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Mechanism of the Rearrangement of 2-(Vinyloxy)alkyl to 4-Ketobutyl Radicals

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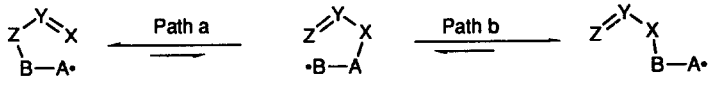
Abstract: The rearrangement of 2-(vinyloxy)alkyl to 4-ketobutyl radicals has been demonstrated to proceed by a two step mechanism involving initial 5-endo-trigonal cyclization to give a tetrahydrofuranyl radical which then fragments to the final radical. Fragmentation of the tetrahydrofuranyl radicals is demonstrated by their generation from the corresponding 2-(ethylthio)-tetrahydrofurans with stannanes and AIBN. The rearrangement reaction is completely blocked when the intermediate tetrahdrofuranyl radical is set up to undergo a 5-hexenyl rearrangement.

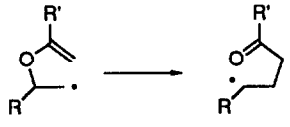
We are interested in the study of a class of free radical rearrangements that may be conveniently generalized by the formalism of Scheme 1.



Scheme 1

The prototypical example of the formal 2,3-type free radical shift (Scheme 1, path a) is the β-(acyloxy)-alkyl radical migration discovered independantly by Surzur[1] and Tanner,[2] studied extensively by Beckwith, Ingold and others,[3] and extrapolated to a very convenient synthesis of 2-deoxy-sugars by Giese.[4] Other, at least formal, examples include the rearrangement of allylperoxy radicals discovered by Schenck[5] and extensively studied by Porter, Davies and Beckwith, and others[6] as well as the (acyloxyalkyl)silyl to (acyloxysilyl)alkyl migration.[7] In parallel with Giese,[8] we have extended this series to include the β-(phosphatoxy)alkyl radical migration[9] and have shown that it proceeds largely via a formal 1,2-shift (Scheme 1, path b). We have also further extrapolated the series to the β-(nitroxy)alkyl and β-(sulfonatoxy)alkyl radical rearrangements.[10]

Using Scheme 1 as a predictive framework we designed and implemented a novel carbon-carbon bond forming radical migration (Scheme 2). In this paper we describe our investigations into the mechanism of this novel free radical rearrangement.[11]

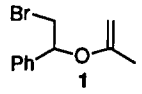
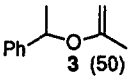
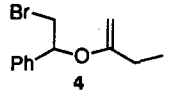
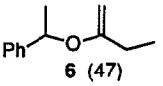
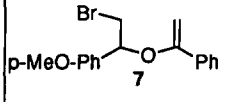
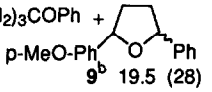
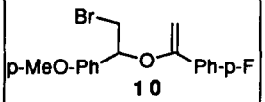
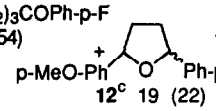
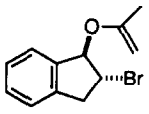
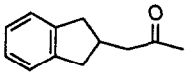
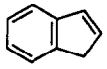
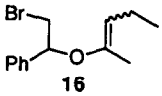
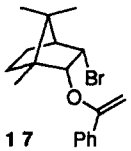
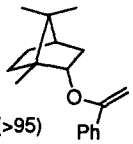


Scheme 2

As previously described, and summarized in Table 1, Scheme 2 was successfully implemented with a number of enol ethers.[11] However, the moderate yields observed and the apparent restriction to terminal enol

ethers limit the practical utility of this interesting migration. The main interest then, especially when considered alongside the various other 2,3-radical shifts delineated above, lies in the reaction mechanism.

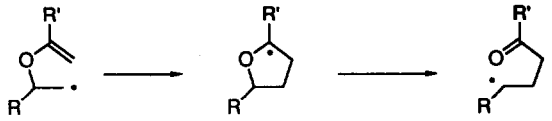
Table 1. Rearrangement of 2-(Vinyloxy)-alkyl to 4-Ketobutyl Radicals

Entry	Substrate	Products (% Yield)[a]
1.	 **1**	$Ph(CH_2)_3COMe$ **2** 32 (50) +  **3** (50)
2.	 **4**	$Ph(CH_2)_3COEt$ **5** 28 (53) +  **6** (47)
3.	 **7**	p-MeO-Ph(CH$_2$)$_3$COPh **8** 39 (50) +  **9**[b] 19.5 (28) + PhCOMe (22) + p-MeO-PhCH=CH$_2$ (24)
4.	 **10**	p-MeO-Ph(CH$_2$)$_3$COPh-p-F **11** 38 (54) +  **12**[c] 19 (22) + p-F-PhCOMe (23) + p-MeO-PhCH=CH$_2$ (13)
5.	 **13**	 **14** 9 (15) +  **15** (85)
6.	 **16**	$PhCH=CH_2$ (>95)
7.	 **17**	 **18** (>95)

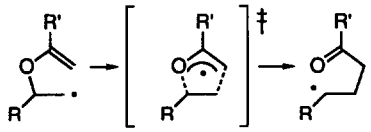
a: Yields refer to isolated products wherever possible. ^{1}H-NMR yields determined on the crude reaction mixtures after removal of volatiles under vacuum are given in parentheses.
b: cis/trans = 1.7/1
c: E/Z = 1/3.5

The various possibilities are: i) a two-step mechanism involving 5-endo-trigonal ring closure onto the enol ether to give a tetrahydrofuranyl radical followed by a retro-5-endo-trigonal ring opening (Scheme 3); ii) a related mechanism in which the tetrahydrofuranyl radical is a transition state in a concerted shift rather than an intermediate (Scheme 4); and two fragmentation/recombination mechanisms (Scheme 5). Previously, we had used a simple crossover experiment to eliminate the possibility of fragmentation to an alkene and carbonyl stabilized radical followed by free diffusion and eventual recombination, leading to the conclusion that any such

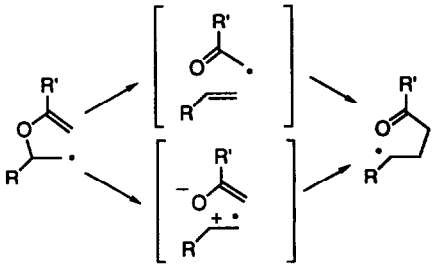
process would need to involve a rapid recoupling of the two species within the solvent cage.[11] A recent study of the phosphatoxy and acyloxy migrations found no evidence for fragmentation / recombination pathways, even within the confines of a solvent cage.[9c]



Scheme 3



Scheme 4



Scheme 5

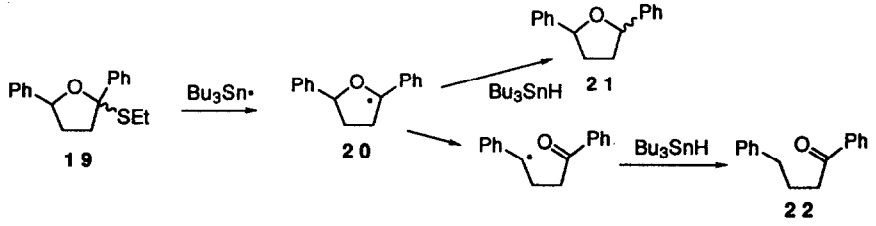
The most intriguing, and most easily tested, pathways are those outlined in Schemes 3 and 4. This is especially the case as such stepwise mechanisms involving ring closure to 1,3-dioxolan-2-yl radicals in the case of the acyloxy migration,[3] to 1,2-dioxolan-4-yl radicals in the case of the allylperoxy migration,[6] and to cyclic phosphoranyl radicals in the case of the phosphatoxy migration[12] have been conclusively excluded.

The mechanism outlined in Scheme 3 would require a relatively facile 5-endo-trigonal radical ring closure which Baldwin has suggested,[13] with good reason,[14] to be disfavored. It would also require a facile ring cleavage of a tetrahydrofuranyl radical. Such ring openings are relatively uncommon and there are many examples of the intermolecular trapping of tetrahydrofuranyl radicals on preparative scales without competitive ring opening,[15] as well as of their observation by ESR spectroscopy.[16] However, there are isolated examples of 5-endo-trigonal ring closure reactions in the literature,[17] some of which proceed with remarkable efficiency under standard preparative conditions.[17a,e,f] Recently, the very rapid 5-endo closure of the 2-formylbenzoyl radical was described.[18] Likewise, there are occasional examples of the seemingly facile cleavage of saturated 5-membered oxygenated heterocyclic radicals in the literature.[19] One especially intriguing case, the cleavage of cyclic thionocarbonates with Bu_3SnH, does not require either high dilution or syringe pump techniques.[20]

In the face of such apparently conflicting reports it is not possible to decide whether the tetrahydrofurans **9** and **12** (Table 1, entries 3 and 4) are the result of detrimental side reactions or that of trapping of tetrahydrofuranyl radicals formed along the main reaction pathway. We therefore began our investigation by probing the stability of appropriately substituted tetrahydrofuranyl radicals under the conditions of the above rearrangement.

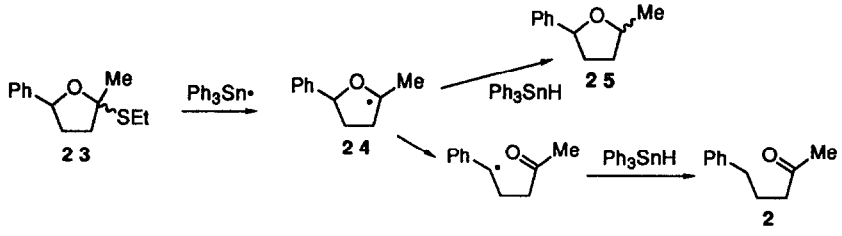
Dropwise addition of Bu_3SnH containing 6 mol% AIBN to a solution of **19** at reflux in benzene under the conditions used to achieve the rearrangement reactions, resulted in conversion of only 36% of the substrate, but clean formation of the ketone **22** and diphenyltetrahydrofuran (**21**) in the ratio 2:1. Repeated addition of Bu_3SnH with the syringe pump eventually lead to complete consumption of the substrate. Examination of the crude reaction mixture by ^1H-NMR lead to the conclusion that the two major products were the ketone (**22**) and

the diphenyltetrahydrofuran (**21**) in the ratio 3:2 (Scheme 6). The tetrahydrofuran was formed as a 3:2 cis trans mixture.[21] The observed ratio of 3:2 for ring opening of **20** versus trapping reflects reasonably the ratio of migration to tetrahydrofuran formation in the reaction of enol ethers **7** and **10** with Bu_3SnH (Table 1, entries 3 and 4) and is strongly suggestive that the tetrahydrofuranyl radical is an intermediate in the migration reaction.



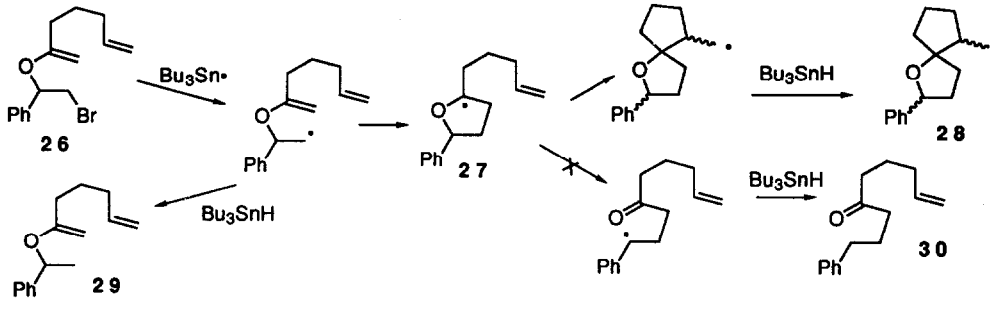
Scheme 6

Following dropwise addition of Ph_3SnH over 18 h to **23** in benzene at reflux the tetrahydrofuran **25** and the ketone **2** were formed in the ratio 50/50 (Scheme 7). The change in stannane was dictated by the poor reactivity of **23**. Unfortunately, a direct comparison of the ring opening reactions of **20** and **24** is not possible owing to the different reaction times and stannanes[22] employed.



Scheme 7

We next investigated the feasibility of the 5-endo-trigonal ring closure required by the stepwise ring closure/fragmentation pathway (Scheme 3) by means of **26** and the 5-hexenyl cyclization. Slow addition of Bu_3SnH and AIBN to **26** over 10 h with the syringe pump followed by examination of the crude reaction mixture by ^1H-NMR spectroscopy revealed the presence of the spirocyclic tetrahydrofuran **28** and the reduction product **29** in the approximate ratio 50:50 (Scheme 8). No evidence for the rearrangement product **30** was found. The inclusion of the 5-hexenyl trap therefore completely suppresses the radical migration and leads to the formation of the spirocyclic tetrahydrofuran **28**. Column chromatography enabled isolation of **28** in 22% yield.



Scheme 8

We conclude that: i) the unique pathway for the radical migration (Scheme 2 and Table 1) is that set out in Scheme 3 and ii) that the opening of the intermediate tetrahydrofuranyl radical **27** is not able to compete with the 5-hexenyl radical rearrangement and hence an upper limit of ~ 10^3 s^{-1} for this ring opening reaction can be set. The various fragmentation products observed in the course of certain migration reactions (Table 1, entries 3 - 6) are the result of minor reaction pathways that become especially prominent when the 5-endo-trigonal closure is retarded more than usual. The formation of tetrahydrofurans results from trapping of ring closed radicals along the main reaction pathway.

Acknowledgements

The Donors of the Petroleum Research Fund, administered by the American Chemical Society, are thanked for partial support of this work. We are grateful to Professor Martin Newcomb, Wayne State University, for helpful discussion.

Experimental Part

General. Melting points were recorded on a Thomas hotstage microscope and are uncorrected. ^1H and ^{13}C-NMR spectra were run in $CDCl_3$ at 300 and 75 MHz respectively. Chemical shifts are downfield from tetramethylsilane as internal standard. All solvents were dried and distilled by standard procedures. All reactions were run under a dry nitrogen or argon atmosphere. THF was distilled, under N_2, immediately prior to use from sodium benzophenone ketyl. Ether refers to diethyl ether. Microanalyses were conducted by Midwest Microanalytical, Indianapolis.

4-Hydroxy-4-phenylbutyrophenone. A solution of 4-phenyl-γ-butyrolactone (0.811 g, 5 mmol) in THF (20 mL) was treated with TMSCl (761 μL, 6 mmol) and cooled to -78 °C. Phenyllithium (1.8 M in cyclohexane /ether 70/30, 3.3 mL, 6mmol) was then added dropwise over 15 min. After being stirred for a further 1 h at -78 °C the reaction was quenched by addition of 2 M HCl (10 mL) and, after being stirred at room temperature for 1 h, was diluted with water (10 mL) and extracted with ethyl acetate (3 x 15 mL). The combined extracts were washed with water, then brine, dried, and concentrated to dryness. Purification by column chromatography on silica gel (eluent: hexane/ether 1/1) gave the title compound[23] (0.765 g, 64%) as an oil with δ_H: 2.22 (2H, m), 2.37 (1H, d, J = 3.7 Hz), 3.13 (2H, t, J = 7.0 Hz), 4.85 (1H, m), 7.28-7.59 (8H, m) and 7.96 (2H, m).

1-Hydroxy-1-phenyl-4-pentanone. A solution of 4-phenyl-γ-butyrolactone (0.811 g, 5 mmol) in THF (20 mL) was treated with TMSCl (761 μL, 6 mmol) and cooled to -78 °C. Methyllithium (1.4 M in ether, 4.5 mL, 6 mmol) was then added dropwise over 15 min. After being stirred for a further 1 h at -78 °C the reaction was quenched by addition of 2 M HCl (10 mL) and, after being stirred at room temperature for 1 h, was diluted with water (10 mL) and extracted with ether (2 x 15 mL). The combined extracts were washed with water, then brine, dried, and concentrated to dryness. Purification by column chromatography on silica gel (eluent: hexane/ether 1/2) gave the title compound[24] (0.705 g, 79%) as a colorless oil with δ_H: 2.03 (2H, q, J = 6.9 Hz), 2.15 (3H, s), 2.57 (2H, t, J = 7.0 Hz), 4.73 (1H, m), and 7.26-7.37 (5H, m).

2-Ethylthio-2,5-diphenyltetrahydrofuran (19). A solution of 4-hydroxy-4-phenylbutyrophenone (100 mg, 0.42 mmol) and anhydrous $ZnCl_2$ (136 mg, 1 mmol) in THF (10 mL) was treated at room temperature with ethanethiol (150 μL, 2 mmol) and the reaction mixture stirred at room temperature overnight. Saturated NH_4Cl

(10 mL) was then added and the reaction mixture extracted with CH_2Cl_2 (3 x 15 mL). The extracts were washed with water and brine, dried (Na_2SO_4), concentrated to dryness and purified by chromatography on silica gel (eluent: hexane/CH_2Cl_2 1/2) to give **19** as a colorless oil (93 mg, 78%) in the form of an unassigned 3/1 anomeric mixture with δ_H: 1.00 (major) and 1.06 (minor) (3H, 2 x t, both with J = 7.5 Hz), 1.77-2.65 (6H, m), 5.18 (minor) and 5.34 (major) (1H, 2 x dd, major has J = 5.8 and 8.2, minor has J = 6.0 and 9.0 Hz) and 7.22-7.65 (10H, m); δ_C (major isomer) : 14.49, 23.74, 33.90, 41.86, 80.03, 95.44, 126.05, 126.20, 126.89, 127.53, 127.86, 128.41 and 145.12, (minor): 14.42, 23.52, 35.62, 42.16, 83.84, 95.70, 125.80, 126.54, 126.93, 127.49, 127.95, 128.36 and 145.54. HRMS. Calc. for $C_{18}H_{20}SO$: 284.12349. Found: 284.12460.

2-Ethylthio-2-methyl-5-phenyltetrahydrofuran (23). A solution of 1-hydroxy-1-phenyl-4-pentanone (142 mg, 1 mmol) in THF (10 mL) was treated with powdered 4Å molecular sieves (~0.5 g), ethanethiol (74 μL, 1 mmol) and BF_3OEt_2 (123 μL, 1 mmol) and the resulting mixture stirred at room temperature for 3 h. K_2CO_3 (10% in H_2O, 15 mL) was then added and the reaction mixture extracted with ethyl acetate (3 x 15 mL). The combined extracts were washed with water and brine, dried (Na_2SO_4) and concentrated to dryness. Chromatography on silica gel (eluent: hexane/CH_2Cl_2 1/1) then gave **23** as a colorless oil (160 mg, 90%) as a 3/1 unassigned mixture of anomers with δ_H: 1.28 (major) and 1.29 (minor) (3H, 2 x t, both with J = 7.4 Hz), 1.77 (minor) and 1.82 (major) (3H, 2 x s), 2.14 (2H, m), 2.31 (1H, m), 2.45 (1H, m), 2.70 (2H, m), 5.08 (minor) and 5.16 (major) (1H, 2 x t, both with J = 7.5 Hz) and 7.24-7.46 (5H, m); δ_C (major isomer): 15.15, 22.77, 28.84, 34.06, 40.25, 80.28, 92.11, 126.00, 127.40, 128.33, and 142.04, (minor): 14.77, 22.68, 29.44, 35.46, 41.30, 83.31, 92.11, 126.52, 127.40, 128.12, and 142.25. Anal. Calc. for $C_{13}H_{18}OS$: C, 70.22; H, 8.16. Found: C, 70.42; H, 8.23.

Reaction of 19 with Bu_3SnH. A solution of Bu_3SnH (127 mg, 0.44 mmol) and AIBN (3 mg) in benzene (20 mL) was added dropwise with the aid of a motor driven syringe pump over 18h to a solution of **19** (83 mg, 0.29 mmol) in benzene (20 mL) at reflux. After a further 2h at reflux the volatiles were removed under vacuum and the crude rection mixture inspected by ^{1}H-NMR spectroscopy which revealed approximately 64% of residual starting material together with the ketone **22** and the tetrahydrofuran **21** (cis and trans). The reaction mixture was again taken up in benzene (20 mL) and heated to reflux with further AIBN (2 mg) for 10h when approximately 70% conversion was achieved. Finally, further tin hydride (44 mg, 0.15 mmol) and AIBN (1 mg) were added in one portion and the reaction mixture heated to reflux for 10h. Removal of the volatiles and inspection of the crude reaction mixture by ^{1}H-NMR revealed the presence of the ketone **22** and the tetrahydrofurans **21** in the ratio 3/2. The tetrahydrofurans **21** were formed in a 60/40 *cis /trans* ratio. Identification of ketone **22** was made by comparison with an authentic commercial sample, whilst the *cis*- and *trans*-tetrahydrofurans **21** were identified according to Schögl.[21]

Reaction of 23 with Ph_3SnH. Dropwise addition of Ph_3SnH (158 mg, 0.45 mmol) and AIBN (10 mg, 0.06 mmol) in benzene (20 mL) over 18 h to a solution of **23** (67 mg, 0.030 mmol) in benzene (20 mL) at reflux followed by a further 2h at reflux gave, after evaporation to dryness and dissolution in $CDCl_3$ a 50/50 ratio of the tetrahydrofuran **25** and the ketone **2** as determined by ^{1}H-NMR spectroscopy. The ketone **2** was identified with the aid of an authentic sample[11] and the tetrahydrofuran **25**, formed as a 1:1.1 mixture of diastereomers, by

comparison with literature data.[25]

2-Bromo-1-phenethyl 5-Hexenoate. To a solution of styrene bromohydrin (1.11 g, 5.5 mmol), Ph_3P (1.44 g, 5.5 mmol) and 5-hexenoic acid (571 mg, 5.0 mmol) in ether (30 mL) was added dropwise diethyl azodicarboxylate (960 mg, 5.5 mmol). After being stirred at room temperature for 20 h the precipitate was filtered off and the solution filtered under reduced pressure to give the crude product, purification of which by chromatography on silica gel (eluent: CH_2Cl_2/hexane 2/3) gave the title compound as a colorless oil (1.25 g, 84%) with δ_H: 1.76 (2H, quintet, J = 7.3 Hz), 2.10 (2H, m), 2.41 (2H, m), 3.59 (1H, dd, J = 4.8 and 10.9 Hz), 3.65 (1H, dd, J = 8.0 and 10.9 Hz), 5.00 (2H, m), 6.77 (1H, tdd, J = 6.7, 10.3 and 17.0 Hz), 6.98 (1H, dd, J = 4.7 and 8.0 Hz) and 7.35 (5H, m); δ_C: 24.00, 32.99, 33.56, 34.39, 74.69, 115.51, 126.54, 128.73, 128.83, 137.59, 137.79 and 172.41. Anal. Calc. for $C_{14}H_{17}BrO_2$: C, 56.58; H, 5.77. Found: C, 56.71; H, 5.84.

Preparation of the Enolether 26. 2-Bromo-1-phenethyl 5-hexenoate (595 mg, 2 mmol) and Cp_2TiMe_2[26] (1.2 g, 5.8 mmol) were heated to reflux in THF (10 mL) in the dark for 60 h. The reaction mixture was then concentrated to ~ 2 mL total volume and dry ether (20 mL) was added causing the formation of a yellow precipitate. The precipitate was removed by filtration and the filtrate was concentrated to dryness. ^{1}H-NMR spectrscopy revealed that the crude product consisted mainly of the required enolether **26**. Purification by chromatography on silica gel (petroleum ether/ether 2/1 with 1% Et_3N) enabled isolation of 130 mg (22%) of **26** which was greater than 95% pure by NMR. It had δ_H: 1.68 (2H, m), 2.07 (2H, q, J = 6.7 Hz), 2.17 (2H, t, J = 7.5 Hz), 3.52 (1H, dd, J = 4.2 and 10.7 Hz), 3.61 (1H, dd, J = 8.2 and 10.7 Hz), 3.68 (1H, d, J = 2.4 Hz), 3.87 (1H, d, J = 2.3 Hz), 4.94-5.03 (3H, m), 5.81 (1H, m) and 7.31 (5H, m); δ_C: 26.38, 33.06, 34.53, 35.87, 78.53, 84.22, 114.68, 126.06, 128.37, 128.70, 138.65 and 161.07. Unfortunately, owing to the instability of this compound, we have not been able to obtain satisfactory microanalytical or HRMS data so far.

Reaction of Enolether 26 with Bu_3SnH. Bu_3SnH (117 mg, 0.40 mmol) and AIBN (2 mg, 4.5 mol%) in benzene (10 mL) were added dropwise, with the syringe pump, over 10 h to a solution of the **26** (80 mg, 0.27 mmol) in benzene (20 mL) at reflux. When the addition was complete reflux was maintained for a further 2 h before the solvent was removed under vacuum. Examination of the crude reaction mixture by ^{1}H-NMR revealed the presence of the spirocyclic tetrahydrofuran **28** and the reduction product **29**. No evidence was found for the formation of the ketone **30**. Preparative tlc on silica gel (eluent: petroleum ether/CH_2Cl_2 9/1 with 1% Et_3N) enabled isolation of pure **28** as a colorless oil (13 mg, 22%). It was an unassigned mixture of all four possible diastereoisomers characterized by four doublets at δ_H: 0.87, 0.89, 0.95 and 0.96 with J = 6.4, 6.1, 6.9 and 7.9 Hz respectively and in the approximate ratio 3:3:1:1 respectively. Other signals were δ_H: 1.2-2.4 (11H, m, 4.87-4.96 (1H, m), 7.20-7.37 (5H, m). HRMS. Calc. for $C_{15}H_{20}O$: 216.15142. Found: 216.14976.

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