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COMMUNICATIONS

Published on Web 01/17/2007

Total Syntheses of Durgamone, Nakorone, and Abudinol B via Biomimetic Oxa- and Carbacyclizations

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A family of oxygenated triterpenoid marine natural products was recently isolated and structurally characterized from Red Sea sponges of the Axinellidae family *Ptilocaulis spiculifer*, including abudinols A and B (**1** and **2**), as well as oxidative degradation products durgamone (**3**) and nakorone (**4**, Figure 1).[1] The unique, highly condensed oxepane−cycloalkane skeleta of these terpenoids were not previously synthetically explored, but given our interest in *endo*-regioselective, biomimetic tandem oxacyclizations,[2] these structures attracted our interest for the potential of combining polyepoxide cyclizations with biomimetic polyene cyclizations.[3]

Our synthesis was inspired by a biosynthetic proposal for abudinols A and B (Figure 2).[4] Tandem oxa- and carbacyclizations of two adjacent epoxides and both alkenes of squalene tetraepoxide (**5**) would provide hypothetical intermediate **6** containing A, B, and C rings, and subsequent tandem cyclization with the remaining two epoxides would complete the biosynthesis of the abudinols. Abudinol A (**1**) corresponds to diepoxide cyclization to form a carbon−oxygen bond at C22, whereas the oxepane ring of abudinol B (**2**) would arise from carbon−oxygen bond formation at the more substituted C23.

The viabilities of these individual cyclization processes for durgamone (**3**) and nakorone (**4**) were tested via diepoxide cyclizations terminated by carbon nucleophiles. The diastereoselective synthesis of keto diepoxide (**8**) was achieved via enantioselective epoxidation methodology[5] (Scheme 1). Tandem cyclization of the enolsilane[6] diepoxide **9** (from the kinetic enolate of **8**) provided bicyclic ketone **10** corresponding to the D and E rings of abudinol B, with optimized conditions using substoichiometric TBSOTf in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP).[7] The structure and absolute stereochemistry of alcohol **11** were substantiated by X-ray diffraction analysis.[8] The enantiomer of durgamone (*ent*-**3**)[9] was then synthesized by zinc acetate-mediated stereospecific ring contraction[10] of the chloromesylate **12**.

For the synthesis of tricyclic *ent*-nakorone (*ent*-**4**), alkylation of the lithium anion of 1-farnesyl *p*-tolyl sulfone (**15**)[11] with 1-bromo-4-trimethylsilyl-2-butyne[12] afforded the triene-yne **16** (Scheme 2), which underwent regio- and stereoselective epoxidation[5] to provide diepoxide **17**, taking advantage of the electron-withdrawing effect of the allylic sulfone to prevent epoxidation of the proximal alkene. After palladium-catalyzed reductive desulfonylation,[13] the resulting enyne diepoxide **18** underwent TMSOTf-promoted cyclization with the propargylsilane nucleophile,[14] resulting in the tricyclic allene **19**, with crystallographic confirmation of structure[8] for the related alcohol **20**. Ozonolysis of the allene of **19** to the tricyclic ketone **21** was followed by desilylation to furnish *ent*-nakorone (*ent*-**4**),[9] which also corresponds to the A, B, and C rings of the abudinols.

We envisioned that abudinols would arise from cross-coupling of bicyclic ketones *ent*-**3** or **10** with tricyclic **21** by a process conceptually equivalent to retro-ozonolysis. Unfortunately, the sterically hindered ketone **21** as well as the enolizable nature of **10** were incompatible with several otherwise reliable transformations of this type.[15] However, palladium-catalyzed cross-coupling[16] effectively united the ABC and DE ring sectors (Scheme 3) through a one-pot sequence in which tricyclic enol triflate **22** was first

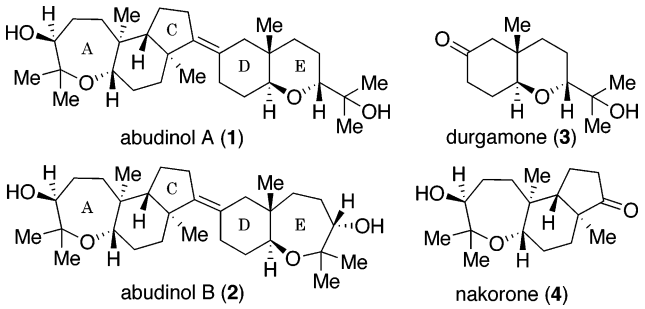


Figure 1. Abudinols A and B, and oxidative degradation natural products.

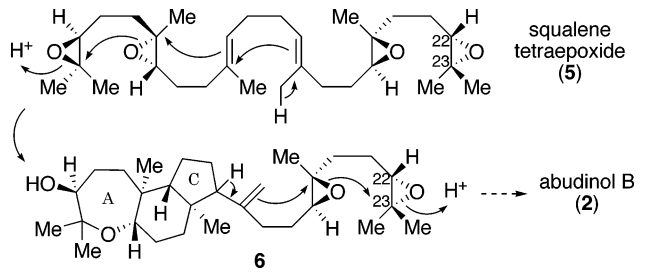
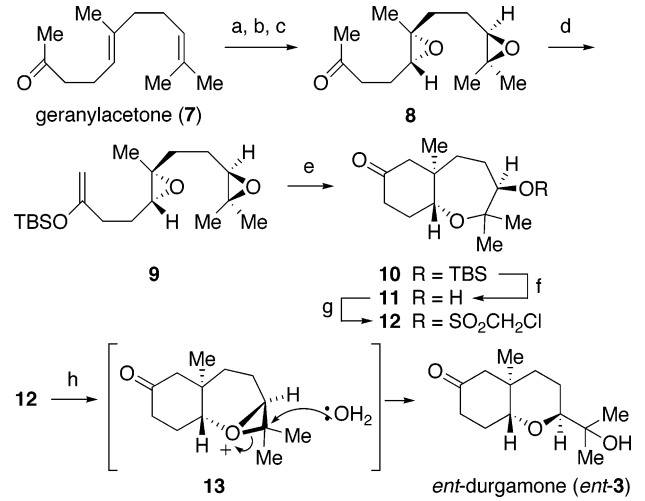


Figure 2. Proposed biosynthetic pathway for abudinols.

Scheme 1. Biomimetic Synthesis of *ent*-Durgamone (*ent*-**3**)[a]



[a] Conditions: (a) $NaBH_4$, MeOH, 0 °C (90% yield); (b) Shi catalyst (0.5 equiv), oxone, K_2CO_3, Na_2EDTA, DMM/MeCN/H_2O, 0 °C (8:1 dr, 95% yield); (c) SO_3−pyridine, DMSO, Et_3N, CH_2Cl_2, 0 °C (95% yield); (d) KHMDS, TBSCl, THF, −78 °C (87% yield); (e) TBSOTf (20 mol %), DTBMP (20 mol %), CH_2Cl_2, −78 °C (60% yield); (f) Bu_4NF, THF (99% yield); (g) $ClSO_2CH_2Cl$, 2,6-lutidine, CH_2Cl_2; (h) $Zn(OAc)_2$, HOAc/H_2O, 50 °C (50% yield).

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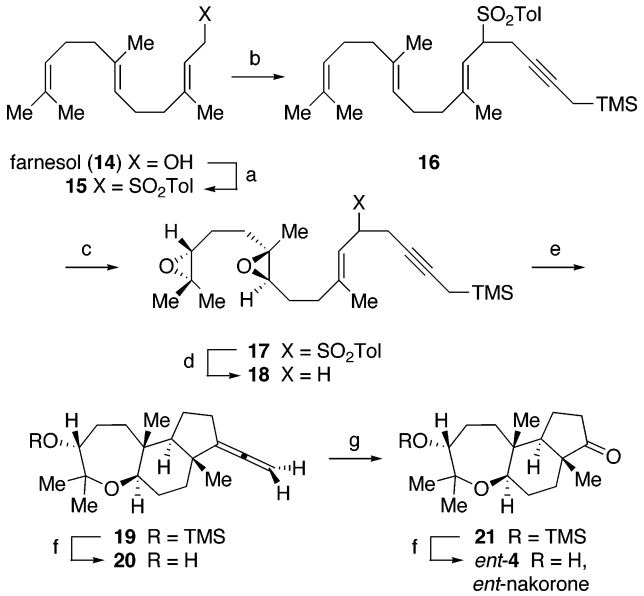
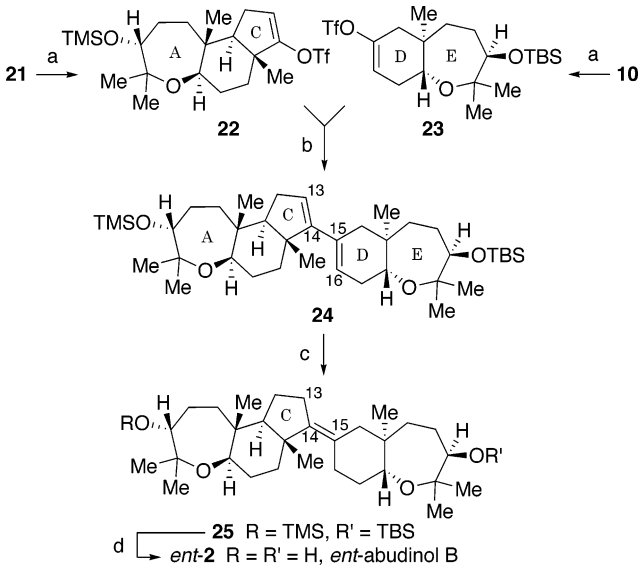
10.1021/ja068826+ CCC: $37.00

Scheme 2. Biomimetic Synthesis of *ent*-Nakorone (*ent*-**4**)[a]



[a] Conditions: (a) Ph_3P, NBS, THF, 0 °C; then cat. Bu_4NI, $NaSO_2Tol$ (99% yield); (b) *n*-BuLi, THF, −78 to −40 °C; then 1-bromo-4-trimethylsilyl-2-butyne, −78 to 20 °C (92% yield); (c) Shi catalyst (0.5 equiv), oxone, K_2CO_3, Na_2EDTA, DMM/MeCN/H_2O, 0 °C (>20:1 dr, 76% yield); (d) $Cl_2Pd(dppp)$ (10 mol %), $LiEt_3BH$, THF, 0 °C (71% yield); (e) TMSOTf (20 mol %), DTBMP (20 mol %), CH_2Cl_2, −78 °C (75% yield); (f) Bu_4NF, THF (99% yield for **20** and for *ent*-**4**); (g) O_3, CH_2Cl_2, −78 °C; then Me_2S, −78 to 20 °C (88% yield).

Scheme 3. Cross-Coupling Synthesis of *ent*-Abudinol B (*ent*-**2**)[a]



[a] Conditions: (a) KHMDS, THF, −78 °C, then $PhNTf_2$, −78 °C (95% yield for **22** and for **23**); (b) **22**, $Cl_2Pd(PPh_3)_2$ (6 mol %), Ph_3P (12 mol %), PhOK (1.5 equiv), bis(neopentylglycolato)diboron (1.1 equiv), toluene, 50 °C; then **23** (1.06 equiv), $Cl_2Pd(dppf)$ (5 mol %), wet K_3PO_4 (4.2 equiv), DMF, 80 °C (70% yield); (c) 5 wt % Pd−C (10 mol %), toluene, H_2 (1 atm), 0 °C (**25**, 30% yield, plus 50% yield of C13−C14 alkene isomer); (d) Bu_4NF (10 equiv), THF, 60 °C (84% yield).

converted into the vinyl boronate by palladium catalysis, and then coupled with bicyclic enol triflate **23** in the presence of $Cl_2Pd(dppf)$ and wet K_3PO_4, to provide pentacyclic diene **24** in good yield.[17] The drawback of this coupling was that hydrogenation of diene **24** was not regioselective, but palladium-catalyzed heterogeneous hydrogenation in toluene[18] provided the bis-silyl ether of abudinol B **25**, along with a substantial amount of the regioisomeric C13−C14 alkene. Desilylation of **25** provided the structure corresponding to *ent*-abudinol B (*ent*-**2**).[9] The alkene geometry and all other structural aspects of our synthetic material were conclusively confirmed by crystallographic analysis of **25**.[8]

In conclusion, cascade cyclizations of diepoxides tethered to enolsilane and to ene-propargylsilane have been developed and applied to the efficient, potentially biomimetic syntheses of several structurally related terpenoid natural product structures. Ongoing explorations include the possibility of direct formation of abudinols and other oxacyclic triterpenoid natural products from polyepoxide substrates similar to squalene tetraepoxide (**5**).

Acknowledgment. This research was supported by the U.S. National Science Foundation (CHE-9982400, CHE-0516793). We also acknowledge the use of shared instrumentation provided by grants from NSF and NIH. We thank Prof. Yoel Kashman (Tel-Aviv University) for his correspondence during the course of our investigations, including spectra of nakorone and abudinol B.

Supporting Information Available: Detailed experimental procedures and characterization (^1H and ^{13}C NMR, HRMS, IR) for all synthetic compounds, crystallography data for compounds **11**, **20**, and **25**, and spectral comparisons of synthetic compounds with naturally derived materials. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) BF_3−Et_2O provided a mixture of silyl ether **10** and the corresponding alcohol **11** in 40% combined yield, whereas Me_2AlCl or TBSOTf favored formation of the silyl ether **10**.
(8) See Supporting Information for details on the crystallographic analyses.
(9) We observed substantial differences in optical rotations for synthetic *ent*-**2**, *ent*-**3**, and *ent*-**4** when compared with reported values for the corresponding natural products **2**, **3**, and **4**. However, spectroscopic data for our synthetic compounds are in good agreement with the natural products (see Supporting Information).
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JA068826+