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A Concise Catalytic Route to the Marine Sesquiterpenoids (–)-Clavukerin A and (–)-Isoclavukerin A

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Dedicated to Professor Günter Domschke on the occasion of his 80th birthday

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Using a combined organocatalytic/metal-catalyzed strategy, the enantiopure title hydroazulenes were prepared in only four steps from (*S*)- and (*R*)-citronellal, respectively. A catalyst-controlled diastereoselective Michael addition of these aldehydes to methyl vinyl ketone followed by chemoselective dibromoolefination and one-pot Wittig olefination/alkyne formation afforded the key dienynes that underwent regioselective domino metathesis to yield the target natural products.

Introduction

The trisnorsesquiterpenes (–)-clavukerin A (**1a**)[1] and (–)-isoclavukerin A (**1b**)[2] were isolated from the soft coral *Clavularia koellikeri* next to the cytotoxic cycloheptenones (+)-clavularin A (**2a**)[3,4] and (–)-clavularin B (**2b**)[3,5] during a search for biologically active substances from marine sources (Figure 1). Because **1a** has already been converted into **2a**,[6a] which can be epimerized to give **2b**,[3] a synthesis of (–)-clavukerin A (**1a**) would also constitute a formal synthesis of clavularins **2a** and **2b**. Hydroazulenes **1a** and **1b** have often been used as testing ground for novel synthetic methods and strategies.[6–9] In this context, several enantioselective syntheses have already been reported for (–)-clavukerin A (**1a**).[7] The most efficient one commenced with limonene oxide to furnish **1a** in nine steps with a good overall yield of 34%.[7c] So far, only two enantioselective syntheses have been published for (–)-isoclavukerin A (**1b**).[7g,8] However, these synthetic routes required at least ten steps and afforded natural product **1b** only in low[7g] to moderate[8] overall yield.

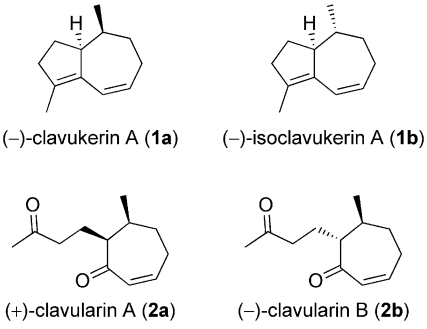

Figure 1. Natural products from the soft coral *Clavularia koellikeri*.

Results and Discussion

We thought that a combined organocatalytic/metal-catalyzed strategy might provide rapid access to both hydroazulenes **1a** and **1b** in enantiopure form (Scheme 1). Domino metathesis[10,11] of acyclic dienynes **3a** or **3b** was envisioned to lead directly to the target bicyclic 1,3-dienes **1a** or **1b**, respectively. In order to achieve selectivity with respect to the handedness of cyclization – from left to right or from right to left – we only added a CH_2 group on the left in a retrosynthetic fashion, while we provided a higher degree of substitution for the olefin on the right by adding an isopropylidene unit. The first intermolecular cycloaddition with a metal carbene complex was then expected to take place preferentially on the less highly substituted olefin to give the desired hydroazulene eventually.[10,11] The terminal alkene and the alkyne of **3a** and **3b** were supposed to originate from elaboration of 1,5-dicarbonyl compounds **4a** or **4b**, which in turn can be derived from (*S*)-citronellal (**5a**) or (*R*)-citronellal (**5b**), respectively, as commercially available starting materials by asymmetric organocatalytic Michael addition to methyl vinyl ketone (MVK).[12,13]

We started our investigations with (*S*)-citronellal (**5a**) that was added to MVK (**7**) in the presence of proline-derived organocatalyst **8** and catechol **9** as a co-catalyst (Scheme 2).[13,14] Using 20 mol-% of catalyst **8** at low tem-

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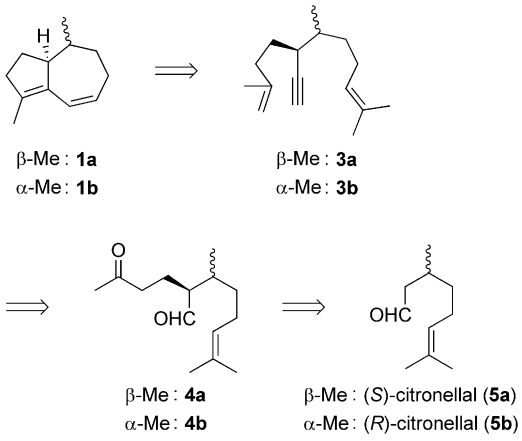
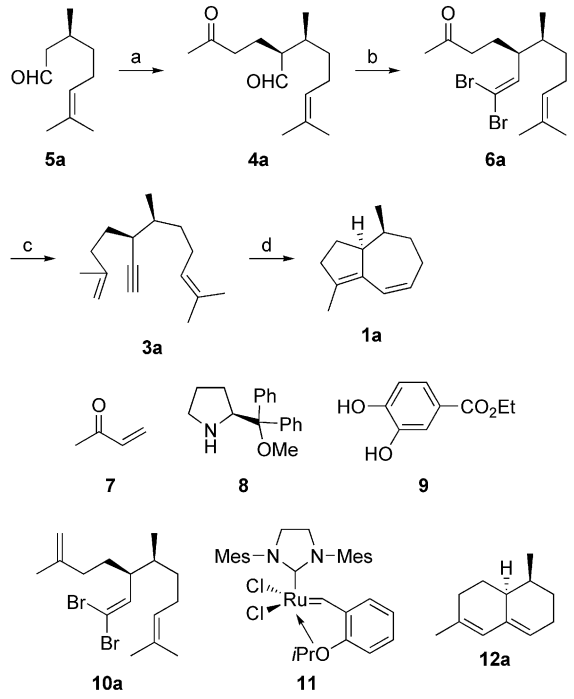


Scheme 1. Retrosynthetic analysis of **1a** and **1b**.

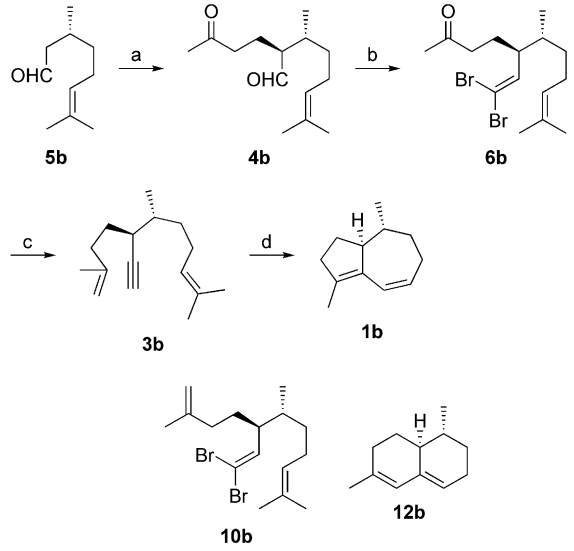
perature, a 90% yield of desired keto aldehyde **4a** was obtained with a catalyst-controlled diastereoselectivity of 18:1. The catalyst loading could be reduced to 1 mol-% of **8** without a significant change in stereoselectivity. However, the yield of **4a** then dropped to 72% even after 4 d at room temperature. A chemoselective dibromoolefination of **4a** as a prelude to alkyne formation[15] left the ketone carbonyl untouched. Much to our surprise, treatment of resultant ketone **6a** with an excess amount of methylene(triphenyl)-phosphorane in benzene at reflux not only caused methylenation of the ketone, but it also converted intermediate dibromoolefin **10a**[16] into halogen-free acetylene **3a**. Although the mechanism of this reaction is not entirely clear,[17,18] this one-pot process directly provided us with the requisite substrate for the crucial domino metathesis. Whereas neither the Grubbs I nor the Grubbs II catalyst effected dienyne metathesis, application of phosphane-free Hoveyda–Blechert catalyst **11**[19] in refluxing toluene brought about the desired transformation of **3a** under an ethylene atmosphere.[20] (–)-Clavukerin A (**1a**), identical to the natural product in all respects, was isolated in 53% yield after straightforward chromatographic separation from minor byproduct **12a**[21] on silica gel impregnated with silver nitrate.[22]

Because our combined organocatalytic/metal-catalyzed strategy provided (–)-clavukerin A (**1a**) in only four steps with a good overall yield of 35%, we decided also to make (–)-isoclavukerin A (**1b**) along these lines (Scheme 3). Now we commenced with (*R*)-citronellal (**5b**) that was added to MVK (**7**) under the conditions already applied for the corresponding reaction of **5a** to give keto aldehyde **4b** in 87% yield with 14:1 *dr*.[13,14] As before, catalyst loading could be reduced to 1 mol-% of **8** without altering the stereoselectivity, but then the yield decreased to 48% even after 10 d at room temperature. Chemoselective dibromoolefination of **4b** to give **6b** followed by one-pot Wittig olefination/alkyne formation and domino metathesis of resultant dienyne **3b** with Hoveyda–Blechert catalyst **11** under an ethylene atmosphere afforded (–)-isoclavukerin A (**1b**), identical to the natural product in all respects, in 55% yield after facile



Scheme 2. Synthesis of (–)-clavukerin A (**1a**). Reagents and conditions: (a) **7**, **8** (20 mol-%), **9** (20 mol-%), 3 °C, 90% (18:1 *dr*); (b) CBr_4, Ph_3P, CH_2Cl_2, 0 °C to r.t., 94%; (c) $Ph_3P{=}CH_2$ (4 equiv.), benzene, reflux, 78% **3a**, 18% **10a**; (d) **11** (4 mol-%), $CH_2{=}CH_2$ (1 atm), toluene, reflux, 53% **1a**.

chromatographic separation[22] from minor byproduct **12b**.[21] Thus, again only four steps were needed with our route to secure a much better overall yield of natural product **1b** compared to the published multistep sequences.[7g,8]



Scheme 3. Synthesis of (–)-isoclavukerin A (**1b**). Reagents and conditions: (a) **7**, **8** (20 mol-%), **9** (20 mol-%), 3 °C, 87% (14:1 *dr*); (b) CBr_4, Ph_3P, CH_2Cl_2, 0 °C to r.t., 92%; (c) $Ph_3P{=}CH_2$ (4 equiv.), benzene, reflux, 78% **3b**, 12% **10b**; (d) **11** (4 mol-%), $CH_2{=}CH_2$ (1 atm), toluene, reflux, 55% **1b**.

Conclusions

In conclusion, we have developed short catalytic routes to the marine sesquiterpenoids (–)-clavukerin A (**1a**) and (–)-isoclavukerin A (**1b**). Application of this technology toward the synthesis of structurally more complex hydroazulenes is currently under investigation.

Experimental Section

Domino Metathesis of Dienynes 3a and 3b: Hoveyda–Blechert catalyst **11**[19,23] (39 mg, 0.062 mmol) and dry toluene (40 mL) were placed under an ethylene atmosphere in a two-necked, 250-mL reactor equipped with a rubber septum, a magnetic stirring bar, a reflux condenser, and a rubber tube on top of the condenser. The green solution was stirred at room temperature for 15 min, and then a solution of dienyne **3a** (340 mg, 1.56 mmol) in dry toluene (10 mL) was added by syringe. The resulting mixture was heated at reflux for 3 h at 125 °C bath temperature. After cooling to room temperature, the reactor was opened, the reaction mixture was transferred into a 250-mL flask, and the volatiles were removed in vacuo. The residue was transferred with a small amount of pentane to a silica gel column (d 2 cm, h 40 cm). Elution with pentane gave a mixture (R_f = 0.51) of isomeric cyclic products as a colorless oil in 91% yield. This mixture was transferred to a column with silica gel impregnated with silver nitrate[22] (d 3 cm, h 17 cm). Elution with pentane/Et_2O, 7:1 (control using TLC plates modified with silver nitrate)[22] afforded two fractions: isomerized hexalin **12a** (R_f = 0.70, 68 mg, 27%) and (–)-clavukerin A (**1a**) (R_f = 0.35, 134 mg, 53%) as the major product. Data for **1a**: $[\alpha]_D^{24}$ = –60.0 (c = 0.55, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3009, 2908, 2870, 2832, 1644, 1607, 1457, 1437, 1381, 1149, 779, 750, 713 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.75 (d, J = 6.9 Hz, 3 H), 1.51–1.60 (m, 1 H), 1.62–1.69 (m, 1 H), 1.72–1.79 (m, 4 H), 1.85–1.94 (m, 2 H), 2.24–2.32 (m, 4 H), 2.85–2.92 (m, 1 H), 5.51–5.56 (m, 1 H), 6.20 (d, J = 12.2 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.4 (CH_3), 14.5 (CH_3), 26.7 (CH_2), 27.2 (CH_2), 34.2 (CH), 34.4 (CH_2), 37.8 (CH_2), 54.5 (CH), 123.8 (CH), 128.8 (CH), 134.9 (C), 138.8 (C) ppm. GC–MS (EI): m/z (%) = 162 (68) $[M]^+$, 147 (70) $[M - CH_3]^+$, 133 (27), 119 (40), 105 (100), 91 (72), 79 (39).

Using the same experimental procedure, treatment of dienyne **3b** (246 mg, 1.13 mmol) with Hoveyda–Blechert catalyst **11** (28 mg, 0.045 mmol) furnished isomerized hexalin **12b** (R_f = 0.70, 60 mg, 33%) and (–)-isoclavukerin A (**1b**) (R_f = 0.35, 101 mg, 55%) as the major product. Data for **1b**: $[\alpha]_D^{24}$ = –100.0 (c = 0.58, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3012, 2951, 2909, 2858, 2828, 1644, 1606, 1456, 1436, 1375, 1133, 779, 738, 713 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 0.95 (d, J = 6.4 Hz, 3 H), 1.24–1.37 (m, 3 H), 1.68–1.73 (m, 4 H), 1.99–2.11 (m, 2 H), 2.20–2.37 (m, 4 H), 5.63–5.66 (m, 1 H), 6.23 (d, J = 11.8 Hz, 1 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.7 (CH_3), 22.0 (CH_3), 29.3 (CH_2), 30.3 (CH_2), 36.69 (CH_2), 36.73 (CH_2), 39.9 (CH), 55.7 (CH), 124.2 (CH), 129.2 (CH), 136.6 (C), 138.6 (C) ppm. GC–MS (EI): m/z (%) = 162 (61) $[M]^+$, 147 (67) $[M - CH_3]^+$, 133 (24), 119 (40), 105 (100), 91 (78), 79 (38).

Both hydroazulenes **1a** and **1b** are rather labile compounds and should be stored at –20 °C with exclusion of oxygen.

Supporting Information (see footnote on the first page of this article): Experimental procedures and ^1H and ^{13}C NMR spectra for compounds **4a**, **6a**, **3a**, **10a**, **1a**, **4b**, **6b**, **3b**, **10b**, **1b**; ^1H NMR spectra of the mixtures **1a/12a** and **1b/12b**.

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[1] M. Kobayashi, B. W. Son, M. Kido, Y. Kyogoku, I. Kitagawa, *Chem. Pharm. Bull.* **1983**, *31*, 2160–2163.
[2] T. Kusumi, T. Hamada, M. Hara, M. O. Ishitsuka, H. Ginda, H. Kakisawa, *Tetrahedron Lett.* **1992**, *33*, 2019–2022.
[3] M. Endo, M. Nakagawa, Y. Hamamoto, T. Nakanishi, *J. Chem. Soc., Chem. Commun.* **1983**, *322–323*, 980.
[4] a) R. Tamura, K. Watabe, N. Ono, Y. Yamamoto, *J. Org. Chem.* **1993**, *58*, 4471–4472; b) H. Weinmann, E. Winterfeldt, *Synthesis* **1995**, 1097–1101.
[5] K. Hiroya, H. Zhang, K. Ogasawara, *Synlett* **1999**, 529–532.
[6] a) S. K. Kim, C. S. Pak, *J. Org. Chem.* **1991**, *56*, 6829–6832; b) I. Shimizu, T. Ishikawa, *Tetrahedron Lett.* **1994**, *35*, 1905–1908; c) J. C. Friese, S. Krause, H. J. Schäfer, *Tetrahedron Lett.* **2002**, *43*, 2683–2685; d) W. Li, X. Liu, X. Zhou, C.-S. Lee, *Org. Lett.* **2010**, *12*, 548–551.
[7] a) M. Asaoka, T. Kosaka, H. Itahana, H. Takei, *Chem. Lett.* **1991**, 1295–1298; b) T. Honda, H. Ishige, H. Nagase, *J. Chem. Soc. Perkin Trans. 1* **1994**, 3305–3310; c) E. Lee, C. H. Yoon, *Tetrahedron Lett.* **1996**, *37*, 5929–5930; d) A. Alexakis, S. March, *J. Org. Chem.* **2002**, *67*, 8753–8757; e) E. L. Grimm, J.-L. Methot, M. Shamji, *Pure Appl. Chem.* **2003**, *75*, 231–234; f) G. Blay, B. Garcia, E. Molina, J. R. Pedro, *J. Nat. Prod.* **2006**, *69*, 1234–1236; g) A. Srikrishna, V. H. Pardeshi, G. Satyanarayana, *Tetrahedron: Asymmetry* **2010**, *21*, 746–750.
[8] B. M. Trost, R. I. Higuchi, *J. Am. Chem. Soc.* **1996**, *118*, 10094–10105.
[9] Recent review on hydroazulene synthesis: D. A. Foley, A. R. Maguire, *Tetrahedron* **2010**, *66*, 1131–1175.
[10] Recent reviews: a) M. Mori, *Materials* **2010**, *3*, 2087–2140; b) M. Mori, *Adv. Synth. Catal.* **2007**, *349*, 121–135.
[11] See also: a) F.-D. Boyer, I. Hanna, *J. Organomet. Chem.* **2006**, *691*, 5181–5188; b) F.-D. Boyer, I. Hanna, *Eur. J. Org. Chem.* **2006**, 471–482.
[12] Y. Chi, S. H. Gellman, *Org. Lett.* **2005**, *7*, 4253–4256.
[13] K. C. Nicolaou, T. R. Wu, D. Sarlah, D. M. Shaw, E. Rowcliffe, D. R. Burton, *J. Am. Chem. Soc.* **2008**, *130*, 11114–11121.
[14] For Michael addition of **5a** and **5b** to **7** in the presence of an achiral amine catalyst, see: a) H. Hagiwara, N. Komatsubara, H. Ono, T. Okabe, T. Hoshi, T. Suzuki, M. Ando, M. Kato, *J. Chem. Soc. Perkin Trans. 1* **2001**, 316–322; b) H. Hagiwara, T. Okabe, H. Ono, V. P. Kamat, T. Hoshi, T. Suzuki, M. Ando, *J. Chem. Soc. Perkin Trans. 1* **2002**, 895–900.
[15] E. J. Corey, P. L. Fuchs, *Tetrahedron Lett.* **1972**, *13*, 3769–3772.
[16] Treatment of **10a** with methylene(triphenyl)phosphorane (3 equiv.) in benzene at reflux for 3 h yielded 75% **3a** next to 7% recovered **10a**.
[17] For conversion of a 1,1-dibromoolefin to a bromoalkyne with methylene(triphenyl)phosphorane, see: W. H. Okamura, G.-D. Zhu, D. K. Hill, R. J. Thomas, K. Ringe, D. B. Borchardt, A. W. Norman, L. J. Mueller, *J. Org. Chem.* **2002**, *67*, 1637–1650.
[18] For generation of halogen-free terminal alkynes as minor products upon treatment of 1,1-dibromoolefins bearing aromatic substituents with methylene(triphenyl)phosphorane (3 equiv.), see: H. J. Bestmann, H. Frey, *Liebigs Ann. Chem.* **1980**, 2061–2071.
[19] a) S. B. Garber, J. S. Kingsbury, B. L. Gray, A. H. Hoveyda, *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179; b) S. Gessler, S. Randl, S. Blechert, *Tetrahedron Lett.* **2000**, *41*, 9973–9976.
[20] G. C. Lloyd-Jones, R. G. Margue, J. G. de Vries, *Angew. Chem.* **2005**, *117*, 7608–7613; *Angew. Chem. Int. Ed.* **2005**, *44*, 7442–7447.

[21] Structures **12a** and **12b** were assigned on the basis of NMR spectroscopic and GC–MS analyses of the crude product mixtures **1a/12a** (ca. 2:1, 91%) and **1b/12b** (ca. 2:1, 91%) prior to purification of **1a** and **1b**, as compounds **12** isomerized during chromatography. Hexalins **12** would result from an initiating intermolecular attack of a ruthenium carbene complex on the more highly substituted olefin of dienynes **3a** and **3b**.[10,11]

[22] T.-S. Li, J.-T. Li, H.-Z. Li, *J. Chromatogr. A* **1995**, *715*, 372–375.

[23] Preparation according to: K. Grela, S. Harutyunyan, A. Michrowska, *Angew. Chem.* **2002**, *114*, 4210–4212; *Angew. Chem. Int. Ed.* **2002**, *41*, 4038–4040.

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