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STEROID CD-RING SYNTHONS FROM PODOCARPIC ACID BY USE OF THE BARTON RADICAL DECARBOXYLATION REACTION

E. Jane Cochrane, S. Warren Lazer, John T. Pinhey*, and John D. Whitby

Department of Organic Chemistry, University of Sydney, Sydney 2006, Australia

Abstract: The ester derived from O-acetylpodocarpic acid (6) and N-hydroxypyridine-2-thione underwent thermal decarboxylation to yield the 2-pyridylthio derivative (7). This compound was converted by *m*-chloroperbenzoic acid into a mixture of sulphoxides, which underwent elimination on mild heating to give the alkene (8) in high yield. This reaction sequence has been used in the production from podocarpic acid of compounds (4) and (5), which are potentially useful for the synthesis of vitamin D analogues and steroids.

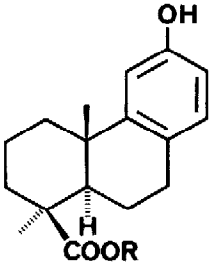
Various attempts have been made to transform the readily available degraded diterpenoids, podocarpic acid (1) and dehydroabietic acid (3), into steroids.[1] The general aim has been to build the five-membered D-ring onto ring C of these tricyclic compounds. In a new approach, which has recently been reported by Matsumoto,[2] the A,B, and C rings of dehydroabietic acid became the D,C, and B rings, respectively, of the steroid. Our aim has been to degrade compounds (1) and (3) to CD-ring synthons for use in the preparation of vitamin D analogues and steroids, and we now report a simple high yielding route from podocarpic acid to the bicyclic compounds (4) and (5).

The major obstacle to the degradation of the acid (1) has been the removal of the CO_2H group with introduction of the exocyclic double bond as in compound (8). The classical method of Curtius degradation, followed by conversion of the resultant 1°-amine to a 3°-amine-N-oxide, and then Cope elimination, is successful in the case of dehydroabietic acid (3),[3] but fails with podocarpic acid (1),[4] in which the CO_2H group has a β-configuration. The sequence proceeds normally to the formation of the β-dimethylamino group, but due to steric crowding by the β-methyl group, oxidation to the N-oxide could not be achieved. This problem has now been solved by use of the highly efficient radical decarboxylation of the ester derived from N-hydroxypyridine-2-thione followed by sulphoxide elimination, a method developed by Barton.[5] This reaction, which is illustrated for O-acetylpodocarpic acid (6) in Scheme 1, gave rise to the α-(2-pyridylthio) derivative (7)† in 98% yield. As expected, compound (7) was readily oxidised by *m*-chloroperbenzoic acid

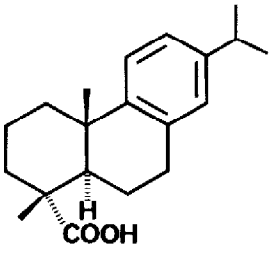
† All new compounds were fully characterised by microanalytical and spectroscopic methods.

to a mixture of sulphoxides, which were unstable and underwent a rapid elimination at 100°C to yield the olefin (8) in 78% yield.#

The actual route from podocarpic acid (1) to synthons (4) and (5) started with degradation of the aromatic ring of the ester (2). This was achieved in good overall yield as outlined in Scheme 2. Ozonolysis of methyl podocarpate (2) proceeded as reported[6] to give a mixture consisting mainly of the hydroperoxide (9), which was oxidised directly with periodate-permanganate to the dicarboxylic acid (10) (75% yield overall). Ring closure in refluxing acetic anhydride containing potassium cyanide and potassium acetate[7] gave the keto ester (11), which was hydrolysed to the carboxylic acid (12) in quinoline and acetic acid.[8]



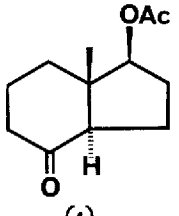
(1) R=H
(2) R=Me



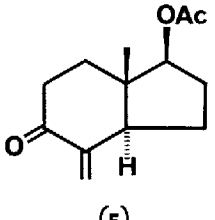
(3)

The production of the olefin (15) from the keto acid (12) proceeded smoothly and is outlined in Scheme 3. The Barton decarboxylation gave the sulphide (13) in 70% yield, and, as with compound (6), attack by the thiyl radical occurred on the less hindered α-face. The carbonyl group was protected at this stage by reduction with sodium borohydride to the β-hydroxy compound, and acetylation to give the sulphide ester (14) in good overall yield. Oxidation of this compound with *m*-chloroperbenzoic acid at -78°C gave a mixture of unstable sulphoxides, which on heating at 100°C yielded the olefin (15) (70% overall).

Ozonolysis of compound (15) in CH_2Cl_2-MeOH at -78°C afforded (74%) the required ketone (4), while a selenium dioxide oxidation produced the allylic alcohol (16) in 55% yield [10% recovery of (15)]. The second target compound (5) was readily obtained from the alcohol (16) in 76% yield by Swern[9] oxidation.

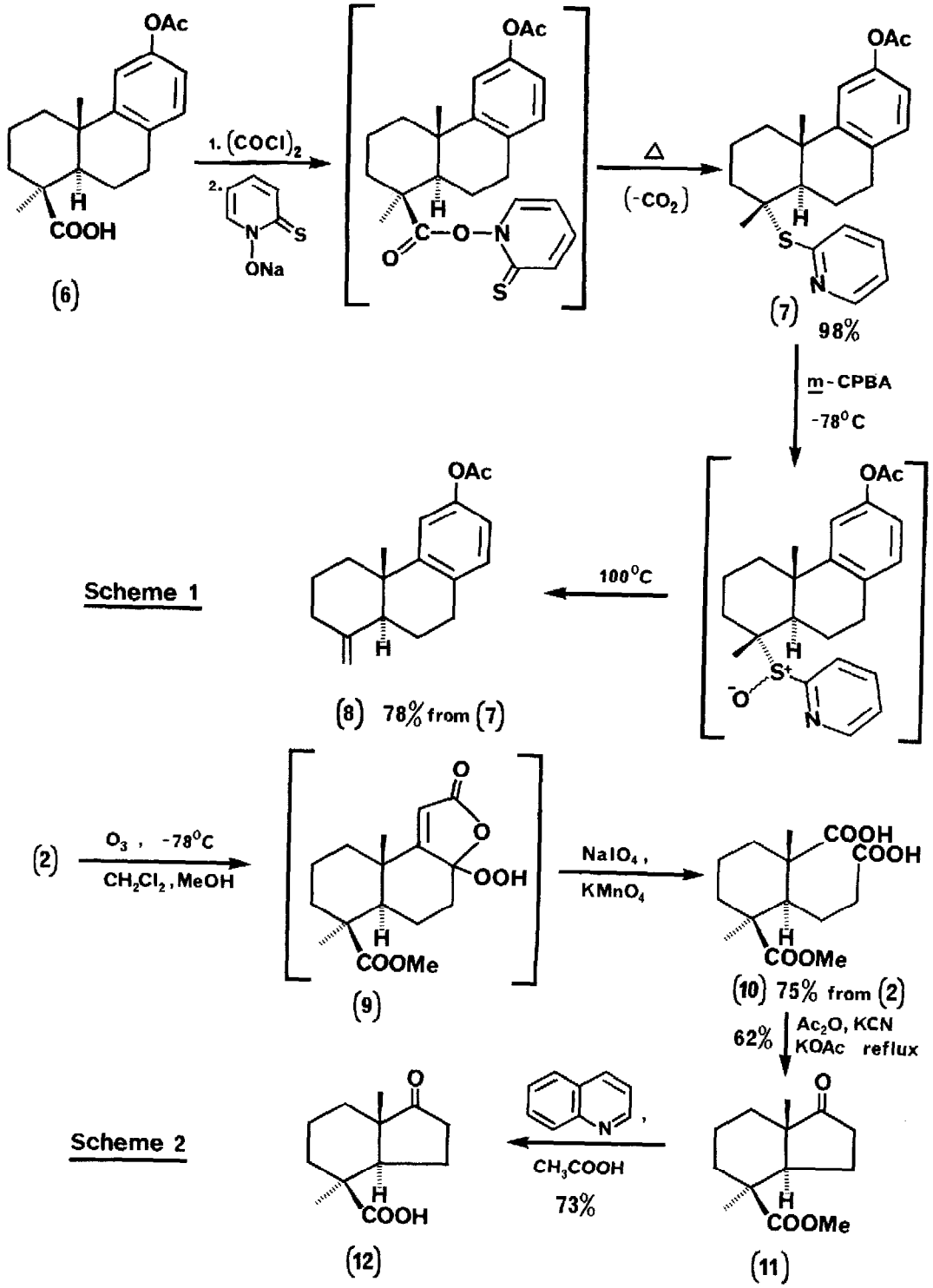


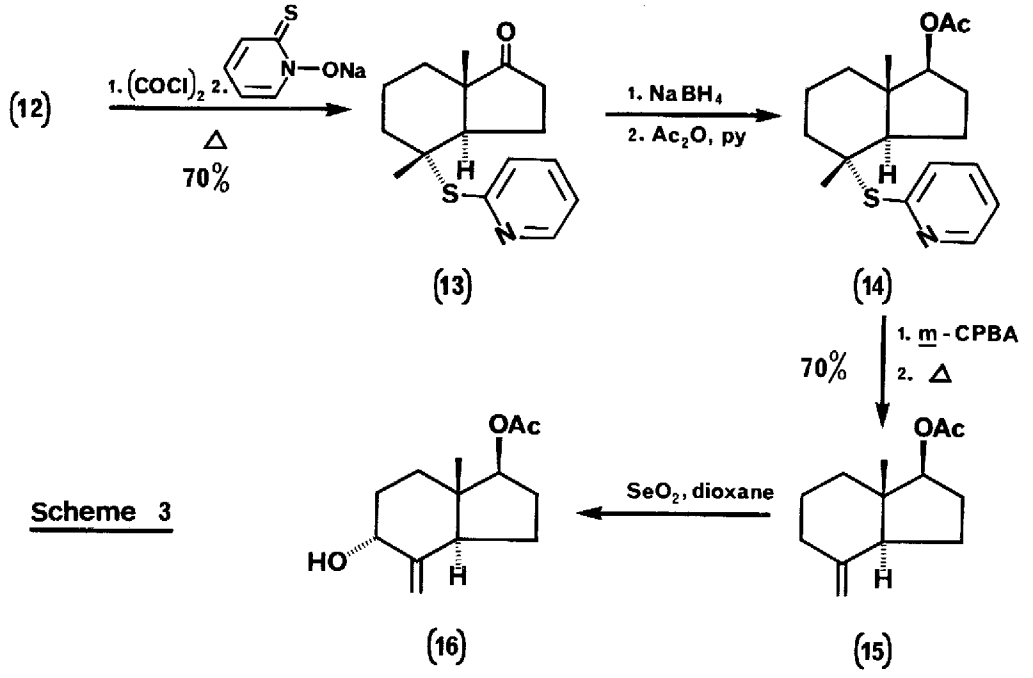
(4)



(5)

This method of degradation of a carboxylic acid to an alkene has also been applied to dehydroabietic acid (3), and the overall yield of the analogous olefin was similar.]


OAc
H
COOH
(6)
1. (COCl)2
2.
N
S
ONa
C–O–N
O
S
Δ
(-CO2)
(7)
98%
m-CPBA
-78°C
100°C
(8) 78% from (7)
Scheme 1
(2)
O3 , -78°C
CH2Cl2 , MeOH
OOH
COOMe
(9)
NaIO4 ,
KMnO4
COOH
(10) 75% from (2)
62%
Ac2O, KCN
KOAc reflux
CH3COOH
73%
(12)
(11)
Scheme 2



Scheme 3

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