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Transfer of Chirality by the Use of an All Carbon Tether

Marie-Gabrielle Braun, Rama Heng, and Samir Z. Zard*

Laboratoire de Synthèse Organique, CNRS UMR 7652, Ecole Polytechnique, 91128 Palaiseau Cedex, France

zard@poly.polytechnique.fr

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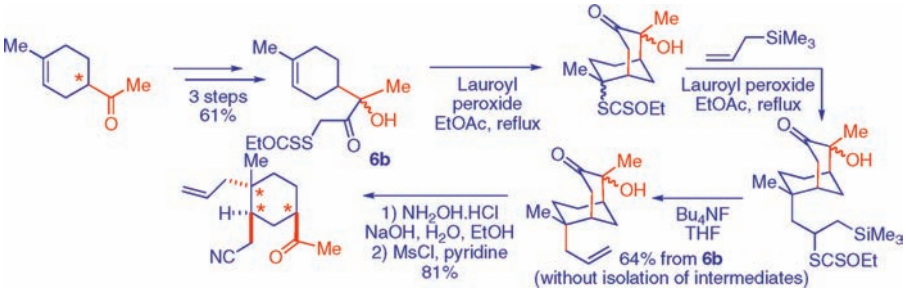
ABSTRACT



Methylketone side chains can be used to direct the creation of one or more chiral centers, including quaternary centers, by exploiting the ability of the radical xanthate transfer process to mediate six-membered ring formation.

In a study related to devising a general approach to the eudesmane class of terpenes,[1] represented by general structure **1** and exemplified by β-eudesmol **2**, pygmol **3**, and kikkanol B **4**,[2] we considered the possibility of combining the power of the Diels–Alder reaction with that of the radical chemistry of xanthates in order to control the relative, and ultimately absolute, stereochemistry around ring B. Our conception, outlined in simplified form in Scheme 1, hinges on exploiting the ready accessibility of the cycloadducts of isoprene such as **5** in enantiopure form[3] and using the methyl ketone to direct a radical carbon–carbon forming process from the same β-side of the cyclohexene ring. A temporary tether based on a vicinal hydroxyketone motif, as in **6** and **7**, would allow through oxidative cleavage the recovery of the methyl ketone in **8**, which could then be easily converted into the isopropyl, isopropenyl, or dimethylcarbinol side chains found in the eudesmanes. The nature of substituents R and R′ can be selected in a manner that allows for the easy construction of ring A. Furthermore, by starting with functionalized isoprenes such as **9** or **10**, the introduction of a hydroxy group in position 6, as in pygmol **3**, or in position 14, as in kikkanol B **4**, respectively, would become very easy.

The sequence in Scheme 1 represents in fact a transfer of chirality using a carbon tether. The use of temporary tethers to control stereochemistry has proven to be a very powerful strategy in organic synthesis.[4] In the case of radical reactions, Stork and Itoh pioneered a quarter of a century ago the use of temporary mixed acetal and, especially, silicon tethers (e.g., **11a** and **11b** in Scheme 2).[5] Their

(1) Wu, Q.-W.; Yan-Ping Shi, Y.-P.; Jia, Z.-J. *Nat. Prod. Rep.* **2006**, *23*, 699.

(2) For a recent discussion of the synthesis of eudesmanes, see: (a) Chen, K.; Baran, P. S. *Nature* **2009**, *459*, 824. (b) Chen, K.; Ishihara, Y.; Galan, M. M.; Baran, P. S. *Tetrahedron* **2010**, *66*, 4738.

(3) For recent reviews on enantioselective Diels–Alder reactions, see: (a) Corey, E. J.; Kürti, L. *Enantioselective Chemical Synthesis*; Direct Book Publishing: 2010. (b) Corey, E. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 2100 and references cited therein.

(4) For reviews, see: (a) Bracegirdle, S.; Anderson, E. A. *Chem. Soc. Rev.* **2010**, *39*, 4114. (b) Gauthier, D. R.; Zandi, K. S.; Shea, K. J. *Tetrahedron* **1998**, *54*, 2289. (c) Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063. (d) Fensterbank, L.; Malacria, M.; Sieburth, S. M. *Synthesis* **1997**, 813. (e) Bols, M.; Skrydstrup, T. *Chem. Rev.* **1995**, *95*, 1253. (f) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237.

(5) (a) Stork, G.; Mook, R., Jr.; Biller, S. A.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1983**, *105*, 3741. (b) Nishiyama, H.; Kitajima, T.; Matsumoto, M.; Itoh, K. *J. Org. Chem.* **1984**, *49*, 2298. (c) Stork, G.; Kahn, M. *J. Am. Chem. Soc.* **1985**, *107*, 500. (d) Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1986**, *108*, 303. (e) Stork, G.; Suh, H. S.; Kim, G. *J. Am. Chem. Soc.* **1991**, *113*, 7054. (f) Stork, G.; Kim, G. *J. Am. Chem. Soc.* **1992**, *114*, 1087.

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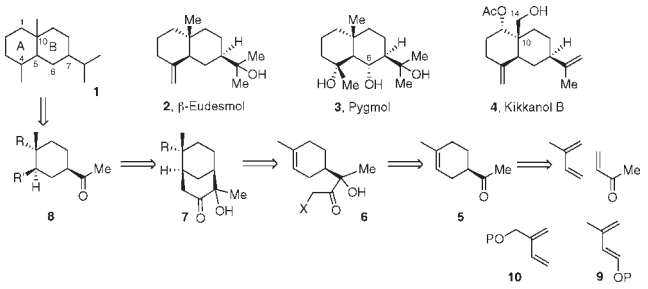
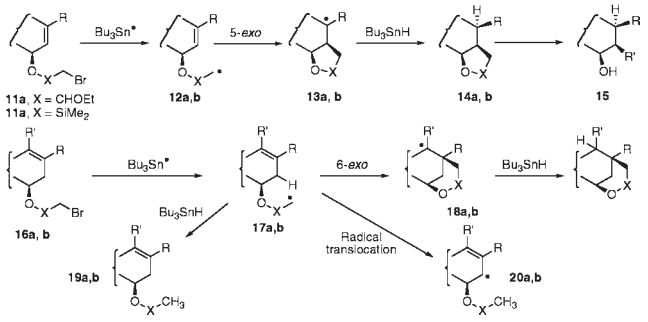
Scheme 1



Scheme 2



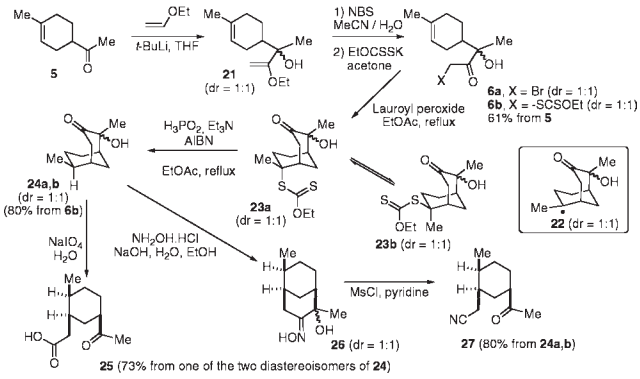
approach, relying mostly on stannanes, starts from allylic alcohols and allows control of the stereochemistry through the creation of a temporary 5-membered ring anchored to the hydroxy group as in **14a** or **14b** and constructed by a 5-*exo*-ring closure onto the adjacent alkene. Cleavage of the linking chain reveals a product, e.g. **15**, where the stereochemistry at one or more chiral centers has been completely controlled.

In very rare instances involving silicon linkages, it was observed that a temporary 6-membered ring may be assembled by a 6-*exo*- (as in **17** → **18**, X = $SiMe_2$) or a 6-*endo*-cyclization process.[6] The main limitation is due to the relative sluggishness of the cyclization step with respect to premature reduction of the intermediate radical **17** by the stannane to give **19a**,**b**. Indeed, in the prototypical 5-hexen-1-yl radical, the 6-*endo*-cyclization is 50 times slower than the 5-*exo*-ring closure.[7] A further serious complication in the 6-*exo*-mode is the possibility of an internal abstraction of an allylic hydrogen to give allylic radical **20a**,**b**.

(6) (a) Koreeda, M.; George, I. A. *J. Am. Chem. Soc.* **1986**, *108*, 8098. (b) Koreeda, M.; Hamann, L. G. *J. Am. Chem. Soc.* **1990**, *112*, 8175. Hanessian, S.; Di Fabio, R.; Marcoux, J. F.; Prud'homme, M. *J. Org. Chem.* **1990**, *55*, 3436.

(7) (a) Newcomb, M. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 1, pp 317−336. (b) Newcomb, M. *Tetrahedron* **1993**, *49*, 1151. (c) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3037.

Scheme 3



In the xanthate transfer process, the reaction of the intermediate radical with its xanthate precursor is reversible and degenerate. This key property contrasts with most other radical based methods. It provides the intermediate radical with an increased lifetime, which hopefully would allow it to overcome the kinetic barrier of a 6-*exo*-ring closure.[8] Moreover, by using a stabilized acetonyl radical in the cyclization step, the undesired competition from the intramolecular abstraction of an allylic hydrogen should be curtailed.[8h]

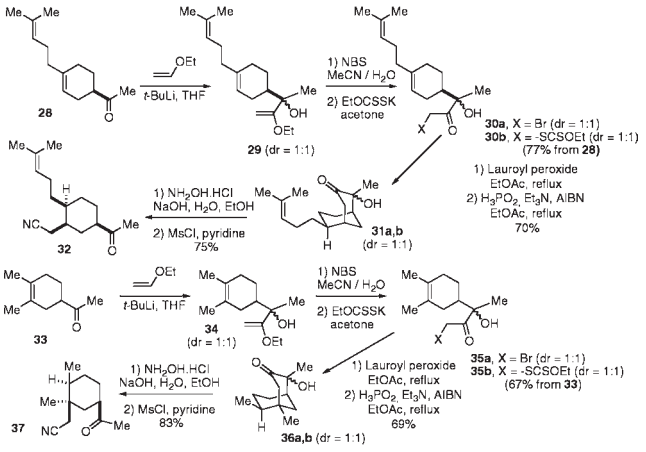
Our projected approach was implemented by first reacting ketone **5** with 1-ethoxyvinyl lithium to give enol ether **21** (Scheme 3). Bromination and displacement with potassium *O*-ethyl xanthate furnished precursor **6b** in a good overall yield as a 1:1 mixture of epimers. Pleasingly, the lauroyl peroxide mediated radical ring closure proceeded smoothly to form the desired [3.2.1] bicyclic structure **23**. Diastereoisomer **23a** is presumably the kinetically favored product, but since the xanthate group exchanges continuously via intermediate radical **22**, the more stable epimer **23b** with the xanthate in the equatorial position accumulates over time. This is of no consequence for the next reduction step. Indeed, treatment with triethylammonium hypophosphite and a small amount of AIBN[9] furnished the reduced material as a separable 1:1 mixture of epimers **24a,b** in an 80% overall yield from **6b**. Clearly, the *irreversible* transfer of the hydrogen atom takes place solely from the least hindered α-side.

In order to regenerate the methylketone side chain, we initially planned to cleave the α-hydroxy-ketone using periodate. However, only one of the two epimers of **24a,**

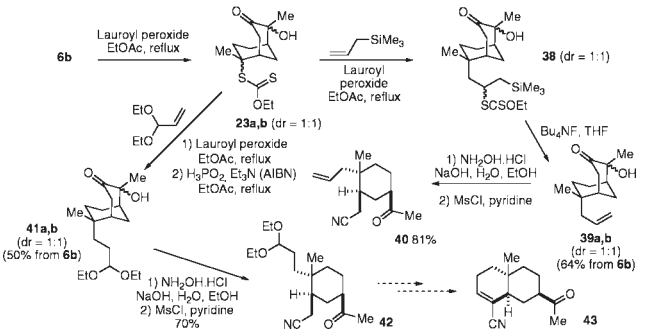
(8) For reviews of the xanthate transfer chemistry, see: (a) Zard, S. Z. *Angew. Chem., Int. Ed.* **1997**, *36*, 672. (b) Zard, S. Z. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 1, p 90. (c) Quiclet-Sire, B.; Zard, S. Z. *Chem.—Eur. J.* **2006**, *12*, 6002. (d) Quiclet-Sire, B.; Zard, S. Z. *Top. Curr. Chem.* **2006**, *264*, 201. (e) Zard, S. Z. *Aust. J. Chem.* **2006**, *59*, 663. (f) Zard, S. Z. *Org. Biomol. Chem.* **2007**, *5*, 205. (g) Quiclet-Sire, B.; Zard, S. Z. *Pure Appl. Chem.* ASAP (doi: 10.1351/PAC-CON-10-08-07). (h) Bergeot, O.; Corsi, C.; El Qacemi, M.; Zard, S. Z. *Org. Biomol. Chem.* **2006**, *4*, 278.

(9) (a) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. Cs. *Tetrahedron Lett.* **1992**, *33*, 5709. (b) Boivin, J.; Jrad, R.; Juge, S.; Nguyen, V. T. *Org. Lett.* **2003**, *5*, 1645.

Scheme 4



Scheme 5



b reacted to give keto acid **25** in 73% yield, while the other remained unscathed under the usual reaction conditions. No attempt to use forcing conditions were made, as our aim was to establish a sequence that would be as mild as possible. An alternative approach was to perform the scission by way of an abnormal Beckmann rearrangement.[10] To this end, the epimeric mixture of ketone **24a,b** was converted into oxime **26**, which was treated with mesyl chloride in pyridine to give keto nitrile **27** in an 80% overall yield. The methyl ketone side chain in the starting cyclohexene **5** could thus be used to introduce a cyanomethyl substituent, while controlling the relative stereochemistry of two new chiral centers in **27**.

The same sequence was applied to the more complex myrcene derived methyl ketone **28** (Scheme 4). Compound **31a,b**, obtained equally efficiently as a separable epimeric mixture, was cleanly converted into ketone **32** by the same modified Beckman rearrangement (Scheme 4). Having established the feasibility of this strategy for the transmission of chirality, we examined some further extensions. One important question concerned the possibility of stereoselectively creating a quaternary center. Placing a substituent on the alkene terminus where the radical addition is to take place slows down considerably the rate of cyclization. For instance, the 5-*exo*-cyclization of the 5-*methyl*-5-hexen-1-yl radical is about 40 times slower than that of the parent 5-hexen-1-yl radical.[11] In the case of the already sluggish 6-*exo*-cyclization, the substitution on the alkene moiety could slow down the rate to a level that would make it synthetically useless.

We were indeed relieved when exposure of xanthate **35b** derived from ketone **33** gave rise to the desired epimeric mixture of bicyclic product **36a,b** following the usual reduction step (Scheme 4), albeit in a slightly reduced overall yield (69%). The ring-opening process to regenerate the methyl ketone side chain in **37** proceeded normally.

The xanthate in the cyclized product may be readily converted into numerous other sulfur groups possessing an exceptionally rich chemistry.[12] Alternatively, another radical carbon−carbon bond forming process may be performed, before the cutting of the linking chain. Two such transformations are displayed in Scheme 5. The first concerns addition of xanthate **23a,b**, prepared above as an epimeric mixture, to allyl trimethylsilane to give derivative **38**, where both the xanthate and the trimethylsilyl groups may be eliminated by treatment with tetrabutylammonium fluoride.[13] In this manner, epimeric allyl derivative **39a,b** was obtained in 64% overall yield from **6b** without isolation of the intermediates. It could be cleaved by the abnormal Beckmann rearrangement to furnish **40** cleanly.

While the addition to allyl trimethylsilane represents a convenient method for introducing an allyl group, numerous other side chains bearing diverse functionalities can be attached by simply using the corresponding alkene trap. For example, the separable 1:1 epimeric mixture of bicyclic compound **41a,b** was produced in 50% overall yield from **6b**, without isolation of the intermediates, by cyclization, *intermolecular* addition to the diethyl acetal of acrolein, and reductive removal of the xanthate. Cleavage of the linking chain furnished **42** (70%). The presence of the masked aldehyde should allow the swift construction of *trans*-decalin **43** through deprotection and condensation of the liberated aldehyde with the acetonitrile side chain.[14] It is worth emphasizing that in both products, **40** and **42**,

(10) (a) Singhal, G. M.; Das, N. B.; Sharma, R. P. *J. Chem. Soc., Chem. Commun.* **1990**, 498. (b) Mulijiani, Z.; Desmukh, A. R. A. S.; Gadre, S. R.; Joshi, V. S. *Synth. Commun.* **1987**, *17*, 25. (c) Forrester, A. R.; Irikawa, H.; Thomson, R. H.; Woo, S.-O.; King, T. J. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1712. (d) Yates, P.; Wong, J.; McLean, S. *Tetrahedron* **1981**, *37*, 3357. (e) Wakamatsu, T.; Fukui, M.; Ban, Y. *Synthesis* **1976**, 341. (f) Shoppee, C. W.; Ram, P.; Roy, S. K. *J. Chem. Soc. (C)* **1966**, 1023. Shoppee, C. W.; Roy, S. K. *J. Chem. Soc.* **1963**, 3774.

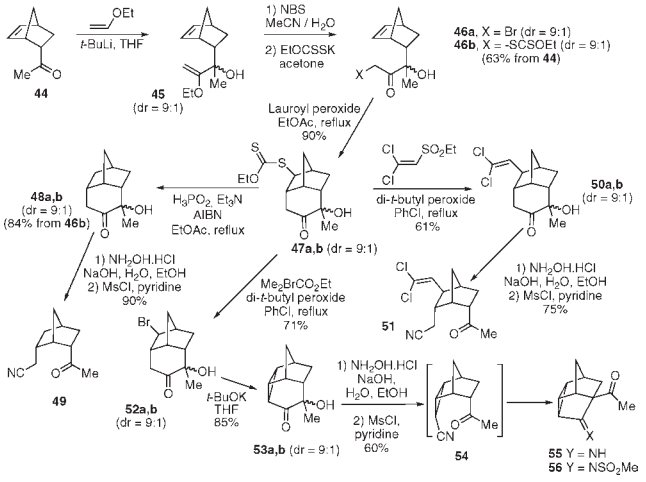
(11) (a) Beckwith, A. L. J.; Easton, C. J.; Serelis, A. K. *J. Chem. Soc., Chem. Commun.* **1980**, 482. (b) Beckwith, A. L. J.; Blair, A. I.; Phillipou, G. *Tetrahedron Lett.* **1974**, 2251.

(12) Zard, S. Z. In *Handbook of RAFT Polymerization*; Barner-Kowollik, C., Ed.; Wiley-VCH: Weinheim, 2008; pp 151−187.

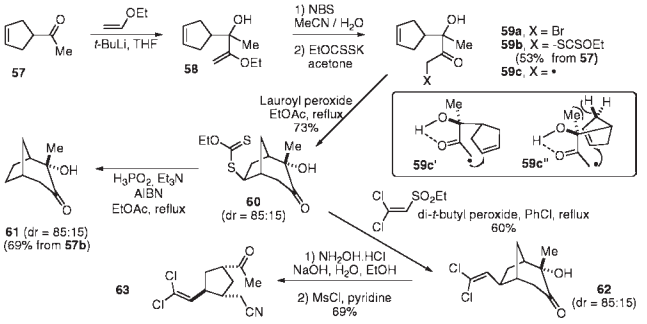
(13) Briggs, M. E.; Zard, S. Z. *Synlett* **2005**, 334.

(14) It is interesting to note in this respect that ozonolysis of the olefin in compound **32** would also give a propionaldehyde side chain that could condense with the acetonitrile moiety, but this time to give a *cis*-decalin.

Scheme 6



Scheme 7



a new quaternary center has been created with complete stereocontrol.

Diels−Alder adducts derived from cyclic dienes such as cyclopentadiene are also suitable substrates for the remote stereochemical control using an all carbon tether, as depicted in Scheme 6. Thus, ketone **44** was converted into xanthate **46b**,[15] which underwent efficient cyclization into separable epimeric mixture **47a,b** and reduction and cleavage to afford methylketone **49** in good yield.

More interesting is the reaction of xanthate **47a,b** with dichlorovinyl ethyl sulfone leading, after scission of the linking chain, to product **51**, where the xanthate group has been replaced by an exceedingly useful dichlorovinyl moiety.[16] The dichlorovinyl group, which exclusively from the least hindered *exo* face may be further elaborated by exploiting various transition metal catalyzed couplings, or converted into a chloroalkyne by treatment with base,[17] or into an alkyne by the powerful Corey-Fuchs reaction,[18] or cleaved by ozone to the nor-aldehyde.

Another manner of exploiting the presence of the xanthate group in **47a,b** is to exchange it with a bromine by heating with ethyl bromoisobutyrate in the presence of stoichiometric amounts of peroxide.[19] The bromine atom in the product, **52a,b**, is also delivered from the *exo* face, and exposure to base induces the formation of cyclopropane derivative **53a,b** in good yield. In this case, however, the abnormal Beckmann rearrangement leading to **54** was followed by a spontaneous ring-closure to give imine **55**, which then reacted with the excess mesyl chloride to give sulfonimide **56** in a 60% overall yield. This remarkaby facile cyclization is no doubt the result of the unbearably strong steric congestion which forces the enolate of the ketone into very close proximity to the nitrile group.

While the combination of the Diels−Alder cycloaddition and the xanthate transfer process constitutes a potent alliance, the present strategy for remote stereochemical control is obviously not limited to cyclohexenyl substrates. Analogous sequences can be accomplished starting with other ring sizes, as indicated by the transformations in Scheme 7 starting with ketone **57** and leading ultimately to products **61** and **63**, where the relative stereochemistry around the cyclopentene ring has been fully controlled. It is interesting to note that the ring closure is quite stereoselective, leading to a major diastereoisomer **58** with the relative stereochemistry indicated. The hydrogen-bonded intermediate radical **59c** is capable of attacking either terminus of the cyclopentene, but the pathway drawn as **59c′** in the box in Scheme 7 appears to be preferred. The alternative mode **59c″** suffers from a destabilizing steric replusion between the methyl group and one of the hydrogens in the ring, as shown.

In summary, we have now in hand a unified, flexible, and convergent strategy for transmitting the stereochemical information from a distal acetyl side chain on a cycloalkene. In contrast to the disposable silicon based tethers, all the elements of the present linking chain are retained in the product. Moreover, the transfer of the xanthate group opens up numerous possibilities for subsequent modifications, including stereoselective carbon−carbon bond formation by an *intermolecular* radical addition and the generation of quaternary centers.

Acknowledgment. We dedicate this paper with respect and admiration to Professor Gilbert Stork (Columbia University). M.-G.B. thanks Ecole Polytechnique for a scholarship.

Supporting Information Available. Experimental procedures, full spectroscopic data, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(15) The addition of the ethoxyvinyllithium to ketone **44** is surprisingly stereoselective. The addition of isopropylmagnesium iodide to the corresponding aldehyde has been reported and appears to give only one epimer, but no comments are given by the authors: Nakazaki, M.; Naemura, K.; Kondo, Y. *J. Org. Chem.* **1976**, *41*, 1229.

(16) Bertrand, F.; Quiclet-Sire, B.; Zard, S. Z. *Angew. Chem., Int. Ed.* **1999**, *38*, 1943.

(17) Carran, J.; Waschbuch, R.; Marinetti, A.; Savignac, P. *Synthesis* **1996**, 1494.

(18) For a recent review, see: Habrant, D.; Rauhala, V.; Koskinen, A. M. P. *Chem. Soc. Rev.* **2010**, *39*, 2007. E. J. Corey, E. J.; P. L. Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769.

(19) Barbier, F.; Pautrat, F.; Quiclet-Sire, B.; Zard, S. Z. *Synlett* **2002**, 811.