m, 6 H), 8.90 (t, J = 9 Hz, 1 H), 9.13 (s, 9 H, $C(CH_3)_3$), 9.13 (m, overlapping with *t*-Bu signal, 3 H, CH_3), 9.96, 9.98 (singlets, 3 H each, $SiCH_3$); mass spectrum *m/e* (rel intensity) 378 (M^+, 3), 321 ($M^+ - t$-Bu, 2), 229 (3.5), 211 (4), 203 (5), 57 (base peak); exact mass *m/e* 321.2229 (calcd for ($C_{23}H_{42}O_2Si$-*t*-Bu), 321.2250).

This aldehyde (**20**, 186 mg) without further purification was reacted with the ylide derived from (4-carboxybutyl)triphenylphosphonium bromide (1.33 g, 1.5 mmol) in dry Me_2SO (1.5 mL) and dimsyl sodium (1.5 mL, 2 M, 3 mmol) at 25 °C. The reaction was complete in 1 h and was then diluted with ice-cold ether (50 mL) and acidified carefully with 1 N oxalic acid to pH 3–4. The organic layer was separated and the aqueous phase extracted with ether (3 × 50 mL); the combined organic solution was washed with water (50 mL) and brine (50 mL) and dried ($MgSO_4$). The solvents were removed and the resulting mixture taken up in ether (20 mL) and esterified with ethereal diazomethane at 0 °C. After complete reaction (TLC) the mixture was concentrated and flash chromatographed (silica, 5% ether in petroleum ether) to afford the methyl ester silyl ether **21** (178 mg, 74%, mixture of silyloxy epimers): R_f 0.28; IR (neat) ν_{max} 3003, 2950, 2925, 2850, 1740 ($COOCH_3$), 1460, 1435, 1360, 1248, 1070, 965, 870, 830, 770 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) τ 4.63 (m, 4 H, olefin), 5.98 (m, 1 H, CHO), 6.33 (s, 3 H, $COOCH_3$), 7.70 (m, 3 H), 7.82 (m, 3 H), 7.98 (m, 3 H), 8.13 (m, 1 H), 8.26 (m, 1 H), 8.33 (t, J = 7.2 Hz, 2 H), 8.50 (m, 5 H), 8.77 (m, 7 H), 9.00 (t, J = 7.2 Hz, 1 H), 9.12 (s, 9 H, $C(CH_3)_3$), 9.12 (m, overlapping with *t*-Bu signal, 3 H, CH_3), 9.95, 9.97 (singlets, 3 H each, $SiCH_3$); mass spectrum *m/e* 389 ($M^+ - t$-Bu − $2CH_3$). Anal. ($C_{29}H_{52}O_3Si$) C, H.

2-(6-Carbomethoxyhex-(2*Z*)-enyl)-3β-(3α-hydroxyoct-(1*E*)-enyl)-bicyclo[3.1.1]heptane (CTA_2 Methyl Ester) (22a) and Its Hydroxy Epimer 22b. The silyl ether **21** (245 mg, 0.5 mmol) in AcOH–THF–H_2O (3:2:2, 14 mL) was stirred under argon at 45 °C for 10 h. After cooling to room temperature the reaction mixture was diluted with dichloromethane (75 mL) and the organic phase separated. The aqueous phase was reextracted with dichloromethane (75 mL) and the combined organic solution was washed with water (50 mL) and brine (50 mL), dried ($MgSO_4$), and concentrated to afford a mixture of hydroxy epimers. Separation of the two isomers was performed by preparative layer chromatography (PLC) (eight silica plates, 20 cm × 20 cm × 0.25 mm, 10% ethyl acetate in petroleum ether, three elutions) furnishing the pure isomers, less polar (**22b**), R_f 0.33 (62 mg, 33%), more polar (**22a**) (assumed to be the 15*S* isomer on the basis of chromatographic mobility and biological activity), R_f 0.29 (123 mg, 65%). **22a**: IR (CCl_4) ν_{max} 3597 (OH), 3414 (OH), 3030, 2967, 2924, 2857, 1736 ($COOCH_3$), 1658, 1475, 1435, 1379, 1348, 1147, 1120, 1072, 971, 909, 845, 728, 674 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) τ 4.52 (m, 2 H, olefin), 4.63 (m, 2 H, olefin), 5.93 (m, 1 H, CHO), 6.30 (s, 3 H, $COOCH_3$), 7.52 (m, 4 H), 7.62 (m, 2 H), 7.80 (m, 3 H), 8.18 (m, 1 H), 8.25 (m, 1 H), 8.30 (t, J = 7.3 Hz, 2 H), 8.47 (m, 5 H), 8.55 (m, 8 H), 9.00 (t, J = 7.5 Hz, 1 H), 9.12 (t, J = 6.7 Hz, 3 H, CH_3); mass spectrum *m/e* (rel intensity) 362 (M^+, 1), 344 ($M^+ - H_2O$, 3), 229 (6), 206 (7), 204 (7), 203 (35), 161 (17), 149 (17), 147 (17), 145 (17), 133 (29), 131 (20), 119 (34), 107 (25), 105 (53), 67 (base peak); exact mass *m/e* 362.2828 (calcd for $C_{23}H_{38}O_3$, 362.2821). Me_3Si derivative: calcd for $C_{26}H_{46}O_3Si$, 434.3217; obsd, 434.3240. The optically active isomer **22a** exhibited $[\alpha]^{30}_D$ +25.80° (CH_3OH, *c* 1.68).

22b: IR (CCl_4) ν_{max} 3597 (OH), 3484 (OH), 3003, 2959, 2933, 2857, 1739 ($COOCH_3$), 1653, 1443, 1435, 1361, 1299, 1203, 1160, 1019, 968, 858, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) τ 4.50 (m, 2 H, olefin), 4.63 (m, 2 H, olefin), 5.93 (m, 1 H, CHO), 6.33 (s, 3 H, $COOCH_3$), 7.68 (m, 4 H), 7.80 (m, 4 H), 7.97 (m, 4 H), 8.15 (m, 1 H), 8.23 (m, 1 H), 8.33 (m, 2 H), 8.48 (m, 4 H), 8.70 (m, 6 H), 9.02 (t, J = 9 Hz, 1 H), 9.12 (t, J = 7.5 Hz, 3 H, CH_3); mass spectrum *m/e* (rel intensity) 344 ($M^+ - H_2O$, 4), 229 (9), 206 (8), 204 (10), 203 (46), 161 (18), 147 (18), 145 (19), 133 (35), 131 (21), 119 (35), 105 (43), 67 (base peak); exact mass *m/e* 344.2704 (calcd for $C_{23}H_{38}O_3 - H_2O$, 344.2715). Me_3Si derivative: calcd for $C_{26}H_{46}O_3Si$, 434.3216; obsd, 434.3208. The optically active isomer **22b** exhibited $[\alpha]^{30}_D$ −16.70° (CH_3OH, *c* 0.75).

2α-(6-Carboxyhex-(2*Z*)-enyl)-3β-(3α-hydroxyoct-(1*E*)-enyl)bicyclo[3.1.1]heptane (CTA_2) (5) and Its Hydroxy Epimer 5b. The methyl ester **22a** (50 mg, 0.14 mmol) in THF (6.5 mL) and water (6.5 mL) was treated at room temperature with stirring under argon with 1 N lithium hydroxide solution (700 μL, 0.70 mmol). After 12 h stirring at ambient temperature (complete reaction by TLC) the THF was removed under vacuum and the aqueous solution mixed with ether (50 mL) was acidified to pH 3–4 with 1 N oxalic acid at 0 °C. The aqueous phase was saturated with solid NaCl to aid extraction of the product into the organic phase and extracted a total of four times (30 mL each). The combined ether solution was washed with water (25 mL) and brine (25 mL) before drying ($MgSO_4$) and concentrated to afford essentially pure carbocyclic thromboxane A_2 (**5**), which was repurified by preparative layer chromatography (PLC) (two silica plates, 20 cm × 20 cm × 0.25 mm, ether–petroleum ether, 1:1) (45 mg, 95%): R_f 0.21; IR (CCl_4) ν_{max} 3333 (OH), 3003, 2959, 2915, 2857, 1709 (COOH), 1618, 1433, 1404, 1256, 1232, 1036, 969 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) τ 2.90 (bs, 2 H, OH, COOH), 4.48 (m, 2 H, olefin), 4.62 (m, 2 H, olefin), 5.85 (q, J = 6 Hz, 1 H, CHO), 7.68 (m, 3 H), 7.75 (m, 1 H), 7.83 (m, 4 H), 8.00 (m, 2 H), 8.27 (m, 2 H), 8.37 (m, 2 H), 8.47 (m, 5 H), 8.70 (m, 6 H), 9.02 (t, J = 9.0 Hz, 1 H), 9.12 (t, J = 7.5 Hz, 3 H, CH_3); mass spectrum *m/e* (rel intensity) 330 ($M^+ - H_2O$, 3), 289 (3), 259 (5), 203 (33), 161 (13), 147 (18), 133 (30), 131 (20), 119 (37), 107 (28), 105 (47), 67 (base peak); exact mass *m/e* 330.2579 (calcd for $C_{22}H_{34}O_2 - H_2O$, 330.2559). The optically active **5** had $[\alpha]^{30}_D$ +32.60° (CH_3OH, *c* 0.95).

The hydroxy epimer of CTA_2 (**5b**) was prepared from **22b** in exactly the same way as above and had the following properties. **5b** (97% from **22b**): R_f 0.25 (silica, ether–petroleum ether, 1:1); IR (CCl_4) ν_{max} 3356 (OH), 3003, 2950, 2924, 2849, 1709 (COOH), 1621, 1401, 1222, 1099, 1022, 969 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) τ 3.23 (bs, 2 H, OH, COOH), 4.38 (m, 2 H, olefin), 4.52 (m, 2 H, olefin), 5.76 (q, J = 7 Hz, 1 H, CHO), 7.63 (m, 5 H), 7.75 (m, 2 H), 7.87 (m, 2 H), 7.98 (m, 1 H), 8.20 (m, 1 H), 8.32 (m, 2 H), 8:47 (m, 6 H), 8.68 (m, 6 H), 8.97 (t, J = 9 Hz, 1 H), 9.08 (t, J = 6 Hz, 3 H, CH_3); mass spectrum

m/e (rel intensity) 348 (M^+, 1), 330 ($M^+ - H_2O$, 3), 289 (3), 203 (32), 161 (12), 147 (16), 133 (28), 131 (17), 119 (34), 107 (23), 105 (41), 67 (base peak); exact mass *m/e* 330.2556 (calcd for $C_{22}H_{36}O_3 - H_2O$, 330.2559). The optically active isomer **5b** had an $[\alpha]^{30}_D$ −23.90° (CH_3OH, *c* 1.20).

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2,4-Methanoproline (2-Carboxy-2,4-methanopyrrolidine) and 2,4-Methanoglutamic Acid (1-Amino-1,3-dicarboxycyclobutane) in Seeds of *Ateleia herbert smithii* Pittier (Leguminosae)

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Abstract: A new acidic amino acid, 2,4-methanoglutamic acid, containing a cyclobutane ring and a new imino acid, 2,4-methanoproline, containing the previously unknown 2-azabicyclo[2.1.1]hexane system have been isolated from seeds of *Ateleia herbert smithii*. The structures of the two compounds were confirmed by X-ray crystallography. Unlike most amino and imino acids the isolated compounds do not show optical activity. Their possible biological significance is discussed.

The seeds of many legume species accumulate high concentrations of nonprotein amino acids and these may play a role in protecting the seeds from insect predation.[2,3] Insects may, however, become adapted to diets containing potentially toxic amino acids as in the case of *Caryedes brasiliensis*, whose larvae live on canavanine-rich seeds.[4,5]

The legume *Ateleia herbert smithii* Pittier, which is a locally common tree found in Costa Rica only in the vicinity of Santa Rosa National Park, Guancaste Province,[6] produces seeds which are ignored by at least 100 seed predators in this habitat, but are preyed on by the larvae of the weevil (Curculionidae) *Apion* sp. nov. In studying the chemistry of these seeds to determine whether the seeds contained secondary compounds likely to deter most predators, we found major concentrations of two acid-stable ninhydrin reacting compounds which could not be identified by their R_f values and ionic mobilities. Lower concentrations of a third ninhydrin-reacting "unknown" were also detected. The present paper describes the isolation and identification of the two major "unknowns" as 2,4-methanoproline and 2,4-methanoglutamic acid. Neither of these

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