ORGANIC LETTERS

2005
Vol. 7, No. 14
3069−3072

An Effective and Highly Stereoselective Julia Olefination of Cyclopropyl Carbinol Mediated by $CeCl_3 \cdot 7H_2O$/NaI

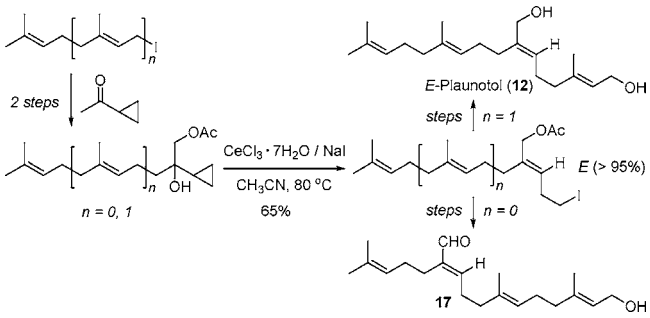
Wei-Dong Z. Li*,†,‡ and Yu Peng†

State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, China, and State Key Laboratory of Elemento-organic Chemistry, Nankai University, Tianjin 300071, China

liwd@lzu.edu.cn; wdli@nankai.edu.cn

Received May 6, 2005

ABSTRACT



An efficient and highly stereoselective synthesis of functionalized trisubstituted *E*-olefins from cyclopropyl carbinol derivatives via a Julia-type olefination mediated by an intriguing Lewis acidic system consisting of $CeCl_3 \cdot 7H_2O$ and NaI in refluxing acetonitrile is reported. This facile olefination allows for the iterative incorporation of methylcyclopropyl ketone as a C_5 prenylation synthon in the synthesis of acyclic terpenoids, as demonstrated in the facile synthesis of plaunotol 6*E*-isomer 12, a biologically significant diterpene diol, and naturally occurring diterpene 17.

The stereoselective synthesis of substituted olefins continues to be an active research subject of methodological development.[1] The classical Julia homoallylic transpositional protocol, involving a protic or Lewis acid-mediated halogenative ring-opening of cyclopropyl carbinol substrates, offered a practical, useful, and versatile method for the stereoselective synthesis of substituted olefins.[2] In connection with an ongoing synthetic program in this laboratory, we present in this paper an effective and highly stereoselective synthesis of bifunctional trisubstituted *E*-olefins from cyclopropyl carbinol derivatives through the Julia-type olefination mediated by an intriguingly mild Lewis acidic system consisting of $CeCl_3 \cdot 7H_2O$ and NaI in refluxing acetonitrile. Since the earlier introduction of $CeCl_3 \cdot 7H_2O$ by Luche[3] to organic synthesis as a mild water-tolerable Lewis acid, this readily available hydrated rare-earth metal halide has emerged as an attractive Lewis acidic mediator in organic synthesis.[4,5] As recently reviewed by Bartoli et al.,[5] the simple combina-

* Fax/Phone: 0086-(0)22-23494613.
† Lanzhou University.
‡ Nankai University.

(1) For general reviews, see: (a) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863. (b) Kelly, S. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 1, pp 729−817. For some recent examples, see: (c) Corey, E. J.; Lee, J.; Roberts, B. *Tetrahedron Lett.* **1997**, *38*, 8915. (d) Tago, K.; Kogen, H. *Org. Lett.* **2000**, *2*, 1975. (e) Taylor, R. E.; Cheng, Y. *Org. Lett.* **2001**, *3*, 2221 and references therein. (f) Das, B.; Banerjee, J.; Mahender, G.; Majhi, A. *Org. Lett.* **2004**, *6*, 3349.

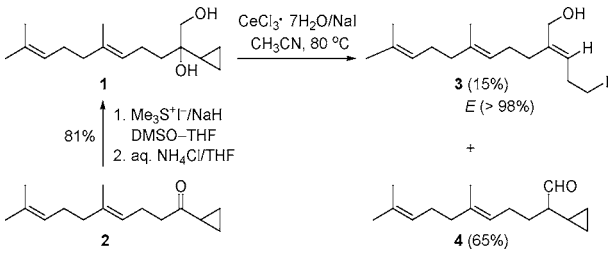
(2) (a) Li, W.-D. Z.; Yang, J.-H. *Org. Lett.* **2004**, *6*, 1849 and ref 4 cited therein. For a general review, see: (b) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C. *Chem. Rev.* **1989**, *89*, 165.

(3) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.

(4) For recent applications, see: (a) Bartoli, G.; Bosco, M.; Giuli, S.; Giuliani, A.; Lucarelli, L.; Marcantoni, E.; Sambri, L.; Torregiani, E. *J. Org. Chem.* **2005**, *70*, 1941. (b) Khosropour, A. R.; Khodaei, M. M.; Ghozati, K. *Chem. Lett.* **2004**, *33*, 1378. (c) Yadav, J. S.; Reddy, B. V. S.;

10.1021/ol051051+ CCC: $30.25
Published on Web 06/15/2005

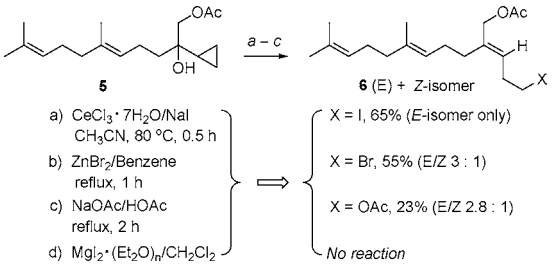
Scheme 1. Julia Olefination of **1** Mediated by $CeCl_3 \cdot 7H_2O$/NaI



tion of $CeCl_3 \cdot 7H_2O$ and NaI in CH_3CN behaves as a uniquely effective and mild Lewis acidic system which promotes various synthetically valuable functional group transformations under mild conditions using convenient procedures. Our current work represents another useful extension of this reagent system in stereoselective olefin synthesis which is applicable in the chemical synthesis of oligoprenylated natural products.

During the screening to find an appropriate reagent system for an effective Julia-type halogenative olefination of prenylated diol **1**, a geraniol-derived cyclopropyl carbinol, readily prepared from homogeranyl cyclopropyl ketone (**2**) in two steps (81% overall), we found that, upon exposure to a slurry mixture of $CeCl_3 \cdot 7H_2O$ (1.0 equiv) and NaI (1.2 equiv) in refluxing CH_3CN for half an hour (Scheme 1), the desired Julia olefination product **3** was obtained in 15% isolated yield as practically pure *E*-isomer[6] and the major product isolated in 65% yield was characterized as a formal pinacol-type rearrangement product **4**. To minimize the unwanted pinacol rearrangement pathway to aldehyde **4**, we then examined the corresponding monoacetylated derivative **5** under identical conditions (a), as shown in Scheme 2. To

Scheme 2. Comparison of Julia Olefination Conditions

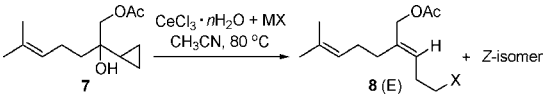


our delight, the corresponding acetoxylated homoallyl iodide **6** was obtained in 65% isolated yield as geometrically pure *E*-isomer as judged by GC and ^{1}H NMR analysis.[7]

To compare the efficiency and stereoselectivity of the reagent system $CeCl_3 \cdot 7H_2O$/NaI in CH_3CN with other frequently used acidic conditions, submission of acetate **5** to conditions b and c, as illustrated in Scheme 2, furnished not only a lower yield of the corresponding Julia olefination product **6** but also a much diminished stereoselectivity (cf. *E*/*Z* ratios),[8] respectively. Notably, many other Lewis acidic conditions that were tested failed to promote the desired Julia olefination to **6**, including MgI_2 etherate in CH_2Cl_2 (condition d), a proven effective Lewis acidic catalyst[2a] for the allylsilane synthesis from the corresponding cyclopropyl carbinol in our previous work.

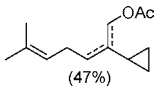
To elucidate the effects of the water content in the reagent system and the alkaline metal halide used, we next examined the Julia olefination of homoprenyl cyclopropyl carbinol acetate **7** under variable conditions. As shown in Table 1,

Table 1. Effects of H_2O and Alkaline Metal Halides



entry	*n*	MX	time (h)	*E*/*Z*[a]	yield (%)[b]
1	7	NaI	1.5	>19:1	66
2	0	NaI	1.5	5:1	61
3	2.5[c]	NaI	1.5	9:1	70
4	7	LiI	2.5	6.3:1	40[e]
5	7	KI	2.5	4.1:1	45[e]
6	7	KBr	5	5.1:1	41[e]
7	7	NaBr	5	4.5:1	42[e]
8	7	^{n}Bu$_4$N$^+$I$^-$	8		trace
9	7	^{n}Bu$_4$N$^+$I$^-$/NaBr	4	4.7:1	57 (2.7:1)[d]

[a] Ratio determined by ^{1}H NMR analysis. [b] Isolated yield recorded. [c] Prepared from $CeCl_3 \cdot 7H_2O$ by partial dehydration. [d] Ratio of X = Br/X = I. [e] Significant amount of dehydration products (below) were formed.



the presence of water in the reaction mixture is obviously essential for a rapid and highly stereoselective olefination in a reproducible yield, while the "dry" conditions (entry 2) led to a much diminished selectivity compared with that of the hydrated $CeCl_3$ (entries 1 and 3). The alkaline metal cations seem to also play a critical role as illustrated in entries 4 and 5, where sodium iodide is proven to be the best halide salt in combination with $CeCl_3 \cdot 7H_2O$ to form an effective, yet mild Lewis acidic system (cf. entries 6 and 7), and the bromo salts are much less effective than iodo salts. Surprisingly, the analogous quaternary ammonium iodide (entry 8) is completely ineffective, while combination with NaBr restored the reactivity but still led to a lower stereoselectivity

Srinivas, M. *Chem. Lett.* **2004**, *33*, 882. (d) Bartoli, G.; Bosco, M.; Giuliani, A.; Marcantoni, E.; Palmieri, A.; Petrini, M.; Sambri, L. *J. Org. Chem.* **2004**, *69*, 1290. (e) Moreno-Dorado, F. J.; Guerra, F. M.; Manzano, F. L.; Aladro, F. J.; Jorge, Z. D.; Massanet, G. M. *Tetrahedron Lett.* **2003**, *44*, 6991.

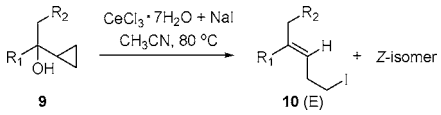
(5) Bartoli, G.; Marcantoni, E.; Sambri, L. *Synlett* **2003**, 2101.

(6) Structure characterized by analysis of ^{1}H NMR and NOE spectrum, and isomeric purity was determined by GC analysis.

(7) Acetylation of **3** afforded an identical acetate **6**.

(8) Stereochemistry of products were assigned by NOE experiments and ratios determined by GC analysis.

Table 2. Effects of Cyclopropyl Carbinol Substituents



9 10 (E)

entry	R_1	R_2	*E*/*Z*[a]	yield (%)[b]
1	homoprenyl	H	3.3:1	83
2	homoprenyl	OBz	10:1	70
3	homogeranyl	OTBDPS	15:1	38
4	4-phenylbutyl	SMe	*E* only	55
5	homogeranyl	Br	2:3	20[c]

[a] Ratio determined by ^{1}H NMR analysis. [b] Isolated yield recorded. [c] Major product isolated is characterized as homofarnesyl iodide (R_2 = H, 51%, *E*/*Z* 3:1), a reductive debromination product (by NaI).

(entry 9). The solvent of choice is proven to be CH_3CN, as demonstrated by Bartoli et al. in their systematic studies.[5]

With the above optimized Julia olefination conditions, we further examined the influence of substituents in the cyclopropyl carbinol substrates. As shown in Table 2, sterically bulkier carbinols (entries 2 and 3 versus entries 1 and 5) appear favorable for the *E*-isomeric product, but apparently are less stereoselective than the corresponding acetoxylated carbinol **7** (cf. entry 1 of Table 1). A stronger carbocation stabilizing group (MeS, entry 4) favors the same *E*-isomer formation equally.

On the basis of the above facts, we rationalized that the highly *E*-selective olefination for substrates **5** and **7** may be attributed to intramolecular acyl participation in the cyclopropylcarbinyl cationic species **i**, as depicted in Figure 1, in

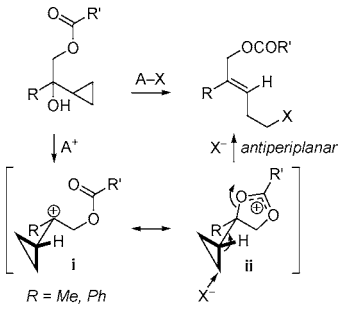
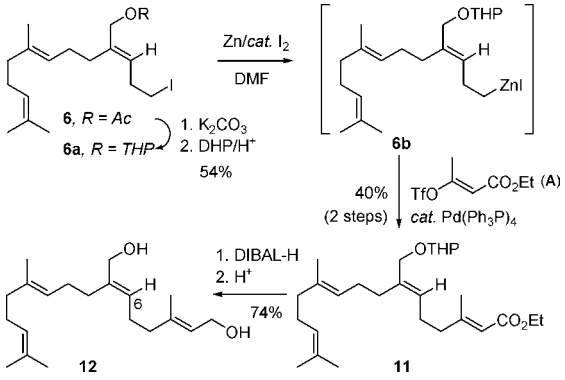


Figure 1. Mechanistic rationale for the highly *E*-selective Julia olefination of cyclopropyl acyloxymethyl carbinols.

which a transient metastable cationic intermediate **ii** thus formed is responsible for the antiperiplanar cyclopropane ring-opening by halide attack, leading to predominantly *E*-olefinic products. The slightly lower *E*-selectivity in the benzoate substrate (entry 2 of Table 2) may be a manifestation of the more significant hyperconjugative cation stabilizing effect of methyl group in the acetate substrates, which may be also reflected in the classical Prévost *trans*-dihydroxylation[9] versus Woodward *cis*-dihydroxylation.[10]

Scheme 3. Synthesis of 6(*E*)-Plaunotol (**12**)



The mild Lewis acidic character of this reagent system may be attributed to the soft activation of hydrated $CeCl_3$ by ligand exchange, with the iodo anion in CH_3CN leading to an effective oxophilic species for the generation of cyclopropylcarbinyl cation **i** and subsequent equilibration to **ii**.

To demonstrate the synthetic usefulness of the now readily available trisubstituted homoallylic iodides **6** and **8** in terpenoid synthesis, we accomplished the synthesis of polyprenylated acyclic diterpenoids **12** and **17** accordingly. As shown in Scheme 3, triene acetate **6** was transformed into the corresponding THP ether **6a** in a routine two-step procedure and, subsequently, into organozinc **6b** by a modified method,[11] which was coupled with a C_4 unit (**A**)[12] under typical Negishi conditions[13] catalyzed by $(Ph_3P)_4Pd$ to give the tetraene **11** in 40% isolated yield from **6a**. Reduction of the ester **11** with DIBAL-H followed by acidic hydrolysis furnished the diterpene diol **12**[14] in good yield, the 6(*E*)-isomer of plaunotol, a naturally occurring antiulcer and antibacterial diterpenol.[15] Similarly, the corresponding organolithium of iodo THP ether **8a** was added to cyclopropylmethyl ketone to give a carbinol **13**, which was subjected to the modified Julia transpositional olefination conditions[16] to afford the homoallyl iodide **14** as a mixture

(9) (a) Prévost, C. *Compt. Rend.* **1933**, *196*, 1129. (b) Campell, M. M.; Sainsburg, M.; Yavarzadeh, R. *Tetrahedron* **1984**, *40*, 5063.

(10) Woodward, R. B.; Brutcher, F. V. *J. Am. Chem. Soc.* **1958**, *80*, 209.

(11) Huo, S.-Q. *Org. Lett.* **2003**, *5*, 423.

(12) (a) Saulnier, M. G.; Kadow, J. F.; Tun, M. M.; Langley, D. R.; Vyas, D. M. *J. Am. Chem. Soc.* **1989**, *111*, 8320. (b) Wada, A.; Fukunaga, K.; Ito, M. *Synlett* **2001**, 800.

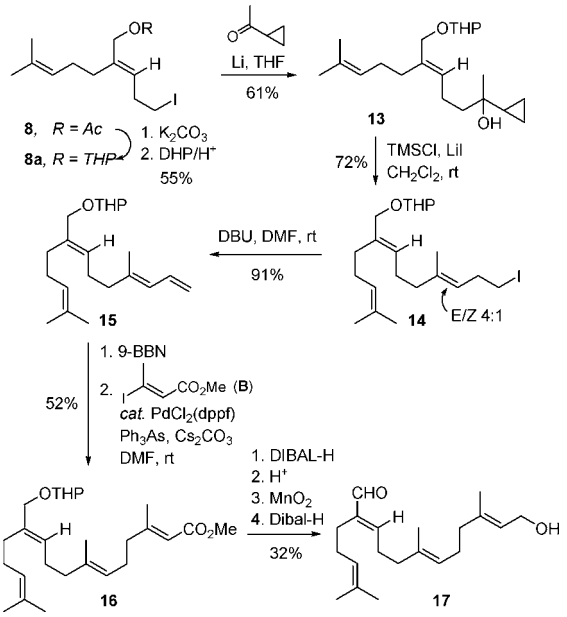
(13) (a) Diederich, F., Stang, P. J., Eds; *Metal-Catalyzed Cross Coupling Reactions*; Wiley-VCH: Weinheim, Germany, 1998. (b) Negishi, E. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Wiley: New York, 2002.

(14) For an earlier alternative synthesis, see: Ogiso, A.; Kitazawa, E.; Kurabayashi, M.; Sato, A.; Takahashi, S.; Noguchi, H.; Kuwano, H.; Kobayashi, S.; Mishima, H. *Chem. Pharm. Bull.* **1978**, *26*, 3117.

(15) For other total synthetic studies, see: (a) Tago, K.; Minami, E.; Masuda, K.; Akiyama, T.; Kogen, H. *Bioorg. Med. Chem.* **2001**, *9*, 1781. (b) Tago, K.; Arai, M.; Kogen, H. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2073. (c) Tago, K.; Kogen, H. *Tetrahedron* **2000**, *56*, 8825. (d) Honda, K.; Igarashi, D.; Asami, M.; Inoue, S. *Synlett* **1998**, 685. (e) Fujiwara, T.; Tsuruta, Y.; Takeda, T. *Tetrahedron Lett.* **1995**, *36*, 8435. (f) Takayanagi, H. *Tetrahedron Lett.* **1994**, *35*, 1581. (g) Inoue, S.; Honda, K.; Iwase, N.; Sato, K. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1629. (h) Sato, K.; Miyamoto, O.; Inoue, S.; Iwase, N.; Honda, K. *Chem. Lett.* **1988**, 1433.

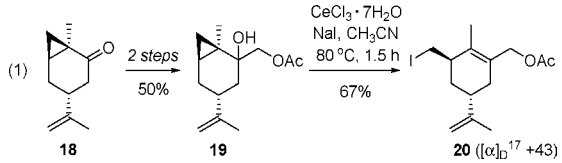
(16) Balme, G.; Fournet, G.; Gore, J. *Tetrahedron Lett.* **1986**, *27*, 1907. These conditions produced the optimal *E*-selective product **14**.

Scheme 4. Synthesis of Natural All-*E* Diterpene **17**



of *E*/*Z* isomers (4:1), which was then treated with DBU in DMF to give the conjugated polyene **15** after chromatography on silica gel in good yield. A Suzuki coupling protocol[17] was employed to elongate the prenylated chain alternatively, as shown in Scheme 4, where 3-methyl-3-iodo acrylate (**B**)[18] was used as a C_4 terminating unit under typical catalytic conditions.[19] The corresponding coupling product **16** was obtained in 52% yield, which was then transformed via a series of routine functional group manipulations into the diterpene aldehyde **17** in an overall yield of 32%,[20] a naturally occurring acyclic diterpenoid[21] possessing similar bioactivity as that of plaunotol.

It is noteworthy that the above facile synthetic sequences (Schemes 3 and 4) allow for the iterative incorporation of methylcyclopropyl ketone as a C_5 prenylation synthon in the synthesis of acyclic prenylated terpenoids,[22] coupled with the use of two readily available C_4 terminating units (**A** or **B**), as illustrated in the above rapid synthesis of plaunotol 6(*E*)-isomer **12** and the first total synthesis of naturally occurring diterpene compound **17**.



This approach is also effective for the Julia olefination of a bicyclic cyclopropyl carbinol derivative **19** prepared similarly from a (−)-carvone-derived ketone **18**[2a] in two steps, and the corresponding iodo acetate **20** was obtained in good overall yield (eq 1). This chiral bifunctional C_{11} synthon may be of value in natural product synthesis.

In summary, the mild Lewis acidic reagent system consisting of $CeCl_3 \cdot 7H_2O$ in refluxing CH_3CN has been proven to be effective for the highly stereoselective synthesis of bifunctional trisubstituted olefins, which add another example in this useful reagent toolbox for functional group manipulation and could find some other applications in the synthesis of terpenoids or another natural products.

Acknowledgment. This paper is dedicated to Professor J.-L. Luche. We thank the National Natural Science Foundation (Distinguished Youth Fund 29925204 and QT 20021001) for financial support. The Cheung Kong Scholars program and the Outstanding Scholars program of Nankai University are gratefully acknowledged.

Supporting Information Available: Experimental procedures and spectral data, copies of spectrum for compounds **1**, **3**−**6**, **6a**, **7**, **8**, **8a**, **9**−**17**, **19**, and **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL051051+

(17) For a review on *B*-alkyl Suzuki coupling, see: Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544.

(18) Ohba, M.; Kawase, N.; Fujii, T. *J. Am. Chem. Soc.* **1996**, *118*, 8250.

(19) (a) Kallan, N. C.; Halcomb, R. L. *Org. Lett.* **2000**, *2*, 2687. (b) Marshall, J. A.; Schaaf, G. M. *J. Org. Chem.* **2003**, *68*, 7428.

(20) The minor *Z*-isomer was separated at the diol stage after reduction of **16** with DIBAL-H and acidic hydrolysis.

(21) (a) Sato, A.; Ogiso, A.; Kuwano, H. *Phytochemistry* **1980**, *19*, 2207. (b) Chiang, Y.-M.; Liu, H.-K.; Lo, J.-M.; Chien, S.-C.; Chan, Y.-F.; Lee, T.-H.; Su, J.-K.; Kuo, Y.-H. *J. Chin. Chem. Soc.* (Taipei) **2003**, *50*, 161. For a relevant diterpene natural product, see: (c) Bohlmann, F.; Zdero, C.; Huneck, S. *Phytochemistry* **1985**, *24*, 1027.

(22) For a review on isoprenoids, see: (a) Cane, D. E., Ed. *Comprehensive Natural Products Chemistry: Isoprenoids including Carotenoids and Steroids*; Pergamon Press: Oxford, 1999; Vol. 2. For recent synthetic studies, see: (b) Negishi, E.; Liou, S.-Y.; Xu, C.; Huo, S. *Org. Lett.* **2002**, *4*, 261. (c) Radetich, B.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 2430. (d) Radetich, B.; Corey, E. J. *Org. Lett.* **2002**, *4*, 3463.