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Enantioselective synthesis of α-terpineol and nephthenol by intramolecular acyloxazolidinone enolate alkylations†

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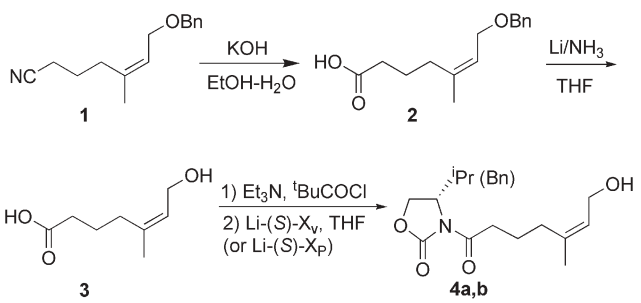
Enolate anions generated from norterpenyl bromides bearing oxazolidinone chiral auxiliaries at the chain termini underwent efficient, stereo-biased cyclizations to form 6- and 14-membered rings in novel synthetic routes to α-terpineol and nephthenol enantiomers.

The asymmetric α-alkylation of carbonyl compounds is widely used for stereocontrolled C–C bond formation in organic synthesis. High levels of enantioselectivity are usually attainable by means of chiral auxiliary-directed enolate alkylation with suitably reactive alkyl halides and sulfonates and other C-electrophiles.[1,2] However, the related intramolecular variants of asymmetric alkylation have been rarely examined,[3] perhaps owing to perceived incompatibilities of the base and a reactive leaving group. Although Solladié-Cavallo *et al.* succeeded in the diastereoselective double alkylation of the Schöllkopf bislactim-derived glycinate with a dibromide alkylating reagent, this protocol was unsuccessful with a hydroxypinone-derived iminoglycinate substrate, the second intramolecular alkylation step forming solely the halide elimination product.[3b] Recently, Vignola and List reported proline-catalyzed intramolecular asymmetric α-alkylation of aldehydes.[3d] Herein, we describe oxazolidinone-directed intramolecular alkylation reactions as key steps in syntheses of the menthane monoterpene alcohol α-terpineol (**9**) and the macrocyclic cembrane diterpene nephthenol (**18**) in high enantiomeric purity.

The feasibility of enantioselective cyclization to form a six-membered ring was examined first with the *N*-acyloxazolidinones **5** (Table 1). Preparation of acyclic precursor imides **4** from the known nitrile **1**[4] was straightforward (Scheme 1), and the latter



Scheme 1

was readily accessible from neryl benzyl ether in five steps following standard procedures similar to those in the literature[4] (see ESI†).

Hydrolysis of nitrile **1** to the acid **2**, followed by removal of the benzyl protecting group (Li/NH_3, −78 °C) provided *cis*-hydroxy acid **3** in good overall yield (81%). Evans' oxazolidinone chiral auxiliaries were then installed in a one-pot procedure through *in situ* formation of the pivalic mixed anhydride intermediate (Et_3N, ^{t}BuCOCl, THF, 0 °C) followed by *N*-acylation of the lithiated (*S*)-oxazolidinones derived from valinol and phenylalaninol (1 equiv. ^{n}BuLi/hexane, X_v or X_p, THF, −78 °C) to afford the imides **4a** and **4b** (72 and 70%).[5]

Various leaving groups, bases, and conditions were evaluated in the intramolecular asymmetric alkylations (Table 1). The allylic hydroxyl was converted to the corresponding diethyl phosphate, chloride and bromide **5** (X = OPO_3Et_2, Cl, and Br) for this purpose.[6] The lithium or sodium enolates of the acyloxazolidinones were generated either by (a) slow addition of the allylic phosphate and chloride to LiHMDS in THF or to a suspension of NaH in THF–DMF at 23 or 50–60 °C or inversely by (b) adding NaHMDS or LiHMDS (1.0 equiv. in THF, over ~20 min) to solutions of the chloride and bromide at −78 °C in THF. The cyclizations gave rise to the known diastereomeric Diels–Alder adducts **6** (1*R*) and **7** (1*S*)[7] in variable proportions. The highest diastereoselectivities and yields were obtained with the sodium enolates of the chloride or bromides at −78 °C (generally >95:5 dr, 65–76%: Table 1, entries 5–7). The reactions proceeded faster with bromide as leaving group (−78 °C, 1 h), and the oxazolidinone bearing the (*S*)-benzyl substituent provided slightly higher diastereoselectivity (entry 7, >99:1 dr) than that with the isopropyl group. Poor yields and diastereoselectivities were observed with sodium hydride as the base and phosphate as the leaving group (entries 1–3).

An authentic sample of the enantiomer of the minor (*S*,*S*)-diastereomer **7** (R = ^{i}Pr) was prepared from the major cyclization product (*R*,*S*)-**6** (Scheme 2). Hydrolysis of carboximide **6** (R = ^{i}Pr; LiOH, H_2O_2, THF–H_2O, rt, 90%)[8] to enantiomerically enriched acid **8**, followed by *in situ* formation of the pivalic mixed anhydride and treatment with the enantiomeric lithiated (*R*)-oxazolidinone (LiX_v) provided (*R*,*R*)-**7** (76%). The expectation that chelation-controlled intramolecular alkylation would take place with the same stereo-bias as an intermolecular reaction was independently verified through conversion of the major isomer (*R*,*S*)-**6** to the natural monoterpene (+)-α-terpineol (**9**). Transformation of **6** (R = ^{i}Pr; LiOBn, THF, 0 °C, 96%) to the benzyl ester, followed by reaction with excess methylmagnesium bromide (15 equiv., THF, 0 °C → rt, 90%) afforded (+)-α-terpineol **9**; $[\alpha]_D^{23}$ + 93.3 (*c* 2.2,

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† Electronic supplementary information (ESI) available: Synthetic procedures, characterization data, and NMR spectra for **3–9** and **13–18**. See DOI: 10.1039/b605346g

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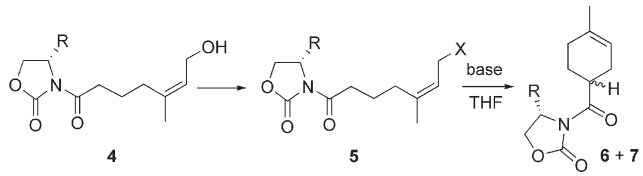
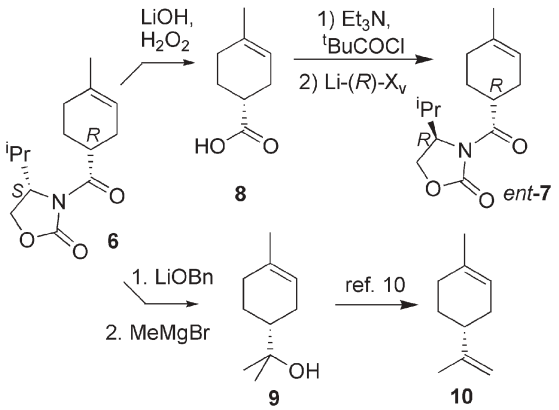
Table 1 Intramolecular asymmetric alkylations of oxazolidinones



Entry	R	X	Base	Solvent	*T*/°C	Time/h	Yield (%)	dr (**6**/**7**)
1[a]	^{i}Pr	OPO_3Et_2	LiHMDS	THF	50–60	1	10	75:25[c]
2[b]	^{i}Pr	OPO_3Et_2	NaH	THF–DMF	23	4	0	
3[b]	^{i}Pr	Cl	NaH	THF–DMF	23	5	12	53:47[c]
4[d]	^{i}Pr	Cl	LiHMDS	THF	−78 → 23	1	60	87:13[e]
5[d]	^{i}Pr	Cl	NaHMDS	THF	−78	12	76	98:2[c]
6[d]	^{i}Pr	Br	NaHMDS	THF	−78	1	65	95:5[c]
7[d]	Bn	Br	NaHMDS	THF	−78	1	67	>99:1[e]

[a] Solution of **5** (X = OPO_3Et_2, 0.01 M in THF) added to LiHMDS (1.5 equiv.) in THF. [b] Solution of **5** (~0.1 M, X = OPO_3Et_2 or Cl) in THF added to NaH suspension. [c] By ^{1}H NMR analysis after column chromatography. [d] Na(Li)HMDS (1 equiv., 1 M in THF) added to **5** (X = Cl or Br, ~0.1 M in THF). [e] By GC analysis of crude product.



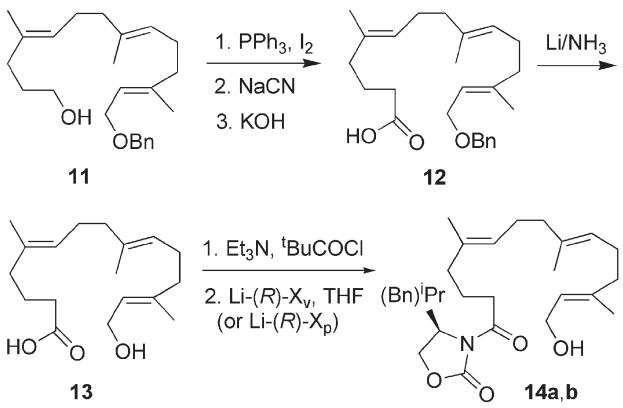
Scheme 2

$CHCl_3$), in good agreement with a literature value $[\alpha]_D^{22}$ + 101 (*c* 0.1, $CHCl_3$).[9] The known dehydration of (+)-α-terpineol (Py, Al_2O_3, 220 °C) constitutes a further correlation with (+)-α-limonene (**10**).[10] An attractive aspect of this approach is the ability to access easily both enantiomeric forms of these naturally occurring menthane monoterpenes simply by altering the chirality of the oxazolidinone auxiliary.

To demonstrate further the utility of this method for asymmetric ring formation, we undertook the asymmetric synthesis of the 14-membered macrocyclic diterpenes, nephthenol and cembrene A (**18** and **19**) through intramolecular alkylation. These diterpenes are the simplest prototypes of the large and diverse cembrane family of natural products and, like the related menthane monoterpenes, they occur in both enantiomeric forms.[11] Although many interesting strategies have been applied to the synthesis of cembrene A,[12] only few asymmetric routes to this diterpene have been reported.[13]

The synthesis of acyclic precursor **13** commenced from (*E*,*E*,*E*)-geranylgeranyl benzyl ether. Selective terminal epoxidation through the 14,15-bromohydrin,[14] hydrolysis and concomitant oxidative cleavage with HIO_4, and $NaBH_4$ reduction furnished benzyloxy alcohol **11** (39% over 3 steps).[15] Conversion to the iodide, cyanide displacement, and alkaline hydrolysis afforded benzyloxy acid **12** (Scheme 3, 81% overall). Deprotection of the benzyl ether gave the hydroxy acid (**13**) and introduction of (*R*)-auxiliaries by the same one-pot procedure provided the valine-derived oxazolidinone **14a** (77% over three steps) and the related benzyl derivative **14b** (80%).

The hydroxy oxazolidinones were converted to allylic bromides **15a**,**b** (Et_3N, $MeSO_2Cl$, −45 °C; LiBr, THF, 0 °C),[6c] and the critical asymmetric macrocyclizations were conducted under conditions similar to those optimized above for 6-membered ring formation (Table 2). The enolates were generated by slow addition of the amide bases (1.0 equiv., THF, over 20 min) to the bromo oxazolidinones (0.1 M, THF) at −78 °C and, after 10–20 min, the solutions were allowed to warm to room temperature. The isomer ratios were determined by integration of the distinctive ring methine signals for the major and minor diastereomers (tt, δ_H 3.70 and 3.80 ppm) in the ^{1}H NMR spectra. The identity of the minor product was established by comparisons with an authentic sample of (*R*,*R*)-**17** obtained from ***ent*-16a** by attachment of the (*R*)-oxazolidinone auxiliary by the procedures outlined above (Schemes 2 and 4). Consistently high levels of asymmetric induction were observed using both chiral auxiliaries and lithium and sodium enolates. However, generation of the enolate at higher temperature reduced the diastereoselectivity somewhat (dr 93:7, entry 1).



Scheme 3

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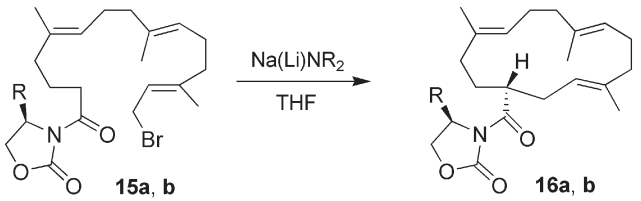
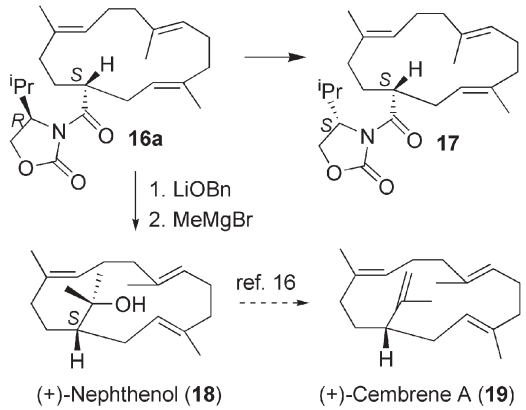
Table 2 Intramolecular asymmetric alkylation of bromo oxazolidinones **15a**,**b**



Entry	R	Base	*T*/°C	Yield (%)	dr[a]
1	^{i}Pr	NaHMDS	23	50	93:7
2	^{i}Pr	NaHMDS	−78 → 23	43	95:5
3	^{i}Pr	NaHMDS	−78 → 0	43	97:3
4	Bn	NaHMDS	−78 → 23	41	97:3
5	Bn	LiHMDS	−78 → 23	45	98:2
6	Bn	LiN(^{i}Pr)$_2$	−78 → 23	46	98:2

[a] By ^{1}H NMR analysis after column chromatography



Scheme 4

The structures and absolute configurations of cyclic products **16** were confirmed by conversion to the natural diterpene (+)-nephthenol (**18**), $[\alpha]_D^{23}$ +48 (*c* 1.24, $CHCl_3$), for ***ent*-18**, lit.[13b] $[\alpha]_{589}$ −43.0 (*c* 0.72, $CHCl_3$), and by comparisons with the reported spectral data (Scheme 4).[11c,13a,b] The (−)-antipode ***ent*-18** $[\alpha]_D^{23}$ −46.3 (*c* 1.20, $CHCl_3$) was also synthesized using the enantiomeric bromo oxazolidinone bearing the (*S*)-X_v auxiliary. Dehydration of (−)-nephthenol to (−)-cembrene A (***ent*-19**) with $SOCl_2$–pyridine has been reported.[13a,b,16]

The cyclizations of bromo oxazolidinones **5** and **15** provide a promising precedent for enantioselective construction of tertiary centers on carbocyclic rings by intramolecular asymmetric alkylation, and open a new approach to the macrocyclic cembrane diterpenes.

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