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Applications of Enantioselective Carbolithiation of Ortho-Substituted β-Methylstyrenes

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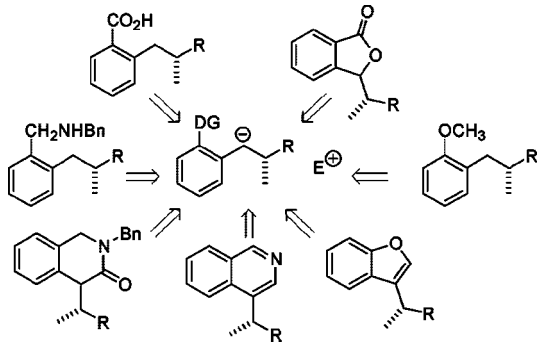
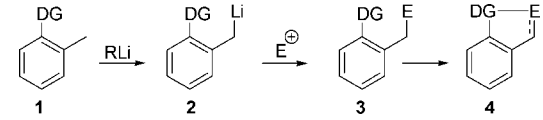


The enantioselective carbolithiation of ortho-substituted (*E*)-β-methylstyrenes provides access to chiral lithiated intermediates with broad synthetic potential. Specifically, β-methylstyrenes with *o*-aminomethyl, ether, and oxazoline groups have been employed in the synthesis of chiral aromatics and heteroaromatics such as isoquinolines, isoquinolinones, benzofurans, and isobenzofuranones.

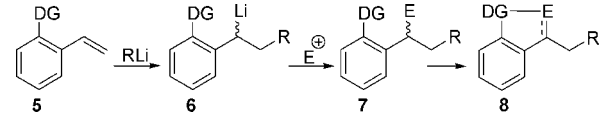
The use of organolithium reagents as strong bases for the generation of benzylic lithium species from ortho-substituted toluenes (2-methylbenzenes) is a versatile synthetic strategy. For example, directed alkyl deprotonation of **1** (DG = directing group) provides the lateral lithiated intermediate **2** which following in situ reaction with suitable electrophiles can generate the substituted aromatics **3**. If a further reaction between the ortho-substituent and reacted electrophile can occur (in situ or in subsequent synthetic steps), this provides an efficient route to the corresponding benzo-fused ring systems **4** (Scheme 1).[1]

Numerous examples of ortho substituents which have been applied to this methodology include substituted anilines,[2] amines,[3] ethers,[4] oxazolines,[5] amides,[6] ureas,[7] carbamates,[8] esters,[9] carboxylates,[10] sulfonamides,[11] and phosphorodiamidate groups.[12] A less commonly utilized approach to the generation of ortho-substituted benzylic lithiated species is the intermolecular carbolithiation of styrenes **5** to provide the lithiated intermediates **6**, which can be transformed into heterocycles **8**following reaction with electrophiles (Scheme 2).[13] This approach offers improved atom efficiency over utilizing the alkyllithium as a base as the product includes an additional functionality from the C−C bond-forming carbolithiation step.

SCHEME 1. Benzylic Lithiums via Lateral Deprotonation



SCHEME 2. Benzylic Lithiums via Carbolithiation of Ortho-Substituted Styrenes



Our current efforts are directed toward the carbolithiation of ortho-substituted β-methylstyrene substrates **9** which offers the opportunity to introduce asymmetry into the C−C bond formation.[14]The goal is to exploit the carbolithiation reaction to provide intermediates **10** containing one configurationally stable chiral center and to utilize in situ reaction with electrophiles at the C−Li center to allow access to a collection of products such as **11** and **12** (Scheme 3).[15] As the chiral center generated during C−C bond formation in the first carbolithiation

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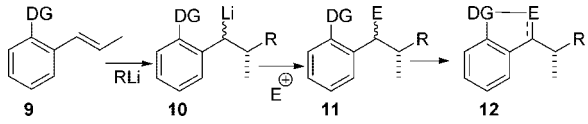
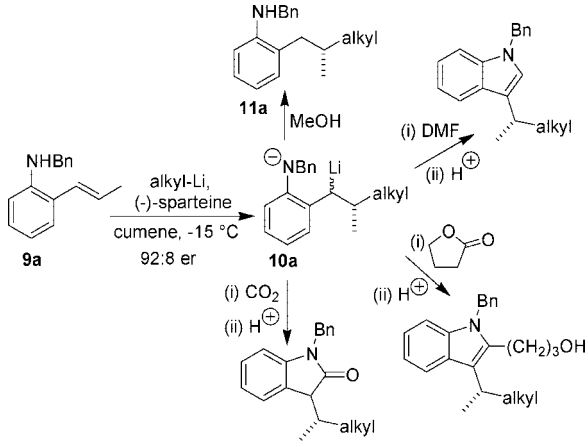
SCHEME 3. Benzylic Lithiums via Enantioselective Carbolithiation of Ortho-Substituted (*E*)-β-Methylstyrenes



step is carried through the electrophile reaction sequence to the final products, selectivity is solely dependent upon achieving an enantioselective alkyllithium addition.

Since a considerable body of literature exists on the synthetic exploitation of benzylic lithiated intermediates such as **2**, our work has focused on the generation of equivalent chiral analogues **10** which could participate in a similar spectrum of transformations but form chiral products. We have recently reported the synthesis of chiral intermediates of this type exploiting a (−)-sparteine-mediated carbolithiation of 2-propenylphenylamine **9a** (DG = NHBn, Scheme 4).[16]

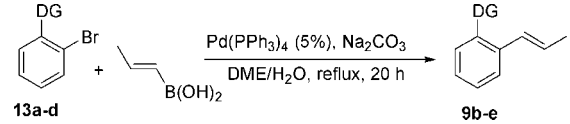
SCHEME 4. Applications of Enantioselective Carbolithiation of 9a



In this case, carbolithiation enables the efficient generation of the chiral lithiated species which following reaction at the C−Li center with varying electrophiles provides access to 2-alkylanilines, 3- and 2,3-substituted indoles, and 3-substituted indol-2-ones with a common er of 92:8 (±1). Herein, we now report the application of this concept to three further important heterocyclic classes, namely the isoquinolines, benzofurans, and isobenzofuranones as representative examples.

The corresponding prochiral β-methylstyrene substrates containing *o*-aminomethyl **9b**,**c**, ether **9d**,**e**, and oxazoline **9f** substituents were prepared by cross-coupling of (*E*)-1-propen-1-ylboronic acid with the corresponding aryl bromides **13a**−**e** (Table 1). Substrates were examined for their ability to undergo (−)-sparteine-mediated asymmetric carbolithiations with *n*-BuLi in coordinating (diethyl ether) and noncoordinating (cumene) solvent conditions.

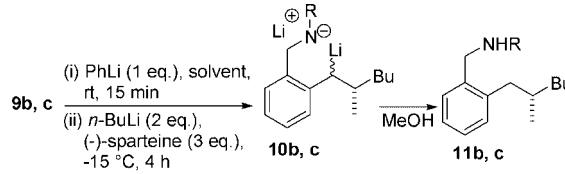
TABLE 1. Synthesis of (*E*)-9b–f



entry	sm	DG	product	yield, %
1	**13a**	CH_2NHBoc	**9b**	84
2	**13b**	CH_2NHBn	**9c**	42
3	**13c**	OMOM	**9d**	95
4	**13d**	OMe	**9e**	83
5	**13e**		**9f**	90

Encouragingly, the enantioselectivity for carbolithiation of **9c** in ether was high with a recorded er of 88:12 and isolated yield of 75% (entry 4). In comparison the *N*-Boc-substituted analogue **9b** has an inferior er of 81:19 and a poorer isolated yield (entry 2). Selectivity was not particularly solvent sensitive as only marginally differing results were obtained in cumene and diethyl ether (Table 2, compare entries 3 and 4). The better selectivity obtained for the *N*-Bn-substituted **9c** over **9b** is consistent with our previously reported aniline analogue **9a**.[16b]

TABLE 2. Enantioselective Carbolithiation of 9b and 9c



entry	sm	solvent	R	product	yield, %	er (*S*:*R*)
1	**9b**	cumene	Boc	**11b**	15[a]	78:22[b]
2	**9b**	Et_2O	Boc	**11b**	46[c]	81:19[b]
3	**9c**	cumene	Bn	**11c**	60	90:10[d]
4	**9c**	Et_2O[e]	Bn	**11c**	75	88:12[d]

[a] Starting material recovered in 82% yield. [b] Determined by chiral HPLC (OD column) and compared to the racemic product generated with TMEDA as additive. [c] Starting material recovered in 15% yield. [d] Determined by conversion to 3-methylheptanoic acid phenylamide and chiral HPLC separation (Supporting Information). [e] Reaction time 2 h.

For the *o*-methoxy and *o*-methoxymethoxy (MOM) examples **9d** and **9e**, no deprotonation of the heteroatom is necessary, and consequently, the reaction sequence involved addition of the substrate to a premixed solution of *n*-BuLi/(−)-sparteine (Table 3). Once again, both cumene and diethyl ether were investigated as solvents, and in this instance, −40 °C was determined as the optimal reaction temperature. Pleasingly, compounds **11d** and **11e** were obtained with high er from the reaction in both solvents. It is interesting to note that the methoxy-substituted **9e** gave a better selectivity (94:6 er) and yield (60%) than that obtained from the MOM-substituted **9d**, which would be considered a stronger coordinating group (Table 3, entries 1 and 3).

Finally, the methodology was extended to the carbolithiation of *o*-oxazoline derivative **9f** using diethyl ether as solvent at −78 °C (Scheme 5). Using 3 equiv of a premixed solution of

(14) For enantioselective carbolithiation of β-methylstyrene, see: (a) Norsikian, S.; Marek, I.; Normant, J. F. *Tetrahedron Lett.* **1997**, *38*, 7523. (b) Norsikian, S.; Marek, I.; Klein, S.; Poisson, J. F.; Normant, J. F. *Chem. Eur. J* **1999**, *5*, 2055.

(15) Carbolithiation results in the formation of a chiral benzylic lithium species **6**; however, this configurationally unstable chiral center is lost if converted to aromatic heterocycle **8**. For examples of resolution of configurationally unstable benzylic lithium centers generated by lateral deprotonation, see: (a) Beak, P.; Anderson, D. R.; Curtis, M. D.; Laumer, J. M.; Pippel, D. J.; Weisenburger, G. A. *Acc. Chem. Res.* **2000**, *33*, 715. For examples by styrene carbolithiation, see: (b) Wei, X.; Taylor, R. J. K. *Tetrahedron: Asymmetry* **1997**, *8*, 665.

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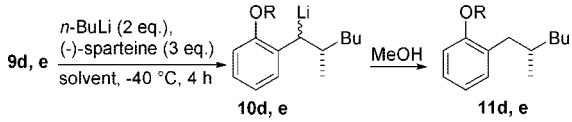
TABLE 3. Enantioselective Carbolithiation of 9d and 9e

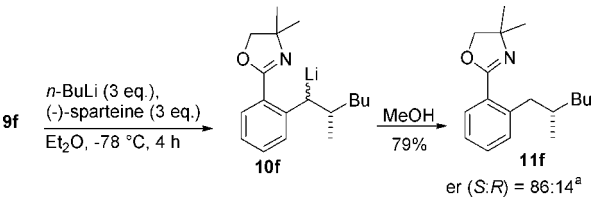


entry	sm	solvent	R	product	yield, %	er[a] (*S*:*R*)
1	**9d**	cumene	MOM	**11d**	42	89:11
2	**9d**	Et_2O	MOM	**11d**	39[b]	89:11
3	**9e**	cumene	Me	**11e**	60	94:6
4	**9e**	Et_2O	Me	**11e**	61[c]	93:7

[a] Determined by conversion to the benzyl-substituted derivative and chiral HPLC (OD column) separation (Supporting Information). [b] Starting material recovered in 50% yield. [c] Starting material recovered in 36% yield.

n-BuLi/(−)-sparteine to ensure a satisfactory conversion, compound **11f** was isolated in 79% yield and with an er of 86:14. The oxazoline moiety, which is generally considered to be the most powerful directing group (for *o*-aryl lithiation) of those tested, appears to increase the carbolithiation reactivity of the substrate without a substantial effect on the selectivity.

SCHEME 5. Enantioselective Carbolithiation of 9f[a]



[a] Determined by chiral HPLC (IA column).

To demonstrate the potential for application of the chiral intermediates **10b**, **10c**, **10e**, and **10f** to fused ring synthesis by electrophile reaction and intramolecular cyclization a number of representative examples have been carried out. Treatment of intermediate **10b** (generated in ether) with DMF as electrophile resulted, following acidification, in the formation of the dihydroisoquinoline **14**. Subsequent Boc deprotection with trifluoroacetic acid (TFA) and reaction with KOAc/iodine gave the aromatic isoquinoline **15** in a 30% overall yield and an er of 81:19, identical to that of **11b** (Scheme 6, A). Treatment of *N*-benzyl lithiated intermediate **10c** (reaction in ether) with CO_2 provides carboxylic acid **16**, which following intramolecular amide coupling with 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide (EDCI) generated the C-3-substituted isoquinolinone **17** as a mixture of diastereoisomers in a 45% overall yield and 88:12 er (Scheme 6, B). In addition, the carbolithiation was tolerant of an alternative alkyllithium as utilizing *n*-HexLi (under identical reaction conditions) provided the chiral lithiated intermediate **10g**, which when applied to the electrophile reaction sequence gave **17b** in 45% yield and an er of 91:9 (Scheme 6B). Treatment of an ethereal solution of **10e** with DMF resulted, following acidification, in the formation of the aldehyde 2-(2-methoxyphenyl)-3-methylheptanal **18a** as a mixture of diastereoisomers (Scheme 6C). Subsequent one-pot demethylation, cyclization, and dehydration to the benzofuran **19a** was achieved by reaction with chlorotrimethylsilane and sodium iodide in acetonitrile at reflux.[17] Separation of the benzofuran enantiomers by chiral HPLC was not achieved, but analysis of **18a** provided the expected er of 93:7. The reaction

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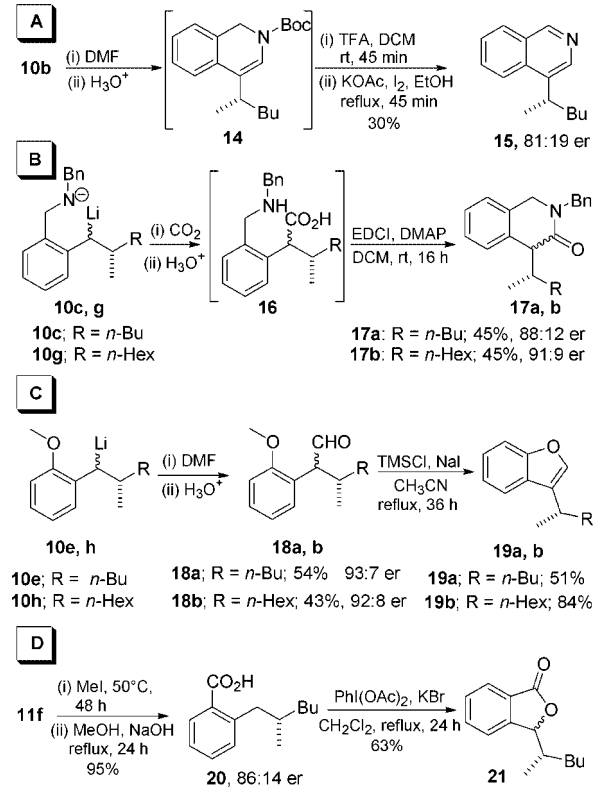
SCHEME 6. Synthesis of Chiral Isoquinolines, Isoquinolinones, Benzofurans, and Isobenzofuranones



sequence was also tolerant to carbolithiation with *n*-HexLi providing the benzofuran **19b** in comparable selectivity. Finally, a representative application of the oxazoline derivative **11f** to heterocyclic synthesis was achieved by deprotection via methyl iodide alkylation and subsequent hydrolysis to afford the benzoic acid **20** (Scheme 6D).[18] Subsequent direct γ-lactone formation with $PhI(OAc)_2$/KBr yielded the isobenzofuranone **21** in 63% yield.[19]

In conclusion, we have shown that an enantioselective carbolithiation of ortho-substituted β-methylstyrenes provides chiral lithiated intermediates of broad synthetic potential which can be applied to the generation of chiral aromatics and heterocycles. Further synthetic applications are currently under investigation and will be reported in due course.

Experimental Section

Representative Carbolithiation Procedure. 1-Methoxy-2-(2-methylhexyl)benzene (11e). A solution of (−)-sparteine (0.47 mL, 2.06 mmol) and *n*-BuLi (0.64 mL, 1.35 mmol) in diethyl ether (2 mL) was cooled to −40 °C. A solution of **9e** (100 mg, 0.68 mmol) in diethyl ether (2 mL) was added dropwise and the reaction mixture stirred at −40 °C for 4 h. The reaction was quenched by the addition of methanol (0.82 mL, 20.28 mmol) and warmed to room temperature, where it was stirred for 10 min. The mixture was diluted with diethyl ether (20 mL), washed with brine (20 mL), dried over sodium sulfate, and concentrated to dryness. The crude product was purified by column chromatography (eluent: 99:1, cyclohexane/ethyl acetate) to afford the product as a colorless oil (127 mg, 61%) (starting material was also recovered in 36% yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.15 (m, 1H), 7.08 (dd, 1H, J =

(18) Meyers, A. I.; Gabel, R.; Mihelich, E. D. *J. Org. Chem.* **1978**, *43*, 1372.
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1.7/ 7.4 Hz), 6.85 (m, 2H), 3.78 (s, 3H), 2.65 (dd, 1H, J = 5.9, 13.2 Hz), 2.34 (dd, 1H, J = 8.3, 13.2 Hz), 1.74 (m, 1H), 1.30 (m, 5H), 1.15 (m, 1H), 0.88 (t, 3H, J = 6.9 Hz), 0.82 (d, 3H, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.0, 131.1, 130.5, 127.0, 120.3, 110.5, 55.4, 38.0, 37.0, 33.6, 29.6, 23.2, 19.8, 14.4; IR (neat) 3021, 2926, 2856, 1600, 1587 cm^{-1}; EI-MS m/z 206.4 $[M]^+$. Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.55; H, 10.78.

Representative Heterocycle Synthesis. 2-(2-Methoxyphenyl)-3-methylheptanal (18a). A solution of (−)-sparteine (0.7 mL, 3.04 mmol) and *n*-BuLi (1.11 mL, 2.03 mmol) in diethyl ether was cooled to −40 °C. A solution of **9e** (150 mg, 1.01 mmol) in diethyl ether (2 mL) was added dropwise and the mixture stirred at −40 °C for 4 h. The reaction mixture was cooled to −78 °C, DMF (0.8 mL) added, and stirring continued at −78 °C for a further 1 h. Aqueous HCl (3 M, 20 mL) was added, the reaction mixture was warmed to room temperature and extracted with diethyl ether (2 × 50 mL), and the combined organic layers were washed with brine (40 mL), dried over sodium sulfate, filtered, and concentrated to dryness. Silica gel chromatography (eluent: 98:2, cyclohexane/ethyl acetate) gave the purified product as a colorless oil (128 mg, 54%) (product analyzed as an equal mixture of diastereoisomers): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.73 (d, 0.5H, J = 2.3 Hz), 9.71 (d, 0.5H, J = 2.7 Hz), 7.26 (m, 1H), 7.09 (m, 1H), 6.93 (m, 2H), 3.81 (s, 1.5H), 3.80 (s, 1.5H), 3.71 (m, 1H), 2.27 (m, 1H), 1.48 (m, 0.5H), 1.24 (m, 3.5H), 1.02 (d, 2H, J = 6.6 Hz), 0.96 (m, 1H), 0.90 (t, 2H, J = 7.0 Hz), 0.80 (t, 2H, J = 7.0 Hz), 0.72 (d, 1H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 202.2, 202.1, 158.0, 157.9, 131.0, 130.5, 128.8, 128.7, 124.9, 124.7, 121.0, 120.9, 111.2, 111.2, 59.1, 58.8, 55.7, 55.6, 35.2, 33.4, 32.8, 32.8, 29.5, 28.9, 23.1, 22.9, 18.1, 16.9, 14.3, 14.2; IR (neat) 3072, 2954, 2859, 1729, 1598 cm^{-1}; ES-MS m/z 235.2 $[M + H]^+$. HRMS $[M + H]^+$ 235.1709, $C_{15}H_{23}O_2$ requires 235.1698. Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.77; H, 9.37.

3-(1-Methylpentyl)benzofuran (19a). A solution of **18a** (50 mg, 0.21 mmol), chlorotrimethylsilane (0.1 mL, 0.8 mmol), and sodium iodide (96 mg, 0.64 mmol) in acetonitrile (5 mL) was heated at reflux for 36 h. The reaction mixture was cooled to room temperature, water (40 mL) was added, and the mixture was extracted with diethyl ether (3 × 20 mL). The combined organic extracts were washed successively with saturated sodium thiosulfate (40 mL) and brine (40 mL), dried over sodium sulfate, filtered and concentrated to dryness. Silica gel chromatography (eluent: 98:2, cyclohexane/ethyl acetate) gave the product as colorless oil (22 mg, 51%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.59 (d, 1H, J = 7.4 Hz), 7.46 (d, 1H, J = 8.2 Hz), 7.24 (m, 3H), 2.92 (m, 1H), 1.78 (m, 1H), 1.62 (m, 1H), 1.35 (d, 3H, J = 11.6 Hz), 1.31 (m, 4H), 0.88 (t, 3H, J = 6.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 155.8, 140.5, 127.9, 126.3, 124.1, 122.2, 120.4, 111.7, 36.6, 30.1, 29.9, 23.0, 20.8, 14.2. IR (neat): 3053, 2960, 2929, 2860, 1454 cm^{-1}. EI-MS: m/z 202.5 $[M]^+$. ES-MS: m/z 405.3 $[2M+H]^+$. HRMS $[2M+H]^+$: 405.2794, $C_{28}H_{37}O_2$ requires 405.2787. $[\alpha]_D$ = −2.0 (c = 0.1, CH_2Cl_2, 20 °C). Chiral HPLC enantiomer separation was not achieved er assigned to be 93:7 by inference from **11e**.

3-(1-Methylpentyl)-3*H*-isobenzofuran-1-one (21). Powdered KBr (43.0 mg, 0.36 mmol, 1.0 equiv) was added to a solution of **20** (80.0 mg, 0.36 mmol) in CH_2Cl_2 (2 mL). $PhI(OAc)_2$ (140 mg, 0.43 mmol) in CH_2Cl_2 (1.5 mL) was added, and the suspension was stirred vigorously under reflux for 24 h. The mixture was cooled to room temperature, satd $NaHCO_3$ solution (4 mL) added, and stirring continued for 5 min. The aqueous layer was extracted with CH_2Cl_2 (2 × 4 mL), and the organic phases were dried over Na_2SO_4 and concentrated to dryness. Purification by chromatography through a short pad of silica gel (prepared with eluent containing 4% NEt_3) eluting with pentane/diethyl ether (70:30) gave the product as colorless oil (51 mg, 63%) (product analyzed as 60:40 mixture of diastereoisomers): ^{1}H NMR ($CDCl_3$, 500 MHz) (60:40 mixture of two diastereomers, signals of the minor isomer are marked with *, signals for both isomers with **) δ 7.94−7.90 (m, 1H)**, 7.71−7.65 (m, 1H)**, 7.57−7.51 (m, 1H)**, 7.46 (br. dd, 0.6H, J = 7.7, 0.8 Hz), 7.43 (br. dd, 0.4H, J = 0.8 Hz)*, 5.51 (d, 0.4H, J' = 2.7 Hz)*, 5.44 (d, 0.6H, J' = 3.8 Hz), 2.22−2.08 (m, 1H)**, 1.72−1.62 (m, 0.4H)*, 1.48−1.16 (m, 5.6H)**, 1.01 (d, 1.8H, J = 6.8 Hz), 0.94 (t, 1.2H, J = 7.1 Hz)*, 0.87 (t, 1.8H, J = 7.1 Hz), 0.68 (d, 1.2H, J = 7.1 Hz)*; ^{13}C NMR ($CDCl_3$, 125 MHz) (peaks of the minor isomer are marked with *) δ 170.9*, 170.7, 149.3*, 148.6, 133.8*, 133.7, 129.0, 128.9*, 127.0, 126.7*, 125.7, 125.6*, 122.2, 121.8*, 85.4, 84.3*, 37.1*, 37.0, 33.1*, 30.1, 29.4*, 29.3, 22.8*, 22.6, 15.3, 14.0*, 13.9, 12.6*; IR (neat) 843, 1072, 1121, 1251, 1404, 1442, 1493, 1591, 2899, 2956, 3019, 3054 cm^{-1}; HRMS $[M - H]^+$ 217.1233, $C_{14}H_{17}O_2$ requires 217.1229.

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Supporting Information Available: Experimental procedures, characterization data, absolute configuration determinations, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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