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Reversal of Diastereoselectivity of Nitrile Oxide 1,3-Dipolar Cycloadditions by Mg(II). Acceleration of Cycloaddition by Microwave Irradiation

Peter Mičúch,[a] L'ubor Fišera,[a,*] Michał K. Cyrański,[b] Tadeusz M. Krygowski[b] and Ján Krajčík[a]

[a]*Department of Organic Chemistry, Slovak University of Technology, 812 37 Bratislava, Slovak Republic*
[b]*Department of Chemistry, University Warsaw, 02 093 Warsaw, Poland*

Dedicated to Professor Rolf Huisgen on the occasion of his 80th birthday

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Abstract—1,3-Dipolar cycloadditions of mesitonitrile oxide to Baylis–Hillman adducts (β-hydroxy-α-methylene esters) proceed regioselectively in good yields. Addition of Grignard reagent reverses the diastereoselectivity of the cycloaddition. Microwave irradiation strongly accelerates the reaction with only a small effect on its diastereoisomeric excess.

Introduction

The 1,3-dipolar cycloaddition of alkenes to nitrile oxides is one of the fundamental reactions since the isoxazolines formed are very useful 'building blocks' in organic synthesis.[1] They can be selectively reduced to 1,3-amino-alcohols,[2,3] β-hydroxycarbonyls[4] and α,β-unsaturated carbonyls.[5] It is also possible to replace hydrogen in position 3 of the isoxazoline ring by an electrophile which extends the scope of using isoxazolines as intermediates in organic synthesis.[6]

If a chiral alkene is used as the dipolarophile, two diastereoisomers can be formed by 1,3-dipolar cycloaddition. Diastereoselectivity of the cycloadditions depends mainly upon the nature of dipole and dipolarophile and several models, which allow the prediction of the main diastereomer, have been published.[7] However, if 1,3-dipolar cycloaddition is used in any synthesis of a complex target molecule, change or even reversal of the ratio of diastereoisomers would be desirable. Although Lewis acids are often used as catalysts in Diels–Alder cycloadditions, use of Lewis acids in 1,3-dipolar cycloaddition of nitrile oxides is the subject of only few reports to the date.[8–10] Kanemasa et al. have controlled the diastereoselectivity of the cycloaddition of nitrile oxides to electron rich alkenes (allylic alcohols) in the presence of a Mg(II) cation.[8,9] They proposed the transition state in which magnesium co-ordinates both nitrile oxide and allylic alcohol (Scheme 1). The transition state containing less steric hindrance between the R^1 group and the terminal hydrogen of the C=C bond should be favoured.[8]

In this paper, we report the ability of Mg(II) to reverse the diastereoselectivity of nitrile oxide 1,3-dipolar cycloaddition and the detailed investigation of the effect of the addition of methylmagnesium bromide upon the induced stereoselectivity in cycloadditions of mesitonitrile oxide with electron deficient dipolarophiles; our preliminary results in this area have been the subject of a recent communication.[10]

Results and Discussion

Baylis–Hillman adducts **1a–f** were chosen as electron deficient dipolarophiles. Baylis–Hillman adducts **1a**,**b** were obtained by a five step procedure from commercial available D-manitol;[11] whereas adducts **1c–f** were prepared via the Baylis–Hillman reaction from the appropriate aldehyde and methyl acrylate or acrylonitrile, respectively.[12,13]

The cycloadditions of mesitonitrile oxide (**4**) with **1a–e** are completely regioselective with only the 5-substituted isoxazolines **2** and **3** being isolated irrespective of the presence or absence of the Mg(II) additive. Changing the solvent, reaction temperature or microwave irradiation has no influence on the regioselectivity of the reaction (Scheme 2).

The cycloadditions were first carried out in the absence of

Keywords: cycloaddition; diastereoselection; nitrile oxides; microwave heating; isoxazolines.

* Corresponding author. Tel.: +421-7-368-560; fax: +421-7-368-560; http://koch.chtf.stuba.sk

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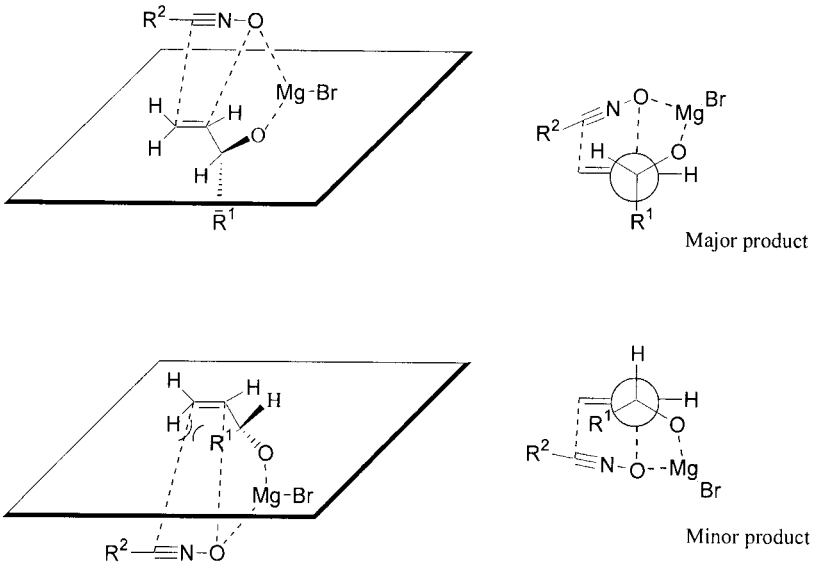
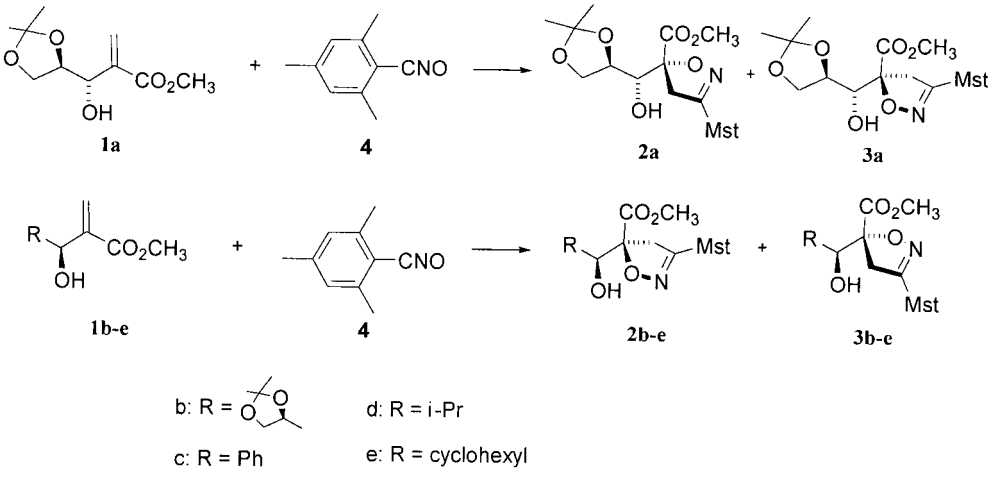


Scheme 1.

any Lewis acid. In the case of isopropyl and cyclohexyl Baylis–Hillman adducts **1d**,**e** single diastereoisomers **3d**,**e** were detected (entries 11 and 15, Table 1) in the crude reaction mixtures. Cycloadditions of mesitonitrile oxide and remaining Baylis–Hillman adducts **1a**–**c** formed mixtures of diastereoisomers (de ranging from 56 to 4%, entries 1, 4, 6 and 8, Table 1). Isoxazolines **3a**–**c** were formed as a main product. The lowest diastereomeric excesses have been observed in the case of phenyl substituted adduct **1c** (de=16%, resp 4%, entries 6 and 8, Table 1). Although Baylis–Hillman adducts **1a** and **1b** are epimers, ratios of diastereoselective isoxazolines **2a**:**3a** and **2b**:**3b** are similar (22:78 for **1a** and 26:74 for **1b**, entries 1 and 4, Table 1). Therefore we gather that the stereogenic centre in β position has only a small influence on the ratio of formed isomers compared to the stereogenic centre in α position.

The addition of a Grignard reagent (MeMgBr) as a Lewis acid affects and can even reverse the sense of induced stereoselectivity: >95:<5 for **1a** and **1d** (entry 2 and 12) or 85:15 for **1b** (entry 5). The stereochemical outcome of the cycloaddition in the absence of Grignard reagent has been rationalised in terms of the presence of hydrogen bonding.[7] The reversal of the stereoselectivity presumably results from the imposition of a chelated transition state with a geometry different from a 'non-chelated' transition state (Scheme 3).

The addition of Grignard reagent (MeMgBr in toluene/THF 3:1, 1 equiv.) to Baylis–Hillman adducts **1a**–**e** at −78°C produces magnesium alkoxides. We presume that magnesium is co-ordinated to the alkoxide as well as to the methoxycarbonyl group and therefore a magnesium alkoxide has a different conformation compared to the free Baylis–Hillman adduct. Mesitonitrile oxide in the presence of the Grignard reagent approaches from the sterically less hindered face to produce isoxazolines **3** as main products (Scheme 3). This means that the addition of Grignard reagent reverses diastereoselectivity of the 1,3-dipolar cycloaddition of nitrile oxide and α-hydroxyalkenes. To the best of our knowledge this unusual reversal of stereoselectivity of the nitrile oxide cycloaddition in the presence of Lewis acids is a very rare phenomenon; having



Scheme 2.

Table 1. 1,3-Dipolar cycloaddition of mesitonitrile oxide to Baylis–Hillman adducts **1a–e**

Entry	Reactant	Solvent[a]	Lewis acid[b]	R. time	R. temp.	Yield (%)	Ratio **2**:**3**[c]
1	**1a**	TOL	–	2 h	80°C	89	22:78
2	**1a**	DCM	MeMgBr	48 h	rt	50	>95:<5
3	**1a**	CLB	MeMgBr	4 min	MW[d]	34	78:22
4	**1b**	TOL	–	2 h	80°C	92	26:74
5	**1b**	DCM	MeMgBr	43 h	rt	62	85:15
6	**1c**	TOL	–	4 h	80°C	92	42:58
7	**1c**	DCM	MeMgBr	24 h	rt	57	61:39
8	**1c**	DCM	–	24 h	rt	96	48:52
9	**1c**	CLB	MeMgBr	4 min	MW[d]	40	70:30
10	**1c**	CLB	–	1.5 min	MW[d]	99	43:57
11	**1d**	TOL	–	2 h	80°C	99	<5:>95
12	**1d**	DCM	MeMgBr	78 h	rt	35	>95:<5
13	**1d**	TCM	MeMgBr	101×20 s	−20–0°C[e]	59	<5:>95
14	**1d**	TCM	–	90 min	MW[d]	46	<5:>95
15	**1e**	TOL	–	3 h	80°C	56	<5:>95
16	**1e**	DCM	MeMgBr	48 h	rt	46	76:24

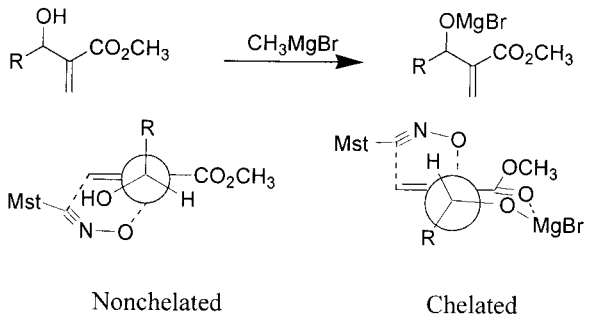
[a] TOL: toluene, CLB: chlorobenzene, DCM: dichloromethane, TCM: tetrachloromethane.
[b] 1 equiv. of MeMgBr was used.
[c] Determined by ^{1}H NMR and/or ^{13}C NMR of crude reaction mixture.
[d] Microwave irradiation.
[e] Reaction mixture was cooled to −20°C, irradiated for 20 s, subsequently cooled to −20°C. The procedure was repeated 101 times.

been observed previously in dipolar cycloaddition of nitrile oxides by Kanemasa[8] and recently by Page.[9]

The most successful example of reversal of diastereoselectivity was found in the cycloaddition to the isopropyl Baylis–Hillman adduct **1d**. With the addition of Mg(II) only isoxazoline **2d** was detected in the crude reaction mixture. On the other hand, in the absence of Mg(II), only isomer **3d** was detected (entries 11 and 12, Table 1). This high diastereoselectivity is probably related to bulkiness of the isopropyl group in the dipolarophile (group R in models from Scheme 3).

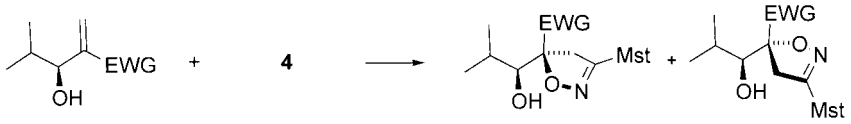
Diastereomeric excesses of the cycloaddition of remaining Baylis–Hillman adducts **1a–c**,**e** with mesitonitrile oxide (**4**) in the presence of Mg(II) additive were found to be in the range of >90% for adduct **1a** (entry 2, Table 1) to 22% for adduct **1c** (entry 7, Table 1). Yields of the cycloaddition in the presence of Mg(II) are smaller (36–62%, entries 2, 5, 7, 12 and 16, Table 1) when compared to yields of the reaction performed without the Mg(II) additive (56–99%, entries 1, 4, 6, 11 and 15, Table 1).

Although mesitonitrile oxide shows moderate reactivity in the catalysed reactions at room temperature, longer reaction times are needed for the completion (24–78 h, entries 2, 5, 7, 12 and 16, Table 1). Acceleration of the reaction by microwave irradiation can be expected when polar molecules join the reaction.[14,15] Our attempts to accelerate the cycloaddition by microwave irradiation were successful. The original solvent (dichloromethane or toluene) was changed to non-flammable chlorobenzene because of its higher boiling point. In the case of chelated cycloaddition provided under the microwave irradiation conditions, the alkoxymagnesium salt was prepared at −20°C; subsequently mesitonitrile oxide was added and the arising homogenous solution was irradiated. Indeed, microwave irradiation decreased reaction times of the chelated as well as non-chelated cycloadditions. For example, in the case of the chelated cycloaddition of dipolarophile **1a**, the reaction time decreased from 48 h to 4 min (entries 2 and 3, Table 1) but diastereomeric excess also dropped from >90 to 56%. In the case of dipolarophile **1c**, microwave irradiation slightly increased diastereomeric excess from 22 to 30% (entries 7 and 9, Table 1) and reaction time also decreased from 24 h to 4 min. Reaction rate of the non-chelated cycloaddition was also increased—Baylis–Hillman adduct **1c** reacted 4 h at 80°C without irradiation, whereas the same cycloaddition under microwave irradiation condition took only 90 s (entries 6 and 10, Table 1). In this case, the diastereomeric excess was nearly unchanged (16 vs 14%, respectively).



Scheme 3.

Intending to investigate the chelated cycloaddition under microwave irradiation conditions at a low temperature, we changed from chlorobenzene as the solvent to non-polar tetrachloromethane (entry 13, Table 1). By the standard procedure, the magnesium alkoxide was prepared from Baylis–Hillman adduct **1d** and the reaction mixture was cooled to −20°C. Afterwards the mixture was microwave irradiated for 20 s (1000 W). The temperature of the mixture raised to 0°C during irradiation and the mixture was subsequently cooled to −20°C. The whole procedure was repeated until the reaction was over (TLC analysis). To our surprise, a single isoxazoline **3d** instead of expected **2d** was isolated. The same product **3d** was isolated when



1d,f **2d,f** **3d,f**

d: EWG = CO_2CH_3
f: EWG = CN

Scheme 4.

Table 2. 1,3-Dipolar cycloaddition of mesitonitrile oxide to Baylis–Hillman adducts **1d**,**f**

Entry	EWG	Solvent[a]	Lewis acid[b]	R. time	R. temp.	Yield (%)	Ratio **2:3**[c]
1	CO_2CH_3	TOL	–	2 h	80	99	<5:>95
2	CO_2CH_3	DCM	MeMgBr	78 h	rt	35	>95:<5
3	CN	TOL	–	3 h	80	71	33:67
4	CN	DCM	MeMgBr	48 h	rt	48	84:16

[a] TOL: toluene, DCM: dichloromethane.
[b] 1 equiv. of MeMgBr was used.
[c] Determined by ^{1}H NMR and/or ^{13}C NMR of crude reaction mixture.

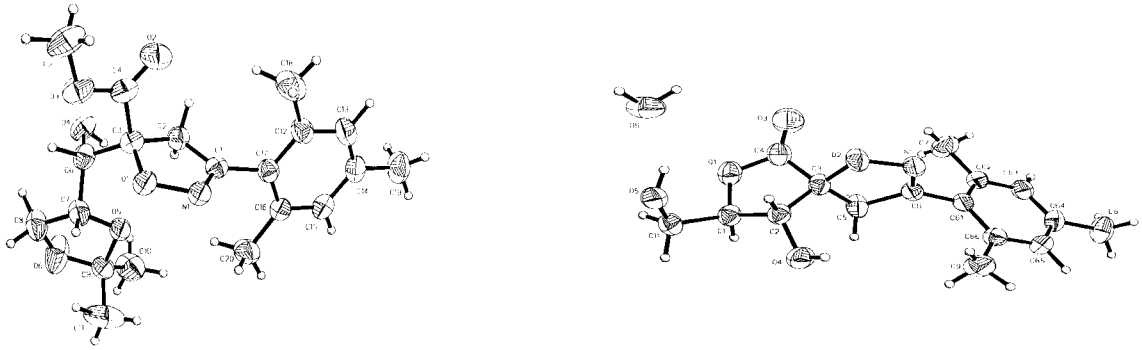
reaction was realised without the presence of Mg(II) additive. In other words, this procedure results in the other diastereoisomer compared to chelated cycloaddition executed in dichloromethane (entry 12, Table 1). This fact could be explained by the co-ordination of tetrachloromethane to Mg(II) and therefore the alkoxide cannot react through the transition state depicted on Scheme 3. A similar effect of THF has been previously found by Kanemasa et al.[8] in the cycloadditions of aromatic nitrile oxides to allylic alcohols. As we expected, cycloaddition performed in tetrachloromethane without the addition of Mg(II) resulted in isoxazoline **3d** as a single product (entry 14, Table 1).

As mentioned above, Baylis–Hillman adduct **1d** offered products with the highest diastereoselectivity under chelated as well as unchelated conditions (entries 11–14, Table 1). To examine the influence of an electron withdrawing group attached to C=C bond, nitrile analogue **1f** was prepared and its cycloaddition to mesitonitrile oxide was performed (Scheme 4).

The Baylis–Hillman adduct **1f** was chosen since we suppose that there is sterical hindrance to overlap of empty orbitals of Mg with a nitrogen sp orbital from a nitrile group along with an sp^3 orbital of oxygen from an alkoxide group of dipolarophile **1f**.

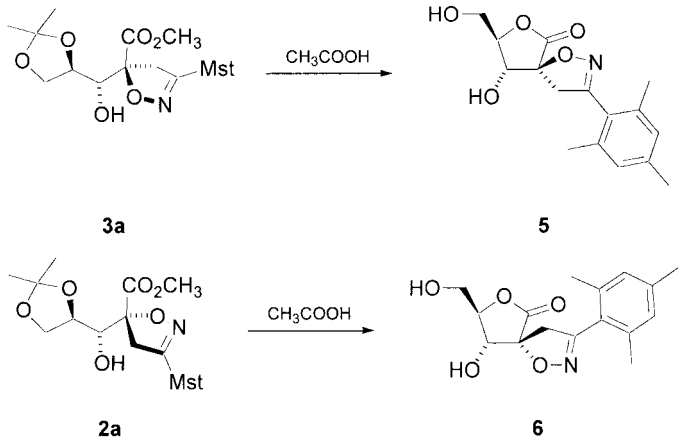
Indeed, diastereomeric excesses of the cycloaddition of the dipolarophile **1f** decreased compared to the dipolarophiles **1d** (entries 4 and 2, Table 2). In the case of non-chelated cycloaddition, diastereomeric excess decreased from >90 to 34% (entries 1 and 3, Table 2) which is probably a result of smaller steric demands of the CN group compared to the CO_2CH_3 group. In the case of chelated cycloaddition diastereomeric excess also dropped from >90 to 68% (entry 2 and 4, Table 2). This fact could be also caused by the impossibility of the realisation of the transition state depicted on Scheme 3 because of its sterical demand as has been mentioned above. However, even in the case of nitrile Baylis–Hillman adduct **1f**, the addition of Mg(II) reverses stereoselectivity of 1,3-dipolar cycloaddition (entries 3 and 4, Table 2). In this case, transition state proposed by Kanemasa et al. could be applied (Scheme 1).

The absolute configuration of the cycloadduct **2b** has been determined directly by X-ray diffraction study (Fig. 1).



2b **5**

Figure 1. X-Ray analysis of **2b** and **5**.[20]



Scheme 5.

Structure of the cycloadduct **3a** is known according to knowledge of the structure of its lactonisation product **5** (Scheme 5), which was also determined by an X-ray diffraction study (Fig. 1). Some spiroisoxazolines occur naturally and they are biologically active, for example, Araplysillins are inhibitors of ATPase.[16] Therefore we have lactonised isoxazolines **2a** and **3a** in 70% aqueous acetic acid (Scheme 5) when only 5-membered spirolactones **5** and **6** were formed.

The absolute configuration of cycloadducts **2a** and **3b** is proposed to be complementary according to the knowledge of structures of their diastereoisomers **2b** and **3a**, respectively. Structures of the other diastereoisomers **2c–f** and **3c–f** were assigned following the analogy with isoxazolines **2a**,**b** and **3a**,**b**. Chemical shifts of carbon at C-5 of the isoxazoline ring in the ^{13}C NMR spectra are lower for isomers **2** compared to the diastereoisomers **3** (Table 3).[17]

Conclusion

1,3-Dipolar cycloadditions of mesitonitrile oxide to Baylis–Hillman adducts **1a–f** proceed regioselectively irrespective of the presence or absence of the Mg(II) additive. Addition of Grignard reagent reverses diastereoselectivity of cycloaddition. The reversal of the stereoselectivity presumably results from the formation of a chelated transition state with a geometry different from a 'non-chelated' transition state. Magnesium is co-ordinated to the alkoxide oxygen as well as to the methoxycarbonyl group and therefore a magnesium alkoxide has a different conformation compared to free Baylis–Hillman adduct. Mesitonitrile oxide in the presence of the Grignard reagent approaches from the sterically less hindered face to produce isoxazolines **3** as main products (Scheme 3). Microwave irradiation strongly accelerates the reaction but has only a small effect concerning the diastereoisomeric excess.

Table 3. Chemical shifts of carbon in the position 5 of the isoxazoline ring in the ^{13}C NMR spectra

	a	**b**	**c**	**d**	**e**	**f**
Isomers **2a–f**	88.6	88.7	89.8	90.6	90.6	82.2
Isomers **3a–f**	90.3	88.9	91.9	91.6	91.3	82.9

Experimental

^1H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra at 75 MHz on a Varian VXR 300 spectrometer at 293 K in $CDCl_3$ solution, unless otherwise stated. Chemical shifts are reported in ppm (δ) downfield from TMS and coupling constants (J) are given in Hz. Optical rotations were measured on a IBZ Messtechnik Polar—LμP instrument at the sodium D line (589 nm). Elemental analyses were obtained on a EA 1108—Elemental Analyzer (Carlo Erba) instrument. Melting points were determined on a Kofler hot plate apparatus and are uncorrected. Commercial reagents were purified before use. Flash chromatography was carried out on silica 60 (40–60 μm, Merck). Eluents are indicated in the text.

Microwave irradiated cycloadditions were executed in a domestic microwave oven in an open reaction vessel without the possibility of stirring, temperature regulation, the use of a cooler or the possibility to work under argon atmosphere.

1,3-Dipolar cycloadditions of Baylis–Hillman adducts 1a–f and mesitonitrile oxide (4). General procedures

Method A: non-chelated cycloaddition. Mesitonitrile oxide (**4**) (161 mg, 1 mmol) and appropriate Baylis–Hillman adduct **1** (1 mmol) are dissolved in toluene (5 ml) and the mixture was stirred at 80°C until the reaction was completed (TLC monitoring). The solvent was evaporated to dryness in vacuum. Diastereoisomers were isolated by column chromatography. Yields, ratio of diastereoisomers and reaction times are summarised in the Tables 1 and 2, respectively. Chromatography conditions and physical properties of products are shown below.

Method B: non-chelated cycloaddition with microwave irradiation. Mesitonitrile oxide (**4**) (161 mg, 1 mmol) and appropriate Baylis–Hillman adduct **1** (1 mmol) were dissolved in chlorobenzene (10 ml) and the mixture was irradiated in an open flask in a domestic microwave oven (500 W) until the reaction was completed (TLC monitoring). The work-up and identification of the reaction mixture accorded to method A above.

Method C: chelated cycloaddition. To the solution of Baylis–Hillman adduct **1** (1 mmol) in dry CH_2Cl_2 (5 ml) under argon atmosphere the solution of methylmagnesium bromide (1.4 M in toluene/THF 3:1, 0.75 ml, 1 mmol) was added dropwise at −78°C. The mixture was stirred for 10 min and the solution of mesitonitrile oxide (**4**) (161 mg, 1 mmol) in CH_2Cl_2 (5 ml) was added dropwise. The resulting homogenous mixture was stirred for an additional 20 min at −78°C, afterward the temperature was allowed to rise and the reaction mixture was stirred until reaction was completed (TLC monitoring) at room temperature. Reaction was quenched by 15 ml of saturated aqueous solution NH_4Cl (20 min), organic phase was separated and aqueous layer was extracted 3×10 ml CH_2Cl_2. Organic layers were dried (Na_2SO_4) and solvent was evaporated in vacuum. The work-up and identification of the reaction mixture accorded to method A above.

Method D: chelated cycloaddition with microwave irradiation. To the solution of Baylis–Hillman adduct **1** (1 mmol) in dry chlorobenzene (5 ml) under argon atmosphere the solution of methylmagnesium bromide (1.4 M in toluene/THF 3:1, 0.75 ml, 1 mmol) was added dropwise at −20°C. The homogenous mixture was stirred for 10 min and the solution of mesitolnitrile oxide (**4**) (161 mg, 1 mmol) in chlorobenzene (5 ml) was added dropwise. The mixture was stirred for an additional 10 min. at −20°C, afterward the mixture was microwave irradiated (500 W) in a domestic microwave oven until the reaction was completed (TLC monitoring). Reaction was quenched by 15 ml of saturated aqueous solution NH_4Cl (20 min), organic phase was separated and aqueous layer was extracted 3×10 ml CH_2Cl_2. Organic layers were dried (Na_2SO_4) and solvent was evaporated in vacuum. The work-up and identification of the reaction mixture accorded to method A above.

(1′*R*,2′*R*,5*S*) Methyl 5-(2,3-*O*-isopropylidene-1,2,3-trihydroxypropyl)-3-(2,4,6-trimethylphenyl)isoxazoline-5-carboxylate (3a). Product was isolated by flash chromatography (silica gel 40–63 μm, hexanes/ethyl acetate 5:1). Mp=119–120°C; $[M^{+\cdot}]$=377. For $C_{20}H_{27}NO_6$, calcd C 63.64, H 7.21, N 3.71; found C 63.57, H 7.21, N 3.71%. ^{1}H NMR ($CDCl_3$), δ: 6.89 (2H, s, H_{Ar}); 4.31 (1H, d, $J_{1',2'}$=8.6 Hz, H-1′); 4.18 (1H, dd, $J_{2',3'a}$=6.5 Hz, $J_{3'a,3'b}$=8.7 Hz, H-3′a); 4.07 (1H, dd, $J_{2',3'b}$=5.1 Hz, $J_{3'a,3'b}$=8.7 Hz, H-3′b); 3.95 (1H, ddd, $J_{2',3'b}$=5.1 Hz, $J_{2',3'a}$=6.5 Hz, $J_{1',2'}$=8.7 Hz, H-2′); 3.82 (3H, s, CO_2CH_3); 3.80 (1H, d, $J_{4a,4b}$=17.7 Hz, H-4a); 3.44 (1H, d, $J_{4a,4b}$=17.7 Hz, H-4b); 2.29 (3H, s, CH_3-*para*); 2.23 (6H, s, CH_3-*ortho*); 1.37, 1.29 (2×3H, 2×s, CH_3CCH_3). ^{13}C NMR ($CDCl_3$), δ: 169.9 (C=O); 159.0 (C-3); 139.1, 136.7, 125.2 (C_{Ar}); 128.4 ($C_{Ar}H$); 110.0 (CH_3CCH_3); 90.3 (C-5); 74.9, 72.7 (C-1′, C-2′); 67.8 (C-3′); 52.9 (OCH_3); 40.2 (C-4); 26.2, 25.0 (CH_3CCH_3); 21.1 (CH_3-*para*); 19.5 (CH_3-*ortho*).

(1′*R*,2′*R*,5*R*) Methyl 5-(2,3-*O*-isopropylidene-1,2,3-trihydroxypropyl)-3-(2,4,6-trimethylphenyl)-isoxazoline-5-carboxylate (2a). The product was isolated by flash chromatography (silica gel 40–63 μm, hexanes/ethyl acetate 4:1). Mp=154–155°C; $[\alpha]_D^{25}$=−7.95 (Z=9.942 mg/ml; $CHCl_3$); $[M^{+\cdot}]$=377. For $C_{20}H_{27}NO_6$, calcd C 63.64, H 7.21, N 3.71; found C 63.50, H 7.22, N 3.68%. ^{1}H NMR ($CDCl_3$), δ: 6.88 (2H, s, H_{Ar}); 4.26–4.22 (1H, m, H-2′); 4.19 (1H, dd, $J_{2',3'a}$=6.0 Hz, $J_{3'a,3'b}$=8.7 Hz, H-3′a); 4.10 (1H, dd, $J_{2',3'b}$=5.4, $J_{3'a,3'b}$=8.7 Hz, H-3′b); 4.03 (1H, d, $J_{1',2'}$=7.5 Hz, H-1′); 3.83 (3H, s, OCH_3); 3.79 (1H, d, $J_{4a,4b}$=18.3 Hz, H-4a); 3.36 (1H, d, $J_{4a,4b}$=18.0 Hz, H-4b); 2.28 (3H, s, CH_3-*para*); 2.20 (6H, s, CH_3-*ortho*); 1.40, 1.34 (2×3H, 2×s, CH_3CCH_3). ^{13}C NMR ($CDCl_3$), δ: 171.1 (C=O); 158.1 (C-3); 139.2, 136.6, 125.0 (C_{Ar}); 128.5 ($C_{Ar}H$); 109.8 (CH_3CCH_3); 88.6 (C-5); 75.4, 74.2 (C-1′, C-2′); 67.0 (C-3′); 52.9 (OCH_3); 46.5 (C-4); 26.4, 25.2 (CH_3CCH_3); 21.2 (CH_3-*para*); 19.6 (CH_3-*ortho*).

(1′*S*,2′*R*,5*R*) Methyl 5-(2,3-*O*-isopropylidene-1,2,3-trihydroxypropyl)-3-(2,4,6-trimethylphenyl)-isoxazoline-5-carboxylate (3b). The product has not been isolated as diastereomeric pure. Following signals came from enriched mixture of diastereoisomers. ^{13}C NMR ($CDCl_3$), δ: 170.9 (C=O); 158.6 (C-3); 139.1, 136.5, 125.1 (C_{Ar}); 128.5 ($C_{Ar}H$); 109.9 (CH_3CCH_3); 88.7 (C-5); 74.1, 72.1 (C-1′, C-2′); 66.2 (C-3′); 53.0 (OCH_3); 44.7 (C-4); 26.0, 25.3 (CH_3CCH_3); 21.0 (CH_3-*para*); 19.5 (CH_3-*ortho*).

(1′*S*,2′*R*,5*S*) Methyl 5-(2,3-*O*-isopropylidene-1,2,3-trihydroxypropyl)-3-(2,4,6-trimethylphenyl)isoxazoline-5-carboxylate (2b). The product was isolated by flash chromatography (silica gel 40–63 μm, hexanes/ethyl acetate 4:1) followed by crystallisation from *n*-hexane. Mp=112–114°C; $[M^{+\cdot}]$=377. For $C_{20}H_{27}NO_6$, calcd C 63.64, H 7.21, N 3.71; found C 63.71, H 7.24, N 3.79%. ^{1}H NMR ($CDCl_3$), δ: 6.90 (2H, s, H_{Ar}); 4.43 (1H, ddd, $J_{1',2'}$=2.2 Hz, $J_{2',3'a}$=6.7 Hz, $J_{2',3'b}$=7.7 Hz, H-2′); 4.21 (1H, d, $J_{1',2'}$=2.2 Hz, H-1′); 4.18 (1H, dd, $J_{2',3'a}$=6.7 Hz, $J_{3'a,3'b}$=8.3 Hz, H-3′a); 3.92 (1H, dd, $J_{2',3'b}$=7.7 Hz, $J_{3'a,3'b}$=8.3 Hz, H-3′b); 3.89 (3H, s, OCH_3); 3.77 (1H, d, $J_{4a,4b}$=18.3 Hz, H-4a); 3.67 (1H, d, $J_{4a,4b}$=18.3 Hz, H-4b); 2.29 (3H, s, CH_3-*para*); 2.25 (6H, s, CH_3-*ortho*); 1.45, 1.39 (2×3H, 2×s, CH_3CCH_3). ^{13}C NMR ($CDCl_3$), δ: 171.1 (C=O); 158.3 (C-3); 139.1, 136.6, 125.1 (C_{Ar}); 128.5 ($C_{Ar}H$); 110.3 (CH_3CCH_3); 88.9 (C-5); 73.4, 70.1 (C-1′, C-2′); 67.3 (C-3′); 53.2 (OCH_3); 43.1 (C-4); 26.2, 25.5 (CH_3CCH_3); 21.1 (CH_3-*para*); 19.5 (CH_3-*ortho*).

(1′*S,5*R**) Methyl 5-(phenylhydroxylmethyl)-3-(2,4,6-trimethylphenyl)-isoxazoline-5-carboxylate (3c).** The mixture of diastereoisomers **2c** and **3c** was isolated by flash chromatography (silica gel 40–63 μm, hexanes/ethyl acetate 5:1). Following NMR signals came from enriched mixture of diastereoisomers. Melting point of diastereoisomer mixture was 135–137°C. For $C_{21}H_{23}NO_4$, calcd C 71.37, H 6.56, N 3.96; found C 71.20, H 6.61, N 3.97%. ^{1}H NMR ($CDCl_3$), δ: 7.54–7.25 (5H, m, $H_{Ar,\ Ph}$); 6.85 (2H, s, $H_{Ar,\ Mst}$); 5.38 (1H, s, CHOH); 3.84 (3H, s, OCH_3); 3.44 (2H, s, H-4); 3.15 (1H, brs, OH); 2.26 (3H, s, CH_3-*para*); 2.12 (6H, s, CH_3-*ortho*). ^{13}C NMR ($CDCl_3$), δ: 170.5 (C=O); 158.5 (C-3); 139.0, 136.9, 136.6, 125.0 ($C_{Ar}H$); 128.6, 128.3, 128.2, 126.8 (C_{Ar}); 91.9 (C-5); 73.9 (*C*HOH); 53.0 (OCH_3); 41.6 (C-4); 21.1 (CH_3-*para*); 19.4 (CH_3-*ortho*).

(1′*S,5*S**) Methyl 5-(phenylhydroxylmethyl)-3-(2,4,6-trimethylphenyl)isoxazoline-5-carboxylate (2c).** Following NMR signals came from an enriched mixture of diastereoisomers. ^{1}H NMR ($CDCl_3$), δ: 7.54–7.25 (5H, m,

$H_{Ar,\,Ph}$); 6.77 (2H, s, $H_{Ar,\,Mst}$); 5.38 (1H, s, C*H*OH); 3.84 (3H, s, OCH_3); 3.58 (1H, d, $J_{4a,4b}$=18.0 Hz, H-4a); 3.31 (1H, d, $J_{4a,4b}$=18.0 Hz, H-4b); 3.07 (1H, brs, O*H*); 2.22 (3H, s, CH_3-*para*); 1.82 (6H, s, CH_3-*ortho*). ^{13}C NMR ($CDCl_3$), δ: 171.7 (C=O); 157.6 (C-3); 138.9, 137.7, 136.6, 125.0 ($C_{Ar}H$); 128.6, 128.4, 128.3, 127.5 (C_{Ar}); 89.8 (C-5); 73.1 (*C*HOH); 53.1 (O*C*H_3); 43.4 (C-4); 21.0 (*C*H_3-*para*); 18.9 (*C*H_3-*ortho*).

(1′*S,5*R**) Methyl 5-(1-hydroxy-2-methylpropyl)-3-(2,4,6-trimethylphenyl)isoxazoline-5-carboxylate (3d).** The product was isolated by flash chromatography (silica gel 40–63 μm, hexanes/ethyl acetate 10:1). Mp=144–145°C; [$M^{+\cdot}$]=319. For $C_{18}H_{25}NO_4$, calcd C 67.69, H 7.89, N 4.39; found C 67.83; H 8.06; N 4.36%. ^{1}H NMR ($CDCl_3$), δ: 6.9 (2H, s, H_{Ar}); 4.1 (1H, d, $J_{1',2'}$=5.1 Hz, H-1′); 3.8 (3H, s, OCH_3); 3.7 (1H, d, $J_{4a,4b}$=17.4 Hz, H-4a); 3.5 (1H, d, $J_{4a,4b}$=17.4 Hz, H-4b); 2.6 (1H, brs, O*H*); 2.3 (3H, s, CH_3-*para*); 2.2 (6H, s, CH_3-*ortho*); 1.7 (1H, m, H-2′); 1.0 (3H, d, *J*=6.9 Hz, CHCH_3); 0.9 (3H, d, *J*=7.2 Hz, CHCH_3). ^{13}C NMR ($CDCl_3$), δ: 171.1 (C=O); 160 (C-3); 139.0, 136.7, 125.5 (C_{Ar}); 128.4 ($C_{Ar}H$); 91.6 (C-5); 75.8 (C-1′); 53.0 (O*C*H_3); 40.7 (C-4); 30.2 (C-2′); 21.1, 19.9, 19.6, 17.5 (C*C*H_3).

(1′*R,5*R**) Methyl 5-(1-hydroxy-2-methylpropyl)-3-(2,4,6-trimethylphenyl)isoxazoline-5-carboxylate (2d).** The product was isolated by flash chromatography (silica gel 40–63 μm, hexanes/ethyl acetate 10:1). Mp=117–118°C; [$M^{+\cdot}$]=319. For $C_{18}H_{25}NO_4$, calcd C 67.69, H 7.89, N 4.39; found C 67.75, H 8.01, N 4.27%. ^{1}H NMR ($CDCl_3$), δ: 6.88 (2H, s, H_{Ar}); 3.83–3.90 (4H, m, H-1′, OCH_3); 3.73 (1H, d, $J_{4a,4b}$=18.0 Hz, H-4a); 3.38 (1H, d, $J_{4a,4b}$=18.0 Hz, H-4b); 2.28 (3H, s, CH_3-*para*); 2.21 (6H, s, CH_3-*ortho*); 2.1 (1H, brs, O*H*); 1.80–1.90 (1H, m, H-2′); 1.06 (3H, d, *J*=6.6 Hz, CHCH_3); 1.03 (3H, d, *J*=6.3 Hz, CHCH_3). ^{13}C NMR ($CDCl_3$), δ: 172.6 (C=O); 158.0 (C-3); 139.1, 136.6, 125.1 (C_{Ar}); 128.5 ($C_{Ar}H$); 90.6 (C-5); 77.4 (C-1′); 52.9 (O*C*H_3); 47.9 (C-4); 31.2 (C-2′); 21.1, 20.9, 19.5, 16.7 (C*C*H_3).

(1′*S,5*R**) Methyl 5-(1-hydroxy-1-cyclohexylmethyl)-3-(2,4,6-trimetylphenyl)isoxazoline-5-carboxylate (3e).** The product is isolated by flash chromatography (silica gel 40–63 μm, hexanes/ethyl acetate 25:1). [$M^{+\cdot}$]=359. For $C_{21}H_{29}NO_4$, calcd C 70.17, H 8.13, N 3.90; found C 70.14, H 8.26, N 3.66%. ^{1}H NMR ($CDCl_3$), δ: 6.88 (2H, s, H_{Ar}); 4.07 (1H, d, *J*=5.4 Hz, C*H*OH); 3.84 (3H, s, OCH_3); 3.67 (1H, d, $J_{4a,4b}$=17.4 Hz, H-4a); 3.43 (1H, d, $J_{4a,4b}$=17.4 Hz, H-4b); 2.5 (1H, brs, O*H*); 2.28 (3H, s, CH_3-*para*); 2.22 (6H, s, CH_3-*ortho*); 1.9–1.0 (11H, m, $H_{cyclohexyl}$). ^{13}C NMR ($CDCl_3$), δ: 171.0 (C=O); 159.1 (C-3); 139.0, 136.6, 125.4 (C_{Ar}); 128.4 ($C_{Ar}H$); 91.3 (C-5); 75.5 (*C*HOH); 53.0 (O*C*H_3); 40.9 (C-4); 40.0 (HOCH*C*H); 29.6, 27.9, 26.3, 26.0, 26.0 ($C_{cyclohexyl}H_2$); 21.1 (*C*H_3-*para*); 19.5 (*C*H_3-*ortho*).

(1′*R,5*R**) Methyl 5-(1-hydroxy-1-cyclohexylmethyl)-3-(2,4,6-trimethylphenyl)isoxazoline-5-carboxylate (2e).** The product was isolated by flash chromatography (silica gel 40–63 μm, hexanes/ethyl acetate 25:1). ^{1}H NMR ($CDCl_3$), δ: 6.88 (2H, s, H_{Ar}); 4.07 (1H, d, *J*=7.2 Hz, C*H*OH); 3.85 (3H, s, OCH_3); 3.73 (1H, d, $J_{4a,4b}$=18.0 Hz, H-4a); 3.37 (1H, d, $J_{4a,4b}$=18.0 Hz, H-4b); 2.3 (1H, brs, O*H*); 2.28 (3H, s, CH_3-*para*); 2.21 (6H, s, CH_3-*ortho*); 2.1–1.0 (11H, m, $H_{cyclohexyl}$). ^{13}C NMR ($CDCl_3$), δ: 172.7 (C=O); 158.0 (C-3); 139.1, 136.6, 126.3 (C_{Ar}); 128.5 ($C_{Ar}H$); 90.6 (C-5); 77.3 (*C*HOH); 52.8 (O*C*H_3); 47.6 (C-4); 40.0 (HOCH*C*H); 30.6, 27.2, 26.4, 26.1, 26.0 ($C_{cyclohexyl}H_2$); 21.1 (*C*H_3-*para*); 19.5 (*C*H_3-*ortho*).

(5*S,1′*S**) 5-(1-Hydroxy-2-methylpropyl)-3-(2,4,6-trimethylphenyl)isoxazoline-5-carbonitrile (3f).** The product was isolated by flash chromatography (silica gel 40–63 μm, hexanes/ethyl acetate 15:1). Mp=145–147°C; [$M^{+\cdot}$]=286. For $C_{17}H_{22}N_2O_4$, calcd C 71.30, H 7.74, N 9.78; found C 71.38, H 7.82, N 10.00%. ^{1}H NMR ($CDCl_3$), δ: 6.91 (2H, s, H_{Ar}); 3.91 (1H, d, $J_{1',2'}$=3.9 Hz, H-1′); 3.76 (1H, d, $J_{4a,4b}$=17.7 Hz, H-4a); 3.33 (1H, d, $J_{4a,4b}$=17.7 Hz, H-4b); 2.5–3.0 (1H, brs, O*H*); 2.29 (3H, s, CH_3-*para*); 2.26 (6H, s, CH_3-*ortho*); 2.1 (1H, m, H-2′); 1.12 (3H, d, *J*=6.9 Hz, CHCH_3-1); 0.99 (1H, d, *J*=6.9 Hz, CHCH_3-3). ^{13}C NMR ($CDCl_3$), δ: 158.6 (C-3); 139.6, 136.6, 124.0 (C_{Ar}); 128.7 ($C_{Ar}H$); 118.5 (CN); 82.9 (C-5); 76.0 (C-1′); 45.4 (C-4); 30.4 (C-2′); 21.1, 20.4 (*C*H_3C*H*CH_3); 19.6 (*C*H_3-*ortho*); 16.4 (*C*H_3-*para*).

(5*R,1′*S**) 5-(1-Hydroxy-2-methylpropyl)-3-(2,4,6-trimethylphenyl)isoxazoline-5-carbonitrile (2f).** The product was isolated by flash chromatography (silica gel 40–63 μm, hexanes/ethyl acetate 15:1). Mp=171–173°C; [$M^{+\cdot}$]=286. For $C_{17}H_{22}N_2O_4$ calcd C 71.30, H 7.74, N 9.78; found C 71.60, H 7.49, N 10.04%. ^{1}H NMR ($CDCl_3$), δ: 6.91 (2H, s, H_{Ar});3.72 (1H, H-1′); 3.69 (1H, d, $J_{4a,4b}$=17.4 Hz, H-4a); 3.52 (1H, d, $J_{4a,4b}$=17.4 Hz, H-4b); 2.29 (3H, s, CH_3-*para*); 2.26 (6H, s, CH_3-*ortho*); 2.2–2.4 (1H, m, H-2′); 1.12 (6H, d, *J*=6.9 Hz, CH_3CHCH_3). ^{13}C NMR ($CDCl_3$), δ: 158.4 (C-3); 139.7, 136.6, 123.7 (C_{Ar}); 128.7 ($C_{Ar}H$); 118.3 (*C*N); 82.2 (C-5); 76.6 (C-1′); 49.2 (C-4); 31.2 (C-2′); 21.1, 20.8 (*C*H_3C*H*CH_3); 19.6 (*C*H_3-*ortho*); 16.4 (*C*H_3-*para*).

(5*S*,8*R*,9*R*) 3-(2,4,6-Trimethylphenyl)-9-hydroxy-8-hydroxymethyl-6-oxo-1,7-dioxa-2-azaspiro[4,4]non-2-ene (5). (1′*R*, 2′*R*,5*S*) Methyl 5-(2,3-*O*-isopropylidene-1,2,3-trihydroxypropyl)-3-(2,4,6-trimethylphenyl)isoxazoline-5-carboxylate (**3a**) (155 mg, 0.411 mmol) was dissolved in 70% acetic acid (2 ml) and the mixture was stirred at 40°C for 2.5 h. The mixture was stirred for an additional 22 h at room temp. Acetic acid was azeotropically evaporated to dryness using toluene at pressure 3300 Pa. The colourless crystalline compound obtained (119 mg, 95%) was spectroscopically pure. Mp=153–156°C; [$M^{+\cdot}$]=305. ^{1}H NMR (DMSO-d^6), δ: 6.94 (2H, s, H_{Ar}); 6.46 (1H, d, *J*=5.4 Hz, O*H*-9); 5.23 (1H, t, *J*=5.2 Hz, CH_2OH); 4.41 (1H, dd, $J_{8,9}$=5.9 Hz, *J*=5.9 Hz, H-9); 4.10 (1H, m, H-8); 3.7–3.8 (2H, m, H-4a, CH_aH_bOH); 3.64 (1H, m, CH_aH_bOH); 3.32 (1H, d, $J_{4a,4b}$=19.2 Hz, H-4b); 2.25 (3H, s, CH_3-*para*); 2.18 (6H, s, CH_3-*ortho*). ^{13}C NMR (DMSO-d^6), δ: 173.3 (C=O); 156.8 (C-3); 138.6, 136.3, 125.0 (C_{Ar}); 128.2 ($C_{Ar}H$); 87.9 (C-5); 82.5 (C-8);69.5 (C-9);58.9 (CH_2OH); 40.0 (C-4); 20.7 (*C*H_3-*para*); 19.1 (*C*H_3-*ortho*).

(5*R*,8*R*,9*R*) 3-(2,4,6-Trimethylphenyl)-9-hydroxy-8-hydroxymethyl-6-oxo-1,7-dioxa-2-azaspiro[4,4]non-2-ene (6). (1′*R*,2′*R*,5*R*)-5-(2,3-*O*-isopropylidene-1,2,3-trihydroxypropyl)-

5-methoxycarbonyl-3-(2,4,6-trimethylphenyl)-4,5-dihydroisoxazoline (**2a**) (135 mg, 0.357 mmol) was dissolved in 70% acetic acid (2 ml) and the mixture is stirred at 40°C for 2.5 h. The mixture was stirred for additional 20 h at room temperature. Acetic acid was azeotropically evaporated to dryness using toluene at pressure 3300 Pa. The colourless crystalline compound (114 mg) obtained was purified by flash chromatography (silica gel 40–63 μm, hexanes/ethyl acetate 1:1). Yield of product is 98 mg (90%). Mp=184°C; $[M^{+\cdot}]$=305. ^{1}H NMR (DMSO-d^6), δ: 6.94 (2H, s, H_{Ar}); 6.02 (1H, d, J=7.5 Hz, O*H*-9); 5.18 (1H, t, J=5.4 Hz, CH_2O*H*); 4.34 (1H, m, H-8); 4.17 (1H, dd, $J_{8,9}$=7.5 Hz, J=7.5 Hz, H-9); 3.78 (1H, m, CH_aH_bOH); 3.60 (1H, m, CH_aH_bOH); 3.55 (1H, d, $J_{4a,4b}$=18.3 Hz, H-4a); 3.36 (1H, d, $J_{4a,4b}$=18.3 Hz, H-4b); 2.26 (3H, s, CH_3-*para*); 2.20 (6H, s, CH_3-*ortho*). ^{13}C NMR (DMSO-d^6), δ: 172.5 (C=O); 157.4 (C-3); 138.5, 136.3, 125.1 (C_{Ar}); 128.2 (C_{Ar}H); 85.4 (C-5); 84.1 (C-8); 70.5 (C-9);59.1 (*C*H_2OH); 43.2 (C-4); 20.7 (*C*H_3-*para*); 19.1 (*C*H_3-*ortho*).

X-Ray diffraction study

The X-ray measurements of the two crystals, **2b** and **5**, were made on a KM-4 KUMA diffractometer with graphite monochromated CuKα radiation[10]. The data were collected at room temperature using $\omega-2\theta$ scan technique. The intensity of the control reflections varied by less than 3%, and the linear correction factor was applied to account for this effect. The data were also corrected for Lorentz and polarisation effects, but no absorption correction was applied (μ=0.775 mm^{-1} and 0.849 mm^{-1} for **2b** and **5**, respectively). The structure was solved by direct methods[18] and refined using SHELXL.[19] The refinement was based on F^2 for all reflections except those with very negative F^2. The weighted R factor, wR and all goodness-of-fit S values are based on F^2. The non-hydrogen atoms were refined anisotropically, whereas the H-atoms were placed in the calculated positions and refined isotropically. **2b**: $C_{20}H_{27}N_1O_6$, colourless crystal 0.15×0.15×0.20 mm^3 (grown from ethanol), M_r=377.43, monoclinic, space group: $P2_1$, a=9.598 (2) A, b=9.951 (2) A, c=10.707 (2) A, β=105.79 (3)°, V=984.0 (3) A^3, Z=2, D_x=1.274 g cm^{-3}. The collected data range: $4.79<\Theta<79.19$ ($-12\leq h\leq 12$, $-12\leq k\leq 12$, $-13\leq l\leq 13$); 5624 reflections, Goodness-of-fit on F^2=1.058; final R=0.0352, wR^2=0.0977 (for all 4779 $F_o>4\ \sigma(F_o)$), R=0.0454 and wR^2=0.1063 (for all 5624 data). Weight=$1/[\sigma^2(F_o^2)+(0.0532P)^2+0.19P]$ where $P=(F_o^2+2F_c^2)/3$. Minimum and maximum difference electron densities were 0.181 and −0.110e A^{-3}. Absolute structure parameter −0.1 (2)[20]. (**5**): $C_{16}H_{21}N_1O_6$, colourless crystal, 0.15×0.20×0.25 mm^3 (grown from ethanol), M_r=323.34, monoclinic, space group $P2_12_12_1$, a=6.933 (1) A, b=9.414 (2) A, c=24.891 (5) A, β=90°, V=1624.6(5) A^3, Z=4, D_x=1.322 g cm^{-3}. The collected data range:$3.55<\Theta<79.25$ ($-8\leq h\leq 8$, $-11\leq k\leq 11$, $-27\leq l\leq 27$); 5219 reflections, Goodness-of-fit on F^2=1.023, final R=0.0328 wR^2=0.0918 (for all 4051 $F_o>4\ \sigma(F_o)$), R=0.0516 and wR^2=0.1036 (for all 5219 data). Weight=$1/[\sigma^2(F_o^2)+(0.0571P)^2+0.23P]$ where $P=(F_o^2+2F_c^2)/3$. Minimum and maximum difference electron densities were 0.157 and −0.136e A^{-3}. Absolute structure parameter 0.0 (2).[20]

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20. Further details of the crystal structure: list of structure factors, anisotropic displacement parameters, H-atom coordinates, complete geometry are deposited with the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 IEZ, UK (on quoting the depository no. CCCD 144970 and HOSSIR).