Pergamon

Tetrahedron Letters 43 (2002) 367–369

TETRAHEDRON LETTERS

Synthesis of montiporynes A and B†

Traci J. Speed and Dasan M. Thamattoor*

Department of Chemistry, Colby College, Waterville, ME 04901, USA

Received 4 September 2001; revised 30 October 2001; accepted 31 October 2001

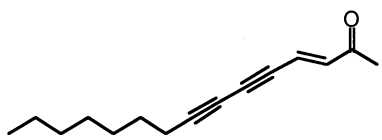
Abstract—Montiporynes A and B, that were among the recently isolated diacetylenic ketones from the stony coral *Montipora* sp., and reported to possess in vitro cytotoxic activity against several human solid tumor cells, have been synthesized in three simple steps from readily available materials.

After being long ignored, hard corals have attracted much attention in recent years as sources of interesting bioactive natural products.[1] Among these marine metabolites are a number of diacetylenic compounds, mostly isolated from hermaphroditic scleractinian corals such as *Montipora digitata*, that have been reported since 1990.[2] There are, however, few synthetic accounts of these naturally occurring diynes.[2b,3]

Recently, there was a report of several new diacetylenic ketones found in the hard coral *Montipora* sp. that were shown to have varying in vitro cytotoxicities against a number of human solid tumor cell lines.[4] The reported biological assay of two of these ketones, (*E*)- and (*Z*)-3-pentadecene-5,7-diyn-2-one, known as montiporyne A (**1**) and montiporyne B (**2**), respectively, are listed in Table 1.

In this communication we describe an expeditious synthesis of **1** and **2**. The first step of the synthetic protocol, as outlined in Scheme 1, is the quantitative conversion of 1-nonyne to 1-iodononyne (**3**) using *N*-iodosuccinimide and a catalytic amount of silver nitrate.[5] This iodination method appears to be superior, in terms of yield as well as experimental convenience, to those that involve the use of butyllithium[3] and ethylmagnesium bromide.[6] In the next step, the improved procedure of Alami and Ferri was employed to couple **3** with propargyl alcohol to afford 2,4-dodecadiynyl alcohol (**4**) in a yield of 89% after purification.[7] Indeed, the unsymmetrical diyne **4** was a key intermediate in the synthesis of montiporic acids A and B,[3] and has been also accessed in other ways.[2b,8] Finally, the Swern oxidation of **4** followed by an in situ Wittig reaction with acetylmethylene-triphenylphosphorane led to **1** in a yield of 58%. However, we noticed that **1**, if allowed to stand at room temperature, began to isomerize to **2** within hours. The ratio of **1**:**2** at equilibrium appears to be approximately 3:1 in favor of the *trans* isomer.[9] The

Table 1. In vitro cytotoxicities (ED50, μg/mL) of **1** and **2** against human solid tumor cells.[a] Data is from Ref. 4



1

2

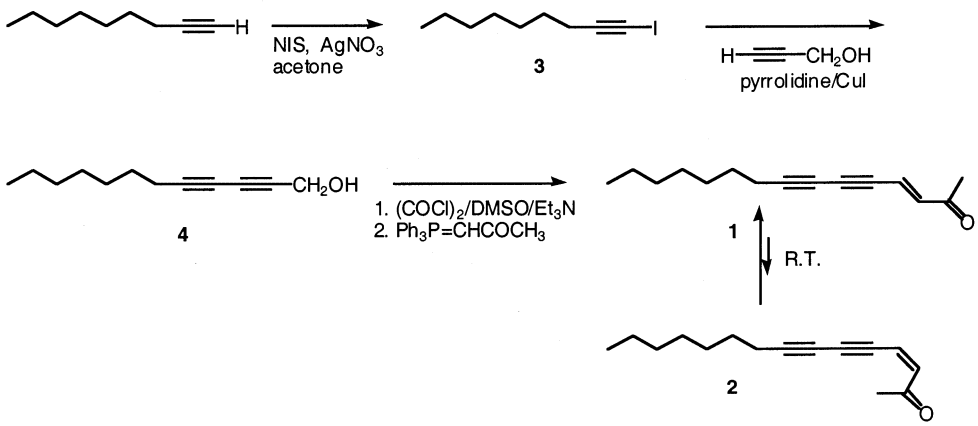
Compound	A549	SK-OV-3	SK-MEL-2	XF498	HCT15
1 (cisplatin)	>50 (0.8)	3.2 (0.8)	1.4 (0.8)	3.2 (0.8)	3.2 (0.8)
2 (cisplatin)	>50 (0.6)	25.9 (0.6)	42.6 (0.6)	>50 (0.6)	>50 (0.6)

[a] A549: human lung cancer; SK-OV-3: human ovarian cancer; SK-MEL-2: human skin cancer; XF498: human CNS cancer; HCT15: human colon cancer. Numbers in parentheses correspond to cisplatin.

* Corresponding author.

† This paper is dedicated to Professor Bradford P. Mundy on the occasion of his retirement from Colby College.

0040-4039/02/$ - see front matter
PII: S0040-4039(01)02143-8



Scheme 1.

separation of **1** and **2** was accomplished by means of flash chromatography over silica gel using ether/hexane (0.5/99.5) as the eluent. The two isomers could be readily distinguished by examining the splitting pattern of the olefinic protons which showed a larger coupling constant ($J=16$ Hz) for the *trans* compound relative to its *cis* isomer ($J=12$ Hz). A comparison of spectral data clearly indicates that our synthetic samples are the same as the naturally occurring materials.[10]

In conclusion, we have developed a convenient procedure that makes available several hundred milligrams of these two interesting marine metabolites which are only found, at this time, in very minute quantities from the natural sources. Further studies toward the synthesis of the other ketones in this family are currently underway in our laboratory.

Supporting information: GC/MS data and ^{1}H, ^{13}C NMR and IR spectra for montiporynes A and B (8 pages) is available upon request.

Acknowledgements

We thank the Research Corporation for a Cottrell College Science Award and financial support from the Division of Natural Sciences at Colby College. T.J.S. thanks the Howard Hughes Medical Institute for a summer research assistantship. The National Science Foundation is gratefully acknowledged for a departmental grant to upgrade our NMR spectrometer. We are indebted to Professor Jee H. Jung of Pusan National University, Korea for sharing spectral data of the naturally occurring montiporynes with us, and helpful discussions. We thank Professor Robert A. Pascal, Jr. and Dr. Dorothy Little for high resolution mass spectrometry analysis.

References

1. For some early examples of metabolites from hard corals, see: (a) Alam, M.; Sanduja, R.; Wellington, G. M. *Heterocycles* **1988**, *27*, 719; (b) Higa, T.; Sakai, R. *Chem. Lett.* **1987**, *127*; (c) Fusetani, N.; Asano, M.; Matsunaga, S.; Hashimoto, K. *Comp. Biochem. Physiol.* **1986**, *85B*, 845; (d) Sanduja, R.; Alam, M.; Wellington, G. M. *J. Chem. Res.* (*S*) **1986**, 450; (e) Sanduja, R.; Martin, G. E.; Weinheimer, A. J.; Alam, M.; Hossain, M. B.; van der Helm, D. *J. Heterocyclic Chem.* **1984**, *21*, 845.
2. (a) Higa, T.; Tanaka, J.; Kohagura, T.; Wauke, T. *Chem. Lett.* **1990**, 145; (b) Coll, J. C.; Bowden, B. F.; Meehan, G. V.; Konig, G. M.; Carroll, A. R.; Tapiolas, D. M.; Alino, P. M.; Heaton, A.; De Nys, R.; Leone, P. A.; Maida, M.; Aceret, T. L.; Willis, R. H.; Babcock, R. C.; Willis, B. L.; Florian, Z.; Clayton, M. N.; Miller, R. L. *Mar. Biol. (Berlin)* **1994**, *118*, 177; (c) Fusetani, N.; Toyoda, T.; Asai, N.; Matsunaga, S.; Maruyama, T. *J. Nat. Prod.* **1996**, *59*, 796.
3. Stefani, H. A.; Costa, I. M.; Zeni, G. *Tetrahedron Lett.* **1999**, *40*, 9215.
4. Bae, B. H.; Im, K. S.; Choi, W. C.; Hong, J.; Lee, C.-O.; Choi, J. S.; Son, B. W.; Song, J.-I.; Jung, J. H. *J. Nat. Prod.* **2000**, *63*, 1511.
5. We are grateful to Professor Nancy Goroff of SUNY, Stony Brook for suggesting this method to us. Trimethylsilylacetylenes also may be used as substrates to carry out such iodinations. See: (a) Gao, K.; Goroff, N. S. *J. Am. Chem. Soc.* **2000**, *122*, 9320; (b) Nishikawa, T.; Shibuya, S.; Hosokawa, S.; Isobe, M. *Synlett* **1994**, 485.
6. Barbu, E.; Tsibouklis, J. *Tetrahedron Lett.* **1996**, *37*, 5023.
7. Alami, M.; Ferri, F. *Tetrahedron Lett.* **1996**, *37*, 2763.
8. (a) Wityak, J.; Chan, J. B. *Synth. Commun.* **1991**, *21*, 977; (b) Doolittle, R. E. *Synthesis* **1984**, 730.
9. The isomerization occurred regardless of whether **1** was in solution or in pure form. Storing **1**, wrapped in aluminum foil, in the refrigerator significantly minimized its isomerization to **2**. Presumably, the isomerization is promoted by light and/or adventitious catalysts.

10. Montiporyne A (**1**): ^{1}H NMR (CD_3OD) δ 0.91 (t, $J=7.0$ Hz, 3H), 1.25–1.44 (m, 8H), 1.57 (q, $J=6.8$ Hz, 2H), 2.27 (s, 2H), 2.40 (t, $J=6.9$, 2H), 6.57 (d, $J=16$ Hz, 1H), 6.73 (d, $J=16$ Hz, 1H). ^{13}C NMR (CD_3OD) δ 20.58, 24.05, 27.87, 27.88, 29.58, 30.23, 30.27, 33.24, 65.96, 73.04, 85.35, 90.88, 124.57, 141.59, 199.39. IR (neat) 2929, 2857, 1677, 1590, 1360, 1248, 1172, 957. HRMS (EI) calcd for $C_{15}H_{20}O$ 216.1515; found 216.1515. Montiporyne B (**2**): ^{1}H NMR (CD_3OD) δ 0.93 (t, $J=4.0$ Hz, 3H), 1.28–1.48 (m, 4H), 1.59 (q, $J=7.2$ Hz, 1H), 2.40–2.45 (m, 2H), 6.31 (d, $J=11.9$ Hz, 1H), 6.48 (d, $J=11.8$ Hz, 1H). ^{13}C NMR (CD_3OD) δ 14.59, 20.42, 23.84, 29.39, 30.03, 30.09, 30.30, 33.04, 65.84, 72.87, 87.50, 91.34, 120.99, 140.80, 199.10. IR (neat) 2929, 2857, 2225, 1670, 1582, 1175. LRMS (EI) 216 (M^+).