Rapid Communication

Ruthenium mediated oxidative fragmentation of the pinane system: An entry into chiral bicyclo[4.2.0]octanes
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(-)-α-Pinene has been restructured in three steps to functionalized bicyclo[4.2.0]octanes via cyclobutane annulation to the tricyclic-[5.1.1.025]nonane system and a novel RuO4 mediated oxidative fragmentation.

Natural products bearing a cyclobutane ring as part of their complex polycyclic framework, once a rarity, are being encountered with increasing regularity from terrestrial as well as marine and microbial sources. Among the terpenes, the presence of a cyclobutane ring in the form of bicyclic, 6-4-fused (bicyclo[4.2.0]octane) sub-structure is quite common as exemplified by sesquiterpenes sterpurene 1, illudol 2, punctatin A 3 and diterpene trihydroxydecipiadiene 4 among others. These and other related structures have generated considerable synthetic interest and several methodologies have been devised to access the functionalized bicyclo[4.2.0]octane framework, many of which are of general nature while a few others have been developed in the context of a specific target. Herein, we report an unanticipated observation that provides short and useful entry into chiral, functionally embellished, bicyclo[4.2.0]octane derivatives from cheap, commercially available (-)-α-pinene 5.

Addition of dichloroketene to (-)-α-pinene 5 under ultrasound irradiation 2a afforded a [2+2]-cycloadduct 6 which underwent smooth reductive dehalogenation to furnish the tricyclic cyclobutanone derivative 7, Scheme I. Our original interest was to effect a two carbon homologation in (-)-α-pinene 5 through C2-C5 bond scission in 7 and for this purpose we sought to functionalize the C5 position through oxidative manoeuvres. Ruthenium tetroxide has been known to oxidize saturated hydrocarbons at CH and CH2 sites. While the selectivity in such oxidations is low and unpredictable, yet ruthenium oxidations of saturated hydrocarbons have found some preparative utility. It was anticipated that C5 of 7 will be particularly amenable to ruthenium oxidation in view of its tertiary nature and additional activation.

When 7 was subjected to oxidation with in situ generated RuO4 for a prolonged period a mixture of 8-10 (2:1:1) was obtained (~50% yield) and could be readily separated by column chromatography on silica gel, Scheme II. The spectral data of 8-10 clearly indicated that while the cyclobutanone moiety present in 7 was fully intact, the pinane portion had undergone oxidative restructuring and the original bridged cyclobutane ring of the natural product has been cleaved. The structures 8-10 were secured on the basis of incisive 1H (1H-1H COSY) and 13C NMR

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Scheme I - Reagents and conditions: (a) Cl₂C-COCl, Zn, ZnCl₂, Et₂O, Zn, 2hr, 40%; (b) Zn, NH₄Cl, MeOH, RT, 70%.

Scheme II - Reagents and conditions: (a) RuCl₃-NaIO₄, CCl₄:CH₃CN:H₂O, RT, 8 days, 50%.

Scheme III - Reagents and conditions: (a) BF₃-Et₂O, CH₂Cl₂, RT, 50%.

(DEPT) spectral data. The regioisomeric hydroxydiones 8 and 9 were particularly difficult to differentiate and to fully secure their formulation a simple chemical transformation was effected. On exposure to Lewis acid (BF₃-etherate), 8 and 9 furnished regioisomeric enones 11 and 12, respectively, which could be identified quite unambiguously by ¹H 2D NMR analysis, Scheme III.

Formation of 8 and 9 from 7 during the catalytic RuO₄ oxidation can be explained through the formation of an alkoxytrioxoruthenium intermediate 13 via the corresponding alkoxyhydroxydioxoruthenium (resulting from the insertion of the bridgehead C₁-H bond into the oxo ruthenium double bond of RuO₄). Fragmentation of the reactive intermediate 13 as shown leads to the bicyclic dione 8, which under the reaction conditions dehydrates and is further oxidised to give 10. Similar insertion of the oxoruthenium double bond into C₁-H and fragmentation (see 14) accounts for the formation of 9. Interestingly, there is approximately 3:1
regiochemical preference for the C₁-H bond insertion. It is noteworthy that oxidation in 7 occurs selectively at the C₁, and C₇ bridgehead tertiary carbon centres of the bridged cyclobutane ring and not at C₅ as was envisaged.

In summary, we have reported a 3-step sequence from (-)-α-pinene 5 in which a new four membered ring is appended but the pre-existing bridged cyclobutane ring is cleaved to furnish highly functionalized and angular methyl bearing bicyclo[4.2.0]octane based chirons of potential synthetic utility. It may be recalled that the skeleton present in 8 is reminiscent of many naturally occurring sesquiterpenoids.

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References
5 All new compounds were fully characterised on the basis of complementary spectral (IR, ¹H & ¹³C NMR and mass) data. Experimental details of the oxidation of 7: To the dechlorinated tricyclic ketene adduct 7 (1g, 5.6 mmole) in 35 mL of ternary solvent mixture of CCl₄, CH₃CN and H₂O (1:1:1.5) was added reoxidising agent NaI₀₄ (12 gm, 10 eq) followed by catalytic amount of RuCl₃ (30 mg, 3 % by wt). The reaction was stirred for 8 days at room temperature and carefully monitored (TLC). When the starting material had largely consumed, the reaction mixture was diluted with dichloromethane (50 mL) and filtered through a celite pad. The organic layer was separated and the aqueous layer was extracted with dichloromethane (25mL x 2). The combined organic extracts were washed with brine and dried over Na₂SO₄. Removal of the solvent under vaccum gave an oily residue which was charged on silica gel column and eluted with 12-15% EtOAc:hexane mixture to give three major products 8 (204 mg), 9(100 mg) and 10 (100 mg) in ratio 2:1:1 in 50% yield (on the basis of recovered starting material). 8: [α]D⁰=+37.4 (c 0.81, CHCl₃); IR(cm⁻¹) 1780, 1703; ¹H NMR (200MHz, CDCl₃): δ 3.49-3.4 (m, 1 H), 3.11 (dq, J=18 , 1.5Hz, 2H), 2.69-2.56 (m, lH ), 2.38-2.19 (m, 2H), 1.80-1.48 (m, 1H), 1.55 (s, 3H), 1.22 (s, 6H); ¹³C NMR (50MHz, CDCl₃): δ 213.7, 208, 71.6, 65.8, 57.1, 44.3, 40.7, 40.5, 27.4, 26.9, 24.1, 23.7; mlz 210(M⁺-18). 9: [α]D⁰=+23.14 (c 0.7, CHCl₃); IR(cm⁻¹) 1774, 1711; ¹H NMR (200MHz, CDCl₃): δ 3.2- 3.1 (m, 3H), 2.7-2.0 (m,5H), 1.54 (s, 3H), 1.33 (s, 3H), 1.3 (s, 3H); ¹³C NMR (50MHz, CDCl₃): δ 209.12, 207.72, 72.8, 64.9, 59.5, 49.37, 38.5, 35.4, 31.8, 29.7, 23.7; mlz 210(M⁺). 10: [α]D⁰=+23.7 (c 0.65, CHCl₃); IR(cm⁻¹) 1782, 1711; ¹H NMR (200MHz, CDCl₃): δ 3.46-3.41 (m, 1H), 3.24 (dq, J=17.7, 2Hz, 2H), 2.8 (m, 1H), 2.56-2.51 (m, 2H), 2.31 (m, 1H), 2.19 (s, 3H), 1.83-1.86 (m, 1H), 1.55 (s, 3H); ¹³C NMR (50MHz, CDCl₃): δ 211.7, 207.2, 206.5, 65.0, 57.1, 46.3, 40.9, 40.0, 28.4, 24.3, 24.2; mlz 166 (M⁺-28).