106. EPC Syntheses[1]) from Bicyclic Dioxanones: (−)-5-Epidehydrofukinone

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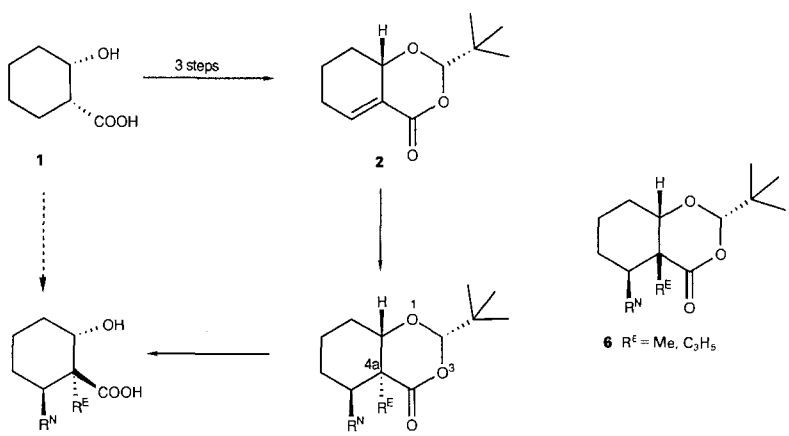
(−)-5-Epidehydrofukinone ((−)-**15**) has been synthesized from (2*S*,4a*S*,5*S*,8a*S*)-4a,5-dimethyl-2-(*tert*-butyl)-perhydro-4*H*-1,3-benzodioxan-4-one (**4a**), a compound readily available by yeast reduction of ethyl 2-oxocyclohexanecarboxylate.

Recently [2], we have synthesized derivatives of (1*S*,2*S*)-2-hydroxycyclohexanecarboxylic acid with three contigous stereogenic centers (compounds **5**, *Scheme 1*) from (1*R*,2*S*)-2-hydroxycyclohexanecarboxylic acid (**1**). The method is based on a highly stereoselective *Michael* addition of lithium dialkylcuprates to the α,β-unsaturated lactone **2** and trapping of the resulting enolates with electrophiles, aqueous NH_4Cl solution, or alkyl halides, giving single diastereoisomers **3** and **4**, respectively.

In [2], the products of double alkylation were tentatively assigned a *cis*-fused perhydro-4*H*-1,3-benzodioxin-4-one structure (see **6** in *Scheme 1*). In this note, we describe the

Scheme 1



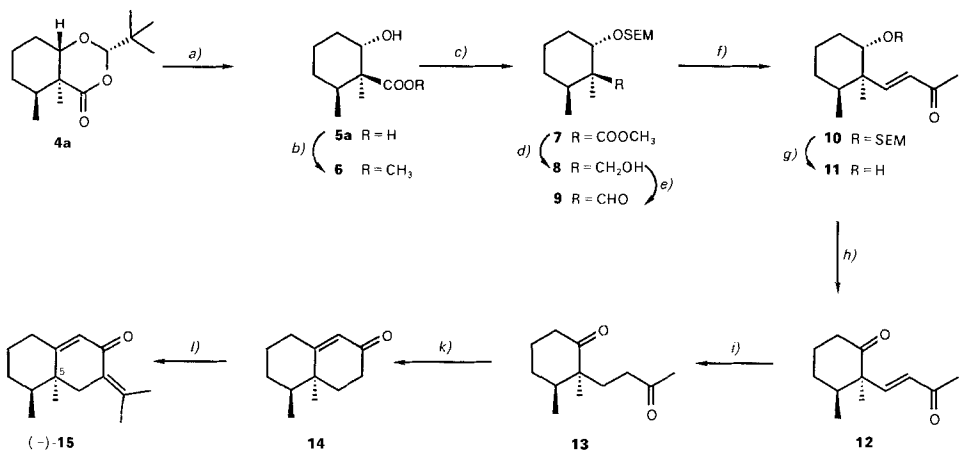
[1]) For definition and discussion of the term, see [1].

[2]) On leave from the *Instituto de Química Orgánica General-C. S. I. C.*, Spain.

transformation of compound **4a** to (−)-5-epidehydrofukinone (= (4a*S*,5*S*)-4,4a,5,6,7,8-hexahydro-4a,5-dimethyl-3-(1-methylethylidene)-2(3*H*)-naphthalenone; (−)-**15**), providing a chemical correlation which proves the (*S*)-configuration of C(4a) in the starting material. Thus, the two six-membered rings of **4a** and of the analogues **4b** and **4c** are *trans*- and not *cis*-fused.

The synthesis[3]) of (−)-5-epidehydrofukinone ((−)-**15**) from **4a** is shown in *Scheme 2*. The bicyclic dioxanone **4a** was first hydrolyzed to the crystalline β-hydroxy acid **5a** (m.p. 106°, $[\alpha]_D = +51.1$)[4]), using acidic or basic conditions. This compound was methylated with ethereal CH_2N_2, in the usual conditions, yielding **6** ($[\alpha]_D = +65.4$). The protected

Scheme 2



a) Dowex 50 × 8, MeOH, r.t., 94%, or LiOH, THF, MeOH, H_2O, r.t., > 98%. *b)* CH_2N_2, Et_2O, 0°, > 99%. *c)* $ClCH_2OCH_2CH_2SiMe_3$ (= SEM-Cl), $(i\text{-}Pr)_2NEt$, CH_2Cl_2, r.t., > 98%. *d)* $LiAlH_4$, THF, 0°, 91%. *e)* PCC, 4 Å molecular sieves, CH_2Cl_2, r.t., 94%. *f)* 1) CH_2COCH_2LiK, Et_2O, from −45° to r.t.; 2) 2N HCl, 0°, 73–83%. *g)* $LiBF_4$, MeCN, 70°, 74%. *h)* PCC, 4 Å molecular sieves, CH_2Cl_2, r.t., 84%. *i)* H_2, Pd/C (cat.), EtOAc, r.t., 91%. *k)* 1) NaOMe, MeOH, r.t.; 2) TsOH, CH_2Cl_2, 92%. *l)* 1) $LiN(i\text{-}Pr)_2$, THF, from −50 to −38°; $ZnCl_2$, −38°; acetone, −38 to 0°; 2) TsOH, C_6H_6, reflux, 77%.

β-hydroxy ester **7** ($[\alpha]_D = -6.4$), which was prepared by reaction with [2-(trimethylsilyl)-ethoxy]methyl chloride (SEM-Cl) using standard conditions [3], was reduced to the corresponding alcohol **8** ($[\alpha]_D = +81.7$), which in turn was oxidized to aldehyde **9** ($[\alpha]_D = +50.3$), using pyridinium chlorochromate (= PCC) [4] in the presence of 4 Å molecular sieves [5]. The chain elongation was complicated by the low reactivity and unstability of the aldehyde **9**. *Wittig* reaction of **9** with (acetylmethylidene)triphenylphosphorane under several different conditions[5]) gave no olefinic compounds, but rather

[3]) All the new compounds gave satisfactory spectroscopic data (^{1}H-NMR, IR, and MS).

[4]) All optical rotations were measured at 25° and with concentrations of *ca.* 1 g/100 ml in $CHCl_3$ solution, except for compound **5a**, which was measured in MeOH solution.

[5]) Toluene, MeCN, and MeOH [6] were used as solvent at different temperatures.

decomposition products; finally, this transformation could be achieved by reaction with doubly deprotonated acetone [7], and quenching with 2N aqueous HCl, to give compound **10** ($[\alpha]_D = +66.8$) as a single stereoisomer in *ca.* 80% yield.

The next step consisted of deprotection of the OH group; it was more difficult than expected: treatment of **10** with Bu_4NF [3] under a variety of conditions caused decomposition. The transformation was eventually accomplished with 10 equiv. of $LiBF_4$ in MeCN at 70° for 8 h [8], with isolation of alcohol **11**, in acceptable purity, by distillation from the crude product mixture. Crude compound **11** was directly oxidized to the diketone **12** ($[\alpha]_D = +204.0$), which in turn was hydrogenated to give the saturated diketone **13** ($[\alpha]_D = 97.1$). Intramolecular aldol condensation with **13** was again tried under a set of different conditions[6]), with the best results being observed by sequential treatment with NaOMe in MeOH[7]) and TsOH in CH_2Cl_2, affording **14** ($[\alpha]_D = -192.0$) in high yield.

Reaction of the enolate of octalone **14**, as generated by treatment with $LiN(i\text{-}Pr)_2$, with acetone [10] in the presence of $ZnCl_2$ [11] gave a 9:1 mixture of aldols (yield: 80%), treatment of which with a catalytic amount of TsOH in refluxing benzene afforded (−)-5-epidehydrofukinone ((−)-**15**; 60%), besides **14** (37%, retroaldol reaction!) which were easily separated by prep. TLC. Spectroscopic data[8]) of (−)-5-epidehydrofukinone agree with those reported for racemic **15** [12].

In conclusion, (−)-5-epidehydrofukinone has been synthesized from the dioxanone **4a** in 13 steps[9]) (28% overall yield). This synthesis also shows that the chiral building blocks available from the bicyclic dioxanone **2** can be used for EPC syntheses of more complex molecules. Work applying compounds **3** and **4** in natural-product synthesis is in progress.

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[6]) The use of catalytic amounts of piperidinium acetate in refluxing benzene [9] or of pyridinium *p*-toluenesulfonate in refluxing toluene (in the presence of molecular sieves) led to compound **14** in unsatisfactory yields.

[7]) At this stage, a single aldol-type product, of unknown configuration, could be isolated.

[8]) Data of (−)-(**15**): M.p. 63–64°. $[\alpha]_D = -178.0$. IR (KBr): 1660, 1620, 1610. ^1H-NMR ($CDCl_3$, 300 MHz): 0.95 (*d*, *J* = 7.I, 3 H); 1.18 (*d*, *J* = 0.7, 3 H); 1.46 (*m*, 1 H); 1.66 (*m*, 2 H); 1.79 (*m*, 1 H); 1.83 (*d*, *J* = 1.2, 3 H); 1.94 (*m*, 1 H); 2.09 (*d*, *J* = 2, 3 H); 2.27 (br. *d*, *J* = 13.5, 1 H); 2.34 (*m*, 2 H); 2.55 (br. *d*, *J* = 13.5, 1 H); 5.81 (*d*, *J* = 2, 1 H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 16.3, 20.9, 22.2, 22.5, 24.3, 28.7, 31.0, 38.7, 39.6, 42.0, 128.3, 128.9, 142.1, 166.9, 191.7. MS: 218 (100, M^+), 203 (20).

[9]) All transformations, except for the preparation of **10** and **11**, could be carried out without purification of intermediates.

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