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Photoinduced radical reactions of α-alkylated ethyl 2-oxo-1-cyclopentanecarboxylate derivatives: α-cleavage and cyclization to the skeleton of linear cyclohexano diquinanes

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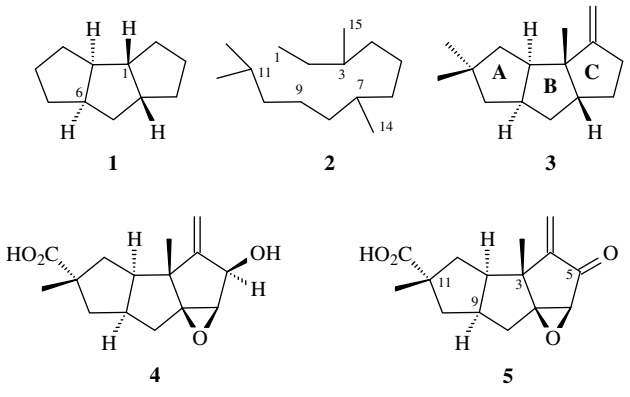
Abstract

The tricyclic core of linear cyclohexano diquinanes was synthesized using photoinduced electron transfer (PET) as a key step. The reaction proceeded in high regioselective manner via ketyl radical anions leading to distonic δ-keto radical anion as reactive intermediates. The irradiation was carried out at a wavelength of 254 nm with triethylamine (TEA) as a strong reducing reagent in acetonitrile. We also showed that the photolysis of the α-alkylated 2-oxocyclopentanecarboxylate derivatives does not lead to any cyclization products via a δ-hydrogen abstraction process. In this case α-C–C bond cleavage as a predominant process was observed.

Among the natural products bearing a tricyclic cyclopentane framework, the linearly fused triquinanes are most versatile and abundant, mostly in microbial sources.[1] The class of linear triquinanes is further divided in four different skeletal types, depending on the location of the four carbon substituents. However, only the thermodynamically favored *cis*,*anti*,*cis*-tricyclo[6.3.0.0^{2,6}]undecane skeleton **1** has been encountered as the basic carbocyclic framework of a large number of naturally occurring triquinanes (Fig. 1).

The hirsutanes[2,3] represent a group of fungal metabolites, whose basic hydrocarbon skeleton biogenetically arises from the connection of the C1–C11, C2–C9, and C3–C7 carbon atoms as well as movement of the methyl groups C14 and C15 in the farnesane sesquiterpene **2** (Fig. 1).[2] The sesquiterpene (±)-hirsutene **3**, isolated[3] from Basidomycetes *Coriolus consors*, is the simplest member of the hirsutane group of linear triquinanes.[1b,3] The epoxide derivatives (±)-hirsutic acid-C **4**, was the first triquinane natural product isolated from Basidomycetes *Stereum hirsutum*[4] and its structure was later confirmed through



1 **2** **3** **4** **5**

Fig. 1. Linear triquinane frameworks.

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spectroscopic and X-ray analysis.[5] The biogenetic precursor of the (±)-hirsutic acid-C **4**, the sesquiterpene (±)-complicatic acid **5**, isolated from the fungus *Stereum complicatum*[6] consist a carbonyl group at position 5.[1d]

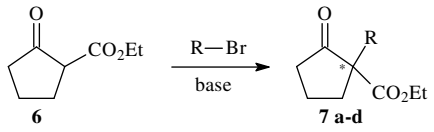
As a result of the promising biological properties of compounds **4** and **5**,[7] several strategies for their synthesis have been employed.[3,8] In recent years, the photoinduced radical/radical anionic cyclization was applied in the synthesis of linear triquinanes.[9] For example, *rac*-hirsutene **4** was synthesized by using of PET process as key step reaction.[9a]

To demonstrate the potential of the PET method, the syntheses of the skeleton of linearly fused cyclopentanoids by PET will be presented in this Letter. Our synthetic concept is illustrated in Scheme 1. We used a two-step convergent strategy[9a] including α-alkylation of differently substituted ($R_1 = R_2 = H$ or Me) β-keto ester derivatives (ring A) with 1-bromomethyl-1-cycloalkenyl reagents (ring C) followed by an intramolecular ring fusion for the construction of ring B. In general, this key step is achieved by a photoinduced electron transfer from TEA (electron donor) to the α-alkylated β-keto ester (electron acceptor) in dry acetonitrile.

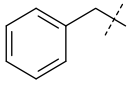
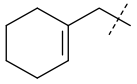
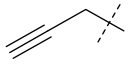
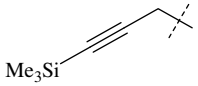
The main challenge in the synthesis of linear triquinanes is the construction of five-membered rings, while the control of the stereochemistry during ring fusion is not a serious problem since *cis*,*anti*,*cis* is the preferred stereochemistry.[1]

The α-substituted β-keto ester derivatives **7a**–**d** were synthesized using ethyl 2-oxocyclopentanecarboxylate **6** as a starting material.[10] The details of α-alkylation reactions with various alkyl bromides are shown in Table 1. The alkylation of the thermodynamically preferred α-position was realized following a modified literature procedure.[11] In general, 1 equiv of the corresponding alkylation reagent and of potassium-*tert*-butylate as base were used under reflux. The best yield (92%) was achieved with propargyl bromide (~80% in toluene). In the case of **7a**, alkylation with benzyl bromide was carried out by using microwave irradiation in the presence of potassium carbonate in DMF.[12]

Table 1
Monoalkylation of ethyl 2-oxo-1-cyclopentanecarboxylate **6**

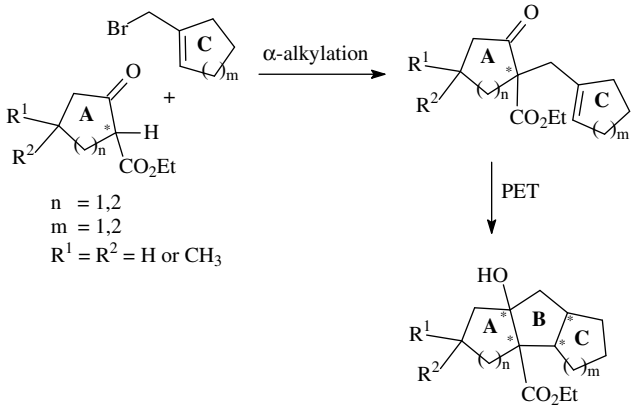


6 **7 a-d**

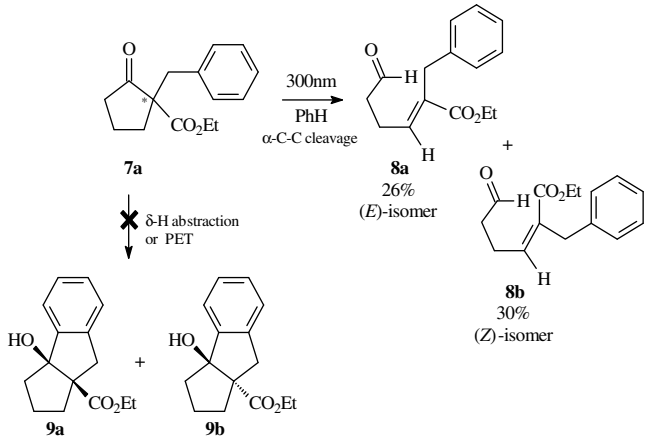
R	Conditions	Product	Yield (%)
1.2 equiv 	K_2CO_3 (2.5 equiv) DMF, microwave 900 W, 4 min	**7a**	97
1.0 equiv 	^{t}BuOK (1.0 equiv) ^{t}BuOH, 24 h reflux	**7b**	25
1.0 equiv 	^{t}BuOK (1.0 equiv) ^{t}BuOH, 2 h reflux	**7c**	92
1.0 equiv 	^{t}BuOK (1.0 equiv) ^{t}BuOH, 1 h reflux	**7d**	74

The synthesis of 2,3-disubstituted cyclopenta-indanes **9a** and **9b** via a photoinduced cyclization failed due to preferred α-C–C-bond cleavage of **7a** and subsequently δ-hydrogen atom abstraction in analogy to earlier results published by us.[13]

The photolysis of **7a** was carried out in accordance to the literature data at a wavelength of 300 nm in dry benzene (Scheme 2).[14] Irradiation for 21 h led to the formation of two isomers: the (*E*)-isomer **8a** and the (*Z*)-isomer **8b** in 26 and 30% yields, respectively, after chromatographic separation. The product ratio was determined by GC as 47:53 (**8a**/**8b**). The stereochemistry of **8a** and **8b** was accomplished by NMR analysis including NOESY experiments. On the other hand, formation of the assumed tricyclic compounds **9a** and **9b** under PET irradiation conditions was not observed by means of GC and GC–MS analysis.



Scheme 1. Retrosynthesis of linear triquinanes using a two-step convergent synthetic concept.

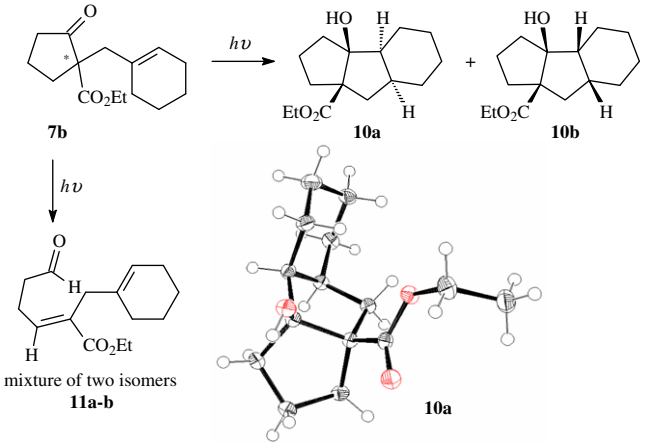


Scheme 2. Photoinitiated α-C–C cleavage of **7a**.

The starting material of this PET reaction was completely reisolated.

In our previous communications, we reported that the basic framework of linear triquinanes is easily accessible by photoreduction of ring-expanded tricyclic alkanone derivatives.[15] Here this concept was applied to 2-oxocyclohexenyl substituted β-keto ester **7b** as starting material. The details of the reductive PET reaction of **7b** are shown in Scheme 3 and Table 2.

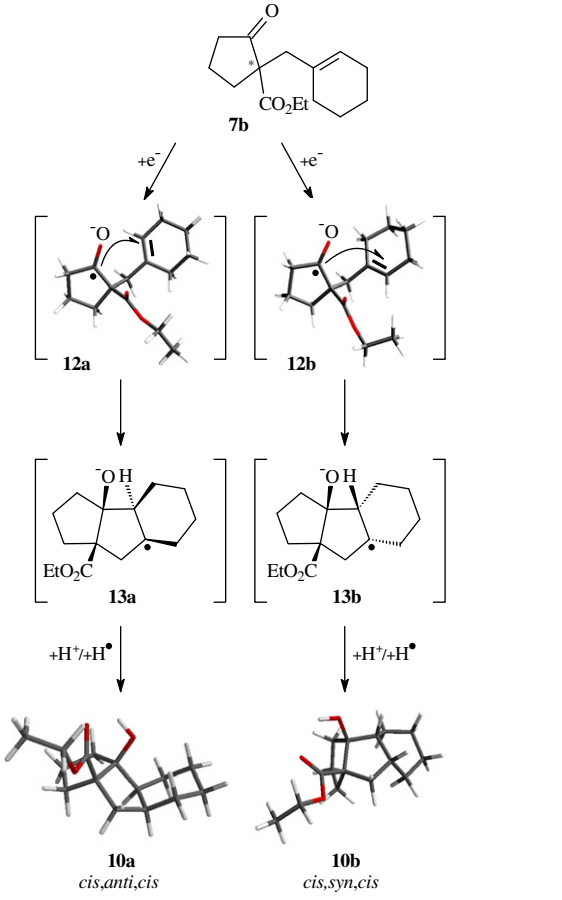
A deoxygenated solution (0.05 M) of **7b** in dry acetonitrile was irradiated in the presence of 10 equiv of TEA in a Rayonet photochemical reactor at 254 nm (quartz tubes). The degree of conversion of the starting material was monitored by GC and GC/MS. The intramolecular radical anion cyclization proceeded highly regioselective and led to a mixture of two diastereoisomers: *cis*,*anti*,*cis* isomer **10a** and *cis*,*syn*,*cis* isomer **10b**.[16] The mixture was purified by column chromatography followed by preparative HPLC separation. The product ratio was determined by GC of the isolated mixture as 59:41 (**10a**/**10b**). The structure determination of **10a** and **10b**[16] was accomplished by spectroscopic analysis using one- and two-dimensional NMR spectroscopy. Additionally, **10a** was confirmed by X-ray crystal structure analysis[17] and shows the thermodynamically preferred *cis*,*anti*,*cis* configuration (Scheme 3).[1b,c] The stereochemistry of **10b** was assigned using qualitative NOESY spectroscopy in combination with ^{1}H NMR analysis supported by molecular modeling of the respective geometries using MMFF94 force field calculations.[18]



Scheme 3. Photoinitiated reactions of **7b**.

The mechanistic details of the reductive PET reaction of **7b** are illustrated in Scheme 4. The initially formed ketyl radical anions **12a**/**12b**, resulting from the corresponding conformers of **7b**, cyclize to form the new distonic γ-radical anions **13a**/**13b** giving **10a** and **10b** in a 5-*endo* fashion after protonation and hydrogen saturation (Scheme 4). In this case, the formation of 5-*endo* fused ring is highly favored according to Baldwin's rules and literature data.[19]

The calculated geometry of the lowest-energy conformers of **10a** (*cis*,*anti*,*cis*) and **10b** (*cis*,*syn*,*cis*) is presented in Scheme 4. The results of the calculates geometry of **10a** were confirmed by analysis of the X-ray data.[16] In general, the photolysis of **7b** shows the same features compared to **7a**, that is, α-C–C-bond cleavage followed by a δ-hydrogen atom abstraction. Consequently, irradiation in dry *n*-hexane without TEA as electron donor led to a mixture of



Scheme 4. Proposed reaction mechanism of reductive PET cyclization of α-substituted ethyl cyclopentanone carboxylate **7b**.

Table 2
Irradiation reactions of ethyl 1-benzyl-2-oxocyclopentanecarboxylate **7b**

Process	Conditions	Product	Yield (%)
PET cyclization	254 nm, TEA (10.0 equiv), MeCN (0.05 M), 1.5 h	**10a**	12
		10b	9
α-C–C cleavage	150 W Hg-lamp, *n*-hexane (0.02 M), 7 h	**11a**,**b**	58[a]

[a] Combined isolated yield of mixture of two isomers.

two *E*-/*Z*-isomer **11a/b** in 58% combined yield after chromatographic purification (Scheme 3/Table 2).

In summary, we have shown that linear cyclohexano diquinane frameworks **10a/10b** are accessible using a two-step convergent synthetic concept, starting from commercially available β-keto ester **6**. Furthermore, the reaction sequence involving a reductive PET cyclization as a key step should be capable for the preparation of other linearly fused tricyclic systems possessing different ring-members and substituents.

Supplementary data

All synthetic procedures and analytical data of compounds **7a–d** and **8a,b** are available from the authors on request, or via http://bieson.ub.uni-bielefeld.de/opus/frontdoor.php?source_opus=639.[20]

Acknowledgments

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References and notes

1. (a) Paquette, L. A.; Doherty, A. M. In *Polyquinane Chemistry*; Springer: New York, 1987; Vol. 26; (b) Mehta, G.; Srikrishna, A. *Chem. Rev.* **1997**, *97*, 671–719; (c) Singh, V.; Thomas, B. *Tetrahedron* **1998**, *54*, 3647–3692; (d) Austin, K. A. B.; Banwell, M. G.; Harfoot, G. J.; Willis, A. C. *Tetrahedron Lett.* **2006**, *47*, 7381–7384; (e) Mehta, G.; Pallavi, K. *Tetrahedron Lett.* **2006**, *47*, 8355–8360.
2. (a) Nuhn, P. In *Natrurstoffe*, 2nd ed.; S. Hirzel: Stuttgart, 1990. Chapter 8; (b) Breitmaier, E. In *Terpene*; Wiley-VCH: Weinheim, 2005; p 48.
3. Nozoe, S.; Furukawa, J.; Sankawa, U.; Shabata, S. *Tetrahedron Lett.* **1976**, 195–198.
4. Heatley, N. G.; Jennings, M. A.; Florey, H. W. *Br. J. Exp. Pathol.* **1947**, *28*, 35–46.
5. Comer, F. W.; Trotter, J. *J. Chem. Soc. B* **1966**, 11–18.
6. Mellows, G.; Mantle, P. G.; Feline, T. C.; Williams, D. J. *Phytochemistry* **1973**, *12*, 2717–2720.
7. Kupka, J.; Anke, T.; Giannetti, B.-M.; Steglich, W. *Arch. Microbiol.* **1981**, *130*, 223–227.
8. (a) Little, R. D.; Muller, G. W. *J. Am. Chem. Soc.* **1981**, *103*, 2744–2749; (b) Curran, D. P.; Rakiewicz, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 1448–1449; (c) Curran, D. P.; Rakiewicz, D. M. *Tetrahedron* **1985**, *41*, 3943–3958.
9. (a) Cossy, J.; Belotti, D.; Pete, J.-P. *Tetrahedron* **1990**, *46*, 1859–1870; (b) Cossy, J.; Belotti, D. *Tetrahedron* **2006**, *62*, 6459–6470.
10. Ethyl 2-oxocyclopentanecarboxylate **6** is commercially available (Fluka Ltd) or can be synthesized following the known three-step procedure, see also (a) Sisido, K.; Utimoto, K.; Isida, T. *J. Am. Chem. Soc.* **1964**, *29*, 2781–2782; (b) Schäfer, J. P.; Bloomfield, I. J. *Org. React.* **1967**, *15*, 1.
11. Klipa, D. H.; Hart, H. *J. Org. Chem.* **1981**, *46*, 2815–2816.
12. Nayyak, S.; Trehan, J.; Kaur, J. *Ind. J. Chem.* **2002**, *41B*, 2342–2345.
13. Tzvetkov, N. T.; Mattay, J. *Tetrahedron Lett.* **2005**, *46*, 7751–7755.
14. (a) Bischof, E. W. Ph.D. Dissertation, Reinisch-westfälische Technische Hochschule, Aaachen, Germany, 1991. For diastereoselective synthesis of functionalized 1,2,3-trisubstituted benzocyclopentenes: (b) Adam, W.; Gogonas, E. P.; Hadjiarapoglon, L. P. *J. Org. Chem.* **2003**, *68*, 9155–9158.
15. (a) Mattay, J.; Banning, A.; Bischof, E. W.; Heidbreder, A.; Runsink, J. *Chem. Ber.* **1992**, *125*, 2119–2127; (b) Bischof, E. W.; Mattay, J. *J. Photochem. Photobiol. A: Chem.* **1992**, *63*, 249–251.
16. (a) *Selected spectral data for compound* **10a**: ^{1}H NMR (500 MHz, C_6D_6) δ 0.91 (t, $J = 7.1$ Hz, 3H, OCH_2CH_3), 1.02–1.10 (m, 1H), 1.18 (dd, $J = 6.5$ and 12.9 Hz, 1H), 1.23 (dd, $J = 6.0$ and 11.1 Hz, 1H), 1.32–1.40 (m, 2H), 1.43 (dd, $J = 4.9$ and 15.5 Hz, 1H), 1.48–1.72 (m, 7H), 1.87 (dd, $J = 6.1$ and 11.0 Hz, 1H), 1.92 (dd, $J = 6.5$ and 11.3 Hz, 1H), 1.98–2.04 (m, 1H), 2.60 (t, $J = 12.8$ Hz, 2H), 2.98 (s, 1H, O*H*), 3.93 (q, $J = 7.1$ Hz, 2H, OCH_2CH_3) ppm; ^{13}C NMR (125 MHz, C_6D_6) δ 14.4 (OCH_2CH_3), 21.8 (CH_2), 22.4 (CH_2), 25.7 (CH_2), 26.2 (CH_2), 27.0 (CH_2), 35.1 (CH), 38.9 (CH_2), 40.5 (CH_2), 44.2 (CH_2), 49.2 (CH), 60.9 (OCH_2CH_3), 62.5 (C), 94.4 (C), 176.8 (CO_2Et) ppm; IR ν_{max} (KBr)/cm^{-1} 3511, 2925, 2875, 2854, 1724, 1704, 1448, 1367, 1255, 1130, 973; GC–MS (EI) *m/z* (%) 252 (6) [M$^+$], 210 (8), 206 (17), 191 (20), 179 (23), 178 (33), 162 (77), 161 (63), 160 (18), 156 (100), 150 (32), 133 (30), 121 (17), 119 (29), 117 (18), 111 (26), 110 (67), 109 (74), 105 (27); HRMS (EI) calcd for $C_{15}H_{24}O_3$ *m/z* 252.1725, *m/z* found 252.1714; (b) *Selected spectral data for compound* **10b**: ^{1}H NMR (500 MHz, C_6D_6) δ 0.92 (t, $J = 7.0$ Hz, 3H, OCH_2CH_3), 1.01–1.10 (m, 1H), 1.11–1.15 (m, 1H), 1.16–1.24 (m, 1H), 1.25–1.31 (m, 1H), 1.38 (d, $J = 12.4$ Hz, 1H), 1.44–1.54 (m, 5H), 1.63 (dd, $J = 7.8$ and 13.6 Hz, 1H), 1.70–1.80 (m, 1H), 1.81–1.88 (m, 1H), 2.02 (dd, $J = 5.6$ and 18.7 Hz, 1H), 2.05 (d, $J = 5.4$ Hz, 1H), 2.33–2.42 (m, 1H), 2.46 (dd, $J = 8.6$ and 11.5 Hz, 1H), 2.67 (dtdd, $J = 2.2$, 12.2, 12.0 and 23.9 Hz, 1H), 2.85 (s, 1H, O*H*), 3.95 (dq, $J = 2.7$ and 9.7 Hz, 2H, OCH_2CH_3) ppm; ^{13}C NMR (125 MHz, C_6D_6) δ 14.2 (OCH_2CH_3), 21.7 (CH_2), 23.8 (CH_2), 25.2 (CH_2), 26.8 (CH_2), 27.3 (CH_2), 37.5 (CH_2), 37.5 (CH_2), 38.3 (CH), 40.0 (CH_2), 49.9 (CH), 60.6 (OCH_2CH_3), 63.7 (C), 96.0 (C), 176.44 (CO_2Et) ppm; IR ν_{max} (neat)/cm^{-1} 3480, 2935, 2856, 1708, 1446, 1367, 1288, 1130, 1029, 977; GC–MS (EI) *m/z* (%) 253 (1) [M$^+$+1H], 252 (4) [M$^+$], 210 (7), 206 (14), 191 (19), 189 (15), 179 (16), 178 (25), 162 (78), 161 (61), 160 (24), 157 (12), 156 (100), 150 (28), 149 (16), 133 (31), 127 (20), 119 (29), 117 (20), 111 (26), 110 (88), 109 (75), 105 (26); HRMS (EI) calcd for $C_{15}H_{24}O_3$ *m/z* 252.1725, *m/z* found 252.1712.
17. *X-ray crystallographic data for compound* **10a**: $C_{15}H_{24}O_3$, $M = 252.34$, $T = 100(2)$ *K*, monoclinic, space group $P2_1/c$, $Z = 4$, $a = 11.7381(3)$, $b = 9.2061(2)$, $c = 12.4965(3)$ Å, ß = 93.4107(15)°, $V = 1348.03(6)$ Å^3, $D_x = 1.243$ g/cm^3, 3923 unique data ($\theta_{max} = 30°$), 2895 with $I > 2\sigma(I)$; $R = 0.0450$, $R_W = 0.1107$.
Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 656838. These data can be obtained free-of-charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.
18. All calculations were carried out with Titan V1.05, Schrödinger Inc., Wavefunction Inc. (18 August 2000). The conformational analysis was accomplished at a semiempirical level (AM1).
19. (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734–736; (b) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073–3100; (c) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925–3941; (d) Surzur, J. M. In *Reactive Intermediates*; Abramovitch, R. A., Ed.; Plenum Press: New York, 1983; Vol. 2, p 164.
20. Tzvetkov, N. T. Ph.D. Dissertation, University of Bielefeld, 2005.