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Stereoselective synthesis of chiral precursors to cyclobutane carbocyclic nucleosides and oligopeptides

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Abstract—Versatile and highly efficient synthetic routes leading to optically active cyclobutanones, γ-amino acids and δ-amino alcohols are described. These compounds are relevant synthetic precursors to enantiopure cyclobutane carbocyclic nucleosides and oligopeptides. (−)-(*S*)-Verbenone is the chiral starting material used and the key synthetic steps involve concerted rearrangements in acidic medium.

Amino acids containing small rings have been used to mimic the skeleton or lateral chains of conformationally restricted peptides. Cyclopentane,[1] cyclobutane[2,3] and cyclopropane derivatives,[4] have been employed for this purpose and several pertinent publications are available. Nevertheless, the literature provides scarce data related to the synthesis of optically active cyclobutane amino acids and related oligopeptides.[3] In nature, cyclobutane amino acids such as 2,4-methanoglutamic acid and 2,4-methanoproline[5] have also been found, as well as enantiomerically pure dipeptides containing the same ring moiety as (1*S*,2*S*)-1-hydroxy-2-[(*S*)-valylamino]cyclobutane-1-acetic acid, produced by *Streptomyces* species X-1092.[6]

Otherwise, the usefulness of carbocyclic nucleosides in the treatment of diverse diseases is well recognized.[7] In particular, carbocyclic analogs (COXT) of oxethanocine A (OXT-A) have received considerable attention due to their wide spectrum of antiviral and antitumoral activity, and numerous syntheses have been described. The earliest nucleoside was described in 1989[8] as a racemate, using cyclobutanone **1a** as an intermediate for the synthesis of COXT-A. That same year Ichikawa et al.[9] described the synthesis of optically active COXT-A and COXT-G by using the enantiopure cyclobutanone **1b** as an intermediate. In 1991 Bristol-Myers-Squibb developed an asymmetric synthesis of **1a**[10] involving an asymmetric cycloaddition. Compound **1a** has been used as a substrate for the preparation of enantiopure COXT-A and COXT-G. In 1995, two achiral carbocyclic nucleosides bearing the guanine or the adenine core were synthesized from cyclobutanone **2a** (Chart 1).[11] Since then, numerous syntheses of COXT have been documented.

Pursuing our ongoing research on the stereoselective synthesis of cyclobutane-containing molecules from terpenes,[12] we describe herein synthetic routes to γ-amino acid derivatives, convenient for incorporation into γ-oligopeptides, as well as amino alcohols and cyclobutanones suitable for use as synthetic precursors to COXT-type nucleosides. Such compounds were obtained starting from (−)-*cis*-pinononic acid, **3**, resultant of the oxidative cleavage of the double bond in (−)-(*S*)-verbenone.[12a] Concerted Baeyer–Villiger oxidation (B–V) and Schmidt rearrangement were the chemi-

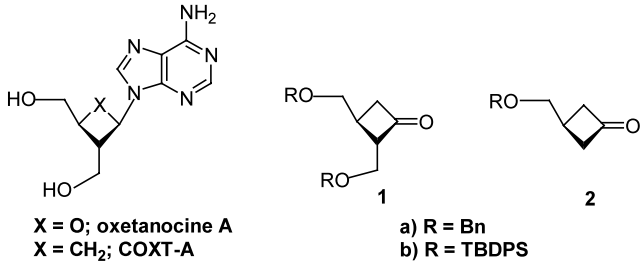

Chart 1.

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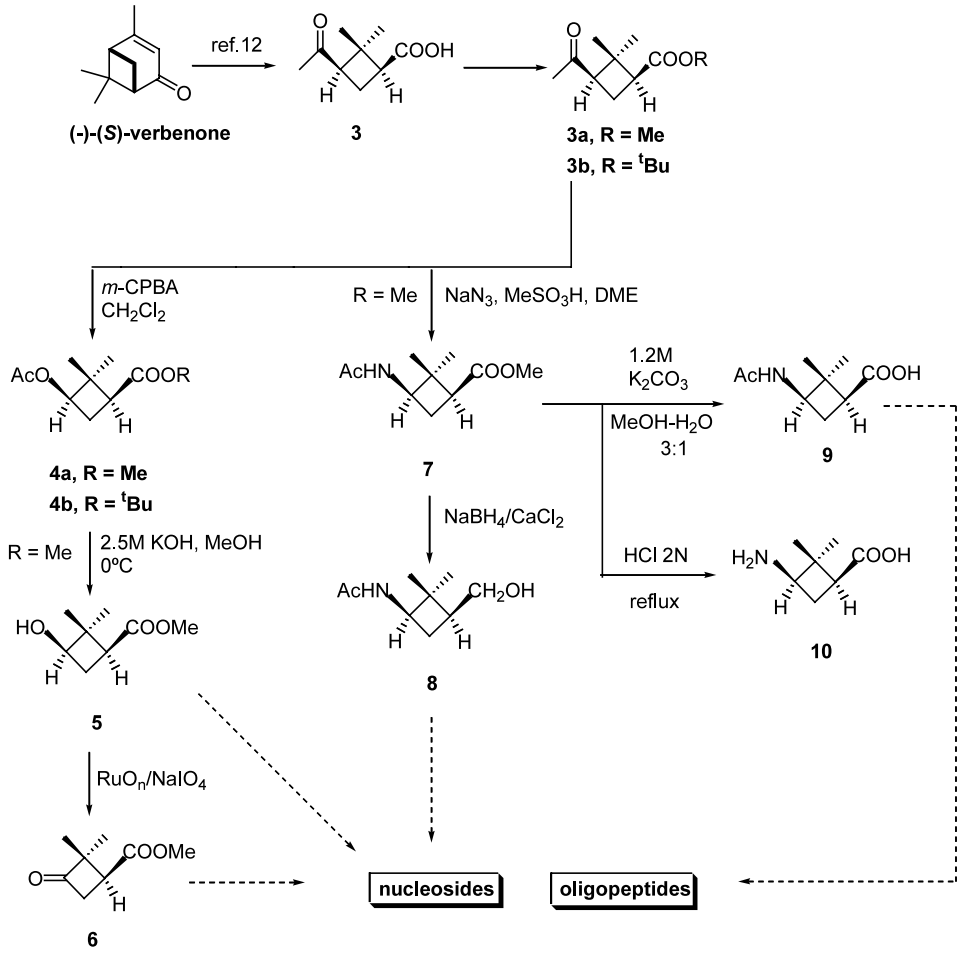
cal transformations involved in the respective key synthetic steps. These reactions were studied with substrates **3**,[12a] **3a**[12a] and **3b**[12f] (Scheme 1).

Under B–V conditions (*m*-chloroperbenzoic acid in CH_2Cl_2, rt, 2 days), compound **3a** rearranged to the corresponding acetate **4a**[13] (90% yield). The same reaction applied to **3b** showed random behavior and proved to be poorly reproducible, **4b** being only sporadically obtained in ca. 10% yield. By controlling the reaction conditions (2.5 M KOH in MeOH at 0°C for 3 h, TLC monitoring),[14] selective saponification of acetate **4a** in the presence of the methyl ester was achieved, leading to alcohol **5**[13] in 82% yield. Subsequent oxidation of **5** with ruthenium oxide afforded ketone **6**.[13] Compound **6**, an analogue of **1** and **2**, was thus prepared from (−)-(*S*)-verbenone in five steps and 55% overall yield. Compounds **5** and **6** are suitable chiral building blocks for the preparation of cyclobutane carbocyclic nucleosides.

According to a second divergent route, compound **3a** underwent Schmidt rearrangement[15] (NaN_3/$MeSO_3H$/DME, −30°C to rt, 12 h) to afford the fully protected γ-amino acid **7**[13] (75% yield), which was thus synthesized in three steps from (−)-(*S*)-verbenone in 67% overall yield. This amino acid is the formal enantiomer of the one described by Burgess,[3a] which was prepared as an *N*-Boc and benzyl ester derivative, starting from (+)-(*R*)-verbenone in five steps and in 25% overall yield. Reduction of compound **7** with $NaBH_4$ and $CaCl_2$[16] led to alcohol **8**, which is a valuable synthetic precursor to carbocyclic nucleosides. Otherwise, when *t*-butyl ester **3b** underwent Schmidt rearrangement, increasing the acidity of the medium led to ester hydrolysis, yielding a mixture of products which were difficult to isolate.

In order to prepare partially protected γ-amino acids, several transformations were tried. Attempts to remove the acetamide group by treatment of **7** with hydrazine proved fruitless. On the other hand, (−)-*cis*-pinononic acid, **3**, was submitted to Schmidt rearrangement conditions affording **9** in very poor yield. In contrast, mild saponification of **7** by using 1.2 M K_2CO_3 in 3:1 MeOH–H_2O provided, in 91% yield, *N*-acetyl γ-*cis* amino acid **9**,[13] homochiral as regards the Burgess compound,[3a] but differently protected. Compound **9** is convenient for incorporation into γ-oligopeptides. Moreover, **9** is one of the enantiomers of the racemate described by Avotins.[2]

Finally, the synthesis of the enantiopure free amino acid **10** was achieved by hydrolysis of **7** with boiling 2 N aqueous HCl (83% yield). The synthesis of this



Scheme 1.

compound in racemic form has also been described by Avotins.[2]

Thus, in this work, highly versatile and efficient synthetic routes from (−)-(*S*)-verbenone, involving concerted rearrangements in acid medium as the key steps, have been accomplished for the preparation of cyclobutanones, amino acids, and amino alcohols. These compounds are relevant precursors to enantiopure nucleosides and oligopeptides and active investigation oriented to the synthesis of such products is being carried out in our laboratories.

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13. All new products were identified and fully characterized by their spectroscopic data and physical constants. Selected data follow.
Compound **4a**: oil; $[\alpha]_D$ +52.6 (*c* 1.40, $CHCl_3$); HRMS calcd for $C_{10}H_{17}O_4$ (MH^+): 201.1127. Found 201.1132.
Compound **5**: oil; $[\alpha]_D$ +18.1 (*c* 5.36, MeOH); HRMS calcd for $C_8H_{15}O_3$ (MH^+): 159.1021. Found 159.0890.
Compound **6**: oil; $[\alpha]_D$ +15.65 (*c* 1.15, MeOH); HRMS calcd for $C_8H_{13}O_3$ (MH^+): 157.0865. Found 157.0855.
Compound **7**: crystals; mp 123–125°C (DMSO); $[\alpha]_D$ +139.4 (*c* 1.03, MeOH); HRMS calcd for $C_{10}H_{17}NO_3$ (MH^+): 200.1287. Found 200.1273.
Compound **9**: oil; $[\alpha]_D$ +38.28 (*c* 2.14, MeOH).
The e.e.s of these compounds was assumed to be 95%, the same as for the verbenone starting material, as determined by ^1H NMR after derivatization. Diastereomeric homogeneity was verified from the corresponding ^{13}C NMR spectra showing a single set of signals in each case.
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