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Synthesis of the first examples of *p*-bromodienone and transannular spirodienone calixarene derivatives

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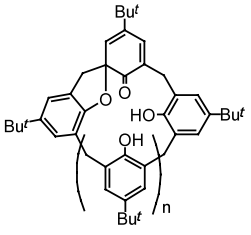
Abstract—The first examples of *p*-bromodienone calixarene derivatives (**6**–**7** and **9**–**10**) have been obtained by treatment of 1,5-dihydroxy-hexaalkoxycalix[8]arenes **5** or tripropoxycalix[4]arene **8** with trimethylphenylammonium tribromide and a saturated solution of $NaHCO_3$. The first transannular spirodienone derivative **11** was only obtained in the presence of NaOH or using the KOH/I_2/PEG-200 oxidizing system.

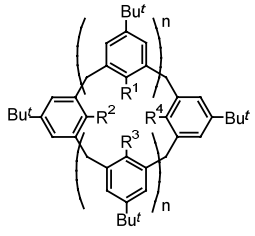
Among the chemical modifications of calixarenes,[1] their mild oxidation to spirodienone derivatives,[2] originally reported by Biali in 1992,[3] is of particular interest since two versatile functionalities (the diene and carbonyl groups) are introduced in a single step. Consequently, these compounds have proved useful key intermediates for the synthesis of calixarenes selectively substituted[4] on the lower rim,[5] extraannular positions,[6] or bridging methylenes.[7]

The formation of spirodienone systems, exemplified by **1**, usually occurs via base-promoted oxidation of the parent *p-tert*-butylcalix[*n*]arene[8,9] **2** with tetraalkylammonium tribromides, but other oxidizing agents, such as $K_3Fe(CN)_6$,[8a] I_2/PEG-200,[10] and O_2/acyl-chloride,[8b] can also be used. In all these reactions, invariably, the spirodienone system is the result of the C(*ortho*)–O bond formation of two *proximal* phenol rings, likely through the intermediacy of phenoxy radicals.[2]

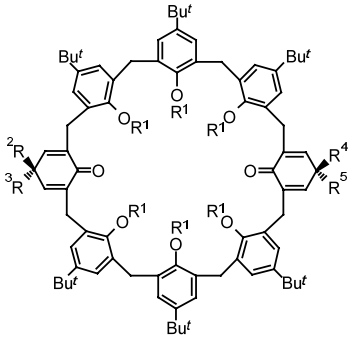
In principle, two *non-proximal* rings could also interact leading to *transannular* spirodienone derivatives like **3**. However, in the case of calix[4]arenes this appears difficult because of the geometrical requirements of the transannular linkage as demonstrated by the finding that 1,3-didehydroxycalix[4]arene **4** does not react under the usual conditions.[11] These observations led Biali to conclude that '*a transannular C–O spiro bond may only be formed in the larger calixarenes*'.[2a]



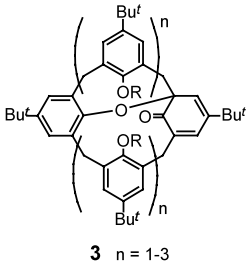
1 n = 1-5



2 n = 1-3; $R^1 = R^2 = R^3 = R^4 = OH$
4 n = 1; $R^1 = R^3 = H$; $R^2 = R^4 = OH$
5a n = 3; $R^1 = R^3 = OPr^n$; $R^2 = R^4 = OH$
5b n = 3; $R^1 = R^3 = OMe$; $R^2 = R^4 = OH$
8 n = 1; $R^1 = R^2 = R^3 = OPr^n$; $R^4 = OH$



6a $R^1 = Pr^n$; $R^2 = R^4 = Br$; $R^3 = R^5 = Bu^t$
6b $R^1 = Me$; $R^2 = R^4 = Br$; $R^3 = R^5 = Bu^t$
7a $R^1 = Pr^n$; $R^2 = R^5 = Br$; $R^3 = R^4 = Bu^t$
7b $R^1 = Me$; $R^2 = R^5 = Br$; $R^3 = R^4 = Bu^t$



3 n = 1-3

Keywords: calixarenes; oxidation; transannular spirodienone; *p*-bromodienone.
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Obviously, the feasibility of this linkage can only be tested on a properly protected derivative. Thus, we realized that the easily available 1,5-dihydroxy-hexaalkoxycalix[8]arenes **5a**–**b**, recently reported by us,[12] are ideal candidates to this end. In fact, the conformational mobility of the calix[8]arene macrocycle allows a spatial proximity of opposite phenol rings as demonstrated by their easy bridging with short spacers.[13]

Therefore, we decided to attempt the transannular spirodienone formation by oxidation of these compounds under conditions usually adopted for monospirodienone synthesis.[9a] Thus, the treatment of **5a** (in CH_2Cl_2 at 25°C) with 3 equiv. of trimethylphenylammonium tribromide and a saturated solution of $NaHCO_3$ resulted in the formation of two yellow derivatives **6a** and **7a** isolated in 30 and 31% yields, respectively, after column chromatography on silica gel.[14] In spite of the yellow color, **6a** and **7a** were not spirodienone derivatives as was indicated by their similar ^{1}H NMR spectra (Fig. 1) containing three 1:1:2 *t*-Bu singlets and which were consistent with a calix[8]arene structure possessing two orthogonal binary symmetry elements.

Elemental analysis and ESI(+) mass spectrometry indicated the stereoisomeric nature of **6a** and **7a** and revealed the presence of bromine, which was confirmed by the ready precipitation of AgBr upon treatment with alcoholic $AgNO_3$. The presence of a dienone chromophore was indicated by UV absorption maximum at 262 nm for **6a** (ε 26,600, *n*-hexane) and 256 nm for **7a** (ε 26,200, *n*-hexane)[15] and was confirmed by a typical ^{13}C NMR resonance for the conjugated carbonyl group at 184.0 and 183.1 ppm for **6a** and **7a**, respectively. These data and the molecular symmetry clearly indicated the presence of a *p*-bromodienone system at the 1,5-positions of the macrocycle. This was confirmed by the presence of a ^{13}C NMR signal at 70.3 and 69.7 ppm, for **6a** and **7a**, respectively, for the bromo-bearing carbon, in accordance with values reported for 4-*tert*-butyl-4-bromo-2,5-cyclohexadienones.[16]

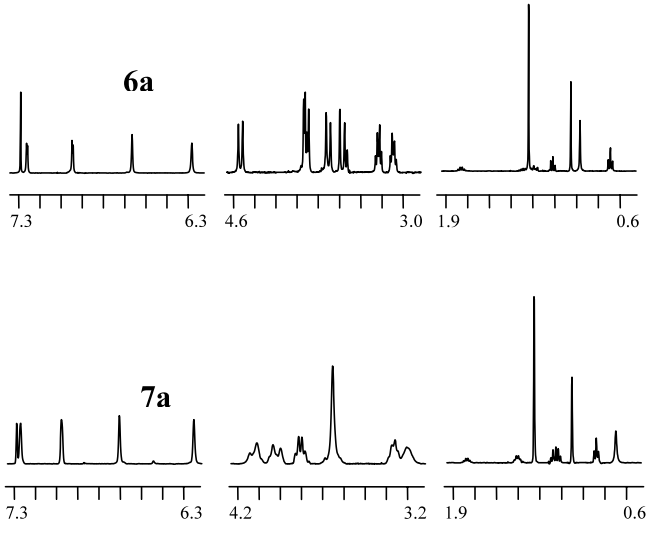


Figure 1. Significant portions of the ^{1}H NMR spectra (400 MHz, $CDCl_3$, 298 K) of compounds **6a** and **7a** (different scales are used).

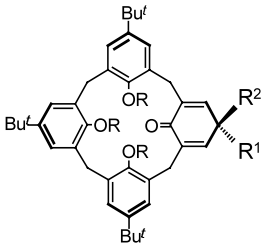
At this point, the stereoisomeric nature of **6a** and **7a** can be easily attributed to the *cis* or *trans* relative geometry of the two bromine atoms of opposite *p*-bromodienone rings. This relative stereochemistry can be assigned on the basis of the diastereotopical resonances of the bridging methylenes. In fact, the presence of one AX system and one AB system for the $ArCH_2Ar$ groups of **6a** (Fig. 1) suggests a *cis* geometry, while the corresponding one AB system and one broad pseudo-singlet for **7a** indicate a *trans* relationship.[17]

It is worth noting that, to the best of our knowledge, **6a** and **7a** represent the first examples of calixarene *p*-bromodienone derivatives.[18,19] Therefore, we decided to verify the extendibility of this *ipso*-bromination procedure to other calixarenes. Thus, similar treatment of **5b**[12] with trimethylphenylammonium tribromide led to the isolation of *cis* and *trans* *p*-bromodienone derivatives **6b** and **7b** in 35 and 38% yields, respectively.[14] Also in this instance, as well as in the above reaction of **5a**, no spirodienone derivative could be detected.

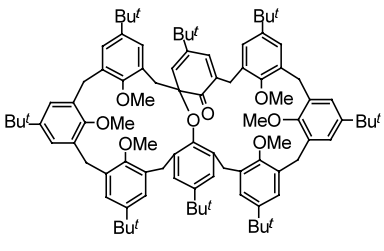
Analogous treatment of tripropoxy-*p*-*t*-butylcalix[4]arene **8**[20] with trimethylphenylammonium tribromide and a saturated solution of $NaHCO_3$ resulted in the formation of a mixture of **9** and **10**, from which **9** could be selectively precipitated by repeated treatment with diethyl ether (81%).[21] Elemental analysis, ESI(+) MS and NMR indicated the *p*-bromodienone stereoisomeric nature of **9** and **10**. Clearly, their stereoisomerism arises from the *exo* or *endo* *ipso*-attack of bromine to the *para* position. The *exo* stereochemistry was attributed to the major product **9** on the basis of thermodynamic and kinetic considerations. In fact, MM3 calculations[22] (in $CHCl_3$ GB/SA model solvent) indicated its lower energy with respect to **10** (2.8 kJ/mol). In addition, and in analogy with other calix[4]arene systems,[23] the *exo* attack to the cavity should also be favored for steric reasons with respect to the hindered *endo* attack.

exo-*p*-Bromodienone **9** displays temperature-dependent ^{1}H NMR spectra due to the easy *through-the-annulus* rotation of the *p*-bromodienone ring. In this way, a cone/partial-cone slow interconversion occurs below the coalescence temperature at 318 K. At higher temperatures the equilibrium becomes fast giving rise to sharp signals for diastereotopical $ArCH_2Ar$ protons. MM3 calculations predict this behavior, giving a small energy difference (0.042 kJ/mol) favoring the cone over the partial-cone conformer of **9**.

From the above results it can be concluded that calixarene *p*-bromodienones should be of general accessibility when isolated, *non-proximal*, phenol rings are present in the starting calixarene. This accessibility seems expandable considering that *p*-bromodienones **6a**–**b** and **7a**–**b** were also obtained by using Br_2/AcOH as the brominating agent.[24]



9 R= *n*-Pr; R^1 = Br; R^2 = Bu^t
10 R= *n*-Pr; R^1 = Bu^t; R^2 = Br



11

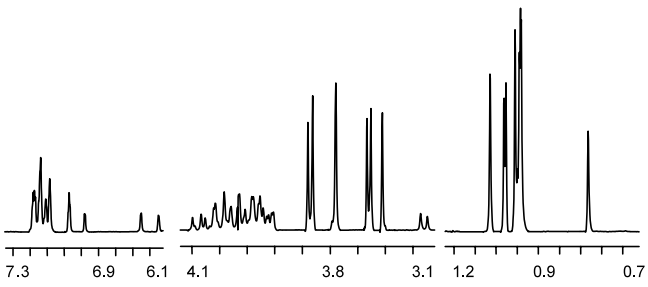


Figure 2. Significant portions of the ^{1}H NMR spectrum (400 MHz, $CDCl_3$, 298 K) of compound **11**.

The non-formation of transannular spirodienone derivatives as a result of the above oxidation conditions can be explained by their probable low stability in conjunction with a faster and more effective concurrent electrophilic *ipso*-bromination. It is likely, that any factor destabilizing the *p*-bromodienone system should favor spirodienone formation. Thus, we decided to investigate the transannular spirodienone formation using the KOH/I_2/PEG-200 oxidizing system.[10] In this instance the alternative route should lead to a *p*-iododienone system which would probably be less stable due to the bulk of the geminal iodine and *t*-Bu groups.

Interestingly, the treatment of **5b** with KOH/I_2/PEG-200 produced a yellow compound **11** (TLC) which was purified by SiO_2-gel chromatography.[25] In accordance with the asymmetry generated by the single spiro stereocenter, the ^{1}H NMR spectrum (Fig. 2) contained six OMe singlets at 3.65, 3.63, 3.52, 3.38, 3.36, and 3.31 ppm and eight *t*-Bu singlets at 1.20, 1.15, 1.14, 1.10, 1.09, 1.08, 1.07, and 0.79 ppm. Typical signals were also found at δ 6.18 and 6.29 confidently assignable to the vinylic protons of the monospirodienone moiety. Moreover, the diastereotopic $ArCH_2Ar$ protons appeared as 16 partially overlapped doublets. The ^{13}C NMR spectrum displayed two resonances at 78.4 and 200.5 ppm relative to the spiro and carbonyl carbons, respectively, and six resonances at 61.3, 61.1, 60.8, 60.5, 60.3, and 60.1 ppm due to the OMe groups.

Further experiments demonstrated that transannular spirodienone **11** could also be obtained (8–10%) with the trimethylphenylammonium tribromide oxidizing system using strongly basic conditions (NaOH),[11] under which no *p*-bromodienone derivatives could be traced (TLC). However, **11** remains undetected in $NaHCO_3$-promoted oxidations even for extended reaction times (up to 24 h). These results suggest that the relative rate of the two concurrent reactions is the major controlling factor.

In conclusion, we have described the first examples of *p*-bromodienone and transannular spirodienone calixarene derivatives. The isolation of the latter compound proves the validity of Biali's hypothesis that non-proximal spirodienones *can* be formed in larger calixarenes.

The calixarene *p*-bromodienones reported here belong to the class of 4-alkyl-4-bromo-2,5-cyclohexadienone derivatives that have proved to be of good synthetic utility. In fact, the easy substitution of bromine with a variety of nucleophiles (including amines,[26a] alcohols,[26b] imidazole,[26c] and pyrazoles[26d]) and the subsequent re-aromatization by transalkylation provide a useful synthetic protocol for functionalization at the *para* position. The application of this procedure to *p*-bromodienone calixarene derivatives should lead to a new route for the upper-rim functionalization of calixarenes. In this instance the complication of stereoisomerism would be overcome in the re-aromatization step.

Acknowledgements

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14. **Procedure for the preparation of 6a–b and 7a–b**. A solution of phenyltrimethylammonium tribromide (360 mg, 0.96 mmol,) in CH_2Cl_2 (27 mL) was added dropwise over 10 min with stirring to a solution of **5a** or **5b**[12] (0.32 mmol) in CH_2Cl_2 (50 mL). Then, 45 mL of saturated aqueous $NaHCO_3$ was added and the mixture was stirred for 15 min at room temperature. The organic phase was washed with H_2O (3×100 mL) and dried. The crude product was subjected to flash column chromatography on silica gel to give the isolated compounds.
From the reaction mixture of **5a** *p*-bromodienones **6a** and **7a** were isolated using dichloromethane/petroleum ether (80:20, *v*/*v*) as eluent. Compound **6a** (164 mg, 30%): ESI(+) MS *m*/*z* 1705 (MH^+); ^1H NMR (400 MHz, $CDCl_3$, 298 K) δ 0.61 (t, $OCH_2CH_2CH_3$, J=7.4 Hz, 12H), 1.09 (t, $OCH_2CH_2CH_3$, J=7.4 Hz, 6H), 0.87 [s, $C(CH_3)_3$, 18H], 0.94 [s, $C(CH_3)_3$, 18H], 1.30 [s, $C(CH_3)_3$, 36H], 1.32 (m, $OCH_2CH_2CH_3$, 8H), 1.88 (m, $OCH_2CH_2CH_3$, 4H), 3.07 (m, $OCH_2CH_2CH_3$, 4H), 3.20 (m, $OCH_2CH_2CH_3$, 4H), 3.54 and 3.87 (AB, $ArCH_2Ar$, J=17.2 Hz, 8H), 3.67 and 4.48 (AX, $ArCH_2Ar$, J=15.9 Hz, 8H), 3.90 (t, $OCH_2CH_2CH_3$, J=6.7 Hz, 4H), 6.30 (s, C=CH, 4H), 6.64 (s, ArH, 4H), 6.97 and 7.23 (AB, ArH, J=2.2 Hz, 8H). Anal. calcd for $C_{106}H_{146}O_8Br_2$: C, 74.54%; H, 8.61%; Br, 9.36%. Found: C, 74.42%; H, 8.72%; Br, 9.23%. Compound **7a** (169 mg, 31%): ESI(+) MS *m*/*z* 1705 (MH^+); ^1H NMR (400 MHz, $CDCl_3$, 298 K) δ 0.61 [s, $C(CH_3)_3$, 18H], 0.98 [s, $C(CH_3)_3$, 18H], 1.30 [s, $C(CH_3)_3$, 36H], 0.77 (t, $OCH_2CH_2CH_3$, J=8.0 Hz, 12H), 1.07 (t, $OCH_2CH_2CH_3$, J=8.0 Hz, 6H), 1.44 (m, $OCH_2CH_2CH_3$, 8H), 1.86 (m, $OCH_2CH_2CH_3$, 4H), 3.28 (m, $OCH_2CH_2CH_3$, 4H), 3.34 (m, $OCH_2CH_2CH_3$, 4H), 3.69 (bs, $ArCH_2Ar$, 8H), 3.85 (m, $OCH_2CH_2CH_3$, 4H), 4.00 and 4.12 (AB, $ArCH_2Ar$, J=15.5 Hz, 8H), 6.27 (s, C=CH, 4H), 6.69 (s, ArH, 4H), 7.01, and 7.24 (AB, ArH, J=2.2 Hz, 8H). Anal. calcd for $C_{106}H_{146}O_8Br_2$: C, 74.54%; H, 8.61%; Br, 9.36%. Found: C, 74.39%; H, 8.74%; Br, 9.20%.
From the reaction mixture of **5b** *p*-bromodienones **6b** and **7b** were isolated using dichloromethane/diethyl ether (95:5, *v*/*v*) as eluent. Compound **6b** (172 mg, 35%): ESI(+) MS *m*/*z* 1537 (MH^+); ^1H NMR (400 MHz, $CDCl_3$, 298 K) δ 0.83 [s, $C(CH_3)_3$, 18H], 0.97 [s, $C(CH_3)_3$, 18H], 1.29 [s, $C(CH_3)_3$, 36H], 3.01 (s, OCH_3, 12H), 3.86 (s, OCH_3, 6H), 3.60 and 3.78 (AB, $ArCH_2Ar$, J=18.0 Hz, 8H), 3.64 and 4.53 (AX, $ArCH_2Ar$, J=15.7 Hz, 8H), 6.26 (s, C=CH, 4H), 6.71, (s, ArH, 4H), 7.01 and 7.23 (AB, ArH, J=2.3 Hz, 8H). Anal. calcd for $C_{94}H_{122}O_8Br_2$: C, 73.31%; H, 7.98%; Br, 10.36%. Found: C, 73.22%; H, 8.11%; Br, 10.21%. Compound **7b** (187 mg, 38%): ESI(+) MS *m*/*z* 1537 (MH^+); ^1H NMR (400 MHz, $CDCl_3$, 298 K) δ 0.69 [s, $C(CH_3)_3$, 18H], 1.07 [s, $C(CH_3)_3$, 18H], 1.24 [s, $C(CH_3)_3$, 36H], 3.34 (s, OCH_3, 12H) 3.65 (s, OCH_3, 6H), 3.69 (bs, $ArCH_2Ar$, 8H), 3.98 and 4.11 (AB, $ArCH_2Ar$, J=15.6 Hz, 8H), 6.35 (s, C=CH, 4H), 6.84, (s, ArH, 4H), 6.97 and 7.14 (AB, ArH, J=2.1 Hz, 8H). Anal. calcd for $C_{94}H_{122}O_8Br_2$: C, 73.31%; H, 7.98%; Br, 10.36%. Found: C, 73.19%; H, 7.81%; Br, 10.19%.
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17. The broad pseudo-singlet observed for **7a** indicates a conformationally averaged *anti*-like relative orientation of the aromatic rings at positions 2 and 3. This is well compatible with the presence of a C_2-axis bisecting the opposite equivalent rings at position 3, in an averaged 'out' orientation, as imposed by the *trans* stereochemistry. Obviously, this feature cannot be compatible with the presence of two-symmetry planes of the C_{2v} *cis* geometry.
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19. The formation of an analogous intermediate *o*-bromocyclohexadienone calixarene derivative by electrophilic bromination was initially hypothesized by Biali to explain spirodienone formation.[2,3] However, currently the phenoxy radicals route is considered more plausible.
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21. **Preparation of *exo*-*p*-bromodienone 9**. Tripropoxycalix[4]arene **8**[19] (1 g, 1.3 mmol) was treated with phenyltrimethylammonium tribromide (488 mg, 1.3 mmol,) as described above for **6a–b**. The crude product was suspended in diethyl ether (10 mL) and the solid precipitated was collected by filtration to give **9**. The filtrate was dried and treatment with Et_2O was repeated three times (3×5 mL) to give an additional amount of **9**. Compound **9** (900 mg, 81%): ESI(+) MS *m*/*z* 853 (MH^+); ^1H NMR (400 MHz, $C_2D_2Cl_4$, 358 K) δ 1.00 [s, $C(CH_3)_3$, 18H], 1.29 [s, $C(CH_3)_3$, 9H], 1.39 [s, $C(CH_3)_3$, 9H], 0.98 (t, $OCH_2CH_2CH_3$, J=7.3 Hz, 3H), 1.09 (t, $OCH_2CH_2CH_3$, J=7.2 Hz, 6H), 1.87 (m, $OCH_2CH_2CH_3$, 4H), 2.39 (m, $OCH_2CH_2CH_3$, 2H), 2.92 and 4.18 (AX, $ArCH_2Ar$, J=13.2 Hz, 4H), 3.14 and 4.36 (AX, $ArCH_2Ar$, J=13.2 Hz, 4H), 3.65 (t, $OCH_2CH_2CH_3$, J=6.8 Hz, 4H), 3.88 (t, $OCH_2CH_2CH_3$, J=8.1 Hz, 2H), 6.55 (bs, ArH, 2H), 6.72 (bs, ArH, 2H), 7.02, (s, C=CH, 2H), 7.13 (s, ArH, 2H). Anal. calcd for $C_{53}H_{73}O_4Br$: C, 74.53%; H, 8.61%; Br, 9.35%. Found: C, 74.31%; H, 8.76%; Br, 9.20%.

22. Molecular modeling was performed with MacroModel-7.2/Maestro-4.1 program: Mohamadi, F.; Richards, N. G.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.
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25. **Procedure for the preparation of transannular spirodienone 11**. A mixture of **5b**[12] (100 mg, 0.075 mmol), I_2 (76 mg, 0.298 mmol), PEG-200 (2 g) in $CHCl_3$ (10 mL) and aqueous KOH (25%, 13 mL), was stirred in the dark for 14 h, at room temperature. The organic phase was separated and washed with brine (3×50 mL) and water (1×50 mL), then dried (Na_2SO_4). The crude product was subjected to flash column chromatography on silica gel, using dichloromethane/diethyl ether (99:1, *v*/*v*) as eluent, to give transannular spirodienone **11** (10 mg, 10%): ESI(+) MS *m*/*z* 1379 (MH^+); ^1H NMR (400 MHz, $CDCl_3$, 298 K) δ 0.79 [s, $C(CH_3)_3$, 9H], 1.07 [s, $C(CH_3)_3$, 9H], 1.08 [s, $C(CH_3)_3$, 9H], 1.09 [s, $C(CH_3)_3$, 9H], 1.10 [s, $C(CH_3)_3$, 9H], 1.14 [s, $C(CH_3)_3$, 9H], 1.15 [s, $C(CH_3)_3$, 9H], 1.20 [s, $C(CH_3)_3$, 9H], 3.31 (s, OCH_3, 3H), 3.36 (s, OCH_3, 3H), 3.38 (s, OCH_3, 3H), 3.52 (s, OCH_3, 3H), 3.63 (s, OCH_3, 3H), 3.65 (s, OCH_3, 3H), 3.12 (d, $ArCH_2Ar$, J=12.4 Hz, 1H), 3.82 (d, $ArCH_2Ar$, J=12.3 Hz, 1H) 3.89 (d, $ArCH_2Ar$, J=12.2 Hz, 1H), 3.90 (d, $ArCH_2Ar$, J=15.7 Hz, 1H), 4.20 (d, $ArCH_2Ar$, J=12.6 Hz, 1H), 3.26-4.12 (overlapped, $ArCH_2Ar$, 11H), 6.18 (bs, C=CH, 1H), 6.29 (bs, C=CH, 1H), 6.67 (d, ArH, J=1.8 Hz, 1H), 6.77–7.10 (overlapped, ArH, 13H). Anal. calcd for $C_{94}H_{122}O_8$: C, 81.81%; H, 8.91%. Found: C, 81.58%; H, 9.03%.
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