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Tetrahedron 60 (2004) 6335–6344
Tetrahedron

Synthesis and antitrypanosomal activity of 2-aminomethyl-1-(2-oxyphenyl)naphthalenes☆

Gerhard Bringmann,[a,*] Robert-Michael Pfeifer,[a] Petra Schreiber,[a] Kristina Hartner,[a] Nikolaus Kocher,[b] Reto Brun,[c] Karl Peters,[d] Eva-Maria Peters[d] and Matthias Breuning[a]

[a]*Institute of Organic Chemistry, University of Würzburg, Am Hubland, D-97074 Würzburg, Germany*
[b]*Institute of Inorganic Chemistry, University of Würzburg, Am Hubland, D-97074 Würzburg, Germany*
[c]*Swiss Tropical Institute, Socinstr. 57, CH-4002 Basel, Switzerland*
[d]*Max Planck Institute for Solid State Research, Heisenbergstraße 1, D-70506 Stuttgart, Germany*

Received 26 December 2003; revised 21 May 2004; accepted 21 May 2004

Dedicated to Professor Dr. Helmut Quast on the occasion of his 70th birthday

Abstract—A broad variety of enantiopure axially chiral 2-aminomethyl-1-(2-oxyphenyl)naphthalenes were prepared via short and efficient synthetic pathways by using the 'lactone method' for the regio- and stereoselective construction of the biaryl axis. Their in vitro activity against *Trypanosoma cruzi*, the causative agent of Chagas' disease, was evaluated. In particular, the *M*-configured atropisomers, with the 2-oxy function equipped with an *O*-triflate group, were found to exhibit good antitrypanosomal activities (down to IC_{50}=1.6 μg/mL), combined with low levels of cytotoxicity.

1. Introduction

Chagas' disease (American trypanosomiasis), caused by the parasitic protozoa *Trypanosoma cruzi*, is a serious threat to people living in Central and South America, where it is endemic in 21 countries.[1] According to the World Health Organization (WHO), a total of 16–18 million people are infected, causing ca. 50.000 casualties a year, and 100 million, that is, one fourth of the population of these countries, are at risk.[1] Current treatments of Chagas' disease are based on nifurtimox (**1**)[2,3] or benznidazol (**2**)[4–6] (Fig. 1). These two compounds show poor clinical efficiency and cause numerous unfavorable side effects, like nausea, skin rashes, peripheral neuritis, bone-marrow depression, weight loss, and sleeping disorders.[7] All this emphasizes the necessity to develop new drugs for the treatment of Chagas' disease.

We have recently discovered a new class of natural products with, in part, high antitrypanosomal activities, the naphthylisoquinoline alkaloids like, for example,

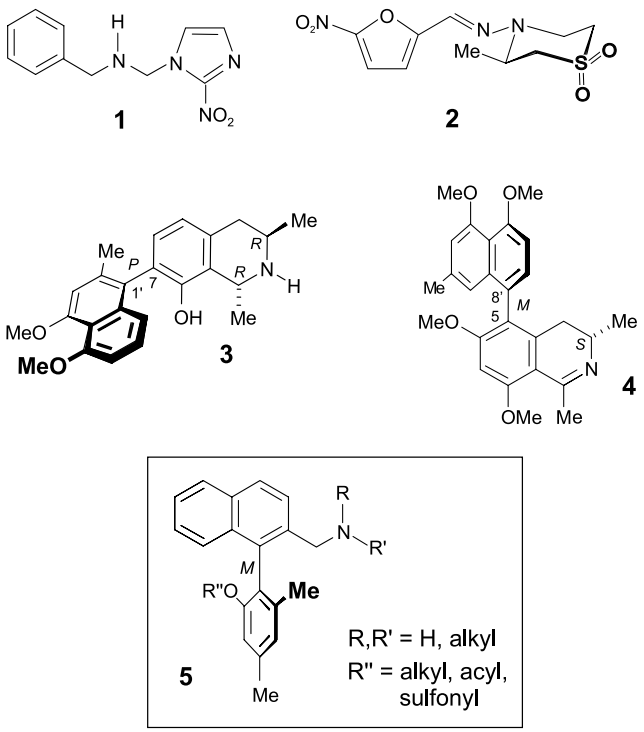


Figure 1. Nifurtimox (**1**) and benznidazol (**2**), drugs currently used for the treatment of Chagas' disease, the likewise antitrypanosomal naphthylisoquinoline alkaloids dioncophylline A (**3**) and ancistrotanzanine B (**4**), and general structure of the simplified target structures **5**.

☆ Part 109 in the series 'Novel Concepts in Directed Biaryl Synthesis', for part 108, see Ref. 20.

Keywords: Axially chiral biaryls; Atropisomerism; Asymmetric synthesis; Antitrypanosomal activity; Chagas' disease.
* Corresponding author. Tel.: +49-931-8885323; fax: +49-931-8884755; e-mail address: bringman@chemie.uni-wuerzburg.de

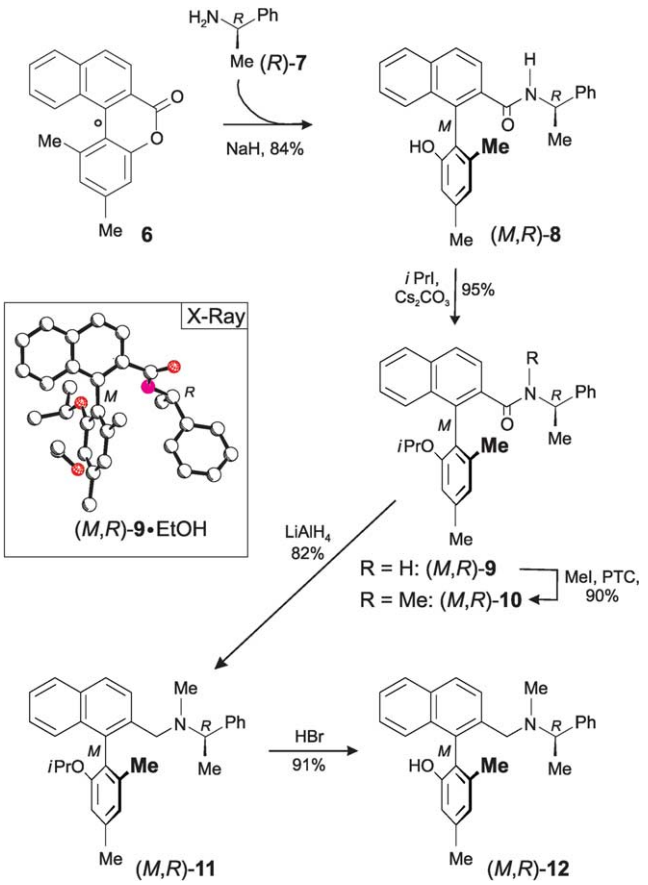
0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.05.076

dioncophylline A (**3**) and ancistrotanzanine B (**4**), which show low IC_{50} values against *T. cruzi* of 0.70 and 1.5 μg/mL, respectively. Although total synthetic pathways have been developed, thus making these and other naphthylisoquinolines accessible,[8] there is urgent demand for the search of even more active analogs with simpler and thus easier-to-access structures. This prompted us to synthesize a variety of closely related biaryls in order to establish structure–activity relationships. In this paper, we report on a group of related, still axially chiral, but simplified 2-aminomethyl-1-(2-oxyphenyl)naphthalenes of type **5**, some of which exhibit excellent antitrypanosomal activities, in particular their *O*-triflate derivatives.

2. Results and discussion

2.1. Chemistry

All biaryls were synthesized in a stereochemically homogeneous form, by using the 'lactone method'.[8] The stereochemical key step of this procedure is the atropo-enantioselective ring cleavage of configurationally unstable biaryl lactones like **6** (Scheme 1), here with the sodium salt of (1*R*)-phenylethylamine [(*R*)-**7**], yielding the dia- and enantiomerically pure biaryl amide (*M*,*R*)-**8** in 84% yield.[9] *O*-Isopropylation of the phenolic hydroxy function of (*M*,*R*)-**8** delivered the protected amide (*M*,*R*)-**9**; its anticipated structure and absolute configuration were confirmed by X-ray diffraction analysis. *N*-Methylation of (*M*,*R*)-**9**, reduction of the amide function, and deprotection of the phenolic OH group delivered the biaryl amide (*M*,*R*)-**12**.



Scheme 1. Synthesis of the enantiopure biaryl aminophenol (*M*,*R*)-**12** and molecular structure of (*M*,*R*)-**9**·EtOH (hydrogen atoms omitted for reasons of clarity).

The secondary biaryl amines (*M*,*R*)-**16** and (*M*,*S*)-**16** were prepared by amination of the enantiopure *O*-benzylated bromide (*M*)-**14**[10] with (*R*)- or (*S*)-phenylethylamine [(*R*)-**7** or (*S*)-**7**] and subsequent deprotection of the phenolic oxygen function with BCl_3 (Scheme 2). The derivative (*M*)-**13**, with the biaryl axis as the only element of chirality, was synthesized by treatment of (*M*)-**14** with benzylamine.

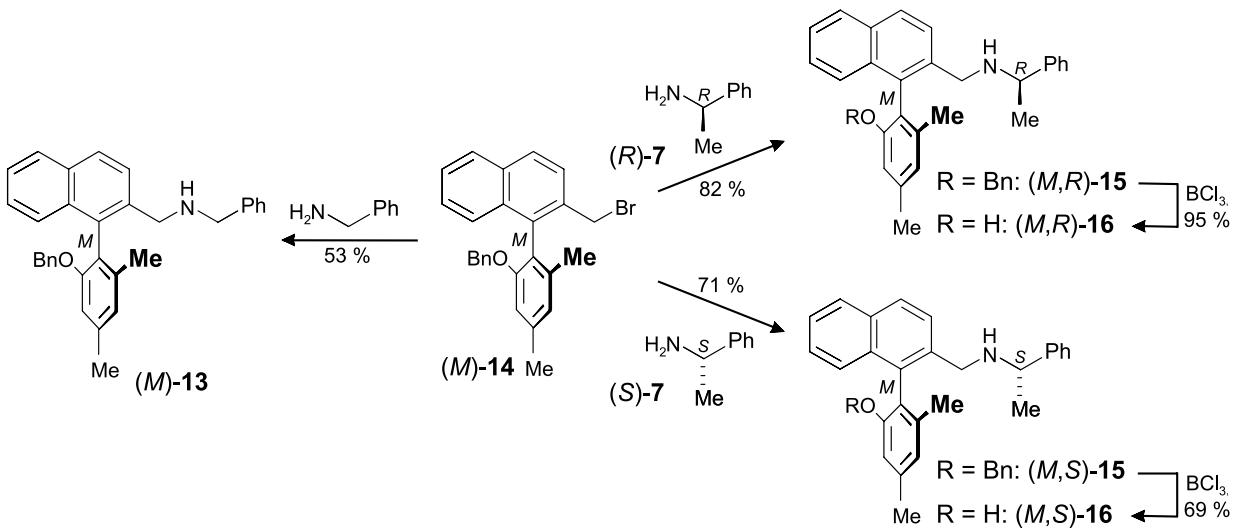
Starting from (*M*,*R*)-**12** and (*M*,*R*)-**16**, a series of differently *O*-functionalized biaryl amines were synthesized, using established standard procedures (Scheme 3). *O*-Sulfonylation of the tertiary biaryl amine (*M*,*R*)-**12** provided (*M*,*R*)-**17**, (*M*,*R*)-**18**, and (*M*,*R*)-**19** (for its molecular structure, see Fig. 2), and acylation with Mosher acid gave (*M*,*R*)-**20**. The MOM ether (*M*,*R*)-**21** and the acetate (*M*,*R*)-**22** were prepared from the secondary amine (*M*,*R*)-**16**.

Since the initial screening against *T. cruzi* had provided the aminotriflate (*M*,*R*)-**19** as the most active compound (see Table 1, Section 2.2), we synthesized several structurally related biarylic triflates. For an investigation of the influence of the two elements of chirality, the biaryl axis and the benzylic stereocenter, we prepared, exemplarily for **19**, all of its four stereoisomers, (*M*,*R*)-**19** (also accessible from (*M*,*R*)-**12**, see Scheme 3), (*M*,*S*)-**19**, (*P*,*S*)-**19**, and (*P*,*R*)-**19**, from the *O*-methylated bromides (*M*)-**23** and (*P*)-**23**[11] by amination and subsequent *O*-deprotection and *O*-triflation (Scheme 4). In order to investigate whether the stereocenter in the *N*-containing side chain is necessary, we analogously

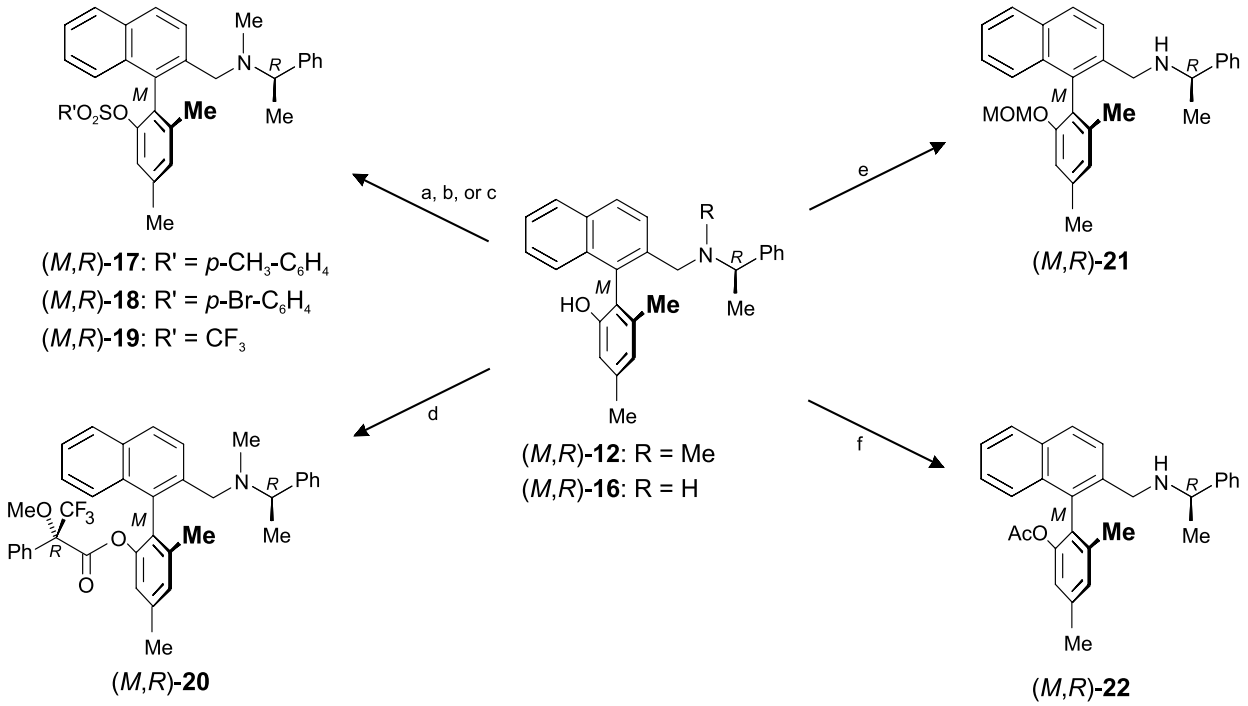
Table 1. Antitrypanosomal activities and cytotoxicities

Compound	IC_{50} [μg/mL] *T. cruzi*	IC_{50}/MIC [μg/mL] cytotoxicity (L6)
Standard	0.4[a]	0.005[b]
(*M*,*R*)-**9**	5.8	92
(*M*)-**13**	5.6	7.2
(*M*,*R*)-**15**	42.9	>90
(*M*,*S*)-**15**	4.6	>90
(*M*,*S*)-**16**	1.8	10
(*M*,*R*)-**17**	14.5	>90
(*M*,*R*)-**18**	37.8	n.e.[c]
(*M*,*R*)-**19**	2.5	>90
(*M*,*S*)-**19**	⇒1.6	⇒>90
(*P*,*R*)-**19**	11.3	>90
(*P*,*S*)-**19**	49.5	n.e.[c]
(*M*,*R*)-**20**	10.9	>90
(*M*,*R*)-**21**	2.1	11.7
(*M*,*R*)-**22**	1.4	2.8
(*M*,*R*)-**24**	2.4	14.1
(*M*,*S*)-**24**	5.3	n.e.[c]
(*P*,*R*)-**24**	1.4	5.5
(*P*,*S*)-**24**	3.4	n.e.[c]
(*M*)-**25**	8.5	n.e.[c]
(*P*)-**25**	2.9	n.e.[c]
(*M*)-**26**	4.6	67
(*P*)-**26**	9.0	>90

[a] Benznidazole (**2**).
[b] Podophyllotoxin.
[c] N.e.=not evaluated.



Scheme 2. Synthesis of the secondary biaryl amines (*M*)-**13**, (*M*,*R*)-**16**, and (*M*,*S*)-**16**.



Scheme 3. Synthesis of (*M*,*R*)-**17**–**22**. (a) *p*-Toluenesulfonic acid, NEt_3; (b) *p*-bromophenylsulfonic acid, NEt_3; (c) Tf_2O, DABCO; (d) (*R*)-Mosher acid, DCC, DMAP; (e) MOMCl, NaH; (f) AcCl, pyridine.

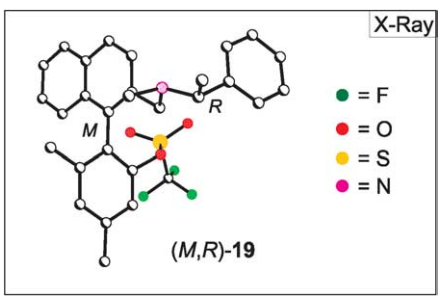
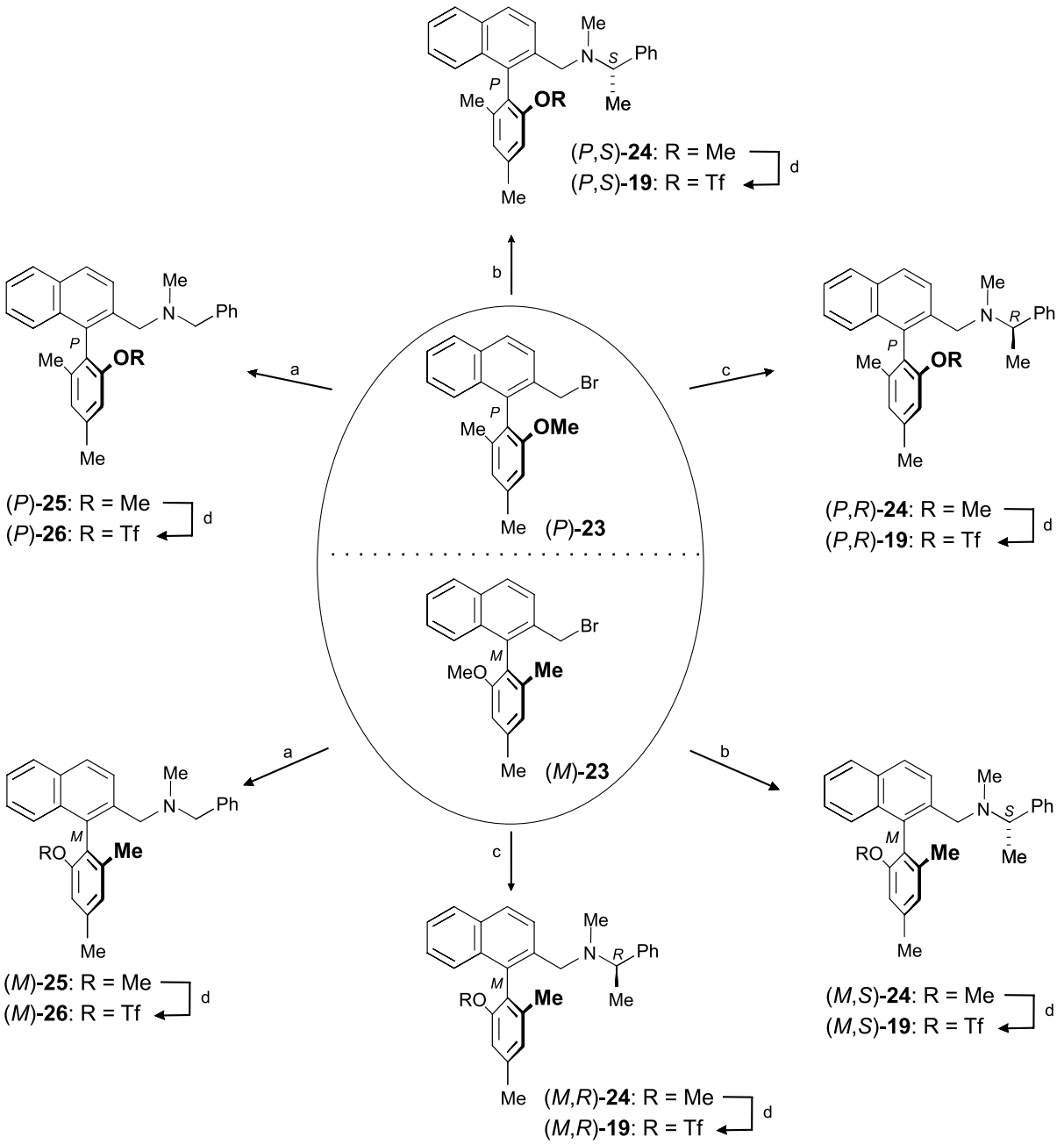


Figure 2. Molecular structure of (*M*,*R*)-**19** in the crystal (hydrogen atoms omitted for reasons of clarity).

synthesized the exclusively axially chiral amines (*M*)-**26** and (*P*)-**26**.

2.2. Antitrypanosomal activity

The 2-aminomethyl-1(2-oxyphenyl)naphthalene derivatives thus synthetically available were evaluated against *T. cruzi* using rat skeletal myoblasts (L-6 cells) in vitro. The results are summarized in Table 1. Good antitrypanosomal activities with IC_{50} values <3 μg/mL were found for the biaryls (*M*,*S*)-**16**, (*M*,*R*)-**19**, (*M*,*S*)-**19**, (*M*,*R*)-**21**, (*M*,*R*)-**22**, (*M*,*R*)-**24**, (*P*,*R*)-**24**, and (*P*)-**25**. Since these compounds possess different substituents on the phenolic oxygen (Me, MOM, Ac, Tf), the substitution pattern at this site does not



Scheme 4. Synthesis of the enantio- and diastereomerically pure triflates **19** and **26**. (a) *N*-methylbenzylamine; (b) (*S*)-*N*-methyl-1-phenylethylamine; (c) (*R*)-*N*-methyl-1-phenylethylamine; (d) 1. HBr; 2. Tf_2O, DABCO.

seem to be essential for attaining high antitrypanosomal activities. The levels of cytotoxicity of these biaryls, by contrast, are significantly influenced by the nature of this substituent: Only the *O*-triflate derivatives (*M*,*R*)-**19** and (*M*,*S*)-**19** were virtually non-toxic (IC_{50}/MIC>90 μg/mL) and exhibited quite promising activity-to-cytotoxicity ratios of more than 35 and 55, respectively. The stereochemical orientation at the biaryl axis plays an important role, too: In the case of the *O*-triflate derivatives **19** and **26**, the *M*-configured biaryls were always more active than their *P*-atropisomers, for example, (*M*,*S*)-**19**: IC_{50}=1.6 μg/mL vs. (*P*,*S*)-**19**: IC_{50}=49.5 μg/mL, while for the *O*-alkyl substituted compounds **24** and **25**, the opposite behavior was observed. No such trend is obvious for the stereogenic center in the *N*-alkyl side chain. Nevertheless, the increased steric demand of the *N*-1-phenylethyl group compared to that of the *N*-benzyl moiety seems to be advantageous, as deduced from their higher activities, for example, (*M*,*S*)-**19** (IC_{50}=1.6 μg/mL) and (*M*,*R*)-**19** (IC_{50}=2.5 μg/mL) vs. (*M*)-**26** (IC_{50}=4.6 μg/mL). Thus, the most promising derivative found within these investigations is the very active and virtually nontoxic, axially chiral and, simultaneously, centrochiral biaryl (*M*,*S*)-**19** (IC_{50}=1.6 μg/mL) possessing an *O*-triflate substituent and the *N*−1-phenylethyl side chain.

3. Conclusion

Axially chiral 2-aminomethyl-1-(2-oxyphenyl)naphthalene

derivatives have proven to be easily prepared in short, directed synthetic sequences, leading to enantio- and diastereomerically pure material. Several representatives of this class of compounds possess significant activities against the protozoan parasite *T. cruzi*, without any notable cytotoxicities. The as yet most promising compound is the *O*-triflated aminophenol (*M*,*S*)-**19**, which provides a good antitrypanosomal activity of IC_{50}=1.6 μg/mL combined with a low level of cytotoxicity (IC_{50}/MIC>90 μg/mL), now making in vivo experiments a rewarding goal. This work is under investigation.

4. Experimental

4.1. General

Melting points were determined with a Kofler melting point apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer polarimeter. IR spectra were scanned from KBr pellets or neat using a Perkin–Elmer spectrophotometer model 1420. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AC 250 (250 MHz) or a Bruker Avance 400 (400 MHz) instrument using the deuterated solvent as an internal reference; *J* values are given in Hertz. Elemental analyses were performed in the Institute of Inorganic Chemistry of the University of Würzburg. Mass spectra were measured on a Finnigan MAT 2000 mass spectrometer at 70 eV. All reactions with moisture and/or air sensitive materials were carried out with flame-dried glassware using the Schlenk tube technique under inert argon atmosphere. The enantiopure biaryls (*M*,*R*)-**8**[9] and (*M*)-**14**[10] were synthesized according to literature procedures. The melting points and elemental analyses of some of the amines were measured using their hydrochlorides or hydrobromides, which were prepared by treatment of an ethereal solution of the free amine with gaseous HCl or aqueous HBr.

4.1.1. (*M*,*R*)-1-(2-Isopropoxy-4,6-dimethylphenyl)-*N*-(1-phenylethyl)naphthalene-2-carboxamide [(*M*,*R*)-9]. A suspension of (*M*,*R*)-**8** (1.16 g, 2.94 mmol), isopropyl iodide (1.18 mL, 11.8 mmol), and Cs_2CO_3 (1.92 g, 5.88 mmol) in acetone (120 mL) was stirred for 2 d at room temperature. The inorganic salts were removed by filtration and the residue was chromatographed on silica gel (petroleum ether/diethyl ether=10:1→1:1) yielding (*M*,*R*)-**9** (1.22 g, 2.79 mmol, 95%) as colorless crystals; mp 143 °C. $[\alpha]_D^{20}$=−16.4 (*c* 1.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.92–7.85 (m, 3H), 7.60–7.21 (m, 6H), 6.91–6.84 (m, 4H), 6.60 (d, *J*=6.0 Hz, 1H), 5.12 (sept., *J*=6.1 Hz, 1H), 4.37 (qui., *J*=6.1 Hz, 1H), 2.49 (s, 3H), 1.76 (s, 3H), 1.45 (d, *J*=6.9 Hz, 3H), 1.10 (d, *J*=6.1 Hz, 3H), 0.92 (d, *J*=6.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 63 MHz): δ 168.6, 155.0, 143.1, 139.2, 138.8, 134.1, 134.0, 132.9, 132.1, 128.1, 127.9, 127.6, 126.7, 126.5, 126.3, 126.2, 126.0, 125.6, 124.8, 123.9, 112.1, 70.3, 49.1, 22.4, 21.7, 21.7, 21.5, 19.7. IR (KBr): ν 3447, 2928, 1649, 1519, 1102, 805 cm^{-1}. MS: *m*/*z* 437 (M^+, 26), 274 (100), 259 (9), 120 (22). Anal. calcd for $C_{30}H_{31}NO_2$: C, 82.34; H, 7.14; N, 3.20; found C, 81.82; H, 7.24; N, 2.94.

4.1.2. (*M*,*R*)-1-(2-Isopropoxy-4,6-dimethylphenyl)-*N*-methyl-*N*-(1-phenylethyl)naphthalene-2-carboxamide [(*M*,*R*)-10]. A suspension of the amide (*M*,*R*)-**9** (1.32 g, 2.94 mmol), MeI (19.8 mL, 835 mg, 5.88 mmol), NaOH (2.41 g, 60.3 mmol), NBu_4I (109 mg, 294 μmol), and K_2CO_3 (4.90 g, 1.23 mmol) in benzene (80 mL) was refluxed for 3 d. Aqueous NH_3 (2 N, 30 mL) was added at room temperature. After 30 min of stirring, the solvent was removed in vacuo, the residue was taken up in diethyl ether (30 mL) and filtered through a plug of celite. The crude product was purified by column chromatography (petroleum ether/diethyl ether=5:1) yielding (*M*,*R*)-**10** as white crystals; mp 156–158 °C. $[\alpha]_D^{20}$=+237.2 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 250 MHz): 5:1-mixture of interconverting rotational isomers with respect to the N–C=O–bond; major isomer: δ 7.91–7.86 (m, 2H), 7.51–7.29 (m, 4H), 7.19–7.16 (m, 3H), 6.83 (br., 3H), 6.62 (s, 1H), 6.02 (q, *J*=7.0 Hz, 1H), 4.25 (sept., *J*=6.1 Hz, 1H), 2.49 (s, 6H), 2.05 (s, 3H), 1.55 (d, *J*=7.0 Hz, 3H), 0.77 (d, *J*=6.1 Hz, 3H), 0.71 (d, *J*=6.1 Hz, 3H); minor isomer: δ 7.81–7.74 (m, 2H), 6.67 (s, 1H), 5.16 (q, *J*=7.0 Hz, 1H), 4.40 (sept., *J*=6.1 Hz, 1H), 2.41 (s, 6H), 2.07 (s, 3H), 0.98 (d, *J*=6.1 Hz, 3H), 0.86 (d, *J*=6.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 63 MHz): major isomer: δ 171.2, 155.6, 141.6, 140.3, 138.4, 138.2, 133.1, 132.9, 132.4, 128.5, 127.8, 127.4, 127.0, 126.4, 126.2, 126.0, 125.9, 124.3, 123.5, 123.0, 110.6, 69.3, 49.4, 30.9, 21.9, 21.7, 21.5, 20.4, 15.4; minor isomer: δ 171.9, 140.6, 140.2, 134.5, 133.1, 132.6, 127.9, 127.1, 126.7, 126.6, 124.0, 123.5, 111.3, 69.9, 55.6, 27.8, 22.8, 22.0, 21.5, 19.3. IR (KBr): ν 3025, 2973, 2922, 1635, 1618, 1449, 1312, 1117, 1083, 817, 758, 703, 597 cm^{-1}. MS: *m*/*z* 451 (M^+, 73), 408 (8), 392 (4), 274 (100). Anal. calcd for $C_{31}H_{33}NO_2$: C, 82.45; H, 7.36; N, 3.10; found C, 81.69; H, 7.06; N, 2.99.

4.1.3. (*M*,*R*)-1-(2-Isopropoxy-4,6-dimethylphenyl)-2-[*N*-methyl-*N*-(1-phenylethyl)aminomethyl]naphthalene [(*M*,*R*)-11]. To a solution of (*M*,*R*)-**10** (1.36 g, 2.94 mmol) in THF (80 mL), LAH (1.12 g, 29.4 mmol) was added and the reaction was stirred for 3 h. After hydrolysis with 0.1 N HCl (20 mL), the aqueous phase was extracted with diethyl ether (100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by chromatography on silica gel (petroleum ether/diethyl ether=3:1→diethyl ether) afforded (*M*,*R*)-**11** (1.23 g, 2.65 mmol, 90%) as a colorless oil; $[\alpha]_D^{20}$=+23.8 (*c* 1.25, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.86–7.80 (m, 3H), 7.40–7.10 (m, 8H), 6.76 (s, 1H), 6.64 (s, 1H), 4.21 (sept., *J*=6.1 Hz, 1H), 3.49 (q, *J*=6.7 Hz, 3H, NC*H*CH_3), 3.38 (d, *J*=14 Hz, 1H), 3.31 (d, *J*=14 Hz, 1H), 2.42 (s, 3H), 2.02 (s, 3H), 1.77 (s, 3H), 1.24 (d, *J*=6.7 Hz, 3H), 0.85 (d, *J*=6.1 Hz, 3H), 0.76 (d, *J*=6.1 Hz, 3H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 155.7, 145.4, 138.6, 137.7, 136.2, 134.3, 132.6, 128.0, 127.7, 127.5, 126.9, 126.7, 126.5, 125.9, 125.3, 125.1, 124.7, 122.7, 111.8, 69.5, 63.2, 56.3, 38.8, 30.9, 21.8, 21.7, 20.0, 18.1. IR (neat): ν 3050, 2970, 1605, 1450, 1308, 1114, 1069, 817, 760, 698 cm^{-1}. MS: *m*/*z* 437 (70, M^+), 422 (73), 332 (34), 303 (95), 259 (100), 43 (3). MS (EI) exact mass calcd for: $C_{31}H_{35}NO$: 437.2719; found 437.2711.

4.1.4. (*M*,*R*)-1-(2-Hydroxy-4,6-dimethylphenyl)-2-[*N*-methyl-*N*-(1-phenylethyl)aminomethyl]naphthalene [(*M*,*R*)-12]. (*M*,*R*)-**11** (524 mg, 1.20 mmol) was dissolved in HBr (20 mL, 48% in HOAc) and heated to reflux

overnight. The solvent was removed under reduced pressure, and the residue was dissolved in MeOH (20 mL) and filtered through a plug of basic alumina (activity 3). Purification by column chromatography (silica gel, petroleum ether/ethyl acetate=1:1) gave (*M*,*R*)-**12** (430 mg, 1.09 mmol, 91%) as a yellow oil; $[\alpha]_D^{20}=-25.8$ (*c* 1.2, $CHCl_3$). ^1H NMR (400 MHz, acetone-d_6): δ 8.12 (s, br., 1H), 7.91–7.88 (m, 2H), 7.78 (d, *J*=12.8 Hz, 1H), 7.44–7.19 (m, 8H), 6.61 (s, 2H), 3.59 (q., *J*=6.8 Hz, 1H), 3.56 (d, *J*=12.1 Hz, 1H), 3.35 (d, *J*=12.1 Hz, 1H), 2.36 (s, 3H), 2.07 (s, 3H), 1.71 (s, 3H), 1.26 (d, *J*=6.8 Hz, 3H). ^{13}C NMR (100 MHz, acetone-d_6): δ 156.0, 144.5, 139.0, 138.7, 136.9, 135.3, 134.1, 133.9, 128.9, 128.8, 128.7, 128.0, 127.7, 126.7, 126.4, 126.1, 123.9, 123.2, 116.0, 64.2, 57.4, 38.8, 21.4, 20.2, 18.3. IR (neat): ν 3057, 2971, 2913, 2846, 1614, 1565, 1494, 1312, 1154, 1048, 838, 809, 762, 702 cm^{-1}. MS: *m*/*z* 395 (M^+, 11), 380 (10), 291 (34), 303 (95), 259 (100). MS (EI) exact mass calcd for: $C_{28}H_{29}NO$ 395.2256; found 395.2257.

4.2. General procedure for the preparation of the arylsulfonic esters (*M*,*R*)-17 and (*M*,*R*)-18

The aminoalcohol (*M*,*R*)-**12** (1.0 equiv.) was treated at 0 °C in dry dichloromethane [5 mL/mmol (*M*,*R*)-**12**] with triethylamine (1.5 equiv.) and *p*-toluenesulfonic acid or *p*-bromophenylsulfonic acid (1.1 equiv.). The reaction mixture was stirred overnight and the solvent was removed in vacuo. The crude product was chromatographed on silica gel (petroleum ether/diethyl ether=5:1) to give (*M*,*R*)-**17** or (*M*,*R*)-**18**.

4.2.1. (*M*,*R*)-2-[*N*-Methyl-*N*-(1-phenylethyl)aminomethyl]-1-(2-(4-methylbenzenesulfonyloxy)-4,6-dimethylphenyl)]naphthalene [(*M*,*R*)-17]. Yield: 53%. $[\alpha]_D^{20}=+17.1$ (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, acetone-d_6): δ 7.89 (s, 1H), 7.87 (s, 1H), 7.78 (d, *J*=8.2 Hz, 1H), 7.44 (t, *J*=7.1 Hz, 1H), 7.31–7.23 (m, 8H), 7.01 (d, *J*=8.4 Hz, 1H), 6.88–6.83 (m, 4H), 1.19 (d, *J*=6.1 Hz, 3H), 3.41 (q, *J*=6.1 Hz, 1H), 3.35 (s, 2H), 2.49 (s, 3H), 2.27 (s, 3H), 1.94 (s, 3H), 1.81 (s, 3H). ^{13}C NMR (400 MHz, acetone-d_6): δ 148.8, 145.6, 145.4, 140.5, 139.7, 137.4, 134.1, 133.6, 133.0, 132.5, 130.7, 130.1, 129.9, 128.9, 128.7, 128.5, 128.2, 127.8, 127.7, 127.5, 126.8, 126.3, 125.9, 120.7, 64.4, 57.5, 38.9, 21.5, 21.2, 20.2, 18.8. IR (neat): ν 3058, 3029, 2973, 2924, 2844, 2782, 1618, 1598, 1493, 1451, 1370, 1284, 1191, 1178, 1155, 1093, 1027, 946, 855, 815, 777, 701, 669 cm^{-1}. MS: *m*/*z* 549 (M^+, 19), 534 (41), 272 (7), 260 (100). MS (EI) exact mass calcd for $C_{35}H_{35}NO_3S$: 549.2338; found 549.2338.

4.2.2. (*M*,*R*)-1-(2-(4-Bromobenzene sulfonyloxy-4,6-dimethylphenyl)-2-[*N*-methyl-*N*-(1-phenylethyl)aminomethyl]naphthalene [(*M*,*R*)-18]. Yield: 40%. $[\alpha]_D^{20}=+29.6$ (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.78–7.68 (m, 3H), 7.40 (t, *J*=7.08 Hz, 1H), 7.32–7.26 (m, 5H), 7.24–7.19 (m, 2H), 7.12 (s, 1H), 6.98 (d, *J*=8.5 Hz, 1H), 6.90 (d, *J*=8.7 Hz, 2H), 6.65 (d, *J*=8.6 Hz, 2H), 3.41 (q, *J*=6.7 Hz, 1H), 3.33 (d, *J*=13.9 Hz, 1H), 3.24 (d, *J*=13.9 Hz, 1H), 2.48 (s, 3H), 1.91 (s, 3H), 1.78 (s, 3H), 1.20 (d, *J*=6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.7, 144.7, 139.7, 138.9, 136.7, 134.8, 132.4, 132.1, 131.3, 131.2, 129.4, 128.2, 128.1, 127.9, 127.8, 127.6, 127.5, 127.0, 126.7, 126.1, 125.5, 125.2, 120.7, 63.5, 56.7, 38.4, 21.3, 20.0, 18.2. IR (neat): ν 3060, 2970, 2925, 2846, 2782, 1641, 1620, 1576, 1453, 1374, 1281, 1190, 1092, 1068, 1027, 947, 788 cm^{-1}. MS: *m*/*z*: 615/613 (9/9, M^+), 600/598 (25/23), 510/508 (7/7), 260 (100), 105 (39). MS (EI) exact mass calcd for $C_{34}H_{32}BrNO_3S$: 613.12862; found 613.12755.

4.2.3. (*M*,*R*)-1-[2-(3,3,3-Trifluoro-2-methoxy-2-phenylpropanoyloxy)-4,6-dimethylphenyl]-2-[*N*-methyl-*N*-(1-phenylethyl)aminomethyl]naphthalene [(*M*,*R*)-20]. A solution of (*M*,*R*)-**12** (50.0 mg, 126 μmol), (*R*)-Mosher acid (32.1 mg, 138 μmol), 29.0 mg DCC (138 μmol), and a catalytic amount of DMAP in dry dichloromethane (2 mL) was stirred for 12 h. The precipitate was filtered off, the mixture concentrated in vacuo and the crude product purified by column chromatography (silica gel, diethyl ether) to give (*M*,*R*)-**20** (65.1 mg, 106 μmol, 84%) as a yellow oil; $[\alpha]_D^{20}=+4.0$ (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.79–7.85 (m, 3H), 7.18–7.43 (m, 9H), 7.12 (s, 1H), 7.03 (t, *J*=7.8 Hz), 6.87 (s, 1H), 6.81 (d, *J*=7.8 Hz), 3.40 (q, *J*=6.6 Hz, 1H), 3.29 (d, *J*=13.9 Hz, 1H), 3.24 (d, *J*=13.9 Hz, 1H), 2.77 (s, 3H), 2.46 (s, 3H), 1.91 (s, 3H), 1.86 (s, 3H), 1.11 (d, *J*=6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.7, 165.0, 148.4, 144.7, 139.5, 138.6, 136.7, 132.7, 132.3, 131.8, 131.5, 129.7, 129.2, 129.0, 128.7, 128.1, 128.0, 127.8, 127.7, 127.5, 127.2, 126.9, 126.6, 126.2, 125.7, 125.4, 124.3, 119.7, 63.4, 56.4, 54.6, 38.6, 29.7, 29.0, 21.3, 19.8, 17.8. IR (neat): ν 3060, 2930, 2854, 1763, 1741, 1712, 1652, 1620, 1508, 1495, 1451, 1360, 1346, 1267, 1228, 1185, 1120, 1080, 1032, 1002, 891, 864, 817, 764, 746, 727, 700 cm^{-1}. MS: *m*/*z* 611 (1, M^+), 189 (17), 83 (100). MS (EI) exact mass calcd for $C_{38}H_{36}F_3NO_3$: 611.2647; found 611.2647.

4.2.4. (*M*)-2-Bromomethyl-1-(2-methoxy-4,6-dimethylphenyl)naphthalene [(*M*)-23]. A suspension of (*M*)-2-hydroxymethyl-1-(2-hydroxy-4,6-dimethylphenyl)naphthalene[12] (320 mg, 1.15 mmol), methyl iodide (220 μL, 490 mg, 3.45 mmol), and Cs_2CO_3 (318 mg, 2.30 mmol) in acetone (20 mL) was stirred for 12 h at room temperature. The solvent was removed in vacuo and the residue purified by column chromatography (silica gel, petroleum ether/ ethyl ether=10:1→1:1) to give a colorless oil, which was dissolved in dichloromethane (10 mL). PPh_3 (520 mg, 1.98 mmol) and $(CBrCl_2)_2$ (646 mg, 1.98 mmol) were added. After 1 h of stirring, the solvent was removed in vacuo and the resulting oil was filtered through a plug of silica gel. Crystallization from dichloromethane/petroleum ether delivered (*M*)-**23** (350 mg, 986 μmol, 99%) as pale yellow needles; mp 148–149 °C. $[\alpha]_D^{20}=+35.1$ (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.87–7.84 (m, 2H), 7.64 (d, *J*=8.4 Hz, 1H), 7.47–7.43 (m, 1H), 7.34–7.30 (m, 2H), 6.82 (s, 1H), 6.71 (s, 1H), 4.41 (d, *J*=9.8 Hz, 1H), 4.37 (d, *J*=9.8 Hz, 1H), 3.60 (s, 3H), 1.83 (s, 3H), 1.49 (s, 3H). ^{13}C NMR (100 MHz, CDCl3): δ 157.2, 138.9, 138.6, 135.2, 133.3, 133.1, 132.5, 128.1, 127.5, 126.4, 126.2, 126.1, 123.4, 122.5, 109.3, 55.6, 33.1, 21.8, 19.9. IR (KBr): ν 3050, 3025, 2912, 1610, 1575, 1460, 1313, 1238, 830, 761 cm^{-1}. MS: *m*/*z* 356/354 (22/23, M^+), 275 (100), 260 (47), 245 (26), 229 (21). Anal. calcd for $C_{20}H_{19}BrO$: C, 67.61; H, 5.39; found C, 68.05; H, 5.67.

4.2.5. (*P*)-2-Bromomethyl-1-(2-methoxy-4,6-dimethylphenyl)naphthalene [(*P*)-23]. In an analogous way, (*P*)-**23** was prepared from (*P*)-2-hydroxymethyl-1-(2-hydroxy-4,6-dimethylphenyl)naphthalene[12] according to procedure 4.9. $[\alpha]_D^{20}=-35.4$ (*c* 1.0, $CHCl_3$). All other spectroscopic and physical data were identical to those of (*M*)-**23**.

4.3. General procedure for the preparation of different amines from the bromides (*M*)-14, (*M*)-23, and (*P*)-23

To a solution of (*M*)-**14**, (*M*)-**23**, or (*P*)-**23** in dichloromethane (2–4 mL/mmol bromide) the respective amine (2.0 equiv.) was added. The reaction mixture was stirred until complete conversion was detected by TLC (deactivated silica gel, petroleum ether/diethyl ether=5:1). The solution was made alkaline with 2 N NaOH and was exhaustively extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$ and the solvent was removed in vacuo. Purification of the crude product by column chromatography (petroleum ether/diethyl ether=10:1) gave the desired amine.

4.3.1. (*M*)-1-(2-Benzyloxy-4,6-dimethylphenyl)-2-(*N*-benzylaminomethyl)naphthalene [(*M*)-13]. Yield: 53%. Characterized as the hydrobromide (*M*)-**13**·HBr. Mp 174 °C (dichloromethane/petroleum ether). $[\alpha]_D^{20}=+39.4$ (*c* 0.9, $CHCl_3$). ^{1}H NMR (400 MHz, actone-d_6): δ 7.92–7.90 (m, 2H), 7.81 (d, *J*=8.6 Hz, 1H), 7.45–7.41 (m_c, 1H), 7.36–7.29 (m, 2H), 7.24–7.16 (m, 5H), 7.11–7.05 (m, 3H), 6.91–6.86 (m, 4H), 4.93 (d, *J*=12.4 Hz, 1H), 4.88 (d, *J*=12.4 Hz, 1H), 3.66–3.64 (m, 4H), 2.40 (s, 3H), 1.80 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 156.2, 139.6, 138.4, 137.1, 135.2, 134.3, 133.0, 132.7, 128.2, 128.1, 128.0, 127.4, 127.3, 126.8, 126.4, 125.9, 125.7, 125.3, 124.6, 124.0, 111.7, 70.1, 53.2, 51.6, 21.7, 19.7. IR (neat): ν 3057, 3031, 2920, 2852, 1607, 1569, 1449, 1313, 1163, 1091, 817, 694 cm^{-1}. MS: *m*/*z* 457 (M^+, 15), 366 (54), 350 (26), 246 (7), 91 (100). Anal. calcd for $C_{33}H_{31}NO$·HBr: C, 73.60; H, 5.99; N, 2.60; found C, 74.31; H, 6.04; N, 2.80.

4.3.2. (*M*,*R*)-1-(2-Benzyloxy-4,6-dimethylphenyl)-2-[*N*-(1-phenylethyl)amino-methyl]naphthalene [(*M*,*R*)-15]. Yield: 82%. $[\alpha]_D^{20}=+59.3$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88–7.83 (m, 2H), 7.57 (d, *J*=8.3 Hz, 1H), 7.44–7.41 (m_c, 1H), 7.39–7.32 (m, 1H), 7.29–7.04 (m, 7H), 6.81–6.72 (m, 4H), 4.78 (s, 2H), 3.60 (q, *J*=6.5 Hz, 1H), 3.51 (d, *J*=12.6 Hz, 1H), 3.47 (d, *J*=12.6 Hz, 1H), 2.43 (s, 3H), 1.79 (s, 3H), 1.13 (d, *J*=6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.4, 145.8, 138.32, 138.26, 137.2, 136.3, 134.2, 132.9, 132.8, 128.2, 128.1, 127.9, 127.18, 127.16, 126.6, 126.3, 125.7, 125.1, 124.7, 123.8, 111.4, 69.8, 57.5, 50.4, 24.3, 21.7, 19.7. IR (neat): ν 3057, 2960, 2920, 1610, 1573, 1493, 1452, 1375, 1315, 1165, 1095, 820, 736 cm^{-1}. MS: *m*/*z*: 471 (M^+, 31) [M^+], 456 (13), 380 (27), 350 (35), 259 (88), 91 (100). Anal. calcd for $C_{34}H_{33}NO$: C, 86.59; H, 7.05; N, 2.97; found C, 87.40; H, 7.15; N, 2.85.

4.3.3. (*M*,*S*)-1-(2-Benzyloxy-4,6-dimethylphenyl)-2-[*N*-(1-phenylethyl)aminomethyl]naphthalene [(*M*,*S*)-15]. Yield: 71%. Characterized as the hydrobromide (*M*,*S*)-**15**·HBr. Mp 156 °C (dichloromethane/petroleum ether). $[\alpha]_D^{20}=+31.4$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, acetone-d_6): δ 7.92–7.88 (m, 2H), 7.70 (d, *J*=8.3 Hz, 1H), 7.45–7.41 (m_c, 1H), 7.36–7.08 (m, 10H), 6.91–6.86 (m, 4H), 4.87 (s, 2H), 3.65 (q, *J*=6.5 Hz, 1H), 3.49 (d, *J*=12.4 Hz, 1H), 3.42 (d, *J*=12.4 Hz, 1H), 2.41 (s, 3H), 1.78 (s, 3H), 1.16 (d, *J*=6.5 Hz, 3H). ^{13}C NMR (100 MHz, acetone-d_6): δ=157.2, 147.0, 139.1, 138.5, 137.7, 133.9, 133.5, 129.0, 128.9, 128.5, 128.1, 127.9, 127.4, 127.33, 127.28, 126.6, 126.3, 126.0, 125.4, 124.4, 111.2, 70.4, 59.0, 51.0, 25.2, 21.7, 20.0. IR (neat): ν 3400, 3012, 2999, 2915, 2895, 1592, 1577, 1478, 1300, 1258, 1082, 1019, 811, 692 cm^{-1}. MS: *m*/*z* 471 (M^+, 43), 456 (23), 380 (29), 350 (43), 259 (100), 91 (84). Anal. calcd for $C_{34}H_{33}NO$·HBr: C, 73.91; H, 6.20; N, 2.53; found C, 73.96; H, 6.48; N, 2.69.

4.3.4. (*M*,*R*)-1-(2-Methoxy-4,6-dimethylphenyl)-2-[*N*-methyl-*N*-(1-phenylethyl)aminomethyl]naphthalene [(*M*,*R*)-24]. Yield: 84%. Characterized as the hydrochloride (*M*,*R*)-**24**·HCl. Mp 141 °C (dichloromethane/petroleum ether). $[\alpha]_D^{20}=-21.7$ (*c* 0.95, $CHCl_3$). ^{1}H NMR (400 MHz, acetone-d_6): δ 7.89–7.87 (m, 3H), 7.43–7.39 (m_c, 1H), 7.35–7.23 (m, 5H), 7.20–7.17 (m, 2H), 6.84 (s, 1H), 6.81 (s, 1H), 3.48 (s, 3H), 3.37 (d, *J*=13.6 Hz, 1H), 3.31 (d, *J*=13.6 Hz, 1H), 2.42 (s, 3H), 2.02 (s, 3H), 1.75 (s, 3H), 1.21 (d, *J*=6.6 Hz, 3H). ^{13}C NMR (100 MHz, acetone-d_6): δ 158.2, 146.0, 139.1, 138.8, 137.0, 135.0, 133.8, 133.5, 128.9, 128.2, 127.9, 127.7, 127.4, 126.5, 126.2, 125.8, 124.6, 123.8, 110.0, 64.0, 57.1, 55.5, 39.1, 21.7, 20.0, 18.4. IR (neat): ν 2929, 2853, 1612, 1573, 1451, 1314, 1239, 1165, 1097, 1028, 941, 830, 814, 763, 701 cm^{-1}. MS: *m*/*z* 409 (M^+, 40), 394 (45), 332 (7), 304 (19), 290 (17), 275 (100), 260 (38), 245 (18), 105 (25). Anal. calcd for $C_{29}H_{31}NO$·HCl: C, 78.09; H, 7.23; N, 3.14; found C, 78.64; H, 7.32; N, 3.18.

4.3.5. (*P*,*S*)-1-(2-Methoxy-4,6-dimethylphenyl)-2-[*N*-methyl-*N*-(1-phenylethyl)aminomethyl]naphthalene [(*P*,*S*)-24]. Characterized as the hydrochloride (*P*,*S*)-**24**·HCl. $[\alpha]_D^{20}=+18.9$ (*c* 0.5, $CHCl_3$). All other spectroscopic and physical data were identical to those of (*M*,*R*)-**24**·HCl.

4.3.6. (*M*,*S*)-1-(2-Methoxy-4,6-dimethylphenyl)-2-[*N*-methyl-*N*-(1-phenylethyl)aminomethyl]naphthalene [(*M*,*S*)-24]. Yield: 75%. Characterized as the hydrochloride (*M*,*S*)-**24**·HCl. Mp 129 °C (dichloromethane/petroleum ether). $[\alpha]_D^{20}=-103.8$ (*c* 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, *J*=8.1 Hz, 1H), 7.82 (d, *J*=8.6 Hz, 1H), 7.81 (d, *J*=8.1 Hz, 1H), 7.38–7.33 (m, 3H), 7.28–7.25 (m, 4H), 7.20–7.15 (m, 1H), 6.77 (s, 1H), 6.66 (s, 1H), 3.52 (s, 3H), 3.44 (q, *J*=6.7 Hz, 1H), 3.39 (d, *J*=13.6 Hz, 1H), 3.20 (d, *J*=13.6 Hz, 1H), 2.43 (s, 3H), 2.04 (s, 3H), 1.60 (s, 3H), 1.26 (d, *J*=6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.2, 145.2, 138.5, 138.0, 136.2, 133.9, 132.7, 132.5, 128.1, 127.9, 127.5, 127.0, 126.5, 125.6, 125.5, 124.9, 123.9, 123.0, 109.0, 63.7, 56.4, 55.2, 38.5, 21.7, 19.7, 18.6. IR (KBr): ν 3056, 3027, 2970, 2932, 1610, 1575, 1452, 1315, 1097, 909, 702 cm^{-1}. MS: *m*/*z* 409 (M^+, 41) [M^+], 394 (41), 275 (100). Anal. calcd for $C_{29}H_{31}NO$·HCl: C, 78.09; H, 7.23; N, 3.14; found C, 77.92; H, 7.33; N, 3.23.

4.3.7. (*M*,*S*)-1-(2-Methoxy-4,6-dimethylphenyl)-2-[*N*-methyl-*N*-(1-phenylethyl)aminomethyl]naphthalene [(*M*,*S*)-24]. Characterized as the hydrochloride (*M*,*S*)-**24**·HCl. $[\alpha]_D^{20}=+99.2$ (*c* 1.0 in $CHCl_3$). All other

spectroscopic and physical data were identical to those of (*P*,*R*)-**24**·HCl.

4.3.8. (*M*)-2-(*N*-Benzyl-*N*-methylaminomethyl)-1-(2-methoxy-4,6-dimethylphenyl)naphthalene [(*M*)-25]. Yield: 94%. Characterized as the hydrochloride (*M*)-**25**·HCl. Mp 126 °C (dichloromethane/petroleum ether). $[\alpha]_D^{20}=-29.1$ (*c* 0.7, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, *J*=8.2 Hz, 1H), 7.87–7.83 (m, 2H), 7.42–7.37 (m_c, 1H), 7.33–7.27 (m, 6H), 7.22 (d, *J*=6.7 Hz, 1H), 6.81 (s, 1H), 6.69 (s, 1H), 3.55 (s, 3H), 3.49–3.30 (m, 4H), 2.46 (s, 3H), 2.08 (s, 3H), 1.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.2, 139.9, 138.4, 138.1, 135.6, 134.0, 132.7, 132.5, 128.8, 128.1, 127.9, 127.2, 126.8, 126.7, 125.0, 123.9, 123.0, 109.1, 62.2, 59.3, 55.3, 42.4, 21.8, 19.7. IR (KBr): ν 3056, 3020, 2945, 2919, 1619, 1575, 1494, 1461, 1097, 789, 735 cm^{-1}. MS: *m*/*z* 395 (M^+, 68), 364 (8), 304 (40), 275 (37), 274 (100), 91 (51). Anal. calcd for $C_{28}H_{29}NO$·HCl: C, 77.85; H, 7.00; N, 3.24; found: C, 77.84; H, 7.21; N, 3.18.

4.3.9. (*P*)-2-(*N*-Benzyl-*N*-methylaminomethyl)-1-(2-methoxy-4,6-dimethylphenyl)naphthalene [(*P*)-25]. $[\alpha]_D^{20}=+27.6$ (*c* 1.0, $CHCl_3$). All other spectroscopic and physical data were identical to those of (*M*)-**25**.

4.4. General procedure for the debenzylation of the amines (*M*)-15

To a solution of the amine (*M*)-**15** in dichloromethane [10 mL/mmol (*M*)-**15**], a 1.0 M solution of BCl_3 in *n*-hexane (2.0 equiv.) was added at 0 °C. After 40 min of stirring, the reaction mixture was cautiously hydrolyzed with water [15 mL/mmol (*M*)-**15**], made alkaline with K_2CO_3, and exhaustively extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$ and the solvent was removed in vacuo. The resulting oily product (*M*)-**16** was purified by chromatography (petroleum ether/diethyl ether=1:1).

4.4.1. (*M*,*R*)-1-(2-Hydroxy-4,6-dimethylphenyl)-2-[*N*-(1-phenylethyl)amino-methyl]naphthalene [(*M*,*R*)-16]. Yield: 95%. Mp 132 °C (dichloromethane/petroleum ether). $[\alpha]_D^{20}=+13.2$ (*c* 1.2, $CHCl_3$). All other spectroscopic and physical data were identical to those reported in ref.[10]

4.4.2. (*M*,*S*)-1-(2-Hydroxy-4,6-dimethylphenyl)-2-[*N*-(1-phenylethyl)amino-methyl]naphthalene [(*M*,*S*)-16]. Yield: 69%. Mp 127 °C (dichloromethane/petroleum ether). $[\alpha]_D^{20}=+35.0$ (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J*=7.9 Hz, 1H), 7.82 (d, *J*=8.2 Hz, 1H), 7.48–7.39 (m_c, 1H), 7.38–7.23 (m_c, 8H), 6.90 (s, 1H), 6.79 (s, 1H), 3.74 (q, *J*=6.7 Hz, 1H), 3.58 (s, 2H), 2.42 (s, 3H), 1.71 (s, 3H), 1.35 (d, *J*=6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.4, 144.2, 138.6, 138.0, 135.0, 133.4, 133.1, 128.8, 128.3, 127.9, 127.4, 126.8, 126.5, 126.3, 126.2, 125.8, 124.7, 123.3, 118.1, 58.7, 51.4, 22.5, 21.3, 20.1. IR (KBr): ν 3500–2200, 3230, 3030, 2930, 2890, 2830, 1595, 1435, 1295, 1085, 1035, 805, 695. MS: *m*/*z*: 381 (M^+, 54) [M^+], 366 (40), 276 (39), 261 (100), 260 (75), 259 (69), 120 (22), 105 (32). Anal. calcd for $C_{27}H_{27}NO$: C, 85.00; H, 7.13; N, 3.67; found C, 85.39; H, 7.37; N, 3.65.

4.4.3. (*M*,*R*)-1-(2-Methoxymethoxy-4,6-dimethylphenyl)-2-[*N*-(1-phenylethyl)aminomethyl]naphthalene [(*M*,*R*)-21]. NaH (9.11 mg, 368 μmol) was added to a solution of (*M*,*R*)-**16** (70.4 mg, 184 μmol) in diethyl ether (10 mL). MOMCl (32 μL, 368 μmol) was added after 30 min and stirring was continued for 16 h. The solvent was removed in vacuo and the residue purified by column chromatography (petroleum ether/diethyl ether=2:1) to give (*M*,*R*)-**21** (62 mg, 146 μmol, 79%) as a yellowish oil; $[\alpha]_D^{20}=+79.5$ (*c* 0.8, $CHCl_3$). ^1H NMR (400 MHz, acetone-d_6): δ 7.91–7.88 (m, 2H), 7.74 (d, *J*=8.6 Hz, 1H), 7.44–7.40 (m_c, 1H), 7.34–7.14 (m, 7H), 6.96 (s, 1H), 6.85 (s, 1H), 4.87 (d, *J*=6.7 Hz, 1H), 4.80 (d, *J*=6.7 Hz, 1H), 3.68 (q, *J*=6.5 Hz, 1H), 3.45 (s, 2H), 2.93 (s, 3H), 2.41 (s, 3H), 1.72 (s, 3H), 1.22 (d, *J*=6.5 Hz, 3H). ^{13}C NMR (100 MHz, acetone-d_6): δ 156.0, 147.1, 139.1, 138.7, 137.7, 134.7, 133.8, 133.5, 129.1, 128.8, 128.3, 127.9, 127.3, 126.6, 126.2, 126.0, 125.7, 125.0, 113.9, 94.9, 58.8, 55.8, 50.6, 25.0, 21.7, 19.9. IR (neat): ν 3054, 2958, 2922, 2855, 1613, 1574, 1491, 1450, 1310, 1209, 1150, 1100, 1049, 991, 820, 757 cm^{-1}. MS: *m*/*z* 425 (M^+, 48), 410 (26), 380 (49), 320 (42), 259 (100), 105 (70). Anal. calcd for $C_{29}H_{31}NO_2$·HCl: C, 75.39; H, 6.98; N, 3.03; found C, 75.17; H, 6.65; N, 2.87.

4.4.4. (*M*,*R*)-1-(2-Acetoxy-4,6-dimethylphenyl)-2-[*N*-methyl-*N*-(1-phenylethyl)aminomethyl]naphthalene [(*M*,*R*)-22]. A solution of (*M*,*R*)-**16** (90.1 mg, 236 μmol), pyridine (38 μL, 472 μmol), and acetyl chloride (34 μL, 472 μmol) in dichloromethane (5 mL) was stirred at room temperature for 16 h, followed by hydrolysis with water (5 mL). After extraction with diethyl ether (20 mL), the combined organic layers were dried over $MgSO_4$, filtered, and evaporated in vacuo. The crude product was purified by column chromatography, affording (*M*,*R*)-**22** (41.3 mg, 97.6 μmol, 41%) as a colorless oil; $[\alpha]_D^{20}=+47.0$ (*c* 0.9, $CHCl_3$). ^1H NMR (400 MHz, acetone-d_6): δ 7.92–7.88 (m, 2H), 7.76 (d, *J*=8.6 Hz, 1H), 7.45–7.41 (m_c, 1H), 7.33–7.16 (m, 7H), 7.07 (s, 1H), 6.94 (s, 1H), 3.71 (q, *J*=6.6 Hz, 1H), 3.47 (d, *J*=12.9 Hz, 1H), 3.42 (d, *J*=12.9 Hz, 1H), 2.42 (s, 3H), 1.79 (s, 3H), 1.51 (s, 3H), 1.24 (d, *J*=6.6 Hz, 3H). ^{13}C NMR (100 MHz, acetone-d_6): δ 169.0, 150.1, 147.0, 139.3, 139.1, 137.9, 133.5, 133.0, 132.8, 129.6, 129.0, 128.9, 128.7, 128.4, 128.1, 127.3, 126.6, 126.5, 126.1, 121.8, 58.7, 50.0, 21.1, 20.2, 19.9. IR (neat): ν 3330, 3057, 2964, 2922, 2857, 1703, 1620. 1453, 1368, 1620, 1453, 1368, 1317, 1246, 1205, 1151, 1107, 1045, 871, 820, 758, 702 cm^{-1}. MS: *m*/*z* 423 (M^+, 20), 408 (30), 318 (100), 259 (37), 105 (37). MS (EI) exact mass calcd for $C_{29}H_{29}NO_2$: 423.2198; found 423.2194.

4.5. General procedure for the preparation of the aminotriflates 19 and 26

A solution of **24** or **25** in 48% aqueous HBr (5 mL/mmol amine) was refluxed for 6 h. The solvent was removed in vacuo, the residue dissolved in MeOH (5 mL/mmol amine) and passed through a plug of celite. The solvent was evaporated under reduced pressure and the residue was dissolved in dry dichloromethane (5 mL/mmol amine) under nitrogen at room temperature. DABCO (2.0 equiv.) and triflic anhydride (2.0 equiv.) were added. The reaction mixture was stirred at room temperature for 16 h, the solvent was removed in vacuo and the product was purified

by column chromatography (petroleum ether/diethyl ether=5:1).

4.5.1. (*M*,*R*)-1-(2-Trifluoromethanesulfonyloxy-4,6-dimethylphenyl)-2-[*N*-methyl-*N*-(1-phenylethyl)aminomethyl]naphthalene [(*M*,*R*)-19]. Yield: 71%. Mp 37 °C (diethyl ether/petroleum ether). $[\alpha]_D^{20}=-14.7$ (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, acetone-d_6): δ 8.00–7.93 (m, 2H), 7.85 (d, *J*=8.6 Hz, 1H), 7.45 (m_c, 1H), 7.41–7.36 (m, 2H), 7.29–7.28 (m, 4H), 7.26–7.18 (m, 3H), 3.46 (q, *J*=6.8 Hz, 1H), 3.39 (d, *J*=11.8 Hz, 1H), 3.35 (d, *J*=11.8 Hz, 1H), 2.52, (s, 3H), 2.01 (s, 3H), 1.90 (s, 3H), 1.21 (d, *J*=6.8 Hz, 3H). ^{13}C NMR (100 MHz, acetone-d_6): δ 148.7, 145.2, 141.7, 140.9, 137.5, 133.8, 133.0, 131.6, 131.2, 129.4, 129.3, 129.2 (q, J_{C-F}=324 Hz), 128.9, 128.3, 128.1, 127.6, 127.1, 126.4, 125.9, 119.7, 64.9, 57.6, 39.1, 21.1, 20.1, 19.1. IR (neat): ν 3005, 2912, 1592, 1395, 1202, 1120, 805 cm^{-1}. MS: *m*/*z* 527 (M^+, 16), 512 (38), 422 (7), 259 (100). Anal. calcd for $C_{29}H_{28}F_3NO_3S$: C, 66.02; H, 5.35; N, 2.65; S, 6.08; found C, 65.87; H, 5.48; N, 2.60; S, 5.94.

O-Triflation of the phenol (*M*,*R*)-**12** according to the general procedure 4.15 delivered (*M*,*R*)-**19** in 89% yield.

4.5.2. (*P*,*S*)-1-(2-Trifluoromethanesulfonyloxy-4,6-dimethylphenyl)-2-[*N*-methyl-*N*-(1-phenylethyl)aminomethyl]naphthalene [(*P*,*S*)-19]. $[\alpha]_D^{20}=+15.2$ (*c* 1.0, $CHCl_3$). All other spectroscopic and physical data were identical to those of (*M*,*R*)-**19**.

4.5.3. (*M*,*S*)-1-(2-Trifluoromethanesulfonyloxy-4,6-dimethylphenyl)-2-[*N*-methyl-*N*-(1-phenylethyl)aminomethyl]naphthalene [(*M*,*S*)-19]. Yield: 76%. $[\alpha]_D^{20}=+22.6$ (*c* 0.8, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.90–7.82 (m, 3H), 7.41 (m_c, 1H), 7.33–7.27 (m, 4H), 7.25–7.24 (m, 1H), 7.20–7.16 (m, 3H), 7.10 (s, 1H), 3.45 (q, *J*=6.5 Hz, 3H), 3.35 (d, *J*=13.9 Hz, 1H), 3.28 (d, *J*=13.9 Hz, 1H), 2.46 (s, 3H), 2.01 (s, 3H), 1.80 (s, 3H), 1.22 (t, *J*=6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.7, 144.6, 140.6, 139.4, 136.6, 132.8, 132.7, 132.1, 130.4, 130.1, 128.7, 128.6, 128.5, 128.0, 127.6, 127.5, 127.2, 127.0, 126.7, 126.4, 126.3, 126.1, 125.4, 125.3, 125.1, 119.0, 118.0, 63.6, 56.5, 38.5, 21.2, 19.8, 18.0. IR (neat): ν 3061, 3029, 2967, 2017, 1631, 1451, 1213, 938, 822 cm^{-1}. MS: *m*/*z* 527 (M^+, 41), 512 (100), 422 (17), 259 (74), 244 (65). Anal. calcd for $C_{29}H_{28}F_3NO_3S$: C, 66.02; H, 5.35; N, 2.65; S, 6.08; found C, 65.95; H, 5.49; N, 2.60; S, 5.94.

4.5.4. (*P*,*R*)-1-(2-Trifluoromethanesulfonyloxy-4,6-dimethylphenyl)-2-[*N*-methyl-*N*-(1-phenylethyl)aminomethyl]naphthalene [(*P*,*R*)-19]. $[\alpha]_D^{20}=-23.5$ (*c* 0.9, $CHCl_3$). All other spectroscopic and physical data were identical to those of (*M*,*S*)-**19**.

4.5.5. (*M*)-1-(2-Trifluoromethanesulfonyloxy-4,6-dimethylphenyl)-2-(*N*-benzyl-*N*-methylaminomethyl)naphthalene [(*M*)-26]. Yield: 82%. Mp 52 °C (diethyl ether/petroleum ether). $[\alpha]_D^{20}=-53.8$ (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, *J*=8.6 Hz, 1H), 7.98 (s, 1H), 7.95 (d, *J*=7.4 Hz, 1H), 7.48 (dt, *J*=7.0, 1.3 Hz, 1H), 7.39 (dt, *J*=7.0, 1.4 Hz, 2H), 7.32–7.30 (m, 7H), 3.46–3.39 (m, 3H), 3.36 (d, *J*=13.7 Hz, 1H), 2.53 (s, 3H), 2.07 (s, 3H), 1.90 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.6, 141.4, 141.0, 140.3, 137.1, 133.9, 133.0, 131.7, 131.2, 129.6, 129.5, 129.2, 129.0, 127.7, 127.2, 126.5, 126.0, 120.5, 119.9, 119.3 (q, J_{C-F}=319 Hz), 63.2, 60.3, 42.5, 21.2, 20.0. IR (neat): ν 3058, 3033, 2924, 2839, 1621, 1556, 1511, 1496, 1225, 945, 822 cm^{-1}. MS: *m*/*z* 513 (M^+, 29), 422 (24), 259 (100), 91 (49). Anal. calcd for $C_{28}H_{26}F_3NO_3S$: C, 65.48; H, 5.10; N, 2.73; S, 6.24; found C, 65.73; H, 5.40; N, 2.59; S, 5.91.

4.5.6. (*P*)-1-(2-Trifluoromethanesulfonyloxy-4,6-dimethylphenyl)-2-(*N*-benzyl-*N*-methylaminomethyl)naphthalene [(*P*)-26]. $[\alpha]_D^{20}=+48.5$ (*c* 0.8, $CHCl_3$). All other spectroscopic and physical data were identical to those of (*M*)-**26**.

4.6. Biological testing

4.6.1. *Trypanosoma cruzi*. Rat skeletal myoblasts (L-6 cells) were seeded in 96-well microtiter plates at 2000 cells/well/100 μL in RPMI 1640 medium with 10% FBS and 2mM L-glutamine. After 24 h of incubation at 37 °C in 5% CO_2 in air, 50 μL of a trypanosome suspension containing 5000 trypomastigote *T. cruzi* [Tulahuen C2C4 strain, containing the β-galactosidase (Lac Z) gene] from culture were added to the wells. 48 h later the medium was removed from the wells and replaced by 100 μL fresh medium with or without a serial drug dilution. Seven 3-fold dilutions were used covering a range from 90 μg/mL to 0.123 μg/mL. Each drug was tested in duplicate. Active compounds were tested twice for confirmation. After 96 h of incubation the plates were inspected under an inverted microscope to assure growth of the controls and sterility. Then the substrate CPRG/Nonidet (50 μL) was added to all wells. The color reaction that developed during the following 2–4 h was read photometrically at 540 nm. Data were transferred into a graphic program (e.g., EXCEL), sigmoidal inhibition curves determined and IC_{50} values calculated.[13]

4.6.2. Cytotoxicity. Cytotoxicity was assessed in the same assay using noninfected L-6 cells and the same serial drug dilution. The MIC was determined microscopically after 4 d.

4.7. Crystallographic part

4.7.1. Crystal structure of (*M*,*R*)-9·EtOH. Crystals of (*M*,*R*)-**9**·EtOH suited for an X-ray structure analysis were obtained from EtOH. The data were collected on a Bruker AXS P4-diffractometer using a graphite monochromated Mo K_α radiation (λ=0.71073 Å) at room temperature. The structure was solved by direct methods and refined by full-matrix anisotropic least square calculations with the aid of the programs SHELXS[14] and SHELXL,[14] respectively.

4.7.2. Crystal structure of (*M*,*R*)-19. Crystal data for compound (*M*,*R*)-**19** were collected from a shock cooled crystal on a BRUKER SMART-APEX diffractometer with a D8-goniometer (graphite Mo K_α radiation, λ=0.71073 Å) equipped with a low temperature device[15] in ω-scan mode at 100(2) K. The data were integrated with SAINT[16] and an empirical adsorption correction was applied (SADABS).[17] The structure was solved by direct methods (SHELXS97)[18]

and refined by full matrix least square calculations against F^2 (SHELXL97).[19] All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were assigned ideal positions using a riding model with U_{iso} constrained to 1.2 (and 1.5) times U_{eq} value of the parent atom.

Crystallographic data (excluding structure factors) reported in this publication have been deposited with Cambridge Crystallographic Data Center as supplementary publication no. CCDC-226172. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: (internat.) +44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk].

Acknowledgements

This work was supported by the Deutsche Forschungsgemeinschaft (SFB 630 'Recognition, Preparation, and Functional Analysis of Agents against Infectious Diseases', by the Ministry of Research (Center of Excellence BIOTEC-marin, by the Fonds der Chemischen Industrie, by the Freistaat Bayern (research fellowship for R.-M.P.), and by the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR). The technical assistance of Elke Gobright is highly acknowledged.

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