Tetrahedron Letters 53 (2012) 4276–4279

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Formation of N-substituted 4- and 7-oxo-4,5,6,7-tetrahydroindoles revisited: a mechanistic interpretation and conversion into 4- and 7-oxoindoles

Antonio Garrido Montalban *, Sven M. Baum, Justin Cowell, Alexander McKillop

School of Chemical Sciences, University of East Anglia, Norwich NR4 7TJ, UK

ARTICLE INFO

Article history:
Received 21 April 2012
Revised 15 May 2012
Accepted 19 May 2012
Available online 1 June 2012

Keywords:
Indoles
Tetrahydroindoles
Cyclization
Aromatization
Chirality

ABSTRACT

An efficient method for the preparation of 4-oxo-4,5,6,7-tetrahydroindoles was successfully applied to the synthesis of N-substituted 7-oxo-4,5,6,7-tetrahydroindoles for the first time. Both isomers where converted into their corresponding 4- and 7-oxoindoles in good yields utilizing a novel aromatization protocol. Based on the impurity profile obtained, however, different mechanisms for the formation of the 4- and 7-oxo-4,5,6,7-tetrahydroindole derivatives are discussed. In addition, the reaction sequences appear to be stereospecific allowing for the direct introduction of a chiral center α to the nitrogen and preparation of enantiomerically enriched products.

Over ten thousand biologically active indole derivatives have been identified to date. Of those, over 200 are currently marked as drugs or undergoing clinical trials.[1] As such, improved or new methods for the construction of this heterocyclic system are constantly needed. This is particularly true for the development of safe and efficient large scale preparations, given the ubiquitous characteristics of indoles among bioactive molecules and natural products.[2] Although a variety of ring-substituted indoles are accessible through classical methods such as the Fischer, Bischler, Madelung, Reissert, Nenitzescu and Gassman procedures,[3] limitations can arise from difficult to obtain precursors and/or low reaction conversions. As part of our pharmacological compound evaluation, we were interested in synthesizing N-substituted 7-alkoxyindoles with the possibility of introducing a chiral center α to nitrogen. The more recent Bartoli indole synthesis is one of the most efficient methods available for the preparation of 7-substituted indoles[4] and has been successfully applied for the synthesis of 7-alkoxy derivatives.[5] As the above syntheses, however, it is mainly suitable for the formation of N-unsubstituted indoles and, to our knowledge, direct methods for the synthesis of N-substituted 7-alkoxyindoles are rare. A survey of the literature revealed that 7-oxotetrahydroindoles could serve as precursors to 7-alkoxyindoles and allow us to directly prepare the compounds of interest. Thus, herein we report our strategy towards the synthesis of N-substituted 7-oxo-4,5,6,7-tetrahydroindoles, an initial mechanistic interpretation and successful conversion of the former into 7-oxoindoles including optically active analogs.

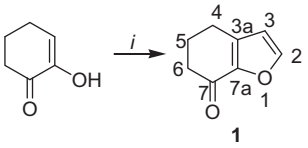
Several examples of laborious multistep Haworth type ring annelations, starting from pyrroles, to give N-unsubstituted 7-oxotetrahydroindoles are known.[6] *N*-Methyl 7-oxo-4,5,6,7-tetrahydroindole, on the other hand, was obtained in low yield through a condensation/cyclization sequence of aminoacetaldehyde dimethyl acetal with 1,2-cyclohexanedione.[7] *N*-Benzyl 7-oxotetrahydroindoles have been prepared in modest yields via reaction of 2,3-epoxy-3-methylcyclohexanones with benzylamine and cyclization of the resulting enamines with dimethylformamide dimethyl acetal (dmfdma) to form the pyrrole ring in a similar manner to the Leimgruber–Batcho[3] indole synthesis. In our hands, however, this procedure resulted in much lower yields than reported.[8] Similar enamines as the ones discussed above, give N-substituted 7-oxotetrahydroindoles when reacted with nitroolefins. Again, this method is limited since it is very substrate dependent and in fact the reaction is reported to only proceed rapidly and almost quantitatively with the enamine derived from benzylamine.[9] In contrast, efficient methods for the synthesis of the 4-oxo isomer are much more abundant, with the first generally useful method appearing in 1962.[10] This procedure and modifications thereof[11] are based on treatment of 4-oxotetrahydrobenzofuran derivatives with ammonia or primary amines in, for example, a sealed vessel at high temperatures. Syntheses involving condensation/cyclization of aminocarbonyl equivalents to 1,3-cyclohexadiones for the formation of 4-oxo-tetrahydroindoles are also known.[12] More recently, Martinelli and co-workers reported a very elegant entry into the 4-oxotetrahydroindole core via a novel intramolecular 1,3-dipolar cycloaddition approach.[13]

The simplicity of Matsumoto and Watanabe[11a] modified procedure for the synthesis of N-substituted 4-oxotetrahydroindoles

* Corresponding author. Tel.: +1 858 453 7200; fax: +1 858 453 7210.
E-mail address: amontalban@arenapharm.com (A.G. Montalban).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.05.090

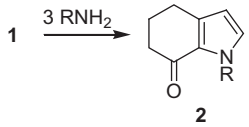
mentioned earlier, however, prompted us to exploit the same strategy for the preparation of N-substituted 7-oxotetrahydroindoles. Thus, treatment of 1,2-cyclohexadione with chloroacetaldehyde in the presence of sodium bicarbonate gave 7-oxo-4,5,6,7-tetrahydrobenzofuran **1** in 40% yield (Scheme 1). At the time we initiated our studies compound **1** had only been prepared via a Friedel-Crafts cyclization approach[14] but reported later in similar yield by Seki et al.[15] using the same modified Feist–Benary furan synthesis. Conversion of **1** into 7-oxotetrahydroindoles, however, was not further investigated. Thus, with the requisite precursor **1** in hand, we embarked onto its conversion into 7-oxotetrahydroindoles. Reactions were carried out in a sealed tube at 150 °C for 36 h. The results obtained from treating **1** with, 3 equiv each, ammonia and a variety of primary amines are summarized in Table 1. To our delight, the expected 7-oxotetrahydroindoles **2** were formed but the yields obtained, were much lower than what Matsumoto and Watanabe[11a] reported for equivalent reactions of the 4-oxo isomer **3**. For comparison, we converted the 4-oxo isomer **3** into the corresponding 4-oxotetrahydroindoles **4** under equivalent conditions and confirmed Matsumoto's observations (Scheme 2, Table 1, yields and products in parentheses). While we believe that the decreased yield of **4c** is due to its lower relative stability, the poor yield of **4g** is most likely associated with sterics (vide infra). Nevertheless, reaction of 4- and 7-oxo-4,5,6,7-tetrahydrobenzofuran **1** and **3**, respectively, with homochiral α-methylbenzylamine (Table 1, entry 6) appeared to proceed stereospecifically, since both products, **2f** ($[\alpha]^{25^\circ C}_{589nm} \approx +140^\circ$ at 6.6 mg/mL in $CHCl_3$) and **4f** ($[\alpha]^{25^\circ C}_{589nm} \approx -16^\circ$ at 6.2 mg/mL in $CHCl_3$), were found to be optically active (vide infra). Furthermore, **2f** obtained from reaction of **1** with homochiral α-methylbenzylamine was not only shown to be optically active but enantiomerically pure by comparing the ^1H NMR spectra of its (+)- and (−)-1-(9-anthryl)-2,2,2-trifluoroethanol (TFAE)[16] diastereomeric solvates with those generated from the racemate. Reaction of **1** and **3** with methyl 2-amino-2-phenylacetate, however, gave only achiral **2d** and **4d**, respectively, from apparent hydrolysis and decarboxylation. Nontheless, in addition to having established that 7-oxotetrahydroindoles **2** can be obtained from its corresponding 7-oxotetrahydrobenzofuran precursor **1**, the reaction proved to be stereospecific for both, **1** and **3** with compounds **4f** and **2f** being the first reported chiral examples of 4- and 7-oxotetrahydroindoles, respectively, utilizing this procedure. Due to the low yields of 7-oxotetrahydroindoles **2** obtained, however, a range of conditions were tried in an attempt to improve upon the original procedure (20% aq EtOH, 3 equiv of amine, 150 °C, 36 h, sealed tube).[17] Decreasing the reaction time to below 24 h and lowering the equivalences of the amine to below 3 led to even lower yields with substantial amounts of unreacted starting material present. No reaction occurred when the temperature was decreased to below 100 °C, whereas aprotic solvents (e.g., dichloroethane) and Lewis acids under anhydrous or aqueous conditions ($AlCl_3$ and $CeCl_3{\cdot}7H_2O$, respectively) tended to stall the transformation. On the other hand, similar yields to the original conditions were obtained when the reaction was carried out in protic solvents (MeOH, EtOH) under anhydrous or aqueous conditions in the presence or absence of small amounts of HCl. Interestingly, in the case of benzylic amines, small amounts of the corresponding carbonyl derivatives **8** could always be detected along with the product under all conditions. This was never observed with the 4-oxo isomer **3**. All of these variations, however, ultimately failed to increase the yield of the desired 7-oxotetrahydroindoles despite the fact that, under the best conditions, the starting material was completely consumed and no other UV-active organic soluble products than **2** and **8** (vide supra) were identifiable from the reaction mixtures. Intrigue by this outcome, we decided to perform a series of additional experiments in order to better understand the formal oxidation to **8**, fate of the starting material **1** and difference in reactivity between the 4- and 7-oxotetrahydrobenzofurans **3** and **1**, respectively. Reactions were carried out according to the most successful anhydrous conditions identified in a sealed tube, with the exception of using an inert atmosphere and open vessel. Under these conditions, reaction of **1** with α-methylbenzylamine did not give the expected product but a more complex mixture of baseline material and three closely running components by tlc. After column chromatography on silica the components were isolated and identified as tetrahydrobenzofuran derivative **5**, the corresponding imine **7** and, as before, acetophenone **8** (Scheme 3). With the less sterically hindered benzylamine, on the other hand, the expected (confirmed after hydrolysis of **6** to **2d** (10%) with aq NH_4Cl) masked oxotetrahydroindole derivative **6** along with the corresponding imine **7** and benzaldehyde **8** were obtained in low yield (Scheme 3). We reasoned that after initial attack of the amine at the 2-position of **1**, as the first step of an ANRORC (Addition of the Nucleophile, Ring Opening and Ring Closure) type mechanism, the enamine **9** should be formed (Fig. 1). In the case of **3**, conjugate addition of the amine at the 7a-position would result in formation of the more reactive for cyclization and stable to tautomerization enamine **14** directly (Fig. 2). Intermediate **14** could, therefore, undergo immediate ring closure to give the corresponding 4-oxotetrahydroindoles in high yield. In contrast, enamine **9** would presumably have to equilibrate first to tautomer **13** (Fig. 1, Path b) before ring closure.



1

Scheme 1. Reagent and condition: (i) chloroacetaldehyde, H_2O, $NaHCO_3$, 0–5 °C → rt overnight; aq H_2SO_4 (40%).

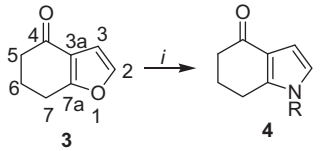
Table 1
Formation of 7-oxotetrahydroindoles **2** from reaction of **1** with aqueous ammonia and primary amines



2

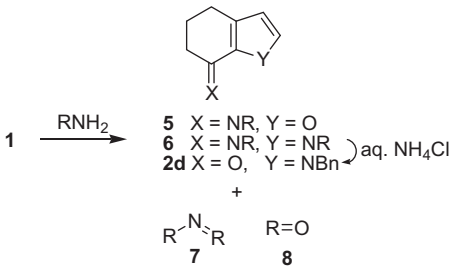
Entry	R	Product	Yield (%)
1	H	**2a**[6] (**4a**[11a])	36 (91)
2	Me	**2b**[7] (**4b**[11a])	22 (89)
3	C_6H_{11}	**2c** (**4c**)	34 (36)
4	Bn	**2d**[8] (**4d**[11a])	30 (83)
5	$PhCH_2\ CH_2$	**2e** (**4e**[22])	46 (71)
6	$PhCHCH_3$	**2f** (**4f**)	23 (83)
7	$PhCHC_4H_9$	**2g** (**4g**)	17 (8)

All reactions were performed in 20% aq EtOH at 150 °C for 36 h in a sealed tube. Yields and products in parentheses are those obtained from reactions with 4-oxotetrahydrobenzofuran **3** after 12 h.



3 4

Scheme 2. Reagent and condition: (i) 3 equiv RNH_2, 20% aq EtOH, 150 °C, 12 h.



Scheme 3. Reagent and condition: (i) excess RNH_2, protic solvent, N_2, Δ.

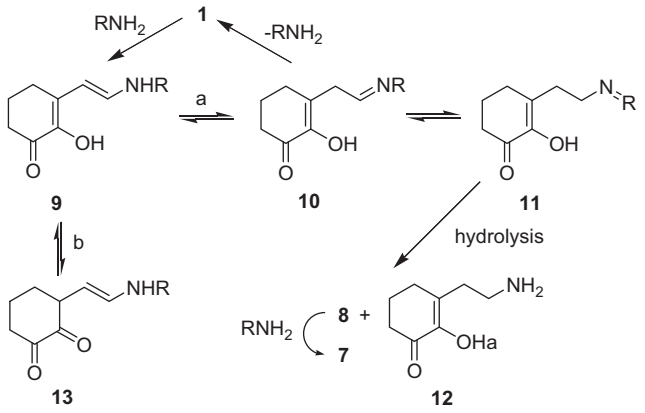


Figure 1. Proposed mechanism for the formation of **7** and **8** from reaction of **1** with primary amines.

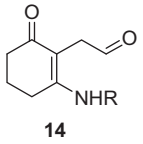
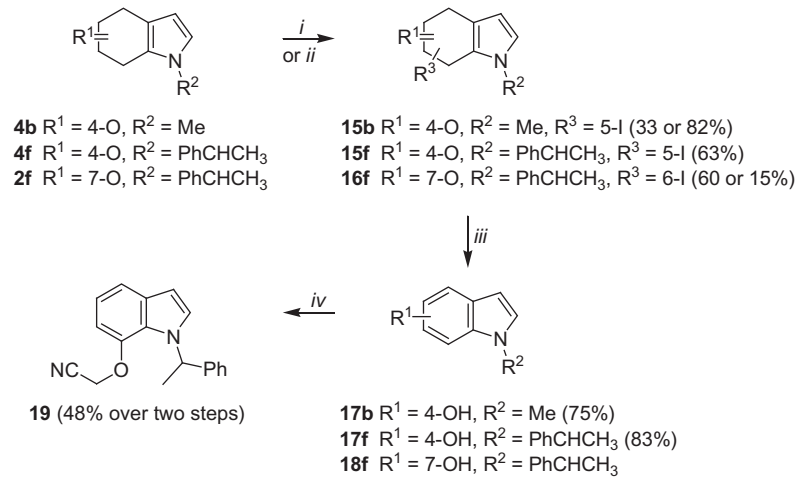


Figure 2. Proposed intermediate from reaction of **3** with primary amines according to an ANRORC type mechanism.

In addition, nucleophilic attack of the enamine moiety onto the ketone (compared to aldehyde) group in **13** is probably kinetically less favorable and the tetrahedral intermediate derived thereof more sterically hindered than the equivalent step in **14**. This may explain why reaction of **1** with α-methylbenzylamine in an open vessel resulted in products from competing lower energy pathways in place of **2f**. Thus, enamine **9** could have instead tautomerize through imine **10** to the more stable (at least when R is benzylic) imine **11** (Fig. 1, Path a) which, in turn, could then have been formally hydrolyzed to **8**. The corresponding carbonyl derivative **8** could then give imine **7** by reacting with excess of the amine. The determined enantiomeric purity of **2f** (vide supra) suggests that formation of the corresponding imine **10** is essentially irreversible (Path a), since no decreased enantiomeric excess or racemization is observed under sealed tube conditions. Thus, it appears that cyclization to oxotetrahydroindole **2f** occurs via the corresponding enamine **13** (Path b) without involvement of the stereogenic center of the starting homochiral α-methylbenzylamine which is, therefore, likely to be transferred to the product unchanged. For the same reasons, we expect the asymmetric center to remain intact over the sequence of reactions leading to oxoindoles **17f** and **19**. Attempts to increase the nucleophilicity of the amine by making the anion led only to deprotonation of **1** instead, as evidenced from the product (6-methyl-7-oxotetrahydrobenzofuran) obtained along with starting material after quenching of the reaction mixture with methyl iodide.

Aromatization of **2** and **4** to 4- and 7-hydroxyindoles, respectively, was not straightforward. While reported methods[6a,18] were, in our hands, not as robust as expected, other dehydrogenation strategies[19] or β-elimination procedures[20] failed. We attributed the limited success, in part, due to the relative instability of the products under the conditions of formation. On the other hand, refluxing **4b** and iodine in methanol[21] gave the corresponding 5-iodo derivative **15b** in 33% yield (Scheme 4).

The yield of **15b** could be further optimized to 82% by reacting **4b** with LDA (lithium diisopropylamide) and trapping of the resulting anion with iodine. Dehydrohalogenation, on the other hand, was best achieved with DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) as the base, thus, giving 4-hydroxyindole **17b** in 75% yield. Similarly, **15f** and enantiomerically enriched **17f** ($[\alpha]_{589nm}^{20^\circ C} \approx -61.4^\circ$ at 6.1 mg/mL in $CHCl_3$) were obtained in 63% (as a separable mixture of diastereoisomers) and 83%, respectively. Interestingly, refluxing **2f** and iodine in methanol gave a mixture of the corresponding 6-iodo analog **16f** (60%) and 3-iodo isomer (10%). The two isomers could easily be separated by column chromatography on silica (5% EtOAc in light petroleum ether as eluent). The diastereomeric



Scheme 4. Reagents and conditions: (i) MeOH, 2 equiv I_2, N_2, reflux, 2–4 h; (ii) LDA, THF, N_2, then I_2, −40 °C → rt, 2 h; (iii) DBU (neat), N_2, rt, 0.25–1 h; (iv) bromoacetonitrile, K_2CO_3, butanone, N_2, reflux, 1 h.

mixture (as confirm by H NMR) of **16f**, however, could not be further resolved. In contrast, deprotonation of **2f** with LDA followed by iodination gave **16f** in much lower yield (15%) along with starting material. Base catalyzed dehydrohalogenation (vide supra) of the diastereomeric mixture **16f** gave, as expected, a single product (**18f**) but again in low yield, especially at higher temperatures. We noticed that both, **16f** and in particular **18f** decomposed readily. Thus, **18f** was converted into its far more stable optically active ($[\alpha]_{589nm}^{20^\circ C} \approx +133^\circ$ at 1.9 mg/mL in $CHCl_3$) alkoxy derivative **19** by reacting it with bromoacetonitrile under basic conditions. The best yields (48% over two steps) of **19** were obtained when both, the dehydrohalogenation and alkylation steps were telescoped.

In Summary, we have developed a new synthesis of N-substituted 7-oxo-4,5,6,7-tetrahydroindoles and gained an understanding of why the relative yields are lower when compared to the corresponding 4-oxo-isomers under the conditions presented. Furthermore, both, 4-, and 7-oxo-4,5,6,7-tetrahydroindoles were successfully aromatized to their corresponding 4- and 7-oxoindoles utilizing a novel protocol. In addition, the reaction sequences appear to be stereospecific in nature resulting in enantiomerically enriched N-substituted derivatives of both, 4-, and 7-oxo-4,5,6,7-tetrahydroindoles and 4-, and 7-oxoindoles. Future work will involve further optimization by, for example, conducting the synthesis of 7-oxo-4,5,6,7-tetrahydroindoles under microwave irradiation as recently demonstrated for the 4-oxo derivatives.[22]

Acknowledgments

We would like to thank Eli Lilly (A.G.M. and J.C.) and the Erasmus Scheme (S.M.B.) for generous support of our studies.

References and notes

1. Bronner, S. M.; Im, G.-Y. J.; Garg, N. K. Indoles and Indolizidines. In *Heterocycles in Natural Product Synthesis*; Majumdar, K. C., Chattopadhyay, S. K., Eds.; Wiley-VCH & Co. KGaA: Weinheim, 2011; pp 221–265. and references cited therein.
2. Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875–2911. and references cited therein.
3. (a) Joule, J. A.; Mills, K.; Smith, G. F. In *Heterocyclic Chemistry*, 3rd ed.; Chapman & Hall: London, 1995; pp 305–349; (b) Gilchrist, G. L. In *Heterocyclic Chemistry*, 2nd ed.; Longman Scientific & Technical: Essex, 1992; pp 223–236; (c) Davies, D. T. In *Aromatic Heterocyclic Chemistry*; Davies, S. G., Ed.; Oxford University Press: Oxford, 1992; pp 53–60.
4. Bartoli, G.; Palmieri, G.; Bosco, M.; Dalpozzo, R. *Tetrahedron Lett.* **1989**, *30*, 2129–2132.
5. Dobson, D.; Todd, A.; Gilmore, J. *Synth. Commun.* **1991**, *21*, 611–617.
6. (a) Berger, J. G.; Teller, S. R.; Pachter, I. J. *J. Org. Chem.* **1970**, *35*, 3122–3126; (b) Murakami, Y.; Tani, M.; Ariyasu, T.; Nishiyama, C.; Watanabe, T.; Yokoyama, Y. *Heterocycles* **1988**, *27*, 1855–1860. and references cited therein.
7. Massa, S.; Stefancich, G.; Artico, M.; Corelli, F.; Silvestri, R. *Farmaco Ed. Sci.* **1987**, *42*, 567–574.
8. Kasum, B.; Prager, R. H.; Tsopelas, C. *Aust. J. Chem.* **1990**, *43*, 355–365.
9. Benedetti, F.; Berti, F.; Nitti, P.; Pitaco, G.; Valentin, D. *Gazz. Chim. Ital.* **1990**, *120*, 25–28.
10. Stetter, H.; Lauterbach, R. *Liebigs Ann. Chem.* **1962**, *655*, 20–26.
11. (a) Matsumoto, M.; Watanabe, N. *Heterocycles* **1984**, *22*, 2313–2316. and references cited therein; (b) Maiti, S.; Perumal, P. T.; Menendez, J. C. *Tetrahedron* **2010**, *66*, 9512–9518; (c) Yadav, P. P.; Gupta, P.; Chaturvedi, A. K.; Shukla, P. K.; Maurya, R. *Bioorg. Med. Chem.* **2005**, *13*, 1497–1505.
12. (a) Edstrom, E. D. *Synlett* **1995**, 49–50. and references cited therein; (b) Masaguer, C. F.; Raviña, E. *Tetrahedron Lett.* **1996**, *37*, 5171–5174. and references cited therein.
13. Nayyar, N. K.; Hutchinson, D. R.; Martinelli, M. J. *J. Org. Chem.* **1997**, *62*, 982–991.
14. Walsh, E. J., Jr.; Stone, G. B. *Tetrahedron Lett.* **1986**, *27*, 1127–1130.
15. Seki, M.; Sakamoto, T.; Suemune, H.; Kanematsu, K. J. *Chem. Soc., Perkin Trans. 1* **1997**, 1707–1714.
16. Pirkle, W. H.; Sikkenga, D. L.; Pavlin, M. S. *J. Org. Chem.* **1977**, *42*, 384–387.
17. *General Procedure for the preparation of 4- and 7-oxotetrahydroindoles:* A solution of 1 or 3 (0.10 g, 0.73 mmol) and the corresponding amine (3 equiv) in 20% aqueous EtOH (~2 mL) was heated in a sealed tube at 150 °C for 12 or 36 h, respectively. The reaction mixture was poured into H_2O (10 mL) and the resulting aqueous solution extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), concentrated and the brown residue subjected to column chromatography (silica) with EtOAc/light petroleum ether as eluent.
18. (a) Plieninger, H.; Klinga, K. *Chem. Ber.* **1968**, *101*, 2605–2607; (b) Remers, W. A.; Weiss, M. J. *J. Org. Chem.* **1971**, *36*, 1241. and references cited therein.
19. (a) Hughes, B.; Suschitzky, H. *J. Chem. Soc.* **1965**, 875–879; (b) Fatiadi, A. J. *Synthesis* **1976**, 133–167; (c) Jung, M. E.; Pan, Y.-G. *J. Org. Chem.* **1977**, *42*, 3961–3963; (d) Fleming, I.; Paterson, I. *Synthesis* **1979**, 736–738; (e) Danishefsky, S.; Chackalamannil, S.; Harrison, P.; Silvestri, M.; Cole, P. *J. Am. Chem. Soc.* **1985**, *107*, 2474–2484; (f) Enda, J.; Kuwajima, I. *J. Am. Chem. Soc.* **1985**, *107*, 5495–5501; (g) Knölker, H.-J. *Synlett* **1992**, 371–387; (h) Knölker, H.-J.; Bauermeister, M.; Pannek, J.-B.; Bläser, D.; Boese, R. *Tetrahedron* **1993**, *49*, 841–862.
20. Williams, D. R.; Nishitani, K. *Tetrahedron Lett.* **1980**, *21*, 4417–4420.
21. Kotnis, A. S. *Tetrahedron Lett.* **1991**, *32*, 3441–3444.
22. Piras, L.; Ghiron, C.; Minetto, G.; Taddei, M. *Tetrahedron Lett.* **2008**, *49*, 459–462.