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Synthetic Approaches to Amino Analogues of *N*-Acetylcolchinol

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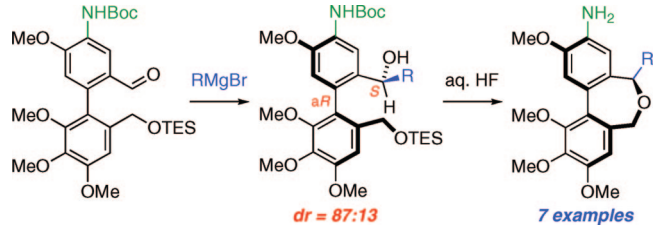
Received March 25, 2009



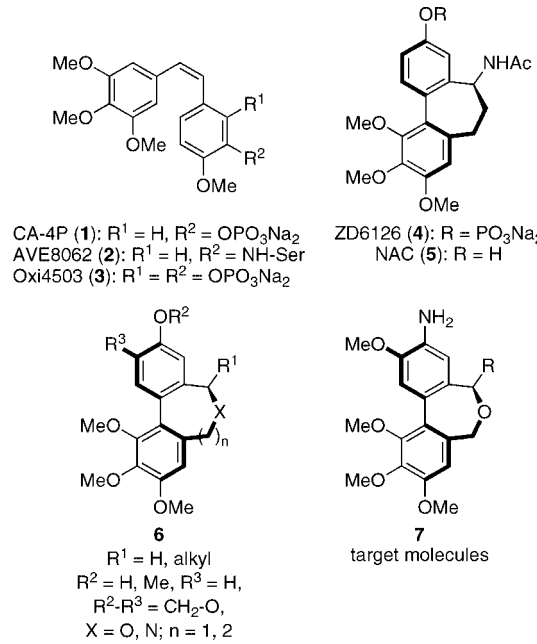
A straightforward synthesis of aminodibenzoxepines, new analogues of *N*-acetylcolchinol, is reported by using two different strategies. The first strategy involves a Grignard addition, a biaryl Suzuki−Miyaura coupling, and a HF-mediated cyclodehydration as key steps. A second strategy, better adapted to the synthesis of analogues bearing a benzylic substituent, was designed by inverting the order of the Grignard addition and the biaryl coupling. This allowed the rapid and reliable production of a series of substituted aminodibenzoxepines. A chelate model was proposed to account for the diastereoselectivity observed in the Grignard addition step.

Introduction

Vascular-disrupting agents (VDAs) are promising anticancer molecules which act by damaging existing tumor vasculature.[1] Among VDAs, compounds that bind to tubulin at the colchicine or vinblastin site and cause microtubule depolymerization showed promising in vitro and in vivo activities.[2] In particular, two series of prodrugs of molecules that bind to the colchicine site have undergone clinical trials (Chart 1): prodrugs of the natural products combretastatin A-1 and A-4 (**1**−**3**) and the allocolchicinoid ZD6126 (**4**), a prodrug of *N*-acetylcolchinol (NAC, **5**).[3]

Whereas the development of combretastatin analogues as VDAs has been the subject of extensive research in the past few years,[4] allocolchicinoid-type molecules have attracted much less attention. This is probably due to synthetic issues, as allocolchicinoids are less readily available than combretastatin

CHART 1



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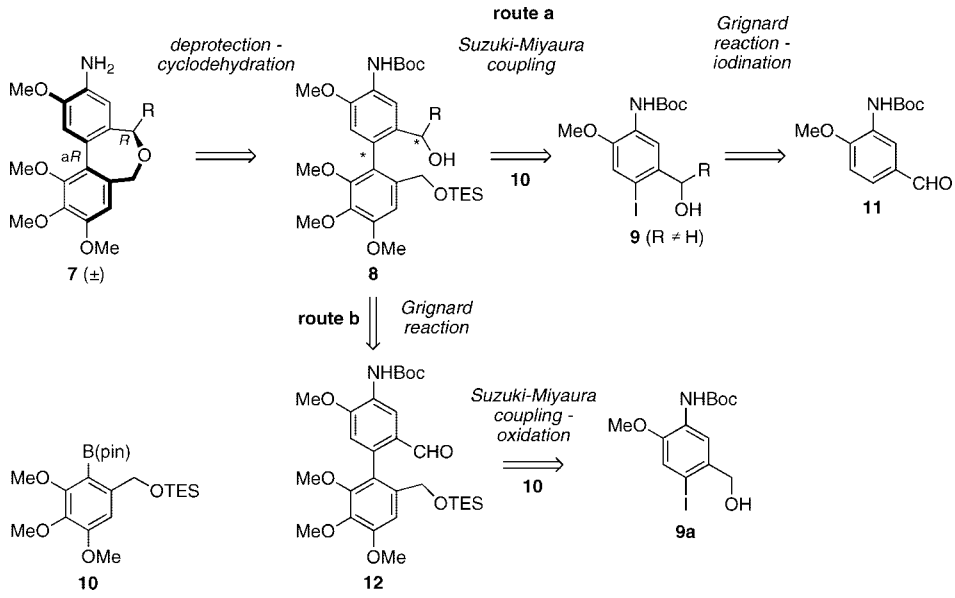
10.1021/jo900632a CCC: $40.75 © 2009 American Chemical Society
Published on Web 05/07/2009

SCHEME 1



analogues. NAC (**5**) itself is derived from colchicine by semisynthesis,[5] a synthetic procedure that intrinsically delivers a limited number of analogues.[6,7] Short and efficient total syntheses of allocolchicinoids that allow the introduction of a variety of functional groups on different parts of the molecule are therefore highly desirable in this context.[8] We recently reported on the racemic and enantioselective synthesis of analogues of NAC having a heterocyclic medium ring (**6**).[9] The most active analogues (R^1 = H or Et, R^2 = Me, R^3 = H, X = O, n = 1) showed activity profiles similar to that of NAC in various in vitro assays.[9c] To further increase the potency and at the same time improve the bioavailability of these molecules, we decided to synthesize the new aminodibenzoxepine analogues **7**. The amino group was chosen to improve the bioavailability by analogy with combretastatin analogues.[10] In addition, preliminary molecular modeling studies[11] indicated that compounds **7** with benzylic substituents (R) of various size could be well accommodated within the colchicine binding pocket of tubulin.[12]

Our retrosynthetic analysis of the target aminodibenzoxepines **7** is depicted in Scheme 1. Following our previous reports,[9] **7** would arise from polyfunctionalized biphenyls **8** by deprotection and cyclodehydration. Whereas dibenzoxepines such as **7** exist as conformational mixtures of a*R* and a*S* atropisomers due to the presence of the 7-membered bridging ring, biphenyls **8** contain two stereogenic elements, i.e., the benzylic stereocenter and the biaryl axis, since there is a much higher rotational barrier in a nonbridged triortho-substituted biaryl system.[9,13] Biphenyls **8** would arise from iodides **9** by Suzuki−Miyaura coupling with boronate **10** as previously described (route a). We have shown that this coupling occurs with moderate to good atropodiastereoselectivity depending on the size of the R group (R = alkyl).[9,13,14] However, both diastereoisomers were converted to the racemic dibenzoxepines (**6**, X = O, n = 1, Chart 1) by cyclodehydration due to the absence of the stereogenic character of the biaryl axis in these bridged biaryls. In turn, iodides **9** would arise from aldehyde **11** by Grignard reaction followed by regioselective iodination. Even though this synthetic route proved applicable to a number of allocolchicinoids **6**, we were concerned about the early introduction of the R benzylic substituent, which is little compatible with diversity-oriented synthesis purposes. In addition, we have shown that the yield and diastereoselectivity of the biaryl coupling from iodoarenes such as **9** rapidly decrease with increasing sizes of the R alkyl group.[9c] We thus considered an alternative pathway (route b,

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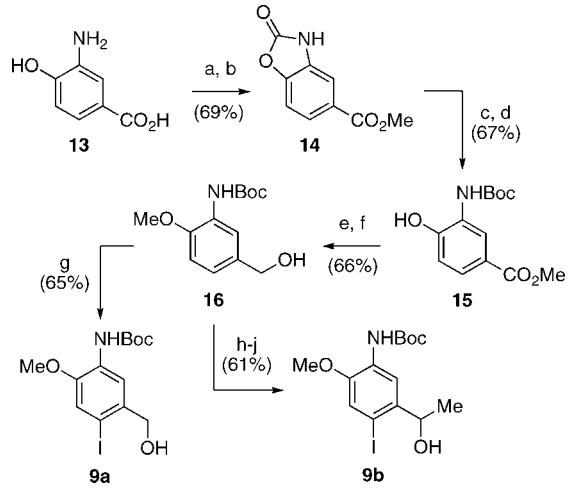
SCHEME 2[a]



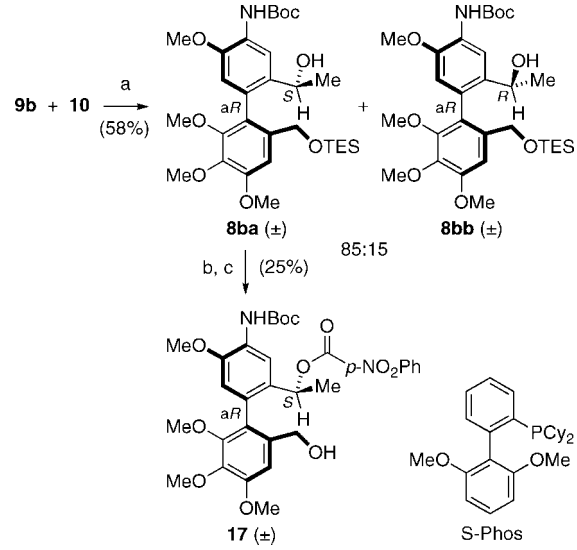
[a] Reaction conditions: (a) AcCl, MeOH, reflux (99%); (b) CDI (2.0 equiv), Et_3N (1.0 equiv), CH_2Cl_2, reflux (70%); (c) Boc_2O (1.05 equiv), Et_3N (2.0 equiv), DMAP (0.1 equiv), THF, 20 °C (95%); (d) Cs_2CO_3 (0.5 equiv), MeOH, 20 °C (71%); (e) MeI (3.0 equiv), K_2CO_3 (3.0 equiv), CH_3CN, 20 °C (91%); (f) DIBALH (4.0 equiv), THF, −78 °C (73%); (g) I_2 (1.0 equiv), CF_3CO_2Ag (1.0 equiv), $CHCl_3$, 0 °C (65%); (h) TPAP (0.02 equiv), NMO (1.5 equiv), CH_2Cl_2, 20 °C (96%); (i) MeMgBr (3.0 equiv), THF, −78 °C (79%); (j) I_2 (1.05 equiv), CF_3CO_2Ag (1.1 equiv), $CHCl_3$, 0 °C (81%). CDI = 1,1′-carbonyldiimidazole, TPAP = tetrapropylammonium perruthenate.

Scheme 1) where biphenyl **8** would arise from aldehyde **12** by Grignard addition, and **12** would be obtained by Suzuki−Miyaura coupling of iodide **9a** and boronate **10** followed by oxidation. Moreover, this new route raised an interesting question on the diastereoselectivity of the Grignard addition with regard to the previous route a. In this paper, we report on the synthesis of various aminodibenzoxepines **7** by route b, and address these diastereoselectivity issues by comparison with route a.

Results and Discussion

1. Comparison of Pathways a and b. For the purpose of comparing routes a and b (Scheme 1), the two iodoarene precursors **9a** and **9b** (i.e., **9** with R = Me) were synthesized from the common primary alcohol precursor **16** (Scheme 2). The synthesis commenced with the esterification of commercially available carboxylic acid **13**,[15] followed by formation of a cyclic carbamate with CDI, which gave ester **14** in 69% overall yield. Ester **14** was converted to the orthogonally functionalized phenol **15** by installation of a Boc group on the carbamate nitrogen and selective cleavage of the cyclic carbamate with methanolic cesium carbonate (67% yield for two steps).[16] The methylation of phenol **15**, followed by the reduction of the ester group with DIBALH furnished the pivotal alcohol **16** in 66% yield from **15** and 31% overall yield from **13**. Iodide **9a** was obtained in 65% yield by regioselective iodination of **16** with use of I_2/CF_3CO_2Ag.[17] The competitive oxidation of the primary alcohol could account for this somewhat moderate yield. On the other hand, iodide **9b** was obtained in three steps, 61% overall yield from **16** by Ley's oxidation,[18] reaction with methylmagnesium bromide, and regioselective iodination.

SCHEME 3[a]



[a] Reaction conditions: (a) $Pd(OAc)_2$ (5 mol %), S-Phos (10 mol %), $Ba(OH)_2 \cdot 8H_2O$ (1.1 equiv), dioxane/H_2O (9:1, c = 0.3 M); (b) ClC(O)*p*-NO_2Ph (1.1 equiv), Et_3N (3.0 equiv), DMAP (0.3 equiv), CH_2Cl_2, 0 °C (48%); (c) TBAF (1.1 equiv), THF, 20 °C (53%).

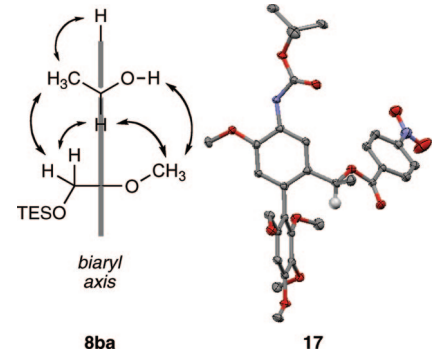


FIGURE 1. Solution (left) and solid-state (right) structures of biaryls **8ba** and **17** from NOESY experiments and X-ray diffraction analysis (30% probability ellipsoids plot, most H atoms were omitted for clarity), respectively.

First, route a (Scheme 1) was investigated with use of iodoarene **9b**. The cross-coupling of **9b** and boronate **10**[9] was performed under conditions previously optimized in our laboratory, using Buchwald's S-Phos[19] as palladium ligand and barium hydroxide as the base (Scheme 3).[9] The two separable diastereoisomeric biaryls **8ba** and **8bb** were isolated in 58% combined yield, and ^{1}H NMR analysis of the crude mixture allowed to measure a 85:15 ratio of **8ba/8bb**. The relative configuration of **8ba** and **8bb** was ascribed to *S*,a*R* and *R*,a*R*, respectively, by NOESY experiments (see Figure 1 for typical correlations observed with **8ba**). The level and sense of the diastereoselectivity observed in the present biaryl coupling are in agreement with those observed on analogous systems.[9]

To confirm the above stereochemical attribution, **8ba** was converted to *p*-nitrobenzoate **17** (Scheme 3), which furnished

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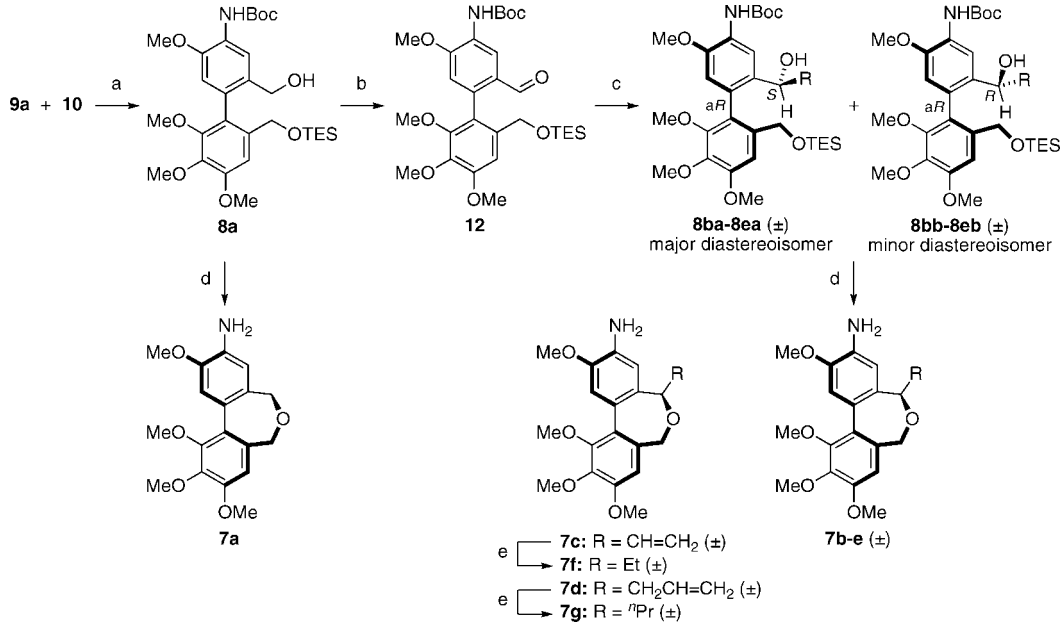
SCHEME 4[a]



[a] Reaction conditions: (a) $Pd(OAc)_2$ (5 mol %), S-Phos (10 mol %), $Ba(OH)_2 \cdot 8H_2O$ (1.1 equiv), dioxane/H_2O (9:1, c = 0.5 M) (63%); (b) TPAP (0.02 equiv), NMO (3.0 equiv), CH_2Cl_2, 20 °C (75%); (c) BrMgR (3.0 equiv), THF, −78 °C (see Table 1); (d) aq HF, CH_3CN, 20 °C (see Table 1); (e) 5% Pd/C, H_2 (1 atm), EtOH, 50 °C, 12 h (72% for **7f**, 90% for **7g**).

TABLE 1. Addition of Grignard Reagents (BrMgR) to Aldehyde 12 and Cyclodehydration[a]

		Grignard addition			cyclodehydration	
entry	R	products	yield (%)[b]	dr[c]	product	yield (%)[d]
1	Me	**8ba**, **8bb**	66	87:13	**7b**	66
2	CH=CH$_2$	**8ca**, **8cb**	86	86:14	**7c**	70
3	CH$_2$−CH=CH$_2$	**8da**, **8db**	66	87:13	**7d**	88
4	Ph	**8ea**, **8eb**	57	87:13	**7e**	67
5	H				**7a**	79

[a] Reaction conditions: see Scheme 4. [b] Combined yield of isolated diastereoisomers. [c] Measured by ^{1}H NMR spectroscopic analysis of the crude mixture. [d] Yield of isolated products.

crystals suitable for X-ray diffraction analysis (Figure 1). In the crystal, the two aryl rings adopt a nearly perpendicular orientation (biaryl torsion angle: ca. 76°) and the C−H bond of the benzylic stereocenter adopts an eclipsed $A^{1,3}$ conformation, which is probably a consequence of the minimization of allylic strain. The *S*,a*R* relative configuration of the stereogenic center and axis can be deduced from this structure, which is in agreement with the NMR attribution.

Route b commenced with the cross-coupling of iodide **9a** with boronate **10** (Scheme 4) which, under the same conditions as above with **9b** and **10**, provided biaryl **8a** in 63% yield. Oxidation of **8a** with TPAP and NMO provided aldehyde **12** in 75% yield. The addition of excess methylmagnesium bromide to **12** furnished a 87:13 diastereoisomeric mixture of **8ba** and **8bb** in 66% combined yield (Scheme 4, step c, and Table 1, entry 1). The overall yield of the **8ba**,**8bb** mixture from alcohol **16** was 35% via route a and 20% via route b. Thus route a is slightly more efficient than route b for the synthesis of biaryls **8ba** and **8bb**, whereas both routes show an almost identical diastereoselectivity (**8ba/8bb**).

2. Addition of Other Grignard Reagents. The addition of other Grignard reagents to aldehyde **12** was next examined (Table 1, entries 2−4). In all cases a mixture of *S*,a*R* and *R*,a*R* diastereoisomers was obtained, with the former being again the major product. Relative configurations were ascribed by NOESY experiments in a similar manner to **8ba** and **8bb** and by comparison of ^{1}H chemical shifts, which were very similar in the same series of diastereoisomers. The reaction diastereoselectivity proved remarkably similar regardless of the structure of the Grignard reagent (entries 1−4). The addition of alkyl Grignard reagents possessing a β-hydrogen (e.g., R = Et, ^{n}Pr) proved troublesome due to the formation of significant amounts of the reduction product (**8a**). Thus, dibenzoxepines bearing linear alkyl groups (**7f**,**g**) were obtained by a different approach (vide infra).

By comparing the relative configuration of diastereoisomers **8ba** and **8bb** obtained by the two different synthetic routes (Schemes 3 and 4), it appears that the diastereoselectivity is comparable and in favor of the same major diastereoisomer (**8ba**). This result is fortuitous, and it was checked that **8ba** and **8bb** do not interconvert by atropisomerization below 100 °C, the temperature of the biaryl coupling, as it was observed before on related biaryls.[9] The stereochemical outcome of the Suzuki−Miyaura coupling of iodide **9b** and boronate **10** might be explained by using the three-element model reported for similar systems.[9b] In contrast, the diastereoselectivity of the Grignard addition to aldehyde **12** deserves a more detailed analysis. Diastereoselective additions of organometallic reagents to *o*-biphenyl aldehydes have been reported before,[20] but to the best of our knowledge the stereoselectivity has never been rationalized. The C(Ar)−C(O)H bond of compound **12** is expected to adopt two favorable *s-trans* and *s-cis* conformations (Scheme 5). In the absence of Grignard reagent, the *s-trans* conformation should prevail due to the minimization of $A^{1,3}$ allylic strain (model A).[9b] The attack of a Grignard reagent such as MeMgBr should occur on the less hindered *si* face of the aldehyde due to the steric repulsion by the silyl group. This

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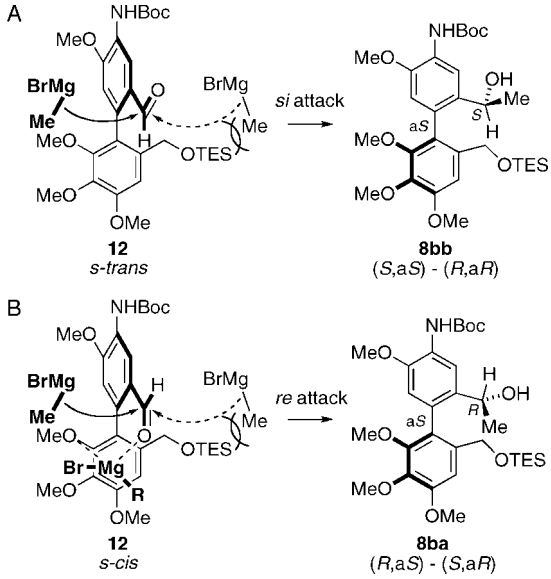
SCHEME 5. Proposed Models for the Grignard Addition to Aldehyde 12



would furnish the *S*,a*S*/*R*,a*R* diastereoisomer **8bb**, which is the minor diastereoisomer observed experimentally. Alternatively, the *s-cis* conformation of **12** could be favored by chelation of magnesium by the oxygen atoms of the aldehyde and of the neighboring methoxy group (model B).[21] Using this chelate model, the attack of the Grignard reagent should occur this time on the more accessible *re* face of the aldehyde, which would give the major *R*,a*S*/*S*,a*R* diastereoisomer **8ba**. Experimentally, it was observed that an excess of Grignard reagent was necessary for a complete conversion, which might be in favor of the chelate model B.

3. Synthesis of Target Dibenzoxepines 7a−g. Dibenzoxepine **7a**, deprived of benzylic substituent (R), was first synthesized from alcohol **8a** (Scheme 4). Treating **8a** with 50% aq HF effected three operations in a single pot: cleavage of TES and Boc groups and cyclodehydration to form the oxepine ring. This process, which was developed before with a triisopropylsilyl ether instead of the Boc-carbamate,[9c] furnished **7a** in 79% yield (Table 1, entry 5). The same method was applied to obtain dibenzoxepines **7b−e** (Table 1, last column, entries 1−4). As illustrated with **7b** (Scheme 6), both *S*,a*R* and *R*,a*R* diastereoisomers of the same biaryl precursor (in this case **8ba** and **8bb**) furnish the same dibenzoxepine upon treatment with aq HF, since the cyclodehydration proceeds via the same carbocationic intermediate **18** (Scheme 6).[9] Thus, depending on the ease of purification after the Grignard addition step, the diastereoisomeric mixture or the isolated diastereoisomers can be employed in the cyclodehydration. For the sake of comparison, yields indicated in Table 1 were obtained starting from the isolated major *S*,a*R* diastereoisomers **8ba−8ea**. These yields ranged from 66% for **8ba** to 88% for **8da**. Dibenzoxepines **7c** and **7d** were then hydrogenated to give the ethyl and *n*-propyl-substituted analogues **7f** and **7g**, respectively, in good yield (Scheme 4, step e). Because the reaction of ethyl and *n*-propylmagnesium bromide with aldehyde **12** failed to give the addition products, this sequence provided a less direct but more reliable method to obtain dibenzoxepines **7f**,**g**.

(21) The coordination of magnesium by *o*-methoxy groups is involved in Meyers' oxazoline biaryl coupling method: (a) Meyers, A. I.; Nelson, T. D.; Moorlag, H.; Rawson, D. J.; Meier, A. *Tetrahedron* **2004**, *60*, 4459. (b) Meyers, A. I. *J. Org. Chem.* **2005**, *70*, 6137.

In contrast to their cyclodehydration precursors, substituted dibenzoxepines **7b−g** occur as conformational mixtures of two interconverting atropisomers (Scheme 6), as evidenced by the presence of exchange correlations on NOESY spectra. The ratio of conformers ranged from 87:13 for **7c** to 98:2 for **7b**, and the major conformer had the *R*,a*R* relative configuration as evidenced by long-distance correlations on NOESY spectra (see Scheme 6 for **7b**), and as observed before with other analogues.[9] All dibenzoxepines **7a−g** could be converted to the more hydrosoluble hydrochlorides upon treatment with dry HCl in diethyl ether. Biological evaluations of these new analogues of *N*-acetylcolchinol analogues will be reported separately.

In conclusion, we reported a straightforward synthesis of new aminodibenzoxepines using two different strategies. The first strategy, in line with our previous reports, involved a Grignard addition, a biaryl Suzuki−Miyaura coupling, and a cyclodehydration as key steps. An alternative strategy was designed by inverting the order of the Grignard addition and the biaryl coupling, which allowed the rapid production of a series of substituted dibenzoxepines **7a−g**. A chelate model was proposed to account for the diastereoselectivity observed in the Grignard addition step. The target dibenzoxepines are potential analogues of *N*-acetylcolchinol, and their evaluation as new vascular-disrupting agents will be reported in due course.

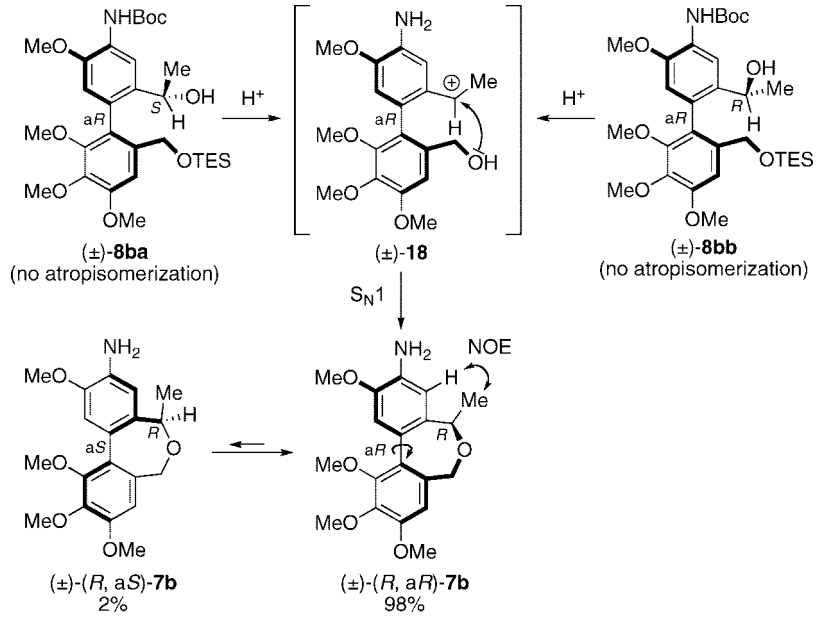
Experimental Section

***tert*-Butyl [2-Hydroxymethyl-2′,3′,4′,5-tetramethoxy-6′-(triethylsilyloxymethyl)biphenyl-4-yl]carbamate (8a).** A sealed tube was charged with iodoarene **9a** (3.00 g, 7.91 mmol), aryl boronate **10** (5.20 g, 11.9 mmol), $Pd(OAc)_2$ (266 mg, 0.40 mmol), S-Phos (325 mg, 0.79 mmol), $Ba(OH)_2 \cdot 8H_2O$ (2.75 g, 8.7 mmol), and dioxane/water (9:1; [**9a**] = 0.5 M). The tube was sealed and placed in an oil bath preheated at 100 °C and stirred for 2.5 h. After cooling to room temperature, the reaction mixture was filtered through Celite and $MgSO_4$. The residue was purified by flash chromatography (silica gel, cyclohexane/EtOAc 93:7) to give alcohol **8a** as an oil (2,79 g, 4.98 mmol, 63%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.11 (s, 1H), 7.60 (s, 1H), 6.60 (s, 1H), 4.37 (d, J = 13.5 Hz, 1H), 4.23 (d, J = 13.5 Hz, 1H), 4.23 (s, 2H), 3.91 (s, 3H), 3.88 (s, 3H), 3.81 (s, 3H), 3.56 (s, 3H), 2.82 (s, 1H), 1.54 (s, 9H), 0.91 (t, J = 7.7 Hz, 9H), 0.56 (q, J = 7.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.1, 152.8, 150.9, 146.9, 141.1, 135.2, 133.0, 128.7, 127.9, 125.3, 119.5, 117.7, 111.8, 106.9, 63.8, 62.5, 61.3, 61.2, 56.0 (2C), 28.5 (3C), 6.8 (3C), 4.4 (3C); IR (neat) ν 3439, 2925, 2874, 1729, 1491, 1048 cm^{-1}; HRMS (ESI) calcd for $C_{29}H_{45}NNaO_8Si^+$ [(MNa^+)] 586.2812, found 586.2813.

***tert*-Butyl [2-Formyl-2′,3′,4′-trimethoxy-6′-(triethylsilyloxymethyl)biphenyl-4-yl]carbamate (12).** Tetrapropylammonium perruthenate (3.74 mg, 0.011 mmol) and *N*-methylmorpholine *N*-oxide (187 mg, 1.59 mmol) were added to a solution of alcohol **8a** (300 mg, 0.53 mmol) in CH_2Cl_2 at 20 °C, under argon. The mixture was stirred at room temperature for 2 h. Water was added, then the aqueous layer was extracted with EtOAc. The combined organic layers were washed with a 1 N aq solution of HCl, dried over $MgSO_4$, filtered, and evaporated under vacuum. The residue was purified by filtration through a short pad of silica (cyclohexane/EtOAc 85:15) to give aldehyde **12** as an oil (240 mg, 80%), which was used directly in the next step. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.60 (s, 1H), 8.69 (s, 1H), 7.10 (s, 1H), 6.97 (s, 1H), 6.66 (s, 1H), 4.31 (d, J = 12.9 Hz, 1H), 4.23 (d, J = 12.9 Hz, 1H), 3.93 (s, 3H), 3.90 (s, 3H), 3.88 (s, 3H), 3.57 (s, 3H), 1.52 (s, 9H), 0.87 (t, J = 8.6 Hz, 9H), 0.52 (q, J = 8.6 Hz, 6H); IR (neat) ν 3438, 1730, 1684, 1525, 1488, 1458 cm^{-1}; HRMS (ESI) calcd for $C_{29}H_{43}NNaO_8Si^+$ [(MNa^+)] 584.2656, found 584.2655.

General Procedure for Grignard Addition to Aldehyde 12. A solution of magnesium bromide was added dropwise to a solution

SCHEME 6. Cyclodehydration of Biaryls 8ba and 8bb



of aldehyde **12** in THF at −78 °C, under argon. The mixture was stirred at −78 °C and then allowed to warm to room temperature for 1−5 h. A saturated aq solution of NH_4Cl was added, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and evaporated under vacuum. The resulting mixture was purified by flash chromatography, using cyclohexane and ethyl acetate as the eluents.

(±)-*tert*-Butyl [2-(1-Hydroxyethyl)-2′,3′,4′,5-tetramethoxy-6′-(triethylsilyloxymethyl)biphenyl-4-yl]carbamate (8ba, 8bb). The addition of methylmagnesium bromide to aldehyde **12** was performed according to the general procedure, starting from methylmagnesium bromide (3 M in diethyl ether, 0.27 mL, 0.81 mmol) and aldehyde **12** (150 mg, 0.27 mmol) in THF (6 mL) at −78 °C for 5 h. After flash chromatography (silica gel, cyclohexane/EtOAc 93:7 then 91:9), alcohols **8ba** and **8bb** were isolated as colorless oils (total mass 101 mg, 66%, diastereoisomeric ratio 87:13). Major diastereoisomer **8ba**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.10 (s, 1H), 7.03 (s, 1H), 6.55 (s, 1H), 4.45 (q, J = 7.1 Hz, 1H), 4.03 (d, J = 13.3 Hz, 1H), 4.15 (d, J = 13.3 Hz, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 3.80 (s, 3H), 3.54 (s, 3H), 2.97 (s, 1H), 1.39 (d, J = 7.1 Hz, 3H), 0.91 (t, J = 7.7 Hz, 9H), 0.57 (q, J = 7.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.1, 152.7, 150.5, 146.6, 140.9, 136.8, 135.4, 128.3, 127.6, 124.9, 115.3, 111.5, 106.3, 80.5, 66.7, 62.4, 61.3, 61.2, 56.0, 55.9, 28.5 (3C), 22.1, 6.9 (3C), 4.5 (3C); IR (neat) ν 3448, 2931, 1732, 1616, 1593, 1397 cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{47}NNaO_8Si^+$ [(MNa^+)] 600.2969, found 600.2968. Minor diastereoisomer **8bb**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.09 (s, 1H), 6.87 (s, 1H), 6.52 (s, 1H), 4.50 (q, J = 6.6 Hz, 1H), 4.29 (s, 2H), 3.91 (s, 3H), 3.89 (s, 3H), 3.80 (s, 3H), 3.61 (s, 3H), 1.55 (s, 9H), 1.40 (d, J = 6.6 Hz, 3H), 0.89 (t, J = 8.1 Hz, 9H), 0.60 (q, J = 8.1 Hz, 6H).

Compounds **8ba** and **8bb** were also obtained by Suzuki−Miyaura coupling in the same manner as above for **8a**, starting from iodoarene **9b** (120 mg, 0.30 mmol), aryl boronate **10** (200 mg, 0.46 mmol), $Pd(OAc)_2$ (10 mg, 0.01 mmol), S-Phos (12 mg, 0.03 mmol), $Ba(OH)_2 \cdot 8H_2O$ (106 mg, 0.33 mmol), and dioxane/water (9:1; [**9b**] = 0.3 M). After flash chromatography (silica gel, cyclohexane/EtOAc 93:7), alcohols **8ba** and **8bb** were isolated as oils (total mass 101 mg, 58%, diastereomeric ratio 85:15).

General Cyclodehydratation Procedure. An aq solution of HF (48% to 51%) was added to a solution of compound **8** in CH_3CN at room temperature, and the mixture was stirred for 48 h. It was cautiously poured into a saturated aq solution of $NaHCO_3$ and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and evaporated under vacuum. The resulting mixture was purified by flash chromatography, using cyclohexane and ethyl acetate as the eluents.

(±)-2,9,10,11-Tetramethoxy-5,7-dihydrodibenzo[*c*,*e*]oxepin-3-amine (7a). The cyclodehydratation of alcohol **8a** was performed according to the general procedure, starting from aq HF (1.13 mL) and compound **8a** (50 mg, 0.09 mmol) in CH_3CN (5.7 mL). After flash chromatography (silica gel, cyclohexane/EtOAc 3:1), compound **7a** was isolated as a colorless oil (23 mg, 79%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (s, 1H), 6.76 (s, 1H), 6.75 (s, 1H), 4.35 (s, 1H), 4.07 (s, 1H), 3.95 (s, 3H), 3.91 (s, 3H), 3.90 (s, 3H), 3.64 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.5, 150.5, 147.0, 142.7, 135.8, 131.5, 128.5, 127.2, 115.7, 111.7, 108.9, 67.7, 67.3, 61.3, 60.8, 56.2, 55.8; IR (neat) ν 3458, 2930, 1621, 1458, 1124 cm^{-1}; HRMS (CI) calcd for $C_{18}H_{22}NO_5^+$ [(MH^+)] 332.1498, found 332.1495.

(±)-5-Ethyl-2,9,10,11-tetramethoxy-5,7-dihydrodibenzo[*c*,*e*]oxepin-3-amine (7f). To a solution of dibenzoxepine **7c** (13 mg, 0.04 mmol) in EtOH at 20 °C under argon atmosphere was added Pd/C (7.5 mg, 0.5 wt equiv). Then H_2 was bubbled into the reaction mixture for 5 min and the reaction mixture was stirred at 50 °C under H_2 atmosphere overnight. The reaction mixture was filtered through a short pad of Celite and evaporated under reduced pressure. The residue was purified by flash chromatography (silica gel, cyclohexane/EtOAc 89:11) to give compound **7f** as an oil (9.4 mg, 72%, conformer ratio 88:12). Major conformer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (s, 1H), 6.81 (s, 1H), 6.74 (s, 1H), 4.36 (d, J = 11.2 Hz, 1H), 3.98−3.87 (m, 2H), 3.96 (s, 3H), 3.90 (s, 3H), 3.89 (s, 3H), 3.66 (s, 3H), 1.97 (quint, J = 7.6 Hz, 1H), 0.95 (t, J = 7.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.6, 150.5, 146.5, 142.7, 135.7, 131.6, 129.8, 127.9, 127.1, 111.8, 111.6, 108.6, 74.5, 68.1, 60.6, 56.2, 56.2, 55.8, 31.1, 29.9; IR (neat) ν 3375, 2930, 1621, 1458, 1124 cm^{-1}; HRMS (CI) calcd for $C_{20}H_{26}NO_5^+$ [(MH^+)] 360.1811, found 360.1812.

(±)-5-Propyl-2,9,10,11-tetramethoxy-5,7-dihydrodibenzo[*c*,*e*]oxepin-3-amine (7g). Compound **7g** was obtained in the same manner as above for **7f**, starting from dibenzoxepine **7d** (16 mg, 0.04 mmol) and Pd/C (8 mg) in EtOH (1 mL). After flash chromatography (silica gel, cyclohexane/EtOAc 89:11), compound **7g** was isolated as an oil (20 mg, 90%, conformer ratio 85:15). Major conformer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (s, 1H), 6.82 (s, 1H), 6.74 (s,

1H), 4.34 (d, $J = 11.1$ Hz, 1H), 4.00 (t, $J = 7.1$ Hz, 1H), 3.96 (s, 3H), 3.95 (d, $J = 11.2$ Hz, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 3.66 (s, 3H), 1.91 (q, $J = 7.6$ Hz, 2H), 1.31 (m, $J = 7.6$ Hz, 2H), 0.95 (t, $J = 7.6$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.6, 150.4, 146.5, 142.6, 135.7, 131.6, 130.0, 127.8, 127.0, 111.8, 111.6, 108.6, 72.5, 68.0, 61.3, 56.0, 55.8, 55.8, 34.4, 19.9, 14.4; IR (neat) ν 3371, 2952, 2931, 2856 cm^{-1}; HRMS (CI) calcd for $C_{21}H_{28}NO_5^+$ [(MH^+)] 374.1967, found 374.1967.

Acknowledgment. We thank Ministère de l'Enseignement Supérieur et de la Recherche (fellowship to V.C.), CNRS (ATIP grant to O.B.), and Johnson Matthey PLC (loan of palladium acetate). We are also grateful to Dr. Erwann Jeanneau for crystallographic data collection, structure solution, and refinement and Dr. Denis Bouchu for mass spectrometry analyses.

Supporting Information Available: Full characterization of all new compounds, detailed experimental procedures, copies of NMR spectra for biaryl intermediates, and target dibenzoxepines and X-ray crystal structure data (CIF) for compound **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO900632A