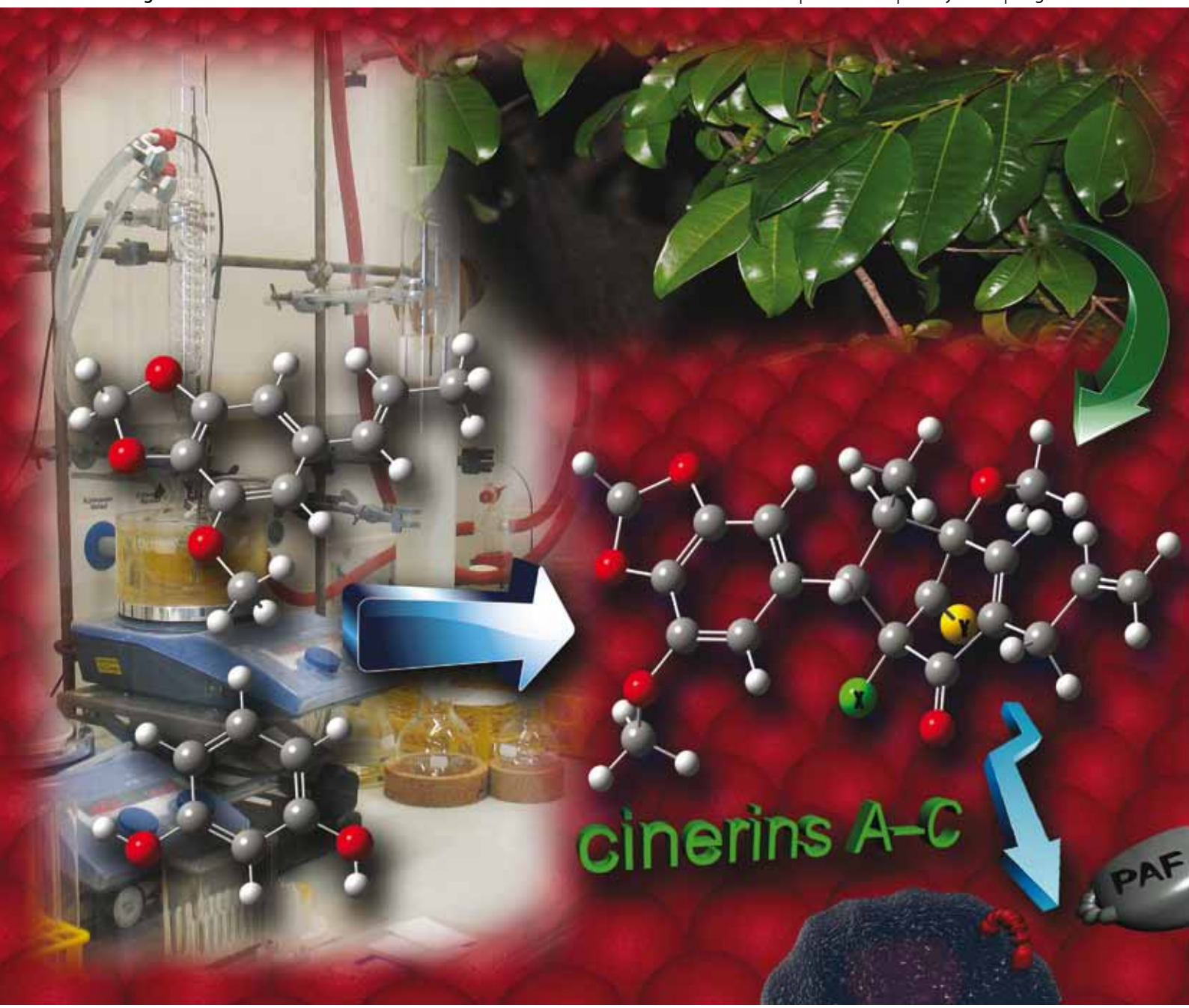
Organic & Biomolecular Chemistry

www.rsc.org/obc

Volume 8 | Number 9 | 7 May 2010 | Pages 1977–2268



ISSN 1477-0520

COMMUNICATION
Ericsson D. Coy B., Luis E. Cuca S. and Michael Sefkow
The first diastereoselective synthesis of cinerins A–C, PAF-antagonistic bicyclo[3.2.1]octane neolignans

EMERGING AREA
Jaskiranjit Kang and Derek Macmillan
Peptide and protein thioester synthesis *via* N→S acyl transfer

RSC Publishing

1477-0520(2010)8:9;1-B

The first diastereoselective synthesis of cinerins A–C, PAF-antagonistic macrophyllin-type bicyclo[3.2.1]octane neolignans, using a novel Pd-catalysed oxyarylation†

Ericsson D. Coy B.,*[a] Luis E. Cuca S.[a] and Michael Sefkow*[b]

Received 8th January 2010, Accepted 2nd February 2010
First published as an Advance Article on the web 12th February 2010
DOI: 10.1039/b927558d

The first diastereoselective synthesis of PAF-antagonistic cinerins A–C, macrophyllin-type bicyclo[3.2.1]octane neolignans from *Pleurothyrium cinereum*, has been accomplished using a novel Pd-catalysed oxyarylation to afford a 2,3-dihydrobenzofuran as the key intermediate.

Neolignans containing a bicyclo[3.2.1]octane core belong to an important class of natural products. These neolignans are further divided into two subgroups, depending on the connectivity of the two phenylpropene moieties: the guianin-type neolignans (8,1′-connected), and the macrophyllin-type neolignans (8,3′-connected).[1] Several syntheses of bicyclo[3.2.1]octane neolignans have been developed in the past.[2] Although guianin-type neolignans are the best known, naturally occurring bicyclooctanoids, several macrophyllin-type neolignans have been shown to exhibit important biological activities[3] (*e.g.* PAF-antagonistic activity), which makes the synthesis of these neolignans particularly interesting. Very recently, four new macrophyllin-type bicyclo[3.2.1]octane neolignans, the cinerins A–D, were characterised as chemical constituents from *Pleurothyrium cinereum* (Lauraceae species).[4] Of these, cinerin B (**1**) and C (**2**) (Fig. 1) exhibit good PAF-antagonistic activities.[4]

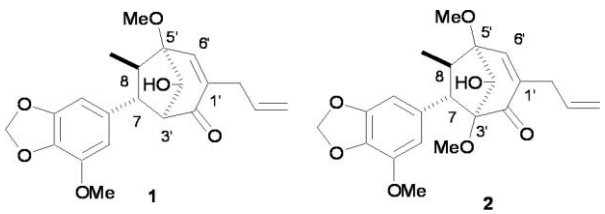
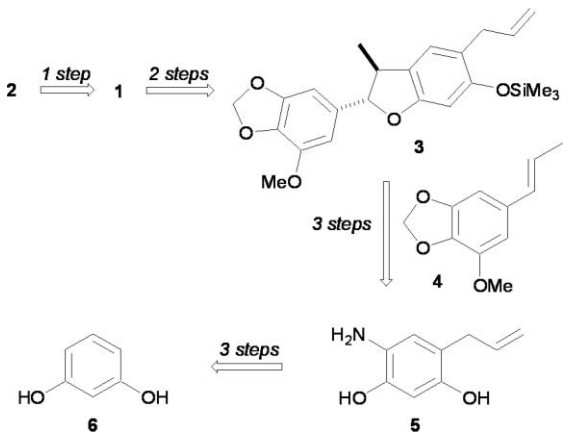


Fig. 1 Macrophyllin-type neolignans cinerin B (**1**) and C (**2**).

Among the reported synthetic approaches, cationic [5+2]-cycloadditions were commonly employed as a strategy for the construction of these bicyclic skeletons. Another, rarely applied route was based on an acid-catalysed rearrangement of 8,3′-neolignans.[5,6] These intermediates can be readily obtained from 8,5′-neolignans, comprising a dihydrobenzofuran core.[5] However, both intermediates, the 8,5′- and 8,3′-neolignans, were generally obtained in low yields.

Recently, we have developed a new and efficient synthesis of *trans*-2-aryl-2,3-dihydrobenzofurans *via* a Pd-catalysed oxyarylation.[7] Obviously this reaction is attractive to develop a stereoselective synthesis for the cinerins B and C from dihydrobenzofuran **3** as precursor, which in turn should be readily available from isomyristicin (**4**) and 2-aminophenol **5**. The highly substituted aminophenol **5**, though previously unknown and expected to be very sensitive towards oxidation,[8] should be available from resorcinol **6**. We further envisioned that cinerin C (**2**) could be prepared from cinerin B (**1**) by α-methoxylation of hindered ketones.[9] The retrosynthetic analysis of the cinerins is shown in Scheme 1.



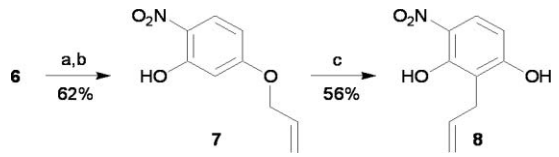
Scheme 1 Retrosynthetic analysis for cinerin B (**1**) and cinerin C (**2**).

Our synthesis of dihydrobenzofurans requires a phenylpropene and an *o*-diazoniumphenol. The latter reagent is prepared *in situ* by treatment of an *o*-aminophenol and a nitrosonium salt.[7] Isomyristicin **4**, the readily substituted phenylpropene, was obtained from myristicin aldehyde and ethylmagnesium bromide followed by dehydratisation with $CuSO_4$ in 61% yield ($E:Z = 14:1$).[10] For the synthesis of **5** from resorcinol **6** a Claisen rearrangement seemed obvious as this reaction is well documented for the corresponding monoallyl ether in diethylaniline.[11] In our hands, the best result was achieved, when the Claisen rearrangement was carried out in a sealed flask at 190 °C with DMF as solvent. However, only a nearly 1 : 1 mixture of 2- and 4-allylresorcinol was obtained in 78% yield. Raising the steric hindrance for C-2 by silylation of O-1 with TBS-Cl (88% yield) didn't affect the regioselectivity of the Claisen rearrangement.[12] Thus, the nitro group was introduced

[a]*Universidad Nacional de Colombia, Facultad de Ciencias, Departamento de Química, Laboratorio de Investigación en Productos Naturales Vegetales, AA 14490, Cra 30 45-03, Bogotá, D.C., Colombia. E-mail: edcoyb@unal.edu.co, lecucas@unal.edu.co*
[b]*Universität Potsdam/UP Transfer GmbH, Am Neuen Palais 10, 14469 Potsdam, Germany. E-mail: sefkow@uni-potsdam.de*

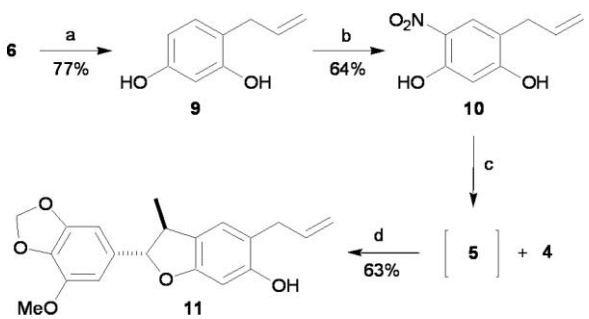
† Electronic supplementary information (ESI) available: Experimental procedures, full spectroscopic data for all new compounds, and copies of ^{1}H and ^{13}C NMR spectra. See DOI: 10.1039/b927558d

at the beginning of the synthesis of **5** (*e.g.* zirconyl nitrate[13] 63%, or bismuth nitrate[14] 78%) to examine the influence of the nitro group in the subsequent reactions. Monoallylation at O-1 was best achieved with tetrabutylammonium hydrogensulfate (TBAHS) affording **7** in 79% yield.[15,16] Unexpectedly, the Claisen rearrangement of **7** provided exclusively 2-allyl-4-nitroresorcinol (**8**) in 56% yield (Scheme 2).



Scheme 2 Synthesis and Claisen rearrangement of allyl ether **7**. (a) $Bi_2(NO_3)_3{\cdot}5H_2O$, Me_2CO, 50 °C, 5 min; (b) 1.1 eq allyl bromide, aq. KOH 50%, TBAHS 1%, Et_2O, 0 °C, 4 h; (c) DMF, 190 °C, 15 h.

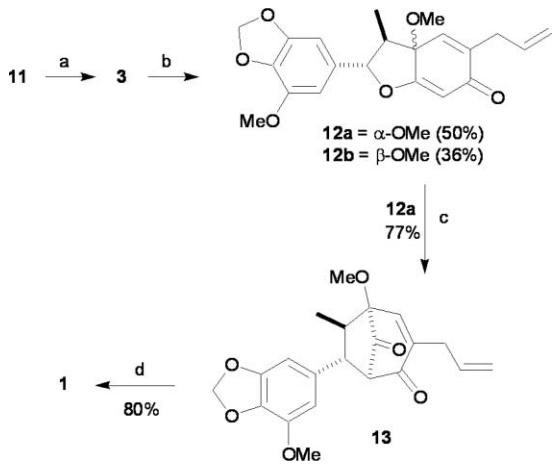
Therefore, the Claisen rearrangement of resorcinol monoallyl ether was not a suitable method to yield **5**. Recently, Kimura *et al.*[17] developed a novel direct C-allylation of arenes, based on a Pd-catalysed, triethylborane promoted reaction of phenols with allyl alcohols. With this reaction, **6** was transformed to 4-allyl-resorcinol (**9**) in 77% yield. Subsequent nitration using zirconyl nitrate gave 6-nitro-4-allyl-resorcinol **10** in 64% yield (Scheme 3).



Scheme 3 Synthesis of dihydrobenzofuran **11**. (a) 1.2 eq. allyl alcohol, 5 mol% $Pd[(Ph_3)P]_4$, 5 eq Et_3B, rt, toluene, 3 h; (b) $ZrO(NO_3)_2{\cdot}xH_2O$, Me_2CO, rt, 2 h; (c) Zn, CH_2Cl_2, AcOH, rt, 1 h; (d) 1 eq $NOPF_6$, MeCN, 0 °C, 2 h; then 1.2 eq **4**, 5 mol% $Pd_2(dba)_3$, 2 eq $ZnCO_3$, rt, 20 h.

With compound **10** in hand, we examined several methods to reduce the nitro group. The best method to obtain amine **5** was Zn/AcOH–CH_2Cl_2,[18] while other methods, such as $NaBH_4$,[19] $Na_2S_2O_3$,[20] Zn/EtOH[21] or NH_4Cl/ultrasound[22] failed to give any desired product.[23] As expected, amine **5** is very unstable and reacts during/after ordinary workup to give intensively colored products.[8] Thus, **5** was used in the next step without workup or purification. The amine was immediately treated with one eq. of $NO^+PF_6^-$ to give the diazonium salt, which in turn was reacted with phenylpropene **4** in the presence of 5 mol% $Pd_2(dba)_3$ and 2 eq. of $ZnCO_3$ (Scheme 3). Dihydrobenzofuran **11** was obtained in 63% overall yield over three steps (corresponds to an average yield of 86% for each step).

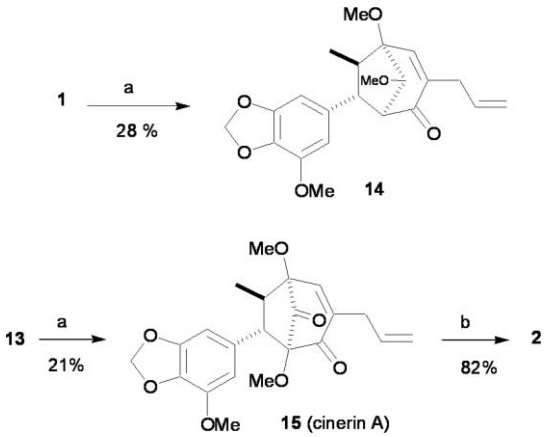
The synthesis of cinerins proceeds with the oxidation of **11** to methoxy dienone **12**. Wang *et al.*[5] reported a procedure for the conversion of similar substrates using phenyliodonium diacetate (PIDA) that provided both, the α- and the β-methoxy epimer at C-3′ with 20 and 50% yield, respectively. However, the subsequent acid catalysed rearrangement is controlled by the relative configuration of C-3′ and only the α-methoxy epimer is suitable for this reaction. Thus, the protocol provided by Wang *et al.* is not sufficient to give the bicyclo[3.2.1]octanes in reasonable yields. Recently, Felpin described that *p*-methoxylation of silyl ether of phenols with PIDA/MeOH gave superior yields compared to the phenol itself.[24] According to Felpin's modification, the oxidative methoxylation of dihydrobenzofuran **11** was carried out using the corresponding trimethylsilyl ether **3**. Indeed, α- and β-methoxy dienone (**12a** and **12b**) were obtained in better total yield (86%) and with a preference for **12a** (**12a** : **12b** ~1.4 : 1) (Scheme 4). The change in stereoselectivity might be due to a change in the mechanism: whereas unprotected phenols (*e.g.* **11**) react with PIDA at the OH group, the corresponding silyl ether (*e.g.* **3**) are attacked by this reagent at the carbon *para* to the silyl ether.[24] As a consequence, cleavage of PIDA-phenol adducts causes an oxo and then a carbocation, which reacts with MeOH under thermodynamic control (with a preference for the β-OMe epimer). On the other hand, the iodonium group in the PIDA-carbon adducts acts as leaving group in a S_N2-like substitution. Assuming the same preference for the β-isomer of the initial PIDA-carbon adducts a reverse orientation in favour of the α-OMe epimer must result.



Scheme 4 Synthesis of cinerin B (**1**). (a) HMDS, $CuSO_4$, CH_2Cl_2, reflux, 4 h; (b) PIDA, MeOH, r.t. 2 h; (c) TsOH, MeOH, reflux, 2 h; (d) $NaBH_4$, EtOH, –15 °C, 15 min.

The acid-catalysed rearrangement was carried out with diastereoisomerically pure α-methoxy neolignan **12a** furnishing the *exo*-aryl bicyclodione skeleton **13** in 77% yield, that is in accord with the reported procedure for analogous substrates.[5,6] Diketone **13** was converted to cinerin B (**1**) in 80% yield by means of a regioselective and diastereoselective reduction using $NaBH_4$ in EtOH. The orientation of the 4′-hydroxy group was determined by its signal pattern in the ^1H NMR spectrum, which is typical for those structures.[25,26]

To obtain cinerin C (**2**), a methoxylation α to the highly hindered ketones was pursued according to the procedure described by Abele *et al.*[9] (Scheme 5). However, starting from cinerin B (**1**) this reaction was not successful. The only product which could be characterised was methyl ether **14**. To avoid the methylation of the hydroxy group at C(4′), diketone intermediate **13** was used as substrate for the α-methoxylation. Indeed, 3′-methoxy-bicyclooctanedione **15**, cinerin A,[4] was isolated in 21% yield



Scheme 5 Synthesis of cinerin C (**2**) and cinerin A (**15**). (a) CCl_4, KOH, MeI, 18-crown-6, reflux, 9 h; (b) $NaBH_4$, EtOH, –15 °C, 15 min.

from **13**. This is an acceptable yield, because the protocol comprises three steps–chlorination, hydroxylation and methylation–in one phase transfer catalysed system.[9] Finally, cinerin A (**15**) was converted into cinerin C (**2**) by reduction of the aliphatic ketone using $NaBH_4$ as described above. The structures **1**, **2** and **15** have been unambiguously established by comparison of their ^1H and ^{13}C NMR spectra with those of the authentic samples.[4]

In summary, we have developed a straightforward synthesis of three recently isolated, naturally-occurring macrophyllin-type bicyclo[3.2.1]octane neolignans from one common precursor. The key step, a novel Pd-catalysed oxyarylation protocol, recently developed in our laboratory, provided a dihydrobenzofuran as the key intermediate from commercially available starting materials. In addition, our route is attractive because the bicyclooctane neolignans are available in good yields and diastereoselectivities and without capricious reaction conditions. The flexibility of our route allows the use of a variety of substrates to be applied to the synthesis of a wide-range of this type of neolignans.

We thank the Institut für Chemie at Universität Potsdam for the analytical support. E.D. Coy acknowledges the DAAD for financing a research stay at the University of Potsdam.

Notes and references

1 R. S. Ward, *Nat. Prod. Rep.*, 1999, **16**, 75.
2 M. Sefkow, *Synthesis*, 2003, 2595.
3 G. Han, *Progr. Nat. Sci.*, 1995, **5**, 299.
4 E. D. Coy, L. E. Cuca and M. Sefkow, *J. Nat. Prod.*, 2009, **72**, 1245.
5 M. Wang, A. Wu, X. Pan and H. Yang, *J. Org. Chem.*, 2002, **67**, 5405.
6 M. A. De Alvarenga, B. U. Brocksom, O. R. Gottlieb, M. Toshida, R. B. Filho and R. J. Figliuolo, *J. Chem. Soc., Chem. Commun.*, 1978, 831.
7 E. D. Coy, L. Jovanovic and M. Sefkow, submitted for publication.
8 (*a*) M. Mure and J. P. Klinman, *J. Am. Chem. Soc.*, 1993, **115**, 7117; (*b*) S. Ma, L. Lin, R. Raghavan, P. Cohenour, P. Y. T. Lin, J. Bennett, R. J. Lewis, E. L. Enwall, R. Kostrzewa, R. E. Lehr and C. L. Blank, *J. Med. Chem.*, 1995, **38**, 4087.
9 E. Abele, K. Rubina, M. Shymanska and E. Lukevics, *Synth. Commun.*, 1995, **25**, 1371.
10 J. Popławski, B. Łozowicka, A. T. Dubis, B. Lachowska, S. Witkowski, D. Siluk, J. Petrusewicz, R. Kaliszan, J. Cybulski, M. Strzałkowska and Z. Chilmonczyk, *J. Med. Chem.*, 2000, **43**, 3671.
11 (*a*) K. D. Kaufman and W. E. Russey, *J. Org. Chem.*, 1965, **30**, 1320; (*b*) F. C. Gozzo, S. A. Fernandes, D. C. Rodrigues, M. N. Eberlin and A. J. Marsaioli, *J. Org. Chem.*, 2003, **68**, 5493.
12 F. Ito, K. Fusegi, T. Kumamoto and T. Ishikawa, *Synthesis*, 2007, 1785.
13 J. P. Selvam, V. Suresh, K. Rajesh, R. S. Ravinder and Y. Venkateswarlu, *Tetrahedron Lett.*, 2006, **47**, 2507.
14 H.-B. Sun, R. Hua and Y. Yin, *J. Org. Chem.*, 2005, **70**, 9071.
15 M.-L. Wang and Z.-F. Lee, *J. Mol. Catal. A: Chem.*, 2007, **264**, 119.
16 The monoallyl ether **7** was accompanied by *ca.* 12% of the corresponding diallyl ether. Other methods, such as phenol allylation with allyl bromide and KOH in acetone, were less efficient and gave higher yields of the undesired diallyl ether.
17 M. Kimura, M. Fukasaka and Y. Tamaru, *Synthesis*, 2006, 3611.
18 H. Gao and J. Kawabata, *Bioorg. Med. Chem.*, 2005, **13**, 1661.
19 B. Zeynizadeh and D. Setamdideh, *Synth. Commun.*, 2006, **36**, 2699.
20 K. A. Monk, R. Siles, M. B. Hadimani, B. E. Mugabe, J. F. Ackley, S. W. Studerus, K. Edvardsen, M. L. Trawick, C. M. Garner, M. R. Rhodes, G. R. Pettit and K. G. Pinney, *Bioorg. Med. Chem.*, 2006, **14**, 3231.
21 R. J. Sundberg and W. J. Pitts, *J. Org. Chem.*, 1991, **56**, 3048.
22 M. A. Pasha and V. P. Jayashankara, *Ultrason. Sonochem.*, 2006, **13**, 42.
23 Interestingly, reduction of **10** with $LiAlH_4$ provided 2-allyl-4-aminophenol in 67% yield.
24 F.-X. Felpin, *Tetrahedron Lett.*, 2007, **48**, 409.
25 G. Q. Han, P. Dai, L. Xu, S. C. Wang and Q. T. Zheng, *Chin. Chem. Lett.*, 1992, **7**, 521.
26 A singlet for the hydrogen at C-4′ is always observed in bicyclooctanoids with an OH group oriented towards the aryl group as the angle between H–C-3′ and H–C-4′ is *ca.* 90°. The diastereoisomer generally shows a doublet in the ^1H NMR spectrum due to a coupling between H–C-3′ and H–C-4′. These results have been independently confirmed by NOESY spectra.