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Introduction of Glyco, Peptido, Carboxy, and Alkyno Substituents at the Calixarene *Exo* Rim via the *p*-Bromodienone Route

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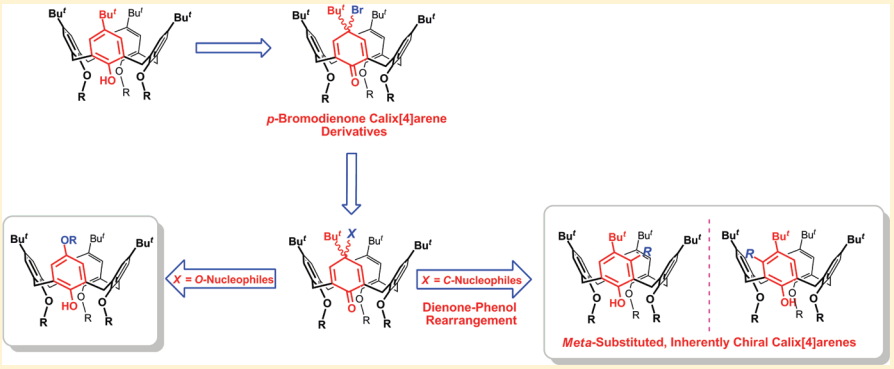
Supporting Information



ABSTRACT: The conceptually novel "*p*-bromodienone route", which allows the direct introduction of nucleophiles at the calixarene *exo* rim, has been extended to anionic *C*-nucleophiles (acetylides) to give chiral *meta*-substituted alkynocalix[4]arenes and to appropriate *O*-nucleophiles to obtain *para*-substituted glyco, peptido, and carboxy derivatives.

Functionalization at the *exo* rim (also called *upper* or *wide* rim)[1] of calixarene macrocycles[2] has been the subject of considerable interest because it is considered the most logical and convenient way to transform their preformed calix cavity in an appropriate recognition site. Usually, this can be achieved with a range of electrophilic aromatic substitutions[3] or with the classical "Claisen rearrangement route",[4] "*p*-quinone-methide route",[5] and "*p*-chloromethylation route".[6]

Very recently, we introduced the "*p*-bromodienone route"[7] as a conceptually novel approach[8] for the direct introduction of nucleophiles at the calixarene *exo* rim using easily accessible calixarene *p*-bromodienone derivatives[9] (exemplified by **1a,b** in Scheme 1). In a similar way, Varma and co-workers concomitantly reported a related procedure in which alkoxy groups are introduced into the calixarene *exo* rim starting from calixarene spirodienone derivatives.[10] In the *p*-bromodienone route, derivatives like **1a** (as well as its *exo*/*endo* mixture **1a,b**) undergo a silver-mediated nucleophilic substitution and a subsequent rearomatization with a range of different *O*-nucleophiles (alcohols and carboxylates) to give *p*-alkoxy- or *p*-acyloxycalixarenes in workable yields.[7a] In a subsequent paper,[7b] we demonstrated that its extension to activated aromatic substrates allows the introduction of aromatic moieties at the *para* or *meta* position of calixarene aromatic rings.[11] In particular, C−C *meta*-coupled products are likely obtained through a dienone−phenol rearrangement of the intermediate dienone derivative.[7b]

In order to expand the potentiality of the *p*-bromodienone route, we decided to investigate the use of appropriate nucleophiles containing glyco, peptido, carboxy, and alkyno substituents, which could be useful for biomimetic recognition[12] or for further synthetic elaboration.

Thus, starting with a sugar moiety, we decided to study the bromine substitution of **1a,b** with the primary hydroxyl group of 1,2,3,4-tetra-*O*-acetyl-β-D-glucose **2a** (TAG, Scheme 1). Therefore, the *exo*/*endo* mixture of calix[4]arene *p*-bromodienone **1a,b** was treated with **2a** in the presence of $AgClO_4$ in DME at 0 °C for 2 h (Scheme 1) to give the corresponding TAG-calixarene derivative **3a** in 60% yield after column chromatography of the reaction mixture. The structure of **3a** was easily assigned by means of spectral analysis. In particular, the presence of a pseudomolecular ion peak at *m*/*z* 1065 in the ESI(+) mass spectrum confirmed the molecular formula. ^{1}H and ^{13}C NMR spectra of **3a** were consistent with an asymmetric calix[4]arene structure due to the presence of the chiral sugar substituent. In particular, the presence of two singlets relative to calixarene *t*-Bu groups at 0.84 and 1.34 ppm (18 and 9H, respectively) was a clear evidence of the displacement of one *t*-Bu group, while the presence of the TAG moiety at the *exo* rim of **3a** was confirmed by the presence of four singlets at 1.99, 2.04, 2.05, and 2.12 ppm relating to acetyl protons and three signals at 169.2, 169.5 (2C), and 170.4 ppm relating to carbonyl groups. In accordance with these results, a specific optical rotation $[\alpha]^{25}_{D}$ of +15.7 (*c* 0.12, $CHCl_3$) was measured for **3a**.

Successively, deacetylation of TAG group at the *exo* rim of **3a** was obtained upon treatment with NaOMe in MeOH as solvent to give glycocalixarene derivative **4** (Scheme 2). Naturally, the glucose moiety of **4** can exist in two α and β anomeric forms. In fact, the ^{1}H NMR spectrum of **4** shows two doublets at 5.17 ppm

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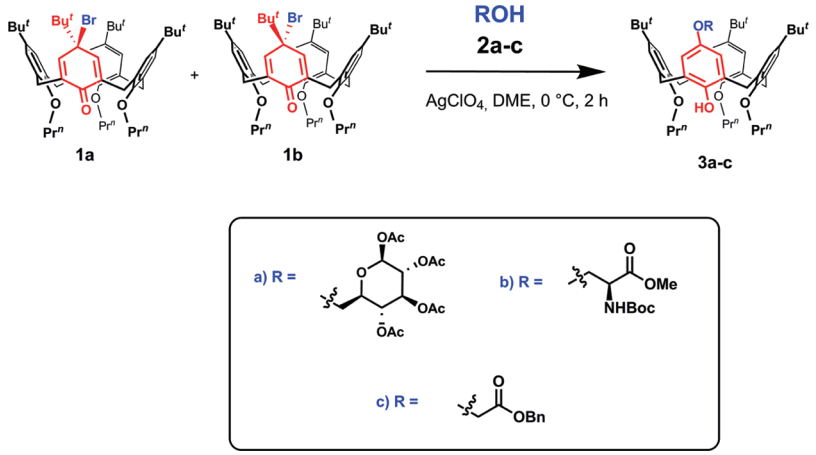
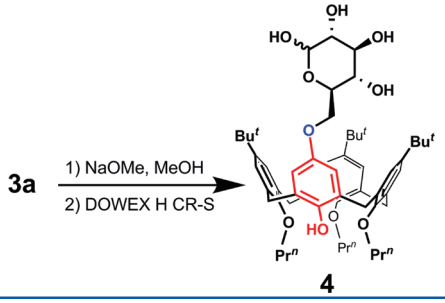
Scheme 1



Scheme 2



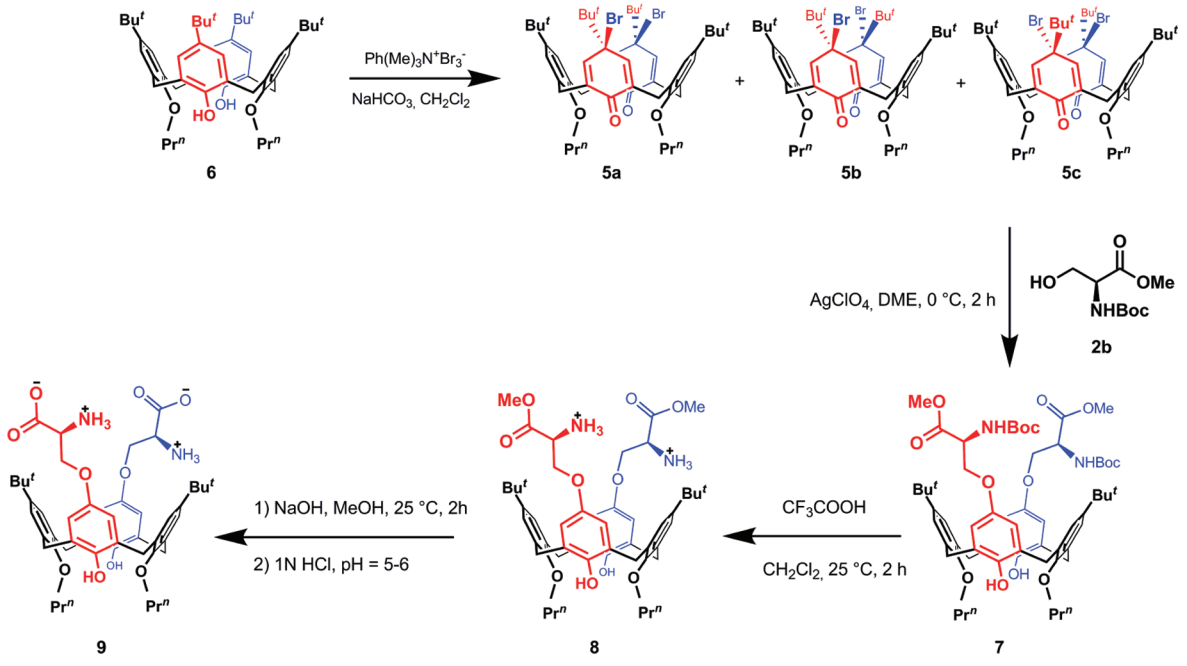
(J = 7.7 Hz) and 5.20 ppm (J = 3.7 Hz) relating to β and α anomeric protons, respectively. Signal integration indicated that the α anomer is preferentially formed over the β one in a ratio of 5:1. It is worth pointing out that, to the best of our knowledge, **4** represents the sole example of glycocalixarene linked by means of a primary alcoholic function and with a free anomeric carbon,[13] which may show new interesting properties.

As previously demonstrated, the introduction of a peptide substituent via the *p*-bromodienone route can be easily obtained using a serine protected with benzyl groups at both the *N*- and *C*-termini.[7a] In order to have a more useful orthogonally protected amino acid derivative, we decided to use *N*-Boc-L-serine methyl ester **2b** as a nucleophile. Thus, the corresponding calixarene amino acid derivative **3b** was obtained in 40% yield under the above conditions ($AgClO_4$, DME, 0 °C, 2 h) (Scheme 1). The structure of **3b** was easily confirmed by spectral analysis, and a specific optical rotation $[\alpha]^{25}_{D}$ = +125.8 (c 0.23, $CHCl_3$) was measured for it.

This approach should be easily extendable to a calixarene bis(amino acid) derivative if the mixture of stereoisomeric distal bis(*p*-bromodienone) calix[4]arene derivatives **5a**–**c**,[7a] easily obtained by treating distal dipropoxycalix[4]arene **6** with trimethylphenylammonium tribromide, is used as the substrate. Therefore, this mixture was treated as above with *N*-Boc-L-serine methyl ester **2b** to give bis(amino acid) derivative **7** in 22% yield (Scheme 3).

As above, the structure of **7** was fully consistent with all spectral data. In particular, its C_2-symmetry was confirmed by

Scheme 3



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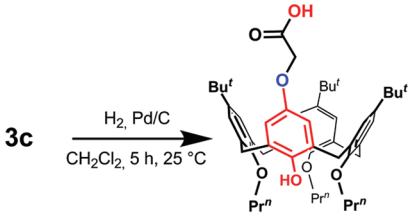
the presence of a single *tert*-butyl singlet (18H) at 1.16 ppm and two $ArCH_2Ar$ AX systems in the ^1H NMR spectrum.

As pointed out previously, calix[4]arene amino acid derivatives **3b** and **7** can be considered a novel type of peptido-calixarenes because, different from other known examples,[12,14,15] in this instance peptide chains can be equally grown either from the *C*- or *N*-terminus through a selective deprotection of amino or carboxy group. Obviously, this kind of linkage of amino acid moieties to calixarene *exo* rim would be more difficult to obtain through synthetic procedures alternative to *p*-bromodienone route.[7b,16]

The selective deprotection of amino groups of **7** was obtained under acid treatment in CH_2Cl_2 to give derivative **8** in 80% yield (Scheme 3). Subsequent basic cleavage of methyl ester groups of **8** led to the formation of zwitterionic derivative **9** in 60% yield (Scheme 3).

Recently, the supramolecular properties of calix[4]arene derivatives bearing anionic carboxylato groups at the *exo* rim (*p*-carboxylatocalixarenes) have attracted considerable interest. In particular, Dalgarno and co-workers[17] have reported a beautiful example of a solid-state nanotube based on a *p*-carboxylatocalix[4]arene, while we have shown that *p*-carboxylatocalix[4]arenes are able to recognize organic cationic guests through an induced-fit mechanism.[18] Thus, prompted by this growing interest, we decided to exploit the *p*-bromodienone route as a simple and direct method to introduce carboxy moieties at the calixarene *exo* rim. Therefore, we reacted benzylglycolate **2c** with the mixture of *p*-bromodienones **1a**,**b** to obtain derivative **3c** in 33% yield (Scheme 1). Then, hydrogenolysis of the benzylic group of **3c** (H_2, Pd/C) gave carboxy derivative **10** in 85% yield (Scheme 4).

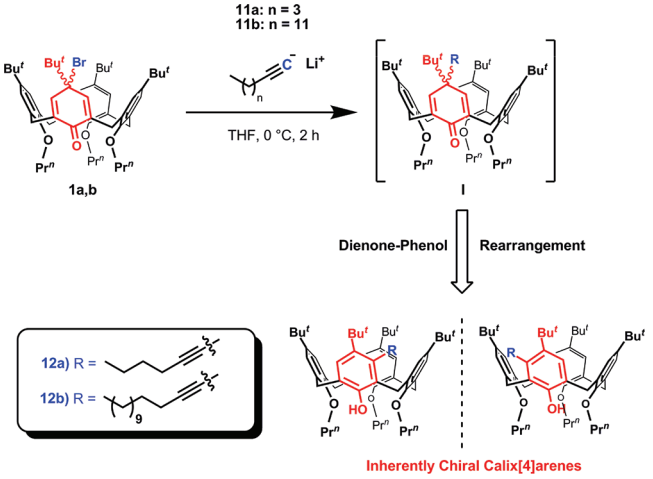
Scheme 4



The structure of **10** was easily assigned in the usual way, and in particular, the presence of a glycolyl group was confirmed by a singlet at 4.66 ppm relating to OCH_2COOH protons. Derivative **10** represents a novel example of carboxycalixarene in which a COOH function is linked to the calixarene aromatic walls through an OCH_2 spacer.

Prompted by these results, we decided to investigate the *p*-bromodienone route with anionic carbon nucleophiles such as acetylide ions. Thus, a THF solution of lithium acetylide **11a**, prepared by reaction of 1-hexyne with *n*-BuLi, was added to a solution of *p*-bromodienone **1a**,**b** in dry THF (Scheme 5). The reaction mixture was kept under stirring for 1 h and then subjected to column chromatography to give derivative **12a** in 48% yield. Derivative **12a** showed an ^1H NMR spectrum consistent with an asymmetric calix[4]arene structure. In fact, diastereotopic $ArCH_2Ar$ protons appeared as eight doublets, while the aromatic protons of the calixarene skeleton gave six doublets with a typical *meta*-coupling and one singlet at 5.94 ppm attributable to an isolated ArH proton of the substituted phenol ring. In addition, four *t*-Bu singlets were present at 0.56,

Scheme 5



1.07, 1.22, and 1.23 ppm (9H each). In analogy with previous results with activated aromatic nucleophiles,[7b] these data were compatible with a chiral asymmetric calix[4]arene structure in which a phenol ring is *meta*- and *para*-substituted with an hexynyl and a *t*-Bu group, respectively, or vice versa.

The real substitution pattern was established by means of a diagnostic NOESY cross-peak between the *t*-Bu group at 0.56 ppm and the isolated ArH singlet at 5.94 ppm, only compatible with a *p*-*t*-Bu and *m*-hexynyl linkage. Interestingly, the unusual high-field positioning (0.56 ppm) of the *t*-Bu group can be explained by the shielding effect of the adjacent triple bond.

As proposed previously for aromatic nucleophiles,[7b] the formation of **12a** can be explained by a dienone-phenol rearrangement[19] of alkyne moiety of intermediate dienone **I** (Scheme 5), which migrates to the adjacent *meta*-position. The migratory aptitude of alkyne moiety was corroborated by a recent report of Kim and co-workers in which a Pt-catalyzed dienone-phenol rearrangement of alkyne-bearing quinols give rise to 5-hydroxybenzofuran systems.[20]

To verify the influence of the alkyne moiety on the reaction outcome, a longer lithium acetylide **11b** was reacted with *exo*/*endo* mixture **1a**,**b**. Also in this instance, a *meta*-substituted calix[4]arene **12b** was obtained in similar yield (43%), thus confirming that the *p*-bromodienone route with carbon nucleophiles provides a practicable method for the synthesis of *meta*-substituted inherently chiral calix[4]arene derivatives.[7c] In addition, the use of acetylide nucleophiles provides an easy entry to calixarenes bearing alkyno substituents at the *meta*-position, which are complementary to those *para*-substituted previously obtained with propargylic alcohol.[7a] All these alkynocalixarenes are particularly interesting as recognition platforms to be used in the fast-expanding field of click chemistry.[16,21]

In conclusion, we have demonstrated that the calixarene *p*-bromodienone route, previously applied to alcohols, carboxylates, and activated aromatic substrates, can be extended to anionic *C*-nucleophiles and can be exploited to append novel functional groups, which would be more difficult to introduce through classical routes. In this way, *para*-substituted glyco, peptido, and carboxy calixarenes were obtained by using appropriate *O*-nucleophiles, while inherently chiral *m*-substituted alkyno-calixarenes were prepared by using acetylide ions as *C*-nucleophiles. We believe that the potentiality of *p*-bromodienone route can be further expanded by using other appropriate nucleophiles including the *N*-, and *S*-ones.

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EXPERIMENTAL SECTION

General: ESI(+)-MS measurements were performed on a quadrupole mass spectrometer equipped with electrospray ion source, using a mixture of H_2O/CH_3CN (1:1) and 5% HCOOH as solvent. Optical rotations were measured at the indicated concentration and temperature using the sodium D line. Flash chromatography was performed on silica gel (40−63 μm). All chemicals were reagent grade and were used without further purification. When necessary, compounds were dried in vacuo over $CaCl_2$. THF was distilled over CaH_2. Reaction temperatures were measured externally. Reactions were monitored by TLC on silica gel plates (0.25 mm) and visualized by UV light or by spraying with H_2SO_4−$Ce(SO_4)_2$. ^{1}H NMR spectra were recorded at 250, 300, or 400 MHz, and ^{13}C NMR spectra were recorded at 63, 75, or 100 MHz. Chemical shifts are reported relative to the residual solvent peak ($CHCl_3$: δ 7.26, $CDCl_3$: δ 77.23). The temperature was maintained at 298 K for all NMR spectra. One-dimensional ^{1}H and ^{13}C spectra, DEPT-90, DEPT-135, COSY-45, heteronuclear multiple-bond correlation (HMBC), heteronuclear single quantum correlation (HSQC), and NOESY were used for NMR peak assignment of all derivatives. COSY-45 spectra were taken using a relaxation delay of 2 s with 30 scans and 170 increments of 2048 points each. HMBC spectra were performed without ^{1}H decoupling, with low-pass J-filter to suppress one-bond correlations, and with a delay of 70 ms for the evolution of long-range couplings. The number of scans taken was 50, with 413 increments of 4096 points each. HSQC spectra were performed with gradient selection, sensitivity enhancement, and phase-sensitive mode using Echo/Antiecho-TPPI procedure. A typical experiment comprised 20 scans with 113 increments of 2048 points each. NOESY spectra were recorded in phase-sensitive mode using a mixing time of 650 ms. A typical experiment comprised 30 scans with 270 increments of 2048 points each. Derivatives **1a,b**,[9] **2a**,[22] and **5a−c**[7a] were synthesized according to literature procedures.

Synthesis of Derivative 3a−c Starting from the Mixture of Stereoisomers 1a,b. A solution of $AgClO_4$ (1.20 mmol) and the appropriate alcohol **2a−c** (5.8 mmol) in DME (7.0 mL) at 0 °C was added to the solid mixture of stereoisomers **1a,b** (0.58 mmol). The reaction mixture was allowed to warm at room temperature and stirred in the dark for 2 h. The reaction was stopped by addition of water (20 mL) and CH_2Cl_2 (20 mL). The organic phase was washed three times with water, dried on Na_2SO_4, and filtered, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel.

Derivative ***3a***. Eluent: CH_2Cl_2, white solid, 0.11 g, 30% yield. $[\alpha]^{25}_D$ = +15.7 (*c* 0.12, $CHCl_3$). Mp: 180−183 °C. ESI(+) MS: *m*/*z* = 1065 (MH^+). ^{1}H NMR ($CDCl_3$, 250 MHz, 298 K): δ 0.84 and 1.34 [s, C(CH_3), 18H and 9H], 0.92 (t, $OCH_2CH_2CH_3$, *J* = 7.5 Hz, 3H), 1.08 (t, $OCH_2CH_2CH_3$, *J* = 7.5 Hz, 6H), 1.79−1.95 (m, $OCH_2CH_2CH_3$, 4H), 1.99, 2.04, 2.05, and 2.12 (s, $COCH_3$, 3H each one), 2.27−2.42 (m, $OCH_2CH_2CH_3$, 2H), 3.17 (overlapped, $ArCH_2Ar$, 4H), 3.71 (t, $OCH_2CH_2CH_3$, *J* = 7.0 Hz, 4H), 3.83 (m, $OCH_2CH_2CH_3$, 2H), 3.95−3.99 (overlapped, CHOAc, 3H), 4.10−4.38 (overlapped, $ArCH_2Ar$, 4H), 5.07 (s, OH, 1H), 5.14−5.33 (overlapped, CHOAc + $-CH_2OAr^{calix}$, 3H), 5.80 (d, −OCHOAc, *J* = 8.0 Hz, 1H), 6.48 (m, ArH, 2H), 6.54 (m, ArH, 2H), 6.65 (s, ArH, 2H), 7.14 (s, ArH, 2H). ^{13}C NMR ($CDCl_3$, 63 MHz, 298 K): δ 9.8, 11.0, 20.8, 20.9, 21.1, 22.6, 23.6, 31.4, 31.7, 31.9, 33.9, 34.3, 68.3, 68.9, 70.7, 73.2, 73.6, 77.4, 77.9, 78.0, 92.1, 115.5, 124.7, 125.1. 125.19, 125.9, 131.5, 131.5, 131.6, 131.7, 132.51, 132.5, 136.2, 136.2, 145.4, 145.4, 145.9, 148.3, 151.2, 152.1, 152.2, 154.1, 169.2, 169.5, 170.4. Anal. Calcd for $C_{63}H_{84}O_{14}$: C, 71.03; H, 7.95. Found: C, 71.13; H, 7.86.

Derivative ***3b***. Eluent: petroleum ether/CH_2Cl_2, (65/35, v/v), white solid, 0.22 g, 40% yield. $[\alpha]^{25}_D$ = +125.8 (*c* 0.23, $CHCl_3$). Mp: 200−203 °C. ESI(+) MS: *m*/*z* = 936 (MH^+). ^{1}H NMR ($CDCl_3$, 400 MHz, 298 K): δ 0.86 (s, *t*-Bu, 9H), 0.87 (s, *t*-Bu, 9H), 0.94 (t, $OCH_2CH_2CH_3$, *J* = 7.6 Hz, 3H), 1.08 (t, $OCH_2CH_2CH_3$, *J* = 7.4 Hz, 6H), 1.32 (s, *t*-Bu, 9H), 1.48 (s, t-Bu^{BOC}, 9H), 1.91 (m, $OCH_2CH_2CH_3$, 4H), 2.31 (m, $OCH_2CH_2CH_3$, 2H), 3.09−3.20 (overlapped, $ArCH_2Ar$, 4H), 3.71−3.86 (overlapped, $OCH_2CH_2CH_3$ + OCH_3, 9H), 4.17 (dd, OCH_2CH(NHBoc)COOMe, J^1 = 9.3 Hz, J^2 = 3.0 Hz, 1H), 4.32−4.38 (overlapped, $ArCH_2Ar$ + OCH_2CH(NHBoc)COOMe, 5H), 4.63 (br d, OCH_2CH(NHBoc)COOMe, 1H) 5.13 (s, OH, 1H), 5.55 (d, OCH_2CH(NHBoc)COOMe, *J* = 8.5 Hz, 1H), 6.50−6.58 (overlapped, ArH, 4H), 6.62 (br s, ArH, 2H), 7.11 (br s, ArH, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ 10.0, 11.0, 22.7, 23.7, 27.5, 28.6, 30.0, 30.2, 31.4, 31.8, 31.9, 34.0, 34.4, 52.8, 54.2, 70.0, 76.6, 78.0, 80.4, 115.0, 115.1, 115.2, 124.9, 125.3, 126.0, 131.6, 131.9, 132.2, 132.8, 136.2, 145.5, 145.9, 147.3, 148.2, 151.3, 152.2, 154.0, 155.8, 171.0. Anal. Calcd for $C_{58}H_{81}NO_9$: C, 74.40; H, 8.72; N, 1.50. Found: C, 74.31; H, 8.81; N, 1.42.

Derivative ***3c***. Eluent: CH_2Cl_2/petroleum ether (8/2, v/v), white solid, 0.25 g, 33% yield. Mp: >180 °C dec. ESI(+) MS: *m*/*z* = 883 (MH^+). ^{1}H NMR ($CDCl_3$, 250 MHz, 298 K): δ 0.84 [s, C(CH_3)$_3$, 18H], 0.95 (t, $OCH_2CH_2CH_3$, *J* = 7.3 Hz, 3H), 1.08 (t, $OCH_2CH_2CH_3$, *J* = 7.4 Hz, 6H), 1.34 [s, C(CH_3)$_3$, 9H], 1.90 (m, $OCH_2CH_2CH_3$, 4H), 2.35 (m, $OCH_2CH_2CH_3$, 2H), 3.17 (br d, overlapped, $ArCH_2Ar$, 4H), 3.73 (t, OCH_2CH_2CH3, *J* = 7.0 Hz, 4H), 3.84 (t, $OCH_2CH_2CH_3$, *J* = 8.2 Hz, 2H), 4.32 (d, $ArCH_2Ar$, *J* = 13.0 Hz, 2H), 4.36 (d, $ArCH_2Ar$, *J* = 12.5 Hz, 2H), 4.63 (s, OCH_2COOR, 2H), 5.16 (s, OH, 1H), 5.26 (s, OCH_2Ph, 2H), 6.49 (d, ArH, *J* = 2.0 Hz, 2H), 6.54 (d, ArH, *J* = 2.0 Hz, 2H), 6.69 (s, ArH, 2H), 7.13 (s, ArH, 2H), 7.38 (overlapped, ArH, 5H). ^{13}C NMR ($CDCl_3$, 63 MHz, 298 K): δ 9.8, 11.0, 22.6, 23.4, 31.1, 31.4, 31.5, 31.9, 33.9, 34.3, 67.01, 67.05, 76.5, 78.0, 115.2, 124.7, 125.2, 125.8, 128.7, 128.8, 131.4, 131.5, 131.7, 132.5, 136.2, 145.8, 148.4, 148.5, 150.7, 151.7, 152.1, 154.0, 169.5. Anal. Calcd for $C_{58}H_{74}O_7$: C, 78.87; H, 8.45. Found: C, 78.96; H, 8.37.

Synthesis of Derivative 4. Compound **3c** (0.11 g, 0.10 mmol) was dissolved in 15 mL of anhydrous methanol at room temperature, and then sodium methoxide (NaOMe) (10 mg) was added to the reaction mixture. The solution was stirred, at room temperature, for 2 h. Dowex H^+ exchange resin, was added until pH = 6−7, and the reaction was stirred for an additional 10 min. The solution was gravity filtered and concentrated in vacuo to give **4** as a white solid, 0.065 g, 72% yield. $[\alpha]^{25}_D$ = +23.7 (*c* 0.12, MeOH). Mp: 170−174 °C. ESI(+) MS: *m*/*z* = 897 (MH^+). ^{1}H NMR (CD_3OD, 400 MHz, 298 K): δ 0.91 [overlapped, C(CH_3)$_3$, 18H], 1.00 (t, $OCH_2CH_2CH_3$, *J* = 7.6 Hz, 3H), 1.17 (t, $OCH_2CH_2CH_3$, *J* = 7.6 Hz, 3H), 1.21 (t, $OCH_2CH_2CH_3$, *J* = 6.8 Hz, 3H), 1.36 [s, C(CH_3)$_3$, 9H], 1.88−2.04 (overlapped, $OCH_2CH_2CH_3$, 4H), 2.31−2.40 (m, $OCH_2CH_2CH_3$, 2H), 3.22 (d, $ArCH_2Ar$, *J* = 10.4 Hz, 2H), 3.25 (d, $ArCH_2Ar$, *J* = 10.4 Hz, 2H), 3.38−3.89 (overlapped, CHOH + $OCH_2CH_2CH_3$, 10H), 4.10−4.22 (m, $-OCH_2-$, 2H), 4.36 (d, $ArCH_2Ar$, *J* = 10.4 Hz, 2H), 4.40 (d, $ArCH_2Ar$, *J* = 10.4 Hz, 2H), 5.17 (d, $-OCHOH^{\beta\text{-anomer}}$, *J* = 7.7 Hz, 0.2 × 1H), 5.20 (d, $-OCHOH^{\alpha\text{-anomer}}$, *J* = 3.7 Hz, 1H), 6.62, 6.67, 6.79, and 7.20 (br s, ArH, 8H). ^{13}C NMR (CD_3OD, 100 MHz, 298 K): δ 10.9, 12.1, 15.3, 16.3, 24.6, 25.4, 31.6, 32.8, 32.9, 33.1, 33.9, 35.5, 35.8, 50.7, 67.7, 70.8, 72.4, 72.8, 74.6, 75.8, 77.1, 78.3, 79.0, 79.7, 79.8, 80.1, 80.4, 94.9, 99.1, 116.9, 126.6, 127.2, 127.7, 133.6, 133.9, 134.8, 137.9, 147.3, 147.8, 149.2, 154.0, 155.9. Anal. Calcd for $C_{55}H_{76}O_{10}$: C, 73.63; H, 8.54. Found: C, 73.72; H, 8.45.

Synthesis of Derivative 7 Starting from the Mixture of Stereoisomers 5a−c. A solution of $AgClO_4$ (0.49 g, 2.4 mmol) and *N*-Boc-L-serine benzyl ester **2b** (1.72 g, 7.9 mmol) in DME (6.0 mL) at 0 °C was added to the solid mixture of stereoisomers **5a−c** (0.70 g, 0.79 mmol). The reaction mixture was allowed to warm at room temperature and stirred in the dark for 2 h. The reaction was stopped by addition of water (20 mL) and CH_2Cl_2 (20 mL). The organic phase was washed three times with water, dried on Na_2SO_4, and filtered, and the solvent was removed under reduced pressure. The crude material was purified by column chromatography on silica gel, eluent CH_2Cl_2/petroleum ether, 65/35, v/v; white solid, 0.18 g, yield, 22%. $[\alpha]^{25}_D$ = +29.0 (*c* 0.20, $CHCl_3$). Mp: >200 °C dec. ESI(+) MS: *m*/*z* = 1055 (MH^+). ^{1}H NMR ($CDCl_3$, 400 MHz, 298 K): δ 1.15 (s, *t*-Bu, 18H), 1.22 (t, $OCH_2CH_2CH_3$, *J* = 8.0 Hz, 6H), 1.42 (s, *t*-Bu, 18H), 2.08 (m, $OCH_2CH_2CH_3$, 4H), 3.26 (d, $ArCH_2Ar$, *J* = 13.2 Hz, 4H), 3.58 (s, OCH_3, 6H), 3.94 (t, $OCH_2CH_2CH_3$, *J* = 6.8 Hz, 4H), 4.01 [dd, OCH_2CHNH(Boc)COOMe, J^1 = 9.2 Hz, J^2 = 2.8 Hz, 2H], 4.22 [dd, OCH_2CH(NHBoc)COOMe, J^1 = 9.2 Hz, J^2 = 2.8 Hz, 2H], 4.32 (d, $ArCH_2Ar$, *J* = 13.2 Hz, 4H), 4.55 [br d, OCH_2CHNH(Boc)-COOMe, 2H], 5.43 [d, OCH_2CH(NHBoc)COOMe, *J* = 8.6, 2H], 6.54 (br s, ArH^{tBu}, 4H), 6.96 (br s, ArH^{OR}, 4H), 8.17 (s, OH, 2H).

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^{13}C NMR ($CDCl_3$, 100 MHz, 298 K): δ 10.7, 11.0, 23.5, 28.5, 31.5, 32.2, 34.4, 52.6, 53.6, 53.8, 68.9, 78.6, 80.3, 114.4, 114.7, 115.1, 126.0, 130.0, 132.7, 133.5, 147.3, 147.6, 150.5, 151.2, 155.6, 170.9. Anal. Calcd for $C_{60}H_{82}N_2O_{14}$: C, 68.29; H, 7.83. Found: C, 68.38; H, 7.74.

Synthesis of Derivative 8. Derivative **7** (0.12 g, 0.12 mmol) was dissolved in CH_2Cl_2 (2 mL) and CF_3COOH (2 mL) was added. The mixture was stirred at room temperature for 2 h. The solvent was removed and the crude material was dissolved in MeOH (0.5 mL) and the product was precipitated by the addition of Et_2O (3 mL) to give derivative **8** as a white solid, 0.082 g; yield 80%. $[\alpha]^{25}_D$ = +76.7 (*c* 0.20, CH_3OH). Mp: >210 °C dec. ESI(+) MS: *m*/*z* = 855 (MH^+). ^{1}H NMR (CD_3OD, 400 MHz, 298 K): δ 1.14 (s, *t*-Bu, 18H), 1.36 (t, $OCH_2CH_2CH_3$, *J* = 7.6 Hz, 6H), 2.10 (m, $OCH_2CH_2CH_3$, 4H), 3.41 (d, $ArCH_2Ar$, *J* = 13.2 Hz, 4H), 3.78 (s, OCH_3, 6H), 3.99 (t, $OCH_2CH_2CH_3$, *J* = 6.8 Hz, 4H), 4.31−4.37 (overlapped, $ArCH_2Ar$ + OCH_2CH, 6H), 4.41−4.48 (overlapped, OCH_2CH + NH_2, 6H), 6.84 (d, ArH^{tBu}, *J* = 2.4 Hz, 2H), 6.85 (d, ArH^{tBu}, *J* = 2.4 Hz, 2H), 7.10 (s, ArH^{OR}, 4H). ^{13}C NMR (CD_3OD, 100 MHz, 298 K): δ 10.9, 22.9, 31.1, 31.2, 34.1, 52.3, 78.2, 114.5, 114.7, 125.5, 125.8, 129.1, 129.9, 133.4, 146.0, 147.2, 150.1, 150.2, 167.0. Anal. Calcd for $C_{50}H_{66}N_2O_{10}$: C, 70.23; H, 7.78. Found: C, 70.32; H, 7.86.

Synthesis of Derivative 9. Derivative **8** (0.082 g, 0.096 mmol) was dissolved in MeOH (2 mL), and a 1 N solution of NaOH (1 mL) was added. The mixture was stirred at room temperature for 2 h. Then a 1 N solution of HCl was added dropwise until pH = 5−6 was reached, and the precipitated product **9** was collected by filtration as a white solid, 0.048 g, 60% yield. $[\alpha]^{25}_D$ = +160.7 (*c* 0.21, CH_3OH). Mp: >220 °C dec. ESI(+) MS: *m*/*z* = 828 (MH^+). ^{1}H NMR (CD_3OD, 400 MHz, 298 K): δ 1.10 (s, *t*-Bu, 18H), 1.33 (t, $OCH_2CH_2CH_3$, *J* = 7.6 Hz, 3H), 2.07 (m, $OCH_2CH_2CH_3$, 4H), 3.37 (d, $ArCH_2Ar$, *J* = 12.4 Hz, 4H), 3.62−3.98 (overlapped, $CHNH$ + $OCH_2CH_2CH_3$, 6H), 4.16−4.35 (overlapped, $NHCHCH_2$ + $ArCH_2Ar$, 8H), 6.81 (d, ArH, *J* = 2.8 Hz, 2H), 6.82 (d, ArH, *J* = 2.8 Hz, 2H), 7.07 (d, ArH, *J* = 2.0 Hz, 2H), 7.08 (d, ArH, *J* = 2.0 Hz, 2H), 7.06 (br s, ArH^{OR}, 4H). ^{13}C NMR (DMSO-d_6, 63 MHz, 298 K): δ 10.8, 28.8, 31.1, 31.2, 34.1, 78.2, 114.5, 114.7, 125.5, 125.7, 129.1, 129.9, 133.4, 146.0, 147.2, 150.1, 150.2, 167.0. Anal. Calcd for $C_{48}H_{62}N_2O_{10}$: C, 69.71; H, 7.56. Found: C, 69.80; H, 7.47.

Synthesis of Derivatives 10. A solution of **3c** (0.025 g, 0.028 mmol) in CH_2Cl_2 (0.4 mL) was stirred in the presence of a catalytic amount of Pd/C (10% w/w) under H_2 for 5 h. Then, the reaction mixture was filtered through Celite and washed three times with CH_2Cl_2. The solvent was removed under reduced pressure to give **10** as a white solid, 0.019 g, 85% yield. Mp: >180 °C dec. ESI(−) MS: *m*/*z* = 791 (M^-). ^{1}H NMR ($CDCl_3$, 400 MHz, 298 K) δ 0.86 [s, $C(CH_3)_3$, 18H], 0.95 (t, $OCH_2CH_2CH_3$, *J* = 7.6 Hz, 3H), 1.09 (t, $OCH_2CH_2CH_3$, *J* = 7.2 Hz, 6H), 1.34 [s, $C(CH_3)_3$, 9H], 1.91 (m, $OCH_2CH_2CH_3$, 4H), 2.32 (m, $OCH_2CH_2CH_3$, 2H), 3.19 (d, $ArCH_2Ar$, *J* = 12.8 Hz, 2H), 3.22 (d, $ArCH_2Ar$, *J* = 12.8 Hz, 2H), 3.71−3.77 (m, $OCH_2CH_2CH_3$, 4H), 3.84 (t, $OCH_2CH_2CH_3$, *J* = 8.0 Hz, 2H), 4.34 (d, $ArCH_2Ar$, *J* = 12.8 Hz, 2H), 4.37 (d, $ArCH_2Ar$, *J* = 12.8 Hz, 2H), 4.66 (s, OCH_2COOH, 2H), 5.28 (s, OH, 1H), 6.50 (d, ArH, *J* = 2.4 Hz, 2H), 6.56 (d, ArH, *J* = 2.4 Hz, 2H), 6.72 (s, ArH, 2H), 7.14 (s, ArH, 2H), 12.1 (broad, COOH). ^{13}C NMR ($CDCl_3$, 63 MHz, 298 K): δ 9.5, 11.2, 22.2, 23.6, 31.2, 31.8, 33.8, 34.2, 66.4, 114.9, 124.6, 125.3, 125.7, 131.2, 131.8, 132.5, 136.0, 145.4, 145.7, 148.6, 150.0, 151.9, 153.9, 173.5. Anal. Calcd for $C_{51}H_{68}O_7$: C, 77.24; H, 8.64. Found: C, 77.32; H, 8.55.

Synthesis of Derivatives 12a,b. *Preparation of Alkynyllithium Derivatives **11a,b**.* An appropriate alkyne (0.84 mmol) was dissolved in dry THF (5 mL), and the solution was cooled at −78 °C. Then a 2.5 M solution of *n*-butyllithium in *n*-hexane (1.38 mL, 3.45 mmol) was added dropwise over 20 min, and the resulting suspension was stirred for 10 min at −78 °C. The solid obtained after decantation was washed two times with dry THF to give a final suspension.

*Synthesis of Derivatives **12a,b**.* A suspension of appropriate alkynyllithium **11a** or **11b** (3.45 mmol) in THF (1.0 mL) at −78 °C was slowly added to the solution of calix[4]arene *p*-bromodienones **1a,b** (0.20 g, 0.23 mmol) in THF (1.0 mL). The reaction mixture was allowed to warm at room temperature and stirred for 1 h. The reaction was stopped by addition of water (20 mL) and CH_2Cl_2 (20 mL). The organic phase was washed three times with water, dried on Na_2SO_4, and filtered, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel (*n*-hexane/CH_2Cl_2, v/v, 2/8).

*Derivative **12a**:* 0.09 g, 48% yield. Mp: >200 °C dec. ESI(+) MS: *m*/*z* = 855 (MH^+). ^{1}H NMR ($CDCl_3$, 400 MHz, 298 K): δ 0.56 [s, $C(CH_3)_3$, 9H], 0.91 (t, $OCH_2CH_2CH_3$, *J* = 7.5 Hz, 3H), 0.95 (overlapped, $OCH_2CH_2CH_3$, 6H), 1.03 (t, $-C\equiv C-CH_2(CH_2)_2CH_3$, *J* = 7.6 Hz, 3H), 1.07 [s, $C(CH_3)_3$, 9H], 1.22 [s, $C(CH_3)_3$, 9H], 1.23 [s, $C(CH_3)_3$, 9H], 1.26−1.53 (overlapped, $C\equiv CCH_2CH_2CH_2CH_3$, 4H), 1.81−2.14 (overlapped, $OCH_2CH_2CH_3$, 6H), 2.19 (t, $C\equiv CCH_2CH_2CH_2CH_3$, *J* = 8.0 Hz, 2H), 2.70 (d, *J* = 12.6 Hz, $ArCH_2Ar$, 1H), 2.97 (d, *J* = 12.5 Hz, $ArCH_2Ar$, 1H), 3.16 (d, *J* = 12.8 Hz, $ArCH_2Ar$, 1H), 3.24 (d, *J* = 12.8 Hz, $ArCH_2Ar$, 1H), 3.58−3.90 (overlapped, $OCH_2CH_2CH_3$, 4H), 3.92 (d, *J* = 12.8 Hz, $ArCH_2Ar$, 1H), 4.08 (m, $OCH_2CH_2CH_3$, 2H), 4.39−4.49 (overlapped, $ArCH_2Ar$, 3H), 5.77 (s, OH, 1H), 5.94 (br s, ArH, 1H), 6.77 (d, ArH, *J* = 2.5 Hz, 1H), 6.80 (d, ArH, *J* = 2.5 Hz, 1H), 6.82 (d, ArH, *J* = 2.5 Hz, 1H), 6.84 (d, ArH, *J* = 2.5 Hz, 1H), 7.03 (d, ArH, *J* = 2.5 Hz, 1H), 7.06 (d, ArH, *J* = 2.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 63 MHz, 298 K). ^{13}C NMR ($CDCl_3$, 63 MHz, 298 K): δ 10.5, 14.4, 19.7, 20.1, 22.9, 23.0, 23.6, 23.8, 28.8, 29.1, 29.4, 29.7, 29.8, 31.8, 31.9, 32.3, 33.8, 34.1, 37.0, 39.1, 48.1, 68.3, 75.3, 79.6, 83.6, 84.5, 86.7, 119.8, 121.9, 123.9, 124.1, 124.6, 124.9, 125.7, 125.8, 132.3, 132.7, 134.5, 135.2, 135.5, 140.2, 140.9, 143.7, 144.9, 145.6, 153.3, 153.4, 153.6, 153.9. Anal. Calcd. for $C_{59}H_{82}O_4$: C, 82.85; H, 9.66. Found: C, 82.94; H, 9.57.

*Derivative **12b**:* white solid, 0.095 g, 43% yield. Mp: >220 °C dec. ESI(+) MS: *m*/*z* = 953 (MH^+). ^{1}H NMR ($CDCl_3$, 250 MHz, 298 K): δ 0.89 (t, $C\equiv CCH_2(CH_2)_9CH_3$, 3H), 0.92 [s, $C(CH_3)_3$, 9H], 1.03 [s, $C(CH_3)_3$, 18H], 1.24 [s, $C(CH_3)_3$, 9H], 0.94−1.11 (overlapped, $OCH_2CH_2CH_3$, 9H), 1.27 (overlapped, $C\equiv CCH_2(CH_2)_9CH_3$, 18H), 1.64 (m, $CH_2CH_2CH_3$, 2H), 1.91 (m, $CH_2CH_2CH_3$, 2H), 2.18 (m, $CH_2CH_2CH_3$, 2H), 2.34 (t, $C\equiv CCH_2(CH_2)_9CH_3$, *J* = 7.1 Hz, 2H), 2.67 (d, *J* = 12.6 Hz, $ArCH_2Ar$, 1H), 2.98 (d, *J* = 12.5 Hz, $ArCH_2Ar$, 1H), 3.15 (d, *J* = 12.8 Hz, $ArCH_2Ar$, 1H), 3.20 (d, *J* = 12.8 Hz, $ArCH_2Ar$, 1H), 3.64−3.92 (overlapped, $OCH_2CH_2CH_3$, 6H), 3.94 (d, *J* = 12.8 Hz, $ArCH_2Ar$, 1H), 4.21 (d, *J* = 12.8 Hz, $ArCH_2Ar$, 1H), 4.37 (d, *J* = 12.8 Hz, $ArCH_2Ar$, 1H), 4.40 (d, *J* = 12.8 Hz, $ArCH_2Ar$, 1H), 5.55 (s, OH, 1H), 5.59 (s, ArH, 1H), 6.69 (d, ArH, *J* = 2.2 Hz, 1H), 6.77 (d, ArH, *J* = 2.3 Hz, 1H), 6.80 (d, ArH, *J* = 2.3 Hz, 1H), 6.96 (d, ArH, *J* = 2.2 Hz, 1H), 6.99 (d, ArH, *J* = 2.3 Hz, 1H), 7.04 (d, ArH, *J* = 2.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 63 MHz, 298 K): δ 10.3, 10.8, 14.3, 19.3, 19.8, 22.8, 22.9, 23.5, 23.6, 28.8, 28.9, 29.4, 29.7, 29.8, 31.6, 31.7, 32.1, 33.8, 33.9, 34.2, 36.9, 38.9, 48.1, 68.3, 75.2, 79.6, 83.4, 84.5, 86.6, 119.6, 121.9, 123.5, 124.1, 124.6, 124.9, 125.7, 125.8, 132.3, 132.8, 134.6, 135.1, 135.4, 140.1, 140.9, 143.6, 144.8, 145.4, 153.1, 153.2, 153.3, 153.8. Anal. Calcd for $C_{66}H_{96}O_4$: C, 83.15; H, 10.15. Found: C, 83.23; H, 10.07.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra of new compounds. 2D NMR spectra and table of all observed HMBC, HSQC, NOE, and COSY interactions used for assignment of **3c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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