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Asymmetric synthesis of (*S*)-(−)-tetrahydropalmatine and (*S*)-(−)-canadine via a sulfinyl-directed Pictet–Spengler cyclization

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ABSTRACT

(*S*)-(−)-Tetrahydropalmatine **2** and (*S*)-(−)-canadine **4** were synthesized in three steps from (*S*)-**6**, in 33% and 34% overall yield, respectively. Thus, condensation of the (*S*)-(*E*)-sulfinylimines **10** and **11** with the carbanion derived from (*S*)-**6** gave the tetrahydroisoquinolines **12** and **13**, respectively, which upon TFA induced N-desulfinylation, and subsequent microwave assisted Pictet–Spengler cyclization effected both cyclization and C-desulfinylation producing (*S*)-(−)-tetrahydropalmatine **2** and (*S*)-(−)-canadine **4** in optically pure form.

1. Introduction

Protoberberines represent a large group of isoquinoline alkaloids occurring in at least eight families of the plant kingdom.[1] These alkaloids possess potent pharmacological properties including antimicrobial, antitumor, antileukemic, and antiinflammatory activities.[2] The tetrahydroprotoberberines **1** are a subclass of protoberberines that possess a unique pharmacological profile as both dopamine D2 receptor antagonists and dopamine D1 receptor agonists.[3] Various alkoxy (methoxy, methylenedioxy) or hydroxy substitution patterns are found in the A- and D-rings, methyl or hydroxyl groups are sometimes present at C-13, and a stereogenic center is found at C-14.[4] (*S*)-(−)-Tetrahydropalmatine **2** and (*S*)-(−)-stepholidine **3**, typical members of the tetrahydroprotoberberine family, were shown to have potential clinical use for the treatment of pain as well as for reducing the addictive potential of drugs of abuse[3] (Fig. 1).

Among the various strategies developed for the asymmetric synthesis of tetrahydroprotoberberines, the Pictet–Spengler[5] and the Bischler–Napieralski cyclization/reduction,[5a,6] are two classical methods, which have been most often used for the construction of the tetrahydroisoquinoline nucleus. A complication of these procedures is the control of the regiochemistry in the closure of ring C when activating substituents are present in the D ring. It is well known, that intramolecular Mannich reactions performed with 3′,4′-dioxygenated 1-benzyltetrahydroisoquinolines yield predominantly or exclusively the 10,11-disubstituted tetrahydroprotoberberines rather than the 9,10-disubstitution products, which structures are found in the majority of the naturally occurring alkaloids. Thus, these methods cannot be used to generate the 9,10-disubstitution pattern found in (*S*)-(−)-tetrahydropalmatine **2** and (*S*)-(−)-canadine **4**. Several approaches have been devised to overcome this problem, one of which involves the use of a bromine atom to prevent cyclization at the undesired site. This procedure, though successful, necessarily adds two steps to the synthetic sequence.[7] Another solution to this problem has been to use a trimethylsilyl moiety as an *ipso* directing group[8] to induce formation of the 9,10-disubstituted product in a Pictet–Spengler cyclization. This strategy has been employed by Schore et al.[9] to synthesize various tetrahydroprotoberberines.

Very recently, we reported the synthesis of (*S*)-(−)xylopinine **5**, a tetrahydroprotoberberine alkaloid isolated from *Xylopia discreta* via a synthetic strategy based on the condensation of the carbanion derived from 2-*p*-tolylsulfinyl-4,5-dimethoxytoluene with the substituted *N*-*p*-tolylsulfinylaldimine (*S*)-**10**, N-desulfinylation of the resulting mixture of products, and subsequent

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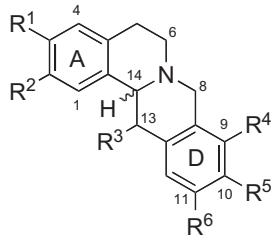
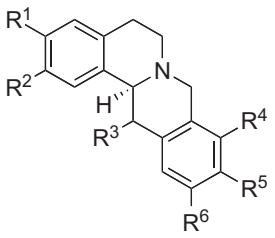


1

R^1 = OH, OMe; R^2 = OMe or $R^1 + R^2 = OCH_2O$
R^3 = H, OH, Me
R^4 = H, OH, OMe; R^5 = OMe or $R^4 + R^5 = OCH_2O$
R^6 = H, OH, OMe



$R^1 = R^2 = R^4 = R^5$ = OMe;
$R^3 = R^6$ = H, (*S*)-(-)-tetrahydropalmatine (**2**)

$R^1 = R^5$ = OH; $R^2 = R^4$ = OMe;
$R^3 = R^6$ = H, (*S*)-(-)-stepholidine (**3**)

$R^1 + R^2 = OCH_2O$; $R^4 = R^5$ = OMe;
$R^3 = R^6$ = H, (*S*)-(-)-canadine (**4**)

$R^1 = R^2 = R^5 = R^6$ = OMe;
$R^3 = R^4$ = H, (*S*)-(-)-xylopinine (**5**)

Fig. 1. Natural tetrahydroprotoberberines.

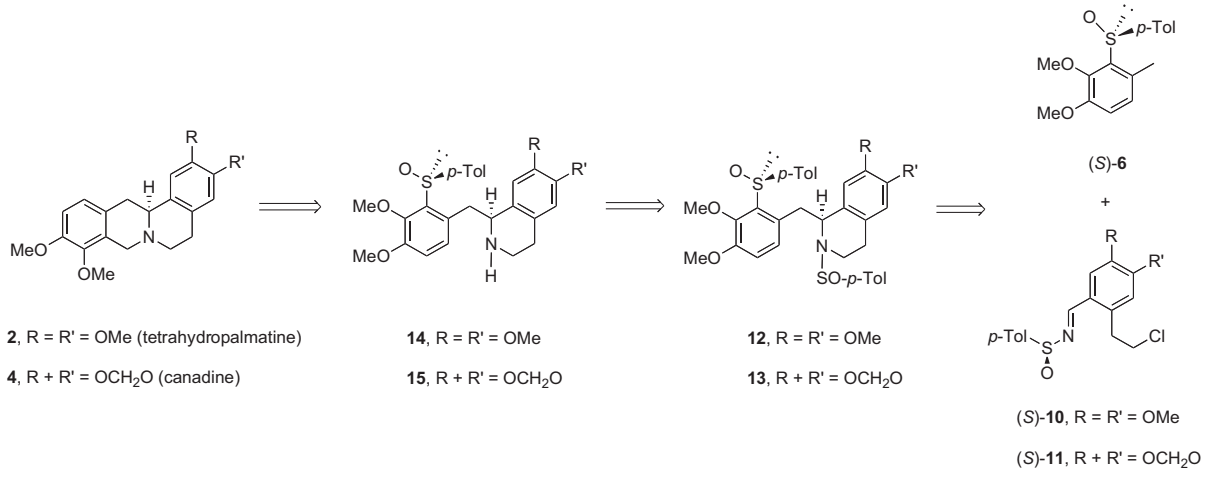
Pictet–Spengler cyclization involving the participation of the sulfinyl group as an *ipso*-director in the electrophilic aromatic substitution reaction.[10] This previously unreported participation of a sulfinyl group in an *ipso* electrophilic aromatic substitution reaction was the key step in the reaction sequence. Herein is described another application of this methodology to the synthesis of optically pure tetrahydroprotoberberines, (*S*)-(−)-tetrahydropalmatine (**2**) and (*S*)-(−)-canadine (**4**), which prove the validity of our synthetic strategy.

The known asymmetric syntheses of tetrahydropalmatine[9,11] and canadine[9,12] are long and/or generate products of low optical purity due to the moderate control of selectivity in the key asymmetric transformation. We hoped to avoid these problems in the manner shown retro-synthetically in Fig. 2 wherein the first disconnection is effected between N-7 and C-8 to give the ring-opened 1-benzylisoquinolines **14** and **15**. Subsequent cleavage of the C-13 and C-14 bond then would give two fragments, the 2-*p*-tolylsulfinyl-3,4-dimethoxytoluene (*S*)-**6**, and the substituted *N*-*p*-tolylsulfinylaldimines (*S*)-**10** and (*S*)-**11**. The first step of the planned synthetic sequence was to involve the nucleophilic addition of the *ortho*-sulfinyl carbanion derived from (*S*)-**6** with the *N*-*p*-tolylsulfinylimines (*S*)-**10** and (*S*)-**11**.

2. Results and discussion

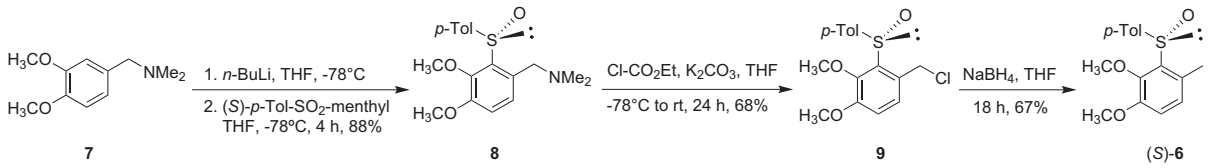
Compound (*S*)-**6**[13] was prepared in 40% overall yield by a three-step sequence starting from 1-(3,4-dimethoxyphenyl)-*N*,*N*-dimethylmethanamine (**7**) (Scheme 1). Doubly *ortho*-directed lithiation at C-2 of **7** followed by treatment with (*S*)-menthyl *p*-toluenesulfinate afforded **8** in 88% yield. Reaction of the tertiary amine **8** with ethyl chloroformate produced the benzylic chloride **9** (68% yield), which upon reductive dehalogenation with $NaBH_4$ in THF gave (*S*)-**6** (67% yield).

The preparation of the intermediates **12** and **13** were performed according to the sequence depicted in Scheme 2. We chose the sulfinylimines (*S*)-**10**[10] and (*S*)-**11** as the electrophiles because of the (*S*) configuration of the tetrahydropalmatine and canadine.[14] The enantiopure sulfinylimine (*S*)-**11** was obtained in 98% yield by condensation of 2-(2-chloroethyl)-4,5-methylenedioxybenzal dehyde with (*S*)-*p*-toluenesulfinamide[15] according to Davis' procedure.[16] Deprotonation of (*S*)-**6** at the benzylic position with LDA at −78 °C, followed by the addition of the *N*-sulfinylimines (*S*)-**10** and (*S*)-**11** at this temperature and stirring overnight at room temperature, produced the 1-benzyltetrahydroisoquinolines **12** and **13** in 71% and 68% isolated yield, respectively. The diastereomeric



2, R = R' = OMe (tetrahydropalmatine)
4, R + R' = OCH_2O (canadine)
14, R = R' = OMe
15, R + R' = OCH_2O
12, R = R' = OMe
13, R + R' = OCH_2O
(*S*)-**6**
(*S*)-**10**, R = R' = OMe
(*S*)-**11**, R + R' = OCH_2O

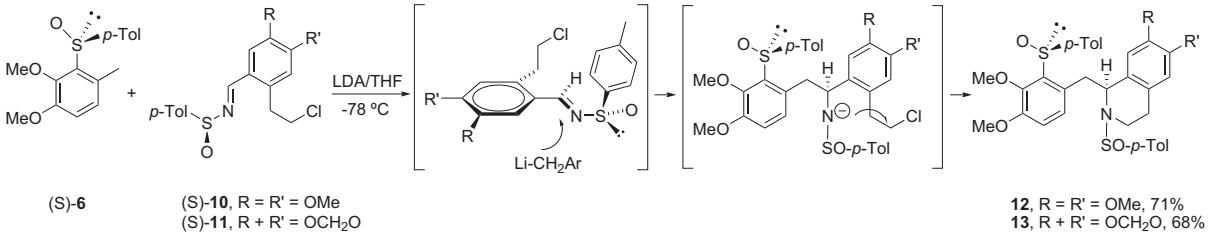
Fig. 2. Retrosynthetic approach to (*S*)-(−)-tetrahydropalmatine (**2**) and (*S*)-(−)-canadine (**4**).



Scheme 1. Synthesis of (*S*)-**6** from 1-(3,4-dimethoxyphenyl)-*N*,*N*-dimethylmethanamine (**7**).

excess of both compounds was excellent (de >96% determined by 300 MHz ^{1}H NMR spectroscopy on the crude product). The almost complete stereoselectivity of these reactions can be explained by assuming the conformational preference of the rotamer with the sulfinyl oxygen adopting a *s*-cis arrangement around the C=N bond (see Scheme 2). In this rotamer, the orientation of the *p*-tolyl group hinders the approach of the benzyllithium species to the upper face, thus providing the *N*-sulfinylamides **12** and **13** with the (*S*) configuration.

sulfinyl directed cyclization to (*S*)-(−)-tetrahydropalmatine (**2**) occurred in 56% yield. (*S*)-(−)-Canadine was similarly obtained from **15** in 53% yield. The spectral properties of **2** and **4** were fully consistent with the literature values and their specific rotations (see Experimental section), were very similar to those reported for the corresponding natural compounds, indicated that both exhibited the (*S*) configuration at their amine bearing carbon atom, and incidentally proves that **12** and **13** also have the (*S*) configuration at this carbon atom.

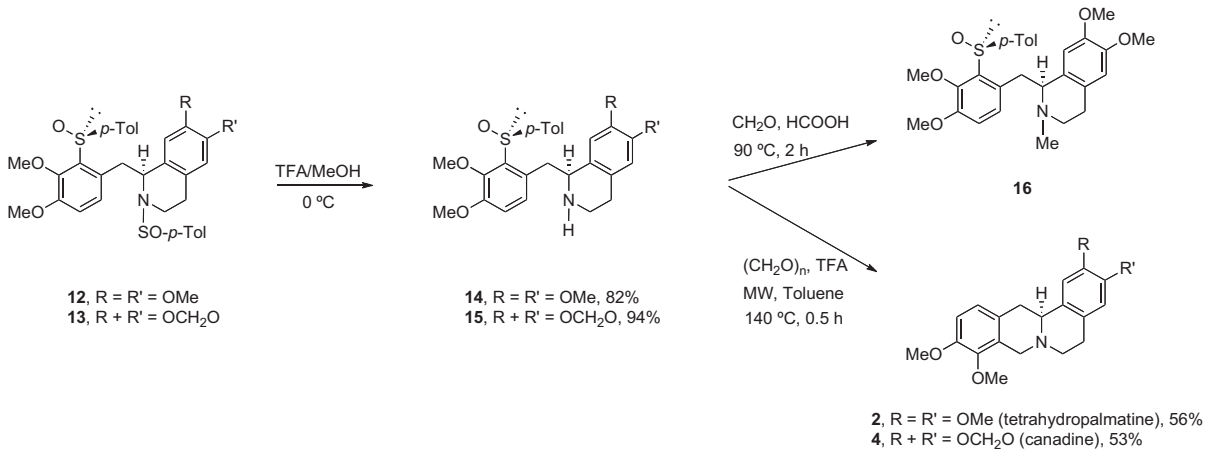


Scheme 2. Synthesis of **12** and **13** from the reactions of (*S*)-**6** with (*S*)-**10** and (*S*)-**11**.

The synthesis of (*S*)-(−)-tetrahydropalmatine **2** and (*S*)-(−)-canadine **4** from **12** and **13** is depicted in Scheme 3. N-Desulfinylation of **12** and **13** was performed with TFA at 0 °C in MeOH, providing the secondary amines **14** and **15** in 82% and 94% yield, respectively. Attempted Pictet–Spengler cyclization of **14** employing aqueous formaldehyde and formic acid at 90 °C for 2 h afforded only the Eschweiler–Clarke N-methylation product **16**, which was isolated in 73% yield. If, however, TFA was utilized instead of formic acid, and the reaction was conducted in toluene solution containing paraformaldehyde under microwave irradiation at 140 °C for 0.5 h,

3. Conclusions

In summary, the synthesis of the optically pure (*S*)-tetrahydropalmatine (**2**) and (*S*)-canadine (**4**) was performed in three steps commencing by reaction of the *ortho*-sulfinyl benzyl carbanion derived from (*S*)-**6** and *N*-sulfinylimines (*S*)-**10** and (*S*)-**11**, N-desulfinylation of the resulting products **12** and **13**, and subsequent sulfinyl-directed microwave assisted Pictet–Spengler cyclization with overall isolated yields of 33% and 34%, respectively. The previously reported participation of the sulfinyl group in an *ipso*



Scheme 3. Preparation of (*S*)-(−)-tetrahydropalmatine (**2**) and (*S*)-(−)-canadine (**4**) from **12** and **13**.

electrophilic aromatic substitution reaction was the key step in the reaction sequence.

4. Experimental section

4.1. General methods

All moisture sensitive reactions were carried out in flame dried glassware under argon atmosphere and monitored by TLC. Flash chromatography was performed with silica gel 60 (230–400 mesh ASTM). Melting points were determined in open capillary tubes and are uncorrected. The optical rotations were measured at room temperature (concentration in g/100 mL). The NMR spectra were acquired in $CDCl_3$ solutions at 300 (or 400) and 75 (or 100) MHz for ^1H and ^{13}C NMR, respectively. *J* values are given in hertz. The diastereomeric excesses were determined by 300 MHz ^1H NMR spectroscopy. Mass spectra were measured at 70 eV and 190 °C. All described compounds were over 97% pure by NMR analysis.

4.2. (*S*)-1-[3,4-Dimethoxy-2-(*p*-tolylsulfinyl)phenyl]-*N*,*N*-dimethylmethanamine 8

To a stirred solution of **7**[17] (1.6 g, 8.20 mmol, 1 equiv) in THF (30 mL) cooled at 0–5 °C a 2.3 M solution in hexanes of *n*-BuLi (4.1 mL, 9.02 mmol, 1.1 equiv) was added dropwise. After 2 h, a solution of (*S*)-menthyl *p*-toluenesulfinate (2.9 g, 9.84 mmol, 1.2 equiv) in THF (10 mL) was added via cannula. The resulting mixture was stirred at room temperature for 4 h. Then, the reaction mixture was quenched with of saturated NH_4Cl (10 mL) and extracted with EtOAc (3×20 mL). The combined organic layers were dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography (99:1 EtOAc/Et_3N) to give **8** as a pale yellow oil (2.4 g, 88% yield), colorless oil, $[\alpha]_D$ −16.5 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 2.19 (s, 6H), 2.34 (s, 3H), 3.20 (d, 1H, *J* 12.9 Hz), 3.69 (s, 3H), 3.80 (s, 3H), 4.08 (d, 1H, *J* 13.2 Hz), 6.93 (d, 1H, *J* 8.5 Hz), 7.07 (d, 1H, *J* 8.5 Hz), 7.20 and 7.59 (AA′BB′, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 44.6 (2C), 56.0, 60.1, 61.2, 115.2, 124.9, 125.5, 129.2, 132.7, 138.6, 139.5, 141.9, 149.1, 153.0; EIMS *m*/*z* 334 (5, M^++1), 316 (100), 195 (27), 151 (83), 58 (16); HRMS-FAB *m*/*z* $[M+1]^+$ calcd for $C_{18}H_{24}NO_3S$ 334.1477, found 334.1487.

4.3. (*S*)-1-(Chloromethyl)-3,4-dimethoxy-2-(*p*-tolylsulfinyl) benzene 9

To a slurry of **8** (4.02 g, 11.98 mmol, 1 equiv) and K_2CO_3 (2.64 g, 19.17 mmol, 1.6 equiv) in THF (10 mL) cooled at −78 °C ethyl chloroformate (2.08 g, 19.17 mmol, 1.6 equiv) was added. The reaction was stirred at room temperature for 12 h. The resulting mixture was quenched with water (10 mL) and extracted with EtOAc (3×15 mL). The combined organic layers were dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography (70:30 hexane/EtOAc) to give **9** as a pale yellow solid (2.66 g, 68% yield); mp 77–78 °C; $[\alpha]_D$ −132.4 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 3H), 3.81 (s, 3H), 3.86 (s, 3H), 5.03 (AB system, 2H, *J* 12.0 Hz), 7.00 (d, 1H, *J* 8.7 Hz), 7.21 (d, 1H, *J* 8.5 Hz), 7.20 and 7.58 (AA′BB′ system, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 41.3, 56.0, 61.2, 115.4, 124.6, 127.6, 129.6, 130.6, 136.9, 140.3, 141.1, 147.8, 153.1; EIMS *m*/*z* 325 (8, M^++1), 288 (100), 271 (88), 240 (31), 209 (19), 197 (14), 105 (13), 91 (10), 77 (7); HRMS-FAB *m*/*z* $[M+1]^+$ calcd for $C_{16}H_{18}ClO_3S$ 325.0665, found 325.0666.

4.4. (*S*)-1,2-Dimethoxy-4-methyl-3-(*p*-tolylsulfinyl)benzene (*S*)-6

A mixture of **9** (1.72 g, 5.29 mmol, 1 equiv) and $NaBH_4$ (1.2 g, 31.77 mmol, 6.0 equiv) in THF (30 mL) was heated at reflux for 18 h. The reaction mixture was quenched with $Na_2SO_4{\cdot}10H_2O$ and filtered through Celite. The filtrate was evaporated under vacuum and the residue purified by flash chromatography (80:20 hexane/EtOAc) to obtain (*S*)-**6** as a white solid (1.03 g, 67%); mp 127–128; $[\alpha]_D$ −198.2 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 2.36 (s, 3H), 2.39 (s, 3H), 3.85 (s, 3H), 3.88 (s, 3H), 6.87 (AB system, 2H, *J* 8.4 Hz), 7.23 and 7.49 (AA′BB′ system, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.6, 21.2, 55.9, 61.4, 115.3, 124.3, 127.5, 129.4, 131.5, 136.2, 139.8, 141.2, 148.0, 151.0; EIMS *m*/*z* 290 (25, M^+), 273 (71), 206 (77), 178 (100), 129 (73), 105 (19), 91 (17), 77 (21); HRMS-FAB *m*/*z* $[M+1]^+$ calcd for $C_{16}H_{19}O_3S$ 291.1055, found 291.1050.

4.5. 2-(2-Chloroethyl)-4,5-methylenedioxybenzaldehyde

To a solution of 3,4-methylenedioxyphenethyl alcohol (1.44 g, 8.66 mmol, 1 equiv) in triethyl orthoformate (1.282 g, 14.4 mL, 86.6 mmol, 10 equiv), $SnCl_4$ (3.38 g, 1.52 mL, 13 mmol, 1.5 equiv) was added quickly at 0–5 °C. The reaction mixture was stirred at 25 °C for 4 h, made basic with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (2×50 mL). The organic layer was washed with water (3×25 mL), dried (Na_2SO_4), and evaporated. The crude reaction mixture (6,7-methylenedioxy-1-ethoxyisochroman, 1.90 g, 8.54 mmol, 1 equiv) in acetyl chloride (10 mL) was refluxed for 4 h. The excess of acetyl chloride was distilled off and the residue was heated at 90–100 °C for 1 h. The residue was purified by flash column chromatography eluting with hexane/EtOAc 4:1 to produce 1.55 g (86%) of 2-(2-chloroethyl)-4,5-methylenedioxybenzaldehyde as a white solid: mp 44–46 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.41 (t, 2H, *J* 6.8 Hz), 3.73 (t, 2H, *J* 6.8 Hz), 6.06 (s, 2H), 6.78 (s, 1H), 7.29 (s, 1H), 10.04 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 35.5, 44.9, 102.1, 111.0, 111.7, 128.6, 137.4, 147.3, 152.1, 189.8; EIMS *m*/*z* 214 (13, M^++2), 212 (35), 177 (100), 163 (15), 148 (23), 135 (25), 119 (13), 91 (15), 77 (14); HRMS-FAB *m*/*z* $[M+1]^+$ calcd for $C_{10}H_{10}ClO_3$ 213.0318, found 213.0322.

4.6. (*S*)-(+)-(*E*)-*N*-[2-(2-Chloroethyl)-4,5-methylenedioxybenzylidene]-4-methylbenzenesulfinamide (*S*)-11

A mixture of (*S*)-(+)-*p*-toluenesulfinamide[15] (0.24 g, 1.55 mmol, 1 equiv), 2-(2-chloroethyl)-4,5-methylenedioxybenzaldehyde (0.33 g, 1.55 mmol, 1 equiv) and titanium (IV) ethoxide (1.77 g, 1.62 mL, 7.75 mmol, 5 equiv) in CH_2Cl_2 (20 mL) was refluxed for 3 h. The reaction mixture cooled at 0 °C was quenched by addition of cold water (10 mL). The mixture was filtered through Celite and the filtrate was washed with CH_2Cl_2. The phases were separated, the aqueous phase was washed with CH_2Cl_2 (15 mL) and the combined organic portions were dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography using hexane/EtOAc 2:1 as eluent to give 0.53 g (98%) of (*S*)-**11** as white solid; mp 107–109 °C; $[\alpha]_D$ +21.5 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 2.40 (s, 3H), 3.24–3.42 (m, 2H), 3.64 (t, 2H, *J* 7.2 Hz), 6.00 and 6.01 (AB system, 2H), 6.74 (s, 1H), 7.31 and 7.62 (AA'BB' system, 4H), 7.39 (s, 1H), 8.82 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.4, 35.9, 44.8, 101.9, 109.3, 111.0, 124.7, 126.2, 129.9, 135.7, 141.7, 142.0, 147.3, 151.1, 157.5; MS-FAB *m*/*z* 350 (51, M^++1), 349 (7), 307 (18), 210 (37), 174 (20), 154 (100), 139 (73), 136 (74), 107 (23), 89 (26), 77 (21); HRMS-FAB *m*/*z* $[M+1]^+$ calcd for $C_{17}H_{17}ClNO_3S$ 350.0618, found 350.0617.

4.7. (1*S*)-1-[3,4-Dimethoxy-2-(*S*)-*p*-tolylsulfinyl]benzyl-6,7-dimethoxy-2-(*S*)-*p*-tolylsulfinyl-1,2,3,4-tetrahydroisoquinoline 12

To a stirred solution of diisopropylamine (0.32 g, 0.44 mL, 3.18 mmol, 1.78 equiv) in THF (10 mL) cooled at −78 °C a solution

1.67 M in hexanes of *n*-BuLi (1.29 mL, 2.15 mmol, 1.2 equiv) was added. After 30 min, a solution of (*S*)-**6** (0.52 g, 1.79 mmol, 1 equiv) in THF (8 mL) was added via cannula. After 1 h at −78 °C, a solution of sulfinylimine (*S*)-**10** (0.653 g, 1.79 mmol, 1 equiv) in THF (10 mL) was added. The resulting solution was stirred at room temperature for 12 h. The reaction mixture was hydrolyzed with saturated aqueous NH_4Cl. The aqueous phase was extracted with CH_2Cl_2 (3×20 mL), washed with brine (2×20 mL), dried (Na_2SO_4), and evaporated. The 300 MHz ^1H NMR spectrum of the crude product revealed a diastereomeric excess >96%. The residue was purified by flash column chromatography using hexane/EtOAc 1:1 as eluent to give 0.79 g (71% yield) of **12** as a white foam; $[\alpha]_D^{20}$ +11.9 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 2.31 (s, 3H), 2.37 (s, 3H), 2.46–2.51 (m, 1H), 3.06–3.39 (m, 4H), 3.70 (dd, 1H, *J* 4.8 and 14.5 Hz), 3.83 (s, 3H), 3.84 (s, 3H), 3.90 (s, 3H), 3.94 (s, 3H), 4.86 (dd, 1H, *J* 4.8 and 10.5 Hz), 6.52 (s, 1H), 6.77 (s, 1H), 6.86 (d, 1H, *J* 8.4 Hz), 6.99 (d, 1H, *J* 8.4 Hz), 7.01–7.12 (AA′BB′ system, 4H), 7.17–7.52 (AA′BB′ system, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.3, 21.4, 29.3, 37.7, 38.0, 55.9, 56.0, 56.2, 61.3, 62.3, 110.1, 111.8, 114.9, 124.6, 126.1, 126.4, 128.9, 129.2 (2C), 129.9, 132.6, 136.7, 140.5, 140.8, 141.4, 142.0, 147.2, 147.7, 148.0, 151.7; MS-FAB *m*/*z* 620 (3, M^++1), 480 (92), 330 (55), 289 (18), 257 (19), 191 (62), 136 (60), 89 (81), 77 (100); HRMS-FAB *m*/*z* $[M+1]^+$ calcd for $C_{34}H_{38}NO_6S_2$ 620.2141, found 620.2137.

4.8. (1*S*)-1-[3,4-Dimethoxy-2-(*S*)-*p*-tolylsulfinyl]benzyl-6,7-methylenedioxy-2-(*S*)-*p*-tolylsulfinyl-1,2,3,4-tetrahydroisoquinoline 13

To a stirred solution of diisopropylamine (0.166 g, 0.23 mL, 1.65 mmol, 1.6 equiv) in THF (5 mL) cooled at −78 °C a solution 1.8 M in hexanes of *n*-BuLi (0.69 mL, 1.24 mmol, 1.2 equiv) was added. After 30 min, a solution of (*S*)-**6** (0.30 g, 1.03 mmol, 1 equiv) in THF (5 mL) was added via cannula. After 1 h at −78 °C, a solution of sulfinylimine (*S*)-**11** (0.395 g, 1.13 mmol, 1.1 equiv) in THF (5 mL) was added. The resulting solution was stirred at room temperature for 12 h. The reaction mixture was hydrolyzed with saturated aqueous NH_4Cl. The aqueous phase was extracted with CH_2Cl_2 (3×20 mL), washed with brine (2×20 mL), dried (Na_2SO_4), and evaporated. The 300 MHz ^1H NMR spectrum of the crude product revealed a diastereomeric excess >96%. The residue was purified by flash column chromatography using hexane/EtOAc 1:1 as eluent to give 0.42 g (68% yield) of **13** as a white solid; mp 182–184 °C; $[\alpha]_D^{20}$ +12.7 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 2.31 (s, 3H), 2.37 (s, 3H), 2.42–2.54 (m, 1H), 3.30–3.26 (m, 3H), 3.29 (dd, 1H, *J* 10.8 and 14.3 Hz), 3.71 (dd, 1H, *J* 4.5 and 14.3 Hz), 3.91 (s, 3H), 3.95 (s, 3H), 4.82 (dd, 1H, *J* 4.5 and 10.8 Hz), 5.89 (AB system, 2H), 6.49 (s, 1H), 6.78 (s, 1H), 6.89 (d, 1H, *J* 8.5 Hz), 6.92–7.10 (AA′BB′ system, 4H), 7.01 (d, 1H, *J* 8.5 Hz), 7.16–7.51 (AA′BB′ system, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.2, 21.3, 29.7, 37.3, 37.8, 56.1, 61.2, 62.6, 100.7, 107.0, 108.9, 114.9, 124.5, 126.2, 127.2, 128.6, 129.1, 129.8, 130.3, 132.5, 136.7, 140.4, 140.7, 141.3, 141.9, 145.8, 146.5, 147.6, 151.6; MS-FAB *m*/*z* 604 (6, M^++1), 464 (100), 314 (64), 289 (19), 176 (38), 154 (65), 136 (47), 77 (23); HRMS-FAB *m*/*z* $[M+1]^+$ calcd for $C_{33}H_{34}NO_6S_2$ 604.1828, found 604.1833.

4.9. General procedure for the preparation of 14 and 15

To a stirred solution of **12** or **13** (1 mmol, 1 equiv) in MeOH (10 mL) cooled at 0 °C trifluoroacetic acid (3 mmol, 3 equiv) was added. The resulting solution was stirred at 0 °C for 3 h. The volatiles were evaporated and the residue was chromatographed in an SCX column affording the corresponding amine.

*4.9.1. (1S)-1-[3,4-Dimethoxy-2-(S)-p-tolylsulfinyl]benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**14**).* Colorless oil, 0.394 g (82% yield); $[\alpha]_D^{20}$ −52.7 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 2.33 (s, 3H), 2.75–2.86 (m, 1H), 2.88–3.08 (m, 2H), 3.24–3.42 (m, 3H), 3.84 (s, 3H), 3.87 (s, 3H), 3.90 (s, 3H), 3.94 (s, 3H), 4.40–4.47 (m, 1H), 5.40–5.90 (br s, 1H), 6.61 (s, 1H), 6.71 (s, 1H), 7.08 (d, 1H, *J* 8.7 Hz), 7.20 (d, 1H, *J* 8.3 Hz), 7.20 and 7.45 (AA′BB′ system, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.3, 27.6, 36.8, 40.8, 55.9, 56.1, 56.2, 56.3, 61.5, 109.6, 111.6, 116.1, 124.4, 126.1, 127.3, 129.0, 129.9, 130.0, 136.0, 140.6, 141.0, 147.8, 147.9, 148.0, 152.0; EIMS *m*/*z* 482 (1, M^++1), 464 (8), 192 (100); HRMS-FAB *m*/*z* $[M+1]^+$ calcd for $C_{27}H_{32}NO_5S$ 482.2001, found 482.1999.

*4.9.2. (1S)-1-[3,4-Dimethoxy-2-(S)-p-tolylsulfinyl]benzyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (**15**).* Colorless oil, 0.437 g (94% yield); $[\alpha]_D^{20}$ −71.9 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.60–2.00 (br, 1H), 2.34 (s, 3H), 2.58–2.83 (m, 3H), 3.09–3.20 (m, 2H), 3.54 (dd, 1H, *J* 3.4 and 14.0 Hz), 3.78 (s, 3H), 3.86 (s, 3H), 4.04 (dd, 1H, *J* 3.4 and 10.5 Hz), 5.89 (s, 2H), 6.54 (s, 1H), 6.76 (s, 1H), 7.01 (d, 1H, *J* 8.6 Hz), 7.07 (d, 1H, *J* 8.6 Hz), 7.21 and 7.52 (AA′BB′ system, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.3, 30.0, 37.7, 40.5, 56.0, 57.2, 61.1, 100.6, 106.6, 108.8, 115.7, 124.5, 127.5, 128.3, 129.6, 131.8, 133.0, 136.7, 140.0, 142.1, 145.8, 145.9, 148.1, 151.7; EIMS *m*/*z* 466 (2, M^++1), 448 (19), 176 (100); HRMS-FAB *m*/*z* $[M+1]^+$ calcd for $C_{26}H_{28}NO_5S$ 466.1688, found 466.1695.

4.10. General procedure for the microwave assisted Pictet–Spengler synthesis of 2 and 4

A solution of the amine **14** or **15** (1 mmol), paraformaldehyde (1.2 mmol 1.2 equiv), TFA (8 mmol, 8 equiv) in toluene (1 mL) was placed in a microwave vial, which was then capped and irradiated in a Monowave 300 microwave equipment at 140 °C for 0.5 h. The volatiles were removed under reduced pressure and the crude reaction mixture was suspended in cold water (3 mL), treated with 2 M aqueous NaOH to pH 8 and extracted with CH_2Cl_2 (3×5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography using hexane/EtOAc 1:1 as eluent.

*4.10.1. (S)-(−)-5,8,13,13a-Tetrahydro-2,3,9,10-tetramethoxy-6H-dibenzo[a,g]quinolizine [(S)-(−)-tetrahydropalmatine (**2**)].* Light yellow solid, 0.199 g (56% yield); mp 142–144 °C (lit.[18] 141–142 °C); $[\alpha]_D^{20}$ −269.1 (*c* 1.0, $CHCl_3$) [lit.[19] $[\alpha]_D^{20}$ −269.0 (*c* 0.8, $CHCl_3$)]; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.61–2.71 (m, 2H), 2.83 (dd, 1H, *J* 11.6 and 15.6 Hz), 3.10–3.24 (m, 2H), 3.27 (dd, 1H, *J* 3.6 and 16.0 Hz), 3.51–3.58 (m, 2H), 3.85 (s, 3H), 3.86 (s, 3H), 3.87 (s, 3H), 3.89 (s, 3H), 4.24 (d, 1H, *J* 16.0 Hz), 6.62 (s, 1H), 6.73 (s, 1H), 6.79 (d, 1H, *J* 8.4 Hz), 6.88 (d, 1H, *J* 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.1, 36.3, 51.5, 54.0, 55.8 (2C), 56.0, 59.3, 60.1, 108.6, 110.9, 111.3, 123.8, 126.7, 127.7, 128.7, 129.7, 145.0, 147.4 (2C), 150.2. These analytical data are in accordance with the values reported in the literature.[11a]

*4.10.2. (S)-(−)-5,8,13,13a-Tetrahydro-9,10-dimethoxy-6H-benzo[g]-1,3-benzodioxolo[5,6-a]quinolizine [(S)-(−)-canadine (**4**)].* Light yellow solid, 0.180 g (53% yield); mp 129–131 °C (lit.[20] 134 °C); $[\alpha]_D^{20}$ −292.0 (*c* 1.0, $CHCl_3$) [lit.[20] $[\alpha]_D^{20}$ −291.0 (*c* 0.93, $CHCl_3$)]; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.56–2.72 (m, 2H), 2.82 (dd, 1H, *J* 11.5 and 15.8 Hz), 3.05–3.22 (m, 2H), 3.22 (dd, 1H, *J* 3.5 and 15.8 Hz), 3.52 (m, 1H), 3.54 (d, 1H, *J* 15.2 Hz), 3.84 (s, 6H), 4.24 (d, 1H, *J* 15.8 Hz), 5.90 (s, 2H), 6.59 (s, 1H), 6.72 (s, 1H), 6.77 (d, 1H, *J* 8.4 Hz), 6.86 (d, 1H, *J* 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.6, 36.5, 51.4, 54.0, 56.0, 59.7, 60.2, 100.8, 105.6, 108.4, 111.1, 123.9, 127.7, 127.8, 128.6, 130.8, 145.2, 146.0, 146.2, 150.4; EIMS *m*/*z* 339 (96, M^+), 338 (51), 308 (14), 205 (13), 174 (19), 164 (100), 149 (65), 105 (35), 77 (8). Analytical data were in agreement with literature values.[11b]

4.11. (1*S*)-1-(3,4-Dimethoxy-2-(*S*)-(*p*-tolylsulfinyl)benzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline 16

A mixture of 37% aqueous CH_2O (1.6 mL), HCOOH (2.4 mL), and **14** (0.1 g, 0.21 mmol) was heated at 90 °C for 2 h. After the resulting mixture had cooled to 25 °C, saturated aqueous $NaHCO_3$ was added until pH >7 was reached. The mixture was then extracted with CH_2Cl_2 (3×20 mL). The organic extracts were dried (Na_2SO_4), and the solvent was evaporated under vacuum. The residue was purified by flash chromatography using EtOAc/NEt_3 as eluent to obtain 0.075 g (73%) of **16** as a pale yellow oil; $[\alpha]_D^{20}$ −25.1 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 2.31 (s, 3H), 2.35 (s, 3H), 2.43–2.51 (m, 1H), 2.64–2.71 (m, 1H), 2.76–2.86 (m, 1H), 3.13 (dd, 1H, *J* 5.4 and 14.2 Hz), 3.20–3.30 (m, 1H), 3.43 (dd, 1H, *J* 8.3 and 14.1 Hz), 3.71 (s, 3H), 3.72 (s, 3H), 3.71–3.82 (m, 1H), 3.78 (s, 3H), 3.82 (s, 3H), 6.43 (s, 1H), 6.54 (s, 1H), 6.81 (d, 1H, *J* 8.6 Hz), 6.91 (d, 1H, *J* 8.6 Hz), 7.21 and 7.54 (AA′BB′ system, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.2, 24.2, 36.8, 42.2, 46.0, 55.8 (2C), 56.0, 61.1, 64.3, 112.2, 115.6, 124.5, 126.3, 127.6, 129.0, 129.3, 129.4, 133.9, 137.2, 139.6, 142.3, 146.8, 147.4, 148.1, 151.4; MS-FAB *m*/*z* 497 (1, M^++2), 215 (5), 165 (8), 153 (10), 109 (28), 69 (65), 55 (100), 41 (69); HRMS-FAB *m*/*z* $[M+1]^+$ calcd for $C_{28}H_{34}NO_5S$ 496.2158, found 496.2147.

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References and notes

1. (a) da-Cunha, E. V. L.; Fechine, I. M.; Guedes, D. N.; Barbosa-Filho, J. M.; da-Silva, M. S. In *The Alkaloids: Chemistry and Biology*; Cordell, G. A., Ed.; Academic: San Diego CA, 2005; Vol. 62, p 1; (b) Bentley, K. W. *The Isoquinoline Alkaloids*; Harwood Academic: Amsterdam, 1998; (c) Hanaoka, M. In *The Alkaloids: Chemistry and Pharmacology*; Brossi, A., Ed.; Academic: Orlando FL, 1988; Vol. 33, p 141; (d) Bhakuni, D. S.; Jain, S. In *The Alkaloids: Chemistry and Pharmacology*; Brossi, A., Ed.; Academic: Orlando FL, 1986; Vol. 28, p 95; (e) Santavy, F. In *The Alkaloids: Chemistry and Physiology*; Manske, R. H. F., Rodrigo, R. G. A., Eds.; Academic: New York, NY, 1979; Vol. 17, p 385; (f) Shamma, M. *The Isoquinoline Alkaloids: Chemistry and Pharmacology*; Academic: New York, NY, 1972; (g) Jeffs, P. W. In *The Alkaloids: Chemistry and Physiology*; Manske, R. H. F., Ed.; Academic: New York, NY, 1967; Vol. 9, p 41.
2. (a) Memetzidis, G.; Stambach, J. F.; Jung, L.; Schott, C.; Heitz, C.; Stoclet, J. C. *Eur. J. Med. Chem.* **1991**, *26*, 605; (b) Suffnees, M. In *The Alkaloids*; Brossi, A., Ed.; Academic: Orlando FL, 1985; Vol. 25, p 3.
3. Chu, H.; Jin, G.; Friedman, E.; Zhen, X. *Cell. Mol. Neurobiol.* **2008**, *28*, 491.
4. *Römpp-Lexikon Naturstoffe*; Fugmann, B., Ed.; Thieme: Stuttgart, 1997; pp 519–520.
5. For a review on Pictet–Spengler cyclization, see: Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797 For examples, see: (a) Awuah, E.; Capretta, A. *J. Org. Chem.* **2010**, *75*, 5627; (b) Mujahidin, D.; Doye, S. *Eur. J. Org. Chem.* **2005**, 2689; (c) Comins, D. L.; Thakker, P. M.; Baevsky, M. F.; Badawi, M. M. *Tetrahedron* **1997**, *53*, 16327; (d) Munchoff, M. J.; Meyers, A. I. *J. Org. Chem.* **1996**, *61*, 4607; (e) Meyers, A. I.; Dickman, D. A.; Boes, M. *Tetrahedron* **1987**, *43*, 5095; (f) Meyers, A. I.; Boes, M.; Dickman, D. A. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 458; (g) McMurtrey, K. D.; Meyerson, L. R.; Cashaw, J. L.; Davies, V. E. *J. Org. Chem.* **1984**, *49*, 947.
6. For examples, see: (a) Venkov, A. P.; Ivanov, I. I. *Tetrahedron* **1996**, *52*, 12299; (b) Larsen, R. D.; Reamer, R. A.; Corley, E. G.; Davis, P.; Grabowski, E. J. J.; Reider, P. J.; Shinkai, I. *J. Org. Chem.* **1991**, *56*, 6034; (c) Pandey, G. D.; Tiwari, K. P. *Heterocycles* **1980**, *14*, 59; (d) Pai, B. R.; Natarajan, S.; Manikumar, G.; Rajaraman, R.; Suguna, H. *J. Org. Chem.* **1978**, *43*, 1992; (e) Rajaraman, R.; Pai, B. R.; Premila, M. S.; Suguna, H. *Indian J. Chem., Sect. B* **1977**, *15*, 876.
7. Kametani, T.; Nakano, K.; Shishido, K.; Fukumoto, K. *J. Chem. Soc. C* **1971**, 3350.
8. Miller, R. B.; Tsang, T. *Tetrahedron Lett.* **1988**, *29*, 6715.
9. Cutter, P. S.; Miller, R. B.; Schore, N. E. *Tetrahedron* **2002**, *58*, 1471.
10. Mastranzo, V. M.; Yuste, F.; Ortiz, B.; Sánchez-Obregón, R.; Toscano, R. A.; García Ruano, J. L. *J. Org. Chem.* **2011**, *76*, 5036.
11. (a) Boudou, M.; Enders, D. *J. Org. Chem.* **2005**, *70*, 9486; (b) Matulenko, M. A.; Meyers, A. I. *J. Org. Chem.* **1996**, *61*, 573; (c) Pyne, S. G.; Dikic, B. *J. Org. Chem.* **1990**, *55*, 1932.
12. (a) Pyne, S. G. *Tetrahedron Lett.* **1987**, *28*, 4737; (b) Iwasa, K.; Gupta, Y. P.; Cushman, M. *J. Org. Chem.* **1981**, *46*, 4744.
13. Mastranzo, V. M.; Olivares, J. L.; Sánchez-Obregón, R.; Yuste, F.; Toscano, R. A. *Acta Crystallogr., Sect. E: Struct. Rep. Online* **2011**, *E67*, o2950.
14. The absolute configuration of the generated stereogenic center could be assigned as (*S*) based on our previous work (see Ref. 10).
15. Fanelli, D. L.; Szewczyk, J. M.; Zhang, Y.; Reddy, G. V.; Burns, D. M.; Davis, F. A. *Org. Synth.* **1999**, *77*, 50.
16. Davis, F. A.; Zhang, Y.; Andemichael, Y.; Fang, T.; Fanelli, D. L.; Zhang, H. *J. Org. Chem.* **1999**, *64*, 1403.
17. (a) Song, Z.; Weng, X.; Huang, J.; Wang, X.; Bai, M.; Zhou, Y.; Yang, G.; Zhou, X. *Chem.—Eur. J.* **2008**, *14*, 5751; (b) Eliel, E. L.; Ferdinand, T. N.; Herrmann, C. *J. Org. Chem.* **1954**, *19*, 1693.
18. Bartley, J. P.; Baker, L. T.; Carvalho, C. F. *Phytochemistry* **1994**, *36*, 1327.
19. Halbsguth, C.; Meissner, O.; Haeberlein, H. *Planta Med.* **2003**, *69*, 305.
20. Baird, P. D.; Blagg, J.; Davies, S. G.; Sutton, K. H. *Tetrahedron* **1988**, *44*, 171.