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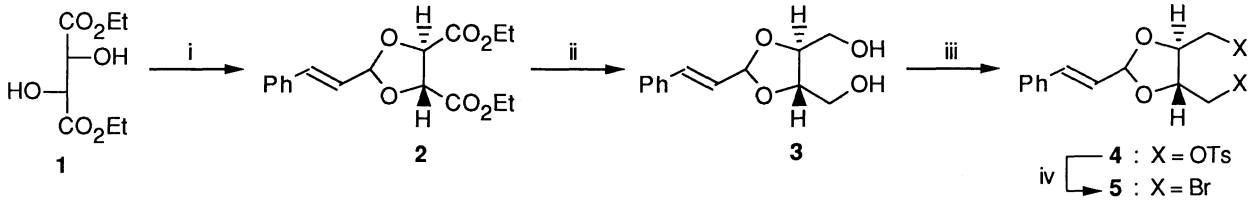
A New Methodology for the Construction of Chiral 4-Benzyl-2-furanone via C_2-Symmetric Bis-Radical Intermediate

Seiichi TAKANO,* Kazuko OHASHI, Takumichi SUGIHARA, and Kunio OGASAWARA
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980

A new methodology leading to optically pure 4-benzyl-2-furanone has been developed by employing intramolecular reaction intervening C_2-Symmetric bis-radical intermediate derived from diethyl (L)-tartrate.

4-Benzyl-2-furanone is the core framework of a variety of the naturally occurring lignans which include some medicinally important compounds.[1] Development of efficient synthetic methods producing the benzylfuranone derivative is, therefore, very important. We report herewith a promising methodology generally applicable to the enantiocontrolled synthesis of the lignan lactones employing a radical cyclization[2] of a substrate with C_2-symmetry.

Owing to its C_2-symmetric structure diethyl (L)-tartrate (**1**) afforded a single acetal **2**, $[\alpha]_D^{27}$ +4.17° (*c* 1.02, $CHCl_3$), on reaction with cinnamic aldehyde diethyl acetal in the presence of pyridinium *p*-toluenesulfonate.[3] Borohydride reduction[4] of **2** gave the diol **3**, mp 66-67 °C, $[\alpha]_D^{31}$ +12.3° (*c* 1.00, $CHCl_3$), which on sequential tosylation and exchange reaction furnished the C_2-symmetric dibromide **5**, $[\alpha]_D^{28}$ +46.6° (*c* 1.03, $CHCl_3$), in 57% overall yield from **1** (Scheme 1).

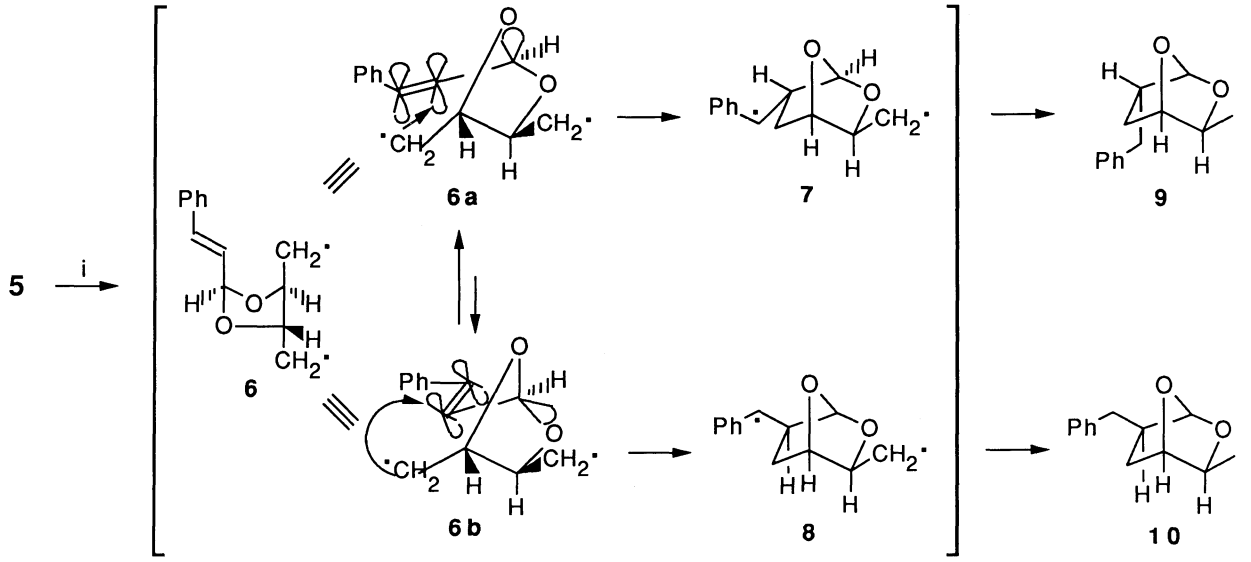


Scheme 1.

Conditions: i) cinnamic aldehyde diethyl acetal, PPTS, benzene, reflux, 5.2 h; ii) $NaBH_4$, MeOH-CH_2Cl_2 (3:1), 0 – 15 °C; iii) TsCl, Et_3N, CH_2Cl_2, 0 °C – r.t.; iv) LiBr, DMF, 60 °C, 24 h.

Despite of anticipated high reactivity of a bis-radical intermediate, clean and facile reaction occurred when **5** was refluxed with 3 equiv. tri-*n*-butyltin hydride in the presence of AIBN to give a readily separable mixture of the *endo*-bicycloacetal **9**, $[\alpha]_D^{28}$ –81.3° (*c* 1.02, $CHCl_3$), and the *exo*-bicycloacetal **10**, $[\alpha]_D^{28}$ –60.3° (*c* 0.85, $CHCl_3$),

in yields of 71.9 and 14.7%. This indicated the intervention of a bis-radical intermediate **6** to give rise to the products **9** and **10** having a bicyclo[2.2.1]heptane framework. Although the reason of the favored formation of the *endo*-isomer **9** over the *exo*-counterpart **10** was uncertain, it was presumed that the orbital effect between the double bond and each of two acetal oxygens played an important role to take the active conformations such as **6a** and **6b** in the reaction (Scheme 2).

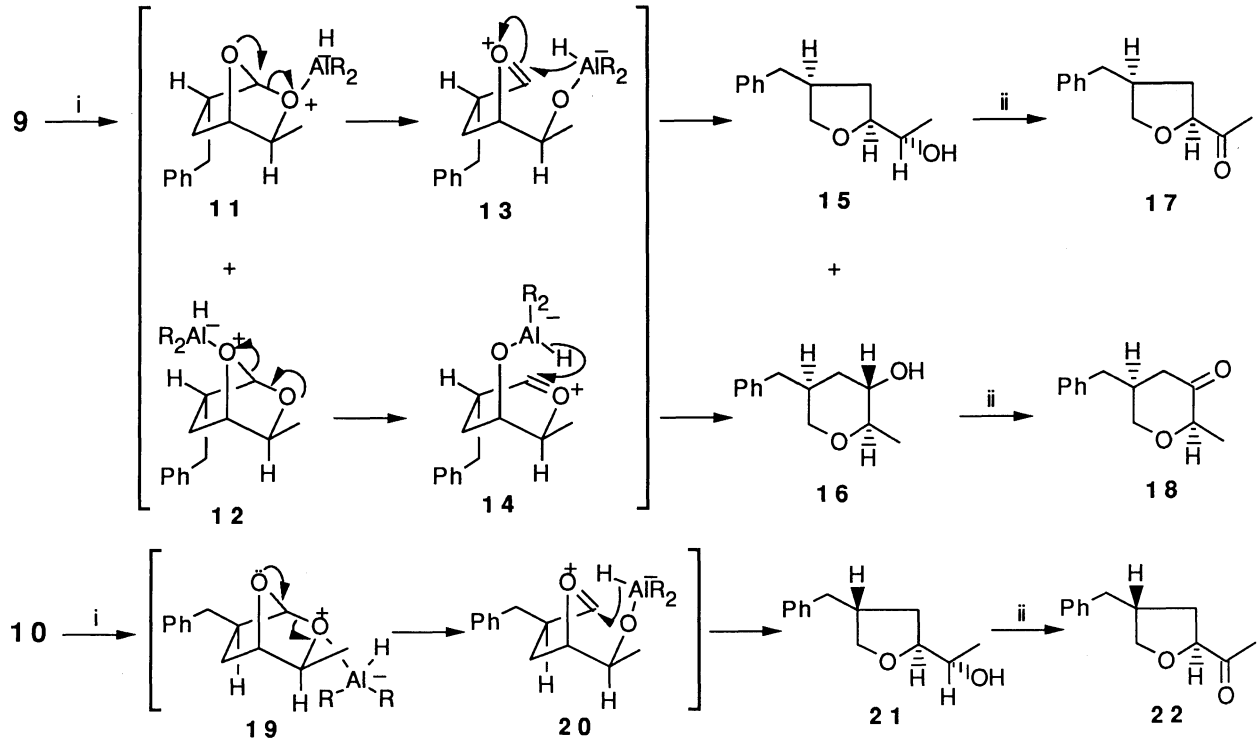


Scheme 2.

Conditions: i) n-Bu_3SnH (3 equiv.), AIBN (0.1 equiv.), benzene, reflux, 10 min.

Structure of the cyclization products could be determined unambiguously by the following sequence of reactions. Thus, the major *endo*-isomer **9** furnished a mixture of the 2,4-disubstituted tetrahydrofuran **15** and the 2,3,5-trisubstituted tetrahydropyran **16** on reductive cleavage with diisobutylaluminum hydride.[4,5] Without separation the mixture was oxidized under the Swern conditions[6] to give a mixture of two isomeric ketones which could be readily separated by silica gel column chromatography to give the five membered ketone **17**, $[\alpha]_D^{30}$ –51.5° (*c* 1.08, $CHCl_3$), and the six membered ketone **18**, $[\alpha]_D^{31}$ +34.3° (*c* 1.0, $CHCl_3$), in overall yields of 42 and 46% from the bicyclic acetal **9**. On the other hand, the reductive cleavage of the *exo*-isomer **10** proceeded in a specific manner to afford the 2,5-disubstituted tetrahydrofuran **21** as a single product under the same reduction conditions which was oxidized to the ketone **22**, $[\alpha]_D^{29}$ –38.2° (*c* 1.45, $CHCl_3$), by the Swern oxidation[6] in 69% overall yield. The observed difference between the *endo*- and the *exo*-acetals may be the reflection of their steric backgrounds. Namely the former formed two complexes such as **11** and **12** with the reducing agent from the less hindered *exo*-face prior to the reduction which resulted in a formation of two products **15** and **16** via **13** and **14**, respectively, while the latter formed a single complex **19** with the reducing agent from the less

hindered *endo*-face which led to a formation of the single product **21** via **20** (Scheme 3).



Scheme 3.

Conditions: i) i-Bu$_2$AlH (2.5 equiv.), toluene, –10 °C, 15 min, r.t., 45 min; ii) Swern oxid., –60 °C, 1 h.

Finally, three isomeric ketones, **17**, **18**, and **22**, thus obtained were transformed into optically pure 4-benzyl-2-furanone **26**, respectively, which clarified the structures of the radical cyclization products, **9** and **10**, eventually. Thus, treatment of the methyl ketone **17** with *m*-chloroperbenzoic acid in the presence of trifluoroacetic acid[7] underwent concurrent Baeyer-Villiger oxidation and peracid mediated acetal oxidation to give (–)-(*S*)-4-benzyl-2-furanone[8,9] [(*S*)-**26**], $[\alpha]_D^{30}$ –8.64° (*c* 0.71, $CHCl_3$), in 70% yield. Upon the same treatment, the isomeric ketone **22** derived from the minor cyclization product **10** afforded the enantiomeric (+)-(*R*)-furanone[8,9] [(*R*)-**26**], $[\alpha]_D^{30}$ +8.79° (*c* 0.71, $CHCl_3$), in 71% yield. The six membered ketone **18**, on the other hand, was treated with *m*-chloroperbenzoic acid under the same conditions to give the seven membered lactone **27** which was sequentially saponified and lactonized to give the (–)-(*S*)-lactone[8,9] [(*S*)-**26**], $[\alpha]_D^{29}$ –8.58° (*c* 0.71, $CHCl_3$), in 42% overall yield (Scheme 4). Synthesis of the naturally occurring lignan lactones employing the present methodology is currently under investigation.

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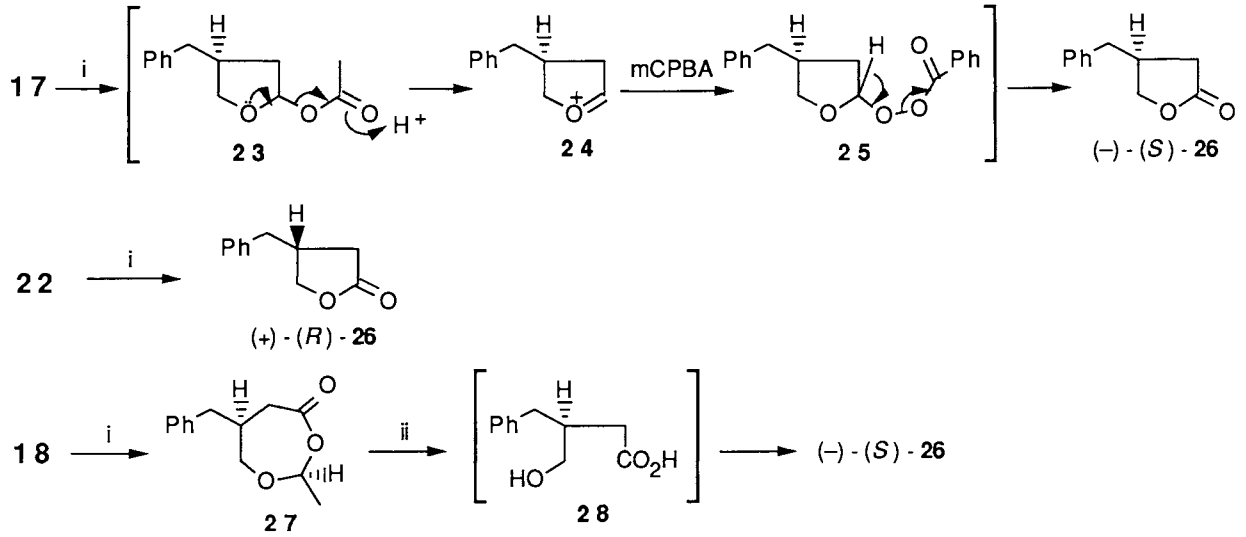


Scheme 4.

Conditions: i) m-CPBA (2.6 equiv.), TFA (1 equiv.), CH_2Cl_2, 0 °C, 10 – 20 min; ii) (a) 10% aq. NaOH, r.t., 5 min, (b) PPTS, toluene, r.t., 15 h.

References

1) Cf. D. A. Whiting, *Nat. Prod. Rep.*, **2**, 191 (1985), **4**, 499 (1987), **7**, 349 (1990).

2) Pertinent reviews for radical reaction in organic synthesis, see: B. Giese, "Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds," Pergamon Press, Oxford (1986); W. P. Neumann, *Synthesis*, **1987**, 665; D. P. Curran, *ibid.*, **1988**, 417, 489.

3) M. Miyashita, A. Yoshikoshi, and P. A. Grieco, *J. Org. Chem.*, **42**, 3772 (1974).

4) S. Takano, A. Kurotaki, Y. Sekiguchi, S. Satoh, M. Hirama, and K. Ogasawara, *Synthesis*, **1986**, 811.

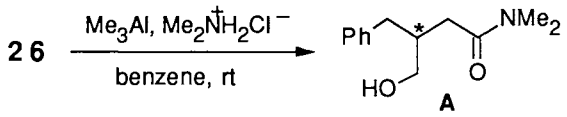
5) S. Takano, M. Akiyama, S. Sato, and K. Ogasawara, *Chem. Lett.*, **1983**, 1593.

6) Cf. A. J. Mancuso and D. Swern, *Synthesis*, **1981**, 165.

7) S. S. C. Koch and A. R. Chamberlin, *Synth. Commun.*, **19**, 829 (1989).

8) Optical purity was estimated to be 100% ee by ^{1}H-NMR analysis.

9) Absolute structure and optical purity of 4-benzyl-2-furanone (**26**) and its congeners having known configuration could be determined unambiguously by ^{1}H-NMR (500 MHz) analysis of the MTPA esters (both enantiomers) of the dimethylamide **A** derived by reaction of **26** with trimethylaluminum and dimethylammonium chloride.[10] Characteristic ABX type signals of MTPA-OC$\underline{H}_2$- of **A** and the congeners possessing substituted aromatic ring appeared at δ ca. 4.16 and δ ca. 4.39 for *R-S* (*S-R*) combination and at δ ca. 4.29 and δ ca. 4.30 for *R-R* (*S-S*) combination.



10) J. I. Levin, E. Turos, and S. M. Weinreb, *Synth. Commun.*, **12**, 989 (1982).

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