Published in final edited form as:
Org Lett. 2007 July 19; 9(15): 2771–2774. doi:10.1021/ol0707259.

Fully Reagent-Controlled Asymmetric Synthesis of (−)-Spongidepsin via the Zr-Catalyzed Asymmetric Carboalumination of Alkenes (ZACA Reaction)

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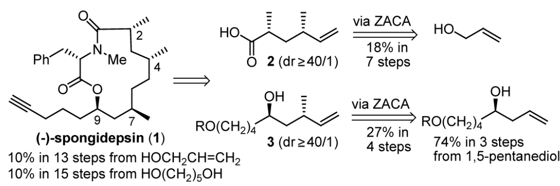
Abstract



The ZACA reaction has been shown to proceed satisfactorily with internally OH-substituted 1-alkenes, provided that the OH group is unprotected and non-allylic. This reaction was used for reagent-controlled asymmetric construction of 3. Allylic alcohol was converted to 2 in 7 steps via iterative ZACA processes and simple chromatography. (−)-Spongidepsin (1) was synthesized by using 2 and 3 through application of the esterification–amidation–ring closing metathesis protocol previously reported.

(−)-Spongidepsin (**1**), isolated from the Vanuatu marine sponge *Spongia* sp., displays cytotoxic and antiproliferative activities against J774.A1, HEK-293, and WEHI-164 cancer cell lines,[1] and its total syntheses and full stereochemical assignments were reported by Forsyth[2] and Ghosh[3] in 2004. More recently, Cossy[4] reported a synthesis featuring a diastereoselective crotylstannation of an α-chiral aldehyde, followed by mesylation and reduction with $LiAlH_4$. Our interest in the synthesis of **1** primarily stemmed from an excellent opportunity for demonstrating the high efficiency in a fully reagent-controlled asymmetric construction of the C1–C9 chiral fragment via recently developed Zrcatalyzed asymmetric carboalumination of alkenes,[5] ZACA reaction hereafter, used in conjunction with simple and ordinary chromatographic purification of 2,4-dimethyl-1-hydroxybutyl[5e-5i] and 2-methyl-1,4-dihydroxybutyl derivatives.

Herein, we report efficient and fully reagent-controlled asymmetric syntheses of the C1–C5 fragment (**2**) and the C6–C13 fragment (**3**) via ZACA reaction and their application to the synthesis of (−)-spongidepsin (**1**) by exploiting the esterification–amidation–ring closing metathesis[6] strategy employed in all three previous syntheses[2-4] (Scheme 1). The detailed schemes for the syntheses of the two key intermediates **2** and **3** are presented in Scheme 2 and 3, respectively. The synthesis of **2** was achieved via the previously reported two-step conversion of allyl alcohol into **4** via **5** in 71% yield and 82% ee,[5i] followed by one-pot

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Supporting Information Available: Experimental procedures and ^{1}H and ^{13}C NMR spectra for compounds **1-3**, **8-10**, **17-23**. This material is available free of charge via the Internet at http://pubs.acs.org.

ZACA–oxidation tandem process and chromatographic purification[5f] to give **6** in 24% overall yield (dr ≥ 40/1) from allyl alcohol (Scheme 2). Compound **6** was converted to **7** via Swern oxidation and Wittig olefination in 80% yield over 2 steps, and **7** was then converted to **2** via desilylation with TBAF, followed by PDC oxidation in 72% yield over 2 steps (18% over 7 steps).

The most distinguishing feature of this synthesis is the efficient and reagent-controlled asymmetric construction of **3** in 7 steps from inexpensive 1,5-pentanediol in 20% overall yield via Brown allylboration[7] to give **8** in 87% yield (74% over 3 steps), and ZACA reaction of **8** to give, after oxidation with O_2, **9** (dr = 3.5/1) in 73% yield (43% after chromatographic purification to dr = 40/1). Oxidation of **9** with $PhI(OAc)_2$ (BAIB) and TEMPO gave **10** in 88% yield, which was then reduced with DIBAL-H and olefinated by the Wittig reaction to give **3** in 73% yield (2 steps). Thus, **3** was obtained in 20% yield from 1,5-pentanediol over 7 steps (Scheme 3). In the Forsyth synthesis, a deliberate stereodivergent construction of the C7 asymmetric center was employed for the establishment of its stereochemistry,[2] while a substrate-controlled diastereoselective construction of the C7 or C9 asymmetric center requiring later Mitsunobu esterification[8] with inversion was used by Ghosh[3] and Cossy.[4] As elegant as these syntheses are, use of the stoichiometric quantitives of rather expensive chiral intermediates left some room for improvement.

We initially opted for the construction of >97% pure **11** as a potential intermediate for the synthesis of **1**, and prepared it in mere 5 steps from TBDPS-protected 3-butene-1-ol, one lipase-catalyzed acetylation, and one chromatographic purification, as recently reported[5k] (Scheme 4). As efficient as this synthesis was, it did not deal with a critically required construction of the C9 asymmetric center. Although the ZACA reaction of proximally oxygenated 1-alkenes, such as the parent allyl alcohol[5i] and homoallyl alcohol[5e] had been successfully developed, the corresponding reactions of the internally oxygenated derivatives remained to be developed. We therefore prepared several racemic ω-vinyl secondary alcohols and their derivatives, such as **12**–**15**, and examined their ZACA reaction. To our disappointment, neither an allylic alcohol (**12a**) nor its TBDPS-protected derivative (**12b**) gave the desired ZACA product in more than 2% yield. Similarly, a TBDPS-protected homoallyl alcohol (**13b**) failed to undergo the ZACA reaction. Fortunately, however, the parent alcohol (**13a**) gave the desired diol (**16**) in 75% yield. The results obtained with **13a** and **13b** provide yet another set of examples of the Zr-catalyzed carboalumination, which demonstrates the desirability of using unprotected alcohols along with the use of one additional equivalent of Me_3Al[5i] rather than their *O*-protetcted derivatives. The ZACA reaction of (2*S*)-5-hexen-2-ol (**14**) with (−)- and (+)-$Zr(NMI)_2Cl_2$[9] as a catalyst provided the desired products **17a** and **17b** in 78-79% yields. The diastereomeric ratio of 7.7/1 observed with (−)-$Zr(NMI)_2Cl_2$ is significantly higher than 4.5/1 observed with (+)-$Zr(NMI)_2Cl_2$. That the sense of asymmetric induction is the same as in the ZACA reaction of 1-hexene has been confirmed by converting the (2*R*,5*S*)-isomer (**17a**) into (2*R*)-2-methyl-1-hexanol by selective protection of the terminal hydroxyl group with TBDPSCl, mesylation of the other hydroxy group, reduction with $LiAlH_4$, and deprotection with TBAF, which yielded (2*R*)-2-methyl-1-hexanol (77% *ee*) exhibiting the identical behavior in analyses of ^1H NMR spectra as that displayed by the product obtained from 1-hexene with (−)-$Zr(NMI)_2Cl_2$ as the catalyst. These exploratory results are summarized in Scheme 5.

Having established that the ZACA reaction of internally hydroxylated 1-alkenes can proceed satisfactorily, as long as the OH group is unprotected and non-allylic, we then applied it to the synthesis of **3**, as shown in detail in Scheme 3. Although not used in our eventual synthesis of **1**, **15** having one less CH_2 group was also prepared and subjected to the ZACA reaction to produce **18a** and **18b**, as shown in eq 5 of Scheme 5.

The following procedure for the conversion of **8** into **9** is representative of the ZACA reaction of internally hydroxylated 1-alkenes. The starting alkenol (**8**) (1.91 g, 5 mmol) dissolved in 5 mL of CH_2Cl_2 was mixed with 1.0 mL (10 mmol) of Me_3Al in 5 mL of CH_2Cl_2 at −78 °C, and the mixture was warmed to 23 °C and stirred for 1 h to generate the Me_2Al-protected alkenol. In a separate reactor, 1.5 mL (15 mmol) of Me_3Al in 5 mL of CH_2Cl_2 was treated with 90 uL (5 mmol) of H_2O to partially convert Me_3Al to methylaluminoxane (MAO).[10] To this was added 167 mg (0.25 mmol) of (+)-$(NMI)_2ZrCl_2$. To a wine-red solution thus formed was added the Me_2Al-protected alkenol solution in CH_2Cl_2, and the resultant mixture was stirred overnight at 23 °C. After confirming the total consumption of the starting alkenol by GC, the mixture was treated at 0 °C with a stream of oxygen bubbled through at the rate of 5 mL per min for 1 h and further stirred at 23 °C for 6 h under O_2 atmosphere. It was quenched with 2 N NaOH, extracted with CH_2Cl_2, washed with saturated aqueous NH_4Cl and brine, dried over $MgSO_4$, and concentrated. After passing it through a short path column of silica gel using EtOAc as an eluent to remove metal-containing impurities, evaporation provided 1.51 g (73%) of the crude product, which essentially consisted of the desired product and its diastereoisomers (dr = 3.5/1). Purification by column chromatography (silica gel, 95/5–85/15 hexanes-EtOAc) provided 872 mg (42%) of the desired product (dr = 40/1, by ^{13}C NMR); $[\alpha]_D^{23}$= −7.5 (*c*, 2.1, $CHCl_3$).

The final assemblage of (−)-spongidepsin (**1**) summarized in Scheme 6 followed closely the strategy developed and demonstrated first by Ghosh[3] and employed recently by Cossy.[4] The final seven steps achieved in 54 % overall yield for the conversion of **19** into **1** confirm this part of the synthesis to be efficient and satisfactory, and the spectral data of **1** thus prepared are in full agreement with those reported previously.[4] The difference between this and the previous syntheses lies in the esterification of *N*-Boc-protected *N*-methylphenylalanine (**20**) with **3** to produce **19** employed in this study. The 89% yield observed for this conversion compares favorably with the Mitsunobu esterification proceeding in about 70% yield employed in the previous syntheses, which, in turn, was dictated by the use of 5-*epi*-**3** prepared via substrate-controlled diastereoselective construction of one or the other asymmetric carbon center.[3,4]

In summary, this work has established that the ZACA reaction[5] is satisfactorily applicable to internally hydroxy-substituted 1-alkenes, in which the OH group is unprotected and non-allylic. Although the extent of asymmetric induction is affected to some extents by the proximal hydroxy-bearing asymmetric carbon center, the reaction is nevertheless reagent-controlled in that the chirality of the newly generated asymmetric carbon center has so far been reliably predictable from the chirality of $Zr(NMI)_2Cl_2$, namely the use of (+)- and (−)-$Zr(NMI)_2Cl_2$ as catalysts leading to the formation of (*S*)- and (*R*)-2-methyl-1-alkylalanes, respectively. This development permits an efficient and fully reagent-controlled asymmetric construction of the C6–C13 fragment of (−)-spongidepsin (**1**), which has not previously been achieved. Together with the previously developed ZACA route to deoxypolypropionates[5e-5i] applied to the efficient and selective synthesis of the C1–C5 fragment (**2**), all three Me-branched asymmetric carbon centers were constructed in a catalytic and enantioface-selective manner through application of the ZACA reaction. Although 5-*epi*-**3** was used in two previous syntheses of **1**,[3,4] **3** was not. So, its applicability to the synthesis of **1** was demonstrated by mostly following the synthetic strategy previously established by other groups.[2-4]

The ZACA reaction of 1-alken-3-ols, except for the case of the parent allyl alcohol,[5i] still remains to be developed and highly desirable. In a more general vein, this study has once again pointed to the desirability of further improving the enantioselectivity of the ZACA reaction. At the current level of enantioselectivity, the ZACA reaction in some cases is limiting the yields of pure chiral products even though the ZACA-based methodology is fundamentally efficient, reasonably general, and potentially economical. Efforts along this line are currently in progress.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the National Institutes of Health (GM 36792), the National Science Foundation (CHE-0309613), and Purdue University for support of this research. We also thank Professor Arun K. Ghosh (Purdue University) for helpful discussion.

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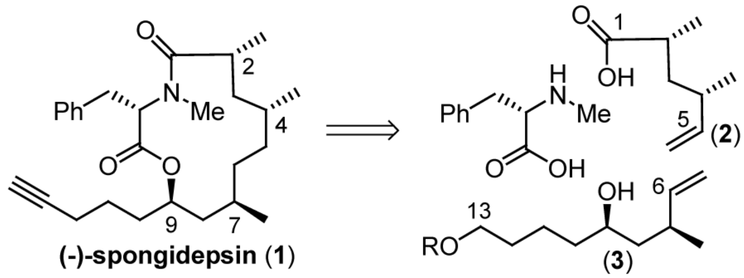
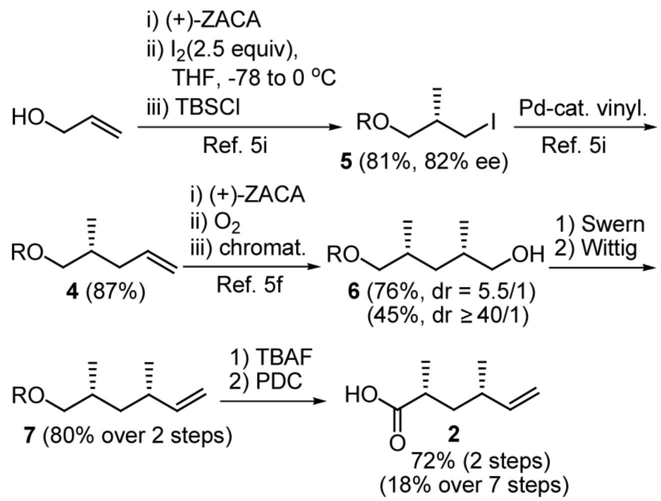
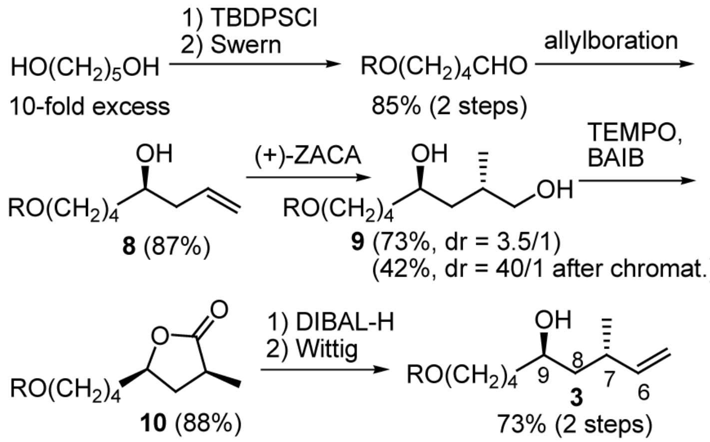


Scheme 1.



R = TBS. (+)-ZACA = Me_3Al (2.5 equiv), (+)-$(NMI)_2ZrCl_2$ (5 mol %), MAO (1.0 equiv), CH_2Cl_2, 23 °C. Pd-cat. vinyl. = i) ^{t}BuLi (2.5 equiv), then $ZnBr_2$ (1.0 equiv), ii) Pd(DPEphos)Cl_2 (5 mol %), DIBAL-H (10 mol %), CH_2=CHBr (3.0 equiv), THF-ether, 23 °C. chromat. = column chromatography (silica gel, 98/2 hexanes-EtOAc). Swern = $(COCl)_2$ (1.2 equiv), DMSO (2.0 equiv), Et_3N (2.2 equiv), CH_2Cl_2. Wittig = Ph_3P=CH_2 (2.0 equiv),THF, 0 to 23 °C. TBAF = tetrabutylammonium fluoride. PDC = pyridinium dichromate.

Scheme 2.



R = TBDPS. Swern = $(COCl)_2$ (1.2 equiv), DMSO (2.0 equiv), Et_3N (2.2 equiv), CH_2Cl_2. allylboration = allylmagnesium bromide (1.2 equiv), (-)-$Ipc_2B(OMe)$ (1.2 equiv), ether, -78 to 23 °C. (+)-ZACA = i) Me_3Al (4.0 equiv), (+)-$(NMI)_2ZrCl_2$ (5 mol %), H_2O (1.0 equiv), CH_2Cl_2, 23 °C, ii) O_2. BAIB = $PhI(OAc)_2$. TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy, Wittig = $Ph_3P{=}CH_2$ (2.0 equiv), THF, 0 °C, 3 h.

Scheme 3.

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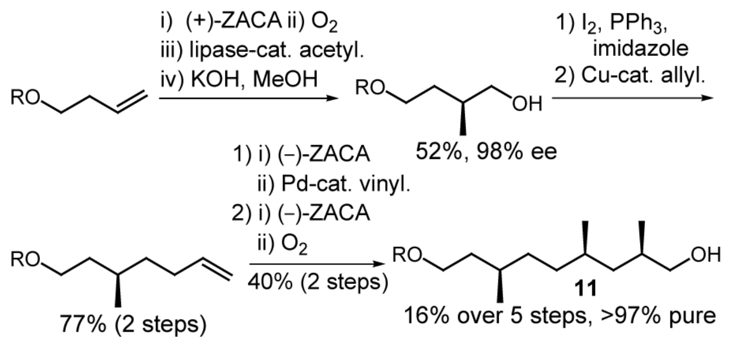
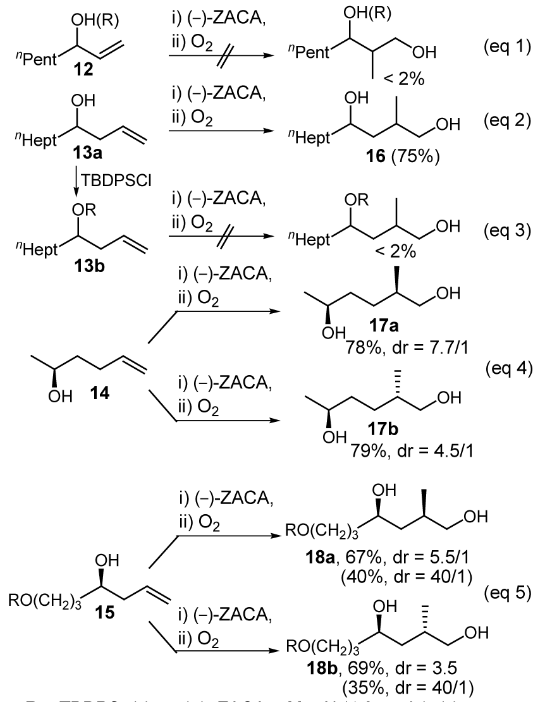


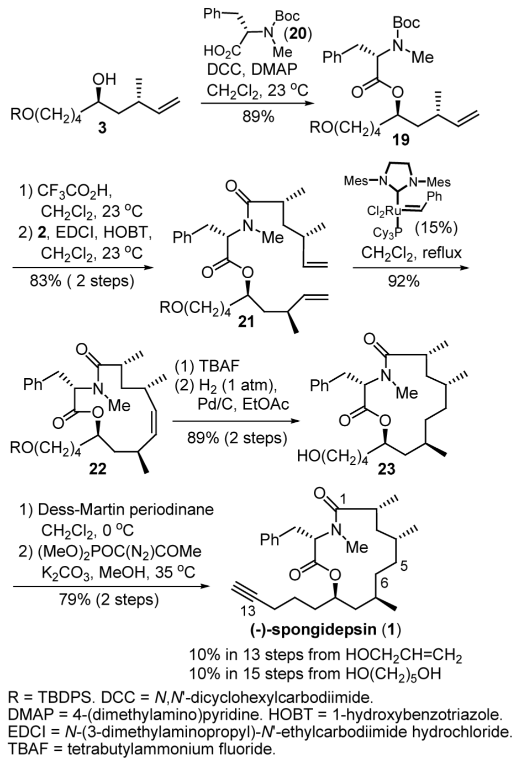
R = TBDPS. (+)- or (−)-ZACA = Me_3Al (2.5 equiv), (+)- or (−)-$(NMI)_2ZrCl_2$ (1 mol %), IBAO (0.5 equiv), CH_2Cl_2, 23 °C, 12 h. lipase-cat. acetyl. = Amano PS lipase (30 mg/mmol), CH_2=CHOAc (5 equiv), CH_2Cl_2, 23 °C. Cu-cat. allyl. = i) ^{t}BuLi (2.5 equiv), ii) CuBr (50 mol %), allyl bromide (1.2 equiv), ether, -78 to 23 °C. Pd-cat. vinyl. = $Zn(OTf)_2$ (1.0 equiv), CH_2=CHBr (6.0 equiv), Pd(DPEphos)Cl_2 (3 mol %), DIBAL-H (6 mol %), DMF-THF-ether, 23 °C, 12 h.

Scheme 4.



R = TBDPS. (−)- or (+)- ZACA = Me_3Al (4.0 equiv), (−)- or (+)-$(NMI)_2ZrCl_2$ (5 mol %), H_2O (1.0 equiv), CH_2Cl_2.

Scheme 5.



RO(CH2)4
3
OH
Ph
Boc
N (20)
HO2C
Me
DCC, DMAP
CH2Cl2, 23 °C
89%
19
1) CF3CO2H,
CH2Cl2, 23 °C
2) 2, EDCI, HOBT,
CH2Cl2, 23 °C
83% (2 steps)
21
Mes−N
N−Mes
Cl2Ru
Cy3P
(15%)
CH2Cl2, reflux
92%
22
(1) TBAF
(2) H2 (1 atm),
Pd/C, EtOAc
89% (2 steps)
HO(CH2)4
23
1) Dess-Martin periodinane
CH2Cl2, 0 °C
2) (MeO)2POC(N2)COMe
K2CO3, MeOH, 35 °C
79% (2 steps)
(-)-spongidepsin (1)
10% in 13 steps from HOCH2CH=CH2
10% in 15 steps from HO(CH2)5OH
R = TBDPS. DCC = N,N'-dicyclohexylcarbodiimide.
DMAP = 4-(dimethylamino)pyridine. HOBT = 1-hydroxybenzotriazole.
EDCI = N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride.
TBAF = tetrabutylammonium fluoride.

Scheme 6.