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Synthesis of Bicyclic *Cis* Fused Dihydrofuran Derivatives *via* the Intramolecular Mitsunobu Reaction

A. Tenaglia,* J.-Y. Le Brazidec and F. Souchon

Laboratoire de Réactivité en Synthèse Organique, associé au CNRS, Faculté de St Jérôme,
Av. Escadrille Normandie-Niemen, Boîte D12, 13397 Marseille Cedex 20, France.

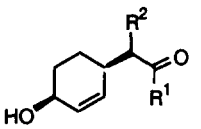
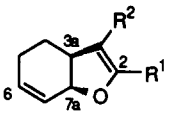
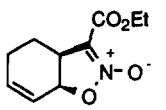
Abstract: Stereoselective dehydrative alkylation/annulation of hydroxy β-diketones, β-ketoesters or β-diesters using Mitsunobu conditions (Bu_3P/DEAD) proceeds under mild and essentially neutral conditions affording *cis* fused bicyclic dihydrofurans in good yields.

Furans and partially reduced furans are important stuctural units in naturally occuring compounds.[1] In connexion with the synthesis of polyoxacyclic compounds, we needed an easy entry into the heteroring system of pyranoids derived from sugars ("off-template"). Although a wide range of synthetic routes to 2,3-dihydrofurans is known,[2] the most straightforward synthesis of such derivatives involves the manganese(III) acetate-promoted oxidative cyclization of β-dicarbonyl compounds with electron rich olefins.[3] Since this process involves monoelectron transfer and oxidative steps which may not be suitable for elaborated and sensitive substrates, we looked for a milder route under neutral conditions. We report here such a method for the construction of *cis* fused bicyclic dihydrofuran derivatives using α-(1,3-dicarbonyl)-substituted allylic alcohols.

First we examined a series of *cis* 4-alkyl cyclohexen-2-ols **1-5**, readily available *via* the well-known palladium-catalyzed alkylation of cyclic vinyl epoxides with soft carbon nucleophiles under neutral conditions.[4] Since these compounds contain a nucleophilic center and an electrophilic counterpart, a dehydrative alkylation/annulation process was anticipated under conditions enhancing the displacement of an activated allylic leaving group. Therefore, the reaction was carried out following Mitsunobu's protocol [5] which provides activation under mild and essentially neutral conditions. The best results were obtained when DEAD and triphenylphosphine (2.2 eq. each) were mixed first[6] before the dropwise addition of the substrate (Table I).

Thus, *cis* 4-alkyl cyclohexen-2-ols **1** and **2** smoothly cyclize (C_6H_6, rt), respectively, into bicyclic tetrahydrobenzofuran derivatives[7] **6** (64%) and **7** (49%). In sharp contrast, **4** was recovered unchanged under the same conditions[8] (Table I, entry 3). As expected, when switching to tributylphosphine as the phosphane component,[9] **10** was obtained in a satisfactory 64% yield from **4**. Using the latter conditions, which were definitely more adapted for our purposes, dehydrative cyclizations of **1** and **2** are dramatically improved (Table I, entry 1-2). The regioselectivity of cyclization was briefly examined with the unsymmetrical β-diketone **3** (Table I, entry 4) which afforded an unseparable 1:1 mixture of bicyclic isomers **8** and **9** in 83% yield.

Table I. Cyclisation of *cis*-4-Alkyl cyclohexen-2-ols under Mitsunobu conditions [a]

Entry	*cis*-4-Alkyl cyclohexen-2--ol	Product(s)	Yield (%) [b] c	Yield (%) [b] d
				
1	**1** R^1 = Me, R^2 = COMe	**6**	64	83
2	**2** R^1 = Me, R^2 = CO_2Me	**7**	49	74
3	**3** R^1 = Me, R^2 = COPh	**8** R^1 = Me, R^2 = COPh **9** R^1 = Ph, R^2 = COMe	-	83 (1:1)
4	**4** R^1 = OMe, R^2 = CO_2Me	**10**	0	64
5	**5** R^1 = OEt, R^2 = NO_2	 **11**	-	82

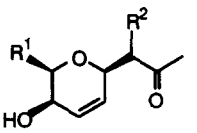
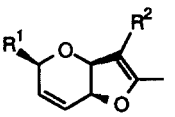
a) DEAD : PR_3 (2.2 molar eq. each), THF, rt, 2-6h; b) isolated yield; c) PPh_3; d) PBu_3

In all cases the expected *O*-alkylation leads to the exclusive formation of a single *cis* fused bicyclic 4,5-dihydrofuran isomer,[10] except when the nucleophilic counterpart is an α-nitroester group, such as in **5**, which affords a *cis* fused bicyclic nitronate[11] **11** in 82% yield. No trace of cyclopropanation resulting from *C*-alkylation was detected. This result is predicted on the basis of stereoelectronic arguments.[12] The *cis* fused ring junction was deduced from NMR NOESY experiments and by comparison with literature data.[13] The resonances of H-3a of compounds **6** and **10** are observed as a dd at δ 2.96 (*J* 4.1, 8.3, 12.1 Hz) and 3.05 (*J* 4.4, 8.1, 11.4 Hz) respectively. In addition, the allylic bridgehread H-7a in **7** and **10** appears as a doublet of doublet at δ 4.70 (*J* 1.6, 8.6 Hz) and as a broad doublet at 4.70 (*J* 8.0 Hz), respectively.

A more general applicability of this method was then tested with β-*C*-glycosides **12-15**[14] which afforded *cis*-fused chiral dihydrofurans[10] branched on the 4-hexenopyranoside moiety[15] (Table II).

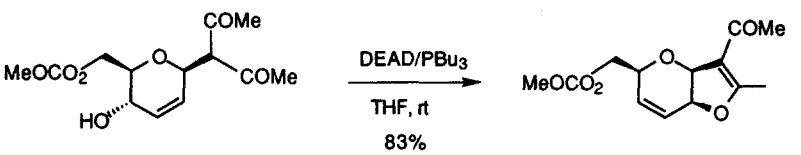
The dehydrative alkylation/annulation process presumably involves a 5-enol *endo-exo*-trig ring closure[16] and delivers the dihydrofuran derivatives rather than an unfavourable 3-enol *exo-exo*-trig pathway giving rise to the cyclopropanated isomer. We assume that this easy heterocyclization is in agreement with a *syn* process which generally prevails in the SN_2' reactions.[12, 17]

Table II. Cyclisation of β-*C*-glycosides under Mitsunobu conditions [a]

Entry	*C*-glycoside	Product	Yield (%) [b]
			
1	**12** $R^1 = CH_2OTBDMS$, $R^2 = COMe$	**16**	71
2	**13** $R^1 = Me$, $R^2 = COMe$	**17**	80
3	**14** $R^1 = H$, $R^2 = COMe$	**18**	60
4	**15** $R^1 = H$, $R^2 = CO_2Me$	**19**	72

a) DEAD : PBu_3 (2.2 molar eq. each), THF, rt, 2-6h; b) isolated yield

This question was examined with the 1,4-*trans*-disubstituted hex-2-enopyranoside derivative **20**,[14] which on treatment under the same conditions cyclized to **21** as a single stereomer in 83% yield.



20 **21**

In this specific case, an *anti* S_N2' process[17] is likely to proceed rather than an unfavourable S_N2 displacement on a distal carbinol center. On the other hand, the *anti* stereochemistry of the nucleophilic attack could be well rationalized *via* a S_N1-type mechanism. The occurence of a contact ion pair or an allylic cation that is not entirely free originating from the solvolysis of the intermediate alkoxyphosphonium ion has been discussed, respectively, in intermolecular Mitsunobu amination[18] and esterification[19] of allylic alcohols. A more detailed investigation is now in progress to clarify this point.

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6. As emphasized earlier, the order mixing of the reagents is crucial for the efficiency . See ref. 5.

7. Intermolecular version of this reaction using β-diketones or β-ketoesters with alcohols was first reported by Misunobu and proceeds mainly or exclusively with *O*-alkylation. See: a) Wada, M.; Mitsunobu, O. *Tetrahedron Lett.* **1972**, *22*, 1279-1282; b) Kurihara, T.; Sugizaki, M.; Kime, I.; Wada, M.; Mitsunobu, O. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2107-2112.

8. O. Mitsunobu has pointed out that ethyl malonate (pK 13.3) was unreactive in the reaction with alcohols, presumably due to low acidity. See ref. 5a.

9. a) For a discussion on the role of the phosphane in the course of the Mitsunobu reaction, see: Tsunoda, T.; Yamamiya,Y.; Itô, S. *Tetrahedron Lett.*, **1993**, *34*, 7639-7642; b) Tributylphosphine generates an alkoxide as intermediate which might be beneficial for the annulation. See: Camp, D.; Jenkins, I. *Aust. J. Chem.* **1992**, *45*, 47-55.

10. All new compounds gave IR, NMR, and elemental analyses consistent with the assigned structures. Selected spectral data. **10**: IR (neat) ν 2956, 1708, 1622, 1470, 1387, 1329, 1271, 1165, 1087 cm^{-1}; RMN ^1H ($CDCl_3$) δ 1.20 (m, 1H), 1.83 (m, 1H), 2.09 (m, 2H), 3.05 (ddd, J = 4.4, 8.1, 11.4 Hz, 1H, H-3a), 3.67 (s, 3H), 3.89 (s, 3H), 4.80 (br d, J = 8.0 Hz, 1H, H-7a), 5.87 (m, 1H), 6.22 (m, 1H); RMN ^{13}C ($CDCl_3$) δ 22.88, 25.15, 38.97, 50.32, 56.47, 77.63, 81.45, 122.17, 135.93, 165.85, 167.52. **16**: mp 63°C; $[\alpha]^{25}_D$ -96° (*c* 0.4, CH_2Cl_2); IR (neat) 2928, 1671, 1593, 1387, 1361, 1254, 1079, 941, 836 cm^{-1}; ^1H RMN ($CDCl_3$) δ 0.03 (s, 6H), 0.86 (s, 9H), 2.27 (s, 3H), 2.28 (s, 3H), 3.53 (dd, 1H, J = 7.1, 10.0 Hz), 3.76 (dd, 1H, J = 6.0, 10.0 Hz), 3.98 (m, 1H), 4.44 (m, 1H), 4.81 (d, 1H, J = 5.4 Hz), 6.11 (ddd, 1H, J = 2.1, 4.0, 10.3 Hz), 6.30 (bd, 1H, J = 10.3 Hz); ^{13}C RMN ($CDCl_3$) δ -5.45, -5.36, 15.28, 18.17, 25.72, 28.87, 64.80, 72.05, 76.26, 76.50, 114.16, 120.71, 134.93, 173.31, 195.08.

11. a) Falck, J. R.; Yu, J. *Tetrahedron Lett.* **1992**, *33*, 6723-6726; b) When reacted with ethyl nitroacetate under Mitsunobu conditions, alcohols are usually oxidized into carbonyl compounds *via* the aci-nitroesters. See: Mitsunobu, O.; Yoshida, N. *Tetrahedron Lett.* **1981**, *22*, 2295-2296.

12. Assuming a chair-like (rather than a twist-boat-like) transition state, incoming nucleophiles prefer attack on γ-position of the allylic moiety from the more "axial" direction, in order to maintain maximum orbital overlap. See: P. Deslongchamps *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983; pp. 174-178.

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14. The β-*C*-glycosides were prepared using a palladium-catalyzed alkylation of 3,4-carbonate glycals. *Submitted for publication.*

15. For a related approach involving *cis*-oriented epoxy pyranose triflates and 1,3-dicarbonyl compounds, see: Al-Tel, T. H.; Al-Abed, Y.; Voelter, W. *J. Chem. Soc., Chem. Commun.*, **1994**, 1735-1736.

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