CHEMISTRY
AN ASIAN JOURNAL

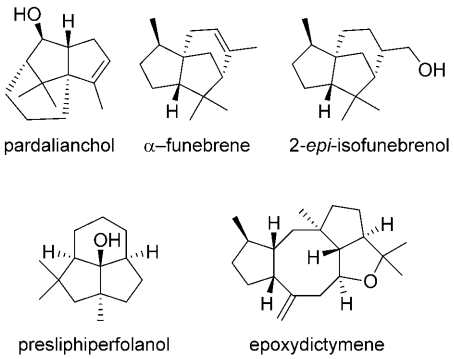
DOI: 10.1002/asia.201100251

Unexpected Formation of a *trans-syn*-Fused Linear Triquinane from a Trimethylenemethane (TMM)-Diyl-Mediated [2+3] Cycloaddition Reaction.

Won-Yeob Kim, Byung Gyu Kim, Taek Kang, and Hee-Yoon Lee*[a]

Dedicated to Professor Eun Lee on the occasion of his retirement and 65th birthday

Polyquinanes, compounds with fused cyclopentane rings intrigue the synthetic chemistry community for their structural complexity and strain associated during the formation of the structures.[1] One of the Platonic solids, dodecahedrane,[2] and many natural products with di-, tri-, and tetraquinane structures have challenged synthetic chemists during last 30 years.[3] The most unique structural feature of polyquinane is that the *cis*-bicyclo[3.3.0]octane is far more stable than its isomer, *trans*-bicyclo[3.3.0]octane (by 6.4 kcal mol^{-1}).[4] This difference in energy ensures a high preference for *cis*-fused polyquinanes and exclusive formation of *cis*-ring junctions during polyquinane synthesis. However, the energy difference has not excluded the existence or the preparation of *trans*-fused polyquinanes in nature and in organic synthesis. There are a few examples of natural products containing the *trans*-bicyclo[3.3.0]octane motif (Scheme 1)[5] and several reports of the formation of the *trans*-bicyclo[3.3.0]octane structure in organic synthesis.[6]



pardalianchol α–funebrene 2-*epi*-isofunebrenol

presliphiperfolanol epoxydictymene

Scheme 1. Natural products with *trans*-bicyclo[3.3.0]octane partial structure.

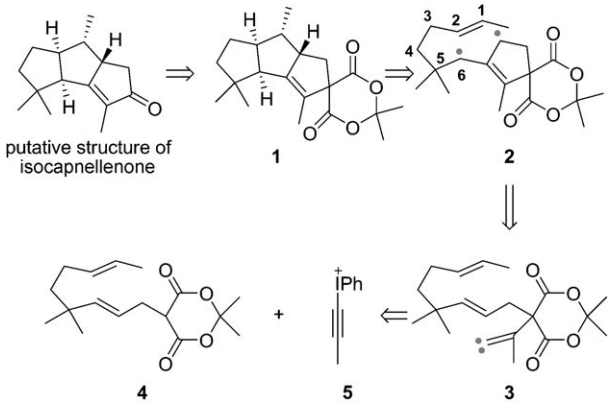
Synthetic *trans*-bicyclo[3.3.0]octane structures were obtained from reactive intermediates via a preformed *trans*-ring junction prior to the cyclization reaction,[6a–e] a ring-contraction reaction from the six-membered ring of a *trans*-fused perhydroindane structure,[6g] or unexpected reactions of an unsaturated ring junction of polyquinane compounds.[6f] There are also few examples of *trans*-bicyclo-[3.3.0]octane formation through transition-metal-catalyzed cycloaddition reactions.[7]

Herein, we report the unexpected formation of a triquinane skeleton containing the *trans*-bicyclo[3.3.0]octane motif from an intramolecular [2+3] cycloaddition reaction of a trimethylenemethane (TMM) diyl with an olefin.[8]

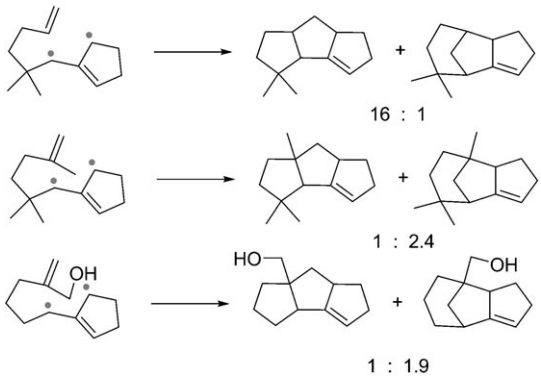
In an ongoing research program directed towards the application of tandem cycloaddition reactions of alkylidene carbenes via TMM diyls to form triquinanes[9] for the total synthesis of natural products, the total synthesis of the putative structure of isocapnellenone[10] was considered. Retrosynthetic analysis showed that the tricyclic structure of isocapnellenone could readily be assembled from **4** and **5** through an alkylidene-carbene-mediated [2+3] TMM cycloaddition reaction, with conversion of the Meldrum's acid unit into the corresponding ketone completing the total synthesis (Scheme 2). This total synthesis would be a testing ground for the efficiency and selectivity of the TMM cycloaddition reaction of a highly congested substrate, and the efficient transformation of the Meldrum's acid unit into the corresponding carbonyl group. As has been observed during the synthesis of capnellene[11] and related compounds, the mode of cycloaddition reaction was greatly affected by the substitution pattern of the diylophile[12] (Scheme 3). Based on these reports, compound **2** was expected to produce cyclized product **1** as the major product.

[a] Dr. W.-Y. Kim, Dr. B. G. Kim, T. Kang, Prof. Dr. H.-Y. Lee
Department of Chemistry
KAIST
373-1 Gusung Dong, Yuseong, Daejeon, 305-701 (Korea)
Fax: (+82) 42-350-2810
E-mail: leehy@kaist.ac.kr

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/asia.201100251.



Scheme 2. Synthetic analysis of the total synthesis of isocapnellenone.

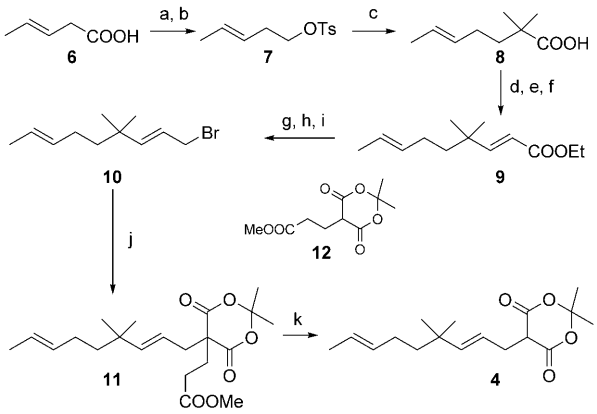


Scheme 3. TMM cycloaddition reaction mode depending on the diylophile substitution.

A successful cycloaddition reaction of **3** into **1** via **2** would expand the scope of the TMM-diyl-mediated [2+3] cycloaddtition reaction for highly substituted substrates, and effective conversion of the dicarboxyl functional group of **1** into the corresponding ketone would broaden the scope of the current synthetic strategy as well.

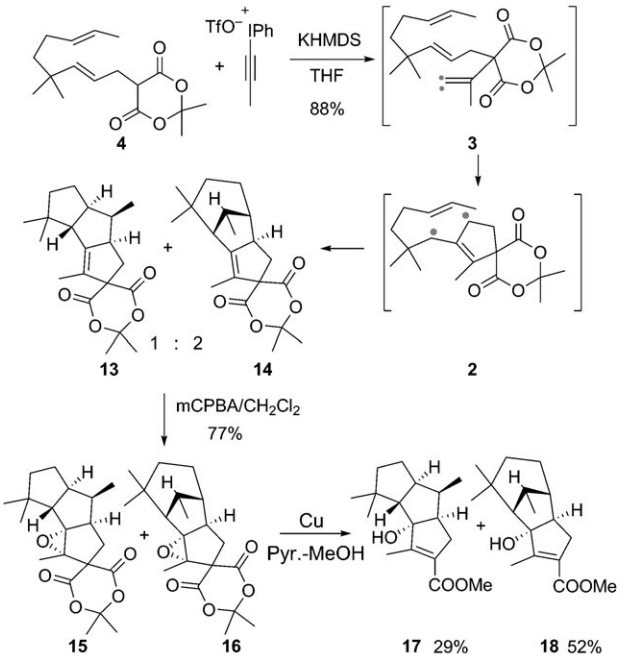
The total synthesis began with the formation of substrate **4** from 3-pentenoic acid, **6** (Scheme 4). Alkylation of isobutyric acid with the tosylate of 3-pentenol, prepared from **6** through $LiAlH_4$ reduction of the carboxylic acid followed by the treatment with TsCl, produced 2,2-dimethyl-5-heptenoic acid **8**. An extension of the carbon chain by two units with the introduction of an olefin was accomplished in a three-step sequence, involving reduction of the acid followed by oxidation after Wittig olefination, to produce unsaturated ester **9**. The ester group of **9** was converted into corresponding bromide **10** through a 3-step sequence of reduction with DIBAL-H, activation as the mesylate, and bromination. Bromide **10** was reacted with Meldrum's acid analog **12** to ensure the mono-alkylation[13] and the acrylate unit of **11** was readily removed by base treatment to produce substrate **4** for the alkylidene-carbene-mediated TMM diyl cycloaddition reaction.

When the anion of **4** was reacted with a propynyl iodonium salt,[14] a mixture of two major products, **13** and **14**, in a 1:2 ratio was obtained in 88% yield through the sequential



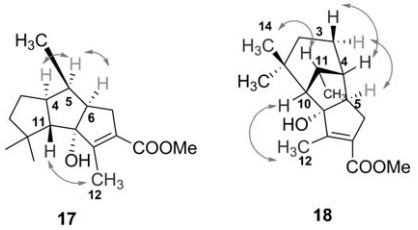
Scheme 4. Preparation of the substrate **4**: a) $LiAlH_4/Et_2O$, 96%; b) TsCl, pyridine/CH_2Cl_2, 93%; c) isobutyric acid, LDA/THF, 87%; d) $LiAlH_4/Et_2O$, 89%; e) PCC/CH_2Cl_2; f) $(EtO)_2POCH_2COOEt$, NaH/THF, 74% for two steps; g) DIBAL-H/CH_2Cl_2, 97%; h) MsCl, Et_3N/CH_2Cl_2; i) LiBr/THF, 70% for two steps; j) **12**, K_2CO_3/DMF, 82% k) LiHMDS/THF, 99%. LDA = lithium diisopropylamide, PCC = pyridinium chlorochromate, DIBAL = diisobutylaluminum hydride, DMF = *N*,*N*-dimethylformamide, Ms = methanesulfonyl.

formation of the alkylidene carbene **3** and the TMM diyl **2** followed by the [2+3] cycloaddition reaction. Owing to the inseparable nature of the products, the mixture was oxidized to the corresponding mixture of epoxides and the Meldrum's acid part was decarboxylated using copper[15] to produce unsaturated alcohols **17** and **18,** in a 1:2 ratio, which were separated by flash chromatography on silica gel (Scheme 5). The structures of alcohols **17** and **18** were deduced to be the expected linearly fused triquinane and a bridged bicyclic compound from their ^1H NMR and COSY



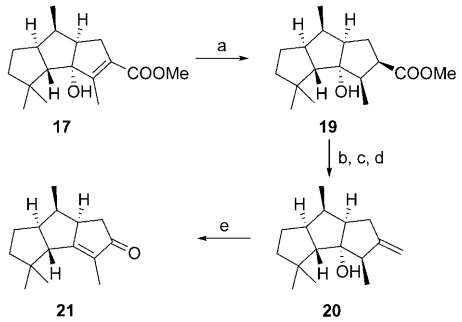
Scheme 5. Tandem cycloaddition reaction of an alkylidene carbene via a TMM diyl.

spectra. Formation of the bridged tricyclic compound **14** as the major product was not expected because the substitution pattern of the diylophile of **4** was believed to favor the formation of the desired linearly fused triquinane **1**. Stereoselective formation of both **13** and **14** was another unexpected result. It was presumed that substituents on the cyclopentene ring of the TMM affected the stereoselectivity during the cycloaddition reaction. The relative stereochemistry of **17** and **18** was deduced through NOE experiments (Scheme 6).



Scheme 6. Key NOE correlation of **17** and **18**.

To our surprise, the NOE experiments indicated that the stereo-structure of **17** should be *trans-syn-cis* at the ring junctions, because NOE correlation from H-5/H-4, H-5/H-6, and H-11/CH_3-12 were observed whilst the expected NOE signal from H-4/H-11 for the *cis* stereochemistry was not observed. The structural integrity of **17** was further confirmed during the conversion of the carboxyl functional group of **17** into the corresponding ketone in the isocapnellenone structure (Scheme 7). As there was no positive sign of the anticipated direct conversion of the carboxylic acid of **17** into the carbonyl group through a decarboxylation reaction,[16] conversion of the carboxylic acid functional group into the corresponding carbonyl group required a five-step detour. In the first step of the transformation, hydrogenation of **17** produced the crystalline saturated ester **19.** The ester of **19** was converted into the corresponding *exo*-olefin **20** through reduction followed by the dehydration procedure reported by Grieco et al.[17] Ozonolysis of the olefin of **20** after an acidic dehydration reaction produced *epi*-isocapnellenone **21**. The spectral data of **21** was distinctively different from the reported data for the putative structure of isocapnellenone.[10b]



Scheme 7. Completion of the total synthesis: a) H_2, Pd/C, EtOAc, 92%; b) $LiBH_4$/THF, 96%; c) *o*-$NO_2PhSeCN$, PBu_3/THF, 89%; d) H_2O_2/THF, 93%; e) O_3 then PPh_3/CH_2Cl_2 −78°C–RT; H_2SO_4, 68%. THF = tetrahydrofuran.

The ultimate confirmation of the stereostructure of the cycloaddition reaction products **13** and compounds derived from **13** was obtained through the single-crystal X-ray analysis of **19**; the analysis clearly showed that the structure of **19** possessed a *trans*-bicyclo[3.3.0]octane skeleton in the triquinane structure (Figure 1).

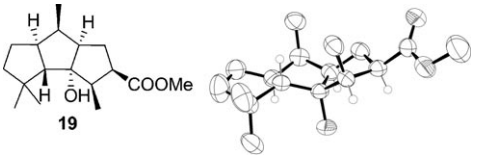
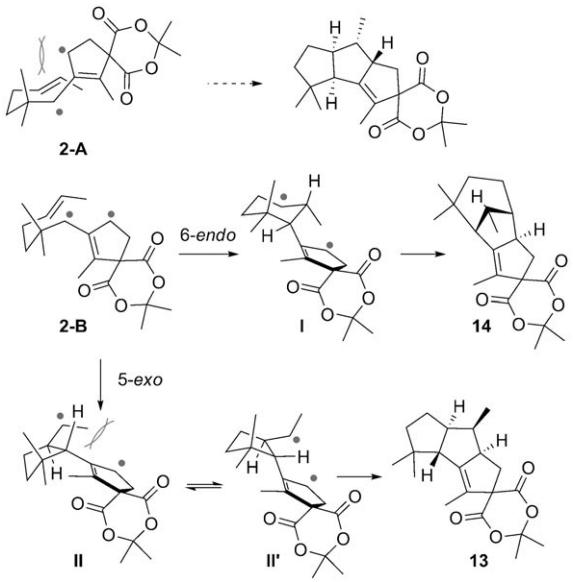


Figure 1. X-ray crystal structure of **19**.

It appears that the *trans* ring junction was established during the TMM-diyl-mediated [2+3] cycloaddition reaction through a sequence of stepwise cyclization reactions rather than a concerted cycloaddition reaction. Transition state models of the cycloaddition reaction explain the formation of the *trans*-fused triquinane structure (Scheme 8). The conformer **2-A** that leads to the regular *cis-anti*-fused linear triquinane structure suffers a 1,3-steric interaction between the methyl group and cyclopentene ring of the TMM–diyl intermediate. The methyl group appended on the end of the olefin also appears to provide extra steric bulk that disfavors the cycloaddition reaction through **2-A**. Thus, conformer **2-B**, which avoids such interactions, becomes the preferred conformer for the cyclization reaction. As has been reported,[18] the cyclization of conformer **2-B** would proceed in a



Scheme 8. Comparison of transition states leading to the products.

stepwise fashion and the first cyclization step could form either intermediate **I** or **II**. Intermediate **I** is produced through 6-*endo-trig*-cyclization that sets the relative stereochemistry between the bridgehead methyl group and the bicyclic structure of **14**. The second cyclization proceeds via the less-sterically demanding 5-*exo-trig*-cyclization to produce **14** stereoselectively. Intermediate **II** is produced through a 5-*exo-trig*-cyclization that sets the *trans*-stereochemistry at the ring junction of the final product. The initially formed intermediate **II** would adopt the sterically less-congested conformer **II'** during the second ring formation. At this stage, the stereochemical integrity of the methyl group attached to the olefin in the substrate was lost. The methyl group adopts the sterically less-congested conformation for the final cyclization reaction to form **13**. This result, along with the previous reports by Little and co-workers,[19] suggests that the cycloaddition reaction pathways to either linearly fused triquinanes or tricyclo[5.3.1.$0^{2,6}$]undecanes could be controlled by judicious choice of the substitution patterns of the tether and the diylophile.

In summary, the high reactivity of the TMM-diyl-mediated [2+3] cycloaddition reaction was demonstrated by the production of *trans-syn*-tricyclo[6.3.0.$0^{2,6}$]undecane without the formation of its *cis* isomer. The formation of the bridged bicyclic, tricyclo[5.3.1.$0^{2,6}$]undecane structure from 1,2-disubstituted diylophile provides another useful information to control the regioselectivity during the [2+3] cycloaddition reaction of the TMM diyl. As the conversion of the Meldrum's acid unit into the corresponding ketone was successful, this synthetic strategy could be applied to the total synthesis of various natural products with related structural features.[20]

Experimental Section

Potassium bis(trimethylsilyl)amide (KHMDS; 2.64 mL of a 0.5 M solution in toluene, 1.32 mmol) was added to a stirred solution of **4** (300 mg, 1.0 mmol) in THF (90 mL) at 0 °C. After being stirred for 30 min at 0 °C, the mixture was warmed to room temperature for 20 min. The solution of propynyl iodonium salt (560 mg, 1.42 mmol) in THF (60 mL) was added for 30 min via cannula. The resulting reaction mixture was stirred for 2 h. The solvent was evaporated in vacuo and purified by flash column chromatography on silica gel (EtOAc/Hexane = 1:10) to give 300 mg (0.90 mmol, 88 %) of a mixture of **13** and **14**. 3-Chloroperoxybenzoic acid (mCPBA; 0.334 g of 77 % contents, 1.35 mmol) was added to a stirred solution of the mixture of **13** and **14** (300 mg, 0.90 mmol) in methylene chloride (10 mL) at room temperature. The mixture was stirred for 24 h and diluted with Et_2O. $Na_2S_2O_3{\cdot}5H_2O$ in H_2O was added to the mixture and stirred for 30 min. The aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic layers were dried over $MgSO_4$, concentrated, and purified by flash column chromatography on silica gel (EtOAc/Hexane = 1:10) to give 241 mg (0.69 mmol, 77 %) of epxodies. Copper powder (5 mg, 0.08 mmol) was added to the stirred solution of epoxides (223 mg, 0.64 mmol) in pyridine/MeOH (5.5 mL, v/v = 10:1) and the mixture was refluxed for 3 h. The reaction mixture was cooled to room temperature. 1 M HCl was added and the aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic layers were dried over $MgSO_4$, and concentrated at reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/Hexane = 1:20 to 1:10) to give **17** (51 mg, 28.5 %) as a white solid and **18** (94 mg, 52.5 %) as a colorless oil.

17: ^{1}H NMR (400 Hz, $CDCl_3$): δ = 3.72 (s, 3H), 2.92 (m, 1H), 2.80 (m, 1H), 2.49 (m, 2H), 2.20 (m, 1H), 2.10 (t, 3H), 1.75 (m, 2H), 1.44 (d, J = 14.45 Hz, 1H), 1.38 (m, 1H), 1.27 (m, 1H), 1.19 (s, 3H), 1.10 (s, 3H), 0.75 ppm (d, J = 7.51 Hz, 3H); ^{13}C NMR (100 Hz, C_6D_6): δ = 166.46, 155.82, 127.49, 93.68, 62.87, 61.80, 52.70, 50.66, 47.84, 35.67, 31.88, 30.86, 30.12, 27.12, 20.97, 13.18, 11.07 ppm; IR (neat): $\tilde{\nu}$ = 3477, 3061, 2982, 2933, 1731, 1490, 1446, 1368, 1247, 1189, 1096, 1032, 932 cm^{-1}; High resolution MS (ESI): Calculated for $C_{17}H_{26}O_3$ $[M+Na]^+$: 301.1780, found: 301.1814.

18: ^{1}H NMR (400 Hz, $CDCl_3$): δ = 3.71 (s, 3H), 2.90–2.83 (m, 1H), 2.32 (m, 1H), 2.20 (m, 2H), 2.10 (t, 3H), 1.78 (m, 2H), 1.60 (m, 1H), 1.35 (d, J = 13.60 Hz, 1H), 1.18 (s, 3H), 1.15 (m, 1H), 1.13 (s, 3H), 1.05 (m, 1H), 1.04 ppm (d, J = 6.44 Hz, 3H); ^{13}C NMR (100 Hz, C_6D_6): δ = 166.63, 156.19, 126.97, 93.95, 68.25, 66.04, 55.62, 50.71, 48.24, 45.48, 37.19, 36.52, 31.80, 27.31, 24.46, 18.67, 13.10 ppm; IR (neat): $\tilde{\nu}$ = 3500, 2949, 2865, 1699, 1645, 1436, 1373, 1347, 1323, 1266, 1220, 1177, 1126, 1109, 1082, 1064, 1036, 1008, 950 cm^{-1}; High resolution MS (ESI): Calculated for $C_{17}H_{26}O_3$ $[M+Na]^+$: 301.1780, found: 301.1814.

Acknowledgements

This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (KRF-2008-314-C00198).

Keywords: cycloaddition · diradicals · fused-ring systems · natural products · triquinanes

[1] a) L. A. Paquette, *Top. Curr. Chem.* **1979**, *79*, 41–165; b) M. Chanon, R. Barone, C. Baralotte, M. Julliard, J. B. Hendrickson, *Synthesis* **1998**, 1559–1583.
[2] L. A. Paquette, *Chem. Rev.* **1989**, *89*, 1051–1065.
[3] a) L. A. Paquette, *Stud. Nat. Prod. Chem.* **1993**, *13*, 3–52; b) G. S. A. Mehta, *Chem. Rev.* **1997**, *97*, 671–719.
[4] S. Chang, C. McNally, S. Shary-Tehrany, M. J. Hickey, R. H. Boyd, *J. Am. Chem. Soc.* **1970**, *92*, 3109–3118.
[5] Pardalianchol: a) F. Bohlmann, W. R. Abraham, *Phytochemistry* **1979**, *18*, 668–671. α-Funebrene: b) H. K. Hariprakasha, P. S. Shanker, G. S. R. S. Rao, *Ind. J. Chem.* **2000**, *39B*, 94–102. 2-*epi*-Isofunebrenol: c) P. S. Beauchamp, J. T. Descalzo, B. C. Dev, B. Dev, C. V. Nguyen, S. L. Midland, J. J. Sim, F. S. Than, *J. Essent. Oil Res.* **2004**, *16*, 571–578. Presilpiperfolanol: d) R. M. Coates, Z. Ho, M. Klobus, S. R. Wilson, *J. Am. Chem. Soc.* **1996**, *118*, 9249–9254; e) F. Bohlmann, C. Zdero, J. Jakupovic, H. Robinson, R. M. King, *Phytochemistry* **1981**, *20*, 2239–2244. Epxoydictymene: f) N. Enoki, A. Furusaki, K. Suehiro, R. Ishida, T. Matsumoto, *Tetrahedron Lett.* **1983**, *24*, 4341–4342.
[6] a) J. C. Tripp, C. H. Schiesser, D. P. Curran, *J. Am. Chem. Soc.* **2005**, *127*, 5518–5527; b) I. Shinohara, M. Okue, Y. Yamada, H. Nagaoka, *Tetrahedron Lett.* **2003**, *44*, 4649–4652; c) E. Piers, A. M. Kaller, *Tetrahedron Lett.* **1996**, *37*, 5857–5860; d) F. Saitoh, M. Mori, K. Okamura, T. Date, *Tetrahedron* **1995**, *51*, 4439–4446; e) W. F. Bailey, A. D. Khanolkar, K. V. Gavaskar, *J. Am. Chem. Soc.* **1992**, *114*, 8053–8060; f) L. Van Hijfte, R. D. Little, J. L. Petersen, K. D. Moeller, *J. Org. Chem.* **1987**, *52*, 4647–4661; g) B. G. Christensen, R. G. Strachan, N. R. Trenner, B. H. Arison, R. Hirschman, J. M. Chemerda, *J. Am. Chem. Soc.* **1960**, *82*, 3995–4000.
[7] a) B. Trillo, M. Gulias, F. Lopez, L. Castedo, J. L. Mascarenas, *Adv. Synth. Catal.* **2006**, *348*, 2381–2384; b) C. M. Yu, J. Youn, J. Jung, *Angew. Chem.* **2006**, *118*, 1583–1586; *Angew. Chem. Int. Ed.* **2006**, *45*, 1553–1556.
[8] S. Yamago, E. Nakamura, *Org. React.* **2002**, *61*, 1–217.

[9] a) Y.-K. Yoon, T. Kang, H.-Y. Lee, *Chem. Asian J.* **2011**, *6*, 645–651; b) H.-Y. Lee, Y. Jung, Y. Yoon, B. G. Kim, Y. Kim, *Org. Lett.* **2010**, *12*, 2672–2674; c) H.-Y. Lee, Y. Kim, *J. Am. Chem. Soc.* **2003**, *125*, 10156–10157.

[10] a) A. Romo de Vivar, D. A. Nieto, R. Gavino, P. C. Ruben, C. A. Perez, *Phytochemistry* **1995**, *40*, 167–170; b) G. Mehta, A. S. K. Murthy, J. D. Umarye, *Tetrahedron Lett.* **2002**, *43*, 8301–8305.

[11] R. D. Little, G. L. Carroll, J. L. Petersen, *J. Am. Chem. Soc.* **1983**, *105*, 928–932.

[12] a) R. D. Little, M. R. Masjedizadeh, K. D. Moeller, I. Dannecker-Doerig, *Synlett* **1992**, 107–113; b) A. K. Allan, G. L. Carroll, R. D. Little, *Eur. J. Org. Chem.* **1998**, 1–12.

[13] H.-Y. Lee, H. S. Tae, B. G. Kim, H.-M. Choi, *Tetrahedron Lett.* **2003**, *44*, 5803–5806.

[14] H.-Y. Lee, Y. Yoon, Y.-H. Lim, Y. Lee, *Tetrahedron Lett.* **2008**, *49*, 5693–5696.

[15] G. Pattenden, S. J. Teague, *Tetrahedron* **1987**, *43*, 5637–5652.

[16] a) D. Naskar, S. Chowdhury, S. Roy, *Tetrahedron Lett.* **1998**, *39*, 699–702; b) P. P. Mahulikar, R. B. Mane, *J. Chem. Res.* **2006**, 15–18; c) Y. Kurasawa, W. Satoh, I. Matsuzaki, Y. Maesaki, Y. Okamoto, H. S. Kim, *J. Heterocycl. Chem.* **2003**, *40*, 837–843.

[17] P. A. Grieco, S. Gilman, M. Nishizawa, *J. Org. Chem.* **1976**, *41*, 1485–1487.

[18] M. R. Masjedizadeh, I. Dannecker-Doerig, R. D. Little, *J. Org. Chem.* **1990**, *55*, 2742–2752.

[19] R. D. Little, M. M. Ott in *Studies in Natural Products Chemistry* (Ed.: Atta-ur-Rahman), Elsevier Health Science, Amsterdam, **2000**, *Vol. 22*, pp. 195–243.

[20] a) J. C. Liermann, A. Schuffler, B. Wollinsky, J. Birnbacher, H. Kolshorn, T. Anke, T. Opatz, *J. Org. Chem.* **2010**, *75*, 2955–2961; b) V. Hellwig, J. Dasenbrock, S. Schumann, W. Steglich, K. Leonhardt, T. Anke, *Eur. J. Org. Chem.* **1998**, 73–79.

Received: March 9, 2011
Published online: June 7, 2011

