LETTER

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A convenient route to optically active γ-substituted γ-lactones

Anil V. Karnik,*[a] Sudhir T. Patil,[a] Subodh S. Patnekar[a] and Abha Semwal[b]

[a] *Department of Chemistry, University of Mumbai, Vidyanagari, Kalina, Mumbai, 400 098 India. E-mail: avkarnik@hotmail.com; Fax: +91-022-26528547; Tel: +91-022-26526091*
[b] *Bio-Organic Division, Bhabha Atomic Research Center, Mumbai, 400085 India*

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Sodium borohydride reduction of 4-substituted (−)-menthyl/(−)-bornyl-4-oxobutanoates followed by simple trituration in acidic medium at low temperature resulted in the formation of optically active γ-substituted γ-lactones.

Substituted γ-lactones are the basic structural units of many complex and challenging biologically active natural products.[1–3] Optically pure substituted γ-lactones have been employed as synthons/intermediates for acquiring many biologically important compounds such as antitumor antibiotic (+)-hitachimycin,[4] an aggregation pheromone *R*-(−)-sulcatol,[5] antileukaemic liganans (+)-*trans*-burseran and (−)-isostegane,[6] a natural product dihydromevinolin,[7] *etc*. Therefore, it is not surprising that various biological and chemical methods have been described in the literature to access these important ring systems in optically active forms.[8–13] The use of chiral reducing agents such as BINAP-Ru(II)-catalyzed hydrogenation,[14,15] hydrosilylation catalyzed by rhodium complexes with chiral phosphine ligands[16] and enzymatic hydrolysis of hydroxy esters[17] are some of the methods that have given satisfactory results. Optically pure γ-substituted γ-lactones have also been obtained from optically pure glutamic acid[18–20] with retention of configuration. However the use of an optically pure alcohol as a chiral auxiliary for the reduction of 4-oxobutanoates **1** using sodium borohydride, followed by hydrolysis, resulted in optically inactive γ-lactones.[21] We describe herein a novel, short and efficient methodology that employs readily available and inexpensive chiral auxiliaries and very mild reaction conditions to achieve the synthesis of optically active γ-substituted γ-lactones **7a–e** with recovery of the chiral auxiliary in an optically pure form.

The secondary carbinol **2** formed by the reduction of 4-oxobutanoates **1** with sodium borohydride is capable of generating an enantiotopic carbocation **3** in acidic medium (Fig. 1). The carbocation so-formed can undergo further reaction with an internal nucleophile if available. If the formation of a stable enantiotopic carbocation is considered as a possibility then its attack in an enantioselective manner by a chiral auxiliary could occur. Based on these considerations, an asymmetric synthesis of γ-substituted γ-lactones **7** was envisaged by using 4-oxobutanoates **1** together with a chiral alcohol auxiliary.

When 4-substituted 4-oxobutanoates **1a–e** in the presence of chiral alcohol auxiliaries were reacted with sodium borohydride and the subsequent acidification was carried out under cold conditions, the formation of optically active lactones was observed. When the reaction was further investigated it was observed that the reaction time required for complete conversion into the lactone varied from 1 to 4.5 h depending on the substitution pattern. In the $NaBH_4$ reduction of **1**, when the reaction mixtures were extracted immediately after acidification, the corresponding γ-hydroxybutanoates **2** were isolated and none (or small amounts, in the case of aryl substituents) of the lactone **7** could be detected. Clearly, lactonization is a slow process occurring during the trituration period in acidic medium.

The overall chemical sequence resembles that of transesterification and hence it is essential, by similarity, to look for the presence of $A_{AL}1$; $A_{AC}1$ and $A_{AC}2$ type mechanisms. The fact

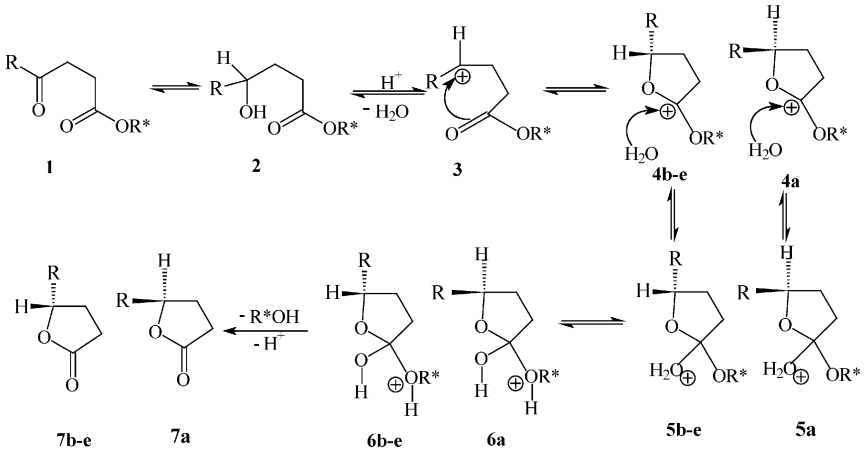

Fig. 1 Proposed mechanism for lactonization *via* a cyclic oxocarbenium ion.

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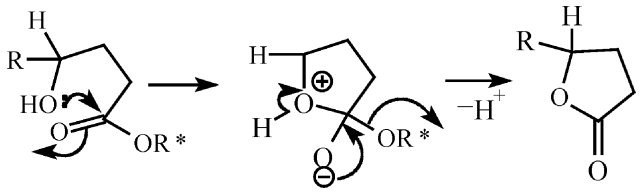


Fig. 2 Mechanism of addition of the hydroxyl group to the ester carbonyl.

that an optically active compound is obtained rules out $A_{AC}1$, where the chiral auxiliary is not a part of the transition state leading to cyclization. The hydroxy ester formed after reduction of the keto carbonyl group can also exhibit addition of the hydroxyl group to the ester carbonyl group as shown in Fig. 2, in a mechanism close to an $A_{AC}2$ type. It is not impertinent to consider the formation of lactone *via* this route. But this route is likely to give racemic lactones if the two diastereomeric hydroxy esters are formed in equimolar proportions. A previous literature report[21] indicates that the optical induction does not occur at the reduction stage, which we further confirmed by isolating the hydroxyesters before cyclization and subjecting them to cyclization at the solvent reflux temperature, leading to the formation of racemic lactones. Relative reaction times required for the formation of γ-lactones **7** should not have been much different in case of $A_{AC}2$ type reactions for **7a** and **7b–e**. Experimental findings show that levulinic acid is 3 to 4 times less reactive. This accounts for the difference in stability of methyl alkyl carbocation **3a** and aryl alkyl carbocations as in the case of **3b–e**, if the formation of a carbocation is to be considered as the rate-determining step. Based on these premises we favour the possibility of the formation of a diastereotopic carbocation followed by enantioselective attack on the carbonyl of the ester group under the influence of the nearby chiral alcohol moiety of the ester. The use of aq. HCl during the second stage (cyclization) favours S_N1 type reactions more strongly. This mechanism is close to the $A_{AL}1$ type mechanism.

In a typical reaction (Scheme 1) **1** was dissolved in methanol and reduction with $NaBH_4$ was carried out as usual. The solution was acidified under cold conditions. The mixture was stirred until the formation of the lactone was complete as monitored by TLC. Extraction followed by column chromatography gave the γ-substituted γ-lactones (**7a–e**; Table 1). The chiral auxiliary, (−)-menthol/(−)-borneol, was also recovered as optically pure by chromatography. The enantiomeric excess for compounds **7a–e** was calculated on the basis of comparison of the optical rotation and chiral HPLC for some of the samples. When (−)-menthol was used as the chiral auxiliary, ee values were found to be in the range from 25% to 63%. The enantioselectivity was enhanced to 61–95% when (−)-borneol was employed as the chiral auxiliary. The configurational outcome depends on the difference in the two diastereomeric transition states involved and incidentally *S* enantiomers were obtained as major products in all cases. In compounds **7b–e** the relative configurations remain the same, however, in **7a** the relative configuration is opposite even though the configuration remains as *S* due to the change in priority order of the ligands. Assignments of configurational descriptors have been done according to comparison with literature reports[5,11,13] for **7a** and **7b** but configurational assignments for compounds **7c**, **7d** and **7e** have not been reported in the literature. These compounds have structural similarities with compound **7b**, the substituents are at the para position of the phenyl ring and by comparison to the sign of optical rotation with **7b** they are considered to have similar configurations, though this has not been established. Spectral details for **7a–e** are found to be in good agreement with the literature.[22]

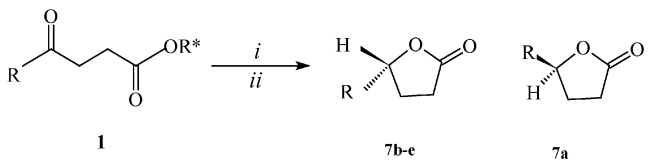
The proposed mechanism, shown in Fig. 1, involving the formation of a diastereomerically enriched cyclic oxocarbenium intermediate **4**, finds support in the following observations: (a) sodium borohydride reduction of (−)-menthyl/(−)-bornyl-4-oxobutanoates **1** followed by acidification and immediate extraction gave γ-hydroxy esters **2** and not the corresponding lactones **7**; (b) γ-hydroxy esters **2** on trituration in an ice-cold HCl mixture gave optically active lactones **7**; (c) γ-hydroxy esters **2** on refluxing in aqueous HCl gave racemic lactones;[21] (d) (−)-menthyl/(−)-bornyl-4-aryl-4-oxobutanoates **1b–e** gave faster formation of lactones (Table 1) compared to (−)-menthyl/(−)-bornyl levulinates **1a**, which indicates the facile formation of a benzyl carbocation from 4-aryl substituted substrates; (e) the γ-substituted γ-lactones formed were configurationally stable and there was no loss of optical activity after standing in aq. HCl (15 ml of 1 : 1 HCl for 10 mmol of product) for a prolonged period (>48 h).

The present asymmetric synthesis of γ-substituted γ-lactones is more convenient relative to other chemical and biological approaches. The easy recovery of the chiral auxiliary in an optically pure form is achieved. The level of enantioselectivity is satisfactory and, moreover, it utilizes readily available and inexpensive chiral auxiliaries. The operation is simple and adaptable to large-scale production. The methodology offers an opportunity for the use of any available chiral alcohol. The methodology is simple enough to be employed for polysubstituted γ-lactones and consequently should open an easier route to many other biologically important compounds and natural products accessible through the intermediacy of substituted γ-lactones. Further work to optimize the chiral induction is in progress.

Experimental

Typical reaction procedure for the synthesis of γ-substituted γ-lactones 7a–e

In a typical experiment (−)-menthyl/(−)-bornyl-4-oxobutanoate (10 mmol) and methanol (15 ml) were placed into a round bottom flask and cooled externally. Sodium borohydride (5 mmol) was added slowly with constant stirring within half an hour. The reaction was monitored by TLC and was complete after 90 min. Then methanol was removed by vacuum distillation. A mixture of ice and HCl (1 : 1, 15 ml) was added to the



1 **7b-e** **7a**

Scheme 1 Conversion of 4-oxobutanoates **1** to γ-substituted γ-lactones **7a–e**. R = CH_3 (a), C_6H_5 (b), 4′-$CH_3C_6H_4$ (c), 4′-$OCH_3C_6H_4$ (d), 4′-BrC_6H_4 (e); R*OH = (−)-menthol, (−)-borneol. Conditions: *i* $NaBH_4$, MeOH, RT; *ii* dilute HCl, −5 to 0 °C, stirring 1–5 h.

Table 1 Formation of γ-substituted γ-lactones **7a–e** from (−)-menthyl/(−)-bornyl-4-oxobutanoates **1**[a]

		(−)-Menthol					(−)-Borneol				
	R	Stirrring time/h	Mp/°C	% Yield	$[\alpha]^{25}_D$	% ee	Stirrring time/h	Mp/°C	% Yield	$[\alpha]^{25}_D$	% ee
7a	CH_3	4.5	Oil	45	−7.84	27[b]	4.5	Oil	50	−17.94	61[b]
7b	C_6H_5	1.25	Oil	61	−8.00	25[c]	1.5	Oil	70	−23.27	72[c]
7c	4-$CH_3C_6H_4$	1	64	66	−5.24	45[c]	1.25	64	69	−12.08	94[c]
7d	4-$OCH_3C_6H_4$	2	49	62	−3.47	63[c]	2.5	49	64	−05.29	95[c]
7e	4-BrC_6H_4	2	85	56	−5.02	33[c]	2.25	85	63	−10.48	69[c]

[a] **7a** and **7b** have *S* configuration; compounds **7c**, **7d** and **7e** are structurally similar to **7b** (the change in structure is away from the chiral center) and have the same sign of optical rotation, hence are considered to be *S* configured, though the configuration has not been established. [b] The ee was calculated on the basis of the optical rotation for **7a** reported in ref. 13 (*i.e* −29.6). [c] The ee for **7b–e** was also calculated by chiral HPLC.[23]

residue and the mixture was stirred continuously until lactone formation was confirmed by comparison with authentic lactone. Time required varied from 1 to 4.5 h depending on the substituent present. The crude product was then dissolved in chloroform and washed with a saturated sodium bicarbonate solution to remove acid, followed by washing with pure water and drying over anhydrous sodium sulfate. The mixture obtained was purified by column chromatography using a 90 : 10 petroleum ether–ethyl acetate eluent system.

γ-Methyl-γ-lactone (7a). IR (oil film): ν = 1780 cm^{-1} (lactone ring). ^1H NMR (300 MHz, $CDCl_3$): δ = 4.52 (m, 1H), 2.6 (t, 2H), 2.18 (m, 1H), 1.8–1.85 (m, 1H), 1.4 (d, 3H).

γ-Phenyl-γ-lactone (7b). IR (oil film): ν = 1785 cm^{-1} (lactone ring). ^1H NMR ($CDCl_3$): δ = 7.35–7.42 (m, 5H), 5.52 (dd, 1H, J = 7 Hz), 2.6–2.7 (m, 3H), 2.18 (m, 1H).

γ-(4-Methylphenyl)-γ-lactone (7c). IR (KBr): ν = 1780 cm^{-1} (lactone ring). ^1H NMR ($CDCl_3$): δ = 7.05 (d, 2H, J = 7.5 Hz), 7.35 (d, 2H, J = 7.5H z), 5.46 (dd, 1H, J = 7 Hz), 2.53–2.68 (m, 3H), 2.34 (s, 3H), 2.18 (m, 1H).

γ-(4-Methoxyphenyl)-γ-lactone (7d). IR (KBr): ν = 1780 cm^{-1} (lactone ring). ^1H NMR ($CDCl_3$): δ = 7.25 (d, 2H), 6.89 (d, 2H), 5.45 (dd, 1H, J = 7 Hz), 3.79 (s, 3H), 2.62–2.88 (m, 3H), 2.20–2.30 (m, 1H).

γ-(4-Bromophenyl)-γ-lactone (7e). The IR (KBr): ν = 1785 cm^{-1} (lactone ring). ^1H NMR ($CDCl_3$): δ = 7.48 (d, 2H), 7.15 (d, 2H), 5.45 (dd, 1H, J = 7.1 Hz), 2.60–2.70 (m, 3H), 2.10–2.15 (m, 1H).

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23 The enantiomeric excess for **7b–e** was calculated by chiral HPLC using a Bruker HPLC V5.205 with a (*R*,*R*) Whelc-01 5 μM (Merck Germany) chiral column. The injection volume is 20 μl, the elution mixture 93 : 7 *n*-hexane : 2-propanol and elution flow rate of 2 ml min^{-1}.