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Resolution and Absolute Configuration of a Tricyclic Lactone. A Potentially Useful Precursor of Highly Functionalized Terpenoids†

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Abstract: *The highly functionalized tricyclic lactone* ***1*** *was obtained in optically pure form by the sulfoximine-mediated resolution of the enone methyl acetal* ***3****. The absolute configuration of (-)-****3*** *and consequently of (+)-****1****, was determined by the transformation of (-)-****3*** *into (-)-****5****, a known intermediate in the total synthesis of forskolin (****2****) and confirmed by application of the high field FT NMR Mosher method to alcohol* ***6****.*

Several years ago we reported a simple approach to the synthesis of the highly functionalized tricyclic lactone **1** involving a sequence of an intramolecular Michael addition in tandem with an aldol condensation.[1,2] We have also shown the utility of **1** as starting material in the synthesis of advanced key intermediates toward the biologically important diterpene forskolin (**2**).[3-5] Very recently Fraser-Reid et al.[6] described a multistep synthesis of **1** in which the key step is an intramolecular Diels-Alder reaction of an appropriate substituted carbohydrate derived α-enone. However and because of the potentiality of **1** as chiral precursor of the functionalized *trans*-decalin system of natural terpenoids, we considered that there still remains a need for a more economical and operationally simple procedure enabling the preparation of optically pure **1**.

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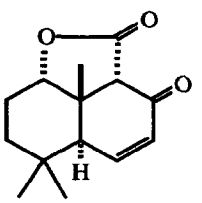
†This paper is dedicated to Professor Alan R. Battersby for his decades of contribution to Organic Chemistry and to commemorate his retirement in 1992.



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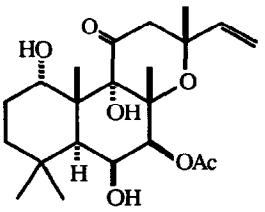

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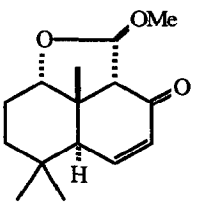

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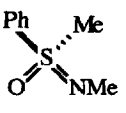
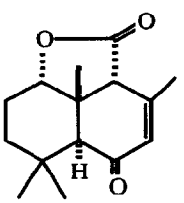
Our plan for the preparation of optically active **1** was to apply the Johnson sulfoximine resolution protocol[7] to the known and readily available derivative (±)-**3**,[3] in which the lactone carbonyl is masked as a methyl acetal. In practice the treatment of (±)-**3** with lithiated (*S*)-sulfoximine **4** proceeded with excellent facial selectivity affording a chromatographically separable mixture of two diastereoisomeric β-hydroxy-sulfoximines.[8] To complete the resolution each oily β-hydroxy-sulfoximine was submitted to thermolysis in refluxing toluene, affording (-)-**3**, mp 89.5-90.5°C, $[\alpha]_D$ -141.3 (c = 0.47, $CHCl_3$), ee>95%[9] and (+)-**3**, mp 89.5-90.5°C, $[\alpha]_D$ +146.7 (c = 0.45, $CHCl_3$), ee>95%[9] from the less and more polar alcohol, respectively.

When (-)-**3** was submitted to acidic hydrolysis followed by Jones oxidation, **1** was obtained in good overall yield (69%), mp 177-180°C, $[\alpha]_D$ +4.36 (c = 0.78, $CHCl_3$). The ^1H, ^{13}C NMR spectra of (+)-**1** are coincident with those previously reported by us for the racemic modification.[1,2] Since the sign of the optical rotation was opposite to that informed by Fraser-Reid [$[\alpha]_D$ -3.03 (c = 0.9, $CHCl_3$)],[12] we concluded that the absolute configuration of (+)-**1** and consequently of (-)-**3** were both the opposite to those depicted in the formulae. Nevertheless, following our previously described sequence,[4] chiral (-)-**3** was converted into (-)-**5**. This enone lactone is a well-known key intermediate previously used in several synthetic sequences toward **2**,[5] that already have been enantioselectively synthesized by Corey et al.[10] and Kanematsu et al..[11] Pure (-)-**5**, mp 170-171°C, $[\alpha]_D$ -42.7 (c = 0.37, $CHCl_3$), ee>95%[9] was found to exhibit ^1H, ^{13}C NMR spectra and optical rotation coincident with those previously reported [lit.[10,11] 164°C, $[\alpha]_D$ -37.8 (c = 0.4, $CHCl_3$); 164°C, $[\alpha]_D$ -37.4 (c= 0.4, $CHCl_3$), respectively]. As expected, when (+)-**3** was submitted to the same reaction sequences described above for (-)-**3**, (+)-**5** [mp 167-169°C, $[\alpha]_D$ +45 (c = 0.4, $CHCl_3$), ee>95%[9]] and (-)-**1** [mp 175.2-179.5°C, $[\alpha]_D$ -4.92 (c = 1.95, $CHCl_3$), ee>95%[9]] were obtained.



(*S*)-4



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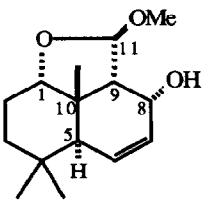

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In view of the foregoing results we decided to establish unambiguously the absolute configuration of (-)-**3** and consequently those of (-)-**5** and (+)-**1** by application of the recently reported extension of the standard Mosher methodology using high field FT NMR techniques[13] to the allylic alcohol **6**,[3] $[\alpha]_D$ -170 (c = 2.38,

acetone) readily obtained by stereospecific reduction of (-)-**3**. Separate *R*-(+)- and *S*-(-)-MTPA [MTPA= α-methoxy-α-(trifluoromethyl)phenylacetic acid] esterification of alcohol **6** followed by an exhaustive ^{1}H NMR analysis (200.13 MHz) of each ester and placing all the assigned protons with positive Δδ values on the right side of the MTPA plane and those with negative values on the left side, as shown in Figure 1, allowed us to conclude that the C-8 alcohol has the *R*-configuration. As the relative stereochemistry of **6** has already been established,[3] we can now confirm that the absolute configuration of (-)-**3** is 1*S*,5*S*,9*R*,10*S*,11*R* and those of (+)-**1** and (-)-**5** are 1*S*,5*S*,9*S*,10*S* and 1*S*,5*S*,9*R*,10*S* respectively as depicted in the corresponding formulae.

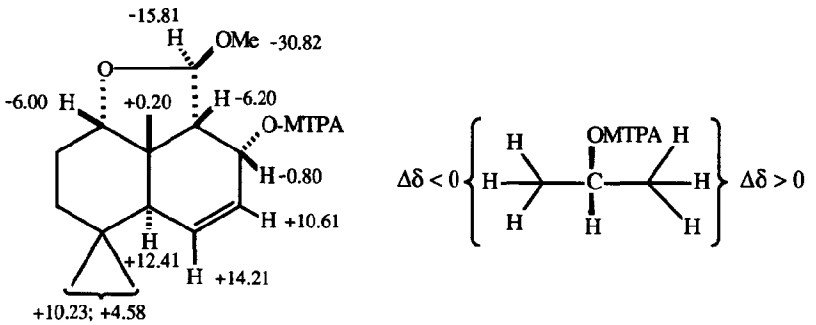

Fig.1 Δδ = δ(*S*-MTPA) - δ(*R*-MTPA); all Δδ values are expressed in Hz

In conclusion, the methodology described above provides a facile entry to optically pure **3**, **1** and **5** by using cheap reagents and extremely simple reaction conditions.

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8. The diastereomeric mixture of hydroxy-sulfoximines obtained from (±)-**3** under standard reaction conditions was chromatographed on silica gel employing increasing amounts of EtOAc in hexane as

solvent to afford two products. The first product to elute (39% yield) was a colorless oil: IR (neat) ν 3441 (br), 3252 (br), 2928, 2870, 1237, 1153, 1104, 1091, 1081, 1037 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.89 (2H, dd, J = 1.5 and 7.48 Hz), 7.62-7.57 (3H, m), 6.69 (1H, dd, J = 3.12 and 9.32 Hz, H-7), 6.08 (1H, dd, J = 3.32 and 9.32Hz, H-6), 5.45 (1H, d, J = 4.42 Hz, H-11), 3.89 (1H, t, J = 3.20 Hz, H-1), 3.43 (1H, d, J = 13.68 Hz, CH_2 sulfoximine, downfield), 3.42 (3H, s, OCH_3), 3.00 (1H, d, J = 13.68 Hz, CH_2 sulfoximine, upfield), 2.63 (3H, s, NCH_3), 2.30 (1H, t, J = 3.32 Hz, H-5), 1.80-1.70 (2H, m, H-2), 1.63 (1H, d, J = 4.42 Hz, H-9), 1.60-1.45 (2H, m, H-3), 0.94 (6H, s), 0.87 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.81 (Ph), 133.81 (Ph), 133.18 (C-6), 131.48 (Ph), 129.83 (C-7), 129.51 (Ph), 105.75 (C-11), 81.74 (C-1), 69.51 (C-8), 67.81 (C-9), 66.06 (CH_2 sulfoximine), 55.64 (OCH_3), 48.73 (C-10), 42.25 (C-5), 34.65 (C-3), 31.73 (4α-Me), 31.04 (C-4), 28.65 (NCH_3), 21.74 (C-2), 21.31 (4β-Me), 19.61 (10-Me).

The second product to elute (35% yield) was a colorless oil: IR (neat) ν 3441 (br), 3223 (br), 2928, 2871, 1241, 1151, 1132, 1108, 1082, 1038 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.90 (2H, dd, J = 1.5 and 7.6 Hz), 7.64-7.58 (3H, m), 5.99 (1H, dd, J = 1.96 and 9.8 Hz, H-6), 5.56 (1H, dd, J = 3.67 and 9.8 Hz, H-7), 5.43 (1H, d, J = 5.5 Hz, H-11), 4.03 (1H, t, J = 3.0 Hz, H-1), 3.50 (3H, s, OCH_3), 3.34 (1H, d, J = 13.98 Hz, CH_2 sulfoximine, downfield), 3.06 (1H, d, J = 13.98 Hz, CH_2 sulfoximine, upfield), 2.88 (1H, d, J = 5.5 Hz, H-9), 2.66 (3H, s, NCH_3), 2.33 (1H, t, J = 3.0 Hz, H-5), 1.95-1.40 (4H, m, H-2, H-3), 1.01 (3H, s), 0.92 (3H, s), 0.84 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 139.52 (Ph), 132.95 (C-6), 131.62 (Ph), 129.97 (C-7), 129.32 (Ph), 128.66 (Ph), 106.82 (C-11), 81.95 (C-1), 69.88 (C-8), 64.60 (CH_2 sulfoximine), 61.85 (C-9), 55.54 (OCH_3), 47.91 (C-10), 42.07 (C-5), 34.70 (C-3), 31.41 (4α-Me), 31.01 (C-4), 28.44 (NCH_3), 21.70 (C-2), 21.28 (4β-Me), 18.73 (10-Me).

9. The enantiomeric purities were established via ^1H NMR analysis employing the shift reagent tris(3-[heptafluoropropyl-hydroxymethylene]-*d*-camphorato) Europium (III) Derivative [Eu(hfc)$_3$].
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