A GREEN REGIO- AND DIASTEREOSELECTIVE SYNTHESIS OF NOVEL TRISPIROHETEROCYCLES IN 2,2,2-TRIFLUOROETHANOL

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Keywords: Spiroheterocycles; cycloaddition; azomethine ylides; 2,2,2-trifluoroethanol; trispiropyrrolidine and thiapyrrolizidine derivatives

A new regio- and diastereoselective 1,3-dipolar cycloaddition reaction of 7,9-bis[(E)-arylidene]-1,4-dioxa-spiro[4,5]decane-8-ones, sarcosine/1,3-thiazolane-4-carboxylic acid and acenapthequinone has been developed for the synthesis of trispiropyrrolidine/thiapyrrolizidine derivatives using 2,2,2-trifluoroethanol as a green solvent. The solvent (TFE) can be readily separated from reaction products and recovered in excellent purity for direct reuse. A regio- and stereochemical outcome of the cycloaddition reaction was ascertained by X-ray crystallographic study.

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INTRODUCTION

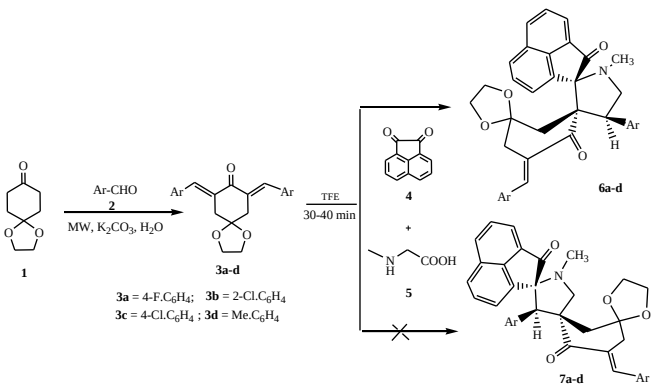
Nitrogen-containing five membered heterocycles are an important class of compounds, not only because of their natural abundance, but also for their chemical and pharmacological significance.[1] Functionalized pyrrolidines are important targets in synthetic chemistry and form the central skeletons of numerous alkaloids and are classes of compounds with significant biological activity.[2-4] On the other hand, spiropyrrolidines have gained significant attention due to their interesting biological activities, such as antimicrobial, antitumor and antibiotic properties.[5-7] Some spiropyrrolidines are potential antileukemic and anticonvulsant agents and antiviral and local anaesthetic activities. Therefore, the synthesis of these compounds has become an important target in recent years.[8-10]

The most developed procedure for construction of spiro-containing compounds depends mainly on cycloaddition reactions, especially 1,3-dipolar cycloaddition to exocyclic double bonds.[11] Azomethine ylides are considered as one of the most important dipole systems which are used intensively for preparation of spiropyrrolidine compounds where, great attention was directed towards their reactions due to their high regio- as well as stereoselective properties.[12-14]

Development of eco-friendly synthetic protocols for the assembly of new chemical entities is of great importance in recent years.[15] In this context, fluorinated alcohols have emerged as new 'green' solvents to replace the conventional volatile organic solvents.[16]

They exhibit a booster effect as a reaction medium and thus, they promote various reactions by pure solvent effect.[17,18] Further, their unique and promising physicochemical properties, such as high selectivity, low nucleophilicity, high hydrogen bonding donor ability, nonvolatility, nonflammability, high ionizing power and recyclability by simple distillation made them well known polar solvent in green synthesis.[19-22]

Recently, our research group has been largely involved in the synthesis of dispiropyrrolidine/pyrrolizidine derivatives via 1,3-cycloaddition reaction.[23,24] Encouraged by these studies and our research program aims to develop new selective and environmental friendly methodologies for synthesis of spiroheterocycles,[25-30] herein we report an expeditious and facile protocol for the synthesis of novel trispiropyrrolidines derivatives through 1,3-dipolar addition reaction of 7,9-bis[(E)-arylidene]-1,4-dioxa-spiro[4,5]-decane-8-ones (**3**), acenapthequinone (**4**) and sarcosine (**5**) using 2,2,2-trifluoroethanol as a reusable solvent for the first time (Scheme 1). To the best of our knowledge, there is no report for the synthesis of novel trispiropyrrolidine derivatives using acenapthequinone, sarcosine and bis-(arylidene substituted)-spiro[4,5]decan-8-ones so far.



Scheme 1. Synthesis of trispiroacenaphthylenepyrrolidines (**6a-d**)

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RESULT AND DISCUSSION

The required dipolarophiles 7,9-bis[(E)-arylidene]-1,4-dioxaspiro[4,5]decane-8-ones (**3a-d)** were prepared by green approach using water and mild base K_2CO_3 under microwaves by the reaction of spiro[4,5]decan-8-one (**1)** with various substituted benzaldehydes **2** in shorter reaction time and in excellent yield as compared to conventional method.[31] The geometry of the olefinic double bond was found to be *E* as evidenced by ^{1}H NMR spectra wherein the olefinic protons appeared at δ 7.64-7.67 (s, 2H) and is found to be identical with those of authentic samples prepared by reported method.

A mixture of 7,9-bis[(E)-4-fluoro-benzylidene]-1,4-dioxa-spiro[4,5]decane-8-one (**3a)**, acenapthequinone (**4)** and sarcosine (**5)** was refluxed for 30-40 minutes in trifluoroethanol to furnish a yellow solid, to be characterized 1-N-methylspiro[2,2′]acenaphthylene-spiro[3,9″]-7″-(4-fluorophenylmethylidene)-1,4-dioxa-spiro-[4″,5″]decan-4-(4-fluorophenyl)-pyrrolidine-8″,2′-dione (**6a)**. The product is isolable simply by filtration with reasonable purity. Initially to study the effect of solvent on present cycloaddition reaction, the reaction was also carried out in different solvents and among them, trifluoroethanol was found to be the best to get a maximum yield of product (Table 1).

Table 1 Preparation of **6a** in different solvents for optimization of reaction conditions[a]

Entry	Solvent	Temp.,^{0}C	Time, h	Yield[b], %
1	ethanol	Reflux	8	78
2	methanol	Reflux	6	75
3	acetonitrile	Reflux	5	69
4	1,4-dioxane	Reflux	6	71
5	THF	Reflux	7	68
6	TFE	Reflux	0.5	92

[a] Reaction conditions: 1mmol of **3a**, **4** and **5;** [b]Isolated yields

Encouraged by these results, the rest of compounds as listed in Table 2 were similarly synthesized using trifluoroethanol as solvent. The reaction gave a single product in all cases as evidenced by thin layer chromatography (TLC). This cycloaddition is also regioselective with the electron rich carbon of the dipole adding to the β-carbon of the α, β-unsaturated moiety of **3** and stereoselective affording only one diastereomer is obtain exclusively, despite the presence of three stereo center in the product **6**. In this cycloaddition only one C=C of **3** is involved, ascribable to steric hindrance encountered for the second cycloaddition resulting in chemoselectivity. The stereochemical information was obtained from an X-ray crystallographic study of a single crystal of **6a** (Fig. 1).[32] The cyclohexanone and the pyrrolidine rings of **6a** are in half chair and envelop forms, respectively. The structures and the regiochemistry of the cycloadducts were also confirmed by spectral analysis. The IR spectrum of **6a** showed two peaks at 1710 and 1680 cm^{-1} due to carbonyl groups of the acenapthequinone and bis (arylidene)-1,4-dioxaspiro[4,5]decane-8-ones. The ^{1}H NMR spectrum of compound **6a** the three *N*-CH_3 hydrogens of the pyrrolidine ring appear as a singlet at δ 1.89 ppm. The –NCH_2 protons and benzylic proton of pyrrolidine ring appeared at δ 3.23 (m, 1H), δ 3.71 (t, 1H, J = 7.2 Hz), δ 4.95 (t, 1H, J = 7.2 Hz) which explained the regiochemistry of the cycloadduct. The ^{13}C NMR spectrum of **6a** showed two signals at δ 163.83, and δ 187.20 for the carbonyl groups.

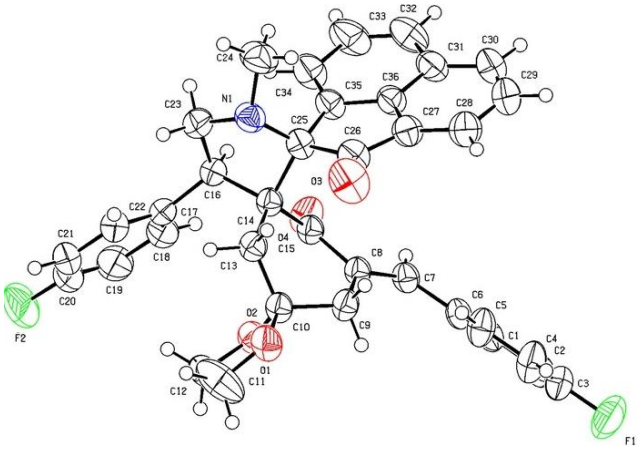
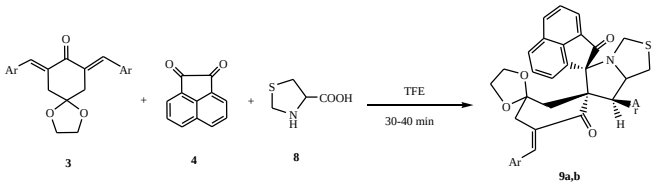


Figure 1. ORTEP diagram of compound **6a**

To further explore the potential of this cycloaddition reaction for synthesis of other spiro-heterocycles, we have investigated the present reaction with thiazolidine-4-carboxylic acid (**8)** in place of sarcosine (**5**) to obtained novel trispirothiapyrrolizidine derivatives listed in table 2 (Scheme 2). The structures of all products were characterized by IR, ^{1}H NMR and ^{13}C NMR spectral analysis.



Scheme 2. Synthesis of trispiroacenaphthylenethiapyrrolizidines **9a, b**

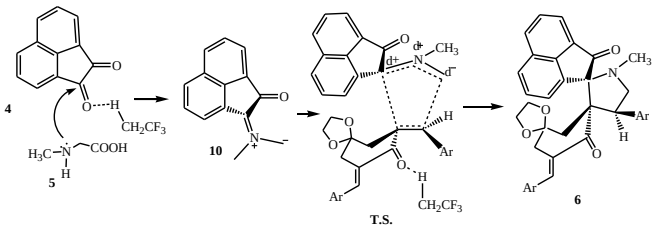
Table 2 Synthetic results of trispiroacenaphthylene-pyrrolidine/thiapyrrolizidines (**6a-d/9a-b)**

No.	Ar	Yield,%	Mp,°C	R_f [a]
6a	4-FC_6H_4	92	228-230	0.85
6b	2-ClC_6H_4	93	234-236	0.81
6c	4-ClC_6H_4	94	188-190	0.87
6d	4-MeC_6H_4	92	196-198	0.83
9a	4-FC_6H_4	89	220-222	0.79
9b	4-MeC_6H_4	90	190-192	0.83

[a](C$_6$H$_6$:EtOAc=8:2)

A plausible mechanism for the formation of the cycloadducts is proposed in Scheme 3. It is known that due to the Bronsted acidity (pKa =12.4) and strong ionizing power 2,2,2-trifluoroethanol play unique behavior in organic transformations.[33] In the present cycloaddition reaction the reaction of acenapthequinone (**4)** with sarcosine (**5)** leads to the "in situ" formation of an azomethine ylide (**10).** Subsequent 1,3-dipolar cycloaddition reaction of dipolarophile **3** and **10** afford trispiropyrrolidine derivative **6.** The hydrogen atom of TFE being electron-deficient and could form hydrogen bonds with carbonyl groups of both acenaphthequinine and dipolarophile **3** thereby catalyses

reaction. Further, the polar transition state of the reaction could be stabilized well by high ionizing solvent TFE. These catalysis presumably expedites the reaction in TFE relative to other solvents**.**



Scheme 3. Plausible mechanism for synthesis of trispiropyrrolidine derivatives

EXPERIMENTAL SECTION

The melting points of all compounds were determined on a Toshniwal apparatus. The purity of compounds was checked on thin layers of silica Gel-G coated glass plates and n-hexane: ethyl acetate (8:2) as eluent. IR spectra were recorded on a Shimadzu FT IR–8400S spectrophotometer using KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 and $CDCl_3$ using TMS as an internal standard on a Bruker Avance spectrophotometer at 300 and 75 MHz, respectively. Mass spectra of representative compounds were recorded on JEOL SX-102 spectrometer at 70 eV. Elemental analyses were carried out on a Carlo-Erba 1108 CHN analyzer. X-ray intensity data were collected on Bruker Kappa Apex II instrument.

General procedure for the synthesis of trispiro-pyrrolidine/thiapyrrolizidines 6/9

An equimolar mixture of appropriate 7,9-bis[(E)-arylidene]-1,4-dioxa-spiro[4,5]decane-8-ones (**3)** (1 mmol), acenapthequinone **(4)** (1 mmol) and sarcosine (**5)**/thiazolidine-4-carboxylic acid (**8)** (1 mmol) in 2,2,2-trifluoroethanol (2-3 ml) was refluxed for the appropriate time (30-40 min). After completion of the reaction as indicated by (TLC), the solid precipitate was filtered and washed with TFE to furnish pure trispiropyrrolidine/thiapyrrolizidine derivatives. The TFE was distilled off (to recover for the next run).

Synthesis of 6a. Yellow Solid; Yield: 92%; IR (KBr, υ cm^{-1}): 3030 (arom-CH), 1710 (>C=O), 1680 (>C=O); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.65(d, 1H, J = 13.8 Hz), 1.89 (s, 3H, N-CH_3), 2.31-2.48 (m, 2H,), 2.90 (m, 1H), 3.23 (m, 1H), 3.29-3.43 (m, 4H, $OCH_2)_2$, 3.71 (t, 1H, J = 7.2 Hz), 4.95 (t, 1H, J = 7.2 Hz), 6.62-8.14 (m, 15H, Ar-H and =CH-Ar); ^{13}C NMR (75 MHz, DMSO-d_6) 35.09, 37.78, 40.33, 47.63, 56.71, 63.18, 63.06, 64.22, 80.54, 105.37, 114.78, 115.06, 115.31, 115.59, 115.90, 119.96, 124.38, 125.16, 127.99, 128.42, 129.73, 130.89, 131.92, 132.04, 132.57, 133.42, 135.30, 135.69, 141.51, 159.58, 198.58, 204.79; Anal.: Calcd for $C_{36}H_{29}F_2NO_4$ C, 74.86; H, 5.06; N, 2.42. Found: C, 74.71; H, 5.02; N, 2.38; Mass (m/z): 578 [M$^+$].

Synthesis of 6b. Yellow Solid; Yield: 93 %; IR (KBr, ν cm^{-1}): 3020 (arom-CH), 1711 (>C=O), 1685 (>C=O); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.23 (d, 1H, J = 13.8 Hz,), 1.78 (s, 3H, N-CH_3), 1.85-1.97 (m, 2H), 2.73-2.79 (m, 1H), 3.02-3.29 (m, 4H, $OCH_2)_2$, 3.43 (t, 1H, J = 8.6 Hz), 3.75 (t, 1H, J = 8.7 Hz), 5.11 (t, 1H, J = 8.7 Hz), 7.01-8.07 (m, 15H, Ar-H and =CH-Ar); ^{13}C NMR (75 MHz, DMSO-d_6) 35.112, 35.89, 37.78, 40.36, 48.61, 57.21, 64.12, 65.18, 80.34, 105.27, 110.10, 122.52, 123.45, 124.69, 125.56, 126.38, 126.71, 126.98, 128.42, 129.14, 130.15, 130.62, 132.65, 133.57, 134.86, 135.08, 136.18, 136.28, 137.26, 137.98, 198.68, 203.42. Anal.: Calcd for $C_{36}H_{29}Cl_2NO_4$ C, 70.82; H, 4.76; N, 2.29. Found: C, 70.98; H, 4.72; N, 2.34; Mass (m/z): 610 [M$^+$].

Synthesis of 6c. Yellow solid; Yield: 94%; IR (KBr, ν cm^{-1}): 3045 (arom-CH), 1708 (>C=O), 1687 (>C=O); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.25 (d, 1H, J = 13.7 Hz), 1.84 (s, 3H, N-CH_3), 2.56-2.65 (m, 2H), 2.95 (m, 1H), 3.09-3.34 (m, 4H, $OCH_2)_2$, 3.46 (m, 1H), 3.78 (t, 1H, J = 8.7 Hz), 5.12 (t, 1H, J = 8.7 Hz), 7.04-8.23 (m, 15H, Ar-H and =CH-Ar); ^{13}C NMR (75 MHz, DMSO-d_6) 35.06, 35.89, 36.28, 42.35, 47.83, 56.61, 63.48, 64.89, 80.14, 105.27, 109.21, 121.51, 121.22, 123.41, 125.35, 126.51, 127.98, 128.99, 129.53, 129.85, 131.42, 132.73, 133.53, 134.46, 135.18, 135.48, 135.97, 136.21, 140.24, 142.54, 198.34, 203.19. Anal.: Calcd for $C_{36}H_{29}Cl_2NO_4$ C, 70.82; H, 4.76; N, 2.29. Found: 70.68; H, 4.72; N, 2.23; Mass (m/z): 610 [M$^+$].

Synthesis of 6d. Yellow Solid; Yield: 92%; IR (KBr, ν cm^{-1}): 3060 (arom-CH), 1710 (>C=O), 1688 (>C=O); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.45 (d, 1H, J = 13.8 Hz), 1.78 (s, 3H, N-CH_3), 2.14 (s, 3H, CH_3), 2.18 (s, 3H, CH_3) 2.32-2.42 (m, 2H,), 2.82 (m, 1H), 3.25-3.43 (m, 4H, $OCH_2)_2$, 3.70 (t, 1H, J = 7.3 Hz), 4.92 (t, 1H, J = 7.3 Hz), 6.65-8.24 (m, 15H, Ar-H and =CH-Ar); ^{13}C NMR (75 MHz, DMSO-d_6) 34.41, 35.55, 37.44, 47.66, 57.29, 61.36, 64.39, 65.18, 76.97, 105.34, 109.21, 115.35, 115.54, 116.26, 116.67, 122.16, 125.17, 127.53, 130.27, 132.76, 133.16, 133.37, 135.87, 138.21, 139.76, 143.32, 134.08, 134.58, 135.28, 137.26, 198.58, 204.79. Anal.: Calcd for $C_{38}H_{35}NO_4$: C, 80.12; H, 6.19; N, 2.46. Found: C, 80.26; H, 6.23; N, 2.41; Mass (m/z): 570 [M$^+$].

Synthesis of 9a. Yellow Solid, Yield: 89%; IR (KBr, ν cm^{-1}): 3070 (arom-CH), 1710 (>C=O), 1685 (>C=O); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.66 (d, 1H, J = 13.8 Hz), 2.56-2.76 (m, 3H), 2.81 (dd, 2H), 3.08 (dd, 1H, J = 6.9 Hz), 3.45 (dd, 1H, J = 7.4 Hz), 3.61-3.72 (m, 4H, $OCH_2)_2$, 4.32 (d, 1H, J = 10.5 Hz), 4.54 (m, 1H), 6.28-7.49 (m, 15H, Ar-H and =CH-Ar), 10.63 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) 31.13, 35.85, 37.46, 48.21, 52.10, 53.01, 63.33, 64.84, 66.60, 76.77, 105.96, 109.59, 114.98, 115.26, 115.94, 116.23, 121.11, 124.23, 129.74, 129.97, 131.38, 132.30, 132.41, 132.60, 132.70, 133.33, 133.52, 133.92, 142.75, 177.93, 197.61. Anal.: Calcd for $C_{37}H_{29}F_2NO_4S$: C, 71.48; H, 4.70; N, 2.25. Found: C, 71.42; H, 4.66; N, 2.21; Mass (m/z): 622 [M$^+$].

Synthesis of 9b. Yellow Solid, Yield: 90%; IR (KBr, ν cm^{-1}): 3055 (arom-CH), 1710 (>C=O), 1684 (>C=O); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.98 (d, 1H, J = 13.8 Hz), 2.05 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 2.24-2.50 (m, 3H), 2.91 (m, 2H), 3.13 (m, 1H), 3.44 (dd, 1H), 3.56-3.69 (m, 4H, $OCH_2)_2$, 4.41 (d, 1H, J = 10.6 Hz), 4.71 (m, 1H), 6.68-8.04 (m, 15H, Ar-H and =CH-Ar); ^{13}C NMR (75 MHz, DMSO-d_6) 19.16, 19.41, 33.77, 35.82, 36.07, 39.00, 50.71, 51.35, 61.28, 62.74, 65.43, 77.42, 103.91, 118.90, 123.70, 124.26, 125.91, 125.91, 126.21, 127.05, 128.00, 128.55, 129.62, 129.81, 130.74, 130.18, 130.63, 131.91, 133.89, 134.62, 136.12, 137.20, 179.50, 196.23. MS (m/z): 611[M$^+$+

1]. Anal.: Calcd for $C_{39}H_{35}NO_4S$: C, 76.32; H, 5.75; N, 2.28. Found: C, 76.20; H, 5.70; N, 2.22; Mass (m/z): 614 [M^+].

CONCLUSION

In conclusion, we have developed an efficient and regioselective three-component 1,3-dipolar cycloaddition reaction for the synthesis of novel trispiro-pyrrolidine and thiapyrrolizidines that incorporate in their structures a 1,3-dioxalane moiety. This method has the advantages of good yield, mild reaction condition, low cost and simplicity in process and handling. The recovered TFE of this method for other useful reactions are currently underway.

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REFERENCES

[1]Vidhya Lakshmi, N., Tamilisai, R., Perumal, P. T., *Tetrahedron Lett.* **2011**, *52*, 5301.

[2]Augustine, T., Kanakam, C. C., Vithiya, S. M., Ramkumar, V., *Tetrahedron Lett.* **2009**, *50*, 5906.

[3]Luibineau, A., Bouchain, G., Queneau, Y., *J. Chem. Soc., Perkin Trans 1*, **1995**, 2433.

[4]Deshong, P., Leginus, J. M., *J. Am. Chem. Soc.* **1983**, *105*, 1686.

[5]Kozikowski, A. P., *Acc. Chem. Res.* **1984**, *17*, 410.

[6]Chande, M. S., Verma, R. S., Barve, P. A., Khanwelkar, R. R., *Eur. J. Med. Chem.* **2005**, *40*, 1143.

[7]Ban, Y., Taga, N., Oishi, T., *Chem. Pharm. Bull.* **1976**, *24*, 736.

[8]Kornet, M. J., Thio, A. P., *J. Med. Chem.* **1976**, *19*, 892.

[9]Bridges, R. J., Lovering, F. E., Humphery, J. M., Stanley, M. S., Blakely, T. N., Cristofaro, M. F., Chamberlin, A. R., *Bioorg. Med. Chem. Lett.* **1993**, *3*, 115.

[10]Rathna, D., Manian, R. S., Jayadevan, J., Kumar, S. S., Raghavachary, R., *Tetrahedron Lett.* **2006**, *47*, 829.

[11]Padwa, A., *In 1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley & Sons: New York **1984**, *2*, 277.

[12]Grigg, R., Sridharan, V., Curran D. P., *(Eds.) Advance in Cycloaddition*, Jai Press, London **1993**, 161.

[13]Coldham, L., Hufton, R., *Chem. Rev.* **2005**, *105*, 2765.

[14]Lashgari, N., Ziarani, G. M., *ARKIVOC* **2012**, (i), 277.

[15]Rajesh, R., Raghunathan, R., *Tetrahedron Lett.* 2010, *51*, 5845.

[16]Khaksar, S., Rouhollahpour, A., Talesh, S. M., *J. Fluorine Chem.* **2012**, *141*, 11.

[17]Vuluga, D., Legros, J., Crousse, B., Slawin, A. M. Z., Laurence, C., Nicolet, P., Bonnet-Delpon, D., *J. Org. Chem.* **2011**, *76*, 1126.

[18]Berkessel, A., Adrio, J. A., Huttenhain, D., Neudorfl, J. M., *J. Am. Chem. Soc.* **2006**, *128*, 8421.

[19]Khaksar, S., Heydari, A., Tajbakhsh, M., Bijanzadeh, H. R., *J. Fluorine Chem.* **2010**, *131*, 106.

[20]Qiao, R. Z., Xu, B. L., Wang, Y. H., *Chinese Chem. Lett.* **2007**, *18*, 656.

[21]Begue, J.P., Bonnet-Delpon, D., Crousse, B., *Synlett* **2004,** 18.

[22]Shuklov, I.A., Dubrovina, N.V., Borner, A., *Synthesis* **2007**, 2925.

[23]Dandia, A., Jain, A. K., Bhati, D. S., *Tetrahedron Lett.* **2011**, *52*, 5333.

[24]Dandia, A., Jain, A. K., Sharma, S., *Tetrahedron Lett.* **2012**, *53*, 5859.

[25]Dandia, A., Laxkar, A. K., Singh, R., *Tetrahedron Lett.* **2012**, *53*, 3012.

[26]Dandia, A., Singh, R., Bhaskaran, S., *Green Chem.* **2011**, *13*, 1852.

[27]Dandia, A., Singh, R., Bhaskaran, S., *Ultrason. Sonochem.* **2010**, *17*, 399.

[28]Dandia, A., Singh, R., Khaturia, S., *J. Fluorine Chem.* **2007**, *128*, 524.

[29]Dandia, A., Gautam, S., Jain, A. K., *J. Fluorine Chem.* **2007**, *128*, 1454.

[30]Dandia, A., Singh, R., Sachdeva, H., Arya K., *J. Fluorine Chem.* **2001**, *111*, 61.

[31]Dimmock, J. R., Padmanilayam, M. P., Zello, G. A., Nienaber, K. H., Allen, T. M., Santos, C. L., DeClerq, E., Balzarini, J., Manavathu, E. K., Stables, J. P., *Eur. J. Med. Chem.* **2003**, *38*, 169.

[32]Crystallographic data (excluding structure factors) for trispiroderivative **6a** in this letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 874669. Copy of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax:+44 (0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

[33]Fustero, S., Roman, R., Sanz-Cervera, J. F., Simon-Fuentes, A., Cunat, A. C., Villanova, S., Murguıa, M., *J. Org. Chem.* **2008**, *73*, 3523.

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