Pergamon

Tetrahedron Letters 42 (2001) 1011–1015

TETRAHEDRON LETTERS

An unusual proximity effect observed in a quinol bis-epoxide series

Guenter Neef,* Siegfried Baesler, Gisbert Depke and Harry Vierhufe

Preclinical Drug Research, Schering AG, D-13353 Berlin, Germany

Received 20 October 2000; accepted 23 November 2000

Abstract—The favorable intramolecular relationship between a benzyl ether group and a chiral quinol bis-epoxide moiety is shown to cause a peculiar type of rearrangement followed by a cascade of acid-catalyzed events that result in the formation of a new, highly strained polycyclic system.

The regio- and stereoselective manipulation of quinol bis-epoxides represents a major challenge to synthetic organic chemists, although a considerable number of terrestrial and marine natural products demonstrate that nature has developed an admirable virtuosity in dealing selectively with the five adjacent electrophilic centers characteristic of the bis-epoxyquinol element. Several compounds of pharmacological interest such as aranorosin[1] and diepoxin σ[2] contain the quinol epoxide moiety as a core element and it appears fairly probable that LL-C10037α,[3] manumycin A[4] and some tyrosine derived metabolites of the agelorin[5] and fistularin[6] series are formed from quinol bis-epoxide precursors (Fig. 1).

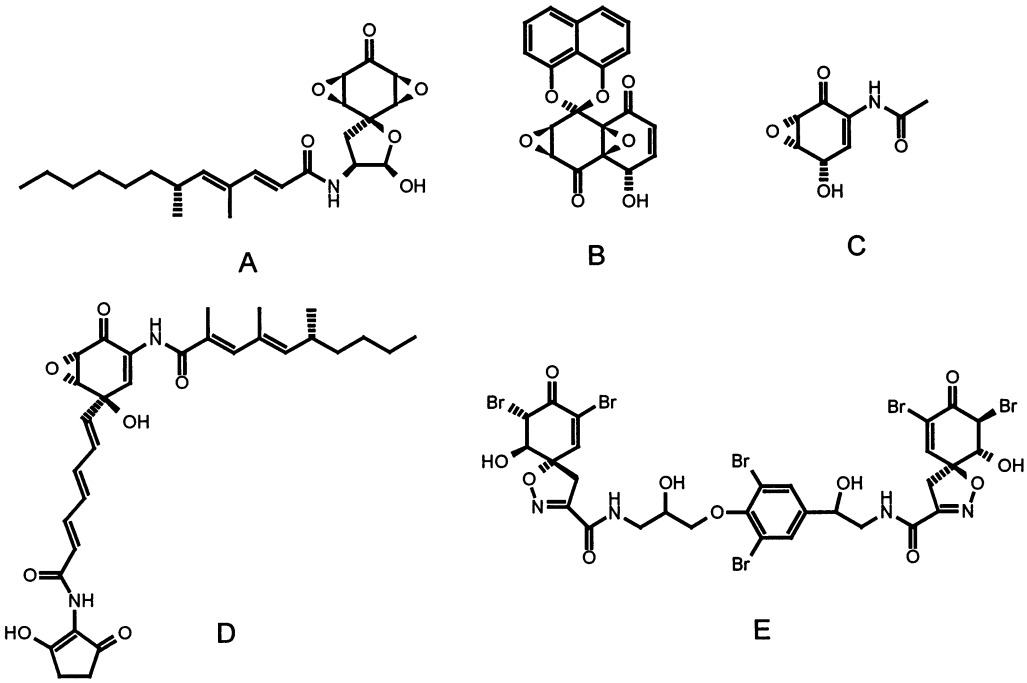


Figure 1. **A**, Aranorosin. **B**, Diepoxin σ. **C**, LL-C10037α. **D**, Manumycin A. **E**, Agelorin A.

Keywords: neighboring group effect; quinol derivatives; microwave-assisted thermolysis.

* Corresponding author.

0040-4039/01/$ - see front matter
PII: S0040-4039(00)02177-8

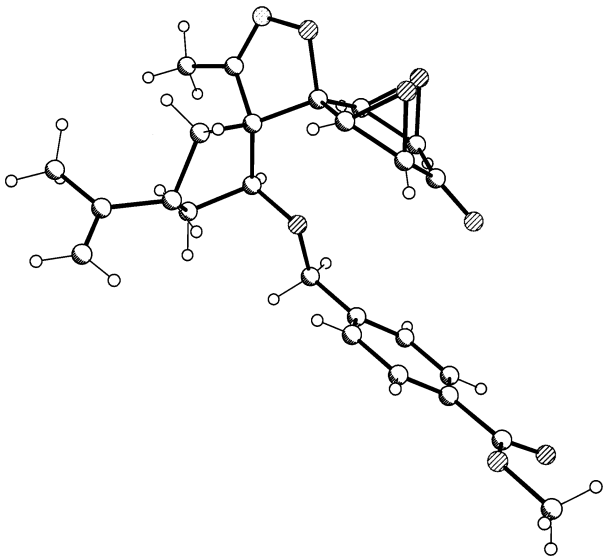
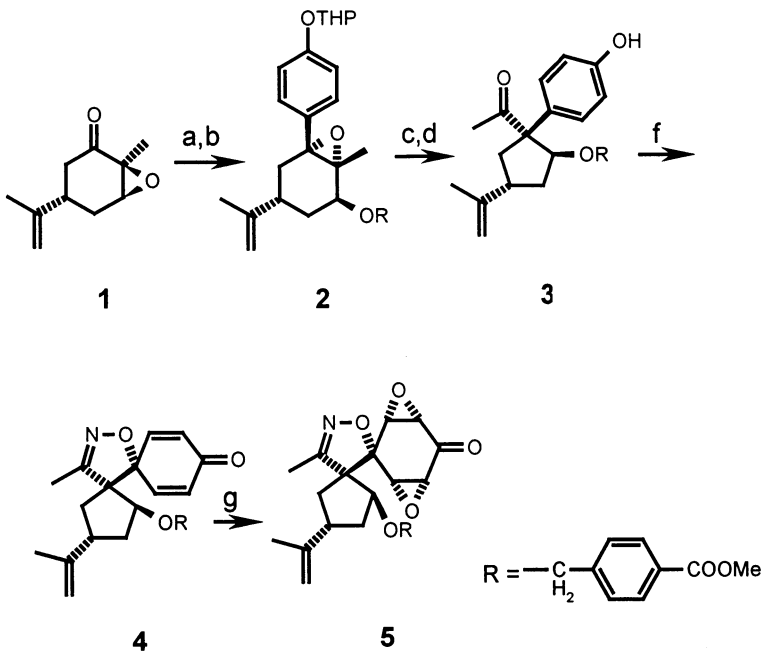


Figure 2. Crystal structure of **5**.

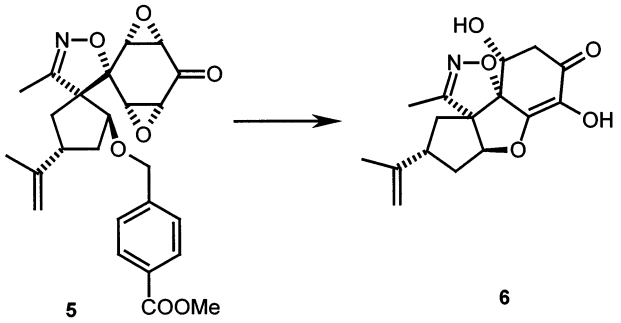
Recently,[7] we described a rearrangement of carvone-derived epoxides that resulted in the stereoselective formation of highly substituted cyclopentane derivatives of type **3**. The newly formed quaternary center bearing a phenyl residue and an acetyl group offered itself to be transformed into a spirocyclohexadienyl isoxazoline intermediate **4**, which after appropriate epoxidation would give rise to quinol bis-epoxide **5** (Fig. 2). The secondary alcohol function originating from the carvone part of the molecule was then expected to act as an internal nucleophile that, for steric reasons, would discriminate between the epoxide moieties and select the β-position of the epoxyketone for nucleophilic attack (Scheme 1).

In order to prepare key precursor **2** we had to modify our recently disclosed protocol[7] by replacing bromobenzene with tetrahydropyranyl-protected 4-bromophenol. As a further slight variation, the secondary alcohol function was protected as a *p*-methoxycarbonylbenzyl ether instead of the unsubstituted benzyl ether group. It must be pointed out that only this combination of protecting groups ensured an uneventful course for the above sequence of reactions. The BF_3–etherate catalyzed rearrangement[8] of epoxide **2** and subsequent THP–ether cleavage resulted in the formation of ring-contracted product **3** that was converted to an *E*/*Z* mixture of oximes. The crude oxime was treated with iodobenzene bis-trifluoroacetate (PIFA)[9] in aqueous acetonitrile to yield the cylohexadienyl isoxazoline **4**. Model considerations suggested a hemiglobal shape for the dispiro compound **4**. Hence, it was no surprise to see epoxidation of cyclohexadienone **4** proceed with formation of a single isomer, the absolute configuration of which was determined later by X-ray crystal structure analysis.[10]

Not unexpectedly, all our initial attempts to cleave the benzyl ether group of compound **5** in the presence of the quinol bis-epoxide met with failure. Nonetheless, we continued our search for appropriate reaction conditions because the X-ray structure revealed a uniquely favorable distance and trajectory for the benzylic ether oxygen to attack one of the epoxide moieties in an S_N2 fashion. A breakthrough was achieved with a solid phase microwave-assisted thermolysis[11] of compound **5** on silica gel. After some optimization work a 60% yield of a nicely crystalline product was obtained to which NMR spectroscopy assigned the structure depicted below (Scheme 2). Again, crystal structure analysis was



Scheme 1. Reaction conditions: (a) *p*-tetrahydropyranyloxy-phenylmagnesium bromide, THF, 55%; (b) *p*-methoxycarbonylbenzyl bromide, NaH, DMF, 92%; (c) BF_3–etherate, $MeCl_2$, −78°C; (d) aqueous HOAc (70%), ambient temp., 67%; (f) PIFA, MeCN–water (4:1), 58%; (g) benzyltrimethylammonium hydroxide, 30% H_2O_2, MeOH, 87%.



Scheme 2. Reaction conditions: **5** (300 mg) on silica gel (5.0 g), 5 min irradiation, 60%.

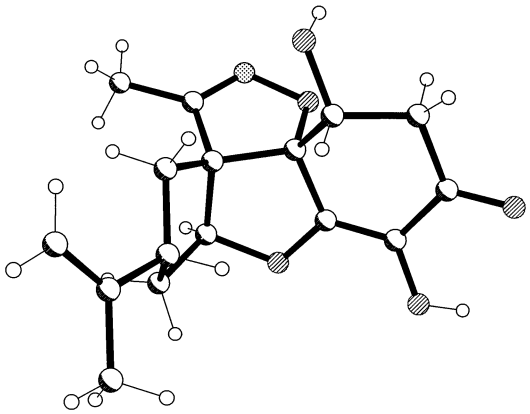


Fig. 3. Crystal structure of **6**.

used to confirm the preliminary assignment for product **6**[12] (Fig. 3).

Although far from being predicted, the formation of product **6** seemed to be easily explainable by assuming an initial benzylic ether cleavage followed by a cascade of mechanistically plausible events as described by the hypothetical sequence of Scheme 3.

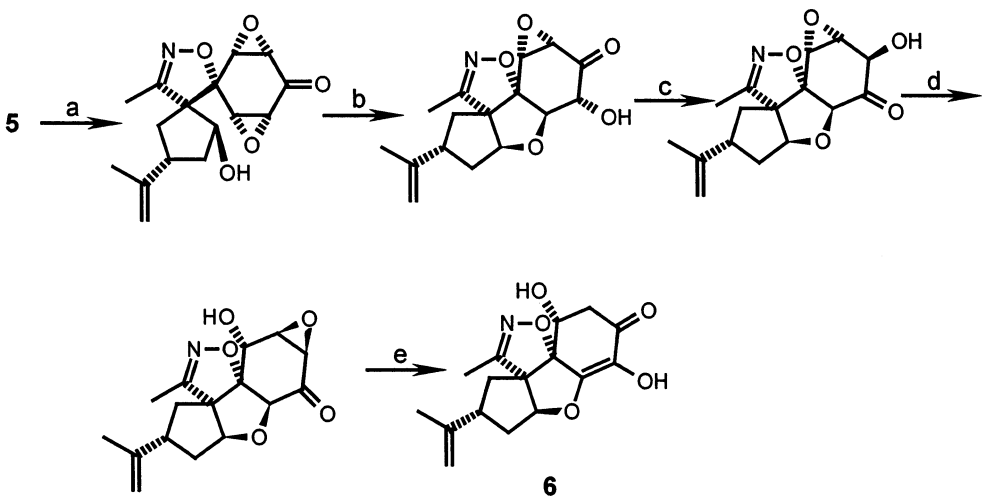
Severe doubts arose, however, when, as a control experiment, an isomer of compound **5** was subjected to the same reaction conditions. After 5 min of microwave irradiation isomer **7** had not undergone a defined transformation (Scheme 4). Only starting material (45%) could be reisolated with no sign of benzyl ether cleaved products in the remainder.

Although the distinctly altered spatial relationship between the benzylic ether oxygen and the epoxy ketone moiety could account for the different chemical reactivity of isomer **7**, benzylic ether cleavage as the initial step in the formation of polycycle **6** became rather questionable.

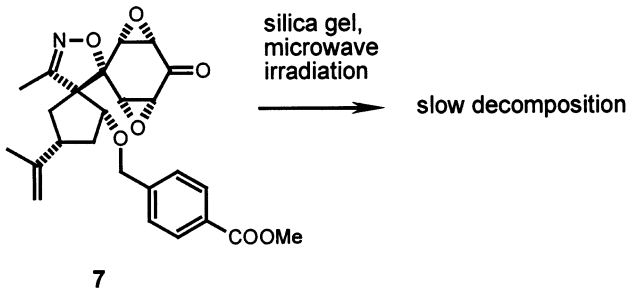
As a consequence, we started a new series of experiments with bis-epoxy ketone **5** aiming no longer at a selective benzyl ether cleavage, but rather trying to activate the epoxide function with Lewis acids in a nucleophile-depleted environment.
Though unsatisfactory from a preparative point of view, the treatment of compound **5** with BF_3–etherate in methylene chloride at −78°C resulted in the formation of an unusual product **8** (Scheme 5). The favorably located epoxide moiety feeling the vicinity of the benzylic oxygen had undergone a new type of rearrangement.

The microwave-assisted thermolysis of **8** on silica gel led to the formation of product **6**, thus making it highly probable that the cascade of product-forming steps in the transformation of **5** and **6** does not start with a benzylic ether cleavage but rather with the rearrangement observed in the BF_3-catalyzed process (**5**–**8**).

These conclusions are further supported by the completely different behavior of isomer **7**, which showed a remarkable resistance to boron trifluoride treatment remaining unchanged for several hours at ambient temperature. With the use of trimethylsilyl triflate as a Lewis acid, it was even possible to isomerize the isopro-



Scheme 3. Hypothetical steps in the formation of **6**. (a) Benzyl ether cleavage. (b) S_N2 epoxide opening. (c) Ene–diol tautomerization. (d) Payne rearrangement. (e) 1,2-H shift.

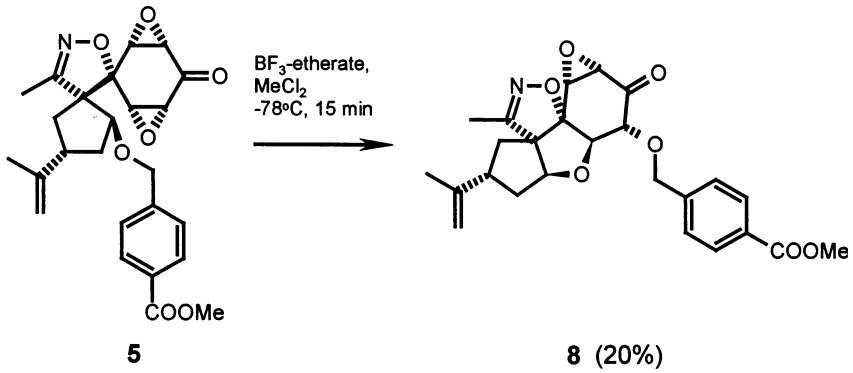


Scheme 4.

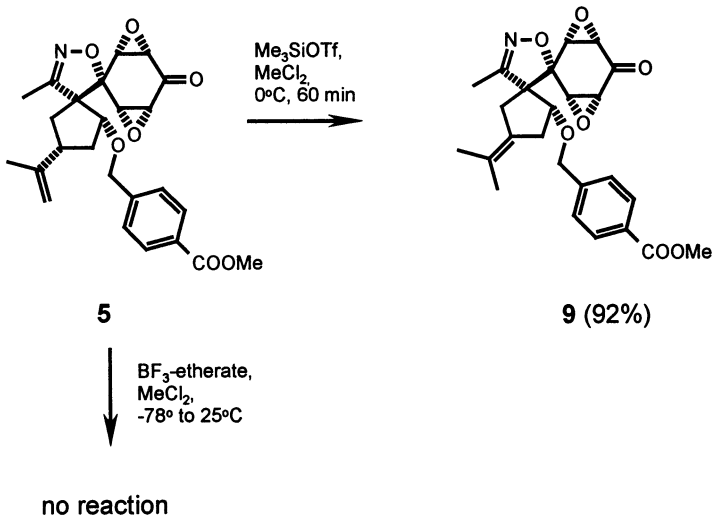
penyl double bond of the molecule **7** without the quinol bis-epoxide element being affected (Scheme 6).

In conclusion, we have been able to demonstrate that a directed intramolecular attack at a quinol bis-epoxide moiety can affect all the electrophilic centers in a way to make them chemically distinguishable and amenable to further structural variation. In that respect, our work can be seen as a complement to the careful analysis reported by Wipf et al.[13] who investigated the intermolecular thiophilic ring-opening and rearrangement reactions of epoxyketone natural products.

It is fairly obvious that the unusual rearrangement product **6** bears the potential of being easily transformed into a number of derivatives that contain the spirocyclohexenone isoxazoline subunit which is a pharmacophoric group of considerable recent interest.[14]



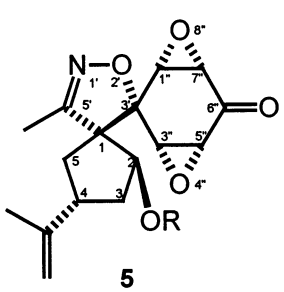
Scheme 5.



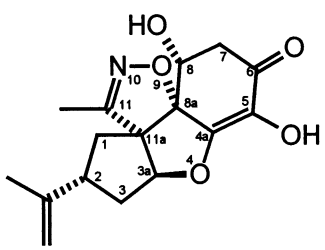
Scheme 6.

References

1. Fehlhaber, H. W.; Kogler, H.; Mukhopadhyay, T.; Vijayakumar, E. K. S.; Ganguli, B. N. *J. Am. Chem. Soc.* **1988**, *110*, 8242.
2. Wipf, P.; Jung, J.-K. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 764.
3. Wipf, P.; Kim, Y. *J. Org. Chem.* **1993**, *58*, 1649.
4. (a) Buzzetti, F.; Gaumann, E.; Hüetter, R.; Keller-Schierlein, W.; Neipp, L.; Prelog, V.; Zaehner, H. *Pharm. Acta Helv.* **1963**, *38*, 871; (b) Wipf, P.; Coish, P. D. G. *Tetrahedron Lett.* **1997**, *38*, 5073.
5. (a) Koenig, G. M.; Wright, A. D. *Heterocycles* **1993**, *16*, 1351; (b) Gao, H.; Kelly, M.; Hamann, M. T. *Tetrahedron* **1999**, *55*, 9717.
6. Mancini, I.; Guella, G.; Laboute, P.; Debitus, C.; Pietra, F. *J. Chem. Soc., Perkin Trans. 1* **1993**, 3121.
7. Neef, G.; Baesler, S.; Depke, G.; Vierhufe, H. *Tetrahedron Lett.* **1999**, *40*, 7969.
8. Domagala, J. M.; Bach, R. D.; Wemple, J. *J. Am. Chem. Soc.* **1976**, *98*, 1975.
9. Kaçan, M.; Koyuncu, D.; McKillop, A. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1771.
10. Crystal data for **5**:[15] $C_{25}H_{27}NO_7$, $M=453.48$, orthorhombic, space group $P2(1)2(1)2(1)$, crystal size $0.7\times0.25\times0.1$ mm^3, unit cell dimensions $a=9.606(2)$, $b=10.482(2)$, $c=22.943(3)$ Å, $\alpha=90$, $\beta=90$, $\gamma=90°$, $V=2310.1(7)$ Å^3, $Z=4$, $D=1.304$ Mg/m^3, absorption coefficient 0.095 mm^{-1}, $T=273(2)$ K, wavelength $\lambda=0.71073$ Å, 3352 reflections collected, 3146 independent reflections [R(int) = 0.0128], R indices (all data) $R_1=0.0505$, $wR_2=0.1210$. The crystallographic data for **5** have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number CCDC 152704.
11. (a) Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathé, D. *Synthesis* **1998**, 1213; (b) The equipment used was a Synthewave 402, ProLabo. After 5 min of irradiation (300 W) the internal temperature of the probe had reached 162°C.
12. Crystal data for **6**·0.5H_2O:[15] $C_{16}H_{19}NO_5$, $M=305.54$, orthorhombic, space group $P2(1)2(1)2(1)$, crystal size $0.7\times0.5\times0.2$ mm^3, unit cell dimensions $a=6.732(1)$, $b=10.576(2)$, $c=21.90(4)$ Å, $\alpha=90$, $\beta=90$, $\gamma=90°$, $V=1559.3(5)$ Å^3, $Z=4$, $D=1.335$ Mg/m^3, absorption coefficient 0.101 mm^{-1}, $T=173(2)$ K, wavelength $\lambda=0.71073$ Å, 2939 reflections collected, 2512 independent reflections [R(int) = 0.0204], R indices (all data) $R_1=0.0309$, $wR_2=0.0734$. The crystallographic data for **6** have been deposited at the CCDC under deposition number CCDC 152705.
13. Wipf, P.; Jeger, P.; Kim, Y. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 351.
14. (a) Goldenstein, K.; Fendert, T.; Proksch, P.; Winterfeldt, E. *Tetrahedron* **2000**, *56*, 4173; (b) Beil, W.; Jones, P. G.; Nerenz, F.; Winterfeldt, E. *Tetrahedron* **1998**, *54*, 7273.
15. Selected physicochemical and spectroscopic data: **5**, mp 191–193°C (ethyl acetate), $[\alpha]_D$ +46.5 ($CHCl_3$, $c=0.505$); ^{1}H NMR ($CDCl_3$, 400 MHz):[16] $\delta=1.55$ ppm (dd, $J=11$ and 14 Hz, 1H, H-5); 1.68 (s, 3H, 4-C[=C]-**CH_3**); 1.78 (ddd, $J=6$, 10, 15 Hz, 1H, H-3); 1.95 (s, 3H, 5′-**CH_3**); 2.03–2.12 (m, 1H, H-3); 2.53 (dd, $J=8$ and 14 Hz, 1H, H-5); 2.09–2.11 (m, 1H, H-4); 3.44 (dd, $J=3$ and 5 Hz, 1H, H-5″); 3.48 (dd, $J=3$ and 5 Hz, 1H, H-7″); 3.77 (t, $J=5$ Hz, 1H, H-1″); 3.93 (s, 3H, COO**CH_3**); 4.07 (t, $J=5$ Hz, 1H, H-3″); 4.18 (dd, $J=6$ and 7 Hz, 1H, H-2); 4.45–4.58 (AB-system, 2H, O-**CH_2**-Ph); 4.69 (s, 1H, C=**CH**[‘Z’]); 4.78 (s, 1H, C=**CH**[‘E’]); 7.34 (d, $J=8$ Hz, 2H, aryl-H); 8.03 (d, $J=8$ Hz, 2H, aryl-H). **6**, mp 192–194°C (MeCN–H_2O), $[\alpha]_D$ +205.5 ($CHCl_3$, $c=0.523$); ^{1}H NMR ($CDCl_3$, 400 MHz):[16] $\delta=1.68$ ppm (ddd, $J=5$, 12.5, 15 Hz, 1H, H-3); 1.77 (s, 3H, 2-C[=C]-**CH_3**); 1.84 (t, $J=12.5$ Hz, 1H, H-5); 2.00 (s, 3H, 11-**CH_3**); 2.33 (d, $J=13$ Hz, 8-**OH**); 2.35–2.45 (m, 2H, H-3 and H-5); 2.45–2.57 (m, 1H, H-4); 2.84–2.90 (m, 2H, H-7); 4.12 (dt, $J=13$ and 7.5 Hz, 1H, H-8); 4.78 (s, 1H, C=**CH**); 4.83 (d, $J=2$ Hz, 1H, C=**CH**); 5.12 (d; $J=5$ Hz, 1H, H-3a); 5.78 (s, 1H, 5-**OH**). **8**, mp 176–179°C (hexane–ethyl acetate), $[\alpha]_D$ +109.0 ($CHCl_3$, $c=0.5$); ^{1}H NMR ($CDCl_3$, 400 MHz):[16] $\delta=1.48$ ppm (ddd, $J=6$, 11, 14 Hz, 1H, H-3); 1.69 (t, $J=14$ Hz, 1H, H-1); 1.73 (s, 3H, 2-C[=C]-**CH_3**); 1.98 (s, 3H, 11-**CH_3**); 2.08 (ddd, $J=2$, 5, 14 Hz, 1H, H-3); 2.23 (ddd, $J=2$, 4, 14 Hz, 1H, H-1); 2.35–2.44 (m, 1H, H-2); 3.53 (dd, $J=1$ Hz and 4 Hz, 1H, H-7); 3.65–3.68 (m, 1H, H-6); 3.80–3.82 (m, 1H, H-5); 3.92 (s, 3H, COO**CH_3**); 4.07 (t, $J=2$ Hz, 1H, H-4a); 4.38 (d, $J=6$ Hz, 1H, H-3a); 4.57 (d, $J=13$ Hz, 1H, O-**CH_2**-Ph); 4.73 (s, 1H, C=**CH** [Z]); 4.74 (d, $J=13$ Hz, 1H, O-**CH_2**-Ph); 4.80 (s, 1H, C=**CH** [E]); 7.44 (d, $J=8$ Hz, 2H, aryl-H); 8.01 (d, $J=8$ Hz, 2H, aryl-H). **9**, mp 172-173 (hexane–ethyl acetate), $[\alpha]_D$ −154.7 ($CHCl_3$, $c=0.506$); ^{1}H NMR ($CDCl_3$, 400 MHz):[16] $\delta=1.64$ ppm (s, 6H, [**H_3C**]$_2$C=C); 2.04 (s, 3H, 5′-**CH_3**); 2.37–2.47 (m, 1H, H-3); 2.46 (d, $J=16$ Hz, 1H, H-5); 2.52 (d, $J=16$ Hz, 1H, H-5); 2.85 (dd, $J=17$ Hz and 8 Hz, 1H, H-3); 2.38 (dd, $J=3$ Hz and 4 Hz, 1H, H-5″); 3.49 (dd, $J=3$ Hz and 4 Hz, 1H, H-7″); 3.60 (t, $J=8$ Hz, 1H, H-1″); 3.86 (t, $J=8$ Hz, 1H, H-3″); 3.92 (s, 3H, COO**CH_3**); 4.18 (t, $J=8$ Hz, 1H, H-2); 4.46 (d, $J=12$ Hz, 1H, O-**CH_2**-Ph); 4.69 (d, $J=12$ Hz, 1H, O-**CH_2**-Ph); 7.34 (d, $J=8$ Hz, 2H, aryl-H); 8.02 (d, $J=8$ Hz, 2H, aryl-H).
16. Atom numbering for compounds **5** and **6**.



5



6