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Asymmetric carbolithiation of 2-phenylselenofumarate derivatives: a short synthesis of (−)-roccellaric acid

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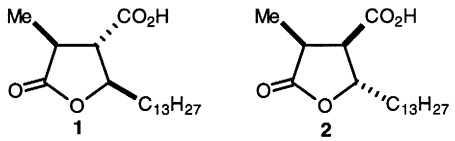
Abstract

(−)-Roccellaric acid and variously substituted succinates are obtained through direct asymmetric carbolithiation of 2-phenylselenofumarate derivatives, followed by reaction with suitable electrophiles.

Keywords: lactones; asymmetric synthesis; selenium; selenium compounds.

Roccellaric and dihydroprotolichesterinic acids **1** and **2** are natural substances belonging to the class of paraconic acids, a kind of compound in which the β-position of the lactone moiety is occupied by a carboxy group. They exhibit a wide range of bioactivities and their stereoselective synthesis is of great interest as shown by a growing literature attention.[1]



In this paper we describe an enantioselective approach both to roccellaric acid and also to chiral 2,3-disubstituted succinates, useful as potential peptidomimetic metalloproteinase inhibitors,[2] using the particular reactivity of 2-phenylselenofumaric diester, as shown in our previous work,[3] affords only conjugate addition products with no detectable traces of 1,2 adducts in the reaction with organolithium compounds.

We developed an asymmetric carbolithiation protocol in which the presence of cyclohexyl based chiral auxiliaries[4] in the ester moieties of 2-phenylselenofumarate provides an excellent stereocontrol in the formation of the two new stereogenic centers. (1*R*,2*S*)-(−)-*trans*-2-Phenyl-1-cyclohexanol proved to be

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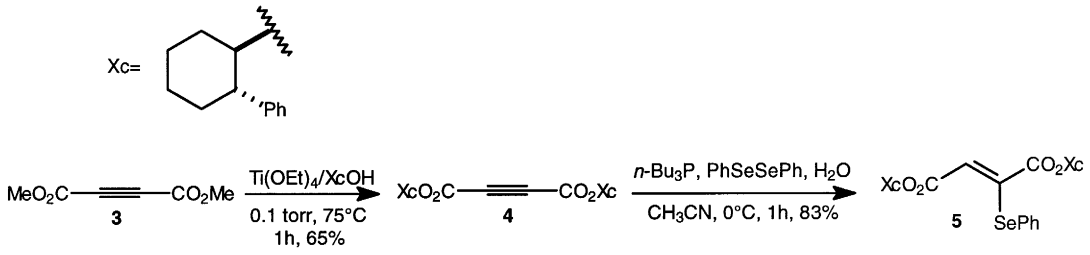
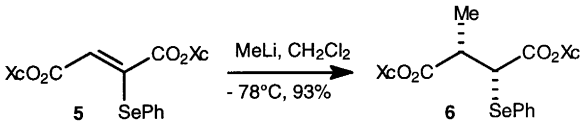
the auxiliary of choice and the corresponding fumaric diester was prepared according to the sequence outlined in Scheme 1.



Scheme 1.

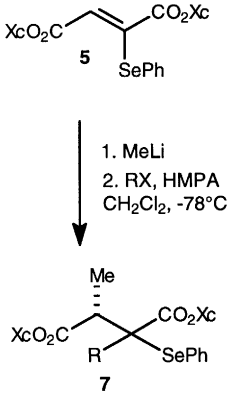
Dimethyl acetylenedicarboxylate **3** was thus transesterified to the corresponding chiral diester **4** via titanium catalyzed methodology;[5] then, nucleophilic addition of in situ generated benzeneselenol[6] proceeded with good yield and stereoselectivity to afford compound **5**. Intermediate **5** was then tested in carbolithiation reactions in the presence of 1 equivalent of organolithium reagent in dichloromethane at −78°C[7] (Scheme 2).



Scheme 2.

Results show that with methyllithium the reaction proceeds with high yield and excellent diastereoselectivity (>15:1)[8] to give succinate **6**. The absolute configuration of C-2 in compound **6** was determined by chemical correlation with the commercially available 2-(*R*)-methyl succinic acid. The relative stereochemistry of C-2 and C-3 was deduced after stereospecific selenoxide *syn*-elimination from the compound **6** that afforded only the 2-methyl maleate derivative, in agreement with an (*S*) C-3 configuration.

To explore the possibility of preparing trisubstituted succinates, we studied the reactivity of the ester enolate resulting from methyllithium addition towards electrophiles (Scheme 3).[9] Interestingly, our data shows that ester enolate reactivity is clearly enhanced by using a commercially available cumene:THF (9:1) methyllithium 1 M solution (Table 1, entries 7 and 8) instead of the usual 1.5 M ethereal solution utilized in our previous reactions (Table 1, entries 1–6).



Scheme 3.

Table 1
Dialkylation of fumarate **5**

Entry	MeLi Solvent	RX	7	T (°C)	Yield (%)	Ratio
1	Et_2O	MeI	**a**	-78 to 0	20	>15:1
2	Et_2O	MeOTf	**a**	-78 to 0	40	>15:1
3	Et_2O	MeOTf	**a**	0	83	>15:1
4	Et_2O	AllI	**b**	-78 to 0	-	-
5	Et_2O	AllI	**b**	0	-	-
6	Et_2O	BnBr	**c**	0	-	-
7	Cumene:THF 9:1	AllI	**b**	-78 to 0	35	>15 :1
8	Cumene:THF 9:1	BnBr	**c**	-78 to 0	51	>15:1

The stereoselectivities are excellent even when low yields are obtained. The stereochemistry of the dialkylation products **7a**–**c** has not yet been determined.

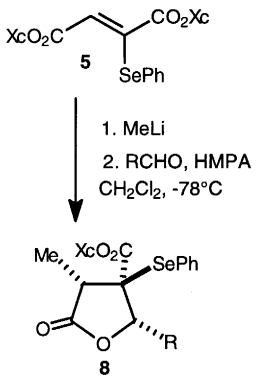
Having established the feasibility of a ‘one pot’ procedure in which an electrophile was used to quench the carbolithiation product, we turned our attention to the synthesis of paraconic acids through reaction of our enolate with a suitable aldehyde, such as myristyl aldehyde. The success of this transformation would have led us to the corresponding 4-carboxy-butano-4-lactones, potential precursors of the naturally occurring roccellaric and dihydroprotolichesterinic acids **1** and **2**.[10]

Again, the use of methyllithium in cumene:THF (9:1) greatly enhanced the reactivity of the ester enolate (Table 2, entry 3) allowing the formation of **8a** in good yield and diastereoselectivity;[11] no formation of **8a** was detected using the ethereal methyllithium solution (Scheme 4, Table 2, entries 1–2). Aromatic aldehydes were unreactive under these conditions (Scheme 4, Table 2, entries 4 and 5). Moreover, recovery of the chiral auxiliary with unaffected optical activity was possible through chromatographic separation.

Table 2
Synthesis of lactone **8**

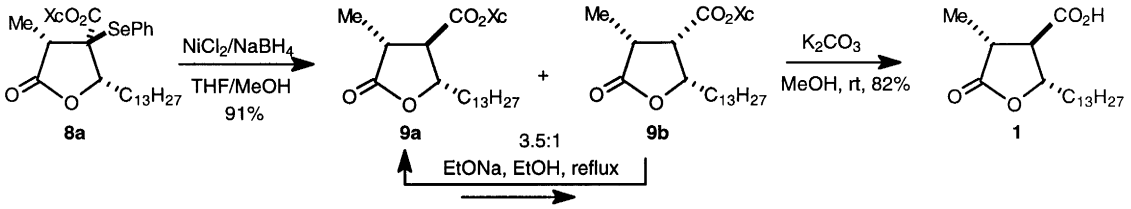
Entry	MeLi Solvent	Time (h)	T (°C)	R	8	Yield (%)	Ratio
1	Et_2O	10	-78	$C_{13}H_{27}$	**a**	-	-
2	Et_2O	20	-78 to 0	$C_{13}H_{27}$	**a**	-	-
3	Cumene:THF 9 :1	0.5	-78 to 0	$C_{13}H_{27}$	**a**	62	>15 :1
4	Et_2O	20	-78 to 0	Ph	**b**	-	-
5	Cumene:THF 9 :1	20	-78 to 0	Ph	**b**	-	-

Compound **8a** was then treated under the usual radical hydrogenolysis conditions (Bu_3SnH, AIBN), but no reaction was observed; however, using another deselenylation protocol based upon the use of in situ generated nickel boride[12] we were able to obtain, in quantitative yield, a diastereomeric mixture of compounds **9a** and **9b** in a 3.5:1 ratio (Scheme 5). The possibility of quantitatively transforming **9b** into



Scheme 4.

9a via subsequent epimerization[13] and separation overcomes the drawback of the limited selectivity of this reaction.



Scheme 5.

Finally, **9a** can be easily transformed into (−)-roccellaric acid, the enantiomer of the natural substance **1,** [mp 107°C, $[\alpha]_D$=−25.4° (c=1.93), lit.[1b] mp 108°C, $[\alpha]_D$=−26° (c=1.93)] by treatment with basic methanol, that allows also the complete recovery of the chiral auxiliary (Scheme 5).

In conclusion, we describe a novel stereoselective protocol to achieve direct asymmetric carbolithiation of 2-phenylseleno fumarate derivatives; the procedure provides a new entry to chiral tri- and disubstituted succinates and proved to be a valuable and straightforward synthetic tool. In fact, (−)-roccellaric acid **1** was easily obtained in three steps from the chiral synthon **5** (overall yield 42%); the sequence allows the recovery of the chiral auxiliary that can be recycled. Studies are in progress to broaden the versatility of the procedure, in order to develop a general method to obtain a wide range of differently 2,3-disubstituted succinates in optically pure form.

Acknowledgements

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7. Typical carbolithiation procedure: diester **5** (587 mg, 1.00 mmol) was dissolved in dry dichloromethane (5 ml, 0.2 M) and the solution cooled to −78°C under an inert atmosphere; methyllithium (0.8 ml of a 1.5 M solution in diethyl ether, 1.2 equiv.) was then added dropwise and the resulting mixture stirred for 10 min. After that, the reaction was quenched by adding methanol, warmed to room temperature and diluted with ethyl acetate; usual work-up (washing with brine, extraction and drying) and chromatography (silica gel column, eluent hexane:ethyl acetate 95:5) afforded pure compound **6** as viscous oil (561 mg, 93%). Selected data for **6**: ^{1}H NMR δ ($CDCl_3$): 0.79 (d, 3H, J=7.0 Hz), 0.9–2.44 (m, 18H), 2.59 (dt, 1H, J_1=12.0 Hz, J_2=4.2 Hz), 3.26 (d, 1H, J=10.0 Hz), 4.70–4.87 (m, 2H), 7.08–7.49 (m, 15H). ^{13}C NMR δ ($CDCl_3$): 16.41, 25.07, 26.02, 26.25, 32.00, 34.00, 34.10, 41.77, 47.36, 49.59, 49.66, 77.21, 78.03, 126.87, 126.95, 128.07, 128.23, 128.66, 128.72, 128.86, 129.51, 135.37, 143.57, 143.85, 171.85, 179.18. $[\alpha]_D$=8.0° (c=1.5 in $CHCl_3$). Anal. calcd for $C_{35}H_{40}O_4Se$: C 69.64, H 6.68. Found C 69.34, H 6.61.
8. All diasteroisomeric ratio were determined via ^{1}H NMR (200 MHz) signals integration.
9. Typical dialkylation procedure: the methodology outlined in Ref. 7 was followed until the addition of methyllithium (in the appropriate solvent, Table 1); the suitable electrophile (3 equiv.) and HMPA (0.1 ml) were then added and the mixture warmed to room temperature. The reaction was then quenched with methanol and diluted with ethyl acetate; usual work-up (washing with brine, extraction and drying) and silica gel chromatography afforded products **7a**–**c** (Table 1).
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11. Typical procedure for the synthesis of lactone **8a**: the methodology outlined in Ref. 7 was followed until the addition of methyllithium (cumene:THF, 9:1 solution); myristyl aldehyde (650 mg, 3 equiv.) dissolved in 1 ml of dichloromethane was then added and the temperature raised to −40°C. After 30 min the reaction was quenched with methanol, diluted with ethyl acetate and warmed to room temperature; the mixture was then neutralized with saturated $NaHCO_3$ solution, washed with brine and the organic layer dried over Na_2SO_4. Silica gel column chromatography (eluent hexane:ethyl acetate, 25:1) afforded pure **8a** as viscous oil (413 mg, 62%). Selected data for **8a**: ^{1}H NMR δ ($CDCl_3$): 0.85–2.27 (m, 38H), 2.70 (dt, 1H, J_1=4.2 Hz, J_2=11.0 Hz), 3.85 (dd, 1H, J_1=1.8 Hz, J_2=10.2 Hz), 5.05 (dt, 1H, J_1=4.2 Hz, J_2=10.4 Hz), 7.13–7.48 (m, 10H). ^{13}C NMR δ ($CDCl_3$): 23.20, 25.13, 25.97, 27.45, 27.80, 29.32, 29.87, 29.99, 30.16, 32.42, 32.79, 34.39, 43.35, 49.67, 61.69, 80.63, 83.54, 125.95, 127.93, 128.36, 128.95, 129.12, 130.15, 130.72, 139.33, 142.99, 168.63, 176.26. $[\alpha]_D$=−27.3° (c=1.3 in $CHCl_3$). Anal. calcd for $C_{37}H_{52}O_4Se$: C 69.46, H 8.19. Found C 69.44, H 8.18.
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