

Highly Efficient Asymmetric Synthesis of Fluvirucinine A₁ via Zr-Catalyzed Asymmetric Carboalumination of Alkenes (ZACA)–Lipase-Catalyzed Acetylation Tandem Process

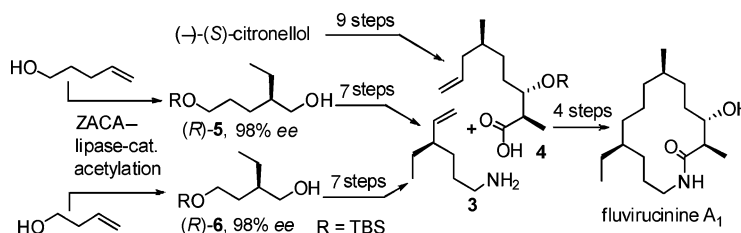
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ABSTRACT



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 A₁ was achieved in four steps via amidation–ring closing metathesis, the overall yield in the longest linear sequence being 34% (13 steps).

Fluvirucinine A₁ (**1a**) is an aglycone of fluvirucin A₁ (**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 Suh² in 22 linear steps in about 3% overall yield. Our recent development of the ZACA–lipase-catalyzed acetylation tandem process³ 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 Et₃-Al (2 equiv), isobutylaluminumoxane (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.

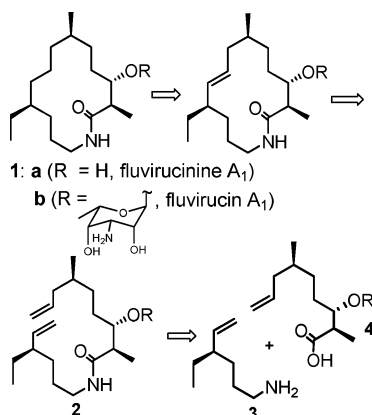
(2) Suh, Y.-G.; Kim, S.-A.; Jung, J.-K.; Shin, D.-Y.; Min, K.-H.; Koo, B.-A.; Kim, H.-S. *Angew. Chem., Int. Ed.* **1999**, *38*, 3545–3547.

(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 methylaluminumoxane (MAO) and H₂O, see: Wipf, P.; Ribe, S. *Org. Lett.* **2000**, *2*, 1713–1716.

Scheme 1



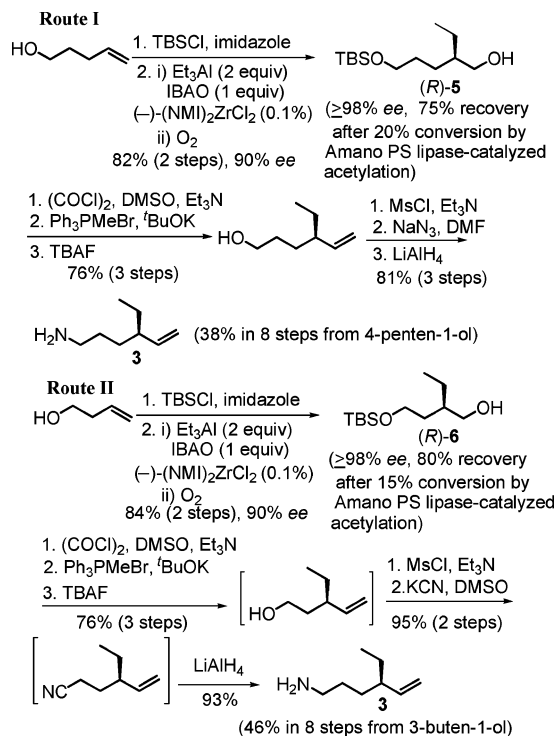
in situ by treating tBu_3Al with 1 molar equiv of H_2O , and just 0.1 mol % of $(-)-(S)\text{-}\beta\text{-citronellol}$, however, its conversion into **4** (dr $\geq 98\%$ by ^{13}C NMR) was performed in nine steps, including the Brown crotylboration⁷ and OsO_4 -

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 $(-)-(S)\text{-}\beta\text{-citronellol}$, however, its conversion into **4** (dr $\geq 98\%$ by ^{13}C NMR) was performed in nine steps, including the Brown crotylboration⁷ and OsO_4 -

(6) For application of the ZACA reaction to the synthesis of deoxy-polypropionates, 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.

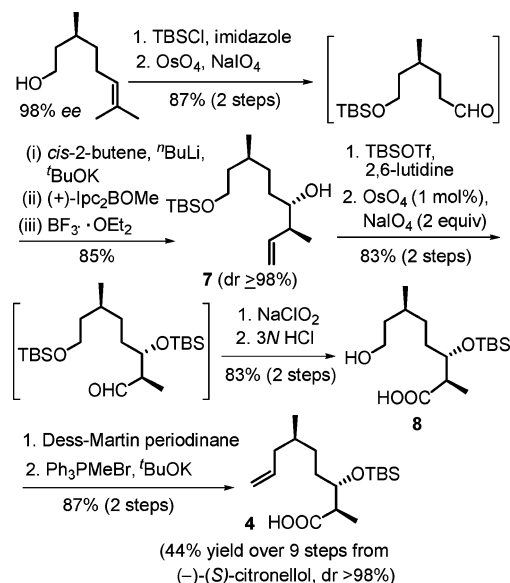
(7) (a) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919–5923. (b) Brown, H. C.; Jadhav, P. K.; Bhat, K. S. *J. Am. Chem. Soc.* **1988**, *110*, 1535–1538.

Scheme 2



catalyzed oxidative alkene cleavage⁸ with NaIO_4 used twice. The whole transformation proceeded satisfactorily in 44% overall yield, as summarized in Scheme 3.

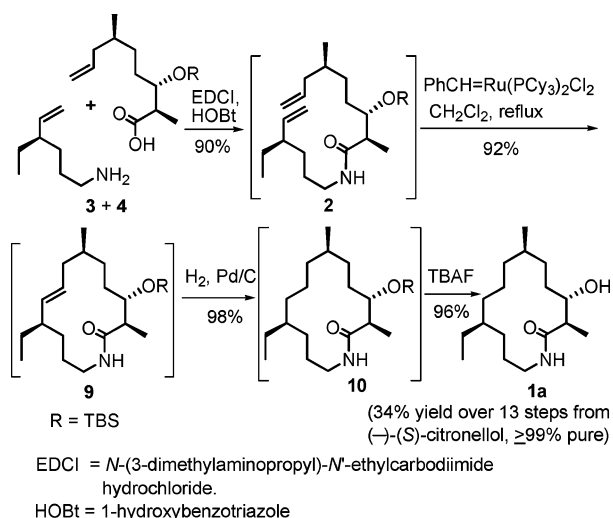
Scheme 3



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

(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



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(PCy₃)₂Cl₂ 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 A₁ (**1a**) in 94% yield over two steps (34% over 13 steps

(9) Sheehan, J. C.; Preston, J.; Cruickshank, P. A. *J. Am. Chem. Soc.* **1965**, *87*, 2492–2493.

(10) (a) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 5426–5427. (b) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446–452.

from (–)-(*S*)-β-citronellol) (Scheme 4). The ¹H and ¹³C NMR spectra as well as the specific rotation [α]_D²³ = +138.6 (*c* 0.2, CH₃OH) 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 Et₃Al, isobutylaluminumoxane (IBAO), and 0.1 mol % of (–)-(NMD)₂ZrCl₂ 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 A₁ (**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 ¹³C 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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