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An Expedient Synthesis of *(R)*-(+)-Umbelactone

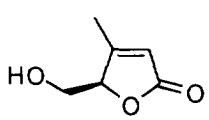
Colin L. Gibson[a]* and Sheetal Handa[b]

[a] Department of Pure & Applied Chemistry, University of Strathclyde, 295 Cathedral Street, Glasgow, G1 1XL, UK.
EMail c.l.gibson@strath.ac.uk

[b] Department of Chemistry, King's College London, The Strand, London, WC2R 2LS, UK. EMail s.handa@uk.ac.kcl.cc.bay

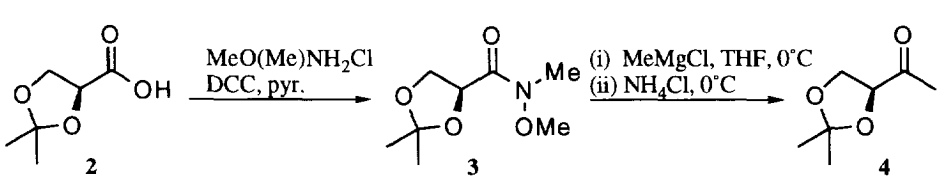
Abstract: The synthesis of the naturally occurring 2(5H)-furanone *(R)*-(+)-umbelactone **1** in five steps and 26.2% overall yield from *(2S)*-2,3-dihydroxy-(2,3-**O**-isopropylidene)propanoic acid **2** is described

The 2(5H)-furanone *(R)*-(+)-umbelactone **1** has been isolated from the alcoholic extracts of *Memycelon umbelatum* Brum.[1] The crude extracts of this plant have shown antiviral, antiamphetamine and spasmolytic activity,[2] consequently, the synthesis of **1** has been the subject of synthetic interest. Thus, the synthesis of the racemic material has been reported[3] and two asymmetric syntheses[4,5] of *(R)*-(+)-**1** and a synthesis of the *(S)*-(-) enantiomer[4] have been described. However, the reported syntheses of *(R)*-(+)-**1** are not particularly efficient and have been achieved in seven steps and 4.4% overall yield from *(R)*-(+)-glutamic acid[4] or in nine steps and 8.7% overall yield[5] from 1,2-dichloroacetone using a Baker's yeast enantioselective reduction. In this communication we report a synthesis of **1** in five steps and in 26.2% overall yield, starting from the *(S)*-acid **2**.



1

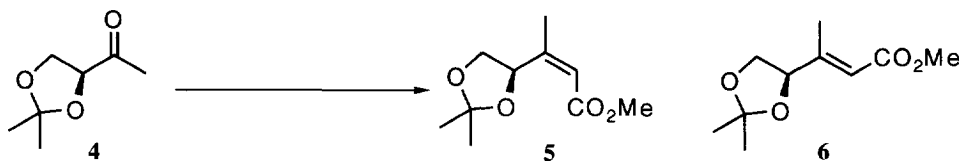
Thus, the *(S)*-acid **2**[6] was converted into the amide **3** by reaction with N,O-dimethylhydroxyamine hydrochloride in pyridine (90%).[7] Subsequent reaction of the amide **3** with excess methylmagnesium chloride in THF and careful evaporation afforded the *(S)*-ketone **4** (86%) (see Scheme 1).[8]



2 **3** **4**

Scheme 1

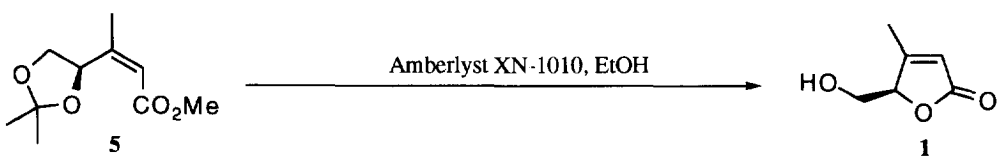
Our original synthetic design required the introduction of the remaining carbon atoms of the umbelactone skeleton through a *(Z)*-selective Wadsworth-Emmons approach on the ketone **4**. We anticipated that the use of Still's bis(2,2,2-trifluoroethyl) (methoxycarbonylmethyl)phosphonate[9] should afford the required *(Z)*-unsaturated ester **5** since α tetrahydropyranyl aldehydes had been shown to give exclusive formation of (Z)-alkenes.[10] However, treatment of the *(S)*-ketone **4** with bis(2,2,2-trifluoroethyl) (methoxycarbonylmethyl)phosphonate and potassium bis(trimethylsilyl)amide in the presence of 18-crown-6, disappointingly, gave predominantly the *(E)*-unsaturated ester **6** (69%) together with the required *(Z)*-unsaturated ester **5** (15%). An alternative Wittig approach with carbomethoxymethylene triphenylphosphorane in acetonitrile at reflux also gave predominantly the *(E)*-unsaturated ester **6** (66%) and a trace of the *(Z)*-unsaturated ester **5** (14%). Conversely, treatment of the *(S)*-ketone **4** with carbomethoxymethylene triphenylphosphorane in methanol at 20°C gave predominantly the required *(Z)*-unsaturated ester **5**, albeit in modest yield (37%), together with the *(E)*-ester **6** (23%) (see Scheme 2).



Conditions	Yield 5	Yield 6
$(CF_3CH_2O)_2P(O)CH_2CO_2Me$, $KN(SiMe_3)_2$, 18-crown-6, -78°C→20°C	15%	69%
$Ph_3P{=}CHCO_2Me$, CH_3CN, 82°C, 20h	14%	66%
$Ph_3P{=}CHCO_2Me$, CH_3OH, 20°C, 24h	37%	23%

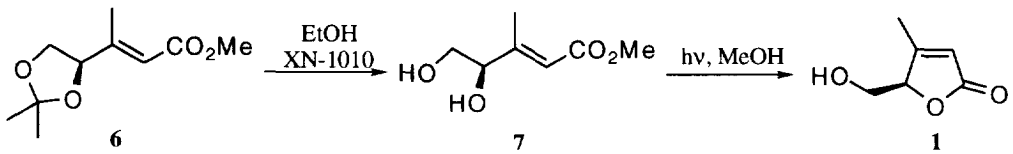
Scheme 2

Removal of the isopropylidene protecting group and lactonization of the *(Z)*-ester **5** was achieved by stirring in an ethanol solution in the presence of an acidic ion exchange resin (Amberlyst XN-1010). This afforded, directly, *(R)*-(+)-umbelactone **1** (73%) which was identical in its spectral and physical properties with those previously reported.[1,4,5]



Scheme 3

Attempts to directly isomerize the *(E)*-unsaturated ester **6** to the isomeric *(Z)*-ester **5** under a variety of conditions (e.g. I_2, tungsten hv[11] or Hg hv[12]) resulted in decomposition of the ester **6**. However, isomerization of the alkene bond in the *(E)*-unsaturated ester **6** could be achieved indirectly. Thus, removal of the isopropylidine protecting group in the *(E)*-unsaturated ester **6** using amberlyst XN-1010 in ethanol afforded the *(E)*-diol ester **7** (87%). Isomerization of the (E)-double bond in diol ester **7** using a medium pressure mercury lamp in methanol with concomitant lactonization afforded *(R)-(+)*-umbelactone **1** (38%) (see Scheme 4) in 17.7% overall yield (26.2% overall including material from the *(Z)*-unsaturated ester **5**) which was identical to that described above.



6 **7** **1**

Scheme 4

In conclusion, a five step synthesis of the naturally occurring *(R)*-(+)-umbelactone **1** has been achieved in 26.2% overall yield staring from the *(S)*-acid **2**. The key steps include Wadsworth-Emmons reaction with bis(2,2,2-trifluoroethyl) (methoxycarbonylmethyl)phosphonate and ketone **4** or a Wittig reaction to give the isomeric esters **4** and **5**. A second key step involves the photochemical isomerization of the *(Z)*-double bond in diol **7** to give *(R)*-(+)-umbelactone **1**.

Acknowledgements: We thank Shell Research Ltd. for generously supplying quantities of the acid **2** and Dr.J. A. Ballantine of the EPSRC Mass Spectrometry Service, University College of Swansea for the accurate mass measurement of **1**.

REFERENCES AND NOTES

1. Agarwal, S. K.; Rastogi, R. P. *Phytochemistry,* **1978**, 17, 1663.
2. Dhar, M. L.; Dhar, M. M.; Dhawan, B. N.; Mehrotra, B. N.; Ray, C. *Indian J. Exp. Biol.*, **1968**, 6, 241.
3. Caine, D.; Frobese, S.; Ukachukwu, V. C. *J. Org. Chem.*, **1983**, 48, 740.
4. Ortuña, R. M.; Bigorra, J. Font, J. *Tetrahedron,* **1987**, 43, 2199.
5. Sato, T.; Okumura, Y.; Itai, J.; Fujisawa, T. *Chem. Lett.*, **1988**, 1537.
6. The *(S)*-acid **2** was available enantiomerically pure in useful quantities (> 100 g) from Shell Research Ltd., Shell Research Centre, Sittingbourne, Kent, ME9 8AG, UK.
7. All new compounds gave satisfactory IR, ^{1}H NMR, ^{13}C NMR and HRMS and/or elemental analysis. Known compounds gave specific rotations in accord, or better than the literature values. The quoted yields are for homogeneous (≥95%) materials isolated by chromatography or kugelrohr distillation or

recrystallization. Selected data: *(S)*-**1** M.p. 58-61°C (white needles, CH_2Cl_2-hexane) lit.[1] 65°C; found $M^{+\cdot}$ 146.0817 $C_6H_8O_3$ requires 146.0817; $[\alpha]_D^{20}$ +12.4 (c=0.96, $CHCl_3$) lit.[4] $[\alpha]_D^{20}$ +11.67 (c=1.84, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 5.89 (m, 1H, H-3), 4.9 (m, 1H, H-5), 4.07 (ddd, J = 12.6, 6.7, 3 Hz, C-5 HCH_a), 3.78 (ddd, J = 12.6, 6.7, 4.2 Hz, C-5 HCH_b), 2.22 (t, J= 6.7 Hz, 1H, OH), 2.11 (m, 3H, C-4 CH_3); δ_H (300 MHz, C_6D_6) 5.38 (m, 1H, H-3), 4.04 (m, 1H, H-5), 3.45 (ddd, J = 12.5, 6.5, 3 Hz, C-5 HCH_a), 3.09 (ddd, J = 12.5, 6.5, 3 Hz, C-5 HCH_b), 2.22 (t, J= 6.5 Hz, 1H, OH), 1.2 (m, 3H, C-4 CH_3); δ_C (62 MHz, $CDCl_3$) 173.68, 166.65, 118.25, 85.63, 61.32, 14.15; ν_{max} (CCl_4) 3603, 3599-3420 (broad), 3024, 3018, 2963, 1759, 1651. *(S)*-**3** B.p. 74-78°C @ 0.2 mm Hg; found C, 50.77, H, 7.76, N, 7.34, MH^+ 190.1071 $C_8H_{15}NO_4$ requires C, 50.78, H, 7.99, N, 7.4 MH^+ 190.1079; $[\alpha]_D^{20}$ -31.28 (c=0.98, $CHCl_3$). *(S)*-**4** B.p. 80°C @ 16 mm Hg (kugelrohr); found MH^+ 145.0877 $C_7H_{13}O_3$ requires 145.0864; $[\alpha]_D^{20}$ -97.78 (c=0.316, $CHCl_3$), lit.[8] $[\alpha]_D^{20}$ -65.8 (c=1, EtOH). *(R)*-**5** found MH^+ 201.1124 $C_{10}H_{17}O_4$ requires 201.1127; $[\alpha]_D^{20}$ -114.35 (c=0.22, $CHCl_3$). *(R)*-**6** found $M^{+\cdot}$ 200.1049 $C_{10}H_{16}O_4$ requires 200.1048; $[\alpha]_D^{20}$ -43.96 (c=0.36, $CHCl_3$). *(R)*-**7** found MH^+ 161.0794 $C_7H_{13}O_4$ requires 161.0814; $[\alpha]_D^{20}$ -13.74 (c=1, $CHCl_3$).

8. Direct reaction of the *(S)*-acid **2** with methyl lithium provides the *(S)*-ketone **4** in poor yield (40%): Handa, S; Hawes, J. E.; Pryce, R. J. *Synth. Commun.*, **1995**, 25, 2837.
9. Still, W. C.; Gennari, C. *Tetrahedron Lett.*, **1983**, 24, 4405
10. Beckmann, M.; Hildebrandt, H.; Winterfeldt, E, *Tetrahedron: Asymm.*, **1990**, 1, 335.
11. Unsaturated *(E)*-amides have been isomerized to the *(Z)*-amides under these conditions: Crombie, L.; Taylor, L, J. Chem. Soc., **1957**, 2761.
12. γ-Hydroxy α,β-unsaturated esters have been isomerized to 2(5H)-furanones under these conditions: Epstein, W. W.; Sonntag, A. C., *J. Org. Chem.*, **1967**, 32, 3390.

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