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Unexpected Stereochemistry in the Lithium Salt Catalyzed Ring Expansion of Nonracemic Oxaspiropentanes. Formal Syntheses of (−)-(4*R*,5*R*)-Muricatacin and the Pheromone (*R*)-Japonilure

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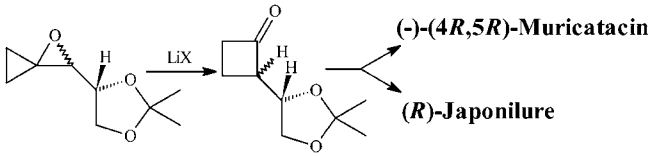
ABSTRACT



(*R*,*R*)-**2** or (*S*,*R*)-**2** **3**

The stereochemistry of the cyclobutanones 3, obtained by lithium salt catalyzed ring expansion of the optically pure oxaspiropentanes 2, depends not only on the lithium salt but also on the stereochemistry of 2. They constitute the starting material for the syntheses of the acetogenin (−)-(4*R*,5*R*)-muricatacin and the pheromone (*R*)-japonilure.

Oxaspiropentanes constitute an important class of compounds in organic synthesis[1,2] and are usually prepared by peracid oxidation of methylenecyclopropanes,[3−9] through nucleophilic addition of 1-bromo-1-lithio-cyclopropanes to ketones at low temperatures[10−12] or through reaction of sulfur ylides with carbonyl compounds.[13−17] They are extremely versatile compounds, as clearly demonstrated by their capability to react with nucleophiles[18] and bases[15−17,19] to give cyclopropanols and to undergo ring expansion to cyclobutanones by reaction with acidic reagents such as protonic acids, lithium or europium salts[1,2,5,6,15−18,20,21] or by thermal treatment.[22,23]

As a result of our interest in oxaspiropentanes,[24,25] we have previously reported[25] the synthesis of the 70:30 mixture of

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(2) Salaun, J. *Top. Curr. Chem.* **1988**, *144*, 1.
(3) Crandall, J. K.; Paulson, D. R. *J. Org. Chem.* **1968**, *33*, 991.
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(11) Dammann, R.; Braun, M.; Seebach, D. *Helv. Chim. Acta* **1976**, *59*, 2821.
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(15) Bogdanowicz, M. J.; Trost, B. M. *Tetrahedron Lett.* **1972**, 887.
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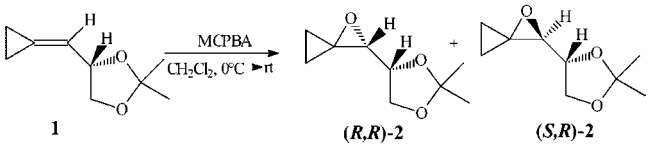
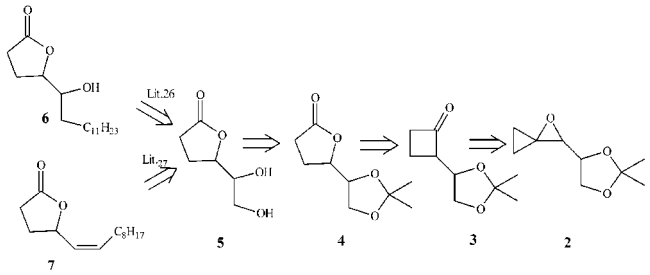
Scheme 1



the oxaspiropentanes (*R*,*R*)-**2** and (*S*,*R*)-**2** (Scheme 1) by epoxidation of (*S*)-4-cyclopropylidene-2,2-dimethyl-1,3-dioxolane **1** and its use in the preparation of chiral cyclobutanols by reaction with Grignard reagents.

With the aim of synthetically exploiting the easy access to the optically pure oxaspiropentanes **2** we planned the synthesis of the substituted γ-lactone **5**, which is a common intermediate for the synthesis of the acetogenin muricatacin (**6**)[26] and the pheromone japonilure (**7**)[27] according to the retrosynthetic analysis reported in Scheme 2.

Scheme 2

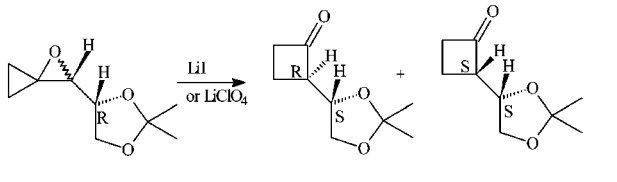


The stereochemistry in the proposed sequence could be in principle easy to forecast and to control. As a matter of fact during the ring expansion of oxaspiropentanes to cyclobutanones by treatment with acidic reagents,[20] lithium salts, or no added reagent,[21,28] the stereochemistry of the chiral epoxide carbon involved in the migration is preferentially inverted. The use of LiI entails the formation of lithio halohydrin-type intermediates,[21] whereas the reaction using $LiClO_4$ occurs through carbocationic species.[1,15−18] Trost and co-workers have clearly demonstrated[1,15−18] that the stereospecificity of the rearrangement strongly depends on the type of acid used.

In this way, changing from protonic acids to the Lewis acidic cations of lithium or europium, the transformation of the oxaspiropentane generates the corresponding cyclobutanones with increasing levels of stereospecificity. On the other hand, the transformation of the cyclobutanone into a γ-lactone through a Baeyer−Villiger oxidation should occurr with retention of configuration at the migrating carbon.[29,30]

Applying the proposed sequence we obtained the interesting and unexpected results, reported in the Table 1, that in

Table 1. Ring Expansion of Oxaspiropentanes **2** with Different Salts



entry	**2**	Li salt	solvent[a]	time (h)	(*R*,*S*)-**3**:(*S*,*S*)-**3**	yields
1	(*R*,*R*)-**2**:(*S*,*R*)-**2** 70:30	$LiClO_4$	C_6H_6	48	50:50	75
2	(*R*,*R*)-**2**	$LiClO_4$	C_6H_6	72	45:55	75
3	(*S*,*R*)-**2**	$LiClO_4$	C_6H_6	24	10:90	85
4	(*R*,*R*)-**2**	LiI	CH_2Cl_2	5	>95:<5	81
5	(*S*,*R*)-**2**	LiI	CH_2Cl_2	5	*b*	
6	(*R*,*R*)-**2**	$MgCl_2$	C_6H_6	24	45:55	90

[a] The reactions were carried out at reflux temperature. [b] Unidentified products.

the ring expansion of the oxaspiropentanes **2** with lithium salts the stereoselectivity[31] depends not only on the lithium salt used but also on the stereochemistry of the oxaspiropentane. Upon treatment of a 70:30 mixture of (*R*,*R*)-**2** and (*S*,*R*)-**2** with $LiClO_4$ (2 equiv) for 2 days a 50:50 mixture of the two diastereoisomeric cyclobutanones (*R*,*S*)-**3** and (*S*,*S*)-**3** was obtained[32] together with substantial amount (25%) of the unreacted (*R*,*R*)-**2** diastereisomerically pure, which was easily separated from the reaction mixture by column chromatography. We did not try to optimize the conditions for this kinetic resolution as (*R*,*R*)-**2** was easily separated from its diastereoisomeric epoxide (*S*,*R*)-**2**. Carrying out the reaction of pure (*S*,*R*)-**2** with $LiClO_4$ in benzene for 24 h led to a 10:90 mixture of the two possible cyclobutanones **3**. Using LiI a product was obtained as a clear oil that gave ^{1}H NMR and ^{13}C NMR spectra with all the signals broadened where unidentified products are present together with traces of a cyclobutanone, to which it was impossible to assign

(20) For a complete discussion dealing with acid-catalyzed rearrangements of epoxides, see: Rickborn, B. in *Comprehensive Organic Chemistry*; Trost, B., Fleming, I., Pattenden, G., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, p 733.

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(31) Assignment of the stereochemistry at this point of the discussion should be, of course, a tentative one, but it is justified by the evidences reported later.

(32) This cyclobutanone has already been prepared through a Kulinkovich reaction, but the stereochemistry is not clearly indicated. Cho, S. Y.; Cha, J. K. *Org. Lett.* **2000**, *2*, 1337.

the configuration. The reaction of the other diastereoisomer (*R*,*R*)-**2** with $LiClO_4$ for 72 h in benzene led to a 45:55 mixture of the two diastereoisomers of **3**. When LiI was used, the diastereoisomer obtained as the minor component in the reaction of $LiClO_4$ with (*S*,*R*)-**2** was isolated, almost pratically pure, as the only component present in the reaction mixture. Using $MgCl_2$ with the oxaspiropentane (*R*,*R*)-**2**, a 45:55 mixture of the cyclobutanones **3** was obtained.

From the data reported in the Table 1 it is clear that the ring expansion of the oxaspiropentanes **2** is occurring in some cases (entries 1, 2, 6) with total or partial epimerization of the chiral epoxide carbon atom, which could be an indication of the intermediacy of a carbonium ion mechanism.

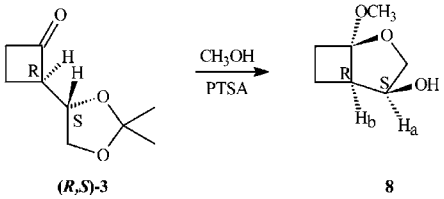
In the cases of entries 3 and 4 the reaction is occurring with preservation of the stereochemical identity of the same carbon atom, either through inversion or retention of the configuration.[33]

This point needs to be examined with great attention in view of the fact that, for what concerns the lithium salts catalyzed epoxide-carbonyl rearrangement,[34−36] the reaction occurs with preservation of configuration through a net double stereochemical inversion at the center adjacent to the carbonyl group in the product. This behavior appears to be in contrast with that proposed in the case of the lithium salts catalyzed ring enlargement of oxaspiropentanes to cyclobutanones, which is reported to occur with inversion of configuration at the migrating terminus.[1,15−18,21,28]

To make this point clear, we concentrated on the optically pure cyclobutanone obtained by reaction of (*R*,*R*)-**2** with lithium iodide, which should have the (*R*,*S*) or the (*S*,*S*) configuration depending on if the reaction occurs with retention or inversion, respectively, of configuration. We first transformed it by treatment with *p*-toluensulfonic acid in methanol into the cyclic acetal **8**, obtained as a single diastereoisomer, to which the configuration was assigned on the basis of a NOE effect present between the H_a and the H_b protons and between the H_b proton and the methoxy group.

As a result of the torsional constraints present in the bicyclic system, the derivative **8** is obtainable only if the starting cyclobutanone is the (*R*,*S*)-**3** diastereoisomer, which can be obtained only if the ring expansion of the oxaspiropentane (*R*,*R*)-**2**, whose stereochemistry has been finally established,[25] is occurring with retention of configuration (Scheme 3).

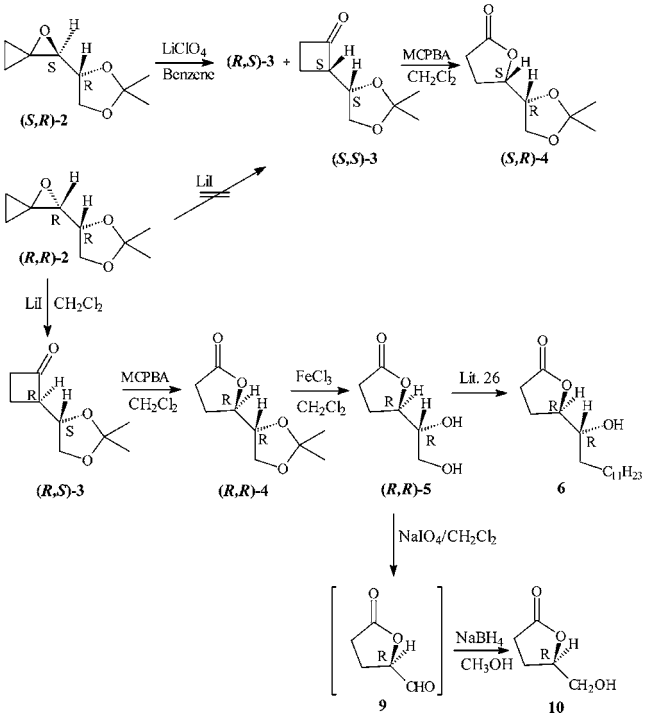
Scheme 3



(*R*,*S*)-**3** **8**

To further confirm the (*R*,*S*)-**3** configuration, the above-mentioned cyclobutanone has been transformed (Scheme 4) into the corresponding γ-lactone through a Baeyer−Villiger oxidation. If the starting cyclobutanone was the (*S*,*S*)-**3** diastereoisomer, it should give the corresponding lactone (*S*,*R*)-**4**, whereas if the starting cyclobutanone was the (*R*,*S*)-**3** diastereoisomer, the lactone (*R*,*R*)-**4** should be obtained.

Scheme 4



(*S*,*R*)-**2** (*R*,*S*)-**3** (*S*,*S*)-**3** (*S*,*R*)-**4**
(*R*,*R*)-**2** (*R*,*S*)-**3** (*R*,*R*)-**4** (*R*,*R*)-**5** **6**
9 **10**

As both lactones (*S*,*R*)-**4** and (*R*,*R*)-**4** are known compounds,[37,38] we found that the obtained lactone was the (*R*,*R*)-**4**, having both ^1H NMR and ^{13}C NMR spectra superimposable with those already published.[37] The optical rotatory power was slightly different (−18 for our product against the reported −20), but the other possible diastereoisomer (*S*,*R*)-**4**, obtainable from the (*S*,*S*)-**3**, has a different ^1H NMR spectrum and an optical rotation of +6. At this point, with the aim of preparing the versatile building block (*R*,*R*)-**5**, we carried out the hydrolysis of the dioxolane ring of (*R*,*R*)-**4** using $FeCl_3$ dispersed in silica gel[39] to avoid epimerization that occurred very easily when the reaction was carried out with aqueous acids. Synthesis of the γ-lactone (*R*,*R*)-**5** constitutes a formal synthesis of (−)-muricatacin **6**, as this natural product has been previously prepared[26a] by using the above-mentioned lactone deprotected at the dioxolane ring.

(33) The stereogenic center of the dioxolane ring is considered to be stereochemically stable toward lithium salts.

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Moreover the γ-lactone (*R*,*R*)-**5** has been very easily oxidized to the corresponding aldehyde **9**, following a reported method[40a] for the oxidation of the diastereoisomer [*R*,*S*]-**5**. This unstable aldehyde, which has been characterized through immediate reduction to the corresponding alcohol **10**,[40] has been previously used as an intermediate in the synthesis of the pheromone japonilure[27] and is a starting material for the synthesis of derivatives of the family of the *(Z)*-5-alken-4-olides.[41]

Using $LiClO_4$ as the acid reagent for the ring expansion of the oxaspiropentane (*S*,*R*)-**2** led preferentially to the cyclobutanone (*S*,*S*)-**3** with retention of configuration (Scheme 4 and Table 1). The configuration of this cyclobutanone has been demonstrated, after obtaining a pure sample by repeated chromatographies, by its oxidation to the corresponding γ-lactone (*S*,*R*)-**4** and comparison with the already reported[37,38] analytical data. This result is complementary to that obtained with LiI and (*R*,*R*)-**2**, and following the same sequence used for the synthesis of (−)-muricatacin should make it possible the synthesis of the epi-(4*S*,5*R*)-muricatacin[42] in enantiomerically pure form. The versatility of the oxadiolane ring makes this procedure very interesting and could, in principle, be extended to the synthesis of other 5-hydroxy-γ-butyrolactones as already previously reported.[26]

As far as we know this is the first report of a ring expansion of an oxaspiropentane into cyclobutanone occurring preferentially with retention of configuration. In this case the different behavior of the two lithium salts could be the consequence of the presence of the two oxygen atoms of the oxadiolane ring that are more basic[43,44] than the epoxide oxygen atom. The lithium atom could therefore undergo a multiple coordination with consequent minor amount of positive charge formed on the chiral epoxide carbon of the oxaspiropentane, which could cause a change in the mechanism of the ring enlargement.

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Supporting Information Available: Detailed descriptions of experimental procedures and characterization of compounds (*R*,*S*)-**3**, (*S*,*S*)-**3**, (*R*,*R*)-**4**, (*R*,*R*)-**5**, and **8**−**10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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