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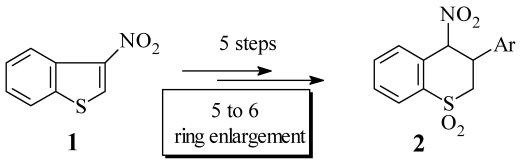
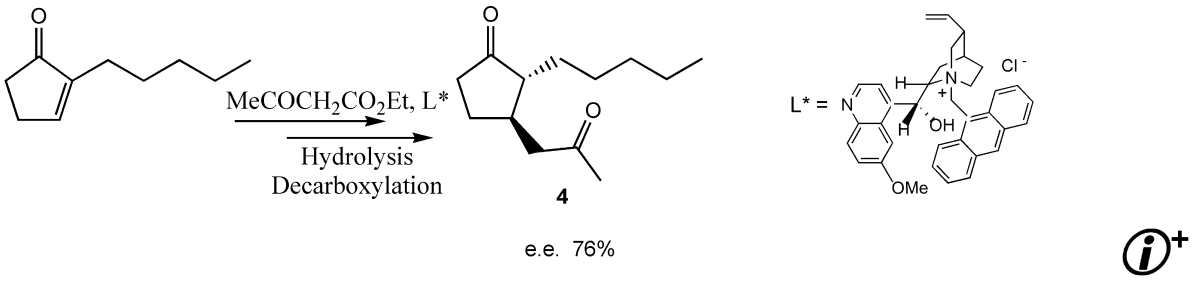
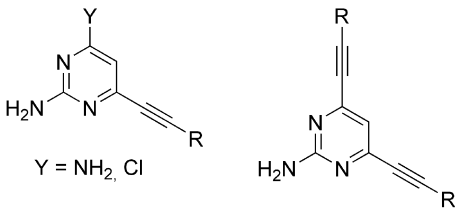
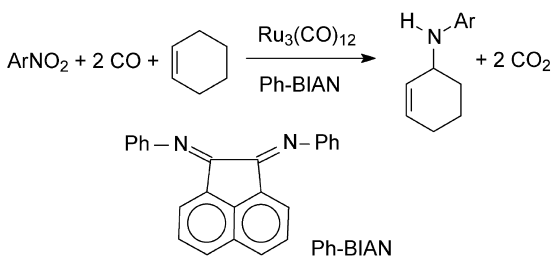
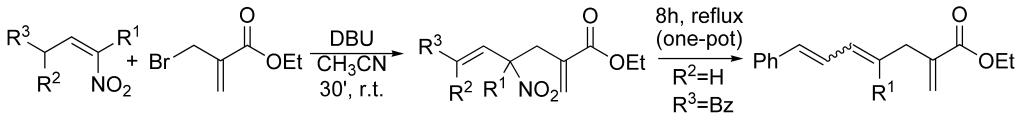


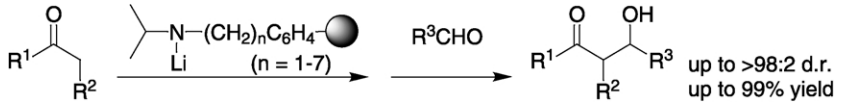


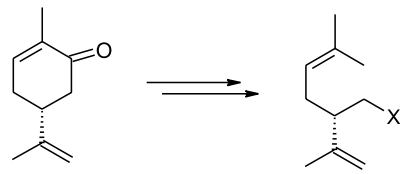


The reaction has been applied to several nitroarenes having strongly electron-withdrawing groups. Only one nitro group reacts when 1,4-dinitrobenzene is employed as substrate, but the second nitro group can be efficiently reduced to amino group in one pot by adding water to the reaction mixture. This circumvents the problem of the low reactivity of nitroarenes having strongly electron donating groups.

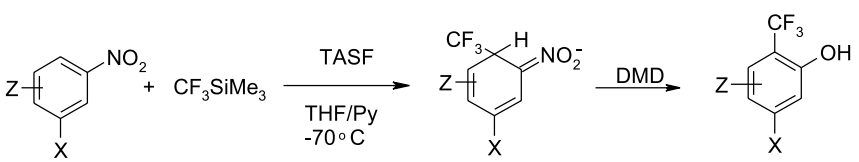


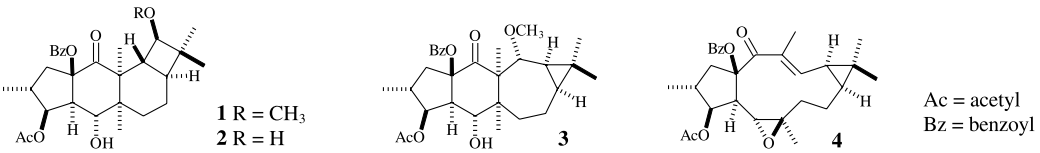




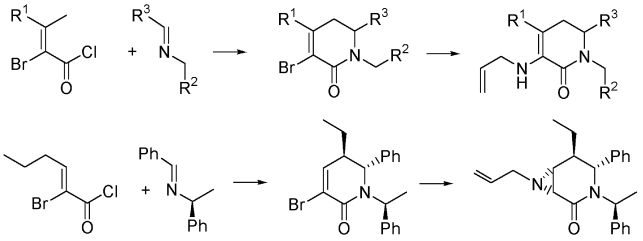


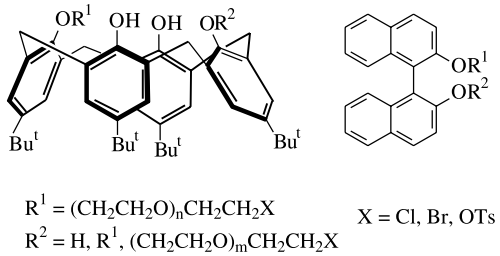
X = $COCH_3$, OAc, NHAc etc.

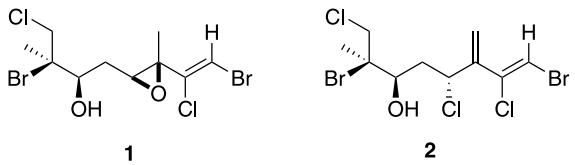


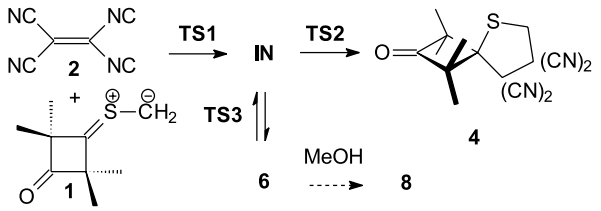


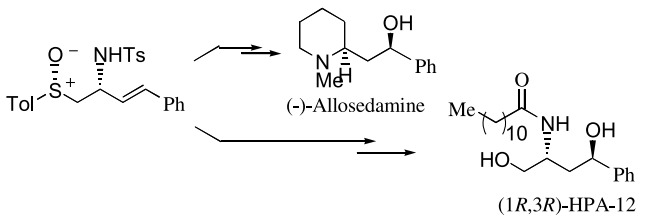
From *Euphorbia villosa* three new tetracyclic diterpenes (**1**–**3**) were isolated together with one new (**4**) and one known lathyrane diterpenes.

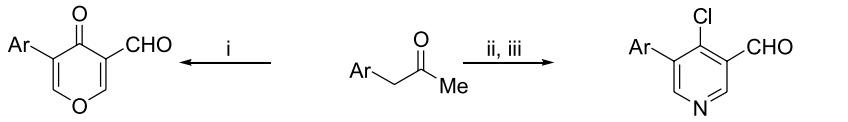




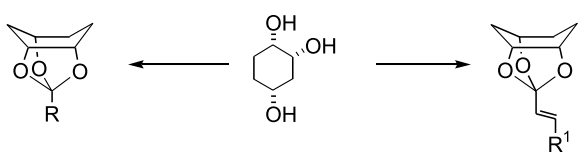


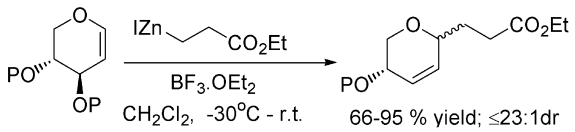


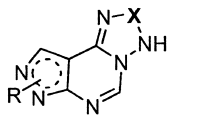


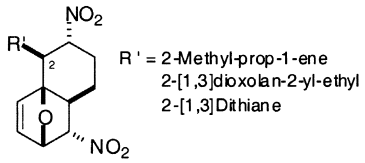


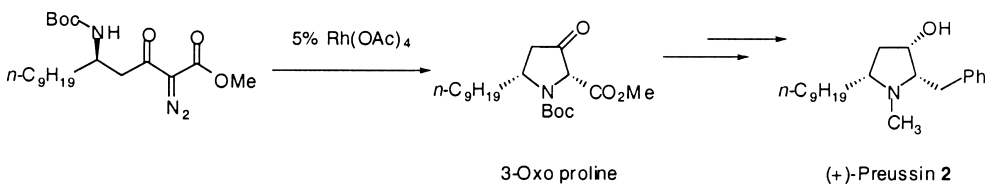
i.DMF/$POCl_3$ (3 equiv.), 72h, rt. ii. DMF/$POCl_3$ (4 equiv.), 48h, rt. iii. NH_4OAc, 0°C, 30 min.











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Simple preparation of 7-alkylamino-2-methylquinoline-5,8-diones: regiochemistry in nucleophilic substitution reactions of the 6- or 7-bromo-2-methylquinoline-5,8-dione with amines☆,☆☆

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Received 16 February 2004; revised 16 April 2004; accepted 16 April 2004

Abstract—7-Alkylamino-2-methylquinoline-5,8-diones (**7**) were prepared from 6-bromo-2-methylquinoline-5,8-dione (**2**) not from 7-bromo-2-methylquinoline-5,8-dione (**1**). The chemistry of the transformation of 6-bromo-2-methylquinoline-5,8-dione (**2**) and various alkylamines, such as piperidine, 2-methylaziridine, benzylamine, *n*-butylamine, cyclohexylamine, *t*-butylamine, and ammonia, to 7-alkylamino compounds **7** as well as the transformation of 7-bromo compound **1** and the alkylamines to 6-alkylamino-2-methylquinoline-5,8-diones **11** was studied. The efficient and simple synthetic routes of the key intermediates, 6- and 7-bromo-2-methylquinoline-5,8-diones (**2** and **1**), from 5,8-dihydroxy-2-methylquinoline (**15**) and 5,7-dibromo-8-hydroxy-2-methylquinoline (**9**), respectively, were developed. We also proposed the mechanism for the unusual regioselectivity on the nucleophilic amination of 6- and 7-bromo-2-methylquinoline-5,8-diones (**2** and **1**).

1. Introduction

Quinoline- and isoquinoline-5,8-diones have wide spectra of biological activities as antitumor, antibacterial, antifungal, antimalarial agents.[1–10] The syntheses and the biological activities of 6,7-functionalized quinoline-5,8-diones such as amino, hydroxyl, methoxy, thiol, and halogen have been reported.[1–4,11–17] As 7-amino group is the most critical segment in determining the antitumor activity of *Streptonigrin*, *Steptonigrone*, and *Lavendamycin*,[18] 7-amino-2-methylquinoline-5,8-dione (**7g**) has been the focus of synthetic efforts. Recently, Behforouz reported a short and efficient synthetic method of 7-amino-2-methylquinoline-5,8-dione (**7g**) as well as *Lavendamycin* from 7-acetylamino-2-methylquinoline-5,8-dione and β-methyltryptophan.[19,20] But to our knowledge, there has been no report on the syntheses of 7-alkylamino-2-methylquinoline-5,8-diones **7** as major products except our previous report[10] due to their synthetic problems such as preferential C6 substitution or addition of nucleophiles,[1,11,13,21] while 7-amino or 7-acetylaminoquinoline-5,8-diones were prepared from the reduction of azide and nitro substituents.[19,20] Recently, we published a report, in which, 7-alkylamino-2-methylquinoline-5,8-diones **7** were synthesized by the new synthetic route—nucleophilic substitution of amines and debromination—from 6,7-dibromo-2-methylquinoline-5,8-dione (**3**).[10] But this method has two drawbacks. First, as there is a regioselectivity between C6 and C7 in amination of 6,7-dibro-2-methylquinoline-5,8-dione (**3**), we could obtain the C7 aminated product only as moderate yields (50–60%) in optimized aprotic solvent such as dioxane. Second, in debromination step, we could not prepare some kinds of alkylamino compounds such as 2-methylaziridine, benzylamine and *t*-butylamine which are unstable in acidic condition because of the prevalently ongoing dealkylation. Thus we tried to discover another synthetic route for the preparation of the 7-alkylamino-2-methylquinoline-5,8-diones **7** including the alkylamino groups which are unstable in acidic conditions.

Herein, we wish to report the preparation of various 7-alkylamino-2-methylquinoline-5,8-diones **7** by a new efficient route. It is noteworthy that the conventional alkylation reactions on 7-amino group do not proceed due to its lack of nucleophilicity. The C2 methyl group could be

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☆☆ Supplementary data associated with this article can be found, in the online version at doi: 10.1016/j.tet.2004.04.041

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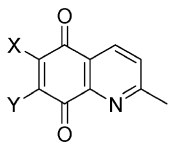
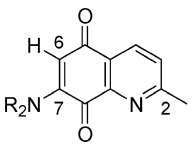
used for coupling with CD ring of *Lavendamycin* by reported method.[19,20]



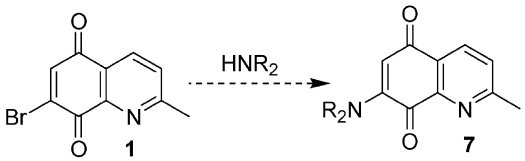
1, X = H, Y = Br,
2, X = Br, Y = H,
3, X = Y = Br,
4, X = Y = H,
5, X = OCH_3, Y = H,
6, X = H, Y = OCH_3



7a, R_2N = piperidinyl,
7b, R_2N = 2-methylaziridinyl,
7c, R_2N = benzylamino,
7d, R_2N = *n*-butylamino,
7e, R_2N = cyclohexylamino,
7f, R_2N = *t*-butylamino,
7g, R_2N = amino

2. Results and discussion

There were many reports on the preparation of 7-amino-quinoline-5,8-dione (**7g**) by nucleophilic azide substitution of 7-bromoquinoline-5,8-dione (**1**) followed by reduction to the amino group[22,23] and 6-aminoquinoline-5,8-dione (**12g**) by direct amine substitution of 6-methoxyquinoline-5,8-dione[21] and we also detected that 7-methoxyquinoline-5,8-dione yields 7-alkylamino-2-methylquinoline-5,8-dione **7** by nucleophilic amine substitution in low yields.[10] Thus to find an efficient synthetic route for the preparation of 7-alkylamino compounds **7**, we have designed a direct amination reaction of 7-bromoquinoline-5,8-dione (**1**) as shown in Scheme 1.

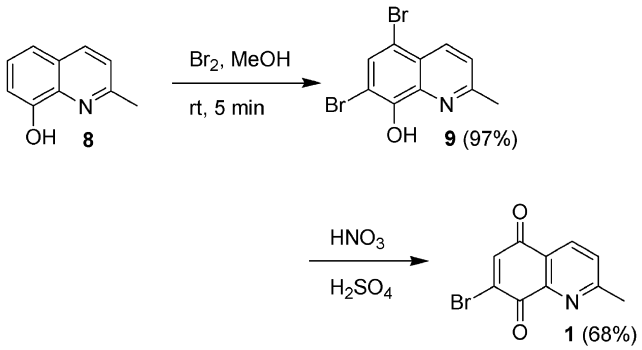


Scheme 1. A proposed new synthetic route for 7-alkylamino-2-methyl-quinoline-5,8-diones.

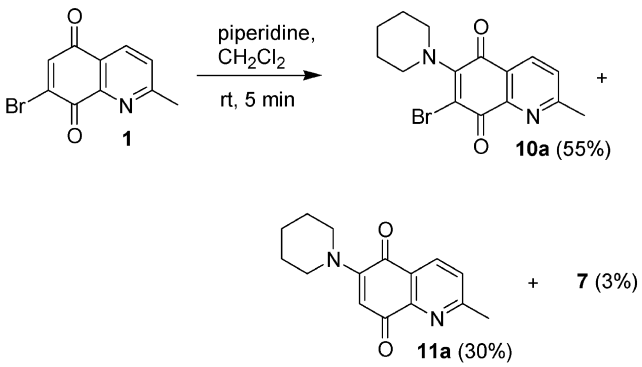
2.1. The preparation of 7-bromoquinoline-5,8-dione (1)

Petrow and Sturgeon reported a synthetic route for the preparation of **1** from 8-hydroxy-5-nitroso-2-methylquinoline by oxidation of nitroso to nitro group, selective bromination on the C7 position, reduction of nitro to the amino group, and oxidation to 7-bromo-2-methylquinoline-5,8-dione (**1**).[24] This procedure contained five steps and produced **1** in low yields. We have tried to discover an efficient and easy synthetic route for 7-bromo-2-methyl-quinoline-5,8-dione (**1**). Various synthetic routes were examined to synthesize 7-bromo compound **1**. Among them, **1** was prepared from very simple starting material, 8-hydroxy-2-methylquinoline (**8**) in two steps with 66% yield as shown in Scheme 2. Simple bromination of **8** gave 5,7-dibromo-8-hydroxy-2-methylquinoline (**9**) in 97% yield at rt for 5 min. The oxidation using 61% of nitric acid in the presence of concentrated sulfuric acid provided **1** in 68% yield.

Surprisingly, direct nucleophilic amination of 7-bromo compound **1** using piperidine gave predominantly the 6-piperidyl compounds **10a** (55%), **11a** (30%), and the

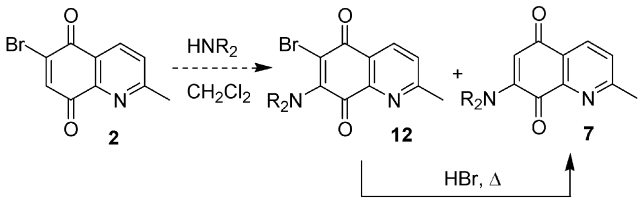


Scheme 2.



Scheme 3. The direct amination of 7-bromo-2-methylquinoline-5,8-dione (**1**).

desired 7-piperidyl compound **7a** in a low yield (3%) as shown in Scheme 3. At this point, the regiochemistry of C6 and C7 positions were thoroughly investigated. Therefore, it was expected the direct nucleophilic amination of 6-bromo-2-methylquinoline-5,8-dione (**2**) would produce 7-amino compounds **12** and **7** (Scheme 4). The debromination reactions of 6-bromo-7-alkylamino compounds **12** to **7** were developed by our group.[10]

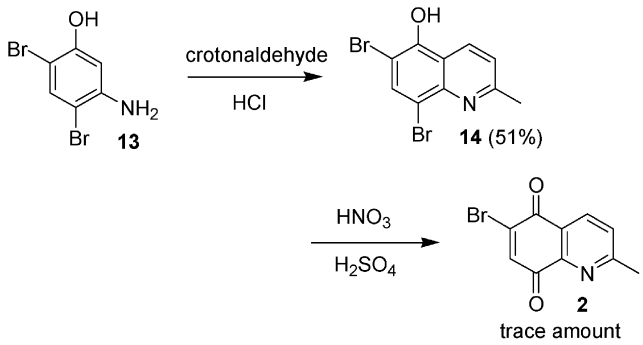


Scheme 4. Another proposed new synthetic route for 7-alkylamino-2-methylquinoline-5,8-diones.

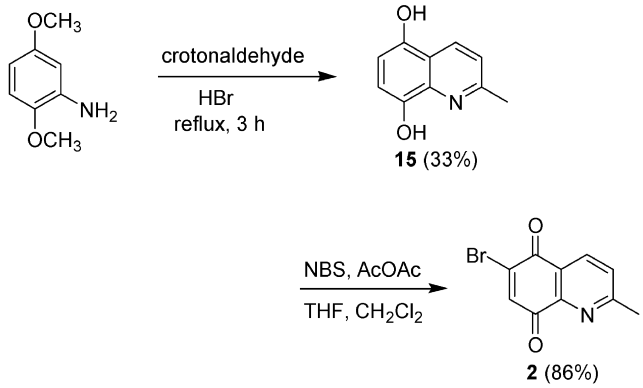
2.2. The preparation of 6-bromoquinoline-5,8-dione (2)

As prepared **1**, we expected that the direct oxidation by nitric acid of 6,8-dibromo-5-hydroxy-2-methylquinoline (**14**) would give **2** (Scheme 5). Unfortunately, we could obtain **2** in a trace amount. The difference of the electron donating abilities between 5-hydroxy and 8-hydroxy groups showed the different reactivities. Generally, it is known that the electron rich aromatic compounds are more easily oxidized. The 8-hydroxy group is thought to have more powerful electron donating ability by the formation of an intramolecular hydrogen bond with N1 nitrogen.

As shown in Scheme 6, we could prepare **2** from



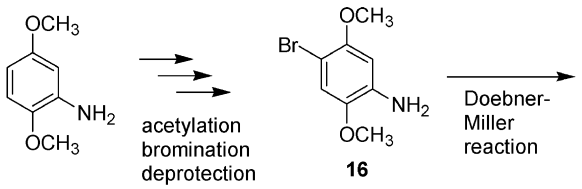
Scheme 5. Oxidation of 6,8-dibromo-5-hydroxy-2-methylquinoline.

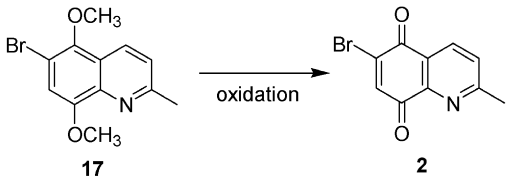


Scheme 6.

2,5-dimethoxyaniline in a reasonable yield by Doebner–Miller reaction[25] followed by oxidation using NBS. The regiochemistry of 6-bromo-2-methylquinoline-5,8-dione synthesized was identified by comparison with the authentic compound prepared by the route as shown in Scheme 7. Using this chemistry only the mono bromo compound **17**, 6-bromo-5,8-dimethoxy-2-methylquinoline was obtained which was oxidized via our recently reported method[26] using NBS with catalytic sulfuric acid and water.

Table 1 shows the results of the various 7-alkylamino compounds **7** prepared by direct nucleophilic aminations from 6-bromo-2-methylquinoline-5,8-dione (**2**). The reaction in the aprotic solvents such as dichloromethane gave the maximum yield of **7**. The addition of triethylamine





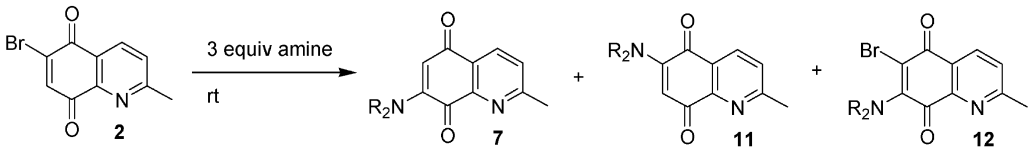
Scheme 7.

increased the selectivity of 7-amino products by trapping the generated HBr that can form the salt with N1 nitrogen. We could also obtain the 6-alkylamino compounds **11** from 6-bromo compound **2** with 40–60% yields by addition of Lewis acid in polar protic solvent as shown in Scheme 8.[28]

2.3. Plausible mechanism for the selective oxidative bromination of 5,8-dihydroxy-2-methylquinoline to 6-bromo-2-methylquinoline-5,8-dione

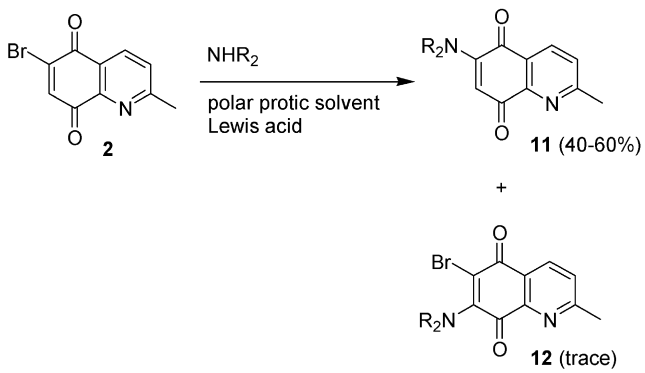
According to Scheme 6, 6-bromo-2-methylquinoline-5,8-dione (**2**) could efficiently and easily be obtained from 5,8-dihydroxy-2-methylquinoline (**15**) in gram-reaction scale. Scheme 9 shows the plausible mechanism for the selective oxidative bromination of **15** to **2**. This mechanism consists

Table 1. Amination of 6-bromo-2-methylquinoline-5,8-dione[a]



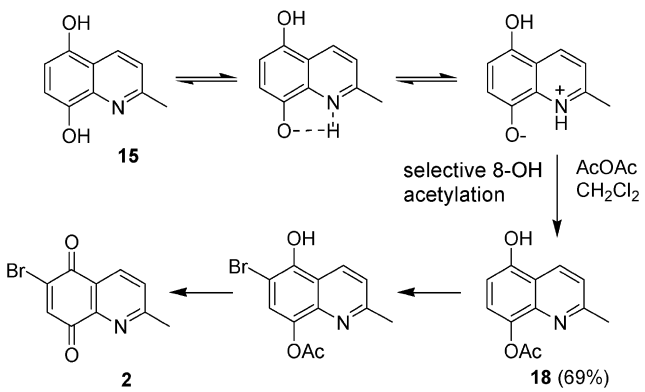
Solvent (25 mL)	Amine (3 equiv.)	Et_3N (mL)	Time (min)	**7** (%)	**11** (%)	**12** (%)	Total yield (%)
MeOH	Piperidine	—	10	**7a** (35)	**11a** (44)	**12a** (trace)	79
Dioxane	Piperidine	—	10	**7a** (70)	**11a** (7)	**12a** (trace)	77
Benzene	Piperidine	—	10	**7a** (75)	**11a** (18)	**12a** (trace)	93
CH_2Cl_2	Piperidine	—	10	**7a** (88)	**11a** (10)	—	98
CH_2Cl_2	2-Methylaziridine	—	15	**7b** (88)	**11b** (11)	—	99
CH_2Cl_2	2-Methylaziridine	0.5	15	**7b** (94)	**11b** (5)	—	99
CH_2Cl_2	Benzylamine	—	10	**7c** (55)	**11c** (5)	**12c** (16)	76
CH_2Cl_2	Benzylamine	0.5	10	**7c** (87)	**11c** (2)	**12c** (3)	92
CH_2Cl_2	*n*-Butylamine	—	10	**7d** (55)	—	**12d** (25)	80
CH_2Cl_2	*n*-Butylamine	0.5	10	**7d** (93)	—	**12d** (6)	99
CH_2Cl_2	Cyclohexylamine	0.5	30	**7e** (74)	—	**12e** (8)	82
CH_2Cl_2	*t*-Butylamine[b]	0.5	48 h	**7f** (48)	—	**12f** (4)	52
CH_2Cl_2	NH_4OH (1.5 mL)	1.5	90	**7g** (34)	—	**12g** (13)	47

[a] See general procedure in Section 4.
[b] 6 equiv. of amine was used.



Scheme 8.

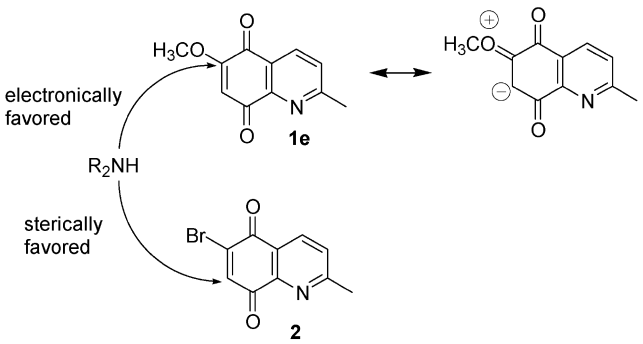
of three steps: (1) selective acetylation of 8-hydroxy group of **15** without base, (2) bromination using NBS onto the C6 position, and (3) oxidation using another equiv of NBS. Therefore, we added 2 equiv. of NBS because it is used as a brominating agent as well as oxidant. The key-intermediate, 5,8-dihydroxy-2-methylquinoline (**15**) could be prepared from 2,5-dimethoxyaniline via Doebner–Miller reaction and demethylation using concentrated HBr in 50–60% yield.[27]



Scheme 9.

When the base such as triethylamine was added, compound **15** was diacetylated on both 5- and 8-hydroxy and this diacetylated compound was not oxidized at the NBS condition. In addition, the direct treatment of NBS in methanol to 5,8-dihydroxy-2-methylquinoline (**15**) provided 2-methylquinoline-5,8-dione (**4**) in a 77% yield. On the inverse regioselectivity of nucleophilic amination of **1** and **2**, some papers reported the prevalent attack on the C6 position[1] is due to the chelation of metal cation between 8-oxygen and 1-nitrogen, and it is generally accepted that chelating effect is important for regioselectivity.[13,28] Actually, we experienced the chelating effect and hydrogen bonding effect in Table 1 (entry 1) and Scheme 8. We also detected that the nucleophilic aminations of 7-bromo-2-methylquinoline-5,8-dione (**1**) yielded the 6-amino compounds **10** and **11**. On the other hand, the neucleophilic aminations of 6-bromo-2-methylquinoline-5,8-dione (**2**) yielded the 7-amino compounds **7** and **12** as major products in non-polar aprotic solvents. It was reported that the 6-methoxy and 7-methoxy compounds each produced 6-amino and 7-amino compounds on the amine substitution of the 6- or 7-methoxy-2-methylquinoline-5,8-dione.[21] From those results, we could conclude that the chelating and intramolecular hydrogen bonding effect in polar protic solvent is important on the regioselectivity, while in non-polar aprotic solvent, the regiochemistry is mainly determined by properties of substituents on C6 or C7 position.

We propose the regioselectivity on the basis of electronic and steric effects. As shown in Scheme 10, the electron donating ability of methoxy group increases the electron density at the C7 position in place of *ortho*-position, consequently making the nucleophilic attack on the *ipso*-position favorable. On the other hand, when the bromine used as a leaving group, the bulkiness of bromine makes the *ipso*-attack difficult, thus it makes the attack at the C7 position in place of *ortho*-position favorable.



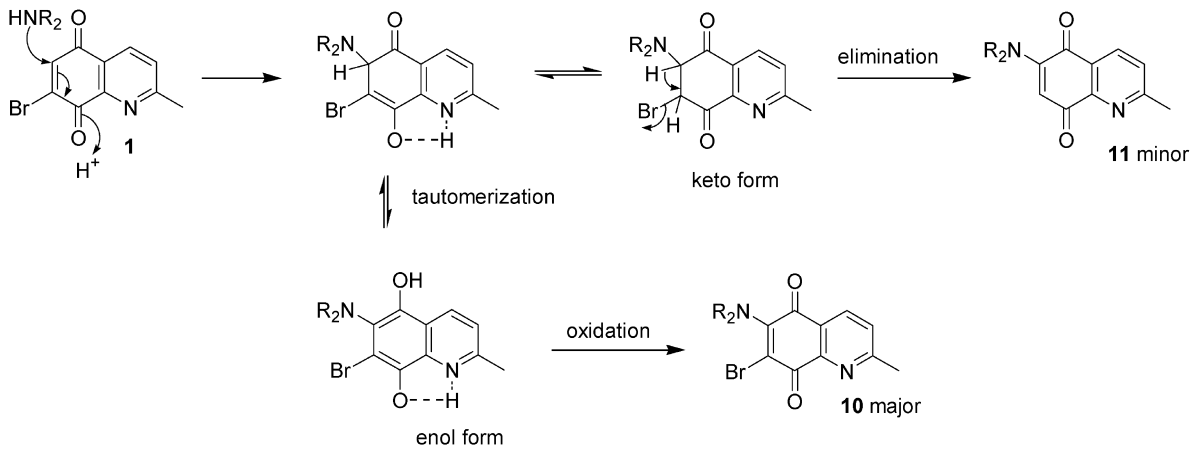
Scheme 10. Regioselectivity by substituent.

Furthermore, we obtained a different result between the 6-bromo (**2**) and 7-bromo-2-methylquinoline-5,8-dione (**1**) on the nucleophilic amination. The 7-bromo-2-methylquinoline-5,8-dione (**1**) yielded the 6-alkylamino-7-bromo-2-methylquinoline-5,8-diones **10** as major products, while 6-bromo-2-methylquinoline-5,8-dione (**2**) produced 7-alkylamino-2-methylquinoline-5,8-diones **7** as major products. We proposed that the different results are due to the intramolecular hydrogen bonding between the OH at the C8 and N1 as shown in Schemes 11 and 12.

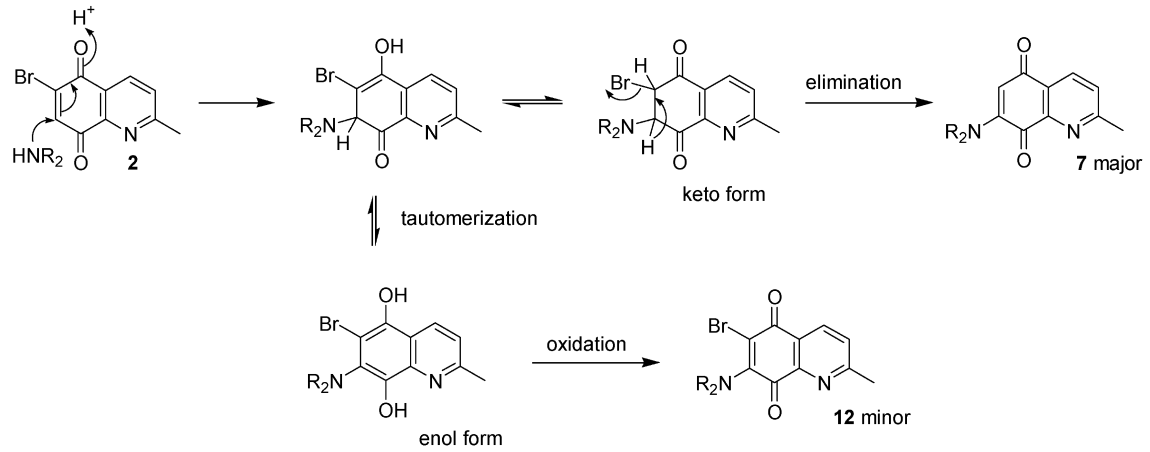
Scheme 11 shows that the intermediate can be in both in keto and enol forms, but the enol form will be more stable due to the intramolecular hydrogen bonding. As a result, following oxidation reaction of enol form provided 6-alkylamino-7-bromo-2-methylquinoline-5,8-dione **10** as a major product. But in case of 6-bromo-2-methylquinoline-5,8-dione (**2**), because there is no possibility for the more stabilizing the enol form, the 7-alkylamino-2-methylquinoline-5,8-diones **7** was obtained as a major product as shown in Scheme 12.

3. Conclusion

Recently, we reported a synthetic method for the preparation of various 7-alkylamino-2-methylquinoline-5,8-diones by nucleophilic amination of 6,7-dibromo-2-methylquinoline-5,8-dione followed by debromination upon treatment with hydrobromic acid.[10] As this synthetic route has some drawbacks, we developed the new synthetic route



Scheme 11. Proposed mechanism on the 6-alkylamino-2-methylquinoline-5,8-diones from 7-bromo-2-methylquinoline-5,8-diones.



Scheme 12. Proposed mechanism of 7-alkylamino-2-methylquinoline-5,8-diones from 6-bromo-2-methylquinoline-5,8-diones.

for 7-alkylamino-2-methylquinoline-5,8-diones by nucleophilic amination from 6-bromo-2-methylquinoline-5,8-dione, not from 7-bromo compound. Using this new method, we could prepare the alkylamino-2-methylquinoline-5,8-diones that could not be prepared by debromination method. During the research for the preparation of 7-alkylamino-2-methylquinoline-5,8-dione, we also discovered a new and efficient synthetic routes for the key intermediates, 6-bromo or 7-bromo-2-methylquinoline-5,8-diones.

4. Experimental

4.1. 5,7-Dibromo-8-hydroxy-2-methylquinoline (9)[29]

Bromine (10 mL) dissolved in MeOH (100 mL) was added into the mixture of 8-hydroxy-2-methylquinoline (**8**, 10.0 g, 62.8 mmol), $NaHCO_3$ (10 g) and MeOH (100 mL). After stirring for 5 min at rt, Na_2SO_3 (5 g) was added and then the mixture was filtered and washed with H_2O (200 mL) and was dried in vacuo to give **9** (19.34 g, 61.0 mmol, 97%) as a white solid.

4.1.1. 7-Bromo-2-methylquinoline-5,8-dione (1).[19] 5,7-Dibromo-8-hydroxy-2-methylquinoline (**9**, 10.8 g, 34.1 mmol) was dissolved in concentrated H_2SO_4 (40 mL), and HNO_3 (61%, 5 mL) was added for 30 min in the ice bath. And ice water (300 mL) was added and extracted with dichloromethane without neutralization and dried by Na_2SO_4 and was concentrated in vacuo to give **1** (5.81 g, 23.1 mmol, 68%) as a yellowish-white solid: ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.30 (d, J=8.2 Hz, 1H), 7.57 (d, J=8.2 Hz, 1H), 7.56 (s, 1H), 2.80 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$ +DMSO-d_6) δ 181.4, 175.9, 164.8, 145.3, 139.4, 139.1, 134.8, 128.1, 126.4, 23.7; MS (EI) 253 (M^+), 251 (M^+, 100), 225, 223, 197, 195, 172, 144, 116, 89, 74, 63, 53, 39. Anal. Calcd for $C_{10}H_6BrNO_2$: C, 47.65; H, 2.40; N, 5.56. Found: C, 47.26; H, 2.52; N, 5.51.

4.2. General procedure for amination of 7-bromo-2-methylquinoline-5,8-dione (1)

4.2.1. 7-Bromo-2-methyl-6-(piperidin-1-yl)quinoline-5,8-dione (10a).[10] 7-Bromo-2-methylquinoline-5,8-dione (**1**, 700 mg, 2.78 mmol) was dissolved in dichloromethane (20 mL) and piperidine (0.7 mL) was added. After stirring for 1 min at rt, H_2O (50 mL) was added into the mixture and extracted with dichloromethane, dried by Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography (40% EtOAc/hexane) to give **10a** (519 mg, 1.55 mmol, 55%), 2-methyl-6-(piperidin-1-yl)-quinoline-5,8-dione (**11a**, 215 mg, 0.84 mmol, 30%),

2-methyl-7-(piperidin-1-yl)quinoline-5,8-dione (**7a**, 22 mg, 0.08 mmol, 3%). See the analytical data in Ref. 10.

4.2.2. 2,4-Dibromo-5-aminophenol (13).[30] The title compound was prepared by acetylation of 3-aminophenol, followed by selective 2,4-dibromination and deacetylation.

4.2.3. 6,8-Dibromo-5-hydroxy-2-methylquinoline (14).[30] Crotonaldehyde (1.5 mL) was added into the mixture of 2,4-dibromo-5-aminophenol (**13**, 1.15 g, 4.31 mmol) and concentrated HCl (10 mL) and AcOH (10 mL), then the reaction mixture was refluxed for 30 min. The reaction mixture was neutralized by $NaHCO_3$ and extracted by EtOAc and was concentrated in vacuo. The residue was purified by flash column chromatography (60% EtOAc/hexane) to give **14** (691 mg, 2.18 mmol, 51%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.07 (bs, 1H), 8.23 (d, J=8.4 Hz, 1H), 7.74 (s, 1H), 7.05 (d, J=8.8 Hz, 1H), 2.49 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$ +DMSO-d_6) δ 159.7, 149.0, 143.7, 134.3, 131.1, 121.5, 119.6, 113.1, 102.9, 24.8; MS (EI) 319 (M^+), 317 (M^+), 315 (M^+), 156, 128, 101, 64, 51, 32 (100). HRMS (EI^+) m/z Calcd for $C_{10}H_7Br_2NO$ (M^+) 316.8874, found 316.8894.

4.2.4. 5,8-Dihydroxy-2-methylquinoline (15).[27] Crotonaldehyde (11.84 g, 169 mmol, 1.3 equiv.) was added into the mixture of 2,5-dimethoxyaniline (20 g, 130 mmol) and concentrated HBr (150 mL), then the reaction mixture was refluxed for 24 h and the reaction mixture was neutralized by $NaHCO_3$ and extracted by EtOAc and was concentrated in vacuo. The residue was purified by flash column chromatography (40% EtOAc/hexane) to give **15** (7.4 g, 42.3 mmol, 33%): ^{1}H NMR (200 MHz, $CDCl_3$ +DMSO-d_6) δ 8.41 (d, J=8.4 Hz, 1H), 7.26 (d, J=8.4 Hz, 1H), 6.93 (d, J=8.2 Hz, 1H), 6.77 (d, J=8.4 Hz, 1H), 2.70 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$ +DMSO-d_6) δ 156.6, 144.8, 144.1, 137.4, 131.3, 120.8, 118.0, 108.9, 107.9, 24.6; MS (EI) 175 (M^+, 100), 146, 118, 87, 74, 52, 39. HRMS m/z (EI^+) 175.0635, Calcd for $C_{10}H_9NO_2$ 175.0633.

4.2.5. 6-Bromo-2-methylquinoline-5,8-dione (2).[26] Acetic anhydride (2 mL) was added into the mixture of 5,8-dihydroxy-2-methylquinoline (**15**, 1.0 g, 5.57 mmol) and dichloromethane (40 mL) and THF (10 mL). After stirring at rt for 5 min, NBS (1.7 g, 9.55 mmol, 1.68 equiv.) was added and was stirred for 10 min and then H_2O (200 mL) including $NaHCO_3$ (3 g) added and extracted by dichloromethane and was concentrated in vacuo. The residue was purified by flash column chromatography (60% EtOAc/hexane) to give **2** (1.23 g, 4.89 mmol, 85.7%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.39 (d, J=8.4 Hz, 1H), 7.65 (s, 1H), 7.59 (d, J=8.0 Hz, 1H), 2.80 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$ +DMSO-d_6) δ 178.6, 175.1, 163.3, 144.3, 137.8, 137.0, 133.3, 125.4, 123.7, 22.9.; MS (EI) 253 (M^+, 100), 251 (M^+), 225, 223, 197, 195, 144, 116, 89, 63, 53, 39. Anal. Calcd for $C_{10}H_6BrNO_2$: C, 47.65; H, 2.40; N, 5.56. Found: C, 47.40; H, 2.55; N, 5.53.

4.3. General procedure for amination of 6-bromo-2-methylquinoline-5,8-dione (2) at Table 1

4.3.1. 2-Methyl-7-(2-methylaziridin-1-yl)quinoline-5,8-dione (7b).[10] 6-Bromo-2-methylquinoline-5,8-dione (**2**, 200 mg, 0.79 mmol) was dissolved in dichloromethane (10 mL) and triethylamine (0.5 mL) then 2-methylaziridine (0.19 mL) was added at rt. After stirring for 5 min, H_2O (100 mL) was added and was extracted with dichloromethane and dried by Na_2SO_4 and was concentrated in vacuo. The residue was purified by flash column chromatography (40% EtOAc/hexane) to give **7b** (170 mg, 0.75 mmol, 94%) as a yellow solid: See detail data are in Ref. 10. 2-Methyl-6-(2-methylaziridin-1-yl)quinoline-5,8-dione (**11b**, 8 mg, 0.04 mmol, 5%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, J=8.0 Hz, 1H), 7.49 (d, J=8.0 Hz, 1H), 6.39 (s, 1H), 2.77 (s, 1H), 2.40–2.43 (m, 1H), 2.20–2.23 (m, 2H), 1.47 (d, J=6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.2, 181.3, 164.9, 157.1, 147.5, 134.5, 126.8, 126.3, 118.9, 36.3, 34.5, 25.2, 17.5; MS (ESI, positive) 229 (M^++1, 100). HRMS (EI^+) m/z Calcd for $C_{13}H_{12}N_2O_2$ (M^+) 228.0899, found 228.0889.

4.3.2. 7-Benzylamino-2-methylquinoline-5,8-dione (7c). ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.29 (d, J=8.0 Hz, 1H), 7.50 (d, J=8.0 Hz, 1H), 7.28–7.40 (m, 5H), 6.42 (bs, 1H), 5.80 (s, 1H), 4.41 (d, J=6.0 Hz, 1H), 2.73 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 182.0, 180.4, 163.0, 147.9, 146.1, 135.6, 134.5, 129.0, 128.4, 128.2, 128.1, 127.6, 100.9, 46.9, 29.6, 24.9; MS (EI) 278 (M^+), 276, 261, 194, 174, 117, 91 (100), 77, 65, 51, 39. HRMS (EI^+) m/z Calcd for $C_{17}H_{14}N_2O_2$ (M^+) 278.1055, found 278.1059.

4.3.3. 6-Benzylamino-2-methylquinoline-5,8-dione (11c). ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.25 (d, J=8.0 Hz, 1H), 7.27–7.45 (m, 6H), 6.20 (bs, 1H), 5.95 (s, 1H), 4.39 (d, J=5.4 Hz, 1H), 2.77 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 181.5, 181.3, 165.4, 148.5, 147.0, 135.4, 134.1, 128.8, 128.0, 127.5, 126.0, 125.0, 102.2, 46.7, 26.3; MS (EI) 278 (M^+, 100), 261, 201, 187, 174, 117, 91, 77, 65. HRMS (EI^+) m/z Calcd for $C_{17}H_{14}N_2O_2$ (M^+) 278.1055, found 278.1056.

Compounds **12a**, **12c-g**, **7d-g**.[10] See detail data are in Ref. 10.

4.3.4. 8-Acetoxy-5-hydroxy-2-methylquinoline (18). Acetic anhydride (2.7 mL, 28.8 mmol, 0.9 equiv.) was added into the mixture of 5,8-dihydroxy-2-methylquinoline (**15**, 5.6 g, 32.0 mmol) and dichloromethane (50 mL). After stirring at rt for 30 min, the reaction mixture was concentrated in vacuo. The residue was purified by flash column chromatography (40% EtOAc/hexane) to give **18** (4.71 g, 22.0 mmol, 69%): ^{1}H NMR (200 MHz, $CDCl_3$ +DMSO-d_6) δ 9.96 (s, 1H), 8.37 (d, J=8.4 Hz, 1H), 7.19 (d, J=8.4 Hz, 1H), 7.10 (d, J=8.6 Hz, 1H), 6.74 (d, J=8.4 Hz, 1H), 2.61 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$ +DMSO-d_6) δ 167.9, 156.9, 149.3, 138.8, 136.8, 129.3, 119.1, 118.9, 116.9, 104.7, 23.3, 18.7; MS (CI) 218 (M^++1, 100), 204, 176. Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 65.98; H, 5.48; N, 6.28.

4.3.5. 6-Bromo-2-methylquinoline-5,8-dione (2) from 8-acetoxy-5-hydroxy-2-methylquinoline (18). NBS (5.47 g, 30.7 mmol, 2.47 equiv.) was added into the mixture of 8-acetoxy-5-hydroxy-2-methylquinoline (2.69 g, 12.4 mmol) and dichloromethane (70 mL). After stirring at rt for 30 min, the solvent was removed in vacuo. The

residue was purified by flash column chromatography (60% EtOAc/hexane) giving **2** (2.30 g, 9.0 mmol, 73%).

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Synthesis and properties of 7,7-bis(heteroazulen-3-yl)-8,8-dicyano-1,4-quinodimethanes

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Abstract—The synthesis and properties of a novel type of 7,7-bis(heteroazulen-3-yl)-8,8-dicyano-1,4-quinodimethanes (**9a**–**c**) are studied. The synthetic method is based on a TFA-catalyzed electrophilic aromatic substitution on the heteroazulenes with 4-(dicyanomethyl)benzaldehyde to afford the corresponding methane derivatives, followed by oxidative hydrogen abstraction with DDQ. The polarization of **9a**–**c** is evaluated by the inspection of their ^{13}C NMR and IR spectra. Based on the investigation of the UV–Vis spectra of **9a**–**c** and protonated cations **10a**–**c**, conformational changes of the heteroazulene-moiety and (dicyanomethyl)phenyl group are suggested. In the CV measurements of **9a**–**c**, two reversible reduction waves are observed, indicating the stabilizing ability of heteroazulenes toward the corresponding radical and anion species. Furthermore, **9a**–**c** exhibit two irreversible oxidation waves, which suggest a conformational change in the radical cation during the redox process. The conformational change is rationalized on the basis of the MO calculations.

1. Introduction

Conjugated π-electron chromophores containing a donor and an acceptor group have attracted current interest in terms of optoelectronic materials,[1] such as non-linear optics[2] and near-infrared dyes.[3] Among numerous classes of these chromophores, compounds containing a quinonoid unit as a spacer are especially promising,[4] because such conjugated systems have generally been recognized to possess marked push–pull electronic effects, which induce large dipole moments leading to a high non-linear response[5] and ready intramolecular charge-transfer transitions resulting in a deep coloration.[6] Gompper and co-workers have reported the synthesis of a number of dicyanoquinodimethanes including 7,7-dicyano-8,8-diphenyl-1,4-quinodimethane (**1a**).[7] Furthermore, Oda and co-workers have reported recently the synthesis and properties of **1a** and its derivatives **1b**,**c** (Fig. 1).[8] Benzoquinonoid compounds have hitherto played the most important role in the development of organic redox chemistry due to their multistage redox properties.[9]

On the other hand, we have studied the synthesis and properties of heteroazulene analogues of the triphenylmethyl cation, i.e. tris(2-oxo-2*H*-cyclohepta[*b*]furan-3-yl)-methyl cation and pyrrole analogues,[10] as well as bis(2-oxo-2*H*-cyclohepta[*b*]furan-3-yl)phenylmethyl cations (**2a**–**e**) and their pyrrole analogues (**3a**–**e**).[11] Through these studies, we clarified the stabilizing ability of heteroazulenes such as **6a**–**c** (Scheme 1) toward the methyl cations and the anomalous substituent effect of the substituted phenyl groups arising from their conformational change. In this context, we also reported the synthesis and properties of heteroazulene-substituted benzene-1,3-bismethylium derivatives[12] and benzene-1,3,5-trismethylium derivatives.[13]

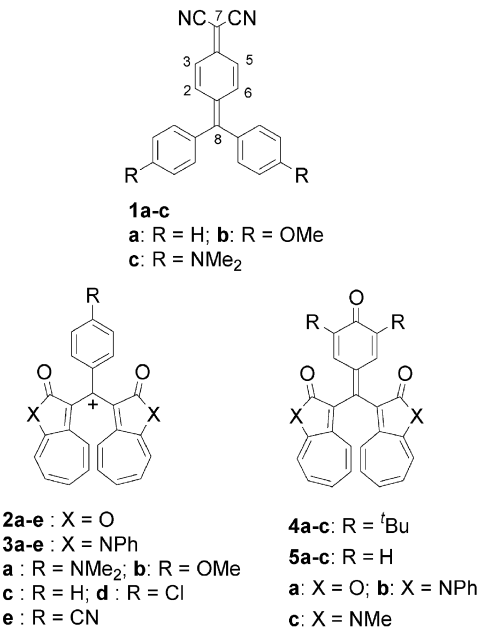

Figure 1.

Keywords: 7,7-Bis(heteroazulen-3-yl)-8,8-dicyano-1,4-quinodimethanes; Heteroazulene; Redox potential; Conformational change.

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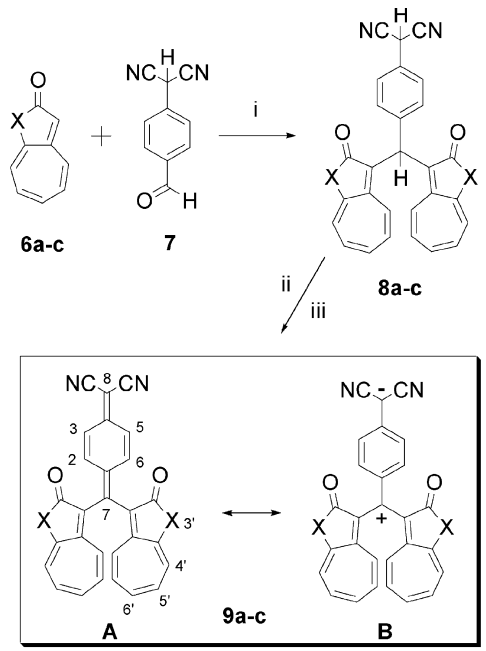
In these cations, two or three methylium units are twisted against the central phenyl group, respectively, and conjugation among the methylium units is not observed. Furthermore, heteroazulenes such as **6a–c** are demonstrated to stabilize not only cations but also radical and anion species based on the studies of the pK_{R+} values and reduction potentials.[11,14] Recently, we have also reported the synthesis and properties of the α,α-bis(heteroazulen-3-yl)-1,4-benzoquinonemethides (**4a–c**) and (**5a–c**) and clarified that the contribution of a polarized structure is small in the ground state but larger in the excited state.[15] The redox property of **4a–c** and **5a–c** was clarified as well (Fig. 1). Thus, heteroazulene-substituted compounds are very interesting for the exploration of novel redox functions. From this viewpoint, we have investigated the synthesis and properties of 7,7-bis(heteroazulen-3-yl)-8,8-dicyano-1,4-quinodimethanes **9a–c**, which are expected to have multistage redox properties and a more highly polarized structure as compared with **4a–c** and **5a–c**.[15] To gain insight into the polarized structural nature of **9a–c**, their ^{13}C NMR and IR spectra are studied. Based on a measurement of the CV, the remarkable redox property of **9a–c** is also demonstrated. We report herein the results in detail.



Scheme 1. Reagents and conditions: (i) TFA–$CHCl_3$ (1/10), 80 °C, 6 h; (ii) DDQ, CH_2Cl_2, rt, 1 h; (iii) Et_3N, CH_2Cl_2, rt, 10 min.

2. Results and discussion

2.1. Synthesis of 7,7-bis(heteroazulen-3-yl)-8,8-dicyano-1,4-quinodimethanes (9a–c)

The preparation of 7,7-bis(heteroazulen-3-yl)-8,8-dicyano-1,4-quinodimethanes was easily accomplished by the TFA-catalyzed electrophilic substitution of heteroazulenes with 4-(dicyanomethyl)benzaldehyde and subsequent oxidation. Reactions of 4-(dicyanomethyl)benzaldehyde (**7**)[16] with 2 M equiv. amounts each of 2*H*-cyclohepta[*b*]furan-2-one (**6a**),[17] 1,2-dihydro-*N*-phenylcyclohepta[*b*]pyrrol-2-one (**6b**),[18] and 1,2-dihydro-*N*-methylcyclohepta[*b*]pyrrol-2-one (**6c**)[19] in $CHCl_3$–TFA (5:1) at 80 °C for 6 h afforded bis(heteroazulen-3-yl)[4-(dicyanomethyl)phenyl]methanes (**8a–c**) in good yields, respectively (Scheme 1, Table 1). Compounds **8a–c** are powdery, orange crystals, the structures of which were assigned on the basis of their IR, ^1H and ^{13}C NMR spectral data as well as the mass spectral data and elemental analyses. The oxidative hydrogen abstraction of **8a–c** with 1.2 M equiv. amounts of DDQ in CH_2Cl_2 at rt for 1 h, followed by addition of Et_3N afforded quinodimethanes **9a–c** in modest to good yields (Scheme 1, Table 1).

Table 1. Results for the preparation of methanes **8a–c** and quinodimethanes **9a–c**

Run	Compound	Condensation		Oxidation	
		Product	Yield (%)	Product	Yield (%)
1	**6a**	**8a**	89	**9a**	95
2	**6b**	**8b**	95	**9b**	75
3	**6c**	**8c**	96	**9c**	50

2.2. Properties of 9a–c

The structures of quinodimethanes **9a–c** were assigned based on their spectral data and elemental analyses. In the ^1H NMR spectra at room temperature, proton signals on the seven-membered ring of **9a–c** appear as broad signals. However, these signals become sharp at elevated temperature (60 °C). Thus, a rapid conformational change of the heteroazulene moieties in these quinodimethanes occurs at that temperature on the NMR time scale. The feature is similar to that of compounds **5a–c**.[15] The ^{13}C NMR spectra of **9a–c** were recorded and the chemical shifts of C8 are summarized in Table 2, along with the corresponding signals of reference compounds **1a–c**.[8] The chemical shifts of C8 become higher in the order **9a**<**9b**<**9c**. Thus, the contribution of the charge-separated ionic forms **9a–c–B** (Scheme 1) becomes larger in this order, depending on the electron-donating ability of the X: O<NPh<NMe. While the chemical shifts of C8 of **9a–c** are higher than those of **1a**,**b**, the values are smaller than that of **1c**, which has two large electron-donating substituents of NMe_2. Furthermore, the IR spectra of **9a–c** exhibit remarkable characteristics. It is well known that there is a good correlation between the

Table 2. ^{13}C NMR and IR spectral data, and the longest wavelength absorption maxima of quinodimethanes **9a–c** and reference compounds **1a–c**

Compound	^{13}C NMR (δ)	ν_{CN} (cm^{-1})	λ_{max} (nm)	
			CH_3CN	CH_3CN+TFA[a]
9a	64.4[b]	2195	531, 663	621
9b	58.4[b]	2196	598, 755	650
9c	56.7[b]	2192	598, 755	647
1a[c]	80.2[d]	2209	495[e]	
1b[c]	66.1[d]	2199	558[e]	
1c[c]	55.1[d]	2186	640sh, 698[e]	

[a] Generation of cations **10a–c**.
[b] Chemical shift of C8-position.
[c] Ref. 8.
[d] Chemical shift of C7-position.
[e] In CH_2Cl_2.

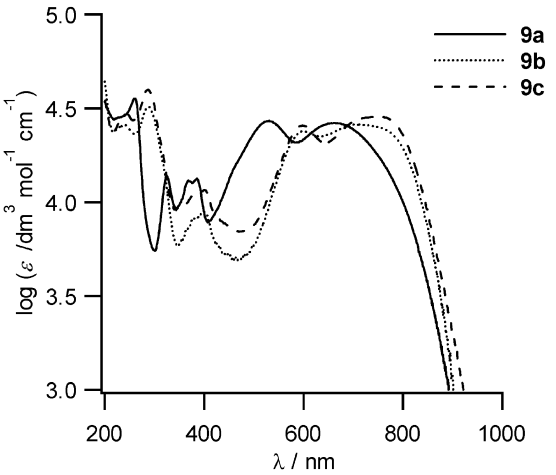


Figure 2. UV–Vis spectra of **9a**–**c** in CH_3CN.

nitrile stretching frequency (ν_{CN}) and the degree of charge transfer in CT-complexes of TCNQ.[20] Thus, in order to evaluate the contribution of the polarized structure **9a**–**c**–**B**, their IR spectra were also recorded in KBr disk, and the nitrile stretching frequencies (ν_{CN}) are summarized in Table 2, along with those of reference compounds **1a**–**c**.[18] While the frequencies (ν_{CN}) of **9a**–**c** are smaller than those of **1a**,**b**, the values are larger than that of **1c**. Thus, the contribution of the polarized structure **9a**–**c**–**B** seems to be larger than those of **1a**,**b** and smaller than that of **1c**. This feature is in good accordance with the consideration based on the ^{13}C NMR spectra.

The UV–Vis spectra of **9a**–**c** in CH_3CN are shown in Figure 2. The longest wavelength absorption maxima of **9a**–**c** are also summarized in Table 2. The spectra of **9b**,**c** are similar, and the longest wavelength absorption maximum of **9a** shows a blue-shift by 92 nm, as compared with those of **9b** and **9c**. By adding a drop of TFA, compounds **9a**–**c** seemed to be completely protonated to give cations **10a**–**c** (Fig. 3, Scheme 2). Upon addition of a drop of Et_3N to the cations **10a**–**c**, **9a**–**c** were regenerated quantitatively (confirmed by UV–Vis measurement). Thus, the protonation–deprotonation cycle is completely reversible. The longest wavelength absorption maxima of **10a**–**c** are also summarized in Table 2. The value of **10a** is similar to those

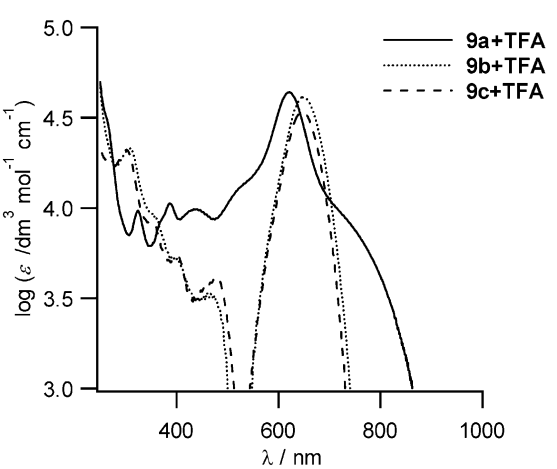
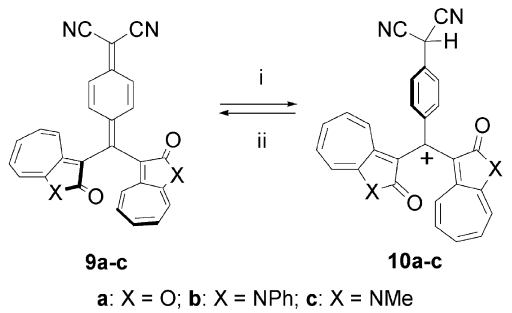


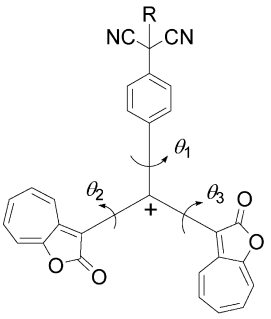
Figure 3. UV–Vis spectra of **9a**–**c** in CH_3CN with TFA.



Scheme 2. Reagents and conditions: (i) TFA, CH_3CN, rt; (ii) Et_3N, CH_3CN, rt.

of **2b**–**e** (621 nm)[11] and the values of **10b**,**c** are similar to those of **3b**–**e** (652 nm),[11] suggesting that the substituent effect of the dicyanomethyl group on the phenyl-moiety is small as in the cases of R=H, Cl, and CN in **2c**–**e** and **3c**–**e**. This feature seems to be reasonable based on consideration of the stable conformation of **2c**–**e** and **3c**–**e**,[11] in which the phenyl group is twisted and the heteroazulene moieties exist in a cationic plane (the cationic plane is defined by the three arylic ipso carbons, cf. Fig. 4). Regarding the charge-separated ionic structures **9a**–**c**–**B**, the benzene-4-(dicyanomethylide)-moiety has a higher electron-donating ability than the heteroazulene-moiety. Thus, the benzene-4-(dicyanomethylide)-moiety exists in a more planar conformation and the heteroazulene-moiety is twisted against the cationic plane due to steric hindrance. On the contrary, the heteroazulene-moiety has a higher electron-donating ability than the 4-(dicyanomethyl)phenyl-moiety in cations **10a**–**c**. Since the heteroazulene-moiety has a more planar conformation and the 4-(dicyanomethyl)phenyl-moiety is twisted against the cationic plane, conjugation between the 4-(dicyanomethyl)phenyl-moiety and the methylium carbon becomes smaller. Thus, the substituent effect of the dicyanomethyl group on the phenyl-moiety becomes less important. In addition, MO calculations of **9a** and **10a** rationalize also this conformational change (Fig. 4, vide infra).

The reduction and oxidation potentials of **9a**–**c** determined by cyclic voltammetry (CV) in CH_3CN are summarized in Table 3, along with those of reference compounds **1a**,**c**[8] and **5a**–**c**.[15] The two reduction waves of **9a**–**c** are reversible



9a (R = **–**)	**10a** (R = H)	**13a** (**13'a**) (R = •)
θ_1 = 0.4 °	θ_1 = 63.0 °	θ_1 = 60.1 °
θ_2 = 99.7 °	θ_2 = 28.9 °	θ_2 = 46.0 °
θ_3 = 80.3 °	θ_3 = -19.0 °	θ_3 = -24.9 °

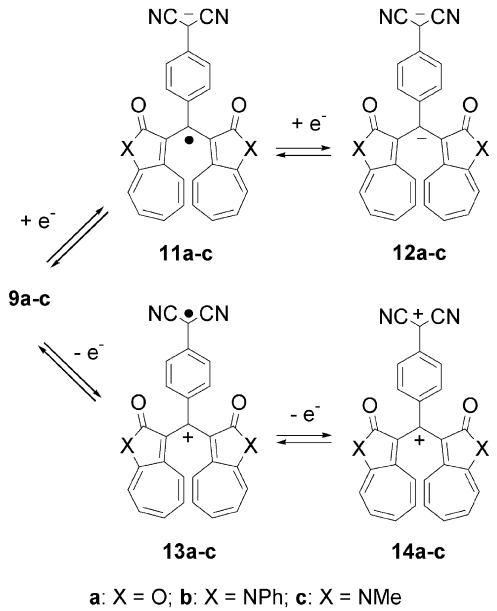
Figure 4. Calculated structural features of **9a**, **10a**, and **13a** (**13a**′).

Table 3. Reduction and oxidation potentials of quinodimethane **9a–c** and reference compounds **1a**,**c** and **5a–c**

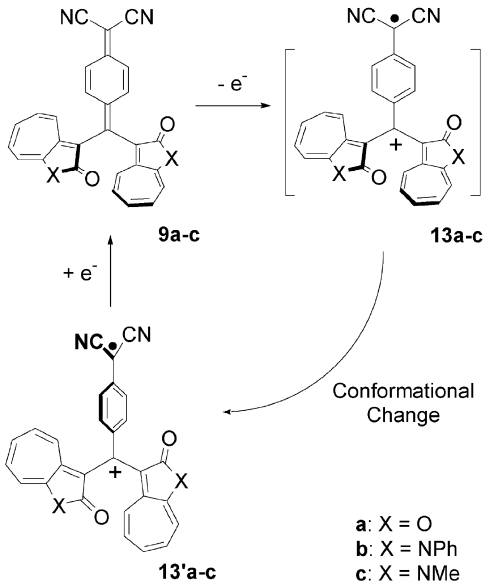
Compound	Reduction potential[a] (V)		Oxidation potential[a] (V)		
	$E1_{red}$	$E2_{red}$	$E1_{ox}$	$[E_{red}]^b$	$E2_{ox}$
9a	−0.70	−1.28	(+0.51)	[(−0.15)]	(+1.55)
9b	−0.82	−1.42	(+0.35)	[(−0.28)]	(+1.27)
9c	−0.98	−1.54	(+0.23)	[(−0.58)]	(+1.21)
1a[c]	−0.44	(−1.46)	(+1.38)		—
1c[c]	−0.72	(−1.60)	(+0.76)		—
5a[d]	−1.07	−1.44	(+0.78)		(+1.47)
5b[d]	−1.22	−1.63	(+0.59)		(+1.11)
5c[d]	−1.26	−1.65	(+0.55)		(+1.06)

[a] V vs. $Ag/AgNO_3$; mean value of the cathodic and anodic peaks. Irreversible processes are shown in parentheses.
[b] Corresponding reduction wave.
[c] Ref. 8.
[d] Ref. 15.

under the conditions of the CV measurements, while the second reduction waves of **1a**,**c** are irreversible. The two waves ($E1_{red}$ and $E2_{red}$) are explained by the formation of stable radical anions **11a–c** and dianions **12a–c**, respectively (Scheme 3). These characteristics are due to the heteroazulenes which stabilize the radical species and anion species.[11,14] Furthermore, the values ($E1_{red}$ and $E2_{red}$) of **9a–c** are less negative than those of **5a–c**, respectively, suggesting the larger electron affinity of **9a–c** as compared with **5a–c**. On the other hand, two oxidation waves were recorded also in the measurements of **9a–c**, as summarized in Table 3. The two oxidation waves ($E1_{ox}$ and $E2_{ox}$) of **9a–c** are irreversible, and can be explained by the formation of radical cations **13a–c** and dications **14a–c**, respectively (Scheme 3). The values ($E1_{ox}$) of **9a–c** are less positive than those of **5a–c**, respectively. The less negative reduction potentials and the less positive oxidation potentials of **9a–c** would be ascribed to the more electron-withdrawing and conjugative nature of the dicyanomethylene group as compared with the oxygen atom in **5a–c**. Furthermore, reduction waves corresponding to the first oxidation waves



Scheme 3.



Scheme 4.

of **9a–c** appeared in a far negative region (**9a**: −0.15 V, **9b**: −0.28 V, **9c**: −0.58 V). These reduction waves are suggested to be the reduction waves of **13′a–c**, which are generated by the conformational change of **13a–c**, respectively, under CV measurement (Scheme 4). In the radical cations **13a–c** generated by the one-electron oxidation of **9a–c**, the heteroazulene-moiety has a larger electron-donating ability than the benzene-4-(dicyanomethyl) radical moiety. Thus, the two heteroazulene units come to have a more planar conformation and the benzene-4-(dicyanomethyl) radical moiety would be twisted against the cationic plane as depicted by **13′a–c**. By this conformational change giving **13′a–c**, the heteroazulene-moiety can stabilize **13a–c** more effectively, and thus, the energy level of the SOMO of **13′a–c** (HOMO of **9a–c**) is raised and the corresponding reduction waves would be shifted to the far negative region. In order to confirm this speculation, MO calculations of **9a**, **10a**, and **13a** were carried out using the AM1 method (MOPAC).[21] The most stable conformations of **9a**, **10a**, and **13a** obtained by MO calculations are depicted in Figure 4. The dihedral angles, θ_1, θ_2, and θ_3, express deviation of the plane of the phenyl group and heteroazulenes from the cationic plane (the plane is defined by the three arylic ipso carbons). The dihedral angle θ_1 of **9a** is 0.4° and the dihedral angles θ_2 and θ_3 of **9a** are much larger to be 99.7 and 80.3°, respectively. Thus, in compound **9a**, the benzene-4-(dicyanomethylide)-moiety has a more planar conformation and the heteroazulene-moiety is twisted against the cationic plane. In contrast, the dihedral angle θ_1 of **10a** becomes much larger to be 63.0° and the dihedral angles θ_2 and θ_3 of **10a** become smaller to be 28.9 and −19.0°, respectively. Thus, in compound **10a**, the heteroazulene-moiety has a more planar conformation and the 4-(dicyanomethyl)phenyl-moiety is twisted against the cationic plane. This fact supports the conformational change discussed in the UV–Vis spectra (vide supra). Furthermore, the geometry optimization starting from the structure of **13a** gave the dihedral angles θ_1, θ_2, and θ_3 to be 60.1, 46.0, and −24.9°, respectively. These values seem to show the structure of **13′a**, and thus, the MO calculations would confirm the conformations of **10a** and **13a**.

3. Conclusion

A convenient preparation of fairly stable 7,7-bis(heteroazulen-3-yl)-8,8-dicyano-1,4-quinodimethanes (**9a–c**) was accomplished. The properties of **9a–c** were clarified by inspection of the ^{13}C NMR and IR spectra as well as the UV–Vis spectra. The contribution of the polarized structure **9a–c–B** was suggested to be larger than that of quinonemethides **5a–c**. Owing to the stabilizing ability of heteroazulenes toward the radical and anion species, **9a–c** exhibited two reversible reduction waves in the CV measurements. Furthermore, **9a–c** exhibited two irreversible oxidation waves, which suggested a conformational change during the redox process. The conformational change is rationalized on the basis of MO calculations. Further studies concerning the synthesis and properties of heteroazulene-substituted quinodimethane analogues are underway.

4. Experimental

4.1. General

IR spectra were recorded on a HORIBA FT-710 spectrometer. Mass spectra and high-resolution mass spectra were run on JMS-AUTOMASS 150 and JMS-SX102A spectrometers. Unless otherwise specified, ^1H and ^{13}C NMR spectra were recorded on JNM-AL400, JNM-lambda500, and AVANCE600 spectrometers using $CDCl_3$ as a solvent, and the chemical shifts are given relative to internal $SiMe_4$ standard; *J*-values are given in Hz. Mps were recorded on a Yamato MP-21 apparatus and were uncorrected. The heteroazulenes, 2*H*-cyclohepta[*b*]furan-2-one (**6a**),[17] 1,2-dihydro-*N*-phenylcyclohepta[*b*]pyrrol-2-one (**6b**),[18] and 1,2-dihydro-*N*-methylcyclohepta[*b*]pyrrol-2-one (**6c**)[19] were prepared as described previously. 4-(Dicyanomethyl)-benzaldehyde (**7**) was prepared as described previously.[16]

4.2. General synthetic procedure for heteroazulene-substituted methane derivatives 8a–f

A solution of each heteroazulenes **6a–c** (2 mmol) and 4-(dicyanomethyl)benzaldehyde **7** (146 mg, 1 mmol) in a mixture of $CHCl_3$ (10 mL) and TFA (2 mL) was stirred at 80 °C for 6 h. After the reaction was completed, the mixture was poured into aqueous $NaHCO_3$ solution. The mixture was extracted with CH_2Cl_2, and the extract was dried over Na_2SO_4 and concentrated in vacuo. The resulting residue was purified by recrystallization to give the products **8a–c** (Table 1, Runs 1–3).

4.2.1. [4-[Bis(2-oxo-2*H*-cyclohepta[*b*]furan-3-yl)methyl]-phenyl]propanedinitrile (8a). Orange prisms; mp 181–184 °C dec (from CH_2Cl_2/Et_2O); ^1H NMR (400 MHz, $CDCl_3$) δ 5.07 (1H, s, CH), 5.72 (1H, s, CH), 6.83–6.90 (2H, m, H-6), 6.98–7.10 (6H, m, H-5, 7, 8), 7.37 (2H, d, *J*=8.3 Hz, Ph-3, 5), 7.47 (2H, d, *J*=8.3 Hz, Ph-2, 6), 7.51 (2H, d, *J*=11.4 Hz, H-4); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 27.8, 34.7, 108.0, 111.7, 114.7, 124.8, 127.6, 128.0, 129.3, 131.3, 132.6, 135.4, 139.8, 148.9, 157.6, 169.4; IR ($CHCl_3$) ν 2357, 1744, 1271 cm^{-1}; MS (rel. int.) *m/z* 444 (M^+, 100%); HRMS calcd for $C_{28}H_{16}N_2O_4$: 445.1189 (M+H). Found: 445.1168 (M^++H). Anal. calcd for $C_{28}H_{16}N_2O_4 \cdot 1/2H_2O$: C, 74.16; H, 3.78; N, 6.18. Found: C, 73.9; H, 3.8; N, 6.1.

4.2.2. [4-[Bis(1,2-dihydro-2-oxo-*N*-phenylcyclohepta[*b*]-pyrrol-3-yl)methyl]phenyl]propanedinitrile (8b). Orange powder; mp 92–98 °C (from AcOEt); ^1H NMR (400 MHz, $CDCl_3$) δ 5.07 (1H, s, CH), 6.28 (1H, s, CH), 6.81 (2H, d, *J*=9.5 Hz, H-8), 6.83 (2H, dd, *J*=11.3, 9.2 Hz, H-6), 6.92 (2H, dd, *J*=11.3, 9.5 Hz, H-7), 6.98 (2H, dd, *J*=11.2, 9.2 Hz, H-5), 7.28–7.55 (14H, m, NPh, Ph-2,3,5,6), 7.91 (2H, d, *J*=11.2 Hz, H-4); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 28.2, 35.9. 112.3, 112.9, 114.2, 124.3, 127.7, 129.1, 129.6, 129.9, 130.1, 130.4, 130.8, 131.3, 132.0, 134.7, 141.8, 142.8, 145.7, 169.1; IR ($CHCl_3$) ν 2300, 1675 cm^{-1}; MS (FAB) *m/z* 595 (M^++H); HRMS calcd for $C_{40}H_{26}N_4O_2$: 595.2134 (M+H). Found: 595.2124 (M^++H). Anal. calcd for $C_{40}H_{26}N_4O_2 \cdot CH_2Cl_2$: C, 72.46; H, 4.15; N, 8.24. Found: C, 74.6; H, 4.3; N, 8.8.

4.2.3. [4-[Bis(1,2-dihydro-*N*-methyl-2-oxocyclohepta[*b*]-pyrrol-3-yl)methyl]phenyl]propanedinitrile (8c). Orange powder; mp 196–199 °C dec (from CH_2Cl_2/Et_2O); ^1H NMR (400 MHz, $CDCl_3$) δ 3.54 (6H, s, Me) 5.05 (1H, s, CH), 6.18 (1H, s, CH), 6.85 (2H, dd, *J*=10.4, 9.2 Hz, H-6), 6.88 (2H, d, *J*=9.2 Hz, H-8), 6.99 (2H, dd, *J*=10.4, 9.2 Hz, H-7), 7.04 (2H, dd, *J*=11.2, 9.2 Hz, H-5), 7.34 (2H, d, *J*=8.0 Hz, Ph-3, 5), 7.39 (2H, d, *J*=8.0 Hz, Ph-2, 6), 7.88 (2H, d, *J*=11.2 Hz, H-4); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 26.6, 35.3, 44.2, 111.8, 113.6, 127.9, 128.4, 128.6, 129.0, 129.2, 129.6, 130.4, 131.0, 141.1, 141.4, 144.6, 168.5; IR ($CHCl_3$) ν 2362, 1669 cm^{-1}; MS (FAB) *m/z* 471 (M^++H); HRMS calcd for $C_{30}H_{22}N_4O_2$: 471.1821 (M+H). Found: 471.1836 (M^++H). Anal. calcd for $C_{30}H_{22}N_4O_2 \cdot 1/2H_2O$: C, 75.14; H, 4.83; N, 11.68. Found: C, 75.3; H, 4.9; N, 11.7.

4.3. Preparation of 9a–c

To a stirred solution of **8a–c** (0.25 mmol) in CH_2Cl_2 (10 mL) was added DDQ (70 mg, 0.30 mmol), and the mixture was stirred at rt for 1 h. To the resulting mixture was added Et_3N (51 mg, 0.5 mmol), and the mixture was stirred at rt for 10 min. The mixture was filtered through Celite and the filtrate was concentrated in vacuo. The resulting residue was purified by column chromatography on SiO_2 using AcOEt as the eluent to give **9a–c** (Table 1, Runs 1–3).

4.3.1. [4-[Bis(2-oxo-2*H*-cyclohepta[*b*]furan-3-yl)methyl]-2,5-cyclohexadiene-1,4-diylidene]propanedinitrile (9a). Dark brown needles; mp >300 °C (from CH_2Cl_2/Et_2O); ^1H NMR (600 MHz, DMSO-d_6, 60 °C) δ 7.01 (2H, d, *J*=9.5 Hz, H-3, 5), 7.40 (2H, d, *J*=9.5 Hz, H-2, 6), 7.38–7.44 (4H, m, H-6′, 8′), 7.56 (2H, dd, *J*=10.2, 10.0 Hz, H-7′), 7.62 (2H, dd, *J*=10.0, 9.7 Hz, H-5′), 7.67 (2H, br d, *J*=9.7 Hz, H-4′); ^{13}C NMR (150.9 MHz, DMSO-d_6, 60 °C) δ 64.4, 105.8, 115.9, 119.6, 122.2, 129.2, 130.2, 135.3, 136.1, 137.3, 139.8, 143.9, 151.6, 155.2, 158.9, 165.6; IR ($CHCl_3$) ν 2195, 1752, 1268 cm^{-1}; MS (rel. int.) *m/z* 443 (M^+H, 100%); HRMS calcd for $C_{28}H_{14}N_2O_4$: 443.1032 (M+H). Found: 443.1064 (M^++H). Anal. calcd for $C_{28}H_{14}N_2O_4 \cdot 1/2H_2O$: C, 74.49; H, 3.35; N, 6.21. Found: C, 74.1; H, 3.7; N, 6.1.

4.3.2. [4-[Bis(1,2-dihydro-2-oxo-*N*-phenylcyclohepta[*b*]-pyrrol-3-yl)methyl]-2,5-cyclohexadiene-1,4-diylidene]-propanedinitrile (9b). Dark brown needles; mp >300 °C (from CH_2Cl_2/Et_2O); ^1H NMR (600 MHz, DMSO-d_6, 60 °C) δ 6.99 (2H, d, J=9.5 Hz, H-8′), 7.20 (2H, d, J=9.5 Hz, H-3, 5), 7.34 (2H, dd, J=10.0, 9.5 Hz, H-6′), 7.42 (4H, d, J=7.7 Hz, NPh-*o*), 7.49 (2H, d, J=9.5 Hz, H-2, 6), 7.50 (2H, dd, J=10.0, 9.5 Hz, H-7′), 7.55 (2H, t, J=7.9 Hz, NPh-*p*), 7.56 (2H, dd, J=10.8, 9.5 Hz, H-5′), 7.60 (2H, d, J=10.8 Hz, H-4′), 7.62 (4H, dd, J=7.9, 7.7 Hz, NPh-*m*); ^{13}C NMR (150.9 MHz, DMSO-d_6, 60 °C) δ 58.4, 111.6, 117.1, 117.7, 120.9, 128.4, 129.0, 129.4, 129.5, 129.6, 133.2, 133.8, 136.5, 136.6, 136.9, 146.4, 148.1, 149.6, 154.9, 165.2; IR ($CHCl_3$) ν 2196, 1684 cm^{-1}; MS (FAB) m/z 593 (M^++H); HRMS calcd for $C_{40}H_{24}N_4O_2$: 593.1977 (M+H). Found: 593.1953 (M^++H). Anal. calcd for $C_{40}H_{24}N_4O_2{\cdot}CH_2Cl_2$: C, 72.68; H, 3.87; N, 8.27. Found: C, 72.2; H, 3.6; N, 8.1.

4.3.3. [4-[Bis(1,2-dihydro-*N*-methyl-2-oxocyclohepta[*b*]-pyrrol-3-yl)methyl]-2,5-cyclohexadiene-1,4-diylidene]-propanedinitrile (9c). Dark brown needles; mp >300 °C (from CH_2Cl_2/Et_2O); ^1H NMR (600 MHz, DMSO-d_6, 60 °C) δ 3.52 (6H, s, Me), 6.92 (2H, d, J=9.5 Hz, H-3, 5), 7.29 (2H, d, J=9.5 Hz, H-8′), 7.34 (2H, dd, J=9.5, 8.2 Hz, H-6′), 7.43 (2H, d, J=9.5 Hz, H-2, 6), 7.45 (2H, dd, J=9.5, 8.2 Hz, H-7′), 7.65 (2H, d, J=10.0 Hz, H-4′), 7.69 (2H, dd, J=10.0, 9.5 Hz, H-5′); ^{13}C NMR (150.9 MHz, DMSO-d_6, 60 °C) δ 26.8, 56.7, 112.2, 114.7, 117.4, 117.5, 120.7, 129.0, 132.6, 136.1, 136.2, 136.6, 143.8, 146.3, 148.0, 154.7, 165.3; IR ($CHCl_3$) ν 2192, 1669 cm^{-1}; MS (FAB) m/z 469 (M^++H); HRMS calcd for $C_{30}H_{20}N_4O_2$: 469.1664 (M+H). Found: 469.1667 (M^++H). Anal. calcd for $C_{30}H_{20}N_4O_2{\cdot}2H_2O$: C, 71.42; H, 4.79; N, 11.10. Found: C, 71.3; H, 4.6; N, 11.0.

4.4. Cyclic voltammetry of 9a–c

The reduction potential of **9a–c** was determined by means of CV-27 voltammetry controller (BAS Co). A three-electrode cell was used, consisting of Pt working and counter electrodes and a reference $Ag/AgNO_3$ electrode. Nitrogen was bubbled through an acetonitrile solution (4 mL) of **9a–c** (0.5 mmol dm^{-3}) and Bu_4NClO_4 (0.1 mol dm^{-3}) to deaerate it. The measurements were made at a scan rate of 0.1 V s^{-1} and the voltammograms were recorded on a WX-1000-UM-019 (Graphtec Co) X-Y recorder. Immediately after the measurements, ferrocene (0.1 mmol) ($E_{1/2}$=+0.083) was added as the internal standard, and the observed peak potential was corrected with reference to this standard. The compounds **9a–c** exhibited two reversible reduction waves and two irreversible oxidation waves, and they are summarized in Table 3.

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In situ 1,3-dipolar azide cycloaddition reaction: synthesis of functionalized D-glucose based chiral piperidine and oxazepine analogues

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Abstract—Functionalized furanose-fused piperidines **4**-**6** and oxazepines **15**-**17**, useful precursors for structurally unique bioactive nucleosides as well as for potential glycosidase inhibitors, have been synthesized by the application of 1,3-dipolar azide cycloaddition (DAC) reaction on D-glucose based substrates. The strategy works well even with the nucleoside analogue **8**, affording the bicyclic nucleoside analogues **11** and **12**.

1. Introduction

The 1,3-dipolar azide cycloaddition (DAC) reaction constitutes a simple method, which has been widely used in the synthesis of alkaloids[1] and many other heterocycles of diverse structures.[2] In recent years, effort has been made to explore cycloaddition on carbohydrate derived alkenes/alkynes. This has led to elegant methodologies for the synthesis of chiral triazoles,[3] azole-piperidinoses,[4] tetrazoles,[5] glucotriazole carboxylate,[6] and various iminosugars[7] en route to nucleoside analogues[8] and inhibitors of glycosidases,[9] glycogen phosphorylases[6] and glycosyl transferases.[10] For our project directed towards the synthesis of new carbohydrate based piperidine and oxazepine analogues, we decided to use this reaction on suitably crafted precursors. The allyl group is easy to introduce into the carbohydrate core and is particularly amenable for such cycloadditions. The precursors **1**-**3**, already used in our laboratory for other synthetic schemes, appeared as convenient starting materials.[11] The expected products could allow introduction of various nucleobases directly onto the anomeric center of a furanose ring or via easy opening of the ring. In this paper, we report the work undertaken to investigate the scope of this reaction for developing functionalized chiral piperidine and oxazepine analogues.

2. Results and discussions

The carbohydrate-derived precursors **1**-**3** on tosylation and subsequent treatment with sodium azide furnished, after column chromatography, TLC pure (in different solvent systems) products. However, these exhibited two sets of ^{1}H and ^{13}C NMR peaks for many of the protons and carbons. The formation of a mixture of enamine and imine **A** and **B** (presumably through the generation of an aziridine ring followed by its opening) was suggested by the fact that the signals at δ 1.78 (s), 2.01 (s), 1.98 (d), and 2.33 (d) in the ^{1}H NMR disappeared on D_2O exchange. In support, the ^{13}C NMR showed signals at δ 143.8 and 164.3, close to the expected shieldings for the enamine and imine carbons, respectively. In addition, the presence of three signals for methylene carbons at δ 35.5, 40.0 and 48.0 indicated formation of the mixture. Acetylation of the mixture, without further purification, furnished single *N*-acetylated products **4**-**6** in fairly good yields (Scheme 1). In the ^{13}C NMR spectrum of **5** for example, the presence of carbon signals at δ 169.4, 142.6, 108.5 and 23.7 suggested the presence of amide carbonyl, olefinic quaternary as well as methine carbons. Additionally, the methyl proton signal at δ 2.17 (d, J=0.9 Hz, allylic coupling) testified to the location of a vinylic methyl group.

When the reaction was performed on a substrate with a pre-installed nucleoside base in the furanose ring, it took an unexpectedly different course. For this study, the tosylate **7** of **1** (Scheme 2) was first treated with acid to remove the isopropylidene protecting group and then subjected to acetylation to furnish **8** as a mixture of anomers. Treatment of this mixture with bis-*O*-trimethylsilyl)uracil

Keywords: DAC reaction; Synthesis; Chiral piperidines and oxazepines; D-Glucose.
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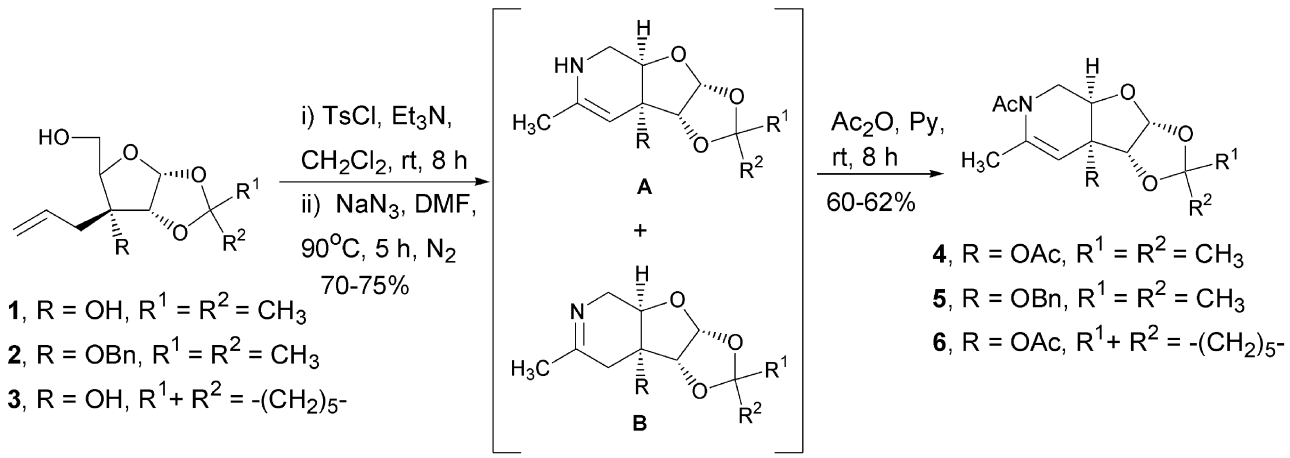
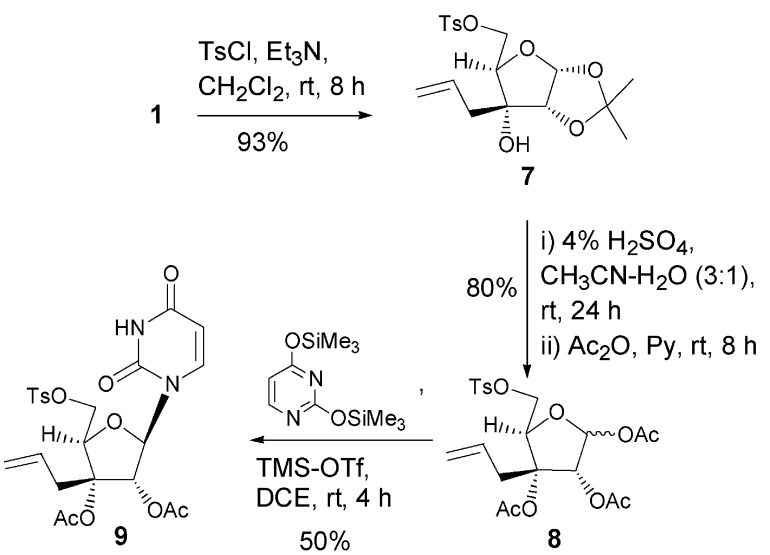


Scheme 1. 1,3-DAC reaction on 3-*C*-allyl glucose precursors.

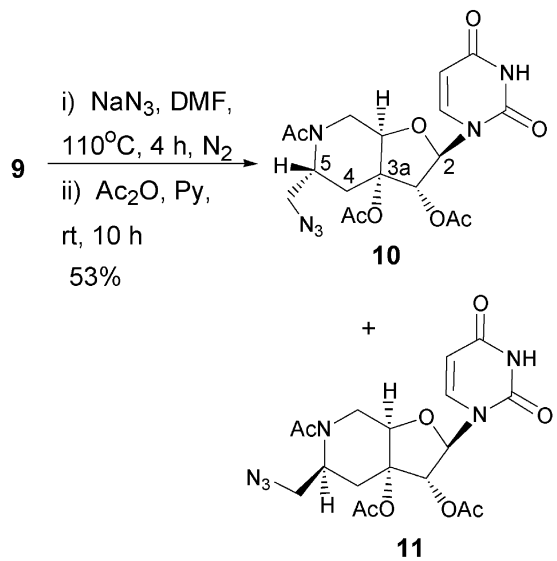


Scheme 2. Preparation of nucleoside derivative **9**.

and TMS-OTf in dichloroethane, under the conditions reported by Vorbrüggen,[12] furnished the nucleoside derivative **9**. The neighbouring acetoxy group, as is known from earlier studies,[13] guides the orientation of the nucleoside base in the product **9**.

On treatment with sodium azide, **9** underwent 1,3-DAC reaction to afford a difficult to purify product, which was therefore directly acetylated. Column chromatographic purification furnished the nucleoside analogues **10** and **11** in 3:1 ratio (Scheme 3).

The peak at $\nu_{max}\sim2106\ cm^{-1}$ in the IR spectra of the products clearly indicated the presence of azide functionality. The FABMS of both the nucleosides showed pseudo molecular ion peaks at *m*/*z* 451 ($M+H^+$) and 473 ($M+Na^+$). Among the three methylene carbon signals in the ^{13}C NMR spectrum, the one at $\delta\sim45.0$ may be assigned to the carbon carrying the azide group. In the ^1H NMR spectrum, the coupling constants $J_{2,3}$ are found to be somewhat different for **10** (6.1 Hz) and **11** (8.5 Hz). This may be due to difference in dihedral angle of the $H-C_2-C_3-H$ unit (40° in **10** and 18° in **11** in the energy-minimized structures



Scheme 3. 1,3-DAC reaction on nucleoside derivative **9**.

obtained using Chem. Office 6.0. For this, a presentation of the structure was created in Chem Draw and transferred to Chem 3D, taking care to ensure that the stereochemistry at different centers of the conformer were correct. After initial energy minimization using MM2 programme, molecular dynamics was run. The generated conformer was tested by MM2 to reach the energy minimized conformer. The piperidine ring in **11** exists in chair conformation ($J_{4a,5a}$=13.0 Hz and $J_{4a,e}$=14.7 Hz), whereas the same ring in **10** is in the twist-boat form ($J_{4a,5a}$=12.3 Hz and $J_{4a,e}$=14.0 Hz), since the chair conformation is destabilized due to 1,3-diaxial interaction between acetoxy group at C-3a and azidomethyl group at C-5.

The formation of the above products may be rationalized by assuming that the 1,3-DAC reaction proceeds through the generation of a triazoline intermediate, which after nitrogen elimination leads to an aziridine intermediate. This quickly isomerizes in case of **1**-**3** to afford imine/enamine mixture (Fig. 1), or is opened by azide attack (in case of **9**).

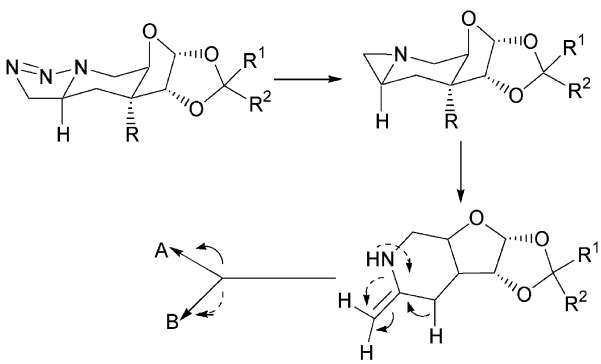


Figure 1. Proposed mechanism for the formation of imine/enamine mixture.

To understand the nature of the aziridine intermediate, we carried out molecular modeling studies. This revealed that the minimium energy conformations of the two *trans*-aziridine isomers (161.3 or 173.9 kcal/mol) are far greater in steric energy than the corresponding *cis*-aziridine isomers (146.6 or 147.1 kcal/mol), which are close to each other in steric energy. The formation of the isomeric mixture of nucleoside derivatives is thus possible through the intermediacy of non-isolable *cis*-aziridines (Figs. 2 and 3).

In another variation of the reaction, the cycloaddition reaction was attempted on substrates carrying *O*-allyl rather

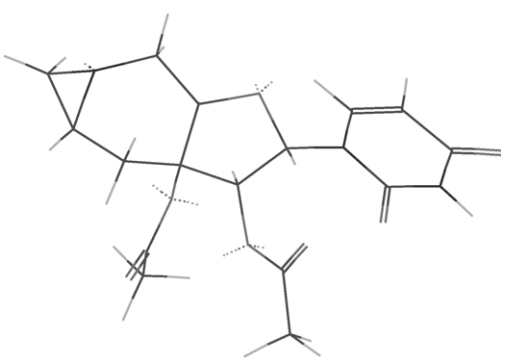


Figure 2. *cis*-Aziridine with N lone pair and ring juncture H α-oriented.

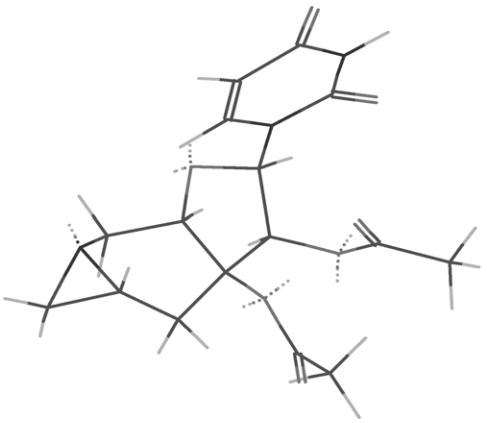


Figure 3. *cis*-Aziridine with N lone pair and ring juncture H β-oriented.

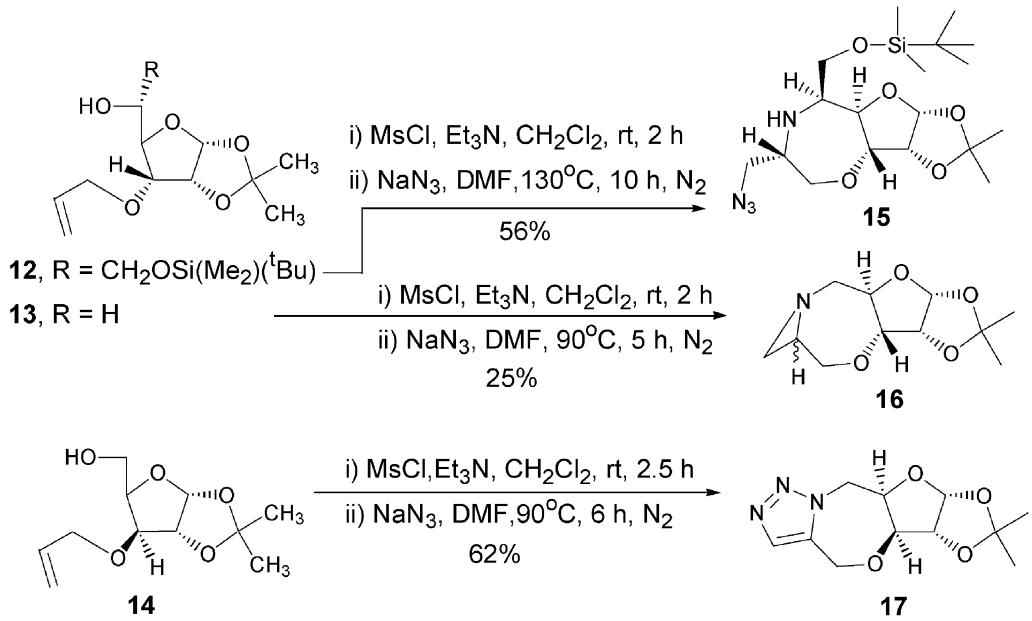
than *C*-allyl group at *C*-3 of the carbohydrate derived precursor. The substrates **12**-**14** were chosen, prepared and characterized according to our established protocols.[14] Both *cis* and *trans* substituted substrates **13** and **14** could be tested besides one (**12**) carrying a bulky group (TBDMS) in one of the substituents.

When **12** was subjected to mesylation followed by reaction with sodium azide, it afforded the oxazepine analogue **15**. However, the aziridino-oxazepine derivative **16** was obtained in low yield by DAC reaction upon **13**, while **14** afforded **17** with triazolo-oxazepine moiety (Scheme 4).

The absence of allyl functionality in **15**-**17** was shown by the disappearance of signals for the vinyl proton(s) in the region between δ 4.84–6.34. Retention of the 1,2-*O*-isopropylidene groups in all the products and the tertiary butyl dimethyl silyl functionality in **15** was evident from their characteristic signals in the ^{1}H NMR spectra. The IR spectrum of **15**, but not those of **16** and **17**, showed a strong band at 2105 cm^{-1} for the azide group. The presence of the CH_2N_3 moiety in **15** was confirmed by the appearance of one double doublet at δ 3.16 (J=7.5, 12.0 Hz) and a doublet at δ 3.28 (J=12.0 Hz) in its ^{1}H NMR spectrum. In the ^{1}H NMR spectrum of **16**, the appearance of two upfield doublets at δ 1.49 and 2.18 clearly indicated the formation of an aziridine moiety. However, the stereochemistry at the aziridine ring juncture could not be ascertained. Mass spectrum as well as ^{13}C NMR spectrum confirmed the structures indicated.

The results of the cycloaddition reactions with *O*-allyl substituted substrates suggest that the course of the reaction remains similar to that observed with the *C*-allyl substituted substrates, that is, initial triazoline formation followed by nitrogen elimination to the aziridine, which could be isolated, albeit in low yield, in case of **13**. In case of **12** the aziridine moiety did not survive under the reaction condition and decomposed in nucleophilic attack by azide ion. The formation of a triazole product **17** from **14** may be explained by assuming that the initial triazoline possibly had a *trans* ring fusion and was therefore prone to oxidation, brought about in this case perhaps by atmospheric oxygen.

In conclusion, we have applied the 1,3-DAC reaction on D-glucose derived unactivated olefin precursors to construct



Scheme 4. 1,3-DAC reaction on glucose derived substrates **12**–**14**.

chiral piperidine and oxazepine rings, fused to ribose moiety, which may be elaborated to iminosugars, oxo-iminosugars and nucleoside analogues. The scope and limitation of the method to synthesize other such systems with different heterocycles of varied ring sizes is under study.

3. Experimental

Melting points were taken in open capillaries and are uncorrected. IR spectra were measured on a JASCO 700 spectrophotometer. ^{1}H and ^{13}C NMR spectra were measured either on a JEOL FX-100 or a Bruker AM 300 L spectrometer using TMS as internal standard. Mass spectra were obtained using a JEOL AX-500 spectrometer operating at 70 eV. Optical rotations were measured in a JASCO DIP 360 polarimeter. HPLC was performed on μ Bondapak™ C_{18} column (7.38×300 mm). Flash chromatography was carried out on LiChroprep® RP-18 (Merck).

3.1. (3a*R*,3b*R*,7a*R*,8a*R*)-Acetic acid 6-acetyl-2,2,5-trimethyl-3a,7,7a,8a-tetrahydro-6*H*-1,3,8-trioxa-6-aza-cyclopenta[*a*]inden-3b-yl ester (4)

3.1.1. Typical procedure for 4. To a stirred solution of **1** (500 mg, 2.17 mmol) in CH_2Cl_2 (30 ml) containing Et_3N (1 ml) was added TsCl (415 mg, 2.18 mmol) and the stirring was continued for 8 h at rt. The mixture was washed with brine (3×10 ml), dried (Na_2SO_4), and concentrated. The crude product was purified by column chromatography using $CHCl_3$ as eluent to furnish **7** (768 mg, 93%). **7** (500 mg, 1.30 mmol) in dry DMF (5 ml) was reacted with NaN_3 (393 mg, 4.7 equiv.) at 90 °C for 5 h under N_2. The solvent was evaporated and the crude mass was extracted with $CHCl_3$ (30 ml). The extract was washed with brine, dried (Na_2SO_4), and concentrated. The residue was subjected to reverse phase flash column chromatography using CH_3CN–H_2O (1:4) to furnish a mixture of enamine and imine **A** and **B** (350 mg). An aliquot of the mixture (50 mg) was then acetylated with Ac_2O/Py. The crude acetylated product was purified by chromatography on silica gel column using Pet. ether–EtOAc (13:7) to yield **4** (35 mg, 61%) as a foamy solid; [Found: C, 57.83; H, 6.73; N, 4.33. $C_{15}H_{21}NO_6$ requires C, 57.87; H, 6.80; N, 4.50%]; (α_D^{20}=−356 (*c* 0.3, $CHCl_3$); IR (KBr): ν_{max} 1733, 1670, 1401, 1380, 1237, 1210, 1067, 1030 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.33 (s, 3H), 1.53 (s, 3H), 2.07 (s, 3H), 2.17 (d, 3H, *J*=0.9 Hz), 2.19 (s, 3H), 3.23 (d, 1H, *J*=13.5 Hz), 4.12 (dd, 1H, *J*=2.7, 13.5 Hz), 4.32 (brs, 1H), 4.86 (d, 1H, *J*=3.6 Hz), 5.47 (s, 1H), 5.70 (d, 1H, *J*=3.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.2(q), 22.3(q), 23.7(q), 26.9(q), 27.1(q), 45.6(t), 76.6(d), 78.6(s), 81.6(d), 105.2(d), 108.5(d), 113.1(s), 142.6(s), 169.4(s), 171.3(s); FABMS: *m*/*z* at 312 (MH^+).

3.1.2. (3a*R*,3b*R*,7a*R*,8a*R*)-1-(3b-Benzyloxy-2,2,5-trimethyl-3a,7,7a,8a-tetrahydro-3b*H*-1,3,8-trioxa-6-aza-cyclopenta[*a*]inden-6-yl) ethanone (5). *Compound* **5**. Yield 60%; sticky mass; [Found: C, 66.62; H, 7.12; N, 3.69. $C_{20}H_{25}NO_5$ requires C, 66.83; H, 7.01; N, 3.90%]; (α_D^{20}=−132 (*c* 0.84, $CHCl_3$); IR (neat): ν_{max} 1673, 1391, 1217, 1135, 1099, 1069, 1026, 1030 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.37 (s, 3H), 1.61 (s, 3H), 2.18 (s, 3H), 2.22 (s, 3H), 3.22 (d, 1H, *J*=13.5 Hz), 4.01 (dd, 1H, *J*=3.0, 13.5 Hz), 4.36 (brs, 1H), 4.45 (d, 1H, *J*=3.3 Hz), 4.65 (d, 1H, *J*=11.0 Hz), 4.69 (d, 1H, *J*=11.0 Hz), 5.16 (s, 1H), 5.68 (d, 1H, *J*=3.3 Hz), 7.32 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.9 (q), 24.1 (q), 27.9 (q), 30.1 (q), 46.6 (t), 66.9 (t), 78.0 (d), 78.5 (s), 82.5 (d), 105.7 (d), 109.9 (d), 114.1 (s), 128.1 (d), 128.2 (d, 2C), 128.7 (d, 2C), 138.9 (s), 142.7 (s), 172.0 (s); FABMS: *m*/*z* at 360 (MH^+).

3.1.3. (3a*R*,3b*R*,7a*R*,8a*R*)-Acetic acid 6-acetyl-2,2-cyclohexylidenyl-5-methyl-3a,7,7a,8a-tetrahydro-6*H*-1,3,8-trioxa-6-aza-cyclopenta[*a*]inden-3b-yl ester (6). *Compound* **6**. Yield 62%; thick liquid; [Found: C, 61.52; H, 7.00; N, 3.83. $C_{18}H_{25}NO_6$ requires C, 61.52; H, 7.17; N,

3.99%]; ($\alpha(^{20}_{D}$=−247 (*c* 0.5, $CHCl_3$); IR (KBr): ν_{max} 1743, 1671, 1399, 1371, 1242, 1128, 1046 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.37 (m, 2H), 1.64 (m, 6H), 1.74 (m, 2H), 2.07 (s, 3H), 2.17 (s, 3H), 2.19 (s, 3H), 3.22 (d, 1H, *J*=13.7 Hz), 4.11 (dd, 1H, *J*=3.0, 13.7 Hz), 4.31 (s, 1H), 4.83 (d, 1H, *J*=3.3 Hz), 5.48 (s, 1H), 5.71 (d, 1H, *J*=3.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.2(q), 22.3(q), 23.6 (t), 23.7(q), 24.0(t), 24.9(t), 36.4(t), 36.9(t), 45.7(t), 76.7(d), 78.8(s), 81.1(d), 104.9(d), 108.8(d), 113.8(s), 142.6(s), 169.4(s), 171.3(s); FABMS: *m*/*z* at 352(MH^+).

3.1.4. Toluene-4-sulfonic acid 6-allyl-6-hydroxy-2,2-dimethyl-tetrahydrofuro[2,3-*d*][1,3]dioxol-5-ylmethyl ester (7). *Compound* **7**. Yield 93%; sticky mass; [Found: C, 56.18; H, 6.00. $C_{18}H_{24}O_7S$ requires C, 56.23; H, 6.29%]; ($\alpha(^{20}_{D}$=+40 (*c* 0.3, $CHCl_3$); IR (neat): ν_{max} 3397 (br), 1599, 1361, 1175, 816, 754 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.32 (s, 3H), 1.52 (s, 3H), 2.40 (s, 3H), 2.45 (dd, 1H, *J*=7.0, 15.5 Hz), 2.52 (dd, 1H, *J*=8.0, 15.5 Hz), 4.17–4.24 (m, 3H), 4.36 (d, 1H, *J*=3.6 Hz), 5.11s, 1H), 5.20 (m, 2H), 5.68 (d, 1H, *J*=3.6 Hz), 5.86 (m, 1H), 7.28 (d, 2H, *J*=8.1 Hz), 7.76 (d, 2H, *J*=8.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.0 (q), 27.0(q), 27.2(q), 35.7 (t), 67.6(t), 79.5 (d), 82.5(d), 84.1(s), 104.5(d), 113.4(s), 119.4(t), 127.9(d, 2C), 130.2(d, 2C), 132.4(d), 133.6(s), 145.0(s); FABMS: *m*/*z* at 385 (MH^+).

3.1.5. (2*R*,3*R*,4*R*,5*R*)-Acetic acid 4-acetoxy-3-allyl-5-(2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-2-(toluene-4-sulfonyloxymethyl)-tetrahydrofuran-3-yl ester (9). Uracil (600 mg, 5.36 mmol) was dissolved in hexamethyl disilazane (10 ml). TMSCl (2 drops) was added to it and the mixture was heated at reflux under N_2 for 12 h. The solvent was evaporated in vacuo, the residue dissolved in DCE (5 ml) and added to a stirred solution of the triacetate mixture **8** (715 mg, 1.52 mmol) in DCE (5 ml). After adding TMS–OTf (0.8 ml) the solution was stirred for 4 h at rt when tlc showed complete disappearance of the starting material. The mixture was neutralized with solid $NaHCO_3$, treated with water (2–3 drops), and the solvent was evaporated in rotary evaporator. The residue was extracted with $CHCl_3$–MeOH mixture (49:1, 20 ml), washed with brine, dried, and concentrated. The crude product was purified by silica gel column chromatography eluting with methanolic $CHCl_3$ (2%) to afford **9** (400 mg, 50%) as a foam; [Found: C, 52.58; H, 5.15; N, 5.21. $C_{23}H_{26}N_2O_{10}S$ requires C, 52.87; H, 5.02; N, 5.36%]; ($\alpha(^{20}_{D}$=−15.9 (*c* 0.49, $CHCl_3$); IR (KBr): ν_{max} 1746, 1696, 1371, 1222, 1179 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.06 (s, 3H), 2.13 (s, 3H), 2.47 (s, 3H, merged with one proton signal), 3.14 (dd, 1H, *J*=7.2, 14.5 Hz), 4.27 (dd, 1H, *J*=2.1, 11.4 Hz), 4.36 (dd, 1H, *J*=2.8, 11.4 Hz), 4.76 (brs, 1H), 5.04 (m, 2H), 5.26 (d, 1H, *J*=8.1 Hz), 5.55 (m, 1H), 5.69 (d, 1H, *J*=8.1 Hz), 6.16 (d, 1H, *J*=8.1 Hz), 7.40 (d, 2H, *J*=8.1 Hz), 7.52 (d, 1H, *J*=8.1 Hz), 7.82 (d, 2H, *J*=8.1 Hz), 7.98 (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.6, 21.7 (2C), 35.6, 67.1, 76.0, 81.0, 84.0, 85.1, 103.5, 119.5, 127.9 (2C), 129.9, 130.3 (2C), 136.0, 139.1, 146.0, 150.6, 162.3, 169.7, 170.2; FABMS: *m*/*z* at 523 (MH^+).

3.1.6. (2*R*,3*R*,3a*R*,5*R*,7a*R*)-Acetic acid 3a-acetoxy-6-acetyl-5-azidomethyl-2-(2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-octahydro-furo[2,3-*c*]pyridin-3-yl ester (10) (2*R*,3*R*,3a*R*,5*S*,7a*R*)-acetic acid 3a-acetoxy-6-acetyl-5-azidomethyl-2-(2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-octahydro-furo[2,3-*c*]pyridin-3-yl ester (11). NaN_3 (50 mg) was added to the uridine derivative **9** (300 mg, 0.57 mmol) in DMF (8 ml) and the mixture was heated at 110 °C for 4 h under N_2. Usual work up followed by purification through reverse phase column chromatography (CH_3CN–H_2O 1:4) afforded a crude residue (175 mg). A part of the residue (60 mg) was acetylated with Ac_2O/Py and the mixture was purified by HPLC (solvent: CH_3CN–H_2O 3:7) to furnish **10** (35 mg, 40%) and **11** (11 mg, 13%).

Compound **10**. Foamy solid; [Found: C, 47.78; H, 4.88; N, 18.38. $C_{18}H_{22}N_6O_8$ requires C, 48.00; H, 4.92; N, 18.66%]; ($\alpha(^{20}_{D}$=+8 (*c* 0.5, $CHCl_3$); IR (KBr): ν_{max} 3453 (br), 2106, 1751, 1691, 1428, 1375, 1230, 1074 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.11 (s, 3H), 2.13 (s, 3H), 2.15 (s, 3H), 2.37 (dd, H, *J*=6.3, 14.0 Hz), 2.57 (t-like, 1H, *J*=12.3, 14.0 Hz), 3.31 (dd, 1H, *J*=2.5, 12.5 Hz), 3.85 (m, 3H), 4.56 (s, 1H), 4.71 (m, 1H), 5.03 (d, 1H, *J*=8.5 Hz), 5.83 (d, 1H, *J*=8.2 Hz), 6.26 (d, 1H, *J*=8.5 Hz), 6.97 (d, 1H, *J*=8.2 Hz), 8.49 (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.4 (q), 21.7(q), 21.9 (q), 28.0 (t), 45.7 (t), 47.5 (d), 53.1(t), 71.9 (d), 80.0 (d), 80.9 (s), 82.6 (d), 104.8 (d), 137.8 (d), 150.4 (s), 161.8 (s) 169.8 (s), 169.9 (s), 171.7 (s); FABMS: *m*/*z* at 451 (MH^+), 473 (MNa^+).

Compound **11**. Foamy solid; [Found: C, 48.12; H, 4.90; N, 18.60. $C_{18}H_{22}N_6O_8$ requires C, 48.00; H, 4.92; N, 18.66%]; ($\alpha(^{20}_{D}$=+15 (*c* 0.54, $CHCl_3$); IR (KBr): ν_{max} 3474 (br), 2106, 1743, 1697, 1634, 1427, 1377, 1236, 1069 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.09 (s, 6H), 2.15 (s, 3H), 2.36 (t-like, 1H, *J*=13.0, 14.7 Hz), 2.70 (dd, 1H, *J*=4.8, 14.8 Hz), 3.34 (dd, 1H, *J*=2, 12.3 Hz), 3.45 (dd, 1H, *J*=10.8, 14.0 Hz), 3.91 (m, 2H), 4.27 (m, 1H), 4.43 (dd, 1H, *J*=6.4, 10.2 Hz), 5.53 (d, 1H, *J*=6.1 Hz), 5.78 (d, 1H, *J*=8.1 Hz), 5.86 (d, 1H, *J*=6.1 Hz), 7.20 (d, 1H, *J*=8.1 Hz), 9.23 (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.7 (q), 21.6 (q), 22.5 (q), 33.3 (t), 45.1(t), 48.2 (d), 52.9 (t), 76.3 (d), 78.8 (d), 81.9 (s), 92.4 (d), 103.7 (d), 142.1 (d), 150.4 (s), 163.0 (s), 169.8 (s), 170.5 (s), 170.9 (s); FABMS: *m*/*z* at 451 (MH^+), 473 (MNa^+).

3.1.7. (3a*R*,3b*R*,6*R*,8*R*,8a*S*,9a*R*)-6-Azidomethyl-8-(*tert*-butyldimethyl-silanyloxymethyl-2,2-dimethyl-octahydro-1,3,4,9-tetraoxa-7-aza-cyclopent[*a*]azulene (15). To a stirred solution of **12** (418 mg, 1.12 mmol) in CH_2Cl_2 (30 ml) containing Et_3N (0.5 ml) was added MsCl (1 equiv.) and the mixture was stirred for 2 h under N_2. The solution was thoroughly washed with brine (3×10 ml), dried (Na_2SO_4), and concentrated to furnish a mesyl derivative. Without further purification this was dissolved in DMF (10 ml) and treated with NaN_3 (300 mg). The reaction mixture was heated at 130 °C under N_2 for 10 h. Usual work up followed by column chromatography using $CHCl_3$–MeOH (99:1) afforded **15** (250 mg, 56%) as a thick liquid; [Found: C, 52.00; H, 8.20; N, 13.21. $C_{18}H_{34}N_4O_5Si$ requires C, 52.15; H, 8.27; N, 13.51%]; ($\alpha(^{20}_{D}$=−9.4 (*c* 0.54, $CHCl_3$); IR (neat): ν_{max} 2100, 1470, 1373, 1255, 1098, 1037, 838 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.063 (s, 3H), 0.076 (s, 3H), 0.91 (s, 9H), 1.35 (s, 3H), 1.60 (s, 3H), 2.99 (m, 1H), 3.16 (dd, 1H, *J*=7.5, 12.0 Hz), 3.27 (d, 1H,

J=12.0 Hz), 3.31(dd, 1H, *J*=4.5, 11.5 Hz), 3.42 (m, 1H), 3.75 (d, 2H, *J*=4.8 Hz), 4.00 (dd, 1H, *J*=1.5, 11.7 Hz), 4.21 (dd, 1H, *J*=4.5, 9.3 Hz), 4.41 (t-like, 1H, *J*=8.1 Hz), 4.58 (t-like, 1H, *J*=3.9 Hz), 5.72 (d, 1H, *J*=3.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ −5.50 (q), −5.54 (q), 18.1(s), 25.8 (q), 26.1 (q, 3C), 26.7 (q), 53.2 (t), 56.2 (d), 57.9 (d), 62.0 (t), 75.3 (t), 78.4 (d), 79.6 (d), 79.7(d), 103.0 (d), 113.0 (d); FABMS: *m/z* at 415 (MH^+).

3.1.8. (3a*R*,3b*R*,7a*R*,8a*R*)-2,2-Dimethyl-3a,5,6,7,7a,8a-hexahydro-3b*H*,5a*H*-1,3,4,8-tetraoxa-6a-aza-cyclopropan[*f*]cyclopent[*a*]azulene (16). MsCl (0.35 ml) and Et_3N (0.5 ml) were added to a solution of **13** (750 mg, 3.26 mmol) in CH_2Cl_2 (30 ml) and the mixture was stirred at rt for 2 h. The solvent was evaporated and the crude mesyl derivative was dissolved in DMF (10 ml). NaN_3 (800 mg) was added to it and the mixture was heated at 90 °C for 5 h. Usual work up and purification afforded **16** (185 mg, 25%) as a gum; [Found: C, 57.86; H, 7.34; N, 5.88. $C_{11}H_{17}NO_4$ requires C, 58.14; H, 7.54; N, 6.17%]; ($\alpha(^{20}_{D}$=−8.8 (*c* 1.17, $CHCl_3$). IR (neat): ν_{max} 1455, 1377, 1216, 1164, 1023, 873 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.35 (s, 3H), 1.49 (d, 1H, *J*=3.3 Hz), 1.64 (s, 3H), 2.18 (d, 1H, *J*=5.1 Hz), 2.34 (t, 1H, *J*=10.8 Hz), 2.44 (m, 1H), 3.21 (dd, 1H, *J*=4.2, 9.0 Hz), 3.27 (dd, 1H, *J*=11.1, 13.2 Hz), 3.83 (d, 1H, *J*=11.1 Hz), 4.23 (t-like, 1H, *J*=9.0 Hz), 4.50 (dd, 1H, *J*=4.5, 13.5 Hz), 4.67 (t-like, 1H, *J*=3.9 Hz), 5.75 (d, 1H, *J*=3.6 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.2 (q), 26.3 (q), 35.4 (d), 35.5 (t), 56.7(t), 72.1(t), 75.3 (d), 78.4 (d), 88.6 (d), 104.0 (d), 113.5 (s); FABMS: *m/z* at 228 (MH^+).

3.1.9. (3a*R*,3b*S*,9a*R*,10a*R*)-2,2-Dimethyl-3a,9,9a,10a-tetrahydro-3b*H*,5*H*-1,3,4,10-tetraoxa-7,8,8a-triaza-cyclopent[*f*]cyclopent[*a*]azulene (17). Compound **17** was prepared from **14** using procedure as adopted in the preparation of **16**.

Yield 62%; gum; [Found: C, 52.08; H, 5.88; N, 16.32. $C_{11}H_{15}N_3O_4$ requires C, 52.17; H, 5.97; N, 16.59%]; ($\alpha(^{20}_{D}$=+9.7 (*c* 0.2, $CHCl_3$); IR (neat): ν_{max} 1644, 1574, 1379, 1218, 1082, 1021, 754 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.29 (s, 3H), 1.47 (s, 3H), 3.78 (d, 1H, *J*=2.6 Hz), 4.51 (dd, 1H, *J*=9.5, 13.0 Hz), 4.54 (d, 1H, *J*=3.7 Hz), 4.64 (m, 1H), 4.77 (dd, 1H, *J*=4.7, 13.0 Hz), 4.84 (d, 1H, *J*=6.8 Hz), 5.54 (d, 1H, *J*=6.8 Hz), 5.97 (d, 1H, *J*=3.6 Hz), 7.31(s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.2, 26.7, 44.4, 79.2, 84.1, 86.8, 88.6, 105.4, 112.6, 121.3, 149.8; FABMS: *m/z* at 254 (MH^+).

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11. Commercially available diacetone glucose was converted[15] to the diol **1** through oxidation of C-3 OH group followed by Grignard reaction with allyl magnesium bromide, selective deprotection of 5,6-ketal, vicinal diol cleavage and sodium borohydride reduction of the aldehyde. Compound **2** was, however, prepared[15] by benzylation of the above Grignard product and thereafter following a sequence of reactions similar to that in case of **1**. 1,2:5,6-Di-*O*-cyclohexylidene-3-*C*-allyl-α-D-allofura-nose was obtained from D-glucose via conventional steps and converted to **3** following a sequence of reactions similar to that in case of **1**. Characteristic data for 1,2:5,6-di-*O*-cyclohexylidene-3-*C*-allyl-α-D allofuranose: mp 106–108 °C; $[\alpha]^{20}_{D}$=+44.8 (*c* 0.85, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.41–1.68 (m, 20H), 2.18 (dd, 1H, *J*=6.0, 14.4 Hz), 2.65 (dd, 1H, *J*=5.4, 14.4 Hz), 2.78 (s, 1H), 3.79 (d, 1H, *J*=7.8 Hz), 3.90 (m, 1H), 4.13 (m, 2H), 4.33 (d,1H, *J*=3.6 Hz), 5.15 (d,1H, *J*=17.3 Hz), 5.19 (d, 1H, *J*=10.2 Hz), 5.77 (d, 1H, *J*=3.6 Hz), 5.99 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.9, 24.26, 24.30, 24.5, 25.3, 25.5, 35.2, 36.4, 36.66, 36.70, 37.3, 68.2, 73.3, 79.1, 81.3, 82.8, 103.7, 110.6, 113.6, 119.1, 133.2. For **3**: mp 155–156 °C; $[\alpha]^{20}_{D}$=+56.6° (*c* 0.54, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.41 (t, 2H, *J*=5.0 Hz), 1.56 (m, 4H), 1.69 (m, 2H), 1.79 (t, 1H, *J*=5.4 Hz), 1.95 (brs, 1H), 2.14 (dd, 1H, *J*=8.2, 14.6 Hz), 2.42 (dd, 1H, *J*=5.9, 14.6 Hz), 2.77 (d, 1H, *J*=1.1 Hz), 3.81 (m, 2H), 3.93 (dd, 1H, *J*=3.8, 7.2 Hz), 4.29

(d, 1H, *J*=3.9 Hz), 5.15 (m, 2H), 5.75 (d, 1H, *J*=3.9 Hz), 5.91 (m, 1H).

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14. The 3-*O*-allylated substrates **12**-**14** were prepared from diacetone D-glucose. The compound **12** was obtained through the oxidation of the hydroxyl group, reduction of the carbonyl group to 3-*epi* alcohol, allylation of the generated hydroxyl group, removal of 5,6-*O*- isopropylidene group, and finally, selective protection of primary hydroxyl group at *C*-6 with *tert*. butyl dimethylsilyl group. The precursors **13** and **14** were generated through allylation of the corresponding hydroxyl groups of diacetone D-glucose/D-allose followed by selective cleavage of 5,6-ketal, vicinal diol cleavage and reduction of the formed aldehyde. **12**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.079 (s, 3H), 0.088 (s, 3H), 0.90, 0.91(2×s, 9H), 1.36 (s, 3H), 1.58 (s, 3H), 2.52 (d, 1H, *J*=2.7 Hz), 3.66 (dd, 1H, *J*=7.5, 10.3 Hz), 3.72 (dd, 1H, *J*=3.8, 10.3 Hz), 3.94 (m, 2H), 4.02 (dd, 1H, *J*=3.8, 8.7 Hz), 4.09 (tdd, 1H, *J*=1.2, 5.9, 12.6 Hz), 4.22 (tdd, 1H, *J*=1.2, 5.9, 12.6 Hz), 4.62 (t, 1H, *J*=3.9 Hz), 5.29 (m, 2H), 5.75 (d, 1H, *J*=3.6 Hz), 5.97 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ −5.4 (2C), 18.4, 25.9 (3C), 26.6, 26.8, 63.8, 71.5, 72.0, 77.8, 77.9, 104.0, 112.9, 117.9, 118.0, 134.5. **13**: ^{1}H NMR ($CDCl_3$+D_2O, 300 MHz): δ 1.32 (s, 3H), 1.47 (s, 3H), 3.75 (dd, 1H, *J*=3.6, 6.0 Hz), 3.82 (dd, 1H, *J*=2.7, 6.0 Hz), 3.87 (m, 1H), 4.03 (dd, 1H, *J*=3.6, 7.5 Hz), 4.08–4.15 (m, 2H), 4.55 (d, 1H, *J*=3.6 Hz), 5.19–5.35 (m, 2H), 5.85–5.98 (m, 2H). **14**: ^{1}H NMR ($CDCl_3$+D_2O, 300 MHz): δ 1.36 (s, 3H), 1.58 (s, 3H), 3.73 (dd, 1H, *J*=3.5, 5.8 Hz), 3.75 (dd, 1H, *J*=2.8, 5.8 Hz), 3.92 (dd, 1H, *J*=4.0, 6.0 Hz), 4.01–4.24 (m, 2H), 4.63 (t-like, 1H, *J*=3.9 Hz), 5.24–5.36 (m, 2H), 5.78 (d, 1H, *J*=3.6 Hz), 5.85–6.01 (m, 1H).
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Easy access to 4-nitrothiochroman *S*,*S*-dioxides via ring-enlargement from 3-nitrobenzo[*b*]thiophene☆

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Abstract—The (*E*)-2-aryl-1-[2-(methylthio)phenyl]-1-nitroethylenes **5** can easily be oxidized to the relevant sulfones **6** and effectively subjected to cyclization via an intramolecular Michael addition after metallation with lithium bis(trimethylsilyl)amide in THF. After quenching with ammonium chloride the 3-aryl-4-nitrothiochroman *S*,*S*-dioxides **2** are obtained as diastereomeric mixtures in good to excellent yields. Both yields and stereochemistry of the ring-closure step appear to be influenced by steric effects of the 3-aryl moiety. As sulfides **5** derive from an initial ring opening of 3-nitrobenzo[*b*]thiophene (**1**), the overall **1** to **2** process can be considered as an effective 5 to 6 ring enlargement of the sulfur heterocycle. A conformational ^{1}H NMR and molecular-mechanics investigation on the isolated diastereomeric **2** has also been accomplished.

1. Introduction

A number of reports from the recent literature clearly testify for a renewed interest in the synthetic approach to thiopyrans and benzothiopyrans (thiochromans).[2,3] The quest for new synthetic routes has been boosted by the importance which has been attached in the last decade to such heterocycles, both in pharmacology and in medicine:[4] an occurrence which has also contributed to partially fill, from both a synthetic and applicative point of view, the gap with the oxygen counterparts (pyrans and benzopyrans, respectively), whose long-recognised abundance in nature has always fostered a good deal of research relevant to preparations and properties.[5]

Many thiochromans have been synthesized through reduction of the corresponding thiochromens[6] and thiochromanones,[7] via Claisen rearrangement of allyl phenyl sulfides,[8] or via thermal decomposition of 2-azidobenzo[*b*]thiophenes in the presence of alkenes.[9] More recent synthetic approaches to thiochromans utilize the cycloaddition of sulfur-stabilized carbocations to alkenes.[2b] Some substituted thiochromans have also been prepared through condensation of dilithiated methylthio- and isopropylthio-benzene with α-diketones.[10]

Within the framework of our long-standing project on the synthetic exploitation of the ring-opening of nitrothiophenes[11] we now report on a novel approach to thiochroman *S*,*S*-dioxides **2** (Scheme 1) which takes advantage of an intramolecular Michael addition of the lithium salts of compounds **6** to the nitrovinyl moiety (Scheme 2) and which can be envisaged, starting from 3-nitrobenzo[*b*]thiophene (**1**), as an overall 5 to 6 enlargement of the sulfur heterocycle. It should be pointed out that, at least to our knowledge, compounds **2** represent the first example of thiochroman derivatives with a nitrogroup at C(4).

2. Results and discussion

Substrates **6** have been prepared (Scheme 1 and Table 1) by oxidation of **5**, in turn easily obtainable via a preliminary ring opening of 3-nitrobenzo[*b*]thiophene (**1**), according to a methodology previously described for the preparation of **5d** (Ar=*p*-tolyl).[12]

Treatment of **6** with lithium bis(trimethylsilyl)amide (LHMDS) in anhydrous THF at room temperature, followed by acidic (NH_4Cl) quenching allowed us to isolate, in good

☆ See Ref. 1.

Keywords: Thiochromans; Nitrothiophenes; 3-Nitrobenzo[*b*]thiophene; Ring-opening/ring-closure reactions; Ring enlargement; Conformations.
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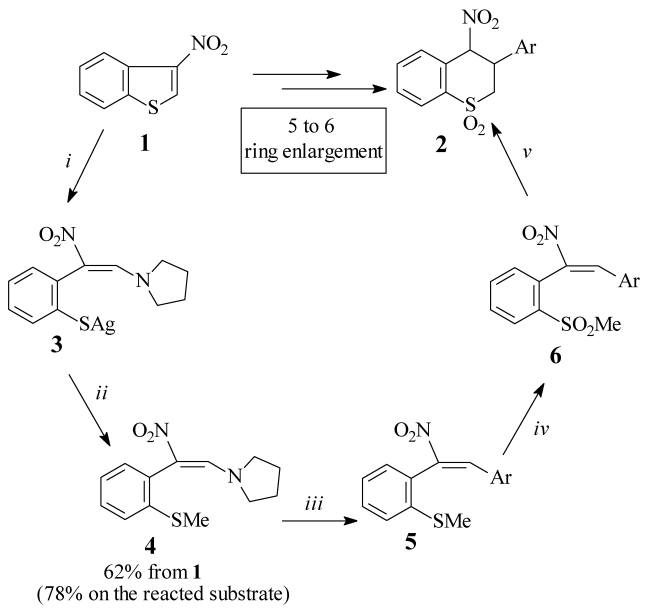


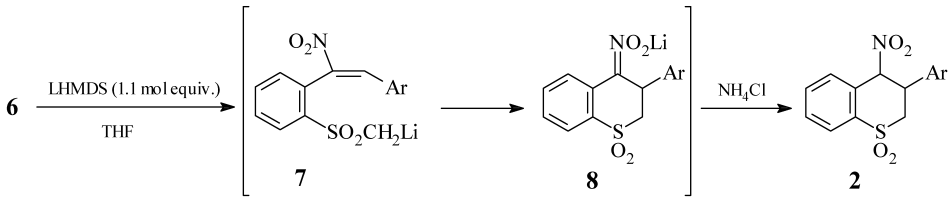
Scheme 1. (i) Pyrrolidine (2 mol equiv.)/$AgNO_3$ (2 mol equiv.), abs. EtOH, rt, overnight; (ii) excess MeI, 0 °C to rt, 2 h; (iii) ArMgX or ArLi (1.1 mol equiv.), THF, −78 °C, 15–45 min, followed by acidic quenching; (iv) MCPBA (2 mol equiv.), CH_2Cl_2, rt; (v) LHMDS (1.1 mol equiv.), THF, rt, 4 h, followed by NH_4Cl quenching.

the mesityl-substituted **6e**, evidencing that the overall process is highly sensitive to the bulk of the aryl moiety in the substrate.

The assignment of the structure to the reaction products is based both on microanalytical results and on spectral data [IR, ^1H and ^{13}C NMR, MS(ESI): see Experimental Section]. In particular, the same molecular weight as for **6**, the absence of the nitrovinyl and of the CH_3SO_2 protons, and the presence of a CH–CH–CH_2 moiety in the ^1H NMR spectra represent definitive confirmation of the proposed structure for **2**.

Nitrothiochromans **2** can be reasonably envisaged to originate from the non isolated nitronates **8**, which are in turn the result of an intramolecular Michael addition undergone by the initially formed lithium salts **7** (Scheme 2). Consistant with this proposed mechanism, if the reaction of **6d** is quenched with ND_4Cl in D_2O, 4-deutero-4-nitro-3-(*p*-tolyl)thiochroman *S*,*S*-dioxide (**2′d**) is formed.

The ^1H NMR spectra of crude nitroderivatives **2** are consistent with the concomitant presence of two racemic diastereoisomers, non separable by chromatography, corresponding to the *trans* and *cis* configurations at the C(3)–C(4) bond; thus, in order to better rationalize the results, it seemed worth carrying out an accurate conformational analysis on such thiochromans. While the sulphur atom and C(4) have to be coplanar with the condensed benzene moiety, C(2) and C(3) can be either on opposite sides with respect to the plane (generating two non equivalent half-chairs) or on the same side (generating two non equivalent boats): in the latter case, though, severe eclipsing at the C(2)–C(3) bond can be expected. Another possibility is represented by sofa conformations, exhibiting just one carbon out of the plane and possibly less effective eclipsing than the boats. For this reason sofa conformations received much attention as possible competitors of half-chairs in related systems.[2b,13]



Scheme 2.

Table 1. Yields of compounds **5**, **6** and **2** (Scheme 1, steps iii, iv and v, respectively)[a]

	Ar	5 (Yield %)	6 (Yield %)	2 (Yield %)[b]	2 *trans*/*cis* Ratio[c]
a	Ph	99	99	78	1:1.4
b	2-MeC_6H_4	95	97	80	1:2.2
c	3-MeC_6H_4	87	99	80	1:1.3
d	4-MeC_6H_4	94[d]	94	88	1:1.2
e	2,4,6-$Me_3C_6H_2$	41 (99)[e]	99	[f]	
f	4-ClC_6H_4	99	99	78	1:1.0
g	1-Naphthyl	99	99	99[g]	1:3.0
h	2-Thienyl	99[h]	99	70	1:0.9

[a] Yields of chromatographically-isolated compounds, if not otherwise stated.
[b] Yields of crude diastereoisomeric mixtures.
[c] Isomeric ratios have been determined by ^1H NMR, on the basis of the ratios of the H(4) signals in the mixture.
[d] See Ref. 12.
[e] Yield based on the reacted substrate.
[f] Unaltered substrate recovered after 48 h, with no trace of products.
[g] Reaction time: 30 h.
[h] Reaction time: 4 h.

to excellent yields, the 3-aryl-4-nitrothiochroman *S*,*S*-dioxides **2** (Scheme 1 and Table 1). It should be pointed out that the formation of the product is much slower for the naphthyl-substituted **6g** and even completely suppressed for

We have approached the problem by running molecular-mechanics calculations (PCMODEL program[14]) for the *trans* and *cis* forms of **2a** (Ar=Ph). Results are collected in Table 2. In both cases the most stable conformation is calculated to be one of the two possible half-chairs, the *trans* form adopting a pseudo-equatorial (*peq*) arrangement of the nitro and the phenyl substituents while the *cis* form prefers a pseudo-axial (*pax*) nitrogroup and a *peq* phenyl moiety (Fig. 1). It stands out that the two forms differ mainly for the orientation of the 4-NO_2 substituent and consequently for the H(3)–C(3)–C(4)–H(4) dihedral angle, which is

Table 2. Calculated dihedral angles (°) and dipole moments (D) for the half-chair conformations of *trans*- and *cis*-**2a**

	C(4a)–C(8a)–S(1)–C(2)	C(8a)–C(4a)–C(4)–C(3)	$H(2)_{pax}$–C(2)–C(3)–H(3)	$H(2)_{peq}$–C(2)–C(3)–H(3)	H(3)–C(3)–C(4)–H(4)	Dipole moment
trans	−17.6	−9.0	172.3	−65.8	164.3	5.054
cis	−16.8	−15.1	173.4	−65.3	55.0	4.341

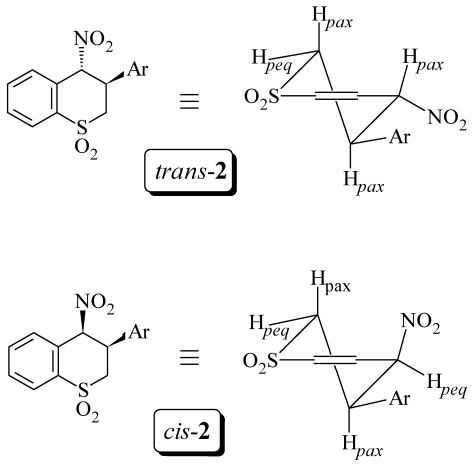


Figure 1. Configuration and preferred half-chair conformation of the two diastereoisomers of **2** (only one enantiomer shown).

calculated to be rather close to 180° for the *trans* form and rather close to 60° for the *cis* one.

Although other conformations cannot be completely ruled out and could be present as minor components, nevertheless these results provide a valuable key to the interpretation of ^{1}H NMR spectra. In fact, the Karplus-Conroy rule[15] predicts high $J_{3,4}$ values (10–15 Hz) for the *quasi-trans* 1,2-pseudodiaxial interaction of H(3) and H(4) in the *trans* form and low values (2–5 Hz) for the staggered 1,2-pseudoaxial-pseudoequatorial interaction of the same protons in the *cis* form. Thus the non aromatic ^{1}H NMR signals of the two racemic pairs of **2** can be fully interpreted and assignments are given in Table 3. It stands out that diastereomeric pairs exhibit striking differences not only, as expected, in $J_{3,4}$ but also in $\delta_{H(2)_{pax}}$ values because of 1,3-pseudodiaxial deshielding interactions between $H(2)_{pax}$ and 4-NO_2 in the *cis* form. Similarly significant variations are observed also in the chemical shifts of H(3) and H(4) on going from *cis*-**2** to *trans*-**2**.

From the *trans*-**2**/*cis*-**2** ratios observed in the crude final mixtures (Table 1) it appears that the cyclization occurs with no significant stereoselectivity but for the 1-naphthyl derivative: in this case, the ca. threefold predominance of the *cis* racemic couple is remarkable and presumably the result of steric effects. It should be also pointed out that a crystallization of the crude from ethanol allows, in the case of the just cited 1-naphthyl derivative, the recovering of an almost pure *cis* isomer, while no appreciable alteration of the *trans*/*cis* ratio has been observed in the other cases; on the other hand, the use of a less polar mixed solvent (viz. ethanol/dioxane) in the case of the model compound **2d** leads to a significant increase in the percentage of the more polar *trans* isomer (see Table 2) in the recovered crystals (the *trans*/*cis* ratio changing from 1:1.2 to 1:0.7 and 1:0.5 after one and two crystallizations, respectively).

3. Conclusions

The results herein enlighten an original and attractive access to the thiochroman *S*,*S*-dioxide ring system, which originates from the ring-opening of 3-nitrobenzo[*b*]thiophene (**1**) and whose key step is represented by an intramolecular Michael-type addition of a sulfonyl-stabilized carbanion onto a nitrovinylic moiety (**6**→**2**: see Schemes 1 and 2).

Table 3. ^{1}H NMR Data (see Section 4) for the non-aromatic protons of the diastereomeric *cis*/*trans* racemic pairs of thiochromans **2**[a]

Isomer	$\delta_{H(2)_{pax}}$	$\delta_{H(2)_{peq}}$	$\delta_{H(3)}$	$\delta_{H(4)}$	$J_{2_{pax},2_{peq}}$	$J_{2_{pax},3}$	$J_{2_{peq},3}$	$J_{3,4}$
trans-**2a**	3.73(dd)	3.60 (dd)	4.62 (app td)	6.13 (d)	14.2	12.0	4.0	11.4
cis-**2a**	4.74 (app t)	3.56 (dd)	4.45 (ddd)	6.00 (d)	13.6	13.8	2.2	4.4
trans-**2b**	3.60 (dd)	3.48[b]	4.99 (app td)	6.30 (d)	14.3	12.1	4.2	11.0
cis-**2b**	4.76 (app t)	3.48[b]	4.62 (dd)	5.94 (d)	12.4	14.0	[c]	4.0
trans-**2c**	3.71 (dd)	3.55[b]	4.56 (app td)	6.14 (d)	13.8	12.5	3.5	11.0
cis-**2c**	4.72 (app t)	3.55[b]	4.39 (ddd)	5.99 (d)	13.6	13.8	2.4	4.1
trans-**2d**	3.71 (dd)	3.58 (dd)	4.57 (app td)	6.10 (d)	14.3	12.0	4.1	11.0
cis-**2d**	4.72 (app t)	3.54 (dd)	4.40 (ddd)	5.97 (d)	13.4	13.6	2.2	4.4
trans-**2f**	3.70 (dd)	3.58 (dd)	4.60 (app td)	6.09 (d)	14.2	11.8	4.4	11.0
cis-**2f**	4.70 (app t)	3.52 (dd)	4.42 (ddd)	5.97 (d)	13.6	13.8	2.2	4.4
trans-**2g**[d]	4.23 (br app t)	3.86 (dd)	5.61 (br app t)	7.03 (d)	14.1	13[e]	2.6	10.6
cis-**2g**[d]	4.78 (app t)	3.88 (dd)	5.36 (ddd)	6.59 (d)	14.0	13.2	2.2	4.1
trans-**2h**[d]	4.21 (dd)	3.87 (dd)	4.9[b]	6.57 (d)	14.2	12.6	3.0	10.2
cis-**2h**[d]	4.57 (app t)	3.91 (dd)	4.9[b]	6.47 (d)	13.6	13.5	2.6	4.4

[a] Chemical shifts as δ ppm from internal TMS, coupling constants in Hz. Solvent: $CDCl_3$, unless otherwise specified; *pax*=pseudoaxial, *peq*=pseudoequatorial. No long-range coupling between non-aromatic and aromatic protons could be detected at 200 MHz (see Ref. 16).
[b] Overlapping signals.
[c] In this product $J_{2_{peq},3}$ is very low and not detectable, possibly because of some little difference in ring conformation as a consequence of the steric requirement of the 2-MeC_6H_4 group.
[d] In acetone-d_6.
[e] Broadening of the relevant triplets does not allow a more accurate measurement.

A ^{1}H NMR study, together with molecular-mechanics calculations, has allowed to gain insights into the configuration of compounds **2** and their conformation.

It should be finally emphasized that the overall **1→2** protocol described herein represents a further example of heterocyclic synthesis by means of a ring-opening/ring-closing procedure which takes advantage of the non-benzenoid behaviour of nitrothiophene derivatives towards secondary nucleophilic amines.[11]

4. Experimental

4.1. General

^{1}H NMR and ^{13}C NMR spectra were recorded at 200 and 50 MHz, respectively; chemical shifts (TMS as internal reference) are reported as δ values (ppm). MS(ESI) analyses were recorded on a Micromass Z0MD Waters instrument (30 V, 13.2 kV). Melting points were determined with a Büchi 535 apparatus and are uncorrected. Petroleum ether and light petroleum refer to the fractions with bp 40–60 and 80–100 °C, respectively. Silica gel 230–400 mesh was used for column chromatography, all solvents being distilled before use. Tetrahydrofuran (THF) was purified by standard methods and distilled over potassium benzophenone ketyl before use. Compound **4** was synthesized as previously reported.[12] Commercial lithium bis(trimethylsilyl)amide (LHMDS, 1 M in THF) was used as received. All other commercially available reagents were used as received.

Organometallic reagents. All the reagents were THF or Et_2O solutions titrated[17] just before use. Phenyl-, 4-methylphenyl-, 2,4,6-trimethylphenyl-, 1-naphthyl-magnesium bromides, 2-methylphenyl-, 3-methylphenyl-magnesium chlorides were commercial solutions in THF; 4-chlorophenylmagnesium bromide and 2-thienyllithium were commercial solutions in Et_2O.

4.2. Reactions of 4 with aromatic organometallic reagents

The reactions were performed on 1 g of compound **4**[12] (3.78 mmol) following the procedure previously reported for the synthesis of **5d**.[12] Yields of compounds **5** are collected in Table 1.

4.2.1. (*E*)-1-[2-(Methylthio)phenyl]-1-nitro-2-phenylethylene (5a). (1.02 g, 99%). Yellow solid, mp 95–96 °C (light petroleum); ν_{max} (Nujol) 1649, 1584, 1513, 1324, 1212, 1166, 1069 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.41 (3H, s), 7.09 (2H, app d), 7.17–7.56 (7H, m), 8.30 (1H, s); ^{13}C NMR (CD_3SOCD_3) δ 14.52, 125.58, 125.99, 128.78, 128.95, 130.70, 130.78, 130.97, 131.02, 131.21, 136.20, 139.50, 147.44. Anal. Calcd for $C_{15}H_{13}NO_2S$: C, 66.4; H, 4.8; N, 5.2%. Found: C, 66.3; H, 4.7; N, 5.2%.

4.2.2. (*E*)-1-[2-(Methylthio)phenyl]-1-nitro-2-(*o*-tolyl)-ethylene (5b). (1.02 g, 95%). Yellow solid, mp 94–96 °C (light petroleum); ν_{max} (Nujol) 1647, 1581, 1513, 1323, 1288, 1228, 1161, 1070 cm^{-1}; ^{1}H NMR (CD_3COCD_3) δ 2.47 (3H, s), 2.51 (3H, s), 6.80–6.99 (2H, m), 7.15–7.32 (4H, m), 7.42–7.53 (2H, m), 8.51 (1H, s); ^{13}C NMR ($CDCl_3$) δ 16.04, 20.15, 125.64, 125.94, 126.84, 129.00, 130.00, 130.23, 130.39, 130.51, 130.58, 131.46, 134.21, 139.10, 140.14, 148.93. Anal. Calcd for $C_{16}H_{15}NO_2S$: C, 67.3; H, 5.3; N, 4.9%. Found: C, 67.5; H, 5.2; N, 4.8%.

4.2.3. (*E*)-1-[2-(Methylthio)phenyl]-1-nitro-2-(*m*-tolyl)-ethylene (5c). (0.94 g, 87%). Yellow solid, mp 65–66 °C (petroleum ether); ν_{max} (Nujol) 1646, 1581, 1504, 1314, 1173, 1070 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.22 (3H, s), 2.42 (3H, s), 6.84 (1H, app d), 6.95 (1H, s), 7.05–7.32 (4H, m), 7.38–7.58 (2H, m), 8.27 (1H, s); ^{13}C NMR ($CDCl_3$) δ 15.99, 21.25, 125.93, 126.92, 127.80, 128.70, 130.23, 130.81, 130.95, 131.16, 131.88, 132.16, 136.48, 138.48, 140.07, 147.80. Anal. Calcd for $C_{16}H_{15}NO_2S$: C, 67.3; H, 5.3; N, 4.9%. Found: C, 67.2; H, 5.2; N, 4.8%.

4.2.4. (*E*)-1-[2-(Methylthio)phenyl]-1-nitro-2-(*p*-tolyl)-ethylene (5d). (1.02 g, 94%). Yellow solid, mp 56–57 °C (light petroleum).[12]

4.2.5. (*E*)-1-[2-(Methylthio)phenyl]-1-nitro-2-(2,4,6-trimethylphenyl)ethylene (5e). [0.49 g, 41% (99% based on the unreacted substrate)]. Yellow solid, mp 128–129 °C (light petroleum); ν_{max} (Nujol) 1645, 1609, 1585, 1518, 1328, 1172, 1067, 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.08 (6H, s), 2.22 (3H, s), 2.44 (3H, s), 6.75–6.83 (3H, m), 7.00 (1H, td, *J*=7.3, 1.4 Hz), 7.31 (1H, td, *J*=7.5, 1.4 Hz), 7.40 (1H, dd, *J*=7.8, 1.4 Hz), 8.18 (1H, s); ^{13}C NMR ($CDCl_3$) δ 17.40, 20.36, 21.01, 125.78, 127.82, 128.59, 129.12, 130.36, 130.93, 131.39, 135.51, 136.16, 138.61, 139.31, 151.87. Anal. Calcd for $C_{18}H_{19}NO_2S$: C, 69.0; H, 6.1; N, 4.5%. Found: C, 69.2; H, 6.0; N, 4.4%.

4.2.6. (*E*)-2-(4-Chlorophenyl)-1-[2-(methylthio)phenyl]-1-nitroethylene (5f). (1.14 g, 99%). Yellow solid, mp 96–98 °C (light petroleum); ν_{max} (Nujol) 1655, 1583, 1519, 1491, 1407, 1325, 1207, 1166, 1092, 1069, 1011 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.42 (3H, s), 7.02 (2H, d, *J*=8.4 Hz), 7.14–7.31 (4H, m), 7.40 (1H, d, *J*=7.8 Hz), 7.52 (1H, td, *J*=7.5, 1.4 Hz), 8.24 (1H, s); ^{13}C NMR ($CDCl_3$) δ 15.79, 125.94, 126.73, 129.18, 129.43, 129.50, 131.01, 131.06, 132.03, 134.87, 137.17, 140.09, 148.29. Anal. Calcd for $C_{15}H_{12}ClNO_2S$: C, 58.9; H, 4.0; N, 4.6%. Found: C, 59.1; H, 3.9; N, 4.7%.

4.2.7. (*E*)-1-[2-(Methylthio)phenyl]-2-(1-naphthyl)-1-nitroethylene (5g). (1.20 g, 99%). Yellow solid, mp 158–159 °C (toluene/light petroleum); ν_{max} (Nujol) 1641, 1584, 1518, 1355, 1322, 1243, 1169, 1071, 1017 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.44 (3H, s), 7.05–7.27 (4H, m), 7.33–7.48 (2H, m), 7.50–7.69 (2H, m), 7.74–7.90 (2H, m), 8.16 (1H, d, *J*=8.4 Hz), 9.01 (1H, s); ^{13}C NMR ($CDCl_3$) δ 16.07, 123.52, 125.13, 125.60, 126.45, 126.77, 127.27, 128.05, 128.21, 128.87, 129.98, 130.55, 130.86, 131.41, 131.95, 133.33, 133.78, 140.31, 150.14. Anal. Calcd for $C_{19}H_{15}NO_2S$: C, 71.0; H, 4.7; N, 4.4%. Found: C, 71.2; H, 4.6; N, 4.4%.

4.2.8. (*E*)-1-[2-(Methylthio)phenyl]-1-nitro-2-(2-thienyl)ethylene (5h). [1.04 g, 99% (reaction time: 4 h)]. Yellow solid, mp 106–108 °C (light petroleum); ν_{max} (Nujol) 1632, 1583, 1500, 1415, 1311, 1286, 1250, 1237, 1214, 1052, 1040 cm^{-1}; ^{1}H NMR (CD_3SOCD_3) δ 2.40 (3H,

s), 7.16 (1H, dd, *J*=4.8, 3.8 Hz), 7.33–7.40 (2H, m), 7.51 (1H, app d, *J*=8.2 Hz), 7.56–7.68 (1H, m), 7.74–7.83 (2H, m), 8.75 (1H, s); ^{13}C NMR (CD_3COCD_3) δ 15.45, 126.90, 127.69, 128.55, 129.80, 131.13, 132.30, 132.75, 135.24, 135.83, 138.07, 141.58, 145.90. Anal. Calcd for $C_{13}H_{11}NO_2S_2$: C, 56.3; H, 4.1; N, 5.1%. Found: C, 56.3; H, 4.0; N, 5.0%.

4.3. Oxidation of compounds 5 to 6

The reaction was performed on 2 mmol of the appropriate **5**, according to the conditions described in Ref. 11. Yields are reported in Table 1.

4.3.1. (*E*)-1-[2-(Methylsulfonyl)phenyl]-1-nitro-2-phenylethylene (6a). (600 mg, 99%). Yellow solid, mp 116–117 °C (ethanol); ν_{max} (Nujol) 1643, 1598, 1512, 1322, 1306, 1213, 1152, 1122 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.97 (3H, s), 7.02 (2H, d, *J*=7.2 Hz), 7.18–7.40 (4H, m), 7.67–7.83 (2H, m), 8.22 (1H, dd, *J*=7.3, 1.9 Hz), 8.37 (1H, s); ^{13}C NMR (CD_3SOCD_3) δ 43.23, 128.99, 129.24, 130.26, 130.39, 131.01, 131.27, 131.75, 133.39, 134.78, 135.09, 139.63, 146.35. Anal. Calcd for $C_{15}H_{13}NO_4S$: C, 59.4; H, 4.3; N, 4.6%. Found: C, 59.3; H, 4.3; N, 4.5%.

4.3.2. (*E*)-1-[2-(Methylsulfonyl)phenyl]-1-nitro-2-(*o*-tolyl)ethylene (6b). (616 mg, 97%). Yellow solid, mp 174–175 °C (ethanol); ν_{max} (Nujol) 1650, 1530, 1336, 1305, 1266, 1232, 1151, 1121, 1073 cm^{-1}; ^{1}H NMR (CD_3SOCD_3) δ 2.47 (3H, s), 3.09 (3H, s), 6.61 (1H, d, *J*=7.6 Hz), 6.95 (1H, t, *J*=7.3 Hz), 7.18–7.33 (2H, m), 7.45 (1H, app dd, *J*=7.0, 1.8 Hz), 7.69–7.86 (2H, m), 8.17 (1H, app dd, *J*=7.4, 1.8 Hz), 8.49 (1H, s); ^{13}C NMR (CD_3SOCD_3) δ 19.54, 43.09, 125.82, 128.60, 128.82, 129.88, 130.06, 130.37, 130.61, 131.46, 133.38, 133.74, 134.19, 139.23, 139.99, 147.78. Anal. Calcd for $C_{16}H_{15}NO_4S$: C, 60.6; H, 4.8; N, 4.4%. Found: C, 60.4; H, 4.7; N, 4.3%.

4.3.3. (*E*)-1-[2-(Methylsulfonyl)phenyl]-1-nitro-2-(*m*-tolyl)ethylene (6c). (630 mg, 99%). Yellow solid, mp 155–156 °C (ethanol); ν_{max} (Nujol) 1646, 1523, 1337, 1307, 1246, 1181, 1150, 1124 cm^{-1}; ^{1}H NMR (CD_3SOCD_3) δ 2.16 (3H, s), 3.00 (3H, s), 6.81 (1H, d, *J*=7.4 Hz), 6.98 (1H, s), 7.13–7.27 (2H, m), 7.56–7.63 (1H, m), 7.84–7.97 (2H, m), 8.19–8.26 (1H, m), 8.36 (1H, s); ^{13}C NMR (CD_3SOCD_3) δ 20.69, 43.25, 127.80, 128.85, 129.39, 130.26, 130.33, 131.71, 131.96, 132.07, 133.41, 134.76, 135.19, 138.27, 139.60, 146.23. Anal. Calcd for $C_{16}H_{15}NO_4S$: C, 60.6; H, 4.8; N, 4.4%. Found: C, 60.7; H, 4.7; N, 4.4%.

4.3.4. (*E*)-1-[2-(Methylsulfonyl)phenyl]-1-nitro-2-(*p*-tolyl)ethylene (6d). (600 mg, 94%). Yellow solid, mp 160–161 °C (ethanol); ν_{max} (Nujol) 1655, 1605, 1513, 1330, 1314, 1192, 1168, 1156, 1125 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.30 (3H, s), 2.95 (3H, s), 6.89 (2H, d, *J*=8.3 Hz), 7.05 (2H, d, *J*=8.3 Hz), 7.35–7.41 (1H, m), 7.67–7.83 (2H, m), 8.18–8.27 (1H, m), 8.35 (1H, s); ^{13}C NMR (CD_3SOCD_3) δ 20.79, 43.23, 127.48, 129.43, 129.56, 130.15, 130.98, 131.54, 133.30, 134.65, 135.09, 139.59, 141.70, 145.47. Anal. Calcd for $C_{16}H_{15}NO_4S$: C, 60.6; H, 4.8; N, 4.4%. Found: C, 60.5; H, 4.8; N, 4.3%.

4.3.5. (*E*)-1-[2-(Methylsulfonyl)phenyl]-1-nitro-2-(2,4,6-trimethylphenyl)ethylene (6e). (684 mg, 99%). Pale yellow solid, mp 202–203 °C (ethanol); ν_{max} (Nujol) 1649, 1611, 1530, 1339, 1305, 1265, 1156, 1119, 1071 cm^{-1}; ^{1}H NMR (CD_3SOCD_3) δ 2.07 (6H, s), 2.17 (3H, s), 3.20 (3H, s), 6.80 (2H, s), 6.94 (1H, dd, *J*=7.7, 1.5 Hz), 7.53 (1H, td, *J*=7.5, 1.3 Hz), 7.69 (1H, td, *J*=7.7, 1.4 Hz), 8.12 (1H, dd, *J*=7.9, 1.3 Hz), 8.36 (1H, s); ^{13}C NMR (CD_3SOCD_3) δ 19.87, 20.47, 43.23, 127.51, 128.26, 128.32, 130.40, 131.32, 132.90, 133.45, 135.59, 135.83, 138.30, 139.21, 149.99. Anal. Calcd for $C_{18}H_{19}NO_4S$: C, 62.6; H, 5.6; N, 4.1%. Found: C, 62.4; H, 5.5; N, 4.0%.

4.3.6. (*E*)-2-(4-Chlorophenyl)-1-[2-(methylsulfonyl)-phenyl]-1-nitroethylene (6f). (670 mg, 99%). Yellow solid, mp 149–150 °C (ethanol); ν_{max} (Nujol) 1649, 1584, 1527, 1407, 1313, 1208, 1151, 1120, 1089, 1011 cm^{-1}; ^{1}H NMR (CD_3SOCD_3) δ 3.04 (3H, s), 7.12 (2H, d, *J*=8.6 Hz), 7.41 (2H, d, *J*=8.6 Hz), 7.54–7.63 (1H, m), 7.83–7.97 (2H, m), 8.19–8.27 (1H, m), 8.43 (1H, s); ^{13}C NMR (CD_3SOCD_3) δ 43.26, 128.84, 129.16, 129.42, 130.32, 131.92, 132.58, 133.32, 133.95, 134.87, 135.99, 139.67, 146.83. Anal. Calcd for $C_{15}H_{12}ClNO_4S$: C, 53.3; H, 3.6; N, 4.1%. Found: C, 53.2; H, 3.6; N, 4.2%.

4.3.7. (*E*)-1-[2-(Methylsulfonyl)phenyl]-2-(1-naphthyl)-1-nitroethylene (6g). (707 mg, 99%). Yellow solid, mp 213–214 °C (ethanol/dioxane); ν_{max} (Nujol) 1646, 1510, 1310, 1243, 1153, 1119, 1069 cm^{-1}; ^{1}H NMR (CD_3SOCD_3) δ 3.12 (3H, s), 7.03 (1H, d, *J*=7.4 Hz), 7.27–7.39 (2H, m), 7.57–7.80 (4H, m), 7.96 (2H, app t, *J*=8.8 Hz), 8.15 (1H, dd, *J*=7.9, 1.3 Hz), 8.22 (1H, d, *J*=7.6 Hz), 8.97 (1H, s); ^{13}C NMR ($CDCl_3$) δ 43.16, 124.06, 125.12, 126.72, 127.39, 127.88, 128.19, 128.63, 128.73, 130.05, 130.62, 131.16, 131.43, 132.89, 133.02, 133.57, 134.08, 140.06, 149.23. Anal. Calcd for $C_{19}H_{15}NO_4S$: C, 64.6; H, 4.3; N, 4.0%. Found: C, 64.4; H, 4.2; N, 4.0%.

4.3.8. (*E*)-1-[2-(Methylsulfonyl)phenyl]-1-nitro-2-(2-thienyl)ethylene (6h). (612 mg, 99%). Yellow solid, mp 151–152 °C (ethanol); ν_{max} (Nujol) 1627, 1337, 1305, 1246, 1152, 1120, 1052 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.93 (3H, s), 7.06 (1H, dd, *J*=5.1, 3.7 Hz), 7.38 (1H, d, *J*=3.7 Hz), 7.42 (1H, dd, *J*=5.1, 0.7 Hz), 7.46–7.55 (1H, m), 7.77–7.89 (2H, m), 8.20–8.29 (1H, m), 8.58 (1H, s); ^{13}C NMR (CD_3SOCD_3) δ 43.48, 128.13, 128.31, 129.88, 130.54, 132.24, 134.04, 134.18, 135.06, 135.27, 138.58, 139.72, 143.04. Anal. Calcd for $C_{13}H_{11}NO_4S_2$: C, 50.5; H, 3.6; N, 4.5%. Found: C, 50.5; H, 3.5; N, 4.4%.

4.4. Reaction of compounds 6 with LHMDS

In a flask, the appropriate **6** (0.3 mmol) was dissolved under Argon in THF (19 mL) and LHMDS 1 M (1.1 mol equiv., 0.33 mL) was added by a syringe under magnetic stirring. The proceeding of the reaction was followed by TLC and, after completion, the mixture was poured into saturated aqueous NH_4Cl (50 mL), and extracted with dichloromethane (2×20 mL), the organic extracts being dried over Na_2SO_4. The crude solid residue, obtained by filtration and removal of the solvent under reduced pressure, was generally pure by ^{1}H NMR analysis, being a diastereomeric *cis*/*trans* mixture of compounds **2**. Yields of compounds **2**

are reported in Table 1 together with the relevant *cis*/*trans* ratios. As mentioned in the text, the crystallization of the crude residues from ethanol brings about only minor variations in the diastereomeric ratio in all cases but for the 1-naphthyl derivative **2g**, for which the pure *cis* stereoisomer can be recovered: therefore, the spectroscopic data reported below refer to the crystallized mixture in every case but for **2g**. For the latter, ^{1}H NMR data for the crude residue, where both diastereoisomers are present, are reported, together with a full spectroscopic characterization of the crystallized *cis* stereoisomer. In the ^{1}H NMR spectra of compounds **2** some signals appeared as triplets, as a consequence of the similar values of the two coupling constants involved; in these cases, as the frequency difference between the outer lines corresponds to the sum of the two *J* values, if one of them was known the other was calculated accordingly.

4.4.1. 4-Nitro-3-phenylthiochroman *S*,*S*-dioxide (2a). (71 mg, 78%, mixture of *trans*:*cis* isomers 1:1.4). White solid, mp 162–170 °C (ethanol); ν_{max} (Nujol) 1556, 1296, 1247, 1225, 1158, 1126, 1070 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.56 (1H *cis*, dd, *J*=13.6, 2.2 Hz), 3.60 (1H *trans*, dd, *J*=14.2, 4.0 Hz), 3.73 (1H *trans*, dd, *J*=14.2, 12.0 Hz), 4.45 (1H *cis*, ddd, *J*=13.8, 4.4, 2.2 Hz), 4.62 (1H *trans*, app td, *J*=12.0, 11.4, 4.0 Hz), 4.74 (1H *cis*, app t, *J*=13.8, 13.6 Hz), 6.00 (1H *cis*, d, *J*=4.4 Hz), 6.13 (1H *trans*, d, *J*=11.4 Hz), 7.18–7.80 (8H *cis* and 8H *trans*), 8.04–8.18 (1H *cis* and 1H *trans*, m); ^{13}C NMR ($CDCl_3$) δ 41.40, 43.13, 48.57, 53.48, 88.55, 90.72, 124.51, 124.59, 127.02, 127.08, 127.25, 127.65, 128.54, 129.21, 129.28, 129.54, 129.61, 129.73, 131.09, 132.16, 133.43, 133.75, 135.45, 136.25, 138.16, 139.05; MS(ESI): *m*/*z* 326.3 (M+Na)$^+$, 302.0 (M−1). Anal. Calcd for $C_{15}H_{13}NO_4S$: C, 59.4; H, 4.3; N, 4.6%. Found: C, 59.2; H, 4.3; N, 4.5%.

4.4.2. 4-Nitro-3-(*o*-tolyl)thiochroman *S*,*S*-dioxide (2b). (76 mg, 80%, mixture of *trans*:*cis* isomers 1:2.2). White solid, mp 187–189 °C (ethanol); ν_{max} (Nujol) 1552, 1413, 1327, 1306, 1267, 1253, 1234, 1197, 1166, 1156, 1132, 1072 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.44 (3H *trans*, s), 2.48 (3H *cis*, s), 3.48 (1H *cis* and 1H *trans*, overlapping multiplets), 3.60 (1H *trans*, dd, *J*=14.3, 12.1 Hz), 4.62 (1H *cis*, dd, *J*=14.0, 4.0 Hz), 4.76 (1H *cis*, app t, *J*=14.0, 12.4 Hz), 4.99 (1H *trans*, app td, *J*=12.1, 11.0, 4.2 Hz), 5.94 (1H *cis*, d, *J*=4.0 Hz), 6.30 (1H *trans*, d, *J*=11.0 Hz), 6.98 (1H *cis*, d, *J*=7.0 Hz), 7.20–7.34 (3H *cis* and 4H *trans*, m), 7.43 (1H *trans*, m), 7.52 (1H *cis*, m), 7.61–7.79 (2H *cis* and 2H *trans*, m), 8.05–8.19 (1H *cis* and 1H *trans*, m); ^{13}C NMR ($CDCl_3$) δ 19.41, 37.64, 38.40, 49.02, 53.97, 86.64, 89.57, 124.52, 124.68, 125.40, 125.81, 127.01, 127.25, 127.44, 127.73, 128.78, 128.83, 129.05, 129.59, 131.08, 131.36, 131.81, 132.14, 133.42, 133.59, 133.69, 134.49, 135.35, 136.44, 139.10 (two pairs of carbons are accidentally isochronous); MS(ESI): *m*/*z* 340.2 (M+Na)$^+$, 316.2 (M−1). Anal. Calcd for $C_{16}H_{15}NO_4S$: C, 60.6; H, 4.8; N, 4.4%. Found: C, 60.6; H, 4.7; N, 4.5%.

4.4.3. 4-Nitro-3-(*m*-tolyl)thiochroman *S*,*S*-dioxide (2c). (76 mg, 80%, mixture of *trans*:*cis* isomers 1:1.3). White solid, mp 179–180 °C (ethanol); ν_{max} (Nujol) 1552, 1300, 1265, 1244, 1219, 1195, 1155, 1129, 1073 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.37 (3H *cis* and 3H *trans*, 2 s overlapped), 3.55 (1H *cis* and 1H *trans*, overlapping multiplets), 3.71 (1H *trans*, dd, *J*=13.8, 12.5 Hz), 4.39 (1H *cis*, ddd, *J*=13.8, 4.1, 2.4 Hz), 4.56 (1H *trans*, app td, *J*=12.5, 11.0, 3.5 Hz), 4.72 (1H *cis*, app t, *J*=13.8, 13.6 Hz), 5.99 (1H *cis*, d, *J*=4.1 Hz), 6.14 (1H *trans*, d, *J*=11.0 Hz), 6.98–7.78 (7H *cis* and 7H *trans*, m), 8.09 (1H *cis* and 1H *trans*, m); ^{13}C NMR (CD_3COCD_3) δ 21.38, 41.54, 44.64, 49.24, 53.41, 89.70, 91.88, 124.69, 124.76, 125.19, 125.47, 128.09, 128.86, 129.18, 129.39, 129.81, 130.04, 130.08, 130.32, 130.89, 131.81, 132.84, 134.16, 134.45, 137.54, 138.15, 139.53, 139.84, 139.88, 140.53 (two pairs of carbons are accidentally isochronous); MS(ESI): *m*/*z* 340.2 (M+Na)$^+$, 316.1 (M−1). Anal. Calcd for $C_{16}H_{15}NO_4S$: C, 60.6; H, 4.8; N, 4.4%. Found: C, 60.4; H, 4.7; N, 4.4%.

4.4.4. 4-Nitro-3-(*p*-tolyl)thiochroman *S*,*S*-dioxide (2d). (84 mg, 88%, mixture of *trans*:*cis* isomers 1:1.2). White solid, mp 194–196 °C (ethanol); ν_{max} (Nujol) 1553, 1513, 1402, 1366, 1343, 1302, 1264, 1247, 1225, 1158, 1131, 1073 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.37 (3H *cis* and 3H *trans*, 2 s overlapped), 3.54 (1H *cis*, dd, *J*=13.4, 2.2 Hz), 3.58 (1H *trans*, dd, *J*=14.3, 4.1 Hz), 3.71 (1H *trans*, dd, *J*=14.3, 12.0 Hz), 4.40 (1H *cis*, ddd, *J*=13.6, 4.4, 2.2 Hz), 4.57 (1H *trans*, app td, *J*=12.0, 11.0, 4.1 Hz), 4.72 (1H *cis*, app t, *J*=13.6, 13.4 Hz), 5.97 (1H *cis*, d, *J*=4.4 Hz), 6.10 (1H *trans*, d, *J*=11.0 Hz), 7.06–7.78 (7H *cis* and 7H *trans*, m), 8.04–8.18 (1H *cis* and 1H *trans*, m); ^{13}C NMR ($CDCl_3$) δ 21.14, 41.05, 42.80, 48.67, 53.57, 88.64, 90.87, 124.47, 124.54, 126.83, 127.03, 127.07, 127.71, 128.58, 129.52, 130.23, 130.34, 131.03, 132.10, 132.45, 133.21, 133.37, 133.68, 138.17, 139.05, 139.12, 139.21 (the methyl carbons of the two isomers are accidentally isochronous); MS(ESI): *m*/*z* 340.3 (M+Na)$^+$, 316.1 (M−1). Anal. Calcd for $C_{16}H_{15}NO_4S$: C, 60.6; H, 4.8; N, 4.4%. Found: C, 60.5; H, 4.8; N, 4.4%. The ^{1}H NMR for the 4-deutero-4-nitro-3-(*p*-tolyl)thiochroman *S*,*S*-dioxide (**2′d**) is analogous to that of **2d** but for the signals at δ 4.40 and 4.57 which are (1H *cis*, dd, *J*=13.6, 2.2 Hz) and (1H *trans*, dd, *J*=12.2, 4.3 Hz), respectively.

4.4.5. 3-(*p*-Chlorophenyl)-4-nitrothiochroman *S*,*S*-dioxide (2f). (79 mg, 78%, mixture of *trans*:*cis* isomers ca. 1:1). White solid, mp 189–195 °C (ethanol); ν_{max} (Nujol) 1552, 1308, 1157, 1131, 1096, 1015 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.52 (1H *cis*, dd, *J*=13.6, 2.2 Hz), 3.58 (1H *trans*, dd, *J*=14.2, 4.4 Hz), 3.70 (1H *trans*, dd, *J*=14.2, 11.8 Hz), 4.42 (1H *cis*, ddd, *J*=13.8, 4.4, 2.2 Hz), 4.60 (1H *trans*, app td, *J*=11.8, 11.0, 4.4 Hz), 4.70 (1H *cis*, app t, *J*=13.8, 13.6 Hz), 5.97 (1H *cis*, d, *J*=4.4 Hz), 6.09 (1H *trans*, d, *J*=11.0 Hz), 7.13–7.80 (7H *cis* and 7H *trans*, m), 8.04–8.17 (1H *cis* and 1H *trans*, m); ^{13}C NMR ($CDCl_3$) δ 40.85, 42.56, 48.44, 53.28, 88.28, 90.53, 124.53, 124.64, 127.02, 127.34, 128.26, 128.41, 128.66, 129.55, 129.86, 129.99, 131.20, 132.28, 133.54, 133.86, 134.70, 135.38, 138.01, 138.90 (two pairs of carbons are accidentally isochronous); MS(ESI): *m*/*z* 360.2 (M+Na)$^+$, 336.2 (M−1). Anal. Calcd for $C_{15}H_{12}ClNO_4S$: C, 53.3; H, 3.6; N, 4.2%. Found: C, 53.2; H, 3.5; N, 4.1%.

4.4.6. 3-(1-Naphthyl)-4-nitrothiochroman *S*,*S*-dioxide (2g). (105 mg, 99%, mixture of *trans*:*cis* isomers 1:3.0). ^{1}H NMR (CD_3COCD_3) δ 3.86 (1H *trans*, dd, *J*=14.1, 2.6 Hz), 3.88 (1H *cis*, dd, *J*=14.0, 2.2 Hz), 4.23 (1H *trans*,

br t, J=13 Hz), 4.78 (1H *cis*, app t, J=14.0, 13.2 Hz), 5.36 (1H *cis*, ddd, J=13.2, 4.1, 2.2 Hz), 5.61 (1H *trans*, br t, J=13 Hz), 6.59 (1H *cis*, d, J=4.1 Hz), 7.03 (1H *trans*, d, J=10.6 Hz), 7.1–8.8 (11H *cis* and 11H *trans*, m) (assignments supported by decoupling experiments). A crystallization from ethanol afforded a white solid, mp 224–226 °C, which was identified as the pure *cis*-diastereoisomer by spectroscopic data; ν_{max} (Nujol) 1551, 1509, 1415, 1305, 1252, 1160, 1133, 1073 cm^{-1}; ^1H NMR (CD_3COCD_3) δ 3.88 (1H, dd, J=14.0, 2.2 Hz), 4.78 (1H, app t, J=14.0, 13.2 Hz), 5.36 (1H, ddd, J=13.2, 4.1, 2.2 Hz), 6.59 (1H, d, J=4.1 Hz), 7.43 (1H, d, J=7.0 Hz), 7.50–7.94 (6H, m), 7.98–8.10 (2H, m), 8.15 (1H, m), 8.56 (1H, m); ^{13}C NMR (CD_3COCD_3) δ 37.69, 49.84, 88.78, 123.36, 124.66, 125.54, 126.44, 127.13, 128.17, 129.54, 130.19, 130.28, 131.24, 131.46, 132.80, 133.40, 134.17, 134.92, 140.57; MS(ESI): *m/z* 376.3 $(M+Na)^+$, 352.2 (M−1). Anal. Calcd for $C_{19}H_{15}NO_4S$: C, 64.6; H, 4.3; N, 4.0%. Found: C, 64.4; H, 4.2; N, 3.9%.

4.4.7. 4-Nitro-3-(2-thienyl)thiochroman *S*,*S*-dioxide (2h). (65 mg, 70%, mixture of *trans*:*cis* isomers 1:0.9). Pale green solid, mp 113–117 °C (ethanol); ν_{max} (Nujol) 1552, 1300, 1246, 1155, 1127, 1069 cm^{-1}; ^1H NMR (CD_3COCD_3) δ 3.87 (1H *trans*, dd, J=14.2, 3.0 Hz), 3.91 (1H *cis*, dd, J=13.6, 2.6 Hz), 4.21 (1H *trans*, dd, J=14.2, 12.6 Hz), 4.57 (1H *cis*, app t, J=13.6, 13.5 Hz), 4.83–4.97 (1H *cis* and 1H *trans*, m), 6.47 (1H *cis*, d, J=4.4 Hz), 6.57 (1H *trans*, d, J=10.2 Hz), 7.10 (1H *cis* and 1H *trans*, m), 7.21 (1H *cis*, m), 7.27 (1H *trans*, m), 7.48–7.57 (2H *cis* and 1H *trans*, m), 7.68–8.12 (3H *cis* and 4H *trans*, m); ^{13}C NMR ($CDCl_3$) δ 37.24, 38.73, 49.56, 53.90, 88.35, 91.32, 124.43, 124.50, 126.09, 126.20, 126.35, 127.00, 127.14, 127.26, 127.58, 127.66, 127.90, 129.63, 131.22, 132.27, 133.47, 133.78, 137.36, 138.07, 138.43, 138.83; MS(ESI): *m/z* 332.2 $(M+Na)^+$, 308.2 (M−1). Anal. Calcd for $C_{13}H_{11}NO_4S_2$: C, 50.5; H, 3.6; N, 4.5%. Found: C, 50.5; H, 3.5; N, 4.6%.

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Enantioselective synthesis and absolute stereochemistry of both the enantiomers of *trans*-magnolione, a fragrance structurally related to *trans*-methyl jasmonate☆,☆☆

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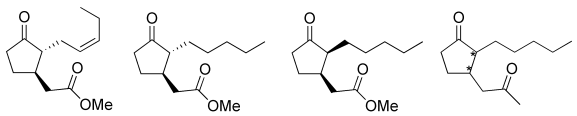
Abstract—Both enantiomers of the *trans* stereoisomer of magnolione **4** have been prepared by asymmetric Michael addition of ethyl acetoacetate to 2-pentylcyclopentenone, followed by hydrolysis/decarboxylation. The Michael reaction occurs under solid/liquid phase transfer catalysis in the presence of *N*-methylanthracenylquininium (or quinidinium) chloride. Enantiomeric excesses up to 76% are obtained. The *trans* structure of the compounds has been fully established by a careful NMR analysis, while the absolute configuration has been assigned as (2*S*,3*S*) for (+)-**4** by the analysis of the CD spectrum.

1. Introduction

(−)-*trans*-Methyl jasmonate (**1**), a natural fragrance isolated from *Jasminum grandiflorum L.*,[1] as well as (−)-*trans*-methyl dihydrojasmonate (**2**) and (+)-*cis*-methyl dihydrojasmonate (**3**), are compounds largely used in the perfume industry owing to their important olfactory properties (jasmine-like fragrances). Magnolione (**4**) is related both in structure and in odour to methyl dihydrojasmonates. In fact, **4** shows an increased odour strength, a better stability, and a more floral, intense, jasmine note (Scheme 1).[2]



(-)-*trans*-methyl jasmonate **1** | (*R*,*R*)-Methyl dihydrojasmonate **2** | (*S*,*R*)-Methyl dihydrojasmonate **3** | Magnolione **4**

Scheme 1.

Until now, magnolione **4** has been prepared and used in the perfume industry as a mixture of stereoisomers: the only known synthetic procedure involves the Michael addition of ethyl acetoacetate to 2-pentyl-2-cyclopenten-1-one (**5**), catalysed by sodium ethoxide.[3] The Michael adduct is successively hydrolysed and decarboxylated to afford the desired compound **4**. Clearly, in this way, a mixture of four diastereoisomers (two *trans* and two *cis* antipodes) results, owing to the presence of the two stereogenic centres at the 2 and 3 positions of the five membered ring. Since the single steroisomers of **4** have not been prepared so far (actually not even the *cis*/*trans* ratio has been reported), nothing is known about the structure/odour relationship of this molecule. We therefore started a research project aimed at preparing the single stereoisomers of **4**, in order to test their perfume properties. In this paper we describe the preparation of the *trans*-stereoisomer of **4** in optically active form, establishing the relative and absolute stereochemistry by means of nuclear magnetic resonance and circular dichroism spectroscopies, respectively. Establishing the absolute strereochemistry of these compounds is certainly of particular value considering that for the related jasmonates the true floral odour is limited to the isomers with a (*R*) configured C(3) carbon atom. So one could expect that in the couple of the *trans* stereoisomers, only the (2*R*,3*R*) configured compound should show the requested perfume properties.

2. Results and discussion

We reasoned that a stereoselective Michael addition of ethyl acetoacetate to 2-pentyl-2-cyclopenten-1-one (**5**) could be carried out following the same procedure which allows the stereoselective Michael addition of dimethyl malonate to **5**, to prepare the *trans* stereoisomers of methyl dihydrojasmonate,

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Keywords: Magnolione; Enantioselective Michael addition; Fragrances; Phase transfer catalysis; Absolute configuration.

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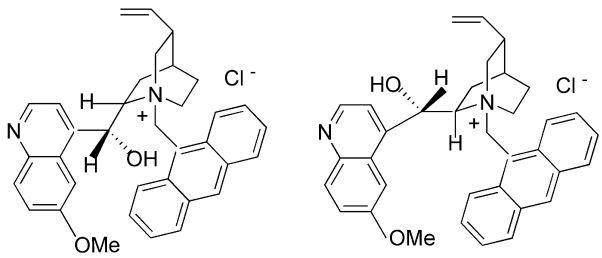
2.[4] Such enantioselective Michael addition has been carried out under phase-transfer catalysis employing, as chiral catalyst, a quaternary ammonium salt derived from quinine or quinidine, *N*-methylanthracenylquininium **6** (or quinidinium **7**) chloride, reported in Scheme 2, affording the best ee's (up to 90%).



N- methyl anthracenyl quininiuim chloride **6**

N- methyl anthracenyl quinidiniuim chloride **7**

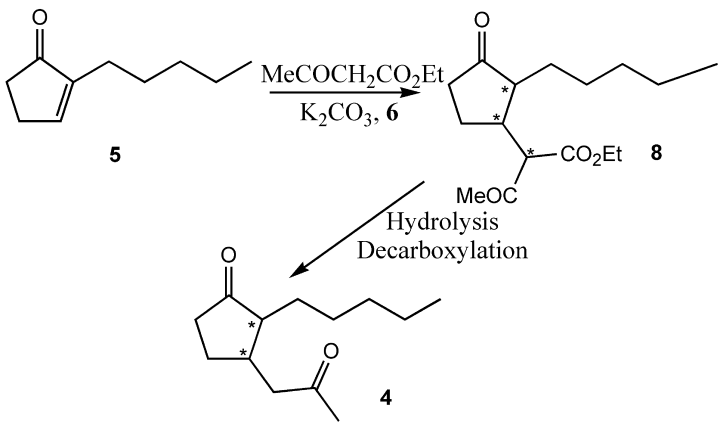
Scheme 2.

The addition of ethyl acetoacetate was carried out, as reported for the synthesis of *trans* methyl dihydrojasmonate, at −20 °C, by adding potassium carbonate (0.28 equiv.) and *N*-methylanthracenyl quininium chloride **6** (0.11 equiv.) to a solution of **5** (1 equiv.) and ethyl acetoacetate (26 equiv.) without any other organic solvent. The resulting mixture was strongly stirred for several days, but no reaction occurred. In the same conditions, at room temperature, the Michael adduct, **8**, was obtained after 96 h with 70% of conversion (GC) and isolated in 65% yield, after column chromatography. With longer time (up to 7 days) the reaction did not proceed further. Gas-chromatographic analysis of purified product reveals the presence of three components in ratio 90/6/4: it is reasonable (vide infra) to assign the major peak to the mixture of four *trans*-stereoisomers, while the two minor components could result from the contribution of the two couples of *cis*-diastereoisomers: in fact **8** possesses three stereogenic centres and then four couples of diastereoisomers have to be expected. Compound **8** has been hydrolysed and decarboxylated to **4**, following the patented method,[3] that is, by adding an equal amount of water and heating the mixture in autoclave up to 180 °C. Product **4** was obtained in 58% yield after purification by column chromatography (Scheme 3).

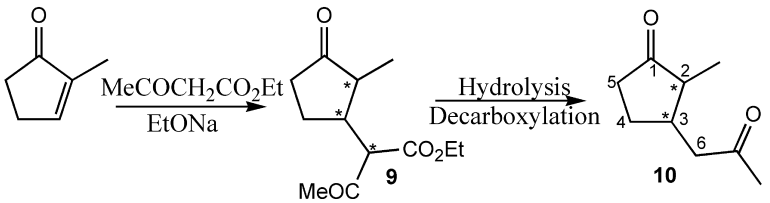
Taking into account that the Michael addition of dimethyl malonate to **5** gives[4] *trans*-methyl dihydrojasmonate it is logical to assume that the same diastereoselection occurs in the present reaction. However an independent structural assignment has been done by means of ^{1}H NMR spectroscopy. The ^{1}H NMR spectrum of **4** is quite complex, since there is a lot of overlap among the proton signals and this makes the structural analysis quite difficult. We thus initially studied the model compound **10**. It has been prepared in racemic form by Michael addition of ethyl acetoacetate to 2-methyl-2-cyclopenten-1-one, using sodium ethoxide as base, in refluxing ethanol for 3 h: **10** is obtained, after hydrolysis and decarboxylation, in 80% yield (Scheme 4).

The ^{1}H NMR spectrum was carefully analysed to assign confidently all the protons present in the molecule. The multiplet at δ 1.68 has been attributed to H2 and showed a ^3J coupling of 11.8 Hz with the vicinal hydrogen H3 at δ 2.04. Molecular mechanics calculations[5] (Fig. 1-top) suggest that for the *cis* isomer it is expected a dihedral angle H2–H3 of −30° to which is associated a ^3J=7.7 Hz, whereas for the more stable *trans* isomer such dihedral angle rises to −164° and the ^3J becomes 11.2 Hz.

The good agreement between the vicinal couplings in the



Scheme 3.



Scheme 4.

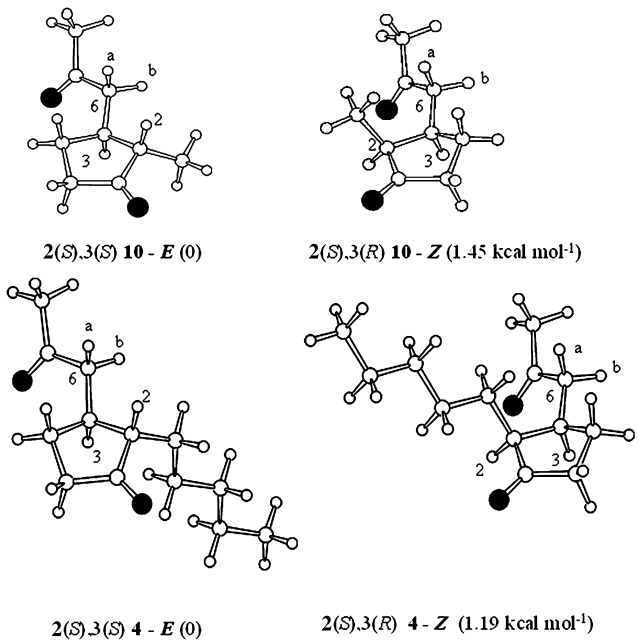


Figure 1. Most stable conformations of the *trans* and *cis* isomers of **10** (top) and **4** (bottom), as obtained by molecular mechanics (MMX) calculations.

computed structures and the determined ^3J=11.8 Hz suggested that in **10** the two substituents on the ring have a *trans* geometry.[6] To substantiate these findings we carried out NOE experiments[7] where the protons at δ 1.68, H2, and δ 0.98, methyl in position 2 of the ring, have been irradiated. Instead the H3 could be not selectively irradiated because of the overlapping with another ring proton. The irradiation of H2 has shown only enhancements of the signals at δ 2.42, 2.73 (H6a and H6b of the CH_2COMe moiety,[6] Fig. 2).

Differently, the irradiation of the methyl at δ 0.98 has produced the enhancements of H6b, at δ 2.73, and H3, at 2.04. These results imply that H2 and the CH_2COMe moieties lie on the same side of the ring, whereas the methyl and H3 must be both situated on the other side and confirm thus that **10** have a *trans* geometry. The same approach was also used to ascertain the geometry for **4**, however the overlapping between the multiplets observed in the ^{1}H NMR spectrum has prevented us from assigning all the protons confidently. Nevertheless, the more isolated multiplets at δ 1.74, 2.46 and 2.75 could be safely and directly assigned to H2 and the geminal protons (H6a, H6b) of the CH_2COMe substituent, by comparison with the chemical shifts found in **10**. The analysis of the H2 multiplet gave a ^3J=10.5 Hz indicating again a *trans* geometry. Molecular mechanics calculations were then carried out to compare the experimental ^3J=10.5 Hz with those computed for the two isomers of **4** (Fig. 1-bottom). The most stable structures obtained showed that in the *cis* isomer H2–H3 are separated by 2.36 Å and form a dihedral angle of −34° to which corresponds a ^3J=7.1 Hz; whereas in the *trans* isomer the same interproton distance rises to 3.08 Å and the two protons are nearly *anti* with a dihedral angle of −167° and a ^3J=11.6 Hz.[8] NOEs experiments have been carried out on several protons and the irradiation of H2 gave the same trend of enhancements observed in **10** (Fig. 3).

The observed NOEs are dependent upon the sixth power of

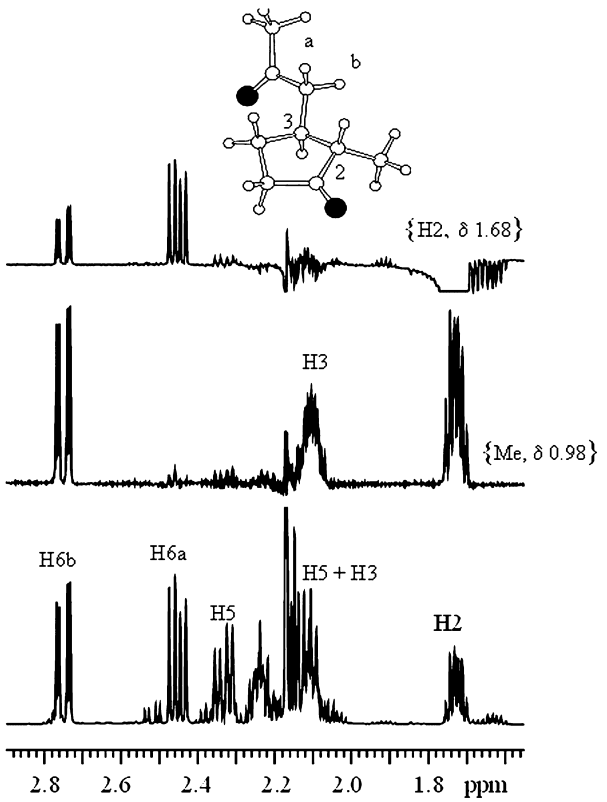


Figure 2. ^{1}H-NOE experiments of **10** irradiating H2 at δ 1.68 (top), 2-Me at δ 0.98 (center) and the ^{1}H NMR (600 MHz) spectrum of **10** is showed at the bottom.

the reciprocal interproton distances.[9] The ratios of independent NOEs were compared in Table 1 with the inverse of the same computed interproton distances for the *cis* and the *trans* isomers of **4**, in order to evaluate the agreement between the experimental NOE and the proposed structure.

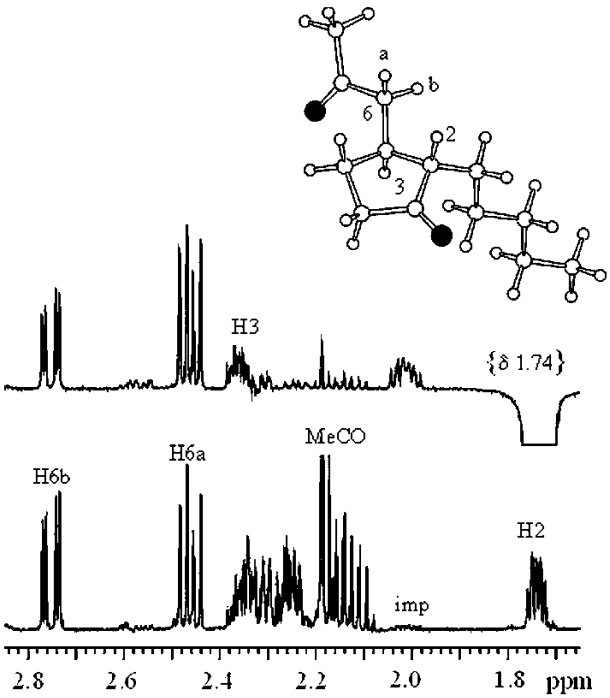


Figure 3. ^{1}H-NOE enhancements observed in **4** by irradiating H2 (δ 1.74, top); ^{1}H NMR spectrum of **4** at 600 MHz (bottom).

Table 1. Columns 1 and 2 refer to the NOE experiments carried out for **4**. In the reported couples of protons the first refer to the irradiated and the second to the observed ones. Columns 3, 4 and 5 refer to the reciprocal computed distances for the two isomers of the same proton couples considered in the NOEs

NOE	Ratio	Distances	*trans*	*cis*
(H2H6b/H2H3)$^{1/6}$	1.06	H2H3/H2H6b	1.05	0.58
(H2H6a/H2H3)$^{1/6}$	1.16	H2H3/H2H6a	1.24	0.65
(H2H6a/H2H6b)$^{1/6b}$	1.09	H2H6b/H2H6a	1.18	0.89
(H6bH3/H6bH2)$^{1/6}$	1.15	H6bH2/H6bH3	1.16	1.64

A good agreement between those ratios could be achieved only for the *trans* geometry. The ee of *trans*-**4**, obtained by the reaction with N-methyl anthracenyl quininium chloride **6**, has been determined to be 76% by means of HPLC upon the chiral stationary phase (Chiralcel OJ-H, hexane/2-propanol=99:1, flow 0.5 mL/min, λ=280 nm). The absolute configuration of *trans*-(+)-**4** has been tentatively assigned as (2*S*,3*S*) taking into account that in the same experimental conditions this enantiomer is obtained in the Michael addition of dimethyl malonate to **5**. The use of the quinidinium salt **7** afforded the (2*R*,3*R*) antipode with 60% ee and 50% yield, determined in the same conditions. Also in this case a 'pseudoenantiomeric effect'[10] was observed when testing the quinidinium catalyst **7** in the reaction, compared to the stereoselectivity of the quininium catalyst **6**, since yield and ee were slightly lower. However, the above configurational assignment has been fully confirmed by a non empirical analysis of the CD spectrum of (+)-**4**. The absorption and CD spectra of (+)-**4**, recorded in hexane between 350 and 250 nm, are reported in Figure 4.

In the UV absorption spectrum, a band at 290 nm ($\varepsilon_{max}\sim60$) is clearly observable: this band, taking into account its position and intensity, can be safely assigned[11] to the n$-\pi^*$ transition of the saturated ketone chromophore. In the CD spectrum a positive Cotton effect, provided with a clear vibrational structure, and having $\Delta\varepsilon_{max}=+1.9$, is present at about ~300 nm. In principle, taking into account that in the structure of (+)-**4** two different ketone chromophores are present, one should think that the positive Cotton effect observed at ~300 nm, results from the contributions of both these chromophores, that is, a first one inserted in the ring and a second one, linked to the 3 position of the ring through a methylene unit, and then having a large conformational freedom. It is well known that simple aliphatic ketones possess weak Cotton effects at about 300 nm, for instance (*S*)-4-methylhexan-3-one shows,[12] at 299 nm, $\Delta\varepsilon=+0.016$ in heptane. On the contrary, (−)-(2*R*,3*S*)-dimethylcyclopentanone has,[13] in the same spectral region, $\Delta\varepsilon\sim-1.8$. Therefore, we can safely assume that the positive Cotton effect measured for (+)-**4** is dominated by the 2,3-disubstituted-cyclopentanone chromophore: in particular, since the C=O linked to the 3 position does not contribute significantly to the CD values at about 300 nm, we can reasonably treat the above substituents as simple aliphatic (methyl) groups. Thus, since (2*R*,3*S*)-dimethylcyclopentanone has[13] a negative CD band at 300 nm, so (+)-**4** must have the opposite (i.e., (2*S*,3*S*), for a formal inversion of configuration following the CIP rules) absolute configuration. The knowledge of the CD spectrum of (2*R*,3*S*)-dimethylcyclopentanone allows us to make a reliable, qualitative configurational assignment for (+)-**4**. However, we decided to do a quantitative analysis of the CD spectrum of (+)-**4**, in order to render it more safe and thus more convincing. We calculated the CD spectrum of (2*R*,3*S*)-dimethylcyclopentanone in the 350–250 nm spectral range. To this end, a conformational analysis of (2*R*,3*S*)-dimethylcyclopentanone was carried out with Gaussian98 package[14] by a DFT method, which uses the B3LYP functional and the 6-31G* basis set. Two conformations with relative populations of 98% (A) and 2% (B) have been found (Fig. 5).

The reduced rotational strength R_{rid} allied to the n$-\pi^*$ transition of (2*R*,3*S*)-dimethylcyclopentanone has been calculated at TDDFT/B3LYP/SV(P) level in the velocity formalism (to get results which are independent of the

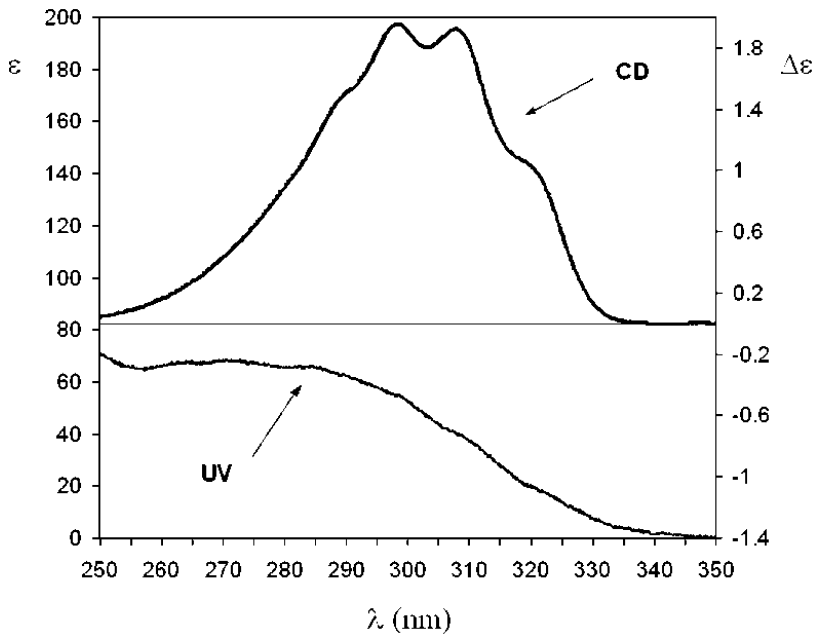


Figure 4. Absorption (lower curve) and CD (upper curve) of (+)-**4** in hexane. CD values have been corrected to 100% ee.

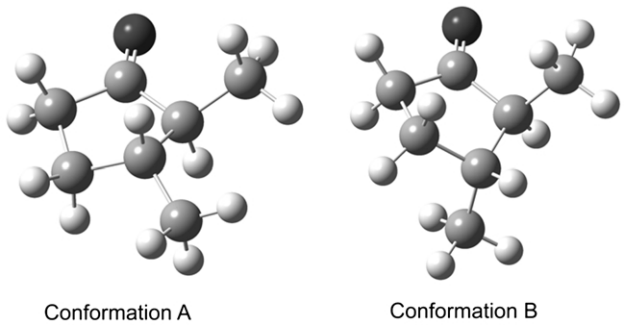


Figure 5. Two calculated conformations (DFT/B3LYP/6-31G*) for (2*R*,3*S*)-dimethylcyclopentanone.

choice of the origin[15]), using the TURBOMOLE 5.6 package,[16] obtaining: for conformation A, R_{rid}=+9.5; for conformation B, R_{rid}=−12.

In Figure 6, the calculated CD spectrum assuming a Boltzmann average of the data relative to the two populations and assuming a Gaussian band shape (with width of the band at half height of 0.15 eV) is reported, together with the experimental one.

Clearly the excellent agreement between calculated and experimental data adds further support to the (2*S*,3*S*) assignment.

3. Conclusions

The most important goal achieved in the present investigation is that a simple route, based on the asymmetric addition of ethyl acetoacetate to 2-pentyl-2-cyclopenten-1-one, under phase transfer catalysis, has been set up to obtain both the *trans* stereoisomers of magnolione **4** in optically active form. In addition, the products obtained have been fully characterized as far as the relative and absolute configuration are concerned: so (+)-**4** has been assigned as the (2*S*,3*S*) stereoisomer. In our opinion even if the diastereomeric and enantiomeric purities reached here are not enough for significant odour tests, this investigation describes the first way to access pure *trans* stereoisomers of **4**. However these results represent a fundamental step to study the structure/odour relationship of **4** in order to make available to the perfume industry other valuable ingredients. Work is now in progress to improve the stereoisomeric purity of *trans*-**4** and to set up an efficient synthesis of *cis*-**4**.

4. Experimental

4.1. General procedures

^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian-Inova spectrometer. UV and CD spectra were recorded in hexane solution on a JASCO J-600 spectropolarimeter. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. Enantiomeric purity of compound **4** was checked by HPLC analyses on a Daicel Chiralcel OJ-H chiral stationary phase using a 99:1 hexane/isopropanol mixture as eluent. Enantiopure *N*-methyl anthracenyl quininium, **6** (or quinidinium, **7**) chloride were prepared according to literature procedures.[4] 2-Pentyl-cyclopenten-1-one and ethyl acetoacetate were distilled before their use. K_2CO_3 was pulverized and dried under vacuum. Analytical TLC were performed on 0.2 mm silica gel plates Merck 60 F-254 and column chromatographies were carried out with silica gel Merck 60 (70–230 mesh). Gas chromatographic analyses were carried out on GC/MS Hewlett–Packard 5080 series II, detector HP 5971, column Supelco 57300-U (polydimethylsiloxane phase, PDMS).

4.1.1. 3-Oxo-2-(3′-oxo-2′-pentyl-cyclopentyl)-butyric acid ethyl ester (8). To a solution of 2-pentyl-2-cyclopenten-1-one (**5**) (2.03 g, 13.3 mmol) in ethyl acetoacetate (45 mL, 350 mmol, 26 equiv.), the catalyst (**6** or **7**, 822 mg,

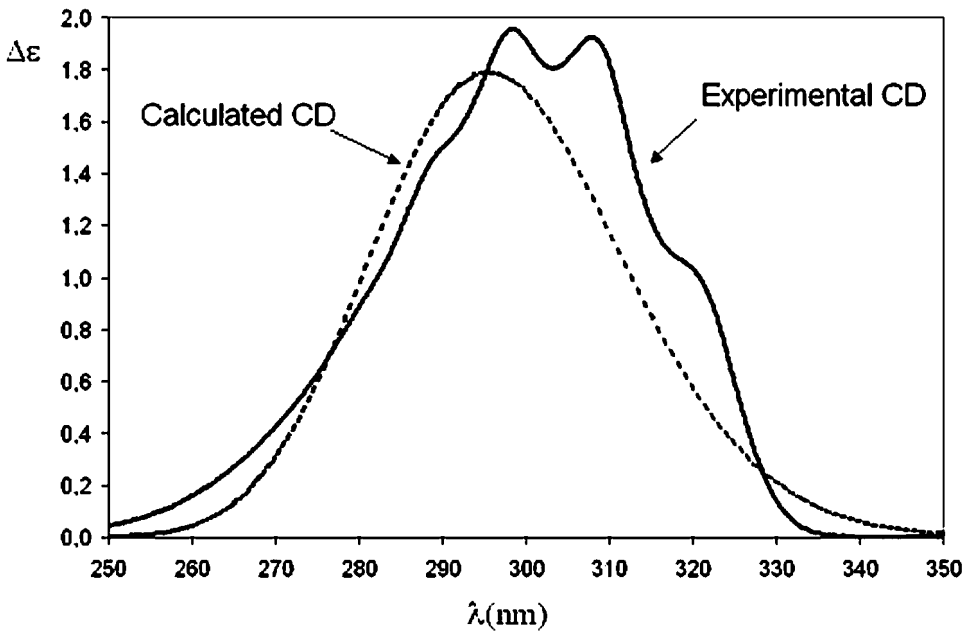


Figure 6. Experimental CD in hexane (solid line) of (+)-**4** and calculated TDDFT/B3LYP/SV(P) (dashed line) of (2*R*,3*S*)-dimethylcyclopentanone.

1.49 mmol, 0.11 equiv.), and potassium carbonate (540 mg, 3.92 mmol, 0.28 equiv.) were successively added. After magnetic stirring at room temperature for 4 days, the reaction mixture was diluted with diethyl ether (400 mL). The organic layer was washed successively by aqueous HCl 10% (2×100 mL), water (100 mL) and brine (2×100 mL). The organic layer was then dried over anhydrous Na_2SO_4, filtered and evaporated. The crude pale yellow oil was distilled under reduced pressure to remove ethyl acetoacetate. Finally chromatography on silica gel (eluent: petroleum ether 70/diethyl ether 30) of the crude residue yielded 2.44 g (65%) of a colourless oil. $[\alpha]_D^{20}=+8.4$ ($c=1.1$; $CHCl_3$). The ^1H and ^{13}C NMR spectra have been characterized by a mixture of the four expected diasteroisomes, of which only the two more abundant have been accounted for their description.

^1H NMR (600 MHz, $CDCl_3$): δ 0.87 (t, $J=7.3$ Hz, 3H); 1.23 (m, 5H); 1.30 (t, $J=7.1$ Hz, 3H); 1.40–1.45 (m, 2H); 1.57–1.70 (m, 2H); 1.96 (m, 1H); 2.16 (m, 2H); 2.27 (s, 3H); 2.33 (m, 1H); 2.65–2.73 (m, 1H); 3.47–3.57 (d, $J=7.1$ Hz, 1H); 4.22 (q, $J=7.3$ Hz, 2H). ^{13}C NMR (150.9 MHz, $CDCl_3$). Isomer **1** δ 13.97 (CH_3); 14.09 (CH_3); 22.41 (CH_2); 23.91 (CH_2); 26.04 (CH_2); 26.04 (CH_2); 28.43 (CH_2); 29.60 (CO*C*H_3); 31.93 (CH_2); 37.18 (CH_2); 39.80 (CH); 52.24 (CH); 61.50 (CO*C*H_2); 62.18 (CH); 168.55 (quat, COO); 201.88 (quat, CO); 219.14 (quat, CO). Isomer **2** δ 13.96 (CH_3); 14.03 (CH_3); 22.39 (CH_2); 24.95 (CH_2); 24.95 (CH_2); 25.89 (CH_2); 28.78 (CH_2); 29.56 (CO*C*H_3); 32.00 (CH_2); 37.03 (CH_2); 39.72 (CH); 52.51 (CH); 61.66 (CO*C*H_2); 63.84 (CH); 168.70 (quat, COO); 201.88 (quat, CO); 219.02 (quat, CO). MS (EI): *m*/*z* 282 (M^+, 1), 239 (1), 212 (1), 169 (62), 153 (79), 139 (67), 131 (100), 123 (19), 97 (25), 83 (43), 55 (27), 43 (72). Anal. Calcd for $C_{16}H_{26}O_4$: C, 68.06; H, 9.28. Found: C, 68.0; H, 9.1.

4.1.2. (*S*,*S*)-3-(2′-Oxo-propyl)-2-pentyl-cyclopentanone (4). Compound **8** (2.0 g, 7.0 mmol) in water (4 mL) was introduced in autoclave: the mixture was stirred and warmed up to 180 °C for 4 h. The cooled mixture was diluted with diethyl ether (20 mL) and dried over anhydrous Na_2SO_4; the organic layer was filtrated and evaporated. The crude residue was purified on silica gel (eluent: petroleum ether 60/diethyl ether 40) to obtain 860 mg (58%) of light yellow oil. $[\alpha]_D^{20}=+22.0$ ($c=1.10$; $CHCl_3$); ee 76%; ^1H NMR (600 MHz, $CDCl_3$): δ 0.88 (t, $J=7.1$ Hz, 3H); 1.25 (m, 2H); 1.29 (m, 3H); 1.38 (m, 2H); 1.53 (m, 2H); 1.74 (m, $J=10.5$, 5.6, 1.5 Hz, 1H); 2.13 (m, $J=8.7$, 10.9, 18.6 Hz, 1H); 2.19 (s, 3H); 2.25 (m, 1H); 2.32 (m, 1H); 2.35 (m, 1H); 2.46 (dd, $J=9.0$, 16.9 Hz, 1H); 2.75 (dd, $J=4.2$, 16.9 Hz, 1H); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ 13.85 (CH_3); 22.30 (CH_2); 26.26 (CH_2); 27.24 (CH_2); 27.77 (CH_2); 30.45 (CO*C*H_3); 36.86 (CH); 37.72 (CH_2); 47.82 (CO*C*H_2); 54.12 (CH); 207.65 (quat, CO); 220.09 (quat, CO). MS (EI): *m*/*z* 210 (M^+, 4), 153 (52), 140 (21), 125 (12), 97 (18), 82 (100), 55 (18), 43 (49). Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.21; H, 10.23.

4.1.3. 2-(2-Methyl-3-oxo-cyclopentyl)-3-oxo-butyric acid ethyl ester (9). To a solution of sodium ethoxide in ethanol, prepared by dissolving sodium (185 mg, 8.05 mmol) in ethanol (10 mL), ethyl acetoacetate (4.4 mL, 32 mmol) was added dropwise at room temperature. 2-Methylciclopenten-1-one (2.25 g, 23.5 mmol) was added successively and the mixture was refluxed for 3 h. To the solution cooled at room temperature acetic acid (2 mL) was added and the mixture was poured onto sodium chloride solution of 10% (50 mL). The mixture was extracted with diethyl ether (2×50 mL) and the organic layer was washed more times with brine (up to neutrality), dried over anhydrous Na_2SO_4, filtrated and evaporated. Excess of ethyl acetoacetate was removed by distillation at reduced pressure and the crude residue was purified by chromatography on silica gel (eluent: petroleum ether 70/diethyl ether 30) to affording **9** with 80% yield. The ^1H and ^{13}C NMR spectra have been characterized by a mixture of the four expected diastereoisomers, of which only the two more abundant have been accounted for their description.

^1H NMR (600 MHz, $CDCl_3$): δ 1.02 (d, $J=7.0$ Hz, 3H); 1.27 (t, $J=7.1$ Hz, 3H); 1.52–1.63 (m, 1H); 1.78–1.93 (m, 1H); 2.15 (m, 2H); 2.25 (s, 3H); 2.34 (m, 1H); 2.44 (m, 1H); 3.48–3.55 (d, $J=7.0$ Hz, 1H); 4.20 (q, $J=7.1$ Hz, 2H). ^{13}C NMR (150.9 MHz, $CDCl_3$). Isomer **1** δ 13.19 (CH_3); 13.98 (CH_3); 24.27 (CH_2); 29.54 (CO*C*H_3); 36.51 (CH_2); 43.25 (CH); 48.00 (CH); 61.51 (CH_2); 63.87 (CH); 168.44 (quat, COO); 201.71 (quat, CO); 220.0 (quat, CO). Isomer **2** δ 13.56 (CH_3); 14.09 (CH_3); 25.29 (CH_2); 29.56 (CO*C*H_3); 36.63 (CH_2); 43.11 (CH); 47.95 (CH); 61.64 (CH_2); 62.40 (CH); 168.69 (quat, COO); 202.00 (quat, CO); 219.54 (quat, CO). MS (EI): *m*/*z* 226 (M^+,1), 181 (29), 169 (10), 139 (15), 130 (53), 110 (20), 97 (100), 81 (13), 55 (13), 43 (60). Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.3; H, 7.9.

4.1.4. 2-Methyl-3-(2-oxopropyl)cyclopentanone (10). 2-(2-Methyl-3-oxo-cyclopentyl)-3-oxo-butyric acid ethyl ester (**9**) was hydrolysed and decarboxylated by the same procedure used for **8** affording the cyclopentanone (**10**) with 58% yield after purification on chromatography column. ^1H NMR (600 MHz, $CDCl_3$) δ 0.98 (t, 3H, CH_3, $J=7.0$ Hz); 1.30 (m, $J=8.5$, 11.4, 12.6 Hz, 1H); 1.68 (m, $J=7.0$, 11.8, 1.4 Hz, 1H); 2.04 (m, 1H); 2.08 (m, $J=9.1$, 11.5, 19.0 Hz 1H); 2.13 (s, 3H); 2.20 (m, 1H); 2.29 (m, $J=8.5$, 18.7, 1.5 Hz 1H); 2.42 (dd, $J=9.2$, 17.1 Hz, 1H); 2.73 (dd, $J=3.9$, 17.1 Hz, 1H). ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 12.15 (CH_3); 27.30 (CH_2); 30.46 (CO*C*H_3); 37.15 (CH_2); 39.70 (CH); 47.82 (CO*C*H_2); 49.40 (CH); 207.75 (quat, CO); 220.11 (quat, CO). MS (EI): *m*/*z* 154 (M^+, 5), 111 (2), 97 (100), 96 (32), 55 (19), 43 (69). Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.58; H, 9.28.

5. Supplementary Material

Details about the optimized input geometries are available.

Acknowledgements

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5. The molecular mechanics calculations were performed using the MMX force field as implemented in PC Model 7.0, Serena Software, Bloomington, IN 47402-3076.
6. From the computed *trans* structure of **10** have also been derived data for the two geminal hydrogens of the CH_2COMe moiety. Indeed, it has been observed that one proton, 6a, is *anti* respect to H3 (dihedral angle of 178° ^3J=12.3 Hz) and distant 2.5 Å from H2. Whereas, the other geminal proton, 6b, is *gauche* (dihedral angle 64° ^3J=2.7 Hz) and distant 2.93 Å from H2. According to the computed and experimental ^3J, H6a and H6b have been assigned at δ 2.42 and 2.73, respectively.
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8. From the calculated minimum energy structures, angles and distances for the geminal protons of the CH_2COMe moiety have be also determined. In the *cis* isomer the proton H6a showed a dihedral angle of 175°, a ^3J with H3 of 12.3 Hz and a distance from H2 of 3.64 Å. The other proton (H6b) is *gauche* to H3 and showed a dihedral angle of 59°, a ^3J=3.4 Hz and a distance from H2 of 4.06 Å. In the *trans* isomer the same geometrical data for H6a become 178°, 12.3 Hz and the distance from H2 is now 2.49 Å; whereas for H6b, *gauche* to H3, it has been found 64°, ^3J=2.6 Hz and a distance from H2 of 2.945 Å. By comparison between computed and experimental ^3J, H6a and H6b were assigned at δ2.46 and 2.75, respectively.
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An efficient synthesis of cytostatic mono and bis-alkynylpyrimidine derivatives by the Sonogashira cross-coupling reactions of 2,4-diamino-6-iodopyrimidine and 2-amino-4,6-dichloropyrimidine

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Abstract—A series of 6-alkynyl-2,4-diaminopyrimidine derivatives bearing various substituents at alkynyl moiety was prepared by the Sonogashira cross-coupling reaction of 2,4-diamino-6-iodopyrimidine using $Pd(PPh_3)_2Cl_2$ as catalyst. The same reaction was applied to 2-amino-4,6-dichloropyrimidine. This compound on reaction with 1 equiv. of alkyne gave 6-alkynyl-2-amino-4-chloropyrimidine derivatives as main products, while reaction with three equivalents of alkyne afforded predominantly 4,6-bis-alkynyl-2-aminopyrimidines. Some of the resulting alkynyl pyrimidines showed considerable cytostatic activity.

1. Introduction

Alkynes are versatile intermediates in synthesis[1,2] as well as an important functional moiety in a wide range of biologically active compounds.[3] The development of methods for alkynyl group introduction into organic molecules is an important target. The widely used Sonogashira reaction typically employs a palladium catalyst and copper iodide to couple a terminal alkyne with an aryl halide.[4] Attractive features of this method include its experimental simplicity and its high atom-economy and functional-group tolerance.[5]

The application of the Sonogashira reaction to pyrimidine bases bearing amino group(s) could provide a broad spectrum of various substituted pyrimidines. Such derivatives may lead to the potential biologically active nucleoside analogues,[6,7] adenosine kinase inhibitors,[8] covalent base-pairs[9,10] or compounds related to enediyne antitumor antibiotics.[11]

2. Results and discussion

In this paper, we report on the synthesis of 2,4,6-trisubstituted pyrimidines via the Sonogashira reaction. We were particularly interested in the introduction of an alkynyl moiety into the 6-position of 2,4-diaminopyrimidine. The only known related cross-coupling is the Suzuki procedure of 2,4-diamino-6-chloropyrimidine with aryl boronic acids.[12] This type of compounds had been synthesized earlier by condensation reactions.[13,14] The purpose of our study—pyrimidines with C–C bond at position 6—required a development of cross-coupling methodology utilizing the Sonogashira reaction.

As a suitable starting material commercially available 2,4-diamino-6-chloropyrimidine was chosen; however, under the standard Sonogashira conditions (ethyne derivative, CuI, DMF, $Pd(PPh_3)_4$ or $Pd(PPh_3)_2Cl_2$, Et_3N or AcOK or Bu_4NF) this compound was unreactive. The problem was solved by conversion of 6-chloro derivative to 2,4-diamino-6-iodopyrimidine by procedure using hydroiodic acid (40%) and sodium iodide.[8] This iodo derivative reacted smoothly at room temperature with a series of substituted ethynes in dimethylformamide in the presence of triethylamine, CuI and $Pd(PPh_3)_2Cl_2$ as a catalyst to give 6-substituted pyrimidines **1a**–**1g** in good yields (Scheme 1).

Identical Sonogashira conditions were a method of choice for preparation of 2-amino-6-alkynyl-4-chloropyrimidine and 2-amino-4,6-bis(alkynyl)pyrimidine derivatives **2** and **3** (Scheme 2). In this case we used 1.1 (Method A) or 3.3 (Method B) equivalents of phenyl-, trimethylsilyl- or hydroxymethyl acetylene. The starting commercially

Keywords: Pyrimidines; Cross-coupling; Sonogashira reaction; Alkynes; Cytostatic activity.
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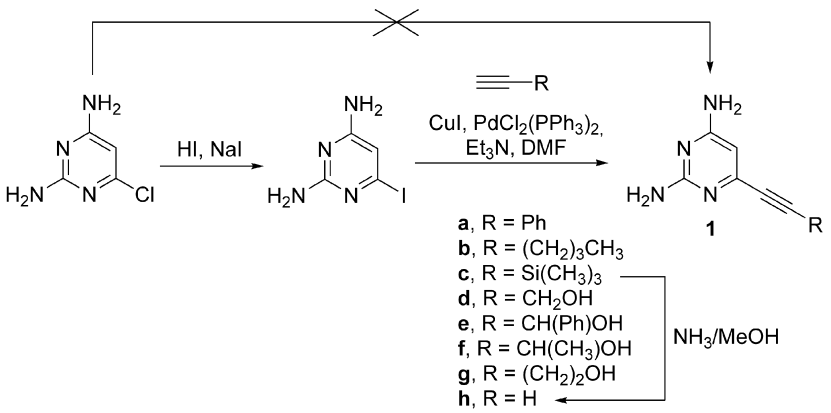
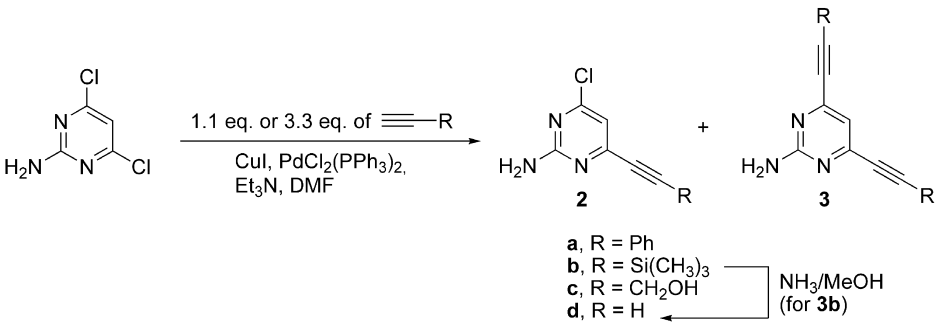


Scheme 1.



Scheme 2.

available 2-amino-4,6-dichloropyrimidine was sufficiently reactive and so the transformation to iodo derivative was not necessary, although the yields of cross-coupling were lower. The selectivity of the mono-alkynylation and bis-alkynylation reaction, taking place under conditions used in Method A and B, respectively, depends on the character of substituent at ethyne group. While the reaction with 1.1 equiv. of ethyne derivative was selective for trimethylsilylethyne and only compound **2b** was isolated, reaction with 3.3 equiv. led selectively to bis-derivatives with phenyl and hydroxymethyl groups **3a** and **3c**. In the remaining cases the both products **2** and **3** were isolated.

The stability in organic solutions of the most of thus prepared compounds was limited. In addition, while the trimethylsilyl derivatives **1c** and **3b** were deprotected under standard conditions in methanolic ammonia to form 2,4-diamino-6-ethynylpyrimidine (**1h**) and 2-amino-4,6-bis(ethynyl)pyrimidine (**3d**), respectively, the attempts to deprotect derivative **2b** under the same conditions led to a complex reaction mixture.

In conclusion, the Sonogashira cross-coupling reaction seems to be the method of choice for C–C bond formation in the positions 4 and 6 of pyrimidine to form 2,4,6-trisubstituted pyrimidines as suitable starting materials for potentially biologically active compounds. To compare the influence of various alkynes on the cross-coupling reaction, the yields of the products **1a**–**1h**, **2a**–**2c** and **3a**–**3c** are summarized in the Table 1.

The title mono and bis-alkynylpyrimidine derivatives **1**, **2** and **3** were tested on their in vitro inhibition of the cell growth in mouse leukemia L1210 cells, human T-lymphoblastoid CCRF-CEM cell line, human promyelocytic leukemia HL-60 cells and human cervix carcinoma HeLa S3 cells (for details see Section 3). The results (Table 2) indicate that compounds **2a**, **3a**, **2c** and **3c** exhibit considerable cytostatic activity (inhibition of the cell growth in vitro) towards human leukemic HL-60 and CCRF-CEM cells, while the L1210 and HeLa S3 cells are less sensitive. The most promising anti-proliferative potency is exerted by compound **3c**. Moderate effects (data not shown) were

Table 1. Summary of the Sonogashira cross-coupling yields

Compound	R	Yield (%)	Compound	Yield (%)	Compound	Yield (%)	R	Method
1a	Ph	84	**2a**	41	**3a**	15	Ph	A
1b	$(CH_2)_3CH_3$	79		—		81		B
1c	$Si(CH_3)_3$	61	**2b**	60	**3b**	—	$Si(CH_3)_3$	A
1d	CH_2OH	61		22		57		B
1e	CH(Ph)OH	66	**2c**	35	**3c**	5	CH_2OH	A
1f	$CH(CH_3)OH$	70		—		39		B
1g	$(CH_2)_2OH$	89			**3d**	36	H (2 steps)	B
1h	H (2 steps)	46						

Table 2. Inhibition of the cell growth in vitro

Compound	IC_{50}, μmol l^{-1}			
	L1210	HL-60	HeLa S3	CCRF-CEM
2a	≫10	6.6	≫10	13.3
3a	≫10	9.0	≫10	6.4
2c	10.9	4.2	10.7	3.8
3c	3.6	2.1	7.6	1.9

observed also for derivatives **1e**, **1h**, **3d** and unstable trimethylsilyl compounds **2b**, **3b**. Their activity can be explained by decomposition under the formation of **2d** and **3d**. The structure-activity relationship of the series of compounds shows that the 4-amino pyrimidines **1** were less active than 4-chloro and 4-alkynyl derivatives **2** and **3**. The active compounds bear mostly unsubstituted ethynyl as the side chain(s) or ethynyl moiety functionalised by phenyl or hydroxymethyl group.

3. Experimental

Unless otherwise stated, solvents were evaporated at 40 °C/2 kPa, and compounds were dried at 2 kPa over P_2O_5. Melting points were determined on a Büchi melting point apparatus. NMR spectra were measured on an FT NMR spectrometer Varian UNITY 500 (^{1}H at 500 M and ^{13}C at 125.7 M frequency) in dimethyl sulfoxide-d_6. Mass spectra were measured on a ZAB-EQ (VG Analytical) spectrometer using FAB (ionization by Xe, accelerating voltage 8 kV, glycerol matrix). 2,4-Diamino-6-chloropyrimidine, 2-amino-4,6-dichloropyrimidine, ethyne derivatives and $Pd(PPh_3)_2Cl_2$ were obtained from Sigma–Aldrich (Praha, Czech Republic). Dimethylformamide was distilled from P_2O_5 and stored over molecular sieves (4 Å) in argon atmosphere.

3.1. 2,4-Diamino-6-ethynylpyrimidines (1a–1g). General procedure

Dimethylformamide (5 ml), the corresponding ethyne derivative (3 mmol) and Et_3N (0.15 ml) were added through septum to an argon purged flask containing 2,6-diamino-6-iodopyrimidine (240 mg, 1 mmol), CuI (10 mg), $PdCl_2$-$(PPh_3)_2$ (50 mg, 0.07 mmol) and the mixture was stirred at room temperature overnight. The solvent was evaporated in vacuo and the residue was chromatographed on a silica gel column (ethyl acetate–methanol) to give compound **1**.

3.1.1. 2,4-Diamino-6-(phenylethynyl)pyrimidine (1a). Yield 180 mg (84%) of a yellow solid, mp 200–203 °C, decomp. IR ν_{max} (KBr) 3468, 3313, 3157, 2214, 1628, 1569, 1541, 1420, 757, 689. MS (FAB) *m/z*: 211 [MH^+] (100). For $C_{12}H_{10}N_4$ (210.2) calculated 68.56% C, 4.79% H, 26.65% N; found 68.23% C, 4.91% H, 26.31% N. ^{1}H NMR (DMSO-d_6): 7.72 (brs, 2H, NH_2); 7.62 (d, 2H, arom. H); 7.53 (t, 1H, arom. H); 7.50 (t, 2H, arom. H); 7.15 (brs, 2H, NH_2); 6.16 (s, 1H, H-5). ^{13}C NMR: 164.58 (2C, C-2 and C-4); 158.16 (C-6); 132.16 (2C, arom. C); 129.24 (2C, arom. C); 120.11 arom. C); 100.03 (C-5); 93.70 and 82.21 (C-1′ and C-2′).

3.1.2. 2,4-Diamino-6-(hex-1-yn-1-yl)pyrimidine (1b). Yield 150 mg (79%) of a white solid, mp 130–133 °C (ethyl acetate). IR ν_{max} (KBr) 3369, 3319, 3166, 2931, 2871, 2232, 1647, 1587, 1525, 1437, 1420. MS (FAB) *m/z*: 191 [MH^+] (100). For $C_{10}H_{14}N_4$ (190.2) calculated 63.13% C, 7.42% H, 29.45% N; found 63.11% C, 7.53% H, 29.14% N. ^{1}H NMR (DMSO-d_6): 7.58 (brs, 2H, NH_2); 6.95 (brs, 2H, NH_2); 5.97 (s, 1H, H-5); 2.47 (t, 2H, $J_{(H\text{-}3',H\text{-}4')}$=7.1 Hz, H-3′); 1.51 and 1.40 (br pent 2H, and br pent, 2H, H-4′ and H-5′); 0.90 (t, 3H, $J_{(H\text{-}5',H\text{-}6')}$=7.36 Hz, H-6′). ^{13}C NMR: 164.67 (C-4); 158.13 (C-2); 139.15 (C-6); 99.46 (C-5); 97.09 and 75.07 (C-1′ and C-2′); 29.62, 21.51 and 18.29 (C-3′, C-4′ and C-5′); 13.54 (C-6′).

3.1.3. 2,4-Diamino-6-[(2-trimethylsilyl)ethynyl]pyrimidine (1c). Yield 125 mg (61%) of yellow foam. IR ν_{max} (KBr) 3467, 3390, 3318, 3182, 2959, 2166, 1622, 1575, 1550, 1407, 1251, 1183, 991, 848. MS (FAB) *m/z*: 207 [MH^+] (100). For $C_9H_{14}N_4Si$ (206) calculated 52.39% C, 6.84% H, 27.16% N; found 52.03% C, 6.83% H, 26.82% N. ^{1}H NMR (DMSO-d_6): 6.42 (brs, 2H, NH_2); 6.02 (brs, 2H, NH_2); 5.80 (s, 1H, H-5); 0.20 (s, 9H, $SiMe_3$). ^{13}C NMR: 164.47 (C-4); 163.56 (C-2); 147.76 (C-6); 104.38 and 92.93 (C-1′ and C-2′); 98.08 (C-5); −0.21 (3C, $SiMe_3$).

3.1.4. 2,4-Diamino-6-(3-hydroxyprop-1-yn-1-yl)pyrimidine (1d). Yield 100 mg (61%) of a white solid, mp 204–206 °C (methanol). IR ν_{max} (KBr) 3427, 3351, 3127, 2236, 2216, 1668, 1639, 1588, 1550, 1431, 1032. MS (FAB) *m/z*: 165 [MH^+] (30). For $C_7H_8N_4O.1/3H_2O$ (170.2) calculated 49.41% C, 5.13% H, 32.92% N; found 49.64% C, 4.89% H, 32.69% N. ^{1}H NMR (DMSO-d_6): 6.40 (brs, 2H, NH_2); 5.98 (brs, 2H, NH_2); 5.78 (s, 1H, H-5); 5.35 (t, 1H, $J_{(OH,\ H\text{-}3')}$= 5.0 Hz, OH); 4.24 (d, 2H, $J_{(OH,\ H\text{-}3')}$=5.0 Hz, H-3′). ^{13}C NMR: 164.48 (C-4); 163.56 (C-2); 148.33 (C-6); 97.59 (C-5); 88.68 and 83.36 (C-1′ and C-2′); 49.38 (C-3′).

3.1.5. 2,4-Diamino-6-(3-hydroxy-3-phenylprop-1-yn-1-yl)pyrimidine (1e). Yield 160 mg (66%) of a yellow amorphous solid. IR ν_{max} (KBr) 3454, 3316, 3124, 2221, 1655, 1622, 1579, 1554, 1440, 1188, 980, 700. MS (FAB) *m/z*: 241 [MH^+] (100). For $C_{13}H_{12}N_4O.2/5H_2O$ (247.5) calculated 63.10% C, 5.21% H, 22.64% N; found 63.12% C, 5.05% H, 22.25% N. ^{1}H NMR (DMSO-d_6): 7.49 (d, 2H, arom. H); 7.38 (t, 2H, arom. H); 7.31 (t, 1H, arom. H); 6.42 (brs, 2H, NH_2); 6.21 (d, 1H, $J_{(OH,\ H\text{-}3')}$=6.0 Hz, H-3′); 6.00 (brs, 2H, NH_2); 5.81 (s, 1H, H-5); 5.55 (d, 1H, $J_{(OH,\ H\text{-}3')}$= 5.0 Hz, OH). ^{13}C NMR: 164.48 (C-4); 163.57 (C-2); 148.11 (C-6); 128.48 (2C, arom. C); 127.88 (arom. C); 126.57 (2C, arom. C); 97.77 (C-5); 89.95 and 84.13 (C-1′ and C-2′).

3.1.6. 2,4-Diamino-6-(3-hydroxybut-1-yn-1-yl)pyrimidine (1f). Yield 125 mg (70%) of yellow foam. IR ν_{max} (KBr) 3401, 3205, 2233, 1622, 1581, 1548, 1418, 1203, 1093, 817. MS (FAB) *m/z*: 179 [MH^+] (100). HRMS (EI): found 178.0842, calculated for $C_8H_{10}N_4O$: 178.0855. ^{1}H NMR (DMSO-d_6): 7.02 (brs, 2H, NH_2); 6.47 (brs, 2H, NH_2); 5.88 (s, 1H, H-5); 5.59 (t, 1H, $J_{(OH,\ H\text{-}3')}$=5.0 Hz, OH); 4.56 (br pent, 1H, J=6.3 Hz, H-3′); 1.35 (d, 3H, $J_{(H\text{-}4',H\text{-}3')}$=6.6 Hz, H-4′). ^{13}C NMR: 164.52 (C-4); 160.85 (C-2); 143.81 (C-6); 98.65 (C-5); 95.22 and 79.21 (C-1′ and C-2′); 56.62 (C-3′); 24.27 (C-4′).

3.1.7. 2,4-Diamino-6-(4-hydroxybut-1-yn-1-yl)pyrimidine (1g). Yield 160 mg (89%) of a yellow solid, mp 155–158 °C, decomp. (ethyl acetate). IR ν_{max} (KBr) 3425, 3324, 3203, 2235, 1627, 1578, 1420, 1046. MS (FAB) *m/z*: 179 [MH^+] (100). For $C_8H_{10}N_4O$ (178.2) calculated 53.92% C, 5.66% H, 31.44% N; found 53.61% C, 5.73% H, 31.19% N. ^{1}H NMR (DMSO-d_6): 7.22 (brs, 2H, NH_2); 6.63 (brs, 2H, NH_2); 5.91 (s, 1H, H-5); 4.95 (br, 1H, OH); 3.56 (t, 2H, $J_{(H\text{-}3',H\text{-}4')}$=6.6 Hz, H-4′); 2.57 (t, 2H, $J_{(H\text{-}4',H\text{-}3')}$= 6.6 Hz, H-3′). ^{13}C NMR: 164.61 (C-4); 159.76 (C-2); 142.04 (C-6); 98.90 (C-5); 93.08 and 77.11 (C-1′ and C-2′); 59.31 (C-4′); 23.23 (C-3′).

3.2. 2-Amino-4-chloro-6-ethynylpyrimidines 2 and 2-amino-4,6-bis(ethynyl)pyrimidines 3. General procedure

Method A. Dimethylformamide (10 ml), the corresponding ethyne derivative (2.2 mmol) and Et_3N (0.3 ml) were added through septum to an argon purged flask containing 2-amino-4,6-dichloropyrimidine (330 mg, 2 mmol), CuI (20 mg), $PdCl_2(PPh_3)_2$ (100 mg, 0.07 mmol) and the mixture was stirred at room temperature overnight. The solvent was evaporated in vacuo and the residue was chromatographed on a silica gel column (ethyl acetate–hexane). Compounds **2** were obtained as major products, small amounts of compounds **3** were isolated as side products.

Method B. Dimethylformamide (10 ml), the corresponding ethyne derivative (6.6 mmol) and Et_3N (0.6 ml) were added through septum to an argon purged flask containing 2-amino-4,6-dichloropyrimidine (330 mg, 2 mmol), CuI (40 mg), $PdCl_2(PPh_3)_2$ (200 mg, 0.14 mmol) and the mixture was stirred at room temperature overnight. The solvent was evaporated in vacuo and the residue was chromatographed on a silica gel column (ethyl acetate–hexane). Compounds **3** were obtained as major products; in the case of **3b**, a small amount of **2b** was isolated as a by-product.

3.2.1. 2-Amino-4-chloro-6-(phenylethynyl)pyrimidine (2a) and 2-amino-4,6-bis(phenylethynyl)pyrimidine (3a).

Method A. 190 mg (41%) of **2a** and 90 mg (15%) of **3a**.

Method B. 480 mg (81%) of **3a**.

Compound **2a**. Yellow needles, mp 145–146 °C (methanol–water). IR ν_{max} (KBr) 3503, 3280, 3139, 2223, 1630, 1551, 1534, 1324, 1229, 1211, 812, 762. MS (FAB) *m/z*: 230 [MH^+] (100). For $C_{12}H_8ClN_3.1/4H_2O$ (234.2) calculated 61.55% C, 3.66% H, 17.94% N; found 61.91% C, 3.53% H, 17.71% N. ^{1}H NMR (DMSO-d_6): 7.62 (d, 2H, arom. H); 7.48 (m, 3H, arom. H); 7.33 (brs, 2H, NH_2); 6.90 (s, 1H, H-5). ^{13}C NMR: 163.50 (C-2); 160.72 (C-4); 152.07 (C-6); 132.26 (2C, arom. C); 130.46 (2C, arom. C); 120.53 (arom. C); 111.05 (C-5); 91.74 and 86.82 (C-1′ and C-2′).

Compound **3a**. Yellow solid, mp 188–189 °C (acetate–hexane). IR ν_{max} (KBr) 3304, 3186, 2216, 1558, 1533, 1522, 1372, 1218, 756, 688. MS (FAB) *m/z*: 296 [MH^+] (100). For $C_{20}H_{13}N_3$ (295.3) calculated 81.34% C, 4.44% H, 14.23% N; found 80.98% C, 4.32% H, 14.01% N. ^{1}H NMR (DMSO-d_6): 7.62 (m, 4H, arom. H); 7.53–7.46 (m, 6H, arom. H); 7.06 (brs, 2H, NH_2); 6.99 (s, 1H, H-5). ^{13}C NMR: 163.86 (C-2); 151.12 (2C, C-4 and C-6); 132.21 (4C, arom. C); 130.32 (2C, arom. C); 129.15 (4C, arom. C); 120.76 (2C, arom. C); 114.45 (C-5); 91.36 and 87.36 (2×2C, C-1′ and C-2′).

3.2.2. 2-Amino-4-chloro-6-[(2-trimethylsilyl)ethynyl]-pyrimidine (2b) and 2-amino-4,6-bis[(2-trimethylsilyl)-ethynyl]pyrimidine (3b).

Method A. 270 mg (60%) of **2b** and traces of **3b**.

Method B. 100 mg (22%) of **2b** and 330 mg (57%) of **3b**.

Compound **2b**. Yellowish solid, unstable. IR ν_{max} (KBr) 3471, 3308, 32031625, 1565, 1532, 1470, 1284, 1252, 892, 848. MS (FAB) *m/z*: 226 [MH^+] (20). HRMS (EI): found 225.0503, calculated for $C_9H_{12}ClN_3Si$: 225.0489. ^{1}H NMR (DMSO-d_6): 7.30 (brs, 2H, NH_2); 6.77 (s, 1H, H-5); 0.23 (s, 9H, $SiMe_3$). ^{13}C NMR: 163.42 (C-2); 160.83 (C-4); 151.47 (C-6); 110.97 (C-5); 101.79 and 98.22 (C-1′ and C-2′); −0.50 (3C, $SiMe_3$).

Compound **3b**. White solid, unstable. IR ν_{max} (KBr) 3501, 3430, 3304, 3194, 2961, 2167, 1620, 1557, 1524, 1335, 1251, 959, 847, 761. MS (FAB) *m/z*: 288 [MH^+] (40). HRMS (EI): found 287.1298, calculated for $C_{14}H_{21}N_3Si_2$: 287.1274. ^{1}H NMR (DMSO-d_6): 7.00 (brs, 2H, NH_2); 6.70 (s, 1H, H-5); 0.23 (s, 18H, $SiMe_3$). ^{13}C NMR: 163.72 (C-2); 150.71 (2C, C-4 and C-6); 114.19 (C-5); 102.31 and 97.78 (2×2C, C-1′ and C-2′); −0.46 (6C, $SiMe_3$).

3.2.3. 2-Amino-4-chloro-6-(3-hydroxyprop-1-yn-1-yl)-pyrimidine (2c) and 2-amino-4,6-bis(3-hydroxyprop-1-yn-1-yl)pyrimidine (3c).

Method A. 130 mg (35%) of **2c** and 20 mg (5%) of **3c**.

Method B. Traces of **2c** and 160 mg (39%) of **3c**.

Compound **2c**. White solid, mp 185–187 °C. IR ν_{max} (KBr) 3421, 3314, 2246, 2224, 1654, 1555, 1539, 1306, 1023, 812. MS (FAB) *m/z*: 184 [MH^+] (100). For $C_7H_6ClN_3O$ (183.6) calculated 45.79% C, 3.29% H, 22.89% N, 19.31% Cl; found 45.52% C, 3.21% H, 22.45% N, 19.34% Cl. ^{1}H NMR (DMSO-d_6): 7.25 (brs, 2H, NH_2); 6.72 (s, 1H, H-5); 5.50 (t, 1H, $J_{(OH,\ H\text{-}3')}$=6.1 Hz, OH); 4.31 (d, 2H, $J_{(OH,\ H\text{-}3')}$=6.1 Hz, H-3′). ^{13}C NMR: 163.44 (C-2); 160.67 (C-4); 152.15 (C-6); 110.68 (C-5); 93.32 and 81.50 (C-1′ and C-2′); 49.38 (C-3′).

Compound **3c**. Yellowish solid, unstable, >300 °C, decomp. IR ν_{max} (KBr) 3466, 3346, 2237, 1637, 1566, 1540, 1360, 1228, 1043. MS (FAB) *m/z*: 204 [MH^+] (100). For $C_{10}H_9N_3O_2$ (203.2) calculated 59.11% C, 4.46% H, 20.86% N; found 58.75% C, 4.52% H, 20.49% N. ^{1}H NMR (DMSO-d_6): 6.90 (brs, 2H, NH_2); 6.62 (s, 1H, H-5); 5.47 (t, 2H, $J_{(OH,\ H\text{-}3')}$=6.1 Hz, OH); 4.30 (d, 4H, $J_{(OH,\ H\text{-}3')}$= 6.1 Hz, H-3′). ^{13}C NMR: 163.68 (C-2); 151.11 (2C, C-4 and C-6); 113.54 (C-5); 92.68 and 81.98 (2×2C, C-1′ and C-2′); 49.38 (2C, C-3′).

3.2.4. 2,4-Diamino-6-ethynylpyrimidine (1h). Solution of 2,4-diamino-6-(2-trimethylsilylethynyl)pyrimidine (**1c**, 100 mg, 0.5 mmol) in methanolic ammonia (15 ml) was stirred at room temperature for 3 h. The solvent was evaporated and the residue subjected to preparative TLC (20% MeOH in ethyl acetate). Yield 50 mg (75%) of **1h** as an unstable yellowish solid. IR ν_{max} (KBr) 3480, 3434, 3326, 3223, 3092, 2107, 1646, 1626, 1574, 1547, 1437, 1402, 1275, 988, 829, 693. MS (FAB) *m/z*: 135 [MH^+] (40). HRMS (EI): found 134.0575, calculated for $C_6H_6N_4$: 134.0592. ^{1}H NMR (DMSO-d_6): 6.48 (brs, 2H, NH_2); 6.05 (brs, 2H, NH_2); 5.85 (s, 1H, H-5); 4.10 (s, 1H, H-2′). ^{13}C NMR: 164.46 (C-4); 163.41 (C-2); 147.40(C-6); 98.36 (C-5); 82.79 (C-1′).

3.2.5. 2-Amino-4,6-bis(ethynyl)pyrimidine (3d). Solution of 2-amino-4,6-bis(2-trimethylsilylethynyl)pyrimidine (**3b**, 220 mg, 0.76 mmol) in methanolic ammonia (20 ml) was stirred at room temperature for 2 h. Solvent was evaporated, the residue in methanol (5 ml) was filtered through a short column of silica gel and purified by preparative HPLC. Yield 90 mg (63%), unstable. IR ν_{max} (KBr) 3497, 3422, 3287, 3175, 2106, 1627, 1559, 1531, 1459, 1321, 1218, 675. MS (EI) *m/z*: 143 [MH^+] (100). HRMS (EI): found 143.0504, calculated for $C_8H_5N_3$: 143.0483. ^{1}H NMR (DMSO-d_6): 7.03 (brs, 2H, NH_2); 6.79 (s, 1H, H-5); 4.54 (s, 2H, H-2′). ^{13}C NMR: 163.72 (C-2); 150.77 (2C, C-4 and C-6); 114.66 (C-5); 81.32 (2C, C-1′); 79.27 (2C, C-2′).

Inhibition of the cell growth was estimated in mouse lymphocytic leukemia L1210 cells (ATCC CCL 219), CCRF-CEM T lymphoblastoid cells (human acute lymphoblastic leukemia, ATCC CCL 119), human promyelocytic leukemia HL-60 cells (ATCC CCL 240) and human cervix carcinoma HeLa S3 cells (ATCC CCL 2.2).[15] L1210 cells, CCRF-CEM cells and HL-60 cells were cultivated in RPMI 1640 medium supplemented with calf foetal serum using 24-well tissue culture plates. The endpoint of the cell growth was 72 h following the drug addition. HeLa S3 cells were seeded to 24-well dishes in RPMI 1640 HEPES modification with foetal calf serum. 48 h following the drug addition the cultivation was stopped and the cell growth was evaluated. An inhibition of the cell growth was determined by cell-counting. In parallel, the cell viability was quantified using XTT (Ref. 16) standard spectrophotometric assay (Roche Molecular Biochemicals). The inhibitory potency of the compound tested was expressed as IC_{50} values.

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Allylic amination of unfunctionalyzed olefins by nitroarenes and CO, catalyzed by $Ru_3(CO)_{12}$/Ph-BIAN (Ph-BIAN=bis(phenylimino)acenaphthenequinone): extension to the synthesis of allylic amines with strongly electron-withdrawing or electron-donating groups on the aryl ring

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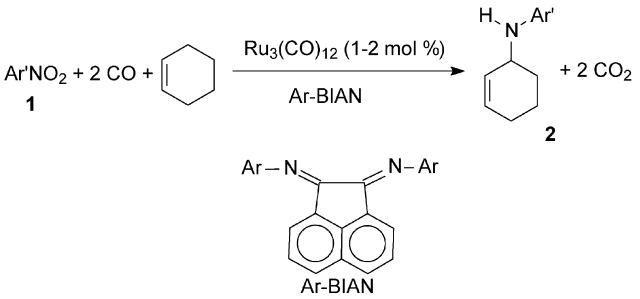
Abstract—The allylic amination of unfunctionalyzed olefins by nitroarenes under CO pressure, catalyzed by $Ru_3(CO)_{12}$/Ph-BIAN (Ph-BIAN=bis(phenylimino)acenaphthenequinone) has been extended to some substrates with strongly electron-withdrawing groups on the nitroarene. Reaction of 1,4-dinitrobenzene selectively affords functionalization of only one nitro group, the other remaining unreacted. However, the second nitro group can be reduced in one pot by CO/H_2O in the presence of the same catalytic system employed in the amination reaction, to afford the corresponding 4-amino derivative. Some attempts to render the reaction enantioselective by employing chiral bis-oxazolines as ligands in place of Ph-BIAN are described. Bis-oxazolines are suitable ligands for the reaction, although not as efficient as Ph-BIAN, but the allylic amine obtained was found to be racemic.

1. Introduction

Allylic amines are important building blocks or final products in organic chemistry and much attention has been devoted to their synthesis.[1] The most often employed synthetic method involves nucleophilic attack of an amine on a π-allyl complex. This is in turn generated by reaction of a suitable metal complex with a prefunctionalized allylic compound, such as an acetate or an halide. The method often gives high yields, but has two limitations. The first is that a prefunctionalized substrate is required, which often needs preliminary steps to be prepared. The second is that the amine must be nucleophilic enough to react with the complex and aromatic amines having electron-withdrawing substituents on the aryl ring are generally poor substrates in these reactions. Some years ago, we reported on a new synthetic way to produce allylic amines, employing a simple unactivated olefin, cyclohexene, and an aromatic nitro compound as the aminating reagent, under reducing conditions (CO pressure). Although the method requires the use of a high-pressure apparatus, the reagents are bulk, cheap commercial products which do not need to be purified (although an higher selectivity can be achieved by purifying the olefin), the experimental operations are simple, the selectivity was high (up to 81.9%), and the turnover numbers were higher than those reported for most C–H activation reactions (Scheme 1).[2–4]



Scheme 1.

One feature of this reaction, which is interesting in view of what said above, apart from the fact of producing CO_2 as the only stoichiometric byproduct, is that nitroarenes bearing electron-withdrawing substituents were those where the highest selectivities were obtained. In this work we have extended the range of nitroarenes for which the reaction may be performed, employing substrates having strongly electron-withdrawing groups on the nitroarene.

Keywords: Allylic amines; Nitroarenes; Carbonylation reactions; Ruthenium; Imines.
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Despite the good results obtained with nitroarenes having electron-withdrawing substituents, substrates with strong electron-donating groups such as methoxy or amino are not suitable substrates for amination reactions of this kind. We have now found a two step-one pot procedure to the 4-amino derivative in good yields. The amino group can be an important entry to a variety of other derivatives. Some preliminary attempts to make the reaction enantioselective are further described.

2. Results and discussion

2.1. Nitroarenes with strongly electron-withdrawing substituents

Four nitroarenes bearing strong electron-withdrawing substituents were employed in this work, 4-$MeOC(O)C_6H_4NO_2$ (**1a**), 3,5-$Cl_2C_6H_3NO_2$ (**1b**), 3,5-$(CF_3)_2C_6H_3NO_2$ (**1c**), and 4-$O_2NC_6H_4NO_2$ (**1d**), none of which has been previously employed in these reactions. The last contains two nitro groups both of which may in principle react. However, we had previously observed that the presence of the strong electron-donating 4-methoxy group on the aryl ring of the nitroarene led to a very slow reaction.[2–4] After one of two nitro groups has reacted, it is converted into an even more electron-releasing amino group. Thus, we deemed a selective reaction of only one nitro group could be feasible.

The results of a series of reactions run under previously optimized conditions (T=160 °C, P_{CO}=40 bar, mol ratios $ArNO_2$/Ph-BIAN/$Ru_3(CO)_{12}$=50:3.75:1)[3] are reported in Table 1. Good selectivities were obtained in all cases and the 84% selectivity in the allylic amine bearing the fluorinated groups is the highest obtained to date in these reactions. As expected, only mono-functionalization was observed for dinitrobenzene and no byproducts were observed in which the second nitro group had been transformed in any way.

When using 4-$MeO_2CC_6H_4NO_2$ as substrate by lowering the temperature a very low conversion results, but with the more reactive 3,5-$(CF_3)_2C_6H_3NO_2$ substrate a significant reaction was observed even at 100 °C.

The only observable byproduct was the aniline corresponding to the nitroarene employed, but small amounts of the corresponding diarylureas are probably also formed, which could not be detected by gas-chromatography. We have previously shown that the hydrogen atoms necessary for the aniline formation come from a ruthenium-catalyzed dehydrogenation of cyclohexene to afford cyclohexadiene and benzene.[3]

Although a complete purification of the allylic amines required chromatography on silica, almost pure samples could be obtained by subsequent acidic extraction with HCl at different concentrations (see Section 4 for details). Indeed, the byproduct anilines are extracted easily into 1 M aqueous HCl, whereas the allylic amines require a more concentrated acid and the presence of methanol as a co-solvent.

2.2. Synthesis of *N*-cyclohex-2-enyl-benzene-1,4-diamine (2e)

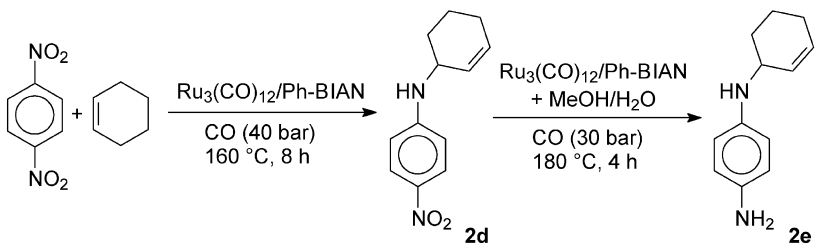
As alluded to in the introduction, the main limit of this type of reaction discussed in this paper is that when it is applied to nitroarenes bearing strongly electron-donating substituents, only very low conversions and selectivities are observed. The reason for this is two-fold. First, the evidence accumulated indicates that the initial reduction of the nitroarene always proceeds by a single electron transfer from the complex to the nitroarene and this is disfavored by electron-donating substituents on the nitroarene.[5] Moreover, coupling between the olefin and the nitrogen-containing complex occurs by a metal catalyzed ene reaction between the olefin and the intermediately formed nitrosoarene and this is also disfavored by the same donating substituents.[1,6] Use of a free amino group in a nitroaniline would further complicate the issue, since the amino group may enter the reaction via an alternative pathway, to yield diarylureas.[5] A different catalytic system, reported by Nicholas for the same reactions, suffers from the same limitations.[7]

Molecules having free amino groups are important both as such and because the amino group can be easily functionalized or transformed (e.g. via an azonium salt) into many other groups. Thus it would be interesting to prepare them by our methodology. The system $Ru_3(CO)_{12}$/Ar-BIAN is also the most active catalyst known to date for the reduction of nitroarenes to anilines by CO/H_2O.[8,9] This reaction proceeds much more easily than the amination reaction and the presence of an electron-donating substituent on the nitroarene is not a major problem here. Since we have now been able to synthesize the 4-nitro derivative **2d**, we effected a two step-one pot reaction from dinitrobenzene. In the first step, **2d** is produced under the

Table 1. Synthesis of allylamines **2** from cyclohexene and different nitroarenes[a]

Run	$Ru_3(CO)_{12}$ (mmol)	Cyclohexene (mL)	Nitroarene	Nitroarene conversion (%)[b]	Allylamine select (%)[c]	Aniline select (%)[c]
1	0.0306	30	3,5-$Cl_2C_6H_3NO_2$ (**1b**)	99.1	57.2 (**2b**)	12.0
2	0.0306	30	4-$MeO_2CC_6H_4NO_2$ (**1a**)	100	42.1 (**2a**)	10.4
3	0.0306	30	1,4-$(NO_2)_2C_6H_4$ (**1d**)	100	52.7(**2d**)	3.2
4	0.0102	10	3,5-$(F_3C)_2C_6H_3NO_2$ (**1c**)	99.9	83.1 (**2c**)	14.4
5[d]	0.0102	10	3,5-$(F_3C)_2C_6H_3NO_2$ (**1c**)	41.9	84.3 (**2c**)	15.7
6[e]	0.0102	10	3,5-$(F_3C)_2C_6H_3NO_2$ (**1c**)	39.7	52.3 (**2c**)	32.8

[a] Experimental conditions: mol ratios $ArNO_2$/Ph-BIAN/$Ru_3(CO)_{12}$=50:3.75:1, T=160 °C, P_{CO}=40 bar, t=6 h.
[b] Calculated with respect to the starting nitroarene by GC analysis (naphthalene as an internal standard).
[c] Calculated with respect to the converted nitroarene by GC analysis (naphthalene as an internal standard).
[d] T=130 °C.
[e] T=100 °C.



Scheme 2.

same conditions reported in this paper (Table 1). Then the autoclave was opened and water and methanol (to improve miscibility) were added. The autoclave was charged again with CO and the reaction run under the temperature and pressure conditions previously shown to give a 99% selectivity in the reduction of nitrobenzene to aniline (Scheme 2).[9]

At the end of the reaction, **2d** had been completely consumed to afford the corresponding amine **2e**. The total selectivity in **2e** (52.8%) is indistinguishable within experimental error from the one in **2d** in the single step reaction, indicating that the reduction step occurs in essentially quantitative yields.

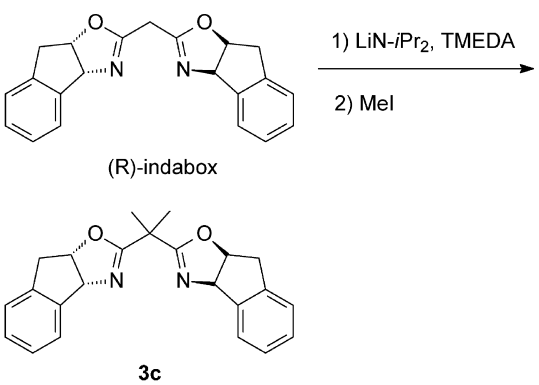
It should be noted that any amination procedure based on a reaction of 1,4-diaminobenzene with a functionalized substrate would surely have to face the problem of multiple substitution not only on the same nitrogen atom, but even on the second one, so that up to four products can be expected, differing in the alkylation extent. On the other hand, with our strategy only the monosubstituted product can be obtained.

During the reaction a small amount of unsubstituted aniline was formed, whose origin is uncertain. Another independent product was formed (as evidenced by GC-MS analysis), which does not include the nitroarene-derived fragment, CyCOOMe. This ester clearly derives from the carboxylation reaction of cyclohexene, which is still present in the reaction mixture in large amount, by CO and methanol. When the reaction was performed by employing ethanol in place of methanol, the reduction reaction proceeded in the same way and CyCOOEt was formed in place of the corresponding methyl ester. This type of carboxylation reactions are typically catalyzed by palladium complexes. By searching through the literature we could only find two examples, both in the patent literature, for ruthenium-catalyzed olefin carboxylation reactions and in none of these examples was a nitrogen ligand present.[10,11] Since this reaction was outside the scope of the present paper, it was not investigated further at the moment, although it surely deserves attention.

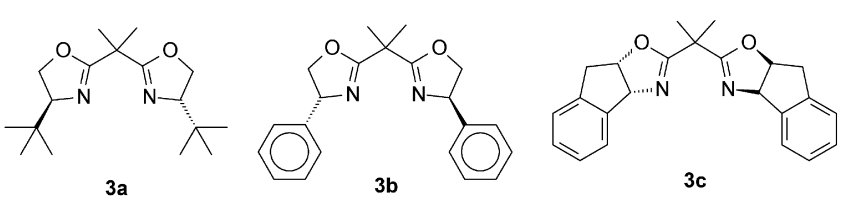
2.3. Use of chiral bis-oxazolines as ligands

Given the importance chiral allylic amines have in pharmaceutical chemistry, we attempted to make our reaction asymmetric by employing a chiral ligand. Since no chiral Ar-BIAN has to date been reported, we decided to use bis-oxazolines as ligands. The choice was motivated by the fact that some years ago we employed similar, although not chiral, ligands in the $Ru_3(CO)_{12}$-catalyzed reduction of nitrobenzene to aniline by CO/H_2O with good results.[12] In the same work, we had noticed that the central $-CH_2-$ moiety of the bis-oxazoline had to be protected by alkylation in order for the catalyst to be active. The ligands employed in this work are shown in Scheme 3.

Two of these, **3a**,**b**, are commercially available, whereas the methylated indabox **3c** is not. Its synthesis from indandiol and dimethylmalononitrile in a low yield has been briefly reported in a communication,[13] but the experimental details and the characterization of the product were not reported. We preferred to start from the commercially available (*R*)-indabox ([3a*R*-[2(3′a*R* *,8′a*S* *),3′aβ,8′aβ]]-(+)-2,2′-methylenebis[3a,8a-dihydro-8*H*-indeno[1,2-*d*]oxazole) and we effected the methylation by deprotonation of the parent ligand by lithium diisopropylamide, followed by reaction with methyl iodide (Eq. (1)). The procedure is a modification of the one reported in the literature for the alkylation of the same or of related bis-oxazolines[14,15] and afforded pure **3c** in a 56.2% isolated yield.



(1)



Scheme 3.

Table 2. Use of bis-oxazolines **3** as ligands[a]

Run	Ligand	T (°C)	t (h)	Nitroarene	Nitroarene conversion (%)[b]	Allylamine select (%)[c]	Aniline select (%)[c]
1	**3c**	160	6	4-$MeO_2CC_6H_4NO_2$	80.9	1.9 (**2a**)	3.0
2	**3b**	160	6	4-$MeO_2CC_6H_4NO_2$	56.4	8.0 (**2a**)	7.0
3	**3a**	160	6	4-$MeO_2CC_6H_4NO_2$	53.4	5.9 (**2a**)	13.6
4	**3a**	130	10	4-$MeO_2CC_6H_4NO_2$	46.4	2.6 (**2a**)	29.1
5	**3c**	130	10	4-$MeO_2CC_6H_4NO_2$	66.2	11.1 (**2a**)	27.8
6	**3c**	160	6	3,5-$Cl_2C_6H_3NO_2$	77.7	31.0 (**2b**)	13.5
7	**3b**	160	6	3,5-$Cl_2C_6H_3NO_2$	99.4	44.5 (**2b**)	22.3
8	**3a**	160	6	3,5-$Cl_2C_6H_3NO_2$	84.4	18.3 (**2b**)	17.7
9	**3c**	130	10	3,5-$Cl_2C_6H_3NO_2$	81.5	37.3 (**2b**)	32.9
10	**3c**	100	10	3,5-$(CF_3)_2C_6H_3NO_2$	12.6	8.9 (**2c**)	37.4

[a] Experimental conditions: $Ru_3(CO)_{12}$=0.65 mg, 1.0×10^{-3} mmol, mol ratio $Ru_3(CO)_{12}$/**3**/$ArNO_2$=1/3/50, P_{CO}=40 bar, in cyclohexene (1 mL).
[b] Calculated with respect to the starting nitroarene; GC analysis.
[c] Calculated with respect to the converted nitroarene; GC analysis.

The reactions with the oxazolines were run in a similar way to the ones with Ar-BIAN ligands. However, in order to be able to perform the reactions on a smaller scale, an aluminum block having three 12 mm holes was prepared that could be fitted in the autoclave. Three small test tubes were placed in the holes (see Section 4 for details), so that three reactions could be run at the same time, each on a 1 mL scale.

The results of reactions run with the bis-oxazoline ligands are reported in Table 2.

The desired products were obtained, but reaction rates and selectivities are in general lower than those achievable with the use of Ph-BIAN. The two enantiomers of **2a** could be separated by chiral HPLC, employing conditions similar to the ones reported for the analogous ethyl ester,[16] but the enantiomers of **2b**–**d** could not be separated by the same technique, nor by chiral phase gas chromatography. Unfortunately the reactions corresponding to entries 1–5 in Table 2 all gave a completely racemic product. At 100 °C, **1a** did not react to any detectable extent and even the more reactive **1c** only gave a low conversion and a very low selectivity in allylic amine. Thus bis-oxazolines are not suitable ligands for an enantioselective modification of our amination reaction. Other chiral ligands have to be developed that also have to impart a reactivity to the catalytic system at least comparable to the one achievable with Ar-BIAN ligands, so that the reaction can be performed at lower temperatures.

3. Conclusions

In this paper, we have expanded the range of successfully converted substrates for the amination of cyclohexene by nitroarenes and CO, including several nitroarenes having strongly electron-withdrawing substituents. A selective reaction of only one nitro group in 1,4-dinitrobenzene was observed. More importantly, a two step-one pot protocol to an amino substituted derivative has been devised, which allows the reaction to be extended to previously inaccessible products, without problems deriving from polysubstitution. Chiral bis-oxazolines were found to be suitable ligands for the catalytic system, but results are inferior to the ones obtainable with Ar-BIAN ligands and the product formed was found to be racemic. We have also determined that carboxylation of cyclohexene is possible using a ruthenium complex as catalyst and this will be studied in further depth.

4. Experimental

4.1. General procedure

Cyclohexene, THF and hexane were purified by distillation over sodium and stored under dinitrogen before use. $Ru_3(CO)_{12}$[17] was synthesized as reported in the literature. Ph-BIAN was prepared as previously reported,[18–20] but employing our protocol based on the use of oxalate to remove the initially present $ZnCl_2$.[21] All other compounds, except for those mentioned below, were commercial products and were used as received. Gas chromatographic analyses were performed on a Perkin Elmer 8420 capillary gas chromatograph equipped with a PS 255 column. Ri values (Ri=response factor, relative to naphthalene as an internal standard) were determined by the use of solutions of known concentrations of the compounds. GC-MS analyses were performed on a Shimadzu GCMS-QP5050A instrument, equipped with an Equity 5 column. NMR spectra were recorded on a Bruker AC 300 FT, operating at 300 MHz for ^{1}H, at 282 MHz for ^{19}F, and at 75 MHz for ^{13}C. Elemental analyses and mass spectra were recorded in the analytical laboratories of Milan University.

4.1.1. Synthesis of 3c. The synthesis was performed in oven-dried glassware working under a dinitrogen atmosphere and employing standard Schlenk and cannula techniques. After the quenching with water, the remaining operations have been conducted in the air. To a Schlenk tube were added (*R*)-indabox ([3a*R*-[2(3′a*R* *,8′a*S* *),3′aβ,8′aβ]]-(+)-2,2′-methylenebis[3a,8a-dihydro-8*H*-indeno[1,2-*d*]-oxazole, 100.0 mg, 0.303 mmol), tetramethylethylendiamine (TMEDA, 92 μL, 0.61 mmol) and THF (12 mL). After the solid was dissolved, the solution was cooled to −78 °C by an acetone–dry ice bath and LiN–iPr$_2$ (0.8 mmol, 0.40 mL of a 2 M solution in THF/heptane/ethylbenzene) was added. The orange suspension was left to stir at −78 °C for 30 min, then at −20 °C for 2.5 h. At this point, the solution was cooled back to −78 °C and MeI (47 μL, 0.75 mmol) was added. The solution was stirred at this temperature for 30 min, then at −20 °C for the same time and finally at room temperature overnight. A saturated

solution of $NaHCO_3$ (7 mL) was added and, after stirring for 10 min, 2 more mL water were added to dissolve a white solid suspended in the aqueous phase. The two phases were separated, the aqueous phase was extracted with THF (3×10 mL) and the combined extracts were joined to the organic phase. After drying with sodium sulfate, the organic solution was evaporated to dryness in vacuo and the resulting solid, consisting of white and orange crystals, was recrystallized from hexane (50 mL) to afford **3c** as colorless needle-like crystals (61.1 mg, 56.2% yield). Anal. Calcd for $C_{23}H_{22}N_2O_2$: C, 77.07; H, 6.19; N, 7.82. Found: C, 76.80; H, 6.09; N, 8.11. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ=1.44 (s, 6H, CH_3), 2.97 (d, J_{gem}=17.9 Hz, 2H, −CHC(H)*H*C), 3.29 (dd, J_{gem}=17.9, J_{12}=7.1 Hz, 2H, −CHC(*H*)HC), 5.29 (pt, 2H, CH−O), 5.54 (d, J_{12}=7.9 Hz, 2H, CH−N), 7.29 (m, 6H, Ar−H), 7.51 (m, 2H, Ar−H). MS (70 eV, EI): *m*/*z*: 358 [M^+].

4.2. Catalytic reactions

In a typical reaction, the nitroarene, $Ru_3(CO)_{12}$ and the ligand (see Tables 1 and 2) were weighed in a glass liner. The liner was placed inside a Schlenk tube with a wide mouth under dinitrogen and was frozen at −78 °C with dry ice, evacuated and filled with dinitrogen, after which the solvent was added. After the solvent was also frozen, the liner was closed with a screw cap having a glass wool-filled open mouth which allows for gaseous reagents exchange and rapidly transferred to a 200 mL stainless steel autoclave with magnetic stirring. The autoclave was then evacuated and filled with dinitrogen three times. CO was then charged at room temperature at the required pressure and the autoclave was immersed in an oil bath preheated at the required temperature. Other experimental conditions are reported in Tables 1 and 2. At the end of the reaction the autoclave was cooled with an ice bath, vented and the products were analyzed by gas chromatography (naphthalene as an internal standard) and then extracted with acids as detailed in the following for each compound. In the case of the synthesis of **2e**, after the amination reaction employing **1d** as substrate was over (conditions as in entry 1 of Table 1), the autoclave was vented, the glass liner moved to the same Schlenk tube employed during the initial preparation and previously placed under a dinitrogen atmosphere and opened in a dinitrogen flux. Water (0.3 mL) and methanol (1.5 mL) were added. The same procedure described before was then employed and the second step was run at 180 °C under 30 bar CO for 4 h. Handling of the reaction solution in the air should be avoided as much as possible, since the catalytically active species Ru(Ph-BIAN)$(CO)_3$ (intense purple color), formed during the reaction, is very air sensitive. The reactions with bis-oxazolines as ligands were performed in a similar way, but on a smaller scale. In this case, three 10 mm wide ×40 mm high test tubes were employed instead of the glass liner, each having a miniature glass wool-filled screw cap similar to the one of the larger liner. The three test tubes were located in the holes of an aluminum block designed to fit the autoclave. Other operations were analogous to the ones described above except that stock solutions of $Ru_3(CO)_{12}$, the ligand and the nitroarene were prepared and the reagent amounts measured by volume to avoid the errors in weighing very small amounts of materials.

4.3. Separation and purification of the allylamines 2

Compounds **2a**, **2b**. The solution after the withdrawal for the GC analysis was extracted with 1 M aqueous HCl (3×5 mL) to remove the byproduct anilines The organic phase was then extracted with ~3 M H_2O/MeOH HCl solution, obtained by mixing 1 volume 37% HCl with 1 volume H_2O and 2 volumes MeOH (3×5 mL). The combined aqueous phases of the second extraction were made basic by the addition of NaOH and back extracted with CH_2Cl_2 (3×5 mL). After drying the organic phase with sodium sulfate, it was evaporated to dryness in vacuo and loaded on a short (7 cm) silica pad. The mixture is eluted with CH_2Cl_2 keeping all the eluate together, until a brown band does not approach the end of the pad, at which point the elution is stopped. The eluate is evaporated to dryness to afford the pure product.

Compounds **2c**, **2d**. The same procedure was employed as above, but a ~6 M H_2O/MeOH HCl solution (obtained by mixing equal volumes of 37% HCl and methanol) was necessary to efficiently extract these allylic amines.

Compound **2e**. A clean separation of **2e** from 1,4-diaminobenzene and aniline could not be achieved by simple acidic extraction. The amines were thus extracted together with 3 M H_2O/MeOH HCl. During the chromatographic separation, a yellow impurity band was first eluted with CH_2Cl_2, after which $CHCl_3$ was added and the red colored **2e** collected. The thus obtained product still contains small amounts of diaminobenzene and aniline. However, heating at 60 °C in vacuo the red oil for 3 h, these more volatile impurity evaporated and the product was shown by GC to contain about 1% of 1,4-diaminobenzene as the only contaminant.

4.4. Identification of the organic products of catalysis

The by-products anilines are all commercial products and were identified by comparison of their CG and CG-MS spectra with those of authentic samples. Compound **2a** is a colorless solid, **2b** and **2c** are colorless oils, **2d** is a yellow solid, and **2e** is a red oil. Compound **2d**[22] has been previously reported in the literature. The ^{1}H NMR spectrum of our sample was consistent with the one reported in the literature. The ^{13}C NMR and mass spectra of **2d** are anyway reported in the following because this data has not been reported previously. After the chromatographic separation, no impurity could be detected in the GC and ^{1}H NMR spectra of the allylamines (except for **2e**, as mentioned above). Thus, the purified compounds are evaluated to be at least 98% pure.

4.4.1. Compound 2a. ^{1}H NMR ($CDCl_3$, 25 °C, TMS): δ=1.65–1.98 (m, 6H, −C*H*$_2$−C*H*$_2$−C*H*$_2$−), 3.87 (s, 3H, $COOCH_3$), 4.08 (s br, 2H, −C*H*−N*H*, 1H exc D_2O), 5.74 (m, 1H, −CH_2−C*H*═CH−CH−), 5.91 (m, 1H, −CH_2−CH═C*H*−CH−), 6.57 (d, J_{ortho}=8.6 Hz, 2H, Ar−H), 7.87 (d, J_{ortho}=8.6 Hz, 2H, Ar−H). ^{13}C NMR ($CDCl_3$, 25 °C, TMS): δ=19.59, 25.12, 28.79, 47.58, 51.58, 111.84, 118.17, 127.64, 131.02, 131.71, 151.01, 167.37. MS (70 eV, EI): *m*/*z*: 231 [M^+]. Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.42; H, 7.50; N, 5.75.

4.4.2. Compound 2b. ^{1}H NMR ($CDCl_3$, 25 °C, TMS): δ=1.60–1.95 (m, 6H, –C*H*$_2$–C*H*$_2$–C*H*$_2$–), 3.82 (s br, 1H, NH, exc D_2O), 3.93 (s br, 1H, –C*H*–NH), 5.70 (m, 1H, –CH$_2$–C*H*=CH–CH–), 5.90 (m, 1H, –CH$_2$–CH=C*H*–CH–), 6.47 (s 2H, Ar–H), 6.65 (s, 1H, Ar–H). ^{13}C NMR ($CDCl_3$, 25 °C, TMS): δ=19.54, 25.10, 28.69, 47.86, 51.58, 111.22, 116.76, 127.48, 131.12, 135.58, 148.87. MS (70 eV, EI): *m*/*z*: 241 [M$^+$]. Anal. Calcd for $C_{12}H_{13}NCl_2$: C, 59.52; H, 5.41; N, 5.78. Found: C, 59.30; H, 5.57; N, 6.12.

4.4.3. Compound 2c. ^{1}H NMR ($CDCl_3$, 25 °C, TMS): δ=1.56–1.96 (m, 6H, –C*H*$_2$–C*H*$_2$–C*H*$_2$–), 4.08 (s br, 2H, –C*H*–N*H*, 1H exc D_2O), 5.72 (m, 1H, –CH$_2$–C*H*=CH–CH–), 5.96 (m, 1H, –CH$_2$–CH=C*H*–CH–), 6.94 (s, 2H, Ar–H), 7.13 (s, 1H, Ar–H). ^{13}C NMR ($CDCl_3$, 25 °C, TMS): δ=19.79, 25.36, 28.83, 48.15, 110.21, 112.45, 123.98 (q, J_{C-F}=272.5 Hz), 127.36, 131.81, 132.88 (q, J_{C-F}=32.8 Hz), 148.15. ^{19}F NMR ($CDCl_3$, 25 °C, TMS): δ=−63.53. MS (70 eV, EI): *m*/*z*: 309 [M$^+$]. Anal. Calcd for $C_{14}H_{13}NF_6$: C, 54.37; H, 4.24; N, 4.53. Found: C, 54.00; H, 4.52; N, 4.80.

4.4.4. Compound 2d. ^{1}H NMR ($CDCl_3$, 25 °C, TMS): δ=1.62–2.02 (m, 6H, –C*H*$_2$–C*H*$_2$–C*H*$_2$–), 4.11 (s br, 1H, NH, exc D_2O), 4.49 (s br, 1H, –C*H*–NH), 5.73 (m, 1H, –CH$_2$–C*H*=CH–CH–), 5.97 (m, 1H, –CH$_2$–CH=C*H*–CH–), 6.55 (d, J_{ortho}=9.2 Hz, 2H, Ar–H), 8.10 (d, J_{ortho}=9.2 Hz, 2H, Ar–H). ^{13}C NMR ($CDCl_3$, 25 °C, TMS): δ=19.36, 24.92, 28.56, 47.78, 111.34, 126.53, 126.65, 131.79, 137.89, 152.29. MS (70 eV, EI): *m*/*z*: 218 [M$^+$]. Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 65.77; H, 6.13; N, 13.16.

4.4.5. Compound 2e. ^{1}H NMR ($CDCl_3$, 25 °C, TMS): δ=1.58–1.92 (m, 6H, –C*H*$_2$–C*H*$_2$–C*H*$_2$–), 3.27 (s br, 3H, NH and NH_2, exc D_2O), 3.90 (s br, 1H, –C*H*–NH), 5.80 (m, 2H, –CH$_2$–C*H*=C*H*–CH–), 6.58 (m, 4H, Ar–H). ^{13}C NMR ($CDCl_3$, 25 °C, TMS): δ=20.24, 25.65, 29.56, 49.68, 115.89, 117.37, 129.55, 130.04, 138.20, 140.87. MS (70 eV, EI): *m*/*z*: 188 [M$^+$]. Anal. Calcd for $C_{12}H_{16}N_2$: C, 76.56; H, 8.57; N, 14.88. Found: C, 76.20; H, 8.22; N, 14.60.

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Fast diastereoselective Baylis–Hillman reaction by nitroalkenes: synthesis of di- and triene derivatives

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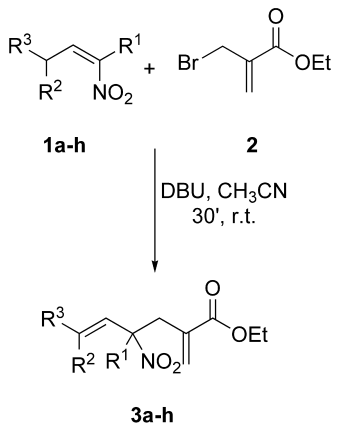
Abstract—The Baylis–Hillman reaction is performed using nitroalkenes as activated alkenes, ethyl-2-bromomethylacrylate as electrophilic acceptor and DBU as catalyst base. Nitro dienes are obtained in good yields and very short reaction times. Moreover, starting from appropriate nitroalkenes it is possible to realize one pot the synthesis of trienic systems.

1. Introduction

Among the various reactions leading to the formation of carbon–carbon bond, the Baylis–Hillman reaction is doubtless one of the most fascinating ones, due to the simplicity through which it is possible to obtain high densely functionalizated products starting from small molecules. The above reaction is a three component reaction resulting in the construction of a carbon–carbon bond between the α-position of an activated alkene and an electrophilic carbon under the influence of a catalyst (most commonly tertiary amines). A variety of activated alkenes have been used such as alkyl vinyl ketones, alkyl (aryl) acrylates, acrylonitrile, vinyl sulfones, acrylamides, allenic esters, vinyl sulfonates, vinyl phosphonates and acrolein.[1,2]

Aliphatic nitro compounds have proven to be valuable intermediates, and the chemical literature continuously reports progress in their utilization for the synthesis of a variety of targets. Moreover, these compounds are very powerful synthetic tools because they facilitate the carbon–carbon bond-forming processes.[3] Surprisingly little attention has been given to conjugated nitroolefines as activated alkenes; anyhow there are two pioneering works of Ono et al. where nitroolefines are reacted with aldehydes or with α,β-unsaturated compounds,[4,5] with the need of long reaction times.

Following our studies in the chemistry of aliphatic nitro compounds we wish here to present an extension of these forerunner works exploiting the reactivity of nitroolefines with a particular carbon electrophile specie, the allyl bromide **2**, whose use has been little explored in the Baylis–Hillman reaction;[6] moreover nothing has been done regarding the study of its behavior with nitroolefins.



Scheme 1.

Table 1. Preparation of nitro dienes **3a–h**

Entry	**1**, **3**	R^1	R^2	R^3	Yield (%) of **3**
1	**1a**, **3a**	Me	Me	Me	63
2	**1b**, **3b**	Me	H	Et	82
3	**1c**, **3c**	Et	H	Et	80
4	**1d**, **3d**	Et	H	*n*-Bu	77
5	**1e**, **3e**	Pr	H	H	80
6	**1f**, **3f**	$-(CH_2)_3-$		H	82
7	**1g**, **3g**	$MeOCCH_2CH_2$	H	Et	84
8	**1h**, **3h**	$MeOOC(CH_2)_4$	H	Et	94

Keywords: Baylis–Hillman reaction; Michael reaction; Nitroalkenes; Nitro dienes; Allylic nitro compounds.
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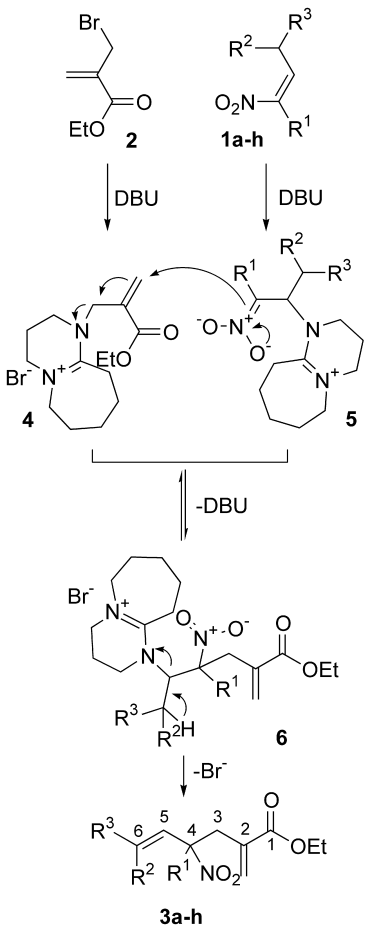
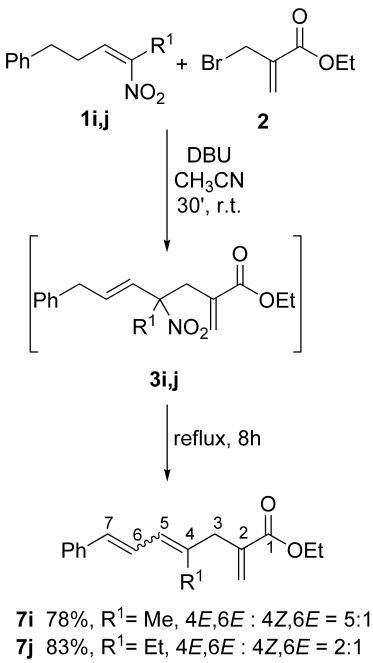
2. Results and discussion

Treatment of 1 equiv. of the nitroalkenes **1a–h** with 1 equiv. of ethyl-2-bromomethylacrylate **2** (Scheme 1), in the presence of DBU (2 equiv.) in acetonitrile and at room temperature affords after 30 min the nitro dienic systems **3a–h** in good yields (63–94%, Table 1).

The choice of DBU as base[7] dramatically improves the efficiency of the method since the reaction can be performed under very short reaction times (30 min) respect to the pioneering work of Ono (24–72 h).[5] It is noteworthy that a variety of nitroalkenes could be successfully employed, even those having other functionalities (entry 7, 8). A plausible mechanism for the formation of **3** is presented in the Scheme 2 (by analogy with Ref. 6). Both the nitroolefin **1** and the bromide **2** are nucleofilically attacked by DBU resulting in the zwitter ionic complexes **4** and **5**; the complex **5** acts as an enolate specie giving the Michael attack to the complex **4** and leading to the dipolar product **6**. Finally, **6** undergoes a base-assisted elimination of the conjugate acid of DBU giving diastereoselectively the nitro dienes **3** with *E* configuration, as evidenced by the H5–H6 coupling constants (14–16 Hz). The compounds **3** contain at least four different functionalities such as: (i) an ester moiety, (ii) an electron rich C–C double bond, (iii) an electron poor C–C double bond, and (iv) a nitro group, so that they can be submitted to several further transformations. Of great interest is the possibility to realize



Scheme 2.

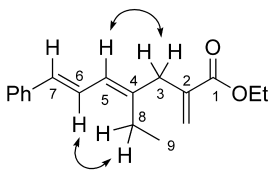


Scheme 3.

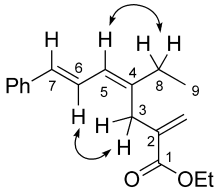
the one-pot preparation of triene derivatives **7** by the appropriate choice of the starting nitroalkenes (Scheme 3).

In fact we observed that if 1-alkyl-1-nitro-4-phenyl-1-butenes **1i,j** are employed, the Baylis–Hillman reaction could give, directly, the compounds **7i,j** as diastereoisomeric mixtures (Scheme 3).

As the ^{1}H and ^{13}C NMR spectra of the diastereomeric mixture **7j** showed better separated sets of signals respect to the **7i** spectra, they could be used for the determination of the configuration of the C4–C5 and the C6–C7 double bonds. The data showed that the major stereoisomer was, as expected, the 4*E*,6*E*. In particular, the *E* configuration of the C6–C7 double bond could be established on the basis of the H6–H7 coupling constant (15.6 Hz for both the diastereoisomers), whereas the C4–C5 configuration was established on the basis of the C3 and C8 chemical shifts. In fact, both the C3 and C8 are deshielded when they are *trans* respect to



7j (4E,6E); C3-39.0 ppm, C8-24.3 ppm



7j (4Z,6E); C3-30.3 ppm, C8-33.0 ppm

Figure 1.

the stirene moiety, as indicated in Figure 1 and according to the data reported for similar compounds.[8a,9] Moreover, the NOESY spectrum of the **7j** mixture showed two remarkably different sets of NOE correlations for the two diastereoisomers. The cross peaks evidenced that for both the diastereoisomers the preferred conformation of the C5–C6 single bond was the *s-trans*. In particular, as depicted in Figure 1, the 4*E* isomer showed the H3–H5 and the H6–H8 NOE correlations, whereas the 4*Z* isomer exhibited the H3–H6 and the H5–H8 NOE correlations.

Compounds **7** are very interesting materials from synthetic point of view because these molecules are recurring structural unit in natural targets of relevant interest and in molecules showing important pharmacological activities.[8] In these cases the energetic gain due to the conjugation of the styrene moiety allows the final spontaneous elimination of nitrous acid leading to trienes **7i,j**. The formation of **7i,j** is strongly helped by heating at reflux and is accomplished in 8 h. Anyway the dienic products **3i,j** could be still obtained and charaterized by stopping the reaction as soon as they were formed.

3. Conclusions

We have reported a new application of the Baylis–Hillman reaction for the diastereoselective, fast, one-pot synthesis of di- and triene derivatives. This procedure works with different conjugated nitroalkenes and affords the title compounds in good yields.

4. Experimental

4.1. General

^{13}C and ^{1}H NMR spectra were recorded in $CDCl_3$ or in C_6D_6 at 200 MHz on a Varian Gemini instrument; the use of C_6D_6 was necessary in the cases in which using $CDCl_3$ olefinic protons signals could not be separated; *J* values are given in Hz. IR spectra were recorded with a Perkin–Elmer 257 spectrophotometer. Mass spectra were determined on a capillary GC/MS operating in split mode with helium carrier gas and fitted with a mass selective detector (MSD). The nitroalkenes used were commercially available or prepared according to literature procedures.[10] The reactions were monitored by TLC. Microanalysis were performed using a Fisons model EA 1108. All the products were purified by flash chromatography on Merck silica gel (cyclohexane/ethyl acetate).

4.2. General procedure for the preparation of nitrodienes 3a–h

The nitroalkene **1** (1 mmol) and the bromide **2** (193 mg, 138 μl, 1 mmol) are dissolved in MeCN (15 ml) and then DBU is added (304 mg, 299 μl, 2 mmol); the obtained solution is magnetically stirred at room temperature for 30 min, then is concentrated under reduced pressure and charged into a flash chromatographic column (cyclohexane/ethyl acetate) giving the pure compound **3**.

4.2.1. Compound 3a. Oil. IR (neat) 1720, 1630, 1543 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 3H, *J*=7.3 Hz); 1.59 (s, 3H), 1.64 (s, 3H), 1.76 (s, 3H), 3.12 (d, 2H, *J*=1.8 Hz), 4.21 (q, 2H, *J*=7.3 Hz), 5.40 (bs, 1H), 5.57 (s, 1H), 6.28 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 167.1, 139.5, 135.1, 129.9, 125.0, 91.1, 61.4, 41.8, 27.4, 24.2, 18.8, 14.3; EI MS 195, 179, 149, 121 (100%), 79. Anal. calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.81. Found: C, 59.98; H, 7.77; N, 5.65.

4.2.2. Compound 3b. Oil. IR (neat) 1719, 1629, 1542 cm^{-1}; ^{1}H NMR (C_6D_6) δ 0.71 (t, 3H, *J*=7.5 Hz); 0.88 (t, 3H, *J*=7.1 Hz), 1.41 (s, 3H), 1.60–1.76 (m, 2H), 2.90 (d, 1H, *J*=13.7 Hz), 3.00 (d, 1H, *J*=13.7 Hz), 3.88 (q, 2H, *J*=7.1 Hz), 5.23 (d, 1H, *J*=1.1 Hz), 5.38 (dt, 1H, *J*=15.7, 6.2 Hz), 5.68 (dt, 1H, *J*=15.7, 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 166.9, 135.8, 135.1, 130.0, 128.4, 91.4, 61.3, 40.8, 25.5, 21.3, 14.3, 13.1; EI MS 195, 149, 121 (100%), 93, 79. Anal. calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.81. Found: C, 60.01; H, 8.12; N, 5.68.

4.2.3. Compound 3c. Oil. IR (neat) 1716, 1630, 1538 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.87 (t, 3H, *J*=7.3 Hz); 1.00 (t, 3H, *J*=7.3 Hz), 1.29 (t, 3H, *J*=7.2 Hz), 1.81–2.20 (m, 4H), 3.02 (dd, 1H, *J*=14.3, 0.7 Hz), 3.16 (dd, 1H, *J*=14.3, 0.7 Hz), 4.17 (q, 2H, *J*=7.2 Hz), 5.53 (bs, 1H), 5.60–5.82 (m, 2H), 6.26 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 167.1, 135.7, 135.4, 129.2, 125.8, 95.3, 61.3, 38.8, 29.9, 25.8, 14.3, 13.2, 8.6; EI MS 209, 163, 135 (100%), 93, 79. Anal. calcd for $C_{13}H_{21}NO_4$: C, 61.16; H, 8.29; N, 5.49. Found: C, 61.34; H, 8.11; N, 5.25.

4.2.4. Compound 3d. Oil. IR (neat) 1716, 1630, 1538 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H, *J*=7.3 Hz); 0.90 (t, 3H, *J*=7.2 Hz), 1.30 (t, 3H, *J*=7.2 Hz), 1.25–1.46 (m, 4H), 1.90–2.22 (m, 4H), 3.04 (dd, 1H, *J*=14.3, 0.7 Hz), 3.16 (dd, 1H, *J*=14.3, 0.7 Hz), 4.19 (q, 2H, *J*=7.2 Hz), 5.53 (bs, 1H), 5.65 (dt, 1H, *J*=16.0, 6.0 Hz), 5.78 (d, 1H, *J*=16.1 Hz), 6.24 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 167.1, 135.4, 134.5, 129.2, 126.6, 95.3, 61.3, 38.7, 32.5, 31.1, 29.9, 22.4, 14.3, 14.1, 8.6; EI MS 252, 237, 179, 123, 93, 79 (100%). Anal. calcd for $C_{15}H_{25}NO_4$: C, 63.58; H, 8.89; N, 4.94. Found: C, 63.75; H, 8.74; N, 5.16.

4.2.5. Compound 3e. Oil. IR (neat) 1718, 1560, 1540 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.91 (t, 3H, *J*=7.1 Hz); 1.12–1.46 (m, 2H), 1.29 (t, 3H, *J*=7.0 Hz), 1.83–2.15 (m, 2H), 3.04 (dd, 1H, *J*=14.6, 0.7 Hz), 3.17 (dd, 1H, *J*=14.6, 0.7 Hz), 4.19 (q, 2H, *J*=7.0 Hz), 5.22 (d, 1H, *J*=17.6 Hz), 5.35 (d, 1H, *J*=11.3 Hz), 5.54 (d, 1H, *J*=0.7 Hz), 6.19 (dd, 1H, *J*=17.8, 11.2 Hz) 6.28 (d, 1H, *J*=0.7 Hz); ^{13}C NMR ($CDCl_3$) δ 166.9, 135.1, 135.0, 129.5, 117.6, 95.0, 61.3, 38.9, 38.8, 17.3, 14.3, 14.2; EI MS 195, 149, 121 (100%), 93, 79. Anal. calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.81. Found: C, 59.89; H, 8.21; N, 5.65.

4.2.6. Compound 3f. Oil. IR (neat) 1716, 1633, 1538 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 3H, *J*=7.1 Hz); 1.46–2.12 (m, 4H), 2.42–2.55 (m, 1H), 3.00 (s, 2H), 4.21 (q, 2H, *J*=7.0 Hz), 5.58 (bs, 1H), 5.91 (m, 1H), 6.06 (m, 1H), 6.31 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 166.8, 134.7, 134.2, 130.0, 125.5, 89.4, 61.4, 41.4, 31.4, 24.9, 19.0, 14.3; EI MS 193, 147, 119 (100%), 91, 79. Anal. calcd for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 59.89; H, 6.97; N, 6.03.

4.2.7. Compound 3g. Oil. IR (neat) 1717, 1628, 1539 cm^{-1}; ^1H NMR (C_6D_6) δ 0.72 (t, 3H, J=7.2 Hz); 0.92 (t, 3H, J=7.2 Hz), 1.50 (s, 3H), 1.64–1.80 (m, 2H), 2.02–2.16 (m, 2H), 2.22–2.36 (m, 2H), 2.96 (d, 2H, J=2.2 Hz), 3.88 (q, 2H, J=7.2 Hz), 5.22 (bs, 1H), 5.35 (dt, 1H, J=16.1, 6.0 Hz), 5.60 (dd, 1H, J=16.1, 6.6 Hz), 6.12 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 206.8, 166.9, 136.2, 134.8, 130.0, 125.6, 94.3, 61.4, 39.6, 38.4, 30.2, 29.5, 25.8, 14.3, 13.1; EI MS 251, 193, 121, 91, 43 (100%). Anal. calcd for $C_{15}H_{23}NO_5$: C, 60.59; H, 7.80; N, 4.71. Found: C, 60.77; H, 8.02; N, 4.51.

4.2.8. Compound 3h. Oil. IR (neat) 1716, 1628, 1538 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (t, 3H, J=7.5 Hz); 1.12–1.46 (m, 2H), 1.29 (t, 3H, J=7.1 Hz), 1.53–1.70 (m, 2H), 1.86–2.37 (m, 4H), 2.30 (t, 2H, J=7.5 Hz), 3.02 (d, 1H, J=14.4 Hz), 3.15 (d, 1H, J=14.4 Hz), 3.67 (s, 3H), 4.18 (q, 2H, J=7.1 Hz), 5.53 (bs, 1H), 5.59–5.72 (m, 1H), 5.76 (d, 1H, J=16.2 Hz), 6.26 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 173.9, 167.0, 135.7, 135.2, 129.4, 125.0, 94.7, 61.3, 51.7, 39.1, 36.3, 33.8, 25.8, 25.0, 23.6, 14.3, 13.2; EI MS 310, 294, 237 (100%), 177, 91. Anal. calcd for $C_{17}H_{27}NO_6$: C, 59.81; H, 7.97; N, 4.10. Found: C, 60.03; H, 8.14; N, 3.98.

4.2.9. Compound 3i. Oil. IR (neat) 1718, 1629, 1542 cm^{-1}; ^1H NMR (C_6D_6) δ 0.86 (t, 3H, J=7.3 Hz); 1.35 (s, 3H); 2.90 (d, 2H, J=3.3 Hz); 2.99 (d, 2H, J=6.2 Hz); 3.87 (q, 2H, J=7.3 Hz); 5.2 (d, 1H, J=1.1 Hz); 5.51 (dt, 1H, J=15.7, 6.6 Hz); 5.73 (dt, 1H, J=15.7, 1.5 Hz); 6.11 (d, 1H, J=1.1 Hz); 6.91–7.15 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 166.9, 139.1, 135.0, 133.0, 130.7, 130.2, 128.9, 128.8, 126.7, 91.3, 61.4, 40.8, 38.9, 21.4, 14.4; EI MS 256, 181, 167, 115, 91. Anal. calcd for $C_{17}H_{21}NO_4$: C, 67.29; H, 6.98; N, 4.62. Found: C, 67.11; H, 7.17; N, 4.47.

4.2.10. Compound 3j. Oil. IR (neat) 1718, 1629, 1542 cm^{-1}; ^1H NMR (C_6D_6) δ 0.63 (t, 3H, J=7.3 Hz); 0.88 (t, 3H, J=7.0 Hz); 1.55–1.95 (m, 2H); 2.89 (d, 1H, J=14.6 Hz); 3.00 (d, 1H, J=14.6 Hz); 3.05 (d, 2H, J=6.6 Hz); 3.88 (q, 2H, J=7.0 Hz); 5.21 (s, 1H); 5.46 (dt, 1H, J=16.0, 6.6 Hz); 5.74 (dt, 1H, J=16.0, 1.5 Hz); 6.09 (s, 1H); 6.96–7.18 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 167.0, 139.3, 135.2, 132.8, 129.5, 128.9, 128.8, 128.1, 126.6, 95.2, 61.4, 39.2, 38.8, 30.0, 14.4, 8.7; EI MS 270, 167, 123, 91, 79. Anal. calcd for $C_{18}H_{23}NO_4$: C, 68.10; H, 7.31; N, 4.42. Found: C, 67.93; H, 7.42; N, 4.57.

4.3. General procedure for the preparation of trienes 7i,j

The nitroalkene **1i,j** (1 mmol) and the bromide **2** (193 mg, 138 μl, 1 mmol) are dissolved in MeCN (15 ml) and then DBU is added (304 mg, 299 μl, 2 mmol); the obtained solution is magnetically stirred at room temperature until the products **3i,j** are formed (30 min., TLC); after that the mixture is refluxed for 8 h to yield the products **7i,j** each as diastereomeric mixture of 4*E*,6*E* and 4*Z*,6*E*. The mixture is finally concentrated and submitted to flash chromatographic column (ciclohexane/ethyl acetate).

4.3.1. Compound 7i. Diastereomeric mixture 4*E*,6*E* and 4*Z*,6*E* (5:1): Oil. IR (neat) 2964, 1715, 1628, 1140 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (t, 3H, J=7.2 Hz), 1.83 (s, 0.5H), 1.86 (s, 2.5H), 3.12 (s, 1.7H), 3.28 (s, 0.3H), 4.22 (q, 1.7H, J=7.2 Hz), 4.23 (q, 0.3H, J=7.2 Hz), 5.53–5.90 (m, 1H), 6.07 (d, 0.83H, J=10.6 Hz), 6.19 (d, 0.17H, J=10.6 Hz), 6.25 (d, 1H, J=1.1 Hz), 6.49 (d, 1H, J=15.4 Hz), 6.99 (dd, 0.17H, J=15.4, 10.6 Hz), 7.01 (dd, 0.83H, J=15.7, 10.6 Hz), 7.16–7.43 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 167.3, 138.8, 138.0, 136.6, 131.1, 128.8, 127.6, 127.3, 126.4, 126.2, 125.5, 61.0, 41.9, 17.1, 14.4. Anal. calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.90; H, 7.99.

4.3.2. Compound 7j. Diastereomeric mixture 4*E*,6*E* and 4*Z*,6*E* (2:1): Oil. IR (neat) 2966, 1716, 1628, 1142 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07 (t, 2H, J=7.3 Hz), 1.08 (t, 1H, J=7.3 Hz), 1.30 (t, 1H, J=7.3 Hz), 1.31 (t, 2H, J=7.3 Hz), 2.13 (q, 1.33H, J=7.3 Hz), 2.29 (q, 0.67H, J=7.3 Hz), 3.14 (s, 0.67H), 3.30 (s, 1.33H), 4.24 (m, 2H), 5.52 (bs, 0.67H), 5.57 (bs, 0.33H), 5.99 (d, 0.33H), 6.20 (d, 0.67H, J=10.7 Hz), 6.23 (bs, 0.67H), 6.27 (bs, 0.33H), 6.49 (d, 0.33H, J=15.3 Hz), 6.53 (d, 0.67H, J=15.6 Hz), 6.97 (dd, 0.67H, J=15.6, 10.7 Hz), 7.02 (dd, 0.33H, J=15.6, 11.0 Hz), 7.16–7.43 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 167.5, 167.4, 142.8, 141.7, 138.3, 138.1, 131.5, 131.3, 128.8 (4C), 127.8, 127.4 (2C), 126.7, 126.5 (2C), 126.4, 125.7, 125.6, 125.2, 61.1, 61.0, 39.0, 33.0, 30.3, 24.3, 14.5 (2C), 13.7, 12.9. Anal. calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 80.21; H, 8.01.

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Crossed aldol reaction using cross-linked polymer-bound lithium dialkylamide

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Abstract—Cross-linked polymer-bound lithium dialkylamides were employed in crossed aldol reaction of various carbonyl compounds with aldehydes to afford the corresponding β-hydroxycarbonyl compounds. The introduction of spacer chains to the polymer-bound lithium dialkylamide between the base moiety and the polystyrene backbone effectively enhanced yields of the desired aldol adducts. Sometimes better yields were obtained by using the polymer-bound reagent having an appropriate spacer-chain with those obtained using lithium diisopropylamide under homogeneous conditions. Repeated use of these polymeric reagents was demonstrated with no loss of efficiency.

1. Introduction

Sterically hindered non-nucleophilic strong bases are useful reagents in preparing carbanions, which undergo various reactions with a variety of electrophiles to afford the corresponding products. Although diisopropylaminomagnesium bromide was first introduced as a sterically hindered non-nucleophilic metal amide in organic synthesis,[1] lithium dialkylamides represented by lithium diisopropylamide (LDA) are widely employed as a hindered non-nucleophilic strong base for the generation of various carbanions by deprotonation of weakly acidic protons in the presence of a variety of functional groups.[2] For example, the lithium dialkylamides form regio- and geometrically controlled enolates from carbonyl compounds,[3,4] which facilitate regio- and stereoselective crossed aldol reactions.[4] Recently, asymmetric synthesis using chiral lithium dialkylamides has been studied extensively.[5–15]

Much attention has been directed to polymer-bound reagents in recent years, because they are easily removed from the reaction medium and can be reused many times easily in comparison with their non-immobilized reagents.[16–24] However, only a few have been reported on the preparation and utilization of polymer-bound metal dialkylamide in organic synthesis in spite of the importance of metal dialkylamides.[25–31] The first attempt to use cross-linked polystyrene-supported lithium dialkylamide as a stronger base than polymer-bound trityllithium for the deprotonation of 1,1-diphenyl-2-chloroethylene was reported in 1981.[25]

Immobilization of chiral metal dialkylamide and its use in enantioselective deprotonation reactions of ketones have emerged.[26,27] In 1999 Majewski et al. prepared soluble and insoluble polymer-supported chiral lithium dialkylamides, then examined the asymmetric crossed aldol reaction of some cyclic ketones to benzaldehyde and enantioselective deprotonation reactions of tropinone, followed by an acylation with trichloroethyl chloroformate.[26] They showed that good enantioselectivity was obtained using the soluble polymer in the presence of lithium chloride. Polymer-supported chiral magnesium dialkylamides were also prepared and were shown to be effective in the deprotonation of 4-substituted and 2,6-disubstituted cyclohexanones, affording the corresponding optically active enol silyl ethers.[27] A stoichiometric amount of polymer-supported chiral lithium dialkylamide has also been employed in the reaction of cyclohexene oxide.[28] During the course of our investigation on the enantioselective isomerization of *meso*-epoxides into highly optically active allylalcohol derivatives, we have already reported the preparation and the use of polymer-bound achiral lithium *N*-alkyl-4-vinylbenzylamide in a catalytic system as an effective regenerator of chiral bases.[29,30]

Although polymer-supported metal dialkylamides were employed in the generation of chiral enolates from cyclic ketones as mentioned above,[26,27] generation of metal enolates by polymer-supported simple achiral metal amides and utilization of the enolate in aldol reaction have not been

Keywords: Supported reagents; Lithium dialkylamides; Aldol reaction; β-Hydroxycarbonyl compounds; Deprotonation; Lithium enolates.
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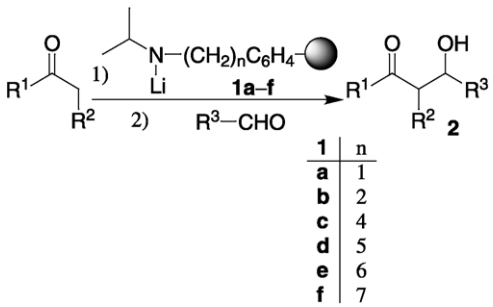
investigated systematically. In this article we report in detail on the preparation of polymer-bound lithium dialkylamides **1a–f** and their use in crossed aldol reactions between various carbonyl compounds such as ketones, esters, and amides, and aldehydes since aldol reaction is one of the most fundamental and important reactions (Scheme 1).[31]



1	n
a	1
b	2
c	4
d	5
e	6
f	7

Scheme 1.

2. Results and discussion

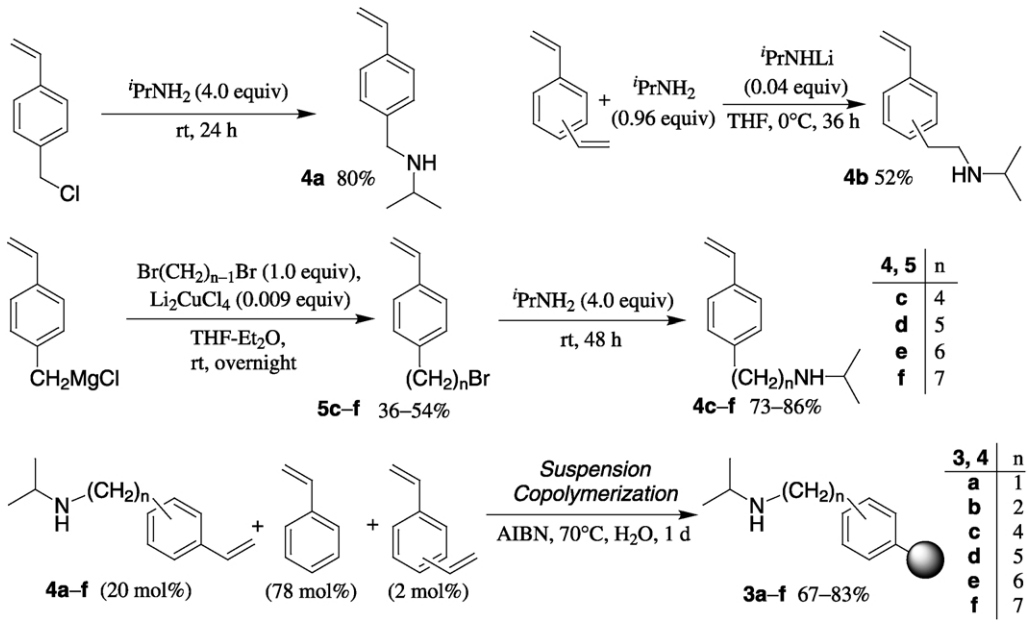
2.1. Synthesis of precursors of lithium dialkylamides

N-Isopropyl-4-vinylbenzylamine (**4a**) (n=1) was easily obtained by the alkylation of isopropylamine (4.0 equiv.) by 4-vinylbenzyl chloride (1.0 equiv.) at rt for 24 h in 80% yield. *N*-Isopropyl-2-(vinylphenyl)ethylamine (**4b**) (n=2) was prepared from isopropylamine (0.96 equiv.) and divinylbenzene (1.0 equiv.) in the presence of a catalytic amount of lithium isopropylamide (0.04 equiv.) according to a procedure similar to that reported by Tsuruta et al.[32] *N*-Isopropyl-ω-(4-vinylphenyl)alkylamines (**4c–f**) (n≥4) were obtained in good yields (73–86%) by the reaction of isopropylamine (4.0 equiv.) and bromoalkylstyrenes **5c–f** (1.0 equiv.) at rt for 48 h. The ω-bromoalkylstyrenes **5c–f** were obtained in reasonable yields (36–54%) by the cross-coupling reaction[33] of α,ω-dibromoalkanes (1.0 equiv.) with 4-vinylbenzylmagnesium chloride (1.0 equiv.) in the presence of lithium tetrachlorocuprate (0.009 equiv.) at rt overnight.

Each of the resulting monomer **4a–f** (20 mol%) was copolymerized with styrene (78 mol%) and divinylbenzene (2 mol%) in the presence of 2,2′-azobisisobutyronitrile (AIBN) according to the method similar to that described previously,[30] and the corresponding polymer-bound dialkylamines **3a–f** were obtained. The procedures are summarized in Scheme 2.

2.2. Crossed aldol reaction between 3-pentanone and benzaldehyde using polymer-bound lithium *N*-isopropyl-4-vinylbenzylamide

In the first place, the aldol reaction of 3-pentanone with benzaldehyde was examined by using 1.2 equiv. of polymer-bound lithium *N*-isopropyl-4-vinylbenzylamide **1a** as a base. Namely, to a suspension of polymer-bound *N*-isopropyl-4-vinylbenzylamine **3a** (amine content: 1.68 mmol/g; particle size: 50–100 mesh; cross-linked with 2 mol% of divinylbenzene, 750 mg, 1.3 mmol) in THF (6 mL) was added a hexane solution of butyllithium (1.54 M, 0.78 mL, 1.2 mmol) dropwise at rt and the reaction mixture was stirred for 0.5 h. A THF (2 mL) solution of 3-pentanone (86.1 mg, 1.0 mmol) was added to the reaction mixture at −78 °C and stirring was continued at the temperature for 15 min. After an addition of THF (2 mL) solution of benzaldehyde (127 mg, 1.2 mmol), the reaction mixture was stirred at −78 °C for 90 min. 1-Hydroxy-2-methyl-1-phenyl-3-pentanone (**2a**) was obtained in 65% yield after the work up of the reaction (Conditions A, Table 1, entry 1). As insufficient formation of the lithium enolate of 3-pentanone was assumed to be the reason for the rather low yield, the reaction temperature was gradually increased to rt during the 15 min in order to complete the generation of the enolate after stirring the mixture at −78 °C for 15 min. The yield of aldol **2a** was increased to 71% (Conditions B, Table 1, entry 2). Although still lower than

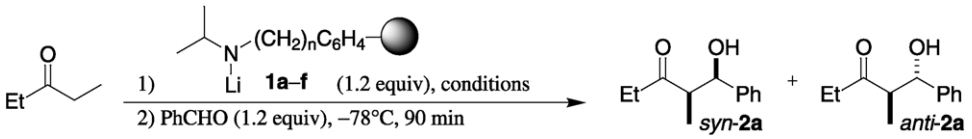


4, 5	n
c	4
d	5
e	6
f	7

3, 4	n
a	1
b	2
c	4
d	5
e	6
f	7

Scheme 2.

Table 1. Aldol reaction of 3-pentanone with benzaldehyde using polymer-bound lithium dialkylamides **1a–f**



Entry	Li-amide	*n*	Conditions[a]	Yield (%)[b]	*syn*:*anti*[c]
1	**1a**	1	A	65	68:32
2	**1a**	1	B	71	69:31
3	**1b**	2	A	65	69:31
4	**1b**	2	B	78	71:29
5	**1c**	4	A	80	68:32
6	**1c**	4	B	87	71:29
7	**1d**	5	A	82	69:31
8	**1d**	5	B	90	69:31
9	**1e**	6	A	80	69:31
10	**1e**	6	B	89	72:28
11	**1f**	7	A	77	68:32
12	**1f**	7	B	87	71:29
13	LDA	—	A	88	62:38
14	LDA	—	B	91	62:38

[a] Conditions A: the enolate was generated at −78 °C for 15 min. Conditions B: the enolate was generated at −78 °C for 15 min and then the resulting mixture was allowed to warm to rt for 15 min.
[b] Isolated yield of aldol **2a**.
[c] Determined by ^{1}H NMR analysis.

those obtained using LDA (Table 1, entries 13 and 14), slightly higher *syn*/*anti* ratios were obtained in the reaction using polymer **1a** (Table 1, entries 1 and 2).

2.3. Effect of spacer-modified polymer-bound lithium dialkylamides on the aldol reaction between 3-pentanone and benzaldehyde

Next, we examined polymer-bound lithium dialkylamide with several spacers between the base site and the polymer support so as to improve the yield of the aldol reaction, since the modification of polymer-bound reagents with spacers sometimes enhance their performance.[34,35] The aldol reaction between 3-pentanone and benzaldehyde was examined using polymer-bound lithium dialkylamide **1b–f** under Conditions A and B as described in Section 2.2. Although the same yield (65%) was observed using polymer **1a** or **1b** under Conditions A (Table 1, entries 1 and 3), the yield was improved to 78% using polymer **1b** under Conditions B (Table 1, entry 4). Then spacer-modified polymer-bound lithium dialkylamide **1c–f** was employed in the reaction under Conditions A as well as Conditions B. As the chain length was elongated up to a pentylene group, the yield of aldol **2a** was gradually improved to 90% under Conditions B (Table 1, entry 8), although longer spacers ($n>5$) had very little influence on the yield (Table 1, entries 10 and 12). Thus, almost the same yield as LDA (Table 1, entries 13 and 14) was realized using **1d** under Conditions B. The *syn*/*anti* ratio of the product **2a** was higher in every case than that observed when LDA was used.

2.4. Aldol reaction of 3-pentanone and cyclohexanone with aldehydes using spacer-modified polymer-bound lithium dialkylamide

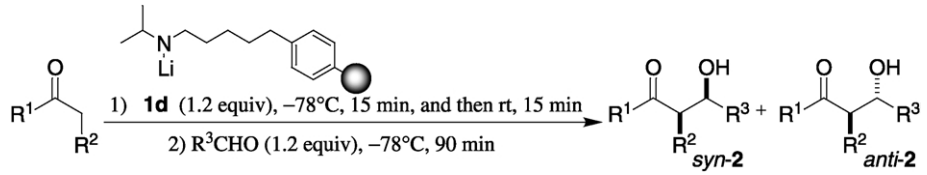
As good results were obtained in the reaction of 3-pentanone and benzaldehyde using **1d**, the reaction of 3-pentanone and cyclohexanone with several aldehydes using **1d** was examined under Conditions B employing a procedure similar to that described in Section 2.2. The results are summarized in Table 2 along with the results obtained using LDA in place of **1d**. In most cases the yields were comparable to those obtained using LDA and slightly higher selectivities were observed in some cases (Table 2, entries 1, 3, 4, 7, and 9) when the spacer-modified polymer-bound reagent **1d** was used.

2.5. Aldol reaction of methyl ketones with several aldehydes using spacer-modified polymer-bound lithium dialkylamide

Next, the aldol reaction of several methyl ketones with aldehydes was investigated in order to examine the regioselectivity of the reaction. The results are summarized in Table 3. At first, the aldol reaction between 2-pentanone and benzaldehyde was carried out using polymer-bound lithium dialkylamide **1a** under Conditions B. The aldol adduct, 1-hydroxy-1-phenyl-3-hexanone (**2k**), was obtained regioselectively in 67% yield (Table 3, entry 1). In contrast to the cases of the reaction of 3-pentanone shown in Table 1, Conditions A gave a better yield (76% yield, Table 3, entry 2). By using spacer-modified polymer-bound lithium dialkylamide **1d** under Conditions A, the yield of aldol **2k** was further increased to 88% (Table 3, entry 3). Then, under Conditions A, the aldol reaction of 2-pentanone with 3-phenylpropanal, cyclohexanecarbaldehyde, or 2-methylpropanal was examined using **1a** as well as **1d**. Corresponding aldol adducts **2l–n** were obtained in good to high yields using **1d**. Better yields as compared to those by using LDA were obtained for all aldehydes examined using **1d** (Table 3, entries 3, 5, 7, and 9).

Enolate was also regioselectively generated from 4-methyl-3-penten-2-one with polymer **1a** and **1d**, and 1-hydroxy-5-

Table 2. Aldol reaction of 3-pentanone and cyclohexanone with aldehydes using spacer-modified polymer **1d**



Entry	Aldol adduct	R^1	R^2	R^3	Yield (%)[a,b]	*syn*:*anti*[b,c]
1	**2a**	Et	Me	Ph	90 (91)	73:27 (62:38)
2	**2b**	Et	Me	*p*-ClC_6H_4	88 (89)	74:26 (77:23)
3	**2c**	Et	Me	*o*-$MeOC_6H_4$	84 (83)	65:35 (53:47)
4	**2d**	Et	Me	*trans*-PhCH=CH	93 (83)	66:34 (60:40)
5	**2e**	Et	Me	*c*-C_6H_{11}	82 (78)	40:60 (29:71)
6	**2f**	Et	Me	$Ph(CH_2)_2$	88 (90)	70:30 (71:29)
7	**2g**	Et	Me	*n*-Pr	65 (70)	72:28 (70:30)
8	**2h**	$-(CH_2)_4-$		Ph	82 (73)	27:73 (25:75)
9	**2i**	$-(CH_2)_4-$		*i*-Pr	59 (61)	3:97 (4:96)
10	**2j**	$-(CH_2)_4-$		$Ph(CH_2)_2$	56 (64)	30:70 (29:71)

[a] Isolated yield of aldol **2a**–**j**.
[b] The figures in parentheses are the results obtained by using LDA in place of polymer-bound lithium dialkylamide **1d**.
[c] Determined by ^1H NMR analysis.

methyl-1-phenyl-4-hexen-3-one (**2o**) was obtained in 81% yield in both cases (Table 3, entries 10–12). A side reaction, e.g. 1,4-addition of polymer **1a** and **1d** to the carbon–carbon bond of 4-methyl-3-penten-2-one, was not problematic (Table 3, entry 11).

Then the reaction of acetone, the least hindered ketone, with benzaldehyde was examined using polymer-bound lithium dialkylamide **1a** and **1d**. The aldol, 4-hydroxy-4-phenyl-2-butanone (**2p**), was obtained only in a moderate yield (60%) when **1a** was used. The yield was improved to 80% using **1d**.

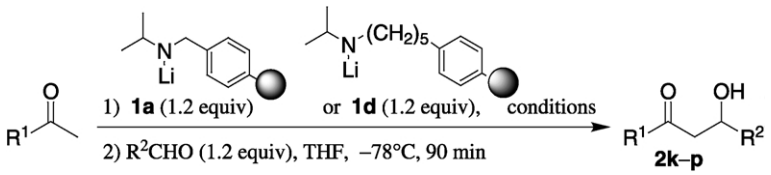
As described above, polymer-bound lithium dialkylamide effectively generates the enolate regioselectively from methyl ketones, and the corresponding aldol products were obtained in good yields by the subsequent reaction with aldehydes.

2.6. Aldol reaction of propionic acid esters with aldehydes using polymer-bound lithium dialkylamides

As polymer-bound lithium dialkylamides **1a** and **1d** were successfully employed to generate enolates from ketones and to afford the corresponding aldols in the reaction with aldehydes, we next examined the generation of enolates from propionic acid esters and their reaction with aldehydes.

Enolate of 2,6-dimethylphenyl propionate (DMP propionate) was generated using **1a** at −78 °C for 15 min

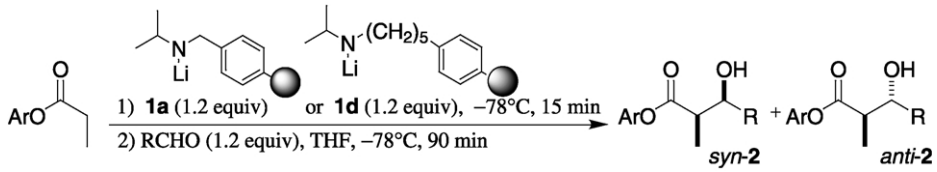
Table 3. Aldol reaction of methyl ketones with several aldehydes using polymer-bound lithium dialkylamides



Entry	Aldol adduct	R^1	R^2	Li-amide	Conditions[a]	Yield (%)[b]
1	**2k**	*n*-Pr	Ph	**1a**	B	67
2	**2k**	*n*-Pr	Ph	**1a**	A	76
3	**2k**	*n*-Pr	Ph	**1d**	A	88 (83)[c]
4	**2l**	*n*-Pr	$Ph(CH_2)_2$	**1a**	A	57
5	**2l**	*n*-Pr	$Ph(CH_2)_2$	**1d**	A	93 (86)[c]
6	**2m**	*n*-Pr	*c*-C_6H_{11}	**1a**	A	63
7	**2m**	*n*-Pr	*c*-C_6H_{11}	**1d**	A	82 (79)[c]
8	**2n**	*n*-Pr	*i*-Pr	**1a**	A	60
9	**2n**	*n*-Pr	*i*-Pr	**1d**	A	79 (73)[c]
10	**2o**	Me_2C=CH	Ph	**1a**	B	81
11	**2o**	Me_2C=CH	Ph	**1d**	B	81 (84)[c]
12	**2o**	Me_2C=CH	Ph	**1d**	A	81
13	**2p**	Me	Ph	**1a**	A	60
14	**2p**	Me	Ph	**1d**	A	80 (85)[c]

[a] Conditions A: the enolate was generated at −78 °C for 15 min. Conditions B: the enolate was generated at −78 °C for 15 min and then the resulting mixture was allowed to warm to rt for 15 min.
[b] Isolated yield of aldol **2k**–**p**.
[c] The figures in parentheses are the results obtained by using LDA in place of polymer-bound lithium amide **1a** and **1d**.

Table 4. Aldol reaction of propionic acid aryl esters with aldehydes using polymer-bound lithium dialkylamides



Entry	Ar[a]	R	Adduct	Base	Yield (%)[b]	*syn*:*anti*[c]
1	DMP	Ph	**2q**	**1a**	32[d]	17:83
2	DMP	Ph	**2q**	**1d**	72 (85)[e]	23:77 (11:89)[e]
3	BHT	Ph	**2r**	**1a**	25[f]	7:93
4	BHT	Ph	**2r**	**1d**	92 (97)[e]	3:97 (<2:98)[e]
5	BHT	*c*-C_6H_{11}	**2s**	**1d**	64	<2:98
6	BHT	*i*-Pr	**2t**	**1d**	79	<2:98
7	BHT	*n*-Pr	**2u**	**1d**	82	3:97

[a] DMP=2,6-dimethylphenyl. BHT=2,6-di-*tert*-butyl-4-methylphenyl.
[b] Isolated yield of aldol **2q**–**u**.
[c] Determined by ^{1}H NMR analysis.
[d] The 2,6-dimethylphenyl propionate was recovered in 68%.
[e] The figures in parentheses are the results obtained by using LDA in place of polymer-bound lithium amides **1a** and **1d**.
[f] The 2,6-di-*tert*-butyl-4-methylphenyl propionate was recovered in 70%.

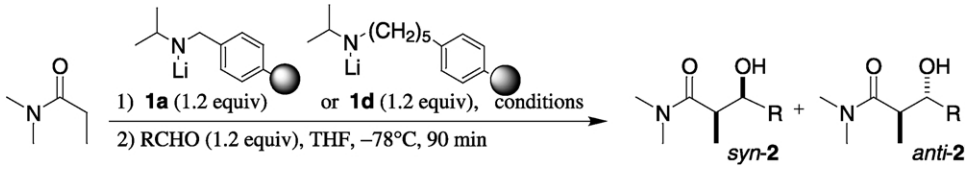
(Conditions A) and the reaction of the enolate with benzaldehyde was carried out at −78 °C for 90 min (Table 4, entry 1). 3-Hydroxy-2-methyl-3-phenylpropionic acid 2,6-dimethylphenyl ester (**2q**) was obtained in only 32% yield (*syn*/*anti*=17:83) with the recovery of the starting material (68%). Then, the reaction temperature was gradually increased to rt during the 15 min after stirring the mixture at −78 °C for 15 min (Conditions B). However, the yield was not improved using **1a**. The yield of **2q** was considerably improved to 72% using spacer-modified polymer **1d** (Table 4, entry 2).

Then, the aldol reaction of more hindered aryl ester, 2,6-di-*tert*-butyl-4-methylphenyl propionate (BHT propionate) with aldehydes was examined to improve *syn*/*anti* ratio of the product. The reaction of BHT propionate and benzaldehyde using polymer **1a** afforded aldol **2r** with higher stereoselectivity (*syn*/*anti*=7:93) but in low yield (25%) (Table 4, entry 3). The yield was enhanced to 92% using spacer-modified polymer **1d** with high *anti*-selectivity (Table 4, entry 4). Then, the aldol reaction of BHT propionate with cyclohexanecarbaldehyde, 2-methylpropanal, and butanal was examined using polymer **1d** and the corresponding *anti*-aldols **2s**–**u** were obtained in good to high yields with very high stereoselectivities (Table 4, entries 5–7).

2.7. Aldol reaction of *N*,*N*-dimethylpropionamide with aldehydes using polymer-bound lithium dialkylamides

The generation of enolate and its reaction was also examined for *N*,*N*-dimethylpropionamide. 3-Hydroxy-2,*N*,*N*-trimethyl-3-phenylpropionamide (**2v**) was obtained in 77% yield (*syn*/*anti*=64:36) by the reaction with

Table 5. Aldol reaction of *N*,*N*-dimethylpropionamide with aldehydes using polymer-bound lithium dialkylamides



Entry	R	Adduct	Base	Conditions[a]	Yield (%)[b]	*syn*:*anti*[c]
1	Ph	**2v**	**1a**	A	77	64:36
2	Ph	**2v**	**1a**	B	96	64:36
3	Ph	**2v**	**1d**	B	99 (97)[d]	62:38 (59:41)[d]
4	$Ph(CH_2)_2$	**2w**	**1a**	B	88	74:26
5	$Ph(CH_2)_2$	**2w**	**1d**	B	83	74:26
6	*c*-C_6H_{11}	**2x**	**1a**	B	93	86:14
7	*c*-C_6H_{11}	**2x**	**1d**	B	93	82:18
8	*i*-Pr	**2y**	**1a**	B	94	85:15
9	*i*-Pr	**2y**	**1d**	B	98	84:16

[a] Conditions A: the enolate was generated at −78 °C for 15 min. Conditions B: the enolate was generated at −78 °C for 15 min and then the resulting mixture was allowed to warm to rt for 15 min.
[b] Isolated yield of aldol **2v**–**y**.
[c] Determined by ^{1}H NMR analysis.
[d] The figures in parentheses are the results obtained by using LDA in place of polymer-bound lithium amides **1a** and **1d**.

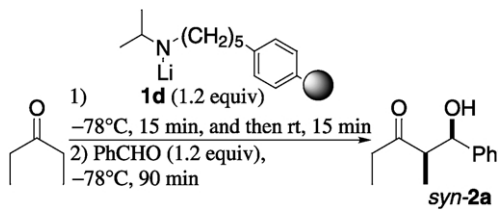
benzaldehyde after the generation of the enolate under Conditions A using **1a** (Table 5, entry 1). The yield was improved to 96% by employing Conditions B (Table 5, entry 2). Almost quantitative yield was achieved when **1d** was used in place of **1a** (Table 5, entry 3).

The reaction was applied to 3-phenylpropanal, cyclohexanecarbaldehyde, and 2-methylpropanal using **1a** and **1d** under Conditions B. Corresponding adducts **2w**–**y** were obtained in high yields with good *syn*/*anti* selectivities (Table 5, entries 4–9).

2.8. Reusability of polymer-bound lithium dialkylamide for the aldol reaction

As the usefulness of spacer-modified polymer-bound lithium dialkylamide **1d** was realized in the aldol reaction of ketones and carboxylic acid derivatives with aldehydes to afford various β-hydroxycarbonyl compounds, its recovery and repeated use were examined in the reaction between 3-pentanone and benzaldehyde under Conditions B. After quenching the aldol reaction using phosphate buffer (pH 7), the mixture was filtered through a glass filter. The recovered spacer-modified polymer-bound amine **3d** was successively rinsed with dichloromethane and water, and then dried under vacuum at 90 °C for 16 h. The dried polymer **3d** swollen in THF was then treated with a hexane solution of butyllithium to regenerate polymer-bound lithium dialkylamide **1d** by the same procedure for the conversion of a new precursor **3d** to polymer **1d**. The regenerated polymer **1d** was used in the aldol reaction between 3-pentanone and benzaldehyde again. The results are shown in Table 6. The yield and *syn*/*anti* selectivity of aldol adduct **2a** scarcely changed after the polymer-bound lithium dialkylamide **1d** was used five times.

Table 6. Reuse of polymer-bound lithium dialkylamide



Batch no.	Yield of **2a** (%)[a]	*syn*:*anti*[b]
1	90	73:37
2	87	70:30
3	89	69:31
4	90	70:30
5	89	71:29
6	89	69:31

[a] Isolated yield of aldol **2a**.
[b] Determined by ^{1}H NMR analysis.

3. Conclusions

Various polymer-bound lithium dialkylamides **1a**–**f** cross-linked with divinylbenzene were derived from the corresponding *N*-isopropyl-ω-(vinylphenyl)alkylamines (**4a**–**f**). The spacer served for an increase of the reactivity of the reagent, and **1b**–**f** was more effective than **1a** in crossed aldol reaction, although polymer **1a** promoted the reaction between *N*,*N*-dimethylpropionamide and aldehydes in good yields. In particular, **1d** modified with a pentamethylene spacer effectively promoted crossed aldol reaction between various carbonyl compounds and aldehydes to afford the corresponding adducts in up to 99% yield. The reagent showed higher *syn*/*anti* selectivities compared to those obtained using LDA under homogeneous conditions in most cases. The method for the recovery and reuse of the base **1d** was also demonstrated. The effect of the alkylene spacers on the reactivity of the polymer-bound lithium dialkylamide revealed by this work would be useful for the attachment of valuable lithium dialkylamides, e.g. chiral lithium dialkylamides, onto the polymer.

4. Experimental

4.1. General

All air-sensitive reactions were carried out under an atmosphere of argon. Tetrahydrofuran (THF) and diethyl ether were distilled under argon over sodium benzophenone ketyl before use. 4-Vinylbenzyl chloride was distilled over calcium hydride under reduced pressure. Lithium tetrachlorocuprate in tetrahydrofuran was purchased from Aldrich. Commercially available solution of butyllithium in hexane (Kanto Chemical Co., Inc.) was used to generate lithium dialkylamides. Proton NMR spectra were measured with a JEOL MY60 spectrometer at 60 MHz, a JEOL EX270 spectrometer at 270 MHz, or with a JEOL AL400 spectrometer at 400 MHz, using $CDCl_3$ as solvent. Carbon NMR spectra were recorded at 68 MHz with a JEOL EX270 spectrometer or at 100 MHz with a JEOL AL400 spectrometer using $CDCl_3$ as solvent. The chemical shifts are given in ppm relative to tetramethylsilane (δ scale) used as an internal standard. Infrared spectra were taken on a Perkin–Elmer Paragon 1000 spectrometer. Mass spectra were measured on a JEOL JMS-600 mass spectrometer using electron impact (EI). Melting points were measured on a Büchi 535 apparatus and are uncorrected. Elemental analyses were carried out on a Perkin–Elmer 2400 CHN analyzer or a Perkin–Elmer 2400 II CHNS/O analyzer. TLC analyses were done on silica-gel 60 F_{254}-coated plates (E. Merck). Column chromatography was carried out with Wakogel C-200 gel unless otherwise specified. Preparative TLC was performed on silica-gel-coated plates (Wakogel B-5F, 20 cm×20 cm).

4.2. Preparation of 4-vinylbenzylmagnesium chloride

A solution of 4-vinylbenzyl chloride (25.0 g, 0.165 mol) in diethyl ether (25 mL) was added dropwise to a mixture of magnesium (4.5 g, 0.19 mol) for 2 h after activation of magnesium with a small piece of iodine in diethyl ether (75 mL) at 0 °C. After stirring for 1 h at 0 °C, the reaction temperature was allowed to increased to rt for 30 min and the mixture was stirred for 1 h. The resulting solution was directly used for the next cross-coupling reaction.

4.3. Synthesis of ω-bromoalkylstyrenes

4.3.1. 1-(4-Bromobutyl)-4-vinylbenzene (5c). A solution of 4-vinylbenzylmagnesium chloride prepared from

0.165 mol of 4-vinylbenzyl chloride in diethyl ether (100 mL) was added dropwise for 3 h to a solution of 1,3-dibromopropane (33.3 g, 0.165 mol) in THF (150 mL) in the presence of lithium tetrachlorocuprate (0.1 M, 15 mL, 1.5 mmol) at 0 °C.[33] After the addition was completed the mixture was stirred overnight at rt. Methanol (5 mL) was then added to cease the reaction. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure in the presence of 2,2-diphenyl-1-picrylhydrazil (DPPH). The resulting mixture was poured into water and extracted with toluene (3×50 mL). The combined organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated. Then the residue was distilled in vacuo in the presence of DPPH to give 1-(4-bromobutyl)-4-vinylbenzene (20.9 g, 53%) as a colorless oil (bp 77 °C/0.028 mmHg). IR (neat): 3085, 3005, 2938, 2858, 1629, 1512, 1458, 1437, 1407, 1251, 991, 907, 844, 827; ^{1}H NMR ($CDCl_3$): 1.70–1.94 (m, 4H), 2.62 (t, J=7.3 Hz, 2H), 3.40 (t, J=6.6 Hz, 2H), 5.19 (dd, J=1.0, 10.9 Hz, 1H), 5.71 (dd, J=1.0, 17.8 Hz, 1H), 6.69 (dd, J=10.7, 17.7 Hz, 1H), 7.13 (d, J=7.9 Hz, 2H), 7.33 (d, J=8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$): 29.7, 32.1, 33.6, 34.6, 113.0, 126.2, 128.5, 135.3, 136.5, 141.5; MS: m/z (%): 240 (M^++2, 23), 238 (M^+, 23), 117 (100), 115 (13), 91 (8). Exact mass for $C_{12}H_{15}Br$: 238.0357. Found 238.0357.

4.3.2. 1-(5-Bromopentyl)-4-vinylbenzene (5d). By a procedure similar to that for 1-(4-bromobutyl)-4-vinylbenzene (**5c**), the cross-coupling reaction with 1,4-dibromobutane (35.6 g, 0.165 mol) and 4-vinylbenzylmagnesium chloride was conducted to give 1-(5-bromopentyl)-4-vinylbenzene as a colorless oil (22.4 g, 54%). Bp 98 °C/0.045 mmHg; IR (neat): 3085, 2934, 2857, 1630, 1512, 1459, 1246, 991, 906, 832; ^{1}H NMR ($CDCl_3$): 1.41–1.54 (m, 2H), 1.58–1.69 (m, 2H), 1.83–1.93 (m, 2H), 2.61 (t, J=7.6 Hz, 2H), 3.40 (t, J=6.8 Hz, 2H), 5.20 (dd, J=0.99, 10.9 Hz, 1H), 5.70 (d, J=0.99, 17.5 Hz, 1H), 6.69 (dd, J=10.9, 12.8 Hz, 1H), 7.13 (d, J=7.9 Hz, 2H), 7.33 (d, J=7.9 Hz, 2H); ^{13}C NMR ($CDCl_3$): 27.8, 30.5, 32.6, 33.8, 35.4, 112.9, 126.1, 128.5, 135.2, 136.6, 142.0; MS: (m/z) %: 254 (M^++2, 23), 252 (M^+, 11), 117 (100), 115 (12), 91 (8). Exact mass for $C_{13}H_{17}Br$: 252.0514. Found 252.0512.

4.3.3. 1-(6-Bromohexyl)-4-vinylbenzene (5e). By a procedure similar to that for 1-(4-bromobutyl)-4-vinylbenzene (**5c**), the cross-coupling reaction with 1,5-dibromopentane (37.9 g, 0.165 mol) and 4-vinylbenzylmagnesium chloride was conducted to give 1-(6-bromohexyl)-4-vinylbenzene as a colorless oil (15.8 g, 36%). Bp 104 °C/0.045 mmHg. IR (neat): 3085, 3006, 2933, 2857, 2361, 1630, 1512, 1458, 1438, 1259, 1225, 991, 907, 839; ^{1}H NMR ($CDCl_3$): 1.26–1.68 (m, 6H), 1.80–1.95 (m, 2H), 2.60 (t, J=7.6 Hz, 2H), 3.40 (t, J=6.9 Hz, 2H), 5.19 (dd, J=0.99, 10.9 Hz, 1H), 5.70 (dd, J=0.99, 17.8 Hz, 1H), 6.69 (dd, J=10.9, 17.8 Hz, 1H), 7.13 (d, J=7.9 Hz, 2H), 7.33 (d, J=8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$): 28.0, 28.3, 31.2, 32.7, 34.0, 35.5, 112.7, 126.0, 128.4, 134.9, 136.5, 142.1; MS: (m/z) %: 268 (M^++2, 25), 266 (M^+, 28), 118 (15), 117 (100), 115 (11), 91 (8). Exact mass for $C_{14}H_{19}Br$: 266.0670. Found: 266.0670.

4.3.4. 1-(7-Bromoheptyl)-4-vinylbenzene (5f). By a similar to that procedure for 1-(4-bromobutyl)-4-vinylbenzene (**5c**), the cross-coupling reaction with 1,6-dibromohexane (40.3 g, 0.165 mol) and 4-vinylbenzylmagnesium chloride was conducted to yield 1-(7-bromoheptyl)-4-vinylbenzene as a colorless oil (18.0 g, 39%). Bp 114 °C/0.060 mmHg. IR (neat): 3085, 3005, 2934, 2858, 1907, 1817, 1629, 1512, 1458, 1437, 1251, 991, 907, 844; ^{1}H NMR ($CDCl_3$): 1.31–1.46 (m, 6H), 1.55–1.66 (m, 2H), 1.84 (quint, J=7.1 Hz, 2H), 2.59 (t, J=7.6 Hz, 2H), 3.39 (t, J=6.9 Hz, 2H), 5.18 (d, J=11.9 Hz, 1H), 5.69 (d, J=16.5 Hz, 1H), 6.68 (dd, J=10.9, 17.5 Hz, 1H), 7.12 (d, J=7.9 Hz, 2H), 7.32 (d, J=8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$): 28.1, 28.7, 29.1, 31.3, 32.8, 34.0, 35.6, 112.7, 126.0, 128.4, 134.9, 136.5, 142.3; MS: (m/z) %: 282 (M^++2, 26), 280 (M^+, 26), 118 (15), 117 (100), 115 (10), 91 (8). Exact mass for $C_{15}H_{21}Br$: 280.0827. Found 280.0829.

4.4. Synthesis of ω-(isopropylamino)alkylstyrenes (4a–f)

4.4.1. *N*-Isopropyl-4-vinylbenzylamine (4a). To isopropylamine (47.3 g, 0.40 mol) was added 4-vinylbenzyl chloride (30.5 g, 0.20 mol) at 0 °C and the mixture was stirred at rt for 24 h. Then dichloromethane and 4 M aqueous solution of sodium hydroxide were added to the reaction mixture. The aqueous solution was extracted with dichloromethane. The combined organic layer was washed with saturated aqueous sodium chloride solution and was dried with anhydrous sodium carbonate. The solvent and isopropylamine were evaporated and the residual oil was purified by column chromatography (silica gel, hexane/ethyl acetate=10:1) and distillation under reduced pressure in the presence of 2,2-diphenyl-1-picrylhydrazil (DPPH) to yield *N*-isopropyl-4-vinylbenzylamine[36,37] as a colorless oil (28.0 g, 80%), bp 66 °C/0.6 mmHg (lit.[36] bp 68 °C/1 mmHg). IR (neat): 3307, 2966, 1630, 1511, 1470, 1380, 1338, 1175, 990, 906, 830, 757, 721; ^{1}H NMR ($CDCl_3$): 1.08 (d, J=6.3 Hz, 6H), 1.36 (br s, 1H), 2.83 (sept, J=6.2 Hz, 1H), 3.75 (s, 2H), 5.20 (dd, J=0.66, 10.9 Hz, 1H), 5.71 (dd, J=1.0, 17.5 Hz, 1H), 6.69 (dd, J=10.9, 17.5 Hz, 1H), 7.27 (d, J=8.2 Hz, 2H), 7.37 (d, J=8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$): 22.8, 47.9, 51.2, 113.2, 126.1, 128.2, 136.1, 136.5, 140.3.

4.4.2. *N*-Isopropyl-2-(vinylphenyl)ethylamine (4b). To 15.4 g of distilled technical 55 wt% divinylbenzene (65 mmol) in THF (48 mL) was added dropwise the mixture of isopropylamine (3.84 g, 65 mmol) in THF (17 mL) and a hexane solution of butyllithium (1.57 M solution, 1.7 mL, 2.6 mmol) for 2 h at 0 °C.[32] After stirring for 36 h at 0 °C, 2-propanol was added to the reaction mixture. The resulting mixture was concentrated under reduced pressure, diluted with ethyl acetate, and washed with water. The organic layer was dried over sodium sulfate and concentrated. The residue was distilled in vacuo in the presence of 2,2-diphenyl-1-picrylhydrazil (DPPH) to give *N*-isopropyl-2-(vinylphenyl)-ethylamine as a colorless oil (6.38 g, 52%), bp 49 °C/0.030 mmHg. IR (neat): 3306, 3087, 3007, 2965, 2867, 2827, 1630, 1512, 1474, 1442, 1379, 1338, 1174, 990, 906, 714; ^{1}H NMR ($CDCl_3$): 1.02 (d, J=6.1 Hz, 6H), 2.38–3.00 (m, 5H), 5.12 (d, J=10.8 Hz, 1H), 5.72 (d, J=17.4 Hz, 1H), 6.64 (dd, J=10.1, 17.5 Hz, 1H), 6.94–7.38 (m, 4H); MS: (m/z) %: 189 (M^+, 2), 131 (15), 117 (10), 115 (12), 91 (13), 72 (100). Exact mass for $C_{13}H_{19}N$: 189.1518. Found 189.1517.

4.4.3. *N*-Isopropyl-4-(4-vinylphenyl)butylamine (4c). To 1-(4-bromobutyl)-4-vinylbenzene (4.78 g, 20 mmol) was added isopropylamine (4.73 g, 80 mmol) at 0 °C. After stirring at room temperature for 48 h, 4 M aqueous solution of sodium hydroxide was added to the reaction mixture until most precipitate dissolved. The aqueous solution was extracted with dichloromethane. The combined organic layer was washed with saturated aqueous sodium chloride solution and was dried with anhydrous sodium carbonate. The solvent and isopropylamine were evaporated, and the residual oil was purified by silica gel chromatography with Chromatorex DM1020 (−100+200 mesh, Fuji Silysia Chemical Ltd) using hexane/ether (1:0–0:1) as eluent, giving *N*-isopropyl-4-(4-vinylphenyl)butylamine as a colorless oil (3.72 g, 86%). IR (neat): 3086, 2932, 2864, 1630, 1512, 1472, 1379, 1174, 990, 904, 842; ^{1}H NMR ($CDCl_3$): 1.04 (d, *J*=6.3 Hz, 6H), 1.48–1.68 (m, 4H), 2.57–2.64 (m, 4H), 2.76 (sept, *J*=6.3 Hz, 1H), 5.18 (dd, *J*=0.66, 10.9 Hz, 1H), 5.70 (dd, *J*=0.50, 17.3 Hz, 1H), 6.20 (dd, *J*=10.9, 17.8 Hz, 1H), 7.13 (d, *J*=8.6 Hz, 2H), 7.31 (d, *J*=7.9 Hz, 2H); ^{13}C NMR ($CDCl_3$): 23.0, 29.3, 30.1, 35.6, 47.4, 48.7, 112.8, 126.1, 128.6, 135.1, 136.7, 142.3; MS: (*m*/*z*) %: 217 (M^+, 40), 202 (57), 117 (34), 72 (100). Exact mass for $C_{15}H_{23}N$: 217.1831. Found 217.1830.

4.4.4. *N*-Isopropyl-5-(4-vinylphenyl)pentylamine (4d). By a procedure similar to that for *N*-isopropyl-4-(4-vinylphenyl)butylamine, alkylation of isopropylamine (4.73 g, 80 mmol) with 1-(5-bromopentyl)-4-vinylbenzene (5.06 g, 20 mmol) was conducted to yield *N*-isopropyl-5-(4-vinylphenyl)pentylamine as a colorless oil (4.07 g, 83%). IR (neat): 3291, 3085, 2964, 2930, 2856, 1630, 1562, 1512, 1461, 1378, 1362, 1174, 990, 905, 842; ^{1}H NMR ($CDCl_3$): 1.04 (d, *J*=6.3 Hz, 6H), 1.26–1.41 (m, 2H), 1.45–1.54 (m, 2H), 1.56–1.68 (m, 2H), 2.57 (t, *J*=7.3 Hz, 2H), 2.60 (t, *J*=7.6 Hz, 2H), 2.77 (sept, *J*=6.3 Hz, 1H), 5.18 (dd, *J*=0.99, 10.9 Hz, 1H,), 5.70 (dd, *J*=0.99, 17.5 Hz, 1H), 6.69 (dd, *J*=10.9, 17.8 Hz, 1H), 7.13 (d, *J*=7.9 Hz, 2H), 7.33 (d, *J*=8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$): 22.9, 27.0, 30.2, 31.2, 35.5, 47.4, 48.6, 112.7, 126.0, 128.4, 135.0, 136.6, 142.3; MS: (*m*/*z*) %: 231 (M^+, 32), 217 (10), 216 (60), 117 (29), 72 (100). Exact mass for $C_{16}H_{25}N$: 231.1987. Found 231.1986.

4.4.5. *N*-Isopropyl-6-(4-vinylphenyl)hexylamine (4e). By a procedure similar to that for *N*-isopropyl-4-(4-vinylphenyl)butylamine, alkylation of isopropylamine (4.73 g, 80 mmol) with 1-(6-bromohexyl)-4-vinylbenzene (5.34 g, 20 mmol) was conducted to yield *N*-isopropyl-6-(4-vinylphenyl)hexylamine as a colorless oil (3.58 g, 73%). IR (neat): 3350, 3085, 2963, 2855, 1630, 1512, 1465, 1406, 1378, 1337, 1262, 1174, 1120, 991, 904, 831; ^{1}H NMR ($CDCl_3$): 1.04 (d, *J*=5.9 Hz, 6H), 1.32–1.64 (m, 8H), 2.54–2.74 (m, 4H), 2.77 (sept, *J*=6.3 Hz, 1H), 5.18 (d, *J*=9.9 Hz, 1H), 5.69 (d, *J*=17.8 Hz, 1H), 6.69 (dd, *J*=10.9, 17.5 Hz, 1H), 7.12 (d, *J*=7.9 Hz, 2H), 7.32 (d, *J*=7.9 Hz, 2H); ^{13}C NMR ($CDCl_3$): 21.6, 27.1, 28.8, 29.0, 31.2, 35.5, 46.5, 49.2, 112.8, 126.1, 128.5, 135.0, 136.6, 142.4; MS: (*m*/*z*) %: 245 (M^+, 28), 231 (11), 230 (58), 128 (16), 117 (28), 72 (100). Exact mass for $C_{17}H_{27}N$: 245.2144. Found 245.2144.

4.4.6. *N*-Isopropyl-7-(4-vinylphenyl)heptylamine (4f). By a procedure similar to that for *N*-isopropyl-4-(4-vinylphenyl)butylamine, alkylation of isopropylamine (4.73 g, 80 mmol) with 1-(7-bromoheptyl)-4-vinylbenzene (5.62 g, 20 mmol) was conducted to yield *N*-isopropyl-7-(4-vinylphenyl)heptylamine as a colorless oil (4.03 g, 78%). IR (neat): 3086, 2932, 2864, 1630, 1512, 1472, 1379, 1174; ^{1}H NMR ($CDCl_3$): 1.04 (d, *J*=6.3 Hz, 6H), 1.25–1.41 (m, 6H), 1.32 (br s, 1H), 1.43–1.51 (m, 2H), 1.54–1.65 (m, 2H), 2.50–2.61 (m, 4H), 2.77 (sept, *J*=6.3 Hz, 1H), 5.18 (dd, *J*=1.0, 10.9 Hz, 1H,), 5.69 (dd, *J*=1.0, 17.5 Hz, 1H), 6.69 (dd, *J*=10.9, 17.5 Hz, 1H), 7.13 (d, *J*=7.9 Hz, 2H), 7.32 (d, *J*=7.9 Hz, 2H); ^{13}C NMR ($CDCl_3$): 23.1, 27.4, 29.2, 29.4, 30.5, 31.4, 35.7, 47.6, 48.7, 112.6, 125.9, 128.4, 134.9, 136.6, 142.4; MS: (*m*/*z*) %: 259 (M^+, 46), 245 (25), 244 (100), 117 (27), 115 (10). Exact mass for $C_{18}H_{29}N$: 259.2300. Found 259.2302.

4.5. Preparation of polymer-bound *N*-isopropyl-ω-(vinylphenyl)alkylamine (3a–f)

Preparation of 2 mol% cross-linked, 20 mol% ring-substituted ω-isopropylaminoalkylated polystyrene in microporous form was carried out by the suspension copolymerization of *N*-isopropyl-ω-(vinylphenyl)alkylamine (20 mol%), styrene (78 mol%), and divinylbenzene (2 mol%) by the procedure described.[30,38] Polymer-bound *N*-isopropyl-4-vinylbenzylamine (**3a**) was prepared according to the literature procedure.[30]

4.5.1. Polymer-bound *N*-isopropyl-5-(4-vinylphenyl)-pentylamine (3d). A solution of gelatin (0.106 g), poly(diallyldimethylammonium chloride-*co*-sulfur dioxide) (1.1 g, from Nittobo, Japan), boric acid (0.41 g, 5.9 mmol), and sodium nitrate (23 mg, 0.33 mmol) in water (33 mL) was adjusted to pH 9.5 with 25 wt% aqueous sodium hydroxide and was placed in a 50 mL round-bottom flask fitted with a reflux condenser and a mechanical stirrer. To the solution was added a mixture of *N*-isopropyl-5-(4-vinylphenyl)pentylamine (1.39 g, 6.0 mmol), styrene (2.44 g, 23.4 mmol), 142 mg of technical 55% divinylbenzene (0.60 mmol), and 2,2′-azobisisobutyronitrile (32 mg, 0.19 mmol). The flask was purged with nitrogen for 40 min at rt, and a nitrogen atmosphere was maintained throughout the polymerization. The mixture was stirred at 70 °C for 1 day. Stirring speed in this preparation was 430 rpm. The insoluble polymer was obtained by filtration with a glass funnel, and it was washed thoroughly with hot water, methanol, THF, and CH_2Cl_2, successively. Cross-linked polymer-bound reagent **3d** was obtained as beads after removal of the solvent under reduced pressure (<1 mmHg) at 90 °C for 16 h. Sieving the polymer beads through a sieve (50–100 mesh) gave the fraction (2.97 g, 76%) of uniform particle size. The amine content determined by elemental analysis (C, 88.51; H, 9.05; N, 2.35) was 1.68 mmol/g. IR (KBr): 3083, 3060, 2925, 1493, 1377, 836, 758, 699.

4.5.2. Polymer-bound *N*-isopropyl-2-(vinylphenyl)ethylamine (3b). The title compound was obtained by a procedure similar to that for polymer-bound *N*-isopropyl-5-(4-vinylphenyl)pentylamine (83% yield). The amine content determined by elemental analysis (C, 88.41; H, 9.06; N, 2.30) was 1.64 mmol/g. IR (KBr): 3433, 3026,

2962, 2924, 2850, 1602, 1493, 1451, 1377, 1174, 1028, 758, 699, 540.

4.5.3. Polymer-bound *N*-isopropyl-4-(4-vinylphenyl)-butylamine (3c). The title compound was obtained by a procedure similar to that for polymer-bound *N*-isopropyl-5-(4-vinylphenyl)pentylamine (82% yield). The amine content determined by elemental analysis (C, 88.97; H, 10.54; N, 2.38) was 1.70 mmol/g. IR (KBr): 3433, 3026, 2962, 2924, 2850, 1602, 1493, 1451, 1377, 1174, 1028.

4.5.4. Polymer-bound *N*-isopropyl-6-(4-vinylphenyl)-hexylamine (3e). The title compound was obtained by a procedure similar to that for polymer-bound *N*-isopropyl-5-(4-vinylphenyl)pentylamine (73% yield). The amine content determined by elemental analysis (C, 86.99; H, 10.41; N, 2.23) was 1.59 mmol/g. IR (KBr): 3313, 3083, 3060, 3027, 2922, 2853, 1666, 1602, 1511, 1492, 1452, 1378, 1362, 1336, 1173, 1029.

4.5.5. Polymer-bound *N*-isopropyl-7-(4-vinylphenyl)-heptylamine (3f). The title compound was obtained by a procedure similar to that for polymer-bound *N*-isopropyl-5-(4-vinylphenyl)pentylamine (67% yield). The amine content determined by elemental analysis (C, 87.99; H, 9.88; N, 2.05) was 1.46 mmol/g. IR (KBr): 3315, 3083, 3061, 3027, 2925, 2853, 1660, 1602, 1511, 1494, 1453, 1378, 1337, 1179, 1029.

4.6. Aldol reactions using polymer-bound lithium dialkylamides (1a–f), general procedure

Conditions A. To a suspension of polymer-bound *N*-isopropyl-4-vinylbenzylamine **3a** (amine content: 1.68 mmol/g; particle size: 50–100 mesh; cross-linked with 2 mol% of divinylbenzene, 750 mg, 1.3 mmol) in THF (6 mL) was added a hexane solution of butyllithium (1.54 M, 0.78 mL, 1.2 mmol) at rt and the reaction mixture was stirred for 0.5 h. Carbonyl compound (1.0 mmol) in THF (2 mL) was added dropwise to the reaction mixture at −78 °C and stirring was continued for 15 min. A THF (2 mL) solution of aldehyde (1.2 mmol) was added to the mixture at −78 °C. After keeping the temperature at −78 °C for 90 min, the reaction was quenched with phosphate buffer (pH 7). The resin was filtered off, washed with CH_2Cl_2 and H_2O, and dried in vacuo at 90 °C for 16 h. The organic filtrate was washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the crude product was purified by preparative TLC or silica-gel chromatography, giving the β-hydroxycarbonyl compound.

Conditions B. To a suspension of polymer-bound *N*-isopropyl-4-vinylbenzylamine **3a** (amine content: 1.68 mmol/g; particle size: 50–100 mesh; cross-linked with 2 mol% of divinylbenzene, 750 mg, 1.3 mmol) in THF (6 mL) was added a hexane solution of butyllithium (1.54 M, 0.78 mL, 1.2 mmol) at rt and the reaction mixture was stirred for 0.5 h. Carbonyl compound (1.0 mmol) in THF (2 mL) was added dropwise to the reaction mixture at −78 °C and stirring was continued for 15 min. The mixture was allowed to warm at rt for 15 min and was cooled to −78 °C again. Then a THF (2 mL) solution of aldehyde (1.2 mmol) was added to the mixture. After keeping the temperature at −78 °C for 90 min, the reaction was quenched with phosphate buffer (pH 7). The resin was filtered off, washed with CH_2Cl_2 and H_2O, and dried in vacuo at 90 °C for 16 h. The organic filtrate was washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the crude product was purified by preparative TLC or silica-gel chromatography, giving the β-hydroxycarbonyl compound.

4.6.1. 1-Hydroxy-2-methyl-1-phenyl-3-pentanone (2a). Yield 90% as a colorless oil (Table 1, entry 8); data consistent with that reported in literatures.[39,40]

4.6.2. 1-(4-Chlorophenyl)-1-hydroxy-2-methyl-3-pentanone (2b). Yield 88% as a colorless oil (Table 2, entry 2); data consistent with that reported in a literature.[39]

4.6.3. 1-Hydroxy-1-(2-methoxyphenyl)-2-methyl-3-pentanone (2c). Yield 84% as a colorless oil (Table 2, entry 3). Aldol **2c** was further purified by preparative thin-layer chromatography (silica-gel, hexane/diethyl ether 3:1) to separate *syn*-**2c** and *anti*-**2c** as colorless oils; data consistent with that reported in a literature.[39]

4.6.4. 5-Hydroxy-4-methyl-7-phenyl-6-hepten-3-one (2d). Yield 93% as a pale yellow oil (Table 2, entry 4); data consistent with that reported in a literature.[39]

4.6.5. 1-Cyclohexyl-1-hydroxy-2-methyl-3-pentanone (2e). Yield 82% as a colorless oil (Table 2, entry 5); data consistent with that reported in literatures.[41,42]

4.6.6. 5-Hydroxy-4-methyl-7-phenyl-3-heptanone (2f). Yield 88% as a colorless oil (Table 2, entry 6); data consistent with that reported in literatures.[39,40]

4.6.7. 5-Hydroxy-4-methyl-3-octanone (2g). Yield 65% as a colorless oil (Table 2, entry 7); data consistent with that reported in literatures.[41,42]

4.6.8. 2-(Hydroxyphenylmethyl)cyclohexanone (2h). Yield 82% as a white solid (Table 2, entry 8). Aldol **2h** was further purified by preparative thin-layer chromatography (silica-gel, hexane/diethyl ether 3:1) to separate *syn*-**2h** and *anti*-**2h** as white crystals; data consistent with that reported in literatures.[43,44]

4.6.9. 2-(1-Hydroxy-2-methylpropyl)cyclohexanone (2i). Yield 59% as a colorless oil (Table 2, entry 9); data consistent with that reported in literatures.[44–46]

4.6.10. 2-(1-Hydroxy-3-phenylpropyl)cyclohexanone (2j). Yield 56% as a viscous oil (Table 2, entry 10); data consistent with that reported in literatures.[47,48]

4.6.11. 1-Hydroxy-1-phenyl-3-hexanone (2k). Yield 88% as a colorless oil (Table 3, entry 3); data consistent with that reported in a literature.[49]

4.6.12. 6-Hydroxy-8-phenyl-4-octanone (2l). Yield 93% as a colorless oil (Table 3, entry 5); IR (neat): 3464, 3027, 2934, 2875, 1708, 1496, 1455, 1408, 1378, 1128, 1098, 1032, 749, 701; ^{1}H NMR ($CDCl_3$): 0.91 (t, J=7.4 Hz, 3H),

1.53–1.89 (m, 4H), 2.39 (t, *J*=7.4 Hz, 2H), 2.47–2.87 (m, 2H), 2.57 (t, *J*=6.1 Hz, 2H), 3.49 (s, 1H), 4.00–4.10 (m, 1H), 7.18–7.31 (m, 5H); ^{13}C NMR ($CDCl_3$): 13.5, 16.8, 31.6, 38.0, 45.3, 48.9, 66.7, 125.6, 128.2, 128.3, 141.7, 212.0; MS: (*m*/*z*) %: 220 (M^+, 8), 203 (13), 202 (72), 159 (15), 149 (22), 131 (24), 117 (23), 115 (15), 105 (11), 104 (11), 92 (23), 91 (86), 72 (14), 71 (100), 57 (16), 55 (11). Exact mass for $C_{14}H_{20}O_2$: 220.1463. Found 220.1465.

4.6.13. 1-Cyclohexyl-1-hydroxy-3-hexanone (2m). Yield 82% as a white solid (Table 3, entry 7); mp 39.2–40.4 °C; IR (neat): 3364, 3289, 2956, 2934, 2894, 2854, 1705, 1447, 1405, 1377, 1353, 1310, 1270, 1127, 1033, 993, 892, 883; ^{1}H NMR ($CDCl_3$): 0.90–1.41 (m, 9H), 1.55–1.87 (m, 7H), 2.42 (t, *J*=7.3 Hz, 2H), 2.48–2.64 (m, 2H), 2.97 (d, *J*=3.6 Hz, 1H), 3.55–3.77 (1H, m); ^{13}C NMR ($CDCl_3$): 13.4, 16.8, 25.9, 26.0, 26.2, 28.0, 28.6, 42.9, 45.4, 46.0, 71.5, 212.4. Exact mass for $C_{12}H_{22}O_2$: 198.1620. Found 198.1593.

4.6.14. 6-Hydroxy-7-methyl-4-octanone (2n). Yield 79% as a colorless oil (Table 3, entry 9); data consistent with that reported in a literature.[50]

4.6.15. 1-Hydroxy-5-methyl-1-phenyl-4-hexen-3-one (2o). Yield 81% as a colorless oil (Table 3, entry 11); IR (neat): 3448, 3086, 3062, 3030, 2975, 2910, 1681, 1618, 1494, 1449, 1383, 1359, 1204, 1115, 1063, 1043, 1013, 824, 800, 701; ^{1}H NMR ($CDCl_3$): 1.91 (d, *J*=1.3 Hz, 3H), 2.18 (d, *J*=1.3 Hz, 3H), 2.82 (s, 1H), 2.84 (d, *J*=0.66 Hz, 1H), 3.71 (d, *J*=2.4 Hz, 1H), 5.15–5.20 (m, 1H), 6.05 (s, 1H), 7.25–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$): 21.0, 27.8, 52.1, 70.1, 123.6, 125.6, 127.4, 128.4, 143.0, 157.6, 200.6; MS: (*m*/*z*) %: 204 (M^+, 16), 186 (14), 162 (18), 120 (35), 107 (15), 106 (13), 105 (38), 83 (100), 79 (16), 77 (28), 55 (22). Exact mass for $C_{13}H_{16}O_2$: 204.1150. Found 204.1153.

4.6.16. 4-Hydroxy-4-phenyl-2-butanone (2p). Yield 80% as a colorless oil (Table 3, entry 14); data consistent with that reported in a literature.[51]

4.6.17. 3-Hydroxy-2-methyl-3-phenylpropionic acid 2,6-dimetylphenyl ester (2q). Yield 72% as a highly viscous colorless oil (Table 4, entry 2); data consistent with that reported in literatures.[52,53]

4.6.18. 3-Hydroxy-2-methyl-3-phenylpropionic acid 2,6-di-*tert*-butyl-4-methylphenyl ester (2r). The *syn*/*anti* ratio was determined by ^{1}H NMR analysis of the crude product in comparison with the ^{1}H NMR data of the 3-hydroxy-2-methyl-3-phenylpropionic acid 2,6-dimethylphenyl ester.[52] Yield 92% as a highly viscous oil (Table 4, entry 4); data consistent with that reported in a literature.[53]

4.6.19. (2*R,3*R**)-3-Cyclohexyl-3-hydroxy-2-methyl-propionic acid 2,6-di-*tert*-butyl-4-methylphenyl ester (2s).** Yield 64% as a highly viscous oil (Table 4, entry 5); IR ($CHCl_3$): 3547, 2930, 2856, 1728, 1599, 1421, 1366, 1128, 1106; ^{1}H NMR ($CDCl_3$): 1.19–1.82 (m, 32H), 2.31 (s, 3H), 2.91 (quint, *J*=7.6 Hz, 1H), 3.53 (d, *J*=4.6 Hz, 1H), 3.59 (dt, *J*=3.7, 7.5 Hz, 1H), 7.12 (d, *J*=3.9 Hz, 2H); ^{13}C NMR ($CDCl_3$): 13.6, 21.6, 25.3, 26.3, 26.5, 26.7, 30.6, 31.48, 31.52, 35.2, 35.3, 39.6, 43.2, 77.8, 126.9, 127.1, 134.7, 141.6, 141.9, 145.7, 176.9; Exact mass for $C_{25}H_{41}O_3$ $(M+H)^+$: 389.3058. Found 389.3056.

4.6.20. (2*R,3*R**)-3-Hydroxy-2,4-dimethylpentanoic acid 2,6-di-*tert*-butyl-4-methylphenyl ester (2t).** Yield 79% as a white solid (Table 4, entry 6); data consistent with that reported in a literature.[53]

4.6.21. 3-Hydroxy-2-methylhexanoic acid 2,6-di-*tert*-butyl-4-methylphenyl ester (2u). Yield 82% as a white solid (Table 4, entry 7); mp 93.5–94.4 °C; IR ($CHCl_3$): 3537, 2965, 2874, 1730, 1482, 1421, 1180, 1103; ^{1}H NMR ($CDCl_3$): 0.95 (t, *J*=7.0 Hz, 3H), 1.19–1.62 (m, 25H), 2.31 (s, 3H), 2.78 (quint, *J*=7.4 Hz, 1H), 3.49 (d, *J*=4.4 Hz, 1H), 3.81–3.89 (m, 0.97H), 4.15–4.19 (m, 0.03H), 7.12 (d, *J*=2.9 Hz, 2H); ^{13}C NMR ($CDCl_3$): 13.5, 14.2, 18.6, 21.6, 31.45, 31.52, 35.2, 35.3, 36.1, 46.3, 72.4, 126.9, 127.1, 134.7, 141.6, 141.9, 145.7, 176.3; Exact mass for $C_{22}H_{37}O_3$ $(M+H)^+$: 349.2743. Found 349.2744.

4.6.22. 3-Hydroxy-2,*N*,*N*-trimethyl-3-phenylpropionamide (2v). Yield 99% as a white solid (Table 5, entry 3); data consistent with that reported in a literature.[54]

4.6.23. 3-Hydroxy-2,*N*,*N*-trimethyl-5-phenylpentanamide (2w). Yield 83% as a colorless oil (Table 5, entry 5); IR (neat): 3416, 2936, 1622, 1496, 1456, 1401, 1147, 1041, 930; ^{1}H NMR ($CDCl_3$): 1.10–1.26 (m, 3H), 1.49–1.99 (m, 2H), 2.55–2.72 (m, 2H), 2.85–3.02 (m, 7H), 3.59–3.65 (m, 0.26H), 3.91 (br d, *J*=9.2 Hz, 0.74H), 4.20–4.41 (m, 0.26H), 4.73 (br s, 0.74H), 7.15–7.30 (m, 5H); ^{13}C NMR ($CDCl_3$): 9.7, 15.2, 32.3, 32.4, 35.3, 35.7, 37.3, 37.7, 40.0, 40.2, 70.3, 73.6, 125.6, 128.1, 128.4, 141.9, 142.1, 176.4, 177.5; MS: (*m*/*z*) %: 235 (M^+, 46), 217 (38), 149 (30), 144 (21), 130 (57), 111 (21), 101 (73), 91 (100), 83 (28), 72 (86), 69 (27), 57 (47), 55 (40). Exact mass for $C_{14}H_{21}NO_2$: 235.1572. Found 235.1570.

4.6.24. 3-Cyclohexyl-3-hydroxy-2,*N*,*N*-trimethyl-propionamide (2x). Yield 93% as a colorless oil (Table 5, entry 7); IR (neat): 3418, 2925, 2852, 1623, 1451, 1418, 1401, 1318, 1259, 1160, 1136, 983, 628; ^{1}H NMR ($CDCl_3$): 0.84–1.26 (m, 7H), 1.35–1.44 (m, 1H), 1.60–1.78 (m, 5H), 1.96–2.04 (m, 0.2H), 2.10–2.21 (m, 0.8H), 2.81–3.11 (m, 7H), 3.15–3.34 (m, 0.18H), 3.42–3.52 (m, 0.82H), 4.28 (d, *J*=8.6 Hz, 0.18H), 4.78 (s, 0.82H); ^{13}C NMR ($CDCl_3$): 9.5, 15.6, 26.1, 26.4, 26.5, 28.5, 28.7, 28.8, 29.9, 30.1, 35.3, 36.1, 37.4, 37.8, 39.5, 42.0, 75.4, 79.1, 177.0, 177.8; MS: (*m*/*z*) %: 214 (M^++1, 8), 213 (M^+, 4), 198 (46), 195 (40), 131 (10), 130 (100), 101 (96), 95 (14), 83 (10), 72 (57), 55 (11). Exact mass for $C_{12}H_{23}NO_2$: 213.1729. Found 213.1726.

4.6.25. 3-Hydroxy-2,4,*N*,*N*-tetramethylpentanamide (2y). Yield 98% as a colorless oil (Table 5, entry 9); IR (neat): 3423, 2961, 2875, 1625, 1508, 1467, 1419, 1401, 1260, 1163, 1103, 1002, 986; ^{1}H NMR ($CDCl_3$): 0.85 (d, *J*=7.3 Hz, 2.5H), 0.90 (d, *J*=6.6 Hz, 0.48H), 0.98 (d, *J*=6.6 Hz, 0.48H), 1.04 (d, *J*=6.6 Hz, 2.5H), 1.13 (d, *J*=7.3 Hz, 2.5H), 1.25 (d, *J*=7.3 Hz, 0.48H), 1.63–1.81 (m, 1H), 2.82–3.10 (m, 7H), 3.20–3.33 (m, 0.16H), 3.41 (d, *J*=9.2 Hz, 0.84H), 4.28 (d, *J*=7.9 Hz, 0.16H), 4.78 (s, 0.84H); ^{13}C NMR ($CDCl_3$): 9.5, 15.6, 18.2, 18.9, 19.8, 19.9,

30.2, 32.2, 35.5, 35.8, 36.7, 37.4, 76.7, 177.7; MS: (*m*/*z*) %: 174 (M^++1), 173 (M^+), 158 (52), 155 (20), 140 (17), 130 (100), 101 (83), 100 (20), 73 (19), 72 (96), 57 (15). Exact mass for $C_9H_{19}NO_2$: 173.1416. Found 173.1418.

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Grob-type fragmentation of a carvone derived β-hydroxymesylate: application to the synthesis of chiral lavandulol derivatives

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Abstract—Grob-type fragmentation of the carvone derived diol-monosulphonate **5** has been utilised for the enantioselective synthesis of various lavandulol derivatives

1. Introduction

Although the cyclic template of the monoterpene carvone has been extensively utilised as a chiral-pool material for the asymmetric synthesis of diverse cyclic structures of interest, its application in the synthesis of acyclic chiral molecules is somewhat less documented.[1] During the course of our studies[2] towards the construction of taxoids from carvone, we were attracted to the possibility of developing new routes to some acyclic chiral molecules of interest from carvone using suitable ring-opening protocol. Herein, we describe our efforts towards the synthesis of various chiral lavandulol derivatives from carvone. Our strategy relied on the identification of the stereogenic center at C-5 of carvone as identical to that of lavandulol at C-2 and some restructuring plans for the synthesis of various lavandulol derivatives could also be envisioned (Fig. 1).

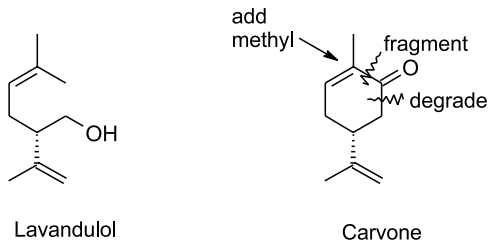

Figure 1. Structural correlation of lavandulol with carvone.

2. Results and discussion

Our synthetic approach commenced from the cheaper, more abundant *R*(−)-carvone (**1**) which was readily elaborated to the hydroxyketone **3** via a two step sequence involving reductive methylation of the derived epoxyketone **2** as described previously.[3] In line with our earlier observation,[2] addition of methylmagnesium iodide to **3** proceeded with high diastereoselectivity and the diol **4** was obtained in good yield after removal of the minor isomer (5%). Selective mesylation of the secondary hydroxy group in the diol **4** could easily be accomplished using conventional conditions to yield the hydroxymesylate **5** in good yield (Scheme 1).

The Grob-type fragmentation of 1,3-diolmonosulphonates has evolved[4] into an outstanding piece and its utility in the construction of functionalised alkenes with defined regio- and/or stereospecificity has rendered it a valuable tool in organic synthesis. Recently an elegant example of this reaction, for the synthesis of some musk compounds, has been reported.[5] We considered application of this type of fragmentation of the hydroxymesylate **5** to unravel the framework of the lavandulyl system. Pleasingly, the hydroxymesylate **5** underwent smooth conversion in refluxing tetrahydrofuran in the presence of sodium hydride to the unsaturated ketone **6** which was obtained as a pleasant smelling colourless liquid.

The ketone **6** contains most of the structural features of the important irregular mono-terpene alcohol lavandulol, therefore, a further degradation to lavandulol[6] was then considered. Although several possibilities exist for this seemingly simple transformation, we argued that a successful Bayer–Villiger oxidation[7] would convert the ketone **6**

Keywords: Fragmentation; Carvone; Lavandulol; Enatioselective.
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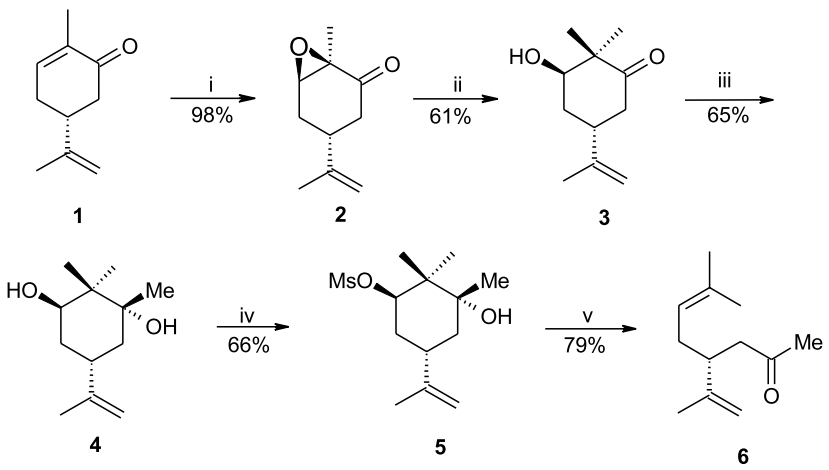
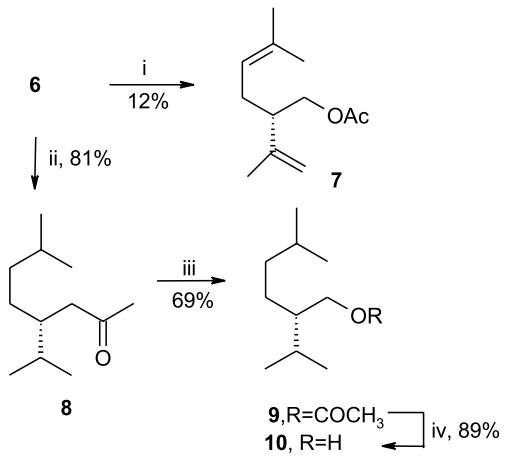


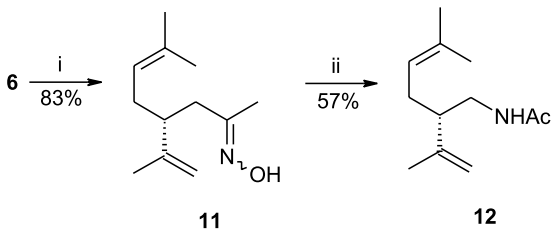
Scheme 1. Reagents and conditions: (i) H_2O_2, NaOH, 0 °C, 4 h, 98%; (ii) Li, NH_3, MeI, −33 °C to room temperature, 3 h, 61%; (iii) MeMgI, 0 °C to room temperature, 12 h, 65%; (iv) MsCl, pyridine, 0 °C to room temperature, 8 h, 66%; (v) NaH, THF, reflux, 8 h, 79%.

into lavandulol acetate. We were aware of the possibility of competing oxidation of the two somewhat activated double bonds present in the molecule, but ample literature precedence in analogous cyclic substrates prompted us to try some of these fruitful conditions. In all of the experiments with *meta*-chloroperbenzoic acid (using sodium bicarbonate, *para*-toluenesulphonic acid, trifluoroacetic acid, etc. as additives) or hydrogen peroxide (in conjunction with acetic or trifluoroacetic acid) epoxidation of the C_6–C_7 double bond was the major phenomenon observed, while from basic conditions (H_2O_2/NaOH) the starting material was recovered unchanged, even after prolonged heating. Bis-trimethylsilyl peroxide has been reported[8] to carry-out Bayer–Villiger oxidation of unsaturated ketones but moderate yields have been recorded in most cases. This reagent in conjunction with $SnCl_4$ did indeed afforded lavandulol acetate, but in poor yield (Scheme 2). On the other-hand, the saturated ketone **8**, obtained by hydrogenation of **6**, underwent smooth Bayer–Villiger oxidation with sodium percarbonate[9] in the presence of trifluoroacetic anhydride[10] to give the acetate **9** in good yield. Hydrolysis of the latter with aqueous potassium carbonate afforded tetrahydrolavandulol in high yield. Tetrahydrolavandulol has been utilised as a key intermediate in the synthesis[11] of tetradesoxybacterioruberin and recently, some interesting biotransformation of the former has also been reported.[12]



Scheme 2. Reagents and conditions: (i) TMS_2O_2, $SnCl_4$, CH_2Cl_2, 24 h, 12%; (ii) H_2, Pd–C, EtOH, room temperature, 4 h, 81% (iii) SPC, TFAA, room temperature, 16 h, 69%; (iv) potassium carbonate, methanol, room temperature, 2 h, 89%.

We also considered the Beckmann-type rearrangement of the oxime of the ketone **6** as an additional possibility. Thus, the ketone **6** was converted into its oxime **11** (~7:1 mixture of E- and Z-) by treatment with hydroxylamine hydrochloride under conventional conditions.[13] Treatment[14] of this mixture with *para*-toluenesulfonyl chloride in pyridine led to smooth formation of the rearranged product **12** as the only isolable product (Scheme 3).



Scheme 3. Reagents and conditions: (i) NH_2OH·HCl, pyridine, ethanol, rt, 6 h, 83%; (ii) *p*-TsCl, pyridine, benzene, rt, 12 h, 57%.

3. Conclusion

In short, we have demonstrated that various chiral lavandulol derivatives could be prepared from carvone through a fragmentation-based approach. Some of the compounds reported here have the potential to find applications in perfumery.

4. Experimental

4.1. General details

Optical rotations were recorded in spectroscopic grade chloroform or dichloromethane on a Jasco DIP-370 polarimeter, $[\alpha]_D$ values are recorded in units of 10^{-1} deg cm^2 g^{-1}. Infrared spectra were obtained using a Perkin–Elmer 1600 series spectrometer as liquid films or

dilute solutions in spectroscopic grade dichloromethane. Proton NMR spectra were recorded on a Bruker DRX-300 spectrometer as dilute solutions in deuterochloroform. The chemical shifts are quoted in parts per million (ppm) relative to tetramethylsilane as the internal standard and the multiplicity of each signal is designated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. All coupling constants are quoted in Hertz. Carbon-13 NMR spectra were recorded on Bruker DPX-300 spectrometer as dilute solutions in deuterochloroform. Chemical shifts are recorded relative to internal chloroform (δ 77.2) or TMS as standard on a broad band decoupled mode, and the multiplicities determined using a DEPT sequence. Mass spectra were recorded on a JEOL-JMS 600 instrument and elemental analyses were obtained on a Perkin–Elmer 204b elemental analyzer.

4.1.1. (1*R*,3*R*,5*R*)-5-isopropenyl-1, 2, 2-trimethylcyclohexane-1,3-diol (4). A solution of methylmagnesium iodide (2 M in THF, 10 ml, 20 mmol) was added dropwise over 20 min to a stirred solution of the hydroxyketone **3**[3] (1.64 g, 9.11 mmol) in dry THF under nitrogen at 0 °C and the resulting yellowish solution was allowed to come to room temperature over 20 h. It was quenched with saturated aqueous NH_4Cl solution (10 ml) and then extracted with ether (2×50 ml). The combined organic extract was washed successively with water (2×50 ml), brine (20 ml) and then dried (Na_2SO_4). It was filtered and the filtrate was concentrated to leave the crude product as a pale yellow oil which on chromatography (SiO_2) (petroleum ether/ethyl acetate, 7:1) afforded the product as a colourless oil (1.17 g, 65%). $[\alpha]_D$ +8.54 (*c*, 0.82 in $CHCl_3$). ν_{max} (neat) 3340, 2920, 1665, 1080 and 885 cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ 4.77 (1H, s), 4.70 (1H, s), 3.62 (1H, t, *J*=9.1 Hz), 3.12 (1H, bs), 2.98–2.64 (1H, m), 1.72 (3H, s), 1.69–1.57 (4H, m), 1.13 (3H, s), 1.10 (3H, s), 0.88 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.3 (s), 108.8 (t), 78.6 (d), 76.0 (s), 40.7 (t), 39.4 (s), 33.9 (t), 33.8 (d), 25.3 (q), 24.0 (q), 21.0 (q), 20.6 (q). Elemental analyses: C, 72.49%; H, 11.04%; $C_{12}H_{22}O_2$ requires C, 72.68%; H, 11.18%. *m/z* (EI, 70 eV) 180 (M^+-H_2O), 145.

4.1.2. (1*R*,3*R*,5*R*)-3-hydroxy-5-isopropenyl-2,2,3-trimethylcyclohexyl methanesulfonate (5). Methanesulfonyl chloride (0.85 ml, 11 mmol) was added in one portion to a stirred solution of the diol **4** (375 mg, 1.89 mmol) in dry pyridine (10 ml) at 0 °C under nitrogen. It was allowed to come to room temperature and stirring continued for 14 h. The brownish mixture was diluted with water (50 ml) and then extracted with ether (3×50 ml). The combined ether extract was washed successively with water (3×25 ml) and saturated aqueous copper sulfate solution (2×25 ml). It was then dried (Na_2SO_4), filtered and the filtrate was concentrated to leave the crude product as a brownish oil which on chromatography (SiO_2) (petroleum ether/ethyl acetate, 6:1) afforded the product as a colourless oil (343 mg, 66%). $[\alpha]_D$ −19.58 (*c*, 2.72 in $CHCl_3$). ν_{max} (neat) 3560, 1660, 1330, 1165 and 880 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.89 (1H, s), 4.64 (1H, s), 3.26–3.06 (1H, m), 3.03 (3H, s), 2.54 (1H, tt, *J*=8.7, 4.2 Hz), 2.11–2.02 (1H, m), 1.82–1.77 (2H, m), 1.73 (3H, s), 1.63–1.48 (1H, m), 1.15 (3H, s), 1.12 (3H, s), 0.99 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.8 (s), 109.6 (t), 90.3 (d), 74.4 (s), 40.5 (t), 40.4 (s), 38.9 (d), 33.7 (q), 32.2 (t), 24.7 (q), 24.3 (q), 21.0 (q), 20.5 (q). Elemental analyses: C, 56.27%; H, 8.44%; S, 11.31%; $C_{13}H_{24}SO_4$ requires C, 56.49%; H, 8.75%; S, 11.60%.

4.1.3. (4*R*)-4-isopropenyl-7-methyl-6-octen-2-one (6). Sodium hydride (130 mg, excess) was added in one portion to a solution of the hydroxymesylate **5** (114 mg, 0.41 mmol) in dry tetrahydrofuran (8 ml) under nitrogen atmosphere and the resulting mixture was heated to reflux for 8 h. It was then cooled in an ice-bath and quenched by slow addition of methanol (1 ml) followed by saturated aqueous ammonium chloride (5 ml). It was then extracted with ether (2×25 ml) and the combined ether extract was washed with water (2×20 ml), brine (1×10 ml) and then dried (Na_2SO_4). It was then filtered and the filtrate was concentrated to leave the crude product as a pale yellow oil which on chromatography (SiO_2) (petroleum ether/ethyl acetate, 20:1) afforded the product as a colourless oil (58 mg, 79%). $[\alpha]_D$ +12.1 (*c*, 2.1 in $CHCl_3$). ν_{max} (neat) 2920, 1720, 1665 and 1645 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.01 (1H, t, *J*=7.2 Hz), 4.73 (1H, s), 4.67 (1H, s), 2.60 (1H, quin., *J*=6.9 Hz), 2.46–2.44 (2H, m), 2.08 (3H, s), 2.03 (2H, t, *J*=7.2 Hz), 1.66 (6H, s), 1.54 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.4 (s), 147.1 (s), 133.0 (s), 122.0 (d), 111.0 (t), 47.5 (t), 42.8 (d), 30.1 (q), 32.0 (t), 25.8 (q), 19.8 (q), 17.8 (q). Elemental analyses: C, 79.69%; H, 10.98%; $C_{12}H_{20}O$ requires C, 79.95%; H, 11.18%. *m/z* (EI, 70 eV) 180 (M^+), 165, 137 (100%).

4.1.4. (2*S*)-2-isopropenyl-5-methyl-4-hexenyl acetate (7). Stannic chloride (130 mg, 0.5 mmol) was added dropwise to a stirred solution of the ketone (90 mg, 0.5 mmol) and bis(trimethylsilyl)peroxide[15] (90 mg, 0.5 mmol) in dichloromethane (5 ml) at 0 °C under nitrogen atmosphere. After stirring for 1 h at that temperature it was allowed to come to room temperature and stirring continued for 24 h. It was then diluted with dichloromethane (25 ml) and then poured into an aqueous solution of sodium thiosulfate (10 ml). The organic layer was separated and washed successively with water (2×10 ml), saturated sodium bicarbonate solution (1×10 ml), water (1×10 ml) and brine (1×10 ml). It was then dried (Na_2SO_4), filtered and the filtrate was concentrated to leave the crude product as a brownish oil which on chromatography (SiO_2) (petroleum ether/ethyl acetate, 12:1) afforded lavandulol acetate as a colourless oil (11 mg, 12%). $[\alpha]_D$ 6.3 (*c*, 1.5 in $CHCl_3$). ν_{max} (neat) 2910, 1708, 1670 and 1645 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.05 (1H, t, *J*=7.5 Hz), 4.82 (1H, d, *J*=1.5 Hz), 4.73 (1H, bs), 4.03 (2H, d, *J*=6.9 Hz) 2.39 (1H, quin., *J*=6.9 Hz), 2.17–2.05 (2H, m), 2.02 (3H, s), 1.69–1.64 (6H, overlapping singlets), 1.59 (3H, s).^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1 (s), 144.9 (s), 132.9 (s), 121.6 (d), 112.4 (t), 65.8 (t), 46.0 (d), 28.5 (t), 25.7 (q), 20.9 (q), 19.9 (q), 17.8 (q). Elemental analyses: C, 73.66%; H, 10.49%; $C_{12}H_{20}O_2$ requires C, 73.43%; H, 10.27%. *m/z* (EI, 70 eV) 196 (M^+), 153, 59 (100%).

4.1.5. (4*R*)-4-isopropyl-7-methyloctan-2-one (8). A solution of the ketone **6** (72 mg, 0.4 mmol) in methanol (5 ml) was vigorously stirred under hydrogen atmosphere in the presence of Pd–C (10%, 5 mg) for 3 h at room temperature. The heterogeneous mixture was then filtered through celite and the filter cake was washed with ether. The combined organic solution was then concentrated to leave the crude

product as a colourless liquid, which was purified by chromatography over silica gel using a mixture of petroleum ether and ethyl acetate (20:1) as eluent. The product was obtained as a colourless liquid (59 mg, 81%). $[\alpha]_D$ +2.1 (*c*, 1.2 in $CHCl_3$). ν_{max} (neat) 1710 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.30 (1H, dd, *J*=15.9, 5.7 Hz), 2.15 (1H, dd, *J*=15.9, 5.7 Hz), 2.03 (3H, s), 1.75 (1H, m), 1.65 (1H, m), 1.36 (1H, m), 1.21 (2H, m), 1.12 (2H, m), 0.8 (12H, overlapping doublets). ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.8 (s), 45.4 (d), 39.6 (t), 36.5 (t), 30.3 (t), 29.5 (q), 28.9 (d), 28.2 (d), 22.6 (q), 22.4 (q), 19.5 (q), 18.4 (q). Elemental analyses: C, 77.88%; H, 12.90%; $C_{12}H_{24}O$ requires C, 78.19%; H, 13.12%. *m/z* (EI, 70 eV) 184 (M^+), 169, 141 (100%), 126.

4.1.6. (2*S*)-2-isopropyl-5-methylhexyl acetate (9). Trifluoroacetic anhydride (0.085 ml) was added to a stirred heterogeneous mixture of the ketone **8** (35 mg, 0.2 mmol) and sodium percarbonate (64 mg, 0.4 mmol) in dry dichloromethane (2 ml) at 0 °C under nitrogen atmosphere. The mixture was allowed to come to room temperature and stirred for 16 h. It was then diluted with dichloromethane (20 ml) and filtered. The filtrate was concentrated in vacuo and the residue was partitioned between ether (20 ml) and water (20 ml). The organic layer was washed successively with saturated sodium bicarbonate solution (2×10 ml), water (10 ml), brine and then dried (Na_2SO_4). It was filtered and the filtrate was concentrated to leave the crude product as a pale yellow oil which on chromatography (SiO_2) (petroleum ether/ethyl acetate, 10:1) afforded tetrahydrolavandulol acetate as a colourless oil (27 mg, 69%). ν_{max} (neat) 1708 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.99–3.84 (2H, m), 2.03 (3H, s), 1.75–1.66 (1H, m), 1.46–1.40 (2H, m), 1.37–1.30 (1H, m), 1.24–1.16 (2H, m), 1.12–1.00 (2H, m), 0.88–0.82 (12H, overlapping doublets), 0.76–0.71 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.3 (s), 65.5 (t), 43.2 (d), 36.7 (t), 28.3 (d), 25.7 (t), 22.6 (d), 22.8 (q), 22.4 (q), 21.0 (q), 19.8 (q), 19.3 (q). Elemental analyses: C, 71.70%; H, 11.89%; $C_{12}H_{24}O_2$ requires C, 71.95%; H, 12.07%.

4.1.7. (2*S*)-2-isopropyl-5-methylhexan-1-ol (10). A solution of the acetate **9** (99 mg, 0.5 mmol) in methanol (5 ml) and saturated aqueous potassium carbonate (2 ml) was stirred at room temperature for 2 h. It was then diluted with water (20 ml) and extracted with ether (2×20 ml). The combined ether extract was washed with brine (1×10 ml) and dried (Na_2SO_4). It was filtered and the filtrate was concentrated to leave the crude product as a pale yellow oil which on chromatography (SiO_2) (petroleum ether/ethyl acetate, 10:1) afforded tetrahydrolavandulol as a colourless oil (71 mg, 89%). $[\alpha]_D$ −9.6 (*c*, 1.4 in $CHCl_3$). ν_{max} (neat) 3320 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.96–3.58 (2H, m), 1.82–1.78 (1H, m), 1.53–1.30 (5H, m), 0.91–0.87 (12H, overlapping doublets). ^{13}C NMR (75 MHz, $CDCl_3$): δ 64.2 (t), 47.3 (d), 37.5 (t), 28.8 (d), 28.3 (d), 25.8 (t), 23.1 (q), 22.9 (q), 20.1 (q), 19.6 (q). Elemental analyses: C, 75.69%; H, 13.82%; $C_{10}H_{22}O$ requires C, 75.88%; H, 14.01%.

4.1.8. (4*R*)-4-isopropenyl-7-methyl-6-octen-2-one oxime (11). Hydroxylamine hydrochloride (232 mg, 3.34 mmol) was added in one portion to a stirred solution of the ketone **6** (500 mg, 2.78 mmol) in pyridine (1.25 ml) and ethanol (1 ml) and the resulting mixture was stirred for 6 h at ambient temperature. It was then cooled to 0 °C, diluted with water (5 ml) and extracted with ethyl acetate (2×10 ml). The combined organic extract was washed successively with aqueous hydrochloric acid (5%, 1×10 ml), sodium bicarbonate solution (5%, 1×10 ml), water (1×10 ml) and then brine (1×10 ml). It was then dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo to leave a pale yellow oil which was purified by chromatography (SiO_2) (petroleum ether/ethyl acetate, 10:1) to leave the product as a colourless oil (0.451 g, 83%). ν_{max} (neat) 3200, 2890, 1625, 1430 and 1360 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): data for the mixture (~7:1 by GC) (data in [] refer to the possible *syn*-isomer) δ 5.05 (1H, br t), 4.75 (1H, s) [4.72, s], 2.43–2.33 (2H, m), [2.10–2.07 (m)], 1.85 (3H, s) [1.84, s], 1.68 (3H, s), 1.65 (3H, s), 1.59 (3H, s). Elemental analyses: C, 73.62%; H, 10.89%; N, 7.46%; $C_{12}H_{21}NO$ requires C, 73.80%; H, 10.84%, N, 7.17%.

4.1.9. N 1-[(2*S*)-2-isopropenyl-5-methyl-4-hexenyl]acetamide (12). *p*-Toluenesulfonyl chloride (341 mg, 1.79 mmol) was added in one portion to a solution of the oxime **11** (350 mg, 1.79 mmol) in a mixture of benzene (1.5 ml) and pyridine (0.4 ml).The resulting homogeneous mixture was stirred at room temperature for 12 h and then diluted with water (10 ml) and ethyl acetate (20 ml). The aqueous phase was extracted with ethyl acetate (2×10 ml) and the combined organic extract was washed successively with aqueous hydrochloric acid solution (5%, 2×10 ml), sodium bicarbonate solution (5%, 1×10 ml), water (2×10 ml) and brine (1×10 ml). It was then dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo to leave the crude product as a brownish oil which was purified by chromatography (SiO_2) (petroleum ether/ethyl acetate, 4:1) to give the product as a colourless oil (202 mg, 57%). $[\alpha]_D$ −7.6 (*c*, 1.4 in $CHCl_3$). ν_{max}(neat) 3280, 2900, 1635 and 1540 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.41 (1H, bs), 5.03 (1H, t, *J*=6 Hz), 4.87 (1H, s), 4.77 (1H, s), 3.42 (1H, dt, *J*=12.6, 5.5 Hz), 3.02 (1H, ddd, *J*=13.4, 9.5, 4.2 Hz), 2.24–2.16 (2H, m), 2.04 (1H, broad t, *J*=6.6 Hz), 1.95 (3H, s), 1.68 (3H, s) 1.65 (3H, s), 1.58 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3 (s), 145.6 (s), 132.9 (s), 121.5 (d), 113.0 (t), 47.1 (d), 40.9 (t), 29.7 (t), 25.6 (q), 23.2 (q), 18.6 (q), 17.8 (q). Elemental analyses: C, 73.53%; H, 11.09%; N, 7.42%; $C_{12}H_{21}NO$ requires C, 73.80%; H, 10.84%; N, 7.17%. *m/z* (EI, 70 eV) 196 (M^+ +1), 123, 69 (100%).

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Oxidative nucleophilic substitution of hydrogen in nitroarenes with trifluoromethyl carbanions. Synthesis of trifluoromethyl phenols

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Abstract—Trifluoromethyl carbanions generated from the Ruppert reagent and TASF add to highly electron-deficient nitroarenes to produce σ^H adducts subsequently oxidized with dimethyldioxirane to substituted trifluoromethyl phenols.

1. Introduction

Pharmaceutical and plant protection agents often contain F or CF_3 substituents and thus methods of introduction of these groups are of great interest in modern organic synthesis.[1,2] Of particular interest are arenes containing CF_3 groups. There are a few general methods of synthesis of such arenes, and the main ones are: exchange of chlorine for fluorine in CCl_3 groups of readily available trichloromethyl arenes and treatment of benzoic acids with SF_4.[3] On the other hand, the direct introduction of a CF_3 group to arenes is also possible via Cu catalyzed replacement of halogen with CF_3^- carbanion generated from the Ruppert reagent, CF_3SiMe_3, or other sources.[4] Attempts to replace halogens or the nitro group in halonitrobenzenes with CF_3^-, generated from the Ruppert reagent without a Cu catalyst, gave the expected products, trifluoromethylnitroarenes, in low yields.[5] There is also one report on oxidative nucleophilic replacement of hydrogen in trinitrobenzene with a CF_3^- anion.[6]

Introduction of carbon substituents into electron-deficient arenes can be efficiently executed via nucleophilic substitution of hydrogen with carbanions[7] or Grignard reagents.[8] The reaction proceeds via addition of these carbon nucleophiles to the electron-deficient rings in the *ortho*- or *para*- positions to the NO_2 group occupied with hydrogen to form σ^H adducts that are converted into the final products in many ways. When the reacting carbanions contain leaving groups X at the carbanion center, base induced β-elimination of HX from the σ^H adducts gives products of vicarious nucleophilic substitution (VNS).[9] On the other hand, oxidation of the σ^H adducts with external oxidants such as $KMnO_4$, DDQ etc. gives substituted nitroarenes, products of oxidative nucleophilic substitution[10] whereas some σ^H adducts oxidized with dimethyldioxirane (DMD) are converted into substituted phenols.[11] Trichloromethyl anions generated by deprotonation of chloroform react with nitroarenes along the VNS pathway affording nucleophilic dichloromethylation.[12] The various ways of transforming σ^H adducts of carbanions to nitroarenes into final products are shown in Scheme 1.

2. Results and discussion

Taking into account the expected higher nucleophilicity of CF_3^- anions, that are less stabilized by fluorine substituents than CCl_3^- anions, and low rate of elimination of HF from σ^H adducts of CF_3^- anions to nitroarenes, we expected that there is a good chance for introduction of CF_3 groups into nitroarenes via an oxidative process. Our first attempts of reaction of CF_3^- anions generated by treatment of CF_3SiMe_3, (**1**) with TASF [tris(dimethylamino)sulfonium difluorotrimethylsilicate] in THF–MeCN with nitrobenzene, 1-nitronaphthalene, 2-and 4-chloronitrobenzenes followed by oxidation with $Bu_4N^+MnO_4^-$ or DMD gave negative results. No CF_3ArNO_2 or CF_3ArOH or other aromatic products containing fluorine were found in the reaction mixtures, although the nitroarenes were partially consumed. Since in the reaction mixture we have found some amounts of nitroaryl acetonitriles it appears that the generated CF_3^- anions afforded deprotonation of acetonitrile and the produced carbanion reacts with nitroarenes. This supposition was confirmed by treatment of CF_3SiMe_3 and 2,4,6-trichloronitrobenzene in THF–MeCN with TASF

Keywords: Ruppert reagent; Nitroarenes; Carbanions; Dimethyldioxirane; Phenols.
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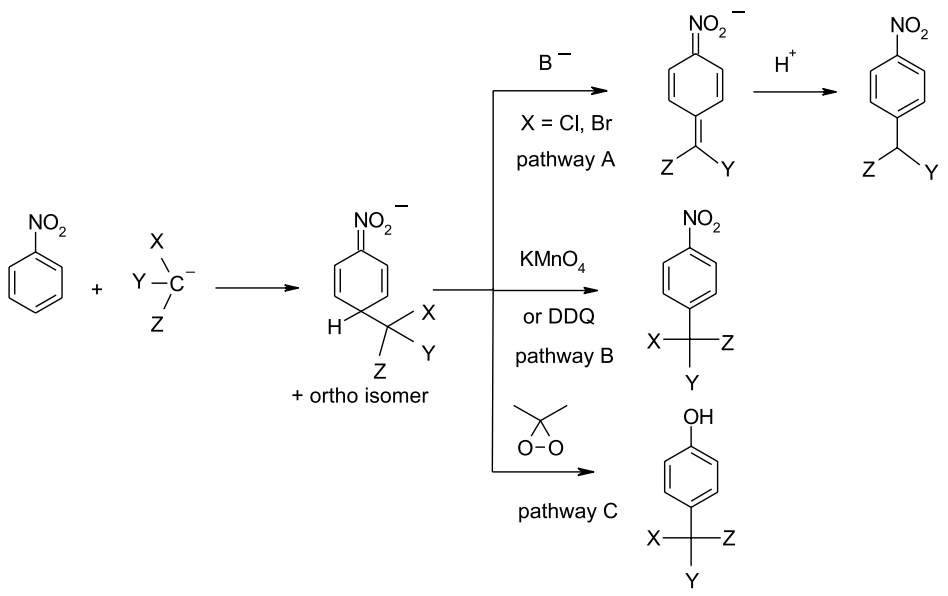


Scheme 1.

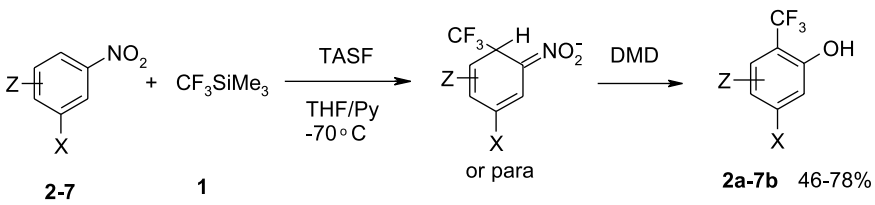
giving 3,5-dichloro-6-nitrophenylacetonitrile in a reasonable yield 46%. Thus, the THF–MeCN solvent system, widely used for reaction of aldehydes and ketones with CF_3^- anion generated from CF_3SiMe_3[13] cannot be used for its reactions with nitroarenes. Perhaps due to low rate and unfavorable equilibrium of the addition of CF_3^- to nitroarenes, the main process was acid–base equilibrium with MeCN. Thus in further studies we used the THF–pyridine solvent system, as neat THF cannot be used because it does not dissolve TASF. However, treatment of nitrobenzene and *p*-chloronitrobenzene with **1** and TASF in THF–Py (1:1) at −70 °C, followed by oxidation with $Bu_4N^+MnO_4^-$ or DMD gave negative results. Since the nitroarenes were mostly recovered we can assume that there was negligible conversion of $ArNO_2$ into σ^H adducts. Hence, we used more electrophilic nitroarenes in our further studies. The results are presented in Table 1.

When a solution of equimolar amounts of the Ruppert reagent **1**, 3-cyanonitrobenzene **2** and TASF in THF–Py (1:1) at −70 °C was treated with an acetone solution of DMD, the reaction resulted in formation of a mixture of three isomeric cyanotrifluoromethyl phenols in a reasonable overall yield 49%. The ratio of 3-cyano-2-trifluoromethyl- **2a**, 3-cyano-4-trifluoromethyl- **2b** and 3-cyano-6-trifluoromethyl phenol **2c** was 5.5:1:6. On the other hand, oxidation of this system with $Bu_4N^+MnO_4^-$ did not produce trifluoromethyl cyanonitrobenzenes, products of ONSH reaction. We have already observed that MnO_4^- oxidation of the anionic σ^H adducts is very sensitive to steric hindrance at the addition site and usually does not proceed with the σ^H adducts of carbanions in *ortho* position to the NO_2 group.[10] Interestingly the addition of CF_3 carbanions took place preferentially *ortho* to the nitro group and as a consequence oxidation of the σ^H adducts to **2** with DMD

Table 1.

Starting nitroarene			Yields of phenols (%)			
X	Z	No.	Total	Isomers		
CN	H	**2**	49	3-CN-2-CF_3	**2a**	22
				3-CN-4-CF_3	**2b**	4
				3-CN-6-CF_3	**2c**	23
CN	4-Cl	**3**	63	3-CN-4-Cl-2-CF_3	**3a**	47
				3-CN-4-Cl-6-CF_3	**3b**	16
NO_2	H	**4**	78	3-NO_2-2-CF_3	**4a**	47
				3-NO_2-4-CF_3	**4b**	18
				3-NO_2-6-CF_3	**4c**	13
NO_2	4-Br	**5**	46	3-NO_2-4-Br-2-CF_3	**5a**	29
				3-NO_2-6-Br-2-CF_3	**5b**	6
				3-NO_2-6-Br-4-CF_3	**5c**	11
NO_2	5-NO_2	**6**	53[a]	3,5di-NO_2-2-CF_3	**6a**	22
				3,5di-NO_2-4-CF_3	**6b**	31
2-Chloro-3-nitropyridine		**7**	57[b]	2-Cl-3-OH-4-CF_3-Py	**7a**	28
				2-Cl-3-OH-6-CF_3-Py	**7b**	29

[a] Additionally α,α,α-trifluoro-2,4,6-trinitrotoluene, 33% was obtained.
[b] Additionally 2,2′-dichloro-3,3′-dinitro-bipyridyl-4,4′, **7c**, 6% was obtained.



Scheme 2.

gave mostly **2a** and **2c**. Under similar conditions, other highly electro-deficient nitroarenes such as *m*-dinitrobenzene **3**, 3-cyano-4-chloronitrobenzene **4**, 2,4-dinitrobromobenzene **5**, 1,3,5-trinitrobenzene **6** and 2-chloro-3-nitropyridine **7** were converted into substituted trifluoromethylphenols as shown in Scheme 2. Also in the reaction of these nitroarenes with CF_3^- anions, the addition proceeded preferentially *ortho* to the nitro groups.

Oxidation of the σ^H adducts of CF_3^- anions to polynitroarenes **4**, **5** and **6** creates an interesting question: which of the negatively charged NO_2 groups is oxidized by DMD and converted into the OH group? Surprising there was not significant difference between rates of oxidation of such nitro groups located *ortho* and *para* to the addition site. For instance in the σ^H adduct of CF_3 to **4** ratio of the corresponding rates equals 0.72.

The structures of the trifluoromethyl phenols obtained by oxidation of the σ^H adducts of CF_3^- anions to nitroarenes were determined on the basis of analysis of ^1H, ^{13}C and ^{19}F NMR spectra. For this purpose, mass spectra were also very helpful. In MS of all *ortho* CF_3 phenols, there were well pronounced ions $[M-20]^+$ formed by elimination of HF.

Although yields of the trifluoromethyl phenols were rather moderate (46–78%), unreacted nitroarenes were recovered and thus there was an excellent material balance of the nitroarenes, usually above 90%. On this basis we suppose that the σ^H adducts of CF_3 anions, once formed, are efficiently oxidized by DMD to phenols. However, the degree of conversion of CF_3^- into the σ^H adducts is not very high in spite of high electrophilicity of the arenes. This is perhaps due to fast dissociation of CF_3^- to difluorocarbene.[14]

Formation of the σ^H adducts of CF_3^- to nitroarenes is accompanied with coloration of the mixture (orange, red, blue, etc) and oxidation of these adducts with DMD results in disappearance of the color. Usually, oxidation is completed within a few min. Only oxidation of σ^H adducts of **6** required a few hours for completion. Because of that, oxidation of the σ^H adducts to 1,3,5-trinitrobenzene with DMD gave, besides the expected phenols **6a** and **6b** substantial quantities of the ONSH product α,α,α-trifluorotrinitrotoluene, **6c**. Surprisingly oxidation of the corresponding σ^H adduct to 2-chloro-3-nitropyridine **7** also gave small amount of the bipyridine **7c**. This byproduct is perhaps formed via oxidation of the deprotonated pyridine by analogy to reported observations.[15] In this case, CF_3^- acted as a base abstracting a proton from the pyridine ring. This process shows that CF_3^- despite being a strong base is a weak nucleophile and can be considered as a hard nucleophile.

Oxidation of σ^H adducts of CF_3^- to **2** and **7** with other oxidants (MnO_4^-, DDQ, Br_2) failed; only when σ^H adducts to **4** were treated with Br_2 and Et_3N, one of the isomeric σ^H adducts was converted into 3,5-dinitro-4-trifluoromethylbromobenzene, **4d**.

3. Conclusion

We have shown that the CF_3^- anion generated by treatment of the Ruppert reagent with TASF adds to nitroarenes provided they show sufficiently high electron deficiency. In our hands the oxidation of such σ^H adducts proceeds satisfactorily only with dimethyldioxirane giving substituted trifluoromethyl phenols.

4. Experimental

4.1. General remarks

Melting points are uncorrected. Infrared spectra were recorded on a Perkin–Elmer FT-IR spectrometer. NMR spectra were measured at 400 MHz on a Mercury-400BB or at 200 MHz on a Gemini-200BB spectrometers. Chemical shifts are reported in ppm relative to tetramethylsilane as internal standard. Mass spectra were obtained on AMD 604 Inectra GmbH instrument using EI, appropriate isotope patterns were observed. Analytical TLC was carried out on Merck alufolien sheets Kieselgel 60 F_{254}. For preparative HPLC Merck-Hitachi equipment was used with pump L-7100 detector VL-7400, using hexane and ethyl acetate as a solvent. For column chromatography silica gel 230–400 mesh, Merck was used. Solvents, nitroarenes and TASF were used as received from the manufacturers except for tetrahydrofuran that was distilled over potassium benzophenone ketyl before use. The Ruppert reagent was a gift from Dr A. Marhold (Bayer AG).

Acetone solution of DMD was prepared according to the described procedure.[16]

4.2. Reaction of the Ruppert reagent with 2,4,6-trichloronitrobenzene in the presence of TASF in THF/MeCN system

To a stirred solution of **1** (0.6 mmol) and nitroarene (0.5 mmol) in THF (5 mL) at −70 °C under argon, TASF (153 mg, 0.5 mmol) dissolved in MeCN (1 mL) was added dropwise, the mixture was stirred for 30 min and the cooling bath was removed. After 30 min of further stirring, aqueous HCl (1 mL) was added. The reaction mixture was dried over anhydrous $MgSO_4$, the solid phase was filtered off and washed with dichloromethane (20 mL). The solvents were

evaporated (25 °C, 15 Torr) and the product was purified by column chromatography using hexane–ethylacetate 20:1 as eluent.

4.2.1. 3,5-Dichloro-2-nitrophenylacetonitrile. Yield 54 mg, 46%, colorless crystals, mp 69–70 °C (EtOH). HR EIMS calcd for $C_8H_4N_2O_2^{35}Cl_2$ M=229.9650. Found: 229.9654. ^{1}H NMR (400 MHz, $CDCl_3$): 7.61–7.59 (m, 1H), 7.85–7.70 (m, 1H), 3.81–3.75 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 137.8, 132.5, 130.8, 128.3, 127.7, 125.7, 114.6, 20.3. Anal. calcd for $C_8H_4N_2O_2Cl_2$: C, 41.59; H, 1.75; N, 12.13, Cl, 30.69. Found: C, 41.68; H, 1.49; N, 12.19, Cl, 30.79.

4.3. General procedure for oxidation of the σ^H adducts of CF_3^- to nitroarenes with DMD

To a stirred solution of **1** (0.6 mmol) and nitroarene (0.5 mmol) in THF (5 mL) at −70 °C under argon, TASF (153 mg, 0.5 mmol) dissolved in pyridine (1 mL) was added dropwise and the mixture was stirred for 5 min. Water (9 μL, 0.5 mmol) and than an acetone solution of DMD (ca. 0.6 mmol, 10 mL of ca. 0.06 M) was added to the mixture. After 15 min of further additional stirring, dilute HCl (1 mL) was added and the cooling bath was removed. A mixture of isomeric trifluoromethylphenols was extracted from the reaction mixture with aqueous NaOH and after acidification of the aqueous layer was separated by preparative HPLC.

The products **7a** and **7b** were isolated in another manner. The reaction mixture was dried over anhydrous $MgSO_4$, the solid phase was filtered off and washed with acetone (20 mL). The solvents were evaporated (25 °C, 15 Torr) and the products were purified by preparative HPLC.

4.3.1. 3-Cyano-2-trifluoromethylphenol (2a). Yield 21 mg, 22%, colorless crystals, mp 157–158 °C (CH_2Cl_2). EIMS m/z (%): 187 (85), 168 (17), 167 (91), 139 (100), 138 (4), 120 (3), 112 (9). HR EIMS calcd for $C_8H_4ONF_3$ M=187.0245. Found: 187.0251. ^{1}H NMR (400 MHz, $CDCl_3$): 7.52 (m, 1H), 7.41 (d, 1H, J=7.7 Hz), 7.24 (d, 1H, J=8.3 Hz), 6.70 (s, broad, 1H). ^{19}F NMR (376 MHz, acetone-d_6): −58.1. Anal. calcd for $C_8H_4F_3NO$: C, 51.35; H, 2.15; N, 7.49. Found: C, 51.17; H, 1.89; N, 7.31.

4.3.2. 3-Cyano-4-trifluoromethylphenol (2b). Yield 4 mg, 4%, colorless crystals. EIMS m/z (%): 187 (100), 168 (8), 139 (75), 120 (10). HR EIMS calcd for $C_8H_4ONF_3$ M=187.0245. Found: 187.0249. ^{1}H NMR (400 MHz, $CDCl_3$): 7.57 (d, 1H, J=8.7 Hz), 7.27 (s, 1H), 7.19 (d, 1H, J=8.7 Hz), 6.68 (s broad, 1H). ^{19}F NMR (376 MHz, acetone-d_6): −60.20.

4.3.3. 3-Cyano-6-trifluoromethylphenol (2c). Yield 22 mg, 23%, colorless crystals, mp 188–189 °C (CH_2Cl_2). EIMS m/z (%): 187 (82), 168 (18), 167 (100), 139 (90), 120 (3), 112 (8). HR EIMS calcd for $C_8H_4ONF_3$ M=187.0245. Found: 187.0249. ^{1}H NMR (400 MHz, $CDCl_3$): 7.64 (d, 1H, J=8.1 Hz), 7.30 (d, 1H, J=8.1 Hz), 7.28 (s, 1H), 6.60 (s broad, 1H). ^{19}F NMR (376 MHz, acetone-d_6): −63.0. ^{13}C NMR (100 MHz, acetone-d_6): 156.7, 128.9 (q, J=5 Hz), 124.1 (q, J=272 Hz), 123.8, 121.6 (q, J=31 Hz), 120.9, 118.0, 96.6. IR (KBr): 3234, 2259, 1980, 1591, 1473, 1316, 1268, 1148, 1108, 1041, 983, 808, 753. Anal. calcd for $C_8H_4F_3NO$: C, 51.35; H, 2.15; N, 7.49. Found: C, 50.99; H, 1.85; N, 7.20.

4.3.4. 4-Chloro-3-cyano-2-trifluoromethylphenol (3a). Yield 52 mg, 47%, yellow crystals, mp 201–202 °C (CH_2Cl_2). EIMS m/z (%): 223 (9), 221 (29), 203 (18), 201 (100), 175 (13), 173 (41). HR EIMS calcd for $C_8H_3ONF_3^{35}Cl$ M=220.9855. Found: 220.9858. ^{1}H NMR (400 MHz, acetone-d_6): 10.50 (s broad, 1H), 7.78 (d, 1H, J=8.9 Hz), 7.48 (d, 1H, J=8.9 Hz). ^{19}F NMR (376 MHz, acetone-d_6): −54.33. ^{13}C NMR (100 MHz, acetone-d_6): 156.6, 135.4, 129.2 (q, J=5 Hz), 124.6, 123.1 (q, J=274 Hz), 123.0 (q, J=30 Hz), 113.8, 96.6. Anal. calcd for $C_8H_3F_3NOCl$: C, 43.37; H, 1.36; N, 6.32. Found: C, 43.16; H, 1.12; N, 6.17.

4.3.5. 4-Chloro-3-cyano-6-trifluoromethylphenol (3b). Yield 18 mg, 16%, yellow crystals, mp 168–169 °C (CH_2Cl_2). EIMS m/z (%): 223 (18), 221 (57), 203 (34), 202 (16), 201 (100), 175 (24), 173 (70). HR EIMS calcd for $C_8H_3ONF_3^{35}Cl$ M=220.9855. Found: 220.9862. ^{1}H NMR (400 MHz, acetone-d_6): 7.84 (d, 1H, J=0.6 Hz), 7.54 (s, 1H), 3.4 (s broad, 1H). ^{19}F NMR (376 MHz, acetone-d_6): −64.5. Anal. calcd for $C_8H_3F_3NOCl$: C, 43.37; H, 1.36; N, 6.32. Found: C, 43.21; H, 1.28; N, 6.34.

4.3.6. 3-Nitro-2-trifluoromethylphenol (4a). Yield 49 mg, 47%, colorless crystals, mp 136–137 °C (CH_2Cl_2/hexane). EIMS m/z (%): 208 (9), 207 (100), 188 (4), 187 (2), 177 (13), 161 (80), 149 (28), 133 (18), 113 (43). HR EIMS calcd for $C_7H_4O_3NF_3$ M=207.0143. Found: 207.0150. ^{1}H NMR (acetone-d_6, 400 MHz): 10.36 (s, 1H), 7.73–7.67 (m, 1H), 7.38 (d, 1H, J=8.4 Hz), 7.28 (d, 1H, J=7.9 Hz). ^{19}F NMR (acetone-d_d, 376 MHz): −59.40. ^{13}C NMR (acetone-d_d, 100 MHz): 157.9, 135.3, 123.0 (q, J=271 Hz), 121.2, 115.1, 108.6 (q, J=34 Hz), 96.6. IR (KBr): 3428, 1617, 1531, 1465, 1376, 1338, 1306, 1154, 1129, 1042, 961, 823, 807, 740.

4.3.7. 3-Nitro-4-trifluoromethylphenol (4b). Yield 19 mg, 18%, colorless crystals, mp 210–211 °C (CH_2Cl_2). EIMS m/z (%): 208 (8), 207 (100), 188 (9), 187 (79), 177 (1), 161 (32), 141 (26), 138 (33), 113 (88). HR EIMS calcd for $C_7H_4O_3NF_3$ M=207.0143. Found: 207.0137. ^{1}H NMR ($CDCl_3$, 400 MHz): 7.69 (d, 1H, J=8.7 Hz), 7.35 (d, 1H, J=2.3 Hz), 7.06–7.00 (m, 1H), 6.38 (s broad, 1H). ^{19}F NMR (acetone-d_d, 376 MHz): −59.56. ^{13}C NMR ($CDCl_3$, 100 MHz): 156.1, 134.8, 129.0, 123.9, 118.79 (q, J=31 Hz), 112.3 (q, J=207 Hz), 96.0.

4.3.8. 3-Nitro-6-trifluoromethylphenol (4c). Yield 14 mg, 13%, yellow oil. EIMS m/z (%): 208 (8), 207 (100), 189 (1), 187 (88), 161 (32), 141 (57), 113 (73). HR EIMS calcd for $C_7H_4O_3NF_3$ M=207.0143. Found: 207.0137. ^{1}H NMR (acetone-d_6, 400 MHz): 7.93–7.91 (m, 1H), 7.87 (d, 1H, J=0.5 Hz), 7.86–7.84 (m, 1H). ^{19}F NMR (acetone-d_{**d}, 376 MHz): −62.92.

4.3.9. 4-Bromo-3-nitro-2-trifluoromethylphenol (5a). Yield 42 mg, 29%, orange oil. EIMS m/z (%): 287 (98), 285 (100), 267 (45), 265 (45), 241 (33), 239 (31), 218 (22), 216 (22), 193 (42), 191 (44), 112 (57), 86 (45). HR EIMS

calcd for $C_7H_3O_3NF_3^{79}Br$ M=284.9248. Found: 284.9253. ^1H NMR (400 MHz, $CDCl_3$): 7.57 (dd, 1H, J=8.9, 0.6 Hz), 6.92 (dd, 1H, J=8.9, 0.4 Hz), 5.10 (s broad, 1H). ^{19}F NMR (376 MHz, $CDCl_3$): −59.46.

4.3.10. 6-Bromo-3-nitro-2-trifluoromethylphenol (5b). Yield 9 mg, 6%, orange oil. EIMS *m/z* (%): 287 (13), 285 (13), 267 (4), 265 (4), 241 (7), 239 (6), 86 (100). HR EIMS calcd for $C_7H_3O_3NF_3^{79}Br$ M=284.9248. Found: 284.9242. ^1H NMR (400 MHz, $CDCl_3$): 8.21 (d, 1H, J=8.8 Hz), 7.95 (d, 1H, J=8.8 Hz), 7.38 (s, 1H). ^{19}F NMR (376 MHz, $CDCl_3$): −59.23.

4.3.11. 6-Bromo-3-nitro-4-trifluoromethylphenol (5c). Yield 17 mg, 11%, orange oil. EIMS *m/z* (%): 287 (13), 285 (13), 257 (4), 255 (4), 241 (7), 239 (7), 229 (4), 227 (4), 101 (23), 100 (25), 86 (100). HR EIMS calcd for $C_7H_3O_3NF_3^{79}Br$ M=284.9248. Found: 284.9257. ^1H NMR (400 MHz, $CDCl_3$): 7.85 (s, 1H), 7.34 (s, 1H), 5.6 (s broad, 1H). ^{19}F NMR (376 MHz, $CDCl_3$): −58.81.

4.3.12. 3,5-Dinitro-4-trifluoromethylphenol (6a). Yield 39 mg, 31%, colorless crystals, mp 163–165 °C (CH_2Cl_2). EIMS *m/z* (%): 253 (9), 252 (100), 183 (22), 160 (39), 159 (9), 135 (20), 132 (54). HR EIMS calcd for $C_7H_3O_5N_2F_3$ M=251.9994. Found: 251.9993. ^1H NMR (200 MHz, acetone-d_6): 7.69 (d, J=0.5 Hz). ^{19}F NMR (376 MHz, acetone-d_6): −55.8 (t, J=0.5 Hz).

4.3.13. 3,5-Dinitro-2-trifluoromethylphenol (6b). Yield 28 mg, 22%, yellow oil. EIMS *m/z* (%): 253 (6), 252 (81), 233 (12), 232 (100), 183 (7), 160 (27), 132 (30). HR EIMS calcd for $C_7H_3O_5N_2F_3$ M=251.9994. Found: 251.9991. ^1H NMR (400 MHz, acetone-d_6): 8.18 (d, 1H, J=0.7 Hz), 7.68 (d, 1H, J=0.7 Hz). ^{19}F NMR (376 MHz, acetone-d_6): −59.2 (t, J=0.7 Hz).

4.3.14. α,α,α-Trifluoro-2,4,6-trinitrotoluene (6c). Yield 46 mg, 33%, colorless crystals, mp 88–89 °C (CH_2Cl_2) (lit.[17] 89 °C). EIMS *m/z* (%): 282 (8), 281 (100), 159 (10), 143 (68), 131 (22). HR EIMS calcd for $C_7H_2O_6N_3F_3$ M=280.9896. Found: 280.9888. ^1H NMR (200 MHz, acetone-d_6): 8.80 (s). ^{19}F NMR (376 MHz, acetone-d_6): −57.5.

4.3.15. 2-Chloro-3-hydroxy-4-trifluoromethylpyridine (7a). Yield 28 mg, 28%, yellow oil. HR EIMS calcd for $C_6H_3NOF_3^{35}Cl$ M=196.9855. Found: 196.9848. ^1H NMR (400 MHz, acetone-d_6): 8.76 (d, 1H, J=5.0 Hz), 7.77 (d, 1H, J=5.0 Hz), 7.40 (s broad, 1H). ^{19}F NMR (376 MHz, acetone-d_6): −65.09.

4.3.16. 2-Chloro-3-hydroxy-6-trifluoromethylpyridine (7b). Yield 28 mg, 28%, yellow oil. HR EIMS calcd for $C_6H_3NOF_3^{35}Cl$ M=196.9855. Found: 196.9843. ^1H NMR (400 MHz, acetone-d_6): 8.59 (s broad, 1H), 8.07 (d, 1H, J=4.8 Hz), 7.33 (d, 1H, J=4.8 Hz). ^{19}F NMR (376 MHz, acetone-d_6): −64.92.

4.3.17. 2,2′-Dichloro-3,3′-dinitro-4,4′-bipyridyl (7c). Orange crystals, mp 189–190 °C (EtOH). EIMS *m/z* (%): 316 (7), 314 (11), 270 (6), 268 (9), 242 (18), 240 (13), 177 (8), 175 (7), 153 (32), 151 (100). HR EIMS calcd for $C_{10}H_4O_4N_4^{37}Cl^{35}Cl$ M=315.9580. Found: 315.9578. ^1H NMR (400 MHz, $CDCl_3$): 8.67 (d, 2H, J=4.9 Hz), 7.32 (d, 2H, J=4.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): 151.0, 143.9, 143.4, 136.1, 122.5. Anal. calcd for $C_{10}H_4O_4N_4O_3Cl_2$: C, 38.12; H, 1.28; N, 17.78. Found: C, 38.08; H, 1.31; N, 17.47.

4.4. Oxidation of σ^H adducts of CF_3^- to *m*-dinitrobenzene with Br_2

To a stirred solution of **1** (0.6 mmol) and nitroarene (0.5 mmol) in THF (5 mL) at −70 °C under argon, TASF (153 mg, 0.5 mmol) dissolved in pyridine (1 mL) was added dropwise and the mixture was stirred for 5 min. Bromine (0.6 mmol, 97 mg) dissolved in THF (1 mL) was added to the mixture and after 5 min triethylamine (0.5 mL) was added. The cooling bath was removed. The solids were filtered off and washed with dichloromethane (20 mL). The solvents were evaporated (25 °C, 15 Torr) and the product was purified by column chromatography using hexane as an eluent. In the cases of use **2** and **7** we could not find any defined products, on GCMS we observed traces (<10%) of products of ONSH process. In case of using **4** we isolated starting nitroarene 25% and **4d** (46%).

4.4.1. 4-Bromo-2,6-dinitro-α,α,α-trifluorotoluene 4d. Yield 73 mg, 46%, yellow crystals, mp 108–109 °C (EtOH). EIMS *m/z* (%): 316 (71), 314 (72), 297 (4), 295 (4), 224 (7), 222 (7), 212 (9), 210 (9), 174 (10), 172 (8), 143 (100). HR EIMS calcd for $C_7H_2O_4N_2F_3^{79}Br$ M=313.9150. Found: 313.9156. ^1H NMR ($CDCl_3$, 400 MHz): 8.09 (d, J=0.6 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz): −57.34. ^{13}C NMR ($CDCl_3$, 100 MHz): 149.8, 130.3, 129.6, 125.4 (q, J=305 Hz), 121.4, 118.7, 116.3 (q, J=36 Hz).

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New tri- and tetracyclic diterpenes from *Euphorbia villosa*

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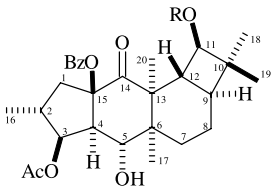
Abstract—Three new tetracyclic diterpenes were isolated from the chloroform-soluble extract of *Euphorbia villosa*, together with one new and one known lathyrane diterpene. The structures were elucidated by means of various spectroscopic methods, including HREI-MS, HRFAB-MS, UV, and 1D and 2D NMR techniques. Spectral analyses revealed that two of the tetracyclic compounds contain the rare 5-6-6-4 fused ring system, while the third has a 5-6-7-3 fused diterpene core. Such diterpene skeletons have previously been found only in euphoractines A-E isolated from *Euphorbia micractina*. As a new structural feature, the diterpene framework described here has a C-2 epimer configuration. The new lathyrane diterpene is a diester of a hitherto unknown polyfunctional parent alcohol.

1. Introduction

The plants of the family Euphorbiaceae (spurges) produce a high diversity of diterpenoids based on various macrocyclic and polycylic skeletons. Characteristic constituents of the family include the tigliane, ingenane and daphnane diterpenes, referred to overall as phorboids,[1] which exhibit strong irritant and tumour-promoting activities as a consequence of their protein kinase C-activating and vanilloid receptor type 1 agonist effect.[2,3] Diterpenes of other skeletal types, e.g. lathyrane, jatrophane, casbane and cembrane derivatives, have also attracted considerable interest because of their complex structures and therapeutically relevant bioactivities. Pharmacological studies have revealed their cytotoxic, antineoplastic, PGE_2-inhibitory, multidrug-resistance-reversing, propyl endopeptidase-inhibitory and various vascular effects.[4–8] As a continuation of our studies on the chemistry and pharmacology of the genus *Euphorbia*, we have now investigated *Euphorbia villosa* W. et K., a stout glabrous or pubescent, rhizomatous perennial plant widely distributed throughout Europe.[9] No chemical and pharmacological investigation has been reported so far on this species. The present paper describes the isolation and structure determination of four new diterpenes (**1**–**4**) and one known diterpene (**5**) from the chloroform-soluble extract of *E. villosa*. We also discuss the conformational behaviour of the compounds, with an interpretation of the results of NOESY experiments and theoretical structure calculations.



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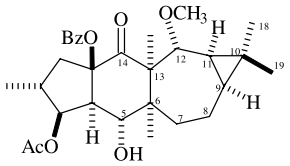
2 R = H



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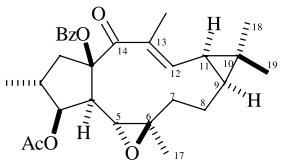

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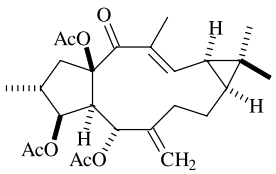

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2. Results and discussion

The chloroform phase of a methanol extract of the dried whole plant of *E. villosa* was fractionated by open column chromatography on polyamide, and then by vacuum liquid chromatography on NP silica gel, and it was further purified by RP HPLC to afford compounds **1**–**5**. Compound **5** ($[\alpha]_D^{28}$=+148, *c* 0.2, $CHCl_3$) was found to be identical in all of its characteristics, including the ^1H and ^{13}C NMR spectral data, with the lathyrane diterpene isolated earlier from *Euphorbia hyberna*.[10]

Keywords: *Euphorbia villosa*; Euphorbiaceae; Terpenes and terpenoids; Lathyrane diterpenes; Tetracyclic diterpenes.
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Table 1. NMR spectral data of **1** in $CDCl_3$ (δ in ppm, multiplicities, J in Hz)

Atom	^{1}H	^{13}C	HMBC (H No.)	NOESY
1α	1.67dd (14.8, 9.6)	38.5	—	1β, 4, 16
1β	3.13dd (14.8, 8.0)	—	3, 16	1α, 2
2	2.25m	38.6	1α, 3, 16	1β, 3, 16
3	5.07dd (5.9, 1.7)	82.1	1β, 5, 16	2, 4, 16, OH
4	2.19m	54.1	1β	1α, 3, 17, OH
5	4.76dd (11.3, 3.1)	62.8	7α, 7β/4, 17	8β, 12, OH, 2′, 6′
6	—	47.4	5, 4/7β, 7α, 17, 20, OH	—
7α	1.16m	32.4	—	7β, 8α, 9, 17
7β	2.19m	—	8α, 8β, 17	7α, 8β
8α	1.42m	21.8	—	7α, 7β, 8β, 9, 18
8β	1.47dd (12.3, 3.2)	—	7α, 12	5, 7β, 8α, 12, 19
9	1.01dt (3.8, 12.3)	38.6	8β, 12, 18, 19	7α, 8α, 11, 20
10	—	41.9	9, 12, 18, 19	—
11	2.83d (8.9)	82.7	12, 18, 19, OMe,	9, 18, 20
12	2.65dd (12.3, 8.9)	46.9	9, 11	5, 8β, 19, 2′, 6′
13	—	56.1	11, 12, 17, 20	—
14	—	205.3	1α	—
15	—	91.2	1β, 3	—
16	1.16d (7.3)	19.8	1α, 3	1α, 2, 3
17	0.76s	17.8	5	4, 7α, 20,
18	0.94s	28.9	9, 11, 19	8α, 11, 19
19	0.38s	14.6	9, 11, 18	8β, 12, 18, 2′, 6′
20	1.14s	13.5	12	9, 11, 17
AcCO	—	172.3	3, AcMe	—
AcMe	2.29s	21.5	—	2′, 6′, 3′, 5′
BzCO	—	163.8	—	—
1′	—	131.6	—	—
2′, 6′	8.07d (7.3)	129.6	—	5, 12, 19, OMe, Ac
3′, 5′	7.41t (7.7)	127.8	—	Ac
4′	7.53t (7.4)	132.6	—	—
OH	2.95d (3.1)	—	—	3, 4, 5,
OMe	2.86s	56.9	12	2′, 6′

2.1. Structure of compound 1

Compound **1** was isolated as colourless prisms with $[\alpha]_D^{28}=-3$ (c 0.1, $CHCl_3$). The molecular formula $C_{30}H_{40}O_7$ was established by HREI-MS, which showed a molecular ion peak at m/z 512.2806 (M^+) (Δ=6.2 ppm). The ^{1}H NMR and JMOD spectra of **1** revealed the presence of one acetate group (δ_H 2.29s; δ_C 172.3 and 21.5) and one benzoate group (δ_H 8.07d, 7.53t and 7.41t; δ_C 163.8, 132.6, 131.6, 129.6, and 127.8) (Table 1). The JMOD and HMQC spectra suggested that the skeleton contained 20 carbons: five methyls, three methylenes, seven methines and five quaternary carbons, with one ketone (δ_C 205.3). The gradient ^{1}H–^{1}H COSY and HMQC spectra demonstrated two structural fragments with correlated protons: $-CH_2-CH(CH_3)-CH(OR)-CH-CH(OR)-$ (A) and $-CH_2-CH_2-CH-CH-CH(OR)-$ (B) (R=H, acyl or methyl). The sequences A and B, tertiary methyls and quaternary carbons were connected by inspection of the long-range C–H correlations observed in a gradient HMBC spectrum, as presented in Figure 1. The correlations of quaternary C-15 with the H-3 and H-1β signals, and of C-4 with the H-1β signal revealed that structural fragment A together with quaternary C-15 forms a methyl-substituted five-membered ring, present in many types of Euphorbiaceae diterpenes. HMBC cross-peaks between C-6 and H-5, C-6 and H-20, C-6 and H-17, and C-13 and H-17, C-13 and H-20, and C-14 and H-1 proved the presence of a six-membered ring B substituted with one keto and two methyl groups. The structure was further elucidated with the aid of two and three-bond correlations between C-6 and H-7, C-13 and H-11, and C-13 and H-12, indicating that structural fragments A and B are connected as depicted in Figure 1. The presence of six-membered ring C and four-membered ring D with geminal dimethyl groups was derived from the HMBC correlations between C-20 and H-12, C-10 and H-18, C-10 and H-19, C-10 and H-12, and C-10 and H-9. The $^2J_{CH}$ and $^3J_{CH}$ correlations between H-1α and the carbon signal at δ_C 205.3 placed the keto group at C-14. The positions of the ester groups were also established via the HMBC experiment. The correlation of the carbonyl signal at δ_C 172.3 (acetyl *C*O) with the proton signal at δ_H 5.07 (H-3) indicated the presence of the acetyl group at C-3. The position of the hydroxy group at C-5 was determined via the coupling constants and the long-range correlations: in the ^{1}H NMR spectrum, the signal of the hydroxy group (δ_H 2.95d) was coupled to H-5 (δ_H 4.76dd), with J=3.2 Hz, while in the HMBC spectrum, the hydroxy proton showed a correlation to C-6. The HMBC correlation between H-11 and the methoxy group pointed to the position of the methoxy group at C-11, and of necessity the benzoyl group was placed at the quaternary C-15. The relative

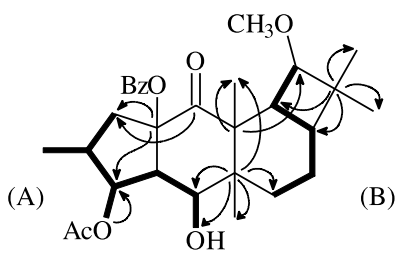

Figure 1. Selected ^{1}H–^{1}H-COSY (▬) and HMBC (C→H) correlations for **1**.

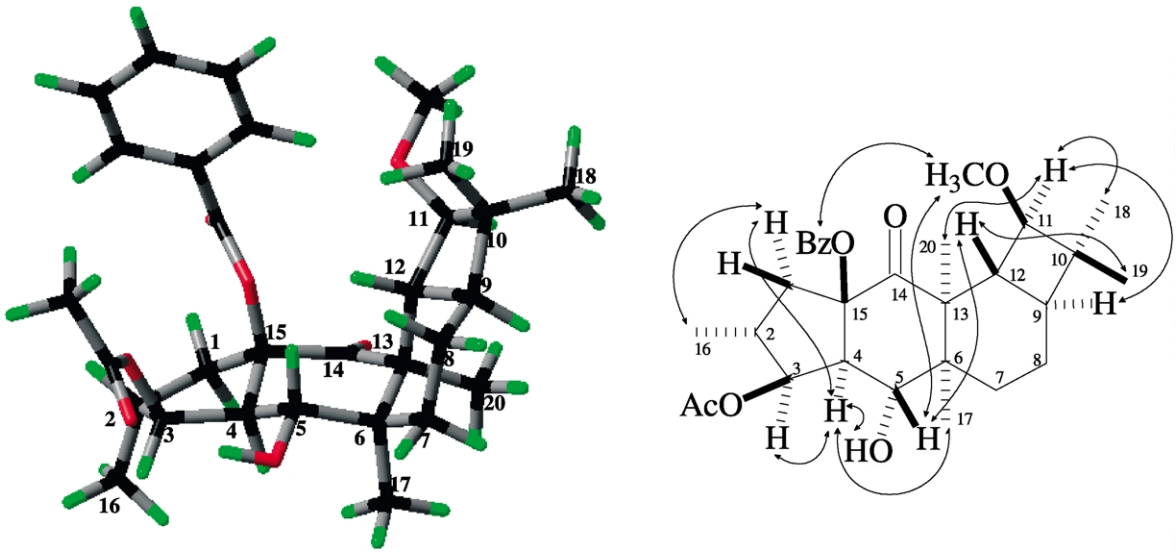

Figure 2. Calculated conformation and significant NOESY correlations (↔) of compound **1**.

configurations of the ten stereogenic centres in **1** were investigated in a phase-sensitive NOESY experiment (Table 1), aided by consideration of the coupling constant values. Conventionally, as reference point, the position of H-4 was chosen to be α. The NOESY correlations observed between H-4 and H-3, H-4 and H-1α, H-4 and 5-OH, and H-4 and H-17 indicated the α stereochemistry of H-3, H-1α, 5-OH and H-17. The NOE interaction between H-1α and H-16 suggested the α position of H-16. A diagnostic NOE interaction was detected between H-5 and H-2′, 6′ (benzoyl), proving the β position of the benzoyl group. The nuclear Overhauser effects observed between H-5 and H-12, H-2′, 6′ and 11-OCH_3 and H-12 and H-19 demonstrated the β position of H-12, 11-OCH_3 and H-19, while the NOEs of H-11 with H-9, H-18 and H-20 were indicative of the α position of H-9, H-18 and H-20. The stereochemistry elucidated from the NOESY experiment was compared with the conformation generated by the semi-empirical PM3[11,12] package of the HyperChem program[13] (Fig. 2). The calculated conformation is in good agreement with the detected nuclear Overhauser effects. Rings B and C are *cis*-fused, and in the model possess a chair–chair conformation. Thus, the distance between H-5 and H-12 is 1.9 Å, and consequently an intense NOESY cross-peak appeared between H-5 and H-12. The calculated conformation indicated the spatial proximity of the benzoyl and C-19 methyl groups in accordance with the observed NOESY correlation between H-2′, 6′ and H-19, and the upfield-shifted methyl signal ($\delta_{H\text{-}19}$ 0.38s) as a result of the anisotropic effect of the aromatic ring. From the above analysis, therefore, the structure of this compound was identified as **1**, moreover complete and unambiguous ^1H and ^{13}C chemical shift assignments were determined as listed in Table 1. Compound **1** has a tetracyclic 5-6-6-4 fused ring system. A similar diterpene core was previously found in euphoractines A, C and D (obtained from *Euphorbia micractina*) with a C-2 epimer configuration.[14]

2.2. Structure of compound 2

Compound **2** was isolated as an amorphous solid with $[\alpha]_D^{28}=+16$ (*c* 0.033, $CHCl_3$). The HRFAB-MS suggested that the molecular formula is $C_{29}H_{39}O_7$, with a molecular ion peak at *m/z* 499.2704 (MH^+) (Δ=1.6 ppm). The ^1H NMR and JMOD spectra of **2** contained signals corresponding to one acetyl (δ_H 2.32s; δ_C 172.1 and 21.5) and one benzoyl group (δ_H 8.12d, 7.58t and 7.44t; δ_C 166.3, 133.4, 130.6, 130.0 and 128.3). Additionally, the ^1H NMR and JMOD spectra exhibited resonances for five methyls, three methylenes, seven methines and five quaternary carbons, including one ketone (δ_C 205.3) (Table 2). The ^1H–^1H COSY spectrum indicated two sequences of correlated protons: $-CH_2-CH(CH_3)-CH(OR)-CH-CH(OR)-$ and $-CH_2-CH_2-CH-CH-CH(OR)-$ (R=H or acyl). After the ^1H and ^{13}C chemical shift assignment of **2** had been achieved via the ^1H–^1H COSY, HSQC and HMBC spectra, it was evident that compounds **1** and **2** differ only in one substituent: the methoxy group of **1** is replaced by a hydroxy group in **2**. The diamagnetically shifted C-11 signal (**2**: $\delta_{C\text{-}11}$ 73.6; **1**: $\delta_{C\text{-}11}$ 82.7) demonstrated a hydroxy group instead of a methoxy group on C-11 in **2**.

The relative configuration of **2** was analysed by a NOESY experiment. Diagnostic nuclear Overhauser effects detected between H-2′, 6′/H-5, H-2′, 6′/H-12, H-2′, 6′/H-19, H-5/H-12, H-12/H-19 and H-1β/H-2 provided evidence of the β orientation, while NOESY cross-peaks between H-1α/H-16, H-1α/H-4, H-4/H-3, H-4/H-17, H-17/H-20, H-20/H-9, H-9/H-18, H-9/H-11 and H-11/H-20 pointed to the α position of these protons and groups. All of the above data indicate structure **2** for this compound.

2.3. Structure of compound 3

Compound **3** was isolated as an amorphous solid with $[\alpha]_D^{28}=-38$ (*c* 0.1, $CHCl_3$). The molecular formula $C_{30}H_{40}O_7$ was established by HREI-MS, with a molecular ion peak at *m/z* 512.2801 (M^+) (Δ=5.2 ppm). In the ^1H NMR and JMOD spectra, signals of one benzoyl, one acetyl and one methoxy group were observed (Table 2). Further analysis of the ^1H NMR and JMOD resonances revealed that the remaining moiety consisted of 20 carbons: five methyls, three methylenes, seven methines and five quaternary carbons (Table 2). A quaternary carbon at δ_C 20.4 and

Table 2. NMR spectral data of **2**–**4** in $CDCl_3$ (δ in ppm, multiplicities, J in Hz)

Atom	**2**		**3**		**4**			
	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H[a]	^{13}C[a]
1α	1.76dd (14.9, 9.4)	39.3	1.70m	38.1	3.09dd (14.4, 4.4)	43.2	2.44dd (14.7, 7.8)	43.8
1β	2.81dd (14.9, 8.1)		3.34dd (14.8, 8.0)		2.31dd (14.4, 7.9)		3.34dd (14.7, 5.5)	
2	2.3m	39.0	2.20m	38.5	2.37m	38.3	2.33m	39.2
3	5.11dd (6.0, 1.7)	82.2	5.03d (5.7)	82.1	5.16dd (5.6, 2.4)	83.4	5.45dd (5.9, 3.0)	83.9
4	2.22m	53.8	2.20m	54.4	1.94m	48.6	2.13dd (9.3, 6.0)	49.5
5	4.73d (11.2)	63.0	4.57brd (10.8)	62.7	3.53d (9.2)	57.8	3.78d (9.3)	58.4
6	—	47.7	—	46.8	—	63.4	—	63.4
7α	1.16m	32.5	2.07dd (14.7, 7.2)	33.8	1.99m	38.7	1.75brt (12.3)	39.7
7β	2.21m		1.43t (13.3)		1.61m		1.58m	
8α	1.44m	22.0	1.69dd (15.0, 9.6)	19.0	1.99m	23.1	1.58m	23.7
8β	1.44m		1.25m		1.34m		1.34m	
9	1.13m	39.1	0.76m	26.3	1.08m	34.3	0.59m	34.3
10	—	41.6	—	20.4	—	26.2	—	25.9
11	3.35d (8.6)	73.6	0.32t (9.5)	26.8	1.45dd (11.2, 8.0)	29.6	1.16dd (11.1, 8.0)	29.9
12	2.47dd (12.1, 8.6)	48.5	3.99d (9.5)	76.7	6.93dd (11.2, 0.6)	144.5	7.03m	143.4
13	—	56.4	—	63.7	—	134.6	—	135.9
14	—	205.3	—	203.5	—	194.4	—	194.4
15	—	92.1	—	91.6	—	93.3	—	94.3
16	1.18d (7.3)	19.8	1.16d (7.3)	19.7	1.06d (7.0)	17.7	0.99d (7.1)	18.0
17	0.77s	17.8	0.76s	19.4	1.15s	20.1	1.05s	20.7
18	0.91s	27.8	0.96s	27.5	1.03s	29.0	0.79s	29.1
19	0.37s	14.2	0.79s	16.2	0.29s	14.8	0.29s	15.4
20	1.16s	13.6	1.25s	12.5	1.90s	12.5	1.96s	13.2
AcCO	—	172.1	—	172.5	—	169.9	—	169.6
AcMe	2.32s	21.5	2.21s	21.4	2.16s	21.3	1.84s	21.2
BzCO	—	166.3	—	163.2	—	164.9	—	165.2
1′	—	130.6	—	131.2	—	130.2	—	131.6
2′, 6′	8.12d (7.2)	130.0	8.11d (7.7)	129.8	8.04d (7.1)	129.6	8.12d (7.2)	130.2
3′, 5′	7.44t (7.7)	128.3	7.43t (7.7)	128.3	7.47t (7.7)	128.7	7.11t (7.4)	129.1
4′	7.58t (7.4)	133.4	7.57t (7.5)	133.1	7.60t (7.5)	133.6	7.03m	133.8
OH	2.84s	—	3.01s	—	—	—	—	—
OMe	—	—	2.52s	54.1	—	—	—	—

[a] In C_6D_6.

two methines at δ_H 0.76 and 0.32, and δ_C 26.3 and 26.8 indicated a *gem*-dimethyl-substituted cyclopropane ring.[10] The gradient ^{1}H–^{1}H COSY and HSQC spectra identified two isolated fragments of correlated protons: $-CH_2-CH(CH_3)-CH(OR)-CH-CH(OR)-$ and $-CH_2-CH_2-CH-CH-CH(OR)-$ (R=H, acyl or methyl). One signal at δ_H 3.01, which did not provide any correlation in the HSQC spectrum, pointed to the presence of one hydroxy group in the molecule. The HMBC correlations between C-15 and H-1, C-15 and H-3 and C-4 and H-1 suggested that structural fragment A, together with a quaternary carbon (C-15), is joined to a methyl-substituted five membered ring in **3**. The long-range correlations between C-5 and H-7, C-5 and H-17, C-17 and H-7, C-6 and OH, C-6 and H-7, C-14 and H-20, C-13 and H-20, C-20 and H-12, and C-6 and H-12 led to the assembly of units A and B together with two methyl groups (C-17 and C-20) through quaternary carbons (C-6, C-13 and C-14), resulting in a 5-6-7-3 condensed ring system. The long-range correlation between the hydroxy group and C-5 clearly indicated that the hydroxy group is located at C-5. The methoxy group was placed at C-12, as shown in the HMBC spectrum by the long-range correlation between the methoxy carbon and H-12. The position of the acetyl group was determined on the basis of the three-bond correlation between the ester carbonyl and H-3. Finally, the benzoyl group, which did not display any long-range correlations, must be on C-15. The relative configuration of the molecule was investigated by a NOESY experiment. Starting from the α position of H-3, the nuclear Overhauser effects between H-3 and 5-OH and H-3 and H-16 were indicative of the α position of the hydroxy group at C-5 and the methyl group at C-2. The NOESY correlations between H-16 and H-1α allowed the conclusion that this H-1 is α-oriented. The NOE effects between H-5 and H-8β, and H-5 and H-12 suggested the β position, and that between H-8α and H-7α the α configuration of these protons. The β orientation of the 19-methyl group followed from the nuclear Overhauser effects between H-12 and H-19. The cross-peaks of the benzoyl protons (H-2′, 6′) with H-5, H-12 and H-19 suggested the β position of the benzoyl group. The α orientation of H-11, H-9 and H-20 was deduced from the NOE correlations between H-18 and H-11, H-11 and H-20, and H-11 and H-9. The overlapping of the ^{1}H signals of H-2, H-4 and 3-OAc at δ_H 2.20 did not allow a conclusion concerning the stereochemistry of H-4, but the coupling constants of H-3 and H-5 in **3** were found to be very similar to those in **1** and **2**, indicating the same α configuration of H-4. Further, the NOESY correlation of the overlapping signal at δ_H 2.20 with that of H-17 can most probably be assigned to the H-4/H-17 correlation, suggesting the α orientation of H-17. All of the above data are compatible with structure **3** for this compound.

2.4. Structure of compound 4

Compound **4**, an amorphous solid with $[\alpha]_D^{28}=-146$ (*c* 0.1, $CHCl_3$), has the molecular formula $C_{29}H_{36}O_6$, determined via the molecular ion peak at *m/z* 480.2526 (M^+)

(Δ=3.0 ppm) in the HREI-MS. Analysis of the ^{1}H NMR and JMOD data revealed that **4** possesses one benzoyl and one acetyl group in the molecule. The diterpene core consists of five methyls, three methylenes, seven methines (one vinylic, δ_C 144.5) and five quaternary carbons, with one ketone (δ_C 194.4) (Table 2). Interpretation of the HSQC and ^{1}H–^{1}H COSY spectra led to the identification of three structural elements with correlated protons: $-CH_2-CH(CH_3)-$ (A), $-CH(OR)-CH-CH-$ (B) and $-CH_2-CH_2-CH-CH-CH=$ (C), (R=acyl). Their connectivities were determined on the basis of the HMBC spectrum. The long-range correlations of the quaternary carbons with the protons of the three fragments (C-6 and H-4, C-6 and H-7, C-6 and H-17, C-10 and H-9, C-10 and H-11, C-10 and H-18, C-10 and H-19, C-13 and H-11, C-13 and H-20, C-14 and H-1, C-14 and H-4, C-14 and H-20, C-15 and H-1, and C-15 and H-3) indicated the bicyclic lathyrane ring system with oxygen functions at C-3, C-5, C-6, C-14 and C-15, and a double bond between C-12 and C-13. The three-bond correlation between H-12 (δ_H 6.93dd) and the carbon signal at δ_C 194.4 placed the keto group at C-14. The chemical shifts of C-5 (δ_C 57.8), C-6 (δ_C 63.4) and H-5 (δ_H 3.53) were indicative of an epoxy group at C-5-C-6.[15] The HMBC correlation between acetyl *C*O and H-3 pointed to the presence of the acetyl group at C-3. The benzoyl group, which did not exhibit any long-range correlations, is located on quaternary C-15. The relative configuration of **4** was determined on the basis of a NOESY experiment. Because of the overlapping of the proton signals in $CDCl_3$ solution, the ^{1}H NMR, JMOD, HSQC and NOESY spectra were also run in C_6D_6, which resulted in better-resolved spectra and unambiguous assignments of all the ^{1}H and ^{13}C NMR signals. Starting from the α position of H-4, the nuclear Overhauser effects between H-4 and H-1α, H-1α and H-16 and H-1α and H-3 indicated the α orientation of H-3 and H-16. The observed correlations of the *ortho*-benzoyl protons with H-5, 3-OAc and H-19, and between H-12 and H-19 proved the β position of H-5 and H-19 and the acetyl group at C-3. The NOE interactions between H-5 and H-7β, H-5 and H-8β and H-5 and H-12 allowed the steric differentiation of the C-7 and C-8 methylene protons and suggested that H-12 is oriented above the plane of the molecule. The NOE interactions between H-18 and H-11 and between H-18 and H-9 suggested the α-oriented H-11 and H-9. As regards the stereochemistry of C-17, the NOESY correlations between H-17 and H-4, and H-17 and H-7α were informative, proving the α orientation of the 17-methyl group. The NOE interaction between H-11 and H-20 revealed that H-20 is oriented below the plane of the macrocycle, thereby confirming the *E* configuration for the C-12/C-13 double bond. As a result of the above NMR study, the structure of this compound was demonstrated to be **4**, and the complete ^{1}H and ^{13}C NMR data were assigned as listed in Table 2. Compound **4** is a lathyrane derivative containing the rare 5,6-epoxy function. The parent diterpene alcohol of **4** has not been described previously.

Biogenetic relationship can be supposed between the isolated compounds, since lathyrane diterpenes are regarded as the biosynthetic progenitors of the naturally occurring polycyclic derivatives. Compounds **1**–**3** can be derived from a lathyrane precursor by transannular cyclization, and in case of **1** and **2**, by expansion of the cyclopropane ring. Similar rearrangement was observed in synthetic studies when acid-catalysed conversion of an epoxylathyrane enone (Euphorbia factor L_1) was performed.[16,17]

3. Experimental

3.1. General

Melting points are uncorrected. HRMS measurements were carried out on a VG ZAB SEQ instrument in EI and FAB ionization mode. The resolution of the instrument was 10,000 (at 10% valley definition). NMR spectra were recorded on a Bruker Avance DRX 500 spectrometer at 500 MHz (^{1}H) and 125 MHz (^{13}C). The signals of the deuterated solvents were taken as reference. Two-dimensional experiments were performed with standard Bruker software. Optical rotations were determined in $CHCl_3$ by using a Perkin–Elmer 341 polarimeter. The UV spectra were recorded on a Shimadzu UV-2101 PC spectrometer. For column chromatography, polyamide (ICN) and silica gel (Kieselgel GF_{254} 15 μm, Merck) were used. HPLC was carried out on a Waters Millipore instrument, with detection at 254 nm on LiChrospher Si 100 and LiChrospher RP-18 (5 μm, 200×4 mm) columns.

3.2. Plant material

E. villosa W. et K. was collected in Vácrátót, Hungary, in June 2000, and identified by Vilmos Miklóssy V. (Institute of Ecology and Botany of the Hungarian Academy of Sciences, Vácrátót). A voucher specimen (No. 550) has been deposited in the Herbarium of the Department of Pharmacognosy, University of Szeged, Szeged.

3.3. Extraction and isolation

The dried plant material (210 g) was percolated with methanol (3 l) at room temperature. The crude extract was concentrated in vacuo to 300 ml and exhaustively extracted with chloroform (1200 ml). On evaporation, the organic phase gave a residue (6.12 g), which was chromatographed on a polyamide column (20 g) with mixtures of MeOH–H_2O (2:3, 3:2 and 4:1) as eluents. The fractions obtained with MeOH–H_2O (3:2) were subjected to silica gel (40 g) flash chromatography, using a gradient system of cyclohexane–EtOAc (19:1, 9:1, 8:2, 7:3 and 6:4). Fractions from cyclohexane–EtOAc (9:1 and 8:2) were further fractionated by reverse-phase HPLC with MeOH–H_2O (8:2 and 9:1) as eluent at a flow rate of 2.0 ml/min. Purification of the peaks observed at retention times of 27.6, 21.1 and 24.7 min yielded compounds **1** (11.0 mg), **5** (13.8 mg), and **3** (3.0 mg), respectively. The fraction eluting at t_R 16.6 min was subjected to NP-HPLC with cyclohexane–CH_2Cl_2–MeOH (70:50:1) as eluent to afford **2** (2.4 mg). The fractions obtained with MeOH–H_2O (4:1) were repeatedly chromatographed on a polyamide column with mixtures of MeOH–H_2O (3:2, 7:3 and 4:1) as eluents. The fractions obtained with MeOH–H_2O (3:2) were separated by flash chromatography on silica gel, using a gradient system of cyclohexane–EtOAc (49:1, 9:1, 4:1 and 7:3). The fractions obtained were further purified by RP-HPLC with

MeOH–H_2O (8:2) as eluent at a flow rate of 1.0 ml/min to afford compound **4** (10.4 mg, t_R=11.5 min).

3.3.1. Compound 1. Colourless prisms; mp 246–248 °C; $[\alpha]_D^{28}=-3$ (*c* 0.1, $CHCl_3$); UV (MeOH): 230 (3.68), 275 (2.91); HREI-MS *m/z* 512.2806 (M^+) (Δ=6.2 ppm). Calcd for $C_{30}H_{40}O_7$: 512.2774. ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) data, see Table 1.

3.3.2. Compound 2. An amorphous solid; $[\alpha]_D^{28}=+16$ (*c* 0.033, $CHCl_3$); UV (MeOH): 231 (3.49), 259 (3.08), 285 (2.43); HRFAB-MS *m/z* 499.2704 (MH^+) (Δ=1.6 ppm). Calcd for $C_{29}H_{38}O_7$: 498.2617. ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$, $^aC_6D_6$) data, see Table 2.

3.3.3. Compound 3. An amorphous solid; $[\alpha]_D^{28}=-38$ (*c* 0.1, $CHCl_3$); UV (MeOH): 232 (3.51), 275 (2.68), 282 (2.67); HREI-MS *m/z* 512.2801 (M^+) (Δ=5.2 ppm). Calcd for $C_{30}H_{40}O_7$: 512.2774. ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) data, see Table 2.

3.3.4. Compound 4. An amorphous solid; $[\alpha]_D^{28}=-146$ (*c* 0.1, $CHCl_3$); UV (MeOH): 233 (336), 271 (3.17); HREI-MS *m/z* 480.2526 (M^+) (Δ=3.0 ppm). Calcd for $C_{29}H_{36}O_6$: 480.2512. ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) data, see Table 2.

3.4. PC model

Molecule conformation of **1** was generated by the semi-empirical PM3[11,12] package of the HyperChem program.[13] The Polak–Ribiere algorithm was used with the termination condition of 0.1 kcal/(A mol) rms gradient. The calculation was performed on a single molecule placed in vacuo.

Acknowledgements

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Practical synthesis of 3-bromo-5,6-dihydropyridin-2-ones via β,γ-unsaturated α-bromo-ketene/imine cycloaddition☆,☆☆

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Abstract—An approach to 3-bromo-4-alkyl-6-aryl-5,6-dihydropyridin-2-ones and 3-bromo-5-ethyl-6-aryl-5,6-dihydropyridin-2-ones starting from β,γ-unsaturated α-bromoketenes and imines is reported. The presence of a bromine atom on the double bond allows performing aziridination or bromine displacement with an amine. The reaction gave fused bicyclic *N*-allyl-aziridines or 3-amino-substituted 5,6-dihydropyridin-2-ones, depending on the substituents on the six-membered ring.

1. Introduction

Nitrogen-containing heterocyclic compounds are important constituents of biologically active natural products[1] and have attracted considerable attention due to their applications in many fields such as pharmaceuticals and synthetic organic chemistry.[2] In particular, several representative pyridin-2-ones possess significant biological activity as antibacterial, antifungal or free radical scavengers,[3] and may be considered starting materials for the synthesis of more complex molecules.[4] Recently, properly substituted examples of 5,6-dihydropyridin-2-ones have been regarded to be useful intermediates for the preparation of spatially defined scaffolds, constrained counterparts of natural amino acids.[5]

Recently, we have been interested in the synthesis of mimetics of the RGD tripeptide, that is the signaling motif in a variety of extracellular matrix proteins involved in the integrin adhesion mechanism.[6] In this paper we report on the synthesis of a new class of 5,6-dihydropyridin-2-ones, aiming to introduce them as non-peptidic scaffolds in mimetics of the RGD β-turn topology. Numerous methods for the preparation of substituted 5,6-dihydropyridin-2-ones starting from acyclic materials have been reported in the literature but they usually require forcing conditions and are non-general.[7]

Ketenes have long been used in the synthesis of various heterocyclic compounds.[8] In the course of our investigation on the chemistry of unsaturated bromo-ketenes,[9] we have developed a good approach to the synthesis of 3-bromo-4-alkyl-5,6-dihydropyridin-2-ones and 3-bromo-5-ethyl-5,6-dihydropyridin-2-ones.

β,γ-Unsaturated α-bromoketenes were prepared starting from the corresponding acyl halides and triethylamine, and their reactivity in the ketene-imine cycloaddition was examined.

2. Results and discussion

2.1. Synthesis of 3-bromo-5,6-dihydropyridin-2-ones

It is known that when an acyl halide is treated with a base, the corresponding ketene is generated. The labile ketene readily reacts with the Schiff base **2** to give a six membered heterocyclic compound. Starting from both 2-bromo-3-methyl-2-butenoyl chloride **1a** and 2-bromo-3-methyl-2-hexenoyl chloride **1b**, deprotonation occurs on the methyl group, to exclusively give the dehydropyridin-2-one **3** in high yield (Scheme 1).

The amounts of Schiff base and TEA and the effect of the temperature were investigated using the reaction of **1a** and **2a**, and selected results are reported in Table 1.

The reaction of **1a** with 2 equiv. of the imine **2a**, carried out at −78 °C in CH_2Cl_2 in the presence of $AlMe_2Cl$, afforded **3a** in 54% yield after silica gel chromatography, and the remaining product was the corresponding benzylamide

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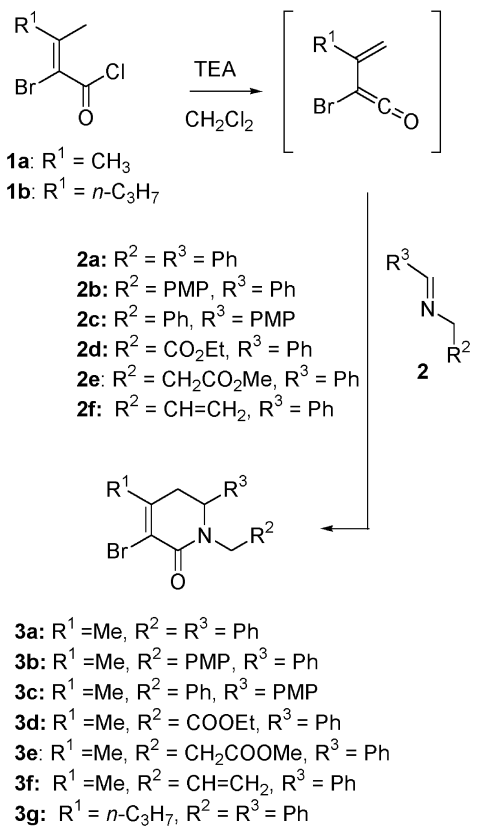


Scheme 1. Formation of β,γ-unsaturated ketenes and reaction with imines **2**.

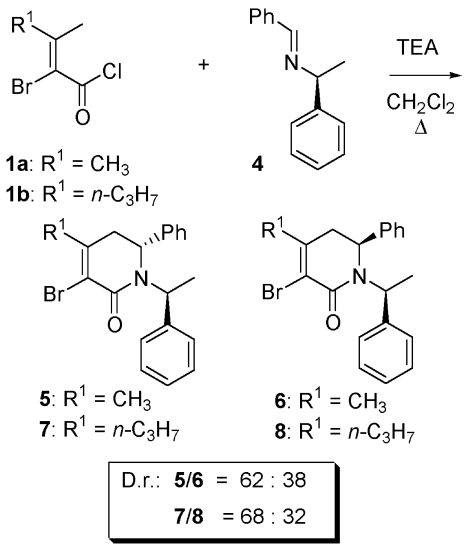
Table 1. Formation of 3-bromo-4-alkyl-5,6-dihydropyridin-2-one **3** via ketene–imine cyclization

Entry[a]	**1** (1 equiv.)	**2** (equiv.)	TEA (equiv.)	*T* (°C)	**3**	Yield (%)[b]
1[c]	**1a**	**2a** (2)	1	−78 to rt	**3a**	54
2	**1a**	**2a** (1)	1	−50 to rt	**3a**	65
3	**1a**	**2a** (1)	2	40	**3a**	92
4	**1a**	**2b** (1)	2	40	**3b**	92
5	**1a**	**2c** (1)	2	40	**3c**	94
6	**1a**	**2d** (1)	2	40	**3d**	34
7	**1a**	**2e** (1)	2	40	**3e**	64
8	**1a**	**2f** (1)	2	40	**3f**	96
9	**1b**	**2a** (1)	2	40	**3g**	94

[a] Reactions were performed in CH_2Cl_2.
[b] Yields correspond to the compounds purified by flash chromatography on silica gel.
[c] Reaction carried out under aluminum-catalyzed conditions.

(entry 1). At −50 °C, in the absence of the Lewis acid, with 1 equiv. of **2a**, dihydropyridinone **3a** was isolated in 65% yield (entry 2). Much better results were obtained when **1a** and **2a** were refluxed in CH_2Cl_2 in the presence of 2 equiv. of TEA (entry 3, 92% yield). These conditions were applied to the reaction of **1a** with imines **2b**-**f**. Excellent results were obtained in both cases, and **3b** and **3c** were obtained in respective yields of 92 and 94% (entries 4 and 5). A lower yield was observed for **3d**, which was obtained from the cyclization of **1a** with the glycine derivative **2d** (entry 6). This result was ascribed to a high degree of autocondensation of the reactive imine. On the other hand, the cycloaddition of **1a** and β-alanine derivative **2e**, gave **3e** in 64% yield (entry 7). When the reaction was performed with the allylamino derivative **2f**, the corresponding dihydropyridinone **3f** was obtained in 96% yield (entry 8). Finally, when acyl chloride **1b** was reacted with **2a** at reflux, **3g** was obtained in 94% yield (entry 9). All of the reactions were monitored by TLC and stopped after disappearance of the imine.

Good yields and moderate diastereoselectivity were observed in the reactions of **1a** and **1b** with the chiral Schiff base **4**, derived by the condensation of benzaldehyde with (*S*)-phenylethylamine, in refluxing CH_2Cl_2. Starting from **1a**, the bromo-dihydropyridin-2-ones **5** and **6** were obtained in a yield of 98% and 62/38 d.r. (Scheme 2).



Scheme 2. Cycloaddition reaction between **1a**-**b** and chiral imine 4″.

Under the same conditions, **1b** gave **7** and **8** in 55% yield and 68/32 d.r. The diastereomeric mixtures of **5/6** and **7/8** were easily separated by flash chromatography and pyridinones were fully characterized by NMR spectroscopy. The isomer **7** was crystallized from ethanol/water. The (6*R*) absolute configuration of the newlycreated stereogenic center in **7** was established by X-ray diffraction,[10] and, according to this result, the (6*S*) configuration to **8** could be assigned (Fig. 1).

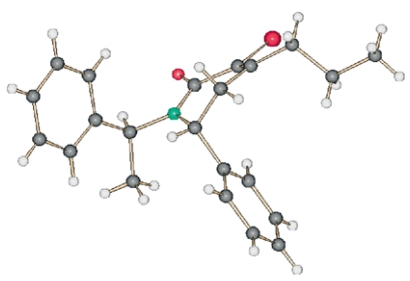


Figure 1. X-ray structure of **7**.

The structure reported in Figure 1, displays **7** in a boat conformation, and the hydrogen of the (*S*)-phenylethylamine group is preferentially in a synperiplanar relationship with the carbonyl of the cycle.

Comparison of the ^{1}H NMR chemical shifts for the pairs of compounds **5/7** and **6/8** revealed a complete regularity and allowed us to confidently attribute the (6*R*) configuration to **5** and the (6*S*) configuration to **6** (Table 2).

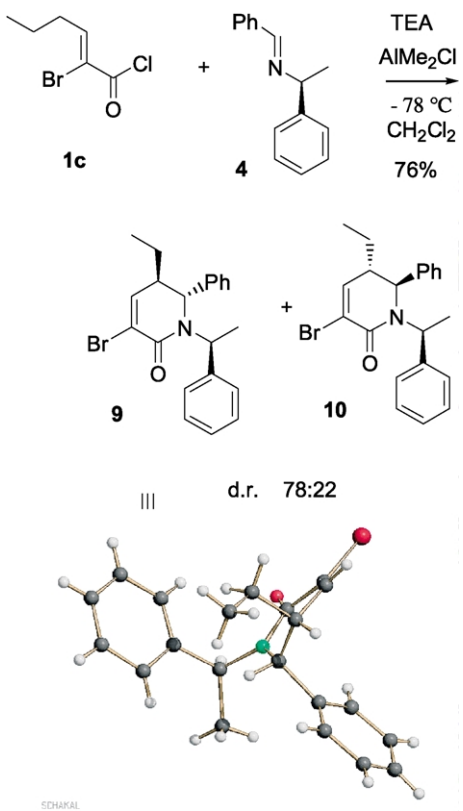
Table 2. ^{1}H NMR data for compounds **5**-**8**

	$\delta^{a}CH_3^{*}$ (ppm)	$\delta^{a}H^{*}$ (ppm)	δH_6 (ppm)	δH_5 (ppm)	$\delta H_{5'}$ (ppm)	J_{5-6} (Hz)	$J_{5'-6}$ (Hz)
5	1.23	6.19	4.39	2.27	2.83	1.2	7.0
6	1.65	5.77	4.57	2.37	3.07	1.5	7.2
7	1.25	6.21	4.42	2.30	2.75	1.8	6.6
8	1.67	5.80	4.60	2.41	3.00	1.5	6.9

[a] Chemical shifts corresponding to (*S*)-phenylethylamino group.

Finally we investigated the behavior of 2-bromo-3-unbranched hexenoyl acyl chloride **1c** in the ketene–imine cyclization with **4**. While the reaction was tested under different conditions, changing the solvent and the temperature, the six-membered heterocyclic compounds **9** and **10** were obtained in 76% total yield and 78:22 d.r. only when the reaction was performed in the presence of one equivalent of $AlMe_2Cl$ at −78 °C and 2 equiv. of **4**.

The two diastereoisomers were easily separated by flash chromatography on silica gel and characterized by ^{1}H NMR analysis, which suggested a 5,6-*trans* relationship for both of them ($J_{5,6}$<0.8 Hz). The major isomer **9** was crystallized from ethanol and its (1′*S*,5*R*,6*R*) absolute configuration was ascertained by X-ray analysis. (Scheme 3).

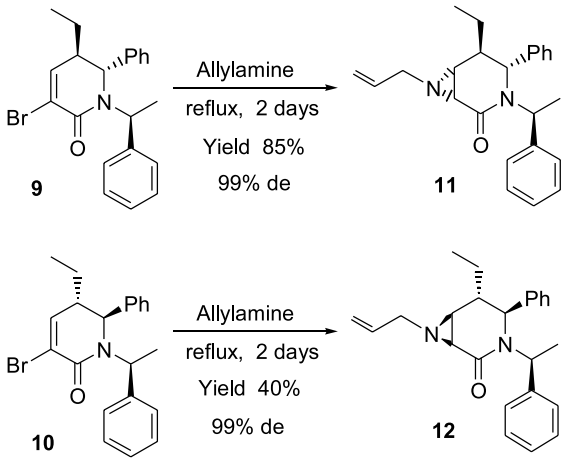


Scheme 3. Synthesis of 5,6-dihydropyridin-2-ones **9** and **10** and X-ray-determined structure of **9**.

2.2. Reactivity of 3-bromo-4-alkyl-5,6-dihydropyridin-2-ones and 3-bromo-5-alkyl-5,6-dihydropyridin-2-ones with allylamine

The presence of the bromine atom on the double bond in the pyridinones makes possible aziridination via the well-known Gabriel–Cromwell reaction.[11] Aziridines have recently received great attention, since they can be considered strained unusual amino acids and they are also useful precursors for the synthesis of various poly-functionalized compounds, such as oxazolines, oxazolidinones, hydroxy amino acids, amino alcohols, etc.[12]

Therefore, we investigated the reactivity of 3-bromo-5,6-dihydropyridin-2-ones in the presence of allylamine. The reaction, carried out on several substrates by refluxing the heterocycle in neat allylamine for 48 h, gave different results depending on the substituents on the six-membered ring. Under these conditions, 3-bromo-5-ethyl-5,6-dihydropyridin-2-ones **9** and **10** gave the corresponding fused bicyclic *N*-allyl-aziridines **11** and **12** in good yield and complete diastereoselectivity (Scheme 4).



Scheme 4. Synthesis of aziridines **11** and **12** via a Gabriel–Cromwell-like reaction.

The assignment of the stereochemistry of the newly created stereocenters in **11** was made by analysis of the coupling constant J_{4-5} and by means of NOESY-1D[13] experiments. The comparison of the vicinal coupling constant (J_{4-5}=1.5 Hz) with literature values[14] referring to similar aziridines, accounted for an anti relationship between the ethyl substituent on C5 and the aziridine ring. Irradiation of the proton at C4 and of the proton at C6 resulted in the enhancement of intensities of the ethyl chain methylene protons, suggesting that they are *cis* to each other. The preferred conformation of (3*R*,4*R*,5*R*,6*R*)-**11**, calculated by means of molecular mechanics energy minimizations of a set of 10^3 geometries generated by Monte Carlo procedure,[15] was in complete agreement with the NOESY-1D signals observed upon irradiation of H_4 and H_5 (Fig. 2). The same considerations allowed to attribute the (3*S*,4*S*,5*S*,6*S*) stereochemistry to **12**.

When the reaction with allylamine was performed on 4-methyl-substituted derivatives, 3-allylamino-4-methyl-5,6-dihydropyridin-2-ones were obtained instead of the

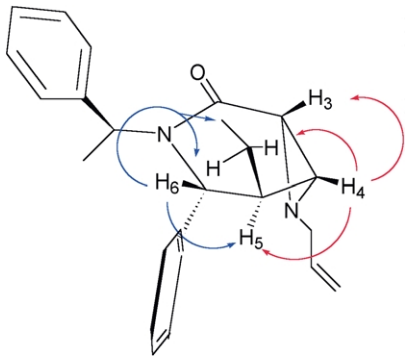
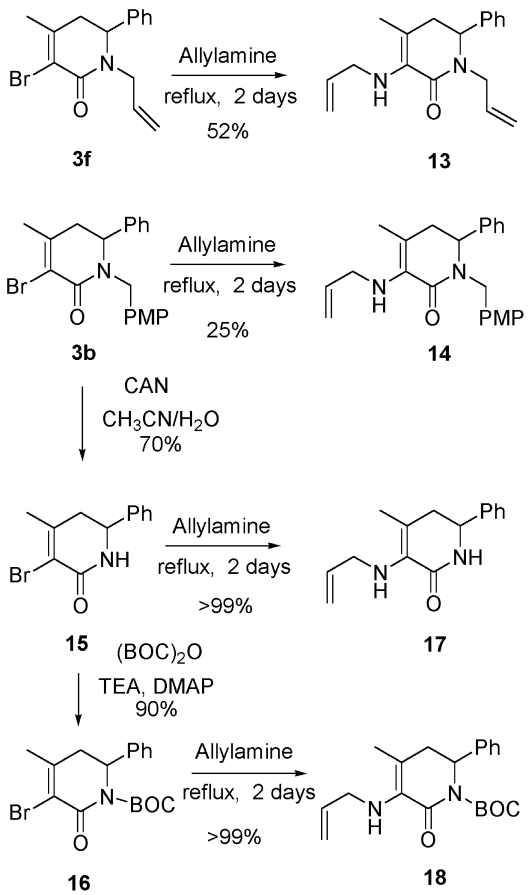


Figure 2. Preferred conformation and NOESY-1D enhancements of **11**.

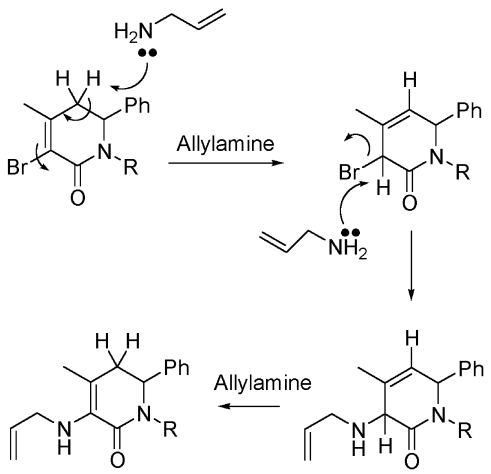
corresponding aziridines. The reaction with **3f** and **3b** gave derivatives **13** and **14** in respective yields of 52 and 25% (Scheme 5).

Finally, deprotection of compound **3b** allowed us to synthesize the dihydropyridin-2-one **15** via cleavage of the *N*-(*p*-methoxybenzyl) group with cerium ammonium nitrate.[16] The reaction carried out in CH_3CN/H_2O at room temperature gave **15** in 70% yield. Upon treatment with TEA, DMAP and di-*tert*-butyldicarbonate in dry THF, **15** was transformed into the corresponding *N*-*tert*-butyloxycarbonyl derivative **16** in 90% yield. The reaction of both **15** and **16** with neat allylamine gave the 3-allylamino-substituted six-membered rings **17** and **18** in quantitative yield (Scheme 5).



Scheme 5. Reactions of allylamine with 3-bromo-4-alkyl-dihydropyridin-2-ones.

The complete chemoselectivity of the reaction between compounds **3b**, **3f**, **15** and **16** and allylamine, can be attributed to the steric hinderance at C_3. In accordance with the nucleophilic substitution of alkyl bromo-2(1*H*)-pyridones and bromo-uracils,[17] a reasonable mechanism could be suggested for the substitution of the vinyl bromide (Scheme 6). The allylamine, acting as a base, promoted the deconjugation of the double bond, so making possible the substitution of the bromine by allylamine itself. Finally the more stable double bond in α,β position was restored.



Scheme 6. Suggested mechanism for the substitution of vinyl bromide by allylamine.

3. Conclusion

A new method for the synthesis of 3-bromo-4-alkyl-5,6-dihydropyridin-2-ones and 3-bromo-5-ethyl-5,6-dihydropyridin-2-ones starting from 3-methyl-β,γ-unsaturated α-bromoketenes and imines has been developed. This one-pot ketene formation/cycloaddition was tested on 2-bromo-3-methyl-2-butenoyl chloride 1a and 2-bromo-3-methyl-2-hexenoyl chloride **1b** in the presence of several different imines. With both substrates, six-membered rings were obtained in good yield. The same reaction gave excellent results even with chiral imines and the ketene derived from 2-bromo-unbranched hexenoyl acyl chloride **1c**. Moreover, the presence of the bromine atom on the double bond makes possible the substitution by allylamine, leading to the formation of aziridines or 3-allylamino derivatives. The reaction gave different results depending on the substituents on the six-membered ring. This class of six membered polyfunctionalized heterocycles could be exploited in the preparation of non-peptidic scaffolds mimicking the β-turn RGD topology.

4. Experimental

4.1. General methods

Unless stated otherwise, solvents and chemicals were obtained from commercial sources and used without further purification. Flash chromatography was performed on silica gel (230–400 mesh). NMR Spectra were recorded with 200, 300, 400 or 600 MHz spectrometers. Chemical shifts were reported as δ values (ppm) relative to the solvent peak of

$CDCl_3$ set at δ=7.27 (^{1}H NMR) or δ=77.0 (^{13}C NMR). Infrared spectra were recorded with an FT-IR spectrometer. Melting points are uncorrected. MS analysis were performed on a liquid chromatograph coupled with an electrospray ionization-mass spectrometer (LC-ESI-MS), using H_2O/CH_3CN as solvent at 25 °C (positive scan 100–500 *m/z*, fragmentor 70 V). Imines **2a-f** and **4** were prepared following a known procedure and characterized by comparison with literature data.[18]

4.2. General procedure for the preparation α-bromo-α,β-unsaturated chlorides 1a-c from α,β-unsaturated acids

To a stirred solution of α,β-unsaturated acid (10 mmol) in CH_2Cl_2 (10 mL), bromine (11 mmol, 0.56 mL) was added dropwise at 0 °C. The mixture was stirred overnight and then washed with a saturated solution of $Na_2S_2O_3$ to remove unreacted bromine. The organic layer was dried over Na_2SO_4 and solvent removed under reduced pressure to give the dibromo acid as a white powder. The product was dissolved in THF (10 mL) then piperidine (40 mmol, 3.9 mL) was added in one portion at 0 °C. The solution was stirred for 24 h at room temperature and then quenched with HCl 6 M (10 mL). After removing THF under reduced pressure, the acid aqueous layer was extracted twice with EtOAc (20 mL). The collected organic layers were dried over Na_2SO_4 and concentrated to give the α-bromo acid as a white powder. $SOCl_2$ (60 mmol, 4.4 mL) was then added to the neat product at 0 °C and the mixture was refluxed for two hours. The α-bromo-α,β-unsaturated chlorides **1a-c** were isolated as *E*/*Z* unseparable mixtures by distilling under reduced pressure.

4.2.1. 2-Bromo-3-methyl-but-2-enoyl chloride 1a. IR (film) ν 2950, 1805 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.11 (s, 3H), 2.13 (s, 3H).

4.2.2. 2-Bromo-3-methyl-hex-2-enoyl chloride 1b. IR (film) ν, 2927, 1811 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H (Major isomer) 0.99 (t, 3H, *J*=7.5 Hz), 1.50–1.60 (m, 2H), 2.08 (s, 3H), 2.40 (m, 2H). (Minor isomer) ^{1}H NMR ($CDCl_3$) δ 0.94 (t, 3H, *J*=7.2 Hz), 1.50–1.60 (m, 2H), 2.05 (s, 3H) 2.40 (m, 2H).

4.2.3. 2-Bromo-hex-2-enoyl chloride 1c. IR (film) ν 2955, 1802 cm^{-}1; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H (Major isomer)1.02 (t, 3H, *J*=7.2 Hz), 1.58–1.68 (m, 2H), 2.47 (m, 2H), 7.8 (t, 1H, *J*=6.9 Hz). (Minor isomer) ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 3H, *J*=7.2 Hz), 1.48–1.57 (m, 2H), 2.40 (m, 2H), 6.68 (t, 1H, *J*=7.8 Hz).

4.3. General procedure for the preparation of 5,6-dihydro-pyridin-2-ones 3a-g and 5-8

Acyl chloride **1a-c** (1 mmol) was added to a refluxing solution of imine **2** or **4** (1 mmol, 1 equiv.) and TEA (0.278 mL, 2 mmol, 2 equiv.) in CH_2Cl_2 (5 mL). The reaction was monitored by TLC and quenched with water after disappearance of the imine reagent. The pH of the water layer was then adjusted to neutrality with 0.1 M HCl and diluted with CH_2Cl_2 (10 mL). The separated organic layer was dried over Na_2SO_4 and the solvent was evaporated under vacuum. 5,6-Dihydro-pyridin-2-one **3a-g** were purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 95/5 as eluant).

4.3.1. 1-Benzyl-3-bromo-4-methyl-6-phenyl-5,6-dihydro-pyridin-2-one 3a. Isolated as a pale yellow oil (327 mg, 92%); IR (film) ν 3029, 2930, 1651, 1608, 1453 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.95 (3H, s), 2.52 (1H, dd, *J*=2.4, 17.2 Hz), 3.03 (1H, dd, *J*=7.5, 17.2 Hz), 3.63 (1H, d, *J*=14.7 Hz), 4.56 (1H, dd, *J*=2.4, 7.5 Hz), 5.63 (1H, d, *J*=14.7 Hz), 7.15–7.18 (2H, m), 7.22–7.40 (8H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 24.7 (q), 39.5 (t), 49.5 (t), 56.6 (d), 115.7 (s), 126.4 (d), 127.6 (d), 128.1 (d), 128.2 (d), 128.7 (d), 129.0 (d), 137.5 (s), 139.6 (s), 145.2 (s), 160.7 (s); GC-MS *m/z* 357 (12), 355 (12), 278 (10), 276 (10), 253 (16), 207 (9), 185 (6), 128 (11), 91 (100). Anal. Calcd for $C_{19}H_{18}BrNO$: C, 64.06; H, 5.09; N, 3.93. Found C, 64.08; H, 5.07; N, 3.92.

4.3.2. 3-Bromo-1-(4-methoxy-benzyl)-4-methyl-6-phenyl-5,6-dihydro-pyridin-2-one 3b. Isolated as a pale yellow oil (356 mg, 92%); IR (film) ν 3031, 2932, 1653, 1593, 1460 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.90 (3H, s), 2.47 (1H, dd, *J*=2.4, 17.4 Hz), 2.96 (1H, dd, *J*=7.6, 17.4 Hz), 3.54 (1H, d, *J*=14.6 Hz), 3.77 (3H, s), 4.52 (1H, dd, *J*=2.4, 7.6 Hz), 5.49 (1H, d, *J*=14.6 Hz), 6.80–6.85 (2H, m), 7.12–7.16 (4H, m), 7.30–7.40 (3H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 24.2 (q), 39.1 (t), 48.4 (t), 55.1 (q), 56.0 (d), 113.8 (d), 115.4 (s), 126.1 (d), 127.7 (d), 128.7 (d), 129.2 (d), 129.4 (s), 139.4 (s), 144.9 (s), 158.9 (s), 160.3 (s); LC-ESI-MS rt 11.9 min, *m/z* 386–388 (M+1), 408–410 (M+Na). Anal. Calcd for $C_{20}H_{20}BrNO_2$: C, 62.19; H, 5.22; N, 3.63. Found C, 62.20; H, 5.21; N, 3.65.

4.3.3. 1-Benzyl-3-bromo-6-(4-methoxy-phenyl)-4-methyl-5,6-dihydro-pyridin-2-one 3c. Isolated as a white solid (364 mg, 94%), mp=105–107 °C; IR (nujol) ν 3031, 2928, 1653, 1611, 1449 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.96 (3H, s), 2.47 (1H, dd, *J*=2.6, 17.2 Hz), 2.98 (1H, dd, *J*=7.2, 17.2 Hz), 3.62 (1H, d, *J*=14.8 Hz), 3.82 (3H, s), 4.49 (1H, dd, *J*=2.6, 7.2 Hz), 6.58 (1H, d, *J*=14.8 Hz), 6.88 (2H, d, *J*=8.8 Hz), 7.07 (2H, d, *J*=8.8 Hz), 7.20–7.40 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 24.4 (q), 39.4 (t), 49.0 (t), 55.2 (d), 55.8 (q), 114.1 (d), 115.5 (s), 127.3 (d), 128.0 (d), 128.5 (d), 131.3 (s), 137.4 (s), 145.2 (s), 159.0 (s), 160.2 (s); LC-ESI-MS rt 12.8 min, *m/z* 386–388 (M+1), 408–410 (M+Na). Anal. Calcd for $C_{20}H_{20}BrNO_2$: C, 62.19; H, 5.22; N, 3.63. Found C, 62.18; H, 5.22; N, 3.62.

4.3.4. (3-Bromo-2-oxo-6-phenyl-4-methyl-5,6-dihydro-pyridin-1-yl)-acetic acid ethyl ester 3d. Isolated as a pale yellow oil (120 mg, 34%); IR (film) ν 3034, 2926, 1741, 1656, 1461 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.22 (t, 3H, *J*=7.0 Hz), 2.01 (s, 3H), 2.66 (dd, 1H, *J*=6.0, 17.2 Hz), 3.07 (dd, 1H, *J*=6.6, 17.2 Hz), 3.37 (d, 1H, *J*=17.6 Hz), 4.15 (q, 2H, *J*=7.0 Hz), 4.77 (d, 1H, *J*=17.6 Hz), 4.80 (dd, 1H, *J*=6.6, 6.0 Hz), 7.18–7.22 (m, 2H), 7.50–7.62 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 14.3 (q), 29.3 (q), 41.8 (t), 52.0 (t), 60.2 (d), 114.7 (s), 127.1 (d), 127.7 (d), 128.0 (d), 140.2 (s), 145.4 (s), 162.6 (s), 166.9 (s). GC-MS *m/z* 353 (15), 351 (15), 280 (13), 278 (13), 266 (15), 264 (15), 185 (5), 110 (10), 91 (100). Anal. Calcd for

$C_{16}H_{18}BrNO_3$: C, 54.56; H, 5.15; N, 3.98. Found C, 54.56; H, 5.18; N, 3.94.

4.3.5. 3-(3-Bromo-2-oxo-6-phenyl-4-methyl-5,6-dihydro-pyridin-1-yl)-propionic acid methyl ester 3e. Isolated as a pale yellow oil (226 mg, 64%); IR (film) ν 3029, 2929, 1730, 1653,1460 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ_H 1.92 (s, 3H), 2.56 (dt, 1H, J=5.7, 16.8 Hz), 2.54 (dd, 1H, J=2.2, 17.4 Hz), 2.86 (ddd, 1H, J=5.7, 8.4, 16.8 Hz), 3.14 (dd, 1H, J=7.4, 17.4 Hz), 3.16 (ddd, 1H, J=5.7, 8.4, 13.6 Hz), 3.74 (s, 3H), 4.07 (dt, 2H, J=5.7, 13.6 Hz), 4.88 (dd, 1H, J=7.4, 2.2 Hz), 7.00–7.12 (m, 2H), 7.20–7.36 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 24.0 (q), 32.6 (t), 39.1 (t), 43.8 (t), 51.3 (q), 59.0 (d), 115.2 (s), 125.8 (d), 127.6 (d), 128.5 (d), 139.8 (s), 145.2 (s), 160.4 (s), 172.2 (s); LC-ESI-MS rt 10.7 min, m/z 352–354 (M+1), 374–376 (M+Na). Anal. Calcd for $C_{16}H_{18}BrNO_3$: C, 54.56; H, 5.15; N, 3.98. Found C, 54.54; H, 5.14; N, 3.97.

4.3.6. 1-Allyl-3-bromo-4-methyl-6-phenyl-5,6-dihydro-pyridin-2-one 3f. Isolated as a pale yellow oil (295 mg, 96%); IR (film) ν 2967, 2926, 1653, 1457 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ_H 1.90 (3H, s), 2.54 (1H, dd, J=2.6, 17.2 Hz), 3.09 (1H, dd, J=7.5, 17.2 Hz), 3.19 (1H, dd, J=7.2, 15.4 Hz), 4.63 (1H, dd, J=2.6, 7.5 Hz), 4.74–4.85 (1H, m), 5.05–5.21 (2H, m), 5.68–5.87 (1H, m), 7.12–7.20 (2H, m), 7.25–7.37 (3H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 24.2 (q), 39.1 (t), 48.4 (t), 56.4 (d), 115.5 (s), 117.5 (t), 126.1 (d), 127.7 (d), 128.6 (d), 132.9 (d), 139.5 (s), 145.0 (s), 160.0 (s); LC-ESI-MS rt 11.6 min, m/z 306–308 (M+1), 328–330 (M+Na). Anal. Calcd for $C_{15}H_{16}BrNO$: C, 58.84; H, 5.27; N, 4.57. Found C, 58.87; H, 5.26; N, 4.55.

4.3.7. 1-Benzyl-3-bromo-6-phenyl-4-propyl-5,6-dihydro-pyridin-2-one 3g. Isolated as a pale yellow oil (362 mg, 94%); IR (film) ν 3029, 2928, 1648, 1611, 1454 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 0.75 (3H, t, J=7.5 Hz,), 1.20–1.30 (2H, m), 2.16 (1H, dt, J=7.6, 13.0 Hz), 2.36 (1H, dt, J=7.8, 13.0 Hz), 2.53 (1H, dd, J=2.1, 17.0 Hz), 2.97 (1H, dd, J=7.4, 17.0 Hz), 3.65 (1H, d, J=15.0 Hz), 4.59 (1H, dd, J=2.1, 7.4 Hz), 5.64 (1H, d, J=15 Hz), 7.14–7.17 (2H, m), 7.3–7.39 (8H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 13.4 (q), 19.2 (t), 37.5 (t), 39.1 (t), 49.2 (t), 56.3 (d), 115.4 (s), 126.1 (d), 127.4 (d), 127.8 (d), 128.0 (d), 128.5 (d), 128.7 (d), 137.4 (s), 139.1 (s), 148.3 (s), 160.7 (s); LC-ESI-MS rt 14.7 min, m/z 384–386 (M+1), 406–408 (M+Na). Anal. Calcd for $C_{21}H_{22}BrNO$: C, 65.63; H, 5.77; N, 3.64. Found C, 65.61; H, 5.79; N, 3.64.

4.3.8. (1′*S*,6*R*)-3-Bromo-4-methyl-6-phenyl-1-(1′-phenyl-ethyl)-5,6-dihydro-pyridin-2-one 5. Isolated as a white solid (226 mg, 61%), mp=120–122 °C; IR (nujol) ν 3028, 2930, 16474, 1630, 1452 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 1.23 (3H, d, J=7.4 Hz,), 1.85 (3H, d, $J_{1,3}$=1.2 Hz), 2.27 (1H, dd,, $J_{1,2}$=17.0 Hz, $J_{1,3}$=1.2 Hz), 2.83 (1H, ddd, J=1.2, 7.0, 17.0 Hz) 4.39 (1H, dd, $J_{1,2}$=7.0 Hz, $J_{1,3}$=1.2 Hz), 6.19 (1H, q, J=7.4 Hz), 7.15–7.18 (2H, m), 7.30–7.42 (8H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 16.3 (q), 24.2 (q), 40.3 (t), 52.4 (d), 53.2 (d), 116.0 (s), 126.1 (d), 127.2 (d), 127.4 (d), 127.5 (d), 128.5 (d), 141.4 (s), 141.8 (s), 144.1 (s), 160.2 (s); $[\alpha]_D^{19}$=+29 (c 1.04, $CHCl_3$); LC-ESI-MS rt 13.4 min, m/z 370–372 (M+1), 392–394 (M+Na). Anal. Calcd for $C_{20}H_{20}BrNO$: C, 64.87; H, 5.44; N, 3.78. Found C, 64.90; H, 5.42; N, 3.79.

4.3.9. (1′*S*,6*S*)-3-Bromo-4-methyl-6-phenyl-1-(1′-phenyl-ethyl)-5,6-dihydro-pyridin-2-one 6. Isolated as a white solid (137 mg, 37%), mp=105–107 °C; IR (nujol) ν 3060, 2976, 1727, 1645, 1494 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 1.65 (3H, d, J=7.0 Hz,), 1.84 (3H, s), 2.37 (1H, dd, J=1.5, 16.8 Hz), 3.07 (1H, dd, J=7.2, 16.8 Hz) 4.57 (1H, dd, J=1.5, 7.2 Hz), 5.77 (1H, q, J=7.0 Hz), 6.78–6.82 (2H, m), 6.95–7.05 (6H, m), 7.15–7.18 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 17.7 (q), 24.1 (q), 40.4 (t), 54.3 (2C, d), 116.6 (s), 126.0 (d), 126.8 (d), 127.4 (d), 127.7 (d), 127.8 (d), 128.4 (d), 138.5 (s), 140.5 (s), 143.9 (s), 159.9 (s); $[\alpha]_D^{19}$=−109 (c 0.99, $CHCl_3$); LC-ESI-MS rt 13.0 min, m/z 370–372 (M+1), 392–394 (M+Na). Anal. Calcd for $C_{20}H_{20}BrNO$: C, 64.87; H, 5.44; N, 3.78. Found C, 64.88; H, 5.45; N, 3.76.

4.3.10. (1′*S*,6*R*)-3-Bromo-6-phenyl-1-(1′-phenyl-ethyl)-4-propyl-5,6-dihydro-pyridin-2-one 7. Isolated as a white solid (147 mg, 37%), mp=116–120 °C; IR (nujol) ν 3059, 2928, 1646, 1624, 1452 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 0.67 (3H, t, J=7.2 Hz,), 1.02–1.15 (2H, m), 1.25 (3H, d, J=7.2 Hz), 2.03 (1H, dt, J=7.0, 13.0 Hz), 2.24–2.31 (1H, m), 2.30 (1H, dd, J=1.8, 16.8 Hz), 2.75 (1H, dd, J=6.6, 16.8 Hz), 4.42 (1H, dd, J=1.8, 6.6 Hz), 6.21 (1H, q, J=7.2 Hz), 7.13–7.17 (2H, m), 7.20–7.40 (8H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 13.4 (q), 16.2 (q), 18.9 (t), 38.6 (t), 38.8 (t), 52.2 (d), 53.2 (d), 115.8 (s), 126.0 (d), 127.2 (d), 127.3 (d), 127.5 (d), 128.3 (d), 128.5(d), 141.3 (s), 141.4 (s), 147.5 (s), 160.4 (s); $[\alpha]_D^{19}$=+34 (c 0.93, $CHCl_3$); LC-ESI-MS rt 12.4 min, m/z 398–400 (M+1), 420–422 (M+Na). Anal. Calcd for $C_{22}H_{24}BrNO$: C, 66.33; H, 6.07; N, 3.52. Found C, 66.32; H, 6.06; N, 3.55.

4.3.11. (1′*S*,6*S*)-3-Bromo-6-phenyl-1-(1′-phenyl-ethyl)-4-propyl-5,6-dihydro-pyridin-2-one 8. Isolated as a white solid (71 mg, 18%), mp=95–99 °C; IR (nujol) ν 3030, 2929, 1643, 1453 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 0.66 (3H, t, J=7.2 Hz,), 1.03–1.15 (2H, m), 1.67 (3H, d, J=7.0 Hz), 2.01–2.11 (1H, m), 2.21–2.30 (1H, m), 2.41 (1H, dd, J=1.5, 16.8 Hz), 3.00 (1H, dd, J=6.9, 16.8 Hz), 4.60 (1H, dd, J=1.5, 6.9 Hz), 5.80 (1H, q, J=7.0 Hz), 6.78–6.80 (2H, m), 6.98–7.04 (6H, m), 7.18–7.20 (2H, m); ^{13}C NMR δ_C (50 MHz, $CDCl_3$) 13.5 (q), 17.8 (q), 19.0 (t), 38.8 (t), 38.9 (t), 54.2 (2C, d), 116.4 (s), 126.0 (d), 126.8 (d), 127.4 (d), 127.7 (2C, d), 128.4 (d), 138.5 (s), 140.1 (s), 147.3 (s), 160.2 (s); $[\alpha]_D^{19}$=−81 (c 1.24, $CHCl_3$); LC-ESI-MS rt 13.6 min, m/z 398–400 (M+1), 420–422 (M+Na). Anal. Calcd for $C_{22}H_{24}BrNO$: C, 66.33; H, 6.07; N, 3.52. Found C, 66.35; H, 6.04; N, 3.56.

4.4. Reaction of 1c with imines in the presence of $AlMe_2Cl$

To a stirred solution of acyl chloride **1c** (0.211 g, 1 mmol) in CH_2Cl_2 at −78 °C, $AlMe_2Cl$ (1 mL of a 1 M solution in hexane, 1 equiv.) was added in one portion. After 10 min, a solution of TEA (0.139 mL, 1 mmol, 1 equiv.) in CH_2Cl_2 (2 mL) and a solution of the imine (2 equiv.) in CH_2Cl_2 (2 mL) were added dropwise at the same time. The reaction was monitored by TLC and quenched, after disappearance

of the imine reagent, with a water solution of Seignette salts (Na/K tartrate). The reaction mixture was filtered through a celite pad, diluted with CH_2Cl_2 and washed twice with water. The organic layer was dried over Na_2SO_4 and solvent was removed under reduced pressure. Compounds **9**, **10** were purifed by flash chromatography on silica gel (cyclohexane/Et_2O, 95/5 as eluant).

4.4.1. (1′*S*,5*R*,6*R*)-3-Bromo-5-ethyl-6-phenyl-1-(1′-phenyl-ethyl)-5,6-dihydro-pyridin-2-one 9. Isolated as a white solid (226 mg, 59%), mp=150–152 °C; IR (nujol) ν 3050, 2923, 1666, 1608, 1421 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 0.49 (3H, t, J=7.2 Hz,), 0.82–1.02 (2H, m), 1.21 (3H, d, J=7.2 Hz), 2.0–2.17 (1H, m), 4.29 (1H, bs), 6.29 (1H, q, J=7.2 Hz), 6.61 (1H, dd, $J_{1,2}$=6.6 Hz, $J_{1,3}$=1.2 Hz), 7.13–7.16 (2H, m), 7.30–7.40 (8H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 10.7 (q), 15.9 (q), 25.7 (t), 47.6 (d), 52.2 (d), 56.7 (d), 118.6 (s), 125.9 (d), 127.1 (d), 127.3 (d), 127.9 (d), 128.2 (d), 128.4 (d), 140.0 (s), 140.5 (s), 142.1 (s), 159.0 (s); $[\alpha]_D^{19}$=−66 (*c* 1.14, $CHCl_3$); LC-ESI-MS rt 15.1 min, *m*/*z* 384–386 (M+1), 406–408 (M+Na). Anal. Calcd for $C_{21}H_{22}BrNO$: C, 65.63; H, 5.77; N, 3.64. Found C, 65.61; H, 5.78; N, 3.63.

4.4.2. (1′*S*,5*S*,6*S*)-3-Bromo-5-ethyl-6-phenyl-1-(1′-phenyl-ethyl)-5,6-dihydro-pyridin-2-one 10. Isolated as a dense yellow oil (65 mg, 17%); IR (film) ν 3031, 2926, 1654, 1616, 1452 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 1.09 (3H, t, J=7.2 Hz,), 1.58–1.73 (2H, m), 1.63 (3H, d, J=7.0 Hz), 2.19 (1H, m), 4.41 (1H, bs), 5.85 (1H, q, J=7.0 Hz), 6.61 (1H, dd, J=6.9 Hz, $J_{1,3}$=1.5 Hz), 6.72–6.78 (2H, m), 6.94–7.06 (6H, m), 7.12–7.18 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 11.5 (q), 16.9 (q), 26.8 (t), 47.2 (d), 53.8 (d), 59.3 (d), 119.4 (s), 125.9 (d), 126.7 (d), 127.5 (d), 127.7 (d), 127.8 (d), 128.6 (d), 138.2 (s), 140.4 (s),140.6 (s), 159.0 (s); $[\alpha]_D^{19}$=−28 (*c* 0.97, $CHCl_3$); LC-ESI-MS rt 14.2 min, *m*/*z* 384–386 (M+1), 406–408 (M+Na). Anal. Calcd for $C_{21}H_{22}BrNO$: C, 65.63; H, 5.77; N, 3.64. Found C, 65.66; H, 5.76; N, 3.62.

4.5. Reaction of 3-bromo-5,6-dihydro-pyridin-2-ones with allylamine

3-Bromo-5,6-dihydro-pyridin-2-one (1 mmol) was refluxed in neat allylamine (5 mL) for 2 days. The excess of amine was then removed by evaporation under reduced pressure. The products were purified by flash chromatography on silica gel (eluant: cyclohexane/Et_2O 9/1 for **11** and **12**, cyclohexane/ethyl acetate 8/2 for **13** and **14**).

4.5.1. (1′*S*,3*R*,4*R*,5*R*,6*R*)-3,4-[*N*-(Allyl)-aziridino]-5-ethyl-6-phenyl-*N*-(1′-phenyl-ethyl)-piperidin-2-one 11. Isolated as a white solid (306 mg, 85%), mp=73–75 °C; IR (nujol) ν 3050, 2921, 1641, 1452 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 0.48 (3H, t, J=7.5 Hz), 0.58–0.69 (1H, m), 0.99–1.09 (1H, m), 1.21 (3H, d, J=7.3 Hz), 1.82 (1H, dd, J=1.5, 6.1 Hz), 2.09–2.17 (1H, m), 2.26 (1H, d, J=6.1 Hz), 2.49 (1H, dd, J=5.2, 14.7 Hz), 3.14 (1H, ddt, J=4.2, 14.7, 2.0 Hz), 4.16 (1H, s), 4.69 (1H, dq, J=17.1, 1.8 Hz), 4.86 (1H, dq, J=10.5, 1.8 Hz), 5.55–5.68 (1H, ddt, J=17.1, 10.5, 4.2 Hz), 6.39 (1H, q, J=7.3 Hz), 7.27–7.35 (10H, m); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 11.5 (q), 17.3 (q), 24.1 (t), 38.9 (d), 43.1 (d), 46.0 (d), 51.2 (d), 58.0 (t), 61.2 (d), 115.5 (t), 126.0 (d), 126.8 (d), 127.8 (d), 128.2 (d), 128.3 (d), 128.4 (d), 134.4 (s), 140.6 (s), 145.1 (d), 169.8 (s); $[\alpha]_D^{19}$=−100.0 (*c* 1.1 $CHCl_3$); LC-ESI-MS rt 15.6 min, *m*/*z* 361 (M+1), 383 (M+Na). Anal. Calcd for $C_{24}H_{28}N_2O$: C, 79.96; H, 7.83; N, 7.77. Found C, 79.98; H, 7.81; N, 7.75.

4.5.2. (1′*S*,3*S*,4*S*,5*S*,6*S*)-3,4-[*N*-(Allyl)-aziridino]-5-ethyl-6-phenyl-*N*-(1′-phenyl-ethyl)-piperidin-2-one 12. Isolated as a white solid (144 mg, 40%), mp=78–80 °C; IR (nujol) ν 3052, 2927, 1639, 1450 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ_H 1.00 (3H, t, J=7.2 Hz,), 1.27 (1H, m), 1.38 (1H, m), 1.70 (3H, d, J=7.2 Hz), 1.90 (1H, dd, J=1.5, 6.0 Hz), 2.18 (1H, d, J=6.0 Hz), 2.31 (1H, bt, J=6.6 Hz), 2.43 (1H, dd, J=15.6, 5.4Hz), 3.10 (1H, dd, J=15.6, 2.4 Hz), 4.35 (1H, s), 4.60 (1H, dd, J=17.4, 1.5 Hz), 4.80 (1H, dd, J=10.8, 1.5 Hz), 5.09 (1H, q, J=7.2 Hz), 5.55 (1H, ddt, J=17.4, 10.8, 4.8 Hz), 7.01–7.15 (7H, m), 7.20–7.35 (3H, m); ^{13}C NMR δ_C (150 MHz, $CDCl_3$) 12.0 (q), 18.2 (q), 25.1 (t), 39.5 (d), 42.9 (d), 46.5 (d), 57.1 (d), 61.1 (t), 62.6 (d), 115.5 (t), 125.6 (d), 126.7 (d), 127.3 (d), 127.8 (d), 128.0 (d), 128.6 (d), 134.4 (s), 140.1 (s), 142.3 (d), 169.6 (s); $[\alpha]_D^{19}$=+11.0 (*c*0.9 $CHCl_3$); LC-ESI-MS rt 17.0 min, *m*/*z* 361 (M+1), 383 (M+Na). Anal. Calcd for $C_{24}H_{28}N_2O$: C, 79.96; H, 7.83; N, 7.77. Found C, 79.95; H, 7.83; N, 7.79.

4.5.3. 1-Allyl-3-allylamino-4-methyl-6-phenyl-5,6-dihydro-pyridin-2-one 13. Isolated as a pale yellow oil (146 mg, 52%); IR (film) ν 3052, 2925, 1638, 1447 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 1.75 (3H, s), 2.35 (1H, dd, J=2.8, 17.2 Hz), 3.05 (1H, dd, J=7.5, 17.2 Hz), 3.16 (1H, dd, J=7.2, 15.3 Hz), 3.42–3.55 (2H, m), 4.58 (1H, dd, J=2.8, 7.5 Hz), 4.76–4.83 (1H, m), 5.04–5.22 (4H, m), 5.68–5.75 (2H, m), 7.18–7.19 (2H, m), 7.22–7.40 (3H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 18.8 (q), 37.2 (t), 47.7 (t), 51.1 (t), 57.0 (d), 115.5 (t), 117.0 (t), 120.8 (s), 126.4 (d), 127.4 (d), 128.4 (d), 133.3 (s), 133.4 (d), 136.6 (d), 140.7 (s), 164.4 (s); LC-ESI-MS rt 12.1 min, *m*/*z* 283 (M+1), 305 (M+Na). Anal. Calcd for $C_{18}H_{22}N_2O$: C, 76.56; H, 7.85; N, 9.92. Found C, 76.55; H, 7.84; N, 9.90.

4.5.4. 3-Allylamino-1-(4-methoxy-benzyl)-4-methyl-6-phenyl-5,6-dihydro-pyridin-2-one 14. Isolated as a pale yellow oil (90 mg, 25%); IR (film) ν 3049, 2932, 1644, 1520 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 1.82 (3H, s), 2.36 (1H, dd, J=2.7, 17.7 Hz), 3.02 (1H, dd, J=7.8, 17.7 Hz), 3.59 (3H, m), 3.90 (3H, s), 4.54 (1H, dd, J=2.7, 7.8 Hz), 5.17 (1H, dq, J=10.5, 1.5 Hz), 5.19 (1H, bs), 5.28 (1H, dq, J=17.1, 1.5 Hz), 5.62 (1H, d, J=15.0 Hz), 6.02 (ddt, J=17.1, 10.5, 6.0 Hz), 6.95 (2H, m), 7.18–7.24 (4H, m), 7.36–7.60 (3H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 18.9 (q), 37.2 (t), 47.8 (t), 51.2 (t), 55.1 (q), 56.6 (d), 113.9 (s), 115.7 (d), 116.1 (t), 120.9 (s), 126.5 (d), 127.2 (d), 128.8 (d), 129.2 (d), 133.4 (s), 136.7 (d), 140.6 (s), 158.9 (s), 164.8 (s); GC-MS *m*/*z* 362(2), 267 (5), 236 (28), 195 (58), 154 (32), 108 (70), 83 (100), 68 (66), 54 (46). Anal. Calcd for $C_{23}H_{26}N_2O_2$: C, 76.21; H, 7.23; N, 7.73. Found C, 76.21; H, 7.22; N, 7.71.

4.6. *N*-*p*-Methoxy-phenyl group removal from dihydro-pyridin-2-one 3b

A solution of CAN (0.548 g, 1 mmol) in water (5 mL) was added dropwise at rt to a stirred solution of **3b** (0.193 g,

0.5 mmol) in CH_3CN (5 mL). After three hours the organic solvent was removed under reduced pressure and the aqueous residue was diluted with ethyl acetate (20 mL) and water (10 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated under reduced pressure. Compound **15** was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 8/2 as eluant).

4.6.1. 3-Bromo-4-methyl-6-phenyl-5,6-dihydro-pyridin-2-one 15. Isolated as a white solid (93 mg, 70%), mp=134–136 °C; IR (film) ν 3304, 3051, 2923, 1640, 1445 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ_H 2.10 (3H, s), 2.63–2.72 (2H, m), 4.74 (1H, t, J=7.8 Hz), 6.00 (1H, bs), 7.35–7.45 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 24.3 (q), 40.6 (t), 54.6 (d), 115.3 (s), 126.2 (d), 128.4 (d), 129.0 (d), 140.2 (s), 148.9 (s), 162.2 (s); GC-MS *m/z* 267 (77), 265 (77), 186 (51), 213 (8), 162 (100), 160 (100), 104 (22), 77 (25), 53 (44). Anal. Calcd for $C_{12}H_{12}NO$: C, 56.16; H, 4.54; N, 5.26. Found C, 56.17; H, 4.55; N, 5.24.

4.7. Preparation of *N-tert*-butyloxycarbonyl-derivative 16

To a stirred solution of **15** (0.267 g, 1 mmol) in CH_2Cl_2 (10 mL) at rt, di-*tert*-butyl dicarbonate (0.436 g, 2 mmol, 2 equiv.), TEA (0.139 mL, 1 mmol, 1 equiv.) and DMAP (0.122 g, 1 mmol, 1 equiv.) were added. After 12 h, the reaction was quenched with water and washed twice with a saturated solution of NH_4Cl (10 mL). The organic layer was dried over Na_2SO_4 and solvent was removed under reduced pressure. Compound **16** was isolated in 90% yield after a quick purification by chromatography on silica gel (cyclohexane/ethyl ether 6/4 as eluant).

4.7.1. 3-Bromo-4-methyl-6-phenyl-1-(*tert*-butyloxycarbonyl)-5,6-dihydro-pyridin-2-one 16. Isolated as a pale yellow oil (328 mg, 90%); IR (film) ν 3042, 2926, 1702, 1644, 1449 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ_H 1.49 (9H, s), 2.02 (3H, s), 2.73 (1H, dd, J=2.6, 17.8 Hz), 3.18 (1H, dd, J=6.6, 17.8 Hz), 5.53 (1H, dd, J=2.6, 6.6 Hz), 7.15–7.45 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 24.7 (q), 27.7 (3C,q), 38.3 (t), 55.5 (d), 83.5 (s), 116.5 (s), 125.4 (d), 128.1 (d), 128.5 (d), 139.9 (s), 149.5 (s), 152.2 (s), 158.8 (s); LC-ESI-MS rt 12.7 min, *m/z* 366–368 (M+1), 388–390 (M+Na). Anal. Calcd for $C_{17}H_{20}NO_3$: C, 55.75; H, 5.50; N, 3.82. Found C, 55.77; H, 5.49; N, 3.79.

4.7.2. 3-Allylamino-4-methyl-6-phenyl-5,6-dihydro-pyridin-2-one 17. Isolated as a pale yellow oil (241 mg, >99%); IR (film) ν 3309, 3050, 2930, 1638, 1441 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 1.92 (3H, s), 2.46 (1H, dd, J=5.4, 16.8 Hz), 2.65 (1H, dd, J=11.7, 16.8 Hz), 3.53 (1H, ddt, J=15.0, 6.0, 1.5 Hz), 3.61 (1H, ddt, J=15.0, 6.0, 1.5 Hz), 4.69 (1H, dd, J=5.4, 11.7 Hz), 5.14 (1H, dq, J=10.2, 1.5 Hz), 5.25 (1H, dq, J=17.1, 1.5 Hz), 5.53 (1H, bs), 5.95 (1H, ddt, J=17.1, 10.2, 6.0 Hz), 7.24–7.45 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 19.0 (q), 39.6 (t), 51.2 (t), 55.5 (d), 113.4 (s), 115.9 (t), 120.4 (s), 126.5 (d), 128.5 (d), 129.1 (d), 136.6 (d), 141.4 (s), 166.7 (d); GC-MS *m/z* 242 (50), 227 (9), 280 (13), 213 (8), 137 (14), 106 (100), 68 (63). Anal. Calcd for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found C, 74.33; H, 7.50; N, 11.55.

4.7.3. 3-Allylamino-4-methyl-6-phenyl-1-(*tert*-butyloxycarbonyl)-5,6-dihydro-pyridin-2-one 18. Isolated as a pale yellow oil (340 mg, >99%); IR (film) ν 3052, 2924, 1710, 1639, 1447 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ_H 1.49 (9H, s), 1.91 (3H, s), 2.45 (1H, dd, J=5.0, 17.1 Hz), 2.63 (1H, dd, J=11.7, 17.1 Hz), 3.55 (1H, ddt, J=14.7, 6.0, 1.5 Hz), 3.58 (1H, ddt, J=14.7, 6.0, 1.5 Hz), 4.69 (1H, dd, J=5.0, 11.7 Hz), 5.20 (1H, dq, J=10.5, 1.5 Hz), 5.22 (1H, dq, J=17.1, 1.5 Hz), 6.08 (1H, ddt, J=17.1, 10.2, 6.0 Hz), 7.21–7.48 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 24.5 (q), 28.2 (3C, q), 40.1 (t), 49.2 (t), 54.9 (d), 82.9 (s), 112.9 (s), 115.8 (t), 121.2 (s), 125.8 (d), 128.2 (d), 128.9 (d), 137.5 (d), 140.0 (s), 153.5 (s), 162.4 (s); LC-ESI-MS rt 12.6 min, *m/z* 343 (M+1), 365 (M+Na). Anal. Calcd for $C_{24}H_{28}N_2O$: C, 79.96; H, 7.83; N, 7.77. Found C, 79.98; H, 7.81; N, 7.75. Anal. Calcd for $C_{20}H_{26}N_2O_3$: C, 70.15; H, 7.65; N, 8.18. Found C, 70.14; H, 7.65; N, 8.17.

4.8. X-ray crystallographic determination of compounds 7 and 9

Data were collected at room temperature on a Bruker AXS CCD diffractometer (Mo K_α radiation, λ=0.71073 Å) for compound **7** and on an Enraf-Nonius CAD4 diffractometer (Mo K_α radiation, λ=0.71073 Å) for compound **9**. The data collection, integration and data reduction for **7** were performed using SMART and SAINT programs[19] and an empirical absorption correction was applied using SADABS.[20] The unit cell parameters for **9** were determined by a least-squares fitting of 25 randomly selected strong reflections and an empirical absorption correction was applied using the azimuthal scan method.[21] The structures were solved by direct methods (SIR97)[22] and subsequent Fourier synthesis and refined by full matrix least-squares on F^2 (SHELXTL) Ref. 23 for all non-hydrogen atoms for **7** whereas for **9** only the bromine atom was treated anisotropically because of the poor data/parameter ratio. Hydrogen atoms were placed in calculated positions except for the hydrogen bound to C9 in compound **7** and to C8 in compound **9**.

4.8.1. Compound 7. $C_{22}H_{23}BrNO$, M=397.32, orthorhombic, space group $P2_12_12_1$, a=9.8512(6) Å, b=11.4055(6) Å, c=17.6739(10) Å, V=1985.8(2) $Å^3$, Z=4, $F(000)$=820, μ=2.079 mm^{-1}, D_c=1.329 g/cm^{-3}. The reflections collected were 26095, of which 5796 unique [$R_{(int)}$ =0.0996]; 2887 reflections $I>2\sigma(I)$, R_1=0.0448 and wR_2=0.0984 for 2887 [$I>2\sigma(I)$] and R_1=0.1048 and wR_2=0.1170 for all (5796) intensity data. Goodness-of-fit=0.867, absolute structure parameter of the model: x=0.018 (12), residual electron density in the final Fourier map was 0.392 and −0.406 e $Å^{-3}$. CCDC number is 229760.

4.8.2. Compound 9. $C_{21}H_{22}BrNO$, M=384.31, orthorhombic, space group $P2_12_12_1$, a=7.659(3) Å, b=12.751(2) Å, c=19.087(4) Å, V=1864.0(9) $Å^3$, Z=4, $F(000)$=792, μ=2.212 mm^{-1}, D_c=1.369 g/cm^{-3}. The reflections collected were 2512, of which 2512 unique; 781 reflections [$I>2\sigma(I)$]. R_1=0.0506 and wR_2=0.1238 for 781 [$I>2\sigma(I)$] and R_1=0.2501 and wR_2=0.1833 for all (2512) intensity data. Goodness-of-fit=0.953, absolute structure parameter of the model: x=0.05(3), residual

electron density in the final Fourier map was 0.311 and −0.235 e Å^{-3}. CCDC number is 229761.

5. Supplementary Material

Crystal data and structure refinement for **7** and **9**. Atomic coordinates (×10^4) and equivalent isotropic displacement parameters (Å^2×10^3) for **7** and **9**.

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Selective O-alkylations with glycol chlorohydrins via the Mitsunobu reaction. A versatile route to calix[4]- and 1,1′-binaphthocrowns

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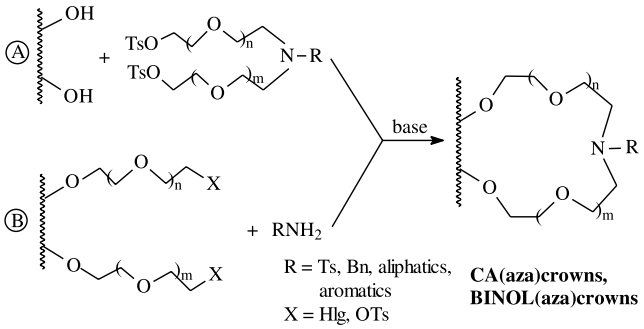
Dedicated to Professor Károly Lempert on his 80th birthday

Abstract—Selective monoalkylation of *p-tert*-butylcalix[4]arene and BINOL with oligoethylene glycol chlorohydrins was achieved under the Mitsunobu protocol using DEAD/TPP. The method provides a simple access to ether precursors capable of cyclising to various crowns.

1. Introduction

In the last decade a large number of supramolecular systems combining the unique properties of calixarenes (CA) and crowns have been described[1,2] and applied in analytical and separation chemistry.[3,4] Recently, calix[4](aza)crowns have attracted great interest due to the easy and versatile derivatisation of the nitrogen atom in the crown ring. N-Alkylation provides a convenient route to the introduction of various side-chains, most frequently additional binding sites or sensing (chromo/fluorophore) units.[5–12]

Although the classical synthesis of azacrown ethers (route A) has also been utilised in the access to calix(aza)crowns,[7] the cyclisation of ω-chloro or tosyloxy-glycolethers with different amine derivatives is preferred (route B)[5,6,8] (Scheme 1). The protecting groups (R=Ts, Bn) can then be removed by reductive methods to afford a free NH in the symmetric position of the crown ring (n=m), which can be further derivatised.[6,8] Although the complexation characteristics of calix(aza)crowns should be infuenced by the position of the nitrogen atom in the ring, asymmetric analogues (where $m \neq n$), still have not been studied. This kind of structure was also found to be essential in chiral 1,1′-binaphtho(crowns), where the recognition of primary amine enantiomers was improved by an asymmetric crown ether binding site.[13] Apart from calix(aza)crowns, the respective 1,1′-binaphthyl analogues have only been examplified by a few racemic derivatives,[14] though these chiral molecules may have potential in designing chromoionophores for the optical recognition of ammonium salt enantiomers.[15]



Scheme 1. Synthetic routes to monoazacrowns.

The synthesis of asymmetric CA- and BINOL-azacrown hosts ($m \neq n$) require precursors with two different ω-halogen/(tosyloxy)ether chains which cannot be introduced either in the CA or in the BINOL molecule by simple stepwise base-promoted alkylations. In both cases protection/deprotection methods[16–18] have to be used to obtain the target compounds. To overcome the inconvenience and low overall yields of the four-step procedures, a rapid alkylation method is herein reported for the selective etherification of *p-tert*-butylcalix[4]arene and BINOL with oligoethylene glycol chlorohydrins.

Keywords: Calix[4]arene; BINOL; O-Alkylation; Mitsunobu reaction; Crown ethers.
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2. Results and discussion

Recently, we have described the convenient application of the Mitsunobu reaction in the selective 1,3-dialkylation- and cycloalkylation of *p-tert*-butylthiacalix[4]arene (TCA) with alcohols and glycols.[19,20] We have shown that quite different results were achieved with the calix[4]arene (CA) counterpart in the same reactions.[20] The higher reactivity and lower selectivity of TCA versus CA were attributed to the more acidic (and less differences in pK_a) OHs and to the 15% larger cavity size. Actually, mono-alkylation of TCA with any alcohols could not be attained, and 1,3-diethers or tetraethers always being formed.[19] These observations prompted us to investigate the possibility of selective alkylation of CA and BINOL[21] with oligoethylene glycol derivatives under the standard Mitsunobu protocol using triphenylphosphine (TPP) and diethyl azodicarboxylate (DEAD) coupling agents (Scheme 2).

2.1. Synthesis of CA- and BINOL mono- and diethers

The reactions were performed at ambient temperature treating CA **1** or (±)-BINOL **2** with glycol chlorohydrins **3a**-**c** and TPP/DEAD (Caution! DEAD may explode if exposed to shock, friction, or heating) in toluene using different molar ratios: (1) **1/3**/(TPP/DEAD)=1:2:2.2, (2) **2/3**/(TPP/DEAD)=1:1.2–1.5:1.3–1.6, respectively. After 2 h reaction (0.5 h was sufficient for **2**) the starting material was consumed and exclusively monoethers **5b**,**c** and **7b**,**c** were formed when **3b**,**c** had been used. In this way, (*S*)-**7b** was prepared in enantiomerically pure form from (*S*)-BINOL. The more reactive **3a** afforded a separable mixture of monoethers **5a** (with a small amount of diether **9a**), and **7a** with diether **10a** in 2:1 ratio, respectively. The generally moderate yields of monoethers (35–50%) refer to 1 mmol scale and can be increased by scaling-up (in 5 mmol scale **5b** and **7b** were obtained in yields of 65–70%).

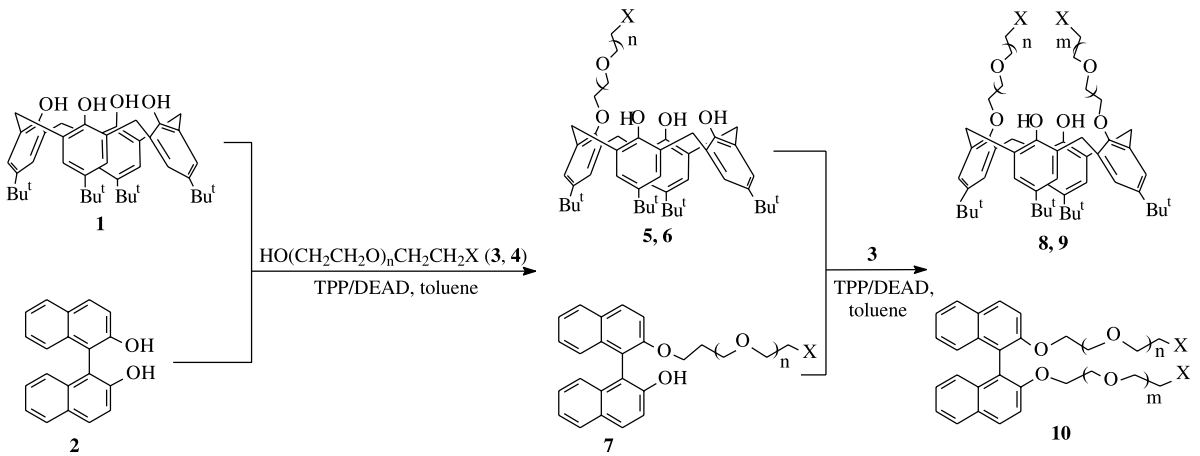
Symmetrical diethers **8a**,**b** and **10a**,**b** were cleanly obtained under the same protocol by increasing the molar ratios to **1**, **2/3**/(TPP/DEAD)=1:3:3.5. On the use of **3b**, however, 1 h reflux was required to complete the reaction. As expected, the long chain chlorohydrin **3c** was not sufficiently reactive to afford CA or BINOL diethers even under vigorous conditions. Making use of the high reactivity of **3a**,**d**, mixed diethers **9a**-**c** and **10c**,**d** including (*S*)-**10c** could easily be prepared by the treatment of monoethers **5b**,**c** and **7b** with 1.5 equiv. of **3a** or **3d** at room temperature. In contrast, the reaction of **7c** with **3a** did not lead to complete conversion even at elevated temperature, and pure asymmetric diether could not be separated from the mixture.

From a synthetic point of view it was of interest to check the reactivity of tosylates **4a** and **4b** under similar conditions. Both analogues reacted more sluggishly with CA **1** as compared with the respective chlorohydrins **3** requiring two molar excess of reagents for the monoether derivatives **6a**,**b**, and four molar excess of reagents for the diethers **8c**,**d** under 2 h reflux in both cases. Notably, these reactions took place in the BINOL series, too, but we failed to obtain pure tosylethers due to separation problems. The molecules containing reactive tosylate end-groups in the chain are regarded as valuable intermediates, albeit they are accessible otherwise, but in significantly longer multi-step reactions.

None of the mono and diethers prepared in this study have been described until now, except for the debutylated analogue of **8a**, which was obtained in a slow, base-promoted alkylation of the parent CA with diethylene glycol monochlorohydrin tosylate.[10]

2.2. Cyclisations of mono- and diethers

The calixarene- and BINOL monoethers and diethers in hand provided a simple access to crowns and azacrowns of different type by self-condensation (monoethers) or by cyclising with *p*-toluenesulfonamide (diethers). Although these reactions were not optimised, they offer a useful synthetic alternative for the preparation of certain crowns.



3a (X = Cl, n = 1)
3b (X = Cl, n = 2)
3c (X = Cl, n = 3)
3d (X = Br, n = 0)
4a (X = TsO, n = 1)
4b (X = TsO, n = 2)

	5a	5b	5c	6a	6b	7a	7b	7c	8a	8b	8c	8d	9a	9b	9c	10a	10b	10c	10d
X	Cl	Cl	Cl	TsO	TsO	Cl	Cl	Cl	Cl	Cl	TsO	TsO	Cl, Br	Cl	Cl	Cl	Cl	Cl	Cl, Br
n	1	2	3	1	2	1	2	3	1	2	1	2	3	2	3	1	2	2	3
m	-	-	-	-	-	-	-	-	1	2	1	2	0	1	1	1	2	1	0
%	83	43	45	47	50	65	43	50	81	77	50	59	42	81	76	64	70	58	53

Scheme 2. Synthesis of CA and BINOL mono- and diethers via the Mitsunobu reaction.

2.3. Calix[4]- and 1,1′-binaphthocrowns

Monoethers **5a**-**c**, and **7b**,**c** exposed to basic conditions underwent intra- and/or intermolecular cyclisations depending on the chain length, affording calix- and binaphthocrowns **11**-**13** (Fig. 1).

The reactions were conducted in MeCN (48 h reflux) using a large excess of K_2CO_3 (equimolar KI was added). Compound **5a** possessing a short chain cyclised to 1,2-calix[4](crown-3) **11a**,[22] while **5c** with a long chain afforded exlusively 1,3-calix[4](crown-5) **12b**.[23] Compound **5b**, which has a medium chain length, gave predominantly also the 1,3-calix[4](crown-4) **12a**[24] with traces of the 1,2-isomer **11b**.[25] Interestingly, we have obtained the same results, when CA was treated with di-, tri- and tetraethylene glycol under the Mitsunobu protocol.[20] The structure of regioisomers **11** and **12** has been determined earlier by others with the aid of the ^{1}H NMR spectra, which display characteristic differences in the splitting pattern of the bridging methylene protons for the proximally-coupled **11**[22,25] versus the distally-coupled **12**.[23,24]

Notably, Shinkai et al.[24] investigated the reaction of calix[4]arene tetrols and triethylene glycol ditosylate in the presence of various alkali carbonate bases to optimise the yield of the 1,3-calix[4](crown-4) **12a**. In these reactions a complex mixture was obtained containing the target **12a** and several side-products, among others 1,2-calixcrown-4 **11b**, non-cyclised intermediate and dimers in comparable amounts. In the light of these results, our indirect method, after optimisation, may have advantages over the traditional direct cyclisations.

Racemic BINOL monoether **7b** and its enantiomer (*S*)-**7b** were smoothly cyclised exclusively to bis(binaphtho-crown-8) (±)-**13b** and (*S*)-**13b**, respectively, which were also the major products in the direct ring closure of 1,1′-bi-2-naphthol with triethylene glycol ditosylate.[26] Compound **7c**, however, gave a 2:1 mixture of mono-(binaphtho-crown-5) **13a** and bis(binaphtho-crown-10) **13c** indicating that the longer tetraethyleneoxy chain of **7c** allows simultaneous intra- and intermolecular reaction pathways. That is the reason why only a low yield of **13a** was achieved in the cyclisation of **2** with tetraethylene glycol ditosylate.[14] Better results were reported for the Okahara cyclisation of *O*,*O*-bis(2-hydroxyethoxyethoxy)-1,1′-bi-2-naphthol.[27]

2.4. Calix[4]- and 1,1′-binaphtho(aza)crowns

Di-chloroethers **8**-**10** were cyclised with *p*-tosylamide ($TsNH_2$) to 1,3-calix[4]- and 1,1′-binaphtho(aza)crown-5,-6, and 7 (**14**, **15**), respectively. This base-promoted ring closure has been used mainly in the case of 1,3-calix[4]arene (bis)chloroethers not containing free phenolic OH groups, probably to avoid a possible self-condensation. Indeed, when the debutylated analogue of **14a** was synthesized by this method using Cs_2CO_3 in DMF solvent, a low yield was reported.[28] Since the N-alkylation of $TsNH_2$ can effectively be performed in the presence of a weaker base, we used a 5-fold excess of K_2CO_3 in DMF at 100 °C (48 h) to effect the cyclisation. Under these conditions the expected N-cyclised products were obtained in good yields. Thus, compounds **8a**,**b** gave the symmetric calix[4](aza)-crowns **14a**,**b**, while **9b** resulted in the asymmetric analogue **14c**. Analogously, BINOL diethers **10a**-**c** cleanly furnished the symmetric- and asymmetric binaphtho(azacrowns) (±)-**15a**-**c** and (*S*)-**15c**. The latter molecule is an appropriate candidate for the synthesis of chiral receptors. Notably, in these experiments, self-cyclised side-products were not formed due to the much higher acidity of the tosylamide NH's versus the remaining calixarene OH's.

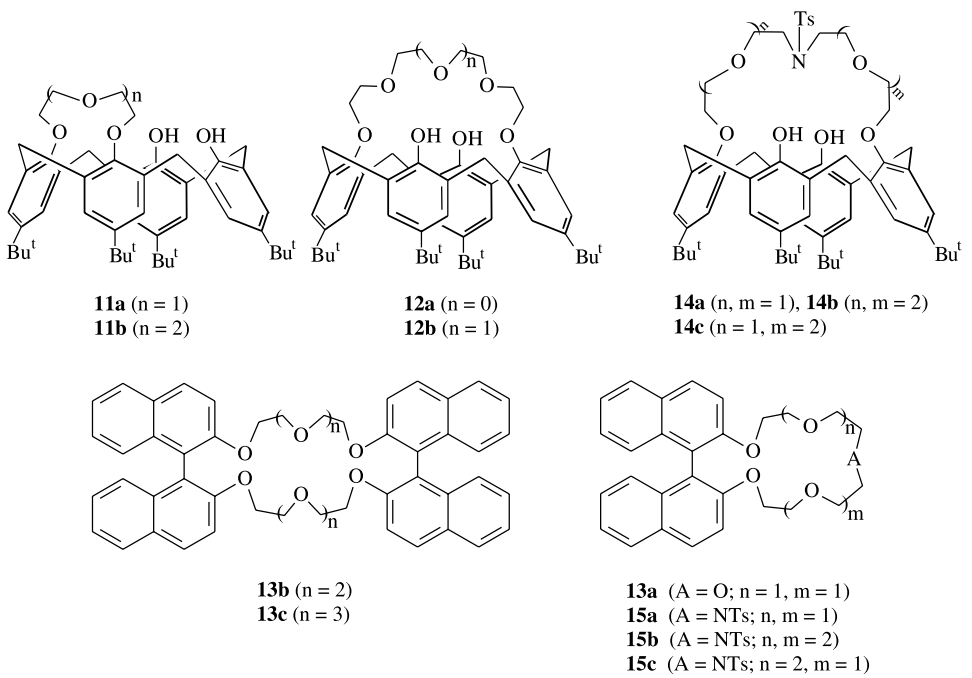


Figure 1. Survey of cyclisation products obtained from monoethers **5**, **7** and diethers **8**-**10**.

With mixed diethers **9a**, **9c** and **10d** an inseparable mixture was obtained and we failed to recover the expected cyclised products. These examples clearly show that the success of ring closure is not dependent on the size of the crown ring being formed, rather on the difference between the chain lengths (n, m) of the precursors. In case of $n-m>1$, for example, in **9c** (2), **9a** and **10d** (3), the cyclisation is not preferred.

3. Conclusions

A series of calixarene- and BINOL mono- and diethers comprised of oligoethylene glycol chains supplied with reactive terminal groups have been synthesized via the Mitsunobu reaction. This selective and rapid alkylation with glycol derivatives provides an easy access to precursors capable of cyclising to various calix[4]- and 1,1′-bi-2-naphthocrowns.

4. Experimental

Melting points are uncorrected. NMR spectra were recorded in $CDCl_3$ at 500:125 MHz on a Bruker Avance DRX-500 spectrometer. Pre-coated silica gel plates (Merck 60 F_{254}) were used for analytical TLC and Kieselgel 60 for column chromatography. All chemicals were reagent grade and used without further purification. TPP, **3a**,**d** were purchased from Merck. *p-tert*-Butylcalix[4]arene **1**,[29] BINOL **2**,[30] glycol chlorohydrins **3b**,**c**[31] tosylates **4**[32] and DEAD[33] were prepared as described in the literature.

4.1. General procedure for the synthesis of monoethers 5, 6, 7 and diethers 8, 9, 10

To the mixture of CA **1** (0.65 g, 1 mmol), glycol derivatives **3** or **4** (2 mmol) and TPP (0.6 g, 2.3 mmol) in toluene (25 ml), a 40% toluene solution of DEAD (1.05 ml, 2.3 mmol) was added dropwise with stirring at room temperature. After 2 h reaction the solution was evaporated to dryness and the residue was separated by column chromatography on silica. The same procedure was applied for the monoalkylation of BINOL **2** (2 mmol) using **3** (1.2 mmol), TPP/DEAD (0.4 g/0.75 ml, 1.5 mmol each) in 0.5 h reactions.

During the synthesis of symmetric diethers **8a**,**b** and **10a**,**b** an enhanced reagent ratio of **1** or **2/3**/(TPP/DEAD)=1:3:3.5 was used. The less reactive **3b** required 0.5 h reflux for completion of the reaction. Mixed diethers **9a**-**c** and **10c**,**d** were prepared by the treatment of monoethers **5b**,**c** or **10b** (1 mmol) with **3a** or **3d** (0.19 g, 1.5 mmoI each) and TPP/DEAD (045 g/0.85 ml, 1.7 mmol each) at ambient temperature.

Tosylethers **6a**,**b** and **8c**,**d** were prepared following the procedures above but using reagent ratios of **1/4a**,**b**/(TPP/DEAD)=1:3:3 (monoethers) and **1/4a**,**b**/(TPP/DEAD)=1:6:6 (diethers), respectively, under 2 h reflux in both cases.

4.2. Calix[4]- and BINOL monoethers

4.2.1. 25-(1-Chloro-3-oxapent-5-yl)oxy-26,27,28-trihydroxy-5,11,17,23-tetra-*tert*-butyl-calix[4]arene (5a). White solid, mp 162–166 °C, (triturated with MeOH); ^{1}H NMR: δ 10.25 (s, 1H, O*H*), 9.38 (s, 2H, O*H*), 7.09 (s, 2H, Ar*H*), 7.05 (m, 4H, Ar*H*), 6.98 (d, 2H, J=2.5 Hz, Ar*H*), 4.47 (d, 2H, J=13 Hz, ArCH_2Ar), 4.31 (m, 2H, CH_2), 4.26 (d, 2H, J=13.5 Hz, ArCH_2Ar), 4.13 (m, 2H, CH_2), 3.97 (t, 2H, J=6 Hz, CH_2), 3.78 (t, 2H, J=5.5 Hz, CH_2), 3.43 (d, 2H, J=14 Hz, ArCH_2Ar), 3.40 (d, 2H, J=14 Hz, ArCH_2Ar), 1.22 (s, 9H, C(CH_3)$_3$), 1.21 (s, 18H, C(CH_3)$_3$), 1.19 (s, 9H, C(CH_3)$_3$); FAB-MS m/z (%): 754.4 (M($^+$(24) (Calcd 754.4). Anal. Calcd for $C_{48}H_{63}O_5Cl$ (755.47): C, 76.31; H, 8.41, found: C, 76.05; H, 8.45%.

4.2.2. 25-(1-Chloro-3,6-dioxaoct-8-yl)oxy-26,27,28-trihydroxy-5,11,17,23-tetra-*tert*-butyl-calix[4]arene (5b). White solid, mp 162–165 °C (eluent: hexane/EtOAc=8:2); ^{1}H NMR: δ 10.27 (s, 1H, O*H*), 9.40 (s, 2H, O*H*), 7.09 (s, 2H, Ar*H*), 7.05 (m, 4H, Ar*H*), 6.98 (d, 2H, J=2 Hz, Ar*H*), 4.47 (d, 2H, J=13 Hz, ArCH_2Ar), 4.32 (m, 2H, CH_2), 4.26 (d, 2H, J=13.5 Hz, ArCH_2Ar), 4.11 (m, 2H, CH_2), 3.87 (m, 2H, CH_2), 3.82 (m, 2H, CH_2), 3.76 (t, 2H, J=6 Hz, CH_2), 3.54 (t, 2H, J=5.5 Hz, CH_2), 3.43 (d, 2H, J=14 Hz, ArCH_2Ar), 3.39 (d, 2H, J=13 Hz, ArCH_2Ar), 1.22 (s, 9H, C(CH_3)$_3$), 1.21 (s, 18H, C(CH_3)$_3$), 1.19 (s, 9H, C(CH_3)$_3$); ^{13}C NMR: δ 149.6, 148.5, 148.3, 148.2, 143.8, 143.3, 133.9, 128.5, 127.9, 126.6, 126.0, 125.9 (Ar*C*), 75.3, 71.7, 71.1, 71.0, 70.3, 42.9 (*C*H$_2$), 34.4, 34.2, 34,1 (*C*CH$_3$), 33.3, 32.3 (Ar*C*H$_2$Ar), 31.7, 31.5 (C*C*H$_3$); FAB-MS m/z (%): 821.5 (M+Na)$^+$ (100) (Calcd 821.5). Anal. Calcd for $C_{50}H_{67}O_6Cl$ (799.53): C, 75.11; H, 8.45, found: C, 74.62; H, 8.38%.

4.2.3. 25-(1-Chloro-3,6,9-trioxaundec-11-yl)oxy-26,27,28-trihydroxy-5,11,17,23-tetra-*tert*-butyl-calix[4]-arene (5c). White solid, mp 103–105 °C (eluent: hexane/EtOAc=7:3); ^{1}H NMR: δ 10.28 (s, 1H, O*H*), 9.40 (s, 2H, O*H*), 7.08 (s, 2H, Ar*H*), 7.05 (m, 4H, Ar*H*), 6.97 (d, 2H, J=2 Hz, Ar*H*), 4.46 (d, 2H, J=13 Hz, ArCH_2Ar), 4.32 (m, 2H, CH_2), 4.26 (d, 2H, J=13.5 Hz, ArCH_2Ar), 4.10 (m, 2H, CH_2), 3.86 (m, 2H, CH_2), 3.81 (m, 2H, CH_2), 3.72 (m, 4H, CH_2), 3.59 (m, 4H, CH_2), 3.43 (d, 2H, J=13.5 Hz, ArCH_2Ar), 3.39 (d, 2H, J=13 Hz, ArCH_2Ar), 1.22 (s, 9H, C(CH_3)$_3$), 1.21 (s, 18H, C(CH_3)$_3$), 1.19 (s, 9H, C(CH_3)$_3$); FAB-MS m/z (%): 865.5 (M+Na)$^+$ (46) (Calcd 865.5), 842.5 (M)$^+$ (49); (Calcd 842.5). Anal. Calcd for $C_{52}H_{71}O_7Cl$ (843.58): C, 74.04; H, 8.48, found: C, 73.98; H, 8.31%.

4.2.4. 25-(1-*p*-Toluenesulfonyloxy-3-oxapent-5-yl)oxy-26,27,28-trihydroxy-5,11,17,23-tetra-*tert*-butyl-calix[4]-arene (6a). White solid, mp 81–84 °C (eluent: hexane/EtOAc=8:2); ^{1}H NMR: δ 10.22 (s, 1H, O*H*), 9.37 (s, 2H, O*H*), 7.80 (d, 2H, J=8 Hz, Ar*H*), 7.25 (d, 2H, J=8 Hz, Ar*H*), 7.08 (s, 2H, Ar*H*), 7.04 (m, 4H, Ar*H*), 6.97 (d, 2H, J=1 Hz, Ar*H*), 4.36 (d, 2H, J=13 Hz, ArCH_2Ar), 4.32 (t, 2H, J=4.5 Hz, CH_2), 4.24 (m, 2H, CH_2), 4.18 (d, 2H, J=14 Hz, ArCH_2Ar), 4.05 (m, 2H, CH_2), 3.91 (t, 2H, J=4.5 Hz, CH_2), 3.39 (d, 2H, J=13.5 Hz, ArCH_2Ar), 3.37 (d, 2H, J=13 Hz, ArCH_2Ar), 2.39 (s, 3H, CH_3), 1.22 (s, 9H, C(CH_3)$_3$), 1.21 (s, 18H, C(CH_3)$_3$), 1.19 (s, 9H, C(CH_3)$_3$);

FAB-MS *m/z* (%): 890.5 (M(+ (71) (Calcd 890.5). Anal. Calcd for $C_{55}H_{70}O_8S$ (891.21): C, 74.12; H, 7.94, found: C, 74.22; H, 7.86%.

4.2.5. 25-(1-1-*p*-Toluenesulfonyloxy-3,6-dioxaoct-8-yl)oxy-26,27,28-trihydroxy-5,11,17,23-tetra-*tert*-butylcalix[4]arene (6b). White solid, mp 160–163 °C (eluent: hexane/ EtOAc=7:3); ^{1}H NMR: δ 10.24 (s, 1H, O*H*), 9.38 (s, 2H, O*H*), 7.78 (d, 2H, *J*=8 Hz, Ar*H*), 7.29 (d, 2H, *J*=8 Hz, Ar*H*), 7.08 (s, 2H, Ar*H*), 7.05 (m, 4H, Ar*H*), 6.97 (d, 2H, *J*=2 Hz, Ar*H*), 4.43 (d, 2H, *J*=13 Hz, ArCH_2Ar), 4.28 (m, 2H, CH_2), 4.23 (d, 2H, *J*=13.5 Hz, ArCH_2Ar), 4.08 (m, 4H, CH_2), 3.79 (m, 2H, CH_2), 3.72 (m, 4H, CH_2), 3.41 (d, 2H, *J*=14 Hz, ArCH_2Ar), 3.38 (d, 2H, *J*=13.5 Hz, ArCH_2Ar), 2.40 (s, 3H, CH_3), 1.22 (s, 9H, C(CH_3)$_3$), 1.20 (s, 18H, C(CH_3)$_3$), 1.19 (s, 9H, C(CH_3)$_3$); FAB-MS *m/z* (%): 957.5 (M+Na)$^+$ (65) (Calcd 957.5). Anal. Calcd for $C_{57}H_{74}O_9S$ (935.26): C, 73.20; H, 7.97, found: C, 72.84; H, 8.03%.

4.2.6. (±)-*O*-(1-Chloro-3-oxapent-5-yl)-1,1′-bi-2-naphthol (7a). Yellow oil (eluent: toluene/MeOH=95:5); ^{1}H NMR: δ 8.02 (d, 1H, *J*=9 Hz, Ar*H*), 7.88 (m, 3H, Ar*H*), 7.45 (d, 1H, *J*=9 Hz, Ar*H*), 7.39–7.20 (m, 6H, Ar*H*), 7.04 (d, 1H, *J*=8.5 Hz, Ar*H*), 5.08 (s, 1H, O*H*), 4.19 (m, 1H, CH_2), 4.10 (m, 1H, CH_2), 3.55 (t, 2H, *J*=4.5 Hz, CH_2), 3.23–3.10 (m, 4H, CH_2); FAB-MS *m/z* (%): 392.1 (M(+ (30) (Calcd 392.1). Anal. Calcd for $C_{24}H_{21}O_3Cl$ (392.88): C, 73.37; H, 5.39, found: C, 73.63; H, 5.44%.

4.2.7. (±)-*O*-(1-Chloro-3,6-dioxaoct-8-yl)-1,1′-bi-2-naphthol (7b). Yellow oil (eluent: hexane/EtOAc=6:4); ^{1}H NMR: δ 7.99 (d, 1H, *J*=9 Hz, Ar*H*), 7.86 (m, 3H, Ar*H*), 7.45 (d, 1H, *J*=9 Hz, Ar*H*), 7.37–7.16 (m, 6H, Ar*H*), 7.04 (d, 1H, *J*=8 Hz, Ar*H*), 5.32 (s, 1H, O*H*), 4.25 (m, 1H, CH_2), 4.10 (m, 1H, CH_2), 3.55 (t, 2H, *J*=4.5 Hz, CH_2), 3.50–3.34 (m, 4H, CH_2), 3.30–3.19 (m, 4H, CH_2); ^{13}C NMR: δ 155.5, 151.6, 134.2, 134.1, 130.9, 129.8, 129.7, 129.3, 128.3, 128.2, 127.4, 126.5, 125.3, 125.1, 124.5, 123.4, 118.1, 116.9, 115.7, 115.6 (Ar*C*), 71.3, 70.6, 70.0, 69.6, 42.6 (*C*H$_2$); FAB-MS *m/z* (%): 436.1 (M)$^+$ (10) (Calcd 436.1). Anal. Calcd for $C_{26}H_{25}O_4Cl$ (436.93): C, 71.47; H, 5.77, found: C, 71.22; H, 5.82%.

4.2.8. (*S*)-*O*-(1-Chloro-3,6-dioxaoct-8-yl)-1,1′-bi-2-naphthol ((*S*)-7b). Yellow oil (eluent: hexane/ EtOAc=6:4), yield: 79%, $[\alpha]_D^{20}$=+21.7 (*c*=1, $CHCl_3$).

4.2.9. (±)-*O*-(1-Chloro-3,6,9-trioxaundec-11-yl)-1,1′-bi-2-naphthol (7c). Yellow oil (eluent: hexane/EtOAc=7:3); ^{1}H NMR: δ 7.99 (d, 1H, *J*=9 Hz, Ar*H*), 7.85 (m, 3H, Ar*H*), 7.46 (d, 1H, *J*=9 Hz, Ar*H*), 7.37–7.17 (m, 6H, Ar*H*), 7.04 (d, 1H, *J*=8.5 Hz, Ar*H*), 5.50 (s, 1H, O*H*), 4.26 (m, 1H, CH_2), 4.10 (m, 1H, CH_2), 3.64–3.22 (m, 14H, CH_2); FAB-MS *m/z* (%): 503.2 (M+Na)$^+$ (16) (Calcd 503.2). Anal. Calcd for $C_{28}H_{29}O_5Cl$ (480.98): C, 69.92; H, 6.08, found: C, 69.31; H, 6.11%.

4.3. Symmetrical calix[4]- and BINOL diethers

4.3.1. 25,27-Bis(1-chloro-3-oxapent-5-yl)oxy-26,28-dihydroxy-5,11,17,23-tetra-*tert*-butyl-calix[4]arene (8a). White solid, mp 110–113 °C (triturated with MeOH); ^{1}H NMR: δ 7.14 (s, 2H, O*H*), 7.07 (s, 4H, Ar*H*), 6.78 (s, 4H, Ar*H*), 4.34 and 3.31 (d+d, 4+4H, *J*=13 Hz, ArCH_2Ar), 4.16 (t, 4H, *J*=4 Hz, CH_2), 4.01 (t, 4H, *J*=4 Hz, CH_2), 3.98 (t, 4H, *J*=6 Hz, CH_2), 3.74 (t, 4H, *J*=6 Hz, CH_2), 1.30 (s, 18H, C(CH_3)$_3$), 0.95 (s, 18H, C(CH_3)$_3$); ^{13}C NMR: δ 150.5, 149.7, 146.9, 141.4, 133.3, 132.5, 127.8, 126.4, 125.6, 125.1 (Ar*C*), 75.5, 71.9, 70.3, 43.1 (*C*H$_2$), 34.2, 34,1 (*C*CH$_3$), 32,1, 31.3 (C*C*H$_3$), 31.8 (Ar*C*H$_2$Ar); FAB-MS *m/z* (%): 860.5 (M(+ (24) (Calcd 860.5). Anal. Calcd for $C_{52}H_{70}O_6Cl_2$ (862.03): C, 72.45; H, 8.18, found: C, 72.96; H, 8.10%.

4.3.2. 25,27-Bis(1-chloro-3,6-dioxaoct-8-yl)oxy-26,28-dihydroxy-5,11,17,23-tetra-*tert*-butyl-calix[4]arene (8b). Yellow oil (eluent: hexane/EtOAc=7:3); ^{1}H NMR: δ 7.09 (s, 2H, O*H*), 7.05 (s, 4H, Ar*H*), 6.75 (s, 4H, Ar*H*), 4.36 and 3.28 (d+d, 4+4H, *J*=13 Hz, ArCH_2Ar), 4.23 (m, 4H, CH_2), 4.15 (t, 4H, *J*=4.5 Hz, CH_2), 3.96 (t, 4H, *J*=5 Hz, CH_2), 3.83 (m, 4H, CH_2), 3.76 (m, 4H, CH_2), 3.53 (t, 4H, *J*=6 Hz, CH_2), 1.31 (s, 18H, C(CH_3)$_3$), 0.93 (s, 18H, C(CH_3)$_3$). Anal. Calcd for $C_{56}H_{78}O_8Cl_2$ (950.13): C, 70.79; H, 8.27, found: C, 70.25; H, 8.36%.

4.3.3. 25,27-Bis(1-*p*-toluenesulfonyloxy-3-oxapent-5-yl)oxy-26,28-dihydroxy-5,11,17,23-tetra-*tert*-butyl-calix[4]arene (8c). White solid, mp 160–163 °C (triturated with MeOH); ^{1}H NMR: δ 7.73 (d, 4H, *J*=7 Hz, Ar*H*), 7.20 (d, 4H, *J*=7 Hz, Ar*H*), 7.17 (s, 2H, O*H*), 7.05 (s, 4H, Ar*H*), 6.77 (s, 4H, Ar*H*), 4.25 (m, 4+4H, ArCH_2Ar, CH_2), 4.05 (m, 4H, CH_2), 3.89 (m, 8H, CH_2), 3.26 (d, 4H, *J*=13 Hz, ArCH_2Ar), 2.37 (s, 6H, CH_2), 1.30 (s, 18H, C(CH_3)$_3$), 0.94 (s, 18H, C(CH_3)$_3$). Anal. Calcd for $C_{66}H_{84}O_{12}S_2$ (1133.50): C, 69.94; H, 7.47, found: C, 69.44; H, 7.52%.

4.3.4. 25,27-Bis(1-*p*-toluenesulfonyloxy-3,6-dioxaoct-8-yl)oxy-26,28-dihydroxy-5,11,17,23-tetra-*tert*-butyl-calix[4]arene (8d). Yellow oil (eluent: hexane/ EtOAc=7:3); ^{1}H NMR: δ 7.79 (d, 4H, *J*=7 Hz, Ar*H*), 7.34 (d, 4H, *J*=7 Hz, Ar*H*), 7.16 (s, 2H, O*H*), 7.06 (s, 4H, Ar*H*), 6.77 (s, 4H, Ar*H*), 4.35 and 3.29 (d+d, 4+4H, *J*=13 Hz, ArCH_2Ar), 4.12 (m, 8H, CH_2), 3.92 (m, 4H, CH_2), 3.77 (m, 4H, CH_2), 3.68 (m, 8H, CH_2), 2.43 (s, 6H, CH_2), 1.31 (s, 18H, C(CH_3)$_3$), 0.95 (s, 18H, C(CH_3)$_3$). Anal. Calcd for $C_{70}H_{92}O_{14}S_2$ (1221.61): C, 68.82; H, 7.59, found: C, 69.19; H, 7.63%.

4.3.5. (±)-*O*,*O*′-Bis(1-chloro-3-oxapent-5-yl)-1,1′-bi-2-naphthol (10a). Yellow oil (eluent: toluene/ MeOH=97:3); ^{1}H NMR: δ 7.94 (d, 2H, *J*=9 Hz, Ar*H*), 7.85 (d, 2H, *J*=8 Hz, Ar*H*), 7.41 (d, 2H, *J*=9.5 Hz, Ar*H*), 7.33 (t, 2H, *J*=7 Hz, Ar*H*), 7.23 (t, 2H, *J*=7 Hz, Ar*H*), 7.17 (d, 2H, *J*=8.5 Hz, Ar*H*), 4.15–4.05 (m, 4H, CH_2), 3.49 (t, 4H, *J*=4.5 Hz, CH_2), 3.15–3.06 (m, 8H, CH_2). Anal. Calcd for $C_{28}H_{28}O_4Cl_2$ (499.43): C, 67.34; H, 5.65, found: C, 67.86; H, 5.70%.

4.3.6. (±)-*O*,*O*′-Bis(1-chloro-3,6-dioxaoct-8-yl)-1,1′-bi-2-naphthol (10b). Yellow oil (eluent: toluene/MeOH=95:5); ^{1}H NMR: δ 7.93 (d, 2H, *J*=9 Hz, Ar*H*), 7.85 (d, 2H, *J*=8 Hz, Ar*H*), 7.41 (d, 2H, *J*=9 Hz, Ar*H*), 7.32 (td, 2H, *J*=7 Hz, 1 Hz, Ar*H*), 7.21 (td, 2H, *J*=8 Hz, 1 Hz, Ar*H*), 7.15 (d, 2H, *J*=8.5 Hz, Ar*H*), 4.09 (m, 4H, CH_2), 3.55–3.45 (m, 12H, CH_2), 3.20 (t, 4H, *J*=4 Hz, CH_2), 3.15–3.05 (m,

4H, CH_2). Anal. Calcd for $C_{32}H_{36}O_6Cl_2$ (587.54): C, 65.42; H, 6.18, found: C, 65.08; H, 6.22%.

4.4. Mixed calix[4]- and BINOL diethers

4.4.1. 25-(1-Chloro-3,6,9-trioxaundec-11-yl)oxy-27-(2-bromoethoxy)-26,28-dihydroxy-5,11,17,23-tetra-*tert*-butyl-calix[4]arene (9a). White solid, mp 57–59 °C (eluent: hexane/EtOAc=7:3); ^{1}H NMR: δ 7.06 (d, 4H, J=0.5 Hz, Ar*H*), 7.01 (s, 2H, O*H*), 6.79 (s, 2H, Ar*H*), 6.73 (s, 2H, Ar*H*), 4.34 and 3.30 (dd, 4H+4H, J=13.5, 3 Hz, ArCH_2Ar), 4.30 (t, 2H, J=6.5 Hz, CH_2), 4.16 (t, 2H, J=4 Hz, CH_2), 4.00 (t, 2H, J=4.5 Hz, CH_2), 3.88 (t, 2H, J=4.5 Hz, CH_2), 3.81 (t, 2H, J=6.5 Hz, CH_2), 3.75 (t, 2H, J=4.5 Hz, CH_2), 3.68 (m, 4H, CH_2), 3.59 (m, 4H, CH_2), 1.30 (s, 18H, C(CH_3)$_3$), 0.96 (s, 9H, C(CH_3)$_3$), 0.90 (s, 9H, C(CH_3)$_3$). Anal. Calcd for $C_{54}H_{74}O_7BrCl$ (950.53): C, 68.23; H, 7.85, found: C, 68.65; H, 7.94%.

4.4.2. 25-(1-Chloro-3-oxapent-5-yl)oxy-27-(1-chloro-3,6-dioxaoct-8-yl)oxy-26,28-dihydroxy-5,11,17,23-tetra-*tert*-butyl-calix[4]arene (9b). White solid, mp 80–82 °C (eluent: hexane/EtOAc=7:3); ^{1}H NMR: δ 7.11 (s, 2H, O*H*), 7.05 (s, 4H, Ar*H*), 6.76 (d, 4H, J=4 Hz, Ar*H*), 4.37 and 4.33 (d+d, 2H+2H, J=13.5 Hz, ArCH_2Ar), 4.15 (m, 4H, CH_2), 3.98 (m, 6H, CH_2), 3.87 (m, 2H, CH_2), 3.75 (m, 6H, CH_2), 3.52 (t, 2H, J=5.5 Hz, CH_2), 3.29 (d, 4H, J=13 Hz, ArCH_2Ar), 1.30 (s, 18H, C(CH_3)$_3$), 0.94 (s, 9H, C(CH_3)$_3$), 0.93 (s, 9H, C(CH_3)$_3$); ^{13}C NMR: δ 150.8, 150.0, 147.1, 141.6, 132.7, 128.0, 125.7, 125.3, (Ar*C*), 75.6, 72.0, 71.7, 71.2, 71.0, 70.3, 43.1, 43.0 (*C*H$_2$), 34.1, 34,0 (*C*CH$_3$), 32,0, 31.2 (C*C*H$_3$), 31.7 (Ar*C*H$_2$Ar). Anal. Calcd for $C_{54}H_{74}O_7Cl_2$ (906.08): C, 71.58; H, 8.23, found: C, 71.11; H, 8.28%.

4.4.3. 25-(1-Chloro-3-oxapent-5-yl)oxy-27-(1-chloro-3,6,9-trioxaundec-11-yl)oxy-26,28-dihydroxy-5,11,17,23-tetra-*tert*-butyl-calix[4]arene (9c). Yellow oil (eluent: hexane/EtOAc=8:2); ^{1}H NMR: δ 7.12 (s, 2H, O*H*), 7.05 (s, 4H, Ar*H*), 6.76 (s, 4H, Ar*H*), 4.35 and 4.33 (d+d, 2H+2H, J=13.5 Hz, ArCH_2Ar), 4.14 (m, 4H, CH_2), 3.99 (m, 4H, CH_2), 3.95 (t, 2H, J=5 Hz, CH_2), 3.85 (t, 2H, J=4.5 Hz, CH_2), 3.72 (m, 4H, CH_2), 3.66 (m, 4H, CH_2), 3.58 (m, 4H, CH_2), 3.28 (dd, 4H, J=13.5, 2.5 Hz, ArCH_2-Ar), 1.29 (s, 18H, C(CH_3)$_3$), 0.94 (s, 9H, C(CH_3)$_3$), 0.93 (s, 9H, C(CH_3)$_3$). Anal. Calcd for $C_{56}H_{78}O_8Cl_2$ (950.13): C, 70.79; H, 8.27, found: C, 70.23; H, 8.32%.

4.4.4. (±)-*O*-(1-Chloro-3-oxapent-5-yl)-*O*′-(1-chloro-3,6-dioxaoct-8-yl)-1,1′-bi-2-naphthol (10c). Yellow oil (eluent: toluene/MeOH=95:5); ^{1}H NMR: δ 7.93 (d, 2H, J=9 Hz, Ar*H*), 7.85 (d, 2H, J=8 Hz, Ar*H*), 7.41 (t, 2H, J=8 Hz, Ar*H*), 7.32 (t, 2H, J=7 Hz, Ar*H*), 7.24–7.14 (m, 4H, Ar*H*), 4.09 (m, 4H, CH_2), 3.56–3.48 (m, 8H, CH_2), 3.21 (t, 2H, J=4.5 Hz, CH_2), 3.16–3.05 (m, 6H, CH_2); ^{13}C NMR: δ 154.5, 154.4, 134.3, 129.7, 129.6, 129.5, 128.0, 126.5, 125.7, 125.6, 124.0, 120.8, 120.7, 115.8, 115.7 (Ar*C*), 71.4, 71.3, 70.7, 70.6, 70.2, 70.1, 69.9, 69.8, 43.0, 42.8 (*C*H$_2$). Anal. Calcd for $C_{30}H_{32}O_5Cl_2$ (543.48): C, 66.30; H, 5.93, found: C, 66.02; H, 5.99%.

4.4.5. (*S*)-*O*-(1-Chloro-3-oxapent-5-yl)-*O*′-(1-chloro-3,6-dioxaoct-8-yl)-1,1′-bi-2-naphthol ((*S*)-10c). Yellow oil (94%), eluent: toluene/MeOH=95:5; $[\alpha]_D^{20}$=−45 (c=1, $CHCl_3$).

4.4.6. (±)-*O*-(1-Chloro-3-oxapent-5-yl)-*O*′-(2-bromoethoxy)-1,1′-bi-2-naphthol (10d). Yellow oil (53%), eluent: toluene/MeOH=95:5; ^{1}H NMR: δ 7.94 (t, 2H, J=9.5 Hz, Ar*H*), 7.85 (d, 2H, J=8 Hz, Ar*H*), 7.41 (m, 2H, Ar*H*), 7.32 (m, 2H, Ar*H*), 7.22 (m, 2H, Ar*H*), 7.14 (m, 2H, Ar*H*), 3.57 (m, 4H, CH_2), 3.48 (m, 4H, CH_2), 3.24–3.09 (m, 6H, CH_2). Anal. Calcd for $C_{30}H_{32}O_5BrCl$ (587.93): C, 61.29; H, 5.49, found: C, 61.11; H, 5.52%.

4.5. General procedure for the self-condensation of mono-chloroethers

The mixture of mono-chloroethers **5a**,**b**,**c** or **7b**,**c** (0.5 mmol), K_2CO_3 (0.7 g, 5 mmol) and KI (0.17 g, 0.5 mmol) in MeCN (20 ml) was stirred for 48 h under reflux. The solvent was then evaporated, the residue was extracted with CH_2Cl_2 (30 ml), washed with dilute aq. HCl, water and dried. The crude products were separated by column chromatography on silica to afford white solids (except for **13c**).

4.6. Calix[4]crowns

4.6.1. 25,26-(3-Oxapenta-1,5-diyl)oxy-27,28-dihydroxy-5,11,17,23-tetra-*tert*-butyl-calix[4]arene (11a). Yield: 69%, mp 152–155 °C (triturated with MeOH). The ^{1}H NMR data are identical to those reported in Ref. 22.

4.6.2. 25,27-(3,6-Dioxaocta-1,8-diyl)oxy-26,28-dihydroxy-5,11,17,23-tetra-*tert*-butyl-calix[4]arene (12a). Yield: 55%, eluent: hexane/EtOAc=8:2, mp 235–237 °C (lit.[24] mp 259–262 °C). The ^{1}H NMR data are identical to those reported in Ref. 24.

4.6.3. 25,27-(3,6,9-Trioxaundeca-1,11-diyl)oxy-26,28-dihydroxy-5,11,17,23-tetra-*tert*-butyl-calix[4]arene (12b). Yield: 35%, eluent: hexane/EtOAc=7:3, mp 224–226 °C (lit.[23] mp 246–248 °C). The ^{1}H NMR data are identical to those reported in Ref. 23.

4.7. 1,1′-Binaphthocrowns

4.7.1. (±)-1,1′-Bi-2-naphtho(17-crown-5) (13a). Yield: 36%, eluent: hexane/EtOAc=3:7, mp 103–105 °C (lit.[24] mp 114–115 °C); ^{1}H NMR: δ 7.92 (d, 2H, J=9 Hz, Ar*H*), 7.84 (d, 2H, J=8 Hz, Ar*H*), 7.47 (d, 2H, J=8.5 Hz, Ar*H*), 7.30 (t, 2H, J=7 Hz, Ar*H*), 7.19 (t, 2H, J=8 Hz, Ar*H*), 7.11 (d, 2H, J=8.5 Hz, Ar*H*), 4.25 (m, 2H, CH_2), 3.99 (m, 2H, CH_2), 3.65 (m, 2H, CH_2), 3.57–3.36 (m, 10H, CH_2); FAB-MS; m/z (%): 467.0 (M+Na)$^+$ (82) (Calcd 467.2). Anal. Calcd for $C_{28}H_{28}O_5$ (444.52): C, 75.66; H, 6.35, found: C, 75.23; H, 6.40%.

4.7.2. (±)-Bis(1,1′-bi-2-naphtho-28-crown-8) (13b). Yield: 21%, eluent: hexane/EtOAc=1:1, mp 119–122 °C; ^{1}H NMR: δ 7.93 (d, 4H, J=8.5 Hz, Ar*H*), 7.85 (d, 4H, J=8 Hz, Ar*H*), 7.49 (d, 4H, J=8.5 Hz, Ar*H*), 7.32–7.05 (m, 12H, Ar*H*), 4.11 (m, 4H, CH_2), 4.03 (m, 4H, CH_2), 3.50–3.34 (m, 8H, CH_2), 3.16 (m, 8H, CH_2); FAB-MS m/z (%): 822.9 (17) (M+Na)$^+$ (Calcd 823.3). Anal. Calcd for

$C_{52}H_{48}O_8$ (800.94): C, 77.98; H, 6.04, found: C, 78.44; H, 6.00%.

4.7.3. (*S*)-Bis(1,1′-bi-2-naphtho-28-crown-8) ((*S*)-13b). Yield: 56%; eluent: hexane/EtOAc=1:1, $[\alpha]_D^{20}=-119$ (c=1, $CHCl_3$).

4.7.4. (±)-Bis(1,1′-bi-2-naphtho-34-crown-10) (13c). Yellow oil (27%), eluent: hexane/EtOAc=3:7; ^{1}H NMR: δ 7.91 (d, 4H, J=9 Hz, Ar*H*), 7.83 (d, 4H, J=8 Hz, Ar*H*), 7.43 (d, 4H, J=9 Hz, Ar*H*), 7.30 (t, 4H, J=7 Hz, Ar*H*), 7.19 (t, 4H, J=8 Hz, Ar*H*), 7.13 (d, 4H, J=8.5 Hz, Ar*H*), 4.12 (m, 4H, CH_2), 4.02 (m, 4H, CH_2), 3.51 (m, 4H, CH_2), 3.42 (m, 4H, CH_2), 3.28–3.16 (m, 16H, CH_2); FAB-MS m/z (%): 927.3 $(M+K)^+$ (15) (Calcd 927.3). Anal. Calcd for $C_{56}H_{56}O_{10}$ (889.05): C, 75.66; H, 6.35, found: C, 75.19; H, 6.40%.

4.8. General procedure for the synthesis of (aza)crowns

The mixture of di-chloroethers **8a**,**b**, **9b** or **10a**-**c** (0.5 mmol), $TsNH_2$ (0.085 g, 0.5 mmol), K_2CO_3 (0.35 g, 2.5 mmol) in DMF (20 ml) was stirred at 100 °C for 48 h. The solvent was then evaporated, the residue was extracted with CH_2Cl_2 (30 ml), washed with dilute aq. HCl, water and dried. The crude products were separated by column chromatography on silica to afford white solids (except for **15b**,**c**).

4.9. Calix[4](aza)crowns

4.9.1. 25,27-(3,9-Dioxa-6-*N*-tosylazaundeca-1,11-diyl)-oxy-26,28-dihydroxy-5,11,17,23-tetra-*tert*-butyl-calix[4]-arene (14a). Yield: 31%, mp 127–129 °C (triturated with MeOH); ^{1}H NMR: δ 7.70 (d, 2H, J=13 Hz, Ar*H*), 7.32 (s, 2H, O*H*), 7.25 (d, 2H, J=13 Hz, Ar*H*), 7.03 (s, 4H, Ar*H*), 6.78 (s, 4H, Ar*H*), 4.29 and 3.27 (d+d, 4+4H, J=21.5 Hz, ArCH_2Ar), 3.99 (m, 12H, CH_2), 3.44 (t, 4H, J=10.5 Hz, CH_2), 2.37 (s, 3H, CH_3), 1.28 (s, 18H, C(CH_3)$_3$), 0.94 (s, 18H, C(CH_3)$_3$). Anal. Calcd for $C_{59}H_{77}NO_8S$ (960.32): C, 73.79; H, 8.08, found: C, 73.21; H, 8.0.2%.

4.9.2. 25,27-(3,6,12,15-Tetraoxa-9-*N*-tosylazaheptadeca-1,17-diyl)oxy-26,28-dihydroxy-5,11,17,23-tetra-*tert*-butyl-calix[4]arene (14b). Yield: 20% (eluent: hexane/EtOAc=6:4), mp 173–176 °C; ^{1}H NMR: δ 7.64 (d, 2H, J=7 Hz, Ar*H*), 7.25 (d, 2H, J=7 Hz, Ar*H*), 7.14 (s, 2H, O*H*), 7.02 (s, 4H, Ar*H*), 6.74 (s, 4H, Ar*H*), 4.36 and 3.26 (d+d, 4+4H, J=12.5 Hz, ArCH_2Ar), 4.12 (m, 4H, CH_2), 3.92 (m, 8H, CH_2), 3.68 (m, 8H, CH_2), 3.19 (m, 4H, CH_2), 2.40 (s, 3H, CH_3), 1.26 (s, 18H, C(CH_3)$_3$), 0.92 (s, 18H, C(CH_3)$_3$). Anal. Calcd for $C_{63}H_{85}NO_{10}S$ (1048.42): C, 72.17; H, 8.17, found: C, 71.73; H, 8.11%.

4.9.3. 25,27-(3,9,12-Trioxa-6-*N*-tosylazatetradeca-1,14-diyl)oxy-26,28-dihydroxy-5,11,17,23-tetra-*tert*-butyl-calix[4]arene (14c). Yield: 36% (eluent: hexane/EtOAc=7:3), mp 76–79 °C; ^{1}H NMR: δ 7.70 (d, 2H, J=8 Hz, Ar*H*), 7.24 (d, 2H, J=6 Hz, Ar*H*), 7.15 (s, 2H, O*H*), 7.05 (s, 4H, Ar*H*), 6.75 (d, 4H, J=2 Hz, Ar*H*), 4.32 (dd, 4H, J=12.5, 5 Hz, ArCH_2Ar), 4.06 (m, 4H, CH_2), 4.01 (m, 2H, CH_2), 3.88 (m, 6H, CH_2), 3.72 (t, 2H, J=5 Hz, CH_2), 3.68 (t, 2H, J=4.5 Hz, CH_2), 3.54 (t, 2H, J=6 Hz, CH_2), 3.49 (t, 2H, J=5 Hz, CH_2), 3.27 and 3.25 (d+d, 2+2H, J=13 Hz, ArCH_2Ar), 2.38 (s, 3H, CH_3), 1.29 (s, 18H, C(CH_3)$_3$), 0.92 (s, 18H, C(CH_3)$_3$); ^{13}C NMR: δ 150.9, 150.1, 150.0, 147.1, 143.2, 141.5, 137.3, 132.8, 132.7, 129.7, 128.0, 127.9, 127.4, 127.3, 125.7, 125.2 (Ar*C*), 76.2, 75.8, 71.3, 71.2, 70.9, 70.6, 70.0, 49.1, 49.0 (*C*H$_2$), 34.1, 34,0 (*C*CH$_3$), 31.9, 31.2 (C*C*H$_3$), 31.7, 31.6 (Ar*C*H$_2$Ar), 21.6 (*C*H$_3$); FAB-MS m/z (%): 1026.5 $(M+Na)^+$ (100) (Calcd 1026.5). Anal. Calcd for $C_{61}H_{81}NO_9S$ (1004.37): C, 72.95; H, 8.13, found: C, 73.24; H, 8.15%.

4.10. 1,1′-Binaphtho(aza)crowns

4.10.1. (±)-*O*,*O*′-(3,9-Dioxa-6-*N*-tosylazaundeca-1,11-diyl)-1,1′-bi-2-naphthol (15a). Yield: 70% (eluent: toluene/MeOH=97:3), mp 71–74 °C; ^{1}H NMR: δ 7.92 (d, 2H, J=9 Hz, Ar*H*), 7.84 (d, 2H, J=8 Hz, Ar*H*), 7.62 (d, 2H, J=8 Hz, Ar*H*), 7.44 (d, 2H, J=9 Hz, Ar*H*), 7.30 (t, 2H, J=7.5 Hz, Ar*H*), 7.24 (d, 2H, J=8.5 Hz, Ar*H*), 7.19 (t, 2H, J=7.5 Hz, Ar*H*), 7.10 (d, 2H, J=8.5 Hz, Ar*H*), 4.22 (m, 2H, CH_2), 3.93 (m, 2H, CH_2), 3.55 (m, 2H, CH_2), 3.46–3.36 (m, 6H, CH_2), 3.24–3.09 (m, 4H, CH_2), 2.40 (s, 3H, CH_3); FAB-MS m/z (%): 597.3 (M(+ (9) (Calcd 597.2). Anal. Calcd for $C_{35}H_{35}NO_6S$ (597.72): C, 70.33; H, 5.90, found: C, 69.89; H, 5.94%.

4.10.2. (±)-*O*,*O*′-(3,6,12,15-Tetraoxa-9-*N*-tosylazaheptadeca-1,17-diyl)-1,1′-bi-2-naphthol (15b). Yellow oil (51%), eluent: hexane/ EtOAc=3:7); ^{1}H NMR: δ 7.92 (d, 2H, J=9 Hz, Ar*H*), 7.84 (d, 2H, J=8 Hz, Ar*H*), 7.69 (d, 2H, J=8 Hz, Ar*H*), 7.43 (d, 2H, J=8.5 Hz, Ar*H*), 7.32–7.26 (m, 4H, Ar*H*), 7.18 (t, 2H, J=7.5 Hz, Ar*H*), 7.13 (d, 2H, J=8.5 Hz, Ar*H*), 4.15 (m, 2H, CH_2), 4.01 (m, 2H, CH_2), 3.64–3.54 (m, 6H, CH_2), 3.42–3.28 (m, 14H, CH_2), 2.41 (s, 3H, CH_3); FAB-MS m/z (%): 724.3 $(M+K)^+$ (35) (Calcd 724.2). Anal. Calcd for $C_{39}H_{43}NO_8S$ (685.83): C, 68.30; H, 6.32, found: C, 68.42; H, 6.28%.

4.11. (±)-*O*,*O*′-(3,9-Dioxa-6-*N*-tosylazaundeca-1,11-diyl)-1,1′-bi-2-naphthol (15c)

Yellow oil (37%), eluent: toluene/MeOH=95:5; ^{1}H NMR: δ 7.91 (t, 2H, J=8.5 Hz, Ar*H*), 7.84 (t, 2H, J=9 Hz, Ar*H*), 7.64 (d, 2H, J=8 Hz, Ar*H*), 7.43 (d, 2H, J=9 Hz, Ar*H*), 7.33–7.12 (m, 8H, Ar*H*), 4.16 (m, 2H, CH_2), 3.95 (m, 2H, CH_2), 3.66–3.16 (m, 16H, CH_2), 2.41 (s, 3H, CH_3); ^{13}C NMR: δ 154.6, 143.3, 136.8, 134.3, 129.8, 129.7, 129.6, 129.5, 129.4, 128.1, 128.0, 127.4, 126.4, 125.6, 125.5, 123.9, 123.8, 121.0, 116.6, 116.4, 116.2 (Ar*C*), 71.0, 70.9, 70.8, 70.4, 70.3, 70.1, 69.8, 49.5, 49.4 (*C*H$_2$), 21.7 (*C*H$_3$); FAB-MS m/z (%): 664.2 $(M+Na)^+$ (59) (Calcd 664.2). Anal. Calcd for $C_{37}H_{39}NO_7S$ (641.77): C, 69.25; H, 6.13, found: C, 69.61; H, 6.07%.

4.12. (*S*)-*O*,*O*′-(3,9-Dioxa-6-*N*-tosylazaundeca-1,11-diyl)-1,1′-bi-2-naphthol (*S*)-15c

Yellow oil (44%), eluent: toluene/MeOH=95:5; $[\alpha]_D^{20}=-94.7$ (c=1, $CHCl_3$).

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Supporting the NMR-based empirical rules to determine the stereochemistry and halogen regiochemistry of vicinal vinyl dihalides. Naturally occurring monoterpenes as chemical models

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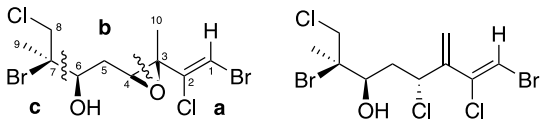
Abstract—Two novel monoterpenes, **1** and **2**, containing an unusual 1,2-bromochloro vinylic portion, were analyzed to study the influence of γ-substituents on the C-1 and H-1 chemical shifts of the 1,2-dihalo vinylic residue. This study reinforces the validity of the empirical rules based on ^{13}C and ^{1}H NMR spectroscopy as a helpful tool for determining the regio- and stereochemistry of substituted vicinal vinyl dihalides. Published by Elsevier Ltd.

1. Introduction

Plocamium cartilagineum (L.) Dixon (Plocamiaceae, order Plocamiales) is characterized by its interesting secondary metabolites, being a rich source of diverse polyhalogenated[1,2] and polyhaloxygenated[3–5] monoterpenes, some of which exhibit an interesting and uncommon vicinal vinyl dihalide functionality.[6]

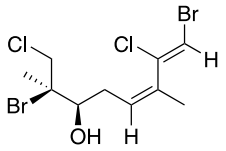
The isolation of prefuroplocamioid **3** has allowed us to establish empirical rules based on ^{13}C NMR and ^{1}H NMR chemical shifts to determine the regiochemistry and geometry of the rare 1,2-bromochloro vinyl system supported by the spectroscopic data of a few examples available at that time.[7] To analyze new model compounds to reinforce these rules, and considering that compounds with this functionality are either infrequently reported in the literature or their ^{1}H NMR and ^{13}C NMR data are incomplete or unassigned, we decided to reexamine *P. cartilagineum* for γ-functionalized 1,2-vinyl dihalides metabolites, our aim being to enhance with new examples the scope of the substituent effects on the chemical shift of C-1 and H-1, the key feature of the method.

In the present work, we report on the chemical and stereochemical characterization of two minor linear dihalo-vinyl monoterpenes, **1** and **2**, isolated from *P. cartilagineum*. Both compounds are structurally related to prefuroplocamioid **3**, featuring novel functionalizations in γ-position.



1

2



3 prefuroplocamioid

2. Results and discussion

Plocamium cartilagineum (L.) Dixon (Plocamiaceae, order Plocamiales) was collected at El Quisco (Chile). From the crude extract, after flash chromatography and successive gel filtration and HPLC, compounds **1** and **2** were isolated.

Compound **1** was obtained as a colourless oil. The EIMS spectrum showed peaks at *m/z* 377/379/381/383 $[M-OH]^+$ with relative intensities indicating the presence of two bromine and two chlorine atoms that correspond to the empirical formula $C_{10}H_{13}{}^{79}Br_2{}^{37}Cl_2O$ $[M-OH]^+$ (HREIMS). Absorbance for a hydroxyl group was observed at 3449 cm^{-1} in the IR spectrum. The ^{13}C NMR spectrum of

Keywords: *Plocamium cartilagineum*; Olefinic proton; Monoterpenes.
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Table 1. ^{1}H and ^{13}C NMR data of compounds **1**-**3** [500 MHz, δ ppm, (J) Hz, $CDCl_3$]

#	**1**			**2**			Prefuroplocamioid (**3**)	
	δ_H	δ_C	HMBC	δ_H[a]	δ_C[a]	HMBC	δ_H[a]	δ_C[a]
1	6.74 s	105.5	C-2, C-3	6.82 s	107.5	C-2, C-3	6.63 s	105.4
2		149.8			137.0			140.3
3		61.3			146.4			132.7
4	3.22 dd (4.7, 7.4)	63.6	C-5	4.88 dd (3.2, 7,7)	68.1	C-3, C-6	6.25 t (7.0)	128.8
5	1.84 m 2.04 m	32.6	C-3, C-4	1.88 m	38.0	C-6	2.44 m	32.7
6	3.86 d (9.7)	72.4	C-4	3.91 dd (2.7, 9.6)	70.2	C-8	2.66 t (7.0)	72.4
7		73.3			73.8			73.3
8	3.80 d (10.9) 4.28 d (10.9)	50.7	C-6, –C-9	3.79 d (10.8) 4.25 d (10.8)	51.1	C-6, C-7	3.77 d (10.7) 4.27 d (10.7)	51.1
9	1.81 s	25.7	C-6, C-8	1.76 s	25.8	C-6, C-7, C-8	1.82 s	26.1
10	1.56 s	15.9	C-2, C-3	5.60 s 5.66 s	117.4	C-2, C-3, C-4	1.88 s	14.9

[a] Spectra taken at $T=-20$ °C.

1 (Table 1), together with the information from a DEPT spectrum, showed the presence of 10 carbon signals assigned to $2CH_3$, $2CH_2$, 3CH (one olefinic and two geminal to a heteroatom), and three quaternary carbons (one olefinic).

The ^{1}H NMR showed a singlet at δ 6.74 attributable to an olefinic proton. A methylene and two methine groups, all bearing a heteroatom, appeared at δ 4.28 (d, J=10.9 Hz), δ 3.80 (d, J=10.9 Hz); and at δ 3.86 (d, J=9.7 Hz) and δ 3.22 (dd, J=4.7, 7.4 Hz), respectively. Additional signals for methylene multiplets at δ 2.04 m and 1.84 m, as well as two upfield singlets at δ 1.81 and 1.56, that correspond to methyl groups geminal to halogen and oxygen, respectively, complete all the protons of **1**.

From the comparison of the ^{1}H and ^{13}C NMR data of **1** with those of prefuroplocamioid **3**, it was observed that these compounds possess identical C-1–C-2 and C-5–C-9 fragments, as can be seen by the similarities of both the protons and carbons NMR signals (Table 1). The ^{1}H NMR showed significant differences in the chemical shifts of H-4 (**1**: $\delta_{H\text{-}4}$ 3.22, dd, J=4.7, 7.4 Hz; **3**: $\delta_{H\text{-}4}$ 6.25, t, J=7.0 Hz) as well as for Me-10, whose chemical shift at δ 1.56 indicates that an oxygen is joined to C-3. The chemical shifts observed at $\delta_{C\text{-}3}$ 61.3 and $\delta_{C\text{-}4}$ 63.6 for **1** suggested that the double bond C-3–C-4 in prefuroplocamoid **3** was epoxydated. This along with the olefinic unsaturation is in agreement with the two degrees of unsaturation required by the molecular formula. The chemical shift of C-3 and C-4 are in good agreement with those found for other epoxymonoterpenes isolated from *P. cartilagineum*.[8,9]

The ^{1}H–^{1}H COSY spectrum allowed us to confirm the connectivities of the H-4–H_2-5–H-6 fragment **b**. The correlations observed in the HMBC experiment of both H-1 and H_3-10 with C-2 and C-3 established the presence of fragment **a**. The C-3/C-4 linkage of fragments **a** and **b** was secured by correlation of H_2-5 with C-3 and C-4. The remaining fragment **c** was confirmed and connected to fragment **b** through the C-6/C-7 bond by the correlations between H_2-8 with C-6 and C-9, and H_3-9 with C-6 and C-8.

The relative stereochemistry of the chiral centers and the geometry of the double bond were determined by a combination of molecular mechanics calculations, a study of the coupling constants, and 2D NOESY experiments. A NOE effect was observed between H-6 with H_3-9 and H-4, suggesting the relative stereochemistry 3*S, 4*R and 6*R for **1**. Also, clear NOE effects were observed between H-1 with H-4 and H_3-10 establishing a Z stereochemistry for the double bond, as shown in Figure 1. Molecular mechanics calculations were performed in order to evaluate a minimized structure compatible with the observed coupling constants of the oxygen-bearing methines with the adjacent methylene and also the observed NOEs, especially that of the vinyl proton. The minimized structure **1**, as represented in Figure 1, shows H-bond interaction of the hydroxylic proton with the oxygen of the oxirane ring and the comparison of the well-resolved J-coupling of methine protons with the theoretical coupling constants [H-4 (J=6.7, 8.9 Hz) and H-6 (J=1.3, 11.2 Hz)] given by the program[10] proved to be in good agreement with the J experimental values of the respective protons given in Table 1. Thus, the structure and stereochemistry of **1** have been characterized as depicted in Figure 1.

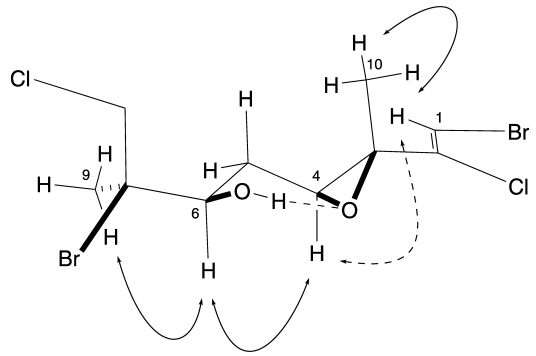


Figure 1. Selected NOEs of compound **1**.

Compound **2** was isolated as a colourless oil and was handled at −20 °C due to its instability at room temperature. The EIMS spectrum showed peaks at m/z 377/379/381/383 $[M-Cl]^+$, whose relative intensities are suggestive of the presence of two chlorine and two bromine atoms, and correspond to the empirical formula $C_{10}H_{13}{}^{81}Br^{79}Br^{37}Cl^{35}ClO$ (HREIMS). An absorbance for a hydroxyl group was observed at 3419 cm^{-1} in the IR spectrum.

Comparison of the ^{1}H and ^{13}C NMR data of compound **2** with those of compound **1** and prefuroplocamioid **3** clearly indicated that all of them have identical C-1–C-2

and C-5–C-9 fragments (Table 1). Significant differences affect fragment C-3–C-4 of compound **2**. Signals observed in their ^{1}H and ^{13}C NMR spectra for a methylene ($\delta_{H\text{-}10}$ 5.60 s, $\delta_{H\text{-}10}$ 5.66 s; $\delta_{C\text{-}10}$ 117.4 and $\delta_{C\text{-}3}$ 146.4) suggest the migration of the double bond C-3–C-4 of prefuroplocamioid **3** to an olefinic methylene C-3–C-10 in compound **2**. On the other hand, ^{1}H NMR and ^{13}C NMR chemical shifts ($\delta_{H\text{-}4}$ 4.88, dd, J=3.2, 7.7 Hz; $\delta_{C\text{-}4}$ 68.1) suggested a C-4 methine bearing chlorine.

^{1}H–^{1}H COSY, HMQC and HMBC experiments were used to confirm the fragments **a**-**c** and establish the connectivities between them.

2D NOESY experiments allowed us to determine the relative stereochemistry of the C-4 and C-6 chiral centers. The NOE effects observed between H-6 with H-4 and H_3-9, and between H-1 with H-4 suggest a relative configuration of 4*R, 6*R for compound **2** and also a Z stereochemistry for the olefin (Fig. 2).

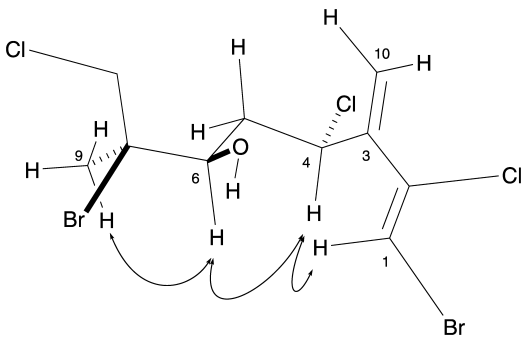
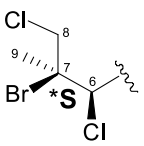
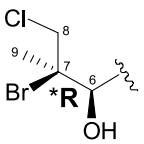


Figure 2. Selected NOEs of compound **2**.

The relative configuration for the quaternary chiral center C-7 of both compounds, **1** and **2**, was established on the basis of the similarities of the ^{13}C NMR chemical shifts of the C-9 methyl group at C-7 (**1**: $\delta_{C\text{-}9}$ 25.7; **2**: $\delta_{C\text{-}9}$ 25.8) compared with the data reported for Me-9: δ_C~25.3 in a series of related monoterpenes whose stereochemistries were determined by X-ray crystallography. As shown in Table 2, the spatial distribution of the substituents joined to C-7 of compounds **1** and **2** and compounds **I**-**IV** must be the same. Thus, establishing priorities around that chiral center, we propose a relative stereochemistry of 7*R. On the basis of the above arguments, the relative stereochemistry of C-7 of the previously described plocamenols A–C,[3] prefuroplocamioid[7] and compounds **V**-**VII**[4] should be revised from 7*S to 7*R.

To confirm the regiochemistry and geometry of the C-1/C-2 double bond we applied the empirical method[7] that permitted us to distinguish a (*Z*)-1,2-bromohalo ($\delta_{C\text{-}1}$~106, $\delta_{H\text{-}1}$~6.74 ppm) from an (*E*)-1,2-bromohalo vinyl system ($\delta_{C\text{-}1}$~101, $\delta_{H\text{-}1}$~6.20 ppm), irrespective of the β-halogen. The H-1 and C-1 chemical shifts of **1** and **2**, Table 1, are concordant with the values proposed by the empirical rule for a *Z* stereochemistry. It may be observed that the effect of the γ-substituents have no significant influence on the chemical shifts of H-1 and C-1 of both compounds. This observation together with the fact that the stereochemistry of the vinyl moiety of these two compounds was supported by NOESY experiments, strongly reinforced the empirical rules, providing a helpful tool for determining the regio- and stereochemistry of substituted vicinal vinyl dihalides, regardless of the substituents at C-3.

Table 2. ^{13}C NMR Chemical shifts for C-9 of 7,8-dihalosubstituted monoterpenes [δ ppm, $CDCl_3$]

Relative configuration	Compound[Ref]	$\delta_{C\text{-}9}$
	**I**[8,9]	25.1[a]
	II[8]	25.0
	III[8]	25.3
	IV[8]	25.1
	Plocamenol A[3]	25.9
	Plocamenol C[3]	25.8
	Prefuroplocamioid[7]	26.1
	V[4]	26.1
	VI[4]	25.7
	VII[4]	25.7

[a] CCl_4.

3. Experimental

3.1. General procedures

Optical rotations were measured on a Perkin–Elmer model 343 Plus polarimeter using a Na lamp at 25 °C. IR spectra were obtained with a Perkin–Elmer 1650/FTIR spectrometer. EIMS and HRMS spectra were taken on a Micromass Autospec spectrometer. ^{1}H NMR and ^{13}C NMR, HMQC, HMBC and COSY spectra were measured employing a Bruker AMX 500 instrument operating at 500 MHz for ^{1}H NMR and at 125 MHz for ^{13}C NMR. Two-dimensional NMR spectra were obtained with the standard Bruker software. HPLC separations were performed with a Hewlett–Packard 1050 (Jaigel-sil semipreparative column 10 μ 20×250 mm) with hexane–EtOAc mixtures. The gel filtration column (Sephadex LH-20) used hexane–MeOH–CH_2Cl_2 (3:1:1) as solvent. Merck Si gels 7734 and 7729 were used in column chromatography. The spray reagent for TLC was H_2SO_4–H_2O–AcOH (1:4:20).

3.2. Plant material

Plocamium cartilagineum was collected off by SCUBA diving at El Quisco, V Region of Chile.

3.3. Extraction and isolation. Air-dried *P. cartilagineum* (327.0 g, dry wt) was extracted with ethyl acetate at room temperature to obtain, after vacuum evaporation, a dark residue (18.8 g). The fraction eluted by flash chromatography on Si gel with hexane–EtOAc (96:4) (669.1 mg) was further separated by gel filtration chromatography to give a fraction (28.8 mg) which was purified by HPLC (Jaigel-sil column 20×250 mm, flow 4 ml/min, hexane–EtOAc (90:10)) to give compound **1** (1.6 mg). Compound **2** (9.0 mg) was obtained after gel filtration chromatography of the fraction eluted with hexane–EtOAc (75:25) by flash chromatography.

3.3.1. Compound 1. Colourless oil; $[\alpha]_D^{25}$=+80 (*c* 0.01,

$CHCl_3$); IR (film) ν_{max} 3449, 2923, 1382, 1074, 1046 cm^{-1}; ^1H and ^{13}C NMR, see Table 1; EIMS *m/z* 377/379/381/383 $[M-OH]^+$ (3, 9, 9, 3), 183/185/187 $[C_4H_5BrClO]^+$ (16, 43, 27), 129/131 (100, 30); HREIMS $[M-OH]^+$ 380.8593 (calcd for $C_{10}H_{13}{}^{79}Br_2{}^{37}Cl_2O$, 380.8651).

3.3.2. Compound 2. Unstable colourless oil; $[\alpha]_D^{25}=+12$ (*c* 0.57, $CHCl_3$); IR (film) ν_{max} 3419, 2969, 1381, 1047 cm^{-1}; ^1H and ^{13}C NMR, see Table 1; EIMS *m/z* 377/379/381/383 $[M-Cl]^+$ (<1, 4, 9, 7), 183/185/187 $[C_4H_5BrClO]^+$ (16, 43, 27); $[M-Cl]^+$ 380.8439 (calcd for $C_{10}H_{13}{}^{81}Br^{79}Br^{37}Cl^{35}ClO$, 380.8474).

Acknowledgements

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A DFT study of the Huisgen 1,3-dipolar cycloaddition between hindered thiocarbonyl ylides and tetracyanoethylene

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Abstract—The mechanism for the 1,3-dipolar cycloaddition between the hindered thiocarbonyl ylide **1** and tetracyanoethylene **2** has been studied at the B3LYP/6-31G* level. Formation of the [3+2] cycloadduct **4** takes place through a stepwise mechanism that is initiated by the nucleophilic attack of the thiocarbonyl ylide **1** to the ethylene derivative **2** to give a zwitterionic intermediate **IN**. The subsequent cyclization of **IN** yields a seven-membered cyclic ketene imine **6**, which equilibrates with the thermodynamically more stable [3+2] cycloadduct **4**. The computed free energies are in agreement with the experimental outcomes.

1. Introduction

Diels–Alder and 1,3-dipolar cycloadditions belong to the most important processes with both synthetic and mechanistic interest in organic chemistry.[1] The usefulness of these cycloaddition reactions arises from its versatility and from its remarkable stereochemistry.[2] By varying the nature of the reagents many different types of carbocyclic structures can be built up. Given the importance of these reactions, a strong effort has been directed toward the characterization of the reagents in these cycloadditions as well as the elucidation of its reaction mechanisms. However, the nature of the 1,3-dipolar cycloaddition mechanism is still an open problem in physical organic chemistry. For instance, the mechanism proposed firstly by Huisgen's group is that of a single-step, four-center cycloaddition, in which two new bonds are both partially formed in the transition state, although not necessarily to the same extent.[3] Thus, for nitrile oxide cycloadditions, experimental data were interpreted either as being consistent with a concerted mechanism[4] or in favor of a stepwise mechanism with diradical intermediates.[5] The high stereoselectivity (over 99.9%) observed in an experiment with diazomethane and methyltiglate excluded the presence of diradical intermediates.[6] On the other hand, Huisgen found a low solvent effects on the 1,3-dipolar cycloadditions.[7] These results were interpreted in terms of early transition structures associated to concerted mechanisms.

The 1,3-dipolar cycloadditions appear to be controlled by frontier molecular orbital (FMO) interactions.[8] In the case of an extremely large difference of the FMO energy of the cycloaddition partners, this model allows one to predict a mechanism via zwitterionic intermediates. For instance, Huisgen reported in 1986 the first experimental evidence for the two-step 1,3-dipolar cycloaddition between the thiocarbonyl ylide **1** and tetracyanoethylene (TCNE, **2**) to afford the thiolane **4** in 84% yield (45 °C, 8 h, THF) (see Scheme 1).[9] In presence of methanol a new product **8**, a spiro seven-membered lactim ether, appears besides **4** (40 °C, 6 h, MeOH/THF 1:99 (v/v), yield 97%, ratio **4**:**8** 34:66).[10] Formation of **8** was rationalized through the irreversible capture by methanol of the seven-membered cyclic ketene imine **6** (see Scheme 1).

Recent studies by these authors for related 1,3-dipolar cycloadditions[11] have shown that they are an example of a switching from a concerted to a two-step mechanism. Thus, the reaction between the thiocarbonyl ylide **1** and 2,3-bis(trifluoromethyl)fumaronitrile **3** affords the seven-membered cyclic ketene imine **7** in 71% yield (50 °C, 7.5 h, cyclohexane), which is stable but rearranged to the thiolane **5** at 60 °C (see Scheme 1).[11b] The large HOMO energy of the thiocarbonyl ylides and the low LUMO energy of these electron-deficient alkenes are responsible for the large zwitterionic participation in theses cycloadditions.[10] For the Huisgen's model the massive steric encumbrance of at least one terminus of the 1,3-dipole is an additional requirement for the occurrence of an intermediate in which only one bond connect the reactants. Even though the presence of significant steric hindrance effects at least at one end of the dipole is an additional requirement for the

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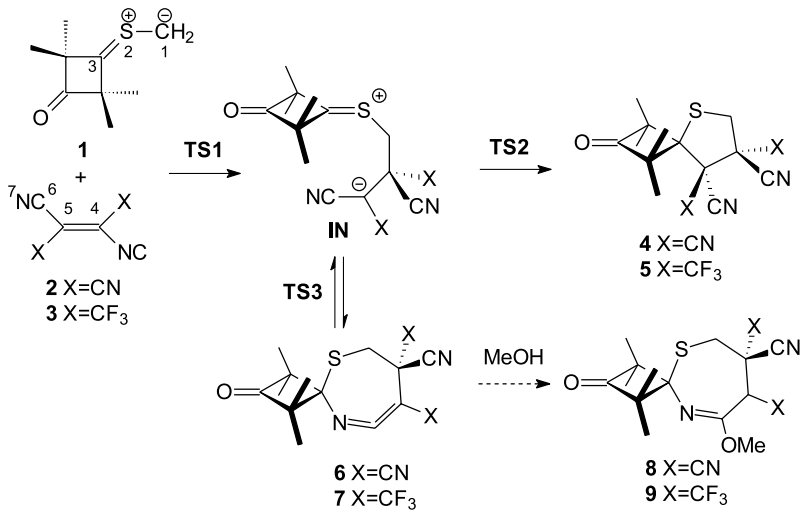


Scheme 1.

Huisgen's stepwise mechanisms, Fokin, Sharpless et al.[12] have recently reported the stepwise copper catalyzed 1,3-dipolar cycloaddition of non-hindered azides with terminal alkenes.

The concerted and biradical stepwise mechanisms for the 1,3-dipolar cycloadditions of thiocarbonyl ylides and thiocarbonyl compounds as dipolarophiles have been recently theoretically studied by Sustmann et al.[13] For the reaction between thiobenzophenone *S*-methylide and thiobenzophenone, the preferred reaction pathway corresponds to the two-step biradical one. The activation barrier for the formation of the biradical intermediate was estimated in 0.4 kcal/mol (UB3LYP/6-31G* calculations).[13a]

Our research program has long maintained an interest in the study of the molecular mechanism of polar cycloaddition reactions in order to provide their regio- and stereochemical outcome and to shed light on the mechanistic details of these important processes. In the present work, a density functional theory (DFT) study for the 1,3-dipolar cycloaddition between the hindered thiocarbonyl ylide **1** and TCNE (**2**) to give the thiolane **4** reported by R. Huisgen et al.[10] has been performed in order to confirm mechanistic details for these stepwise 1,3-dipolar cycloadditions (Scheme 1).

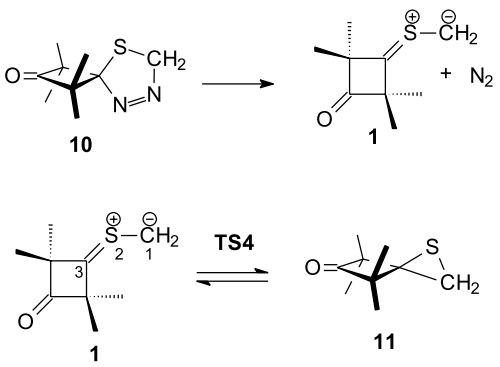
2. Computational methods

In recent years, theoretical methods based on the density functional theory[14] have emerged as an alternative to traditional ab initio methods in the study of structure and reactivity of chemical systems. Diels–Alder and 1,3-dipolar cycloaddition reactions have been the object of several DFT studies showing that functionals that include gradient corrections and hybrid functional, such as B3LYP,[15] together the standard 6-31G* basis set,[16] lead to potential energy barriers in good agreement with the experimental results.[17] Thus, in the present study geometrical optimizations of the stationary points were carried out using this methodology. The stationary points were characterized by frequency calculations in order to verify that minima and transition structures (TS) have zero and one imaginary frequency, respectively. The optimizations were carried out using the Berny analytical gradient optimization method.[18] The transition vectors (TV),[19] for example, the eigenvector associated to the unique negative eigenvalue of the force constants matrix, have been characterized. The electronic structures of stationary points were analyzed by the natural bond orbital (NBO) method.[20] All calculations were carried out with the Gaussian 98 suite of programs.[21]

The solvent effects have been considered by B3LYP/6-31G* single point calculations on the gas-phase stationary points using a relatively simple self-consistent reaction field[22] (SCRF) based on the polarizable continuum model (PCM) of the Tomasi's group.[23] The solvent used in the experimental work was tetrahydrofuran.[10] Therefore, we have used its dielectric constant at 298.0 K, ε=7.58.

The computed values of free energies were estimated by means of the B3LYP/6-31G* potential energy barriers including solvent effects, along with the zero-point energies and the thermal corrections to the free energies, which were evaluated at the experimental temperature of 318.15 K.[10] To calculate free energies at that temperature, the difference between the values at the temperature and 0 K was evaluated according standard thermodynamics.[24] A scaling factor[25] of 0.96 for the vibrational energies was used.

The global electrophilicity index ω,[26] which measures the stabilization in energy when the system acquires an additional electronic charge ΔN from the environment, has been given the following simple expression,[26] $\omega=\mu^2/2\eta$, in terms of the electronic chemical potential (and the chemical hardness η. Both quantities may be approached in terms of the one electron energies of the frontier molecular orbital HOMO and LUMO, ε_H and ε_L, as $\mu\approx(\varepsilon_H+\varepsilon_L)/2$ and $\eta\approx(\varepsilon_H-\varepsilon_L)$, respectively.[14a,27] Electrophilic and nucleophilic Fukui functions[28] condensed to atoms have been evaluated from single point calculations performed at the ground state of molecules at the same level of theory, using a method described elsewhere.[29] This method evaluates the Fukui functions using the coefficients of the frontier



Scheme 2.

molecular orbitals involved in the reaction and the overlap matrix.

3. Results and discussions

3.1. Structure and stability of the thiocarbonyl ylide 1

The thiocarbonyl ylide **1** was prepared in situ by the thermal extrusion of N_2 through the 1,3-dipolar cycloreversion of **10** (40 °C, THF) (see Scheme 2).[10] Huisgen et al. found that in absence of a dipolarophile, the thiocarbonyl ylide **1** undergoes an electrocyclization to the thiirane **11**. Therefore, previous to consider the reaction of **1** with TCNE, the thermodynamic and kinetic stability of **1** were studied. In Table 1 the relative energies of **1**, **11** and the TS associated to the electrocyclization process of **1**, **TS4**, are given, while the corresponding geometries are shown in Figure 1.

The activation energy associated to the electrocyclization process, via **TS4**, is 16.3 kcal/mol. This barrier is closer to that obtained by Sustmann et al. for the electrocyclization of the simplest thiocarbonyl ylide, 17.2 kcal/mol (B3LYP/6-31G*).[13b] The thiirane **11** is 45.3 kcal/mol lower in energy than the thiocarbonyl ylide **1**; the electrocyclization process being strongly exothermic. Inclusion of solvent effects and thermal corrections to the free energies does not modify these relative energies. These energetic results indicate that in absence of intercepting reagents the thiocarbonyl ylide **1** by heating undergoes electrocyclization furnishing the thiirane **11** (see Scheme 2).[10,11b]

At the thiocarbonyl ylide **1**, the C1–S2 and S2–C3 bond lengths are 1.651 and 1.640 Å, respectively, while the bond order[30] (BO) between these atoms are ca. 1.45. The natural population analysis (NPA) gives a larger negative charge at the methylene C1 carbon atom, 0.85 e, than at the disubstituted C3 one, 0.38 e. This dissymmetric charge distribution, together the larger nucleophilic Fukui function at the C1 atom (see later), makes the methylene group the most nucleophilic center of this ylide. The geometry of the thiocarbonyl ylide **1** shows the hindrance around the C3 carbon atom, dues to the presence of the four methyl substituents on the cyclobutanone ring (see **1** in Figure 1). At **TS4** the length of the C1–C3 forming-bond is 2.393 Å, while the BO between these atoms is 0.62. This distance at the TS associated to the electrocyclization of the simplest thiocarbonyl ylide is 2.371 Å.[13b]

Table 1. Total (*E*, in au) and relative[a] (Δ*E*, in kcal/mol) energies in vacuum and in tetrahydrofuran, and free (*G*, in au) and relative free[a] (Δ*G*, in kcal/mol) energies at 318.15 K for the reaction between the thiocarbonyl ylide **1** and TCNE (**2**)

	In vacuum		In THF			
1	*E*	Δ*E*	*E*	Δ*E*	*G*	Δ*G*
1	−824.692022		−824.694410		−824.538931	
TS4	−824.665969	16.3	−824.668604	16.2	−824.512352	16.7
11	−824.764256	−45.3	−824.767446	−45.8	−824.606509	−42.4
2	−447.518276		−447.524025		−447.517518	
TS1	−1272.219495	−5.8	−1272.231388	−8.1	−1272.045631	6.8
IN	−1272.242190	−20.0	−1272.258145	−24.9	−1272.069266	−8.0
TS2	−1272.231537	−13.3	−1272.248092	−18.6	−1272.057443	−0.6
4	−1272.293901	−52.5	−1272.300797	−51.7	−1272.102849	−29.1
TS3	−1272.239206	−18.1	−1272.252443	−21.3	−1272.059405	−1.9
6	−1272.274671	−40.4	−1272.284387	−41.4	−1272.088670	−20.2
8	−1388.055750	−82.2	−1388.065727	−81.3	−1387.817690	−42.9

[a] Relatives to **1**, **1**+**2** and **1**+**2**+methanol.

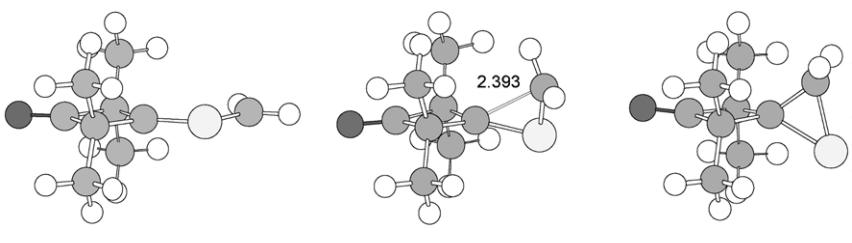


Figure 1. Geometries of the thiocarbonyl ylide **1**, the thiirane **11**, and the transition structure corresponding to the electrocyclization conversion of **1** in **11**, **TS4**. The bond lengths directly involved in the reaction are given in angstroms.

3.2. Study of the reaction between the thiocarbonyl ylide 1 and TCNE (2)

An analysis of the gas-phase results for the reaction between the thiocarbonyl ylide **1** and TCNE indicates that the 1,3-dipolar cycloaddition takes place by a stepwise process. Therefore, two TSs, **TS1** and **TS2**, a zwitterionic intermediate **IN**, and the corresponding [3+2] cycloadduct **4** were located and characterized. The different stationary points of this cycloaddition are depicted in Scheme 1 together with the atom numbering, while the geometries of the TSs and intermediate are presented in Figure 3. The energetic results are summarized in Table 1 and in Figure 2.

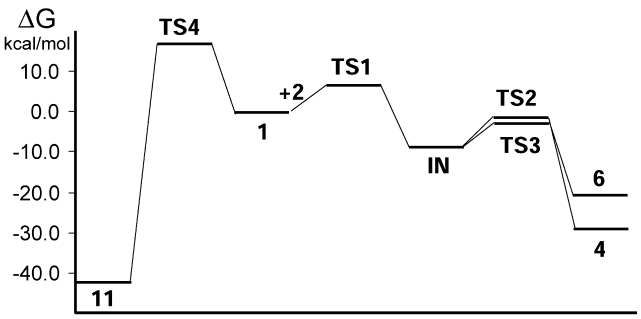


Figure 2. Free energy profile for the reaction of thiocarbonyl ylide **1** in absence and in presence of TCNE (**2**), in THF at 45 °C.

The first step is the nucleophilic attack of the electrophilically activated methylene of the thiocarbonyl ylide **1** to one of the two symmetrically substituted ethylene carbon atoms of TCNE to give the zwitterionic intermediate **IN** via **TS1**. The TS is located 5.8 kcal/mol below reactants. The TS associated to the birradical stepwise 1,3-dipolar cycloaddition between thiobenzophenone *S*-methylide and thiobenzophenone has been estimated to be 0.4 kcal/mol (UB3LYP/6-31G* calculations) above reactants.[13a] Inclusion of solvent effects and thermal corrections to the free energies brings the activation free energy associated to **TS1** to 6.8 kcal/mol. Formation of the zwitterionic intermediate **IN** is exergonic in 8.0 kcal/mol. The second step that yields the formation of the [3+2] cycloadduct **4** is the ring-closure process on this zwitterionic intermediate. The free activation energy for the intramolecular nucleophilic attack of the C5 carbon atom of the TCNE moiety to the hindered C3 carbon atom via **TS2** is 7.4 kcal/mol. Formation of the [3+2] cycloadduct **4** is exergonic in 29.1 kcal/mol.

In presence of methanol the adduct **8** appeared beside **4** by capture of the seven-membered cyclic ketene imine **6** (see Scheme 1).[10] **6** is formed through the electrophilic attack of the nitrile N7 nitrogen atom to the C3 carbon atom at the intermediate **IN**, via **TS3** (see Scheme 1). The free activation energy for this cyclization, 6.1 kcal/mol, is lower than that for the formation of the five-membered ring via **TS2**, because of the lesser hindrance for the electrophilic attack of the terminal N7 nitrogen atom than the attack of the C5 carbon atom of TCNE moiety in **IN**. The ketene imine **6** is ca. 12.2 kcal/mol lesser in free energy than **IN**. However, the [3+2] cycloadduct **4** is 8.9 kcal/mol more stable than the seven-membered cyclic ketene imine **6**. Therefore, by heating formation of **6** can be reversible, and formation of the more favorable [3+2] cycloadduct **4** takes place by thermodynamic control (see Fig. 2). Note that the activation free energy for the retrocyclization of **6**, 18.3 kcal/mol, is closer to that for the electrocyclization of **1**, 16.7 kcal/mol. On the other hand, in presence of methanol formation of the product **8** by capture of **6** can be irreversible. The difference of activation free energies for the formation of **4** and **6**, 1.3 kcal/mol, is in reasonable agreement with the ratio for the formation of the cycloadducts **4** and **8** in presence methanol (23:66).[10]

The geometries of the TSs and intermediate corresponding to the reaction between the thiocarbonyl ylide **1** and TCNE are given in Figure 3. The length of the C1–C4 forming-bond at **TS1** is 2.209 Å, while the distance between the C3 and C5 atoms is 3.825 Å. At the intermediate **IN** the C1–C4 bond length, 1.558 Å, indicates that these atoms are already bonded, while the distance between the C3 and C5 atoms remains to 3.847 Å. At **TS2** the distance between the C3 and C5 atoms is 3.486 Å. At **TS3** the distance between the N7 and C3 atoms is 2.520 Å, while this distance at **6** is 1.432 Å, indicating that these atoms are already bonded.

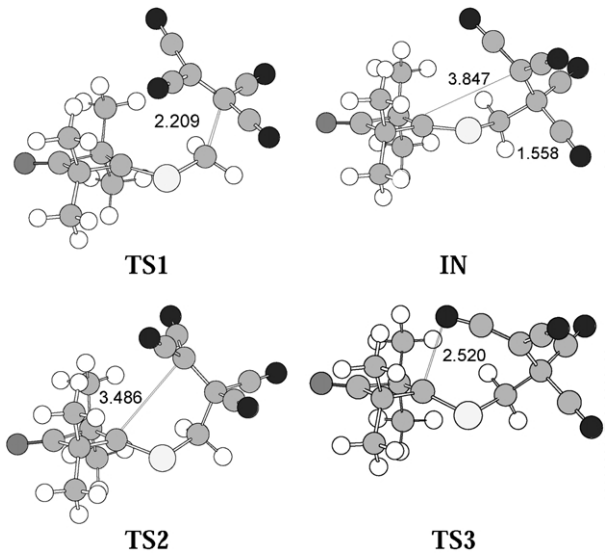


Figure 3. Geometries of the transition structures and intermediate involved in the stepwise 1,3-dipolar cycloaddition between the thiocarbonyl ylide **1** and TCNE (**2**). The bond lengths directly involved in the reaction are given in angstroms.

The C5–C6 and C6–N7 bond lengths at the ketene imine **6**, 1.320 and 1.214 Å, respectively, are closer to those found at the crystalline structure of a stable seven-membered cyclic ketene imine derived from the reaction between 1,1,3,3-tetramethylindan-2-thione *S*-methylide and **3**, 1.33 and 1.20 Å, respectively.[11b] The involvement of the allenic type bond system into a seven-membered ring creates strain. At the ketene imine **6** the C5=C6=N7 bond system is not linear but ratter bent to 160.5°; this value at the X-ray is 163.8°.[11b]

An analysis of the atomic motions along the unique imaginary vibrational frequency associated with **TS1** (217.8i cm^{-1}) indicates that it is mainly associated with the motion of the C1 and C4 carbon atoms along the C–C bond-formation process, the motion of the C3 and C5 atoms

is negligible. At **TS2** (18.7i cm^{-1}) this frequency is mainly associated to the C1–C4 bond rotation. However, the analysis of the corresponding TV shows the participation of the C3–C5 length associated to the C3–C5 bond-formation.[31]

The BO value of the C1–C5 forming-bond at **TS1** is 0.37, while this value between the C3 and C5 atoms is 0.0. At the intermediate **IN** the BO value of the C1–C4 bond is 0.95. While the BO value between the C1 and S2 atoms decreases along the nucleophilic attack, 1.45 (**1**) 1.22 (**TS1**) and 0.97 (**IN**), this value between the S2 and C3 atoms increases, 1.45 (**1**) 1.54 (**TS1**) and 1.57 (**IN**), as a consequence of the stabilization of the positive charge that is developing at C3 carbon atom by delocalization of the lone-pair of the S2 sulphur atom on the C3 carbon atom. The BO values between the C3 and C5 atoms at **TS2**, and the C3 and N7 atoms at **TS3**, which will be bonded, are 0.17 and 0.19, respectively. The BO values between C6 and N7 atoms at **IN**, **TS3** and **6**, 2.76, 2.56 and 2.06, respectively, indicate the evolution from the nitrile N≡C– triple bond at **IN** to –N=C– double bond at **6**.

Finally, the NPA allows us to evaluate the charge transfer (CT) along the 1,3-dipolar cycloaddition process. The B3LYP/6-31G* atomic charges at the TSs and intermediate were shared between the donor thiocarbonyl ylide **1** and the acceptor TCNE. Along this stepwise cycloaddition the charge transferred from the ylide **1** to TCNE is 0.50 e at **TS1**, 0.70 e at **IN**, and 0.71 e at **TS2**, indicating the large zwitterionic character of these species. The CT increases along this polar process to the formation of the intermediate **IN**. These results are in agreement with the Huisgen's proposal, being the hindrance to the ring-closure process via **TS2** responsible for the presence of **IN**.

The larger dipole moment of the TSs and the intermediate, 7.88 D (**TS1**), 10.14 D (**IN**), 10.35 D (**TS2**) and 9.08 D (**TS3**), than of the cycloadducts, 3.56 D (**3**) and 6.38 D (**6**), are in agreement with the large zwitterionic character of the former, and with the faster rearrangement of the ketene imine **7** to the thiolane **5** in acetonitrile than in cyclohexane.[11b,c]

3.3. Global and local electrophilicity/nucleophilicity analysis

This cycloaddition reaction has been also analyzed using the global and local indexes defined in the context of density functional theory.[32] Recent studies carried out on cycloaddition reactions with a polar character have shown that these indexes are powerful tools to study both reactivity,[31,33] and regioselectivity.[34] In Table 2 the static global properties, electronic chemical potential μ, chemical hardness η, and global electrophilicity ω, and the electrophilic and nucleophilic Fukui functions for the thiocarbonyl ylide **1** and TCNE (**2**) are presented.

The electronic chemical potential of TCNE, −0.2587 au, is lower than the electronic chemical potential of the thiocarbonyl ylide **1** (μ=−0.1168 au) thereby indicating that the net charge transfer will take place from **1** to TCNE in agreement with the NPA at **TS1**. The TCNE has a very large electrophilicity value, ω=5.95 eV, it being a strong electrophile within the ω scale.[33a,c] On the other hand, the electrophilicity value of the thiocarbonyl ylide **1** is 1.44 eV. The large difference in electrophilicity,[33a,c] $\Delta\omega$, for the TCNE (**2**)/thiocarbonyl ylide **1** pair, 4.51 eV, indicates that this cycloaddition will take place with a large CT, in clear agreement with the NPA performed at the TSs and intermediate.

Table 2. Global[a] and local properties of the thiocarbonyl ylide 1 and TCNE (2). *k* defines the site in the molecule where the property is being evaluated

	Global properties			Local properties		
	μ	η	ω	*k*	$f+$	$f-$
Ylide 1	−0.1168	0.1285	1.44	1	0.2770	0.4837
				2	0.2344	0.0309
				3	0.2023	0.3956
TCNE **2**	−0.2587	0.1529	5.95	4	0.2570	0.1770
				5	0.2570	0.1770

[a] Electronic chemical potential, μ, and chemical hardness, η, in atomic units; global electrophilicity, ω, in eV. See the text for definitions.

The thiocarbonyl ylide **1** has the largest value of f_k^- at the C1 position, 0.4837; in consequence, this is the more reactive site for a nucleophilic attack (see Table 2). The presence of the two electron-releasing alkyl groups at the C3 carbon atom polarizes the thiocarbonyl ylide framework through the C1 one. On the other hand, the symmetric TCNE (**2**) has the same nucleophilic activation at the C4 and C5 carbon atoms, f_k^+=0.2570. This symmetric distribution has been used recently to explain the synchronicity on the bond-formation process in polar Diels–Alder reactions involving symmetric reagents.[33d] However, the hindrance present at the C3 carbon atom of the thiocarbonyl ylide **1** prevents the synchronous bond formation, and therefore, this polar cycloaddition reaction takes place through the initial Michael-type addition of the thiocarbonyl ylide **1** to TCNE.

4. Conclusions

The mechanism for the 1,3-dipolar cycloaddition between the hindered thiocarbonyl ylide **1** and TCNE reported by R. Huisgen has been studied by using density functional theory at B3LYP/6-31G* level. In absence of TCNE, the thiocarbonyl ylide **1** by heating yields the thermodynamically more stable thiirane **11** through an electrocyclization process. In presence of TCNE formation of the [3+2] cycloadduct **3** takes place through a stepwise mechanism with a large polar character, which is initialized by the nucleophilic attack of the thiocarbonyl ylide **1** to the electrophilically activated TCNE to give a zwitterionic intermediate **IN**. The subsequent ring closure affords a seven-membered cyclic ketene imine **6**, which can be captured in presence of methanol. By heating **6** equilibrates with the thermodynamically more stable [3+2] cycloadduct **4**. The activation free energies associated to the cyclization reactions of **IN** to yield the cycloadducts **4** and **6** are in acceptable agreement with the formation of the thiolane **4** and the seven-membered lactim ether **8** in presence of methanol.

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Stereoselective synthesis of (−)-allosedamine and (1*R*,3*R*)-HPA-12 from β-*p*-toluenesulfonamido-γ,δ-unsaturated sulfoxide☆

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Abstract—A stereoselective synthesis of (−)-allosedamine and HPA-12 is disclosed. The key steps of the synthesis include the diastereoselective synthesis of a β-sulfonamido unsaturated sulfoxide, elaboration of a bromohydrin via intramolecular sulfinyl group participation and a ring-closing metathesis reaction for the construction of the piperidine ring of allosedamine.

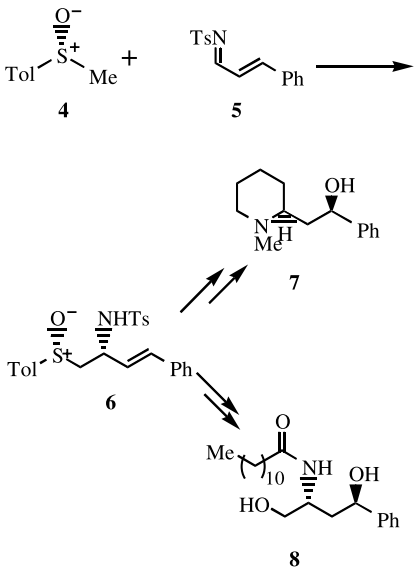
1. Introduction

1,3-Aminoalcohols are constituents of many synthetic[1] and natural products[2] possessing potent physiological activity. They are useful as ligands and as chiral auxiliaries in asymmetric synthesis.[3] We recently disclosed the preparation of protected β-amino γ,δ-unsaturated sulfoxides **2** and their regio- and stereoselective elaboration into 1,3-aminoalcohol derivatives **3**.[4] The unsaturated sulfoxides **2** were prepared from the Garner aldehyde **1** using a multistep sequence of straightforward reactions (Scheme 1). This study demonstrated the potential of the sulfinyl group as an intramolecular nucleophile to regio- and stereoselectively functionalize an olefin and the importance of the relative configurations of the sulfinyl group and the carbon bearing the amino substituent on the stereoselectivity of bromohydrin formation.

However, for protected β-amino γ,δ-unsaturated sulfoxides **2** to be useful synthons, it is important that they be accessible in one or two steps from readily available starting materials.

An attractive route to synthon **2** would be the direct addition of sulfoxide stabilized anions to *N*-substituted imines. The use of chiral sulfoxide stabilized carbanions for asymmetric C–C bond formation, via alkylation or addition to C=O and activated C=C bonds has been studied extensively.[5] However, the addition of sulfoxide stabilized carbanions to imines has received less attention.[6] Most of the literature reports are concerned with the addition of sulfoxide anions to imines derived from aromatic aldehydes[7] and to the best of our knowledge there is only one report on the addition of the carbanion derived from (*S*)-*tert*-butyl phenylmethyl-sulfoxide to imines derived from α,β-unsaturated aldehydes.[8]

We disclose herein the diastereoselective addition of the anion of methyl *p*-tolyl sulfoxide **4** with *N*-Ts imine **5**, derived from cinnamaldehyde, to yield the protected β-amino γ,δ-unsaturated sulfoxide **6** and its elaboration to (−)-allosedamine **7** and (1*R*,3*R*)-HPA-12, **8** (Eq. (1)).



(1)

☆ IICT Communication No. 040317.

Keywords: (−)-Allosedamine; (1*R*,3*R*)-HPA-12; Protected β-amino sulfoxide; Bromohydrin; Pummerer reaction; Ring-closing metathesis reaction.

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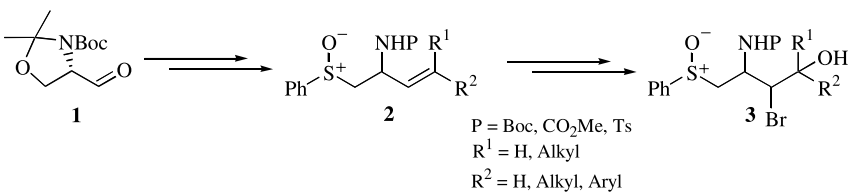
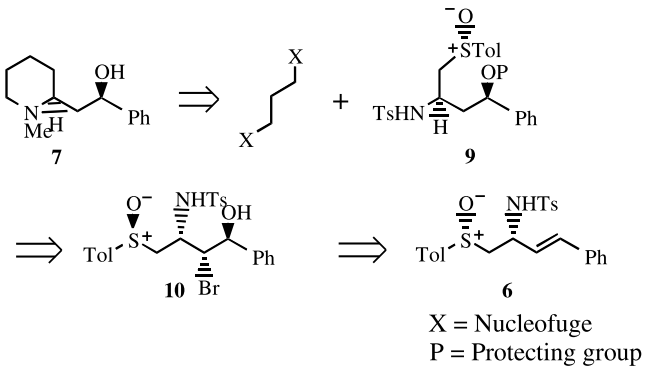


Scheme 1.



Scheme 2.

Table 1. Reaction of lithium anion of (*R*)-methyl *p*-tolyl sulfoxide **4** and imine **5**

Entry	T_1[a] (°C)	T_2[b] (°C)	Time (min)	Yield (%)	Ratio[c]	
					6s	**6a**
1	−30	−78	15	82	70	30
2	−78	−78	15	81	75	25
3	−78	−78	90	71	60	40
4	−30	−78–80	120	53	53	47
5	−42	−42	30	62	58	42

[a] Temperature at which lithium anion of (*R*)-methyl *p*-tolyl sulfoxide was generated.
[b] Temperature at which the reaction was carried out.
[c] Ratios were determined by ^{1}H NMR analysis of the crude reaction mixture.

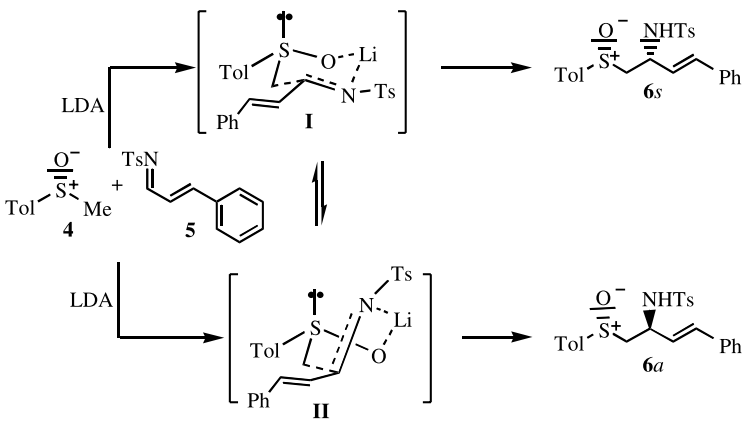
2. Results and discussion

2.1. Synthesis of (−)-allosedamine

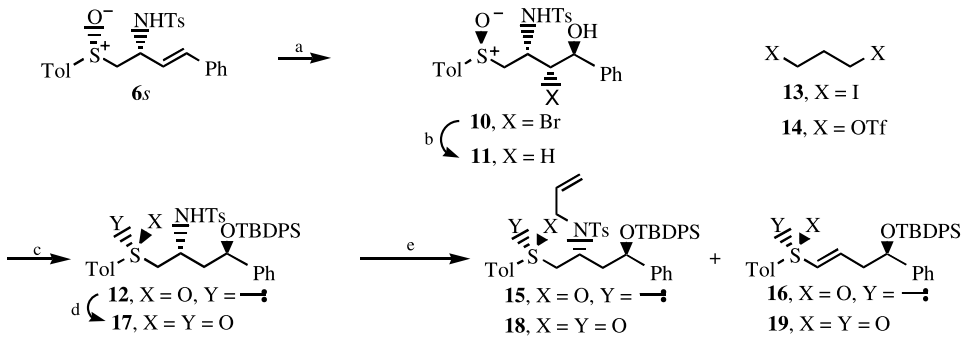
Allosedamine **7**, was isolated from *Lobelia inflata*,[9] the crude extract of which has been utilized for the treatment of asthma, bronchitis and pneumonia.[10] Though several routes to racemic allosedamine have been disclosed,[11] stereoselective asymmetric syntheses are few in number.[12,13] We describe herein a stereoselective synthesis of (−)-allosedamine taking advantage of the potential of the sulfinyl group as an intramolecular nucleophile to regio- and stereoselectively functionalize an olefin[4,14] (Scheme 2, retrosynthetic analysis). The piperidine ring of allosedamine was envisaged to be elaborated via dialkylation of the dianion derived from **9** using a suitable 1,3-dielectrophile.

The first step of the synthesis required the stereoselective preparation of the unsaturated sulfoxide **6**. Kagan and co-workers[6b] have pointed out the influence of temperature, both during anion generation from the chiral sulfoxide and addition of the anion with the imine, on the diastereoselectivity of β-amino sulfoxide formation. Thus anion generation from **4** and subsequent addition of the anion with the imine **5**[15] were conducted at different temperatures and the results are tabulated in Table 1. Not surprisingly, the best diastereoselectivity (ca. 3:1 of **6*s*/6*a***) was observed when the anion was generated at −78 °C and subsequently reacted with the imine at −78 °C over a period of 15 min (entry 2). The diastereoselectivity eroded when the reaction was allowed to proceed for longer periods of time at −78 °C (entry 3) or when the reaction was carried out at higher temperatures (entries 4 and 5). The temperature at which the anion was generated did not profoundly influence the diastereoselectivity (entry 1). The observed results can be rationalized by invoking intermediates **I** and **II** which are in equilibrium, higher temperatures favour more rapid equilibration to give the thermodynamic isomer **II** (Scheme 3).

The diastereomers **6*s*** and **6*a*** were readily separated by column chromatography and the structures assigned to them by comparison of their ^{1}H NMR data with that of related compounds previously synthesized by us.[4,16] The



Scheme 3.



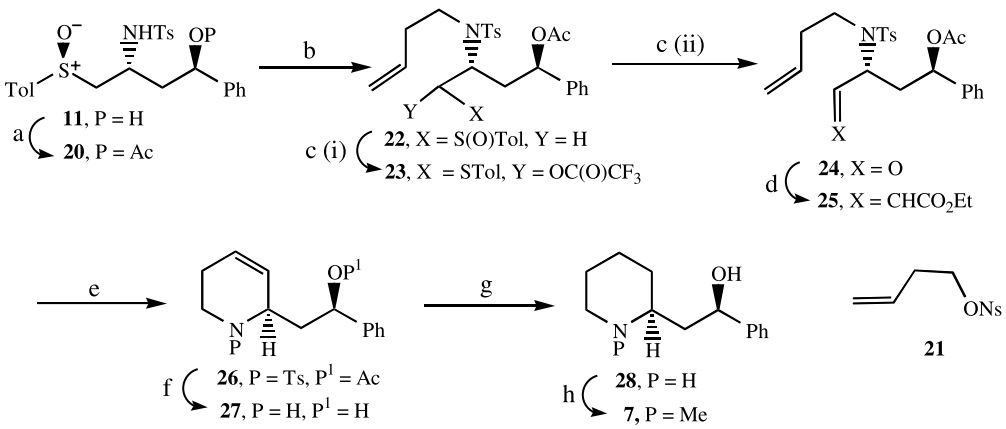
Scheme 4. Reagents and conditions: (a) NBS, H_2O, toluene, rt, 1 h, 84%; (b) *n*-Bu_3SnH, AIBN, benzene, reflux, 1.5 h, 76%; (c) TBDPS-Cl, imidazole, DCM, rt, 2 h, 80%; (d) *m*-CPBA, $CHCl_3$, 0 °C, 10 min, 93%; (e) LDA, HMPA, $I(CH_2)_3I$ **13** or $TfO(CH_2)_3OTf$ **14**, THF, −78 to −20 °C, 2 h.

unsaturated sulfoxide **6*s*** on treatment with NBS afforded regio- and stereospecifically the bromohydrin **10**. The structure was assigned to **10** based on our studies on the related unsaturated sulfoxide prepared from methyl phenyl-sulfoxide.[4] The bromine atom in **10** was removed by treatment with *n*-tributyltin hydride to afford the amino-alcohol **11**. Protection of the hydroxy group in **11** by treatment with *t*-butyldiphenylchlorosilane in dichloro-methane as the solvent afforded the silyl ether **12**. Generation of the dianion of **12** using excess LDA and subsequent treatment with 1,3-diiodopropane **13**, with the intention of elaborating the piperidine ring did not bear fruit. The products isolated were the *N*-allylation product **15** and the eliminated product **16**. The use of 1,3-propane di triflate **14**, HMPA as the co-solvent and bases such as LiHMDS, NaHMDS or KHMDS also gave the same result (Scheme 4). Attempted elaboration of the piperidine ring on sulfone **17**, obtained from **12** by *m*-CPBA oxidation, using a variety of bases and dielectrophiles **13/14** proved disappointing. The *N*-allylated product **18** and the elimination product **19** were the only products obtained. Similar results have been observed by Najera and co-workers in the attempted dialkylation of protected β-amino sulfones.[17]

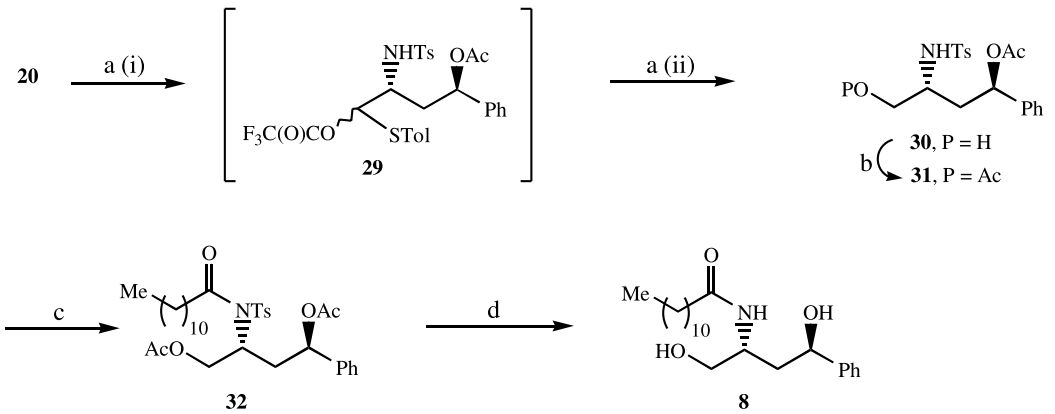
In the search for an alternative route for the construction of the piperidine ring on **11**, we zeroed in on the ring-closing metathesis (RCM) reaction.[18] The aminoalcohol **11**, on treatment with acetic anhydride yielded the acetate **20**. *N*-Alkylation of **20** with homoallyl nosylate **21**, yielded the compound **22** which on treatment with trifluoroacetic anhydride in the presence of Et_3N yielded the Pummerer intermediate **23**.[19] Hydrolysis of **23** with saturated aq. $NaHCO_3$ and treatment of the resulting aldehyde **24** with ethyl (triphenylphosphoranylidene)acetate yielded the (*E*)-ester **25** as the sole product. RCM reaction of **25** in the presence of 5 mol% of Grubbs' catalyst (first generation) proceeded uneventfully to yield **26** which was elaborated to allosedamine **7** using a straightforward sequence of reactions. It is noteworthy that an electron deficient olefin participates in the RCM reaction to afford the product cleanly.[20] Deprotection of the *p*-toluenesulfonyl group in **26** with Na–Hg[21] yielded alcohol **27** by concomitant deacetyl-ation. Subsequent reduction of the double bond by treatment with Pt/C under an atmosphere of hydrogen followed by reductive alkylation with aq. formaldehyde in the presence of sodium cyanoborohydride[22] yielded (−)-allosedamine **7**, with physical characteristics that were in good agreement to those reported in the literature[12d] (Scheme 5).

2.2. Synthesis of (1*R*,3*R*)-HPA-12

(1*R*,3*R*)-*N*-(3-Hydroxy-1-hydroxymethyl-3-phenylpropyl)-dodecanamide (HPA-12), **8** is an inhibitor of ceramide movement from the endoplasmic reticulum to the site of sphingomyelin synthesis and is a specific inhibitor of sphingomyelin synthesis in mammalian cells.[23] Kobayashi and co-workers have reported three routes to HPA-12, all of them exploiting the enantioselective Mannich reaction as



Scheme 5. Reagents and conditions: (a) Ac_2O, pyridine, DCM, rt, 4 h, 96%; (b) **21**, K_2CO_3, CH_3CN, reflux, 2 h, 90%; (c) (i) TFAA, Et_3N, CH_3CN, 0 °C, 50 min; (ii) aq. $NaHCO_3$, 0 °C, 20 min; (d) Ph_3PCHCO_2Et, PhH, rt, 30 min, 75% for two steps; (e) Grubbs' catalyst, toluene, reflux, 16 h, 80%; (f) Na–Hg, Na_2HPO_4, MeOH, reflux, 6 h, 78%; (g) H_2, Pt/C, AcOEt, rt, 3 h, 90%; (h) 37% aq. HCHO, $NaCNBH_3$, AcOH, CH_3CN, rt 4 h, 70%.



Scheme 6. Reagents and conditions: (a) (i) TFAA, 2,6-Lutidine, CH_3CN, 0 °C, 5 min; (ii) 20% aq. K_2CO_3, $NaBH_4$, 0 °C to rt, 15 min, 78%; (b) Ac_2O, pyridine, rt, 2 h, 97%; (c) Et_3N, DMAP, $C_{11}H_{23}COCl$, 0 °C to rt, 4 h, 91%; (d) Na-naphthalenide, DME, −20 °C, 2 min, K_2CO_3, 24 h, 55%.

the key step.[24] While the C–N bond was introduced with high selectivity, the diastereoselectivity of C–OH bond formation was modest. We describe herein a highly stereoselective route to HPA-12 using the acetate **20** as the key intermediate (Scheme 6). The Pummerer intermediate **29** without isolation was subjected to treatment with aq. K_2CO_3 and $NaBH_4$ to yield the alcohol **30**, which was protected as its acetate **31**. Treatment of **31** with dodecanoyl chloride in the presence of Et_3N and catalytic amounts of DMAP afforded the compound **32**. Reductive removal of the *p*-toluenesulfonyl group using freshly prepared sodium naphthalenide[25] led to the removal of the acetyl group during workup to yield (1*R*,3*R*)-HPA-12, which had physical characteristics in excellent agreement to that reported in the literature.[24a]

In conclusion, we have described a stereoselective route to (−)-allosedamine and (1*R*,3*R*)-HPA-12 using the bromosulfonamide **10** as the key intermediate. Efforts are in progress to prepare diastereomerically pure protected β-amino sulfoxide **2** and the results will be disclosed in the future.

3. Experimental

3.1. General

All air or moisture sensitive reactions were carried out under nitrogen atmosphere. Solvents were freshly distilled, THF over Na/benzophenone ketyl, DCM over P_2O_5 followed by CaH_2 and toluene over P_2O_5. Commercially available reagents were used without further purification except NBS, which was freshly recrystallized from hot water before use. Thin layer chromatography was performed with precoated silica gel plates. Column chromatography was carried out using silica gel (60–120 mesh). NMR spectra were recorded on a 200, 300 or 400 MHz spectrometer. ^1H NMR and ^{13}C NMR samples were internally referenced to TMS (0.00 ppm). Melting points are uncorrected.

3.1.1. *N*-[3-Phenyl-(2*E*)-2-propenylidene]-4-methyl-1-benzenesulfonamide, 5. To a solution of cinnamaldehyde (1.32 g, 10 mmol) and *p*-toluenesulfonamide (1.71 g, 10 mmol) in benzene (60 mL) under reflux in a Dean and Stark apparatus was added $BF_3{\cdot}Et_2O$ (50 mg, 0.4 mmol). The reflux was continued for 2 h and the solution was cooled to 0 °C. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with cold 1 N NaOH (2×50 mL) solution. The organic layer was washed with water (75 mL), brine (50 mL) and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure afforded a solid that was crystallized from chloroform–petroleum ether to afford the imine **5**[15] (2.08 g, 7.3 mmol) as colorless crystals in 73% yield. Mp 202–204 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 8.75 (d, J=9.4 Hz, 1H), 7.82 (d, J=8.3 Hz, 2H), 7.57–7.38 (m, 6H), 7.32 (d, J=8.3 Hz, 2H), 6.97 (dd, J=15.9, 9.4 Hz, 1H), 2.45 (s, 3H).

3.2. Experimental procedure for the reaction of anion generated from 4 with imine 5

Diisopropylamine (2.4 mL, 18 mmol) in THF (27 mL) was cooled at 0 °C and *n*-BuLi (9 mL, 2.0 M, 18 mmol) was added dropwise over 10 min. The reaction mixture was allowed to stir for 10 min at 0 °C and then cooled to −78 °C. (*R*)-Methyl *p*-tolylsulfoxide **4**, (1.85 g, 12 mmol) in THF (18 mL) was added dropwise via a syringe and stirred for 20 min at this temperature. A solution of the imine **5** (2.65 g, 12 mmol) in THF (12 mL) was added dropwise over a period of 5 min. After 15 min of stirring at −78 °C, the reaction mixture was quenched by the addition of aq. saturated NH_4Cl solution (5 mL). The aqueous layer was extracted with ethyl acetate (75 mL) and the combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and evaporated under reduced pressure. The diastereomeric sulfonamides **6*s*** and **6*a*** were separated by column chromatography using AcOEt/chloroform (23:2, v/v) as the eluent. The diastereomer **6*a*** eluted first followed by **6*s*** in 20 and 61% yields, respectively (combined yield 81%).

3.2.1. 4-Methyl-1-[2-(S_R)(4-methylphenylsulfonamido)-4-phenyl-(2*R*,3*E*)-3-butenylsulfinyl]benzene, 6*s*. Pale yellow solid. Mp 187–188 °C. 61% (2.6 g). ^1H NMR (200 MHz, $CDCl_3$) δ 7.74 (d, J=8.2 Hz, 2H), 7.49 (d, J=8.2 Hz, 2H), 7.36–7.04 (m, 9H), 6.30 (d, J=15.6 Hz, 1H), 6.09 (d, J=5.9 Hz, NH), 5.88 (dd, J=15.6, 7.4 Hz, 1H), 4.43–4.26 (m, 1H), 3.11 (dd, J=13.4, 7.4 Hz, 1H), 2.89 (dd, J=13.4, 6.7 Hz, 1H), 2.40 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.6, 141.8, 141.4, 141.1, 131.9, 129.8, 129.2, 128.4, 127.8, 126.7, 126.5, 126.3, 125.6,

124.0, 62.2, 51.7, 20.9, 20.8. $[\alpha]_D^{25}=+75.0$ (*c* 0.7, $CHCl_3$). *m/z* LSIMS 440 $[M^+ +H]$. IR (neat) 3453, 1597, 1493, 1365, 1338, 1158 cm^{-1}. Anal. calcd For $C_{24}H_{25}NO_3S_2$: C, 65.58; H, 5.73; N, 3.19; S, 14.59. Found: C, 65.43; H, 5.65; N, 3.12; S, 14.51.

3.2.2. 4-Methyl-1-[2-(S_R)(4-methylphenylsulfonamido)-4-phenyl-(2*S*,3*E*)-3-butenylsulfinyl]benzene, 6*a*. Colorless solid. Mp 208–209 °C. 20% (853 mg). ^1H NMR (200 MHz, $CDCl_3$) δ 7.72 (d, *J*=8.2 Hz, 2H), 7.44 (d, *J*=8.2 Hz, 2H), 7.36–7.10 (m, 9H), 6.48 (d, *J*=6.7 Hz, NH), 6.41 (d, *J*=15.6 Hz, 1H), 6.03 (dd, *J*=15.6, 6.7 Hz, 1H), 4.58–4.42 (m, 1H), 2.94–2.85 (m, 2H), 2.43 (s, 3H), 2.33 (s, 3H). $[\alpha]_D^{25}=+91.8$ (*c* 1.5, $CHCl_3$). *m/z* LSIMS 440 $[M^+ +H]$. IR (neat) 3340, 1593, 1488, 1363, 1340, 1157 cm^{-1}.

3.2.3. *N*-[2-Bromo-3-hydroxy-1-(S_S)(4-methylphenylsulfinylmethyl)-3-phenyl-(1*S*,2*R*,3*S*)-propyl]-4-methyl-1-benzenesulfonamide, 10. To a solution of sulfoxide **6*s*** (3.07 g, 7 mmol) in toluene/chloroform (2:1, 35 mL) was added water (210 μL, 11.7 mmol) followed by *N*-bromosuccinimide (1.58 g, 8.4 mmol) and the reaction mixture stirred at room temperature for 1 h. Then the reaction mixture was quenched by the addition of aqueous saturated $NaHCO_3$ (10 mL) solution. The mixture was diluted with chloroform (40 mL) and the organic layer was washed with water (25 mL), brine (25 mL) and dried over Na_2SO_4. Evaporation of the solvent afforded the crude bromohydrin, which was purified by column chromatography using AcOEt/petroleum ether (7:13, v/v) as the eluent to yield bromohydrin **10** (3.15 g, 5.88 mmol) in 84% yield. Colorless solid. Mp 180–182 °C. ^1H NMR (200 MHz, $CDCl_3$) δ 7.86 (d, *J*=8.2 Hz, 2H), 7.48–7.24 (m, 11H), 5.32 (d, *J*=10.4 Hz, NH), 4.85 (dd, *J*=9.7, 5.2 Hz, 1H), 4.70–4.56 (m, 1H), 4.06 (d, *J*=9.7 Hz, 1H), 3.84 (d, *J*=5.2 Hz, OH), 3.01 (dd, *J*=13.4, 6.0 Hz, H), 2.68 (dd, *J*=13.4, 7.4 Hz, 1H), 2.47 (s, 3H), 2.43 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 143.2, 142.6, 141.4, 140.8, 138.6, 130.1, 129.8, 128.1, 127.9, 127.5, 127.0, 123.8, 73.6, 62.6, 61.9, 49.9, 21.2, 21.0. $[\alpha]_D^{25}=-38.8$ (*c* 1, acetone). *m/z* LSIMS 536 $[M+H]^+$. IR (neat) 3405, 3221, 1589, 1370, 1341, 1159 cm^{-1}. Anal. calcd for $C_{24}H_{26}BrNO_4S_2C$, 53.73; H, 4.88; N, 2.61; S, 11.95. Found: C, 53.69; H, 4.84; N, 2.62; S, 11.95.

3.2.4. *N*-[3-Hydroxy-1-(S_S)(4-methylphenylsulfinylmethyl)-3-phenyl-(1*R*,3*R*)-propyl]-4-methyl-1-benzenesulfonamide, 11. To a stirred solution of bromohydrin **10** (2.68 g, 5 mmol) in benzene (30 mL) were added successively at room temperature *n*-Bu_3SnH (1.53 g, 5.25 mmol) and AIBN (41 mg, 0.25 mmol). The solution was refluxed for 90 min when TLC examination revealed complete consumption of starting material. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column using AcOEt/petroleum ether (2:3, v/v) as the eluent to afford the product **11** (1.73 g, 3.8 mmol) in 76% yield. Colorless solid. Mp 55–56 °C. ^1H NMR (200 MHz, $CDCl_3$) δ 7.77 (d, *J*=8.2 Hz, 2H), 7.32 (d, *J*=8.2 Hz, 2H), 7.26–7.11 (m, 9H), 6.86 (d, *J*=8.9 Hz, NH), 4.87 (d, *J*=8.9 Hz, 1H), 4.58–4.52 (m, 1H), 3.75 (bs, OH), 2.79–2.67 (m, 2H), 2.39 (s, 6H), 2.12–1.96 (m, 1H), 1.91–1.75 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.8, 143.4, 142.0, 139.8, 137.6, 130.2, 129.7, 128.3, 127.3, 127.2, 125.5, 123.9, 70.0, 60.9, 49.0, 43.4, 21.4, 21.3. $[\alpha]_D^{25}=-63.7$ (*c* 1, acetone). *m/z* LSIMS 458 $[M+H]^+$. IR (neat) 3540, 3272, 1598, 1494, 1398, 1327, 1159 cm^{-1}. Anal. calcd for $C_{24}H_{27}NO_4S_2C$, 62.99; H, 5.95; N, 3.06; S, 14.07. Found: C, 63.03; H, 5.91; N, 3.05; S, 14.06.

3.2.5. 1-[4-*tert*-Butyldiphenylsilyloxy-2-(4-methylphenylsulfonamido)-4-phenyl-(2*R*,4*R*)-butyl-(S_S)-sulfinyl]-4-methylbenzene, 12. To a solution of the sulfoxide **11** (457 mg, 1 mmol) in dichloromethane (4 mL) was added imidazole (136 mg, 2 mmol) and TBDPS-Cl (275 mg, 1 mmol) at ambient temperature. The reaction mixture was stirred for 2 h at room temperature and solvent was removed under reduced pressure. The residue was diluted with ether (15 mL) and washed with water (2×10 mL), brine (10 mL), dried over Na_2SO_4 and evaporated to afford the crude product mixture. Purification on silica gel column using AcOEt/petroleum ether (3:17, v/v) as the eluent afforded the silyl ether **12** (557 mg, 0.8 mmol) in 80% yield. Viscous oil. ^1H NMR (200 MHz, $CDCl_3$) δ 7.72–7.60 (m, 4H), 7.57–6.97 (m, 17H), 6.79 (d, *J*=8.2 Hz, 2H), 5.94 (bs, NH), 4.70 (t, *J*=4.7 Hz, 1H), 3.32–3.26 (m, 1H), 2.92–2.85 (m, 2H), 2.47 (s, 3H), 2.45–2.42 (m, 4H), 2.25–2.18 (m, 1H), 1.06 (s, 9H). *m/z* LSIMS 696 $[M+H]^+$. IR (neat) 3522, 1585, 1491, 1398, 1335, 1155 cm^{-1}. Anal. calcd for $C_{40}H_{45}NO_4S_2Si$: C, 69.03; H, 6.52; N, 2.01; S, 9.21. Found: C, 68.83; H, 6.61; N, 2.08; S, 9.02.

3.2.6. 3-Trifluoromethanesulfonyloxypropyl trifluoromethanesulfonate, 14. To a solution of Tf_2O (5.64 g, 20 mmol) in dry dichloromethane (20 mL) cooled at 0 °C under nitrogen atmosphere was added 1,3-propanediol (760 mg, 10 mmol) via a syringe and stirred for 40 min. A solution of pyridine (1.58 g, 20 mmol) in dry dichloromethane (4 mL) was added to the above stirred solution over a period of 5 min and stirred further for a period of 1 h. The reaction mixture was allowed to attain room temperature over a period of 30 min and the solvent was evaporated under reduced pressure. The residue was diluted with ethyl acetate (20 mL) and washed successively with aq. $CuSO_4$ solution (2×20 mL), water (2×10 mL), brine (10 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford **14** (2.71 g, 8 mmol) in 80% yield which was used in the next step without further purification. Liquid. ^1H NMR (200 MHz, $CDCl_3$) δ 4.67 (t, *J*=6.8 Hz, 4H), 2.33 (quintet, *J*=6.8 Hz, 2H).

3.3. General procedure for the dialkylation of 12 and 17

To a solution of sulfoxide **12** (35 mg, 0.05 mmol) in THF (0.5 mL) was added LDA (0.1 mL, 0.1 mmol, 1 M) dropwise at −78 °C. After stirring for 30 min at this temperature, a solution of diiodopropane (33 mg, 0.11 mmol) in THF (0.1 mL) was added dropwise, and stirring was continued. As the TLC revealed no reaction at −78 °C, the reaction mixture was warmed to −20 °C and stirred for 3 h. The reaction mixture was quenched by addition of saturated aq. NH_4Cl solution (0.2 mL) and extracted with ether (2×10 mL). The ether extracts were washed with brine (10 mL), dried and evaporated. Column chromatography on silica gel eluting with AcOEt/petroleum ether (1:9, v/v) afforded the products.

3.3.1. 1-[2-Allyl(4-methylphenyl)sulfonamido-4-(*tert*-butyldiphenylsilyloxy)-4-phenyl-(2*R*,4*R*)-butyl-(S_S)-sulfinyl]-4-methylbenzene, 15. 32% (12 mg). Low melting solid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.62–7.57 (m, 2H), 7.46 (d, J=8.1 Hz, 2H), 7.40–7.08 (m, 19H), 5.56–5.42 (m, 1H), 4.82 (d, J=9.8 Hz, 1H), 4.57 (d, J=16.9 Hz, 1H), 4.27 (dd, J=9.8, 3.7 Hz, 1H), 3.86–3.73 (m, 1H), 3.58 (dd, J=15.4, 6.4 Hz, 1H), 3.51 (dd, J=15.4, 6.4 Hz, 1H), 3.32 (dd, J=15.1, 6.4 Hz, 1H), 2.78 (dd, J=15.1, 11.7 Hz, 1H), 2.49 (s, 3H), 2.43 (s, 3H), 2.12–1.96 (m, 2H), 0.98 (s, 9H). *m*/*z* LSIMS 758 $[M+Na]^+$. IR (neat) 2945, 2826, 1598, 1490, 1393, 1329, 1157 cm^{-1}. Anal. calcd for $C_{43}H_{49}NO_4S_2Si$: C, 70.17; H, 6.71; N, 1.90; S, 8.71. Found: C, 69.78; H, 6.33; N, 1.75; S, 8.56.

3.3.2. 4-(*tert*-Butyldiphenylsilyloxy)-1-(S_S)(4-methylphenylsulfinyl)-4-phenyl-(*E*)-1-(4*R*)-butene, 16. 16% (4 mg). Viscous oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.73–7.62 (m, 2H), 7.47–7.18 (m, 17H), 6.27 (dt, J=15.8, 8.2 Hz, 1H), 5.93 (d, J=15.8 Hz, 1H), 4.71 (dd, J=7.6, 3.8 Hz, 1H), 2.40 (s, 3H), 2.12–1.96 (m, 2H), 0.98 (s, 9H). *m*/*z* LSIMS 524 $[M+H]^+$. IR (neat) 2848, 1595, 1498, 1357 cm^{-1}.

3.3.3. 1-[4-(*tert*-Butyldiphenylsilyloxy)-2-(4-methylphenylsulfonamido)-4-phenyl-(2*R*,4*R*)-butylsulfonyl]-4-methylbenzene, 17. To a solution of sulfoxide **12** (350 mg, 0.5 mmol) in chloroform (2 mL), *m*-CPBA (123 mg, 0.5 mmol, 60%) was added at 0 °C and the reaction mixture was stirred at 0 °C for 10 min. The reaction mixture was diluted with chloroform (15 mL) and washed successively with 10% aq. sodium bisulfite solution (2×10 mL), 10% aq. sodium bicarbonate solution (2×10 mL), water (10 mL) and brine (10 mL). The reaction mixture was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to afford crude product. Column chromatography using AcOEt/petroleum ether (1:4, v/v) afforded sulfone **17** (330 mg, 0.47 mmol) in 93% yield. Viscous oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.77–7.65 (m, 2H), 7.54–7.28 (m, 9H), 7.27–6.97 (m, 10H), 6.76 (d, J=8.2 Hz, 2H), 5.72 (d, J=5.9 Hz, NH), 4.80 (t, J=4.6 Hz, 1H), 3.63 (dd, J=13.4, 3.1 Hz, 1H), 3.24–3.13 (m, 1H), 2.77 (dd, J=13.4, 8.9 Hz, 1H), 2.48 (s, 6H), 2.46–2.40 (m, 1H), 2.14–2.07 (m, 1H), 0.97 (s, 9H). *m*/*z* LSIMS 712 $[M+H]^+$. IR (neat) 3522, 1597, 1498, 1398, 1347, 1171 cm^{-1}. Anal. calcd for $C_{40}H_{45}NO_5S_2Si$: C, 67.48; H, 6.37; N, 1.97; S, 9.01. Found: C, 67.03; H, 6.11; N, 2.05; S, 9.26.

3.3.4. 1-[2-Allyl(4-methylphenyl)sulfonamido-4-(*tert*-butyldiphenylsilyloxy)-4-phenyl-(2*R*,4*R*)-butylsulfonyl]-4-methylbenzene, 18. 30% (11 mg). Low melting solid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.78–7.60 (m, 4H), 7.54–7.13 (m, 19H), 5.49–5.28 (m, 1H), 4.75 (d, J=10.2 Hz, 1H), 4.59 (d, J=16.5 Hz, 1H), 4.24 (dd, J=7.9, 4.9 Hz, 1H), 3.90–3.72 (m, 1H), 3.56–3.50 (m, 1H), 3.42 (dd, J=15.4, 6.8 Hz, 1H), 3.21 (dd, J=15.1, 6.8 Hz, 1H), 2.62 (dd, J=15.1, 4.5 Hz, 1H), 2.46 (s, 3H), 2.41 (s, 3H), 2.35–2.26 (m, 1H), 2.10–2.01 (m, 1H), 0.97 (s, 9H). *m*/*z* LSIMS 775 $[M+Na]^+$. IR (neat) 2956, 2843, 1591, 1398, 1333, 1171 cm^{-1}. Anal. calcd for $C_{43}H_{49}NO_5S_2Si$: C, 68.67; H, 6.57; N, 1.86; S, 8.53. Found: C, 68.43; H, 6.33; N, 1.75; S, 8.56.

3.3.5. 4-(*tert*-Butyldiphenylsilyloxy)-1-(4-methylphenylsulfonyl)-4-phenyl-(*E*)-1-(4*R*)-butene, 19. 14% (4 mg). Viscous oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.73–7.62 (m, 2H), 7.47–7.18 (m, 17H), 6.27 (dt, J=15.7, 7.9 Hz, 1H), 5.93 (d, J=15.7 Hz, 1H), 4.79 (t, J=6.3 Hz, 1H), 2.47 (s, 3H), 2.37–2.04 (m, 2H), 0.98 (s, 9H). *m*/*z* LSIMS 541 $[M+H]^+$. IR (neat) 2867, 1592, 1334, 1167 cm^{-1}.

3.3.6. 3-Butenyl 4-nitro-1-benzenesulfonate, 21. To a solution of 3-buten-1-ol (360 mg, 5 mmol) in dry dichloromethane (20 mL) was added successively Et_3N (1.01 g, 10 mmol) and *p*-nitrobenzenesulfonyl chloride (1.11 g, 5 mmol) at room temperature under N_2. The reaction mixture was stirred for a period of 4 h. The reaction mixture was washed with water (10 mL), brine (10 mL) and evaporated to dryness under reduced pressure. The crude product mixture was chromatographed on silica gel using AcOEt/petroleum ether (1:4, v/v) as the eluent to afford the nosylate **21** (4 mmol) as a pale yellow solid in 80% yield. Mp 122 °C. ^{1}H NMR (200 MHz, $CDCl_3$) 8.42 (d, J=8.8 Hz, 2H), 8.19 (d, J=8.8 Hz, 2H), 5.78–5.55 (m, 1H), 5.18–5.05 (m, 2H), 4.21–4.11 (m, 2H), 2.51–2.36 (m, 2H). *m*/*z* LSIMS 258 $[M^+ + H]$.

3.3.7. 4-(S_S)(4-Methylphenylsulfinyl)-3-(4-methylphenylsulfonamido)-1-phenyl-(1*R*,3*R*)-butyl acetate, 20. To a stirred solution of **11** (1.37 g, 3 mmol) in dichloromethane (12 mL) were added successively pyridine (474 mg, 6 mmol) and acetic anhydride (331 mg, 3.25 mmol). The reaction mixture was stirred for 4 h and then diluted with dichloromethane (20 mL). The organic layer was washed successively with aqueous saturated $CuSO_4$ solution (2×15 mL), water (15 mL), 5% aq. $NaHCO_3$ solution (2×10 mL), water (10 mL), brine (10 mL) and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure followed by column chromatography using AcOEt/petroleum ether (1:1, v/v) as the eluent afforded the acetate **20** (1.44 g, 2.88 mmol) in 96% yield. White solid. Mp 70–72 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.72 (d, J=8.2 Hz, 2H), 7.36–7.13 (m, 11H), 6.16 (d, J=8.2 Hz, NH), 5.71 (dd, J=8.9, 4.5 Hz, 1H), 3.98–3.81 (m, 1H), 2.78 (d, J=5.2 Hz, 2H), 2.45 (s, 3H), 2.42 (s, 3H), 2.41–2.14 (m, 2H), 2.02 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 143.3, 142.0, 139.9, 139.8, 137.9, 130.0, 129.7, 128.5, 128.0, 127.2, 126.1, 123.9, 72.4, 60.1, 48.3, 41.2, 21.4, 21.3, 21.0. $[\alpha]_D^{25}=-71.8$ (*c* 0.75, $CHCl_3$). *m*/*z* LSIMS 500 $[M+H]^+$. IR (neat) 3249, 1741, 1596, 1493, 1371, 1327, 1152 cm^{-1}. Anal. calcd for $C_{26}H_{29}NO_5S_2$: C, 62.50; H, 5.85; N, 2.80; S, 12.83. Found: C, 62.43; H, 5.91; N, 2.84; S, 12.80.

3.3.8. 3-[3-Butenyl(4-methylphenyl)sulfonamido)-4-(S_S)(4-methylphenylsulfinyl)-1-phenyl-(1*R*,3*R*)-butyl acetate, 22. Homoallyl nosylate **21** (566 mg, 2.2 mmol) was added to a stirred mixture of acetate **20** (1.1 g, 2.2 mmol) and K_2CO_3 (456 mg, 3.3 mmol) in dry acetonitrile (8.8 mL) and the reaction mixture was allowed to reflux for 2 h. The reaction mixture was diluted with ethyl acetate (20 mL) and washed with water (2×15 mL) followed by brine (15 mL) solution. After drying over Na_2SO_4, evaporation of the solvent under reduced pressure afforded the crude compound which on column chromatography using AcOEt/petroleum ether (3:7, v/v) as the eluent afforded the *N*-alkylated product **22** (1.1 g, 1.98 mmol) in 90% yield. Viscous oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.67 (d,

J=8.2 Hz, 2H), 7.45 (d, J=8.2 Hz, 2H), 7.36–7.11 (m, 9H), 5.68–5.48 (m, 2H), 5.04–4.90 (m, 2H), 4.21–4.04 (m, 1H), 3.32–3.24 (m, 1H), 3.19–3.11 (m, 1H), 2.94 (dd, J=13.4, 7.4 Hz, 1H), 2.79 (dd, J=13.4, 6.7 Hz, 1H), 2.42 (s, 6H), 2.36–2.10 (m, 4H), 2.02 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 143.7, 141.7, 140.4, 139.8, 137.5, 134.2, 130.0, 129.8, 128.5, 128.1, 127.5, 126.3, 123.9, 117.2, 72.8, 62.5, 52.1, 47.1, 40.9, 34.1, 21.5, 21.4, 21.0. $[\alpha]_D^{25}=-45.5$ (c 2.2, $CHCl_3$). m/z LSIMS 554 [M^++H]. IR (neat) 2977, 1752, 1595, 1488, 1449, 1337, 1142, 1083 cm^{-1}. Anal. calcd for $C_{30}H_{35}NO_5S_2$: C, 65.07; H, 6.37; N, 2.53; S, 11.58. Found: C, 65.43; H, 5.75; N, 2.21; S, 12.01.

3.3.9. Ethyl 4-[3-butenyl(4-methylphenyl)sulfonamido]-6-acetoxy-6-phenyl-(*E*,4*R*,6*R*)-2-hexenoate, 25. To a solution of the *N*-homoallyl compound **22**, (664 mg, 1.2 mmol) in acetonitrile (6 mL) cooled at 0 °C was added triethylamine (364 mg, 3.6 mmol) followed by trifluoroacetic anhydride (1.26 g, 6 mmol) and the mixture stirred for 50 min. An aq. 5% $NaHCO_3$ solution (2 mL) was added at 0 °C and stirred for another 20 min. The reaction mixture was then extracted into benzene (10 mL) and washed successively with water (5 mL), brine (5 mL) and dried over Na_2SO_4. The benzene solution of the aldehyde was directly taken ahead to the next step and reacted with ethyl (triphenylphosphoranylidene)acetate (498 mg, 1.2 mmol). The reaction was stirred at room temperature for 30 min. The solvent was removed under reduced pressure to afford a residue which was purified by column chromatography using EtOAc/petroleum ether (1:9) as the eluent to afford the α,β-unsaturated ester **25** (449 mg, 0.9 mmol) in 75% yield (for the two steps). Pale yellow solid. Mp 59–61 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.63 (d, J=8.2 Hz, 2H), 7.39–7.20 (m, 7H), 6.54 (dd, J=15.6, 5.2 Hz, 1H), 5.76–5.56 (m, 3H), 5.08–4.93 (m, 2H), 4.64–4.47 (m, 1H), 4.12 (q, J=6.7 Hz, 2H), 3.18 (ddd, J=15.6, 11.1, 5.9 Hz, 1H), 2.92 (ddd, J=15.6, 10.4, 5.9 Hz, 1H), 2.56–2.16 (m, 6H), 2.06–1.91 (m, 4H), 1.24 (t, J=6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 165.9, 144.7, 144.0, 140.1, 137.5, 134.8, 130.2, 129.1, 128.7, 127.7, 126.8, 124.3, 117.7, 73.0, 61.0, 55.8, 45.2, 39.5, 36.0, 21.9, 21.5, 14.6. $[\alpha]_D^{25}=+58.7$ (c 2.25, $CHCl_3$). m/z LSIMS 500 [M^++H]. IR (neat) 2957, 2887, 1745, 1590, 1498, 1450, 1343, 1140, 1078 cm^{-1}. Anal. calcd for $C_{27}H_{36}NO_6S$: C, 64.91; H, 6.66; N, 2.80; S, 6.42. Found: C, 65.08; H, 6.85; N, 2.71; S, 6.46.

3.3.10. 2-[1-(4-Methylphenylsulfonyl)-(2*R*)-1,2,5,6-tetrahydropyridin-2-yl]-1-phenyl-(1*R*)-ethyl acetate, 26. Bis-(tricyclohexylphosphine)benzylideneruthenium(IV)dichloride $\mathbf{G_1}$ (25 mg, 0.032 mmol) was added to a solution of diene **25** (324 mg, 0.65 mmol) in toluene and refluxed for 16 h, when TLC revealed the complete consumption of the starting material. The solvent was removed under reduced pressure. Column chromatography using EtOAc/petroleum ether (1:4, v/v) as the eluent afforded the product **26** (207 mg, 0.52 mmol) in 80% yield. Pale yellow solid. Mp 75–76 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.67 (d, J=8.9 Hz, 2H), 7.36–7.16 (m, 7H), 5.74 (dd, J=9.7, 4.5 Hz, 1H), 5.66–5.54 (m, 2H), 4.54–4.41 (m, 1H), 3.77 (dd, J=14.9, 5.2 Hz, 1H), 3.08 (ddd, J=14.9, 11.9, 5.2 Hz, 1H), 2.42 (s, 3H), 2.20–1.60 (m, 7H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 143.2, 140.5, 138.1, 129.5, 128.5, 128.0, 127.3, 127.2, 126.5, 125.5, 72.7, 50.2, 41.4, 38.0, 29.7, 21.5, 21.2. $[\alpha]_D^{25}=-119.0$ (c 0.75, $CHCl_3$). m/z LSIMS 400 [M+H]$^+$. IR (neat) 3032, 2925, 2853, 1744, 1598, 1494, 1374, 1345, 1159, 1096 cm^{-1}. Anal. calcd for $C_{22}H_{25}NO_4S$: C, 66.14; H, 6.31; N, 3.51; S, 8.02. Found: C, 66.03; H, 6.55; N, 3.41; S, 8.07.

3.3.11. 2-[(2*R*)-1,2,5,6-Tetrahydropyridin-2-yl]-1-phenyl-(1*R*)-ethan-1-ol, 27. Freshly prepared Na–Hg (6%, 150 mg) was added to a well-stirred mixture of **26** (179 mg, 0.45 mmol) and anhydrous Na_2HPO_4 (319 mg, 2.25 mmol) in methanol (9 mL) at room temperature and allowed to reflux for 6 h. The reaction mixture was quenched with water (3 mL) and extracted into ethyl acetate (2×15 mL). The organic layer was washed with brine (15 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was chromatographed on a small pad of silica gel using CH_2Cl_2: MeOH (50:1 then 1:10, v/v) as the eluent to afford **27** (71 mg, 0.35 mmol) in 78% yield. Viscous liquid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40–7.12 (m, 5H), 5.97–5.82 (m, 1H), 5.58–5.44 (m, 1H), 5.12–4.96 (m, 1H), 4.04–3.88 (m, 1H), 3.43–3.24 (m, 1H), 3.03–2.83 (m, 1H), 2.56–1.85 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.0, 128.3, 127.1, 126.3, 125.4, 69.4, 51.1, 41.3, 40.3, 29.6. $[\alpha]_D^{25}=-39.1$ (c 0.8, $CHCl_3$). m/z LSIMS 204 [M^++H]. IR (neat) cm^{-1} 3331, 2972, 2845, 1591, 1494. Anal. calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.57; H, 8.15; N, 6.66.

3.3.12. 1-Phenyl-2-[(6*S*)-tetrahydro-6-piperidin-2-yl]-(1*R*)-ethan-1-ol, 28. To a solution of **27** (15 mg, 0.075 mmol) in ethyl acetate (1.5 mL) was added Pt/C (5 mg, 10% w/w) and the reaction mixture was allowed to stir under H_2 atmosphere for 3 h. The reaction mixture was filtered through celite and evaporated to dryness under reduced pressure to afford **28** (14 mg, 0.068 mmol) in 90% yield. Viscous liquid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.42–7.18 (m, 5H), 5.22 (bd, J=7.4 Hz, 1H), 3.44 (bd, J=11.7 Hz, 1H), 3.36–3.21 (m, 1H), 2.91–2.71 (m, 1H), 2.42–2.22 (m, 1H), 2.04–1.66 (m, 6H), 1.51–1.32 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.0, 22.5, 29.6, 42.1, 44.9, 54.4, 68.4, 125.5, 127.2, 128.4, 143.6. $[\alpha]_D^{25}=-28.1$ (c 0.2, methanol). m/z EI 206 [M^++H]. Anal. calcd for $C_{13}H_{19}NO$, C, 76.06; H, 9.33; N, 6.82. Found: C, 76.57; H, 9.15; N, 6.66.

3.3.13. 2-[1-Methyl-(6*S*)-tetrahydro-6-piperidin-2-yl]-1-phenyl-(1*R*)-ethan-1-ol, 7. To a solution of the substrate **28** (12 mg, 0.06 mmol) in acetonitrile (0.9 mL) was added 37% aq. HCHO (0.28 mL, 3.43 mmol), AcOH (20 μL) and $NaCNBH_3$ (19 mg, 0.33 mmol). The resulting reaction mixture was stirred at room temperature for 4 h and then concentrated under reduced pressure. The residue was extracted into dichloromethane (2×10 mL) and the solvent was evaporated under reduced pressure. Column chromatography using MeOH/DCM (first with 1:10 v/v then methanol alone) as the eluent afforded the product **7** in 70% yield as a solid. Mp 78–80 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40–7.21 (m, 5H), 5.10 (dd, J=10.4, 3.4 Hz, 1H), 3.02 (d, J=10.4 Hz, 1H), 2.46 (s, 3H), 2.45–3.32 (m, 1H), 2.17 (ddd, J=14.9, 10.9, 4.3 Hz, 1H), 1.96–1.53 (m, 6H), 1.32–1.20 (m, 2H). $[\alpha]_D^{25}=-28.8$ (c 0.4, MeOH) [lit.[12d] $[\alpha]_D^{25}=-29.8$ (c 0.2, MeOH)]. m/z LSIMS 220 [M+H]$^+$.

3.3.14. 4-Hydroxy-3-(4-methylphenylsulfonamido)-1-phenyl-(1*R*,3*R*)-butyl acetate, 30. To a stirred solution of **20** (1.05 g, 2.1 mmol) and dry 2,6-lutidine (674 mg, 6.3 mmol) in acetonitrile (15 mL) under a nitrogen atmosphere at 0 °C, neat trifluoroacetic anhydride (1.5 mL, 10.5 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 5 min. Aq. 20% K_2CO_3 solution was added to adjust pH to 7. Then $NaBH_4$ (400 mg, 10.5 mmol) was added portionwise and the reaction mixture allowed to attain room temperature. After 15 min the reaction was quenched with an aqueous saturated ammonium chloride solution (5 mL). The reaction mixture was extracted with ethylacetate (2×15 mL) and the collected organic layers dried over anhydrous sodium sulfate. Evaporation of the solvent followed by purification on a silica gel column using acetone/petroleum ether (1:4, v/v) afforded the β-amino alcohol **29** (617 mg, 1.64 mmol) in 78% yield. Solid. Mp 159–161 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.69 (d, J=8.2 Hz, 2H), 7.34–7.12 (m, 7H), 7.01 (d, J=8.2 Hz, NH), 5.60 (dd, J=10.4, 4.4 Hz, 1H), 4.13–4.04 (m, 1H), 3.38–3.16 (m, 2H and 1-OH), 2.44 (s, 3H), 2.09–1.72 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 142.6, 141.6, 138.9, 129.7, 128.5, 127.5, 126.4, 125.6, 72.1, 63.7, 51.7, 38.1, 21.1, 20.8. $[\alpha]_D^{25}$=+13.6 (*c* 0.6, acetone). *m/z* LSIMS 378 $[M+H]^+$. IR (neat) 3421, 3249, 1745, 1598, 1496, 1152 cm^{-1}. Anal. calcd for $C_{19}H_{23}NO_5S$: C, 60.46; H, 6.14; N, 3.71; S, 8.49. Found: C, 60.48; H, 6.03; N, 3.79; S, 8.33.

3.3.15. 4-Acetoxy-3-(4-methylphenylsulfonamido)-1-phenyl-(2*R*,4*R*)-butyl acetate, 31. To a stirred solution of **30** (377 mg, 1 mmol) in dichloromethane (4 mL) was added successively pyridine (158 mg, 2 mmol) and acetic anhydride (122 mg, 1.1 mmol) at room temperature under N_2. The reaction mixture was stirred for a period of 2 h at room temperature. The reaction mixture was then diluted with dichloromethane (16 mL) and washed sequentially with aq. saturated $CuSO_4$ solution (2×10 mL), water (10 mL), aq. 5% $NaHCO_3$ solution (2×10 mL), water (10 mL), brine (10 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure followed by purification on a silica gel column using AcOEt/petroleum ether (1:3, v/v) as the eluent afforded the diacetate **31** (406 mg, 0.97 mmol) in 97% yield. Viscous liquid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.74 (d, J=8.2 Hz, 2H), 7.48–7.12 (m, 7H), 5.68 (dd, J=9.7, 4.5 Hz, 1H), 5.58 (d, J=8.9 Hz, NH), 4.0–3.84 (m, 2H), 3.76–3.52 (m, 1H), 2.44 (s, 3H), 2.12–1.80 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 169.8, 143.6, 140.0, 137.7, 129.8, 128.6, 128.1, 127.0, 126.2, 72.6, 65.7, 49.8, 39.2, 21.5, 21.0, 20.6. $[\alpha]_D^{25}$=+11.4 (*c* 0.75, $CHCl_3$). *m/z* LSIMS 420 $[M+H]^+$. IR (neat) 3324, 1754, 1590, 1493, 1148 cm^{-1}. Anal. calcd for $C_{21}H_{25}NO_6S$: C, 60.13; H, 6.01; N, 3.34; S, 7.64. Found: C, 60.43; H, 5.91; N, 2.94; S, 7.80.

3.3.16. 2-Dodecanoyl-(4-methylphenyl)sulfonamido-4-acetoxy-4-phenyl-(2*R*,4*R*)-butyl acetate, 32. A solution of dodecanoyl chloride (110 mg, 0.5 mmol) in dichloromethane (0.25 mL) was added dropwise to a mixture of the diacetate **31** (210 mg, 0.5 mmol), Et_3N (101 mg, 1 mmol) and DMAP (cat.) in dichloromethane (1.5 mL) at 0 °C under N_2. The reaction mixture was gradually allowed to attain room temperature and stirred further for a period of 4 h. The reaction mixture was diluted with dichloromethane (10 mL) and washed successively with water (2×5 mL), 10% aq. citric acid solution (5 mL), brine (5 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography on silica gel with AcOEt/petroleum ether (1:9, v/v) to afford the amide **31** (274 mg, 0.46 mmol) in 91% yield. Liquid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.72 (d, J=8.2 Hz, 2H), 7.40–7.22 (m, 7H), 5.57 (dd, J=9.7, 4.5 Hz, 1H), 4.73–4.58 (m, 1H), 4.50–4.32 (m, 2H), 2.60–2.16 (m, 7H), 2.11 (s, 3H), 2.0 (s, 3H), 1.71–1.11 (m, 18H), 0.88 (t, J=6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 170.5, 170.2, 144.9, 140.2, 137.2, 129.9, 128.6, 128.1, 127.7, 126.3, 73.4, 64.2, 56.0, 38.3, 31.9, 29.6, 29.4, 29.2, 29.0, 28.9, 24.7, 22.6, 21.6, 21.2, 20.8, 14.1. $[\alpha]_D^{25}$=+9.66 (*c* 2.0, acetone). *m/z* LSIMS 542 $[M-OAc]^+$. Anal. calcd for $C_{33}H_{47}NO_7S$: C, 65.86; H, 7.87; N, 2.33; S, 5.33. Found: C, 65.66; H, 7.42; N, 2.13; S, 5.47.

3.3.17. *N*-[3-Hydroxy-1-hydroxymethyl-3-phenyl-(1*R*,3*R*)-propyl]dodecanamide, 8. To the substrate **31** (30 mg, 0.05 mmol) in dimethoxyethane (0.5 mL) was added freshly prepared Na-naphthalenide in dimethoxyethane (the solution of sodium naphthalenide in dimethoxyethane was prepared by adding dimethoxyethane (10 mL) to a mixture of Na (300 mg, 13 mmol) and naphthalene (2.05 g, 16 mmol) and stirring the mixture at room temperature for 2 h) at −20 °C under nitrogen atmosphere until light green color persisted (ca 2 min). The reaction mixture was quenched by the addition of water (1 mL). Solid K_2CO_3 (140 mg) was added and the reaction mixture stirred at room temperature for 24 h. The solvent was evaporated under reduced pressure and the residue was extracted into ethylacetate (2×5 mL). Column chromatography using hexane/isopropylalcohol (4:1, v/v) afforded the product **30** (10 mg, 0.27 mmol) in 55% yield. Solid. Mp 76–78 °C [lit.[24a] mp 75.5–77 °C]. ^{1}H NMR (200 MHz, $CDCl_3$) 7.40–7.12 (m, 5H), 6.19 (d, J=5.9 Hz, NH), 4.62 (bd, J=7.5 Hz, 1H), 4.19–4.08 (m, 1H), 3.77–3.62 (m, 2H), 2.31–2.13 (m, 2H), 1.68–1.45 (m, 2H), 1.42–1.20 (m, 18H), 0.86 (t, J=6.7 Hz, 3H). $[\alpha]_D^{25}$=−36.6 (*c* 0.56, $CHCl_3$) [lit.[24a]=−35.1 (*c* 0.8, $CHCl_3$)].

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Vilsmeier–Haack reactions of carbonyl compounds: synthesis of substituted pyrones and pyridines

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Abstract—Vilsmeier–Haack reaction of substituted phenylacetones leads to the formation of conjugated iminium salts which on aqueous basic work up afford 3-formyl-4-pyrones and on ammonium acetate-induced cyclization afford 5-aryl-4-chloronicotinaldehydes in good yields.

1. Introduction

The Vilsmeier–Haack reaction is a widely used method for the formylation of activated aromatic and heteroaromatic compounds.[1,2] The reactions of aliphatic substrates,[3] particularly carbonyl compounds[4] with chloromethyleneiminium salts are highly versatile. They lead to multiple iminoalkylations in the presence of excess reagent and the resulting intermediates undergo cyclization to afford aromatic or heterocyclic compounds.[5,6] Multifunctional intermediates derived from these reactions (e.g., β-chloroenaldehydes) are subsequently exploited for the synthesis of functionalized heterocycles or other valuable target molecules.[7,8] Dibenzyl ketone on treatment with chloromethyleneiminium salt undergo multiple iminoalkylations followed by cyclization to afford 3,5-diphenyl-4*H*-pyran-4-one.[9,10] The reaction of *o*-hydroxyacetophenones with Vilsmeier-reagent also involve an iminoalkylation cyclization sequence, leading to the formation of 3-formyl chromones.[11–14]

We envisaged that methyl ketones having an additional enolizable methylene group at the α′ position should undergo multiple iminoalkylations on treatment with chloromethyleneiminium salt and the resultant intermediate on hydrolysis with saturated aq. potassium carbonate and subsequent cyclization should afford α-formyl-4-pyrones. Alternatively, cyclization of the multiple iminoalkylated intermediate induced by ammonium acetate prior to the work up would afford substituted pyridines. In this paper, we describe the reactions of some carbonyl compounds having two enolizable sp^2 or sp^3 hybridized carbons adjacent to the carbonyl group, and the cyclization reactions of the resulting iminoalkylated intermediates to substituted pyrones and pyridines.[15]

One of the general methods for the preparation of 4-pyrones involve cyclization of 1,3-dicarbonyl compounds obtained either by the addition of acyl ketenedithioacetals,[16] enamines[17] or enol ethers[18] to carboxylates or acid chlorides or by the addition of enamines to diketene.[19] Another approach towards the synthesis of 4-pyrones, particularly those having substituents at 2 and 6 positions, involve cyclization of 1,3,5-tricarbonyl compounds.[20–22] We have shown earlier that epoxidation of alkenoyl ketenedithioacetals followed by Lewis acid catalyzed rearrangement and cyclization leads to 2,5-disubstituted-4-pyrones.[23]

When benzyl methyl ketone was treated with 3 equiv. of the Vilsmeier–Haack reagent, prepared from DMF and $POCl_3$, for 72 h in DMF, 4-oxo-5-phenyl-4*H*-pyran-3-carbaldehyde **2a** was obtained in 59% yield (Scheme 1). Other substituted aryl acetones **1b-c** also reacted similarly to afford respective 3-formyl pyrones **2b-c**. We have recently shown that treatment of the multiple iminoalkylated intermediates derived from tertiary alcohols readily undergo cyclization in the presence of ammonium acetate to afford substituted pyridines.[24,25] We have therefore examined the reactivity of the intermediate iminium salt derived from aryl acetones towards similar cyclization. The reaction mixture after treatment of aryl acetones **1a** and **1c** with chloromethyleneiminium salt for 48 h at room temperature was cooled to 0–5 °C, and 40 equiv. of ammonium acetate was added and stirred for another 30 min, to afford the 5-aryl-4-chloro nicotinaldehydes **3a-b**.

Enolization of aryl acetones promoted in the presence of a

Keywords: Pyridines; Pyrones; Vilsmeier–Haack reagents; Iminoalkylations; Iminium salts; Aryl acetones.
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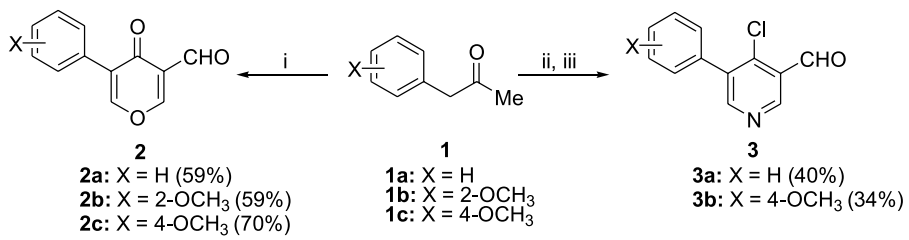
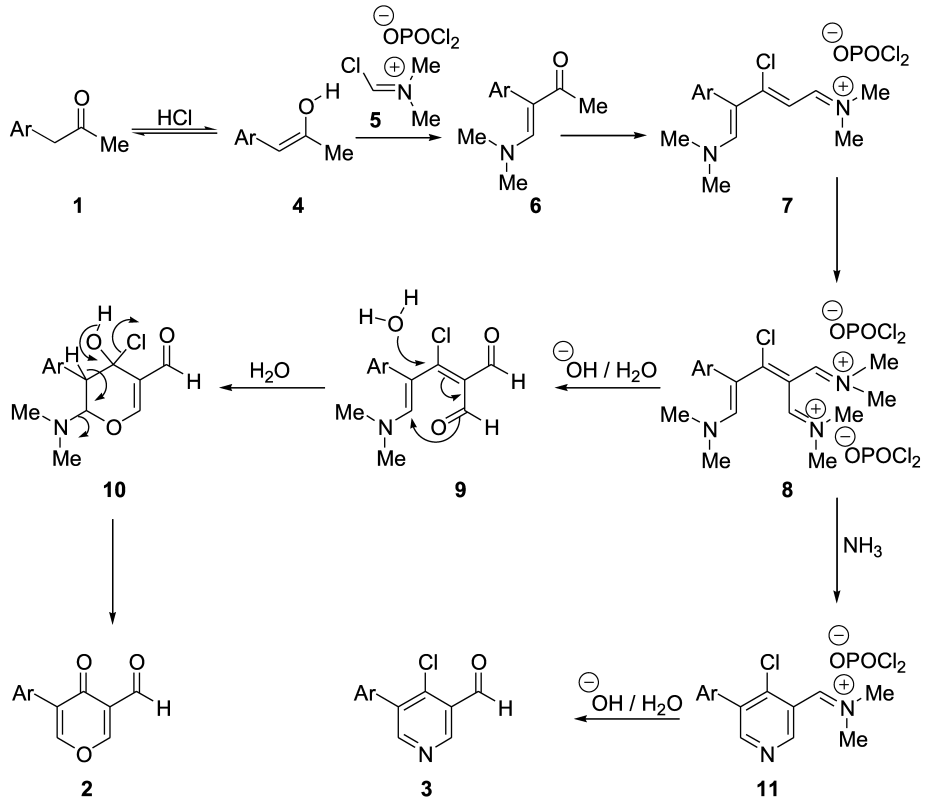


Scheme 1. Reagents and conditions: (i) DMF/$POCl_3$ (3 equiv.), 72 h, rt; (ii) DMF/$POCl_3$ (4 equiv.), 48 h, rt; (iii) NH_4OAc, 0 °C, 30 min.

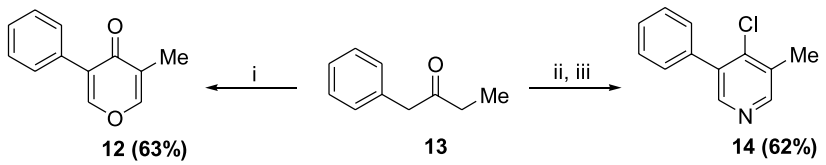
small amount of HCl followed by the addition of the enol to chloromethyleneiminium salt leads to the formation of the enaminoketone **6**. Sequential addition of this enaminoketone to 2 mol of chloromethyleneiminium salt results in the formation of the bis-iminium salt **8**. Hydrolysis of **8** should lead to the formation of the pentadienaldehyde **9** which undergo addition of a molecule of water followed by ring closure to afford an intermediate pyran **10**. Loss of HCl and dimethyl amine from **10** should lead to the formation of pyran-4-one **2**. Alternatively, cyclization of the intermediate bis-iminium salt **8** induced by ammonium acetate would give the iminium salt **11** which on aqueous work-up afford the substituted nicotinaldehydes **3** (Scheme 2).

Treatment of benzyl ethyl ketone **13** with the Vilsmeier–Haack reagent followed by hydrolysis gave the expected 3-methyl-5-phenyl-4*H*-pyran-4-one **12** in 63% yield. Alternatively, treatment of **13** with chloromethyleneiminium salt followed by ammonium acetate induced cyclization gave 4-chloro-3-methyl-5-phenylpyridine **14** in 62% yield (Scheme 3).

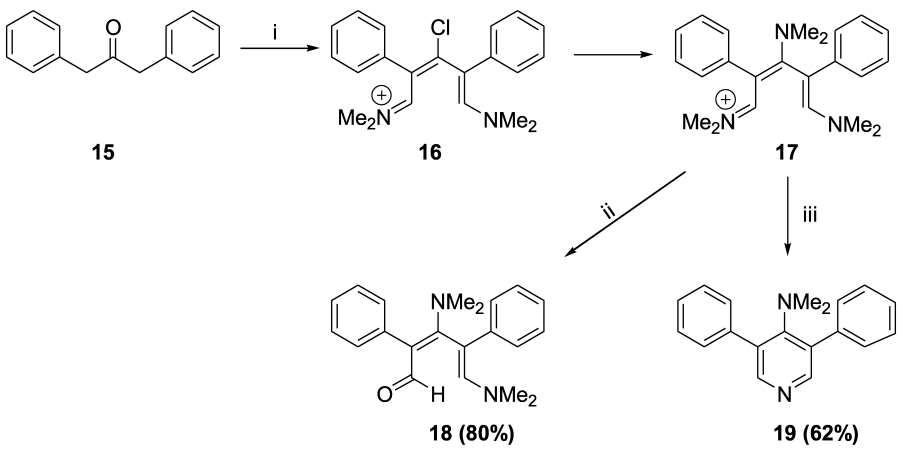
The formation of 3,5-diphenyl-4*H*-pyran-4-one from dibenzyl ketone on treatment with Vilsmeier reagent has been reported in the literature.[9,10] However, under our reaction conditions 3,5-bis(dimethylamino)-2,4-diphenyl-2,4-pentadienal **18** was formed as the only product in high



Scheme 2.



Scheme 3. Reagents and conditions: (i) DMF/$POCl_3$ (3 equiv.), 72 h, rt; (ii) DMF/$POCl_3$ (4 equiv.), 48 h, rt; (iii) NH_4OAc, 0 °C, 30 min.



Scheme 4. Reagents and conditions: (i) DMF/$POCl_3$ (3 equiv.), 72 h, rt; (ii) DMF/$POCl_3$ (4 equiv.), 48 h, rt; (iii) NH_4OAc, 0 °C, 30 min.

yield. It is interesting to note the introduction of *N*,*N*-dimethylamino substituent at the 3-position. Apparently, cyclization to the expected 4-pyrone is not favored by the presence of the dimethylamino group at the 3-position. However, the iminium salt **17** did undergo cyclization in the presence of ammonium acetate to afford 3,5-diphenyl-4-(*N*,*N*-dimethylamino)pyridine **19** (Scheme 4).

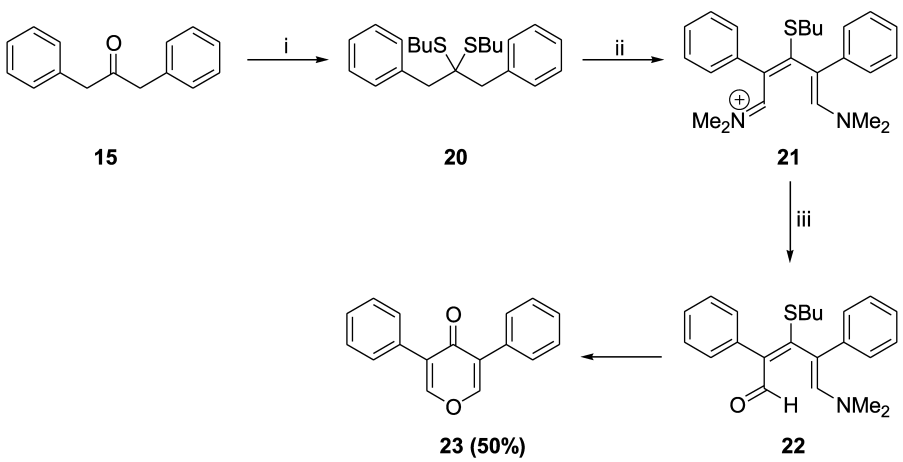
In a related experiment the dithioketal **20**, derived from the dibenzyl ketone **15** and butanethiol,[26] was subjected to Vilsmeier–Haack reaction in the presence of 3 equiv. of reagent prepared from $POCl_3$ and DMF for 16 h at room temperature. Subsequent basic hydrolysis gave 3,5-diphenyl-4*H*-pyran-4-one **23** in 50% yield. Obviously, **23** has been formed by the cyclization of the intermediate butylthio substituted pentadienaldehyde **22** (Scheme 5).

Phenoxyacetone **24** on treatment with Vilsmeier–Haack reagent followed by saturated aq. potassium carbonate gave 2[1-chloro-3-(dimethylamino)-2-phenoxy-2-propenylidene] malonaldehyde **26** as a pale yellow crystalline solid in 72% yield (Scheme 6). The fact that pentadienaldehyde **26**, formed by the hydrolysis of the bisiminium salt **25**, did not undergo further cyclization to give the expected 3-formyl pyrone **27** may be attributed to the reduced electrophilicity of C_5 of the pentadienaldehyde **26** due to the presence of the phenoxy substituent at C_4.

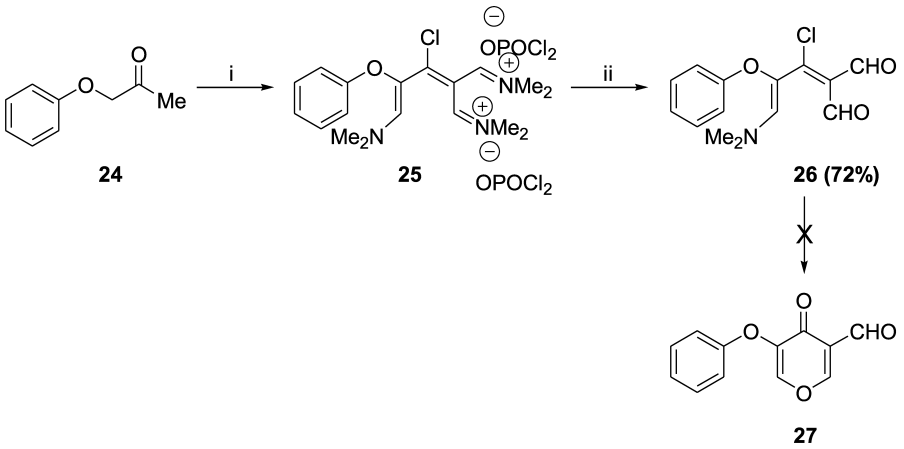
The reaction of benzylacetone **28** with Vilsmeier–Haack reagent under these conditions gave an unexpected product, 5-benzyl-4-hydroxy-6-(phenylethyl)isophthalaldehyde **33** in low yield among other unidentified products. The substituted phenol **33** must have resulted from the reaction of the α,β-unsaturated ketone **29**, which is the aldol type self-condensation product of benzylacetone, with chloromethyleneiminium salt. The bisiminium salt **30** formed by the multiple iminoalkylation of this ketone undergo cyclization and elimination of dimethylamine to afford the iminium salt **32** which on basic hydrolysis leads to the formation of **33** (Scheme 7). Similar cyclizations involving α,β-unsaturated ketones such as mesityloxide have been reported earlier.[27,28]

There are several approaches to the synthesis of 4-pyrones starting from but-3-ene-2-ones having an amino or alkoxy substituent at the 4-position.[17,29] The acyl ketenedithioacetals have alkylthio substituents at the β-position making them suitable candidates for the synthesis of 4-pyrones.[16] Against this background we have attempted to employ the Vilsmeier–Haack protocol for the synthesis of 4-pyrones starting from some substituted acyl ketenedithioacetals.

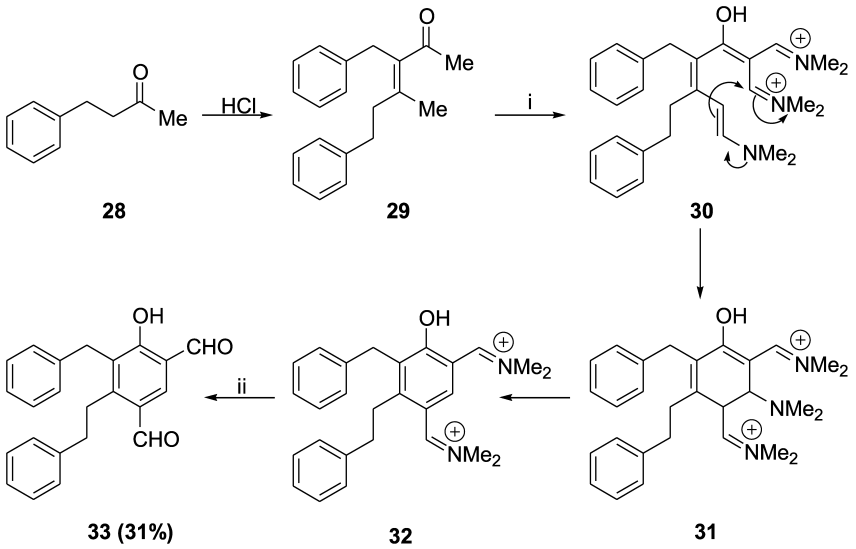
The ketenedithioacetal **36a** which was prepared from phenylacetone was allowed to react with 3 equiv. of Vilsmeier reagent for 72 h at room temperature. After the



Scheme 5. Reagents and conditions: (i) BuSH, $TiCl_4$, $CHCl_3$; (ii) DMF/$POCl_3$ (3 equiv.), 16 h, rt; (iii) $^-OH/H_2O$.



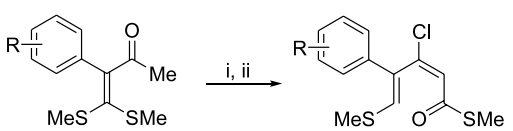
Scheme 6. Reagents and conditions: (i) DMF/$POCl_3$ (3 equiv.), 72 h, rt; (ii) $^{-}OH/H_2O$.



Scheme 7. Reagents and conditions: (i) DMF/$POCl_3$ (3 equiv.), 72 h, rt; (ii) $^{-}OH/H_2O$.

usual alkaline work up the S^1-methyl 3-chloro-5-(methylsulfanyl)-4-phenyl-2,4-pentadienethioate **37a** was isolated in 70% yield. Similarly *p*-methoxyphenyl substituted acyl ketenedithioacetal afforded the corresponding thiol ester **37b** (Scheme 8).

A plausible mechanism involving a 1,5-methylthio migration for the formation of the thiol ester **37** is depicted in Scheme 9. The initial iminoalkylation of the ketenedithioacetal leads to the formation of the iminium salt **38**. The presence of aryl substituent at the α-position of the ketenedithioacetal reduces the extent of delocalization of



36a: R = H
36b: R = 4-OCH_3

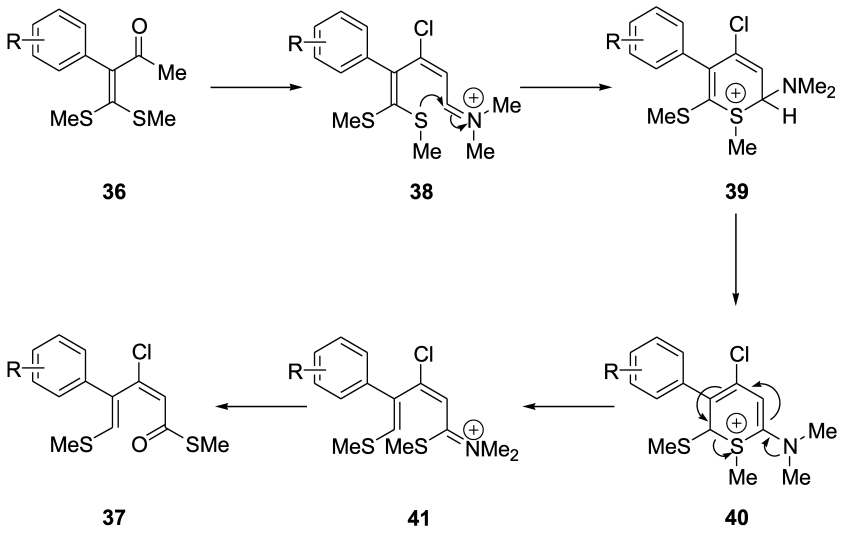
37a: R = H (70%)
37b: R = 4-OCH_3 (71%)

Scheme 8. Reagents and conditions: (i) DMF/$POCl_3$ (3 equiv.), 72 h, rt; (ii) $^{-}OH/H_2O$.

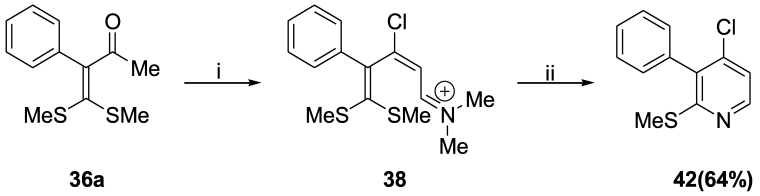
the carbonyl group from the ketenedithioacetal moiety. This favors enolization of the ketenedithioacetal **36** which is essential for the formation of iminium salt **38**. An intramolecular attack of the methylthio group to the iminium moiety results in the migration of the methylthio group which eventually lead to the formation of the iminium salt **41** which on hydrolysis gives the thiol ester **37**.

Treatment of the product mixture obtained by the addition of Vilsmeier reagent to the acyl ketenedithioacetal **36a** with excess ammonium acetate prior to the basic hydrolysis gave 4-chloro-2-(methylsulfanyl)-3-phenylpyridine **42** in 64% yield (Scheme 10). It is important to note that substituted nicotinaldehyde was not formed when ketenedithioacetal **36a** was used as the starting substrate, instead of phenylacetone. This could be attributed to the higher selectivity of ketenedithioacetals towards iminoalkylation compared to the corresponding enaminoketones which are the proposed intermediates involved in the direct reaction of ketones with chloromethyleneiminium salt.

In summary, we have shown that the Vilsmeier–Haack



Scheme 9.



Scheme 10. Reagents and conditions: (i) DMF/$POCl_3$ (3 equiv.), 72 h, rt; (ii) NH_4OAc, 0 °C, 30 min.

reactions of substituted phenylacetones followed by treatment with aq. K_2CO_3 or anhydrous NH_4OAc lead to the formation of 3-formyl-4-pyrones and 5-aryl-4-chloronicotinaldehydes, respectively, in good yields. The formation of 3-methyl-5-phenyl-4*H*-pyran-4-one and 4-chloro-3-methyl-5-phenylpyridine were observed in the case of benzyl ethyl ketone. However, other aliphatic ketones on treatment with the Vilsmeier reagent gave rather complex product mixtures. The reaction of phenoxyacetone and dibenzyl ketone did undergo multiple iminoalkylations under these conditions, but failed to give the expected pyran-4-one derivatives. But when the reaction was carried out using dibenzyl ketone followed by treatment with ammonium acetate 3,5-diphenyl-4-(*N*,*N*-dimethylamino)-pyridine was obtained instead of the corresponding chlorosubstituted pyridine. Nevertheless, the dithioketal of dibenzyl ketone gave 3,5-diphenyl-4*H*-pyran-4-one. We have also carried out some reactions on substituted ketenedithioacetals expecting the formation of substituted pyran-4-ones. Though the substituted ketenedithioacetals underwent Vilsmeier reaction smoothly, the product obtained were the substituted conjugated pentadiene thioicacid S-methyl esters on usual alkaline workup. However, on treatment with the Vilsmeier reagent followed by ammonium acetate, acyl ketenedithioacetal derived from phenylacetone afforded 4-chloro-2-(methylsulfanyl)-3-phenylpyridine.

2. Experimental

2.1. General

Melting points are uncorrected and were obtained on a Buchi-530 melting point apparatus. IR spectra were recorded on a Shimadzu IR-470 spectrometer. NMR spectra were recorded in deutereochloroform (internal standard TMS) on JEOL EX90 or Bruker WM200 or Bruker WM300 spectrometers; ^1H spectra at 90 or 200 or 300 MHz and ^{13}C spectra at 22.4 or 50.3 or 75.5 MHz, respectively, and coupling constants are given in Hz. Electron impact mass spectra were obtained on a Finnigan-MAT 312 spectrometer. Solvents were dried and distilled before use: *N*,*N*-dimethylformamide from $P_2O_5{\cdot}CHCl_3$ from anhydrous $CaCl_2$. Organic extracts were dried over anhydrous Na_2SO_4.

2.1.1. 4-Oxo-5-phenyl-4*H*-pyran-3-carbaldehyde (2a). Vilsmeier reagent was prepared by mixing ice-cold, dry DMF (50 mL) and $POCl_3$ (2.8 mL, 30 mmol). The mixture was then stirred for 15 min at room temperature. 1-Phenylacetone **1a** (1.34 g, 10 mmol) was dissolved in dry DMF (5 mL) and added over about 15 min at 0–5 °C. The reaction mixture was stirred for 72 h at room temperature. The mixture was then added to cold, saturated aq. K_2CO_3 (200 mL) and extracted with diethyl ether (3×50 mL). The organic layer was washed with water, dried over anhydrous Na_2SO_4, and evaporated to afford the crude product, which was column chromatographed over silica gel using hexane/ethyl acetate (9:1) as eluent to give the title compound **2a** (1.1 g, 59%), as a colorless crystalline solid, mp 148–149 °C. [Found: C, 71.92; H, 3.96. $C_{12}H_8O_3$ requires C, 72.0; H, 4.03%]; ν_{max}(KBr) 3020, 1700, (C=O), 1640, (C=O), 1540, 1320, 1270, 1010 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ 7.10–7.80 (5H, m, arom. H), 7.90 (1H, s, vinylic), 8.40 (1H, s, vinylic), 10.35 (1H, s, CHO); ^{13}C NMR (22.64 MHz, $CDCl_3$): δ 124.32, 128.50, 129.00, 129.60, 132.55, 152.87, 159.20 (arom. and vinylic), 175.21

(C═O), 188.70 (C═O); EI-MS *m/z*: 200 (M^+), 172 (100%), 115 (50%), 102 (22%), 89 (11%).

2.1.2. 5-(2-Methoxyphenyl)-4-oxo-4*H*-pyran-3-carbaldehyde (2b). The title compound **2b** (1.1 g, 59%) a pale yellow crystalline solid, mp 127–129 °C was obtained by the same procedure as **2a** except using 1-(2-methoxyphenyl)acetone **1b** (1.64 g, 10 mmol) instead of **1a**. [Found: C, 67.75; H, 4.27. $C_{13}H_{10}O_4$ requires C, 67.82; H, 4.38%]; ν_{max}(KBr) 3015, 1685 (C═O), 1640 (C═O), 1600, 1540, 1485, 1455, 1305, 1285, 1260, 1240, 1080, 1020, 1005 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 3.80 (3H, s, OCH_3); 6.90–7.60 (4H, m, arom. H); 7.90 (1H, s, vinylic); 8.40 (1H, s, vinylic); 10.35 (1H, s, CHO); ^{13}C NMR (22.64 MHz, $CDCl_3$) δ 55.64 (OCH_3), 111.28, 118.74, 120.56, 124.17, 130.41, 130.52, 131.12, 154.30, 157.14, 159.17 (arom. and vinylic), 175.10 (C═O), 189.09 (C═O); EI-MS *m/z*: 230 (10%, M^+), 216 (20%), 202 (90%), 185 (21%), 159 (11%), 131 (66%), 115 (19%), 97 (18%), 85 (53%), 71 (56%).

2.1.3. 5-(4-Methoxyphenyl)-4-oxo-4*H*-pyran-3-carbaldehyde (2c). The title compound **2c** (1.61 g, 70%) a pale yellow crystalline solid, mp 153–154 °C was obtained by the same procedure as **2a** except using 1-(4-methoxyphenyl)acetone **1c** (1.64 g, 10 mmol) instead of **1a**. [Found: C, 67.76; H, 4.29. $C_{13}H_{10}O_4$ requires C, 67.82; H, 4.38%]; ν_{max}(KBr) 3060, 1685, (C═O), 1630, (C═O), 1600, 1535, 1500, 1350, 1320, 1290, 1275, 1250, 1180, 1100, 1030, 1015, 1005 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 3.8 (3H, s, OCH_3); 6.95 (2H, d, J=8 Hz, arom. H); 7.45 (2H, d, J=8 Hz, arom. H); 7.85 (1H, s, vinylic); 8.35 (1H, s, vinylic), 10.35 (1H, s, CHO); ^{13}C NMR (22.64 MHz, $CDCl_3$) δ 55.16 (OCH_3), 114.00, 121.78, 124.17, 129.72, 132.14, 152.18, 159.05 (arom. and vinylic), 160.24, 175.10 (C═O), 188.82 (C═O); EI-MS *m/z*: 230 (48%, M^+), 202 (100%), 187 (21%), 159 (15%), 145 (13%), 132 (17%), 117 (12%), 89 (19%).

2.1.4. 4-Chloro-5-phenylnicotinaldehyde (3a). Vilsmeier reagent was prepared by mixing ice-cold, dry DMF (50 mL) and $POCl_3$ (3.7 mL, 40 mmol). The mixture was then stirred for 15 min at room temperature. 1-Phenylacetone **1a** (1.34 g, 10 mmol) was dissolved in dry DMF (5 mL) and added over about 15 min at 0–5 °C. The reaction mixture was stirred for 48 h at room temperature and was cooled to 0–5 °C in an ice bath and excess solid ammonium acetate (40 equiv., 31 g) was slowly added to the reaction mixture and stirred for another 30 min. The mixture was then added to cold, saturated aq. K_2CO_3 (200 mL) and the white precipitate formed was filtered and dried. It was further purified by column chromatography over silicagel using hexane/ethylacetate (19:1) as eluent to give the title compound **3a** (1.74 g, 40%) as a white crystalline solid, mp 81–83 °C. [Found: C, 66.14; H, 3.68; N, 6.36. $C_{12}H_8ClNO$ requires C, 66.22; H, 3.70; N, 6.44%]; ν_{max}(KBr) 1690, 1550, 1430, 1380, 1305, 1260, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27–7.50 (5H, m, arom.); 8.72 (1H, s, Py 6-H); 9.02 (1H, s, Py 2-H); 10.59 (1H, s, CHO); ^{13}C NMR (75.48 MHz, $CDCl_3$) δ 127.87, 128.60, 128.92, 129.48, 134.14, 137.40, 144.90, 149.63, 155.20 (arom.), 189.06 (CHO); EI-MS *m/z*: 219 (M^++2, 10%), 218 (M^++1, 33%), 217 (M^+, 30%) 216 (100%, M^+−1), 215 (64%), 198 (41%), 187 (33%), 152 (29%), 125 (53%), 77 (18%).

2.1.5. 4-Chloro-5-(4-methoxyphenyl)nicotinaldehyde (3b). The title compound **3b** (1.57 g, 34%, a white solid, mp 94–96 °C) was obtained by the same procedure as **3a** except using 1-(4-methoxyphenyl)acetone **1c** (1.64 g, 10 mmol) instead of **1a**. [Found: C, 62.91; H, 3.93; N, 5.57. $C_{13}H_{10}ClNO_2$ requires C, 63.04; H, 4.07; N, 5.66%]; ν_{max}(KBr) 1685, 1610, 1550, 1510, 1430, 1380, 1295, 1250, 1180, 1025 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.89 (s, 3H, OCH_3); 7.04 (d, 2H, J=8 Hz, arom.); 7.39 (, d, 2H, J=8 Hz, arom.); 8.64 (1H, s, Py 6-H); 9.17 (1H, s, Py 2-H); 10.59 (1H, s, CHO); EI-MS *m/z*: 249 (M^++2, 3%), 248 (M^++1, 33%), 247 (M^+, 10%) 246 (100%, M^+−1), 228 (83%), 140 (17%), 112 (18%).

2.1.6. 3-Methyl-5-phenyl-4*H*-pyran-4-one (12). The title compound **12** (1.45 g, 63%, a colorless crystalline solid, mp 90–92 °C) was obtained by the same procedure as **2a** except using 1-phenyl-2-butanone (1.48 g, 10 mmol) instead of **1a**. [Found: C, 77.36; H, 5.38. $C_{12}H_{10}O_2$ requires C, 77.40; H, 5.41%]; ν_{max}(KBr) 3010, 1640, 1610, 1490, 1410, 1330, 1290, 1040, 1000 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.0 (3H, s, CH_3); 7.2–7.9 (7H, m, arom. and vinylic); ^{13}C NMR δ (50.3 MHz, $CDCl_3$) 11.24 (CH_3), 126.28, 128.30, 128.41, 128.62, 128.80, 131.49, 151.24, 152.94 (arom. and vinylic), 177.50 (C═O); EI-MS *m/z*: 186 (100%, M^+), 129 (12%), 102 (84%), 89 (24%), 76 (19%).

2.1.7. 4-Chloro-3-methyl-5-phenylpyridine (14). Vilsmeier reagent was prepared by mixing ice-cold, dry DMF (50 mL) and $POCl_3$ (3.7 mL, 40 mmol). The mixture was then stirred for 15 min at room temperature. 1-Phenyl-2-butanone (1.48 g, 10 mmol) was dissolved in dry DMF (5 mL) and added over 15 min at 0–5 °C. The reaction mixture was stirred for 48 h at room temperature. It was then cooled to 0–5 °C in an ice bath and excess solid ammonium acetate (40 equiv., 31 g) was slowly added to the reaction mixture and stirred for another 30 min. The mixture was then added to cold, saturated aq. K_2CO_3 (200 mL) and extracted with diethyl ether (3×50 mL). The organic layer was washed with water, dried over anhydrous Na_2SO_4, and evaporated to afford the crude product, which was column chromatographed over silica gel using hexane/ethyl acetate (19:1) as eluent to give the title compound **14** (1.27 g, 62%) a brown viscous oil. [Found: C, 70.65; H, 4.88; N, 6.79. $C_{12}H_{10}ClN$ requires C, 70.77; H, 4.95; N, 6.88%]; ν_{max}(neat) 1550, 1450, 1400, 1270, 1230, 1170, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.45 (3H, s, CH_3), 7.39–7.44 (5H, m, arom.), 8.37 (1H, s, Py 6-H), 8.62 (1H, s, Py 2-H); ^{13}C NMR (75.48 MHz, $CDCl_3$) δ 17.91 (CH_3), 128.68, 128.73, 129.93, 130.01, 136.34, 142.97, 149.01; 149.11, 150.12; EI-MS *m/z*: 205 (M^++2, 8%), 204 (M^++1, 33%), 203 (M^+, 25%) 202 (100%, M^+−1), 201 (24%), 185 (46%), 167 (54%), 141 (41%), 115 (45%).

2.1.8. 3,5-Bis(dimethylamino)-2,4-diphenyl-2,4-pentadienal (18). To the Vilsmeier reagent prepared from $POCl_3$ (2.8 mL, 30 mmol) and dry DMF (50 mL) 1,3-diphenylacetone (2.1 g, 10 mmol) was added in dry DMF (5 mL) at 0–5 °C and the reaction mixture was stirred at room temperature for 72 h. It was then worked up using

cold, saturated aq. K_2CO_3 (200 mL) and extracted with diethyl ether (3×50 mL). The organic layer was washed with water, dried over anhydrous Na_2SO_4, and evaporated to afford the yellow crystals of the product, which was recrystallized from benzene to give the title compound **18** (2.56 g, 80%) a yellow crystalline solid, mp 140–142 °C. [Found: C, 78.68; H, 7.47; N, 8.63. $C_{21}H_{24}N_2O$ requires C, 78.72; H, 7.55; N, 8.74%]; ν_{max}(KBr) 2900, 1620 (C═O), 1580, 1380, 1285, 1085 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 2.4 (6H, s, $N(CH_3)_2$), 2.8 (6H, s, $N(CH_3)_2$), 6.8 (1H, s, vinylic), 7.0–7.5 (10H, m, arom.), 9.1 (1H, s, CHO); ^{13}C NMR (22.4 MHz, $CDCl_3$) δ 43.08 (CH_3), 43.50 (CH_3), 108.48, 121.22, 124.53, 125.30, 125.72, 127.51, 127.72, 128.29, 129.27, 129.96, 138.46, 138.70, 151.86, 173.84 (vinylic and arom.) 186.64 (CHO); EI-MS *m/z*: 320 (M^+, 35%), 303 (13%), 276 (54%), 202 (19%), 178 (11%), 145 (73%), 103 (21%), 89 (23%), 72 (98%).

2.1.9. 3,5-Diphenyl-4-(*N*,*N*-dimethylamino)pyridine (19). To the Vilsmeier reagent prepared from $POCl_3$ (3.7 mL, 40 mmol) and dry DMF (50 mL) 1,3-diphenylacetone (2.1 g, 10 mmol) was added in dry DMF (5 mL) at 0–5 °C and the reaction mixture was stirred at room temperature for 48 h. It was then cooled to 0–5 °C in ice and excess solid ammonium acetate (40 equiv., 31 g) was slowly added to the reaction mixture and stired for 30 min more. The mixture was then added to cold, saturated aq. K_2CO_3 (200 mL) and extracted with diethyl ether (3×50 mL). The organic layer was washed with water, dried over anhydrous Na_2SO_4, and evaporated to afford the product, which was column chromatographed over silicagel using hexane/ethylacetate (19:1) as eluent to give the title compound **19** (1.75 g, 62%) a brown viscous oil. [Found: C, 83.13; H, 6.57; N, 10.14. $C_{19}H_{18}N_2$ requires C, 83.18; H, 6.61; N, 10.21%]; ν_{max}(neat) 1580, 1510, 1435, 1420, 1310, 1230, 1135, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.24 (6H, s, $N(CH_3)_2$), 7.25–7.33 (10H, m, arom.), 8.19 (2H, s, Py, 2-H and 6-H); EI-MS *m/z*: 274 (100%, M^+), 273 (82%), 271 (21%), 259 (36%), 105 (59%), 91 (26%), 77 (30%).

2.1.10. 3,5-Diphenyl-4*H*-pyran-4-one (23). To the Vilsmeier reagent prepared from $POCl_3$ (2.8 mL, 30 mmol) and dry DMF (50 mL) dithioketal of 1,3-diphenylacetone (3.7 g, 10 mmol) was added in dry DMF (5 mL) at 0–5 °C and the reaction mixture was stirred at room temperature for 72 h. It was then worked up using cold, saturated aq. K_2CO_3 (200 mL) and extracted with diethyl ether (3×50 mL). The organic layer was washed with water, dried over anhydrous Na_2SO_4, and column chromatographed over silica gel using hexane/ethyl acetate (9:1) as eluent to give the title compound **23**. (1.3 g, 50%) a colorless crystalline solid, mp 185–186 °C (lit.,[10] 186–187 °C).

2.1.11. 2-[1-Chloro-3-(dimethylamino)-2-phenoxy-2-propenylidene]malonaldehyde (26). To the Vilsmeier reagent prepared from $POCl_3$ (2.8 mL, 30 mmol) and dry DMF (50 mL) 1-phenoxyacetone (1.5 g, 10 mmol) was added in dry DMF (5 mL) at 0–5 °C and the reaction mixture was stirred at room temperature for 72 h. It was then worked up using cold, saturated aq. K_2CO_3 (200 mL) and extracted with diethyl ether (3×50 mL). The organic layer was washed with water, dried over anhydrous Na_2SO_4, and evaporated to afford the yellow crystals of the product, which was recrystallized from benzene to give the title compound **26** (2 g, 72%) a pale yellow crystalline solid, mp 161–162 °C. [Found: C, 60.10; H, 4.92; N, 4.93. $C_{14}H_{14}ClNO_3$ requires C, 60.11; H, 5.04; N, 5.01%]; ν_{max}(KBr) 2980, 2700, 1720, 1680, 1580, 1480, 1400, 1260, 1250, 1210, 1180, 1130, 1010 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.25 (6H, s, $N(CH_3)_2$); 6.95–7.35 (6H, m, arom. and vinylic); 9.05 (1H, s, CHO), 9.45 (1H, s, CHO); ^{13}C NMR (75.48 MHz, $CDCl_3$) δ 39.81 (CH_3), 47.59 (CH_3), 115.21, 122.15, 129.66, 135.31, 147.51, 156.28, 160.11 (arom. and vinylic), 184.37 (CHO), 185.75 (CHO); EI-MS *m/z*: 281 (M^++2, 3) 279 (M^+, 12%), 278 (68%), 249 (27%), 186 (100%), 157 (38%), 94 (34%), 77 (56%).

2.1.12. 5-Benzyl-4-hydroxy-6-(phenylethyl)isophthalaldehyde (33). To the Vilsmeier reagent prepared from $POCl_3$ (2.8 mL, 30 mmol) and dry DMF (50 mL) 4-phenyl-2-butanone (1.48 g, 10 mmol) was added in dry DMF (5 mL) at 0–5 °C and the reaction mixture was stirred at room temperature for 72 h. It was then worked up using cold, saturated aq. K_2CO_3 (200 mL) and extracted with diethyl ether (3×50 mL). The organic layer was washed with water, dried over anhydrous Na_2SO_4, and column chromatographed using hexane/ethyl acetate (9:1) as eluent to give the title compound **33** (0.53 g, 31%) a colorless crystalline solid. [Found: C, 80.14; H, 5.79. $C_{23}H_{20}O_3$ requires C, 80.21; H, 5.85%]; ν_{max}(KBr) 1680, 1620, 1580, 1480, 1400, 1365, 1265, 1245, 1200, 1180, 1165, 1125, 1000 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.03 (2H, t, J=7 Hz, CH_2), 3.20 (2H, t, J=7 Hz, CH_2), 4.03 (2H, s, CH_2), 7.23–7.25 (10H, m, arom.), 7.99 (1H, m, OH), 8.06 (1H, m, arom.), 9.91 (1H, s, CHO), 11.73 (1H, s, CHO); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 30.29, 34.99, 40.15 (CH_2), 119.76, 126.29, 126.52, 128.46, 128.62, 128.64, 128.90, 129.11, 130.83, 132.93, 136.77, 139.19, 141.10, 163.27 (arom. and vinylic), 196.52, 196.78 (CHO); EI-MS *m/z*: 344 (44%, M^+), 239 (100%), 161 (28%), 91 (32%).

2.1.13. S[1]-Methyl 3-chloro-5-(methylsulfanyl)-4-phenyl-2,4-pentadienethioate (37a). To the Vilsmeier reagent prepared from $POCl_3$ (2.8 mL, 30 mmol) and dry DMF (50 mL) 4,4-bis(methylsulfanyl)-3-phenyl-3-buten-2-one **36a** (2.38 g, 10 mmol) was added in dry DMF (5 mL) at 0–5 °C and the reaction mixture was stirred at room temperature for 72 h. It was then worked up using cold, saturated aq. K_2CO_3 (200 mL) and extracted with diethyl ether (3×50 mL). The organic layer was washed with water, dried over anhydrous Na_2SO_4, and column chromatographed over silica gel using hexane/ethyl acetate (9:1) as eluent to give the title compound **37a** (1.98 g, 70%) a yellow crystalline solid, mp 97–98 °C. [Found: C, 54.78; H, 4.57. $C_{13}H_{13}ClOS_2$ requires C, 54.82; H, 4.60%]; ν_{max}(KBr) 1636 (C═O), 1555, 1520, 1480, 1430, 1310, 1260, 1220, 1080, 1045, 1025, 920, 845 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 2.2 (3H, s, SCH_3), 2.4 (3H, s, SCH_3), 7.0–7.8 (7H, m, arom. and vinylic); ^{13}C NMR (22.64 MHz, $CDCl_3$) δ 13.21 (SCH_3), 14.88 (SCH_3), 118.74, 127.96, 128.44, 130.79, 131.63, 136.43, 140.61, 141.21 (arom. and vinylic), 191.42 (C═O); EI-MS *m/z*: 284 (2%, M^+), 237 (100%), 189 (20%), 174 (46%), 115 (22%).

2.1.14. S[1]-Methyl 3-chloro-4-(4-methoxyphenyl)-5-(methyl-sulfanyl)-2,4-pentadienethioate (37b). The title

compound **37b** (2.24 g, 71%) a yellow crystalline solid, mp 97–99 °C was obtained by the same procedure as **37a** except using 3-(4-methoxyphenyl)-4,4-bis(methylsulfanyl)-3-buten-2-one **36b** (2.68 g, 10 mmol) instead of **36a**. [Found: C, 53.38; H, 4.76. $C_{14}H_{15}ClO_2S_2$ requires C, 53.41; H, 4.8%]; ν_{max}(KBr) 2900, 1630 (C=O), 1600, 1555, 1525, 1490, 1290, 1240, 1170, 1050, 1030, 925 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 2.2 (3H, s, SCH_3), 2.4 (3H, s, SCH_3), 3.85 (3H, s, OCH_3), 6.8–7.6 (6H, m, arom. and vinylic); ^{13}C NMR (22.64 MHz, $CDCl_3$) δ 13.27 (SCH_3), 14.85 (SCH_3), 55.01 (OCH_3), 113.37, 118.83, 128.53, 130.41, 131.36, 132.11, 140.49, 140.82, 159.67 (arom. and vinylic), 191.89 (C=O); EI-MS *m/z*: 316 (2%, M^++2), 314 (6%, M^+), 313 (14%), 266 (100%), 238 (17%), 223 (21%), 203 (78%), 188 (32%), 180 (18%), 160 (15%), 145 (45%).

2.1.15. 4-Chloro-2-(methylsulfanyl)-3-phenylpyridine (42). To the Vilsmeier reagent prepared from $POCl_3$ (2.8 mL, 30 mmol) and dry DMF (50 mL) 4,4-bis(methylsulfanyl)-3-phenyl-3-buten-2-one **36a** (2.38 g, 10 mmol) was added in dry DMF (5 mL) at 0–5 °C and the reaction mixture was stirred at room temperature for 72 h. It was then cooled to 0–5 °C in ice and solid ammonium acetate (40 equiv., 31 g) was slowly added to the reaction mixture in excess and stirred 30 min more. The reaction mixture was then worked up using cold, saturated aq. K_2CO_3 (200 mL) and extracted with diethyl ether (3×50 mL). The organic layer was washed with water, dried over anhydrous Na_2SO_4, and column chromatographed over silica gel using hexane as eluent to give the title compound **42** (1.5 g, 64%) a red liquid which turns to a purple colored liquid on solvent evaporation. [Found: C, 61.11; H, 4.21; N, 5.86. $C_{12}H_{10}ClNS$ requires C, 61.14; H, 4.28; N, 5.94%]; ν_{max}(neat) 2923, 1676, 1547, 1437, 1359, 1207 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.38 (3H, s, SCH_3); 7.05 (1H, d, *J*=5.5 Hz, Py 5-H); 7.17–7.21 (2H, m, Ph); 7.36–7.42 (3H, m, Ph); 8.24 (1H, d, *J*=5.5 Hz, Py 6-H); ^{13}C NMR (75.48 MHz, $CDCl_3$) δ 13.11 (SCH_3), 118.96, 127.67, 128.57, 132.91, 133.84, 141.36, 147.31, 160.18 (arom.); EI-MS *m/z*: 237 (M^++2, 8%), 236 (M^++1, 44%), 235 (M^+, 36%) 234 (100%, M^+−1), 233 (50%), 201 (58%), 200 (29%), 199 (50%), 154 (79%), 127 (24%), 105 (57%), 77 (43%).

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Synthesis of 1-substituted 2,9,10-trioxatricyclo[4.3.1.0^{3,8}]decanes

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Abstract—A series of 1-alkyl- and 1-alkenyl-2,9,10-trioxatricyclo[4.3.1.0^{3,8}]decanes, models for the core orthoester structural moiety of resiniferatoxin and synaptolepis factors, was prepared by a transetherification reaction of (±)-all-*cis*-cyclohexane-1,2,4-triol and trimethyl orthocarboxylates. The synthesis of the starting trimethyl orthocarboxylates is also given in detail.

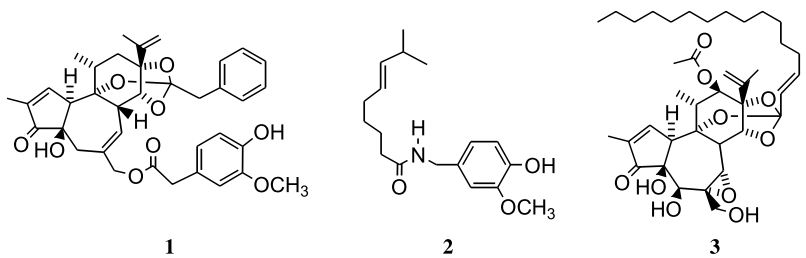
1. Introduction

The polycyclic orthoesters, 2,9,10-trioxatricyclo[4.3.1.0^{3,8}]-decanes, attracted a lot of attention since it has been shown that this structural unit is incorporated in diterpenes with a daphnane skeleton such as resiniferatoxin (**1**, resiniferonol-9α,13α,14α-orthophenylacetate-20-(4-hydroxy-3-methoxy)-phenylacetate, RTX),[1–3] daphnetoxin and its 12-hydroxy derivative, 1-alkyldaphnanes, etc.[3–10] Most of these daphnanes exhibit various physiological activities.[7,11,12] RTX **1** has been isolated from Euphorbium,[1] the dried latex of *Euphorbia resinifera*, which has been in medicinal use since ancient times and as a matter of fact can be regarded as one of the oldest medicines known to man.[13] The recent interest in RTX **1** arises from its biological activity to relieve pain, especially in connection to diabetic neuropathy.[14] A similar biological activity is exhibited by capsaicin **2**.[14] RTX **1** seems to be more promising from a pharmaceutical point of view than capsaicin **2**, because it is more potent and at the same time better tolerated by the patients in clinical trials.[14]

While there are numerous investigations on structure–activity relationships of **2**,[15] less is known about that of RTX **1**.[16,17] It is assumed that the homovanillyl residue at C-20 and the lipophilic orthoester group on ring C of RTX are both necessary for the activity.[2,8,13,14] The tricyclic diterpene skeleton contributes also to the activity.[16] However, some derivatives of RTX **1** (e.g., compounds **5**) were synthesized and some of them showed similar activity as compared to RTX **1** in the irritation test on mouse ear.[2,18]

Other naturally occurring daphnanes with orthoester moiety such as kirkinine **3** and a series of structurally similar compounds isolated from the Kenyan plant *Synaptolepis kirkii* were shown to possess neurotrophic activity.[10,19] The latter structures of them incorporate a long chain attached to the orthoester C-atom, including often a double bond at the α-position (Fig. 1).[3,10,19]

It is difficult to study the structure–activity relationships because of the limited accessibility of RTX **1** and kirkinine



1 **2** **3**

Figure 1.

Keywords: Cage orthoesters; Resiniferatoxin; Pinner reaction; Transetherification; All-*cis*-cyclohexane-1,2,4-triol.
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3 from natural sources and the high price of the synthetic material. Thus, in this paper, the preparation of a series of 1-substituted 2,9,10-trioxatricyclo[4.3.1.0^{3,8}]decanes of types **16** and **17** from (±)-all-*cis*-cyclohexane-1,2,4-triol **15**[28] as partial structural units of RTX **1** and kirkinine **3** is described.

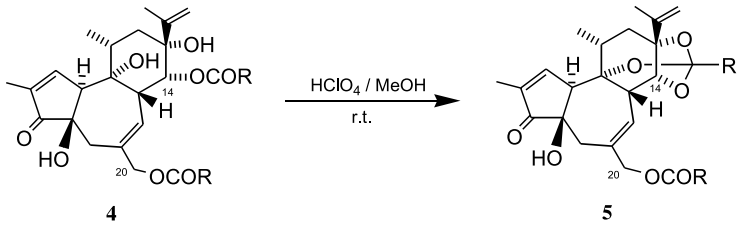
2. Results and discussion

There are few examples in the literature about the preparation of RTX derivatives and their more simple structural analogs. Adolf and co-workers treated a series of 14,20-diacylresiniferonols **4** with a solution of perchloric acid in methanol at room temperature to give the analogous compounds **5** of RTX in good yields (Scheme 1).[2,18] The formation of the orthoester moiety via mild acid treatment of the monoacylated cyclohexane-1,2,4-triol moiety, introduced by Adolf,[2,18] was used as well by Wender and co-workers in the key step of their synthesis of (+)-RTX **1**.[20,21] Reflux 14,20-dibenzoylresiniferonol **6** with *p*-toluenesulfonic acid in dichloroethane afforded also a good yield of the corresponding orthoester **7** (Scheme 2).[16]

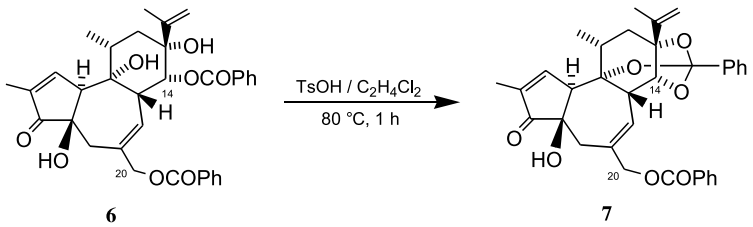
The polyhydroxylated ceverathrum alkaloids give readily orthoacetates[22–25] by treatment with acetic anhydride–pyridine[22,23] or by means of acetic anhydride–perchloric acid.[24,25] The formation of orthoesters in this group of alkaloids is used for stereochemical assignments based on the presumption that *cis*-orientation of the hydroxyl groups with respect to the polycyclic skeleton of the alkaloids obviously favours the formation of the orthoester moiety.[22–25]

However, not always the *cis*-configuration of the oxygenated functional groups towards the cyclohexane ring is a prerequisite condition for the formation of the cage type of orthoesters. For example, the synthesis of (±)-7-substituted 1-benzyl-2,9,10-trioxatricyclo[4.3.1.0^{3,8}]-decanes **9** modelling the core orthoester structure of RTX was performed from the diacylated derivative of cyclohexane-r-1,t-2,c-4-triol **8** as starting compound.[26] It was shown that compound **8** underwent a cyclization to orthophenylacetate **9** at 170 °C accompanied by a configurational change from 1,2-*trans* in **8** to 1,2-*cis* in **9** (Scheme 3). The harsh reaction conditions necessary to convert **8** into **9** are explained by the energetically unfavourable change of the conformation of the cyclohexane ring from chair in **8** to boat in **9**.[26]

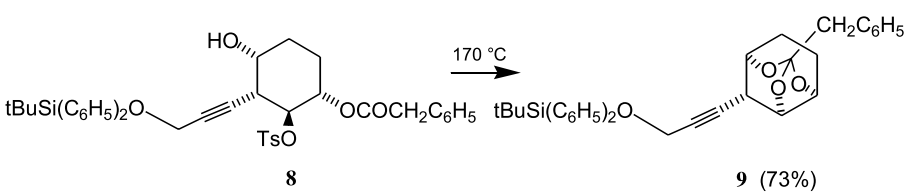
As pointed out above, the formation of the orthoester moiety in the synthetic studies related to RTX **1** is strongly dependent on the conformation of ring C of RTX **1**.[2,15,22–26] Until now, there are few evidences about the stereochemistry of **1** and other daphnane compounds with orthoester functionality probably because of the complexity of the molecule, low isolation yields from the plant material and non-crystallizability of the compounds. NMR investigations in combination with molecular modelling studies are carried out in order to throw more light at the stereochemistry of RTX **1**.[27] It is suggested that the orthophenylacetate group can act as a conformational lock



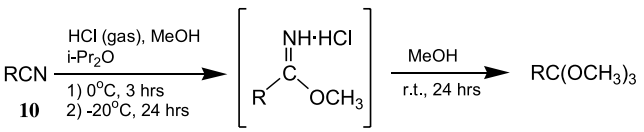
Scheme 1.



Scheme 2.



Scheme 3.



11a R = $CH_3(CH_2)_4$ (52%) **12a** (72%)
11b R = $CH_3(CH_2)_5$ (62%) **12b** (79%)
11c R = $CH_3(CH_2)_8$ (75%) **12c** (60%)
11d R = $CH_3(CH_2)_{14}$ (87%) **12d** (72%)
11e R = *E*-$CH_2CH{=}CHCH_3$ (86%) **12e** (70%)

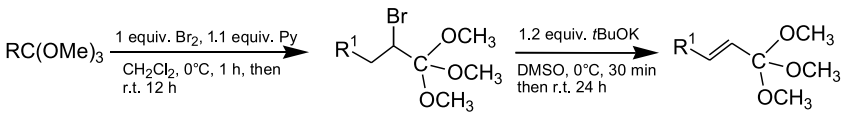
Scheme 4.

for the six-membered ring C forcing it to adopt boat conformation.[27]

Our approach to synthesize cage compounds of type **16** and **17** involved an acid catalysed transetherification reaction of (±)-all-*cis*-cyclohexane-1,2,4-triol **15**[28] with a series of trimethyl orthoesters of saturated and unsaturated carboxylic acids **12** and **14**, respectively (Scheme 6). These orthoesters were synthesized as outlined in Schemes 4 and 5. Except for trimethyl orthovalerate **12f**, trimethyl orthoformate **12g** and trimethyl orthobenzoate **12h**, which are commercially available, trimethyl orthoesters of hexanoic,[29] heptanoic, decanoic and hexadecanoic acids **12a**–**d**, as well as trimethyl ortho-3*E*-pentenoic acid **12e** were synthesized for the purposes of this investigation from the corresponding nitriles **10** using the Pinner reaction (Scheme 4).[30,31] A solution of the appropriate nitrile **10** in methanol and diisopropyl ether was treated with a slight molar excess of dry hydrogen chloride. The precipitated hydrochlorides of methyl imidates of type **11** were subjected to methanolysis to give the desired orthoesters **12**. It should be underlined that the formation of orthoesters is not well documented in the literature. Although being reported in some articles and books,[32–36] the literature is devoid of detailed and reliable description for the isolation of the pure orthoesters. In our hands, in most cases the Pinner reaction was accompanied by the formation of small quantities of the corresponding amides and methyl esters as side products.[30,31]

The introduction of the double bond in α-position to the orthoester functionality to give the trimethyl orthoesters of 2*E*-hexenoic, 2*E*-heptenoic and 2*E*-pentenoic acids **14a**–**c** was carried out using literature procedures (Scheme 5).[37,38] Thus, orthoesters **12a**,**b**,**f** were brominated by means of bromine in the presence of pyridine at room temperature[37] to give trimethyl ortho-2-bromocarboxylates **13a**–**c**, which were purified by means of vacuum distillation. Subsequent dehydrobromination by the use of potassium *tert*-butoxide in DMSO afforded trimethyl *E*-α,β-unsaturated orthoesters **14a**–**c** purified by means of vacuum distillation.

The synthesis of cage compounds of types **16** and **17** was carried out in the presence of an acid catalyst (Scheme 6). In order to find suitable reaction conditions for the preparation of **16** and **17**, different acid catalysts, such as perchloric acid in acetic anhydride, boron trifluoride–etherate, *p*-toluenesulfonic acid and Amberlite IR-120 (plus) were evaluated. The molar ratio of the all-*cis*-cyclohexane-1,2,4-triol **15** to the orthoesters **12** and **14**, the temperature, the solvent and the reaction time were also varied (Table 1). The highest degree of conversion of the starting triol **15** was achieved when trimethyl orthoester **12** or **14** was used in 1.5–3.0 molar excess with 10% of catalyst Amberlite IR-120 (plus) in the presence of molecular sieves 4 Å. The reaction mixture was heated at 20–120 °C, mostly at 80–100 °C, in DMF as solvent under inert atmosphere (Scheme 6). Such vigorous reaction conditions force the conformational change of the cyclohexane ring towards the less favoured boat form fixed by the orthoester cage.[26] Orthoesters of type **16** were isolated from the reaction mixtures by means of bulb-to-bulb vacuum distillation, or by means of flash silica gel column chromatography. In some cases, the millimole scale of the experiment made the purification of the

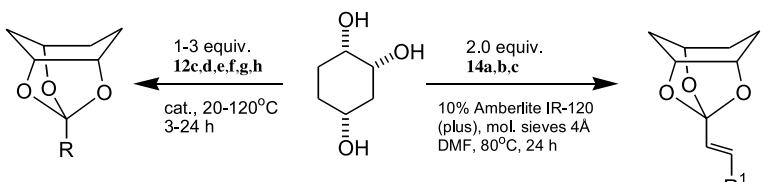


12a R = $CH_3(CH_2)_4$
12b R = $CH_3(CH_2)_5$
12f R = $CH_3(CH_2)_3$

13a R^1 = $CH_3(CH_2)_2$ (86%)
13b R^1 = $CH_3(CH_2)_3$ (71%)
13c R^1 = CH_3CH_2 (86%)

14a (80%)
14b (57%)
14c (65%)

Scheme 5.



15

16c R = $CH_3(CH_2)_8$ (50%)
16d R = $CH_3(CH_2)_{14}$ (66%)
16e R = *E*-$CH_2CH{=}CHCH_3$ (65)%
16f R = $CH_3(CH_2)_3$ (36%)
16g R = H (28%)
16h R = C_6H_5 (80%)

17a R^1 = $CH_3(CH_2)_2$ (10%)
17b R^1 = $CH_3(CH_2)_3$ (10%)
17c R^1 = CH_3CH_2 (20%)

Scheme 6.

Table 1. Synthesis of polycyclic orthoesters **16** and **17** from all-*cis*-cyclohexane-1,2,4-triol **15** with orthoesters **12** and **14**, respectively

No	Compound (equiv.)	Cat. (equiv.)	Solvent	Temperature (°C)	Time (h)	Compounds **16**, **17** (yield, %)
1	**12c** (1.2)	Amberlite IR-120 (plus) (10%) mol. sieves 4 Å	DMF	100	7	**16c** (50)[a]
2	**12d** (1.5)	Amberlite IR-120 (plus) (10%) mol. sieves 4 Å	DMF	100	8	**16d** (66)[a]
3	**12e** (1.2)	Amberlite IR-120 (plus) (10%) mol. sieves 4 Å	DMF	100	4.5	**16e** (37)[a,b]+20% **15**[c]
4	**12e** (1.2)	Amberlite IR-120 (plus) (10%) mol. sieves 4 Å	DMF	100	7	**16e** (57)[a,b]+40% **15**[c]
5	**12e** (2.0)	Amberlite IR-120 (plus) (10%) mol. sieves 4 Å	DMF	100	7	**16e** (65)[a,b]+17% **15**[c]
6	**12e** (3.0)	Amberlite IR-120 (plus) (10%) mol. sieves 4 Å	DMF	100	4	**16e** (50)[a,b]+17% **15**[c]
7	**12e** (3.0)	Amberlite IR-120 (plus) (10%) mol. sieves 4 Å	DMF	100	14	Complex mixture
8	**12f** (1.5)	Amberlite IR-120 (plus) (10%) mol. sieves 4 Å	DMF	120	3	**16f** (36)[a]
9	**12g** (1.8)	*p*-TsOH (0.26)	THF	60	5	**16g** (9)[b]
10	**12g** (1.0)	$BF_3{\cdot}Et_2O$ (1 drop)	THF	20	22	**16g** (9)[b]
11	**12g** (1.8)	$BF_3{\cdot}Et_2O$ (1 drop)	THF	60	48	Complex mixture
12	**12g** (2.0)	Amberlite IR-120 (plus) (10%)	DMF	100	8	**16g** (28)[b]
13	**12h** (1.05)	*p*-TsOH (0.26)	DMF	100	4	**16h** (10)[b]
14	**12h** (1.05)	$BF_3{\cdot}Et_2O$ (0.25)	DMF	100	4	**16h** (4)[b]
15	**12h** (1.05)	$BF_3{\cdot}Et_2O$ (1.0)	THF	20	15	**16h** (5)[b]
16	**12h** (1.1)	$BF_3{\cdot}Et_2O$ (0.3)	DMF	100	8	**16h** (5)[b]
17	**12h** (1.8)	*p*-TsOH (0.3)	DMF	120	7	Complex mixture
18	**12h** (1.5)	*p*-TsOH (0.25)	DMF	100	4	**16h** (18)[b]
19	**12h** (1.5)	Amberlite IR-120 (plus) (10%)	DMF	100	7	**16h** (6)[d]
20	**12h** (1.5)	Amberlite IR-120 (plus) (10%) mol. sieves 4 Å	DMF	100	9	**16h** (22)[a]
21	**12h** (1.5)	Amberlite IR-120 (plus) (10%) mol. sieves 4 Å	DMF	100	24	**16h** (80)[a]
22	**14a** (2.0)	Amberlite IR-120 (plus) (10%) mol. sieves 4 Å	DMF	80	24	**17a** (10)[a]
23	**14b** (2.0)	Amberlite IR-120 (plus) (10%) mol. sieves 4 Å	DMF	80	24	**17b** (10)
24	**14c** (2.0)	Amberlite IR-120 (plus) (10%) mol. sieves 4 Å	DMF	80	24	**17c** (20)

[a] Isolated after preparative gas chromatography.
[b] Isolated after flash column chromatography.
[c] Unreacted (±)-all-*cis*-cyclohexane-1,2,4-triol **15**.
[d] Isolated by means of recrystallization from ethyl acetate–petroleum ether (bp 40–60 °C).

orthoesters **16** and **17** by means of vacuum distillation very difficult. The yields of **16** varied from 28 to 80%. Trioxatricyclo[4.3.1.$0^{3,8}$]decane **16g** was accompanied by a side product as a result of a partial transetherification, as identified by GC–MS spectra of the crude reaction mixtures. Unlike the orthoesters **16**, the preparation of compounds **17a–c** containing a double bond at the α-position of the 1-substituent gave rise to much more complex reaction mixtures, as evidenced by the ^{1}H NMR spectra of the crude mixtures. While **17c** could be isolated by means of bulb-to-bulb vacuum distillation in ca. 20% yield, the higher homologues **17a**,**b** could only be isolated by MPLC in much lower yields.

All cage orthoesters **16** and **17** were characterized by ^{1}H NMR, ^{13}C NMR, IR and mass spectroscopy.

In conclusion, from (±)-all-*cis*-cyclohexane-1,2,4-triol **15** a series of 1-substituted 2,9,10-trioxatricyclo[4.3.1.$0^{3,8}$]-decanes of types **16** and **17** as partial structural units of RTX **1** and kirkinine **3**, models for the core orthoester structural moiety of resiniferatoxin and synaptolepis factors, was synthesized.

3. Experimental

3.1. General remarks

^{1}H NMR spectra (270 MHz) and ^{13}C NMR spectra (68 MHz) were taken with a JEOL JNM-EX 270 NMR spectrometer as solutions in $CDCl_3$, chemical shifts in δ-values with TMS as internal standard, *J* in Hz. IR spectra (ν, cm^{-1}) were obtained from a Perkin–Elmer 983 G infrared spectrophotometer (liquid film). Mass spectra (MS) were measured with a Varian MAT-112 spectrometer (70 eV) using GC–MS coupling (RSL 200, 20 m×0.53 mm, i.d.; He as carrier gas), *m*/*z* (relative intensities in %) are given. All reactions were performed in oven-dried glassware. Solvents were dried using standard techniques. Medium pressure liquid chromatography (MPLC) on reversed phase (Lichroprep RP-18, 40–63 μm, Merck) was executed with a Büchi system consisting of a 688 chromatography pump, a 687 gradient former, a 684 fraction collector (Büchi, Switzerland) and a SEDEX 55 evaporative light scattering detector (LSD) (SEDERE, France) (40 °C, 2 bar N_2 flow and split 1/50). Solvents (HPLC grade) used are from Ruthburn, Germany. Flash chromatography was performed on silica gel 35–70 μm (pore diameter ca. 6 nm, Acros Chimica). TLC plates from Merck with silica (mobile phase: ethyl acetate containing 3% MeOH) and with reverse phase RP-18 (mobile phase: MeOH–H_2O 3:7) were used for qualitative analysis of the reaction products. All the orthoesters **12** and **14**, and the cage orthoesters **16** and **17**, were stored under dry conditions over a small amount of anhydrous potassium carbonate in order to avoid possible hydrolysis of the orthoester function.

3.2. Synthetic procedures

3.2.1. Preparation of hydrochlorides of methyl imidates 11.[30,31] Through a solution of 0.05 mol of the appropriate nitrile in 18 ml of dry diisopropylether and 0.06 mol (1.2 equiv.) of dry MeOH was bubbled at 0 °C ca. 0.075 mol gaseous HCl (1.5 equiv.). The reaction mixture was kept 3 h at 0 °C and then overnight at −20 °C, after which it was diluted with dry diethyl ether and left to stand at −20 °C for 3–4 days. Afterwards, it was warmed to room temperature and filtered. The imidate hydrochlorides thus

obtained were dried for 3–4 days in a vacuum desiccator charged with P_2O_5 and KOH. Yields are given in Scheme 4.

3.2.2. Methanolysis of the imidates 11.[30,31] To 0.02 mol of imidate hydrochloride, prepared as above, 0.12 mol of dry MeOH was added, and the mixture was stirred at room temperature. Gradually, NH_4Cl precipitated with chilling of the reaction mixture. After 24 h 40 ml of dry ether was added to the mixture, which was stirred further for 3 days. Then the salt was filtered and the filtrate was evaporated to a small volume. Usually, at this point, a precipitation of a little amount of the corresponding amide was observed, which was removed by filtration. The filtrate was diluted with ether and washed twice with saturated aqueous $NaHCO_3$ and dried (K_2CO_3). After removal of the solvent, the residue was purified by means of a vacuum distillation.

Trimethyl orthohexanoate **12a**.[29] 72%, 82–84 °C/15 mm Hg. ^{1}H NMR δ ($CDCl_3$) 0.90 (3H, t, J=7.0 Hz, CH_3), 1.28–1.32 (6H, m, $3CH_2$), 1.68–1.73 (2H, m, $CH_2C(OCH_3)_3$), 3.23 (9H, s, $3OCH_3$). ^{13}C NMR δ ($CDCl_3$) 13.9 (CH_3), 22.4, 22.5, 30.2, 31.6 ($4CH_2$), 49.2 ($3OCH_3$), 115.6 ($C(OCH_3)_3$). IR (NaCl): 1072, 1096 and 1120 (C–O–C) cm^{-1}. MS *m/z*: no M$^+$, 130 (12), 101 (13), 99 (32), 89 (48), 74 (100), 59 (26), 55 (17). Anal. calcd for $C_9H_{20}O_3$: C 61.31%, H 11.44%; found C 60.93%, H 11.60%.

Trimethyl orthoheptanoate **12b**. 79%, 95–98 °C/15 mm Hg. ^{1}H NMR δ ($CDCl_3$) 0.89 (3H, t, J=7.0 Hz, CH_3), 1.29 (8H, broad s, $4CH_2$), 1.68–1.71 (2H, m, $CH_2C(OCH_3)_3$), 3.23 (9H, s, $3OCH_3$). ^{13}C NMR δ ($CDCl_3$) 13.8 (CH_3), 22.4, 22.5, 28.9, 30.1, 31.5 ($5CH_2$), 48.9 ($3OCH_3$), 115.6 ($C(OCH_3)_3$). IR (NaCl): 1072, 1123, 1154 and 1188 (C–O–C) cm^{-1}. MS *m/z*: no M$^+$, 160 (54), 160 (71), 106 (100), 102 (94), 75 (16), 75 (21), 59 (11), 55 (17). Anal. calcd for $C_{10}H_{22}O_3$: C 63.11%, H 11.66%; found C 63.42%, H 11.52%.

Trimethyl orthodecanoate **12c**. 60%, 60 °C/0.01 mm Hg. ^{1}H NMR δ ($CDCl_3$) 0.88 (3H, t, J=7.0 Hz, CH_3), 1.26 (14H, broad s, $7CH_2$), 1.65–1.78 (2H, m, $CH_2C(OCH_3)_3$), 3.23 (9H, s, $3OCH_3$). ^{13}C NMR δ ($CDCl_3$) 13.8 (CH_3), 22.5, 22.6, 29.1, 29.3. 29.3, 29.3, 30.9, 31.6 ($8CH_2$), 48.9 (OCH_3), 49.0 ($2OCH_3$), 115.6 ($C(OCH_3)_3$). IR (NaCl): 1049, 1161 and 1240 (C–O–C) cm^{-1}. MS *m/z*: no M$^+$, 202 (13), 201 (76), 200 (10), 115 (11), 106 (17), 105 (100), 102 (20), 101 (96). Anal. calcd for $C_{13}H_{28}O_3$: C 67.18%, H 12.15%; found C 67.32%, H 12.03%.

Trimethyl orthohexadecanoate **12d**. 72%, 105 °C/0.05 mm Hg. ^{1}H NMR δ ($CDCl_3$) 0. 90 (3H, t, J=7.0 Hz, CH_3), 1.26 (26H, broad s, $13CH_2$), 1.65–1.78 (2H, m, $CH_2C(OCH_3)_3$), 3.22 (9H, s, $3OCH_3$). ^{13}C NMR δ ($CDCl_3$) 14.1 (CH_3), 22.8, 23.1, 29.3, 29.5, 29.7, 29.7, 29.7, 29.7, 29.9, 29.9, 29.9, 30.2, 30.6, 32.1 ($14CH_2$), 49.2 ($3OCH_3$), 115.9 ($C(OCH_3)_3$). IR (NaCl): 1062, 1155 and 1240 (C–O–C) cm^{-1}. MS *m/z*: 316 (M$^+$, 1), 270 (8), 143 (14), 111 (17), 105 (39), 101 (100), 97 (12), 91 (23). Anal. calcd for $C_{19}H_{40}O_3$: C 72.08%, H 12.75%; found C 72.23%, H 12.59%.

Trimethyl ortho-3E-pentenoate **12e**. 70%, 35 °C/0.05 mm Hg. ^{1}H NMR δ ($CDCl_3$) 1.71 (3H, d, J=7.0 Hz, CH_3), 2.48–2.50 (2H, m, CH_2CH=), 3.25 (9H, s, $3OCH_3$), 5.40 (1H, d×m, J=15.8Hz, CH=), 5.55 (1H, d×m, J=15.8 Hz, CH=). ^{13}C NMR δ ($CDCl_3$) 17.3 (CH_3), 33.5 (CH_2), 48.6 ($3OCH_3$), 114.4 ($C(OCH_3)_3$), 123.6 (C=), 127.3 (C=). IR (NaCl): 966 (C=C), 1004, 1080 and 1231 (C–O–C), 1774 (CH=CH) cm^{-1}. MS *m/z*: 160 (M$^+$, 6), 145 (9), 129 (54), 128 (11), 127 (11), 105 (100), 91 (20), 87 (23). Anal. calcd for $C_8H_{16}O_3$: C 59.96%, H 10.07%; found C 60.17%, H 10.19%.

3.2.3. Trimethyl ortho-2-bromoalkanoates 13. *General procedure*.[37] Bromine (0.05 mol) was added dropwise with stirring to a 5% solution of the orthoester **12** (0.05 mol) in CH_2Cl_2 containing pyridine (0.055 mol) at 5 °C. Afterwards, the reaction mixture was left overnight at room temperature. Then it was poured into 100 ml of light petroleum ether (bp 40–60 °C) with stirring. The precipitated pyridinium salt was filtered off, and was washed with 25 ml of petroleum ether, and then with 2×25 ml of dry diethyl ether. The combined filtrates were washed successively with 15 ml of saturated aqueous $NaHCO_3$ containing a small amount of $Na_2S_2O_3$, 15 ml of water and finally dried ($MgSO_4$). After removal of the solvents in vacuum, the residue was purified by means of vacuum distillation.

Trimethyl ortho-2-bromohexanoate **13a**. 86%, 45–50 °C/0.01 mm Hg. ^{1}H NMR δ ($CDCl_3$) 0.95 (3H, t, J=7.0 Hz, CH_3), 1.25–1.43 (2H, m, CH_2), 1.60–2.08 (4H, m, $2CH_2$), 3.41 (9H, s, $3OCH_3$), 4.02 (1H, d×d, J=2.5 Hz, J=11.0 Hz, CHBr). ^{13}C NMR δ ($CDCl_3$) 13.9 (CH_3), 22.2, 30.2, 32.8 ($3CH_2$), 51.0 ($3OCH_3$), 56.1 (CBr), 112.2 ($C(OCH_3)_3$). IR (NaCl): 1070, 1089, 1120 and 1159 (C–O–C) cm^{-1}. MS *m/z*: no M$^+$, 225 (33), 223 (32), 181 (15), 179 (15), 105 (100). Anal. calcd for $C_9H_{19}O_3Br$: C 42.51%, H 7.54%; found C 42.56%, H 7.49%.

Trimethyl ortho-2-bromoheptanoate **13b**. 71%, 55–57 °C/0.03 mm Hg. ^{1}H NMR δ ($CDCl_3$) 0.95 (3H, t, J=7.0 Hz, CH_3), 1.30–1.34 (4H, m, $2CH_2$), 1.61–2.05 (4H, m, $2CH_2$), 3.40 (9H, s, $3OCH_3$), 4.02 (1H, d×d, J=2.5 Hz, J=11 Hz, CHBr). ^{13}C NMR δ ($CDCl_3$) 13.9 (CH_3), 22.4, 27.6, 31.1, 32.9 ($4CH_2$), 50.9 ($3OCH_3$), 56.0 (CBr), 112.1 ($C(OCH_3)_3$). IR (NaCl): 1080, 1092, 1122, 1157 and 1195 (C–O–C) cm^{-1}. MS *m/z*: no M$^+$, 239 (17), 238 (16), 237 (12), 105 (100), 101 (30), 59 (21), 55 (20). Anal. calcd for $C_{10}H_{21}O_3Br$: C 44.76%, H 7.90%; found C 44.86%, H 7.88%.

Trimethyl ortho-2-bromopentanoate **13c**.[31] 86%, 93–96 °C/15 mm Hg. ^{1}H NMR δ ($CDCl_3$) 0.95 (3H, t, J=7.0 Hz, CH_3), 1.17–1.27 (2H, m, CH_2), 1.60–2.05 (2H, m, CH_2), 3.20 (9H, s, $3OCH_3$), 4.05 (1H, d×d, J=2.5, 11 Hz, CHBr). ^{13}C NMR δ ($CDCl_3$) 13.3 (CH_3), 21.1, 34.9 ($2CH_2$), 50.1 (CBr), 55.6 ($3OCH_3$), 112.1 ($C(OCH_3)_3$). IR (NaCl): 1072, 1096 and 1120 (C–O–C) cm^{-1}. MS *m/z*: no M$^+$, 211 (85) and 209 (84) (both M$^+-OCH_3$), 179 (10), 129 (12), 106 (15), 105 (100), 101 (38). Anal. calcd for $C_8H_{17}O_3Br$: C 39.99%, H 7.14%; found C 39.69%, H 7.04%.

3.2.4. Trimethyl ortho-2*E*-alkenoates 14. *General procedure*.[38] An appropriate 2-bromo orthoester **13**

(0.05 mol) was added dropwise to a stirred mixture of 0.06 mol potassium *tert*-butoxide in 12 ml of DMSO at 0 °C. Stirring was continued for 24 h at room temperature, after which the reaction mixture was poured into an equal volume of water and extracted with ether. The dried ($MgSO_4$) extract was evaporated in vacuum and the product was purified by means of vacuum distillation providing the products **14a–c**.

Trimethyl ortho-2E-hexenoate **14a**. 80%, 85–92 °C/15 mm Hg. ^{1}H NMR δ ($CDCl_3$) 0.93 (3H, t, J=7.0 Hz, CH_3), 1.38–1.49 (2H, m, CH_2), 2.06–2.14 (2H, m, CH_2), 3.23 (9H, s, $3OCH_3$), 5.23 (1H, d×d, J=1.3, 15.8 Hz, $(CH_3O)_3CCH$=), 6.10 (1H, d×t, J=6.9, 15.8 Hz, CH=). ^{13}C NMR δ ($CDCl_3$) 13.2 (CH_3), 21.7, 33.6 ($2CH_2$), 49.0 ($3CH_3O$), 113.1 ($C(OCH_3)_3$), 124.8 (CH=), 137.2 (CH=). IR (NaCl): 1091 and 1182 (C–O–C), 1673 (C=C) cm^{-1}. MS *m/z*: no M$^+$, 144 (11), 143 (100), 142 (89), 141 (23), 127 (47), 113 (11), 105 (21), 101 (26). Anal. calcd for $C_9H_{18}O_3$: C 62.02%, H 10.42%; found C 61.90%, H 10.22%.

Trimethyl ortho-2E-heptenoate **14b**. 57%, 102–112 °C/15 mm Hg. ^{1}H NMR δ ($CDCl_3$) 0.93 (3H, t, CH_3, J=7.0 Hz), 1.29–1.44 (4H, m, $2CH_2$), 2.08–2.16 (2H, m, CH_2), 3.22 (9H, s, $3OCH_3$), 5.24 (1H, d×d, J=1.3, 15.5 Hz, $(CH_3O)_3CCH$=), 6.04 (1H, d×t, J=6.9, 15.8 Hz, CH=). ^{13}C NMR δ ($CDCl_3$) 13.6 (CH_3), 21.9, 30.8, 30.9 ($3CH_2$), 49.2 ($3CH_3O$), 113.2 ($C(OCH_3)_3$), 124.7 (CH=), 137.5 (CH=). IR (NaCl): 1092 and 1180 (C–O–C), 1673 (C=C) cm^{-1}. MS *m/z*: 188 (M$^+$, 1), 173 (M$^+-CH_3$, 0.6), 157 (M$^+-CH_3O$, 100), 127 (25), 106 (10). Anal. calcd for $C_{10}H_{20}O_3$: C 63.78%, H 10.71%; found C 63.92%, H 10.69%.

Trimethyl ortho-2E-pentenoate **14c**.[38] 65%, 88–90 °C/40 mm Hg. ^{1}H NMR δ ($CDCl_3$) 1.04 (3H, t, J=7.0 Hz, CH_3), 2.10–2.28 (2H, m, CH_2), 3.20 (9H, s, $3OCH_3$), 5.24 (1H, d×d, J=1.7, 15.8 Hz, $(CH_3O)_3CCH$=), 6.10 (1H, d×t, J=6.6, 15.8 Hz, CH=). ^{13}C NMR δ ($CDCl_3$) 13.1 (CH_3), 24.9 (CH_2), 40.7 (CH_3O), 49.2 ($2CH_3O$), 113.3 ($C(OCH_3)_3$), 123.6 (CH=), 139.0 (CH=). IR (NaCl): 1023, 1047 and 1184 (C–O–C), 1674 (CH=CH) cm^{-1}. MS *m/z*: 160 (M$^+$, 5), 144 (67), 130 (20), 129 (23), 128 (10), 114 (48), 113 (100). Anal. calcd for $C_8H_{16}O_3$: C 59.96%, H 10.07%; found C 59.81%, H 10.18%.

3.2.5. 1-Alkyl- and 1-alkenyl-2,9,10-trioxatricyclo-[4.3.1.0^{3,8}]decanes 16c–h, 17a–b. *General procedure*. To a stirred solution of (±)-all-*cis*-cyclohexane-1,2,4-triol **15**[28] (0.195 g, 1.5 mmol) in DMF (3 ml), containing dry Amberlite IR-120 (plus) (0.02 g), and molecular sieves 4 Å, the orthoester **12** or **14** (1–3 equiv.) was added at room temperature. The reaction mixture was stirred and heated at 80–100 °C for 24 h under nitrogen. After cooling, the reaction mixture was filtered through a sintered glass filter and the solid was rinsed with dry dichloromethane (3×5 ml). After evaporation of the volatiles by rotavapour, high vacuum was necessary to remove DMF from the filtrate. The reaction products **16c–h** and **17a–c** were isolated by means of recrystallisation, vacuum distillation ('bulb-to-bulb' distillation), preparative gas chromatography, flash chromatography or MPLC.

1-Nonyl-2,9,10-trioxatricyclo[4.3.1.0^{3,8}]decane **16c**. 50%, bp 145 °C/1 mm Hg. ^{1}H NMR δ ($CDCl_3$) 0.87 (3H, t, J=6.5 Hz, CH_3), 1.25 (12H, broad s, $6CH_2$), 1.38–1.60 (4H, m, CH_2CH_2CHO), 1.71–1.85 (5H, m, CH_2 and *H*CH), 2.10–2.30 (3H, m, CH_2 and HC*H*), 4.24–4.28 (1H, m, H-6), 4.50–4.61 (2H, m, H-3 and H-8). ^{13}C NMR δ ($CDCl_3$) 14.1 (CH_3), 22.1, 21.7, 23.5, 27.9, 28.4, 29.3, 29.5, 29.5, 29.6, 31.9, 34.7 ($11CH_2$), 69.4, 72.2, 73.7 (C-3, C-6 and C-8), 119.5 (C-1). IR (NaCl): 1004, 1094 and 1245 (C–O–C) cm^{-1}. MS *m/z*: 268 (M$^+$, 15), 169 (22), 156 (41), 155 (83), 98 (87), 96 (10), 87 (14), 85 (43). Anal. calcd for $C_{16}H_{28}O_3$: C 71.59% C, H 10.52%; found C 71.41%, H 10.68%.

1-Pentadecyl-2,9,10-trioxatricyclo[4.3.1.0^{3,8}]decane **16d**. 66%, bp 150 °C/1 mm Hg. ^{1}H NMR δ ($CDCl_3$) 0.88 (3H, t, J=7.0 Hz, CH_3), 1.25 (26H, broad s, $13CH_2$), 1.38–1.85 (5H, m, $2CH_2$ and *H*CH), 2.10–2.37 (3H, m, CH_2 and HC*H*), 4.26–4.28 (1H, m, H-6), 4.51–4.62 (2H, m, H-3 and H-8). ^{13}C NMR δ ($CDCl_3$) 14.1 (CH_3), 22.1, 22.7, 23.5, 25.0, 25.1, 27.9, 28.4, 29.2, 29.3, 29.4, 29.5, 29.6, 29.7, 29.7, 29.7, 32.0, 34.7 ($17CH_2$), 69.4, 72.2, 73.7 (C-3, C-6 and C-8), 119.5 (C-1). IR (NaCl): 1092 and 1259 (C–O–C) cm^{-1}. MS *m/z*: 352 (M$^+$, 1), 97 (51), 96 (21), 87 (19), 83 (25), 81 (16), 69 (31), 55 (100). Anal. calcd for $C_{22}H_{40}O_3$: C 74.94% C, H 11.44%; found C 74.61%, H 11.89%.

1-(2E-Buten-1-yl)-2,9,10-trioxatricyclo[4.3.1.0^{3,8}]decane **16e**. 65%, bp 120 °C/3 mm Hg. ^{1}H NMR δ ($CDCl_3$) 1.38–1.81 (3H, m, CH_2 and *H*CH), 1.69 (3H, d, J=5.0 Hz, CH_3), 2.11–2.27 (3H, m, CH_2, *H*CH), 2.56–2.58 (2H, m, CH_2CH=), 4.28 (1H, t, J=5.6 Hz, H-6), 4.52–4.64 (2H, m, H-3 and H-8), 5.29–5.56 (2H, m, CH=CH). ^{13}C NMR δ ($CDCl_3$) 18.1 (CH_3), 22.0, 27.7, 28.3 ($3CH_2$), 38.2 (CH_2CH=), 69.7, 72.3, 73.9 (C-3, C-6 and C-8), 118.7 (C-1), 124.1, 128.5 (CH=CH). IR (NaCl): 958 (CH=CH), 1021, 1092 and 1255 (C–O–C) cm^{-1}. MS *m/z*: 196 (M$^+$, 16), 97 (69), 88 (30), 86 (87), 84 (95), 83 (29), 69 (47), 55 (100). Anal. calcd for $C_{11}H_{16}O_3$: C 67.31%, H 8.22%; found C 67.12%, H 8.29%.

1-Butyl-2,9,10-trioxatricyclo[4.3.1.0^{3,8}]decane **16f**. 36%, bp 90 °C/0.5 mm Hg. ^{1}H NMR δ ($CDCl_3$) 0.90 (3H, t, J=7.2 Hz, CH_3), 1.29–1.61 (6H, m, $3CH_2$), 1.71–1.86 (3H, m, CH_2 and *H*CH), 2.10–2.29 (3H, m, CH_2 and HC*H*), 4.25–4.29 (1H, m, H-6), 4.51–4.62 (2H, m, H-3 and H-8). ^{13}C NMR δ ($CDCl_3$) 13.9 (CH_3), 22.1, 22.6, 25.6, 27.8, 28.4, 34.4 ($6CH_2$), 69.5, 72.2, 73.7 (C-3, C-5 and C-8), 119.5 (C-1). IR (NaCl): 1015, 1092 and 1260 (C–O–C) cm^{-1}. MS *m/z*: 198 (M$^+$, 2), 97 (19), 96 (31), 85 (100), 68 (20), 67 (13), 57 (62), 55 (16). Anal. calcd for $C_{11}H_{18}O_3$: C 66.62%, H 9.16%; found C 66.37% C, H 9.31%.

2,9,10-Trioxatricyclo[4.3.1.0^{3,8}]decane **16g**. 28%, bp 90 °C/2 mm Hg. ^{1}H NMR δ ($CDCl_3$) 1.41–1.83 (4H, m, CH_2CH_2CHO), 2.11–2.36 (2H, m, $OCHCH_2CHO$), 4.26 (1H, t, J=5.1 Hz, H-6) and 4.52–4.59 (2H, m, H-3 and H-8), 5.97 (1H, s, 1-H). ^{13}C NMR δ ($CDCl_3$) 21.8, 27.1, 29.0 ($3CH_2$), 69.5, 71.0, 73.0 (C-3, C-6 and C-8), 110.9 (C-1). MS *m/z*: 142 (M$^+$, 14), 97 (46), 96 (44), 70 (66), 69 (27), 68 (79), 67 (65), 57 (87). Anal. calcd for $C_7H_{10}O_3$: C 59.13%, H 7.09%; found C 60.15%, H 7.01%.

1-Phenyl-2,9,10-trioxatricyclo[4.3.1.0^{3,8}]decane **16h**. 80%,

bp 100 °C/0.01 mm Hg. ^{1}H NMR δ ($CDCl_3$) 1.50–1.68 (2H, m, CH_2), 1.83–1.92 (1H, m, *H*CH), 2.16–2.42 (3H, m, HC*H* and O–CHCH_2CH–O), 4.47 (1H, t, *J*=5.3 Hz, H-6), 4.72–4.82 (2H, m, H-3 and H-8), 7.35–7.37 (3H, m, arom. H), 7.68–7.70 (2H, m, arom. H). ^{13}C NMR δ ($CDCl_3$) 22.1, 27.8, 28.3 ($3CH_2$), 70.4, 72.8, 74.3 (C-3, C-6 and C-8), 117.5 (C-1), 125.8 (CH═), 128.0 (2CH═), 129.3 (2CH═), 135.8 (C_{quat}). IR (NaCl): 970, 1004 and 1090 (C–O–C) cm^{-1}. MS *m*/*z*: 218 (M^+, 4), 105 (100), 96 (32), 77 (28), 68 (13). Anal. calcd for $C_{13}H_{14}O_3$: C 71.53%, H 6.47%; found C 71.90%, H 6.89%.

1-(1E-Penten-1-yl)-2,9,10-trioxatricyclo[4.3.1.0^{3,8}]decane **17a**. 10%. ^{1}H NMR δ ($CDCl_3$) 1.03 (3H, t, *J*=7.3 Hz, CH_3), 1.42–2.25 (10H, m, $5CH_2$), 3.94–4.06 (2H, m), 4.87–4.92 (m, 1H) (H-3, H-6 and H-8), 5.88 (1H, d×d, *J*=1.7, 15.8 Hz, CH═), 7.01 (1H, d×t, *J*=6.1, 15.5 Hz, CH═). ^{13}C NMR δ ($CDCl_3$) 13.6 (CH_3), 21.0, 21.3, 30.4, 34.1, 36.4 ($5CH_2$), 66.5, 69.0, 72.9 (C-3, C-6 and C-8), 121.0 (C-1), 135.2, 135.4 (CH═CH). IR (NaCl): 976 (CH═CH), 1030, 1074, 1113, 1180 and 1227 (C–O–C), 1653 (CH═CH) cm^{-1}. GC–MS *m*/*z*: 211 (M^++1, 2), 115 (16), 114 (35), 113 (47), 97 (100), 96 (60), 71 (17), 69 (22), 55 (58). Anal. calcd for $C_{12}H_{18}O_3$: C 68.53%, H 8.63%; found C 68.75%, H 8.51%.

1-(1E-Hexen-1-yl)-2,9,10-trioxatricyclo[4.3.1.0^{3,8}]decane **17b**. 10%. ^{1}H NMR δ ($CDCl_3$) 0.91 (3H, t, *J*=7.2 Hz, CH_3), 1.10–2.42 (12H, m, $6CH_2$), 3.96–4.01 (2H, m) and 4.90–4.92 (1H, m) (H-3, H-6 and H-8), 5.85 (1H, d, *J*=15.8 Hz, CH═), 7.02 (1H, d×t, *J*=6.9, 15.5 Hz, CH═). ^{13}C NMR δ ($CDCl_3$) 14.1 (CH_3), 22.5, 22.7, 30.3, 30.8, 32.2, 36.4 ($6CH_2$), 69.4, 73.3, 76.9 (C-3, C-6 and C-8), 121.2 (C-1), 133.7, 134.0 (CH═CH). IR (NaCl): 981 (CH═CH), 1033, 1113, 1214 and 1279 (C–O–C), 1653 (CH═CH) cm^{-1}. GC–MS *m*/*z*: 225 (M^++1, 3), 130 (18), 115 (49), 114 (62), 112 (100), 97 (58), 73 (15), 70 (13). Anal. calcd for $C_{13}H_{20}O_3$: C 69.60%, H 8.99%; found C 69.92%, H 8.82%.

1-(1E-Buten-1-yl)-2,9,10-trioxatricyclo[4.3.1.0^{3,8}]decane **17c**. 20%. ^{1}H NMR δ ($CDCl_3$) 1.03 (3H, t, *J*=7.3 Hz, CH_3), 1.42–2.38 (8H, m, $4CH_2$), 4.36 (1H, t, *J*=5.6 Hz, H-6), 4.54–4.71 (2H, m, H-3 and H-8), 5.60 (1H, d×d, *J*=1.7, 15.8 Hz, CH═), 6.30 (1H, d×t, *J*=6.1, 15.8 Hz, CH═). ^{13}C NMR δ ($CDCl_3$) 12.4 (CH_3), 21.2, 24.7, 27.7, 28.3 ($4CH_2$), 73.8, 76.5, 77.0 (C-3, C-6 and C-8), 116.2 (C-1), 122.6, 137.9 (CH═CH). IR (NaCl): 964 (CH═CH), 1022, 1045, 1092, 1137, 1182 and 1196 (C–O–C), 1686 (CH═CH) cm^{-1}. MS *m*/*z*: 196 (M^+, 6), 97 (18), 96 (34), 84 (51), 83 (100), 69 (14), 68 (26), 67 (10). Anal. calcd for $C_{11}H_{16}O_3$: C 67.31%, H 8.22%; found C 67.48%, H 8.38%.

Acknowledgements

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Highly stereoselective addition of organozinc reagents to pentopyranose derived glycals: effect of protecting group and assignment of *C*-glycoside stereochemistry

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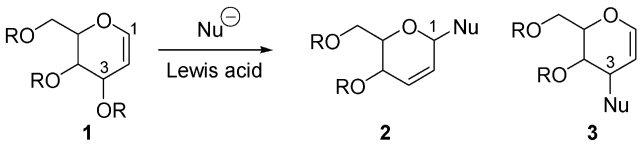
Abstract—The nucleophilic addition of ethyl 3-propionylzinc iodide to a variety of differently protected pentopyranose derived D-glycals **6a**–**g** proceeds with good to high levels of diastereoselectivity to provide the corresponding β-*C*-glycosides **7**. The stereochemistry of the *para*-nitrobenzoate derivative **7d** has been confirmed by X-ray crystallography, and the stereochemistry of the other β-*C*-glycoside products has been correlated to **7d**. The stereochemical outcome observed supports the earlier suggestion by Isobe that through-space effects are important in stabilising and controlling the reactivity of the intermediate oxonium species represented by **11**.

1. Introduction

Glycals **1** are ambident carbohydrate electrophiles capable of reacting with nucleophiles either at *C*(1) or *C*(3) either directly or via the intermediacy of a Ferrier rearrangement product (a $\Delta^{2,3}$ glycal) to provide the branched derivatives **2** and **3** (Scheme 1). Use of carbon nucleophiles provides access to unsaturated *C*-glycosides (such as **2**), which have, in turn, found applications in a range of areas, including natural products synthesis.[1]



Scheme 1.

There have been many reports in the literature involving the addition of silicon-based nucleophiles[2] to glycals. In particular, allyl silanes, silyl enol ethers, propargyl silanes and silyl acetylenes have found applications in this area, with a variety of Lewis acids, ranging from $BF_3{\cdot}OEt_2$ to montmorillonite, being employed.[3] Silyl-based nucleophiles provide *C*-glycosides incorporating alkene, ketone, allene and alkyne moieties but more complex (or more remote) functionality can present an issue. Other organometallic nucleophiles have been evaluated for this type of transformation, but there are several properties an organometallic nucleophile must possess in order to be effective in the context of the chemistry shown in Scheme 1. The nucleophile must be reasonably Lewis acid tolerant, soluble in a solvent that does not interact significantly with a Lewis acid and must not react with functionality on the glycal substrate, which is commonly associated with *O*-acetyl protecting groups. The organometallic nucleophiles reported that satisfy these criteria are boronic acids (in the presence of Pd(II)),[4] organoaluminium,[5] organocopper[6] and organozinc reagents. Zinc-based reagents are particularly attractive for this type of transformation, being readily available and tolerant of both a wide range of solvents and functional groups.[7] The first reports of organozinc additions to glycals employed simple Reformatsky reagents,[8] but arylzincs[9] and more complex functionalised zinc nucleophiles have also been used successfully.

We described the reactivity of a range of organozinc reagents towards various glycals as an entry to *C*-glycosides analogous to **2**.[10] This chemistry complements the silyl based methodology (see above) and has been applied by ourselves[11a] and Jackson[11b] to the synthesis of *C*-glycosyl tyrosine and *C*-glycosyl serine derivatives, the former providing building blocks for *C*-glycopeptides.[11a] Further, modification of an organozinc reagent with Cu(I) cyanide provides access to the isomeric *C*(3) substituted product (cf. **3**, Scheme 1).[12]

Keywords: *C*-Glycosides; Glycals; Organozinc.
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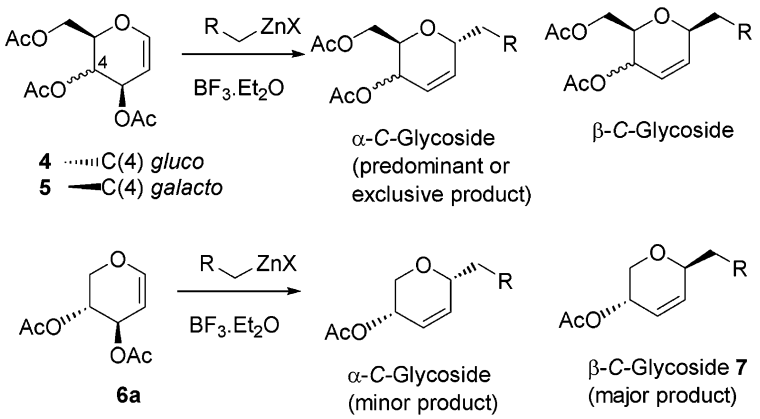


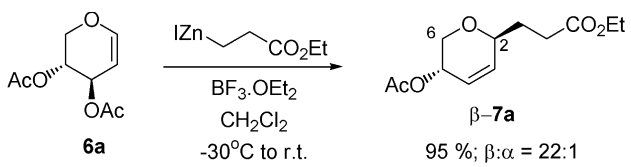
Scheme 2.

Earlier work has demonstrated that tri-*O*-acetyl-D-glucal **4** and tri-*O*-acetyl-D-galactal **5** (as well as disaccharide variants) react with organozinc halides in the presence of $BF_3{\cdot}Et_2O$ with good to excellent levels of stereocontrol, depending on the carbohydrate configuration employed (Scheme 2). In the *gluco* series, the α-*C*-glycoside was favoured by typically 4:1 over the corresponding β-*C*-glycoside. In the *galacto* series, **5** produced the α-*C*-glycoside exclusively.

We had also examined briefly the viability of pentopyranose-derived D-glycals, such as di-*O*-acetyl-D-xylal **6a**,[13] which reacts in a highly selective fashion, showing a significant bias for the β-*C*-glycoside. Isobe[2d] and others[14] have also observed this high β-selectivity, and we were interested to probe the origins of this stereochemical outcome. The results of this study are presented in this paper.

2. Results and discussion

We have found that the Lewis acid mediated addition of ethyl 3-propionylzinc iodide to di-*O*-acetyl-D-xylal **6a**[12] proceeds in excellent yield with a high level of stereocontrol leading to the β-*C*-glycoside β-**7a**, with the α-*C*-glycoside (α-**7a**) produced as the minor component. (Scheme 3).

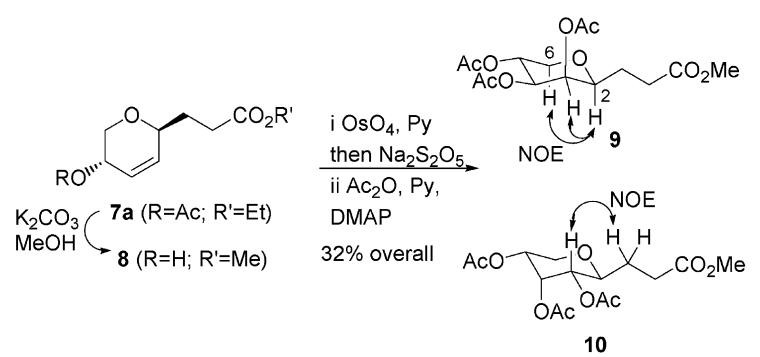


Scheme 3.

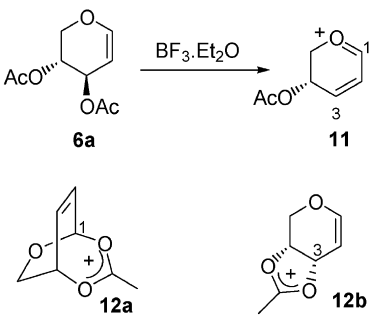
The stereochemistry of **7a** was initially assigned using the γ-*gauche* effect, which relies on the ^{13}C NMR signal for *C*-6 (pyran numbering) of the *C*-2 α-isomer being more shielded than the analogous signal for the β-isomer.[15] Although this holds true for *C*-glycosides where a *C*-6 substituent is present (such as those derived from **4** and **5**, Scheme 2), there are conflicting reports[3f] regarding the applicability of this rule when no *C*-6 substituent is present (as in **7a**).

To confirm the stereochemistry of *C*-glycoside **7a**, the acetate group was cleaved and the resulting alcohol **8** (as the methyl ester) was dihydroxylated[16] to enable diagnostic NOE experiments to be carried out (Scheme 4). Following complete *O*-acetylation, the 3,4-*cis*-4,5-*trans* **9** and the 3,4-*cis*-4,5-*cis* **10** diastereomers were isolated as a 1:1 mixture in 32% yield. An alternative two step dihydroxylation protocol developed by Donohoe[17] gave only the 3,4-*cis*-4,5-*cis* product **10**.

NOE experiments showed two strong interactions for **9** associated with *H*-2 and *H*-3, and *H*-2 and *H*-6_{ax} which supports β stereochemical assignment for the *C*-glycoside linkage. This conclusion is supported by the results obtained with diastereomer **10**, in which *H*-3 interacts only with the protons of the propionyl side chain. This assignment was subsequently confirmed by crystallographic analysis, which is discussed below.



Scheme 4.

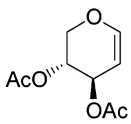
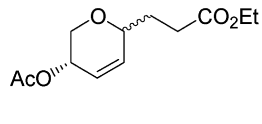
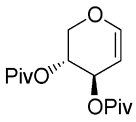
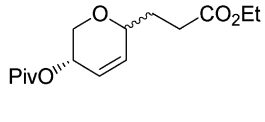
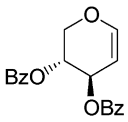
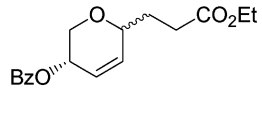
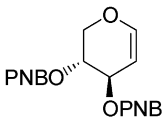
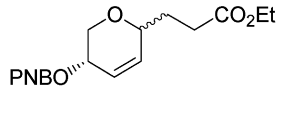
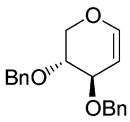
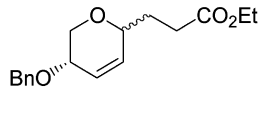
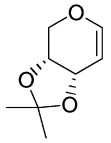
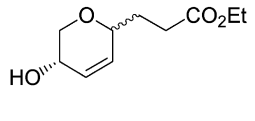
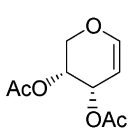
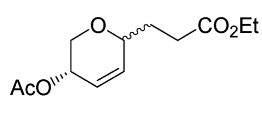


Scheme 5.

The β-selectivity associated with the transformation shown in Scheme 3 is interesting and raises the question of the origin of this effect. One possibility, given that *O*-acetyl groups are present, is neighbouring group participation, whereby the *C*-4 acetate stabilises the intermediate oxonium species by direct interaction via the carbonyl oxygen (Scheme 5). This could involve carbonyl participation at the *C*-1 position of **11**, forming a 7-membered intermediate **12a**, or at *C*-3 leading to a 5-membered intermediate **12b**.

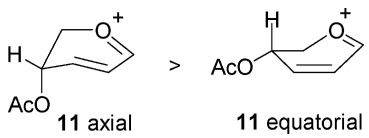
An alternative explanation for the high β-selectivity associated with nucleophilic additions to pentopyranose-derived glycals has been proposed by Isobe,[2d–g] who has

Table 1. *C*-Glycosides **7** derived from pentopyranose-derived glycals **6**

Entry	Glycal	*C*-Glycoside	α:β Ratio[a]	Yield (%)[b]
1[c]	 **6a**	 **7a**	1:22	95
2[c]	 **6b**[18]	 **7b**	1:23	71
3[c]	 **6c**	 **7c**	1:14	91
4[c]	 **6d**[19]	 **7d**	1:15	82
5[c]	 **6e**[20]	 **7e**	1:15	73
6[c]	 **6f**[21]	 **7f**	1:15	66
7	 **6g**	 **7a**	1:15	76

[a] α:β Ratio determined by ^{1}H NMR of the crude reaction mixture.
[b] Yields quoted as a mixture of diastereomers. In the case of **6a**, both *C*-1 α- and β-adducts were isolated and characterised, but in the other cases only the major β-*C*-glycoside was characterised.
[c] Ac=acetyl; Piv=pivaloyl; Bz=benzoyl; PNB=*para*-nitrobenzoyl; Bn=benzyl.

suggested that this stereochemical outcome is based on the preferential pseudoaxial orientation of the *C*-4 substituent (OAc). This conformer (**11** axial) has been calculated to be 1.5 kcal/mol more stable that the corresponding equatorial variant (**11** equatorial), and this preference then positions the *C*-4 OAc moiety effectively to interact and stabilise the oxonium species.[2e]



This interaction operates in a through-space manner to stabilise (via the alkyl-oxygen lone pair) the developing oxonium species, and the origin of this stereoelectronic interaction is based on the work of Miljkovic and Deslongchamps.[22] In the case of *O*-acetyl, this stabilisation can be viewed as being similar to **12a**, although it should be appreciated that the through-space effect is suggested to involve the alkyl (rather than acyl) oxygen atom.

It was of interest to test these explanations experimentally, and we speculated that replacing the *O*-acetyl protecting groups on the glycal with another substituent might influence the α/β ratio of *C*-glycoside products that are obtained. Reducing the ability of the carbonyl oxygen to participate directly (as in **12a** or **12b**) might be achieved using a bulky or more electron deficient ester, or use of an alkyl ether (or variant) would remove the carbonyl component altogether. The Miljkovic and Deslongchamps hypothesis[22] is, however, anticipated to be less dependent on the nature of the oxygen protecting group.

To probe this mechanism, a series of glycals were synthesised with a range of different esters (acetate **6a**, pivalate **6b**, benzoate **6c**, and *para*-nitrobenzoate **6d**), and the di-*O*-benzyl-protected glycal **6e** was also prepared. We also examined the arabinal isopropylidene variant **6f**, and corresponding the *O*-acetylated arabinal isomer **6g** as substrates for the zinc-mediated *C*-glycosylation reaction. All glycals were reacted under the same conditions as described for acetate **6a**: treatment of the glycal with 2 equiv. of organozinc reagent and 2 equiv. of $BF_3{\cdot}OEt_2$ at −30 °C, then the mixture was allowed to warm to room temperature (as in Scheme 3).

The results are shown in Table 1, and the *C*-glycosides were obtained in 66–95% yield. In all cases, the β-isomer predominated and this has been established unambiguously (see below). Interestingly, there is not a significant difference in the level of selectivity observed as a function of the *O*-protecting group. All ester derivatives **6a**–**d** give broadly similar results (favouring the β-isomer by 14–23:1), and the benzyl ether derivative **6e** preferentially gave the β-*C*-glycoside **7e** as a 15:1 ratio of isomers. In the case of the arabinal derivatives **6f** and **6g**, good β-selectivity was still observed. Interestingly, the level of selectivity associated with **7a** was slightly higher starting from **6a** than from the isomeric glycal **6g**, (and indeed a lower yield −76 vs. 95%—was also observed in the latter case). These could be within experimental error or may be associated with an as yet undefined factor. Assignment of the structures of **7b**–**f** was achieved in two ways. The *para*-nitrobenzoate **7d** was crystalline and its structure was established by crystallographic analysis, which clearly shows the 2,5-*trans* relationship between the two stereocentres on the dihydropyran ring (Figure 1).

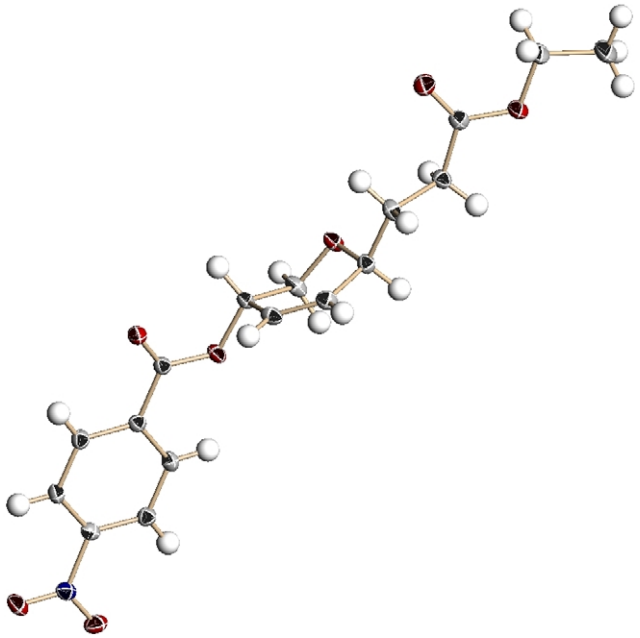
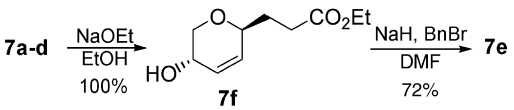


Figure 1. Structure of β-*C*-glycoside **7d**.

Following this, the remaining *C*-glycosides were correlated to **7e** by a series of straightforward transformations as outlined in Scheme 6.



Scheme 6.

3. Conclusions

We have developed a robust and highly stereoselective procedure for the formation of *trans*-2,5-substituted dihydropyrans based on the Lewis acid mediated addition of organozinc halides to pentopyranose-derived glycals. The stereochemical outcome of this reaction is not significantly influenced by the nature of the *O*-protecting group which suggests that direct neighbouring group participation (as in **12a** or **12b**) is not necessary to achieve high β-selectivity. Our observations provide further support for the mechanistic proposal suggested earlier by Isobe,[2e] which is based on a conformational preference and a stabilising through-space interaction.

4. Experimental

Infrared spectra were recorded in the range of 4000–600 cm^{-1} on a Perkin–Elmer FT-IR infrared spectrophotometer and the peaks are reported (ν_{max}) in wave numbers (cm^{-1}). Mass spectra were recorded using a Fisons V. G. Analytical Autospec instrument. High-resolution

mass determinations were performed on the same instrument. Optical rotations were recorded on a Perkin–Elmer 141 polarimeter. Proton nuclear magnetic resonance (^{1}H NMR) and carbon-13 nuclear magnetic resonance (^{13}C NMR) were recorded on JEOL JNM-GX270, JEOL JNM-LA300, JEOL JNM-GX400 or JEOL JNM ECP-400 spectrometers. Both ^{1}H and ^{13}C NMR chemical shifts are quoted in parts per million (δ) downfield from internal tetramethylsilane (TMS) standard. Assignments are based on COSY experiments, and carbohydrate and pyran numbering conventions have been used where appropriate to indicate proton and carbon signals in the Section 4. Coupling constants (J), expressed in Hertz, have been approximated to the nearest 0.5 Hz. Unless stated, flash chromatography was carried out using Merck 60 silica gel.

4.1. General method: preparation of ethyl 3-iodozinc-propionate

In a dry degassed flask, acid washed zinc dust (4.8 equiv.) was activated by heating (at ca. 250 °C) under vacuum (<1 mm Hg) for 20 min, then allowed to cool to room temperature. Anhydrous tetrahydrofuran (0.5 mL/1 mmol of Zn) was added followed by distilled 1,2-dibromoethane (0.2 equiv.) and the mixture was heated to reflux 4 times. Distilled chlorotrimethylsilane (0.15 equiv.) was added and the reaction mixture sonicated at 40 °C for 40 min. The suspension was brought to reflux and ethyl 3-iodopropionate (2.4 equiv.) in tetrahydrofuran (2 mL/1 mmol of iodide) was added via syringe pump over 90 min, refluxed for another 2 h and cooled to room temperature. Once cool, the solution was filtered and the solvent was removed in vacuo (using a nitrogen-purged rotary evaporator). The gel-like residue was redissolved in anhydrous dichloromethane (2 mL/0.5 mmol of glycal) and used immediately.

Details of the individual reactions using ethyl 3-iodozinc-propionate are given below.

4.1.1. (2*S*, 5*S*) Ethyl 3′-(5-acetoxy-5,6-dihydro-2*H*-pyran-2-yl) propionate (β 7a) and (2*R*, 5*S*) ethyl 3′-(5-acetoxy-5,6-dihydro-2*H*-pyran-2-yl) propionate (α 7a). Ethyl 3-iodozincpropionate (prepared according to the general procedure from ethyl 3-iodopropionate (11.4 g, 50 mmol)) was cooled to −30 °C and di-*O*-acetyl D-xylal (**6a**) (5 g, 25 mmol) in dichloromethane (25 mL) was added followed by $BF_3{\cdot}OEt_2$ (7.1 g, 50 mmol). The solution was allowed to warm to room temperature over 12 h, then washed with ice cold brine (2×100 mL), dried (Na_2SO_4) and concentrated in vacuo. The resulting residue was subjected to column chromatography (9:1 petroleum ether–ethyl acetate) to afford the title compounds (5.756 g, 95%) as a separable 22:1 mixture of β and α diastereomers.

(2*S*, 5*S*) Ethyl 3′-(5-acetoxy-5,6-dihydro-2*H*-pyran-2-yl) propionate (β-**7a**) was isolated as the major component and as a colourless oil: R_f 0.45 (7:3 petroleum ether–ethyl acetate); $[\alpha]_D^{23}$=+115 (*c* 0.34, $CHCl_3$); IR: ν_{max} (neat)/cm^{-1} 2981w (C–H), 1728s (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 5.91–5.82 (2H, m, H-3 and H-4), 5.23–5.19 (1H, m, H-5), 4.20–4.14 (1H, m, H-2), 4.13 (2H, q, *J*=7.0 Hz, OEt), 4.07 (1H, dd, *J*=11.5, 5.0 Hz, H-6a), 3.52 (1H, dd, 11.5, 6.5, H-6b), 2.43 (2H, t, *J*=7.5 Hz, H-2′), 2.07 (3H, s, Ac), 1.91–1.82 (2H, m, H-3′), 1.26 (3H, t, *J*=7.0 Hz, OEt); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 173.3 (C-1′), 170.4 (C=O, Ac), 133.4 (C-3), 124.6 (C-4), 72.3 (C-2), 64.8 (C-5), 64.6 (C-6), 60.3 (CH_2O, Et), 29.7 (C-2′), 28.6 (C-3′), 20.9 (CH_3, Ac), 14.1 (CH_3, Et); MS (CI$^+$) *m*/*z*: 243 (5%, MH$^+$), 197 (11%, [M−OEt]$^+$), 183 (41%, [M−OAc]$^+$), 137 (100%, [M−EtOH−OAc]$^+$), 129 (62%); HRMS (CI$^+$) *m*/*z*: $C_{12}H_{19}O_5$ (MH$^+$) requires: 243.1232. Found: 243.1232.

(2*R*, 5*S*) Ethyl 3′-(5-acetoxy-5,6-dihydro-2*H*-pyran-2-yl) propionate (α-**7a**) was isolated as the minor component and as a colourless oil: R_f 0.38 (7:3 petroleum ether–ethyl acetate); $[\alpha]_D^{23}$=+128 (*c* 0.40, $CHCl_3$); IR: ν_{max} (neat)/cm^{-1} 2980w, (C–H), 1727s (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 5.97–5.94 (2H, m, H-3 and H-4), 5.01–4.98 (1H, m, H-5), 4.13 (2H, q, *J*=7.0 Hz, OEt), 4.10–4.06 (1H, m, H-2), 4.03 (1H, d, *J*=12.5 Hz, H-6a), 3.73 (1H, dd, *J*=12.5, 2.5 Hz, H-6b), 2.48 (2H, t, *J*=7.5 Hz, H-2′), 2.10 (3H, s, Ac), 2.04–1.80 (2H, m, H-3′), 1.26 (3H, t, *J*=7.0 Hz, OEt); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 174.4 (C-1′), 170.9 (C=O, Ac), 135.7 (C-3), 122.9 (C-4), 72.7 (C-2), 67.7 (C-6), 64.7 (C-5), 60.4 (OCH_2), 29.7 and 29.7 (C-2′ and C-3′), 21.2 (CH_3, Ac), 14.2 (CH_3, Et); MS (FAB) *m*/*z*: 265 (19%, [M+Na]$^+$), 243 (35%, MH$^+$), 197 (17%, [M−OEt]$^+$), 183 (100%, [M−OAc]$^+$), 141 (10%), 129 (58%). Anal. calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.29: H, 7.83.

4.1.2. (2*S*, 5*S*) Methyl 3′-(5-hydroxy-5,6-dihydro-2*H*-pyran-2-yl) propionate (8). A mixture of acetate β-**7a** (102 mg, 0.42 mmol), potassium carbonate (5.8 mg, 0.0421 mmol) and methanol (1 mL) was stirred at 25 °C for 4 h. Addition of diethyl ether (2 mL) and petroleum ether (2 mL), followed by filtration through a pad of celite and concentration afforded the title compound (84 mg, 100%) as colourless crystals. Mp: 54 °C (ethyl acetate–petroleum ether): R_f 0.15 (4:1 hexane–isopropyl ether); $[\alpha]_D^{23}$=+102 (*c* 0.1, $CHCl_3$); IR: ν_{max} (thin film)/cm^{-1} 3417br s (O–H), 3031w, 2955m, 2857m (C–H), 1726s (C=O); ^{1}H NMR (400 MHz, *d*6-DMSO): δ_H 5.84 (1H, dtd, *J*=10.5, 2.5, 1.5 Hz, H-4), 5.73 (1H, dt, *J*=10.5, 2.0 Hz, H-3), 4.18–4.06 (1H, m, H-5), 4.14–2.01 (1H, m, H-2), 3.98 (1H, ddd, *J*=11.0, 4.5, 1.0 Hz, H-6$_{eq}$), 3.63 (3H, s, OMe), 3.28 (1H, dd, *J*=11.0, 8.0 Hz, H-6$_{ax}$), 2.40 (2H, t, *J*=7.5 Hz, H-2′), 1.91–1.82 (1H, m, H-3′a), 1.80–1.71 (1H, m, H-3′b) (O*H* was not observed); ^{13}C NMR (100 MHz, *d*6-DMSO): δ_C 175.7 (C-1′), 131.8 (C-3), 130.9 (C-4), 74.1 (C-2), 69.9 (C-6), 53.4 (C-5), 52.1 (OMe), 30.7 (C-3′), 30.3 (C-2′); MS (CI$^+$) *m*/*z*: 187 (1%, MH$^+$), 169 (6%, [M−OH]$^+$), 155 (12%, [M−OMe]$^+$), 137 (66%), 115 (61%), 85 (100%). Anal. calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 58.05; H, 7.59.

4.1.3. (2*S*, *3R*, 4*R*, 5*R*) Methyl 3′-(3,4,5-triacetoxytetrahydropyran-2-yl)propionate (9) and (2*S*, 3*R*, 4*S*, 5*R*) methyl 3′-(3,4,5-triacetoxytetrahydropyran-2-yl)propionate (10). To a solution of allylic alcohol **8** (146 mg, 0.78 mmol) at 0 °C in anhydrous pyridine (2 mL) was added a solution of osmium tetroxide (200 mg, 0.78 mmol) in pyridine (6 mL). The mixture was warmed to room temperature and stirred for 18 h. Sodium metabisulfite (3 g) was added and the mixture stirred for a further 2 h. The solvent was removed in vacuo, and the residue was

dissolved in methanol (10 mL), 12 M HCl (6 drops) was added and the mixture stirred for 1 h. The mixture was filtered through a plug of celite and the solvents removed in vacuo. The residue was dissolved in acetic anhydride (10 mL), to this was added pyridine (6 mL) and DMAP (22 mg, 0.18 mmol) and the solution was stirred for 18 h. The solvents were removed in vacuo and the residue diluted with CH_2Cl_2 (80 mL) which was washed with $NaHCO_3$ (2×80 mL) and brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified via column chromatography (4:1 petroleum ether–ethyl acetate) to afford a 1:1 mixture of diastereomers (88 mg, 32% combined yield), which were separable.

(2*S*, 3*R*, 4*R* 5*R*) Methyl 3′-(3,4,5-triacetoxytetrahydropyran-2-yl)propionate (**9**) was isolated as a colourless solid: R_f 0.35 (1:1 ethyl acetate–petroleum ether); IR: ν_{max} (neat)/cm^{-1} 2925w, 2858w (C–H), 1748s (C═O); ^1H NMR (400 MHz, $CDCl_3$): δ_H 5.34 (1H, dd, *J*=3.5, 1.0 Hz, H-3), 5.20 (1H, td, *J*=10.0, 5.5 Hz, H-5), 5.03 (1H, dd, *J*=10.0, 3.5 Hz, H-4), 4.14 (1H, dd, *J*=11.0, 5.5 Hz, H-6_{eq}), 3.67 (3H, s, OMe), 3.58 (1H, ddd, *J*=9.5, 4.5, 1.0 Hz, H-2), 3.23 (1H, dd, *J*=11.0, 10.0 Hz, H-6_{ax}), 2.42 (2H, m, H-2′), 2.16, 2.03, and 2.00 (9H, 3×s, Ac), 1.91–1.83 and 1.75–1.67 (2H, 2×m, H-3′); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 172.6 (C-1′), 169.9, 169.5 and 169.4 ($MeCO_2$), 75.8 (C-2), 71.4 (C-4), 69.4 (C-3), 66.7 (C-6), 66.2 (C-5), 51.2 (OMe), 29.2 (C-2′), 25.5 (C-3′), 20.3, 20.2 and 20.1 (O_2CMe); MS (CI^+) *m*/*z*: 347 (1%, MH^+), 315 (26%, $[M-OMe]^+$), 273 (8%), 226 (56%), 184 (100%); HRMS (CI^+) *m*/*z*: $C_{15}H_{23}O_9$ (MH^+) requires: 347.1342; found: 347.1349.

(2*S*, 3*S*, 4*S*, 5*R*) Methyl 3′-(3,4,5-triacetoxytetrahydropyran-2-yl)propionate (**10**) isolated as a colourless oil: R_f 0.40 (1:1 ethyl acetate–petroleum ether); IR: ν_{max} (neat)/cm^{-1} 2954w, 2882w (C–H), 1749s (C═O); ^1H NMR (400 MHz, $CDCl_3$): δ_H 5.62 (1H, t, *J*=3.0 Hz, H-4), 4.97 (1H, ddd, *J*=10.5, 5.5, 3.0 Hz, H-5), 4.68 (1H, dd, *J*=10.0, 3.0 Hz, H-3), 3.83 (1H, ddd, *J*=10.5, 5.5, 1.0 Hz, H-6_{eq}), 3.68 (3H, s, OMe), 3.66 (1H, td, *J*=10.0, 3.0 Hz, H-2), 3.59 (1H, t, *J*=10.5 Hz, H-6_{ax}), 2.48 (1H, m, H-2′), 2.42 (1H, m, H-2′), 2.16, 2.02, and 2.01 (9H, 3×s, Ac), 1.99–1,91 and 1.68–1.60 (2H, 2×m, H-3′); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 173.1 (C-1′), 169.4, 168.8, and 168.7 ($MeCO_2$), 72.4 (C-2), 70.1 (C-3), 68.0 (C-4), 66.7 (C-5), 63.4 (C-6), 51.6 (OMe), 29.4 (C-2′) 26.6 (C-3′), 20.8, 20.7, and 20.6 (O_2CMe); MS (CI^+) *m*/*z*: 347 (4%, MH^+), 315 (33%, $[M-OMe]^+$), 287 (13%, $[M-OAc]^+$), 273 (10%), 213 (12%), 185 (40%), 167 (86%), 61 (100%); HRMS (CI^+) *m*/*z*: $C_{15}H_{23}O_9$ (MH^+) requires: 347.1342; found: 347.1342.

4.1.4. Di-*O*-benzoyl D-xylal (6c). Di-*O*-acetyl D-xylal (**6a**) (1.5 g, 7.5 mmol), was treated with sodium methoxide solution (20 mg of Na/20 mL of MeOH) and stirred for 3 h. The mixture was passed through a plug of celite, then concentrated in vacuo and redissolved in dichloromethane (20 mL) to which pyridine (10 mL) and DMAP (100 mg, 0.82 mmol) were added. The solution was cooled to 0 °C, and benzoyl chloride (5.22 mL, 6.37 g, 45 mmol) was added slowly over 20 min. The mixture was stirred for 16 h, then concentrated in vacuo and chromatographed directly (2:1 40–60 petroleum ether–dichloromethane) to afford **6c** (1.68 g, 69%) as a colourless crystalline solid. Mp: 113–115 °C (dichloromethane–40–60 petroleum ether): R_f 0.15 (2:1 40–60 petroleum ether–dichloromethane); $[\alpha]_D^{20}$=−87.3 (*c* 1.58, $CHCl_3$); IR: ν_{max} (thin film)/cm^{-1} 1716s (C═O), 1639m, 1450w, 1299m, 1237s, 1173w, 1087s, 1066s, 1022m, 953m; ^1H NMR: ($CDCl_3$, 400 MHz): δ_H 8.05 (4H, d, *J*=8.5 Hz, *H*Ar), 7.58 (2H, tq, *J*=6.0 Hz, 1.5, *H*Ar), 7.45 (4H, t, *J*=8.0 Hz, *H*Ar), 6.72 (1H, d, *J*=6.5 Hz, H-1), 5.43–5.39 (1H, m, H-3), 5.39–5.36 (1H, m, H-4), 5.15 (1H, ddd, *J*=7.5, 5.0, 1.5 Hz, H-2), 4.42 (1H, ddd, *J*=13.0, 3.0, 1.5 Hz, H-5), 4.22 (1H, dd, *J*=13.0, 2.0 Hz, H-5′); ^{13}C NMR: ($CDCl_3$, 75 MHz): δ_C 165.5 (*C*═O), 165.4 (*C*═O), 148.3 (C-1), 133.4, 133.2, 129.9, 129.8, 129.7, 129.4, 128.5, and 128.4 (*C*Ar), 97.5 (C-2), 67.6 (C-4), 64.0 (C-3), 63.9 (C-5); LRMS *m*/*z*: (CI) 283 (1%), 203 (65%, $[M-PhCO_2]^+$), 161 (10%), 123 (100%), 105 (95%), 81 (95%); HRMS (CI) $C_{12}H_{11}O_3$ $[M-(PhCO_2)]^+$ requires: 203.0708; found: 203.0711.

4.1.5. 3,4-*O*,*O*′-Isopropylidene D-arabinal (6g).[21] Di-*O*-acetyl D-arabinal (**6a**) (1.0 g, 5 mmol), was treated with sodium methoxide solution (20 mg of Na/20 mL of MeOH) and stirred for 3 h. The mixture was passed through a plug of celite, then concentrated in vacuo and redissolved in dry dichloromethane (30 mL), then 2,2-dimethoxypropane (1.23 mL, 1.04 g, 10 mmol) and 2,3-dichloro-5,6-dicyano-*para*-benzoquinone (114 mg, 0.5 mmol) were added and the mixture was stirred for 12 h. The resulting dark green solution was concentrated in vacuo and chromatographed directly (dichloromethane) to afford **6g** (562 mg, 72%) as a colourless oil: R_f 0.3 (dichloromethane); $[\alpha]_D^{22}$=+52 (*c* 0.8, CH_2Cl_2); IR: ν_{max} (thin film)/cm^{-1} 2985w, 1456w, 1380m, 1371m, 1245m, 1215m, 1108m, 1059s, 995s, 933w; ^1H NMR: (300 MHz, $CDCl_3$): δ_H 6.55 (1H, dd, *J*=6.0, 1.0 Hz, H-1), 5.12 (1H, dd, *J*=6.0, 4.0 Hz, H-2), 4.49 (1H, dd, *J*=6.0, 5.0 Hz, H-3), 4.20 (1H, ddd, *J*=8.0, 6.0, 5.5 Hz, H-4), 4.03 (1H, ddd, *J*=11.0, 4.0, 1.0 Hz, H-5a), 3.63 (1H, dd, *J*=11.0, 8.0 Hz, H-5b), 1.49 (3H, br. s, CH_3), 1.39 (3H, br.s, CH_3); ^{13}C NMR: (75 MHz, $CDCl_3$): δ_C 147.7 (C-1), 108.9 (CCH_3), 100.0 (C-2), 70.5 (C-3), 67.1 (C-4), 65.0 (C-5), 28.4 (CH_3), 26.1 (CH_3); LRMS *m*/*z*: (CI) 157 ($[M+H]^+$, 3%) 149 (4%), 137 (8%), 99 (45%, $[M-(CH_3)_2CO+H]^+$), 84 (80%), 59 (100%); HRMS (CI) $C_8H_{13}O_3$ $[M+1]^+$ requires 157.0865; found: 157.0866.

4.1.6. (2*S*, 5*S*)-Ethyl 3′-(5,6-dihydro-5-(trimethylacetoxy)-2*H*-pyran-2-yl) propionate (7b). Ethyl 3-iodozincpropionate (prepared according to the general procedure from ethyl 3-iodopropionate (483 mg, 2.12 mmol)) was cooled to −30 °C and di-*O*-(trimethylacetyl) D-xylal (**6b**)[18] (300 mg, 1.06 mmol) in dichloromethane (2 mL) was added followed by $BF_3{\cdot}OEt_2$ (301 mg, 2.12 mmol). The solution was allowed to warm to room temperature over 12 h, then washed with ice cold brine (2×10 mL), dried (Na_2SO_4) and concentrated in vacuo. The resulting residue was subjected to column chromatography (9:1 petroleum ether–ethyl acetate) to afford the title compounds (213 mg, 0.752 mmol, 71%) as a 23:1 mixture of β and α diastereomers. Only the major component β-**7b** could be isolated in pure form, however, ^1H NMR of the crude reaction mixture indicated the presence of the other diastereomer.

(2*S*, 5*S*) Ethyl 3′-(5,6-dihydro-5-(trimethylacetoxy)-2*H*-pyran-2-yl)-propionate β-**7b**, was isolated as a colourless

oil: R_f 0.15 (9:1 40–60 petroleum ether–ethyl acetate); $[\alpha]_D^{20}=-6.2$ (*c* 0.32, $CHCl_3$); IR: ν_{max} (neat)/cm^{-1} 2976, 1726s, 1480w, 1395w, 1277m, 1148s, 1093m, 1032m, 939w, 915w; ^1H NMR: ($CDCl_3$, 400 MHz): δ_H 5.81–5.71 (2H, m, H-3 and H-4), 5.16–5.10 (1H, m, H-5), 4.12–4.07 (1H, m, H-2), 4.05 (2H, q, *J*=7.0 Hz, H-4′), 4.01 (1H, dd, *J*=12.0, 4.0 Hz, H-6a), 3.38 (1H, dd, *J*=12.0, 7.0 Hz, H-6b), 2.35 (2H, t, *J*=7.5 Hz, H-2′), 1.88–1.71 (2H, m, H-3′), 1.18 (3H, t, *J*=7.0 Hz, H-5′), 1.11 (9H, s, H-3″); ^{13}C NMR: (100 MHz, $CDCl_3$): δ_C 177.8 (C-1″), 173.1 (C-1′), 132.9 (C-4), 125.0 (C-3), 72.3 (C-2), 64.9 (C-6), 64.4 (C-5), 60.1 (C-2), 38.5 (C-2″), 29.5 (C-2′), 28.9 (C-3′), 26.9 (C-3″), 14.0 (C-5′); LRMS (CI) *m/z*: 313 (4%, $[M+C_2H_5]^+$), 285 (3%, $[M+H]^+$), 239 (15%), 183 (65%, $[M-Me_3CCO_2]^+$), 137 (100%), 129 (90%); HRMS: (CI) $C_{15}H_{25}O_5$ $[M+1]^+$ requires 285.1701; found: 285.1691.

4.1.7. (2*S*, 5*S*) Ethyl 3′-(5-benzoyloxy-5,6-dihydro-2*H*-pyran-2-yl) propionate (7c). Ethyl 3-iodozincpropionate (prepared according to the general procedure from ethyl 3-iodopropionate (422 mg, 1.852 mmol)) was cooled to −30 °C and di-*O*-benzoyl-D-xylal (**6c**) (300 mg, 0.926 mmol) in dichloromethane (2 mL) was added followed by $BF_3{\cdot}OEt_2$ (259 mg, 1.852 mmol). The solution was allowed to warm to room temperature over 12 h, then washed with ice cold brine (2×10 mL), dried over sodium sulfate and concentrated in vacuo. The resulting residue was subject to column chromatography (8:2 petroleum ether–ethyl acetate) to afford the title compounds (256 mg, 91% yield) as a 14:1 mixture of β and α diastereomers. Only the major component β-**7c** could be isolated in pure form, however, ^1H NMR of the crude reaction mixture indicated the presence of the other diastereomer.

(2*S*, 5*S*) Ethyl 3′-(5,6-dihydro-5-benzoyloxy-2*H*-pyran-2-yl)-propionate **7c**, was isolated as a colourless gum: R_f 0.2 (8:2 40–60 petroleum ether–ethyl acetate); $[\alpha]_D^{20}=-3.0$ (*c* 0.66, $CHCl_3$); IR: ν_{max} (neat)/cm^{-1} 2981w (C–H), 1715s (C=O), 1451w, 1316w, 1264s, 1175m, 1093m, 1025m, 992w, 918w; ^1H NMR: (400 MHz, $CDCl_3$): δ_H 8.15–8.02 (2H, m, *H*Ar), 7.64–7.52 (1H, 2×m, *H*Ar), 7.50–7.39 (2H, m, *H*Ar), 6.02–5.89 (2H, 2×m, H-3 and H-4), 5.52–5.45 (1H, m, H-5), 4.27–4.20 (2H, m, H-2 and H-6a), 4.15 (2H, q, *J*=7.5 Hz, H-4′), 3.66 (1H, dd, *J*=11.0, 6.5 Hz, H-6b), 2.47 (2H, t, *J*=7.5 Hz, H-2′), 1.92 (2H, m, H-3′), 1.27 (3H, t, *J*=7.5 Hz, H-5′); ^{13}C NMR: (100 MHz, $CDCl_3$): δ_C 173.4 (C-1′), 166.0 (Ar*C*O$_2$), 132.3 (C-3), 132.1 (*C*Ar), 130.1 (*C*Ar), 129.6 (*C*Ar), 128.2 (*C*Ar), 124.8 (C-4), 72.4 (C-2), 65.3 (C-5), 64.8 (C-6), 60.4 (C-4′), 29.7 (C-2′), 28.8 (C-3′), 14.1 (C-5′); LRMS (CI) *m/z*: 333 (3%, $[M+C_2H_5]^+$), 305 (2.5%, $[M+H]^+$), 259 (10%, $[M-EtO]^+$), 183 (55%, $[M-PhCO_2]^+$), 137 (100%), 129 (80%), 123 (50%), 105 (60%); HRMS: (CI) $C_{17}H_{21}O_5$ $[M+1]^+$ requires: 305.1389; found: 305.1390.

4.1.8. (2*S*, 5*S*) Ethyl 3′-(5,6-dihydro-5-(*para*-nitrobenzoyloxy)-2*H*-pyran-2-yl) propionate (7d). Ethyl 3-iodozincpropionate (prepared according to the general procedure from ethyl 3-iodopropionate (331 mg, 1.45 mmol)) was cooled to −30 °C and di-*O*-(4-nitrobenzoyl)-D-xylal (**6d**)[19] (300 mg, 0.725 mmol) in dichloromethane (2 mL) was added followed by $BF_3{\cdot}OEt_2$ (206 mg, 1.45 mmol). The solution was allowed to warm to room temperature over 12 h, then washed with ice cold brine (2×10 mL), dried (Na_2SO_4) and concentrated in vacuo. The resulting residue was subjected to column chromatography (7:3 petroleum ether–ethyl acetate) to afford the title compounds (207 mg, 0.594 mmol, 82% yield) as a 15:1 mixture of β and α diastereomers. Only the major component β-**7d** could be isolated in pure form, however, ^1H NMR of the crude reaction mixture indicated the presence of the other diastereomer.

(2*S*, 5*S*) Ethyl 3′-(5,6-dihydro-5-(para-nitrobenzyloxy)-2*H*-pyran-2-yl)-propionate **7d**, was isolated as a yellow/green solid. Mp: 83–84 °C (dichloromethane–hexanes): R_f 0.15 (7:3 40–60 petroleum ether–ethyl acetate); $[\alpha]_D^{20}=+32.0$ (*c* 0.25, $CHCl_3$); IR: ν_{max} (neat)/cm^{-1} 2982w (C–H), 1720s (C=O), 1609w, 1530s (NO_2), 1320m, 1266s, 1163m, 1100s, 972m, 921m; ^1H NMR (300 MHz, $CDCl_3$): δ_H 8.19–8.15 (2H, m, H-4″), 8.09–8.04 (2H, m, H3″) 6.00 (2H, s, H-3 and H-4), 5.51–5.48 (1H, m, H-5), 4.38–4.19 (2H, m, H-2 and H-6a), 4.15 (2H, q, *J*=7.0 Hz, H-4′), 3.71 (1H, dd, *J*=11.5, 6.0 Hz, H-6b), 2.47 (2H, t, *J*=7.5 Hz, H-2′), 1.97–1.85 (2H, m, H-3′), 1.28 (3H, t, *J*=7.0 Hz, H-5′); ^{13}C NMR: (75 MHz, $CDCl_3$): δ_C 173.3 (C-1′), 164.1 (C-1″), 150.5 (C-3″), 135.3 (C-4″), 134.4 (C-4), 130.8 (C-2″), 123.9 (C-3), 123.4 (C-5″), 72.4 (C-2), 66.3 (C-5), 64.4 (C-6), 60.4 (C-4′), 29.8 (C-2′), 28.5 (C-3′), 14.1 (C-5′); MS (CI) *m/z*: 378 (2%, $[M+C_2H_5]^+$), 350 (0.5%, $[M+H]^+$), 304 (2%), 183 (40%), 168 (50%), 137 (100%), 129 (60%); HRMS: (CI) $C_{17}H_{20}NO_7$ $[M+1]^+$ requires: 350.1240; found: 350.1242.

4.1.9. (2*S*, 5*S*) Ethyl 3′-(5,6-dihydro-5-benzyloxy-2*H*-pyran-2-yl) propionate (7e). Ethyl 3-iodozincpropionate (prepared according to the general procedure from ethyl 3-iodopropionate (461 mg, 2.02 mmol)) was cooled to −30 °C and di-*O*-benzyl-D-xylal (**6e**)[20] (300 mg, 1.01 mmol) in dichloromethane (2 mL) was added followed by $BF_3{\cdot}OEt_2$ (287 mg, 2.02 mmol). The solution was allowed to warm to room temperature over 12 h, then washed with ice cold brine (2×10 mL), dried (Na_2SO_4) and concentrated in vacuo. The resulting residue was subjected to column chromatography (9:1 petroleum ether–ethyl acetate) to afford the title compounds (214 mg, 0.734 mmol, 73%) as a 15:1 mixture of β and α diastereomers. Only the major component β-**7e** could be isolated in pure form, however, ^1H NMR of the crude reaction mixture indicated the presence of the other diastereomer.

(2*S*, 5*S*) Ethyl 3′-(5,6-dihydro-5-benzyloxy-2*H*-pyran-2-yl)-propionate β-**7e**, was isolated as a colourless oil: R_f 0.2 (3:1 40–60 petroleum ether–diethyl ether); $[\alpha]_D^{20}=+4.0$ (*c* 1.50, $CHCl_3$); IR: ν_{max} (neat)/cm^{-1} 2860w (C–H), 1730s (C=O), 1454w, 1372w, 1253m, 1160m, 1087s, 1027m, 907s; ^1H NMR: (300 MHz, $CDCl_3$): δ_H 7.36–7.27 (5H, m, *H*Ar), 5.96 (1H, ddd, *J*=10.5, 2.0, 1.5 Hz, H-3 or H-4), 5.75 (1H, dt, *J*=10.5, 1.5 Hz, H-3 or H-4), 4.60 (2H, dd, *J*=16.5, 11.5 Hz, PhC*H*$_2$O), 4.19–4.02 (5H, m, H-2, H-6a, and H-5′), 3.47 (1H, dd, *J*=13.0, 9.5 Hz, H-6b), 2.40 (2H, t, *J*=7.5 Hz, H-2′), 1.96–1.72 (2H, m, H-3′), 1.24 (3H, t, *J*=7.5 Hz, H-6′); ^{13}C NMR: (75 MHz, $CDCl_3$): δ_C 173.5 (C-1′), 138.3 (*C*Ar), 131.6 (C-3), 128.4 (*C*Ar), 127.8 (*C*Ar), 127.7 (*C*Ar), 127.2 (C-4), 72.8 (C-2), 70.9 (Ph*C*H$_2$O), 69.5

(C-5), 66.6 (C-6), 60.3 (C-5′), 29.7 (C-2′ or C-3′), 29.5 (C-2′ or C-3′), 14.2 (C-6′); LRMS (CI) *m/z*: 291 (2, M+H), 260 (2%), 245 (4%, $[M-OEt]^+$), 183 (40%), 137 (65%), 129 (60%), 91 (100%, $[PhCH_2]^+$); HRMS (CI) $C_{17}H_{23}O_4$ $[M+1]^+$ requires: 291.1596; found: 291.1596.

4.1.10. (2*S*, 5*S*) Ethyl 3′-(5,6-dihydro-5-hydroxy-2*H*-pyran-2-yl) propionate (7f). Ethyl 3-iodozincpropionate (prepared according to the general procedure from ethyl 3-iodopropionate (146 mg, 0.642 mmol)) was cooled to −30 °C and 3,4-isopropylidene D-arabinal (**6f**)[21] (50 mg, 0.321 mmol) in dichloromethane (1 mL) was added followed by $BF_3{\cdot}OEt_2$ (91 mg, 0.642 mmol). The solution was allowed to warm to room temperature over 12 h, then washed with ice cold brine (2×10 mL), dried over sodium sulfate and concentrated in vacuo. The resulting residue was subject to column chromatography (7:3 petroleum ether–ethyl acetate) to afford the title compounds (42 mg, 0.212 mmol, 66% yield) as a 15:1 mixture of β and α diastereomers. Only the major component β-**7f** could be isolated in pure form, however, ^{1}H NMR of the crude reaction mixture indicated the presence of the other diastereomer.

(2*S*, 5*S*) Ethyl 3′-(5,6-dihydro-5-hydroxy-2*H*-pyran-2-yl)-propionate **6f**, was isolated as a colourless oil: R_f 0.35 (1:1 ethyl acetate–40–60 petroleum ether); $[\alpha]_D^{20}=+29.1$ (*c* 0.12, $CHCl_3$); IR: ν_{max} (thin film)/cm^{-1} 3437br s (O–H), 2925m (C–H), 1731s (C=O), 1377w, 1261w, 1184m, 1041w; ^{1}H NMR: ($CDCl_3$, 400 MHz): δ_H 5.92 (1H, dtd, *J*=10.5, 3.0, 0.5 Hz, H-4), 5.76 (1H, ddd, *J*=10.5, 4.0, 1.4 Hz, H-3), 4.20–4.11 (2H, m, H-2 and H-5), 4.13 (2H, q, *J*=7.0 Hz, H-4′), 4.12 (1H, ddd, *J*=11.5, 4.0, 1.0 Hz, H-6a), 3.41 (1H, dd, *J*=11.5, 6.5 Hz, H-6b), 2.42 (2H, t, *J*=8.0 Hz, H-2′), 1.92–1.80 (2H, m, H-3′), 1.25 (3H, t, *J*=7.0 Hz, H-5′) (OH was not observed); ^{13}C NMR: ($CDCl_3$, 100 MHz): δ_C 173.8 (C-1′), 131.7 (C-4), 128.7 (C-3), 72.5 (C-2), 68.2 (C-6), 62.8 (C-5), 60.4 (C-4′), 29.9 (C-2′), 28.9 (C-3′), 14.2 (C-5′); LRMS (CI) *m/z*: 183 (2.5%, $[M-OH]^+$), 149 (10%), 137 (35%), 84 (100%); HRMS: (CI) $C_{10}H_{15}O_3$ $[M-OH]^+$ requires 183.1021; found 183.1023.

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Synthesis of new pyrazolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidines and related heterocycles

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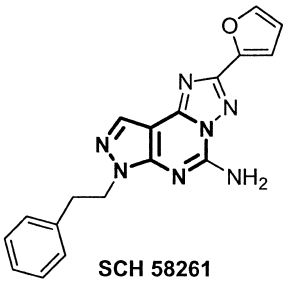
Abstract—The reaction between 5-amino-4-imino-1(2)-substituted-1(2)*H*-4,5-dihydropyrazolo[3,4-*d*]pyrimidines and several commercially available reactants afforded new heterocycles with a conserved pyrazolo[3,4-*d*]pyrimidine nucleus. The key intermediates employed proved to be suitable compounds by virtue of their two vicinal amino and imino groups that were used to obtain five, six and seven-membered rings.

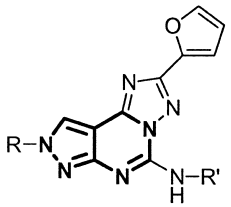
1. Introduction

Adenosine is present in different tissues in the mammalian organism where it has a variety of important physiological functions such as the synthesis of nucleic acids or implications in energy metabolism production.[1–3] Adenosine interacts with four cell surface receptor subtypes (ARs) classified as A_1, A_{2A}, A_{2B} and A_3, belonging to the family of G protein-coupled receptors.[4] Efforts made in medicinal chemistry in the past 20 years have led to the discovery of a variety of selective antagonists for the A_{2A} and the A_3 adenosine receptor subtypes. Among these, it was demonstrated that the structural requirement for reaching A_{2A} and A_3 antagonist behavior is the tricyclic heterocyclic pyrazolo[1,5-*c*]-1,2,4-triazolo[4,3-*e*]pyrimidine structure, N^7-substituted for molecules designed as A_{2A} antagonists and N^8-substituted for molecules planned as A_3 antagonists.[5–14] Until now, the best results in terms of A_{2A} and A_3 antagonistic affinity and selectivity are respectively achieved by the synthesis of **SCH 58261**[5] and the 5-*N*-(substituted-phenylcarbamoyl)amino-N^8-substituted-pyrazolo-triazolo-pyrimidines, belonging to **MRE** analogs (Fig. 1).[10,11] Along with the tricyclic structure, another structural requirement necessary for the activity and, above all, the receptor anchorage was found to be the presence of the 2-furyl group at the 2-position of the tricyclic core.[5]

Starting from these SAR observations and in continuation to



SCH 58261



MRE series

R= alkyl, R'= (substituted)phenyl urea or amide

Figure 1. Potent and selective A_{2A} and A_3 adenosine receptor antagonists.

Keywords: Reactivity studies; Adenosine antagonists; Pyrazolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidines; 5-Amino-4-imino-1(2)-substituted-1(2)*H*-pyrazolo[3,4-*d*]pyrimidines.
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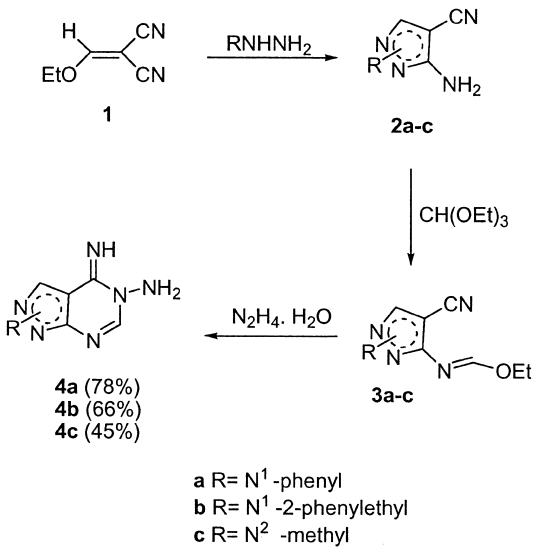


Scheme 1.

our interest in the synthesis of pyrazolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidines[15] we decided to design and synthesize new adenosine ligands, maintaining the pyrazolo[3,4-*d*]pyrimidine nucleus and to replace the 2-(2-furyl)-triazole moiety with other five, six and seven-membered rings, fused to the pyrazolo[3,4-*d*]pyrimidine ring system and functionalized by the introduction of several functions, such as ester, acid, amide, hydrazide, and alkyl groups.

For this purpose we started from the key intermediates **4a–c** (5-amino-4-imino-1(2)-substituted-1(2)*H*-pyrazolo[3,4-*d*]pyrimidines), easily obtained from the N^1 or N^2-substituted amino-cyano-pyrazoles (Scheme 1).[16,17] These substrates proved to be versatile compounds by virtue of their vicinal amino and imino functions, evaluating the reactivity in several cyclization reactions performed with the aim of obtaining new heterocycles with a conserved pyrazolo[3,4-*d*]pyrimidine core. The substituents selected for the pyrazole nitrogen of **4a–c** were mainly 1-phenyl but 1-(2-phenylethyl) like SCH 58261, and 2-methyl like the MRE series were also chosen for comparison reasons.

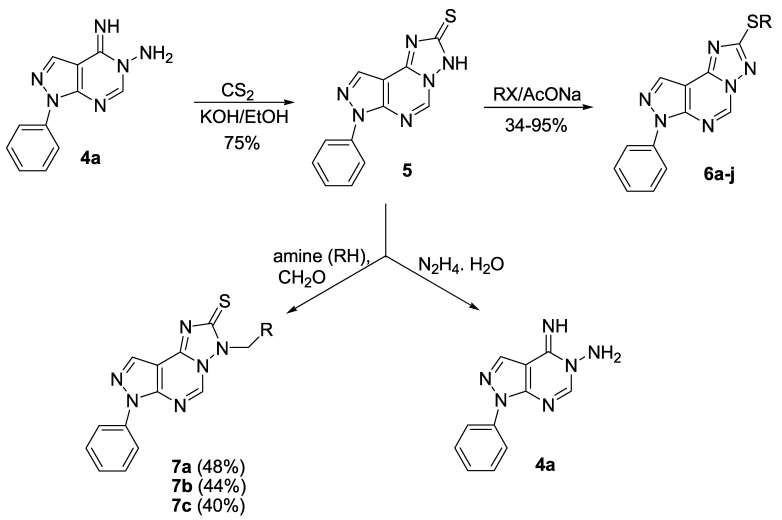
In our chemical reactivity studies described here, we principally employed the intermediate **4a** (5-amino-4-imino-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine), due to its easy preparation, high reactivity and good yield of reactions. The major limitations of compounds **4b** and **4c** were their low solubility in organic solvents employed in the clusters of reactions performed and, at the same time, the restricted yield of reactions.

The new heterocycles obtained will be evaluated in pharmacological assays to determine their antagonist properties versus the A_{2A} and A_3 adenosine receptor subtypes.

2. Results and discussions

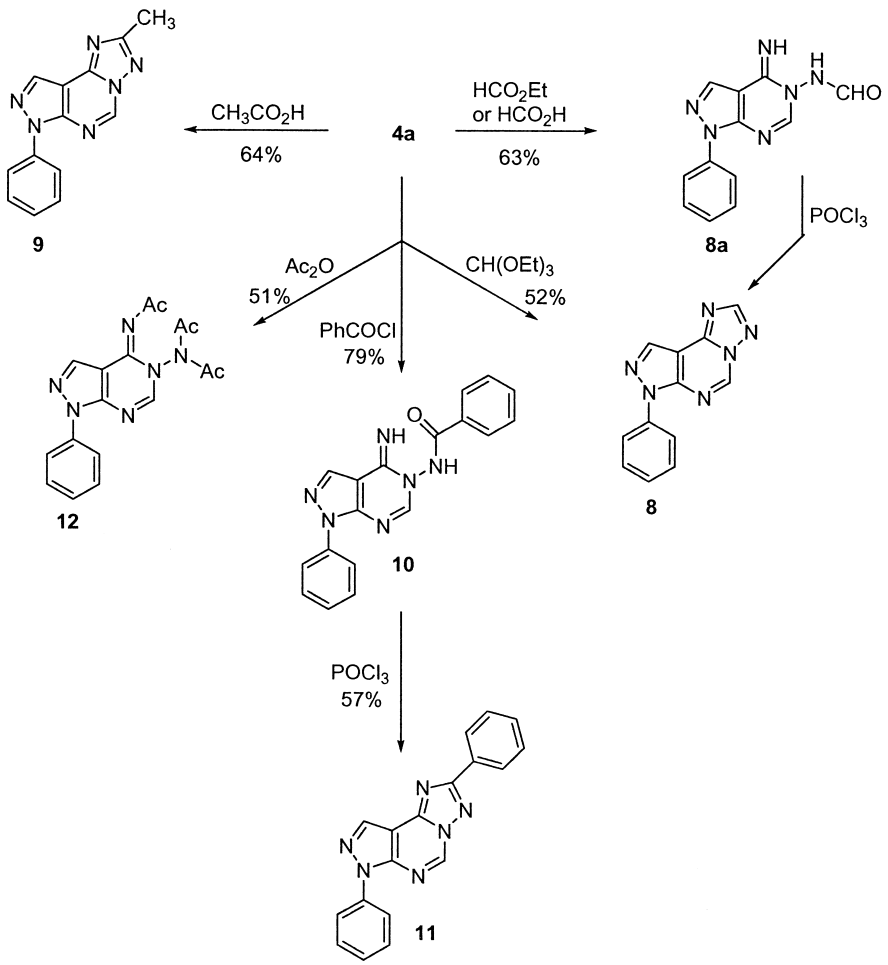
The N^1 or N^2-substituted amino-cyano-pyrazoles[16,17] were reacted with triethylorthoformate to give the corresponding ethoxymethylene amino derivatives **3a–c**. These latter compounds were used as intermediates for the preparation of the key compounds **4a–c** by cyclization with hydrazine hydrate, as depicted in Scheme 1.

When **4a** was allowed to react with CS_2, the pyrazolo-triazolo-pyrimidine-2-thione **5** was obtained. This latter compound, was alkylated using several alkylating agents (RX) in refluxing ethanol in the presence of anhydrous sodium acetate to give the corresponding derivatives **6a–j**. The Mannich bases **7a–c** were obtained via the reaction of the thione **5** with formaldehyde and the corresponding amines. In a trial to prepare the hydrazino derivative via the



6a R= CH_2CO_2Et, 34%; **6b** R= CH_2CO_2H, 80%; **6c** R= CO_2Et, 48%; **6d** R= CH_2COCH_3, 42%; **6e** R= CH_2CONH_2, 39%; **6f** R= CH_2CN, 91%; **6g** R= CH_3, 95%; **6h** R= Et, 48%; **6i** R= $CH_2CONHC_6H_4CH_3$, 56%; **6j** R= $CH(CN)_2$, 37%.
7a R= NC_4H_8O, **7b** R= $NHCH_2C_6H_5$, **7c** R= NHC_6H_5

Scheme 2.



Scheme 3.

reaction of **5** with hydrazine hydrate, unexpectedly the reaction product was found to be compound **4a** (Scheme 2).

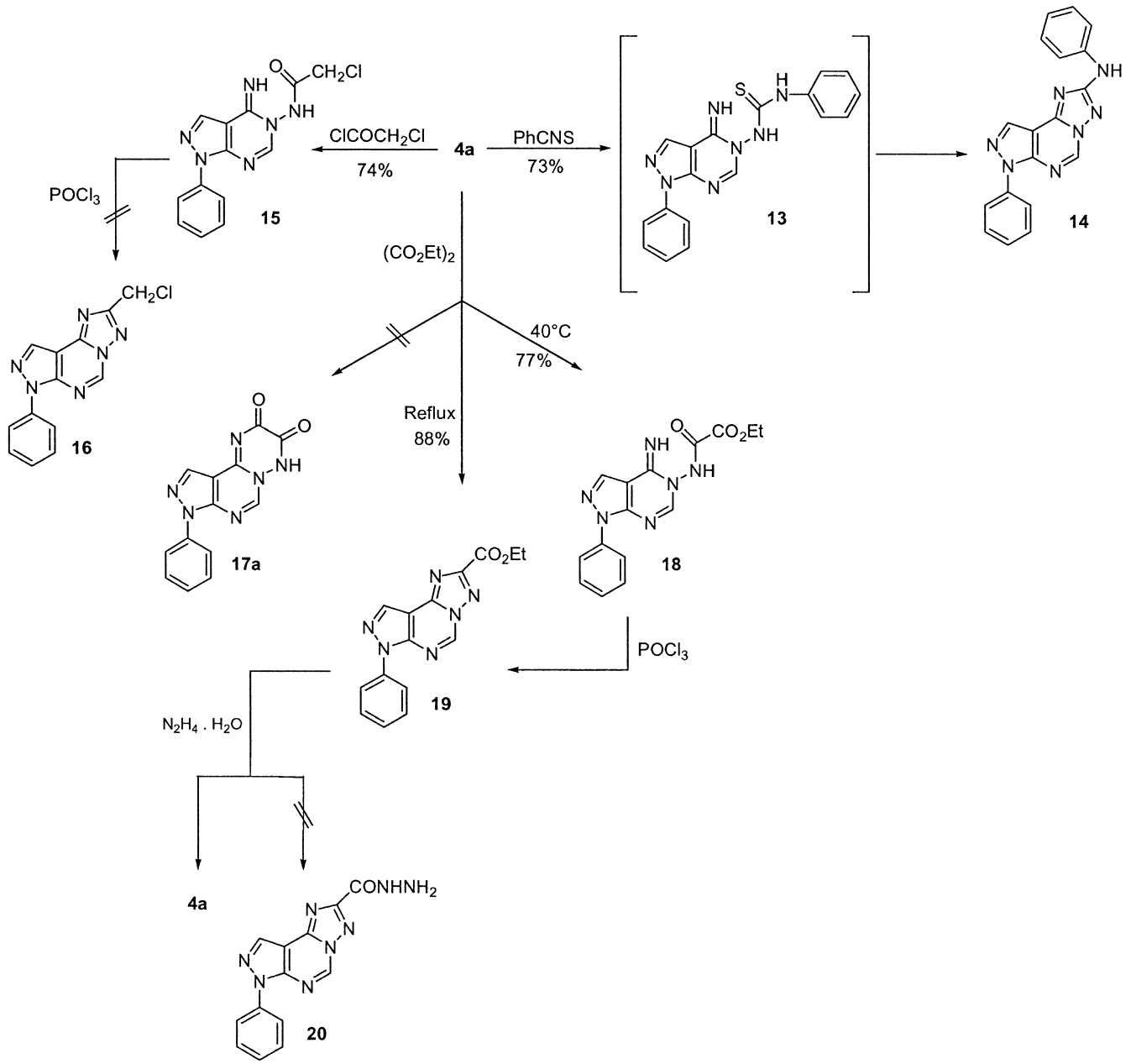
As described in Scheme 3, reaction of **4a** with triethylorthoformate afforded the corresponding 7-phenyl-7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine **8**; however, its reaction with ethyl formate did not afford **8** but gave the intermediate formylamino derivative **8a** which could be ring closed in refluxing phosphoryl chloride to give **8**. Other 2-substituted derivatives of **8** could be synthesized as shown in Scheme 3. The 2-methyl derivative **9** was obtained by boiling **4a** in glacial acetic acid. However, upon heating compound **4a** in refluxing acetic anhydride the reaction product was identified as the triacetyl derivative **12** and not the expected product **9**. Compound **11** (the 2-phenyl analog of **9**) could not be obtained directly by the reaction of **4a** with benzoylchloride which gave the benzoylamino derivative **10**. This latter compound could be cyclized into **11** in boiling $POCl_3$ (Scheme 3).

On the other hand, as depicted in Scheme 4, the 2-phenylamino derivative **14** was obtained when **4a** was treated with phenylisothiocyanate in refluxing pyridine. Obviously this reaction proceeded via the thiourea intermediate **13** with concomitant dehydrosulfurization. Also, the reaction of **4a** with chloroacetyl chloride did not afford the chloromethyl derivative **16** but resulted in the formation of chloroacetylamino derivative **15**, which could not be cyclized into **16** in boiling $POCl_3$. Interestingly, upon warming **4a** in diethyl oxalate the intermediate **18** was obtained. This upon heating in boiling $POCl_3$ gave the ester **19**. Alternatively, compound **19** could be obtained directly from **4a** by heating under reflux with diethyl oxalate and no evidence for the formation of the possible dioxotriazine derivate **17a** was observed.

Interestingly, hydrazinolysis of the ester **19** did not afford the expected carbohydrazide derivative **20** but resulted in ring opening of the triazole ring giving back the aminoimino compound **4a**.

In Scheme 5, reaction of **4a** with an excess of diethyl malonate gave directly the ester **23**. As was the case with compound **19**, hydrazinolysis of compound **23** did not afford the expected hydrazide derivative but also resulted in opening of the triazole ring with the formation of the aminoimino compound **4a**. The interaction of compounds **4a–c** with an equimolar ratio of ethyl chloroformate gave the corresponding triazino derivative **21a–c**, whereas the reaction of **4a** with an excess of same reagent gave the diethoxycarbonylamino compound **22**. When compound **4a** was subjected to the diazotization reaction conditions, the tetrazolo derivative **24** was formed.

Treatment of compounds **4a–c** with oxalyl chloride in refluxing dry benzene afforded the corresponding dioxo-

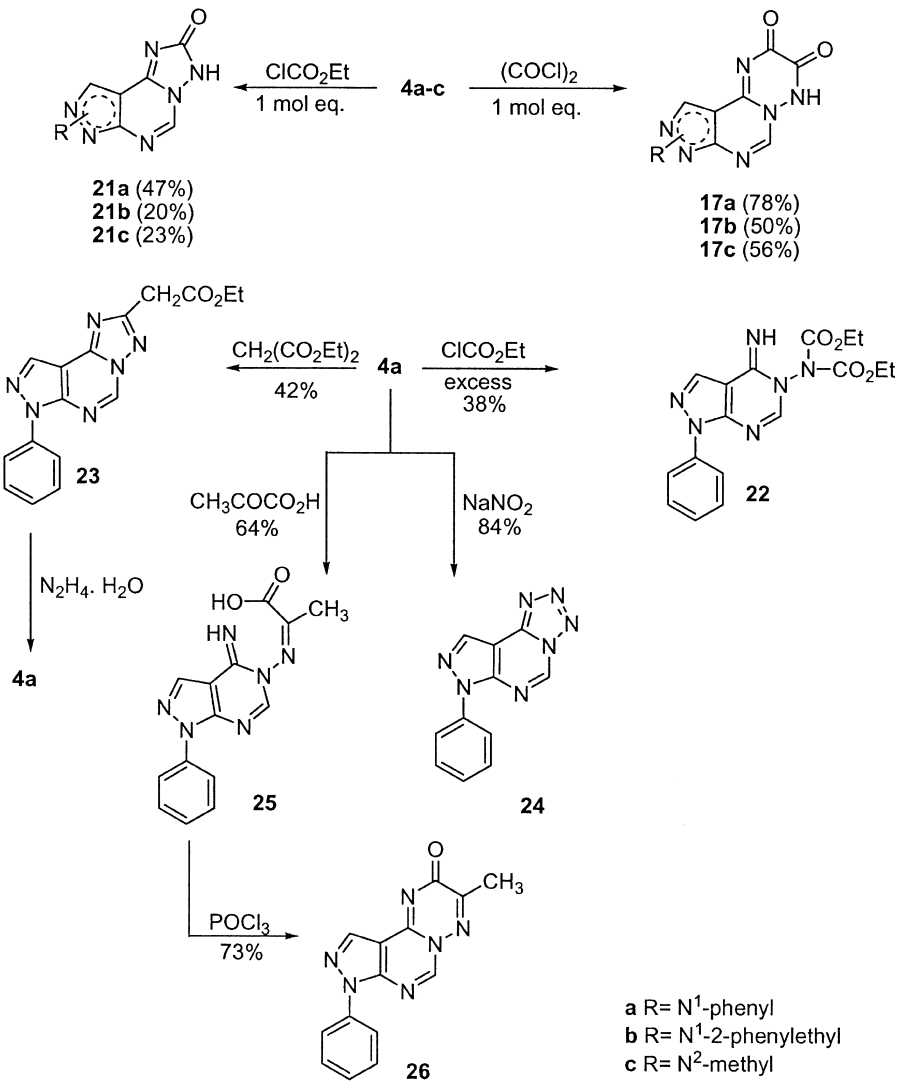


Scheme 4.

triazine compounds **17a–c**. However, reaction of **4a** with pyruvic acid gave the intermediate **25**, which was cyclized in boiling $POCl_3$ to give the triazinone compound **26** (Scheme 5).

In a comparative study,[18] it was reported that the reaction of the 3-amino-4-imino-3,4-dihydrothieno[2,3-*d*]pyrimidine with acetylacetone gave 2-methythieno[3,2-*e*]-[1,2,4]triazolo[1,5-*c*]pyrimidine and its reaction with ethoxymethylenemalononitrile or ethyl ethoxymethylenecyanoacetate led to the formation of the parent thieno[3,2-*e*] [1,2,4]triazolo[1,5-*c*]pyrimidine.

In contrast, in our hands when the aminoimino compound **4a** was allowed to react with acetylacetone under the same reaction conditions reported for the reaction described above we got a product with a different mp and spectral data to those obtained for **9**. The NMR spectrum of the products formed from the reaction between **4a–c** and acetylacetone (compounds **27a–c**) showed two additional methyl signals. This is in agreement with the structure of 5,7-dimethyl-1(2)-substituted-1(2)*H*-azolo[3′,4′:4,5]pyrimido[1,6-*b*]triazepines **27a–c**. It is noteworthy that when the reaction was carried out with **4a** in benzoylacetone, the product was identified as the intermediate azomethine compound **28** which could be cyclized to the corresponding triazepine **29** by heating in refluxing phosphoryl chloride (Scheme 6). The reaction between **4a** and ethyl benzoylacetate led to the formation of the triazepine **31**. On the other hand the reaction of **4a** with ethoxymethylenemalononitrile or ethyl ethoxymethylenecyano-acetate did not afford the triazolo derivative **8**, as would be expected from the same reaction reported for the amino-imino derivative of the thieno-pyrimidine,[18] however the reaction products were identified



Scheme 5.

as the triazepine–aminonitrile and aminoester derivatives **30a**,**b**, respectively. Compound **32** was finally obtained from the reaction between **4a** and benzoylacetonitrile.

In conclusion, the amino ester **30b** could be hydrolyzed to the corresponding amino acid **30c**, however, the hydrazinolysis of the ester function of **30b** did not lead to the corresponding amino hydrazide derivative but gave back the amino imino derivative **4a**.

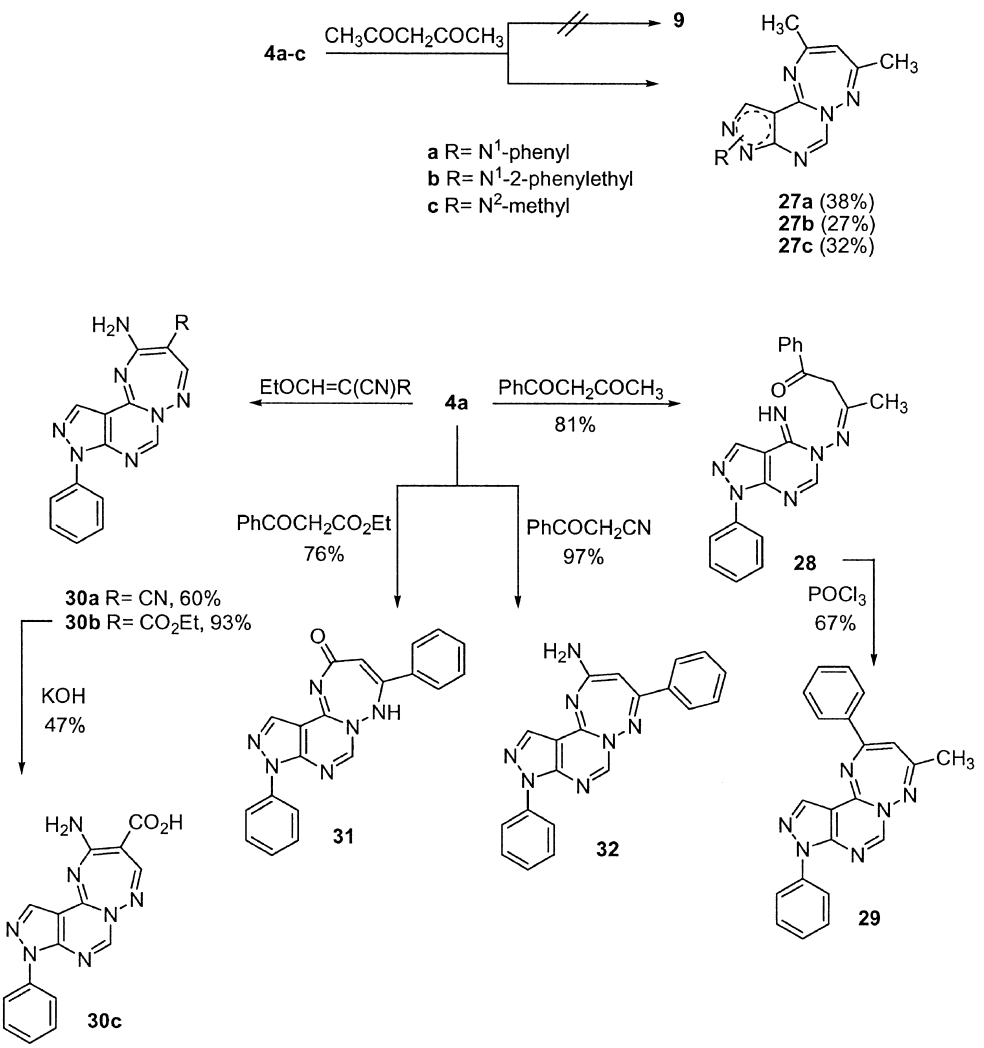
3. Conclusion

New heterocycles were obtained from the reaction between 5-amino-4-imino-1(2)-substituted-1(2)*H*-4,5-dihydropyrazolo[3,4-*d*]pyrimidines **4a**–**c** and several commercially available reactants. All the compounds obtained and described in this work retain the pyrazolopyrimidine core while third fused heterocyclic nucleus (five, six or seven-membered) was constructed via easily accessible intermediates. A SAR study of the newly synthesized compounds to evaluate their affinity and selectivity toward A_{2A} and A_3 adenosine receptor subtypes will be the subject of another publication.

4. Experimental

4.1. General

Reactions were routinely monitored by thin-layer chromatography (TLC) on silica gel (precoated F_{245} Merck plates) and products visualized with iodine or potassium permanganate solution. ^{1}H NMR spectra were determined in $CDCl_3$, CF_3COOD or DMSO-d_6 solutions with a Bruker AC 200 spectrometer. Peak positions are given in parts per million (δ) downfield from tetramethylsilane as internal standard, and J values are given in Hz. IR spectra were recorded on Pye Unicam SP 300 spectrometer using KBr Wafer technique. Mass spectra were obtained with a Shimadzu QP5050 DI 50 spectrometer. Light petroleum ether refers to the fractions boiling at 40–60 °C. Melting points were determined on a Buchi–Tottoli instrument and are uncorrected. Chromatographies were performed using Merck 60–200 mesh silica gel. All products reported



Scheme 6.

showed ^{1}H NMR spectra in agreement with the assigned structures. Analyses were performed by the micro-analytical laboratory of Dipartimento di Chimica, University of Ferrara. Compounds **3a–c** were prepared according to known procedures.[16,17]

4.1.1. General procedures for the preparation of 5-amino-4-imino-1(2)-substituted-1(2)*H*-4,5-dihydropyrazolo[3,4-*d*]pyrimidines 4a–c. A mixture of compounds **3a–c** (5.24 g, 22 mmol) and hydrazine hydrate (8 mL, 80%) in ethanol (20 mL) was heated under reflux for 2 h. The white precipitate formed after cooling was filtered off and dried. Recrystallization from ethanol afforded the required products **4a–c** as white crystals.

5-Amino-4-imino-1-phenyl-1H-4,5-dihydropyrazolo[3,4-d]pyrimidine **4a**. Yield 78% (3.84 g), white crystals, mp 235 °C. [Found: C, 58.56; H, 4.35; N, 37.10. $C_{11}H_{10}N_6$ requires: C, 58.39; H, 4.46; N, 37.15]. IR cm^{-1}: 3330, 3200 (NH and NH_2), 1630 (C=N); ^{1}H NMR (DMSO-d_6): δ 4.90 (s, 2H, NH_2), 7.63–7.17 (m, 5H, phenyl), 8.23 (s, 1H, CH-pyrazole), 8.30 (s, 1H, CH-pyrimidine), 9.43 (s, 1H, NH). MS: *m*/*z* 226.24 (M^+).

5-Amino-4-imino-1-(2-phenylethyl)-1H-4,5-dihydropyrazolo[3,4-d]pyrimidine **4b**. Yield 66% (3.27 g), white crystals, mp 264 °C. [Found: C, 61.33; H, 5.24; N, 32.88. $C_{13}H_{14}N_6$ requires: C, 61.40; H, 5.55; N, 33.05]. IR cm^{-1}: 3260, 3180 (NH and NH_2), 1590 (C=N); ^{1}H NMR DMSO-d_6): δ 3.14 (t, 2H, CH_2, J=7.2 Hz), 4.49 (t, 2H, CH_2, J=7.2 Hz), 4.82 (bs, 2H, NH_2), 7.12–7.23 (m, 5H, phenyl), 8.03 (s, 1H, CH-pyrazole), 8.28 (s, 1H, CH-pyrimidine), 9.07 (s, 1H, NH). MS: *m*/*z* 255.2 (M^+).

5-Amino-4-imino-2-methyl-2H-4,5-dihydropyrazolo[3,4-d]pyrimidine **4c**. Yield 45% (1.95 g), white crystals, mp >300 °C. [Found: C, 43.79; H, 4.80; N, 50.98. $C_6H_8N_6$ requires: C, 43.90; H, 4.91; N, 51.19]. IR cm^{-1}: 3320, 3210 (NH and NH_2), 1615 (C=N); ^{1}H NMR (DMSO-d_6): δ 3.74)s, 3H, CH_3), 6.56 (bs, 2H, NH_2), 7.98 (s, 1H, CH-pyrazole), 8.20 (s, 1H, CH-pyrimidine), 11.78 (s, 1H, NH). MS: *m*/*z* 165.2 (M^+).

4.1.2. 7-Phenyl-7*H*-2,3-dihydro-2-thioxopyrazolo[4,3-*e*]-[1,2,4]triazolo[1,5-*c*]pyrimidine 5. To a stirred suspension of compound **4a** (5.24 g, 22 mmol) in ethanol (20 mL), ethanolic potassium hydroxide (30 mL, 0.01 mol) and CS_2 (2 mL) were added dropwise. The reaction mixture was then heated under reflux for 6 h. After cooling and evaporation of the solvent, the potassium salt obtained was dissolved in

water and acidified with 2 N aqueous HCl. The solid product formed was collected and recrystallized from ethanol into yellow crystals. Yield 0.30 g (75%), mp 275–277 °C. [Found: C, 53.50; H, 3.36; N, 31.19. $C_{12}H_8N_6S$ requires: C, 53.72; H, 3.01; N, 31.33]. IR; cm^{-1} 3350 (NH), 1630 (C═N), 1190 (C═S). ^1H NMR (DMSO-d_6): δ 7.55 (m, 3H, phenyl), 7.93–8.13 (m, 2H, phenyl), 8.60 (s, 1H, CH-pyrazole), 9.03 (s, 1H, CH-pyrimidine), 9.47 (s, 1H, NH). MS: *m/z* 268.27 (M^+).

4.1.3. General procedures for the preparation of 7-phenyl-7*H*-2-substituted-mercaptopyrazolo[4,3-*e*]-[1,2,4]triazolo[1,5-*c*] pyrimidines 6a–j. To a mixture of compound **5** (0.228 g, 0.001 mol) and sodium acetate (1.64 g, 0.02 mol) in ethanol (15 mL) was added the respective halo compound (RX, 0.001 mol), then the reaction mixture was heated under reflux for 4 h. After cooling the solid products formed were filtered, washed with water and recrystallized from the proper solvent.

2-(7-Phenyl-7H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidin-2-yl)-thioethyl acetate **6a**. Using ethyl chloroacetate, compound **6a** was obtained as white crystals from ethanol. Yield 34% (0.10 g), mp 133–135 °C. [Found: C, 54.42; H, 4.20; N, 23.50. $C_{16}H_{14}N_6SO_2$ requires: C, 54.22; H, 3.98; N, 23.72]. IR cm^{-1}: 3050 (CH arom.), 2950 (CH aliph.), 1750 (C═O); ^1H NMR ($CDCl_3$): δ 1.30 (t, 3H, CH_2CH_3, J=7.3 Hz), 4.07 (s, 2H, CH_2), 4.20 (q, 2H, CH_2CH_3, J=7.3 Hz), 7.43 (m, 3H, phenyl), 8.03 (m, 2H, phenyl), 8.37 (s, 1H, CH-pyrazole), 8.93 (s, 1H, CH-pyrimidine). MS: *m/z* 355.19 (M^+).

2-(7-Phenyl-7H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidin-2-yl)-thioacetic acid **6b**. Using chloroacetic acid **6b** was obtained as yellow crystals from ethanol–dioxane (1:1). Yield 0.26 g, (80%), mp 295–297 °C. [Found: C, 51.44; H, 2.98; N, 25.56. $C_{14}H_{10}N_6SO_2$ requires: C, 51.52; H, 3.08; N, 25.76]. IR cm^{-1} 3050 (CH arom.), 2900–2820 (CH aliph.), 3100–2400 (OH), 1700 (C═O), 1640 (C═N). ^1H NMR (DMSO-d_6): δ 4.13 (s, 2H, CH_2), 5.07 (m, 1H, OH), 7.57 (m, 3H, phenyl), 8.10 (m, 2H, phenyl), 8.70 (s, 1H, CH-pyrazole), 9.57 (s, 1H, CH-pyrimidine).

Ethyl-2-(7-phenyl-7H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidin-2-yl)-thio formate **6c**. Using ethylchloroformate **6c** was obtained as yellow crystals from benzene. Yield 0.163 g, (48%), mp 295–297 °C. [Found: C, 52.75; H, 3.70; N, 24.46. $C_{15}H_{12}N_6SO_2$ requires: C, 52.93; H, 3.55; N, 24.69]. IR cm^{-1} 3080 (CH arom.), 1730 (C═O), 1640 (C═N). ^1H NMR ($CDCl_3$): δ 1.37 (t, 3H, CH_2CH_3, J=7.2 Hz), 4.37 (q, 2H, CH_2CH_3, J=7.2 Hz), 7.47 (m, 3H, phenyl), 8.13 (m, 2H, phenyl), 8.53 (s, 1H, CH-pyrazole), 9.20 (s, 1H, CH-pyrimidine).

1-(7-Phenyl-7H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidin-2-yl)-thiopropanone **6d**. Using chloroacetone **6d** was obtained as buff crystals from ethanol. Yield 0.131 g, (42%), mp 188–189 °C. [Found: C, 53.70; H, 3.61; N, 26.80. $C_{14}H_{12}N_6SO$ requires: C, 53.83; H, 3.87; N, 26.91]. IR cm^{-1} 3050 (CH arom.), 1700 (C═O), 1640 (C═N). ^1H NMR ($CDCl_3$): δ 2.37 (s, 3H, CH_3), 4.13 (s, 2H, CH_2), 7.43 (m, 3H, phenyl), 8.13 (m, 2H, phenyl), 8.43 (s, 1H, CH-pyrazole), 9.00 (s, 1H, CH-pyrimidine).

2-(7-Phenyl-7H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidin-2-yl)thio acetamide **6e**. Using chloroacetamide **6e** was obtained as fluffy yellow crystals from dioxane. Yield 0.126 g, (39%), mp 255–57 °C. [Found: C, 51.53; H, 3.38; N, 29.97. $C_{14}H_{11}N_7SO$ requires: C, 51.68; H, 3.41; N, 30.14]. IR cm^{-1} 3350, 3180 (NH_2), 3050 (CH arom.), 2900 (CH aliph.), 2220 (C≡N), 1640 (C═N). ^1H NMR (CF_3-COOD): δ 4.40 (s, 2H, CH_2), 5.15 (bs, 2H, NH_2), 7.77 (m, 5H, phenyl), 9.07 (s, 1H, CH-pyrazole), 9.53 (s, 1H, CH-pyrimidine).

2-(7-Phenyl-7H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidin-2-yl)-thioacetonitrile **6f**. Using chloroacetonitrile **6f** was obtained as pale yellow crystals from ethanol. Yield 0.28 g, (91%), mp 180–182 °C. [Found: C, 54.53; H, 2.88; N, 31.67. $C_{14}H_9N_7S$ requires: C, 54.71; H, 2.95; N, 31.90]. IR cm^{-1} 3080 (CH arom.), 2950, 2900 (CH aliph.) and 2220 (C≡N). ^1H NMR ($CDCl_3$): δ 4.05 (s, 2H, CH_2), 7.48 (m, 3H, phenyl), 8.03 (m, 2H, phenyl), 8.07 (s, 1H, CH-pyrazole), 9.07 (s, 1H, CH-pyrimidine).

2-Methylthio-7-phenyl-7H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidine **6g**. Using methyl iodide **6g** was obtained as white platelets from ethanol. Yield 0.27 g, (95%), mp 208–210 °C. [Found: C, 55.16; H, 3.46; N, 29.59. $C_{13}H_{10}N_6S$ requires: C, 55.30; H, 3.57; N, 29.70]. IR cm^{-1} 3050 (CH arom.), 2980 (CH aliph.), 1640 (C═N). ^1H NMR ($CDCl_3$): δ 2.73 (s, 3H, CH_3), 7.47 (m, 3H, phenyl), 8.17 (m, 2H, phenyl), 8.43 (s, 1H, CH-pyrazole), 8.83 (s, 1H, CH-pyrimidine).

2-Ethylthio-7-phenyl-7H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidine **6h**. Using ethyl iodide **6h** was obtained as white crystals from ethanol. Yield 0.14 g, (48%), mp 168–170 °C. [Found: C, 56.60; H, 4.18; N, 28.14. $C_{14}H_{12}N_6S$ requires: C, 56.74; H, 4.08; N, 28.36]. IR cm^{-1} 3050 (CH arom.), 2950 (CH aliph.), 1640 (C═N). ^1H NMR ($CDCl_3$): δ 1.5 (t, 3H, CH_3, J=7.2 Hz), 3.30 (q, 2H, CH_2, J=7.2 Hz), 7.43 (m, 3H, phenyl), 8.03 (m, 2H, phenyl), 8.40 (s, 1H, CH-pyrazole), 8.98 (s, 1H, CH-pyrimidine).

N-(p-Tolyl)-2-(7-phenyl-7H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidin-2-yl)-thioacetamide **6i**. Using 2-chloro-*N*-(*p*-tolyl)-acetamide **6i** was obtained as yellow crystals from ethanol. Yield 0.13 g, (56%), mp 183–185 °C. [Found: C, 60.62; H, 3.98; N, 23.42. $C_{21}H_{17}N_7SO$ requires: C, 60.70; H, 4.12; N, 23.60]. IR cm^{-1} 3300 (NH), 3030 (CH arom.), 2900 (CH aliph.), 1650 (C═O). ^1H NMR (DMSO-d_6): δ 2.33 (s, 3H, CH_3), 4.37 (s, 2H, CH_2), 7.03 (m, 2H, phenyl), 7.47 (m, 5H, phenyl), 8.10 (m, 2H, phenyl), 8.60 (s, 1H, CH-pyrazole), 8.77 (s, 1H, CH-pyrimidine), 10.57 (s, 1H, NH).

(7-Phenyl-7H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidin-2-ylthio) malononitrile **6j**. Using bromomalononitrile **6j** was obtained as buff crystals from ethanol–dioxane (1:1). Yield 0.122 g, (36.7%), mp 205–207 °C. [Found: C, 53.99; H, 2.60; N, 33.84. $C_{15}H_8N_8S$ requires: C, 54.21; H, 2.43; N, 33.72]. IR cm^{-1} 3080 (CH arom.), 2900 (CH aliph.), 2200 (C≡N), 1640 (C═N). ^1H NMR (DMSO-d_6): δ 7.51 (m, 4H, phenyl and $CH(CN)_2$), 8.01 (m, 2H, phenyl), 8.60 (s, 1H, CH-pyrazole), 9.03 (s, 1H, CH-pyrimidine).

4.1.4. General procedure for the preparation of 3-substituted-7-phenyl-7*H*-2,3-dihydro-2-thioxo-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines 7a–c. A mixture of **5** (0.268 g, 0.001 mol), 36% aqueous formaldehyde (1 mL), methanol (20 mL) and selected amines (0.001 mol) was stirred at room temperature for about 3 h. The solid products formed were filtered off and recrystallized from the proper solvent.

3-(Morpholin-4-yl-methyl)-7-phenyl-7H-2,3-dihydro-2-thioxopyrazolo[4,3-e][1,2,4] triazolo[1,5-c]pyrimidine **7a**. Using morpholine **7a** was obtained as white crystals (methanol). Yield 0.174 g, (48%), mp 152–154 °C. [Found: C, 55.40; H, 4.42; N, 26.71. $C_{17}H_{17}N_7SO$ requires: C, 55.57; H, 4.66; N, 26.68]. IR cm^{-1} 2900, 2800 (CH aliph.), 1640 (C═N), 1150 (C═S). ^1H NMR ($CDCl_3$): δ 2.67 (t, 4H, NCH_2, J=3.2 Hz), 3.67 (t, 4H, OCH_2, J=3.2 Hz), 5.03 (s, 2H, CH_2), 7.40 (m, 3H, Phenyl), 7.98 (m, 2H, Phenyl), 8.40 (s, 1H, CH-pyrazole), 8.93 (s, 1H, CH-pyrimidine).

3-(Benzylaminomethyl)-7-phenyl-7H-2,3-dihydro-2-thioxo-pyrazolo[4,3-e][1,2,4] triazolo[1,5-c]pyrimidine **7b**. Using benzylamine **7b** was obtained as white crystals (ethanol–dioxane 2:1). Yield 0.17 g, (44%), mp 218–220 °C. [Found: C, 61.70; H, 4.25; N, 25.54. $C_{20}H_{17}N_7S$ requires: C, 61.99; H, 4.42; N, 25.31]. IR cm^{-1} 3100 (NH), 3050 (CH arom.), 2980 (CH aliph.), 1640 (C═N), 1210 (C═S). ^1H NMR (CF_3COOD): δ 5.00 (s, 2H, CH_2), 6.30 (s, 2H, CH_2), 7.66 (m, 10H, phenyl), 8.93 (s, 1H, CH-pyrazole), 9.43 (s, 1H, CH-pyrimidine).

3-(Phenylaminomethyl)-7-phenyl-7H-2,3-dihydro-2-thioxo-pyrazolo[4,3-e][1,2,4] triazolo[1,5-c]pyrimidine **7c**. Using aniline **7c** was obtained as white crystals (ethanol–dioxane; 1:1). Yield 0.15 g, (40%), mp 170–173 °C. [Found: C, 61.31; H, 4.20; N, 26.39. $C_{19}H_{15}N_7S$ requires: C, 61.11; H, 4.05; N, 26.26]. IR cm^{-1} 3100 (NH), 3030 (CH arom.), 2900 (CH aliph.), 1640 (C═N), 1230 (C═S). ^1H NMR (CF_3COOD): δ 4.03 (s, 2H, CH_2), 7.70 (m, 10H, Phenyl), 8.93 (s, 1H, CH-pyrazole), 9.46 (s, 1H, CH-pyrimidine).

4.1.5. 7-Phenyl-7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]-pyrimidine 8. A mixture of **4a** (0.226 g, 0.001 mol) and triethylorthoformate (5 mL) in dimethylformamide (5 mL) was refluxed for 1 h. After cooling and dilution with ice/water (30 mL), the solid product formed was filtered off and recrystallized from ethanol to furnish **8** as gray crystals. Yield 0.123 g, (52%), mp 178–180 °C. [Found: C, 61.25; H, 3.56; N, 35.31. $C_{12}H_8N_6$ requires: C, 61.01; H, 3.41; N, 35.58]. IR cm^{-1} 3050 (CH-arom.), 1630 (C═N).^1H NMR ($CDCl_3$): δ 7.46 (m, 3H, phenyl), 8.65 (m, 2H, phenyl), 8.36 (s, 1H, CH-pyrazole), 8.50 (s, 1H, CH-pyrimidine), 9.17 (s, 1H, CH-triazole). MS: m/z 236.2 (M^+).

4.1.6. 5-Formylamino-4-imino-1-pheny-1*H*-4,5-dihydro-pyrazolo[3,4-*d*]pyrimidine 8a. A mixture of **4a** (0.226 g, 0.001 mol) and ethyl formate (5 mL) in dimethylformamide (5 mL) was heated under reflux for about 5 h. After cooling, the solid product formed was collected, washed with water (30 mL) and recrystallized from ethanol to afford **8a** as white crystals. Yield 0.16 g, (63%), mp 271–273 °C. [Found: C, 56.83; H, 3.92 N, 32.98. $C_{12}H_{10}N_6O$ requires: C, 56.68; H, 3.96; N, 33.06]. IR cm^{-1} 3200 (NH), 3020 (CH-arom.), 1630 (C═N), 1660 (C═O). ^1H NMR ($CDCl_3$): δ 7.55 (m, 3H, phenyl), 8.11 (m, 2H, phenyl), 8.33 (s, 1H, CHO), 8.36 (s, H, CH-pyrazole), 8.40 (s, 1H, CH-pyrimidine), 10.24 (m, 2H, 2NH). MS: m/z 254.25 (M^+).

4.1.7. 2-Methyl-7-phenyl-7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine 9. A mixture of **4a** (0.226 g, 0.001 mol) and acetic acid (15 mL) was refluxed for 5 h. After cooling and dilution with ice/water (20 mL), the white precipitate formed was filtered off and recrystallized from ethanol to give white crystals. Yield 0.16 g, (64%), mp 185–187 °C. [Found: C, 62.53; H, 4.29 N, 33.35. $C_{13}H_{10}N_6$ requires: C, 62.39; H, 4.03; N, 33.58]. IR cm^{-1} 3050 (CH-arom.), 1640 (C═N).^1H NMR ($CDCl_3$): δ 2.65 (s, 3H, CH_3), 7.46 (m, 3H, phenyl), 8.13 (m, 2H, phenyl), 8.48 (s, 1H, CH-pyrazole), 9.06 (s, 1H, CH-pyrimidine). MS: m/z 250 (M^+).

4.1.8. *N*-(4-Imino-1-phenyl-1*H*-4,5-dihydropyrazolo[3,4-*d*]pyrimidin-5-yl)benzamide 10. To a stirred solution of **4a** (0.452 g, 0.002 mol) in pyridine (5 mL), benzoyl chloride (0.28 g, 0.002 mol) was added dropwise and stirring was continued for 6 h. After dilution with ice/water mixture (35 mL) the solid product formed was collected by filtration and recrystallized from ethanol to furnish white crystals. Yield 0.52 g, (79%), mp 265–267 °C. [Found: C, 65.27; H, 4.42 N, 25.32. $C_{18}H_{14}N_6O$ requires: C, 65.44; H, 4.27; N, 25.44]. IR cm^{-1} 3230 (NH), 3050 (CH-arom.), 1700 (C═O), 1630 (C═N). ^1H NMR (DMSO-d_6): δ 7.51 (m, 6H, phenyl), 8.06 (m, 4H, phenyl), 8.26 (s, 1H, CH-pyrazole), 8.50 (s, 1H, CH-pyrimidine), 10.33 (s, 1H, NH), 10.83 (bs, 1H, N*H*CO). MS: m/z 330.95 (M^+).

4.1.9. 2,7-Diphenyl-7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine 11. A solution of **10** (0.20 g, 0.64 mmol) in $POCl_3$ was heated under reflux for 8 h. After cooling, the reaction mixture was poured into ice/water mixture (35 mL) and neutralized with ammonium hydroxide solution. The solid product formed was filtered off and recrystallized from ethanol to give buff crystals. Yield 0.18 g, (57%), mp 178–180 °C. [Found: C, 69.50; H, 3.77: N, 26.74. $C_{18}H_{12}N_6$ requires: C, 69.22; H, 3.87; N, 26.91]. IR cm^{-1} 3230 (NH), 3050 (CH-arom.), 1700 (C═O), 1630 (C═N). ^1H NMR (DMSO-d_6): δ 7.50 (m, 6H, phenyl), 8.04 (m, 4H, phenyl), 8.36 (s, 1H, CH-pyrazole), 8.47 (s, 1H, CH-pyrimidine). MS: m/z 312.32 (M^+).

4.1.10. 4-(Acetyl-imino)-5-diacetylamino-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine 12. A suspension of **4a** (0.45 g, 0.002 mol) in acetic anhydride (10 mL) was heated under reflux for 1 h. After cooling, the solvent was concentrated under reduced pressure, then the reaction mixture was poured into ice-water (40 mL) to give a solid precipitate which was filtered off and recrystallized from petroleum ether 60/80 to furnish **12** as buff crystals. Yield 0.36 g, (51%), mp 112–115 °C. [Found: C, 57.76; H, 4.62; N, 23.76. $C_{17}H_{16}N_6O_3$ requires C, 57.95; H, 4.58; N, 23.85]. IR cm^{-1} 3100 (CH arom.), 2910 (CH aliph.), 1718 (C═O). ^1H NMR ($CDCl_3$): δ 2.43 (s, 6H, 2CH_3), 2.50 (s, 3H, CH_3), 7.52 (m, 3H, phenyl), 8.06 (m, 2H, phenyl), 8.23 (s, 1H, CH-pyrazole), 8.72 (s, 1H, CH-pyrimidine). MS: m/z 352 (M^+).

4.1.11. 2-Phenylamino-7-phenyl-7*H*-pyrazolo[4,3-*e*]-[1,2,4]triazolo[1,5-*c*]pyrimidine 14. A suspension of **4a** (0.226 g, 0.001 mol) and phenylisothiocyanate (0.135 g, 0.001 mol) in pyridine (10 mL) was heated under reflux for 5 h. After cooling the reaction mixture was poured into ice/water (30 mL) and neutralized with diluted 10% HCl to give a buff solid precipitate. This product was collected and crystallized from ethanol–DMF (3:1) to furnish **14** as a buff powder. Yield 0.24 g, (73.4%), mp 274–276 °C. [Found: C, 65.94; H, 3.86; N, 29.76. $C_{18}H_{13}N_7$ requires C, 66.04; H, 4.00; N, 29.95]. IR cm^{-1} 3100 (NH), 3050 (CH arom.), 1650 (C═N). ^1H NMR (DMSO-d_6): δ 7.50 (m, 8H, phenyl), 8.04 (m, 2H, phenyl), 8.22 (s, 1H, NH), 8.63 (s, 1H, CH-pyrazole), 9.03 (s, 1H, CH-pyrimidine). MS: *m/z* 371.94 (M^+).

4.1.12. *N*-(4-Imino-1-phenyl-1*H*-4,5-dihydropyrazolo[3,4-*d*]pyrimidin-3-yl)-2-chloro acetamide 15. A mixture of **4a** (0.226 g, 0.002 mol) and chloroacetyl chloride (0.112 g, 0.001 mol) in dioxane (10 mL) was refluxed for 6 h. The white precipitate formed was collected and recrystallized from ethanol to give fluffy white crystals. Yield 0.22 g, (74%), mp 205–208 °C. [Found: C, 55.52; H, 3.77; N, 27.55. $C_{13}H_{11}ClN_6O$ requires C, 55.86; H, 3.66; N, 27.76]. IR cm^{-1} 3150 (NH), 2980, 2780 (CH-aliph.), 1710 (C═O), 1630 (C═N). ^1H NMR (DMSO-d_6): δ 4.50 (s, 2H, CH_2), 7.58 (m, 3H, phenyl), 8.12 (m, 2H, phenyl), 8.45 (s, 1H, CH-pyrazole), 8.80 (s, 1H, CH-pyrimidine), 8.91–9.1 (bs, 2H, 2NH). MS: *m/z* 302.76 (M^+).

4.1.13. General procedure for the synthesis of 1(2)-substituted-1(2)*H*,7*H*-5,6-dioxo-5,6-dihydropyrazolo[3′,4′:4,5]pyrimido[1,6-*b*] [1,2,4]triazine 17a–c. To a solution of **4a–c** (0.001 mol) in dry benzene (10 mL), oxalyl chloride (0.126 g, 0.001 mol) was added. The reaction mixture was heated under reflux for 8 h. The solids formed were collected by filtration and recrystallized from a mixture of ethanol/benzene (1:1) to afford **17a–c** as yellow crystals

1-Phenyl-1H,7H-5,6-dioxo-5,6-dihydropyrazolo[3′,4′:4,5]pyrimido[1,6-b] [1,2,4]triazine **17a**. Yield 0.23 g, (78%), yellow crystals, mp >300 °C. [Found: C, 55.60; H, 2.68; N, 29.79. $C_{13}H_8N_6O_2$ requires: C, 55.71; H, 2.88; N, 29.99]. IR cm^{-1} 3200 (NH), 3080 (CH arom.), 2900 (CH aliph.), 1730 (C═O), 1710 (C═O). ^1H NMR (DMSO-d_6): δ 7.48 (m, 5H, arom.); 7.98 (s, 1H, CH-pyrazole), 8.23 (s, 1H, CH-pyrimidine), 10.82 (bs, 1H, NH). MS: *m/z* 280 (M^+).

1-(2-Phenylethyl)-1H,7H-5,6-dioxo-5,6-dihydropyrazolo[3′,4′:4,5]pyrimido[1,6-b] [1,2,4]triazine **17b**. Yield 0.135 g (50.52%), yellow crystals, mp >300 °C. [Found C, 58.22; H, 3.81; N, 27.02. $C_{15}H_{12}N_6O_2$ requires: C, 58.44; H, 3.92; N, 27.26]. IR cm^{-1} 3400 (NH), 2920 (CH arom.), 2650 (CH aliph.), 1740 (C═O), 1700 (C═O). ^1H NMR (DMSO-d_6): δ 3.23 (t, 2H, CH_2, J=7.2 Hz), 4.67 (t, 2H, CH_2, J=7.2 Hz), 7.24 (m, 5H, arom.), 8.09 (s, 1H, CH-pyrazole), 8.35 (s, 1H, CH-pyrimidine), 9.32 (bs, 1H, NH). MS: *m/z* 309.2 (M^+).

2-Methyl-2H,7H-5,6-dioxo-5,6-dihydropyrazolo[3′,4′:4,5]pyrimido[1,6-b] [1,2,4]triazine **17c**. Yield 0.166 g (56%), yellow crystals, mp >300 °C. [Found: C, 43.92; H, 2.51; N, 38.65. $C_8H_6N_6O_2$ requires: C, 44.04; H, 2.77; N, 38.52]. IR cm^{-1} 3340 (NH), 1700 (C═O), 1660 (C═O). ^1H NMR (DMSO-d_6): δ 3.40 (s, 3H, CH_3), 8.20 (s, 1H, CH-pyrazole), 8.45 (s, 1H, CH-pyrimidine), 9.30 (bs, 1H, NH). MS: *m/z* 219.3 (M^+).

4.1.14. Ethyl *N*-(4-imino-1-phenyl-1*H*-4,5-dihydropyrazolo[3,4-*d*]pyrimidin-5-yl)-carbamoyl formate 18. A mixture of **4a** (0.226 g, 0.001 mol) and diethyl oxalate (5 mL) was warmed with stirring at 40 °C for 30 min. The solid precipitate formed was collected and recrystallized from dioxane to furnish **18** as buff crystals. Yield 0.25 g, (77%), mp 298–300 °C. [Found: C, 55.41; H, 4.56 N, 25.46. $C_{15}H_{14}N_6O_3$ requires C, 55.21; H, 4.32; N, 25.76]. IR cm^{-1} 3200 (NH), 3050 (CH arom.), 1710 (C═O), 1670 (C═O) and 1630 (C═N). ^1H NMR (DMSO-d_6): δ 1.33 (t, 3H, CH_2CH_3, J=7.3 Hz), 4.30 (q, 2H, CH_2H_3, J=7.3 Hz), 7.40 (m, 3H, phenyl), 8.08 (m, 2H, phenyl), 8.23 (s, 1H, CH-pyrazole), 8.37 (s, 1H, CH-pyrimidine), 8.88 (s, 2H, 2NH). MS: *m/z* 326 (M^+).

4.1.15. Ethyl (1-phenyl-1*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidin-5-yl) carboxylate 19. A mixture of **4a** (0.226 g, 0.001 mol) and diethyl oxalate (5 mL) was refluxed for 8 h. The reaction mixture was then concentrated at reduced pressure and left to cool. The solid product formed was filtered off and recrystallized from ethanol to furnish **19** as buff crystals. Yield 0.27 g, (88%), mp 212–214 °C. [Found: C, 58.34; H, 3.96 N, 26.99. $C_{15}H_{12}N_6O_2$ requires: C, 58.43; H, 3.92; N, 27.26]. IR cm^{-1} 3050 (CH-arom.), 1730 (C═O). 1650 (C═N).^1H NMR ($CDCl_3$): δ 1.52 (t, 3H, CH_2CH_3, J=7.4 Hz), 4.55 (q, 2H, CH_2H_3, J=7.4 Hz), 7.46 (m, 3H, phenyl), 8.06 (m, 2H, phenyl), 8.53 (s, 1H, CH-pyrazole), 9.23 (s, 1H, CH-pyrimidine).

4.1.16. General procedure for the preparation of 7(8)-substituted-7(8)*H*-2-oxo-2,3-dihydropyrazolo[4,3-*e*]-[1,2,4]triazolo[1,5-*c*]pyrimidines 21a–c. A mixture of **4a–c** (0.001 mol) and ethyl chloroformate (0.001 mol) in dry benzene (10 mL) was heated under reflux for 8 h. After cooling and triturating with ethanol the solid formed was filtered off and recrystallized from dioxane/ethanol (1:2) to furnish compounds **21a–c** as crystals.

7-Phenyl-7H-2-oxo-2,3-dihydropyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidine **21a**. Yield 0.13 g (47%), buff crystals, mp 258–260 °C. [Found: C, 57.30; H, 2.98; N, 33.18. $C_{12}H_8N_6O$ requires: C, 57.14; H, 3.19; N, 33.32]. IR cm^{-1} 3300 (NH), 1680 (C═O), 1640 (C═N). ^1H NMR (DMSO-d_6): δ 7.44 (m, 3H, phenyl), 7.98 (m, 2H, phenyl), 8.40 (s, 1H, CH-pyrazole), 8.63 (s, 1H, CH-pyrimidine), 10.52 (bs, 1H, NH). MS: *m/z* 252.23 (M^+).

7-(2-phenylethyl)-7H-2-oxo-2,3-dihydropyrazolo[4,3-e]-[1,2,4]triazolo[1,5-c]pyrimidine **21b**. Yield 0.10 g (20%), buff crystals, mp 290 °C. [Found: C, 59.71; H, 4.26; N, 29.95. $C_{14}H_{12}N_6O$ requires: C, 59.99; H, 4.32; N, 29.98]. IR cm^{-1} 3440 (NH), 3090 (CH arom.), 1685 (C═O). ^1H NMR (DMSO-d_6): δ 3.21 (t, 2H, CH_2, J=7.2 Hz), 4.60 (t, 2H, CH_2, J=7.2 Hz), 7.23 (m, 5H, arom.), 7.88 (s, 1H, CH-pyrazole), 8.11 (s, 1H, CH-pyrimidine), 11.41 (bs, 1H, NH). MS: *m/z* 281.32 (M^+).

8-Methyl-8H-2-oxo-2,3-dihydropyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidine **21c**. Yield 60 mg (23%), buff crystals, mp >300 °C. [Found: C, 44.35; H, 3.02; N, 44.08. $C_7H_6N_6O$ requires: C, 44.21; H, 3.18; N, 44.19]. IR cm^{-1} 3450 (NH), 3180 (CH aliph.), 1690 (C=O). ^1H NMR (DMSO-d_6): δ 3.73 (s, 3H, CH_3), 7.43 (s, 1H, CH-pyrazole), 8.01 (s, 1H, CH-pyrimidine), 11.79 (bs, 1H, NH). MS: *m/z* 191.16 (M^+).

4.1.17. 5-(*N*,*N*-Diethoxycarbonylamino)-4-imino-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine 22. A mixture of **4a** (0.226 g, 0.001 mol) and ethyl chloroformate (0.162 g, 0.0015 mol) in dry benzene (10 mL) was heated under reflux for 8 h. The reaction mixture was concentrated to one-third its volume and triturated with ethanol to give buff solid product which was filtered off and recrystallized from petroleum ether 60/80 to furnish **22** as buff crystals. Yield 0.14 g (38%), mp 118–120 °C. [Found: C, 55.30; H, 4.79: N, 22.45. $C_{17}H_{18}N_6O_4$ requires: C, 55.13; H, 4.90; N, 22.69]. IR cm^{-1} 3290 (NH), 3050 (CH-arom.), 3980, 3910 (CH-aliph.), 1740 (C=O), 1630 (C=N). ^1H NMR (DMSO-d_6): δ 1.30 (m, 6H, $2CH_2CH_3$), 4.26 (m, 4H, $2CH_2CH_3$), 7.36 (m, 3H, phenyl), 8.06 (m, 2H, phenyl), 8.37 (s, 1H, CH-pyrazole), 8.73 (s, 1H, CH-pyrimidine), 8.92 (bs, 1H, NH). MS: *m/z* 370.1 (M^+).

4.1.18. Ethyl (1-phenyl-1*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidin-5-yl)acetate 23. A suspension of **4a** (0.226 g, 0.001 mol) and diethyl malonate (5 mL) was heated under reflux over its boiling point for 10 h. The yellow solid product formed was filtered off and crystallized from dioxane into yellow crystals. Yield 0.14 g, (42%), mp >300 °C. [Found: C, 59.48; H, 4.50: N, 25.99. $C_{16}H_{14}N_6O_2$ requires: C, 59.62; H, 4.38; N, 26.08]. IR cm^{-1} 3050 (CH arom.), 2950, 2800 (CH aliph.), 1730 (C=O), 1630 (C=N). ^1H NMR (DMSO-d_6): δ 1.23 (t, 3H, CH_2CH_3), 4.11 (q, 2H, CH_2CH_3), 5.15 (s, 2H, CH_2), 7.46 (m, 3H, phenyl), 8.13 (m, 2H, phenyl), 8.40 (s, 1H, CH-pyrazole), 8.70 (s, 1H, CH-pyrimidine). MS: *m/z* 322.32 (M^+).

4.1.19. 7-Phenyl-7*H*-pyrazolo[4,3-*e*]-1,2,3,4-tetrazolo[1,5-*c*]pyrimidine 24. To a cold solution of **4a** (0.226 g, 0.001 mol) in acetic acid (10 mL) was added an ice-cold solution of sodium nitrite (0.21 g/5 mL H_2O, 0.003 mol) with stirring during five minutes. Stirring was then continued for 2 h. The reaction mixture was poured into water (60 mL) and the solid formed was filtered off and recrystallized from ethanol to afford **24** as buff crystals. Yield 0.20 g, (84%), mp 200–202 °C. [Found: C, 55.47; H, 2.89; N, 41.29. $C_{11}H_7N_7$ requires: C, 55.69; H, 2.97; N, 41.34]. IR cm^{-1} 3060 (CH arom.), 2910 (CH aliph.), 1640 (C=N). ^1H NMR (DMSO-d_6): δ 7.56 (m, 3H, phenyl), 8.01 (m, 2H, phenyl), 8.90 (s, 1H, CH-pyrazole), 10.16 (s, 1H, CH-pyrimidine). MS: *m/z* 237.22 (M^+).

4.1.20. 2-(4-Imino-1-phenyl-1*H*-4,5-dihydropyrazolo[3,4-*d*]pyrimidin-5-ylimino) propionic acid 25. A solution of **4a** (0.45 g, 0.002 mol) and pyruvic acid (0.208 g, 0.002 mol) in ethanol (15 mL) was heated under reflux for 5 h. After cooling, the reaction mixture was poured into water (60 mL). The solid precipitate formed was filtered off and recrystallized from ethanol–dioxane (1:1) to give buff crystals. Yield 0.38 g, (64.4%), mp 258–260 °C. [Found: C, 56.78; H, 3.96; N, 28.30. $C_{14}H_{12}N_6O_2$ requires: C, 56.75; H, 4.08; N, 28.37]. IR cm^{-1} 3150 (NH), 2600–2400 (OH), 1695 (C=O), 1600 (C=N). ^1H NMR (DMSO-d_6): δ 2.21 (s, 3H, CH_3), 7.47 (m, 3H, phenyl), 8.20 (m, 2H, phenyl), 8.57 (s, 1H, CH-pyrazole), 8.80 (s, 1H, CH-pyrimidine), 9.12 (bs, 1H, NH), 11.20 (bs, 1H, OH). MS: *m/z* 296.87 (M^+).

4.1.21. 6-Methyl-1-phenyl-1*H*-5-oxo-pyrazolo[3′,4′:4,5]-pyrimido[1,6-*b*]-1,2,4-]triazine 26. A solution of **25** (0.18 g, 0.0006 mol) and $POCl_3$ (10 mL) was heated under reflux for 1 h. After cooling, the reaction mixture was poured into ice-water (50 mL) and neutralized with ammonia solution to give dark buff precipitate. The solid was filtered off and recrystallized from ethanol to afford **26** as buff crystals. Yield 0.124 g (73.4%), mp 294–296 °C. [Found: C, 60.88; H, 3.98; N, 28.30. $C_{14}H_{10}N_6O$ requires: C, 60.42; H, 4.08; N, 28.37]. IR cm^{-1} 3050 (CH arom.), 2900 (CH aliph.), 1640 (C=O). ^1H NMR (CF_3COOD): δ 2.73 (s, 3H, CH_3), 7.70 (m, 3H, phenyl), 7.90 (m, 2H, phenyl), 9.13 (s, 1H, CH-pyrazole), 9.23 (s, 1H, CH-pyrimidine). MS: *m/z* 278.20 (M^+).

4.1.22. General procedure for the preparation of 5,7-dimethyl-1(2)-substituted-1(2)*H*-pyrazolo[4′,3′:4,5]-pyrimido[1,6-*b*][1,2,4]triazepines 27a–c. A mixture of **4a–c** (0.001 mol) and acetylacetone (0.01 mol) in ethanol (15 mL) was heated under reflux for 1 h. After cooling, the solid formed was collected and crystallized from ethanol to afford **27a–c** as crystals.

5,7-Dimethyl-1-phenyl-1H-pyrazolo[4′,3′:4,5]pyrimido-[1,6-b][1,2,4]triazepine **27a**. Yield 0.112 g, (38%), white crystals, mp 152–153 °C. [Found: C, 65.95; H, 4.70; N, 28.68. $C_{16}H_{14}N_6$ requires: C, 66.19; H, 4.86; N, 28.95]. IR cm^{-1} 3050 (CH arom.), 2900 (CH aliph.), 1565 (C=N). ^1H NMR ($CDCl_3$): δ 2.37 (s, 3H, CH_3), 2.80 (s, 3H, CH_3), 6.03 (s, 1H, CH-triazepine), 7.34 (m, 3H, phenyl), 8.15 (m, 2H, phenyl), 8.73 (s, 1H, CH-pyrazole), 8.82 (s, 1H, CH-pyrimidine). MS: *m/z* 290 (M^+).

5,7-Dimethyl-1-(2-phenylethyl)-1H-pyrazolo[4′,3′:4,5]-pyrimido[1,6-b][1,2,4]triazepine **27b**. Yield 85 mg (27%), white crystals, mp 210 °C. [Found: C, 67.72; H, 5.36; N, 26.66. $C_{18}H_{18}N_6$ requires: C, 67.90; H, 5.70; N, 26.40]. IR cm^{-1} 3250 (CH arom.), 2940 (CH aliph.), 1580 (C=N). ^1H NMR ($CDCl_3$): δ 2.36 (s, 3H, CH_3), 2.79 (s, 3H, CH_3), 3.26 (t, 2H, CH_2, J=7.3 Hz), 4.73 (t, 2H, CH_2, J=7.3 Hz), 6.07 (s, 1H, CH-triazepine), 7.23 (m, 5H, arom.), 8.66 (s, 1H, CH-pyrazole), 8.68 (s, 1H, CH-pyrimidine). MS: *m/z* 319.2 (M^+).

2,5,7-Trimethyl-2H-pyrazolo[4′,3′:4,5]pyrimido[1,6-b]-[1,2,4]triazepine **27c**. Yield 90 mg (32%), white crystals, mp 255 °C. [Found: C, 57.97; H, 5.11; N, 36.97. $C_{11}H_{12}N_6$ requires: C, 57.88; H, 5.30; N, 36.82]. IR cm^{-1} 3000 (CH aliph.), 1610 (C=N). ^1H NMR (DMSO-d_6): δ 2.41 (s, 3H, CH_3), 2.82 (s, 3H, CH_3), 3.32 (s, 3H, N–CH_3), 6.21 (s, 1H, CH-triazepine), 8.38 (s, 1H, CH-pyrazole), 8.51 (s, 1H, CH-pyrimidine). MS: *m/z* 228.3 (M^+).

4.1.23. 3-(4-Imino-1-phenyl-1*H*-1,4-dihydropyrazolo[3,4-*d*]pyrimidin-5-yl-imino)-1-phenylbutan-1-one 28. A mixture of **4a** (0.226 g, 0.001 mol) and benzoylacetone (0.162 g, 0.001 mol) in ethanol (20 mL) was

refluxed for 10 h. The solvent was evaporated under reduced pressure and the solid formed was collected and recrystallized from ethanol to give white crystals. Yield 0.3 g, (81%), mp 150–152 °C. [Found: C, 67.95; H, 4.70; N, 22.58. $C_{21}H_{18}N_6O$ requires: C, 68.09; H, 4.90; N, 22.69]. IR cm^{-1} 3400 (NH), 3030 (CH arom.), 2900 (CH aliph.), 1605 (C═O), 1585 (C═N). ^1H NMR ($CDCl_3$): δ 2.33 (s, 3H, CH_3), 3.27 (s, 2H, CH_2), 6.43 (s, 1H, NH), 7.43 (m, 8H, Phenyl), 8.23 (m, 2H, Phenyl), 8.28 (s, 1H, CH-pyrazole), 8.63 (s, 1H, CH-pyrimidine). MS: *m/z* 370.2 (M^+).

4.1.24. 1,5-Diphenyl-7-methyl-1*H*-pyrazolo[3′,4′:4,5]pyrimido[1,6-*b*][1,2,4]triazepine 29. A mixture of **28** (0.19 g, 0.512 mmol) and $POCl_3$ (15 mL) was heated under reflux for 2 h. After cooling, the reaction mixture was poured into a mixture of ice-cold water and neutralized with ammonium hydroxide solution. The solid formed was collected and recrystallized from petroleum ether (60/80) to afford **29** as white crystals. Yield 0.12 g, (67%), mp 113–115 °C. [Found: C, 71.38; H, 4.60; N, 23.58. $C_{21}H_{16}N_6$ requires C, 71.57; H, 4.58; N, 23.85]. IR cm^{-1} 3030 (CH arom), 1590 (C═N). ^1H NMR (DMSO-d_6): δ 2.42 (s, 3H, CH_3), 6.50 (s, 1H, CH-triazepine), 7.42 (m, 6H, Phenyl), 7.53 (m, 2H, Phenyl), 8.20 (m, 2H, Phenyl), 8.57 (s, 1H, CH-pyrazole), 8.77 (s, 1H, CH-pyrimidine). MS: *m/z* 352.38 (M^+).

4.1.25. 5-Amino-1-phenyl-1*H*-pyrazolo[3′,4′:4,5]pyrimido[1,6-*b*][1,2,4]triazepine-6-carbonitrile 30a. A mixture of **4a** (0.226 g, 0.001 mol) and ethoxymethylene malononitrile (0.122 g, 0.001 mol) in ethanol (10 mL) was refluxed for 4 h. The precipitate formed after cooling was filtered off and recrystallized from methanol to furnish **30a** as white crystals. Yield 0.18 g, (60%), mp 288–290 °C. [Found: C, 59.31; H, 3.48; N, 36.88. $C_{15}H_{10}N_8$ requires C, 59.59; H, 3.33; N, 37.07]. IR cm^{-1} 3400, 3300 (NH_2), 1620 (NH_2), 2220 (C≡N). ^1H NMR (CF_3CO_2D): δ 5.80 (bs, 2H, NH_2), 7.70 (s, 5H, phenyl), 8.10 (s, 1H, CH-triazepine), 9.23 (s, 1H, CH-pyrazole), 9.30 (s, 1H, CH-pyrimidine). MS: *m/z* 302.29 (M^+).

4.1.26. Ethyl (5-amino-1-phenyl-1*H*-pyrazolo[3′,4′:4,5]pyrimido[1,6-*b*][1,2,4]triazepin-6-yl)carboxylate 30b. A mixture of compound **4a** (0.226 g, 0.001 mol) and ethyl ethoxymethylene cyanoacetate (0.16 g, 0.001 mol) in ethanol (10 mL) was refluxed for 4 h. After cooling, the solid precipitate was filtered off and recrystallized from ethanol to furnish **30b** as white crystals. Yield 0.28 g, (93%), mp 215–217 °C. [Found: C, 58.67; H, 4.54; N, 28.40. $C_{12}H_{15}N_7O_2$ requires C, 58.44; H, 4.33; N, 28.07]. IR cm^{-1} 3300, 3400 (NH_2), 1680 (C═O). ^1H NMR (CF_3CO_2D): δ 1.50 (t, 3H, CH_2CH_3, J=7.2 Hz), 4.46 (q, 2H, CH_2CH_3, J=7.2 Hz), 7.67 (s, 5H, phenyl), 8.27 (s, 1H, CH-triazepine), 9.20 (s, 1H, CH-pyrazole), 9.30 (s, 1H, CH-pyrimidine). MS: *m/z* 349.35 (M^+).

4.1.27. 5-Amino-1-phenyl-1*H*-pyrazolo[3′,4′:4,5]pyrimido[1,6-*b*][1,2,4]triazepin-6-carboxylic acid 30c. A mixture of **30b** (0.349 g, 0.001 mol) and potassium hydroxide (0.56 g, 0.01 mol) in ethanol (15 mL) was heated under reflux for 1 h. The solvent was evaporated and the solid precipitate formed was dissolved in water and the aqueous phase was acidified with acetic acid. The precipitate was filtered off and crystallized from ethanol to afford **30c** as white crystals. Yield 0.15 g (47%), mp 295–297 °C. [Found: C, 56.14; H, 3.74; N, 29.98. $C_{15}H_{11}N_7O_2$ requires: C, 56.07; H, 3.45; N, 30.52]. IR cm^{-1} 3050 (CH arom.), 1720 (C═O). ^1H NMR (DMSO-d_6): δ 5.31 (bs, 2H, NH_2), 7.52 (m, 3H, phenyl), 8.09 (m, 2H, phenyl), 8.23 (s, 1H, CH-pyrazole), 8.37 (s, 1H, CH-pyrimidine), 8.50 (s, 1H, CH-triazepine), 12.47 (bs, 1H, OH).

4.1.28. 1,7-Diphenyl-1*H*,8*H*-5-oxopyrazolo[3′,4′:4,5]-pyrimido[1,6-*b*][1,2,4]triazepine 31. A suspension of **4a** (0.226 g, 0.001 mol) and ethylbenzoyl acetate (1.66 g, 0.009 mol) in ethanol (7 mL) was heated under reflux for 10 h. After concentration, the solid product formed was filtered off and recrystallized from methanol to give **31** as yellow crystals. Yield 0.27 g, (76%,), mp 192–94 °C. [Found: C, 67.58; H, 4.11; N, 23.56. $C_{20}H_{14}N_6O$ requires: C, 67.78; H, 3.98; N, 23.72]. IR cm^{-1} 3080 (CH arom.), 1730 (C═O), 1640 (C═N). ^1H NMR ($CDCl_3$): δ 5.97 (s, 1H, CH-triazepine), 7.43 (m, 6H, Phenyl), 7.83 (m, 2H, Phenyl), 8.20 (m, 2H, Phenyl), 8.67 (s, 1H, CH-pyrazole), 8.93 (s, 1H, CH-pyrimidine), 11.06 (bs, 1H, NH). MS: *m/z* 354.10 (M^+).

4.1.29. 5-Amino-1,7-diphenyl-1*H*-pyrazolo[3′,4′:4,5]-pyrimido[1,6-*b*][1,2,4]triazepine 32. A suspension of **4a** (0.45 g, 0.002 mol) and benzoylacetonitrile (0.290 g, 0.002 mol) in ethanol (20 mL) was heated under reflux for 10 h. After concentration and cooling, the solid formed was filtered off and recrystallized from ethanol to give **32** as scarlet red crystals. Yield 0.68 g, (97%), mp 141–143 °C. [Found: C, 67.61; H, 4.58; N, 27.51. $C_{20}H_{15}N_7$ requires C, 67.97; H, 4.28; N, 27.75]. IR cm^{-1} 3400, 3280 (NH_2), 3040 (CH arom.), 1600 (C═N). ^1H NMR ($CDCl_3$): δ 4.00 (s, 2H, NH_2), 5.77 (s, 1H, CH-triazepine), 7.43 (m, 5H, Phenyl), 7.83 (m, 3H, Phenyl), 8.23 (m, 2H, Phenyl), 8.70 (s, 1H, CH-pyrazole), 9.00 (s, 1H, CH-pyrimidine). MS: *m/z* 353.10 (M^+).

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2-Substituted-3,7-dinitro-11-oxatricycloundec-9-ene: an approach towards the synthesis of Ergot alkaloids

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Abstract—A simple and versatile method for the preparation of various ergoline or secoergoline skeleton, using 2-substituted-3,7-dinitro-11-oxatricycloundec-9-ene as key intermediates, is described. The key step involves an IMDAF reaction with an excellent stereocontrol. This novel synthetic route provides new cycloadducts as useful scaffolds for Ergot alkaloids synthesis.

1. Introduction

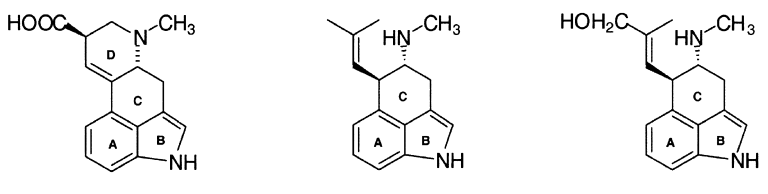
With respect to their structures and biological activities, the Ergot alkaloids derived from *Claviceps* species, are one of the most prolific groups of alkaloids. The potential of this group of alkaloids as medicinal agents is very high based on their broad spectrum of pharmaceutical activities. They respond to such physiologically important biosubstances as noradrenaline, serotonine and/or dopamine and their receptors.[1]

The key structural feature of Ergot alkaloids, exemplified by lysergic acid **1**, is a tetracyclic ergoline ring system. In addition to tetracyclic derivatives, a number of tricyclic analogues were the D ring is open are also found in nature. The representatives of secoergoline group, such as seco-agroclavine **2** or chanoclavine **3**, are of particular interest because of their role as biosynthetic precursors of lysergic acid **1** (Fig. 1).

Since the first total synthesis of lysergic acid **1** by Kornfeld and Woodward,[2] several independent approaches have been developed.[3] Two main strategies have been utilized, each defined by the choice of the starting material, either an indole or indoline nucleus which preform the **A** and **B** rings (Fig. 1). Oppolzer[4] and Genet[5] successfully achieved the synthesis of the Ergot alkaloids starting from an indole nucleus, thus avoiding the aromatization of ring C, through careful choice of their synthetic methods. But to date there are few synthetic approaches to the framework of lysergic acid beginning with other subunits: a 5-nitro-2-tetralone,[6] a β-naphtol nucleus,[7] a 2-bromoaniline constructed for a triple radical cyclization,[8] and a suitably functionalized aryne for an intramolecular Diels–Alder cyclization.[9]

2. Synthetic design

We designed a general and versatile method for preparing



1 2 3

Figure 1.

Keywords: Ergot alkaloids; Ergoline; Secoergoline; Lysergic acid; IMDAF; Oxatricycloundec-9-ene compounds.
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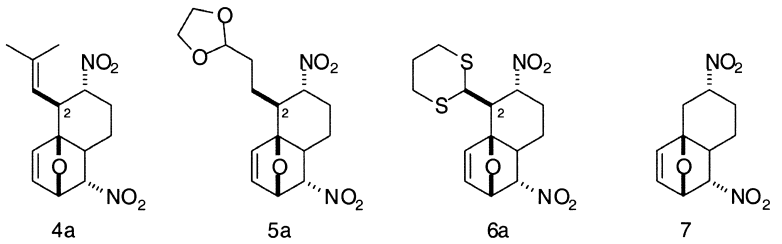


Figure 2.

various ergoline or secoergoline alkaloids, using 2-substituted-3,7-dinitro-11-oxatricycloundec-9-ene (**4a**, **5a** and **6a**) as the key intermediates (Fig. 2).

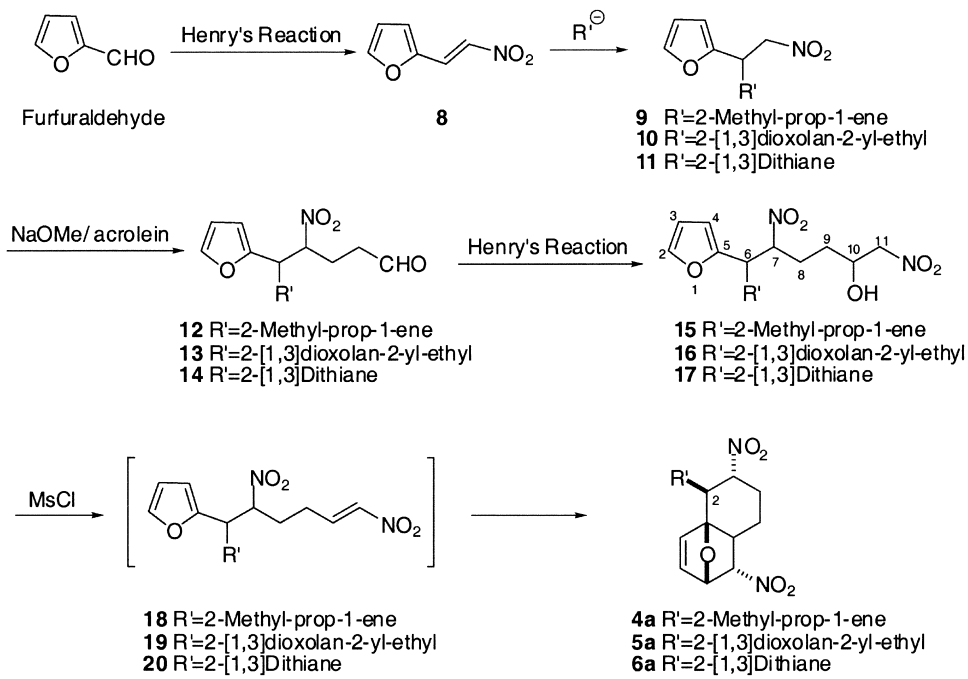
Indeed, we have recently shown that 3,7-dinitro-11-oxatricycloundec-9-ene **7** could be readily prepared[10] in 7 steps from furfuraldehyde with excellent stereocontrol by applying the IMDAF methodology[11] to compounds bearing a nitro group on the side chain. This method utilized cheap and easily available starting materials. We present here the extension of this methodology for the synthesis of various 2-substituted-3,7-dinitro-11-oxatricycloundec-9-ene compounds such as **4a**, **5a** and **6a**, by using appropriate reagents at the very beginning of the previously reported synthesis[10] (Scheme 1).

3. Results and discussion

The first step for these syntheses was the preparation of 2-(2-nitroethyl)-furan **8** starting from furfuraldehyde and nitromethane. This was achieved by a Henry's reaction to yield the desired nitro-olefin compound **8** in 88% yield.[12]

The reactivity of **8** towards nucleophiles was then studied, particularly with the use of achiral organometallic reagents. We describe here three variations, using either Grignard reagents derived from 2-(2-bromoethyl)-1,3-dioxolane and 4-bromo-2-methyl-2-butene, or 2-lithio-l,3-dithiane, for the synthesis of secoergoline and ergoline derivatives. Grignard reagents represent one of the most important and versatile class of organic intermediates known to the synthetic chemist. In spite of this, several types of Grignard reagents are not readily available due to the lack or slowness of the reaction of certain types of halides with magnesium metal. We synthesized through classic methods the terminal acetal[13] and butene[14] substituted organomagnesium halides. Attempts to form the Grignard reagents required high temperatures and extended reaction times before the starting material was fully consumed. The condensation reactions were carried out, after cooling the organometallic for several hours, affording compounds **9** and **10** in 85 and 53% yield, respectively. The most successful sulphur stabilized acyl anion equivalent in terms of availability, ease of preparation and general suitability, was the cyclic 2-lithio-1,3-dithiane.[15] It reacted with nitroalkene **8** to afford **11** in 70% yield.

As outlined in Scheme 1, the next steps followed the same synthetic route as that described in the previous publication.[10] Treatment of compounds **9**, **10** or **11** with sodium methanolate and acrolein provided the required



Scheme 1.

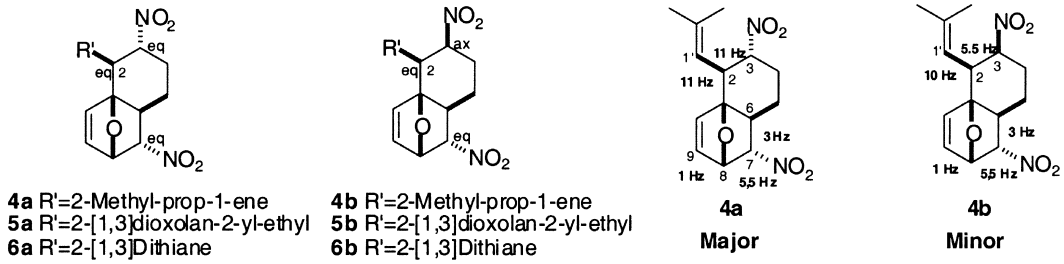


Figure 3.

5-(2-furyl)-5-*R*-4-nitropentanal **12**, **13**, or **14**. A second Henry's reaction with nitromethane yielded the condensation products **15**, **16**, or **17** as diastereoisomeric mixtures. Classical mesyl chloride dehydration applied to nitroalcohols furnished the none isolated desired nitroolefins **18**, **19**, or **20**, which were correctly functionalized for the IMDAF reaction, thus permitting the synthesis at room temperature of **4**, **5**, or **6**. Under these conditions two diastereisomers of **4**, **5**, or **6** were obtained in a 15:1 ratio (Fig. 3).

A careful analysis by 1D or 2D ^{1}H NMR of cycloadducts **4** showed that both of them possessed the expected *endo* structures, as the main product **4a** ($J_{H\text{-}8/H\text{-}7}$=5.5 Hz), previously observed for the unsubstituted compound **7** (Fig. 2). The substitution at the C-2 position was deduced from the two couplings of H-2 with H-3 and the H-1′ ($J_{H\text{-}2/H\text{-}3}$, $J_{H\text{-}2/H\text{-}1'}$=11 Hz for **4a**; $J_{H\text{-}2/H\text{-}3}$=11 Hz, $J_{H\text{-}2/H\text{-}1'}$=5.5 Hz for **4b**). The same study was performed on the other cycloadducts and provided the same result, *endo* attack for the cycloaddition with all substituents in equatorial position for the major products. It should be noted that compounds **5b** and **6b** could not be isolated as pure compounds, due to the small amount of starting material.

4. Conclusions

In summary, we have developed a direct and efficient strategy for the synthesis of 2-substituted-3,7-dinitro-11-oxatricycloundec-9-ene, which were easily prepared froth furfuraldehyde. This strategy is intended to permit in the future the access to different Ergot alkaloid derivatives, by introducing substituants at the beginning of the synthesis. The construction of indole nucleus from the nitro group at C-7, using the isocyanate route,[16] is currently under investigation. Other applications of these general methods for the synthesis of others alkaloids are in progress, the results of which will be reported in due course.

5. Experimental

5.1. General

The melting points were determined on a Leica VM apparatus and are not corrected. IR spectra (ν_{max} in cm^{-1}) were obtained on a Nicolet FT-IR instrument. ^{1}H NMR (δ [ppm], J [Hz]) and ^{13}C NMR spectra were recorded at 400 and 100 MHz respectively, using a Bruker Avance 400 spectrometer. When necessary, the signals were unambiguously assigned by 2D NMR techniques: COSY, NOESY, HMQC, and HMBC. These experiments were performed using standard Bruker microprograms. Mass spectra were recorded with a Nermag R-10-10C spectrometer using chemical ionization technique (reagent gas: NH_3) (CI/MS) and with a ZQ 2000 Waters using a Zspray (ESI-MS). Microanalyses were performed on a Perkin–Elmer 2400 CHN. Column chromatographies were conducted using silica gel 60 Merck (35–70 μm) with an overpressure of 200 mbars.

5.2. General procedure for the preparation of Diels–Alder adducts

To a solution of nitroalcohol (9.4 mmol), in 60 mL of ethyl acetate at −60 °C under an argon atmosphere was added triethylamine (37.6 mmol). After 15 min of stirring at the same temperature, mesyl chloride (37.4 mmol) was added over 25 min. The temperature was allowed to rise to −5 °C and the stirring was continued for 1 more hour. The mixture was then filtered through celite. The resulting solution was washed by 200 mL of saturated aqueous sodium bicarbonate solution and 100 mL of water. The organic layers were dried on Na_2SO_4, evaporated under reduced pressure to obtain a brownish oil. The resulting oil was slowly stirred in dichloromethane at room temperature for 15–20 days, then the product was purified by recrystallization, afforded the Diels–Alder products in 15:1 ratio with around 41% yield.

5.2.1. 2-(3-Methyl-but-1-enyl)-3,7dinitro-11-oxa-tricyclo[6.2.1.0^{1,6}] undec-9-ene (4a and 4b). *Compound* **4a**. (1.2 g): IR (film) ν_{max} cm^{-1}: 2934, 1672, 1552, 1532, 1448, 1376, 1218, 1082, 854; ^{1}H NMR ($CDCl_3$) δ: 1.31 (dq, 1H, J=3.5, 11 Hz, H-5ax), 1.66 (s, 3H, H-3′), 1.70 (s, 3H, H-4′), 2.10 (dq, 1H, J=3.5, 10 Hz, H-4ax), 2.3–2.6 (m, 3H, H-6 and H-5eq and H-4eq), 3.57 (t, 1H, J=11 Hz, H-2), 4.51 (dt, 1H, J=3.5, 11 Hz, H-3), 4.63 (dd, 1H, J=3, 5.5 Hz, H-7), 5.08 (dt, 1H, J=1.5, 11 Hz, H-1′), 5.30 (dd, 1H, J=1, 5.5 Hz, H-8), 6.2–6.3 (m, 2H, H-9 and H-10); ^{13}C NMR ($CDCl_3$) δ: 17.8 (C-4′), 25.8 (C-3′), 27.4 (C-5), 29.8 (C-4), 40.7 (C-6), 41.8 (C-2), 79.1 (C-8), 86.5 (C-3), 89.7 (C-7), 91.5 (C-1), 117.9 (C-1′), 133.1 (C-9), 138.3 (C-2′), 140.9 (C-10); MS (CI/NH_3) m/z 295 [MH]$^+$. Anal. calcd for $C_{14}H_{18}N_2O_5$: C, 57.13; H, 6.16; N, 9.52. Found: C, 57.29; H, 6.16; N, 9.50.

Compound **4b**. (80 mg). IR (film) ν_{max} cm^{-1}: 2918, 1673, 1552, 1532, 1448, 1376, 1218, 1081, 855; ^{1}H NMR ($CDCl_3$) δ: 1.66 (s, 3H, H-3′), 1.75 (s, 3H, H-4′), 2.1–2.2 (m, 2H,

H-5), 2.3–2.5 (m, 3H, H-6 and H-4), 3.84 (dd, 1H, *J*=5.5, 10 Hz, H-2ax), 4.6–4.7 (m, 2H, H-3 and H-7), 5.24 (d, 1H, *J*=10 Hz, H-1′), 5.33 (dd, 1H, *J*=1, 5.5 Hz, H-8), 6.21 (dd, 1H, *J*=1, 4.5 Hz, H-9), 6.34 (d, 1H, *J*=4.5 Hz, H-10); ^{13}C NMR ($CDCl_3$) δ: 18.1 (C-3′), 22.6 (C-5), 26.1 (C-4′), 27.5 (C-4), 37.5 (C-6), 40.2 (C-2), 79.3 (C-8), 82.6 (C-3), 89.7 (C-7), 90.4 (C-1), 115.0 (C-1′), 133.7 (C-9), 140.0 (C-2′), 141.2 (C-10); MS (CI/NH_3) *m/z* 295 $[MH]^+$. Anal. calcd for $C_{14}H_{18}N_2O_5$: C, 57.13; H, 6.16; N, 9.52. Found: C, 57.32; H, 6.19; N, 9.55.

5.2.2. 2-(2-[1,3]Dioxolan-2-yl-ethyl)-3,7-dinitro-11-oxa-tricyclo[6.2.1.0^{1,6}]undec-9-ene (5a). (15 mg). IR (film) ν_{max} cm^{-1}: 2892, 1549, 1377, 1145, 1034, 745; ^{1}H NMR ($CDCl_3$) δ: 1.58 (m, 2H, H-1′ and H-2′), 1.75 (m, 2H, H-1′ and H-2′), 2.09 (td, 1H, *J*=10, 2 Hz, H-5), 2.22 (m, 2H, H-5 and H-4), 2.27 (m, 2H, H-4 and H-7), 2.65 (dt, 1H, *J*=10, 2 Hz, H-6), 3.45 (m, 1H, H-2), 3.83 (m, 2H, H-5′ and H-6′), 3.94 (m, 2H, H-5′ and H-6′), 4.61 (td, 1H, *J*=8, 3 Hz, H-3), 4.79 (t, 1H, *J*=3 Hz, H-3′), 5.02 (d, 1H, *J*=2 Hz, H-8), 6.28 (d, 1H, *J*=5 Hz, H-10), 6.56 (dd, 1H, *J*=5, 2 Hz, H-9); ^{13}C NMR ($CDCl_3$) δ: 23.3 (C-2′), 27.5 (C-4), 31.2 (C-1′), 35.1 (C-5 and C-6), 38.8 (C-2), 42.1 (C-7), 64.8 (C-5′ and C-6′), 78.8 (C-8), 87.1 (C-3), 91.2 (C-1), 104.0 (C-3′), 136.0 (C-10), 138.4 (C-9); ESI-MS *m/z*: 379 $[MK]^+$. Anal. calcd for $C_{15}H_{20}N_2O_7$: C, 52.94; H, 5.92; N, 8.23. Found: C, 53.02; H, 5.93; N, 8.24.

5.2.3. 2-[1,3]Dithian-2-yl-3,7-dinitro-11-oxa-tricyclo-[6.2.1.0^{1,6}]undec-9-ene (6a). (25 mg). IR (film) ν_{max} cm^{-1}: 1548; ^{1}H NMR ($CDCl_3$) δ: 1.4–2.5 (m, 7H, H-4, H-5, H-6 and H-4′), 2.85 (m, 4H, H-3′ and H-5′), 3.27 (dd, 1H, *J*=3, 11.5 Hz, H-2), 4.25 (d, 1H, *J*=3 Hz, H-1′), 4.59 (dd, 1H, *J*=2, 6 Hz, H-7), 5.04 (ddd, 1H, *J*=4, 11.5, 12 Hz, H-3), 5.46 (dd, 1H, *J*=2, 6 Hz, H-8), 6.38 (dd, 1H, *J*=2, 8 Hz, H-9), 6.62 (d, 1H, *J*=8 Hz, H-10); ^{13}C NMR ($CDCl_3$) δ: 25.4 (C-4′), 26.8 (C-5), 30.9 (C-4), 32.1–32.4 (C-3′, C-5′), 42.0 (C-6), 46.5 (C-2), 49.1 (C-1′), 79.4 (C-8), 83.3 (C-3), 89.2 (C-7), 90.8 (C-1), 132.7 (C-9), 140.5 (C-10); MS (CI/NH_3) *m/z* 376 $[M+18]^+$. Anal. calcd for $C_{14}H_{18}N_2O_5S_2$: C, 46.91; H, 5.06; N, 7.82. Found: C, 46.97; H, 5.07; N, 7.83.

5.2.4. 2-(2-Nitro-vinyl)-furan (8). Nitromethane (27 mL, 30.5 g, 0.5 mol) was slowly added to 250 mL of a 20% aqueous KOH solution and the reaction mixture was cooled to 0 °C. Freshly distilled furfuraldehyde (41.4 mL, 48 g, 0.5 mol) was added at such a rate that the temperature was maintained at 0 °C. The reaction was then vigorously stirred for 10 min at the same temperature, then poured into 600 mL of ice cooled 50% aqueous HCl. The yellow precipitate was filtered off and washed with water. Crystallization from methanol afforded **8** as yellow needles (61.1 g, 88%). Mp: 74–75 °C. IR (film) ν_{max} cm^{-1}: 3125, 1636, 1502–1330, 740; ^{1}H NMR ($CDCl_3$) δ: 6.57 (dd, 1H, *J*=3.5, 1.5 Hz, H-3), 6.89 (d, 1H, *J*=3.5 Hz, H-4), 7.50 (d, 1H, *J*=13 Hz, H-6), 7.59 (dd, 1H, *J*=3.5, 0.5 Hz, H-2), 7.77 (d, 1H, *J*=13.5 Hz, H-7); ^{13}C NMR ($CDCl_3$) δ: 113.2 (C-3), 119.9 (C-4), 125.3 (C-7), 134.7 (C-6), 146.7 (C-2, C-5); CI-MS *m/z*: 157 $[M+18]^+$. Anal. calcd for $C_6H_5NO_3$: C, 51.80; H, 3.62; N, 10.07. Found: C, 51.42; H, 3.71; N, 10.01.

5.2.5. 2-(3-Methyl-1-nitromethyl-but-enyl)-furan (9). To a suspension of 5 g of crushed magnesium turnings (207 mmol) in 20 mL of dry THF at 25 °C under an argon atmosphere, was added 5 mL of 1-bromo-3-methyl-1-propene (49 mmol). To initialize the reaction, 2–3 small crystals of iodine were added. The remaining of 1-bromo-3-methyl-1-propene (12.6 mL, 131 mmol) was diluted by 20 mL of THF and added dropwise to the reaction mixture, which was refluxed for 5 h until green-gray solution was obtained. The temperature was allowed to rise to room temperature. The vinyl magnesium suspension was added dropwise under an argon atmosphere with stirring at −20 °C to a solution of **8** (3 g; 21.6 mmol) in 40 mL of THF. The stirring was continued at 0 °C for 2 h. The reaction was quenched by adding 60 mL of saturated ammonium chloride solution. The mixture was extracted with CH_2Cl_2 (100 mL×3). The combined organic layers were dried on Na_2SO_4, filtered and evaporated under reduced pressure. Flash chromatography of the residue on silica gel (CH_2Cl_2/cyclohexane: 1/1) yielded **9** (3.58 g, 85%) as a pale yellow oil. IR (film) ν_{max} cm^{-1}: 3121, 1674, 1552, 1506, 1375, 820, 738; ^{1}H NMR ($CDCl_3$) δ: 1.71 (d, 3H, *J*=1.5 Hz, H-4′), 1.75 (d, 3H, *J*=1.5 Hz, H-3′), 4.46 (dd, 1H, *J*=8.5, 11 Hz, H-7), 4.50 (m, 1H, H-6), 4.73 (dd, 1H, *J*=6, 11 Hz, H-7), 5.25 (dt, 1H, *J*=1.5, 9 Hz, H-1′), 6.13 (d, 1H, *J*=3 Hz, H-4), 6.32 (dd, 1H, *J*=2, 3 Hz, H-3), 7.33 (dd, 1H, *J*=1, 2 Hz, H-2); ^{13}C NMR ($CDCl_3$) δ: 17.9 (C-4′), 25.6 (C-3′), 37.1 (C-6), 77.9 (C-7), 106.2 (C-3), 110.2 (C-4), 118.9 (C-1′), 137.9 (C-2′), 142.0 (C-2), 152.2 (C-5); MS (CI/NH_3) *m/z* 196 $[MH]^+$.

5.2.6. 2-(3-Furan-2-yl-4-nitro-butyl)-[1,3]dioxolane (10). To a suspension of 2.4 g of crushed magnesium turnings (100 mmol) in 24 mL of dry THF at 25 °C was added 1 mL of 2-(2-bromoethyl)-[1,3]dioxolane (part of 14.2 g, 78.4 mmol) and three small crystals of iodine. The solution was stirred at 25 °C for 5 min, under an argon atmosphere, before addition of dry THF (126 mL). The remaining 8.2 mL were added dropwise over 40 min period to the reaction mixture which was stirring for 20 min. After cooling at −60 °C, compound **8** (4.8 g, 34.5 mmol) in 30 mL of dry THF was slowly added over 30 min period and the mixture was stirred for 5 h at −60 °C under an argon atmosphere. The temperature was allowed to rise to room temperature and the stirring was continued for 18 h. The reaction was quenched by adding 180 mL of saturated ammonium chloride solution. The mixture was extracted with CH_2Cl_2 (150 mL×4) and the combined organic layers were dried on Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. Flash chromatography of the residue on silica gel (CH_2Cl_2/cyclohexane: 6/4) yielded **10** (5.2 g, 53%) as a yellow oil. IR (film) ν_{max} cm^{-1}: 2890, 1552, 1378, 1143, 1033, 741; ^{1}H NMR ($CDCl_3$) δ: 1.63 (dd, 1H, *J*=8. 4 Hz, H-2′), 1.65 (dd, 1H, *J*=8, 4 Hz, H-2′), 1.83 (m, 2H, H-1′), 3.65 (m, 1H, H-6), 3.85 (m, 2H, H-5′ and H-6′), 3.94 (m, 2H, H-5′ and H-6′), 4.55 (dd, 1H, *J*=13, 7 Hz, H-7), 4.63 (dd, 1H, *J*=13, 8 Hz, H-7), 4.85 (t, 1H, *J*=4 Hz, H-3′), 6.17 (d, 1H, *J*=3 Hz, H-4), 6.29 (dd, 1H, *J*=3, 2 Hz, H-3), 7.35 (d, 1H, *J*=2 Hz, H-2); ^{13}C NMR ($CDCl_3$) δ: 25.0 (C-1′), 30.7 (C-2′), 37.6 (C-6), 64.9 (C-5′ and C-6′), 78.3 (C-7), 103.7 (C-3′), 107.6 (C-4), 110.2 (C-3), 142.3 (C-2), 152.0 (C-5); ESI-MS *m/z*: 264 $[MNa]^+$.

5.2.7. 2-(1-[1,3]Dithian-2-yl-2-nitro-ethyl)-furan (11). A solution of 1,3-dithiane (6.20 g, 51.5 mmol) in 120 mL of

dry THF under an argon atmosphere was added dropwise with stirring at −20 °C to 20.1 mL (51.5 mmol) of *n*-butyllithium (2.5 M) solution in hexane. The stirring was continued for 4 h 30 min at −20 °C. Then the reaction mixture was cooled to −60 °C and compound **8** (6 g, 43 mmol) in 20 mL of dry THF was added dropwise. After the addition the temperature was allowed to rise to room temperature and the stirring was continued under argon for 18 h. The reaction was quenched by adding 20 mL of a saturated aqueous sodium bicarbonate solution. The mixture was extracted with CH_2Cl_2 (200 mL×3) and the combined organic layers were dried on Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. Flash chromatography of the resulting brownish oil on silica gel (CH_2Cl_2) yielded **11** (6.65 g, 70%) as white-yellow amorphous compound. IR (film) ν_{max} cm^{-1}: 1550, 1420; ^1H NMR ($CDCl_3$) δ: 1.7–2.2 (m, 2H, H-4′), 2.8–3.0 (m, 4H, H-3′ and H-5′), 4.08 (ddd, 1H, *J*=5, 7, 9.5 Hz, H-6), 4.32 (d, 1H, *J*=7 Hz, H-1′), 4.79 (dd, 1H, *J*=9.5, 13.5 Hz, H-7), 4.98 (dd, 1H, *J*=5, 13.5 Hz, H-7), 6.29 (dd, 1H, *J*=1, 3 Hz, H-4), 6.31 (dd, 1H, *J*=2, 3 Hz, H-3), 7.37 (dd, 1H, *J*=1, 2 Hz, H-2); ^{13}C NMR ($CDCl_3$) δ: 25.2 (C-4′), 29.6 (C-3′, C-5′), 42.1 (C-7), 47.7 (C-1′), 75.5 (C-6), 109.2 (C-4), 110.4 (C-3), 142.6 (C-2), 149.1 (C-5); MS (CI, NH_3) *m*/*z* 277 $[M+18]^+$.

5.2.8. 5-Furan-2-yl-7-methyl-4-nitro-oct-6-enal (12). A solution of compound **9** (3.5 g, 18 mmol) in 20 mL of methanol was added dropwise with stirring under an argon atmosphere to a sodium methanolate solution (0.15 g of sodium metal in 14 mL of methanol). The reaction mixture was cooled to −20 °C and freshly distilled acrolein (2 mL, 30 mmol) in 20 mL of methanol was added dropwise over 1 h. The temperature was allowed to rise to 0 °C and the stirring continued for 2 h. Addition of 1 mL of glacial acetic acid neutralized the solution. The resulting mixture was concentrated under reduced pressure and extracted with CH_2Cl_2 (100 mL×3). The combined organic layers were dried on Na_2SO_4, filtered and evaporated under reduced pressure. Flash chromatography of the residue on silica gel (CH_2Cl_2/cyclohexane: 1/1) yielded **12** (2.84 g, 63%) as a diastereisomeric mixture of aldehydes. IR (film) ν_{max} cm^{-1}: 3050, 1719, 1549, 1500, 1374, 1009, 856, 740; ^1H NMR ($CDCl_3$) δ: 1.7–1.9 (m, 12H, H-4 and H-4), 2.0–2.3 (m, 4H, H-8), 2.5–2.6 (m, 4H, H-9), 4.25 (t, 1H, *J*=9.5 Hz, H-6), 4.34 (t, 1H, *J*=9.5 Hz, H-6), 4.7–4.9 (m, 2H, H-7), 5.3–5.4 (m, 2H, H-1′), 6.14 (d, 1H, *J*=3 Hz, H-4), 6.24 (d, 1H, *J*=3 Hz, H-4), 6.31 (dd, 1H, *J*=2, 3 Hz, H-3), 6.36 (dd, 1H, *J*=2, 3 Hz, H-3), 7.3–7.4 (m, 2H, H-2), 9.70 (s, 1H, H-10), 9.74 (s, 1H, H-10); ^{13}C NMR ($CDCl_3$) δ: 17.6 (C-4′), 18.1 (C-4′), 23.0 (C-8), 23.8 (C-8), 25.7 (C-3′), 39.5 (C-9), 39.6 (C-9), 42.2 (C-6), 89.7 (C-7), 90.0 (C-7), 106.5 (C-3 or C-4), 107.1 (C-3 or C-4), 110.1 (C-4 or C-3), 110.3 (C-4 or C-3), 118.0 (C-1′), 119.0 (C-1′), 137.1 (C-2′), 137.8 (C-2′), 142.0 (C-2), 151.7 (C-5), 152.2 (C-5), 199.4 (C-10), 199.5 (C-10); MS (CI/NH_3) *m*/*z* 252 $[MH]^+$.

5.2.9. 7-[1,3]Dioxolan-2-yl-5-furan-2-yl-4-nitro-heptanal (13). To a stirred solution of compound **10** (4.13 g, 17.1 mmol) in 20 mL of dry THF under an argon atmosphere was added 0.025 N sodium methanolate solution (31.5 mL). The reaction mixture was cooled to 0 °C and a solution of freshly distilled acrolein (1.8 mL, 1.5 g, 27 mmol) was added dropwise over 1 h (keep the temperature between 0–5 °C). After stirring for 1 h, the solution was acidified by adding 1 mL of glacial acetic acid. The resulting mixture was concentrated under reduced pressure and extracted with CH_2Cl_2 (100 mL×3). The combined organic layers were washed with 50 mL of water, dried on Na_2SO_4, filtered, and the solvent was evaporated under reduced pressure. Flash chromatography of the residue on silica gel (CH_2Cl_2/cyclohexane: 6/4) yielded a diastereisomeric mixture of aldehydes **13** (2.65 g, 52%) as a yellow oil. IR (film) ν_{max} cm^{-1}: 3427, 3120, 2958, 2889, 2734, 1724, 1551, 1362, 1144, 1034, 744; ^1H NMR ($CDCl_3$) δ: 1.47 (dd, 1H, *J*=8, 4 Hz, H-2′), 1.50 (dd, 1H, *J*=8, 4 Hz, H-2′), 1.66 (m, 1H, H-1′), 1.82 (m, 1H, H-1′), 1.89 (m, 1H, H-8), 2.02 (m, 1H, H-8), 2.42 (m, 2H, H-9), 3.35 (td, 1H, *J*=10, 4 Hz, H-6), 3.78 (m, 2H, H-5′ and H-6′), 3.88 (m, 2H, H-5′ and H-6′), 4.67 (td, 1H, *J*=10, 4 Hz, H-7), 4.77 (t, 1H, *J*=4 Hz, H-3′), 6.20 (d, 1H, *J*=3 Hz, H-4), 6.30 (d, 1H, *J*=2 Hz, H-3), 7.35 (d, 1H, *J*=2 Hz, H-2), 9.36 (s, 1H, H-10); ^{13}C NMR ($CDCL_3$) δ: 24.0 (C-8), 24.6 (C-1′), 30.7 (C-2′), 39.4 (C-9), 42.7 (C-6), 64.7 (C-5′ and C-6′), 90.3 (C-7), 103.5 (C-3′), 109.0 (C-4), 110.2 (C-3), 142.4 (C-2), 150.8 (C-5), 199.4 (C-10); ESI-MS *m*/*z*: 320 $[MNa]^+$.

5.2.10. 5-[1,3]Dithian-2-yl-5-furan-2-yl-4-nitro-pentanal (14). A solution of compound **11** (3 g, 11 mmol) in 12 mL of dry THF was added under an argon atmosphere to 20 mL of 0.4 N sodium methanolate solution. The reaction mixture was cooled to 0 °C and a solution of freshly distilled acrolein (1.16 mL, 17 mmol) was added dropwise over 1 h (keeping the temperature between 0 and 5 °C). The stirring was continued for 1 h. Addition of 1 mL of glacial acetic acid neutralized the solution. The resulting mixture was concentrated under reduced pressure and the residue was extracted with CH_2Cl_2 (100 mL×3). The combined organic layers were washed, dried by Na_2SO_4, filtered and the solvents were evaporated to obtain a yellow oil. Flash chromatography on silica gel (dichloromethane/cyclohexane: 6/4) yielded **14** (2.7 g, 74%) as a yellow oil. IR (film) ν_{max} cm^{-1}: 1725, 1548, 1419, 708; ^1H NMR ($CDCl_3$) δ: 1.78 (m, 2H, H-4′), 1.95 (m, 2H, H-9), 2.43 (m, 2H, H-8), 2.77 (m, 4H, H-3′ and H-5′), 3.90 (dd, 1H, *J*=7, 8.5 Hz, H-6), 4.17 (d, 1H, *J*=7 Hz, H-1′), 5.13 (ddd, 1H, *J*=3.5, 6, 8.5 Hz, H-7), 6.30 (m, 2H, H-4 and H-3), 7.38 (dd, 1H, *J*=0.5, 2 Hz, H-2), 9.62 (s, 1H, H-10); ^{13}C NMR ($CDCl_3$) δ: 23.0 (C-8), 25.3 (C-4′), 29.7 (C-3′, C-5′), 39.7 (C-9), 46.8 (C-6), 47.7 (C-1′), 87.0 (C-7), 110.5 (C-3), 110.7 (C-4), 142.8 (C-2), 147.6 (C-5), 206.6 (C-10); MS (CI/NH_3) *m*/*z* 333 $[M+18]^+$.

5.2.11. 6-Furan-2-yl-8-methyl-1,5-dinitro-non-7-en-2-ol (15). A solution of compound **12** (2.75 g, 11 mmol) in 40 mL of isopropanol, under argon at 25 °C, was added dropwise to a stirred suspension of nitromethane (3.6 mL, 66.6 mmol) and 40% potassium fluoride on alumina (1.6 g) in 10 mL of isopropanol. After 3 days, the mixture was filtered through celite. The filtrate was concentrated under reduced pressure. Flash chromatography of the residue on silica gel (diethyl ether/cyclohexane: 1/1) yielded **15** (3.16 g, 92%) as a diastereoisomers mixture of alcohols. IR (film) ν_{max} cm^{-1}: 1671, 1549, 1506, 1377, 1010, 817, 738; ^1H NMR ($CDCl_3$) δ: 1.2–1.3 (m, 2H, H-8), 1.6–1.9 (m, 14H, H-4′, H-3′ and H-8), 1.9–2.2 (m, 4H, H-9), 2.8–3.1 (s, 1H, OH), 4.1–4.3 (m, 6H, H-11 and H-6), 4.5–4.8

(m, 2H, H-7), 5.21 (dd, 1H, J=1.2, 9 Hz, H-1′), 5.31 (dd, 1H, J=1.2, 9 Hz, H-1′), 6.1–6.2 (m, 2H, H-3 or H-4), 6.2–6.3 (m, 2H, H-4 or H-3), 7.3–7.4 (m, 2H, H-2); ^{13}C NMR ($CDCl_3$) δ: 17.7 (C-4′), 18.2 (C-4′), 25.7 (C-3′), 26.7 (C-3′), 27.1 (C-8), 27.7 (C-8), 29.5 (C-9), 29.8 (C-9), 42.2 (C-6), 67.8 (C-10), 68.1 (C-10), 80.1 (C-11), 80.8 (C-11), 90.1 (C-7), 90.4 (C-7), 106.6 (C-3 or C-4), 107.1 (C-3 or C-4), 110.2 (C-4 or C-3), 110.5 (C-4 or C-3), 117.8 (C-1′), 118.9 (C-1′), 137.4 (C-2′), 138.0 (C-2′), 142.1 (C-2), 151.7 (C-5), 152.2 (C-5); MS (CI/NH_3) m/z 313 $[MH]^+$.

5.2.12. 8-[1,3]Dioxolan-2-yl-6-furan-2-yl-1,5-dinitro-octan-2-ol (16). A solution of compound **13** (0.48 g, 1.62 mmol) in 6 mL of a mixture of isopropanol and CH_2Cl_2 (2/1), under argon at 25 °C, was added dropwise to a stirred suspension of 0.51 mL of nitromethane (0.57 g, 9.42 mmol) and 0.18 g of 40% potassium fluoride on alumina. After stirring for 24 h, the mixture was filtered through celite. The filtrate was concentrated under reduced pressure. Flash chromatography of the residue on silica gel (CH_2Cl_2/cyclohexane: 6/4) yielded a diastereoisomeric mixture of alcohols **16** (0.46, 80%) as a yellow oil. IR (film) ν_{max} cm^{-1}: 3437, 2958, 2889, 1722, 1556, 1368, 1144, 1034, 744; ^{1}H NMR ($CDCl_3$) δ: 1.41 (m, 2H, H-9), 1.50 (m, 2H, H-1′ and H-2′), 1.68 (m, 2H, H-1′ et H-8), 1.84 (m, 2H, H-2′ and H-8), 3.36 (m, 1H, H-6), 3.80 (m, 2H, H-5′ and H-6′), 3.90 (m, 2H, H-5′ and H-6′), 4.20 (m, 1H, H-10), 4.30 (m, 2H, H-11), 4.70 (td, 1H, J=10, 3 Hz, H-7), 4.48 (t, 1H, J=4 Hz, H-3′), 6.20 (t, 1H, J=3 Hz, H-4), 6.32 (m, 1H, H-3), 7.37 (m, 1H, H-2); ^{13}C NMR ($CDCl_3$) δ: 24.8 (C-8), 25.3 (C-1′), 28.0 (C-2′), 29.7 (C-9), 43.0 (C-6), 64.9 (C-5′ and C6′), 67.3 and 68.0 (C-10), 80.5 (C-11), 91.0 and 91.5 (C-7), 103.7 (C-3′), 109.3 (C-4), 110.5 (C-3), 142.7 (C-2), 151.1 (C-5); ESI-MS m/z: 397 $[MK]^+$.

5.2.13. 6-[1,3]Dithian-2-yl-6-furan-2-yl-1,5-nitro-hexan-2-ol (17). A solution of compound **14** (2.68 g, 8.5 mmol) in 30 mL of a mixture isopropanol and dichloromethane (2/1), under argon at 25 °C, were added dropwise to a stirred suspension of nitromethane (2.54 mL, 47 mmol) and of 40% potassium fluoride on alumina (0.93 g). After stirring for 24 h, the mixture was filtered through celite. The filtrate was concentrated under reduced pressure. Flash chromatography of the residue on silica gel (dichloromethane/cyclohexane 6/4) yielded a diastereoisomeric mixture of alcohols **17** (2.32 g, 73%) as a yellow oil. IR (film) ν_{max} cm^{-1}: 3447, 1557, 1421; ^{1}H NMR ($CDCl_3$) δ: 1.5 (m, 6H, H-9, H-8 and H-4′), 2.78 (m, 4H, H-3′ and H-5′), 3.90 (m, 1H, H-6), 4.15 (d, 1H, J=9 Hz, H-1′), 4.35 (m, 3H, H-10 and H-11), 5.15 (m, 1H, H-7), 6.30 (m, 2H, H-3 and H-4), 7.38 (d, 1H, J=1.5 Hz, H-2); ^{13}C NMR ($CDCl_3$) δ: 25.0–25.2 (C-4′), 26.1–26.6 (C-8), 27.1–27.6 (C-9), 29.6 (C-3′, C-5′), 47.5–47.7 (C-1′), 67.1–67.8 (C-10), 77.4 (C-6), 80.5 (C-11), 87.5–87.9 (C-7), 110.1 (C-3), 110.5 (C-4), 142.7–142.8 (C-2), 147.8–148.3 (C-5); MS (CI/NH_3) m/z: 394 $[M+18]^+$.

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Asymmetric synthesis of (+)-preussin from *N*-sulfinyl δ-amino β-ketoesters

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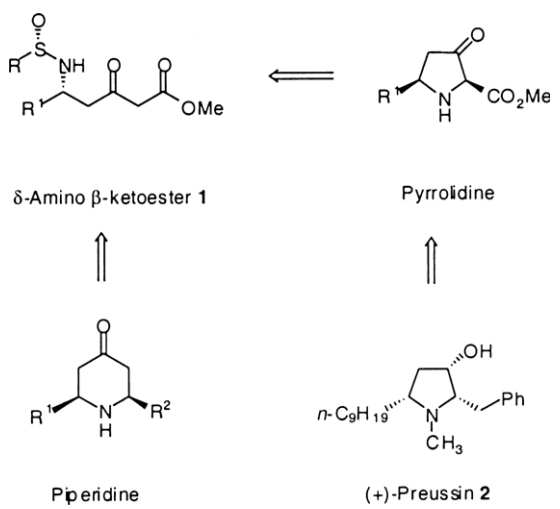
Abstract—The efficient asymmetric synthesis of the antifungal pyrrolidine alkaloid (+)-preussin (**2**) was accomplished via the stereoselective reduction of a 5-substituted 3-oxo proline. The oxo proline was prepared from an *N*-sulfinyl δ-amino β-ketoester, a sulfinimine derived polyfunctionalized chiral building block.

1. Introduction

Recent results in our laboratory have demonstrated the utility of *N*-sulfinyl δ-amino β-ketoesters as valuable chiral building blocks for the concise asymmetric synthesis of polysubstituted piperidine[1] and pyrrolidine alkaloids[2] (Scheme 1).[3] The piperidine structure is rapidly assembled via an intramolecular Mannich reaction of the amine salt of **1** and diverse carbonyl compounds.[1] Construction of the pyrrolidine framework (5-substituted 3-oxo prolines) involves a novel intramolecular metal carbenoid NH insertion reaction of the α-diazo δ-amino β-ketoester corresponding to **1**.[2] The fact that the NH insertion reaction is highly stereoselective and exclusively affords the *cis*-2,5-disubstituted product suggested the possibility of efficient asymmetric syntheses of 2,3,5-trisubstituted pyrrolidines such as (+)-preussin (**2**).[2a]



Scheme 1.

(+)-Preussin (**2**) has been the subject of a number of asymmetric syntheses[4] of varying degrees of conciseness because it is a potent antifungal agent with significant broad-spectrum antibiotic activity against yeast and filamentous fungi.[5] To prepare (+)-**2** from the oxo proline requires (i) a stereoselective reduction of the 3-oxo unit, (ii) conversion of the carbomethoxy group into a benzyl group, and (iii) *N*-methylation. We describe here the realization of this objective with a highly efficient asymmetric synthesis of (+)-preussin (**2**) from a sulfinimine derived δ-amino β-ketoester.

The δ-amino β-ketoester (R_S,5*S*)-(−)-**5** was prepared as previously described except that the sulfinimine (*R*)-(−)-**3** was prepared from commercially (Scheme 2) available (*R*)-(−)-*p*-toluenesulfinamide and 2,4-*trans*,*trans*-decadienal.[1d] The deprotection/protection sequence performed on (−)-**5** gave the *N*-Boc derivative (*S*)-(+)-**6** in 86% yield, and hydrogenation afforded (*S*)-(+)-**7** in nearly quantitative yield.

With the requisite *N*-Boc δ-amino β-ketoester (*S*)-(+)-**7** in hand, treatment with commercially available 4-carboxybenzenesulfonylazide (4-CBSA)[2] in the presence of Et_3N gave the key α-diazo derivative (*S*)-(+)-**8** in 94% isolated yield (Scheme 3). On treatment of (+)-**8** with 5 mol% $Rh_2(OAc)_4$ at rt in DCM the oxo proline **9** was isolated as a single diastereoisomer in 96% crude yield.[2] A concerted or nearly concerted metal carbenoid N–H insertion reaction mechanism was proposed earlier for the high stereoselectivity of this reaction.[2b] The crude ^1H NMR exhibits

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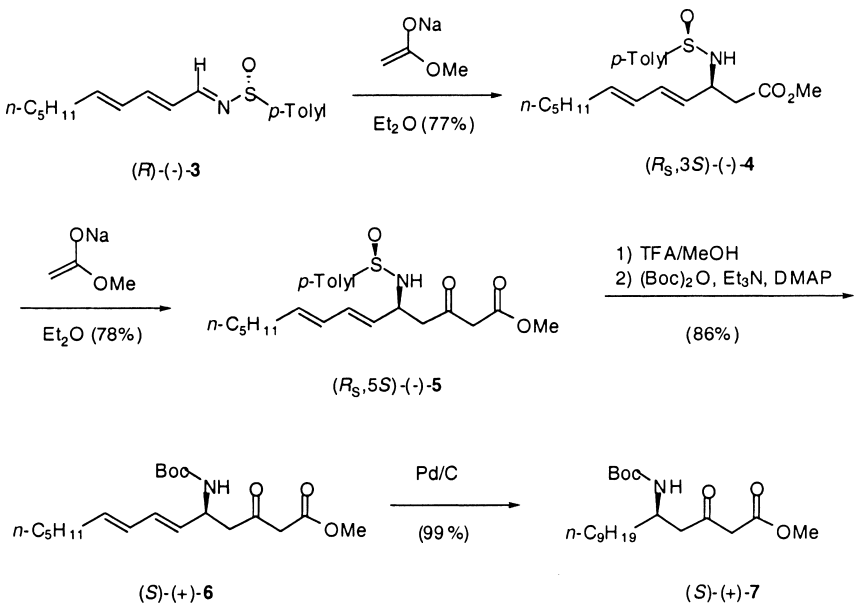
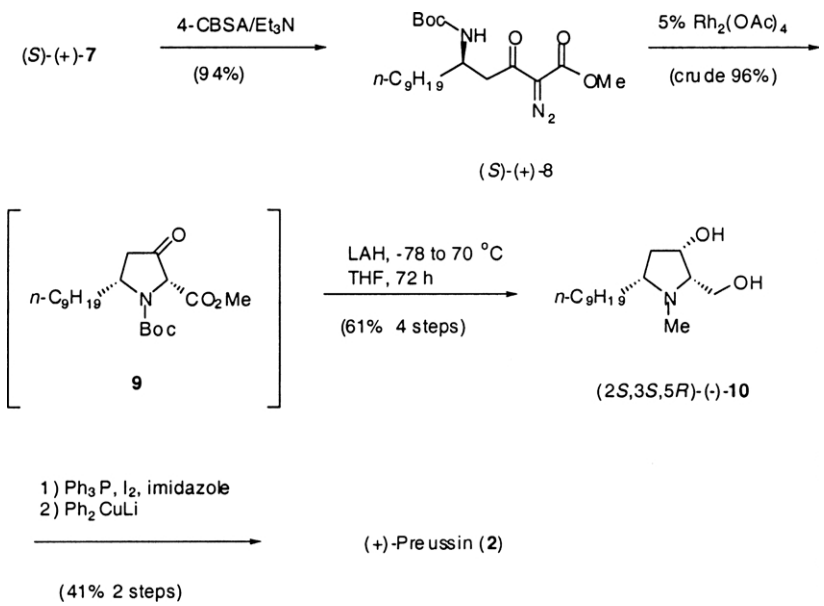


Scheme 2.

broadening of peaks due, we believe, to the presence of rotomers at the Boc group. However, attempts at purification by silica gel chromatography resulted in epimerization at C-2 to give **9** as 6:1 mixture of inseparable *cis*/*trans* isomers as suggested by ^{1}H NMR of the carboxyl methyl group. The presence of rotomers and peak broadening made the spectra quite complex to analyze. Facile epimerization at C-2 on purification was noted earlier for the 5-phenyl substituent,[2a] but not the 5-*tert*-butyl derivative,[2b] and may be due to the larger sized of the *tert*-butyl group. To avoid having to separate the diastereoisomers later in the synthesis, the crude oxo proline was taken on to the next step without purification. The fact at crude **9** was stable in solution for several hours suggest that epimerization occurs under acidic, silica gel, conditions.

Because lithium aluminum hydride (LAH) reduces ketones to alcohols, carboxylic esters to hydroxy methylene groups, and *N*-Boc to *N*-methyl groups[6] the possibility that all three reductions could be carried out stereoselectivity in one pot to give (−)-**10** was next explored. Initial studies with 10.0 equiv. of LAH at rt for 12 h resulted in reduction of both the oxo and carbomethoxy groups; however, poor stereoselectivity for the reduction of the 3-oxo group afforded a 4:1 mixture of isomers. Furthermore, the *N*-Boc group was not reduced. When the reduction was carried out at −78 °C for 4 h with slow warming to room temperature the oxo group was reduced with complete *cis* selectivity. Continued heating of the reaction mixture for 72 h at 70 °C afforded the desired dihydroxy *N*-methyl pyrrolidine (−)-**10**, in one pot, in 61% isolated yield for the four steps.

Conversion of diol (−)-**10** to (+)-preussin (**2**) requires selective conversion of the primary alcohol, in the presence



Scheme 3.

of the secondary alcohol, into a leaving group that will facilitate coupling with the phenyl group. Initial attempts to tosylate the primary alcohol in the presence of the secondary alcohol using *p*-toluenesulfonyl chloride and various bases (pyridine, Et_3N, and *i*-Pr_2NEt) resulted in extensive decomposition. Iodination with 4 equiv. of I_2, Ph_3P and imidazole appeared to be successful, but the product decomposed on work-up. For this reason, the crude iodide was immediately treated with 10 equiv. Ph_2CuLi at −78 °C and warmed to rt and stirred for 8 h, which afforded, following chromatography, (+)-preussin (**2**) in 40% yield for the two steps. This material had properties consistent with literature values.[4e]

In summary, a concise asymmetric synthesis of the pyrrolidine antifungal agent (+)-preussin (**2**) was accomplished from the sulfinimine derived δ-amino β-ketoester (+)-**7** with an overall yield of 23% for the seven steps, a number of steps being carried out in one pot.

2. Experimental

2.1. General procedures

Column chromatography was performed on silica gel, Merck grade 60 (230–400 mesh). TLC plates were visualized with UV, in an iodine chamber, or with phosphomolybdic acid, unless noted otherwise. Melting points were recorded on a Mel-Temp apparatus and are uncorrected. Optical rotations were measured on a Perkin–Elmer 341 polarimeter and IR spectra were recorded, using NaCl plates or as KBr disks, on a Mattson 4020 FTIR. ^1H NMR and ^{13}CNMR spectra were recorded on a GE Omega 500, operating at 500 and 125 MHz, respectively. HR-MS was performed in the Department of Chemistry, Drexel University, Philadelphia, PA, using a Fissions ZAB HF double-focusing mass spectrometer. Elemental analyses were performed in the Department of Chemistry, University of Pennsylvania, Philadelphia, PA.

Solvents were purified using the Glass Contour solvent dispensing system. Unless stated otherwise, all reagents were purchased from commercial sources and used without additional purification.

2.1.1. (*R*)-(−)-*N*-(2,4-Decaylidene)-*p*-toluenesulfinamide (3). In an oven-dried, 25-mL one-necked, round-bottomed flask equipped with a magnetic stirring bar was placed *E*,*E*-2,4-decadienal (0.360 mL, 2.0 mmol, Aldrich) in CH_2Cl_2 (10 mL). Titanium(IV) ethoxide (0.22 mL, 1.0 mmol) and (*R*)-(−)-*p*-toluenesulfinamide (0.283 g, 2.0 mmol, Aldrich) were added and the reaction mixture was stirred at rt for 12 h.[7] At this time, the reaction was quenched by addition of ice-H_2O (4 mL) and filtered through Celite. The organic phase was washed with brine (4 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (30% EtOAc/hexanes) afforded 0.435 g (75%) of (*R*)-(−)-**3** as an oil; $[\alpha]_D^{20}=-820.0$ (*c* 1.2, $CHCl_3$); IR (neat): 2927, 2857, 1608, 1560, 1094 cm^{-1}; ^1H NMR ($CHCl_3$) δ 0.87 (t, *J*=7.0 Hz, 3H), 1.29 (m, 4H), 1.42 (m, 2H), 2.16 (dd, *J*=7.0, 14.0 Hz, 2H), 2.39 (s, 3H), 6.11 (m, 1H), 6.19 (m, 1H), 6.37 (dd, *J*=10.0, 16.0 Hz, 1H), 6.87 (dd, *J*=10.0, 16.0 Hz, 1H), 7.28 (d, *J*=8.0 Hz, 2H), 7.55 (d, *J*=8.0 Hz, 2H), 8.35 (d, *J*=8.5 Hz, 1H); ^{13}C NMR δ 14.4, 21.8, 22.9, 28.8, 31.8, 33.5, 125.0, 127.2, 129.6, 130.2, 142.0, 142.5, 145.3, 147.9, 162.1. HR-MS calcd for $C_{17}H_{23}NOSNa$ (M+Na): 312.1398. Found: 312.1396.

2.1.2. (R_S,3*S*)-(−)-Methyl-3-*N*-(*p*-toluenesulfinyl)amino-3-dodeca-4,6-dienoate (4). In a 50-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar and an argon balloon was placed NaHMDS (1.80 mL, 1.0 M solution in THF) in ether (20 mL) and the solution was cooled to −78 °C. Anhydrous methyl acetate (0.15 mL, 1.80 mmol) was added dropwise and the reaction mixture was stirred at −78 °C for 50 min. At this time, sulfinimine (*R*)-(−)-**3** (0.35 g, 1.22 mmol) in ether (5 mL) was added dropwise and the reaction mixture was stirred for 4 h and quenched at −78 °C with sat. NH_4Cl solution (6 mL). The aqueous phase was washed with EtOAc (2×8 mL) and the combined organic phases were washed with brine (8 mL), dried (Na_2SO_4), and concentrated. Chromatography (50% EtOAc/hexanes) afforded 0.34 g (77%) of an oil; $[\alpha]_D^{20}=-114.0$ (*c* 1.1, $CHCl_3$); IR (KBr): 3198, 2927, 1734, 1437 cm^{-1}; ^1H NMR ($CHCl_3$) δ 0.87 (t, *J*=7.0 Hz, 3H), 1.27 (m, 4H), 1.38 (m, 2H), 2.05 (dd, *J*=7.5, 15.0 Hz, 2H), 2.39 (s, 3H), 2.61 (m, 2H), 3.63 (s, 3H), 4.27 (m, 1H), 4.75 (d, *J*=6.0 Hz, 1H), 5.58 (dd, *J*=8.0, 16.5 Hz, 1H), 5.73 (m, 1H), 6.01 (m, 1H), 6.28 (dd, *J*=10.5, 15.0 Hz, 1H), 7.28 (d, *J*=8.0 Hz, 2H), 7.55 (d, *J*=8.0 Hz, 2H); ^{13}C NMR δ 14.4, 20.9, 21.8, 22.9, 29.2, 31.8, 33.0, 41.2, 52.2, 53.4, 125.9, 126.8, 129.4, 129.6, 130.0, 133.7, 137.2, 141.7, 142.6, 171.8. HR-MS calcd for $C_{20}H_{29}NO_3SNa$ (M+Na): 386.1766. Found: 386.1756.

2.1.3. (R_S,5*S*)-(−)-Methyl-3-oxo-5-(*p*-toluenesulfinyl-amino)-tetradeca-6,8-dienoate (5). In a 25-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed NaHMDS (2.60 mL, 1.0 M solution in THF) in THF (6 mL) and the solution was cooled to −78 °C. Methyl acetate (0.21 mL, 2.60 mmol) was added and the reaction mixture was stirred for 1 h and (R_S,3*S*)-(−)-**4** (0.23 g, 0.60 mmol) in THF (4 mL) was added. The reaction mixture was stirred at −78 °C for 2.0 h, for 50 min at −15 °C or until completed (monitored by TLC), and quenched by the addition of sat. NH_4Cl (4.0 mL). The aqueous phase was extracted with EtOAc (3×8 mL), the combined organic phases were dried (Na_2SO_4), and concentrated.

Chromatography (20% EtOAc/hexane) gave 0.195 g (78%) of an oil; $[\alpha]_D^{20}=-91.6$ (*c* 1.0, $CHCl_3$); IR (neat): 3211, 2926, 1718, 1653 cm^{-1}; ^1H NMR ($CHCl_3$) δ 0.87 (t, *J*=7.0 Hz, 3H), 1.27 (m, 4H), 1.38 (m, 2H), 2.05 (dd, *J*=7.5, 15.0 Hz, 2H), 2.39 (s, 3H), 2.88 (d, *J*=6.0 Hz, 2H), 3.40 (s, 2H), 3.70 (s, 3H), 4.31 (m, 1H), 4.63 (d, *J*=6.0 Hz, 1H), 5.58 (dd, *J*=8.0, 16.5 Hz, 1H), 5.73 (m, 1H), 6.01 (m, 1H), 6.22 (dd, *J*=10.5, 15.0 Hz, 1H), 7.28 (d, *J*=8.0 Hz, 2H), 7.57 (d, *J*=8.0 Hz, 2H); ^{13}C NMR δ 14.4, 21.8, 22.9, 29.2, 31.8, 33.1, 49.4, 49.9, 52.8, 52.9, 125.9, 129.3, 129.6, 130.0, 133.7, 137.2, 141.8, 142.6, 167.6, 201.2. HR-MS calcd for $C_{22}H_{31}NO_4SNa$ (M+Na): 428.1872. Found: 428.1871.

2.1.4. (*S*)-(+)-Methyl-3-oxo-5-(*tert*-butyloxycarbonyl-amino)-tetradeca-6,8-dienoate (6). In a 25-mL,

one-necked, round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and argon-filled balloon was placed (R_S,5*S*)-(−)-**5** (0.170 g, 0.40 mmol) in MeOH (8 mL). The reaction mixture was cooled to 0 °C, TFA (0.156 mL, 2.0 mmol) was added, and the reaction mixture was stirred at rt for 2 h. At this time the solution was concentrated, the residue was dissolved in THF (8 mL), cooled to 0 °C, and Et_3N (0.330 mL, 2.4 mmol), DMAP (ca. 0.005 g), and di-*tert*-butyldicarbonate (0.132 g (0.60 mmol) were added. The reaction mixture was stirred for 2 h at 0 °C and quenched by the addition of sat. NH_4Cl (3.0 mL). The aqueous phase was extracted with EtOAc (2×8 mL), and the combined organic phases were washed with H_2O (8 mL), brine (8 mL), dried (Na_2SO_4), and concentrated. Chromatography (5–30% EtOAc/hexanes) gave 0.130 g (86%) of a yellow solid; mp 57.0–58.0 °C; $[\alpha]_D^{20}$=+3.60 (*c* 0.7, $CHCl_3$); IR (KBr): 3349, 2924, 1751, 1684, 1525 cm^{-1}; ^1H NMR ($CHCl_3$) δ 0.87 (t, *J*=7.0 Hz, 3H), 1.24 (m, 4H), 1.38 (m, 2H), 1.43 (s, 9H), 2.05 (dd, *J*=7.5, 15.0 Hz, 2H), 2.86 (d, *J*=5.0 Hz, 2H), 3.46 (dd, *J*=20.0, 16.0 Hz, 2H), 3.73 (s, 3H), 4.50 (m, 1H), 5.01 (bs, 1H), 5.53 (dd, *J*=8.0, 16.5 Hz, 1H), 5.69 (m, 1H), 5.98 (m, 1H), 6.12 (dd, *J*=10.5, 15.0 Hz, 1H); ^{13}C NMR δ 14.4, 23.0, 29.0, 29.4, 32.0, 33.0, 48.4, 49.5, 50.0, 52.8, 80.2, 91.7, 129.8, 129.9, 132.2, 136.5, 155.7, 167.8, 201.1. Anal calcd for $C_{21}H_{37}NO_5$: C, 65.77; H, 9.72; N, 3.65. Found: C, 65.55; H, 9.29; N, 3.72.

2.1.5. (*S*)-(+)-Methyl-3-oxo-5-(*tert*-butyloxycarbonylamino)-5-nonylpentanoate (7). In a 50-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar and rubber septum was placed (*S*)-(+)-**6** (0.40 g, 1.04 mmol) in MeOH (20 mL). To the solution was added 10% Pd/C and the reaction mixture was stirred under an H_2 balloon for 2 h. At this time, the solution was filtered through Celite and concentrated to give 0.404 g (100%) of a white solid; mp 48.0–49.0 °C; $[\alpha]_D^{20}$=+27.2 (*c* 1.1, $CHCl_3$); IR (KBr): 3353, 2923, 1684 cm^{-1}; ^1H NMR ($CHCl_3$) δ 0.87 (t, *J*=7.0 Hz, 3H), 1.24 (b, 14H), 1.41 (b, 9H), 1.50 (b, 2H), 2.74 (m, 2H), 3.47 (m, 2H), 3.73 (s, 3H), 3.89 (m, 1H), 4.79 (d, *J*=8.0 Hz, 1H); ^{13}C NMR δ 14.5, 23.1, 26.6, 28.8, 29.7, 29.9, 32.3, 35.0, 47.8, 48.0, 49.7, 52.8, 79.7, 91.4, 155.8, 167.9, 202.2. Anal calcd for $C_{21}H_{41}NO_5$: C, 65.08; H, 10.66; N, 3.61. Found: C 64.83; H, 10.24; N, 4.01.

2.1.6. (*S*)-(+)-Methyl-2-diazo-3-oxo-5-(*tert*-butyloxycarbonylamino)-5-nonylpentanoate (8). In a 25-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and argon balloon was placed (*S*)-(+)-**7** (0.400 g, 1.08 mmol) and *p*-carboxybenzenesulfonyl azide (*p*-CBSA) (0.277 g, 1.18 mmol) in acetonitrile (8 mL). The reaction mixture was cooled to 0 °C and Et_3N (0.44 mL, 3.24 mmol) was added and the reaction mixture was stirred for 2 h. At this time, the white precipitate was removed by filtration, the filtrate was concentrated, and EtOAc (20 mL) was added to the residue. The organic phase was washed with H_2O (2×8 mL), 1 N NaOH (2×8 mL), brine (10 mL), dried (Na_2SO_4), and concentrated to give 0.400 g (94%) of a gel; $[\alpha]_D^{20}$=+26.4 (*c* 1.0, $CHCl_3$); IR (KBr): 3376, 2928, 2855, 2135, 1718, 1172 cm^{-1}; ^1H NMR ($CHCl_3$) δ 0.87 (t, *J*=7.0 Hz, 3H), 1.24 (b, 14H), 1.41 (b, 9H), 1.50 (b, 2H), 3.00 (m, 2H), 3.73 (s, 3H), 3.89 (m, 1H), 4.79 (d, *J*=8.0 Hz, 1H); ^{13}C NMR δ 14.5, 23.1, 26.6, 29.8, 29.9, 30.0, 32.4, 36.1, 45.7, 49.0, 52.6, 76.9, 79.6, 156.0, 162.3, 191.3. HR-MS calcd for $C_{20}H_{35}NO_5Na$ (M+Na): 420.2474. Found: 420.2468.

2.1.7. Methyl-*N*-(*tert*-butyloxycarbonyl)-3-oxo-5-nonylpyrrolidine-2-carboxylate (9). In a 50-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar and argon-filled balloon was placed (*S*)-(+)-**8** (0.250 g, 0.63 mmol) in DCM (20 mL). To the solution was added $Rh_2(OAc)_4$ (0.028, 5 mol%) and the reaction mixture was stirred for 2 h at rt. At this time, the solution was concentrated. The ^1H NMR spectra indicated the presence of a single isomer as a mixture of rotomers suggested by peak broadening; major rotomer: ^1H NMR ($CHCl_3$) δ 0.87 (t, *J*=7.0 Hz, 3H), 1.29 (m, 24H), 1.95 (b, 1H), 2.40 (b, 1H), 2.80 (b, 1H), 3.80 (s, 3H), 4.28 (b, 1H), 4.60 (b, 1H); minor rotomer: δ 0.87 (t, *J*=7.0 Hz, 3H), 1.29 (m, 24H), 1.95 (b, 1H), 2.38 (b, 1H), 2.82 (b, 1H), 3.80 (s, 3H), 4.28 (b, 1H), 4.68 (b, 1H). Chromatography (10% EtOAc/hexanes) resulted in a 6:1 mixture of isomers; major isomer: ^1H NMR ($CHCl_3$) δ 0.87 (t, *J*=7.0 Hz, 3H), 1.29 (m, 24H), 1.95 (b, 1H), 2.40 (b, 1H), 2.80 (b, 1H), 3.80 (s, 3H), 4.28 (b, 1H), 4.60 (b, 1H); minor isomer: δ 0.87 (t, *J*=7.0 Hz, 3H), 1.29 (m, 24H), 1.82 (b, 1H), 2.38 (b, 1H), 2.90 (b, 1H), 3.76 (s, 3H), 4.40 (b, 1H), 4.60 (b, 1H).

2.1.8. (2*S*,3*S*,5*R*)-(−)-*N*-Methyl-2-hydroxymethyl-3-hydroxy-5-nonylpyrrolidine (10). To crude **9** was added THF (20 mL), the solution was cooled to −78 °C, LAH (0.120 g, 3.15 mmol) was added, and the reaction mixture was stirred for 4 h. At this time, the solution was slowly warmed to 0 °C, stirred at this temperature for 2 h, cooled to −78 °C, and LAH (0.120 g, 3.15 mmol) was added. The reaction mixture was heated at 70 °C for 72 h at which time the reaction was quenched by the addition of H_2O (0.24 mL) and 10% NaOH (0.72 mL), and H_2O (0.24 mL). The solution was stirred for 1 h, passed through Celite, the organic phase was washed with brine (5 mL), and (Na_2SO_4), and concentrated. Chromatography (2% MeOH/EtOAc) afforded 0.099 g (61%) of an oil $[\alpha]_D^{20}$=−37.8 (*c* 0.7, $CHCl_3$); IR (KBr): 3379, 2925, 2854, 2791, 1030 cm^{-1}; ^1H NMR ($CHCl_3$) δ 0.87 (t, *J*=7.0 Hz, 3H), 1.29 (b, 16H), 1.41 (b, 9H), 1.70 (m, 1H), 2.25 (m, 1H), 2.27 (s, 3H), 2.39 (m, 1H), 2.44 (m, 1H), 3.11 (b, 2H), 3.73 (dd, *J*=3.5, 11.5 Hz, 1H), 3.80 (dd, *J*=2.0, 11.5 Hz, 1H), 4.29 (dd, *J*=7.0, 14.0 Hz, 1H); ^{13}C NMR δ 14.5, 23.1, 26.5, 29.7, 29.98, 30.02, 30.4, 32.3, 34.1, 39.0, 42.3, 59.5, 64.4, 70.1, 72.3. HR-MS calcd for $C_{15}H_{31}NO_2Na$ (M+Na): 280.2252. Found: 280.2260.

2.1.9. (2*S*,3*S*,5*R*)-(+)-Preussin (2). In a 10-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and argon balloon was placed (−)-**10** (0.031 g, 0.120 mmol) in DCM (5 mL), the solution was cooled to 0 °C, Ph_3P (0.160 g, 0.60 mmol), imidazole (0.041 g, 0.60 mmol), and I_2 (0.150 g, 0.60 mmol) were added. The reaction mixture was stirred at this temperature for 4 h and the solution was filtered. The filtrate was concentrated, dissolved in THF (3 mL), and cooled to −78 °C. In a separate 10-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and argon balloon was placed CuI (0.230 g, 1.20 mmol) in THF (2 mL). The solution was cooled to 0 °C, and PhLi (1.5 mL, 2.40 mmol, 1.6 M in cyclohexane and ether) was

added dropwise. The suspension, which turned to a clear green solution after stirring at 0 °C for 10 min, was cooled to −78 °C, and the I_2 solution mixture was added dropwise. After stirring the reaction mixture at rt for 8 h the solution was cooled to −78 °C, stirred for 30 min, and poured into sat. aq. NH_4Cl (4 mL). The aqueous phase was extracted with EtOAc (2×10 mL), the combined organic phases were washed with brine (8 mL), dried (Na_2SO_4), and concentrated. Chromatography (30% EtOAc/hexane) afforded 0.016 g (41%) of an oil; $[\alpha]_D^{20}=+30.8$ (*c* 0.7, $CHCl_3$) [lit.[4e] +31.5 (*c* 1.0, $CHCl_3$)]. Spectral properties were consistent with literature values.[4e]

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Corrigendum

Corrigendum to "Aryl-2,3-oxaphosphabicyclo[2.2.2]octene derivatives—the precursors of oxoarylphosphine oxides (aryl metaphosphonates)" [Tetrahedron 60 (2004) 2789]☆

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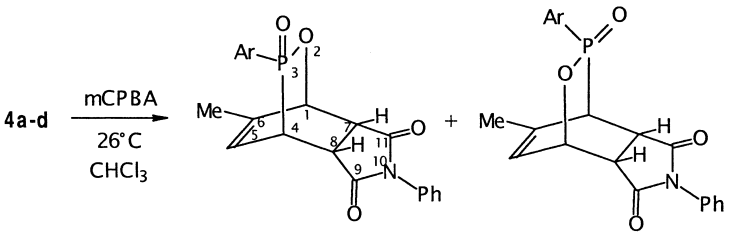
The following scheme describing time of reaction and ratio of regioisomers is missing from the above article:



Ar = as in Scheme 1 **5Aa-d** **5Ba-d**

Ar	Time[a] [h/min]	Yield of **5Aa-d** and **5Ba-d** [%]	**5Aa-d** [%][b]	**5Ba-d** [%][b]
a	1/15	77	45	55
b	5/50	21	26	74
c	8/20	22	17	83
d	0/25	79	44	56

[a] the time after which the product of epoxidation appeared in the mixture
[b] on the basis of relative ^{31}P NMR intensities

Scheme 2.

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