Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 5605–5609
Tetrahedron Letters

Intramolecular reactions of 2-indolylacyl radicals: cyclisation upon aromatic rings

M.-Lluïsa Bennasar,* Tomàs Roca and Francesc Ferrando

Laboratory of Organic Chemistry, Faculty of Pharmacy, University of Barcelona, Barcelona 08028, Spain

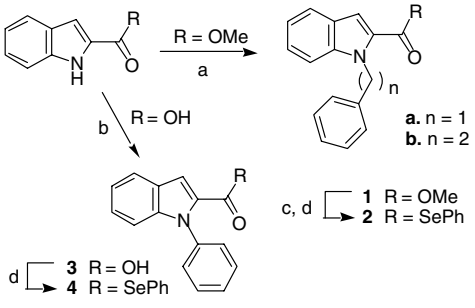
Received 5 May 2004; accepted 26 May 2004
Available online 15 June 2004

Abstract—The generation of 2-indolylacyl radicals from the corresponding selenoesters under reductive (tributyltin hydride–AIBN) and nonreductive (hexabutylditin, 300 W) conditions and their behaviour in cyclisation reactions upon benzene rings attached either to the indole nitrogen or the C-3 ring position have been studied.

Intramolecular reactions of nucleophilic carbon-centred radicals with aromatic systems have received considerable synthetic attention for the construction of complex polycyclic molecules incorporating aromatic rings.[1] Fully aromatic products are generally obtained after the in situ oxidation of the initially formed cyclohexadienyl radicals, which occurs even under the apparently reductive tributyltin hydride–AIBN conditions.[2] Most of the examples reported in the literature deal with cyclisations of aryl and, to a lesser extent, alkyl radicals upon arenes[1,3] and heteroarenes,[1] including pyridines,[4] quinolines,[5] azoles,[6] or indoles.[7,8] However, similar processes involving acyl radicals, which have an enhanced synthetic potential due to their intrinsic functionalisation,[9] have scarcely been studied.[10]

In the last few years we have been actively studying the generation of 2- and 3-indolylacyl radicals from the corresponding phenyl selenoesters and their reactions with alkene acceptors under reductive conditions.[11] Our continuing interest in this area led us to explore intramolecular reactions of these radical intermediates with aromatic and heteroaromatic rings, as a general approach to polycyclic aryl or heteroaryl indolyl ketones. We herein report our preliminary results using 2-indolylacyl radicals in cyclisation reactions upon benzene rings located in chains attached either to the indole nitrogen or the C-3 ring position.

Selenoesters **2a**,**b** and **4**, bearing a phenyl moiety separated by one or two methylene groups or directly attached to the indole nitrogen, were selected as radical precursors for cyclisations leading to 1,2-fused ring indole derivatives. These compounds were efficiently prepared from simple starting products as shown in Scheme 1. Thus, *N*-alkylation of the sodium salt of methyl indole 2-carboxylate with benzyl or 2-phenylethyl bromide gave esters **1a** and **1b**, which were converted into **2a** and **2b** by hydrolysis and subsequent reaction of the resulting carboxylic acids with Et_3N, PhSeCl and PBu_3.[12] On the other hand, Ullman reaction of indole 2-carboxylic acid with bromobenzene gave acid **3**,[13] which was converted as above into selenoester **4**.

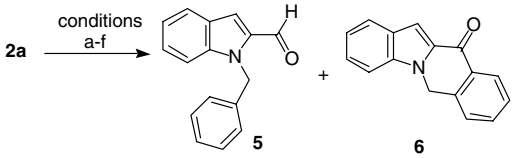


Scheme 1. Reagents and conditions: (a) $Ph(CH_2)_nBr$, NaH, THF, rt, 93% (**1a**), 60% (**1b**); (b) PhBr, K_2CO_3, CuO, DMF, reflux, 71%; (c) 2 N KOH, MeOH–dioxane, reflux, then, 2 N HCl; (d) Et_3N, then PhSeCl, PBu_3, THF, rt, 95% (**2a** from **1a**), 80% (**2b** from **1b**), 75% (**4**).

Keywords: Radicals; Radical cyclisation; Aromatic polycyclic compounds.
* Corresponding author. Tel.: +34-934024540; fax: +34-934024539; e-mail: bennasar@ub.edu

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.05.133

Table 1. Radical cyclisation of selenoester **2a**



Entry	Radical mediator	Conditions[a]	Products (yields, %)[b]
1	*n*-Bu_3SnH	a or b	**5** (90)
2	*n*-Bu_3SnH	c	**5** + **2a** (1:1)[c]
3	TTMSS	d	**5** + **6** (4:1)[c]
4	*n*-Bu_6Sn_2	e	**5** (10), **2a** (25), **6** (40)
5	*n*-Bu_6Sn_2	f	**6** (65)

[a] Conditions a: *n*-Bu_3SnH (1.5 mol), AIBN (0.1 mol), benzene, 0.03 M, reflux, syringe pump, 2 h; b: *n*-Bu_3SnH (1.8 mol), AIBN (1.8 mol), MeCN–hexane, 0.06 M, reflux, syringe pump, 4 h; c: *n*-Bu_3SnH (1.2 mol), AIBN (0.1 mol), Ph_2Se_2 (cat), benzene, 0.01 M reflux, syringe pump, 20 h; d: TTMSS (1.2 mol), AIBN (2 mol), benzene, 0.03 M, reflux, syringe pump, 4 h; e: *n*-Bu_6Sn_2 (0.2 mol), 300 W, benzene, 0.01 M, reflux, 24 h; f: *n*-Bu_6Sn_2 (2.2 mol), 300 W, benzene, 0.01 M, reflux, 24 h.

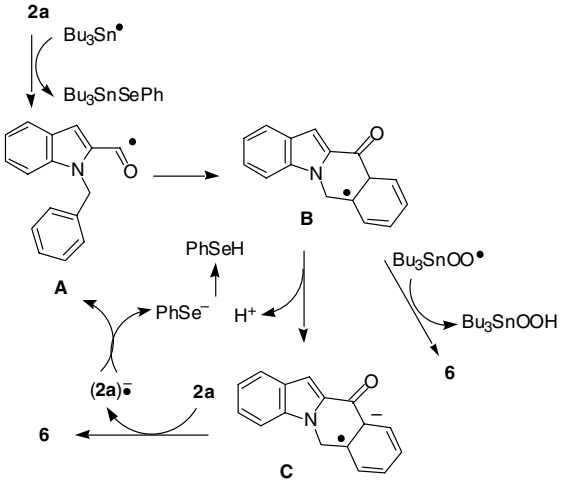
[b] Isolated yields.

[c] Ratio determined by ^1H NMR analysis of the reaction mixtures.

We set out to examine several experimental conditions from selenoester **2a** to achieve the desired cyclisation (Table 1). Considering the literature precedents,[1] the use of standard reductive (tributyltin hydride–AIBN) conditions was first investigated. Unsatisfactorily, using different amounts of the initiator either in benzene (entry 1, conditions a) or in acetonitrile–hexane[10d] (entry 1, conditions b) aldehyde **5**, coming from simple reduction of the initially formed 2-indolylacyl radical, was isolated in high yield as the only product. This premature reduction was also observed in the presence of catalytic phenylselenol under conditions reported by Crich and Hwang,[14] although significant amounts of the starting substrate **2a** were also recovered even after 20 h reaction (entry 2). On the other hand, the use of the poorer hydrogen-atom donor tris(trimethylsilyl)silane (TTMSS, entry 3)[15] as the radical mediator gave a reaction mixture, in which aldehyde **5** could be identified as the major product along with minor amounts of the desired tetracycle **6**.

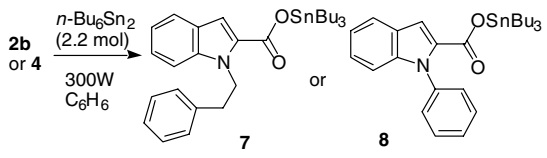
The above results prompted us to investigate the cyclisation of **2a** under non reductive conditions (*n*-Bu_6Sn_2, 300 W sun lamp, entries 4 and 5).[16] We expected that this process was now favoured due to the comparatively longer effective lifetime of the indolylacyl radical. Our first experiments were promising, as treatment of **2a** with a substoichiometric amount of *n*-Bu_6Sn_2 gave the cyclised product **6**[17] in 40% yield. However, significant amounts of recovered **2a** (25%), indicative of a poor chain, and aldehyde **5** (10%, see below) were also formed. Satisfactorily, complete conversion of the substrate **2a** was achieved using 2.2 mol of the radical mediator to give tetracycle **6** (65% isolated yield) with no trace of reduction product.

The above results can be rationalised as depicted in Scheme 2. After cleavage of *n*-Bu_6Sn_2 under the influence of heat and/or light, the resulting tributyltin radical generates the 2-indolylacyl radical **A**, which in absence of competitive reactions can intramolecularly react upon the benzene ring to give the cyclohexadienyl radical **B**.[18] When substoichiometric amounts of the radical mediator are used, conversion of **B** into **6** must be described, at least in part, through a chain propagation mechanism, which may involve a $S_{RN}1$ type reaction very similar to the one first proposed by Bowmann for tributyltin hydride–AIBN mediated aromatic substitutions.[19] Thus, deprotonation of radical **B**, followed by a SET reaction from the resulting radical anion **C** to selenoester **2a** would generate tetracycle **6** and a new radical anion, which would lose phenylselenolate anion to give radical **A** to propagate the chain. Phenylselenol thus formed could reduce radical **A**, thereby accounting for the formation of aldehyde **5**. However, under conditions of Table 1, entry 5, this oxidative step can also occur by a simple hydrogen abstraction,[16] for instance, by peroxy radical *n*-$Bu_3SnOO^{\cdot}$ coming from reaction of tin radicals with oxygen, which was not rigorously excluded from the reaction mixture.

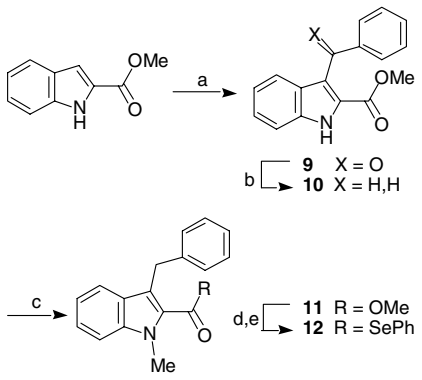


Scheme 2. Proposed mechanism for the *n*-Bu_6Sn_2-mediated cyclisation of selenoester **2a**.

The cyclisation method that had allowed the efficient preparation of isoquinolinoindole **6** was next extended to selenoesters **2b** and **4**, having a different tether between the phenyl ring and the radical centre (Scheme 3). However, all attempts to create a seven-membered or a strained benzo fused five-membered ring met with failure. Thus, when **2b** or **4** were treated with 2.2 mol of *n*-Bu_6Sn_2 under sun lamp irradiation tributyltin esters **7**[20] (80%) or **8** (40%) were isolated as the only reaction products. These compounds probably are formed by



Scheme 3.



Scheme 4. Reagents and conditions: (a) benzoic acid, trifluoroacetic anhydride, H_3PO_4, CH_3CN, rt, 70%; (b) Et_3SiH, TFA, rt, 93%; (c) MeI, NaH, THF, 0 °C to rt, 90%; (d) 2 N KOH, reflux, then, 2 N HCl; (e) Et_3N, then PhSeCl, PBu_3, THF, rt, 95%.

reaction of the starting selenoesters with *n*-Bu_6Sn_2, followed by oxidation of resulting 2-indolylacyltin with molecular oxygen.[21]

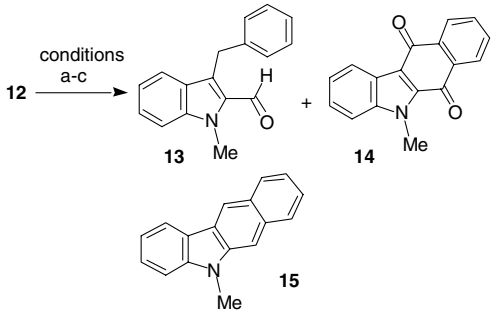
Attention was next turned to cyclisations leading to 2,3-fused ring indole derivatives. For this purpose, selenoester **12**, which incorporates a benzyl group at the 3-position of the indole ring, was prepared from methyl indole 2-carboxylate as depicted in Scheme 4. Friedel–Crafts acylation with benzoic acid[22] followed by reduction of the resulting 2,3-diacylindole **9** with triethylsilane gave ester **10**, which, after *N*-methylation, was converted into **12** following the same procedure previously used for selenoesters **2** and **4**.

We examined the behaviour of **12** in both reductive and non reductive conditions (Table 2). In contrast to the above 1-benzyl series, the desired cyclisation did take place when *n*-Bu_3SnH was used as the radical mediator to give tetracycle **14**[23] in 40% yield along with significant amounts of aldehyde **13** (50% yield, entry 1). These results clearly indicated that intramolecular reaction of the 2-indolylacyl radical **D** (Scheme 5) to give the cyclohexadienyl radical **E** is now more favoured, although reduction to **13** is still a competing pathway. Considering the recent mechanistic findings on the *n*-Bu_3SnH-mediated homolytic aromatic substitutions,[2] the initiator AIBN, which is present in stoichiometric amounts, is probably responsible for the regeneration of the aromaticity of the phenyl ring. Nevertheless, the initially formed tetracycle **F** was not observed since an additional oxidation at the benzylic position spontaneously occurred to give **14**.

Under nonreductive conditions the cyclisation course of selenoester **12** was similar to that of **2a**. As can be observed in Table 2, entry 2, exposure of **12** to a substoichiometric amount of *n*-Bu_6Sn_2 resulted in incomplete conversion to give the overoxidised tetracycle **14** in a modest 30% yield and minor amounts of two reduction products: aldehyde **13** (14% yield) and tetracycle **15**[24] (5%). Satisfactorily, the yield of **14** increased to 50% when 2.2 mol of the radical mediator were used (entry 3), neither the starting product **12** nor aldehyde **13** being observed.[25] Significantly, tetracycle **15** was again formed in 10% yield. From the mechanistic point of view, regeneration of the aromaticity from the cyclised cyclohexadienyl radical **E** can be described as in the 1-benzyl series, by hydrogen abstraction or via a $S_{RN}1$ type chain reaction to initially produce tetracycle **F**, which would now undergo an additional oxidation to give tetracycle **14** (Scheme 6). However, in this series reduction of radical **E** (or **G**), probably by phenylselenol[14] produced from the chain reaction (see Scheme 2), partially competes with the oxidative step to give **15** after dehydration.

In summary, the intramolecular homolytic acylation of benzene rings has been studied from several indolyl selenoesters. This reaction efficiently occurs from selenoesters **2a** and **12** under nonreductive conditions (*n*-Bu_6Sn_2, 300 W) to give tetracyclic phenyl indolyl

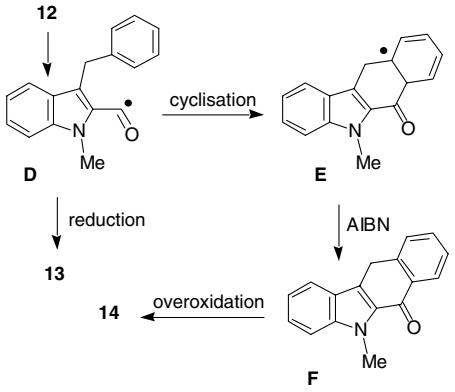
Table 2. Radical cyclisation of selenoester **12**



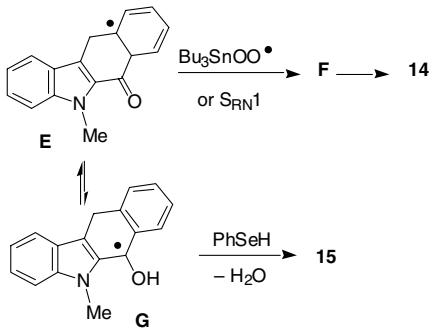
Entry	Radical mediator	Conditions[a]	Products (yields, %)[b]
1	*n*-Bu_3SnH	a	**13** (50), **14** (40),
2	*n*-Bu_6Sn_2	b	**12** (25), **13** (14), **14** (30), **15** (5)
3	*n*-Bu_6Sn_2	c	**14** (50), **15** (10)

[a] Conditions a: *n*-Bu_3SnH (1.8 mol), AIBN (1.8 mol), MeCN–hexane, 0.06 M, reflux, 4 h, syringe pump; b: *n*-Bu_6Sn_2 (0.2 mol), 300 W, benzene, 0.01 M, reflux, 24 h; c: *n*-Bu_6Sn_2 (2.2 mol), 300 W, benzene, 0.01 M, reflux, 24 h.

[b] Isolated yields.



Scheme 5. Probable mechanism for the *n*-Bu_3SnH–AIBN mediated cyclisation of **12**.



Scheme 6. Proposed mechanism for the formation of tetracycles **14** and **15** under *n*-Bu_6Sn_2–hν conditions.

ketones **6** and **14**, which deserve interest due to their potential pharmacological activities.[26] Further extension of this reaction to heterocyclic systems is currently underway in our laboratory.

Acknowledgements

Financial support from the 'Ministerio de Ciencia y Tecnología', Spain, and the 'Fondo Europeo de Desarrollo Regional' (FEDER) through project BQU2003-04967-C02-02 is gratefully acknowledged. We also thank the DURSI (Generalitat de Catalunya) for Grant 2001SGR00084. F.F. thanks the University of Barcelona for a grant.

References and notes

1. Studer, A.; Bossart, M. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 2, pp 62–80.
2. For a recent discussion, see: Beckwith, A. L. J.; Bowry, V. W.; Bowman, W. R.; Mann, E.; Parr, J.; Storey, J. M. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 95–98, and references cited therein.
3. For recent leading references, see: (a) Fiumana, A.; Jones, K. *Tetrahedron Lett.* **2000**, *41*, 4209–4211; (b) Kaoudi, T.; Quiclet-Sire, B.; Seguin, S.; Zard, S. Z. *Angew. Chem., Int. Ed.* **2000**, *39*, 731–733; (c) Harrowven, D. C.; L'Helias, N.; Moseley, J. D.; Blumire, N. J.; Flanagan, S. R. *Chem. Commun.* **2003**, 2658–2659.
4. For instance, see: (a) Minisci, F.; Vismara, E.; Fontana, F. *Heterocycles* **1989**, *28*, 489–519; (b) Murphy, J. A.; Sherburn, M. S. *Tetrahedron* **1991**, *47*, 4077–4088; (c) Harrowven, D. C.; Nunn, M. I. T.; Blumire, N. J.; Fenwick, D. R. *Tetrahedron* **2001**, *57*, 4447–4454; (d) Harrowven, D. C.; Sutton, B. J.; Coulton, S. *Tetrahedron Lett.* **2001**, *42*, 9061–9064.
5. Harrowven, D. C.; Sutton, B. J.; Coulton, S. *Tetrahedron* **2002**, *58*, 3387–3400.
6. (a) Aldabbagh, F.; Bowman, W. R.; Mann, E.; Slawin, A. M. Z. *Tetrahedron* **1999**, *55*, 8111–8128; (b) Escolano, C.; Jones, K. *Tetrahedron* **2002**, *58*, 1453–1464; (c) Allin, S. M.; Barton, W. R. S.; Bowman, W. R.; McInally, T. *Tetrahedron Lett.* **2002**, 4191–4193.
7. For instance, see: (a) Kraus, G. A.; Kim, H. *Synth. Commun.* **1993**, *23*, 55–64; (b) Artis, D. R.; Cho, I.-S.; Jaime-Figueroa, S.; Muchowski, J. M. *J. Org. Chem.* **1994**, *59*, 2456–2466; (c) Wang, S.-F.; Chuang, C.-P. *Tetrahedron Lett.* **1997**, *38*, 7597–7598; (d) Moody, C. J.; Norton, C. L. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2639–2643; (e) Caddick, S.; Shering, C. L.; Wadman, S. N. *Tetrahedron* **2000**, *56*, 465–473; See also: (f) Hilton, S. T.; Ho, T. C. T.; Pljevaljcic, G.; Schulte, M.; Jones, K. *Chem. Commun.* **2001**, 209–210.
8. For the isolation of dihydro derivatives of indole, see: (a) Ziegler, F. E.; Jeroncic, L. O. *J. Org. Chem.* **1991**, *56*, 3479–3486; (b) Gribble, G. W.; Fraser, H. L.; Badenock, J. C. *Chem. Commun.* **2001**, 805–806; (c) Flanagan, S. R.; Harrowven, D. C.; Bradley, M. *Tetrahedron Lett.* **2003**, *44*, 1795–1798.
9. For reviews on acyl radical chemistry, see: (a) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177–194; (b) Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, *99*, 1991–2069.
10. Upon arenes: (a) Motherwell, W. B.; Vázquez, S. *Tetrahedron Lett.* **2000**, *41*, 9667–9671, and references cited therein; Upon pyridines: (b) Fontana, F.; Minisci, F.; Barbosa, M. C. N.; Vismara, E. *J. Org. Chem.* **1991**, *56*, 2866–2869; Upon indoles and pyrroles: (c) Miranda, L. D.; Cruz-Almanza, R.; Pavón, M.; Alva, E.; Muchowski, J. M. *Tetrahedron Lett.* **1999**, *40*, 7153–7157; (d) Allin, S. M.; Barton, W. R. S.; Bowman, W. R.; McInally, T. *Tetrahedron Lett.* **2001**, *42*, 7887–7890; Upon pyridines: (e) Doll, M. K.-H. *J. Org. Chem.* **1999**, *64*, 1372–1374.
11. (a) Bennasar, M.-L.; Roca, T.; Griera, R.; Bosch, J. *Org. Lett.* **2001**, *3*, 1697–1700; (b) Bennasar, M.-L.; Roca, T.; Griera, R.; Bassa, M.; Bosch, J. *J. Org. Chem.* **2002**, *67*, 6268–6271; (c) Bennasar, M.-L.; Roca, T.; Ferrando, F. *Org. Lett.* **2004**, *6*, 759–762.
12. Batty, D.; Crich, D. *Synthesis* **1990**, 273–275.
13. Olgen, S.; Akaho, E.; Nebioglu, D. *Eur. J. Med. Chem.* **2001**, *36*, 747–770.
14. Crich, D.; Hwang, J.-T. *J. Org. Chem.* **1998**, *63*, 2765–2770.
15. Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188–194.
16. (a) Josien, H.; Ko, S.-B.; Bom, D.; Curran, D. P. *Chem. Eur. J.* **1998**, *4*, 67–83; (b) Miranda, L. D.; Cruz-Almanza, R.; Pavón, M.; Romero, Y.; Muchowski, J. M. *Tetrahedron Lett.* **2000**, *41*, 10181–10184; (c) Bowman, W. R.; Bridge, C. F.; Cloonan, M. O.; Leach, D. C. *Synlett* **2001**, 765–768; (d) Bennasar, M.-L.; Roca, T.; Griera, R.; Bosch, J. *J. Org. Chem.* **2001**, *66*, 7547–7551.
17. Compound **6**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.46 (s, 2H), 7.23 (m, 1H), 7.40–7.55 (m, 4H), 7.51 (s, 1H), 7.66 (ddd, $J = 1.6$, 7.6, 7.8 Hz, 1H), 7.80 (d, $J = 8.2$ Hz, 1H), 8.38 (dd, $J = 1.6$, 7.8 Hz, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 44.4 (CH_2), 105.9 (CH), 110.1 (CH), 121.5 (CH), 123.4 (CH), 125.6 (CH), 126.3 (CH), 127.2 (C), 127.3 (CH), 128.0 (CH), 130.6 (C), 132.6 (C), 133.2 (CH), 136.3 (C), 137.4 (C), 177.3 (CO); HRMS calcd for $C_{16}H_{11}NO$ 233.0841, found 233.0834.
18. An electrophilic substitution mechanism can be excluded as no cyclisation was observed after heating **2a** under 300 W sunlamp irradiation without *n*-Bu_6Sn_2.
19. Bowman, W. R.; Heaney, H.; Jordan, B. M. *Tetrahedron* **1991**, *47*, 10119–10128, See also Ref. 6a.
20. Compound **7**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, $J = 7.2$ Hz, 9H), 1.39 (m, 12H), 1.68 (m, 6H), 3.05 (t, $J = 7.8$ Hz, 2H), 4.81 (t, $J = 7.8$ Hz, 2H), 7.13 (m, 1H), 7.35–7.55 (m, 8H), 7.65 (d, $J = 7.8$ Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 13.7 (CH_3), 16.8 (CH_2), 27.1 (CH_2), 27.9 (CH_2), 37.1 (CH_2), 46.1 (CH_2), 110.2 (CH), 110.6 (CH), 120.1 (CH), 122.3 (CH), 124.2 (CH), 126.1 (C), 126.3 (CH), 128.4 (CH), 128.8 (CH), 129.4 (C), 138.6 (C), 139.2 (C), 166.2 (CO); CI-MS m/z 556 (MH^+).
21. Kosugi, M.; Naka, H.; Sano, H.; Migita, T. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3462–3464.

22. Murakami, Y.; Tani, M.; Suzuki, M.; Sudoh, K.; Uesato, M.; Tanaka, K.; Yokoyama, Y. *Chem. Pharm. Bull.* **1985**, *33*, 4707–4715.
23. Boogaard, A. T.; Pandit, U. K.; Koomen, G.-J. *Tetrahedron* **1994**, *50*, 4811–4828.
24. Markgraf, J.-H.; Patterson, D.-E. *J. Heterocycl. Chem.* **1986**, *33*, 109–111.
25. However, no cyclisation was observed when a selenoester related to **12**, having a 3-benzoyl instead of a 3-benzyl substituent, was subjected to the experimental conditions of Table 2, entry 3.
26. For instance, see: Fernández, M.; Barcia, C.; Estévez, J. C.; Estévez, R. J.; Castedo, L. *Synlett* **2004**, 267–270, and references cited therein.