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Synthesis of (+)-Siphonarienone: Asymmetric Alkylation using a Chiral Benzopyrano-isoxazolidine Auxiliary

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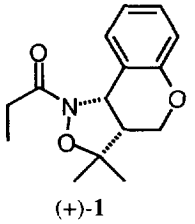
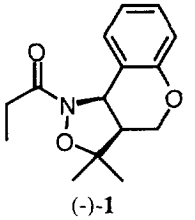
Abstract: Asymmetric alkylation of the potassium enolates derived from N-propionyl benzopyrano-[4,3-c]-isoxazolidine derivatives with chiral alkyl triflates proceeded smoothly with high diastereoselectivity. The stereochemistry of the newly formed stereogenic center was fully controlled by the facial selectivity of the enolate according to the rule of double asymmetric synthesis. The application of this methodology led to the first synthesis of (+)-siphonarienone, a marine polypropionate natural product.

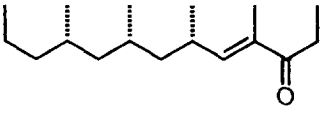
We have recently demonstrated that alkylation of (+)- and (-)-N-propionyl isoxazolidines **1** proceeds with high facial selectivity and, more importantly, the potassium enolate of **1** appears to have enhanced reactivity for alkylation as compared to other chiral reagents including those derived from oxazolidinone and sultam heterocycles.[1] The enolate of **1** reacted with the triflate of β-branched alchohols, rather unreactive electrophiles which usually do not undergo alkylation with the majority of known chiral reagents.[2] Numerous polyketide natural products contain branched methyl groups with a 1, 3 relationship, the construction of which has been achieved with multi-step transformations including asymmetric alkylation with allylic electrophiles and subsequent asymmetric hydrogenation.[2] The high reactivity of the enolate of **1** enhances its utility in the synthesis of polyketide-type natural products, as it directly inserts the structural unit [-*$CH(CH_3)CH_2$-] into the alkylating agent. Here, we would like to report, as further applications of the asymmetric alkylation of **1**, the synthesis of fully reduced polypropionate units, including the first synthesis of (+)-siphonarienone **7**,[3] a marine natural product.



(+)-**1**



(-)-**1**

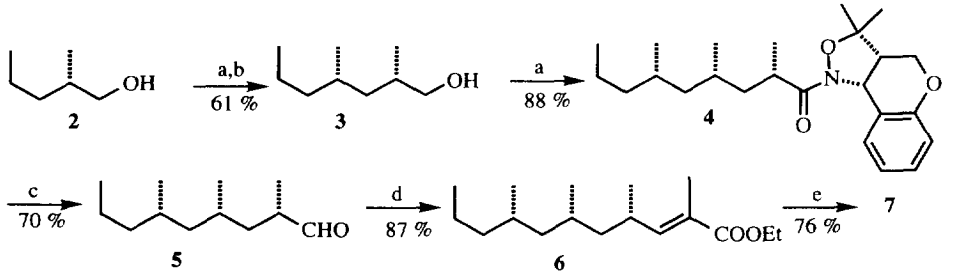


siphonarienone **7**

The synthesis of siphonarienone began with the chiral alcohol **2**.[4] A series of transformations, 1) preparation of the corresponding triflate, 2) reaction with the potassium enolate of (-)-**1**, and 3) reduction with $LiBH_4$ and EtOH in ether, afforded homologated alcohol **3** with high diastereoselectivity (ds >97%). The optimized reaction conditions for the alkylation required the use of diethyl ether as a solvent in the presence of 3 equiv of HMPA, and the maintenance of low temperature (-78 °C) throughout the reaction to minimize fragmentation of the enolate.[5] Under these conditions, the triflate, reacted with the enolate almost instantaneously

(see below). The same asymmetric alkylation of **3** provided **4** (ds >97%). Reduction of **4** with excess DIBAH in diethyl ether afforded aldehyde **5** ($[\alpha]_D$ -0.99, c 2.11, $CHCl_3$), which was converted to ester **6** ($[\alpha]_D$ 36.1, c 2.01, $CHCl_3$) by a Wittig reaction. Application of the Weinreb procedure[6] to **6** afforded ethyl ketone **7** ($[\alpha]_D$ 27.5, c 2.00, $CHCl_3$). During these transformations, the integrity of the stereochemistry was retained. The ^1H and ^{13}C NMR of the synthetic material were identical to those reported for siphonarienone[3] (Scheme 1).

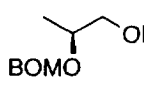
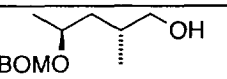
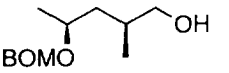
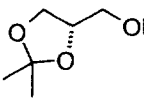
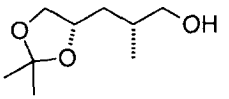
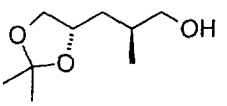
Scheme 1



Key: a) 1) Tf_2O, 2,6-t-Bu_2Pyridine; 2) K-enolate of (-)-**1**, ether, HMPA. b) $LiBH_4$-EtOH, ether. c) DIBAH, ether, 0 °C. d) Ethoxycarbonylethylidenetriphenylphosphorane, toluene, reflux, 3 h. e) 1) Me_3Al, MeNH(OMe)•HCl, benzene, reflux, 2 h; 2) EtMgBr, THF, rt, 2 h.

The application of the asymmetric alkylation of **1** is not limited to the construction of the unfunctionalized syn 1,3-dimethyl structures. The potassium enolates of both (+)- and (-)-**1** cleanly reacted with the triflates of chiral, functionalized alcohols **8** and **9** in high yield and with excellent diastereoselectivity (Table 1). Note that the stereochemical outcome of each alkylation was fully governed by the high facial selectivity of the enolate (double asymmetric synthesis).[7] The alkylated products were reduced by the combination of $LiBH_4$ and EtOH to provide high yields of the extended alcohols **10~13** with the recovery of the chiral auxiliary. The stereostructures of **10~13** were established by comparison with literature data.[8]

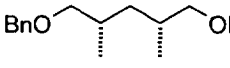
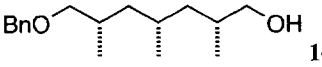
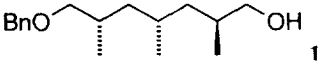
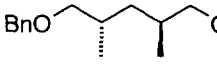
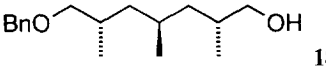
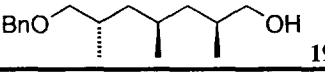
Table 1: Double Asymmetric Alkylations

ROH	Reagent	yield (ds) alkylation; reduction	Product[a)]	
 **8**	(+)-**1**	85 %, 94 % (>98 %)		**10**
	(-)-**1**	88 %, 96 % (>98 %)		**11**
 **9**	(+)-**1**	65 %, 69 % (>98 %)		**12**
	(-)-**1**	54 %, 64 % (>98 %)		**13**

a) Product after alkylation and reduction (see text).

The above sequence of reactions can be reiterative. Thus, the asymmetric alkylation was exectuted on the isomeric chiral alcohols **14** and **15**, which were prepared by the alkylation of the triflate of (*S*) 3-benzyloxy-2-methylpropanol with (+)- and (-)-**1**, respectively, followed by reduction.[1] Under the standard reaction conditions the potassium enolates of both (+)- and (-)-**1** reacted with the triflates of **14** and **15** without problem[9] (Table 2). The four chiral alcohols **16~19**, obtained after reductive cleavage, represent all the stereoisomers of 2,4,6-trimethyl-heptane-1,7-diol monobenzyl ether. The stereostructures of **16~19** were established through those of the corresponding diols **16a~19a**, of which the meso and chiral isomers were easily ascertained by ^{13}C NMR and optical rotation data: **16a** and **18a** were meso compounds and **17a** and **19a** were identical.[10]

Table 2: Reiterative Asymmetric Alkylations to Synthesize 2,4,6-Trimethyl-heptane-1,7-diol Derivatives

ROH	Reagent	overall yield (ds)	Product[a)]
 **14**	(+)-**1**	79 % (>98 %)	 **16**
	(-)-**1**	75 % (>98 %)	 **17**
 **15**	(+)-**1**	65 % (>98 %)	 **18**
	(-)-**1**	62 % (>98 %)	 **19**

a) Product after alkylation and reduction (see text).

In summary, the asymmetric alkylation of **1** constitutes a useful method for the construction of fully reduced polypropionate units, which led to the first synthesis of siphonarienone. Furthermore, the products shown in Table 1 and 2 represent useful synthons which are now readily accessible through the alkylation of **1**. The high diastereoselection achieved by double asymmetric synthesis is noteworthy.

A general procedure of the alkylation and reduction is described below:

Preparation of the triflate: Triflic anhydride (1.2 equiv) was added dropwise to a stirred solution of the alcohol and 2,6-di-*tert*-butylpyridine (1.5 equiv) in CH_2Cl_2 at -78 °C. After 30 min the reaction was diluted with hexane and washed with aqueous $NaHCO_3$. The organic solution was dried and concentrated, and a trace amount of the remaining salt was removed. After concentration, the triflate was used immediately in the next step.

Alkylation of the enolate of **1**: To a stirred suspension# of **1** (1.2 equiv of the triflate) in diethyl ether (~0.1 M) at -78 °C, was transferred *via* cannula a precooled solution of KHMDS (1.0 equiv, 0.25 M) in a 1:1 mixture of diethyl ether and toluene. After 30 min the reaction mixture became a clear solution, and HMPA (3 equiv) was added dropwise, which solidified upon addition. After 10 min the reaction mixture became a clear solution, and a precooled solution of the triflate in diethyl ether was transferred *via* cannula. Usually the reaction was complete within 30 min and quenched by the addition of aqueous NH_4Cl. The usual work-up followed by column chromatography afforded the alkylation product and unreacted **1**.

1 was not very soluble in diethyl ether at -78 °C.

Reductive cleavage of the auxiliary: To a solution of the alkylated product and EtOH (3 equiv) in diethyl

ether was added a solution of $LiBH_4$ (3 equiv) in THF at room temperature. The resulting cloudy mixture was stirred at room temperature overnight and quenched by the careful addition of 2M HCl. After 2 h, the usual worked-up followed by silica gel chromatography afforded the alcohol and the auxiliary was recovered from the basified aqueous layer.

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References and Notes:

1. Abiko, A.; Moriya, O.; Filla, S. A.; Masamune, S. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 793.
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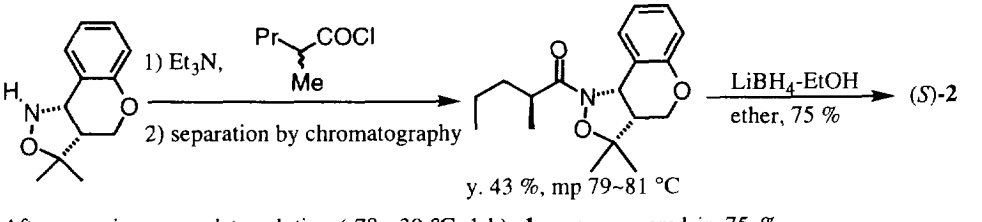
3. Norte, M.; Cataldo, F.; Gonzalez, A. G.; Rodriguez, M. L.; Ruiz-Perez, C. *Tetrahedron* **1990**, *46*, 1669. Optical rotation of the natural product was reported as $[\alpha]_D$ 13.3 (c 0.7, $CHCl_3$).
4. (*S*)-**2** was prepared in multi-gram quantity by resolution of (±)-2-methylpentanoic acid with the (-)-isoxazolidine, followed by reduction.



5. After warming an enolate solution (-78~-30 °C, 1 h), **1** was recovered in 75 % yield along with fragmentation products, from which **20** was isolated.

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8. **10** was converted to the corresponding known diol: Chiarello, J.; Joullie. M. M. *Synth. Commun.* **1989**, *19*, 3379. ent-**12**: Tsuda, M.; Sasaki, T.; Kobayashi, J. *J. Org. Chem.* **1994**, *59*, 3734.
9. The triflate of anti-alcohol **15** was prepared in diethyl ether at -78 °C and 2.5 eq. of the enolate solution in diethyl ether was transferred *via* cannula.
10. Optical rotatory and ^{13}C NMR data for the alcohols: **16a**; meso, ^{13}C NMR δ 67.7, 41.2, 33.1, 27.8, 20.9, 17.7. **17a**; $[\alpha]_D$ -33.5 (c 2.75, $CHCl_3$), ^{13}C NMR δ 69.0, 68.0, 41.4, 40.6, 33.0, 32.9, 27.2, 20.3, 17.2, 16.5. **18a**; meso, ^{13}C NMR δ 68.9, 41.5, 33.1, 27.1, 19.1, 16.4. **19a**; $[\alpha]_D$ -32.1 (c 1.50, $CHCl_3$), ^{13}C NMR δ 69.0, 68.0, 41.4, 40.6, 33.0, 32.9, 27.2, 20.3, 17.2, 16.5.

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