Pergamon

Tetrahedron Letters 43 (2002) 8697–8700

TETRAHEDRON LETTERS

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

Hua Mao, Mohamed Koukni, Tomasz Kozlecki, Frans Compernolle* and Georges J. Hoornaert

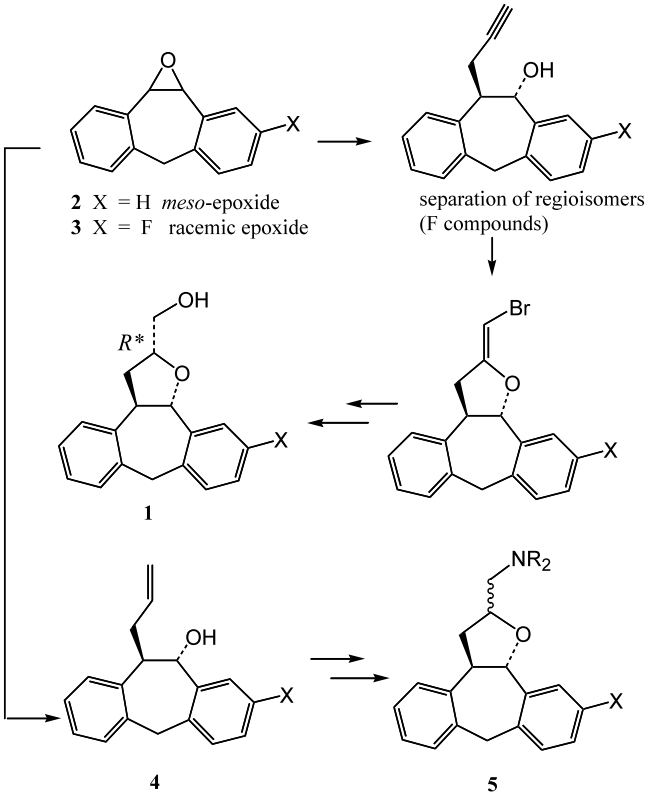
Laboratorium voor Organische Synthese, K.U. Leuven, Celestijnenlaan 200F, B-3001 Leuven, Belgium

Received 20 September 2002; revised 24 September 2002; accepted 25 September 2002

Abstract—The epoxides derived from 5*H*-dibenzo[*a*,*d*]cycloheptene and its 2-fluoro derivative were converted into the *trans*-fused hydropyran-3-one compounds (4a*R**,13b*S**)-(12-fluoro-)4,4a,9,13b-tetrahydrodibenzo[3,4:6,7]cyclohepta[1,2-*b*]pyran-3(2*H*)-one and the corresponding 3-amino derivative via two separate sequences. These involved opening of the epoxide by either a propargyl or allylmagnesium reagent followed by tungsten-mediated cyclisation of the alkynol or OsO_4-catalysed transformation into the diol.

Recently we described a stereoselective synthesis of the racemic *trans*-fused hydrofuran alcohols **1**.[1] Our approach was based on ring opening of the epoxides **2** and **3** by reaction with propargylmagnesium bromide followed by mercury(II) induced cyclisation and further elaboration of the 2-(bromomethylene)-hydrofuran ring system (Scheme 1). The incentive for this work came from a recent finding that *trans*-fused tetracyclic hydrofuran compounds of type **5** exhibit potent activity in the central nervous system,[2] to be compared with that of similar well-known tricyclic and tetracyclic antidepressants like mianserin and mirtazapine.[3] In the original patent[2] compounds **5** were accessed via a non-stereoselective route which involved initial opening of epoxides **2** and **3** by allylmagnesium chloride, followed by bromination of the 11-allyl substituted tricyclic alcohols **4**. This led to concomitant cyclisation to give the epimeric 2-(bromomethyl) substituted hydrofurans, which upon further reaction with various amines were converted to an epimeric mixture of 2-(aminomethyl) compounds **5**.

In the present work our aim was to develop a route providing access to tetrahydropyran-fused analogues of tetracyclic compounds **1**. To this end, we envisaged two different strategies starting from either the 11-propargyl or 11-allyl substituted compounds **6** or **7** (Scheme 2). Each of these strategies could lead to the corresponding *trans*-fused hydropyran-3-one precursors **8a**,**b** by using either tungsten-mediated[4,5] cyclisation of the alkyne or OsO_4-catalysed oxidation[6] of the alkene group to form

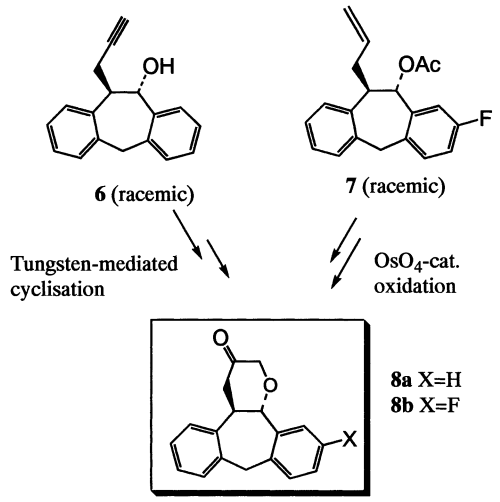


Scheme 1. Reported syntheses of hydrofuran-fused compounds **1** and **5**.

Keywords: tetrahydropyran; tricyclic compounds; heterocyclic compounds.

* Corresponding author. Tel.: +32-16-327407; fax: +32-16-327990; e-mail: frans.compernolle@chem.kuleuven.ac.be

0040-4039/02/$ - see front matter
PII: S0040-4039(02)02111-1



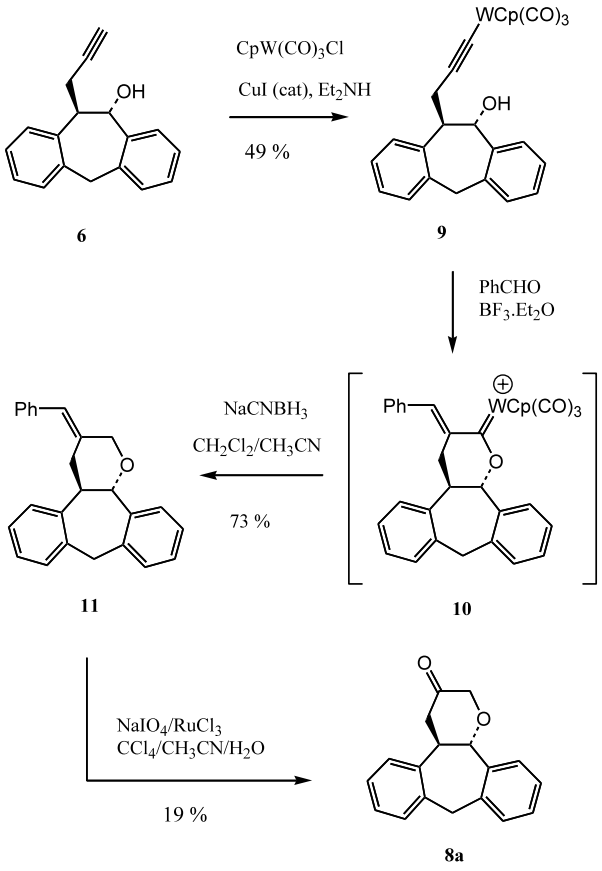
Scheme 2. Two different approaches used in this work to construct the tetrahydropyran-fused ketones **8a**,**b**.

the corresponding diol, followed by selective manipulation of the primary and secondary alcohol groups.

In our first approach proceeding via tungsten-mediated cyclisation, alkyne **6** was converted to the corresponding tungsten-η^1-alkynol derivative **9** by reaction with $CpW(CO)_3Cl$ (1.1 equiv.) and CuI (0.2 equiv.) in diethylamine according to the published procedure (Scheme 3).[4,5] Following chromatographic purification (EtOAc/hexane, 3:7) **9** was isolated in 49% yield. Compound **9** then was subjected to reaction with benzaldehyde and $BF_3{\cdot}Et_2O$ in diethyl ether at −40°C, which led to precipitation of the oxacarbenium salt **10**. This intermediate was not isolated but was directly converted to the benzylidene product **11** in a one-pot procedure, i.e. by replacing the diethyl ether mother liquor with dichloromethane and further reaction with $NaCNBH_3$ in acetonitrile at −40°C for 2 h. Following aqueous workup and chromatographic purification (silica gel column using diethyl ether/hexane, 1:9, followed by preparative TLC using dichloromethane/hexane, 7:3), compound **11** was isolated as a single isomer in 73% yield. The (*E*)-configuration of **11** was inferred from comparison with previous assignments for similar transformations.[5,7]

Oxidative cleavage of the benzylidene double bond was effected by reaction of **11** with $NaIO_4$ and catalytic $RuCl_3$. Unfortunately, this reaction led to formation of at least three products, from which the desired ketone **8a** could be isolated in only 19% yield (column chromatography using dichloromethane/hexane, 7:3).

In our second approach we started from the *O*-acetylated 11-allyl compound **7**, prepared by acetylation of the corresponding alcohol **4** (X = F). The latter was isolated by column chromatographic separation of the 7:3 mixture of regioisomers obtained from ring opening of epoxide **3** with allylmagnesium bromide (see before, Scheme 1).

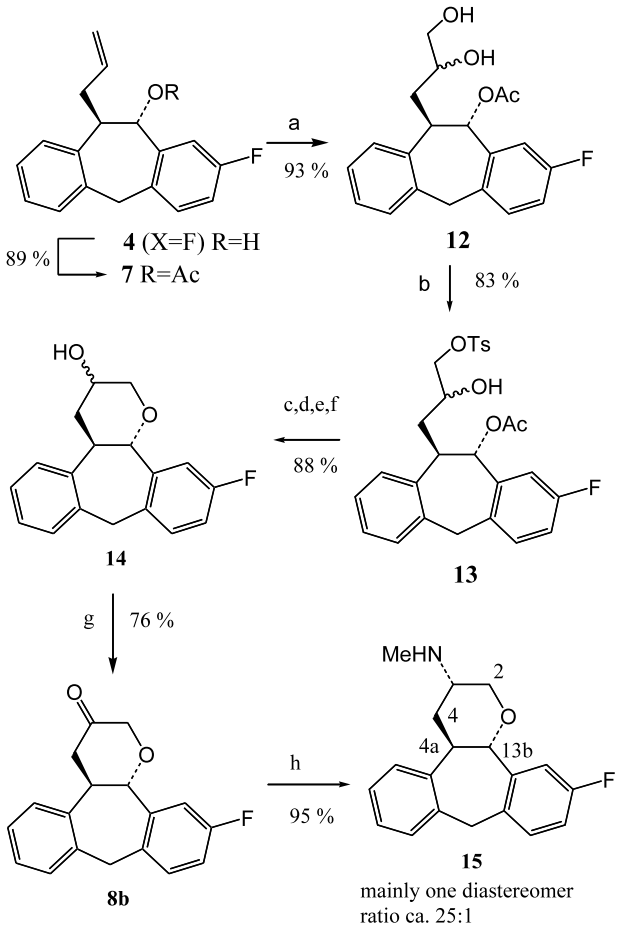


Scheme 3. Synthesis of ketone **8a** proceeding via tungsten-mediated cyclisation of alkyne **6**

Compound **7** was subjected to a catalytic OsO_4 dihydroxylation of the double bond to give diol **12** as a ca. 1:1 mixture of diastereoisomers, as seen from ^1H NMR analysis (Scheme 4). To achieve the desired ring closure to form the tetrahydropyran ring we envisioned regioselective activation of the primary OH-group using the selective *O*-tosylation procedure developed by Martinelli et al.,[8,9] followed by protection of the remaining secondary OH group as the corresponding tetrahydropyranyl (THP) ether. Subsequent base-induced removal of the acetate group then could result in concomitant cyclisation.

Without further separation of its epimeric components, diol **12** was submitted to Bu_2SnO catalysed *O*-tosylation to give the mono *O*-tosylated compound **13** in 83% yield. Subsequent protection of the free OH group as the THP ether followed by deacetylation—effected by reaction with K_2CO_3 in methanol—afforded the corresponding benzylic alcohol. However, in contrast to the fast cyclisation observed for the hydrofuran analogues,[1] no ring closure was observed under these conditions. Instead, this step required a separate treatment of the benzylic alcohol with NaH in THF for 3 days. Final acid-catalysed removal of the THP group furnished the epimeric mixture of *trans*-fused secondary alcohols **14** in 88% yield (four steps).

This diastereomeric complexity could be lifted by further oxidation of the epimeric alcohols **14** with pyri-



Scheme 4. *Reagents and conditions*: (a) OsO_4, NMO, CH_2Cl_2, rt, 20 h; (b) TsCl, Et_3N, Bu_2SnO, toluene, rt, 24 h; (c) DHP, CSA, CH_2Cl_2, rt, 2 h; (d) K_2CO_3, MeOH, rt, 16 h; (e) NaH, THF, rt, 3 days; (f) Dowex, MeOH, H_2O, 50°C, 2 h; (g) PCC, CH_2Cl_2, rt, 18 h; (h) $MeNH_2{\cdot}HCl$, Et_3N, MeOH, H_2/Pd–C, rt, 20 h.

dinium chlorochromate (PCC) affording pure ketone **8b** in racemic form. Final reductive amination of ketone **8b** was effected by Pd-catalysed hydrogenation with $MeNH_2{\cdot}HCl$ to give *N*-methylamino compound **15** mainly as one diastereomer (diastereomeric ratio 25:1).[10]

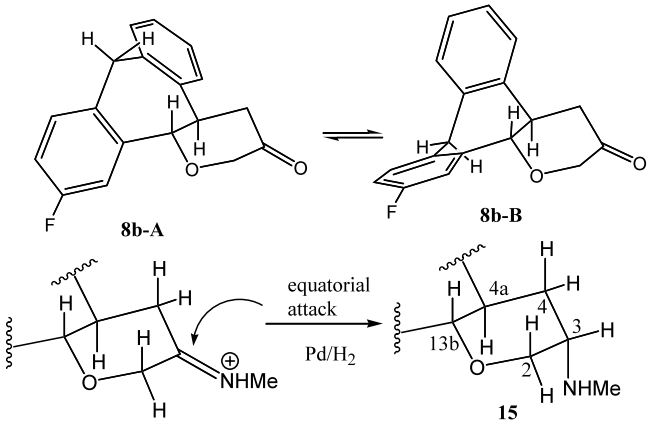
The stereochemical structure of **15** was established on the basis of the coupling constant values observed in the ^1H NMR spectrum. The ^3J value (10.7 Hz) found for the angular protons H-4a and H-13b indicates a 1,2-diaxial relationship consistent with *trans*-fusion of the tetrahydropyran ring. The equatorial protons H-2eq and H-4eq could be identified by a mutual long-range coupling (W-pattern, $^4J = 1.2$ Hz), while the ^3J coupling values found for the axial hydrogens H-2ax and H-4ax revealed an ax, eq disposition relative to proton H-3 ($^3J_{2ax,3} = 2.2$ Hz; $^3J_{4ax,3} = 3.3$ Hz). This clearly demonstrated the equatorial position of H-3 and hence the axial orientation of the amino group. The fixed *gauche* relationship between the *N* and *O* heteroatoms in target compound **15** stands in contrast to the conformational freedom of the 2-(aminomethyl) substituted tetrahydrofuran analogues **5**, allowing for both *anti* and *gauche* orientations of the heteroatoms. In fact, compound **15** was inactive.

To explain the diastereoselectivity of the hydrogenation we examined the preferred conformations of ketone **8b** and the corresponding iminium intermediate, as well as those of the axial and equatorial amine reduction products. From molecular mechanics calculations[11] it appears that all of these can exist as two almost isoenergetic conformational structures **A** and **B** with an opposite mode of bending for the diarylmethylene bridge. Apparently, such different bending does not significantly affect the shape of the ring-fused tetrahydropyran chair moiety. Consequently the stereochemical course of the hydrogenation is probably governed by a favourable equatorial approach of the palladium catalyst to either conformer **A** or **B** (Scheme 5).

In summary, we developed two different routes providing access to *trans*-fused tetrahydropyran derivatives of 5*H*-dibenzo[*a*,*d*]cycloheptene by using tungsten-mediated cyclisation of alkynol **6** or OsO_4-catalysed transformation of alkenol acetate **7** into the corresponding diol. Only the latter approach was fully exploited to obtain ketone precursor **8b**, which subsequently was converted to target amino compound **15**. According to molecular mechanics calculations these compounds can exist as two isoenergetic conformers **A** and **B** that have the same shape for the *trans*-fused chair moiety of the hydropyran ring but an opposite mode of bending for the diarylmethylene bridge.

Acknowledgements

The authors wish to thank the F.W.O. (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.



Scheme 5. Favoured conformations **A** and **B** of ketone **8a** and its iminium derivative favouring equatorial approach of Pd-catalyst.

References

1. Compernolle, F.; Mao, H.; Tahri, A.; Kozlecki, T.; Van der Eycken, E.; Medaer, B.; Hoornaert, G. J. *Tetrahedron Lett*. **2002**, *43*, 3011–3015.
2. Andrés-Gil, J. I.; Fernandez-Gadea, F. J.; Gil-Lopetegui, P.; Diaz-Martinez, A. Janssen Pharmaceutica, N. V. Patent Application PCT/EP98/06352; WO 99/19317 22 April, 1999.
3. Kaspersen, F. M.; Van Rooij, F. A. M.; Sperling, E. G. M.; Wieringa, J. H. *J. Label. Comp. Radiopharm*. **1989**, *9*, 1055–1068.
4. Liang, K.-W.; Li, W.-T.; Peng, S.-M.; Wang, S.-L.; Liu, R.-S. *J. Am. Chem. Soc*. **1997**, *119*, 4404–4412.
5. Liang, K.-W.; Chandrasekharam, M.; Li, C.-L.; Liu, R.-S. *J. Org. Chem*. **1998**, *63*, 7289–7293.
6. Broom, N.; O'Hanlon, P. J.; Simpson, T. J.; Stephen, R.; Willis, C. L. *J. Chem. Soc., Perkin Trans. 1* **1995**, 3067–3072.
7. Spectral data for analytically pure compounds **9** and **11**:
   9: oil; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 2.87 (dd, 1H, $J=8.0$, 16.7 Hz, CH_2), 3.07 (dd, 1H, $J=4.4$, 16.7 Hz, CH'_2), 3.21–3.25 (m, 1H, CH), 3.58 (s, 1H, OH), 3.76 (d, 1H, $J=14.1$ Hz, CH_2-5), 4.16 (d, 1H, $J=14.1$ Hz, CH'_2-5), 5.46 (d, 1H, $J=9.2$ Hz, C$\underline{H}$-OH), 5.48 (s, 5H, -Cp), 7.02–7.22 (m, 7H, H-Ar), 7.58 (d, 1H, $J=7.7$ Hz, H-Ar); ^{13}C NMR (100 MHz, $CDCl_3$): 30.04 (CH_2), 40.44 (CH_2-5), 51.25 (CH), 61.00 (≡C-W), 73.63 (CH-OH), 84.04 (C≡C-W), 91.37 (-Cp), 126.20, 126.25, 126.53, 126.89, 127.06, 127.23, 128.28, 130.38 (CH-Ar), 139.53, 139.58, 140.09 (C-Ar), 211.77, 211.92 (CO); MS (CI, methane), m/z (%): 581 (MH^+, 1%), 553 (MH^+–CO, 5%), 525 (MH^+–2CO, 1%), 497 (MH^+–3CO, 1%).
   11: oil; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 2.69 (t, 1H, $J=13.8$ Hz, CH_2-4), 3.37–3.44 (m, 2H, CH_2-4+CH-4a), 3.93 (d, 1H, $J=14.6$ Hz, CH_2-9), 4.22 (d, 1H, $J=14.6$ Hz, CH'_2-9), 4.48 (d, 1H, $J=12.4$ Hz, CH_2-2), 4.58 (d, 1H, $J=12.4$ Hz, CH'_2-2), 4.80 (d, 1H, $J=10.4$ Hz, CH-13b), 6.53 (s, 1H, C=CH), 7.08–7.38 (m, 12H, H-Ar), 7.46 (d, 1H, $J=7.8$ Hz, H-Ar); ^{13}C NMR (100 MHz, $CDCl_3$): 34.12 (CH_2-4), 40.81 (CH_2-9), 45.40 (CH-4a), 72.12 (CH_2-2), 81.88 (CH-13b), 125.01 (C=CH), 126.60, 126.79, 126.84, 127.42, 127.48, 127.62, 127.77, 128.18, 128.32, 128.39, 128.42, 128.93, 128.96 (CH-Ar), 136.55, 136.69, 137.87, 138.37, 138.65 (C-Ar), 140.43 (C=CH); MS (CI, methane), m/z (%): 339 (MH^+, 100%), 321 (MH^+–H_2O, 81%).
8. Martinelli, M. J.; Nayyar, N. K.; Moher, E. D.; Dhokte, U. P.; Pawlak, J. M.; Vaidyanathan, R. *Org. Lett*. **1999**, *1*, 447–450.
9. Martinelli, M. J.; Vaidyanathan, R.; Khau, V. V. *Tetrahedron Lett*. **2000**, *41*, 3733–3776.
10. Spectral data for analytically pure compounds **8b** and **15**:
    8b: oil; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 2.90 (dd, 1H, $J=16.3$, 12.0 Hz, H-4ax), 3.01 (ddbr, 1H, $J=16.3$, 4.5 Hz, H-4eq), 3.75 (dt, 1H, $J=12.0$, 4.5 Hz, H-4a), 4.03 (d, 1H, $J=15.3$ Hz, H-2), 4.08 (d, 1H, $J=15.3$ Hz, H′-2), 4.23 (d, 1H, $J=16.3$ Hz, CH_2-9), 4.42 (d, 1H, $J=16.3$ Hz, CH'_2-9), 4.94 (d, 1H, $J=10.5$ Hz, H-13b), 6.86 (dt, 1H, $J=8.3$, 2.7 Hz, H-Ar), 7.08–7.26 (m, 6H, H-Ar); ^{13}C NMR (100 MHz, $CDCl_3$): 39.99 (CH_2-9), 43.80 (CH-4a), 45.31 (CH_2-4), 74.64 (CH_2-2), 78.82 (CH-13b), 114.22 (d, $^2J_{CF}=$ 12.38 Hz, CH-Ar-F), 114.44 (d, $^2J_{CF}=10.61$ Hz, CH-Ar-F), 127.14, 127.33, 127.49, 128.13 (CH-Ar), 129.67 (d, $^3J_{CF}=7.83$ Hz, CH-Ar-F), 113.94 (d, $^4J_{CF}=3.08$ Hz, C-Ar-F), 137.27, 138.51 (C-Ar), 139.07 (d, $^3J_{CF}=7.33$ Hz, C-Ar-F), 162.02 (d, $^1J_{CF}=244.52$ Hz, C-Ar-F), 206.62 (C=O). MS (CI, methane), m/z (%):283 (MH^+, 25%), 265 (MH^+–H_2O, 100%); EI: m/z 282 ($M^{+\bullet}$, 39%), 209 (100%); IR: (NaCl, cm^{-1}): 3432 (br), 3060, 1728 (s), 1495, 1266, 1088.
    15: oil, ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 2.13 (td, 1H, $J=12.9$, 3.3 Hz, H-4ax), 2.38 (dddd, 1H, $J=12.9$, 5, 2.6, 1.2 Hz, H-4eq), 2.54 (s, 3H, CH_3), 2.84–2.86 (m, 1H, H-3), 3.49 (td, 1H, $J=10.7$, 2.6 Hz, H-4a), 3.81 (dd, 1H, $J=11.8$, 2.2 Hz, H-2ax), 3.93 (d, 1H, $J=14.8$ Hz, CH_2-9), 4.15 (d, 1H, $J=14.8$ Hz, CH'_2-9), 4.25 (ddd, 1H, $J=11.8$, 2.0, 1.2 Hz, H-2eq), 4.53 (d, 1H, $J=10.7$ Hz, H-13b), 6.81 (dt, $J=8.4$, 2.7 Hz, H-Ar), 7.07–7.20 (m, 6H, H-Ar); ^{13}C NMR (100 MHz, $CDCl_3$): 33.89 (CH_3), 35.45 (CH_2-4), 38.61 (CH-4a), 40.04 (CH_2-9), 54.46 (CH-3), 70.83 (CH_2-2), 81.61 (CH-13b), 113.97 (d, $^2J_{CF}=21.11$ Hz, CH-Ar-F), 115.25 (d, $^2J_{CF}=22.63$ Hz, CH-Ar-F), 126.54, 126.91, 127.69, 128.48 (CH-Ar), 129.51 (d, $^3J_{CF}=7.73$ Hz, CH-Ar-F), 134.08 (d, $^4J_{CF}=3.16$ Hz, C-Ar-F), 138.82, 140.18 (C-Ar), 140.42 (d, $^3J_{CF}=7.18$ Hz, C-Ar-F), 162.00 (d, $^1J_{CF}=243.87$ Hz, C-Ar-F); MS (CI, methane), m/z (%):298 (MH^+, 100%); EI: m/z 209 (100%); IR: (NaCl, cm^{-1}): 2495, 1495, 1250, 1055
11. Calculations were carried out using the Hyperchem™ molecular mechanics method.