JOC Notes

Diels−Alder Approach to Tetra-ortho-Substituted Biaryls Employing Propargylic Tertiary Alcohols as Dienophiles

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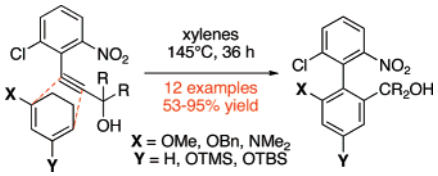
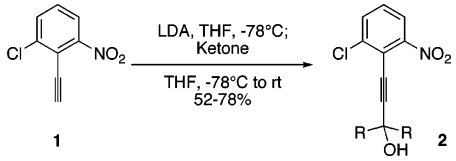


The efficient synthesis of a series of tetra-ortho-substituted biaryls is described utilizing a Diels−Alder reaction between propargylic tertiary alcohols and cyclic oxygenated dienes. The successful resolution of one of the biaryls is achieved through derivatization with menthyl chloroformate followed by crystallization. The menthyl carbamate is cleaved under basic conditions to reveal enantiomerically pure biaryl compounds.

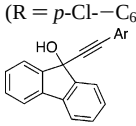
Diels−Alder cycloaddition has been shown to be an effective method for the formation of sterically challenging carbon−carbon bonds.[1] Our laboratory[2] and others[3] have exploited this unique reactivity for the construction of biaryl compounds. This Diels−Alder approach to biaryls (DAB) has allowed us to construct biaryl compounds possessing four different substituents at the four ortho positions[2a,c]—a feat that has not been previously reported. Our previous cases have focused on the cycloaddition of disubstituted alkynes with oxygenated, cyclic, and acyclic dienes to yield (after aromatization) the required tetra-ortho-substituted biaryls. In each case, both substituents on the alkyne were able to activate the dienophile via their resonance-based, electron-withdrawing character. In this Note, we describe for the first time the ability to construct tetra-ortho-substituted biaryl compounds using alkynes possessing just one resonance-based, electron-withdrawing group.

The synthesis of the propargylic tertiary alcohols is shown in Table 1. Starting from the known alkyne **1** (available in one step[2b] from the commercially available 2-chloro-6-nitrobenzaldehyde), deprotonation with our standard conditions (LDA, THF, −78 °C followed by the addition of the electrophile, −78 °C to rt) generated the propargylic alcohols in moderate to good yield (52−78%). Both acyclic and cyclic ketones with either alkyl or aromatic substituents were tolerated in this transformation. It should be noted that attempts at formation of the secondary alcohol derived from trapping the lithiated acetylene with benzaldehyde led to extensive decomposition—possibly due to Oppenhauer-type[4] hydride transfer by the resultant propargylic secondary alkoxide.

TABLE 1. Synthesis of Propargyl Alcohols



1 **2**

entry	ketone	yield
a	acetone	71% (R = Me)
b	3-pentanone	63% (R = Et)
c	cyclobutanone	60% (R = $(CH_2)_3$)
d	cyclopentanone	52% (R = $(CH_3)_4$)
e	cyclohexanone	68% (R = $(CH_2)_5$)
f	benzophenone	77% (R = Ph)
g	4,4′-dimethylbenzophenone	78% (R = *p*-Me-C_6H_4)
h	4,4-dichlorobenzophenone	69% (R = *p*-Cl-−C_6H_4)
i	9-fluorenone	77% 

With the alkynes in hand, we turned our attention to the key Diels−Alder cycloaddition (Table 2). We were gratified to find that treatment of the propargyl alcohols **2** with the commercially

(1) (a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388−401. (b) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369−96.

(2) (a) Ashburn, B. O.; Carter, R. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 6737−41. (b) Naffziger, M. R.; Ashburn, B. O.; Perkins, J. R.; Carter R. G. *J. Org. Chem.* **2007**, *129*, 9109−9116. (c) Ashburn, B. O.; Carter, R. G.; Zakharov, L. N. *J. Am. Chem. Soc.* **2007**, *72*, 9857−9865.

(3) Prior examples of using a Diels−Alder reaction to construct a biaryl: (a) Reed, J. A.; Schilling, C. L.; Tarvin, R. F.; Rettig, T. A.; Stille, J. K. *J. Org. Chem.* **1969**, *34*, 2188−92. (b) McDonald, E.; Suksamrarn, A.; Wylie, R. D. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1893−900. (c) Weinreb, S. M.; Basha, F. Z.; Hibino, S.; Khatri, N. A.; Kim, D.; Pye, W. E.; Wu, T.-T. *J. Am. Chem. Soc.* **1982**, *104*, 536−44. (d) Boger, D. L.; Panek, J. S.; Duff, S. R. *J. Am. Chem. Soc.* **1985**, *107*, 5745−54. (e) Effenberger, F.; Ziegler, T. *Chem. Ber.* **1987**, *120*, 1339−46. (f) Kanakam, C. C.; Mani, N. S.; Ramanathan, H.; Subba Rao, G. S. R. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1907−13. (g) Sain, B.; Sandhu, J. S. *J. Org. Chem.* **1990**, *55*, 2545−46. (h) Bateson, J. H.; Smith, C. F.; Wilkinson, J. B. *J. Chem. Soc., Perkin Trans 1* **1991**, 651−53. (i) Smith, D. M.; Royles, B. J. L. *J. Chem. Soc., Perkin Trans. 1* **1994**, 355−58. (j) D'Auria, M. *Tetrahedron Lett.* **1995**, *36*, 6567−70. (k) Knolker, H.-J.; Baum, E.; Hopfmann, T. *Tetrahedron Lett.* **1995**, *36*, 5339−42. (l) Avenoza, A.; Busto, J. H.; Cativiela, C.; Peregrina, J. M. *Synthesis* **1995**, 671−74. (m) Balázs, L.; Kádas, I.; Tõke, L. *Tetrahedron Lett.* **2000**, *41*, 7583−87. (n) Watson, M. D.; Fechtenkotter, A.; Mullen, K. *Chem. Rev.* **2001**, *101*, 1267−300. (o) Min, S.-H.; Kim, Y.-W.; Choi, S.; Park, K. B.; Cho, C.-G. *Bull. Korean Chem. Soc.* **2002**, *23*, 1021−22. (p) Hilt, G.; Smolko, K. I. *Synthesis* **2002**, 686−92. (q) Hilt, G.; Smolko, K. I.; Lotsch, B. V. *Synlett* **2002**, 1081−84. (r) Moore, J. E.; York, M.; Harrity, J. P. A. *Synlett* **2005**, 860−62. (s) Yamato, T.; Miyamoto, M.; Hironaka, T.; Miura, Y. *Org. Lett.* **2005**, *7*, 3−6. (t) Hilt, G.; Galbiati, F.; Harms, K. *Synthesis* **2006**, 3575−84. (u) Liu, Y.; Lu, K.; Dai, M.; Wang, K.; Wu, W.; Chen, J.; Quan, J.; Yang, Z. *Org. Lett.* **2007**, *9*, 805−08.

(4) (a) Augé, J.; Lubin-Germain, N.; Seghrouchni, L. *Tetrahedron Lett.* **2003**, *44*, 819−21. For reviews on Oppenauer oxidations, see: (b) de Graauw, C. F.; Peters, J. A.; Huskens, B. J. *Synthesis* **1994**, 1007−17. (c) Djerassi, C. *Org. React.* **1951**, *6*, 207−72.

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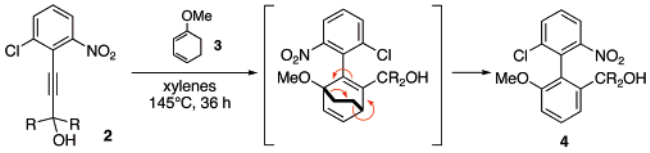
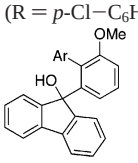
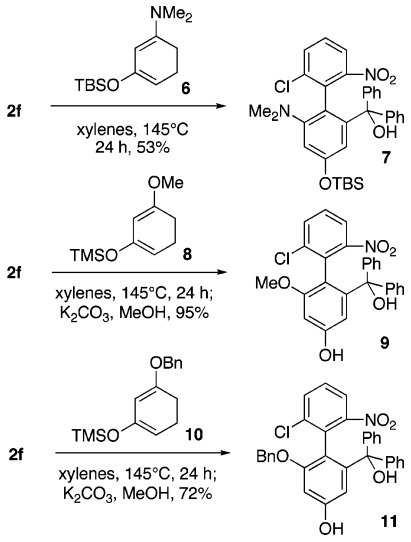
TABLE 2. Diels−Alder Construction of Biaryls



entry	alkyne	yield
a	**2a**	72% (R = Me)
b	**2b**	58% (R = Et)
c	**2c**	67% (R = $(CH_2)_3$)
d	**2d**	55% (R = $(CH_3)_4$)
e	**2e**	62% (R = $(CH_2)_5$)
f	**2f**	80% (R = Ph)
g	**2g**	79% (R = *p*-Me−C_6H_4)
h	**2h**	67% (R = *p*-Cl−C_6H_4)
i	**2i**	68% 

SCHEME 1. Diene Scope in Diels−Alder Construction of Biaryls



available 1-methoxy-1,3-cyclohexadiene (**3**) in xylenes at 145 °C cleanly generated the tetra-ortho-substituted biaryls **4**. The yields for this transformation were generally high (55−80%). Of note is the fact that the significant steric requirement for the construction of the tetra-ortho-substituted biaryl with a tertiary alcohol moiety is nicely addressed through this DAB strategy. The regiochemistry from the Diels−Alder process was confirmed for each product by HMBC analysis. These reactions are believed to proceed through a bicyclic intermediate followed by the extrusion of ethylene to generate the biaryl **4**. If the reaction is conducted initially at a lower temperature (e.g., 100 °C, 25 h), the intermediate bicycle can be observed via NMR analysis of the crude mixture. One possible explanation for the facile nature of these transformations could be internal hydrogen bond activation between the propargylic alcohol and either the nitro or chloro moieties. Support for this working hypothesis can be found in the inability of the TMS silylated alcohol (TMSCl, imidazole, cat. DMAP, CH_2Cl_2, 65%, 88% borsm) version of **2f** to undergo the same cycloaddition (130−150 °C over 43 h).

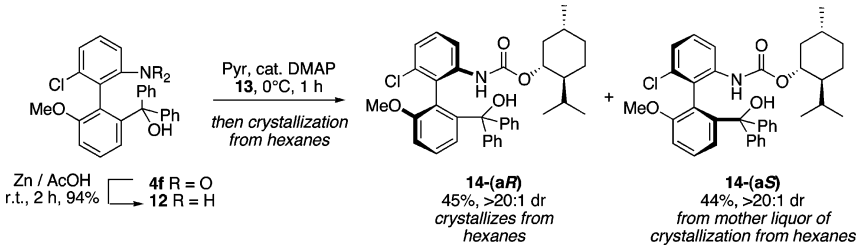
We also explored the degree of diene variation that was tolerated under the reaction process (Scheme 1). We initially screened our standard acyclic dienes[2] (Brassard's diene[5] and commercially available TBS Danishefsky's diene[6]); however, we found that they were not amenable to the cycloaddition process. We have previously observed a similar behavior for our carbonyl-containing alkyne series.[2c] A range of cyclic dienes did successfully undergo the Diels−Alder reaction and gave rise to highly functionalized biaryls. We were pleased to find that an *o*-amino functionality could be incorporated via the previously unknown diene **6** (synthesized from 1,3-cyclohexanedione in three steps) in reasonable yield. Dioxygenated dienes **8**[7] and **10**[2b] also cleanly yielded their requisite biaryl products **9** and **11** in excellent yields (95% and 72%, respectively).

One important attribute of highly substituted biaryls is the restricted rotation around the σ aryl−aryl linkage. Consequently, enantiomerically enriched biaryls have proven useful as chiral ligands in a range of enantioselective pathways.[8] We have developed an efficient protocol to obtain enantiomerically enriched biaryls from our DAB process (Scheme 2). Biaryl **4f** was chosen as a representative example. After reduction of **4f** with zinc in acetic acid (94%), the resultant aniline moiety was treated with commercially available (−)-menthyl chloroformate **13** (Scheme 2). After standard column chromatography, the diastereomeric carbamates were dissolved in hexanes. We were pleased to observe crystallization of a single diastereomer **14-(a*R*)** from the mother liquor in excellent yield and diastereoselectivity (45%, >20:1 dr). Confirmation of the absolute stereochemistry was obtained by X-ray crystallographic analysis of biaryl **14-(a*R*).** Concentration of the mother liquor and a second recrystallization from hexanes revealed that the remaining material consisted of the alternate diastereomer **14-(a*S*)**—again in excellent yield and diastereoselectivity (44%, >20:1 dr).

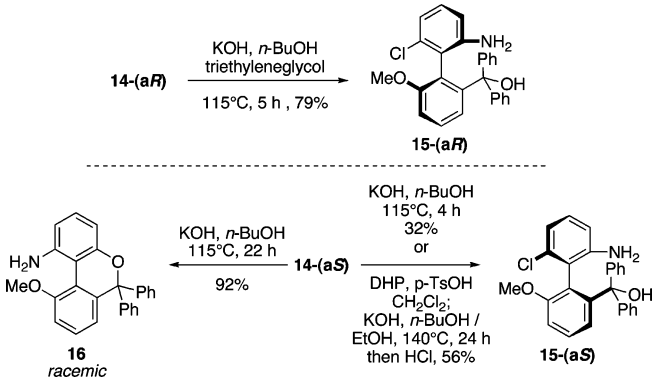
Cleavage of the carbamate was possible under basic conditions (Scheme 3). Treatment of diastereomer **14-(a*R*)** with KOH in hot *n*-butanol/triethyleneglycol provided a 79% yield of the amino alcohol **15-(a*R*)**. Confirmation that no racemization had occurred under the reaction conditions was achieved by reacylation of **15-(a*R*)** with (−)-menthyl chloroformate (**13**) to provide **14-(a*R*)** as a single diastereomer (86%). Attempted cleavage of the diastereomeric carbamate **14-(a*S*)** gave the desired product **15-(a*S*)** in only modest yield (32%). A second product **16** was competitively produced under the reaction conditions (57%). Extended reaction time led to exclusive formation of this dibenzo[*b*,*d*]pyran **16** in 92% yield. This product **16** is presumably formed via nucleophilic aromatic substitution by the tertiary alcohol on the aryl chloride. It is worth noting that this compound is formed as the racemate. The added strain induced by the dibenzopyran ring system presumably lowered the activation energy for racemization of the atropic diastereomers. Fortunately, this side product can be surpressed by protection of the tertiary alcohol as its THP ether

(5) Savard, J.; Brassard, P. *Tetrahedron* **1984**, *40*, 3455−64.
(6) Ireland, R. E.; Aristoff, P. A.; Hoyung, C. F. *J. Org. Chem.* **1979**, *44*, 4318−22.
(7) Freskos, J. N.; Morrow, G. W.; Swenton, J. S. *J. Org. Chem.* **1985**, *50*, 805−10.
(8) (a) Wallace, T. W. *Org. Biomol. Chem.* **2006**, *4*, 3197−210. (b) Shimizu, H.; Nagasaki, I.; Saito, T. *Tetrahedron* **2005**, *61*, 5405−32. (c) McCarthy, M.; Guiry, P. J. *Tetrahedron* **2001**, *57*, 3809−44.

SCHEME 2. Resolution of Atropic Isomers via Derivatization and Crystallizaton



SCHEME 3. Cleavage of the Menthyl Carbamate



followed by saponification and acidic workup [56% yield from **14-(a*S*)**]. Again, conversion back to its menthyl carbamate **14-(a*S*)** confirmed no racemization had occurred under the reaction process (83%, >20:1 dr).

In summary, the efficient synthesis of tetra-ortho-substituted biaryl compounds has been reported utilizing propargyl tertiary alcohols as dienophiles. A range of substituents is tolerated for the tertiary alcohols; however, cyclic dienes are required to facilitate effective cycloaddition. Facile resolution of the Diels−Alder adduct **12** provided a rapid synthesis of enantiomerically enriched biaryls **14** and **15**. Continued exploration into the scope of the DAB strategy will be reported in due course.

Experimental Section

Acetylene 2f. To a stirred solution of **1** (2.05 g, 11.3 mmol) and THF (56.5 mL) was added LDA (11.3 mL, 11.3 mmol, 1.0 M in THF/hexanes) at −78 °C. After 10 min, the solution was transferred via cannulation into a stirred solution of benzophenone (3.09 g, 16.9 mmol) in THF (16.9 mL) at −78 °C. After 30 min, the dark brown solution was allowed to warm to rt. After an additional 1 h, the mixture was quenched with sat. aq NH_4Cl (100 mL), diluted with EtOAc (100 mL), and washed with H_2O (100 mL) and sat. aq NaCl (100 mL). The dried extract ($MgSO_4$) was concentrated in vacuo and purified by chromatography over silica gel, eluting with 25−75% CH_2Cl_2/hexanes to give **2f** (3.16 g, 8.69 mmol, 77%) as a white crystalline solid. Mp 134−35 °C; IR (neat) 3524, 3077, 2220, 1531 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, J = 8.2, 1.4 Hz, 1H), 7.75−7.77 (m, 4H), 7.73 (dd, J = 8.2, 1.0 Hz, 1H), 7.39−7.44 (m, 5H), 7.29−7.35 (m, 2H), 3.11 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.0, 144.1, 139.1, 133.8, 128.9, 128.5, 128.0, 126.2, 122.9, 117.8, 105.7, 79.3, 75.3; HRMS (CI^+) calcd for $C_{21}H_{15}NO_3Cl$ (M + H) 364.0740, found 364.0748.

Biaryl 4f. To a pressure vessel containing **2f** (3.16 g, 8.69 mmol) and xylenes (17.4 mL) was added diene **3** (2.87 g, 3.01 mL, 26.1 mmol) at rt. The mixture was heated at 145 °C for 36 h. The crude material was purified by chromatography over silica gel, eluting with 10−40% CH_2Cl_2/hexanes to give **4f** (2.78 g, 6.23 mmol, 72%) as a yellow crystalline solid. Mp 152−53 °C; IR (neat) 3552, 3053, 1528, 1355 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, J = 8.2, 1.2 Hz, 1H), 7.44 (dd, J = 8.0, 1.2 Hz, 1H), 7.31−7.35 (m, 5H), 7.23−7.29 (m, 3H), 7.13−7.18 (m, 4H), 6.99 (d, J = 7.9 Hz, 1H), 6.63 (dd, J = 8.0, 0.6 Hz, 1H), 3.74 (s, 3H), 2.65 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 150.6, 147.0, 144.4, 144.3, 136.9, 133.8, 133.0, 128.3, 128.1, 128.0, 127.8, 127.7, 127.6, 127.4, 127.0, 124.4, 123.4, 122.0, 109.9, 82.9, 56.3; HRMS (CI^+) calcd for $C_{26}H_{20}NO_4Cl$ (M + H) 445.1081, found 445.1078.

Anilino Alcohol 12. To a stirred solution of **4f** (2.78 g, 6.23 mmol) and glacial acetic acid (62.4 mL) was added Zn dust (2.04 g, 31.2 mmol) at rt. After 2 h, the mixture was quenched with sat. aq $NaHCO_3$ (250 mL), diluted with EtOAc (200 mL), and washed with $NaHCO_3$ (200 mL), H_2O (200 mL), and sat. aq NaCl (200 mL). The dried extract ($MgSO_4$) was concentrated in vacuo and purified by chromatography over silica gel, eluting with 50−80% CH_2Cl_2/hexanes to give **12** (2.45 g, 5.86 mmol, 94%) as a white crystalline solid. Mp 110−11 °C; IR (neat) 3528, 3333, 2825, 1623, 1572 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.16−7.31 (m, 11H), 6.99 (t, J = 8.0 Hz, 1H), 6.98 (dd, J = 8.3, 1.0 Hz, 1H), 6.73 (dd, J = 7.9, 1.0 Hz, 1H), 6.66 (dd, J = 8.0, 1.0 Hz, 1H), 6.54 (dd, J = 8.0, 1.1 Hz, 1H), 4.59 (br s, 1H), 3.73 (s, 3H), 3.17 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 147.1, 146.9, 146.3, 145.1, 135.8, 129.2, 128.7, 127.83, 127.81, 127.6, 127.5, 126.9, 126.8, 124.1, 123.3, 123.1, 120.0, 114.2, 110.6, 82.9, 56.4; HRMS (CI^+) calcd for $C_{26}H_{22}NO_2Cl$ (M + H) 415.1339, found 415.1359.

Carbamates 14-(a*R*) and 14-(a*S*). To a stirred solution of **12** (1.54 g, 3.71 mmol), DMAP (45.3 mg, 0.371 mmol), and pyridine (18.6 mL) was slowly added (−)-menthyl chloroformate (4.06 g, 3.94 mL, 18.5 mmol) at 0 °C. After 1 h, the mixture was quenched with NH_4Cl (60 mL), diluted with Et_2O (80 mL), and washed with NH_4Cl (60 mL), H_2O (2 × 60 mL), and sat. aq NaCl (60 mL). The dried extract ($MgSO_4$) was purified by chromatography over silica gel, eluting with 50−75% CH_2Cl_2/hexanes. The mixture of diastereomers was crystallized from hot hexanes to give **14-(a*R*)** (996 mg, 1.67 mmol, 45%) as white crystals, and after recrystallization of the mother liquor, **14-(a*S*)** (975 mg, 1.63 mmol, 44%) was obtained. **14-(a*R*)** isomer: Mp 162−163 °C; $[\alpha]^{23}_D$ −77.6 (*c* 2.08, $CHCl_3$); IR (neat) 3569, 3414, 2954, 1727, 1575 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 7.7 Hz, 1H), 7.35 (t, J = 8.1 Hz, 1H), 7.18−7.33 (m, 11H), 7.08 (d, J = 7.9 Hz, 1H), 6.99 (d,

J = 7.7 Hz, 1H), 6.66 (d, J = 7.9 Hz, 1H), 5.79 (s, 1H), 4.54 (td, J = 10.9, 4.4 Hz, 1H), 3.67 (s, 3H), 2.70 (s, 1H), 2.03 (d, J = 11.7 Hz, 1H), 1.65−1.72 (m, 3H), 1.27−1.33 (m, 1H), 0.93−1.13 (m, 3H), 0.97 (d, J = 6.5 Hz, 3H), 0.85 (d, J = 7.0 Hz, 3H), 0.74 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 153.1, 146.8, 146.1, 145.9, 138.0, 134.8, 128.9, 128.1, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 126.9, 123.9, 123.5, 122.6, 117.9, 110.4, 83.5, 74.8, 56.2, 47.3, 41.5, 34.3, 31.4, 26.7, 24.1, 22.1, 20.5, 17.40; HRMS (EI$^+$) calcd for $C_{37}H_{40}NO_4Cl$ (M + H) 597.2646, found 597.2642. **14-(a*S*)** isomer: Mp 88−90 °C; $[\alpha]^{23}_D$ +18.8 (*c* 2.14, $CHCl_3$); IR (neat) 3556, 3415, 2955, 1727, 1575 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (br s, 1H), 7.36 (t, J = 8.1 Hz, 1H), 7.19−7.34 (m, 11H), 7.05 (dd, J = 7.9, 0.7 Hz, 1H), 7.01 (d, J = 8.1 Hz, 1H), 6.68 (d, J = 8.0 Hz, 1H), 6.01 (s, 1H), 4.61 (td, J = 10.9, 4.3 Hz, 1H), 3.70 (s, 3H), 2.73 (s, 1H), 1.97−2.06 (m, 3H), 1.73 (d, J = 11.7 Hz, 2H), 1.49−1.54 (m, 1H), 1.33−1.41 (m, 1H), 1.01 (d, J = 7.0 Hz, 3H), 0.94 (d, J = 6.4 Hz, 3H), 0.88−1.16 (m, 2H), 0.85 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 153.2, 146.8, 146.4, 145.7, 138.3, 134.8, 128.9, 128.8, 128.1, 127.9, 127.8, 127.7, 127.4, 127.3, 126.8, 123.9, 123.4, 122.8, 117.7, 110.6, 83.5, 75.1, 56.3, 47.1, 41.1, 34.3, 31.4, 25.9, 23.2, 22.1, 21.1, 16.3; HRMS (EI$^+$) calcd for $C_{37}H_{40}NO_4Cl$ (M + H) 597.2646, found 597.2651.

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Supporting Information Available: All remaining experimental procedures are provided, including ^{1}H and ^{13}C spectra, of all new compounds, as well as crystallographic data with details of data collections and refinements for crystal structures of the compounds **14-(a*R*)** and **15-(a*R*)** and the corresponding CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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