Tetrahedron: Asymmetry Vol. 4, No. 5, pp. 1043-1046, 1993
Printed in Great Britain

0957-4166/93 $6.00+.00
Pergamon Press Ltd

Enantiocomplementary Preparation of Optically Pure 2-Trimethylsilylethynyl-2-cyclopentenol by Homochiralization of Racemic Precursors: A New Route to the Key Intermediate of 1,25-Dihydroxycholecalciferol and Vincamine

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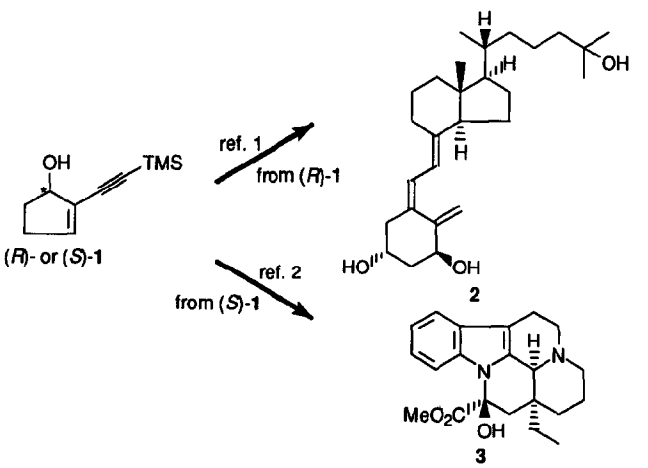
(*Received* 19 *January* 1993; *accepted* 23 *March* 1993)

Abstract: Treatment of racemic 2-trimethylsilylethynyl-2-cyclopentenol [(±)-**1**] with vinyl acetate in the presence of lipase PS in toluene yielded a 1:1 mixture of the unreacted (*S*)-alcohol [(*S*)-**1**] and the (*R*)-acetate [(*R*)-**7**] which without isolation afforded the chirally homogeneous (*R*)-alcohol [(*R*)-**1**] in 73% overall yield on reaction with acetic acid in the same reaction medium in the presence of diisopropyl azodicarboxylate and triphenylphosphine, followed by reductive deacylation of the resulting (*R*)-acetate [(*R*)-**7**]. On the other hand, hydrolysis of the racemic acetate [(±)-**7**], obtained from [(±)-**1**], in a phosphate buffer solution in the presence of lipase PS yielded a 1:1 mixture of the (*R*)-alcohol [(*R*)-**1**] and the unreacted (*S*)-acetate [(*S*)-**7**] which without separation, furnished the enantiomerically homogeneous (*S*)-alcohol [(*S*)-**1**] in 75% overall yield on treatment with acetic acid under the above Mitsunobu conditions, followed by reductive deacylation of the resulting (*S*)-acetate [(*S*)-**7**].

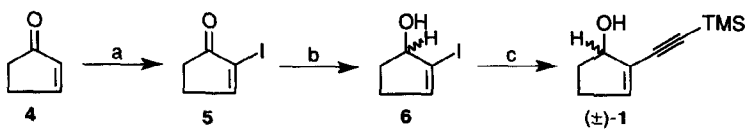
Optically active 2-trimethylsilylethynyl-2-cyclopentenol (**1**) is a potentially useful chiral building block owing to the presence of an allylic double bond and an ethynyl side chain nearby the secondary hydroxy group on the chiral center. So far its potential has already been demonstrated by the synthesis of two medicinally important materials, 1,25-dihydroxycholecalciferol (**2**) and vincamine (**3**), in which the (*R*)-enantiomer was used for the construction of the A ring moiety of the former[1] and the (*S*)-enantiomer was used for the construction of the non-tryptamine moiety of the latter[2] (**Scheme 1**). Intending to exploit **1** and the related chiral compounds more extensively as versatile chiral building blocks, we have been investigated enantiotopical preparation of these compounds[3] and, herewith, wish to report an expeditious enantiocomple-



Scheme 1

mentary preparation of both enantiomers of optically pure **1** by homochiralization of the racemic substrate [(±)-**1**] by employing lipase mediated enantiospecific acylation and deacylation reactions as the key steps. The basic concept of the present preparation is that lipases can both acylate and hydrolyze an appropriate substrate depending on the conditions employed.[4,5]

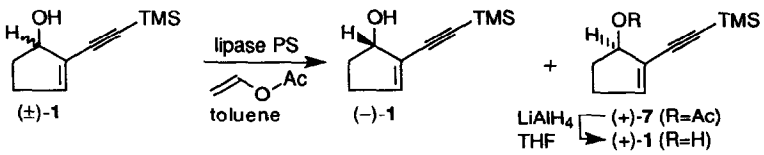
Cross-coupling[6] of the racemic 2-iodo-2-cyclopentenol (**6**), obtained from cyclopentenone (**4**) in 58% overall yield *via* the iodide[7] (**5**), with trimethylsilylacetylene in DMF in the presence of palladium catalyst, copper(I) iodide, and Hünig base afforded the racemic cyclopentenol [(±)-**1**] in 78.9% yield (**Scheme 2**).



Scheme 2

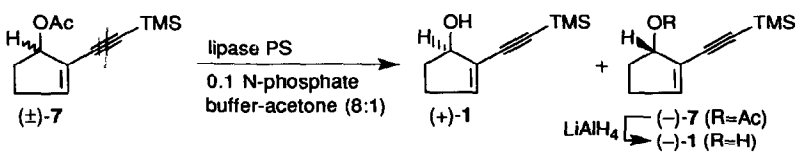
Reagents and conditions: (a) I_2, pyridine, CCl_4; (b) $NaBH_4$, $CeCl_3$, MeOH; (c) TMS-acetylene, $Pd(PPh_3)_4$ (cat.), CuI (cat.), *i*-Pr_2NEt, DMF.

When (±)-**1** was stirred with two equivalents of vinyl acetate in the presence of lipase PS (Amano, *Pseudomonas* sp.) in toluene at 30 °C, the reaction terminated after 120 h to afford the unreacted (–)-**1**, mp 43 °C, $[\alpha]_D^{30}$ –19.8 (*c* 0.59, $CHCl_3$), ≥99% ee[8] and the acetate [(+)-**7**], $[\alpha]_D^{27}$ +52.4 (*c* 1.00, $CHCl_3$), ≥99% ee,[8] in yields of 47 and 48% after separation by silica gel column chromatography. The latter compound could be transformed into (+)-**1**, mp 43.5 °C, $[\alpha]_D^{30}$ +19.5 (*c* 0.59, $CHCl_3$), ≥99% ee,[8] in 85% yield by reductive deacylation using lithium aluminum hydride in THF (**Scheme 3**).



Scheme 3

On the other hand, when the racemic acetate (±)-**7**, obtained in 91% yield from the racemic alcohol [(±)-**1**], was stirred with the same lipase (lipase PS) in 0.1 N phosphate buffer solution at 30 °C, the reaction terminated after 48 h to afford the (+)-alcohol [(+)-**1**], mp 43.5 °C, $[\alpha]_D^{32}$ +19.5 (*c* 0.80, $CHCl_3$), >99% ee,[8] and the unreacted acetate [(–)-**7**], $[\alpha]_D^{29}$ –53.6 (*c* 1.08, $CHCl_3$), ≥99% ee,[8] in yields of 46.2 and 43.0% after separation by silica gel column chromatography. The latter furnished (–)-**1**, mp 43.5 °C, $[\alpha]_D^{29}$ –19.4 (*c* 1.19,

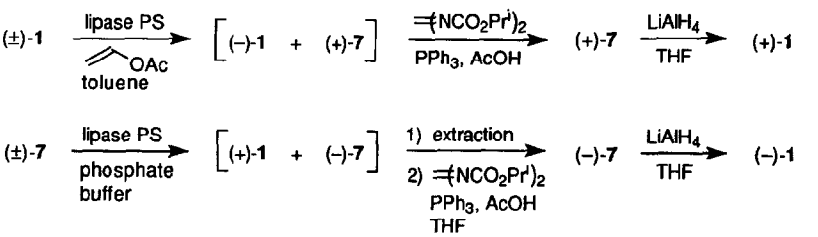


Scheme 4

$CHCl_3$), ≥99% ee,[8] in 86% yield on reductive deacylation with lithium aluminum hydride in THF (**Scheme 4**).

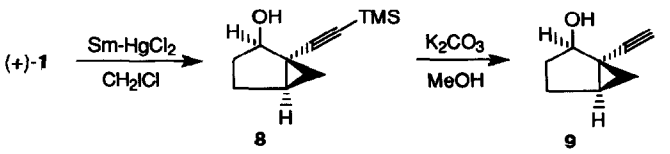
Because both of the acylation and the deacylation brought about clear-cut enantiotopical discrimination of the specific enantiomers giving rise enantiocomplementarily to the alcohol (**1**) and the acetate (**7**) as a 1:1 mixture, we next attempted to make these two approaches complementary so as to produce a single product being enantiomeric to each other. Thus, the racemic alcohol [(±)-**1**] was reacted with vinyl acetate as above in the presence of lipase PS in toluene. The reaction mixture, after removal of the insoluble material by filtration, was then subjected to the Mitsunobu reaction[9] using 1.6 equivalent of acetic acid in the presence of diisopropyl azodicarboxylate and triphenylphosphine to convert the unreacted (–)-alcohol [(–)-**1**] into the (+)-acetate [(+)-**7**] with inversion of configuration.[10] The reaction proceeded in the expected way with consumption of the alcohol to furnish the (+)-acetate [(+)-**7**] which after isolation was reduced with lithium aluminum hydride to give the (+)-alcohol [(+)-**1**] having an optical purity of 87.5% ee[8] in an excellent yield. Very fortunately, purification by a single recrystallization gave an optically pure (+)-**1** (≥99% ee[8]) in 73% overall yield from the racemic substrates [(±)-**1**]. Since the Mitsunobu reaction of the optically pure (–)-**1** (≥99% ee) under the same conditions was found to proceed but losing some extent of the original chiral integrity to afford the inverted acetate [(+)-**7**] having optical purity of 89% ee, the resulting stereochemical outcome above may be reconcilable.

The racemic acetate [(±)-**7**] , on the other hand, was treated with lipase PS as above in a phosphate buffer solution to give a mixture of the (+)-alcohol [(+)-**1**] and the unreacted (–)-acetate [(–)-**7**] . The mixture, without separation, was reacted with acetic acid in THF solution in the presence of diisopropyl azodicarboxylate and triphenylphosphine to convert the former [(+)-**1**] into the latter [(–)-**7**] with inversion of chirality. The single (–)-acetate [(–)-**7**] thus obtained was reductively deacylated with lithium aluminum hydride to give the (–)-alcohol [(–)-**1**] having optical purity of 89% ee[8] which on a single recrystallization afforded the optically pure (–)-alcohol [(–)-**1**] in ≥99% ee.[8] Overall yield of optically pure (–)-**1** from the racemic acetate (±)-**7** was 75% (**Scheme 5**).



Scheme 5

Stereochemistry of the products could be determined by transforming the (+)-alcohol [(+)-**1**] into the key intermediate (**9**) of 1,25-dihydroxycholecalciferol (**2**) *via* **8** by the established routes[1,3] which indicated unambiguously the (+)-enantiomer [(+)-**1**] to have *R*-configuration and thereby (–)-**1** to have *S*-configuration (**Scheme 6**).



Scheme 6

In conclusion, we have developed an enantiocomplementary preparation of optically pure 2-trimethylsilylethynyl-2-cyclopentenol (**1**) by homochiralization of the racemic precursors *via* sequential kinetic resolution using the same lipase and the Mitsunobu inversion without separation of the reaction intermediates. Utilization of the optically pure compounds for the construction of optically active materials as well as application of the present technology to the preparation of other chiral building blocks are currently under investigation.

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