ORGANIC LETTERS

2013
Vol. 15, No. 17
4327–4329

"One-Pot" Reductive Lactone Alkylation Provides a Concise Asymmetric Synthesis of Chiral Isoprenoid Targets

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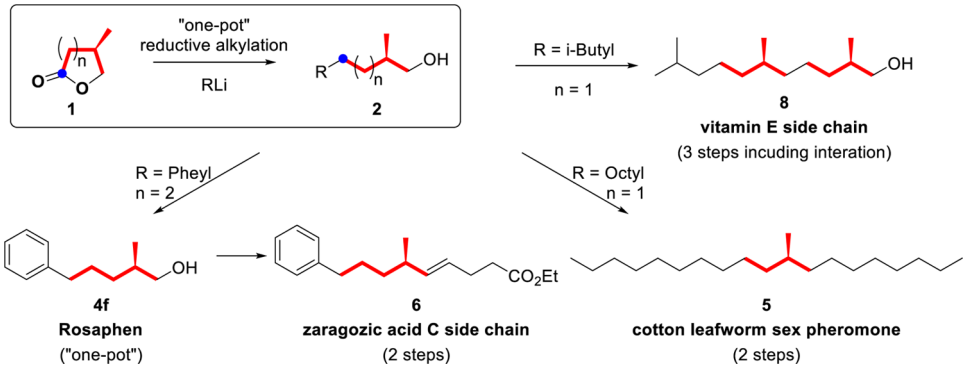
Received June 26, 2013

ABSTRACT

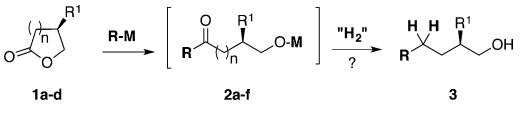


An efficient method, based on nucleophilic addition to lactones followed by modified in situ Clemmensen reduction, provides a short synthetic route to chiral isoprenoid targets. The efficacy of this method has been exemplified through the synthesis of several targets including the commercial fragrance Rosaphen, the side chain of Zaragozic acid C, the cotton leaf sex pheromone, and the side chains of vitamin E.

Chiral isoprenoid units are important structural fragments in natural products, such as pheromones, fragrances, and vitamins. Previous approaches have employed chiral auxiliaries,[1] biocatalysis,[2,3] transition metal catalysis,[4,5] or the chiral pool.[6] Despite significant reports on the synthesis of chiral isoprenoid compounds, considering the numerous natural products with such moieties and the disadvantages of existing methods, there is still room to explore more efficient approaches for general methyl-branched compounds with short synthetic routes, cheap starting materials, and feasible scale-up procedures.

The proposed process is outlined in Scheme 1. This involves monoaddition of an organometallic reagent to a lactone carbonyl followed by in situ reduction of the intermediate keto-alcohol.

Scheme 1. Proposed "One-Pot" Reductive Alkylation of Chiral Lactones



Additions of both Grignard reagents and alkyllithiums were evaluated. This apparently simple process is often plagued by overaddition leading to tertiary alcohols. This is especially so for Grignard additions. We found that Xu's method gave the monoadduct reproducibly in acceptable yields.[7] However this required the use of 8 equiv of amine

(1) Yadav, J. S.; Gayathri, K. U.; Thrimurtulu, N.; Prasad, A. R. *Tetrahedron* **2009**, *65*, 3536.
(2) Hoegberg, H. E.; Hedenstroem, E.; Faegerhag, J.; Servi, S. *J. Org. Chem.* **1992**, *57*, 2052.
(3) Ferraboschi, P.; Grisenti, P.; Manzocchi, A.; Santaniello, E. *J. Org. Chem.* **1990**, *55*, 6214.
(4) Takaya, H.; Ohta, T.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Inoue, S.; Kasahara, I.; Noyori, R. *J. Am. Chem. Soc.* **1987**, *109*, 1596.
(5) Kondakov, D. Y.; Negishi, E.-i. *J. Am. Chem. Soc.* **1995**, *117*, 10771.
(6) Liu, X. Y.; Stocker, B. L.; Seeberger, P. H. *J. Am. Chem. Soc.* **2006**, *128*, 3638.
(7) Yang, S. B.; Gan, F.-F.; Chen, G. J.; Xu, P. F. *ChemInform* **2009**, *40*, 2532–2534.

10.1021/ol401801g
Published on Web 08/19/2013

salt, *N*,*O*-dimethylhydroxylamine·HCl. In our hands, employing alkyllithiums, either commercially available or generated from the iodide and *t*-BuLi,[8] gave the monoadduct, reproducibly, in good yields.

The more problematic step involved the in situ reduction of the adduct. The generated keto-alcohol can undergo deoxygenation under the modified Clemmensen reduction as reported by Arimoto and co-workers,[9] ultimately giving the best results. Unlike their original report, which required 100 equiv of TMSCl and Zn dust, we found that 10 equiv were more than satisfactory giving the corresponding reduction products in >95% yields.

As outlined in Scheme 2 the initial adduct is in equilibrium with the ring-closed, lithiated acetal. As the reducing system requires access to the free ketone, it is possible that the cyclic acetal is not present in appreciable amounts and/or the silylated derivative is able to rearrange to the free ketone prior to reduction.

Scheme 2. Nucleophilic Addition to Lactones, Followed by in Situ Silylation and Modified Arimoto–Clemmenson Reduction

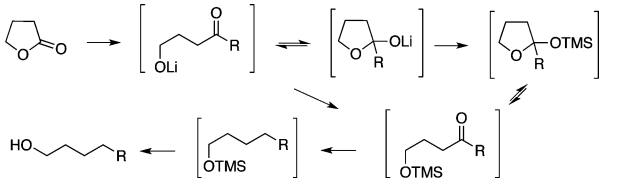


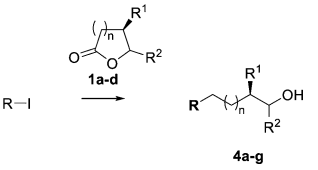
Table 1 lists examples of the reductive alkylation procedure outlined in Scheme 1. In all cases the overall yields for a one-pot sequence of lithiation, addition, and reduction are excellent. For alkyllithiums which are not commercially available, the corresponding iodides were converted to their alkyllithiums by reacting with *t*-BuLi (2.2 equiv) at −78 °C in Et_2O for 1 h, followed by warming to rt for 30 min. During warming, the Et_2O served as a scavenger to consume any excess *t*-BuLi, generating the corresponding alkyllithium in >95% yield. The two homochiral lactones used, (*R*)-3-methylbutyrolactone and (*R*)-4-methyl-δ-valerolactone, can be derived from tigogenin, a byproduct from sisal industrial waste.[10,11] The (*R*)-3-methylbutyrolactone also can be prepared via asymmetric synthesis, as reported by Helmchen.[12]

It is noteworthy that this process works well for five-, six-, and seven-membered lactones (Table 1).

Each alcohol synthesized from **1a** and **1c** was produced in high enantiomeric purity evidenced by, for example, Mosher ester analysis of **4a** shown in Figure 1 with Negishi's

(8) Cavicchioli, S.; Savoia, D.; Trombini, C.; Umani-Ronchi, A. *J. Org. Chem.* **1984**, *49*, 1246.
(9) Xu, S.; Toyama, T.; Nakamura, J.; Arimoto, H. *Tetrahedron Lett.* **2010**, *51*, 4534.
(10) Cheng, L. L.; Gu, C. Y.; Li, M.; Jin, R. H.; Lin, J. R.; Tian, W. S. *Huaxue Shiji* **2010**, *32*, 305.
(11) Yu, S.; Pan, X.; Lin, X.; Ma, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 135.
(12) Ostermeier, M.; Brunner, B.; Korff, C.; Helmchen, G. *Eur. J. Org. Chem.* **2003**, 3453.
(13) Huo, S. Q.; Negishi, E. I. *Org. Lett.* **2001**, *3*, 3253.

Table 1. Reductive Alkylation of Sample Lactones[a]



entry	1	*n*	R^1	R^2	R	4	yield (%)
1	**1a**	1	Me	H	*i*-Bu	**4a**	79
2	**1a**	1	Me	H	*n*-Pr	**4b**	73
3	**1a**	1	Me	H	*n*-Hex	**4c**	75
4	**1a**	1	Me	H	*n*-Oct	**4d**	78
5	**1b**	1	H	Me	*n*-Bu[b]	**4e**	79
6	**1c**	2	Me	H	Ph	**4f**	76
7	**1d**	3	H	H	*n*-Bu[b]	**4g**	83

[a] Reagents and conditions: (i) *t*-BuLi (2.2 equiv), Et_2O, −78 °C, 1 h; (ii) **1** (1.1 equiv), Et_2O, −78 °C, 3 h; (iii) TMSCl (10 equiv), Zn (10 equiv), MeOH/Et_2O (3:1), 0 °C, 1 h. [b] Commercial 1 M solution of *n*-BuLi in hexanes was used.

results for comparison.[13] The absence of peaks at 4.15 ppm indicated the high enantiomeric purity of alcohol **4a**.

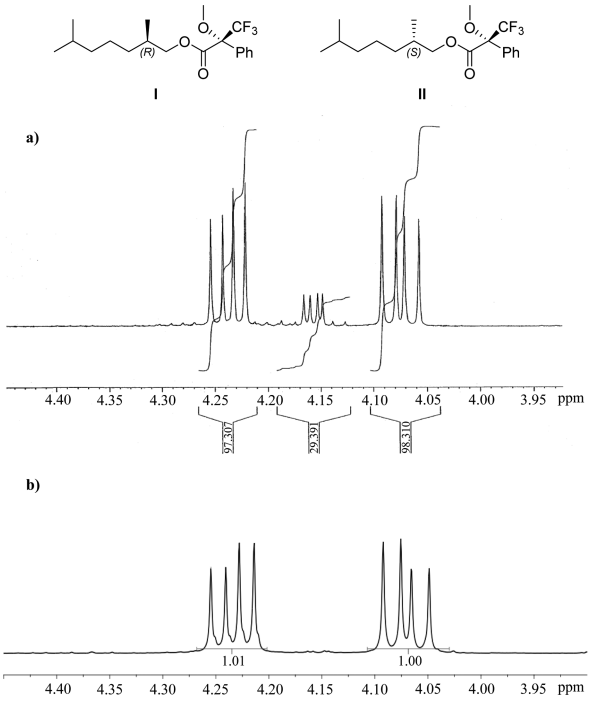
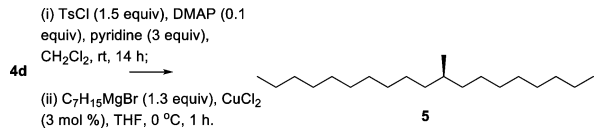


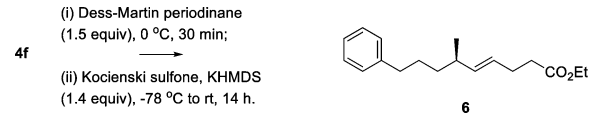
Figure 1. Spectroscopic analysis of the Mosher ester of **4a**.[13] (a) The ^{1}H NMR spectrum reported by Negishi for the mixture of the *R*-enantiomer (**I**, major) and *S*-enantiomer (**II**, minor). (b) The ^{1}H NMR spectrum of the crude ester from our alcohol **4a** synthesized from the "one-pot" procedure.

Alcohol **4c** is an advanced intermediate in the total synthesis of tuberculostearic acid, (*R*)-10-methylstearic acid originally isolated from *Mycobacterium tuberculosis*.[14]

Scheme 3. Synthesis of the Cotton Leafworm Sex Pheromone



Scheme 4. Synthesis of the C6 Side Chain of Zaragozic Acid C

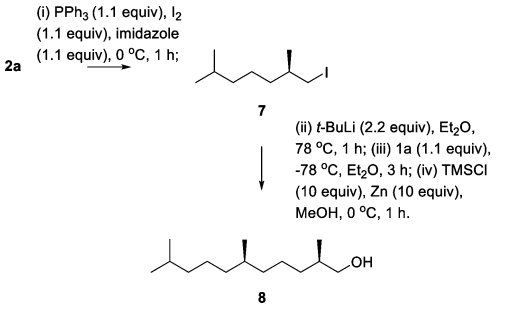


Significantly, **4f** is the commercially important fragrance (*R*)-Rosaphen which has been prepared previously by several groups.[15−17]

Simple activation of the alcohol produced in our procedure allows for the direct incorporation of the chiral isoprene unit in other natural product targets. For example, tosylation of **4d**, followed by Cu(II)-catalyzed displacement with *n*-heptylmagnesium bromide, provides (*S*)-9-methylnonadecane, **5** (>99% ee), in a total of three steps from (*R*)-3-methylbutyrolactone (Scheme 3). Product **5** is the major sex pheromone of female moths and larvae of the cotton leafworm (*Alabama argillacea*),[18] pests which feed on cotton leaves, twigs, and buds. Our synthesis of **5** (3 steps, 57%) is a substantial improvement over a previous synthesis (15 steps, 6%).[14]

Alternatively, Dess-Martin oxidation of **4f** gave the corresponding aldehyde, which was used without purification in a Kocienski-modified Julia olefination (Scheme 4).[19] This provided alkene **6**, the C6 side chain of Zaragozic acid C, a potent inhibitor of squalene synthase isolated from a sterile fungal culture of *Leptodontium elatius*,[20] in 81% yield and 98% ee over the two steps.

Scheme 5. Synthesis of the Vitamin E Side Chain



Given the occurrence of repeating chiral isoprene units in Nature, it was of obvious interest to establish whether or not our reductive alkylation methodology could be applied in an iterative manner to the undecanol **7**. This was chosen as a representative target, as it is the side chain moiety employed by Noyori's group in their total synthesis of *R*,*R*,*R*-α-tocopherol.[3] Thus conversion of **2a** into its corresponding iodide, employing Appel's procedure followed by lithiation, provided the nucleophile required to enter the next reductive alkylation cycle (Scheme 5). This process gave **8** in 41% overall yield from **2a**.

In summary, we have developed a very short, two-step protocol for reductively alkylating lactones employing a sequence of nucleophilic addition followed by modified in situ Clemmensen reduction. This has provided the basis for a simple and versatile method for synthesizing enantiomerically pure chiral isoprenoids.

Acknowledgment. J.C. is grateful to the China Scholarship Council and Monash University for financial support.

Supporting Information Available. Experimental procedures and ^{1}H NMR spectra for **4a**−**4f**, **5**−**9** as well as ^{13}C NMR spectra for **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

(14) Anderson, R. J.; Chargaff, E. *J. Biol. Chem.* **1929**, *85*, 77.
(15) Santini, C.; Ball, R. G.; Berger, G. D. *J. Org. Chem.* **1994**, *59*, 2261.
(16) Nicewicz, D. A.; Satterfield, A. D.; Schmitt, D. C.; Johnson, J. S. *J. Am. Chem. Soc.* **2008**, *130*, 17281.
(17) Matteoli, U.; Beghetto, V.; Scrivanti, A.; Aversa, M.; Bertoldini, M.; Bovo, S. *Chirality* **2011**, *23*, 779.
(18) Lamers, Y. M. A. W.; Rusu, G.; Wijnberg, J. B. P. A.; de Groot, A. *Tetrahedron* **2003**, *59*, 9361.
(19) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, *1998*, 26.
(20) Dufresne, C.; Wilson, K. E.; Zink, D.; Smith, J.; Bergstrom, J. D.; Kurtz, M.; Rew, D.; Nallin, M.; Jenkins, R.; Bartizal, K.; Trainor, C.; Bills, G.; Meinz, M.; Huang, L.; Onishi, J.; Milligan, J.; Mojena, M.; Pelaez, F. *Tetrahedron* **1992**, *48*, 10221.

The authors declare no competing financial interest.