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Highly Efficient Asymmetric Synthesis of Fluvirucinine A_1 via Zr-Catalyzed Asymmetric Carboalumination of Alkenes (ZACA)–Lipase-Catalyzed Acetylation Tandem Process

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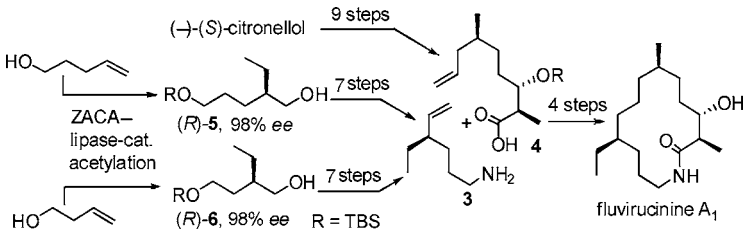
ABSTRACT



ZACA–lipase-catalyzed acetylation tandem process has been shown to proceed satisfactorily with either TBS-protected 4-penten-1-ol or 3-buten-1-ol to provide the corresponding enantiomerically pure (*R*)-2-ethyl-1-alkanols. Either (*R*)-5 or (*R*)-6 was converted to 3 in seven steps. The other fragment 4 was synthesized in nine steps from (−)-(*S*)-citronellol. Conversion of 3 and 4 into 99% pure fluvirucinine A_1 was achieved in four steps via amidation–ring closing metathesis, the overall yield in the longest linear sequence being 34% (13 steps).

Fluvirucinine A_1 (**1a**) is an aglycone of fluvirucin A_1 (**1b**), a member of antibiotics isolated from the fermentation broth of unidentified actinomycete strains exhibiting considerable inhibitory activity against influenza A virus.[1] It has recently been synthesized by Suh[2] in 22 linear steps in about 3% overall yield. Our recent development of the ZACA−lipase-catalyzed acetylation tandem process[3] permitting efficient and selective syntheses of enantiomerically pure 2-methyl-1-alkanols prompted us to see if this tandem process would be readily adaptable to the synthesis of 2-alkyl-1-alkanols, where the 2-alkyl group is ethyl or a higher primary alkyl group. If so, a convergent and highly efficient synthesis of **1a** via **2**, which in turn should be obtained from **3** and **4**, as outlined in a retrosynthetic analysis shown in Scheme 1 would be feasible.

The first crucial task of devising efficient and enantioselective routes to **3** was achieved in two similar manners, as summarized in Scheme 2. In Route I, commercially available 4-penten-1-ol was protected with TBSCl and imidazole in 98% yield and subjected to the ZACA reaction[4−6] with Et_3-Al (2 equiv), isobutylaluminoxane (IBAO, 1 equiv) generated

(1) (a) Naruse, N.; Tenmyo, O.; Kawauo, K.; Tomita, K.; Ohgusa, N.; Miyaki, T.; Konishi, M.; Oki, T. *J. Antibiot.* **1991**, *44*, 733−740. (b) Naruse, N.; Tsuno, T.; Sawada, Y.; Konishi, M.; Oki, T. *J. Antibiot.* **1991**, *44*, 741−755. (c) Naruse, N.; Konishi, M.; Oki, T.; Inouye, Y.; Kakisawa, H. *J. Antibiot.* **1991**, *44*, 756−761. (d) Tomita, K.; Oda, N.; Hoshino, Y.; Ohgusa, N.; Chikazawa, H. *J. Antibiot.* **1991**, *44*, 940−948.

(2) Suh, Y.-G.; Kim, S.-A.; Jung, J.-K.; Shin, D.-Y.; Min, K.-H.; Koo, B.-A.; Kim, H.-S. *Angew. Chem., Int. Ed.* **1999**, *38*, 3545−3547.

(3) Huang, Z.; Tan, Z.; Novak, T.; Zhu, G.; Negishi, E. *Adv. Synth. Catal.* **2007**, *349*, 539−545. ZACA stands for Zr-catalyzed asymmetric carboalumination of alkenes.

(4) (a) Kondakov, D.; Negishi, E. *J. Am. Chem. Soc.* **1995**, *117*, 10771−10772. (b) Kondakov, D.; Negishi, E. *J. Am. Chem. Soc.* **1996**, *118*, 1577−1578. (c) Huo, S.; Negishi, E. *Org. Lett.* **2001**, *3*, 3253−3256.

(5) (a) For the use of IBAO as a promotor, see: Huo, S.; Shi, J.; Negishi, E. *Angew. Chem., Int. Ed.* **2002**, *41*, 2141−2143. (b) For a seminal contribution on the use of promotors, such as methylaluminoxane (MAO) and H_2O, see: Wipf, P.; Ribe, S. *Org. Lett.* **2000**, *2*, 1713−1716.

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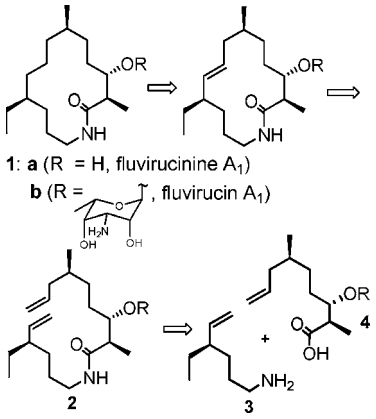
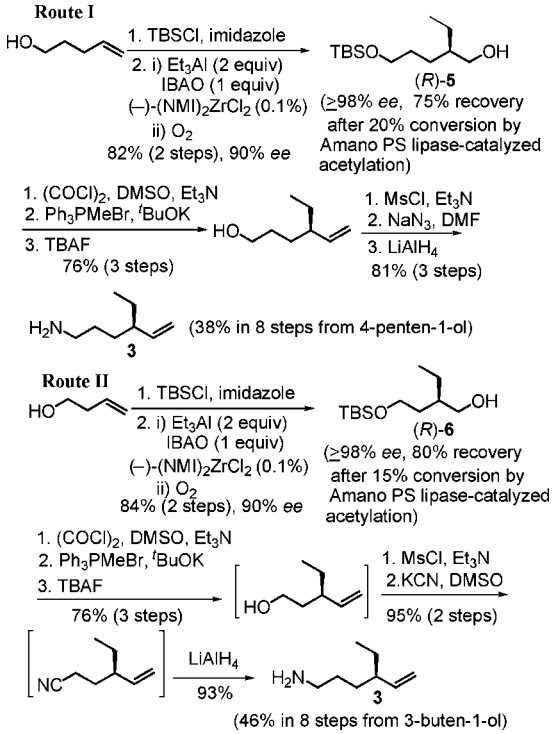
Scheme 1



in situ by treating $^{i}Bu_3Al$ with 1 molar equiv of H_2O, and just 0.1 mol % of (−)-$(NMI)_2ZrCl_2$. The crude product isolated in 82% yield was shown to be 90% ee or 95% *R* and purified by selective acetylation with vinyl acetate (5 equiv) and Amano PS lipase (30 mg/mmol) to give enantiomerically pure (≥98% ee) (*R*)-**5** in 75% recovery. The results clearly indicate that the ZACA−lipase-catalyzed acetylation tandem process promises to provide a very favorable route to a wide range of (*R*)-2-ethyl-1-alkanols. After six additional and conventional steps, including formation and reduction of an azide, (*R*)-**3** of ≥98% ee was obtained in 38% yield over eight steps from 4-penten-1-ol (Route I in Scheme 2). Similarly, 3-buten-1-ol (Aldrich) was converted to 4-TBS-protected (*R*)-2-ethyl-1,4-butanediol (**6**) of ≥98% ee in 67% yield in just two steps and one purification with vinyl acetate and Amano PS Lipase. Conversion of **6** into **3** also required six well-known steps, including cyanation and reduction with $LiAlH_4$ of the nitrile thus formed. Thus, (*R*)-**3** of ≥98% ee was produced in 46% yield over eight steps from 3-buten-1-ol. A somewhat higher product yield of 46% and the use of less expensive 3-buten-1-ol make Route II in Scheme 2 somewhat more attractive than Route I. It should also be noted that both **5** and **6** promise to serve as potentially versatile Et-branched difunctional chiral synthons.

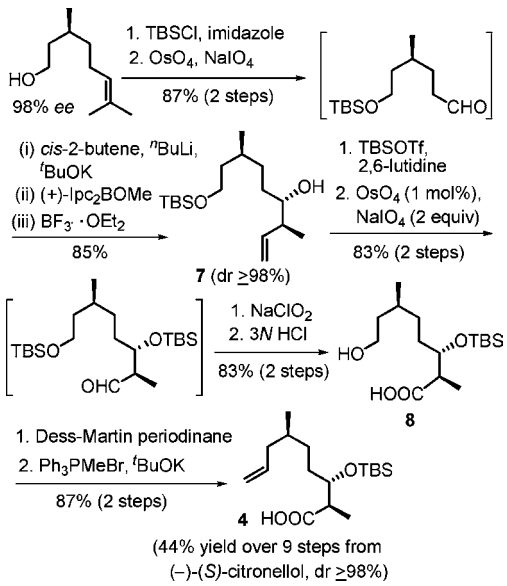
Preparation of the other key intermediate **4** via ZACA reaction of TBS-protected 3-buten-1-ol with Me_3Al in a manner similar to that employed in Route II in Scheme 2 is conceivable and was indeed considered first. In view of the ready availability of (−)-(*S*)-*β*-citronellol, however, its conversion into **4** (dr ≥98% by ^{13}C NMR) was performed in nine steps, including the Brown crotylboration[7] and OsO_4-

Scheme 2



catalyzed oxidative alkene cleavage[8] with $NaIO_4$ used twice. The whole transformation proceeded satisfactorily in 44% overall yield, as summarized in Scheme 3.

Scheme 3



Conversion of the two key intermediates **3** and **4** into a 14-membered lactam **9** was achieved in two steps in 83%

(6) For application of the ZACA reaction to the synthesis of deoxypolypropionates, see: (a) Negishi, E.; Tan, Z.; Liang, B.; Novak, T. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5782−5787. (b) Tan, Z.; Negishi, E. *Angew. Chem., Int. Ed.* **2004**, *43*, 2911−2914. (c) Magnin-Lachaux, M.; Tan, Z.; Liang, B.; Negishi, E. *Org. Lett.* **2004**, *6*, 1425−1427. (d) Novak, T.; Tan, Z.; Liang, B.; Negishi, E. *J. Am. Chem. Soc.* **2005**, *127*, 2838−2839. (e) Liang, B.; Novak, T.; Tan, Z.; Negishi, E. *J. Am. Chem. Soc.* **2006**, *128*, 2770−2771. (f) Zhu, G.; Negishi, E. *Org. Lett.* **2007**, *9*, 2771−2774.

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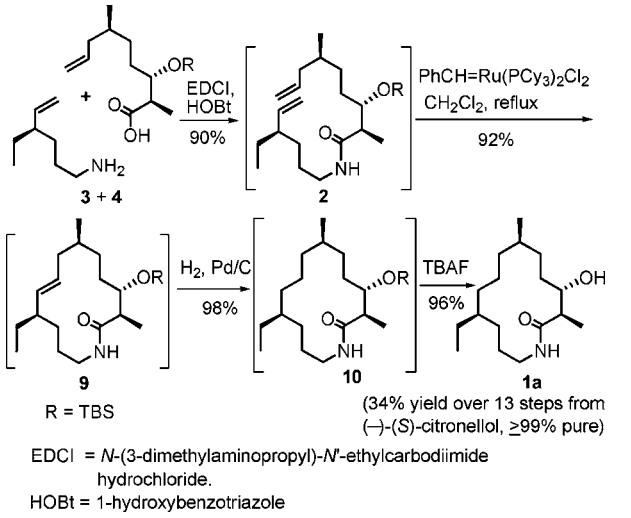
(8) (a) Pappo, R.; Allen, D. S., Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478−479. (b) Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett.* **2004**, *6*, 3217−3219.

Scheme 4



EDCI = *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride.
HOBt = 1-hydroxybenzotriazole

combined yield. Thus, amidation of **3** with **4** by the use of *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDCI) and 1-hydroxybenzotriazole (HOBt)[9] produced **2** in 90% yield, which was then subjected to the Ru-catalyzed ring closing metathesis (RCM)[10] with 10 mol % of PhCH=$Ru(PCy_3)_2Cl_2$ as a catalyst to produce the desired macrolactam **9** in 92% yield. Its hydrogenation over Pd/C (5%) followed by desilylation with TBAF furnished fluvirucinine A_1 (**1a**) in 94% yield over two steps (34% over 13 steps from (−)-(*S*)-*β*-citronellol) (Scheme 4). The ^1H and ^{13}C NMR spectra as well as the specific rotation $[\alpha]^{23}_D = +138.6$ (*c* 0.2, CH_3OH) are in good agreement with those reported in the literature.[1,2]

In summary, the ZACA reaction of TBS-protected 3-buten-1-ol or 4-penten-1-ol with Et_3Al, isobutylaluminoxane (IBAO), and 0.1 mol % of (−)-$(NMI)_2ZrCl_2$ proceeds in about 85% yield and in 90% ee. Furthermore, the crude product thus obtained can be readily purified by Amano PS lipase-catalyzed acetylation with vinyl acetate to give (*R*)-**5** or (*R*)-**6**, respectively, of ≥98% ee in 75−80% recovery. The ready access to enantiomerically pure (*R*)-**5** or (*R*)-**6** permits the preparation of (*R*)-**3** of ≥98% ee in 46 or 38% yield over eight steps from 3-buten-1-ol or 4-penten-ol, respectively. Another satisfactory, albeit conventional, preparation of isomerically pure **4** from (−)-(*S*)-*β*-citronellol in 44% yield over nine steps followed by a three-step conversion of **3** and **4** into fluvirucinine A_1 (**1a**) in 78% yield over four steps has provided **1a** of ≥99% isomeric purity in 34% overall yield in 13 steps from (−)-(*S*)-*β*-citronellol.

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Supporting Information Available: Experimental procedures and ^1H and ^{13}C NMR spectra of the reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

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