Pergamon

Tetrahedron Letters 43 (2002) 4535–4536

TETRAHEDRON
LETTERS

A novel short synthesis of norbisabolide[†]

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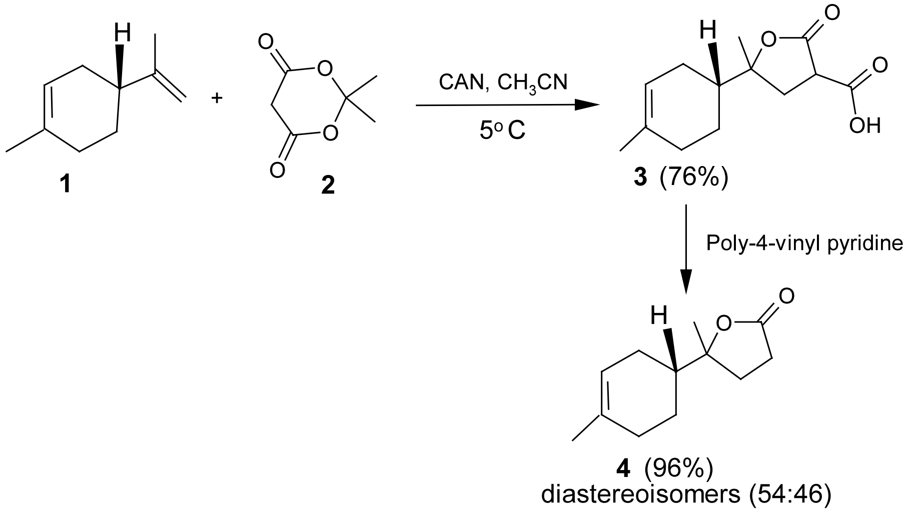
Received 14 December 2001; revised 17 April 2002; accepted 25 April 2002

Abstract—A novel two-step synthesis of norbisabolide is reported involving free radical addition of Meldrum's acid to (*R*)-(+)-limonene using cerium(IV) ammonium nitrate (CAN) followed by decarboxylation with poly-4-vinylpyridine. © 2002 Elsevier Science Ltd. All rights reserved.

Norbisabolide **4** is a C_{12}-terpene lactone isolated from the root bark of *Atalantia monophylla*.[1] It has been synthesised by Kocienski[2] and Ho[3] from limonene via limonene epoxide by eight and five steps, respectively, in moderate yields. Limonene has also been directly converted into norbisabolide by Fukamiya[4] and Gardrat[5] in 7% and 43% yields, respectively. We report here a short and efficient synthesis of norbisabolide from (*R*)-(+)-limonene **1** and Meldrum's acid **2** mediated by cerium(IV) ammonium nitrate (CAN).

CAN is a well known oxidant used in many organic transformations[6] and also for the generation of free radicals which add to carbon–carbon double bonds to yield interesting products.[7] Meldrum's acid is a versatile reagent, which has attracted considerable attention in organic synthesis.[8] Our interest[9] in Meldrum's acid has prompted us to exploit this highly acidic active methylene compound in a free radical addition reaction using CAN. This is the first report of the free radical addition of Meldrum's acid to olefins.

CAN-mediated free radical addition of Meldrum's acid to (*R*)-(+)-limonene **1** yielded the lactone carboxylic



Scheme 1.

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[†] Dedicated to the memory of the late Dr. Nitiraj R. Mane.

PII: S0040-4039(02)00814-6

acid[†] **3** which on decarboxylation with poly-4-vinyl pyridine in DMF or pyridine furnished norbisabolide[‡] **4** (diastereoisomeric mixture, 54:46) (Scheme 1) in good yields (96 and 62%). Decarboxylation using poly-4-vinylpyridine gave pure product in higher yield in comparison to decarboxylation in pyridine. The probable mechanism[7] involves addition of Meldrum's acid radical to the double bond followed by cyclisation to give a γ-lactone. The regioselectivity of addition can be explained on the basis of a steric effect where the bulky Meldrum's acid radical adds to the less hindered double bond in the chain.

Advantages of the method are that the lactone carboxylic acid is obtained in a pure form by bicarbonate extraction from the unreacted starting materials and that decarboxylation is almost quantitative. γ-Lactones constitute important structural features of many natural products and also serve as intermediates in the synthesis of important compounds. The generality of this reaction for the synthesis of other γ-lactones will be explored.

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[†] Lactone carboxylic acid **3**: To a stirred mixture of (*R*)-(+)-limonene (2.72 g, 0.02 mole) and Meldrum's acid (2.88 g, 0.02 mole) in acetonitrile (40 ml) was added cerium(IV) ammonium nitrate (21.92 g, 0.04 mole) batchwise at 5°C over 15 min. The reaction mixture was stirred for an additional 30 min until completion of the reaction (TLC and disappearance of the CAN colour). It was then diluted with water (50 ml) and extracted with ether. The ether extract was washed with sodium bicarbonate solution and the bicarbonate layer was acidified and extracted with ether. The ether layer was washed with water, dried (anhydrous sodium sulphate), and the solvent removed to furnish the lactone carboxylic acid **3** (3.6 g, 76%) as a viscous liquid. IR (neat): 3650–3000 (broad, -COOH), 1750 (broad and strong carbonyl group of lactone and carboxylic group), 1610, 1190, 904 and 728 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.36 and 1.43 (54:46, 3H, two singlets for methyl groups in two diastereoisomers), 1.57 (3H, br. s, vinylic-CH_3), 1.25–2.65 (9H, m, 4 methylenes and methine-H), 3.85 (1H, m, methine-H), 5.29 (1H, br. s, vinylic-H), 8.83 (1H, br. s, -COOH). ^{13}C NMR ($CDCl_3$, DEPT spectrum): δ 21.61, 22.30, 22.89, 23.41 (two methyl groups in two diastereoisomers); 23.89, 25.61, 29.99, 33.89, 34.55, 34.91 (methylenes); 43.06, 43.26 (methine-C); 46.57, 47.30 (methine-C); 88.43 (quaternary C); 119.09, 119.31 (vinylic-CH); 133.61, 133.86 (vinylic-C); 170.55 (carbonyl); 171.98 (carbonyl). Further signals are observed due to diastereoisomers. Anal. $C_{13}H_{18}O_4$: requires: C, 65.55; H, 7.56%; found: C, 65.67; H, 7.48%.

[‡] Norbisabolide **4**: By decarboxylation of **3** with poly-4-vinylpyridine: To the lactone carboxylic acid **3** (0.952 g, 4 mmole) in DMF (5 ml) was added poly-4-vinylpyridine (0.5 g) and the mixture stirred for 2 h at 80°C after which the reaction was complete (TLC). The reaction mixture was cooled, filtered and the filtrate diluted with water (20 ml) and extracted with ether. The ether extract was washed with aqueous sodium bicarbonate, water and dried (anhydrous sodium sulphate). Removal of ether furnished norbisabolide **4** (diastereoisomeric mixture) as a single product as indicated by TLC (0.742 g, 96%). An analytical sample was prepared by passing it through a column of silica gel using pet-ether. Bp 170–175°C/8 mm. IR (neat): 1770 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30 and 1.33 (54:46, 3H, two singlets for methyl groups in two diastereoisomers), 1.61 and 1.64 (54:46, 3H, two singlets for vinylic methyl groups in two diastereoisomers), 1.65–2.30 (9H, m, four methylenes and one methine-H), 2.58 (2H, m, methylene adjacent to keto group), 5.38 (1H, m, vinylic-H). ^{13}C NMR ($CDCl_3$, DEPT spectrum): δ 21.83, 22.71, 23.04, 23.19 (two methyl groups in two diastereoisomers); 25.76, 28.52, 29.88, 30.13, 30.76 (methylenes); 42.74 and 42.89 (methine-C); 88.26 (quaternary C); 119.09 and 119.38 (vinylic-CH); 133.24 and 133.53 (vinylic-C); 176.06 (lactone carbonyl). Further signals were observed due to diastereoisomers. MS: m/e 194 (M^+), 99 (100). Anal. $C_{12}H_{18}O_2$: requires: C, 74.23; H, 9.28%; found: C, 74.34; H, 9.32%.