Lewis Acid-Promoted Reactions of γ-Lactols with Silyl Enol Ethers — Stereoselective Formation of Functionalized Tetrahydrofuran Derivatives

Andreas Schmitt[a][‡] and Hans-Ulrich Reißig*[a]

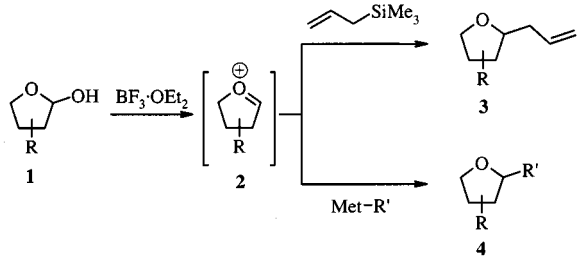
Dedicated to Professor Horst Kunz on the occasion of his 60th birthday

Keywords: Asymmetric synthesis / Lewis acids / Tetrahydrofuran / Enols / Felkin−Anh model / Carbocations

The monosubstituted γ-lactols **1a**, **1b**, **1c**, and **1d** and the disubstituted γ-lactol **1e** were converted into tetrahydrofuran derivatives by reaction with typical silyl enol ethers in the presence of Lewis acids. Although the most suitable Lewis acid appears to be zinc chloride, $BF_3{\cdot}Et_2O$ or diethylaluminium chloride are also suitable under appropriate conditions. The stereoselectivities of these substitution reactions are similar to those observed with other silylated nucleophiles; however, there are several important differences. A comparison of the diastereoselectivities of different γ-lactols and of various silylated nucleophiles and organometallic compounds will also be presented in this paper.

Introduction

In preceding publications we reported the Lewis acid-induced reactions of substituted γ-lactols **1** with silylated nucleophiles (e.g. allyl- and propargylsilanes), which furnished di- and trisubstituted tetrahydrofuran derivatives such as **3** in good yields and very often excellent diastereoselectivities (Scheme 1).[1] Also, substitution reactions with suitable organometallic compounds affording products **4** with good selectivity are possible.[2] These systematic studies with several monosubstituted (and one disubstituted) γ-lactols supplemented our earlier investigations,[3] which employed highly substituted γ-lactols. In all these experiments good evidence was gained that oxocarbenium ions of type **2** are intermediates in these transformations. The observed stereoselectivities could plausibly be explained by a modified Felkin-Anh model.[4]

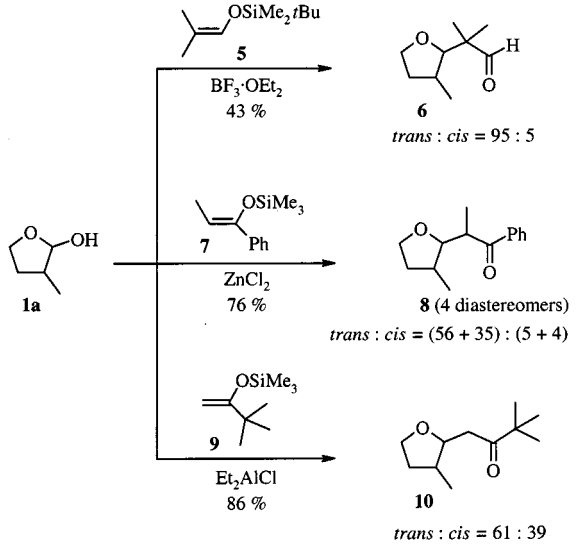


Scheme 1

In this final paper of the series we present our experiments with silyl enol ethers as nucleophiles, which should provide tetrahydrofuran derivatives with a carbonyl group in the side chain introduced by this substitution reaction.[5] Since the stereoselective synthesis of tetrahydrofurans is of considerable interest for the preparation of natural products and other biologically active compounds, our approach to this product class should have some practical relevance.[6]

Results

Treatment of γ-lactol **1a** with an excess of boron trifluoride (3 equivalents) in the presence of silyl enol ether **5** (2 equivalents) provided the expected disubstituted tetrahydrofuran **6** (Scheme 2) with very high *trans* selectivity, albeit in only moderate yield. In the course of these investigations we found that zinc chloride appears to be the Lewis acid of choice when silyl enol ethers are employed as nucleophiles.[7] This may be due to the sensitivity of the enol ethers and of the products to strong Lewis acids. However, in our earlier studies we demonstrated that the influence of the



Scheme 2

[a] Freie Universität Berlin, Institut für Chemie − Organische Chemie,
Takustr. 3, 14195 Berlin, Germany
Fax: (internat.) +49-30/8385-5367
E-mail: hans.reissig@chemie.fu-berlin.de
[‡] See Ref.[8]

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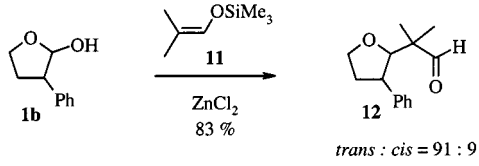
Lewis acid employed on the diastereoselectivity is only marginal. Thus, the diastereoselectivities as observed in the subsequent experiments should be similar even when performed with different Lewis acids.

The reaction of γ-lactol **1a** with the prochiral propiophenone-derived silyl enol ether **7** in the presence of $ZnCl_2$ gave compound **8** in good yield (Scheme 2). Here we recognized that reactions performed with this mild Lewis acid required temperatures higher than −20 °C. Product **8** was formed as a mixture of four diastereomers; however, the *trans:cis* (diastereofacial) selectivity was very high (91:9), whereas the simple diastereoselectivity was rather low (60:40). An attempted equilibration of this mixture with DBU did not change the initial ratio.

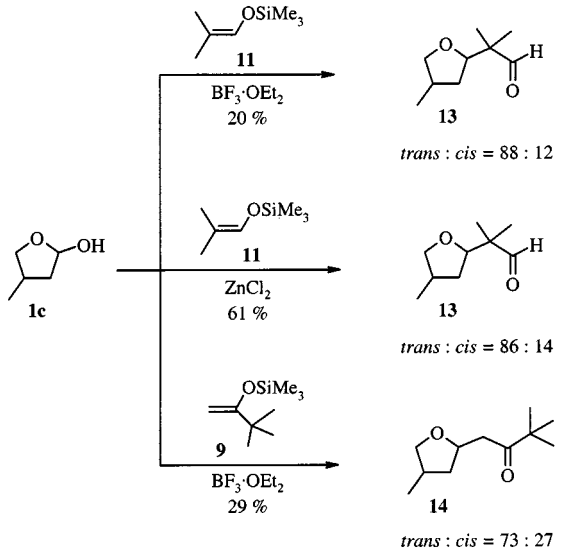
The β-unsubstituted silyl enol ether **9** was also combined with **1a** in the presence of diethylaluminium chloride as Lewis acid (Scheme 2). In this case it is important to use only one equivalent of the aluminium reagent since an excess seems to cause addition of the ethyl group to the carbonyl function of **10**.[8] However, under appropriate conditions this reaction produces a very good yield of disubstituted tetrahydrofuran **10**, but the diastereoselectivity (*trans*-:*cis* = 61:39) was rather disappointing.

The second model compound studied was phenyl-substituted γ-lactol **1b**. In general, it seems to behave like **1a**, thus giving a fairly high *trans*-selective reaction with silyl enol ether **11** in the presence of zinc chloride (Scheme 3).[9] Compound **12** was obtained in good yield with a *trans*:*cis* ratio of 91:9. Under similar conditions lactol **1b** was also treated with the parent silyl enol ether, trimethylsiloxyethene.[8] However, only oligomeric material was obtained, which is probably due to subsequent reactions of the resulting product containing a sterically unhindered aldehyde function.



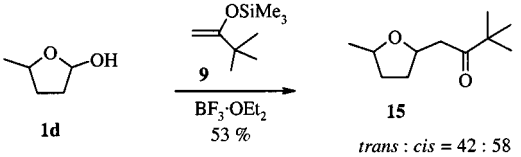
Scheme 3

γ-Lactol **1c** was the most selective model substrate in reactions with other nucleophiles providing excellent *trans*:*cis* ratios of at least 95:5.[1] Thus, we were rather surprised (and disappointed) that **1c** reacts with silyl enol ethers with only moderate to good stereoselectivity. The transformation of the silyl enol ether **11** into substitution product **13** (Scheme 4) proved again that the diastereoselectivity of the γ-lactol reactions is independent of the Lewis acid employed. With $BF_3{\cdot}Et_2O$ and with $ZnCl_2$ almost identical *trans*:*cis* ratios were observed, but the milder zinc Lewis acid afforded a considerably higher yield. Whereas the β-disubstituted silyl enol ether **11** still gave a rather good *trans*-selectivity, it was remarkably lower with the β-unsubstituted nucleophile **9**, furnishing the tetrahydrofuran derivative **14** in a *trans*:*cis* selectivity of only 73:27.



Scheme 4

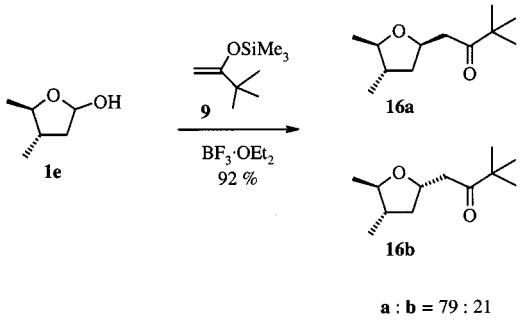
As expected from our experience[1,2] with other nucleophiles, the γ-lactol **1d** gave only poor diastereoselectivities. Its substitution reaction with the silyl enol ether **9** (Scheme 5) furnished a 42:58 mixture of two diastereomers **15** in moderate yield. In this case the configuration of the major product is not definite, since the criteria we use for structural assignments of the other tetrahydrofuran derivatives in this publication as well as in our earlier work[1,2,8] do not allow an unambiguous decision. However, due to the very low diastereoselectivity observed in the formation of **15** this is of no concern.



Scheme 5

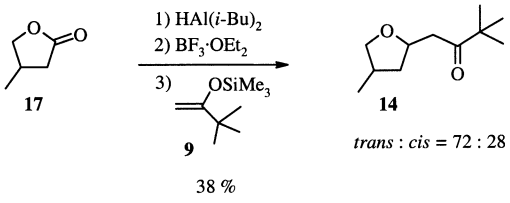
We also introduced the *trans*-4,5-disubstituted γ-lactol **1e** into the reaction under investigation. To our pleasure the substitution of **1e** with the silyl enol ether **9** (Scheme 6) afforded the tetrahydrofuran derivative **16** in excellent yield, even with BF_3 as the Lewis acid, and a moderate diastereoselectivity (79:21) in favour of **16a** was observed. However, again the reaction of **1e** with allyltrimethylsilane had given a significantly higher selectivity (86:14). The influence on the stereoselectivity of the 4-methyl group in **1e** seems to be higher than the effect of the 5-methyl group, in accordance with our earlier published examples.[1]

Finally, we examined a one-pot procedure which combines generation of the γ-lactol and its substitution reaction with a silyl enol ether. For this purpose the γ-lactone **17** was first treated with diisobutylaluminium hydride, then with $BF_3{\cdot}Et_2O$, and finally nucleophile **9** was added (Scheme 7). Product **14** was obtained in a similar *trans*:*cis* ratio of isomers (72:28) as observed in the two-step sequence (see



Scheme 6

above). The yield was rather low, and therefore the one-pot procedure seems not to be superior to the normal protocol. However, we did not try the one-pot reaction with other (milder) Lewis acids which might give better results.

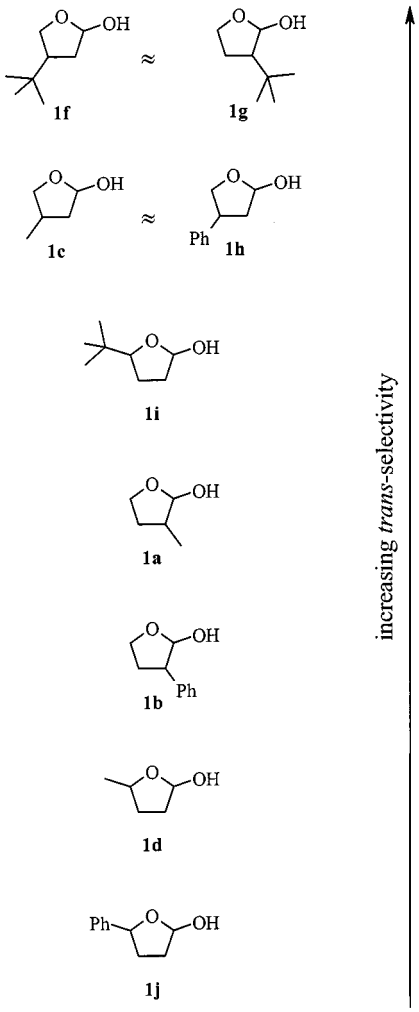


Scheme 7

Discussion

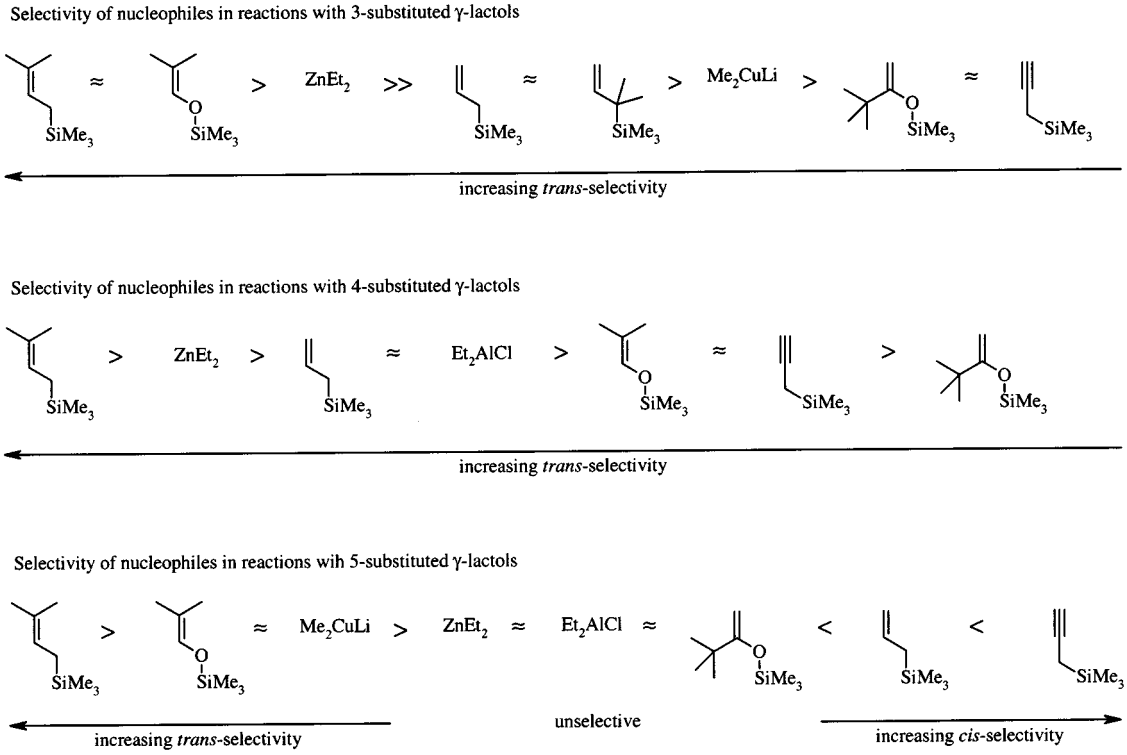
The reactions of silyl enol ethers with γ-lactols generally proceed with lower yield than those of **1** with allylsilanes. This may be due to the higher sensitivity of silyl enol ethers and their reaction products to Lewis acids. The observed diastereoselectivities do not completely fit in the pattern observed for reactions of **1** with allylsilanes or propargylsilanes.[1] They are generally slightly higher for 3-substituted γ-lactols like **1a** and **1b**, but are significantly lower for the 4-substituted γ-lactol **1c**. The one example presented here with the 5-substituted γ-lactol **1d** demonstrates that with this electrophile the selectivity is low (and relatively unpredictable); with other nucleophiles we have also observed low diastereoselectivities or moderate *cis*- or *trans*-selective reactions depending on the size of the nucleophile and the substituent at the γ-lactol.[1,2]

We do not want to repeat our interpretation of γ-lactol substitutions as discussed earlier.[1,2] The Felkin-Anh model[4] should also explain the results observed here, although no obvious arguments can be given for deviations in selectivity. The lower selectivities of silyl enol ethers as observed in the majority of examples may be due to their higher nucleophilicity,[10] but we hesitate to discuss further this apparently delicate balance between steric and electronic effects due to the relatively small number of experimental results available. However, there is a general trend with β-disubstituted silyl enol ethers as **5** and **11** are the most diastereoselective species, whereas the β-unsubstituted silyl enol ethers such as **9** are relatively unselective.[11] Of more importance may be the qualitative selectivity pattern which can be gained from comparison of all our model reactions employing different γ-lactols **1** and the various (silylated) nucleophilic components.[1,2] Scheme 8 reveals that the *tert*-butyl-substituted lactols **1f** and **1g** are the most *trans* selective as to be expected with this bulky group. Surprisingly, the 4-substituted lactols **1c** and **1h** are very close with respect to their *trans* selectivity. At the end of this sequence we find the 5-substituted compounds **1d** and **1j**, whereas the γ-lactols **1a** and **1b** bearing the substituent relatively close to the reacting anomeric centre generally showed only moderate selectivity.



Scheme 8

The selectivity pattern with respect to the nucleophiles employed is more difficult to understand and should be divided into three parts according to the γ-lactol type (see Scheme 9). Thus, for reactions of 3-substituted γ-lactols the β-disubstituted nucleophiles are most *trans* selective, whereas slim silylated components such as propargylsilane are the least *trans*-selective reagents. For the 4-substituted γ-lactols, the sequence is roughly similar although there are deviations in detail (e.g. the surprisingly low *trans* selectivity of the β-disubstituted silyl enol ether). The reactions of the 5-substituted γ-lactols are the least predictable transformations: sterically hindered nucleophiles are *trans* selective, the



Scheme 9

reagents of apparently moderate steric demand are unselective, whereas silylated components with little hindrance at the reacting carbon are slightly *cis* selective.[12] As mentioned above, it is difficult to discuss these effects in detail. Nevertheless, the pattern as presented as result of our model reactions may be used as a guide for predicting the stereochemical outcome of other reactions at the anomeric centre of γ-lactols or similar cyclic acetals.

Conclusions

In our model reactions we could demonstrate that a variety of silylated nucleophiles or organometallic compounds can be employed for direct substitution of the HO group at the anomeric centre of γ-lactols. By use of the appropriate Lewis acid — in most cases $BF_3{\cdot}Et_2O$ is sufficient — this nucleophilic substitution is possible without conversion of the hydroxy group into a better leaving group; the involvement of an oxocarbenium ion as intermediate is plausible and supported by experimental facts. We could gain information about the diastereoselectivity of this process and its dependence on the substitution of the γ-lactol and the type of nucleophile employed. The most surprising result was the very high *trans* selectivity observed with the 4-substituted γ-lactols, which is often higher than those recorded for the corresponding 3-substituted γ-lactols. A mechanistic rationalization for this effect has been presented. Our results obtained with model compounds may help to design syntheses of advanced tetrahydrofuran derivatives.

Experimental Section

General Remarks: See ref.[2] NMR spectroscopic data of mixtures of diastereomers are given in the following manner: signal of *trans* isomer/signal of *cis* isomer. The tetrahydrofuran derivatives prepared are rather sensitive to oxygen. Therefore, for most compounds no correct elemental analysis could be obtained (see compound **12**); instead, they were converted into crystalline 2,4-dinitrophenylhydrazones by a standard procedure which, after recrystallization, provided correct elemental analyses.

Starting Materials: The preparation of the γ-lactols **1a**, **1b**, **1c**, and **1d** is described in ref.[2] Compound **1e** was described in ref.[1]

General Procedure for the Reactions of γ-Lactols with Silyl Enol Ethers: To a solution of the corresponding γ-lactol **1** in dry dichloromethane (2 mL/mmol) was added 2 equivalents of the corresponding silyl enol ether and the mixture was cooled to −78 °C. Then, 3 equivalents of the Lewis acid were added from a syringe and the mixture was allowed to warm to room temperature within 16 h. After addition of water (2 mL/mmol) and extraction with dichloromethane (3 × 20 mL) the organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was carefully distilled in a kugelrohr oven. Boron trifluoride and zinc dichloride were used as their etherates. For the amounts of starting materials used and the resulting products see Table 1.

2-Methyl-2-(3-methyl-2-tetrahydrofuranyl)propanal (6): ^{1}H NMR ($CDCl_3$): δ = 0.99, 1.01 (2 s, 3 H each, Me), 1.02 (d, J = 7.0 Hz, 3 H, 3′-Me), 1.42−1.52, 1.84−2.17 (2 m, 1 H, 2 H, 3′-H, 4′-H), 3.46 (d, J = 6.0 Hz, 1 H, 2′-H), 3.60−3.80 (m, 2 H, 5′-H), 9.52 (s, 1 H, 1-H); the signals of *cis*-**6** are not detectable. − ^{13}C NMR ($CDCl_3$): δ = 16.8/17.7, 18.7/18.5, 19.7/20.8 (3 q, Me), 33.8/33.3 (d, C-3′), 34.9/35.0 (t, C-4′), 49.4 (s, C-2), 67.2/67.3 (t, C-5′), 89.3/90.7 (d, C-2′), 205.5 (d, C-1). − IR (neat): $\tilde{\nu}$ = 2980−2830 cm^{-1} (CH), 1710 (C=O).

Table 1. Reactions of γ-lactols **1a**−**1e** with silyl enol ethers in the presence of Lewis acids according to the general procedure

γ-Lactol [mg (mmol)]	Silyl enol ether [2 equiv.]	Lewis acid [3 equiv.]	Product	Yield (%) [mg (%)]	*trans*:*cis*	b.p. [° C/Torr]
1a [500 (4.90)]	**5**	$BF_3{\cdot}OEt_2$	**6**	327 (43)[a]	95:5	70/4.5
1a [420 (4.12)]	**7**	$ZnCl_2$	**8**	687 (76)	(56 + 35): (5 + 4)[b]	90/0.01
1a [190 (1.86)]	**9**	Et_2AlCl[c]	**10**	250 (86)[d]	61:39[e]	90/0.01
1b [260 (1.59)]	**11**	$ZnCl_2$	**12**	288 (83)	91:9	95/0.01
1c [350 (3.43)]	**11**	$BF_3{\cdot}OEt_2$	**13**	107 (20)	88:12	70/0.4
1c [400 (3.92)]	**11**	$ZnCl_2$	**13**	374 (61)	86:14	70/0.4
1c [300 (1.83)]	**9**	$BF_3{\cdot}OEt_2$	**14**	187 (29)	73:27	70/0.4
1d [250 (2.45)]	**9**	$BF_3{\cdot}OEt_2$	**15**	241 (53)	42:58	70/0.4
1e [135 (1.16)]	**9**	$ZnCl_2$	**16**	212 (92)	79:21[f]	75/0.4

[a] Product contains *tert*-butyldimethylsilanol. − [b] Four diastereomers. − [c] One equivalent. − [d] Product was impure. − [e] Determined by ^{13}C NMR of the distilled sample. − [f] *Trans:cis* with respect to substituents at C-2 and C-4.

2,4-Dinitrophenylhydrazone of **6** (m.p. 110−112 °C). − $C_{15}H_{20}N_4O_5$ (336.3): calcd. C 53.57, H 5.99, N 16.66; found C 53.39, H 5.92, N 16.78.

2-(3-Methyl-2-tetrahydrofuranyl)-1-phenylpropanone (8) (four diastereomers): ^1H NMR ($CDCl_3$): δ = 1.04 (d, *J* = 6.0 Hz, 0.11 H, 3′-Me), 1.04 (d, *J* = 6.5 Hz, 1.69 H, 3′-Me), 1.07 (d, *J* = 6.5 Hz, 1.06 H, 3′-Me), 1.16 (d, *J* = 7.0 Hz, 0.14 H, 3′-Me), 1.20 (d, *J* = 7.0 Hz, 0.14 H, 3-Me), 1.21 (d, *J* = 7.0 Hz, 1.06 H, 3-Me), 1.29 (d, *J* = 7.0 Hz, 1.69 H, 3-Me), 1.38 (d, *J* = 7.0 Hz, 0.11 H, 3-Me), 1.45−1.60, 1.94−2.24 (2 m, 3 H, 3′-H, 4′-H), 3.50−3.90 (m, 4 H, 2′-H, 5′-H, 3-H), 7.40 −7.60, 7.90−8.00 (2 m, 5 H, Ph). − ^{13}C NMR ($CDCl_3$): δ = 13.7* + 13.0 (q, C-3), 18.4* + 19.1 (q, 3′-Me), 35.0* + 34.9/31.1# + 33.0 (t, C-4′), 36.9* + 36.0/33.8# +33.6 (d, C-3′), 44.4* + 45.2/41.9# + 41.5 (d, C-2), 66.7/65.7# + 65.8 (t, C-5′), 86.7* + 87.0/83.4# + 83.8 (d, C-2′), 128.2* + 127.9/127.7, 128.3* + 128.1/128.5, 132.7* + 132.5/132.9, 136.8* + 137.1 (3 d, s, Ph), 202.5 + 202.6 (s, C-1); *major *trans* isomer/#major *cis* isomer. − IR (neat): $\tilde{\nu}$ = 3080−3000 cm^{-1} (=CH), 3000−2800 (CH), 1670 (C=O). − $C_{14}H_{18}O_2$ (218.3): calcd. C 77.03, H 8.31; found C 77.10, H 8.33.

3,3-Dimethyl-1-(3-methyl-2-tetrahydrofuranyl)-2-butanone (10): ^1H NMR ($CDCl_3$): δ = 1.05/0.87 (d, *J* = 7.0 Hz, 3 H, 3′-Me), 1.14/1.15 (s, 9 H, *t*Bu), 1.48−1.65, 2.00−2.20 (2 m, 1 H each, 4′-H), 1.85/2.32−2.45 (sept/m, *J* = 7.0 Hz, 1 H, 3′-H), 2.53/2.50 (dd, *J* = 4.5, 16.5 Hz/6.5, 17.5 Hz, 1 H, 1-H), 2.80/2.87 (dd, *J* = 7.5, 16.5 Hz/7.0, 17.5 Hz, 1 H, 1-H), 3.80−3.90/3.75−3.90 (m, 1 H, 2′-H), 3.80−3.90/3.70, 4.23 (m/dt, q, *J* = 6.0, 8.0 Hz, *J* = 6.0 Hz, 2 H, 5′-H). − ^{13}C NMR ($CDCl_3$): δ = 14.4/17.0 (q, 3′-Me), 25.9, 44.0/26.2, 43.9 (q, s, *t*Bu), 34.1/33.6 (t, C-4′), 39.0/34.6 (d, C-3′), 41.0/37.3 (t, C-1), 66.5/65.7 (t, C-5′), 77.3/81.3 (d, C-2′), 213.6/213.7 (s, C-2). − IR (neat): $\tilde{\nu}$ = 2990−2810 cm^{-1} (CH), 1700 (C=O).
2,4-Dinitrophenylhydrazone of **10** (m.p. 122−125 °C). − $C_{17}H_{24}N_4O_5$ (364.4): calcd. C 56.03, H 6.64, N 15.37; found C 55.82, H 6.65, N 15.50.

2-Methyl-2-(3-phenyl-2-tetrahydrofuranyl)propanal (12): ^1H NMR ($CDCl_3$): δ = 0.79, 0.89 (2 s, 3 H each, Me), 1.88, 2.19/1.56−1.80 (qd, dddd/m, *J* = 8.0, 12.5 Hz, *J* = 5.0, 7.0, 8.0, 12.5 Hz, 2 H, 4′-H), 3.04/3.00−3.10 (q/m, *J* = 8.0 Hz, 1 H, 3′-H), 3.78 (dt, *J* = 7.0, 8.0 Hz, 1 H, 5′-H), 3.90 (dt, *J* = 5.0, 8.0 Hz, 1 H, 5′-H), 3.98 (d, *J* = 8.0 Hz, 1 H, 2′-H), 7.00−7.40 (m, 5 H, Ph), 9.36 (s, 1 H, 1-H). − ^{13}C NMR ($CDCl_3$): δ = 17.5/18.5, 19.0/19.7 (2 q, 2 Me), 37.4/32.6 (t, C-4′), 46.5/46.4 (d, C-3′), 49.4 (s, C-2), 68.5/67.6 (t, C-5′), 89.0/88.9 (d, C-2′), 126.5, 127.5/127.0, 128.6/128.1, 142.7/142.8 (3 d, s, Ph), 205.5 (d, C-1). − IR (neat): $\tilde{\nu}$ = 3080−3000 cm^{-1} (=CH), 2980−2840 (CH), 1725 (C=O). − $C_{14}H_{18}O_2$ (218.3): calcd. C 77.03, H 8.31; found C 74.94, H 8.15. No correct elemental analysis could be obtained of this compound.

2-Methyl-2-(4-methyl-2-tetrahydrofuranyl)propanal (13): ^1H NMR ($CDCl_3$): δ = 0.97, 0.99 (2 s, 2 H each, Me), 0.97 (d, *J* = 7.0 Hz, 3 H, 4′-Me), 1.48 (td, *J* = 8.0, 13.0 Hz, 1 H, 3′-H), 2.14−2.28/2.30−2.40 (m, 1 H, 4′-H), 2.80 (td, *J* = 8.0, 13.0 Hz, 1 H, 3′-H), 3.23/3.20, 3.88/3.95 (dd/t, dd, *J* = 6.5, 8.5/8.5 Hz, *J* = 6.5, 8.5 Hz/6.0, 8.5 Hz, 1 H each, 5′-H), 4.01 (t, *J* = 7.5 Hz, 1 H, 2′-H), 9.53/9.54 (s, 1 H, 1-H). − ^{13}C NMR ($CDCl_3$): δ = 18.0, 18.2, 19.2 (3 q, 3 Me), 33.2/34.2 (d, C-4′), 34.5/35.4 (t, C-3′), 49.3/49.1 (s, C-2), 75.3/75.1 (t, C-5′), 82.4 (d, C-2′), 205.9/205.2 (d, C-1). − IR (neat): $\tilde{\nu}$ = 2980−2940 cm^{-1} (CH), 1720 (C=O).
2,4-Dinitrophenylhydrazone of **13** (m.p. 116−117 °C). − $C_{15}H_{20}N_4O_5$ (336.3): calcd. C 53.57, H 5.99, N 16.66; found C 53.72, H 5.90, N 16.54.

3,3-Dimethyl-1-(4-methyl-2-tetrahydrofuranyl)-2-butanone (14): ^1H NMR ($CDCl_3$): δ = 1.04 (d, *J* = 6.5 Hz, 3 H, 4′-Me), 1.13/1.14 (s, 9 H, *t*Bu), 1.65, 1.75 (2 ddd, *J* = 7.0, 8.5, 12.5 Hz, *J* = 6.0, 7.0, 12.5 Hz, 1 H each, 3′-H), 2.24−2.39 (m, 1 H, 4′-H), 2.53/2.58, 2.92/2.97 (2 dd, *J* = 7.0, 17.0/6.5, 17.0 Hz, *J* = 6.0, 17.0 Hz, 1 H each, 1-H), 3.25/3.33, 3.97/3.87 (dd/t, dd/t, *J* = 7.0, 8.5 Hz/7.5 Hz, *J* = 7.0, 8.5/8.0 Hz, 1 H each, 5′-H), 4.38/4.23- 4.33 (tt/m, *J* = 6.0, 7.0 Hz, 1 H, 2′-H). − ^{13}C NMR ($CDCl_3$): δ = 17.9/17.8 (q, 4′-Me), 26.2, 44.2 (q, s, *t*Bu), 33.2/34.3 (d, C-4′), 39.8/41.0 (t, C-3′), 42.9/43.0 (t, C-1), 74.8/74.3 (t, C-5′), 74.8/75.9 (d, C-2′), 214.1 (s, C-2). − IR (neat): $\tilde{\nu}$ = 2980−2820 cm^{-1} (CH), 1705 (C=O).
2,4-Dinitrophenylhydrazone of **14** (m.p. 129−131 °C). − $C_{17}H_{24}N_4O_5$ (364.4): calcd. C 56.03, H 6.64, N 15.37; found C 55.89, H 6.59, N 15.31.

3,3-Dimethyl-1-(5-methyl-2-tetrahydrofuranyl)-2-butanone (15): ^1H NMR ($CDCl_3$): δ = 1.14/1.13 (s, 9 H, *t*Bu), 1.21/1.23 (d, *J* = 6.0 Hz, 3 H, 5′-Me), 1.34−1.56, 1.94−2.26 (2 m, 2 H each, 3′-H, 4′-H), 2.57/2.54, 2.94/2.98 (2 dd, *J* = 7.5, 17.0 Hz, *J* = 5.5, 17.0 Hz, 1 H each, 1-H), 4.03−4.18/3.88−3.97, 4.36−4.45, 4.19−4.26 (2 m, 1 H each, 5′-H, 2′-H). − ^{13}C NMR ($CDCl_3$): δ = 21.4/21.3 (q, 5′-Me), 26.2, 44.2 (q, s, *t*Bu), 32.6/31.6, 33.8/32.8 (2 t, C-3′, C-4′), 42.9 (t, C-1), 74.7/74.6, 75.6/75.4 (2 d, C-5′, C-2′), 214.1/214.2 (s, C-2). − IR (neat): $\tilde{\nu}$ = 3000−2840 cm^{-1} (CH), 1700 (C=O).
2,4-Dinitrophenylhydrazone of **15** (m.p. 121−122 °C). − $C_{17}H_{24}N_4O_5$ (364.4): calcd. C 56.03, H 6.64, N 15.37; found C 55.85, H 6.54, N 15.33.

3,3-Dimethyl-1-(4,5-dimethyl-2-tetrahydrofuranyl)-2-butanone (16): ^1H NMR ($CDCl_3$): δ = 0.76/0.77, 1.14 (2 d, *J* =

6.5 Hz, J = 6.0 Hz, 3 H each, 4′-Me, 5′-Me), 0.95/0.96 (s, 9 H, *t*Bu), 1.40−1.70/2.17 (m/broad quint, $J \approx$ 6.0 Hz, 2 H, 3′-H), 2.28/2.27, 2.83/2.81 (2 dd, J = 6.0, 17.0 Hz/6.0, 16.5 Hz, 1 H each, 1-H), 3.27/3.45 (qd, J = 6.0, 7.0 Hz/6.0, 9.0 Hz, 1 H, 5′-H), 4.49/4.59 (tt/dq, J = 6.0, 7.5 Hz/3.0, 6.0 Hz, 1 H, 2′-H). − ^{13}C NMR ($CDCl_3$): δ = 16.8/16.2, 19.3/19.2 (2 q, 5′-Me, 4′-Me), 26.2, 44.1 (q, s, *t*Bu), 40.2/42.0 (d, C-4′), 40.2/42.0 (t, C-3′), 43.5 (t, C-1), 73.7/74.0 (d, C-2′), 82.0/80.9 (d, C-5′), 214.2 (s, C-2). − IR (neat): $\tilde{\nu}$ = 2980−2820 cm^{-1} (CH), 1700 (C=O).

2,4-Dinitrophenylhydrazone of **16** (m.p. 134−138 °C). − $C_{18}H_{26}N_4O_5$ (378.4): calcd. C 57.13, H 6.92, N 14.81; found C 56.92, H 6.87, N 14.76.

Preparation of 14 by a One-Pot Procedure: γ-Lactone **17** (500 mg, 5.00 mmol) was dissolved in 10 mL of toluene and cooled to −80 to −90 °C. Then, diisobutylaluminium hydride (1 M solution in toluene, 6.0 mL, 6.0 mmol) was added within 30 min. The resulting solution was stirred for 30 min. at −78 °C and then boron trifluoride etherate (2.11 g,15.0 mmol) and, after 15 min., **9** (1.72 g, 10.0 mmol) were added. The mixture was warmed to −30 °C within 2 h, then hydrolysed with 10 mL of water and warmed to room temperature. After precipitation of the aluminium hydroxides the mixture was filtered through a pad of Celite and the filtrate was extracted with *tert*-butyl methyl ether. The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was distilled by kugelrohr (70 °C/0.4 Torr) distillation to give 300 mg (38%) of pure **14** (*trans:cis* = 72:28).

Acknowledgments

Generous support by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is most gratefully acknowledged. We thank Dr. R. Zimmer for his help during preparation of this manuscript.

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Received October 6, 2000
[O00518]