Pergamon

Tetrahedron Letters 43 (2002) 3011–3015

TETRAHEDRON LETTERS

Stereoselective synthesis of *trans*-fused tetrahydrofuran derivatives of 5*H*-dibenzo[*a*,*d*]cycloheptene

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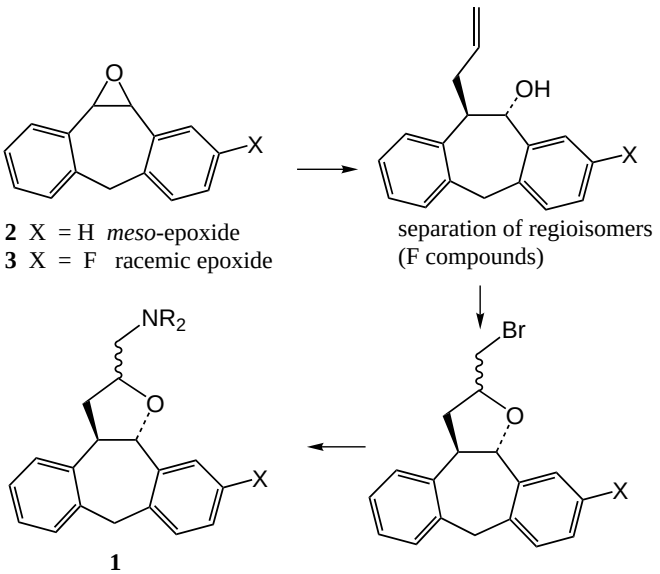
Received 25 January 2002; revised 25 February 2002; accepted 26 February 2002

Abstract—The epoxides derived from 5*H*-dibenzo[*a*,*d*]cycloheptene and its 2-fluoro derivative were converted to *trans*-fused hydrofurans **4a**,**b** (55 and 44% overall yields) via a five-step sequence, i.e. (i) epoxide ring opening using propargylmagnesium bromide, (ii) mercury(II)-induced cyclisation and in situ bromination to give the bromomethylene substituted hydrofurans, (iii, iv) acid catalysed hydration and stereoselective reduction of the hemiacetal intermediates, and (v) base promoted cyclisation. © 2002 Elsevier Science Ltd. All rights reserved.

In a recent patent, *trans*-fused tetracyclic hydrofuran compounds of type **1** were shown to exhibit potent activity in the central nervous system, especially with regard to their potential use as antidepressants.[1] The structures of these compounds are similar to those of well-known tricyclic and tetracyclic antidepressants like mianserin and mirtazapine.[2] They were accessed via epoxidation of 5*H*-dibenzo[*a*,*d*]cycloheptene or its 2-fluoro derivative, followed by opening of the epoxides **2** and **3** by reaction with allylmagnesium chloride and separation of the regioisomers derived from fluoro epoxide **3**. Subsequent bromination of the allyl side chain resulted in ring closure to form the bromomethyl substituted tetrahydrofuran ring. Final substitution of the bromo substituent with amines afforded an isomeric mixture of amines, from which the various stereoisomers could be isolated by using highly demanding chromatographic procedures (Scheme 1).

At the outset of this work our aim was to develop regio and stereocontrolled synthetic routes providing access to each of the stereoisomers of hydrofuran compounds **1**. Here we present a successful five-step sequence leading to the racemic precursor alcohols **4**, ready for conversion to the corresponding amino analogues. Our approach is based on the stereoselective generation and ring opening of the epoxide intermediates **5**, derived from propargylic alcohols **6** by elaboration of the terminal acetylene function to form the corresponding bromo-diol intermediates (Scheme 2).

Our synthesis also started with nucleophilic opening of epoxides **2** and **3**, using propargylmagnesium instead of



Scheme 1. Reported synthesis of hydrofuran-fused compounds **1**.

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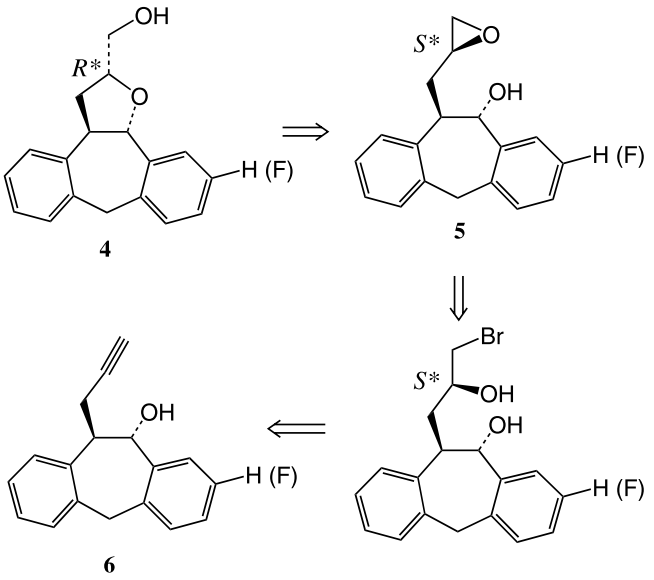
PII: S0040-4039(02)00404-5



Scheme 2. Synthetic approach for precursor alcohols **4** proceeding via alcohols **6** and epoxides **5**.

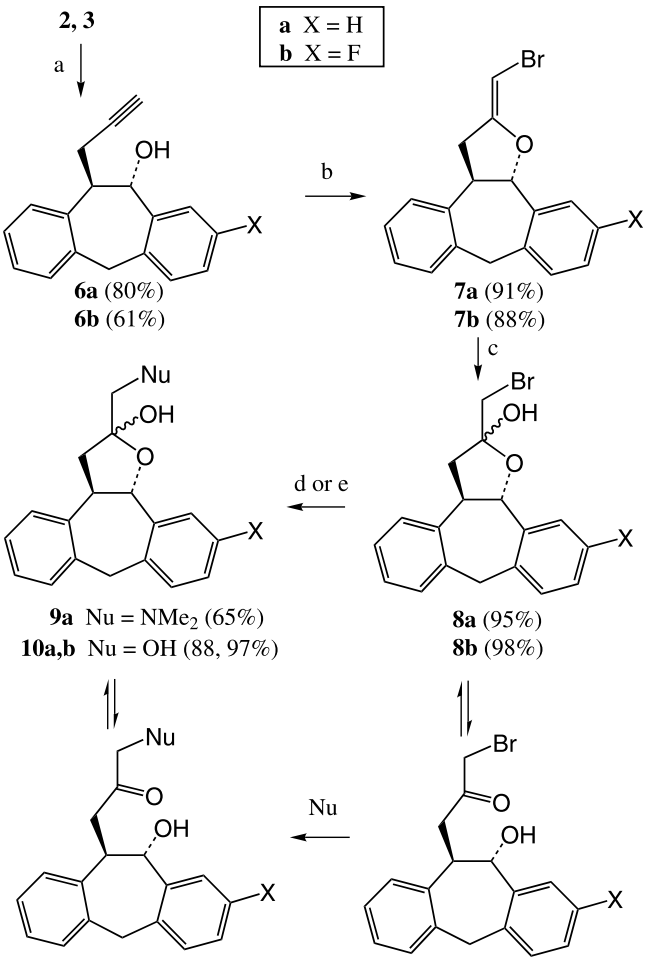
allylmagnesium reagent (Scheme 3). Interestingly, opening of fluoro epoxide **3** occurred with marked regioselectivity to give the desired isomer **6b** in a favourable ratio of ca. 7:3. To explain the preferential attack at the less electron deficient benzylic position of **3**, one may invoke the operation of an S_N1-like mechanism, due to co-ordination of magnesium to the epoxide *O*-atom. Application of HPLC was required to separate **6b** from its unwanted regioisomer. The desired *trans*-type acetylenic alcohols **6a**,**b** were isolated in 80 and 61% yield, respectively.

Mercury(II) induced cyclisation[3] of **6a** apparently led to formation of the expected enol ether as indicated by TLC analysis, but this unstable product did not survive column chromatography. However, the corresponding bromo alkenes **7a**,**b** were isolated in excellent yield when the cyclisation of **6a**,**b** was carried out in the presence of *N*-bromosuccinimide. The amount of $HgCl_2$ applied (0.5 equiv.) was found to be critical. Indeed, dibrominated side products were formed when using more than 1 equiv., whereas with a lesser amount (0.1 equiv.) a prolonged reaction time of 5–6 days was required for complete conversion. The (*Z*)-configuration of **7a**,**b** was demonstrated by a NOE relating the vinylic proton with the nearby methylene protons.

Compounds **7a**,**b** are subject to acid catalysed nucleophilic addition to the double bond of the enol ether. Thus, hydration of **7a**,**b** was effected by treatment with water and camphorsulfonic acid to produce hemiacetal compounds **8a**,**b** in nearly quantitative yield. The hemiacetal structure was demonstrated by CI mass spectral data (MH^+ 345 for **8a** and MH^+ 363 for **8b**) and by ^1H NMR analysis, which clearly revealed the presence of a ca. 1:1 mixture of the two 'anomeric' products.

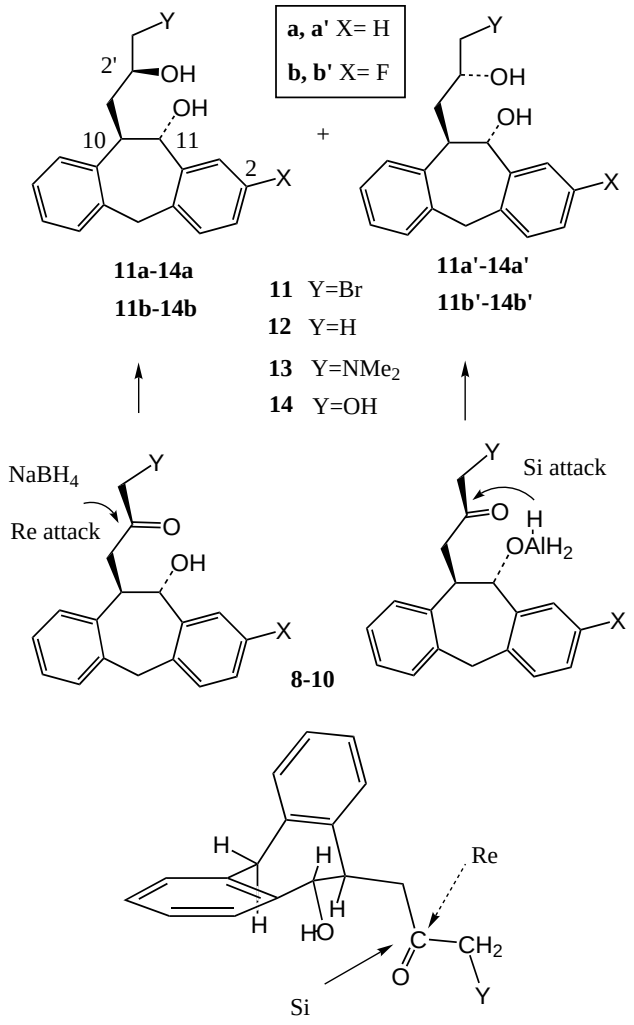
From their hemiacetal structure, compounds **8a**,**b** are expected to be in tautomeric equilibrium with the corresponding ketone forms, resulting in the observation of characteristic reactivities for both nucleophilic substitution of the α-bromo position and reduction of the ketone function. Thus, alternate treatment of compound **8a** with either Me_2NH or sodium hydroxide produced amine **9a** and diol **10a**, respectively. The fluoro diol analogue **10b** was prepared in a similar way. However, we were unable to convert **9a** or **10a**,**b** into a target structure via reduction of an intermediate cation formed at the 'anomeric' centre. For example, ionic hydrogenolysis of the 'anomeric' hydroxyl group was attempted by treating **9a** with trifluoroacetic acid and Et_3SiH,[4] but this resulted in elimination of the benzylic alcohol group from the open-chain ketone tautomer of **9a** to produce the corresponding cycloheptenyl amino ketone.

An obvious alternative strategy, as indicated already in our retrosynthetic analysis (Scheme 2), is to reduce the hidden ketone function of hemiacetals **8** to generate the



Scheme 3. *Reagents and conditions*: (a) $CH{\equiv}CCH_2Br$, Mg, $HgCl_2$, Et_2O, THF, reflux; (b) $HgCl_2$ (0.5 equiv.), NBS (1 equiv.), DMAP (2 equiv.), CH_2Cl_2; (c) CSA, CH_2Cl_2, H_2O; (d) $Me_2NH{\cdot}HCl$, Et_3N, THF, MeOH, 2 days; (e) 10% NaOH, THF, 2 h.

corresponding bromo diols, followed by base-catalysed conversion into epoxides **5** and cyclisation to form the hydrofuran ring. Treatment of hemiacetal **8a** with $NaBH_4$ in THF/MeOH led to formation of alcohols **11a** and **11a′** in a diastereomeric ratio of 4:1 (Scheme 4 and Table 1). Similar reduction of the fluoro analogue **8b** afforded the bromo alcohols **11b**,**b′** with an epimeric ratio of ca. 20:1, as inferred from the ratio found for the corresponding hydrofuran products **4b**,**b′** (see below). When hemiacetal **8a** was reduced with $LiAlH_4$ instead of $NaBH_4$, debrominated epimeric alcohols **12a**,**a′** were generated, but interestingly with opposite diastereoselectivity (1:10).



Scheme 4.

The epimeric ratios were determined by integration of the ^1H NMR signals corresponding to the benzylic proton H11 next to the OH group (Table 1). For epimers **11a** and **12a**, this proton was observed as a doublet ($^3J=9.2$ Hz) at ca. 5.00 ppm whereas the corresponding signal for alcohols **11a′** and **12a′** was found at ca. 5.20 ppm ($^3J=8.2$ Hz). It should be noticed that the structures of the epimeric alcohols could be assigned only in an indirect way through intercomparison of the ^1H NMR spectra before and after further cyclisation of bromo alcohols **11a**,**a′** to produce tetrahydrofuran compounds **4a**,**a′** (see NOE of **4a**). Similar reductions using $NaBH_4$ and $LiAlH_4$ were carried out also for the amino hemiacetal compound **9a**, which equally resulted in opposite diastereoselectivities (9:1 and 1:4, respectively) for the epimeric alcohols **13a** and **13a′**. The assignment of the diastereoisomers again relied on the observation of the benzylic H-atom next to OH as a doublet ($^3J=9.1$ Hz) at 5.10 ppm for amino alcohol epimer **13a** and as a doublet ($^3J=8.8$ Hz) at 5.35 ppm for the other epimer **13a′**. Similar treatment of the diol hemiacetal **10a** with $LiAlH_4$ and $NaBH_4$ in THF also gave satisfactory results. However, the ratio of the two diastereoisomers **14a**,**a′**was about 1:1 for the $LiAlH_4$ reduction, whereas the $NaBH_4$ reduction gave mainly **14a** (ratio about 8:1).

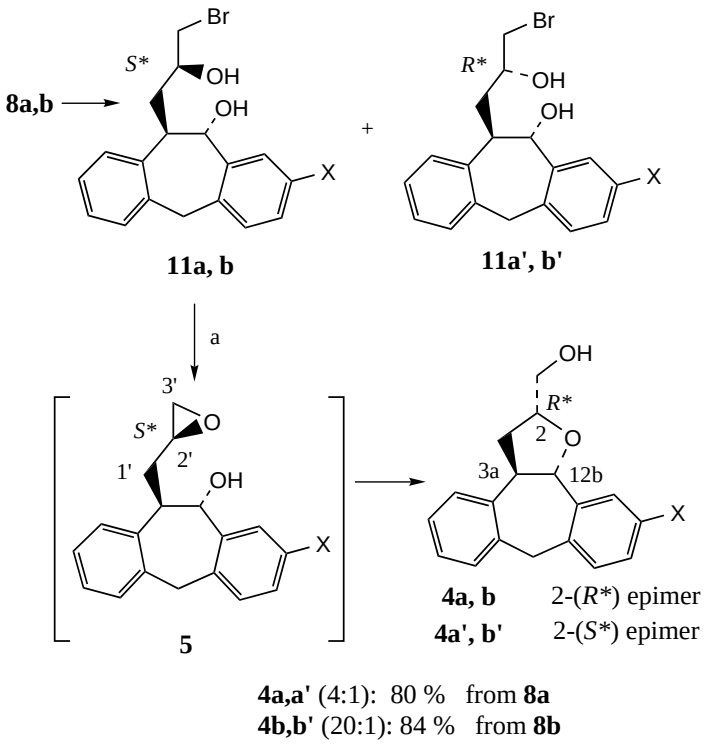
The reason for the observed stereoselectivities may be that the attack of $NaBH_4$ would occur from the more accessible 'outside' *Re*-face of the carbonyl group to give the corresponding 2′-(*S**)-alcohol, whereas reduction with $LiAlH_4$ probably proceeds via complexation of the reagent with the benzylic alcohol group, resulting in internal attack from the opposite *Si*-face. Conformational calculations[5] indicated that the tricylic moiety of the ketone adopts a bent conformation showing a convex and a concave side; the equatorial side chain has an extended zigzag form oriented in the main plane of the seven-membered ring, implying that the carbonyl group is oriented downward.

In the next step of our sequence the 4:1 mixture **11a**,**a′** obtained with $NaBH_4$ was subjected to treatment with base (NaH in THF). According to our synthetic plan, this afforded a mixture of two diastereoisomers **4a** and **4a′**, exhibiting the same isomeric ratio 4:1 as the starting bromo diols (Scheme 5). Prominent features in the ^1H NMR spectrum of the epimeric mixture are the doublet signals found for the benzylic H-atom H12b at 5.08 ppm ($^3J=11.1$ Hz) for **4a** and at 5.12 ppm ($^3J=11.1$ Hz) for **4a′**, confirming its *trans*-diaxial relation-

Table 1. Diastereoselective reductions of **8a**–**10a**[a]

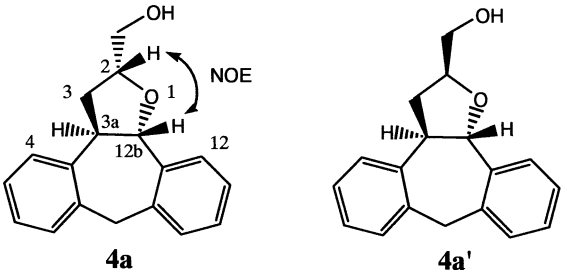
Start. comp.	2′-(*S**)-epimer (H11: δ, ^3J)	2′-(*R**)-epimer (H11: δ, ^3J)	Yield (%) (epim. ratio)	
			$NaBH_4$	$LiAlH_4$
8a	**11a** (5.00, 9.2)	**11a′** (5.20, 8.2)	77 (4:1)	
8a	**12a** (5.05, 9.2)	**12a′** (5.23, 8.2)		49 (1:10)
9a	**13a** (5.10, 9.1)	**13a′** (5.35, 8.8)	77 (9:1)	91 (1:4)
10a	**14a** (4.92, 9.1)	**14a′** (5.18, 8.8)	88 (8:1)	92 (1:1)

[a] The unstable intermediate **8b** could not be isolated in pure form.



Scheme 5. Reagents and conditions: (a) NaH, THF.

ship with H3a. A cross peak in the NOESY spectrum clearly revealed the *cis* orientation of protons H12b and H2 for the main epimer **4a**.[6]



When the reduction/cyclisation sequence (**8**→**11**→**4**) was applied to the fluoro analogue **8b**, an increased selectivity in favour of **4b** was apparent from ^{1}H NMR analysis of the epimeric hydrofuran products (**4b**:**4b**′ = 20:1). It should be noticed that the $NaBH_4$ reduction and NaH promoted cyclisation could be combined in a one-pot reaction to give a satisfactory yield of cyclic products **4a**,**a**′ and **4b**,**b**′ (80 and 84% over two steps). When the ring closure reaction was carried out using only 1 equiv. of NaH and for a short period of time, the product isolated by column chromatography also contained the epoxide intermediate **5**. It had the same R_f value as the cyclised compounds but also displayed characteristic high field NMR signals.[7] Upon standing of the product mixture, this was converted completely to the hydrofuran compounds.

In summary, both the fluoro and non-fluoro epoxides **2** and **3** were opened successfully by reaction with propargylmagnesium bromide to give the acetylenic alcohols **6a**,**b**. The latter were converted into tetrahydrofuran hemiacetals **8a**,**b** via mercury(II)-induced cyclisation and bromination of the enol ether intermediate. Subsequent acid catalysed hydration and stereoselective reduction of the hidden ketone group enabled final base promoted cyclisation of the bromo diol intermediates **11a**,**b** to produce target alcohols **4a**,**b** in good yields. In future work we intend to study the synthesis of other stereoisomers, including the epimeric compounds **4a**′,**b**′ and *cis*-fused hydrofuran compounds.

Acknowledgements

The authors wish to thank the FWO (Fund for Scientific Research, Flanders, Belgium) and the Janssen Research Foundation for financial support. We are indebted to R. De Boer and Professor S. Toppet for mass and NMR measurements. H. Mao also thanks the K.U.Leuven for a fellowship.

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5. Calculations were carried out using the Hyperchem™ molecular mechanics method.
6. All compounds gave satisfactory analytical data.
   Selected data for compound **7a**: mp 131–132 °C; HRMS calcd $C_{18}H_{15}BrO$ ($M^{+\bullet}$): 326.0306. Found: 326.0316 (2%);
   ^{1}H NMR: (δ, $CDCl_3$, 400 MHz): 3.02 (ddd, 1H, J=14.7, 12.2, 2.2 Hz, CH_2-3), 3.22 (dd, 1H, J=14.7, 6.8 Hz, CH'_2-3), 3.67 (dt, 1H, J=12.2, 6.8 Hz, CH-3a), 4.14 (d, 1H, J=16.3 Hz, CH_2-8), 4.26 (d, 1H, J=16.3 Hz, CH'_2-8), 5.10 (dd, 1H, J=2.2, 0.6 Hz, CH-Br), 5.46 (d, 1H, J=11.2 Hz, CH-12b), 7.15–7.33 (m, 7H, H-Ar), 7.66 (d, 1H, J=7.5 Hz, H-Ar)
   ^{13}C NMR: (δ, $CDCl_3$, 100 MHz): 35.54 (CH$_2$-3), 41.57 (CH$_2$-8), 47.32 (CH-3a), 72.57 (CH-Br), 83.69 (CH-12b), 124.95, 126.99, 127.08, 127.20, 127.32, 127.69, 129.22, 130.10 (CH-Ar), 134.84, 135.87, 137.35, 137.48 (C-Ar), 156.24 (C=CHBr).
   Selected data for compound **4a**: HRMS calcd $C_{18}H_{18}O_2$ ($M^{+\bullet}$) 266.1307. Found: 266.1309 (100%);
   ^{1}H NMR: (δ, $CDCl_3$, 400 MHz): 2.43–2.49 (m, 2H, CH_2-3), 3.40 (q, 1H, J=11.1 Hz, CH-3a), 3.69 (dd, 1H, J=11.5, 5.4 Hz, CH_2-OH), 3.85 (dd, 1H, J=11.5, 3.5 Hz, CH'_2-OH), 4.07 (d, 1H, J=16.0 Hz, CH_2-8), 4.27 (d, 1H, J=16.0 Hz, CH'_2-8), 4.40–4.46 (m, 1H, CH-2), 5.08 (d, 1H, J=11.1 Hz, CH-12b), 7.14–7.28 (m, 7H, H-Ar), 7.54 (d, 1H, J=7.60 Hz, H-Ar).
   ^{13}C NMR: (δ, $CDCl_3$, 100 MHz): 33.59 (CH$_2$-3), 41.66 (CH$_2$-8), 47.31 (CH-3a), 65.85 (CH$_2$-OH), 77.51 (CH-2), 81.22 (CH-12b), 124.52, 126.69, 126.84, 126.93, 127.21, 127.77, 129.03, 129.85 (CH-Ar), 135.52, 137.06, 137.64, 139.13 (C-Ar).
   Selected data for compound **4b**: HRMS calcd $C_{18}H_{17}FO_2$ ($M^{+\bullet}$): 284.1213. Found: 284.1213 (100%);
   ^{1}H NMR: (δ, $CDCl_3$, 400 MHz): 2.37–2.50 (m, 2H, CH_2-3), 3.32 (q, 1H, J=11.0 Hz, CH-3a), 3.69 (dd, 1H, J=11.6, 5.5 Hz, CH_2-OH), 3.82 (dd, 1H, J=11.6, 3.9 Hz, CH'_2-OH), 3.95 (d, 1H, J=16.2 Hz, CH_2-8), 4.23 (d, 1H, J=16.2 Hz, CH'_2-8), 4.37–4.42 (m, 1H, CH-2), 5.03 (d, 1H, J=11.0 Hz, CH-12b), 6.84 (dt, 1H, J=8.5, 2.9 Hz, H-Ar), 7.12–7.20 (m, 5H, H-Ar), 7.27 (dd, 1H, J=9.8, 2.4 Hz, H-Ar).
   ^{13}C NMR: (δ, $CDCl_3$, 100 MHz): 33.80 (CH$_2$-3), 40.75 (CH$_2$-8), 47.21 (CH-3a), 65.69 (CH$_2$-OH), 77.73 (CH-2), 80.59 (CH-12b), 111.37 (d, $^2J_{CF}$=22.75 Hz, CH-Ar-F), 113.49 (d, $^2J_{CF}$=21.23 Hz, CH-Ar-F), 126.71, 126.89, 128.06, 129.82 (CH-Ar), 130.34 (d, $^3J_{CF}$=8.34 Hz, CH-Ar-F), 131.11 (d, $^4J_{CF}$=2.27 Hz, C-Ar-F), 136.49, 137.47 (C-Ar), 141.61 (d, $^3J_{CF}$=7.58 Hz, C-Ar-F), 161.97 (d, $^1J_{CF}$=242.65 Hz, C-Ar-F).
7. Characteristic high field signals for epoxide intermediate **5a** in ^{1}H NMR spectrum of the mixture of **4a** and **5a** (δ, $CDCl_3$, 250 MHz): 2.0–2.3 (m, 3H, CH_2-1′, CH_2-3′), 2.80 (t, 1H, ^2J=^3J=4.8 Hz, CH_2-3′), 3.1–3.2 (m, 1H, CH-2′).