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Efficient Oxidative Radical Cyclizations of Ester Enolates with Carbocation Desilylation as Termination: Synthesis of Cyclopentanoid Monoterpenes and Analogues†

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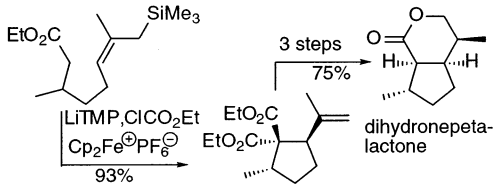
ABSTRACT



An efficient oxidative radical cyclization approach for the synthesis of 2-alkenyl cyclopentane or cyclohexane carboxylates from ω-silylallyl ester enolates induced by recyclable SET oxidant ferrocenium hexafluorophosphate has been developed. A new tandem alkoxycarbonylation/oxidative radical cyclization/cationic termination process forms the basis for a five-step synthesis of the cyclopentanoid monoterpene dihydronepetalactone and analogues.

The development of new radical reaction methodology that provides an alternative to tin-based reactions becomes increasingly important as a result of ecological reasons.[1] Electron transfer seems to be especially promising because radicals can be generated from and converted to other reactive intermediates.[2] This in turn allows the combination of ionic and radical reactions to many new domino processes.

These perspectives spurred our interest in oxidative radical cyclizations and tandem anionic/radical/cationic reactions.[3] We found that annulated butyrolactones **6** can be synthesized through SET oxidation of enolates **1**/radical 5-*exo* cyclization/SET oxidation/lactonization induced by mild and recyclable SET oxidant ferrocenium hexafluorophosphate **2** (Scheme 1).[4]

A side reaction in this method is the competitive deprotonation of cyclized tertiary trialkylcarbenium ions **5** to alkenylcyclopentanes **7**. The partial formation of **7** led us to the question whether the reaction path can also be diverted to the exclusive synthesis of synthetically versatile 2-alkenylcyclopentanecarboxylates **7** via oxidative radical cyclizations of enolates. A solution for the selective generation of the alkenyl function offered itself through desilylation of β-silylcarbenium ions, which is precedented in ionic allylsilane chemistry by examples such as the Sakurai−Hosomi and related reactions[5] and in Moeller's electrooxidative cyclizations.[6]

† Dedicated to Professor Dr. Werner Schroth on the occasion of his 75th birthday.

(1) (a) Studer, A.; Amrein, S. *Synthesis* **2002**, 835−849. (b) Murphy, J. A. *Pure Appl. Chem.* **2000**, *72*, 1327−1334. (c) Baguley, P. A.; Walton, J. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3072−3082.

(2) (a) Mikami, T.; Narasaka, K. In *Advances in Free Radical Chemistry*; Zard, S. Z., Ed.; Jai Press Inc.: Stamford, 1999; Vol. 2, pp 45−88. (b) Molander, G. A.; Harris, C. R. *Tetrahedron* **1998**, *54*, 3321−3354. (c) Melikyan, G. G. *Org. React.* **1997**, *49*, 427−675. (d) Dalko, P. I. *Tetrahedron* **1995**, *51*, 7579−7653.

(3) (a) Jahn, U. *Chem. Commun.* **2001**, 1600−1601. (b) Jahn, U.; Müller, M.; Aussieker, S. *J. Am. Chem. Soc.* **2000**, *122*, 5212−5213.

(4) (a) Jahn, U.; Hartmann, P.; Dix, I.; Jones, P. G. *Eur. J. Org. Chem.* **2001**, 3333−3355. (b) Jahn, U.; Hartmann, P. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2277−2282.

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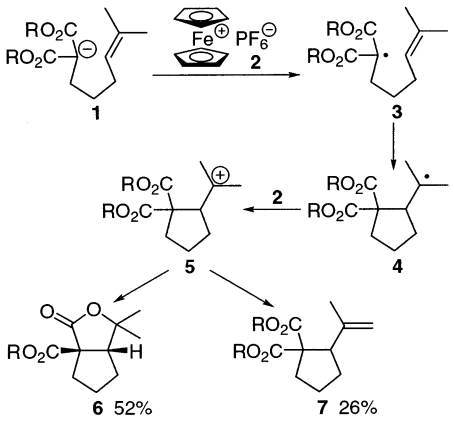
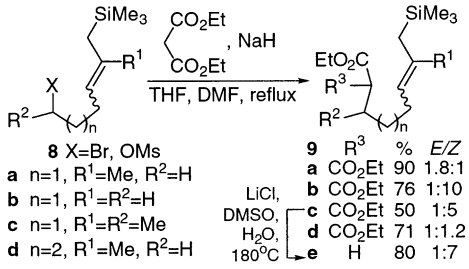
Scheme 1. Oxidative Radical Cyclizations of Malonate Enolates with Cationic Termination



Here we report the realization of selective oxidative enolate cyclizations to 2-alkenylcyclopentanecarboxylates and alkenylcyclohexanecarboxylates under very mild conditions by using ω-silylalkenylesters **9**. Our results indicate that even slow radical cyclizations such as 6-*endo* or 6-*exo* cyclizations can be performed efficiently. Moreover, in contrast to our earlier results,[4] even secondary alkyl radicals can be oxidized. The methodology is applied to a short approach to iridoid monoterpenes and analogues.[7]

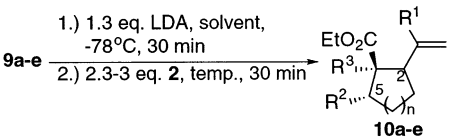
Initial investigations focused on oxidative radical cyclizations of malonates **9a**−**d**, which are easily available through standard alkylation of malonic esters by silylated alkenyl bromides or mesylates **8a**−**d** (Scheme 2).

Scheme 2. Synthesis of Cyclization Precursors **9**



Deprotonation of **9a**−**c** by LDA and treatment with 2−3 equiv of ferrocenium hexafluorophosphate **2** in DME gave the 2-alkenylcyclopentan-1,1-dicarboxylates **10a**−**c** in good yields as the sole products (Table 1, entries 1−3). It is especially noteworthy that the disubstituted allylsilyl ester

Table 1. Oxidative Radical Cyclizations of ω-Silyl Ester Enolates **9**



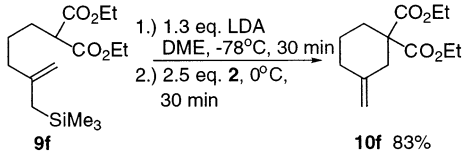
entry	9	solvent/temp	10 (%)[a]	2,5-*trans*/*cis*
1	**a**	DME/0 °C	**a** (86)	
2	**b**	DME/0 °C	**b** (98)	
3	**c**	DME/0 °C	**c** (59)[b]	2.5:1[c]
4	**d**	DME/0 °C	**d** (68)	
5	**e**	THF/−78 °C	**e** (53)[d]	2.1:1[c,e]

[a] Isolated yields. [b] 30% of **9c** recovered. [c] Determined by NOE difference spectroscopy for both isomers. [d] 40% of **9e** recovered. [e] The 1,5-diastereoselectivity of both isomers is *trans* (NOE).[8]

9b underwent oxidative cyclization with the same efficiency as triple-substituted **9a** (entry 2). Through introduction of the silyl group in the β-position, radical oxidation is facilitated considerably and thus even secondary alkyl radicals are made amenable to oxidation by **2**.[9] Branched malonate enolate **9c** cyclized in a somewhat lower yield of 59% to a 2.5:1 *trans/cis*-diastereomeric mixture of cyclopentanedicarboxylate **10c**;[10] the remainder of the mass balance was recovered starting material (entry 3). The methodology was equally well applicable to the homologous 6-*exo* cyclization. When the malonate enolate of **9d** was reacted with **2**, 68% of cyclohexane derivative **10d** was isolated as the exclusive product (entry 4). Compounds resulting from either dimerization of malonyl radicals or 1,5-hydrogen transfer, often competing with radical 6-*exo* cyclizations, were not detected.

A similar oxidative 6-*endo* cyclization of malonate enolate **9f** afforded 3-methylenecyclohexane-1,1-dicarboxylate **10f** in a yield as high as 83% (Scheme 3).

Scheme 3. 6-*endo* Cyclization of **9f**



We provide the first evidence that simple, less stabilized ester enolates can also be oxidatively cyclized under similar conditions. When ω-silyl ester **9e** was deprotonated by LDA in THF and treated with **2** at −78 °C, cyclic compound **10e** was isolated in 53% yield as an inseparable mixture of two

(5) (a) Marko, I. E.; Mekhalfia, A.; Murphy, F.; Bayston, D. J.; Bailey, M.; Janousek, Z.; Dolan, S. *Pure Appl. Chem.* **1997**, *69*, 565−570. (b) Langkopf, E.; Schinzer, D. *Chem. Rev.* **1995**, *95*, 1375−1408.

(6) For a review, see: Moeller, K. D. *Tetrahedron* **2000**, *56*, 9527−9554.

(7) For synthetic approaches, see: (a) Nangia, A.; Prasuna, G.; Rao, P. B. *Tetrahedron* **1997**, *53*, 14507−14545. (b) Thomas, A. F.; Bessiere, Y. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley: New York, 1988; Vol. 7, pp 275−454.

(8) Published NMR data of **10e**: Sakai, T.; Morita, K.; Matsumura, C.; Sudo, S.; Tsuboi, S.; Takeda, A. *J. Org. Chem.* **1981**, *46*, 4774−4779.

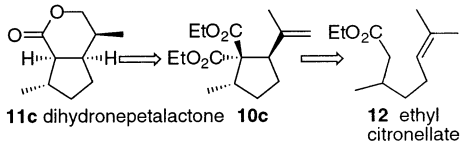
(9) Oxidation potentials of some silylated radicals compared to alkyl radicals, see: Zhang, S.; Bordwell, F. G. *J. Org. Chem.* **1996**, *61*, 51−54.

(10) The configuration of **10c** was assigned on the basis of NOE experiments (Supporting Information).

major diastereomers in a ratio of 2.1:1 (Table 1, entry 5).[8] In addition, trace amounts of a third unassigned diastereomer were detected by NMR spectroscopy. However, from this reaction, although 2.5 equiv of **2** were consumed as in the cyclization reactions above, ca. 40% of **9e** was recovered consistently. At present, we cannot provide a reason for the somewhat lower cyclization yield of **10e** compared to that of **10a**−**d**. A change of the base to LiTMP, change of the solvent to THF-d_8, or a quench of the reaction mixture with D_2O did not improve the yields. With HMPA as additive or in DME as the solvent, the yield of **10e** decreased to 34%, while 64% of **9e** was recovered. Future work must investigate the reaction parameters including enolate aggregation and ligands more thoroughly to further optimize this cyclization protocol.

On the basis of the cyclization results of ω-silylalkenylmalonates **9**, we envisaged an application to a short access to cyclopentanoid monoterpenes, namely, dihydronepetalactone **11c** and its nor-methyl analogues **11a,b** (Scheme 4).

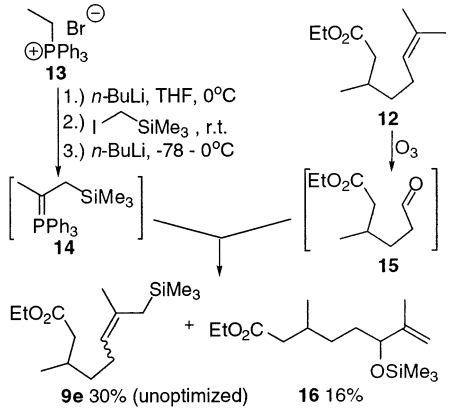
Scheme 4. Retrosynthesis of Dihydronepetalactone **11c**



A retrosynthetic disconnection called for a hydroboration/oxidation/lactonization of 2-alkenylcyclopentanecarboxylates **10c** to synthesize the valerolactone moiety of **11c**, while ethyl citronellate **12** should serve as the precursor for the two-step construction of the cyclopentane ring **10c** in a new tandem alkoxycarbonylation/oxidative cyclization protocol.

Because the preparation of **9e** via **9c** was lengthy, an alternative synthesis of **9e** started with a one-pot sequential ozonolysis/Wittig reaction (Scheme 5). Phosphorane **14**,

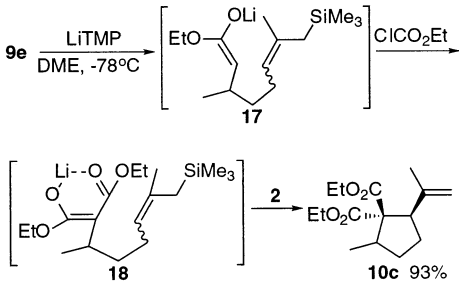
Scheme 5. Synthesis of ω-Silylcitronellate **9e**



which was generated from salt **13** through sequential deprotonation/alkylation/deprotonation with BuLi/(iodomethyl)trimethylsilane/BuLi underwent Wittig reaction with the crude aldehyde **15** derived from ozonolysis of **12**. In this way, ω-silylated citronellate **9e** was obtained as a 1:1 *E/Z*-mixture in unoptimized 30% yield based on phosphonium salt **13**. As a side product, compound **16** was formed as a 1:1 *syn/anti*-diastereomeric mixture.[11]

ω-Silylcitronellate **9e** was subjected to the key tandem alkoxycarbonylation/oxidative cyclization reaction by deprotonating with 2.6 equiv of LiTMP, adding 1.2 equiv of ethyl chloroformate followed by 2.3 equiv of **2** (Scheme 6). After

Scheme 6. Tandem Alkoxycarbonylation/Oxidative Radical Cyclization of **9e**



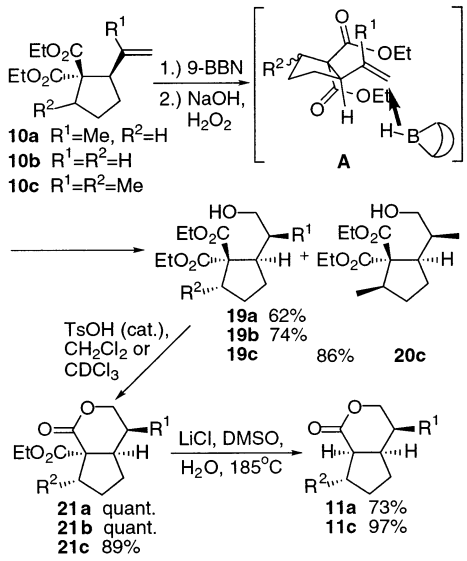
conventional workup, 93% of substituted cyclopentane-1,1-dicarboxylate **10c** was isolated as a 2:1 *trans/cis*-diastereomeric mixture. It is especially noteworthy that the tandem sequence **9e** → [**17**] → [**18**] → **10c** gave considerably better results than the oxidative cyclization of the corresponding malonate **9c**.

Because the *cis*- and *trans*-diastereomers of **10c** were not separable at this stage, the mixture was carried through to hydroboration/oxidation with 9-BBN to provide the separable alcohols **19c** and **20c**[12] in a combined yield of 86% as single diastereomers at the newly created stereocenter (Scheme 7). The hydroboration/oxidation was also conducted with alkenylcyclopentanes **10a,b** and proved to be highly diastereoselective for **10a**. The diastereoselectivity can be easily rationalized by assuming a strongly preferred conformation **A** of **10** to avoid ^{1,3}A-strain.[13] From this conformation, one face is effectively shielded by the two ester groups so that the borane can only attack from the opposite face. Thus, the two ester groups prove to be much more effective than a monoester or a carboxylic acid in a related synthesis.[14]

The alcohols **19a**−**c** were submitted to lactonization induced by catalytic amounts of p-TsOH in CH_2Cl_2 or $CDCl_3$ and provided the lactones **21a**−**c** in high yields as single diastereomers as indicated by NMR and GC. Finally, Krapcho dealkoxycarbonylation afforded dihydronepetalactone **11c** and its nor-methyl analogue **11a** in good to excellent yields. Synthetic **11c** was identical with respect to the reported data of the natural product.[15]

(11) For similar products from silylated phosphoranes, see: Iio, H.; Ishii, M.; Tsukamoto, M.; Tokoroyama, T. *Tetrahedron Lett.* **1988**, *29*, 5965−5968 and references therein.
(12) This alcohol may be useful for the synthesis of other iridoids.
(13) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841−1860.
(14) Wolinsky, J.; Eustace, E. J. *J. Org. Chem.* **1972**, *37*, 3376−3378.

Scheme 7. Completion of the Synthesis of Dihydronepetalactone **11c**



To summarize, silylated esters are convenient starting materials for the high-yielding synthesis of alkenylcyclopentane and alkenylcyclohexanecarboxylates through an oxidative enolate cyclization with cationic desilylation. In contrast to the known methods, secondary alkyl radicals can now be oxidized to carbenium ions. A new tandem alkoxycarbonylation/oxidative cyclization serves to synthesize dihydronepetalactone in only five steps from ethyl citronellate. At the same time this strategy should allow a unified approach to cyclopentanoid monoterpenes, since related natural products such as iridomyrmecin, mitsugashiwalactone, actinidine and others share the same skeleton. Work along these lines is underway.

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Supporting Information Available: Spectroscopic and analytical data of compounds **9a**−**f**, **10a**−**f**, **11a,c**, **16**, **19**−**21a**−**c** and experimental procedures for their preparation. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Compare: (a) Fleming, I.; Terrett, N. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2645−2649. (b) Uyehara, T.; Shida, N.; Yamamoto, Y. *J. Org. Chem.* **1992**, *57*, 3139−3145.