Tetrahedron

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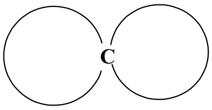
Rosy Pradhan, Manabendra Patra, Ajaya K. Behera, Bijay K. Mishra* and Rajani K. Behera*



Synthesis of spiro and hetero spiro compounds has been reviewed on the basis of a synthon approach along with their biological activities and photochromism.

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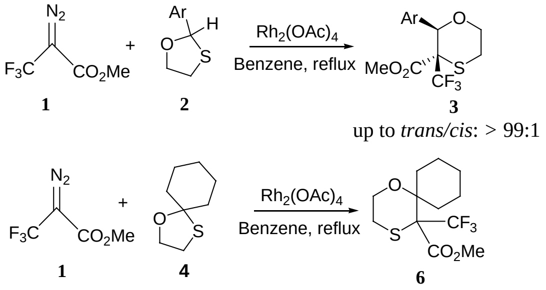

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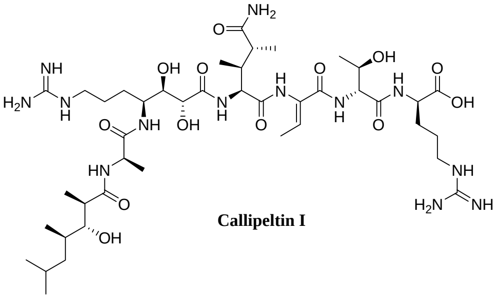
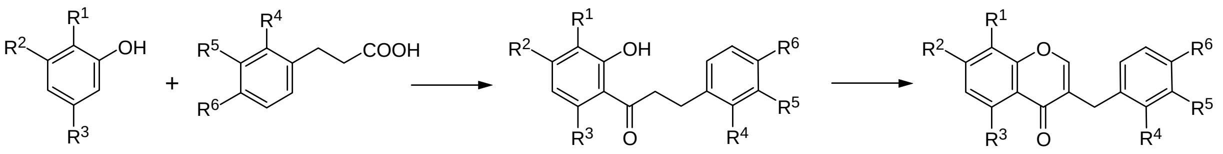
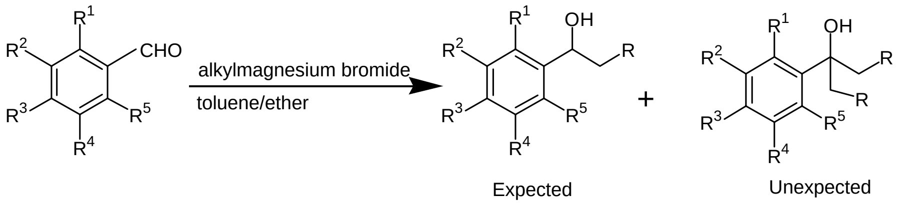
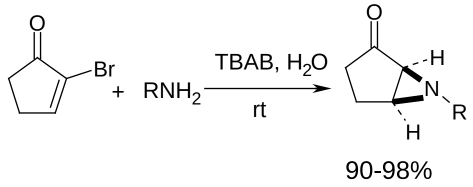


Callipeltin I







$$R^1C\equiv CH + (CH_2O)_n + HNR^2R^3 \xrightarrow[MW]{CuI/Al_2O_3} R^1C\equiv CCH_2NR^2R^3$$

Chiral bisphospholane ligands (Me-ketalphos): synthesis of their Rh(I) complexes and applications in asymmetric hydrogenation

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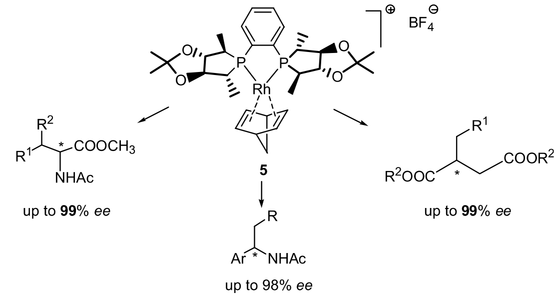
Qian Dai, Chun-Jiang Wang and Xumu Zhang*



A highly active ionic liquid catalyst for Morita–Baylis–Hillman reaction

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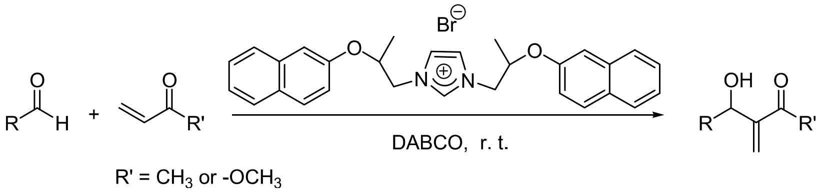
Yu-Sheng Lin, Chiao-Yang Lin, Chih-Wei Liu and Thomas Y. R. Tsai*



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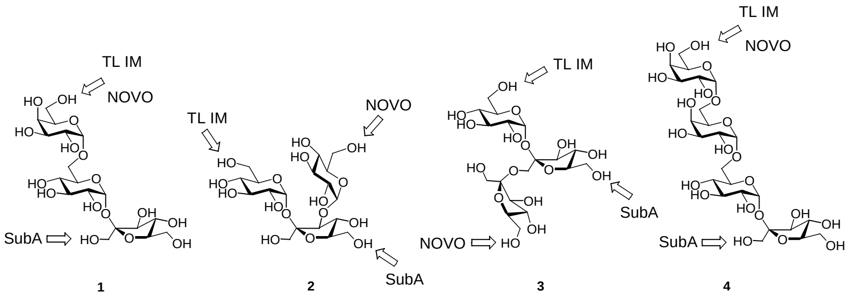
Ignacio Pérez-Victoria and Juan Carlos Morales*



NOVO = Novozym 435; TL IM = Lipozyme TL IM; SubA = MβCD-subtilisin Carlsberg

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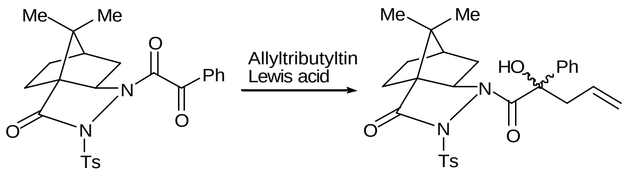
Jung-Hsuan Chen, Uppala Venkatesham, Li-Chen Lee and Kwunmin Chen*



$Sn(OTf)_2$: β-OH/α-OH = 99:1
$PdCl_2$: β-OH/α-OH = 4:96

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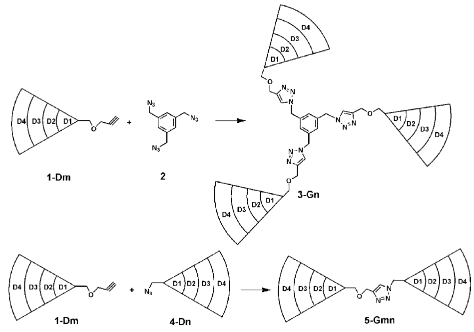

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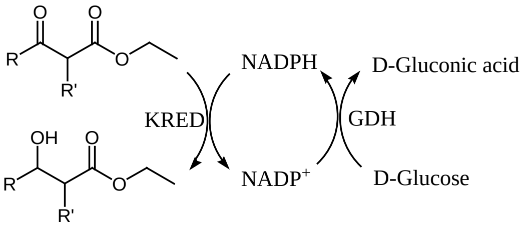

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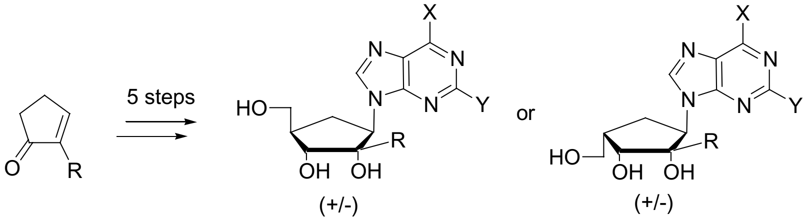

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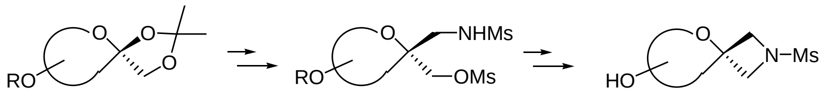

Pyranoid and furanoid rings. Conf. D-*ribo* and D-*arabino*

Reaction of α,β-unsaturated Fischer carbene complexes with allyl alkoxide

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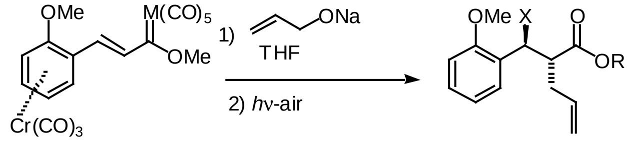
Ken Kamikawa,* Atsushi Tachibana, Yasunori Shimizu, Kazuya Uchida, Masaru Furusyo and Motokazu Uemura*

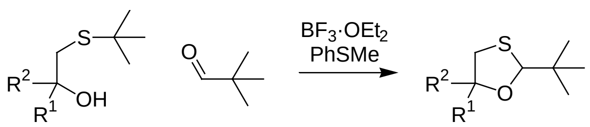


M = Cr X = H, R = CH_2=CHCH_2; 68%, 95% ee
M = W X = OH, R = CH_3; 65%, anti/syn = 92/8

Direct conversion of *tert*-butyl 2-hydroxyalkyl sulfides to 1,3-oxathiolanes

pp 931–936

Michael J. Porter,* Fabienne Saez and Amandeep Kaur Sandhu



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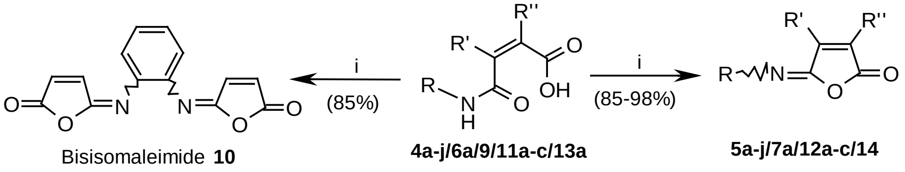
Kishan P. Haval, Santosh B. Mhaske* and Narshinha P. Argade*



R = aryl, alkyl, benzyl, *o*-C_6H_4-NHCOCH=CHCOOH; R' = H, Ph; R'' = H, Me; R'R'' =

(i) Cyanuric chloride, NEt_3, DCM, 0 °C to rt, 8 h (85-98%)

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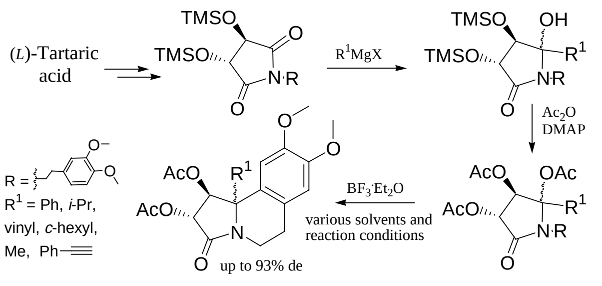
Zbigniew Kałuża,* Danuta Mostowicz, Grzegorz Dołęga, Katarzyna Mroczko and Robert Wójcik



Baylis–Hillman adducts between pyridine carboxaldehyde derivatives and cyclic enones

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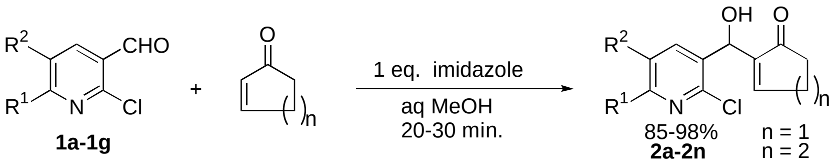
P. Narender, B. Gangadasu, M. Ravinder, U. Srinivas, G. Y. S. K. Swamy, K. Ravikumar* and V. Jayathirtha Rao*



α-Amido sulfones from natural α-amino acids and their reaction with carbon nucleophiles

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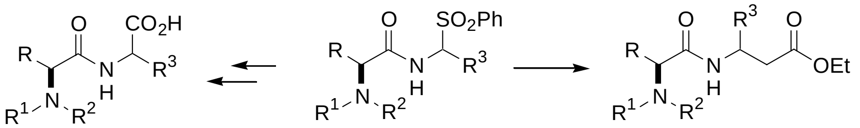
Marino Petrini* and Mirko Seri



α-Amino acid amides can be easily converted into α-amido sulfones that upon reaction with different nucleophiles lead to the corresponding substitution products such as α,α and α,β-dipeptides.

Synthesis of atropoisomeric pyridines via cobalt-catalyzed cocyclotrimerization of diynes with benzonitrile

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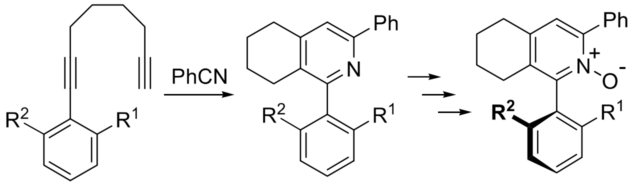

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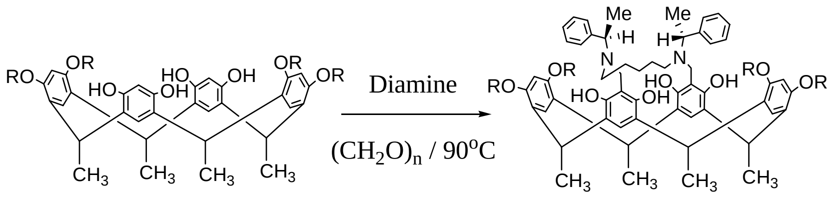
Gareth Arnott, Roger Hunter* and Hong Su



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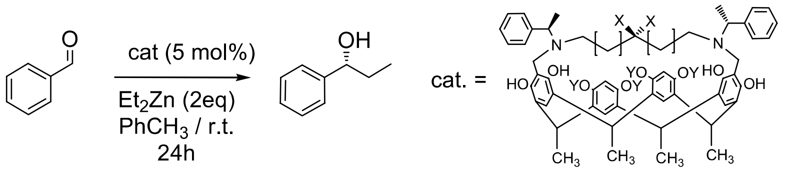
Gareth Arnott and Roger Hunter*



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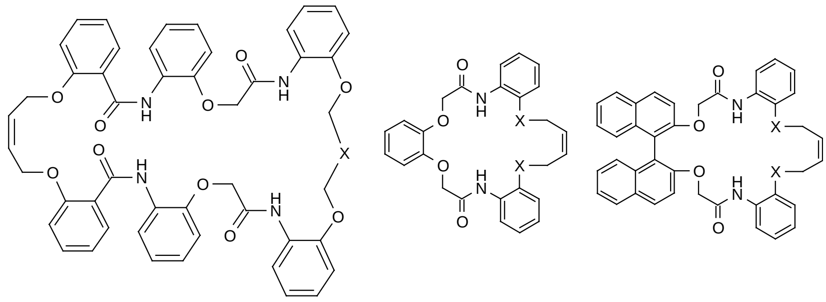

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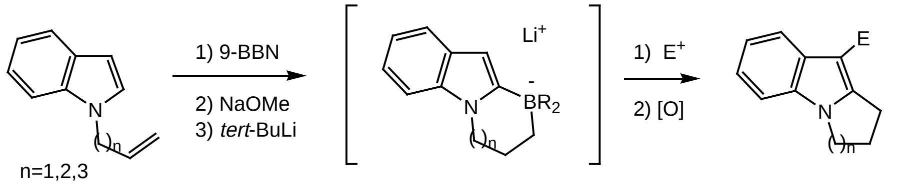

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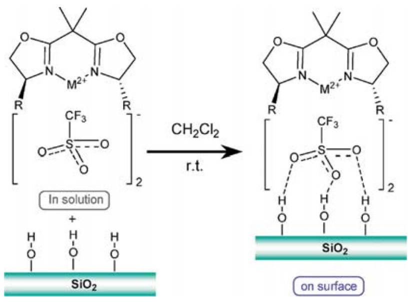
Hong Wang, Xiaojing Liu, Haian Xia, Peng Liu, Jinbo Gao, Pinliang Ying, Jianliang Xiao* and Can Li*



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*Corresponding author
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A synthon approach to spiro compounds

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Keywords: Photochromism; Synthon; Spiro compounds.

Abbreviations: BINAP, 2,2′-bis(diphenylphosphospiro)-1,1′-binaphthalene; Boc, *t*-butoxycarbonyl; CTAB, cetyltrimethylammonium bromide; DEAD, diethylazodicarboxylate; 4-DMAP, 4-(dimethylamino)pyridine; Fmoc, 9-fluorenylmethoxycarbonyl; HMPA, hexamethylphosphoric amide; HMPT, hexamethylphosphorous triamide; KHDMS, potassium hexamethyldisilazide; LAH, lithium aluminium hydride; LDA, lithium diisopropylamide; LiHDMS, lithium hexamethyldisilazide; *m*-CPBA, *m*-chloroperbenzoic acid; NaHMDS, sodium hexamethyldisilazane; NBS, *N*-bromosucinimide; NCS, *N*-chlorosuccinimide; NMO, *N*-methylmorpholine *N*-oxide; PCC, pyridinium chlorochromate; PDC, pyridinium dichromate; Ph, phenyl; PhH, benzene; PhMe, toluene; PLG, L-propyl-leucyl-glycinamide; PMP, 1,2,2,6,6-pentamethylpiperidine; PPTS, pyridinium toluene-4-sulphonate; rt, room temperature; TFA, trifluoro acetic acid; THF, tertrahydrafuran; TMEDA, *N,N,N′,N′*-tetramethylethylene diamine; TMPA, tetramethylene phosphoramide; Tol, *p*-tolyl; TPAP, tetrapropylammonium perruthenate; *p*-TSA, *p*-toluene sulphonic acid; Z, benzyloxycarbonyl.

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1. Introduction

In 1900, Bayer created the first spiran described as a bicyclic hydrocarbon connected by a single carbon. The term spirocyclanes was used to describe the family of such hydocarbon. Due to the tetrahedral nature of the spiro-linked carbon, the ring planes are nearly perpendicular to each other.

Spiro compounds having cyclic structures fused at a central carbon are of recent interest due to their interesting conformational features and their structural implications on biological systems. The asymmetric characteristic of the molecule due to the chiral spiro carbon is one of the important criteria of the biological activities. The retention of neurotoxic properties of perhydrohistrionicotoxin (**1**), an analogue of a natural product **2**, is clear evidence of the role of the spiro carbon in steering the biological activity.[1]

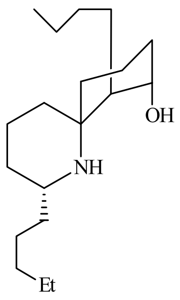
The presence of the sterically constrained spiro structure in various natural products also adds to the interest in the investigations of spiro compounds.[2] Spiro compounds represent an important class of naturally occurring substances characterised by their highly pronounced biological properties.[3–5]

In the arena of photochromism, spiro compounds, due to their steric constraints, equilibrate with the corresponding non-spiro analogue and exhibit various photochemical phenomena. The discovery of the photochromic reactions of spiropyrans[6] (Scheme 1) during 1952 initiated the work in the area of photochemical erasable memory.[7]

Some more related applications based on the equilibrium are self-development photography, actinometry, displays, filters and lenses of variable optical density etc.[8]

2. Biological activities

The spiro functionality has been known for a long time to be present in phytochemicals either in alkaloids, lactones or terpenoids. The spirocyclic alkaloid (−)-histrionicotoxin (**2**), isolated from skin extracts of the poison dart frog, *Dendrobats histrionius*, found in Columbia, is a very potent nicotinic receptor antagonist.[9] Spiroketals are reported to be the sub-units of many naturally occurring substances of biological interest such as insect pheromones, antifeedants and polyether antibiotics.[10] A series of spiroketals (**3**–**6**) have been isolated from *Chrysanthemum coronanium*, a common vegetable of South China.[11] Some of these compounds are found to have antifeeding activity towards silkworm[12] and spasmolytic and antiphlogistic activity.[13,14] Unsaturated spiroacetals such as 1,6-dioxaspiro[4.4]nona-3,8-diene[15] and 1,6-dioxaspiro[4.5]decane[16] have also been isolated from *Artemisia sp.*



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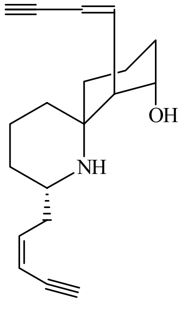

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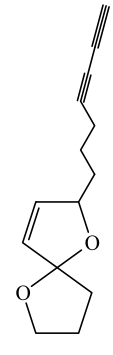

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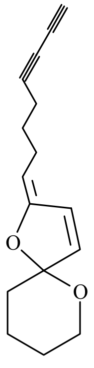

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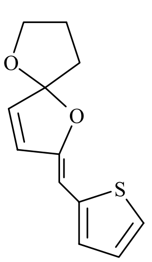

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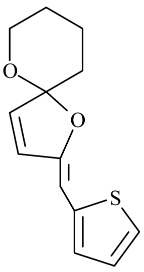
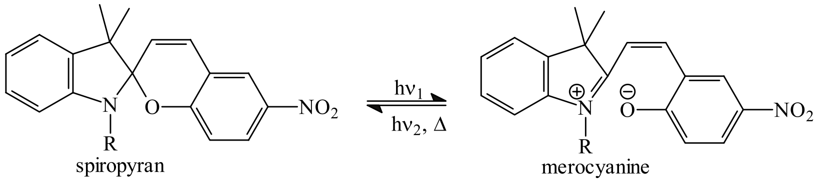


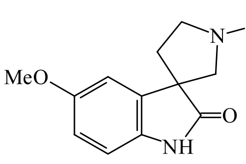
6

The spiro [pyrrolidin-3,3′-indole] ring system is a recurring structural motif in a number of natural products such as vinblastine and vincristine, that function as cytostatics and are of prime importance in cancer chemotherapy.[17] The derivatives of spiro-oxindole find very wide biological application as antimicrobial, antitumour, and antibiotic agents, and inhibitors of human NK-1 receptor etc.[18–20] Horsfiline (**7**), an oxindole alkaloid containing a spiro-[indole-pyrrolidone] nucleus, has been isolated by Bodo and co-workers[21] from *Horsfieldia superba*, a tree from Malaysia, the extracts of which are commonly employed in local medicine.

The saponaceolides (A–D), **8** are found to possess antitumour activity in 60 human cancer cell lines.[22] Each of these compounds contains a unit of tricyclic trioxaspiroketal.



Scheme 1.



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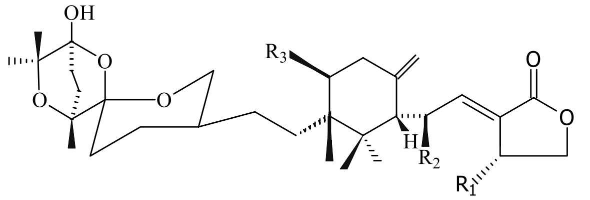
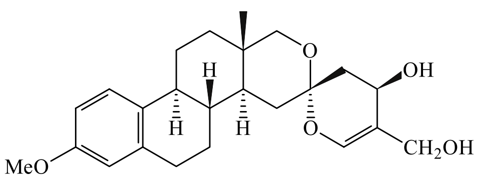


8: A: $R_1 = OH, R_2 = R_3 = H$ C: $R_1 = R_2 = OH, R_3 = H$
B: $R_1 = R_2 = R_3 = H$ D: $R_1 = R_3 = OH, R_2 = H$

The alkaloids containing a spiro[indole-pyrrolidine] nucleus are cell-cycle-specific cytostatic agents that arrest mitosis and metaphase by acting as spindle poisons. They are also found to be useful in cancer chemotherapy.[23]

Some spiroacetals (**9**) and (**10**) show strong cytotoxic activity against human cancer cells.[24] These compounds are hybrid natural products made from estrone (**11**) and a highly biologically active mycotoxin, talaromycin B (**12**).[25]



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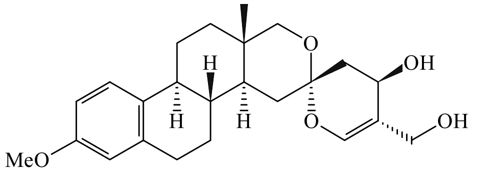

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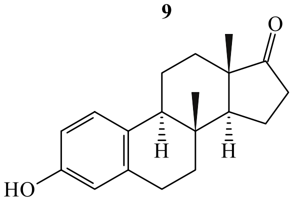

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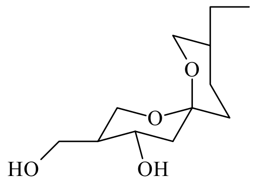

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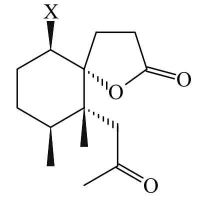
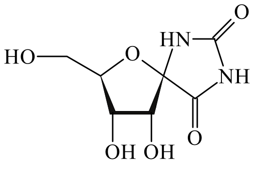


13: X = Cl
14: X = OH



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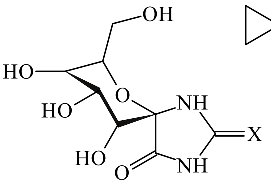
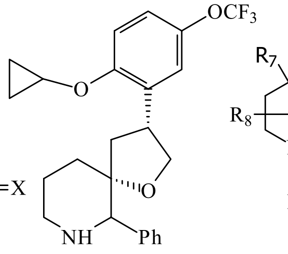


16: X = O
17: X = S



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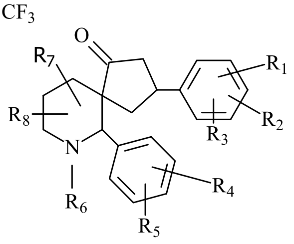


19

R_1 = OH, (flouro)alkyl, cycloalkyl, alkenyl, (flouro)alkoxy, PhCO, CN, halo, NH_2,alkylthio, carbamoyl, acyl, etc.
R_2 = H, halo, alkyl, alkoxy, etc.
R_3 = H, halo, (flouro)alkyl, cycloalkyl, alkoxy, NH_2, alkylthio, carbamoyl, acyl, etc.
R_4 = H, halo, alkyl, alkoxy, CF_3, OCF_3, NO_2, CN, alkylthio, carbamoyl, carboxy etc.
R_5 = H, halo, alkyl, CF_3, etc.
R_6 = H, acyl, carboxy, carbamoyl, phenyl, etc.
R_7 and R_8 = H, halo, alkyl, carboxy, alkoxy methyl, carbamoyl, etc.

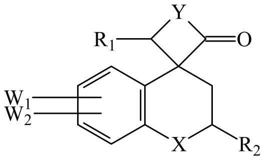
Napalilactone (**13**)[26] and pathylactone A (**14**)[27] are novel norsesquiterpenoid spirolactones isolated from marine sources and **14** was reported to be a Ca^{2+} antagonist.[28] (+)-Hydantocidin (**15**), which contains a unique spiro-nucleoside structure, possesses potent herbicidal and plant-growth regulatory activity.[29] The D-glucopyranosylidene-spiro-hydantoin analogue (**16**) of hydantocidin was shown to be the most efficient inhibitor of muscle glycogen phosphorylase B known to date. The thio-analogue (**17**) is a potent inhibitor of glycogen phosphorylase B and glycogen phosphorylase A, not only from muscle, but also of liver origin.[30]

A research group at Merck[31] has developed a neuropeptide antagonist, which exhibits antidepressant activity.

Maligres and coworkers[32] have synthesised a non-peptidal (−)-spirobyclic NK-1 (**18**) receptor antagonist, which is required for their clinical programme.

The azaspiro compounds (**19**) are reported[33] to be tachykinin antagonists and are of particular use in the treatment of depression, anxiety, pain, inflammation, migraine, emesis or postherpetic neuralgia.

Some spiroheterocycles, benzopyrans (**20**) and (**21**), are aldose reductase inhibitors, which are found to be useful as antidiabetics.[34] Several potent reductase inhibitors based on spirosuccinimide, spiropyridazine and spiroazetidine have been reported for the prevention of secondary complications of diabetes.[35]



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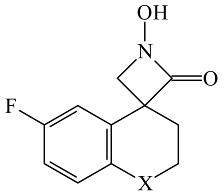
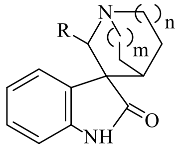


21

R_1& R_2 = H, C_{1-6} alkyl, aryl; W_1 & W_2 = H, halo, NO_2;
Y = NOH, CH_2NOH, C ONOH, NHO, CH:COH; X = O, CO;

Spirobicyclic lactam peptidomimetics[36] (**22**) and (**23**) of L-prolyl-leucyl-glycinamide (PLG) were found to exhibit a pharmacological profile similar to PLG (**24**) in terms of their [^{3}H]-spiroperidol/*N*-propylnorapomorphine D_2 receptor competition binding assay[37,38] and the 6-hydroxydopamine-lesioned animal model of Parkinson's disease. Both (**22**) and (**23**) produced a greater shift from the low-affinity state to the high-affinity state of the dopamine D_2 receptor than PLG. Spirocyclic quinuclidines (**25**) containing spiro-fused indoles are important for muscarinic receptor binding.[39] Substituted quinuclidines exhibit selective muscarinic receptor binding properties.[40]



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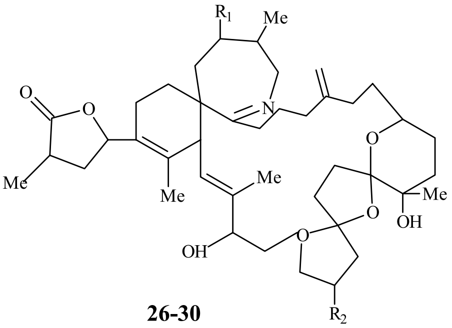
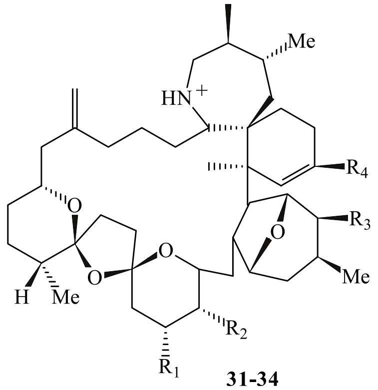


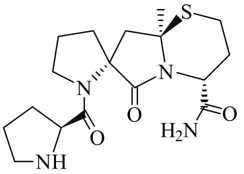
26-30

R = H, C_5H_9, C_6H_5, *i*-Pr, 4,4-diethoxy butyl		Spirolide		R_1	R_2
	26	A	$\Delta^{2,3}$	H	CH_3
m = 1,2	**27**	B		H	CH_3
n = 0,1	**28**	C	$\Delta^{2,3}$	Me	CH_3
	29	D		Me	CH_3
	30	13-des Me C	$\Delta^{2,3}$	C Me	H



31-34

Pinnatoxin	R_1	R_2	R_3	R_4
A (**31**)	H	H	OH	COO^-
B (**32**)	H	H	OH	$CH(OH)COO^-$
C (**33**)	H	H	OH	$CH(OH)COO^-$
D (**34**)	Me	OH	H	$CO(CH_2)_2COO^-$



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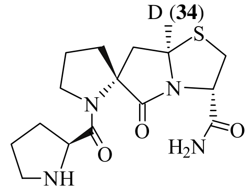

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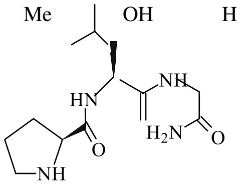


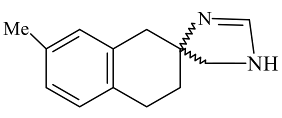
24

Spirolides A–D (**26–29**) and 13-desmethyl spirolide C (**30**) are toxic in a mouse bioassay for lipophilic toxins.[41–44] These compounds were first found in the extract of shellfish from aquaculture sites and, subsequently, they were shown to be produced by dianoflagellates such as *Alexandrium ostenofeldii*. All the compounds (**26–29**) contain an unusual seven-membered spiro-linked cyclic imine moiety with the same atomic connectivity as found in pinnatoxins A–D (**31–34**), which are potent calcium channel activators and are responsible for outbreaks of shellfish poisoning in China and Japan.[45]

Cordi and co-workers[46] have reported some spiro-imidazoline compounds endowed with α-adrenergic agonist activities. They have also reported that (*R*,*S*)-spiro(1,3-diazacyclopent-1-ene)-5,2′-(7′-methyl-1′,2′,3′,4′-tetrahydronaphthalene) (**35**) is a prototype of venospecific constrictors as it is able to constrict the saphenous vein of dogs without noticeable effects on the mean arterial pressure.[47]

Synthetic compounds with a 2-spiropiperidine moiety also possess interesting pharmacological activities.

Spiro[piperidine-2,2′-adamantane] (**36**) proved to be active against influenza viruses[48] and the spiro[piperidine-2,3′(2′H)-benzopyran] (**37**) showed a significant and selective affinity for the 5-HT$_{1A}$ receptors[49] and, therefore, serves as an anxiolytic agent.



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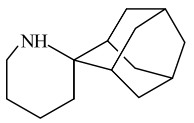

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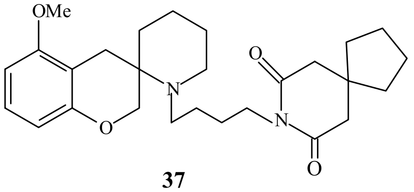
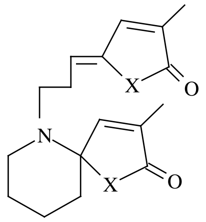


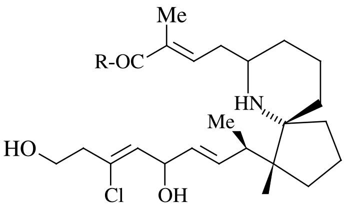
37

Interesting biological activities have been found in the piperidine alkaloids, (±)-pandamarine (**38**) and (−)-pandamarilactone (**39**), which contain an azaspiro[4.5]-decane structural unit.[50] The alkaloids (**38**) and (**39**) are isolated from *Pandanus sp.*[51] Pinnaic acid (**40**) and tauropinnaic acid (**41**), isolated from *Pinna muricata*,[52] are found to exhibit inhibitory activity against a cytosolic 85 kD phospholipase (cPLA$_2$).[53] Halichlorine (**42**), isolated from the marine sponge *Halichondria okadi*, is an inhibitor of the vascular cell adhesion molecule.[54]



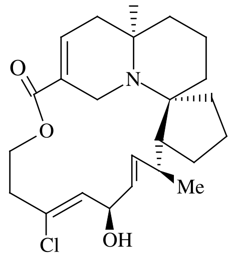
38 X: NH

39 X: O



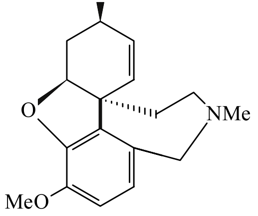
40 R: OH

41 R: NHCH$_2$CH$_2$SO$_3$H



42

Galanthamine (**43**), which contains the basic spiro[5*H*-2-benzazepine-5′,1′-cyclohexene] tricyclic fragment, is among some of the most widely used and most effective experimental drugs in the treatment of Alzheimer’s disease, because of its potent acetylcholinesterase activities.[55]

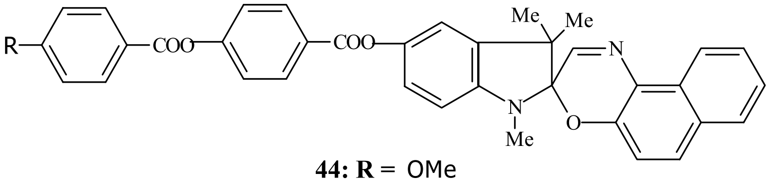


43

3. Photochromism

Optical memory systems including molecular memory switches impact upon photochromism.[56–58] It has been proposed[59,60] that information storage systems are based on a combination of two types of reversible process, namely photochemical cis/trans isomerisation and electrochemical oxidation and reduction, offering the possibility of readout and writing in either optical or electrical mode. The photoisomerisation of the azo group, however, has been shown to have the disadvantages of relatively low photosensitivity and a limited wavelength region for the coloured form.[61] These difficulties hinder the development of azo compounds for practical molecular switching devices. In contrast, a feature making spiropyrans one of the most widely studied classes of photochromic compounds is the intense absorption of the coloured form in the visible region. This is of great importance for practical applications of spiropyrans in display and photochromic memory systems.[62] Spiro compounds, due to their equilibrating cyclic and acyclic structures, are well established as photochromic materials.[63–67]

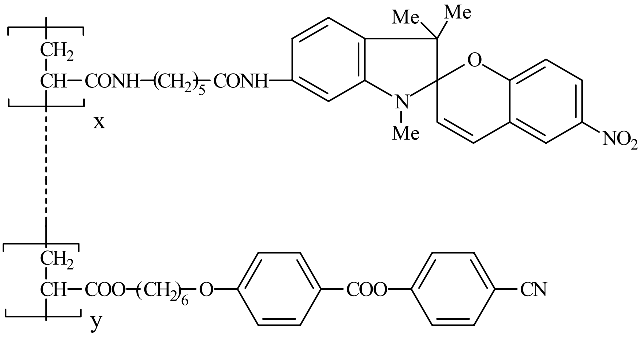
The spiro compounds exhibit photochromism when irradiated by photons. These characteristics have been exploited to study liquid crystals. Shragina et al.[68] have studied the photochromic molecules (**44**) and (**45**), which represent quasi-liquid crystals. The supercooled films of these compounds form blue merocyanine molecules on UV irradiation, which are spontaneously converted back into a non-coloured spiro-oxazine form in the dark.



44: R = OMe

45: R = C$_7$H$_{15}$

The side-chain liquid-crystal polymers (**46**), (**47**) and (**48**) contain mesogenic and photochromic groups.[69,70] The photochromic liquid-crystal polymers open up many possibilities in molecular engineering because the mesogenic and photochromic groups are more autonomous in this case.



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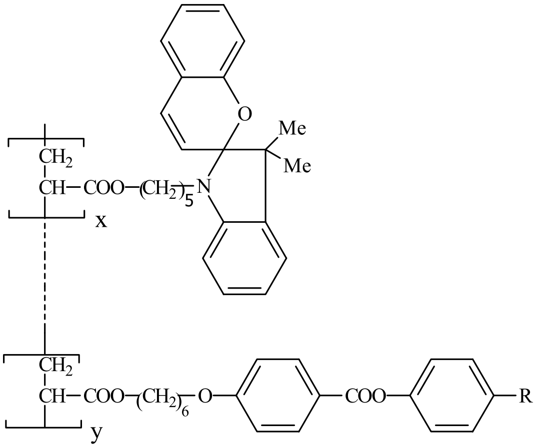

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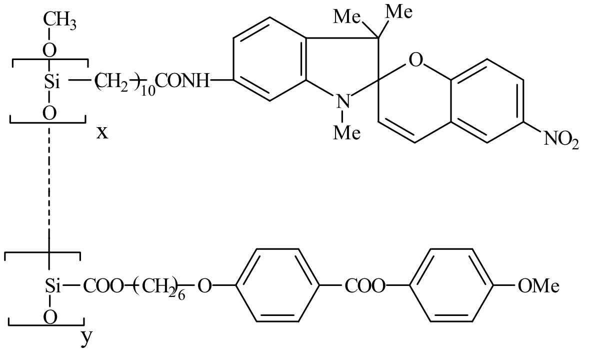
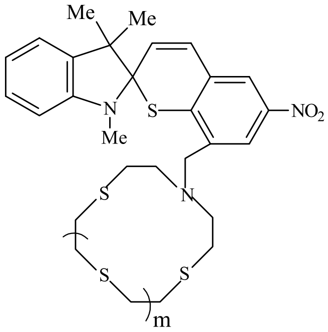


48

It has been reported that the incorporation of a crown ether moiety into a spirobenzopyran affords ion-responsive photochromic materials.[71] The spirobenzopyrans (**49**) and (**50**) showed a selective binding ability to Mg^{2+} and Ag^{+} with negative and positive photochromism, respectively. Among the metal ions, only Ag^{+} facilitated photoisomerisation to the corresponding merocyanine form.[72] In the case of the spirobenzopyran **51**, thermal isomerisation and facilitated photoisomerisation to the merocyanine form were observed in presence of Ag^{+}.



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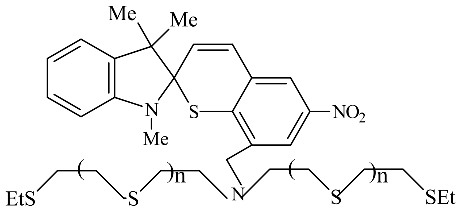

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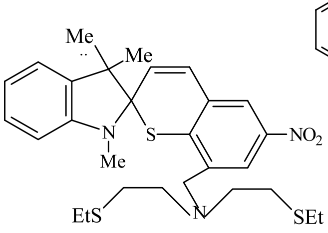

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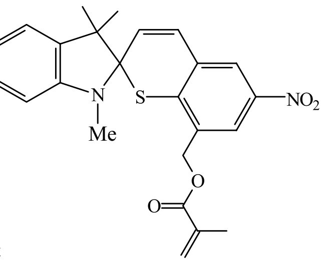


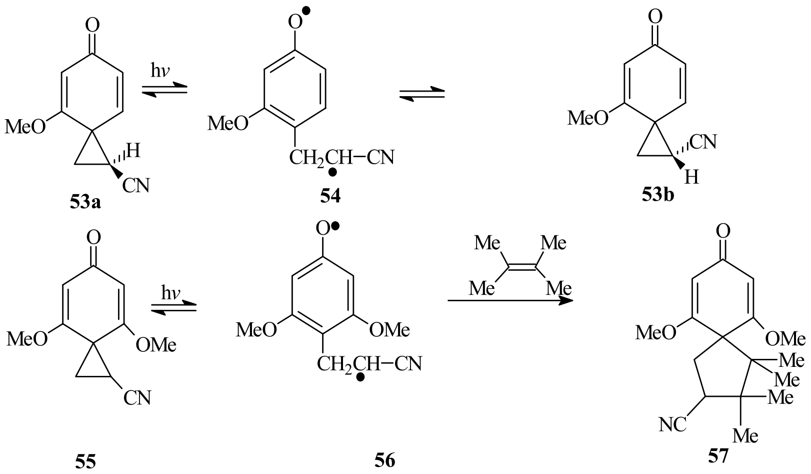
52

Masafumi et al.[73] have reported that, on exposure of the spirobenzothiapyran **52** to UV light in polar solvents like methanol and acetone, the light-yellow solution turned to blue-green. The colour was spontaneously bleached at room temperature when the irradiation was turned off.

Photolysis of the spiro compound (**53**) results in photoisomerisation via the nitrile-stabilised biradical (**54**). Photolysis of the dienone (**55**) in the presence of tetramethylethylene gave the spiro compound (**57**)[74] through the biradical (**56**), as shown in Scheme 2.

4. Synthesis

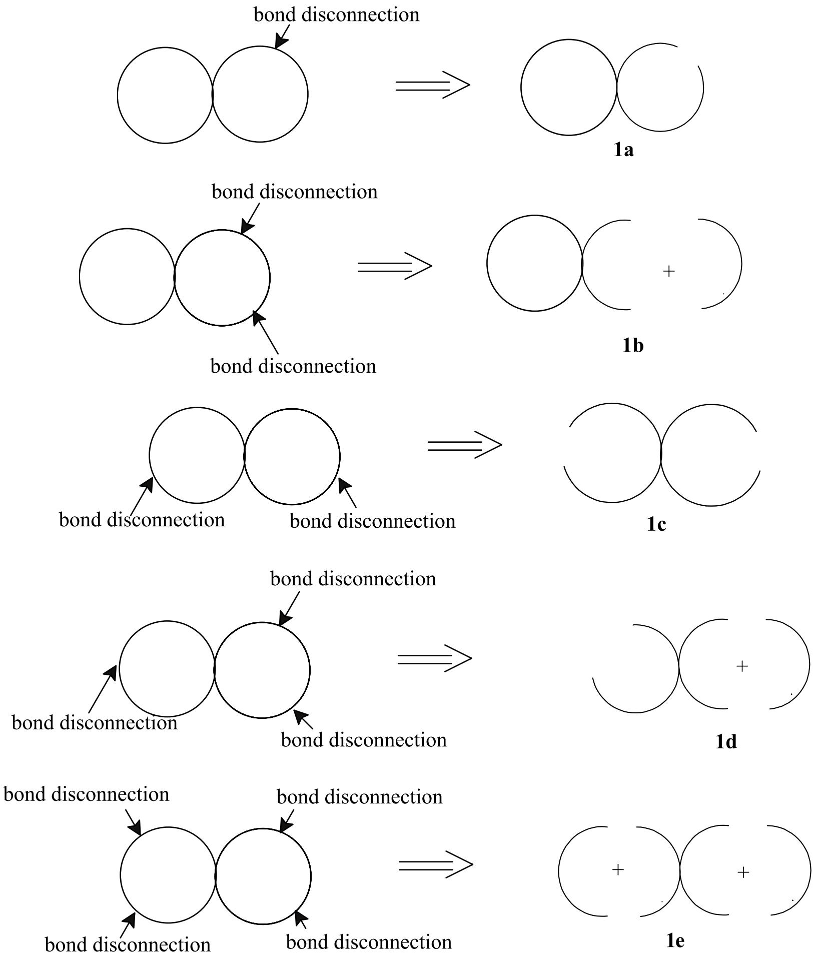
A spiro compound contains two rings fused at a common point, mostly a carbon atom. The antithetic analysis of a spiro unit may result in a large number of possible prestructs, which can be used for the synthesis of target spiro molecules. The analysis can be undertaken by bond disconnection either at branch appendages (bond other than exocyclic) or ring appendages (exocyclic bond) or at both.[75] The process leads to the prediction of several synthon components, which include cyclic compounds on which a spiro unit can be generated or acyclic derivatives, which can cyclise to yield the target spiro compound.



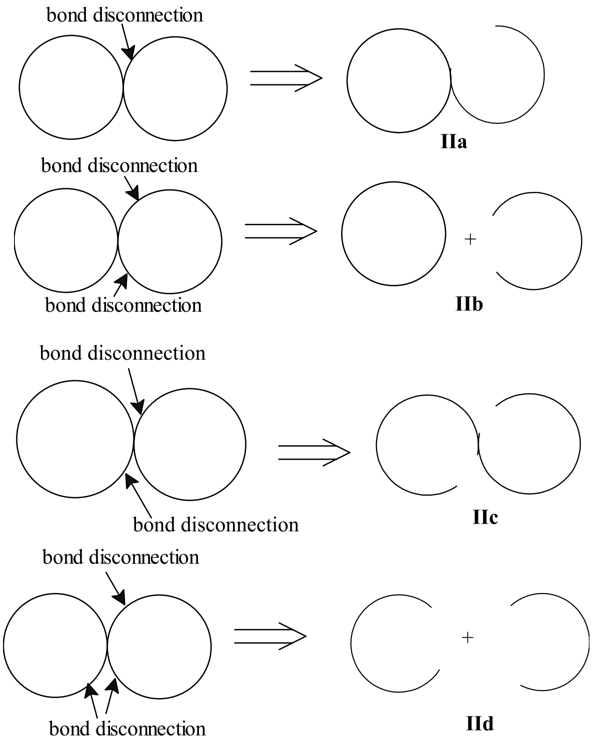
Scheme 2.

4.1. Antithetic analysis of spiro unit

4.1.1. Cleavage at branch appendage(s). Bond disconnection at a bond of any ring of the spiro unit other than exocyclic will lead to a prestruct (**Ia**) having a single synthon component with a ring and two alkyl units. In prestruct **Ia**, the cyclisation may occur due to the reconnection of the terminal point of the pendant alkyl groups to achieve the target. Bond disconnections at two branch appendages in a single ring lead to the prestruct (**Ib**) with two synthon components, one being similar to **Ia** and the other an alkyl unit. Bond disconnection at branch appendages in both rings results in the generation of acyclic prestructs (**Ic**, **Id** and **Ie**). Prestruct **Ic** may have a single synthon component, whereas **Id** and **Ie** may have two and three acyclic components, respectively (Scheme 3).



Scheme 3.

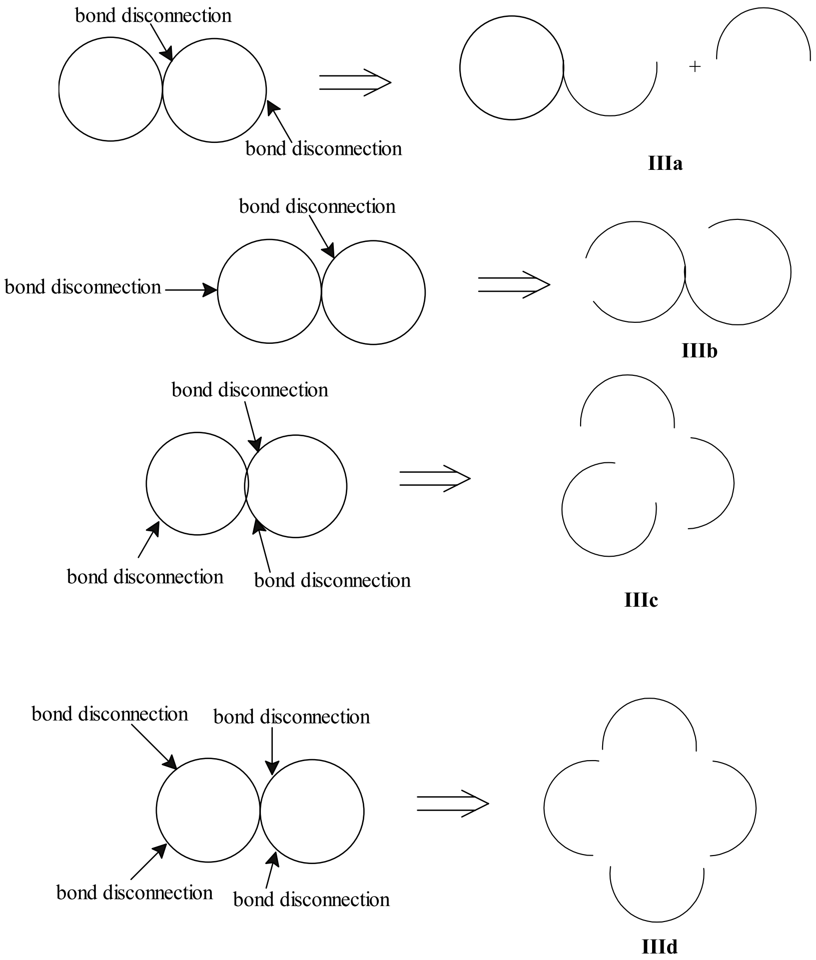


Scheme 4.

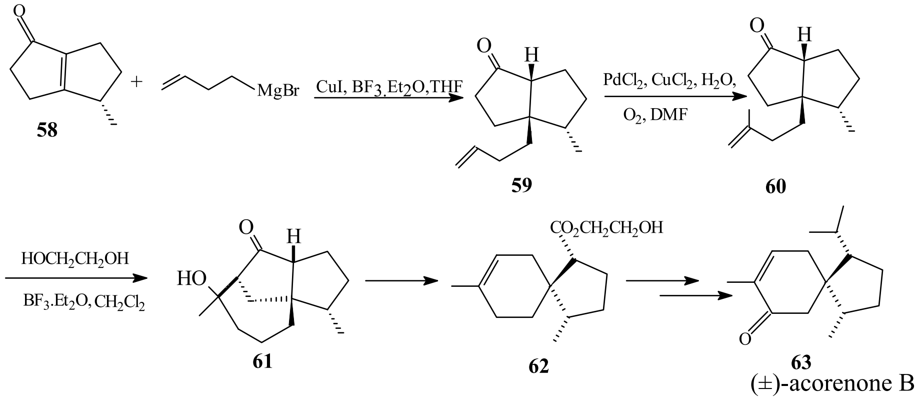
4.1.2. Cleavage at ring appendage(s). A spiro compound has four ring appendages having the possibilities of four types of bond disconnections (Scheme 4). A single bond disconnection in a single ring will lead to the formation of a prestruct (**IIa**) having a synthon component with a ring attached with a pendant alkyl group. Bond disconnection at two ring appendages of a single ring generates a prestruct (**IIb**) with two synthon components, one being a ring and the other an alkyl group. From this prestruct, the synthesis may occur either in a single step or in a tandem synthesis involving two steps. Disconnection at two ring appendages in two different rings may lead to an acyclic prestruct (**IIc**), which contains all the atoms of the spiro-skeleton. The target molecule can be synthesised either in a single step or in a two-step process.

Three bond disconnections, two at one ring and one at the other ring, lead to the prestruct (**IId**) with two acyclic alkyl groups.

4.1.3. Disconnection at both branch and ring appendage(s). Bond disconnections at a ring appendage and a branch appendage in a single ring lead to the prestruct (**IIIa**) having synthon components, a ring with a pendant alkyl group and an acyclic alkyl fragment. Two bond disconnections in two different rings at one ring appendage and the other at branch appendage will lead to a prestruct (**IIIb**) with



Scheme 5.



Scheme 6.

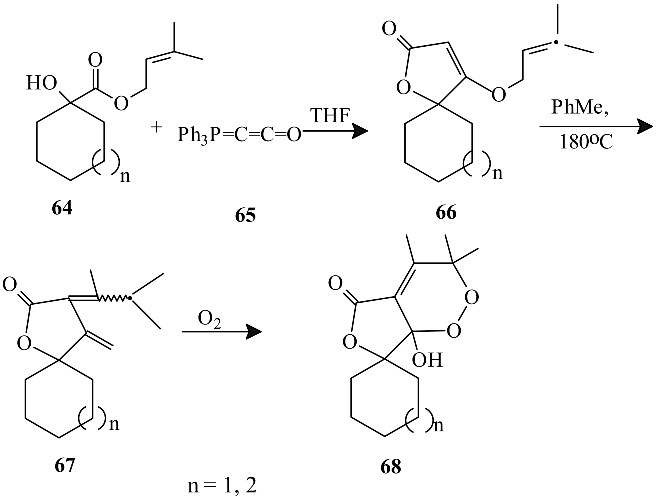
an acyclic synthon component having a branched alkyl group. Cleavage at two ring appendages and one branch appendage gives rise to the prestruct (**IIIc**) with all alkyl synthon components, while disconnections at two ring and two branch appendages engender a prestruct (**IIId**) with four synthon components (Scheme 5).

4.2. Synthesis of spiro compounds by using prestruct Ia

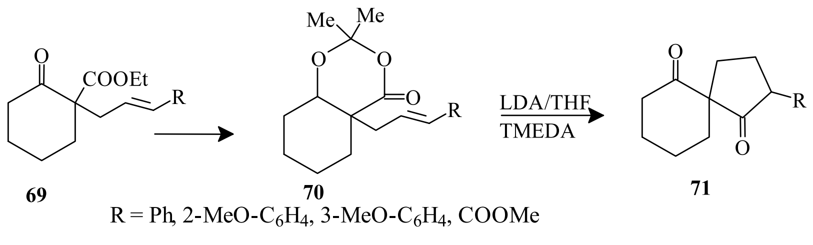
The prestruct **Ia** is due to bond disconnection at a branch appendage in a single ring. The corresponding synthon component has mostly a ring and two pendant alkyl groups attached at the carbon, which becomes the bridge head in the spiro nucleus. The synthesis of **63** from a spirogenic compound (**60**) is an example of the use of prestruct **Ia**. The synthon component **60**, obtained from **58** through an intermediate **59**, cyclises by an attack of a methylene unit on a carbonyl group to yield **61**, which, after derivatisation with ethylene glycol, cleaves to yield the spiro compound **62** and, on subsequent work up, produces (±)-acorenone B (**63**)[76] (Scheme 6).

Schobert and co-workers[77] have reported the synthesis of spirodiones **68** by using an α-hydroxy allyl ester (**64**) as the ring synthon component. Intramolecular Wittig olefination between **64** and the phosphorous ylide (**65**) afforded **66**. Heating a solution of **66** in toluene to 180 °C in a sealed glass tube yielded **67**, which undergoes autoxidation to the hemiketal endoperoxide (**68**) (Scheme 7).

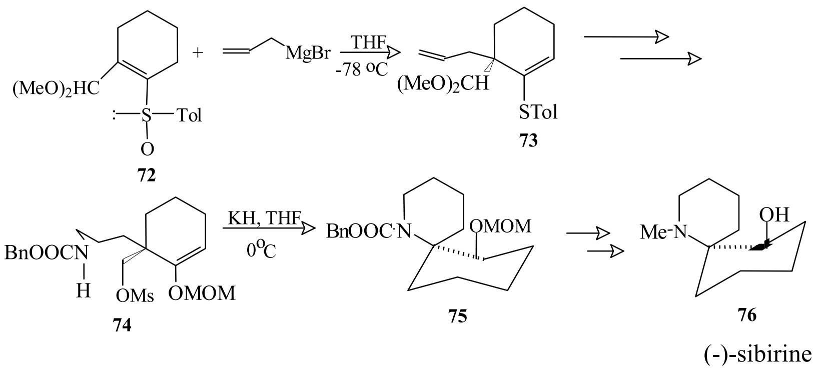
A convenient synthesis of spirodiones **71** has been achieved by a one-pot tandem cyclisation–elimination process starting from the allyl-lacto acetals **70**, prepared from the commercial ethyl 2-cyclohexanone carboxylates (**69**)[78] (Scheme 8).



Scheme 7.



Scheme 8.



Scheme 9.

(−)-Sibirine (**76**) was synthesised from a chiral sulphoxide (**72**) used as a synthon component. The sulphoxide **72** was converted into **73** by the reaction of allylmagnesium bromide and subsequently into **74**. The key transformation for this purpose was the conjugate addition Pummerer reaction[79] involving the transformation of **74** into spiro compound **75** (Scheme 9).

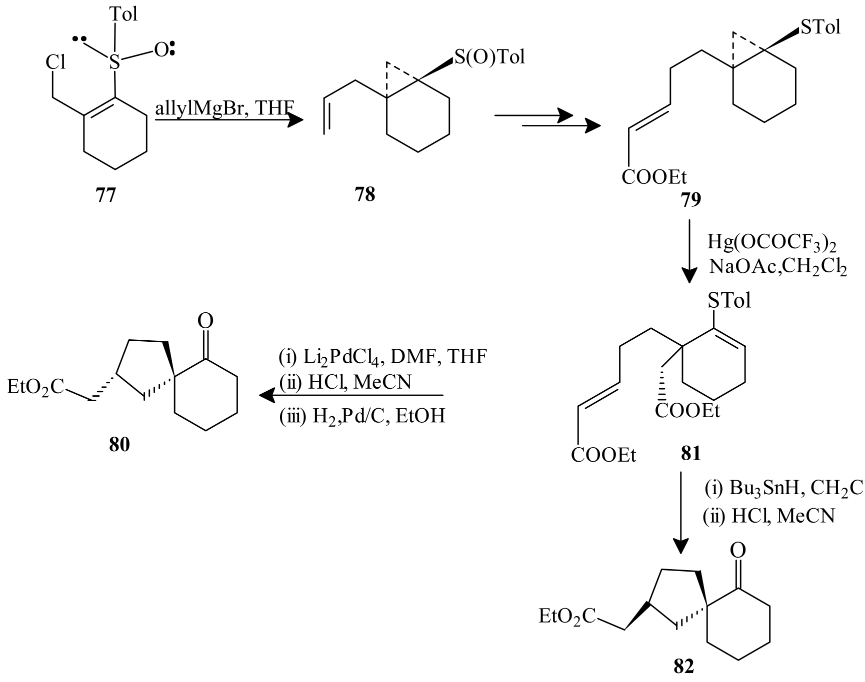
When the chiral sulfoxide **77** was used instead of **72**, the spiro compound **78** was formed as a single stereoisomer on reaction with allylmagnesium bromide. Compound **78** was converted into **79** on treatment with mercuric(II) trifluoroacetate, which underwent ring opening to form **80** in high yield. The spirodecanes **81** and **82** have been prepared from **80**, as shown in Scheme 10.

Sharma et al.[80] have achieved the synthesis of spiro carbon-linked disaccharides (**86**) and (**87**) starting from a chiral ketone (**83**) and furan through **84** and **85**, as shown in Scheme 11.

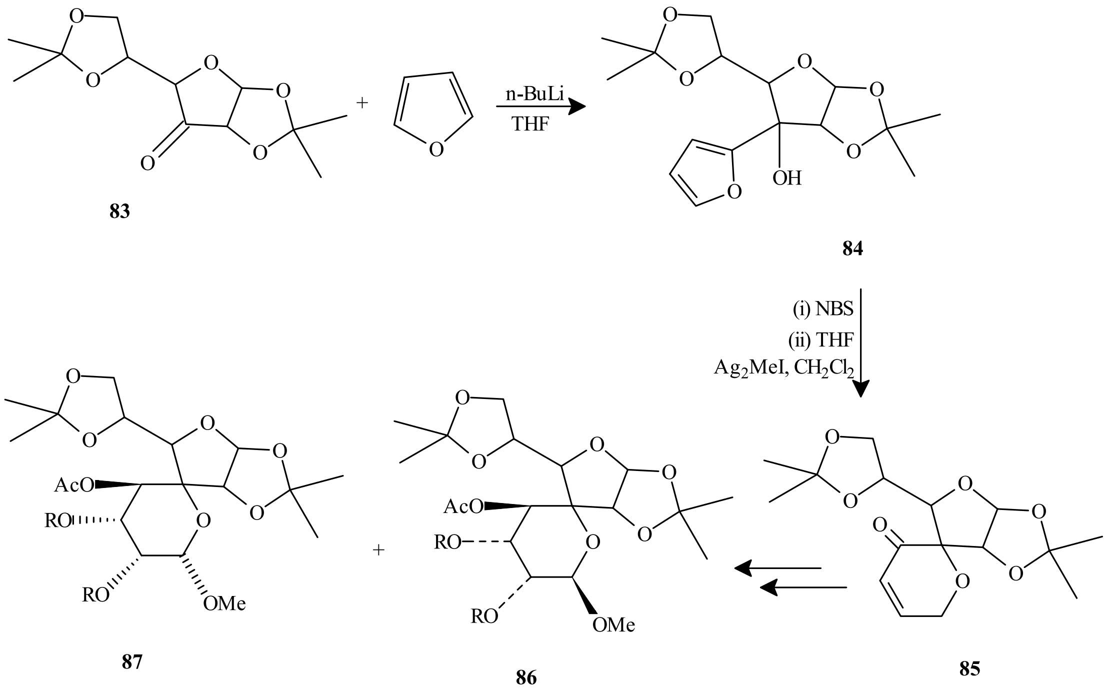
Ortho-substituted aminobenzenes (**88**) were used to synthesise spiro compounds containing a 2,3-dihydroindole unit (**89**), which occurs in the intermediates for the synthesis of *Aspidosperma* alkaloids, by using a steroselective 1,5-electrocyclisation, which can be brought about thermally or by deprotonation[81] using *t*-BuOLi and *t*-BuOH (Scheme 12).

Zubkov et al.[82] have synthesised the spiro compounds (**94**) and (**95**) by Wagner–Meerwein rearrangement of the diepoxy derivatives (**93**). Compound **93** was synthesised from furfurylamine (**90**) and cycloalkanones through **91** and **92**, as shown in Scheme 13.

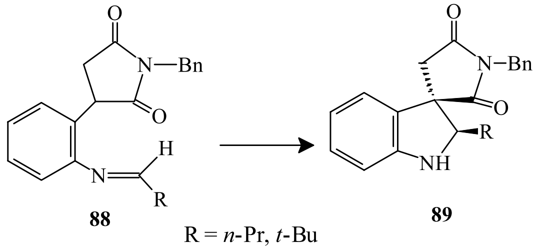
Cossy et al.[83] have used a cyclic α-keto ester as the synthon component for the synthesis of spirodiols **98**. The alkylation



Scheme 10.



Scheme 11.

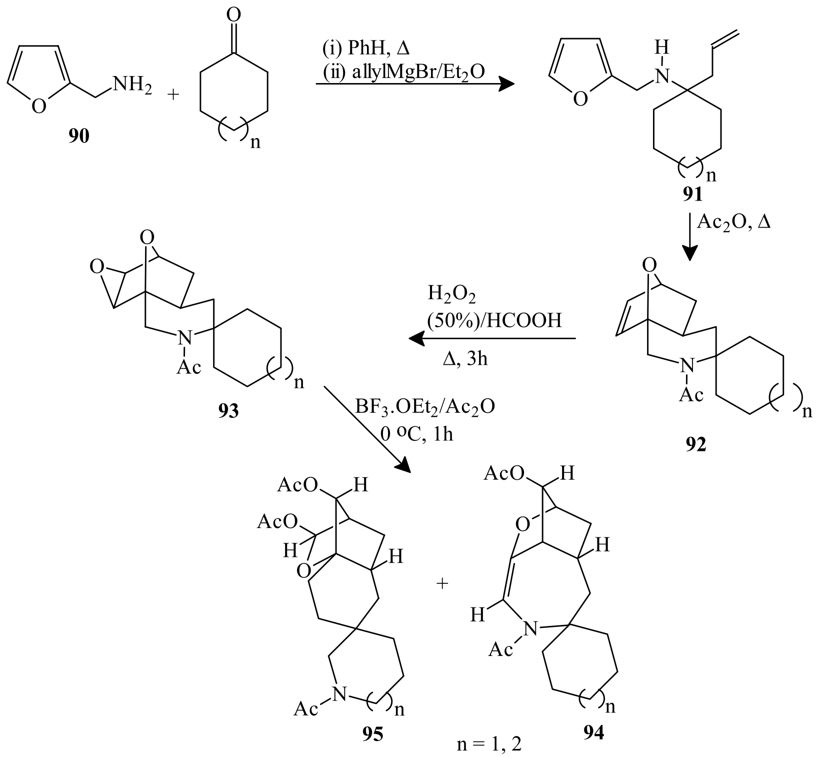


Scheme 12.

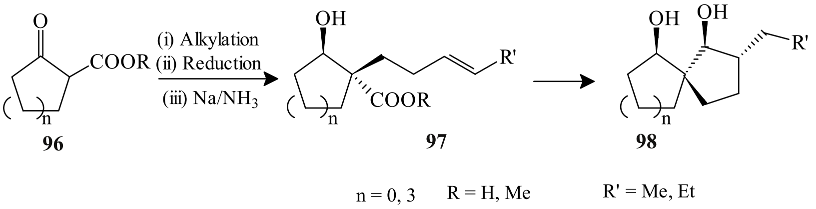
and reduction of **96** generated the hydroxy esters **97**, which, on cyclisation, furnished the spirodiols **98** (Scheme 14).

4.3. Synthesis of spiro compounds by using prestruct Ib

The prestruct **Ib** is due to the bond disconnection at two branch appendages of one ring in the spiro unit. Therefore, the synthon component has one ring unit similar to prestruct **Ia** and the other an alkyl unit. A number of spiropyrans were synthesised by Padmavathi et al.[84] using prestruct **Ib**. They



Scheme 13.



Scheme 14.

have taken the 2,6-diaryl-4,4-disubstituted-4*H*-pyrans (**102**) and (**109**) as the synthon components. The synthesis of **102** and **109** were achieved by the reaction of **99** with **100** and **107**, respectively, through the formation of **101** and **108**, respectively. Cyclocondensation of **102** and **109** with $NH_2NH_2\cdot H_2O$, $NH_2OH\cdot HCl$, NH_2CONH_2 and NH_2CSNH_2 in the presence of base afforded the desired spiro compounds **103–106** and **110–113**, respectively, as shown in Schemes 15 and 16.

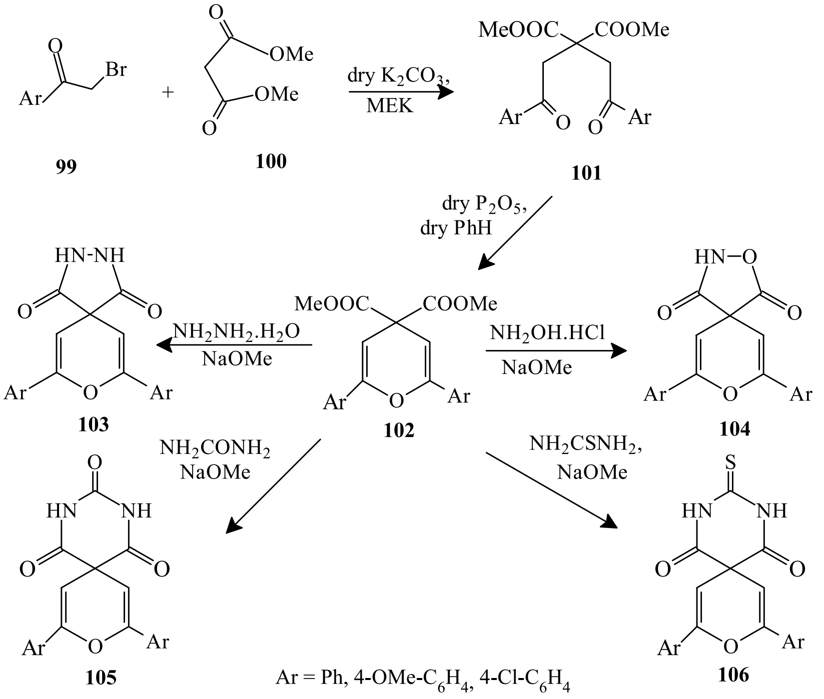
Prestruct **Ib** was also used by Coelho et al.[85] for the synthesis of spiro[thioxanthene-napththopyrans] (**116**). The spiro compounds were synthesised from substituted naphthols (**115**) and an intermediate, obtained from thioxanthone (**114**), using a one-step reaction (Scheme 17). The photochromic properties of these compounds were studied under flash photolysis and continuous irradiation.

Kurth and co-workers[86] have reported the synthesis of spiro-fused (C_5)-isoxazolino-(C_4)-pyrazolones(1-oxa-2,7,8-triazaspiro[4,4]-2,8-nonadien-6-ones) **119**, by using β-ketoesters (**117**) as the ring synthon component. The reaction of **117** with hydrazine results in the intermediate hydrazone **118**. This hydrazone undergoes cyclo-elimination to give the isoxazolinopyrazolones (**119**) (Scheme 18).

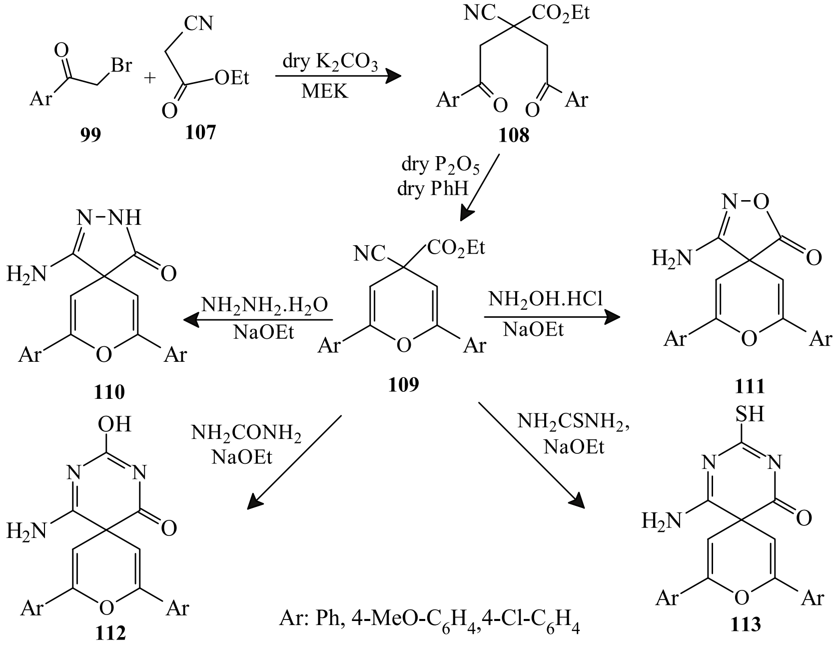
4.4. Synthesis of spiro compounds by using prestruct Ic

Bond disconnection at branch appendages of two different rings engenders prestruct **Ic**. The corresponding synthon component is an acyclic branched compound having a quaternary carbon. The synthesis of 4,9-dimethylspiro[4.4]-nonane-2,7-dione (**125**) is an example of the use of prestruct **Ic**. The synthon component **120** was synthesised from acetylacetone. The 4-pentenal (**121**) was formed from **122** by monoacetylation and subsequent oxidation. The compound **123** undergoes Rh-mediated cyclisation twice to form the desired spirodiketone (**124**)[87] (Scheme 19).

The tricyclic sila-alkane (**128**)[88] and bicyclic sila-alkane (**129**) were synthesised from bis(phenylethynyl)-silanes (**126**) through an intermediate (**127**), as shown in Scheme 20.

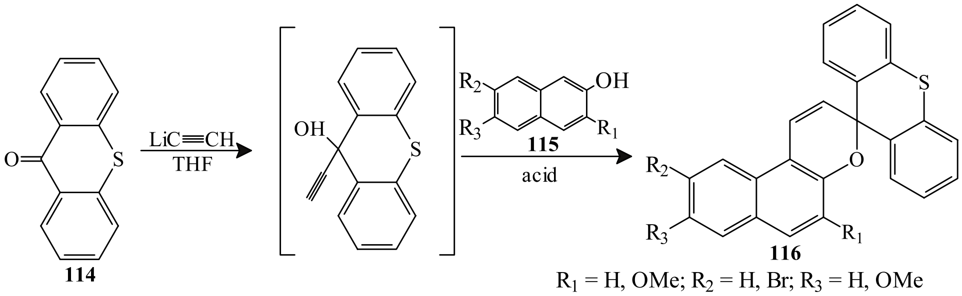


Scheme 15.



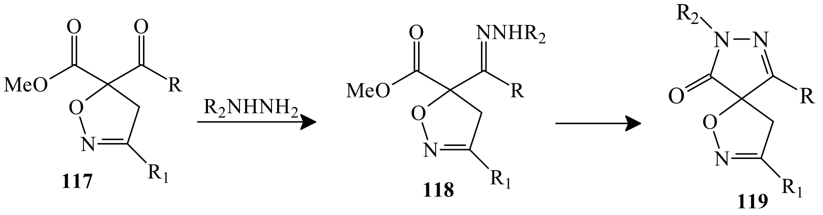
Ar: Ph, 4-MeO-C_6H_4,4-Cl-C_6H_4

Scheme 16.



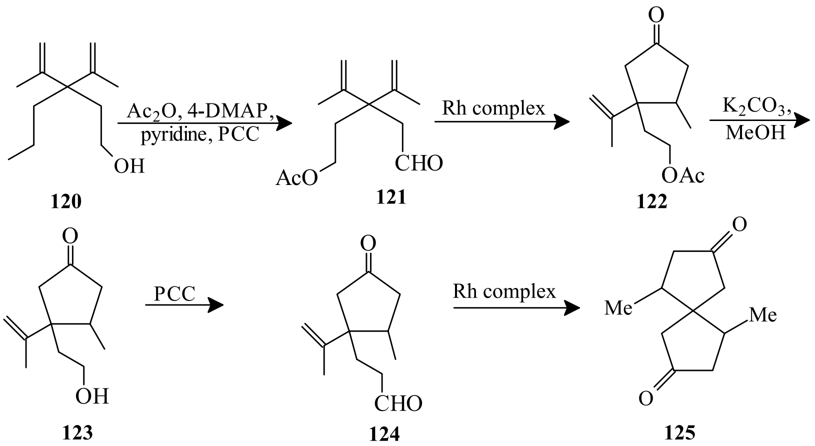
R_1 = H, OMe; R_2 = H, Br; R_3 = H, OMe

Scheme 17.

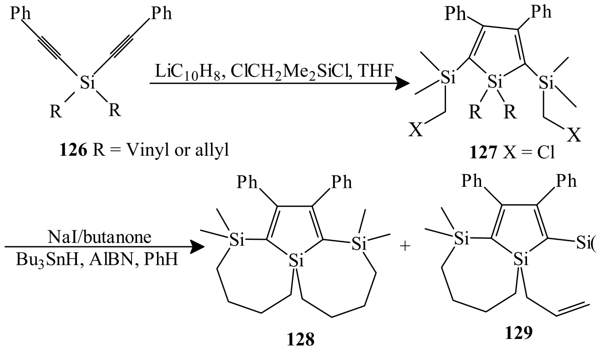


R = Me, Et, Ph, 4-MePh, 4-MeOPh
R_1 = 2-Ph, 4-MeOPh ,2-pyridyl,2-(4-BrBnO)Ph
R_2 = H, Me, Ph, Bn, 4-MeOPh

Scheme 18.



Scheme 19.



Scheme 20.

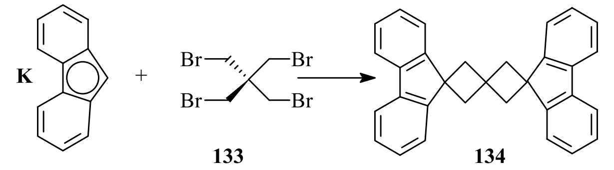
4.5. Synthesis of spiro compounds by using prestruct Id

The prestruct **Id** is due to bond disconnections at three branch appendages of two rings, that is, two bond disconnections at one ring and the third bond disconnection at the other ring. In this case, one of the synthon components is similar to prestruct **Ic** and the other component is an alkyl unit. To the best of our knowledge, no report is available describing the synthesis of spiro compounds by using synthon components corresponding to prestruct **Id**.

4.6. Synthesis of spiro compounds by using prestruct Ie

When the bond disconnections take place at four different branch appendages, the prestruct **Ie** is generated. An example of the use of prestruct **Ie** is the synthesis of spirobiscalix[4]crowns (**132**) from the synthon components **130** and **131**, as shown in Scheme 21.[89]

Moll et al.[90] have also used pentaerythrityl tetrabromide (**133**) as one of the synthon components for the synthesis of spiro[3,3]heptane-2,6-dispirofluorene (**134**) (Scheme 22).



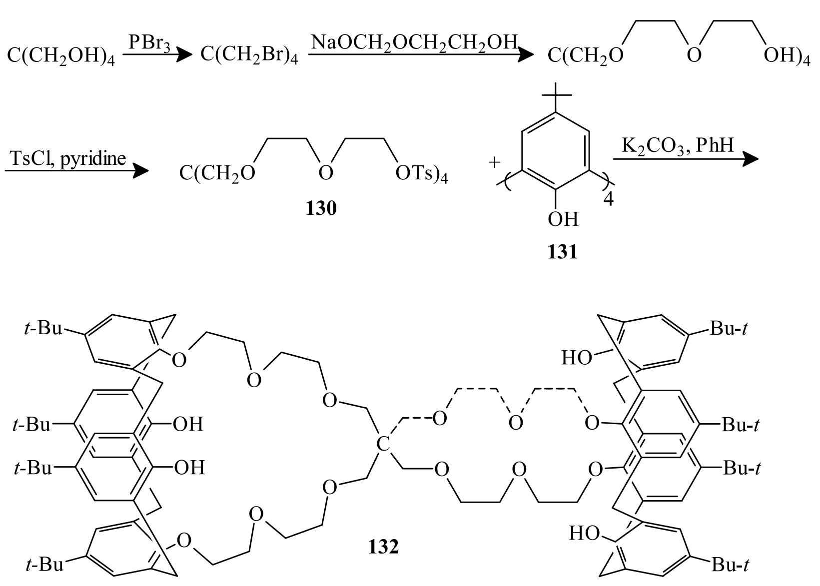
Scheme 22.

The novel spiro-compounds (**139a–f**) have been prepared by Schulte et al.[91] using pentaerythrityl tetrabromide as the synthon component. The synthesis has been carried in three steps by one-pot oxidative coupling of guaiacol (**135**) and 1,2-dialkoxybenzenes (**136a–f**), followed by dimethylation of triphenylenes (**137**) to **138** and subsequent etherification with tetrabromide (Scheme 23).

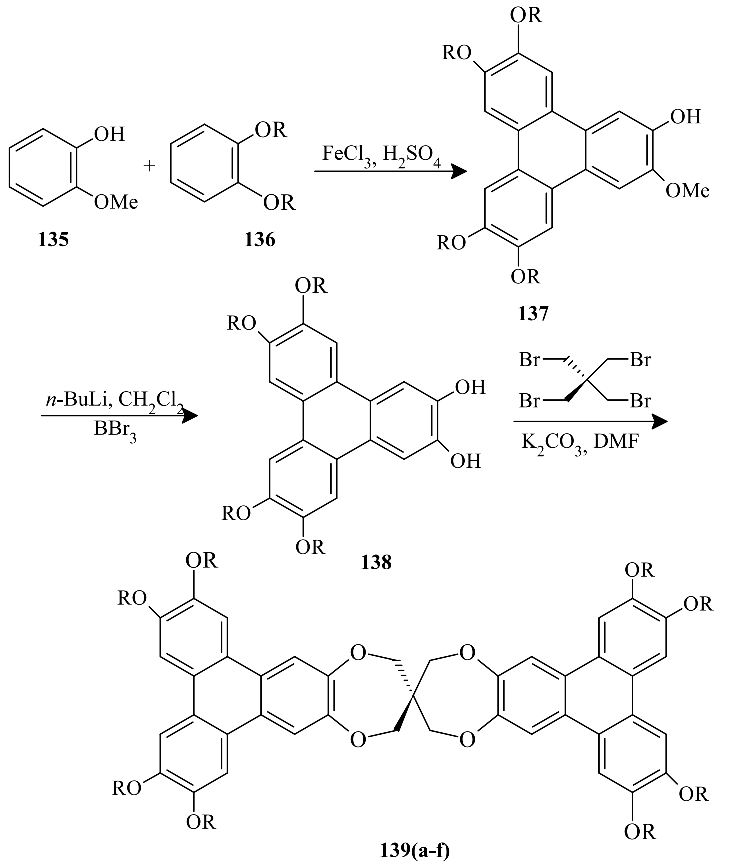
4.7. Synthesis of spiro compounds by using prestruct IIa

The prestruct **IIa** is due to bond disconnection at a ring appendage in one ring. The corresponding synthon component has mostly a ring and an alkyl group attached at carbon, which subsequently becomes the spiro centre. Prestruct **IIa** is used in the synthesis of (−)-perhydrohistrionicotoxin from **142**. The synthon component **142**, an amine, was synthesised from **140**. Hydrolysis of the thioketal moiety of **140** by treatment with *N*-chlorosuccinimide (NCS) and silver nitrate gave **141**, which was treated with triphenylphosphine to yield **142**. Spirocyclisation of **142** was carried by treatment with dichlorotitanium(IV) diisopropoxide to furnish the spirocycle **143**. Catalytic hydrogenation of the double bond in **143** resulted in perhydrohistrionicotoxin (**144**) (Scheme 24).[92]

A number of tetraazaspiro[5,5]trione compounds (**146**) or (**147**) were synthesised from **145** in the presence of diethyl azodicarboxylate (DEAD) or NCS or *N*-bromosuccinimide

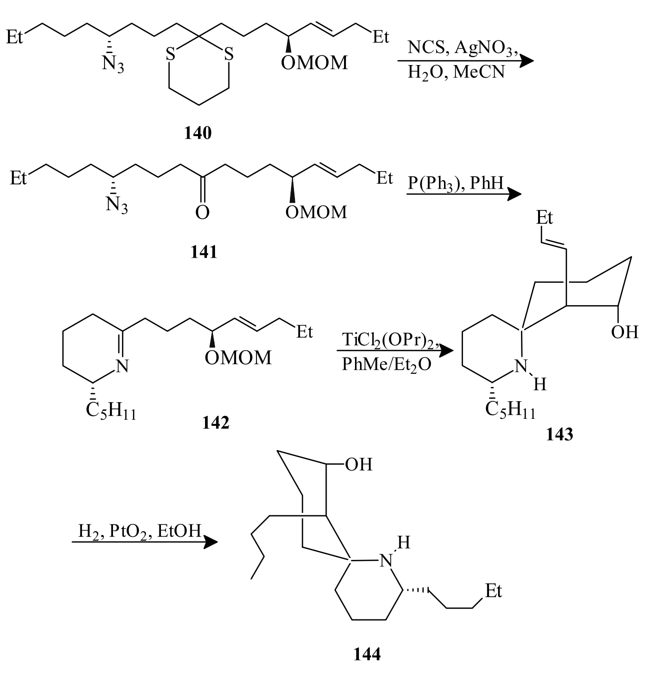


Scheme 21.



a : R = C_5H_{11} ; b : R = C_6H_{13}; c : R = C_7H_{15}; d : R = C_8H_{17} ; e : R = C_9H_{19}; f : R = $C_{10}H_{21}$

Scheme 23.



Scheme 24.

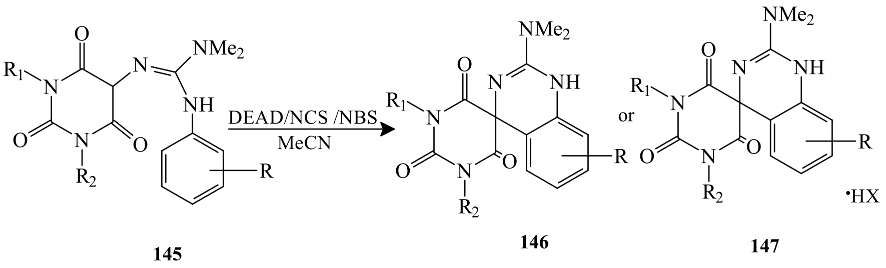
(NBS) as dehydrogenating agents. The compounds **145** were synthesised from barbituric acid (Scheme 25).[93]

Kido et al.[94] have developed a new method for the synthesis of (+)-acorenone B (**151**) through a spiro compound (**150**) based on spiroannulation of a cyclic arylsulphonium ylide (**149**) obtained from the diazo ketoester **148** (Scheme 26).

Prestruct **IIa** has been used by Pigge et al.,[95] who have synthesised novel cyclohexadienyl azaspirocyclic ruthenium complexes (RuCP) (**153**) by using the corresponding *N*-benzyl acetoacetamide derivatives (**152**) as the synthon component. Demetalation of 153 to provide **154** has been accomplished by several oxidants, out of which $CuCl_2$ proved to be the most efficient (Scheme 27).

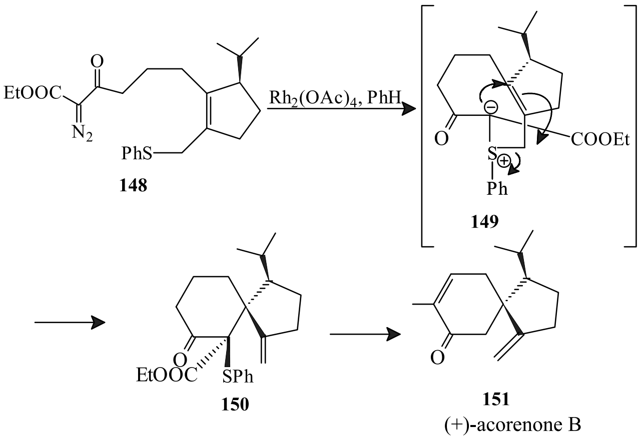
A synthon component corresponding to prestruct **IIa** has been used to form stabilised Meisenheimer-type salts[96] (**156**) by anionic spirocyclisation of 3-nitro-4-(2-hydroxyphenoxy)-2*H*-1-benzopyran-2-ones (**155**) (Scheme 28).

Spiro-oxindoles (**159**) and (**160**) have been synthesised from acryloyl-2′-iodoanilide (**158**) by an asymmetric Heck reaction[97] using BINAP (**157**). The synthon component



R = H, 2'-Me, 3'-Me, 4'-Me, 2',3'-(Me)$_2$, Et, OMe, 2',3',4'-(OMe)$_3$;
R$_1$ = Me; R$_2$ = H, Me; X = Cl, Br

Scheme 25.



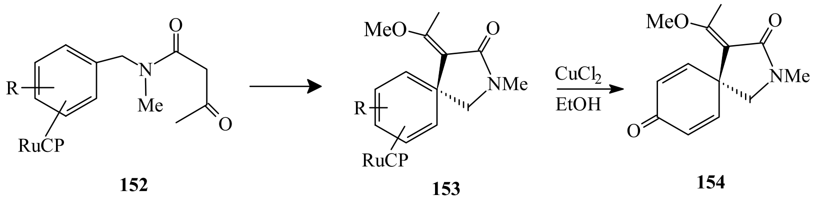
Scheme 26.

158 undergoes palladium catalysed cyclisation to form the dispiro compounds (**159**) and (**160**), as shown in Scheme 29.

The formation of spiro [4.4] compounds **163** and **164** has been achieved by Mori et al.[98] by enantioselective spirocyclisation of the diene **161** in the presence of a catalyst **162** (Scheme 30).

Pearson et al.[99] have explored the possibility of making thiol lactones (**167**) starting from an iron-complexed allyl thio ester (**165**) through corresponding spiro intermediate (**166**) as shown in Scheme 31.

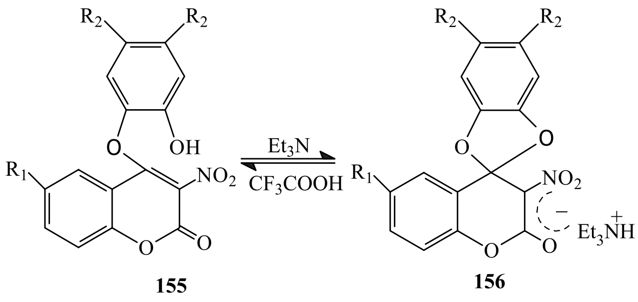
In an effort to synthesise the biologically active spiro alkaloids, nitramine, isonitramine and sibirine, Cossy et al.[100] have chosen β-ketoamide (**168**) as a synthon component of the prestruct **IIa** for the preparation of chiral lactams (**171**) and (**172**). The ketoamide (**168**) was heated with 1 equiv of manganese(III) acetate in ethanol and a mixture of imines (**169**) and (**170**) was produced. These latter imines have been separated and hydrolysed with aqueous acetic acid to afford the spiro-lactams (**171**) and (**172**) (Scheme 32).



R = H, OMe

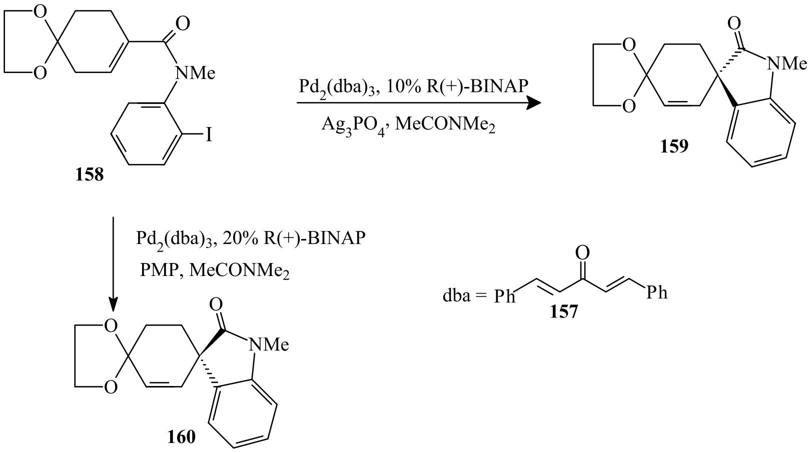
Scheme 27.

A recent approach reported by Simpkins[101] involves the use of prestruct **IIa** to generate a range of spirocyclic ethers **174** of different ring size. Intramolecular conjugate addition of an alkyl radical derived from the phenylselenyl compound (**173**) to an enone system afforded the desired spiro ethers **174** (Scheme 33).

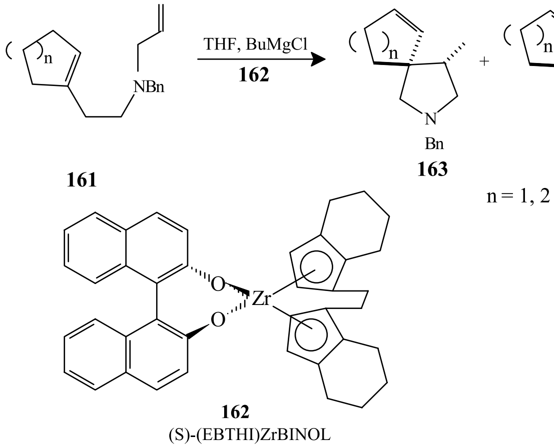


R$_1$ = H, NO$_2$; R$_2$ = H, Cl

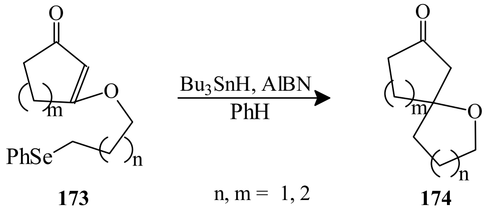
Scheme 28.



Scheme 29.

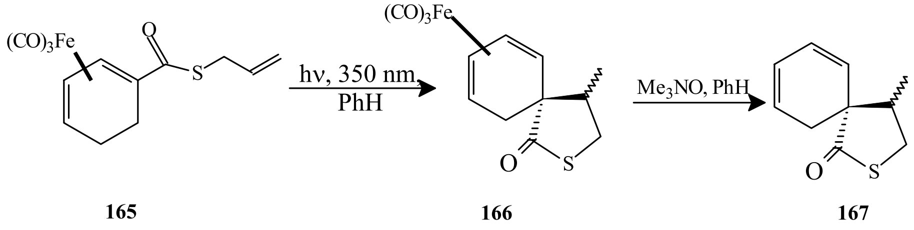


Scheme 30.

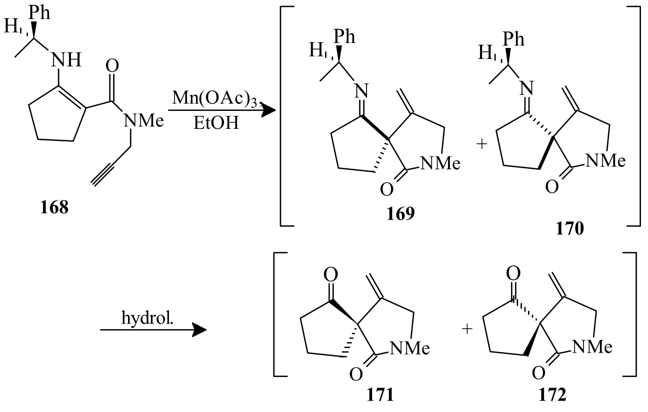


Scheme 33.

Martin-Lopej and Bermezo.[102] have described the synthesis of the 1,6-diazaspiro[4.5]decane (**178**) and 6-aza-1-oxaspiro[4.5]decane (**179**) systems by oxidative cyclisation of **176** and **177**, respectively, which are obtained from an N-substituted tetrahydropyridine derivative (**175**) (Scheme 34).

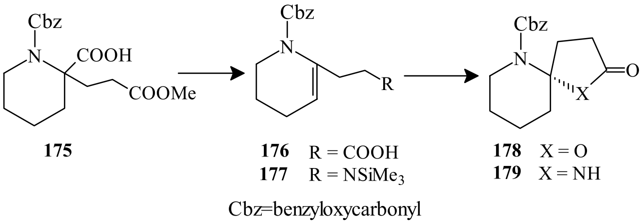


Scheme 31.

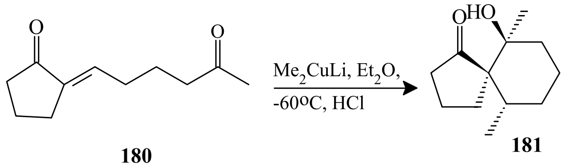


Scheme 32.

Naf et al.[103] have used an enone system **180** to prepare the spiro hydroxy ketone **181** in a single step. Conjugate addition of lithium dimethylcuprate to **180** and spontaneous intramolecular aldol condensation furnishes the desired spiro compound **181** with high yield (Scheme 35).



Scheme 34.

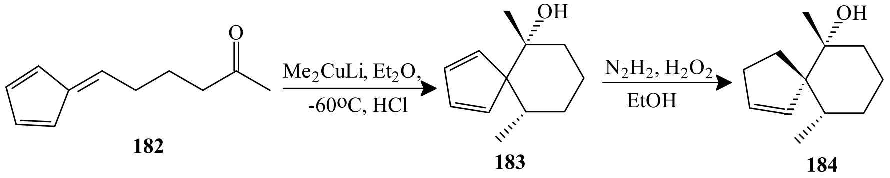


Scheme 35.

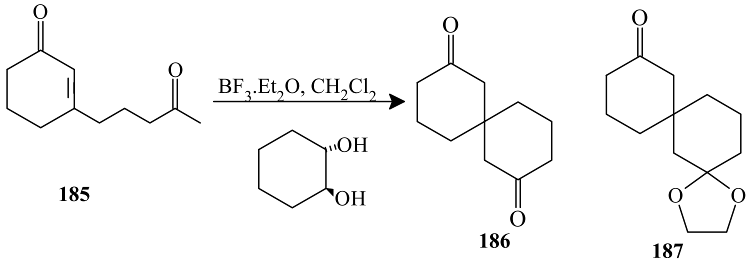
Similarly, Buchi et al.[104] have used a fulvene (**182**) to obtain a spiro compound **183** by using the same reagents, which, on subsequent treatment with N_2H_2 and H_2O_2 yields a single stereoisomer **184** in high yield (Scheme 36).

The synthesis of a spiro diketone (**186**) with good enantioselectivity (85%) has been achieved[105] from a cyclohexanone ring system **185** on treatment with a Lewis acid in the presence of optically pure (*S*,*S*)-cyclohexane-1,2-diol by way of a Michael addition mechanism. The reaction when carried out in the presence of ethylene glycol forms the spiro compound **186** (55% of yield) along with a minor product **187** (16% of yield)[106] (Scheme 37).

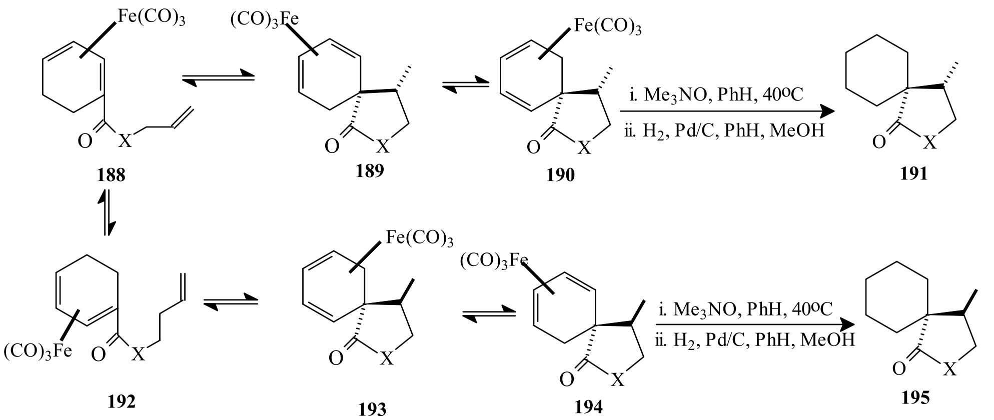
Iron-complexed allyl amides or esters (**188** and **192**) have been found to undergo thermally induced stereospecific spirocyclisation to afford spiro compounds (**189** and **190**, and **193** and **194**, respectively), which on further demetalisation resulted in formation of (**191**) and (**195**), respectively, as shown in Scheme 38.[107]



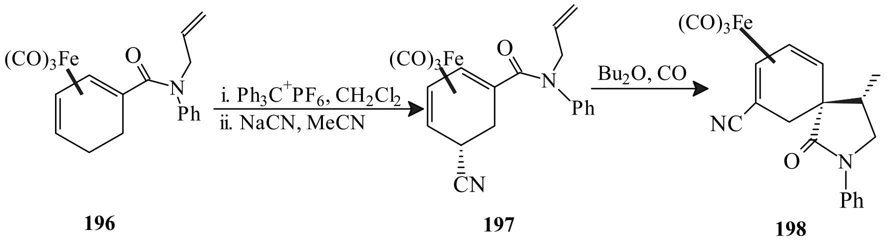
Scheme 36.



Scheme 37.



Scheme 38.

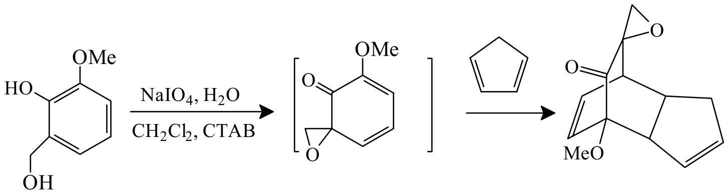


Scheme 39.

The products **190**, **194** and the starting material undergo competing rearrangements of the complexed diene unit. When the optically pure amide **196** was taken as the starting material, these competing processes were suppressed by incorporating an electron-withdrawing CN group at C_5 to form **197**, which yielded an enantiomerically pure spiro compound (**198**) (Scheme 39).

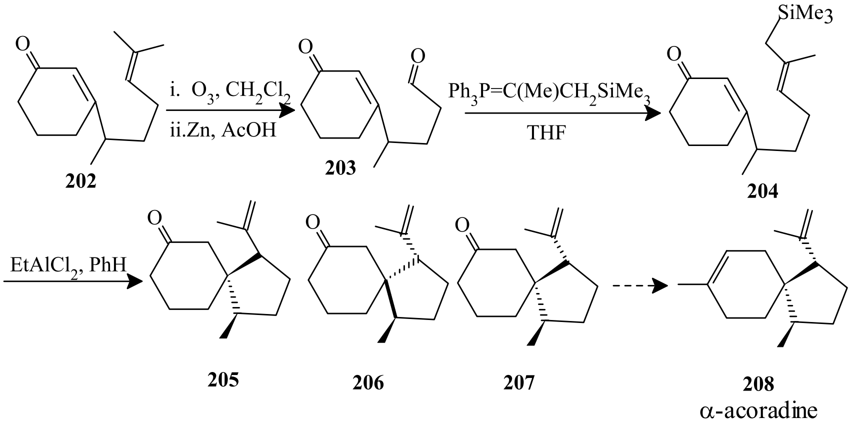
Singh[108] has also used prestruct **IIa** in the oxidation of *O*-vanillyl alcohol (**199**) with aqueous sodium meta-periodate to produce a spiro intermediate (**200**) in the presence of cyclopentadiene in a biphasic (CH_2Cl_2/H_2O) medium containing cetyltrimethyl ammonium bromide (CTAB) as a phase-transfer catalyst, furnished the adduct **201** in 70% yield (Scheme 40).

Yamamoto et al.[109] have synthesised α-acoradine (**208**) from a cyclohexane ring system **202** containing a long side chain by an intramolecular Sakurai–Hosomi reaction (Scheme 41). An allylsilane (**204**) has been made from **202** through an aldehyde intermediate (**203**) followed by cyclisation in the presence of ethylalumium dichloride to afford the spiro compounds (**205**), (**206**) and (**207**). Unfortunately, the stereoselectivity was poor and **207** is convertible into α-acoradine **208**.



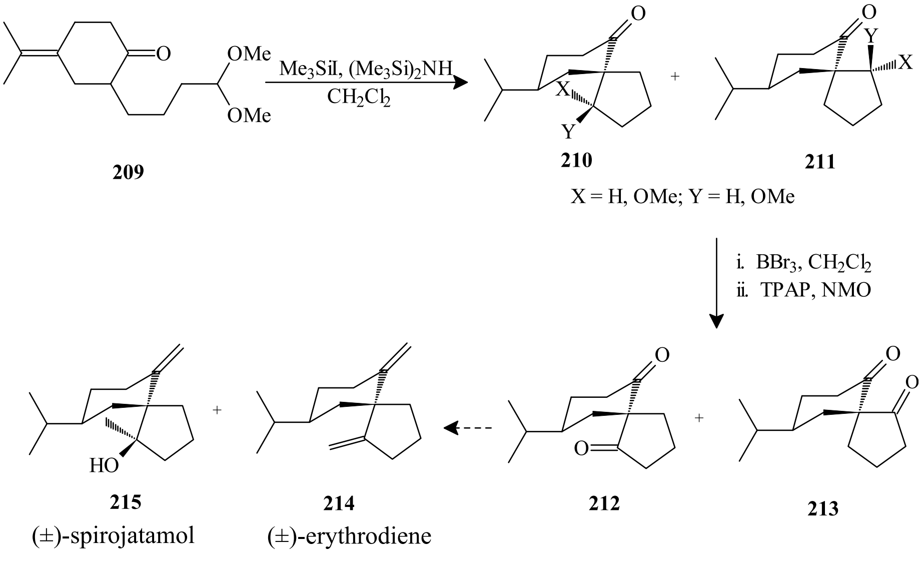
199 **200** **201**

Scheme 40.



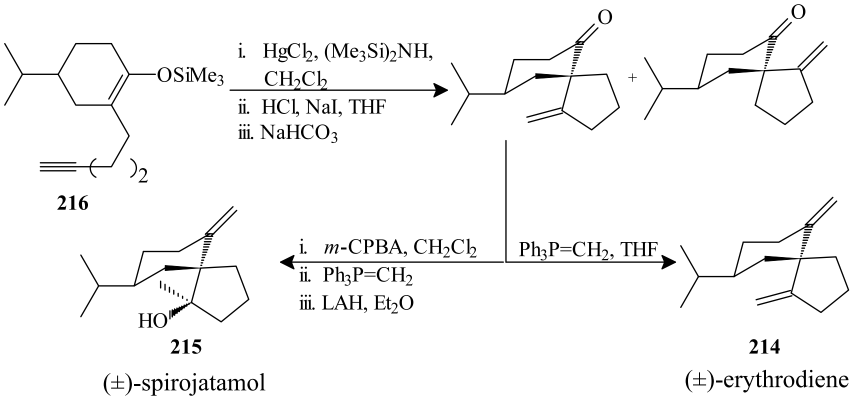
202 **203** **204** **205** **206** **207** **208**

Scheme 41.



209 **210** **211** **215** **214** **212** **213**

Scheme 42.



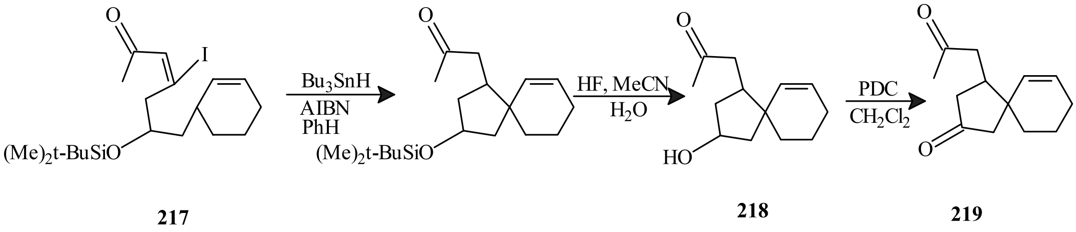
Scheme 43.

Ihara's group[110] has reported the synthesis of the sesquiterpenes (±)-erythrodiene (**214**) and (±)-spirojatamol (**215**) by the use of an intramolecular Mukaiyama aldol reaction, as shown in Scheme 42. The acetal **209** when treated with $Me_3SiI/(Me_3SiI)_2NH$ gave a mixture of **210** and **211**, which, on demethylation and oxidation, yielded the ketones **212** and **213**. These latter ketones have been converted into **214** and **215**.

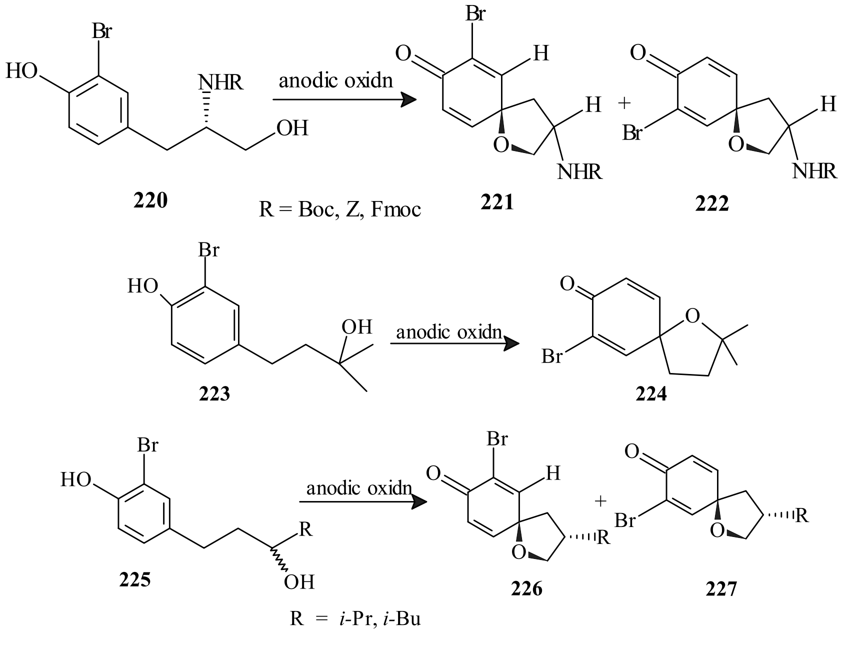
Another method was used for the synthesis of the sesquiterpenes (±)-erythrodiene (**214**) and (±)-spirojatamol (**215**) by Huang and Forsyth.[111] The precursor **216** when allowed to react with a mercuric salt followed by photodimerisation gave a mixture of spiroketones out of which one derivative was elaborated into **214** and **215**, as shown in Scheme 43.

Philip and Stephen[112] have reported the synthesis of a spirocyclic system (**219**) from the compound **217**, which was converted to the spiro compound (**218**) through a free radical approach, as shown in Scheme 44.

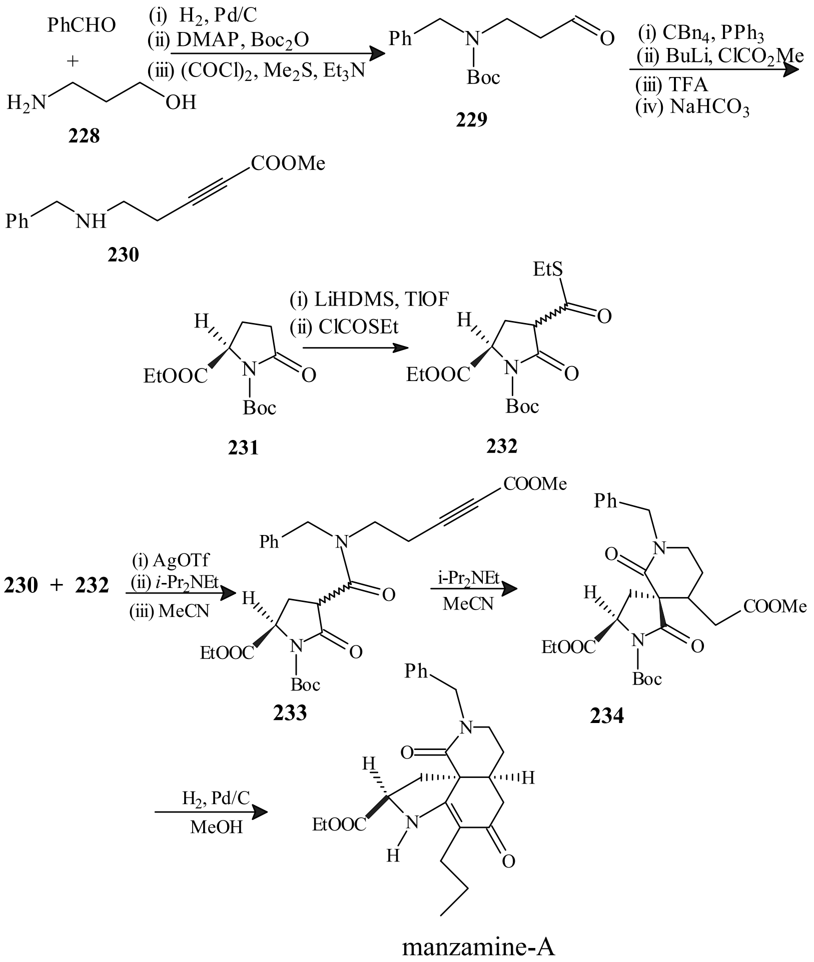
Nishiyama et al.[113] have constructed the spirodienones (**221**) and (**222**); (**224**); (**226**) and (**227**) by aniodic oxidation



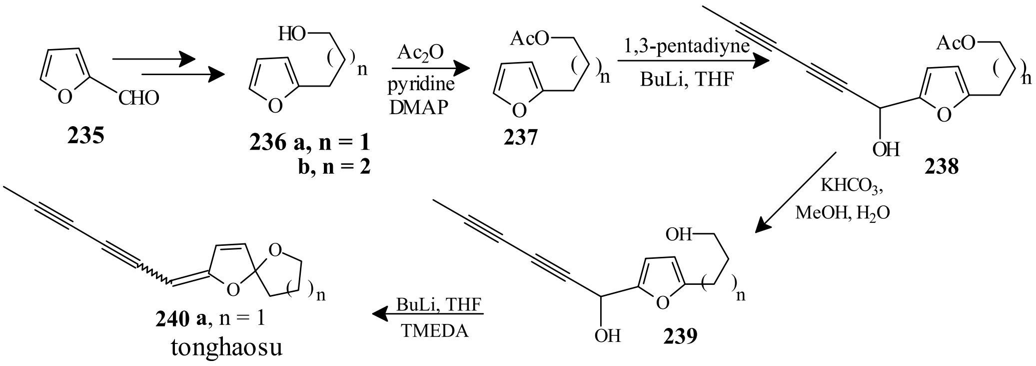
Scheme 44.



Scheme 45.



Scheme 46.



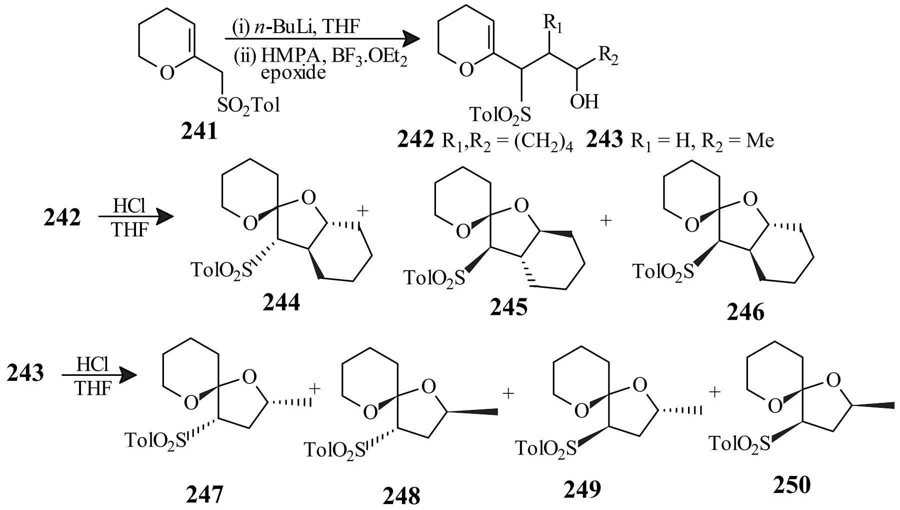
Scheme 47.

of the corresponding alcohol derivatives (**220**), (**223**) and (**225**), respectively, as shown in Scheme 45.

In the synthesis of manzamine-A, Brands and Dimichele[114] used **230** and **232** as the synthon components to synthesise a spirogenic compound (**233**) for the construction of the spirocentre in **234** with the desired stereochemistry. One of the synthon components **230** was prepared from 3-amino-1-propanol (**228**) through **229** and the other unit **232** was synthesised from a pyroglutamic acid derivative (**231**) (Scheme 46).

Tonghaosu (**240a**), a natural product isolated from several plants of the tribe *Athemdeae*, is a [4.4]spiroketal. The spiroketal was synthesised from furfuraldehyde (**235**) through a series of reactions involving intermediate (**236–239**), as shown in Scheme 47.[115]

Craig et al.[116] have prepared 6,6- and 6,5-spiroketals (**244–250**) by acid-catalysed cyclisation of **242** and **243**, which were obtained by alkylation and epoxide-opening reactions of 3,4-dihydro-6-[(*p*-toluenesulfonyl)methyl]-2*H*-pyran (**241**) (Scheme 48).



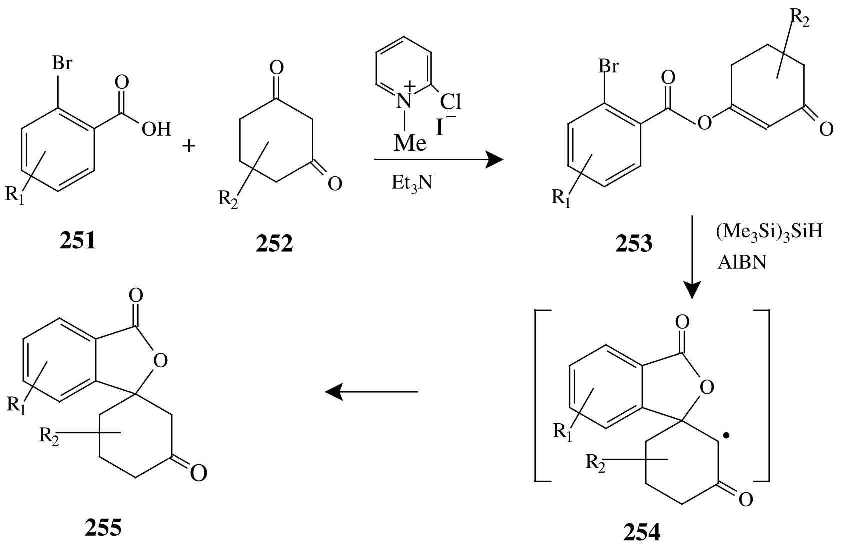
Scheme 48.

Zhang et al.[117] have built a spiro centre in a cyclohexanone ring through a stepwise process using prestruct **IIa**. The precursor (**253**) of the spiro compound (**255**) was prepared by alkylating at the oxygen function of the cyclohexanone (**252**) using a substituted *o*-bromobenzoic acid (**251**). The cyclisation was proposed to proceed via a free-radical intermediate (**254**),[118] as shown in Scheme 49.

In the synthesis of spirotryprostatin, Edmonson and Danishefsky[119] have used a 6-methoxytryptophan (**256**) as one of the synthon components for the synthesis of the spiro-oxindole unit **260**. The synthesis commenced with a Pictet–Spengler reaction[120] of the aldehyde **257** with **256** to yield **258**, which on further hydroxybromination resulted in the spirogenic compound (**259**) (Scheme 50). The spiro compound **260** serves as an intermediate for the synthesis of spirotryprostatin.

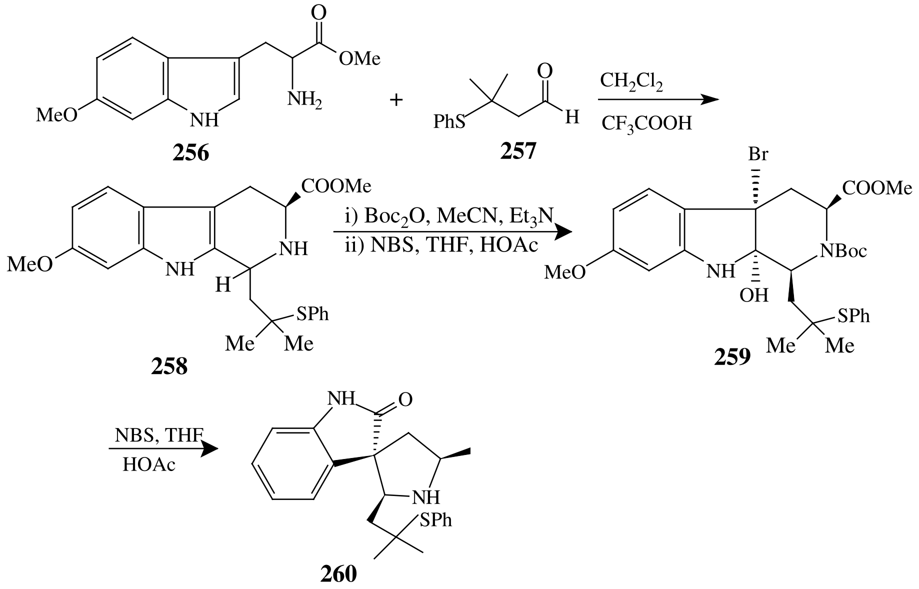
Semmelhack[121] has explored the synthesis of (±)-acorenone and (±)-acorenone B (Scheme 51) using the prestruct **IIa**. The diastereoisomers **262** and **263**, on treatment of an anisole (**261**) with chromium hexacarbonyl, were converted into the spiroketones **264** and **265**, respectively, through a variety of reactions, as shown in Scheme 51.

(±)-Acorenone B (**271**) was synthesised stereoselectively by Trost et al.[122] by using a ketone **266** and cyclopropylidenediphenylsulphonium fluoroborate (**267**)

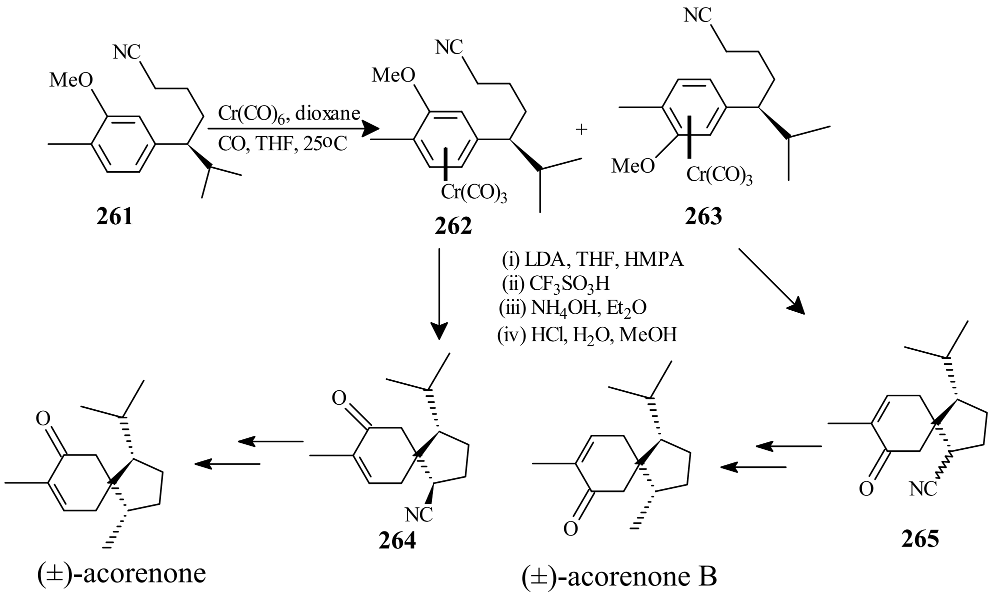


R_1 = H, OMe, Boc;
R_2 = 2,4-$Cl_2C_6H_3$, 2-ClC_6H_4, 2-$CF_3C_6H_4$, 4-$MeOC_6H_4$

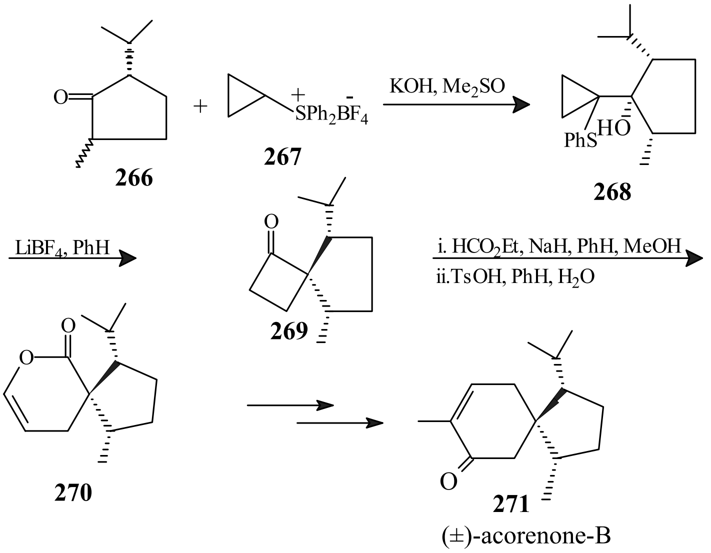
Scheme 49.



Scheme 50.



Scheme 51.



Scheme 52.

through various intermediates (**268–270**), as shown in Scheme 52.

4.8. Synthesis of spiro compounds by using prestruct IIb

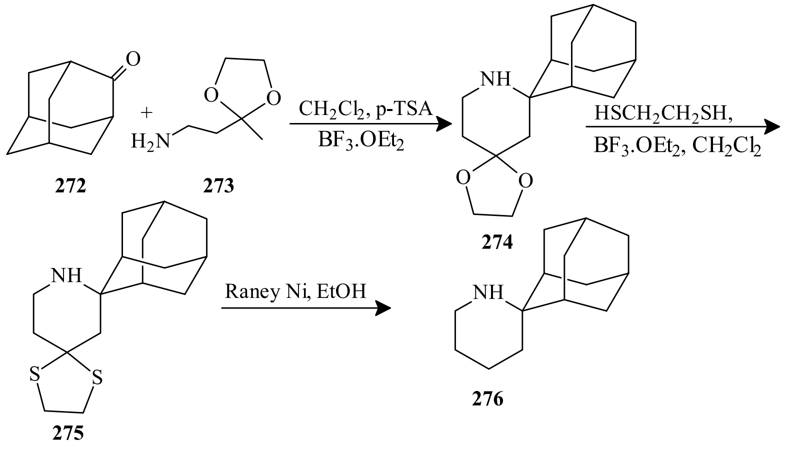
Prestruct **IIb** is due to bond disconnection at two ring appendages at one ring. The two synthon components consist of a ring and an alkyl group.

Adamantanone (**272**) and an amine **273** have been used as synthon components in the synthesis of spiro[piperidine-2,2′-adamantane] (**276**)[123] as shown in Scheme 53. The reaction of **272** and **273** gave the expected product **274**, which was converted into the dithiolane derivative (**275**). Subsequent hydrogenolysis of **275** furnished the desired spiro compound **276**.

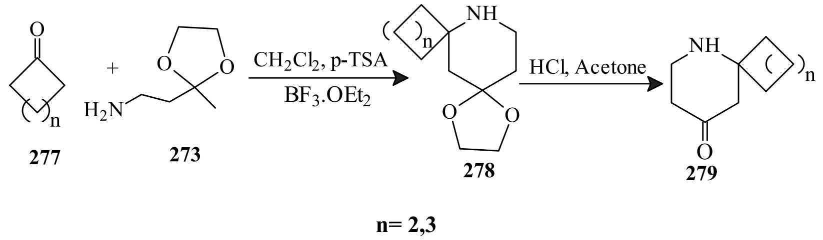
The same strategy was adopted for the synthesis of a 2,2′-spiropiperidine skeleton (**278**) by taking cyclic ketones **277**. Subsequent keto-deprotection resulted in the formation of **279** (Scheme 54).

Prestruct **IIb** has been used by Stork et al.[124] for the synthesis of (±) β-vetivone (**285**). One of the synthon components, enone **280**, was alkylated with homoallylic dichloride (**281**), the other synthon. The spiroketone **284** was formed via **282** and **283**. Addition of methyllithium to **283** and subsequent treatment with acid gave (±)-β-vetivone (**285**) (Scheme 55).

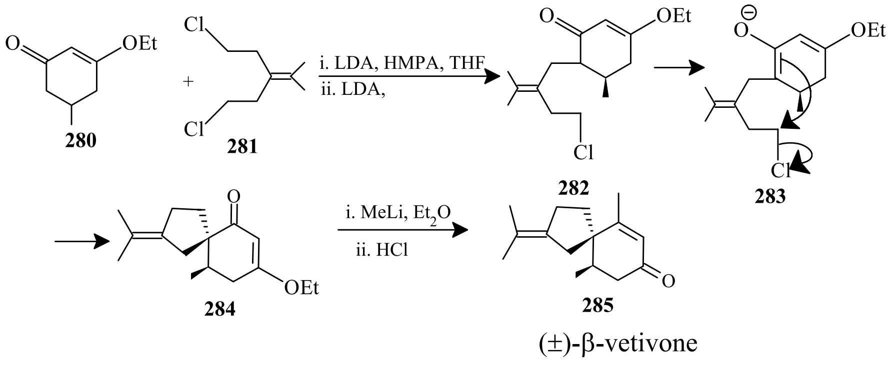
Posner et al.[125] have reported a similar method for the synthesis of (±) β-vetivone (**285**) starting from a lactone (**286**) instead of the enone **280**. The lactone (**286**) on alkylation with the allylic-homoallylic dibromide (**287**) forms the spiro-lactone (**288**), which has been converted into (±) β-vetivone (**285**) by a series of reactions, as shown in Scheme 56. Asaoka et al.[126] used the same dihalide (**287**) to alkylate a different substrate **291** for the



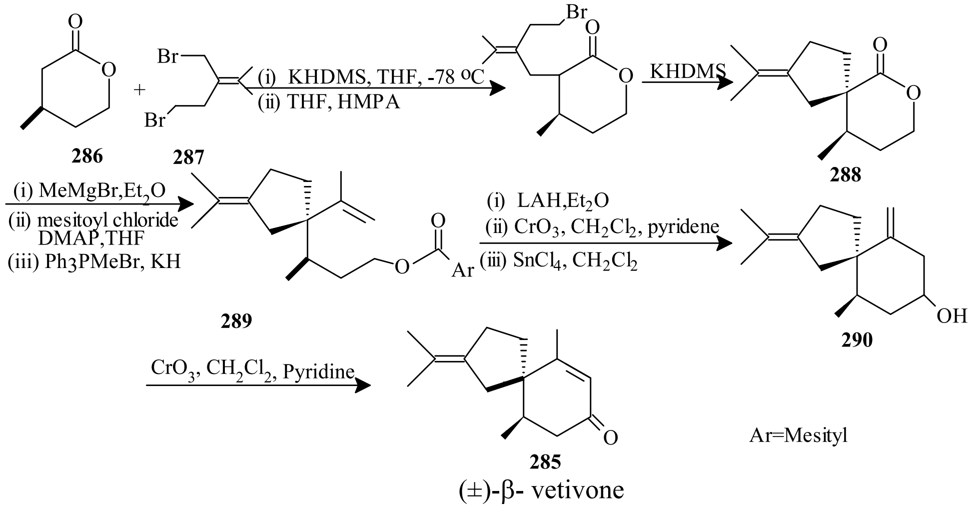
Scheme 53.



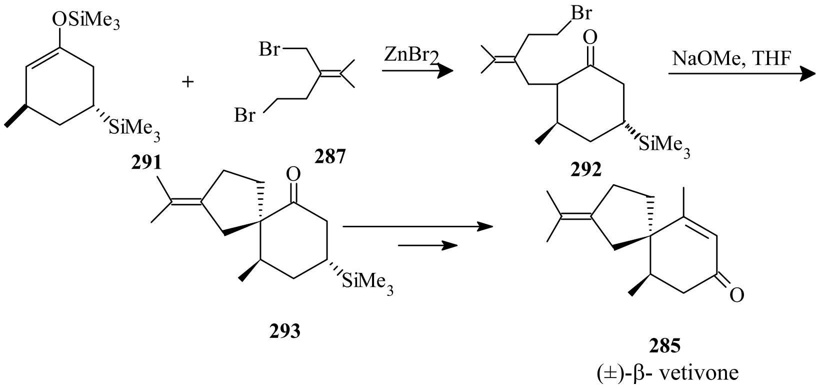
Scheme 54.



Scheme 55.



Scheme 56.



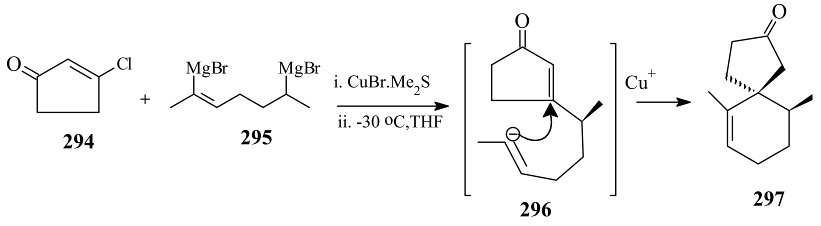
Scheme 57.

synthesis of (±) β-vetivone (**285**) through **292** and **293** (Scheme 57).

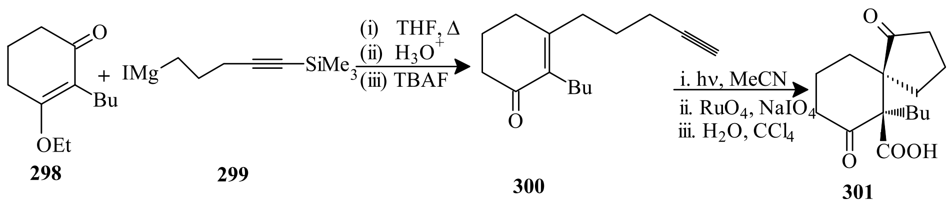
A spiro[4.5] skeleton **297** was constructed steroselectively by the reaction of a bis-Grignard reagent **295** and ketone **294** in the presence of CuBr·Me_2S through an intermediate **296** (Scheme 58).[127]

A steroselective construction of spiro[4.5]decanones (**301**) was established by Koft and Smith[128] by spirocyclisation of **300**, which was obtained by the reaction of enone **298** with Grignard reagent **299** (Scheme 59).

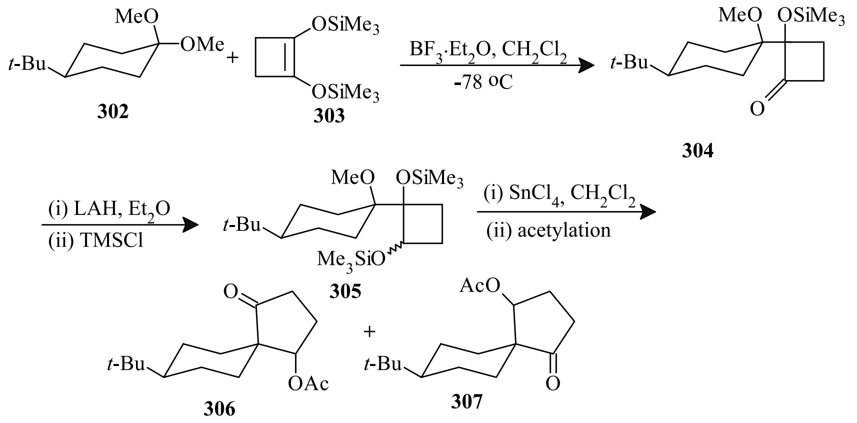
Burnell and co-workers[129,130] have synthesised a number of spiro[4.5]decanes, which have been employed as the key



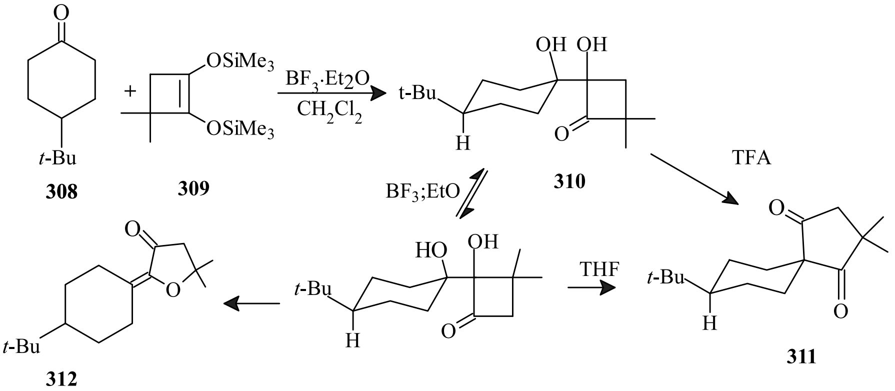
Scheme 58.



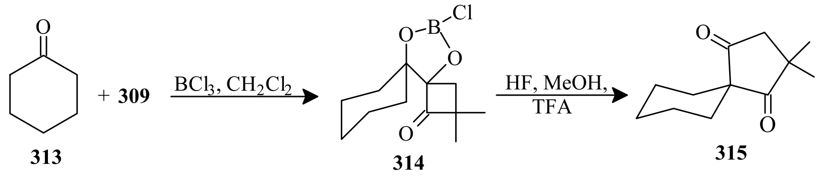
Scheme 59.



Scheme 60.



Scheme 61.

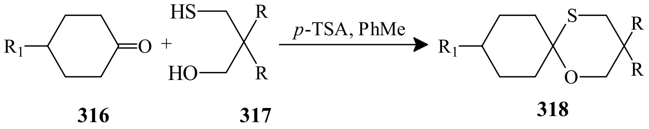


Scheme 62.

step in the synthesis of various natural products. The construction of the simple spiro systems **306** and **307** can be achieved by using acetal **302** and a silylated acyloin (**303**) through a series of reaction furnishing intermediates **304** and **305** (Scheme 60).

The same group[131,132] has also reported the synthesis of spiro compound **311** by the reaction of a ketone **308** and a silyated compound **309** through the intermediate **310**. A significant amount of the byproduct **312** was also formed (Scheme 61). This problem has been avoided[133] by using BCl_3 instead of $BF_3{\cdot}Et_2O$ in a reaction of cyclohexanone (**313**) with **309**, which traps the initial adduct as a cyclic ester **314** (Scheme 62). The spirocycle **315** was formed by treatment of the cyclic ester **314** with hydrogen fluoride in methanol, followed by TFA.

Some spiro-1,3-oxathiane derivatives (**318**) were obtained by the condensation reaction of cyclohexanones (**316**) with 3-mercapto-1-propanols (**317**)[134] (Scheme 63).

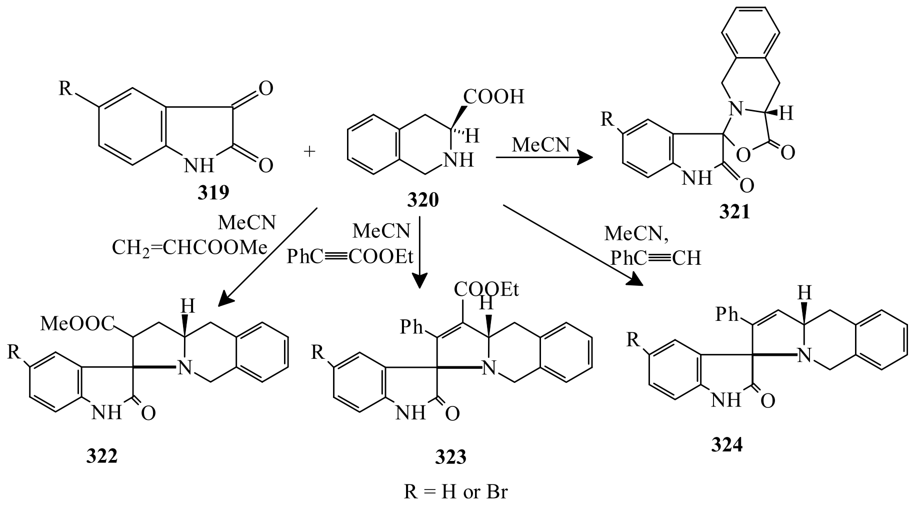


R = H, Me; R_1 = H, Me, Ph, *t*-Bu

Scheme 63.

The investigation revealed that compound **318** (R = Me, R_1 = H) exhibits helical chirality (due to the spiro skeleton) and a virtual triligand chiral centre (belonging to the 1,3-oxathiane ring) whereas compounds **318** exhibit semi-flexible structure.

Prestruct **IIb** has been used by Pardasani et al.[135] for the synthesis of spiro-oxazolidinone (**321**) and spiro-pyrrolidine derivatives (**322–324**). The reaction of the synthon components, isatin (**319**) and a secondary cyclic α-amino



Scheme 64.

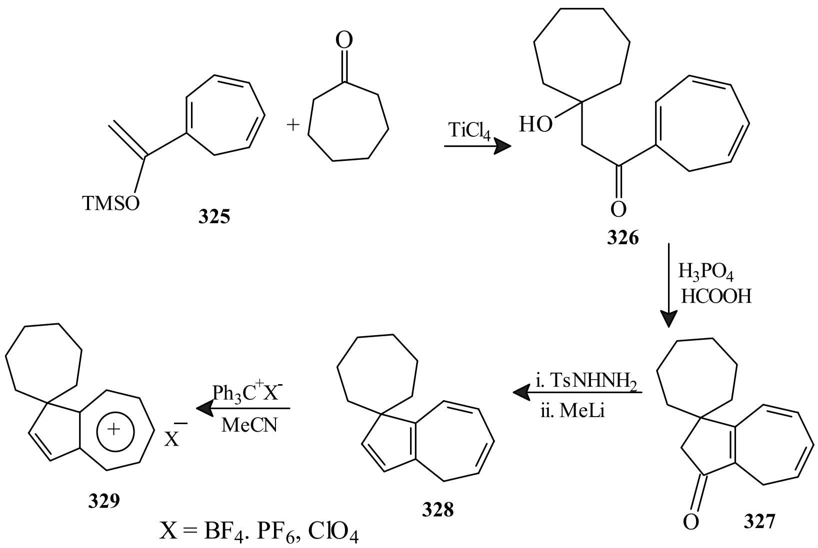
acid, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**320**), gives rise to an azomethine ylide, which underwent [3+2] cycloaddition reaction with various dipolarophiles affording an inseparable stereoisomeric mixture of spiro-oxazolidinone (**321**) and spiro-pyrrolidine derivatives (**322–324**), as shown in Scheme 64.

Oda et al.[136] have generated a spirocentre by using a cycloheptatriene derivative **325** and cycloheptanone. The rection of **325** and cycloheptanone yielded **326**, which on Mukaiyama aldol reaction and Nazarov cyclisation furnished **327**. Shapiro reaction of **327** yielded **328**, which was converted to an azulenium ion **329** by hydride abstraction (Scheme 65).

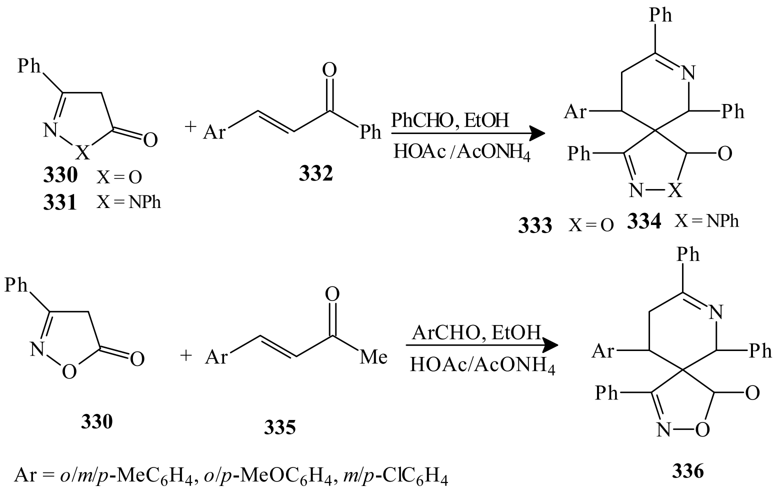
Spirotetrahydropyridine derivatives (**333**) and (**334**) were synthesised diastereoselectively in good yield by the reaction of chalcones (**332**), azolin-5-ones (**330**) and (**331**), benzaldehyde and ammonium acetate in ethanol. When benzalacetone (**335**) was used, the reaction occurred only with isoxazolin-5-ones such as **330** leading to spirans (**336**)[137] (Scheme 66).

Spiroketones (**340**) were constructed stereoselectively using cyclopentanone or cyclohexanone (**337**) and a substituted bromoepoxide (**338**) in the presence of potassium hydride (Scheme 67). The spiroketones (**340**) can be used as key intermediates for the synthesis of different alkaloids, viz (−)-histrionicotoxin.[138]

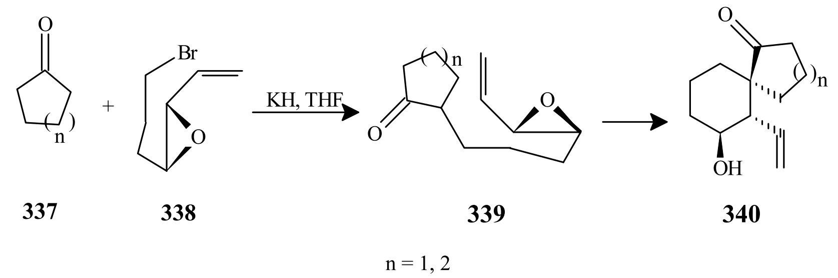
Cannone et al.[139] have used prestruct **IIb** in a stereoselective spirocyclisation of enones. Enone **341** was alkylated by the dibromide **342** to form the spiro



Scheme 65.



Scheme 66.

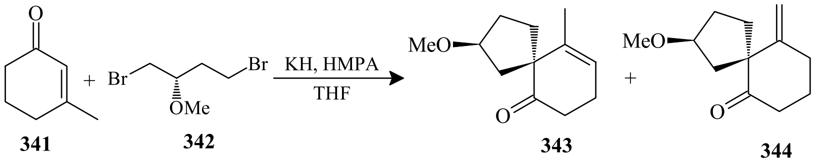


Scheme 67.

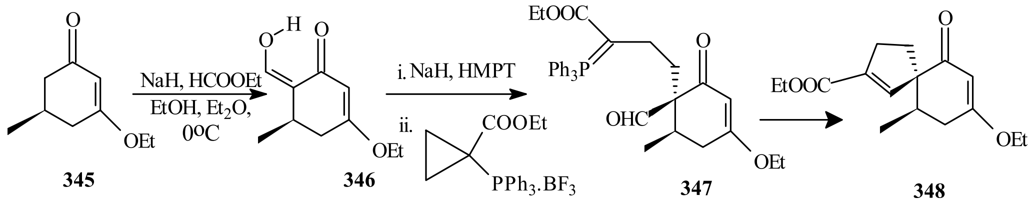
compounds **343** and **344**. The spiro compound **343** can serve as a precursor to sesquiterpenes with a spiro[4.5] skeleton (Scheme 68).

The common intermediate (**348**), a spiro[4.5] system, can be utilised in the synthesis of α-vetispirene, β-vetispirene, β-vetivone and hinesole. The spiro compound (**348**) can be synthesised from the ketone (**345**)[140] through the intermediates **346** and **347**, as shown in Scheme 69.

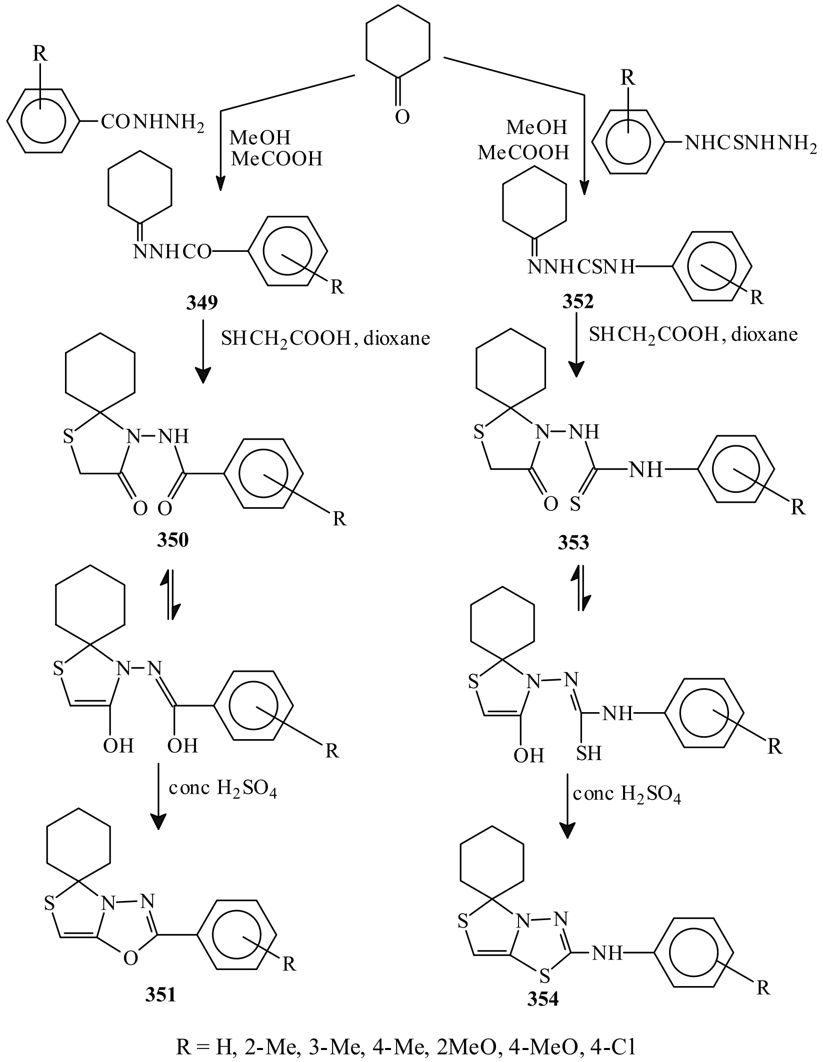
Nizamuddin et al.[141] have prepared several spiro-oxadiazolothiazoline and spiro-thiadiazolothiazoline derivatives (**351**) and (**354**) from cyclohexanone. 1-Aroyl-cyclohexane-hydrazones (**349**) and 1-aryl-cyclohexane-thiosemicarbazones (**352**) when separately treated with mercaptoacetic



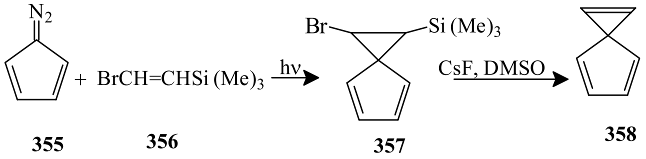
Scheme 68.



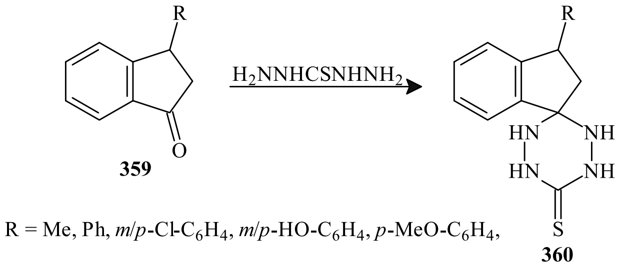
Scheme 69.



Scheme 70.



Scheme 71.



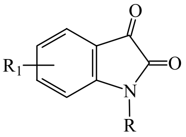
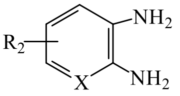
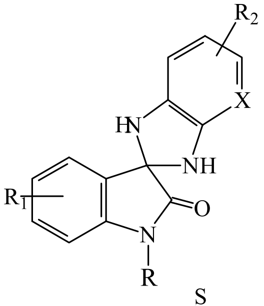
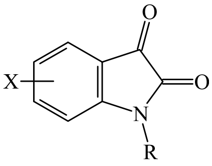
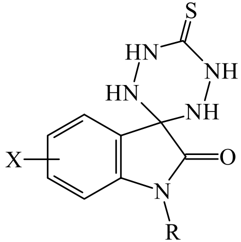
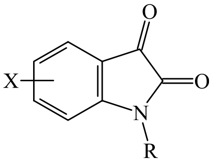
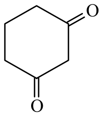
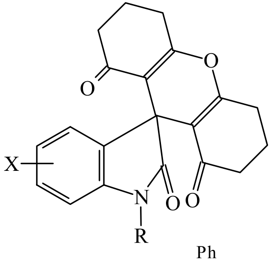
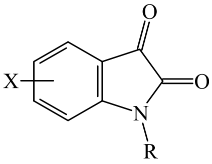
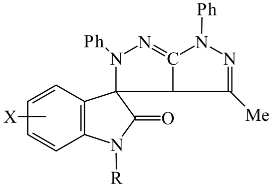
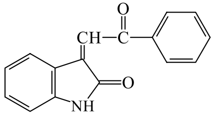
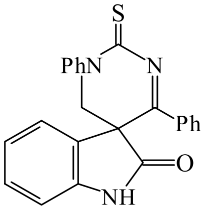
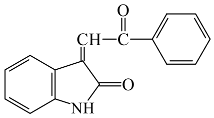
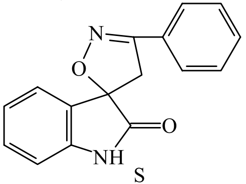
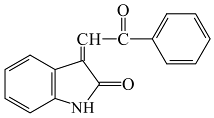
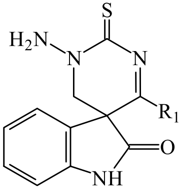
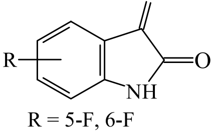
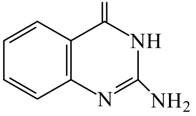
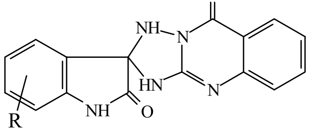
Scheme 72.

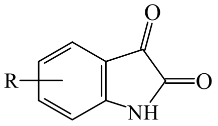
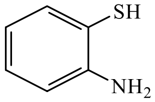
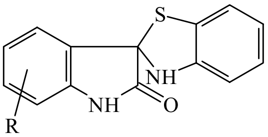
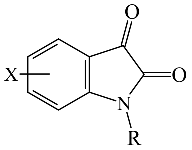
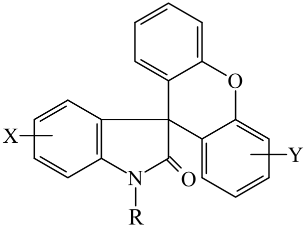
acid afforded **350** and **353**, respectively. On subsequent treatment with concentrated H_2SO_4 spiro-oxadiazolothiazolines (**351**) and spiro-thiadazolothiazolines (**354**) were obtained (Scheme 70).

The synthesis and thermal rearrangement of spiro[2.4] hepta-1,4,6-triene (**358**) has been studied by Billups et al.[142] Photolysis of diazocyclopentadiene (**355**) in (2-bromovinyl)trimethylsilane (**356**) forms the intermediate **357**, which, on treatment with CsF, gives the desired spiro compound **358** (Scheme 71).

Pujari et al.[143,144] have synthesised spiro tetrazine compounds (**360**) by taking the 3-aryl/alkylindan-1-one (**359**) and thiocarbohydrazide as the synthon components (Scheme 72).

Joshi and co-workers have used prestruct **IIb** for the synthesis of several spiro compounds as given below.

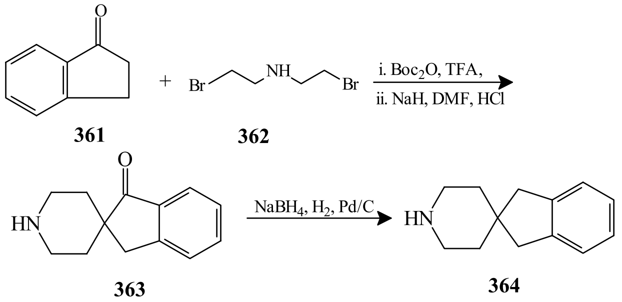
Sl No	Synthon component I	Synthon component II	Product	Reference
1	 R = COMe, H R_1 = H, 4-F, 5-F, 3CF$_3$	 X = CH or N R_2 = H, F, CF$_3$		145
2	 R = COMe, H X = 5-F,6-F	$H_2NNHCSNHNH_2$		146
3	 R = COMe, H X = 5-F,6-F	 1,3-cyclohexanedione		147, 148
4	 R = COMe, H X = 5-F,6-F	(i) $PhNHNH_2$; (ii) $MeCOCH_2CO_2Et$		149
5		$PhNHCSNH_2$, phenyl thiourea		150
6		$NH_2OH \cdot HCl$		151
7		$NH_2NHCSNH_2$	 R_1 = H, Me	152
8	 R = 5-F, 6-F	 2,3-Amino-4(3)-quinazolone	 R = 5-F, 6-F	153

Sl No	Synthon component I	Synthon component II	Product	Reference
9	 R = 5-F, 6-F	 2-aminothiophenol	 R = 5-F, 6-F	154
10	 X = 5-F, 6-F, 4-CF_3 R = H, Me, COMe, COPh	*m*/*p*-Cresol or α-naphthol	 X = 5 -F, 6-F,4 -CF_3 Y = 2,7-Me_2,3,6-Me_2, 2,7-F_2 R = H, Me, COMe, COPh	155

Spiropiperidine (**364**) was obtained by the reduction of the **363**, which was obtained by the reaction of 1-indanone (**361**) and an amine (**362**) (Scheme 73).[156]

The reaction of steroidal 6-ketones (**365**) with R(−)-2-aminobutanol in the presence of *p*-TsOH as catalyst affords selectively the respective steroidal (6*R*)-spiro-4′-ethyl-1′,3′-oxazolidines (**366**) (Scheme 74).[157]

Shamuzzaman et al.[158] have used prestruct **IIa** for the synthesis of cholest-5-en-(3*R*)-Δ^2-1′,3′,4′-oxadiazoline (**369**) by taking cholest-5-en-3-one (**367**) and semicarbazide hydrochloride as the synthon components. Compound **368** was obtained by the condensation of **367** with semicarbazide hydrochloride. The spiro compound **369** was synthesised by the cyclisation of **368** with acetic anhydride and pyridine (Scheme 75).



Scheme 73.

4.9. Synthesis of spiro compounds by using prestruct IIc

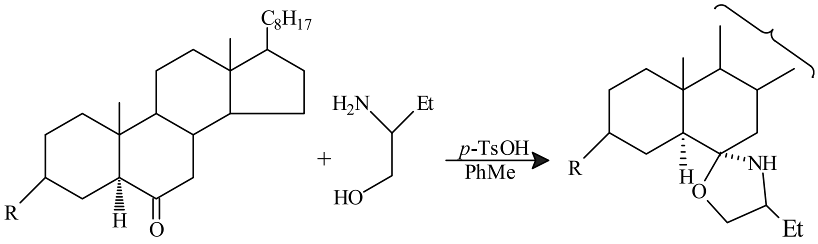
The bond disconnections at the ring appendages of two different rings generate the prestruct **IIc**. The synthon component may be a long acyclic compound.

Nagashi et al.[159] have used titanium-catalysed cascade carboalumination of trienes (**370**) and (**374**) to generate the spirobicycles (**372**), (**373**), (**375**) and (**376**), respectively, through an intermediate (**371**)(Scheme 76).

Trost et al.[160] have reported the formation of two spiro centres in tandem by using prestruct **IIc**, which is an example of building two spiro units by tricyclisation. The synthon component **377** undergoes cyclisation in presence of palladium to form the dispiro compound **378** (Scheme 77).

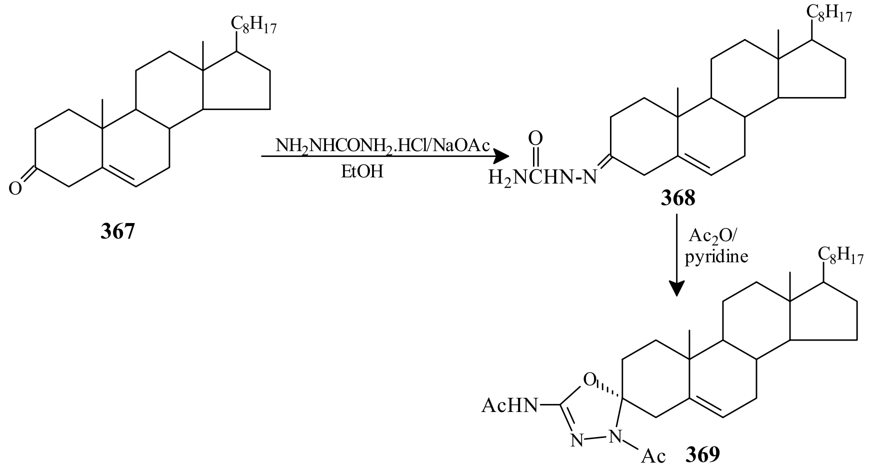
(*E*)- and (*Z*)-2-methoxycarbonylmethylene-1,6-dioxaspiro[4.5]decanes (**381**) and (**382**) have been synthesised from an equilibrium mixture of acyclic keto alcohol (**379**) and hemiacetal (**380**) via intermolecular conjugate addition[161] (Scheme 78).

The (*E*) isomer could be obtained in a 52:1 ratio under thermodynamically controlled conditions using *t*-BuOK in THF, whereas a catalytic amount of $Pd(OAc)_2$ resulted in the (*Z*) isomer in a 95:1 ratio.

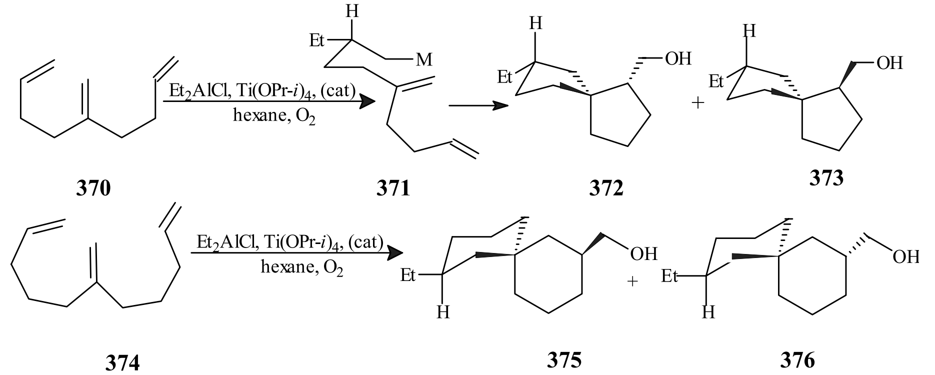


365 R = H, Cl, OAc **366**

Scheme 74.

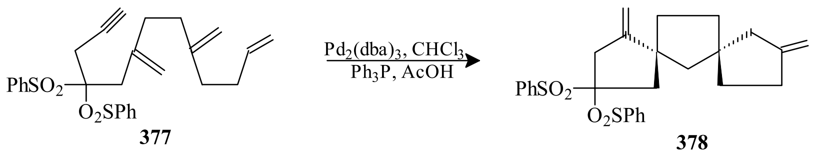


Scheme 75.

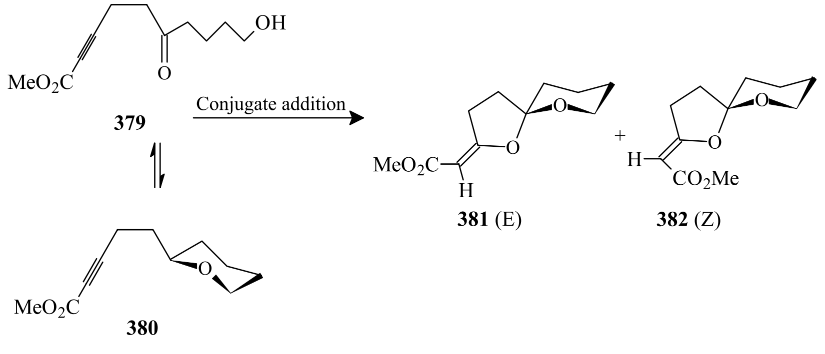


M = Al and/or Ti group

Scheme 76.



Scheme 77.



Scheme 78.

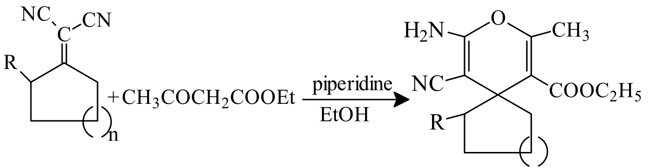
4.10. Synthesis of spiro compounds by using prestruct IId

The prestruct **IId** is due to bond disconnections at three ring appendages of two rings, that is, two bond disconnections at one ring and the third bond disconnection at the other ring. In this case, the synthon components are two acyclic groups. No report has been available to us, however, describing the synthesis of spiro compounds by using synthon components corresponding to prestruct **IId**.

4.11. Synthesis of spiro compounds by using prestruct IIIa

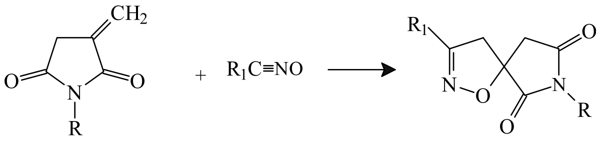
The bond disconnections at a ring appendage and also a branch appendage at the same ring lead to prestruct **IIIa**.

A series of spiroheterocycles **384** were synthesised by the reaction of cycloalkylidenemalononitriles (**383**) with an active methylene compound, $MeCOCH_2CO_2Et$, as shown in Scheme 79.[162]



383 R = H, Me; n = 1,2 **384**

Scheme 79.



385 **386**

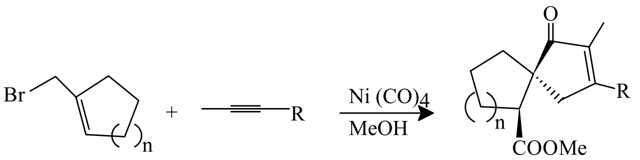
R = Ph, *o*/*m*-Cl-Ph; R_1 = Me, COOEt

Scheme 80.

Some spiroheterocycles, 1-oxa-2,7-diazaspiro[4.4]non-2-ene-6,8-diones (**386**), were synthesised by the reaction of itaconimides (**385**) with nitrile oxides using prestruct **IIIa** (Scheme 80).[163]

An approach to the creation of a spirocentre in an asymmetric fashion by taking a prestruct **IIIa** has been reported by Moreto et al.[164] This method involves nickel-catalysed addition of halomethylcycloalkanes (**387**) to one end of the triple bond and carbonylation of the other end of the acetylenic sulfoxide (**388**) to form **389** in a stereo-controlled manner. Demetallation of **389** gives a byproduct **390** and a spiro compound **391**, which is converted to the desired spiro compound **392** (Scheme 81).

A similar study by the same workers has been reported[165] using an achiral acetylenic system (**393**) to synthesise spirocyclopentanones (**394**) by a similar type of intra-molecular carbonylative cycloaddition (Scheme 82).

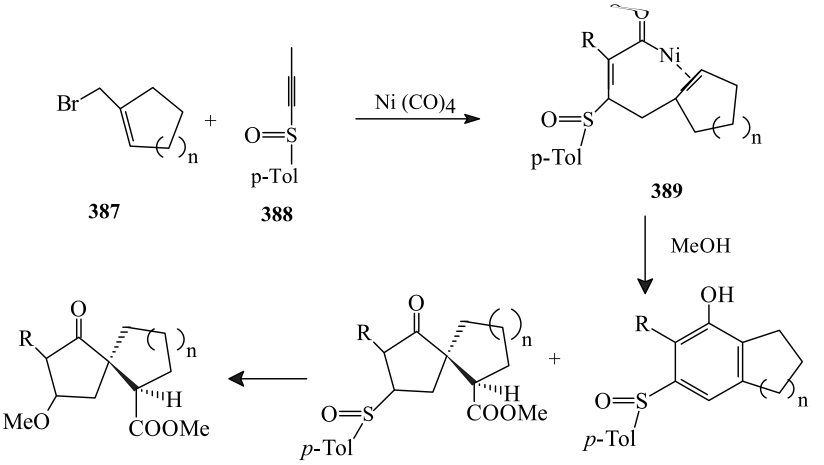


387 **393** **394**

R = CH_2OH, COOMe,: n = 1,2,3,4

Scheme 82.

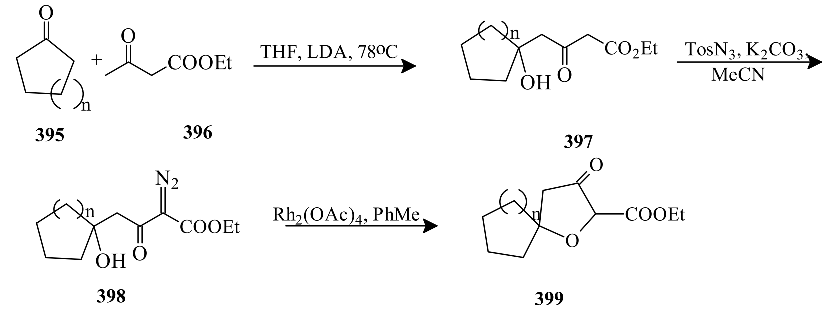
Functionalised spirocyclic tetrahydrofurans (**399**) have been obtained by Jones and Toutounji[166] by using prestruct **IIIa**. The synthon components, cycloalkanones **395** and ethyl acetoacetate (**396**), undergo an acetoacetate ester dianion–aldol reaction to form **397**, which is transformed into an α-diazo-β-keto ester (**398**). The carbene O–H insertion of **398** engenders the spiro compound **399**, as shown in Scheme 83.



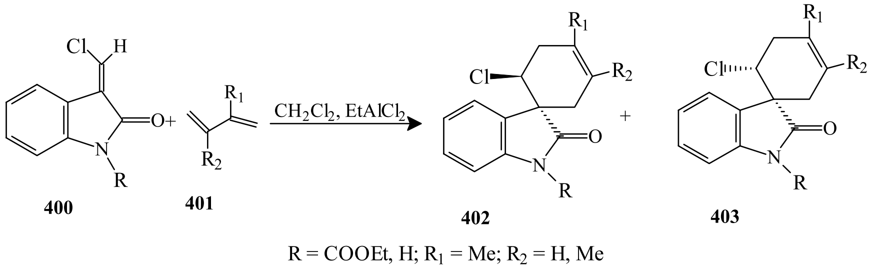
387 **388** **389** **392** **391** **390**

R = Me, n-Bu; n = 1,2,3,4

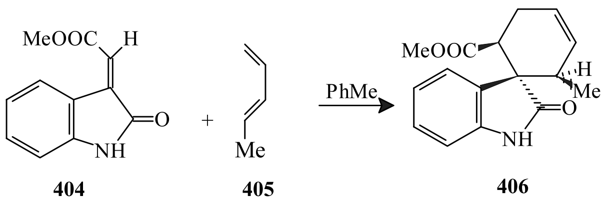
Scheme 81.



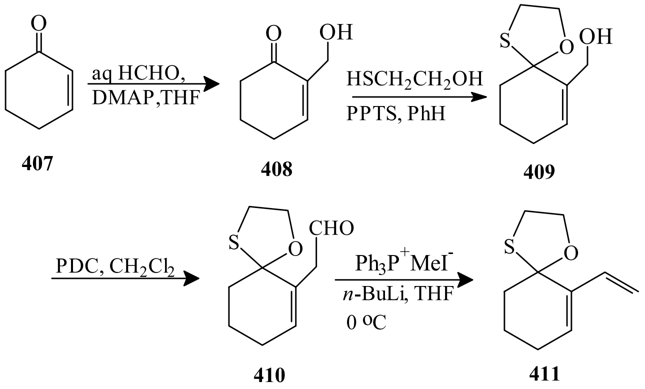
Scheme 83.



Scheme 84.



Scheme 85.



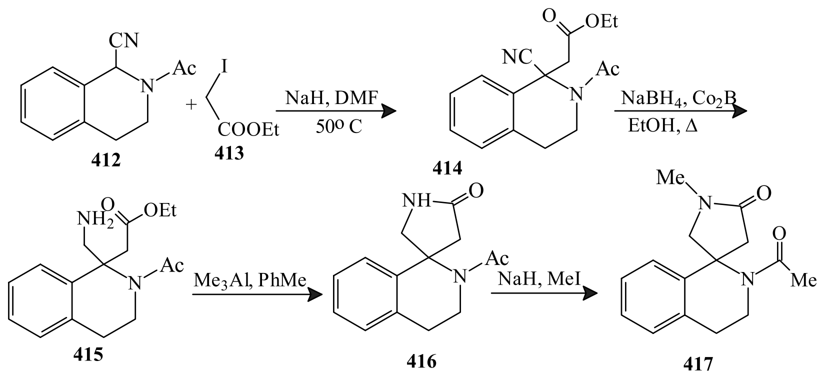
Scheme 86.

The synthesis of spiro compounds **402** and **403** using prestruct **IIIa** has been reported by Gelmi et al.[167] The synthon components, 3-chloromethylenindolones (**400**) and dienes (**401**), undergo Diels–Alder cycloaddition reactions in the presence of an ethylaluminium dichloride catalyst to furnish the desired spiro compounds (Scheme 84).

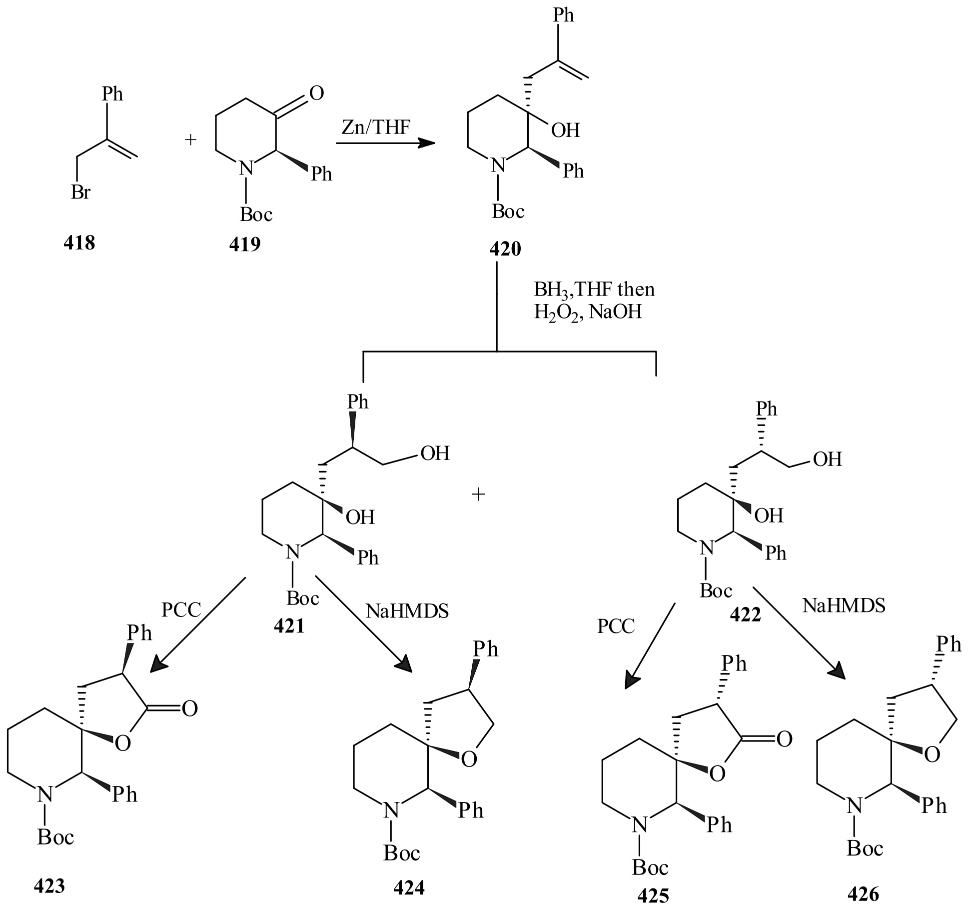
Okada and co-workers[168] have reported the synthesis of the spiro adduct **406** as a single product by the reaction of dienophile (**404**) with the pure (*E*) isomer of piperylene (**405**) (Scheme 85).

Yadav and co-workers[169] have used prestruct **IIIa** for the synthesis of spirodiene (**411**). Baylis–Hillman reaction of 2-cyclohexenone (**407**) with formalin furnished **408**, which underwent spirocyclocondensation with 2-mercaptoethanal to give the spiro-alcohol **409**. Oxidation of **409** furnished an aldehyde **416**, which on Wittig olefination furnished the desired spirodiene **411** (Scheme 86).

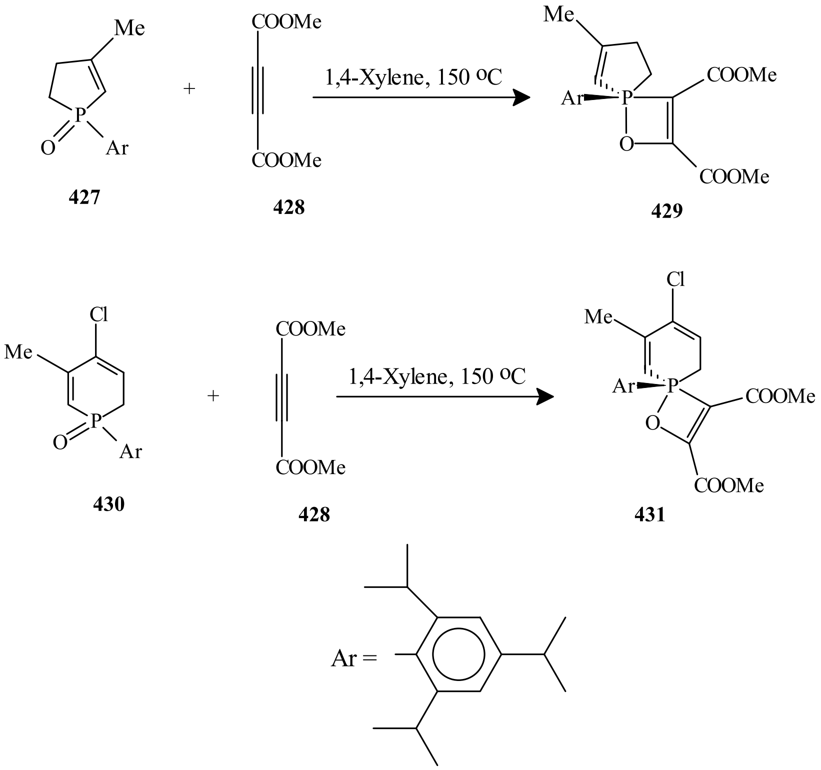
A convenient synthetic strategy for the synthesis of a new spiroheterocyclic system **417** has been developed by Campiani et al.[170] The target compound (**417**) has been prepared by using a tetrahydroisoquinoline derivative (**412**)



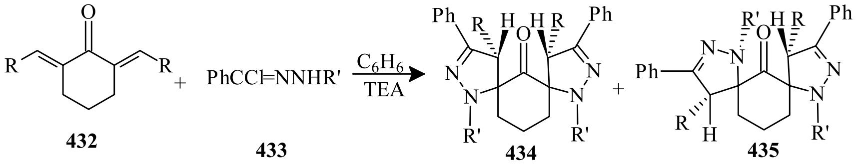
Scheme 87.



Scheme 88.



Scheme 89.



R = C_6H_5, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-FC_6H_4
R' = C_6H_5, 4-MeC_6H_4,

Scheme 90.

and ethyl iodoacetate (**413**) as the starting materials through intermediates **414**, **415** and **416** (Scheme 87).

In the synthesis of NK-1 receptor antagonists, Maligres et al.[171] have used prestruct **IIIa** for the synthesis of a spirobicyclic ether unit. Condensation of 2-phenylallyl bromide (**418**) with ketopiperidine (**419**) in the presence of zinc dust in THF furnished the homoallylic alcohol (**420**). Hydroboration/oxidation of **420** with $BH_3\cdot THF$ or $BH_3\cdot Me_2S$ gave **421** or **422**, respectively. Oxidation of **421** and **422** with PCC gave the spirobicyclic lactone units (**423**) and (**425**), respectively. Similarly reaction of **421** and **422** with NaHMDS afforded the spiro compounds (**424**) and (**426**) (Scheme 88).

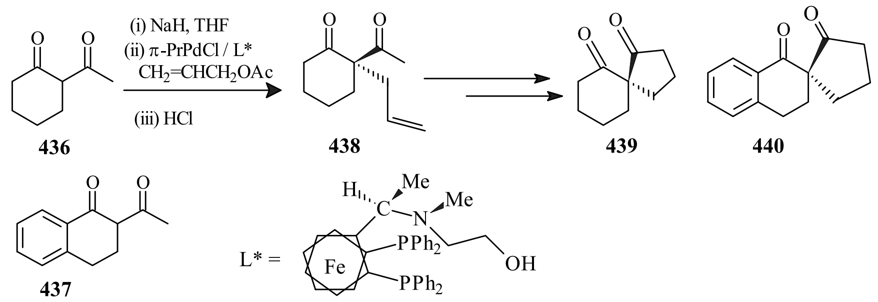
Keglevich and co-workers[172] have reported the synthesis of phosphorous-heterocycles (**429**) and (**431**) by a [2+2] cycloaddition reaction of 2,3-dihydrophosphole oxides (**427**) or 1,2-dihydrophosphonil oxides (**430**) with dimethyl acetylenedicarboxylate (**428**) (Scheme 89). In the spiro-1,2-oxaphosphetes (**429**) and (**431**) the phosphorous atom has a trigonal bipyramidal geometry. The 1,2-oxaphosphetanes are well-known intermediates for the Wittig reaction.[173]

Two spirocentres are generated by the 1,3-dipolar cycloaddition of 2,6-bis(aryl methylidene)cyclohexanones (**432**) and hydrazonyl chlorides (**433**). The reaction proceeded regioselectively affording the tetraazadispiro compounds (**434**) and (**435**)[174] (Scheme 90).

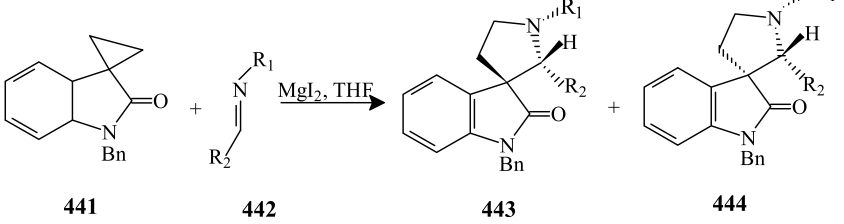
The spirodiones **439** and **440** were synthesised by Hayashi et al.[175] using 2-acetylcyclohexane (**436**) or 2-acetyltetralone (**437**) on reaction with allyl acetate in the presence of a chiral phosphine ligand (**L***) and subsequent cleavage of the double bond followed by Aldol condensation of the resulting aldehyde through an intermediate **438** (Scheme 91).

Carreira and co-workers[176] have synthesised spiro[pyrrolidin-3,3′-oxindoles] (**443**) and (**444**) by using spiro[cyclopropane-1,3′-oxindole] (**441**) as the ring synthon component. Treatment of **441** and *N*-alkylsulfonylaldimines (**442**) with a catalytic amount of MgI_2 in THF afforded the desired spiro compounds (**443**) and (**444**) (Scheme 92).

A number of diastereomeric spiro tricyclic nitroso acetals (**446** and **447**) have been synthesised by the reaction of

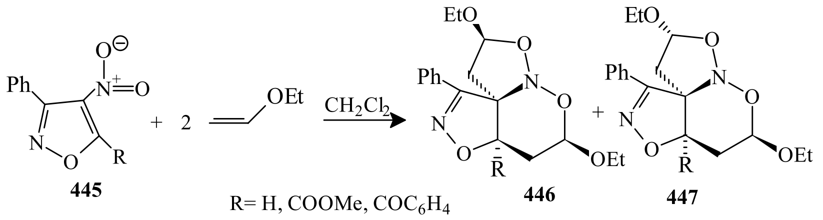


Scheme 91.



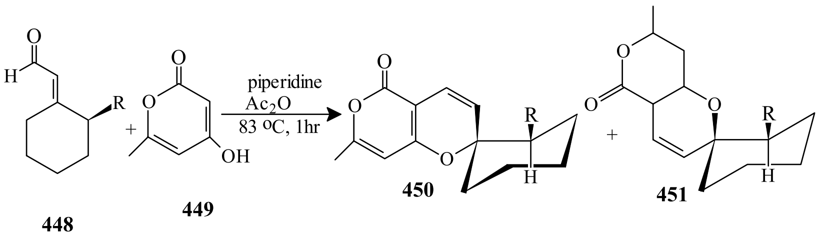
R_1 = allyl, Bn, p-$TolSO_2$;
R_2 = Et, Ph, 4-MeC_6H_4, 2-MeC_6H_4, 2-BrC_6H_4, 4-BrC_6H_4, 4-$CF_3C_6H_4$, 4-$MeOC_6H_4$, furyl

Scheme 92.



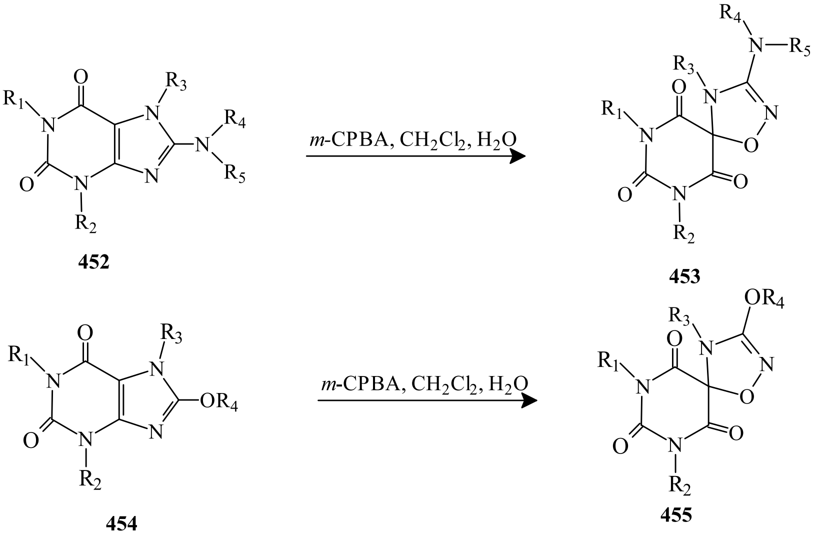
R= H, COOMe, COC_6H_4

Scheme 93.



R = Me, *n*-Bu, Bn, *t*-Bu, OMe

Scheme 94.



R_1, R_2, R_3 = Me, Et

R_4, R_5 = Me, Et, $(CH_2)_2Cl$, CH_2CHMe_2, $CH_2(CH_2)_3Me$, $CH_2OC(O)Me$

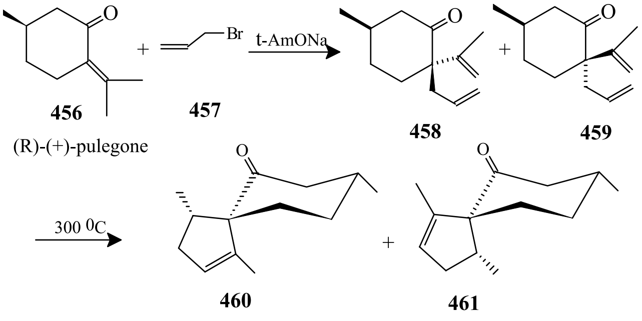
Scheme 95.

4-nitrosoxazoles (**445**) and ethyl vinyl ether in dichloromethane,[177] as shown in Scheme 93.

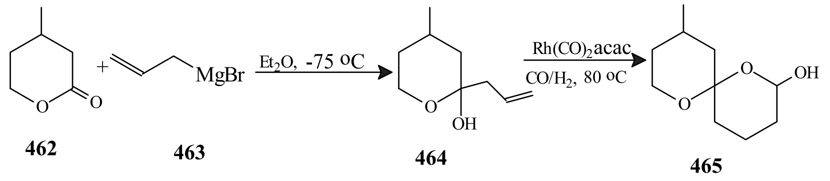
The syntheses of spiroheterocycles **450** and **451** have been achieved by Richard et al.[178] through the reaction of aldehydes **448** and the pyrone **449** by the use of Ac_2O and piperidine (Scheme 94).

Zimmer et al.[179] have reported that oxidation of 8-substituted xanthines (**452**) by *m*-CPBA to give the spiro compound **453**, whereas the xanthines **454** underwent rearrangement under similar conditions to yield **455** (Scheme 95).

(+)-Pulegone (**456**) was used as the synthon component for the synthesis of spiro compounds **460** and **461**. Pulegone has been alkylated with **457** to obtain the diastereomers **458** and **459**, which, on thermolysis, underwent a Conia-type cyclisation to yield a separable mixture of **460** and **461** (Scheme 96).[180]

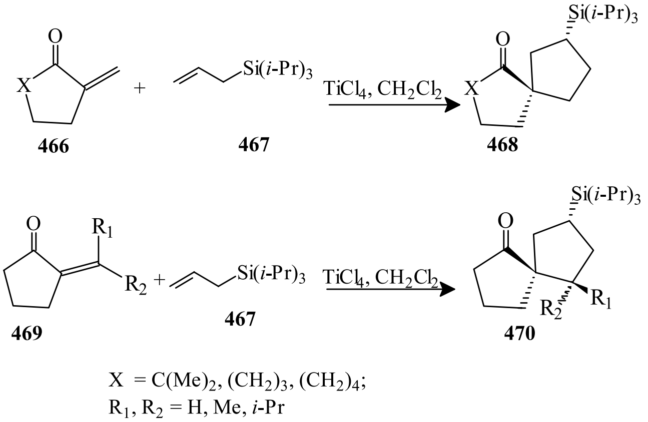


Scheme 96.



Scheme 97.

Eilbracht et al.[181] have also used prestruct **IIIa** by using lactone (**462**) and allylmagnesium bromide (**463**) as the synthon components for the synthesis of spiroketal (**465**). The addition of **463** to lactone **462** leads to a hemiacetal **464** as a single diastereoisomer.[182] The intramolecular ring-closure reaction of **464** in the presence of $Rh(CO)_2acac$ gives the spiroketal (**465**) (Scheme 97).



X = $C(Me)_2$, $(CH_2)_3$, $(CH_2)_4$;
R_1, R_2 = H, Me, *i*-Pr

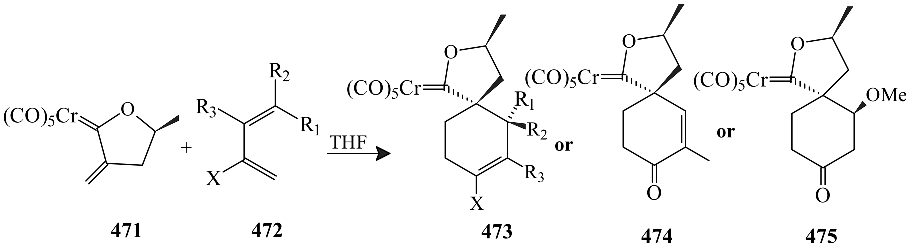
Scheme 98.

Knolker et al.[183] have used a similar prestruct to synthesise spirocyclopentanes (**468**) and (**470**) by the reaction of an allylsilane (**467**) with 2-alkylidenecycloalkanones (**466**) and disubstituted exomethylene compounds (**469**), respectively, as shown in Scheme 98.

Barluenga et al.[184] have used an α,β-unsaturated exocyclic chromium carbene complex (**471**) and butadienes (**472**) to construct spirolactones (**473**), (**474**) and (**475**) (Scheme 99).

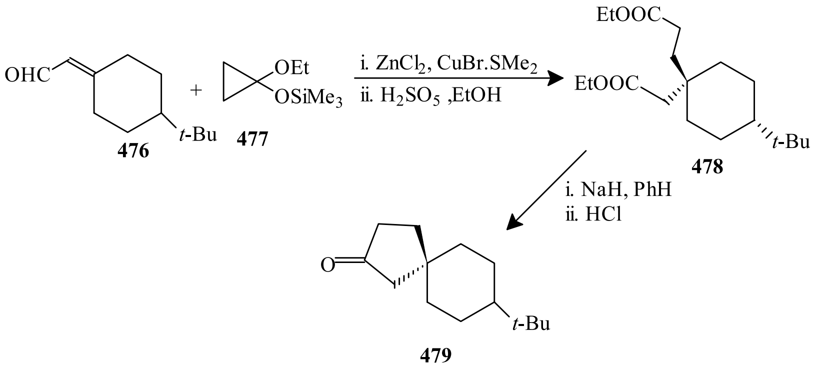
Provencal and Leahy[185] have used an unsaturated aldehyde (**476**) for the synthesis of the spiro compound **479**. Compound **476** has been subjected to copper-catalysed conjugate addition to **477**, followed by treatment with Caro's acid to form the diester **478**, which, on Dieckmann condensation, followed by decarboxylation, furnished **479** (Scheme 100).

During a study of spirobenzopyran[186] analogues as 5-HT_{1A} receptor ligands and potential anxiolytic agents, a series of spiro[pyrrolidine and piperidine 2,3′(2′H)-benzopyrans] (**483**) were synthesised and evaluated for their serotonergic and dopaminergic activities. Michael condensation of benzopyrans **480** with methyl acrylate (**481**) in the presence

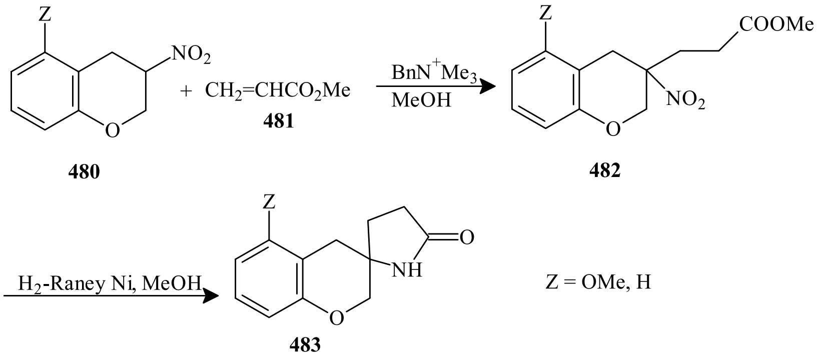


R_1 = H, CH_2OMe;
R_2 = H, OMe, CH_2OMe, $CH_2OTBDMS$, 1-morpholino;
R_3 = H, Me, $CH_2(CH_2)_2Me$;
X = 1-morpholino, $OSiMe_3$

Scheme 99.



Scheme 100.

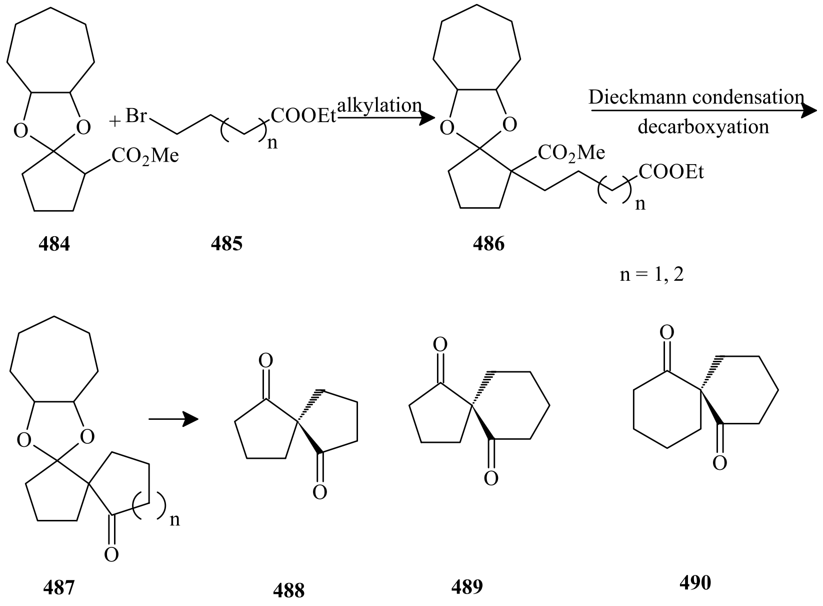


Scheme 101.

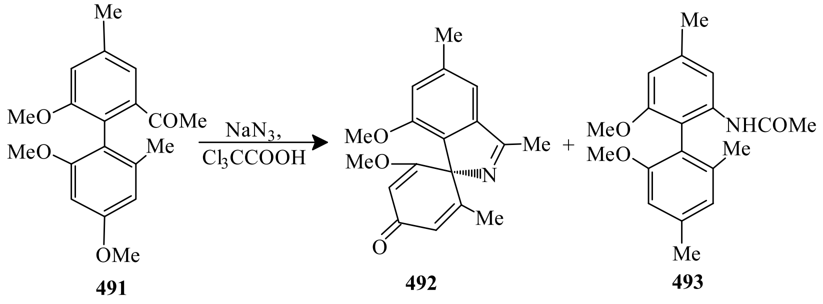
of benzyltrimethylammonium methoxide afforded the nitroester derivatives (**482**). Compounds **482** were reductively cyclised with Raney nickel in methanol to give oxospiropyrrolidine benzopyran derivatives (**483**) (Scheme 101).

Suemune et al.[187] have reported the synthesis of a series of optically active spirocyclic diones (**488–490**). When acetal (**484**) was alkylated with bromoesters (**485**), it gave rise to the generic diesters (**486**). Dieckmann condensation of **486**, followed by decarboxylation, produced the spiroketones (**487**). Acetal cleavage of **483** furnished the spirodiones (**488–490**) (Scheme 102).

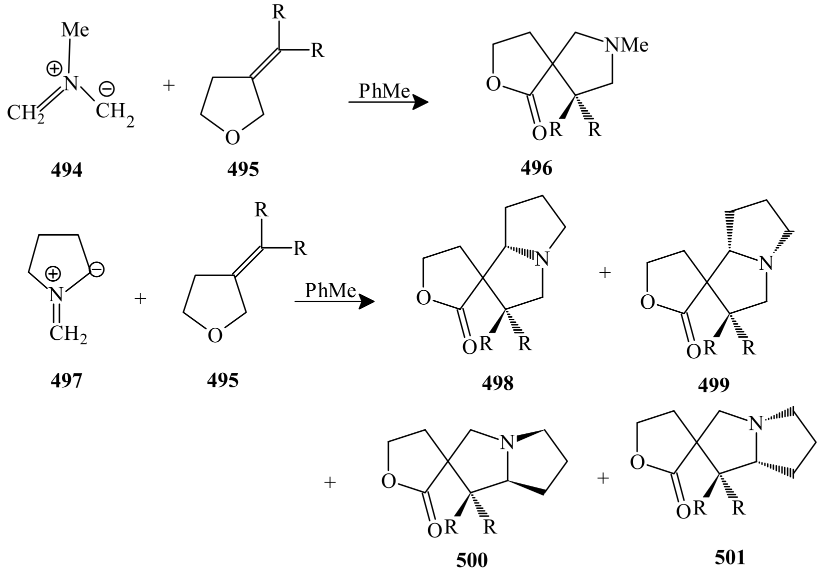
Baker and co-workers[188] have explored one of the aborative synthetic routes for the synthesis of spiro compounds, which involved a Schmidt rearrangement. Schmidt rearrangement of **491** with sodium azide and trichloroacetic acid gave **493** and spiroisoindolyl cyclohexadienone (**492**) in 30% yield. The formation of **492** involves a self-immolative intramolecular chirality transfer from a biphenyl axis to a spirocentre (Scheme 103).



Scheme 102.



Scheme 103.

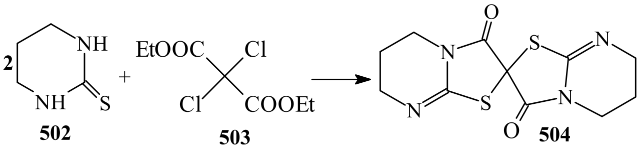


R = H, Tosyloxy, 2-thienyl, C≡CPh, C≡CTMS

Scheme 104.

The syntheses of spiropyrrolidines (**496**) and (**498–501**) were achieved by Mazal et al.[189] from azomethine ylides (**494**) and (**497**). The 1,3-dipolar cycloaddition of **494** or **497** with α-methylene-γ-lactones (**495**) gave the desired spiro compounds **496** and **498–501**, respectively, with various extents of stereoselectivity and regioselectivity, as shown in Scheme 104.

Pujari et al.[190] have also used prestruct **IIIa** for the synthesis of spiro compound **504** by the reaction of 3,4,5,6-tetrahydro-pyrimidine-2-thione (**502**) with dichloromalonate (**503**) (Scheme 105).



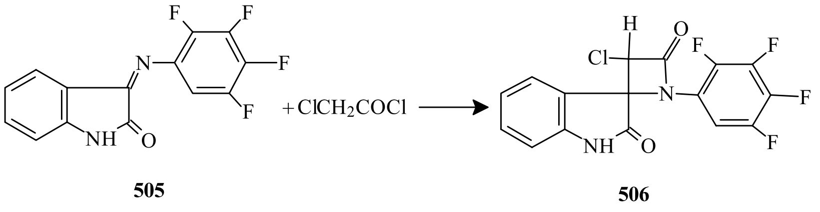
Scheme 105.

Joshi et.al.[191] have used prestruct **IIIa** for the synthesis of a spiro[azetidine-2,3′-3*H*-indole]-2′,4(1*H*)-dione (**506**) by the reaction of anil (**505**) with $ClCH_2COCl$ (Scheme 106).

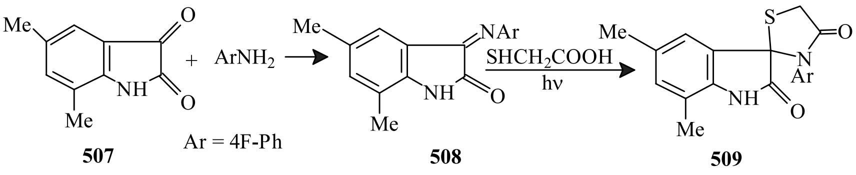
Spiro[3*H*-3,2′-thiazolidines] (**509**) were synthesised by the treatment of mercaptoacetic acid with indolylimines (**508**) under microwave irradiation. Imines (**508**) were prepared from indole-2,3-dione (**507**) and aromatic amines, as shown in Scheme 107.[192]

Takshi and co-workers[193] have reported the synthesis of spiroheterocycles (**512**) by the cycloaddition of *o*-chloranil (**510**) with tricarbonyliron complexes (**511**) (Scheme 108).

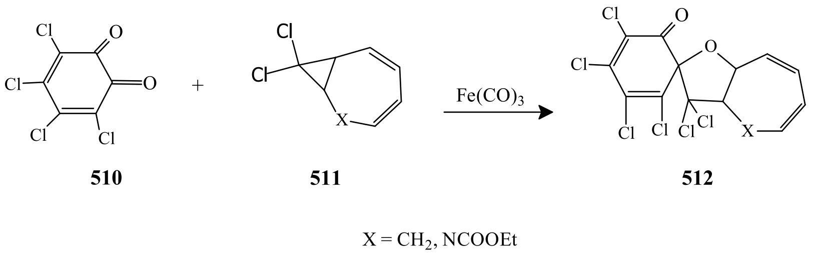
Sasaki et al.[194] have explored the synthesis of spiro-adamantane–aziridine, –azetidine, –triazabicycloheptadione,



Scheme 106.

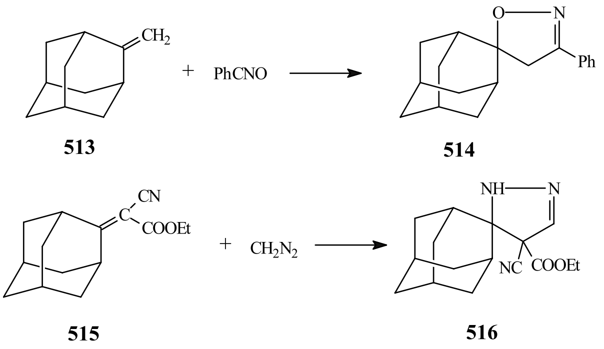


Scheme 107.



Scheme 108.

–isoxazoline and –pyrazoline derivatives by ionic or cycloaddition reactions of methyleneadamantane (**513**) or ethyl adamantylidenecyanoacrylate (**515**). When methyleneadamantane (**513**) is treated with PhCNO, it gives spiroisoxazoline (**514**), whereas treatment of ethyl adamantylidenecyanoacrylate with CH_2N_2 affords spiropyrazoline (**516**) (Scheme 109).



Scheme 109.

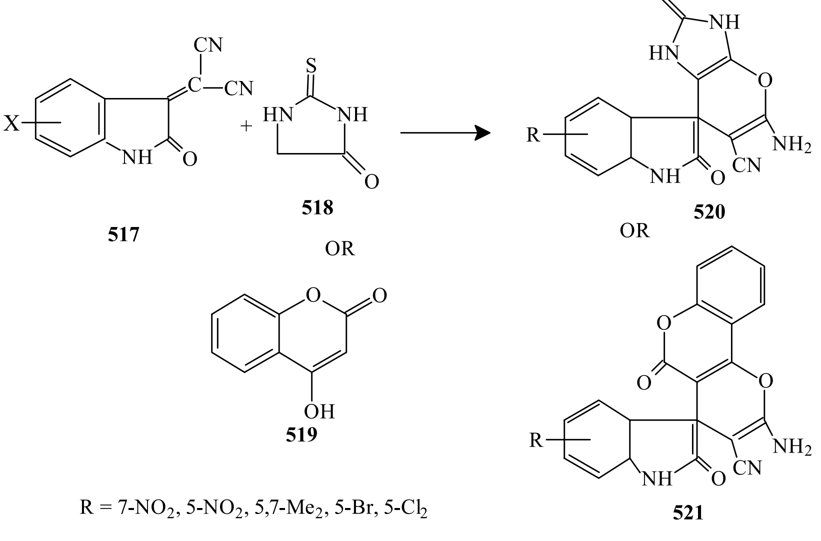
Dandia and co-workers[195] have reported the synthesis of spiro compound **520** and **521** using prestruct **IIIa**. Michael condensation of 3-dicyanomethylene-2*H*-indol-2-ones (**517**) with 2-thiohydantoin (**518**) or 4-hydroxy-2*H*-1-benzopyran-2-one (**519**) affords spiro compounds **520** and **521**, respectively, under microwave irradiation (Scheme 110).

The reaction of 3-benzoylcyanomethylidine-1(*H*)-indol-2-one (**522**) with a number of active methylene compounds leads to the formation of spiro compounds **523–525**, whereas the reaction of mercaptoacetic acid, an α-amino acid and hydrazine hydrate furnishes the spiro compounds **526** and **527**, respectively. Compound **522** is generated by condensation of 1*H*-indole-2,3-dione with benzoyl acetatonitrile (Scheme 111).[196]

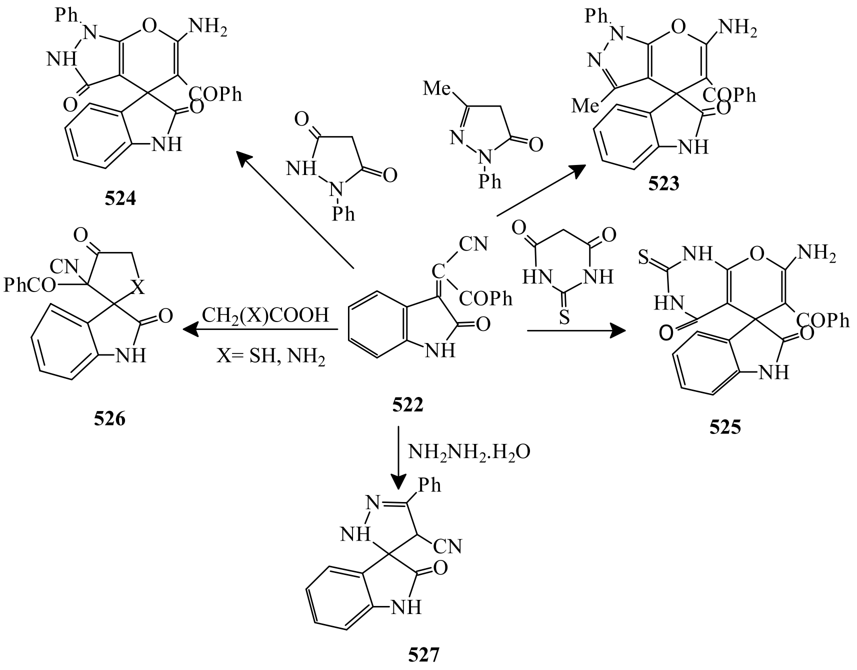
Arturo and co-workers[197] have studied the synthesis of thiaspirohexane (**529**) and azaspirohexane (**530**) by the cycloaddition of *N*-mesityl cyclopropylideneazomethine (**528**) with $Ph_2C{=}S$ and $PhN{=}C(CN)_2$, respectively. Compound **528** is synthesised by the reaction of mesitylcyclopropyl formimidoyl chloride with Me_3COK in THF (Scheme 112).

Chen et al.[198] have reported an efficient synthesis of (±) alantrypinone (**534**) by a hetero Diels–Alder reaction of a novel pyrazine diene (**531**) with a 3-alkylideneoxindole (**532**) through a spiro intermediate (**533**) (Scheme 113).

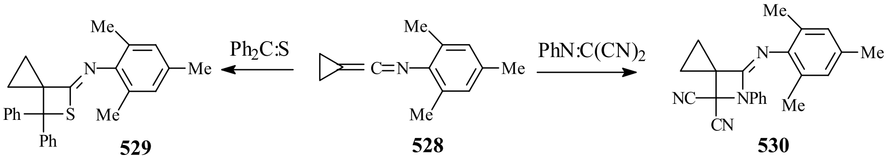
In a sequential process, an imine (**535**) prepared from isatin and *n*-butylamine undergoes cycloaddition with chloroacetyl chloride to afford a mixture of stereoisomeric



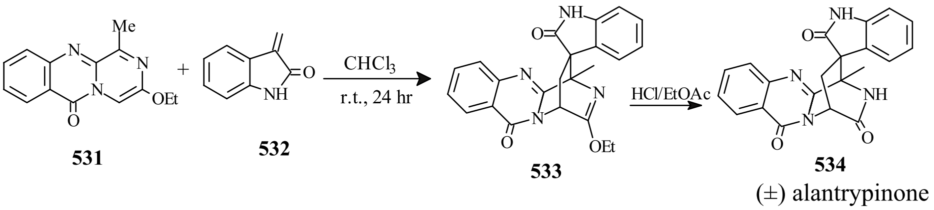
Scheme 110.



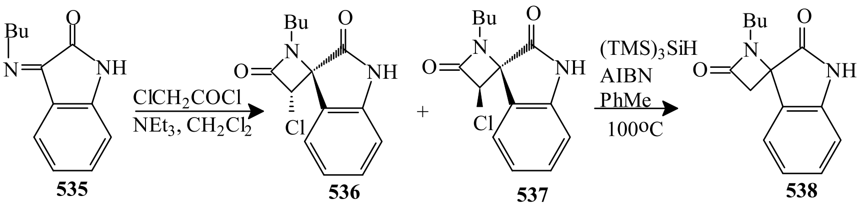
Scheme 111.



Scheme 112.



Scheme 113.

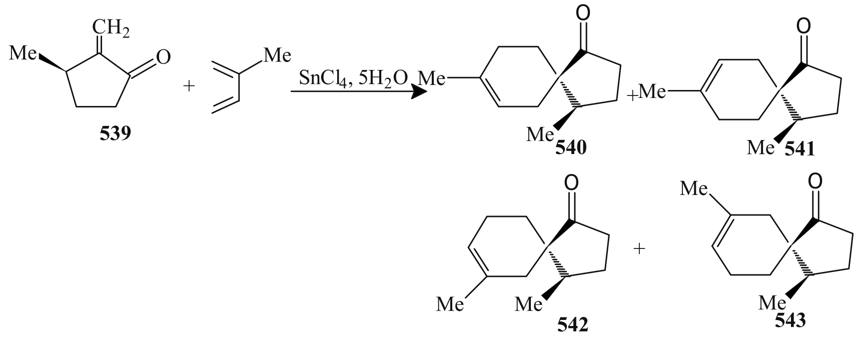


Scheme 114.

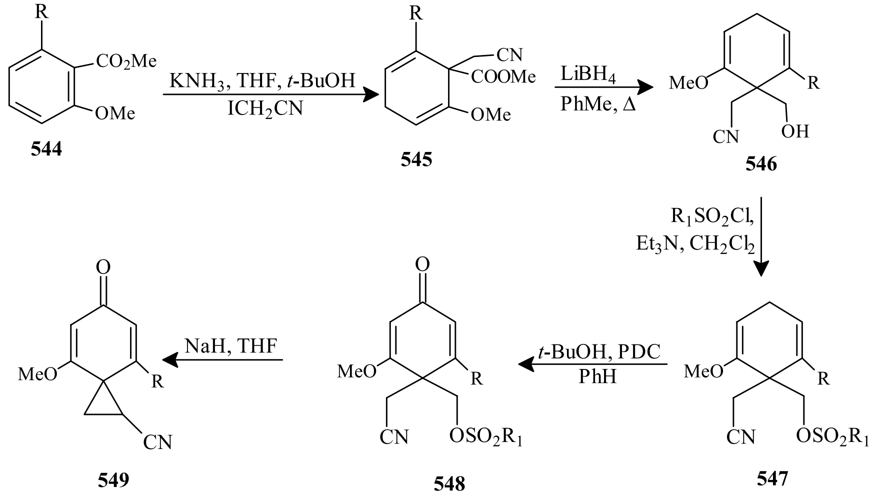
α-chloro-β-lactams (**536** and **537**). A free radical reduction of the mixture with tris(trimethylsilyl)silane leads to the formation of a spirocyclic β-lactam (**538**) (Scheme 114).[199]

In the synthesis of (−)-acorone and several spirosesquiterpenes, Marx and Norman[200] have used enone **539** as one of the synthon components. Enone **539** underwent a Lewis acid-catalysed Diels–Alder reaction with isoprene to give **540–543** (Scheme 115).

Schultz and Taveras[74] have reported the synthesis of spiro[2,5]octa-1,4-dien-3-ones (**549**) from methyl



Scheme 115.



$R = H, OMe; R_1 = Me, Ph$

Scheme 116.

2-methoxybenzoate (**544**) and iodoacetonitrile, through different intermediates **545–548** as shown in Scheme 116.

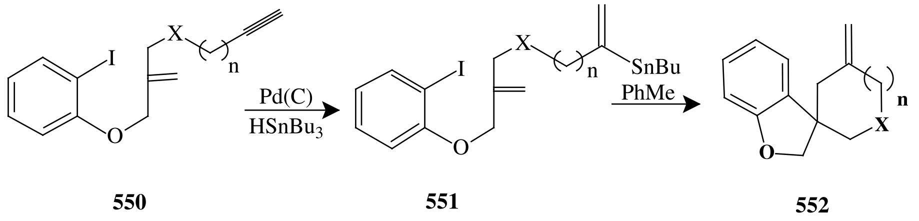
4.12. Synthesis of spiro compounds by using prestruct IIIb

Bond disconnections at a ring appendage as well as a branch appendage at two different rings generate prestruct **IIIb**. The synthon component consists of a branched acyclic compound. Grigg et al.[201] have synthesised a series of 5/6 and 5/12–17-membered bicyclospiro compounds using prestruct **IIIb**. The enynes (**550**) undergo regiospecific hydrostannylation to afford the α-vinylstannanes (**551**), which, on bis-cyclisation-anion capture, yield the spirocyles (**552**) via 5-*exo-trig* cyclisation followed by sp^3–sp^2 intramolecular Stille coupling (Scheme 117).

4.13. Synthesis of spiro compounds by using prestruct IIIc

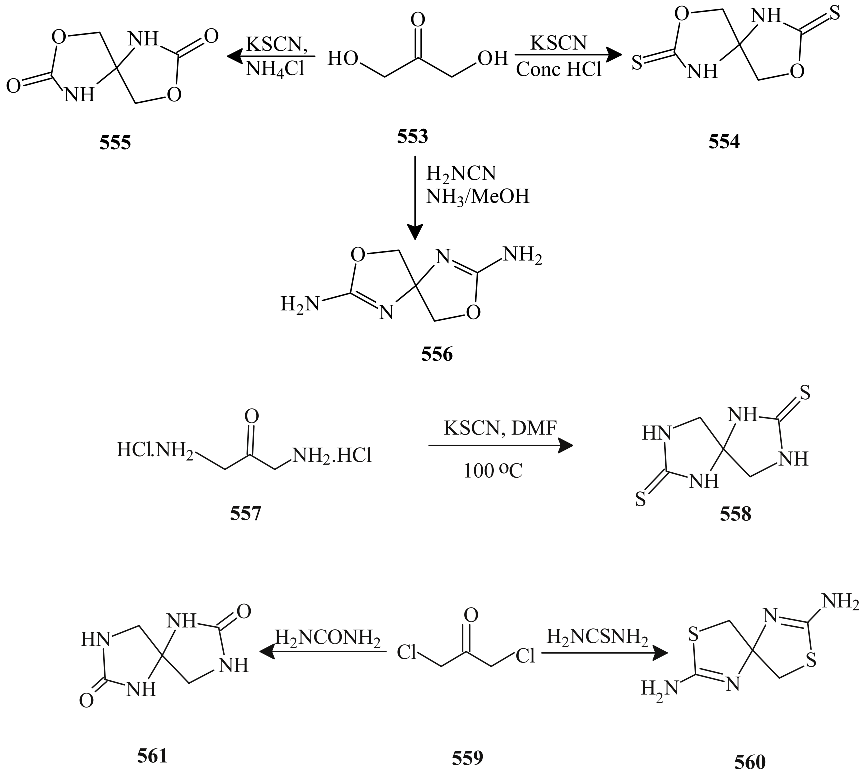
When bond disconnections take place at two ring appendages of one ring and a branch appendage of another ring, prestruct **IIIc** is generated. The synthon components are all alkyl groups.

From open-chain 1,3-disubstituted acetone derivatives (**553** and **557**), Saul et al.[202] have synthesised spirobisoxazolidine (**554–556**) and spirobisimidazolidine derivatives (e.g., **558**)

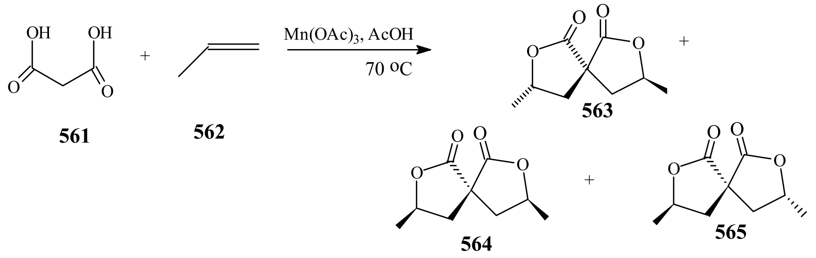


$n = 1,2; X = O, NCOPh, NSO_2Ph$

Scheme 117.



Scheme 118.



Scheme 119.

by reaction with different reagents. From a prochiral 1,3-dichloroacetone (**559**), the chiral spiro derivative **560** and **561** were obtained as racemic mixtures, which were further resolved by using brucine (Scheme 118).

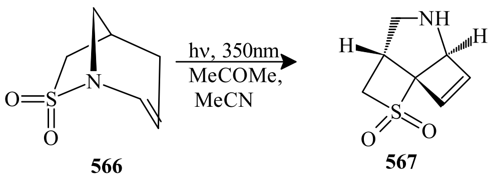
A similar strategy[203] has been followed for the synthesis of spirodilactones. A mixture of spirodilactones (**563**), (**564**) and (**565**) were synthesised using malonic acid (**561**) and an alkene (**562**) by heating at 70 °C in the presence of glacial acetic acid and manganese(III) acetate. The spiro centre is generated at the –CH$_2$– of malonic acid (Scheme 119). Of the possible three stereoisomers **563**, **564** and **565**, the unsymmetrical species **564** was the major product.

4.14. Synthesis of spiro compounds by using prestruct IIId

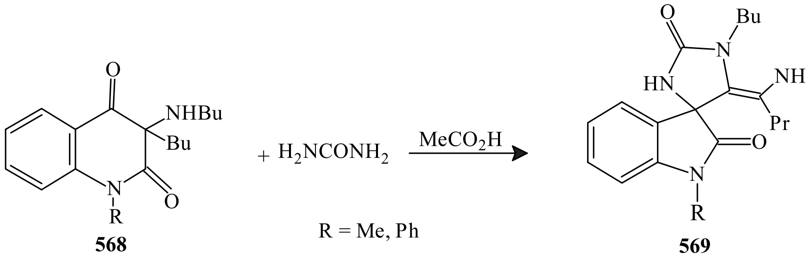
The prestruct **IIId** is due to bond disconnections at two ring appendages and two branch appendages, that is, two bond disconnections at one ring and two bond disconnections at the other ring. In this case the synthon components are four acyclic groups. No report has been available to us, however, describing the synthesis of spiro compounds by using synthon components corresponding to prestruct **IIId**.

4.15. Synthesis of spiro compounds by using a different type of prestruct

The synthesis of a strained spirocycle (**567**)[204] via photoinduced SO$_2$–N bond cleavage of **566** was carried out using a prestruct, which is due to three bond disconnections at three ring appendages of different rings. This is an unique example, which used a different type of prestruct (Scheme 120).



Scheme 120.



Scheme 121.

Some novel spirodiones (**569**) were synthesised using a different type of synthon component, **568**. 1-Alkyl/aryl-3-amino-1*H*,3*H*-quinolin-2,4-diones (**568**) react with urea in boiling acetic acid to form the spiro compounds (**569**)[205] (Scheme 121).

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References and notes

1. Takahashi, K.; Witkop, B.; Brossi, A.; Maleque, M. A.; Albuquerque, E. X. *Helv. Chim. Acta* **1982**, *65*, 252.
2. Srivastav, N.; Mittal, A.; Kumar, A. *J. Chem. Soc., Chem. Commun.* **1992**, 493.
3. Longeon, A.; Guyot, M.; Vacelet, J. *Experentia* **1990**, *46*, 548.
4. Kobayashi, J.; Tsuda, M.; Agemi, K.; Shigemiri, H.; Ishibashi, M.; Sasaki, T.; Mikami, Y. *Tetrahedron* **1991**, *47*, 6617.
5. James, D. M.; Kunze, H. B.; Faulkner, D. J. *J. Nat. Prod.* **1991**, *54*, 1137.
6. Fisher, E.; Hirshberg, Y. *J. Chem. Soc.* **1952**, 4522.
7. Hinshberg, Y. *Bull. Res. Council. Isr.* **1956**, *5A*, 188. *J. Am. Chem. Soc.* **1956**, *78*, 2304.
8. Berkovic, G.; Krongauz, V.; Weiss, V. *Chem. Rev.* **2000**, *100*, 1741.
9. Daly, J. W.; Kale, I. L.; Myers, C. W.; Tokueyama, T.; Waters, J. A.; Witkop, B. *Proc. Natl. Acad. Sci. U.S.A.* **1971**, *68*, 1870.
10. Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617.
11. (a) Hegnauer, R. In *Chemotaxonomie der Pflanzen*, *Vol. 3*; Birkhauser: Basel, 1964; p 447. (b) Zedero, C.; Bohlmann, F. *Plant Syst.* **1990**, *1*, 171.
12. Tada, M.; Chiba, K. *Agric. Biol. Chem.* **1984**, *26*, 1987.
13. Martinez, V.; Barbera, O.; Sanchez-Parareda, J.; Marco, J. A. *Phytochemistry* **1987**, *26*, 2619.
14. Breinclich, J.; Schannagel, K. *Arznei,-Forsch.* **1968**, *18*, 429.
15. Weyerstahl, P.; Wahlburg, H.; Kaut, V. K.; Lochynski, S. *Liebigs Ann. Chem.* **1992**, 279.
16. Tan, R.-X.; Jia, Z.-J.; Zhao, Y.; Feng, S.-L. *Phytochemistry* **1992**, *31*, 3405.
17. Cordell, G. A., Ed.; The Alkaloids: Chemistry and Biology; Academic: San Diego, 1998; Vol. 5.
18. Okita, T.; Isobe, M. *Tetrahedron* **1994**, *50*, 11143.
19. Rosemmond, P.; Hossemi, M. M.; Bub, C. *Liebigs Ann. Chem.* **1992**, *2*, 151.
20. Kornet, M. J.; Tnio, A. P. *J. Med. Chem.* **1976**, *19*, 892.
21. Jossang, A.; Jossang, P.; Hadi, H. A.; Sevenet, T.; Bodo, B. *J. Org. Chem.* **1991**, *56*, 6527.
22. Vidari, G.; Larfranchi, G.; Santori, P.; Serra, S. *Tetrahedron: Asymmetry* **1995**, *6*, 2977.
23. Fisher, C.; Meyers, C.; Carreira, E. M. *Helv. Chim. Acta* **2000**, *83*, 1175.
24. Tietze, L. F.; Schneider, G.; Wolfling, J.; Nobel, T.; Wulff, C.; Schubert, I.; Rubeling, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 2469.
25. (a) Lynn, G. D.; Phillips, N. J.; Hutton, W. C.; Shabanowitz, J.; Fennel, D. L.; Cole, R. J. *J. Am. Chem. Soc.* **1982**, *104*, 7319. (b) Tietze, L. F.; Schneider, G. *J. Org. Chem.* **1991**, *56*, 2476.
26. Carney, J. R.; Pham, A. T.; Yoshida, W. Y.; Scheuer, P. J. *Tetrahedron Lett.* **1992**, *33*, 7115.
27. Su, J.-Y.; Zhong, Y.-I.; Zeng, L.-M. *J. Nat. Prod.* **1993**, *56*, 288.
28. Vyvyan, J. R.; Rubens, C. A.; Halfen, J. A. *Tetrahedron Lett.* **2002**, *43*, 221.
29. Osz, E.; Szilagyi, L.; Somsak, L.; Benyei, A. *Tetrahedron* **1999**, *55*, 2419.
30. (a) Bichard, C. J. F.; Mitchell, E. P.; Wormald, M. R.; Watson, K. A.; Johnson, L. N.; Zographos, S. E.; Koutra, D. D.; Oikonomakos, N. G.; Fleet, G. W. J. *Tetrahedron Lett.* **1995**, *36*, 2145. (b) Parly, J. P.; Faure, R.; Josheph, B.; Kiss, L.; Rollin, P. *Tetrahedron* **1994**, *50*, 6559.
31. Karmer, M. S.; Cutler, N.; Feighner, J.; Shrivastava, R.; Carman, J.; Sramek, J. J.; Reines, S. A.; Liu, G.; Snavely, D.; Wyatt-Knowles, E.; Hale, J. J.; Mills, G. G.; Maccoss, M.; Swain, C. J.; Harrisson, T.; Hill, R. G.; Hefti, F.; Scolnick, E. M.; Cascieri, M. A.; Chicchi, G. G.; Sadowski, S.; Williams, A. R.; Hewson, L.; Smith, D.; Carlson, E. J.; Hargreves, R. J.; Rupniak, N. M. J. *Science.* **1998**, *281*, 1640.
32. Maligres, P. E.; Waters, M. M.; Lee, J.; Reamer, R. A.; Askin, D.; Ashwood, M. S.; Cameron, M. *J. Org. Chem.* **2002**, *67*, 1093.
33. Kulagowski, J. J. (PCT Int.Appl. W00047,562 (Cl. CO7 D221/20), Aug 17, 2000, GB Appl. 1999/2,881, Feb 9, 1999, p 80; *Chem. Abstr.* **1992**, *116*, 177116h.
34. Eggler, J. F.; Larson, E. R. US Patent 5,039,672 (Cl.514-210, CO7D498/10). Appl. 505, 304, April 05, 1990, p 15; *Chem. Abstr.* **1992**, *116*, 59214q.
35. (a) Malamas, M. S.; Hohman, T. C. *J. Med. Chem.* **1994**, *37*, 2059. (b) Malamas, M. S.; Hohman, T. C.; Miller, J. *J. Med. Chem.* **1994**, *37*, 2043.

36. Khalil, E. M.; Ojala, W. H.; Pradhan, A.; Nair, V. D.; Gleason, W. B.; Mishra, R. K.; Johnson, R. L. *J. Med. Chem.* **1999**, *42*, 628.
37. Srivastav, L. K.; Bajwa, S. B.; Johnson, R. L.; Mishra, R. K. *J. Neurochem.* **1988**, *50*, 960.
38. Baures, P. W.; Ojala, W. H.; Costain, W. J.; Ott, M. C.; Pradhan, A.; Gleason, W. B.; Mishra, R. K.; Johnson, R. L. *J. Med. Chem.* **1997**, *40*, 3594.
39. Rival, Y.; Hoffmann, R.; Didier, B.; Rybaltchenko, V.; Bourguignon, J.-J.; Wermuth, C. G. *J. Med. Chem.* **1998**, *41*, 311.
40. (a) Street, L. J.; Baker, R.; Book, T.; Kneen, C. O.; Macleod, A. M.; Merchant, K. J.; Showell, G. A.; Saunders, J.; Herbert, R. H.; Freedman, S. B.; Harley, E. A. *J. Med. Chem.* **1990**, *33*, 2690. (b) Swain, C.; Baker, R.; Kneen, C.; Herbert, R.; Moseley, J.; Seward, E. M.; Stevenson, G. I.; Beer, M.; Stanton, J.; Watling, K.; Ball, R. G. *J. Med. Chem.* **1992**, *35*, 1019.
41. Hu, T.; Curtis, J. M.; Walter, J. A.; Wright, J. L. C. *J. Chem. Soc., Chem. Commun.* **1995**, 2159.
42. Hu, T.; Curtis, J. M.; Walter, J. A.; Wright, J. L. C. *Tedrahedron Lett.* **1996**, *37*, 7671.
43. Hu, T.; Burton, I. W.; Cembella, A.; Curtis, J. M.; Quilliam, M. A.; Walter, J. A.; Wright, J. L. C. *J. Nat. Prod.* **2001**, *64*, 308.
44. Yasumoto, T.; Oshima, Y.; Yamaguchi, M. *Bull. Jpn. Soc. Sci. Fish.* **1978**, *44*, 1249.
45. (a) Uemura, D.; Chou, T.; Haino, T.; Nagatsu, A.; Fukuzawa, S.; Zheng, S.; Chen, H. *J. Am. Chem. Soc.* **1995**, *117*, 1155. (b) Chou, T.; Haino, T.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 4023.
46. Cordi, A. A.; Lacoste, J. M.; Descombees, J.-J.; Courchay, C.; Vanhoute, P. M.; Laubie, M.; Verbeuren, T. J. *J. Med. Chem.* **1995**, *38*, 4056.
47. Cordi, A. A.; Lactose, J.-M.; Le Borgne, F.; Herve. Y.; Vaysse-Ludot, L.; Descombes, J.-J.; Courchay, C.; Laubie, M.; Verbeuren, T. J. *J. Med. Chem.* **1997**, *40*, 2931.
48. Kolocouris, N.; Kolocouris, A.; Foscolos, G. B.; Fytas, G.; Neyts, J.; Padalko, E.; Balzarini, J.; Snoeck, R.; Andrei, G.; De Clercq, E. *J. Med. Chem.* **1996**, *39*, 3307.
49. Comey, C.; Marot, C.; Podona, T.; Baudin, M.-L.; Morin-Allory, L.; Guillaumet, G.; Pfeiffer, B.; Caignard, H.; Renard, P.; Rettoni, M.-C.; Adam, G.; Guardida-Lemaitri, B. *J. Med. Chem.* **1996**, *39*, 4285.
50. Karmer, R. M. *Exp. Med. Biol.* **1990**, *275*, 35.
51. (a) Nonato, M. G.; Garson, M. J.; Truscott, J. W.; Carver, J. A. *Phytochemistry* **1993**, *34*, 1159. (b) Buttery, R. G.; Juliano, B. O.; Ling, L. C. *Chem. Ind.* **1983**, 478.
52. Chou, T.; Kuramoto, M.; Otani, Y.; Shikano, M.; Yazawa, K.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 3871.
53. Kim, D. K.; Kudo, I.; Fujimori, Y.; Mizushima, H.; Masuda, M.; Kikuchi, R.; Ikizawa, K.; Inoue, K. *J. Biochem.* **1990**, *108*, 903.
54. Kuramoto, M.; Tong, C.; Yamada, K.; Chiba, T.; Hayashi, Y.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 3867.
55. Maelicke, A.; Albuquereque, X. *Drug Discovery Today* **1996**, *1*, 53.
56. *Molecular Electronics Devices, Molecular Electronics Devices II*; Carter, F. L., Ed.; Marcel Dekker: New York, 1982; p 1987.
57. Kawai, S. H.; Gilat, S. L.; Lehn, J. M. *J. Chem. Soc., Chem. Commun.* **1994**, 1011.
58. Newell, A. K.; Utley, J. H. P. *J. Chem. Soc., Chem. Commun.* **1992**, 800.
59. Liu, Z. F.; Hashimoto, K.; Fujishima, A. *Nature* **1990**, *658*, 347.
60. Saika, T.; Iyoda, T.; Honda, K.; Shimdzu, T. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1181.
61. Bisle, H.; Romer, M.; Rau, H. *Ber. Bunsenges. Phys. Chem.* **1976**, *80*, 301.
62. Durr, H.; Bouas-Laurent, H. *Photochromism, Molecule and Systems*; Elsevier: , 1990; Chapter 8 and references cited there in.
63. El'tsov, A. V. *Organic Photochromes*; Consultant Bureau: New York, 1990.
64. *Applied Photochromic Polymer Systems*; McArdle, C. B., Ed.; Blackie: London, 1992.
65. Proceedings of the 1st International Symposim on Photo-Chromism, *Mol. Cryst. Liq. Cryst.* **1994**, *246*.
66. Proceedings of the 2nd International symposim on photochromism, *Mol. Cryst. Liq. Cryst.* **1997**, *297*.
67. Carno, J. C.; Guglielmetti, R. J. Ed.; *Organic Photochromic and Thermochromic Compound*; Plenum: New York, 1998, Vol. 1 and 1999, Vol. 2.
68. Shragina, L.; Buchholtz, F.; Yitzchaik, S.; Krongauz, V. *Liq. Cryst.* **1990**, *7*, 643.
69. (a) Cabera, I.; Krongauz, V. *Macromolecules* **1987**, *20*, 2713. (b) Yitzchaik, S.; Cabera, I.; Buchholtz, F.; Krongaur, V. *Macromolecules* **1990**, *23*, 707.
70. Cabera, I.; Krongauz, V.; Ringsdorf, H. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1178.
71. (a) Kimura, K.; Kado, S.; Sakamota, H.; Sakai, A.; Yokoyama, M.; Tanaka, M. *J. Chem. Soc., Perkin Trans. 2* **1999**, 2539. (b) Sakamota, H.; Tanaka, M.; Kimura, K. *Chem. Lett.* **2000**, 928.
72. Tanaka, M.; Ikeda, T.; Xu, Q.; Ando, H.; Shibutani, Y.; Nakamura, M.; Sakamoto, H.; Yajima, S.; Kimura, K. *J. Org. Chem.* **2002**, *67*, 2223.
73. Hirano, M.; Osakada, K.; Nohira, H.; Miyashita, A. *J. Org. Chem.* **2002**, *67*, 533.
74. Schultz, G. A.; Taveras, G. A. *Tetrahedron Lett.* **1996**, *37*, 5853.
75. Corey, E. Z.; Jorgenson, W. L. *J. Am. Chem. Soc.* **1976**, *98*, 189.
76. Nagumo, S.; Suemune, H.; Sakai, K. *J. Chem. Soc., Chem. Commun.* **1990**, 1778.
77. Schobert, R.; Siegfried, S.; Gordon, G.; Mulholland, D.; Nieuwenhuyzen, M. *Tetrahedron Lett.* **2001**, *42*, 4561.
78. Jaivisuthunza, W.; Tarnchompo, B.; Thebtaranonth, C.; Thebtaranonth, Y. *Tetrahedron Lett.* **1996**, *37*, 3199.
79. Imanishi, T.; Kurumada, T.; Maezaki, N.; Sugiyama, K.; Iwata, C. *J. Chem. Soc., Chem. Commun.* **1991**, 1409.
80. Sharma, G. V. M.; Reddy, V. G.; Krishna, P. R. *Tetrahedron Lett.* **1999**, *40*, 1783.
81. Speckamp, W. N. *Heterocycles* **1984**, *21*, 211.
82. Zubkov, F. I.; Nikitina, E. V.; Turchin, K. F.; Aleksandrov, G. G.; Safronova, A. A.; Borisov, R. S.; Varlamov, A. V. *J. Org. Chem.* **2004**, *69*, 432.
83. Cossy, J.; Gille, B.; Bellosta, V. *J. Org. Chem.* **1998**, *63*, 3141.
84. Padmavati, V.; Balaiah, A.; Reddy, K. V.; Pdmaja, K.; Reddy, K. V. *Indian J. Chem.* **2002**, *41B*, 1670.
85. Coelho, P. J.; Carvalho, L. M.; Abrantes, S.; Oliveria, M. M.; Oliveria-Campos, A. M. F.; Samat, A.; Guglielmetti, R. *Tetrahedron* **2002**, *58*, 9505.

86. Sammelson, R. A.; Gurusinghe, C. D.; Kurth, J. M.; Olmstead, M. M.; Kurth, M. J. *J. Org. Chem.* **2002**, *67*, 876.
87. Tanaka, M.; Takahashi, M.; Sakamoto, E.; Imail, M.; Matsui, A.; Fujio, M.; Funakoshi, K.; Sakai, K.; Suemune, H. *Tetrahedron* **2001**, *57*, 1197.
88. Teng, Z.; Keese, R.; Stoeckli, E. H. *Tetrahedron* **1998**, *54*, 10699.
89. Li, J.; Zhang, Z.; Chen, Y.; Lu, X. *Tetrahedron Lett.* **1998**, *39*, 6507.
90. Moll, O. P. Y.; Borgne, T. L.; Thuery, P.; Ephritikhine, M. *Tetrahedron Lett.* **2001**, *42*, 3855.
91. Schulte, J. L.; Laschat, S.; Vill, V.; Nishikawa, E.; Finkelmam, H.; Nimtz, M. *Eur. J. Org. Chem.* **1998**, 2499.
92. Tanner, D.; Hagberg, L. *Tetrahedron* **1998**, *54*, 7907.
93. Koke, B. *Tetrahedron Lett.* **1996**, *37*, 3849.
94. Kido, S.; Abiko, P.; Kato, M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 229.
95. Pigge, F. C.; Coniglio, J. J.; Rath, N. P. *J. Org. Chem.* **2004**, *69*, 1161.
96. Drozd, V. N.; Knyazev, V. N.; Nam, N. L.; Yufit, D. S.; Struchkov, Y. T.; Stankevich, I. V.; Chistyakov, L. A. V. P.; Mozhaeva, T. Ya.; Saveljev, V. L. *Tetrahedron* **1992**, *48*, 469.
97. (a) Ashimori, A.; Overman, L. E. *J. Org. Chem.* **1992**, *57*, 4571. (b) Ashimori, A.; Bachand, B.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6477.
98. Yamaura, Y.; Hyakutake, M.; Mori, M. *J. Am. Chem. Soc.* **1997**, *119*, 7615.
99. Pearson, A. J.; Alimardonov, A.; Pinkerton, A. A.; Parrish, D. A. *J. Org. Chem.* **1998**, *63*, 6601.
100. Cossy, J.; Bouzide, A.; Leblanc, C. *Synlett* **1993**, 202.
101. Middleton, D.; Simpkins, N.; Begley, M.; Terrett, N. K. *Tetrahedron* **1990**, *46*, 545.
102. Martin-Lopej, M. J.; Bermejo, F. *Tetrahedron* **1998**, *54*, 12379.
103. Naf, F.; Decorzant, R.; Thommen, W. *Helv. Chim. Acta* **1975**, *58*, 1808.
104. Buchi, G.; Berthet, D.; Decorzant, R.; Grieder, A.; Hauser, A. *J. Org. Chem.* **1976**, *41*, 3208.
105. Suemune, H.; Takahashi, Y.; Sakai, K. *J. Chem. Soc., Chem. Commun.* **1993**, 1858.
106. Yamada, S.; Karasawa, S.; Takahashi, Y.; Aso, M.; Suemune, H. *Tetrahedron* **1998**, *54*, 15555.
107. Pearson, A. J.; Zettler, M. W. *J. Chem. Soc., Chem. Commun.* **1987**, 1243.
108. Singh, V. *Acc. Chem. Res.* **1999**, *32*, 324.
109. (a) Yamamoto, Y.; Furuta, T. *J. Org. Chem.* **1990**, *55*, 3971. (b) Schinzer, D. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 308.
110. Tokunaga, Y.; Yagihashi, M.; Ihara, M.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1997**, 189.
111. (a) Huang, H.; Forsyth, C. J. *J. Org. Chem.* **1995**, *60*, 2773. (b) Huang, H.; Forsyth, C. J. *Tetrahedron Lett.* **1993**, *34*, 7889.
112. Parsons, P. J.; Caddick, S. *Tetrahedron* **1994**, *50*, 13523.
113. Mori, K.; Yamamura, S.; Nishiyama, S. *Tetrahedron* **2001**, *57*, 5533.
114. Brands, K. M. J.; Dimichele, L. M. *Tetrahedron Lett.* **1998**, *39*, 1677.
115. Gao, Y.; Wu, W.-L.; Wu, Y.-L.; Ye, B.; Zhou, R. *Tetrahedron* **1998**, *54*, 12523.
116. Craig, D. C.; Edwards, G. L.; Sinclair, D. J. *Tetrahedron* **2001**, *57*, 563.
117. Zhang, W.; Pugh, G. *Tetrahedron Lett.* **1999**, *40*, 7595.
118. (a) Ladlow, M.; Pattenden, G. *Tetrahedron Lett.* **1984**, *25*, 4317. (b) Lee, E.; Tae, J. S.; Lee, C.; Park, C. M. *Tetrahedron Lett.* **1993**, *34*, 4831.
119. Edmonson, S. D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1138.
120. (a) Taniguchi, M.; Hino, T. *Tetrahedron* **1981**, *37*, 1487. (b) Taniguchi, M.; Anjiki, T.; Nakagawa, M.; Hino, T. *Chem. Pharm. Bull.* **1984**, *32*, 2544.
121. Semmelhack, M. F.; Yamashita, A. J. *J. Am. Chem. Soc.* **1980**, *102*, 5924.
122. Trost, B. M.; Hiroi, K.; Holy, N. *J. Am. Chem. Soc.* **1975**, *97*, 5873.
123. Ciblat, S.; Canet, J.-L.; Troin, Y. *Tetrahedron Lett.* **2001**, *42*, 4815.
124. Stork, G.; Danheiser, R. L.; Ganem, B. *J. Am. Chem. Soc.* **1973**, *95*, 3414.
125. Posner, G. H.; Hamill, T. G. *J. Org. Chem.* **1988**, *53*, 6031.
126. Asaoka, M.; Takenouchi, K.; Takei, H. *Chem. Lett.* **1988**, 1225.
127. Canonne, P.; Boulanger, R.; Angers, P. *Tetrahedron Lett.* **1991**, *32*, 5861.
128. Koft, E. R.; Smith, A. B. *J. Org. Chem.* **1984**, *49*, 832.
129. Shimada, J. I.; Hashimoto, K.; Kim, B. H.; Nakamura, E.; Kawajima, I. *J. Am. Chem. Soc.* **1984**, *106*, 1759.
130. Wu, Y.-J.; Zhu, Y.-Y.; Burnell, D. J. *J. Org. Chem.* **1994**, *59*, 104.
131. Zhu, Y.-Y.; Burnell, D. J. *Tetrahedron: Asymmetry* **1996**, *7*, 3295.
132. (a) Burnell, D. J.; Crane, S. N. *J. Org. Chem.* **1998**, *63*, 1352. (b) Crane, S. N.; Jenkins, T. J.; Burnell, D. J. *J. Org. Chem.* **1997**, *62*, 8722.
133. Burnell, D. J.; Crane, S. N. *J. Org. Chem.* **1998**, *63*, 5708.
134. Terec, A.; Grosu, I.; Muntean, L.; Toupet, L.; Ple, G.; Socaci, C.; Mager, S. *Tetrahedron* **2001**, *57*, 8751.
135. Pardasani, P.; Pardasani, R. T.; Chaturvedi, V.; Sexena, A. *Indian J. Chem.* **2003**, *42B*, 412.
136. Oda, M.; Fukuta, A.; Kajioka, T.; Uchiyama, T.; Kainuma, H.; Miyatake, R.; Kuroda, S. *Tetrahedron* **2000**, *56*, 9917.
137. Risitano, F.; Grassi, G.; Foti, F.; Romeo, R. *Synthesis* **2002**, 116.
138. Furuta, K.; Ikeda, Y.; Meguriya, N.; Ikeda, N.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2781.
139. Galvez, J. M. G.; Angers, P.; Canonne, P. *Tetrahedron Lett.* **1994**, *35*, 2849.
140. Dauben, W. G.; Hart, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 7307.
141. Nizamuddin, S. A. *Indian J. Chem.* **2004**, *43B*, 901.
142. Billups, W. E.; Saini, R. K.; Litosh, V. A.; Alemary, L. B.; Wilson, W. K.; Wiberg, K. B. *J. Org. Chem.* **2002**, *67*, 4436.
143. Kumar, S.; Pujari, H. K. *Indian J. Chem.* **1988**, *27B*, 912.
144. Sharma, R.; Kumar, S.; Pujari, H. K. *Indian J. Chem.* **1990**, *29B*, 440.
145. Joshi, K. C.; Chand, P.; Dandia, A. *Indian J. Chem.* **1984**, *23B*, 743.
146. Joshi, K. C.; Jain, R.; Dandia, A.; Sharma, V. *J. Heterocycl. Chem.* **1986**, *23*, 97.
147. Joshi, K. C.; Jain, R.; Dandia, A.; Arora, S. *J. Fluorine Chem.* **1989**, *42*, 149.
148. Joshi, K. C.; Jain, R.; Dandia, A.; Sharma, V. *Indian J. Heterocycl. Chem.* **1991**, *1*, 95.
149. Joshi, K. C.; Dandia, A.; Sharma, C. S.; Joshi, R. J. *Indian Chem. Soc.* **1994**, *71*, 459.
150. Joshi, K. C.; Jain, R.; Arora, S. J. *Indian Chem.* **1990**, *29B*, 369.

151. Joshi, K. C.; Jain, R.; Sharma, K.; Jain, S. C. *J. Indian Chem. Soc.* **1988**, *65*, 640.
152. Joshi, K. C.; Jain, R.; Sharma, K. *Heterocycles* **1990**, *31*, 473.
153. Joshi, K. C.; Dandia, A.; Khanna, S. *Indian J. Chem.* **1992**, *31B*, 105.
154. Joshi, K. C.; Dandia, A.; Khanna, S. *Indian J. Chem.* **1990**, *29B*, 824.
155. Joshi, K. C.; Jain, R.; Dandia, A.; Garg, S.; Ahmed, N. *J. Heterocycl. Chem.* **1989**, *26*, 1799.
156. Yang, L.; Morriello, G.; Prandergast, K.; Cheng, K.; Jacks, T.; Chan, W. W.-S.; Schleim, K. D.; Smith, R. G.; Patchett, A. A. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 107.
157. Sharma, K.; Saleem, A.; Salim, A. *Indian J. Chem.* **2003**, *42B*, 2866.
158. Shamuzzaman, S. N.; Salim, A. *Indian J. Chem.* **2004**, *43B*, 410.
159. Kondakov, D. Y.; Wang, S.; Negashi, E. *Tetrahedron Lett.* **1996**, *37*, 3803.
160. Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1991**, *113*, 701.
161. Toshima, H.; Aramaki, H.; Furumoto, Y.; Inamura, S.; Ichihara, A. *Tetrahedron* **1998**, *54*, 5531.
162. El-Shafei, A. K.; Sultan, A. A.; Soliman, A. M.; Ahmed, E. A. *Synth. Commun.* **1995**, *25*, 3211.
163. Svetlik, J.; Liptaj, T.; Hanus, V. *Czech. Liebigs Ann. Chem.* **1992**, *6*, 591.
164. Villar, J. M.; Delgado, A.; Llebaria, A.; Moreto, J. M.; Molins, E.; Miravitlles, C. *Tetrahedron* **1996**, *52*, 10525.
165. Pages, L.; Llebaria, A.; Camps, F.; Molins, E.; Miravitlles, C.; Moreto, J. M. *J. Am. Chem. Soc.* **1992**, *114*, 10449.
166. Jones, K.; Toutounji, T. *Tetrahedron* **2001**, *57*, 2427.
167. Baccalli, E. M.; Clerici, F.; Gelmi, M. L. *Tetrahedron* **1999**, *55*, 8579.
168. Okada, K.; Kondo, M.; Tanino, H.; Inoue, S. *Heterocycles* **1992**, *34*, 589.
169. Yadav, V. K.; Senthil, G.; Ganesh, B. K.; Parvez, M.; Reid, J. L. *J. Org. Chem.* **2002**, *67*, 1109.
170. Gemma, S.; Campiani, G.; Butini, S.; Morelli, E.; Minetti, P.; Tinti, O.; Nacci, V. *Tetrahedron* **2002**, *58*, 3689.
171. Maligres, P. E.; Waters, M. M.; Lee, J.; Reamer, R. A.; Askin, D.; Ashwood, M. S.; Cameron, M. *J. Org. Chem.* **2002**, *67*, 1093.
172. Keglevich, G.; Forintos, H.; Keseru, G. M.; Hegedus, L.; Toke, L. *Tetrahedron* **2000**, *56*, 4823.
173. Vedejs, E.; Marth, C. F. In *Phosphorus-31 NMR Spectral Properties in Compound Characterisation and Structural Analysis*; Quin, L. D., Verkade, J. G., Eds.; VCH: New York, 1994; Chapter 23, p 297.
174. Girgis, A. S.; Ibrahim, Y. A.; Mishriky, N.; Lisgarten, J. N.; Potter, B. S.; Palmer, R. A. *Tetrahedron* **2001**, *57*, 2015.
175. Hayashi, T.; Kanehira, H.; Hagihara, T.; Kumada, M. *J. Org. Chem.* **1988**, *53*, 113.
176. Alper, P. B.; Meyers, C.; Lerchner, A.; Siegel, D. R.; Carreira, E. M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3186.
177. Giomi, D.; Turchi, S.; Danesi, A.; Faggi, C. *Tetrahedron* **2001**, *57*, 4237.
178. Mclaughlin, M. J.; Shen, H. C.; Hsung, R. P. *Tetrahedron Lett.* **2001**, *42*, 609.
179. Zimmer, H.; Amer, A.; Baumann, F. M.; Haecker, M.; Hess, C. G. M.; Ho, D.; Huber, H. J.; Koch, K.; Mahnke, K.; Schumacher, C.; Wingfield, R. C. *Eur. J. Org. Chem.* **1999**, 2419.
180. Conia, J.-M.; Le Perchec, P. *Bull. Chim. Soc. Fr.* **1996**, 278.
181. Rzychon, B. K.; Eilbracht, P. *Tetrahedron* **1998**, *54*, 10721.
182. Schmidt, B.; Kocienski, P.; Reid, G. *Tetrahedron* **1996**, *52*, 1617.
183. Knolker, H.-J.; Jones, P. G.; Graf, R. *Synlett* **1996**, 1155.
184. Barluenga, J.; Aznar, F.; Barluenga, S.; Garcia-Granda, S.; Alvarez-Rua, C. *Synlett* **1997**, 1040.
185. Provencal, D. P.; Leahy, J. W. *J. Org. Chem.* **1994**, *59*, 5496.
186. Corinne, C.; Christophe, M.; Techao, P.; Marie-Laure, B.; Luc Morin-Allory, G. G.; Bruno, P.; Daniel-Henry, C.; Pierre, R. *J. Med. Chem.* **1996**, *39*, 4285.
187. (a) Suemune, H.; Maeda, K.; Kato, K.; Sakai, K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3441. (b) Kato, K.; Suemune, H.; Sakai, K. *Tetrahedron Lett.* **1992**, *33*, 3481. (c) Kato, K.; Suemune, H.; Sakai, K. *Heterocycles* **1994**, *37*, 413.
188. Baker, R. W.; Kyasnoor, R. V.; Sergeant, M. V. *Tetrahedron Lett.* **1999**, *40*, 3475.
189. Castulik, J.; Marck, J.; Mazal, C. *Tetrahedron* **2001**, *57*, 8339.
190. Chadha, V. K.; Sharma, K. S.; Pujari, H. K. *Indian J. Chem.* **1971**, *9B*, 1216.
191. Joshi, K. C.; Dandia, A.; Bhagat, S. *J. Fluorine Chem.* **1990**, *48*, 169.
192. Dandia, A.; Singh, R.; Arya, K. *Org. Prep. Proced. Int.* **2003**, *35*, 401.
193. Takshi, I.; Kazunohu, H.; Naniyuki, H.; Masami, Y.; Ken, J. K. *Tetrahedron* **1983**, *39*, 1281.
194. Sasaki, T.; Eguchi, S.; Hirako, Y. *Tetrahedron* **1976**, *32*, 437.
195. Dandia, A.; Singh, R.; Sachdev, H.; Gupta, R.; Paul, S. *J. Chin. Chem. Soc.* **2003**, *50*, 273.
196. El-Mary, T. I.; Ahmed, R. A.; Bakhite, E. A. *J. Chin. Chem. Soc.* **2001**, *48*, 921.
197. Arturo, B.; Gaetano, B.; Patrizia, G.; Elisabeta, F.; Piera, S.; Alessandro, D. *J. Org. Chem.* **1985**, *50*, 5368.
198. Chen, Z.; Fan, J.; Kende, A. S. *J. Org. Chem.* **2004**, *69*, 79.
199. Lin, X.; Weinreb, M. *Tetrahedron Lett.* **2001**, *42*, 2631.
200. Marx, J.; Norman, L. R. *J. Org. Chem.* **1975**, *40*, 1602.
201. Casaschi, A.; Grigg, R.; Sansano, J. M.; Vilson, D.; Redpath, J. *Tetrahedron* **2000**, *56*, 7541.
202. Saul, R.; Kern, T.; Kopf, J.; Pinter, I.; Koll, P. *Eur. J. Org. Chem.* **2000**, 205.
203. Fristad, W. E.; Hershberger, S. S. *J. Org. Chem.* **1985**, *50*, 1026.
204. Paquette, L. A.; Barton, W. R.; Gallucci, J. C. *Org. Lett.* **2004**, *6*, 1313.
205. Klasek, A.; Koristek, K.; Lycka, A.; Holcapek, M. *Tetrahedron* **2003**, *59*, 5279.

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Stereoselective preparation of trifluoromethyl containing 1,4-oxathiolane derivatives through ring expansion reaction of 1,3-oxathiolanes

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Abstract—Trifluoromethyl containing 1,4-oxathiolanes are synthesized in excellent yields and high stereoselectivities from the expansion reactions of sulfur ylide intermediates, which were prepared from the reaction of 2-diazo-3,3,3-trifluoro-propionic acid methyl ester and 1,3-oxathiolanes in the presence of $Rh_2(OAc)_4$.

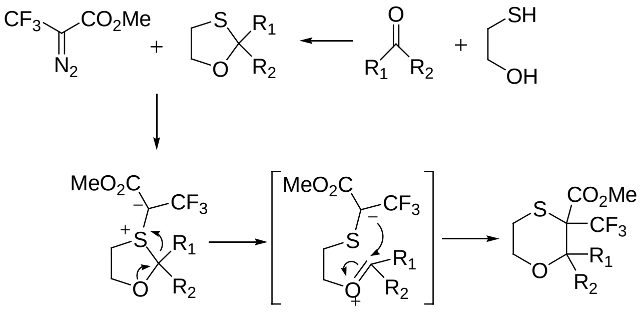
1. Introduction

Considerable attention has been given to trifluoromethyl containing organic compounds as agrochemical and pharmaceutical agents due to their unique properties arising from altered electron density, acidity, and lipophilicity.[1] Accordingly, the development of new methods for the synthesis of the trifluoromethyl containing organic compounds is continuous to be a an important area of research in agricultural, medicinal, and organic chemistry.[2] 1,4-Oxathiolanes are important heterocycles occurring in natural and medicinal molecules,[3] for example, RNA polymerase inhibitor tagetitoxin.[4] Although the preparation of nonfluoro-1,4-oxathiolane are well documented, however, the stereoselective ratio of the products mostly is still low, in particular to those containing quaternary carbons.[5] Furthermore, it is difficult to introduce fluorine atoms into 1,4-oxathiolanes.[6]

2. Results and discussion

As part of a project on synthesis of fluorine-containing molecules using fluorinated diazocompounds, we wish to develop a method to synthesize trifluoromethyl containing 1,4-oxathiolane through ring expansion of 1,3-oxathiolane started from 2-diazo-3,3,3-trifluoro-propionic acid methyl ester.

Porter et al. reported 1,4-oxathiolanes could be synthesized from the reaction of 1,3-oxathiolanes and a silylated diazoacetate in the presence of a copper catalyst in moderate yield and low diastereomeric ratio.[5] In this paper, we will report the stereoselective synthesis trifluoromethyl containing 1,4-oxathiolane from the reaction of 2-diazo-3,3,3-trifluoro-propionic acid methyl ester and 1,3-oxathiolanes (Scheme 1).



Scheme 1.

1,3-Oxathiolane **2** can be readily obtained from the reaction of 2-mercapto ethanol and carbonyl compounds in the presence of CAN in excellent yields. Initial studies were focus on the reaction of 1,3-oxathiolanes **2** derived from aromatic aldehydes and diazocompounds **1**. To a refluxing benzene solution of 1,3-oxathilane **2** and catalyst was added a benzene solution of diazocompound **1** in 2 h. The stirring continues for an additional 2 h. $Rh_2(OAc)_4$ is a superior catalyst than the copper catalysts, for example, $Cu(acac)_2$, which is contradict to the results reported by Porter.[5]

Keywords: Stereoselective synthesis; Diastereomeric ratio; Lipophilicity; Sulfur ylide; Diazo; Trifluoromethyl; 1,4-Oxathiolane.

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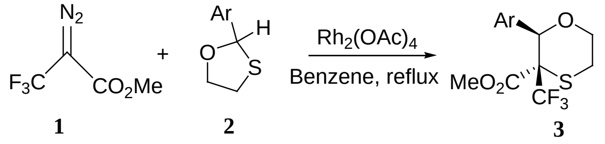
The reaction gives 1,4-oxathiolanes **3** in high yields with excellent diastereomeric ratio. 1,3-Oxathiolanes derived from the aromatic aldehydes substituted with electron-withdrawing groups lead to the products in relatively higher yields than those electron-donating ones, but with lower diastereometric ratio (Table 1, entries 6–8). Chemical shift data from the NMR spectrum of the products suggests that the major isomer is the one in which the carbmethoxy and phenyl groups are trans-oriented. Those electron-rich substrates give 1,4-oxathiolanes in higher trans/cis ratio than those electron-poor ones. For example, it gives to almost exclusively trans diastereoselective products when the aromatic ring was substituted with methoxy group (Table 1, entry 8). The nitro-substituted substrate, however, it gives only 3:2 trans/cis diastereoselective ratio (Table 1, entry 8).

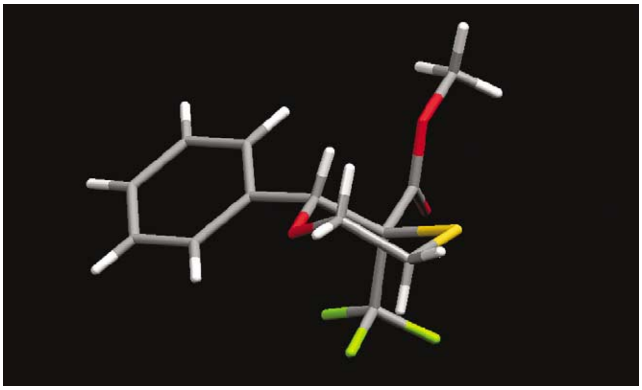
Table 1.



Entry	1,3-Oxathiolanes	Product	Yield (%)[a]	trans/cis[b]
1	Ar = Ph (**2a**)	**3a**	93	96:4
2	Ar = *o*-F–C_6H_4–(**2b**)	**3b**	65	97:3
3	Ar = *o*-Cl–C_6H_4–(**2c**)	**3c**	75	98:2
4	Ar = *o*-Br–C_6H_4–(**2d**)	**3d**	75	97:3
5	Ar = *p*-Br–C_6H_4–(**2e**)	**3e**	92	92:8
6	Ar = *p*-NO_2–C_6H_4–(**2f**)	**3f**	100	2:1
7	Ar = *p*-CH_3–C_6H_4–(**2g**)	**3g**	88	92:8
8	Ar = *p*-MeO–C_6H_4–(**2h**)	**3h**	83	> 99:1

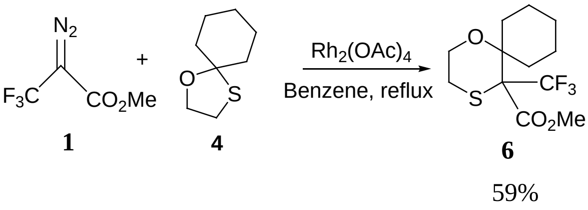
[a] All products were fully characterized by spectroscopic methods. The yields were isolated yields.
[b] Determined by ^{1}H NMR integration of the reaction mixture.

The relative stereochemistry of **3** was further confirmed by a X-ray crystal diffraction analysis of compound **3a** (Scheme 2). The structural analysis clearly shows the 1,4-oxathiolane ring of **3a** keeps in a thermodynamic stable chair conformation. The large groups, methoxyl carbonyl and phenyl ring, lie in the equatorial position of six-member ring. Trifluoromethyl group, smaller than methoxyl carbonyl group, situates in the axial position. What resulted in the low diastereomeric ratio (2:1) with regard to the reaction of 2-(4-nitro-phenyl)-1,3-oxathiolane with 1,4-oxathiolane? We know that the trifluoromethyl and aromatic ring are in cis position according to the crystallographic study. The electrostatic repulsion between the trifluoromethyl and nitrophenyl, an electron-deficient group, makes the relatively bulky methoxyl carbonyl group tend to be axial set, in order to reduce such repulsion.



Scheme 2. The molecular structure of **3a**.

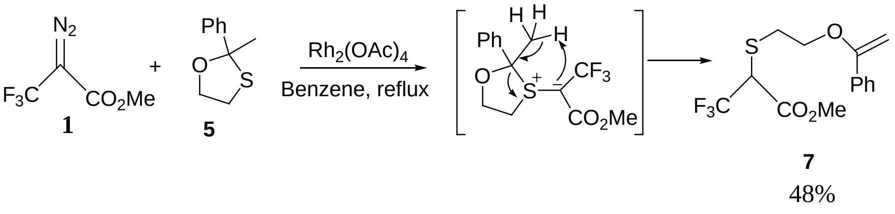
Spiro structures existed in many medicinally or biologically important molecules.[7] How to efficiently synthesize such compounds is still a challenge subject. It is in particular difficult to introduce fluorine atom into spiro-molecules. Spiro 1,3-oxathiolanes can be easily available from cyclic ketone with 2-mercapto ethanol. Based on the above experiments, the [1,2]-rearrangement of the intermediate sulfur ylides of spiro 1,3-oxathiolanes should give the trifluoromethyl containing spiro 1,4-oxatiolane. Under the same reaction conditions, the spiro compound **6** was indeed obtained in 59% yield, which was in line with our initial speculations (Scheme 3).



Scheme 3.

For comparison, 1,3-oxathiolane **5** was treated with trifluoromethyl diazoacetate **1** under similar reaction conditions, no [1,2]-rearrangement of intermediate sulfur ylides was not observed. The elimination product **7** was dominant (48%) (Scheme 4). The reaction might be preceded through a five-membered ring intermediate.

In summary, we have developed an efficient method for the stereoselective synthesis of trifluoromenthyl 1,4-oxathiolane through ring expansion of 1,3-oxathiolane ylide using



Scheme 4.

trifluoromethyl diazoactetate in the presence of $Rh_2(OAc)_4$. This catalytic, stereoselective and mild reaction will be the method of choice in many instances.

3. Experimental

Melting points were measured on a Temp-Melt apparatus and are uncorrected. Solvents were dried before use. ^1H, ^{19}F, and ^{13}C NMR spectra were recorded on a Varian-360L instrument or Bruker DRX-400 spectrometer with TMS and TFA ($\delta CFCl_3 = \delta TFA + 76.8$) as the internal and external standards and the upfield as negative. IR spectra were obtained with an IR-440 Shimadzu spectrophotometer. Low-resolution mass spectra and high-resolution mass spectra (HRMS) were obtained on a Finnigan GC–MS 4021 and Finnigan MAT-8430 instrument, respectively. The X-ray structural analysis was performed with a Rigaku/AFC 7R Diffractometer. Elemental analyses were performed by this Institute.

3.1. General procedure for ring expansion

A mixture of 1,3-oxathiolane (**2**) (1 mmol) and $Rh_2(OAc)_4$ (5 mg, 0.01 mmol) in dry benzene (2 mL) was heated to reflux under a nitrogen atmosphere. A solution of 2-diazo-3,3,3-trifluoro-propionic acid methyl ester (**1**) (201 mg, 1.2 mmol) in benzene (2 mL) was added dropwise over 2 h through syringe. Reflux was continued for 2 h, and then the mixture was allowed to cool to rt. The solvent was removed under reduced pressure and the residue was purified by a flash chromatography on silica gel (petroleum–ethyl acetate) to give the ring expansion product 1,4-oxathiolane (**3**). The procedure for the preparation of products **6** and **7** are similar to that of **3**.

3.1.1. 2-Phenyl-3-trifluoromethyl-1,4-oxathiinane-3-carboxylic acid methyl ester (3a). Colorless crystal with mp: 59–61 °C, yield: 93%, IR (KBr): 2987, 2957, 2924, 1747, 1498, 1455, 1432, 1253, 1164 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.44 (d, 1H, $J = 13.5$ Hz), 3.41 (t, 1H, $J = 12.3$ Hz), 3.80 (s, 3H), 4.07 (t, 1H, $J = 11.7$ Hz), 4.49 (d, 1H, $J = 11.4$ Hz), 5.49 (s, 1H), 7.32–7.46 (m, 5H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.7, 53.4, 55.8 (d, $J_{F\text{–}C} = 24.8$ Hz), 69.5, 82.4, 125.1 (q, $J_{F\text{–}C} = 283.3$ Hz), 127.2, 128.0, 128.5, 137.5, 166.1 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ −59.89 (s) ppm. EI-MS (*m/z*, %): 306 (M^+, 6), 200 (100), 172 (21), 105 (42), 77 (15), 59 (21). Anal. Calcd for $C_{13}H_{13}F_3O_3S$: C; 50.98, H; 4.28%. Found: C; 51.10, H; 4.25%.

X-ray data of **3a**

$C_{13}H_{13}F_3O_3S$: $M_w = 306.29$, CCDC no. 284941, orthorhombic, space group: $P2(1)2(1)2(1)$, $a = 6.755(10)$ Å $b = 7.867(11)$ Å, $c = 12.937(18)$ Å; $\alpha = 91.464(3)°$, $\beta = 92.651(3)°$, $\gamma = 108.662(2)°$; $V = 650.06(16)$ Å^3, $Z = 1$, $D_c = 1.794$ g/cm^3, $F(000) = 348$. Radiation, Mo Kα ($\lambda = 0.71073$ Å). Crystal dimension, $0.58 \times 0.44 \times 0.34$ mm.

Intensity data were collected at 293(2) K with a Bruker P4 four-circle diffractometer with graphite monochromator and Mo Kα radiation ($\lambda = 0.71073$ Å). A total of 8147 independent reflection were measured in range $2.36 < \theta < 27.0°$. The structure was solved by directed methods and expanded using Fourier techniques. The nonhydrogen atoms were refined anisotropically, hydrogen atoms were included but not refined. The final cycle of fullmatrix least-square refinement was base on F^2. The final R and wR value were 0.0490 and 0.1128, respectively. All calculations were performed using the SHELX-97 program.

3.1.2. 2-(2-Fluoro-phenyl)-3-trifluoromethyl-1,4-oxathiinane-3-carboxylic acid methyl ester (3b). Colorless crystal with mp: 71–73 °C, yield: 65%, IR (KBr): 3001, 2955, 2923, 1750, 1491, 1458, 1434, 1258, 1164 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.48 (d, 1H, $J = 13.2$ Hz), 3.43 (t, 1H, $J = 15.0$ Hz), 3.77 (s, 3H), 4.06 (t, 1H, $J = 12.0$ Hz), 4.49 (d, 1H, $J = 11.7$ Hz), 5.48 (s, 1H), 6.94–7.59 (m, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.1, 53.6, 57.2 (d, $J_{F\text{–}C} = 26.5$ Hz), 70.0, 82.3, 114.4, 114.7, 123.9, 129.1 (q, $J_{F\text{–}C} = 283.4$ Hz), 129.5, 130.8, 130.9, 165.0 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ −60.3 (s, 3F) −116.8 (s, 1F) ppm. EI-MS (*m/z*, %): 324 (M^+, 6), 200 (100), 172 (23), 123 (46), 113 (12), 59 (45). Anal. Calcd for $C_{13}H_{12}F_4O_3S$: C; 48.15, H; 3.73%. Found: C; 47.97, H; 3.84%.

3.1.3. 2-(2-Chloro-phenyl)-3-trifluoromethyl-1,4-oxathiinane-3-carboxylic acid methyl ester (3c). Colorless crystal, mp: 69–71 °C, yield: 75%, IR (KBr): 3011, 2958, 2967, 1934, 1740, 1478, 1437, 1258, 1160 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.49 (d, 1H, $J = 12.6$ Hz), 3.47 (t, 1H, $J = 13.5$ Hz), 3.75 (s, 3H), 4.06 (t, 1H, $J = 11.7$ Hz), 4.49 (d, 1H, $J = 11.7$ Hz), 5.59 (s, 1H), 7.25–7.65 (m, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.7, 54.0, 58.1, 70.2, 79.8, 125.4 (q, $J_{F\text{–}C} = 282.9$ Hz), 126.4, 128.5, 129.8, 130.5, 132.8, 135.3, 164.7 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ −59.7 (s, 3F) ppm. EI-MS (*m/z*, %): 340 (M^+, 2), 200 (100), 172 (20), 139 (27), 113 (11), 59 (34). Anal. Calcd for $C_{13}H_{12}ClF_3O_3S$: C; 45.82, H; 3.55%. Found: C; 45.85, H; 3.62%.

3.1.4. 2-(2-Bromo-phenyl)-3-trifluoromethyl-1,4-oxathiinane-3-carboxylic acid methyl ester (3d). Colorless crystal, mp: 97–99 °C, yield: 75%, IR (KBr): 3062, 2995, 2920, 1745, 1474, 1431, 1262, 1225, 1170, 1153, 1095 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.48 (d, 1H, $J = 13.8$ Hz), 3.46 (t, 1H, $J = 12.0$ Hz), 3.75 (s, 3H), 4.05 (t, 1H, $J = 12.0$ Hz), 4.49 (d, 1H, $J = 11.7$ Hz), 5.59 (s, 1H), 7.15–7.56 (m, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.7, 54.1, 58.0, 70.2, 82.4, 123.6, 125.5 (q, $J_{F\text{–}C} = 285.1$ Hz), 126.9, 130.1, 130.9, 131.8, 136.9, 164.6 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ −59.5 (s) ppm. EI-MS (*m/z*, %): 340/342 (M^+, 1/1), 200 (100), 185 (15), 183 (16), 172 (19), 113 (8), 59 (29). Anal. Calcd for $C_{13}H_{12}BrF_3O_3S$: C; 40.54, H; 3.14%. Found: C; 40.69, H; 3.27%.

3.1.5. 2-(4-Bromo-phenyl)-3-trifluoromethyl-1,4-oxathiinane-3-carboxylic acid methyl ester (3e). Colorless crystal, mp: 62–64 °C, yield: 92%, IR (KBr): 2996, 2957, 1749, 1489, 1338, 1249, 1173, 1162, 1099 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.44 (d, 1H, $J = 13.5$ Hz), 3.37 (t, 1H, $J = 12.3$ Hz), 3.78 (s, 3H), 4.02 (t, 1H, $J = 11.7$ Hz), 4.46 (d, 1H, $J = 11.7$ Hz), 5.41 (s, 1H), 7.24–7.26 (m, 2H), 7.41–7.44 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.0, 53.7, 55.3, 69.4, 85.8, 125.0 (q, $J_{F\text{–}C} = 283.4$ Hz), 129.1, 131.0, 131.4, 136.6, 166.0 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ -59.8 (s) ppm. EI-MS (*m*/*z*, %): 340/342 (M^+, 4/4), 200 (100), 185 (26), 183 (24), 172 (21), 113 (17), 77 (7), 59 (35). HR-EI-MS calcd for $C_{13}H_{12}BrF_3O_3S$ (M^+): 383.9643; found: 383.9657.

3.1.6. 2-(4-Nitro-phenyl)-3-trifluoromethyl-1,4-oxathiinane-3-carboxylic acid methyl ester (3f). Colorless crystal, mp: 77–79 °C, yield: 100%, IR (KBr): 3000, 2961, 2914, 1751, 1744, 1608, 1517, 1350, 1251, 1157, 1104, 1032 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.50 (d, 1H, $J=13.8$ Hz), 3.42 (t, 1H, $J=12.3$ Hz), 3.83 (s, 3H), 4.06 (t, 1H, $J=12.0$ Hz), 4.52 (d, 1H, $J=11.7$ Hz), 5.57 (s, 1H), 7.58–7.61 (m, 2H), 8.14–8.18 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.7, 53.8, 55.2, 69.3, 80.9, 123.0, 126.8, 130.5, 144.6, 147.8, 165.9 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ -59.7 (s) ppm. EI-MS (*m*/*z*, %): 351 (M^+, 1), 200 (100), 172 (17), 113 (3), 77 (1), 59 (5). Anal. Calcd for $C_{13}H_{12}NF_3O_5S$: C; 44.45, H; 3.44, N; 3.99%. Found: C; 44.36, H; 3.27, N; 3.89%.

3.1.7. 2-(4-Methyl-phenyl)-3-trifluoromethyl-1,4-oxathiinane-3-carboxylic acid methyl ester (3g). Pale yellow liquid, yield: 88%, IR (KBr): 3009, 2958, 2865, 2253, 1749, 1715, 1616, 1516, 1437, 1363, 1264, 1224, 1171, 1105 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.35 (s, 3H), 2.44 (d, 1H, $J=12.6$ Hz), 3.42 (t, 1H, $J=11.2$ Hz), 3.80 (s, 3H), 4.06 (t, 1H, $J=11.7$ Hz), 4.49 (d, 1H, $J=12.0$ Hz), 5.45 (s, 1H), 7.12–7.15 (m, 2H), 7.26–7.35 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.2, 24.7, 53.5, 55.8, 69.6, 82.4, 123.3, 127.1, 128.6, 134.6, 138.2, 166.2 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ -59.9 (s) ppm. EI-MS (*m*/*z*, %): 320 (M^+, 8), 200 (100), 172 (15), 119 (50), 91 (17), 84 (19), 59 (27). HR-MALDI-MS calcd for $C_{14}H_{15}F_3O_3SNa$ ($M+Na^+$): 343.0592; found: 343.0593.

3.1.8. 2-(4-Methoxyl-phenyl)-3-trifluoromethyl-1,4-oxathiinane-3-carboxylic acid methyl ester (3h). Pale yellow solid with mp: 82–84 °C, yield: 83%, IR (KBr): 3021, 2982, 2841, 1743, 1616, 1515, 1436, 1293, 1261, 1171, 1156, 1103 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.45 (d, 1H, $J=13.5$ Hz), 3.41 (t, 1H, $J=12.0$ Hz), 3.80 (s, 6H), 4.06 (t, 1H, $J=11.7$ Hz), 4.49 (d, 1H, $J=13.5$ Hz), 5.41 (s, 1H), 6.82–6.85 (m, 2H), 7.27–7.31 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.8, 53.4, 55.2, 55.7, 69.6, 82.1, 113.2, 125.2 (q, $J_{F-C}=281.2$ Hz), 128.5, 129.6, 159.6, 166.2 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ -59.8 (s) ppm. EI-MS (*m*/*z*, %): 336 (M^+, 18), 200 (100), 172 (16), 136 (98), 135 (82), 113 (10), 77 (9), 59 (21). Anal. Calcd for $C_{14}H_{15}F_3O_4S$: C; 50.00, H; 4.50%. Found: C; 50.00, H; 4.47%.

3.1.9. 5-Trifluoromethyl-1-oxa-4-thia-spiro[5.5]undecane-5-carboxylic acid methyl ester (6). Pale yellow liquid, yield: 59%, IR (KBr): 3403, 2959, 2881, 1750, 1708, 1440, 1354, 1282, 1252, 1147, 1111 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.38–1.87 (m, 6H), 2.01–2.05 (m, 2H) 2.30–2.34 (m, 2H), 2.86–3.04 (m, 2H), 3.76 (s, 3H), 3.86 (t, 1H, $J=5.7$ Hz), 4.18 (t, 1H, $J=8.1$ Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.6, 22.6, 27.6, 32.9, 53.2, 60.0, 77.1, 124.0 (q, $J_{F-C}=277.7$ Hz), 165.7 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ -52.1 (dd, $J^1=10.1$ Hz, $J^2=36.7$ Hz) ppm. EI-MS (*m*/*z*, %): 298 (M^+, 3), 200 (100), 188 (20), 159 (18), 142 (71), 91 (29), 59 (53), 45 (64). HR-MALDI-MS calcd for $C_{12}H_{17}F_3O_3SNa$ ($M+Na^+$): 321.0748; found: 321.0759.

3.1.10. 3,3,3-Trifluoro-2-[2-(1-phenyl-vinyloxy)-ethylsulfanyl]-propionic acid methyl ester (7). Pale yellow oil (152 mg, 48%), IR (KBr): 3467, 2959, 1751, 1713, 1686, 1439, 1361, 1269, 1147, 1111 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.21 (q, 2H, $J=4.8$ Hz), 3.80 (s, 3H), 3.82 (s, 1H), 4.10 (t, 2H, $J=6.0$ Hz), 4.23 (d, 1H, $J=3.0$ Hz), 4.72 (d, 1H, $J=3.3$ Hz), 7.34–7.62 (m, 5H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.4, 49.7, 53.2, 63.2, 83.2, 127.8 (q, $J_{F-C}=282.8$ Hz), 125.0, 125.4, 128.2, 128.6, 159.6, 165.6 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ -52.5 ppm. EI-MS (*m*/*z*, %): 321 (M^+, 15), 201 (100), 179 (6), 141 (17), 77 (5), 59 (8). HR-MALDI-MS calcd for $C_{14}H_{15}F_3O_3SNa$: 343.0592; found: 343.0598.

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References and notes

1. (a) *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; ACS Symposium Series 639; American Chemical Society: Washington, DC, 1996. (b) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123–3197. (c) *Synthesis and Chemistry of Agrochemical III*; Baker, D. R., Fenyes, J. G., Steffens, J. J., Eds.; ACS Symposium Series 504; American Chemical Society: Washington, DC, 1992.
2. (a) *Asymmetric Fluoroorganic Chemistry*; Ramachandran, P. V., Ed.; ACS Symposium Series 746; American Chemical Society: Washington, DC, 1999. (b) Kitazume, T.; Yamazaki, T. *Experimental Methods in Organic Fluorine Chemistry*; Gordon and Breach Science: Amsterdam, 1998. (c) Burton, D. J.; Yang, Z. Y.; Qiu, W. *Chem. Rev.* **1996**, *96*, 1641–1716.
3. Miyauchi, H.; Tanio, T.; Ohashi, N. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2377–2380.
4. (a) Mitchell, R. E.; Durbin, R. D. *Physiol. Plant Pathol.* **1981**, *18*, 157–168. (b) Mitchell, R. E.; Coddington, J. M.; Young, H. *Tetrahedron Lett.* **1989**, *30*, 501–504.
5. Ioannou, M.; Porter, M. J.; Saez, F. *Chem. Commun.* **2002**, 346–347.
6. Kawa, H.; Hamouda, H. A.; Ishikawa, N. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1694–1697.
7. Dandia, A.; Sachdeva, H.; Ahmed, N.; Joshi, K. C. *Heterocycl. Commun.* **2000**, *6*, 181–188.

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Tetrahedron

Callipeltins F–I: new antifungal peptides from the marine sponge *Latrunculia* sp.

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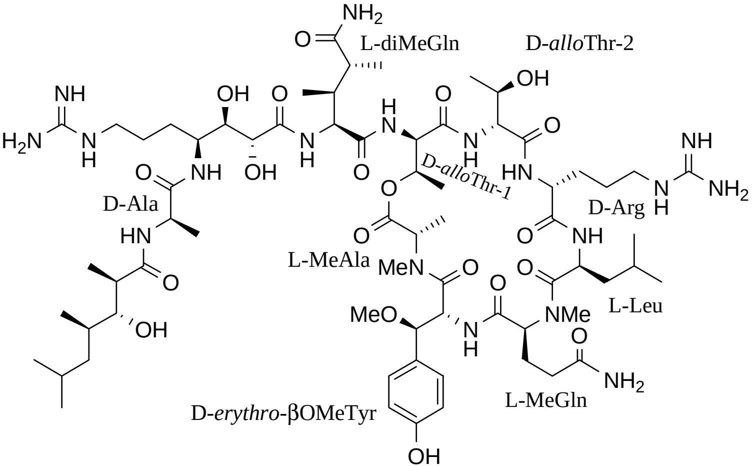
Abstract—Four new antifungal peptides, callipeltins F–I, were isolated from the marine sponge *Latrunculia* sp., collected off Vanuatu islands. Their structures were elucidated by NMR and MS analysis. The new callipeltins exhibited anti *Candida* activity in the 10^{-4} M range.

1. Introduction

Callipeltin A (**1**) and its congeners were isolated in our laboratories from the sponges *Callipelta* sp.[1,2] and *Latrunculia* sp.[3] Callipeltin A, that contains some unusual structural features such as the presence of numerous non-ribosomial amino acids and a unique N-terminal aliphatic hydroxy acid moiety, represents the first member of a class of potent antiviral marine peptides. This growing family comprises papuamides A–D, obtained from Papua New Guinea collections of the sponge *Theonella mirabilis* and *T. swinhoei*,[4] microspinamide from the Indonesian sponge *Sidonops microspinosa*[5] and neamphamide, from the Papua New Guinea sponge *Neamphius huxleyi*,[6] all sharing more or less a degree of structural homology suggesting a common pharmacophore. Recently, callipeltin A (**1**) was found to be a potent inotropic agent making it of interest as a regulator of myocardial contractility.[7,8] The combination of interesting biological activity, unsual aminoacids and complex molecular architecture have attracted the interest of the synthetic chemistry community. [9–19]



Callipeltina A (**1**)

Keywords: Callipeltin; Peptides; Antifungal.

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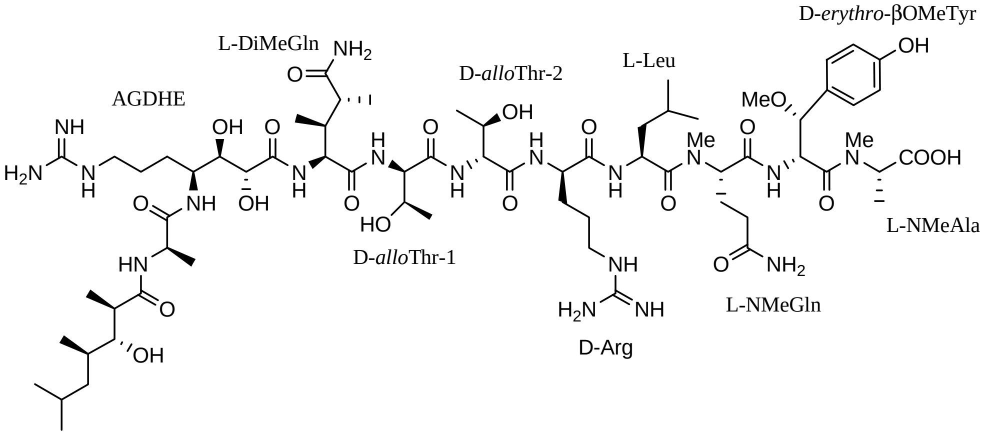
These synthetic efforts have enabled the confirmation of the absolute stereochemistry of the 3,4-dimethylglutamine residue,[10] the revision of the 3-hydroxy-2,4,6-trimethylheptanoic acid end group,[16–18] and the definition of the absolute stereochemistry of the β-OMeTyr unit.[19]

Callipeltin C (**2**), which is the acyclic derivative of callipeltin A, displays antifungal activity against *Fusarium oxysporum*, *Helminthosporium sativum*, *Phytophtora hevea*, and *Candida albicans*.

The absolute configurations of D-Ala, D-Arg and two D-*allo*Thr residues were determined by LC–MS analysis of the acid hydrolysate derivatized with Marfey's reagent (1-fluoro-2,4-dinitrophenyl)-5-L-alaninamide; L-FDAA)[20] and comparison with appropriate amino acid standards. To establish the absolute configuration of 3,4-diMeGln and AGDHE residues, an authentic sample of callipeltin A was hydrolysed and derivatised with L-FDAA. The configuration of the remaining stereocentres in callipeltin F was assumed to be the same of callipeltin A.



Callipeltin C (**2**)

In order to re-isolate further amounts of callipeltins for additional pharmacological studies, we re-examined the polar extracts of the sponge *Latrunculia* sp., still available in our laboratories in large amounts. After a careful sequential HPLC separation on Vydac and Thermo HyPurity columns, we were able to isolate minor callipeltin-related open-chain derivatives, named callipeltins F–I (**3**–**6**).

In this paper, we describe the isolation and the structure determination of the new compounds.

2. Results and discussion

The lyophilised sponge was extracted with methanol and the crude methanolic extract was subjected to a modified Kupchan's partitioning procedure. Fractionation of the butanol-soluble material (ca. 4 g) by DCCC ($CHCl_3$/MeOH/H_2O, 7:13:8 ascending mode) followed by repeated reversed phase HPLC afforded pure callipeltins F–I (**3**–**6**).

Callipeltin F (**3**) was obtained as colourless amorphous solid and its molecular formula was determined to be $C_{42}H_{79}N_{13}O_{14}$ by HR ESIMS. Extensive analysis of the ^{1}H and ^{13}C NMR data of **3**, including ^{1}H–^{1}H COSY, HMQC, HMBC spectra (see Table 1), by comparison with those of callipeltin C (**2**), disclosed the presence of one residue each of alanine (Ala), arginine (Arg), 3,4-dimethylglutamine (diMeGln), 4-amino-7-guanidino-2,3-dihydroxyheptanoic acid (AGDHE), 3-hydroxy-2,4,6-trimethylheptanoic acid, and of two residues of threonine (Thr). The amino acid sequence of **3** and placement of acyl substituent were assigned from the analysis of the fragmentation pattern in the ESI MS/MS mass spectrum (Fig. 1).

The molecular formula $C_{54}H_{100}N_{16}O_{17}$ of callipeltin G (**4**) was deduced by HR ESIMS [*m/z* 1245.7532 $(M+H)^+$]. COSY, HOHAHA, HMQC, HMBC experiments readily disclosed the presence, in addition to the same residues found in callipeltin F of one residue of leucine (Leu) and *N*-methylglutamine (MeGln). The sequencing of these units by the analysis of ESI MS/MS fragmentation peaks led to the structure as shown in Figure 2.

The stereochemistry of the amino acid residues was determined by Marfey's method to be D-*allo*Thr, D-Arg, L-Leu, L-MeGln, D-Ala.

Callipeltin H (**5**) analyzed for the molecular formula $C_{68}H_{116}N_{18}O_{20}$ by HR ESIMS. The NMR data for **5** were consistent with those of callipeltin C, except for the presence of a signal relative at a methyl group downfield shifted to $\delta=1.79$ and of an olefinic signal at $\delta=6.70$. One 2-amino-2-butenoic acid (dAbu) unit was assigned from the TOCSY and HMBC data, which provided correlations from the methyl signal at $\delta_H=1.79$ to the olefinic carbon signals at δ 134.4 and 131.0 and from the olefinic proton to carbonyl signal a δ 166.6. ROESY correlations (in CD_3OH) between the –NH signal at $\delta=9.74$ and the methyl signal at 1.79 indicated the (*Z*)-geometry for dAbu unit. The 2-amino-2-butenoic unit was found as common amino acid component of cyanobacteria hepatotoxins mycrocystins,[21–23] where is present in both geometrical isomers, whereas in the sponge peptides aciculitins it was found as (*E*) isomer.[24]

Comparison of the reported NMR data of the two geometrical isomers of the dAbu unit allowed a

Table 1. ^{1}H and ^{13}C NMR data (500 MHz, CD_3OD) for compounds **3**, **4** and **6**

aa	**3**		**4**		aa	**6**	
	δ_H[a]	δ_C	δ_H	δ_C		δ_H	δ_C
MeGlu					**MeGlu**		
α			5.14	57.6	α		
β			2.36, 2.02m	25.1	β		
γ			2.20 ovl	32.9	γ		
NMe			3.08	32.1	NMe		
CO				173.8	CO		
$CONH_2$				178.2	$CONH_2$		
Leu					**Leu**		
α			4.84dd (9.7, 3.1)	49.7	α		
β			1.72, 1.52m	40.8	β		
γ			1.70m	25.7	γ		
Me-γ			0.98d	23.4	Me-γ		
Me-ψ			0.96d	21.6	Me-ψ		
CONH				172.7	CONH		
Arg					**Arg**		
α	4.48t (7.8)	54.2	4.38 ovl	53.9	α	4.40m	58.0
β	1.97, 1.68m	29.2	1.93, 1.68m	29.6	β	1.96, 1.80m	29.6
γ	1.60m	25.2	1.67m	26.4	γ	1.68m	26.4
δ	3.24m	41.9	3.19m	41.9	δ	3.22m	41.9
CONH		173.0		173.2	CONH		173.0
Guan		157.8		157.4	Guan		157.8
***Allo*Thr-1**					***Allo*Thr**		
α	4.33 ovl	59.4	4.36 ovl	60.5	α	4.31 ovl d	60.1
β	4.13m	67.4	4.12m	68.6	β	4.17m	68.0
γ	1.27d (7.0)	18.7	1.27d (7.0)	20.4	γ	1.29d (7.0)	20.1
CONH		171.7		172.7	CONH		172.1
***Allo*Thr-2**					**dAbu**		
α	4.33 ovl	59.7	4.22d (6.1)	61.2	α	—	130.0
β	4.09 ovl	67.4	4.05m	68.4	β	6.71q (7.9)	133.1
γ	1.26d (6.0)	20.1	1.31d (6.0)	20.4	γ	1.78d (7.9)	13.2
CONH		171.5		171.5	CONH		171.5
DiMeGln					**DiMeGln**		
α	4.44 ovl	57.6	4.45d (9.7)	57.8	α	4.32 ovl	58.0
β	2.23m	39.1	2.21 ovl	39.6	β	2.30m	37.1
βMe	1.02d (6.8)	14.0	1.01d (6.8)	13.8	βMe	1.13d (7.4)	14.0
γ	2.63m	41.8	2.63m	42.0	γ	2.67m	42.6
γMe	1.20d (7.0)	19.9	1.18d (7.0)	15.8	γMe	1.25d (7.4)	15.0
CONH		174.1		175.4	CONH		171.9
$CONH_2$		179.3		179.2	$CONH_2$		180.0
AGDHE					**AGDHE**		
α	3.98d (7.1)	73.4	3.98d (7.1)	72.9	α	4.02d (7.1)	73.4
β	3.70dd (7.1, 2.7)	75.0	3.76dd (7.1, 2.7)	75.3	β	3.80dd (7.1, 2.1)	74.0
γ	4.15 ovl	50.2	4.15d (2.7)	50.7	γ	4.08m	51.0
δ	1.67, 1.30m	26.4	1.68, 1.30m	29.8	δ	1.67, 1.30m	29.6
ε	1.67m	25.7	1.65m	25.4	ε	1.67m	26.4
ζ	3.25m	42.0	3.19m	41.9	ζ	3.19m	42.0
CO		175.0		175.8	CO		176.1
Guan		157.8		157.8	Guan		157.8
Ala					**Ala**		
α	4.32 ovl	51.3	4.31q (7.3)	51.9	α	4.32 ovl	50.1
β	1.40d (7.3)	17.6	1.42d (7.3)	17.6	β	1.42d (7.6)	17.6
CONH		175.0		176.0	CONH		174.8
TMHEA					**TMHEA**		
1		177.9		178.8	1		177.9
2	2.63m	44.9	2.62m	44.9	2	2.63m	44.5
3	3.50dd (8.7, 2.7)	78.9	3.51dd (8.7, 2.7)	76.5	3	3.50dd (8.7, 2.9)	78.9
4	1.77m	34.0	1.76m	33.7	4	1.75m	32.6
5	1.26m	40.4	1.23m	39.8	5	1.20m	38.4
6	1.69m	24.8	1.69m	26.5	6	1.69m	25.7
7	0.97d (6.2)	23.8	0.95d (6.2)	24.5	7	0.97d (6.7)	23.7
8	1.08d (6.0)	14.4	1.08d (6.0)	14.6	8	1.08d (6.9)	14.4
9	1.01d (6.5)	17.5	0.99d (6.5)	17.4	9	0.99d (6.9)	17.3
10	0.88d (6.5)	21.8	0.88d (6.5)	21.6	10	0.88d (6.7)	20.9

[a] Coupling constants are in parentheses and given in Hz. ^{1}H and ^{13}C assignments aided by COSY, TOCSY, HMQC and HMBC experiments. ovl: signal overlapped.

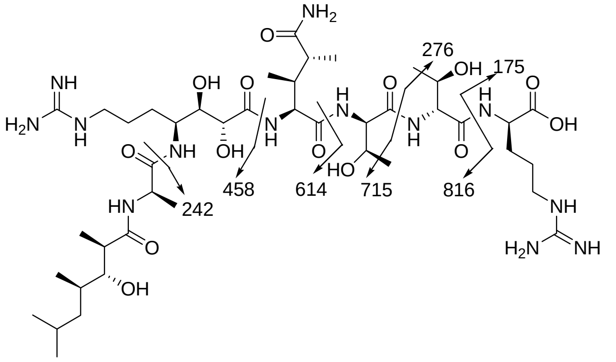


Figure 1. Callipeltin F (**3**) with ES MS/MS fragmentations.

confirmation of the proposed stereochemistry. The vinyl proton was observed at δ_H 6.5 ppm in the (*Z*)-isomer and at δ_H 5.7 ppm in the (*E*)-isomer. Similarly the C-3 carbon is downfield shifted in the (*Z*)-isomer (δ_C 129.3 vs 123.8 ppm). NMR chemical shifts of the dAbu unit in callipeltin H (Table 2) well mach those reported for the (*Z*)-isomer. It has been suggested that the dAbu residue could biogenetically arise by anti-dehydradation of the threonine[23] affording the *E* isomer from *allo*Thr end the *Z* isomer from Thr. The co-occurrence in the same sponge of callipeltins containing D-*allo*Thr residue and of the corresponding derivatives containing the (*Z*)-dAbu residue rules out the hypothesis of a direct origin of callipeltin H and I from callipeltin C and F, respectively.

The amino acid sequence of **4** and placement of the acyl moiety were assigned from a combination of ESI MS/MS data, interesidue NOE interactions and HMBC correlations (Table 2 and Figure 3). The alignment of amino acid residues from the C-terminus *N*-MeAla to *allo*Thr was the same as that of callipeltin C as secured by diagnostic b type fragmentations depicted in Figure 3.

ROESY cross-peak between the *allo*Thr-NH (δ 7.86) and the dAbu-NH (δ 9.74) established an amide linkage between these two residues. The sequence of remaining units in callipeltin H was deduced from inter-residue NOE interaction NH/CHα as shown in Table 2.

The absolute configuration of the amino acid residues was determined by Marfey's method to be D-*allo*Thr, D-Arg, L-Leu, L-MeGlu, D-Ala.

To define the chirality of β-OMeTyr residue, a sample of **4** was ozonised and hydrolysed and subjected to Marfey's analysis. Ion selective monitoring for L-FDAA-OMeAsp (*m/z* 416) showed a peak at t_R 17.30 corresponding to 2*R*,3*S* β-OMeAsp, indicating a 2*R*,3*R* stereochemistry of β-OMeTyr residue.[19]

The molecular formula $C_{42}H_{77}N_{13}O_{13}$ of callipeltin I (**6**), deduced by HR ESIMS, indicated the loss of one water molecule from callipeltin F. The presence of a 2-amino-2-butenoic acid (dAbu) unit was clearly inferred by the inspection of the ^1H NMR spectrum. The sequencing of the amino acid units was determined by the analysis of ESI MS/MS fragmentation peaks (Fig. 4). The stereochemistry of the amino acid residues was determined by Marfey's method to be D-Ala, D-*allo*Thr, D-Arg.

The finding of D-*allo*Thr in all new callipeltins is in contrast with our previous studies on callipeltin A–E[3] and this results prompted us to reinvestigate the stereochemistry of the threonine residues in callipeltin A. Thus, callipeltin A was subjected to acid hydrolysis, Marfey's derivatisation and LC–MS analysis. A single peak corresponding to D-*allo*Thr was observed by ion-selective monitoring for FDAA-Thr (*m/z* 372). Our original misassignment (L-Thr vs D-*allo*Thr) was due likely to the presence of an unassigned peak,[3] probably arising from a side reaction of a residue in callipeltin A during the hydrolysis. This fortuitously had the same retention time of FDAA derivative of L-Thr (12.5 min), but different molecular weight (*m/z* 292).

The new callipeltin derivatives were tested for the anti HIV1 activity measured on infected human T-lymphoblasoid cells. No inhibition was observed even at high tested concentration of 2 μg/mL, indicating the importance of the conformationally constrained cyclic structure for the antiviral activity observed for callipeltin A and related cyclodepsipetides.

Callipeltins F–I inhibit the growth of *Candida albicans* (ATCC24433) in the standard disk assay with a MIC of 10^{-4} M.

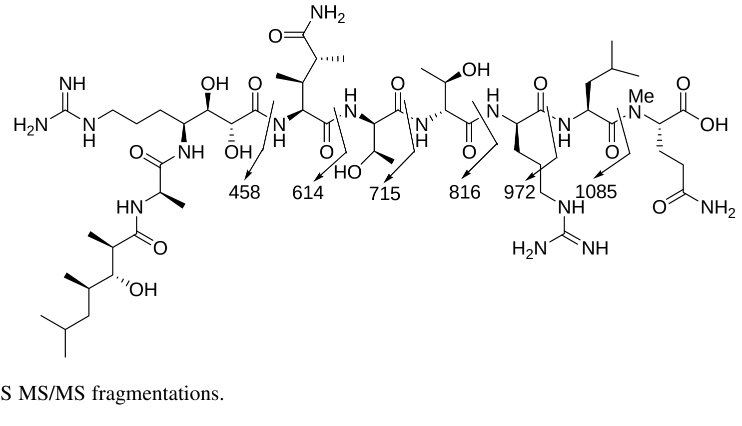


Figure 2. Callipeltin G (**4**) with ES MS/MS fragmentations.

Table 2. ^{1}H and ^{13}C NMR data (500 MHz, CD$_3$OD) for callipeltin H (**5**) in CD$_3$OH

Residue	δ_H^{a}	δ_C	HMBC (^{1}H to ^{13}C)	NOE^b
TMHEA				
1		179.2		
2	2.61m	44.6	C1	Ala-N*H*
3	3.51dd (8.5, 2.4)	79.5		
4	1.76m	33.5		
5	1.19m	39.1		
6	1.69m	26.1		
7	0.98d (6.2)	24.2		
8	1.11d (6.0)	14.5	C1	
9	1.10d (6.5)	17.2		
10	0.88d (6.5)	21.2		
OH	na			
Ala				
α	4.33 ovl	51.2	C1-TMHEA	AGDHE-*NH*-4
β	1.41d (6.7)	17.6	CO	
CONH	8.30d (6.5)	175.6		TMHEA-2
AGDHE				
α	4.07 ovl	73.6	CO	DiMeGln-N*H*
β	3.79dd (6.2, 2.6)	75.1		
γ	4.09 ovl	50.7		
δ	1.69, 1.30m	26.1		
ε	1.62m	26.1		
ζ	3.17m	41.6	Guan	
CO		176.6		
Guan	7.26 br s	157.8		
OH-2	7.72 br s			
OH-3	na			
NH-4	7.76 br s			α-Ala
DiMeGln				
α	4.34 ovl	58.5	CONH	*allo*Thr-N*H*
β	2.29m	38.5	CONH$_2$	
βMe	1.13d (6.8)	14.8	Cγ, Cα	
γ	2.70m	43.4	CONH$_2$	CO*NH$_2$*
γMe	1.25d (6.3)	15.4	CONH$_2$	CO*NH$_2$*
CONH	8.91 br s	173.1		
CONH$_2$	7.61 br s	180.8		
dAbu				
α		131.0		
β	6.70q (7.3)	134.4	CO	
γ	1.79d (7.3)	14.2	Cβ, Cα	NH
CONH	9.74s	166.6		*allo*Thr-N*H*, DiMeGln-N*H*
***Allo*Thr**				
α	4.24t (6.7)	61.4	CO	
β	4.14m	68.8		
γ	1.34d (7.7)	20.5		N*H*
CONH	7.86d (6.7)	173.1		
Arg				
α	4.35t (7.8)	54.1		NH-leu
β	1.91, 1.74m	29.2		
γ	1.60m	25.2		
δ	3.17m	41.9	Guan	
CONH	7.66 ovl	na		
Guan	7.26 br s	157.8		
Leu				
α	4.70dd (9.5, 4.1)	50.2		
β	1.61, 1.44m	40.1		
γ	1.65m	25.8		
Me-γ	0.95d (7.0)	21.2		
Me-ψ	0.98d (6.8	24.2		
CONH	8.20d (6.3)	172.9		α-Arg
MeGlu				
α	4.97dd (10.4, 4.5)	55.2		
β	1.72, 1.51m	25.6		
γ	1.93, 2.04m	32.1	CONH$_2$	
NMe	3.09s	32.3	CO-Leu	
CO		na		
CONH$_2$	na	176.9		
β-OMeTyr				
α	5.22d (10.7)	54.2	CO	
β	4.34d (10.7)	85.1	CO, C4	
C4		129.7		

(*continued on next page*)

Table 2 (*continued*)

Residue	δ_H[a]	δ_C	HMBC (^1H to ^{13}C)	NOE[b]
C5	7.21d (6.8)	129.7	C7	
C6	6.78d (6.8)	115.9		
C7		159.4		
OH	na			
OMe	3.14s	56.7	C2	
CONH	7.67 ovl	175.8		
MeAla				
α	5.12q (6.7)	57.7		
β	1.41d (6.7)	14.4	COOH	
NMe	2.84s	31.4	Cα, CO-βOMeTyr	
COOH		170.7		

[a] Coupling constants are in parentheses and given in Hz.

[b] Correlations were obtained by NOESY with a 400 ms mixing time. na: not assigned. ovl: signal overlapped.

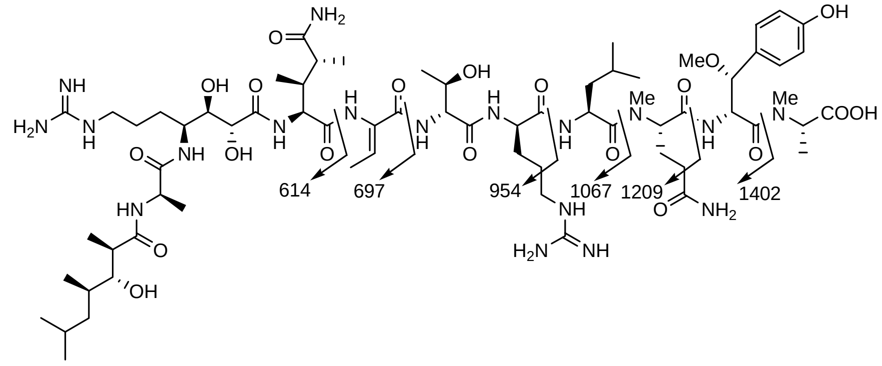


Figure 3. Callipeltin H (**5**) with ES MS/MS fragmentations.

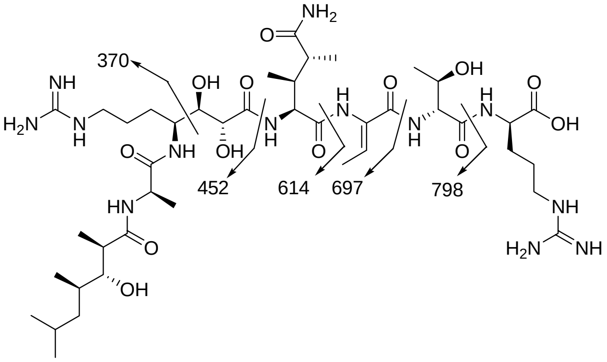


Figure 4. Callipeltin I (**6**) with ES MS/MS fragmentations.

3. Experimental

3.1. General experimental procedures

Specific rotations were measured on a Perkin-Elmer 243 B polarimeter. High-resolution ESI-MS spectra were performed with a Micromass QTOF Micro mass spectrometer. ESI MS experiments were performed on a Applied Biosystem API 2000 triple-quadrupole mass spectrometer. NMR spectra were obtained on a Varian Mercury-400 and Inova- 500 NMR spectrometers (^1H at 400 and 500 MHz, ^{13}C at 100 and 125 MHz, respectively) equipped with a Bruker X-32 hardware, δ (ppm), J in Hz, spectra referred to CD_2HOD as internal standards ($\delta_H = 3.30$). HPLC was performed using a Waters Model 6000 A pump equipped with U6K injector and a differential refractometer, model 401.

3.2. Sponge material and separation of individual peptides

Latrunculia sp. (Family Latrunculidae, Demospongiae: Poecilosclerida) was collected at a depth of 15–20 m at Emae, Vanuatu South Pacific, in June 1996. The samples were frozen immediately after collection and lyophilised to yield 800 g of dry mass. Taxonomic identification was performed by Prof. John Hooper of Queensland Museum, Brisbane, Australia and reference specimens are on file (R1642) at the ORSTOM Centre of Noumea. Preliminary tests of bioactivity on polar extracts showed antifungal activity against *Candida albicans* and cytotoxic activity against L16 cells (10 μg/mL, 100% inhibition).

The lyophilised material (800 g) was extracted with methanol (4×2.5 L) at room temperature and the crude methanolic extract (80 g) was subjected to a modified Kupchan's partitioning procedure as follows. The methanol extract was dissolved in a mixture of $MeOH/H_2O$ containing 10% H_2O and partitioned against *n*-hexane. The water content (% v/v) of the MeOH extract was adjusted to 20 and 40%, and partitioned against CCl_4 and $CHCl_3$, respectively. The aqueous phase was concentrated to remove MeOH and then extracted with *n*-BuOH. The buthanol-soluble material (ca. 4 g) was chromatographated by DCCC in five runs

($CHCl_3$/MeOH/H_2O, 7:13:8, ascending mode) and fractions of 4 mL were collected.

Fractions 10–11 were purified by HPLC on a Vydac C18 column (10 μ, 250×10 mm, 4 mL/min) with CH_3CN/H_2O 28% (0.1% TFA) as eluent to give 4.8 mg of pure callipeltin F **3** ($t_R = 5.0$ min). The additional peak at $t_R = 5.2$ min was further purified by HPLC on a Thermo-Hypurity column (5 μ, 250×4.6 mm) eluting with CH_3CN/H_2O 24% containing 0.01% TFA (flow rate 1.2 mL/min) to give 2.4 mg of pure callipeltin I **6** ($t_R = 3.0$ min).

Fractions 12–13 were purified by HPLC on a Vydac C18 column (10 μ, 250×10 mm, 4 mL/min) with CH_3CN/H_2O 28% (0.1% TFA) as eluent to give a peak at $t_R = 5.0$ min containing mainly callipeltin G (**4**) that was further purified by HPLC on a Thermo-Hypurity column (5 μ, 250×4.6 mm) eluting with CH_3CN/H_2O 27% containing 0.05% TFA (flow rate 1.2 mL/min) to give 4.9 mg of pure **4** ($t_R = 4.0$ min).

Fractions 14–15 were purified by HPLC on a Vydac C18 column (10 μ, 250×10 mm, 4 mL/min) eluting with CH_3CN/H_2O 30% (0.1% TFA) to give a peak at $t_R = 10.8$ min containing a mixture of callipeltin C (**2**) and callipeltin H. Further purification by HPLC on a Thermo-Hypurity column (5 μ, 250×4.6 mm) eluting with CH_3CN/H_2O 27% containing 0.05% TFA (flow rate 1.2 mL/min) gave 9.3 mg of pure callipeltin H **5** ($t_R = 6.2$ min).

3.3. Characteristic of each compounds

3.3.1. Callipeltin F (3). 4.8 mg, white amorphous solid; $[\alpha]_D^{25}$ −4.3 (*c* 0.35, methanol); ^1H and ^{13}C NMR data in CD_3OD given in Table 1; ESI-MS: m/z (%) 990.6 (35) $[M+H]^+$, 496.0 (100) $[M+2H]^{++}$. HRMS (ESI): calcd for $C_{42}H_{80}N_{13}O_{14}$: 990.5942; found 990.5938 $[M+H]^+$.

3.3.2. Callipeltin G (4). 4.9 mg, white amorphous solid; $[\alpha]_D^{25}$ −5.3 (*c* 0.26, methanol); ^1H and ^{13}C NMR data in CD_3OD given in Table 1. ESI-MS: m/z (%) 1245.7 (100) $[M+H]^+$. HRMS (ESI): calcd for $C_{54}H_{101}N_{16}O_{17}$: 1245.7525; found 1245.7532 $[M+H]^+$.

3.3.3. Callipeltin H (5). 9.3 mg, white amorphous solid; $[\alpha]_D^{25}$ −4.5 (*c* 0.71, methanol); ^1H and ^{13}C NMR data in CD_3OH given in Table 2. ESI-MS: m/z (%) 1505.7 (25) $[M+H]^+$, 753.7 (100) $[M+2H]^{++}$. HRMS (ESI): calcd for $C_{68}H_{117}N_{18}O_{20}$: 1505.8686; found 1505.8677 $[M+H]^+$.

3.3.4. Callipeltin I (6). 2.4 mg, white amorphous solid; $[\alpha]_D^{25}$ 1.3 (*c* 0.37, methanol); ^1H and ^{13}C NMR data in CD_3OD given in Table 1. ESI-MS: m/z (%) 972.5 (100) $[M+H]^+$. HRMS (ESI): calcd for $C_{42}H_{78}N_{13}O_{13}$: 972.5837; found 972.5848 $[M+H]^+$.

3.4. Determination of absolute stereochemistry

3.4.1. General procedure for peptide hydrolysis. Peptide samples (200 μg) were dissolved in degassed 6 N HCl (0.5 mL) in an evacuated glass tube and heated at 160 °C for 16 h. The solvent was removed in vacuo and the resulting material was subjected to further derivatisation.

3.4.2. General procedures for LC–MS analysis of Marfey's (FDAA) derivatives. A portion of the hydrolysate mixture (800 μg) or the aminoacid standard (500 μg) was dissolved in 80 μL of a 2:3 solution of TEA/MeCN and treated with 75 μL of 1% 1-fluoro-2,4-dinitrophenyl-5-L-alaninamide (FDAA) in 1:2 MeCN/acetone. The vials were heated at 70 °C for 1 h, and the contents were neutralised with 0.2 N HCl (50 μL) after cooling to room temperature. An aliquot of the L-FDAA derivative was dried under vacuum, diluted with MeCN/5% HCOOH in H_2O (1:1), and separated on a Vydac C18 (25×1.8 mm i.d.) column by means a linear gradient from 10 to 50% aqueous acetonitrile containing 5% formic acid and 0.05% trifluoracetic acid, over 45 min at 1 mL/min. The RP-HPLC system was connected to the electrospray ion source by inserting a splitter valve and the flow going into the mass spectrometer source was set at a value of 100 μL/min. Mass spectra were acquired in positive ion detection mode (*m*/*z* interval of 320–900) and the data were analyzed using the suite of programs Xcalibur (ThermoQuest, San José, California); all masses were reported as average values. Capillary temperature was set at 280 °C, capillary voltage at 37 V, tube lens offset at 50 V and ion spray voltage at 5 V.

Retention times of authentic FDAA-amino acids (min): L-Thr (12.5), D-Thr (17.6), L-*a*Thr (13.1), D-*a*Thr (14.1), L-Ala (16.6 min), D-Ala (20.0 min), L-NMeAla (18.7 min), D-NMeAla (19.4 min), L-Arg (11.7 min), D-Arg (13.08 min), L-Leu (28.9 min), D-Leu (34.8 min).

The hydrolysate of callipeltin A contained: D-Arg (13.1), D-*a*Thr (14.0), (3*S*,4*R*)-3,4-diMe-L-Glu (17.7), L-*N*MeAla (18.5), D-Ala (20.1), L-Leu (28.7).

The hydrolysate of callipeltin F contained: D-Arg (13.2), D-*a*Thr (14.5), (3*S*,4*R*)-3,4-diMe-L-Glu (17.8).

The hydrolysate of callipeltin G contained: D-Arg (13.0), D-*a*Thr (14.5), (3*S*,4*R*)-3,4-diMe-L-Glu (18.0), D-Ala (20.5) L-Leu (29.3).

The hydrolysate of callipeltin H contained: D-Arg (13.1), D-*a*Thr (14.0), (3*S*,4*R*)-3,4-diMe-L-Glu (18.0), D-Ala (20.2), L-*N*MeAla (18.5 min), L-Leu (29.7).

The hydrolysate of callipeltin I contained: D-Arg (13.4), D-*a*Thr (14.2), (3*S*,4*R*)-3,4-diMe-L-Glu (18.5).

3.5. Determination of the absolute stereochemistry of β-OMeTyr residue in callipeltin H (5)

A stream of ozone in O_2 was bubbled through a cooled solution of callipeltin H (0.5 mg) or of all four diastereomers of β-OMeTyr (1 mg)[19] in MeOH (0.5 mL) at −78 °C for 1 h. Hydrogen peroxide (35%, 10 drops) was added to the reaction mixture with then allowed to stand at room temperature overnight. The solvent was removed under a stream of N_2 and the resulting β-methoxyaspartates were immediately subjected to Marfey derivatization. The ozonolysis product of callipeltin H was then dissolved in degassed 6 N HCl (0.5 mL) in an evacuated glass tube and heated at 160 °C for 16 h. The solvent was removed in vacuo and the resulting material was subjected to further derivatisation.

A portion of callipeltin H hydrolizate mixture or the β-methoxyaspartates (500 μg) was subjected to Marfey's derivatization and LC–MS analysis.

Retention times of authentic L-FDAA-β-OMeAsps (min): (2*S*,3*S*)-β-OMeAsp (10.23 min), (2*S*,3*R*)-β-OMeAsp (16.06 min), (2*R*,3*R*)-β-OMeAsp (9.86 min), (2*R*,3*S*)-β-OMeAsp (17.30 min). The hydrolysate of ozonolysis product of callipeltin H contained: (2*R*,3*S*)-β-OMeAsp (17.30 min).

3.6. Antifungal tests

The broth macrodilution test was performed by using the NCCLS standard reference method for broth dilution antifungal susceptibility testing of yeasts.[25] Stock solutions of callipeltins F–I (10^{-3} M) were prepared, divided into aliquots, and stored at −80 °C. A new aliquot was thawed on each day of use. Before testing, *Candida albicans* (ATCC 24433) were maintained on Sabouraud's agar slants and periodically transferred to Sabouraud's agar plates and incubated for 48 h at 28 °C. To prepare stationary growth phase yeast, a colony was taken from the agar plate and transferred into 30 mL Sabouraud-dextrose broth (DIFCO laboratories, Detroit, MI) and incubated for 72 h at 35 °C. Cells were centrifuged at $1000\times g$ for 10 min and the pellet was washed twice with distilled water. Cells were counted and suspended in RPMI 1640 plus 0.165 M MOPS buffer at a density of 5000 CFU/mL. One hundred microlitres of the yeast suspension was transferred into control wells or wells containing the callipeltins 10^{-4}–10^{-8} M final concentrations. The plates were incubated in air at 35 °C without agitation for 48 h. The experiments were run in triplicate. Negative growth corresponded to no visible growth in the well.

Acknowledgements

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References and notes

1. Zampella, A.; D'Auria, M. V.; Gomez-Paloma, L.; Casapullo, A.; Minale, L.; Debitus, C.; Henin, Y. *J. Am. Chem. Soc.* **1996**, *118*, 6202–6209.
2. D'Auria, M. V.; Zampella, A.; Gomez-Paloma, L.; Minale, L.; Debitus, C.; Roussakis, C.; Le Bert, V. *Tetrahedron* **1996**, *52*, 9589–9596.
3. Zampella, A.; Randazzo, A.; Borbone, N.; Luciani, S.; Trevisi, L.; Debitus, C.; D'Auria, M. V. *Tetrahedron Lett.* **2002**, *43*, 6163–6166.
4. Ford, P. W.; Gustafson, K. R.; McKee, T. C.; Shigematsu, N.; Maurizi, L. K.; Pannell, L. K.; Williams, D. E.; de Silva, E. D.; Lassota, P.; Allen, T. M.; Van Soest, R.; Andersen, R. J.; Boyd, M. R. *J. Am. Chem. Soc.* **1999**, *121*, 5899–5909.
5. Rashid, M. A.; Gustafson, K. R.; Cartner, L. K.; Shigematsu, N.; Pannell, L. K.; Boyd, M. R. *J. Nat. Prod.* **2001**, *64*, 117–121.
6. Oku, N.; Gustafson, K. R.; Cartner, L. K.; Wilson, J. A.; Shigematsu, N.; Hess, S.; Pannell, L. K.; Boyd, M. R.; McMahon, J. B. *J. Nat. Prod.* **2004**, *67*, 1407–1411.
7. Trevisi, L.; Bova, S.; Cargnelli, G.; Danieli-Betto, D.; Floreani, M.; Germinario, E.; D'Auria, M. V.; Luciani, S. *Biochem. Biophys. Res. Commun.* **2000**, *279*, 219–222.
8. Trevisi, L.; Cargnelli, G.; Ceolotto, G.; Papparella, I.; Semplicini, A.; Zampella, A.; D'Auria, M. V.; Luciani, S. *Biochem. Pharmacol.* **2004**, *68*, 1331–1338.
9. Liang, B.; Carroll, P. J.; Joullie, M. M. *Org. Lett.* **2000**, *2*, 4157–4160.
10. Okamoto, N.; Hara, O.; Makino, K.; Hamada, Y. *Tetrahedron: Asymmetry* **2001**, *12*, 1353–1358.
11. Acevedo, C. M.; Kogut, E. F.; Lipton, M. A. *Tetrahedron* **2001**, *57*, 6353–6359.
12. Chandrasekhar, S.; Ramachandar, T.; Rao, B. V. *Tetrahedron: Asymmetry* **2001**, *12*, 2315–2321.
13. Guerlavais, V.; Carroll, P. J.; Joullie, M. M. *Tetrahedron: Asymmetry* **2002**, *13*, 675–680.
14. Thoen, J. C.; Morales-Ramos, A. I.; Lipton, M. A. *Org. Lett.* **2002**, *4*, 4455–4458.
15. Zampella, A.; Sorgente, M.; D'Auria, M. V. *Tetrahedron: Asymmetry* **2002**, *13*, 681–685.
16. Zampella, A.; D'Auria, M. V. *Tetrahedron: Asymmetry* **2002**, *13*, 1237–1239.
17. Ravi, K. A.; Venkateswara, R. B. *Tetrahedron Lett.* **2003**, *44*, 5645–5647.
18. Turk, J. A.; Visbal, G. S.; Lipton, M. A. *J. Org. Chem.* **2003**, *68*, 7841–7844.
19. Zampella, A.; D'Orsi, R.; Sepe, V.; Casapullo, A.; Monti, M. C.; D'Auria, M. V. *Org. Lett.* **2005**, *16*, 3585–3588.
20. Marfey, P. *Carlsberg Res. Commun.* **1984**, *49*, 591–596.
21. Sano, T.; Kaya, K. *Tetrahedron Lett.* **1995**, *36*, 8603–8606.
22. Sano, T.; Kaya, K. *Tetrahedron* **1998**, *54*, 463–470.
23. Sano, T.; Beattie, K. A.; Codd, G. A.; Kaya, K. *J. Nat. Prod.* **1998**, *61*, 851–853.
24. Bewley, C. A.; He, H.; Williams, D. H.; Faulkner, D. J. *J. Am. Chem. Soc.* **1996**, *118*, 4314–4321.
25. Tentative standard M27-T, Vol. 15, no. 10. National Committee for Clinical Laboratory Standards: Villanova, Pa.

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A concise synthesis of polyhydroxydihydrochalcones and homoisoflavonoids

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Abstract—A general and single step synthesis of polyhydroxydihydrochalcones from the readily available phenols and dihydrocinnamic acids using $BF_3 \cdot Et_2O$ is described. The method allows the synthesis of a wide range of compounds with multiple phenolic hydroxyls and other substituents. These dihydrochalcones are converted into homoisoflavonoids by DMF/PCl_5 and the methodology has been applied to the synthesis of naturally occurring phloretin and 5,7-dihydroxy-3-[(4-hydroxyphenyl)methyl]-4*H*-chromen-4-one. The antioxidant activity of dihydrochalcones and homoisoflavonoids was determined by superoxide free radical (NBT) and DPPH free radical scavenging methods. Polyhydroxydihydrochalcones **3c**, **3f**, **3g** and homoisoflavonoids **4c**, **4f**, **4g** displayed excellent antioxidant activity.

1. Introduction

Naturally occurring polyphenolic compounds display wide spectrum of biological activities. Polyphenolic flavonoids have gained increasing importance in view of their strong antioxidant activity and preventing role in free radical mediated disorders such as cancer, Alzheimer's, Parkinson's, and cardiovascular diseases.[1] Dihydrochalcones (DHCs), the reduced form of chalcones, have been known to occur widely in nature and are important intermediates for many natural products and pharmaceutical drugs.[1] DHCs have been reported to have various biological activities[2,3] and have received considerable attention as food sweeteners (neohesperidin).[4] Up to now, DHCs were mostly synthesized through a Claisen–Schmidt condensation[5,6] to obtain chalcone, followed by reduction to DHC or through the alkaline reduction of a corresponding flavanone.[7,8] Although widely used, the procedures are not suitable for polyhydroxyDHCs, as these methods require protection of all phenolic hydroxyls. Recently, palladium mediated coupling of iodobenzenes and the enol of acetophenone was reported[9] as an alternative route to DHCs. The homoisoflavonoids (3-benzylchromen-4-ones), are naturally occurring compounds and are structurally related to flavonoids,[10] and display a wide spectrum of biological activities.[11–15] A few methods of synthesis have been reported in the literature for homoisoflavonoids and these were based on (i) the condensation of 4-chromanones with arylaldehydes in methanol by passing HCl gas or by using piperidine as a base[16,17] followed by isomerisation of the double bond using Pd/C at 250 °C, (ii) hydrogenation of chalcones followed by one carbon extension using ethyl formate/sodium[18] or methanesulfonyl chloride/DMF.[19] Both the methods have disadvantages; while the first method has multiple steps, in the second method, the phenolic hydroxyls have to be protected to get chalcones in good yield. Our interest in the chemistry of the flavonoids[20] and an increasing demand for a short, and efficient method prompted us to develop a simple and general method for the synthesis of DHCs and homoisoflavonoids. The methodology has been applied to the synthesis of phloretin,[21] a naturally occurring DHC and 5,7-dihydroxy-3-[(4-hydroxyphenyl)-methyl]-4*H*-chromen-4-one, a homoisoflavonoid from *Ophiopogon jaburan*.[22] Moreover, to the best of our knowledge, there is no report in the literature on the antioxidant activity of homoisoflavonoids. So we report in this paper, the details of synthesis of DHCs, homoisoflavonoids and their antioxidative activity results.

Keywords: Dihydrochalcones; Homoisoflavonoids; Boron trifluoride etherate; Antioxidant activity.

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2. Results and discussion

2.1. Synthesis

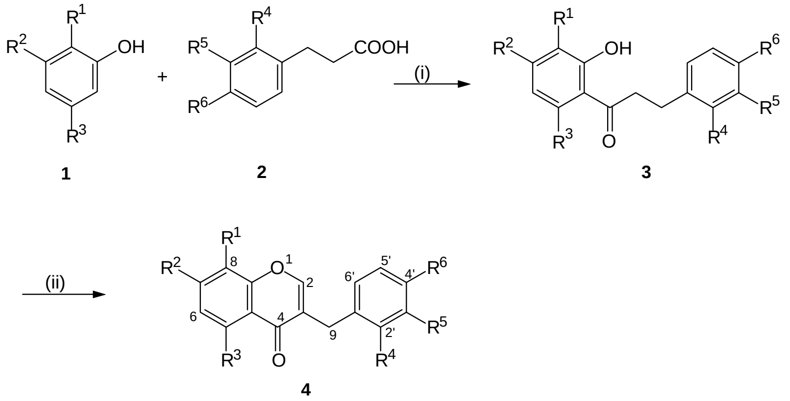
During the course of our investigations of new synthetic routes to flavonoids, we have found that a Friedel-Crafts reaction constitutes a novel and efficient approach to DHCs. The method involves the preparation of DHCs in a single step from phenols and dihydrocinnamic acids by Friedel-Crafts acylation using boron trifluoride etherate, which serves as the Lewis acid for the acylation and as solvent for the reaction (Scheme 1). In this method, protection of the phenolic hydroxyls is not necessary. In a typical experiment, substituted phenol (**1**, 3 mmol) and dihydrocinnamic acid (**2**, 3 mmol) was treated with boron trifluoride etherate at 80–90 °C for 90 min. After completion of the reaction (monitored by TLC), it was poured into aqueous sodium acetate and extracted with ethyl acetate to give DHCs (**3**). The generality of the reaction was established with various phenols and substituted dihydrocinnamic acids and in all cases (Table 1, 7 examples) the reaction was completed within 90 min. In the second step, the DHCs (**3a**–**3g**) were treated with *N*,*N*′-dimethyl(chloromethylene)ammonium chloride[23] generated in situ from DMF and PCl_5 for one carbon extension to get homoisoflavonoids (**4a**–**4g**) in 78–88% yield (Table 1). In all cases the reaction was complete in 2 h and the products were characterized by their spectral data (IR, NMR and Mass). The methodology has been applied to the synthesis of naturally occurring phloretin,[21] a DHC and 5,7-dihydroxy-3-[(4-hydroxyphenyl)methyl]-4*H*-chromen-4-one (**4h**), isolated from *Ophiopogon jaburan*.[22] Reaction of phloroglucinol and 4-hydroxydihydrocinnamic acid with $BF_3 \cdot Et_2O$ gave phloretin (**3h**), which was converted further into **4h** (85% yield) using *N*,*N*′-dimethyl(chloromethylene)ammonium chloride. The spectral data of synthetic **3h** and **4h** were found to be identical with those of the corresponding natural products.[19]

2.2. Antioxidant activity

We have determined the antioxidative activity of DHCs (**3a**–**3h**) and homoisoflavonoids (**4a**–**4h**) by nitro blue tetrazolium (NBT)[24,25] and 1,1-diphenyl-2-picrylhydrazyl (DPPH)[26] free radical scavenging methods. The IC_{50} values of these compounds are presented in Table 2. DHCs **3f** (IC_{50}: 12.9 μM), **3g** (IC_{50}: 19.6 μM) and **3c** (IC_{50}: 30.2 μM) and homoisoflavonoids **4f** (IC_{50}: 6.3 μM), **4g** (IC_{50}: 8.2 μM) and **4c** (IC_{50}: 24.8 μM) having catechol moieties were the most active compounds. Interestingly **3f**, **3g** and **3c** and **4f**, **4g** and **4c** showed several-fold more potent activity than vitamin C (IC_{50}: 852 μM), vitamin E (IC_{50}: 726 μM), BHA (IC_{50}: 966 μM) and BHT (IC_{50}: 381 μM). The same order of activity was followed by DHCs **3a**–**3h** and homoisoflavonoids **4a**–**4h** with the DPPH method. Again **3c**, **3f** and **3g** and **4c**, **4f** and **4g** showed good DPPH free radical scavenging activity. The superior antioxidative activity of these compounds lends further support to the fact that the catechol system enhances the antioxidative activity.[27]

3. Conclusions

In conclusion, we have described a general, single step method for the synthesis of polyhydroxydihydrochalcones using phenols and dihydrocinamic acids with $BF_3 \cdot Et_2O$. One carbon extension of these dihydrochalcones into homoisoflavonoids by DMF/PCl_5 was achieved in good yields. The DHCs and homoisoflavonoids were evaluated for their antioxidative potential by two commonly used



Scheme 1. Reagents and conditions: (i) $BF_3 \cdot Et_2O$, 80–90 °C, 90 min, 30–71% (ii) $BF_3 \cdot Et_2O$, DMF/PCl_5, rt, 2 h, 78–88%.

Table 1. Dihydrochalcones **3** and homoisoflavonoids **4**

S.no.	Entry	R_1	R_2	R_3	R_4	R_5	R_6	**3** Yield (%)[a]	**4** Yield (%)[a]
1	a	H	OH	H	H	H	OH	62	85
2	b	H	OH	H	H	H	OCH_3	71	88
3	c	H	OH	H	H	OH	OH	55	82
4	d	H	OH	H	H	OCH_3	OCH_3	68	87
5	e	H	OH	H	OCH_3	H	OCH_3	61	78
6	f	OH	OH	H	H	H	OH	58	80
7	g	OH	OH	H	H	H	OCH_3	65	81
8	h	H	OH	OH	H	H	OH	30	85

[a] Unoptimized isolated yields.

Table 2. Antioxidant activity of homoisoflavonoids

Compound no.	NBT superoxide scavenging activity (IC$_{50}$ in μM)	DPPH free radical scavenging activity (IC$_{50}$ in μM)
3a	>100	>100
3b	>100	>100
3c	30.2	7.8
3d	>100	>100
3e	>100	>100
3f	12.9	11.3
3g	19.6	14.9
3h	16.6	95
4a	>100	>100
4b	>100	>100
4c	24.8	13.4
4d	>100	>100
4e	>100	>100
4f	6.3	19.0
4g	8.2	19.6
4h	17.6	>100
Vitamin C	852	25.1
Vitamin E	726	>100
BHA	966	34.0
BHT	381	22.5

BHA, butylated hydroxyanisole; BHT, butylated hydroxytoluene; NBT, nitro blue tetrazolium; DPPH, 1,1-diphenyl-2-picrylhydrazyl. The lower the IC$_{50}$ values, the higher is the antioxidant activity.

methods, the superoxide and DPPH free radical scavenging methods. DHCs **3c**, **3f** and **3g** and homoisoflavonoids **4c**, **4f** and **4g** were potent antioxidants.

4. Experimental

4.1. General

Melting points were recorded on a Mel-Temp melting point apparatus, in open capillaries and are uncorrected. IR spectra were recorded on a Perkin-Elmer BX1 FTIR Spectrophotometer and ^{1}H NMR (400 MHz), ^{13}C NMR-DEPT (100 MHz) spectra were recorded on a Bruker AMX 400 MHz NMR spectrometer using TMS as internal standard and the values for chemical shifts (δ) being given in ppm and coupling constants (J) in Hertz (Hz). Mass spectra were recorded on an Agilent 1100 LC/MSD. Acme silica gel G and silica gel (100–200 mesh) were used for analytical TLC and column chromatography, respectively.

4.2. General procedure for dihydrochalcones (3)

A mixture of phenol (**1**, 3 mmol), 3-phenylpropanoic acid (**2**, 3 mmol) and $BF_3\cdot Et_2O$ (1.94 mL, 15.3 mmol) was stirred at 80–90 °C for 90 min under N_2. The reaction mixture was poured into 10% aqueous NaOAc solution (100 mL) and allowed to stand for 4 h and the solution was extracted with EtOAc (3×100 mL). The combined EtOAc layer was washed with water (20 mL), brine (20 mL) and dried over Na_2SO_4. The residue obtained after evaporation of the solvent was chromatographed over silica gel column using hexane–EtOAc mixtures as eluent to give **3a–h**.

4.2.1. 1-(2,4-Dihydroxyphenyl)-3-(4-hydroxyphenyl)-propan-1-one (3a). Light brown powder (480 mg, 62%), mp 140–142 °C; IR (KBr): 3456, 3270, 1626, 1214, 1165, 1134, 987 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 12.63 (1H, s, Ar-OH), 11.69 (1H, s, Ar-OH), 10.60 (1H, s, Ar-OH), 7.79 (1H, d, $J=8.8$ Hz, H-6″), 7.04 (2H, d, $J=8.3$ Hz, H-2′,6′), 6.65 (2H, d, $J=8.3$ Hz, H-3′,5′), 6.35 (1H, dd, $J=8.8$, 2.4 Hz, H-5″), 6.24 (1H, d, $J=2.4$ Hz, H-3″), 3.20 (2H, t, $J=7.6$ Hz, H-3), 2.81 (2H, t, $J=7.6$ Hz, H-2); ^{13}C NMR (DMSO-d_6): δ 203.9, 164.7, 164.3, 155.5, 133.0, 131.0, 129.3, 115.1, 112.6, 108.2, 102.4, 39.1, 29.1; MS (ESI, negative ion mode): m/z 257 $(M-H)^-$. Analysis found: C, 69.68; H, 5.52%. Calcd for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46%.

4.2.2. 1-(2,4-Dihydroxyphenyl)-3-(4-methoxyphenyl)-propan-1-one (3b). Light brown powder (580 mg, 71%), mp 58–60 °C; IR (KBr): 3456, 3105, 1629, 1225, 1131, 1029, 990 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 12.60 (1H, s, Ar-OH), 10.61 (1H, s, Ar-OH), 7.79 (1H, d, $J=8.8$ Hz, H-6″), 7.16 (2H, d, $J=8.3$ Hz, H-2′,6′), 6.82 (2H, d, $J=8.3$ Hz, H-3′,5′), 6.34 (1H, dd, $J=8.8$, 2.0 Hz, H-5″), 6.23 (1H, d, $J=2.0$ Hz, H-3″), 3.69 (3H, s, Ar-OCH_3), 3.22 (2H, t, $J=7.5$ Hz, H-3), 2.84 (2H, t, $J=7.5$ Hz, H-2); ^{13}C NMR (DMSO-d_6): δ 203.7, 164.8, 164.3, 157.6, 132.9, 129.4, 114.2, 113.7, 112.6, 108.2, 102.5, 55.0, 40.1, 29.0; MS (ESI, negative ion mode): m/z 271 $(M-H)^-$. Analysis found: C, 70.52; H, 5.97%. Calcd for $C_{16}H_{16}O_4$: C, 70.58; H, 5.92%.

4.2.3. 1-(2,4-Dihydroxyphenyl)-3-(3,4-dihydroxyphenyl)-propan-1-one (3c). Colorless powder (450 mg, 55%), mp 108–110 °C; IR (KBr): 3339, 1638, 1605, 1286, 1222, 1200, 1174, 1141, 968 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 12.63 (1H, s, Ar-OH), 8.72 (1H, s, Ar-OH), 8.56 (1H, s, Ar-OH), 8.29 (1H, s, Ar-OH), 7.77 (1H, d, $J=8.8$ Hz, H-6″), 7.10–7.20 (2H, m, H-2′,5′), 6.47 (1H, dd, $J=7.8$, 1.5 Hz, H-6′), 6.34 (1H, dd, $J=8.8$, 2.0 Hz, H-5″), 6.23 (1H, d, $J=2.0$ Hz, H-3″), 3.16 (2H, t, $J=7.6$ Hz, H-3), 2.74 (2H, t, $J=7.6$ Hz, H-2); ^{13}C NMR (DMSO-d_6): δ 205.0, 165.9, 165.4, 146.1, 144.5, 134.1, 133.0, 120.1, 117.0, 116.6, 113.7, 109.3, 103.6, 40.4, 30.4; MS (ESI, negative ion mode): m/z 273 $(M-H)^-$. Analysis found: C, 65.64; H, 5.18%. Calcd for $C_{15}H_{14}O_5$: C, 65.69; H, 5.15%.

4.2.4. 1-(2,4-Dihydroxyphenyl)-3-(3,4-dimethoxyphenyl)-propan-1-one (3d). Light brown powder (615 mg, 68%), mp 128–130 °C; IR (KBr): 3371, 1631, 1257, 1235, 1209, 1137, 1026, 991 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 12.64 (1H, s, Ar-OH), 10.63 (1H, s, Ar-OH), 7.82 (1H, d, $J=8.8$ Hz, H-6″), 6.88 (1H, d, $J=1.8$ Hz, H-2′), 6.83 (1H, d, $J=8.0$ Hz, H-5′), 6.76 (1H, dd, $J=8.0$, 1.8 Hz, H-6′), 6.37 (1H, dd, $J=8.8$, 2.1 Hz, H-5″), 6.26 (1H, d, $J=2.1$ Hz, H-3″), 3.73 (3H, s, Ar-OCH_3), 3.70 (3H, s, Ar-OCH_3), 3.25 (2H, t, $J=7.6$ Hz, H-3), 2.86 (2H, t, $J=7.6$ Hz, H-2); ^{13}C NMR (DMSO-d_6): δ 203.8, 164.8, 164.3, 148.7, 147.2, 133.5, 133.0, 120.2, 112.6, 112.4, 111.9, 108.2, 102.5, 55.5, 55.4, 39.2, 29.5; MS (ESI, negative ion mode): m/z 301 $(M-H)^-$. Analysis found: C, 67.52; H, 6.04%. Calcd for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00%.

4.2.5. 1-(2,4-Dihydroxyphenyl)-3-(2,4-dimethoxyphenyl)-propan-1-one (3e). Colorless powder (555 mg, 61%), mp 110–112 °C; IR (Neat): 3347, 1626, 1290, 1208, 1153, 1037, 990 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 12.72 (1H, s, Ar-OH), 9.99 (1H, s, Ar-OH), 7.60 (1H, d, $J=8.5$ Hz, H-6″), 7.00 (1H, d, $J=8.5$ Hz, H-5″), 6.20–6.40 (4H, m, H-3′,5′,6′,3″), 3.81 (3H, s, Ar-OCH_3), 3.78 (3H, s, Ar-OCH_3), 3.10 (2H, t, $J=7.5$ Hz, H-3), 2.90 (2H, t, $J=7.5$ Hz, H-2); ^{13}C NMR (DMSO-d_6): δ 204.2, 164.8, 164.4, 159.2, 158.0, 132.9, 130.0, 120.8, 112.5, 108.2, 104.3, 102.5, 98.3, 55.5, 55.3, 38.0, 24.8; MS (ESI, negative ion mode): *m/z* 301 (M−H)$^-$. Analysis found: C, 67.51; H, 6.05%. Calcd for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00%.

4.2.6. 1-(2,3,4-Trihydroxyphenyl)-3-(4-hydroxyphenyl)-propan-1-one (3f). Pale green powder (475 mg, 58%), mp 158–160 °C; IR (KBr): 3440, 3246, 1633, 1243, 1213, 1118, 1044, 1004, 899 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 12.63 (1H, s, Ar-OH), 10.06 (1H, s, Ar-OH), 9.15 (1H, s, Ar-OH), 8.59 (1H, s, Ar-OH), 7.34 (1H, d, J=8.8 Hz, H-6″), 7.04 (2H, d, J=8.3 Hz, H-2′,6′), 6.66 (2H, d, J=8.3 Hz, H-3′,5′), 6.38 (1H, d, J=8.8 Hz, H-5″), 3.20 (2H, t, J=7.5 Hz, H-3), 2.82 (2H, t, J=7.5 Hz, H-2); ^{13}C NMR (DMSO-d_6): δ 204.9, 155.7, 152.6, 152.4, 132.5, 131.2, 129.4, 122.6, 115.2, 113.0, 107.9, 39.0, 29.4; MS (ESI, negative ion mode): *m/z* 273 (M−H)$^-$. Analysis found: C, 65.66; H, 5.20%. Calcd for $C_{15}H_{14}O_5$: C, 65.69; H, 5.15%.

4.2.7. 1-(2,3,4-Trihydroxyphenyl)-3-(4-methoxyphenyl)-propan-1-one (3g). Light brown oil (560 mg, 65%), IR (Neat): 3396, 2928, 1632, 1244, 1178, 1114, 1033, 999 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 12.60 (1H, s, Ar-OH), 10.08 (1H, s, Ar-OH), 8.61 (1H, s, Ar-OH), 7.33 (1H, d, J=8.8 Hz, H-6″), 7.16 (2H, d, J=7.8 Hz, H-2′,6′), 6.81 (2H, d, J=7.8 Hz, H-3′,5′), 6.38 (1H, d, J=8.8 Hz, H-5″), 3.69 (3H, s, Ar-OCH$_3$), 3.20 (2H, t, J=7.5 Hz, H-3), 2.85 (2H, t, J=7.5 Hz, H-2); ^{13}C NMR (DMSO-d_6): δ 204.8, 157.8, 152.7, 152.6, 133.1, 132.6, 129.6, 122.6, 114.0, 113.1, 108.0, 55.2, 39.4, 29.3; MS (ESI, negative ion mode): *m/z* 287 (M−H)$^-$. Analysis found: C, 66.62; H, 5.62%. Calcd for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59%.

4.2.8. 1-(2,4,6-Trihydroxyphenyl)-3-(4-hydroxyphenyl)-propan-1-one (3h). Pale yellow solid (245 mg, 30%), mp 258–260 °C (lit.[19] mp 257–258 °C); IR (KBr): 3268, 1630, 1606, 1296, 1209, 1163, 1076 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 12.23 (2H, s, Ar-OH), 10.36 (1H, s, Ar-OH), 9.13 (1H, s, Ar-OH), 7.00 (2H, d, J=8.3 Hz, H-2′,6′), 6.65 (2H, d, J=8.3 Hz, H-3′,5′), 5.79 (2H, s, H-3″, 5″), 3.20 (2H, t, J=7.8 Hz, H-3), 2.74 (2H, t, J=7.8 Hz, H-2); ^{13}C NMR (DMSO-d_6): δ 204.4, 164.8, 164.4, 155.6, 131.9, 129.4, 115.3, 103.9, 94.9, 45.7, 29.6; MS (ESI, negative ion mode): *m/z* 273 (M−H)$^-$.

4.3. General procedure for homoisoflavonoids (4)

A mixture of **3** (3 mmol) and $BF_3\cdot Et_2O$ (1.2 mL, 9 mmol) was cooled to 10 °C and DMF (4.6 mL) was added drop wise for 5 min. In another flask, DMF (8 mL) was cooled to 10 °C and PCl_5 (0.939 g, 4.5 mmol) was added in small portions. The mixture was then allowed to stand to 55 °C for 20 min. The light yellow colored solution containing *N,N*′-dimethyl(chloromethylene)ammonium chloride was then added to the above reaction mixture slowly at 20–25 °C. The mixture was stirred at rt for 2 h and poured into boiling dil HCl slowly and cooled. The solution was extracted with EtOAc (3×50 mL) and the combined EtOAc layer was washed with water (20 mL), brine (20 mL) and dried over sodium sulfate. The residue obtained after evaporation of the solvent was chromatographed over silica gel column using chloroform–methanol mixtures as eluent to give **4a**–**h**.

4.3.1. 7-Hydroxy-3-[(4-hydroxyphenyl)methyl]-4*H*-chromen-4-one (4a). Colorless powder (680 mg, 85%), mp 212–214 °C; IR (KBr): 3430, 1628, 1600, 1267, 1244, 1176, 1140, 1099, 960 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 10.73 (2H, br s, Ar-OH), 8.04 (1H, s, H-2), 7.86 (1H, d, J=8.8 Hz, H-5), 7.06 (2H, d, J=8.3 Hz, H-2′,6′), 6.88 (1H, dd, J=8.8, 2.2 Hz, H-6), 6.79 (1H, d, J=2.2 Hz, H-8), 6.65 (1H, d, J=8.3 Hz, H-3′,5′), 3.53 (2H, s, H-9); ^{13}C NMR (CDCl$_3$+DMSO-d_6): δ 176.3, 162.2, 157.8, 155.4, 152.2, 129.4, 128.9, 126.6, 123.8, 116.3, 115.1, 114.6, 102.0, 30.2; MS (ESI, negative ion mode): *m/z* 267 (M−H)$^-$. Analysis found: C, 71.59; H, 4.55%. Calcd for $C_{16}H_{12}O_4$: C, 71.64; H, 4.51%.

4.3.2. 7-Hydroxy-3-[(4-methoxyphenyl)methyl]-4*H*-chromen-4-one (4b). Light brown powder (740 mg, 88%), mp 162–164 °C; IR (KBr): 3433, 1631, 1248, 1161, 1132, 1096, 1034 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 10.55 (1H, s, Ar-OH), 7.96 (1H, s, H-2), 7.87 (1H, d, J=8.8 Hz, H-5), 7.19 (2H, d, J=8.3 Hz, H-2′,6′), 6.86 (1H, dd, J=8.8, 2.0 Hz, H-6), 6.80 (2H, d, J=8.3 Hz, H-3′,5′), 6.71 (1H, d, J=2.0 Hz, H-8), 3.72 (3H, s, Ar-OCH$_3$), 3.61 (2H, s, H-9); ^{13}C NMR (CDCl$_3$+DMSO-d_6): δ 176.2, 162.2, 157.8, 157.6, 152.1, 130.6, 129.4, 126.6, 123.5, 116.3, 114.6, 113.4, 102.0, 54.7, 30.2; MS (ESI, negative ion mode): *m/z* 281 (M−H)$^-$. Analysis found: C, 72.29; H, 5.04%. Calcd for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00%.

4.3.3. 7-Hydroxy-3-[(3,4-dihydroxyphenyl)methyl]-4*H*-chromen-4-one (4c). Colorless powder (695 mg, 82%), mp 192–194 °C; IR (KBr): 3393, 1627, 1239, 1180, 1113, 967 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 10.73 (1H, s, Ar-OH), 8.72 (1H, s, Ar-OH), 8.61 (1H, s, Ar-OH), 8.07 (1H, s, H-2), 7.86 (1H, d, J=8.8 Hz, H-5), 6.88 (1H, dd, J=8.8, 2.2 Hz, H-6), 6.79 (1H, d, J=2.2 Hz, H-8), 6.63 (1H, d, J=2.1 Hz, H-2′), 6.59 (1H, d, J=8.3 Hz, H-5′), 6.51 (1H, dd, J=8.3, 2.1 Hz, H-6′), 3.47 (2H, s, H-9); ^{13}C NMR (CDCl$_3$+DMSO-d_6): δ 176.4, 162.1, 157.8, 152.3, 144.4, 142.9, 129.9, 126.6, 123.7, 119.8, 116.3, 115.7, 115.1, 114.6, 102.0, 30.3; MS (ESI, negative ion mode): *m/z* 283 (M−H)$^-$. Analysis found: C, 67.58; H, 4.29%. Calcd for $C_{16}H_{12}O_5$: C, 67.60; H, 4.26%.

4.3.4. 7-Hydroxy-3-[(3,4-dimethoxyphenyl)methyl]-4*H*-chromen-4-one (4d). Colorless powder (815 mg, 87%), mp 180–182 °C; IR (KBr): 3245, 1632, 1262, 1244, 1175, 1140, 1094, 1026, 963 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 10.62 (1H, s, Ar-OH), 8.01 (1H, s, H-2), 7.88 (1H, d, J=8.8 Hz, H-5), 6.78–6.90 (5H, m, Ar-H), 3.75 (3H, s, Ar-OCH$_3$), 3.72 (3H, s, Ar-OCH$_3$), 3.61 (2H, s, H-9); ^{13}C NMR (CDCl$_3$+DMSO-d_6): δ 176.0, 162.3, 157.8, 152.4, 148.4, 147.1, 131.4, 126.6, 123.3, 120.5, 116.3, 114.7, 112.2, 111.2, 102.0, 55.4, 55.3, 30.6; MS (ESI, negative ion mode): *m/z* 311 (M−H)$^-$. Analysis found: C, 69.19; H, 5.21%. Calcd for $C_{18}H_{16}O_5$: C, 69.22; H, 5.16%.

4.3.5. 7-Hydroxy-3-[(2,4-dimethoxyphenyl)methyl]-4*H*-chromen-4-one (4e). Colorless powder (730 mg, 78%), mp 182–184 °C; IR (KBr): 3224, 1631, 1241, 1207, 1158, 1124, 1040 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 10.72 (1H, s, Ar-OH), 7.86 (1H, d, J=8.8 Hz, H-5), 7.85 (1H, s, H-2), 7.02 (1H, d, J=8.3 Hz, H-6′), 6.88 (1H, dd, J=8.8, 2.0 Hz, H-6), 6.79 (1H, d, J=2.0 Hz, H-8), 6.51 (1H, d, J=2.1 Hz, H-3′), 6.42 (1H, dd, $J=8.3$, 2.1 Hz, H-5′), 3.77 (3H, s, Ar-OCH$_3$), 3.70 (3H, s, Ar-OCH$_3$), 3.51 (2H, s, H-9); MS (ESI, negative ion mode): m/z 311 $(M-H)^-$. Analysis found: C, 69.18; H, 5.20%. Calcd for $C_{18}H_{16}O_5$: C, 69.22; H, 5.16%.

4.3.6. 7,8-Dihydroxy-3-[(4-hydroxyphenyl)methyl]-4*H*-chromen-4-one (4f). Colorless powder (680 mg, 80%), mp 251–253 °C; IR (KBr): 3458, 1628, 1201, 1175, 1156, 1047, 985 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 10.17 (1H, s, Ar-OH), 9.15 (2H, br s, $2\times$Ar-OH), 8.14 (1H, s, H-2), 7.37 (1H, d, $J=8.6$ Hz, H-5), 7.07 (2H, d, $J=8.3$ Hz, H-2′,6′), 6.91 (1H, d, $J=8.6$ Hz, H-6), 6.65 (2H, d, $J=8.3$ Hz, H-3′,5′), 3.56 (2H, s, H-9); ^{13}C NMR (CDCl$_3$+DMSO-d_6): δ 176.1, 155.6, 152.9, 149.9, 147.1, 132.9, 129.9, 129.5, 123.0, 117.1, 115.2, 115.0, 114.1, 30.0; MS (ESI, negative ion mode): m/z 283 $(M-H)^-$. Analysis found: C, 67.57; H, 4.30%. Calcd for $C_{16}H_{12}O_5$: C, 67.60; H, 4.26%.

4.3.7. 7,8-Dihydroxy-3-[(4-methoxyphenyl)methyl]-4*H*-chromen-4-one (4g). Colorless powder (725 mg, 81%), mp 252–254 °C; IR (KBr): 3320, 3150, 1631, 1241, 1172, 1155, 1047, 980 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 10.25 (1H, s, Ar-OH), 9.39 (1H, s, Ar-OH), 8.21 (1H, s, H-2), 7.38 (1H, d, $J=8.8$ Hz, H-5), 7.21 (2H, d, $J=8.3$ Hz, H-2′,6′), 6.92 (1H, d, $J=8.8$ Hz, H-6), 6.82 (1H, d, $J=8.3$ Hz, H-3′,5′), 3.70 (3H, s, Ar-OCH$_3$), 3.61 (2H, s, H-9); ^{13}C NMR (CDCl$_3$+DMSO-d_6): δ 176.2, 157.4, 152.1, 149.4, 146.8, 132.5, 130.9, 129.3, 122.7, 117.0, 115.1, 113.7, 113.3, 54.6, 30.0; MS (ESI, negative ion mode): m/z 297 $(M-H)^-$. Analysis found: C, 68.41; H, 4.79%. Calcd for $C_{17}H_{14}O_5$: C, 68.45; H, 4.73%.

4.3.8. 5,7-Dihydroxy-3-[(4-hydroxyphenyl)methyl]-4*H*-chromen-4-one (4h). Pale yellow powder (725 mg, 85%), mp 215–217 °C (lit.[19] mp 218–219 °C); IR (KBr): 3283, 1667, 1620, 1314, 1282, 1233, 1174, 1053 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 12.73 (1H, s, Ar-OH), 10.83 (1H, s, Ar-OH), 9.19 (1H, s, Ar-OH), 8.13 (1H, s, H-2), 7.06 (1H, d, $J=8.3$ Hz, H-2′,6′), 6.65 (2H, d, $J=8.3$ Hz, H-3′,5′), 6.32 (1H, d, $J=2.0$ Hz, H-6), 6.17 (1H, d, $J=2.0$ Hz, H-8), 3.53 (2H, s, H-9); ^{13}C NMR (CDCl$_3$+DMSO-d_6): δ 180.8, 164.0, 161.6, 157.8, 155.6, 153.3, 129.3, 128.5, 122.3, 115.1, 104.4, 98.7, 93.5, 29.3; MS (ESI, negative ion mode): m/z 283 $(M-H)^-$.

4.4. Antioxidant activity

4.4.1. Superoxide free radical scavenging activity. The superoxide free radical scavenging activity was determined by the NBT method.[24,25] The reaction mixture contained EDTA (6.6 mM), NaCN (3 μg), riboflavin (2 μM), NBT (50 μM), various concentrations of the test drug in ethanol and a phosphate buffer (58 mM, pH 7.8) in a final volume of 3 mL. Optical density was measured at 560 nm. The test tubes were uniformly illuminated with an incandescent lamp for 15 min, after which the optical density was measured again at 560 nm. The percent inhibition of superoxide radical generation was measured by comparing mean absorbance values of the control and those of the test substances. IC$_{50}$ values were obtained from the plot drawn of concentration in μg versus percentage inhibition and were converted into μM. All the tests were run in triplicate and averaged.

4.4.2. DPPH free radical scavenging activity. DPPH radical scavenging activity was measured based on the reduction of methanolic solution of the colored DPPH.[26] Free radical scavenging ability of the test drug in ethanol added to the methanolic solution of DPPH is inversely proportional to the difference in initial and final absorption of DPPH solution at 516 nm. Drug activity is expressed as the 50% inhibitory concentration (IC$_{50}$). The reaction mixture contained 1×10^{-4} mM methanolic solution of DPPH and various concentrations of test drugs. The percentage inhibition was determined by comparing the absorbance values of test and control tubes. IC$_{50}$ values were obtained from the plot, drawn for concentration in microgram versus percentage inhibition.

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References and notes

1. Harborne, J. B.; Baxter, H. In *The Handbook of Natural Flavonoids*, *Vol. 2*; Wiley: New York, 1999; and references cited therein.
2. Kabori, M.; Shinmoto, H.; Tsushida, T.; Shinohara, K. *Cancer Lett.* **1997**, *119*, 207.
3. Mathiesen, L.; Malterud, K. E.; Sund, R. B. *Free Radic. Biol. Med.* **1997**, *22*, 307.
4. DuBois, G. E.; Crosby, G. A.; Stephenson, R. A. *J. Med. Chem.* **1981**, *24*, 408.
5. Wattanasin, S.; Murphy, W. S. *Synthesis* **1980**, 647.
6. Bohlmann, F.; Paul, A. H. K. *Leibigs Ann. Chem.* **1984**, 1382.
7. Krbechek, L.; Inglett, G.; Holik, M.; Dowling, B.; Wagner, R.; Riter, R. *J. Agric. Food Chem.* **1968**, *16*, 108.
8. DuBois, G. E.; Crosby, G. A.; McGrraugh, G. V.; Ng, S. Y. W.; Stephenson, R. A.; Wang, P. C.; Wingard, R. E. *J. Org. Chem.* **1982**, *47*, 1319.
9. Briot, A.; Baehr, C.; Brouillard, R.; Wagner, A.; Mioskowski, C. *J. Org. Chem.* **2004**, *69*, 1374.
10. Lockhart, I. M. In *The Chemistry of Heterocyclic Compounds Chromenes, Chromanones and Chromones*; Ellis, G. P., Ed.; Wiley: New York, 1977.
11. Al Nakib, T.; Bezjak, V.; Meegan, M. J.; Chandy, R. *Eur. J. Med. Chem.* **1990**, *25*, 455.
12. Middleton, E., Jr.; Kandaswami, C. *Biochem. Pharmacol.* **1992**, *43*, 1167.
13. Verma, A.; Johnson, J. A.; Gould, M. N.; Tanner, M. A. *Cancer Res.* **1988**, *48*, 5754.
14. Kandaswami, C.; Perkins, E.; Solonuik, D. S.; Drzewiecki, G.; Middleton, E., Jr. *Cancer Lett.* **1991**, *56*, 147.
15. Kirkiacharian, S.; Tongo, H. G.; Bastide, J.; Bastide, P.; Grenie, M. M. *Eur. J. Med. Chem.* **1989**, *24*, 541.

16. Malhotra, S.; Sharma, V. K.; Parmar, V. S. *J. Chem. Res. (S)* **1988**, 179.
17. Farkas, L.; Gottsegen, A.; Nogradi, M. *Tetrahedron* **1970**, *26*, 2787.
18. Davis, F. A.; Chen, B.-C. *J. Org. Chem.* **1993**, *58*, 1751.
19. Jain, A. C.; Paliwal, P. *Indian J. Chem., Sect B* **1989**, *28*, 416.
20. Venkateswarlu, S.; Panchagnula, G. K.; Guraiah, M. B.; Subbaraju, G. V. *Tetrahedron* **2005**, *61*, 3013.
21. Woodcock, D. *Nature* **1947**, *159*, 100.
22. Watanabe, Y.; Sanada, S.; Ida, Y.; Shoji, J. *Chem. Pharm. Bull.* **1985**, *33*, 5358.
23. Balasubramanian, S.; Nair, M. G. *Synth. Commun.* **2000**, *30*, 469.
24. McCord, J. M.; Fridovich, I. *J. Biol. Chem.* **1969**, *244*, 6049.
25. Venkateswarlu, S.; Raju, M. S. S.; Subbaraju, G. V. *Biosci. Biotechnol. Biochem.* **2002**, *66*, 2236.
26. Lamaison, J. I.; Ptijean-Freytet, C.; Carnet, A. *Pharm. Act. Helv.* **1991**, *66*, 185.
27. Wang, M.; Jin, Y.; Ho, C.-T. *J. Agric. Food Chem.* **1999**, *47*, 3974.

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Unexpected formation of aryl dialkyl carbinol as a side product from the reaction of methoxyarylaldehydes with Grignard reagents☆

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Abstract—In the attempted formation of secondary aryl alkyl carbinols from the reaction of methoxyarylaldehydes with Grignard reagents, aryl dialkyl carbinols were formed as unexpected side products. A mechanism for their formation is proposed.

1. Introduction

Hypercholesterolemia has been accountable for as much as 50% mortality in both developing and developed nations. A number of drugs such as statins, clofibrate and niacins have been developed for improving plasma lipid levels in human beings.[1] In this regard, some natural phenylpropanoids[2] (C_6–C_3 units) such as α-asarone and elemicin have also evolved as extremely efficient hypolipidemic *trans*-arylalkenes, although their activity is somewhat marred by genotoxicity of the compounds. As a result, a number of other phenylpropanoids such as arylalkanones and arylalkanols (C_6–C_3 units) have been synthesized and have shown promising hypolipidemic activity with reduced toxicity.[2d] Among these analogues, arylalkanols are important hypolipidemic compounds and are precursors for the synthesis of all above phenylpropanoids. The preparation of arylalkanols[3] would generally involve reaction of Grignard reagents[4] with arylaldehydes. Although these Grignard reactions are clean and moderately yielding, formation of various side products[5] is one problem generally encountered. In most cases, the side products remain unrevealed[3a] and in others, where they are identified, numerous mechanisms underlying their formation create considerable ambiguity regarding their formation. From an industrial point of view, endeavours towards identification of such side products during the development of chemical processes for bioactive compounds holds considerable importance, as side product detection is highly crucial for quality approval by relevant agencies. When studying reaction of methoxylated arylaldehydes **2a**–**2g** with alkylmagnesium halides for the formation of aryl alkyl carbinols **3a**–**3i**, we encountered an interesting class of side products, aryl dialkyl carbinol derivatives **1a**–**1g**, along with above expected products **3a**–**3i** (Scheme 1).

2. Results and discussion

In continuation of our ongoing studies on the chemical synthesis of phenylpropanoids[6] and the associated scale up and yield enhancement for various biological activities, we were interested to prepare intermediate 1-(3,4,5-trimethoxyphenyl)-1-propanol **3a** for the synthesis of either 1-(3,4,5-trimethoxyphenyl)-1-propene (commonly known as elemicin) or 1-(3,4,5-trimethoxyphenyl)-1-propanone. The methodology for the aforementioned synthesis would comprise Grignard reaction of 3,4,5-trimethoxybenzaldehyde **2a** with ethylmagnesium bromide in ether to provide **3a**, which upon either dehydration or oxidation would provide bioactive[2] elemicin or phenylpropanone **4a**. The first step of Grignard reaction in ether was critically evaluated and this idea was informed by matters emerging in Grignard chemistry wherein a lot of modifications[4,5] have come to the fore. For example, change of the ether solvent in the Grignard process was attempted by replacing this with a mixture of ether and a hydrocarbon of high boiling point such as toluene.[7] The reaction kinetics and, in turn, yield emanating from such a change of solvent would be

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Keywords: Aryl dialkyl carbinol; Aryl alkyl carbinol; Arylaldehyde; Grignard reaction.

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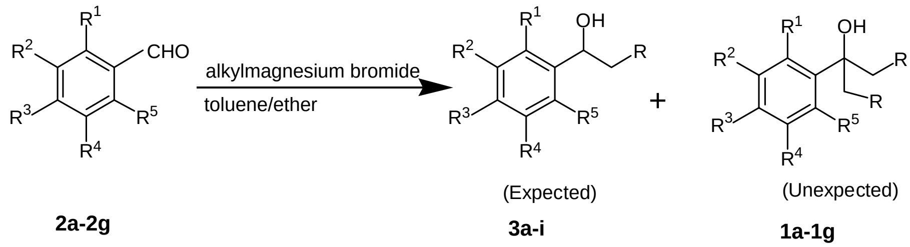


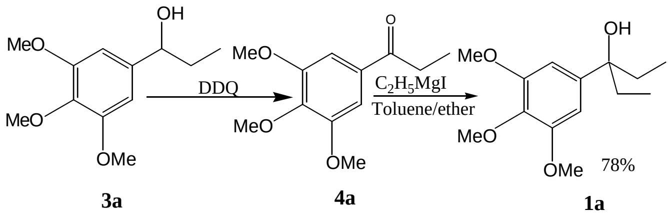
	R^1	R^2	R^3	R^4	R
(a)	H	OMe	OMe	OMe	Me
(b)	OMe	H	OMe	OMe	Me
(c)	OMe	OMe	OMe	H	Me
(d)	H	OMe	OMe	H	Me
(e)	H	(R^2+R^3) -OCH$_2$O-		H	Me
(f)	OMe	H	OMe	H	Me
(g)	H	H	OMe	H	Me
(h)	OMe	H	OMe	OMe	Et
(i)	OMe	H	OMe	OMe	H

Scheme 1.

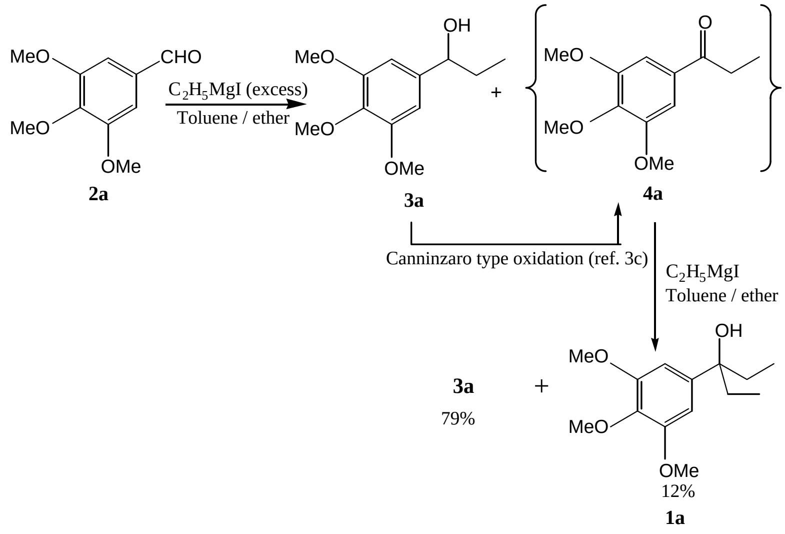
explored. In addition we and others have already reported on formation of methoxylated aryl alkyl carbinols[2a,8] through Grignard reaction of the corresponding arylaldehydes, wherein the effect of reverse addition of Grignard reagent led to an enhancement in yield of the product carbinols, for example, **3a** in 79% yield was observed. In order to further increase the yield of the product **3a**, a lot of variants in the reaction (increasing time of addition, changing the amount of the solvents and the amount of the Grignard reagent etc.) were performed. However, success kept eluding us in our endeavour. In due course, we thought that the presence of side product formation in the product mixture was responsible for the comparatively low yield of **3a** (79% yield). Unfortunately, we had missed the side product formation during our previous report[8b] because of performing the Grignard reactions on a small scale (0.012 mol of substrate) and subsequent formation of **1a** in minute traces. However, performing the above reactions on a greater preparative scale (0.12 mol of substrate) allowed us to detect the side product **1a** in 12% yield. Delving deep into literature studies, one report was found confirming formation of dimer[3c] as a side product in 30% yield during reaction of arylaldehyde **2b** with a large excess of Grignard reagent. This encouraged us to identify the side product, once again, in the present study and attempt to formulate the underlying mechanism for its formation and, subsequently, eliminate production of this side product, so that the yield of the expected product **3a** can be improved further.

Surprisingly, the side product formed during reaction of 3,4,5-trimethoxybenzaldehyde **2a** with ethylmagnesium bromide was not the expected dimer[3c] (as reported in the case of 2,4,5-trimethoxybenzaldehyde **2b**) but instead 3-(3,4,5-trimethoxyphenyl)-3-pentanol **1a**, a tertiary carbinol. Purification of the crude product by column chromatography provided **3a** in 79% and **1a** in 12% yield. The ^{1}H and ^{13}C NMR spectra of **3a** matched well with the reported values.[8b] The ^{1}H NMR spectrum of **1a** indicated a 6H triplet at δ 0.73 and also a quartet of 4H at 1.76, which indicated the presence of 2 equiv –CH$_2$–CH$_3$ groups. The presence of two ethyl groups was further confirmed by the DEPT ^{13}C NMR spectrum of **1a**. The DEPT spectrum in d_6-DMSO confirmed the point of attachment of the additional –CH$_2$–CH$_3$ group at C-1 as the signal at 77.2 disappeared due to its quaternary nature. HRMS of **1a** also supported the proposed structure of the aryl dialkyl carbinol.

The formation of the unexpected product **1a** was unequivocally confirmed by its synthesis starting from **3a**. Oxidation of **3a** with DDQ[9] afforded **4a** in 89% yield, which upon treatment with ethylmagnesium bromide provided **1a** in 78% yield (Scheme 2), whose TLC, mixed TLC, co-mp and NMR spectra were identical to side product **1a** discussed above.

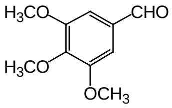
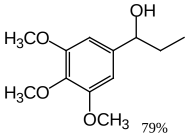
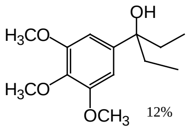
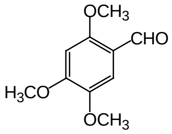
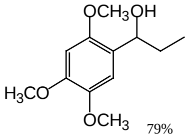
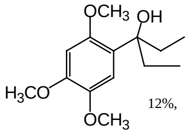
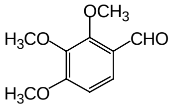
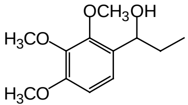
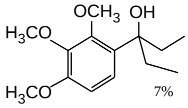
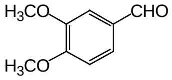
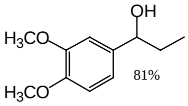
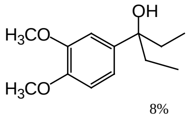
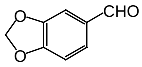
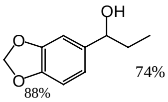
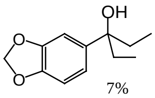
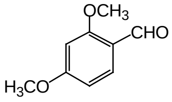
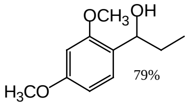
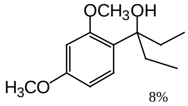
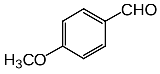
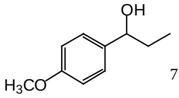
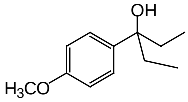
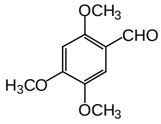
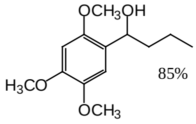
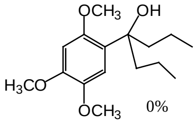
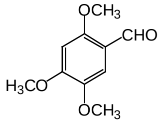
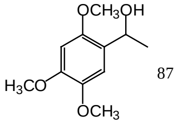
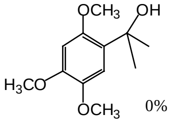


Scheme 2.



Scheme 3.

Table 1. Grignard reaction of arylaldehydes (**2a**–**2i**) into aryl alkyl carbinols (**3a**–**3i**) and unexpected side product aryl dialkyl carbinols (**1a**–**1g**)

Run	Arylaldehyde (**2**)	Aryl alkyl carbinol (**3**)	Aryl dialkyl carbinols (**1**)
a		 79%	 12%
b		 79%	 12%,
c		 84%	 7%
d		 81%	 8%
e		 88% 74%	 7%
f		 79%	 8%
g		 78%	 8%
h		 85%	 0%
i		 87%	 0%

The mechanism for formation of dialkyl carbinol **1a** is believed to proceed through an internal Canninzaro-type reaction[3c] of some of the secondary alcohol **3a** to afford the corresponding oxidized product **4a** (Scheme 3).

After successful isolation of the side product **1a**, the Grignard reaction was performed with 2,4,5-trimethoxybenzaldehyde **2b** and, once again, tertiary carbinol (**1b**) was obtained as a side product in 12% yield but not the dimer as previously isolated by Francisco et al.[3b] The plausible reason for the absence of any dimeric side product in our case may be due to the reverse addition of Grignard reagent to **2b**, in comparison to the reported method.[3b] In order to check the generality of the above reaction, some other substituted arylaldehydes **2c**–**2g** were also studied and the formation of the tertiary alcohols **1c**–**1g** was detected along with the major products **3c**–**3i** (Table 1). In contrast, no aryl dialkyl carbinols **1h**–**1i** were detected in the case of Grignard reaction with both propylmagnesium bromide and methylmagnesium bromide, and arylaldehyde **2b**. However, the normal aryl alkyl carbinols **3h**–**3i** were both formed in these cases in better yields than the other reactions described. This finding further strengthens our hypothesis of formation of the side product at the cost of the normal expected product. Further studies to eliminate the side product **1a**–**1g** in order to enhance the yield of carbinols **3a**–**3g** are in progress.

3. Conclusion

In conclusion, we have discovered the formation of aryl dialkyl carbinols **1a**–**1g** from the reaction of methoxyarylaldehydes **2a**–**2g** with alkylmagnesium halides during the formation of aryl alkyl carbinols **3a**–**3i**. The formation of tertiary alcohols is reported from acyl, carboxylic acid, ketone and ester derivatives, but their direct formation from aldehydes is a new finding. Overall, identification of such side products during development of chemical processes for the synthesis of bioactive compounds holds much importance.

4. Experimental

4.1. General

Melting points were determined with a Mettler FP80 micromelting point apparatus and are uncorrected. Column chromatography was performed on silica gel (60–120 mesh size). ^{1}H (300 MHz) NMR spectra were recorded in $CDCl_3$ and d_6-DMSO on a Bruker Avance-300 spectrometer. HRMS were determined using a Micromass Q-TOF Ultima spectrometer.

4.2. Representative experimental for the synthesis of 3a–3i and 1a–1g

Alkylmagnesium bromide (prepared from 30.5 mL of alkyl bromide and 9.91 g Mg in 70 mL of ether) in toluene (40 mL) was added dropwise in 15–20 min to a cooled mixture of methoxy arylaldehyde (**2a**–**2g**, 0.102 mol) in ether (80 mL) and toluene (125 mL) and finally the mixture was stirred for 12–14 h at room temperature under a nitrogen atmosphere. The cooled mixture was poured into a saturated solution of ammonium chloride (2×15 mL) and stirred for 20 min. The mixture was extracted with ethyl acetate (3×50 mL) and the combined extracts were washed with brine (2×15 mL), dried over Na_2SO_4 and filtered. The residue obtained upon evaporation was chromatographed by neutral alumina column using a hexane–ethyl acetate mixture, with increasing proportions of ethyl acetate up to 25%, to afford pure secondary alcohols **3a**–**3i** and tertiary alcohols **1a**–**1g**. Spectral data for aryl alkyl carbinols (**3a**–**3i**) was found to match with the reported values.[8b]

4.2.1. Compound 1a. White solid, 3.1 g (12%); mp 60–62 °C; $\nu_{max}(CHCl_3)$ 3571 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.52 (2H, s, H-2 and H-6), 3.78 (9H, s, 3,4,5-OCH_3), 1.76 (4H, q, $J=6.85$ Hz, H-2′ and H-2′), 0.73 (6H, t, $J=6.85$ Hz, H-3′ and H-3′); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 153.05 (C-3 and C-5), 142.2 (C-4), 136.5 (C-1), 103.2 (C-2 and C-6), 77.2 (C-1′), 61.1 (4-OCH_3), 56.4 (3, 5-OCH_3), 35.3 (C-2′ and C-2′), 8.2 (C-3′ and C-3′); HRMS (M+Na) *m/z*: 277.3176 (Calcd for $C_{14}H_{22}O_4Na$: 277.3160).

4.2.2. Compound 1b. White solid, 3.1 g (12%); mp 107–110 °C; $\nu_{max}(CHCl_3)$ 3568 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.02 (1H, s, H-6), 6.38 (1H, s, H-3), 3.83 (6H, s, 4 and 5-OCH_3), 3.79 (3H, s, 2-OCH_3), 2.34 (4H, q, $J=7.3$ Hz, H-2′ and H-2′), 1.12 (6H, t, $J=7.3$ Hz, H-3′ and H-3′); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 160.0 (C-2), 156.5 (C-4), 141.8 (C-5), 111.1 (C-1), 110.9 (C-6), 100.6 (C-3), 78.0 (C-1′), 56.7 (4, 5-OCH_3), 56.1 (C-2-OCH_3), 31.3 (C-2′ and C-2′), 8.3 (C-3′ and C-3′); HRMS (negative) *m/z*: 253.3201 (Calcd for $C_{14}H_{22}O_4$: 253.3182).

4.2.3. Compound 1c. Colourless liquid, 1.8 g (7%); $\nu_{max}(CHCl_3)$ 3575 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.80 (1H, d, $J=8.9$ Hz, H-6), 6.48 (1H, d, $J=8.9$ Hz, H-2), 3.81 (3H, s, 3-OCH_3), 3.70 (6H, s, 2 and 4-OCH_3), 1.87–1.75 (2H, m, H-2′), 1.69–1.57 (2H, m, H-2′), 0.63 (6H, t, $J=7.3$ Hz, H-3′ and H-3′); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 152.3 (C-5), 151.8 (C-4), 142.1 (C-3), 128.9 (C-6), 122.0 (C-1), 106.5 (C-2), 78.0 (C-1′), 60.6 (3-OCH_3), 60.4 (2-OCH_3), 55.7 (4-OCH_3), 33.9 (C-2′ and C-2′), 8.2 (C-3′ and C-3′); HRMS (M+Na) *m/z*: 277.3158 (Calcd for $C_{14}H_{22}O_4Na$: 277.3160).

4.2.4. Compound 1d. Colourless liquid, 1.8 g (8%); $\nu_{max}(CHCl_3)$ 3572 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.82 (1H, d, $J=8.1$ Hz, H-6), 6.74 (1H, d, $J=8.1$ Hz, H-5), 6.24 (1H, s, H-2), 3.82 (6H, s, 3 and 4-OCH_3), 1.81–1.78 (4H, m, H-2′ and H-2′), 0.92 (6H, t, $J=7.3$ Hz, H-3′ and H-3′); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 149.0 (C-3), 148.1 (C-4), 131.1 (C-1), 130.6 (C-6), 123.8 (C-5), 118.6 (C-2), 77.2 (C-1′), 55.9 (4-OCH_3), 55.7 (3-OCH_3), 29.7 (C-2′ and C-2′), 13.2 (C-3′ and C-3′); HRMS (posative) *m/z*: 225.3012 (Calcd for $C_{13}H_{20}O_3$: 225.3079).

4.2.5. Compound 1e. Colourless liquid, 1.5 g (7%); $\nu_{max}(CHCl_3)$ 3567 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ

6.83 (1H, s, H-6), 6.76 (2H, m, H-2 and H-5), 5.91 (2H, s, –OCH_2O–), 1.79–1.73 (4H, m, H-2′ and H-2′), 0.89 (6H, t, $J=6.9$ Hz, H-3′ and H-3′); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 149.0 (C-3), 148.2 (C-4), 134.5 (C-1), 121.6 (C-6), 112.3 (C-5), 105.1 (C-2), 98.5 (–OCH_2O–), 77.1 (C-1′), 30.7 (C-2′ and C-2′), 11.4 (C-3′ and C-3′); HRMS (negative) *m*/*z*: 207.2419 (Calcd for $C_{12}H_{16}O_3$: 207.2493).

4.2.6. Compound 1f. Colourless liquid, 1.8 g (8%); ν_{max} ($CHCl_3$) 3571 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.20 (1H, d, $J=8.5$ Hz, H-6), 6.5 (1H, d, $J=8.5$ Hz, H-5), 6.39 (1H, s, H-3), 3.69 (6H, s, 2 and 4 –OCH_3), 1.71–1.69 (4H, m, H-2′ and H-2′), 0.92 (6H, t, $J=7.3$ Hz, H-3′ and H-3′); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 159.7 (C-2), 158.8 (C-4), 129.4 (C-6), 117.2 (C-1), 102.2 (C-5), 99.1 (C-3), 72.6 (C-1′), 55.8 (2-OCH_3), 55.2 (4-OCH_3), 33.1 (C-2′ and C-2′), 8.1 (C-3′ and C-3′); HRMS (positive) *m*/*z*: 225.3012 (Calcd for $C_{13}H_{20}O_3$: 225.3079).

4.2.7. Compound 1g. Colourless liquid, 1.6 g (8%); ν_{max}($CHCl_3$) 3571 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.21 (2H, d, $J=8.5$ Hz, H-6 and H-2), 6.79 (2H, d, $J=8.5$ Hz, H-5 and H-3), 3.72 (3H, s, 4′-OCH_3), 1.74 (4H, m, H-2′ and H-2′), 0.69 (6H, t, $J=7.3$ Hz, H-3′ and H-3′); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 158.0 (C-4), 137.9 (C-1), 126.6 (C-6 and C-2), 113.3 (C-5 and 3), 77.1 (C-1′), 55.1 (4-OCH_3), 34.8 (C-2′ and C-2′), 7.8 (C-3′ and C-3′); HRMS (M+Na) *m*/*z*: 217.2595 (Calcd for $C_{12}H_{18}O_2Na$: 217.2634).

4.3. Synthesis of 1-(3,4,5-trimethoxy)phenyl-1-propanone (4a) and 1a from 3a

A mixture of aryl alkyl carbinol (**3a**) (2.4 mmol) and DDQ (4.8 mmol) in wet dioxane (30 mL) was stirred at room temperature for 14 h. The precipitated $DDQH_2$ was filtered and the red coloured filtrate was evaporated and subsequently chromatographed on silica gel (hexane/ethyl acetate 7:3) to provide phenylpropanone **4a** in 89% whose spectral data was found matching with the reported values. Further treatment of ketone **4a** with excess of ethylmagnesium bromide in ether and toluene provided **1a** in 78% yield.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.10.051.

References and notes

1. (a) Neil, H. A.; Mant, D.; Jones, L.; Morgan, B.; Mann, J. I. *Br. Med. J.* **1990**, *301*, 584. (b) Mantell, G.; Burke, M. T.; Staggers, J. *Am. J. Cardiol.* **1990**, *66*, B11. (c) McCully, K. S. *Nat. Med.* **1996**, *2*, 386. (d) Chrysselis, M. C.; Rekka, E. A.; Kourounakis, P. N. *J. Med. Chem.* **2000**, *43*, 609. (e) Ceska, R.; Melenovsky, V.; Malik, J.; Kralikova, E.; Stulc, T.; Vrablik, M. *Int. Congress Series* **2004**, *1262*, 458.
2. (a) Poplawski:, J.; Lozowicka, B.; Dubis, A. T.; Lachowska, B.; Witkowski, S.; Siluk, D.; Petrusenict, J.; Kaliszan, R.; Cybulski, J.; Stralkowska, M.; Chilmonczylc, Z. *J. Med. Chem.* **2000**, *43*, 3671. (b) Chilmonczyk, Z.; Siluk, D.; Kaliszan, R.; Łozowicka, B.; Popławski, J.; Filipek, S. *Pure Appl Chem.* **2001**, *73*, 1445. (c) Cassani-Galindo, M.; Madrigal-Bujaidar, E.; Chamorro, G.; Díaz, F.; Tamariz, J.; Espinosa-Aguirre, J. J. E. *Toxicol. In Vitro* **2005**, *19*, 547. (d) Medina-Franco, J. L.; López-Vallejo, F.; Rodríguez-Morales, S.; Castillo, R.; Chamorro, G.; Tamariz, J. *Bioorg. Med. Chem.* **2005**, *15*, 989.
3. (a) Sharma, P. K.; Dandiya, P. C. *Indian J. Appl. Chem.* **1969**, *32*, 236. (b) Barata, L. E. S.; Baker, M. B.; Gottlieb, O. R.; Rureda, K. A. *Phytochemistry* **1978**, *17*, 783. (c) Francisco, D.; Leticia, C.; Rosa, F.; Joaquin, T.; Fernando, L.; German, C.; Heber, M. *Org. Prep. Proced. Int.* **1991**, *23*, 133. (d) Patel, S.; Panda, M. P.; Kuanar, M.; Mishra, B. K. *Ind. J. Chem.* **2004**, 1299.
4. (a) Hamdouchi, C.; Warborsky, H. M. In *Handbook of Grignard Reagents*; Silverman, G. S., Rakita, P. E., Eds.; Dekker: New York, 1996. (b) Garst, J. F.; Soriaga, M. P. *Coord. Chem. Rev.* **2004**, *248*, 623.
5. (a) Lajis, N. H.; Khan, M. N.; Hassan, H. A. *Tetrahedron* **1993**, *49*, 3405. (b) Lesce, M. R.; Graziano, M. L.; Cermola, F.; Montella, S.; Giola, L. D. *Tetrahedron Lett.* **2003**, *44*, 5781. (c) Vícha, R.; Potáček, M. *Tetrahedron* **2005**, *61*, 83.
6. (a) Sharma, A.; Joshi, B. P.; Sinha, A. K. *Chem. Lett.* **2003**, *32*, 1186. (b) Pathania, V.; Sharma, A.; Sinha, A. K. *Helv. Chim. Acta* **2005**, *88*, 811. (c) Joshi, B. P.; Sharma, A.; Sinha, A. K. *Tetrahedron* **2005**, *61*, 3075.
7. Canonne, P.; Foscolos, G.; Caron, H.; Lemay, G. *Tetrahedron* **1982**, *38*, 3563.
8. (a) Nishiguchi, I.; Sakai, M.; Maekawa, H.; Ohno, T.; Yamamoto, Y.; Ishino, Y. *Tetrahedron Lett.* **2002**, *43*, 635. (b) Sharma, A.; Joshi, B. P.; Sinha, A. K. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 2231.
9. (a) Walker, D.; Hiebert, J. D. *Chem. Rev.* **1967**, *67*, 153. (b) Fu, P. P.; Harvey, R. G. *Chem. Rev.* **1978**, *78*, 317.

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Tetrahedron

Phase transfer catalyzed aziridination of α-bromo-2-cyclopenten-1-one

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Abstract—An efficient and highly selective synthesis of bicyclic-α-keto aziridines from 2-bromo-2-cyclopentenone and aliphatic primary amines mediated by phase transfer catalysts (PTCs) in water at room temperature is demonstrated. Bicyclic-α-keto-aziridines are highly strained and reactive compounds that can be used in the synthesis of biologically active compounds. Therefore, the present strategy with its mild reaction conditions opens up a new entry to the synthesis of unusual aziridines using inexpensive reagents.

1. Introduction

Three-membered-heterocycles such as epoxides and aziridines are versatile intermediates in organic synthesis because they can be converted into a variety of multifunctional compounds.[1,2] The ability of aziridines to undergo highly regio- and stereoselective ring-opening reaction renders them useful as precursors for chiral substrates, auxiliaries, reagents and ligands in stereoselective synthesis for a variety of *N*-containing compounds.[3,4] The nucleophilic ring-opening of *N*-substituted aziridines in the presence of Lewis acids regioselectively affords substituted α-functionalized β-amino acid or β- functionalized α-amino acid precursors, depending on the nature of the nucleophile, the Lewis acid and the three-membered ring substituents. Through ring expansion, aziridines could also give amido derivatives and oxazolines, as a protected form of hydroxyl amino compounds.[5–7] In addition, β-lactam antibiotics, pyrrolidine alkaloids, polymers and chiral amines as chiral auxiliaries for asymmetric alkylation and aldol transformations could be obtained from aziridines.[8,9] Enantiopure aziridines are also currently of interest as enzyme substrates and enzyme inhibitors.[9] Consequently, novel types of peptidic cysteine protease inhibitors containing aziridine-2,3-dicarboxylic acid have been designed and recently synthesized.[10] The development of efficient synthetic routes to aziridines is therefore a worthy target for the synthetic organic chemist.[11,12] It is essential that efficient methods exist for the facile synthesis of a range of structurally diverse aziridines, with the added requirement that any available methods should also allow stereoselective aziridine formation.[1] Like their epoxide counterparts, aziridines can be prepared by a number of methods most of which start from easily available enantiomerically pure compounds. Olefins, imines and β-amino alcohols are the most common and attractive precursors of aziridine derivatives due to low cost, wide availability and their ability to undergo direct [2+1] aziridination reactions.[12a]

Although the stereoselective synthesis of activated aziridines from olefins, alcohols and imines has been widely investigated,[13–15] to the best of our knowledge, studies on non-activated aziridines (*N*-alkyl or aryl) are very rare.[3,16] Aziridination of 2-iodo-α, β-unsaturated ketones using Cs_2CO_3 and xylene in the presence of 1,10-phenanthroline refluxing at 90 °C was reported by Barros and co-workers.[3] We have, however, found that bicyclic-α-keto-aziridines are unstable and decompose to form non-homogenous mixtures within few days even when kept in a refrigerator. This shows that their synthesis requires mild reaction conditions in order to make it possible to isolate reasonable yields.

Nowadays, the demand for environmentally benign organic chemical transformations and organizating research with the aim of keeping pollution effects to a minimum, together with a reduction of energy and raw materials consumption has increased.[17,18] In this respect, the procedure developed by Barros et al.[3] suffers from several disadvantages such as

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Keywords: Aziridination; Phase transfer catalysis; Primary aliphatic amines; Conjugate addition-imitated ring closure reaction; Bicyclic-α-keto-aziridines.
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long reaction time, use of toxic and organic solvent, difficulty of recovery of high boiling solvent relative to the stability of aziridines, high reaction temperature and use of additives. These indicate that a better method for this transformation is desired. We have developed a practical, highly efficient and simple aziridinaton protocol of α-bromo-2-cyclopenetenone **2**. We have assessed different reaction conditions to apply tandem conjugate addition-initiated ring closure (CAIRC) reactions and in the present paper we wish to report the synthesis of *N*-substituted bicyclic-α-keto-aziridines from a series of primary amines applying various PTCs particularly using tetrabutylammonium bromide, TBAB in H_2O.

2. Results and discussion

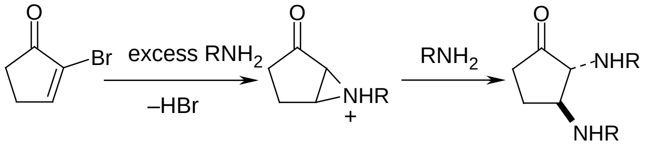
One of the long standing goals of our research has been the development of a mild and general protocol for the selective functionalization of α-donor substituted 2-cyclopentenones **2** with different nucleophiles. Our recent findings have led us to pose several fundamental questions that relate to the stereoselective synthesis of *N*, *S* and *O*-containing heterocycles through conjugate addition-initiated ring closure reactions (CAIRC). Specifically, we are interested in the construction of aziridines from amines since *N*-substituted aziridines are important building blocks for the synthesis of α and β-amino acids. It occurred to us that 2-bromo-2-cyclopentenone **2** could be a suitable substrate for the synthesis of bicyclic α-keto-aziridines.

Initially we chose a model reaction: the addition of benzylamine **1a** to **2** and we investigated different molar ratio of reactants. We also scanned several non-polar and polar solvents such as CH_2Cl_2, CH_3CN, THF, Et_2O, EtOAc, toluene, C_6H_6, CH_3OH, acetone and $CHCl_3$, as well as H_2O. It was noteworthy that the reaction proceeded smoothly only in H_2O. In all the cases, the presence of PTC was found to be essential to promote these reactions. Therefore, we further explored the catalytic activities of various quaternary ammonium salts in the presence of water in tandem conjugate addition-initiated ring closure reaction to give aziridines and the results are summarized in Table 1. The experiments reported in Table 1 were all carried out in water and yields were not optimized. Most of the reactions gave similar results using various PTCs. Especially, the aziridination reactions mediated by Bu_4NBr, Bu_4NI, Hex_4NBr and benzyldimethyl-2-hydroxyethyl ammonium chloride (entries 1, 3, 6 and 8, respectively) proceeded in a similar manner with comparable yields. Bu_4NF showed slow conversion in which most unreacted materials were recovered together with significant amount of amination products. However, for convenience and simplicity, we chose TBAB in H_2O to perform the aziridination reaction of 2-bromo-2-cyclopentenone **2** with other amines.

Table 1. Screening of some phase transfer catalysts on aziridination of **2** with the model amine **1a** in the presence of H_2O at room temperature

Entry	Phase transfer catalysts	Yield (%)
1	Tetrabutylammonium bromide	91
2	Tetrabutylammonium fluoride	54
3	Tetrabutylammonium iodide	88
4	Tetrabutylammonium tetrafluoroborate	79
5	Tetrabutylammonium hydrogensulphate	82
6	Tetrahexylammonium bromide	87
7	Benzyltriaethylammonium chloride	74
8	Benzyldimethyl 2-hydroxyethylammonium chloride	89

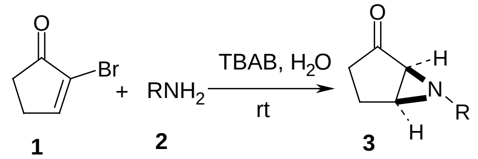
After choosing water as solvent and TBAB as catalyst, we next observed the reaction between **2** and **1a** at room temperature. The reactions were fast giving high yields of the desired products after a reasonable time of reaction. When the reactions were run in water using TBAB as a catalyst, we found that the stoichiometry of the reactants was critical. The use of excess amounts or even equimolar amount of amines leads to substantial amounts of byproducts through transamination or alkylation or bis-addition. This is probably due to HBr liberated during the reaction that protonates the aziridine formed, which is subsequently ring opened by the excess amine (Scheme 1). Therefore, the relief of ring-strain is a factor that provides a driving force for ring-opening after protonation. Primary amines can also be protonated by HBr to give self-alkylated tri- and diamines. For instance, when excess **1c** was reacted with **2**, $(C_5H_5O)_3N$ was obtained as a major byproduct, which was identified by GC–MS.



Scheme 1.

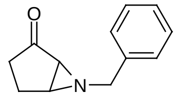
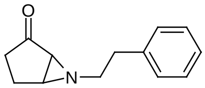
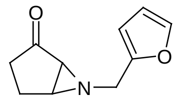
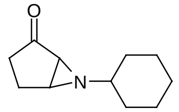
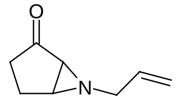
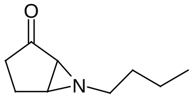
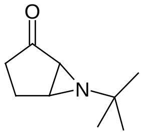
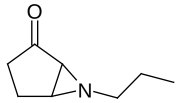
When a slight excess of acceptor (1:1.25 mmol) and 10 mmol % TBAB was used, the side reactions was totally suppresses and no byproducts were obtained. This showed that the course of the reaction was highly dependent on the amount of reactants used. Slight excess of enone provided a good compromise between conversion, yield and suppression of side products so that aziridines can be obtained in 90–98% isolated yields in reactions carried out at room temperature.

To determine the scope and generality of the protocol with respect to amines variation, a series of aliphatic primary amines **1a–h** (phenethyl, benzyl, furayl, cyclohexyl, allyl, butyl, *tert*-butyl and propyl amines, respectively) were reacted with **2** under the above-mentioned conditions and the results are summarized in Table 2. As shown in Table 2, we observed very good to excellent reactivity with all the tested amines. Particularly, the reaction of *t*-$BuNH_2$ was very fast and the reaction was completed within 1 h. The use of aromatic amines such as aniline, 2, 3-dimethylaniline and 2, 6-dimethylaniline under the same reaction conditions did not produce any aziridines nor even after 3 days of stirring. This can be explained by the lower solubility and the less nucleophilc nature of the aromatic amines compared to aliphatic amines towards the first conjugate addition. The effect of solubility in water is also clearly seen among the reactivity of aliphatic amines. Aliphatic amines containing aromatic groups in their chain were found to be relatively less reactive than others (Table 2, entries 1, 2 and 3). This



Scheme 2.

Table 2. TBAB catalyzed aziridination of **2** with amines **1a**–**h** in H_2O at room temperature

Entry	Amine	Time (h)	Product	Yield (%)
1	**1a**	5	 **3a**	98
2	**1b**	5	 **3b**	93
3	**1c**	5	 **3c**	91
4	**1d**	3	 **3d**	90
5	**1e**	3	 **3e**	96
6	**1f**	3	 **3f**	95
7	**1g**	1	 **3g**	94
8	**1h**	3	 **3h**	97

indicates that the quaternary ammonium salts are suitable catalysts to active aliphatic amines and not aromatic amines. This observed selectivity could be useful to differentiate the two types of amines for synthetic applications (Scheme 2).

Generally, this procedure is used to introduce aliphatic amines having different functionality such as allyl and furfuryl groups. Particularly, allyl containing aziridines are useful and versatile synthetic intermediates since this group can be derivatized into interesting functionalities.

3. Conclusion

In this paper, we show that highly reactive bicyclic α-keto-aziridines can be synthesized from α-bromo-enones via a simple 'one pot' procedure. This is the first strategy where aziridines have been synthesized from 2-bromo-2-cyclopentenone and amines mediated by PTCs in water. We believe that this method offers advantages for the development of a direct diastreoselective synthesis of substituted aziridines in high yields under very mild and simple conditions. Further studies will focus on the development of asymmetric aziridination reaction of amines and on the extension of the reaction scope to other amines.

4. Experimental

4.1. General methods

All ^1H and ^{13}C NMR spectra were recorded on a JEOI JNM-EX 400 FT NMR system using $CDCl_3$ as a solvent. Chemical shifts are given in ppm and *J*-values in Hz. Analytical TLC were carried out on precoated (0.25 mm) Merck silica gel F-254 plates. Flash chromatography was carried out using Merck's Kiegelgel 60 (230–400mesh). GLC analyses were performed on a varian 3300 chromatograph equipped with split injector, FID detector and a varian 4400 integrator. IR spectra were recorded on a FT-IR spectrometer and are reported as wave number. GC–MS spectra were registered on a Hewlett 5890 Packard series II CP Sil 5 CB column (25 m) followed by VG Quattro mass spectrometer. Finnigan-MAT-95XL mass spectrometer was used to obtain HREIMS data and the spectra were obtained at 250 °C and 70 eV. All reagents and solvents except 2-bromo-cyclopentenone **2** were obtained from commercial sources and used as received without further purification. Compound **2** was prepared according to literature procedure.[19]

4.2. General procedure for the reaction of 2-bromo-2-cyclopenten-2-one 2 with various amines (1a–h)

A mixture of the bromo-ketone **2** (1.25 mmol), TBAB (10 mmol %) and aliphatic primary amines (1.0 mmol) in H_2O (5 mL) was stirred at room temperature for the specified time until the amine was consumed (see Table 2). The reaction mixture was extracted with Et_2O (3×5 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The expected aziridines (**3a**–**h**) were obtained in quantitative yields after flash chromatography on silica gel (pentane/diethyl ether, 4:1). Each aziridine was characterized by the analysis of HREIMS, DEPT, ^1H and ^{13}C NMR data except **3a** and **3e** that showed very short life spans in the HREIMS.

4.2.1. 6-Benzyl-6-aza-bicyclo[3.1.0]hexan-2-one (3a). (0.181 g, 98%) as a brown oil, R_f 0.46 (3:7 Et_2O/pentane); IR (neat, NaCl plates, ν_{max}, cm^{-1}): 3028, 2930, 1738, 1601, 1451, 1351; ^1H NMR (δ): δ 1.95–2.10 (m, 2H), 2.24–2.35 (m, 2H), 2.40 (d, $J=4.0$ Hz, 1H), 2.80 (t, $J=3.6$ Hz, 1H), 3.40 (d, $J=13.6$ Hz, 1H), 3.80 (d, $J=13.6$ Hz, 1H), 7.27–7.34 (m, 1H), 7.35–7.42 (m, 4H); ^{13}C NMR: δ 212.1 (CO), 139.7 (C), 129.2 (CH), 128.5 (CH), 127.3 (CH), 60.2 (CH_2Ph), 47.6 (CH), 46.5 (CH), 32.6 (CH_2), 24.2 (CH_2); MS (EI): 187% (M^+, 35), 131 (15), 92 (83), 91 (100), 77 (16), 65 (89), 51 (21).

4.2.2. 6-(Phenethyl)-6-aza-bicyclo[3.1.0]hexan-2-one (3b). (0.187 g, 93%) as brown oil, R_f (0.41 Et_2O/pentane); IR (neat, NaCl plates, ν_{max}, cm^{-1}): 2929, 1712, 1421, 1360, 1220; ^{1}H NMR (δ): δ 1.82–2.20 (m, 2H), 2.06 (d, $J=4.0$ Hz, 1H), 2.13–2.21 (m, 1H), 2.25–2.35 (m, 1H), 2.46 (t, $J=3.6$ Hz, 1H), 2.52–2.60 and 2.63–2.71 (m, $-CH_2$Ph), 2.92 (t, $J=7.6$ Hz, 2H), 7.18–7.26 (m, 2H), 7.28–7.39 (m, 3H); ^{13}C NMR: δ 212.0 (–CO), 139.5 (C), 129.0 (CH), 128.5 (CH), 126.2 (CH), 60.2 (CH), 47.0 (CH), 46.4 (CH_2), 36.5 (CH_2), 32.6 (CH_2), 24.2 (CH_2); HRMS: found for $C_{13}H_{15}NO$: 201.1152, calcd: 201.1154.

4.2.3. 6-Furan-2-ylmethyl-6-aza-bicyclo[3.1.0]hexan-2-one (3c). (0.162 g, 91%) as a brown oil, R_f 0.79 (3:7 Et_2O/pentane); IR (neat, NaCl plates, ν_{max}, cm^{-1}): 3116, 2932, 1739, 1590, 1503, 1446, 1405, 1344; ^{1}H NMR (δ): δ 1.96–2.05 (m, 2H), 2.22–2.36 (m, 2H), 2.35 (d, $J=3.6$ Hz, 1H), 2.82 (t, $J=3.6$ Hz, 1H), 3.42 (d, $J=14.2$ Hz, 1H), 3.63 (d, $J=14.2$ Hz, 1H), 6.13 (d, $J=3.0$ Hz, 1H), 6.22 (dd, $J=3.0$, 1.0 Hz, 1H), 7.17 (d, $J=1.0$ Hz, 1H); ^{13}C NMR: δ 212.0, 152.2 (C), 142.5 (CH), 110.5 (CH), 108.3 (CH), 54.1 ($-NCH_2$), 46.8 (CH), 45.3 (CH), 33.1 (CH_2), 24.2 (CH_2); HRMS: found for $C_{10}H_{11}NO_2$: 177.0796, calcd: 77.0790.

4.2.4. 6-Cyclohexyl-6-aza-bicyclo[3.1.0]hexan-2-one (3d). (0.161 g, 90%) as a yellow oil, R_f 0.72 (1:4 Et_2O/pentane); IR (neat, NaCl plates, ν_{max}, cm^{-1}): 2926, 2853, 1738, 1449, 1353, 1165, 1112; ^{1}H NMR (δ): δ 1.12–1.26 (m, 2H), 1.28–1.48 (m, 4H), 1.59–1.68 (m, 4H), 1.75–1.89 (m, 2H), 1.94–2.04 (m, 1H), 2.10 (d, $J=3.6$ Hz, 1H), 2.14–2.36 (m, 2H), 2.62 (t, $J=3.6$ Hz, 1H); ^{13}C NMR: δ 212.3, 66.5 (–NCH), 46.2 (CH), 45.4 (CH), 33.5 (CH_2), 33.0 (CH_2), 24.9 (CH_2), 24.7 (CH_2), 24.5 (CH_2); HRMS: found for $C_{11}H_{17}NO$: 179.1314, calcd: 179.1310.

4.2.5. 6-Allyl-6-aza-bicyclo[3.1.0]hexan-2-one (3e). (0.131 g, 96%) as a yellow oil, R_f 0.62 (1:9 Et_2O/pentane); IR (neat, NaCl plates, ν_{max}, cm^{-1}): 2929, 1738, 1642, 1448; ^{1}H NMR (δ): δ 1.92–2.04 (m, 2H), 2.13 (d, $J=4.0$ Hz, 1H), 2.20–2.36 (m, 2H), 2.63 (t, $J=3.6$ Hz, 1H), 2.99 (d, $J=5.6$ Hz, 2H), 5.17 (dd, $J=9.2$, 1.2 Hz, 1H), 5.26 (dd, $J=16.0$, 1.6 Hz, 1H), 5.70–5.95 (m, $CH{=}CH_2$); ^{13}C NMR: δ 212.0, 134.4 ($CH{=}CH_2$), 117 ($CH{=}CH_2$), 60.6 ($-NCH_2$), 47.0 (CH), 46.2 (CH), 33.3 (CH_2), 24.2 (CH_2); MS: *m/z* % 137 (M^+, 25), 136 (M^+-H, 6), 71 (11), 57 (12), 41 (24).

4.2.6. 6-Butyl-6-aza-bicyclo[3.1.0]hexan-2-one (3f). (0.145 g, 95%) as a yellow oil, R_f 0.52 (1:9 Et_2O/pentane); IR (neat, NaCl plates, ν_{max}, cm^{-1}): 2930, 2867, 1739, 1615, 1456, 1407, 1353; ^{1}H NMR (δ): δ 0.90 (t, $J=14.8$ Hz, 3H) 1.32–1.41 (m, 2H), 1.50–1.60 (m, 2H), 1.88–1.97 (m, 2H), 2.02 (d, $J=4.0$ Hz, 1H), 2.14–2.26 (m, 2H), 2.31 (t, $J=6.8$ Hz, 2H), 2.54 (t, $J=3.6$ Hz, 1H); ^{13}C NMR: δ 212.2, 58.5 ($-NCH_2$), 47.2 (CH), 46.1 (CH), 33.2 (CH_2), 32.5 (CH_2), 24.1 (CH_2), 20.5 (CH_2), 14.3 (CH_3); HRMS: found for $C_9H_{15}NO$: 153.1155, calcd: 153.1154.

4.2.7. 6-*tert*-Butyl-6-aza-bicyclo[3.1.0]hexan-2-one (3g). (0.143 g, 94%) as a yellow oil, R_f 0.55 (1:9 Et_2O/pentane); IR (neat, NaCl plates, ν_{max}, cm^{-1}): 2968, 1737, 1612, 1362, 1213, 1091; ^{1}H NMR (δ): δ 1.03 (s, 9H), 1.92–2.14 (m, 2H), 2.27 (d, $J=4.0$ Hz, 1H), 2.33–2.42 (m, 2H), 2.78 (t, $J=3.6$ Hz, 1H); ^{13}C NMR: δ 214.5, 54.2 (C), 41.5 (CH), 39.4 (CH), 35.7 (CH_2), 27.8 (CH_3), 24.5 (CH_2); GC–MS: *m/z%* 154 (M^++H, 2), 153 (M^+, 5), 97 (100), 68 (34), 57 (34), 41 (30).

4.2.8. 6-Propyl-6-aza-bicyclo[3.1.0]hexan-2-one (3h). (0.135 g, 97%) as a yellow oil, R_f 0.69 (1:9 Et_2O/pentane); IR (neat, NaCl plates, ν_{max}, cm^{-1}): 2958, 1740, 1680, 1633, 1460, 1352, 1190; ^{1}H NMR (δ): δ 0.94 (t, $J=14.8$ Hz, 3H), 1.54–1.66 (m, 2H), 1.90–1.97 (m, 2H), 2.03 (d, $J=3.6$ Hz, 1H), 2.10–2.24 (m, 2H), 2.30 (t, $J=11.2$ Hz, 1H), 2.55 (t, $J=3.6$ Hz, 2H); ^{13}C NMR: δ 212.2, 60.5 ($-NCH_2$), 37.2 (CH), 36.2 (CH), 33.0 (CH_2), 24.1 (CH_2), 23.3 (CH_2), 12.4 (CH_3); HRMS: found for $C_8H_{13}NO$: 139.0998, calcd: 139.0997.

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References and notes

1. Sugihara, H.; Daikai, K.; Jin, X.; Furuno, H.; Inanaga, J. *Tetrahedron Lett.* **2002**, *43*, 2735.
2. (a) Aggarwal, V. K.; Stenson, R. A.; Jones, R. V. H.; Fieldhouse, R.; Blacker, J. *Tetrahedron Lett.* **2001**, *42*, 1587. (b) Fazio, A.; Loreto, M. A.; Tardella, P. A. *Tetrahedron Lett.* **2001**, *42*, 2185. (c) Carducci, M.; Fioravanti, S.; Loreto, M. A.; Pellacani, L.; Tardella, P. A. *Tetrahedron Lett.* **1996**, *37*, 3777. (d) Fujisawa, T.; Hayakawa, R.; Shimizu, M. *Tetrahedron Lett.* **1992**, *33*, 7903.
3. Barros, M. T.; Maycock, C. D.; Ventura, M. R. *Tetrahedron Lett.* **2002**, *43*, 4329.
4. Bongini, A.; Cardillo, G.; Gentilucci, L.; Tomasini, C. *J. Org. Chem.* **1997**, *62*, 9148.
5. Cardillo, G.; Gentilucci, L.; Tomasini, C.; Pilar, M.; Castejon-Bordas, V. *Tetrahedron: Asymmetry* **1996**, *7*, 755.
6. Chen, D.; Timmons, C.; Guo, L.; Xu, X.; Li, G. *Synthesis* **2004**, 2479.
7. (a) Ley, S. V.; Middleton, B. *Chem. Commun.* **1998**, 1995. (b) Tanner, D.; Birgersson, C.; Dhaliwal, H. K. *Tetrahedron Lett.* **1990**, *31*, 1903. (c) Chandrasekhar, M.; Sekar, G.; Singh, V. K. *Tetrahedron Lett.* **2000**, *41*, 10079.
8. Gillespie, K. M.; Sanders, C. J.; O'Shaughnessy, P.; Westmoreland, I.; Thickitt, C. P.; Scott, P. *J. Org. Chem.* **2002**, *67*, 3450.
9. Osborn, H. M. I.; Sweeney, J. *Tetrahedron: Asymmetry* **1997**, *8*, 1693.
10. Cardillo, G.; Gentilucci, L.; Gianotti, M.; Perciaccante, R.; Tolomelli, A. *J. Org. Chem.* **2001**, *66*, 8657.
11. (a) Xie, W.; Fang, J.; Li, J.; Wang, P. G. *Tetrahedron* **1999**, *55*, 12929. (b) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Am.*

Chem. Soc. **1994**, *116*, 2742. (c) Antunes, A. M. M.; Marto, S. J. L.; Branco, P. S.; Prabhakar, S.; Lobo, A. M. *Chem. Commun.* **2001**, 405.

12. (a) Garner, P.; Dogan, O.; Pillai, S. *Tetrahedron Lett.* **1994**, *35*, 1653. (b) Fioravanti, S.; Pellacani, L.; Stabile, S.; Tardella, P. A.; Ballini, R. *Tetrahedron* **1998**, *54*, 6169. (c) Xu, J.; Jiao, P. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1491. (d) Fioravanti, S.; Morreale, A.; Pellacani, L.; Tardella, P. A. *J. Org. Chem.* **2002**, *67*, 4972.
13. Fioravanti, S.; Pellacani, L.; Tabanella, S.; Tardella, P. A. *Tetrahedron* **1998**, *54*, 14105.
14. Dahanukar, V. H.; Zavialov, L. A. *Curr. Opin. Drug Discovery Dev.* **2002**, *5*, 918.
15. Atkinson, R. S.; Grimshire, M. J.; Kelly, B. J. *Tetrahedron* **1989**, *45*, 2875.
16. Barros, M. T.; Matias, P. M.; Maycock, C. D.; Ventura, M. R. *Org. Lett.* **2003**, *5*, 4321.
17. Minakata, S.; Kano, D.; Oderaotoshi, Y.; Komatsu, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 79.
18. Bensa, D.; Rodriguez, J. *Synth. Commun.* **2004**, *34*, 1515.
19. Kowalski, C. J.; Weber, A. E.; Fields, K. W. *J. Org. Chem.* **1982**, *47*, 5088.

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A microwave-enhanced, solventless Mannich condensation of terminal alkynes and secondary amines with *para*-formaldehyde on cuprous iodide doped alumina

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Abstract—A microwave-enhanced, solventless Mannich condensation of terminal alkynes and secondary amines with *para*-formaldehyde on cuprous iodide doped alumina has been developed. β-Aminoalkynes are generated in good yields. The reaction can be extended to include a cyclization, which affords 2-substituted benzo[*b*]furans. The chemoselectivity of the reaction indicates that terminal alkynes are much more reactive than enolizable ketones under the reaction conditions.

1. Introduction

The Mannich reaction is a classic example of a three-component condensation reaction.[1] In general, formaldehyde (or *para*-formaldehyde), an amine, and an 'active-hydrogen' component such as an enolizable ketone or terminal alkyne are allowed to react to afford the corresponding β-aminoketone or β-aminoalkyne. The latter Mannich adduct contains at least two potential sites for further modification: the amine and the alkyne.[2] In addition, β-aminoalkynes and their derivatives have a wide range of applications including use as pharmaceutical intermediates[3] and as general synthetic building blocks.[4] Moreover, the alkyne moieties may be functionalized in various ways.

The traditional Mannich method for synthesizing β-aminoalkynes often requires drastic reaction conditions and generally is run in dioxane, a toxic solvent. The organic solvent and the metal catalyst can be difficult to handle and often difficult to dispose of safely.

We have found alumina to be a particularly useful reagent in organic synthesis because it can be modified in a variety of ways that enhance its reactivity. It also obviates a number of environmental problems.[5] For example, using a commercially available alumina/potassium fluoride mixture to which palladium powder was added, we were able to carry out Suzuki and Sonogashira coupling reactions on a wide variety of aromatic moieties without the use of solvents.[6]

Microwave irradiation of organic reactions has gained in popularity in recent years since it was found to accelerate a wide variety of transformations.[7] Early experiments utilized solvents with high dielectric constants, which permitted rapid heating of the reaction solution. In recent years, a number of reports have appeared in which reactants are coated on to surfaces, which themselves absorb little or no microwave energy; in these instances, the reactive species absorb the microwave energy but the temperature of the reaction mixture tends to rise only modestly. This results in relatively large energy saving as well as making it possible to carry out reactions in relatively simple glassware such as open beakers and flasks.[8]

We now wish to report the details of a microwave-enhanced Mannich condensation of terminal alkynes with amines and *para*-formaldehyde on CuI-doped alumina in the absence of solvents that produces the corresponding aminomethylated adducts in good yields. The reaction can be extended to a Mannich condensation cyclization sequence that generates 2-substituted benzo[*b*]furans in one-pot and in good yields. The process is highly efficient, does not require pre-forming the iminium species, and is not hampered by the heterogeneity of the reaction medium (Scheme 1).

$$R^1C{\equiv}CH + (CH_2O)_n + HNR^2R^3 \xrightarrow[\text{MW}]{\text{CuI/Al}_2\text{O}_3} R^1C{\equiv}CCH_2NR^2R^3$$

Scheme 1.

Keywords: Cuprous salts; Mannich reaction; Solventles; Microwave.

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Table 1. A Effect of cuprous salts on the Mannich condensation[a]

Entry	Cuprous salt	Yield (%)[b]
a	Cu_2Cl_2	28
b	CuBr	26
c	CuI	82
d	None	0

[a] Reaction conditions: dibenzylamine (1.00 mmol), 1-decyne (1.00 mmol), *para*-formaldehyde (3.00 mmol), cuprous salt (3.00 mmol), Al_2O_3 (1.00 g), irradiated at 300 W for 10 min.

[b] Isolated yields.

2. Results and discussion

2.1. Effect of cuprous salts on the Mannich condensation of terminal alkynes with amines and *para*-formaldehyde

We initially explored the affect of the cuprous salts on the Mannich condensation of terminal alkynes with amines and *para*-formaldehyde. The results are listed in Table 1. Dibenzylamine, *para*-formaldehyde and 1-decyne were chosen as the model reactants for this investigation.

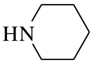
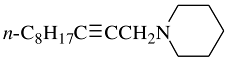
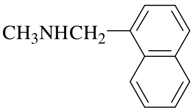
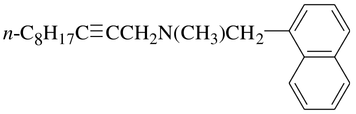
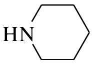
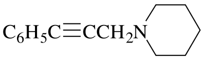
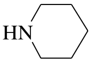
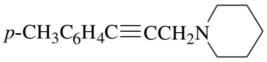
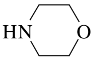
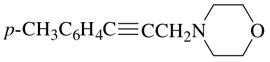
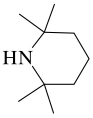
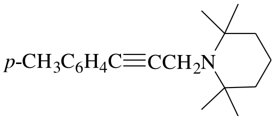
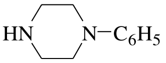
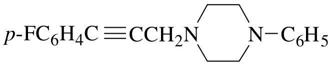
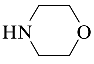
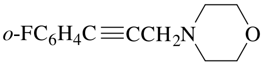
It is evident that the Mannich reaction requires a cuprous salt to 'active' the terminal alkyne carbon–hydrogen bond to promote aminomethylation. Among the cuprous salts we tested, cuprous iodide was most effective and was chosen for further study.

2.2. Mannich condensation of terminal alkynes with secondary amines and *para*-formaldehyde

Table 2 contains a summary of the experimental results. A number of terminal alkynes were successfully condensed with secondary amines and *para*-formaldehyde in good yields. Dibenzylamine, methylbenzylamine, morpholine, piperidine, 1-phenylpiperazine, *N*-methyl-1-naphthalenemethylamine, di(*iso*-propyl)amine all reacted smoothly with terminal alkynes and *para*-formaldehyde to generate the corresponding Mannich products. It should be noted that the reaction tolerated many functional groups and that the sterically hindered 2,2,6,6-tetramethylpiperidine smoothly produced the corresponding Mannich adduct.

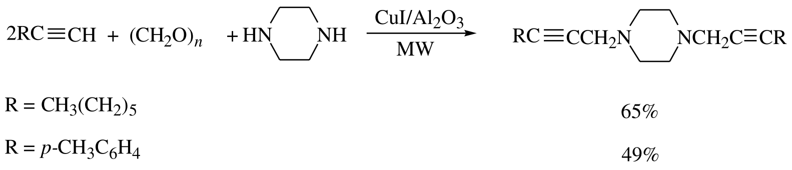
During the investigation, we found that piperazine reacts with terminal alkynes (2 equiv) and *para*-formaldehyde (excess) to afford the diaminomethylation adducts [bis-(β-aminoalkyne)] (Scheme 2) and 1,9-decadiyne reacted with secondary amines (2 equiv) and *para*-formaldehyde (excess) to generate the bis-Mannich products in moderate to good yields (Scheme 3).

Table 2. Mannich condensation reaction of terminal alkynes with secondary amine and *para*-formaldehyde[a]

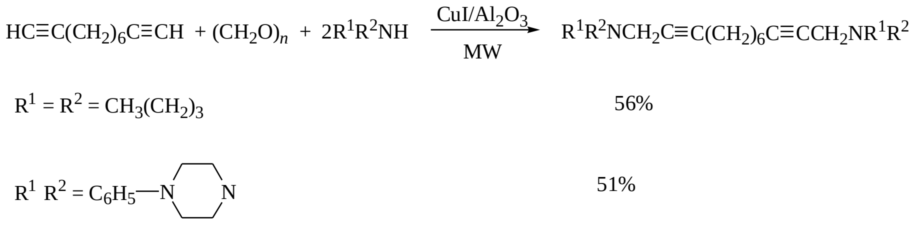
Entry	Alkyne	Amine	Product	Yield (%)[b]
a	$n\text{-}C_8H_{17}C\equiv CH$	$(n\text{-}C_4H_9)_2NH$	$n\text{-}C_8H_{17}C\equiv CCH_2N(n\text{-}C_4H_9)_2$	88
b	$n\text{-}C_8H_{17}C\equiv CH$	$(C_6H_5CH_2)_2NH$	$n\text{-}C_6H_{13}C\equiv CCH_2N(CH_2CH_6H_5)_2$	82
c	$n\text{-}C_6H_{13}C\equiv CH$	$(C_6H_5CH_2)_2NH$	$n\text{-}C_8H_{17}C\equiv CCH_2(CH_2C_6H_5)_2$	81
d	$n\text{-}C_8H_{17}C\equiv CH$	$C_6H_5CH_2NHCH_3$	$n\text{-}C_8H_{17}C\equiv CCH_2N(CH_3)CH_2C_6H_5$	89
e	$n\text{-}C_8H_{17}C\equiv CH$			82
f	$n\text{-}C_8H_{17}C\equiv CH$			71
g	$C_6H_5C\equiv CH$	$(C_6H_5CH_2)_2NH$	$C_6H_5C\equiv CCH_2N(CH_2C_6H_5)_2$	79
h	$C_6H_5C\equiv CH$			88
i	$p\text{-}CH_3C_6H_4C\equiv CH$			80
j	$p\text{-}CH_3C_6H_4C\equiv CH$	$(C_6H_5CH_2)_2NH$	$p\text{-}CH_3C_6H_4C\equiv CCH_2N(CH_2C_6H_5)_2$	83
k	$p\text{-}CH_3C_6H_4C\equiv CH$			92
l	$p\text{-}CH_3C_6H_4C\equiv CH$			74
m	$p\text{-}FC_6H_4C\equiv CH$			90
n	$p\text{-}FC_6H_4C\equiv CH$	$(C_6H_5CH_2)_2NH$	$p\text{-}FC_6H_4C\equiv CCH_2N(CH_2C_6H_5)_2$	85
o	$o\text{-}FC_6H_4C\equiv CH$			72
p	$p\text{-}BrC_6H_4C\equiv CH$	$(n\text{-}C_4H_9)_2NH$	$p\text{-}BrC_6H_4C\equiv CCH_2N(n\text{-}C_4H_9)_2$	89

[a] Reaction conditions: secondary amine (1.00 mmol), terminal alkyne (1.00 mmol), *para*-formaldehyde (3.00 mmol), cuprous iodide (3.00 mmol), Al_2O_3 (1.00 g).

[b] Isolated yields.



Scheme 2.



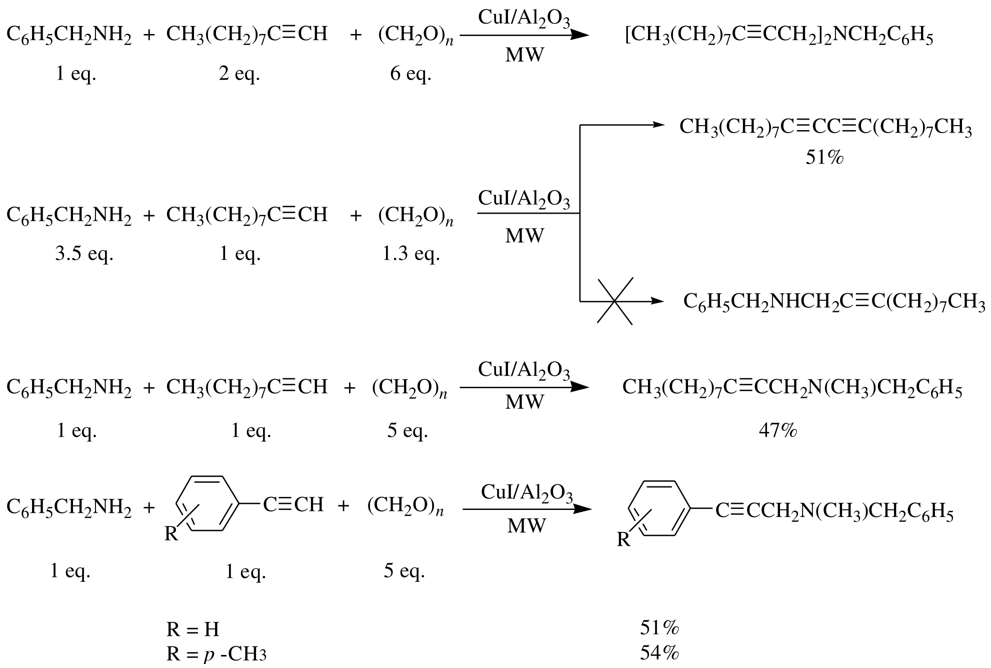
Scheme 3.

2.3. Mannich condensation of terminal alkynes with primary amines and *para*-formaldehyde

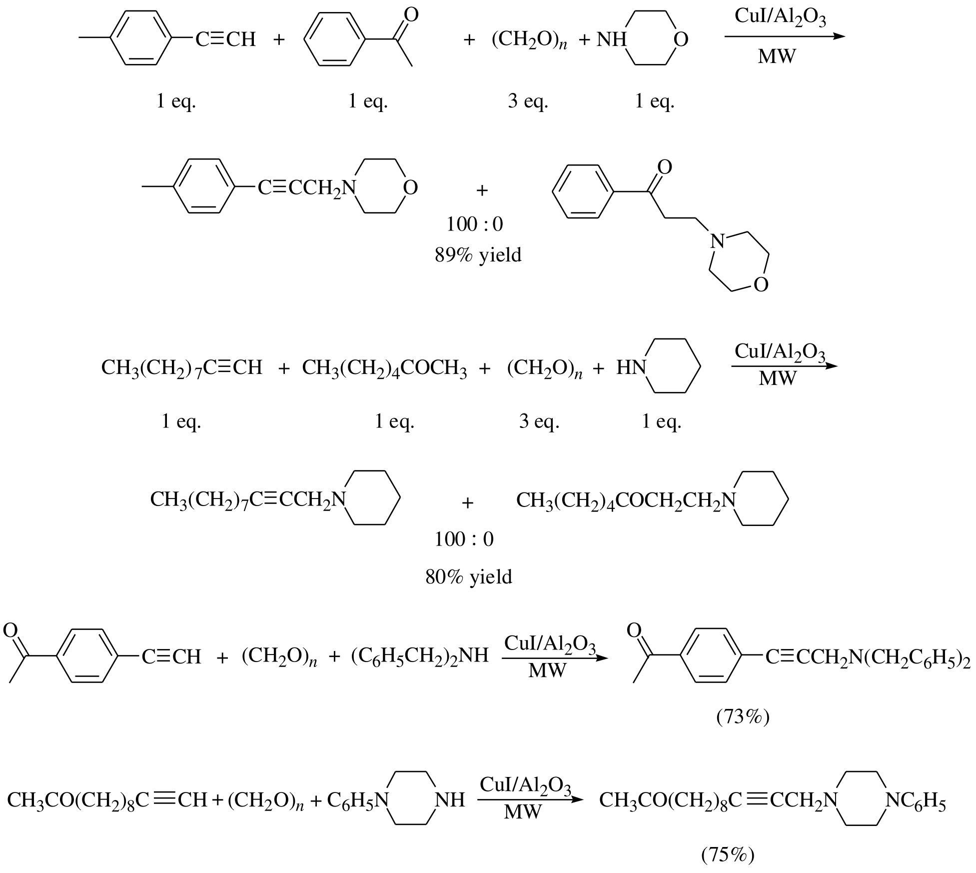
As anticipated, benzylamine (1 equiv), a primary amine, reacted with 1-decyne (2 equiv) and *para*-formaldehyde (6 equiv) to produce the bis-Mannich condensation because there are two nitrogen–hydrogen bonds in the primary amine (Scheme 4). Interestingly, when the ratio of reactants is changed alternative reations occur. For example, benzylamine (1 equiv) reacted with 1-decyne (1 equiv) and *para*-formaldehyde (5 equiv) to generate the Mannich condensation product followed reductive methylation (Scheme 4) phenylacetylene derivatives also afforded methylation products in fair yields (Scheme 4). The reaction provides an alternative route to *N*-methyl-β-aminoalkynes in a convenient and straightforward fashion.[9]

2.4. The chemoselectivity of the Mannich condensation of terminal alkynes with secondary amines and *para*-formaldehyde

The chemoselectivity of the reaction was investigated. When a mixture of acetophenone and 4-ethynyltoluene (or a mixture of 1-decyne and 2-heptanone) served as competitive acidic substrates for the Mannich reaction, only the β-aminoalkynes were formed (Scheme 5). As anticipated, the Mannich reaction of 4-acetyl-1-ethynylbenzene with dibenzylamine and *para*-formaldehyde (or 11-dodecyn-2-one



Scheme 4.



Scheme 5.

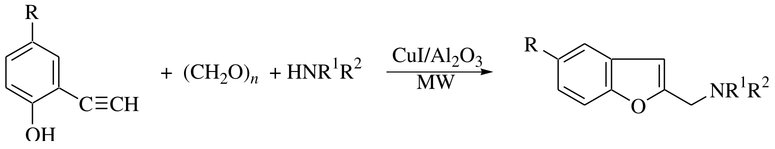
with 1-phenylpiperazine and *para*-formaldehyde) generated β-aminoalkyne products exclusively (Scheme 5).

2.5. 2-Subsitituted benzo[*b*]furans from the Mannich condensation of *o*-ethynylphenol with secondary amines and *para*-formaldehyde

Benzo[*b*]furans and their derivatives have received much attention in recent years because of their occurrence in natural products and their physiological activity.[10] They are widely used as antitumor agents,[11] as ligands of the adenosine A_1 receptor,[12] and as calcium entry blockers.[13] General routes to benzo[*b*]furans involve reductive cyclization of ketoesters by low-valent titanium,[14] photochemically induced rearrangement of phosphate esters,[15] palladium catalyzed Suzuki coupling of boronic acids with organic halides or triflates,[16] and palladium catalyzed Sonogashira coupling (followed by cyclization) of *o*-iodophenol and terminal alkynes.[17] No report has appeared describing the synthesis of 2-substituted benzo[*b*]furans using a Mannich condensation reaction.

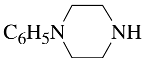
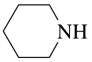
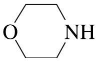
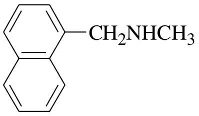
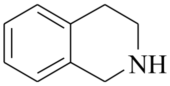
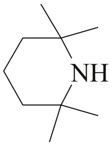
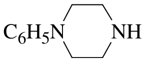
The Mannich condensation–cyclization of *o*-ethnylphenol with secondary amines and *para*-formaldehyde on cuprous iodide doped alumina under solvent free and microwave irradiation conditions generates 2-(dialkylaminomethyl)-benzo[*b*]furans in good yields (Scheme 6 and Table 3).

Table 3 contains a summary of the results. Under microwave irradiation and solvent free conditions, *o*-ethynylphenol (as well as *p*-acetyl-*o*-ethynylphenol) reacts smoothly with *para*-formaldehyde and a variety of secondary amines, such as 1-phenylpiperizine, piperdine, morpholine, dibutylamine, di(*iso*-propyl)amine, and *N*-methylaniline, methylbenzylamine, 1,2,3,4-tetrahydroisoquioine, and *N*-methylnaphthylmethylamine to afford the desired 2-substituted benzo[*b*]furans in one-pot. It should be noted that the highly sterically encumbered 2,2,6,6-tetramethylpiperidine also smoothly undergoes the reaction to generate the corresponding 2-substituted-benzo[*b*]furan, which was characterized by ^{1}H, ^{13}C NMR, MS and microanalysis, and confirmed by X-ray crystal diffraction. Interestingly, when *o*-ethynylphenol (2 equiv) was allowed



Scheme 6.

Table 3. Mannich condensation–cyclization reaction of *o*-ethnylphenol and its deriatives with secondary amines and *para*-formaldehyde (see Scheme 6)[a]

Entry	R	Amine	Yield (%)[b]
a	H		65
b	H	$(n\text{-}C_4H_9)_2NH$	68
c	H		65
d	H	$CH_5CH_2NHCH_3$	62
e	H		55
f	H		70
g	H		59
h	H	$(i\text{-}C_3H_7)_2NH$	56
i	H		52
j	H	$C_6H_5NHCH_3$	36
k	H		65

[a] Reaction condition: secondary amine (1.00 mmol), *o*-ethynylphenol (1.00 mmol), *para*-formaldehyde (3.00 mmol), cuprous iodide (3.00 mmol), Al_2O_3 (1.00 g), irradiated at 300 W for 10 min.

[b] Isolated yields.

to react with *para*-formaldehyde (excess) and piperazine (1 equiv), a bis-Mannich condensation cyclization product was formed (Scheme 7).

2.6. Surface recyclability

We utilized a surface containing 3 mmol of cuprous iodide per gram of alumina for 1 mmol scale reactions. In an effort to enhance the efficiency of the new solid-state Mannich condensation reaction and reduce waste, recycling was investigated. Table 4 contains a summary of the results. It can be seen that the catalyst and alumina remain active through at least eight cycles. After the product was removed from the surface using an organic solvent, the surface was used directly for the next trial without further treatment.

Table 4. Successive trials for Mannich condensation using CuI/Al_2O_3[a]

Trial	Yield (%)[b]
1	82
2	80
3	81
4	79
5	80
6	82
7	80
8	79

[a] Experiment were carried out as described in the Section 4 by using 1-decyne (1 mmol), dibenzylamine (1.00 mmol), *para*-formaldehyde (3.00 mmol), cuprous iodide (3.00 mmol), Al_2O_3 (1.00 g), microwave irradiation at 300 W for 10 min.

[b] Isolated yields.

3. Conclusion

A reliable, rapid, practical, and environmentally benign method for the synthesizing β-aminoalkynes and 2-substituted benzo[*b*]furans has been developed, which involves the use of a solvent-free mixture of cuprous iodide and alumina under microwave irradiation conditions. The process is highly efficient, does not require pre-forming the iminium species, and is not hampered by the heterogeneity of the reaction.

4. Experimental

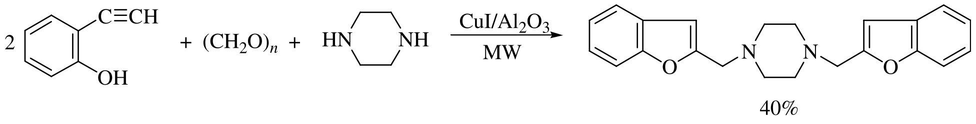
Melting points were recorded on a MEL-TEMP melting point apparatus and are uncorrected. IR were recorded on a Bomem MB 100 FT-IR. All ^1H and ^{13}C NMR spectra were recorded on a 250 MHz Bruker AC 250 or Avance 400 MHz spectrometer. Chemical shift are given as δ value with reference to tetramethylsilane (TMS) as internal standard. GC/MS data were obtained by using a Hewlett-Packard 6890 series GC equipped with a 5973 mass selective detector. Microanalyses were performed by Atlantic Microlabs, Norcross, GA. A commercially available Ethos E Touch Control microwave unit (Milestone) was utilized.

Al_2O_3 and cuprous iodide were purchased from Aldrich Chemical Co. The organic reagents were analytical grade and used as received (Aldrich Chemical Co.).

Products were purified, if applicable, by flash chromatography on 230–400 mesh ASTM 60 Å silica gel, SiO_2.

4.1. General procedure for Mannich condensation of terminal alkynes with amines and *para*-formaldehyde

Secondary amine (1.00 mmol) and terminal alkyne (1.00 mmol) were added to a mixture of cuprous iodide (0.572 g, 3.00 mmol), *para*-formaldehyde (0.09 g, 3.00 mmol)



Scheme 7.

and alumina (1.00 g) contained in a clean, dry, 10 mL round-bottomed flask. The mixture was stirred at room temperature to ensure efficient mixing. The flask was then fitted with a septum (punctured by an 18 gauge needle to serve as a pressure release valve), placed in the microwave oven and irradiated at 300 W for 10 min [caution: heating volatile materials in commercial microwave ovens for extended periods can be hazardous]. After cooling, ether (4 mL) was added and the slurry stirred at room temperature to ensure product removal from the surface. The mixture was vacuum filtered using a sintered glass funnel and the product was purified by flash chromatography to yield the desired β-aminoalkyne.

4.1.1. Dibutyl(undec-2-ynyl)amine.[18] Oil; ^{1}H NMR (250 MHz, CDCl$_3$): δ 3.35 (s, 2H), 2.38–2.49 (t, 4H), 2.12–2.21 (t, 3H), 1.19–1.60 (m, 20H), 0.88–0.94 (m, 9H); ^{13}C NMR (62.5 MHz, CDCl$_3$): δ 84.9, 74.7, 53.5, 42.3, 31.7, 29.7, 29.2, 29.1, 29.0, 28.8, 22.7, 20.7, 18.7, 14.1.

4.1.2. Dibenzyl(undec-2-ynyl)amine. Oil; IR (film, CHCl$_3$) 2261 cm^{-1} (C≡C); ^{1}H NMR (250 MHz, CDCl$_3$) δ 7.40–7.16 (m, 10H), 3.65 (s, 2×2H), 3.22 (s, 2H), 2.24 (t, J=6.6 Hz, 2H), 1.55–1.30 (m, 12H), 0.88 (t, J=6.8 Hz, 3H); ^{13}C NMR (62.5 MHz, CDCl$_3$): δ 139.1, 128.9, 128.1, 126.9, 85.7, 74.4, 57.5, 41.6, 31.8, 29.3, 29.1, 28.9, 22.6, 18.7, 14.1; MS *m/z* (relative intensity) 347 (M$^+$, 3), 270 (6), 256 (10), 194 (7), 91 (100). Anal. Calcd for C$_{25}$H$_{33}$N: C, 86.40; H, 9.57; N, 4.03. Found: C, 86.34; H, 9.68; N, 4.09.

4.1.3. Dibenzyl(non-2-ynyl)amine. Oil; IR (film, CHCl$_3$) 2260 cm^{-1} (C≡C); ^{1}H NMR (250 MHz, CDCl$_3$): δ 7.40–7.18 (m, 10H), 3.65 (s, 2×2H), 3.22 (s, 2H), 2.25 (t, J=6.7 Hz, 2H), 1.59–1.31 (m, 8H), 0.91 (t, J=6.7 Hz, 3H); ^{13}C NMR (62.5 MHz, CDCl$_3$): δ 139.1, 129.0, 128.2, 126.9, 85.8, 74.4, 57.5, 41.6, 31.4, 29.1, 28.6, 22.6, 18.7, 14.1; MS *m/z* (relative intensity) 319 (M$^+$, 3), 242 (7), 228 (9), 194 (6), 91 (100). Anal. Calcd for C$_{23}$H$_{29}$N: C, 86.47; H, 9.15; N, 4.38. Found: C, 86.24; H, 9.22; N, 4.41.

4.1.4. Benzylmethyl(undec-2-ynyl)amine. Oil; IR (film, CHCl$_3$) 2261 cm^{-1} (C≡C); ^{1}H NMR (250 MHz, CDCl$_3$): δ 7.34–7.21 (m, 5H), 3.55 (s, 2H), 3.25 (s, 2H), 2.30 (s, 3H), 2.23 (t, J=6.8 Hz, 2H), 1.56–1.28 (m, 12H), 0.88 (t, J=6.0 Hz, 3H); ^{13}C NMR (62.5 MHz, CDCl$_3$): δ 138.6, 129.1, 128.1, 127.0, 85.7, 74.5, 60.1, 45.4, 41.7, 31.8, 29.2, 29.0, 28.9, 28.8, 22.6, 18.7, 14.0; MS *m/z* (relative intensity) 271 (M$^+$, 7), 194 (26), 158 (21), 120 (19), 91 (100). Anal. Calcd for C$_{19}$H$_{29}$N: C, 84.07; H, 10.77; N, 5.16. Found: C, 84.21; H, 10.88; N, 5.23.

4.1.5. 1-(Undec-2-ynyl)piperidine. Oil; IR (film, CHCl$_3$) 2188 cm^{-1} (C≡C); ^{1}H NMR (250 MHz, CDCl$_3$): δ 3.20 (t, J=1.8 Hz, 2H), 2.47 (s, br, 2×2H), 2.18 (t, J=6.8 Hz, 2H), 1.66–1.28 (m, 18H), 0.88 (t, J=6.5 Hz, 3H); ^{13}C NMR (62.5 MHz, CDCl$_3$): δ 84.9, 75.0, 53.1, 47.9, 31.6, 29.0, 28.9, 28.7, 25.7, 23.8, 22.4, 18.5, 13.8; MS *m/z* (relative intensity) 235 (M$^+$, 22), 234 (M$^+$−1, 74), 150 (30), 136 (59), 122 (58), 98 (23), 84 (100). Anal. Calcd for C$_{16}$H$_{29}$N: C, 81.63; H, 12.42; N, 5.95. Found: C, 81.45; H, 12.55; N, 6.02.

4.1.6. Methyl-1-(naphthalenemethyl)(undec-2-ynyl)-amine. Oil; IR (film, CHCl$_3$) 2259 cm^{-1} (C≡C); ^{1}H NMR (250 MHz, CDCl$_3$): δ 8.29 (d, J=8.1 Hz, 1H), 7.82–7.73 (m, 2H), 7.52–7.34 (m, 4H), 3.96 (s, 2H), 3.30 (s, 2H), 2.34 (s, 3H), 2.26 (t, J=6.7 Hz, 2H), 1.62–1.28 (m, 12H), 0.87 (t, J=6.6 Hz, 3H); ^{13}C NMR (62.5 MHz, CDCl$_3$): δ 134.5, 133.8, 132.6, 128.3, 128.0, 127.5, 125.8, 125.5, 125.0, 124.6, 85.9, 74.7, 58.1, 45.6, 41.9, 31.8, 29.2, 29.0, 28.9, 22.6, 18.8, 14.1; MS *m/z* (relative intensity) 321 (M$^+$, 5), 306 (1), 208 (17), 180 (50), 141 (100), 115 (19). Anal. Calcd for C$_{23}$H$_{31}$N: C, 85.92; H, 9.72; N, 4.36. Found: C, 85.84; H, 9.90; N, 4.44.

4.1.7. Dibenzyl(3-phenylprop-2-ynyl)amine.[19] Oil; ^{1}H NMR (250 MHz, CDCl$_3$): δ 7.45–7.18 (m, 15H), 3.72 (s, 4H), 3.43 (s, 2H); ^{13}C NMR (62.5 MHz, CDCl$_3$): δ 138.8, 131.7, 129.0, 128.3, 127.9, 127.1, 123.4, 85.9, 84.4, 57.9, 42.0.

4.1.8. 1-(3-phenylprop-2-ynyl)piperidine.[20] Oil; IR (film, CHCl$_3$) 2188 cm^{-1} (C≡C); ^{1}H NMR (250 MHz, CDCl$_3$): δ 7.45–7.41 (m, 2H), 7.27–7.25 (m, 3H), 3.46 (s, 2H), 2.55 (s, br, 2×2H), 1.67–1.59 (m, 2×2H), 1.45 (t, J=5.5 Hz, 2H); ^{13}C NMR (62.5 MHz, CDCl$_3$): δ 131.4, 127.9, 127.7, 123.1, 84.8, 84.7, 53.2, 48.2, 25.7, 23.7; MS *m/z* (relative intensity) 199 (M$^+$, 42), 170 (11), 157 (25), 130 (7), 122 (13), 115 (100).

4.1.9. 1-[3-(*p*-Tolyl)prop-2-ynyl]piperidine.[21] Oil; ^{1}H NMR (250 MHz, CDCl$_3$): δ 7.34–7.30 (d, 2H), 7.11–7.07 (d, 2H), 3.46 (s, 2H), 2.50–2.61 (t, 3H), 2.32 (s, 3H), 1.59–1.70 (t, 4H), 1.36–1.48 (m, 2H); ^{13}C NMR (62.5 MHz, CDCl$_3$): δ 137.7, 131.5, 128.8, 120.2, 85.0, 84.2, 53.4, 48.4, 25.9, 23.7, 21.3.

4.1.10. Dibenzyl[3-(*p*-tolyl)prop-2-ynyl]amine. Oil; IR (film, CHCl$_3$) 2229 cm^{-1} (C≡C); ^{1}H NMR (250 MHz, CDCl$_3$): δ 7.44–7.20 (m, 12H), 7.11 (d, J=7.9 Hz, 2H), 3.74 (s, 2×2H), 3.45 (s, 2H), 2.33 (s, 3H); ^{13}C NMR (62.5 MHz, CDCl$_3$): δ 138.9, 138.0, 131.6, 129.0, 128.2, 127.0, 120.3, 86.0, 83.6, 57.7, 42.0, 21.4; MS *m/z* (relative intensity) 325 (M$^+$, 6), 234 (11), 194 (9), 129 (45), 91 (100). Anal. Calcd for C$_{24}$H$_{23}$N: C, 88.57; H, 7.12; N, 4.30. Found: C, 88.45; H, 7.21; N, 4.27.

4.1.11. 4-[(3-*p*-Tolyl)prop-2-ynyl]morpholine. Oil; IR (film, CHCl$_3$) 2204 cm^{-1} (C≡C); ^{1}H NMR (250 MHz, CDCl$_3$): δ 7.32 (d, J=8.1 Hz, 2H), 7.09 (d, J=8.0 Hz, 2H), 3.75 (t, J=4.7 Hz, 2×2H), 3.48 (s, 2H), 2.62 (t, J=4.6 Hz, 2×2H), 2.32 (s, 3H); ^{13}C NMR (62.5 MHz, CDCl$_3$): δ 138.0, 131.4, 128.9, 119.8, 85.5, 83.2, 66.7, 52.3, 47.9, 21.3; MS *m/z* (relative intensity) 215 (M$^+$, 29), 184 (32), 170 (26), 157 (40), 129 (100). HRMS Calcd for C$_{14}$H$_{17}$NO: 215.1310, found: 215.1310.

4.1.12. 2,2,6,6-Tetramethyl-1-[3-(*p*-tolyl)prop-2-ynyl]-piperdine. Mp 178–180 °C; IR (KBr, CHCl$_3$) 2401 cm^{-1} (C≡C); ^{1}H NMR (250 MHz, CDCl$_3$): δ 7.27 (d, J=7.9 Hz, 2H), 7.06 (d, J=7.8 Hz, 2H), 3.55 (s, 2H), 2.31 (s, 3H), 1.54–1.44 (m, 6H), 1.17 (s, 12H); ^{13}C NMR (62.5 MHz, CDCl$_3$): δ 137.3, 131.3, 128.8, 121.2, 92.2, 81.0, 54.9, 41.2, 33.8, 27.5, 21.4, 17.8; MS *m/z* (relative intensity) 269 (M$^+$, 2), 254 (7), 129 (100). Anal. Calcd for $C_{19}H_{27}N$: C, 84.70; H, 10.10; N, 5.20. Found: C, 84.56; H, 10.23; N, 5.11.

4.1.13. 1-[3-(4-Fluorophenyl)prop-2-ynyl]-4-phenylpiperazine. Mp 80.5–81.5 °C; IR (KBr) 2253 cm^{-1} ($C\equiv C$); ^1H NMR (250 MHz, $CDCl_3$): δ 7.44–7.38 (m, 2H), 7.29–7.23 (m, 2H), 7.01–6.83 (m, 5H), 3.55 (s, 2H), 3.25 (t, $J=4.8$ Hz, 2×2H), 2.78 (t, $J=4.8$ Hz, 2×2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 164.3, 160.3, 151.1, 133.6, 133.4, 129.0, 119.7, 119.0 (d, $J=3.3$ Hz), 116.1, 115.6, 115.2, 84.4, 83.9, 52.0, 49.0, 47.6; MS *m/z* (relative intensity) 294 (M^+, 12), 252 (6), 188 (11), 176 (14), 159 (100), 133 (84), 106 (60). Anal. Calcd for $C_{19}H_{19}N_2F$: C, 77.52; H, 6.51; N, 9.52. Found: C, 77.60; H, 6.66; N, 9.55.

4.1.14. Dibenzyl[(3-*p*-fluorophenyl)prop-2-ynyl]amine.[22] Oil; ^1H NMR (250 MHz, $CDCl_3$): δ 7.44–7.01 (m, 14H), 3.74 (S, 2×2H), 3.46 (s, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 164.3, 160.4, 138.8, 129.9, 129.8, 129.0, 128.3, 127.6, 127.2, 125.2, 118.7, 118.4, 115.5, 115.2, 85.6, 84.7, 57.8, 41.9.

4.1.15. 4-[3-(2-Fluorophenyl)prop-2-ynyl)]morpholine. Oil; IR (film, $CHCl_3$) 2205 cm^{-1} ($C\equiv C$); ^1H NMR (250 MHz, $CDCl_3$): δ 7.46–7.39 (m, 1H), 7.33–7.24 (m, 1H), 7.10–7.02 (m, 2H), 3.77 (t, $J=4.6$ Hz, 2×2H), 3.56 (s, 2H), 2.66 (s, br, 2×2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 162.8 (d, $J=250.3$ Hz), 133.4, 129.8 (d, $J=7.6$ Hz), 123.8 (d, $J=3.4$ Hz), 115.3 (d, $J=20.8$ Hz), 111.4 (d, $J=15.4$ Hz), 89.3, 78.9, 66.8, 52.2, 48.0; MS *m/z* (relative intensity) 219 (M^+, 16), 188 (17), 161 (16), 133 (100), 86 (26). Anal. Calcd for $C_{13}H_{14}NFO$: C, 71.21; H, 6.44; N, 6.39. Found: C, 70.93; H, 6.50; N, 6.28.

4.1.16. [3-(4-Bromophenyl)prop-2-ynyl]dibutylamine. Oil; IR (film, $CHCl_3$) 2190 cm^{-1} ($C\equiv C$); ^1H NMR (250 MHz, $CDCl_3$): δ 7.41 (d, $J=8.5$ Hz, 2H), 7.27 (d, $J=8.5$ Hz, 2H), 3.58 (s, 2H), 2.51 (t, $J=7.3$ Hz, 2×2H), 1.51–1.27 (m, 8H), 0.93 (t, $J=7.1$ Hz, 2×3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 133.0, 131.3, 122.3, 121.9, 86.2, 83.8, 53.6, 42.6, 29.6, 20.6, 14.0; MS *m/z* (relative intensity) 323, 321 (M^+, 4, 4), 280, 278 (97, 100), 195, 193 (78, 79), 114 (26), 84 (20). Anal. Calcd for $C_{17}H_{24}NBr$: C, 63.36; H, 7.51; N, 4.35. Found: C, 63.31; H, 7.53; N, 4.37.

4.2. General procedure for the Mannich condensation of terminal alkyne with piperazine and *para*-formaldehyde

Terminal alkyne (2.00 mmol), *para*-formaldehyde (6.00 mmol) and piperazine (1.00 mmol) were mixed well with Al_2O_3 (2.00 g) and cuprous iodide (1.16 g, 6.00 mmol) and placed in the microwave oven and irradiated at 30% power for 10 min.

4.2.1. 1,4-Di(non-2-ynyl)piperazine. Oil; IR (film, $CHCl_3$) 2196 cm^{-1} ($C\equiv C$); ^1H NMR (250 MHz, $CDCl_3$): 3.25 (s, 2×2H), 2.62 (s, br, 4×2H), 2.17 (t, $J=6.9$ Hz, 2×2H), 1.52–1.26 (m, 16H), 0.89 (t, $J=6.7$ Hz, 2×3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 85.3, 74.5, 51.7, 47.1, 31.1, 28.6, 28.4, 22.3, 18.5, 13.8; MS *m/z* (relative intensity) 330 (M^+, 3), 287 (10), 260 (9), 231 (10), 207 (100), 178 (26), 108 (20). Anal. Calcd for $C_{22}H_{38}N_2$: C, 79.94; H, 11.59; N, 8.47. Found: C, 76.69; H, 11.68; N, 8.43.

4.2.2. 1,4-Di[3-(*p*-tolyl)prop-2-ynyl]piperazine. Mp 119–121 °C; IR (film, $CHCl_3$) 2199 cm^{-1} ($C\equiv C$); ^1H NMR (250 MHz, $CDCl_3$) 7.32 (d, $J=8.0$ Hz, 2×2H), 7.08 (d, $J=8.1$ Hz, 2×2H), 3.52 (s, 2×2H), 2.74 (s, br, 2×4H), 2.32 (s, 2×3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 138.0, 131.5, 128.9, 120.0, 85.4, 83.5, 51.9, 47.6, 21.3; MS *m/z* (relative intensity) 342 (M^+, 2), 341 (M^+-1, 5), 272 (3), 223 (5), 213 (11), 129 (100), 115 (8). Anal. Calcd for $C_{24}H_{26}N_2$: C, 84.17; H, 7.65; N, 8.18. Found: C, 83.96; H, 7.85; N, 8.03.

4.3. General procedure for the Mannich condensation of α,ω-dialkyne with secondary amine and *para*-formaldehyde

α,ω-Dialkyne (1.00 mmol), *para*-formaldehyde (6.00 mmol) and secondary amine (2.00 mmol) were mixed well with Al_2O_3 (2.00 g) and cuprous iodide (1.16 g, 6.00 mmol) and placed in the microwave oven and irradiated at 300 W for 10 min.

4.3.1. *N*,*N*,*N*,*N*-Tetrabutyl-2,10-dodecadiynyl-1,12-diamine. Oil; IR (film, $CHCl_3$) 2189 cm^{-1} ($C\equiv C$); ^1H NMR (250 MHz, $CDCl_3$) 3.34 (t, $J=1.9$ Hz, 2×2H), 2.43 (t, $J=7.3$ Hz, 4×2H), 2.19 (t, $J=6.5$ Hz, 2×2H), 1.53–1.25 (m, 24H), 0.92 (t, $J=7.1$ Hz, 4×3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 84.5, 74.7, 53.3, 42.0, 29.5, 28.7, 28.1, 20.6, 18.5, 13.9; MS *m/z* (relative intensity) 246 (M^+-170, 21), 112 (12), 84 (100), 70 (29), 57 (66). Anal. Calcd for $C_{28}H_{52}N_2$: C, 80.70; H, 12.58; N, 6.72. Found: C, 80.50; H, 12.62; N, 6.69.

4.3.2. 1,12-Di(4-phenylpiperazino)-2,10-dodecadiyne. Mp 81–82 °C; IR (film, $CHCl_3$) 2204 cm^{-1} ($C\equiv C$); ^1H NMR (250 MHz, $CDCl_3$) 7.28–7.21 (m, 2×2H), 6.93–6.81 (m, 2×3H), 3.29 (s, 2×2H), 3.22 (t, $J=7.7$ Hz, 4×2H), 2.69 (t, $J=4.6$ Hz, 4×2H), 2.20 (t, $J=6.8$ Hz, 2×2H), 1.53–1.39 (m, 8H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 151.1, 128.9, 119.5, 85.4, 74.5, 51.9, 48.9, 47.2, 28.5, 28.1, 18.5; MS *m/z* (relative intensity) 322 (M^+-160, 17), 216 (10), 159 (94), 120 (66), 106 (100), 77 (70). Anal. Calcd for $C_{32}H_{42}N_4$: C, 79.62; H, 8.77; N, 11.61. Found: C, 79.60; H, 8.76; N, 11.55.

4.4. Mannich condensation reaction of terminal alkyne with primayl amine and *para*-formaldehyde

(a) 1-Decyne (2.00 mmol), *para*-formaldehyde (6.00 mmol) and benzylamine (2.00 mmol) were mixed well with Al_2O_3 (2.00 g) and cuprous iodide (1.16 g, 6.00 mmol) and placed in the microwave oven and irradiated at 300 W for 10 min, worked up the same as the general procedure. (b) Terminal alkyne (1.00 mmol), *para*-formaldehyde (5.00 mmol) and benzylamine (1.00 mmol) were mixed well with Al_2O_3 (1.00 g) and cuprous iodide (0.58 g, 3.00 mmol) and placed in the microwave oven and irradiated at 30% power for 10 min.

4.4.1. Benzyldi(undec-2-ynyl)amine. Oil; IR (film, $CHCl_3$) 2232 cm^{-1} ($C\equiv C$); ^1H NMR (250 MHz, $CDCl_3$) 7.38–7.20 (m, 5H), 3.66 (s, 2H), 3.35 (s, 2×2H), 2.21 (t, $J=6.7$ Hz, 2×2H), 1.55–1.28 (m, 2×12H), 0.88 (t, $J=6.6$ Hz, 2×3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 138.3, 129.3, 128.1, 127.1, 85.3, 75.0, 56.9, 42.3, 31.8, 29.2, 29.1, 28.9, 22.6, 18.7, 14.0; MS *m/z* (relative intensity) 322 ($M^+ - 85$, 6), 294 (7), 184 (5), 156 (8), 91 (100). Anal. Calcd for $C_{29}H_{45}N$: C, 85.44; H, 11.13; N, 3.44. Found: C, 85.37; H, 11.24; N, 3.52.

4.4.2. Benzylmethyl(undec-2-ynyl)amine. Oil; IR (film, $CHCl_3$) 2260 cm^{-1} ($C{\equiv}C$); ^1H NMR (250 MHz, $CDCl_3$): δ 7.35–7.22 (m, 5H), 3.55 (s, 2H), 3.26 (t, $J = 2.0$ Hz, 2H), 2.30 (s, 3H), 2.26–2.20 (m, 2H), 1.59–1.28 (m, 12H), 0.88 (t, $J = 6.5$ Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 138.6, 129.2, 128.2, 127.1, 85.8, 74.6, 60.2, 45.5, 41.8, 31.8, 29.2, 29.1, 29.0, 28.9, 22.6, 18.7, 14.0; MS *m/z* (relative intensity) 271 (M^+, 7), 194 (25), 158 (22), 120 (18), 91 (100). Anal. Calcd for $C_{19}H_{29}N$: C, 84.07; H, 10.77; N, 5.16. Found: C, 83.96; H, 10.85; N, 5.19.

4.4.3. Benzylmethyl[3-(phenyl)prop-2-ynyl]amine. Oil; IR (film, $CHCl_3$) 2235 cm^{-1} ($C{\equiv}C$); ^1H NMR (250 MHz, $CDCl_3$): δ 7.48–7.44 (m, 2H), 7.38–7.23 (m, 8H), 3.62 (s, 2H), 3.49 (s, 2H), 2.38 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 138.3, 131.6, 129.1, 128.1, 127.9, 127.1, 123.2, 85.6, 84.3, 60.1, 45.6, 41.8; MS *m/z* (relative intensity) 235 (M^+, 18), 158 (41), 144 (27), 115 (100), 91 (64). Anal. Calcd for $C_{17}H_{17}N$: C, 86.77; H, 7.28; N, 5.95. Found: C, 86.66; H, 7.43; N, 6.01.

4.4.4. Benzylmethyl[3-(*p*-tolyl)prop-2-ynyl]amine. Oil; IR (film, $CHCl_3$) 2247 cm^{-1} ($C{\equiv}C$); ^1H NMR (250 MHz, $CDCl_3$): δ 7.37–7.24 (m, 7H), 7.09 (d, $J = 7.94$ Hz, 2H), 3.62 (s, 2H), 3.49 (s, 2H), 2.38 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 138.4, 137.9, 131.5, 129.1, 128.9, 128.2, 127.1, 120.2, 85.7, 83.6, 60.2, 45.7, 41.9, 21.3; MS *m/z* (relative intensity) 249 (M^+, 17), 172 (32), 158 (36), 129 (100), 91 (73). Anal. Calcd for $C_{18}H_{19}N$: C, 86.70; H, 7.68; N, 5.62. Found: C, 86.42; H, 7.60; N, 5.57.

4.4.5. Preparation of 4-acetyl-1-ethynylbenzene.[23] To a stirred solution of *p*-bromoacetophone (1.00 g, 5.00 mmol) and Et_3N–dioxane (4 mL/4 mL), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol) and CuI (0.019 g, 0.100 mmol) were added in one portion. Then (trimethylsilyl)acetylene (0.85 mL, 6.00 mmol) was added dropwise at room temperature under nitrogen. The reaction mixture was stirred overnight. Et_3N, dioxane and unreacted (trimethylsilyl)acetylene were removed under reduced pressure. The product extracted with Et_2O (3×20 mL). The combined organic phase was washed with H_2O, dried (Na_2SO_4) and concentrated under vacuum. The residue was purified by column chromatography to generate 0.820 g (85% yield) of 4-acetyl-1-((trimethylsilyl)ethynyl)benzene. Oil; ^1H NMR (250 MHz, $CDCl_3$): δ 7.87 (d, $J = 7.9$ Hz, 2H), 7.52 (d, $J = 8.4$ Hz, 2H), 2.57 (s, 3H), 0.27 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 196.9, 136.3, 131.9, 128.0, 127.8, 103.9, 97.9, 26.4, -0.29; MS *m/z* (relative intensity) 216 (M^+, 15), 201 (100), 158 (10), 143 (8), 93 (9).

4-Acetyl-1-((trimethylsilyl)ethynyl)benzene (0.648 g, 3.00 mmol) was added to KF/Al_2O_3 (2.00 g, 40% by weight) and stirred at room temperature to ensure efficient mixing. The result mixture was placed in the microwave oven and irradiated at 30% power for 3 min. After cooling, hexane (10 mL) was added and the slurry stirred at room temperature to ensure product removal from the surface. The product was purified by chromatography to afford 0.415 g (97% yield) of 4-acetyl-1-ethynylbenzene. Mp 68–70 °C (lit.[23] 69–70 °C); ^1H NMR (250 MHz, $CDCl_3$): δ 7.90 (d, $J = 8.3$ Hz, 2H), 7.57 (d, $J = 8.4$ Hz, 2H), 3.27 (s, 1H), 2.59 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 197.1, 136.7, 132.2, 128.1, 126.8, 82.7, 80.3, 26.5; MS *m/z* (relative intensity) 144 (M^+, 31), 129 (100), 101 (54), 75 (21).

4.4.6. Preparation of 11-dodecyn-2-one.[24] To a suspension of dry pyridinium chlorochromate (4.85 g, 22.5 mmol) in dry CH_2Cl_2 (20 mL), 10-undecyn-1-ol (2.50 g, 15 mmol) and dry CH_2Cl_2 (5 mL) were added dropwise. The reaction mixture was stirred at room temperature for 3 h and the solution was then extracted with ether (3×20 mL). The combined organic layer was dried with Na_2SO_4 and the solvent removed under reduced pressure. The product was purified by column chromatography (hexane/ethyl acetate 9:1) to afford 2.00 g (80% yield) of 10-undecyn-1-al.

To a solution of 10-undecyn-1-al (1.50 g, 9.04 mmol) in dry Et_2O (15 mL), CH_3MgBr in ether (3 M, 3.67 mL, 11 mmol) was added at 0 °C over a 1 h period. The reaction mixture was then refluxed for 3 h. Aqueous ammonium chloride was then added to quench the reaction and the mixture was extracted with ether (3×20 mL). The combined organic layer was washed with water and dried with Na_2SO_4 and then the solvent removed under reduced pressure (2 mmHg for 2 h). The crude product was used without purification.

11-Dodecyn-2-ol (crude, 1.4 g) in dry CH_2Cl_2 (5 mL) was added dropwise to a suspension of pyridinium chlorochromate (2.26 g, 10.5 mmol) in dry CH_2Cl_2 (10 mL) dropwise at room temperature. The reaction mixture was stirred at room temperature for 2 days and then extracted with ether (3×20 mL). The combined organic layer was dried with Na_2SO_4 and then the solvent removed under reduced pressure. The product was purified by column chromatography (hexane/ethyl acetate 85:15) to afford 1.20 g (combined yield 74%) of 11-dodecyn-2-one. Oil; ^1H NMR (250 MHz, $CDCl_3$): δ 2.41 (t, $J = 7.4$ Hz, 2H), 2.18–2.12 (m, 5H), 1.93 (t, $J = 2.4$ Hz, 1H), 1.55–1.28 (m, 12H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 208.5, 84.2, 67.9, 43.4, 29.5, 28.9, 28.8, 28.6, 28.3, 28.1, 23.5, 18.0; MS *m/z* (relative intensity) 165 ($M^+ - C_2H_5$, 2), 147 (2), 122 (6), 107 (9), 95 (15), 81 (23), 58 (100).

4.5. Chemoselectivity of Mannich Condensation

(a) *Intermolecular chemoselectivity*. A secondary amine (morpholine or piperazine, 1.00 mmol), terminal alkyne (4-ethynyltoluene or 1-decyne, 1.00 mmol) and an enolizable ketone (acetophone or 2-heptone, 1.00 mmol) were mixed with a mixture of cuprous iodide (0.572 g, 3.00 mmol), *para*-formaldehyde (0.09 g, 3.00 mmol) and alumina (1.00 g) in a clean, dry, 10 mL round-bottomed flask at room temperature. The flask was then fitted with a septum (punctured by an 18 gauge needle), placed in the microwave oven and irradiated at 30% power for 10 min.

(b) *Intramolecular chemoselectivity*. Dibenzylamine or 1-phenylpiperazine (1.00 mmol) and 4-acetyl-1-ethynylbenzene or 11-dodecyn-2-one (1.00 mmol) were added to a mixture of cuprous iodide (0.572 g, 3.00 mmol), *para*-formaldehyde (0.09 g, 3.00 mmol) and alumina (1.00 g) contained in a clean, dry, 10 mL round-bottomed flask. The mixture was stirred at room temperature to ensure efficient mixing. The flask was then fitted with a septum (punctured by an 18 gauge needle), placed in the microwave oven and irradiated at 30% power for 10 min.

4.5.1. [3-(4-Acetylphenyl)prop-2-ynyl]dibenzylamine.

Oil; IR (film, $CHCl_3$) 2230 cm^{-1} (C≡C), 1683 cm^{-1} (C═O); ^1H NMR (250 MHz, $CDCl_3$): δ 7.92 (d, $J=8.3$ Hz, 2H), 7.56 (d, $J=8.2$ Hz, 2H), 7.45–7.23 (m, 10H), 3.76 (s, 2×2H), 3.50 (s, 2H), 2.60 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 197.2, 138.7, 136.1, 131.9, 129.0, 128.3, 128.2, 127.2, 88.3, 85.2, 57.8, 42.1, 26.6; MS *m/z* (relative intensity) 194 (M^+-159, 11), 158 (15), 143 (25), 115 (20), 91 (100). Anal. Calcd for $C_{25}H_{23}NO$: C, 84.95; H, 6.56; N, 3.96. Found: C, 85.11; H, 6.66; N, 3.94.

4.5.2. 1-Phenyl-4-(tridec-12-oxo-2-ynyl)piperazine.

Mp 33–34 °C; IR (film, $CHCl_3$) 2208 cm^{-1} (C≡C), 1711 cm^{-1} (C═O); ^1H NMR (250 MHz, $CDCl_3$): δ 7.29–7.22 (m, 2H), 6.95–6.82 (m, 3H), 3.31 (s, 2H), 3.23 (t, $J=4.9$ Hz, 2×2H), 2.71 (t, $J=4.9$ Hz, 2×2H), 2.39 (t, $J=7.4$ Hz, 2H), 2.19 (t, $J=6.7$ Hz, 2H), 2.11 (s, 3H), 1.58–1.28 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 209.2, 151.1, 129.0, 119.6, 116.0, 85.6, 74.5, 51.9, 48.9, 47.3, 43.6, 29.7, 29.2, 29.0, 28.8, 28.7, 28.6, 23.7, 18.6; MS *m/z* (relative intensity) 354 (M^+, 18), 248 (35), 160 (53), 159 (94), 130 (38), 120 (71), 105 (100). Anal. Calcd for $C_{23}H_{34}N_2O$: C, 77.92; H, 9.67; N, 7.90. Found: C, 77.98; H, 9.61; N, 8.02.

4.5.3. Iodination of phenols: preparation of 4-hydroxy-3-iodoacetophenone (representative procedure).

4-Hydroxyacetophenone (1.36 g, 10 mmol) was dissolved in 10 mL of THF–H_2O (50/50, V/V) and I_2 (2.80 g, 11 mmol) and $NaHCO_3$ (0.92 g, 11 mmol) were crushed together and added to the solution. After the mixture was stirred for 3 h at room temperature, residual I_2 was destroyed by addition of a 5% aqueous solution of $Na_2S_2O_3$ until the brown color disappeared. The mixture was extracted with ether (3× 50 mL). The organic phase was dried with Na_2SO_4 and the solvent was removed under pressure. 4-Hydroxy-3-iodo-acetophenone (1.23 g, 47% yield) was isolated by column chromatography (silica gel, hexane/ethyl acetate 95:5). Mp 152–154 °C (lit.[25] 153–155 °C); ^1H NMR (250 MHz, CD_3OD): δ 8.29 (s, 1H), 7.82 (d, $J=8.5$ Hz, 1H), 6.86 (d, $J=8.4$ Hz, 1H), 4.91 (s, br, 1H), 2.51 (s, 3H); MS *m/z* (relative intensity) 262 (M^+, 36), 247 (100), 219 (16), 127 (7), 120 (23), 92 (40).

4.5.4. Preparation of *o*-ethynylphenol and *p*-acetyl-*o*-ethynylphenol via a Sonogashira coupling followed by desilylation: synthesis of *o*-ethynylphenol as representative.

To a stirred solution of 2-iodophenol (1.10 g, 5.00 mmol) and Et_3N–dioxane (4 mL/4 mL), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol) and CuI (0.019 g, 0.10 mmol) were added in one portion. Then (trimethylsilyl)acetylene (0.85 mL, 6.00 mmol) was added dropwise at room temperature under nitrogen. The reaction mixture was stirred overnight. Et_3N, dioxane and unreacted (trimethylsilyl)-acetylene were removed under reduced pressure. The product was extracted with Et_2O (3×20 mL) and the combined organic phase washed with H_2O, dried (Na_2SO_4) and concentrated under vacuum. The residue was purified by column chromatography to afford 0.87 g (86% yield) of *o*-((trimethylsilyl)ethynyl)phenol. Mp 46–48 °C (lit.[26] 46–47 °C); ^1H NMR (250 MHz, $CDCl_3$): δ 7.32 (dd, $J=6.3$ Hz, $J=1.4$ Hz, 1H), 7.20 (dt, $J=7.0$ Hz, $J=1.5$ Hz, 1H), 6.93 (d, $J=8.2$ Hz, 1H), 6.82 (t, $J=7.6$ Hz, 1H), 5.90 (s, 1H), 0.26 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 157.0, 131.6, 130.6, 120.1, 114.5, 109.5, 102.2, 99.0, −0.1; MS *m/z* (relative intensity) 190 (M^+, 18), 175 (100), 159 (19), 135 (13), 115 (16), 77 (14).

o-[(Trimethylsilyl)ethynyl]phenol (0.61 g, 3.00 mmol) was added to KF/Al_2O_3 (2.00 g, 40% by weight) and stirred at room temperature to ensure efficient mixing. The resultant mixture was placed in the microwave oven and irradiated at 30% power for 3 min. After cooling, hexane (10 mL) was added and the slurry stirred at room temperature to ensure product removal from the surface. The product was purified by chromatography to afford 0.365 g (92% yield) of *o*-ethynylphenol. Oil;[27] ^1H NMR (250 MHz, $CDCl_3$): δ 7.38 (d, $J=7.5$ Hz, 1H), 7.27 (dt, $J=7.7$ Hz, $J=1.0$ Hz, 1H), 6.95 (d, $J=8.2$ Hz, 1H), 6.87 (t, $J=7.5$ Hz, 1H), 5.80 (s, br, 1H), 3.46 (s, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 157.4, 132.0, 130.9, 120.3, 114.8, 108.3, 84.3, 78.3; MS *m/z* (relative intensity) 118 (M^+, 100), 89 (44), 63 (21).

4.5.5. *p*-Acetyl-*o*-[(trimethylsilyl)ethynyl]phenol.

Mp 127–129 °C; ^1H NMR (250 MHz, $CDCl_3$): δ 8.00 (d, $J=1.4$ Hz, 1H), 7.87 (d, $J=8.7$ Hz, 1H), 7.00 (d, $J=8.7$ Hz, 1H), 6.63 (s, br, 1H), 2.55 (s, 3H), 0.29 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 196.2, 160.9, 133.0, 131.1, 129.9, 114.8, 109.9, 103.2, 97.8, 26.2, −0.2; MS *m/z* (relative intensity) 232 (M^+, 24), 217 (100), 174 (8), 115 (10), 101 (19). Anal. Calcd for $C_{13}H_{16}O_2Si$: C, 67.20; H, 6.94. Found: C, 67.40; H, 6.84.

4.5.6. *p*-Acetyl-*o*-ethynylphenol.

Mp 100–102 °C; ^1H NMR (250 MHz, $CDCl_3$): δ 8.05 (d, $J=1.5$ Hz, 1H), 7.91 (d, $J=8.7$ Hz, 1H), 7.37 (s, 1H), 7.03 (d, $J=8.6$ Hz, 1H), 3.50 (s, 1H), 2.57 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 196.7, 161.6, 133.8, 131.3, 129.6, 115.2, 108.8, 84.4, 77.5, 26.1; MS *m/z* (relative intensity) 160 (M^+, 40), 145 (100), 117 (48), 89 (31). HRMS Calcd for $C_{10}H_8O_2$ 160.0524, found 160.0520.

4.6. One-pot synthesis of 2-substitutited benzo[*b*]furans via the Mannich condensation cyclization sequence reaction of *o*-ethynylphenol with secondary amines and *para*-formaldehyde: general procedure

o-Ethynylphenol (0.18 g, 1.00 mmol) and the secondary amine (1.00 mmol) were added to a mixture of cuprous iodide (0.57 g, 3.00 mmol), *para*-formaldehyde (0.09 g, 3.00 mmol) and alumina (1.00 g) contained in a clean, dry, 10 mL round-bottomed flask. The mixture was stirred at room temperature to ensure efficient mixing. The flask was then fitted with a septum (punctured by an 18 gauge needle), placed in the microwave oven and irradiated at 30% power for 10 min. After cooling, ether (4 mL) was added and the slurry stirred at room temperature to ensure product removal from the surface. The mixture was vacuum filtered using a sintered glass funnel and the product purified by flash chromatography (hexane/EtOAc as eluting agent) to afford the desired 2-substituted-benzo[*b*]furan.

4.6.1. 1-(Benzofuran-2-ylmethyl)-4-phenylpiperazine. Mp 75–76 °C; ^{1}H NMR (250 MHz, CDCl$_3$): δ 7.53–7.46 (m, 2H), 7.26–7.18 (m, 4H), 6.90–6.80 (m, 3H), 6.59 (s, 1H), 3.70 (s, 2H), 3.20 (t, J=4.8 Hz, 2×2H), 2.67 (t, J=4.8 Hz, 2×2H); ^{13}C NMR (62.5 MHz, CDCl$_3$): δ 155.0, 154.2, 151.1, 129.0, 128.1, 123.9, 122.6, 120.6, 119.6, 116.0, 111.2, 105.7, 55.3, 52.9, 48.9; MS *m/z* (relative intensity) 292 (M^{+}, 33), 186 (12), 173 (22), 159 (98), 131 (100), 106 (54), 77 (56). Anal. Calcd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.89; N, 9.58. Found: C, 78.04; H, 6.89; N, 9.47.

4.6.2. (Benzofuran-2-ylmethyl)dibutylamine.[28] Oil; ^{1}H NMR (250 MHz, CDCl$_3$): δ 7.50–7.43 (m, 2H), 7.22–7.17 (m, 2H), 6.54 (s, 1H), 3.77 (s, 2H), 2.50 (t, J=7.5 Hz, 2×2H), 1.53–1.46 (m, 2×2H), 1.35–1.27 (m, 2×2H), 0.90 (t, J=7.2 Hz, 2×3H); ^{13}C NMR (62.5 MHz, CDCl$_3$): δ 156.2, 154.9, 128.5, 123.5, 122.4, 120.5, 111.1, 104.8, 53.7, 50.7, 29.2, 20.6, 14.0; MS *m/z* (relative intensity) 259 (M^{+}, 2), 216 (10), 131 (100), 77 (9).

4.6.3. 1-(Benzofuran-2-ylmethyl)piperidine.[29] Oil; ^{1}H NMR (250 MHz, CDCl$_3$): δ 7.53–7.45 (m, 2H), 7.27–7.15 (m, 2H), 6.56 (s, 1H), 3.64 (s, 2H), 2.46 (s, br, 2×2H), 1.63–1.57 (m, 2×2H), 1.44–1.42 (m, 2H); ^{13}C NMR (62.5 MHz, CDCl$_3$): δ 155.0, 128.3, 123.7, 122.5, 120.5, 111.2, 105.3, 56.1, 54.3, 25.8, 24.1; MS *m/z* (relative intensity) 251 (M^{+}, 10), 131 (100), 84 (26), 77 (15).

4.6.4. (Benzofuran-2-ylmethyl)benzylmethylamine. Oil; ^{1}H NMR (250 MHz, CDCl$_3$): δ 7.52–7.18 (m, 9H), 6.57 (s, 1H), 3.70 (s, 2H), 3.60 (s, 2H), 2.29 (s, 3H); ^{13}C NMR (62.5 MHz, CDCl$_3$): δ 155.4, 155.0, 138.4, 129.0, 128.3, 128.2, 127.1, 123.7, 122.5, 120.6, 111.2, 105.2, 61.3, 53.7, 42.1; MS *m/z* (relative intensity) 251 (M^{+}, 10), 160 (13), 131 (100), 91 (27), 77 (13). Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.25; H, 6.82; N, 5.56.

4.6.5. 4-(Benzofuran-2-ylmethyl)morpholine. Mp 50–51 °C (lit.[30] 51–52 °C); ^{1}H NMR (250 MHz, CDCl$_3$): δ 7.54–7.46 (m, 2H), 7.28–7.17 (m, 2H), 6.60 (s, 1H), 3.74 (t, J=4.6 Hz, 2×2H), 3.67 (s, 2H), 2.54 (t, J=4.5 Hz, 2×2H); ^{13}C NMR (62.5 MHz, CDCl$_3$): δ 155.1, 154.0, 128.1, 123.9, 122.6, 120.6, 111.2, 105.8, 66.7, 55.8, 53.4; MS *m/z* (relative intensity) 217 (M^{+}, 14), 144 (9), 131 (100), 86 (26), 77 (17).

4.6.6. (Benzofuran-2-ylmethyl)methyl(1-naphthalenemethyl)amine. Oil; ^{1}H NMR (250 MHz, CDCl$_3$): δ 8.20–8.17 (m, 1H), 7.80–7.70 (m, 2H), 7.50–7.32 (m, 6H), 7.26–7.14 (m, 2H), 6.57 (s, 1H), 3.94 (s, 2H), 3.76 (s, 2H), 2.30 (s, 3H); ^{13}C NMR (62.5 MHz, CDCl$_3$): δ 155.5, 155.0, 134.3, 133.8, 132.4, 128.3, 128.0, 127.4, 125.9, 125.5, 125.0, 124.5, 123.8, 122.5, 120.6, 111.1, 105.4, 59.4, 54.2, 42.3; MS *m/z* (relative intensity) 301 (M^{+}, 9), 207 (8), 160 (42), 141 (61), 131 (100), 115 (19), 77 (13). Anal. Calcd for $C_{21}H_{19}NO$: C, 83.69; H, 6.35; N, 4.65. Found: C, 83.71; H, 6.53; N, 4.68.

4.6.7. 2-(Benzofuran-2-ylmethyl)-1,2,3,4-tetrahydroisoquinoline. Mp 58–59 °C; ^{1}H NMR (250 MHz, CDCl$_3$): δ 7.53–7.45 (m, 2H), 7.25–6.95 (m, 6H), 6.62 (s, 1H), 3.83 (s, 2H), 3.71 (s, 2H), 2.90 (t, J=5.3 Hz, 2H), 2.82 (t, J=5.4 Hz, 2H); ^{13}C NMR (62.5 MHz, CDCl$_3$): δ 155.0, 154.6, 134.3, 133.9, 128.5, 128.2, 126.5, 126.1, 125.5, 123.8, 122.5, 120.6, 111.2, 105.4, 55.6, 54.9, 50.5, 28.8; MS *m/z* (relative intensity) 263 (M^{+}, 5), 145 (19), 131 (100), 104 (23), 77 (21). Anal. Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 81.96; H, 6.57; N, 5.30.

4.6.8. (Benzofuran-2-ylmethyl)di(isopropyl)amine. Oil; ^{1}H NMR (250 MHz, CDCl$_3$): δ 7.50–7.41 (m, 2H), 7.20–7.16 (m, 2H), 6.57 (s, 1H), 3.77 (d, J=0.59 Hz, 2H), 3.18–3.08 (m, 2H), 1.06 (d, J=6.6 Hz, 4×3H); ^{13}C NMR (62.5 MHz, CDCl$_3$): δ 160.2, 154.8, 128.9, 123.0, 122.3, 120.3, 110.9, 103.2, 49.0, 42.9, 20.7; MS *m/z* (relative intensity) 231 (M^{+}, 3), 216 (9), 131 (100). Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 78.16; H, 9.36; N, 5.97.

4.6.9. 1-(Benzofuran-2-ylmethyl)-2,2,6,6-tetramethylpiperidine. Mp 88–89 °C; ^{1}H NMR (250 MHz, CDCl$_3$): δ 7.48–7.36 (m, 2H), 7.17–7.14 (m, 2H), 6.63 (s, 1H), 3.81 (s, 2H), 1.60–1.51 (m, 6H), 1.06 (s, 4×3H); ^{13}C NMR (62.5 MHz, CDCl$_3$): δ 163.5, 154.5, 129.1, 122.7, 122.2, 120.2, 110.7, 102.9, 54.9, 42.4, 41.2, 27.4, 17.8; MS *m/z* (relative intensity) 271 (M^{+}, 2), 256 (15), 131 (100), 77 (7). Anal. Calcd for $C_{18}H_{25}NO$: C, 79.66; H, 9.28; N, 5.16. Found: C, 79.40; H, 9.36; N, 4.91.

4.6.10. (Benzofuran-2-ylmethyl)methylaniline. Oil; ^{1}H NMR (250 MHz, CDCl$_3$): δ 7.48–7.41 (m, 2H), 7.28–7.15 (m, 4H), 6.86–6.72 (m, 3H), 6.49 (s, 1H), 4.61 (s, 2H), 3.08 (s, 3H); ^{13}C NMR (62.5 MHz, CDCl$_3$): δ 155.2, 154.9, 149.1, 129.2, 128.4, 123.7, 122.6, 120.6, 117.3, 112.9, 111.0, 103.9, 50.5, 38.6; MS *m/z* (relative intensity) 237 (M^{+}, 13), 207 (26), 131 (100), 96 (9), 77 (23). Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 81.17; H, 6.61; N, 5.63.

4.6.11. 1-(5-Acetylbenzofuran-2-ylmethyl)-4-phenylpiperazine. Mp 111–113 °C; ^{1}H NMR (250 MHz, CDCl$_3$): δ 8.19 (s, 1H), 7.93 (d, J=8.6 Hz, 1H), 7.52 (d, J=8.7 Hz, 1H), 7.25 (t, J=7.7 Hz, 2H), 6.93–6.82 (m, 3H), 6.17 (s, 1H), 3.76 (s, 2H), 3.24 (t, J=4.7 Hz, 2×2H), 2.72 (t, J=4.7 Hz, 2×2H), 2.65 (s, 3H); ^{13}C NMR (62.5 MHz, CDCl$_3$): δ 197.5, 157.6, 156.1, 151.1, 132.6, 129.0, 128.3, 124.7, 122.0, 119.7, 116.1, 111.2, 106.2, 55.3, 53.0, 49.0, 26.7; MS *m/z* (relative intensity) 334 (M^{+}, 25), 228 (11), 201 (55), 173 (64), 130 (36), 106 (87), 56 (100). HRMS Calcd for $C_{21}H_{22}N_2O_2$ 334.1681, found 334.1690.

4.6.12. 1,4-Bis(benzofuran-2-ylmethyl)piperazine. Mp 143–144 °C; ^{1}H NMR (250 MHz, CDCl$_3$): δ 7.52–7.44 (m, 4H), 7.29–7.15 (m, 4H), 6.58 (s, 2×1H), 3.69 (s, 2×2H), 2.62 (s, br, 4×2H); ^{13}C NMR (62.5 MHz, CDCl$_3$): δ 155.0, 154.3, 128.2, 123.8, 122.6, 120.6, 111.2, 105.6, 55.3, 52.7; MS *m/z* (relative intensity) 346 (M^{+}, 2), 215 (46), 131 (100), 77 (15). Anal. Calcd for $C_{22}H_{22}N_2O_2$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.05; H, 6.51; N, 7.99.

4.7. General procedure for recycling

After carried out a Mannich condensation, ether was added to remove the product from the cuprous iodide and alumina surface. After filtration, the Cu/Al_2O_3 was directly used for the next trial.

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References and notes

1. (a) Tramonitini, M.; Angiolini, L. *Mannich-Bases, Chemistry and Uses*; CRC: Boca Raton, FL, 1994. (b) Lehmann, F.; Pilotti, Å. ; Luthman, K. *Mol. Diversity* **2003**, *7*, 145. (c) Hayashi, Y.; Tsuboi, W.; Ashimine, I.; Urushima, T.; Shoji, M.; Sakai, K. *Angew. Chem.* **2003**, *115*, 3805. (d) Padwa, A.; Waterson, A. G. *J. Org. Chem.* **2000**, *65*, 235. (e) Hwang, D. R.; Uang, B. J. *Org. Lett.* **2002**, *4*, 463.
2. (a) McNally, J. J.; Youngman, M. A.; Dax, S. L. *Tetrahedron Lett.* **1998**, *39*, 967. (b) Youngman, M. A.; Dax, S. L. *Tetrahedron Lett.* **1997**, *38*, 6347. (c) Youngman, M. A.; Dax, S. L. *J. Comb. Chem.* **2001**, *3*, 469.
3. (a) Bieber, L. W.; da Silva, M. F. *Tetrahedron Lett.* **2004**, *45*, 8281. (b) Sanders, K. B.; Thomas, A. J.; Pavia, M. R.; Davis, R. E.; Coughenour, L. L.; Myers, S. L.; Fischer, S.; Moos, W. H. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 803. (c) Miura, M.; Enna, M.; Okuro, K.; Nomura, M. *J. Org. Chem.* **1995**, *60*, 4999.
4. (a) Zhang, H.-C.; Brumfield, K. K.; Jaroskova, L.; Maryanoff, B. E. *Tetrahedron Lett.* **1998**, *39*, 3449. (b) Dyatkin, A. B.; Rivero, R. A. *Tetrahedron Lett.* **1998**, *39*, 3647. (c) Black, D. A.; Arndtsen, B. A. *Org. Lett.* **2004**, *6*, 1107. (d) Gao, G.; Sanda, F.; Masuda, T. *Macromolecules* **2003**, *36*, 3932. (e) Tabei, J.; Nomura, R.; Masuda, T. *Macromolecules* **2002**, *35*, 5405.
5. (a) Kabalka, G. W.; Pagni, R. M. *Tetrahedron* **1997**, *53*, 7999. (b) Bartoli, G.; Bartolacci, M.; Giuliani, A.; Marcantoni, E.; Massaccesi, M.; Torregiani, E. *J. Org. Chem.* **2005**, *70*, 169. (c) Navratilova, H.; Kriz, Z.; Potacek, M. *Synth. Commun.* **2004**, *34*, 2101. (d) Pala Wilgus, C.; Downing, S.; Molitor, E.; Bains, S.; Pagni, R. M.; Kabalka, G. W. *Tetrahedron Lett.* **1995**, *36*, 3469.
6. (a) Kabalka, G. W.; Pagni, R. M.; Hair, C. M. *Org. Lett.* **1999**, *1*, 1423. (b) Kabalka, G. W.; Pagni, R. M.; Wang, L.; Namboodiri, V.; Hair, C. M. *Green Chem.* **2000**, *2*, 120. (c) Kabalka, G. W.; Wang, L.; Namboodiri, V.; Pagni, R. M. *Tetrahedron Lett.* **2000**, *41*, 5151. (d) Wang, M.; Li, P. H.; Wang, L. *Synth. Commun.* **2004**, *34*, 2803. (e) Kabalka, G. W.; Wang, L.; Pagni, R. M. *Synlett* **2001**, 108. (f) Kabalka, G. W.; Wang, L.; Pagni, R. M. *Synlett* **2001**, 676.
7. (a) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250. (b) Blettner, C. G.; Koenig, W. A.; Wilfried, A.; Stenzel, W.; Schotten, T. *J. Org. Chem.* **1999**, *64*, 3885. (c) Xu, G.; Wang, Y. G. *Org. Lett.* **2004**, *6*, 985.
8. Varma, R. S. *Green Chem.* **1999**, *1*, 43 and references cited therein.
9. (a) Djuric, S. W. *J. Org. Chem.* **1984**, *49*, 1311. (b) Gribble, G. W.; Nutaitis, C. F. *Synthesis* **1987**, 709. (c) Loibner, H.; Pruckner, A.; Stutz, A. *Tetrahedron Lett.* **1984**, *25*, 1535.
10. (a) Pu, Y. M.; Grieme, T.; Gupta, A.; Plata, D.; Bhatia, A. V.; Cowart, M.; Ku, Y. Y. *Org. Process Res. Dev.* **2005**, *9*, 45. (b) Macleod, C.; McKiernan, G. J.; Guthrie, E. J.; Farrugia, L. J.; Hamprecht, D. W.; Macritchie, J.; Hartley, R. C. *J. Org. Chem.* **2003**, *68*, 387. (c) Oka, T.; Yasusa, T.; Ando, T.; Watanabe, M.; Yoneda, F.; Ishida, T.; Knoll, J. *Bioorg. Med. Chem.* **2001**, *9*, 1213.
11. (a) Gangjee, A.; Zeng, Y. B.; McGuire, J. J.; Mehraein, F.; Kisliuk, R. L. *J. Med. Chem.* **2004**, *47*, 6893. (b) Gangjee, A.; Devraj, R.; McGuire, J. J.; Kisliuk, R. L. *J. Med. Chem.* **1995**, *38*, 3798.
12. (a) Lütjens, H.; Scammells, P. J. *Synlett* **1999**, 1079. (b) Chang, J. Y.; Chang, C. Y.; Kuo, C. C.; Chen, L. T.; Wein, Y. S.; Kuo, Y. H. *Mol. Pharmacol.* **2004**, *65*, 77.
13. (a) Kozikowsky, A. P.; Ma, D.; Du, L.; Lewin, N. E.; Blumberg, P. M. *J. Am. Chem. Soc.* **1995**, *117*, 6666. (b) Pal, M.; Subramanian, V.; Yeleswarapu, K. R. *Tetrahedron Lett.* **2003**, *44*, 8221.
14. (a) Fürstner, A.; Jumbam, D. N. *Tetrahedron* **1992**, *48*, 5991. (b) Bosch, J.; Roca, T.; Catena, J.-L.; Farrerons, C.; Miquel, I. *Synthesis* **2000**, 721.
15. (a) Givens, R. S.; Athey, P. S.; Matuszewski, B.; Kueper, L. W., III; Xue, J.-Y.; Fister, T. *J. Am. Chem. Soc.* **1993**, *115*, 6001. (b) Givens, R. S.; Athey, P. S.; Matuszewski, B.; Kueper, L. W., III; Xue, J.-Y. *J. Am. Chem. Soc.* **1992**, *114*, 8708.
16. (a) Jinno, S.; Okita, T.; Inouye, K. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1029. (b) Cockerill, G. S.; Easterfield, H. J.; Percy, J. M. *Tetrahedron Lett.* **1999**, *40*, 2601.
17. (a) Larock, R. C.; Yum, E. K.; Doty, M. J.; Sham, K. K. C. *J. Org. Chem.* **1995**, *60*, 3270. (b) Kundu, N. G.; Pal, M.; Mahanty, J. S.; Dasgupta, S. K. *J. Chem. Soc., Chem. Commun.* **1992**, 41. (c) Kabalka, G. W.; Wang, L.; Pagni, R. M. *Tetrahedron* **2001**, *57*, 8017. (d) Fancelli, D.; Fagnola, M. C.; Severino, D.; Bedeschi, A. *Tetrahedron Lett.* **1997**, *38*, 2311.
18. Andreev, V. P.; Vuks, E. M.; Kochetkova, E. V.; Remizova, L. A.; Favorskaya, I. A. *Zh. Org. Khim.* **1979**, *15*, 464.
19. Hiroyuki, N.; Takaya, K.; Makoto, I.; Jean-Francois, B. *J. Am. Chem. Soc.* **2004**, *126*, 5958.
20. Mannich, C.; Chang, F. T. *Ber.* **1933**, *66B*, 418.
21. Chukhadzhyan, El. O.; Chukhadzhyan, E. O.; Babayan, A. T. *Zh. Org. Khim.* **1974**, *10*, 46.
22. Xu, Q.; Borremans, F.; Devreese, B. *Tetrahedron Lett.* **2001**, *42*, 7261.
23. Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1980**, 627.
24. Trost, B. M.; Pinkerton, A. B. *J. Am. Chem. Soc.* **1999**, *121*, 1988.
25. Zenner, J. M.; Larock, R. C. *J. Org. Chem.* **1999**, *64*, 7312.
26. Arcadi, A.; Cacchi, S.; Rasario, M. D.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, *61*, 9280.
27. Alberola, A.; Calvo, B.; Ortega, A. G.; Pedrosa, R. *J. Chem. Soc., Perkin Trans. 1* **1992**, 3075.
28. Chow, C.-T.; Chi, J.-Y. *Huaxue Xuebao* **1962**, *28*, 236.
29. Ziegler, H. J.; Inion, H.; Aussems, G.; Christiaens, A.; Chaillet, F.; Charlier, R. *Chim. Ther.* **1971**, *6*, 159.
30. Bardamova, M. I.; Myasnikova, R. N.; Kotlyarevskii, I. L. *Khim. Geterotsikl. Soedin.* **1972**, 1457.

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Chiral bisphospholane ligands (Me-ketalphos): synthesis of their Rh(I) complexes and applications in asymmetric hydrogenation

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Abstract—Rhodium complexes of functionalized bisphospholane ligands (*S*,*S*,*S*,*S*-Me-ketalphos) **1** and (*R*,*S*,*S*,*R*-Me-ketalphos) **2** have been used as catalyst precursors for the asymmetric hydrogenation of several different types of functionalized olefins and have achieved high enantioselectivities.

1. Introduction

Development of new chiral phosphine ligands has played a significant role in the transition metal catalyzed asymmetric reactions during the last several decades.[1] Chiral C_2-symmetric bisphospholane ligands such as DuPhos[2] and its analogues RoPhos,[3a] BASPhos[3b,4] and MalPhos[5] have attracted much attention due to their effectiveness for asymmetric hydrogenation of functionalized olefins and ketones.[6] Recently, our group[7,8] and RajanBabu[9] reported a series of modified DuPhos ligands with ketal (**1** and **2**, named as ketalphos, prepared from inexpensive *D*-mannitol) or hydroxyl groups at the 3 and 4 positions of the phospholanes. In our previous reports, only one enantiomer of the ligands was synthesized. Designing a catalytic system that can obtain both enantiomers of the hydrogenation products is desired. Since preparation of the enantiomer of **1** may require the expensive *L*-mannitol, it is more practical to use its diastereomer **2** as ligand candidate to achieve opposite enantioselectivities in asymmetric hydrogenation. Rhodium complexes prepared in situ with ligand **1** and **2** gave good ee's in asymmetric hydrogenation reactions.[10] However, only some preliminary results for the asymmetric hydrogenation of α-dyhydroamino acid derivatives were given. A systematic study of both diastereomers of Me-ketalphos in the hydrogenation of different kinds of unsaturated compounds is of significant importance.

According to the literature,[2c,11] the use of in situ metal–ligand complexes generally leads to slightly less ee values in comparison to the corresponding isolated complexes. A possible reason is that the formation of the achiral rhodium catalyst species competes with the chiral active catalyst. In our previous attempts to prepare the complexes in situ, we found that the catalysts were inactive in the asymmetric hydrogenation possibly due to the short incubation time of metal precursor and the ligands. Based on a more recent report,[9] we were able to obtain the active species by extending the incubation time. However, the asymmetric hydrogenation results through the in situ method of mixing metal precursors with ligands **1** and **2** leads to relatively lower ee's compared with the ones achieved by the isolated complexes. Also, the results of the in situ method were not easily reproducible. In this paper, we reported our studies based on the preparation of isolated metal complexes of Me-ketalphos ligands for asymmetric hydrogenation. The advantage of using the isolated complexes is high reproducibility, enantioselectivity and ease of operation (Fig. 1).

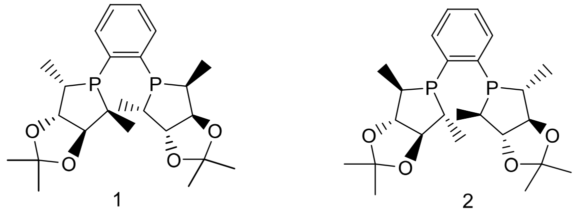
1
(2*S*, 3*S*, 4*S*, 5*S*)-Me-Ketalphos
2
(2*R*, 3*S*, 4*S*, 5*R*)-Me-Ketalphos

Figure 1. Structure of both diastereomers of Me-ketalphos.

2. Results and discussion

(*S*,*S*,*S*,*S*)-Me-ketalphos and its diasteromer were prepared from commercially available *D*-mannitol.[8,9] Since the Rh-NBD complex precursor is more reactive than the Rh-COD

Keywords: Hydrogenation; Catalyst; Rhodium.

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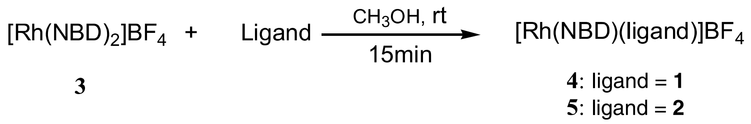


$$\underset{\mathbf{3}}{[Rh(NBD)_2]BF_4} + \text{Ligand} \xrightarrow[\text{15min}]{CH_3OH,\ rt} [Rh(NBD)(ligand)]BF_4$$

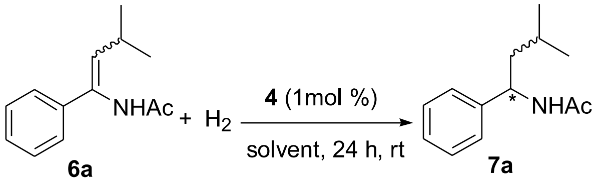
4: ligand = **1**
5: ligand = **2**

Scheme 1. Synthesis of rhodium bisphospholane complex **4** and **5**.

complex in the initiation reaction,[12] we selected $[Rh(NBD)_2]BF_4$ as the complex precursor in our catalyst precursor preparation (Scheme 1). To a solution of ligand in methanol was added 1 equiv of the complex precursor and stirred at rt for 15 min. After removal of the solvent, the Rh-Me-ketalphos complex gave a clean phosphorus NMR at 100 ppm. These Rh-Me-ketalphos complexes were characterized by ^{1}H, ^{31}P NMR and HRMS.

Using an enamide **6a** as the substrate, we have performed the condition optimization. As shown in Table 1, almost all the solvents gave good to excellent ee's except for ethanol (87% ee). In screening of solvents, we initially used methanol and found out that the results were not very consistent.[13] Both methylene chloride and isopropanol were found to be solvents of the choice.

Table 1. Rhodium catalyzed asymmetric hydrogenation of an enamide **6a**[a]



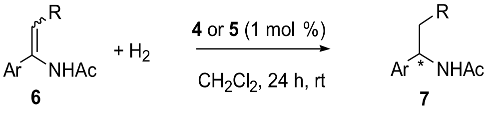
Entry	Solvent	ee (%)[b]
1	CH_2Cl_2	97
2	CH_3OH	92
3	C_2H_5OH	87
4	*i*-PrOH	97
5	THF	94
6	Toluene	92

[a] The reactions were carried out at rt under 10 atm of H_2 pressure for 24 h with 100% conversions.
[b] Enantiomeric excesses were determined by chiral GC using a Supelco Chiral Select 1000 (0.25 mm×30 m) column.

Under the optimized conditions, we have investigated asymmetric hydrogenation of enamides with both **4** and **5** as catalysts (Table 2). Complete conversions and very high enantioselectivities were observed with complex **4** (92–98% ee's). The reaction time was not optimized to ensure the complete conversion. A more detailed study on substrate **6d** showed that a TON of 1000 can be achieved without any deterioration of the enantioselectivity [14] and a TOF of 70 h^{-1}.[15] Catalyst **5** also behaved in a similar fashion, even though the enantioselectivities were slightly lower.

For hydrogenation of dehydroamino acid derivatives, complex **5** was found to be an excellent complex and high ee's for the substrates in Table 3 have been achieved (entries 1–7). In asymmetric hydrogenation, tetra-substituted substrates usually are more challenging in both reactivity and selectivity compared with tri-substituted ones. In our case, entry 8 showed high enantioselectivity (92%) under mild reaction condition, which is comparable to the best results

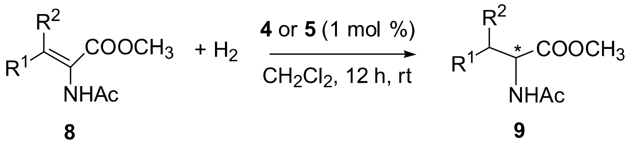
Table 2. Asymmetric hydrogenation of enamides by **4** and **5**[a]



Entry	Substrate	Complex	ee (%)[b]	Confign.[c]
1	Ar = Ph, R = isopropyl **6a**	**4**	96	*S*
2	Ar = Ph, R = H **6b**	**4**	92	*S*
3	Ar = *p*-CF_3-Ph, R = H **6c**	**4**	96	*S*
4	Ar = *p*-OMe-Ph, R = CH_3 **6d**	**4**	97	*S*
5	Ar = *p*-CF_3-Ph, R = CH_3 **6e**	**4**	97	*S*
6	Ar = Ph, R = CH_3 **6f**	**4**	98	*S*
7	**6a**	**5**	93	*R*
8	**6b**	**5**	94	*R*
9	**6c**	**5**	93	*R*
10	**6d**	**5**	94	*R*
11	**6e**	**5**	95	*R*
12	**6f**	**5**	93	*R*

[a] The reactions were carried out at rt under 10 atm of H_2 pressure for 24 h with 100% conversions.
[b] Enantiomeric excesses were determined by chiral GC using a Supelco Chiral Select 1000 (0.25 mm×30 m) column.
[c] The absolute configurations were assigned by comparision of the sign of optical rotation with reported data.

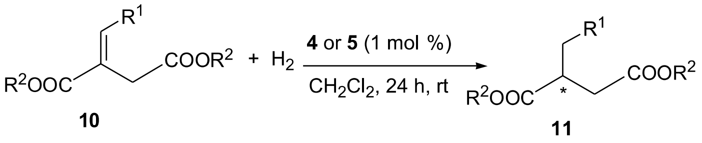
Table 3. Asymmetric hydrogenation of dehydroamino acid derivates by **4** and **5**[a]



Entry	Substrate	Complex	ee (%)[b]	Confign.[c]
1	R^1 = H, R^2 = H **8a**	**5**	99	*R*
2	R^1 = Ph, R^2 = H **8b**	**5**	99	*R*
3	R^1 = *o*-Cl-Ph, R^2 = H **8C**	**5**	98	*R*
4	R^1 = *p*-F-Ph, R^2 = H **8d**	**5**	99	*R*
5	R^1 = *m*-Br-Ph, R^2 = H **8e**	**5**	99	*R*
6	R^1 = 2-Thienyl, R^2 = H **8f**	**5**	99	*R*
7	R^1 = 2-Napthyl, R^2 = H **8g**	**5**	99	*R*
8	R^1 = CH_3, R^2 = CH_3 **8h**	**5**	92	*R*
9	**8a**	**4**	74	*S*
10	**8b**	**4**	59	*S*
11	**8c**	**4**	89	*S*
12	**8d**	**4**	76	*S*
13	**8e**	**4**	81	*S*
14	**8f**	**4**	96	*S*
15	**8h**	**4**	69	*S*

[a] The reactions were carried out at rt under 3 atm of H_2 pressure for 12 h.
[b] Enantiomeric excesses were determined by chiral GC using a Chirasil-Val III column.
[c] The absolute configurations were assigned by comparing the sign of optical rotation with reported data.

Table 4. Asymmetric hydrogenation of itaconic acid derivatives by complex **4** and **5**[a]



Entry	Substrate	Complex	ee (%)[b]	Confign.[c]
1	$R^1=H$, $R^2=CH_3$ **10a**	**4**	98	*R*
2	$R^1=i$-Pr, $R^2=H$ **10b**	**4**	99[d]	*R*
3	**10a**	**5**	99	*S*
4	**10b**	**5**	98[d]	*S*

[a] The reactions were carried out at rt under 10 atm of H_2 pressure for 24 h with 100% conversions.

[b] Enantiomeric excesses were determined by chiral GC using a Gamma-DEX 225 column.

[c] The absolute configurations were assigned by comparing the sign of optical rotation with reported data.

[d] Enantiomeric excesses were determined on the corresponding methyl esters.

that have been reported.[7,16] However, the complex **4** of diastereomeric phospholane **1**, only gave opposite selectivities in much lower ee values. The detailed reason for these results is still not clear. We have also explored hydrogenation of itaconic acid derivatives with catalysts **4** and **5**. Excellent results (up to >98% ee) were achieved with **10a** and **10b** (Table 4).

3. Conclusion

In summary, rhodium complexes **4** and **5** of (*S*,*S*,*S*,*S*)-Me-ketalphos and its diastereomer (*R*,*S*,*S*,*R*)-Me-ketalphos were prepared and characterized by NMR spectroscopy. The investigation of **4** and **5** in asymmetric hydrogenation of several different types of functionalized alkenes showed that catalyst **4** was highly enantioselective for the hydrogenation of enamides, while catalyst **5** performed very well for both enamides and dehydroamino acid derivatives.

4. Experimental

4.1. General methods

All reactions and manipulations were performed in a nitrogen-filled glovebox or using standard schlenk techniques. GC analysis was carried out using chiral capillary columns: Chirasil-Val III FOST (Dimensions: 30 m× 0.25 mm) for dehydroamino acid derivatives; Chiral Select 1000 column (dimensions: 15 m×0.25 mm) for enamides; γ-225 (dimensions: 30 m×0.25 mm) for itaconic acid derivatives. Chemical shifts were reported in ppm downfield from tetramethylsilane with the solvent resonance as the internal standard.

4.2. General procedure for the synthesis of 4 and 5

To a solution of Me-ketalphos **1** (135 mg, 0.3 mmol) in 20 mL of methanol was added $[Rh(NBD)_2]BF_4$ (112.2 mg, 0.3 mmol) [NBD=norbornadiene], and the resulting bright orange solution was stirred at rt for 15 min. Solvent was removed under reduced pressure.

4.2.1. Rh(NBD)(1)]BF_4. ^{1}H NMR (360 MHz, CD_3OD) δ 7.91–7.96 (m, 2H), 7.78–7.82 (m, 2H), 6.13 (s, 2H), 5.91 (s, 2H), 4.72 (dd, $J=8.04$, 10.49 Hz, 2H), 4.29 (dd, $J=7.41$, 10.31 Hz, 4H), 3.26–3.32 (m, 2H), 2.77–2.86 (m, 2H), 1.93 (s, 2H), 1.55 (s, 6H), 1.54 (s, 6H), 1.30–1.37 (m, 6H), 0.73–0.79 (m, 6H). ^{31}P NMR (CD_3OD) δ 100.1 (d, $J_{\text{Rh-P}}=$ 153.5 Hz); HRMS (cation) *m*/*z* calcd for $C_{31}H_{44}O_4P_2Rh$ 645.1770, found 645.1737; HRMS (anion) *m*/*z* calcd for BF_4 87.0029, found 87.0024.

4.2.2. Rh(NBD)(2)]BF_4. ^{1}H NMR (360 MHz, CD_3OD) δ 8.04–8.28 (m, 2H), 7.86–7.88 (m, 2H), 6.14 (s, 2H), 4.40 (s, 2H), 4.28 (dd, $J=10.1$, 18.9 Hz, 2H), 3.76 (dd, $J=8.9$, 11.4 Hz, 4H), 2.81–2.92 (m, 2H), 2.62–2.79 (m, 2H), 2.06 (s, 2H), 1.64 (s, 6H), 1.62 (s, 6H), 1.30–1.60 (m, 6H), 0.87–0.93 (m, 6H). ^{31}P NMR (CD_3OD) δ 100.8 (d, $J_{\text{Rh-P}}=$ 158.0 Hz); HRMS (cation) *m*/*z* calcd for $C_{31}H_{44}O_4P_2Rh$ 645.1770, found 645.1752; HRMS (anion) *m*/*z* calcd for BF_4 87.0029, found 87.0021.

4.3. General hydrogenation procedure using 4 or 5

In a glove box, a solution of 0.005 mmol of catalyst in 1 mL of CH_2Cl_2 was added 0.5 mmol of substrate. The resulting mixture was transferred to an autoclave. The hydrogenation was performed at rt under 3–10 atm of hydrogen for 12–24 h. The hydrogen was carefully released and the reaction mixture was passed through a short silica gel plug to remove the catalyst. The ee were measured by GC with a chiral column directly without any further purification. The absolute configurations of the products were determined by comparing the sign of optical rotation with the reported values.

All the physical characterization data for substrates and products can be found in Ref. 17 and the references therein.

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References and notes

1. Brunner, H.; Zettlmeier, W. In *Handbook of Enantioselective Catalysis with Transition Metal Compounds*, *Vol. 2*; VCH Verlagsgesellschaft: Weinheim, 1993; Ligands-References, p 359.

2. (a) Burk, M. J.; Feaster, J. E.; Harlow, R. L. *Organometallics* **1990**, *9*, 2653. (b) Burk, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 8518. (c) Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 10125. (d) Burk, M. J.; Lee, J. R.; Martine, J. P. *J. Am. Chem. Soc.* **1994**, *116*, 10847. (e) Burk, M. J.; Wang, Y. M.; Lee, J. R. *J. Am. Chem. Soc.* **1996**, *118*, 5142.
3. (a) Holz, J.; Quirmbach, M.; Schmidt, U.; Heller, D.; Stürmer, R.; Börner, A. *J. Org. Chem.* **1998**, *63*, 8031. (b) Holz, J.; Stürmer, R.; Schmidt, U.; Drexler, H.-J.; Heller, D.; Krimmer, H.-P.; Börner, A. *Eur. J. Org. Chem.* **2001**, *24*, 4615.
4. Holz, J.; Heller, D.; Stürmer, R.; Börner, A. *Tetrahedron Lett.* **1999**, *40*, 7059.
5. Holz, J.; Monsees, A.; Jiao, H.; You, J.; Komarov, I. V.; Fischer, C.; Drauz, K.; Borner, A. *J. Org. Chem.* **2003**, *68*, 1701.
6. Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029.
7. Liu, D.; Li, W.; Zhang, X. *Org. Lett.* **2002**, *4*, 4471.
8. (a) Li, W.; Zhang, Z.; Xiao, D.; Zhang, X. *Tetrahedron Lett.* **1999**, *40*, 6701. (b) Li, W.; Zhang, Z.; Xiao, D.; Zhang, X. *J. Org. Chem.* **2000**, *65*, 3489.
9. (a) Shin, S.; RajanBabu, T. V. *Org. Lett.* **1999**, *1*, 1229. (b) Yan, Y.; RajanBabu, T. V. *J. Org. Chem.* **2000**, *65*, 900.
10. RajanBabu, T. V.; Yan, Y.; Shin, S. *J. Am. Chem. Soc.* **2001**, *123*, 10207.
11. Brunner, H. *Applied Homogeneous Catalysis with Organometallic compounds*. In Cornils, B., Herrmann, W. A., Eds. 2nd ed.; Wiley-VCH: Weinheim, 2001; p 209.
12. Cobley, C. J.; Lennon, I. C.; McCague, R.; Ramsden, J. A.; Zannotti-Gerosa, A. *Tetrahedron Lett.* **2001**, *42*, 7481.
13. Phosphorus NMR showed that the complex was decomposed after certain period of time with detection of a small peak at 83 ppm.
14. The hydrogenation reaction was performed with 0.1 mol% loading of complex **4** at standard reaction condition for enamides for 16 h with 100% conversion.
15. The hydrogenation reaction was performed with 0.1 mol% loading of complex **4** at standard reaction condition for enamides for 2 h with 14% conversion.
16. (a) Evans, D. A.; Michael, F. E.; Tedrow, J. S.; Campos, K. R. *J. Am. Chem. Soc.* **2003**, *125*, 3534. (b) Ohashi, A.; Imamoto, T. *Org. Lett.* **2001**, *3*, 373. (c) Imamoto, T.; Watanabe, J.; Wada, Y.; Masuda, H.; Yamada, H.; Tsuruta, H.; Matsukawa, S.; Yamaguchi, K. *J. Am. Chem. Soc.* **1998**, *120*, 1635. (d) Burk, M. J.; Gross, M. F.; Martinez, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 9375. (e) Sawamura, M.; Kuwano, R.; Ito, Y. *J. Am. Chem. Soc.* **1995**, *117*, 9602.
17. (a) Zhu, G.; Zhang, X. *J. Org. Chem.* **1998**, *63*, 3133. (b) Li, W.; Zhang, X. *J. Org. Chem.* **2002**, *65*, 5871. (c) Wu, S.; Wang, W.; Tang, W.; Lin, M.; Zhang, X. *Org. Lett.* **2002**, *4*, 4495.

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A highly active ionic liquid catalyst for Morita–Baylis–Hillman reaction

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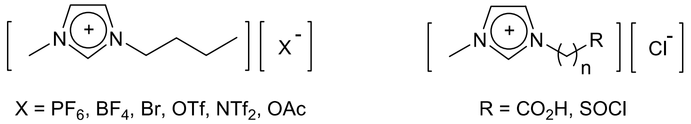
Abstract—The Morita–Baylis–Hillman reaction is an efficient carbon–carbon bond forming reaction for the preparation of α-methylene-β-hydroxycarbonyl compounds. A new and highly active di-naphthalene imidazolium salt has been synthesized. We have found that 1,3-bis[2-(naphthalene-2-yloxy)propyl]imidazolium bromid promoted the Morita–Baylis–Hillman reaction of various aryl aldehyde compounds in the absence of solvents. Our studies show that the Morita–Baylis–Hillman reaction by the influence of ionic liquid to give a high yield and short reaction time.

1. Introduction

The Morita–Baylis–Hillman (MBH) reaction is a particularly powerful transformation because it permits the coupling of various activated aldehydes and α,β-unsaturated ketones, a process that has a great synthetic advantage.[1] This reaction involves three components: an activated alkene, an electrophile, and a tertiary amine. Lewis bases, such as 1,4-diazabicyclo[2.2.2]octane (DABCO),[2] DMAP,[3] DBU,[4] 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP),[5] and imidazole,[6] are frequently used in these reactions as catalysts. In addition, Lewis acid-accelerated reactions were also reported, such as $TiCl_4$,[7] Et_2AlI,[8] and BF_3.[9] In a general process, the MBH reaction suffers from poor reaction rates and long reaction time. For this reason, modifications such as the use of high pressure,[10] microwave irradiation[11] and ultrasound[12] have given some promising results. In recent years, room temperature ionic liquids (RTILs) have been gaining exposure for their potential in organic synthesis. From both an environmental and an economical point of view, the concept of recoverable and recyclable catalysis has become increasingly important.[13] RTILs have received considerable attention for applications as green solvents[14] and replacements for traditional organic solvents.[15] Their properties, negligible vapor pressure, high polarity, non-flammable, and easy handling, and the fact that ionic liquids can often act as catalysts as well as reaction media, enable them to be used as solvents for a variety of transition metal catalyzed reactions (e.g., esterification,[16] alkylation,[17] oxidation,[13a] and hydrogenation[18]). There are many reports concerning the applications of RTILs in organic reactions, such as the Diels–Alders reaction,[19] Friedel-Crafts reaction,[20] Suzuki cross-coupling,[21] Mannich reaction,[22] Heck reaction,[23] and Baeyer–Villiger reaction[24] that often afford greater yields, product selectivity[25] and accelerated reaction rates. A recent report described the acceleration of the DABCO-catalysed MBH reaction in ionic liquids[26] and led us to investigate the effects of ionic liquids. Beside, RTILs were usually based on the 1-*n*-alkyl-3-methylimidazolium cation, which can be synthesized easily from the commercially available starting material, 1-methylimidazole. Scheme 1 has shows general RTILs applied in organic synthesis in literatures and reported that ionic liquids such as [bmim][PF_6] or [bdmim][PF_6] accelerate the rates and improve the yields of MBH reaction.[27]

A common MBH reaction carried out with [bmim][X] to give lower yield (13–78%)[26b] and a longer reaction time.



Scheme 1. Ionic liquids.

Keywords: Morita–Baylis–Hillman reaction; Ionic liquids; DABCO.

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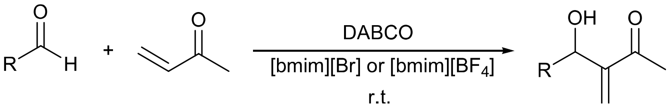
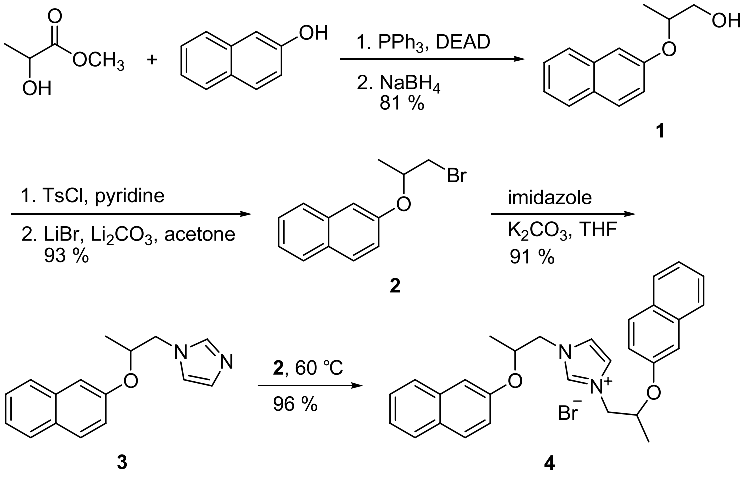
Table 1. Reaction of various aldehydes with methyl vinyl ketone in the presence of [bmim][Br] or [bmim][BF_4]



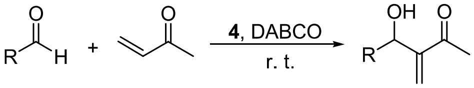
Aldehyde	[bmim][Br]		[bmim][BF_4]	
	Time (h)	Yield (%)	Time (h)	Yield (%)
2-Pyridinecarboxaldehyde	32	46	29	57
4-Chlorobenzaldehyde	46	72	35	68
4-Biphenylcarboxaldehyde	36	58.5	34	66
2-Naphthaldehyde	78	26	69	33
Methyl 4-formylbenzoate	57	18	71	13
4-Methoxybenzaldehyde	112	9	89	11

We prepared [bmim][Br][28a] and [bmim][BF_4][28b] and then carried out the reactions of these RTILs with aldehydes and α,β-unsaturated ketones in the presence of DABCO (Table 1). Since we were not satisfied with the results, we synthesized a new imidazolium salt for the MBH reaction (Scheme 2). The reaction of methyl lactate with 2-naphthol in the presence of DEAD[29] is followed by sodium borohydride reduction yields the primary alcohol **1**.[30]



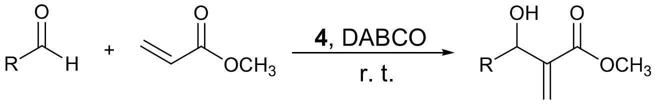
Scheme 2. Synthesis of di-naphthalene imidazolium salt.

Table 2. Reaction of various aldehydes with methyl vinyl ketone in the presence of 1,3-bis[2-(naphthalene-2-yloxy)propyl]imidazolium bromide



Entry	Aldehyde	Product	Time (h)	Yield (%)
1	*p*-Nitrobenzaldehyde	**5**	0.1	99
2	Methyl 4-formylbenzoate	**6**	0.5	96
3	4-(Trifluoromethyl)benzaldehyde	**7**	2.8	99
4	2-Naphthaldehyde	**8**	0.7	79
5	3-Phenylpropionaldehyde	**9**	28	82
6	4-Biphenylcarboxaldehyde	**10**	18	87
7	4-Methylbenzaldehyde	**11**	29	79
8	4-Chlorobenzaldehyde	**12**	20	81
9	4-Methoxybenzaldehyde	**13**	18	58
10	3,4,5-Trimethoxybenzaldehyde	**14**	27	89
11	4-(Methylthio)benzaldehyde	**15**	15	87
12	2-Pyridinecarboxaldehyde	**16**	7	85
13	3-Pyridinecarboxaldehyde	**17**	12	81
14	4-Bromo-2-thiophenecarbozaldehyde	**18**	0.5	94
15	5-(3-Chlorophenyl)furfural	**19**	18	97

Table 3. Reaction of various aldehydes with methyl acrylate in the presence of 1,3-bis[2-(naphthalene-2-yloxy)propyl]imidazolium bromide



Entry	Aldehyde	Product	Time (h)	Yield (%)
1	*p*-Nitrobenzaldehyde	**20**	0.5	98
2	Methyl 4-formylbenzoate	**21**	2.5	92
3	4-(Trifluoromethyl)benzaldehyde	**22**	1.1	91
4	2-Naphthaldehyde	**23**	20	81
5	3-Phenylpropionaldehyde	**24**	30	71
6	4-Biphenylcarboxaldehyde	**25**	12	86
7	4-Methylbenzaldehyde	**26**	18	59
8	4-Chlorobenzaldehyde	**27**	27	58
9	4-Methoxybenzaldehyde	**28**	22	47
10	3,4,5-Trimethoxybenzaldehyde	**29**	71	93
11	4-(Methylthio)benzaldehyde	**30**	22	83
12	2-Pyridinecarboxaldehyde	**31**	10	87
13	3-Pyridinecarboxaldehyde	**32**	16	79
14	4-Bromo-2-thiophenecarbozaldehyde	**33**	3	92
15	5-(3-Chlorophenyl)furfural	**34**	22.4	89

The tosylation of the primary alcohol followed by a treatment with 1.3 equiv of lithium bromide in acetone produced bromide **2**. The reaction of imidazole with compound **2** afforded the imidazole derivative, isolated as compound **3**. Finally, the treatment of **3** with bromide **2** at 60 °C gave 1,3-bis[2-(naphthal-2-yl-oxy)propyl]imidazolium bromide **4** in 96% yield after purification.

The treatment of various aryl aldehydes with methyl vinyl ketone (MVK) or methyl acrylate in the presence of hydrophilic ionic liquid **4** not only produced the desired product in moderate to high yield but also reduced the side products. For example, in the reaction of methyl 4-formylbenzoate (1.0 equiv) with MVK (2.0 equiv), entry 2 (Table 2) can be obtained in 96% yield in the presence of compound **4** (0.2 equiv) for 0.5 h at room temperature. We also prepared MBH reaction with methyl acrylate (Table 3), our condition goes very smoothly, producing high yields and also accelerating the reaction rate. The recovered ionic liquid was reused for subsequent runs.[16b]

In conclusion, the present procedure catalyzed by a hydrophilic RTIL, 1,3-bis[2-(naphthal-2-yl-oxy)propyl]-imidazolium bromide provides an efficient and general methodology for the MBH reaction of aryl aldehydes and MVK or methyl acrylate to yield α-methylene-β-hydroxycarbonyl compounds. The results presented in this paper, demonstrate that the MBH reaction works well in the presence of ionic liquid.

2. Experimental

All reagents were purchased from Acros, Aldrich Chimie, Fluka and used without further purification. IR spectra were taken as KBr plates. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution at 300 and 75 MHz spectrometer. TLC analysis was performed used glass plate with silica gel 60 F_{254}. Flash column chromatography was carried out using 200–300 mesh silica gel.

2.1. Typical procedure for the ionic liquid promoted Morita–Baylis–Hillman reaction

In a dried flask, aldehyde (1 mmol), DABCO (224 mg, 2 mmol), and 1,3-bis[2-(naphthal-2-yl-oxy)propyl]imidazolium bromide (129.3 mg, 0.25 mmol) were measured together. Methyl vinyl ketone (105 mg, 1.5 mmol) was added, and the reaction mixture was stirred for 7–20 h at ambient temperature in all cases. The mixture was washed with ether (3×10 mL), and the solid was separated by vacuum filtration. Then the solid was extracted with 130 mL dichloromethane and followed by a general procedure to recover the catalyst. The ethereal phase was concentrated, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (Hexane/ethyl acetate, 7:3, v/v).

2.1.1. Synthesis of 1. Methyl lactate (10.40 g, 0.1 mol) was added to a solution of 2-naphthol (14.40 g, 0.11 mmol) and triphenyl phosphine (31.44 g, 0.12 mol) in dichloromethane (100 mL). The reaction mixture was stirred at 0 °C and diethyl azodicarboxylate (17.04 g, 0.12 mol) was added. After the mixture was stirred for 2 h at room temperature and the white solid ($Ph_3P{=}O$) was separated by vacuum filtration. The organic layer was evaporated under vacuum, the crude dissolved in a co-solvent (200 mL tetrahydrofuran and 20 mL methol), sodium tetrahydridoborate (3.8 g, 0.1 mol) was added, and stirred at ambient temperature for 3.5 h. The organic phase was washed with 100 mL of water and dried over anhydrous $MgSO_4$. The organic solvent was evaporated under reduced pressure to give 2-(1-methoxy-propan-2-yloxy)naphthalene (17.56 g, 81%) as yellow oil.

IR (KBr) ν_{max}: 3420 (OH), 3056, 1215, 2975, 2931, 1627, 1598, 1509, 1467, 1256, 1215, 1180, 1050, 970, 839, 748; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.39–1.37 (d, $J=7.0$ Hz, 3H), 3.85–3.82 (d, $J=7.8$ Hz, 2H), 4.70–4.63 (m, 1H), 7.22–7.15 (m, 2H), 7.45–7.35 (m, 2H), 7.79–7.71 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: 155.59, 134.60, 129.71, 127.74, 126.88, 126.53, 123.93, 119.62, 109.03, 74.83, 66.20, 15.81; MS (EI, 70 eV, *m/z*, %): 202 (M^+, 65), 171 (28), 143 (100), 127 (55), 115 (77), 101 (11); HRMS calcd for $C_{13}H_{14}O_2$: 202.0994. Found: 202.0998.

2.1.2. Synthesis of 2. A mixture of 2-(1-methoxypropan-2-yloxy)naphthalene (10.80 g, 0.05 mol), tosyl chloride (11.44 g, 0.06 mol), and pyridine (5.3 mL, 0.06 mol) was stirred in 100 mL of dichloromethane at room temperature for 18 h. The organic phase was washed with 150 mL water, dried over anhydrous $MgSO_4$ and concentrated. Then the tosylate crude mixture wit lithium bromide (5.66 g, 0.065 mol) was diluted in 50 mL of acetone, and lithium carbonate (0.37 g, 0.05 mol) added. The mixture was stirred at ambient temperature for 24 h. When the reaction was completed by a TLC analysis, the solvent was evaporated and a dark yellow oil was purified via flash chromatography (Hexane/ethyl acetate, 9:1, v/v), producing a light yellow oil, 2-(1-bromopropan-2-yloxy)naphthalene (12.28 g, 93%).

IR (KBr) ν_{max}: 1627, 1598, 1509, 1466, 1255, 1214, 1177, 838, 747; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.54 (d, $J=6.2$ Hz, 3H), 3.53–3.48 (m, 1H), 3.67–3.61 (m, 1H), 4.76–4.70 (m, 1H), 7.19–7.15 (m, 2H), 7.39–7.36 (m, 1H), 7.46–7.43 (m, 1H), 7.79–7.72 (m, 3H); ^{13}C NMR ($CDCl_3$) δ: 155.12, 134.43, 129.77, 129.13, 127.67, 126.82, 126.49, 124.02, 119.54, 109.15, 73.53, 35.31, 18.79; MS (FAB, *m*/*z*): 266 (M^+), 264, 145, 144, 127; HRMS calcd for $C_{13}H_{13}BrO$: 264.0150. Found: 264.0151.

2.1.3. Synthesis of 3 and 4. Bromide **2** (5.30 g, 0.02 mol) was injected into a flask containing tetrahydrofuran (55 mL) followed by potassium carbonate (0.55 g, 8 mmol) and stirred at room temperature for 24 h. After completion of the reaction, as indicated by TLC, the product was quenched with 50 mL water and extracted with dichloromethane (3× 50 mL). The organic layer was dried over anhydrous $MgSO_4$, concentrated under reduced pressure and purified by chromatography on silica gel to afford imidazole **3** (4.59 g, 91%). The combined bromide **2** (2.52 g, 0.01 mol) and imidazole **3** (2.65 g, 0.01 mol) was stirred at 60 °C for 2 h. The mixture was washed with diethyl ether (3× 100 mL) and evaporated under vacuum. A brown solid, 1,3-bis[2-(naphthalene-2-yloxy)propyl]imidazolium bromide, was obtained (9.93 g, 96%).

Compound **3**. IR (KBr) ν_{max}: 2924, 1735, 1508, 1255, 1214, 748; ^1H NMR ($CDCl_3$) δ: 1.37 (d, $J=6.0$ Hz, 3H), 4.22–4.19 (m, 2H), 4.70–4.80 (m, 1H), 7.09–7.03 (m, 4H), 7.44–7.35 (m, 2H), 7.58 (s, 1H), 7.78–7.68 (m, 3H); ^{13}C NMR ($CDCl_3$) δ: 156.52, 137.89, 134.00, 129.89, 128.62, 129.60, 127.69, 126.75, 126.58, 124.11, 120.00, 119.31, 108.95, 73.21, 51.66, 17.15; MS (EI, 70 eV, *m*/*z*, %): 252 (M^+, 83), 171 (46), 144 (93), 127 (56), 109 (100); HRMS calcd for $C_{16}H_{16}N_2O$: 252.1263. Found: 252.1259.

Compound **4**. IR (KBr) ν_{max}: 3056, 2195, 1626, 1598, 1509, 1467, 1255, 1180, 1119, 1078, 972, 732; ^1H NMR ($CDCl_3$) δ: 1.44 (d, $J=6.2$ Hz, 6H), 4.47–4.39 (m, 2H), 4.96–4.89 (m, 4H), 7.01–6.98 (m, 2H), 7.13–7.12 (m, 2H), 7.44–7.34 (m, 8H), 7.71–7.62 (m, 8H); ^{13}C NMR ($CDCl_3$) δ: 154.15, 132.24, 129.92, 128.80, 127.60, 126.88, 126.68, 124.27, 122.56, 118.80, 109.13, 72.41, 67.99, 54.21, 25.62, 16.63; MS (FAB, *m*/*z*): 517 $(M)^+$, 437 $(M-Br)^+$, 293, 253, 185, 144, 109. Anal. Calcd for $C_{29}H_{29}BrN_2O_2$: C, 67.31; H, 5.65. Found: C, 67.35; H, 5.68; mp: 178 °C.

Compounds **5**,[31] **7**,[31] **9**,[32] **11**,[33] **12–13**,[34] **16–17**,[35] **20**,[36] **22**,[2f] **23**,[37] **24**,[38] **26**,[12a] **27**,[39] **28–29**,[40] and **31–32**,[41] were identical to authentic samples by comparison of their spectral date.

2.1.4. Methyl 4-[(1-hydroxy)(2-methylene)butyl-3-one]-benzoate (6). IR (KBr) ν_{max}: 3460 (OH), 1719 (C=O), 1677 (C=O), 1434, 1283, 1115, 960, 766, 707; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.01 (d, $J=6.6$ Hz, 2H), 7.44 (d, $J=8.3$ Hz, 1H), 6.22 (s, 1H), 5.97 (s, $J=5.97$ Hz, 1H), 5.65 (s, 1H), 3.91 (s, 1H), 2.34 (s, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 200.29 (C=O), 168.89, 149.46, 146.63, 129.72, 129.48, 127.32, 126.44, 72.64, 52.13, 26.44; MS (FAB, *m*/*z*): 217 $(M^+ + 1 - H_2O)$; HRMS calcd for $C_{13}H_{14}O_4$: 234.0892. Found: 234.0897.

2.1.5. 3-(Hydroxy(naphthalene-2-yl)methyl)but-3-en-2-one (8). IR (KBr) ν_{max}: 3436 (OH), 3055, 1672 (C=O), 1363, 1125, 1041, 952, 824, 747; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.85–7.80 (m, 4H), 7.49–7.23 (m, 4H), 6.23 (s, 1H), 6.01 (s, $J=1.1$ Hz, 1H), 5.80 (s, 1H), 2.35 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 200.46 (C=O), 149.92, 138.84, 133.26, 132.92, 128.17, 128.12, 127.67, 127.00, 126.18, 126.03, 125.47, 124.56, 72.91, 26.54; MS (EI, 70 eV, *m*/*z*, %): 226 (M^+, 84), 225 (100), 211 (14), 166 (15), 165 (34), 155 (23), 128 (54), 127 (43), 84 (50); HRMS calcd for $C_{17}H_{16}O_2$: 226.0994. Found: 226.0996.

2.1.6. 3-[Hydroxy(4-phenylphenyl)methyl]but-3-en-2-one (10). IR (KBr) ν_{max}: 3436 (OH), 3029, 1672 (C=O), 1485, 1363, 1038, 763, 700; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.60–7.56 (m, 4H), 7.45–7.43 (m, 4H), 7.42 (d, 1H), 6.23 (s, 1H), 6.05 (d, $J=1.1$ Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 200.39 (C=O), 149.90, 140.80, 140.65, 140.59, 128.78, 127.33, 127.12, 127.11, 126.97, 126.80, 72.73, 26.55; MS (EI, 70 eV, *m*/*z*, %): 252 (M^+, 87), 251 (100), 191 (22), 175 (75), 152 (35), 77 (26); HRMS calcd for $C_{17}H_{16}O_2$: 252.1150. Found: 252.1150.

2.1.7. 2-[Hydroxy(3,4,5-trimethoxyphenyl)methyl]-cyclohex-2-enone (14). IR (KBr) ν_{max}: 3480 (OH), 2937, 2838, 1672 (C=O), 1591, 1506, 1459, 1418, 1325, 1231, 1125, 1008, 843; ^1H NMR (300 MHz, $CDCl_3$), δ 6.58 (s, 2H), 6.17 (s, 1H), 5.96 (s, 1H), 3.85, (s, 6H), 3.83 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 200.53 (C=O), 153.24, 149.90, 137.36, 137.10, 126.88, 103.54, 72.75, 60.83, 56.12, 26.56; MS (70 eV, *m*/*z*, %): 266 (M^+, 54), 235 (74), 196 (100), 181 (49), 169 (28), 138 (18), 125 (31), 110 (19), 84 (70); HRMS calcd for $C_{14}H_{18}O_5$: 266.1154. Found: 266.1147.

2.1.8. 3-[Hydroxy(4-methylthiophenyl)methyl]but-3-en-2-one (15). IR (KBr) ν_{max}: 3437 (OH), 2920, 1673 (C=O), 1596, 1493, 1403, 1364, 1092, 1038, 972, 820; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.29–7.20 (dd, 4H), 6.19 (s, 1H), 5.99 (s, 1H), 5.58 (s, 1H), 2.49 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 200.33 (C=O), 149.88, 138.46, 137.87, 127.08, 126.63, 126.57, 72.46, 26.52, 15.84; MS (EI, 70 eV, *m*/*z*, %): 222 (M^+, 39), 221 (42), 207 (8), 175 (100), 153 (37), 151 (37), 124 (21), 109 (30), 77 (18); HRMS calcd for $C_{12}H_{14}O_2S$: 222.0715. Found: 222.0718.

2.1.9. 3-[(4-Bromothiophen-2-yl)(hydroxy)methyl]but-3-en-2-one (18). IR (KBr) ν_{max}: 3421 (OH), 3106, 2919, 1672 (C=O), 1367, 1033, 971, 821; ^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.16 (s, J=1.4 Hz, 1H), 6.85 (s, J=1.2 Hz, 1H), 6.38 (s, 1H), 5.96 (s, 1H), 5.68 (s, 1H), 3.77 (s, 3H); ^{13}C NMR (75.4 MHz, CDCl$_3$) δ: 166.37 (C=O), 147.28, 140.35, 127.14, 127.03, 122.59, 109.35, 69.83, 52.27; MS (FAB, *m/z*): 243 (M$^+$+1−H$_2$O); HRMS calcd for C$_9$H$_9$BrO$_2$S: 259.9507. Found: 259.9512.

2.1.10. 3-{[5-(3-Chlorophenyl)furan-2-yl](hydroxy)-methyl}but-3-en-2-one (19). IR (KBr) ν_{max}: 3429 (OH), 2919, 2365, 1672 (C=O), 1605, 1430, 1367, 1019, 781; ^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.6 (d, J=1.3 Hz, 1H), 7.48 (t, 1H), 7.31–7.19 (m, 2H), 6.61 (d, J=3.3 Hz, 1H), 6.34 (d, J=3.3 Hz, 1H), 6.29 (s, 1H), 6.17 (s, 1H), 5.67 (s, 1H), 2.41 (s, 3H); ^{13}C NMR (75.4 MHz, CDCl$_3$) δ: 200.02 (C=O), 154.48, 152.17, 147.05, 134.69, 132.28, 129.96, 127.70, 123.70, 127.33, 121.80, 109.44, 106.94, 67.51, 26.42; MS (70 eV, *m/z*, %): 278 (M+2, 33), 276 (M$^+$, 100), 247 (6), 233 (19), 215 (18), 207 (72), 191 (12), 178 (74), 165 (8), 152 (21), 149 (32), 139 (89), 137 (40), 115 (69), 111 (29), 98 (81), 70 (38); HRMS calcd for C$_{15}$H$_{13}$ClO$_3$: 276.0553. Found: 276.0556.

2.1.11. Methyl 4-[2-(methoxycarbonyl)hydroxyallyl]-benzoate (21). IR (KBr) ν_{max}: 3491 (OH), 2955, 1723 (C=O), 1436, 1283, 1110, 1019, 818; ^{1}H NMR (300 MHz, CDCl$_3$) δ: 8.03 (s, 1H), 8.00 (s, 1H), 7.47 (s, 1H), 7.45 (s, 1H), 6.36 (s, 1H), 5.83 (s, 1H), 5.60 (s, 1H), 3.91 (s, 1H), 3.71 (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ: 166.9 (C=O), 166.6 (C=O), 146.3, 141.4, 129.8, 129.6, 126.9, 126.5, 73.13, 52.2, 52.1; MS (EI, 70 eV, *m/z*, %): 250 (M$^+$, 35), 235 (18), 219 (25), 191 (31), 190 (35), 165 (18), 163 (100), 131 (13), 105 (31), 77 (30), 59 (21); HRMS calcd for C$_{13}$H$_{14}$O$_5$: 250.0841. Found: 250.0849.

2.1.12. Methyl 2-[hydroxy(4-phenylphenyl)methyl]-acrylate (25). IR (KBr) ν_{max}: 3370 (OH), 2952, 1719 (C=O), 1434, 1268, 1151, 1030, 766; ^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.64 (m, 4H), 7.50 (m, 4H), 7.37 (t, J=1.2 Hz, 1H), 6.38 (s, 1H), 5.91 (s, 1H), 5.62 (s, 1H), 3.75 (s, 3H); ^{13}C NMR (75.4 MHz, CDCl$_3$) δ: 166.82 (C=O), 141.84, 140.78, 140.76, 140.30, 128.80, 127.37, 127.25, 127.12, 127.03, 126.30, 73.18, 52.06; MS (EI, 70 eV, *m/z*, %): 268 (M$^+$, 70), 236 (22), 208 (21), 191 (27), 181 (100), 153 (20), 77 (18); HRMS calcd for C$_{17}$H$_{16}$O$_3$: 268.1099. Found: 268.1097.

2.1.13. Methyl 2-{hydroxy[4-(methylthio)phenyl]-methyl}acrylate (30). IR (KBr) ν_{max}: 3458 (OH), 2952, 2919, 1715 (C=O), 1631, 1495, 1434, 1287, 1435, 1287, 1146, 1037, 957, 818; ^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.28 (dd, 2H), 7.22 (dd, 2H), 6.33 (s, 1H), 5.85 (d, J=1.0 Hz, 1H), 5.52 (s, 1H), 3.72 (s, 3H), 3.07 (d, 1H), 2.47 (s, 3H); ^{13}C NMR (75.4 MHz, CDCl$_3$) δ: 166.77 (C=O), 141.76, 138.07, 127.15, 126.45, 126.18, 72.92, 52.08, 15.75; MS (FAB, *m/z*): 221 (M$^+$+1−H$_2$O); HRMS calcd for C$_{12}$H$_{14}$O$_3$S: 238.0664. Found: 238.0668.

2.1.14. Methyl 2-[hydroxy(4-bromothiophen-2-yl)methyl]acrylate (33). IR (KBr) ν_{max}: 3447 (OH), 3110, 2952, 1712 (C=O), 1437, 1335, 1151, 1038,818; ^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.13 (s, J=1.3 Hz, 1H), 6.83 (s, J=0.9 Hz, 1H), 6.24 (s, 1H), 6.12 (s, 1H), 5.72 (s, 1H), 2.37 (s, 3H); ^{13}C NMR (75.4 MHz, CDCl$_3$) δ: 200.17 (C=O), 148.30, 147.49, 127.40, 127.04, 122.36, 109.30, 69.53, 26.50; MS (EI, 70 eV, *m/z*, %): 278 (M+2, 100), 276 (M$^+$, 97), 261 (71), 246 (52), 218 (42), 191 (57), 166 (30), 121 (26), 109 (25), 97 (10), 84 (48); HRMS calcd for C$_9$H$_9$BrO$_3$S: 275.9456. Found: 275.9453.

2.1.15. Methyl 2-[(5-(3-chlorophenyl)furan-2-yl)-(hydroxy)methyl]acrylate (34). IR (KBr) ν_{max}: 3449 (OH), 2947, 1715 (C=O), 1628, 1438, 1286, 1202, 783; ^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.6 (d, J=1.7 Hz, 1H), 7.48 (t, 1H), 7.31–7.19 (m, 2H), 6.61 (d, J=3.3 Hz, 1H), 6.34 (d, J=3.3 Hz, 1H), 6.29 (s, 1H), 6.17 (s, 1H), 5.67 (s, 1H), 2.41 (s, 3H); ^{13}C NMR (75.4 MHz, CDCl$_3$) δ: 200.02 (C=O), 154.48, 152.17, 147.05, 134.69, 132.28, 129.96, 127.70, 123.70, 127.33, 121.80, 109.44, 106.94, 67.51, 26.42; MS (70 eV, *m/z*, %): 294 (M+2, 21), 292 (M$^+$, 70), 260 (25), 232 (27), 207 (89), 205 (70), 178 (74), 153 (40), 149 (40), 141 (77), 139 (100), 115 (78), 113 (30), 111 (31), 75 (22); HRMS calcd for C$_{15}$H$_{13}$ClO$_3$: 292.0502. Found: 292.0509.

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References and notes

1. Anand, R. V.; Baktharaman, S.; Singh, V. K. *Tetrahedron Lett.* **2002**, *43*, 5393.
2. (a) Faltin, C.; Fleming, E. M.; Connon, S. J. *J. Org. Chem.* **2004**, *69*, 6496. (b) Alcaide, B.; Almendros, P.; Aragoncillo, C.; Rodriguez-Acebes, R. *J. Org. Chem.* **2004**, *69*, 826. (c) Chandrasekhar, S.; Narsihmulu, C.; Saritha, B.; Sultana, S. S. *Tetrahedron Lett.* **2004**, *45*, 5865. (d) Shi, M.; Zhao, G.-L. *Tetrahedron* **2004**, *60*, 2083. (e) Maher, D. J.; Connon, S. J. *Tetrahedron Lett.* **2004**, *45*, 1301. (f) Patra, A.; Roy, A. K.; Joshi, B. S.; Roy, R.; Batra, S.; Bhaduri, A. P. *Tetrahedron* **2003**, *59*, 663. (g) Yu, C.; Hu, L. *J. Org. Chem.* **2002**, *67*, 219.
3. (a) Sohtome, Y.; Tanatani, A.; Hashimoto, Y.; Nagasawa, K. *Tetrahedron Lett.* **2004**, *45*, 5589. (b) Rezgui, F.; El Gaïed, M. M. *Tetrahedron Lett.* **1998**, *39*, 5965.
4. (a) Ballini, R.; Barboni, L.; Bosica, G.; Fiorini, D.; Mignini, E.; Palmieri, A. *Tetrahedron* **2004**, *60*, 4995. (b) Aggarwal, V. K.; Mereu, A. *Chem. Commun.* **1999**, 2311.
5. Hayase, T.; Shibata, T.; Soai, K.; Wakasuki, Y. *Chem. Commun.* **1998**, 1271.
6. (a) Gatri, R.; El Gaïed, M. M. *Tetrahedron Lett.* **2002**, *43*, 7835. (b) Luo, S.; Zhang, B.; He, J.; Janczuk, A.; Wang, P. G.; Cheng, J.-P. *Tetrahedron Lett.* **2002**, *43*, 7369.
7. (a) Basavaiah, D.; Sreenivasulu, B.; Rao, A. J. *J. Org. Chem.* **2003**, *68*, 5983. (b) Patra, A.; Batra, S.; Joshi, B. S.; Roy, R.; Kundu, B.; Bhaduri, A. P. *J. Org. Chem.* **2002**, *67*, 5783. (c) Shi, M.; Feng, Y.-S. *J. Org. Chem.* **2001**, *66*, 406. (d) Shi, M.; Jiang, J. K.; Cui, S.-C. *Tetrahedron* **2001**, *57*, 7343. (e) Kataoka, T.; Kinoshita, H.; Kinoshita, S.; Iwamura, T.; Watanabe, S.-i. *Angew. Chem., Int. Ed.* **2000**, *39*, 2358. (f)

Shi, M.; Jiang, J.-K.; Feng, Y.-S. *Org. Lett.* **2000**, *2*, 2397. (g) Shi, M.; Jiang, J.-K. *Tetrahedron* **2000**, *56*, 4793. (h) Li, G.; Wei, H.-X.; Gao, J. J.; Caputo, T. D. *Tetrahedron Lett.* **2000**, *41*, 1.

8. (a) Pei, W.; Wei, H.-X.; Li, G. *Chem. Commun.* **2002**, 1856. (b) Pei, W.; Wei, H.-X.; Li, G. *Chem. Commun.* **2002**, 2412.
9. (a) Kinoshita, H.; Kinoshita, S.; Munechika, Y.; Iwamura, T.; Watanabe, S.-i.; Kataoka, T. *Eur. J. Org. Chem.* **2003**, 4852. (b) Kinoshita, H.; Osamura, T.; Kinoshita, S.; Iwamura, T.; Watanabe, S.-i.; Kataoka, T.; Tanabe, G.; Muraoka, O. *J. Org. Chem.* **2003**, *68*, 7532.
10. (a) Hayashi, Y.; Okado, K.; Ashimine, I.; Shoji, M. *Tetrahedron Lett.* **2002**, *43*, 8683. (b) Oishi, T.; Oguri, H.; Hirama, M. *Tetrahedron: Asymmetry* **1995**, *6*, 1241.
11. Kundu, M. K.; Mukherjee, S. B.; Balu, N.; Padmakumar, R.; Bhat, S. V. *Synlett* **1994**, 444.
12. (a) Coelho, F.; Almeida, W. P.; Veronese, D.; Mateus, C. R.; Silva Lopes, E. C.; Rossi, R. C.; Silveira, G. P. C.; Pavam, C. H. *Tetrahedron* **2002**, *58*, 7437. (b) Almeida, W. P.; Coelho, F. *Tetrahedron Lett.* **1998**, *39*, 8609.
13. (a) Yadav, J. S.; Reddy, B. V. S.; Basak, A. K.; Narsaiah, A. V. *Tetrahedron* **2004**, *60*, 2131. (b) Khan, F. A.; Dash, J.; Satapathy, R.; Upadhyay, S. K. *Tetrahedron Lett.* **2004**, *45*, 3055. (c) Zhu, H.-P.; Yang, F.; Tang, J.; He, M.-Y. *Green Chem.* **2003**, *5*, 38. (d) Audic, N.; Clavier, H.; Mauduit, M.; Guillemin, J.-C. *J. Am. Chem. Soc.* **2003**, *125*, 9248. (e) Leadbeater, N. E.; Marco, M. *Chem. Rev.* **2002**, *102*, 3217.
14. Wang, Y.; Li, H.; Wang, C.; Jiang, H. *Chem. Commun.* **2004**, 1938.
15. Nguyen, H.-P.; Matondo, H.; Baboulène, M. *Green Chem.* **2003**, *5*, 303.
16. (a) Itoh, T.; Han, S.; Matsushita, Y.; Hayase, S. *Green Chem.* **2004**, *6*, 437. (b) Imrie, C.; Elago, E. R. T.; McClelland, C. W.; Williams, N. *Chem. Commun.* **2002**, 159.
17. (a) Law, M. C.; Wong, K.-Y.; Chan, T. H. *Green Chem.* **2004**, *6*, 241. (b) Yoo, K.; Namboodiri, V. V.; Varma, R. S.; Smirniotis, P. G. *J. Catal.* **2004**, *222*, 511.
18. (a) Anderson, K.; Fernández, S. C.; Hardacre, C.; Marr, P. C. *Inorg. Chem. Commun.* **2004**, *7*, 73. (b) Berthod, M.; Joerger, J.-M.; Mignani, G.; Vaultier, M.; Lemaire, M. *Tetrahedron: Asymmetry* **2004**, *15*, 2219. (c) Lee, S.-g.; Zhang, Y. J.; Piao, J. Y.; Yoon, H.; Song, C. E.; Choi, J. H.; Hong, J. *Chem. Commun.* **2003**, 2624. (d) Wolfson, A.; Vankelecom, I. F. J.; Jacobs, P. A. *Tetrahedron Lett.* **2003**, *44*, 1195.
19. (a) Kumar, A.; Pawar, S. S. *J. Org. Chem.* **2004**, *69*, 1419. (b) Yadav, J. S.; Reddy, B. V. S.; Reddy, J. S. S.; Rao, R. S. *Tetrahedron* **2003**, *59*, 1599. (c) Meracz, I.; Oh, T. *Tetrahedron Lett.* **2003**, *44*, 6465.
20. (a) Baleizão, C.; Pires, N.; Gigante, B.; Curto, M. J. M. *Tetrahedron Lett.* **2004**, *45*, 4375. (b) Gmouh, S.; Yang, H.; Vaultier, M. *Org. Lett.* **2003**, *5*, 2219.
21. (a) Wang, A.-E.; Zhong, J.; Xie, J.-H.; Li, K.; Zhou, Q.-L. *Adv. Synth. Catal.* **2004**, *346*, 595. (b) Arentsen, K.; Caddick, S.; Cloke, F. G. N.; Herring, A. P.; Hitchcock, P. B. *Tetrahedron Lett.* **2004**, *45*, 3511. (c) Jensen, J. F.; Johannsen, M. *Org. Lett.* **2003**, *5*, 3025. (d) Miao, W.; Chan, T. H. *Org. Lett.* **2003**, *5*, 5003. (e) Rajagopal, R.; Jarikote, D. V.; Srinivasan, K. V. *Chem. Commun.* **2002**, 616.
22. (a) Zhao, G.; Jiang, T.; Gao, H.; Han, B.; Huang, J.; Sun, D. *Green Chem.* **2004**, *6*, 75. (b) Kabalka, G. W.; Venkataiah, B.; Dong, G. *Tetrahedron Lett.* **2004**, *45*, 729. (c) Yang, X.-F.; Wang, M.; Varma, R. S.; Li, C.-J. *Org. Lett.* **2003**, *5*, 657.
23. (a) Xiao, J.-C.; Twamley, B.; Shreeve, J. M. *Org. Lett.* **2004**, *6*, 3845. (b) Xie, X.; Lu, J.; Chen, B.; Han, J.; She, X.; Pan, X. *Tetrahedron Lett.* **2004**, *45*, 809. (c) Xie, X.; Chen, B.; Lu, J.; Han, J.; She, X.; Pan, X. *Tetrahedron Lett.* **2004**, *45*, 6235. (d) Park, S. B.; Alper, H. *Org. Lett.* **2003**, *5*, 3209.
24. Bernini, R.; Coratti, A.; Fabrizi, G.; Goggiamani, A. *Tetrahedron Lett.* **2003**, *44*, 8991.
25. Song, C. E.; Shim, W. H.; Roh, E. J.; Lee, S.-g.; Choi, J. H. *Chem. Commun.* **2001**, 1122.
26. (a) Hsu, J.-C.; Yen, Y.-H.; Chu, Y.-H. *Tetrahedron Lett.* **2004**, *45*, 4673. (b) Kim, E. J.; Ko, S. Y. *Helv. Chim. Acta* **2003**, *86*, 894. (c) Pégot, B.; Vo-Thanh, G.; Gori, D.; Loupy, A. *Tetrahedron Lett.* **2004**, *45*, 6425–6428. (d) Aggarwal, V. K.; Emme, I. *Chem. Commun.* **2002**, 1612–1613.
27. (a) Boovanahalli, S. K.; Kim, D. W.; Chi, D. Y. *J. Org. Chem.* **2004**, *69*, 3340. (b) Li, D.; Shi, F.; Peng, J.; Guo, S.; Deng, Y. *J. Org. Chem.* **2004**, *69*, 3582. (c) Yadav, J. S.; Reddy, B. V. S.; Premalatha, K. *Adv. Synth. Catal.* **2003**, *345*, 948. (d) Kawanami, H.; Sasaki, A.; Matsui, K.; Ikushima, Y. *Chem. Commun.* **2003**, 896. (e) Kim, D. W.; Song, C. E.; Chi, D. Y. *J. Org. Chem.* **2003**, *68*, 4281. (f) Chiappe, C.; Pieraccini, D.; Saullo, P. *J. Org. Chem.* **2003**, *68*, 6710. (g) Zerth, H. M.; Leonard, N. M.; Mohan, R. S. *Org. Lett.* **2003**, *5*, 55.
28. (a) Bortolini, O.; Bottai, M.; Chiappe, C.; Conte, V.; Pieraccini, D. *Green Chem.* **2002**, *4*, 621. (b) Lévêque, J.-M.; Luche, J.-L.; Pétrier, C.; Roux, R.; Bonrath, W. *Green Chem.* **2002**, *4*, 357.
29. Lizarzaburu, M. E.; Shuttleworth, S. J. *Tetrahedron Lett.* **2002**, *43*, 2157.
30. Heidelberg, T.; Martin, O. R. *J. Org. Chem.* **2004**, *69*, 2290.
31. Iwamura, T.; Fujita, M.; Kawakita, T.; Kinoshita, S.; Watanabe, S.-i.; Kataoka, T. *Tetrahedron* **2001**, *57*, 8455.
32. Eggert, U.; Poly, W.; Hoffmann, H. M. R. *Angew. Chem.* **1987**, *99*, 1047.
33. Huang, J.-W.; Shi, M. *Adv. Synth. Catal.* **2003**, *345*, 953.
34. Basavaiah, D.; Hyma, R. S.; Kumaragurubaran, N. *Tetrahedron* **2000**, *56*, 5905.
35. Shi, M.; Jiang, J.-K.; Li, C.-Q. *Tetrahedron Lett.* **2002**, *43*, 127.
36. Yu, C.; Liu, B.; Hu, L. *J. Org. Chem.* **2001**, *66*, 5413.
37. Nascimento, M. G.; Zanotto, S. P.; Melegari, S. P.; Fernandes, L.; Sá, M. M. *Tetrahedron: Asymmetry* **2003**, *14*, 3111.
38. Poly, W.; Schomburg, D.; Hoffmann, H. M. R. *J. Org. Chem.* **1988**, *53*, 3701.
39. Basavaiah, D.; Muthukumaran, K. *Tetrahedron* **1998**, *54*, 4943.
40. Rosa, J. N.; Afonso, C. A. M.; Santos, A. G. *Tetrahedron* **2001**, *57*, 4189.
41. Yu, C.; Liu, B.; Hu, L. *J. Org. Chem.* **2001**, *66*, 5413.

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Complementary regioselective esterification of non-reducing oligosaccharides catalyzed by different hydrolases

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Abstract—The enzymatic transesterification of several tri- and tetrasaccharides with vinyl laurate is described. The lipases from *Candida antarctica* B (Novozym 435) and *Thermomyces lanuginosus* (Lipozyme TL IM) and the alkaline protease from *Bacillus licheniformis* (subtilisin Carlsberg) have been used with each carbohydrate to obtain different regioisomers. By using the sugars in their amorphous form, complete solubility is achieved in the reaction media (*tert*-butanol/pyridine mixtures for the lipases and pyridine for the protease) and high isolated yields of the corresponding monoesters are obtained. Good to excellent regioselectivity is observed for all the enzymes, showing a final complementary picture respect to the primary hydroxyls of the oligosaccharides studied.

1. Introduction

Carbohydrate fatty acid esters are non-ionic surfactants with broad applications in food, cosmetic and pharmaceutical industries.[1] They are biodegradable, non-toxic and can be produced from inexpensive and renewable raw materials.[2] Their emulsifying and surfactant properties[3] may be modulated by the type of fatty acid, the sugar moiety, the degree of substitution and the position of attachment to the fatty acid (for instance regioisomeric sucrose monoesters present different CMC values).[4]

Regioselective chemical acylation of carbohydrates is a particular challenging task due to their multifunctionality.[5] For this reason, tedious multi-step synthesis based on protection/deprotection reactions is usually required.[6] The use of enzymes in organic solvents has helped to solve this problem and both, lipases[7] and proteases[8] have been employed for the regioselective acylation of carbohydrates.[9] Different factors affect the activity, stability and selectivity of hydrolases in non-aqueous media.[10] The nature of the solvent is particularly important since a compromise between enzyme activity and saccharide solubility is required. This is even more important in the case of lipases that are active in hydrophobic solvents limiting acylation mainly to mono- and disaccharides.[11] To our knowledge, only three previous examples of enzymatic acylation of tri- and tetrasaccharides have been described in the literature. Riva et al.[12,13] synthesized a series of esterified tri- and tetrasaccharides by using subtilisin in dimethylformamide and trihaloethyl butyrates as the acylating agents to get ca. 29–50% isolated yields. Subtilisin showed a strong preference towards the regioselective esterification of the primary hydroxyls of the fructose unit in fructose-containing oligosaccharides and to the $6''$-OH in the non-reducing glucose of maltotriose. Ferrer et al.[14] prepared long-chain fatty acid esters of maltotriose using the lipase from *Thermomyces lanuginosus* (previously *Humicola Lanuginosa*) in a medium constituted by two miscible solvents (2-methyl-2-butanol/dimethylsulfoxide). The hydroxyl $6''$-OH in the non-reducing end of the trisaccharide was acylated in low yields with 20% DMSO mixtures. Higher yields could be obtained by using 5% DMSO mixtures, but 10% of diesters were formed under these reaction conditions. Recently, Gustavsson et al.[15] reported similar reaction conditions using the lipase from *Candida antarctica* B for the transesterification of xyloglucan oligosaccharides mixtures with vinyl stearate obtaining 14% yield and some disubstitution (less than 10% of the total acylated products).

We were interested in preparing fatty acid esters of tri- and tetrasaccharides in order to study the relevance of the specific carbohydrate, its size and acylation position in the physicochemical properties of this type of non-ionic

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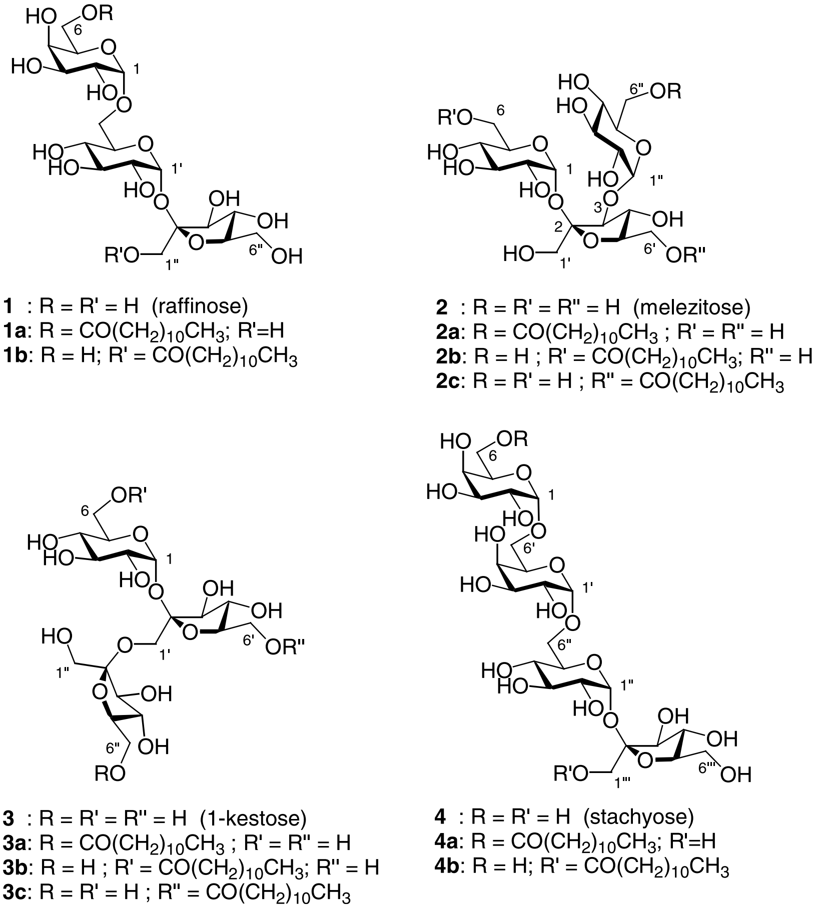

1 : R = R' = H (raffinose)
1a: R = $CO(CH_2)_{10}CH_3$; R'=H
1b: R = H; R' = $CO(CH_2)_{10}CH_3$

2 : R = R' = R'' = H (melezitose)
2a: R = $CO(CH_2)_{10}CH_3$; R' = R'' = H
2b: R = H ; R' = $CO(CH_2)_{10}CH_3$; R'' = H
2c: R = R' = H ; R'' = $CO(CH_2)_{10}CH_3$

3 : R = R' = R'' = H (1-kestose)
3a: R = $CO(CH_2)_{10}CH_3$; R' = R'' = H
3b: R = H ; R' = $CO(CH_2)_{10}CH_3$; R'' = H
3c: R = R' = H ; R'' = $CO(CH_2)_{10}CH_3$

4 : R = R' = H (stachyose)
4a: R = $CO(CH_2)_{10}CH_3$; R'=H
4b: R = H; R' = $CO(CH_2)_{10}CH_3$

Scheme 1.

surfactants. Moreover, recently reported antibacterial activity of 6″-*O*-laourylmaltotriose[16] and antitumoral activity of 6″-*O*-palmitoylmaltotriose[17] confirm the interest in developing selective methods for the preparation of large-oligosaccharide fatty acid esters. In this work, we present the enzymatic transesterification of the non-reducing oligosaccharides raffinose, melezitose, 1-kestose and stachyose with vinyl laurate. The reactions were performed in *tert*-butanol/pyridine mixtures with lipases from *Thermomices lanuginosus* (Lipozyme TL IM) and from *Candida antarctica* B (Novozym 435), and in pyridine with the alkaline protease from *Bacillus licheniformis* (subtilisin Carlsberg). The three enzymes studied gave high isolated yields of the sugar monoesters and only small amounts of diesters were produced. Regioselectivity for each oligosaccharide and enzyme is also discussed showing a complementary behaviour that allows the access to a particular regioisomer by selecting the appropriate hydrolase.

2. Results and discussion

All the commercially available non-reducing oligosaccharides considered in this investigation contain a sucrose moiety in their chemical structure (Scheme 1) The tri- and tetrasaccharides raffinose (**1**) and stachyose (**4**) can be considered as sucrose molecules substituted at the C-6 hydroxyl group while the trisaccharides melezitose (**2**) and 1-kestose (**3**) can be considered as a C-3′ hydroxyl-glucosylated sucrose and a C-1′ hydroxyl-fructosylated sucrose, respectively. This common structural feature led us to select the three different hydrolases indicated in the introduction because they have previously shown different regioselectivity in the acylation of sucrose.[12,18]

In all these enzyme-catalyzed transesterifications, vinyl laurate was chosen as acyl donor. We decided to use the amorphous form of each oligosaccharide obtained by lyophilization to increase the solubility of the sugars in organic solvents with the additional advantage of removing almost all the water of crystallization.[19] The regioisomeric distribution in the isolated products was determined by HPLC/MS (see Supplementary data) and the structure of main regioisomers was established by NMR. The position of esterification was determined by correlation bidimensional analysis ^1H–^1H (COSY) and ^1H–^{13}C NMR (HSQC, HMBC) and in some cases using 1D selective TOCSY and HSQC-TOCSY experiments.

Transesterifications catalyzed by Candida antarctica lipase B

First, we investigated the esterification of raffinose (**1**) with lipase Novozym 435, an immobilized preparation of *C. antarctica* lipase B on a macroporous acrylic resin. Due to the low solubility of trisaccharides in the relatively apolar solvents needed to use lipases, we tried a *tert*-butanol/pyridine (55:45) mixture at 60 °C to carry out the enzymatic reaction. The specific ratio of solvents and temperature were selected since Novozym 435 shows the highest enzyme activity in the acylation of glucose with myristic acid in the above reaction conditions.[20]

Using 0.04 M of **1** and 0.2 M acyl donor as starting concentrations, complete solubilization of the sugar was observed in the reaction media, and 48% isolated yield of raffinose monoester was obtained after 72 h of reaction (Table 1). A small proportion of starting material and diester was also observed by TLC. Analysis of raffinose monolaurate showed that only the regioisomer possessing the ester substitution at the 6-OH of the galactose unit was formed. The reaction processing is very simple since it only requires filtration, rotary-evaporation of the solvents and column chromatography of the residue. Interestingly, only one regioisomer was obtained, whereas for sucrose this lipase produces a 1:1 mixture of the 6 and 6′ esters.[11]

We extended the same reaction conditions to the other two trisaccharides: melezitose (**2**) and 1-kestose (**3**). Similarly to raffinose, a small proportion of diester and remaining starting sugar was detected by TLC. The isolated yield of monoester was 38% for melezitose and 54% for 1-kestose. The acylation of melezitose went preferentially to the 6″-OH of the glucose linked 1→3 to the fructose (69% selectivity), to some extent to the 6′-OH of the fructose unit (22% selectivity) and a small proportion to the 6-OH of the other glucose residue (9% selectivity). In the case of 1-kestose, the esterification goes to the 6″-OH of the terminal fructose with high selectivity (90%), with only 7% to the 6′-OH of the middle fructose and 3% of other regioisomers. It is remarkable the strong preference for the fructofuranosyl ring compared with the results obtained with raffinose and melezitose.

The tetrasaccharide stachyose (**4**) was the last carbohydrate tested. We used slight modifications in the reaction conditions (see Table 1) in order to achieve complete solubility of this larger oligosaccharide. After 8 days the majority of the sugar remained unreacted (as seen by TLC) giving the lowest yield (26%) of isolated monoester amongst all the oligosaccharide tested. The regioselectivity partially correlates with that observed for raffinose; 79% of the esterification went to the 6-OH of the terminal galactose and 14% to the 6‴-OH of the fructose unit.

Transesterifications catalyzed by Thermomices lanuginosus lipase

Next, we studied the esterification of the selected oligosaccharides with the immobilized form of *T. lanuginosus* lipase on granulated silica (currently commercialized under the trade name Lipozyme TL IM). We selected this type of immobilization since it has higher selectivity to monoesters than other supported preparations when used in the synthesis of sucrose esters in two-solvent mixtures.[21] In addition, it has been reported[18] that lipases from *T. lanuginosus* and *C. antarctica* acylate sucrose in the same 2-methyl-2-butanol/DMSO mixtures. This observation lead us to use Lipozyme TL IM in the same *tert*-butanol/pyridine reaction mixtures described above for Novozym 435.

When we carried out the esterification reaction with Lipozyme TL IM for raffinose (**1**), the same regioisomer as for lipase Novozym 435 was obtained, but the isolated yield was much higher (79%) and the reaction time much shorter (24 h). Actually, the conversion of the reaction was 89% as determined by HPLC and no diester formation was detected (by TLC or HPLC) even at prolonged reaction times (Fig. 1).

In the case of trisaccharides melezitose (**2**) and 1-kestose (**3**), similar reactivity was found for both sugars, although this was lower than for raffinose, requiring longer reaction time to reach the plateau of conversion (Fig. 1). The isolated yield of monoester after 72 h was 54% for melezitose and 57% for 1-kestose. Some starting material remained unreacted and only traces of diester were observed. The preferred position of acylation in the case of melezitose was the 6-OH of the glucose linked 1→2 to the fructose (61% selectivity) while partial acylation occured at the primary hydroxyl of the other glucose unit (33% selectivity) and at the fructosyl 6′-OH (4% selectivity). On the other hand, 1-kestose was acylated at the 6-OH of the terminal glucose with 87% selectivity along with 13% of other unidentified regioisomers. This can be considered a high regioselectivity taking into account that 1-kestose has four primary hydroxyls (one more than raffinose) in its structure.

The esterification of the tetrasaccharide stachyose (**4**) with Lipozyme TL IM was also carried out using the same reaction conditions as with Novozym 435. Surprisingly, the initial reaction rate was very similar to the rate observed for **2** and **3** but after 3 days higher isolated yield of monoester was obtained (68%) with an excellent selectivity (96%)

Table 1. Acylation of tri- and tetrasaccharides using Novozym 435 and vinyl laurate as acylating agent

Carbohydrate	Solvent	Temperature (°C)	Reaction time (h)	Yield (%)	Position of acylation	Selectivity (%)
Raffinose	*t*-BuOH–pyridine (55/45)	60	72	48	Galactosyl 6-OH	>99
Melezitose	*t*-BuOH–pyridine (55/45)	60	72	38	Glucosyl linked 1→3, 6″-OH	69
					Fructosyl 6′-OH	22
					Glucosyl linked 1→2, 6-OH	9
Kestose	*t*-BuOH–pyridine (55/45)	60	72	54	Terminal Fructosyl 6″-OH	90
					Middle Frutosyl 6′-OH	7
Stachyose	*t*-BuOH–pyridine (50/50)	65	192	26	Galactosyl 6-OH	79
					Fructosyl 6‴-OH	14

Yields are referred to isolated monoester and selectivity corresponds to percentage of each regioisomer of saccharide monoester as found by HPLC/MS.

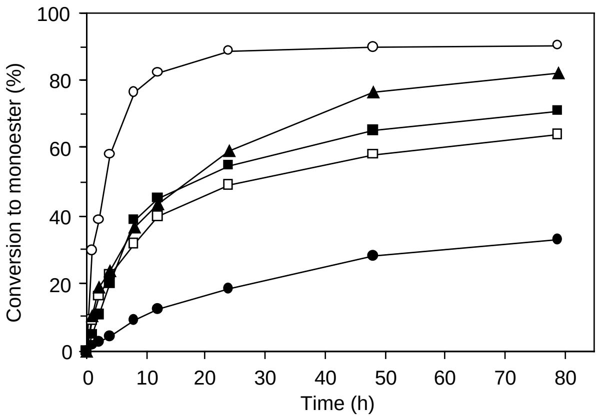

Figure 1. Kinetics of transesterification of the non-reducing oligosaccharides with vinyl laurate catalysed by Lipozyme TL IM. Conditions: (A) 0.04 M trisaccharide, 0.2 M vinyl laurate, 10 mg/ml biocatalyst, 10 mg/ml 3 Å molecular sieves, *t*-BuOH/pyridine (55:45), 60 °C. [raffinose (○), melezitose (□), 1-kestose (■)]. (B) 0.026 M tetrasaccharide, 0.131 M vinyl laurate, 8 mg/ml biocatalyst, 8 mg/ml 3 Å molecular sieves, *t*-BuOH–pyridine (50/50), 65 °C [stachyose (▲)]. (C) 0.1 M trisaccharide, 0.5 M vinyl laurate 25 mg/ml biocatalyst, 25 mg/ml 3 Å molecular sieves, pyridine, 60 °C [raffinose (●)].

towards the 6-OH of the terminal galactose. A negligible amount of diacylated product was formed in this case.

T. lanuginosus lipase (immobilized on Celite) has previously shown better conversion than Novozym 435 in the acylation of sucrose with vinyl laurate,[18] what clearly agrees with the results we have obtained for the tri- and tetrasaccharides studied. It is also important to note that our isolated yields (54–79%) are higher than the previously reported in the literature[14] for the transesterification of maltotriose with vinyl laurate employing *T. lanuginosus* lipase (immobilized on Celite) in 2-methyl-2-butanol containing 20% DMSO, although we use longer reaction times and lower substrate concentration, what may be important for scale-up reactions. In any case, the *tert*-butanol/pyridine mixtures seem to be a good reaction media. In fact, we have observed that Lipozyme TL IM has significant activity in the transesterification of raffinose in pyridine (Fig. 1).

The regioselectivity we have found (Tables 1 and 2) is different for both lipases (with the only exception of raffinose). Although the overall fold and catalytic machinery of the two enzymes are very similar, there are important structural differences that may explain the different behaviour. *C antarctica* lipase has a large binding pocket and likely no amphiphilic lid over it while in *T. lanuginosus* lipase the binding pocket is less spacious and occluded by an helical lid.[22,23] Furthermore, computational studies of sucrose transesterification with vinyl laurate catalyzed by these lipases[24] have shown that not only the different binding pocket shape but also the different motion of the pocket during catalysis may explain the different regioselectivity observed with each lipase.

Transesterifications catalyzed by subtilisin Carlsberg

It has been reported that co-lyophilization of subtilisin Carlsberg with methyl-β-cyclodextrin (MβCD) improves the enzyme activity and enantioselectivity in organic solvents.[25] This form of the biocatalyst is superior to both the simple lyophilised powder and the cross-linked enzyme crystals (CLEC) preparations.[26] We decided to employ the MβCD-subtilisin Carlsberg preparation in our oligosaccharide acylations expecting to obtain good yields with high levels of regioselectivity.

Subtilisin catalyzes carbohydrate acylation in DMF and pyridine;[12] although the former is a better solvent for oligosaccharides, the use of the amorphous form of the sugars allowed us to employ pyridine at 40 °C facilitating the processing of the reaction. Using 0.2 M of raffinose (**1**) and 0.6 M of vinyl laurate in the presence of 22 mg/ml biocatalyst under vigorous stirring, high conversion was observed by TLC after 24 h and only traces of diester were noticed. Raffinose monoester was isolated in 74% yield with excellent regioselectivity (98%) towards the 1″-OH of the fructose moiety (Table 3).

Similar reaction conditions were employed for the remaining oligosaccharides. After 48 h, reactions were stopped when traces of diester were observed, although a small amount of starting material remained unreacted. Reaction over the tetrasaccharide stachyose (**4**) showed a great correlation with that of raffinose producing acylation in the same hydroxyl of the fructose unit (98% selectivity) and similar isolated yield (76%). On the other hand, acylation of melezitose and kestose went preferentially towards the 6′-OH of the central fructose in both cases.

The regioselectivity observed for stachyose is similar to the reported by Riva et al.[13] for acylation with trifluoroethyl butyrate in DMF, but for raffinose and melezitose our esterification conditions with vinyl laurate produce higher regioselectivity. Futhermore, we have obtained higher isolated yields by using MβCD-subtilisin Carlsberg preparation than those described for carbohydrate acylation using a CLEC preparation of subtilisin[27] or a lyophilized

Table 2. Acylation of tri- and tetrasaccharides using Lipozyme TL IM and vinyl laurate as acylating agent

Carbohydrate	Solvent	Temperature (°C)	Reaction time (h)	Yield (%)	Position of acylation	Selectivity (%)
Raffinose	*t*-BuOH–pyridine (55/45)	60	24	79	Galactosyl 6-OH	>99
Melezitose	*t*-BuOH–pyridine (55/45)	60	72	54	Glucosyl linked 1→2, 6-OH	61
					Glucosyl linked 1→3, 6″-OH	33
					Fructosyl 6′-OH	4
Kestose	*t*-BuOH–pyridine (55/45)	60	72	57	Glucosyl 6-OH	87
Stachyose	*t*-BuOH–pyridine (50/50)	65	72	68	Galactosyl 6-OH	96
					Fructosyl 1‴-OH	4

Yields are referred to isolated monoester and selectivity corresponds to percentage of each regioisomer of saccharide monoester as found by HPLC/MS.

Table 3. Acylation of tri- and tetrasaccharides using MβCD-Subtilisin Carlsberg preparation and vinyl laurate as acylating agent

Carbohydrate	Solvent	Temperature (°C)	Reaction time (h)	Yield (%)	Position of acylation	Selectivity (%)
Raffinose	Pyridine	40	24	74	Fructosyl 1″-OH	98
Melezitose	Pyridine	40	48	69	Fructosyl 6′-OH	73
					Glucosyl linked 1→2, 6-OH	16
					Glucosyl linked 1→3, 6″-OH	6
Kestose	Pyridine	40	48	55	Middle Fructosyl 6′-OH	69
					Glucosyl 6-OH	11
					Terminal Fructosyl 6″-OH	10
Stachyose	Pyridine	40	48	76	Fructosyl 1‴-OH	98

Yields are referred to isolated monoester and selectivity corresponds to percentage of each regioisomer of saccharide monoester as found by HPLC/MS.

subtilisin powder.[13] Computational studies of Subtilisin-catalyzed transesterification of sucrose[28] have shown that entropic factors are crucial in the enzyme regioselectivity. Modelling of the possible tetrahedral transition-state adducts find that in the 1′OH-adduct the sucrose moiety is the most solvent exposed. This exposure confers a higher mobility upon the sucrose, which translates into a larger entropic stabilization. This approach also explains the results obtained with raffinose and stachyose as these compounds can be considered as sucrose derivatives modified at their glucosyl C-6 hydroxyl. It is probable than the 6′-OH adduct in both melezitose and 1-kestose is also the most solvent exposed.

In summary, we have carried out one-step acylation of tri- and tetrasaccharides catalyzed by hydrolases in good isolated yields. Key aspects in the reaction conditions are the use of the amorphous form of the saccharides and the specific solvent (*tert*-butanol/pyridine mixtures for lipases and pyridine for the protease). Moreover, it is the first time that these non-reducing oligosaccharides are acylated using lipases and are transesterified with a long chain acyl donor using subtilisin. High selectivity has been obtained for acylation with all the enzymes employed. This allows the access to a particular regioisomer by selecting the appropriate hydrolase, showing a picture of complementary regioselective acylation of the primary hydroxyl groups. At the same time, a correlation in the enzymatic behaviour towards the pair raffinose–stachyose is observed for all used hydrolases, and to a less extent for the pair 1-kestose-melezitose. Studies of the biological and physical properties of these new non-ionic surfactants are in progress.

3. Experimental

3.1. General methods

Anhydrous pyridine and vinyl laurate were supplied by Fluka; anhydrous *tert*-butanol, molecular sieves (3 Å, 8–12 mesh) and methyl-β-cyclodextrin from Aldrich; raffinose and melezitose from Sigma and stachyose and 1-kestose from TCI Chemicals. All the carbohydrates were used in their amorphous form prepared by lyophilization of the corresponding aqueous solutions. Granulated lipase from *T. lanuginosus* (Lipozyme TL IM), immobilized lipase from *C. antarctica* B (Novozym 435) and subtilisin Carslberg (purified powder) were kindly donated by Novozymes A/S. Molecular sieves were preactivated at ca. 350 °C for 12 h. All reactions were monitored by TLC on precoated Silica-Gel 60 plates (Alugram Sil G/UV$_{254}$ supplied by Macherey-Nagel), and detected by heating with Mostain (500 ml of 10% H_2SO_4, 25 g of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, 1 g $Ce(SO_4)_2\cdot 4H_2O$). The elution system was $CHCl_3$–MeOH (2.5/1) for the reactions involving trisaccharides and EtOAc–MeOH–H_2O (7/5/1) for the reactions with stachyose. Products were purified by flash chromatography with Aldrich Silica gel 60 (200–400 mesh) using a gradient of chloroform/methanol 5:1 to 2:1 (v/v) for the trisaccharides monolaurates and 5:1 to 1:1 v/v for the stachyose monolaurates.

NMR spectra were recorded on either a Bruker AVANCE 300 or ARX 400 [300 or 400 MHz (^{1}H) and 75 or 100 (^{13}C)] at room temperature for solutions in CD_3OD. Chemical shifts are referred to the methanol multiplet, centered at 3.31 ppm for ^{1}H NMR and 49.0 ppm for ^{13}C NMR. Optical rotations (Sodium D line) were measured at 20 °C with a Perkin-Elmer 241 for pure regioisomers (those oligosaccharide monolaurates obtained with $>95\%$ regioselectivity). High resolution FAB (+) mass spectral analyses were obtained on a Micromass AutoSpec-Q spectrometer. Infrared spectra were recorded using a Nicolet 20SXB FTIR spectrophotometer.

Analysis of the regioisomeric distribution of the isolated monoesters and the kinetic study of reactions catalyzed by Lipozyme TL IM were carried out by HPLC/MS. A Waters Alliance 2695 separation module was employed with a Waters Spherisorb 3 μm ODS2 column (4.6×250 mm) and a Waters Micromass ZQ mass spectrometer detector. The temperature of the column was set to 40 °C. Flow rate was 1.1 ml/min with splitting before the detection module. Mobile phases were acetonitrile/water mixtures in isocratic conditions. The ratio changed depending on the application as follows: for the analysis of the regioisomeric distribution of trisaccharide monolaurates, acetonitrile/water 35:65 (v:v) and for the more polar stachyose monolaurates, 30:70 (v:v); for the analysis of the kinetics of trisaccharide reactions, acetonitrile/water 45:55 (v:v) and for the stachyose reaction, 40:60 (v:v). Detection was done with positive ESI ionization in both Scan and SIR modes. For the kinetics studies, alliquots were concentrated to dryness, diluted with water and extracted with hexane to remove excess of vinyl laurate, prior to analysis.

3.2. General method for the transesterifications catalyzed by Novozym 435

Raffinose, melezitose or 1-kestose (202 mg, 0.4 mmol) were dissolved in anhydrous pyridine (4.5 ml) at 60 °C before careful addition of preheated (60 °C) anhydrous *tert*-butanol (5.5 ml). Novozym 435 (100 mg) and 3 Å molecular sieves (100 mg) were then added and the suspension maintained 30 min at 60 °C with orbital shaking (250 rpm). Finally, vinyl laurate (457 mg, 2 mmol) was added. When conversion stopped by TLC, the mixture was cooled and filtered. The solvent was evaporated under vacuum at 45 °C eliminating last traces of pyridine by co-evaporation with toluene. The remaining residue was subjected to flash chromatography. Concentration of pure fractions in vacuo afforded the monolaurates as amorphous white solids.

The tetrasaccharide stachyose (210 mg, 0.315 mmol) was dissolved in anhydrous pyridine (6 ml) at 65 °C before careful addition of preheated (65 °C) anhydrous *tert*-butanol (6 ml). Novozym 435 (100 mg) and 3 Å molecular sieves (100 mg) were then added and the suspension maintained 30 min at 65 °C with orbital shaking (250 rpm). Finally, vinyl laurate (360 mg) was added. The reaction was monitored and processed as described for trisaccharides.

3.2.1. 6-*O*-Lauroylraffinose (1a). The general procedure outlined above was followed. After 3 days the reaction was stopped and the monoester isolated (132 mg, 48%). Only regioisomer **1a** was obtained (HPLC/MS). $R_f=0.34$; $[\alpha]_D$ +80.7 (*c* 7 in methanol); ν_{max} (cm^{-1}) (KBr disks): 3410 br (O–H), 1730 (C=O); HRMS (FAB): calcd for $C_{30}H_{54}O_{17}Na$ $(M+Na^+)$ 709.325871, found 709.324561; ^1H NMR (CD_3OD, 400 MHz): δ 5.40 (d, 1H, $J_{1'-2'}=3.7$ Hz, H-1′), 4.87 (d partially overlapped with residual water, 1H, H-1), 4.24 (m, 1H, H-6a), 4.22 (dd, 1H, $J_{6a-b}=11.3$ Hz, $J_{6b-5}=2.6$ Hz, H-6b), ca. 4.10 (m, 2H, H-3″, H-4″); ca. 4.04 (m, 2H, H-5, H-5′), 3.88 (br.d, 1H, $J=3.0$ Hz, H-4), 3.83 (dd, 1H, $J_{6'a-b}=11.1$ Hz, $J_{6'a-5'}=6.1$ Hz, H-6′a), ca. 3.81 (m, 1H, H-3), ca. 3.76 (m, 3H, H-5″, H6″a, H6″b), ca. 3.73 (m, 1H, H-2), 3.71 (t, 1H, $J_{2'-3'}=J_{3'-4'}=9.4$ Hz, H-3′) ca. 3.70 (m, 1H, H-6′b), 3.64 (d, 1H, $J_{1''a-b}=12.3$ Hz, H-1″a), 3.60 (d, 1H, $J_{1''a-b}=12.3$ Hz, H-1″b), 3.43 (dd, 1H, $J_{2'-3'}=9.7$ Hz, $J_{1'-2'}=3.7$ Hz, H-2′), 3.26 (t, 1H, $J_{3'-4'}=J_{4'-5'}=9.5$ Hz, H-4′), 2.34 (t, 2H, $J=7.4$ Hz, –CH_2–CO–), 1.61 (m, 2H, CH_2–CH_2–CO–), 1.29 (m, 16H, –CH_2– chain), 0.90 (t, 3H, $J=6.8$ Hz, CH_3–); ^{13}C NMR (CD_3OD, 100 MHz): δ 175.4 (C=O), 105.3 (C-2″), 100.5 (C-1), 93.4 (C-1′), 83.5 (C-5″), 79.1 (C-3″), 75.4 (C-4″), 74.4 (C-3′), 73.2 (C-5′), 73.1 (C-2′), 72.1 (C-4′), 71.1 (C-3), 70.9 (C-4), 70.3 (C-2), 69.9 (C-5), 68.5 (C-6′), 64.9 (C-6), 64.2 (C-1″), 63.3 (C-6″), 35.0 (–CH_2–CO–), 33.1, 30.7, 30.6, 30.5, 30.4, 30.2, 26.0, 23.7 (–*C*H_2-lauroyl backbone), 14.5 (*C*H_3-lauroyl).

3.2.2. 6″-*O*-Lauroylmelezitose (2a). The general procedure outlined above was followed. After 3 days the reaction was stopped and the monoester isolated (104 mg, 38%). $R_f=0.63$; ν_{max} (cm^{-1}) (KBr disks): 3400 br (O–H), 1725 (C=O); HRMS (FAB): calcd for $C_{30}H_{54}O_{17}Na$ $(M+Na^+)$ 709.325871, found 709.326346. Regioisomeric proportion 6″/6′/6=69/22/9 (HPLC/MS). NMR assignments of main regioisomer **2a** ^1H NMR (CD_3OD, 400 MHz): δ 5.47 (d, 1H, $J_{1-2}=3.8$ Hz, H-1), 5.08 (d, 1H, $J_{1''-2''}=3.6$ Hz, H-1″), 4.42 (dd, 1H, $J_{6''a-b}=11.6$ Hz, $J_{6''a-5''}=1.5$ Hz, H-6″a), 4.29 (t, 1H, $J_{3'-4'}=J_{4'-5'}=7.7$ Hz, H-4′), 4.24 (dd, 1H, $J_{6''a-b}=11.6$ Hz, $J_{6''b-5''}=6.4$ Hz, H-6″b), 4.19 (d, 1H, $J_{3'-4'}=7.7$ Hz, H-3′), 4.11 (m, 1H, H-5″), 3.91 (m, 1H, H-5), 3.85 (dd, 1H, $J_{6a-b}=11.9$ Hz, $J_{6a-5}=1.4$ Hz, H-6a), ca. 3.78 (m, 2H, H6′a, H6′b), ca. 3.73 (m, 1H, H-5′) ca. 3.72 (m, 1H, H1′a), 3.70 (dd, 1H, $J_{6a-b}=11.9$ Hz, $J_{6b-5}=4.9$ Hz, H-6b), 3.69 (t, 1H, $J_{2''-3''}=J_{3''-4''}=9.6$ Hz, H-3″), 3.62 (t, 1H, $J_{2-3}=J_{3-4}=9.6$ Hz, H-3), 3.58 (d, 1H, H-1′b), 3.43 (dd, 1H, $J_{2-3}=9.7$ Hz, $J_{1-2}=3.8$ Hz, H-2), 3.41 (dd, 1H, $J_{2''-3''}=9.7$ Hz, $J_{1''-2''}=3.8$ Hz, H-2″), 3.35 (t, 1H, $J_{3''-4''}=J_{4''-5''}=9.6$ Hz, H-4″), 3.31 (t, 1H, $J_{3-4}=J_{4-5}=9.6$ Hz, H-4), 2.37 (t, 2H, $J=7.5$ Hz, –CH_2–CO–), 1.61 (m, 2H, CH_2–CH_2–CO–), 1.29 (m, 16H, –CH_2– chain), 0.90 (t, 3H, $J=6.8$ Hz, CH_3–); ^{13}C NMR (CD_3OD, 100 MHz): δ 175.5 (C=O), 105.3 (C-2′), 101.6 (C-1″), 93.2 (C-1), 85.7 (C-3′), 83.7 (C-5′), 75.1 (C-3), 74.8 (C-3″, C-4′), 74.2 (C-5), 73.6 (C-2″), 73.2 (C-2), 71.8 (C-4″), 71.7 (C-5″, C-4), 64.8 (C-6″), 64.6 (C-1′), 63.3 (C-6′), 62.6 (C-6), 35.0 (–*C*H_2–CO–), 33.1, 30.7, 30.6, 30.4, 30.2, 26.0, 23.7 (–*C*H_2-lauroyl backbone), 14.4 (*C*H_3-lauroyl).

3.2.3. 6″-*O*-Lauroyl(1-kestose) (3a). The general procedure outlined above was followed. After 3 days the reaction was stopped and the monoester isolated (148 mg, 54%). $R_f=0.33$; ν_{max} (cm^{-1}) (KBr disks): 3400 br (O–H), 1730 (C=O); HRMS (FAB): calcd for $C_{30}H_{54}O_{17}Na$ $(M+Na^+)$ 709.325871, found 709.324767. Main regioisomer **3a** was produced with 90% regioselectivity (HPLC/MS). NMR assignments of **3a** ^1H NMR (CD_3OD, 400 MHz): δ 5.38 (d, 1H, $J_{1-2}=3.8$ Hz, H-1), 4.41 (dd, 1H, $J_{6''a-b}=11.8$ Hz, $J_{6''a-5''}=8.0$ Hz, H-6″a), 4.23 (dd, 1H, $J_{6''a-b}=11.8$ Hz, $J_{6''b-5''}=3.0$ Hz, H-6″b), 4.19 (d, 1H, $J_{3'-4'}=8.4$ Hz, H-3′), 4.12 (d, 1H, $J_{3''-4''}=8.1$ Hz, H-3″), 4.02 (m, 1H, H4′), 4.00 (m, 1H, H4″), 3.91 (td, 1H, $J_{4''-5''}=J_{5''-6''a}=7.9$ Hz, $J_{5''-6''b}=3.0$ Hz, H-5″), 3.81 (m, 2H, H-5, H1′a), ca. 3.77 (m, 1H, H-1′b), ca. 3.76 (m, 3H, H-5′, H6′a, H-6′b), ca. 3.71 (m, 2H, H-6a, H-6b), 3.67 (t, 1H, $J_{2-3}=J_{3-4}=9.4$ Hz, H-3), 3.65 (d, 1H, $J_{1''a-b}=12.0$ Hz, H-1″a), 3.58 (d, 1H, $J_{1''a-b}=12.0$ Hz, H-1″b), 3.38 (dd, 1H, $J_{2-3}=9.6$ Hz, $J_{1-2}=3.8$ Hz, H-2), 3.34 (t, 1H, $J_{3-4}=J_{4-5}=9.4$ Hz, H-4), 2.36 (t, 2H, $J=7.5$ Hz, –C*H_2*–CO–), 1.61 (m, 2H, C*H_2*–CH_2–CO–), 1.29 (m, 16H, –CH_2– chain), 0.90 (t, 3H, $J=6.8$ Hz, CH_3–); ^{13}C NMR (CD_3OD, 100 MHz): δ 175.5 (C=O), 105.6 (C-2″), 104.9 (C-2′), 94.1 (C-1), 83.6 (C-5′), 80.7 (C-5″), 79.5 (C-3′), 78.6 (C-3″), 77.3 (C-4″), 75.6 (C-4′), 74.8 (C-3), 74.4 (C-5), 73.3 (C-2), 71.5 (C-4), 66.8 (C-6″), 63.2 (C-6′), 62.9 (C-1′), 62.3 (C-6), 61.9 (C-1″), 35.0 (–*C*H_2–CO–), 33.1, 30.7, 30.6, 30.4, 30.2, 26.0, 23.7 (–*C*H_2-lauroyl backbone), 14.4 (*C*H_3-lauroyl).

3.2.4. 6-*O*-Lauroylstachyose (4a). The general procedure outlined above was followed. After 8 days the reaction was stopped and the monoester isolated (69 mg, 26%). Regioisomeric proportion 6/6‴=79/14%+7% other regioisomers (HPLC/MS). See characterization of main regioisomer **4a** in next section.

3.3. General method for the transesterifications catalyzed by Lipozyme TL IM

Exactly the same method as the Novozym 435 catalyzed reactions was used changing just the biocatalyst to Lipozyme TL IM.

3.3.1. 6-*O*-Lauroylraffinose (1a). The general procedure outlined above was followed. After 24 h the reaction was stopped and the monoester isolated (217 mg, 79%).

Only one regioisomer **1a** was obtained (HPLC/MS), which is the same obtained with Novozym 435 catalysis.

3.3.2. 6-*O*-Lauroylmelezitose (2b). The general procedure outlined above was followed. After 3 days the reaction was stopped and the monoester isolated (148 mg, 54%). R_f= 0.33; ν_{max} (cm^{-1}) (KBr disks): 3400 br (O–H), 1725 (C=O); HRMS (FAB): calcd for $C_{30}H_{54}O_{17}Na$ (M+Na$^+$) 709.325871, found 709.326346. Regioisomeric proportion 6/6″/6′=61/33/4%+2% other regioisomers (HPLC/MS). NMR assignments of main regioisomer **2b** ^{1}H NMR (CD_3OD, 400 MHz): δ 5.42 (d, 1H, J_{1-2}=3.8 Hz, H-1), 5.08 (d, 1H, $J_{1''-2''}$=3.8 Hz, H-1″), 4.44 (dd, 1H, J_{6a-b}= 12.0 Hz, J_{6a-5}=1.4 Hz, H-6a), 4.16 (dd, 1H, J_{6a-b}= 12.0 Hz, J_{6b-5}=5.6 Hz, H-6b), ca. 4.23 (m, 1H, H-4′), ca. 4.20 (m, 1H, H-3′), 4.04 (m, 1H, H-5), 3.97 (m, 1H, H-5″), ca. 3.91 (m, 1H, H-6″a), ca. 3.87 (m, 1H, H-1′a), ca. 3.85 (m, 1H, H-5′), ca. 3.70 (m, 2H, H-6′a, H-6′b), 3.69 (t, 1H, $J_{2''-3''}$=$J_{3''-4''}$=9.3 Hz, H-3″), 3.65 (dd, 1H, $J_{6''a-b}$= 12.0 Hz, $J_{6''b-5''}$=5.2 Hz, H-6″b), 3.61 (t, 1H, J_{2-3}= J_{3-4}=9.3 Hz, H-3), 3.57 (d, 1H, $J_{1'a-b}$=12.1 Hz, H-1′b), 3.43 (dd, 1H, $J_{2''-3''}$=9.8 Hz, $J_{2''-1''}$=3.7 Hz, H-2″), 3.41 (dd, 1H, J_{2-3}=9.8 Hz, J_{2-1}=3.9 Hz, H-2), 3.27 (t, 1H, $J_{3''-4''}$=$J_{4''-5''}$=9.4 Hz, H-4″), 3.26 (t, 1H, J_{3-4}=J_{4-5}= 9.4 Hz, H-4), 2.37 (t, 2H, J=7.5 Hz, –CH_2–CO–), 1.62 (m, 2H, CH_2–CH_2–CO–), 1.29 (m, 16H, –CH_2– chain), 0.90 (t, 3H, J=6.8 Hz, CH_3–); ^{13}C NMR (CD_3OD, 100 MHz): δ 175.5 (C=O), 105.4 (C-2′), 102.2 (C-1″), 93.2 (C-1), 86.1 (C-3′), 83.4 (C-5′) 75.0 (C-3), 74.7 (C-3″), 74.6 (C-4′), 73.9 (C-5″), 73.7 (C-2″), 73.1 (C-2), 72.1 (C-4″), 71.9 (C-5), 71.6 (C-4), 64.8 (C-6), 64.0 (C-1′, C-6′), 62.9 (C-6″), 34.9 (–CH_2–CO–), 33.1, 30.8, 30.7, 30.5, 30.4, 30.3, 26.0, 23.7 (–CH_2-lauroyl backbone), 14.5 (CH_3-lauroyl).

3.3.3. 6-*O*-Lauroyl(1-kestose) (3b). The general procedure outlined above was followed. After 3 days the reaction was stopped and the monoester isolated (157 mg, 57%). R_f= 0.33; ν_{max} (cm^{-1}) (KBr disks): 3400 br (O–H), 1730 (C=O); HRMS (FAB): calcd for $C_{30}H_{54}O_{17}Na$ (M+Na$^+$) 709.325871, found 709.324767. Main regioisomer **3b** was produced with 87% regioselectivity (HPLC/MS). NMR assignments for main regioisomer **3b** ^{1}H NMR (CD_3OD, 400 MHz): δ 5.39 (d, 1H, J_{1-2}=3.8 Hz, H-1), 4.39 (dd, 1H, J_{6a-b}=12.0 Hz, J_{6a-5}=1.5 Hz, H-6a), 4.20 (d, 1H, $J_{3'-4'}$= 8.4 Hz, H-3′), 4.18 (dd, 1H, J_{6a-b}=12.0 Hz, J_{6b-5}=5.0 Hz, H-6b), 4.13 (d, 1H, $J_{3''-4''}$=8.3 Hz, H-3″), ca. 4.01 (m, 1H, H-4″), 4.00 (m, 1H, H-5), ca. 3.99 (m, 1H, H-4′), 3.82 (d, 1H, $J_{1'a-b}$=10.4 Hz, H-1′a), ca. 3.77 (m, 1H, H1′b), ca. 3.76 (m, 1H, H5′), ca. 3.75 (m, 4H, H6′a, H6′b, H6″a, H6″b), ca. 3.74 (m, 1H, H-5″), 3.69 (t, 1H, J_{2-3}=J_{3-4}=9.4 Hz, H-3), 3.64 (d, 1H, $J_{1''a-b}$=12.0 Hz, H-1″a), 3.59 (d, 1H, $J_{1''a-b}$= 12.0 Hz, H-1″b), 3.39 (dd, 1H, J_{2-3}=9.7 Hz, J_{1-2}=3.8 Hz, H-2), 3.30 (t, 1H, J_{3-4}=J_{4-5}=9.4 Hz, H-4), 2.37 (t, 2H, J= 7.5 Hz, –CH_2–CO–), 1.61 (m, 2H, CH_2–CH_2–CO–), 1.29 (m, 16H, –CH_2– chain), 0.90 (t, 3H, J=6.7 Hz, CH_3–); ^{13}C NMR (CD_3OD, 100 MHz): δ 175.5 (C=O), 105.3 (C-2′), 104.9 (C-2″), 93.8 (C-1), 83.7 (C-5′), 83.4 (C-5″), 79.2 (C-3′), 78.7 (C-3″), 76.3 (C-4″), 75.7 (C-4′), 74.5 (C-3), 73.2 (C-2), 72.0 (C-5), 71.6 (C-4), 64.6 (C-6), 63.9 (C-6″), 63.7 (C-6′), 63.0 (C-1′), 62.3 (C-1″), 34.9 (–CH_2–CO–), 33.1, 30.7, 30.6, 30.5, 30.2, 26.0, 23.7 (–CH_2-lauroyl backbone), 14.4 (CH_3-lauroyl).

3.3.4. 6-*O*-Lauroylstachyose (4a). The general procedure outlined above was followed. After 3 days the reaction was stopped and the monoester isolated (183 mg, 68%). Regioisomer **4a** was obtained with >95% regioselectivity (HPLC/MS). R_f=0.63; $[\alpha]_D$ +106.9 (*c* 7 in methanol); ν_{max} (cm^{-1}) (KBr disks): 3410 br (O–H), 1730 (C=O); HRMS (FAB): calcd for $C_{36}H_{64}O_{22}Na$ (M+Na$^+$) 871.378694, found 871.378528; ^{1}H NMR (CD_3OD, 400 MHz): δ 5.41 (d, 1H, $J_{1''-2''}$=3.7 Hz, H-1″), 4.86 (d, 1H, H-1), 4.85 (d, 1H, $J_{1'-2'}$=3.6 Hz, H-1′), 4.27 (dd, 1H, J_{6a-b}=11.2 Hz, J_{6a-5}= 4.7 Hz, H-6a), 4.21 (dd, 1H, J_{6a-b}=11.2 Hz, J_{6b-5}=7.5 Hz, H-6b), 4.12 (m, 1H, H-5), ca. 4.10 (m, 2H, H-3‴, H-4‴), ca. 4.05 (m, 1H, H-5″), ca. 4.04 (m, 1H, H-5′), 3.90 (m, 1H, H-4), 3.88 (dd, 1H, 1H, $J_{6''a-b}$=11.0 Hz, $J_{6''a-5''}$=5.9 Hz, H-6″a), ca. 3.87 (m, 1H, H-4′), 3.85 (m, 1H, H-6′a), 3.83 (m, 1H, H-3), 3.81 (m, 1H, H-3′), ca. 3.77 (m, 3H, H-6‴a, H-6‴b, H-2), ca. 3.76 (m, 1H, H-5‴), ca. 3.75 (m, 1H, H-2′), 3.71 (m, 2H, H-3″, H-6″b), 3.63 (d, 1H, $J_{1'''a-b}$=12.4 Hz, H-1‴a), 3.62 (m, 1H, H-6′b), 3.60 (d, 1H, $J_{1'''a-b}$=12.4 Hz, H-1‴b), 3.44 (dd, 1H, $J_{2''-3''}$=9.7 Hz, $J_{1''-2''}$=3.7 Hz, H-2″), 3.29 ((t, 1H, $J_{3''-4''}$=$J_{4''-5''}$=9.5 Hz, H-4″), 2.37 (t, 2H, J=7.5 Hz, –CH_2–CO–), 1.62 (m, 2H, CH_2–CH_2–CO–), 1.29 (m, 16H, –CH_2– chain), 0.90 (t, 3H, J=6.8 Hz, CH_3–); ^{13}C NMR (CD_3OD, 100 MHz): δ 175.4 (C=O), 105.3 (C-2‴), 100.4 (C-1′), 99.8 (C-1), 93.4 (C-1″), 83.5 (C-5‴), 79.1 (C-3‴), 75.3 (C-4‴), 74.5 (C-3″), 73.1 (C-5″), 73.0 (C-2″), 72.1 (C-4″), 71.3 (C-3′)^a, 71.2 (C-3)^a, 71.0 (C-4, C-4′), 70.6 (C-2)^b, 70.5 (C-5′)^b, 70.1 (C-2′)^b, 69.9 (C-5), 68.4 (C-6″), 68.0 (C-6′), 64.9 (C-6), 64.2 (C-1‴), 63.2 (C-6‴), 35.0 (–CH_2–CO–), 33.1, 30.8, 30.7, 30.5, 30.3, 26.0, 23.7 (–CH_2-lauroyl backbone), 14.5 (CH_3-lauroyl). Note: ^{13}C NMR assignments marked with the same letter may be interchangeable.

3.4. General method for the transesterifications catalyzed by subtilisin Carslberg

MβCD-subtilisin Carlsberg preparation was obtained as previously described[26] using 0.1 M KOH instead of phosphate buffer for the pH adjustment in order to prevent side alkaline catalysis in the transesterificatin reactions, which would promote competitive non-regioselective acylations and even more substitution.[29]

In a typical experiment a solution of raffinose, melezitose or 1-kestose (125 mg, 0.25 mmol) in anhydrous pyridine (2 ml) and vinyl laurate (170 mg, 0.74 mmol) were shaken with vigorous magnetic stirring at 40 °C in the presence of MβCD-subtilisin Carlsberg (45 mg). When conversion stopped by TLC, the mixture was cooled and filtered. The solution was concentrated under vacuum at 45 °C eliminating last traces of pyridine by co-evaporation with toluene. The remaining residue was subjected to flash chromatography. Concentration of pure fractions in vacuo afforded the monolaurates as amorphous white solids.

For the tetrasaccharide transesterification, the enzyme (70 mg), stachyose (150 mg, 0.225 mmol) and vinyl laurate (156 mg, 0.68 mmol) were mixed in anhydrous pyridine (2 ml). The same reaction conditions and work-up described for the trisaccharides was followed.

3.4.1. 1″-*O*-Lauroylraffinose (1b). The general procedure outlined above was followed. After 24 h the reaction was stopped and the monoester isolated (127 mg, 74%). Regioisomer **1b** was obtained with 98% regioselectivity (HPLC/MS). $R_f=0.30$; $[\alpha]_D$ +94 (*c* 7 in methanol); ν_{max} (cm^{-1}) (KBr disks): 3410 br (O–H), 1735 (C=O); HRMS (FAB): calcd for $C_{30}H_{54}O_{17}Na$ (M+Na$^+$) 709.325871, found 709.326289; ^1H NMR (CD$_3$OD, 300 MHz): δ 5.41 (d, 1H, $J_{1'-2'}=3.8$ Hz, H-1′), 4.89 (d, 1H, $J_{1-2}=3.2$ Hz, H-1), 4.35 (d, 1H, $J_{1''a-b}=12.2$ Hz, H-1″a), 4.12 (d, 1H, $J_{1''a-b}=12.2$ Hz, H-1″b), 4.10 (m, 1H, H-4″), 4.09 (m, 1H, H-3″), 4.05 (m, 1H, H-5′), 3.91 (m, 1H, H-3), 3.87 (dd, 1H, $J_{6'a-b}=11.5$ Hz, $J_{6'a-5'}=6.0$ Hz, H-6′a), 3.85 (m, 1H, H-5), 3.78 (m, 1H, H-4), ca. 3.77 (m, 1H, H-2), ca. 3.75 (m, 2H, H-6″a, H-6″b), ca. 3.75 (m, 1H, H6′-b), ca. 3.73 (m, 1H, H-5″), 3.70 (m, 2H, H-6a, H-6b), 3.69 (t, 1H, $J_{2'-3'}=J_{3'-4'}=9.4$ Hz, H-3′), 3.43 (dd, 1H, $J_{2'-3'}=9.6$ Hz, $J_{1'-2'}=3.8$ Hz, H-2′), 3.32 (t, 1H, $J_{3'-4'}=J_{4'-5'}=9.2$ Hz, H-4′), 2.37 (t, 2H, $J=7.4$ Hz, –C*H*$_2$–CO–), 1.62 (m, 2H, C*H*$_2$–CH$_2$–CO–), 1.29 (m, 16H, –CH$_2$– chain), 0.90 (t, 3H, $J=6.7$ Hz, CH$_3$–); ^{13}C NMR (CD$_3$OD, 75 MHz): δ 174.8 (C=O), 104.4 (C-2″), 100.5 (C-1), 93.9 (C-1′), 83.6 (C-5″), 78.6 (C-3″), 74.7 (C-4″), 74.4 (C-3′), 73.3 (C-5′), 72.8 (C-2′), 72.4 (C-5), 72.0, (C-4′), 71.4 (C-3), 71.0 (C-4), 70.5 (C-2), 68.3 (C-6′), 64.1 (C-1″), 63.0 (C-6″), 62.8 (C-6), 35.0 (–*C*H$_2$–CO–), 33.0, 30.7, 30.6, 30.4, 30.2, 26.0, 23.7 (–*C*H$_2$-lauroyl backbone), 14.4 (*C*H$_3$-lauroyl).

3.4.2. 6′-*O*-Lauroylmelezitose (2c). The general procedure outlined above was followed. After 48 h the reaction was stopped and the monoester isolated (119 mg, 69%). $R_f=0.32$; ν_{max} (cm^{-1}) (KBr disks): 3400 br (O–H), 1725 (C=O); HRMS (FAB): calcd for $C_{30}H_{54}O_{17}Na$ (M+Na$^+$) 709.325871, found 709.325243. Regioisomeric proportion 6′/6/6″=73/16/6%+5% other regioisomers (HPLC/MS). NMR assignments of main regioisomer **2c**, ^1H NMR (CD$_3$OD, 300 MHz): δ 5.41 (d, 1H, $J_{1-2}=3.8$ Hz, H-1), 5.12 (d, 1H, $J_{1''-2''}=3.7$ Hz, H-1″), 4.43 (dd, 1H, $J_{6'a-b}=11.8$ Hz, $J_{6'a-5'}=7.7$ Hz, H-6′a), 4.35 (dd, 1H, $J_{6'a-b}=11.8$ Hz, $J_{6'a-5'}=3.7$ Hz, H-6′b), 4.34 (t, 1H, $J_{3'-4'}=J_{4'-5'}=8.1$ Hz, H-4′), 4.23 (d, 1H, $J_{3'-4'}=8.1$ Hz, H-3′), 3.95 (m, 1H, H-5′), ca. 3.90 (m, 2H, H-5, H-5″), ca. 3.88 (m, 2H, H-6a, H-6″a), 3.82 (d, 1H, $J_{1'a-b}=12.3$ Hz, H-1′a), ca. 3.69 (m, 1H, H-3″), ca. 3.68 (m, 2H, H-6b, H-6″b), ca. 3.63 (m, 1H, H-3), 3.60 (d, 1H, $J_{1'a-b}=12.3$ Hz, H-1′b), 3.42 (dd, 1H, H-2″), 3.40 (dd, 1H, H-2), ca. 3.28 (m, 2H, H-4, H-4″), 2.35 (t, 2H, $J=7.5$ Hz, –C*H*$_2$–CO–), 1.62 (m, 2H, C*H*$_2$–CH$_2$–CO–), 1.29 (m, 16H, –CH$_2$– chain), 0.90 (t, 3H, $J=6.8$ Hz, CH$_3$–); ^{13}C NMR (CD$_3$OD, 75 MHz): δ 175.5 (C=O), 105.6 (C-2′), 101.7 (C-1″), 93.1 (C-1), 85.2 (C-3′), 80.4 (C-5′), 75.7 (C-4′), 75.1 (C-3), 74.9 (C-3″), 74.0 (C-5, C-5′), 73.7 (C-2″), 73.3 (C-2), 72.1 (C-4″), 72.0 (C-4), 66.6 (C-6′), 64.2 (C-1′), 62.9 (C-6″), 62.8 (C-6), 35.0 (–*C*H$_2$–CO–), 33.1, 30.7, 30.6, 30.4, 30.2, 26.0, 23.7 (–*C*H$_2$-lauroyl backbone), 14.4 (*C*H$_3$-lauroyl).

3.4.3. 6′-*O*-Lauroyl(1-kestose) (3c). The general procedure outlined above was followed. After 48 h the reaction was stopped and the monoester isolated (94 mg, 55%). $R_f=0.33$; ν_{max} (cm^{-1}) (KBr disks): 3400 br (O–H), 1730 (C=O); HRMS (FAB): calcd for $C_{30}H_{54}O_{17}Na$ (M+Na$^+$) 709.325871, found 709.324767. Main regioisomer **3c** was produced with 69% regioselectivity (HPLC/MS). NMR assignments for main regioisomer **3c**: ^1H NMR (CD$_3$OD, 400 MHz): δ 5.37 (d, 1H, $J_{1-2}=3.8$ Hz, H-1), 4.31 (m, 2H, H6′a, H6′b), 4.20 (d, 1H, $J_{3'-4'}=8.3$ Hz, H-3′), 4.13 (d, 1H, $J_{3''-4''}=8.1$ Hz, H-3″), 4.01 (m, 1H, H-4″), 3.99 (m, 1H, H-4′), 3.89 (m, 1H, H-5′), 3.86 (d, 1H, $J_{1'a-b}=11.8$ Hz, H-1′a), 3.80 (m, 1H, H-5), ca. 3.74 (m, 3H, H-5″, H6″a, H6″b), 3.70 (m, 3H, H-1′b, H-6a, H-6b), 3.67 (t, 1H, $J_{2-3}=J_{3-4}=9.6$ Hz, H-3), 3.65 (d, 1H, $J_{1''a-b}=11.9$ Hz, H-1″a), 3.58 (d, 1H, $J_{1''a-b}=11.9$ Hz, H-1″b), 3.38 (dd, 1H, $J_{2-3}=9.7$ Hz, $J_{1-2}=3.8$ Hz, H-2), 3.33 (t, 1H, $J_{3-4}=J_{4-5}=9.6$ Hz, H-4), 2.37 (t, 2H, $J=7.5$ Hz, –C*H*$_2$–CO–), 1.61 (m, 2H, C*H*$_2$–CH$_2$–CO–), 1.29 (m, 16H, –CH$_2$– chain), 0.90 (t, 3H, $J=6.7$ Hz, CH$_3$–); ^{13}C NMR (CD$_3$OD, 100 MHz): δ 175.5 (C=O), 105.3 (C-2″), 105.2 (C-2′), 94.0 (C-1), 83.5 (C-5″), 80.5 (C-5′), 78.8 (C-3′), 78.7 (C-3″), 76.5 (C-4′), 76.3 (C-4″), 74.8 (C-3), 74.2 (C-5), 73.4 (C-2), 71.5 (C-4), 66.5 (C-6′), 63.9 (C-6″), 62.6 (C-1′), 62.4 (C-1″), 62.3 (C-6), 34.9 (–*C*H$_2$–CO–), 33.1, 30.8, 30.6, 30.5, 30.2, 26.0, 23.7 (–*C*H$_2$-lauroyl backbone), 14.4 (*C*H$_3$-lauroyl).

3.4.4. 1‴-*O*-Lauroylstachyose (4b). The general procedure outlined above was followed. After 48 h the reaction was stopped and the monoester isolated (145 mg, 76%). Regioisomer **4b** was obtained with 98% regioselectivity (HPLC/MS). $R_f=0.63$; $[\alpha]_D$ +105.4 (*c* 7 in methanol); ν_{max} (cm^{-1}) (KBr disks): 3410 br (O–H), 1735 (C=O); HRMS (FAB): calcd for $C_{36}H_{64}O_{22}Na$ (M+Na$^+$) 871.378694, found 871.378598; ^1H NMR (CD$_3$OD, 400 MHz): δ 5.41 (d, 1H, $J_{1''-2''}=3.7$ Hz, H-1″), 4.88 (d, 1H, $J_{1-2}=3.2$ Hz, H-1), 4.86 (d, 1H, $J_{1'-2'}=3.7$ Hz, H-1′), 4.35 (d, 1H, $J_{1'''a-b}=12.1$ Hz, H-1‴a), 4.11 (d, 1H, $J_{1'''a-b}=12.1$ Hz, H-1‴b), ca. 4.08 (m, 2H, H-3‴, H-4‴), 4.07 (m, 1H, H-5′), 4.05 (m, 1H, H-5″), 3.93 (m, 1H, H-4′), 3.91 (dd, 1H, $J_{6''a-b}=11.1$ Hz, $J_{6''a-5''}=5.6$ Hz, H-6″a), ca. 3.89 (m, 1H, H-5), ca. 3.85 (m, 1H, H-6′a), 3.83 (m, 1H, H-3), 3.80 (m, 1H, H-4), ca. 3.76 (m, 4H, H-2, H-2′, H-6‴a, H-6‴b), ca. 3.73 (m, 1H, H-3′), ca. 3.72 (m, 1H, H-5‴), ca. 3.71 (m, 2H, H-6a, H-6b), 3.69 (m, 1H,, H-6″b), 3.67 (t, 1H, $J_{2''-3''}=J_{3''-4''}=9.5$ Hz, H-3″), ca. 3.65 (m, 1H, H-6′b), 3.43 (dd, 1H, $J_{2''-3''}=9.7$ Hz, $J_{1''-2''}=3.7$ Hz, H-2″), 3.32 (t, 1H, $J_{3''-4''}=J_{4'-5'}=9.5$ Hz, H-4″), 2.37 (t, 2H, $J=7.5$ Hz, –C*H*$_2$–CO–), 1.63 (m, 2H, C*H*$_2$–CH$_2$–CO–), 1.29 (m, 16H, –CH$_2$– chain), 0.90 (t, 3H, $J=6.8$ Hz, CH$_3$–); ^{13}C NMR (CD$_3$OD, 60 MHz): δ 174.8 (C=O), 104.1 (C-2‴), 100.4 (C-1′), 100.1 (C-1), 93.9 (C-1″), 83.7 (C-5‴), 78.6 (C-3‴), 74.7 (C-4‴), 74.5 (C-3″), 73.1 (C-5″), 72.8 (C-2″), 72.4 (C-5), 72.0 (C-4″), 71.5 (C-3)[a], 71.3 (C-3′)[a], 71.0 (C-4)[b], 70.9 (C-4′)[b], 70.5 (C-5′)[c], 70.2 (C-2, C-2′)[c], 68.2 (C-6″), 67.8 (C-6′), 64.0 (C-1‴), 63.1 (C-6‴), 62.6 (C-6), 35.0 (–*C*H$_2$–CO–), 33.1, 30.8, 30.6, 30.5, 30.3, 26.0, 23.7 (–*C*H$_2$-lauroyl backbone), 14.5 (*C*H$_3$-lauroyl). Note: ^{13}C NMR assignments marked with the same letter may be interchangeable.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.10.046

References and notes

1. Watanabe, T. *Foods Food Ingr. J. Jpn.* **1999**, *180*, 18–25.
2. Björkling, F.; Godtfredsen, S. E.; Kirk, O. *Trends Biotechnol.* **1991**, *9*, 360–363.

3. Ferrer, M.; Comelles, F.; Plou, F. J.; Cruces, M. A.; Fuentes, G.; Parra, J. L.; Ballesteros, A. *Langmuir* **2002**, *18*, 667–673.
4. Garofalakis, G.; Murria, B. S.; Sarney, D. B. *J. Colloid Interface Sci.* **2000**, *229*, 391–398.
5. Haines, A. H. *Adv. Carbohydr. Chem. Biochem.* **1976**, *33*, 11–109.
6. Haines, A. H. *Adv. Carbohydr. Chem. Biochem.* **1981**, *39*, 13–70.
7. Schmid, R. D.; Verger, R. *Angew. Chem., Int. Ed.* **1998**, *37*, 1608–1633.
8. Bordusa, F. *Chem. Rev.* **2002**, *102*, 4817–4867.
9. Plou, F. J.; Cruces, M. A.; Ferrer, M.; Fuentes, G.; Pastor, E.; Bernabé, M.; Christensen, M.; Comelles, F.; Parra, J. L.; Ballesteros, A. *J. Biotechnol.* **2002**, *96*, 55–66.
10. Carrea, G.; Riva, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 2226–2254.
11. Woudenberg-van Oosterom, M.; van Rantwijk, F.; Sheldon, R. A. *Biotechnol. Bioeng.* **1996**, *49*, 328–333.
12. Riva, S.; Chopineau, J.; Kieboom, A. P. G.; Klibanov, A. M. *J. Am. Chem. Soc.* **1988**, *110*, 584–589.
13. Riva, S.; Nonini, M.; Ottolina, G.; Danieli, B. *Carbohydr. Res.* **1998**, *314*, 259–266.
14. Ferrer, M.; Cruces, M. A.; Plou, F. J.; Bernabé, M.; Ballesteros, A. *Tetrahedron* **2000**, *56*, 4053–4061.
15. Gustavsson, M. T.; Persson, P. V.; Iversen, T.; Martinelle, M.; Hult, K.; Teeri, T. T.; Brumer, H. *Biomacromolecules* **2005**, *6*, 196–203.
16. Devulapalle, K. S.; Gómez de Segura, A.; Ferrer, M.; Alcalde, M.; Mooser, G.; Plou, F. J. *Carbohydr. Res.* **2004**, *339*, 1029–1034.
17. Ferrer, M.; Perez, G.; Plou, F. J.; Castell, J. V.; Ballesteros, A. *Biotechnol. Appl. Biochem.* **2005**, *42*, 35–39.
18. Ferrer, M.; Cruces, M. A.; Bernabé, M.; Ballesteros, A.; Plou, F. J. *Biotechnol. Bioeng.* **1999**, *65*, 10–16.
19. Saleki-Gerhardt, A.; Stowell, J. G.; Byrn, S. R.; Zografi, G. *J. Pharm. Sci.* **1995**, *84*, 318–323.
20. Degn, P.; Zimmermann, W. *Biotechnol. Bioeng.* **2001**, *74*, 485–491.
21. Ferrer, M.; Plou, F. J.; Fuentes, G.; Cruces, M. A.; Andersen, L.; Kirk, O.; Christensen, M.; Ballesteros, A. *Biocatal. Biotransform.* **2002**, *20*, 63–71.
22. Pleiss, J.; Fischer, M.; Schmid, R. D. *Chem. Phys. Lipids* **1998**, *93*, 67–80.
23. Muralidhar, R. V.; Chirumamilla, R. R.; Marchant, R.; Ramachandran, V. N.; Ward, O. P.; Nigam, P. *World J. Microbiol. Biotechnol.* **2002**, *18*, 81–97.
24. Fuentes, G.; Ballesteros, A.; Verma, C. S. *Protein Sci.* **2004**, *13*, 3092–3103.
25. Griebenow, K.; Laureano, Y. D.; Santos, A. M. Montanez Clemente. *I., Rodríguez, L., Vidal, M. W., Barletta, G., J. Am. Chem. Soc.* **1999**, *121*, 8157–8163.
26. Montanez Clemente, I.; Alvira, E.; Macias, M.; Ferrer, A.; Fonseca, M.; Rodríguez, J.; Gonzalez, A.; Barletta, G. *Biotechnol. Bioeng.* **2002**, *78*, 53–59.
27. Polat, T.; Bazin, H. G.; Linhardt, R. J. *J. Carbohydr. Chem.* **1997**, *16*, 1319–1325.
28. Fuentes, G.; Cruces, M. A.; Plou, F. J.; Ballesteros, A.; Verma, C. S. *ChemBioChem* **2002**, *9*, 907–910.
29. Potier, P.; Bouchu, A.; Gagnaire, J.; Queneau, Y. *Tetrahedron: Asymmetry* **2001**, *12*, 2409–2419.

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Tetrahedron

Diastereoselective allylation of α-ketoamides bearing camphor *N*-tosylpyrazolidinone auxiliary: efficient synthesis of highly optically active two stereoisomers

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Abstract—Complementary allylation conditions were developed for the synthesis of both diastereomers of tertiary homoallylic alcohols. Treatment of camphor *N*-tosylpyrazolidinone derived α-ketoamides with allyltributylstannane afforded both the individual homoallylic alcohols in high optical purity (up to 98% de) when the reaction was carried out in the presence of $Sn(OTf)_2$ and $PdCl_2$, respectively. The stereochemical outcome and reversal of stereoselectivity in the reaction are proposed based on ^{13}C NMR and FTIR studies.

1. Introduction

The development of novel chiral auxiliaries that provide practical routes for the preparation of synthetically useful intermediates remains one of the most important fields in organic synthesis.[1] The fact that there are no universal chiral auxiliaries for all asymmetric transformations is a compelling reasons for discovering novel chiral auxiliaries for specific reactions.[2] From a practical synthetic point of view, the synthesis of both stereoisomers from the same chiral resources is attractive and has been a subject of considerable interest in recent years.[3] The reversal of stereochemistry from a single chiral starting material can be achieved by careful manipulation of the reaction components, especially the control of the architecture of the ligand-Lewis acid complex. The asymmetric allylation of ketones,[4] aldehydes[5] and imine[6] functionalities for the formation of homoallyl alcohols and homoallyl amines are well documented in the literature. The corresponding secondary and tertiary homoallylic alcohols are versatile intermediates that have been further used in organic synthesis.[7] However, allyl metal addition to α-keto esters and amides is a less well investigated topic.[8] Diastereoselective allylation of camphor *N*-phenylpyrazolidinone derived α-ketoamides was examined recently by us.[9] The corresponding quarternary α-hydroxy carbonyls were obtained with good to excellent stereoselectivity. However, to the best of our knowledge, a diastereoselective allylation of α-ketoamides with reversal of stereoselectivity has not been achieved to date. Here, we wish to report the asymmetric allylation of a novel camphor auxiliary derived α-ketoamides in the presence of a Lewis acid. The desired products were obtained in excellent diastereomeric excess in good to excellent chemical yields. The facial stereoselectivity and the stereochemical course of the reactions are discussed.

2. Results and discussion

The preparation of camphor *N*-tosylpyrazolidinone **4** followed the same synthetic route as described previously (Scheme 1).[2g] The treatment of (+)-ketopinic acid **1** with *p*-toluenesulfonhydrazide producing the desired hydrazone **2** in nearly quantitative chemical yield. Cyclization was carried out by treatment with $SOCl_2$ in EtOAc at 75 °C for 4 h. The corresponding C–N double bond was reduced with $NaCNBH_3$ in acetic acid to give the chiral camphor *N*-tosylpyrazolidinone **4** in 75% material yield. The desired α-ketoamides **5** are readily prepared by coupling the camphor *N*-tosylpyrazolidinone **4** with the freshly prepared α-ketocarboxylic acid chlorides at room temperature in 49–97% yields. It is noteworthy that both camphor *N*-tosylpyrazolidinone **4** and camphor *N*-tosylpyrazolidinone phenylglyoxylate **5a** exist as two structural conformers in the asymmetric unit as indicated by X-ray crystallographic analyses.[10] Two distinct *N*-invertomers of camphor *N*-tosylpyrazolidinone **4** were observed in which the tosyl group is oriented toward and away from the C7 dimethyl group (Scheme 1, the dihedral angles of $NNSC^2_{SP}$ are −72.0 and +84.1°, respectively).[11] On the other hand,

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Keywords: Allylation; Reversal of stereoselectivity; Chiral auxiliary.

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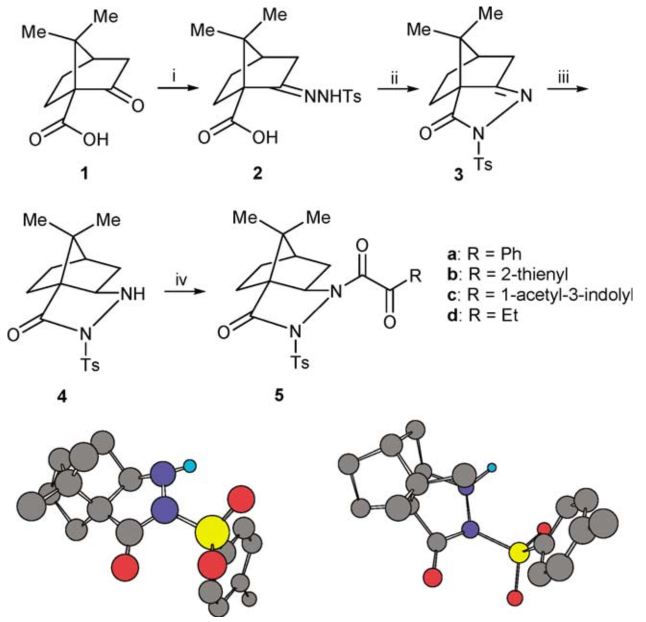


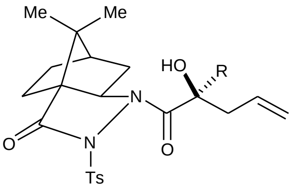
Scheme 1. Reagents and conditions: (i) *p*-toluenesulfonhydrazide, CH_2Cl_2, rt, 99%; (ii) $SOCl_2$, EtOAc, 75 °C, 90%; (iii) $NaCNBH_3$, AcOH, rt, 75%; (iv) RCOCOCl, CH_2Cl_2, base, rt, 49–97%.

the tosyl group points away from the C7 dimethyl group in **5a**, thus avoiding the electrostatic repulsion with the dicarbonyl groups (the dihedral angles of $NNSC^2_{SP}$ are -69.9 and $-83.0°$, respectively). In addition, the amide carbonyl group in **5a** is oriented away from the *N*-tosyl group with the dicarbonyl groups in an *s*-trans arrangement (the dihedral angles of COCO are 137.6 and 143.5°, respectively. See supporting information).

With the desired chiral α-ketoamides **5a–d** in hand, we examined the diastereoselective allylation. The camphor *N*-tosylpyrazolidinone phenylglyoxylate **5a** was chosen as a probe substrate. No reaction products were obtained when **5a** was treated with allyltributylstannane in the absence of a Lewis acid. Various metal triflates such as $Sc(OTf)_3$, $Sm(OTf)_3$, $Zn(OTf)_2$ and $Eu(OTf)_3$ were systematically screened, but resulted in either low to moderate chemical yields or a low level of diastereoselectivities (data not shown). A satisfactory result was obtained when the reaction was carried out in the presence of 2.0 equiv of $Yb(OTf)_3$ for 24 h (Table 1, entry 1). The stereoselectivity was further improved to an excellent level when $Sn(OTf)_2$ was employed in a 5 min reaction (entry 2). The diastereoselectivity was determined by ^{1}H NMR and HPLC studies of relevant peaks. The absolute stereochemistry of the newly generated stereogenic center in the major diasteoreomer **6a** was assigned to have an *R* configuration, deduced from the single crystal X-ray analysis. Interestingly, the sense of stereoinduction was reversed with less reactivity when the reaction was carried out in the presence of $PdCl_2$ and the structure of product **7a** was again confirmed by single crystal X-ray analysis (entry 3). A careful examination of the ^{1}H NMR spectra indicates that the characteristic C-2 methine proton (camphor numbering) appears at 3.16 ppm for the *R* isomer while at 4.32 ppm for the counter *S* isomer.[9,12] The diamagnetic anisotropy effect of the aromatic substituent may account for the shielding effect.

Having identified two discrete Lewis acids [$Sn(OTf)_2$ and $PdCl_2$] that can produce complementary diastereomers of the allylation reactions, we sought to examine the nature of the architecture of the chiral auxiliary backbone. Toward this end, the allylation proceeded smoothly when camphor *N*-tosylpyrazolidinone derived 2-thienylglyoxylate **5b** was used under the optimum reaction conditions, providing **6b** with excellent selectivity in the presence of $Sn(OTf)_2$ (entry 4). The opposite diasteoreomer with a similar selectivity was produced when $PdCl_2$ was used (entry 5).

Table 1. Diastereoselective allylation of camphor *N*-tosylpyrazolidinone derived α-ketoamides **5a**–**d** in the presence of a Lewis acid[a]



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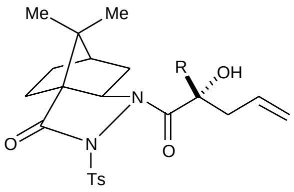

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Entry		R=	Lewis acid	*t*	Yield (%)[b]	Configuration[c]	Ratio (**6**:**7**)[d]
1	**5a**	Phenyl	$Yb(OTf)_3$	24 h	90	*R*	91:09
2	**5a**	Phenyl	$Sn(OTf)_2$	5 min	92	*R*	99:01
3	**5a**	Phenyl	$PdCl_2$	24 h	60	*S*	06:94
4	**5b**	2-Thienyl	$Sn(OTf)_2$	5 min	95	*S*	99:01
5	**5b**	2-Thienyl	$PdCl_2$	24 h	88	*R*	01:99
6	**5c**	1-Acetyl-3-indolyl	$Sn(OTf)_2$	5 min	98	*R*[f]	99:01
7	**5c**	1-Acetyl-3-indolyl	$PdCl_2$	24 h	—[e]	—	—
8	**5d**	Ethyl	$Sn(OTf)_2$	5 min	95	*S*	89:11
9	**5d**	Ethyl	$PdCl_2$	24 h	<10	*R*[f]	15:85

[a] Unless otherwise specified, all reactions were carried out in a solvent [in CH_3CN when $Sn(OTf)_2$ was used and in CH_2Cl_2 when $PdCl_2$ was used] at room temperature using **5** (0.11 mmol), allyltributylstannane (1.06 mmol) and a Lewis acid (0.22 mmol).

[b] Total isolated yield (**6**+**7**).

[c] The absolute stereochemistry of the newly generated stereogenic center was deduced by X-ray crystallographic analyses.

[d] Ratios of diastereomers were determined by ^{1}H NMR analysis of relevant peaks and HPLC analyses of crude products.

[e] The deacylated compound *N*-tosylcamphorpyrazolidinone-3-indoloylglyoxylate was isolated in 50%.

[f] Absolute stereochemistry are assigned by analogy.

It is noteworthy that, under either reaction conditions, no desired allylation product was observed with camphor *N*-tosylpyrazolidinone derived 3-indoloylglyoxylate. This was presumably due to the presence of an active hydrogen atom that decreases the reactivity. This problem was eliminated when NH protected analogue was used. Thus, camphor *N*-tosylpyrazolidinone-1-acetyl-3-indoloylglyoxylate **5c** upon allylation afforded the expected product with fairly high yield and selectivity in the presence of $Sn(OTf)_2$ (entry 6). However, no desired reaction products were observed when $PdCl_2$ was employed and the deacylation product was isolated (entry 7). Finally, the aliphatic substrate **5d** efficiently participates in the reaction, leading to the desired products with good diastereoselectivity, but the reactivity decreased dramatically when $PdCl_2$ was used as a Lewis acid (entries 8–9).

The high degree of stereoselectivity and the reversal of stereoselectivity can be rationalized by the chelation and non-chelation control of the Lewis acid with α-ketoamides **5** as shown in Figure 1. Among the possible conformations, the pseudo planar *s*-trans conformer of the α-dicarbonyl group in **5** is electronically favored over its *s*-cis conformer to avoid electrostatic repulsive interactions between the adjacent carbonyl groups. This was confirmed by X-ray crystallographic analyses of **5a**,**b** in the solid states. The reversal of stereoselectivity can be explained by simple ^{13}C NMR and FTIR studies. When a mixture of $Sn(OTf)_2$ and **5a** in CD_3CN was examined by ^{13}C NMR, no significant chemical shift difference in the carbonyl region was observed (<0.05 ppm) in comparison with a spectrum of the pure substrate.[13] This indicates that there is little chelation of Lewis acid metal atom with the carbonyl oxygen atoms. In addition, no significant carbonyl group stretching band changes in the infrared spectrum of the mixture were observed. However, a new stretching band corresponding to an S=O group developed at 1272 cm^{-1}, which is different from the stretching band of 1240 cm^{-1} in **5a**.[14] On the other hand, a mixture of $PdCl_2$ and substrate **5a** give no significant carbonyl signal shift difference or absorption band changes (carbonyl and sulfonyl groups) by ^{13}C NMR and FTIR spectroscopy. These data indicate a strong coordination of the $Sn(OTf)_2$ with sulfonyl oxygen atoms and this may account for the much faster reaction in the presence of $Sn(OTf)_2$ in comparison to the use of $PdCl_2$ (5 min vs 24 h). The coordination of the tin to the sulfonyl group resulted in the rapid release of the nucleophilic allyl group. The allyl group then attacks the α-carbonyl amide group from the bottom *si* face to afford the desired product. While, in the case of $PdCl_2$, the electronic rich tosyl group prevents nucleophilic addition from the *si* face, leading to the addition from the top *re* face.[15]

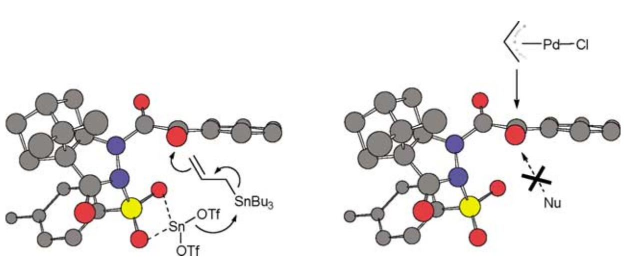

Figure 1. Proposed mechanistic explanation of the diastereoselective allylation. The stereoview of the Chem3D structure of **5a** was generated from the X-ray crystal coordinates. All hydrogen atoms are omitted for the sake of clarity.

3. Conclusion

In conclusion, a new camphor-based chiral auxiliary *N*-tosylpyrazolidinone was synthesized, and tested as a stereocontrolling element in allylation reactions across a range of substrates. The present work confirms that the correct choice of Lewis acid is essential in determining the diastereoselective outcome of the allylation.[16] The strongly chelating $Sn(OTf)_2$ led to the *si* face addition diastereomer, while the non-chelating $PdCl_2$ gave the counter diastereomer with allyltributyltin. Further synthetic applications are currently underway.

4. Experimental

4.1. General methods

All reagents were used as purchased from the commercial suppliers without further purification. NMR spectra were recorded on a Bruker Avance 400 NMR spectrometer (400 MHz for ^1H, and 100 MHz for ^{13}C). Chemical shifts are reported in δ ppm referenced to an internal TMS standard for ^1H NMR and chloroform-*d* (δ 77.0) for ^{13}C NMR. Optical rotations were measured on a JASCO P-1010 polarimeter. Infrared spectra were recorded on a Perkin-Elmer FTIR spectrum 500 spectrometer. Only the characteristic peaks are quoted. EI mass spectra were recorded on Finnigan TSQ-700 at an ionizing energy of 70 eV and HRMS spectra were recorded on JEOL SX-102A. Routine monitoring of reactions was performed using silica gel, glass-backed TLC plates (Merck Kieselgel 60 F254) and visualized by UV light (254 nm). Analytical high-performance liquid chromatography was performed on a JASCO PU-1580 HPLC (ZORBAX analytical NH_2 column). Solutions were evaporated to dryness under reduced pressure with a rotary evaporator and the residue was purified by flash column chromatography on silica gel (230–400 mesh) with the indicated eluents. Air and/or moisture sensitive reactions were performed under usual inert atmosphere conditions.

Crystallographic data for the structures in this paper have been deposited at the Cambridge Crystallographic Data Center and allocated the deposit numbers CCDC 281384-281390, and 284467.[17]

4.1.1. 2-(2-Tosylhydrazono)-7,7-dimethylbicyclo[2.2.1]-heptane-1-carboxylic acid (2). To a solution of (+)-ketopinic acid **1** (20 g, 109.9 mmol) in CH_2Cl_2 (300 mL) was added *p*-toluenesulfonhydrazide (22.5 g, 120.9 mmol) in one portion and the mixture was allowed to stir for 4 h at room temperature. The reaction mixture was diluted with water (500 mL) and extracted with dichloromethane (3×500 mL), the organic layer was separated and dried over anhydrous $MgSO_4$ and concentrated to give ketopinic acid tosylhydrazone **2** as a white solid (38.1 g; 99%); mp: 114–115 °C. $R_f=0.29$ (1:1 hexanes/EtOAc). $[\alpha]_D^{27}$ +47.1

(*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, 2H, $J=7.6$ Hz), 7.74 (br s, 1H, –NH–, D_2O exchangeable), 7.35 (d, 2H, $J=7.6$ Hz), 2.51–2.39 (m, 2H), 2.43 (s, 3H), 2.09–2.03 (m, 2H), 1.94 (d, 1H, $J=17.4$ Hz), 1.68–1.62 (m, 1H), 1.33–1.28 (m, 1H), 1.20 (s, 3H), 0.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 169.0, 145.0, 134.3, 130.1, 127.9, 61.1, 51.7, 44.3, 33.9, 31.1, 27.5, 21.5, 19.7, 18.3; IR (neat, cm^{-1}): 3436–2408 (br), 1715, 1597, 1416, 1337, 1166, 1088, 920; HRMS (EI) calcd for $C_{17}H_{22}N_2O_4S$ 350.1295. Found 350.1283.

4.1.2. 10,10-Dimethyl-3-*N*-tosyl-4-aza-tricyclo[5.2.1.0^{1,5}]-dec-4-en-2-one (3). The above prepared ketopinic acid tosylhydrazone **2** (20 g, 57.14 mmol) was dissolved in ethyl acetate (300 mL). To this solution was added thionyl chloride (15.8 mL, 217.14 mmol) slowly and the reaction mixture was brought to reflux at 75 °C for 4 h under N_2 atmosphere. The reaction mixture quenched with water (600 mL) and extracted with ethyl acetate (3×600 mL). The dried $MgSO_4$ extract was concentrated in vacuo and purified by flash column chromatography, eluted with (1:1 hexanes/EtOAc) afforded the cyclized product **3** as a colorless solid (17.07 g; 90%).; mp: 83–84 °C. $R_f=0.44$ (1:1 hexanes/EtOAc). $[\alpha]_D^{27}$ −99.6 (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, 2H, $J=7.9$ Hz), 7.32 (d, 2H, $J=7.9$ Hz), 2.59 (d, 1H, $J=18.0$ Hz), 2.43 (s, 3H), 2.22–2.20 (m, 2H), 2.15 (d, 1H, $J=18.0$ Hz), 2.10–2.05 (m, 1H), 1.76–1.69 (m, 1H), 1.52–1.45 (m, 1H), 1.12 (s, 3H), 0.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 172.2, 145.2, 135.3, 129.7, 127.9, 64.0, 50.9, 48.7, 32.2, 26.8, 26.0, 21.5, 18.5, 18.1; IR (neat, cm^{-1}): 3065, 2961, 2923, 2853, 1760, 1747, 1645, 1598, 1455, 1373, 1295, 1258, 1178, 1082, 959, 814, 705; HRMS (EI) calcd for $C_{17}H_{20}N_2O_3S$ 332.1189. Found 332.1190; Crystal data for **3** (colorless crystal, recrystallized from hexanes/EtOAc) at 25 °C: $C_{17}H_{20}N_2O_3S$, *M* 332.422, Orthorhombic, $P2_12_12_1$, $a=10.1101(2)$ Å, $b=12.9076(3)$ Å, $c=25.9674(8)$ Å, $V=3388.67$ (15) Å^3, $Z=8$, $D_x=1.303$ Mg/m^3, $\mu=0.21$ mm^{-1}, 2336 reflections, 416 parameters, $R=0.058$, $R_w=0.096$.

4.1.3. 10,10-Dimethyl-3-*N*-tosyl-4-aza-tricyclo[5.2.1.0^{1,5}]-decan-2-one (4). To a stirred solution of cyclized substrate **3** (5.05 g, 15.21 mmol) in AcOH (75 mL) at room temperature was added slowly $NaBH_3CN$ (13.19 g, 210 mmol). The reaction mixture was stirred at room temperature for 30 min until the reaction was completed and diluted with H_2O (750 mL) and extracted with CH_2Cl_2 (3×600 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated to give a crude product, which is purified by flash column chromatography eluted with (2:1 hexanes/EtOAc) to yield **4** (3.75 g; 75%) as a white solid; mp: 118–119 °C. $R_f=0.38$ (2:1 hexanes/EtOAc). $[\alpha]_D^{27}$ +14.4 (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, 2H, $J=8.0$ Hz), 7.32 (d, 2H, $J=8.0$ Hz), 5.05 (br s, 1H, –NH–), 3.5 (dd, 1H, $J=8.4$, 4.0 Hz), 2.44 (s, 3H), 2.11–2.02 (m, 2H), 1.89–1.80 (m, 2H), 1.66 (dd, 1H, $J=13.2$, 8.4 Hz), 1.26–1.15 (m, 2H), 0.94 (s, 3H), 0.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 145.2, 134.5, 129.4, 128.4, 64.5, 58.9, 52.5, 47.2, 36.4, 29.0, 26.4, 21.6, 20.4, 19.7; IR (neat, cm^{-1}): 3323, 3302, 2958, 2899, 1757, 1747, 1598, 1481, 1360, 1173, 1075, 863, 817; HRMS (EI) calcd for $C_{17}H_{22}N_2O_3S$ 334.1346. Found 334.1350. Anal. Calcd for $C_{17}H_{22}N_2O_3S$: C, 61.05; H, 6.63; N, 8.38. Found: C, 61.07; H, 6.60; N, 8.20; Crystal data for **4** (colorless crystal, recrystallized from hexanes/EtOAc) at 25 °C: $C_{17}H_{22}N_2O_3S$, *M* 334.438, Monoclinic, $P2_1$, $a=9.7297(3)$ Å, $b=14.6999(4)$ Å, $c=12.2705(5)$ Å, $V=1714.77(10)$ Å^3, $Z=4$, $D_x=1.295$ Mg/m^3, $\mu=0.205$ mm^{-1}, 5864 reflections, 415 parameters, $R=0.0643$, $R_w=0.1547$.

4.2. General procedure for the synthesis of compounds 5a–c

Under N_2 atmosphere a mixture of benzoylformic acid (2.25 g, 15.0 mmol) and thionyl chloride (15.27 mL, 209.29 mmol) was refluxed at 75 °C for 2 h and concentrated on rotary evaporator to remove $SOCl_2$. The resulting crude mixture was dissolved in CH_2Cl_2 (15 mL) and added to a solution of camphor *N*-tosylpyrazolidinone **4** (1.0 g, 2.99 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was allowed to stir for 15 min and quenched with water (50 mL) and extracted with CH_2Cl_2 (3×75 mL). The organic extracts were combined, dried over anhydrous $MgSO_4$ and concentrated to give crude products, which were subject to flash column chromatography eluted with (2:1 hexanes/EtOAc) afforded the pure product **5a** (1.35 g, 97%) as a white solid.

4.2.1. 10,10-Dimethyl-3-*N*-tosyl-4-*N*-(2-oxo-2-phenyl-acetyl)-tricyclo[5.2.1.0^{1,5}]decan-2-one (5a). $R_f=0.38$ (2:1 hexanes/EtOAc); mp: 179–181 °C. $[\alpha]_D^{27}$ −194.6 (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, 2H, $J=7.6$ Hz), 7.92 (s, 2H), 7.65 (t, 1H, $J=7.2$ Hz), 7.53 (t, 2H, $J=7.6$ Hz), 7.37 (d, 2H, $J=8.4$ Hz), 4.07 (s, 1H), 2.46 (s, 3H), 2.11 (t, 1H, $J=9.8$ Hz), 1.95–1.90 (m, 2H), 1.77 (dd, 1H, $J=13.4$, 8.2 Hz), 1.26 (s, 3H), 1.26–1.22 (m, 2H), 1.08 (m, 1H), 1.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 162.2, 146.0, 134.4, 133.6, 133.0, 130.5, 130.3, 130.0, 128.6, 128.4, 70.0, 60.0, 52.8, 47.5, 36.1, 28.8, 26.5, 21.6, 20.1, 20.0; IR (neat, cm^{-1}): 3065, 3003, 2964, 2925, 1768, 1680, 1652, 1594, 1483, 1450, 1385, 1241, 1173, 1083, 946, 816, 732; HRMS (EI) calcd for $C_{25}H_{26}N_2O_5S$ 466.1557. Found 466.1574. Anal. Calcd for $C_{25}H_{26}N_2O_5S$: C, 64.36; H, 5.62; N, 6.00. Found: C, 64.33; H, 5.62; N, 5.75; Crystal data for **5a** (colorless crystal, recrystallized from hexanes/EtOAc) at 20 °C: $C_{25}H_{26}N_2O_5S$, *M* 466.54, Monoclinic, $P2_1$, $a=10.1710(5)$ Å, $b=11.8910(5)$ Å, $c=19.5700(12)$ Å, $V=2360.8(2)$ Å^3, $Z=4$, $D_x=1.313$ Mg/m^3, $\mu=0.176$ mm^{-1}, 7815 reflections, 596 parameters, $R=0.1298$, $R_w=0.1964$.

4.2.2. 10,10-Dimethyl-3-*N*-tosyl-4-*N*-[2-oxo-2-(thiophen-2-yl)acetyl]-tricyclo[5.2.1.0^{1,5}]decan-2-one (5b). White solid. $R_f=0.35$ (2:1 hexanes/EtOAc); mp: 180–182 °C. $[\alpha]_D^{27}$ −232.7 (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, 1H, $J=3.6$ Hz), 7.93 (s, 2H), 7.81 (d, 1H, $J=4.4$ Hz), 7.37 (d, 2H, $J=8.0$ Hz), 7.2 (t, 1H, $J=4.4$ Hz), 4.11 (d, 1H, $J=6.8$ Hz), 2.46 (s, 3H), 2.09–2.06 (m, 1H), 1.94–1.92 (m, 2H), 1.82 (dd, 1H, $J=14.0$, 8.4 Hz), 1.26–1.22 (m, 2H), 1.18 (s, 3H), 1.05 (m, 1H), 1.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.1, 174.3, 161.4, 146.0, 139.5, 137.0, 134.6, 129.8, 129.1, 128.9, 128.7, 70.5, 60.3, 52.6, 47.4, 36.8, 28.8, 26.7, 21.8, 20.3, 20.0; IR (neat, cm^{-1}): 3106, 2997, 2962, 2920, 2884, 1766, 1652, 1596, 1409, 1380, 1357, 1246, 1175, 1083, 1055, 815; HRMS (EI) calcd for $C_{23}H_{24}N_2O_5S_2$ 472.1127. Found 472.1129. Anal. Calcd for $C_{23}H_{24}N_2O_5S_2$: C, 58.45; H, 5.12; N, 5.93. Found:

C, 58.68; H, 5.11; N, 5.88; Crystal data for **5b** (colorless crystal, recrystallized from hexanes/EtOAc) at 20 °C: $C_{23}H_{24}N_2O_5S_2$, *M* 472.56, Monoclinic, $P2_1$, $a=12.5900(4)$ Å, $b=6.6550(2)$ Å, $c=13.2260(5)$ Å, $V=1107.62(6)$ Å^3, $Z=2$, $D_x=1.417$ Mg/m^3, $\mu=0.279$ mm^{-1}, 3697 reflections, 285 parameters, $R=0.0735$, $R_w=0.1837$.

4.2.3. 10,10-Dimethyl-3-*N*-tosyl-4-*N*-[2-(1-acetyl-1*H*-indol-3-yl)-2-oxoacetyl]-tricyclo[5.2.1.0^{1,5}]decan-2-one (5c). White solid. $R_f=0.59$ (2:1 hexanes/EtOAc); mp: 194–195 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.49–8.47 (m, 1H), 8.36–8.34 (m, 1H), 7.94 (s, 2H), 7.48–7.42 (m, 2H), 7.36 (d, 2H, $J=7.6$ Hz), 4.22 (s, 1H), 2.75 (s, 3H), 2.46 (s, 3H), 2.12 (td, 1H, $J=11.7$, 3.9 Hz), 1.96–1.93 (m, 2H), 1.86 (dd, 1H, $J=13.7$, 8.0 Hz), 1.31–1.24 (m, 3H), 1.21 (s, 3H), 1.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.0, 169.0, 162.2, 146.1, 136.2, 135.9, 129.8, 129.0, 127.1, 126.7, 125.6, 122.0, 117.7, 116.6, 70.7, 60.4, 52.7, 47.6, 29.7, 28.9, 26.7, 23.9, 21.8, 20.3, 20.1; IR (neat, cm^{-1}): 3059, 2962, 2925, 1768, 1732, 1652, 1539, 1448, 1379, 1212, 1175, 1008, 756; HRMS (EI) calcd for $C_{29}H_{29}N_3O_6S$ 547.1777. Found 547.1779.

4.2.4. 10,10-Dimethyl-3-*N*-tosyl-4-*N*-(2-oxobutanoyl)-tricyclo[5.2.1.0^{1,5}]decan-2-one (5d). Under N_2 atmosphere a mixture of 2-ketobutyric acid (3.00 g, 29.30 mmol) and thionyl chloride (32.1 mL, 440.7 mmol) was refluxed at 75 °C for 2 h and concentrated on rotary evaporator to remove $SOCl_2$. The resulting crude product was dissolved in CH_2Cl_2 (5 mL) and added to a solution of camphor *N*-tosylpyrazolidinone **4** (0.20 g, 0.59 mmol) in CH_2Cl_2 (5 mL). This was added pyridine (2.30 mL, 29.50 mmol) and the reaction was allowed to stir at room temperature for 12 h. The reaction mixture was then quenched with H_2O (20 mL) and extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts dried over anhydrous $MgSO_4$ and the crude products were purified by flash column chromatography eluted with (2:1 hexane/EtOAc) provided product **5d** (0.12 g; 50%) as a colorless oil. $R_f=0.38$ (2:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, 2H, $J=8.2$ Hz), 7.40 (d, 2H, $J=8.2$ Hz), 3.78 (m, 1H), 3.11 (dq, 1H, $J=19.0$, 7.2 Hz), 2.81 (dq, 1H, $J=19.0$, 7.2 Hz), 2.48 (s, 3H), 2.03–1.86 (m, 4H), 1.81 (dd, 1H, $J=14.3$, 8.2 Hz), 1.26–1.20 (m, 2H), 1.16 (t, 3H, $J=7.2$ Hz), 1.16 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.0, 174.9, 162.3, 146.4, 133.9, 130.0, 128.6, 70.3, 60.0, 52.4, 47.3, 35.2, 31.7, 28.7, 26.6, 21.6, 20.2, 19.8, 6.9; IR (neat, cm^{-1}): 2964, 2941, 2889, 1769, 1726, 1660, 1596, 1458, 1379, 1189, 1175, 1086, 964, 815; HRMS (EI) calcd for $C_{21}H_{26}N_2O_5S$ 418.1562. Found 418.1560.

4.3. Typical procedure for the synthesis of compounds 6a and 7a

To a solution of camphor *N*-tosylpyrazolidinone derived α-ketoamide (51.27 mg, 0.11 mmol) in CH_3CN (4 mL) was added allyltributylstannane (0.37 mL, 1.06 mmol) and tin(II) triflate (91.7 mg, 0.22 mmol). The reaction was allowed to stir for 5 min at room temperature. The mixture was quenched with H_2O (15 mL) and extracted with CH_2Cl_2 (3×20 mL). The organic layers were separated and dried over anhydrous $MgSO_4$ and concentrated to give crude products. Further purificatin by flash column chromatography eluted with (3:1 hexanes/EtOAc) afforded **6a** and **7a** as a white solid (51.42 mg; 92%, ratio of diastereomers 99:01).

4.3.1. 10,10-Dimethyl-3-*N*-tosyl-4-*N*-[(*R*)-2-hydroxy-2-phenylpent-4-enoyl]-tricyclo[5.2.1.0^{1,5}]decan-2-one (6a). $R_f=0.54$ (2:1 hexanes/EtOAc); mp: 170–172 °C. $[\alpha]_D^{27}$ +142.0 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, 2H, $J=8.0$ Hz), 7.54 (d, 2H, $J=7.2$ Hz), 7.37 (d, 2H, $J=8.0$ Hz), 7.33–7.26 (m, 3H), 5.92 (m, 1H), 5.35 (d, 1H, $J=9.6$ Hz), 5.28 (d, 1H, $J=16.8$ Hz), 3.34 (dd, 1H, $J=13.2$, 5.5 Hz), 3.16 (s, 1H), 3.02 (s, 1H), 2.76–2.73 (m, 1H), 2.46 (s, 3H), 2.46–2.42 (m, 1H), 2.00–1.94 (m, 1H), 1.81–1.78 (m, 3H), 1.27 (s, 3H), 1.05 (s, 3H), 0.97–0.91 (m, 1H), 0.86–0.81 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 153.0, 144.8, 139.5, 136.0, 132.6, 129.3, 129.1, 128.4, 128.0, 124.7, 122.1, 78.4, 67.5, 59.0, 55.1, 49.5, 46.3, 41.5, 28.0, 26.2, 21.7, 20.7, 19.7; IR (neat, cm^{-1}): 3530, 3065, 2965, 2884, 1748, 1703, 1450, 1368, 1173, 1083, 814, 739; HRMS (EI) calcd for $C_{28}H_{32}N_2O_5S$ 509.2060. Found 509.2053; Crystal data for **6a** (colorless crystal, recrystallized from hexanes/EtOAc) at 20 °C: $C_{28}H_{32}N_2O_5S$, *M* 508.62, Monoclinic, $P2_1$, $a=8.6460(2)$ Å, $b=11.5040(3)$ Å, $c=13.4890(3)$ Å, $V=1301.10(5)$ Å^3, $Z=2$, $D_x=1.298$ Mg/m^3, $\mu=0.165$ mm^{-1}, 4476 reflections, 326 parameters, $R=0.0652$, $R_w=0.1377$.

4.3.2. 10,10-Dimethyl-3-*N*-tosyl-4-*N*-[(*S*)-2-hydroxy-2-phenylpent-4-enoyl]-tricyclo[5.2.1.0^{1,5}]decan-2-one (7a). White solid. $R_f=0.46$ (2:1 hexanes/EtOAc); mp: 194–195 °C. $[\alpha]_D^{27}$ −71.3 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, 2H, $J=7.8$ Hz), 7.67 (d, 2H, $J=7.8$ Hz), 7.39–7.28 (m, 5H), 5.94 (m, 1H), 5.32 (d, 1H, $J=10.1$ Hz), 5.26 (d, 1H, $J=17.2$ Hz), 4.32 (t, 1H, $J=6.2$ Hz), 3.27 (dd, 1H, $J=13.4$, 6.2 Hz), 2.93 (br s, 1H), 2.66 (dd, 1H, $J=13.4$, 8.4 Hz), 2.46 (s, 3H), 2.08–2.02 (m, 1H), 1.89–1.74 (m, 3H), 1.56 (s, 1H), 1.27–1.16 (m, 2H), 0.90 (s, 3H), 0.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 172.9, 145.2, 140.2, 135.6, 133.0, 129.5, 128.9, 128.1, 127.6, 125.4, 121.9, 78.7, 72.5, 60.3, 51.7, 51.1, 47.0, 39.5, 29.1, 26.5, 21.8, 20.2, 19.5; IR (neat, cm^{-1}): 3504, 3065, 2965, 2935, 1755, 1668, 1447, 1379, 1295, 1189, 1174, 1086; HRMS (EI) calcd for $C_{28}H_{32}N_2O_5S$ 508.2026. Found 508.2009; Crystal data for **7a** (colorless crystal, recrystallized from hexanes/EtOAc) at −73 °C: $C_{28}H_{32}N_2O_5S$, *M* 508.62, Orthorhombic, $P2_12_12_1$, $a=6.3790(2)$ Å, $b=18.5760(6)$ Å, $c=21.1690(8)$ Å, $V=2508.45(15)$ Å^3, $Z=4$, $D_x=1.347$ Mg/m^3, $\mu=0.172$ mm^{-1}, 4409 reflections, 326 parameters, $R=0.1054$, $R_w=0.1766$.

4.3.3. 10,10-Dimethyl-3-*N*-tosyl-4-*N*-[(*S*)-2-hydroxy-2-(thiophen-2-yl)pent-4-enoyl]-tricyclo[5.2.1.0^{1,5}]decan-2-one (6b). White solid. $R_f=0.51$ (2:1 hexanes/EtOAc); mp: 163–165 °C. $[\alpha]_D^{27}$ +122.8 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, 2H, $J=8.0$ Hz), 7.35 (d, 2H, $J=8.0$ Hz), 7.20 (d, 1H, $J=4.8$ Hz), 7.01 (d, 1H, $J=3.7$ Hz), 6.92 (t, 1H, $J=4.8$ Hz), 5.89 (m, 1H), 5.36 (d, 1H, $J=10.1$ Hz), 5.31 (d, 1H, $J=17.2$ Hz), 3.52 (s, 1H), 3.35 (dd, 1H, $J=13.3$, 5.1 Hz), 3.25 (br s, 1H), 2.72–2.65 (m, 2H), 2.44 (s, 3H), 2.06–1.98 (m, 2H), 1.87–1.81 (m, 2H), 1.25 (s, 3H), 1.12–1.06 (m, 1H), 1.06 (s, 3H), 0.97 (t, 1H, $J=10.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6, 171.8, 144.9, 144.3, 135.8, 132.0, 129.2, 129.1, 127.3, 125.0, 124.2, 122.4, 78.0, 68.2, 59.0, 55.1, 49.7, 46.3, 41.7, 28.0, 26.2, 21.7, 20.6, 19.7; IR (neat, cm^{-1}): 3516, 2992, 2966, 2884, 1748, 1698, 1452, 1368, 1207, 1173, 1086, 815; HRMS (EI) calcd for $C_{26}H_{30}N_2O_5S_2$ 514.1591. Found 514.1599; Crystal data for **6b** (colorless crystal, recrystallized from hexanes/EtOAc) at −123 °C: $C_{26}H_{30}N_2O_5S_2$, *M* 514.64, Monoclinic, $P2_1$, $a=8.5300(3)$ Å, $b=11.2470(4)$ Å, $c=13.4740(7)$ Å, $V=1247.57(9)$ Å^3, $Z=2$, $D_x=1.370$ Mg/m^3, $\mu=0.254$ mm^{-1}, 4278 reflections, 317 parameters, $R=0.0625$, $R_w=0.1386$.

4.3.4. 10,10-Dimethyl-3-*N*-tosyl-4-*N*-[(*R*)-2-hydroxy-2-(thiophen-2-yl)pent-4-enoyl]-tricyclo[5.2.1.0^{1,5}]decan-2-one (7b). White solid. $R_f=0.41$ (2:1 hexanes/EtOAc); mp: 167–168 °C. $[\alpha]_D^{27}$ −50.1 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, 2H, $J=8.2$ Hz), 7.37 (d, 2H, $J=8.2$ Hz), 7.25 (dd, 1H, $J=5.0$, 1.0 Hz), 7.17 (dd, 1H, $J=3.5$, 1.0 Hz), 6.95 (dd, 1H, $J=5.0$, 3.5 Hz), 5.95 (m, 1H), 5.34 (d, 1H, $J=10.8$ Hz), 5.30 (d, 1H, $J=18.0$ Hz), 4.34 (s, 1H), 3.25 (dd, 1H, $J=13.6$, 7.5 Hz), 3.18 (br s, 1H), 2.89 (dd, 1H, $J=13.6$, 7.5 Hz), 2.46 (s, 3H), 2.19–2.16 (m, 1H), 2.09–2.04 (m, 1H), 1.92 (dd, 1H, $J=14.4$, 8.1 Hz), 1.87–1.81 (m, 1H), 1.67 (t, 1H, $J=3.7$ Hz), 1.30–1.19 (m, 2H), 0.94 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 172.8, 145.3, 144.5, 135.4, 132.4, 129.5, 128.9, 126.8, 125.3, 124.4, 122.3, 78.3, 72.8, 60.4, 51.7, 51.5, 47.0, 39.9, 29.1, 26.6, 21.8, 20.3, 19.5; IR (neat, cm^{-1}): 3501, 3054, 2992, 2961, 1741, 1683, 1380, 1175, 1080, 1039, 936, 827, 752; HRMS (EI) calcd for $C_{26}H_{30}N_2O_5S_2$ 514.1591. Found 514.1598. Anal. Calcd for $C_{26}H_{30}N_2O_5S_2$: C, 60.68; H, 5.88; N, 5.44. Found: C, 60.82; H, 5.85; N, 5.45; Crystal data for **7b** (colorless crystal, recrystallized from hexanes/EtOAc) at −73 °C: $C_{26}H_{30}N_2O_5S_2$, *M* 514.64, Orthorhombic, $P2_12_12_1$, $a=9.8170(2)$ Å, $b=12.1720(2)$ Å, $c=21.7010(5)$ Å, $V=2593.11(9)$ Å^3, $Z=4$, $D_x=1.318$ Mg/m^3, $\mu=0.244$ mm^{-1}, 4469 reflections, 316 parameters, $R=0.0531$, $R_w=0.1272$.

4.3.5. 10,10-Dimethyl-3-*N*-tosyl-4-*N*-[(*R*)-2-(1-acetyl-1*H*-indol-3-yl)-2-hydroxypent-4-enoyl]-tricyclo[5.2.1.0^{1,5}]-decan-2-one (6c). White solid. $R_f=0.60$ (2:1 hexanes/EtOAc); mp: 153–155 °C. $[\alpha]_D^{16}$ +157.3 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, CDCl3) δ 8.44 (d, 1H, $J=7.9$ Hz), 8.10 (d, 2H, $J=8.2$ Hz), 7.96 (d, 1H, $J=7.9$ Hz), 7.49 (s, 1H), 7.38 (d, 2H, $J=8.2$ Hz), 7.35 (t, 1H, $J=7.9$ Hz), 7.26 (t, 1H, $J=7.9$ Hz), 5.94 (m, 1H), 5.35 (d, 1H, $J=10.4$ Hz), 5.30 (d, 1H, $J=17.4$ Hz), 3.54 (dd, 1H, $J=7.7$, 5.1 Hz), 3.43 (dd, 1H, $J=12.6$, 4.1 Hz), 3.25 (br s, 1H), 2.80–2.75 (m, 1H), 2.69 (d, 1H, $J=12.6$ Hz), 2.61 (s, 3H), 2.47 (s, 3H), 1.98 (td, 1H, $J=12.0$, 4.8 Hz), 1.83–1.78 (m, 3H), 1.30–1.26 (m, 1H), 1.16 (s, 3H), 1.03 (s, 3H), 1.00–0.96 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 172.2, 168.6, 145.2, 136.4, 135.5, 132.0, 129.3, 129.2, 127.3, 125.5, 123.8, 122.9, 122.1, 121.9, 121.7, 116.5, 77.4, 59.2, 47.4, 46.4, 41.2, 31.5, 28.1, 26.3, 22.6, 21.7, 20.5, 19.7, 14.1; IR (neat, cm^{-1}): 3418, 3080, 2962, 2930, 2894, 1748, 1710, 197, 1451, 1382, 1331, 1225, 1173, 1083, 815; HRMS (EI) calcd for $C_{32}H_{35}N_3O_6S$ 589.2247. Found 589.2240.

4.3.6. 10,10-Dimethyl-3-*N*-tosyl-4-*N*-[(*S*)-2-ethyl-2-hydroxypent-4-enoyl]-tricyclo[5.2.1.0^{1,5}]decan-2-one (6d). White solid. $R_f=0.42$ (2:1 hexanes/EtOAc); mp: 138–140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, 2H, $J=8.2$ Hz), 7.35 (d, 2H, $J=8.2$ Hz), 6.05 (m, 1H), 5.34 (d, 1H, $J=10.0$ Hz), 5.24 (d, 1H, $J=17.1$ Hz), 3.90 (s, 1H), 2.87 (dd, 1H, $J=13.3$, 5.2 Hz), 2.67–2.58 (m, 1H), 2.44 (s, 3H), 2.38–2.28 (m, 1H), 2.22–2.11 (m, 2H), 1.98–1.87 (m, 2H), 1.70–1.65 (m, 1H), 1.34 (s, 3H), 1.30–1.23 (m, 3H), 1.13 (s, 3H), 0.93 (t, 3H, $J=7.4$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 144.8, 136.0, 132.7, 129.1, 129.0, 121.3, 78.5, 59.1, 46.2, 42.3, 32.1, 28.0, 27.8, 26.3, 21.7, 20.8, 19.8, 17.5, 13.6, 8.2; IR (neat, cm^{-1}): 3535, 2968, 2941, 2884, 1747, 1695, 1597, 1456, 1373, 1295, 1173, 1083, 814, 737; HRMS (EI) calcd for $C_{24}H_{32}N_2O_5S$ 460.2032. Found 460.2035.

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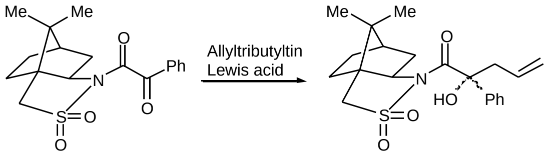
References and notes

1. (a) Oppolzer, W.; Lienard, P. *Helv. Chim. Acta* **1992**, *75*, 2572–2582. (b) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 876–889. (c) Evans, D. A. *Aldrichim. Acta* **1982**, *15*, 23–32.
2. (a) Dixon, D. J.; Horan, R. A. J.; Monck, N. J. T. *Org. Lett.* **2004**, *6*, 4423–4426. (b) Boeckman, R. K., Jr.; Reeder, L. M. *Synlett* **2004**, 1399–1403. (c) Akkari, R.; Calmes, M.; Escale, F.; Iapichella, J.; Rolland, M.; Martinez, J. *Tetrahedron: Asymmetry* **2004**, *15*, 2515–2525. (d) Kotake, T.; Rajesh, S.; Hayashi, Y.; Mukai, Y.; Ueda, M.; Kimura, T.; Kiso, Y. *Tetrahedron Lett.* **2004**, *45*, 3651–3654. (e) Martinez, A. G.; Vilar, E. T.; Fraile, A. G.; Cerero, S.de la M.; Morillo, C. D.; Morillo, R. P. *J. Org. Chem.* **2004**, *69*, 7348–7351. (f) Boeckman, R. K. Jr.; Boehmler, D. J.; Musselman, R. A. *Org. Lett.* **2001**, *3*, 3777–3780. (g) Yang, K.-S.; Chen, K. *Org. Lett.* **2000**, *2*, 729–731.
3. (a) Fan, C. L.; Lee, W.-D.; Teng, N.-W.; Sun, Y.-C.; Chen, K. *J. Org. Chem.* **2003**, *68*, 9816–9818. (b) Sibi, M. P.; Liu, M. *Curr. Org. Chem.* **2001**, *5*, 719–755. (c) Yabu, K.; Masumoto, S.; Yamasaki, S.; Hamashima, Y.; Kanai, M.; Du, W.; Curran, D. P.; Shibasaki, M. *J. Am. Chem.* **2001**, *123*, 9908–9909. (d) Adam, W.; Pastor, A.; Peters, K.; Peters, E.-M. *Org. Lett.* **2000**, *2*, 1019–1022. (e) Chu, Y.-Y.; Yu, C.-S.; Chen, C.-J.; Yang, K.-S.; Lain, J.-C.; Lin, C.-H.; Chen, K. *J. Org. Chem.* **1999**, *64*, 6993–6998. (f) Evans, D. A.; Murry, J. A.; Kozlowski, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 5814. (g) Alvarez-Ibarra, C.; Csaky, A. G.; Maroto, R.; Quiroga, M. L. *J. Org. Chem.* **1995**, *60*, 7934–7940.
4. (a) Kim, J. G.; Waltz, K. M.; Garcia, I. F.; Kwiatkowski, D.; Walsh, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 12580–12585. (b) Wada, R.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8910–8911 and references therein.
5. (a) Lu, J.; Ji, S.-J.; Teo, Y.-C.; Loh, T.-P. *Org. Lett.* **2005**, *7*, 159–161. (b) Nishiyama, Y.; Kakushou, F.; Sonoda, N. *Tetrahedron Lett.* **2005**, *46*, 787–789. (c) Wong, W.-L.; Lee, C.-S.; Leung, H.-K.; Kwong, H.-L. *Org. Biomol. Chem.* **2004**, *2*, 1967–1969. (d) Aoyama, N.; Hamada, T.; Manabe, K.;

Kobayashi, S. *Chem. Commun.* **2003**, 676–677. (e) Thadani, A. N.; Batey, R. A. *Org. Lett.* **2002**, *4*, 3827–3830.

6. (a) Shimizu, M.; Kimura, M.; Watanabe, T.; Tamaru, Y. *Org. Lett.* **2005**, *7*, 637–640. (b) Solin, N.; Wallner, O. A.; Szabo, K. J. *Org. Lett.* **2005**, *7*, 689–691. (c) Miyabe, H.; Yamaoka, Y.; Naito, T.; Takemoto, Y. *J. Org. Chem.* **2004**, *69*, 1415–1418. (d) Cook, G. R.; Maity, B. C.; Kargbo, R. *Org. Lett.* **2004**, *6*, 1741–1743. (e) Fernandes, R. A.; Yamamoto, Y. *J. Org. Chem.* **2004**, *69*, 735–738.
7. (a) Nicolaou, K. C.; Kim, D. W.; Baati, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 3701. (b) Hornberger, K. R.; Hamblett, C. L.; Leighton, J. L. *J. Am. Chem. Soc.* **2000**, *122*, 12894–12895. (c) Felpin, F.-X.; Lebreton, J. *J. Org. Chem.* **2002**, *67*, 9192–9199.
8. (a) Kulesza, A.; Mieczkowski, A.; Jurczak, J. *Tetrahedron: Asymmetry* **2002**, *13*, 2061–2069. (b) Basavaiah, D.; Sreenivasulu, B. *Tetrahedron Lett.* **2002**, *43*, 2987–2990. (c) Shin, J. A.; Cha, J. H.; Pae, A. N.; Choi, K. I.; Koh, H. Y.; Kang, H.-Y.; Cho, Y. S. *Tetrahedron Lett.* **2001**, *42*, 5489–5492. (d) Kiegiel, K.; Jurczak, J. *Tetrahedron Lett.* **1999**, *40*, 1009–1012. (e) Soai, K.; Ishizaki, M. *J. Org. Chem.* **1986**, *51*, 3290–3295.
9. Wang, S.-G.; Tsai, H. R.; Chen, K. *Tetrahedron Lett.* **2004**, *45*, 6183–6185.
10. Lavallee, D. K.; Zeltmann, A. H. *J. Am. Chem. Soc.* **1974**, *96*, 5552–5556.
11. Yang, K.-S.; Chen, K. *J. Org. Chem.* **2001**, *66*, 1676–1679.
12. Additional data for C-2 methine protons are as follows: **6b** (3.52 ppm), **7b** (4.34 ppm), **6c** (3.54 ppm), and **6d** (3.90 ppm).
13. (a) Kobayashi, S.; Nagayama, S. *J. Am. Chem. Soc.* **1997**, *119*, 10049–10053. (b) Nakamura, H.; Iwama, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **1996**, *118*, 6641–6647.
14. In infrared spectra stretching bands shift toward lower absorption frequency for carbonyl and imino band are observed commonly in the presence of a Lewis acid. See: (a) Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 4548–4549. (b) Van Vliet, R. P.; Van Koten, G.; Modder, J. F.; Van Beek, J. A. M.; Klaver, W. *J. Organomet. Chem.* **1987**, *319*, 285–301.
15. Kim, K. S.; Kim, B. H.; Park, W. M.; Cho, S. J.; Mhin, B. J. *J. Am. Chem. Soc.* **1993**, *115*, 7472–7477.
16. The diastereoselective allylation of the camphorsultam derived phenylglyoxylate was carried out under similar reaction conditions. The reversal of stereoselectivity was observed and the results are as follows.



Sn(OTf)$_2$: β-OH/α -OH = 13:87 (62%)
Zn(OTf)$_2$: β-OH/ α-OH = 86:14 (87%)

17. Compounds **3** (CCDC 284467), **4** (CCDC 281390), **5a** (CCDC 281384), **5b** (CCDC 281386), **6a** (CCDC 281385), **6b** (CCDC 281387), **7a** (CCDC 281388), **7b** (CCDC 281389). TOC.

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Synthesis of Fréchet type dendritic benzyl propargyl ether and Fréchet type triazole dendrimer

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Abstract—Fréchet type dendritic benzyl propargyl ethers were synthesized by the reaction of propargyl bromide with the corresponding Fréchet type dendritic benzyl alcohol. A propargyl focal point functionalized dendrons were applied for the construction of symmetric and unsymmetric dendrimers containing 1,2,3-triazole rings as connectors via click chemistry with a tripodal azide core or a azide focal point functionalized Fréchet type dendrons.

1. Introduction

Terminal alkynes are versatile intermediates in synthetic organic and material chemistry due to their characteristic reactions such as metathesis reaction, metal-catalyzed coupling reactions including sonogashira coupling reaction and oxidative homocoupling, and so on. Another important viewpoint in synthetic chemistry is 1,3-dipolar cycloaddition reaction with organoazides to provide heterocyclic five membered rings. Since the 1,3-dipolar cycloaddition of alkynes with azides was investigated by Huisgen et al.[1] it has been attracted much attention because of the synthetic importance of the aromatic and nonaromatic five-membered [1,2,3]-triazole heterocycles.[2] The traditional method for producing the triazole by cycloaddition requires elevated temperature, typically in refluxing conditions and also provides a mixture of 1,4-disubstituted and 1,5-disubstituted triazoles.

Recently, Tornøe and Sharpless independently reported a copper(I)-catalyzed Huisgen [2+3] dipolar cycloaddition reaction between an terminal alkyne and an organic azide in which the 1,4-regioisomer is exclusively formed and which also allows the rapid synthesis of compound libraries.[3] The reaction is highly chemoselective affording only the desired 1,2,3-triazole even in the presence of a large variety of other functional groups. In addition, the reaction is high yielding and can be carried out in water. The Cu(I)-catalyzed Huisgen's 1,3-dipolar cycloaddition reaction between alkynes and azides is one of the prototype reactions in click chemistry.[4] This click chemistry is a modular approach that uses the most practical and reliable chemical transformations and has found in many applications in organic chemistry,[5] drug discovery,[6] bioconjugations,[7] material science,[8] and synthesis of polymer[9] and dendrimer.[10]

Because dendrimers contain three distinct structural parts that are the core, end-groups, and branched units connecting core and periphery, there are three strategies for triazole dendrimers. Therefore, three types of triazole dendrimer having triazole unit(s) at core(s), every branching points, and peripheries, have been synthesized convergently and/or divergently. The convergent method for dendrimer containing triazole unit(s) at core can be facilitated by fewer coupling reaction(s) between a dendron-azide and a dendron-alkyne, between a dendron-azide and multi-alkynes, or between a dendron-alkyne and multi-azides and by convenient purifications. A relatively few applications using the alkynyl-dendron in dendrimer synthesis have been reported. Because of the high yields and lack of byproducts provided by the click chemistry for stitching together dendrons and core unit, the various dendrimers having functional building block at core could be obtained easily and shown the characteristic behaviors. Due to our interest in developing new functional dendrimers, we became involved in exploring efficient cycloaddition reaction that provides an easy access to dendrimers. Here we present the synthesis of propargyl-functionalized Fréchet-type

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Keywords: Alkyne; Azide; Cycloaddition; Dendrimer; 1,2,3-Triazoles.

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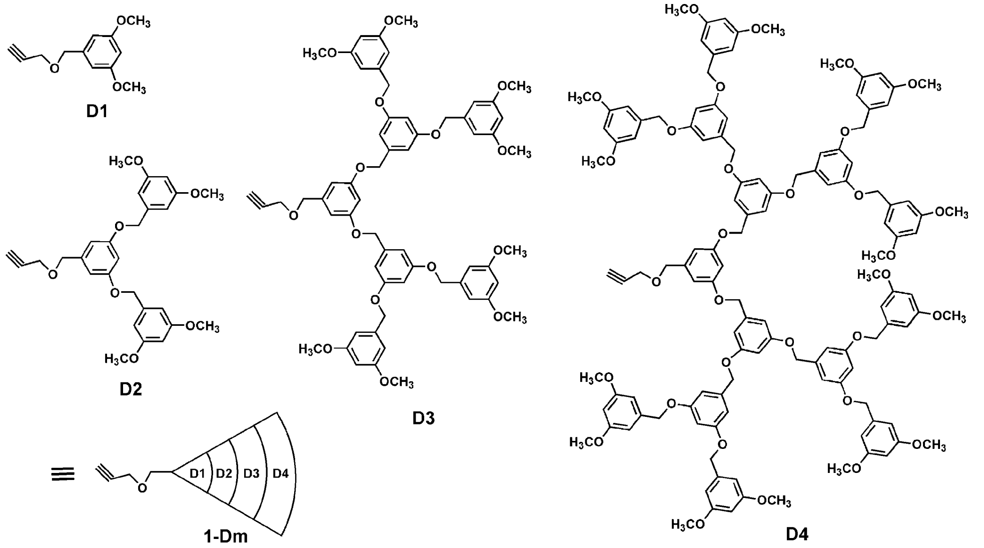


Figure 1. Structures of acetylenic-dendrons **1-Dm** ($m=1$–4: generation of dendron).

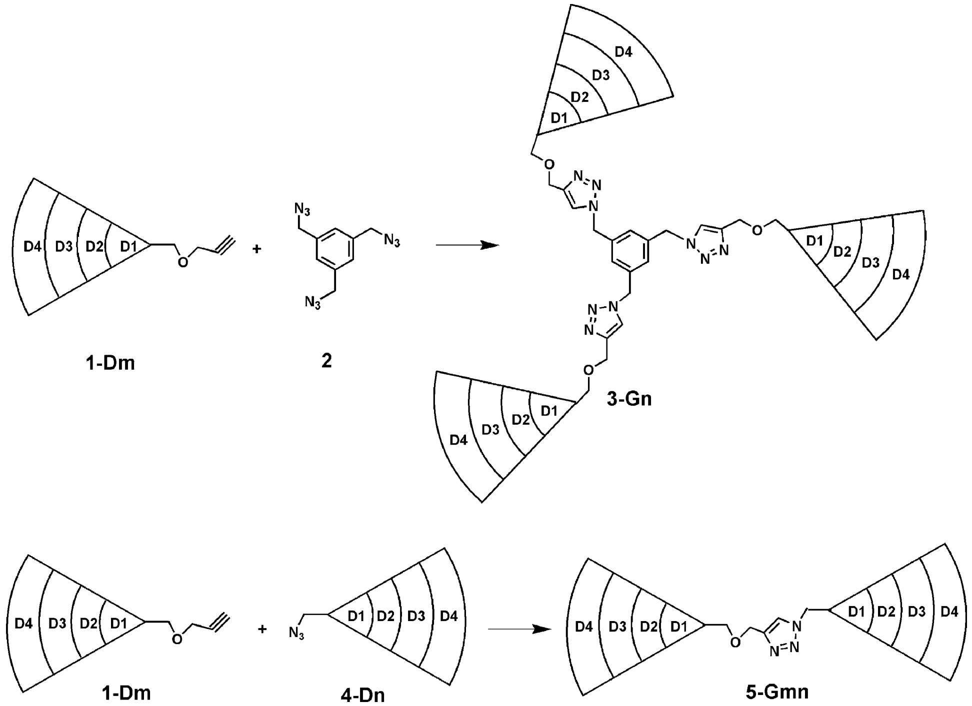
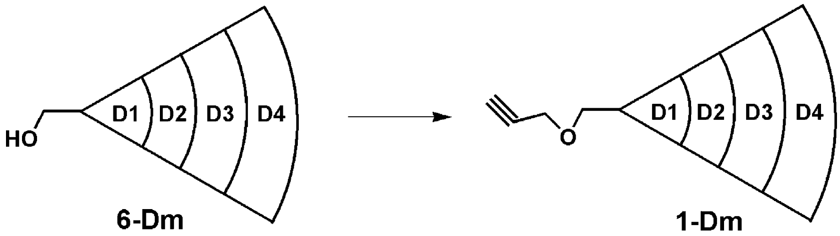


Figure 2. Synthetic strategies of triazole dendrimers via the Cu(I)-catalyzed 1,3-dipolar cycloaddition reactions. Conditions: 5 mol% $CuSO_4\cdot 5H_2O$/10 mol% sodium ascorbate with respect to alkyne, DMF/H_2O (4:1), 50–60 °C.

dendrons **1-Dm** (Fig. 1) and their application to the convergent synthesis of dendrimers using click chemistry with a tripodal azide core or an azide focal point functionalized Fréchet type dendrons (Fig. 2). The fundamental study reported herein details the growth of dendrimers convergently with triazole linkages between the core and dendrons.

2. Results and discussion

The poly(benzyl ether) dendrons, now frequently referred to as Fréchet-type dendrons, have been utilized by a number of groups because they are relatively readily accessed and exhibit the chemical stability associated with ether linkages and good solubility in organic solvents.[11] Due to these reasons we selected the Fréchet-type dendrons in the design and synthesis of the propargyl focal point functionalized dendrons. The terminal acetylenic Fréchet-type dendrons **1-Dm** ($m=1$–4: generation of dendron) were synthesized by the propargylation of the corresponding dendritic benzyl alcohols with propargyl bromide (Scheme 1). The Fréchet-type benzyl alcohols **6-Dm** ($m=1$–4: generation of dendron) were prepared according to the reported procedure.[12] For the synthesis of the propargyl focal point functionalized Fréchet-type dendrons **1-Dm**, we have reacted the corresponding dendritic benzyl alcohols **6-Dm** with propargyl bromide in the presence of NaH in THF.



Scheme 1. Synthesis of acetylenic-dendrons **1-Dm**. Conditions: NaH, THF, propargyl bromide, rt, ~10 h.

The reaction of propargyl bromide with first generation dendritic benzyl alcohol **6-D1** in THF in the presence of NaH provided the first generation dendritic benzyl propargyl ether **1-D1** in 97% yield. Next, we conducted the reaction for the preparation of higher generation dendrons. The reactions of propargyl bromide with **6-D2**, **6-D3**, and **6-D4** in the same condition gave the dendritic benzyl propargyl ether **1-D2**, **1-D3**, and **1-D4** in yields of 92, 93, and 88%, respectively. All dendrons were confirmed by ^{1}H and ^{13}C NMR spectroscopy, IR spectroscopy, and their FAB mass spectra.

For the construction of the triazole dendrimer **3-Gn** via the 1,3-dipolar cycloaddition reactions between acetylene-dendrons **1-Dm** and the tripodal azide **2**, we simply utilized the click chemistry condition, which is well-documented. The active Cu(I) species, generated in situ by reacting $CuSO_4 \cdot 5H_2O$ with sodium ascorbate as the reducing agent, provide the 1,4-disubstituted 1,2,3-triazole in excellent yield.[3a] We carried out the reactions in a 4:1 solvent ratio of DMF to H_2O using 5 mol% $CuSO_4 \cdot 5H_2O$ with 10 mol% sodium ascorbate with respect to alkyne at 50–60 °C. The reaction progress could be checked by TLC. The generation and disappearance of the intermediates, which are mono- and/or di-triazole derivatives, were monitored by TLC runs of the reaction mixture. The reaction of 1,3,5-tris(azidomethyl)benzene **2** with **1-D1** in 0.1 M solution provided the triazole dendrimer **3-G1** having just 1,4-disubstituted 1,2,3-triazole units in yield of 89% after 18 h. Given the success in using cycloaddition reaction in the synthesis of first generation dendrimer, we expanded this reaction to get higher generation dendrimers. Reaction of 1,3,5-tris(azidomethyl)benzene **2** with **1-D2** and **1-D3** afforded the triazole dendrimers **3-G2** and **3-G3** in yields of 88 and 80%, respectively, after 26 h. In case of **1-D4**, the triazole dendrimer **3-G4** was obtained in 80% yield after 28 h. For completion of the reaction between the dendritic acetylene and the tripodal core, the higher generation dendron takes longer time than the lower generation dendron. This observation led us to imagine that the reaction between the dendritic acetylene and the tripodal azide core was kinetically controlled by the accessibility of acetylide due to the steric hindrance (bulkiness) of dendron and spatial congestion of tripodal core region. Therefore, the results showed that the formation of triazole between tripodal azide and propargyl-dendrons can be regarded as a new connector to construct various dendrimers and functional materials.

All dendrimers **3-Gn** were confirmed by ^{1}H and ^{13}C NMR spectroscopy. From their ^{1}H NMR spectra ($CDCl_3$), the peaks of the benzene protons of core and the triazole protons in dendrimers **3-Gn** were found at 7.11 and 7.49 ppm for **3-G1**, 7.11 and 7.49 ppm for **3-G2**, 7.04 and 7.39 ppm for **3-G3**, and 6.96 and 7.34 ppm for **3-G4**, respectively. The peaks of the benzylic protons adjacent to the nitrogen of triazole in dendrimers **3-Gn** were found at 5.43 ppm for **3-G1**, 5.42 ppm for **3-G2**, 5.32 ppm for **3-G3**, and 5.22 ppm for **3-G4**, respectively. As the dendrimer generation increased, the peaks of the benzene protons of core, the triazole protons, and the benzylic protons adjacent to the nitrogen of triazole showed up-field shift. In third and fourth generation dendrimers it is observed that the benzene protons of core, the triazole protons, and the benzylic protons adjacent to the nitrogen of triazole are influenced by the larger dendritic effect changing their microenvironment.[13] Analysis of the dendrimers by FAB or MALDI-TOF mass spectrometry as well as by gel-permeation chromatography (GPC) provides no signs of products with defects that would arise from incomplete coupling (Fig. 3). As expected, the obtained dendrimer possessed a very well-defined molecular structure with very low polydispersity values (PDI = 1.01–1.04). IR data also confirmed that neither alkyne (~3285 cm^{-1}) nor azide (2098 cm^{-1}) residues remain in the final dendrimer.

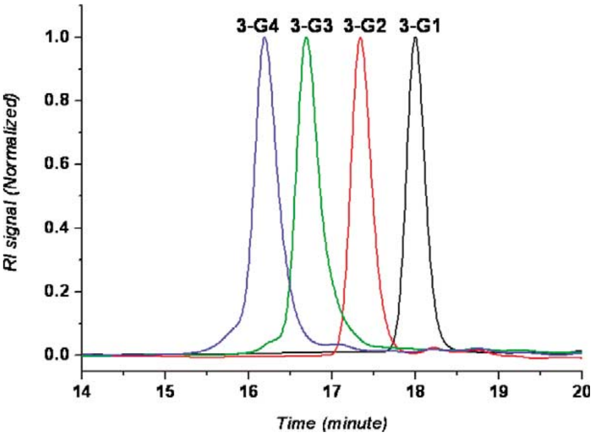


Figure 3. GPC diagrams of dendrimers **3-Gn** obtained from THF eluent.

To probe the viability of our approach, we next investigated the synthesis of triazole dendrimer **5-Gmn** from the coupling reactions between acetylenic-dendron **1-Dm** and azido-dendron **4-Dn** (entries 1–4 in Table 1). The same reaction condition as the previous trimerization was utilized in the hetero-dimerization reaction between an azide and an alkyne. The reaction of **1-D1** with **4-D1** in a 4:1 solvent ratio of DMF to H_2O using 5 mol% $CuSO_4 \cdot 5H_2O$ with 10 mol% sodium ascorbate at 50–60 °C provided the just 1,4-disubstituted 1,2,3-triazole product **5-G11** in 90% yield. Given the success in using cycloaddition reaction in the synthesis of first generation dendrimer, we expanded this reaction to get higher generation dendrimers (entries 2–4 in Table 1). Reactions of **1-D2** with **4-D2**, **1-D3** with **4-D3**, and **1-D4** with **4-D4** in a same conditions provided 1,4-disubstituted 1,2,3-triazole symmetrical dendrimers **5-G22**, **5-G33**, and **5-G44** in yields of 89, 94, and 95%, respectively. For completion of the reaction between two dendrons, the higher generation dendrons take slightly longer time than the lower generation dendrons which can be imagined by the simple steric hindrance of dendrons. Whereas the trimerization reaction between dendrons and core to provide **3-Gn** is more sluggish than the coupling reaction between two dendrons because there are some limitation in the accessibility of acetylide due to the additional spatial congestion of core region. All symmetric dendrimers were also confirmed by ^{1}H and ^{13}C NMR spectroscopy and FAB and MALDI mass spectra. From their ^{1}H NMR spectra ($CDCl_3$), the peaks of the benzylic protons adjacent to the nitrogen of triazole and the triazole proton in dendrimers **5-Gmn** were found at 5.42 and 7.48 ppm for **5-G11**, 5.42 and 7.44 ppm for **5-G22**, 5.39 and 7.44 ppm for **5-G33**, and 5.34 and 7.42 ppm for **5-G44**, respectively. As the dendrimer generation increased, the peaks of the benzylic protons adjacent to the nitrogen of triazole and the triazole proton showed slightly up-field shift. Analysis of the higher dendrimers by gel-permeation chromatography (GPC) shows very low polydispersity values, PDI = 1.02 and 1.04 for **5-G33** and **5-G44**, respectively (Fig. 4).

Table 1. Synthesis of triazole dendrimers **5-Gmn** from azido-dendrons **1-Dm** and acetylenic-dendrons **4-Dn**

Entry	1-Dm	4-Dn	Rxn time (h)	Product	Yield (%)[a]
1	**1-D1**	**4-D1**	5	**5-G11**	90
2	**1-D2**	**4-D2**	6	**5-G22**	89
3	**1-D3**	**4-D3**	7	**5-G33**	94
4	**1-D4**	**4-D4**	8	**5-G44**	95
5	**1-D1**	**4-D2**	6	**5-G12**	84
6	**1-D1**	**4-D3**	6	**5-G13**	90
7	**1-D1**	**4-D4**	7	**5-G14**	85
8	**1-D2**	**4-D1**	6	**5-G21**	85
9	**1-D2**	**4-D4**	7	**5-G24**	92
10	**1-D3**	**4-D1**	7	**5-G31**	92
11	**1-D4**	**4-D2**	7	**5-G42**	88

[a] Isolated yields.

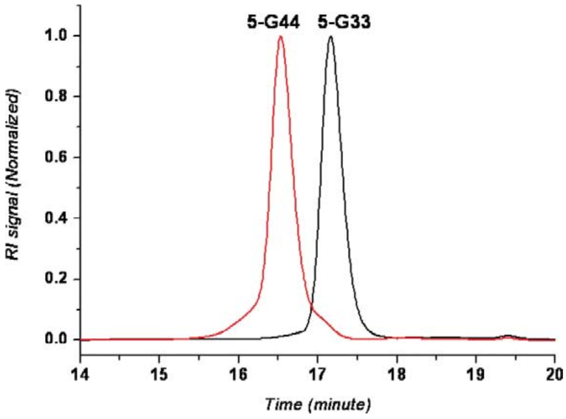


Figure 4. GPC diagrams of dendrimers **5-Gmn** obtained from THF eluent.

Next, we turned our attention toward the formation of unsymmetrical 1,2,3-triazole dendrimers. We have investigated two synthetic strategies. The first one is based on the reactions of lower generations acetylenic-dendrons **1-D1** or **1-D2** with **4-Dn** (entries 5–9 in Table 1). The second strategy involves the reactions using higher generations acetylenic dendrons **1-D3** and **1-D4** (entries 10–11 in Table 1). The reactions of **1-D1** with **4-D2**, **4-D3**, and **4-D4** provided 1,4-disubstituted 1,2,3-triazole unsymmetrical dendrimers **5-G12**, **5-G13**, and **5-G14** in yields of 84, 90, and 85%, respectively. The reactions of **1-D2** with **4-D1** and **4-D4** provided 1,4-disubstituted 1,2,3-triazole unsymmetrical dendrimers **5-G21** and **5-G24** in yields of 85 and 92%, respectively. The reactions of **1-D3** with **4-D1** and of **1-D4** with **4-D2** provided 1,4-disubstituted 1,2,3-triazole unsymmetrical dendrimers **5-G31** and **5-G42** in yields of 92 and 88%, respectively. Therefore, the results showed that the formation of triazole between azide-dendrons and propargyl-dendrons are found to be an efficient connector to construct various unsymmetric dendrimers and may be applied for the synthesis of functional materials. We are currently investigated the synthesis of various unsymmetric functional dendrimers using the different kinds of dendrons. All unsymmetric dendrimers were confirmed by ^{1}H and ^{13}C NMR spectroscopy and FAB mass spectra.

3. Conclusion

We have demonstrated that the propargyl-functionalized Fréchet-type dendrons are synthesized by the propargylation of the corresponding Fréchet type dendritic benzyl alcohol and that the trimerization reactions between tripodal azide and acetylene-dendrons and the coupling reactions between azido dendrons and acetylenic dendrons lead to the formation of symmetric triazole dendrimers in high yields. Furthermore, such reactions between dendrons of different size afford unsymmetrical triazole dendrimers. This reaction may then provide an insight into designing various (un)symmetrical dendrimers such as amphiphilic dendrimers. We are currently working towards various functional dendrimers using this strategy for various applications.

4. Experimental

^{1}H NMR spectra were recorded on a 300 or 500 MHz NMR spectrometer using the residual proton resonance of the solvent as the internal standard. Chemical shifts are reported in parts per million (ppm). When peak multiplicities are given, the following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; d of d, doublet of a doublet; m, multiplet; br, broad. ^{13}C NMR spectra were proton decoupled and recorded on a 75 or 125 MHz NMR spectrometer using the carbon signal of the deuterated solvent as the internal standard. EI, FAB, and MALDI mass spectra were obtained from Korea Basic Science Institute in Daegu or Daejeon and POSTECH. Flash chromatography was performed with 37–75 μm silica gel. Analytical thin layer chromatography was performed on silica plates with F-254 indicator and the visualization was accomplished by UV lamp or using an iodine chamber. Polydispersity (PDI) of dendrimers was determined by gel permeation chromatography (GPC) analysis relative to polystyrene calibration (Agilent 1100 series GPC, Plgel 5 μm MIXED-C, refractive index detector) in THF solution. All chemicals were obtained from commercial sources and used as received, unless otherwise mentioned. THF was distilled over Na/Ph_2CO ketyl. Dendritic benzyl alcohols **6-Dm** and azides **4-Dn**[12] and 1,3,5-tris(azidomethyl)benzene[14] used here were prepared according to previously reported procedure.

4.1. Synthesis of dendritic benzyl propargyl ether (1-Dm)

General procedure. Dendritic benzyl alcohol **6-Dm** (1 mmol) was added to a THF (10 mL) solution of sodium hydride (1.2 mmol). After stirred under nitrogen for 30 min, propargyl bromide (1.2 mmol) was added and the mixture was stirred for ∼10 h. The reaction mixture was poured slowly into cold brine (20 mL) and the resulting solution was extracted with EtOAc (20 mL × 3). The combined organic phase was dried with sodium sulfate, concentrated, and purified by column chromatography (EtOAc/Hex system) to afford the desired product **1-Dn**.

4.1.1. Compound 1-D1. A colorless oil; 97% yield; IR 3286, 2942, 2840, 2115, 1599, 1463, 1205, 1155, 1067 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.47 (t, J = 2.4 Hz, 1H), 3.79 (s, 6H), 4.18 (d, J = 2.4 Hz, 2H), 4.56 (s, 2H), 6.40 (d, J = 2.1 Hz, 1H), 6.52 (d, J = 2.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.9, 139.6, 105.7, 100.0, 79.6, 74.6, 71.5, 57.0, 55.3; MS (EI): *m/z* 206 [M^+], 166, 152, 137; HRMS (EI) Calcd for $C_{12}H_{14}O_3$: 206.0943. Found: 206.0943.

4.1.2. Compound 1-D2. A colorless oil; 92% yield; IR 3285, 2939, 2838, 2116, 1598, 1459, 1204, 1154, 1054 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.46 (t, J = 2.4 Hz, 1H), 3.80 (s, 12H), 4.16 (d, J = 2.4 Hz, 2H), 4.55 (s, 2H), 4.98 (s, 4H), 6.41 (d, J = 2.1 Hz, 2H), 6.55 (d, J = 2.1 Hz, 1H), 6.57(m, 4H), 6.60 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.0, 160.0, 139.7, 139.2, 106.9, 105.2, 101.7, 100.0, 79.6, 74.7, 71.4, 70.0, 57.1, 55.4; MS (EI): *m/z* 478 [M^+], 438, 301, 151; HRMS (EI) Calcd for $C_{28}H_{30}O_7$: 478.1992. Found: 478.1992.

4.1.3. Compound 1-D3. A colorless gum; 93% yield; IR 3284, 2938, 2838, 2117, 1598, 1458, 1203, 1153, 1050 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.46 (t, J = 2.4 Hz, 1H), 3.79 (s, 24H), 4.16 (d, J = 2.4 Hz, 2H), 4.55 (s, 2H), 4.97 (s, 12H), 6.41 (m, 4H), 6.53–6.60 (m, 13H), 6.67 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.0, 160.1, 160.0, 139.7, 139.2, 139.1, 106.9, 106.4, 105.2, 101.6, 100.0, 79.6, 74.7, 71.4, 70.04, 70.0, 57.1, 55.3; MS (FAB): *m/z* 1021.5 [M^+], 966.7, 572.9 410.2, 340.2; HRMS (FAB) Calcd for $C_{60}H_{62}O_{15}$: 1022.4089. Found: 1023.4167 [M^+ + H].

4.1.4. Compound 1-D4. A colorless gum; 88% yield; IR 3285, 2942, 2840, 2116, 1599, 1458, 1206, 1153, 1069, 1054 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.44 (t, J = 2.4 Hz, 1H), 3.77 (s, 48H), 4.14 (d, J = 2.3 Hz, 2H), 4.53 (s, 2H), 4.95 (s, 28H), 6.39 (m, 8H), 6.55–6.60 (m, 26H), 6.66 (m, 11H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.0, 160.1, 160.0, 139.7, 139.2, 139.1, 107.0, 106.4, 105.2, 101.6, 100.0, 79.6, 74.7, 71.4, 70.03, 70.0, 75.1, 55.3; MS (FAB): *m/z* 2110.9 [M^+], 1960.9, 1687.9; HRMS (FAB): Calcd for $C_{124}H_{126}O_{31}$: 2110.8283. Found: 2111.8361 [M^+ + H].

4.2. Synthesis of 1,2,3-triazole dendrimers 3-Gn by reaction between 1,3,5-tris(azidomethyl)benzene 2 and acetylene-dendrons 1-Dm

General procedure: A solution of 1,3,5-tris(azidomethyl)-benzene **2** (0.01 mmol) and acetylene-dendrons **1-Dm** (0.03 mmol) in DMF–H_2O (4:1, 1 mL) in the presence of 15 mol% $CuSO_4 \cdot 5H_2O$ with 30 mol% sodium ascorbate was stirred at 50–60 °C for 18–28 h. The reaction was monitored by TLC regarding on the disappearance of **1-Dm** and the generation and disappearance of mono- and/or di-triazole derivatives. The reaction mixture was poured into brine (20 mL) and the resulting solution was extracted with EtOAc (20 mL × 3). The combined organic phase was dried with sodium sulfate, concentrated, and purified by column chromatography (EtOAc/Hex system) to afford the desired product.

4.2.1. Compound 3-G1. A yellowish gum; 89% yield; IR 2923, 2854, 1597, 1465, 1203, 1154, 1067, 1051 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.75 (s, 18H), 4.51 (s, 6H), 4.62 (s, 6H), 5.43 (s, 6H), 6.36 (m, 3H), 6.48 (m, 6H), 7.11 (s, 3H), 7.49 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.3, 146.2, 140.5, 137.3, 128.0, 123.2, 106.1, 100.1, 73.0, 64.0, 55.7, 53.7; MS (FAB): *m/z* 862.3 [M^+], 694.2, 647.4, 544.2; HRMS (FAB) Calcd for $C_{45}H_{51}N_9O_9$: 861.3810. Found: 862.3888 [M^+ + H]. PDI: 1.01.

4.2.2. Compound 3-G2. A yellowish gum; 88% yield; IR 2926, 2854, 1596, 1461, 1203, 1156, 1054 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.77 (s, 36H), 4.50 (s, 6H), 4.61 (s, 6H), 4.94 (s, 12H), 5.42 (s, 6H), 6.39 (m, 6H), 6.52 (m, 3H), 6.55 (m, 12H), 6.57 (m, 6H), 7.11 (s, 3H), 7.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.4, 160.4, 146.2, 140.6, 139.6, 137.3, 128.0, 123.1, 107.2, 105.7, 101.9, 100.3, 72.9, 70.4, 64.0, 55.8, 53.6; MS (FAB): *m/z* 1678.9 [M^+], 663.5, 647.5; HRMS (FAM) Calcd for $C_{93}H_{99}N_9O_{21}$: 1677.6956. Found: 1678.7034 [M^+ + H]. PDI: 1.01.

4.2.3. Compound 3-G3. A yellowish gum; 80% yield; IR 2923, 2854, 1596, 1461, 1203, 1153, 1050 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.75 (s, 72H), 4.48 (s, 6H), 4.59 (s, 6H), 4.92 (s, 36H), 5.32 (s, 6H), 6.38 (m, 12H), 6.49–6.64 (m, 39H), 6.64 (m, 12H), 7.04 (s, 3H), 7.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.4, 160.47, 160.37, 146.1, 140.6, 139.7, 139.5, 137.3, 131.2, 128.0, 123.1, 107.1, 106.8, 105.7, 105.4, 102.0, 101.9, 100.4, 72.9, 70.5, 70.3, 64.0, 55.8, 53.6; MS (MALDI): Calcd for $C_{189}H_{195}N_9O_{45}$: 3310.3247. Found: 3333.2024 [M^+ + Na]. PDI: 1.03.

4.2.4. Compound 3-G4. A yellowish solid; mp 78–80 °C; 80% yield; IR 2933, 2839, 1599, 1462, 1203, 1157, 1051 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.72 (s, 144H), 4.44 (s, 6H), 4.54 (s, 6H), 4.89 (s, 84H), 5.22 (s, 6H), 6.36 (m, 24H), 6.52 (m, 73H), 6.62 (m, 38H), 6.96 (s, 3H), 7.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.4, 160.45, 160.37, 146.2, 146.0, 140.7, 139.7, 139.63, 139.56, 137.2, 132.6, 129.0, 128.9, 127.9, 123.2, 107.1, 106.8, 105.7, 105.4, 102.0, 101.9, 101.8, 100.3, 72.8, 70.4, 70.3, 69.9, 64.0, 55.7, 55.3, 55.1, 53.5; MS (MALDI): Calcd for $C_{381}H_{387}N_9O_{93}$: 6580.15. Found: 6603.42 [M$^+$ + Na]. PDI: 1.04.

4.3. Synthesis of 1,2,3-triazole dendrimers 5-Gmn by reaction between propargyl-dendrons 1-Dm and azido-dendrons 4-Dn

General procedure: A mixture of propargyl-dendrons **1-Dm** (0.10 mmol) and azido-dendrons **4-Dn** (0.10 mmol) in DMF–H_2O (4:1, 1 mL) in the presence of 5 mol% $CuSO_4\cdot 5H_2O$ with 10 mol% sodium ascorbate was stirred at 50 °C for $\sim$8 h. The reaction was monitored by TLC regarding on the disappearance of **4-Dn**. The reaction mixture was poured into brine (20 mL) and the resulting solution was extracted with EtOAc (20 mL×3). The combined organic phase was dried with sodium sulfate, concentrated, and purified by column chromatography (EtOAc/Hex system) to afford the desired product.

4.3.1. Compound 5-G11. A colorless oil; 90% yield; IR 2939, 2839, 1599, 1462, 1203, 1157, 1066, 1047 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.75 (s, 6H), 3.78 (s, 6H), 4.52 (s, 2H), 4.65 (s, 2H), 5.42 (s, 2H), 6.37 (m, 1H), 6.40 (m, 3H), 6.49 (m, 2H), 7.48 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.4, 161.0, 145.6, 140.2, 136.7, 122.5, 106.2, 105.6, 100.5, 99.9, 72.6, 63.8, 55.5, 55.4, 54.3; MS (EI): m/z=399 [M$^+$], 233, 151; HRMS (EI): m/z Calcd for $C_{21}H_{25}N_3O_5$: 399.1794. Found: 399.1796.

4.3.2. Compound 5-G22. A yellowish gum; 89% yield; IR 2939, 2839, 1596, 1458, 1206, 1153, 1050 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.78 (s, 24H), 4.52 (s, 2H), 4.64 (s, 2H), 4.92 (s, 4H), 4.95 (s, 4H), 5.42 (s, 2H), 6.40 (m, 4H), 6.49–6.60 (m, 14H), 7.44 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.0, 160.96, 160.3, 159.97, 145.5, 139.2, 138.8, 136.7, 122.5, 107.2, 106.8, 105.2, 102.1, 101.5, 100.0, 99.9, 72.6, 70.1, 70.0, 63.7, 55.4, 54.1; MS (FAB): m/z=944.4 [M$^+$]; HRMS (FAB): m/z Calcd for $C_{53}H_{57}N_3O_{13}$: 943.3891. Found: 944.3970 [M$^+$ +H].

4.3.3. Compound 5-G33. A yellowish gum; 94% yield; IR 2939, 2840, 1597, 1456, 1203, 1154, 1051 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.77 (s, 48H), 4.51 (s, 2H), 4.63 (s, 2H), 4.89 (s, 4H), 4.94 (s, 20H), 5.39 (s, 2H), 6.40 (m, 6H), 6.45 (m, 2H), 6.55 (m, 24H), 6.62 (m, 4H), 6.65 (m, 6H), 7.44 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.1, 160.4, 160.2, 160.1, 160.0, 145.6, 140.4, 139.6, 139.4, 139.23, 139.2, 139.0, 136.9, 122.7, 107.2, 106.8, 106.5, 105.3, 102.2, 101.8, 101.7, 100.03, 100.0, 72.4, 70.1, 70.0, 63.7, 55.4, 54.1; MS (MALDI): Calcd for $C_{117}H_{121}N_3O_{29}$: 2031.8086. Found: 2054.7959 [M$^+$ + Na]. PDI: 1.02.

4.3.4. Compound 5-G44. A yellowish solid; mp 76–78 °C; 95% yield; IR 2936, 2836, 1596, 1456, 1206, 1153, 1051 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.75 (s, 96H), 4.49 (s, 2H), 4.61 (s, 2H), 4.86 (s, 6H), 4.92 (s, 50H), 5.34 (s, 2H), 6.38 (m, 16H), 6.42 (m, 2H), 6.55 (m, 54H), 6.60 (m, 4H), 6.65 (m, 14H), 7.42 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.7, 161.4, 161.1, 160.7, 160.5, 160.4, 160.2, 145.9, 140.8, 139.8, 139.7, 139.63, 139.59, 139.3, 137.4, 123.1, 108.1, 107.5, 107.1, 106.8, 105.9, 105.7, 105.4, 102.4, 102.1, 101.9, 100.4, 72.7, 70.444, 70.37, 64.0, 55.7, 54.4; MS (MALDI): Calcd for $C_{245}H_{249}N_3O_{61}$: 4211.58. Found: 4234.70 [M$^+$ +Na]. PDI: 1.04.

4.3.5. Compound 5-G12. A yellowish gum; 84% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.76 (s, 6H), 3.79 (s, 12H), 4.53 (s, 2H), 4.65 (s, 2H), 4.93 (s, 4H), 5.42 (s, 2H), 6.37 (m, 1H), 6.41 (m, 2H), 6.49 (m, 4H), 6.54 (m, 4H), 6.57 (m, 1H), 7.45 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.4, 161.3, 160.8, 146.0, 140.6, 139.2, 137.1, 122.9, 107.7, 106.0, 105.6, 102.6, 100.4, 100.3, 73.0, 70.5, 64.1, 55.8, 55.7, 54.6; MS (FAB): m/z=672.3 [M$^+$ +H]; HRMS (FAB): m/z Calcd for $C_{37}H_{41}N_3O_9$: 671.2843. Found: 672.2921 [M$^+$ +H].

4.3.6. Compound 5-G13. A yellowish gum; 90% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.75 (s, 6H), 3.78 (s, 24H), 4.52 (s, 2H), 4.64 (s, 2H), 4.92 (s, 4H), 4.97 (s, 8H), 5.41 (s, 2H), 6.36 (m, 1H), 6.41 (m, 4H), 6.46–6.49 (m, 4H), 6.57 (m, 11H), 6.54 (m, 4H), 7.46 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.7, 161.4, 161.3, 160.7, 160.5, 160.49, 160.4, 146.0, 140.7, 139.7, 139.6, 139.5, 139.3, 137.1, 122.9, 107.7, 107.2, 106.83, 106.8, 106.5, 106.0, 105.7, 102.1, 102.0, 101.9, 100.8, 100.38, 100.35, 100.27, 72.9, 72.8, 70.5, 70.4, 64.1, 55.8, 55.7, 54.6; MS (FAB): m/z=1216.4 [M$^+$ +H], 663.5; HRMS (FAB): m/z Calcd for $C_{69}H_{73}N_3O_{17}$: 1215.4940. Found: 1216.5018 [M$^+$ +H].

4.3.7. Compound 5-G14. A yellowish gum; 85% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.72 (s, 6H), 3.77 (s, 48H), 4.50 (s, 2H), 4.63 (s, 2H), 4.91 (s, 4H), 4.96 (s, 24H), 5.38 (s, 2H), 6.35 (m, 1H), 6.40 (m, 8H), 6.48 (m, 3H), 6.56 (m, 22H), 6.63 (m, 4H), 6.67 (m, 10H), 7.45 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.0, 160.9, 160.3, 160.1, 145.6, 140.2, 139.2, 139.1, 138.7, 136.8, 122.6, 107.3, 106.4, 105.6, 105.2, 102.0, 101.7, 101.6, 99.9, 99.8, 99.6, 72.5, 70.04, 70.0, 63.6, 55.33, 55.27, 54.1; MS (FAB): m/z= 1216.4 [M$^+$ +H], 663.5; MS (FAB): Calcd for $C_{133}H_{137}N_3O_{33}$: 2305.5. Found: 2305.9 [M$^+$].

4.3.8. Compound 5-G21. A yellowish gum; 85% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.73 (s, 6H), 3.78 (s, 12H), 4.51 (s, 2H), 4.63 (s, 2H), 4.95 (s, 4H), 5.41 (s, 2H), 6.40 (m, 5H), 6.53–6.59 (m, 7H), 7.47 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.3, 161.0, 160.7, 160.0, 145.5, 140.3, 139.2, 139.1, 136.7, 136.5, 122.5, 106.7, 106.1, 105.9, 105.2, 105.0, 101.5, 100.4, 99.9, 72.4, 70.0, 63.7, 55.4, 55.3, 54.2; MS (FAB): m/z=672.3 [M$^+$ +H]; HRMS (FAB): m/z Calcd for $C_{37}H_{41}N_3O_9$: 671.2843. Found: 672.2921 [M$^+$ +H].

4.3.9. Compound 5-G24. A yellowish gum; 92% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.75 (s, 12H), 3.78 (s, 48H), 4.49 (s, 2H), 4.62 (s, 2H), 4.91 (s, 8H), 4.95 (s, 24H), 5.39 (s, 2H), 6.40 (m, 10H), 6.47 (m, 2H), 6.56 (m, 30H), 6.62 (m, 4H), 6.66 (m, 8H), 7.44 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.4, 161.36, 160.7, 160.5, 160.4, 146.0, 140.7, 139.7, 139.6, 139.55, 139.3, 137.3, 123.0, 107.6, 107.1, 106.8, 106.1, 105.7, 102.5, 102.0, 101.9, 100.3, 72.8, 70.5, 70.4, 64.0, 55.7, 54.5; MS (FAB): Calcd for $C_{149}H_{153}N_3O_{37}$: 2577.8. Found: 2577.4 [M$^+$].

4.3.10. Compound 5-G31. A yellowish gum; 92% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.73 (s, 6H), 3.78 (s, 24H), 4.52 (s, 2H), 4.64 (s, 2H), 4.96 (s, 4H), 4.98 (s, 8H), 5.40 (s, 2H), 6.39–6.41 (m, 7H), 6.52 (m, 1H), 6.57 (m, 13H), 6.67 (m, 3H), 7.46 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.7, 161.4, 160.5, 160.4, 145.9, 140.7, 139.7, 139.6, 137.1, 122.9, 107.2, 106.8, 106.6, 105.7, 102.0, 101.9, 100.9, 100.4, 72.9, 70.5, 70.4, 64.1, 55.8, 54.6; MS (FAB): $m/z =$ 1216.4 $[M^+ + H]$, 753.5, 647.5; HRMS (FAB): m/z Calcd for $C_{69}H_{73}N_3O_{17}$: 1215.4940. Found: 1216.5018 $[M^+ + H]$.

4.3.11. Compound 5-G42. A yellowish gum; 88% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.75 (s, 12H), 3.77 (s, 48H), 4.52 (s, 2H), 4.63 (s, 2H), 4.87 (s, 8H), 4.95 (s, 24H), 5.36 (s, 2H), 6.40 (m, 10H), 6.45 (m, 2H), 6.51 (m, 4H), 6.56 (m, 24H), 6.60 (m, 2H), 6.66 (m, 12H), 7.43 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.1, 160.6, 160.4, 160.1, 160.0, 145.6, 140.4, 139.4, 139.3, 139.2, 138.9, 136.9, 122.6, 107.6, 107.2, 106.8, 106.5, 105.3, 102.2, 102.0, 101.7, 100.0, 72.5, 70.1, 69.8, 63.7, 55.4, 54.1; MS (FAB): Calcd for $C_{149}H_{153}N_3O_{37}$: 2577.8. Found: 2577.4 $[M^+]$.

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References and notes

1. Huisgen, R. *1,3-Dipolar Cycloaddition Chemistry*; Wiley: New York, 1984.
2. Katritzky, A. R.; Zhang, Y.; Singh, S. K. *Heterocycles* **2003**, *60*, 1225.
3. (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596. (b) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057.
4. Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004.
5. (a) Kacprzak, K. *Synlett* **2005**, 943. (b) Li, Z.; Seo, T. S.; Ju, J. *Tetraheron Lett.* **2004**, *45*, 3143. (c) Suarez, P. L.; Gándara, Z.; Gómez, G.; Fall, Y. *Tetraheron Lett.* **2004**, *45*, 4619. (d) Bodine, K. D.; Jin, D. Y.; Gin, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 1638. (e) Loren, J. C.; Sharpless, K. B. *Synthesis* **2005**, 1514. (f) Wu, Y.-M.; Deng, J.; Li, Y.; Chen, Q.-Y. *Synthesis* **2005**, 1314.
6. (a) Lenda, F.; Guenoun, F.; Tazi, B.; Larbi, N. B.; Martinezd, J.; Lamatyd, F. *Tetrahedron Lett.* **2004**, *45*, 8905. (b) Manetsch, R.; Krasinński, A.; Radić, Z.; Raushel, J.; Taylor, P.; Sharpless, K. B.; Kolb, H. C. *J. Am. Chem. Soc.* **2004**, *126*, 12809. (c) Kolb, H. C.; Sharpless, K. B. *Drug Discov. Today* **2003**, *8*, 1128.
7. (a) Wang, Q.; Chan, T. R.; Hilgraf, R.; Fokin, V. V.; Sharpless, K. B.; Finn, M. G. *J. Am. Chem. Soc.* **2003**, *125*, 3192. (b) Meng, J.-C.; Siuzdak, G.; Finn, M. G. *Chem. Commun.* **2004**, 2108. (c) Link, A. J.; Vink, M. K. S.; Tirrell, D. A. *J. Am. Chem. Soc.* **2004**, *126*, 10598. (d) Sivakumar, K.; Xie, F.; Cash, B. M.; Long, S.; Barnhill, H. N.; Wang, Q. *Org. Lett.* **2004**, *6*, 4603 and references therein.
8. (a) Parent, M.; Mongin, O.; Kamada, K.; Katan, C.; Blanchard-Desce, M. *Chem. Commun.* **2005**, 2029. (b) Englert, B. C.; Bakbak, S.; Bunz, U. H. F. *Macromolecules* **2005**, *38*, 5868.
9. (a) Díaz, D. D.; Punna, S.; Holzer, P.; McPherson, A. K.; Sharpless, K. B.; Fokin, V. V.; Finn, M. G. *J. Polym. Sci., Part A* **2004**, *42*, 4392. (b) Helms, B.; Mynar, J. L.; Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **2004**, *126*, 15020. (c) Opsteen, J. A.; van Hest, J. C. M. *Chem. Commun.* **2005**, 57. (d) Mantovani, G.; Ladmiral, V.; Tao, L.; Haddleton, D. M. *Chem. Commun.* **2005**, 2089. (e) Lutz, J.-F.; Börner, H. G.; Weichenhan, K. *Macromol. Rapid Commun.* **2005**, *26*, 514. (f) Binder, W. H.; Kluger, C. *Macromolecules* **2004**, *37*, 9321. (g) Tsarevsky, N. V.; Sumerlin, B. S.; Matyjaszewski, K. *Macromolecules* **2005**, *38*, 3558.
10. (a) Wu, P.; Feldman, A. K.; Nugent, A. K.; Hawker, C. J.; Scheel, A.; Voit, B.; Pyun, J.; Fréchet, J. M. J.; Sharpless, K. B.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2004**, *43*, 3928. (b) Malkoch, M.; Schleicher, K.; Drockenmuller, E.; Hawker, C. J.; Russell, T. P.; Wu, P.; Fokin, V. V. *Macromolecules* **2005**, *38*, 3663. (c) Joralemon, M. J.; O'Reilly, R. K.; Matson, J. B.; Nugent, A. K.; Hawker, C. J.; Wooley, K. L. *Macromolecules* **2005**, *38*, 5436. (d) Lee, J. W.; Kim, B. K. *Bull. Korean Chem. Soc.* **2005**, *26*, 658. (e) Lee, J. W.; Kim, B. K.; Jin, S. H. *Bull. Korean Chem. Soc.* **2005**, *26*, 833.
11. (a) Grayson, S. M.; Fréchet, J. M. J. *Chem. Rev.* **2001**, *101*, 3919. (b) Tozawa, T. *Chem. Commun.* **2004**, 1904. (c) Liao, L.-X.; Stellacci, F.; McGrath, D. V. *J. Am. Chem. Soc.* **2004**, *126*, 2181. (d) Hara, M.; Samori, S.; Cai, X.; Tojo, S.; Arai, T.; Momotake, A.; Hayakawa, J.; Uda, M.; Kawai, K.; Endo, M.; Fujitsuka, M.; Majima, T. *J. Am. Chem. Soc.* **2004**, *126*, 14217. (e) Díez-Barra, E.; González, R.; Sánchez-Verdú, P.; Tolosa, J. *Tetrahedron* **2004**, *60*, 1563. (f) Momotake, A.; Arai, T. *Tetrahedron Lett.* **2004**, *45*, 4131. (g) Balzani, V.; Ceroni, P.; Giansante, C.; Vicinelli, V.; Klärner, F.-G.; Verhaelen, C.; Vögtle, F.; Hahn, U. *Angew. Chem., Int. Ed.* **2005**, *44*, 4574. (h) Li, W.-S.; Jiang, D.-L.; Suna, Y.; Aida, T. *J. Am. Chem. Soc.* **2005**, *70*, 7700. (i) Shanahan, C. S.; McGrath, D. V. *J. Org. Chem.* **2005**, *70*, 1054. (j) Lee, J. W.; Kim, B. K.; Jin, S. H. *Bull. Korean Chem. Soc.* **2005**, *26*, 715.
12. Stewart, G. M.; Fox, M. A. *J. Am. Chem. Soc.* **1996**, *118*, 4354.
13. (a) Jansen, J. F. G. A.; de Brabander van den Berg, E.; Meijer, E. W. *Science* **1994**, *266*, 1226. (b) Mattei, S.; Seiler, P.; Diederich, F.; Gramlich, V. *Helv. Chim. Acta* **1995**, *78*, 1904. (c) Wooley, K. L.; Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1993**, *115*, 11496. (d) Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1990**, *112*, 7638.
14. Heyer, H.; Lehn, J. M. *Tetrahedron Lett.* **1986**, *27*, 5869.

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A recombinant ketoreductase tool-box. Assessing the substrate selectivity and stereoselectivity toward the reduction of β-ketoesters

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Abstract—The substrate selectivity and stereoselectivity of a series of ketoreductases were evaluated toward the reduction of two sets of β-ketoesters. Both the structural variety at β-position and the substituent at α-position greatly affected the activity and stereoselectivity of these ketoreductases. For the first set of β-ketoesters, at least one ketoreductase was found that catalyzed the formation of either (D) or (L) enantiomer of β-hydroxyesters from each substrate with high optical purity, with the only exception of ethyl (D)-3-hydroxy-3-phenylpropionate. For the second set of β-ketoesters with α-substituents, the situation is more complex. More commonly, a ketoreductase was found that formed one of the four diastereomers in optically pure form, with only a few cases in which enzymes could be found that formed two or more of the diastereomers in high optical purity. The continued development of new, more diverse ketoreductases will create the capability to produce a wider range of single diastereomers of 2-substituted-3-hydroxy acids and their derivatives.

1. Introduction

With the advantages of environmentally benign reaction conditions, broad reaction scope, and high stereo- and regioselectivity, biocatalytic reductions of prochiral ketones offer significant potential in the synthesis of optically pure alcohols.[1] A biocatalytic reduction can be carried out using either whole cell systems[2] or isolated ketoreductases.[3] Since a whole cell may contain more than one ketoreductases, frequently with opposing stereoselectivities, not all whole-cell-mediated ketone reductions provide product chiral alcohols in high optical purity.[4] A straightforward approach to solve this problem is to carry out the reduction with an isolated ketoreductase in an in vitro reaction system. However, until recently the application of isolated ketoreductases to ketone reduction has been hampered by their limited availability.[3] In this context, we have developed an 'easy-to-use' ketoreductase tool-box consisting of more than 30 recombinant ketoreductases **KRED101–131** by genome mining and protein engineering, and have shown that these isolated recombinant ketoreductase enzymes efficiently catalyze the enantioselective reduction of a variety of substituted aryl ketones to optically pure aryl alcohols.[5] Since optically pure β-hydroxy carboxylic acids and their derivatives are key building blocks in the synthesis of bioactive compounds,[6] many efforts have been made to develop effective methods for their synthesis in enantiomerically pure form.[7] Enzymatic reduction of β-ketoesters catalyzed by ketoreductases represents an attractive approach to enantiomerically pure β-hydroxy carboxylic acids and their derivatives. The β-ketoester starting materials are readily available in many cases, and the environmentally friendly reaction conditions are easily introduced in an industrial setting and can be scaled to commercial volumes.[3a,8] In this study, we report on the substrate selectivity and stereoselectivity of a recombinant ketoreductase tool-box by evaluating the reduction of a series of diverse β-ketoesters. These studies represent a systematic look at enzyme-catalyzed stereoselective ketone reduction, which will serve as a useful guideline for developing enzymatic processes for the production of optically pure β-hydroxy carboxylic acid esters and also guide the needs for future development of new ketoreductase enzymes.

2. Results and discussion

Two sets of β-ketoesters have been chosen as substrates to evaluate the activity and stereoselectivity of the

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Keywords: Ketoreductase; Stereoselectivity; β-Ketoesters.

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ketoreductase tool-box, which comprises 31 recombinant ketoreductase enzymes **KRED101–131**. The first set of β-ketoesters **1–8** have diverse structure at the β-position, while the second ones **9–15** possess different substituents at the α-position as shown in Figure 1. The activity and stereoselectivity of the ketoreductases toward these two sets of β-ketoesters will be presented separately.

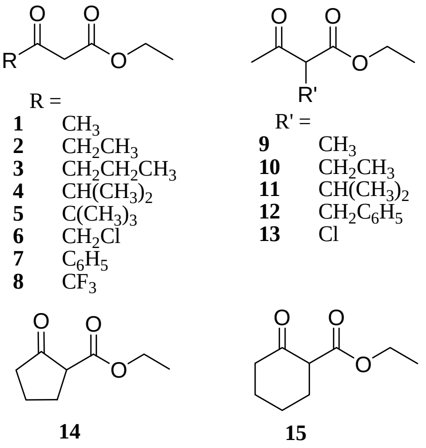
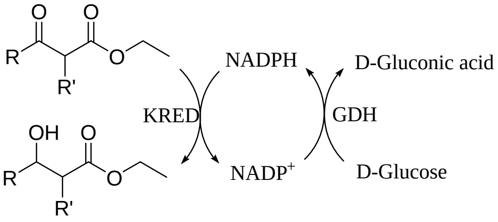


Figure 1. β-Ketoesters **1**–**15**.

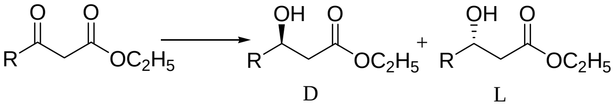


Scheme 1. Reduction of β-ketoesters catalyzed by ketoreductases with NADPH recycle system.

The activities of the ketoreductases toward the reduction of β-ketoesters **1–8** were determined by spectrophotometrically measuring the oxidation of NADPH at 340 nm at room temperature. The relative activity of **KRED101** in the reduction of ethyl 3-oxobutyrate **1** was defined as 100. The enantioselectivity of the ketoreductase-catalyzed reduction of β-ketoesters **1–8** were studied using an NADPH recycle system as shown in Scheme 1.

The selected data of the relative activity and enantioselectivity for the reduction of β-ketoesters **1–8** are presented together in Table 1. From Table 1 it can be seen that most of the ketoreductases effectively catalyzed the reduction of ethyl 3-oxobutyrate **1**. When the chain length of the β-ketoesters increases or become branched (from **1**→**2**→**3**→**4**→**5**), three major trends were observed for the ketoreductase activities. For example, the activity of **KRED108** followed a descending order from **1**→**2**→**3**→**4**→**5** as shown in Figure 2. Several other ketoreductases, **KRED102**,**103**,**106**, and **KRED107**, followed the same decreasing order. This may be due to the alkyl group at β-position becoming more bulky from **1** to **5**. An interesting trend was observed for **KRED112** and **KRED118**, which showed an overall decrease in activity from **1**→**2**→**3**→**4**→**5**, but with an unexpected increase in activity for substrate **3** (**KRED112** is shown in Fig. 2 as an example). **KRED114**,**121**,**123**, and **KRED130** did not show significant activity change across the series of β-ketoesters **1–5** (**KRED114** is shown in Fig. 2 as an example). Interestingly, **KRED101** showed the highest activity toward the reduction of ethyl 4,4-dimethyl-3-oxo-pentanoate **5**. For the reduction of ethyl 4-chloro-3-oxo-butyrate **6** and ethyl 4,4,4-trifluoro-3-oxo-butyrate **8**, most of the ketoreductases were efficient catalyst, while only a few ketoreductases were effective in the reduction of ethyl benzoylacetate **7**.

Table 1. The relative activity and enantioselectivity of the ketoreductases toward the reduction of β-ketoesters **1–8**



KRED	**1** (CH_3)	**2** (CH_2CH_3)	**3** ($CH_2CH_2CH_3$)	**4** ($CH(CH_3)_2$)	**5** ($C(CH_3)_3$)	**6** (CH_2Cl)	**7** (C_6H_5)	**8** (CF_3)
101	37[a] (100)[b]	−65 (154)	75 (120)	−99 (170)	−>99 (277)	−>99 (394)	−61 (94)	−88 (71)
102	>99 (51)	>99 (16)	—[c]	—	—	99 (226)	—	87 (9)
103	>99 (97)	>99 (13)	—	—	—	99 (311)	—	96 (9)
106	>99 (67)	>99 (24)	—	—	—	97 (353)	—	98 (4)
107	−>99 (60)	−>99 (21)	−>99 (7)	−>99 (3)	−>99 (1)	−>99 (271)	−54 (3)	−97 (6)
108	>99 (354)	>99 (114)	95 (34)	—	—	98 (406)	66 (29)	83 (77)
110	>99 (13)	—	—	—	—	−8 (14)	99 (10)	—
112	84 (361)	23 (210)	96 (355)	−89 (127)	−>99 (29)	−9 (516)	−68 (93)	−75 (237)
113	89 (318)	52 (60)	97 (296)	−87 (79)	−99 (29)	−89 (24)	−67 (60)	−65 (203)
114	37 (43)	−56 (51)	−6 (61)	−73 (45)	−99 (54)	−63 (263)	73 (174)	−46 (27)
118	>99 (630)	>99 (516)	>99 (617)	>99 (369)	99 (13)	97 (396)	−77 (136)	91 (224)
121	−23 (30)	−90 (47)	−72 (46)	−>99 (20)	−>99 (71)	−82 (164)	80 (189)	−91 (49)
123	−22 (17)	−78 (27)	−62 (51)	−97 (41)	−>99 (17)	−93 (174)	—	−89 (29)
128	96 (200)	98 (223)	>99 (149)	65 (16)	—	79 (137)	—	64 (63)
130	70 (20)	0 (14)	−88 (20)	−99 (16)	−>99 (7)	−8 (294)	—	−90 (81)
131	−52 (16)	−91 (34)	−98 (41)	−>99 (16)	—	−94 (404)	—	35 (337)

[a] ee%, the positive ee value indicates that L-enantiomer is the major product, while the negative ee value indicates that D-configuration is the major enantiomer.

[b] The initial reaction rate was measured by the procedure described in the Section 4, the relative activity of **KRED101** in the reduction of ethyl 3-oxobutyrate **1** was defined as 100 and its specific activity was 88 nmol min^{-1} mg^{-1}.

[c] The conversion of the reduction was less than 20% after 24 h, the ee value and relative activity was thus not reported.

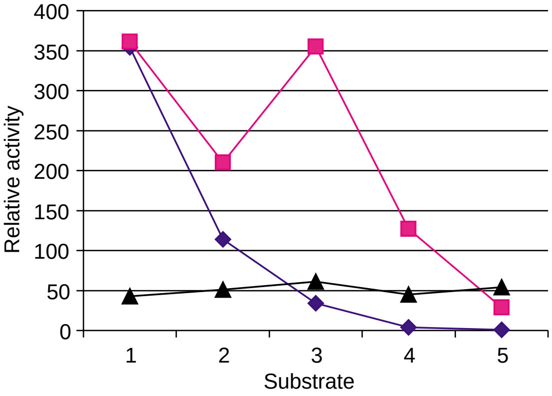


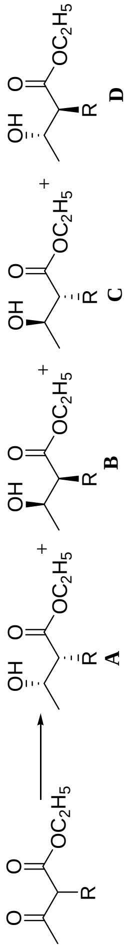
Figure 2. Three major patterns for the structural effect on the activity of ketoreductases toward the reduction of β-ketoesters (**1**–**5**). **KRED108** (diamond), **KRED112** (square), and **KRED114** (triangle).

Reduction of the first set of β-ketoesters produced two enantiomers (L and D) of β-hydroxyesters, since the enzyme delivered the hydride either from the *re*- or *si*-face of the prochiral ketone. The enantioselectivity of the enzymatic reduction was clearly dependent on the structure of the β-ketoesters. In some cases, structure of the β-ketoesters also affected the stereochemical preference, that the enzyme delivered the hydride preferentially at the *re*- or *si*-side of the carbonyl group. For example, **KRED101**-catalyzed reductions of β-ketoesters **1** and **3** gave (L)-enantiomer as the major product, resulting from the hydrogen transfer occurring at the *re*-face of the carbonyl group; while (D)-enantiomer was obtained as the major product in the **KRED101**-catalyzed reduction of β-ketoesters **2**, **4**, and **5**, indicating that the hydrogen transfer occurred at the *si*-face of the carbonyl group. Similar structure-induced inversion of configuration was observed for **KRED112**,**113**,**114**, and **KRED130**. From the results, it can be found that both enantiomers of β-hydroxyesters were obtained in high optical purity by one or more ketoreductases for each of the tested β-ketoesters, the only exception was ethyl (D)-3-hydroxy-3-phenylpropionate. The breadth of scope offered by ketoreductases demonstrates that such a group of enzymes can serve as a useful tool-box for the synthesis of optically pure β-hydroxyesters.

The selected data for the relative activity and stereoselectivity of the ketoreductase-catalyzed reduction of α-substituted-β-ketoesters **9**–**15** are presented in Table 2. When the size of the alkyl group at the α-position of ethyl 3-oxo-butyrate increased (from **9**→**10**→**11**), the activity of most ketoreductases showed a decreasing trend. The benzyl group at the α-position **12** had an unexpectedly diverse effect on the enzyme activity when compared with the introduction of an α-methyl group **9**. Most of the ketoreductases showed high activity toward the reduction of ethyl 2-chloro-3-oxo-butyrate **13**. Both ethyl 2-oxo-cyclopentanecarbonate **14** and ethyl 2-oxo-cyclohexane-carbonate **15** were good substrates for most of the tested ketoreductases, although the activities toward these two substrates were significantly varied.

The reduction of the second set of β-ketoesters generated two chiral carbon atoms, with the possible formation of four diastereomers (Table 2). In many cases, a single

Table 2. Stereoselectivity of ketoreductase-catalyzed reduction of ethyl 2-substituted-3-oxo-butyrate



KRED	**9** (CH$_3$)	**10** (CH$_2$CH$_3$)	**11** (CH(CH$_3$)$_2$)	**12** (CH$_2$Ph)	**13** (Cl)	**14**	**15**
102	100/0/0/0[a] (116)[b]	100/0/0/0 (81)	3.3/0/96.7/0 (13)	95.6/0/4.4/0 (37)	100/0/0/0 (191)	97.7/2.3/0/0 (76)	100/0/0/0 (133)
103	100/0/0/0 (130)	95.5/0/4.5/0 (19)	3.4/0/96.6/0 (10)	95.3/0/4.7/0 (4)	100/0/0/0 (180)	98.0/1.1/0/0.9 (43)	100/0/0/0 (33)
106	100/0/0/0 (186)	100/0/0/0 (49)	4.5/0/95.5/0 (13)	94.2/0/5.8/0 (29)	100/0/0/0 (404)	99.0/1.0/0/0 (126)	100/0/0/0 (191)
107	3.0/0/92.1/4.9 (198)	0/18.5/57.8/23.7 (36)	28.6/12.0/59.4/0 (7)	80.6/0/19.4/0 (13)	—[c]	28.0/72/0/0 (96)	71.2/19.7/0/9.1 (153)
111	19.1/10.6/21.3/49.0 (64)	8.7/14.0/60.8/16.5 (41)	1.0/66.6/3.1/29.2 (23)	15.6/0/84.4/0 (67)	100/0/0/0 (301)	2.6/13.1/39.3/45.0 (44)	8.9/35.1/32.1/23.9 (451)
113	56.4/2.7/26.0/14.8 (393)	4.1/26.9/5.0/64.0 (121)	—	34.8/0/64.1/1.1 (281)	100/0/0/0 (443)	0/24.2/0/75.8 (167)	0.5/32.1/0.3/66.1 (397)
114	16.7/2.7/71.0/9.7 (183)	15.3/5.4/70.5/8.8 (194)	0.9/35.3/6.7/57.1 (23)	5.8/0/94.0/0.2 (206)	100/0/0/0 (257)	2.9/12.8/42.5/41.8 (53)	9.2/27.5/33.4/30.0 (633)
115	17.9/10.7/49.8/21.5 (94)	9.1/13.9/59.6/17.4 (66)	0.7/63.6/1.6/34.1 (33)	5.4/0/94.2/0.4 (124)	95.5/2.0/2.5/0 (327)	2.6/13.2/39.4/44.8 (77)	10.4/31.9/29.3/28.3 (580)
117	89.0/0/11.0/0 (41)	10.4/0/89.6/0 (43)	—	65.3/0/34.7/0 (6)	100/0/0/0 (464)	100/0/0/0 (207)	100/0/0/0 (36)
118	72.0/0/28.0/0 (653)	10.4/3.0/85.6/1.0 (601)	—	9.3/0/90.7/0 (114)	100/0/0/0 (487)	100/0/0/0 (354)	95.9/0/4.1/0 (324)
121	13.5/4.0/70.7/11.8 (104)	7.6/5.6/78.9/7.9 (99)	0/44.8/9.0/46.2 (18)	7.9/0/92.1/0 (140)	100/0/0/0 (1414)	1.1/19.4/10.6/68.9 (36)	3.8/36.2/7.7/52.3 (557)
129	—	—	—	—	100/0/0/0 (27)	—	5.0/95.0/0/0 (54)
131	49.5/39.3/11.1/0 (16)	73.9/2.3/23.8/0 (13)	—	4.0/0/96.0/0 (21)	100/0/0/0 (129)	19.8/80.2/0/0 (40)	42.6/57.4/0/0 (574)

[a] The data were presented as the ratio of diastereomers (**A**/**B**/**C**/**D**).

[b] The initial reaction rate was measured by the procedure described in the Section 4, the relative activity of **KRED101** in the reduction of ethyl 3-oxobutyrate **1** was defined as 100 and its specific activity was 88 nmol min^{-1} mg^{-1}.

[c] The conversion was less than 20% after 20 h, so the ratio and relative activity are not reported.

diastereomer was obtained with very high diastereoselectivity. Mechanistically, the high diastereoselectivity results from the acidity of the α-proton in the β-ketoester, allowing the epimerization of the α-carbon of the β-ketoester starting material, but not the β-hydroxyester product, under the reaction conditions. Especially for ethyl 2-chloro-3-oxo-butyrate **13**, almost every ketoreductase showed high diastereoselectivity. In most cases, diastereomer **A** was obtained. A few exceptions were **KRED102**- and **KRED103**-catalyzed reduction of ethyl 2-isopropyl-3-oxo-butyrate **11**, in which diastereomer **C** was obtained with selectivity greater than 96%. Although the other diastereomers were also obtained as the major product in other cases, the diastereoselectivity was not as high, ranging from 40–95% in most cases. This indicates that while this current group of ketoreductases show high stereoselectivity and good diversity in terms of the substrate acceptance toward the reduction of 2-substituted-3-ketoesters, further efforts are required to develop ketoreductases with high and diverse diastereoselectivities, that is, for the production of diastereomers **B**, **C**, and **D**.

3. Conclusion

The substrate selectivity and stereoselectivity of a series of ketoreductases have been studied toward the reduction of two sets of β-ketoesters. Both the structural variety at β-position and the substituent at α-position greatly affect the activity and stereoselectivity of these reductions. For the synthetic purposes, the ability to prepare each stereoisomer of β-hydroxyester building blocks in homochiral form is important. For the first set of β-ketoesters, our ketoreductase collection has been demonstrated to be a useful tool-box for this goal. For the second set of β-ketoesters with α-substituent, one of the four diastereomers was produced in optically pure form, although diastereomer **A** was obtained in most cases. We are continuing efforts to develop new ketoreductases with differing diastereoselectivity in the reduction of α-substituted-β-ketoesters.

4. Experimental

The chiral GC analysis was performed on a Hewlett Packard 5890 series II plus gas chromatograph equipped with autosampler, EPC, split/splitless injector, FID detector and 25 m×0.25 mm CP-Chirasil-Dex CB chiral capillary column. The ketoreductase activities toward the reduction of β-ketoesters (Tables 1 and 2) were assayed using SpectraMax M2 microplate reader (Molecular Devices). All the ketoreductases were purified recombinant enzymes, which were developed by genome mining and protein engineering, and are commercially available from BioCatalytics, Inc. All the β-ketoesters were purchased from Aldrich and the β-hydroxyester standards were prepared by following the literature procedures.[9–18]

4.1. Activity assay of the ketoreductases

The activities of the ketoreductases toward the reduction of β-ketoesters (Tables 1 and 2) were determined by spectrophotometrically measuring the oxidation of NADPH at 340 nm ($\varepsilon = 6.22\ \mathrm{mM}^{-1}\ \mathrm{cm}^{-1}$) in the presence of excess β-ketoesters. The activity was measured at room temperature in 96-well plate, in which each well contained β-ketoester (6.25 mM), NADPH (0.25 mM) in potassium phosphate buffer (100 mM, pH 7.0, 180 μl). The reaction was initiated by the addition of the ketoreductase (20 μl solution containing 2.5–100 μg of enzyme). The specific activity was defined as the number of nmol of NADPH converted in one minute by 1 mg of enzyme ($\mathrm{nmol\ min}^{-1}\ \mathrm{mg}^{-1}$).

4.2. Stereoselectivity of the enzymatic reduction of β-ketoesters

The stereoselectivity of the enzymatic reduction of β-ketoesters was studied using an NADPH recycle system. The general procedure was as follows: D-glucose (4 mg), D-glucose dehydrogenase (0.5 mg), NADPH (0.5 mg), ketoreductase (0.5 mg) and β-ketoester solution in DMSO (50 μl, 0.25 M) were mixed in a potassium phosphate buffer (1 ml, 100 mM, pH 7.0) and the mixture was shaken at 25 °C overnight. The mixture was extracted with methyl *tert*-butyl ether (1 ml). The organic extract was dried over anhydrous sodium sulfate and was subjected to chiral GC analysis. The absolute configuration of ethyl 3-hydroxybutyrate, ethyl 3-hydroxypentanoate were determined by comparison of the chiral GC data with that in the literature.[19] The absolute configuration of other β-hydroxyesters were identified by comparing the chiral GC data with the standard samples. The racemate and enantiomers or diastereomers of the β-hydroxyesters were prepared by sodium borohydride reduction or following the literature methods: ethyl 3-hydroxyhexanoate,[9] ethyl 3-hydroxy-4-methylpentanoate,[10] ethyl 4-chloro-3-hydroxybutyrate,[9a,11] ethyl 3-hydroxy-3-phenylpropionate,[12] ethyl 3-hydroxy-4,4,4-trifluorobutyrate[13] ethyl 3-hydroxy-2-methylbutyrate,[9a,14] ethyl 2-ethyl-3-hydroxybutyrate,[9a,14a] ethyl 2-isopropyl-3-hydroxybutyrate,[14a,15] ethyl 2-benzyl-3-hydroxybutyrate,[16] ethyl 2-chloro-3-hydroxybutyrate,[17] ethyl 2-hydroxycyclopentanecarboxylate[18] and ethyl 2-hydroxycyclohexanecarboxylate.[18]

4.3. Preparative scale reduction of ethyl 4,4-dimethyl-3-oxo-pentanoate and absolute configuration determination of ethyl 4,4-dimethyl-3-hydroxy-pentanoate

D-Glucose (400 mg), D-glucose dehydrogenase (5 mg), NADPH (5 mg), **KRED101** (5 mg) and ethyl 4,4-dimethyl-3-oxo-pentanoate (200 mg) were mixed in a potassium phosphate buffer (50 ml, 100 mM, pH 7.0) and the mixture was stirred at room temperature with pH being controlled by 0.5 M sodium hydroxide solution. After 24 h, GC analysis indicated that reduction was complete. The reaction mixture was extracted with MTBE (30 ml×2). The organic extract was dried over anhydrous Na_2SO_4 and removal of the solvent gave product β-hydroxyester as clear oil (185 mg, 92% yield). ^1H and ^{13}C NMR ($CDCl_3$) are in accordance with literature data.[20] The ester was then hydrolyzed in H_2O with 1.5 equiv of NaOH solution to give (D)-4,4-dimethyl-3-hydroxy-pentanoic acid. ^1H and ^{13}C NMR ($CDCl_3$) are in accordance with literature data.[21] $[\alpha]_D^{22}$ −53.4 (*c* 1.0, $CHCl_3$); lit.[21] $[\alpha]_D^{25}$ 53.0 (*c* 1.0, $CHCl_3$) for L-enantiomer.

References and notes

1. For reviews, see: (a) Kroutil, W.; Mang, H.; Edegger, K.; Faber, K. *Curr. Opin. Chem. Biol.* **2004**, *8*, 120–126. (b) Nakamura, K.; Yamanaka, R.; Matsuda, T.; Harada, T. *Tetrahedron: Asymmetry* **2003**, *14*, 2659–2681. (c) Patel, R. N. *Curr. Opin. Biotechnol.* **2001**, *12*, 587–604. (d) Kula, M.-R.; Kragl, U. In *Stereoselective Biocatalysis*; Patel, R. N., Ed.; Marcel Dekker: New York, 2000; pp 839–866.
2. For recent examples of microbial and whole cell reduction, see: (a) Ernst, M.; Kaup, B.; Müller, M.; Bringer-Meyer, S.; Sahm, H. *Appl. Microbiol. Biotechnol.* **2005**, *66*, 629–634. (b) van Deursen, R.; Stampfer, W.; Edegger, K.; Faber, K.; Kroutil, W. *J. Mol. Catal. B: Enzym.* **2004**, *31*, 159–163. (c) Stampfer, W.; Edegger, K.; Kosjek, B.; Faber, K.; Kroutil, W. *Adv. Synth. Catal.* **2004**, *346*, 57–62. (d) Stampfer, W.; Kosjek, B.; Faber, K.; Kroutil, W. *J. Org. Chem.* **2003**, *68*, 402–406. (e) Patel, R. N.; Chu, L.; Mueller, R. *Tetrahedron: Asymmetry* **2003**, *14*, 3105–3109. (f) Katz, M.; Frejd, T.; Hahn-Hägerdal, B.; Gorwa-Grauslund, M. F. *Biotechnol. Bioeng.* **2003**, *84*, 573–582. (g) Wolberg, M.; Kaluzna, I. A.; Müller, M.; Stewart, J. D. *Tetrahedron: Asymmetry* **2004**, *15*, 2825–2828. (h) Carballeira, J. D.; Alvarez, E.; Campillo, M.; Pardo, L.; Sinistera, J. V. *Tetrahedron: Asymmetry* **2004**, *15*, 763–770. (i) Lagos, F. M.; Carballeira, J. D.; Bermudez, J. l.; Alvarez, E.; Sinistera, J. V. *Tetrahedron: Asymmetry* **2004**, *15*, 951–962. (j) Perrone, M. G.; Santandrea, E.; Scilimati, A.; Tortorella, V.; Capitelli, F.; Bertolasi, V.; Lagos, F. M.; Carballeira, J. D.; Bermudez, J. L.; Alvarez, E.; Sinistera, J. V. *Tetrahedron: Asymmetry* **2004**, *15*, 3501–3510. (k) Zhang, J.; Duetz, W. A.; Witholt, B.; Li, Z. *Chem. Commun.* **2004**, 2120–2121. (l) Haberland, J.; Kriegesmann, A.; Wolfram, E.; Hummel, W.; Liese, A. *Appl. Microbiol. Biotechnol.* **2002**, *58*, 595–599.
3. For recent examples of isolated ketoreductase reduction, see: (a) Gröger, H.; Hummel, W.; Rollmann, C.; Chamouleau, F.; Hüsken, H.; Werner, H.; Wunderlich, C.; Abokitse, K.; Drauz, K.; Buchholz, S. *Tetrahedron* **2004**, *60*, 633–640. (b) Shorrock, V. J.; Chartrain, M.; Woodley, J. M. *Tetrahedron* **2004**, *60*, 781–788. (c) Eckstein, M.; Filho, M. V.; Liese, A.; Kragl, U. *Chem. Commun.* **2004**, 1084–1085. (d) Gröger, H.; Hummel, W.; Buchholz, S.; Drauz, K.; Nguyen, T. V.; Rollmann, C.; Hüsken, H.; Abokitse, K. *Org. Lett.* **2003**, *5*, 173–176. (e) Kaluzna, I. A.; Andrew, A. A.; Bonilla, M.; Martzen, M. R.; Stewart, J. D. *J. Mol. Catal. B: Enzym.* **2002**, *17*, 101–105. (f) Schubert, T.; Hummel, W.; Kula, M.-R.; Müller, M. *Eur. J. Org. Chem.* **2001**, *22*, 4181–4187. (g) Wolberg, M.; Hummel, W.; Müller, M. *Chem. Eur. J.* **2001**, *7*, 4562–4571. (h) Wolberg, M.; Hummel, W.; Wandrey, C.; Müller, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4306–4308.
4. (a) Shieh, W. R.; Sih, C. J. *Tetrahedron: Asymmetry* **1993**, *4*, 1259–1269. (b) Nakamura, K.; Kawai, Y.; Nakajima, N.; Ohno, A. *J. Org. Chem.* **1991**, *56*, 4778–4783. (c) Shieh, W. R.; Gopalin, A. S.; Sih, C. J. *J. Am. Chem. Soc.* **1985**, *107*, 2993–2994.
5. Zhu, D.; Rios, B. E.; Rozzell, J. D.; Hua, L. *Tetrahedron: Asymmetry* **2005**, *16*, 1541–1546.
6. (a) Bertau, M.; Bürli, M.; Hungerbühler, E.; Wagner, P. *Tetrahedron: Asymmetry* **2001**, *12*, 2103–2107. (b) Palomo, C.; Oiarbide, M.; Garcia, J. M.; Gonzalez, A.; Pazos, R.; Odriozola, J. M.; Banuelos, P.; Tello, M.; Linden, A. *J. Org. Chem.* **2004**, *69*, 4126–4134. (c) Pereira, R. *Crit. Rev. Biotechnol.* **1998**, *18*, 25–83. (d) Rabasseda, X.; Sorbera, L. A.; Castaner, J. *Drugs Future* **1999**, *24*, 1057.
7. For some of the recent examples, see: (a) Junge, K.; Hagemann, B.; Enthaler, S.; Oehme, G.; Michalik, M.; Monsees, A.; Riermeier, T.; Dingerdissen, U.; Beller, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 5066–5069. (b) Hu, A.; Ngo, H. L.; Lin, W. *Angew. Chem., Int. Ed.* **2004**, *43*, 2501–2504. (c) Fujiwara, Y.; Katagiri, T.; Uneyama, K. *Tetrahedron Lett.* **2003**, *44*, 6161–6163.
8. (a) Kaluzna, I. A.; Feske, B. D.; Wittayanan, W.; Ghiviriga, I.; Stewart, J. D. *J. Org. Chem.* **2005**, *70*, 342–345. (b) Kaluzna, I. A.; Matsuda, T.; Sewell, A. K.; Stewart, J. D. *J. Am. Chem. Soc.* **2004**, *126*, 12827–12832.
9. (a) Dahl, A. C.; Madsen, J. O. *Tetrahedron: Asymmetry* **1998**, *9*, 4395–4417. (b) Crump, D. R. *Aust. J. Chem.* **1982**, *35*, 1945.
10. Burk, M. J.; Harper, T. G. P.; Kalberg, C. S. *J. Am. Chem. Soc.* **1995**, *117*, 4423–4424.
11. Zhou, B.; Gopalan, A. S.; VanMiddlesworth, F.; Shieh, W. R.; Sih, C. J. *J. Am. Chem. Soc.* **1983**, *1057*, 5925.
12. (a) Sterk, D.; Stephan, M. S.; Mohar, B. *Tetrahedron: Asymmetry* **2002**, *13*, 2605–2608. (b) Deol, B. S.; Ridley, D. D.; Simpson, G. W. *Aust. J. Chem.* **1976**, *29*, 2459.
13. (a) Seebach, D.; Renaud, P.; Schweizer, W. B.; Züger, M. F.; Brienne, M.-J. *Helv. Chim. Acta* **1984**, *67*, 1843–1853. (b) Bertau, M.; Bürli, M.; Hungerbühler, E.; Wagner, P. *Tetrahedron: Asymmetry* **2001**, *12*, 2103–2107.
14. (a) Hamdani, M.; De Jeso, B.; Deleuze, H.; Maillard, B. *Tetrahedron: Asymmetry* **1993**, *4*, 1229–1232. (b) Nakamura, K.; Miyai, T.; Nozaki, K.; Oshio, K.; Oka, K.; Ohno, K. *Tetrahedron Lett.* **1986**, *27*, 3155.
15. Mangone, C. P.; Pereyra, E. N.; Argimon, S.; Moreno, S.; Baldessari, A. *Enzyme Microb. Technol.* **2002**, *30*, 596–601.
16. (a) Frater, G.; Müller, U.; Grunther, W. *Tetrahedron* **1984**, *40*, 1269–1277. (b) Shieh, W. R.; Sih, C. J. *Tetrahedron: Asymmetry* **1993**, *4*, 1259–1269.
17. (a) Cabon, O.; Buisson, D.; Larcheveque, M.; Azerad, R. *Tetrahedron: Asymmetry* **1995**, *6*, 2199–2210. (b) Hamdani, M.; De Jeso, B.; Deleuze, H.; Saux, A.; Maillard, B. *Tetrahedron: Asymmetry* **1993**, *4*, 1233–1236. (c) Akita, H.; Todoroki, R.; Endo, H.; Ikari, Y.; Oishi, T. *Synthesis* **1993**, 513–516.
18. (a) Levy, L. M.; Dehli, J. R.; Gotor, V. *Tetrahedron: Asymmetry* **2003**, *14*, 2053–2058. (b) Sato, T.; Maeno, H.; Noro, T.; Fujisawa, Y. *Chem. Lett.* **1988**, 1739–1742.
19. Rodriguez, S.; Schroeder, K. T.; Kayer, M. M.; Stewart, J. D. *J. Org. Chem.* **2000**, *65*, 2586–2587.
20. Wan, X.; Sun, Y.; Luo, Y.; Li, D.; Zhang, Z. *J. Org. Chem.* **2005**, *70*, 1070–1072.
21. Palomo, C.; Oiarbide, M.; Aizpurua, J. M.; González, A.; Garcia, J. M.; Landa, C.; Odriozola, I.; Linden, A. *J. Org. Chem.* **1999**, *64*, 8193–8200.

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A short and novel synthesis of carbocyclic nucleosides and 4′-*epi*-carbocyclic nucleosides from 2-cyclopenten-1-ones☆

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Abstract—Carbocyclic nucleoside analogues remain interesting target molecules having the potential to combine biological activity with greater metabolic stability than their sugar counterparts. This paper describes a rapid and versatile synthetic approach to such compounds based on commercial cyclopentenones (e.g., **1**) that has been developed in our laboratory. Carbocyclic nucleosides like 2′-methyl-aristeromycin **6** were synthesized in racemic form in 5 steps via key intermediate **4**. The procedure was also adapted to the preparation of 4′-epi-carbocyclic nucleosides using epoxide **17** instead of **4** and employing the same methodology.

1. Introduction

Modified nucleosides are presently the object of intense research activity in medicinal chemistry due to their potential as antiviral agents. As part of our on-going antiviral program, we have found that 2′-methyl-branched nucleosides showed particularly promising potential.[1–3] Most notably to date, a prodrug of 2′-methyl-cytidine is currently in Phase II clinical trials as an anti-hepatitis C drug.[4] It was therefore relevant to consider the preparation of carbocyclic analogues of our lead compounds. Since 2′-branched carbocycles[5] had not been reported when this work was initiated, it was necessary to design a synthetic route giving rapid access to this class of molecules. Many enantioselective syntheses of carbocycles have been reported starting with D- or L-ribose[6–9] and D- or L-ribonolactone.[10–13] All of them are non-trivial or lengthy and, appeared difficult to adapt to the preparation of branched carbocycles. Furthermore, the powerful antiviral activity of some L-nucleosides like Telbivudine[14–16] or Lamivudine[17,18] prompted us to opt for a synthesis of our targets as racemic mixtures in the first instance. Most synthetic procedures for racemic preparation of carbocycles use either Vince lactam[19–22] or cyclopentadiene.[23,24] Again, the adaptation of a known procedure to the synthesis of our molecules seemed to be problematic and would have led to synthetic routes of more than 15 steps. It was therefore decided to try and find a novel approach allowing a rapid and efficient access to 2′-branched carbocycles. This research resulted in the shortest synthesis of racemic carbocycles reported so far and is disclosed herein.

2. Results and discussion

2.1. General strategy

In every approach we considered, introduction of the 2′-branching seemed to be the weak link of the synthesis and it was therefore decided to opt for a starting compound already bearing it. The retrosynthetic analysis for purine derivatives is shown in Figure 1. Epoxide ring opening was

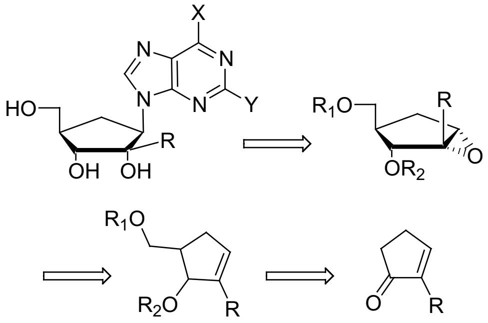

Figure 1. Retrosynthetic analysis.

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Keywords: Nucleoside analogues; Carbocycles; Aristeromycin; Hepatitis C; Antivirals.

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chosen as the means of introduction of the base[25–27] taking advantage of the presence of the 2′-branching to control the regioselectivity of the reaction. The core of carbocyclic pseudo-nucleosides being a cyclopentane, we were naturally led to cyclopentenones, appropriately substituted in position 2, as our starting point. This class of molecules present several key advantages (a) bearing the targeted 2′-branching, which can be changed by switching to another ketone, (b) having the 3′-oxygen of the future carbocycle, (c) having a double bond ready for epoxidation, (d) having a keto group making possible an α-alkylation for introduction of the 5′-carbon, (e) being achiral and (f) being commercially available at a reasonable price.

2.2. Preparation of key epoxide 4

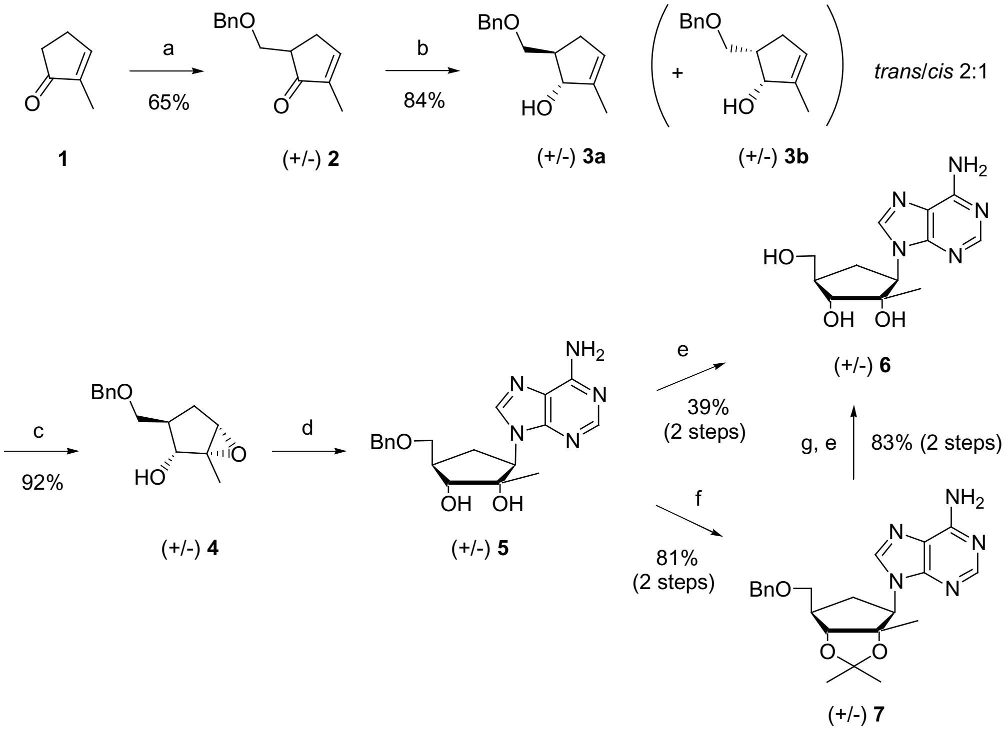
Introduction of the nucleoside 4′-hydroxymethyl group on ketone **1** (Scheme 1) was not a trivial task: 2-cyclopenten-1-ones are notoriously troublesome substrates for α-alkylation reactions.[28,29] For instance, attempts to react gaseous formaldehyde on the enolate of **1** failed. The successful method came from the use of benzyloxymethyl (BOM) halides as the alkylating agent, which would potentially help introduce an already protected 4′-hydroxymethyl group. Whilst this reaction failed when attempted with BOM chloride at −50 °C and the formation of a complex mixture of products was observed at higher temperatures, freshly prepared BOM bromide[30] gave acceptable yields when it was reacted with the lithium enolate of **1** at −78 °C. When ketone **2** was treated with $LiAlH_4$ at −78 °C, alcohols **3** were obtained in 84% yield as a 2:1 mixture of diastereoisomers favoring the desired trans. The ratio remained similar at −30 and 0 °C with the concomitant formation of side products. To our delight, alcohols **3a/3b** were very easily separated on silica gel chromatography. The two last nucleoside stereogenic carbons were introduced in one step during the peroxy acid-promoted epoxidation of **3a**. The allylic alcohol allowed perfect control on the stereochemistry of the reaction and epoxide **4** was obtained as the sole product in excellent yield.

2.3. Synthesis of carbocyclic nucleosides

Having everything in place for the introduction of the base, **4** was treated with the sodium salt of adenine in DMF at 100 °C. The 2′-methyl induced a perfect regio- and stereoselectivity, the attack occurring from the β-face on the 1′-carbon exclusively. Due to its poor solubility, purification of nucleoside **5** from the excess of adenine was not satisfactory but could be made much easier when crude **5** was directly protected as its 2′,3′-isopropylidene derivative **7**. Target compound **6** was obtained by either palladium-catalyzed hydrogenolysis of the benzyl protecting group of **5** or double deprotection of **7**. This synthesis resulted in the efficient first synthesis of (+/−)-2′-methyl-aristeromycin **6** in 5–7 steps and 23% overall yield.

A confirmation of the structure of this series of molecules was given by X-ray analysis performed on a single-crystal of **7** grown in DCM/acetone (Fig. 2).

This synthetic method is applicable to other purines, sometimes with minor changes. For instance, guanine reacted very poorly with **4** (ca. 6% yield) but after protection



Scheme 1. Reagents and conditions: (a) LDA, BOM bromide, THF, −78 to −50 °C; (b) $LiAlH_4$, ether, −78 to −60 °C; (c) *m*-CPBA, DCM, 0 °C; (d) NaH, adenine, DMF, 100 °C; (e) palladium hydroxide on charcoal, cyclohexene, MeOH, reflux; (f) *p*-toluenesulfonic acid, 2,2-dimethoxypropane, acetone, RT; (g) trifluoroacetic acid 90%, 0 °C.

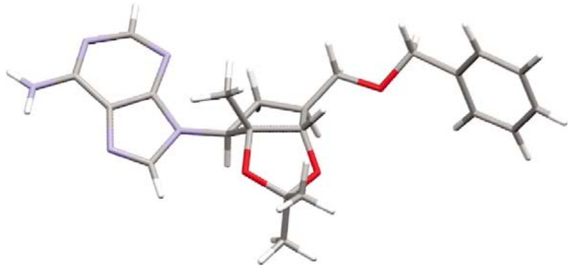
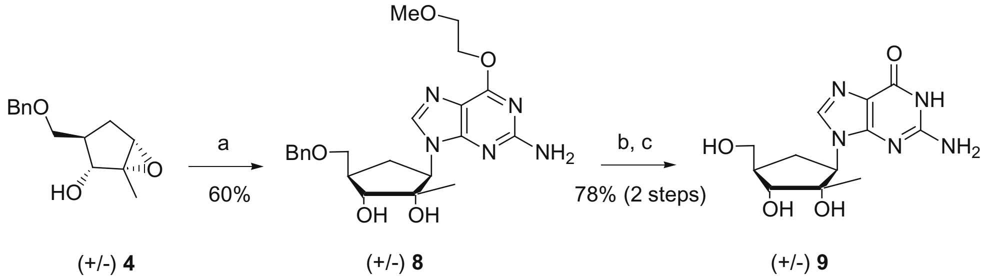


Figure 2. Single-crystal structure of fully protected carbocycle **7** (1′*S*,2′*R*,3′*S*,4′*S* enantiomer).

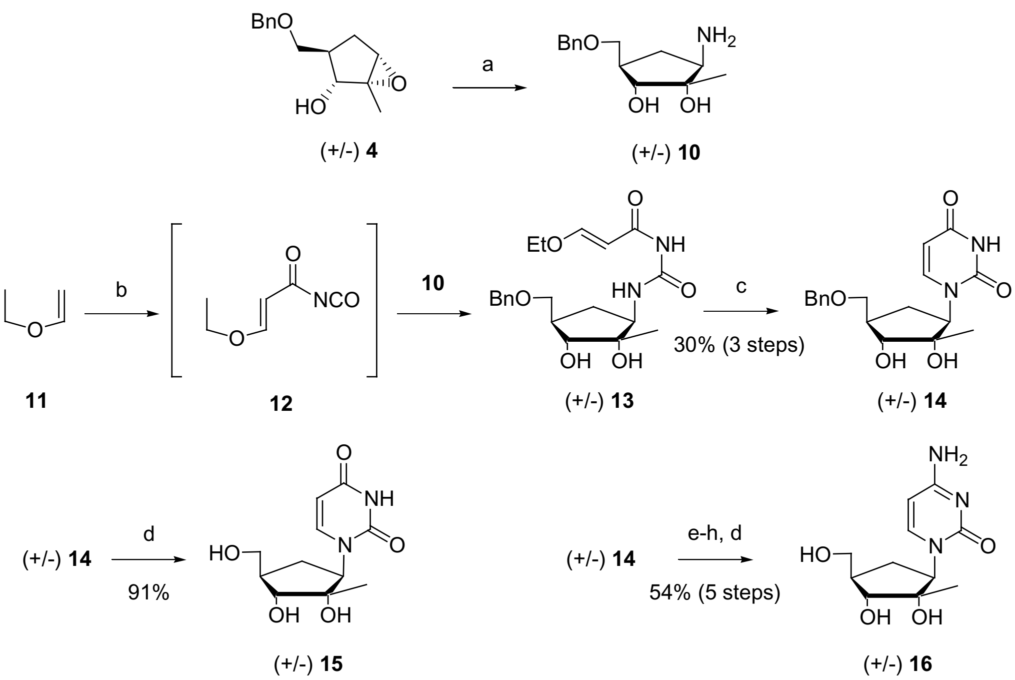
of the base with a methoxyethoxy group,[31,32] the reaction proceeded smoothly and **8** was obtained in reasonable yield (Scheme 2). Carbocycle **8** was then deprotected to afford racemic 2′-methyl-guanosine analogue **9**.

We then turned our attention to the preparation of carbocyclic nucleosides having a pyrimidine base. A slight modification to the general synthesis proved necessary to get acceptable yields. Even though uracil salts were shown to react slowly with epoxides,[32] it was found more advantageous to build the pyrimidine ring by elaboration of the amine group of **10** (Scheme 3). Key epoxide **4** was opened with ammonia with perfect regio- and stereoselective control. Cyclopentylamine **10** was used without purification in a uracil ring-construction process. In order to do that, we adapted previously described procedures:[33–35] ethylvinyl ether **11** was reacted with chlorocarbonyl isocyanate then treated with triethylamine to give isocyanate **12**. The latter compound was directly condensed with **10** in situ. Without prior purification, **13** was cyclized under acidic conditions to afford carbocycle **14**. This 3-step-1-pot synthesis gave access to two pyrimidine derivatives. First, removal of the benzyl-protecting group of **14** afforded uridine analogue **15** in 27% yield from **4**.

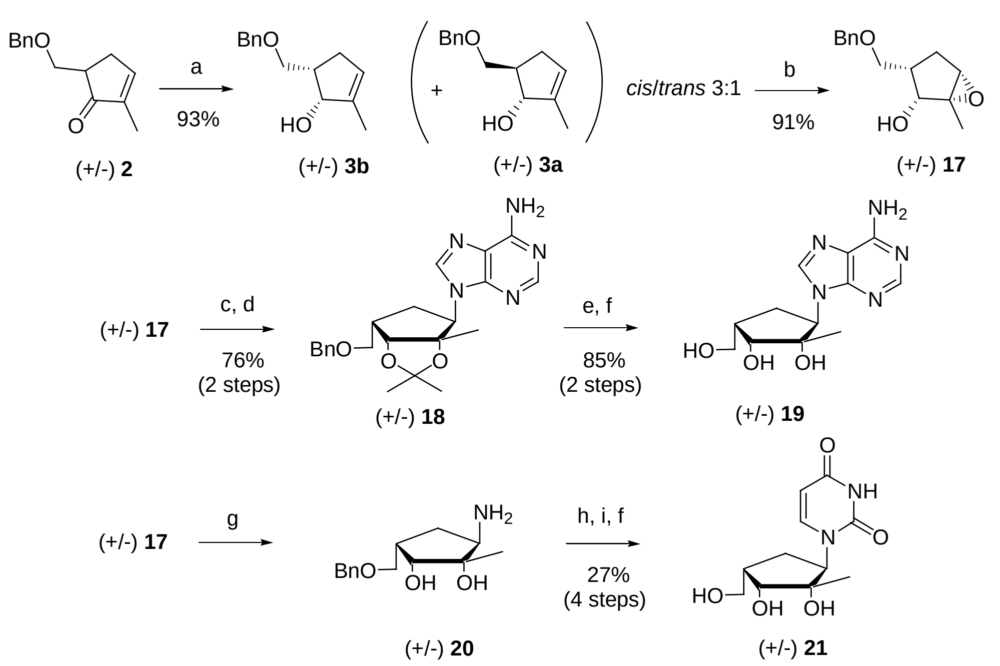
On the other hand, a simple adaptation of the method of Miah et al.[36] provided the cytidine analogue. After protection with an isopropylidene, **14** was activated with *p*-nitrophenol and treated with ammonia. The product was



Scheme 2. Reagents and conditions: (a) NaH, 2-amino-6-(methoxyethoxy)-purine, DMF, 125 °C; (b) 3 N HCl, dioxane, 80 °C; (c) palladium hydroxide on charcoal, cyclohexene, MeOH, reflux.



Scheme 3. Reagents and conditions: (a) NH_3, MeOH, 130 °C; (b) *N*-(chlorocarbonyl)-isocyanate, THF, 0 °C then Et_3N, 0 °C then **10**, −40 °C; (c) 1 N H_2SO_4, dioxane, 100 °C; (d) palladium hydroxide on charcoal, cyclohexene, MeOH, reflux; (e) *p*-toluenesulfonic acid, 2,2-dimethoxypropane, acetone, RT; (f) trifluoroacetic anhydride, *N*-methylpyrrolidine then *p*-nitrophenol, MeCN, 0 °C; (g) NH_3, MeOH, 60 °C; (h) trifluoroacetic acid 90%, 0 °C.



Scheme 4. Reagents and conditions: (a) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH, 0 °C; (b) *m*-CPBA, DCM, 0 °C; (c) NaH, adenine, DMF, 100 °C; (d) *p*-toluenesulfonic acid, 2,2-dimethoxypropane, acetone, RT; (e) trifluoroacetic acid 90%, 0 °C; (f) palladium hydroxide on charcoal, cyclohexene, MeOH, reflux; (g) NH_3, MeOH, 130 °C; (h) *N*-(chlorocarbonyl)-isocyanate, THF, 0 °C then Et_3N, 0 °C then **20**, −40 °C; (i) 1 N H_2SO_4, dioxane, 100 °C.

directly deprotected to give (+/−)-2′-methyl-carbodine **16** in 5 steps and 54% yield from **14**.

2.4. Synthesis of 4′-epi-carbocyclic nucleosides

An interesting feature of our carbocycle synthesis is the possibility of using the minor product of the reduction step of ketone **2** (Scheme 1), cis-alcohol **3b**, for the straightforward preparation of seldom reported 4′-epi-carbocycles.[37] Moreover, after reinvestigation of the reduction of **2**, it proved possible to change dramatically the stereochemical outcome of the reaction. When **2** was subjected to Luche's reduction conditions ($NaBH_4$ in presence of Ce^{3+}),[38,39] **3b** was obtained as the major product of a 3:1 mixture in excellent yield (Scheme 4). Diol **3b** was epoxidized with *m*-chloroperoxybenzoic acid to give **17** as the sole product of the reaction. Then, the chemistry previously described for **4** was applied to **17**. Reaction with adenine sodium salt followed by protection led to carbocycle **18**. In a similar fashion to **7**, the structure of this compound was confirmed by X-ray diffraction of a single crystal grown in DCM/acetone. After two deprotections, racemic 2′-methyl-4′-epi-aristeromycin **19** was obtained in good yield. On the other hand, when submitted to epoxide-opening conditions with ammonia, **17** led to cyclopentylamine **20**. The latter was used in the uracil-ring construction process described for **10** to afford uridine derivative **21** in moderate yield.

3. Conclusion

We have developed a new route for the synthesis of carbocyclic nucleosides. This method was also used for the preparation of 4′-epi-carbocycles. 2-Cyclopenten-1-ones give rapid access to a large number of compounds of potential antiviral interest through key intermediates **4** and **17**. Furthermore, the introduction of any 2′-branching-group can be achieved by using the appropriate ketone as a starting material. This versatile approach gives the shortest access to racemic carbocylic nucleosides reported so far.

Compounds **6**, **9**, **15**, **16**, **19** and **21** were evaluated for antiviral activity in cell culture experiments toward the following viruses: Bovine Viral Diarrhea, Hepatitis B, Human Immunodeficiency, Dengue and West Nile. No activity was found for any of these molecules, nor was there any cytotoxicity to the host cells.

4. Experimental

4.1. General

All ^1H chemical shifts are reported in δ relative to $CHCl_3$ (δ 7.26) or DMSO (δ 2.55). All ^{13}C chemical shifts are reported in δ relative to $CDCl_3$ (centre of triplet, δ 77.2) or DMSO-d_6 (centre of septet, δ 39.5). The spin multiplicities are indicated by the symbols s (singlet), d (doublet), t (triplet), m (multiplet) and, br (broad). Reactions were monitored by thin-layer chromatography (TLC) using Merck silica gel 60-F_{254} precoated plates with visualization by irradiation with a UV lamp or by charring after immersion in a solution of $(NH_4)_2SO_4$ and H_2SO_4 in aqueous EtOH or by charring after immersion in a 5% solution of ninhydrin in EtOH. TLC plates were developed with solvent systems (A) EtOAc/hexanes 1:1, (B) DCM/MeOH 9:1 or (C) DCM/MeOH 8:2. Column chromatographies were performed on either silica gel 60 (normal phase) or C_{18}-branched silica gel 40–63 μm (reverse phase) and eluted with the indicated solvent system. Yields refer to chromatographically and spectroscopically (NMR) homogeneous materials. The reactions were generally carried out in an argon atmosphere using Fluka dry solvents. BOM bromide was synthesized according to Ref. 30 using either paraformaldehyde or trioxane indifferently. 2-Amino-6-(methoxyethoxy)-purine was synthesized according to Ref. 31. All other chemicals were purchased from Sigma-Aldrich or Acros.

4.1.1. (+/−)-2-Methyl-5-(benzyloxymethyl)-2-cyclopenten-1-one (2). To a solution of 2-methyl-2-cyclopenten-1-one **1** (15.0 g, 156 mmol) in THF (600 mL) was added dropwise a 1.8 M solution of LDA in hexanes (87 mL, 157 mmol) at −78 °C over 10 min. The solution was stirred for 1 h at −78 °C. Then, freshly prepared BOM bromide (purity ca. 70% by NMR) (48.0 g, 167 mmol) was added dropwise over 10 min. The solution was stirred for 3 h at −78 °C then allowed to warm up to −50 °C over 1.5 h. The reaction was quenched with sat. $NaHCO_3$ solution (300 mL) and THF was evaporated. The residue was taken up in EtOAc (400 mL) and the solution was extracted with sat. $NaHCO_3$ solution (2×400 mL) and brine (400 mL). The organic phase was dried over Na_2SO_4 and the solvent was evaporated. The residue was purified by column chromatography (hexanes/EtOAc 9:1) to afford **2** (22.0 g, 65%) as a pale yellow oil: TLC $R_f=0.47$ (A); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.81 (m, 3H), 2.55–2.80 (m, 3H), 3.64 (dd, 1H, $J=6.4$, 9.2 Hz), 3.77 (dd, 1H, $J=3.8$, 9.2 Hz), 4.52 (s, 2H), 7.36 (m, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 9.6, 30.6, 45.1, 69.2, 72.4, 126.9, 127.6, 137.5, 140.7, 157.2, 208.7; HRMS(FAB) Calcd $[M+H]^+$ ($C_{14}H_{17}O_2$): 217.1229, found: 217.1216.

4.1.2. (+/−)-2-Methyl-5-(benzyloxymethyl)-2-cyclopenten-1-ol (3). *Method A*. To a suspension of $LiAlH_4$ (2.2 g, 57.1 mmol) in ether (175 mL) at −78 °C was added dropwise a solution of **2** (12.3 g, 57.0 mmol) in ether (75 mL) over 10 min. The slurry was stirred and slowly warmed up to −60 °C over 2 h. Then, the reaction was quenched with successive careful additions of EtOAc (30 mL), MeOH (30 mL) and H_2O (200 mL). The milky aqueous phase was washed with ether (2×100 mL). The organic phases were pooled and washed with H_2O (2×300 mL), dried over Na_2SO_4 and the solvents were evaporated. The residue was purified by column chromatography (hexanes/EtOAc 9:1). The first eluted product was **3b** (3.5 g, 28%), which was obtained as a colorless oil: TLC $R_f=0.47$ (A); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.81 (m, 3H), 2.26 (m, 2H), 2.59 (m, 2H), 3.69 (m, 2H), 4.57 (s, 2H), 4.61 (br, 1H), 5.52 (m, 1H), 7.36 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.4, 33.0, 40.8, 69.8, 72.6, 79.1, 126.5, 127.1, 127.8; 137.6, 141.3; HRMS(FAB) Calcd $[M+H]^+$ ($C_{14}H_{19}O_2$): 219.1385, found: 219.1403. This product was followed by **3a** (7.0 g, 56%) as a colorless oil: TLC $R_f=0.42$ (A); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.78 (m, 3H), 1.96 (m, 1H), 2.12 (br, 1H), 2.37–2.59 (m, 2H), 3.56 (m, 2H), 4.46 (br, 1H), 4.58 (s, 2H), 5.45 (m, 1H), 7.35 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.0, 32.6, 47.6, 72.3, 72.4, 81.7, 125.5, 127.0, 127.1, 127.7, 137.8, 140.5; HRMS(FAB) Calcd $[M+H]^+$ ($C_{14}H_{19}O_2$): 219.1385, found: 219.1404.

Method B. To a solution of **2** (2.0 g, 9.2 mmol) in MeOH (55 mL) was added $CeCl_3\cdot 7H_2O$ (3.4 g, 14.0 mmol) at 0 °C. The solution was stirred for 30 min at this temperature. Then, $NaBH_4$ (0.7 g, 18.4 mmol) was carefully added portionwise. The milky suspension was allowed to warm up to room temperature and stirred for 3 h. The reaction was quenched by addition of acetic acid (3 mL) and MeOH was evaporated. The remaining solid was taken up in EtOAc (100 mL) and extracted with sat. NH_4Cl solution (2×100 mL), sat. $NaHCO_3$ solution (100 mL) and brine (100 mL). The organic phase was dried over Na_2SO_4 and the solvent was evaporated. The residue was purified by column chromatography (hexanes/EtOAc 9:1) to afford **3b** (1.4 g, 70%) and **3a** (0.5 g, 23%) as colorless oils.

4.1.3. (+/−)-(1α,2β,3α,5α)-1-Methyl-2-hydroxy-3-(benzyloxymethyl)-6-oxabicyclo[3.1.0]hexane (4). To a solution of **3a** (2.0 g, 9.2 mmol) in DCM (45 mL) was added *m*-chloroperoxybenzoic acid 77% (2.8 g, 12.0 mmol) at 0 °C. The solution was stirred at 0 °C for 1 h and then allowed to warm-up to room temperature over 2 h. To the white suspension was added sat. $NaHCO_3$ solution (50 mL). The mixture was extracted with EtOAc/sat. $NaHCO_3$ solution (100 mL each). The organic phase was washed with H_2O (2×100 mL), dried over Na_2SO_4 and evaporated to dryness. The residue was purified by column chromatography (hexanes/EtOAc 8:2) to afford **4** (2.0 g, 92%) as a colorless oil, which solidified in the fridge: TLC $R_f=0.25$ (A); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51 (s, 3H), 1.56 (m, 1H), 1.89 (m, 1H), 2.12 (m, 1H), 2.29 (br, 1H), 3.31 (s, 1H), 3.49 (dd, 1H, $J=6.3$, 9.1 Hz), 3.62 (dd, 1H, $J=5.1$, 9.1 Hz), 3.90 (d, 1H, $J=7.4$ Hz), 4.54 (s, 2H), 7.36 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 27.9, 40.9, 60.7, 64.6, 69.9, 72.4, 76.6, 126.9, 127.7; 137.7; HRMS(FAB) Calcd $[M+H]^+$ ($C_{14}H_{19}O_3$): 235.1334, found: 235.1348.

4.1.4. (+/−)-2′-*C*-Methyl-5′-*O*-benzyl-aristeromycin (5). *Method A*. To a suspension of adenine (1.75 g, 12.9 mmol) in DMF (30 mL) was added NaH (60% oil dispersion) (0.43 g, 10.8 mmol) at room temperature. After the evolution of hydrogen had ceased, the creamy suspension was stirred at 80 °C for 20 min. Epoxide **4** (1.04 g, 4.3 mmol) dissolved in DMF (20 mL) was added via a syringe. The resulting suspension was stirred at 100 °C for 18 h then cooled down to room temperature. The solid was filtered over celite and rinsed with DCM. The filtrate was evaporated. The brown residue was purified by column chromatography (DCM/MeOH 94:6) to afford **5** (0.65 g, 41%) as a beige powder: TLC $R_f=0.20$ (B); mp 180.4–181.5 °C; ^{1}H NMR (200 MHz, DMSO) δ 0.68 (s, 3H), 2.09–2.46 (m, 3H), 3.65–3.74 (m, 3H), 4.56 (s, 2H), 4.65 (s, 1H), 4.73 (m, 1H), 4.90 (d, 1H, $J=6.3$ Hz), 7.23 (br, 2H), 7.32 (m, 5H), 8.12 (s, 1H), 8.16 (s, 1H); ^{13}C NMR (75.5 MHz, DMSO) δ 20.6, 28.9, 42.0, 60.8, 70.7, 72.0, 76.2, 78.4, 118.5, 127.2, 127.3, 128.1, 138.4, 139.8, 149.7, 152.0, 155.8; HRMS(FAB) Calcd $[M+H]^+$ ($C_{19}H_{24}N_5O_3$): 370.1879, found: 370.1861.

Method B. A solution of **7** (500 mg, 1.22 mmol) in TFA 90% (8 mL) was stirred for 1 h at 0 °C. Then, the solution was basified by the addition of ammonia-saturated methanol and the solvents were evaporated. The residue was taken up in cold H_2O (ca. 10 mL) and filtered. The solid was washed with cold H_2O and dried in the oven at 60 °C under vacuum. Carbocyclic nucleoside **5** was obtained (400 mg, 90%) as a white solid.

4.1.5. (+/−)-2′-*C*-Methyl-aristeromycin (6). A solution of **5** (330 mg, 0.89 mmol) in MeOH (30 mL) was treated with palladium hydroxide (20% on charcoal) (200 mg) at 0 °C. Cyclohexene (10 mL) was added and the mixture was refluxed for 15 h. The suspension was cooled down to room temperature, filtered over celite and the solvents were evaporated. The residue was crystallized from H_2O to afford **6** (228 mg, 92%) as a white powder: TLC $R_f = 0.21$ (C); mp 209.1–210.2 °C; UV (H_2O) $\lambda_{max} = 259$ nm ($\varepsilon = 13{,}100$); ^1H NMR (300 MHz, DMSO) δ 0.68 (s, 3H), 1.95–2.22 (m, 2H), 2.38 (m, 1H), 3.58–3.77 (m, 3H), 4.62 (m, 1H), 4.68–4.89 (m, 3H), 7.23 (br, 2H), 8.14 (s, 1H), 8.26 (s, 1H); ^{13}C NMR (75.5 MHz, DMSO) δ 20.6, 28.4, 44.0, 60.6, 61.1, 75.7, 78.7, 118.4, 139.8, 149.8, 152.0, 155.8; HRMS(FAB) Calcd $[M+H]^+$ ($C_{12}H_{18}N_5O_3$): 280.1410, found: 280.1402.

4.1.6. (+/−)-2′-*C*-Methyl-2′,3′-*O*-isopropylidene-5′-*O*-benzyl-aristeromycin (7). This synthesis began like the preparation of **5** using 500 mg (2.13 mmol) of epoxide **4**. After evaporation of DMF, the brown residue was suspended in acetone (32 mL) and 2,2-dimethoxypropane (8 mL). The suspension was acidified with *p*-toluenesulfonic acid (300 mg, 1.75 mmol) and stirred for 2 h at room temperature. The mixture was filtered, the solid was washed with acetone and the filtrate was neutralized with pyridine (300 μL). The solvents were evaporated. The residue was taken up in DCM (100 mL) and extracted successively with H_2O (100 mL), 1 N HCl (100 mL), sat. $NaHCO_3$ solution (100 mL) and brine (100 mL). The organic phase was dried over Na_2SO_4 and the solvent was evaporated. The remaining solid was purified by column chromatography (DCM/MeOH 96:4) to afford **7** (695 mg, 81%) as a beige powder: TLC $R_f = 0.38$ (B); mp 200.4–201.3 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.19 (s, 3H), 1.39 (s, 3H), 1.68 (s, 3H), 2.46 (m, 1H), 2.57 (m, 1H), 2.85 (m, 1H), 3.65 (m, 2H), 4.27 (d, 1H, $J = 2.7$ Hz), 4.63 (s, 2H), 5.05 (dd, 1H, $J = 6.7$, 13.5 Hz), 5.97 (br, 2H), 7.35 (m, 5H), 7.87 (s, 1H), 8.36 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.7, 25.9, 27.8, 30.3, 40.2, 63.9, 70.1, 72.6, 86.3, 88.3, 112.4, 119.2, 127.0, 127.1, 127.8, 137.4, 139.8, 150.3, 151.5, 154.4; HRMS(FAB) Calcd $[M+H]^+$ ($C_{22}H_{28}N_5O_3$): 410.2192, found: 410.2203.

4.1.7. (+/−)-2-Amino-6-deamino-6-(methoxyethoxy)-2′-*C*-methyl-5′-*O*-benzyl-aristeromycin (8). A suspension of 2-amino-6-(methoxyethoxy)-purine (950 mg, 4.54 mmol) in DMF (8 mL) was treated with NaH (60% oil dispersion) (160 mg, 4.00 mmol) at room temperature. After the evolution of hydrogen had ceased, the suspension was stirred at 80 °C for 20 min. Epoxide **4** (375 mg, 1.60 mmol) dissolved in DMF (8 mL) was added via a syringe. The resulting brown solution was stirred at 125 °C for 48 h then cooled down to room temperature. The DMF was evaporated. The brown residue was purified by column chromatography (DCM/MeOH 96:4) to afford **8** (425 mg, 60%) as a beige powder: TLC $R_f = 0.45$ (B); mp 175.7–176.6 °C; ^1H NMR (200 MHz, DMSO) δ 0.70 (s, 3H), 1.94 (m, 1H), 2.23 (m, 1H), 2.44 (m, 1H), 3.32 (s, 3H), 3.62–3.72 (m, 5H), 4.49–4.66 (s, 6H), 4.91 (d, 1H, $J = 6.4$ Hz), 6.41 (br, 2H), 7.33 (m, 5H), 7.92 (s, 1H); ^{13}C NMR (75.5 MHz, DMSO) δ 20.6, 29.2, 41.9, 57.9, 59.8, 64.4, 69.9, 70.8, 72.0, 76.2, 78.5, 113.3, 127.2, 128.1, 138.3, 138.4, 154.5, 159.3, 160.0; HRMS(FAB) Calcd $[M+H]^+$ ($C_{22}H_{30}N_5O_5$): 444.2247, found: 444.2254.

4.1.8. (+/−)-2′-*C*-Methyl-carbocyclic guanosine (9). A solution of **8** (400 mg, 0.90 mmol) in 3 N HCl (70 mL) was stirred for 3 h at 80 °C. Then, the solution was cooled down, evaporated and the residue was basified with ammonia-saturated MeOH. The solvent was evaporated and the residue was rapidly purified by column chromatography (DCM/MeOH 88:12) to afford 2′-*C*-methyl-5′-*O*-benzyl-carbocyclic guanosine as a beige solid: TLC $R_f = 0.30$ (C); ^1H NMR (200 MHz, DMSO) δ 0.71 (s, 3H), 1.88 (m, 1H), 2.23 (m, 1H), 2.40 (m, 1H), 3.59–3.66 (m, 3H), 4.49–4.55 (m, 4H), 4.93 (d, 1H, $J = 6.2$ Hz), 6.52 (br, 2H), 7.34 (m, 5H), 7.75 (s, 1H), 10.64 (br, 1H). A solution of the above 2′-*C*-methyl-5′-*O*-benzyl-carbocyclic guanosine (295 mg, 0.77 mmol) in MeOH (20 mL) was treated with palladium hydroxide (20% on charcoal) (150 mg) at 0 °C. Cyclohexene (5 mL) was added and the mixture was refluxed for 15 h. The suspension was cooled down to room temperature, filtered over celite and the solvents were evaporated. The residue was purified by reverse phase column chromatography (H_2O/MeOH 95:5) to afford **9** (205 mg, 78% from **8**) as a white solid: TLC $R_f = 0.10$ (C); mp > 230 °C (dec); UV (H_2O) $\lambda_{max} = 252$ nm ($\varepsilon = 11{,}200$); ^1H NMR (300 MHz, DMSO) δ 0.73 (s, 3H), 1.88 (m, 1H), 2.06 (m, 1H), 2.36 (m, 1H), 3.60–3.66 (m, 3H), 4.42 (s, 1H), 4.52 (m, 1H), 4.73–4.79 (m, 2H), 6.42 (br, 2H), 7.82 (s, 1H), 10.56 (br, 1H); ^{13}C NMR (75.5 MHz, DMSO) δ 15.7, 20.6, 43.9, 59.5, 60.7, 75.6, 78.8, 116.1, 135.8, 151.5, 153.3, 157.1; HRMS(FAB) Calcd $[M+H]^+$ ($C_{12}H_{18}N_5O_4$): 296.1359, found: 296.1339.

4.1.9. (+/−)-(1β,2β,3α,5α)-1,2-Dihydroxy-1-methyl-3-(benzyloxymethyl)-5-amino-cyclopentane (10). A solution of **4** (900 mg, 3.84 mmol) in ammonia-saturated MeOH (20 mL) was heated at 130 °C under pressure for 3 h. The solution was cooled down, degassed and evaporated to dryness to get 960 mg of **10** as an oily brown residue, which was found homogeneous by TLC and used in the next step without purification: TLC $R_f = 0.14$ (C).

4.1.10. (+/−)-2′-*C*-Methyl-5′-*O*-benzyl-carbocyclic uridine (14). To a solution of *N*-(chlorocarbonyl) isocyanate (894 mg, 8.51 mmol) in THF (9 mL) was slowly added a solution of ethylvinyl ether (804 mg, 11.15 mmol) in THF (6 mL) at 0 °C. The resulting solution was stirred for 20 min at 0 °C. Then, triethylamine (852 mg, 8.42 mmol) in THF (9 mL) was slowly added. The resulting suspension was stirred for 5 min at 0 °C and then, cooled down to −40 °C. A solution of amine **10** (1.920 g, 7.64 mmol) in THF (9 mL) was rapidly added to the mixture and the suspension was allowed to slowly warm up to room temperature. Then, THF was evaporated and the residue was dissolved in dioxane (6 mL). To this solution was added 1 N H_2SO_4 (9 mL) and the mixture was heated at 100 °C for 2 h. Then, the solution was cooled down to room temperature and basified with 3 N ammonia (7 mL). The ammonium salts were precipitated with MeOH and the suspension was filtered. The filtrate was evaporated to dryness and the crude material was purified by column chromatography (DCM/MeOH 96:4) to afford **14** (798 mg, 30%) as a white solid: TLC $R_f = 0.32$ (B); mp

183.1–184.2 °C; ^{1}H NMR (300 MHz, DMSO) δ 0.89 (s, 3H), 1.61 (m, 1H), 2.16 (m, 1H), 2.29 (m, 1H), 3.48 (d, 1H, $J=9.5$ Hz), 3.62 (m, 2H), 4.52 (s, 2H), 4.67 (m, 1H), 5.25 (dd, 1H, $J=2.2$, 8.1 Hz), 7.34 (m, 5H), 7.66 (d, 1H, $J=$ 8.1 Hz), 11.26 (br, 1H); ^{13}C NMR (75.5 MHz, DMSO) δ 20.4, 27.5, 41.8, 61.2, 70.0, 72.2, 76.0, 78.6, 100.7, 127.3, 127.4, 128.1, 138.2, 142.9, 151.2, 162.7; HRMS(FAB) Calcd $[M+H]^+$ ($C_{18}H_{23}N_2O_5$): 347.1607, found: 347.1616.

4.1.11. (+/−)-2′-*C*-Methyl-carbocyclic uridine (15). A solution of **14** (250 mg, 0.72 mmol) in MeOH (20 mL) was cooled down to 0 °C and treated with palladium hydroxide (20% on charcoal) (180 mg). Cyclohexene (7 mL) was added and the mixture was refluxed for 15 h. The suspension was cooled down to room temperature, filtered on celite and the solvents were evaporated. The residue was crystallized from MeOH/*i*-propyl ether to afford **15** (164 mg, 91%) as white crystals: TLC $R_f=0.27$ (C); mp 181.6–182.5 °C; UV (H_2O) $\lambda_{max}=267$ nm ($\varepsilon=9900$); ^{1}H NMR (200 MHz, DMSO) δ 0.92 (s, 3H), 1.61 (m, 1H), 2.00 (m, 1H), 2.17 (m, 1H), 3.44 (m, 1H), 3.56 (m, 2H), 4.39 (s, 1H), 4.67–4.76 (m, 3H), 5.59 (d, 1H, $J=8.0$ Hz), 7.72 (d, 1H, $J=8.0$ Hz), 11.29 (br, 1H); ^{13}C NMR (75.5 MHz, DMSO) δ 20.6, 27.0, 43.6, 60.4, 61.1, 75.8, 78.6, 100.9, 142.9, 151.2, 162.8; HRMS(FAB) Calcd $[M+H]^+$ ($C_{11}H_{17}N_2O_5$): 257.1137, found: 257.1139.

4.1.12. (+/−)-2′-*C*-Methyl-carbodine (16). A suspension of **14** (300 mg, 0.87 mmol) in acetone (25 mL) and 2,2-dimethoxypropane (8 mL) was treated with *p*-toluenesulfonic acid (50 mg, 0.3 mmol). After dissolution of the materials, the solution was stirred for 1 h at room temperature. Then, the mixture was neutralized with pyridine (50 μL) and the solvents were evaporated. The residue was rapidly purified by column chromatography (DCM/MeOH 95:5) to afford 2′-*C*-methyl-2′,3′-*O*-isopropylidene-5′-*O*-benzyl-carbocyclic uridine as a white solid: TLC $R_f=0.48$ (B); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.27 (s, 3H), 1.37 (s, 3H), 1.61 (s, 3H), 2.12–2.22 (m, 2H), 2.47 (m, 1H), 3.51–3.67 (m, 2H), 4.17 (d, 1H, $J=2.9$ Hz), 4.58 (s, 2H), 5.13 (m, 1H), 5.67 (dd, 1H, $J=2.3$, 8.1 Hz), 7.22 (d, 1H, J = 8.1 Hz), 7.36 (m, 5H), 9.29 (br, 1H). To a solution of the above 2′-*C*-methyl-2′,3′-*O*-isopropylidene-5′-*O*-benzyl-carbocyclic uridine (280 mg, 0.73 mmol) in MeCN (8 mL) was added *N*-methylpyrrolidine (700 μL) and trifluoroacetic anhydride (300 μL, 2.12 mmol) at 0 °C. The mixture was stirred for 30 min then *p*-nitrophenol (300 mg, 2.16 mmol) was added. The yellow solution was stirred for 3 h at 0 °C. The mixture was diluted with DCM (20 mL) and extracted with 1 N HCl (20 mL), sat. $NaHCO_3$ solution (3×20 mL) and brine (20 mL). The organic phase was dried over Na_2SO_4 and the solvents were evaporated. The residue was taken up in ammonia-saturated MeOH (30 mL) and stirred at 60 °C for 15 h. The solvent was evaporated and the residue was purified by column chromatography (DCM/MeOH 94:6) to afford 2′-*C*-methyl-2′,3′-*O*-isopropylidene-5′-*O*-benzyl-carbodine as a yellowish solid: TLC $R_f=0.23$ (B); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.23 (s, 3H), 1.36 (s, 3H), 1.60 (s, 3H), 2.09–2.22 (m, 2H), 2.44 (m, 1H), 3.51–3.64 (m, 2H), 4.15 (d, 1H, $J=$ 3.5 Hz), 4.57 (s, 2H), 5.18 (m, 1H), 5.72 (d, 1H, $J=7.4$ Hz), 7.21 (d, 1H, $J=7.4$ Hz), 7.35 (m, 5H). A solution of the above 2′-*C*-methyl-2′,3′-*O*-isopropylidene-5′-*O*-benzyl-carbodine (202 mg, 0.52 mmol) in TFA 90% (5 mL) was stirred for 1 h at 0 °C. Then, the solution was basified by the addition of ammonia-saturated methanol and the solvents were evaporated. The residue was taken up in cold H_2O and filtered. The solid was washed with cold H_2O and dried in the oven at 60 °C under vacuum. 2′-*C*-methyl-5′-*O*-benzyl-carbodine was obtained as an off-white solid and used directly in the next step: TLC $R_f=0.51$ (C). A solution of 2′-*C*-methyl-5′-*O*-benzyl-carbodine (172 mg, 0.50 mmol) in MeOH (20 mL) was cooled down to 0 °C and treated with palladium hydroxide (20% on charcoal) (120 mg). Cyclohexene (7 mL) was added and the mixture was refluxed for 15 h. The suspension was cooled down to room temperature, filtered on celite and the solvents were evaporated. The residue was crystallized from MeOH/*i*-propyl ether to afford **16** (112 mg, 54% from **14**) as a white powder: TLC $R_f=0.20$ (C); mp >200 °C (dec); UV (H_2O) $\lambda_{max}=274$ nm ($\varepsilon=7400$); ^{1}H NMR (200 MHz, DMSO) δ 0.85 (s, 3H), 1.60 (m, 1H), 1.92–2.19 (m, 2H), 3.49–3.63 (m, 3H), 4.54–4.79 (m, 4H), 5.73 (d, 1H, $J=7.4$ Hz), 7.26 (br, 2H), 7.66 (d, 1H, $J=7.4$ Hz); ^{13}C NMR (75.5 MHz, DMSO) δ 20.9, 27.4, 44.0, 60.8, 62.3, 76.1, 78.5, 93.4, 143.8, 155.4; 164.0; HRMS(FAB) Calcd $[M+H]^+$ ($C_{11}H_{18}N_3O_4$): 256.1297, found: 256.1302.

4.1.13. (+/−)-(1β,2β,3α,5β)-1-Methyl-2-hydroxy-3-(benzyloxymethyl)-6-oxabicyclo[3.1.0]hexane (17). The preparation was carried out as described for **4**, using **3b** in place of **3a**. Epoxide **17** was obtained in 91% yield as a colorless oil, which solidified in the fridge: TLC $R_f=0.25$ (A); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.53 (s, 3H), 1.75 (dd, 1H, $J=2.1$, 14.9 Hz), 1.98 (dd, 1H, $J=9.5$, 14.9 Hz), 2.51 (m, 1H), 3.29 (s, 1H), 3.38 (dd, 1H, $J=5.3$, 9.0 Hz), 3.94 (dd, 1H, $J=9.0$, 9.5 Hz), 4.29 (d, 1H, $J=8.2$ Hz), 4.46 (d, 1H, $J=11.7$ Hz), 4.58 (d, 1H, $J=11.7$ Hz), 7.36 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.3, 28.7, 37.0, 61.4, 66.8, 72.4, 72.5, 75.6, 127.1, 127.8; 137.1; HRMS(FAB) Calcd $[M+H]^+$ ($C_{14}H_{19}O_3$): 235.1334, found: 235.1343.

4.1.14. (+/−)-2′-*C*-Methyl-2′,3′-*O*-isopropylidene-4′-epi-5′-*O*-benzyl-aristeromycin (18). The preparation was carried out as described for **7**, using **17** in place of **4**. Carbocyclic nucleoside **18** was obtained in 76% yield (2 steps) as a beige powder: TLC $R_f=0.37$ (B); mp 104.8–105.7 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.01 (s, 3H), 1.40 (s, 3H), 1.56 (s, 3H), 2.34 (m, 1H), 2.48 (m, 1H), 3.11 (m, 1H), 3.74 (m, 2H), 4.44 (d, 1H, $J=4.0$ Hz), 4.62 (m, 2H), 5.01 (dd, 1H, $J=2.2$, 7.1 Hz), 6.38 (br, 2H), 7.35 (m, 5H), 7.88 (s, 1H), 8.40 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.0, 25.3, 26.9, 31.9, 42.3, 63.9, 68.9, 72.7, 85.9, 91.6, 110.5, 118.9, 127.0, 127.7, 137.6, 138.7, 149.9, 152.1, 154.7; HRMS(FAB) Calcd $[M+H]^+$ ($C_{22}H_{28}N_5O_3$): 410.2192, found: 410.2173.

4.1.15. (+/−)-2′-*C*-Methyl-4′-epi-aristeromycin (19). The preparation was carried out as described for **6**, using **18** in place of **7**. Carbocyclic nucleoside **19** was obtained in 85% yield (2 steps) as a white powder: TLC $R_f=0.23$ (C); mp 254.3–255.2 °C; UV (H_2O) $\lambda_{max}=260$ nm ($\varepsilon=13{,}600$); ^{1}H NMR (200 MHz, DMSO) δ 0.88 (s, 3H), 1.95 (m, 1H), 2.56 (m, 2H), 3.44 (m, 1H), 3.61 (m, 1H), 3.71 (m, 1H), 4.50 (t, 1H, $J=5.1$ Hz), 4.80 (s, 1H), 4.87 (m, 1H), 4.90 (d, 1H,

$J=5.1$ Hz), 7.21 (br, 2H), 8.12 (s, 1H), 8.17 (s, 1H); ^{13}C NMR (75.5 MHz, DMSO) δ 20.4, 27.5, 40.5, 60.9, 61.4, 76.5, 80.1, 118.7, 140.7, 150.0, 151.8, 155.8; HRMS(FAB) Calcd $[M+H]^+$ ($C_{12}H_{18}N_5O_3$): 280.1410, found: 280.1417.

4.1.16. (+/−)-(1β,2β,3β,5α)-1,2-Dihydroxy-1-methyl-3-(benzyloxymethyl)-5-amino-cyclopentane (20). The preparation was carried out as described for **10**, using **17** in place of **4**. Cyclopentylamine **20** was obtained as a brown oil and directly used in the next step without purification: TLC $R_f=0.13$ (C).

4.1.17. (+/−)-2′-*C*-Methyl-4′-epi-carbocyclic uridine (21). The preparation was carried out as described for **15**, using **17** in place of **4**. Carbocyclic nucleoside **21** was obtained in 27% yield (4 steps from **17**) as a white powder: TLC $R_f=0.29$ (C); mp 195.5–196.4 °C; UV (H_2O) $\lambda_{max}=267$ nm ($\varepsilon=10{,}400$); ^{1}H NMR (200 MHz, DMSO) δ 1.00 (s, 3H), 1.87 (m, 2H), 2.31 (m, 1H), 3.40 (dd, 1H, $J=6.8$, 10.5 Hz), 3.60 (m, 2H), 4.49 (m, 2H), 4.82 (d, 1H, $J=4.2$ Hz), 4.89 (m, 1H), 5.54 (d, 1H, $J=8.0$ Hz), 7.67 (d, 1H, $J=8.0$ Hz), 11.23 (br, 1H); ^{13}C NMR (75.5 MHz, DMSO) δ 20.4, 27.1, 40.5, 60.7, 61.0, 76.5, 79.9, 100.3, 143.5, 151.4, 162.9; HRMS(FAB) Calcd $[M+H]^+$ ($C_{11}H_{17}N_2O_5$): 257.1137, found: 257.1140.

4.2. X-ray crystallographic data

Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 284302 and 284303.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.10.037

References and notes

1. Sommadossi, J.-P.; La Colla, P. WO PCT Int. Appl. 0190121, 2001.
2. Sommadossi, J.-P.; La Colla, P.; Storer, R.; Gosselin, G. WO PCT Int. Appl. 2004003000, 2004.
3. Sommadossi, J.-P.; La Colla, P.; Standring, D. N.; Bichko, V. V.; Qu, L. WO PCT Int. Appl. 2004058792, 2004.
4. Afdhal, N. H.; Rodriguez-Torres, M.; Lawitz, E. J.; Godofsky, E. W.; Chao, G.; Fielman, B. A.; Knox, S.; Brown, N. A. *Enhanced Antiviral Efficacy for Valopicitabine (NM283) Plus PEG-Interferon in Hepatitic C Patients with HCV Genotype-1 Infection: Results of a Phase IIa Multicenter Trial*; 39th Annual Meeting of the European Association for the Study of the Liver; Paris, France; 13–17 April, 2005.
5. In this paper, numbering of compounds is given by analogy with the parent ribonucleosides.
6. Wang, P.; Gullen, B.; Newton, M. G.; Cheng, Y.-C.; Schinazi, R. F.; Chu, C. K. *J. Med. Chem.* **1999**, *42*, 3390–3399.
7. Wang, P.; Agrofoglio, L. A.; Newton, M. G.; Chu, C. K. *J. Org. Chem.* **1999**, *64*, 4173–4178.
8. Song, G. Y.; Paul, V.; Choo, H.; Morrey, J.; Sidwell, R. W.; Schinazi, R. F.; Chu, C. K. *J. Med. Chem.* **2001**, *44*, 3985–3993.
9. Jin, Y. H.; Liu, P.; Wang, J.; Baker, R.; Huggins, J.; Chu, C. K. *J. Org. Chem.* **2003**, *68*, 9012–9018.
10. Borcherding, D. R.; Scholtz, S. A.; Borchardt, R. T. *J. Org. Chem.* **1987**, *52*, 5457–5461.
11. Ali, S. M.; Ramesh, K.; Borchardt, R. T. *Tetrahedron Lett.* **1990**, *31*, 1509–1512.
12. Wolfe, M. S.; Blake, L. A.; Borcherding, D. R.; Borchardt, R. T. *J. Org. Chem.* **1990**, *55*, 4712–4717.
13. Song, G. Y.; Naguib, F. N. M.; El Kouni, M. H.; Chu, C. K. *Nucleosides Nucleotides Nucleic Acids* **2001**, *20*, 1915–1925.
14. Bryant, M. L.; Bridges, E. G.; Placidi, L.; Faraj, A.; Loi, A.-G.; Pierra, C.; Dukhan, D.; Gosselin, G.; Imbach, J.-L.; Hernandez, B.; Juodawlkis, A.; Tennant, B.; Korba, B.; Cote, P.; Marion, P.; Cretton-Scott, E. M.; Schinazi, R. F.; Sommadossi, J.-P. *Antimicrob. Agents Chemother.* **2001**, *45*, 229–235.
15. Bryant, M. L.; Bridges, E. G.; Placidi, L.; Faraj, A.; Loi, A.-G.; Pierra, C.; Dukhan, D.; Gosselin, G.; Imbach, J.-L.; Hernandez, B.; Juodawlkis, A.; Tennant, B.; Korba, B.; Cote, P.; Marion, P.; Cretton-Scott, E. M.; Schinazi, R. F.; Sommadossi, J.-P. *Nucleosides Nucleotides Nucleic Acids* **2001**, *20*, 597–607.
16. Hernandez-Santiago, B.; Placidi, L.; Cretton-Scott, E. M.; Faraj, A.; Bridges, E. G.; Bryant, M. L.; Rodriguez-Santiago, J.; Imbach, J.-L.; Gosselin, G.; Pierra, C.; Dukhan, D.; Sommadossi, J.-P. *Antimicrob. Agents Chemother.* **2002**, *46*, 1728–1733.
17. De Clercq, E. *J. Clin. Virol.* **2004**, *22*, 73–89.
18. Dybul, M.; Nies-Kraske, E.; Dewar, R.; Maldarelli, F.; Hallahan, C. W.; Daucher, M.; Piscitelli, S. C.; Ehler, L.; Weigand, A.; Palmer, S.; Metcalf, J. A.; Davey, R. T.; Rock Kress, D. M.; Powers, A.; Beck, I.; Frenkel, L.; Baseler, M.; Coffin, J.; Fauci, A. S. *J. Infect. Dis.* **2004**, *189*, 1974–1982.
19. Vince, R.; Daluge, S. *J. Org. Chem.* **1980**, *45*, 531–533.
20. Montgomery, J. A.; Clayton, S. J.; Thomas, H. J.; Shannon, W. M.; Arnett, G.; Bodner, A. J.; Kion, I.-K.; Cantoni, G. L.; Chiang, P. K. *J. Med. Chem.* **1982**, *25*, 626–629.
21. Secrist, J. A.; Comber, R. N.; Gray, R. J.; Gilroy, R. B.; Montgomery, J. A. *J. Med. Chem.* **1993**, *36*, 2102–2106.
22. Katagiri, N.; Ito, Y.; Shiraishi, T.; Maruyama, T.; Sato, Y.; Kaneko, C. *Nucleosides Nucleotides* **1996**, *15*, 631–647.
23. Madhavan, G. V. B.; Martin, J. C. *J. Org. Chem.* **1986**, *51*, 1287–1293.
24. Ludek, O. R.; Meier, C. *Synthesis* **2003**, 2101–2109.

25. Martin, J. C.; Smee, D. F.; Verheyden, J. P. H. *J. Org. Chem.* **1985**, *50*, 755–759.
26. Madhavan, G. V. B.; McGee, D. P. C.; Rydzewski, R. M.; Boehme, R.; Martin, J. C.; Prisbe, E. J. *J. Med. Chem.* **1988**, *31*, 1798–1804.
27. Hutchison, A.; Grim, M.; Chen, J. *J. Heterocycl. Chem.* **1989**, *26*, 451–452.
28. Koreeda, M.; Liang, Y.; Akagi, H. *J. Chem. Soc., Chem. Commun.* **1979**, 449–450.
29. Brown, D. W.; Campbell, M. M.; Taylor, A. P.; Zhang, X.-A. *Tetrahedron Lett.* **1987**, *28*, 985–988.
30. Visscher, J.; Schwartz, A. W. *Nucleosides Nucleotides* **1993**, *12*, 107–114.
31. Kjellberg, J.; Johansson, N. G. *Nucleosides Nucleotides* **1989**, *8*, 225–256.
32. Biggadike, K.; Borthwick, A. D.; Exall, A. M.; Kirk, B. E.; Roberts, S. M.; Youds, P. *J. Chem. Soc., Chem. Commun.* **1987**, 1083–1084.
33. Shealy, Y. F.; O'Dell, C. A. *J. Heterocycl. Chem.* **1976**, *13*, 1015–1020.
34. Lin, T.-S.; Zhang, X.-H.; Wang, Z.-H.; Prusoff, W. H. *J. Med. Chem.* **1988**, *31*, 484–486.
35. Wyatt, P. G.; Anslow, A. S.; Coomber, B. A.; Cousins, R. P. C.; Evans, D. N.; Gilbert, V. S.; Humber, D. C.; Paternoster, I. L.; Sollis, S. L.; Tapolczay, D. J.; Weingarten, G. G. *Nucleosides Nucleotides* **1995**, *14*, 2039–2049.
36. Miah, A.; Reese, C. B.; Song, Q.; Sturdy, Z.; Neidle, S.; Simpson, I. J.; Read, M.; Rayner, E. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3277–3283.
37. Only one example could be found in the literature reporting on the synthesis of the 4′-epimer of carbodine obtained by reduction of cyclopentenyl cytosine: Russ, P. L.; Hegedus, L.; Kelley, J. A.; Barchi, J. J.; Marquez, V. E. *Nucleosides Nucleotides* **1992**, *11*, 351–363.
38. Kobayashi, Y.; Miyazaki, H.; Shiozaki, M. *J. Org. Chem.* **1994**, *59*, 813–822.
39. Sirbu, D.; Falck-Pedersen, M. L.; Romming, C.; Undheim, K. *Tetrahedron* **1999**, *55*, 6703–6712.

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Expeditious synthesis of sulfoazetidine spiro-*C*-glycosides from ketose acetals

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Abstract—Pyranoid and furanoid spiro-*N*-mesyl azetidines, a new type of water-soluble spiro-*C*-nucleoside, have been prepared from easily available sugar spiroacetals (or glycosyl cyanides). The synthetic pathway involves opening of the acetalic ring with trimethylsilylcyanide, reduction, formation of an *N*,*O*-dimesylate, cyclization with sodium hydride in anhydrous DMF, and *O*-deprotection.

1. Introduction

The azetidine ring is an important target of synthetic organic chemistry due to the significant pharmaceutical activities of this four-membered heterocycle. Thus, the β-lactams are well-known antibiotics,[1] and take part in the structure of anticancer drugs;[2] and dihydroazetidines have been recently reported as probiotics.[3] *N*-Tosylazetidines have been used as masked dipoles in heterocyclization reactions.[4] The data on carbohydrate derivatives with azetidine rings are scarce; they are mainly on fused azetidines,[5] and in one case on alditol–azetidines biologically active as glycosidase inhibitors.[6] We have not found antecedents either on spiroazetidine sugar derivatives or on sugar *N*-sulfoazetidines. In this communication, we report the preparation of the water-soluble *N*-sulfospirosugarazetidines **6**, **12**, and **24**, as representative examples of azetidine spiro-*C*-glycosides.[7] The starting materials are the easily available pyranoid (**1**, **7**, and **13**) and furanoid (**18**) sugarspiroacetals with β-D-*ribo* (**1**, **18**) and β-D-*arabino* (**7**, **13**) configurations. The synthetic pathway involves a cyclization step to form the azetidine ring based on reported[8–10] preparations of simple monocyclic azetidines from 1,3 aminoalcohols.

2. Results and discussion

Treatment of the diisopropylidene acetal **1**[11] with trimethylsilyl cyanide, followed by *O*-desilylation with SiO_2 gave the β-D-ribohexulopyranosyl cyanide **2** in 81% yield (Scheme 1). The standard desilylation with tetrabutylammonium fluoride (TBAF)[12] was also attempted, but decomposition took place and the yield was very low. Reduction of **2** with lithium–aluminium hydride gave the non-isolated 1,3-aminohydroxy derivative, which was directly transformed into the sulfoamidoester **4** by reaction with mesyl chloride at rt. Basic treatment (NaH) of **4** in anhydrous DMF produced the spirosulfonamide **5**. Simultaneous removals of the isopropylidene and benzyl groups afforded the water-soluble sulfoazetidine spiro-*C*-nucleoside **6** in 40% overall yield from **1** (six steps).

The ^{13}C NMR spectrum of **2** presented a signal at 118.9 ppm for the cyano group, and the β-configuration for this compound was based on NOE experiments performed on **4**. The two mesyl groups of **4** resonated at 2.99, 2.97 (^{1}H), 40.5 and 37.6 (^{13}C) ppm and its 2D-NOESY spctrum showed strong NOE contacts between the CH_2NHMs and H-3 of the sugar ring confirming β configuration for this group, and consequently for the C≡N group of **2**. The signal for the resonance of the spiro carbon atom of **5** appeared at 72.0 ppm. The ^{13}C NMR spectrum of **6** showed the resonance for C-4 (anomeric carbon in the sugar ring) at 76.4 ppm, this being the sugar carbon atom resonating at lowest field, as in related *O*-unprotected pyranoid spiro-*C*-glycosides of different five-membered heterocycles.[13,14] The resonances for the mesyl group of **6** appeared at 2.93 (CH_3) and 33.9 (CH_3) ppm.

To obtain the *arabino*-spirosulfoazetidine **12** we have started (Scheme 1) from two differently O-protected D-fructose derivatives, the tri-*O*-benzyl spiroacetal **7**[15] and the 4,5-*O*-isopropylidenefructopyranosyl cyanide **14**, which was easily prepared[14] from the spiroacetal **13**.[16] The overall yield was better in the case of **7**. The opening of the spiroacetal ring of **7** to obtain **8** was performed with

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Keywords: Azetidines; Glycosides; Spirosugars.

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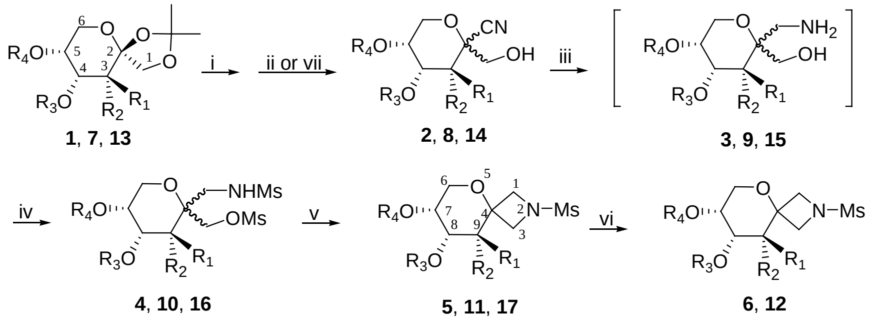


Compound	R_1	R_2	R_3	R_4	Anomers
1	H	OBn	CMe_2		β
2	H	OBn	CMe_2		β
3	H	OBn	CMe_2		β
4	H	OBn	CMe_2		β
5	H	OBn	CMe_2		–
6	H	OH	H	H	–
7	OBn	H	Bn	Bn	β
8	OBn	H	Bn	Bn	α:β
9	OBn	H	Bn	Bn	α:β
10	OBn	H	Bn	Bn	α:β
11	OBn	H	Bn	Bn	–
12	OH	H	H	H	–
13	OBn	H	CMe_2		β
14	OBn	H	CMe_2		β
15	OBn	H	CMe_2		β
16	OBn	H	CMe_2		β
17	OBn	H	CMe_2		–

Scheme 1. Reagents and conditions: (i) TMSCN, TfOTMS, CH_2Cl_2, −20 °C, 2.5 h; (ii) SiO_2, CH_2Cl_2, rt, 24 h; (iii) $LiAlH_4$, Et_2O, rt, 2.5 h; (iv) ClMs/Py, rt, 12 h; (v) NaH, DMF, 2.5 h; (vi) H_2, Pd/C; MeOH, AcOH, rt, 12 h; (vii) TBAF, CH_2Cl_2, rt, 0.5 h.

trimethylsilyl cyanide, but in this case, the use of TBAF was possible. Product **8** was a mixture of anomers (α/β ratio 1:3); the attack of the TMSCN took place preferably by the less hindered pathway to give the β anomer. The mixture was directly used in the next steps, as in both cases the same spiroazetidine is obtained. The ^{13}C NMR spectrum of **8** showed signals at 117.9 (α-anomer) and 116.2 ppm (β-anomer) for the C≡N group. The treatment of **8** and **14** with lithium–aluminium hydride (→ **9**, **15**) followed by reaction with mesyl chloride gave the pair of anomers **10** (β) and **10a** (α), as isolated products, and **16**, respectively.

Cyclization of **10** and **16** (→ **11**, **17**) followed by O-deprotection gave the target spiroazetidine **12** in high yield. The NMR data of **12** supported the proposed structure, being also C-4 the ring carbon atom whose resonance appeared at lowest field (75.7 ppm). The values of the coupling constants $J_{7,8}$ and $J_{8,9}$ (3.0 and 8.5 Hz, respectively) were indicative of *gauche* and antiperiplanar relationships, respectively, between the corresponding protons, and consequently the pyranoid ring of **12** is in the $^1C_4$ (numbering of the sugar ring) conformation in methanol (see Fig. 1).

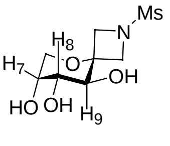


Figure 1. Conformation of compound **12**.

With the aim of preparing furanoid spiroazetidines we have started with the furanosyl cyanide **19**, which was easily prepared[17] from the furanoid spiroacetal **18**.[18] When the same reactions (Scheme 2) were performed on **19**, the sulfonamide spiro-*C*-glycoside **24** was obtained in 37% overall yield from **19**. In this case, the removal of the isopropylidene group was performed with MeOH/HCl (89% yield) and the *O*-debenzoylation with H_2/Pd/C in AcOEt (quantitative).

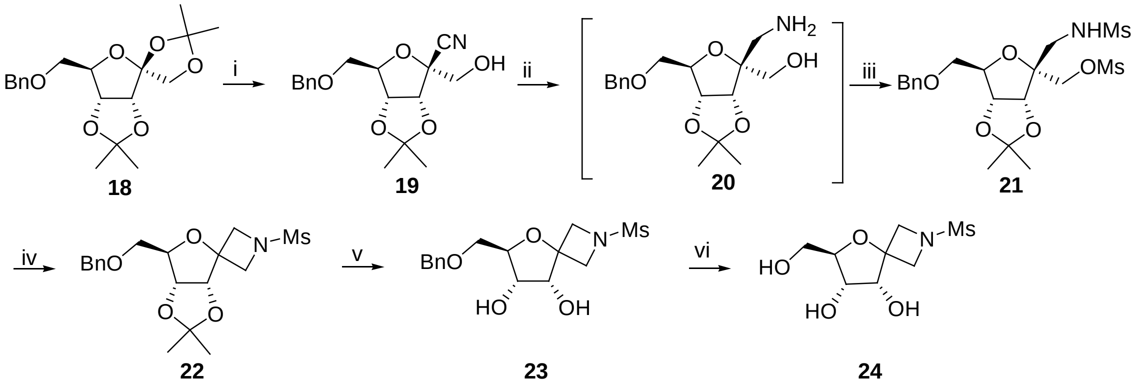
The key step is the cyclization (Scheme 3) by internal nucleophilic displacement of the mesyloxy group, to afford the spiroazetidine (**5**, **11**, **17**, and **23**). A preparation of *N*-mesylaminoglycosides through non-isolated *N*-mesylaziridines obtained by a related cyclization, has been recently communicated.[19]

In conclusion, we have developed a high yielding six-step synthesis of water-soluble pyranoid and furanoid spiro-*C*-glycosides derived of *N*-sulfoazetidines. The key step is the formation of the azetidine ring, which is promoted by NaH. The stereochemistry is defined by the starting sugar derivative and the reactions are experimentally easy.

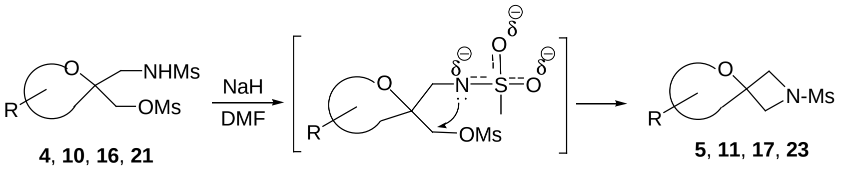
3. Experimental

3.1. General methods

A Perkin-Elmer Model 141 MC polarimeter, 1-cm tubes, at 589 nm, was used for measurement of specific rotations.



Scheme 2. Reagents and conditions: (i) Ref. 17; (ii) $LiAlH_4$, Et_2O, rt, 2.5 h; (iii) MsCl/Py, rt, 12 h; (iv) NaH, DMF, 2.5 h; (v) MeOH, HCl; (vi) H_2, Pd/C, AcOEt, rt, 3 h.



Scheme 3. Key step in the formation of the azetidine ring of **5**, **11**, **17**, and **23**.

IR spectra were recorded for KBr discs on a Bomen Michelson MB-120 FTIR spectrophotometer. Mass spectra (CI, and FAB) were recorded with or a Micromass AutoSpecQ instrument with a resolution of 1000 or 60,000 (10% valley definition). For the FAB spectra, ions were produced by a beam of xenon atoms (6–7 K eV), using 3-nitrobenzyl alcohol or thioglycerol as matrix and NaI as salt. TLC was performed on Silica Gel HF254, with detection by UV light or charring with H_2SO_4. Silica Gel 60 (Merck, 70–230 and 230–400 mesh) was used for preparative chromatography. NMR experiments were recorded on Bruker AMX or Avance AV 500 spectrometers (500.13 MHz for ^{1}H and 125.75 MHz for ^{13}C). Sample concentrations were typically in the range 10–15 mg per 0.6 mL of solvent. Chemical shifts are given in ppm, using the residual protonated solvent signal as reference. ^{1}H and ^{13}C assignments were confirmed by 2D conventional COSY and HSQC experiments, 2D NOESY experiments were carried out on a 5 mm inverse detection probe operating at 303 K, by using the double-pulsed field gradient spin-echo technique (DPFGSE-NOE).[20] A mixing time of 400 ms, a recycle delay of 2 s, and 1024 transients per spectrum, were used in all cases. Selective inversions were performed by using Gaussian-shaped soft pulses (50 ms).

3.2. General procedure for the preparation of compounds 2 and 8

A solution of **1** or **7** (2.85 mmol) in CH_2Cl_2 (13.0 mL) was stirred at −20 °C under argon and 4 Å molecular sieve. TMSCN (1200 μL, 8.81 mmol), and TMSOTf (847 μL, 4.4 mmol) were added and the stirring was maintained for 2 h. The mixture was neutralized with Et_3N (694 μL), diluted with Et_2O, washed with water, dried ($MgSO_4$), and concentrated to dryness. The residue was solved in CH_2Cl_2 (20.0 mL), and silica gel 60 (Merck, 70–230 and 230–400 mesh) (15.0 g) was added, for **2**, and a catalytic amount of TBAF·$3H_2O$ for **8**. The mixture was stirred at rt, 24 h for **2**, and 1 h for **8**, then washed with water and brine, dried ($MgSO_4$), and concentrated to dryness. The residue was purified by column chromatography using Et_2O:hexane 1/1 as eluent.

3.2.1. 3-*O*-Benzyl-2-cyano-2-deoxy-4,5-*O*-isopropylidene-β-D-psicopyranose 2.

Colorless syrup. Yield 81%; $[\alpha]_D^{29}$ −111 (*c* 0.6, CH_2Cl_2); CIMS *m*/*z* 319 [$(M+H)^+$]; IR 2984, 2911, 2114, 1740, 1678, 1651, 1561, 1516, 1456, 1395, 1262, 1100, 864, 801 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.36 (m, 5H, Ph),4.86, 4.71 (each d, each 1H, $J_{gem}=12$ Hz, CH_2Ph), 4.57 (dd, 1H, $J_{3,4}=3.5$ Hz, $J_{4,5}=7.5$ Hz, H-4), 4.31 (ddd, 1H, $J_{5,6a}=1.5$ Hz, $J_{5,6b}=2.5$ Hz, H-5), 3.99 (m, 4H, H-3, H-1a, H-1b, H-6a), 3.83 (dd, 1H, $J_{6a,6b}=13$ Hz, H-6b), 1.55, 1.36 (each s, each 3H, *C*$(CH_3)_2$) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 136.3–128.6 (Ar), 118.9 (C≡N), 110.7 ($C(CH_3)_2$), 75.9 (C-2), 74.1 (C-3), 73.9 (CH_2Ph), 72.3 (C-5), 71.1 (C-4), 64.8 (C-6), 64.5 (C-1), 26.1, 25.0 (C(*C*$H_3)_2$) ppm; HRCIMS *m*/*z* obsd 320.1488, calcd for $C_{17}H_{22}NO_5$ 320.1498.

3.2.2. 3,4,5-Tri-*O*-benzyl-2-cyano-2-deoxy-α,β-D-fructofuranose 8.

Colorless syrup. Yield 85%; α/β (1:3); CIMS: *m*/*z* 459 [$(M+H)^+$]; IR 3030, 2917, 2874, 2114, 1740, 1699, 1651, 1516, 1456, 1397, 1262, 1092, 868, 739, 671 cm^{-1}; ^{13}C NMR for α anomer (125.7 MHz, $CDCl_3$) δ 138.0–127.7 (Ar), 117.9 (CN), 75.2 (C-4*), 74.7 (C-2), 73.7 (*C*H_2Ph), 72.8 (C-3), 71.9 (C-5*), 71.5, 71.4 (2 *C*H_2Ph), 64.5 (C-6), 62.3 (C-1) ppm. For β anomer (125.7 MHz, $CDCl_3$) δ 130.0–127.7 (Ar), 116.2 (CN), 80.5 (C-4*), 80.1 (C-2), 75.5 (*C*H_2Ph), 73.3 (C-3), 72.7 (C-5*), 72.5, 72.0 (2 *C*H_2Ph), 65.8 (C-6), 64.7 (C-1) ppm; HRCIMS *m*/*z* obsd 460.2132, calcd for $C_{28}H_{30}NO_5$ 460.2124. Anal. Calcd for $C_{28}H_{29}NO_5$: C, 73.18; H, 6.36; N, 3.05. Found: C, 72.76; H, 6.28; N, 3.10.

3.3. General procedure for the preparation of compounds 4, 10, 16, and 21

A solution of **2**, **8**, or **14** (1.69 mmol) in diethyl ether (18 mL) was cooled to 0 °C, then $LiAlH_4$ (334 mg, 8.63 mmol) was added and the resulting mixture was stirred 3 h at rt. Treatment with K_2CO_3 1 M (0.87 mL) gave a white precipitate that was removed by filtration through Celite. The organic layer was washed with brine, dried on $MgSO_4$ and concentrated. The residue was dissolved in pyridine (6.5 mL) under argon, and a solution of mesyl chloride (1.1 mL) was dropped. The mixture was stirred at rt for 24 h. The solution was poured into ice-water and extracted with CH_2Cl_2, the organic layer was separated, washed with 1 M sulphuric acid, saturated aqueous sodium hydrogencarbonate, and water, dried ($MgSO_4$), filtered and evaporated to dryness. The residue was purified by column chromatography as indicated in each case.

3.3.1. 3-*O*-Benzyl-2-deoxy-4,5-*O*-isopropylidene-1-*O*-mesyl-2-mesylaminomethyl-β-D-psicopyranose 4. Column chromatography (AcOEt/hexane 1:1) of the residue gave **4** as a amorphous solid. Yield 80%; $[\alpha]_D^{31}$ −23 (c 0.9, CH_2Cl_2); CIMS m/z 480 $[(M+H)^+]$; IR 3422, 3119, 2963, 1773, 1699, 1649, 1557, 1520, 1458, 1398, 1262, 1090, 1032, 872, 801 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40–7.30 (m, 5H, Ph), 5.09 (d, 1H, $J_{1a,1b}=12$ Hz, H-1a), 4.76, 4.64 (each d, each 1H, $J_{gem}=11.5$ Hz, CH_2Ph), 4.57 (dd, 1H, $J_{NH,CH_{2a}}=9$ Hz, $J_{NH,CH_{2b}}=4.5$ Hz, NH), 4.52 (dd, 1H, $J_{3,4}=3.5$ Hz, $J_{4,5}=6$ Hz, H-4), 4.33 (d, 1H, H-1b), 4.23 (m, 1H, H-5), 3.99 (d, 1H, H-3), 3.75 (dd, 1H, $J_{5,6a}=5.5$ Hz, $J_{6a,6b}=13$ Hz, H-6a), 3.66 (dd, 1H, $J_{5,6b}=7$ Hz, H-6b), 3.44 (dd, 1H, $J_{gem}=13$ Hz, *H*CHNH), 3.38 (dd, 1H, HC*H*NH), 2.99, 2.97 (each s, each 3H, CH_3SO_2–), 1.58, 1.33 (each s, each 3H, $C(CH_3)_2$) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 137.3–128.3 (Ar), 110.5 ($C(CH_3)_2$), 75.2 (C-2), 72.6 (C-3), 72.4 (CH_2Ph), 71.8 (C-5), 71.2 (C-4), 67.7 (C-1), 62.0 (C-6), 45.2 (CH_2NH), 40.5, 37.6 (2 CH_3SO_2), 27.3, 25.3 ($C(CH_3)_2$) ppm; HRCIMS m/z obsd 480.1381, calcd for $C_{19}H_{30}NO_9S_2$ 480.1362. Anal. Calcd for $C_{19}H_{29}NO_9S_2$: C, 47.59; H, 6.10; N, 2.92; S, 13.37. Found: C, 47.25; H, 5.96; N, 2.90; S, 12.95%.

3.3.2. Tri-*O*-benzyl-2-deoxy-1-*O*-mesyl-2-mesylaminomethyl-α-D-fructopyranose 10a and tri-*O*-benzyl-2-deoxy-1-*O*-mesyl-2-mesylaminomethyl-β-D-fructopyranose 10. Column chromatography (AcOEt/hexane 1:1) of the residue gave **10** and **10a** as amorphous solids. Data for **10a**. Yield 16%; $[\alpha]_D^{26}$ −29 (c 0.94, CH_2Cl_2); FABMS: m/z 642 $[(M+Na)^+]$; IR 3117, 2963, 2874, 1740, 1678, 1645, 1626, 1561, 1516, 1456, 1397, 1092, 1024, 870, 801 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36–7.28 (m, 15H, Ph), 4.87–4.56 (m, 6H, 3 CH_2Ph), 4.53 (d, 1H, $J_{1a,1b}=11.5$ Hz, H-1a), 4.46 (dd, 1H, $J_{NH,CH_{2a}}=7.5$ Hz, $J_{NH,CH_{2b}}=5$ Hz, NH), 4.23 (d, 1H, H-1b), 4.17 (d, 1H, $J_{3,4}=8.5$ Hz, H-3), 3.88 (dd, 1H, $J_{5,6a}=4$ Hz, $J_{6a,6b}=13$ Hz, H-6a), 3.82 (m, 1H, H-5), 3.77 (dd, 1H, $J_{4,5}=3$ Hz, H-4), 3.65 (d, 1H, H-6b), 3.42 (dd, 1H, $J_{gem}=13$ Hz, *H*CHNH), 3.32 (dd, 1H, HC*H*NH), 2.96, 2.86 (each s, each 3H, CH_3SO_2) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 149.5–123.9 (Ar), 78.2 (C-4), 77.9 (C-2), 75.5 (CH_2Ph), 74.5 (C-3), 72.6 (C-5), 72.1 (CH_2Ph), 71.8 (CH_2Ph), 66.5 (C-1), 62.2 (C-6), 44.8 (CH_2NH), 40.6, 37.7 (2 CH_3SO_2) ppm; HRFABMS m/z obsd 642.1806, calcd for $C_{30}H_{37}NO_9NaS_2$ 642.1807. Anal. Calcd for $C_{30}H_{37}NO_9S_2$: C, 58.14; H, 6.02; N, 2.26; S, 10.35. Found: C, 57.76; H, 5.98; N, 2.40; S, 10.11%. Data for **10**. Yield 50%; $[\alpha]_D^{24}$ −34 (c 1, CH_2Cl_2); FABMS: m/z 642 $[(M+Na)^+]$; IR 3117, 2963, 2874, 1740, 1678, 1645, 1626, 1561, 1516, 1456, 1397, 1092, 1024, 870, 801 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36–7.26 (m, 15H, Ph), 4.85–4.57 (m, 7H, 3 CH_2Ph, NH), 4.52 (d, 1H, $J_{1a,1b}=11.5$ Hz, H-1a), 4.36 (d, 1H, H-1b), 4.04 (d, 1H, $J_{3,4}=7.5$ Hz, H-3), 3.92 (dd, 1H, $J_{5,6a}=4.5$ Hz, $J_{6a,6b}=13$ Hz, H-6a), 3.84 (m, 1H, H-5), 3.82 (m, 1H, H-4), 3.65 (d, 1H, H-6b), 3.51 (dd, 1H, $J_{NH,CH_2}=5$ Hz, $J_{gem}=14$ Hz, *H*CHNH), 3.34 (dd, 1H, $J_{NH,CH_2}=7.5$ Hz, HC*H*NH), 2.98, 2.96 (each s, each 3H, CH_3SO_2) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 137.8–127.8 (Ar), 77.8 (C-4), 77.2 (C-2), 75.3 (CH_2Ph), 75.1 (C-3), 72.4 (CH_2Ph), 72.3 (C-5), 71.7 (CH_2Ph), 69.4 (C-1), 61.6 (C-6), 41.4 (CH_2NH), 40.6, 37.9 (2 CH_3SO_2) ppm; HRFABMS m/z obsd 642.1793, calcd for $C_{30}H_{37}NO_9NaS_2$ 642.1807.

3.3.3. 3-*O*-Benzyl-2-deoxy-4,5-*O*-isopropylidene-1-*O*-mesyl-2-mesylaminomethyl-β-D-fructopyranose 16. Column chromatography (CH_2Cl_2/MeOH 60:1) of the residue gave **16** as amorphous solid. Yield 66%; $[\alpha]_D^{31}$ −10 (c 0.9, CH_2Cl_2); CIMS m/z 480 $[(M+H)^+]$; IR 3422, 3119, 2963, 1740, 1678, 1651, 1618, 1561, 1516, 1456, 1397, 1262, 1092, 870, 802 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39–7.32 (m, 5H, Ph), 4.81 (d, 1H, $J_{gem}=11.5$ Hz, CH_2Ph), 4.66 (dd, 1H, $J_{NH,CH_{2a}}=6$ Hz, $J_{NH,CH_{2b}}=7$ Hz, NH), 4.57 (d, 1H, CH_2Ph), 4.47 (dd, 1H, $J_{3,4}=5.5$ Hz, $J_{4,5}=7$ Hz, H-4), 4.35 (d, 1H, $J_{1a,1b}=10.5$ Hz, H-1a), 4.31 (m, 1H, H-5), 4.26 (d, 1H, H-1b), 3.94 (dd, 1H, $J_{5,6a}=3$ Hz, $J_{6a,6b}=13$ Hz, H-6a), 3.82 (d, 1H, H-3), 3.81 (dd, 1H, $J_{5,6b}=3$ Hz, H-6b), 3.52 (dd, 1H, $J_{gem}=14$ Hz, *H*CHNH), 3.20 (dd, 1H, HC*H*NH), 3.00, 2.95 (each s, each 3H, CH_3SO_2–), 1.52, 1.37 (each s, each 3H, $C(CH_3)_2$) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 137.1–128.3 (Ar), 109.9 ($C(CH_3)_2$), 76.3 (C-2), 74.6 (C-3), 74.1 (C-4), 73.7 (CH_2Ph), 72.3 (C-5), 69.6 (C-1), 62.4 (C-6), 42.3 (CH_2NH), 40.7, 37.7 (2 CH_3SO_2–), 26.9, 25.0 ($C(CH_3)_2$) ppm; HRCIMS m/z obsd 480.1346, calcd for $C_{19}H_{30}NO_9S_2$ 480.1362.

3.3.4. 6-*O*-Benzyl-2-deoxy-3,4-*O*-isopropylidene-1-*O*-mesyl-2-mesylaminomethyl-β-D-psicofuranose 21. Column chromatography (Et_2O/hexane 4:1) of the residue gave **21** as amorphous solid. Yield 66%. $[\alpha]_D^{31}$ +8 (c 0.9, CH_2Cl_2); CIMS m/z 480 $[(M+H)^+]$; IR 3121, 2963, 2868, 1740, 1651, 1561, 1518, 1456, 1395, 1358, 1262, 1092, 868, 802, 669 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38–7.32 (m, 5H, Ph), 5.75 (dd, 1H, $J_{NH,CH_{2a}}=8.5$ Hz, $J_{NH,CH_{2b}}=3.5$ Hz, NH), 4.94 (dd, 1H, $J_{3,4}=6.5$ Hz, $J_{4,5}=5.5$ Hz, H-4), 4.79 (d, 1H, H-3), 4.60, 4.56 (each d, each 1H, $J_{gem}=11.5$ Hz, CH_2Ph), 4.37, 4.31 (each d, each 1H, $J_{1a,1b}=10.5$ Hz, H-1a, H-1b), 4.14 (m, 1H, H-5), 3.74 (dd, 1H, $J_{5,6a}=2.5$ Hz, $J_{6a,6b}=10.5$ Hz, H-6a), 3.60 (dd, 1H, $J_{5,6b}=2.5$ Hz, H-6b), 3.38 (dd, 1H, $J_{gem}=13$ Hz, *H*CHNH), 3.32 (dd, 1H, HC*H*NH), 3.06, 2. 74 (each s, each 3H, CH_3SO_2–), 1.52, 1.33 (each s, each 3H, $C(CH_3)_2$) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 136.9–128.3 (Ar), 114.2 ($C(CH_3)_2$), 84.6 (C-5), 83.6 (C-3), 81.6 (C-4), 73.9 (CH_2Ph), 69.6 (C-6), 69.0 (C-1), 47.2 (CH_2NH), 40.2, 37.6 (2 CH_3SO_2), 27.2, 25.3 ($C(CH_3)_2$) ppm. Anal. Calcd for $C_{19}H_{29}NO_9S_2$: C, 47.59; H, 6.10; N, 2.92; S, 13.37. Found: C, 47.38; H, 6.12; N, 2.91; S, 13.25%.

3.4. General procedure for the preparation of compounds 5, 11, 17, and 22

To a stirred solution of the corresponding -*N* and *O*-mesylated compound **4**, **10**, **16**, or **21** (0.15 mmol) in DMF (3.6 mL) at rt, sodium hydride (60 mg, 1.50 mmol) was added for compounds **11**, **17**, and **22**. For compound **5**, the sodium hydride was added in three portions (20 mg at 0, 5, and 10 h of reaction). The reaction mixture was stirred at rt. When monitoring of the reaction by TLC (AcOEt/hexane 1:1) indicated that all starting material had been consumed, the mixture was poured into ice-water and extracted with CH_2Cl_2. The organic layer was separated, washed with water, dried ($MgSO_4$), filtered, and evaporated to dryness. The residue was purified by column chromatography (AcOEt/hexane 1:1).

3.4.1. (7*R*,8*R*,9*R*)-2-Aza-9-benzyloxy-7,8-(dimethylmethylenedioxy)-2-*N*-mesyl-5-oxaspiro[3.5]nonane 5. Column chromatography (AcOEt/hexane 1:1) of the residue gave **5** as amorphous solid. Yield 54%; $[\alpha]_D^{31}$ −31 (*c* 0.96, CH_2Cl_2); FABMS *m/z* 406 $[(M+Na)^+]$; IR 3119, 2959, 2880, 1740, 1678, 1651, 1626, 1516, 1464, 1397, 1335, 1262, 1092, 856, 799 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37–7.35 (m, 5H, Ph), 4.88, 4.65 (each d, each 1H, $J_{gem}=11.5$ Hz, CH_2Ph), 4.55 (dd, 1H, $J_{7,8}=5.5$ Hz, $J_{8,9}=3$ Hz, H-8), 4.38 (d, 1H, $J_{3a,3b}=9$ Hz, H-1a), 4.22 (dt, 1H, $J_{6a,7}=5.5$ Hz, $J_{6b,7}=8$ Hz, H-7), 3.99 (d, 1H, $J_{1a,1b}=9$ Hz, H-3a), 3.95 (d, 1H, H-1b), 3.77 (d, 1H, H-3b), 3.73 (dd, 1H, $J_{6a,6b}=12$ Hz, H-6a), 3.51 (d, 1H, H-9), 3.49 (dd, 1H, H-6b), 2.75 (s, 3H, CH_3SO_2), 1.50, 1.35 (each s, each 3H,) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 137.0–128.5 (Ar), 110.6 ($C(CH_3)_2$), 73.1 (C-9), 72.0 (C-4), 71.7 (C-7), 71.6 (C-8), 71.5 (CH_2Ph), 62.5 (C-6), 58.9 (C-3), 56.1 (C-1), 34.7 (CH_3SO_2–), 28.1, 25.9 ($C(CH_3)_2$) ppm; HRFABMS *m/z* obsd 406.1304, calcd for $C_{18}H_{25}NO_6NaS$ 406.1300. Anal. Calcd for $C_{18}H_{25}NO_6S$: C, 56.38; H, 6.57; N, 3.65; S, 8.36. Found: C, 55.94; H, 6.45; N, 3.65; S, 8.21%.

3.4.2. (7*R*,8*R*,9*S*)-2-Aza-7,8,9-tribenzyloxy-2-*N*-mesyl-5-oxaspiro[3.5]nonane 11. Column chromatography (Et_2O/hexane 4:1) of the residue gave **11** as amorphous solid. Yield 76%; $[\alpha]_D^{31}$ −28 (*c* 1.0, CH_2Cl_2); FABMS *m/e* 546 $[(M+Na)^+]$; IR 3117, 2961, 2874, 1740, 1699, 1651, 1626, 1561, 1506, 1456, 1397, 1262, 1092, 799, 669 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35–7.38 (m, 15H, Ph), 4.79–4.57 (m, 6H, CH_2Ph), 4.05 (d, 1H, $J_{3a,3b}=9.5$ Hz, H-3a), 4.01 (d, 1H, $J_{1a,1b}=9$ Hz, H-1a), 3.90–3.85 (m, 2H, H-6a, H-7), 3.88 (d, 1H, H-3b), 3.85 (d, 1H, $J_{8,9}=6$ Hz, H-9), 3.75 (d, 1H, H-1b), 3.70 (dd, 1H, $J_{7,8}=2$ Hz, H-8), 3.58 (dd, 1H, $J_{6a,6b}=11$ Hz, $J_{6b,7}=2$ Hz, H-6b), 2.76 (s, 3H, CH_3SO_2) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 138.0–127.9 (Ar), 76.6 (C-9), 76.0 (C-8), 74.5 (CH_2Ph), 73.5 (C-4), 72.8 (CH_2Ph), 72.2 (C-7), 71.7 (CH_2Ph), 61.4 (C-6), 58.7 (C-3), 56.8 (C-1), 35.4 (CH_3SO_2) ppm; HRFABMS *m/z* obsd 546.1901, calcd for $C_{29}H_{33}NO_6NaS$ 546.1926.

3.4.3. (7*R*,8*R*,9*S*)-2-Aza-9-benzyloxy-7,8-(dimethylmethylenedioxy)-2-*N*-mesyl-5-oxaspiro[3.5]nonane 17. Column chromatography (Et_2O/hexane 2:1) of the residue gave **17** as amorphous solid. Yield 64%; $[\alpha]_D^{29}$ −44 (*c* 0.9, CH_2Cl_2); FABMS *m/z* 406 $[(M+Na)^+]$; IR 3117, 2963, 2878, 1699, 1645, 1559, 1516, 1464, 1397, 1339, 1262, 1092, 1022, 870, 801, 685 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37–7.30 (m, 5H, Ph), 4.93, 4.66 (each d, each 1H, $J_{gem}=11.5$ Hz, CH_2Ph), 4.26 (t, 1H, $J_{7,8}=J_{8,9}=6$ Hz, H-8), 4.20 (m, 1H, H-7), 4.02 (d, 1H, $J_{3a,3b}=8.5$ Hz, H-3a), 4.01 (d, 1H, $J_{1a,1b}=9$ Hz, H-1a), 3.96 (dd, 1H, $J_{6a,6b}=13.5$ Hz, $J_{6a,7}=2$ Hz, H-6a), 3.83 (m, 3H, H-1b, H-3b, H-6b), 3.66 (d, 1H, H-9), 2.73 (s, 3H, CH_3SO_2–), 1.51, 1.36 (each s, each 3H, $C(CH_3)_2$) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 137.4–128.30 (Ar), 110.0 ($C(CH_3)_2$), 76.5 (C-9), 75.0 (C-8), 73.5 (CH_2Ph), 72.4 (C-4), 72.3 (C-7), 62.0 (C-6), 59.6 (C-3), 55.7 (C-1), 35.2 (CH_3SO_2-), 27.7, 25.8 (2 ($C(CH_3)_2$) ppm; HRFABMS *m/z* obsd 406.1314, calcd for $C_{18}H_{25}NO_6NaS$ 406.1300.

3.4.4. (6*R*,7*S*,8*R*)-2-Aza-6-benzyloxymethyl-7,8-(dimethylmethylenedioxy)-2-*N*-mesyl-5-oxaspiro[3.4]-octane 22. Column chromatography (Et_2O/hexane 2:1) of the residue gave **22** as amorphous solid. Yield 63%; $[\alpha]_D^{31}$ −76 (*c* 0.8, CH_2Cl_2); FABMS *m/z* 406 $[(M+Na)^+]$; IR 3117, 2940, 2866, 1846, 1740, 1699, 1651, 1626, 1561, 1516, 1456, 1395, 1339, 1273, 1092, 1026, 872, 797 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41–7.28 (m, 5H, Ph), 4.81 (dd, 1H, $J_{6,7}=0.5$ Hz, $J_{7,8}=6$ Hz, H-7), 4.75 (d, 1H, H-8), 4.53, 4.43 (each d, each 1H, $J_{gem}=11.5$ Hz, CH_2Ph), 4.25 (m, 2H, H-6, H-3a), 3.95 (d, 1H, $J_{3a,3b}=9$ Hz, H-3b), 3.86 (d, 1H, $J_{1a,1b}=9$ Hz, H-1a), 3.69 (d, 1H, H-1b), 3.55, 3.51 (each dd, each 1H, $J_{gem}=10$ Hz, $J_{6,CH_2}=2.5$ Hz, *H*CHOB*n*, HC*H*OB*n*), 2.88 (s, 3H, CH_3SO_2), 1.45, 1.38 (each s, each 3H, $C(CH_3)_2$) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 137.1–128.2 (Ar), 112.8 ($C(CH_3)_2$), 85.7 (C-8), 83.9 (C-6), 83.3 (C-7), 81.0 (C-4), 74.1 (CH_2Ph), 71.7 (CH_2OBn), 63.7 (C-1), 57.2 (C-3), 36.2 (CH_3SO_2), 26.5, 25.2 ($C(CH_3)_2$) ppm; HRFABMS *m/z* obsd 406.1305, calcd for $C_{18}H_{25}NO_6NaS$ 406.1300. Anal. Calcd for $C_{18}H_{25}NO_6S$: C, 56.38; H, 6.57; N, 3.65; S 8.36. Found: C, 56.18; H, 6.42; N, 3.67; S, 8.34.

3.5. General procedure for the preparation of compounds 6 and 12

To a solution of the corresponding O-protected compound **5**, **11** or **17** (0.14 mmol) in dry methanol (3.7 mL), acetic acid (370 μL) and C/Pd (122 mg) were added. The reaction mixture was stirred at rt, under hydrogen for 12 h, and controlled by TLC (AcOEt/MeOH 15:1) until total consumption of the starting material. The mixture was diluted with methanol (25 mL) and neutralized with basic resin Amberlite IR-400(OH^-), filtered, and evaporated to dryness. The residue was purified by column chromatography (AcOEt/MeOH 15:1).

3.5.1. (7*R*,8*R*,9*R*)-2-Aza-7,8,9-trihydroxy-2-*N*-mesyl-5-oxaspiro[3.5]nonane 6. Amorphous solid. Yield 93%; $[\alpha]_D^{30}$ +4 (*c* 1.2, MeOH); CIMS *m/z* 254 $[(M+H)^+]$; IR 3420, 3121, 2963, 1740, 1699, 1651, 1626, 1539, 1516, 1456, 1397, 1262, 1092, 1028, 870, 801, 685 cm^{-1}; ^1H NMR (500 MHz, MeOD) δ 4.28 (d, 1H, $J_{3a,3b}=9.5$ Hz, H-

1a), 4.05 (d, 1H, $J_{1a,1b}=9.0$ Hz, H-3a), 3.94 (t, 1H, $J_{6a,7}=J_{7,9}=2.5$ Hz, H-7), 3.78 (d, 1H, H-1b), 3.68 (d, 1H, H-3b), 3.65 (m, 2H, H-6a, H-8), 3.55 (d, 1H, $J_{6a,6b}=8.5$ Hz, H-6b), 3.45 (d, 1H, H-9), 2.93 (m, 3H, CH_3SO_2) ppm; ^{13}C NMR (125.7 MHz, MeOD) δ 76.4 (C-4), 73.6 (C-7), 71.5 (C-9), 68.5 (C-8), 63.3 (C-6), 59.1 (C-3), 57.5 (C-1), 33.9 (CH_3SO_2 ppm; HRCIMS *m/z* obsd 254.0703, calcd for $C_8H_{16}NO_6S$ 254.0698.

3.5.2. (7*R*,8*R*,9*S*)-2-Aza-7,8,9-trihydroxy-2-*N*-mesyl-5-oxaspiro[3.5]nonane 12. Amorphous solid. Yield 93% (from **11**), 92% (from **17**). $[\alpha]_D^{29}$ −47 (*c* 0.9, MeOH); CIMS *m/z* 254 [(M+H)$^+$]; IR 3422, 2963, 1834, 1740, 1651, 1561, 1516, 1456, 1397, 1262, 1092, 1024, 870, 796 cm^{-1}; ^{1}H NMR (500 MHz, MeOD) δ 4.13 (dd, 1H, $J_{3a,3b}=9.5$ Hz, $J_{1a,3a}=1.0$ Hz, H-3a), 4.10 (dd, 1H, $J_{1a,1b}=9.0$ Hz, H-1a), 3.83 (m, 1H, H-7), 3.79 (dd, 1H, $J_{1b,3b}=1.0$ Hz, H-3b), 3.77 (dd, 1H, H-1b), 3.72 (m, 2H, H-6a, H-9), 3.60 (dd, 1H, $J_{6a,6b}=12.5$ Hz, $J_{6a,7}=2.5$ Hz, H-6b), 3.52 (dd, 1H, $J_{7,8}=3.0$ Hz, $J_{8,9}=8.5$ Hz, H-8), 2.94 (s, 3H, CH_3SO_2) ppm; ^{13}C NMR (125.7 MHz, MeOD) δ 75.7 (C-4), 72.3 (C-8), 70.7 (C-9), 68.9 (C-7), 65.8 (C-6), 59.5 (C-3), 56.1 (C-1), 34.2 (CH_3SO_2) ppm; HRCIMS *m/z* obsd 254.0710, calcd for $C_8H_{16}NO_6S$ 254.0698.

3.5.3. (6*R*,7*S*,8*R*)-2-aza-6-benzyloxymethyl-7,8-dihydroxy-2-*N*-mesyl-5-oxaspiro[3.4]octane 23. To a solution of **22** (0.45 mmol) in methanol (12.0 mL), concentrated hydrochloric acid (946 μL) was added. The reaction mixture was stirred at rt for 12 h. The process was controlled by TLC (CH_2Cl_2/MeOH, 15:1 as eluent). The solution was neutralized with $NaHCO_3$, filtered, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (CH_2Cl_2/MeOH, 30:1) as eluent to give **23** as amorphous solid. Yield 89%. $[\alpha]_D^{29}$ −5 (*c* 0.9, CH_2Cl_2); CIMS *m/z* 344 [(M+H)$^+$]; IR 3447, 3030, 2924, 2870, 1653, 1507, 1456, 1404, 1339, 1092, 1026, 874, 756, 712 cm^{-1}; ^{1}H NMR (500 MHz, MeOD) δ 7.35–7.25 (m, 5H, Ph), 4.53 (s, 2H, CH_2Ph), 4.30 (d, 1H, $J_{3a,3b}=9$ Hz, H-3a), 4.05 (m, 2H, H-7, H-8), 3.99 (m, 1H, H-6), 3.90 (dd, 1H, $J_{1a,1b}=9$ Hz, $J_{1a,3b}=1$ Hz, H-1a), 3.86 (d, 1H, H-1b), 3.80 (dd, 1H, H-3b), 3.60 (dd, 1H, $J_{gem}=10.5$ Hz, $J_{6,CH_2}=3.0$ Hz), 3.53 (dd, 1H, $J_{6,CH_2}=4$ Hz, HC*H*OH), 2.92 (s, 3H, CH_3SO_2) ppm; ^{13}C NMR (125.7 MHz, MeOD) δ 139.5–128.7 (Ar), 84.3 (C-6), 80.0 (C-4), 75.6 (C-7*), 74.5 (CH_2Ph), 72.9 (C-8*), 71.4 (CH_2OH), 61.8 (C-1), 59.2 (C-3), 34.3 (CH_3SO_2) ppm; HRCIMS *m/z* obsd 344.1164, calcd for $C_{15}H_{22}NO_6S$ 344.1168.

3.5.4. (6*R*,7*S*,8*R*)-2-Aza-7,8-dihydroxy-6-hydroxymethyl-2-*N*-mesyl-5-oxaspiro[3.4]octane 24. To a solution of **23** (0.397 mmol) in AcOEt (27.0 mL), C/Pd (27 mg) was added. The reaction mixture was stirred at rt, under hydrogen for 1.5 h, and controlled by TLC (AcOEt/MeOH 15:1 as eluent), until total consumption of the starting material, filtered through Celite and concentrated. The residue was purified by column chromatography (AcOEt/MeOH 15:1) to give **24** as amorphous solid. Yield 99%. $[\alpha]_D^{29}$ +6 (*c* 0.9, MeOH); CIMS *m/z* 254 [(M+H)$^+$]; IR 3422, 3121, 2963, 1740, 1694, 1645, 1551, 1464, 1397, 1262, 1092, 1024, 801 cm^{-1}; ^{1}H NMR (500 MHz, MeOD) δ 4.31 (dt, 1H, $J_{3a,3b}=9.0$ Hz, $J_{1a,3a}=J_{1b,3a}=1.0$ Hz, H-3a), 4.03 (m, 2H, H-7, H-8), 3.96 (dd, 1H, $J_{1a,1b}=9.0$ Hz, H-1a), 3.88 (dt, 1H, $J_{1a,1b}=9.0$ Hz, $J_{1b,3b}=1.0$ Hz, H-1b), 3.87 (m, 1H, H-6), 3.80 (dd, 1H, H-3b), 3.66 (dd, 1H, $J_{gem}=12$ Hz, $J_{6,CH_2}=3$ Hz, *H*CHOH), 3.54 (dd, 1H, $J_{6,CH_2}=4$ Hz, HC*H*OH), 2.94 (s, 3H, CH_3SO_2) ppm; ^{13}C NMR (125.7 MHz, MeOD) δ 85.6 (C-6), 79.8 (C-4), 75.7 (C-7), 72.4 (C-8), 62.9 (CH_2OH), 61.6 (C-1), 59.2 (C-3), 34.3 (CH_3SO_2) ppm; HRCIMS *m/z* obsd 254.0708, calcd for $C_8H_{16}NO_6S$ 254.0698.

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References and notes

1. (a) For a recent reference, see as example: Venkateson, A. M.; Agarwal, A.; Abe, T.; Ushirogochi, H.; Yamamura, I.; Kumogai, T.; Petersen; Peter, J.; Weis, W.; Lenoy, E.; Yang, Y.; Shlaes, D. M.; Ryan, J. L.; Mansour, T. S. *Bioorg. Med. Chem.* **2004**, *12*, 5807–5817. (b) Tuta, E.; Wittigens, A.; Maffii, G.; Blanchi, G. In Gallo, V., Santamaría, L., Eds.; Research Progress in Organic, Biological and Medicinal Chemistry; North-Holland: Amsterdan, 1964; Vol. 1, p 477.
2. Barbaro, G.; Battaglia, A.; Di Giuseppe, F.; Giorgianni, P.; Guerrini, A.; Bertucci, C.; Geremia, S. *Tetrahedron: Asymmetry* **1999**, *10*, 2765–2773.
3. Ozone, F.; Inoue, Y.; Shiraishi, A.; Hamashima, H.; Masuda, K.; Shiojima, K.; Sasatsu, M. *J. Microbiol. Meth.* **2002**, *50*, 91–95.
4. Ungureanu, I.; Klotz, Ph.; Schoenfelder, A.; Mann, A. *Tetrahedron Lett.* **2001**, *42*, 6087–6091.
5. See as examples: (a) Furman, B.; Thürmer, Z. K.; Lysek, R. L.; Voelter, W.; Chmielewski, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 1121–1123. (b) Obika, S.; Andoh, J.; Onoda, M.; Nakagawa, O.; Hiroto, A.; Sugimoto, T.; Imanishi, T. *Tetrahedron Lett.* **2003**, *44*, 5267–5270.
6. Eniade, A.; Martin, O. R. *Carbohydr. Res.* **2002**, *337*, 273–277.
7. For the term spironucleoside, see: Gasch, C.; Pradera, M. A.; Salameh, B. A. B.; Molina, J. L.; Fuentes, J. *Tetrahedron: Asymmetry* **2001**, *12*, 1267–1277.
8. Barluenga, J.; Fernández-Marí, F.; Viado, A. L.; Aguilar, E.; Olano, B. *J. Org. Chem.* **1996**, *61*, 5659–5662.
9. Huszthy, P.; Bradshaw, J. S.; Krakowiak, K. E.; Wang, T.; Dalley, N. K. *J. Heterocycl. Chem.* **1993**, *30*, 1197–1207.
10. Thompso, H. W.; Swistok, J. *J. Org. Chem.* **1981**, *46*, 4907–4911.
11. Elliot, R. D.; Niwas, S.; Riordan, J. M.; Montgomery, J. A.; Secrist, J. A. *Nucleosides Nucleotides* **1992**, *11*, 98–119.
12. Corey, E. J.; Snider, B. B. *J. Am. Chem. Soc.* **1972**, *94*, 2549–2550.

13. Gasch, C.; Salameh, B. A. B.; Pradera, M. A.; Fuentes, J. *Tetrahedron Lett.* **2001**, *42*, 8615–8617.
14. Gasch, C.; Pradera, M. A.; Salameh, B. A. B.; Molina, J. L.; Fuentes, J. *Tetrahedron: Asymmetry* **2001**, *12*, 1267–1277.
15. Campbell, M. M.; Hefferman, G. D.; Lewis, T. *Carbohydr. Res.* **1994**, *251*, 243–250.
16. Prisbe, E. J.; Smejkal, J.; Verheyden, J. P. H.; Moffat, J. G. *J. Org. Chem.* **1976**, *41*, 1836–1846.
17. Sano, H.; Mio, S.; Kitagawa, J.; Sugai, S. *Tetrahedron: Asymmetry* **1994**, *5*, 2233–2240.
18. Mio, S.; Kumagawa, Y.; Sugai, S. *Tetrahedron* **1991**, *47*, 2133–2144.
19. Di Bussolo, V.; Romano, M. R.; Pineschi, M.; Crotti, P. *Org. Lett.* **2005**, *7*, 1299–1302.
20. Stott, K.; Keeler, J.; Van Q, N.; Shaka, A. J. *J. Magn. Reson.* **1997**, *125*, 302–324.

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Reaction of α,β-unsaturated Fischer carbene complexes with allyl alkoxide

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Abstract—Optically enriched homo-binuclear Fischer chromium carbene complexes with planar chiral arene chromium complexes gave α-allyl β-arylpropionates up to 97% ee by reaction with allyl alkoxide and subsequent photo-oxidative demetalation. The chiral hetero-binuclear tungsten carbene complexes afforded *anti* α-allyl β-hydroxy β-arylpropionates as a major product up to 92/8 dr by the same reaction sequence. High diastereoselectivity in these reactions is contributed to the planar chirality of the arene chromium complex, even though the reaction was carried out under vigorous basic media. The reaction products, α-allyl β-arylpropionates were derived by 1,3-$M(CO)_5$ shift and subsequent [3,3]-sigmatropic rearrangement. Also, the corresponding chromium-uncomplexed α,β-unsaturated Fischer carbene complexes afforded α-allyl β-arylpropionates under the same conditions. Formation of β-allyl β-arylpropionates via 1,2-$M(CO)_5$ shift followed by [3,4]-sigmatropic rearrangement was not observed in both reactions of chromium-coordinated and the corresponding chromium-uncoordinated α,β-unsaturated Fischer carbene complexes with allyl alkoxide in the presence of base.

1. Introduction

Fischer carbene complexes are one of the most versatile organometallic reagents for organic synthesis,[1] and a number of novel reactions using Fischer carbene complexes have been reported.[2] For instance, α,β-unsaturated Fischer carbene complexes are significant for organic synthesis such as Michael addition reaction,[3] [3+2]-, [4+2]- and [3+2+1]-cycloaddition reactions.[4–6] Furthermore, optically active Fischer carbene complexes have attracted increasing attention as powerful tool of asymmetric reaction, and various chiral carbene complexes have been developed to date. Most of these chiral α,β-unsaturated Fischer carbene complexes have chiral alcohols or amines at the carbene carbon atom as a stabilizing substituent (type I) due to their easy preparation (Fig. 1). On the other hand, there are few examples of the other type of chiral α,β-unsaturated Fischer carbene complexes, in which a chiral auxiliary is directly attached to the α,β-unsaturated bond.[7] As a synthetic development of the planar chiral arene chromium complexes, we have investigated asymmetric reaction of optically pure α,β-unsaturated Fischer carbene complexes with planar chirality (Type II, $R^* = ArCr(CO)_3$). We expected that these type of chiral Fischer carbene complexes would become promising chiral reagents, since a reactive site is located closely to the chiral auxiliary. Moreover, these binuclear chiral complexes would be expected to develop interesting asymmetric reactions based on the combined nature of two metallic moieties. However, to best of our knowledge, there is no report on asymmetric reactions utilizing α,β-unsaturated binuclear Fischer carbene complexes[8] with a planar chiral transition metal π-complex. Herein, we wish to report asymmetric reaction utilizing planar chiral binuclear Fischer carbene complexes with allyl alkoxides.[9]

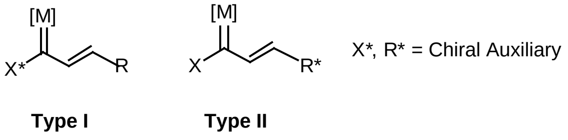

Figure 1. Chiral α,β-unsaturated Fischer carbene complexes.

2. Results and discussion

Barluenga et al. reported[10] that aryl α,β-unsaturated Fischer carbene complexes **1** were treated with allyl alcohol in the

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Keywords: Fischer carbene complexes; Binuclear carbene complexes; Planar chirality; 1,3-Metal shift; 3,4-Sigmatropic rearrangement; Enantiomeric excess.

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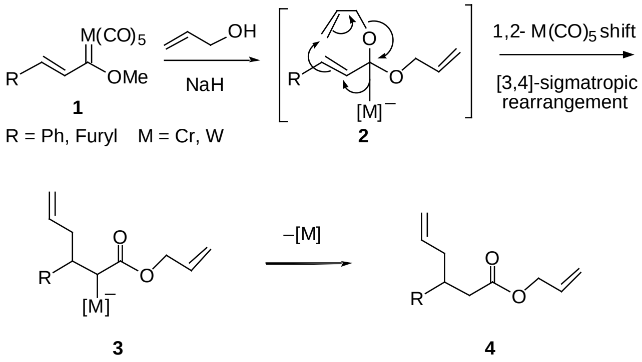
presence of a base to give β-allyl β-arylpropionate **4** via concerted 1,2-M(CO)$_5$ shift followed by [3,4]-sigmatropic rearrangement (Scheme 1). The allyl group was introduced at the β-carbon to the ester carbonyl group. Therefore, β-allyl β-arylpropionates **4** would be expected to obtained as optically active compounds by utilizing α,β-unsaturated binuclear Fischer carbene complexes with planar chiral arene chromium complex as a chiral auxiliary.

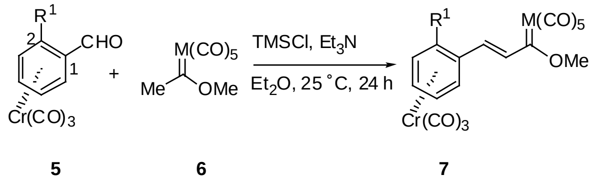


Scheme 1. [3,4]-Sigmatropic rearrangement promoted by [1,2]-metal shift reported by Barluenga.

2.1. Synthesis of α,β-unsaturated binuclear Fischer carbene complexes

Chiral binuclear α,β-unsaturated Fischer carbene complexes **7** as starting materials were easily prepared by aldol condensation of planar chiral *o*-substituted benzaldehyde chromium complexes **5** with methylmethoxycarbene complexes **6** in the presence of triethylamine and trimethylsilyl chloride in reasonable yields (Table 1).[11] The geometry of the double bond of complexes **7** was determined as (*E*)-configuration by ^{1}H NMR.

Table 1. Preparation of chiral α,β-unsaturated binuclear Fischer carbene complexes[a]



Entry	Compound	M	R^1	Yield **7** (%)
1	**7a**	Cr	H	55
2	**7b**	Cr	OMe	74
3	**7c**	Cr	Me	60
4	**7d**	Cr	OPr-*i*	31
5	**7e**	W	H	40
6	**7f**	W	OMe	59
7	**7g**	W	Me	65
8	**7h**	W	OPr-*i*	30

[a] Planar chiral (1*R*,2*S*)-enantiomer was used as starting materials in this study.

2.2. Reactions of binuclear Fischer carbene complexes with allyl alkoxides

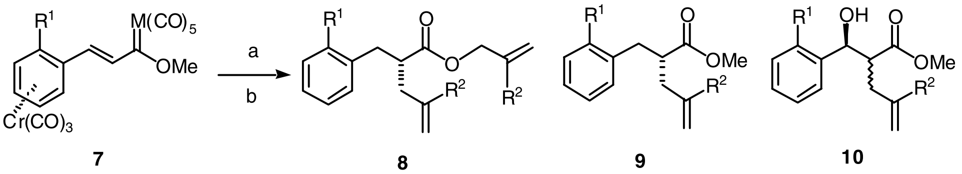
Since we have chiral binuclear α,β-unsaturated Fischer carbene complexes in hand, we examined an asymmetric version of [3,4]-sigmatropic rearrangement reaction of these chiral binuclear α,β-unsaturated Fischer carbene complexes with allyl alkoxides. Initially, we studied the synthesis of β-allyl β-phenyl propionate **4** (R = Ph) by using nonchiral binuclear Fischer carbene complex **7a** according to Barluenga's conditions. A reaction was carried out by stirring a solution of the binuclear carbene complex **7a** and allyl alcohol in the presence of NaH under inert gas in a balloon, and subsequently exposed to sunlight. Surprisingly, α-allyl β-phenyl propionate **8a** was obtained in 75% yield without formation of β-allyl β-phenyl propionate **4** (R = Ph) (Table 2, entry 1). Thus, the allyl group was regioselectively introduced at the α position to the ester group. The structure of α-allyl β-phenyl propionate **8a** was absolutely confirmed by comparison with both authentic samples **8a** and **4** (R = Ph).[12] Both compounds **4** and **8a** could be cleanly distinguished by ^{1}H NMR spectra. The formation of α-allyl β-phenyl propionate **8a** is in sharp contrast to Barluenga's report, in which the allyl group was introduced at the β-position.

We initially imagined that the distinct difference of two reaction pathways of α,β-unsaturated Fischer carbene complexes with allyl alkoxide might be attributed to the strong electron-withdrawing ability of the tricarbonylchromium fragment. Hence, we examined the reaction of α,β-unsaturated chromium carbene complex **11** having *p*-nitrophenyl group with allyl alkoxide. However, only ester exchange product **12** was obtained (Scheme 2). Thus, the electronic effect of the arene ring of α,β-unsaturated binuclear Fischer carbene complexes does not seem to control the two reaction pathways. Surprisingly, the tricarbonylchromium-uncomplexed α,β-unsaturated Fischer carbene complex **1** (R = Ph, M = Cr) gave only α-allyl β-phenyl propionate **8a** in 68% yield without detection of β-allyl β-phenyl propionate **4** (R = Ph) by the reaction with allyl alkoxide under identical conditions with Barluenga's report. In this way, we obtained only α-allyl β-phenyl propionate by reaction with allyl alkoxide in both cases of α,β-unsaturated Fischer carbene complex **1** and the corresponding tricarbonylchromium coordinated α,β-unsaturated Fischer carbene complex **7**. Consequently, we concluded that the structural assignment of the reaction products is wrong in Barluenga's report.[10]

We next extended this interesting reaction to the asymmetric synthesis of α-allyl β-phenyl propionate by using planar chiral binuclear carbene complexes. When enantiomerically pure binuclear Fischer carbene complex **7b** ($[\alpha]_D^{24}$ −3400 (*c* 0.001, CHCl$_3$)), derived from a planar chiral (−)-(*R*)-*o*-methoxybenzaldehyde chromium complex, was reacted with allyl alkoxide at 25 °C, α-allyl β-(*o*-methoxyphenyl)propionate (**8b**) ($[\alpha]_D^{23}$ −25.2 (*c* 0.09, CHCl$_3$)) was obtained in 68% yield with 95% ee[13] (entry 2). Expectedly, the α-allyl phenyl propionate **8b** was obtained with high ee despite severe basic conditions.

The absolute stereochemistry of the compound **8b** was determined as (*R*)-configuration by comparison of an optical rotation of authentic (*S*)-configurated allyl 2-allyl *o*-methoxyphenylpropionate (**15**) ($[\alpha]_D^{23}$ +27.1 (*c* 0.38, CHCl$_3$)) prepared from Evans' oxazolidone derivative **13** (Scheme 3).[14]

Table 2. Reaction of binuclear carbene complexes **7** with allyl alcohols[a]

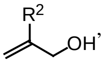


7 **8** **9** **10**

7a; R^1 = H, M = Cr
7b; R^1 = OMe, M = Cr
7c; R^1 =Me, M = Cr
7d; R^1 = OPr-*i*, M = Cr
7e; R^1 = H, M = W
7f; R^1 = OMe, M = W
7g; R^1 = Me, M = W
7h; R^1 = OPr-*i*, M = W

Alphabetical numbering for compounds **8**, **9** and **10** is as follows;
a: R^1 = R^2 = H; **b:** R^1 = OMe, R^2 = H; **c:** R^1 = OMe, R^2 = Me;
d: R^1 = Me, R^2 = H; **e:** R^1 = OPr-*i*, R^2 = H

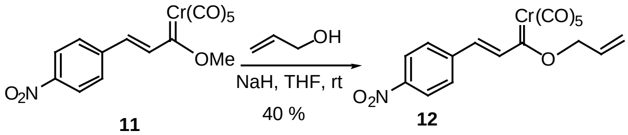
Entry	Complex	Temperature (°C)[b]	Yield **8** (%)	Yield **9** (%)	Yield **10** (%)	ee (%) of **8** or **9**[c]	*anti*/*syn* Ratio of **10**[d]
1	**7a**	25	**8a** (75)	—	—	—	—
2	**7b**	25	**8b** (68)	—	—	95	—
3	**7b**	0	—	**9b** (40)	**10b** (40)	97	78/22
4	**7b**	25	**8c** (85)	—	—	72	—
5	**7b**	0	—	—	**10c** (45)	—	83/17
6	**7c**	25	**8d** (83)	—	—	77	—
7	**7c**	0	—	**9d** (55)	**10d** (40)	93	83/17
8	**7c**	−30	—	**9d** (33)	**10d** (30)	97	80/20
9	**7d**	0	—	**9e** (10)	**10e** (51)	—	85/15
10	**7e**	25	—	**9a** (10)	**10a** (71)	—	63/37
11	**7e**	−30	—	—	**10a** (75)	—	92/8
12	**7f**	−30	—	—	**10b** (65)	—	92/8
13	**7g**	−30	—	—	**10d** (70)	—	92/8
14	**7h**	−30	—	—	**10e** (31)	—	75/25

[a] Reagents and conditions: (a) , NaH, THF, under inert gas in ballon; (b) *h*ν air, ether

[b] Reaction time; 30 min for the reaction at 25 °C: 1.5 h for the reaction at 0 or −30 °C.

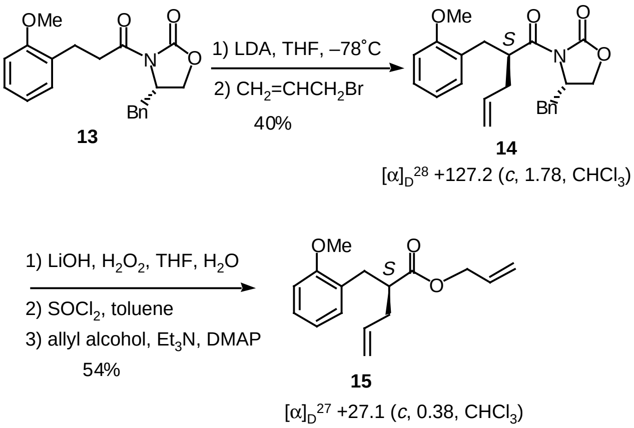
[c] Determined by chiral HPLC.

[d] Determined by integration of representative signals by ^{1}H NMR of the product.



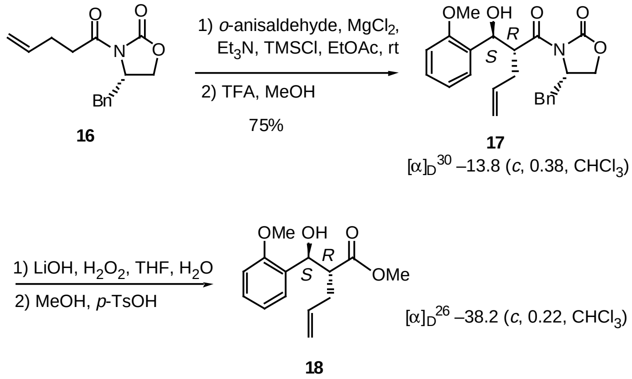
11 **12**

Scheme 2. Reaction of electron deficient mononuclear carbene complex with allyl alkoxide.



Scheme 3. Absolute configuration of α-allyl β-(2-methoxyphenyl) propionate.

When the reaction was performed at 0 °C, the corresponding α-allyl methyl ester **9b** was obtained in 40% yield with 97% ee along with formation of α-allyl β-hydroxy ester **10b** as an easily separable diastereomeric mixture in 40% yield (entry 3). The stereochemistry of the major α-allyl β-hydroxy ester **10b** ($[\alpha]_D^{30}$ −36.0 (*c* 0.23, $CHCl_3$)) was determined to possess the *anti* (2*R*,3*S*)-configuration by comparison with authentic compound. The authentic methyl 2(*R*)-allyl-3(*S*)-hydroxy-3(*o*-methoxyphenyl)propionate (**18**) was prepared by *anti* selective aldol reaction of chiral oxazoline derivative **16** according to the reported procedure[15] (Scheme 4).



Scheme 4. Absolute configuration of α-allyl-β-hydroxy ester.

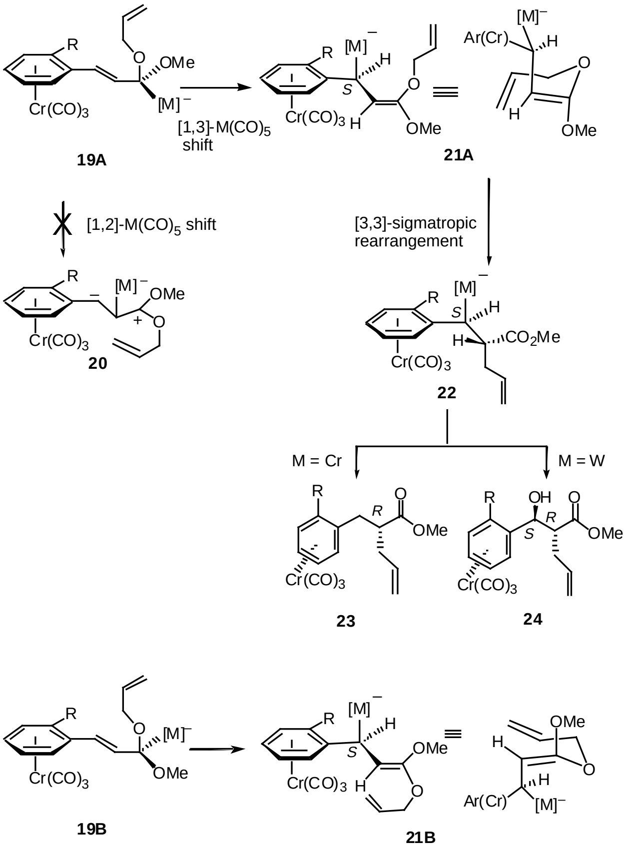
Similarly, with 2-methyl-2-propen-1-ol at 25 °C, the corresponding β-allyl β-arylpropionate **8c** was obtained in 85% yield with 72% ee (Table 2, entry 4). On reaction of **7b** with 2-methyl-2-propen-1-ol at 0 °C, the corresponding α-allyl-β-hydroxy ester **10c** was only obtained with 83/17 dr (entry 5). Similarly, with *o*-methyl substituted-arene chromium complex **7c**, the reaction products were controlled by reaction temperature. Thus, α-allyl-β-hydroxy ester **8d** was obtained at 25 °C (entry 6), while the corresponding α-allyl methyl ester **9d** and diastereomeric α-allyl-β-hydroxy ester **10d** were obtained at lower reaction temperature (entries 7 and 8). The optical yield of **9d** increased to 97% ee in the reaction at −30 °C (entry 8). When the *ortho* substituent of the arene chromium complex was changed to an isopropoxy group, aldol type product **10e** was obtained as a major product in 51% yield with 85/15 dr (entry 9). In this way, binuclear α,β-unsaturated chromium carbene complexes with planar chiral arene chromium complex were reacted with allyl alcohols in the presence of a base to give [3,3]-sigmatropic rearrangement products, α-allyl *o*-substituted phenyl propionate esters, with high ee without formation of β-allyl β-arylpropionates. Furthermore, when the reaction was performed at lower temperature under longer reaction time, methyl α-allyl β-hydroxy-β-arylpropionates **10**, were obtained with high *anti* selectivity in moderate yield. Thus, the coordination of the tricarbonylchromium fragment to the arene ring of α,β-unsaturated Fischer carbene complexes gave optically active α-allyl β-arylpropionates and α-allyl β-aryl β-hydroxypropionates, respectively, with high selectivity by reaction with allyl alkoxides depending on the reaction temperature.

To further pursue this unique reaction, we next turned our attention to the reaction of hetero-binuclear tungsten carbene complexes having planar chiral arene chromium complexes with allyl alkoxides. A hetero-binuclear tungsten carbene complex **7e** was reacted with allyl alkoxide to give [3,3]-sigmatropic rearranged products, **9a** and **10a**. In analogy with α,β-unsaturated chromium carbene complex **1** (M = Cr), the corresponding tungsten carbene complex **1** (R = Ph, M = W) gave still α-allyl β-phenyl propionate in 55% yield without detection of β-allyl β-phenyl propionate reported by Barluenga.[10] Thus, α,β-unsaturated chromium or tungsten carbene complexes afforded always α-allyl propionates via metal 1,3-shift and subsequent [3,3]-sigmatropic rearrangement by reaction with allyl alkoxides, regardless of the coordination of the tricarbonylchromium fragment to the arene ring. In the case of binuclear tungsten carbene complex, methyl α-allyl-β-hydroxy-β-aryl propionate **10a** was predominantly obtained even at room temperature (entry 10). The aldol type product **10a** was obtained as sole product with higher diastereoselectivity at lower reaction temperature (entry 11). Similarly, optically active tungsten carbene complexes with planar chiral arene chromium complexes **7f**, **7g** gave the corresponding α-allyl-β-aryl-β-hydroxypropionates **10b**, **10d** in good yields with high diastereoselectivity by reaction with allyl alkoxide at −30 °C (entries 12 and 13). Compared with homo-binuclear chromium complexes, the hetero-binuclear tungsten carbene complexes having planar chiral arene chromium complex gave predominantly *anti* α-allyl-β-hydroxy-β-arylpropionates as major reaction product with high selectivity in spite of vigorous basic conditions. With a sterically bulky *ortho* isopropoxy substituent of the arene chromium complex, diastereomeric ratio decreased to 75/25 (entry 14).

A clarification of origin of the benzylic oxygen of α-allyl-β-hydroxy-β-arylpropionates **10** in the reaction of the binuclear carbene complexes **7** is significant for the reaction mechanism. Although the reaction was carried out under an inert atmosphere in a balloon, trace amounts of oxygen might be present in the solvent and/or inert gas. Therefore, the reaction mixture of **7g**, allyl alcohol and NaH in dry THF was carefully degassed by an inert gas/freeze/vacuum technique, and the reaction was carried out in a well-degassed glove box. Consequently, it was found that the aldol-type product **10d** decreased to 15% yield, and the α-allyl product **9d** was obtained in 50% yield. This result indicates obviously that the benzylic hydroxy group was introduced from oxygen in the solvent and/or inert gas. The oxygenated product **10** in the reaction with hetero-binuclear tungsten carbene complexes was obtained with higher yield than the reaction with chromium complexes.

3. Reaction mechanism

On the basis of these results, we propose the reaction mechanism of α,β-unsaturated binuclear Fischer carbene complexes with allyl alkoxide in Scheme 5. Nucleophilc addition of allyl alkoxide at the metal carbene fragment of



Scheme 5. Proposed mechanism.

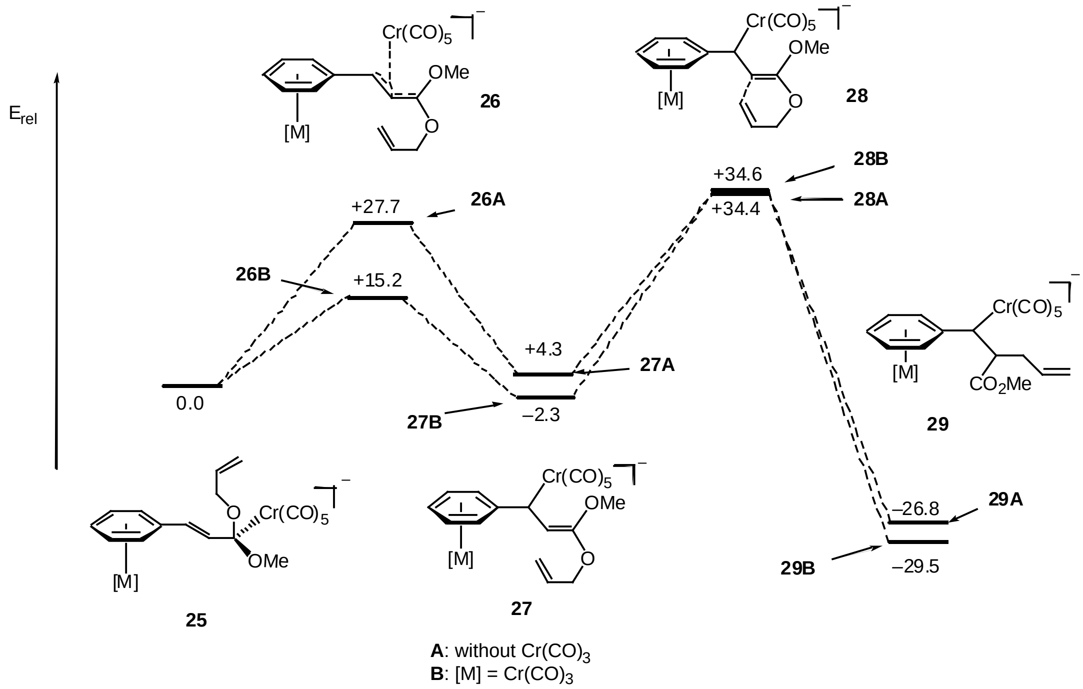


Figure 2. Ab initio calculation.

α,β-unsaturated Fischer carbene complex **7** is initiated to give tetrahedral intermediates **19A** and **19B**. A tetrahedral intermediate **19A** would be formed by the addition to *s-transoid* configurated carbene carbon of the complex **7**, and another intermediate **19B** is formed from *s-cisoid* conformer of the complex **7**. Generally, [1,2]-M$(CO)_5$ shift[16] in α,β-unsaturated Fischer carbene complexes is a concerted process accompanied with sigmatropic rearrangement. The products derived from this process were not observed in the reaction of α,β-unsaturated carbene complexes **1** and **7** with allyl alkoxides. The formation of (*R*)-configurated α-allyl arylpropionates **8**, **9** and **10** would be explained by 1,3-metal shift[17] followed by [3,3]-sigmatropic rearrangement reaction. 1,3-Metal shift from the tetrahedral intermediate **19A** generates an intermediate **21** with *anti* conformation between the tricarbonylchromium fragment and the pentacarbonylmetal group due to steric repulsion. Consequently, benzylic position of the resulting σ-allyl chromium complex **21** is *S*-configuration. Subsequent [3,3]-sigmatropic rearrangement produces α-allyl β-aryl propionate complex **22** with (*R*)-configuration at the α-position via 6-membered chair form **21A**. Furthermore, in the case of the chromium carbene complexes, protonation and the following reductive elimination of the intermediate **22** occur to give complex **23** as the major product. On the other hand, with tungsten carbene complexes, the anionic tungsten species is easily trapped with oxygen followed by reductive elimination to give *anti* aldol type products **24**. Similarly, the intermediate **19B** affords α-allyl β-aryl propionate complex **22** via [3,3]-sigmatropic rearrangement from the transition state **21B**.

4. Computational studies

We, furthermore, studied ab initio calculation in this unique 1,3-metal shift process of α,β-unsaturated unsaturated Fischer carbene complex (Fig. 2).[18,19] The complex **26A** and **26B** were transition states for the 1,3-metal shift step of tetrahedral non-chromium coordinated intermediate **25A** and the corresponding $Cr(CO)_3$-complexed intermediate **25B**. Activation energies for the 1,3-metal shift step are 27.7 and 15.2 kcal mol^{-1}, respectively.[20] On the other hand, the structures **27A** and **27B** are the 1,3-metal shifted stable intermediate of **25A** and **25B**. The corresponding chromium-coordinated intermediate **27B** is 6.6 kcal mol^{-1} more stable than non-chromium complexed intermediate **27A**. Following [3,3]-sigmatropic rearrangement takes place with exothermicity of almost same energy in both $Cr(CO)_3$-complexed and non-complexed intermediates to give rearranged products **29A** and **29B**. In contrast, we could not find out the transition state structures for concerted 1,2-metal shift and 3,4 sigmatropic rearrangemet giving β-allyl arylpropionate. Theoretical study also supports that 1,3-metal shift process in the reaction of α,β-unsaturated Fischer carbene complexes with allyl alkoxides is favorable reaction path than 1,2-metal shift.

5. Conclusions

The binuclear α,β-unsaturated carbene complexes with arene chromium complex afforded α-allyl β-arylpropionates and *anti* α-allyl-β-hydroxy-β-arylpropionates as optically enriched compounds via 1,3-M$(CO)_5$ shift and [3,3]-sigmatropic rearrangement. The corresponding α,β-unsaturated carbene complexes without tricarbonylchromium coordination gave also α-allyl β-aryl propionate without detection of β-allyl β-aryl propionate under the same reaction conditions.

6. Experimental

6.1. General

All manipulations involving organometallics were carried out under an atmosphere of nitrogen or argon and using inert gas/vacuum double manifold techniques. All NMR spectra were recorded in $CDCl_3$ or acetone-d_6 solvent with tetramethylsilane as an internal reference. Mass spectra were determined with EI or FAB mode. Optical rotations were obtained at wavelength 589 nm (sodium D line) using a 1.0-dm cell with a total volume of 5 mL. Diethyl ether and tetrahydrofuran were distilled from sodium/benzophenone ketyl immediately before use.

6.2. General procedure for preparation of binuclear α,β-unsaturated Fischer carbene complexes

Binuclear Fischer carbene complexes were prepared by reported procedure.[8a,11] To an equimolar solution of pentacarbonyl[(methoxy)(methyl)carbene]chromium(0) (1 mmol) and the corresponding benzaldehyde chromium complex in anhydrous Et_2O (0.1 M) was added Et_3N (4 mmol) at room temperature. Then, TMSCl (3 mmol) was added dropwise at the same temperature, and the reaction mixture was stirred until disappearance of the starting material. The solvent was removed in vacuo and the residue was purified by silica gel chromatography.

6.2.1. Binuclear carbene complex 7a. Mp 116 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 4.87 (3H, s), 5.69 (2H, t, $J=6.0$ Hz), 5.89 (1H, t, $J=6.0$ Hz), 6.20 (2H, d, $J=6.0$ Hz), 6.79 (1H, d, $J=15.6$ Hz), 7.98 (1H, d, $J=15.6$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 66.68, 90.74, 93.43, 94.08, 98.33, 125.36, 138.67, 216.39, 224.28, 231.58, 332.02; IR ($CHCl_3$) 3034, 2957, 2058, 2000, 1586, 1453, 1225, 986 cm^{-1}. Anal. Calcd for $C_{18}H_{10}O_9Cr_2$: C, 45.59; H, 2.13. Found: C, 45.64; H, 2.41.

6.2.2. Binuclear carbene complex 7b. $[\alpha]_D^{24}$ -3400 (c 0.001, $CHCl_3$); mp 88 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 3.84 (3H, s), 4.82 (3H, s), 4.99 (1H, t, $J=6.3$ Hz), 5.10 (1H, d, $J=6.3$ Hz), 5.72 (1H, t, $J=6.3$ Hz), 5.94 (1H, d, $J=6.3$ Hz), 6.94 (1H, d, $J=15.3$ Hz), 7.78 (1H, d, $J=15.3$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 56.06, 66.56, 73.22, 84.87, 88.73, 93.39, 93.97, 122.39, 138.73, 143.65, 211.55, 216.60, 231.93, 331.83; IR ($CHCl_3$) 2957, 2058, 2000, 1580, 1464, 1213, 992 cm^{-1}. Anal. Calcd for $C_{19}H_{12}O_{10}Cr_2$: C, 45.25; H, 2.40. Found: C, 45.51; H, 2.41.

6.2.3. Binuclear carbene complex 7c. $[\alpha]_D^{24}$ -5600 (c 0.001, $CHCl_3$); mp 95 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 2.34 (3H, s), 4.83 (3H, s), 5.14 (1H, d, $J=6.3$ Hz), 5.25 (1H, t, $J=6.3$ Hz), 5.58 (1H, t, $J=6.3$ Hz), 5.79 (1H, d, $J=6.3$ Hz), 6.79 (1H, d, $J=15.2$ Hz), 7.68 (1H, d, $J=15.2$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.39, 66.56, 88.92, 92.19, 92.63, 94.46, 98.00, 111.28, 124.60, 139.66, 216.49, 224.27, 232.05, 332.38; IR ($CHCl_3$) 3032, 2959, 2058, 2000, 1580, 1451, 1225, 992 cm^{-1}. Anal. Calcd for $C_{19}H_{12}O_9Cr_2$: C, 46.74; H, 2.48. Found: C, 46.48; H, 2.43.

6.2.4. Binuclear carbene complex 7d. $[\alpha]_D^{24}$ -2400 (c 0.001, $CHCl_3$); mp 112 °C; ^1H NMR (500 MHz, acetone-d_6) δ 1.42–1.48 (6H, m), 4.72–4.75 (1H, m), 4.81 (3H, s), 5.29 (1H, t, $J=6.4$ Hz), 5.69 (1H, d, $J=6.9$ Hz), 6.13 (1H, t, $J=6.4$ Hz), 6.48 (1H, d, $J=6.9$ Hz), 7.41 (1H, d, $J=15.6$ Hz), 7.97 (1H, d, $J=15.6$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.78, 22.41, 66.38, 72.93, 74.94, 84.43, 94.42, 94.60, 125.26, 138.78, 142.87, 216.67, 232.15, 245.56, 332.18; IR ($CHCl_3$) 2986, 2056, 2000, 1580, 1454, 1252, 992 cm^{-1}. Anal. Calcd for $C_{21}H_{16}O_{10}Cr_2$: C, 47.38; H, 3.03. Found: C, 47.57; H, 2.86.

6.2.5. Binuclear carbene complex 7e. Mp 117 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 4.72 (3H, s), 5.68 (2H, t, $J=6.3$ Hz), 5.90 (1H, t, $J=6.3$ Hz), 6.21 (2H, d, $J=6.3$ Hz), 6.97 (1H, d, $J=15.5$ Hz), 7.95 (1H, d, $J=15.5$ Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 59.87, 90.24, 93.24, 93.90, 98.08, 113.36, 148.91, 197.22, 231.53, 233.37, 305.15; IR ($CHCl_3$) 2953, 2067, 2000, 1586, 1451, 1215, 988 cm^{-1}. Anal. Calcd for $C_{18}H_{10}O_9CrW$: C, 35.67; H, 1.66. Found: C, 35.71; H, 1.88.

6.2.6. Binuclear carbene complex 7f. $[\alpha]_D^{24}$ -4000 (c 0.001, $CHCl_3$); mp 148 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 2.34 (3H, s), 4.64 (3H, s), 5.14 (1H, d, $J=6.6$ Hz), 5.24 (1H, t, $J=6.2$ Hz), 5.59 (1H, t, $J=6.2$ Hz), 5.80 (1H, d, $J=6.6$ Hz), 7.07 (1H, d, $J=15.3$ Hz), 7.58 (1H, d, $J=15.3$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 56.09, 69.09, 73.23, 84.89, 88.62, 93.28, 94.00, 127.49, 142.65, 143.49, 197.43, 203.93, 231.90, 305.60; IR ($CHCl_3$) 3032, 2951, 2066, 2000, 1580, 1464, 1252, 995 cm^{-1}. Anal. Calcd for $C_{19}H_{12}O_{10}CrW$: C, 35.87; H, 1.90. Found: C, 35.82; H, 1.93.

6.2.7. Binuclear carbene complex 7g. $[\alpha]_D^{24}$ -3800 (c 0.001, $CHCl_3$); mp 145 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 2.34 (3H, s), 4.64 (3H, s), 5.14 (1H, d, $J=6.6$ Hz), 5.24 (1H, t, $J=6.3$ Hz), 5.59 (1H, t, $J=6.3$ Hz), 5.80 (1H, d, $J=6.6$ Hz), 7.07 (1H, d, $J=15.3$ Hz), 7.58 (1H, d, $J=15.3$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.45, 69.19, 88.84, 92.04, 92.57, 94.49, 97.74, 111.11, 129.64, 143.69, 197.31, 203.67, 231.97, 305.87; IR ($CHCl_3$) 3032, 2953, 2073, 2000, 1580, 1449, 1219, 995 cm^{-1}. Anal. Calcd for $C_{19}H_{12}O_9CrW$: C, 36.80; H, 1.95. Found: C, 36.70; H, 2.03.

6.2.8. Binuclear carbene complex 7h. $[\alpha]_D^{23}$ -2600 (c 0.001, $CHCl_3$); mp 129 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.39 (3H, d, $J=6.0$ Hz), 1.49 (3H, d, $J=6.0$ Hz), 4.48 (1H, sep, $J=6.0$ Hz), 4.63 (3H, s), 4.94 (1H, t, $J=6.5$ Hz), 5.10 (1H, d, $J=6.5$ Hz), 5.74 (1H, t, $J=6.5$ Hz), 5.92 (1H, d, $J=6.5$ Hz), 7.28 (1H, d, $J=15.6$ Hz), 7.66 (1H, d, $J=15.6$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.80, 22.43, 69.02, 72.98, 74.89, 84.43, 88.06, 94.26, 130.85, 142.56, 142.73, 197.48, 203.88, 232.12, 306.23; IR ($CHCl_3$) 3025, 2988, 2066, 1971, 1941, 1578, 1452, 1219 cm^{-1}; MS (relative intensity) m/z, 664 (M^+, 5), 167 (30), 149 (100), 81 (41); HRMS calcd for $C_{21}H_{16}O_{10}CrW$ 663.9658, found 663.9651.

6.3. General procedure for stereoselective [3,3]-sigmatropic reactions utilizing binuclear Fischer carbene complexes

A solution of complex **7** (0.082 mmol) in dry THF (2.0 mL) was added dropwise to a solution of NaH (66 mg, 60% in oil, 1.6 mmol) in allyl alcohol (2.0 mL) under argon. The solution immediately turned from dark purple to yellow.

The reaction mixture was stirred and quenched with aqueous NH_4Cl. The resulting mixture was extracted with EtOAc and washed with brine. The organic layer was dried over anhydrous $MgSO_4$ and filtered and concentrated under reduced pressure. The yellow residue was pushed a plug of silica gel with EtOAc, and all yellow bands were collected. Without further purification, the crude reaction mixture was diluted with ether (5.0 mL) and was exposed to sunlight until yellow solution became colorless. The precipitate was filtered off, and the solution was evaporated under reduced pressure and purified by silica gel chromatography to give a demetallated product.

6.3.1. Allyl 2-allyl-3-phenylpropionate (8a). (Lit. Ref. 21) ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.26–2.42 (2H, m), 2.76–2.81 (2H, m), 2.93–2.98 (1H, m), 4.50 (2H, dd, *J* = 6.0, 1.4 Hz), 5.03–5.09 (2H, m), 5.15–5.22 (2H, m), 5.72–5.83 (2H, m), 7.15–7.28 (5H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ 36.01, 37.75, 47.23, 64.95, 117.18, 118.08, 126.35, 128.37, 128.93, 132.13, 135.05, 139.06, 174.49.

6.3.2. (−)-(*R*)-Allyl 2-allyl-3-(2-methoxyphenyl)propionate (8b). $[\alpha]_D^{23}$ −25.2 (*c* 0.09, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.25–2.30 (1H, m), 2.36–2.42 (1H, m), 2.86–2.91(3H, m), 3.82 (3H, s), 4.49 (2H, ddd, *J* = 4.6, 3.3, 1.4 Hz), 5.02–5.09 (2H, m), 5.14–5.22 (2H, m), 5.73–5.83 (2H, m), 6.82–6.86 (2H, m), 7.09 (1H, dd, *J* = 7.3, 1.8 Hz), 7.19 (1H, dt, *J* = 7.3, 1.8 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 32.84, 36.29, 45.17, 55.16, 64.77, 110.19, 116.75, 117.81, 120.24, 127.44, 127.71, 130.79, 132.33, 135.42, 157.59, 174.89; IR ($CHCl_3$) 3013, 2942, 1728, 1495, 1466, 1246, 1163, 922, 742 cm^{-1}; MS (relative intensity) (FAB) *m/z*, 260 (M$^+$, 44), 203 (32), 121 (100), 91 (31); HRMS calcd for $C_{16}H_{20}O_3$ 260.1412, found 260.1416. HPLC conditions; Chiralcel OD; hexane/2-propanol = 100:1; flow rate 1.0 mL/min; column temperature 40 °C; UV detector 254 nm, retention time, racemate, 14.3 min, 16.9 min: **8b**, 16.9 min.

6.3.3. (−)-(*R*)-2-Methylpropenyl 2-(2-methylpropenyl)-3-(2-methoxyphenyl)propionate (8c). $[\alpha]_D^{27}$ −50.0 (*c* 0.02, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.62 (3H, s), 1.74 (3H, s), 2.21 (1H, dd, *J* = 14.2, 6.4 Hz), 2.43 (1H, dd, *J* = 14.2, 8.7 Hz), 2.81 (1H, dd, *J* = 13.3, 8.7 Hz), 2.89 (1H, dd, *J* = 13.3, 6.4 Hz), 3.01–3.07 (1H, m), 3.82 (3H, s), 4.37 (2H, s), 4.76 (2H, d, *J* = 6.0 Hz), 4.84 (2H, s), 6.82–6.85 (2H, m), 7.09 (1H, d, *J* = 7.3 Hz), 7.18 (1H, t, *J* = 7.3 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 19.40, 22.16, 33.32, 40.75, 43.96, 55.19, 67.50, 110.19, 112.17, 112.82, 120.31, 127.56, 127.70, 130.73, 140.06, 143.02, 157.59, 175.30; IR ($CHCl_3$) 3000, 2920, 1724, 1648, 1491, 1460, 1240, 1160, 899, 739 cm^{-1}; MS (relative intensity) *m/z*, 288 (M$^+$, 25), 232 (38), 187 (36), 161 (48), 121 (100), 91 (64), 55 (12); HRMS calcd for $C_{18}H_{24}O_3$ 288.1726, found 288.1723. HPLC conditions; Chiralcel OD; hexane/2-propanol = 20:1; flow rate 1.0 mL/min; column temperature 40 °C; UV detector 254 nm, retention time, racemate, 5.2 min, 6.3 min: **8c**, 6.3 min.

6.3.4. (−)-(*R*)-Allyl 2-allyl-3-(2-methylphenyl)propionate (8d). $[\alpha]_D^{26}$ −17.7 (*c* 0.26, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.27–2.32 (4H, m), 2.41–2.47 (1H, m), 2.74–2.82 (2H, m), 2.92–2.97 (1H, m), 4.50 (2H, d, *J* = 5.5 Hz), 5.04–5.22 (4H, m), 5.73–5.83 (2H, m), 7.10–7.13 (4H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ 19.41, 35.32, 45.89, 64.96, 117.20, 118.05, 125.85, 126.50, 129.58, 130.34, 132.16, 135.11, 136.18, 137.29, 174.67; IR ($CHCl_3$) 3013, 2930, 1730, 1495, 1456, 1229, 1165, 924, 741 cm^{-1}; MS (relative intensity) *m/z*, 244 (M$^+$, 4), 203 (20), 157 (53), 105 (100), 121 (100), 91 (14); HRMS calcd for $C_{16}H_{20}O_2$ 244.1463, found 244.1459. HPLC conditions; Chiralcel OD; hexane/2-propanol = 20:1; flow rate 1.0 mL/min; column temperature 40 °C; UV detector 254 nm, retention time, racemate, 4.1 min, 4.7 min: **8d**, 4.1 min.

6.3.5. Methyl 2-allyl-3-phenylpropionate (9a). (Lit. Ref. 22) ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.26–2.40 (2H, m), 2.73–2.81 (2H, m), 2.91–2.99 (1H, m), 3.59 (s, 3H), 5.01–5.09 (2H, m), 5.70–5.80 (1H, m), 7.13–7.29 (5H, m); IR (neat) 3018, 2961, 1722, 1212.

6.3.6. (−)-(*R*)-Methyl 2-allyl-3-(2-methoxyphenyl)propionate (9b). $[\alpha]_D^{27}$ −53.6 (*c* 0.056, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.24–2.40 (2H, m), 2.82–2.88 (3H, m), 3.58 (3H, s), 3.82 (3H, s), 5.00–5.08 (2H, m), 5.72–5.80 (1H, m), 6.82–6.87 (2H, m), 7.08 (1H, dd, *J* = 7.8, 1.4 Hz), 7.19 (1H, dt, *J* = 7.8, 1.4 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 32.85, 36.31, 45.26, 51.25, 55,20, 110.12, 116.54, 120.15, 127.58, 130.56, 135.35, 157.42, 175.48; IR ($CHCl_3$) 3013, 2953, 1728, 1601, 1494, 1466, 1439 cm^{-1}; MS (relative intensity) *m/z*, 234 (M$^+$, 25), 116 (37), 121 (100), 91 (68); HRMS calcd for $C_{14}H_{18}O_3$ 234.1256, found 234.1256. HPLC conditions; Chiralcel OD; hexane/2-propanol = 9:1; flow rate 1.0 mL/min; column temperature 40 °C; UV detector 254 nm, retention time, racemate, 6.4 min, 7.2 min: **9b**, 7.2 min.

6.3.7. (+)-(*R*)-Methyl 2-(2-methylpropenyl)-3-(2-methoxyphenyl)propionate (9c). $[\alpha]_D^{30}$ +24.0 (*c* 0.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 1.72 (3H, s), 2.14–2.21(1H, m), 2.35–2.44 (1H, m), 2.73–2.93 (2H, m), 2.96–3.02 (1H, m), 3.54 (3H, s), 3.81 (3H, s), 4.74 (2H, d, *J* = 7.2 Hz), 6.82 (1H, d, *J* = 7.8 Hz), 6.84 (1H, t, *J* = 7.8 Hz), 7.07 (1H, dd, *J* = 7.8, 1.7 Hz), 7.18 (1H, dt, *J* = 7.8, 1.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 22.17, 33.27, 40.72, 43.99, 51.27, 55.20, 110.14, 111.99, 120.20, 127.52, 127.62, 130.56, 143.00, 157.44, 175.89; IR ($CHCl_3$) 3379, 2928, 1728, 1601, 1464, 1217 cm^{-1}; MS (relative intensity) *m/z*, 248 (M$^+$, 18), 217 (13), 192 (96), 161 (100), 121 (86), 91 (65); HRMS calcd for $C_{15}H_{20}O_3$ 248.1413, found 248.1417. HPLC conditions; Chiralcel OD; hexane/2-propanol = 20:1; flow rate 1.0 mL/min; column temperature 40 °C; UV detector 254 nm, retention time, racemate, 6.7 min, 12.0 min: **9c**, 12.0 min.

6.3.8. (−)-(*R*)-Methyl 2-allyl-3-(2-methylphenyl)propionate (9d). $[\alpha]_D^{20}$ −62.5 (*c* 0.01, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.23–2.31 (1H, m), 2.31 (3H, s), 2.34–2.46 (1H, m), 2.70–2.80 (1H, m), 2.78 (1H, dd, *J* = 7.9, 20.4 Hz), 2.94 (1H, dd, *J* = 7.9, 13.3 Hz), 3.59 (3H, s), 5.02–5.10 (2H, m), 5.70–5.80 (1H, m), 7.08–7.14 (4H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ 19.45, 29.76, 35.23, 36.36, 45.95, 51.46, 117.06, 125.80, 126.45, 129.43, 130.28, 135.08, 137.26, 175.37; IR ($CHCl_3$) 3027, 3013, 2928, 1730, 1213 cm^{-1}; MS (relative intensity) *m/z*, 218 (M$^+$, 28), 177 (32), 159 (25), 158 (89), 145 (54), 113 (48), 106

(28), 105 (100); HRMS calcd for $C_{14}H_{18}O_2$ 218.1310, found 218.1310. HPLC conditions; Chiralcel OD; hexane/2-propanol = 100:1; flow rate 1.0 mL/min; column temperature 40 °C; UV detector 254 nm, retention time, racemate, 7.5 min, 9.1 min: **9d**, 7.5 min.

6.3.9. (−)-(*R*)-Methyl 2-allyl-3-(2-isopropoxyphenyl)-propionate (9e). $[\alpha]_D^{26}$ −29.6 (*c* 0.054, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 1.25–1.30 (6H, m), 2.17–2.32 (2H, m), 2.77–2.80 (2H, m), 3.51 (3H, s), 4.44–4.52 (1H, m), 4.92–5.19 (3H, m), 5.13–5.68 (1H, m), 6.73–7.10 (4H, m); IR ($CHCl_3$) 3373, 2983, 1728, 1601, 1454 cm^{-1}; MS (relative intensity) *m/z*, 262 (M^+, 18), 188 (24), 147 (29), 146 (100), 107 (40); HRMS calcd for $C_{16}H_{22}O_3$ 262.1569, found 262.1570.

6.3.10. Methyl 2-allyl-3-hydroxy-3-phenylpropionate (10a). (Lit. Ref. 23) ^1H NMR (500 MHz, $CDCl_3$) δ 2.11–2.17 (1H, m), 2.25–2.31 (1H, m), 2.84–2.88 (2H, m), 3.69 (3H, s), 4.83 (1H, dd, *J* = 7.8, 5.0 Hz), 5.00–5.04 (2H, m), 5.64–5.72 (1H, m), 7.29–7.38 (5H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ 33.75, 51.71, 52.77, 74.85, 117.33, 126.41, 128.13, 128.57, 134.30, 141.63, 174.96.

6.3.11. (−)-(2*R*,3*S*)-Methyl 2-allyl-3-hydroxy-3-(2-methoxyphenyl)propionate (10b). $[\alpha]_D^{30}$ −36.0 (*c* 0.23, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 2.09–2.14 (1H, m), 2.32–2.38 (1H, m), 3.04 (1H, ddd, *J* = 12.8, 7.3, 5.0 Hz), 3.34 (1H, d, *J* = 9.2 Hz), 3.66 (3H, s), 3.86 (3H, s), 4.97–5.04 (3H, m), 5.65–5.73 (1H, m), 6.89 (1H, d, *J* = 8.7 Hz), 6.96 (1H, t, *J* = 7.3 Hz), 7.26–7.28 (2H, m); IR ($CHCl_3$) 3555, 2953, 1730, 1641, 1215 cm^{-1}; MS (relative intensity) *m/z*, 250 (M^+, 2), 138 (10), 137 (100), 135 (19), 107 (21); HRMS calcd for $C_{14}H_{18}O_4$ 250.1205, found 250.1171. HPLC conditions; Chiralcel OD; hexane/2-propanol = 9:1; flow rate 1.0 mL/min; column temperature 40 °C; UV detector 254 nm, retention time, racemate, 10.2 min, 11.1 min: **10b**, 10.2 min.

6.3.12. (−)-(2*R*,3*S*)-Methyl 2-(2-methylpropenyl)-3-hydroxy-3-(2-methoxyphenyl)propionate (10c). $[\alpha]_D^{30}$ −34.3 (*c* 0.07, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 1.61 (3H, s), 1.95–2.01 (1H, m), 2.29–2.37 (1H, m), 3.01–3.16 (1H, m), 3.32 (1H, d, *J* = 9.1 Hz), 3.55 (3H, s), 3.79 (3H, s), 4.66 (2H, d, *J* = 1.0 Hz), 4.91 (1H, dd, *J* = 9.1, 7.0 Hz), 6.79–6.91 (2H, m), 7.17–7.22 (2H, m); IR ($CHCl_3$) 3013, 2957, 1730, 1240, 1215 cm^{-1}; MS (relative intensity) *m/z*, 264 (M^+, 1), 208 (22), 137 (100), 135 (23), 107 (41); HRMS calcd for $C_{15}H_{20}O_4$ 264.1361, found 264.1360. HPLC conditions; Chiralcel OD; hexane/2-propanol = 9:1; flow rate 1.0 mL/min; column temperature 40 °C; UV detector 254 nm, retention time, racemate, 6.3 min, 7.0 min: **10c**, 6.3 min.

6.3.13. (−)-(2*R*,3*S*)-Methyl 2-allyl-3-hydroxy-3-(2-methylphenyl)propionate (10d). $[\alpha]_D^{27}$ −40.2 (*c* 0.48, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 2.09–2.15 (1H, m), 2.32–2.37 (4H, m), 2.82 (1H, d, *J* = 5.5 Hz), 2.87–2.92 (1H, m), 3.68 (3H, s), 4.99–5.10 (3H, m), 5.63–5.71 (1H, m), 7.14–7.38 (4H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ 19.33, 33.61, 51.68, 52.24, 71.08, 117.29, 125.85, 126.39, 127.77, 130.59, 134.37, 135.22, 139.67, 175.07; IR ($CHCl_3$) 3470, 3081, 3013, 2953, 1723, 1644, 1441 cm^{-1}; MS (relative intensity) *m/z*, 234 (M^+, 2), 157 (10), 121 (100), 114 (91), 93 (66); HRMS calcd for $C_{14}H_{18}O_3$ 234.1256, found 234.1251.

6.3.14. (−)-(2*R*,3*S*)-Methyl 2-allyl-3-hydroxy-3-(2-isopropoxyphenyl)propionate (10e). $[\alpha]_D^{27}$ −34.8 (*c* 0.48, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.36 (3H, d, *J* = 6.1 Hz), 1.39 (3H, d, *J* = 6.1 Hz), 2.12 (1H, quin, *J* = 7.2 Hz), 2.34 (1H, quin, *J* = 7.2 Hz), 3.06 (1H, ddd, *J* = 9.2, 7.2, 6.1 Hz), 3.44–3.54 (1H, m), 3.65 (3H, s), 4.64 (1H, sep, *J* = 6.1 Hz), 4.94–5.05 (3H, m), 5.65–5.75 (1H, m), 6.87 (1H, d, *J* = 7.9 Hz), 6.91 (1H, t, *J* = 7.9 Hz), 7.20–7.26 (2H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ 22.07, 22.29, 34.17, 51.56, 69.84, 72.27, 112.33, 116.74, 120.28, 128.11, 128.59, 129.99, 134.81, 154.52, 174.94; IR ($CHCl_3$) 3366, 3025, 3013, 1730, 1601, 1238 cm^{-1}; MS (relative intensity) *m/z*, 278 (M^+, 2), 165 (43), 149 (8), 123 (100), 121 (15); HRMS calcd for $C_{16}H_{22}O_4$ 278.1518, found 278.1514. HPLC conditions; Chiralcel OD; hexane/2-propanol = 9:1; flow rate 1.0 mL/min; column temperature 40 °C; UV detector 254 nm, retention time, racemate, 6.1 min, 7.5 min: **10e**, 6.1 min.

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References and notes

1. Some selected reviews: (a) Doyle, M. P. In Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Comprehensive Organometallic Chemistry II; Pergamon: New York, 1995; Vol. 12, pp 387–420. (b) Wulff, W. D. In Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Comprehensive Organometallic Chemistry II; Pergamon: New York, 1995; Vol. 12, pp 469–547. (c) Hegedus, L. S. In Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Comprehensive Organometallic Chemistry II; Pergamon: New York, 1995; Vol. 12, pp 549–600. (d) *Metal Carbons in Organic Synthesis*; Dötz, K.-H., Ed.; Topics in Organometallic Chemistry; Springer: Berlin, 2004; Vol. 13. (e) Bertrand, G. (Guest Ed.); *J. Organomet. Chem.* **2001**, *617/618*, 3–754.
2. Some selected references: (a) Miura, T.; Iwasawa, N. *J. Am. Chem. Soc.* **2002**, *124*, 518–519. (b) Iwasawa, N.; Shido, M.; Kusama, H. *J. Am. Chem. Soc.* **2001**, *123*, 5814–5815. (c) Barluenga, J.; López, L. A.; Löber, O.; Tomás, M.; García-Granda, S.; Alvarez-Rúa, C.; Borge, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 3392–3394. (d) Barluenga, J.; Aznar, F.; Palomero, M. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4346–4348. (e) Barluenga, J.; Aznar, F.; Gutiérrez, I.; Martín, A.; García-Granda, S.; Llorca-Baragaño, M. A. *J. Am. Chem. Soc.* **2000**, *122*, 1314–1324. (f) Barluenga, J.; Ballesteros, A.; Santamaría, J.; Bernardo de la Rúa, R.; Rubio, E.; Tomás, M. *J. Am. Chem. Soc.* **2000**, *122*, 12874–12875. (g) Barluenga, J.; Rodríguez, F.; Fañanás, F. J.; Rubio, E. *Angew. Chem., Int. Ed.* **1999**, *38*, 3084–3086.
3. Some selected references for Michael reactions: (a) Barluenga, J.; Montserrat, J. M.; Flórez, J.; García-Granda, S.; Martin, E.

Chem. Eur. J. **1995**, *1*, 236–242. (b) Barluenga, J.; Montserrat, J. M.; Flórez, J.; García-Granda, S.; Martín, E. *Angew. Chem., Int. Ed. Engl.* **1994**, *23*, 1392–1394. (c) Barluenga, J.; Bernad, P. L., Jr.,; Concellón, J. M.; Piñera-Nicolás, A.; García-Granda, S. *J. Org. Chem.* **1997**, *62*, 6870–6875. (d) Ezquerra, J.; Pedregal, C.; Merino, I.; Flórez, J.; Barluenga, J.; García-Granda, S.; Llorca, M.-A. *J. Org. Chem.* **1999**, *64*, 6554–6565. (e) Shi, Y.; Wulff, W. D.; Yap, G. P. A.; Rheingold, A. L. *Chem. Commun.* **1996**, 2601–2602.

4. Some selected references for [3+2]-cycloaddition: (a) Barluenga, J.; Fernández-Marí, F.; Viado, A. L.; Aguilar, E.; Olano, B.; García-Granda, S.; Moya-Rubiera, C. *Chem. Eur. J.* **1999**, *5*, 883–896. (b) Kagoshima, H.; Okamura, T.; Akiyama, T. *J. Am. Chem. Soc.* **2001**, *123*, 7182–7183. (c) Merino, I.; Laxmi, Y. R. S.; Flórez, J.; Barluenga, J. *J. Org. Chem.* **2002**, *67*, 648–655.
5. Some selected references for [4+2]-cycloaddition: (a) Powers, T. S.; Jiang, W.; Su, J.; Wulff, W. D.; Waltermire, B. E.; Rheingold, A. L. *J. Am. Chem. Soc.* **1997**, *119*, 6438–6439. (b) Wulff, W. D.; Bauta, W. E.; Kaesler, R. W.; Lankford, P. J.; Miller, R. A.; Murray, C. K.; Yang, D. C. *J. Am. Chem. Soc.* **1990**, *112*, 3642–3659. (c) Hsung, R. P.; Wulff, W. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **1994**, *116*, 6449–6450. (d) Beddoes, R. L.; King, J. D.; Quayle, P. *Tetrahedron Lett.* **1995**, *36*, 3027–3028. (e) Hsung, R. P.; Wulff, W. D.; Challener, C. A. *Synthesis* **1996**, 773–789.
6. Some selected references for [3+2+1]-cycloaddition: (a) Quinn, J. F.; Powers, T. S.; Wulff, W. D.; YAP, G. P. A.; Rheingold, A. L. *Organometallics* **1997**, *16*, 4945–4947. (b) Dötz, K. H.; Stinner, C.; Nieger, M. *J. Chem. Soc., Chem. Commun.* **1995**, 2535–2536. (c) Bao, J.; Wulff, W. D.; Fumo, M. J.; Grant, E. B.; Heller, D. P.; Whitcomb, M. C.; Yeung, S.-M. *J. Am. Chem. Soc.* **1996**, *118*, 2166–2181.
7. (a) Vorogushin, A. V.; Wulff, W. D.; Hansen, H.-J. *J. Am. Chem. Soc.* **2002**, *124*, 6512–6513. (b) Dötz, K. H.; Jäkel, C.; Hasse, W.-C. *J. Organomet. Chem.* **2001**, *617–618*, 119–132. (c) Janes, E.; Dötz, K. H. *J. Organomet. Chem.* **2001**, *622*, 251–258.
8. Some selected α,β-unsaturated binuclear Fischer carbene complexes with arene tricarbonylchromium complex or ferrocene: (a) Sierra, M. A.; del Amo, J. C.; Mancheño, M. J.; Gómez-Gallego, M. *J. Am. Chem. Soc.* **2001**, *123*, 851–861. (b) Barluenga, J.; López, S.; Trabanco, A. A.; Fernández-Acebes, A.; Flórez, J. *J. Am. Chem. Soc.* **2000**, *122*, 8145–8154. (c) Barluenga, J.; Fernández-Acebes, A.; Trabanco, A. A.; Flórez, J. *J. Am. Chem. Soc.* **1997**, *119*, 7591–7592.
9. A preliminary report: Kamikawa, K.; Tachibana, A.; Shimizu, Y.; Uchida, K.; Furusyo, M.; Uemura, M. *Org. Lett.* **2004**, *6*, 4307–4310.
10. Barluenga, J.; Rubio, E.; López-Pelegrín, J. A.; Tomás, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 1091–1093.
11. Aumann, R.; Heinen, H. *Chem. Ber.* **1987**, *120*, 537–540 and Ref. 8a.
12. Authentic samples **4** (R=Ph) and **8a** were prepared by allyl esterification of 3-phenyl-hex-5-enoic acid and LDA-mediated α-allylation of β-phenyl propionate, respectively. 3-Phenyl-hex-5-enoic acid; Majetich, G.; Casares, A. M.; Chapman, D.; Behnke, M. *Tetrahedron Lett.* **1983**, *24*, 1909–1912.
13. Enantiomeric excess was determined by chiral HPLC with Chiralcel OD; hexane/2-propanol=100:1; flow rate 1.0 mL/min; column temperature 40 °C; UV detector 254 nm, retention time, racemate, 14.3 min, 16.9 min: **8b**, 16.9 min.
14. Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737–1739.
15. Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2002**, *124*, 392–393.
16. (a) Dötz, K. H.; Christoffers, C.; Knochel, P. *J. Organomet. Chem.* **1995**, *489*, C84–C86. (b) Iwasawa, N.; Ochiai, T.; Maeyama, K. *J. Org. Chem.* **1998**, *63*, 3164–3165. (c) Iwasawa, N.; Maeyama, K.; Saitou, M. *J. Am. Chem. Soc.* **1997**, *119*, 1486–1487. (d) Iwasawa, N.; Ochiai, T.; Maeyama, K. *Organometallics* **1997**, *16*, 5137–5139. (e) Barluenga, J.; Trabanco, A. A.; Flórez, J.; Gracía-Granda, S.; LLlorca, M.-A. *J. Am. Chem. Soc.* **1998**, *120*, 12129–12130. (f) Barluenga, J.; Tomás, M.; Rubio, E.; López-Pelegrín, J. L.; García-Granda, S.; Priede, M. P. *J. Am. Chem. Soc.* **1999**, *121*, 3065–3071.
17. (a) Hegedus, L. S.; Lundmark, B. R. *J. Am. Chem. Soc.* **1989**, *111*, 9194–9198. (b) Sleiman, H. F.; McElwee-White, L. *J. Am. Chem. Soc.* **1988**, *110*, 8700–8701. (c) Maxey, C. T.; Sleiman, H. F.; Massey, S. T.; McElwee-White, L. *J. Am. Chem. Soc.* **1992**, *114*, 5153–5160. (d) Fischer, H.; Schlageter, A.; Bidell, W.; Früh, A. *Organometallics* **1991**, *10*, 389–391.
18. All calculations were performed with Gaussian 98: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, Jr., J. A.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, Revision A. 5; Gaussian, Inc.: Pittsburgh, PA, 1998.
19. Geometry optimizations for Cr complexes **25**–**29** were carried out with RHF level theory on using 3-21G(d) basis sets.
20. Total energies of compounds **25A** and **25B** were −2245.7650 H and −3620.2431 H, respectively. Relative energies were including zero point energy correction.
21. Zou, X.-W.; Lu, T.-M.; Song, J.; Wu, F.-H.; Shen, Y.-J. *Huadong Ligong Daxue Xuebao* **2003**, *29*, 210–213.
22. Kim, D. H.; Li, Z.-H.; Lee, S. S.; Park, J.-Il.; Chung, S. J. *Bioorg. Med. Chem.* **1998**, *6*, 239–249.
23. (a) Hart, D. J.; Krishnamurthy, R. *J. Org. Chem.* **1992**, *57*, 4457–4470. (b) Urabe, H.; Takeda, T.; Hideura, D.; Sato, F. *J. Am. Chem. Soc.* **1997**, *119*, 11295–11305.

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Direct conversion of *tert*-butyl 2-hydroxyalkyl sulfides to 1,3-oxathiolanes

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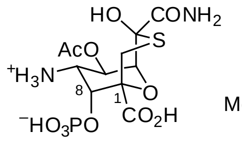
Abstract—*tert*-Butyl 2-hydroxyalkyl sulfides, prepared by reaction of epoxides with 2-methylpropane-2-thiol, are converted directly to 1,3-oxathiolanes upon treatment with pivalaldehyde and boron trifluoride diethyl etherate in the presence of thioanisole.

1. Introduction

As part of a research programme[1] targeted towards the synthesis of the RNA polymerase inhibitor tagetitoxin **1**,[2] we wished to synthesise the cis-disubstituted 1,3-oxathiolane ester **2-c** as a single enantiomer. It was hoped that subsequent deprotonation and reaction with an appropriate aldehyde would allow stereospecific construction of the C1–C8 bond of tagetitoxin.[3] Literature reports concerning the enolates of related sulfur-containing heterocycles left some doubt as to whether the proposed coupling would be feasible. Seebach et al. reported that the lithium enolate of thiazolidine **3** rapidly decomposed by a β-elimination process and could not be induced to react with electrophiles.[4] Conversely, Pattenden et al. were successful in alkylating the enolate of thiazolidine **4**, which differs from **3** only in the nature of the nitrogen protecting group.[5] It was thus unclear prior to this study whether the enolate of **2-c** would be sufficiently stable to allow reaction with an aldehyde to take place. While **2-c** had not previously been synthesised, it was anticipated that it should be readily prepared by acid-catalysed condensation of the corresponding β-hydroxythiol with pivalaldehyde.



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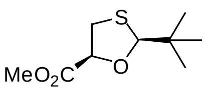
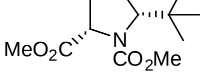


2-*c*



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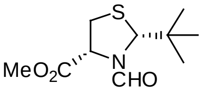

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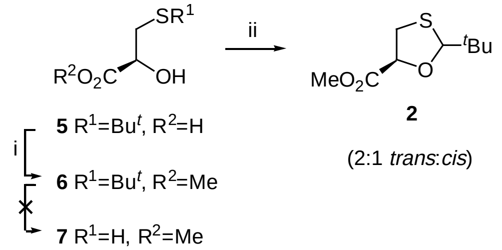
2. Results and discussion

L-Serine was converted via potassium (*R*)-glycidate to carboxylic acid **5** by literature procedures.[6] Esterification was accomplished with thionyl chloride/methanol to afford ester **6** (Scheme 1).[7]



Scheme 1. Reagents and conditions: (i) SOCl$_2$, MeOH, 45%; (ii) ^{t}BuCHO (1 equiv), BF$_3$·OEt$_2$ (2 equiv), PhSMe (1 equiv), CH$_2$Cl$_2$, 55%.

Keywords: Heterocycles; Sulfur; Protecting groups; *tert*-Butyl sulfides; Lewis acids.

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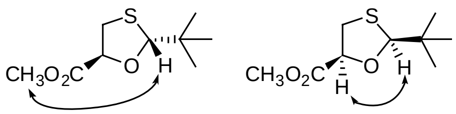
The next step, removal of the *tert*-butyl protecting group to generate a vicinal hydroxythiol **7**,[7] proved problematic. Treatment of **6** with a range of protic and Lewis acids (including $Hg(OAc)_2$/TFA followed by H_2S;[7b] TFA/Et_3SiH,[7c] and HBF_4/TFA)[7d] failed to give efficient deprotection, and attempts to generate the corresponding disulfide by treatment with oxidising agents (I_2 or $PhI(OAc)_2$)[7e] were also unsuccessful. We were thus forced to develop a new method for removal of the *tert*-butyl group, and were gratified to discover that treatment of **6** with pivalaldehyde, $BF_3 \cdot OEt_2$ and thioanisole in dichloromethane led directly to the formation of the desired 1,3-oxathiolane **2**, which was obtained as a 2:1 mixture of isomers. NOE experiments on this mixture (Fig. 1), together with analysis of ^1H–^1H coupling constants,[8] indicated that the major component was the trans-isomer **2-t**.



2-*t* (major) **2-*c*** (minor)

Figure 1. Selected nuclear Overhauser enhancements in **2-t** and **2-c**.

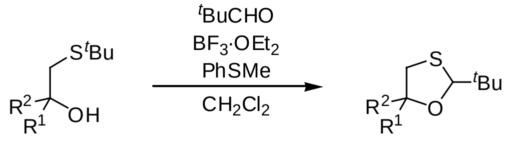
Attempts to improve the yield of the reaction by use of other Lewis or Brønsted acids ($ZnCl_2$, $InCl_3$, $ZrCl_4$, Dowex-50) were unsuccessful, with only boron trifluoride, of the acids investigated, giving the desired product. Replacement of pivalaldehyde with other aldehydes or ketones also proved unsuccessful, while omission of the thioanisole gave a much slower reaction, with appreciable quantities of starting material still present after 40 h.

Our attention next turned to the scope of this transformation. A range of racemic or achiral *tert*-butyl 2-hydroxyalkyl sulfides was prepared by opening of the corresponding mono- or 1,1-disubstituted epoxides with 2-methylpropane-2-thiol under basic conditions.[9] These compounds were subjected to the deprotection–cyclisation conditions developed for compound **6**: the results are summarised in Table 1.

Sulfides derived from monosubstituted epoxides (**8a**–**8g**) were converted to the corresponding 1,3-oxathiolanes **9a**–**9g** as mixtures of diastereomers, which were in general not separable by column chromatography. In the case of **9a**, as for **2**, the trans-isomer was the major one; in all other cases, the cis-isomer predominated. Achiral sulfide **8h**, which incorporates a tertiary alcohol, could also be converted to the corresponding 1,3-oxathiolane in high yield under the same conditions.

Given the ready interconversion of 1,3-oxathiolane stereoisomers in the presence of $BF_3 \cdot OEt_2$,[8] the product ratios observed may reflect the relative thermodynamic stability of the two diastereomers. Indeed, previous equilibration studies have indicated that the cis-isomer of 2,5-dialkyl-1,3-oxathiolanes is the more stable.[8] By contrast, Brønsted acid-catalysed condensation of methyl 3-mercapto-2-hydroxypropanoate with acetaldehyde was reported to give the trans-isomer, analogous to **2-t**, as the major isolated product.[10]

Table 1. Conversion of *tert*-butyl sulfides to 1,3-oxathiolanes



8a-8h **9a-9h**

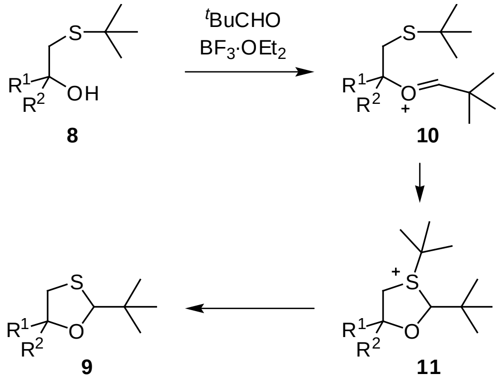
Sulfide	R^1	R^2	Time (h)	Yield (%) (trans:cis)[a]
8a	CO_2Et	H	4	67 (2.2:1)
8b	n-C_3H_7	H	4	15 (1:2.5)[b]
8c	CH_2Ph	H	22	47 (1:3.8)
8d	CH_2OPh	H	5	74 (1:3.1)
8e	CH_2OBn	H	24	82 (1:3.0)
8f	$CH_2OCH_2CH{=}CH_2$	H	25	36 (1:2.9)
8g	$(CH_2)_6CH{=}CH_2$	H	5	12 (1:3.7)
8h	CH_2OPh	CH_2OPh	23	91

[a] Isolated yields of mixtures of diastereomers. The figures in parentheses represent the trans:cis isomeric ratio in the crude reaction mixture, as determined by ^1H NMR spectroscopy.

[b] Isolated yield of cis-isomer.

Yields of oxathiolanes were moderate to good, with the exceptions of **9b**, whose volatility made isolation troublesome, and of **9g**, where isolation of a pure product was hampered by problems in separating the oxathiolane product from non-polar impurities.

The mechanism for this combined deprotection–cyclisation transformation is presumed to be that outlined in Scheme 2. Condensation of the alcohol functionality of **8** with pivalaldehyde, catalysed by the Lewis acid, gives cation **10**, which is attacked in an intramolecular fashion by the sulfur atom to afford **11**. Loss of a *tert*-butyl cation, which is scavenged by thioanisole, leads to the observed product **9**.



Scheme 2. Proposed mechanism for deprotection–cyclisation.

An alternative mechanism in which acid-catalysed removal of the *tert*-butyl group to yield a hydroxythiol is followed by condensation with pivalaldehyde was ruled out by a control experiment carried out in the absence of pivalaldehyde; in this case, no reaction occurred and the starting material was recovered unchanged.

We have investigated the possibility of generating the lithium enolate of **2** with LDA (for initial studies a mixture of **2-c** and **2-t** was employed) and reacting it with an aldehyde electrophile. Under all conditions tested to date[11] (temperatures from −90 to −78 °C, in the presence or absence of DMPU and lithium bromide as additives; trapping by addition of isobutyraldehyde, or in situ with benzaldehyde), decomposition of the starting material **2** occurred, but none of the desired adduct was formed. These results suggest that the lithium enolate of oxathiolane ester **2**, like that of thiazolidine **3**, decomposes more rapidly than it reacts with aldehyde electrophiles, presumably through β-elimination.

3. Conclusions

We have developed a mild method for the direct conversion of *tert*-butyl 2-hydroxyalkyl sulfides into 1,3-oxathiolanes in a single step. This method circumvents the difficulties encountered in removal of the *tert*-butyl group to form a thiol. A variety of functional groups is tolerated, and yields of up to 91% are obtained for the reaction.

4. Experimental

4.1. General

Reactions were performed under an atmosphere of nitrogen or argon. Methanol and ethanol were dried by distillation from the corresponding magnesium alkoxides. Dichloromethane was dried by passage through an alumina column. Triethylamine was distilled from calcium hydride prior to use. Other reagents were used as obtained from commercial sources.

All new compounds or mixtures of stereoisomeric compounds were judged to contain <5% impurities by ^{1}H NMR.

The relative stereochemistries of compounds **9a–9g** were ascertained by the observation of nuclear Overhauser enhancements in each diastereomer.

4.2. Synthesis of sulfides 6 and 8a–8h

4.2.1. Methyl (2*S*)-3-*tert*-butylsulfanyl-2-hydroxypropanoate (6). (2*S*)-3-*tert*-Butylsulfanyl-2-hydroxypropanoic acid[6b] (**5**, 2.0 g, 11 mmol) was added to a solution of thionyl chloride (8.3 mL, 11.4 mmol) in methanol (50 mL), and the mixture was heated to reflux for 18 h. After cooling to room temperature, the reaction mixture was concentrated in vacuo. Purification by flash chromatography (silica, hexane/ethyl acetate 2:1) afforded **6** (0.98 g, 45%); as a colourless oil; $[\alpha]_D^{25}$ +28.3 (*c* 0.92, EtOH); ν_{max}/cm^{-1} (film) 3444, 2960, 1743, 1460, 1365, 1215, 1096; δ_H (300 MHz; CDCl$_3$) 1.33 (9H, s), 2.87 (1H, dd, J=13.1, 6.0 Hz), 3.01 (1H, dd, J=13.1, 4.3 Hz), 3.81 (3H, s), 4.39 (1H, dd, J=6.0, 4.4 Hz); δ_C (75 MHz; CDCl$_3$) 31.0 (CH$_3$), 38.5 (CH$_2$), 44.6 (C), 52.7 (CH$_3$), 70.3 (CH), 173.7 (C); *m/z* (CI+) 193 (MH$^+$, 35%), 137 (100).

4.2.2. Ethyl 3-*tert*-butylsulfanyl-2-hydroxypropanoate (8a). A solution of sodium ethoxide was prepared by adding sodium (11.86 mg, 0.5 mmol) to dry ethanol (0.26 mL) at 0–5 °C. 2-Methylpropane-2-thiol (0.43 mL, 3.8 mmol) was then added and the resultant solution was stirred for 30 min at room temperature. A solution of ethyl glycidate (400 mg, 3.4 mmol) in dry ethanol (6.9 mL) was added dropwise to the ethoxide/thiol solution, and heated under reflux for 2 h. The reaction mixture was quenched with water (10 mL) and the ethanol removed in vacuo. The aqueous layer was then extracted with diethyl ether (2×10 mL). The combined organic extracts were washed with brine (10 mL), dried (MgSO$_4$) and concentrated. Purification by flash chromatography (silica, petroleum ether/ethyl acetate 85:15) afforded **8a** (193 mg, 27%) as a colourless oil; ν_{max}/cm^{-1} (film) 3444, 2962, 2931, 2902, 1732, 1461; δ_H (300 MHz; CDCl$_3$) 1.31 (3H, t, J=7.2 Hz), 1.32 (9H, s), 2.85 (1H, dd, J=13.0, 5.8 Hz), 3.02 (1H, dd, J=13.0, 4.3 Hz), 4.26 (2H, q, J=7.1 Hz), 4.37–4.40 (1H, m); δ_C (75 MHz; CDCl$_3$) 14.2, 30.9, 33.0, 42.4, 62.0, 69.9, 173.1; *m/z* (CI+) 207 (MH$^+$, 10%), 188 (11), 151 (100), 133 (81), 105 (25); HRMS (CI+) found 207.1048; $C_9H_{19}O_2S$ (MH$^+$) requires 207.1055.

4.2.3. 1-*tert*-Butylsulfanylpentan-2-ol (8b) (general procedure A). 1,2-Epoxypentane (1.12 g, 13.0 mmol) was dissolved in methanol (130 mL). 2-Methylpropane-2-thiol (1.46 mL, 13.0 mmol) and triethylamine (0.91 mL, 6.5 mmol) were added and the resulting mixture was heated under reflux for 5 h. The solvent was then removed in vacuo to give the crude product. Flash chromatography (silica, petroleum ether/ethyl acetate 95:5) afforded **8b** as a colourless oil (1.76 g, 77%); ν_{max}/cm^{-1} (film): 3385, 2929, 2872, 1460, 1363, 1163; δ_H (300 MHz; CDCl$_3$) 0.92 (3H, broad t, J=7.0 Hz), 1.32 (9H, s), 1.37–1.53 (4H, m), 2.35 (1H, s), 2.50 (1H, dd, J=12.8, 8.6 Hz), 2.76 (1H, dd, J=12.7, 3.6 Hz), 3.61–3.69 (1H, m); δ_C (75 MHz; CDCl$_3$) 14.1, 19.0, 31.1, 36.6, 38.7, 42.4, 69.8; *m/z* (EI) 176 (M$^+$, 93%), 133 (43), 119 (52); HRMS (EI) found 176.1239; $C_9H_{20}OS$ (M$^+$) requires 176.1235.

4.2.4. 1-*tert*-Butylsulfanyl-3-phenylpropan-2-ol (8c). Prepared in 72% yield from 2-benzyloxirane by general procedure A, using ethanol as solvent; colourless oil; ν_{max}/cm^{-1} (film) 3418, 2899, 2864, 1456, 1366, 1163, 1032; δ_H (300 MHz; CDCl$_3$) 1.31 (9H, s), 2.26 (1H, broad s), 2.58 (1H, dd, J=12.8, 7.8 Hz), 2.75 (1H, dd, J=12.8, 4.4 Hz), 2.84 (2H, app. d, J=6.4 Hz), 3.87–3.96 (1H, m), 7.20–7.26 (3H, m), 7.29–7.35 (2H, m); δ_C (75 MHz; CDCl$_3$) 31.1, 35.6, 42.5, 42.9, 71.3, 126.6, 128.5, 129.4, 138.0; *m/z* (EI) 224 (M$^+$, 21%), 206 (100), 150 (83), 133 (70), 117 (100); HRMS (EI) found 224.1239; $C_{13}H_{20}OS$ (M$^+$) requires 224.1235.

4.2.5. 1-*tert*-Butylsulfanyl-3-phenoxypropan-2-ol (8d).[12] Prepared in 97% yield from glycidyl phenyl ether by general procedure A, using ethanol as solvent; yellow oil; ν_{max}/cm^{-1} (film) 3395, 2926, 2864, 1601, 1495, 1245; δ_H (300 MHz; CDCl$_3$) 1.38 (9H, s), 2.51 (1H, broad s), 2.78 (1H, dd, J=13.0, 6.9 Hz), 2.89 (1H, dd, J=13.0, 5.6 Hz), 3.97–4.14 (3H, m), 6.90–6.99 (3H, m), 7.26–7.32 (2H, m); δ_C (75 MHz; CDCl$_3$) 31.0, 32.3, 42.7, 69.3, 70.6, 114.6, 121.2, 129.5, 158.5; *m/z* (FAB+) 240 (M$^+$, 20%), 222 (22), 149 (29), 133 (49), 94 (100); HRMS (FAB+) found 240.1186; $C_{13}H_{20}O_2S$ (M^+) requires: 240.1184.

4.2.6. 1-Benzyloxy-3-*tert*-butylsulfanylpropan-2-ol (8e).[13] Prepared in 53% yield from benzyl glycidyl ether by general procedure A; colourless oil; ν_{max}/cm^{-1} (film) 3443, 2961, 2924, 2862, 2899, 1454, 1364; δ_H (300 MHz; $CDCl_3$) 1.33 (9H, s), 2.40 (1H, broad s), 2.67 (1H, dd, J=12.8, 7.1 Hz), 2.75 (1H, dd, J=12.8, 5.9 Hz), 3.49 (1H, dd, J=9.6, 6.3 Hz), 3.58 (1H, dd, J=9.6, 4.0 Hz), 3.87–3.95 (1H, m), 4.57 (2H, s), 7.27–7.38 (5H, m); δ_C (75 MHz; $CDCl_3$) 31.0, 32.3, 42.4, 69.7, 73.1, 73.5, 127.8, 128.5, 137.9; *m/z* (CI+) 255 (MH^+, 32%), 289 (28), 236 (100), 199 (20), 181 (69), 147 (40); HRMS (CI+) found 255.1412; $C_{14}H_{23}O_2S$ (MH^+) requires 255.1419.

4.2.7. 1-Allyloxy-3-*tert*-butylsulfanylpropan-2-ol (8f). Prepared in 80% yield from allyl glycidyl ether by general procedure A; colourless oil; ν_{max}/cm^{-1} (film) 3445, 2961, 2899, 2862, 1645, 1460, 1366; δ_H (300 MHz; $CDCl_3$) 1.32 (9H, s), 2.54 (1H, broad s), 2.66 (1H, dd, J=12.8, 7.0 Hz), 2.74 (1H, dd, J=12.8, 5.9 Hz), 3.44 (1H, dd, J=9.6, 6.4 Hz), 3.54 (1H, dd, J=9.6, 4.0 Hz), 3.84–3.92 (1H, m), 4.01–4.04 (2H, m), 5.17–5.31 (2H, m), 5.84–5.97 (1H, m); δ_C (75 MHz; $CDCl_3$) 31.0, 32.3, 42.4, 69.7, 72.3, 73.0, 117.3, 134.5; *m/z* (CI+) 205 (MH^+, 10%), 159 (20), 149 (45), 131 (100), 97 (38); HRMS (CI+) found 205.1259; $C_{10}H_{21}O_2S$ (MH^+) requires 205.1262.

4.2.8. 1-*tert*-Butylsulfanyldec-9-en-2-ol (8g). Prepared in 98% yield from 1,2-epoxydec-9-ene by general procedure A, using ethanol as solvent; pale yellow oil; ν_{max}/cm^{-1} (film) 3404, 2928, 2856, 1639, 1458, 1364, 1163; δ_H (300 MHz; $CDCl_3$) 1.31–1.40 (10H, m), 1.33 (9H, s), 2.00–2.07 (2H, m), 2.50 (1H, dd, J=12.8, 8.6 Hz), 2.77 (1H, dd, J=12.8, 3.6 Hz), 3.59–3.67 (1H, m), 4.90–5.02 (2H, m), 5.80 (1H, ddt, J=17.0, 10.3, 6.7 Hz); δ_C (75 MHz; $CDCl_3$) 25.7, 28.9, 29.0, 29.5, 31.2, 33.8, 36.6, 36.7, 42.4, 70.0, 114.2, 139.2; *m/z* (FAB+) 245 (MH^+, 100%), 227 (23), 187 (25), 171 (68); HRMS (FAB+) found 245.1928; $C_{14}H_{29}OS$ (MH^+) requires 245.1939.

4.2.9. 2-(*tert*-Butylsulfanylmethyl)-1,3-diphenoxypropan-2-ol (8h). 1,3-Diphenoxy-2-methylenepropane[14] (802 mg, 3.3 mmol) was dissolved in CH_2Cl_2 (8 mL) and the solution was cooled to 0 °C. MCPBA (70–75%, 902 mg, 3.7 mmol) and saturated aqueous $NaHCO_3$ (5 mL) were added and the resulting mixture was stirred for 5 h at room temperature. The mixture was cooled to 0 °C and another equivalent of MCPBA was added. After stirring at room temperature for 21 h, the mixture was cooled to 0 °C and treated with a further equivalent of MCPBA and saturated aqueous $NaHCO_3$ (2 mL). After stirring at room temperature for 3 h, the reaction mixture was filtered through Celite® and the filtrate was washed with brine (10 mL) and dried ($MgSO_4$). The solvent was removed in vacuo and purification by flash chromatography (silica, petroleum ether/ethyl acetate 94:6) afforded 2,2-di(phenoxymethyl)-oxirane (415 mg, 49%); ν_{max}/cm^{-1} (film) 3057, 3040, 2930, 1587, 1497, 1242; δ_H (300 MHz; $CDCl_3$) 3.02 (2H, s), 4.24 (2H, d, J=10.6 Hz), 4.28 (2H, d, J=10.6 Hz), 6.92–7.01 (6H, m), 7.26–7.33 (4H, m); δ_C (75 MHz; $CDCl_3$) 49.5, 56.9, 68.0, 114.7, 121.4, 129.5, 158.5; *m/z* (CI+) 256 (M^+, 100%), 181 (29), 183 (29), 185 (23), 173 (67); HRMS (CI+) found 257.1169; $C_{16}H_{17}O_3$ (MH^+) requires 257.1178.

Sulfide **8h** was prepared from 2,2-di(phenoxymethyl)-oxirane by general procedure A; white solid (mp 68–70 °C); ν_{max}/cm^{-1} (KBr) 3377, 2951, 2924, 2932, 1599, 1590, 1497; δ_H (400 MHz; $CDCl_3$) 1.33 (9H, s), 3.04 (2H, s), 4.11 (4H, s), 6.94–6.98 (6H, m), 7.26–7.31 (4H, m); δ_C (75 MHz; $CDCl_3$) 30.9, 33.3, 42.6, 70.0, 72.8, 114.7, 121.2, 129.5, 158.5; *m/z* (EI) 346 (M^+, 13%), 235 (100), 179 (46), 131 (65), 107 (84), 94 (58); HRMS (EI) found 346.1610; $C_{20}H_{26}O_3S$ (M^+) requires 346.1603.

4.3. Conversion of sulfides to 1,3-oxathiolanes

4.3.1. Methyl (5*S*)-2-*tert*-butyl-1,3-oxathiolane-5-carboxylate (2) (general procedure B). To a solution of methyl (2*S*)-3-*tert*-butylsulfanyl-2-hydroxypropanoate (**6**, 0.38 g, 2 mmol) in dry dichloromethane (5 mL) were added successively pivalaldehyde (0.22 mL, 2 mmol), thioanisole (0.24 mL, 2 mmol) and boron trifluoride diethyl etherate (0.50 mL, 4 mmol). The mixture was stirred at room temperature for 3 h then quenched with saturated aqueous $NaHCO_3$ (5 mL). The aqueous phase was extracted with dichloromethane (3×10 mL), and the combined extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated in vacuo. ^1H NMR analysis showed the ratio of products to be 2:1 in favour of the trans isomer. Purification of the residue by flash chromatography (silica, hexane/ethyl acetate 90:10) afforded **2** (0.22 g, 55%) as a colourless oil, as a 2:1 trans:cis diastereomeric mixture: ν_{max}/cm^{-1} (film) 2962, 1743, 1365, 1209, 1107; δ_H (500 MHz; $CDCl_3$); *(2R,5S)-trans-isomer* **2-t**. 0.98 (9H, s), 3.12 (1H, dd, J=10.8, 6.6 Hz), 3.26 (1H, dd, J=10.8, 2.5 Hz), 3.77 (3H, s), 4.97 (1H, dd, J=6.5, 2.5 Hz), 5.22 (1H, s). *(2S,5S)-cis-isomer* **2-c**. 1.02 (9H, s), 3.00 (1H, dd, J=10.4, 9.1 Hz), 3.23 (1H, dd, J=10.4, 5.8 Hz), 3.78 (3H, s), 4.49 (1H, dd, J=9.1, 5.8 Hz), 4.99 (1H, s); δ_C (125 MHz; $CDCl_3$); *(2R,5S)-trans-isomer* **2-t**. 25.6, 34.3, 35.7, 52.3, 80.6, 95.9, 171.3; *(2S,5S)-cis-isomer* **2-c**. 25.8, 34.6, 35.3, 52.4, 80.8, 96.3, 169.6; *m/z* (electrospray) 227 (M+Na, 100%), 217 (30); HRMS (electrospray) found: 227.0714; $C_9H_{16}O_3SNa$ (M+Na) requires 227.0712.

4.3.2. Ethyl 2-*tert*-butyl-1,3-oxathiolane-5-carboxylate (9a). Prepared as a 2.2:1 trans:cis mixture (crude) from **8a** by general procedure B and isolated in 67% yield as a 2.4:1 trans:cis mixture; colourless oil; ν_{max}/cm^{-1} (film) 2957, 2868, 1744, 1364, 1186, 1144; δ_H (500 MHz; $CDCl_3$); *(2RS, 5SR)-trans-isomer*. 0.99 (9H, s), 1.23–1.31 (3H, m), 3.12 (1H, dd, J=10.7, 6.6 Hz), 3.24–3.28 (1H, m), 4.18–4.28 (2H, m), 4.94 (1H, dd, J=6.6, 2.5 Hz), 5.23 (1H, s); *(2RS, 5RS)-cis-isomer*. δ 1.02 (9H, s), 1.23–1.31 (3H, m), 2.99 (1H, app. dd, J=10.4, 9.0 Hz), 3.22–3.25 (1H, m), 4.18–4.28 (2H, m), 4.47 (1H, dd, J=9.0, 5.8 Hz), 4.99 (1H, s); δ_C (75 MHz; $CDCl_3$); *(2RS, 5SR)-trans-isomer*. 14.2, 25.7, 34.3, 35.7, 61.5, 80.6, 95.9, 170.9; *(2RS, 5RS)-cis-isomer*. 14.2, 25.9, 34.7, 35.4, 61.5, 80.9, 96.4, 169.2; *m/z* (CI+) 219 (MH^+, 16%), 161 (81), 149 (24), 133 (100), 101 (41); HRMS (CI+) found 219.1056; $C_{10}H_{19}O_3S$ (MH^+) requires: 219.1055.

4.3.3. 2-*tert*-Butyl 5-propyl-1,3-oxathiolane (9b). Prepared as a 2.5:1 cis:trans mixture from **8b** by general procedure B; from this mixture a pure sample of the cis-diastereomer could be isolated in 15% yield by flash chromatography. Colourless oil; ν_{max}/cm^{-1} (film) 2957, 2930, 2864, 1479, 1464, 1362; δ_H (500 MHz; CDCl$_3$) 0.92 (3H, broad t, *J*=7.4 Hz), 0.95 (9H, s), 1.33–1.50 (2H, m), 1.53–1.60 (1H, m), 1.68–1.75 (1H, m), 2.47 (1H, app. t, *J*=9.9 Hz), 2.94 (1H, dd, *J*=9.8, 4.7 Hz), 3.83–3.88 (1H, m), 4.90 (1H, s); δ_C (75 MHz; CDCl$_3$) 14.2, 19.6, 25.8, 35.1, 35.9, 36.9, 84.0, 95.4; *m/z* (EI) 188 (M$^+$, 23%), 131 (100), 103 (31); HRMS (EI) found 188.1235; $C_{10}H_{20}OS$ (M$^+$) requires 188.1235.

4.3.4. 5-Benzyl-2-*tert*-butyl-1,3-oxathiolane (9c). Prepared as a 3.8:1 cis:trans mixture (crude) from **8c** by general procedure B and isolated in 47% yield as a 3.8:1 cis:trans mixture; colourless oil; ν_{max}/cm^{-1} (film) 2930, 2864, 1497, 1479, 1454, 1362, 1182, 1076; δ_H (500 MHz; CDCl$_3$); *(2RS, 5RS)-cis isomer*. 0.96 (9H, s), 2.56 (1H, app. t, *J*=9.9 Hz), 2.85–2.89 (2H, m), 3.11 (1H, dd, *J*=13.8, 6.2 Hz), 4.06–4.11 (1H, m), 4.92 (1H, s), 7.19–7.24 (3H, m), 7.26–7.30 (2H, m); *(2RS, 5SR)-trans-isomer*. 0.96 (9H, s), 2.77–2.83 (2H, m), 2.85–2.89 (1H, m), 2.99 (1H, dd, *J*=13.5, 6.1 Hz), 4.57–4.59 (1H, m), 5.04 (1H, s), 7.19–7.24 (3H, m), 7.26–7.30 (2H, m); δ_C (75 MHz; CDCl$_3$); *(2RS, 5RS)-cis-isomer*. 25.8, 35.9, 36.6, 40.1, 84.4, 95.4, 126.5, 128.4, 129.4, 137.9; *(2RS, 5SR)-trans-isomer*. 25.9, 35.2, 36.6, 39.2, 84.3, 94.6, 126.5, 128.5, 129.3, 138.1; *m/z* (CI+) 237 (MH$^+$, 7%), 151 (55), 117 (100), 91 (50); HRMS (CI+) found 237.1314; $C_{14}H_{21}OS$ (MH$^+$) requires 237.1313.

4.3.5. 2-*tert*-Butyl-5-phenoxymethyl-1,3-oxathiolane (9d). Prepared as a 3.1:1 cis:trans mixture (crude) from **8d** by general procedure B and isolated in 74% yield as a 2.2:1 cis:trans mixture; colourless oil; ν_{max}/cm^{-1} (CDCl$_3$ cast) 2957, 2870, 1599, 1497, 1244, 1049, 908; δ_H (500 MHz; CDCl$_3$); *(2RS, 5RS)-cis-isomer*. 0.97 (9H, s), 2.79 (1H, app. t, *J*=9.6 Hz), 3.11 (1H, dd, *J*=10.3, 5.2 Hz), 4.05 (1H, dd, *J*=9.8, 5.6 Hz), 4.19 (1H, dd, *J*=9.8, 5.3 Hz), 4.29–4.34 (1H, m), 5.00 (1H, s), 6.89–6.96 (3H, m), 7.25–7.29 (2H, m); *(2RS, 5SR)-trans-isomer*. 0.97 (9H, s), 3.03 (1H, dd, *J*=10.8, 4.3 Hz), 3.05–3.11 (1H, m), 3.99 (1H, dd, *J*=9.4, 6.8 Hz), 4.03–4.08 (1H, m), 4.72–4.77 (1H, m), 5.00 (1H, s), 6.89–6.96 (3H, m), 7.25–7.29 (2H, m); δ_C (75 MHz; CDCl$_3$); *(2RS, 5RS)-cis-isomer*. 25.9, 34.4, 35.2, 68.6, 81.7, 96.1, 114.7, 121.1, 129.5, 158.6; *(2RS, 5SR)-trans-isomer*. 25.9, 34.2, 36.1, 67.6, 81.2, 95.4, 114.7, 121.1, 129.5, 158.6; *m/z* (FAB+) 252 (M$^+$, 30%), 195 (100), 154 (56) 137 (33); HRMS (FAB+) found 253.1254; $C_{14}H_{21}O_2S$ (MH$^+$) requires 253.1262.

4.3.6. 5-Benzyloxymethyl-2-*tert*-butyl-1,3-oxathiolane (9e). Prepared as a 3.0:1 cis:trans mixture (crude) from **8e** by general procedure B and isolated in 82% yield as a 2.7:1 cis:trans mixture; colourless oil; ν_{max}/cm^{-1} (film) 2955, 2864, 1479, 1454, 1364, 1090; δ_H (500 MHz; CDCl$_3$); *(2RS, 5RS)-cis-isomer*. 0.97 (9H, s), 2.65 (1H, app. t, *J*=9.8 Hz), 2.99 (1H, dd, *J*=10.1, 5.2 Hz), 3.60 (1H, dd, *J*=10.4, 4.7 Hz), 3.67 (1H, dd, *J*=10.4 5.7 Hz), 4.12–4.17 (1H, m), 4.55–4.62 (2H, m), 4.97 (1H, s), 7.31–7.37 (5H, m); *(2RS, 5SR)-trans-isomer*. 0.96 (9H, s), 2.90 (1H, dd, *J*=10.7, 4.6 Hz), 2.99 (1H, dd, *J*=10.7, 5.9 Hz), 3.49 (1H, dd, *J*=9.8, 6.2 Hz), 3.55 (1H, dd, *J*=9.8, 5.8 Hz), 4.55–4.62 (3H, m), 4.93 (1H, s), 7.31–7.37 (5H, m); δ_C (75 MHz; CDCl$_3$); *(2RS, 5RS)-cis-isomer*. 25.9, 34.3, 35.1, 70.9, 73.5, 82.9, 96.0, 127.7, 128.4, 138.1; *(2RS, 5SR)-trans-isomer*. 25.9, 34.1, 36.0, 70.0, 73.4, 82.0, 95.3, 127.7, 128.4, 138.1; *m/z* (CI+) 267 (MH$^+$, 15%), 271 (61), 209 (100), 181 (43); HRMS (CI+) found 267.1410; $C_{15}H_{23}O_2S$ (MH$^+$) requires 267.1419.

4.3.7. 5-Allyloxymethyl-2-*tert*-butyl-1,3-oxathiolane (9f). Prepared as a 2.9:1 cis:trans mixture (crude) from **8f** by general procedure B and isolated in 36% yield as a 2.8:1 cis:trans mixture; colourless oil; ν_{max}/cm^{-1} (film) 2955, 2951, 2926, 1724, 1641, 1479, 1464; δ_H (500 MHz; CDCl$_3$); *(2RS, 5RS)-cis-isomer*. 0.96 (9H, s), 2.63 (1H, app. t, *J*=9.8 Hz), 2.98 (1H, dd, *J*=10.1, 5.2 Hz), 3.56 (1H, dd, *J*=10.5, 4.8 Hz), 3.64 (1H, dd, *J*=10.5, 5.7 Hz), 4.02–4.05 (2H, m), 4.08–4.13 (1H, m), 4.95 (1H, s), 5.16–5.29 (2H, m), 5.84–5.92 (1H, m); *(2RS, 5SR)-trans-isomer*. 0.96 (9H, s), 2.89 (1H, dd, *J*=10.7, 4.7 Hz), 2.98 (1H, dd, *J*=10.7, 5.9 Hz), 3.46 (1H, dd, *J*=9.9, 6.3 Hz), 3.51 (1H, dd, *J*=9.9, 5.7 Hz), 4.00–4.02 (2H, m), 4.51–4.55 (1H, m), 4.94 (1H, s), 5.16–5.29 (2H, m), 5.84–5.92 (1H, m); δ_C (75 MHz; CDCl$_3$); *(2RS, 5RS)-cis-isomer*. 25.9, 34.4, 35.1, 70.9, 72.5, 82.9, 96.0, 117.2, 134.6; *(2RS, 5SR)-trans-isomer*. 25.9, 34.1, 36.0, 70.1, 72.4, 82.0, 95.3, 117.2, 134.6; *m/z* (DCI): 235 (18%), 217 (MH$^+$, 9), 159 (100), 131 (19), 97 (57).

4.3.8. 2-*tert*-Butyl-5-(oct-7-enyl)-1,3-oxathiolane (9g). Prepared as a 3.7:1 cis:trans mixture (crude) from **8g** by general procedure B and isolated in 12% yield as a 14:1 cis:trans mixture; colourless oil; ν_{max}/cm^{-1} (film) 2928, 2856, 1641, 1479, 1362, 1072; δ_H (400 MHz; CDCl$_3$); *(2RS, 5RS)-cis-isomer*. 0.97 (9H, s), 1.25–1.79 (10H, m), 2.02–2.07 (2H, m), 2.49 (1H, app. t, *J*=9.9 Hz), 2.96 (1H, dd, *J*=9.8, 4.7 Hz), 3.83–3.90 (1H, m), 4.92 (1H, s), 4.94–5.02 (2H, m), 5.81 (1H, ddt, *J*=17.0, 10.3, 6.7 Hz); δ_C (75 MHz; CDCl$_3$); *(2RS, 5RS)-cis-isomer*. 25.8, 26.2, 28.8, 29.0, 29.5, 33.7, 33.8, 35.1, 36.9, 84.2, 95.4, 114.2, 139.1; *m/z* (CI+) 257 (MH$^+$, 15%), 199 (80), 171 (100), 137 (31); HRMS (CI+) found 257.1934; $C_{15}H_{29}OS$ (MH$^+$) requires 257.1939.

4.3.9. 2-*tert*-Butyl-5,5-di(phenoxymethyl)-1,3-oxathiolane (9h). Prepared in 91% yield from **8h** by general procedure B; colourless oil; ν_{max}/cm^{-1} (film) 2955, 2932, 1599, 1587, 1497, 1244; δ_H (400 MHz; CDCl$_3$) 0.99 (9H, s), 3.13 (1H, d, *J*=11.4 Hz), 3.27 (1H, d, *J*=11.4 Hz), 4.13 (1H, d, *J*=9.4 Hz), 4.19 (1H, d, *J*=9.4 Hz), 4.21 (2H, s), 5.08 (1H, s), 6.92–6.80 (6H, m), 7.26–7.30 (4H, m); δ_C (75 MHz; CDCl$_3$) 26.0, 35.2, 35.4, 67.6, 69.0, 87.8, 96.1, 114.8, 114.9, 121.1, 129.5, 158.7, 158.8; *m/z* (EI) 358 (M$^+$, 50%), 301 (100), 145 (98), 107 (53), 94 (30); HRMS (EI) found 358.1592; $C_{21}H_{26}O_3S$ (M$^+$) requires 358.1603.

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References and notes

1. Ioannou, M.; Porter, M. J.; Saez, F. *Tetrahedron* **2005**, *61*, 43–50.
2. (a) Mitchell, R. E.; Durbin, R. D. *Physiol. Plant Pathol.* **1981**, *18*, 157–168. (b) Mitchell, R. E.; Coddington, J. M.; Young, H. *Tetrahedron Lett.* **1989**, *30*, 501–504.
3. For a review of related reactions, see: Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem., Int. Ed.* **1996**, *35*, 2708–2748.
4. Jeanguenat, A.; Seebach, D. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2291–2298.
5. Pattenden, G.; Thom, S. M.; Jones, M. F. *Tetrahedron* **1993**, *49*, 2131–2138.
6. (a) Petit, Y.; Larchevêque, M.; *Organic Syntheses*; Wiley: New York, 2004; Collect. Vol. 10, pp 401–404. (b) Cavelier, F.; Yim, A.-M. *Org. Prep. Proced. Int.* **1998**, *30*, 103–106.
7. For deprotection conditions, see: Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley-Interscience: New York, 1999; pp 470–471. (b) Nishimura, O.; Kitada, C.; Fujino, M. *Chem. Pharm. Bull.* **1978**, *26*, 1576–1585. (c) Mehta, A.; Jaouhari, R.; Benson, T. J.; Douglas, K. T. *Tetrahedron Lett.* **1992**, *33*, 5441–5444. (d) Akaji, K.; Yoshida, M.; Tatsumi, T.; Kimura, T.; Fujiwara, Y.; Kiso, Y. *J. Chem. Soc., Chem. Commun.* **1990**, 288–290. (e) Kolovos, M. G.; Moutevelis-Minakakis, P. *Tetrahedron Lett.* **1984**, *25*, 4153–4156.
8. Keskinen, R.; Nikkilä, A.; Pihlaja, K. *Tetrahedron* **1972**, *28*, 3943–3955.
9. Luly, J. R.; Yi, N.; Soderquist, J.; Stein, H.; Cohen, J.; Perun, T. J.; Plattner, J. J. *J. Med. Chem.* **1987**, *30*, 1609–1616.
10. Teodori, E.; Gualtieri, F.; Angeli, P.; Brasili, L.; Giannella, M.; Pigini, M. *J. Med. Chem.* **1986**, *29*, 1610–1615.
11. For typical reaction conditions, see: (a) Corey, E. J.; Reichard, G. A. *J. Am. Chem. Soc.* **1992**, *114*, 10677–10678. (b) Seebach, D.; Weber, T. *Tetrahedron Lett.* **1983**, *24*, 3315–3318. (c) Seebach, D.; Amstutz, R.; Laube, T.; Schweizer, W. B.; Dunitz, J. D. *J. Am. Chem. Soc.* **1985**, *107*, 5403–5409; see also Ref. 3.
12. Wielechowska, M.; Plenkiewicz, J. *Tetrahedron: Asymmetry* **2003**, *14*, 3203–3210.
13. Kraynack, E. A.; Pedersen, S. F. *J. Org. Chem.* **1993**, *58*, 6114–6117.
14. Weiss, F.; Isard, A. *Bull. Soc. Chim. Fr.* **1967**, *6*, 2033–2038.

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Tetrahedron

Cyanuric chloride: decent dehydrating agent for an exclusive and efficient synthesis of kinetically controlled isomaleimides☆

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Abstract—Starting from maleanilic and maleamic acids, a facile general approach to kinetically controlled isomaleimides has been described for the first time using cyanuric chloride as a dehydrating agent with 85–98% yields. The effect of a variety of substituents present on the aromatic ring in amine and maleic anhydride moiety, on these kinetic/thermodynamic dehydration processes of anilic acids has been also described. Under the same set of reaction conditions the phthalanilic acid gave kinetically controlled product, isophtalimide in 91% yield, while the corresponding succinanilic acid furnished the thermodynamically more stable succinimide in high yield.

1. Introduction

Anilic acids on dehydration under kinetically controlled conditions form isoimides while under thermodynamically controlled conditions they furnish the corresponding imides (Scheme 1).[1,2] A large number of applications of imides are known and plenty of methods to design them are well established.[2] The first isomaleimide synthesis was reported in 1955 by Tsou et al.[1a] using trifluroacetic anhydride as a dehydrating agent and to the best of our knowledge a natural product with an isoimide moiety is not known. In comparison with imide, the isoimide chemistry is less explored and only limited isoimide chemistry is known, as a general and efficient method to exclusively design isoimides is still elusive. Presently isomaleimides have been synthesized from the corresponding maleamic acids by using (i) $COCl_2/Et_3N$,[3] (ii) DCC,[4] (iii) $Ac_2O/NaOAc$,[5] (iv) CH_3COCl/Et_3N,[6] (v) $EtOCOCl/Et_3N$,[6] (vi) $(CF_3CO)_2O/Et_3N$,[7] (vii) ketenes[8] and (viii) 2-chloro-1,3-dimethylimidazolinium chloride[9] in pyridine as dehydrating agents. In the synthesis of isomaleimides,[3–9] the use of above mentioned dehydrating reagents have the following limitations (a) large excess amount of reagent is required, (b) tedious workup and purification procedures are involved, (c) low yields of isoimides with decomposition of anilic acids, (d) formation of inseparable mixtures of imides and isoimides in varying proportions, (e) addition of liberated hydrochloric acid to the carbon–carbon double bond and (f) 2+2 cycloaddition reactions of formed imine with ketenes, chlorsulfonylisocyanates, chloroacetyl or 2-chlorophenoxyacetyl chlorides.[10] Recently isoimides have found applications in preparation of surfmers,[11] novel polyimides,[12] novel polyisoimides,[5d,13] agro-chemicals,[9a] pharmaceuticals,[9a] spiro β-lactams,[6,10a,b] resins,[14] polyhydrazides,[15] herbicidal anti-dotes,[16] membranes,[13b] adhesives,[13b] diagnosis and cancer treatment and in vivo photodynamic therapy.[4d,17] Isoimides are useful in the detection and measurement of biological materials such as bacteria, enzymes and hormones.[7b] To focus on the unique butiminolide functional moiety and to explore the chemistry of this important functional group, a search for readily available, cheap, efficient and general quantized reagent is a task of significant challenge.[1–9] Cyanuric chloride has been used earlier as dehydrating agent on several type of organic compounds.[18] The predominance of deprotonation of the amide groups or conversion of carboxylic hydroxyl group into good leaving groups results in predominant formation of the imides or isoimides, respectively.[19] In this context, we reasoned that in comparison with acid anhydrides, acid chlorides, ketenes and carbodiimides, the optimum reactive chloroimines will be soft and the best dehydrating agents to obtain these kinetically controlled isomaleimide products. We chose cyanuric chloride with three inherently present chloro-imine units for this kinetic dehydrative cyclization purpose and now we herein report first simple and efficient method for the synthesis of isoimides (Schemes 2–6).

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Keywords: Maleamic acids; Cyanuric chloride; Dehydration; Kinetic products; Isomaleimides.

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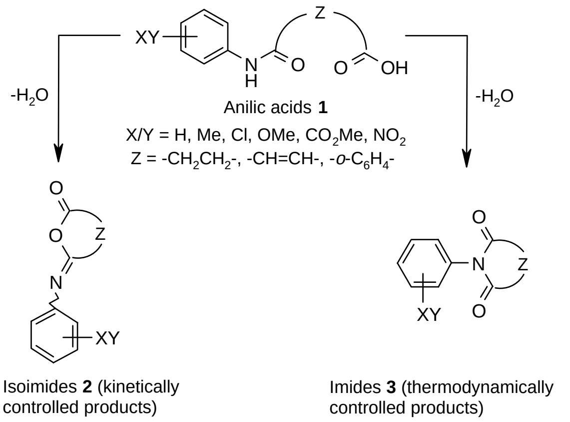
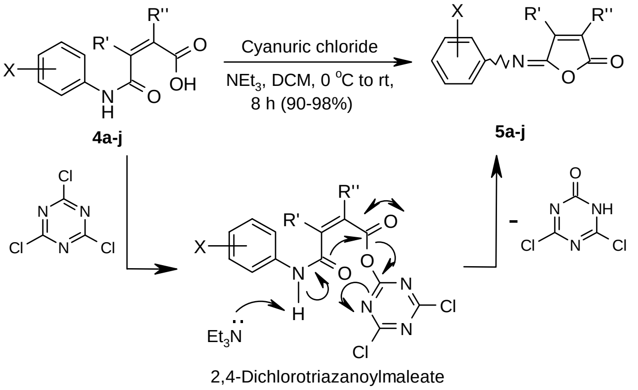


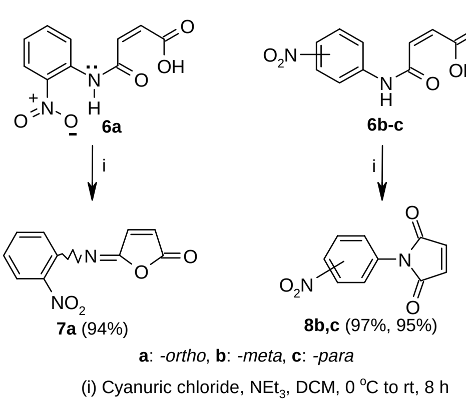
Scheme 1.



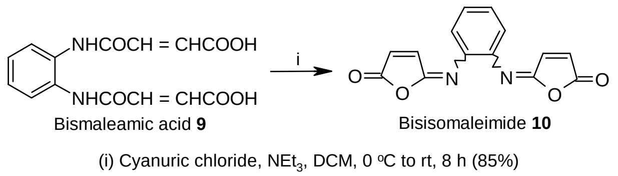
Scheme 2.

Table 1

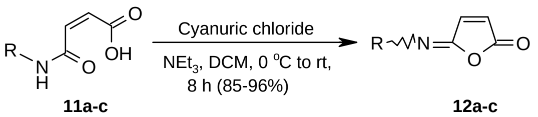
Sr. no.	Acid	X	R′	R″	Product (%)
1	**4a**	H	H	H	**5a** (90)
2	**4b**	*o*-CH_3	H	H	**5b** (98)
3	**4c**	*p*-CH_3	H	H	**5c** (93)
4	**4d**	*o*-OCH_3	H	H	**5d** (90)
5	**4e**	*p*-OCH_3	H	H	**5e** (91)
6	**4f**	*p*-Cl	H	H	**5f** (93)
7	**4g**	*o*-CO_2CH_3	H	H	**5g** (94)
8	**4h**	H	H	CH_3	**5h** (97)
9	**4i**	*p*-CH_3	H	CH_3	**5i** (90)
10	**4j**	*p*-CH_3	Ph	H	**5j** (95)



Scheme 3.



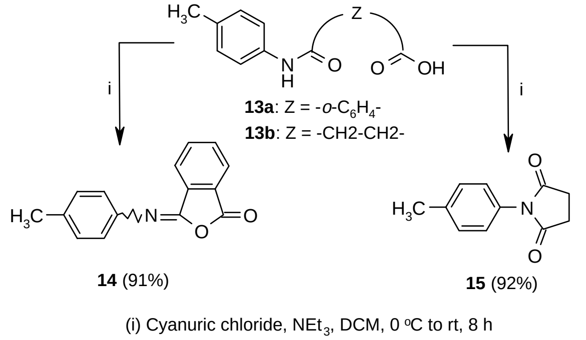
Scheme 4.



Scheme 5.

Table 2

Sr. no.	Acid	R	Product (%)
1	**11a**	CH_3	**12a** (87)
2	**11b**	*p*-$H_3CO–C_6H_4–CH_2$	**12b** (85)
3	**11c**	(*R*)-$PhC(H_3)CH_2$	**12c** (96)



Scheme 6.

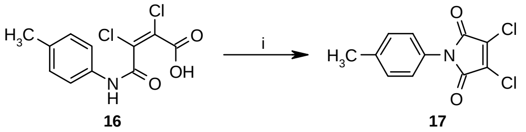
2. Results and discussion

In our research group we have been using cyclic anhydrides as potential precursors for the synthesis of recently isolated bioactive natural and unnatural products[20] and the reactions of cyclic anhydrides with a variety of aromatic and aliphatic amines are known to furnish the corresponding anilic and amic acids in high yields.[20f] In accordance with our aim, we performed the reaction of *N*-phenylmaleanilic acid (**4a**) in DCM with cyanuric chloride (1.1 equiv) in the presence of triethylamine (3.0 equiv) at room temperature and exclusively obtained the corresponding *N*-phenylisomaleimide (**5a**) in 90% yield (Scheme 2). We believe that the present kinetic dehydration must be proceeding via the formation of intermediate 2,4-dichlorotriazinoylmaleate and both the leaving group ability of 2,4-dichlorotrazine-2-ol and the stability of the formed 4,6-dichlorotriazin-2-one must be responsible for this quantitative and exclusive formation of isoimide. In the same conversion, use of half an equivalent of cyanuric chloride also furnished the isoimide **5a** but in less than 50% yield, revealing that 1.1 equiv of cyanuric chloride is necessary for the quantitative conversion of maleanilic acid to the corresponding isoimide, indicating that the in situ generated 4,6-dichlorotriazin-2-one does not further act as a dehydrating agent with same reactivity. To establish the generality of this new set of reaction conditions, we prepared several maleanilic acids **4b–g** and all of them on treatment with cyanuric chloride furnished exclusively the corresponding desired *N*-arylisomaleimides **5b–g** in 90–98% yields (Table 1). The structures of these butiminolides **5a–g** were established from the characteristic lactone carbonyl and imine double bond stretching frequencies in infra-red spectra, presence of two doublet peaks for the vinylic protons in ^{1}H NMR spectra and ^{13}C NMR data. The presence of *syn* and *anti* isomerism was observed in ^{1}H NMR spectra of some of the isoimides. We prepared the mono-substituted methyl and phenyl maleanilic acids **4i** and **4j** from the reactions of *p*-toluidine with methylmaleic and phenylmaleic anhydrides, respectively.[21] These acids **4h–j** on treatment with cyanuric chloride also gave the corresponding mono-substituted isomaleimides **5h–j** in 90–97% yields.

Generally, the isomaleimides with a nitro group on aromatic ring are prepared directly from the corresponding diacid-chlorides and nitro anilines.[22] We planned to study the effect of electron withdrawing *o*-/*m*-/*p*-nitro groups on these cyanuric chloride induced dehydration reactions and prepared the corresponding *o*-/*m*-/*p*-nitromaleanilic acids **6a–c**. The treatment of *o*-nitromaleanilic acid (**6a**) with cyanuric acid chloride exclusively gave the corresponding *o*-nitroisomaleimide **7a** in 94% yield, while *m*-nitromaleanilic acid (**6b**) and *p*-nitromaleanilic acid (**6c**) under the same set of reaction conditions gave only the corresponding nitromaleimides **8b**,**c** in quantitative yields (Scheme 3). Herein, we were unable to obtain the corresponding isomaleimides from acids **6b**,**c** even after carrying out the addition of cyanuric chloride at −20 or −78 °C and we always ended-up with formation of maleimides **8b**,**c**. We reason that the *o*-nitromaleanilic acid **6a** exclusively provides isoimide **7a** due to the intramolecular hydrogen bonding of –NH proton with the *o*-nitro group forming a stable six-membered cyclic structure. This makes the –NH proton less accessible to the base and isoimide formation takes place via the participation of lone pair of electrons on the nitrogen atom. The diacid **9** on treatment with cyanuric chloride (2.2 equiv) also smoothly furnished the bis-isomaleimide **10** in 85% yield (Scheme 4). It appears that the bisisoimide **10** will be a potential substrate to attempt novel 2+2 intramolecular cycloaddition reaction.

The reaction of cyanuric chloride with maleamic acids **11a–c** also gave the corresponding *N*-alkylisomaleimides **12a–c** in 85–96% yields (Scheme 5, Table 2) indicating that the present kinetic dehydration condition works equally well with maleamic acids to design *N*-alkylisomaleimides in very good yields.

We studied the dehydration reactions of phthalanilic acid **13a** and succinanilic acid **13b** using cyanuric chloride as a dehydrating agent under the same set of reaction conditions. The acid **13a** furnished the desired isophthalimide **14** in 91% yield, while the acid **13b** gave exclusively the corresponding succinimide **15** in 92% yield (Scheme 6). Here we surmise that for isolation of these kinetically controlled butiminolides, a strong carbon–carbon double bond support to the backbone is essential. Alternatively, the formed relatively less stable isosuccinimide might be undergoing an in situ isomerization to the corresponding succinimide. In our hands reaction of dichloromaleanilic acid **16** with cyanuric chloride also gave the corresponding dichloromaleimide **17** in 97% yield[23] (Scheme 7). We feel that the present imide formation could be due to the extra thermodynamic stability of disubstitued maleimides, indicating that the present conditions are also useful to design the corresponding succinimides and disubstituted maleimides. The conversion of kinetically controlled isoimides to the corresponding thermodynamically more stable imides is known in the literature.[24]



(i) Cyanuric chloride, NEt$_3$, DCM, 0 °C to rt, 8 h (97%)

Scheme 7.

3. Conclusions

In summary, we have demonstrated an elegant general approach to exclusively design kinetically controlled *N*-aryl/*N*-alkyl isomaleimides and isophthalimides using readily available cyanuric chloride as a dehydrating agent and the present approach has several advantages over earlier approaches. We feel that the present new clean and efficient route to isoimides will be highly useful to further explore the important field of isoimide chemistry as they are dissymmetric in nature, nucleophilic ring openings under neutral conditions are feasible and both carbonyl and imine functionalities will be accessible. Our further studies on isoimide synthesis and the first intramolecular cyclization on isomaleimide skeleton to design the heterocyclic systems via the Michael additions, by taking the advantage of *syn-anti* equilibrium are in progress.

4. Experimental

4.1. General

Commercially available cyclic anhydrides and aromatic/aliphatic amines were used. Freshly recrystallized cyanuric chloride (CCl_4) was used. Column chromatographic separations were carried out on ACME silica gel (60–120 mesh/100–200 mesh). Melting points are uncorrected. FT-IR spectra were recorded on a FT-IR-8300 Shimadzu spectrometer. ^{1}H NMR spectra were recorded in $CDCl_3$ using TMS as an internal standard on a Brucker AC 200 and MSL 300 NMR spectrometers (200 and 300 MHz, respectively). ^{13}C NMR spectra were recorded on a Brucker AC 200, MSL 300 and Brucker AV 400 NMR spectrometers (50, 75 and 100 MHz, respectively). The presence of *syn* and *anti* isomerism was observed in ^{1}H NMR spectra of some of the isoimides.

4.2. General procedure for preparation of isoimides

To a slurry of amic acid (10 mmol) in DCM (30 mL) was added Et_3N (30 mmol) in a drop-wise fashion with constant stirring at 0 °C. To the resulting reaction mixture was added a solution of cyanuric chloride (11 mmol) in DCM (20 mL) and the reaction mixture was further stirred for 8 h at room temperature. The reaction mixture was concentrated in vacuo and the residue was dissolved in ethyl acetate (50 mL). The organic layer was washed with water, 5% aqueous bicarbonate, brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo and the obtained product was purified by silica gel column chromatography using a mixture of petroleum ether and ethyl acetate (9:1) to obtain pure isoimide (85–98% yields). Satisfactory IR, ^1H and ^{13}C NMR and elemental analysis data were obtained for all the newly synthesized compounds.

4.2.1. 5-Phenylimino-5*H*-furan-2-one (5a). Pale yellow solid (1.56 g, 90%), mp 65–67 °C (pet. ether); ^1H NMR ($CDCl_3$, 200 MHz) δ 6.70 (d, $J=8$ Hz, 0.95H), 6.80 (d, $J=8$ Hz, 0.05H), 7.20–7.60 (m, 6H); IR (nujol) ν_{max} 1819, 1798, 1724, 1678 cm^{-1}. Anal. Calcd for $C_{10}H_7NO_2$: C, 69.36; H, 4.08; N, 8.09. Found: C, 69.29; H, 3.97; N, 8.11.

4.2.2. 5-*o*-Tolylimino-5*H*-furan-2-one (5b). Yellow thick oil (1.83 g, 98%); ^1H NMR ($CDCl_3$, 200 MHz) δ 2.31 (s, 3H), 6.71 (d, $J=6$ Hz, 0.96H), 6.83 (d, $J=6$ Hz, 0.04H), 7.05–7.44 (m, 4H), 7.44 (d, $J=6$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 17.7, 121.7, 125.9, 126.2, 128.0, 130.2, 132.0, 142.3, 142.6, 149.7, 166.9; IR (neat) ν_{max} 1801, 1794, 1688 cm^{-1}. Anal. Calcd for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.42; H, 4.81; N, 7.53.

4.2.3. 5-*p*-Tolylimino-5*H*-furan-2-one (5c). Pale yellow solid (1.74 g, 93%), mp 76–78 °C (pet. ether); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.37 (s, 3H), 6.66 (d, $J=6$ Hz, 0.9H), 6.74 (d, $J=6$ Hz, 0.1H), 7.20 (d, $J=6$ Hz, 2H), 7.35–7.40 (m, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.0, 125.5, 127.2, 129.5, 137.6, 140.7, 143.1, 149.4, 167.2; IR (nujol) ν_{max} 1796, 1763, 1676 cm^{-1}. Anal. Calcd for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.43; H, 4.92; N, 7.36.

4.2.4. 5-(2-Methoxy-phenylimino)-5*H*-furan-2-one (5d). Yellow thick oil (1.83 g, 90%); ^1H NMR ($CDCl_3$, 200 MHz) δ 3.87 (s, 3H), 6.66 (d, $J=6$ Hz, 1H), 6.90–7.00 (m, 2H), 7.19 (dd, $J=8$, 2 Hz, 1H), 7.33 (dd, $J=8$, 2 Hz, 1H), 7.47 (d, $J=6$ Hz, 1H); IR (neat) ν_{max} 1807, 1794, 1690 cm^{-1}. Anal. Calcd for $C_{11}H_9NO_3$: C, 65.01; H, 4.46; N, 6.89. Found: C, 64.94; H, 4.51; N, 6.92.

4.2.5. 5-(4-Methoxy-phenylimino)-5*H*-furan-2-one (5e). Pale yellow solid (1.85 g, 91%), mp 75 °C (pet. ether + ethyl acetate); ^1H NMR ($CDCl_3$, 200 MHz) δ 3.84 (s, 3H), 6.62 (d, $J=6$ Hz, 0.96H), 6.74 (d, $J=6$ Hz, 0.04H), 6.92 (d, $J=8$ Hz, 2H), 7.38 (d, $J=6$ Hz, 1H), 7.56 (d, $J=8$ Hz, 2H); IR (nujol) ν_{max} 1796, 1665 cm^{-1}. Anal. Calcd for $C_{11}H_9NO_3$: C, 65.01; H, 4.46; N, 6.89. Found: C, 64.92; H, 4.32; N, 6.97.

4.2.6. 5-(4-Chloro-phenylimino)-5*H*-furan-2-one (5f). Pale yellow solid (1.93 g, 93%), mp 100–102 °C (pet. ether + ethyl acetate); ^1H NMR ($CDCl_3$, 200 MHz) δ 6.71 (d, $J=6$ Hz, 0.94H), 6.78 (d, $J=6$ Hz, 0.06H), 7.37 (s, 4H), 7.40 (d, $J=6$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 126.7, 128.0, 129.2, 133.2, 141.9, 143.2, 150.4, 166.8; IR (nujol) ν_{max} 1825, 1801, 1759, 1678 cm^{-1}. Anal. Calcd for $C_{10}H_6NO_2Cl$: C, 57.85; H, 2.91; N, 6.75. Found: C, 58.01; H, 3.01; N, 6.66.

4.2.7. Methyl 2-(5-oxo-5*H*-furan-2-ylideneamino)-benzoate (5g). Yellow thick oil (2.17 g, 94%); ^1H NMR ($CDCl_3$, 200 MHz) δ 3.83 (s, 3H), 6.73 (d, $J=6$ Hz, 1H), 7.02 (d, $J=8$ Hz, 1H), 7.24 (t, $J=8$ Hz, 1H), 7.44–7.57 (m, 2H), 7.98 (d, $J=8$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 51.8, 121.3, 121.7, 124.8, 129.2, 130.5, 132.5, 141.7, 145.3, 151.3, 165.7, 166.1; IR (neat) ν_{max} 1801, 1720, 1713 cm^{-1}. Anal. Calcd for $C_{12}H_9NO_4$: C, 62.34; H, 3.92; N, 6.06. Found: C, 62.43; H, 3.81; N, 5.97.

4.2.8. 3-Methyl-5-phenylimino-5*H*-furan-2-one (5h). Off white solid (1.81 g, 97%), mp 110–112 °C (pet. ether); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.16 (s, 3H), 7.04 (s, 1H), 7.15–7.45 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 10.9, 124.5, 126.7, 128.8, 136.4, 139.3, 143.8, 149.6, 168.6; IR (nujol) ν_{max} 1780, 1674 cm^{-1}. Anal. Calcd for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.43; H, 4.66; N, 7.59.

4.2.9. 3-Methyl-5-*p*-tolylimino-5*H*-furan-2-one (5i). Off white solid (1.81 g, 90%), mp 115–116 °C (pet. ether); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.15 (s, 3H), 2.36 (s, 3H), 7.02 (s, 1H), 7.19 (d, $J=9$ Hz, 2H), 7.32 (d, $J=9$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.7, 20.9, 125.0, 129.4, 136.5, 136.9, 138.7, 141.2, 148.9, 168.7; IR (nujol) ν_{max} 1778, 1674 cm^{-1}. Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.70; H, 5.63; N, 7.07.

4.2.10. 4-Phenyl-5-*p*-tolylimino-5*H*-furan-2-one (5j). Yellow solid (2.50 g, 95%), mp 174–176 °C (pet. ether + ethyl acetate); ^1H NMR ($CDCl_3$, 200 MHz) δ 2.37 (s, 3H), 7.15–7.30 (m, 2H), 7.35–7.55 (m, 6H), 7.85–8.05 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.2, 125.6, 127.9, 128.1, 129.0, 129.6, 130.9, 133.0, 137.5, 137.8, 141.3, 148.7, 166.7; IR (nujol) ν_{max} 1771, 1657 cm^{-1}. Anal. Calcd for $C_{17}H_{13}NO_2$: C, 75.55; H, 4.98; N, 5.32. Found: C, 75.71; H, 5.06; N, 5.38.

4.2.11. 5-(2-Nitro-phenylimino)-5*H*-furan-2-one (7a). Pale yellow solid (2.05 g, 94%), mp 113–115 °C (pet. ether + ethyl acetate); ^1H NMR ($CDCl_3$, 200 MHz) δ 6.80 (d, $J=6$ Hz, 1H), 7.17 (d, $J=8$ Hz, 1H), 7.34 (t, $J=8$ Hz, 1H), 7.50 (d, $J=6$ Hz, 1H), 7.62 (t, $J=8$ Hz, 1H), 8.06 (d, $J=8$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 123.4, 124.9, 125.8, 129.9, 133.7, 139.3, 141.4, 141.8, 152.8, 165.6; IR (nujol) ν_{max} 1817, 1801, 1702, 1527, 1377 cm^{-1}. Anal. Calcd for $C_{10}H_6N_2O_4$: C, 55.05; H, 2.77; N, 12.84. Found: C, 54.97; H, 2.88; N, 12.97.

4.2.12. 1-(3-Nitro-phenyl)-pyrrole-2,5-dione (8b). Off white solid (2.12 g, 97%), mp 132–134 °C (pet. ether + ethyl acetate); ^1H NMR ($CDCl_3$, 200 MHz) δ 6.94 (s, 2H), 7.66 (t, $J=8$ Hz, 1H), 7.80 (d, $J=8$ Hz, 1H), 8.24 (d, $J=8$ Hz, 1H), 8.34 (t, $J=2$ Hz, 1H); IR (nujol) ν_{max} 1724, 1533, 1346 cm^{-1}. Anal. Calcd for $C_{10}H_6N_2O_4$: C, 55.05; H, 2.77; N, 12.84. Found: C, 55.09; H, 2.82; N, 12.90.

4.2.13. 1-(4-Nitro-phenyl)-pyrrole-2,5-dione (8c). Golden yellow solid (2.07 g, 95%), mp 173–175 °C (pet. ether + ethyl acetate); ^1H NMR ($CDCl_3$, 200 MHz) δ 6.94 (s, 2H), 7.68 (d, $J=10$ Hz, 2H), 8.33 (d, $J=10$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 124.4, 125.4, 134.6, 137.1, 146.2, 168.5; IR (nujol) ν_{max} 1780, 1715, 1521, 1348 cm^{-1}. Anal.

Calcd for $C_{10}H_6N_2O_4$: C, 55.05; H, 2.77; N, 12.84. Found: C, 55.17; H, 2.87; N, 12.92.

4.2.14. *N*,*N*′-Bis-(5-imino-5*H*-furan-2-one)-benzene-1,2-diamine (10). Golden yellow solid (2.28 g, 85%), mp 143–145 °C (benzene); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.70 (d, $J=8$ Hz, 1.92H), 6.80 (d, $J=8$ Hz, 0.08H), 7.10–7.55 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 121.8, 127.0, 128.5, 137.2, 142.5, 151.4, 166.6; MS (*m*/*e*) 268, 207, 170, 142, 115, 102, 90, 82, 64, 54. IR ($CHCl_3$) ν_{max} 1813, 1796, 1720, 1686, 1678 cm^{-1}. Anal. Calcd for $C_{14}H_8N_2O_4$: C, 62.69; H, 3.00; N, 10.44. Found: C, 62.82; H, 3.11; N, 10.57.

4.2.15. 5-Methylimino-5*H*-furan-2-one (12a). Yellow thick oil (0.97 g, 87%); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.88 (s, 3H), 6.21 (d, $J=12$ Hz, 1H), 7.01 (d, $J=12$ Hz, 1H); IR (nujol) ν_{max} 1711, 1618 cm^{-1}. Anal. Calcd for $C_5H_5NO_2$: C, 54.05; H, 4.54; N, 12.61. Found: C, 54.11; H, 4.60; N, 12.49.

4.2.16. 5-(4-Methoxy-benzylimino)-5*H*-furan-2-one (12b). Thick oil (1.85 g, 85%); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.80 (s, 3H), 4.76 (s, 2H), 6.64 (d, $J=6$ Hz, 1H), 6.90 (d, $J=8$ Hz, 2H), 7.15–7.35 (m, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 52.7, 55.0, 113.8, 128.4, 129.0, 130.1, 142.1, 151.9, 158.6, 166.5; IR ($CHCl_3$) ν_{max} 1773, 1709, 1630 cm^{-1} Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.11; N, 6.45. Found: C, 66.24; H, 5.09; N, 6.42.

4.2.17. 5-(1-Phenyl-ethylimino)-5*H*-furan-2-one (12c). Yellow thick oil (1.93 g, 96%); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.55 (d, $J=6$ Hz, 3H), 5.19 (q, $J=6$ Hz, 1H), 6.62 (d, $J=6$ Hz, 0.95H), 6.73 (d, $J=6$ Hz, 0.05H), 7.15–7.60 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.0, 58.4, 126.5, 127.2, 128.5, 128.8, 142.5, 143.7, 150.9, 166.7; IR (nujol) ν_{max} 1711, 1634 cm^{-1}. Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.11; N, 6.96. Found: C, 71.77; H, 5.03; N, 7.06.

4.2.18. 3-*p*-Tolylimino-3*H*-isobenzofuran-1-one (14). Off white solid (2.16 g, 91%), mp 125–127 °C (pet. ether); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.39 (s, 3H), 7.23 (d, $J=8$ Hz, 2H), 7.41 (d, $J=8$ Hz, 2H), 7.79 (t, $J=8$ Hz, 1H), 7.85 (t, $J=6$ Hz, 1H), 7.99 (d, $J=6$ Hz, 1H), 8.10 (d, $J=8$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.0, 123.4, 124.9, 125.1, 127.4, 129.4, 132.7, 135.2, 136.4, 137.1, 140.9, 146.1, 164.9; IR (nujol) ν_{max} 1811, 1792, 1705 cm^{-1}. Anal. Calcd for $C_{15}H_{11}NO_2$: C, 75.93; H, 4.67; N, 5.90. Found: C, 76.06; H, 4.71; N, 5.85.

4.2.19. 1-*p*-Tolyl-pyrrolidine-2,5-dione (15). White solid (1.74 g, 92%), mp 158–160 °C (pet. ether); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.38 (s, 3H), 2.88 (s, 4H), 7.16 (d, $J=8$ Hz, 2H), 7.28 (d, $J=8$ Hz, 2H); IR (nujol) ν_{max} 1770, 1705, 1600 cm^{-1}. Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.99; H, 5.72; N, 7.33.

4.2.20. 3,4-Dichloro-1-*p*-tolyl-pyrrole-2,5-dione (17). White solid (2.48 g, 97%), mp 152–154 °C (pet. ether); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.40 (s, 3H), 7.22 (d, $J=8$ Hz, 2H), 7.30 (d, $J=8$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.2, 125.9, 127.8, 130.0, 133.5, 138.6, 162.1; IR (nujol) ν_{max} 1730 cm^{-1}. Anal. Calcd for $C_{11}H_7NO_2Cl_2$: C, 51.59; H, 2.76; N, 5.47. Found: C, 51.62; H, 2.81; N, 5.55.

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References and notes

1. (a) Tsou, K. C.; Barnett, R. J.; Seligman, A. M. *J. Am. Chem. Soc.* **1955**, *77*, 4613. (b) Sauers, C. K.; Cotter, R. J. *J. Org. Chem.* **1961**, *26*, 6. (c) Cotter, R. J.; Sauers, C. K.; Whelan, J. M. *J. Org. Chem.* **1961**, *26*, 10. (d) Curtin, D. Y.; Miller, L. L. *Tetrahedron Lett.* **1965**, 1869. (e) Hedaya, E.; Hinman, R. L.; Theodoropulos, S. *J. Org. Chem.* **1966**, *31*, 1311. (f) Hedaya, E.; Hinman, R. L.; Theodoropulos, S. *J. Org. Chem.* **1966**, *31*, 1317. (g) Ernst, M. L.; Schmir, G. L. *J. Am. Chem. Soc.* **1966**, *88*, 5001. (h) Curtin, D. Y.; Miller, L. L. *J. Am. Chem. Soc.* **1967**, *89*, 637. (i) Barratt, M. D.; Davies, A. P.; Evans, M. T. A. *Eur. J. Biochem.* **1971**, *24*, 280. (j) Anderson, N. H.; Ollis, W. D.; Thorpe, J. E.; Ward, A. D. *J. Chem. Soc., Perkin Trans. 1* **1975**, 825. (k) Boyd, G. V.; Monteil, R. L. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1338. (l) Mazurkiewicz, R. *Wiad. Chem.* **1987**, *41*, 755. (m) Nielsen, O.; Buchardt, O. *Synthesis* **1991**, 819. (n) Ezzell, S. A.; Hansen, R. G.; Anderson, G. J. PCT Int. Appl. WO 9720832 A1, 1997, 51; *Chem. Abstr.* **1997**, *127*, 109325. (o) Fruk, L.; Graham, D. *Heterocycles* **2003**, *60*, 2305. (p) Conley, N. R.; Hung, R. J.; Willson, C. G. *J. Org. Chem.* **2005**, *70*, 4553 and references cited therein 1a–p.
2. (a) Searle, N. E. U.S. Patent 2,444,536, 1948; *Chem. Abstr.* **1948**, *42*, 7340. (b) Mehta, N. B.; Phillips, A. P.; Lui, F. F.; Brooks, R. E. *J. Org. Chem.* **1960**, *25*, 1012. (c) Braish, T. F.; Fox, D. E. *Synlett* **1992**, 979. (d) Reddy, P. Y.; Kondo, S.; Toru, T.; Ueno, Y. *J. Org. Chem.* **1997**, *62*, 2652. (e) Le, Z.-G.; Chen, Z.-C.; Hu, Y.; Zheng, Q.-G. *Synthesis* **2004**, 995 and references cited therein 2a–e.
3. Nagata, T.; Tamaoki, A.; Kajimoto, N.; Wada, M. Jpn. Kokai Tokkyo Koho JP 61022074 A2 4, 1986; *Chem. Abstr.* **1986**, *105*, 24175.
4. (a) Awad, W. I.; Wasfi, A. S.; Ewad, M. J. S. *J. Iraqi Chem. Soc.* **1977**, *2*, 5. (b) Harris, F. W.; Karnavas, A. J.; Cucuras, C. N.; Das, S. *Polym. Prepr.* **1985**, *26*, 287. (c) Oishi, T.; Fujimoto, M.; Yoshimoto, N.; Kimura, T. *Polym. J.* **1989**, *21*, 655. (d) Pandey, R. K.; Kozyrev, A. N.; Dougherty, T. J. PCT Int. Appl. WO 9732885 A1 47, 1997; *Chem. Abstr.* **1997**, *127*, 247962.
5. (a) Baumann, M. Eur. Pat. Appl. EP 38303 A2 16, 1981; *Chem. Abstr.* **1982**, *96*, 52172. (b) Raetzsch, M.; Krahl, K. *Acta Polym.* **1984**, *36*, 91. (c) Kurimoto, I.; Yoshimura, M.; Inoue, K. Yamaguchi, T. Jpn. Kokai Tokkyo Koho JP 01056670 A2 8, 1989; *Chem. Abstr.* **1989**, *111*, 175922. (d) Kurita, K.; Suzuki, Y.; Enari, T.; Kikuchi, M.; Nishimura, S.; Ishii, S. *J. Polym. Sci., Part A: Polym. Chem.* **1994**, *32*, 393. (e) Corrie, J. E. T.; Moore, M. H.; Wilson, G. D. *J. Chem. Soc., Perkin Trans. 1* **1996**, 777.

6. Capraro, H. G.; Winkler, T.; Martin, P. *Helv. Chim. Acta* **1983**, *66*, 362.
7. (a) Aziz, T.; Shubber, A. *Iraqi J. Sci.* **1981**, *22*, 340. (b) Theodoropulos, S. U.S. US 4789742 A6 7, 1988; *Chem. Abstr.* **1989**, *111*, 97063.
8. Roth, M. Ger. Offen. DE 2705186 18, 1977; *Chem. Abstr.* **1977**, *87*, 167864.
9. (a) Ikeda, K.; Yamashita, W.; Tamai, S. Eur. Pat. Appl. EP 846714 A1 36, 1998; *Chem. Abstr.* **1998**, *129*, 68137. (b) Ikeda, K.; Yamashita, W.; Tamai, S. U.S. US 5892061 A6 24, 1999; *Chem. Abstr.* **1999**, *130*, 281980.
10. (a) Capraro, H. G.; Rhis, G.; Martin, P. *Helv. Chim. Acta* **1983**, *66*, 633. (b) Barba, V.; Hernandez, C.; Rojas-Lima, S.; Fartin, N.; Norberto, S. R. *Can. J. Chem.* **1999**, *77*, 2025.
11. Klimenkovs, I.; Zicmanis, A.; Uzulina, I.; Graillat, C.; Guyot, A. *J. Dispersion Sci. Technol.* **2004**, *25*, 119.
12. Marasco, J.-P.; Garapon, J.; Sillion, B. *Polym. Bull.* **1995**, *35*, 285.
13. (a) Mochizuki, A.; Teranishi, T.; Ueda, M. *Polym. Prepr.* **1994**, *35*, 371. (b) Kasai, T. Jpn. Kokai Tokkyo Koho JP A2 7, 1994; *Chem. Abstr.* **1995**, *122*, 163013.
14. Domeier, L. A.; Clark, E. M. Eur. Pat. Appl. Ep 277013 A1 6, 1988; *Chem. Abstr.* **1989**, *110*, 76676.
15. Nagarathinam, R.; Viswanathan, S. *Polym. Bull.* **1986**, *16*, 147.
16. Kirino, O.; Rubin, B.; Casida, J. E. *Agric. Biol. Chem.* **1985**, *49*, 267.
17. Kozyrev, A. N.; Zheng, G.; Lazarou, E.; Dougherty, T. J.; Smith, K. M.; Pandey, R. K. *Tetrahedron Lett.* **1997**, *38*, 3335.
18. (a) De Luca, L.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* **2001**, *3*, 1519. (b) De Luca, L.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* **2002**, *4*, 553. (c) Porcheddu, A.; Giacomelli, G.; Salaris, M. *J. Org. Chem.* **2005**, *70*, 2361 and references cited therein 18a–c.
19. Koton, M. M.; Kudryavtsev, V. V.; Zubkov, V. A.; Yakimanskii, A. V.; Meleshko, T. K.; Bogorad, N. N. *Vysokomol. Soedin., Ser. A* **1984**, *26*, 2534.
20. (a) Kar, A.; Gogoi, S.; Argade, N. P. *Tetrahedron* **2005**, *61*, 5297. (b) Mondal, M.; Argade, N. P. *Tetrahedron Lett.* **2004**, *45*, 5693. (c) Kar, A.; Argade, N. P. *Tetrahedron* **2003**, *59*, 2991. (d) Kar, A.; Argade, N. P. *J. Org. Chem.* **2002**, *67*, 7131. (e) Mhaske, S. B.; Argade, N. P. *J. Org. Chem.* **2001**, *66*, 9038. (f) Argade, N. P.; Balasubramaniyan, V. *Hetereocycles* **2000**, *53*, 475 and references cited therein.
21. Balasubramaniyan, V.; Argade, N. P. *Tetrahedron* **1989**, *45*, 835 and references cited therein.
22. Ganin, E. V. *Chem. Heterocycl. Compd.* **1998**, *33*, 1092.
23. Ganin, E. V. *Ukr. Khim. Zh.* **1997**, *63*, 39.
24. (a) McCormack, M. T.; Hegarty, A. F. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1701. (b) Kehrbach, W.; Alexandrou, N. E. *J. Heterocycl. Chem.* **1978**, *15*, 1255. (c) Hegarty, A. F.; Tynan, N. M.; Fergus, S. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1328 and references cited therein 24a–c.

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10b-Substituted hexahydropyrrolo-isoquinolines: studies on diastereoselective formation of a quaternary carbon stereocenter via *N*-acyliminium ion cyclization

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Abstract—The stereoselective synthesis of hexahydro-pyrroloisoquinolines with a quaternary carbon stereocenter is described. The presented methodology employs the addition of a Grignard reagent to the carbonyl group of imide **1**, derived from L-tartaric acid, followed by acetylation and $BF_3 \cdot Et_2O$ induced cyclization. The acetylation–cyclization sequence can be run either as a one-pot process, or stepwise in a selected solvents. The crucial step, an acid-catalyzed carbon–carbon bond-forming reaction via an *N*-acyliminium ion offers high stereoselectivity, which has been shown to be strongly dependent on the size of the R^1 substituents and the reaction conditions, that is, choice of solvent, amount of a Lewis acid, temperature, and concentration of the substrate. Based on the results observed, participation of solvent in the cyclization, via an *N*-acyliminium cation is proposed.

1. Introduction

The numerous syntheses of chiral, nitrogen-containing heterocycles that involve an iminium ion cyclization in the construction of a new stereogenic center are widely reported.[1,2] The isoquinoline[3] and pyrrolo[2,1-*a*]isoquinoline[4] alkaloids with significant bioactivity often have the stereocenters located at the tertiary or quaternary carbon atom, in the α-nitrogen position. Consequently, iminium ion chemistry is widely utilized in preparation of such compounds.[5] The asymmetric construction of a quaternary carbon stereocenter, frequently present in a variety of naturally occurring products, is a challenging task by itself. During the last decade, special attention has been paid to the development of both catalytic[6] and non-catalytic[7] methods for the asymmetric synthesis of compounds containing carbon atoms with four different non-hydrogen substituents.

We have recently described the stereocontrolled synthesis of hexahydro-pyrrolo[2,1-*a*]isoquinolines that contain a quaternary carbon stereocenter.[8] Our methodology employs the addition of a Grignard reagent to imide **1**, derived from L-tartaric acid, followed by the one-pot acetylation–cyclization sequence (Scheme 1). Herein we detail the utility of this methodology and disclose further findings that the reaction conditions, that is, choice of solvent, amount of a Lewis acid, temperature, and even concentration of the substrate, have a great impact on the stereoselectivity of an *N*-acyliminium ion cyclization, the key step of the synthesis of 10b-substituted hexahydropyrrolo-isoquinolines.

2. Results and discussion

A preliminary study on the preparation of pyrroloisoquinolines **4a–f** from imide **1**, derived from L-tartaric acid, was carried out employing procedure analogous to that reported by Lete and co-workers[5f–g] (Scheme 1). The nucleophilic addition of a Grignard reagent to the carbonyl group of **1** led to hydroxylactam **2a–f**, which, in case of **2a**, was isolated and analysed. However, we found that the use of crude reaction product directly in the next step was more practical. Hydroxylactam **2a**, subjected to the cyclization in the presence of trifluoroacetic acid in dichloromethane at reflux,[9] led to the expected **5a** in a trace amounts only. Changing of the reaction conditions, that is, solvent, temperature, time, protic and/or Lewis acid did not improve the yield of **5a**.

We assumed that acetylation of the hydroxyl group of **2a** would increase the rate of the slowest step of the reaction,

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Keywords: *N*-Acyliminium ion cyclization; Diastereoselective synthesis; Isoquinoline alkaloids.

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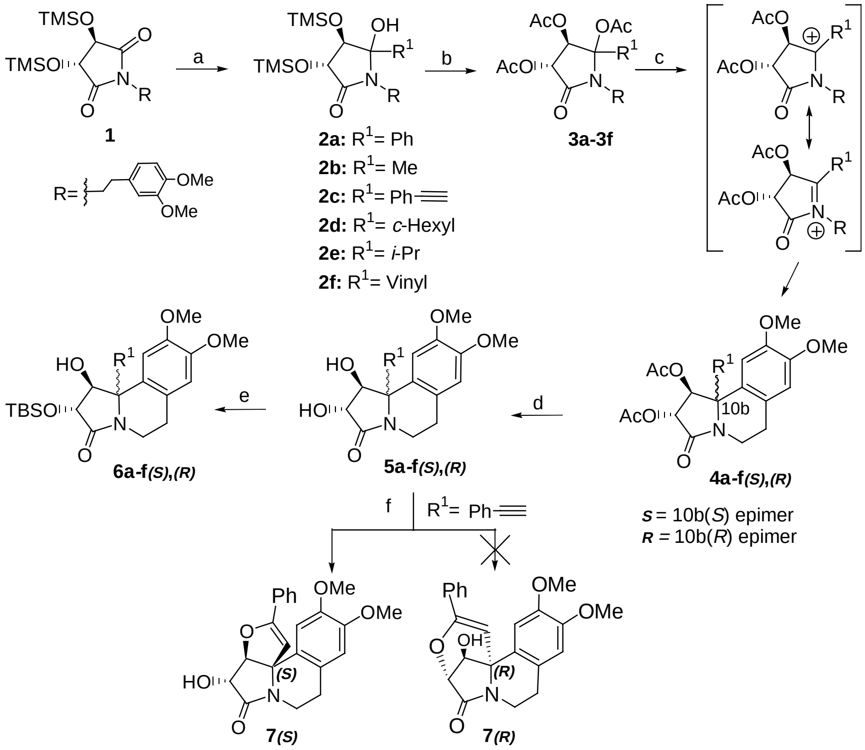


Scheme 1. Reagents and conditions: (a) R^1MgBr (1.5 equiv), THF, 0 °C gradually to rt, 1–2 h; (b) Ac_2O (4 equiv), DMAP (1.1 equiv), MeCN or Me_2CO rt, 3–4 h; (c) $BF_3 \cdot Et_2O$ (4 equiv), rt, 10 min then semi-satd aq $NaHCO_3$; (d) MeONa, MeOH; (e) TBS-Cl, imidazole, DMF, rt, 24 h; (f) $Pd(OAc)_2$ (0.2 equiv), TEA, THF, rt, 2 h.

namely the *N*-acyliminium ion formation,[10] thus facilitating the subsequent cyclization. Treatment of **2a** with acetic anhydride and DMAP in acetonitrile gave unstable triacetate **3a**, which was isolated by the chromatography on silica gel in only a 15% yield. Consequently, the crude triacetate **3a** in acetonitrile was treated with $BF_3 \cdot Et_2O$ to give hexahydro-pyrroloisoquinolines **4a**(*S*) and **4a**(*R*) in a 3:1 ratio, respectively. Several other 10b-substituted pyrroloisoquinolines **4b**–**f**(*S*),(*R*) were obtained as a mixture of diastereoisomers, utilizing the modified procedure consisting of addition of Grignard reagent to the imide **1** followed by the one-pot acetylation–cyclization of crude **2a**–**f**. The results are summarized in Table 1. The overall yields of **4a**–**f**(*S*),(*R*), based on the starting imide **1**, were high, except for entry 6. Although the 10b-epimers **4a**–**f**(*S*),(*R*) or their respective dihydroxy derivatives **5a**–**f**(*S*),(*R*) can be separated by tedious chromatography on silica gel, we have found that the respective 2-*t*-butyldimethylsilyloxy-pyrroloisoquinolines **6a**–**f**(*S*),(*R*) are much easier to purify due to the improved differentiation of the polarity of the **10b** epimers. The alkaline hydrolysis of the acetates **4a**–**f**(*S*),(*R*) followed by the silylation of the crude diols and separation of the resulting 2-silylethers gave optically pure pyrroloisoquinolines **6a**–**f**(*S*) and **6a**–**f**(*R*) in a high yield (Scheme 1, Table 1). The assignment of the configuration at the bridgehead carbon atom C-10b in pyrroloisoquinolines **4a**–**f**(*S*),(*R*) can be accomplished by NOESY experiment carried out with the mixture of diastereomers. However, due to the overlapping of the signals of epimers, only selected data of the major component can be collected and analysed, which may lead to some degree of uncertainty over data interpretation. The isolation of pure **6a**–**f**(*S*) and **6a**–**f**(*R*) allowed for an easy and unequivocal assignment of the configuration at C-10b of the obtained pyrroloisoquinolines.

The NOESY experiments, carried out with **6a**–**b**,**d**–**f**(*S*) showed an interaction between protons of the R^1 substituent (both α and β) at the C-10b-position with protons at C-2 and the OH group, as exemplified for **6f**(*S*) (Fig. 1). For the

Table 1. Stereocontrolled synthesis of hexahydro-pyrroloisoquinolines **4a**–**f**(*S*),(*R*) and separation of diastereomers as an optically pure 2-silyloxy-derivatives **6a**–**f**(*S*),(*R*)[a]

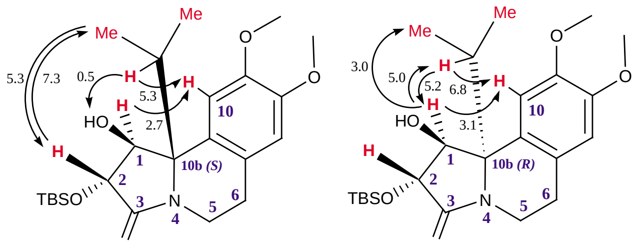
Entry	R^1	**4**(*S*),(*R*) Yield (%)[b]	*S*:*R*[c]	**6**(*S*) Yield (%)[d]	**6**(*R*) Yield (%)[d]
1	Ph	82	3:1	71	23
2	Me	85	5.6:1	61	11
3	PhC≡C	81	9.5:1	68	7.4
4	*c*-Hexyl	50	1:10	6.5	74
5	*i*-Pr	80	1:6.3	10	67
6	Vinyl	38	4.6:1	60	13

[a] General procedure A, for details see Section 4.

[b] Isolated yields of the mixture of diastereomers calculated for three-steps starting from **1**.

[c] Diastereomeric ratio was determined by ^1H NMR analysis.

[d] Isolated yields of pure diastereomers calculated for two-steps starting from **4**.



6f(*S*) **6f(*R*)**

Figure 1.

C-10b*R* epimers, the respective protons of the R^1 substituent interact only with proton at C-1.

The 10b-phenylethynyl-substituted pyrroloisoquinolines **6c**(*S*),(*R*) do not possess diagnostic protons that are able to interact with protons at C-1 or C-2, thus it is impossible to carry out the direct assignment of configuration at C-10b solely on the basis of NOE experiments. However, the β-ethynyl-substituted alcohols easily undergo cyclization to give the respective dihydrofurans.[11] The epimeric mixture of **5c**(*S*),(*R*) was subjected to the palladium-catalyzed cyclization to give the dihydrofuranyl derivative **7**(*S*) in 82% yield. The epimeric **7**(*R*) compound was not detected in the crude reaction mixture. The exclusive formation of **7**(*S*)-isomer indicates that the major diastereomer of **4c**(*S*),(*R*) possesses the *S*-configuration at the C-10b.

Careful analysis of spectroscopic data of both the pyrroloisoquinolines **4a–f**(*S*),(*R*) and respective 2-silyloxy derivatives **6a–f**(*S*),(*R*) revealed an interesting regularity in their $J_{1,2}$ values (Tables 2 and 3). The $J_{1,2}$ values of **4a–f**(*S*) were in the range of 6.8 Hz (R^1=Ph) to 8.0 Hz (R^1=*i*-Pr), while the respective coupling constants of 10b(*R*)-series compounds were substantially smaller: 2.7 and 2.3 Hz (R^1=Ph, *c*-hexyl, respectively) and 0.0 Hz for the remaining compounds. The same regularity, even more pronounced, was observed for the 2-silyloxy derivatives **6a–f**(*S*),(*R*) (Table 3). The $J_{1,2}$ values of all 10b(*S*)-epimers were 8.3 Hz, while compounds of 10b(*R*)-series showed $J_{1,2}$ values in the range of 3.1–0.0 Hz. The large vicinal coupling constants (~8 Hz) of pyrroloisoquinolines of 10b(*S*) series indicate pseudo-equatorial arrangement of the substituents at C1 and C2, constrained by the steric interaction of the C-10b and C1 groups. Similar steric interactions lead to the pseudo-axial arrangement of the substituents at C1 and C2 of 10b(*R*) epimers, which is indicated by a small $J_{1,2}$ values (0–3.1 Hz).

Our observation that the values of $J_{1,2}$ coupling constants of all 10b(*S*) epimers **4a–f** and **6a–f** are large (6.8–8.3 Hz) and the respective values of compounds 10b(*R*) series are small (3.1–0.0 Hz) confirmed the above assignment. In addition, this regularity can be used as a rule for easy determination of the configuration at C-10b of pyrroloisoquinolines of this structure.

The unequivocal assignment of the configuration at C-10b for all pyrroloisoquinolines **4a–f** allowed for the rationalization of the observed stereoselectivity of cyclization reaction (Table 1). The plausible transition state of the cyclization is depicted on Figure 2. The internal nucleophile (dimethoxyphenyl moiety) may approach the *N*-acyliminium ion **A** either *anti*- or *syn*- with respect to the acetoxy group involved in the bridging of adjacent cationic center.[12] The diastereomer C-**10b**(*S*) and C-**10b**(*R*) is a product of *anti*- and *syn*-addition of the nucleophile, respectively.

The stereochemical outcome of the cyclization reactions described in this paper, can be rationalized by assuming the importance of differences in the steric interactions of the approaching nucleophile with the R^1 substituent versus the acetoxy group. The prevalent *anti*-addition of the nucleophile was observed for relatively small R^1 groups (phenyl, methyl, vinyl, phenylethynyl, entries 1–3, 6 Table 1). In contrast, when bulky R^1 groups (*c*-hexyl, *i*-propyl, entries 4 and 5) are present, *syn*-addition takes place primarily.

Our methodology of a simple, three-step synthesis of the C-10b-substituted-1,2-diacetoxy-hexahydro-pyrrolo-isoquinolines **4a–f**(*S*),(*R*) offers good overall chemical yield, but only moderate stereoselectivity. To improve the stereoselectivity of the key step, namely the acid-catalysed cyclization via *N*-acyliminium ion, we decided to re-investigate the reaction conditions.

The main question always associated with the nucleophilic addition to the *N*-acyliminium ion derived from 3-substituted-,[12,13] 3,4-disubstituted-pyrrolidine[14] or 3-substituted-piperdines,[15] is whether to expect *syn*- or *anti*-stereoselection in relation to the substituent adjacent to the cationic center. In general, the stereoselection primarily

Table 2. The $J_{1,2}$ coupling constants of hexahydro-pyrroloisoquinolines **4a–f**(*S*),(*R*)

C-10b	*R*^{1}						
	Ph	Me	Ph≡	*c*-Hexyl	*i*-Pr	Vinyl	
(*S*)	6.8	7.9	7.8	7.9	8.0	7.9	$J_{1,2}$ (Hz)
(*R*)	2.7	0	0	2.3	0	0	

Table 3. The $J_{1,2}$ coupling constants of hexahydro-pyrroloisoquinolines **6a–f**(*S*),(*R*)

C-10b	*R*^{1}						
	Ph	Me	Ph≡	*c*-Hexyl	*i*-Pr	Vinyl	
(*S*)	8.3	8.3	8.3	8.3	8.3	8.3	$J_{1,2}$ (Hz)
(*R*)	3.1	0	0	2.0	2.2	0	

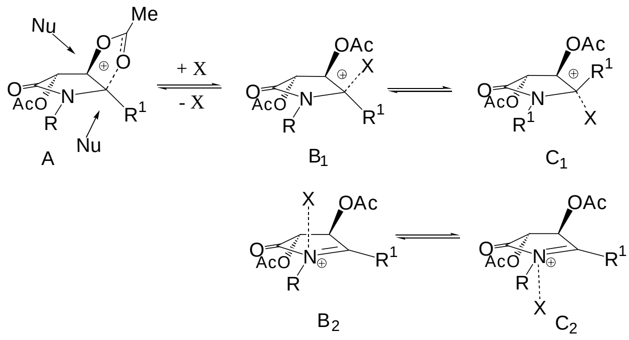


Figure 2.

depends on the C-3 substituent. Thus, the acetoxy-substituent should induce the high *anti* selectivity via neighboring group participation, while the 3-benzyloxy- or silyloxy- derivatives should prefer the moderate *syn*-addition of the nucleophile. However, the C-3 silyloxy-[14b] or benzyloxy-[15] substituent can induce the same level of trans-selectivity as the acetoxy group. Recently, Kobayashi and co-workers proposed a rationalization of this phenomenon by assuming a strong dependence of the stereochemistry on the nucleophile steric demand.[15] Additional factors, such as choice of acid catalyst, temperature, or solvent will usually influence the stereoselectivity to a limited degree only. In spite of the impressive number of reported fine syntheses based on chiral *N*-acyliminium ions where *syn*- versus *anti*- stereoselection was concerned, the reports presenting in-depth study of this important issue are rare as far as we know.[12,13e,14b,15]

The most frequently utilized solvent for reactions involving the *N*-acyliminium ion is dichloromethane, while other solvents, such as acetonitrile, toluene, diethyl ether or formic acid are less common.[12–15] For the initial evaluation of the influence of solvent choice on the stereoselectivity of the discussed cyclization, we selected compound **3a** as the *N*-acyliminium cation precursor. Due to its thermal and chemical instability, we used crude **3a**, which can be stored for weeks in a deep-freeze (−18 to −22 °C). The results of the $BF_3 \cdot Et_2O$ induced cyclization of **3a** in a variety of solvents are summarized in Table 4.

Table 4. $BF_3 \cdot Et_2O$ promoted cyclization of **3a**. The effect of solvent on the diastereoselectivity[a]

Entry	Solvent	*S*:*R*[b]
1	CH_2Cl_2	16.1:1
2	1,2-Dichloroethane	10.5:1
3	Toluene	7.7:1
4	Methyl pivaloate	6.8:1
5	$MeNO_2$	5.8:1
6	MeCN	3.3:1
7	Acetic acid	2.9:1
8	Tetrahydrofuran	2.5:1
9	Methyl acetate	2.6:1
10	Ethyl acetate	2.2:1
11	3-Pentanone	2.0:1
12	Acetone	1.9:1
13	Pinacolone	1.7:1
14	DMF	No reaction

[a] All reactions were carried out using standard procedure: crude acetate **3a** (0.1 M/solvent) obtained via procedure A or B was treated at rt with $BF_3 \cdot Et_2O$ (4 equiv), stirred for 10 min then quenched by the addition of satd aq $NaHCO_3$. Isolated yields were always ≥80%.

[b] Diastereomeric ratio was determined by HPLC analysis.

The cyclization of **3a** conducted in CH_2Cl_2 gave a mixture of the product *anti*- [10b(*S*)] and *syn*-addition [10b(*R*)] in the ratio of 16.1:1, respectively (entry 1). When 1,2-dichloroethane was used the amount of *anti*-product decreased substantially (10.5:1, entry 2). The change to a more polar solvent such as acetonitrile, nitromethane, acetic acid, tetrahydrofuran or ethyl acetate, resulted in further decrease of *anti* selectivity (entries 3–10). The lowest *anti* selectivity was observed in unusual solvents such as 3-pentanone, acetone and pinacolone (entries 11–13). Although in the presence of a Lewis acid these ketones can undergo self-condensation, it apparently did not affect the very fast *N*-acyliminium cyclization.

We believe that solvents utilized in runs 3–10 may have stabilized the cationic center in direct competition to the acetoxy group, via proposed structures B_1, B_2, or C_1, C_2 (Fig. 2). Consequently, the acetoxy bridge in **A** may become broken, resulting in a decreased *anti*-stereoselection. Such participation of a solvent in the reaction involving the *N*-acyliminium cation was never before postulated, as far as we know. However, cases of a similar solvent participation are well documented in glycosylation reactions proceeding via an oxonium ion.[16]

In the course of the work presented in the above investigation, we have found that reliable and well-reproducible results can be realized only when $BF_3 \cdot Et_2O$ is quickly injected via syringe directly into a vigorously stirred solution of **3a**. This observation can be rationalized by assumption that the stereoselectivity of a fast reaction (< 10 min) depends on a concentration of the Lewis acid catalyst. The cyclization of **3a** in the presence of 1 equiv of $BF_3 \cdot Et_2O$ yielded a mixture of C-10b epimers in a ratio *S*:*R* = 12.5:1 (Table 5, entry 1). An increase in the amount of Lewis acid led to the improvement of *anti* selection, which reached the maximum when 4 equiv of Lewis acid were used (entry 3). Further increase of the catalyst up to 10 equiv did not change the proportion of diastereomers significantly. Applying a sub-molar amount of $BF_3 \cdot Et_2O$ (0.3 equiv) resulted in a sluggish reaction. In addition the substrate was not consumed completely, even when allowing the cyclization to run for up to 18 h. The triacetate **3a**, when treated with 4 equiv of $BF_3 \cdot 2AcOH$ gave mixture of C-10b epimers *S* and *R* in a 8.6:1 ratio, respectively (Table 5, entry 4). In comparison with the result of run 3, the reaction catalyzed with $BF_3 \cdot 2AcOH$ was slower and less selective.

Table 5. Cyclization of **3a**. The effect of varying amounts of $BF_3 \cdot Et_2O$ on diastereoselectivity[a]

Entry	Catalyst, (equiv)	*S*:*R*[b]
1	$BF_3 \cdot Et_2O$, 1	12.5:1
2	$BF_3 \cdot Et_2O$, 2	13.6:1
3	$BF_3 \cdot Et_2O$, 4	16.1:1
4[c]	$BF_3 \cdot 2AcOH$, 4	8.6:1
5	$BF_3 \cdot Et_2O$, 10	15.9:1

[a] Standard procedure of Table 4 was utilized, concd **3a** 0.1 M/CH_2Cl_2, rt. Isolated yields were always ≥80%.

[b] Diastereomeric ratio was determined by HPLC analysis.

[c] The cyclization required at least 30 min for completion.

The results presented in Table 4 (entry 7) and Table 5 indicated that the acetic acid evolved during carbon–carbon bond formation caused the decrease *anti* selectivity of cyclization either via formation of a less selective catalyst $BF_3 \cdot 2AcOH$, or by the complexation of *N*-acyliminium ion in competition to the adjacent acetoxy group.

In the course of our efforts to enhance the diastereoselectivity of the cyclization, we unexpectedly noticed that small changes in the concentration of **3a** in dichloromethane led to the substantial modification of the stereoselectivity of the reaction. Consequently, we carried out a series of cyclization experiments varying the concentration of **3a**. The results, presented in Table 6, can be rationalized as follows: the rate of intramolecular reaction, like the discussed cyclization, should not depend on the concentration of the iminium ion precursor. Acetic acid, evolved during carbon–carbon bond formation, could affect the stabilization of the cationic center competitively to the acetoxy group as depicted in Figure 2. A reversible cation complexation, responsible for the decreased *anti*-stereoselection, is a second-order reaction, and as such should depend on the reactant concentration.

Table 6. Cyclization of **3a**. The effect of a concentration of the substrate on diastereoselectivity[a]

Entry	Concd **3a** [M]/CH_2Cl_2	*S*:*R*[b]
1	0.5	7.6:1
2	0.25	8.9:1
3	0.1	12.6:1
4	0.05	14.8:1
5	0.05[c]	11.0:1
6	0.005	28.6:1

[a] Standard procedure of Table 4 was followed, using 1.1 equiv of $BF_3 \cdot Et_2O$, rt. Isolated yields were always ≥80%.

[b] Diastereomeric ratio was determined by HPLC analysis.

[c] Reaction was run in the presence of acetic acid (4 equiv).

The above rationalization may explain why the reaction carried out under high-dilution conditions (0.005 M, entry 6) led to a considerable improvement in *anti* selectivity over the one conducted under a higher concentration (0.5 M, entry 1). The outcome of entries 4 and 5 showed that the presence of a small amount of cation-complexing solvent (4 equiv of acetic acid) can decrease the *anti* selectivity of the cyclization. The reported effect of concentration on the stereoselectivity was not observed in other polar solvents such as acetic acid, ethyl acetate or acetone, supporting our rationale.

Table 7. Cyclization of **3a**. The effect of the reaction temperature on diastereoselectivity[a]

Entry	Temperature (°C)	Reaction time (min)	*S*:*R*[b]
1	23	10	16.1:1
2	0	15	23.0:1
3	−10	20	17.3:1
4	−20	30	17.8:1
5	−40	60	17.6:1

[a] Standard procedure of Table 4 was utilized, concd **3a** 0.1 M/CH_2Cl_2, 4 equiv of $BF_3 \cdot Et_2O$. Isolated yields were always ≥80%.

[b] Diastereomeric ratio was determined by HPLC analysis.

Table 7 presents the effect of temperature on the stereoselectivity. A decrease in the reaction temperature from 23 to 0 °C enhanced the *anti* selectivity (entries 1 and 2). However, further cooling to −10 °C resulted in a diminished selectivity, which remained unchanged for the other reactions carried out at −20 and −40 °C. Our results appear to be in agreement with a recent report by Wistrand, who observed that the *syn*/*anti*-stereoselections of the diastereoselective allylation of *N*-acyliminium ion at rt and at −78 °C were nearly the same.[13a]

The outcome of our optimization experiments, presented in Tables 4–7 allows the precise definition of the reaction conditions, which facilitate either *syn* or *anti* selectivity of the cyclization. Thus, to emphasize the *syn*-addition of the nucleophile, a solution of *N*-acyliminium ion precursor **3** in a polar solvent such as ethyl acetate, acetone or pinacolone (concentration is not important), should be treated at rt with $BF_3 \cdot Et_2O$ (1–2 equiv). In contrast, if the *anti*-addition product is required, the $BF_3 \cdot Et_2O$ (4 equiv) has to be added at 0 °C into a dilute solution of **3** in such a solvent as dichloromethane or 1,2-dichloroethane.

In order to assess the scope of the optimized reaction conditions, several other 10b-substituted pyrroloisoquinolines were prepared applying procedures B and C (Table 8). Procedure B, favoring the *syn*-addition, consists of the use of crude hydroxy-lactams **2a–e** in a 0.2 M acetone solution for the one-pot acetylation–cyclization reaction sequence. The acetone was used as a solvent of choice, since it is inexpensive, non-toxic and offers fast and clean conversion of trimethylsilylated hydroxy-lactams **2a–e** into respective triacetates **3a–e**. Furthermore, as evident from Table 4, entry 13, cyclization performed in acetone yields a relatively higher than expected proportion of *syn*-addition product. Procedure C, that favors the *anti*-addition of the nucleophile, is based on the use of crude triacetates **3a–e**, obtained applying procedure A or B. The cyclization step is conducted at 0 °C by treating the 0.05 M solution of **3a–e** in dichloromethane with 4 equiv of $BF_3 \cdot Et_2O$. Experiments using procedure B led to the epimeric mixtures **4a–e** (Table 8). The product of the *anti*-addition of the nucleophile was obtained preferentially when small C-10b substituents (R^1 = Ph, Me, PhC≡C, entries 1–3) were present. However, the values of de for the obtained products were very low. The reverse stereoselection was observed when the bulky R^1 groups (*c*-Hexyl, *i*-Pr, entries 4 and 5) were present. The **4d**(*R*) and **4e**(*R*) epimers were formed predominantly in a high de. The cyclization of triacetates **3a–e**, utilizing procedure C resulted in a remarkable increase in *anti* selectivity for the small R^1 (entries 1–3) and, as expected, the decrease of *syn* selectivity for bulky C-10b substituents (entries 4 and 5).

Analyzing the results of the cyclization experiments (Tables 4–8) it is possible to conclude that the *syn*- versus *anti*-stereoselection of this process is controlled to a major extent by the steric requirements of susbtituent R^1, and the acetoxy group forming the bridge with neighboring cationic center. However, the choice of solvent as well as other experimental parameters can have an effect of a lesser magnitude.

Table 8. The optimized synthesis of optical pure hexahydro-pyrroloisoquinolines **4a**(*S*), **4b**(*S*), **6c**(*S*), **7c**(*S*), **5d**(*R*), and **6e**(*R*)

Entry	R^1	Cyclization product	Procedure[a]	*R*:*S*[b]	Isolated product	Yield (%)[c]
1	Ph	**4a**(*S*),(*R*)	B	1:1.9		
			C	1:24	**4a**(*S*)	69
2	Me	**4b**(*S*),(*R*)	B	1:3.4		
			C	1:17.9	**4b**(*S*)	73
3	PhC≡C	**4c**(*S*),(*R*)	B	1:9.2		
			C	1:22	**6c**(*S*), [**7c**(*S*)]	69, (52)
4	*c*-Hexyl	**4d**(*S*),(*R*)	B	19:1	**5d**(*R*)	50
			C	4.5:1		
5	*i*-Pr	**4e**(*S*),(*R*)	B	11:1	**6e**(*R*)	42
			C	2.5:1		

[a] Procedure B: crude hydroxylactams **2a–e** were acetylated (0.2 M/acetone, DMAP 1.1 equiv, Ac_2O, 4.0 equiv, rt, 3 h) and treated at rt with $BF_3\cdot Et_2O$ (3 equiv), stirred for 15 min then quenched with satd aq $NaHCO_3$. Procedure C: crude acetylated lactams **3a–e** obtained following Method A or B were isolated, then dissolved in CH_2Cl_2 (0.05 M), cooled to 0 °C, treated with $BF_3\cdot Et_2O$ (4 equiv) in one portion, stirred for 15 min and then quenched with satd aq $NaHCO_3$.

[b] Diastereomeric ratio of pyrroloisoquinolines **4a–f** was determined by HPLC analysis.

[c] Isolated yield of optically pure product, based on the imide **1**.

We were pleased to see that the main products **4a**(*S*) and **4b**(*S*) can be isolated in a high overall yield as optically pure compounds after a single crystallization from ethanol (entries 1 and 2, procedure C). Also, the cyclohexyl derivative **4d**(*R*), after hydrolysis of the acetate groups can be isolated via crystallization from acetone as a dihydroxy derivative **5d**(*R*) (entry 4, procedure B). The remaining pyrroloisoquinolines **4c** and **4e** can be isolated by chromatography as respective derivatives **6c**(*S*), **7c**(*S*) and **6e**(*R*) (entries 3 and 5, procedure B).

3. Concluding remarks

In summary, we have successfully developed a simple, three-step synthesis of hexahydro-pyrroloisoquinolines with a quaternary carbon stereocenter at the C-10b carbon atom. The presented methodology utilizes the addition of a Grignard reagent to the carbonyl group of imide **1**, derived from L-tartaric acid, followed by acetylation and $BF_3\cdot Et_2O$ induced cyclization. The acetylation–cyclization sequence can be run either stepwise or as a one-pot process, in selected solvents. The crucial step, an acid-catalysed carbon–carbon bond-forming reaction via an *N*-acyliminium ion offers high stereoselectivity. The degree of stereoselectivity was shown to be strongly dependent on the size of the R^1 substituent and, to a lesser degree, on the reaction conditions, that is, choice of solvent, amount of Lewis acid, temperature, and even concentration of the substrate. Based on the observed results, participation of solvent in the cyclization via *N*-acyliminium cation is proposed.

Our observation that the values of $J_{1,2}$ coupling constants of all 10b(*S*) epimers **4a–f** and **6a–f** are large (6.8–8.3 Hz), and the respective values of compounds 10b(*R*) series are small (3.1–0.0 Hz), can be used as a rule for the easy determination of the configuration at C-10b of pyrroloisoquinolines of this structure. The obtained pyrroloisoquinolines **4a**(*S*), **4b**(*S*) and **5d**(*R*) can be isolated in a high overall yield as optically pure compounds after a single crystallization, while the remaining compounds can be isolated by chromatography as their respective 2-silyloxy-derivatives.

4. Experimental

4.1. General

Melting points are uncorrected. Optical rotations were measured at 23 °C with a JASCO Dip-360 digital polarimeter. IR spectra were obtained using an FT-IR-1600 Perkin-Elmer spectrophotometer. ^1H NMR spectra were recorded in $CDCl_3$ (except where indicated otherwise) using a Bruker AM 500 spectrometer. Chemical shifts are quoted in δ ppm relative to TMS for ^1H and $CDCl_3$ for ^{13}C NMR. Coupling constants *J* are reported in Hertz. Mass spectra were recorded using an AMD 640 or a Mariner mass spectrometer. Kugelrohr distillation was performed using Buchi glass oven B585. HPLC analyses were preformed with a Shimadzu LC-8A chromatograph with Hibar® 250-4 LiChrosob® Si 60 (5 μm). Thin-layer chromatography was carried out on precoated silica gel (Merck Kieselgel 60 F_{254}, 0.2 mm layer thickness). Flash column chromatography was preformed using Merck Kieselgel (230–400 mesh). All reactions were carried out under an argon atmosphere using anhydrous solvents. Most reagents were obtained from commercial suppliers and were used without further purification, unless noted. THF was distilled from Na and benzophenone, dichloromethane and toluene were distilled from CaH_2.

4.1.1. Preparation of (2*R*,3*R*)-1-[2-(3,4-dimethoxy-phenyl)-ethyl]-3,4-trimethylsilanyloxy-pyrrolidine-2,5-dione (1). To a stirred suspension of (2*R*,3*R*) 3,4-dihydroxy-1-[2-(3,4-dimethoxy-phenyl)-ethyl]-pyrrolidine-2,5-dione[5k] (29.5 g, 0.1 mol) in pyridine (50 mL, ~0.6 mol) and CH_2Cl_2 (300 mL) at 0 °C, trimethylsilyl chloride (33 mL, 0.26 mol) was added dropwise. The reaction mixture was stirred at 0 °C for 15 min followed by an additional 1 h at rt. The solution was poured into ice-water mixture (~500 mL). The organic phase was separated, washed with cold water (3× ~300 mL), saturated sodium bicarbonate (200 mL), dried ($MgSO_4$), filtered and evaporated.

The crude product was purified by Kugelrohr distillation (oven temperature 150–160 °C, 0.1 Torr).

Yield: 41.3 g, 94%. Viscous oil, solidified on storage at rt, mp 60–61 °C; $[\alpha]_D$ +126.8 (*c* 1.1, CH_2Cl_2); IR (CH_2Cl_2): 3055, 2961, 1721 cm^{-1}; ^1H NMR: 0.22 (s, 18H), 2.83 (m, 2H), 3.66 (m, 1H), 3.72 (m, 1H), 3.64 and 3.86 (two s, 6H), 4.33 (s, 2H), 6.75 (m, 3H); ^{13}C NMR: −0.01, 33.03 (t), 39.89 (t), 55.83, 55.89, 76.37, 111.37, 112.07, 120.91, 129.96 (s), 147.88 (s), 148.95 (s), 173.21 (s); MS (EI, HR) *m/z*: (M^+) calcd for $C_{20}H_{33}NO_6Si_2$: 439.1846. Found: 439.1842.

4.2. General procedures for the preparation of hexahydropyrrolo-isoquinolines [4a–f(*S*),(*R*)]

4.2.1. Procedure A. To a solution of imide **1** (878 mg, 2 mmol) in dry THF (3 mL), an organomagnesium bromide (3 mmol) in THF (3 mL) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 15 min, gradually warmed up to rt, and stirring was continued until TLC indicated the disappearance of **1** (approx. 0.5 h). The reaction mixture was poured into ice-cold semi-satd aq $NaHCO_3$ (30 mL) and extracted with *t*-butyl methyl ether (3×30 mL). The combined extracts were washed with ice-cold water, dried ($MgSO_4$), filtered and evaporated in vacuo. The crude hydroxy-lactam **2a–f** was dissolved in dry MeCN (10 mL), and after cooling to 0 °C, dimethylaminopyridine (270 mg, 2.2 mmol) and Ac_2O (756 μL, 8 mmol) were added. The cooling bath was removed and stirring was continued at rt for 3 h, then $BF_3\cdot Et_2O$ (1.14 mL, 8 mmol) was added in one portion. The mixture was stirred at rt for 10 min then cooled to 0 °C, quenched with satd aq $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3×20 mL). The combined extracts were washed with water (2×20 mL), dried ($MgSO_4$), filtered and evaporated in vacuo. The product was purified by flash column chromatography on silica gel to yield pyrroloisoquinolines as a mixture of epimers. The yields of **4a–f**(*S*),(*R*) are calculated based on a sequence of three-steps from **1**.

4.2.2. Procedure B. The crude hydroxylactam **2**, obtained according to procedure A was acetylated in acetone (0.2 M/ acetone, DMAP 1.1 equiv, Ac_2O, 4.0 equiv, 0 °C→rt, 3 h) and treated at rt with $BF_3\cdot Et_2O$ (3 equiv) added in one portion. Workup and purification of obtained pyrroloisoquinolines **4a–f**(*S*),(*R*) as in procedure A.

4.2.3. Procedure C. The acetylated lactam **3**, obtained according to procedure A or B was isolated as follows: the reaction mixture was poured into ice-cold water and extracted twice with CH_2Cl_2, collected extracts were washed with cold water, satd aq sodium bicarbonate, and again with water, dried ($MgSO_4$) and evaporated. Crude **3** was carefully dried at rt under high vacuum (0.1 Torr, 2 h), then dissolved in CH_2Cl_2 (0.05 M), cooled to 0 °C and with vigorous stirring, $BF_3\cdot Et_2O$ (4 equiv) was added in one portion. Stirring at 0 °C was continued for 15 min and then the reaction mixture was quenched by the addition of satd aq $NaHCO_3$. Workup and purification of the obtained pyrroloisoquinolines **4a–f**(*S*),(*R*) was as in procedure A.

4.2.4. Preparation of (2*R*,3*R*)-1-[2-(3,4-dimethoxy-phenyl)-ethyl]-5-hydroxy-5-phenyl-3,4-bis-trimethyl-silanyloxy-pyrrolidin-2-one (2a). The crude hydroxy-lactam **2a** was obtained following procedure A from imide **1** (439 mg, 1 mmol) and filtered through a silica gel pad using *t*-butylmethyl ether/hexane = 1:1 as eluent to give **2a** as a 10:1 mixture of epimers.

Yield: 388 mg, 75%, white solid, crystallization from hexane gave analytical pure sample of main epimer. Colourless crystals, mp 90–92 °C; $[\alpha]_D$ +23.0 (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2): 3499, 2961, 1717 cm^{-1}; ^1H NMR: −0.11 and 0.26 (two s, 18H), 2.74 (m, 2H), 2.86 (m, 1H), 3.58 (m, 1H), 3.76 and 3.80 (two s, 6H), 4.01 (s, 1H, exchangeable with D_2O), 4.14 (d, 1H, $J=6.7$ Hz), 4.31 (d, 1H, $J=6.7$ Hz), 6.52 (m, 2H), 6.68 (d, 1H, $J=8.0$ Hz), 7.32–7.49 (m, 5H); ^{13}C NMR: −0.23, 0.41, 34.40, 42.79, 55.77, 55.87, 75.50, 82.43, 88.69, 111.18, 111.94, 120.58, 126.77, 128.49, 128.61, 131.75, 139.98, 145.42, 148.79, 172.24; MS (LSIMS, HR) *m/z*: ($M+Na^+$) calcd for $C_{26}H_{39}NO_6NaSi_2$: 540.2214. Found: 540.2221.

4.2.5. Preparation of (2*R*,3*R*)-3,4,5-triacetoxy-1-[2-(3,4-dimethoxy-phenyl)-ethyl]-5-phenyl-pyrrolidin-2-one (3a). Crude **3a** was obtained from **1** (439 mg, 1 mmol) according to procedure C and purified by flash column chromatography on silica gel using ethyl acetate/hexane = 1:1 as an eluent.

Yield: 75 mg, 15%; white semisolid; IR (CH_2Cl_2): 2977, 1755, 1731 cm^{-1}.

Selected data of the main product taken from the 8:1 mixture of epimers.

^1H NMR: 2.06, 2.17 and 2.21 (three s, 9H), 2.68 (m, 2H), 3.05 (m, 1H), 3.42 (m, 1H), 3.79 and 3.81 (two s, 6H), 5.66 (d, 1H, $J=5.9$ Hz), 5.56 (d, 1H, $J=5.9$ Hz), 6.51 (m, 2H), 6.70 (d, 1H, $J=6.7$ Hz), 7.43 (m, 3H), 7.53 (m, 2H); ^{13}C NMR: 20.41, 20.68, 21.77, 33.25, 43.48, 55.80, 55.90, 74.87, 78.15, 93.34, 111.26, 111.92, 120.49, 125.77, 128.90, 129.36, 131.03, 138.36, 147.67, 149.93, 168.98, 169.43, 169.50, 170.09.

4.2.6. Preparation of (1*S*,2*R*,10b*S* and 10b*R*)-1,2-di-acetoxy-8,9-dimethoxy-10b-phenyl-1,2,3,5,6,10b-hexa-hydro-pyrrolo [2,1-*a*]isoquinolin-3-one [4a(*S*) and 4a(*R*)]. Procedure A, yield: 82%, **4a**(*S*): **4a**(*R*) = 3:1,

Procedure B, yield: 83%, **4a**(*S*): **4a**(*R*) = 1.9:1.

Procedure C, The crude reaction mixture of **4a**(*S*): **4a**(*R*) = 24:1 was crystallized from ethanol to give pure **4a**(*S*). Yield: 69% (three-steps), white solid. The spectroscopic and physical properties of **4a**(*S*) and **4a**(*R*) were previously reported.[8]

4.2.7. Preparation of (1*S*,2*R*,10b*S* and 10b*R*)-1,2-di-acetoxy-8,9-dimethoxy-10b-methyl-1,2,3,5,6,10b-hexa-hydro-pyrrolo[2,1-*a*]isoquinolin-3-one [4b(*S*) and 4b(*R*)]. Procedure A, yield: 85%, **4b**(*S*): **4b**(*R*) = 5.6:1.

Procedure B, yield: 83%, **4b**(*S*): **4b**(*R*) = 3.4:1.

Procedure C, the isolation procedure of hydroxyamide **2b** was modified: for the extraction of **2b** dichloromethane was used. The crude reaction mixture of **4b**(*S*): **4b**(*R*) = 17.9:1 was crystallized from ethanol to give pure **4b**(*S*). Yield: 73% (three-steps).

Compound **4b**(*S*). Colourless crystals, mp 168–169 °C (ethanol); $[\alpha]_D$ +152 (*c* 1.2, CH$_2$Cl$_2$); IR (CH$_2$Cl$_2$): 2939, 1752, 1715 cm^{-1}; ^{1}H NMR: 1.65 (s, 3H), 2.14 and 2.24 (two s, 6H), 2.71 (m, 1H), 2.96 (m, 1H), 3.12 (m, 1H), 3.81 and 3.82 (two s, 6H), 4.41 (dd, 1H, J = 13.1, 6.2 Hz), 5.46 (d, 1H, J = 7.9 Hz), 5.67 (d, 1H, J = 7.9 Hz), 6.26 and 6.58 (two s, 2H); ^{13}C NMR: 20.68, 20.86, 23.44, 27.85 (t), 34.57 (t), 55.86, 55.89, 59.52 (s), 72.34, 79.32, 107.41, 111.73, 124.41 (s), 131.24 (s), 148.26 (s), 148.52 (s), 164.32 (s), 169.70 (s), 170.47 (s); MS (ES, HR) *m*/*z*: (M + H$^+$) calcd for C$_{19}$H$_{24}$NO$_7$: 378.1547. Found: 378.1552. Anal. Calcd for C$_{19}$H$_{23}$NO$_7$: C, 60.47; H, 6.14; N, 3.71. Found: C, 60.51; H, 6.08; N, 3.70.

Compound **4b**(*R*). Selected data taken from the mixture of epimers **4b**(*S*): **4b**(*R*) = 5.6:1

^{1}H NMR: 1.68 (s, 3H), 1.69 and 2.20 (two s, 6H), 5.17, 5.55, 6.47, and 6.59 (four s, 4H).

4.2.8. Preparation of (1*S*,2*R*,10b*S* and 10b*R*)-1,2-di-acetoxy-8,9-dimethoxy-10b-phenylethynyl-1,2,3,5,6,10b-hexahydro-pyrrolo [2,1-*a*]isoquinolin-3-one [4c(*S*) and 4c(*R*)]. Procedure A, yield: 81%, **4c**(*S*): **4c**(*R*) = 9.5:1.

Procedure B, yield: 83%, **4c**(*S*): **4c**(*R*) = 9.2:1.

Procedure C, yield: 78%, **4c**(*S*): **4c**(*R*) = 23:1

Oil; IR (CH$_2$Cl$_2$): 3008, 2939, 2232, 1754, 1722 cm^{-1}; MS (EI, HR) *m*/*z*: (M$^+$) calcd for C$_{26}$H$_{25}$NO$_7$: 463.1631. Found: 463.1646.

Selected data for the mixture of epimers **4c**(*S*): **4c**(*R*) = 9.2:1.

Compound **4c**(*S*). ^{1}H NMR: 2.14 and 2.25 (two s, 6H), 2.75 (m, 1H), 2.98, (m, 1H), 3.32 (m, 1H), 3.83 and 3.87 (two s, 6H), 4.40 (ddd, 1H, J = 13.1, 6.2, 1.6 Hz), 5.84 (d, 1H, J = 7.8 Hz), 5.80 (dd, 1H, J = 7.8, 1.1 Hz), 6.60 (s, 1H), 6.86 (s, 1H), 7.30–7.43 (m, 5H); ^{13}C NMR: 20.66, 20.92, 27.56 (t), 35.48 (t), 55.92 (overlapped signals of two carbons), 58.43 (s), 74.38, 78.82, 85.44 (s), 87.37 (s), 108.14, 111.67, 121.81 (s), 124.77 (s), 127.44 (s), 128.35, 128.97, 131.86, 148.46 (s), 149.10 (s), 167.62 (s), 169.76 (s), 170.20 (s).

Compound **4c**(*R*). ^{1}H NMR: 1.67 and 2.16 (two s, 6H), 3.85 and 3.88 (two s, 6H), 2.90 (m, 1H), 5.13 (s, 1H), 6.61 (s, 1H).

4.2.9. Preparation of (1*S*,2*R*,10b*S* and 10b*R*)-1,2-di-acetoxy-10b-cyclohexyl-8,9-dimethoxy-1,2,3,5,6,10b-hexahydro-pyrrolo[2,1-*a*]isoquinolin-3-one [4d(*S*) and 4d(*R*)]. Procedure A, yield: 50%, **4d**(*S*): **4d**(*R*) = 1:10.

Procedure B, yield: 80%, **4d**(*S*): **4d**(*R*) = 1:19.

Procedure C, yield: 77%, **4d**(*S*): **4d**(*R*) = 1:4.5.

Oil; IR (CH$_2$Cl$_2$): 2936, 2857, 1753, 1702 cm^{-1}; MS (ES, HR) *m*/*z*: (M + Na$^+$) calcd for C$_{24}$H$_{31}$NO$_7$Na: 468.1993. Found: 468.2013.

Selected data for the mixture of epimers **4d**(*S*): **4d**(*R*) = 1:4.5.

Compound **4d**(*S*). ^{1}H NMR: 2.08 and 2.22 (two s, 6H), 3.79 and 3.85 (two s, 6H), 4.50 (m, 1H), 5.48 (d, 1H, J = 7.9 Hz), 5,76 (d, 1H, J = 7.9 Hz), 6.48 and 6.55 (two s, 2H).

Compound **4d**(*R*). ^{1}H NMR: 1.83 and 2.18 (two s, 6H), 2.66 (dd, 1H, J = 16.1, 3.9 Hz), 2.91 (m, 1H), 3.25 (m, 1H), 3.80 and 3.86 (two s, 6H), 4.44 (ddd, 1H, J = 13.3, 7.0, 1.3 Hz), 5.15 (d, 1H, J = 2.3 Hz), 5,65 (d, 1H, J = 2.3 Hz), 6.54 and 6.58 (two s, 2H); ^{13}C NMR: 20.71, 20.69, 26.15 (s), 26.57 (t), 27.23 (t), 27.60 (t), 28.07 (t), 29.86 (t), 37.67 (t), 49.64, 55.74, 55.93, 69.35 (s), 75.10, 75.92, 109.85, 111.57, 126.11 (s), 126.65 (s), 146.97 (s), 147.94 (s), 167.44 (s), 167.44 (s), 169.67 (s), 169.85 (s).

4.2.10. Preparation of (1*S*,2*R*,10b*S* and 10b*R*)-1,2-diacetoxy-10b-isopropyl-8,9-dimethoxy-1,2,3,5,6,10b-hexahydro-pyrrolo[2,1-*a*]isoquinolin-3-one [4e(*S*) and 4e(*R*)]. Method A, yield: 80%, **4e**(*S*): **4e**(*R*) = 1:6.3.

Method B, yield: 80%, **4e**(*S*): **4e**(*R*) = 1:11.

Method C, yield: 77%, **4e**(*S*): **4e**(*R*) = 1:2.5.

Oil; IR (CH$_2$Cl$_2$): 2966, 2939, 1753, 1704 cm^{-1}; MS (ES, HR) *m*/*z*: (M + Na$^+$) calcd for C$_{21}$H$_{27}$NO$_7$Na: 428.1680. Found: 428.1704.

Selected data for the mixture of epimers **4e**(*S*): **4e**(*R*) = 1:2.5.

Compound **4e**(*S*). ^{1}H NMR: 0.82 (d, 1H, J = 7.3 Hz), 1.19 (d, 1H, J = 7.3 Hz), 2.09 and 2.21 (two s, 6H), 3.78 and 3.85 (two s, 6H), 4.52 (m, 1H), 5.50 (d, 1H, J = 8.0 Hz), 5.73 (d, 1H, J = 8.0 Hz), 6.50 and 6.57 (two s, 2H).

Compound **4e**(*R*). ^{1}H NMR: 0.89 (d, 3H, J = 7.0 Hz), 1.09 (d, 3H, J = 7.0 Hz), 1.83 and 2.18 (two s, 6H), 2.68 (m, 1H), 2.92 (m, 1H), 3.25 (m, 1H), 3.80 and 3.87 (two s, 6H), 4.46 (dd, 1H, J = 13.3, 6.3 Hz), 5.17 (d, 1H, J = 2.0 Hz), 5.61 (s, 1H), 6.55 and 6.59 (two s, 2H); ^{13}C NMR: 17.38, 20.02, 20.64, 20.90, 28.12, 37.54, 39.11, 55.69, 55.78, 69.48, 74.92, 75.89, 109.57, 111.46, 126.30, 126.50, 146.92, 147.84, 167.42, 169.61, 169.82.

4.2.11. Preparation of (1*S*,2*R*,10b*S* and 10b*R*)-1,2-diacetoxy-8,9-dimethoxy-10b-vinyl-1,2,3,5,6,10b-hexahydro-pyrrolo[2,1-*a*]isoquinolin-3-one [4f(*S*) and 4f(*R*)]. Procedure A, yield: 38%; **4f**(*S*): **4f**(*R*) = 4.6:1.

Oil; IR (CH$_2$Cl$_2$): 2939, 2855, 1753, 1716 cm^{-1}; MS (ES, HR) *m*/*z*: (M + Na$^+$) calcd for C$_{20}$H$_{23}$NO$_7$Na: 412.1367. Found: 412.1380.

Selected data for the mixture of epimers **4f**(*S*): **4f**(*R*) = 4.6:1.

Compound **4c**(*S*). ^{1}H NMR: 2.12 and 2.19 (two s, 6H), 2.69

(m, 1H), 2.95 (m, 1H), 3.08 (m, 1H), 3.80 and 3.86 (two s, 6H), 4.31 (ddd, 1H, $J=12.9$, 6.3, 2.5 Hz), 5.04 (d, 1H, $J=17.1$ Hz), 5.36 (d, 1H, $J=10.4$ Hz), 5.54 (d, 1H, $J=7.9$ Hz), 5.63 (dd, 1H, $J=7.9$, 1.1 Hz), 6.09 (dd, 1H, $J=17.1$, 10.4 Hz), 6.59 and 6.64 (two s, 2H); ^{13}C NMR: 20.67, 20.86, 24.51 (t), 35.15 (t), 55.79, 55.89, 63.53 (s), 74.08, 79.82, 108.02, 111.74, 117.23 (t), 125.58 (s), 127.88 (s), 136.19 (s), 148.12 (s), 148.71 (s), 168.12 (s), 169.72 (s), 170.38 (s).

Compound **4f**(*R*) *epimer*. ^1H NMR: 1.70 and 2.14 (two s, 6H), 3.79 and 3.87 (two s, 6H), 4.38 (ddd, 1H, $J=12.8$, 6.0, 1.0 Hz), 5.05 (d, 1H, $J=17.0$ Hz), 5.15 (s, 1H), 5.29 (d, 1H, $J=10.4$ Hz), 5.62 (s, 1H), 6.06 (dd, 1H, $J=17.0$, 10.4 Hz), 6.47 and 6.60 (two s, 2H).

4.2.12. Preparation of (1*S*,2*R*,10b*R*)-10b-cyclohexyl-1,2-dihydroxy-8,9-dimethoxy-1,2,3,5,6,10b-hexahydro-pyrrolo[2,1-*a*]isoquinolin-3-one [5d(*R*)]. The crude mixture of **4d**(*S*),(*R*) obtained from imide **1** (878 mg, 2 mmol) using procedure B, was dissolved at rt in dry MeOH (20 mL) containing MeONa (54 mg, 1 mmol). The solution was stirred until TLC indicated the disappearance of the substrate (~0.5 h), then the reaction was quenched by the addition of a small piece of dry ice and evaporated in vacuo. The residue was dissolved in CH_2Cl_2 (~20 mL), the precipitate was filtered off, washed with CH_2Cl_2 and the filtrate was evaporated. The residue was crystallized from methanol–ethyl acetate mixture to give pure dihydroxy-pyrroloisoquinoline **5d**(*R*).

Yield: 368 mg, 51%; colourless crystals; mp 236–238 °C; $[\alpha]_D$ −115.3 (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2): 3565, 3357, 2935, 1685 cm^{-1}.

^1H NMR ($CDCl_3+D_2O$): 1.12 (m, 4H), 1.25 (m, 1H), 1.45 (m, 1H), 1.65 (m, 1H), 1.78 (m, 3H), 2.02 (m, 1H), 2.64 (dd, 1H, $J=16.4$, 5.0 Hz), 2.93 (m, 1H), 3.18 (m,1H), 3.83 and 3.87 (two s, 6H), 4.04 (d, 1H, $J=5.8$ Hz), 4.26 (m, 1H), 4.41 (d, 1H, $J=5.8$ Hz), 6.55 and 7.27 (two s, 2H); ^{13}C NMR: 26.32 (t), 26.84 (t), 27.00 (t), 27.21 (t), 27.54 (t), 28.64 (t), 36.05 (t), 47.51, 55.71, 56.15, 66.63 (s), 76.11, 76.65, 111.86, 111.98, 126.72 (s), 127.63 (s), 146.48 (s), 147.98 (s), 172.75 (s); MS (ES, HR) *m*/*z*: (M^+) calcd for $C_{20}H_{27}NO_5$: 361.1889. Found: 361.1903. Anal. Calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88. Found: C, 66.35; H, 7.38; N, 3.84.

4.3. General procedure for the preparation of 2-(*tert*-butyl-dimethyl-silanyloxy)-hexahydropyrrolo-iso-quinolines [6a–f(*S*),(*R*)]

The mixture of diacetoxy-pyrroloisoquinolines **4a–f**(*S*),(*R*) (0.5 mmol) was dissolved at rt in dry MeOH (10 mL) containing MeONa (16 mg, 0.3 mmol). The solution was stirred until TLC indicated the disappearance of the substrate (~0.5 h), then the reaction was quenched by the addition of a small piece of dry ice and evaporated in vacuo. The residue was dissolved in CH_2Cl_2 (~5 mL), the precipitate was filtered off and the filtrate was evaporated to yield the crude mixture of dihydroxy-pyrroloisoquinolines **5a–f**(*S*),(*R*). The obtained mixture was dissolved in DMF (3 mL) and imidazole (102 mg, 1.5 mmol) was added followed by the *tert*-butyldimethylchlorosilane (120 mg, 0.8 mmol). The stirring was continued for 24 h at rt. The mixture was poured into water, extracted with ethyl acetate (2×10 mL), washed with water and brine then dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by flash column chromatography to give optical pure derivatives **6a–f**(*S*) and **6a–f**(*R*)

4.3.1. Preparation of (1*S*,2*R*,10b*S* and 10b*R*)-2-(*tert*-Butyl-dimethyl-silanyloxy)-1-hydroxy-10b-phenyl-8,9-dimethoxy-1,2,3,5,6,10b-hexahydro-pyrrolo[2,1-*a*]iso-quinolin-3-one [6a(*S*)] and [6a(*R*)]. The spectroscopic and physical properties of **6a**(*S*) and **6a**(*R*) were previously reported.[8]

4.3.2. Preparation of (1*S*,2*R*,10b*S* and 10b*R*)-2-(*tert*-butyl-dimethyl-silanyloxy)-1-hydroxy-8,9-dimethoxy-10b-methyl-1,2,3,5,6,10b-hexahydro-pyrrolo[2,1-*a*]iso-quinolin-3-one [6b(*S*)] and [6b(*R*)]. *Compound* **6b**(*S*). Yield: 61%; oil; $[\alpha]_D$ +195.0 (*c* 1.1, CH_2Cl_2); IR (CH_2Cl_2): 3685, 3610, 2932, 1704 cm^{-1}; ^1H NMR: 0.17 and 0.21 (two s, 6H), 0.92 (s, 9H), 1.52 (s, 3H), 2.57 (br s, 1H, exchangeable with D_2O), 2.64 (m, 1H), 2.88 (m, 1H), 2.99 (m, 1H), 3.84 and 3.85 (two s, 6H), 4.03 (d, 1H, $J=8.3$ Hz), 4.30 (ddd, 1H, $J=11.4$, 6.1, 1.4 Hz), 4.37 (d, 1H, $J=8.3$ Hz), 6.53 and 6.97 (two s, 2H); ^{13}C NMR: −5.01, −4.21, 18.34 (s), 21.82, 25.87, 28.03 (t), 33.87 (t), 55.84, 56.02, 59.33 (s), 76.93, 82.50, 108.07, 111.48, 124.17 (s), 133.00 (s), 148.02 (s), 168.22 (s); MS (EI, HR) *m*/*z*: (M^+) calcd for $C_{21}H_{33}NO_5Si$: 407.2128. Found: 407.2138.

Compound **6b**(*R*). Yield: 11%; white crystals; mp 158–160 °C (*t*-butylmethylether–hexane); $[\alpha]_D$ −126.8 (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2): 3685, 3560, 2934, 1697 cm^{-1}; ^1H NMR: 0.20 and 0.22 (two s, 6H), 0.93 (s, 9H), 1.67 (s, 3H), 2.65 (dd, 1H, $J=15.8$, 3.8 Hz), 2.83 (m, 1H), 3.05 (m, 1H), 3.85 and 3.89 (two s, 6H), 4.05 and 4.09 (two s, 2H), 4.32 (dd, 1H, $J=13.2$, 5.5 Hz), 6.57 and 6.63 (two s, 2H); ^{13}C NMR: −5.24, −4.67, 18.07 (s), 25.72, 26.71, 28.58 (t), 34.29 (t), 55.89, 56.22, 66.00 (s), 77.83, 78.01, 108.03, 112.46, 127.46 (s), 128.03 (s), 148.50 (s, overlapped signals of two carbons), 170.07 (s); MS (EI, HR) *m*/*z*: (M^+) calcd for $C_{21}H_{33}NO_5Si$: 407.2128. Found: 42.2133.

4.3.3. Preparation of (1*S*,2*R*,10b*S* and 10b*R*)-2-(*tert*-butyl-dimethyl-silanyloxy)-1-hydroxy-8,9-dimethoxy-10b-phenylethynyl-1,2,3,5,6,10b-hexahydro-pyrrolo[2,1-*a*]isoquinolin-3-one [6c(*S*) and 6b(*R*)]. *Compound* **6c**(*S*). Yield: 68%; oil; $[\alpha]_D$ +129.7 (*c* 1, CH_2Cl_2); IR (CH_2Cl_2): 3603, 3544, 2958, 2858, 1713 cm^{-1}; ^1H NMR: 0.21 and 0.24 (two s, 6H), 0.958 (s, 9H), 2.63 (br d, 1H, $J=10.0$ Hz, exchangeable with D_2O), 2.74 (ddd, 1H, $J=16.1$, 4.4, 1.8 Hz), 2.93 (m, 1H), 3.24 (m, 1H), 3.87 and 3.90 (two s, 6H), 4.05 (m, 1H), 4.34 (ddd, 1H, $J=13.0$, 6.3, 1.9 Hz), 4.42 (dd, 1H, $J=8.3$, 1.2 Hz), 6.58 (s, 1H), 7.19 (s, 1H), 7.3–7.43 (m, 5H); ^{13}C NMR: −4.97, −4.36, 18.39 (s), 25.73, 27.59 (t), 35.04 (t), 55.90, 56.08, 59.06 (s), 77.38, 82.48, 85.64 (s) 88.33 (s), 108.35, 111.42, 121.45 (s), 124.54 (s), 128.31 (s), 128.42, 129.12, 131.91, 148.38 (s), 148.81 (s), 168.54 (s); MS (ES, HR) *m*/*z*: ($M+Na^+$) calcd for $C_{28}H_{35}NO_5NaSi$: 516.2177. Found: 516.2182.

Compound **6c**(*R*). Yield: 7.4%; oil; $[\alpha]_D$ −86.7 (*c* 1, CH_2Cl_2);

IR (CH_2Cl_2): 3558, 3054, 2932, 2857, 1705 cm^{-1}; ^{1}H NMR: 0.20 and 0.22 (two s), 0.91 (s, 9H), 2.69 (dd, 1H, *J*=5.9, 3.5 Hz), 2.87 (m, 1H), 3.26 (m, 1H), 3.26 (m, 1H), 3.88 and 3.92 (two s, 6H), 4.16 (s, 1H), 4.35 (dd, 1H, *J*=13.1, 5.4 Hz), 4.46 (br s, 1H), 6.66 (s, 1H), 6.87 (s, 1H), 7.27–7.35 (m, 5H); ^{13}C NMR: −5.15, −4.60, 18.16 (s), 25.71, 28.16 (t), 35.14 (t), 55.94, 56.31, 63.00 (s), 77.38, 78.79, 85.66 (s), 89.20 (s), 108.46, 112.35, 122.41 (s), 124.51 (s), 128.05 (s), 128.13, 128.46, 131.67, 148.84 (s), 149.04 (s), 170.44 (s); MS (ES, HR) *m/z*: (M+Na$^+$) calcd for $C_{28}H_{35}NO_5NaSi$: 516.2177. Found: 516.2191.

4.3.4. Preparation of (1*S*,2*R*,10b*S* and 10b*R*)-2-(*tert*-butyl-dimethyl-silanyloxy)-10b-cyclohexyl-1-hydroxy-8,9-dimethoxy-1,2,3,5,6,10b-hexahydro-pyrrolo[2,1-*a*]isoquinolin-3-one [6d(*S*) and 6d(*R*)]. *Compound* **6d**(*S*). Yield: 6.5%; oil; [*α*]$_D$ +103 (*c* 1.4, CH_2Cl_2); IR (CH_2Cl_2): 3609, 2932, 2856, 1700 cm^{-1}; ^{1}H NMR: 0.20 and 0.23 (two s, 6H), 0.94 (s, 9H), 0.9–1.4 (m, 6H), 1.69 (m, 2H), 1.90 (m, 2H), 2.27 (m, 1H), 2.64 (dd, 1H, *J*=16.2, 4.0 Hz), 1.88 (m, 1H), 3.18 (m, 1H), 3.87 and 3.91 (two s, 6H), 4.13 (d, 1H, *J*=8.3 Hz), 4.47 (ddd, 1H, *J*=13.2, 5.9, 1.2 Hz), 4.62 (d, 1H, *J*=8.3 Hz), 6.55 and 6.96 (two s, 2H); ^{13}C NMR: −4.94, −4.14, 18.38 (s), 25.84, 26.36 (t), 26.58 (t), 27.66 (t, overlapped signals of two carbons), 29.11 (t), 30.627 (t), 36.21 (t), 44.76, 55.81, 56.17, 65.74 (s), 76.829, 84.86, 107.36, 111.36, 124.87 (s), 132.53 (s), 147.82 (s), 148.23 (s), 170.57 (s); MS (ES, HR) *m/z*: (M+Na$^+$) calcd for $C_{26}H_{41}NO_5NaSi$: 498.2644. Found: 498.2632.

Compound **6d**(*R*). Yield: 74%; oil; [*α*]$_D$ −75.2 (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2): 3557, 2933, 2857, 1692 cm^{-1}; ^{1}H NMR: 0.19 and 0.20 (two s, 6H), 0.93 (s, 9H), 0.8–1.3 (m, 5H), 1.60 (m, 2H), 1.75 (m, 2H), 1.94 (m, 1H), 2.11 (m, 1H), 2.67 (ddd, 1H, *J*=16.2, 5.3, 2.0 Hz), 2.84 (m, 1H), 3.25 (m, 1H), 3.87 and 3.88 (two s, 6H), 4.01 (d, 1H, *J*=2.0 Hz), 4.26 (dd, 1H, *J*=3.5, 2.0 Hz), 4.32 (ddd, 1H, *J*=13.3, 7.2, 2.0 Hz), 6.63 and 6.79 (two s, 2H); ^{13}C NMR: −5.17, −4.52, 18.12 (s), 25.73, 26.29 (t), 26.74 (t), 27.78 (t), 28.30 (t), 30.22 (t), 36.95 (t), 49.26, 55.79, 56.24, 70.17 (s), 77.16, 78.24, 109.70, 112.37, 125.75 (s), 128.39 (s), 147.47 (s), 148.26 (s), 171.42; MS (ES, HR) *m/z*: (M+H$^+$) calcd for $C_{26}H_{42}NO_5Si$: 476.2827. Found: 476.2842.

4.3.5. Preparation of (1*S*,2*R*,10b*S* and 10b*R*)-2-(*tert*-butyl-dimethyl-silanyloxy)-1-hydroxy-10b-isopropyl-8,9-dimethoxy-1,2,3,5,6,10b-hexahydro-pyrrolo[2,1-*a*]isoquinolin-3-one [6e(*S*) and 6e(*R*)]. *Compound* **6e**(*S*). Yield: 10%; oil; [*α*]$_D$ +167.7 (*c* 0.7, CH_2Cl_2); IR (CH_2Cl_2): 3687, 3605, 2960, 2857, 1701 cm^{-1}; ^{1}H NMR: 0.17 and 0.2 (two s, 6H), 0.78 (d, 1H, *J*=7.3 Hz), 0.92 (s, 9H), 1.10 (d, 1H, *J*=6.6 Hz), 2.40 (d, 1H, *J*=5.3 Hz, exchangeable with D_2O), 2.65 (m, 2H), 2.87 (m, 1H), 3.11 (m, 1H), 3.85 and 3.87 (two s, 6H), 4.11 (dd, 1H, *J*=8.3, 5.3 Hz), 4.45 (dd, 1H, *J*=13.0, 6.1 Hz), 4.56 (d, 1H, *J*=8.3 Hz), 6.54 and 6.94 (two s, 2H).

^{13}C NMR: −4.98, −4.19, 18.39 (s), 18.73, 20.72, 25.83, 27.77 (t), 34.40, 36.20 (t), 55.81, 56.06, 65.46 (s), 76.73, 84.60, 107.29, 111.39, 124,70 (s), 132.94 (s), 145.93 (s), 148.25 (s), 170.59 (s); MS (ES, HR) *m/z*: (M+Na$^+$) calcd for $C_{23}H_{37}NO_5NaSi$: 458.2333. Found: 458.2339.

Compound **6e**(*R*). Yield: 67%; oil; [*α*]$_D$ −77.9 (*c* 1.3, CH_2Cl_2); IR (CH_2Cl_2): 3558, 2960, 2857, 1693 cm^{-1}; ^{1}H NMR: 0.18 and 0.19 (two s, 6H), 0.91 (d, 3H, *J*=7.0 Hz), 0.93 (s, 9H), 1.05 (d, 3H, *J*=6.8 Hz), 1.62 (d, 1H, *J*=3.8 Hz, exchangeable with D_2O), 2.33 (m, 1H), 2.65 (dd, 1H, *J*=16.0, 5.2 Hz), 2.85 (m, 1H), 3.21 (m, 1H), 3.85 and 3.86 (two s, 6H), 4.02 (d, 1H, *J*=2.2 Hz), 4.23 (dd, 1H, *J*=3.8, 2.2 Hz), 6.62 and 6.81 (two s, 2H); ^{13}C NMR: −5.17, −4.54, 18.14, 18.16 (s), 20.34, 25.74 (t), 27.89 (t), 36.66 (t), 38.66, 55.78, 56.16, 69.96 (s), 77.16, 78.35, 108.70, 112.39, 125.91 (s), 128.35 (s), 147.49 (s), 148.28 (s), 171.35 (s); MS (ES, HR) *m/z*: (M+H$^+$) calcd for $C_{23}H_{38}NO_5Si$: 436.2514. Found: 436.2526.

4.3.6. Preparation of (1*S*,2*R*,10b*S* and 10b*R*)-2-(*tert*-butyl-dimethyl-silanyloxy)-1-hydroxy-8,9-dimethoxy-10b-vinyl-1,2,3,5,6,10b-hexahydro-pyrrolo[2,1-*a*]isoquinolin-3-one [6f>(*S*) and 6f(*R*)]. *Compound* **6f**(*S*). Yield: 60%; oil; [*α*]$_D$ +107.5 (*c* 1.1, CH_2Cl_2); IR (CH_2Cl_2): 3608, 2933, 2858, 1709 cm^{-1}; ^{1}H NMR (C_6D_6): 0.17 and 0.22 (two s, 6H), 0.93 (s, 9H), 2.31 (d, 1H, *J*=6.8 Hz, exchangeable with D_2O), 2.66 (m, 1H), 2.90 (m, 1H), 3.00 (m, 1H), 3.86 and 3.88 (two s, 6H), 4.12 (dd, 1H, *J*=8.3, 6.8 Hz), 4.25 (m, 1H), 4.32 (d, 1H, *J*=8.3, 1.1 Hz), 5.07 (d, 1H, *J*=17.2 Hz), 5.33 (d, 1H, *J*=10.5 Hz), 6.11 (dd, 1H, *J*=17.2, 10.5 Hz), 6.58 and 7.10 (two s, 2H); ^{13}C NMR: −5.01, −4.24, 18.35 (s), 25.27, 27.69 (t), 34.76 (t), 55.87, 56.09, 63.65 (s), 76.58, 83.33, 108.39, 111.56 (t), 125.17 (s), 129.73 (s), 136.70, 148.06 (s), 148.31 (s), 169.04 (s); MS (EI, HR) *m/z*: (M+H$^+$) calcd for $C_{22}H_{34}NO_5Si$: 420.2201. Found: 420.2216.

Compound **6f**(*R*). Yield: 13%; oil; [*α*]$_D$ −111.0 (*c* 0.6, CH_2Cl_2); IR (CH_2Cl_2): 3558, 2932, 2858, 1699 cm^{-1}; H NMR: 0.29 and 0.37 (two s, 6H), 1.05 (s, 9H), 1.80 (br s, 1H, exchangeable with D_2O), 2.09 (dd, 1H, *J*=15.8, 3.8 Hz), 2.61 (m, 1H), 2.81 (dt, 1H, *J*=12.7, 4.3 Hz), 3.36 and 3.37 (two s, 6H), 4.28 (br s, 1H), 4.35 (dd, 1H, *J*=12.7, 5.5 Hz), 4.50 (s, 1H), 4.90 (dd, 1H, *J*=17.2, 1.0 Hz), 5.069 (dd, 1H, *J*=10.4, 1.0 Hz), 6.23 (s, 1H), 6.30 (dd, 1H, *J*=17.2, 10.4 Hz), 6.49 (s, 1H); ^{13}C NMR: −5.25, −4.67, 18.05 (s), 25.69, 28.28 (t), 34.11 (t), 55.86, 56.18, 70.30 (s), 76.91, 77.97, 109.19, 112.42, 117.44 (t), 123.43 (s), 129.12 (s), 139.37, 148.10 (s), 148.66 (s), 170.36 (s); MS (EI, HR) *m/z*: (M+H$^+$) calcd for $C_{22}H_{34}NO_5Si$: 420.2201. Found: 420.2210.

4.3.7. Preparation of (1*R*,8b*S*,11a*S*)-1-hydroxy-6,7-dimethoxy-10-phenyl-1,3,4,11a-tetrahydro-11-oxa-2a-aza-pentaleno[6a,1-*a*]naphthalen-2-one (7). The epimeric mixture of **4c**(*S*),(*R*) (232 mg, 0.5 mmol), obtained applying procedure A, was dissolved at rt in dry MeOH (10 mL) containing MeONa (16 mg, 0.3 mmol). The solution was stirred until TLC indicated the disappearance of the substrate (∼0.5 h), then the reaction was quenched by the addition of a small piece of dry ice and evaporated in vacuo. The residue was dissolved in CH_2Cl_2 (∼5 mL), the precipitate was filtered off and the filtrate was evaporated to yield the crude mixture of dihydroxy-pyrroloisoquinolines **5c**(*S*),(*R*). The obtained mixture was then dissolved in THF (3 mL) and $Pd(OAc)_2$ (23 mg, 0.1 mmol) was added followed by triethylamine (28 μl, 0.2 mmol) and stirring was continued for 2 h at rt. The mixture was poured into water and extracted with CH_2Cl_2 (2×15 mL). Collected extracts were washed with water, semi-satd aq $NaHCO_3$ and water again then dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by flash column chromatography to give **7**.

Yield: 155 mg, 82%; oil; $[\alpha]_D$ +247.0 (*c* 0.9, CH_2Cl_2); IR (CH_2Cl_2): 3556, 3330, 2985, 2939, 1732, 1699 cm^{-1}; ^1H NMR: 2.69 (dd, 1H, *J*=16.5, 3.6 Hz), 2.99 (m, 1H), 3.15 (m, 1H), 3.77 and 3.86 (two s, 6H), 3.94 (br s, 1H, exchangeable with D_2O), 4.38 (dd, 1H, *J*=13.0, 5.2 Hz), 4.64 (br s, 1H), 5.03 (d, 1H, *J*=3.9 Hz), 5.70 (s, 1H), 6.56 (s, 1H), 6.64 (s, 1H), 7.39 (m, 3H), 7.66 (m, 2H); ^{13}C NMR: 27.53 (t), 36.74 (t), 55.94, 56.14, 73.06 (s), 77.68, 92.06, 101.56, 108.59, 111.23, 124.80 (s), 125. 84, 128.48, 129.53 (s), 129.70 (overlapped signals of two carbons), 148.63 (s) 148.80 (s), 157.29 (s), 170.97 (s); MS (EI, HR) *m/z*: (M^+) calcd for $C_{22}H_{21}NO_5$: 379.1420. Found: 379.1429.

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References and notes

1. Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817–3856.
2. Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev.* **2004**, *104*, 2311–2352.
3. Bentley, K. W. *The Isoquinoline Alkaloids*; Harwood Academic, Amsterdam, 1998; pp 255–361.
4. Dyke, S. F.; Quessy, S. N. In Rodrigo, R. G. A., Ed.; The Alkaloids; Academic: New York, 1981; Vol. 18, p 1.
5. (a) Chrzanowska, M.; Rozwadowska, M. *Chem. Rev.* **2004**, *104*, 3341–3370. (b) Padwa, A.; Henning, R.; Kappe, C. O.; Reger, T. S. *J. Org. Chem.* **1998**, *63*, 1144–1155. Allin, S. M.; Streetley, G. B.; Slater, M.; James, S. L.; Martin, W. P. *Tetrahedron Lett.* **2004**, *45*, 5493–5496. (c) Allin, S. M.; Vaidya, D. G.; James, S. L.; Allard, J. E.; Smith, T. A. D.; McKee, V.; Martin, W. P. *Tetrahedron Lett.* **2002**, *43*, 3661–3663. (d) Allin, S. M.; James, S. L.; Elsegood, M. J.; Martin, W. P. *J. Org. Chem.* **2002**, *67*, 9464–9467. (e) Gill, Ch.; Greenhalgh, D. A.; Simpkins, N. S. *Tetrahedron Lett.* **2003**, *44*, 7803–7807. (f) Manteca, I.; Sotomayor, N.; Villa, M.-J.; Lete, E. *Tetrahedron Lett.* **1996**, *37*, 7841–7844. (g) Collado, M. I.; Manteca, I.; Sotomayor, N.; Villa, M.-J.; Lete, E. *J. Org. Chem.* **1997**, *62*, 2080–2092. (h) Garcia, E.; Arrasate, S.; Ardeo, A.; Lete, E.; Sotomayor, N. *Tetrahedron Lett.* **2001**, *42*, 1511–1513. (i) Bailey, P. D.; Morgan, K. M.; Smith, D. I.; Vernon, J. M. *Tetrahedron Lett.* **1994**, *35*, 7115–7118. (j) Bailey, P. D.; Morgan, K. M.; Smith, D. I.; Vernon, J. M. *Tetrahedron* **2003**, *59*, 3369–3378. (k) Lee, J. Y.; Lee, Y. S.; Chung, B. Y.; Park, H. *Tetrahedron* **1997**, *53*, 2449–2458. (l) Lee, Y. S.; Lee, J. Y.; Kim, D. W.; Park, H. *Tetrahedron* **1999**, *55*, 4631–4636.
6. Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388–401.
7. (a) Fuji, K. *Chem. Rev.* **1993**, *93*, 2032066. (b) Schuch, C. M.; Pilli, R. A. *Tetrahedron: Asymmetry* **2000**, *11*, 753–764.
8. Mostowicz, D.; Wójcik, R.; Dołęga, G.; Kałuża, Z. *Tetrahedron Lett.* **2004**, *45*, 6011–6015.
9. For leading references of the use of trifluoroacetic acid as an *N*-acylimimium ion promoter see: 5e, 5g– j.
10. Hiemstra, H.; Speckamp, W. N. In Trost, B. M., Fleming, I., Eds.; Comprehensive Organic Synthesis; Pergamon: Oxford, 1991; Vol. 2, pp 1047–1082.
11. Saito, T.; Suzuki, T.; Morimoto, M.; Akiyama, C.; Ochiai, T. *J. Am. Chem. Soc.* **1998**, *120*, 11633–11644.
12. Bernardi, A.; Micheli, F.; Potenza, D.; Scolastico, C.; Villa, R. *Tetrahedron Lett.* **1990**, *31*, 4949–4952.
13. (a) Thaning, M.; Wistrand, L. G. *Org. Chem.* **1999**, *55*, 1406–1408. (b) Koot, W.-J.; Ginkel, R.; Kranenburg, M.; Hiemstra, H.; Louwrier, S.; Moolenaar, M. J.; Speckamp, W. N. *Tetrahedron Lett.* **1991**, *32*, 401–404. (c) Huang, J.-M.; Hong, S.-C.; Wu, K.-l.; Tsai, Y.-M. *Tetrahedron Lett.* **2004**, *45*, 3047–3050. (d) Schuch, C. M.; Pilli, R. A. *Tetrahedron: Asymmetry* **2002**, *13*, 1973–1980. (e) Klitzke, C. F.; Pilli, R. A. *Tetrahedron Lett.* **2001**, *42*, 5605–5608.
14. (a) Pilli, R. A. *Tetrahedron: Asymmetry* **2000**, *11*, 753–764. (b) Othman, R. B.; Bousquet, T.; Fousse, A.; Othman, M.; Dalla, V. *Org. Lett.* **2005**, *7*, 2825–2828.
15. Okitsu, O.; Suzuki, R.; Kobayashi, S. *Org. Chem.* **2001**, *66*, 809–823.
16. Schmit, R. R.; Behrendt, M.; Toepfer, A. *Synlett* **1990**, 694–696 and references citated there.

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Baylis–Hillman adducts between pyridine carboxaldehyde derivatives and cyclic enones☆

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Abstract—Baylis–Hillman (BH) adducts were synthesized using pyridinecarboxaldehyde derivatives and cyclic enones. The Baylis–Hillman reaction was examined by employing various organic tertiary bases and solvents. It was observed that DBU in MeOH as well as imidazole and *N*-methylimidazole in aqueous MeOH are very effective. These pyridinecarboxaldehydes were reactive and efficient towards the Baylis–Hillman reaction and the resulting adducts are highly stable. The crystal structure for one of the BH adducts was determined.

1. Introduction

The Baylis–Hillman (BH) reaction is one that results in the formation of a carbon–carbon bond between the α-position of an activated alkene and carbon electrophile containing an electron-deficient sp^2 carbon atom under the influence of a suitable catalyst. The Baylis–Hillman (BH) and related processes have become increasingly important for synthetic organic chemists because the resulting adducts are packed with functional groups and stereochemistry, which can be subjected to numerous transformations.[1] Cyclic enones are also activated alkenes but the Baylis–Hillman reaction of 2-cyclopenten-1-one or 2-cyclohexen-1-one is sluggish or does not occur at all under traditional conditions.[2] To make the reaction more efficient, a variety of methods including physical as well as chemical attempts have been explored. Recently, various organic bases and methods for the synthesis of the Baylis–Hillman adducts of cyclic enones have been developed. Methoxide anion in MeOH solvent,[3] imidazole in aqueous media,[4] azoles in basic water solution,[5] imidazole in basic water solution,[6] the combination of 2,6-diphenyl-4*H*-chalcogeno-4-ones and $TiCl_4$ in methylene chloride,[7] the combination of $LiClO_4$ and DABCO in ether,[8] the use of Et_2AlI in CH_2Cl_2,[9] tributylphosphine combined with 1,1-bi-naphthol,[10] Lewis base effects including DMAP, tributylphosphines and DBU,[11] $TiCl_4$ (Lewis acid) without the use of Lewis base have all been applied to highly reactive aldehydes.[12] Lithium phenylselenide (PhSeLi) catalyzed Baylis–Hillman reaction with cyclic enones,[13] DMAP in aqueous THF used as a catalyst for the Baylis–Hillman reaction between aldehydes (aromatic and aliphatic) and cyclic enones[14] have also been reported. The Baylis–Hillman reactions involving cyclic enones and heterocyclic compounds are less explored. Only Kim et al. reported with quinolinecarboxaldehyde[14b] and Batra et al. reported using 5-isoxazolecarboxaldehyde.[15] To the best of our knowledge there are no other BH reactions involving heterocyclic compounds and cyclic enones reported in the literature. The Baylis–Hillman reaction between pyridine carboxaldehyde/furfuraldehyde and cyclic enones are reported to produce unstable BH adducts.[16] In contrast to earlier reports, we have successfully synthesized Baylis–Hillman adducts between pyridinecarboxaldehyde derivatives and cyclic enones under a variety of conditions. Synthesized Baylis–Hillman adducts containing a pyridine moiety are very stable and for one of the BH adducts an X-ray structure was also determined. The formation of these Baylis–Hillman adducts is found to be very fast and with high yields compared to earlier reports. Such Baylis–Hillman adducts have wide applicability in organic synthesis in preparation of quinolines, naphthyridines, and aza pyrazoles.

2. Results and discussions

The Baylis–Hillman (BH) reaction was conducted using various substituted 2-chloro-pyridine-3-carboxaldehydes[17]

☆ IICT communication no. 050919.

Keywords: Baylis–Hillman reaction; Substituted 2-chloropyridine-3-carboxaldehydes; Cyclic enones; Organic tertiary bases; Solvents; Baylis–Hillman adducts; X-ray crystal structure.

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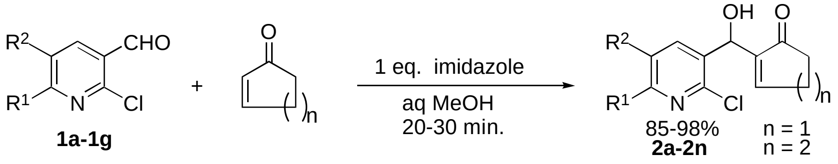


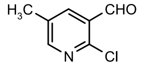
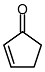
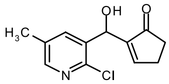
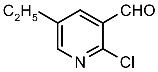
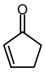
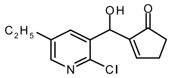
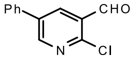
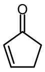
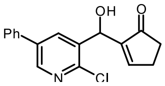
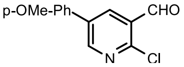
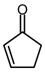
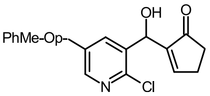
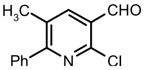
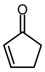
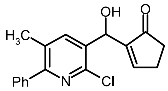
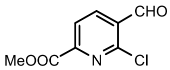
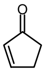
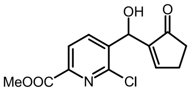
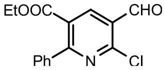
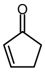
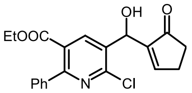
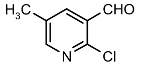
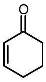
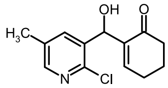
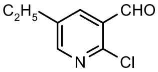
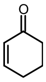
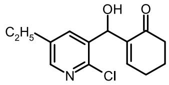
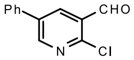
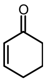
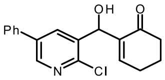
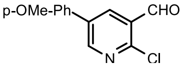
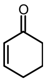
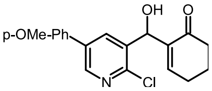
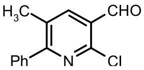
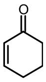
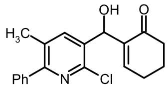
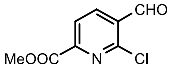
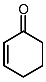
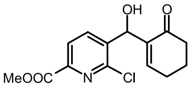
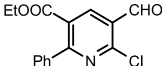
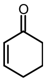
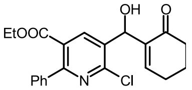
1a-1g **2a-2n**

1a: $R^1 = H, R^2 = CH_3$
1b: $R^1 = H, R^2 = C_2H_5$
1c: $R^1 = H, R^2 = Ph$
1d: $R^1 = H, R^2 = 4\text{-OMe-}C_6H_4$
1e: $R^1 = Ph, R^2 = CH_3$
1f: $R^1 = COOMe, R^2 = H$
1g: $R^1 = Ph, R^2 = COOEt$

2a: $R^1 = H, R^2 = CH_3$, n = 1; **2h:** n = 2
2b: $R^1 = H, R^2 = C_2H_5$, n = 1; **2i:** n = 2
2c: $R^1 = H, R^2 = Ph$, n = 1; **2j:** n = 2
2d: $R^1 = H, R^2 = 4\text{-OMe-}C_6H_4$, n = 1; **2k:** n = 2
2e: $R^1 = Ph, R^2 = CH_3$, n = 1; **2l:** n = 2
2f: $R^1 = COOMe, R^2 = H$, n = 1; **2m:** n = 2
2g: $R^1 = Ph, R^2 = COOEt$, n = 1; **2n:** n = 2

Scheme 1.

Table 1. The Baylis–Hillman reaction between substituted pyridinecarboxaldehyde (**1a**–**1g**) and cyclic enones in the presence of imidazole[a,b]

Entry	Aldehyde (**1a**–**1g**)	Cyclic enone	Product (**2a**–**2n**)	Time (min)	Yield (%)[c]
1				20	98
2				20	98
3				25	96
4				20	90
5				25	90
6				15	85
7				20	82
8				25	90
9				25	92
10				30	96
11				25	95
12				30	92
13				22	80
14				25	78

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[a] The reactions were conducted in $MeOH–H_2O$, (1/1, v/v) system at room temperature and the reaction was monitored by TLC.
[b] Mole ratio of aldehyde/cycloalkenone/imidazole = 1:1.2:1.
[c] Isolated yields.

(**1a–g**) and cyclic enones (2-cyclopenten-1-one; 2-cyclohexen-1-one) in the presence of 1 equiv imidazole as an organic base in aqueous methanol solvent system at room temperature (Scheme 1). The BH adducts (**2a–n**) were readily formed (within 15–30 min) in high yields (80–98%). A slight excess of cyclic enone (1.2 equiv) was found to give higher yields in these reactions. The results of these studies are shown in Table 1. The reaction time indicated in Table 1 represents the reactivity and efficiency of the aldehydes towards BH reaction. The yields are somewhat lower for entries 6, 7, 13 and 14 in Table 1 and this may be due to the presence of the ester functionality, which can lead to other products, which were not analyzed. All the BH adducts were found to be stable and we determined an X-ray crystal structure for **2a**.

On crystallization, compound **2a** led to crystals suitable for single-crystal X-ray diffraction studies.[19] The molecular configuration of **2a** is shown in Figure 1. Although the molecule contains a chirotopic stereogenic atom, C6, the crystal belongs to a centro-symmetric space group and thus represents a racemate. The dihedral angle formed by the plane of the pyridine ring and the cyclopent-2-enone plane is 78.1(1)°. The hydroxyl oxygen is tilted towards the cyclopent-2-enone due to steric interactions between the hydroxyl group and the Cl atom as the C4–C6–O1 [111.7(1)°] bond angle is distinctly larger than that of the C7–C6–O1 [106.6(2)°]. The C6–H6···Cl intra-molecular interaction closes the five-membered pseudo-ring Cl–C5–C4–C6–H6 according to the S(5) pattern.[20] Similar interactions were noted in the literature.[21] The crystal structure of (**2a**) is stabilized by O–H···O intermolecular interactions forming hydrogen-bonded dimmers.[22]

The Baylis–Hillman reaction between 2-chloro-5-methylpyridine-3-carboxaldehyde and cyclopent-2-enone using a variety of organic bases in MeOH:H_2O (1:1) and MeOH was carried out to understand the role of the organic tertiary base (Table 2). The three bases imidazole, *N*-methylimidazole and DMAP readily gave Baylis–Hillman adducts in MeOH–H_2O (1/1) in excellent yields (entries 1–3; Table 2). DABCO, DBU, trimethylamine and triethylamine (entries 4–7; Table 2) gave Baylis–Hillman adduct (**2a**) in MeOH–H_2O (1/1) with lower yields along with Aldol-type product (**2o**) (Scheme 2). The reaction was found to be complete within 45 min for all these above-mentioned bases. Other bases such as 1,2,3-triazole, 1,2,4-triazole and pyridine in MeOH–H_2O (1/1) were found to be non-effective in the formation of BH adducts (entries 8–10; Table 2) even after 5 h. To know the role of water, the reaction was conducted in pure MeOH using DBU and DMAP. The DBU base in MeOH gave the BH adduct in excellent yield (entry 11; Table 2) without any Aldol-type product formation, whereas DMAP gave the BH adduct albeit in lower yield, but without formation of the Aldol-type product. These observations show that the polar nature of the medium used and as well as the water present are important. To probe further the role of water, we conducted reactions in various solvents with and without water using 2-chloro-5-methylpyridine-3-carboxaldehyde, cyclopent-2-enone and imidazole as an organic base (Table 3). The Baylis–Hillman adduct formation is facile in all the pure solvents selected (Table 3), but the reaction time differs. The presence of water in all these solvents accelerates the formation of the BH adduct with a given selected organic base. Particularly striking are the THF and dioxane solvents, where the reaction time for BH adduct formation is reduced by 6–7 times by the presence of water (entries 3–6; Table 3). The solvents like sulfolane and DMSO have comparable reaction times leading towards formation of BH adducts (Table 3). It has been reported that protic solvents or polar solvents with water accelerate BH adduct formation, through either stabilization of enolate by hydrogen bonding or by activation of the aldehyde through hydrogen

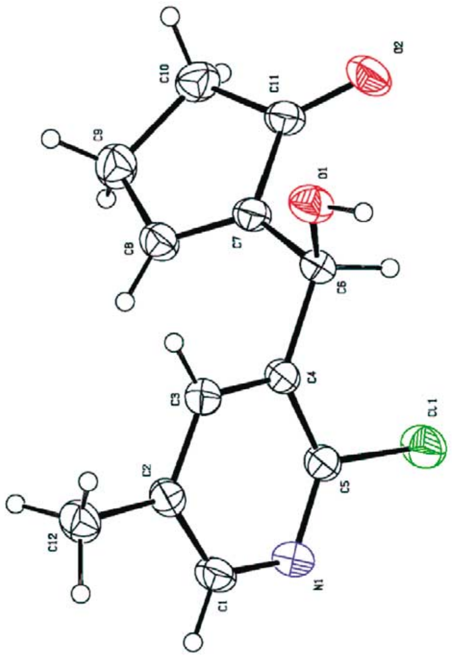


Figure 1. A view of product **2a** with the atomic numbering scheme. Displacement ellipsoids are drawn at the 30% probability level.

Table 2. Effect of base on Baylis–Hillman reaction[a]

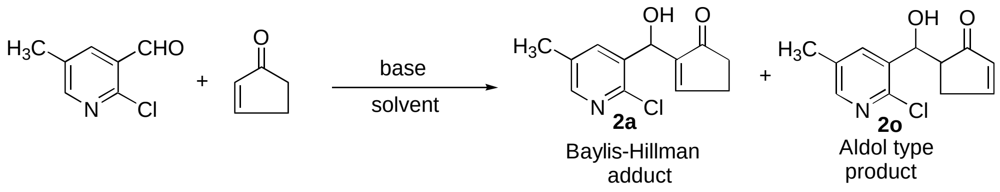
Entry	Base	Time (min)	Yield (%)[b]	
			Baylis–Hillman adduct (**2a**)	Aldol type adduct (**2o**)
1	Imidazole	30	98	None
2	*N*-Methylimidazole	45	95	None
3	4-Dimethylamino-pyridine (DMAP)	40	90	None
4	Diazabicyclooctane (DABCO)	35	55	40
5	DBU	30	38	25
6	Me_3N/H_2O	25	45	40
7	Et_3N	25	35	38
8	1,2,3-Triazole	300	None[c]	None
9	1,2,4-Triazole	300	None[c]	None
10	Pyridine	300	15[c]	None
11	DBU (in MeOH)[d]	20	98	None
12	DMAP (in MeOH)[d]	120	35	None

[a] The reaction was conducted between 2-chloro-5-methyl-3-pyridine-carboxaldehyde (**1a**; 1 equiv) and cyclopent-2-enone (1.2 equiv) in the presence of 1 equiv of base in MeOH–H_2O (1/1, v/v) solvent system at room temperature and the reaction was monitored by TLC.

[b] Isolated yields.

[c] Aldehyde was recovered.

[d] Pure MeOH as medium.



Scheme 2.

Table 3. Effects of medium on the BH reaction[a]

Entry	Solvent	Time (min)	Yield (%)[b]
1	MeOH	90	95
2	MeOH/H_2O	30	98
3	THF	360	65
4	THF/H_2O	50	90
5	Dioxane	300	75
6	Dioxane/H_2O	45	82
7	Dimethylformamide (DMF)	360	65
8	DMF/H_2O	120	90
9	Sulpholane	100	80
10	DMSO	110	75

[a] The reaction was conducted using 2-chloro-5-methyl-3-pyridinecarboxaldehyde (**1a**; 1 mmol) and cyclopent-2-enone (1.2 mmol) in the presence of 1 mmol of imidazole at room temperature and the reaction was monitored by TLC.

[b] Isolated yields.

bonding.[18] All these observations show that it is important to choose the correct organic base and solvent for a given aldehyde in conducting the Baylis–Hillman reaction.

3. Summary

2-Chloropyridine-3-carboxaldehyde derivatives were investigated as highly reactive substrates toward Baylis–Hillman reaction with cyclic enones. The influence of organic tertiary base and reaction media was significant. This may be the fastest Baylis–Hillman reaction with cyclic enones observed with respect to aldehyde substrates. The Baylis–Hillman adducts involving pyridine heterocycle are found to be stable and an X-ray structure for one of the Baylis–Hillman adducts was solved.

4. Experimental

4.1. General methods

All activated alkenes and tertiary amines were obtained commercially. The melting points were determined on a Mel-Temp apparatus and are uncorrected. IR was recorded with a Perkin-Elmer model 1600 series FTIR spectrometer using KBr optics. All ^{1}H NMR and ^{13}C NMR spectra were recorded on a 200 and 50 MHz, respectively. EIMS were detected on VG Micromass 7070H (70 eV). Aldehydes were synthesized according to the earlier published work by us.[17]

4.2. Typical experimental procedure

The clear solution of aldehyde (**1a–1g**) (1 mmol) and imidazole (1 equiv) in 5 mL of MeOH was slowly charged with 5 mL of deionized water. To a stirred homogeneous reaction mixture was added cyclic enone (1.2 mmol) at room temperature and the reaction progress was monitored by TLC. Upon completion of the reaction, the reaction mixture was acidified with aqueous HCl (5 mL) and extracted with $CHCl_3$ (3×20 mL). Combined organic layers were washed with brine solution (2×10 mL). The organic layer was concentrated and column chromatography of the crude product on silica gel, using 30% ethyl acetate in hexane as eluent, gave pure Baylis–Hillman adduct (**2a**–**2n**).

4.3. Characterization data

4.3.1. 2-[(2-Chloro-5-methylpyridine-3-yl)(hydroxy) methyl]cyclopent-2-en-1-one (2a). White Solid; Mp 120–123 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.16 (d, J=2.3 Hz, 1H), 7.82 (d, J=2.3 Hz, 1H), 7.14 (t, J=3.4 Hz, 1H), 5.78 (s, 1H), 4.18 (s, 1H), 2.65 (m, 2H), 2.52 (m, 2H), 2.4 (s, 3H); ^{13}C NMR: (50 MHz, $CDCl_3$): δ 209.6, 160.5, 148.7, 146.1, 145.0, 137.6, 134.9, 132.8, 65.6, 35.1, 26.7, 17.7; MS EI (*m/z*): 237 (M^+), 202, 156, 117, 92, 39; IR (KBr): 3436, 2983, 1683 cm^{-1}. Anal. Calcd for $C_{12}H_{12}ClNO_2$: C, 60.61; H, 5.13; N, 5.89%; Found: C, 60.80; H, 5.23; N, 5.98%.

4.3.2. 2-[(2-Chloro-5-ethylpyridine-3-yl)(hydroxy)-methyl]cyclopent-2-en-1-one (2b). White Solid; Mp 107–110 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.08 (d, J=2.3 Hz, 1H), 7.78 (d, J=2.3 Hz, 1H), 7.07 (t, J=3.7 Hz, 1H), 5.70 (s, 1H), 4.42 (br, 1H), 2.66 (q, J=7.4 Hz, 2H), 2.54 (m, 2H), 2.4 (m, 2H), 1.20 (t, J=7.4 Hz, 3H); ^{13}C NMR: (50 MHz, $CDCl_3$): δ 209.3, 160.6, 147.6, 145.9, 145.0, 138.8, 136.4, 135.1, 65.1, 34.8, 26.5, 25.2, 14.8; MS EI (*m/z*): 251 (M^+), 216, 170, 131, 104, 53; IR (KBr): 3462, 2921, 1662 cm^{-1}. Anal. Calcd for $C_{13}H_{14}ClNO_2$: C, 62.03; H, 5.61; N, 5.56%; Found: C, 62.44; H, 5.98; N, 5.74%.

4.3.3. 2-[(2-Chloro-5-phenylpyridine-3-yl)(hydroxy)-methyl]cyclopent-2-en-1-one (2c). White solid; Mp 112–114 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.53 (d, J=3.0 Hz, 1H), 8.21 (d, J=3.0 Hz, 1H), 7.36–7.59 (m, 5H), 7.16 (t, J=3.2 Hz, 1H), 5.83 (s, 1H), 4.34 (s 1H), 2.46–2.72 (m, 4H); ^{13}C NMR: (50 MHz, $CDCl_3$): δ 209.0, 160.1, 147.1, 146.1, 144.4, 135.8, 135.7, 135.5, 135.0, 128.6, 128.0, 126.6, 126.5, 65.1, 34.6, 26.1; MS (EI) *m/z*: 299 (M+), 264, 236, 153, 77; IR (KBr): 3432, 2989, 1643 cm^{-1}. Anal. Calcd for $C_{17}H_{14}ClNO_2$: C, 68.18; H, 4.70; N, 4.67%; Found: C, 68.24; H, 4.83; N, 4.87%.

4.3.4. 2-[(2-Chloro-5-(4-methoxyphenyl)pyridine-3-l)-(hydroxy)methyl]cyclopent-2-en-1-one (2d). White solid; Mp 110–114 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.43 (d, J=2.3 Hz, 1H), 8.13 (d, J=2.3 Hz, 1H), 7.49 (m, 2H), 7.17 (t, J=3.9 Hz, 1H), 6.92 (m, 2H), 5.8 (s, 1H), 3.81 (s, 3H), 2.53 (m, 2H), 2.45 (m, 2H); MS (EI) *m/z*: 329 (M+), 294, 276, 251, 107, 65; IR (KBr): 3487, 2993, 1674, 1323 cm^{-1}.

Anal. Calcd for $C_{18}H_{16}ClNO_3$: C, 65.56; H, 4.89; N, 4.25%; Found: C, 65.87; H, 5.12; N, 4.45%.

4.3.5. 2-[(2-Chloro-5-methyl-6-phenylpyridine-3-yl)-(hydroxy)methyl]cyclopent-2-en-1-one (2e). White solid; Mp 138–142 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.85 (s, 1H), 7.35–7.55 (m, 5H), 7.23 (t, J=3.0 Hz, 1H), 5.81 (s, 1H), 4.09 (s, 1H), 2.62–2.68 (m, 2H), 2.48–2.55 (m, 2H), 2.4 (s, 3H); ^{13}C NMR: (50 MHz, $CDCl_3$): δ 210.0, 160.4, 157.9, 145.5, 144.7, 139.4, 138.8, 133.3, 130.4, 129.0, 128.4, 128.2, 66.2, 35.1, 26.7, 19.4; MS (EI) *m/z*: 313 (M+), 278, 50, 235, 193, 115, 77; IR (KBr): 3402, 2981, 1663 cm^{-1}. Anal. Calcd for $C_{18}H_{16}ClNO_2$: C, 68.90; H, 5.14; N, 4.46%; Found: C, 69.12; H, 5.43; N, 4.76%.

4.3.6. Methyl-6-chloro-5-[hydroxy(5-oxo-cyclopent-1-en-1-yl)methyl]pyridine-2-carboxylate (2f). Pale yellow solid; Mp 76–79 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.22 (d, J=7.7 Hz, 1H), 8.13 (d, J=7.7 Hz, 1H), 7.17 (t, J=2.2 Hz, 1H), 5.89 (s, 1H), 4.01 (s, 3H), 2.65 (m, 2H), 2.5 (m, 2H); ^{13}C NMR: (50 MHz, $CDCl_3$): δ 209.3, 164.2, 160.7, 148.8, 146.9, 144.2, 139.8, 137.9, 124.1, 65.7, 52.9, 34.9, 26.7; MS (EI) *m/z*: 281 (M+), 246, 218, 202, 188, 122, 69; IR (KBr): 3414, 2954, 1723, 1689, 1315 cm^{-1}. Anal. Calcd for $C_{13}H_{12}ClNO_4$: C, 55.43; H, 4.29; N, 4.97%; Found: C, 55.67; H, 4.67; N, 5.14%.

4.3.7. Ethyl 6-chloro-5-[hydroxy(5-oxo-1-cyclopentenyl)-methyl]-2-phenyl nicotinate (2g). Pale yellow; Mp 123–126 °C; ^{1}H NMR (200 Hz, $CDCl_3$): δ 8.87 (s, 1H), 7.6 (m, 2H), 7.42 (m, 3H), 7.22 (t, J=3.7 Hz, 1H), 5.92 (s, 1H), 4.2 (q, J=6.8 Hz, 2H), 2.65 (m, 2H), 2.5 (m, 2H), 1.1 (t, J=6.7 Hz, 3H). ^{13}C NMR: (50 MHz, $CDCl_3$): δ 209.6, 165.6, 161.2, 149.1, 148.1, 145.8, 139.2, 136.4, 134.4, 132.7, 129.1, 128.4, 124.7, 65.5, 54.2, 36.0, 25.2, 14.3; MS (EI) *m/z*: 371 (M+), 336, 318, 275, 263, 178, 77; IR (KBr): 3423, 2967, 1733, 1646, 1328 cm^{-1}. Anal. Calcd for $C_{20}H_{18}ClNO_4$: C, 64.61; H, 4.88; N, 3.77%; Found: C, 64.92; H, 5.09; N, 3.78%.

4.3.8. 2-[(2-Chloro-5-methylpyridine-3-yl)(hydroxy)-methyl]cyclohex-2-en-1-one (2h). White solid; Mp 105–107 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.11 (d, J=2.3 Hz, 1H), 7.78 (d, J=2.3 Hz, 1H), 6.47 (t, J=4.1 Hz, 1H), 5.72 (s, 1H), 2.5 (m, 2H), 2.38 (s, 3H), 2.38 (m, 2H), 2.03 (m, 2H); ^{13}C NMR: (50 MHz, $CDCl_3$): δ 200.2, 148.5, 148.2, 138.7, 137.9, 134.7, 132.5, 68.4, 38.3, 25.7, 22.3, 17.7; MS EI (*m/z*): 251 (M$^+$), 216, 198, 116, 84, 65, 48; IR (KBr): 3425, 2957, 1673 cm^{-1}. Anal. Calcd for $C_{13}H_{14}ClNO_2$: C, 62.01; H, 5.64; N, 5.56%; Found: C, 62.24; H, 5.74; N, 5.68%.

4.3.9. 2-[(2-Chloro-5-ethyl pyridine-3-yl)(hydroxy)-methyl]cyclohex-2-ene-1-one (2i). Pale yellow; Mp 98–102 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.06 (d, J=2.4 Hz, 1H), 7.76 (d, J=2.4 Hz, 1H), 6.5 (t, J=4.0 Hz, 1H), 5.72 (s, 1H), 4.22 (br, 1H), 2.64 (q, J=8.0 Hz, 2H), 2.5 (m, 2H), 2.38 (m, 2H), 1.99 (m, 2H), 1.28 (t, J=8.0 Hz, 3H); ^{13}C NMR: (50 MHz, $CDCl_3$): δ 200.2, 149.4, 148.9, 139.1, 138.8, 135.3, 134.2, 128.1, 67.7, 38.0, 25.9, 25.8, 22.3, 14.9; MS EI (*m/z*): 265 (M+), 230, 212, 130, 98, 79, 62. Anal. Calcd for $C_{14}H_{16}ClNO_2$: C, 63.28; H, 6.07; N, 5.27%; Found: C, 63.54; H, 6.42; N, 5.44%.

4.3.10. 2-[(2-Chloro-5-phenylpyridine-3-yl)(hydroxy)-methyl]cyclohex-2-en-1-one (2j). White solid; Mp 116–118 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.51 (d, J=2.6 Hz, 1H), 8.19 (d, J=2.6 Hz, 1H), 7.34–7.64 (m, 5H), 6.54 (t, J=4.3 Hz, 1H), 5.8 (s, 1H), 3.88 (br, 1H), 2.35–2.6 (m, 4H), 2.05 (m, 2H); ^{13}C NMR: (50 MHz, $CDCl_3$): δ 200.3, 148.5, 148.0, 146.4, 138.6, 136.4, 136.0, 135.8, 135.4, 129.0, 128.4, 127.0, 68.5, 38.3, 25.8, 22.3; MS (EI) *m/z*: 313 (M+), 278, 260, 217, 71, 57; IR (KBr): 3424, 2924, 1685 cm^{-1}. Anal. Calcd for $C_{18}H_{16}ClNO_2$: C, 68.90; H, 5.14; N, 4.46%; Found: C, 69.12; H, 5.27; N, 4.48%.

4.3.11. 2-[(2-Chloro-5-(4-methoxyphenyl) pyridine-3-yl)-(hydroxy)methyl]cyclohex-2-en-1-one (2k). Pale yellow; Mp 110–113 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.45 (d, J=2.1 Hz, 1H), 8.12 (d, J=2.1 Hz, 1H), 7.5 (m, 2H), 6.95 (m, 2H), 6.55 (t, J=4.3 Hz, 1H), 5.78 (s, 1H), 3.82 (s, 3H), 2.3–2.6 (m, 4H), 2.02 (m, 2H); ^{13}C NMR: (50 MHz, $CDCl_3$): δ 200.5, 160.1, 148.5, 147.4, 146.1, 138.7, 135.7, 135.3, 135.2, 128.8, 128.2, 114.6, 68.8, 55.4, 38.4, 25.8, 22.4, 19.1; MS (EI) *m/z*: 343 (M+), 308, 290, 247, 107, 65. Anal. Calcd for $C_{19}H_{18}ClNO_3$: C, 66.38; H, 5.28; N, 4.07%; Found: C, 66.97; H, 5.56; N, 4.34%.

4.3.12. 2-[(2-Chloro-5-methyl-6-phenylpyridine-3-yl)-(hydroxy)methyl]cyclohex-2-en-1-one (2l). White solid; Mp 134–136 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.87 (s, 1H), 7.35–7.55 (m, 5H), 6.65 (t, J=3.9 Hz, 1H), 5.80 (s, 1H), 3.86 (br, 1H), 2.5 (m, 2H), 2.41 (m, 2H), 2.4 (s, 3H), 2.0 (m, 2H); ^{13}C NMR: (50 MHz, $CDCl_3$): δ 200.6, 157.7, 148.5, 146.0, 139.9, 138.9, 138.7, 133.4, 130.2, 129.0, 128.4, 128.2, 68.7, 38.4, 25.8, 22.4, 19.4; MS (EI) *m/z*: 327 (M$^+$), 311, 291, 273, 249, 218, 117; IR (KBr): 3405, 2912, 1612 cm^{-1}. Anal. Calcd for $C_{19}H_{18}ClNO_2$: C, 69.62; H, 5.53; N, 4.27%; Found: C, 70.07; H, 5.74; N, 4.56%.

4.3.13. Methyl-6-chloro-5-[hydroxy(6-oxo-cyclohex-1-en-1-yl)methyl]pyridine-2-carboxylate (2m). Pale yellow; Mp 67–70 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.18 (d, J=7.5 Hz, 2H), 8.12 (d, J=7.5 Hz, 1H), 6.56 (t, J=3.8 Hz, 1H), 5.85 (s, 1H), 4.00 (s, 3H), 2.5 (m, 2H), 2.4 (m, 2H), 2.05 (m, 2H); ^{13}C NMR: (50 MHz, $CDCl_3$): δ 199.9, 164.3, 149.2, 148.7, 146.8, 139.9, 138.3, 123.9, 68.5, 52.9, 38.2, 25.7, 22.2; MS (EI) *m/z*: 295 (M+), 260, 232, 229, 201, 160, 112, 59; IR (KBr): 3494, 2953, 1727, 1651, 1315 cm^{-1}. Anal. Calcd for $C_{14}H_{14}ClNO_4$: C, 56.86; H, 4.77; N, 4.74%; Found: C, 57.12; H, 4.98; N, 4.98%.

4.3.14. Ethyl 6-chloro-5-[hydroxy(5-oxo-1-cyclohexenyl)methyl]-2-phenyl nicotinate (2n). Pale yellow; Mp 112–115 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.87 (s, 1H), 7.6 (m, 2H), 7.4 (m, 3H), 6.60 (t, J=4.4 Hz, 1H), 5.95 (s, 1H), 4.2 (q, J=7.5 Hz, 2H), 2.38–2.57 (m, 4H), 2.02 (m, 2H), 1.1 (t, J=7.5 Hz, 3H); MS (EI) *m/z*: 385 (M+), 350, 332, 321, 278, 165, 73; IR (KBr): 3421, 2949, 1746, 1678, 1347 cm^{-1}. Anal. Calcd for $C_{21}H_{20}ClNO_4$: C, 65.37; H, 5.22; N, 3.63%; Found: C, 65.78; H, 5.67; N, 3.78%.

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References and notes

1. (a) Baylis, A. B.; Hillman, M. E. D. German Patent 2,155,113, 1972; *Chem. Abstr.* **1972**, *77*, 34174q. (b) Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653. (c) Basavaiah, D.; Dharma Rao, P.; Suguna, Hy. *Tetrahedron* **1996**, *52*, 8001. (d) Ciganek, E. *Org. React.* **1997**, *51*, 201. (e) Basavaiah, D.; Jaganmohan Rao, A.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811.
2. (a) Shi, M.; Li, C.-Q.; Jiang, J.-K. *Chem. Commun.* **2001**, 833. (b) Langer, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 3049.
3. Luo, S.; Mi, X.; Xu, H.; Wang, P. G.; Cheng, J.-P. *J. Org. Chem.* **2004**, *69*, 8413.
4. Gatri, R.; EI Gaied, M. M. *Tetrahedron Lett.* **2002**, *43*, 7835.
5. Luo, S.; Mi, X.; Xu, H.; Wang, P. G.; Cheng, J.-P. *Tetrahedron Lett.* **2004**, *45*, 5171.
6. Luo, S.; Wang, P. G.; Cheng, J.-P. *J. Org. Chem.* **2004**, *69*, 555.
7. Iwama, T.; Kinoshita, H.; Kataoka, T. *Tetahedron Lett.* **1999**, *40*, 3741.
8. Kawamura, M.; Kobayashi, S. *Tetrahedron Lett.* **1999**, *40*, 1539.
9. Zhu, Y.-H.; Vogel, P. *Synlett* **2001**, 79.
10. Yamada, Y. M. A.; Ikegami, S. *Tetrahedron Lett.* **2000**, *41*, 2165.
11. Shi, M.; Xu, Y.-M. *Chem. Commun.* **2001**, 1876.
12. Li, G.; Wei, H.-X.; Gao, J. J.; Caputo, T. D. *Tetrahedron Lett.* **2000**, *41*, 1.
13. Jauch, J. *J. Org. Chem.* **2001**, *66*, 609.
14. (a) Rezgui, F.; EI Gaied, M. M. *Tetrahedron Lett.* **1998**, *39*, 5965. (b) Lee, K. Y.; Gong, J. H.; Kim, J. N. *Bull. Korean. Chem. Soc.* **2002**, *23*, 659.
15. Patra, A.; Batra, S.; Joshi, B. S.; Roy, R.; Kundu, B.; Bhaduri, A. *J. Org. Chem.* **2002**, *67*, 5783.
16. Luo, S.; Zhang, B.; He, J.; Janczuk, A.; Wang, P. G.; Cheng, J.-P. *Tetrahedron Lett.* **2002**, *43*, 7369.
17. Gangadasu, B.; Chinaraju. B.; Jayathirtha Rao. V., U.S. Patent 6,479,664, 2002; *Chem.Abstr.* **2002**, *137*, 352892.
18. Aggarwal, V. K.; Dean, D. K.; Mereu, A.; Williams, R. *J. Org. Chem.* **2002**, *67*, 510.
19. A colorless cube crystal of compound **1** was obtained from chloroform. The crystal belongs to the triclinic crystal system, space group P-1 with $a=7.6654$ (7), $b=7.8985$ (7), $c=10.6559$ (9) Å, $\alpha=79.675(1)°$, $\beta=77.282(1)°$, $\gamma=62.600(1)°$; $V=556.47(8)$ Å^3, $Z=2$, $\lambda=0.71073$ Å, μ(Mo Kα)= 0.326 mm^{-1}, $F_{000}=246$, $T=273(2)$ K. Data collection yielded 4029 reflections resulting in 1955 unique ($I>2\sigma I$), θ range: 1.97–25.0°. Full matrix least-squares refinement led to a final $R=0.0364$, $wR=0.0960$ and GOF = 1.042. Intensity data were measured on Bruker Smart Apex [Bruker, 2001, SAINT (version 6.28a) and SMART (version 5.625) Bruker AXS inc., Madison, Wisconsin, USA.] with CCD area-detector. Crystallographic data for the structure of **2a** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 275627.
20. Bernstein, J.; Davis, R. E.; Shimoni, L.; Chang, N. L. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1555.
21. Palinko, I. *Acta Crystallogr., sect. B* **1999**, *55*, 216.
22. Etter, M. C. *Acc. Chem. Res.* **1990**, *23*, 120.

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α-Amido sulfones from natural α-amino acids and their reaction with carbon nucleophiles

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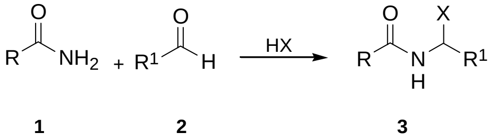
Abstract—Amides obtained from *N*-carbamoyl α-amino acids react with aldehydes in the presence of benzenesulfinic acid to give α-amido sulfones in good yield. These derivatives act as equivalents of *N*-acylimines in the reaction with nucleophiles leading to the corresponding addition products. The utilization of the lithium enolate of alkyl acetates as a nucleophile allows the preparation of α,β-dipeptides, while a two-step procedure involving nitromethylation and Nef conversion leads to the synthesis of α,α-dipeptides.

1. Introduction

α-Amino acids contain a well-known structural unit, which is present in a plethora of important biologically active compounds. Furthermore, natural α-amino acids represent a valuable and cheap source of enantiomerically pure compounds suitable for diastereoselective syntheses.[1] Recently proline and other peptide derivatives have been successfully employed as organocatalysts in a number of processes devoted to the synthesis of enantiomerically enriched compounds.[2] The carboxylic group in α-amino acids offers a number of synthetic opportunities of linkage with other organic frameworks such as amino derivatives giving *N*-substituted amides and peptides. A complementary approach consists of the conversion of the carboxylic group into an amido group that can be used as substrate in different coupling processes leading to a functional implementation of the original α-amino acid framework. Coupling reactions with diazoesters represent an effective procedure for the synthesis of peptides and oxazole derivatives.[3] Optically active α-amino amides are known to react with glyoxalate esters giving α-hydroxy *N*-acylamino derivatives that, after acetylation, are converted into biologically active compounds.[4] Condensation of *N*-unsubstituted amides **1** with aldehydes **2** in the presence of a nucleophile HX provides a general and straightforward entry to α-substituted *N*-acylamino derivatives **3** (Scheme 1).



Scheme 1.

Compounds **3** can be considered as stable precursors of reactive *N*-acylimines that are obtained by elimination of HX from **3** under basic conditions. *N*-Acylimines are strong electrophiles that quickly react with a large variety of nucleophilic reagents giving the corresponding addition products.[5] The utilization of α-amino acid amides in the synthesis of compounds **3** has been exploited several years ago by Katritzy et al. who prepared a number of those derivatives using benzotriazole as nucleophilic reagent.[6]

2. Results and discussion

In this paper, we report the synthesis of α-amidoalkylphenyl sulfones from optically active α-amino acid amides and their utilization as *N*-acylimino equivalents in the reaction with different nucleophiles.[7] Condensation of *N*-protected amino acid amides **4**[8] with aldehydes **5** in the presence of benzenesulfinic acid affords the corresponding sulfones **6** in good yield (Scheme 2, Table 1).

Contrary to what was observed in the synthesis of α-amido sulfones from chiral aldehydes that usually occurs with high *syn* diastereoselectivity, reaction of amides **4** gives rise to an almost equimolar mixture of diastereomers in sulfones **6**.[9] Grignard reagents are particularly effective in promoting

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Keywords: Amino acids; Carbanions; Dipeptides; Imines; Sulfones.

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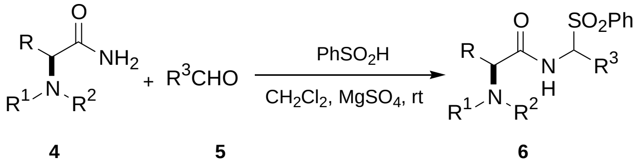


4	R	R^1	R^2
a	$PhCH_2$	H	Boc
b	$PhCH_2$	H	Cbz
c	$PhCH_2$	Phth	
d	Me_2CH	H	Boc
e	Ph	H	Boc
f	$-(CH_2)_3-$		Boc

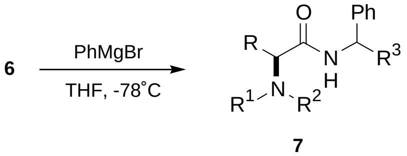
Scheme 2.

Table 1. Synthesis of α-amido sulfones **6** from α-amino acid amides **4**

Entry	Amide **4**	Aldehyde **5**, R^3	Sulfone **6**	Yield (%)[a]
1	**4a**	Et	**6a**	85
2	**4a**	$Ph(CH_2)_2$	**6b**	95
3	**4a**	Me_2CHCH_2	**6c**	81
4	**4a**	Me	**6d**	93
5	**4a**	Ph	**6e**	81
6	**4b**	Et	**6f**	88
7	**4b**	$Ph(CH_2)_2$	**6g**	89
8	**4c**	Et	**6h**	78
9	**4d**	Et	**6i**	91
10	**4d**	$Ph(CH_2)_2$	**6j**	87
11	**4d**	c-C_6H_{11}	**6k**	90
12	**4d**	n-C_9H_{19}	**6l**	83
13	**4e**	Et	**6m**	92
14	**4f**	Et	**6n**	90

[a] Yields of pure, isolated products.

the tandem elimination–addition from α-amido sulfones and therefore, this class of nucleophilic reagents has been initially tested for the reaction with sulfones **6**.[10] Reaction of phenylmagnesium bromide with α-amido sulfones **6** leads to the corresponding adducts **7** in good yield but poor diastereoselectivity (dr = 3:2) (Scheme 3, Table 2).



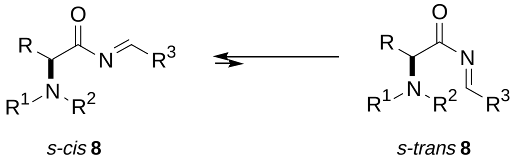
Scheme 3.

Table 2. Reaction of α-amido sulfones **6** with PhMgBr

Entry	Sulfone **6**	Amide **7**	Yield (%)[a]
1	**6a**	**7a**	85
2	**6b**	**7b**	90
3	**6c**	**7c**	77
4	**6d**	**7d**	84
5	**6f**	**7e**	88
6	**6h**	**7f**	71
7	**6i**	**7g**	91
8	**6j**	**7h**	82
9	**6n**	**7i**	87

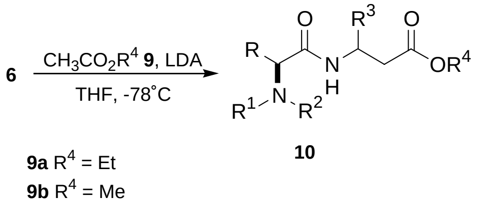
[a] Yields of pure, isolated products.

The disappointing stereochemical outcome of this reaction may be ascribed to the equilibrium in which rotamers **8** of the intermediate *N*-acylimine are involved (Scheme 4).



Scheme 4.

As demonstrated for the reaction of structurally related *N*-arylacyliminium ion derivatives with nucleophiles, high diastereoselectivities are obtained when the conformation of the imino intermediate is locked as in rotamer *s-trans*-**8**.[11] However, the preferred conformation in *N*-acylimines is usually *s-cis*-**8** owing to the lower steric repulsion between the imino and the chain frameworks. In conformation *s-cis*-**8** the electrophilic carbon is located too far from the stereogenic center to ensure a consistent diastereoselection in the subsequent nucleophilic addition.[12] Direct coupling of amino acids usually represents the most exploited procedure to prepare dipeptides and related compounds. Functionalization at the α-position in *N*-substituted glycine derivatives also provides a complementary approach to the synthesis of dipeptide systems.[13] Sulfones **6** are amenable to be used as valuable substrates for the preparation of α,β-dipeptides using a synthetic approach based on the direct addition of an ester enolate to the corresponding *N*-acylimine. The interest in α,β-dipeptides is justified by their potential biological activity, furthermore these compounds are key intermediates in the synthesis of some interesting molecular targets.[14] Thus, reaction of sulfones **6** with the lithium enolate of alkyl acetates **9** at −78 °C affords the corresponding adducts **10** in good yield (Scheme 5, Table 3).



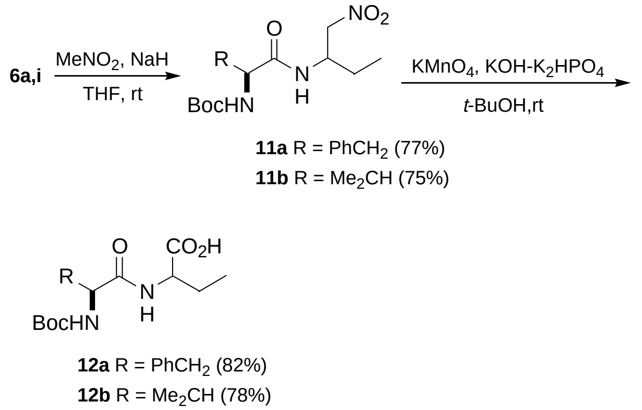
Scheme 5.

Table 3. Reaction of α-amido sulfones **6** with lithium enolate of alkyl acetates **9**

Entry	Sulfone **6**	Acetate **2**	Dipeptide **10**	Yield (%)[a]
1	**6e**	**9a**	**10a**	76
2	**6f**	**9a**	**10b**	72
3	**6g**	**9b**	**10c**	69
4	**6h**	**9a**	**10d**	72
5	**6i**	**9a**	**10e**	67
6	**6k**	**9a**	**10f**	75
7	**6l**	**9b**	**10g**	65
8	**6m**	**9a**	**10h**	78

[a] Yields of pure, isolated products.

Similarly to what was observed in the formation of derivatives **7**, the formation of α,β-dipeptides **10** occurs with poor diastereoselectivity. Attempt to use other metals such as zinc or titanium enolates did not provide any improvement in the efficiency of the process both in terms of chemical yield or in diastereoselectivity. Finally, we decided to apply our two-step procedure for the synthesis of α-amino acids to sulfones **6** with the aim to prepare α,α-dipeptides.[7h,15] Thus, representative sulfones **6a,i** have been made to react with nitromethane in the presence of sodium hydride to give the corresponding nitro derivatives **11** (Scheme 6). Nef conversion[16] of the nitromethyl group into a carboxylic group has been realized in oxidative conditions using $KMnO_4$ giving dipeptides **12**, once again as a diastereomeric mixture.



Scheme 6.

3. Conclusions

In conclusion, α-amido sulfones **6** can be prepared by reaction of *N*-carbamoyl amino acid amides with aldehydes in the presence of benzenesulfinic acid. These sulfones act as *N*-acylimino equivalents in the reaction with nucleophiles giving the corresponding adducts in good yield albeit with poor diastereoselectivity. Grignard reagents, lithium enolates of esters and sodium methanenitronate efficiently add to α-amido sulfones **6**. Among the products obtained with this procedure there are α,α- and α,β-dipeptide systems that are valuable synthetic intermediates and biologically active compounds.

4. Experimental

4.1. General

^1H NMR were recorded at 300 MHz on a Varian VXR300 in $CDCl_3$ as solvent. ^{13}C NMR were recorded at 75 MHz in $CDCl_3$ as solvent. Microanalyses were performed with a CHNS-O analyzer Model EA 1108 from Fisons Instruments. IR spectra were recorded with a Perkin-Elmer Paragon 500 FT-IR. GLC analyses were performed on a Hewlett-Packard 5890 equipped with a capillary column of fused silica (0.32 mm×25 m), stationary phase SE54. THF was dried by heating over sodium wire then distilled. Dichloromethane was dried by heating over calcium hydride and then distilled. Ethyl acetate was dried by heating over P_2O_5 and then distilled All chemicals used are available commercially. *N*-Carbamoyl α-amino acid amides **4** were prepared as described.[8]

4.2. General procedure for the preparation of phenylsulfonyl derivatives 6

Amide **4** (6 mmol) was dissolved in dichloromethane (30 mL) and then benzenesulfinic acid (7.5 mmol), the appropriate aldehyde **5** (5 mmol) and anhydrous $MgSO_4$ (0.5 g) were sequentially added at room temperature. The mixture was stirred for 12 h at room temperature and then filtered over a short pad of Florisil. Removal of the solvent afforded the crude sulfone **6**, which was purified by column chromatography (7:3 hexanes/ethyl acetate).

4.2.1. *tert*-Butyl *N*-(1-benzyl-2-oxo-2-[1-(phenylsulfonyl)propyl]aminoethyl)carbamate, 6a. Yield 85%. White solid mp 85–87 °C. IR (cm^{-1}, KBr) 3400, 1690, 1370, 1145. ^1H NMR diast. A. δ (ppm) 0.86 (t, 3H, $J=7.3$ Hz); 1.49 (s, 9H); 1.60–1.83 (m, 2H); 2.79–2.95 (m, 2H); 4.15–4.26 (m, 1H); 4.73 (d, 1H, $J=8.9$ Hz); 5.02–5.19 (m, 1H); 6.55 (d, 1H, $J=11.0$ Hz); 7.06–7.18 (m, 2H); 7.20–7.37 (m, 3H); 7.48–7.67 (m, 3H); 7.87 (dt, 2H, $J=1.8$, 7.0 Hz). Diast. B δ: 0.95 (t, 3H, $J=7.3$ Hz); 1.49 (s, 9H); 1.60–1.83 (m, 2H); 2.79–2.95 (m, 2H); 4.15–4.26 (m, 1H); 4.66 (d, 1H, $J=8.7$ Hz); 5.02–5.19 (m, 1H); 6.75 (d, 1H, $J=11.0$ Hz); 7.06–7.18 (m, 2H); 7.20–7.37 (m, 3H); 7.48–7.67 (m, 3H); 7.87 (dt, 2H, $J=1.8$, 7.0 Hz). ^{13}C NMR δ: 9.8, 10.0, 20.3, 20.4, 28.4, 28.5, 37.0, 38.1, 55.4, 56.3, 70.0, 70.3, 81.0, 81.4, 127.3, 129.0, 129.2, 129.4, 129.5, 134.3, 134.4, 136.2, 136.3, 155.4, 155.6, 171.3, 171.5. Anal. Calcd for $C_{23}H_{30}N_2O_5S$ (446.56): C, 61.86; H, 6.77; N, 6.27. Found: C, 61.93; H, 6.73; N, 6.31.

4.2.2. *tert*-Butyl *N*-(1-benzyl-2-oxo-2-[3-phenyl-1-(phenylsulfonyl)propyl]aminoethyl)carbamate, 6b. Yield 95%. White solid mp 115–117 °C. IR (cm^{-1}, KBr) 3405, 1693, 1376, 1148. ^1H NMR δ (ppm) 1.39 (s, 9H); 1.60–1.83 (m, 2H); 1.88–2.15 (m, 1H); 2.15–2.95 (m, 5H); 4.15–4.40 (m, 1H); 4.84–4.98 (m, 1H); 5.05–5.26 (m, 1H); 5.77–5.86 (m, 1H); 7.06–7.38 (m, 10H); 7.40–7.72 (m, 3H); 7.78–7.95 (m, 2H). Anal. Calcd for $C_{29}H_{34}N_2O_5S$ (522.66): C, 66.64; H, 6.56; N, 5.36. Found: C, 66.70; H, 6.61; N, 5.33.

4.2.3. *tert*-Butyl *N*-(1-benzyl-2-[3-methyl-1-(phenylsulfonyl)butyl]amino-2-oxoethyl)carbamate, 6c. Yield 81%. Colorless oil. IR (cm^{-1}, neat) 3390, 1698, 1372, 1145. ^1H NMR δ (ppm) 0.70–1.03 (m, 6H); 1.45 (s, 9H); 1.55–1.78 (m, 1H); 1.89–2.12 (m, 2H); 2.65–3.04 (m, 2H); 4.08–4.25 (m, 1H); 4.55–4.78 (m, 1H); 5.15–5.36 (m, 2H); 6.30–6.50 (m, 1H); 7.06–7.18 (m, 2H); 7.20–7.40 (m, 3H); 7.44–7.78 (m, 3H); 7.82–7.95 (m, 2H). Anal. Calcd for $C_{25}H_{34}N_2O_5S$ (474.61): C, 63.27; H, 7.22; N, 5.90. Found: C, 63.22; H, 7.26; N, 5.95.

4.2.4. *tert*-Butyl *N*-(1-benzyl-2-oxo-2-[1-(phenylsulfonyl)ethyl]aminoethyl)carbamate, 6d. Yield 93%. White solid mp 103–105 °C. IR (cm^{-1}, KBr) 3380, 1695, 1375, 1145. ^1H NMR diast. A. δ (ppm) 1.40 (s, 9H); 1.45 (d, 3H, $J=6.6$ Hz); 2.62–2.91 (m, 2H); 4.11–4.30 (m, 1H); 4.78 (d, 1H, $J=8.1$ Hz); 5.19–5.37 (m, 1H); 6.64 (d, 1H, $J=10.3$ Hz);

7.06–7.12 (m, 2H); 7.18–7.33 (m, 3H); 7.48–7.67 (m, 3H); 7.85–7.93 (m, 2H). Diast. B. δ: 1.41 (s, 9H); 1.60 (d, 3H, $J=7.0$ Hz); 2.75–2.98 (m, 2H); 4.15–4.28 (m, 1H); 4.71 (d, 1H, $J=8.1$ Hz); 5.25–5.30 (m, 1H); 6.84 (d, 1H, $J=10.2$ Hz); 7.06–7.12 (m, 2H); 7.18–7.33 (m, 3H); 7.48–7.67 (m, 3H); 7.85–7.93 (m, 2H). ^{13}C NMR δ: 13.0, 13.3, 28.4, 37.4, 38.4, 55.4, 56.0, 64.8, 65.0, 80.7, 81.0, 127.2, 127.3, 128.9, 129.2, 129.3, 129.4, 129.5, 134.1, 134.3, 136.2, 136.4, 155.4, 155.6, 170.7, 170.9. Anal. Calcd for $C_{22}H_{28}N_2O_5S$ (432.53): C, 61.09; H, 6.52; N, 6.48. Found: C, 61.14; H, 6.56; N, 6.53.

4.2.5. Benzyl *N*-(1-benzyl-2-oxo-2-[phenyl(phenylsulfonyl)methyl]aminoethyl)carbamate, 6e. Yield 81%. White solid mp 126–128 °C. IR (cm^{-1}, KBr) 3405, 1690, 1378, 1150. ^{1}H NMR δ (ppm) 1.40 (s, 9H); 2.80–3.03 (m, 2H); 4.25–4.40 (m, 1H); 4.70–5.05 (m, 2H); 6.23 (d, 1H, $J=11.3$ Hz); 7.10–7.70 (m, 12H); 7.80–7.97 (m, 2H); 8.10–8.18 (m, 1H). Anal. Calcd for $C_{30}H_{28}N_2O_5S$ (528.62): C, 68.16; H, 5.34; N, 5.30. Found: C, 68.21; H, 5.37; N, 5.26.

4.2.6. Benzyl *N*-(1-benzyl-2-oxo-2-[1-(phenylsulfonyl)propyl]aminoethyl)carbamate, 6f. Yield 88%. White solid mp 138–140 °C. IR (cm^{-1}, KBr) 3400, 1690, 1370, 1145. ^{1}H NMR δ (ppm) 0.72 (t, 3H, $J=7.3$ Hz, diast. A); 0.93 (t, 3H, $J=7.3$ Hz, diast. B); 1.53–1.86 (m, 1H); 2.08–2.40 (m, 1H); 2.65–2.97 (m, 2H); 4.40–4.58 (m, 1H); 5.00–5.30 (m, 3H); 5.46 (d, 1H, $J=8.7$ Hz, diast. B); 5.52 (d, 1H, $J=8.9$ Hz, diast. A); 7.06–7.70 (m, 13H); 7.80–7.98 (m, 2H). Anal. Calcd for $C_{26}H_{28}N_2O_5S$ (480.58): C, 64.98; H, 5.87; N, 5.83. Found: C, 65.03; H, 5.83; N, 5.88.

4.2.7. Benzyl *N*-(1-benzyl-2-oxo-2-[3-phenyl-1-(phenylsulfonyl)propyl]aminoethyl)carbamate, 6g. Yield 89%. White solid mp 121–123 °C. IR (cm^{-1}, KBr) 3390, 1696, 1370, 1145. ^{1}H NMR δ (ppm) 2.37–2.50 (m, 2H); 2.61–2.69 (m, 2H); 2.80–3.00 (m, 2H); 4.22–4.50 (m, 1H); 4.97 (d, 1H, $J=8.9$ Hz); 5.06–5.35 (m, 3H); 6.83–7.70 (m, 19H); 7.79–7.90 (m, 2H). ^{13}C NMR δ: 28.4, 28.5, 31.2, 31.5, 35.4, 37.3, 38.5, 55.9, 56.4, 67.5, 68.4, 68.8, 126.6, 127.4, 128.3, 128.6, 128.7, 128.8, 129.0, 129.2, 129.3, 129.4, 129.5, 134.3, 134.4, 135.9, 136.0, 136.4, 136.6, 139.9, 140.0, 156.0, 156.3, 170.9. Anal. Calcd for $C_{32}H_{32}N_2O_5S$ (556.67): C, 69.04; H, 5.79; N, 5.03. Found: C, 69.00; H, 5.82; N, 4.99.

4.2.8. *N*1-[1-(Phenylsulfonyl)propyl]-2-(1,3-dioxo-2,3-dihydro-1*H*-2-isoindolyl)-3-phenylpropanamide, 6h. Yield 78%. Colorless oil. IR (cm^{-1}, neat) 3300, 1690, 1370, 1145. ^{1}H NMR δ (ppm) 0.98 (t, 3H, $J=7.3$ Hz, diast. B); 1.06 (t, 3H, $J=7.3$ Hz, diast. A); 1.65–1.90 (m, 1H); 2.20–2.44 (m, 1H); 3.29–3.35 (m, 2H); 4.79 (t, 1H, $J=8.1$ Hz, diast. A); 4.92 (dd, 1H, $J=7.0$, 9.5 Hz, diast. B); 5.18–5.25 (m, 1H); 7.00–7.20 (m, 5H); 7.40–7.90 (m, 9H). ^{13}C NMR δ: 10.0, 10.1, 20.1, 20.3, 34.7, 34.7, 55.8, 55.9, 70.3, 70.5, 123.7, 123.8, 127.2, 127.3, 128.7, 128.9, 129.1, 129.3, 134.2, 134.4, 134.5, 134.6, 136.1, 136.2, 136.4, 136.8, 167.9, 168.2, 168.5. Anal. Calcd for $C_{26}H_{24}N_2O_5S$ (476.55): C, 65.53; H, 5.08; N, 5.88. Found: C, 65.59; H, 5.12; N, 5.91.

4.2.9. *tert*-Butyl *N*-[2-methyl-1-([1-(phenylsulfonyl)propyl]aminocarbonyl)propyl]carbamate, 6i. Yield 91%. White solid mp 152–154 °C. IR (cm^{-1}, KBr) 3405, 1694, 1373, 1145. ^{1}H NMR δ (ppm) diast. A. 0.64–0.88 (m, 6H); 1.04 (t, 3H, $J=7.3$ Hz); 1.49 (s, 9H); 1.75–1.95 (m, 1H); 1.98–2.10 (m, 2H); 3.80–3.98 (m, 1H); 4.67 (d, 1H, $J=8.5$ Hz); 5.08–5.27 (m, 1H); 6.58 (d, 1H, $J=9.9$ Hz); 7.46–7.70 (m, 3H); 7.85–7.96 (m, 2H). Diast. B. δ: 0.64–0.88 (m, 6H); 1.02 (t, 3H, $J=7.3$ Hz); 1.47 (s, 9H); 1.75–1.95 (m, 1H); 2.20–2.43 (m, 2H); 3.63–3.79 (m, 1H); 4.82 (d, 1H, $J=8.6$ Hz); 5.08–5.27 (m, 1H); 6.58 (d, 1H, $J=9.9$ Hz); 7.46–7.70 (m, 3H); 7.85–7.96 (m, 2H). ^{13}C NMR δ: 10.0, 17.5, 19.4, 20.5, 20.7, 28.4, 28.5, 29.6, 30.3, 60.2, 70.0, 81.4, 129.3, 129.4, 134.2, 136.9, 155.3, 155.5, 171.5, 171.6. Anal. Calcd for $C_{19}H_{30}N_2O_5S$ (398.53): C, 57.26; H, 7.59; N, 7.03. Found: C, 57.31; H, 7.63; N, 6.98.

4.2.10. *tert*-Butyl *N*-[2-methyl-1-([3-phenyl-1-(phenylsulfonyl)propyl]aminocarbonyl)propyl] carbamate, 6j. Yield 87%. White solid mp 112–114 °C. IR (cm^{-1}, KBr) 3450, 1695, 1375, 1145. ^{1}H NMR δ (ppm) diast. A. 0.70 (d, 3H, $J=7.0$ Hz); 0.84 (d, 3H, $J=7.0$ Hz); 1.48 (s, 9H); 1.80–2.25 (m, 3H); 2.42–2.90 (m, 2H); 3.83–3.90 (m, 1H); 4.85 (d, 1H, $J=8.9$ Hz); 5.10–5.37 (m, 1H); 7.08–7.30 (m, 6H); 7.46–7.66 (m, 3H); 7.85–7.96 (m, 2H). Diast. B. 0.73 (d, 3H, $J=6.6$ Hz); 0.76 (d, 3H, $J=6.6$ Hz); 1.43 (s, 9H); 1.80–2.25 (m, 3H); 2.42–2.90 (m, 2H); 3.70–3.79 (m, 1H); 5.02 (d, 1H, $J=8.9$ Hz); 5.10–5.37 (m, 1H); 7.08–7.30 (m, 6H); 7.46–7.66 (m, 3H); 7.85–7.96 (m, 2H). ^{13}C NMR δ: 14.3, 17.6, 19.4, 21.2, 28.4, 28.5, 28.6, 28.8, 30.6, 31.5, 59.8, 60.6, 68.3, 68.4, 80.5, 80.6, 126.6, 126.7, 128.4, 128.8, 129.1, 129.3, 134.2, 134.3, 136.6, 139.8, 140.0, 156.0, 156.2, 171.5, 171.9. Anal. Calcd for $C_{25}H_{34}N_2O_5S$ (474.61): C, 63.27; H, 7.22; N, 5.90. Found: C, 63.33; H, 7.19; N, 5.94.

4.2.11. *tert*-Butyl *N*-[1-([cyclohexyl(phenylsulfonyl)methyl]aminocarbonyl)-2-methylpropyl] carbamate, 6k. Yield 90%. Waxy solid. IR (cm^{-1}, neat) 3400, 1690, 1375, 1145. ^{1}H NMR δ (ppm) diast. A. 0.66 (d, 3H, $J=7.0$ Hz); 0.81 (d, 3H, $J=7.0$ Hz); 0.98–1.45 (m, 5H); 1.50 (s, 9H); 1.60–1.88 (m, 4H); 1.89–2.07 (m, 1H); 2.10–2.22 (m, 1H); 2.40–2.58 (m, 1H); 3.70 (dd, 1H, $J=6.6$, 8.8 Hz); 4.68 (d, 1H, $J=8.1$ Hz); 5.13 (dd, 1H, $J=3.7$, 10.6 Hz); 6.79 (d, 1H, $J=11.0$ Hz); 7.47–7.65 (m, 3H); 7.88–7.95 (m, 2H). Diast. B. ^{1}H NMR δ: 0.69 (d, 3H, $J=6.6$ Hz); 0.78 (d, 3H, $J=6.6$ Hz); 0.98–1.45 (m, 5H); 1.48 (s, 9H); 1.60–1.88 (m, 4H); 1.89–2.07 (m, 1H); 2.10–2.22 (m, 1H); 2.40–2.58 (m, 1H); 3.87 (dd, 1H, $J=5.8$, 8.1 Hz); 4.85 (d, 1H, $J=8.7$ Hz); 5.13 (dd, 1H, $J=3.7$, 10.6 Hz); 6.79 (d, 1H, $J=11.0$ Hz); 7.47–7.65 (m, 3H); 7.88–7.95 (m, 2H). ^{13}C NMR δ: 17.6, 19.4, 19.5, 25.5, 25.8, 27.5, 28.5, 30.9, 36.8, 37.0, 60.2, 72.2, 80.7, 128.7, 128.9, 129.2, 134.1, 137.9, 156.0, 156.2, 171.4, 171.5. Anal. Calcd for $C_{25}H_{36}N_2O_5S$ (476.63): C, 63.00; H, 7.61; N, 5.88. Found: C, 63.06; H, 7.65; N, 5.82.

4.2.12. *tert*-Butyl *N*-[2-methyl-1-([1-(phenylsulfonyl)decyl]aminocarbonyl)propyl]carbamate, 6l. Yield 83%. White solid mp 95–98 °C. IR (cm^{-1}, KBr) 3400, 1690, 1370, 1145. ^{1}H NMR δ (ppm) diast. A. 0.72 (d, 3H, $J=6.6$ Hz); 0.84 (t, 3H, $J=7.0$ Hz); 0.88–0.95 (m, 3H); 1.20–1.38 (m, 14H); 1.49 (s, 9H); 1.60–1.70 (m, 2H); 1.90–2.10 (m, 1H); 3.82–3.90 (m, 1H); 4.71 (d, 1H, $J=8.6$ Hz); 5.17–5.35 (m, 1H); 6.64–6.80 (m, 1H); 7.50–7.73 (m, 3H); 7.86–7.95 (m, 2H). Diast. B. 0.71 (d, 3H, $J=6.6$ Hz); 0.84

(t, 3H, $J=7.0$ Hz); 0.88–0.95 (m, 3H); 1.20–1.38 (m, 14H); 1.46 (s, 9H); 1.60–1.70 (m, 2H); 2.13–2.35 (m, 1H); 3.69–3.76 (m, 1H); 4.86 (d, 1H, $J=8.8$ Hz); 5.17–5.35 (m, 1H); 6.64–6.80 (m, 1H); 7.50–7.73 (m, 3H); 7.86–7.95 (m, 2H). ^{13}C NMR δ: 14.3, 17.5, 19.4, 19.5, 22.8, 24.9, 25.3, 27.0, 28.4, 30.4, 59.9, 60.0, 76.9, 81.4, 81.5, 129.1, 129.3, 129.4, 131.7, 134.2, 136.8, 155.9, 156.0, 171.4, 171.5. Anal. Calcd for $C_{26}H_{44}N_2O_5S$ (496.70): C, 62.87; H, 8.93; N, 5.64. Found: C, 62.93; H, 8.89; N, 5.61.

4.2.13. *tert*-Butyl *N*-(2-oxo-1-phenyl-2-[1-(phenylsulfonyl)propyl]aminoethyl)carbamate, 6m. Yield 92%. White solid mp 143–146 °C. IR (cm^{-1}, KBr) 3390, 1695, 1370, 1145. ^{1}H NMR δ diast. A. 0.81 (t, 3H, $J=7.3$ Hz); 1.41 (s, 9H); 1.63–1.90 (m, 1H); 2.16–2.47 (m, 1H); 5.08–5.25 (m, 2H); 5.42 (d, 1H, $J=8.0$ Hz); 6.60–6.78 (m, 1H); 7.15–7.37 (m, 5H); 7.44–7.67 (m, 3H); 7.87–7.98 (m, 2H). Diast. B. 1.06 (t, 3H, $J=7.3$ Hz); 1.41 (s, 9H); 1.63–1.90 (m, 1H); 2.16–2.47 (m, 1H); 5.08–5.25 (m, 2H); 5.59 (d, 1H, $J=8.3$ Hz); 6.60–6.78 (m, 1H); 7.15–7.37 (m, 5H); 7.44–7.67 (m, 3H); 7.87–7.98 (m, 2H). ^{13}C NMR δ: 9.6, 10.0, 20.3, 20.6, 28.4, 58.6, 58.9, 70.2, 70.3, 77.4 80.5, 80.6, 127.3, 127.4, 128.5, 128.9, 129.3, 133.9, 134.2, 136.4, 136.6, 137.1, 137.2, 155.1, 155.2, 170.4, 171.4. Anal. Calcd for $C_{22}H_{28}N_2O_5S$ (432.53): C, 61.09; H, 6.52; N, 6.48. Found: C, 61.13; H, 6.58; N, 6.52.

4.2.14. *tert*-Butyl 2-([1-(phenylsulfonyl)propyl]amino carbonyl)-1-pyrrolidinecarboxylate, 6n. Yield 90%. Yellow oil. IR (cm^{-1}, neat) 3400, 1690, 1370, 1148. ^{1}H NMR δ diast. A. 1.00 (t, 3H, $J=7.3$ Hz); 1.48 (s, 9H); 1.63–1.93 (m, 4H); 2.19–2.40 (m, 2H); 3.16–3.45 (m, 2H); 4.08–4.30 (m, 2H); 5.02–5.29 (m, 1H); 7.44–7.70 (m, 3H); 7.80–7.96 (m, 2H). Diast. B. 1.07 (t, 3H, $J=7.3$ Hz); 1.53 (s, 9H); 1.63–1.93 (m, 4H); 2.19–2.40 (m, 2H); 3.16–3.45 (m, 2H); 4.08–4.30 (m, 2H); 5.02–5.29 (m, 1H); 7.44–7.70 (m, 3H); 7.80–7.96 (m, 2H). Anal. Calcd for $C_{19}H_{28}N_2O_5S$ (396.50): C, 57.56; H, 7.12; N, 7.07. Found: C, 57.61; H, 7.16; N, 7.03.

4.3. General procedure for the reaction of phenylsulfonyl derivatives 6 with PhMgBr

Sulfone **6** (1 mmol) was dissolved in dry THF (15 mL) and the solution was cooled to −78 °C. Phenylmagnesium bromide (2 mmol, 1 M in THF) was then added dropwise over 5 min and after 1 h at −78 °C the mixture was quenched with saturated aqueous NH_4Cl (8 mL). After extraction of the aqueous phase with CH_2Cl_2 (3×15 mL) the organic extracts were dried over $MgSO_4$. Evaporation of the solvent at reduced pressure gave the crude phenyl derivative, which was purified by column chromatography (hexanes/ethyl acetate 8:2).

4.3.1. *tert*-Butyl *N*-1-benzyl-2-oxo-2-[(1-phenylpropyl) amino]ethylcarbamate, 7a. Yield 85%. Colorless oil. IR (cm^{-1}, neat) 3405, 1695. ^{1}H NMR δ (ppm) 0.74 (t, 3H, $J=7.3$ Hz, diast. A); 0.83 (t, 3H, $J=7.3$ Hz, diast. B); 1.41 (s, 9H); 1.57–1.85 (m, 2H); 2.95–3.18 (m, 2H); 4.23–4.40 (m, 1H); 4.70–4.90 (m, 1H); 5.03–5.21 (m, 1H); 6.10–6.22 (m, 1H); 7.05–7.38 (m, 10H). ^{13}C NMR δ: 10.6, 10.7, 27.0, 28.4, 29.2, 38.5, 55.0, 55.1, 56.2, 80.8, 126.7, 127.0, 127.1, 127.3, 127.4, 128.6, 128.8, 128.9, 129.4, 129.5, 136.8, 136.9, 141.7, 141.8, 155.6, 170.4, 170.5. Anal. Calcd for $C_{23}H_{30}N_2O_3$ (382.50): C, 72.22; H, 7.91; N, 7.32. Found: C, 72.27; H, 7.96; N, 7.33.

4.3.2. *tert*-Butyl *N*-1-benzyl-2-[(1,3-diphenylpropyl) amino]-2-oxoethylcarbamate, 7b. Yield 90%. Waxy solid. IR (cm^{-1}, neat) 3400, 1695. ^{1}H NMR δ (ppm) 1.40 (s, 9H); 1.85–2.10 (m, 2H); 2.38–2.65 (m, 2H); 4.2–4.43 (m, 1H); 4.80–5.10 (m, 2H); 6.00–6.18 (m, 1H); 7.05–7.38 (m, 15H). ^{13}C NMR δ: 28.45, 32.4, 32.6, 37.9, 38.4, 53.3, 53.4, 56.3, 80.2, 126.1, 126.7, 127.1, 127.6, 127.8, 128.5, 128.6, 128.8, 128.9, 129.4, 129.5, 133.4, 136.8, 136.9, 141.3, 141.6, 157.1, 170.4, 170.5. Anal. Calcd for $C_{29}H_{34}N_2O_3$ (458.60): C, 75.95; H, 7.47; N, 6.11. Found: C, 76.01; H, 7.43; N, 6.13.

4.3.3. *tert*-Butyl *N*-1-benzyl-2-[(3-methyl-1-phenylbutyl) amino]-2-oxoethylcarbamate, 7c. Yield 77%. White solid mp 148–151 °C. IR (cm^{-1}, KBr) 3400, 1690. ^{1}H NMR δ (ppm) 0.86 (d, 3H, $J=6.6$ Hz); 0.89 (d, 3H, $J=6.6$ Hz); 1.44 (s, 9H); 1.5–1.83 (m, 3H); 2.91–3.15 (m, 2H); 4.20–4.36 (m, 1H); 4.80–5.20 (m, 2H); 5.90–6.10 (m, 1H); 7.05–7.38 (m, 10H). ^{13}C NMR δ: 22.4, 22.5, 24.9, 25.0, 28.4, 38.4, 45.7, 51.7, 51.9, 56.2, 80.4, 126.6, 1271, 127.3, 128.7, 128.9, 129.5, 129.6, 142.4, 142.6, 155.9, 170.3, 170.4. Anal. Calcd for $C_{25}H_{34}N_2O_3$ (410.55): C, 73.14; H, 8.35; N, 6.82. Found: C, 73.19; H, 8.31; N, 6.85.

4.3.4. *tert*-Butyl *N*-1-benzyl-2-oxo-2-[(1-phenylpropyl) amino]methylcarbamate, 7d. Yield 84% Spectroscopic data are in full agreement with those reported.[17]

4.3.5. Benzyl *N*-1-benzyl-2-oxo-2-[(1-phenylpropyl) amino]ethyl carbamate, 7e. Yield 88%. White solid mp 110–112 °C. IR (cm^{-1}, KBr) 3405, 1690. ^{1}H NMR δ (ppm) 0.72 (t, 3H, $J=7.5$ Hz, diast. A); 0.80 (t, 3H, $J=7.3$ Hz, diast. B); 1.55–1.80 (m, 2H); 2.85–3.20 (m, 2H); 4.33–4.56 (m, 1H); 4.68–4.90 (m, 1H); 5.05 (s, 2H); 5.45–5.70 (m, 1H); 6.15–6.38 (m, 1H); 7.02–7.40 (m, 15H). ^{13}C NMR δ: 10.6, 10.7, 29.1, 38.8, 39.0, 55.1, 55.3, 56.6, 67.2, 126.6, 127.0, 127.4, 128.1, 128.3, 127.7, 128.9, 129.4, 129.5, 136.3, 136.7, 141.8, 156.1, 170.2, 170.3. Anal. Calcd for $C_{26}H_{28}N_2O_3$ (416.52): C, 74.98; H, 6.78; N, 6.73. Found: C, 74.92; H, 6.73; N, 6.75.

4.3.6. *N*1-(1-Phenylpropyl)-2-(1,3-dioxo-2,3-dihydro-1*H*-2-isoindolyl)-3-phenylpropanamide, 7f. Yield 71%. Waxy solid. IR (cm^{-1}, neat) 3400, 1695. ^{1}H NMR δ (ppm) 0.70 (t, 3H, $J=7.3$ Hz, diast. A); 0.81 (t, 3H, $J=7.3$ Hz, diast. B); 1.50–1.80 (m, 2H); 3.33–3.84 (m, 2H); 4.20–4.36 (m, 1H); 4.55–4.77 (m, 1H); 5.47–5.55 (m, 1H, diast. A); 5.75–5.85 (m, 1H, diast. B); 6.80–7.30 (m, 11H); 7.38–7.60 (m, 2H); 7.78–7.90 (m, 1H). Anal. Calcd for $C_{26}H_{24}N_2O_3$ (412.48): C, 75.71; H, 5.86; N, 6.79. Found: C, 75.77; H, 6.85; N, 6.82.

4.3.7. *tert*-Butyl *N*-(2-methyl-1-[(1-phenylpropyl) amino] carbonylpropyl)carbamate, 7g. Yield 91%. Yellow oil. IR (cm^{-1}, neat) 3390, 1695. ^{1}H NMR δ (ppm) 0.83–1.10 (m, 9H); 1.41 (s, 9H); 1.73–1.89 (m, 2H); 2.05–2.22 (m, 1H); 3.78–3.90 (m, 1H); 4.80–4.97 (m, 1H); 5.00–5.18 (m, 1H); 6.30 (d, 1H, $J=8.4$ Hz); 7.18–7.40 (m, 5H). ^{13}C NMR δ: 10.9, 11.0, 18.2, 19.5, 19.6, 27.1, 28.5, 29.3, 29.5, 30.6, 30.8, 55.0, 55.2, 60.6, 80.1, 126.7, 126.8, 127.4, 127.5, 128.8, 142.2, 156.2, 156.3, 171.1, 171.2. Anal. Calcd for $C_{19}H_{30}N_2O_3$ (334.45): C, 68.23; H, 9.04; N, 8.38. Found: C, 68.26; H, 9.00; N, 8.40.

4.3.8. *tert*-Butyl *N*-(1-[(1,3-diphenylpropyl)amino] carbonyl-2-methylpropyl)carbamate, 7h. Yield 82%. White solid 133–135 °C. IR (cm^{-1}, KBr) 3395, 1690. ^{1}H NMR δ (ppm) 0.88 (d, 3H, $J=7.0$ Hz); 0.98 (d, 3H, $J=7.0$ Hz); 1.41 (s, 9H); 1.62–1.81 (m, 1H); 2.07–2.30 (m, 2H); 2.50–2.76 (m, 2H); 3.78–3.90 (m, 1H); 4.92–5.15 (m, 2H); 6.26–6.42 (m, 1H); 7.15–7.40 (m, 10H). ^{13}C NMR δ: 19.5, 19.7, 28.4, 30.5, 30.7, 32.6, 37.9, 38.1, 53.3, 53.4, 60.6, 80.2, 126.2, 126.7, 127.6, 128.5, 128.6, 128.9, 141.4, 141.5, 142.0, 156.1, 171.0. Anal. Calcd for $C_{25}H_{34}N_2O_3$ (410.55): C, 73.14; H, 8.35; N, 6.82. Found: C, 73.18; H, 8.36; N, 6.88.

4.3.9. *tert*-Butyl 2-[(1-phenylpropyl)amino]carbonyl-1-pyrrolidinecarboxylate, 7i. Yield 87%. Yellow oil. IR (cm^{-1}, neat) 3405, 1695. ^{1}H NMR δ (ppm) 0.86 (t, 3H, $J=7.3$ Hz, diast. A); 0.88 (t, 3H, $J=7.5$ Hz, diast. B); 1.44 (s, 9H); 1.65–1.98 (m, 4H); 2.10–2.45 (m, 2H); 3.20–3.50 (m, 3H); 4.18–4.45 (m, 1H); 4.80–4.95 (m, 1H); 7.18–7.37 (m, 5H). Anal. Calcd for $C_{19}H_{28}N_2O_3$ (332.44): C, 68.65; H, 8.49; N, 8.43. Found: C, 68.68; H, 8.53; N, 8.39.

4.4. General procedure for the preparation of α,β-dipeptides 10

To a solution of diisopropylamine (3 mmol) in dry THF (12 mL), BuLi (1.6 M in hexanes, 3.2 mmol, 2.0 mL) was added at 0 °C and stirring was continued for 0.5 h at 0 °C. Dry alkyl acetate **9** (3 mmol) was then added at −78 °C and after stirring at the same temperature for 0.5 h sulfone **6** (1 mmol) dissolved in dry THF (5 mL) was added. Stirring was continued for 1 h at −78 °C and then the mixture was quenched by addition of saturated aqueous NH_4Cl (6 mL).The mixture was extracted with CH_2Cl_2 (4× 15 mL) and dried over $MgSO_4$. The crude product obtained after evaporation of the solvent was purified by column chromatography (hexanes/ethyl acetate 75:25).

4.4.1. Ethyl 3-(2-[(*tert*-butoxycarbonyl)amino]-3-phenylpropanoylamino)-3-phenylpropanoate, 10a. Yield 76%. Colorless oil. IR (cm^{-1}, neat) 3405, 1735, 1690. ^{1}H NMR δ (ppm) 1.12 (t, 3H, $J=7.3$ Hz, diast A); 1.13 (t, 3H, $J=7.3$ Hz, diast. B); 1.41 (s, 9H); 2.65–2.85 (m, 2H); 2.93–3.20 (m, 2H); 3.96–4.10 (m, 2H); 4.27–4.44 (m, 1H); 5.05–5.22 (m, 1H); 5.28–5.43 (m, 1H); 6.80–7.00 (m, 1H); 7.05–7.40 (m, 10H). ^{13}C NMR δ: 14.0, 14.1, 28.2, 39.7, 39.9, 40.4, 49.3, 49.4, 55.9, 60.6, 60.7, 80.0, 80.1, 126.2, 126.3, 128.5, 128.6, 129.0, 1239.2, 129.3, 129.6, 129.7, 139.0, 140.0, 155.3, 170.3, 170.4, 170.5, 170.7. Anal. Calcd for $C_{25}H_{32}N_2O_5$ (440.53): C, 68.16; H, 7.32; N, 6.36. Found: C, 68.14; H, 7.35; N, 6.40.

4.4.2. Ethyl 3-[(2-[(benzyloxy)carbonyl]amino-3-phenyl propanoyl)amino]pentanoate, 10b. Yield 72%. Colorless oil. IR (cm^{-1}, neat) 3400, 1735, 1690. ^{1}H NMR δ (ppm) 0.65–0.82 (m, 3H); 1.17 (t, 3H, $J=7.0$ Hz, diast A); 1.19 (t, 3H, $J=7.0$ Hz, diast B); 1.28–1.40 (m, 2H); 2.30–2.48 (m, 2H); 2.90–4.10 (q, 2H, $J=7.0$ Hz + m, 1H); 4.23–4.42 (m, 1H); 5.02 (s, 2H); 5.63–5.75 (m, 1H); 6.47–6.78 (m, 1H); 7.10–7.38 (m, 10H). ^{13}C NMR δ: 10.4, 10.5, 14.2, 26.9, 38.0, 38.3, 38.8, 47.5, 47.7, 56.5, 60.5, 66.8, 126.9, 128.0, 128.1, 128.5, 128.6, 129.3, 136.3, 136.7, 136.8, 155.9, 170.4, 171.4, 171.5. Anal. Calcd for $C_{24}H_{30}N_2O_5$ (426.51): C, 67.59; H, 7.09; N, 6.57. Found: C, 67.55; H, 7.05; N, 6.60.

4.4.3. Methyl 3-[(2-[(benzyloxy)carbonyl]amino-3-phenylpropanoyl)amino]-5-phenylpentanoate, 10c. Yield 69%. White solid mp 89–93 °C. IR (cm^{-1}, KBr) 3405, 1738, 1695. ^{1}H NMR δ (ppm) 1.62–1.81 (m, 2H); 2.35–2.57 (m, 4H); 3.00–3.35 (m, 2H); 3.61 (s, 3H); 4.10–4.25 (m, 1H); 4.28–4.47 (m, 1H); 5.10 (s, 2H); 5.30–5.43 (m, 1H); 6.28–6.40 (m, 1H); 7.10–7.40 (m, 15H). ^{13}C NMR δ: 32.4, 32.6, 35.7, 35.9, 38.2, 38.4, 45.9, 46.1, 51.8, 56.8, 60.0, 60.3, 67.2, 67.5, 126.2, 126.3, 127.0, 127.1127.5, 128.2, 128.3, 128.5, 128.7, 128.8, 128.9, 129.4, 129.5, 136.3, 136.6, 141.3, 141.4, 156.8, 170.3, 170.5, 171.8, 172.0. Anal. Calcd for $C_{29}H_{32}N_2O_5$ (488.58): C, 71.29; H, 6.60; N, 5.73. Found: C, 71.28; H, 6.63; N, 5.70.

4.4.4. Ethyl 3-[2-(1,3-dioxo-2,3-dihydro-1*H*-2-isoindolyl)-3-phenylpropanoyl]aminopentanoate, 10d. Yield 72%. Waxy solid. IR (cm^{-1}, neat) 3395, 1740, 1690. ^{1}H NMR δ (ppm) 0.88 (t, 3H, $J=7.4$ Hz, diast. A); 0.89 (t, 3H, $J=7.4$ Hz, diast. B); 1.18 (8t, 3H, $J=7.0$ Hz); 1.45–1.78 (m 2H); 2.43–2.55 (m, 2H); 3.50–3.63 (m, 2H); 3.95–4.10 (m, 1H); 4.13–4.21 (m, 1H); 5.05–5.15 (m, 1H); 6.68–6.78 (m, 1H); 7.07–7.22 (m, 5H); 7.65–7.70 (m, 2H); 7.75–7.80 (m, 2H). ^{13}C NMR δ: 10.7, 10.8, 14.2, 27.0, 27.2, 34.7, 34.9, 37.9, 34.1, 48.1, 48.2, 55.7, 56.0, 60.8, 123.6, 127.0, 128.7, 128.8, 129.0, 129.7, 131.6, 134.3, 136.9, 137.0, 168.0, 168.1, 170.7, 170.8, 171.8, 172.0. Anal. Calcd for $C_{24}H_{26}N_2O_5$ (422.48): C, 68.23; H, 6.20; N, 6.63. Found: C, 68.28; H, 6.17; N, 6.66.

4.4.5. Ethyl 3-(2-[(*tert*-butoxycarbonyl)amino]-3-methyl-butanoylamino)pentanoate, 10e. Yield 67%. White solid mp 83–86 °C. IR (cm^{-1}, KBr) 3400, 1734, 1695. ^{1}H NMR δ (ppm) 0.88–0.98 (m, 9H); 1.25 (t, 3H, $J=7.0$ Hz, diast. B); 1.26 (t, 3H, $J=7.3$ Hz, diast. A); 1.44 (s, 9H); 1.50–1.65 (m, 2H); 2.08–2.25 (m, 1H); 2.52 (d, 1H, $J=5.1$ Hz, diast. B); 2.53 (d, 2H, $J=5.5$ Hz, diast. A); 3.80–3.95 (m, 1H); 4.10–4.25 (m, 3H); 5.03–5.15 (m, 1H); 6.37–6.57 (m, 1H). ^{13}C NMR δ: 10.7, 10.8, 14.3, 19.4, 27.2, 28.4, 30.8, 31.1, 38.3, 38.5, 60.2, 60.3, 79.9, 155.9, 171.1, 171.2, 171.7. Anal. Calcd for $C_{17}H_{32}N_2O_5$ (344.45): C, 59.28; H, 9.36; N, 8.13. Found: C, 59.26; H, 9.33; N, 8.15.

4.4.6. Ethyl 3-(2-[(*tert*-butoxycarbonyl)amino]-3-methyl butanoylamino)-3-cyclohexylpropanoate, 10f. Yield 75%. Colorless oil. IR (cm^{-1}, neat) 3405, 1735, 1690. ^{1}H NMR δ (ppm) 0.85–1.00 (m, 8H); 1.10–1.22 (m, 3H); 1.25 (t, 3H, $J=7.3$ Hz); 1.42 (s, 9H); 1.60–1.80 (m, 6H); 2.08–1.30 (1H); 2.50–2.55 (m, 2H); 3.75–3.96 (m, 1H); 4.00–4.20 (m, 3H); 4.95–5.15 (m, 1H); 6.45 (d, 1H, $J=9.1$ Hz). Anal. Calcd for $C_{21}H_{38}N_2O_5$ (398.54): C, 63.29; H, 9.61; N, 7.03. Found: C, 63.33; H, 9.58; N, 7.00.

4.4.7. Ethyl 3-(2-[(*tert*-butoxycarbonyl)amino]-3-methyl butanoylamino)dodecanoate, 10g. Yield 65%. Spectroscopic data are in full agreement with those reported.[14c]

4.4.8. Ethyl 3-(2-[(*tert*-butoxycarbonyl)amino]-2-phenyl acetylamino)pentanoate, 10h. Yield 78%. Waxy solid. IR (cm^{-1}, neat) 3405, 1735, 1690. ^{1}H NMR δ (ppm) diast. A. 0.67 (t, 3H, J=7.0 Hz); 1.23 (dt, 3H, J=1.1, 7.0 Hz); 1.40 (s, 9H); 1.41–1.60 (m, 2H); 2.50 (d, 2H, J=5.1 Hz); 4.13 (dq, 2H, J=1.1, 7.0 Hz); 4.14–4.25 (m, 1H); 5.00–5.17 (m, 1H); 5.78–5.95 (m, 1H); 6.41 (d, 1H, J=10.0 Hz); 7.22–7.36 (m, 5H). Diast. B. 0.89 (t, 3H, J=7.0 Hz); 1.15 (dt, 3H, J=1.1, 7.0 Hz); 1.40 (s, 9H); 1.41–1.60 (m, 2H); 2.39 (d, 2H, J=5.1 Hz); 3.95 (dq, 2H, J=1.1, 7.0 Hz); 4.14–4.25 (m, 1H); 5.00–5.17 (m, 1H); 5.78–5.95 (m, 1H); 6.31 (d, 1H, J=10.0 Hz); 7.22–7.36 (m, 5H). ^{13}C NMR δ: 10.4, 10.8, 14.2, 14.3, 27.1, 28.4, 37.9, 38.4, 47.9, 48.0, 58.9, 60.7, 60.7, 77.4, 80.1, 127.6, 128.3, 128.4, 129.0, 129.1, 138.7, 138.9, 155.2, 169.7, 169.8, 171.6, 171.8. Anal. Calcd for $C_{20}H_{30}N_2O_5$ (378.46): C, 63.47; H, 7.99; N, 7.40. Found: C, 63.43; H, 8.02; N, 7.44.

4.5. General procedure for preparation of nitro derivatives 11

To a stirred suspension of NaH (3 mmol) in dry THF (10 mL), nitromethane (3 mmol) was added dropwise at room temperature. After stirring for 30 min, the appropriate sulfone **6** (1 mmol) dissolved in dry THF (5 mL) was added and the white suspension was stirred at room temperature for 30 min. The reaction was quenched by addition of saturated aqueous NH_4Cl (4 mL), was extracted with $CHCl_3$ (4×15 mL) and then dried over $MgSO_4$. The crude nitro derivative **11** obtained after removal of the solvent was purified by column chromatography (hexanes/ethyl acetate 7:3).

4.5.1. *tert*-Butyl *N*-(2-[1-(nitromethyl)propyl]amino-2-oxo-1-phenylethyl)carbamate, 11a. Yield 77%. White solid mp 73–77 °C. IR (cm^{-1}, KBr) 3400, 1695, 1550. ^{1}H NMR δ (ppm) 0.87 (t, 3H, J=7.3 Hz, diast. A); 0.92 (t, 3H, J=7.3 Hz, diast. B); 1.42 (s, 9H, diast. A); 1.43 (s, 9H, diast. B); 1.50–1.70 (m, 2H); 2.98–3.17 (m, 2H); 4.20–4.42 (m, 3H); 4.45–4.55 (m, 1H); 4.90–5.08 (m, 1H); 6.23–6.42 (m, 1H); 7.16–7.40 (m, 5H). Anal. Calcd for $C_{17}H_{25}N_3O_5$ (351.40): C, 58.11; H, 7.17; N, 11.96. Found: C, 58.15; H, 7.20; N, 11.99.

4.5.2. *tert*-Butyl *N*-[2-methyl-1-([1-(nitromethyl)propyl] aminocarbonyl)propyl]carbamate, 11b. Yield 75%. White solid mp 105–107 °C. IR (cm^{-1}, KBr) 3400, 1690, 1555. ^{1}H NMR δ: 0.90–1.03 (m, 9H); 1.44 (s, 9H, diast. A); 1.45 (s, 9H, diast. B); 1.50–1.78 (m, 2H); 2.10–2.25 (m, 1H); 3.82–3.96 (m, 2H); 4.28–4.42 (m, 1H); 4.55–4.63 (m, 1H); 5.03–5.18 (m, 1H); 6.59 (d, 1H, J= 8.1 Hz). Anal. Calcd for $C_{14}H_{17}N_3O_5$ (317.38): C, 52.98; H, 8.57; N, 13.24. Found: C, 53.00; H, 8.55; N, 13.26.

4.6. General procedure for preparation of α,α-dipeptides 12

Nitroderivative **11** (0.5 mmol) dissolved in *t*BuOH (4 mL) was treated with aqueous buffered KOH (0.5 M in KOH and 1.25 M in K_2HPO_4, 3 mL) at room temperature. The mixture was stirred for 5 min and then aqueous $KMnO_4$ (0.5 M, 4 mL, 2 mmol) was added dropwise mantaining the temperature below 25 °C by occasional cooling. After stirring at room temperature for 1 h the mixture was cooled by ice bath and then saturated Na_2SO_3 (10 mL) was added. The mixture was then acidified with 2 M HCl until pH ∼5 and then extracted with ethyl acetate (4×15 mL). The organic solutuion was dried over $MgSO_4$ and after evaporation of the solvent the crude acid **12** was purified by column chromatography (dichloromethane/methanol 9:1).

4.6.1. 2-(2-[(*tert*-Butoxycarbonyl)amino]-2-phenylacetyl amino)butanoic acid, 12a

Yield 82%. Waxy solid. IR (cm^{-1}, neat) 3400, 1710, 1690. ^{1}H NMR δ: 0.78 (t, 3H, J=7.0 Hz, diast. A); 0.96 (t, 3H, J=7.0 Hz, diast. B); 1.39 (s, 9H); 1.65–2.00 (m, 2H); 2.95–3.18 (m, 2H); 4.45–4.68 (m, 2H); 5.36 (m, 1H, diast. A); 5.58–5.70 (m, 1H, diast. B); 6.55 (br s, 1H); 6.95–7.15 (m, 1H); 7.20–7.35 (m, 5H). Anal. Calcd for $C_{17}H_{24}N_2O_5$ (336.38): C, 60.70; H, 7.19; N, 8.33. Found: C, 60.66; H, 7.20; N, 8.29.

4.6.2. 2-(2-[(*tert*-Butoxycarbonyl)amino]-3-methyl butanoylamino)butanoic acid, 12b

Yield 78%. Spectroscopic data are in full agreement with those reported.[18]

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References and notes

1. (a) O'Donnell, M. J. *Acc. Chem. Res.* **2004**, *37*, 506–517. (b) Lygo, B.; Andrews, B. I. *Acc. Chem. Res.* **2004**, *37*, 518–525. (c) Abellán, T.; Chinchilla, R.; Galindo, N.; Guillena, G.; Nájera, C.; Sansano, J. M. *Eur. J. Org. Chem.* **2000**, 2689–2697.
2. (a) List, B. *Acc. Chem. Res.* **2004**, *37*, 548–557. (b) Notz, W.; Tanaka, F.; Barbas, C. F. *Acc. Chem. Res.* **2004**, *37*, 580–591. (c) List, B. *Tetrahedron* **2002**, *58*, 5573–5590. (d) Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2441–2495. (e) Gröger, H.; Wilken, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 529–532.
3. (a) Buck, R. T.; Clarke, P. A.; Coe, D. M.; Drysdale, M. J.; Ferris, L.; Haigh, D.; Moody, C. J.; Pearson, N. D.; Swann, E. *Chem. Eur. J.* **2000**, *6*, 2160–2167. (b) Bagley, M. C.; Hind, S. L.; Moody, C. J. *Tetrahedron Lett.* **2000**, *41*, 6897–6900. (c) Falorni, M.; Giacomelli, G.; Porcheddu, A.; Dettori, G. *Eur. J. Org. Chem.* **2000**, 3217–3222.
4. (a) Priem, G.; Rocheblave, L.; De Michelis, C.; Courcambeck, J.; Kraus, J. L. *J. Chem.Soc., Perkin Trans. 1* **2000**, 819–824. (b) Niddam, V.; Camplo, M.; Le Nguyen, D.; Chermann, J.-C.; Kraus, J. L. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 609–614. (c) Nichifor, M.; Schacht, E. H. *Tetrahedron* **1994**, *50*, 3747–3760. (d) Kingsbury, W. D.; Boehm, J. C.; Mehta, R. J.; Grappel, S. *J. Med. Chem.* **1984**, *27*, 1447–1451. α-Hydroxy *N*-acylamines can be also prepared

by oxidative decarboxylation of serine derivatives: (e) Troast, D. M.; Porco, J. A. *Org. Lett.* **2002**, *4*, 991–994. (f) Paulitz, C.; Steglich, W. *J. Org. Chem.* **1997**, *62*, 8474–8478. (g) Bogenstätter, M.; Steglich, W. *Tetrahedron* **1997**, *53*, 7267–7274. (h) Apitz, G.; Jäger, M.; Jaroch, S.; Kratzel, M.; Schäffeler, L.; Steglich, W. *Tetrahedron* **1993**, *49*, 8223–8232.

5. (a) Fišera, L. In Padwa, A., Ed.; Science of Synthesis; Thieme: Stuttgart, 2004; Vol. 27, pp 349–373. (b) Zaugg, H. A. *Synthesis* **1984**, 85–110 and pp 181–212.
6. (a) Katritzky, A. R.; Manju, K.; Singh, S. K.; Meher, N. K. *Tetrahedron* **2005**, *61*, 2555–2581. (b) Katritzky, A. R.; Shobana, N.; Harris, P. A.; Hill, J. B.; Ager, D. J. *Org. Prep. Proced. Int.* **1992**, *24*, 121–126. (c) Katritzky, A. R.; Urogdi, L.; Mayence, A. *J. Org. Chem.* **1990**, *55*, 2206–2214.
7. For some very recent applications of α-amidialkylphenyl sulfones see: (a) Mennen, S. M.; Gipson, J. D.; Kim, Y. R.; Miller, S. J. *J. Am. Chem. Soc.* **2005**, *127*, 1654–1655. (b) Zhang, H.-L.; Liu, H.; Cui, X.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *Synlett* **2005**, 615–618. (c) Côté, A.; Boezio, A. A.; Charette, A. B. *Proc. Nat. Acad. Sci.* **2004**, *101*, 5405–5410. (d) Shiraishi, Y.; Yamauchi, H.; Takamura, T.; Kinoshita, H. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 2219–2229. (e) Zawadzki, S.; Zwierzak, A. *Tetrahedron Lett.* **2004**, *45*, 8505–8506. (f) Zhao, Y.; Ma, Z.; Zhang, X.; Zou, Y.; Jin, X.; Wang, J. *Angew. Chem., Int. Ed. Engl.* **2004**, *43*, 5977–5980. (g) Banphavichit, V.; Chaleawlertumpon, S.; Bhanthumnavin, W.; Vilaivan, T. *Synth. Commun.* **2004**, *34*, 3147–3160. (h) Giri, N.; Petrini, M.; Profeta, R. *J. Org. Chem.* **2004**, *69*, 7303–7308. (i) Pesenti, C.; Arnone, A.; Arosio, P.; Frigerio, M.; Meille, S. V.; Panzeri, W.; Viani, F.; Zanda, M. *Tetrahedron Lett.* **2004**, *45*, 5125–5129. (j) Frantz, D. E.; Morency, L.; Soheili, A.; Murry, J. A.; Grabowski, E. J. J.; Tillyer, R. D. *Org. Lett.* **2004**, *6*, 843–846. (k) Gizeki, P.; Youcef, R. A.; Poulard, C.; Dhal, R.; Dujardin, G. *Tetrahedron Lett.* **2004**, *45*, 9589–9592.
8. Pozdnev, V. F. *Tetrahedron Lett.* **1995**, *36*, 7115–7118.
9. Aldehydes bearing a cyclic framework as (*R*)-2,3-isopropylideneglyceraldehyde or (L)-prolinal give the best results in term of diastereoselectivity. On the other hand reaction of *N*-Boc-phenylalaninal with benzyl carbamate in the presence of benzenesulfinic acid gives the corresponding sulfone in good yield but poor diastereoselectivity: Foresti, E.; Palmieri, G.; Petrini, M.; Profeta, R. *Org. Biomol. Chem.* **2003**, *1*, 4275–4281. See also Ref. 7h.
10. (a) Mecozzi, T.; Petrini, M. *J. Org. Chem.* **1999**, *64*, 8970–8972. (b) Morton, J.; Rahim, A.; Walker, E. R. H. *Tetrahedron Lett.* **1982**, *23*, 4123–4126. (c) Weygand, F.; Steglich, W.; Oettmeier, W. *Chem. Ber.* **1970**, *103*, 818–826.
11. Müller, R.; Röttele, H.; Henke, H.; Waldmann, H. *Chem. Eur. J.* **2000**, *6*, 2032–2043.
12. Seebach, D.; Renaud, P. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 843–844.
13. (a) Dialer, H.; Steglich, W.; Beck, W. *Tetrahedron* **2001**, *57*, 4855–4862. (b) Schumann, S.; Zeitler, K.; Jäger, M.; Polborn, K.; Steglich, W. *Tetrahedron* **2000**, *56*, 4187–4196. (c) Apitz, G.; Jäger, M.; Jaroch, S.; Kratzel, M.; Schäffleler, L.; Steglich, W. *Tetrahedron* **1993**, *49*, 8223–8232.
14. (a) Huang, L.; Brinen, L. S.; Ellmann, J. A. *Bioorg. Med. Chem.* **2003**, *11*, 21–29. (b) Palomo, C.; Oiarbide, M.; Landa, A.; González-Rego, M. C.; García, J. M.; González, A.; Odriozola, J. M.; Martín-Pastor, M.; Linden, A. *J. Am. Chem. Soc.* **2002**, *124*, 8637–8643. (c) Chiba, H.; Agematu, H.; Sakai, K.; Dobashi, K.; Yoshioka, T. *J. Antibiot.* **1999**, *52*, 710–720. (d) Shibata, N.; Das, B. K.; Takeuchi, Y. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4234–4236.
15. Ballini, R.; Petrini, M. *Tetrahedron Lett.* **1999**, *40*, 4449–4452.
16. Ballini, R.; Petrini, M. *Tetrahedron* **2004**, *60*, 1017–1047.
17. Katritzky, A. R.; Wang, M.; Yang, H.; Zhang, S.; Akhmedov, N. G. *ARKIVOC* **2002**, *(viii)*, 134–142.
18. Ward, D. E.; Vàxquez, A.; Pedras, M. S. C. *J. Org. Chem.* **1999**, *64*, 1657–1666.

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Synthesis of atropoisomeric pyridines via cobalt-catalyzed cocyclotrimerization of diynes with benzonitrile

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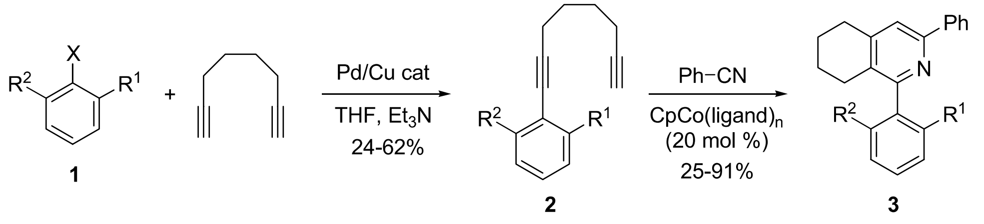
Abstract—Arylpyridines (precursors for potential organocatalysts) are easily accesible by cobalt-catalyzed cocyclotrimerization of *ortho*-substituted 1-aryl-1,7-octadiynes with benzonitrile. The scope of the reaction with respect to the *ortho* substituents (OMe, Me, COOMe, NHCOMe, F, etc.) was investigated. Three potentially atropoisomeric arylpyridines were prepared and one of them was converted into the corresponding *N*-oxide and resolved into its enantiomers. The absolute configuration of the *N*-oxide was established by X-ray crystal structure analysis. Preliminary results of its application in asymmetric organocatalysis are presented.

1. Introduction

The interest in the field of organocatalysis (acceleration of a reaction by a catalytic amount of an organic compound) has increased in the last few years. In particular, organocatalysis is gaining importance in asymmetric synthesis, complementing bio- and metal-catalysis.[1] Out of several concepts of organocatalysis, a significant role is played by activation of a Lewis acid by a Lewis base. One type of the typical Lewis base organocatalysts are pyridine *N*-oxides with a biaryl framework.[2–5] Since pyridine *N*-oxides are easily accessible from pyridines, there is general interest in the development of new synthetic methods for pyridine preparation. One of them is based on [2+2+2] cocyclotrimerization of two C–C-triple bonds with a nitrile.[6] The use of the most widely and generally utilized cobalt catalysts was pioneered by Wakatsuki,[7] Vollhardt,[8] and Bönnemann.[9] Over the years a number of other transition metal compounds such as Ti,[10] Zr,[11] Fe,[12] Ta,[13] and Rh[14] were shown to catalyze or mediate the cyclotrimerization. Recently, a Ru-based catalyst has been shown to be suitable for cyclotrimerization of diynes with electron-deficient nitriles.[15,16] Cocyclotrimerization has also been used for preparation of oligopyridines (namely bipyridines) either by cocyclotrimerization of diynes with dinitriles,[17] or alkynylnitriles with diynes,[18] or cyanopyridines with alkynes.[19] The synthesis of chiral pyridines is based either on cyclotrimerization with chiral nitriles[20] or enantioselective cyclotrimerization by treatment with chiral cyclopentadienyl cobalt complexes.[21] Herein, we report on the cobalt-catalyzed cyclotrimerization of substituted aryldiynes with nitriles to potentially atropoisomeric pyridines, conversion



Scheme 1. Preparation of diynes **2** and their cocyclotrimerization with nitriles to arylpyridines **3** under Co-catalysis.

Keywords: Pyridine; Cocyclotrimerization; Cobalt; Catalysis; Organocatalysis.

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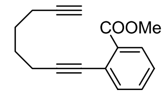
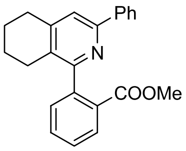
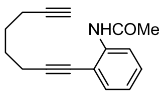
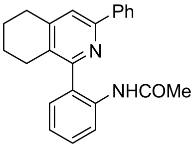
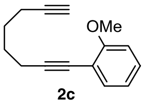
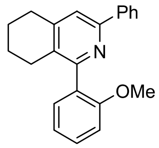
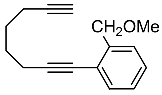
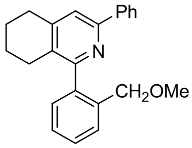
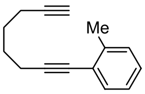
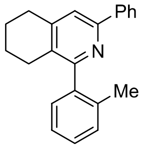
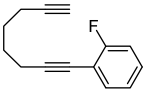
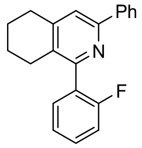
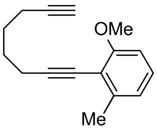
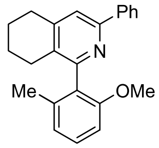
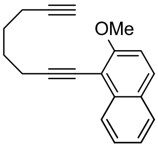
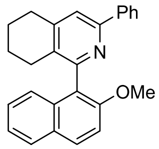
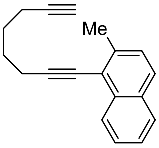
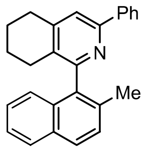
Table 1. Cobalt-catalyzed cocyclotrimerization of diynes **2** with benzonitrile to arylpyridines **3**

Entry	Diyne **2a**	Product **3**	Conditions[a]	Yield %[b]
1	 **2a**	 **3a**	A	54
2	 **2b**	 **3b**	A	35
3	 **2c**	 **3c**	A	76
4	 **2d**	 **3d**	A	33
5	 **2e**	 **3e**	A	91
6	 **2f**	 **3f**	A	46
7	 **2g**	 **3g**	A, B, C	30, 25, 62
8	 **2h**	 **3h**	A, B, C	75 (54)[c], 67, 0
9	 **2i**	 **3i**	A, B, C	30, 69, 48

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[a] Conditions: A = $CpCo(CO)_2$ (20 mol%), PPh_3 (40 mol%), 140 °C, 48 h; B = CpCo(COD) (20 mol%), 140 °C, 48 h; C = $CpCo(CH_2{=}CH_2)_2$ (10 mol%), 20 °C, 30 min.

[b] Isolated yields.

[c] $CpCo(CO)_2$ (10 mol%), 140 °C, 48 h.

of one of them into a pyridine *N*-oxide, its resolution into enantiomers, and preliminary results of its application in enantioselective additions to benzaldehyde.

2. Results and discussion

We envisioned that one of the possible pathways to potentially atropoisomeric arylpyridines could be based on the reaction of nitriles with properly substituted α,ω-diynes,[22,23] such as 1-(*ortho*-substituted-aryl)-1,7-octadiynes (Scheme 1). This strategy is similar to that used by Heller et al.[21] but its scope is limited only to a methoxy group as the substituent in the *ortho*-position. It is reasonable to assume that *ortho*-substitution may affect the course of cyclotrimerization by steric and electronic effects. These effects are important in the search for new synthetic methods for preparation of potentially atropoisomeric biaryls. Recently, they have been studied in the Dötz reaction of *ortho*-substituted arylalkynes with chromium carbenes[24] and in the CuCl mediated reaction of zirconacyclopentadienes with *ortho*-substituted arylpropynoates.[25] Furthermore, the synthetic usefulness of the commercially available $CpCo(CO)_2$ was explored.

The required *ortho*-substituted 1-aryl-1,7-octadiynes were prepared by palladium-catalyzed Krause modification[26] of the Sonogashira coupling[27] of 1,7-octadiyne with arylhalides **1** (Scheme 1). Usually, the coupling proceeded smoothly to afford the desired diynes **2** in moderate to reasonable isolated yields (24–62%) and selectivity. To accomplish the cyclotrimerization of the diynes with nitriles, the standard conditions (20 mol% of commercially available $CpCo(CO)_2$, 40 mol% of PPh_3 as a ligand, 140 °C, 2 days) were used (Scheme 1). It has been shown that the catalytically active species are formed in a reasonable reaction rate at this temperature.[6a] Other cobalt complexes such as CpCo(COD) and $CpCo(CH_2{=}CH_2)_2$ (Jonas catalyst)[28,29] were used in order to compare the catalytic activity. The cocyclotrimerizations were carried out in benzonitrile as solvent to minimize homocyclotrimerization of diyne, to ensure a high selectivity ratio for pyridine formation.

The results of cocyclotrimerizations are presented in Table 1. The reaction with the diyne bearing an ester group **2a** afforded the corresponding product **3a** in acceptable yield of 54% (entry 1). In the case of the diyne with a nitrogen substituent such as **2b**, the reaction proceeded only in moderate yield of 35% (entry 2). The cocyclotrimerizations with alkynes bearing methoxy **2c** and methoxymethyl substituents **2d** differed considerably (entries 3 and 4); the product **3c** was obtained in good yield of 76%, whereas the arylpyridine **3d** was isolated in significantly lower yield of 33%. In the case of 1-(*ortho*-tolyl)-1,7-octadiyne **2e** the arylpyridine **3e** was furnished in high yield of 91% (entry 5). The cocyclotrimerization of the fluorine substituted diyne **2f** with benzonitrile also proceeded to give the corresponding arylpyridine **3f** in moderate 46% yield (entry 6).

Cocyclotrimerizations of diynes that were expected to give sterically hindered arylpyridines with restricted rotation about the bond connecting two aromatic rings were far more intriguing (entries 7–9). The reaction of the methoxymethyl substituted diyne **2g** afforded the desired product **3g** in 30% yield (entry 7, conditions A). The use of CpCo(COD) under the same reaction conditions afforded the product in a similar yield of 25% (conditions B). A considerably different result was obtained when the Jonas catalyst (condition C) was used. The full conversion of the starting material was observed within 30 min and **3g** was isolated in good 62% yield. The structure of **3g** was unequivocally confirmed by crystalographic analysis (Fig. 1).

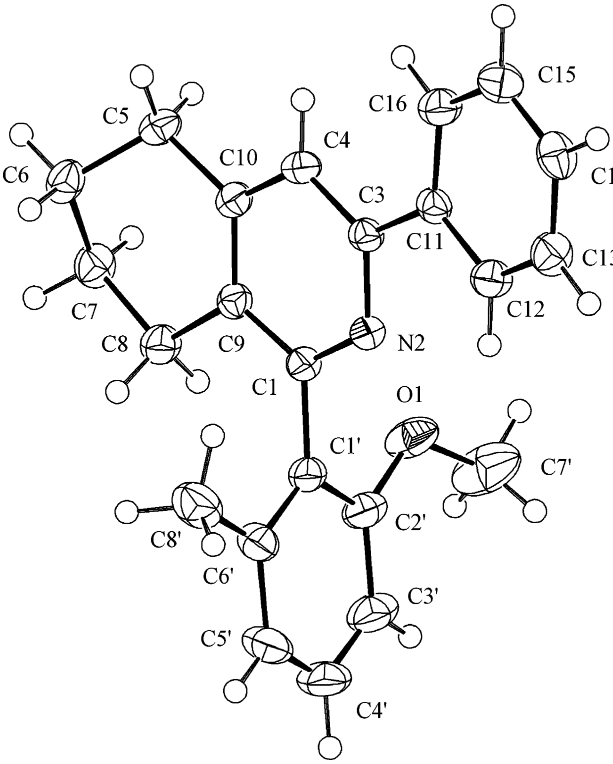
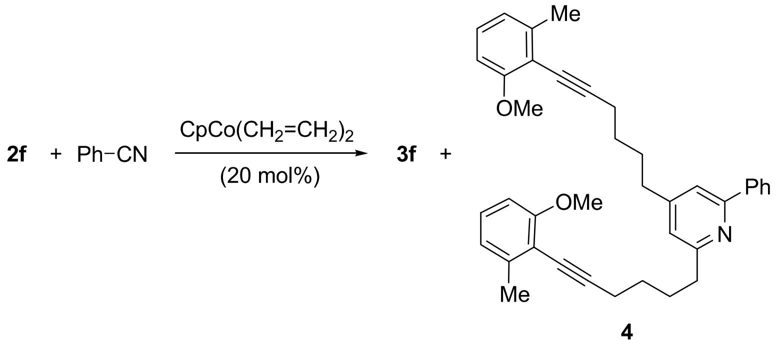


Figure 1. An ORTEP diagram of **3g**. Displacement parameters are shown at the 50% probability level.

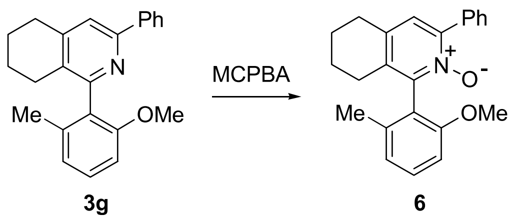
The cyclotrimerization of diyne **2g** was also carried out on 10 mmol scale and the product **3g** was isolated in 45% yield. In addition, it was possible to isolate the compound **4** in 6% yield, which was the product of the cocyclotrimerization of two molecules of **2g** with benzonitrile (Scheme 2). As expected, the reaction with the methoxynaphthyldiyne **2h** furnished the corresponding product **3h** in very good yield of 75% (entry 8, conditions A), which is close to the yield obtained by Heller under different reaction conditions.[21] The similar result was observed under conditions B (67% yield). Surprisingly, the reaction carried out in the presence of the Jonas catalyst did not proceed and the starting material was quantitatively recovered (entry 8, conditions C). The reaction with methylnaphthyldiyne **2i** gave the corresponding product **3i** in rather low yield of 30% (entry 9, conditions A). Again the use the Jonas catalyst (conditions C) resulted in increase of the reaction rate and the conversion of the starting material; the product **3i** was isolated in 48% yield. However, in this instance CpCo(COD) proved to be the catalyst of choice, because



Scheme 2. Formation of **4** in cocyclotrimerization of **2g** and benzonitrile.

its use afforded the corresponding product in 69% yield (conditions B).

The question is what factors are mainly responsible for the observed difference in the yields of the arylpyridines in entries 1–6. Obviously, the differences cannot be simply explained by steric factors, since it is known that for example methyl group occupies larger space than methoxy or ester groups.[30] Although we do not have any spectroscopic evidence for the following hypothesis, it is sensible to assume that the course of the reaction is influenced (retarded) by the strengh of the coordination of the lone electron pair on the heteroatom of the *ortho*-substituent to the cobalt atom in the intermediate cobaltacyclopentadiene.



Scheme 3. Oxidation of the pyridine **3g** to **6**.

Since our initial impetus for this work was to develop an alternative method for the preparation of chiral pyridine oxides as potential organocatalysts, we chose pyridine **3g** for further investigation in this direction. Its oxidation with *m*-chloroperoxobenzoic acid (MPCBA) proceeded smoothly to give the corresponding *N*-oxide **6** in 54% isolated yield (Scheme 3). The *N*-oxide **6** was resolved by cocrystallization with (*S*)-(−)-binol **7** (binol = 2,2′-dihydroxy-1,1′-binaphthyl),[2–5] which gave the crystalline

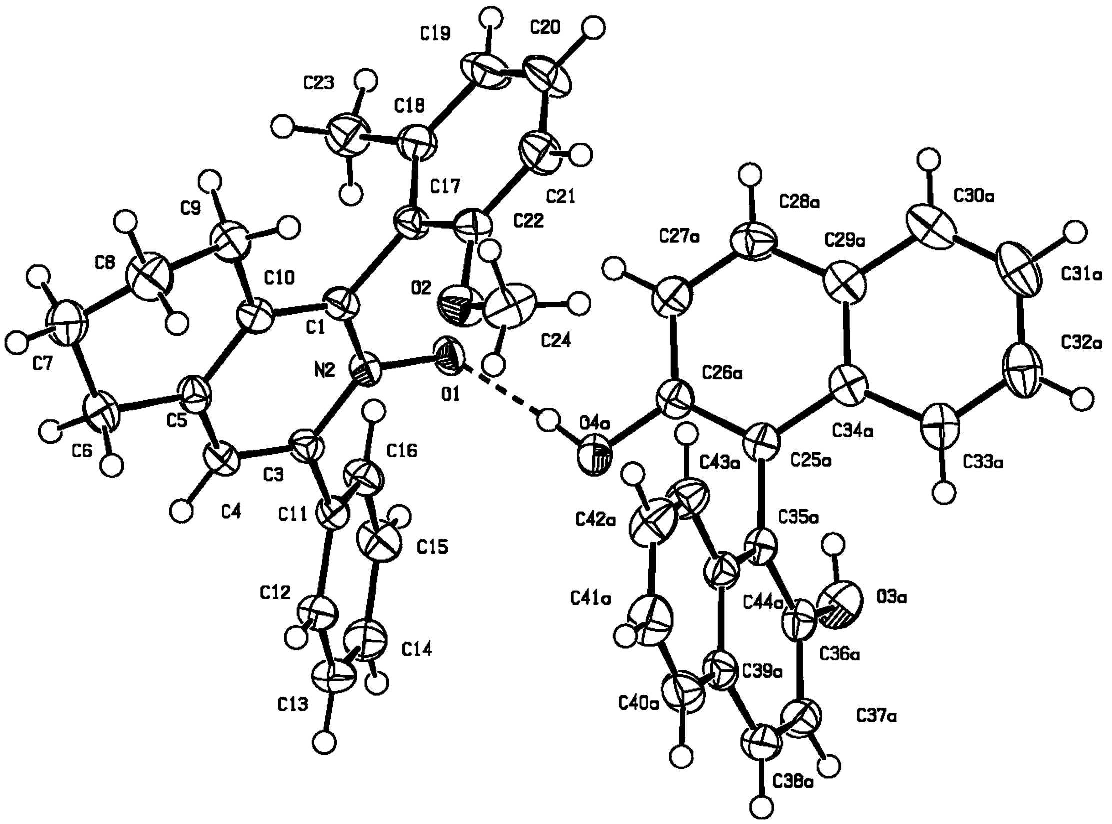
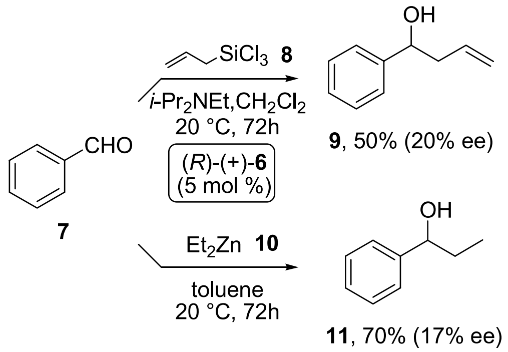


Figure 2. An ORTEP diagram illustrating the interaction of (*R*)-(+)-**6** (on the left) with (*S*)-(−)-**7** (right), in particular the hydrogen bonding N–O···H–O; O(1)···O(4a) 2.606(2) Å, O(1)···H–O(4a) 176(2)°. Displacement parameters are shown at the 50% probability level.

material containing (*S*)-(−)-binol **7** and (+)-**6** (in 1:1 ratio), while (−)-**6** remained in the solution. This cocrystallization, followed by a chromatographic separation of (+)-**6** from (*S*)-(−)-binol **7**, furnished pure (+)-**6** of 95% ee (as detected by chiral HPLC, Chiracel OD-H) in 30% yield. The absolute configuration was found to be (*R*)-(+)-**6** by crystallographic analysis of the molecular crystal of (+)-**6** with (*S*)-(−)-**7** (Fig. 2) of known absolute configuration. The configurational stability of the compound (*R*)-(+)-**6** was quantitatively evaluated by an analytical chiral HPLC. Preliminary data were obtained by heating samples of (*R*)-(+)-**6** and injecting them on the chiral column. The (*R*)-(+)-**6** showed no racemization in toluene at 110 °C after 12 h.

The catalytic activity of the pyridine *N*-oxide (*R*)-(+)-**6** (5 mol%) was preliminarly tested in the addition of allytrichlorosilane **8** to benzaldehyde **7** in dichloromethane (Scheme 4). The attempt to carry out the reaction under usual conditions (−40 °C)[5] was not successful. The reaction proceeded at room temperature only, but even then the reaction rate was rather low, 50% yield of the corresponding alcohol **9** was obtained after 72 h with the modest asymmetric induction of 20% ee. The enantioselectivity of (*R*)-(+)-**6** was also tested in the reaction of diethylzinc **10** with benzaldehyde **7**.[31] The resulting asymmetric induction was again modest (17% ee).



Scheme 4. Enantioselective additions to benzaldehyde **7**.

3. Conclusion

This work has shown that cobalt-catalyzed [2+2+2] cocyclotrimerization of diynes with benzonitrile is a convenient and straightforward method for preparation of not only mono-*ortho*-substituted arylpyridines but also potentially atropoisomeric bis-*ortho*-substituted arylpyridines (entries 7–9, Table 1) in reasonable yields. The starting diynes are easily prepared from the corresponding substituted arylhalides and 1,7-octadiyne in good yields and the use of the commercially available $CpCo(CO)_2$ catalysts gave good yields of the cyclotrimerization products in most cases. Other types of $CpCo(ligand)_n$ (ligand = ethylene, COD) catalysts were tested in cyclotrimerization with bis-*ortho*-substituted aryldiynes but their activity was highly dependent on the structure of the substrate. Last but not least, the racemic arylpyridine-*N*-oxide **6** was resolved into enantiomers and its absolute configuration was unequivocally determined by X-ray structure analysis. Despite the fact that the result of enantioselective additions were not too high, it is premature to rule out the synthetic utility of the pyridine *N*-oxide (*R*)-(+)-**6** at this moment. Further experiments investigating its reactivity and structural modifications will follow in the near future.

4. Experimental

All reactions were carried out under a protective atmosphere of Ar in 20 mL Schlenk flasks. Unless mentioned, reagents were used as obtained without further purification.

4.1. General procedure for catalytic cyclotrimerization of aryl-substituted 1,7-octadiynes with benzonitrile

1-Aryl-1,7-octadiyne (0.4 mmol) and PPh_3 (42 mg, 0.16 mmol) were added to a dry Schlenk tube under argon and dissolved in benzonitrile (2 mL, 19.4 mmol). Then $CpCo(CO)_2$ (14 mg, 0.08 mmol) was added. The reaction mixture was heated for 48 h at 140 °C. After cooling down it was quenched with water and volatiles were removed under reduced pressure. Column chromatography on silica gel was used to isolate products.

4.1.1. Methyl 2-(5,6,7,8-tetrahydro-3-phenylisoquinolin-1-yl)benzoate (3a). Column chromatography on silica gel (7:1 hexane/EtOAc) afforded 192 mg (54%) of the title compound as a viscous liquid: ^1H NMR (400 MHz, $CDCl_3$) δ 1.74–1.84 (m, 4H), 2.44–2.47 (m, 2H), 2.87–2.90 (m, 2H), 3.61 (s, 3H), 7.30–7.47 (m, 6H), 7.54–7.59 (m, 1H), 7.93–7.95 (m, 2H), 7.99–8.01 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.4, 23.0, 26.7, 29.5, 52.0, 119.8, 126.9 (2C), 127.7, 128.1, 128.4 (2C), 129.4, 130.0, 130.1, 130.3, 131.6, 139.7, 142.3, 146.6, 153.1, 159.0, 167.7; IR ($CHCl_3$) ν 3523, 3367, 3064, 3005, 2952, 1721, 1590, 1576, 1434, 1295, 1275, 1130, 1084, 1052, 966, 908 cm^{-1}; FAB-MS *m/z* 241 ($M+H^+$), 225, 165, 128, 115; HR-MS (FAB) calculated for $C_{16}H_{17}O_2$ ($M+H^+$) 241.1239, found 241.1229.

4.1.2. *N*-(2-(5,6,7,8-Tetrahydro-3-phenylisoquinolin-1-yl)phenyl)acetamide (3b). Column chromatography on silica gel (1:1 hexane/EtOAc) afforded 96 mg (35%) of the title compound as a pale yellow solid: mp 130–132 °C (hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 1.72–1.76 (m, 2H), 1.83–1.89 (m, 2H), 1.92 (s, 3H), 2.66–2.69 (m, 2H), 2.92–2.95 (m, 2H), 7.13–7.17 (m, 1H), 7.35–7.51 (m, 6H), 8.01–8.03 (m, 2H), 8.33 (d, $J=8.4$ Hz, 1H), 9.61 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.1, 22.9, 24.8, 27.6, 29.7, 119.7, 122.4, 123.0, 126.2 (2C), 128.4, 128.7 (2C), 128.8, 128.9, 129.9, 131.5, 135.8, 138.5, 149.5, 152.5, 156.0, 168.1; IR ($CHCl_3$) ν 3325, 3065, 3011, 2943, 2864, 1682, 1590, 1521, 1448, 1303, 1242 cm^{-1}; EI-MS *m/z* (% relative intensity) 342 (M^+, 100), 327 (95), 299 (28), 284 (20), 271 (9), 225 (16), 171 (8), 149 (32), 105 (86), 77 (52), 57 (26), 55 (19), 43 (27); HR-MS calculated for $C_{23}H_{22}N_2O$ 342.1732, found 342.1749.

4.1.3. 5,6,7,8-Tetrahydro-1-(2-methoxyphenyl)-3-phenylisoquinoline (3c). Column chromatography on silica gel (4:1 hexane/EtOAc) afforded 97 mg (76%) of the title compound as a viscous liquid: ^1H NMR (400 MHz, $CDCl_3$) δ 1.65–1.85 (m, 4H), 2.33–2.40 (m, 1H), 2.60–2.66 (m, 1H), 2.85–2.90 (m, 2H), 3.77 (s, 3H), 6.95–6.97 (m, 1H), 7.04–7.07 (m, 1H), 7.30–7.42 (m, 6H), 7.96–7.98 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.4, 22.9, 25.7, 29.6, 55.5, 110.8, 120.0, 120.7, 127.0 (2C), 128.1, 128.4 (2C), 129.2, 130.4, 130.7, 131.0, 139.9, 146.5, 153.6, 156.6, 157.0; IR ($CHCl_3$) ν 3530, 3063, 2940, 2863, 2837, 1697, 1589, 1555, 1495, 1463, 1278, 1244, 1180, 1109, 1027, 955 cm^{-1}; EI-MS *m/z* (% relative intensity) 315 (M$^+$, 100), 298 (10), 284 (30), 210 (13); HR-MS calculated for $C_{22}H_{21}NO$ 315.1623, found 315.1638.

4.1.4. 5,6,7,8-Tetrahydro-1-(2-(methoxymethyl)phenyl)-3-phenylisoquinoline (3d). Column chromatography on silica gel (5:2 hexane/EtOAc) afforded 56 mg (33%) of the title compound as a viscous liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.71–1.88 (m, 4H), 2.35–2.58 (m, 2H), 2.87–2.91 (m, 2H), 3.25 (s, 3H), 4.33 (s, 3H), 7.16–7.43 (m, 7H), 7.56–7.57 (m, 1H), 7.95–7.97 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.3, 23.0, 26.7, 29.6, 58.3, 72.2, 119.9, 125.3, 126.8, 127.2, 127.9, 128.1, 128.2, 128.3, 128.5 (2C), 128.8, 129.0, 130.2, 136.3, 139.4, 153.1, 158.3; IR ($CHCl_3$) ν 3063, 3008, 2935, 2862, 1589, 1432, 1090, 956 cm^{-1}; EI-MS *m/z* (% relative intensity) 329 (M$^+$, 16), 314 (100), 277 (9), 149 (11), 69 (25), 55 (20), 43 (23); HR-MS calculated for $C_{23}H_{23}NO$ 329.1780, found 329.1768.

4.1.5. 5,6,7,8-Tetrahydro-3-phenyl-1-*o*-tolylisoquinoline (3e). Column chromatography on silica gel (4:1 hexane/EtOAc) afforded 110 mg (91%) of the title compound as a viscous liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.71–1.83 (m, 4H), 2.14 (s, 3H), 2.30–2.45 (m, 2H), 2.86–2.89 (m, 2H), 7.19–7.29 (m, 4H), 7.33–7.42 (m, 4H), 7.95–7.98 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.6, 22.3, 23.0, 26.5, 29.6, 119.7, 125.5, 126.8 (2C), 127.6, 128.2, 128.5 (2C), 128.6, 129.7, 130.2, 135.7, 139.8, 140.5, 147.1, 153.5, 159.5; IR ($CHCl_3$) ν 3523, 3063, 2942, 2863, 1692, 1589, 1580, 1554, 1432, 1387, 1247, 1178, 1072, 1026 cm^{-1}; EI-MS *m/z* (% relative intensity) 299 (M$^+$, 100), 284 (65), 270 (20), 257 (26), 165 (9), 128 (8), 103 (8), 84 (27), 49 (7); HR-MS calculated for $C_{22}H_{21}N$ 299.1674, found 299.1672.

4.1.6. 5,6,7,8-Tetrahydro-1-(2-fluorophenyl)-3-phenylisoquinoline (3f). Column chromatography on silica gel (4:1 hexane/EtOAc) afforded 122 mg (46%) of the title compound as a viscous liquid: ^{1}H NMR (400 MHz, C_6D_6) δ 1.41–1.46 (m, 4H), 2.41–2.50 (m, 4H), 2.60–2.66 (m, 1H), 6.63–6.67 (m, 1H), 6.79–6.83 (m, 1H), 6.90–6.96 (m, 2H), 7.16–7.20 (m, 1H), 7.24–7.29 (m, 2H), 7.40–7.45 (m, 1H), 8.16–8.19 (m, 2H); ^{13}C NMR (100 MHz, C_6D_6) δ 23.3, 23.8, 27.0, 30.3, 116.9, 121.5, 125.7 (d, $J=3$ Hz), 128.6 (2C), 130.2 (2C), 131.2, 132.4, 133.4 (d, $J=18$ Hz), 141.4, 148.5, 155.5, 156.2, 161.7 (d, $J=246$ Hz); IR ($CHCl_3$) ν 2941, 1713, 1617, 1590, 1580, 1553, 1494, 1452, 1432, 1423, 1386, 1226, 1099 cm^{-1}; EI-MS *m/z* (% relative intensity) 303 (35), 133 (10), 103 (M$^+$, 100), 76 (32), 50 (16); HR-MS calculated for $C_{21}H_{18}FN$ 303.1423, found 303.1435.

4.1.7. 5,6,7,8-Tetrahydro-1-(2-methoxy-6-methylphenyl)-3-phenylisoquinoline (3g). Column chromatography on silica gel (4:1 hexane/EtOAc) afforded 121 mg (30%) of the title compound as a white solid: mp 138–139 °C (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.69–1.83 (m, 4H), 2.03 (s, 3H), 2.04–2.27 (m, 1H), 2.43–2.49 (m, 1H), 2.86–2.89 (m, 2H), 3.71 (s, 3H), 6.81 (d, $J=8.4$ Hz, 1H), 6.91 (d, $J=7.6$ Hz, 1H), 7.23–7.27 (m, 1H), 7.31–7.42 (m, 4H), 7.94–7.97 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7, 22.3, 22.8, 25.4, 29.6, 55.6, 108.4, 120.1, 122.7 (2C), 127.1, 128.2, 128.3, 128.4 (2C), 128.6, 131.1, 137.6, 139.8, 146.9, 153.7, 156.4, 156.7; IR ($CHCl_3$) ν 3065, 3025, 3016, 2941, 2863, 2839, 2357, 1591, 1581, 1556, 1470, 1434, 1422, 1387, 1297, 1261, 1230, 1221, 1212, 1087 cm^{-1}; EI-MS *m/z* (% relative intensity) 329 (M$^+$, 29), 314 (20), 298 (12), 284 (10), 256 (15), 242 (6), 148 (31), 135 (9), 123 (10), 111 (13), 97 (24), 81 (42), 69 (100), 57 (67), 43 (77); HR-MS calculated for $C_{23}H_{23}NO$ 329.1780, found 329.1784. EA calculated for $C_{23}H_{23}NO$ C, 83.85; H, 7.04; N, 4.25. Found C, 83.59; H, 7.08; N, 3.99.

4.1.8. 5,6,7,8-Tetrahydro-1-(2-methoxynaphthalen-1-yl)-3-phenylisoquinoline (3h). Spectral characteritics were in agreement with the previously published data.[21]

4.1.9. 5,6,7,8-Tetrahydro-1-(2-methylnaphthalen-1-yl)-3-phenylisoquinoline (3i). Column chromatography on silica gel (10:1 hexane/EtOAc) afforded 125 mg (30%) of the title compound as a white solid: mp 175–176 °C (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.63–1.69 (m, 2H), 1.77–1.83 (m, 2H), 2.13–2.22 (m, 2H), 2.22 (s, 3H), 2.91–2.94 (m, 2H), 7.22–7.24 (m, 1H), 7.29–7.50 (m, 7H), 7.79–7.84 (m, 2H), 7.96–7.98 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.0, 22.3, 22.9, 25.6, 29.7, 120.1, 124.7, 125.1, 126.0, 126.9 (2C), 127.6, 127.9, 128.3, 128.5 (2C), 128.8, 131.0, 131.9, 132.1, 133.1, 136.6, 139.8, 147.2, 154.3, 158.1; IR ($CHCl_3$) ν 3059, 3024, 3015, 2941, 2356, 1591, 1556, 1508, 1494, 1381, 1315, 1260, 1229, 1219, 1205, 1198, 1085, 915, 866, 813 cm^{-1}; EI-MS *m/z* (% relative intensity) 349 (M$^+$, 100), 334 (65), 320 (16), 307 (14), 256 (7), 166 (8), 149 (46), 139 (8), 111 (10), 97 (16), 83 (24), 69 (42), 57 (56), 43 (59); HR-MS calculated for $C_{26}H_{23}N$ 349.1830, found 349.1839. EA calculated for $C_{26}H_{23}N$ C, 89.36; H, 6.63; H 4.01. Found C, 88.86; H, 6.67; H, 3.76.

4.1.10. (±)-5,6,7,8-Tetrahydro-1-(2-methoxy-6-methylphenyl)-3-phenylisoquinoline-*N*-oxide (6). To a solution of pyridine **3f** (160 mg, 0.48 mmol) in dichloromethane (2 mL) was added MCPBA (purity 70%) (220 mg, 0.93 mmol) at 0 °C. After stirring of the resulting mixture at room temperature for 1 h it was quenched by the saturated water solution of $NaHCO_3$ (1 mL) and the crude product was extracted with dichloromethane (5 mL). The organic layer was separated and column chromatography on silica gel (ethyl acetate) afforded 90 mg (54%) of the title compound **6** as a viscous liquid: ^{1}H NMR (400 MHz, C_6D_6) δ 1.32–1.44 (m, 4H), 2.06–2.14 (m, 2H), 2.16 (s, 3H), 2.26–2.33 (m, 2H), 3.25 (s, 3H), 6.56 (d, $J=8.2$ Hz, 1H), 6.91 (d, $J=7.6$ Hz, 1H), 7.01–7.06 (m, 1H), 7.10–7.22 (m, 4H), 7.96–7.98 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 23.1, 23.3, 27.1, 29.2, 56.2, 109.8, 123.6, 123.9, 126.8, 128.6 (2C), 129.5, 130.3, 130.6 (2C), 134.0, 134.7, 135.4, 139.5, 146.9, 148.0, 158.0; IR ($CHCl_3$) ν 3614, 3010, 2971, 1582, 1467, 1387, 1257, 1127, 1080, 945 cm^{-1}; EIS-MS *m/z* 346 (M$^+$ + H), 352 (M$^+$ − O + Na), 368 (M$^+$ + Na).

4.1.11. (*R*)-(+)-5,6,7,8-Tetrahydro-1-(2-methoxy-6-methylphenyl)-3-phenylisoquinoline-*N*-oxide ((*R*)-(+)-6). To a solution of (*S*)-(−)-binol **7** (293 mg, 0.99 mmol) and racemic 5,6,7,8-tetrahydro-1-(2-methoxy-6-methylphenyl)-3-phenylisoquinoline-*N*-oxide **6** (340 mg, 0.99 mmol) in dichloromethane (5 mL) heptane (10 mL) was added, the flask was closed with a septum with a needle and set aside to allow slow evaporation of dichloromethane through the needle. The molecular complex (*R*)-(+)-**6**·(*S*)-(−)-**7** crystallized within 5 days as colorless needles that were collected by suction filtration. Individual components were collected by column chromatography on silica gel (ethyl acetate), which afforded 105 mg (30%) of (*R*)-(+)-**6**. Chiral HPLC (Chiralcel OD-H, 0.46×25 cm, 8:1 heptane/2-propanol, 1.2 mL min^{-1}) showed 95% ee depending on the batch (t_S = 8.01 min, t_R = 9.12 min).

4.2. Enantioselective allylation of benzaldehyde with allyltrichlorosilane to (*R*)-(+)-1-phenyl-but-3-en-1-ol (9)

To a solution of (*R*)-(+)-**6** (5 mg, 0.014 mmol) in dichloromethane (1.4 mL) were added benzaldehyde (40 μL, 0.4 mmol), diisopropylethylamine (87 μL, 0.5 mmol), and allyltrichlorosilane (75 μL, 0.47 mmol) at 0 °C. The reaction mixture was stirred at 20 °C for 72 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (1 mL), the layers were separated and dried over $MgSO_4$. GC yield of **9** was 50%. Chiral GC (HP-Chiral *β* 30 m×0.25 mm, oven: 80 °C for 15 min, then 1 °C/min to 150°C, 5 min at that temperature) showed 20% ee (t_R = 57.55 min, t_S = 56.03 min).

4.3. Enantioselective alkylation of benzaldehyde with diethylzinc to (*R*)-(+)-1-phenyl-1-propanol (11)

To a solution of (*R*)-(+)-**6** (7 mg, 0.02 mmol) in toluene (0.6 mL) 1 M solution of diethyl zinc hexane (0.68 mL, 0.68 mmol) was added at 0 °C and the reaction mixture was stirred for 20 min. Then benzaldehyde (33 μL, 0.33 mmol), was added and the reaction mixture was stirred for 72 h at 20 °C. The reaction was quenched with 10% H_2SO_4 (0.5 mL), the organic layer was separated and the aqueous phase was extracted with diethylether, the combined organic layers were dried over $MgSO_4$. GC yield of the 1-phenyl-1-propanol was 62%. Chiral GC (HP-Chiral *β* 30 m×0.25 mm, oven: 80 °C for 15 min, then 1 °C/min to 150 °C, 5 min at that temperature) showed 17% ee (t_R = 49.78 min, t_S = 51.09 min).

4.4. Crystallography

Crystal data for: **3g**. $C_{23}H_{23}NO$, $M = 329.42$, monoclinic, $P2_1/n$, $a = 13.1910(3)$ Å, $b = 8.6090(2)$ Å, $c = 16.4300(4)$ Å, $\beta = 107.1860(11)°$, $V = 1782.50(7)$ Å^3, $Z = 4$, $D_x = 1.228$ Mg m^{-3}. A colorless prism dimensions 0.5×0.25×0.2 mm was mounted on glass capillary with epoxy glue and measured at Nonius KappaCCD diffractometer by monochromatized Mo Kα radiation ($\lambda = 0.71073$ Å) at 150(2) K. An absorption was neglected ($\mu = 0.074$ mm^{-1}); a total of 26146 measured reflections in the range $h = -17$ to 17, $k = -11$ to 11, $l = -21$ to 21 ($\theta_{max} = 27.5°$), from which 4076 were unique ($R_{int} = 0.015$), 3294 observed according to the $I > 2\sigma(I)$ criterion. The structure was solved by direct methods (SIR92)[32] and refined by full-matrix least squares based on F^2 (SHELXL97).[33] The hydrogen atoms were recalculated into idealised positions (riding model) and assigned displacement parameter either $H_{iso}(H) = 1.2\ U_{eq}$(pivot atom) or $H_{iso}(H) = 1.5\ U_{eq}$(pivot atom) for methyl moiety. The refinement converged ($\Delta/\sigma_{max} = 0.001$) to $R = 0.0447$ for observed reflections and $wR = 0.124$, $S = 1.038$ for 229 parameters and all 4076 reflections. The final difference map displayed no peaks of chemical significance ($\Delta\rho_{max} = 0.252$, $\Delta\rho_{min}$ -0.246 eÅ^{-3}).

Crystal data for (*R*)-(+)-**6**·(*S*)-(−)-**7**: $C_{23}H_{23}NO_2 \cdot C_{20}H_{14}O_2$, $M = 631.74$, monoclinic, $P2_1$, $a = 11.5900(3)$ Å, $b = 9.0280(2)$ Å, $c = 16.0570(4)$ Å, $\beta = 104.4160(13)°$, $V = 1627.22(7)$ Å^3, $Z = 2$, $D_x = 1.289$ Mg m^{-3}. A colorless plate of dimensions 0.37×0.2×0.15 mm was mounted on glass capillary with epoxy glue and measured at Nonius KappaCCD diffractometer by monochromatized Mo Kα radiation ($\lambda = 0.71073$ Å) at 150(2) K. An absorption was neglected ($\mu = 0.082$ mm^{-1}); a total of 19962 measured reflections in the range $h = -15$ to 15, $k = -11$ to 11, $l = -20$ to 20 ($\theta_{max} = 27.5°$), from which 7408 were unique ($R_{int} = 0.028$), 6678 observed according to the $I > 2\sigma(I)$ criterion. The structure was solved by direct methods (SIR92)[32] and refined by full-matrix least squares based on F^2 (SHELXL97).[33] The absolute configuration of the crystal has been assigned by reference of known configuration of (*S*)-(−)-binol **7**. The hydrogen atoms were found on difference Fourier map, those on carbon atoms were recalculated into idealised positions (riding model) and assigned displacement parameter either $H_{iso}(H) = 1.2\ U_{eq}$(pivot atom) or $H_{iso}(H) = 1.5\ U_{eq}$(pivot atom) for methyl moiety. The hydrogen of the hydroxyl moiety was refined isotropically. The refinement converged ($\Delta/\sigma_{max} = 0.000$) to $R = 0.0378$ for observed reflections and $wR = 0.0956$, $S = 1.001$ for 443 parameters and all 7408 reflections. The final difference map displayed no peaks of chemical significance ($\Delta\rho_{max} = 0.259$, $\Delta\rho_{min}$ -0.181 eÅ^{-3}).

Crystallographic data for structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC no. 283868 and 283869 for **3g** and (*R*)-(+)-**6**·(*S*)-(−)-**7**, respectively. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EY, UK (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.10.034. Preparation and spectral characteristics of the starting 1-aryl-1,7-diynes **2** and the pyridine **4**.

References and notes

1. For a general concept of organocatalysis and typical examples, see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726–3748. (b) Malkov, A.; Kočovský, P. *Curr. Org. Chem.* **2003**, *7*, 1737–1757. (c) Palomo, C.; Oiarbide, M.; Garcia, J. M. *Chem. Soc. Rev.* **2004**, *33*, 65–75. (d) Chelucci, G.; Murineddu, G.; Pinna, G. A. *Tetrahedron: Asymmetry* **2004**, *15*, 1373–1389. (e) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5135–5175. (f) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719–724.
2. (a) Nakajima, M.; Saito, M.; Shiro, M.; Hashimoto, S. *J. Am. Chem. Soc.* **1998**, *120*, 6419–6420. (b) Nakajima, M.; Saito, M.; Hashimoto, S. *Chem. Pharm. Bull.* **2000**, *48*, 306–307. (c) Nakajima, M.; Saito, M.; Hashimoto, S. *Tetrahedron: Asymmetry* **2002**, *13*, 2449–2452. (d) Nakajima, M.; Saito, M.; Uemura, M.; Hashimoto, S. *Tetrahedron Lett.* **2002**, *43*, 8824–8827. (e) Nakajima, M.; Yokota, T.; Saito, M.; Hashimoto, S. *Tetrahedron Lett.* **2004**, *45*, 61–64.
3. (a) Shimada, T.; Kina, A.; Ikeda, S.; Hayashi, T. *Org. Lett.* **2002**, *4*, 2799–2801. (b) Shimada, T.; Kina, A.; Hayashi, T. *J. Org. Chem.* **2003**, *68*, 6329–6337.
4. (a) Malkov, A. V.; Orsini, M.; Pernazza, D.; Muir, K. W.; Langer, V.; Meghani, P.; Kočovský, P. *Org. Lett.* **2002**, *2*, 1047–1049. (b) Malkov, A. V.; Bell, M.; Orsini, M.; Pernazza, D.; Massa, A.; Herrmann, P.; Meghani, P.; Kočovský, P. *J. Org. Chem.* **2003**, *68*, 9659–9668. (c) Malkov, A. V.; Pernazza, D.; Bell, M.; Bella, M.; Massa, A.; Teplý, F.; Meghani, P.; Kočovský, P. *J. Org. Chem.* **2003**, *68*, 4727–4742. (d) Malkov, A. V.; Bell, M.; Vassieu, M.; Bugatti, V.; Kočovský, P. *J. Mol. Catal. A* **2003**, *196*, 179–186.
5. Malkov, A.; Dufková, L.; Farrugia, L.; Kočovský, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 3674–3677.
6. For reviews see: (a) Bönnemann, H.; Brijoux, W. *Adv. Heterocycl. Chem.* **1990**, *48*, 177–222. (b) Shore, N. E. In *[2+2+2] Cycloadditions*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Comprehensive Synthesis; Pergamon: Oxford, 1991; Vol. 5, pp 1129–1162. (c) Grotjahn, D. B. In *Transition Metal Alkyne Complexes: Transition Metal-Catalyzed Cyclotrimerization*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Hegedus, L. S., Eds.; Comprehensive Organometallic Chemistry II; Pergamon: Oxford, 1995; Vol. 12, p 741. (d) Bönnemann, H.; Brijoux, W. In *Cyclomerization of Alkynes*; Beller, M., Bolm, C., Eds.; Transition Metals for Organic Synthesis; Wiley: Weinheim, Germany, 1998; Vol. 1, pp 114–135. (e) Varela, J. A.; Saá, C. *Chem. Rev.* **2003**, *103*, 3787–3801.
7. (a) Wakatsuki, Y.; Yamazaki, H. *J. Chem. Soc., Chem. Commun.* **1973**, 280. (b) Wakatsuki, Y.; Yamazaki, H. *Tetrahedron Lett.* **1973**, 3383–3384. (c) Wakatsuki, Y.; Yamazaki, H. *J. Chem. Soc., Dalton Trans.* **1978**, 1278–1282.
8. Vollhardt, K. P. C.; Bergman, R. G. *J. Am. Chem. Soc.* **1974**, *96*, 4996–4998.
9. Bönnemann, H.; Brinkmann, R.; Schenkluhn, H. *Synthesis* **1974**, 575–577.
10. Ti-mediated. (a) Hill, J. E.; Balaich, G.; Fanwick, P. E.; Rothwell, I. P. *Organometallics* **1993**, *12*, 2911–2924. (b) Suzuki, D.; Tanaka, R.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **2002**, *124*, 3518–3519.
11. Zr-mediated. (a) Takahashi, T.; Tsai, F.; Kotora, M. *J. Am. Chem. Soc.* **2000**, *122*, 4994–4995. (b) Takahashi, T.; Tsai, F.; Li, Y.; Wang, H.; Kondo, Y.; Yamanaka, M.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc.* **2002**, *124*, 5059–5067.
12. Fe-mediated. Ferré, K.; Toupet, L.; Guerchais, V. *Organometallics* **2002**, *21*, 2578–2580.
13. Ta-mediated. (a) Smith, D. P.; Strickler, J. R.; Gray, S. D.; Bruck, M. A.; Holmes, R. S.; Wigley, D. E. *Organometallics* **1992**, *11*, 1275–1288. (b) Takai, K.; Yamada, M.; Utimoto, K. *Chem. Lett.* **1995**, 851–852.
14. Rh-catalyzed. (a) Cioni, P.; Diversi, P.; Ingrosso, G.; Lucherini, A.; Ronca, P. *J. Mol. Catal.* **1987**, *40*, 337–357. (b) Cioni, P.; Diversi, P.; Ingrosso, G.; Lucherini, A.; Ronca, P. *J. Mol. Catal.* **1987**, *40*, 359–377. (c) Diversi, P.; Ermini, L.; Ingrosso, G.; Lucherini, A. *J. Organomet. Chem.* **1993**, *447*, 291–298. (d) Costa, M.; Dias, F. S.; Chiusoli, G. P.; Gazzola, G. L. *J. Organomet. Chem.* **1995**, *488*, 47–53. (e) Costa, M.; Dalcanale, E.; Dias, F. S.; Graiff, C.; Tiripicchio, A.; Bigliardi, L. *J. Organomet. Chem.* **2001**, *619*, 179–193. (f) Rh-mediated. Bianchini, C.; Meli, A.; Peruzzini, M.; Vacca, A.; Vizza, F. *Organometallics* **1991**, *10*, 645–651.
15. (a) Yamamoto, Y.; Okuda, S.; Itoh, K. *Chem. Commun.* **2001**, 1102–1103. (b) Yamamoto, Y.; Ogawa, R.; Itoh, K. *J. Am. Chem. Soc.* **2001**, *123*, 6189–6190. (c) Yamamoto, Y.; Takagishi, H.; Itoh, K. *Org. Lett.* **2001**, *3*, 2117–2119. (d) Yamamoto, Y.; Takagishi, H.; Itoh, K. *J. Am. Chem. Soc.* **2002**, *124*, 28–29. (e) Yamamoto, Y.; Kinpara, K.; Saigoku, T.; Takagishi, T.; Okuda, S.; Nishiyama, H.; Itoh, K. *J. Am. Chem. Soc.* **2005**, *127*, 605–613.
16. Varela, J. A.; Castedo, L.; Saá, C. *J. Org. Chem.* **2003**, *68*, 8595–8598.
17. (a) Varela, J. A.; Castedo, L.; Saá, C. *J. Org. Chem.* **1997**, *62*, 4189–4192. (b) Varela, J. A.; Castedo, L.; Saá, C. *J. Am. Chem. Soc.* **1998**, *120*, 12147–12148. (c) Varela, J. A.; Castedo, L.; Maestro, M.; Mahía, J.; Saá, C. *Chem. Eur. J.* **2001**, *7*, 5203–5213.
18. Varela, J. A.; Castedo, L.; Saá, C. *Org. Lett.* **1999**, *1*, 2141–2143.
19. Bönnemann, H.; Brinkmann, R. *Synthesis* **1975**, 600–602.
20. (a) Heller, B.; Sundermann, B.; Fischer, C.; You, J.; Chen, W.; Drexler, H.-J.; Knochel, P.; Bonrath, W.; Gutnov, A. *J. Org. Chem.* **2003**, *68*, 9221–9225. (b) Hoshi, T.; Katano, M.; Nozawa, E.; Suzuki, T.; Hagiwara, H. *Tetrahedron Lett.* **2004**, *45*, 3489–3491.
21. Gutnov, A.; Heller, B.; Fischer, C.; Drexler, H.-J.; Spannenberg, A.; Sundermann, B.; Sundermann, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 3795–3797.
22. For reaction of α,ω-diynes with nitriles, see: (a) Naiman, A.; Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 708–709. (b) Brien, D. J.; Naiman, A.; Vollhardt, K. P. C. *J. Chem. Soc., Chem. Commun.* **1982**, 133–134. (c) Chiusoli, G. P.; Pallini, L.; Terenghi, G. *Transition Met. Chem.* **1983**, *8*, 250–252. (d) Battaglia, L. P.; Delledonne, D.; Nardelli, M.; Predieri, G.; Chiusoli, G. P.; Costa, M.; Pelizzi, C. *J. Organomet. Chem.* **1989**, *363*, 209–222. (e) Zhou, Z.; Battaglia, L. P.; Chiusoli, G. P.; Costa, M.; Nardelli, M.; Pelizzi, C.; Predieri, G. *J. Organomet. Chem.* **1991**, *417*, 51–63. (f) Vitulli, G.; Bertozzi, S.; Lazzaroni, R.; Salvadori, P. *J. Organomet. Chem.* **1986**, *307*, C35–C37. (g) Vitulli, G.; Bertozzi, S.; Vignali, M.; Lazzaroni, R.; Salvadori, P. *J. Organomet. Chem.* **1987**, *326*, C33–C36. (h) Moretto, A. F.; Zhang, H.-C.; Maryanoff, B. E. *J. Am. Chem. Soc.* **2001**, *123*, 3157–3158. (i) Yong, L.; Butenschön, H. *Chem. Commun.* **2002**, 2852–2853. (j) Hoshi, T.; Katano, M.; Nozawa, E.; Suzuki, T.; Hagiwara, H. *Tetrahedron Lett.* **2004**, *45*, 3489–3491.

23. For reaction of α,β-diynes with nitriles in natural product synthesis, see: (a) Parnell, C. A.; Vollhardt, K. P. C. *Tetrahedron* **1985**, *41*, 5791–5796. (b) Geiger, R. E.; Lalonde, M.; Stoller, H.; Schleich, K. *Helv. Chim. Acta* **1984**, *67*, 1274–1282. (c) Saá, C.; Crotts, D. D.; Hsu, G.; Vollhardt, K. P. C. *Synlett* **1994**, 487–489.
24. (a) Anderson, J. C.; Cran, J. W.; King, N. P. *Tetrahedron Lett.* **2002**, *43*, 3849–3852. (b) Anderson, J. C.; Cran, J. W.; King, N. P. *Tetrahedron Lett.* **2003**, *44*, 7771–7774.
25. Dufková, L.; Kotora, M.; Císařová, I. *Eur. J. Org. Chem.* **2005**, 2491–2499.
26. Thorand, S.; Krause, N. *J. Org. Chem.* **1998**, *63*, 8851–8853.
27. (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467–4470. (b) Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1980**, 627–630.
28. For preparation see: (a) Jonas, K.; Deffense, D.; Habermann, D. *Angew. Chem., Int. Ed. Eng.* **1983**, *22*, 716–718. (b) Cammack, J. K.; Jalisatgi, S.; Matzger, A. J.; Negrón, A.; Vollhardt, K. P. C. *J. Org. Chem.* **1996**, *61*, 4798–4800.
29. Jonas catalyst is very reactive and promotes cocyclotrimerization of alkynes with nitriles already at 20 °C. (a) See Ref. 28a. (b) Diversi, P.; Ingrosso, G.; Lucherini, A.; Vanacore, D. *J. Mol. Catal.* **1987**, *41*, 261–270. (c) Bönnemann, H.; Brijoux, W. *New J. Chem.* **1987**, *11*, 549–559. (d) Schulz, W.; Preacejus, H.; Oehme, G. *Tetrahedron Lett.* **1989**, *30*, 1229–1232. (e) See Ref. 18
30. *Stereochemistry of Organic Compounds*; Eliel, E. L., Wilen, S. H., Eds.; Wiley: New York, 1994; p 1144.
31. For leading reference, see: Derdau, V.; Laschat, S.; Hupe, E.; König, W. A.; Dix, I.; Jones, P. G. *Eur. J. Inorg. Chem.* **1999**, 1001–1007.
32. Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Burla, M. C.; Polidori, G.; Camalli, M. *J. Appl. Cryst.* **1994**, *27*, 435.
33. Sheldrick, G. M. *SHELXL97*: *Program for crystal structure refinement from refraction data*; University of Göttingen: Germany, 1997.

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Synthesis and characterization of chiral, bridged resorcinarenes as templates for asymmetric catalysis

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Abstract—A full study of the synthesis of chiral, bridged resorcinarenes (**3a**–**3l**, **13a**, **13b**) is presented using Mannich condensation of C_{2v}-tetraprotected resorcinarenes with chiral 1,*n*-diamines bearing homochiral α-methylbenzyl auxiliaries at each terminal nitrogen. The study has revealed the methodology to be applicable to preparing a broad range of bridged structures with varying lengths of bridge, different functionality in the bridge and various protecting groups on the upper rim. Reproducible and satisfactory yields in the reaction were only obtained with the pendant R group as methyl. The bridged adducts have been fully characterized by a range of spectroscopic techniques, and NMR has revealed varying trends in the way the various bridges protrude into the cavity. Low temperature NMR as well as X-ray structures of tetramesylate **15** and tetratoluate **3g** has revealed hydrogen bonding to the amine nitrogens in the bridge to be an important control element for positioning the bridge relative to the cavity of the bowl. The derivatives provide chiral templates for asymmetric catalysis studies using cooperative effects in the bowl.

1. Introduction

It has long been a desire for synthetic chemists to achieve in the laboratory what is seemingly so effortlessly achieved in biological systems. While it is well known that enzymes can efficiently regio- and stereoselectively catalyse a vast array of organic transformations under mild conditions, a synthetic example has yet to be produced that can match an enzyme in rate acceleration, turnover and specificity.[1] Recently, attention has been directed at utilizing calixarenes and resorcinarenes as platforms for asymmetric processes with many examples now reported on the use of these frameworks for chiral recognition and discrimination studies.[2] Regarding catalysis, while the literature contains examples of calixarenes and resorcinarenes that are used as catalysts,[3] few of them describe asymmetric catalysis. In this regard, Matt has shown that a lower-rim, inherently chiral calixarene scaffold can be used in allylic alkylation (palladium) and hydrogenation (rhodium), although low ees were obtained.[4] Others have shown that cooperative effects may potentially be provided by supramolecular interactions involving the concave bowl.[5] However, a comprehensive picture has yet to emerge regarding application of directing effects in the bowl towards designing superior asymmetric catalysts for carrying out reactions rather than purely for recognition phenomenon. We have recently reported the first example of an asymmetric reaction taking place in the bowl,[6] which we have termed intracavity asymmetric catalysis, using chiral, distally-bridged resorcinarenes of the type shown in Figure 1. In this paper we discuss the scope of the methodology used for the synthesis of chiral bridged resorcinarenes, along with new examples for use in the study of asymmetric reactions occurring in the bowl.

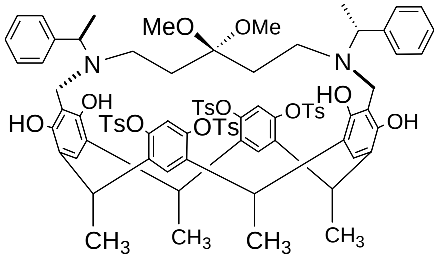

Figure 1. Example of a chiral, distally-bridged resorcinarene.

2. Strategy

Our strategy (Scheme 1) involved using the Mannich reaction to prepare chiral, bridged resorcinarenes[6] as C_{2v}-symmetric templates for catalysis, in which a functional group in the middle of the bridge would offer opportunities for intracavity catalysis. Our choice of Mannich

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Keywords: Resorcinarene; Catalytic template; Mannich reaction.

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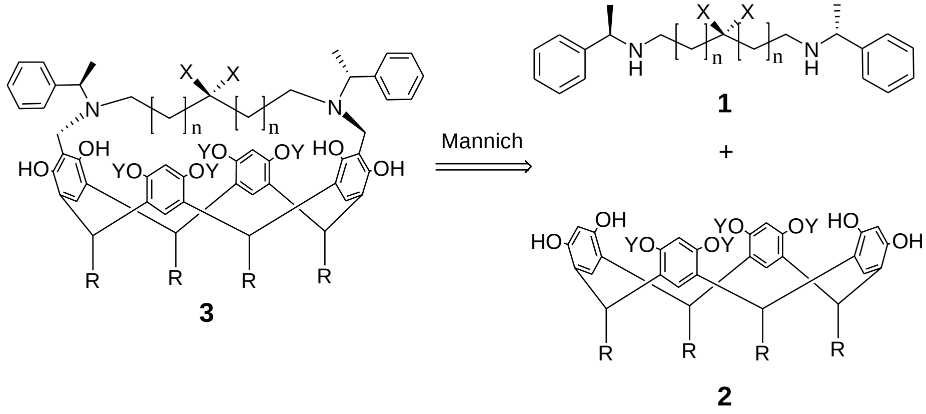


Scheme 1. Retrosynthetic strategy for formation of bridged resorcinarenes.

methodology for bridge introduction was inspired by a precedent set by Böhmer and Shivanyuk,[7,8] who demonstrated that primary diamines undergo Mannich reactions with C_{2v}–tetraprotected resorcinarenes and formaldehyde to afford bridged bis-benzoxazines. We sought to adapt this precedent to using secondary 1,*n*-diamines bearing a chiral α-methylbenzyl unit at each nitrogen as a chiral auxiliary for generation of enantiomerically pure C_{2v}-symmetric bridged resorcinarenes as catalyst templates. This methodology would provide the opportunity to incorporate desirable functionality in the bridge by using functionalized diamine lines of type **1** (varying *n* and X). In addition, other structural parameters for developing a structure–activity profile of catalysis included the choice of upper-rim protecting groups Y in the C_{2v}–array of resorcinarene **2**, as well as the pendant benzylic R groups.

Our previous work[6] described the synthesis of bridged resorcinarenes with Y = tosylate, $n = 1$ and varying length of benzylic R with or without ketal X groups in the bridge as described in Table 1. In the comprehensive study described in this paper, emphasis was focused on two parameters, namely the length and nature of the bridge (*n* and X) and the size and nature of the upper-rim protecting groups (Y).

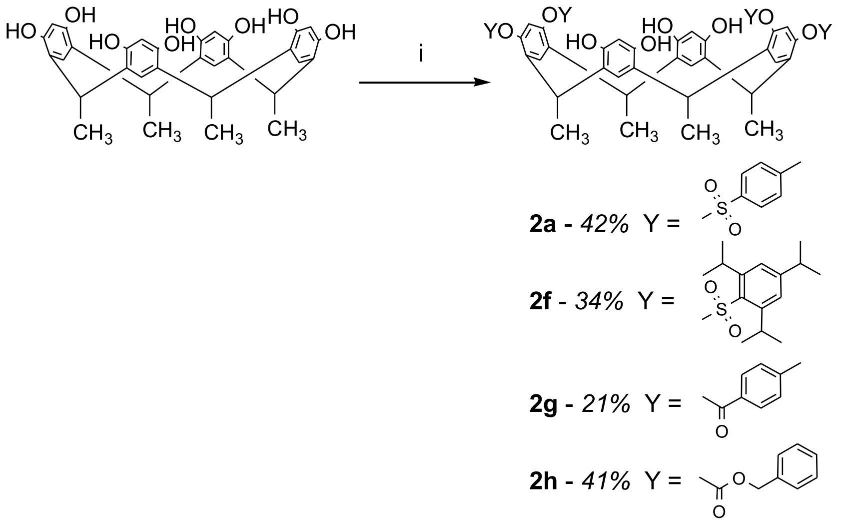
Table 1. Previously synthesized chiral bridged resorcinarenes

	Y	R	*n*	X, X
3a	Tos	CH_3	1	H
3b	Tos	C_5H_{11}	1	H
3c	Tos	$C_{11}H_{23}$	1	H
3d	Tos	CH_3	1	OMe
3e	Tos	CH_3	1	$OCH_2C(CH_3)_2CH_2O$

In order to install different upper-rim protecting groups on the bridged resorcinarenes, it was necessary to synthesize a series of appropriately C_{2v}-protected resorcinarenes, which could be used in the Mannich reaction with suitable diamines (cf. Scheme 1). This could be achieved by using and expounding methodology developed by Shivanyuk and Böhmer in 1998,[9] involving either direct functionalisation with 4 equiv of electrophile or through formation of the tetra-Cbz derivative, which may then be used to form other C_{2v}-protected resorcinarenes via a protection, deprotection (CBz) protocol. The latter methodology is powerful in view of its practical simplicity, since the desired C_{2v}–tetra-Cbz derivative intermediate precipitates out of the reaction medium as a complex with 2 equiv triethylammonium hydrochloride, thus ensuring high purity and easy access to the desired product. After functionalising the remaining four hydroxyl groups with a suitable electrophile, the Cbz groups can be removed by facile hydrogenolysis furnishing new C_{2v}-tetraprotected resorcinarenes.

There were many possible protecting-group targets for our study, but essentially the aim was to evaluate a selection of both large and small ones that might affect the steric environment in the bowl of the final catalyst. One restriction in setting about these syntheses was that the methodology was only really practical on the tetramethylresorcinarene (**2**; $R = CH_3$, $Y = H$), since resorcinarenes with longer pendant chains generally gave little or no product in the acylation reactions.[9] Further studies in this area, though, may result in C_{2v}-protected resorcinarenes with longer pendant chains such as the tetraundecylresorcinarene tetratosylate (**2c**; $R = C_{11}H_{23}$, Y = Tos) used to synthesize **3c**.[10]

The large number of possibilities for protecting groups resulted in the decision to evaluate other sulfonates of varying sizes, in view of the success of the tetratosylates. A methanesulfonyl group (Mes) was identified as a good example of a smaller protecting group than tosylate, with 2,4,6-triisopropylbenzenesulfonate (Trips) as one with greater steric bulk. It was also thought desirable to evaluate groups other than the sulfonate functionality in order to probe electronic effects. Thus the bridged resorcinarene tetrabenzyloxycarbonate (Cbz) was identified, also in view of its ready availability[9] as already mentioned, as well as the resorcinarene tetra(*p*-tolyl) (Tol) ester since it was also available by direct acylation of the parent resorcinarene with *p*-toluoyl chloride.[9] It was thought that evaluating this bridged analogue would provide an interesting comparison to the resorcinarene tetratosylate **3a** in view of similarity in steric size but difference in donor character around the respective oxygen atoms. Likewise, the resorcinarene tetraacetate (Ac) was also considered as one for making an informative comparison with the resorcinarene tetramesylate on steric grounds while at the same time complementing the ester series. A tetramethylated resorcinarene was also targeted for this study.



Scheme 2. Direct synthesis of C_{2v}-protected resorcinarenes. Reagents and conditions: (i) YCl (4 equiv), Et_3N (4 equiv), CH_3CN, rt.

3. Results and discussion

3.1. Synthesis of alternative C_{2v}-protected resorcinarenes

Formation of the sterically demanding C_{2v}-symmetrical resorcinarene tetratripsylate **2f** (2,4,6-triisopropyl-benzenesulfonate) was gratifyingly achieved in 34% yield[†] using the methodology developed by Shivanyuk for tetratosylation (Scheme 2).[11] Similarly, both the C_{2v}-resorcinarene tetratoluate **2g** as well as the all-important C_{2v}-resorcinarene tetrabenzyloxycarbonate (CBz) **2h** could be readily obtained via the said literature procedure in 21 and 41% yields, respectively.[9]

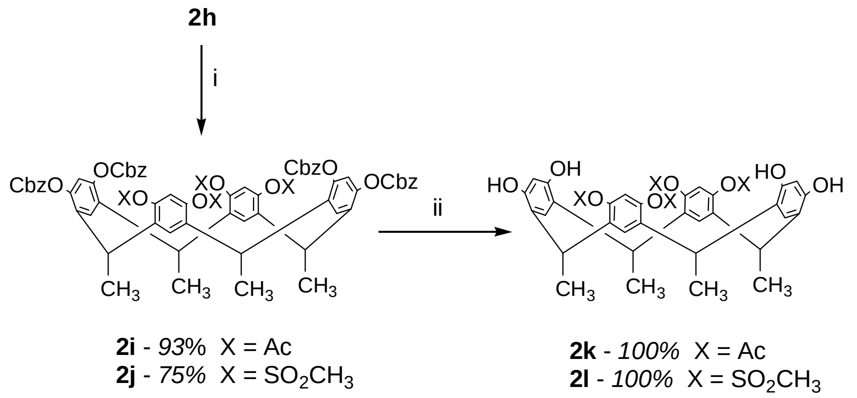
The resorcinarene tetraacetate **2k** could be synthesized by the method reported by Shivanyuk, involving acetylation of the tetracarbonate **2h** to give **2i** in excellent yield followed by quantitative cleavage of the protecting groups.[9] For this reaction, the authors used catalytic hydrogenolysis over palladium supported on carbon in dioxane as a solvent. This was probably due to the compound's poor solubility in ethanol. In the present work it was found that performing the reaction in a solvent mixture of ethanol and THF (1:1 v:v) at room temperature gave a better reaction profile than that from using dioxane. Formation of the resorcinarene tetramesylate **2l** was also achieved in the same way as the resorcinarene tetraacetate **2k** (Scheme 3). To this end, mesyl chloride was reacted with resorcinarene tetracarbonate **2h** in the presence of Hünig's base to give the required tetramesylate derivative **2j** in a good yield (75% after recrystallization of the crude reaction product). The mesylation was rapid being finished by tlc within 30 min (from 0 °C to rt). Removal of the carbonate groups could likewise be achieved as before using catalytic hydrogenolysis. Once again, a 1:1 mixture of ethanol and THF was the preferred solvent, cleanly affording the desired tetramesylate **2l** after 6 h at room temperature.

It was also thought desirable to tetramethylate the resorcinarene. Though resorcinarene tetratosylate **2a** could be tetramethylated using dimethyl sulphate, the tosyl groups failed to be cleaved under basic conditions, a fact already noted by Shivanyuk.[9] Tetramethylation of the resorcinarene tetracarbonate **2h** or tetratoluate **2g** unfortunately failed to give the desired C_{2v}-symmetrical product. Many conditions were tried, using both dimethyl sulfate or methyl iodide as methylating agent, and varying the type of base used (sodium hydride, triethylamine, Hünig's Base). In one case the reaction was attempted in neat methyl iodide, but in all attempts the reactions gave mixtures of 3–5 unidentified products, which were inseparable by chromatography. It became clear, after stirring the tetracarbonate with sodium hydride that the failure of these reactions was due to the starting material undergoing some manner of transformation. Tentatively it could be suggested that this was due to the carbonate groups migrating around the resorcinarene ring. Unfortunately, the phenolic hydroxyl oxygens are not nucleophilic enough for direct alkylation and thus require the use of a base to form the phenoxide, which resulted in starting-material transformation. Direct methylation of tetramethylresorcinarene (**2**; $R=CH_3$ and $Y=H$) did not give the desired product; one isolated product revealed tetramethylation by ^1H NMR but did not show C_{2v}-symmetry.

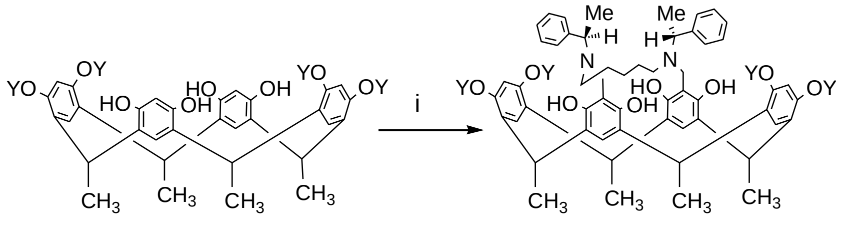
3.2. Synthesis of bridged resorcinarenes

The synthesis of bridged resorcinarenes containing different protecting groups, $n=1$ and $X=H$, was achieved using the methodology already described for synthesizing the bridged resorcinarene tetratosylates.[10] Thus each C_{2v}-symmetrical tetraprotected resorcinarene **2a–2l** was heated in acetonitrile with a slight excess of the diamine and paraformaldehyde in large excess to yield distally-bridged products **3a–3l** (Scheme 4). Such conditions were found to be superior to reaction with aqueous formaldehyde in ethanol, which resulted in resorcinarene ethoxymethylation. Yields were generally good except for the resorcinarene tetraacetate, which was not optimized (Table 2).

[†] Yields for these types of reactions are typically less than 50% even dropping to less than 10% owing to the formation of isomeric products.



Scheme 3. Reagents on conditions: (i) XCl (5 equiv), *i*-Pr$_2$NEt (6 equiv), DCM, rt; (ii) H$_2$, Pd/C (10%), TH–FEtOH (1:1), rt.



2 **3**

Scheme 4. Reagents and conditions: (i) diamine **1** (1.2 equiv), (CH$_2$O)$_n$ (10 equiv), 90 °C.

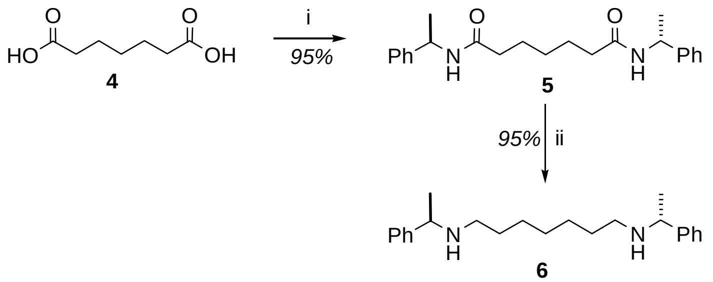
Table 2. Results for bridging reactions

	Y	Yield (%)
3a	Tos	60
3f	Trips	78
3g	Tol	55
3h	Cbz	70
3k	Ac	20
3l	Mes	51

3.3. Synthesis of longer diamines

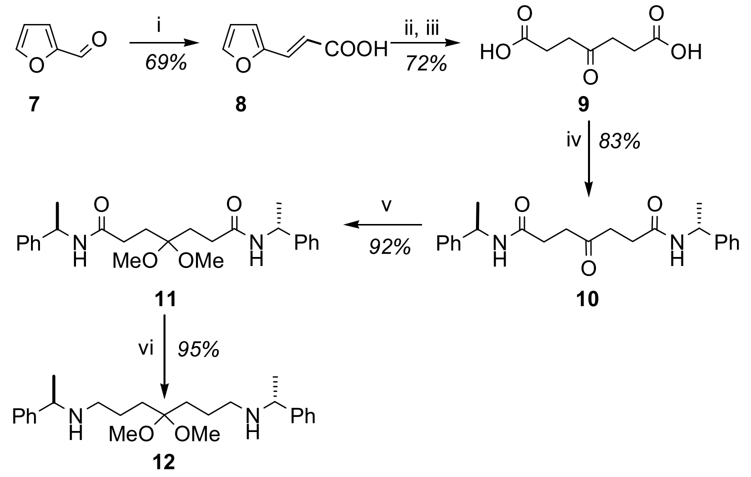
The second parameter evaluated was the synthesis of bridged resorcinarenes with longer bridges. Therefore it became necessary to synthesize a longer diamine than type **1**. This could be achieved using pimelic acid (heptanedioic acid) **4** as starting material as shown in Scheme 5. Thus pimelic acid was readily coupled to α-methylbenzylamine under DCC conditions yielding the desired diamide **5** in excellent yield. In this reaction the addition of hydroxybenzotriazole (HOBt) was found to be important for preventing the formation of the *N*-acylated urea side-product. Reduction of the diamide was achieved using lithium aluminium hydride in refluxing THF to give diamine **6** in 95% yield for each step.

In a similar fashion, synthesis of the dimethoxy ketal-functionalized diamine required 4-oxopimelic acid, which could be derived from furfural in three steps. The first of the steps converted furfural **7** into 3-(2-furyl)acrylic acid **8** via a Knoevenagel reaction,[12] by heating furfural with malonic acid in pyridine at 100 °C for 2 1/2 h to give **8** in a good overall yield (69% after recrystallization). Conversion of acid **8** into the desired oxopimelic acid **9** was efficiently carried out in two further steps by first refluxing the acid **8** in ethanol using a continuous passage of HCl gas.[13] Distillation of the crude material obtained gave diethyl pimelate as a clear oil which was readily saponified with aqueous potassium hydroxide (3 M) at room temperature in under 30 min, resulting in 4-oxopimelic acid **9** in 72% overall yield. The coupling of α-methylbenzylamine was again accomplished via a DCC coupling with the diacid to give diamide **10** in good yield (83%). The penultimate step required protection of the ketone carbonyl group as its dimethoxy ketal, prior to reduction of the diamide. This was



4 **5** **6**

Scheme 5. Reagents and conditions: (i) α-methylbenzylamine, DCC, HOBt, CH$_2$Cl$_2$; (ii) LiAlH$_4$, THF, reflux.



Scheme 6. Reagents and conditions: (i) malonic acid, pyridine, 100 °C; (ii) EtOH, HCl, reflux; (iii) KOH, H_2O, rt; (iv) α-methylbenzylamine, DCC, HOBt, CH_2Cl_2, rt; (v) $CH(OCH_3)_3$, MeOH, *p*-TsOH (cat), reflux; (vi) $LiAlH_4$, THF, reflux.

achieved by refluxing **10** in excess trimethyl orthoformate and catalytic *p*-toluenesulfonic acid overnight. This cleanly afforded the desired ketal **11** in yields of up to 92%. Finally, reduction of diamide **11** to diamine **12** was found to be possible using lithium aluminium hydride in refluxing diethyl ether, with the addition of triethylamine to attenuate the slight Lewis acidity of the metal salts, Scheme 6.

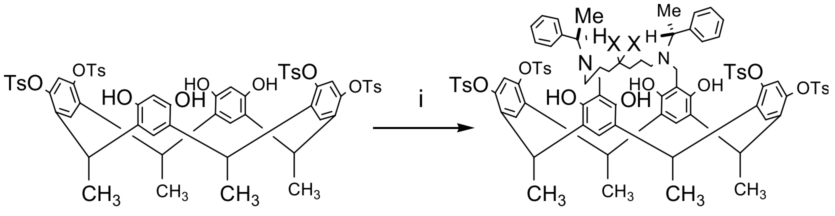
3.4. Synthesis of longer bridged resorcinarenes

The newly prepared longer chiral diamine line **6** was used to bridge resorcinarene tetratosylate **2** (Y=Tos, R=CH_3). Using the standard reaction conditions, a maximum yield of 36% of the bridged product **13a** was obtained (Scheme 7). The low yield of bridged resorcinarene **13a** was in contrast to the better yields that were obtained for the bridged resorcinarene using the shorter diamine line **3a**.

This lower yield deserves mechanistic comment. It is reasonable to assume that the bridging process is achieved via two discrete steps, the first being the initial aminomethylation, which is followed by a second, rate-determining aminomethylation step to close the bridge. The lower yield for **13a** from the longer line **6** may be accounted for by assuming closure to be slower than for **3a** on entropic grounds (larger $\Delta S\#$ −ve). The longer lifetime for the mono-adduct from **6**, would then increase the chances of an intermolecular reaction. Careful scrutiny of the reaction tlc revealed another product, which was slightly more polar than the bridged product **13a**. It had virtually identical ^1H and ^{13}C NMR spectra to the bridged product **13a**, the only difference being that the signals in the ^1H NMR were a little less resolved. Its IR spectrum was no different to **13a**, but its optical rotation was opposite in sign and different in magnitude (−7.0° vs +13.2° for **13a**). MALDI-TOF mass spectrometry revealed that this compound had a molecular mass of 3047 amu corresponding to exactly twice the molecular mass of bridged resorcinarene **13a**. This prompted us to conclude that the side-product isolated in 5% yield was dimer **14** (Fig. 2).

This structure seems plausible as similar examples exist in the literature, which have been well-documented and reviewed.[14] In 1998, Böhmer demonstrated this type of dimerisation with tetrapentylresorcinarene **2** (Y=H, R=C_5H_{11}) and ethylenediamine under Mannich conditions, giving an octabenzoxazine dimer linked by four bridges.[15] Böhmer reported that only ethylenediamine worked, whereas 1,3-diaminopropane, and ethylenediamine derivatives such as 1,2-diaminocyclohexane or *N*,*N*′-dimethylethylenediamine failed to give any defined reaction product.[15] This chiral resorcinarene dimer linked by two bridges represents the first example of a dimer of this type.

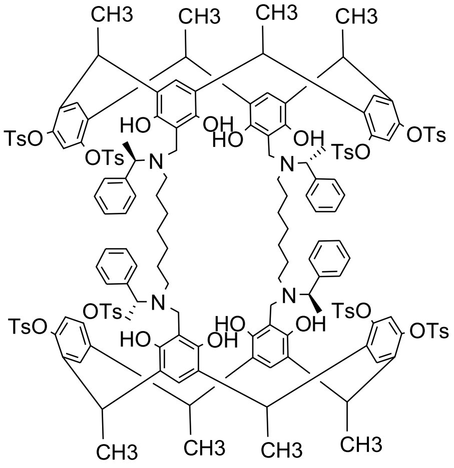
In a similar fashion, the functionalized, longer ketal-diamine **12** could be used to bridge resorcinarene **2** (Y=Tos, R=CH_3). This was performed in the usual manner at 90 °C and gave 10% of the desired product **13b** after one hour. Increasing the number of equivalents of diamine from one to three gave a vastly improved yield of 48%. With a slight



2

13a X = H (*36%*)
13b X = OMe (57%)

Scheme 7. Reagents and conditions: (i) diamine **6**/**12**, $(CH_2O)_n$, CH_3CN, 80 °C, 2 h.



14

Figure 2. Proposed structure of dimer **14**.

decrease in reaction temperature, the yield could be further optimized to 57%. Interestingly, in this case no dimer like **14** was observed, presumably because of the steric presence of the ketal in the middle of the line.

4. Spectroscopic and conformational aspects

The NMR spectra of the bridged resorcinarenes were remarkably straightforward to assign, owing to the high degree of symmetry; a typical example of a ^{1}H NMR spectrum is shown in Figure 3 for resorcinarene **3h** (Y = CBz). All of the NMR signals could be unambiguously assigned using 2D-NMR techniques (HSQC and HMBC). A few significant features of the ^{1}H NMR spectra deserve comment. Firstly, the three singlets (marked with *) for the resorcinarene aromatic methine protons of the bridged products were used as markers to indicate that reaction had successfully taken place at the positions *ortho* to both hydroxyl groups of the tetraprotected resorcinarene.

Secondly, a new signal between 3.71 and 3.78 ppm (singlet in Figure 3, although in some cases appearing as a pair of doublets owing to diastereotopicity; marked with ↓) was always observed for these structures corresponding to the methylene protons on the carbon attaching the bridge to the resorcinarene. Thirdly, no hydroxyl signals were observed suggesting a fast interconversion between hydrogen-bonded modes to be occurring that creates very broad peaks on the timescale of the NMR experiment. Fourthly, there was an upfield shift of all the methylene protons on the bridge relative to the starting diamine, with the central methylenes experiencing the greatest shift; this feature is an important indication that the bridge resides over the bowl, resulting in anisotropic shielding by the aromatic rings comprising the bowl.[16] An increase in upfield shift from one resorcinarene to another was interpreted as indication of the bridge spending more time deeper within the cavity of the bowl. Table 3 shows the variation in the chemical shift of the central methylene group for the bridged resorcinarenes synthesized. Going from **3a** to **3b** and then to **3c** involving lengthening of the pendant alkyl chain creates a conformational change that encourages the bridge to spend more time lower within the cavity. This may be due to increased repulsion between the pendant R groups, resulting in the upper-rim aromatic rings to fold inwards slightly forcing the bridge to bury itself more into the cavity. In the case of **3a** versus **3h** it would appear that the CBz protecting groups have a similar effect, also resulting in the bridge to lie lower in the cavity. Conversely, the sterically undemanding mesyl groups with CH_3 as the pendant R group (**3l**) releases the line out of the cavity as indicated by a weaker shielding effect compared to **3a**. In the case of the longer bridge **13a**, the central methylene protons do not exhibit as great an upfield chemical shift as **3a**, indicating that the longer bridge prefers to sit higher above the cavity than deeper in it, presumably to maximize entropy.

Table 3. Comparison of chemical shifts for central methylene protons

	n	Y	R	Central methylene (ppm)	Central methylene Δppm
1	1	—	—	1.27	—
3a	1	Tos	CH_3	0.90	−0.37
3b	1	Tos	C_5H_{11}	0.72	−0.55
3c	1	Tos	$C_{11}H_{23}$	0.70	−0.57
3f	1	Trips	CH_3	0.99	−0.28
3g	1	Tol	CH_3	0.93	−0.34
3h	1	Cbz	CH_3	0.77	−0.50
3k	1	Ac	CH_3	0.84	−0.43
3l	1	Ms	CH_3	1.05	−0.22
6	2	—	—	1.32	—
13a	2	Tos	CH_3	1.10	−0.17

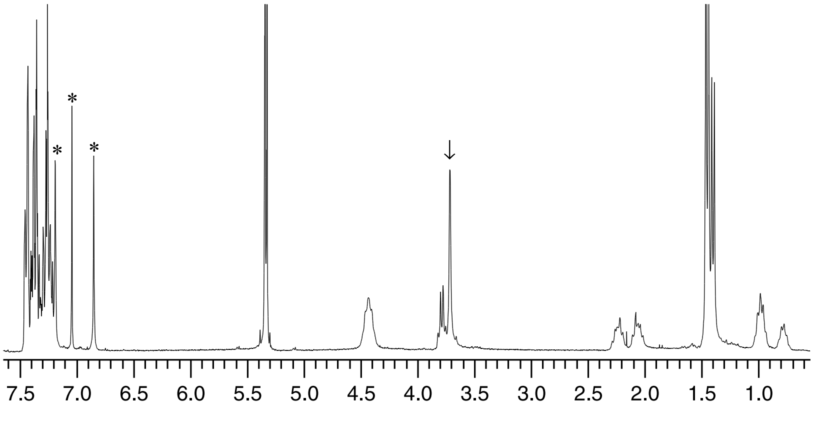


Figure 3. ^{1}H NMR spectrum of resorcinarene **3h**.

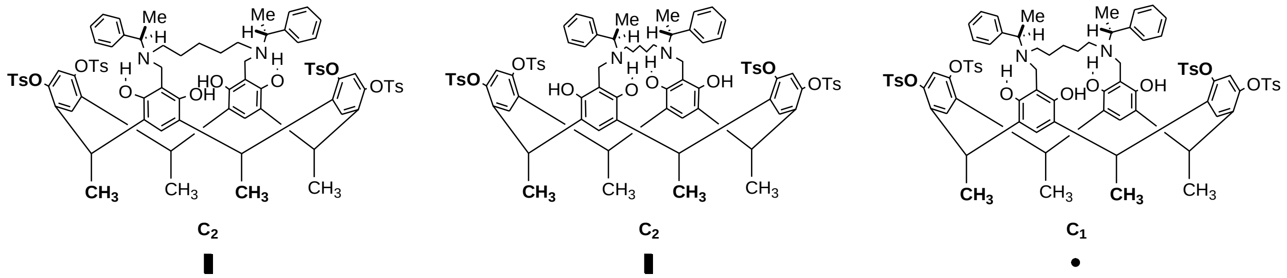


Figure 4. Hydrogen bonded conformers of **3a**.

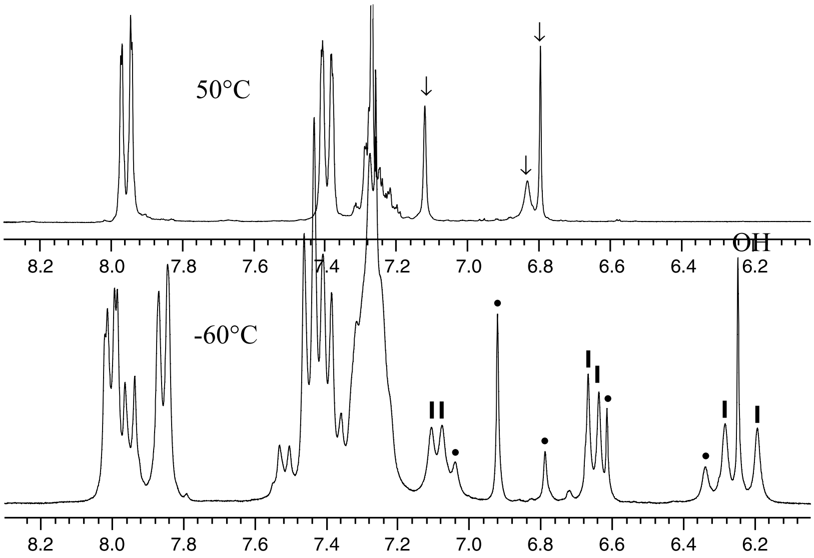


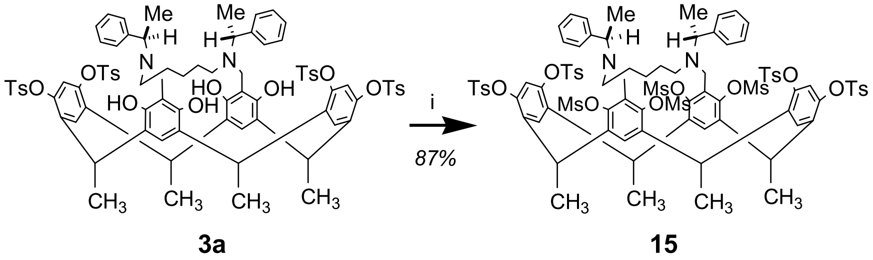
Figure 5. High and low temperature ^{1}H NMR spectra of **3a**.

Finally, another important observation was the downfield shift (>0.5 ppm) of the protons on the lower rim of the protected resorcinol rings. Prior to bridging they were found around 6.25 ppm, significantly upfield to what would be expected. The reason for this has been attributed to the resorcinarene existing in a boat conformation,[17] since the aromatic groups that are most horizontal have their protons on the lower rim in the shielding zone of the vertical aromatic rings. In the bridged compounds, the protons appeared downfield at around 6.85 ppm (+/−0.20 ppm), suggesting a change in shape towards the crown conformation, though to what extent this change had occurred was not pursued any further by NMR studies.

The possibility of hydrogen bonding between the tertiary amine nitrogens on the bridge and the phenolic hydroxyl groups on the resorcinarene was also considered as an important structural feature. Such bonding would generate three diastereomeric structures as shown in Figure 4; two with C_2 symmetry and one with C_1 symmetry. The C_1-symmetric structure would be expected to show 5 singlets for its aromatic methine protons in its ^{1}H NMR spectrum, while the C_2-symmetric isomers would show three singlets each. This distribution as expected was not seen at temperatures above room temperature, owing to conformational exchange. However, on cooling to 0 °C the resorcinarene aromatic signals became very broad and indistinct. Further cooling to −60 °C revealed a far more complex picture, in which the rate of 'flipping' between the different hydrogen bonded modes slowed enough for the individual diastereomers in Figure 4 to be observed. Figure 5 shows the aromatic region of the ^{1}H NMR spectrum of **3a** at 50 and −60 °C. At 50 °C there are 3 signals (marked with ↓) at 6.79, 6.83 and 7.11 ppm for the average of the conformers. On cooling, the signals become increasingly broadened and then resolved below −40 °C into separate signals, becoming clear at −60 °C. By careful inspection and integration it was possible to assign the signals for the C_1 conformer (5 signals marked with ●), while 2 sets of 3 signals each could be seen for the C_2 conformers (marked with ▮) One extra signal could be attributed to a hydroxyl proton.[‡] Integration revealed that the different conformers existed in an approximate ratio of 1:1:1 (C_2:C_2:C_1). The signal at $\delta = 6.92$ ppm integrates for 2H.

It is possible that H-bonding could affect the conformation of the bridged resorcinarene, and therefore the hydroxyl substituents were suitably protected. The latter are however not easy to functionalize,[18] and it was thus decided to use mesyl chloride as a small reactive electrophile. Mesylation using excess mesyl chloride and Hünig's base in dichloromethane was successful in furnishing the desired tetramesylated product **15** in a favourable 87% yield (Scheme 8).

[‡] As mentioned, the hydroxyl protons are invisible at normal NMR temperatures owing to the rapid hydrogen bonding exchange. On cooling, the signals at 6.24 ppm and at 13.10 ppm (not shown) become visible.



Scheme 8. Reagents and conditions: (i) mesyl chloride (20 equiv), i-Pr_2EtN (20 equiv), DCM, rt.

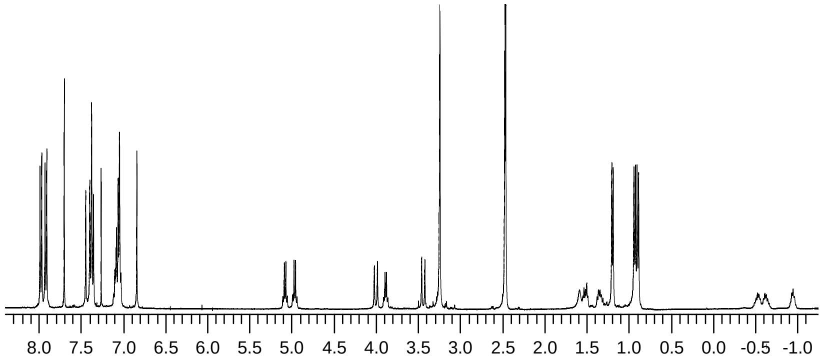


Figure 6. ^{1}H NMR spectrum of resorcinarene **15**.

The ^{1}H NMR spectrum (Fig. 6) of **15** provided some surprises, notably that the methylene protons in the centre of the bridge were now found at −0.95 ppm, representing a massive 2.22 ppm upfield shift from the diamine **1** (prior to bridging). This could only be attributed to the bridge spending a much higher percentage of its time deep within the resorcinarene cavity. This might arise from the disruption of the hydrogen bonding with the amines, allowing the bridge to 'collapse' into the cavity, analogous to what happens if the supports of a suspension bridge are removed.

Furthermore, another intriguing spectroscopic observation was a 0.45 ppm upfield shift of the signals for the pendant methyl groups on the resorcinarene (from 1.37 to 0.89 and 0.93 ppm). The reason for this was not made clear until a single crystal X-ray structure determination was realised. Great difficulty was experienced in trying to grow suitable crystals for X-ray diffraction. Eventually a suitable crystal was found in a solution of toluene, acetone and dichloromethane. **15** crystallized in the space group $P2_12_12$ with $Z{=}4$, with two dichloromethane molecules of solvation which were located in five different positions in the unit cell with partial occupancies. As a result, the structure could not be refined satisfactorily because the dichloromethane molecules were highly disordered with large temperature factors. Therefore, the fractional atomic coordinates of the structure are not reported. Only the unit cell parameters are listed in the supplementary data. The positions of the resorcinarene atoms alone were located unambiguously and its molecular conformation can thus be reported. This is given by the torsion angles listed in the supplementary data.

The X-ray picture of **15** as an ORTEP diagram (ellipsoidal model at 30% probability level) revealed the bridge to be positioned inside the cavity in accordance with predictions from the ^{1}H NMR, and also provided the answer to the upfield shift of the pendant methyl groups. As can be seen in Figure 7, the aromatic groups of the tosylate groups are pointing downwards towards the lower rim in order to

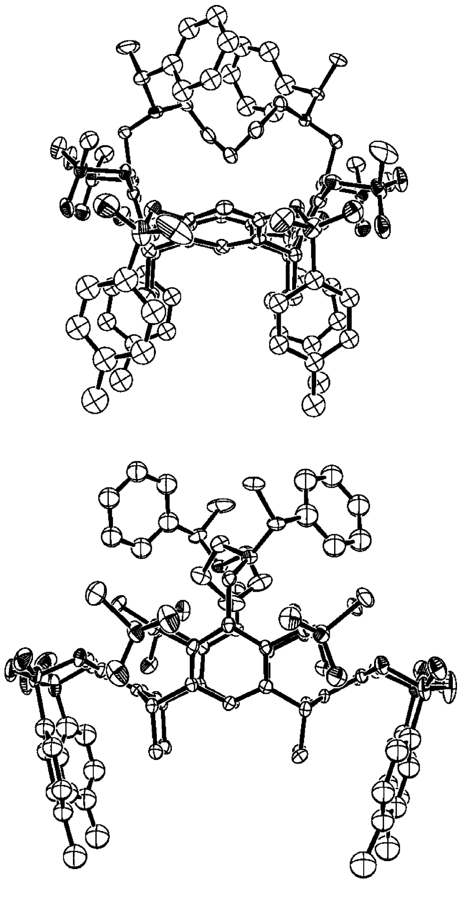


Figure 7. X-ray structure of **15**.

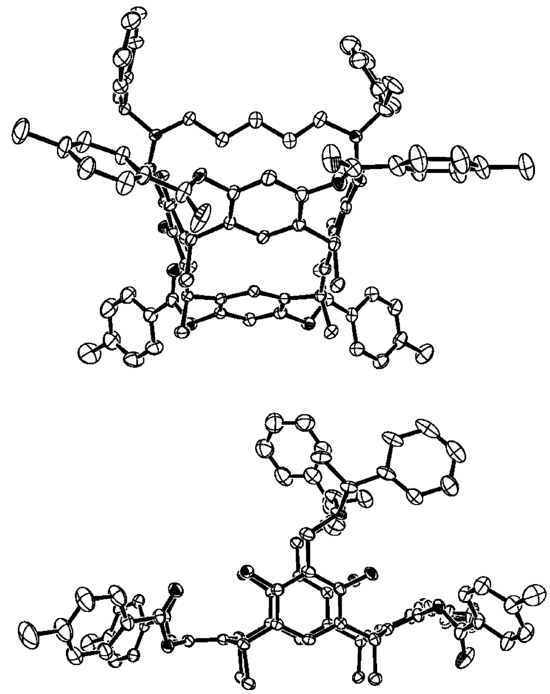


Figure 8. X-ray structure of **3g**.

minimize repulsion with the mesylate groups. As a result, they are in a position to anisotropically shield the pendant methyl groups.

It is clear from this X-ray structure that the hydrogen bonding in the bridged resorcinarene is important in maintaining a preferred shape by: (a) keeping the bridge above the cavity, potentially allowing reactions to be accommodated there; and (b) holding the protecting groups up instead of down allowing for potential cooperative effects in the bowl.

It was thus hoped that an X-ray structure of a hydrogen-bonded bridged resorcinarene could be obtained. Suitable crystals were not readily obtainable, but eventually slow evaporation of a solution of tetratoluate **3g** in diisopropyl ether, pentane and dichloromethane resulted in the formation of diffraction-quality crystals, although they were very unstable outside their mother liquor. Bridged resorcinarene **3g** crystallized in the space group $P1$ with $Z=2$ as a dipentane solvate. There are thus two independent resorcinarene host molecules and four pentane guest molecules in the unit cell, all located at general positions. We note that the comformation of the two independent resorcinarene molecules are very similar, and Figure 8 shows one of these structures. The unit cell parameters and other crystal data and refinement data are given in the supplementary data.

The X-ray structure of **3g** reveals a boat-like conformation and demonstrates the effect that hydrogen bonding has on the positioning of the bridge, sustaining it over the cavity and with the protecting toluate ester groups held up towards the cavity (as apposed to hanging downwards as in **15**).

5. Conclusions

This paper has extended the methodology developed previously,[6,9] to the synthesis of a range of new, chiral, bridged resorcinarenes, which have been fully characterized by NMR and X-ray techniques resulting in the observation of some interesting aspects of bridge-positioning relative to the cavity of the bowl. In the following paper, a comprehensive study is presented on the use of these derivatives as asymmetric templates for the catalyzed enantioselective addition reaction of diethylzinc to benzaldehyde, which is considered to be one the first reported examples of using the bowl of an asymmetrically functionalized resorcinarene for promoting asymmetric catalysis,[6] as suggested recently by Iwanek.[19] The results are rationalized using a stereoselectivity model.

6. Experimental

6.1. General remarks

All reactions were carried out under nitrogen using dry solvents. Nuclear Magnetic Resonance spectra were recorded on a Varian Unity 400 (100 MHz for ^{13}C) or Varian Mercury 300 MHz (75 MHz for ^{13}C) and were carried out in chloroform-*d*. Optical rotations were obtained using a Perkin Elmer 141 polarimeter at 20 °C. Melting points were obtained using a Reichert Jung Thermovar hot-stage microscope and are uncorrected. Elemental analyses were performed using a Fisons EA 1108 CHN elemental analyser. Infrared spectra were recorded on a Perkin–Elmer Paragon 1000 FT-IR spectrometer in either dichloromethane or chloroform. Resorcinarenes **2a**,**g–i** were synthesized according to the literature procedures.[9] Bridged resorcinarenes **3a–e** have been reported previously.[6,10] Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 273318 and 273319. Copies of the data can be obtained free of charge from CCDC via www.ccdc.cam.ac.uk/data_request/cif. Names and numbering of compounds follows IUPAC 'phane' nomenclature rules;[§] Figure 9 shows two examples of this.

6.1.1. 3^4,3^6,7^4,7^6-Tetrahydroxy-2,4,6,8-tetramethyl-1^4,1^6,5^4,5^6-tetra(2′,4′,6′-triisopropylbenzene-sulfonyl-oxy)-1,3,5,7(1,3)tetrabenzenacyclooctaphane (2f). Tetramethyl-resorcinarene **2** ($R=CH_3$, $Y=H$) (3.27 g, 6 mmol) was dissolved in acetonitrile (60 mL) and triethylamine (3.35 mL, 24 mmol) added. The pink, heterogeneous solution was stirred at room temperature for 15 min and then 2,4,6-triisopropylbenzenesulfonyl chloride (5.16 g, 6 mmol) was added in one portion. The reaction was allowed to stir at room temperature overnight, followed by filtration of the solid precipitate formed. The precipitate was washed with cold acetonitrile (2×20 mL) and then dissolved in dichloromethane (75 mL). 1 M HCl (100 mL) was added and the product extracted into dichloromethane (3×50 mL). After drying ($MgSO_4$) and evaporation, the crude product was further purified by column

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[§] For a full description see http://www.chem.qmul.ac.uk/iupac/

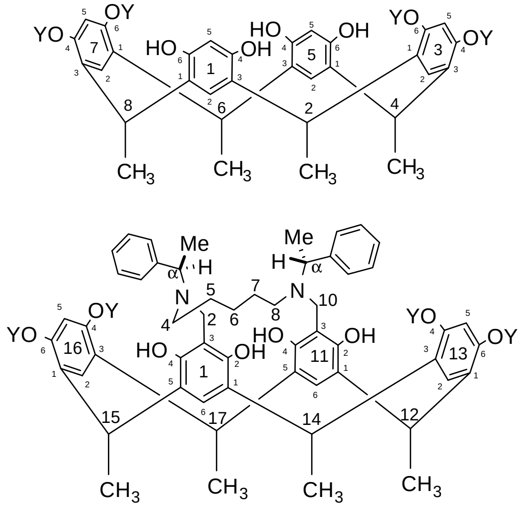

Figure 9. Example of numbering format for resorcinarenes.

chromatography (60 g silica gel, eluting with ethyl acetate/petroleum ether 1:4). In this way, tetratripsylresorcinarene **2f** (3.3 g, 34%) could be prepared as a white solid. Mp 190–192 °C (from DMF/ethyl acetate/petroleum ether); ν_{max}/cm^{-1} (CHCl$_3$) 3476s+3387s (O–H, H-bonded), 3015s (C–H, aromatic), 2964s+2931 (CH$_3$), 1599m+1514s (aryl stretch), 1346s+1180s (–SO$_2$–); δ_H (300 MHz, CDCl$_3$) 1.11+1.13 (48H, 2×d, J=6.8 Hz, 7′/9′-*i*-Pr), 1.21 (24H, d, J=6.8 Hz, 8′-*i*-Pr), 1.38 (12H, d, J=6.8 Hz, –CH_3), 2.88 (4H, spt, J=6.8 Hz, H-8′), 3.93 (8H, spt, J=6.8 Hz, H-7′/9′), 4.39 (4H, q, J=6.8 Hz, H-2,4,6,8), 6.02 (2H, s, H-1^5,5^5), 6.31 (2H, s, H-3^2,7^2), 6.57 (2H, s, H-3^5,7^5), 7.03 (2H, s, H-1^2,5^2), 7.16 (4H, br, –OH), 7.18 (8H, s, H-3′,5′); δ_C (75 MHz, CDCl$_3$) 20.0 (CH$_3$), 23.4 (8′*i*-Pr), 24.4 (7′/9′*i*-Pr), 29.9 (C-7′/9′), 31.9 (C-2,4,6,8), 34.2 (C-8′), 102.0 (C-1^5,5^5), 113.5 (C-3^5,7^5), 119.0 (C-1^1,1^3,5^1,5^3), 124.1 (C-3′,5′), 125.2 (C-1^2,5^2), 127.0 (C-3^2,7^2), 129.5 (C-1′), 139.1 (C-3^1,3^3,7^1,7^3), 144.8 (C-3^4,3^6,7^4,7^6), 151.2 (C-2′,6′), 153.2 (C-1^4,1^6,5^4,5^6), 154.5 (C-4′); MALDI TOF: *m*/*z* (rel. int.) 1609.4 [M$^+$−H] (81), 1342.91 [M$^+$−SO$_2$Ar] (69), 1076.09 [M$^+$−SO$_2$Ar×2] (70), 809.27 [M$^+$−SO$_2$Ar×3] (53), 542.06 [M$^+$−SO$_2$Ar×4] (45). Found: C, 68.58; H, 7.54; S, 7.71%; C$_{92}$H$_{120}$O$_{16}$S$_4$ requires C, 68.63; H, 7.51; S, 7.97%.

6.1.2. 3^4,3^6,7^4,7^6-Tetraacetoxy-1^4,1^6,5^4,5^6-tetrahydroxy-2,4,6,8-tetramethyl-1,3,5,7(1,3)tetrabenzenacyclooctaphane (2k)[9]. Resorcinarene **2i** (1 g, 0.8 mmol) was dissolved in a 1:1 solvent mixture of THF and ethanol (50 mL). 10% Palladium on carbon (100 mg, 0.1 mmol) was added and the solution stirred at room temperature under a positive pressure of hydrogen. After 4 h the reaction was checked for completion (tlc) and the catalyst filtered off through Celite®, washing with dichloromethane (100 mL). Evaporation of the solvent afforded tetraacetate **2k** (570 mg, 100%) as a pale pink solid. The ^{1}H NMR spectrum corresponded to that published in the literature.[9] δ_H (300 MHz, DMSO-d_6) 1.39 (12H, d, J=7.1 Hz, CH$_3$), 2.11 (12H, s, OAc), 4.39 (4H, q, J=7.1 Hz), 6.30 (2H, s, Ar-H), 6.41 (2H, s, Ar-H), 6.58 (2H, s, Ar-H), 7.33 (2H, s, Ar-H), 8.82 (4H, br s, –OH).

6.1.3. 3^4,3^6,7^4,7^6-Tetra(benzyloxycarbonyloxy)-1^4,1^6,5^4,5^6-tetra(methylsulfonyloxy)-2,4,6,8-tetramethyl-1,3,5,7 (1,3)tetrabenzenacyclooctaphane (2j). Diisopropylamine (3.06 mL, 17.6 mmol) and resorcinarene tetra-Cbz **2h** (3.46 g, 3.2 mmol) were added to dry dichloromethane (40 mL) and the solution cooled to 0 °C. Mesyl chloride (1.24 mL, 16 mmol) was added slowly and the reaction allowed to warm to room temperature. After 30 min the reaction was checked for completion (tlc) and then poured into 1 M HCl (100 mL). The product was then extracted into dichloromethane (3×70 mL), dried with magnesium sulphate and the solvent evaporated in the usual way. Recrystallization of the crude product from DMF/ethyl acetate/petroleum ether gave the title compound **2j** (3.34 g, 75%) as a white powder. Mp 246–248 °C (from DMF/ethyl acetate/petroleum ether); ν_{max}/cm^{-1} (CHCl$_3$) 1763s (C=O, ester), 1375s+1169s (–SO$_2$–); δ_H (300 MHz, CDCl$_3$) 1.50 (12H, d, J=7.1 Hz, –CH_3), 2.88 (12H, s, –SO$_2$CH_3), 4.65 (4H, q, J=7.1 Hz, H-2,4,6,8), 5.25+5.30 (8H, 2×d, J_{AB}= 12 Hz, H-2′), 6.19+7.26 (4H, s, H-1^2,5^2 and H-3^2,7^2), 7.21+7.23 (4H, s, H-1^5,5^5 and H-3^5,7^5), 7.34–7.47 (20H, m, Ph); δ_C (75 MHz, CDCl$_3$) 20.0 (–CH$_3$), 31.9 (C-2,4,6,8), 38.1 (–SO$_2$$C$H3), 70.7 (C-2′), 116.1+116.4, 125.6, 126.6, 128.6, 128.7, 128.8 (Ph+C-1^2,5^2 and C-3^2,7^2 and 3^5,7^5 and C-1^5,5^5), 134.6 (Ph), 134.3+135.5 (C-1^1,1^3,3^1,3^3,5^1,5^3, 7^1,7^3), 145.5+146.6 (C-3^4,3^6,7^4,7^6 and C-1^4,1^6,5^4,5^6), 153.2 (C-1′); MALDI-TOF *m*/*z* (rel. int.) 1431.51 [M+K]$^+$(28), 1415.20 [M+Na]$^+$(100). Found: C, 58.81; H, 4.66; S, 9.05%; C$_{68}$H$_{64}$O$_{24}$S$_4$ requires C, 58.61; H, 4.63; S, 9.20%.

6.1.4. 3^4,3^6,7^4,7^6-Tetrahydroxy-1^4,1^6,5^4,5^6-tetra(methylsulfonyloxy)-2,4,6,8-tetramethyl-1,3,5,7(1,3)tetrabenzenacyclooctaphane (2l). Resorcinarene **2j** (1.4 g, 1 mmol) was dissolved in a 1:1 solvent mixture of THF and ethanol (60 mL). 10% Palladium on carbon (100 mg, 0.1 mmol) was added and the solution stirred at room temperature under a positive pressure of hydrogen. After 6 h the reaction was checked for completion (tlc) and the catalyst filtered off through Celite®, washing with dichloromethane (100 mL). Evaporation of the solvent afforded tetramesylate **2l** (850 mg, 99%) as an off-white solid. Mp >300 °C (dec.); ν_{max}/cm^{-1} (KBr) 3494s+3389s (O–H, H-bonded), 3032s (C–H, aromatic), 2968s+2933s (CH$_3$), 1619m+1520s (aryl stretch), 1354s+1184s (–SO$_2$–) δ_H (300 MHz, DMSO-d_6) 1.42 (12H, d, J=6.9 Hz, –CH$_3$), 2.93 (12H, s, –SO$_2$CH$_3$), 4.63 (4H, q, J=6.9 Hz, H-2,4,6,8), 6.12 (2H, s, H-1^2,5^2), 6.42 (2H, s, 1^5,5^5), 7.18 (2H, s, 3^5,7^5), 7.48 (2H, s, 3^2,7^2), 9.16 (4H, s, –OH); δ_C (75 MHz, DMSO-d_6) 20.3 (CH$_3$), 29.7 (C-2,4,6,8), 37.0 (SO$_2$CH$_3$), 102.0 (C-1^5,5^5), 114.0 (C-3^5,7^5), 122.6 (C-1^1,1^3,5^1,5^3), 125.2 (C-1^2,5^2), 126.8 (C-3^2,7^2), 136.3 (C-3^1,3^3,7^1,7^3), 144.4 (C-3^4,3^6,7^4,7^6), 152.4 (C-1^4,1^6,5^4,5^6); MALDI-TOF *m*/*z* (rel. int.) 896.04 [M$^+$+K$^+$] (48), 879.94 [M$^+$+Na$^+$] (100). Found: C, 50.28; H, 4.64; S, 14.85%; C$_{36}$H$_{40}$O$_{16}$S$_4$ requires C, 50.46; H, 4.70; S, 14.97%.

6.2. General procedure for the synthesis of bridged resorcinarenes (3)

Tetraprotectedresorcinarene **2** (0.25–0.5 mmol, 1 equiv), diamine **1**, **6** or **12** (1.2 equiv) and paraformaldehyde (10 equiv) were added to a high-pressure glass reaction vessel with a screw top. Acetonitrile (40 mL) was added and the vessel sealed and placed in an oil bath at 90 °C. After 40 min the reaction was checked by tlc for complete consumption of **2**. Silica gel (1–2 g) was then added and the solvent removed under reduced pressure. The solid-supported crude material was then finely ground and subjected to column chromatography (30 g silica gel eluting with ethyl acetate–petroleum ether 1:9–1:1) to furnish bridged derivatives **3**.

6.2.1. (*R*,*R*)-$1^2,1^4,11^2,11^4$-Tetrahydroxy-12,14,15,17-tetra-methyl-3,9-bis(1-phenylethyl)-$13^4,13^6,16^4,16^6$-tetra(2′,4′,6′-triisopropylbenzenesulfonyloxy)-3,9-diaza-1,11(1,3,5),13,16(1,3)tetrabenzenabicyclo[9.3.3]heptadecaphane (3f). Yield 78%. Mp 232–233 °C (from diethyl ether–petroleum ether); $[\alpha]_D$ +67.6 (*c* 1.40 in $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 3516s (O–H, H-bonded), 2964s+2872s (C–H), 1599m+1481m (aryl stretch), 1376s+1180s (–SO_2–O–); δ_H (300 MHz, $CDCl_3$) 0.99 (2H, m, H-6), 1.11 (4H, m, H-5,7), 1.18 (24H, d, *J*=6.6 Hz, 7′/9′ *i*-Pr), 1.31 (60H, br d, *J*=6.6 Hz, 7′/8′/9′ *i*-Pr+–C*H*$_3$), 1.37 (6H, d, *J*=6.6 Hz, NCHC*H*$_3$), 2.12 and 2.35 (4H, m, H-4,8), 2.96 (4H, m, H-8′), 3.66 and 3.77 (4H, d, J_{AB}=15.4 Hz, H-2,10), 3.74 (2H, m, NC*H*CH$_3$), 4.13 (8H, m, H-7′/9′), 4.52 and 4.54 (4H, 2×q, *J*=6.6 Hz, H-12,14,15,17), 6.74 (2H, s, H-$13^5,16^5$), 6.80 (2H, s, H-$13^2,16^2$), 7.09 (2H, s, H-$1^6,11^6$), 7.18–7.31 (18H, m, Ph+H-3′,5′); δ_C (75 MHz, $CDCl_3$) 18.6 (NCHC*H*$_3$), 21.6 and 22.3 (–CH$_3$), 23.1 (C-6), 23.5 (8′ *i*-Pr), 24.7 (7′/9′ *i*-Pr), 26.3 (C-5,7), 30.0 (C-7′/9′), 31.0 and 31.3 (C-12,14,15,17), 34.3 (C-8′), 48.4 (C-2,10), 49.5 (C-4,8), 61.7 (N*C*HCH$_3$), 108.4 (C-$1^3,11^3$), 115.6 (C-$13^5,16^5$), 118.1 and 119.1 (C-$1^1,1^5,11^1,11^5$), 123.7 (C-$1^6,11^6$), 124.0 and 124.1 (C-3′,5′), 127.3 (C-$13^2,16^2$), 128.0 and 128.5 (Ph), 130.3 and 130.6 (C-1′), 139.6 and 140.2 (C-$13^1,13^3,16^1,16^3$), 142.2 (Ph), 144.5 and 144.6 (C-$13^4,13^6,16^4,16^6$), 151.0 and 151.2 (C-2′,6′), 153.0 (C-$1^2,1^4,11^2,11^4$), 154.3 and 154.4 (C-4′); MALDI TOF: *m/z* (rel. int.) 1942.89 [M$^+$] (53), 1838.6 [M$^+$ −PhCHCH$_3$] (10). Found: C, 71.04; H, 7.72; N, 1.46; S, 6.38%; $C_{115}H_{150}N_2O_{16}S_4$ requires C, 71.03; H, 7.77; N, 1.44; S, 6.60%

6.2.2. (*R*,*R*)-$1^2,1^4,11^2,11^4$-Tetrahydroxy-$13^4,13^6,16^4,16^6$-tetra(4-methylbenzoyloxy)-12,14,15,17-tetramethyl-3,9-bis(1-phenylethyl)-3,9-diaza-1,11(1,3,5),13,16(1,3)tetra-benzenabicyclo[9.3.3]heptadecaphane (3g). Yield 55%. Mp 193–195 °C (from diisopropyl ether–dichloromethane); $[\alpha]_D$ +7.8 (*c* 2.64 in $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 3480s (O–H, H-bonded), 2972s+2873s (C–H, aliphatic), 1729s (C=O, ester); δ_H (300 MHz, $CDCl_3$) 0.93 (2H, m, H-6), 1.10 (4H, m, H-5,7), 1.40 (6H, d, *J*=6.7 Hz, NCHC*H*$_3$), 1.54 (12H, d, *J*=6.7 Hz, –C*H*$_3$), 2.19 and 2.33 (4H, m, H-4,8), 2.46 (12H, s, H-7′), 3.78 (6H, br, NC*H*CH$_3$ and H-2,10), 4.49 (4H, br m, H-12,14,15,17), 7.04 (2H, s, H-$13^2,16^2$), 7.14 (2H, s, H-$13^5,16^5$), 7.22–7.30 (12H, br m, H-$1^6,11^6$+Ph) 7.34 (8H, m, H-3′,5′), 8.23 (8H, m, H-2′,6′); δ_C (100 Hz, $CDCl_3$) 17.7 (NCHC*H*$_3$), 21.7 (C-7′), 22.2 and 22.4 (–CH$_3$), 24.8 (C-5,7), 25.9 (C-6), 30.6+30.7 (C-12,14,15,17), 49.8 (C-2,10), 52.0 (C-4,8), 62.3 (N*C*HCH$_3$), 108.8 (C-$1^3,11^3$), 115.8 (C-$13^5,16^5$), 119.8 (C-$1^1,1^5,11^1,11^5$), 122.7 (C-$1^6,11^6$), 126.9 (C-1′), 127.0 (Ph), 127.2 (C-$13^2,16^2$), 128.0+128.4 (Ph), 129.4 (C-3′,5′), 130.5 (C-2′,6′), 137.7 (C-$13^1,13^3,16^1,16^3$), 141.9 (Ph), 144.6 (C-4′), 146.1 (C-$13^4,13^6,16^4,16^6$), 152.9 (C-$1^2,1^4,11^2,11^4$), 165.8 (C=O); MALDI TOF: *m/z* (rel. int.) 1350.65 [M$^+$] (79), 1247.25 (44). Found: C, 77.53; H, 6.54; N, 2.03%; $C_{87}H_{86}N_2O_{12}$ requires C, 77.31; H, 6.41; N, 2.07%.

6.2.3. (*R*,*R*)-$13^4,13^6,16^4,16^6$-Tetra(benzyloxycarbonyloxy)-$1^2,1^4,11^2,11^4$-tetrahydroxy-12,14,15,17-tetramethyl-3,9-bis(1-phenylethyl)-3,9-diaza-1,11(1,3,5),13,16(1,3)tetra-benzenabicyclo[9.3.3]heptadecaphane (3h). Yield 70%. Mp 117–119 °C (from diethyl ether); $[\alpha]_D$ +6.7 (*c* 1.00, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 3502s (O–H, H-bonded), 2971s (C–H, aliphatic), 1757s (C=O, ester); δ_H (300 MHz, $CDCl_3$) 0.77 (2H, qu, *J*=7.1 Hz, H-6), 0.98 (4H, qu, *J*=7.1 Hz, H-5,7), 1.40 (6H, d, *J*=6.5 Hz, NCHC*H*$_3$), 1.45 (12H, d, *J*=6.5 Hz, –C*H*$_3$), 2.06 and 2.23 (4H, m, H-4,8), 3.71 (4H, s, H-2,10), 3.79 (2H, q, *J*=6.5 Hz, H-α), 4.43 (4H, m, H-12,14,15,17), 5.32 and 5.34 (8H, 2×s, H-2′), 6.85 (2H, s, H-$13^2,16^2$), 7.04 (2H, s, H-$13^5,16^5$), 7.19 (2H, s, H-$1^6,11^6$), 7.20–7.48 (30H, m, Ph); δ_C (75 Hz, $CDCl_3$) 18.0 (NCHC*H*$_3$), 22.0 and 22.1 (–*C*H$_3$), 24.8 (C-5,7), 25.5 (C-6), 30.5 (C-12,14,15,17), 49.5 (C-2,10), 51.6 (C-4,8), 62.1 (N*C*HCH$_3$), 70.6 (2′), 109.0 (C-$1^3,11^3$), 115.2 (C-$13^5,16^5$), 119.5 (C-$1^1,1^5,11^1,11^5$), 123.0 (C-$1^6,11^6$), 127.2 (C-$13^2,16^2$), 127.4+128.1+128.4+128.5+128.7 (Ph), 135.0 (Ph), 137.7 (C-$13^1,13^3,16^1,16^3$), 141.5 (Ph), 146.3 (C-$13^4,13^6,16^4,16^6$), 152.9 (C-$1^2,1^4,11^2,11^4$), 154.1 (C-1′); MALDI-TOF *m/z* (rel. int.) 1416.36 [M$^+$ +2H] (100). Found: C, 73.88; H, 6.17; N, 2.02%; $C_{87}H_{86}N_2O_{16}$ requires C, 73.82; H, 6.12; N, 1.98%.

6.2.4. (*R*,*R*)-$13^4,13^6,16^4,16^6$-Tetraacetoxy-$1^2,1^4,11^2,11^4$-tetra-hydroxy-12,14,15,17-tetramethyl-3,9-bis(1-phenylethyl)-3,9-diaza-1,11(1,3,5),13,16(1,3)tetra-benzenabicyclo-[9.3.3]heptadecaphane (3k). Yield 20%. Mp 162–164 °C (from diethyl ether - petroleum ether); $[\alpha]_D$ +8.1 (*c* 1.62, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 3502s (O–H, H-bonded), 2972s+2874s (C–H, aliphatic), 1747s (C=O, ester); δ_H (300 MHz, $CDCl_3$) 0.84 (2H, m, H-6), 0.97 (4H, m, H-5,7), 1.40 (6H, d, *J*=7.0 Hz, NCHC*H*$_3$), 1.48 (12H, d, *J*=7.1 Hz, –C*H*$_3$), 2.08 and 2.24 (4H, m, H-4,8), 2.39 (12H, s, OC(O)C*H*$_3$), 3.73 (4H, s, H-2,10), 3.81 (2H, q, *J*=7.0 Hz, H-α), 4.35 (4H, m, H-12,14,15,17), 6.85 (2H, s, H-$13^5,16^5$), 6.89 (2H, s, H-$13^2,16^2$), 7.28 (2H, s, H-$1^6,11^6$), 7.19–7.34 (10H, m, Ph); δ_C (75 MHz, $CDCl_3$) 17.5 (NCHC*H*$_3$), 21.0 (OC(O)*C*H$_3$), 22.0 and 22.1 (–*C*H$_3$), 25.0 and 25.7 (C-5, 6,7), 30.5 (C-12,14,15,17), 49.4 (C-2,10), 52.0 (C-4,8), 62.2 (N*C*HCH$_3$), 109.2 (C-$1^3,11^3$), 115.9 (C-$13^5,16^5$), 119.9 (C-$1^1,1^5,11^1,11^5$), 122.7 (C-$1^6,11^6$), 127.1 (Ph), 127.3 (C-$13^2,16^2$), 128.0 and 128.4 (Ph), 137.1 and 137.2 (C-$13^1,13^3,16^1,16^3$), 141.5 (Ph), 145.8 and 145.9 (C-$13^4,13^6,16^4,16^6$), 153.0 (C-$1^2,1^4,11^2,11^4$), 170.0 (C=O); MALDI-TOF *m/z* (rel. int.) 1047.75 [M$^+$] (100), 1003.60 [M$^+$ −COCH$_3$] (20), 943.60 [M$^+$ −CHCH$_3$Ph] (75). Found: C, 72.17; H, 6.59; N, 2.75%; $C_{63}H_{70}N_2O_{12}$ requires C, 72.26; H, 6.74; N, 2.67%.

6.2.5. (*R*,*R*)-$1^2,1^4,11^2,11^4$-Tetrahydroxy-12,14,15,17-tetra-methyl-$13^4,13^6,16^4,16^6$-tetra(methylsulfonyl-oxy)-3,9-bis(1-phenylethyl)-3,9-diaza-1,11(1,3,5),13,16(1,3)-tetra-benzenabicyclo[9.3.3]hepta-decaphane (3l). Yield 51%. Mp 201–203 °C (from dichloromethane–diethyl ether); $[\alpha]_D$ +8.1 (*c* 2.13, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 3523s (O–H, H-bonded), 2975s+2875s (C–H), 1606m+1481m (aryl stretch), 1370s+1183s (–SO_2–O–); δ_H

(300 MHz, CDCl$_3$) 1.05 (2H, m, H-6), 1.19 (4H, m, H-5,7), 1.37 (6H, d, J=6.8 Hz, NCHCH_3), 1.50 (12H, d, J=7.1 Hz, –CH_3), 2.18 and 2.37 (4H, m, H-4,8), 2.37 and 2.40 (12H, 2×s, –SO$_2$Me), 3.78 (4H, s, H-2,10), 3.81 (2H, q, J=6.8 Hz, NCHCH$_3$), 4.56 and 4.59 (4H, 2×q, J=7.1 Hz, H-12,14, 15,17), 6.80 (2H, s, H-13^2,16^2), 7.15 (2H, s, H-1^6,11^6), 7.17–7.32 (10H, m, Ph), 7.47 (2H, s, H-13^5,16^5); δ_C (75 MHz, CDCl$_3$) 16.8 (NCHCH$_3$), 21.8 and 22.0 (–CH$_3$), 24.5 (C-5,7), 25.0 (C-6), 31.7 (C-12,14,15,17), 38.1 (SO$_2$Me), 48.9 (C-2,10), 49.8 (C-4,8), 61.1 (NCHCH$_3$), 108.5 (C-1^3,11^3), 116.4 (C-13^5,16^5), 118.2 (C-1^1,1^5, 11^1,11^5), 124.3 (C-1^6,11^6), 127.1 (C-13^2,16^2), 127.5 127.9 and 128.4 (Ph), 140.2 (C-13^1,13^3,16^1,16^3), 141.3 (Ph), 144.6 (C-13^4,13^6,16^4,16^6), 153.6 (C-1^2,1^4,11^2,11^4); MALDI-TOF m/z (rel. int.) 1192.1 [M$^+$+2H] (100). Found: C, 59.48; H, 5.98; N, 2.36; S, 10.52%; $C_{59}H_{70}N_2O_{16}S_4$ requires C, 59.48; H, 5.92; N, 2.35; S, 10.76%.

6.2.6. Heptanedioic acid bis[(1-phenylethyl)amide] (5). Pimelic acid **4** (641 mg, 4 mmol) and hydroxybenzotriazole (270 mg, 2 mmol) were dissolved in dry dichloromethane (50 mL) and cooled to 0 °C. Dicyclohexylcarbodiimide (2.06 g, 10 mmol) was added, followed by slow addition of (*R*)-α-methylbenzylamine (1.08 mL, 8.4 mmol). The reaction was allowed to warm to room temperature slowly overnight. On completion, the reaction was added to aqueous sodium carbonate (100 mL) and extracted with dichloromethane (3×70 mL). The organic layers were combined and dried with magnesium sulphate and then reduced to yield a crude white product, which was purified by column chromatography (60 g silica gel, eluting with methanol–ethyl acetate 2:98), to afford diamide **5** (1.40 g, 95%) as a colourless powder. Mp 157–158 °C (ethyl acetate–ethanol); [α]$_D$ +108.5 (*c* 2.50, EtOH); ν_{max}/cm^{-1} (CH$_2$Cl$_2$) 1670s (C=O stretch, amide I), 1506s (C=O, amide II), 1262s; δ_H (300 MHz, CDCl$_3$) 1.33 (2H, m, H-4), 1.46 (6H, d, J=6.9 Hz, –CH_3), 1.62 (4H, m, H-3,5), 2.14 (4H, m, H-2,6), 5.10 (2H, q, J=6.9 Hz, H-α), 5.86 (2H, br d, J=~7 Hz, NH), 7.21–7.35 (10H, m, Ph); δ_C (75 MHz, CDCl$_3$) 21.8 (–CH$_3$), 25.1 (C-3,5), 28.5 (C-4), 36.3 (C-2,6), 48.6 (C-α), 126.1, 127.3, 128.6 and 143.4 (Ph), 171.9 (C=O); m/z (rel. int.) 367.2 [M$^+$+H] (57), 263.2 (8), 246.2 (9), 142 (12), 120 [PhCH(NH)CH$_3$] (18), 105 [PhCHCH$_3$] (100), 91 [PhCH$_2$] (47). Found C, 75.49; H, 8.26; N, 7.60%; $C_{23}H_{30}N_2O_2$ requires C, 75.38; H, 8.25; N, 7.64%.

6.2.7. *N*,*N*′-Bis(1-phenylethyl)heptane-1,5-diamine (6). Di-amide **5** (4.30 g, 11.7 mmol) was dissolved in dry THF (150 mL) and cooled to 0 °C. Lithium aluminium hydride (1.78 g, 46.9 mmol) was added portion-wise to the reaction, which was then heated to reflux for 18 h. After the reaction was complete (tlc), it was cooled to 0 °C and quenched by the slow addition of water (1.7 mL), 1 M sodium hydroxide (3.4 mL) followed by water (3.4 mL). The reaction was stirred at room temperature for 1 h, the salts removed via filtration through Celite®, washing with dichloromethane (100 mL), to afford diamine **6** (3.78 g, 95%) as a clear oil, which was judged to be >95% pure for the next step. The product was characterized as its ditosylate. Mp 137–138 °C (ethanol–dichloromethane); [α]$_D$ +18.8 (*c* 2.6, CHCl$_3$); ν_{max}/cm^{-1} (CHCl$_3$) 3024s (C=C–H), 2940s+2856s (C–H, aliphatic), 1599s (aryl), 1380s+1162s (SO$_2$–O); δ_H (400 MHz, CDCl$_3$) 0.84 (6H, br m, H-3,4,5), 1.06 and 1.28 (4H, m×2, H-2,6), 1.35 (6H, d, J=7.1 Hz, –CH_3×2), 2.41 (6H, s, -Tos-CH_3×2), 2.92 (4H, m, H-1,7), 5.15 (2H, q, J=7.1 Hz, H-α), 7.18–7.25 (10H, m, Ph), 7.28 (4H, d, J=8.0 Hz, –Tos), 7.71 (4H, d, J=8.0 Hz, -Tos); δ_C (75 MHz, CDCl$_3$) 16.6 (–CH$_3$), 21.4 (Tos-CH$_3$), 26.6 (C-3,5), 28.2 (C-4), 30.4 (C-2,6), 44.1 (C-1,7), 55.2 (C-α), 127.1, 127.5, 128.2, 129.5, 138.4, 140.3 and 142.9 (Ph); m/z (rel. int.) 669 [M$^+$+Na] (100). Found C, 68.68; H, 7.16; N, 4.32; S, 9.92%; $C_{37}H_{46}N_2O_4S_2$ requires C, 68.70; H, 7.17; N, 4.33; S, 9.91%.

6.2.8. 4-Oxo-heptanedioic acid bis[(1-phenylethyl)-amide] (10). Oxo-pimelic acid **9** (3.49 g, 20 mmol) and hydroxybenzotriazole (1.35 g, 10 mmol) were dissolved in dry dichloromethane (200 mL) and cooled to 0 °C. Dicyclohexylcarbodiimide (10.3 g, 50 mmol) was added, followed by slow addition of (*R*)-α-methylbenzylamine (5.4 mL, 42 mmol). The reaction was allowed to warm to room temperature slowly overnight. On completion, the reaction was added to aqueous sodium carbonate (200 mL) and extracted with dichloromethane (3×100 mL). The organic layers were combined and dried with magnesium sulphate and then reduced to yield a crude white product, which was purified by column chromatography (100 g silica gel, eluting with methanol–ethyl acetate 2:98). In this way, diamide **10** (6.30 g, 83%) was obtained as a white powder. Mp 160–161 °C (ethyl acetate–ethanol); [α]$_D$ +121.5 (*c* 2.20, EtOH); ν_{max}/cm^{-1} (CHCl$_3$) 3432m (N–H), 1716s (C=O, ketone), 1672s (C=O, amide), 1508s (NH bend); δ_H (400 MHz, CDCl$_3$) 1.45 (6H, d, J=6.9 Hz, 2×NCHCH_3), 2.45 (4H, m, H-3,5), 2.76 (4H, m, H-2,6), 5.06 (2H, q, J=7.0 Hz, 2×H-α), 5.94 (2H, br d, J=6.9 Hz, 2×N–H), 7.21–7.34 (10H, m, Ph); δ_C (100 MHz, CDCl$_3$) 21.8 (–CH$_3$), 30.2 (C-3,5), 37.6 (C-2,6), 48.9 (C-α), 126.1, 127.2, 128.6 and 143.3 (Ph), 170.7 (C-1,7), 208.8 (C-4); m/z (rel. int.) 381.2 [M$^+$+H] (42), 260.1 [M$^+$−PhCH(CH$_3$)NH] (17), 156.0 (21), 120.0 [PhCH(CH$_3$)NH] (25), 105.0 [PhCHCH$_3$] (100). Found C, 72.58; H, 7.26; N, 7.29%; $C_{23}H_{28}N_2O_3$ requires C, 72.61; H, 7.42; N, 7.36%.

6.2.9. 4,4-Dimethoxy-heptanedioic acid bis[(1-phenyl-ethyl)-amide] (11). Diamide **10** (0.98 g, 2.5 mmol) was dissolved in dry methanol (30 mL) with a catalytic amount of *p*-toluenesulfonic acid (40 mg, 0.2 mmol). Trimethyl orthoformate (2 mL, 18 mmol) was added and the reaction heated to gentle reflux overnight. On completion of the reaction, solid sodium carbonate was added and the methanol reduced on a rotary evaporator. Ethyl acetate (100 mL) was added to the crude material, which was then washed with water (25 mL) and brine (25 mL). The organic layer was then dried with magnesium sulphate and reduced to give a crude oil which was purified via column chromatography (50 g silica gel, eluting with methanol–ethylacetate 2:98), to give dimethoxyketal diamide **11** (0.98 g, 92%) as fine white needles. Mp 129–131 °C (ethyl acetate–ethanol); [α]$_D$ +86.9 (*c* 2.05, EtOH); ν_{max}/cm^{-1} (CHCl$_3$), 1663s (C=O, amide), 1505s (N–H bend); δ_H (400 MHz, CDCl$_3$) 1.45 (6H, d, J=6.9 Hz, 2×NCHCH_3), 1.89 (4H, m, H-3,5), 2.19 (4H, m, H-2,6), 3.13 (6H, s, OCH_3), 5.03 (2H, q, J=7.0 Hz, 2×H-α), 6.13 (2H, br d, J=7.7 Hz, 2×N–H), 7.18–7.33 (10H, m, Ph); δ_C (100 MHz, CDCl$_3$) 21.8 (–CH$_3$), 28.1 (C-3,5), 31.2 (C-2,6), 47.9 (–OCH$_3$), 48.8 (C-α), 102.5 (C-4), 126.1, 127.3, 128.6 and 143.2 (Ph), 171.7 (C-1,7); *m/z* (rel. int.) 449.2 [M$^+$+Na] (5), 395.2 [M$^+$−OCH$_3$] (56), 259.1 (19), 142.0 (15), 105.0 [PhCHCH$_3$] (100). Found C, 70.71; H, 8.01; N, 6.74%; $C_{25}H_{34}N_2O_4$ requires C, 70.40; H, 8.03; N, 6.57%.

6.2.10. 4,4-Dimethoxy-*N*,*N*′-bis-(1-phenylethyl)heptane-1,7-diamine (12). Diamide **11** (1.11 g, 2.6 mmol) and triethylamine (1.8 mL, 13 mmol) were added to dry diethyl ether (100 mL) and cooled to 0 °C. Lithium aluminium hydride (395 mg, 10.4 mmol) was added to the solution in small portions. Thereafter, the reaction was heated to reflux for 4–6 h until reduction was complete (tlc control). The reaction was then cooled to 0 °C and quenched by the addition of H_2O (0.4 mL), 1 M NaOH (0.8 mL) and H_2O (0.8 mL) in that order. The heterogeneous solution was allowed to stir at room temperature for approximately one hour until all the salts had turned white. These were then filtered off through Celite® and washed with dichloromethane (200 mL). The filtrate was then reduced to afford diamine **12** (880 mg, 85%) as an oil. $[\alpha]_D$ +37.5 (*c* 2.92, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 3013s (aromatic C–H), 2954s+2831s (aliphatic C–H), 1602w (aryl ring), 1188m (C–N), 1113s (C–O–C); δ_H (400 MHz, $CDCl_3$) 1.39 (3H, d, J=6.6 Hz, –C*H*$_3$), 1.32–1.61 (10H, m, H-2,3,5,6+NH×2), 2.42+2.50 (4H, 2×dt, J=11.4, 7.1 Hz, H-1,7), 3.08 (6H, s, OC*H*$_3$), 3.78 (2H, q, J=6.6 Hz, NC*H*CH$_3$), 7.20–7.35 (10H, m, Ph); δ_C (100 MHz, $CDCl_3$) 23.9 (CH$_3$), 24.1 (C-2,6), 30.2 (C-3,5), 47.6 (C-1,7+OMe), 58.4 (N*C*HCH$_3$), 103.1 (C-3), 126.6, 127.0, 128.4 and 144.8 (Ph).

6.2.11. (*R*,*R*)-1^2,1^4,13^2,13^4-Tetrahydroxy-14,16,17,19-tetra-methyl-3,11-bis(1-phenylethyl)-15^4,15^6,18^4,18^6-tetra-(*p*-toluenesulfonyloxy)-3,11-diaza-1,13(1,3,5),15,18(1,3) tetrabenzenabicyclo[11.3.3]nona-decaphane(13a). Tetratosylresorcinarene **2a** (465 mg, 0.5 mmol), diamine **6** (203 mg, 0.6 mmol) and paraformaldehyde (300 mg, 10 mmol) were added to a high-pressure glass reaction vessel with a screw top. Acetonitrile (40 mL) was added and the vessel sealed and placed in an oil bath at 80 °C. After two hours the reaction was checked by tlc for complete consumption of **2a**. Silica gel (2–3 g) was then added and the solvent removed under reduced pressure. The solid-supported crude material was then finely ground and subjected to column chromatography (40 g silica gel eluting with ethyl acetate–petroleum ether 3:7). In this manner, bridged resorcinarene **13a** (220 mg, 36%) eluted first, followed by dimer **14** (80 mg, 5%). Mp 133–137 °C (diisopropyl ether–dichloromethane); $[\alpha]_D$ +13.2 (*c* 2.40, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$): 3528s (O–H, H-bonded), 2974m+2932m (C–H, aliphatic), 1598s (aryl-H), 1371s+1176s (–SO$_2$–O–); δ_H (300 MHz, $CDCl_3$) 1.07–1.44 (10H, m, H-5,6,7,8,9), 1.30 (6H, d, J=6.9 Hz, NCHC*H*$_3$), 1.41 (12H, d, J=7.0 Hz, –C*H*$_3$), 1.99 and 2.40 (4H, m, H-4,10), 2.47 and 2.49 (12H, 2×s, H-7′), 3.60 and 3.69 (4H, AB d, J_{AB}=14.6 Hz, H-2,12), 3.79 (2H, q, J=6.9 Hz, H-α), 4.52 and 4.55 (4H, 2×q, J=7.0 Hz, H-14,16,17,19), 6.45 (2H, s, H-15^2,18^2), 6.78 (2H, s, H-15^5,18^5), 7.07 (2H, s, H-1^6,13^6), 7.17–7.33 (10H, m, Ph), 7.39 and 7.41 (8H, 2×d, J=∼8.0 Hz, H-3′,5′), 7.94 (8H, 2×d, J=∼8.0 Hz, H-2′,6′); δ_C (75 MHz, $CDCl_3$) 14.1 (NCH*C*H$_3$), 20.6 and 20.7 (–*C*H$_3$), 21.7 (C-7′), 25.0, 25.8 and 26.4 (C-5,6,7,8,9), 31.8 and 31.9 (C-14,16,17,19), 46.4 (C-2,12), 48.4 (C-4,10), 57.1 (C-α), 108.8 (C-1^3,13^3), 114.8 (C-15^5,18^5), 118.5 and 118.9 (C-1^1,1^5,13^1,13^5), 123.6 (C-1^6,13^6), 127.0 (Ph),127.4 (C-15^2,18^2), 128.0 (Ph), 128.4, 128.5 and 128.6 (C-2′,6′+Ph), 130.1 (C-3′,5′), 132.9 (C-1′), 139.8 and 140.0 (C-15^1, 15^3,18^1,18^3), 140.2 (Ph), 144.8 and 145.0 (C-15^4,15^6, 18^4,18^6), 145.6 (C-4′), 153.1 and 153.8 (C-1^2,1^4,13^2,13^4); MS: *m/z* (rel. int.) 1523.4 [M$^+$] (55), 1417.3 [M$^+$−H–PhCHCH$_3$] (13), 1370.3 (7), 1185.1 (7), 1028.3 (3), 875.1 (3), 547.1 (7), 339.3 (57), 105.1 [PhCHCH$_3$] (100). Found C, 66.98; H, 5.98; N, 1.84; S, 8.05%; $C_{85}H_{90}N_2O_{16}S_4$ requires C, 66.99; H, 5.95; N, 1.84; S, 8.42%.

6.2.12. (*R*,*R*,*R*,*R*)-1^2,1^4,13^2,13^4,17^2,17^4,29^2,29^4-Octa-hydroxy-14,16,30,32,33,35,36,38-octamethyl-3,11,19,27-tetra(1-phenylethyl)-15^4,15^6,31^4,31^6,34^4,34^6,37^4,37^6-octa-(*p*-toluenesulfonyloxy)-3,11,19,27-tetraaza-1,13,17,29 (1,3,5),15,31,34,37(1,3)tricyclo[27.3.3.3^{13,17}]octatriaconta-phane (14). From synthesis of bridged resorcinarene **13a**. Mp 161–165 °C (diisopropyl ether–dichloromethane); $[\alpha]_D$ −7.0 (*c* 1.33 in $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$): 3527s (O–H, H-bonded), 3022s (C–H, aromatic), 2930m (C–H, aliphatic), 1598s (aryl stretch), 1371s+1177s (–SO$_2$–);δ_H (300 MHz, $CDCl_3$) 1.03 (4H, m, H-7,23), 1.21 (12H, d, J=6.8 Hz, NCHC*H*$_3$), 1.27 (8H, m, C-5,6,8,9,21,22,24,25), 1.36 and 1.39 (24H, d, J=6.7 Hz, −C*H*$_3$), 2.02 and 2.40 (8H, br m, H-4,10,20,26), 2.45 (24H, s, H-7′), 3.34 (8H, s, H-2,12,18,28), 3.65 (4H, q, J=6.8 Hz, NC*H*CH$_3$), 4.43 and 4.48 (8H, 2×q, J=7.0 Hz, H-14,16,30,32,33,35,36,38), 6.44 (4H, s, H-15^2,31^2,34^2,37^2), 6.72 (4H, s, H-15^5,31^5, 34^5,37^5), 7.00 (4H, s, H-1^6,13^6,17^6,29^6), 7.02–7.17 (20H, m, Ph), 7.35 (16H, d, J=∼8.1 Hz, H-3′,5′), 7.88 (16H, d, J=∼8.1 Hz, H-2′,6′); δ_C (75 MHz, $CDCl_3$) 16.0 (NCH*C*H$_3$), 20.4+20.6 (–*C*H$_3$), 21.7 (C-7′), 26.7, 27.4 and 30.0 (C-5,6,8,9,21,22,24,25), 31.7 and 31.9 (C-14,16,30,32,33, 35, 36,38), 46.9 (C-2,12,18,28), 49.3 (C-4,10,20,26), 58.1 (C–N*C*HCH$_3$), 109.0 (C-1^3,13^3,17^3,29^3), 114.5 (C-15^5,31^5, 34^5, 37^5), 118.9 (C-1^1,1^5,13^1,13^5,17^1,17^5,29^1,29^5), 123.3 (C-1^6,13^6,17^6,29^6), 127.2 (Ph), 127.4 (C-15^2,31^2,34^2,37^2), 128.1 (Ph), 128.4, 128.4 and 128.5 (C-2′,6′+Ph), 130.0 (C-3′,5′), 133.2 and 133.4 (C-1′), 139.7 and 140.1 (C-15^1,15^3, 31^1,31^3,34^1,34^3, 37^1,37^3), 140.4 (Ph), 144.9 and 145.1 (C-15^4,15^6,31^4,31^6,34^4,34^6,37^4,37^6), 145.5 and 145.6 (C-4′), 153.5 and 153.8 (C-1^2,1^4,13^2,13^4,17^2, 17^4,29^2,29^4); MALDI TOF: *m/z* (rel. int.) 3047.3 [M$^+$] (15), 1524.7 [M$^+$/2+H] (72). Found C, 66.52; H, 5.96; N, 1.86; S, 8.16%; $C_{170}H_{180}N_4O_{32}S_8\cdot H_2O$ requires C, 66.60; H, 5.98; N, 1.83; S, 8.37%.

6.2.13. (*R*,*R*)-1^2,1^4,13^2,13^4-Tetrahydroxy-14,16,17,19-tetra-methyl-7,7-dimethoxy-3,11-bis(1-phenyl-ethyl)-15^4,15^6, 18^4,18^6-tetra(*p*-toluenesulfonyloxy)-3,11-diaza-1,13(1,3,5),15,18(1,3)tetrabenzenabicyclo[11.3.3]nona-decaphane (13b). Tetratosylresorcinarene **2a** (580 mg, 0.5 mmol), diamine **12** (590 mg, 1.48 mmol) and para-formaldehyde (300 mg, 10 mmol) were added to a high-pressure glass reaction vessel with a screw top. Acetonitrile (40 mL) was added and the vessel sealed and placed in an oil bath at 80 °C. After 1 1/2 h the reaction was checked by tlc for complete consumption of **2a**. Silica gel (2–3 g) was then added and the solvent removed under reduced pressure. The solid-supported crude material was then finely ground and subjected to column chromatography (50 g silica gel eluting with ethyl acetate–petroleum ether 3:7), to afford bridged resorcinarene **13b** (450 mg, 57%). Mp 146–148 °C (diisopropyl ether–dichloromethane); $[\alpha]_D$ +1.0 (*c* 2.40, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$): 3526s (O–H, H-bonded), 2971m (C–H, aliphatic), 1599s (aryl stretch), 1371s+1177s (–SO_2–), 1092s (C–O–C, ether); δ_H (300 MHz, $CDCl_3$) 1.29 (6H, d, *J*=6.9 Hz, NCHC*H*$_3$), 1.26–1.37 (8H, m, H-5,6, 8,9), 1.42 (12H, d, *J*=7.1 Hz, –C*H*$_3$), 2.02 and 2.45 (4H, m, H-4,10), 2.48 and 2.49 (12H, 2×s, H-7′), 3.02 (6H, s, –OC*H*$_3$), 3.60 and 3.66 (4H, AB d, J_{AB}=14.8 Hz, H-2,12), 3.80 (2H, q, *J*=6.9 Hz, H-α), 4.52 and 4.57 (4H, 2×q, *J*=7.1 Hz, H-14,16,17,19), 6.44 (2H, s, H-15^2,18^2), 6.73 (2H, s, H-15^5,18^5), 7.07 (2H, s, H-1^6,13^6), 7.17–7.30 (10H, m, Ph), 7.40 (8H, 2×d, *J*=8.4 Hz, H-3′,5′), 7.94 (8H, 2×d, *J*=8.3 Hz, H-2′,6′); δ_C (75 MHz, $CDCl_3$) 14.0 (NCHCH_3), 20.3 and 20.5 (–CH_3), 21.6 (C-5,9), 21.7 (C-7′), 30.8 (C-6,8), 31.9 and 32.1 (C-14,16,17,19), 46.3 (C-2,12), 47.6 (–OCH_3), 48.7 (C-4,10), 57.1 (C-α), 103.0 (C-7), 108.7 (C-1^3,13^3), 115.1 (C-15^5,18^5), 118.6 and 119.1 (C-1^1,1^5, 13^1,13^5), 123.6 (C-1^6,13^6), 127.1 (Ph),127.5 (C-15^2,18^2), 128.0 (Ph), 128.4, 128.5 and 128.6 (C-2′,6′+Ph), 130.1 (C-3′,5′), 133.3 (C-1′), 139.9 and 140.1 (C-15^1,15^3,18^1, 18^3), 140.2 (Ph), 145.0 and 145.1 (C-15^4,15^6,18^4,18^6), 145.6 (C-4′), 153.1 and 154.0 (C-1^2,1^4,13^2,13^4); MS: *m*/*z* (rel. int.)=1584.1 [M^++H] (4), 1520.9 (3), 1413.8 (3), 1185.5 (5), 1031.5 [-Tos] (3), 875.4 [–Tos] (3), 719.4 [–Tos] (3), 335.4 (70), 175.1 (67), 105.1 [$PhCHCH_3$] (100). Found C, 65.98; H, 5.96; N, 1.76; S, 7.76%; $C_{87}H_{94}N_2O_{18}S_4$ requires C, 65.97; H, 5.98; N, 1.77; S, 8.10%.

6.2.14. (*R*,*R*)-1^2,1^4,11^2,11^4-Tetramethanesulfonyloxy-12, 14,15,17-tetramethyl-3,9-bis(1-phenylethyl)-13^4,13^6,16^4, 16^6-tetra(*p*-toluenesulfonyloxy)-3,9-diaza-1,11(1,3,5), 13,16 (1,3)tetrabenzenabicyclo[9.3.3]heptadecaphane (15). Bridged resorcinarene **3a** (450 mg, 0.3 mmol) and diisopropylethylamine (1.05 mL, 6 mmol) were dissolved in dry dichloromethane (15 mL). The solution was cooled to 0 °C in an ice-water bath and methanesulfonyl chloride (0.46 mL, 6 mmol) was added dropwise. The solution was then allowed to warm to room temperature. After the reaction was complete (tlc), it was poured into sat. $NaHCO_3$ (25 mL) and extracted with dichloromethane (3×25 mL) in the usual manner. After drying the organic layers with magnesium sulphate, and evaporation of the dichloromethane, the crude product was purified via column chromatography (40 g silica gel eluting with ethyl acetate–petroleum ether 1:1). The resulting material was then recrystallized (dichloromethane/ethyl acetate/petroleum ether) to give **15** (470 mg, 87%). Mp 194–195 °C (dichloromethane/ethyl acetate/petroleum ether); $[\alpha]_D$ −20.0 (*c* 2.9, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$): 3021m (aryl stretch), 2940s (C–H aliphatic), 1598m (aryl stretch), 1452s (CH_3), 1377s+1178s (–SO_2–O–); δ_H (400 MHz, $CDCl_3$) −0.95 (2H, m, H-6), −0.62 and −0.54 (4H, m, H-5,7), 0.89 and 0.93 (12H, 2×d, *J*=7.1 Hz, –C*H*$_3$), 1.20 (6H, d, *J*=6.8 Hz, NCHC*H*$_3$), 1.35 and 1.52 (4H, m, H-4,8), 2.46 and 2.47 (12H, 2×s, H-7′), 3.24 (12H, s, –SO_2C*H*$_3$), 3.44 and 4.00 (4H, d, J_{AB}=14.7 Hz, H-2,10), 3.88 (2H, q, *J*=6.8 Hz, NC*H*CH$_3$), 4.96 and 5.08 (4H, 2×q, *J*=7.1 Hz, H-12,14,15,17), 6.84 (2H, s, H-13^2,16^2), 7.01–7.12 (10H, m, Ph), 7.36 and 7.39 (8H, 2×d, *J*=8.5 Hz, H-3′,5′), 7.44 (2H, s, H-1^6,11^6), 7.70 (2H, s, H-13^5,16^5), 7.91 and 7.97 (8H, d, *J*=8.5 Hz, H-2′,6′); δ_C (75 MHz, $CDCl_3$) 13.7 (NCHCH_3), 21.2 (C-6), 21.4 (C-7′), 21.7 and 22.2 (–CH_3), 25.1 (C-5,7), 30.0 (C-12,14,15,17), 38.0 and 38.6 (–SO_2Me), 48.4 (C-4,8), 51.8 (C-2,10), 62.9 (NCHCH$_3$), 116.5 (C-13^5, 16^5), 123.7 (C-1^6,11^6), 126.5 (C-13^2,16^2), 127.0 (Ph), 127.7 (Ph), 129.2 (C-2′,6′), 130.0 (C-3′,5′), 132.6 and 132.8 (C-1′), 134.8 (C-1^3,11^3), 136.6 and 137.2 (C-1^1,1^5,11^1,11^5,13^1, 13^3,16^1,16^3), 143.0 (Ph), 143.4, 144.3, 144.8 and 144.7 (C-1^2,1^4,11^2,11^4,13^4,13^6,16^4,16^6), 145.9 (C-4′); *m*/*z* (rel. int.)=1807.9 $[M+H]^+$(57), 1728.9 (21), 1653.0 (12), 510.4 (12), 105.1 [$PhCHCH_3$] (100). Found C, 57.18; H, 5.31; N, 1.72; S, 14.05%; $C_{87}H_{94}N_2O_{24}S_8\cdot H_2O$ requires C, 57.22; H, 5.30; N, 1.53; S, 14.05%.

References and notes

1. For reviews see: (a) Motherwell, W. B.; Bingham, M. J.; Six, Y. *Tetrahedron* **2001**, *57*, 4663–4686. (b) Breslow, R.; Dong, S. D. *Chem. Rev.* **1998**, *98*, 1997–2012.
2. (a) Tanaka, Y.; Aoyama, Y. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 3343–3344. (b) Kobayashi, K.; Asakawa, Y.; Kikushi, Y.; Toi, H.; Aoyama, Y. *J. Am. Chem. Soc.* **1993**, *115*, 2648–2654. (c) Pappalardo, S.; Parisi, M. F. *Tetrahedron Lett.* **1996**, *37*, 1493–1496. (d) Arnaud-Neu, F.; Caccamese, S.; Fuangswasdi, S.; Pappalardo, S.; Parisi, M. F.; Petringa, A.; Principato, G. *J. Org. Chem.* **1997**, *62*, 8041–8048. (e) Tairov, M. A.; Vysotsky, M. O.; Kalchenko, O. I.; Pirozhenko, V. V.; Kalchenko, V. I. *J. Chem. Soc., Perkin Trans. 1* **2002**, *11*, 1405–1411. (f) He, Y.; Xiao, Y.; Meng, L.; Zeng, Z.; Wu, X.; Wu, C.-T. *Tetrahedron Lett.* **2002**, *43*, 6249–6253.
3. (a) Steyer, S.; Jeunesse, C.; Matt, D.; Welter, R.; Wesolek, M. *J. Chem. Soc., Dalton Trans.* **2002**, *22*, 4264–4274. (b) Cobley, C. J.; Ellis, D. D.; Orpen, A. G.; Pringle, P. G. *J. Chem. Soc., Dalton Trans.* **2000**, *20*, 1109–1112. (c) Parlevliet, F. J.; Kiener, C.; Fraanje, J.; Goubitz, K.; Lutz, M.; Spek, A. L.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *J. Chem. Soc., Dalton Trans.* **2000**, *20*, 1113–1122. (d) Shimizu, S.; Shirakawa, S.; Sasaki, Y.; Hirai, C. *Angew. Chem., Int. Ed.* **2000**, *39*, 1256–1259. (e) Baldini, L.; Bracchini, C.; Cacciapaglia, R.; Casnati, A.; Mandolini, L.; Ungaro, R. *Chem. Eur. J.* **2000**, *6*, 1322–1330. (f) Dospil, G.; Schatz, J. *Tetrahedron Lett.* **2001**, *42*, 7837–7840. (g) Frank, M.; Maas, G.; Schatz, J. *Eur. J. Org. Chem.* **2004**, *3*, 607–613.
4. Dieleman, C.; Steyer, S.; Jeunesse, C.; Matt, D. *J. Chem. Soc., Dalton Trans.* **2001**, 2508–2517.
5. For examples see: (a) Löffler, F.; Hagen, M.; Lüning, U. *Synlett* **1999**, *11*, 1826–1828. (b) Gibson, C.; Rebek, J. *Org. Lett.* **2002**, *4*, 1887–1890.
6. Arnott, G.; Page, P. C. B.; Heaney, H.; Hunter, R.; Eur *J. Org. Chem.* **2004**, 5126–5134.
7. Shivanyuk, A.; Schmidt, C.; Böhmer, V.; Paulus, E. F.; Lukin, O.; Vogt, W. *J. Am. Chem. Soc.* **1998**, *120*, 4319–4326.
8. For other examples of Mannich chemistry in resorcinarenes see: (a) Matsushita, Y.; Matsui, T. *Tetrahedron Lett.* **1993**, *34*, 7433–7436. (b) Leigh, D. A.; Linnane, P.; Pritchard, R. G.; Jackson, G. *J. Chem. Soc., Chem. Commun.* **1994**, 389–390. (c) Arnecke, R.; Böhmer, V.; Paulus, E. F.; Vogt, W. *J. Am. Chem. Soc.* **1995**, *117*, 3286–3287. (d) Schneider, U.; Schneider, H.-J. *Chem. Ber.* **1994**, *127*, 2455–2469. (e) Luostarinen, M.; Shivanyuk, A.; Rissanen, K. *Org. Lett.* **2001**, *3*, 4141–4144.
9. Shivanyuk, A.; Paulus, E. F.; Böhmer, V.; Vogt, W. *J. Org. Chem.* **1998**, *63*, 6448–6449.

10. Arnott, G.; Page, P. C. B.; Heaney, H.; Hunter, R.; Sampler, E. *Synlett* **2001**, 412–414.
11. Lukin, O. V.; Pirozhenko, V. V.; Shivanyuk, A. N. *Tetrahedron Lett.* **1995**, *36*, 7725–7728.
12. Rajagopalan, S.; Raman, P. V. A. In *Organic Syntheses*, *Collect. Vol. III*; Wiley: New York, 1955–1961.
13. Emerson, W. S.; Longley, R. I. In *Organic Syntheses*, *Collect. Vol. IV*; Wiley: New York, 1963–1970.
14. Sherman, J. C.; Chapman, R. G. *Chem. Rev.* **1999**, *99*, 931–967.
15. Schmidt, C.; Thondorf, I.; Kolehmainen, E.; Böhmer, V.; Vogt, W.; Rissanen, K. *Tetrahedron Lett.* **1998**, *39*, 8833–8836.
16. Steed, J. W.; Atwood, J. L. *Supramolecular Chemistry*; Wiley: New York, 2000.
17. (a) Högberg, A. G. S. *J. Org. Chem.* **1980**, *45*, 4498–4500. (b) Högberg, A. G. S. *J. Am. Chem. Soc.* **1980**, *102*, 6046–6050. (c) Abis, L.; Dalcanale, E.; Du Vosel, A.; Spera, S. *J. Chem. Soc., Perkin Trans. 2* **1990**, 2075–2080. (d) Abis, L.; Dalcanale, E.; Du Vosel, A.; Spera, S. *J. Org. Chem.* **1988**, *53*, 5475–5479. (e) Shivanyuk, A. N.; Pirozhenko, V. V.; Kalchenko, V. I.; Markovsky, L. N. *J. Chem. Res., Synop.* **1995**, 374–375. (f) Lukin, O.; Shivanyuk, A.; Pirozhenko, V. V.; Tsymbal, I. F.; Kalchenko, V. I. *J. Org. Chem.* **1998**, *63*, 9510–9516.
18. For a similar difficulty see: Page, P. C. B.; Heaney, H.; Sampler, E. P. *J. Am. Chem. Soc.* **1999**, *121*, 6751–6752.
19. Iwanek, W.; Urbaniak, M.; Grawdzik, B.; Schurig, V. *Tetrahedron: Asymmetry* **2003**, *14*, 2787–2792.

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Enantioselective addition of diethylzinc to benzaldehyde catalysed by chiral, bridged resorcinarenes: a stereoselectivity model based on chirality transfer

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Abstract—The enantioselective addition of diethylzinc to benzaldehyde catalysed by a range of chiral bridged resorcinarenes has been studied, and the results used as a means of probing cooperative effects in the resorcinarene bowl. A structure–activity relationship has emerged in which bridged resorcinarenes with little available room in the bowl (e.g., **3b**, **3c**) favour *R*-enantioselectivity in the product, while those promoting cooperative effects in the bowl via coordination sites in the bridge (**3e**) or strong donor protecting groups (**3j**) favour *S*-enantioselectivity. A mechanistic hypothesis based on Noyori's model to account for these trends has been put forward in which stereoselectivity is dependent on two factors as the ratio of axially diastereomeric anti-zincoxazines as well as the *exo* or *endo* bias of active zinc. The model explains why ee's are never greater than around 50% and indicates asymmetric induction to be due to the axial chirality in the bowl as a result of chirality transfer from the bridge, rather than due to induction via the central chirality in the line of the bridge. As a result, the model stimulates some new fascinating possibilities in enzyme mimicry.

1. Introduction

In the previous paper,[1] we described the synthesis and characterization of a range of chiral bridged resorcinarenes using Mannich technology for bridge incorporation. Emphasis was placed on varying the protecting groups on the upper rim as well as the length and nature of the chiral diamine line used to construct the bridge. Although a range of pendant lower-rim groups were screened in the simple model, only $R=CH_3$ was used for the full set of derivatives. Our purpose for synthesizing these derivatives was to investigate the potential use of such structures as templates for asymmetric catalysis. The literature contains very few examples of calixarenes and resorcinarenes in asymmetric catalysis. For instance, Matt has shown that a lower-rim, inherently chiral calixarene scaffold can be used in allylic alkylation (palladium) and hydrogenation (rhodium), although low ees were obtained.[2] Others have shown that cooperative effects may potentially be provided by supramolecular interactions involving the concave bowl.[3] Of particular interest for us was the possibility of using cooperative effects, which could be investigated using an asymmetric reaction as a probe. Given the presence of tertiary amino and phenolic hydroxyl functionality in a 1,3-relationship near to the chiral auxiliaries in the bridge, it was decided to use the enantioselective addition of diethylzinc to benzaldehyde as this probe reaction, given that this reaction is mechanistically well-documented and known to work with γ-amino alcohols.[4,5]Many catalysts based on chiral β- and γ-amino alcohols have been reported for the enantioselective addition reaction of diethylzinc to benzaldehyde (aldehydes), with many of them now able to achieve ee's in excess of 95%.[6] A comprehensive mechanistic picture has now emerged in which the amino alcohol functionality is postulated to form a zincoxazine intermediate that acts as a template for catalysis.[7]

To this end we have recently reported evidence for the first example of a cavity-controlled addition of diethylzinc to benzaldehyde involving ketal functionality in the bridge.[8] In this paper, we present results on a comprehensive study of the diethylzinc reaction using our bridged resorcinarenes as catalyst templates, and use the trends in stereoselectivity to develop a mechanistic model that offers insights into the origin of the enantioselectivity, and hence ideas on future design.

Keywords: Resorcinarene; Catalytic template; Diethylzinc; Enzyme mimicry; Cavity control.

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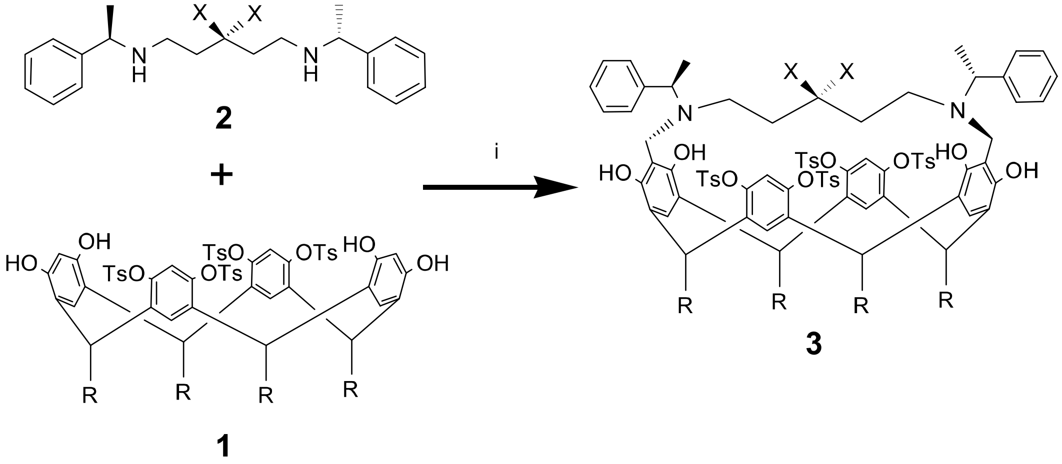


Scheme 1. Synthesis of bridged resorcinarenes. Reagents and conditions: (i) $(CH_2O)_n$, CH_3CN, 90 °C.

2. Results

Our first studies were conducted on bridged resorcinarene tetratosylates **3a–e**.[8] These could be synthesized by the Mannich reaction between resorcinarene tetratosylate **1**, diamine **2** and excess paraformaldehyde in moderate to good yields (Scheme 1, Table 1),[8,9] in which the resorcinarene tetratosylates **1** could themselves be synthesized by known methodology.[9–11] The derivatives chosen aimed to firstly probe communication between lower and upper-rims by varying the pendant R group, while keeping the bridge constant, and secondly to probe the influence of having a coordinating (to zinc) group (X) in the middle of the bridge while keeping the pendant R group constant (as methyl).

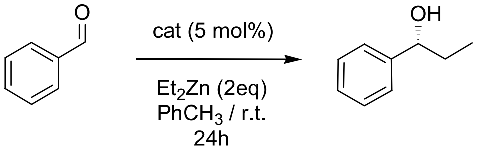
Table 1. Yields for bridged resorcinarenes synthesized

	R	X	Yield (%)
3a	CH_3	H	60
3b	C_5H_{11}	H	80
3c	$C_{11}H_{23}$	H	67
3d	CH_3	$OCH_2C(CH_3)_2CH_2O$	47
3e	CH_3	OMe	57

Addition reactions were carried out in all cases using benzaldehyde as limiting reagent with diethylzinc (2 equiv) and a resorcinarene loading of 5 mol% in toluene at room temperature for 24 h. Yields of 1-phenyl-1-propanol were ascertained from purification using column chromatography while ee's were determined by chiral GC using a modified β-cyclodextrin glass capillary column (Heptakis-2,3-di-*O*-acetyl-6-*O*-TMBMS-β-CD). The results can be found in Table 2.

Two important trends emerge from these results. The first was that the enantioselectivity increased with lengthening of the resorcinarene pendant R groups, which drew attention to the possible involvement of the cavity in influencing the stereochemical outcome of the reaction. This was because ^{1}H NMR spectroscopic studies on resorcinarenes **3a–c**, as described in a previous paper,[1] had revealed an increasing downfield shift of the bridge methylenes (X = H in **3**) going from **3a** to **3c**, indicating that the bridge spent more time in the cavity for **3c**.[12] This trend was rationalized by invoking increased lower-rim repulsions for **3c** resulting in the upper rim phenyl groups being pushed closer together. Importantly for these results, the increase in ee on going from **3a** to **3c** would thus be associated with minimizing room in the bowl, which has implications for the mechanistic model proposed later. The second trend identified, intriguingly, was that the dimethoxy ketal on the bridge of **3e** effected a complete reversal of the enantioselectivity of the reaction. We have recently proposed that this result suggests intracavity catalysis in view of the position of the ketal in the middle of the line and the possibility therefore of direct involvement of the ketal group as a coordination site to zinc.[8]

Table 2. Results for the asymmetric addition of diethylzinc to benzaldehyde



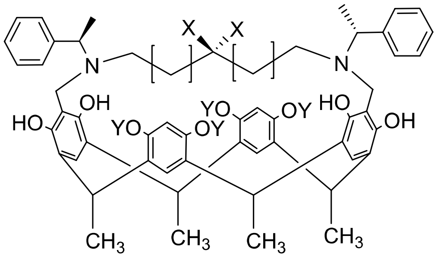
	R	X	Yield (%)	ee (%) (enantiomer)
3a	CH_3	H	91	12 (*R*)
3b	C_5H_{11}	H	94	41 (*R*)
3c	$C_{11}H_{23}$	H	99	52 (*R*)
3d	CH_3	$OCH_2C(CH_3)_2CH_2O$	85	34 (*R*)
3e	CH_3	OMe	85	51 (*S*)

Satisfied that the enantioselective addition of diethylzinc to benzaldehyde could indeed be used as a mechanistic probe reaction, we elected to broaden the study to other structural changes, notably to address the influence of the upper-rim protecting groups as well as the length of the bridge. These changes were addressed in that order.

Alternatives to the tosylate 'protecting' group were selected for ease of synthesis and potential for providing different steric and electronic environments near the cavity. Their synthesis and characterization has been described in a previous paper.[1] Thus, methanesulfonate (OMs, **3f**) and triisopropylbenzenesulfonate (OTrips, **3g**) were chosen to sterically complement the *p*-toluenesulfonate (OTs, **3a**) groups already used. In addition, ester derivatives such as acetate (OAc, **3h**) and tolyl (OTol, **3i**) were synthesized, along with a benzyl carbonate (OCBz, **3j**) in order to investigate electronic effects around the group directly attached to the phenolic oxygen. Attempts at synthesizing an alkyl methyl analogue failed. Slightly longer diamine lines for bridging were synthesized and characterized, including an example with a dimethoxy ketal in the centre of the bridge (**3l**) for comparison with the shorter-bridged resorcinarene **3e**. In all these cases the pendant R group was kept as methyl.

These new compounds were then evaluated out as before for their ability to catalyze the asymmetric addition of diethylzinc to benzaldehyde. The results are shown in Table 3, along with a comparison with compound **4**, an *o*-hydroxybenzylamine containing a chiral α-methylbenzyl auxiliary at nitrogen, which was prepared by Palmieri and investigated in the same reaction.[13] Compound **4** modelled a structural fragment of bridged resorcinarene **3**.

Table 3. Results for the asymmetric addition of diethylzinc to benzaldehyde



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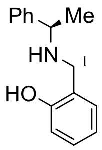


4

	n	Y	X	Yield (%)	ee (%) (enantiomer)
3f	1	OMs	H	84	5 (*S*)
3g	1	OTrips	H	73	14 (*R*)
3h	1	OAc	H	75	12 (*S*)
3i	1	OTol	H	79	20 (*S*)
3j	1	OCbz	H	99	49 (*S*)
3k	2	OTs	H	41[a]	19 (*S*)
3l	2	OTs	OMe	3[b]	21 (*S*)
4	—	—	—	92	16 (*S*)

[a] Benzyl alcohol (46%) obtained as byproduct.
[b] Benzyl alcohol (91%) obtained as byproduct.

Table 3 reveals that the ee's showed no quantitative improvement compared to those obtained previously. An important observation though was that the results with **4** indicated that the resorcinarene skeleton does indeed influence the enantioselectivity. Palmieri found that the best results (>90% ee) were obtained when a chiral group was attached to position 1 (marked on table diagram) indicating that the resorcinarene structure plays a pivotal role in the asymmetric induction.

The trend in ee's provided an opportunity to draw some interesting conclusions. In this regard, the derivatives should be viewed as four sets as: **3f/3g**; **3h–3j**, **3k** and **3l**. Firstly, the **3f/3g** comparison: increasing the steric bulk of the sulfonate protecting group from tosylate (**3a**, Table 2) to the triisopropylbenzenesulfonate (Trips, **3g**), did not significantly alter the reaction stereo-outcome. However, reducing its size to the methanesulfonate (Ms, **3f**), resulted in a reversal in the sense of enantioselectivity in the product towards favouring the *S*-enantiomer. In the **3h–3j** set, changing the protecting group from a sulfonate to an ester (Ac, Tol) or carbonate (Cbz), resulted in the product always favouring the *S*-configuration rather than *R*-, with the carbonate returning the best and significantly higher ee for the unfunctionalised (X=H) bridged resorcinarenes. Thirdly, increasing the length of the unfunctionalised bridge by two methylene groups as **3k** while keeping tosylate as protecting group also resulted in a reversal of enantioselectivity from *R* to *S*. Lengthening the functionalised bridge of **3e** by two methylene groups to **3l** resulted in retention of the *S*-enantioselectivity but at a reduced level (51 vs 21%).

In our previous work focusing on compound **3e**,[8] we suggested that a transition-state occurring in the resorcinarene cavity equated with reversal of enantioselectivity. Thus, in accordance with this hypothesis, the results above would be rationalised as follows. Firstly, changing from the larger tosylate to the smaller mesylate group decreases steric bulk near the cavity and thus allows for a greater chance of an intracavity transition-state. Secondly, changing from sulfonate to ester protecting groups (i.e., from tetratosylate **3a** to tetratolate **3i**), results in oxygen donor atoms near the cavity with increased Lewis basicity, thus directing the diethylzinc into the cavity (see Fig. 1). This is particularly poignant for the tetrabenzylcarbonate **3j**, which returned an ee of 49% (*S*), as a result of having two mesomeric oxygen donors to the carbonyl group.

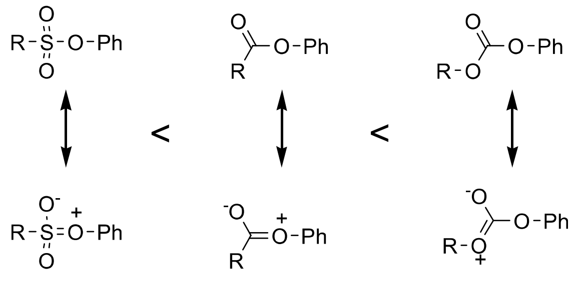


Figure 1. Relative donor strengths of protecting group oxygens.

Similarly for the longer-bridged resorcinarene **3k**, the selectivity shift from *R* to *S* was also indicative of more available room in the cavity in keeping with the NMR trends.[1] The upfield shift for the longer bridge **3k** was less (−0.22 ppm) compared to that of the shorter bridged **3a** (−0.37 ppm) indicating that the bridge of **3k** lies on average more out of the cavity compared to **3a**, probably to maximize entropy. Furthermore, the longer-bridged **3l** containing the ketal in the centre of the bridge also returned an *S*-enantioselectivity indicating a predominantly cavity-controlled process. However, the ee was lower than that of the shorter bridged compound **3e** (21 vs 51%) presumably as a result of the ketal coordinating group being on average further out of the cavity. All of these results appeared to corroborate our hypothesis for **3e** put forward to explain the trends in enantioselectivity as *S*-enantioselectivity indicating a preferred cavity-controlled process. A further important observation made from the results, in particular for the longer-bridged resorcinarenes **3k** and **3l**, was the reduction in chemical yield compared to other bridged resorcinarenes. For **3k** and **3l**, the byproduct produced in these reactions was determined to be benzyl alcohol, produced via hydride reduction of the substrate benzaldehyde. Ridley and Coates, in their study of organozinc compounds, have proposed that diethylzinc can do this via a β-elimination of hydride from diethylzinc with concomitant release of ethylene.[14] This was supported by the observation that the reaction of diethylzinc with benzophenone gave the reduced product quantitatively, whereas no reaction (addition or reduction) was observed with dimethylzinc, which lacks β-hydrogens. The authors proposed a cyclic transition-state shown in Figure 2.

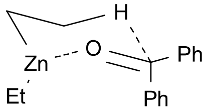


Figure 2. Proposed six-membered transition-state for reduction of benzophenone.

In the case of **3k** and **3l**, presumably the longer and hence larger bridges make it energetically more difficult to accommodate the benzaldehyde substrate inside the cavity. The result is that the diethylzinc favours the less sterically demanding hydride delivery option compared to the ethyl transfer. This scenario is particularly significant for ketal **3l** in which the ketal attempts to direct zinc coordination and hence reaction from within the cavity of the bowl, but the larger line promotes a favoured hydride delivery on steric grounds.

3. Mechanistic model

In order to consolidate our thoughts into a mechanistic model, attention was turned towards the current mechanistic view on this reaction. Of particular significance for our results was the observation that ee's were never higher than around 50%, which made us uncomfortable when referring to a 'cavity-controlled' process. Thus, we considered this feature to be highly significant. Although several reaction mechanisms involving various ligands have appeared in the literature, that of Noyori's utilizing amino alcohols as ligands[7] has received the widest recognition. This mechanism postulates that two molecules of dialkylzinc per catalyst are required for a reaction to occur, the first forming a zinc-chelate complex with expulsion of alkane to provide a zincoxazine template (template-zinc) for the complexation of the second equivalent that generates the active zinc-entity (active-zinc) responsible for alkyl group transfer. Palmieri,[8] working on derivatives of **4** as catalysts for the same reaction, has also postulated an analogous 'zincoxazine' template formation with dimethylzinc, based on Noyori's work. The full mechanism is depicted in Figure 3.

For mechanistic studies regarding the ratio of diethylzinc to the pre-catalyst resorcinarene, a series of reactions were conducted a using a 1:1 ratio of catalyst: benzaldehyde, so as to be able to determine the number of equivalents of diethylzinc required for the reaction to go to completion. Two resorcinarenes were studied on a 0.5 mmol scale, **3b** (R = *n*-pentyl) and **3e** (R = CH_3) with the dimethoxy ketal in the bridge. The pendant R group and the group in the bridge were varied in this study in order to probe their importance. Moreover, carrying out the reactions on a 0.5 mmol scale

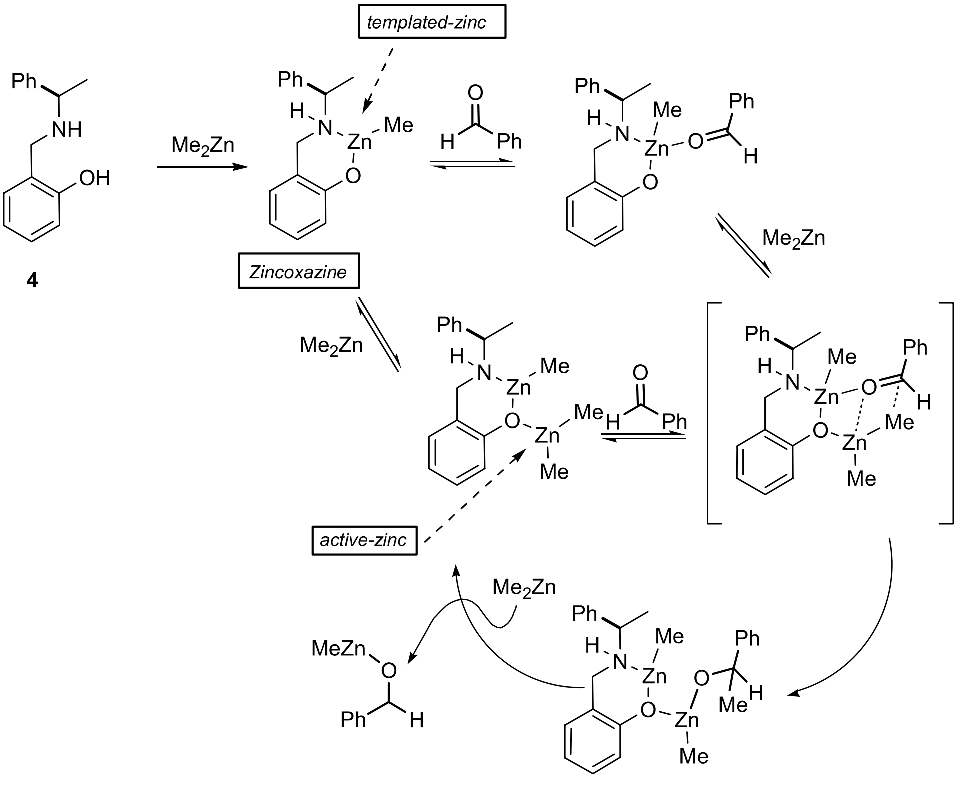


Figure 3. Palmieri's template and active zincoxazines.

minimized errors of judgment that might be incurred in the syringing of the reactants. Reactions were left the customary 24 h after the addition of each equivalent of diethylzinc to allow the possibility of reaction to proceed before monitoring by TLC. The results are shown in Table 4.

Table 4. Equivalents diethylzinc required to ensure complete reaction

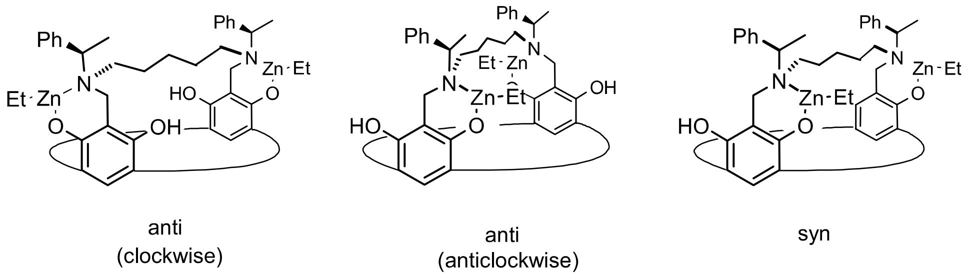
Et_2Zn (equiv)	Resorcinarene **3b**	Resorcinarene **3e**
2	No reaction	No reaction
3	Partial[a]	No reaction
4	Complete reaction	No reaction
5	—	Complete reaction

[a] Judged by TLC to be ~10%.

With a ratio of 2:1:1 Et_2Zn/resorcinarene/benzaldehyde, neither resorcinarene produced any reaction. At 3:1:1, **3b** showed partial reaction (~10% by TLC), while **3e** showed no conversion of starting material. At 4:1:1, **3b** showed complete conversion to the product 1-phenyl-1-propanol, while **3e** remained at 0% conversion, Addition of the fifth equivalent of diethylzinc to **3e** finally resulted in complete conversion of benzaldehyde. These trends were considered to be highly significant indicators for constructing a mechanistic model, which we now delineate.

In keeping with the Noyori mechanistic model, these results support the notion of initial consumption of 2 equiv of diethylzinc to form a bis-zincoxazine template intermediate, for which theoretically there are three possible arrangements, as one *syn* and two axially diasterisomeric *anti*-zincoxazine templates (Fig. 4).

The third equivalent of diethylzinc could either coordinate to a zincoxazine oxygen to form 'active-zinc' (see Fig. 3), resulting in alkyl addition to benzaldehyde (once coordinated), or it could react with one of the unreacted, poorly nucleophilic hydroxyl groups, resulting in an inactive site in view of the inability to form a chelate. Figure 5 shows three possible pathways that might exist for the reaction of


anti
(clockwise)

anti
(anticlockwise)

syn

Figure 4. The three possible arrangements of the bis-zincoxazine resorcinarene templates.

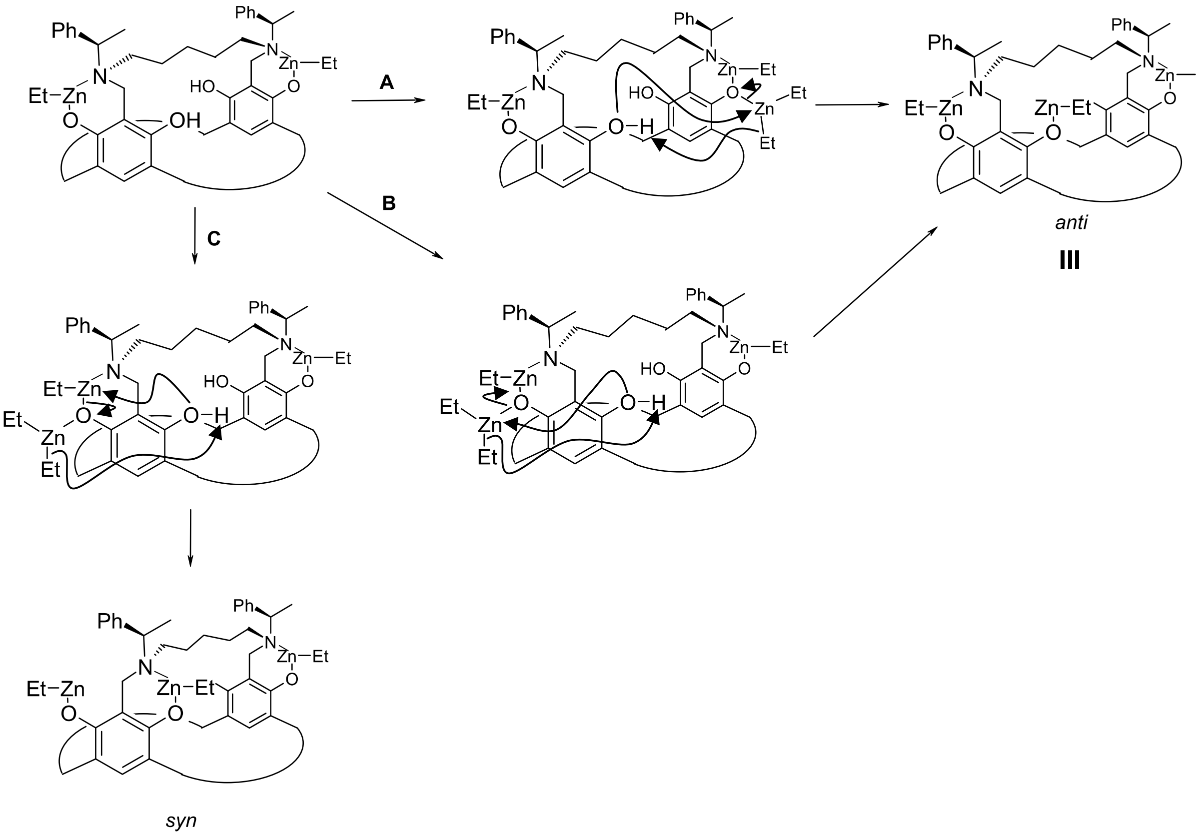


Figure 5. Possible mechanism for coordination of third diethylzinc molecule.

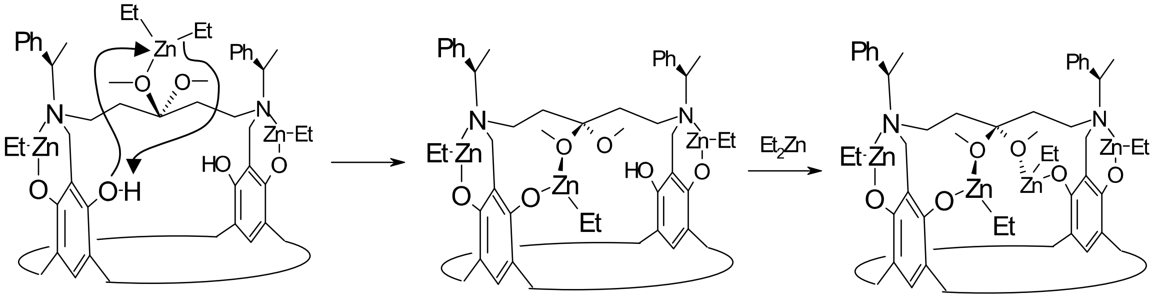


Figure 6. Possible mechanism or the coordination of third and fourth diethylzine molecules in **3e**.

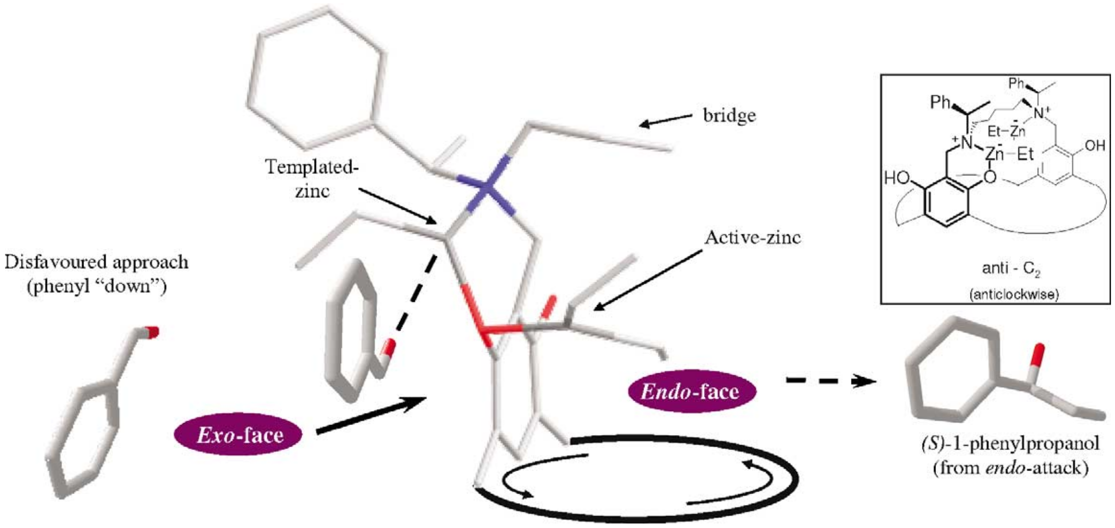


Figure 7. 3D-representation of *endo* versus *exo* facial delivery for zincoxazine in the anthoclockwise configuration (showing only one of the zincoxazines and including coordinated 'active-zinc').

the third equivalent of diethylzinc. Mechanistically, these suggest an initial coordination of the diethylzinc to the oxygen of one of the zincoxazines, followed by an intramolecular rearrangement of the 'active-zinc' onto a free hydroxyl group either on the opposite side of the bowl (pathway A) or on the same side (pathway B). This complexation offers a plausible mechanism for the interconversion of the *syn*/*anti*-bis-zincoxazine arrangements as shown by pathway C. Evidently a competition exists between active-zinc formation and hydroxyl exchange, with the latter being favoured, since the third equivalent of diethylzinc resulted in only partial conversion of benzaldehyde to 1-phenylpropanol for **3b** and none for **3e**. It was only on addition of the fourth equivalent of diethylzinc that the **3b** reaction went to completion, now indicating a greater preference for activation of 'templated-diethylzinc' to form 'active-zinc' compared to reaction with the final free hydroxyl group.

For **3e**, however, conversion was still blocked, either as a result of exchange with the remaining phenolic hydroxyl or because of competing coordination of diethylzinc by the dimethoxy ketal. We consider the latter to be more plausible, particularly in view of the results with **3b**. Finally, addition of the fifth equivalent to the **3e** reaction successfully brought about full conversion indicating that active-zinc is only set up after the fourth equivalent of diethylzinc with this template. Figure 6 shows how these processes might possibly occur.

The next step in the Noyori model requires coordination of the benzaldehyde oxygen to the zinc of the templated-zinc. In our case it seems reasonable to postulate that the benzaldehyde approaches the zincoxazine in a preferred orientation governed by steric interactions, regardless of inter- versus intracavity reaction preference. Consideration of molecular models suggests this to involve an orientation in which the phenyl group points away from both the bridge and the lower rim. Once both 'active-zinc' has been set up and benzaldehyde coordination to 'templated-zinc' has taken place, ethyl group transfer may proceed from the *exo*- or *endo*-face of the zincoxazine,[†] depending on the positioning of 'active-zinc' *endo*-face attachment of 'active-zinc' is shown in Figure 7.

Of the three diastereoisomeric bis-zincoxazines depicted in Figure 4, literature precedent suggests that the *anti*-arrangement predominates. Böhmer has demonstrated that Mannich condensation of resorcinarene tetratosylates (**1**) with achiral primary diamines and formaldehyde gave predominantly bridged *anti* bis-benzoxazines with

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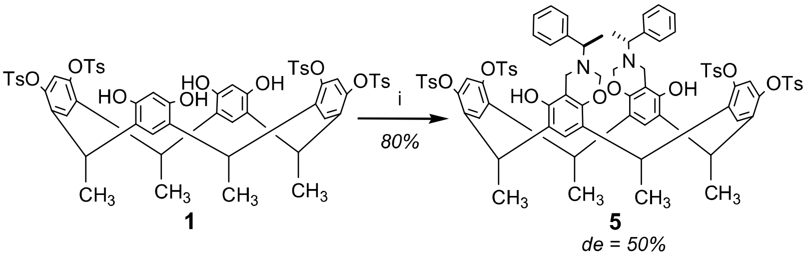
[†] The *endo*-face is synonymous with the cavity, while the *exo*-face effectively places the active diethylzinc on the outside of the perimeter.



Scheme 2. Reagents and conditions: (i) (*R*)-α-methylbenzylamine, formaldehyde, AcOH (cat.), EtOH, rt.

the *syn*-isomer only being detected by ^{1}H NMR (<5%) when the length of the polymethylene spacer is five or more carbons long.[15] Further support for discounting the *syn*-diastereomer comes from our own work in which condensation of resorcinarene tetratosylate **1** with chiral (*R*)-α-methylbenzylamine and formaldehyde gave a 3:1 mixture of the *anti* bis-benzoxazine **5** with no trace of the *syn*-isomer, Scheme 2. The ^{1}H NMR spectrum (Fig. 8) showed three sets of aromatic methine singlets in the 6.2–7.0 ppm range, which is characteristic of the *anti*-bisbenzoxazine arrangement of a mixture of diastereomers (the *syn*-arrangement would have resulted in the appearance of five signals in this region).

Thus, in this transition-state model the enantioselectivity of the reaction is determined by the interplay between the *exo*- versus *endo*-delivery bias of 'active-zinc', together with the diastereomeric excess of the two *anti* bis-zincoxazines, which together account for the large range of ee's from *R* to *S*. It is likely that the latter is primarily due to the *exo*/*endo* factor rather than a shift in the *anti* bis-zincoxazine equilibrium, as the *exo*/*endo* bias would presumably be more responsive towards structural changes affecting the space in the cavity, and hence the positioning of active zinc inside or outside. Consequently, this model indicates that enantioselectivity is not as a result of the sp^3 asymmetric chirality in the bridge but rather due to axial chirality in the bowl[16]—as a result of chirality transfer from the bridge—working in conjunction with cavity effects. Such a model neatly explains why ee's are never greater than 50%. For instance, the ketal-bridged template **3e** result, with an ee of 51% in favour of the *S*-enantiomer, may be rationalized as proceeding via two axially diastereomeric zincoxazines, one giving rise to 75% *S* and the other 25% *R*, but both via *endo*-delivery of ethyl to a benzaldehyde positioned in both cases with its phenyl group pointing away from the resorcinarene.

Similarly, our hypothesis that *S*-enantioselectivity is synonymous with *endo* delivery of the ethyl group, allows prediction that the dominant bis-zincoxazine diastereomer of the 3:1 mixture is the anticlockwise one. This correlates with Heaney's work on resorcinarene tetrabenzoxazines in which the *R*-auxiliary promoted a bias to the anticlockwise isomer.[17]

The present transition-state model may be thus summarised as follows:

- Reaction proceeds via two axially-chiral, diastereomeric *anti* bis-zincoxazines, whose ratio is estimated to be 75:25 in favour of the 'anti-clockwise'— isomer when the bridge is (*R*, *R*). This would explain why ee's were never greater than about 50%.
- The stereo-positioning of active zinc as either *exo* or *endo* with respect to the cavity (bowl) is a crucial feature in determining *R* or *S* enantioselectivity. Delivery of ethyl from *exo*-'active-zinc' is considered to produce an excess of the *R*-enantiomer of 1-phenyl-1-propanol. Thus, compounds **3b** and **3c** with long pendant chains and minimised room in the bowl set up a predominance of *exo*-active zinc, which results in *exo*-delivery of ethyl favouring the *R*-products.

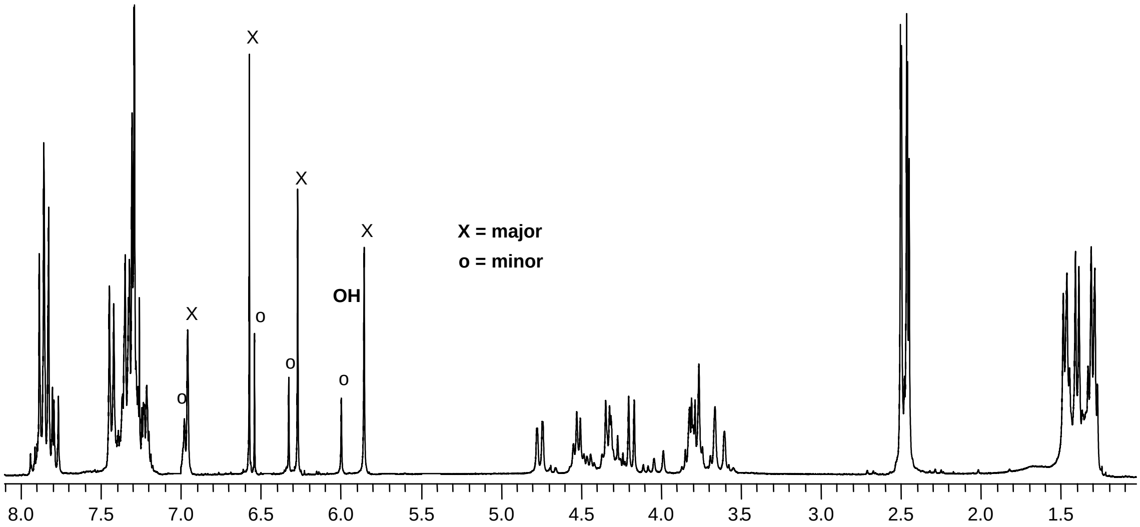


Figure 8. ^{1}H NMR spectrum of **5** showing the major and minor isomers.

- Conversely, *endo*-attachment of active zinc resulting in *endo* delivery of ethyl favours the *S*-configuration in the product. This is the case for compounds **3e** and **3j** involving cooperative cavity effects—the former from donor methoxy groups in the bridge, and the latter from the electron-donating carbonate groups—which promote the kinetic formation of *endo*-'active-zinc'.

4. Conclusion

The enantioselectivities achieved by these catalysts for the reaction in question by no means compare with the high values (>95% ee) achievable for many other systems.[4] However, this study has allowed generation of a working model alluding to some interesting cavity effects operating in conjunction with axial chirality in the resorcinarene bowl, as a result of chirality transfer from the asymmetry in the bridge, as being responsible for the enantioselectivity. The study[8,9] represents the first reported example of using the bowl of an asymmetrically functionalised resorcinarene for promoting asymmetric catalysis,[8] a desirable research objective suggested recently by Iwanek.[18] In this regard, these catalysts open up a new dimension in resorcinarene asymmetric catalysis and synthetic enzyme mimicry.

5. Experimental

5.1. General remarks

All diethylzinc reactions were carried out under argon using dry toluene. Nuclear magnetic resonance spectra were recorded on a Varian Unity 400 (100 MHz for ^{13}C) or Varian Mercury 300 MHz (75 MHz for ^{13}C) and were carried out in chloroform-*d*. Optical rotations were obtained using a Perkin Elmer 141 polarimeter at 20 °C. Melting points were obtained using a Reichert Jung Thermovar hot-stage microscope and are uncorrected. Elemental analyses were performed using a Fisons EA 1108 CHN elemental analyser. Infrared spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrometer in either dichloromethane or chloroform. Enantiomeric excesses were determined by chiral GC on a Hewlett Packard HP 5890 Gas Chromatagraph, using a modified β-cyclodextrin glass capillary column (Heptakis-2,3-di-*O*-acetyl-6-*O*-TMBMS-β-CD) and helium as a carrier gas. Bridged resorcinarenes **3** were synthesised according to reported procedures.[1,8]

5.2. General procedure for the synthesis of 1-phenylpropanol

To a pre-dried Schlenk tube was added catalyst (0.025 mmol) and 1 M diethylzinc in toluene (1 mmol, 1 mL) at −20 °C. The solution was allowed to stir for 15 min followed by the addition of 1 M benzaldehyde in toluene (0.5 mmol, 0.5 mL). The reaction vessel was then sealed and allowed to warm slowly to room temperature. After 16 h the reaction was checked (TLC) for complete consumption of benzaldehyde. On completion, the reaction was cooled to 0 °C and quenched by the slow addition of 1 M HCl (1 mL), and then extracted from water (20 mL) with dichloromethane (3×20 mL). The organic extracts were dried over magnesium sulphate and reduced in the usual manner. Flash chromatography (5 g SiO_2, eluting with ethyl acetate/petroleum ether 3:17) afforded 1-phenylpropanol as a clear oil. The enantiomeric excess was determined by chiral GC.

5.2.1. (*R*,*R*)-1^5,5^5-Dihydroxy-2,4,6,8-tetramethyl-1^3,5^3-bis(1-phenylethyl)-3^4,3^6,7^4,7^6-tetra(*p*-toluene-sulfonyloxy)-3,7 (1,3)benzena-1,5(6,8)-(3,4-dihydro-2H-benzo[*e*]-[1,3]oxa-zina)cyclooctaphane (5). Tetramethylresorcinarene tetratosylate (290 mg, 0.25 mmol) and (*R*)-α-methylbenzylamine (0.2 mL, 1.5 mmol) were added to ethanol (30 mL) and 32% aqueous formaldehyde (8 mL). Glacial acetic acid (0.5 mL) was added and the reaction allowed to stir at room temperature overnight. The product that precipitated was filtered and washed with ethanol to give the title compound (280 mg, 80%) as an off-white powder. Mp 152–155 °C (from ethanol–dichloromethane); $[\alpha]_D$ −6.7 (*c* 1.67 in $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 3514s (O–H, H-bonded), 2930s+2853s (C–H), 1598m+1483m (aryl stretch), 1371s+1186s ($-SO_2-O-$); δ_H (300 MHz, $CDCl_3$) 1.26–1.34 (6H, m, C-4/8 $-CH_3$), 1.40 (6H, d, J=6.6 Hz, NCHCH_3), 1.43–1.50 (6H, m, C-2/6 $-CH_3$), 2.45, 2.46, 2.48 and 2.50 (12H, 4×s, H-7′), 3.36 and 3.80 (4H, 2×d, J_{AB}=17.6 Hz, H-1^4,5^4 -major), 3.77 and 4.02 (4H, 2×d, J_{AB}=17.6 Hz, H-1^4,5^4 -minor) 3.80 (2H, q, J=6.6 Hz, NC*H*CH_3), 4.09 and 4.67 (4H, 2×d, J_{AB}=8.9 Hz, H-1^2,5^2 -minor), 4.18–4.76 (4H, 2×d, J_{AB}=10.3 Hz, H-1^2,5^2 -major), 4.33 (2H, q, J=6.8 Hz, H-4,8 -major), 4.52 (2H, q, J=6.8 Hz, H-2,6 -major), 4.25 and 4.45 (4H, m, H-2,4,6,8 -minor), 5.85 (2H, s, –OH -major), 6.00 (2H, s, –OH -minor), 6.27 (2H, s, H-3^2 -major), 6.32 (2H, s, H-3^2 -minor), 6.54 (2H, s, H-3^5 -minor), 6.57 (2H, s, H-3^5 -major), 6.96 (2H, s, H-1^7 -major), 6.98 (2H, s, H-1^7 -minor), 7.18–7.47 (18H, m, Ph +H-3′/5′), 7.76–7.94 (8H, m, H-2′/6′); δ_C (75 MHz, $CDCl_3$) 19.1, 20.5 (CH_3 major), 20.6, 20.9 (CH_3 minor), 31.4 (C-4,8 minor), 31.7 (C-4,8 major), 32.2 (C-2,6 minor), 32.4 (C-2,6 major), 43.8 (C-1^4 minor), 45.4 (C-1^4 major), 58.4 (N*C*HCH_3), 78.6 (C-1^2 major), 79.8 (C-1^2 minor), 108.9 (C-1^{10} major), 109.0 (C-1^{10} minor), 114.6 (C-3^5 minor), 114.8 (C-3^5 major), 116.7 (C-1^6 minor), 116.9 (C-1^6 major), 121.3 (C-1^8 major), 121.6 (C-1^8 minor), 122.2 (C-1^7 major), 122.3 (C-1^7 major), 126.6 (C-3^2 major), 126.9, 127.2, 127.6, 128.0, 128.1, 128.3, 128.4, 128.6, 128.7, 129.8, 130.3, 130.4 (Ph +C-2′/3′/5′/6′), 131.5+133.8 (C-1′ minor), 131.6+134.1 (C-1′ major), 138.2 (C-3^1 minor), 138.3 (C-3^1 major), 141.7 (C-3^3 minor), 142.1 (C-3^3 major), 143.9 (C-3^6 minor), 144.2 (C-3^6 major), 144.3, 145.2+145.3 (C-4′+ Ph), 145.6 (C-3^4 major), 146.3 (C-4′), 150.3 (C-1^5 minor), 150.7 (C-1^5 major), 151.8 (C-1^9 minor), 152.3 (C-1^9 major); MALDI TOF: *m/z* (rel int.) 1450.51 [$M^+ - H$] (5); Found: C, 65.95; H, 5.41; N, 1.94; S, 8.34%; $C_{80}H_{78}N_2O_{16}S_4$ requires C, 66.19; H, 5.42; N, 1.93; S, 8.83%.

References and notes

1. Arnott, G.; Hunter, R.; Hong, S., *Tetrahedron*, **2006**, 62, preceding paper. doi: 10.1016/j.tet.2005.10.029.

2. Dieleman, C.; Steyer, S.; Jeunesse, C.; Matt, D. *J. Chem. Soc., Dalton Trans.* **2001**, 2508–2517.
3. For examples see: (a) Löffler, F.; Hagen, M.; Lüning, U. *Synlett* **1999**, *11*, 1826–1828. (b) Gibson, C.; Rebek, J. *Org. Lett.* **2002**, *4*, 1887–1890.
4. For recent reviews of the asymmetric addition of dialkylzincs see: (a) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757–824. (b) Walsh, P. J. *Acc. Chem. Res.* **2003**, *36*, 739–749.
5. A few examples include: (a) Cardellicchio, C.; Ciccarella, G.; Naso, F.; Perna, F.; Tortorella, P. *Tetrahedron* **1999**, *55*, 14685–14692. (b) Zhang, H.; Chan, K. S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 381–382. (c) Mino, T.; Oishi, K.; Yamashita, M. *Synlett* **1998**, 965–966. (d) Cozzi, P. G.; Papa, A.; Umani-Ronchi, A. *Tetrahedron Lett.* **1996**, *37*, 4613–4616.
6. For a sample of recent examples see: (a) Kang, S.-W.; Ko, D.-H.; Kim, K. H.; Ha, D.-C. *Org. Lett.* **2003**, *5*, 4517–4519. (b) Fonseca, M. H.; Eibler, E.; Zabel, M.; Kőnig, B. *Tetrahedron: Asymmetry* **2003**, *14*, 1989–1994. (c) Fu, B.; Du, D.-M.; Wang, J. *Tetrahedron: Asymmetry* **2004**, *15*, 119–126. (d) Scarpi, D.; Galbo, F. L.; Occhiato, E. G.; Guarna, A. *Tetrahedron: Asymmetry* **2004**, *15*, 1319–1324. (e) Sibi, M. P.; Stanley, L. M. *Tetrahedron: Asymmetry* **2004**, *15*, 3353–3356. (f) Bauer, T.; Gajewiak, J. *Tetrahedron* **2004**, *60*, 9163–9170. (g) Casey, M.; Smyth, M. P. *Synlett* **2003**, *1*, 102–106. (h) Wipf, P.; Pierce, J. G.; Wang, X. *Tetrahedron: Asymmetry* **2003**, *14*, 3605–3611.
7. (a) Noyori, R.; Kawai, S. K.; Okada, S.; Kitamura, M. *Pure Appl. Chem.* **1988**, *60*, 1597–1606. (b) Yamakawa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 6327–6335. (c) Yamakawa, M.; Noyori, R. *Organometallics* **1999**, *18*, 128–133.
8. Arnott, G.; Page, P. C. B.; Heaney, H.; Hunter, R. *Eur. J. Org. Chem.* **2004**, 5126–5134.
9. Arnott, G.; Page, P. C. B.; Heaney, H.; Hunter, R.; Sampler, E. *Synlett* **2001**, 412–414.
10. Lukin, O. V.; Pirozhenko, V. V.; Shivanyuk, A. N. *Tetrahedron Lett.* **1995**, *36*, 7725–7728.
11. Shivanyuk, A.; Paulus, E. F.; Böhmer, V.; Vogt, W. *J. Org. Chem.* **1998**, *63*, 6448–6449.
12. Morikawa, O.; Nakanishi, K.; Miyashiro, M.; Kobayashi, K.; Konishi, H. *Synthesis* **2000**, *2*, 233–236 for an analogous system.
13. Palmieri, G. *Tetrahedron: Asymmetry* **2000**, *11*, 3361–3373.
14. Coates, G. E.; Ridley, D. *J. Chem. Soc. (A)* **1966**, 1064–1069.
15. Shivanyuk, A.; Schmidt, C.; Böhmer, V.; Paulus, E. F.; Lukin, O.; Vogt, W. *J. Am. Chem. Soc.* **1998**, *120*, 4319–4326.
16. For an example of an axially chiral resorcinarene see: Page, P. C. B.; Heaney, H.; Sampler, E. P. *J. Am. Chem. Soc.* **1999**, *121*, 6751–6752.
17. El Gihani, M. T.; Heaney, H.; Slawin, A. M. Z. *Tetrahedron Lett.* **1995**, *36*, 4905–4908. Heaney found that (*R*)-α-methly-benzylamine favoured the formation of the anticlockwise resorcinarene tetrabenzoxazine.
18. Iwanek, W.; Urbaniak, M.; Grawdzik, B.; Schurig, V. *Tetrahedron: Asymmetry* **2003**, *14*, 2787–2792.

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Efficient synthesis of 18–40 membered macrocyclic polyoxadiamides and polyoxatetraamides via ring closing metathesis

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Abstract—Ring closing metathesis of the appropriate 1,ω-dienes led to efficient synthetic approaches towards the corresponding macrocyclic polyoxadiamides and tetraamides with 18–40 membered ring sizes in good to excellent yields using Grubbs' catalyst.

1. Introduction

Recently, ring closing metathesis (RCM)[1] has found increasing application in the synthesis of macrocyclic compounds.[2–12] The application of RCM as the key macrocyclization step in the synthesis of crown compounds has opened efficient routes towards macrocyclic crown compounds of important applications in supramolecular chemistry.[6,13–16]

The present work describes new routes for the synthesis of macrocyclic polyethers containing diamide and tetraamide groups inside the macrocyclic ring via RCM using Grubbs'catalyst **I** as the key macrocyclization step. The results obtained provide an efficient synthetic procedure to the macrocyclic polyoxadiamides **3b–e**, **4**, **5**, **6a**,**b**, **7a**,**b**, **9a**,**b** with 18–34 membered ring sizes and the macrocyclic polyoxatetraamides **1a–e**, **2b**,**d**, **8a**,**b** with 28–40 membered ring sizes. The new macrocyclic crown-amides **1–9** synthesized in the present investigation are of potential interesting diverse applications, which have been reviewed in our recent publications (Fig. 1).[16]

2. Results and discussion

Scheme 1 illustrates our synthetic routes towards the precursors 1,ω-dienes **15a–e** needed for the RCM synthesis of **1a–e**. Thus, acylation of *o*-aminophenol **10** with *o*-allyloxybenzoyl chloride **11** afforded *o*-(*o*-allyloxybenzamido)phenol **12**. The latter was converted into its potassium salt **13**, which was then reacted with the appropriate bis-chloroacetanilide derivatives **14a–e** to afford the corresponding 1,ω-dienes **15a–e** in 63–93% yields. RCM of **15a–e** proceeded smoothly to give the corresponding macrocycles **1a–e** in 52–97% yields with Grubbs' catalyst **I** (2.5–5 mol%) in refluxing CH_2Cl_2 for 24 h. The results are presented in Table 1.

On the other hand, 1,ω-dienes **17b**,**d** were readily obtained as outlined in Scheme 2. Thus, reacting the potassium salt of *o*-allyloxyacetamidophenol **8** with each of **14b**,**d** afforded the corresponding desired 1,ω-dienes **17b**,**d**. RCM of the latter dienes proceeded smoothly to give the corresponding macrocycles **2b**,**d** in 70 and 60% yields, respectively, upon heating with Grubbs' catalyst **I** (5 mol%) in refluxing CH_2Cl_2 for 24 h. The results are presented in Table 1.

Scheme 3 outlines the synthetic routes followed for the synthesis of the 1,ω-dienes **21–23**, required for the RCM synthesis of macrocycles **3b–e**, **4** and **5**. Thus, alkylation of methyl salicylate **18** with 2-allyloxyethyl *p*-toluenesulfonate afforded methyl 2-(2-allyloxyethoxy)benzoate, which was hydrolysed to the corresponding acid. The latter was then converted to the corresponding acid chloride **19** by the action of $SOCl_2$. Reaction of **19** with each of the amines **20b–e**, ethylenediamine and *o*-phenylenediamine afforded the corresponding 1,ω-dienes **21b–e**, **22** and **23**, respectively. Compounds **22** and **23** were also, prepared by reacting the dipotassium salts of each of 1,2-bis(2-hydroxybenzamido)ethane and 1,2-bis(2-hydroxybenzamido)benzene with 2-allyloxyethyl *p*-toluenesulfonate. RCM of

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Keywords: Ring closing metathesis; 1,ω-Dienes; Bis-anilides; Diazapolyoxacycloalkenediones; Tetraazapolyoxacycloalkenetetraones.

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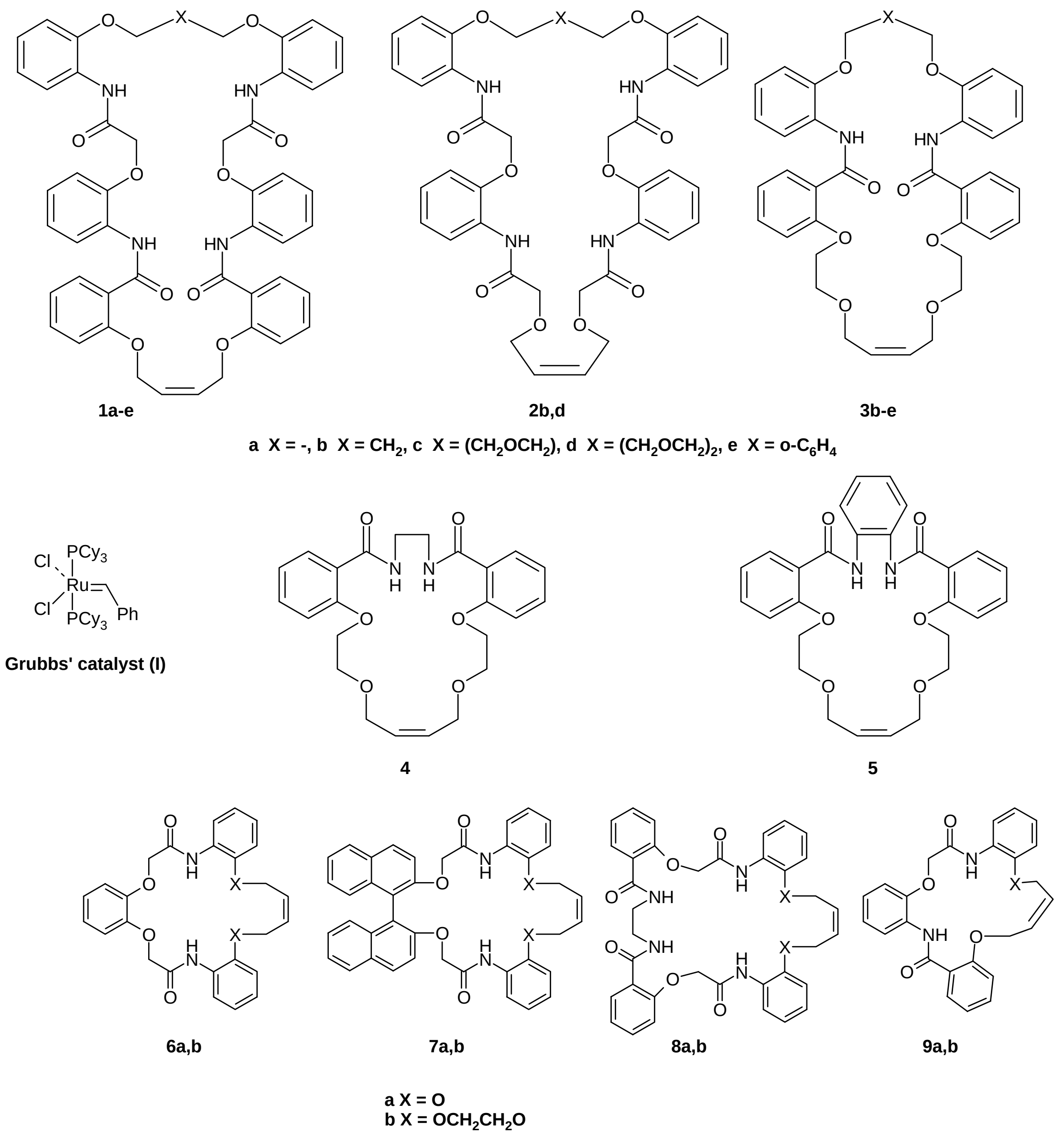


Figure 1.

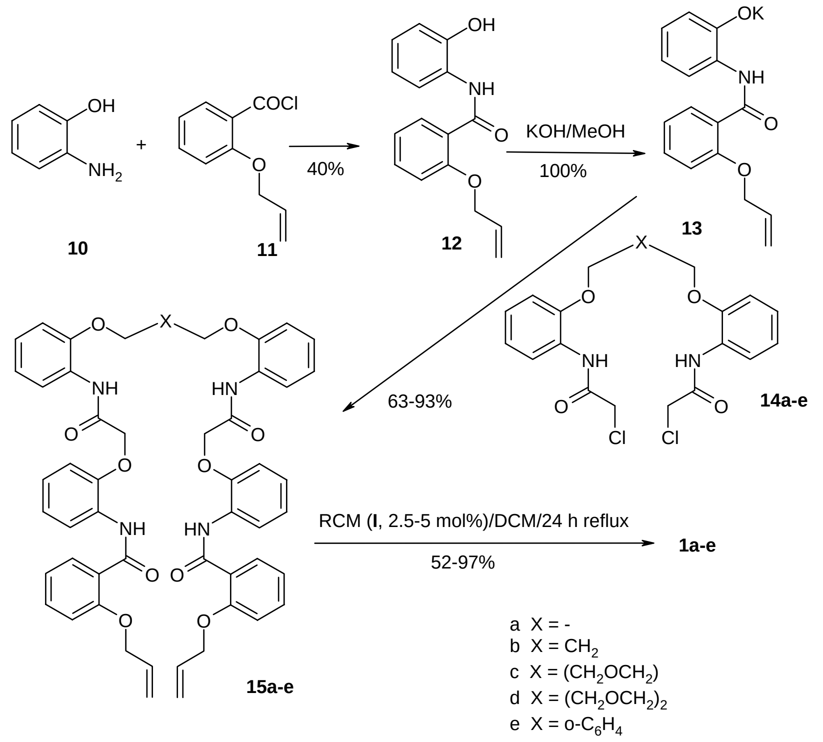
compounds **21–23** afforded corresponding macrocyclic compounds **3–5** in 60–99% yields upon heating with Grubbs' catalyst **I** (2.5–5 mol%) in refluxing CH_2Cl_2 for 4–24 h. The results are presented in Table 2.

On the other hand, 1,ω-dienes **30–33** were readily obtained as outlined in Scheme 4. Thus, acylation of each of the *o*-allyloxyaniline **24a** and *o*-(2-allyloxyethoxy)aniline **24b** with chloroacetyl chloride afforded the corresponding chloroacetanilide derivatives **25a**,**b**, respectively. Reacting the latter with the potassium salt of the appropriate phenolic compounds **26–29** afforded the corresponding desired 1,ω-dienes **30–33**. RCM of the latter dienes proceeded smoothly to give the corresponding macrocycles **6–9** in 73–100% yields upon heating with Grubbs' catalyst **I** (2.5–7.5 mol%) in refluxing CH_2Cl_2 for 2–24 h (Table 3).

In all RCM reactions, the progress of the reaction was monitored by TLC and ^{1}H NMR analysis where no further increase in products was noticed (after the time indicated in Tables 1–3) of reflux in CH_2Cl_2. The RCM products **1–9** were shown from their ^{1}H and ^{13}C NMR to consist of the *E* and *Z* isomers in different ratios as shown in Tables 1–3.

The *E*:*Z* isomers of the olefinic crown-diamides were readily assigned and their ratios were determined from the ^{1}H and ^{13}C NMR spectra. The major products in all RCM reactions were shown to be the *E* isomers with the characteristic ^{13}C signal of the OCH_2 (of the $OCH_2CH{=}CHCH_2O$), which appears further downfield than that for the corresponding *Z* isomer. In ^{1}H NMR the $O\mathit{CH_2}CH{=}$ and $OCH_2\mathit{CH}{=}$ signals of *E* isomers appear as broad singlets. On the other hand, those similar proton signals for the *Z* isomer split into a doublet and triplet with $J=3$–5 Hz.

The present work describes an efficient synthetic access towards macrocyclic crown-diamide and crown-tetraamide



Scheme 1.

Table 1. Catalyst %, yields and *E*/*Z* ratios of macrocycles **1a**–**e**, **2b**,**d**

Entry	Substrate	(mol%) Catalyst/substrate, reaction time (h)	Yield (%)	Product *E*:*Z* ratio
1	**15a**	2.5, 24	97	**1a** 5:1
2	**15b**	5.0, 24	91	**1b** 7:1
3	**15c**	2.5, 24	52	**1c** 5:1
4	**15d**	2.5, 24	78	**1d** 5:1
5	**15e**	2.5, 24	88	**1e** 13:1
6	**17b**	5.0, 24	70	**2b** 2.5:1
7	**17d**	5.0, 24	60	**2d** 3.5:1

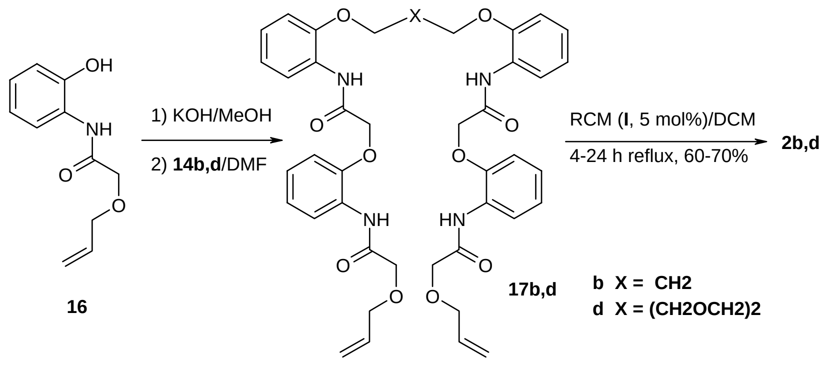
derivatives, with potential diverse applications in supramolecular chemistry and as starting compounds for further synthetic transformations utilizing the RCM techniques for the macrocyclization step. The examples of RCM presented here represent one of the best macrocyclization reaction techniques for the synthesis of crown compounds. It also, expands the utility of RCM methodology and its application to the synthesis of cyclic olefins of large ring sizes with different functional groups.

3. Experimental

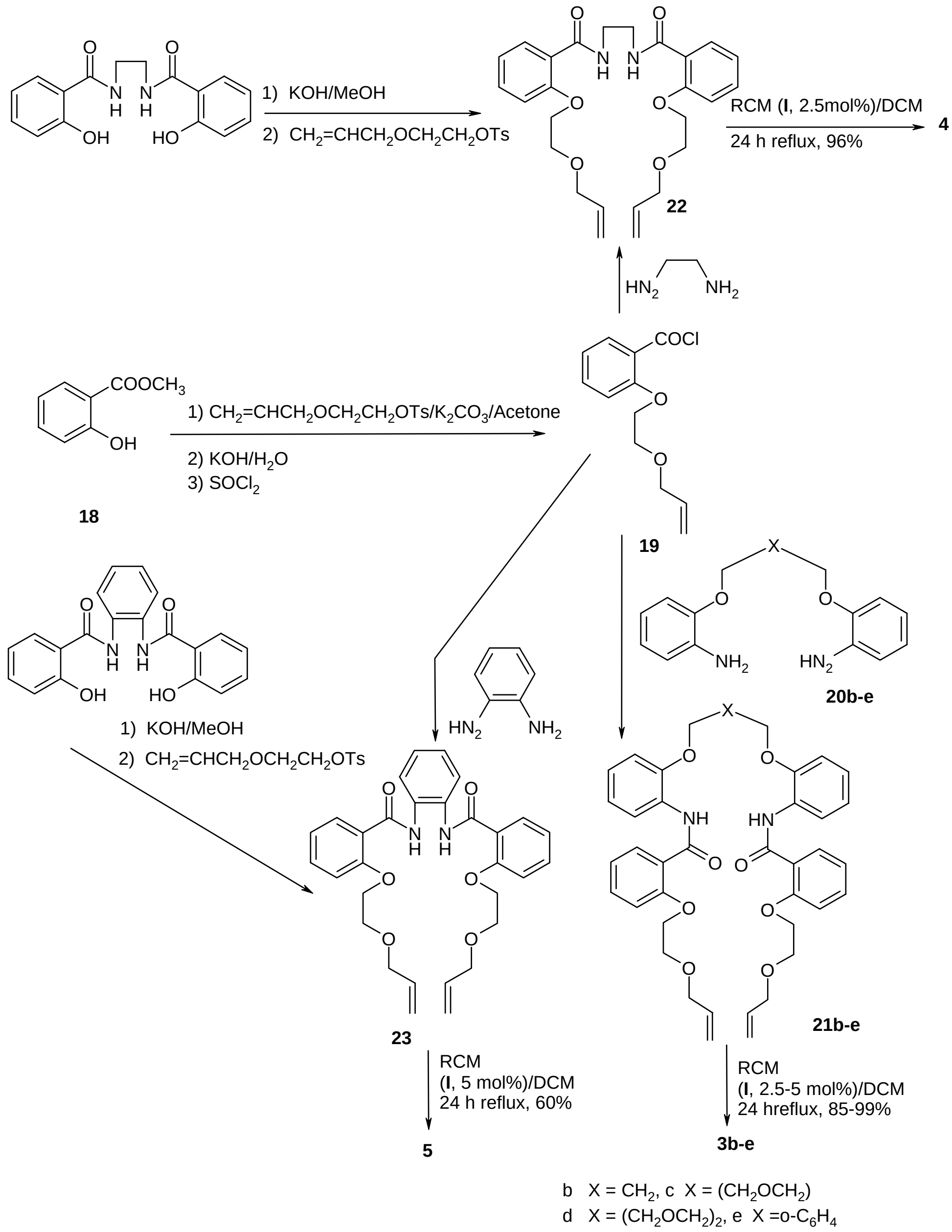
3.1. General

All melting points are uncorrected. IR spectra were recorded in KBr disks using Perkin Elmer System 2000 FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 400, 400 MHz super-conducting NMR spectrometer. Mass spectra were measured on VG Autospec-Q (high resolution, high performance, tri-sector GC/MS/MS) and with LCMS using Agilent 1100 series LC/MSD with an API-ES/APCI ionization mode. Microanalyses were performed on LECO CH NS-932 Elemental Analyzer. The starting *o*-allyloxybenzoyl chloride **11**,[17] bis-amines **14a–e**,[16e] bis-amides **20b–e**,[18] 1,2-bis(2-hydroxybenzamido)ethane[19] and 1,2-bis(2-hydroxybenzamido)benzene[19] were prepared as reported.

3.1.1. 2-(*o*-Allyloxybenzamido)phenol 12. To an ice cold (0–5 °C) stirred solution of **10** (5.3 g, 49 mmol) and



Scheme 2.



Scheme 3.

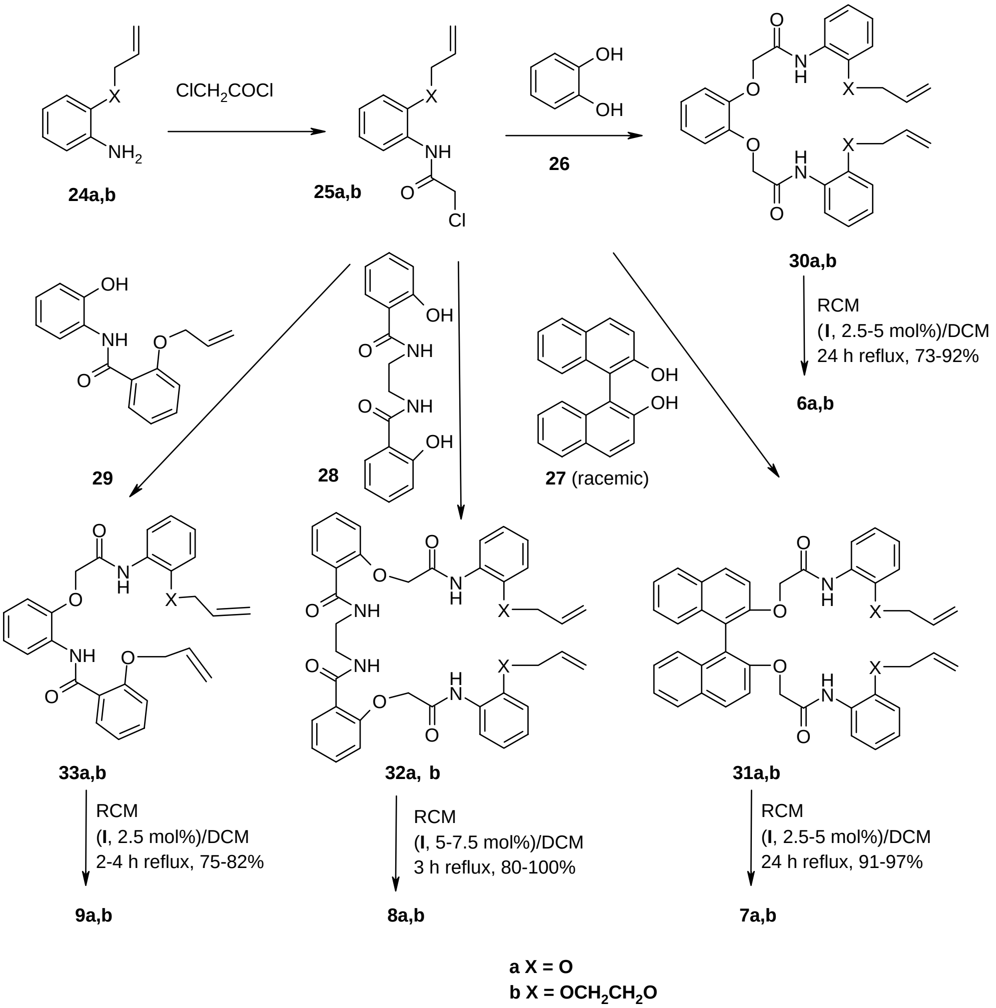
Table 2. Catalyst %, yields and *E*/*Z* ratios of macrocycles **3b–e**, **4**, **5**

Entry	Substrate	(mol%) Catalyst/substrate, reaction time (h)	Yield (%)	Product *E*:*Z* ratio
1	**21b**	2.5, 24	99	**3b** 3:1
2	**21c**	5.0, 24	85	**3c** 1.7:1
3	**21d**	2.5, 24	99	**3d** 2:1
4	**21e**	2.5, 24	98	**3e** 3:1
5	**22**	2.5, 4	96	**4** 2.5:1
6	**23**	5.0, 24	60	**5** 1.4:1

triethylamine (6.8 mL, 50 mmol) in DCM (20 mL) was added **11** (9.5 g, 48 mmol) in DCM (15 mL). The reaction mixture was stirred for 1 h in ice and stirring was continued overnight at room temperature. The resulting solution was extracted with DCM, neutralized with concd HCl, washed with water, Na_2CO_3 solution and water again and then dried over anhydrous sodium sulfate. The solvent was then removed in vacuo and remaining precipitate was crystallized from DCM/pet. ether (40–60) to give 5.5 g (42%) of colorless crystals, mp 130–131 °C. MS: $m/z=269$ (M^+, 30%). IR: 3326, 3077, 1640, 1598, 1542, 1482, 1457, 1329, 1283, 1232, 1162, 1089, 997, 786, 762, 722. ^{1}H NMR ($CDCl_3$): δ 10.38 (s, 1H, NH), 9.61 (s, 1H, OH), 8.33 (dd, 1H, $J=8.0$, 1.5 Hz), 7.55 (dt, 1H, $J=8.3$, 1.5 Hz), 7.19 (t, 2H, $J=7.6$ Hz), 7.09 (m, 2H), 6.98 (d, 1H, $J=7.7$ Hz), 6.91 (t, 1H, $J=7.5$ Hz), 6.21 (m, 1H, CH=), 5.57 (d, 1H, $J=17.2$ Hz, CH_2=), 5.50 (d, 1H, $J=10.3$ Hz, CH_2=), 4.80 (d, 2H, $J=6.0$ Hz, OCH_2). Anal. Calcd for $C_{16}H_{15}NO_3$ (269.3): C 71.36; H 5.61; N 5.20. Found: C 71.10; H 5.61; N 5.44.

3.1.2. Synthesis of 15a–e and 17b,d. General procedure.

To a solution of KOH (0.13 g, 2.2 mmol) in methanol (5 mL) was added **12** or **16** (2.2 mmol). The mixture was stirred at room temperature for 15 min and the solvent was



Scheme 4.

Table 3. Catalyst %, yields and *E*/*Z* ratios of macrocycles **6**–**9**

Entry	Substrate	(mol%) Catalyst/substrate, reaction time (h)	Yield (%)	Product *E*:*Z* ratio
1	**30a**	2.5, 24	92	**6a** 3.6:1
2	**30b**	5, 24	73	**6b** 2:1
3	**31a**	2.5, 24	91	**7a** 3:1
4	**31b**	5, 24	97	**7b** 3:1
5	**32a**	7.5, 3	100	**8a** 2:1
6	**32b**	5, 3	80	**8b** 2.6:1
7	**33a**	2.5, 4	75	**9a** 1:1
8	**33b**	2.5, 2	82	**9b** 2.5:1

then removed in vacuo. To the remaining potassium salt was added DMF (2 mL) and the appropriate dichloro derivatives **14a–e** (1 mmol). The reaction mixture was then heated under reflux for 5 min. The mixture was then cooled, diluted with water (20 mL) and the precipitate was collected, washed with cold water and finally crystallized (except **17d**, which was obtained as an oil) to give the corresponding dienes **15a–e** and **17b**, which were also characterized by their R_f values using DCM–pet. ether (40–60)–EtOAc (6/4/3).

3.1.2.1. Compound 15a. Yield 0.8 g (93%); colorless crystals (EtOH), mp 130–131 °C, R_f=0.7. LCMS; *m*/*z*=863 (M+1). IR: 3400, 3344, 3071, 2933, 2875, 1688, 1663, 1600, 1536, 1482, 1455, 1331, 1293, 1252, 1229, 1163, 1118, 1093, 1047, 999, 915, 750. ^{1}H NMR (CDCl$_3$): δ 10.19 (s, 2H, NH), 8.56 (s, 2H, NH), 8.48 (m, 2H), 8.25 (d, 2H, J=7.6 Hz), 8.20 (d, 2H, J=7.6 Hz), 7.42 (t, 2H, J=7.8 Hz), 7.09 (t, 2H, J=7.4 Hz), 7.02 (m, 6H), 6.71 (m, 6H), 6.42 (d, 2H, J=7.5 Hz), 5.83 (m, 2H, CH=), 5.13 (m, 4H, =CH$_2$), 4.44 (s, 4H, OCH$_2$CO), 4.25 (d, 4H, J=4.5 Hz, OCH_2CH=), 3.19 (s, 4H, OCH$_2$). Anal. Calcd for $C_{50}H_{46}N_4O_{10}$ (862.9): C 69.59; H 5.37; N 6.49. Found: C 69.50; H 5.52; N 6.77.

3.1.2.2. Compound 15b. Yield 0.8 g (91%); colorless crystals (EtOH), mp 130–131 °C, R_f=0.6. LCMS; *m*/*z*=877 (M+1). IR: 3400, 3344, 3064, 2937, 1674, 1601, 1536, 1484, 1456, 1335, 1293, 1227, 1120, 1051, 998, 931, 851, 752. ^{1}H NMR (CDCl$_3$): δ 10.52 (s, 2H, NH), 8.70 (dd, 2H, J=7.8, 1.7 Hz), 8.63 (s, 2H, NH), 8.29 (d, 4H, J=7.8 Hz), 7.51 (dt, 2H, J=7.7, 1.8 Hz), 7.09 (m, 6H), 6.95 (d, 2H, J=8.3 Hz), 6.86 (m, 4H), 6.67 (dt, 2H, J=7.8, 1.4 Hz), 6.34 (d, 2H, J=8.0 Hz), 5.98 (m, 2H, CH=), 5.30 (d, 2H, J=17.2 Hz, =CH$_2$), 5.19 (d, 2H, J=10.5 Hz, =CH$_2$), 4.69 (s, 4H, OCH$_2$CO), 4.57 (d, 4H, J=5.7 Hz, OCH_2CH=), 3.43 (t, 4H, J=5.2 Hz, OCH$_2$CH$_2$), 1.18 (quint, 2H, J=5.2 Hz, OCH$_2$CH_2). Anal. Calcd for $C_{51}H_{48}N_4O_{10}$ (876.9): C 69.85; H 5.52; N 6.39. Found: C 69.63; H 5.43; N 6.29.

3.1.2.3. Compound 15c. Yield 0.7 g (77%); colorless crystals (EtOH), mp 160–161 °C, $R_f=0.6$. LCMS; $m/z=907$ (M+1). IR: 3391, 3341, 3069, 2936, 2874, 1691, 1658, 1601, 1535, 1483, 1455, 1333, 1295, 1254, 1229, 1135, 1118, 1047, 753. ^{1}H NMR (CDCl$_3$): δ 10.49 (s, 2H, NH), 8.67 (d, 2H, $J=8.0$ Hz), 8.63 (s, 2H, NH), 8.36 (d, 2H, $J=8.0$ Hz), 8.27 (d, 2H, $J=8.0$ Hz), 7.48 (t, 2H, $J=8.0$ Hz), 7.13 (t, 2H, $J=8.0$ Hz), 7.05 (m, 4H), 6.92 (m, 8H), 6.41 (d, 2H, $J=8.0$ Hz), 5.99 (m, 2H, CH=), 5.29 (d, 2H, $J=16.5$ Hz, =CH$_2$), 5.19 (d, 2H, $J=10.4$ Hz, =CH$_2$), 4.64 (s, 4H, OCH$_2$CO), 4.53 (d, 4H, $J=5.6$ Hz, OCH_2CH=), 3.43 (t, 4H, $J=4.4$ Hz, OCH$_2$CH$_2$O), 3.95 (t, 4H, $J=4.4$ Hz, OCH$_2$CH$_2$O). Anal. Calcd for $C_{52}H_{50}N_4O_{11}$ (907.0): C 68.86; H 5.56; N 6.18. Found: C 68.71; H 5.45; N 6.47.

3.1.2.4. Compound 15d. Yield 0.6 g (63%); colorless crystals (EtOH/CHCl$_3$), mp 143–144 °C, $R_f=0.4$. LCMS; $m/z=952$ (M+1). IR: 3396, 3344, 3064, 3012, 2920, 1663, 1600, 1535, 1483, 1456, 1333, 1293, 1254, 1226, 1117, 1048, 932, 752. ^{1}H NMR (CDCl$_3$): δ 10.49 (s, 2H, NH), 8.83 (s, 2H, NH), 8.67 (dd, 2H, $J=7.6$, 1.9 Hz), 8.40 (dd, 2H, $J=7.7$, 1.6 Hz), 8.29 (dd, 2H, $J=7.8$, 1.6 Hz), 7.45 (dt, 2H, $J=8.0$, 1.6 Hz), 7.10 (t, 2H, $J=7.6$ Hz), 7.02 (m, 8H), 6.92 (m, 4H), 6.76 (dd, 2H, $J=8.0$, 1.2 Hz), 6.05 (m, 2H, CH=), 5.33 (d, 2H, $J=17.2$ Hz, =CH$_2$), 5.24 (d, 2H, $J=10.5$ Hz, =CH$_2$), 4.72 (s, 4H, OCH$_2$CO), 4.57 (d, 4H, $J=5.6$ Hz, OCH_2CH=), 3.67 (t, 4H, $J=5.2$ Hz, OCH$_2$CH$_2$O), 3.15 (t, 4H, $J=5.2$ Hz, OCH$_2$CH$_2$O), 3.07 (s, 4H, OCH$_2$CH$_2$O). Anal. Calcd for $C_{54}H_{54}N_4O_{12}$ (951.0): C 68.20; H 5.72; N 5.89. Found: C 67.98; H 5.57; N 6.10.

3.1.2.5. Compound 15e. Yield 0.8 g (85%); colorless crystals (EtOH), mp 228–229 °C, $R_f=0.8$. LCMS; $m/z=939$ (M+1). IR: 3393, 3322, 3070, 3005, 2935, 2884, 1691, 1654, 1599, 1527, 1482, 1454, 1332, 1290, 1248, 1231, 1188, 1136, 1114, 1091, 1044, 997, 949, 929, 895, 790, 753. ^{1}H NMR (CDCl$_3$): δ 10.20 (s, 2H, NH), 8.78 (d, 2H, $J=7.7$ Hz), 8.62 (s, 2H, NH), 8.43 (m, 2H), 8.23 (d, 2H, $J=7.5$ Hz), 7.45 (t, 2H, $J=7.5$ Hz), 6.96 (m, 16H), 6.43 (m, 2H), 6.38 (m, 2H), 5.73 (m, 2H, CH=), 5.20 (d, 2H, $J=17$ Hz, =CH$_2$), 5.08 (d, 2H, $J=10.2$ Hz, =CH$_2$), 4.62 (s, 4H, OCH$_2$CO), 4.36 (s, 4H, OCH$_2$Ar), 4.27 (d, 4H, $J=5.5$ Hz, OCH_2CH=). Anal. Calcd for $C_{56}H_{50}N_4O_{10}$ (939): C 71.63; H 5.37; N 5.97. Found: C 71.34; H 5.46; N 6.20.

3.1.2.6. Compound 17b. Yield 0.4 g (53%); colorless crystals (EtOH), mp 126–127 °C, $R_f=0.7$. LCMS; $m/z=753$ (M+1). IR: 3388, 3270, 3070, 2934, 2879, 1679, 1603, 1537, 1486, 1456, 1290, 1260, 1119, 750. ^{1}H NMR (CDCl$_3$): δ 9.03 (s, 2H, NH), 8.63 (s, 2H, NH), 8.44 (m, 2H), 8.30 (m, 2H), 7.06 (m, 4H), 6.97 (m, 4H), 6.92 (m, 2H), 6.58 (m, 2H), 5.82 (m, 2H, CH=), 5.27 (d, 2H, $J=17.2$ Hz, =CH$_2$), 5.15 (d, 2H, $J=10.4$ Hz, =CH$_2$), 4.74 (s, 4H, OCH$_2$CO), 4.06 (t, 4H, $J=5.6$ Hz, OCH_2CH=), 4.05 (s, 4H, OCH$_2$CO), 3.71 (t, 4H, $J=5.5$ Hz, OCH_2CH$_2$), 1.72 (quint, 2H, $J=5.5$ Hz, OCH$_2$CH_2). Anal. Calcd for $C_{41}H_{44}N_4O_{10}$ (752.8): C 65.41; H 5.89; N 7.44. Found: C 65.32; H, 5.85; N 7.60.

3.1.2.7. Compound 17d. Yield 0.12 g (15%); pale yellow oil purified using column chromatography using EtOAc/pet. ether (40–60) as an eluent, $R_f=0.6$/EtOAc. LCMS; $m/z=827$ (M+1). IR: 3389, 3070, 2923, 2854, 1689, 1603, 1535, 1486, 1456, 1292, 1255, 1207, 1117, 1045, 930, 750. ^{1}H NMR (CDCl$_3$): δ 9.06 (s, 2H, NH), 8.76 (s, 2H, NH), 8.43 (m, 2H), 8.34 (d, 2H, $J=7.9$ Hz), 6.92 (m, 12H), 5.80 (m, 2H, CH=), 5.25 (dd, 2H, $J=17.3$, 1.0 Hz, =CH$_2$), 5.11 (d, 2H, $J=10.2$ Hz, =CH$_2$), 4.71 (s, 4H, OCH$_2$CO), 4.08 (s, 4H, OCH$_2$CO), 4.04 (d, 4H, $J=5.6$ Hz, OCH_2CH=), 3.99 (t, 4H, $J=4.8$ Hz, OCH$_2$CH$_2$O), 3.49 (t, 4H, $J=4.8$ Hz, OCH$_2$CH$_2$O), 3.33 (s, 4H, OCH$_2$CH$_2$O). Anal. Calcd for $C_{44}H_{50}N_4O_{12}$ (826.9): C 63.91; H 6.09; N 6.78. Found: C 63.68; H 6.31; N 6.77.

3.1.3. Methyl 2-(2-allyloxyethoxy)benzoate. A mixture of methyl salicylate (10 g, 65 mmol), 2-allyloxyethyl *p*-toluenesulfate (8.5 g, 33 mmol) and anhydrous K$_2$CO$_3$ (4.5 g, 33 mmol) in dry acetone (50 mL) was heated under reflux for 48 h. The solid precipitate was filtered off and the solvent was evaporated in vacuo. The remaining oil was dissolved in DCM, washed twice with aq KOH (10%), dried over anhydrous Na$_2$SO$_4$ and the solvent was then removed in vacuo and the remaining oil was purified by column chromatography over silica gel using DCM/pet ether (40–60) as an eluent to give 6.8 g (87%) of colorless oil, $R_f=0.3$ [DCM/pet. ether (40–60) 2:1]. LCMS; $m/z=251$ (M+1). IR: 3078, 2947, 2871, 1727, 1600, 1491, 1450, 1304, 1252, 1133, 1088, 1050, 926, 758. ^{1}H NMR (CDCl$_3$): δ 7.80 (dd, 1H, $J=8.0$, 1.6 Hz), 7.46 (dt, 1H, $J=8.8$, 1.7 Hz), 7.01 (m, 2H), 5.97 (m, 1H, CH=), 5.33 (dd, 1H, $J=17.2$, 1.6 Hz, CH$_2$=), 5.22 (dd, 1H, $J=9.4$, 0.9 Hz, CH$_2$=), 4.23 (t, 2H, $J=5.08$ Hz, CH$_2$), 4.15 (d, 2H, $J=5.5$ Hz, CH$_2$), 3.89 (m, 4H, CH$_2$), 3.89 (s, 3H, CH$_3$). Anal. Calcd for $C_{13}H_{16}O_4$ (236.3): C 66.09; H 6.83. Found: C 65.95; H 6.62.

3.1.4. 2-(2-Allyloxyethoxy)benzoic acid. A mixture of methyl 2-(2-allyloxyethoxy)benzoate (1.2 g, 5 mmol) in aq KOH (10%, 10 mL) was heated under reflux for 24 h. The mixture was neutralized with concd HCl and extracted with DCM, washed with water, separated and dried over anhydrous sodium sulfate. The solvent was then removed in vacuo to give 0.8 g (72%) of colorless oil, which was used in the next step without further purification. LCMS; $m/z=223$ (M+1). IR: 3300–2871 (br) 3071, 2928, 2871, 1731, 1603, 1486, 1456, 1387, 1351, 1297, 1240, 1162, 1124, 1038, 926, 756. ^{1}H NMR (CDCl$_3$): δ 9.89 (br, 1H), 8.17 (dd, 1H, $J=7.8$, 1.1 Hz), 7.56 (dt, 1H, $J=7.9$, 1.6 Hz), 7.15 (t, 1H, $J=7.4$ Hz), 7.06 (d, 1H, $J=8.4$ Hz), 5.93 (m, 1H, CH=), 5.32 (dd, 1H, $J=16$, 1.1 Hz, CH$_2$=), 5.24 (d, 1H, $J=10.4$ Hz, CH$_2$=), 4.39 (t, 2H, $J=4.5$ Hz, CH$_2$), 4.09 (d, 2H, $J=5.8$ Hz, CH$_2$), 3.87 (t, 2H, $J=4.5$ Hz, CH$_2$).

3.1.5. 2-(2-Allyloxyethoxy)benzoyl chloride 19. A mixture of 2-(2-allyloxyethoxy)benzoic acid (2.22 g, 10 mmol) and SOCl$_2$ (1.5 mL, 20 mmol) was heated under reflux at 100 °C for 1.5 h. The excess SOCl$_2$ was removed in vacuo to give 2.2 g (92%) of colorless oil, which was used directly in the next step without further purification.

3.1.6. Preparation of the bis-amides 21–23. General procedure. A. To a cold solution (0–5 °C) of each of **20b–e**, ethylenediamine or *o*-phenylenediamine (0.8 mmol) and triethylamine (0.25 g, 2.5 mmol) in DCM (20 mL), was added **19** (0.44 g, 1.7 mmol) in DCM (5 mL) dropwise with stirring. After complete addition the reaction mixture was stirred for 1 h at 0–5 °C and stirring was continued overnight at room temperature. The organic layer was extracted with DCM, washed with concd HCl (5 mL), water twice, $NaHCO_3$ solution and finally water. The organic layer was separated, dried over anhydrous sodium sulfate, the solvent was then removed in vacuo and the remaining material was purified by column chromatography. All compounds were characterized by R_f values using the solvent mixture DCM–pet. ether (40–60)–EtOAc in (6/4/2).

B. To a mixture of each of 1,2-bis(2-hydroxybenzamido)-ethane and 1,2-bis(2-hydroxybenzamido)benzene (0.8 mmol), anhydrous K_2CO_3 (0.4 g, 3 mmol) and 2-allyloxyethyl *p*-toluenesulfonate (0.5 g, 2 mmol) in dry DMF (2 mL) was heated at 100 °C for 10 h. The product was then extracted with DCM, washed several times with water, separated and dried over anhydrous sodium sulfate. The solvent was then removed in vacuo and the remaining product was purified to give the corresponding products **22** and **23**, respectively.

3.1.6.1. Compound 21b. Yield 0.26 g (50%), colorless oil, $R_f=0.8$. LCMS; $m/z=667$ (M+1). IR: 3346, 3072, 2938, 2878, 1660, 1599, 1535, 1481, 1454, 1332, 1291, 1252, 1234, 1162, 1134, 1117, 1091, 1048, 995, 927, 753. ^1H NMR ($CDCl_3$): δ 10.22 (s, 2H, NH), 8.46 (d, 2H, $J=7.6$ Hz), 8.27 (dd, 2H, $J=8.0$, 1.8 Hz), 7.45 (dt, 2H, $J=7.9$, 1.7 Hz), 7.14 (t, 2H, $J=7.5$ Hz), 6.98 (m, 6H), 6.87 (dd, 2H, $J=8.0$, 1.4 Hz), 5.67 (m, 2H, CH=), 5.06 (dd, 2H, $J=17.3$, 1.5 Hz, CH_2=), 4.99 (dd, 2H, $J=10.4$, 1.2 Hz, CH_2=), 4.30 (m, 8H, CH_2), 3.86 (d, 4H, $J=5.6$ Hz), 3.72 (t, 4H, $J=4.8$ Hz), 2.33 (quint, 2H, $J=4.6$ Hz). ^{13}C/DEPT NMR ($CDCl_3$): δ 163.1 (C), 156.4 (C), 147.9 (C), 133.9 (CH), 132.9 (CH), 132.1 (CH), 128.2 (C), 123.9 (CH), 122.7 (C), 121.8 (CH), 121.7 (CH), 121.2 (CH), 117.1 (CH_2), 113.9 (CH), 111.6 (CH), 72.0 (CH_2), 69.2 (CH_2), 67.7 (CH_2), 65.0 (CH_2), 28.7 (CH_2). Anal. Calcd for $C_{39}H_{42}N_2O_8$ (666.8): C 70.25; H 6.35; N 4.20. Found: C 69.89; H 6.33; N 4.09.

3.1.6.2. Compound 21c. Yield 0.33 g (59%), colorless oil, $R_f=0.7$. LCMS; $m/z=697$ (M+1). IR: 3342, 3072, 2932, 2874, 1660, 1599, 1534, 1481, 1454, 1332, 1291, 1235, 1132, 1093, 1048, 929, 753. ^1H NMR ($CDCl_3$): δ 10.24 (s, 2H, NH), 8.53 (m, 2H), 8.22 (dd, 2H, $J=7.6$, 1.6 Hz), 7.40 (dt, 2H, $J=7.8$, 2 Hz), 7.10 (t, 2H, $J=7.6$ Hz), 7.04 (m, 4H), 6.95 (d, 2H, $J=8.4$ Hz), 6.86 (m, 2H), 5.72 (m, 2H, CH=), 5.11 (dd, 2H, $J=17.3$, 1.6 Hz, CH_2=), 5.03 (dd, 2H, $J=10.5$, 1 Hz, CH_2=), 4.31 (t, 4H, $J=4.9$ Hz, OCH_2CH_2), 4.16 (t, 4H, $J=4.7$ Hz, OCH_2CH_2), 3.90 (dd, 4H, $J=5.7$, 1 Hz, OCH_2CH=), 3.84 (t, 4H, $J=4.7$ Hz, OCH_2CH_2), 3.78 (t, 4H, $J=4.9$ Hz, OCH_2CH_2). Anal. Calcd for $C_{40}H_{44}N_2O_9$ (696.8): C 68.95; H 6.36; N 4.02. Found: C 69.15; H 6.18; N 3.98.

3.1.6.3. Compound 21d. Yield 0.26 g (44%), colorless crystals, mp 56–57 °C, $R_f=0.5$. LCMS; $m/z=741$ (M+1). IR: 3340, 3073, 2927, 2874, 1660, 1599, 1536, 1480, 1456, 1333, 1291, 1254, 1235, 1221, 1162, 1134, 1115, 1091, 1048, 997, 928, 754. ^1H NMR ($CDCl_3$): δ 10.24 (s, 2H, NH), 8.54 (dd, 2H, $J=7.4$, 2.3 Hz), 8.24 (dd, 2H, $J=7.8$, 1.4 Hz), 7.43 (dt, 2H, $J=8.4$, 1.5 Hz), 7.12 (t, 2H, $J=7.5$ Hz), 7.05 (m, 6H), 6.92 (dd, 2H, $J=7.7$, 2.3 Hz), 5.76 (m, 2H, CH=), 5.14 (dd, 2H, $J=17.2$, 1.3 Hz, CH_2=), 5.06 (d, 2H, $J=10.3$ Hz, CH_2=), 4.38 (t, 4H, $J=4.9$ Hz, CH_2), 4.19 (t, 4H, $J=4.7$ Hz, OCH_2), 3.95 (d, 4H, $J=5.6$ Hz, OCH_2CH=), 3.83 (t, 4H, $J=4.9$ Hz, OCH_2), 3.75 (t, 4H, $J=4.7$ Hz, OCH_2), 3.52 (s, 4H, CH_2). ^{13}C NMR ($CDCl_3$): δ 163.3, 156.6, 148.0, 134.2, 132.9, 132.3, 128.8, 124.8, 123.9, 121.8, 121.6, 121.5, 117.2, 113.6, 112.3, 72.2, 70.8, 69.4, 69.1, 68.5, 68.0. Anal. Calcd for $C_{42}H_{48}N_2O_{10}$ (740.9): C 68.09; H 6.53; N 3.78. Found: C 67.87; H 6.65; N 3.86.

3.1.6.4. Compound 21e. Yield 0.27 g (46%), colorless oil, $R_f=0.9$. LCMS; $m/z=729$ (M+1). IR: 3343, 3072, 2933, 2874, 1661, 1599, 1535, 1480, 1454, 1332, 1293, 1233, 1162, 1133, 1092, 1046, 100, 922, 752. ^1H NMR ($CDCl_3$): δ 10.40 (s, 2H, NH), 8.54 (d, 2H, $J=8.0$ Hz), 8.30 (dd, 2H, $J=7.8$, 1.2 Hz), 7.53 (m, 2H), 7.45 (dt, 2H, $J=7.7$, 1.4 Hz), 7.39 (m, 2H), 7.13 (t, 2H, $J=7.5$ Hz), 6.98 (m, 4H), 6.87 (m, 4H), 5.63 (m, 2H, CH=), 5.29 (s, 4H, OCH_2Ar), 5.04 (dd, 2H, $J=17.5$, 1 Hz, CH_2=), 4.98 (d, 2H, $J=10.3$ Hz, CH_2=), 3.87 (t, 4H, $J=4.7$ Hz, OCH_2), 3.76 (d, 4H, $J=5.4$ Hz, OCH_2), 3.37 (t, 4H, $J=4.7$ Hz, OCH_2). Anal. Calcd for $C_{44}H_{44}N_2O_8$ (728.9): C 72.51; H 6.09; N 3.84. Found: C 72.56; H 5.99; N 4.10.

3.1.6.5. Compound 22. Yield 0.19 g (51%, A), 0.2 g (52%, B), colorless crystals from EtOAc, mp 95–96 °C. LCMS; $m/z=469$ (M+1). IR: 3354, 3071, 2943, 2861, 1646, 1600, 1539, 1483, 1448, 1296, 1245, 1087, 1051, 1020, 999, 925, 766. ^1H NMR ($CDCl_3$): δ 8.46 (s, 2H, NH), 8.19 (dd, 2H, $J=7.7$, 1.3 Hz), 7.42 (dt, 2H, $J=7.7$, 1.3 Hz), 7.08 (t, 2H, $J=7.5$ Hz), 6.96 (d, 2H, $J=8.2$ Hz), 5.85 (m, 2H, CH=), 5.27 (d, 2H, $J=17.7$ Hz, CH_2=), 5.20 (d, 2H, $J=13.8$ Hz, CH_2=), 4.23 (t, 4H, $J=4.6$ Hz, OCH_2CH_2), 3.97 (d, 4H, $J=5.6$ Hz, OCH_2CH=), 3.73 (t, 4H, $J=4.6$ Hz, OCH_2CH_2), 3.68 (m, 4H, NCH_2). Anal. Calcd for $C_{26}H_{32}N_2O_6$ (468.5): C 66.65; H 6.88; N 5.98. Found: C 66.52; H 6.84; N 6.11.

3.1.6.6. Compound 23. Yield 0.88 g (85%, A), 0.74 g (71%, B), colorless oil, $R_f=0.8$. LCMS; $m/z=517$ (M+1). IR: 3320, 3075, 2934, 2869, 1662, 1598, 1529, 1510, 1480, 1454, 1300, 1231, 1111, 1045, 927, 756. ^1H NMR ($CDCl_3$): δ 10.02 (s, 2H, NH), 8.22 (dd, 2H, $J=7.8$, 1.4 Hz), 7.80 (m, 2H), 7.46 (dt, 2H, $J=8.0$, 1.5 Hz), 7.26 (m, 2H), 7.10 (t, 2H, $J=7.5$ Hz), 7.03 (d, 2H, $J=8.2$ Hz), 5.68 (m, 2H, CH=), 5.11 (dd, 2H, $J=17.3$, 1.4 Hz, CH_2=), 5.05 (d, 2H, $J=10.3$ Hz, CH_2=), 4.22 (t, 4H, $J=4.8$ Hz, OCH_2CH_2), 3.86 (d, 4H, $J=5.6$ Hz, OCH_2CH=), 3.65 (t, 4H, $J=4.8$ Hz, OCH_2CH_2). Anal. Calcd for $C_{30}H_{32}N_2O_6$ (516.6): C 69.75; H 6.24; N 5.42. Found: C 69.50; H 6.28; N 5.70.

3.1.7. 2-(2-Allyloxyethoxy)acetanilide. A. A mixture of *o*-acetamidophenol (1.5 g, 10 mmol), 2-allyloxyethyl *p*-toluenesulfate (2.56 g, 10 mmol) and anhydrous K_2CO_3 (5.5 g) in dry DMF (5 mL) was heated at 100 °C for 4 h. Crushed ice was then added to the mixture, the precipitate was washed three times with cold KOH soln (10%) and then with cold water twice and then extracted with DCM, and dried over anhydrous Na_2SO_4. The solvent was then removed in vacuo to give 1.98 g (86%) of the product as a pale yellow oil, which was used in the next step without further purification. MS: $m/z=235.1$ (M^+, 70%). IR: 3531, 3423, 3309, 2932, 2872, 1684, 1601, 1531, 1487, 1450, 1371, 1327, 1289, 1255, 1213, 1118, 1036, 929, 752.

^{1}H NMR (CDCl$_3$): δ 8.27 (dd, 1H, J=7.6, 1.5 Hz), 8.24 (s, 1H, NH), 6.90 (m, 2H), 6.82 (dd, 1H, J=7.6, 1.5 Hz), 5.83 (m, 1H, =CH), 5.23 (dd, 1H, J=17.1, 1.2 Hz, =CH$_2$), 5.13 (d, 1H, J=10.3 Hz, =CH$_2$), 4.04 (t, 2H, J=4.5 Hz, OCH$_2$CH$_2$), 3.97 (d, 2H, J=5.6 Hz, CH$_2$CH=), 3.66 (t, 2H, J=4.5 Hz, OCH$_2$CH$_2$), 2.07 (s, 3H, CH$_3$).

B. To a solution of KOH (0.56 g, 10 mmol) in methanol (15 mL), was added *o*-acetamidophenol (1.5 g, 10 mmol). The mixture was then stirred at room temperature for 15 min and the solvent was then removed in vacuo. To the remaining potassium salt was added DMF (2 mL) and 2-allyloxyethyl *p*-toluenesulfate (2.56 g, 10 mmol). The reaction mixture was then heated under reflux for 5 min. The mixture was cooled, diluted with water (20 mL) and extracted with DCM, washed with cold water, dried over Na$_2$SO$_4$ and evaporated to give 2.09 g (91%) of the product as a pale yellow oil, which was used in the next step without further purification.

3.1.8. 2-(2-Allyloxyethoxy)aniline hydrochloride 24b. A mixture of 2-(2-allyloxyethoxy)acetanilide (10 mmol) and concd HCl (2 mL) in ethanol (10 mL) was heated under reflux for 2 h. The solvent was then removed in vacuo and the residue obtained was washed with ether and crystallized from ethyl acetate to give 1.5 g (65%) of the product as colorless crystals, mp 124 °C. MS: *m*/*z*=193 [(C$_{11}$H$_{15}$NO$_2$)$^+$, 30%]. IR: 3412, 2873, 2591, 1630, 102, 1461, 1267, 1098, 1026, 931, 755. ^{1}H NMR (CDCl$_3$): δ 10.49 (br s, 3H, NH$_2$HCl), 7.74 (d, 1H, J=7.5 Hz), 7.33 (t, 1H, J=7.5 Hz), 7.00 (m, 2H), 5.84 (m, 1H, CH=), 5.21 (d, 1H, J=17.2 Hz, CH$_2$=), 5.09 (d, 1H, J=10.2 Hz, CH$_2$=), 4.25 (br, 2H, OCH$_2$CH$_2$), 4.03 (d, 2H, J=5 Hz, CH$_2$CH=), 3.92 (br, 2H, OCH$_2$CH$_2$). Anal. Calcd for C$_{11}$H$_{16}$NO$_2$Cl (229.7): C 57.52; H 7.02; N 6.10. Found: C 57.26; H 6.90; N 6.28.

3.1.9. Chloroacetanilides 25a,b. General procedure. To a cold (0–5 °C) solution of each of **24a**,**b** (50 mmol) and triethylamine (10.6 mL, 76 mmol) in DCM (25 mL) was added dropwise with stirring chloroacetyl chloride (3.8 mL, 50 mmol) in DCM (25 mL). The reaction mixture was stirred for 1 h in ice and stirring was continued overnight at room temperature. The resulting solution was neutralized with HCl, washed with Na$_2$CO$_3$ solution and water, extracted with DCM, dried over sodium sulfate and the solvent was removed in vacuo to give the corresponding product **25a**,**b**.

3.1.9.1. *o*-Allyloxychloroacetanilide 25a. Yield 10.8 g (96%), pale yellow oil. MS: *m*/*z*=225 (M$^+$, 20%). IR: 3388, 2872, 1683, 1603, 1537, 1487, 1456, 1411, 1337, 1291, 1255, 1207, 1117, 997, 914, 748. ^{1}H NMR (CDCl$_3$): δ 9.06 (s, 1H, NH), 8.35 (dd, 1H, J=8, 1.2 Hz), 7.07 (dt, 1H, J=8, 1.2 Hz), 6.98 (t, 1H, J=8 Hz), 6.88 (d, 1H, J=8 Hz), 6.06 (m, 1H, CH=), 5.47 (dd, 1H, J=16, 1.1 Hz, CH$_2$=), 5.32 (dd, 1H, J=9.4, 1 Hz, CH$_2$=), 4.58 (d, 2H, J=4.9 Hz, CH$_2$CH=), 4.20 (s, 2H, COCH$_2$). Anal. Calcd for C$_{11}$H$_{12}$NO$_2$Cl (225.7): C 58.55; H 5.36; N 6.21. Found: C 58.32; H 5.37; N 6.40.

3.1.9.2. *N*-[2-(2-Allyloxyethoxy)phenyl]chloroacetamide 25b. Yield 11.3 g (84%), pale yellow oil. MS: *m*/*z*=271 (M+1, 25%), 269 (M$^+$, 78%). IR: 3505, 3383, 3075, 3014, 2938, 2871, 1763, 1689, 1603, 1534, 1487, 1454, 1408, 1338, 1290, 1257, 1210, 1118, 1043, 996, 928, 752. ^{1}H NMR (CDCl$_3$): δ 9.11 (s, 1H, NH), 8.34 (d, 1H, J=7.8 Hz), 7.09 (t, 1H, J=7.8 Hz), 7.01 (t, 1H, J=7.8 Hz), 6.92 (d, 1H, J=7.8 Hz), 5.96 (m, 1H, CH=), 5.32 (d, 1H, J=17.3 Hz, CH$_2$=), 5.23 (d, 1H, J=10.4 Hz, CH$_2$=), 4.23 (t, 2H, J=4.5 Hz, OCH$_2$CH$_2$), 4.20 (s, 2H, COCH$_2$), 4.10 (d, 2H, J=5.6 Hz, CH$_2$CH=), 3.83 (t, 2H, J=4.5 Hz, OCH$_2$CH$_2$). ^{13}C NMR (CDCl$_3$): δ 163.6, 147.5, 133.3, 127.2, 124.5, 121.5, 119.7, 117.5, 112, 72.4, 68.6, 68.4, 43.1. Anal. Calcd for C$_{13}$H$_{16}$NClO$_3$ (269.7): C 57.89; H 5.98; N 5.19. Found: C 57.62; H 5.75; N 5.40.

3.1.10. Synthesis of compounds 30–33. General procedures. A mixture of each of the appropriate chloroacetanilide **25a**,**b** (1 mmol) and the appropriate phenolic derivative **26–29** (1 mmol) and powdered K$_2$CO$_3$ (4 mmol) in anhydrous DMF (1.5 mL) was stirred at 100 °C for 1 h. After cooling crushed ice was added and the mixture was extracted with DCM. The organic layer was separated, washed with water and dried over anhydrous sodium sulfate. The solvent was removed in vacuo and remaining product was crystallized from the proper solvent.

3.1.10.1. Compound 30a. Yield 0.24 g (49%), colorless crystals (EtOH), mp 144 °C. LCMS; *m*/*z*=489 (M+1). IR: 3436, 3383, 3023, 2970, 2868, 1684, 1601, 1539, 1503, 1485, 1456, 1421, 1336, 1292, 1253, 1203, 1131, 1115, 1046, 1017, 928, 751. ^{1}H NMR (CDCl$_3$): δ 9.19 (s, 2H, NH), 8.43 (dd, 2H, J=7.5, 1.9 Hz), 7.03 (m, 8H), 6.59 (dd, 2H, J=7.8, 1.5 Hz), 5.86 (m, 2H, =CH), 5.30 (dd, 2H, J=17.3, 1.1 Hz,=CH$_2$), 5.16 (dd, 2H, J=10.6, 0.9 Hz, =CH$_2$), 4.70 (s, 4H, OCH$_2$CO), 4.15 (d, 4H, J=5.0 Hz, O*CH$_2$*CH=). Anal. Calcd for C$_{28}$H$_{28}$N$_2$O$_6$ (488.6): C 68.84; H 5.78; N 5.73. Found: C 68.62; H 5.88; N 5.76.

3.1.10.2. Compound 30b. Yield 0.5 g (87%), pale yellow. MS: *m*/*z*=576.2 (M$^+$, 100%). IR: 3393, 3070, 2932, 2863, 1690, 1601, 1536, 1503, 1486, 1457, 1256, 1211, 1118, 1048, 928, 750. ^{1}H NMR (CDCl$_3$): δ 9.18 (s, 2H, NH), 8.39 (dd, 2H, J=7.8, 1.6 Hz), 7.01 (m, 8H), 6.67 (d, 2H, J=7.9 Hz), 5.74 (m, 2H, =CH), 5.14 (dd, 2H, J=17.2, 1.4 Hz, =CH$_2$), 5.02 (d, 2H, J=10.4 Hz, =CH$_2$), 4.72 (s, 4H, OCH$_2$CO), 3.91 (d, 4H, J=5.5 Hz, O*CH$_2$*CH=), 3.83 (t, 4H, J=4.7 Hz, OCH$_2$CH$_2$O), 3.63 (t, 4H, J=4.7 Hz, OCH$_2$CH$_2$O). Anal. Calcd for C$_{32}$H$_{36}$N$_2$O$_8$ (576.7): C 66.65; H 6.29; N 4.86. Found: C 64.18; H 5.93; N 5.86.

3.1.10.3. Compound 31a. Yield 0.12 g (18%), colorless crystals (acetone), mp 141–142 °C. LCMS; *m*/*z*=665 (M+1). IR: 3387, 3061, 2918, 2852, 1690, 1599, 1534, 1507, 1483, 1457, 1360, 1326, 1272, 1253, 1210, 1149, 1121, 1066, 992, 924, 813, 751. ^{1}H NMR (CDCl$_3$): δ 8.42 (s, 2H, NH), 8.08 (dd, 2H, J=7.9, 1.4 Hz), 7.97 (d, 2H, J=9.0 Hz), 7.87 (d, 2H, J=8.2 Hz), 7.43 (d, 2H, J=9 Hz), 7.37 (t, 2H, J=7.4 Hz), 7.28 (t, 2H, J=9 Hz), 7.18 (d, 2H, J=8.4 Hz), 6.98 (t, 2H, J=7.8 Hz), 6.89 (d, 2H, J=7.6 Hz), 6.72 (d, 2H, J=7.8 Hz), 5.57 (m, 2H, CH=), 5.07 (dd, 2H, J=17.3, 1.3 Hz, =CH$_2$), 4.95 (dd, 2H, J=10.6, 1.2 Hz, =CH$_2$), 4.59, 4.52 (2d, 4H, J=15.5 Hz, OCH$_2$CO), 4.25 (d, 4H, J=5 Hz, O*CH$_2$*CH=). Anal. Calcd for C$_{42}$H$_{36}$N$_2$O$_6$ (664.8): C 75.89; H 5.46; N 4.21. Found: C 75.67; H 5.62; N 4.22.

3.1.10.4. Compound 31b. Yield 0.7 g (93%), colorless crystals (EtOH), mp 144–145 °C. LCMS; *m*/*z*=753 (M+1). IR: 3391, 3063, 2870, 1693, 1601, 1533, 1484, 1457, 1325, 1254, 1211, 1147, 1114, 1063, 927, 754. ^{1}H NMR ($CDCl_3$): δ 8.47 (s, 2H, NH), 8.07 (dd, 2H, *J*=7.9, 1.2 Hz), 7.97 (d, 2H, *J*=9 Hz), 7.88 (d, 2H, *J*=8.2 Hz), 7.44 (d, 2H, *J*=9 Hz), 7.39 (t, 2H, *J*=7.6 Hz), 7.28 (t, 2H, *J*=7.6 Hz), 7.20 (d, 2H, *J*=8.4 Hz), 7.03 (dt, 2H, *J*=7.8, 1.2 Hz), 6.92 (t, 2H, *J*=7.7 Hz), 6.81 (d, 2H, *J*=8.0 Hz), 5.70 (m, 2H, CH=), 5.09 (dd, 2H, *J*=17.4, 1.6 Hz, CH_2=), 5.04 (d, 2H, *J*=10.5 Hz, CH_2=), 4.55 (s, 4H, OCH_2CO), 3.89 (m, 4H, OCH_2CH_2), 3.67 (d, 4H, *J*=5.5 Hz, $\mathrm{O}\mathit{CH}_2\mathrm{CH}$=), 3.22 (m, 4H, OCH_2CH_2). Anal. Calcd for $C_{46}H_{44}N_2O_8$ (752.9): C 73.39; H 5.89; N 3.72. Found: C 73.07; H 5.96; N 3.91.

3.1.10.5. Compound 32a. Yield 0.2 g (29%), colorless crystals (EtOH), mp 167–168 °C. LCMS; *m*/*z*=679 (M+1). IR: 3397, 3374, 3350, 1698, 1640, 1602, 1542, 1489, 1453, 1299, 1254, 1223, 1116, 1043, 1005, 750. ^{1}H NMR ($CDCl_3$): δ 8.65 (s, 2H, NH), 8.53 (s, 2H, NH), 8.25 (d, 2H, *J*=7.8 Hz), 8.11 (d, 2H, *J*=7.4 Hz), 7.35 (t, 2H, *J*=7.5 Hz), 7.03 (m, 4H), 6.92 (t, 2H, *J*=7.7 Hz), 6.83 (d, 2H, *J*=8.2 Hz), 6.78 (d, 2H, *J*=8.0 Hz), 5.81 (m, 2H, CH=), 5.19 (m, 4H, CH_2=), 4.72 (s, 4H, OCH_2CO), 4.41 (d, 4H, *J*=4.7 Hz, $\mathrm{O}\mathit{CH}_2\mathrm{CH}$=), 3.82 (s, 4H, NCH_2). Anal. Calcd for $C_{38}H_{38}N_4O_8$ (678.8): C 67.24; H 5.64; N 8.25. Found: C 66.98; H 5.71; N 8.46.

3.1.10.6. Compound 32b. Yield 0.65 g (85%), colorless crystals (EtOAc), mp 67–68 °C. LCMS; *m*/*z*=767 (M+1). IR: 3385, 3334, 2929, 2862, 1692, 1642, 1601, 1537, 1485, 1453, 1295, 1255, 1206, 1161, 1117, 1046, 928, 752. ^{1}H NMR ($CDCl_3$): δ 8.86 (s, 4H, NH), 8.14 (d, 2H, *J*=7.8 Hz), 8.03 (dd, 2H, *J*=7.7, 1 Hz), 7.28 (t, 2H, *J*=8.1 Hz), 6.96 (m, 4H), 6.85 (t, 2H, *J*=7.7 Hz), 6.77 (d, 2H, *J*=8.3 Hz), 6.74 (d, 2H, *J*=8.4 Hz), 5.77 (m, 2H, CH=), 5.18 (d, 2H, *J*=17.2 Hz, CH_2=), 5.10 (d, 2H, *J*=10.4 Hz, CH_2=), 4.66 (s, 4H, $\mathrm{O}\mathit{CH}_2\mathrm{CO}$), 3.98 (t, 4H, *J*=4.7 Hz, $\mathrm{OCH_2}\mathit{CH}_2$), 3.90 (d, 4H, *J*=5.5 Hz, $\mathrm{O}\mathit{CH}_2\mathrm{CH}$=), 3.78 (s, 4H, NCH_2), 3.58 (t, 4H, *J*=4.7 Hz, OCH_2CH_2). Anal. Calcd for $C_{42}H_{46}N_4O_{10}$ (766.9): C 65.78; H 6.05; N 7.31. Found: C 66.01; H 5.93; N 7.22.

3.1.10.7. Compound 33a. Yield 0.2 g (44%), colorless crystals (EtOH), mp 128 °C. LCMS; *m*/*z*=459 (M+1). IR: 3396, 3333, 3071, 2873, 1685, 1659, 1601, 1531, 1483, 1457, 1334, 1293, 1253, 1226, 1163, 1132, 1091, 1046, 998, 753. ^{1}H NMR ($CDCl_3$): δ 10.54 (s, 1H, NH), 8.88 (s, 1H, NH), 8.71 (dd, 1H, *J*=7.7, 1.6 Hz), 8.43 (dd, 1H, *J*=7.8, 1.3 Hz), 8.35 (dd, 1H, *J*=7.9, 1.5 Hz), 7.49 (dt, 1H, *J*=8.6, 1.5 Hz), 7.06 (m, 7H), 6.79 (d, 1H, *J*=8.0 Hz), 6.07 (m, 1H, CH=), 5.56 (m, 1H, CH=), 5.37 (d, 1H, *J*=17.3 Hz, CH_2=), 5.27 (d, 1H, *J*=10.3 Hz, CH_2=), 5.04 (dd, 1H, *J*=17.2, 0.8 Hz, CH_2=), 4.94 (dd, 1H, *J*=10.5, 0.6 Hz, CH_2=), 4.77 (s, 2H, OCH_2CO), 4.61 (d, 2H, *J*=5.6 Hz, OCH_2CH=), 4.20 (d, 2H, *J*=5.3 Hz, OCH_2CH=). Anal. Calcd for $C_{27}H_{26}N_2O_5$ (458.5): C 70.73; H 5.72; N 6.11. Found: C 70.71; H 5.82; N 6.21.

3.1.10.8. Compound 33b. Yield 0.2 g (40%), colorless crystals (EtOH), mp 126 °C. LCMS; *m*/*z*=503 (M+1). IR: 3398, 3353, 3015, 2922, 2852, 1665, 1602, 1539, 1482, 1458, 1332, 1294, 1254, 1216, 1117, 1094, 1046, 996, 930, 755. ^{1}H NMR ($CDCl_3$): δ 10.54 (s, 1H, NH), 8.91 (s, 1H, NH), 8.72 (dd, 1H, *J*=8.8, 1.2 Hz), 8.43 (d, 1H, *J*=7.6 Hz), 8.34 (d, 1H, *J*=8.0 Hz), 7.50 (t, 1H, *J*=8.0 Hz), 7.09 (m, 5H), 6.95 (d, 2H, *J*=8.5 Hz), 6.84 (d, 1H, *J*=8.0 Hz), 6.06 (m, 1H, CH=), 5.63 (m, 1H, CH=), 5.36 (d, 1H, *J*=17.2 Hz, CH_2=), 5.27 (d, 1H, *J*=10.4 Hz, CH_2=), 5.06 (d, 1H, *J*=17.2 Hz, CH_2=), 4.98 (d, 1H, *J*=10.4 Hz, CH_2=), 4.75 (s, 2H, OCH_2CO), 4.60 (d, 2H, *J*=5.5 Hz, $\mathrm{O}\mathit{CH}_2\mathrm{CH}$=), 3.82 (t, 2H, *J*=4.9 Hz, OCH_2CH_2), 3.71 (d, 2H, *J*=5.5 Hz, $\mathrm{O}\mathit{CH}_2\mathrm{CH}$=), 3.29 (t, 2H, *J*=4.9 Hz, OCH_2CH_2). Anal. Calcd for $C_{29}H_{30}N_2O_6$ (502.6): C 69.31; H 6.02; N 5.57. Found: C 69.05; H 5.77; N 5.78.

3.1.11. Ring closing metathesis of 15a–e, 17b,d, 21b–e, 22, 23, 30a,b, 31a,b, 32a,b and 33a,b. General procedure. A solution of each of the substrates **15a**–**e**, **17b**,**d**, **21b**–**e**, **22**, **23**, **30a**,**b**, **31a**,**b**, **32a**,**b** and **33a**,**b** (0.2 mmol) in DCM (25 mL) and Grubbs' catalyst (4–12 mg, ca. 2.5–7.5 mol% of the substrate) was heated under reflux for 2–24 h (Tables 1–3). The reaction mixture was then mixed with silica gel (100–200 mm, 0.5 g), stirred for 30 min, filtered and the silica was extracted twice with DCM (50 mL). After removing the solvent from the DCM extract, the remaining products were analyzed by ^{1}H NMR (Tables 1–3). All macrocycles were characterized by their R_f. All *E* and *Z* isomers were identified by their ^{1}H and ^{13}C NMR signals in their mixture.

3.1.11.1. Compound 1a. (*E* and *Z*): Yield 162 mg (97%), colorless crystals (EtOH), mp 243–244 °C, R_f=0.6 [EtOAc/pet. ether (40–60) 2:1]. LCMS; *m*/*z*=835 (M+1). IR: 3394, 3356, 3068, 2929, 1688, 1663, 1600, 1532, 1482, 1455, 1330, 1294, 1250, 1222, 1119, 1092, 1046, 1008, 955, 748. ^{1}H NMR ($CDCl_3$) (*E* isomer): δ 9.97 (s, 2H, NH), 8.78 (s, 2H, NH), 8.53 (dd, 2H, *J*=8.0, 1.3 Hz), 8.11 (dd, 2H, *J*=7.7, 1.5 Hz), 7.80 (dd, 2H, *J*=7.9, 1.2 Hz), 7.41 (dt, 2H, *J*=8.0, 1.6 Hz), 7.07 (m, 4H), 6.92 (dt, 2H, *J*=7.4, 1.3 Hz), 6.79 (m, 4H), 6.70 (d, 2H, *J*=7.9 Hz), 6.43 (d, 2H, *J*=7.8 Hz), 6.33 (t, 2H, *J*=7.8 Hz), 6.27 (s, 2H, CH=), 4.73 (s, 4H, OCH_2CO), 4.53 (s, 4H, CH_2CH=), 3.52 (s, 4H, OCH_2CH_2). ^{13}C NMR ($CDCl_3$) (*E* isomer): δ 165.7, 162.6, 156.0, 146.5, 146.2, 133.3, 132.8, 128.6, 128, 125.2, 124.8, 123.9, 122.8, 121.9, 121.5, 121.1, 120.9, 118.3, 112.2, 111.4, 109.6, 69.6, 69.1, 66.6. ^{1}H NMR ($CDCl_3$) (*Z* isomer): δ 10.19 (s, 2H, NH), 8.74 (s, 2H, NH), 8.57 (d, 2H, *J*=8.3 Hz), 8.18 (d, 2H, *J*=7.8 Hz), 7.98 (d, 2H, *J*=7.8 Hz), 7.41 (t, 2H, *J*=8.0 Hz), 7.08 (m, 4H), 6.98 (t, 2H, *J*=7.8 Hz), 6.82 (m, 4H), 6.64 (d, 2H, *J*=8.8 Hz), 6.52 (d, 2H, *J*=7.5 Hz), 6.33 (t, 2H, *J*=7.8 Hz), 5.89 (t, 2H, *J*=3.6 Hz, CH=), 4.75 (s, 4H, $\mathrm{O}\mathit{CH}_2\mathrm{CO}$), 4.61 (d, 4H, *J*=3.6 Hz, CH_2CH=), 3.80 (s, 4H, OCH_2CH_2). ^{13}C NMR ($CDCl_3$) (*Z* isomer): δ 165.7, 165.69, 155.7, 146.7, 146.6, 133.3, 132.8, 129.6, 127.8, 125.9, 124.9, 123.6, 122.8, 121.7, 121.6, 121.1, 120.9, 119.3, 113.2, 112.1, 110.9, 70.1, 67.3, 64.9. Anal. Calcd for $C_{48}H_{42}N_4O_{10}$ (834.9): C 69.06; H 5.07; N 6.71. Found: C 69.01; H 5.03; N 6.45.

3.1.11.2. Compound 1b. (*E* and *Z*): Yield 154 mg (91%), purified using column chromatography with eluent DCM–pet. ether (40–60)–EtOAc (6/4/3), colorless crystals [DCM/pet. ether (40–60)] mp 176–177 °C, R_f=0.6 [EtOAc/pet. ether (40–60) 2:1]. LCMS; *m*/*z*=849 (M+1). IR: 3399, 3353, 3069, 3034, 2931, 1686, 1664, 1601, 1534, 1483, 1455, 1330, 1293, 1252, 1214, 1116, 1092, 1048, 1004, 751. ^{1}H NMR (CDCl$_3$) (*E* isomer): δ 10.14 (s, 2H, NH), 8.85 (s, 2H, NH), 8.71 (d, 2H, $J=8.0$ Hz), 8.24 (m, 4H), 7.42 (t, 2H, $J=7.7$ Hz), 7.17 (m, 4H), 7.10 (t, 2H, $J=7.8$ Hz), 6.99 (d, 2H, $J=8.2$ Hz), 6.81 (d, 2H, $J=8.3$ Hz), 6.72 (m, 4H), 6.47 (m, 2H), 6.01 (s, 2H, CH=), 4.72 (s, 4H, OCH$_2$CO), 4.48 (s, 4H, OCH_2CH=), 3.82 (t, 4H, $J=5.5$ Hz, OCH$_2$), 1.78 (quint, 2H, $J=5.5$ Hz, OCH$_2$CH$_2$). ^{1}H NMR (CDCl$_3$) (*Z* isomer): δ 10.09 (s, 2H, NH), 8.83 (s, 2H, NH), 8.77 (d, 2H, $J=9.3$ Hz), 8.29 (m, 2H), 7.44 (t, 2H, $J=8.6$ Hz), 7.25 (m, 4H), 7.17 (d, 2H, $J=8.8$ Hz), 7.05 (t, 2H, $J=8.3$ Hz), 6.81 (d, 2H, $J=4$ Hz), 6.72 (m, 4H), 6.61 (t, 2H, $J=8.8$ Hz), 6.05 (t, 2H, $J=7.8$ Hz), 5.55 (br, 2H, CH=), 4.65 (s, 4H, OCH$_2$CO), 4.52 (s, 4H, OCH_2CH=), 3.91 (t, 4H, $J=6.1$ Hz, OCH$_2$), 1.78 (quint, 2H, $J=5.5$ Hz, OCH$_2$CH$_2$). Anal. Calcd for $C_{49}H_{44}N_4O_{10}$ (848.9): C 69.33; H 5.22; N 6.60. Found: C 69.11; H 5.54; N 6.31.

3.1.11.3. Compound 1c. (*E* and *Z*): Yield 91 mg (52%), colorless crystals [DCM/pet. ether (40–60)], mp 237 °C, $R_f=0.6$ [EtOAc/pet. ether (40–60) 2:1]. LCMS; $m/z=879$ (M+1). IR: 3406, 3067, 2926, 1694, 1659, 1601, 1534, 1482, 1454, 1333, 1293, 1253, 1219, 1130, 1048, 752. ^{1}H NMR (CDCl$_3$) (*E* isomer): δ 10.33 (s, 2H, NH), 8.80 (s, 2H, NH), 8.71 (d, 2H, $J=7.2$ Hz), 8.23 (dd, 2H, $J=8.0$, 1.6 Hz), 8.19 (m, 2H), 7.29 (dt, 2H, $J=8.0$, 1.5 Hz), 7.19 (t, 2H, $J=7.6$ Hz), 7.07 (t, 2H, $J=7.6$ Hz), 7.01 (dt, 2H, $J=7.8$, 1.3 Hz), 6.90 (d, 2H, $J=7.8$ Hz), 6.74 (m, 6H), 6.46 (m, 2H), 6.22 (t, 2H, $J=3.8$ Hz, =CH), 4.72 (s, 4H, OCH$_2$CO), 4.60 (d, 4H, $J=3.8$ Hz, OCH_2CH=), 3.74 (t, 4H, $J=4$ Hz, OCH$_2$CH$_2$O), 3.40 (t, 4H, $J=4$ Hz, OCH$_2$CH$_2$O). ^{13}C NMR (CDCl$_3$) (*E* isomer): δ 166, 163.1, 156.3, 147.1, 146.6, 133.4, 132.3, 129.5, 129.4, 126.4, 124.6, 124, 124, 122, 122, 121.2, 119.5, 114, 113.1, 111.6, 70.5, 70.1, 70, 68.4. ^{1}H NMR (CDCl$_3$) (*Z* isomer): δ 10.26 (s, 2H, NH), 8.88 (s, 2H, NH), 8.71 (d, 2H, $J=7.2$ Hz), 8.23 (dd, 2H, $J=8.0$, 1.6 Hz), 8.19 (m, 2H), 7.39 (m, 2H), 7.20 (m, 6H), 7.05 (m, 2H), 6.74 (m, 6H), 6.35 (m, 2H), 5.67 (t, 2H, $J=3.5$ Hz, CH=), 4.64 (d, 4H, $J=3.5$ Hz, OCH_2CH=), 4.61 (s, 4H, OCH$_2$CO), 3.74 (t, 4H, $J=4$ Hz, OCH$_2$CH$_2$O), 3.40 (t, 4H, $J=4$ Hz, OCH$_2$CH$_2$O). Anal. Calcd for $C_{50}H_{46}N_4O_{11}$ (878.9): C 68.33; H 5.28; N 6.37. Found: C 67.97; H 5.06; N 6.19.

3.1.11.4. Compound 1d. (*E* and *Z*): Yield 144 mg (78%), colorless crystals [DCM/pet. ether (40–60)], mp 201–202 °C, $R_f=0.4$ [EtOAc/pet. ether (40–60) 2:1]. LCMS; $m/z=923$ (M+1). IR: 3392, 3342, 3068, 2936, 2875, 1686, 1659, 1600, 1532, 1481, 1456, 1330, 1293, 1254, 1220, 1163, 1134, 1118, 1092, 1048, 750. ^{1}H NMR (CDCl$_3$) (*E* isomer): δ 10.35 (s, 2H, NH), 8.81 (s, 2H, NH), 8.71 (dd, 2H, $J=8.1$, 1.3 Hz), 8.38 (dd, 2H, $J=7.9$, 1.4 Hz), 8.23 (dd, 2H, $J=7.7$, 1.6 Hz), 7.00 (m, 14H), 6.86 (d, 2H, $J=8.1$ Hz), 6.68 (d, 2H, $J=7.6$ Hz), 6.43 (m, 2H, =CH), 4.82 (s, 4H, OCH$_2$CO), 4.67 (m, 4H, OCH_2CH=), 3.84 (t, 4H, $J=3.9$ Hz, OCH$_2$CH$_2$), 3.45 (t, 4H, $J=3.9$ Hz, OCH$_2$CH$_2$), 3.32 (s, 4H, OCH$_2$CH$_2$O). ^{13}C NMR (CDCl$_3$) (*E* isomer): δ 166.3, 163.2, 156.1, 147.0, 146.8, 133.6, 132.6, 129.7, 128.9, 126.7, 124.6, 123.7, 123.0, 121.7, 121.4, 121.1, 120.0, 112.2, 112.1, 112.0, 111.9, 70.3, 69.5, 69.4, 69.3, 68.3. ^{1}H NMR (CDCl$_3$) (*Z* isomer): δ 10.40 (s, 2H, NH), 8.75 (s, 2H, NH), 8.71 (dd, 2H, $J=8.1$, 1.3 Hz), 8.32 (d, 2H, $J=6$ Hz), 8.25 (d, 2H, $J=7.7$ Hz), 7.21 (t, 2H, $J=7.3$ Hz), 7.00 (m, 14H), 6.73 (d, 2H, $J=7$ Hz), 6.09 (t, 2H, $J=3.7$ Hz, =CH), 4.82 (d, 4H, $J=3.7$ Hz, OCH_2CH=), 4.75 (s, 4H, OCH_2CO), 3.88 (t, 4H, $J=4$ Hz, OCH$_2$$CH_2$), 3.43 (t, 4H, $J=4$ Hz, OCH$_2$$CH_2$), 3.23 (s, 4H, OCH$_2CH_2$O). ^{13}C NMR (CDCl$_3$) (*Z* isomer): δ 166.1, 163.2, 156.1, 147.0, 146.8, 133.2, 132.4, 129.2, 128.7, 126.8, 123.9, 123.2, 121.9, 121.8, 121.6, 121.2, 120.3, 112.6, 112.5, 112.0, 70.4, 69.1, 65.0. Anal. Calcd for $C_{52}H_{50}N_4O_{12}$ (923): C 67.67; H 5.46; N 6.07. Found: C 67.69; H 5.49; N 6.12.

3.1.11.5. Compound 1e. (*E*): Yield 160 mg (88%), colorless crystals (EtOH), mp 229–230 °C, $R_f=0.8$ [EtOAc/pet. ether (40–60) 2:1]. LCMS; $m/z=911$ (M+1). IR: 3401, 3347, 3070, 3023, 2934, 1695, 1651, 1599, 1536, 1482, 1455, 1332, 1295, 1250, 1220, 1163, 1138, 1116, 1092, 1047, 1008, 751. ^{1}H NMR (DMSO-d_6): δ 10.31 (s, 2H, NH), 9.50 (s, 2H, NH), 8.39 (d, 2H, $J=7.7$ Hz), 8.02 (d, 2H, $J=7.4$ Hz), 7.92 (d, 2H, $J=7.4$ Hz), 7.30 (m, 2H), 7.26 (t, 2H, $J=7.3$ Hz), 7.08 (m, 14H), 6.93 (d, 4H, $J=7.3$ Hz), 6.02 (br, 2H, =CH), 5.15 (s, 4H, OCH$_2$Ar), 4.83 (s, 4H, OCH$_2$CO), 4.59 (s, 4H, OCH_2CH=). ^{13}C NMR (DMSO-d_6 $\delta=39.5$): δ 166.5, 162.4, 155.9, 148.8, 147.2, 134.4, 133.3, 131.5, 129.1, 128.1, 127.9, 127.8, 126.4, 125.4, 124.1, 122.7, 121.6, 121.5, 121.2, 120.8, 120.7, 113.3, 112.9, 112.3, 68.7, 67.9, 67.7. ^{1}H NMR (DMSO-d_6): δ 10.41 (s, 2H, NH), 9.66 (s, 2H, NH), 8.50 (d, 2H, $J=7.7$ Hz), 8.02 (d, 2H, $J=7.4$ Hz), 7.92 (d, 2H, $J=7.4$ Hz), 7.30 (m, 2H), 7.26 (t, 2H, $J=7.3$ Hz), 7.08 (m, 14H), 6.93 (d, 4H, $J=7.3$ Hz), 5.57 (br, 2H, =CH), 5.15 (s, 4H, OCH$_2$Ar), 4.83 (s, 4H, OCH$_2$CO), 4.82 (br, 4H, OCH_2CH=). Anal. Calcd for $C_{54}H_{46}N_4O_{10}$ (910.9): C 71.20; H 5.09; N 6.15. Found: C 70.45; H 5.12; N 6.33.

3.1.11.6. Compound 2b. (*E* and *Z*): Yield 101 mg (70%), colorless crystals mp 217–218 °C, purified using column chromatography using DCM/pet. ether (40–60)/EtOAc, $R_f=0.4$ [EtOAc/pet. ether (40–60) 2:1]. LCMS; $m/z=725$ (M+1). IR: 3396, 3379, 3067, 2960, 2860, 1691, 1602, 1529, 1487, 1456, 1331, 1291, 1253, 1200, 1093, 1047, 750. ^{1}H NMR (CDCl$_3$) (*E* isomer): δ 8.86 (s, 2H, NH), 8.79 (s, 2H, NH), 8.51 (dd, 2H, $J=7.2$, 1.4 Hz), 8.40 (dd, 2H, $J=7$, 2 Hz), 7.07 (m, 10H), 6.66 (d, 2H, $J=8.5$ Hz), 5.68 (s, 2H, CH=), 4.67 (s, 4H, OCH$_2$CO), 3.98 (t, 4H, $J=5.6$ Hz, OCH_2CH$_2$), 3.78 (s, 4H, OCH$_2$CO), 3.65 (s, 4H, OCH_2CH=), 2.00 (quint, 2H, $J=5.6$ Hz, OCH$_2$$CH_2$). ^{13}C NMR (CDCl$_3$) (*E* isomer): δ 167.3, 165.6, 147.0, 146.0, 128.4, 128.2, 126.4, 124.9, 124.4, 123.9, 121.5, 120.2, 120.0, 114.2, 110.8, 70.9, 70.4, 69.9, 64.1, 29.0. ^{1}H NMR (CDCl$_3$) (*Z* isomer): δ 8.86 (s, 2H, NH), 8.72 (s, 2H, NH), 8.40 (dd, 2H, $J=7$, 2 Hz), 8.32 (d, 2H, $J=7.38$ Hz), 7.07 (m, 10H), 6.69 (d, 2H, $J=8.1$ Hz), 5.44 (t, 2H, $J=3.8$ Hz, CH=), 4.72 (s, 4H, OCH$_2$CO), 3.98 (m, 8H, OCH_2CH$_2$, OCH_2CH=), 3.89 (s, 4H, OCH$_2$CO), 2.00 (quint, 2H, $J=5.6$ Hz, OCH$_2$$CH_2$). ^{13}C NMR (CDCl$_3$) (*Z* isomer): δ 167.1, 165.6, 147.4, 146.1, 128.3, 127.6, 126.2, 125.0, 124.6, 123.5, 121.0, 120.7, 120.5, 113.5, 110.7, 69.7, 69.6, 66.7, 64.3, 28.9. Anal. Calcd for $C_{39}H_{40}N_4O_{10}$ (724.8): C 64.63; H 5.56; N 7.73. Found: C 64.48; H 5.74; N 7.78.

3.1.11.7. Compound 2d. (*E* and *Z*): Yield 96 mg (60%), colorless crystals mp 198–199 °C, purified using column chromatography using DCM/pet. ether (40–60)/EtOAc, $R_f=0.1$ [EtOAc/pet. ether (40–60) 2:1]. LCMS; $m/z=799$

(M+1). IR: 3386, 2920, 1687, 1601, 1533, 1454, 1254, 1202, 1117, 1052, 955, 750. ^{1}H NMR ($CDCl_3$) (*E* isomer): δ 9.04 (s, 2H, NH), 8.77 (s, 2H, NH), 8.40 (m, 2H), 8.35 (d, 2H, $J=7.6$ Hz), 7.02 (m, 10H), 6.86 (d, 2H, $J=8.2$ Hz), 5.87 (s, 2H, CH=), 4.77 (s, 4H, OCH_2CO), 4.05 (m, 12H, OCH_2CH_2, $OCH_2CH=$, OCH_2CO), 3.63 (t, 4H, $J=4.3$ Hz, OCH_2CH_2), 3.50 (s, 4H, OCH_2CH_2O). ^{1}H NMR ($CDCl_3$) (*Z* isomer): δ 9.05 (s, 2H, NH), 8.96 (s, 2H, NH), 8.40 (m, 2H), 8.35 (d, 2H, $J=7.6$ Hz), 7.02 (m, 10H), 6.86 (d, 2H, $J=8.2$ Hz), 5.70 (t, 2H, $J=3.9$ Hz, CH=), 4.76 (s, 4H, OCH_2CO), 4.19 (d, 4H, $J=3.9$ Hz, $OCH_2CH=$), 4.05 (m, 8H, OCH_2CH_2, OCH_2CO), 3.59 (t, 4H, $J=4.3$ Hz, OCH_2CH_2), 3.49 (s, 4H, OCH_2CH_2O). Anal. Calcd for $C_{42}H_{46}N_4O_{12}$(798.9): C 63.15; H 5.80; N 7.01. Found: C 63.32; H 5.85; N 7.60.

3.1.11.8. Compound 3b. (*E* and *Z*): Yield 0.127 g (99%), colorless crystals (EtOH), mp 79–80 °C, purified using column chromatography with eluent DCM/pet. ether (40–60)/EtOAc, $R_f=0.7$ [DCM/pet. ether (40–60)/EtOAc 6:4:2]. LCMS; $m/z=639$ (M+1). IR: 3346, 2928, 2862, 1659, 1598, 1531, 1480, 1453, 1291, 1233, 1047, 752. ^{1}H NMR ($CDCl_3$) (*E* isomer): δ 10.11 (s, 2H, NH), 8.47 (d, 2H, $J=7.8$ Hz), 8.30 (dd, 2H, $J=7.8$, 1.4 Hz), 7.51 (dt, 2H, $J=7.6$, 1.6 Hz), 7.18 (t, 2H, $J=7.6$ Hz), 6.99 (m, 6H), 6.88 (d, 2H, $J=8.0$ Hz), 5.58 (s, 2H, CH=), 4.34 (m, 8H, OCH_2CH_2), 3.87 (br, 4H, $O\mathit{CH}_2CH=$), 3.77 (m, 4H, OCH_2), 2.33 (quint, 2H, $J=6$ Hz, $OCH_2\mathit{CH}_2CH_2O$). ^{13}C NMR ($CDCl_3$) (*E* isomer): δ 163.4, 156.5, 148.2, 132.9, 132.6, 129.2, 128.3, 124.1, 123.2, 122.2, 122.0, 121.2, 113.8, 111.7, 71.1, 69.3, 67.8, 65.4, 28.8. ^{1}H NMR ($CDCl_3$) (*Z* isomer): δ 10.09 (s, 2H, NH), 8.51 (d, 2H, $J=7.9$ Hz), 8.30 (dd, 2H, $J=7.8$, 1.4 Hz), 7.49 (t, 2H, $J=7.5$ Hz), 7.18 (t, 2H, $J=7.6$ Hz), 6.99 (m, 6H), 6.89 (d, 2H, $J=8.0$ Hz), 5.56 (t, 2H, $J=4.2$ Hz, CH=), 4.34 (m, 4H, OCH_2), 4.27 (t, 4H, $J=4.5$ Hz, OCH_2), 4.04 (d, 4H, $J=4.2$ Hz, $O\mathit{CH}_2CH=$), 3.77 (m, 4H, OCH_2), 2.41 (quint, 2H, $J=6.4$ Hz, OCH_2). ^{13}C NMR ($CDCl_3$) (*Z* isomer): δ 163.4, 156.5, 148.0, 133.0, 132.5, 129.7, 128.2, 124.2, 122.9, 122.1, 121.9, 121.4, 113.6, 111.6, 69.2, 67.7, 66.3, 65.4, 29.1. Anal. Calcd for $C_{37}H_{38}N_2O_8$ (638.7): C 69.58; H 6.00; N 4.39. Found: C 69.56; H 6.13; N 4.25.

3.1.11.9. Compound 3c. (*E* and *Z*): Yield 110 mg (85%), colorless oil, purified using column chromatography with eluent DCM/pet. ether (40–60)/EtOAc, $R_f=0.5$[DCM/pet. ether (40–60)/EtOAc 6:4:2]. LCMS; $m/z=669$ (M+1). IR: 3343, 2926, 2872, 1658, 1598, 1532, 1480, 1454, 1221, 1130, 1092, 1047, 771. ^{1}H NMR ($CDCl_3$) (*E* isomer): δ 10.21 (s, 2H, NH), 8.55 (m, 2H), 8.29 (m, 2H), 7.51 (dt, 2H, $J=8.2$, 1.1 Hz), 7.17 (t, 2H, $J=7.5$ Hz), 7.07 (m, 6H), 6.91 (m, 2H), 5.70 (br, 2H, CH=), 4.41 (t, 4H, $J=4.9$ Hz, OCH_2CH_2), 4.27 (t, 4H, $J=4.9$ Hz, OCH_2CH_2), 3.96 (br, 4H, $O\mathit{CH}_2CH=$), 3.91 (t, 4H, $J=4.9$ Hz, OCH_2CH_2), 3.86 (t, 4H, $J=4.9$ Hz, OCH_2CH_2). ^{13}C NMR ($CDCl_3$) (*E* isomer): δ 163.4, 156.6, 148.1, 132.9, 132.5, 129.3, 128.6, 124.0, 123.1, 122.0, 121.8, 121.4, 113.8, 112.2, 71.1, 69.5, 69.3, 68.2, 67.8. ^{1}H NMR ($CDCl_3$) (*Z* isomer): δ 10.26 (s, 2H, NH), 8.55 (m, 2H), 8.29 (m, 2H), 7.51 (dt, 2H, $J=8.2$, 1.1 Hz), 7.17 (t, 2H, $J=7.5$ Hz), 7.07 (m, 6H), 6.91 (m, 2H), 5.55 (t, 2H, $J=4$ Hz, CH=), 4.38 (t, 4H, $J=4.9$ Hz, OCH_2CH_2), 4.27 (t, 4H, $J=4.9$ Hz, OCH_2CH_2), 4.08 (d, 4H, $J=4$ Hz, $O\mathit{CH}_2CH=$), 3.91 (t, 4H, $J=4.9$ Hz, OCH_2CH_2), 3.86 (t, 4H, $J=4.9$ Hz, OCH_2CH_2). ^{13}C NMR ($CDCl_3$) (*Z* isomer): δ 163.3, 156.7, 147.9, 133.0, 132.5, 129.4, 128.7, 123.9, 123.0, 122.0, 121.8, 121.6, 113.8, 112.4, 69.7, 69.2, 68.4, 68.0, 66.7. Anal. Calcd for $C_{38}H_{40}N_2O_9$ (668.7): C 68.25; H 6.03; N 4.19. Found: C 68.56; H 5.92; N 4.31.

3.1.11.10. Compound 3d. (*E* and *Z*): Yield 140 mg (99%), colorless oil, purified using column chromatography with eluent DCM/pet. ether (40–60)/EtOAc, $R_f=0.4$ [DCM/pet. ether (40–60)/EtOAc 6:4:2]. LCMS; $m/z=713$ (M+1). IR: 3340, 2924, 2872, 1659, 1598, 1533, 1480, 1454, 1292, 1234, 1119, 1048, 753. ^{1}H NMR ($CDCl_3$) (*E* isomer): δ 10.27 (s, 2H, NH), 8.58 (d, 2H, $J=7.2$ Hz), 8.28 (dd, 2H, $J=8.0$, 1.6 Hz), 7.48 (t, 2H, $J=7.8$ Hz), 7.15 (t, 2H, $J=7.6$ Hz), 7.10–7.02 (m, 6H), 6.95 (m, 2H), 5.74 (s, 2H, CH=), 4.42 (t, 4H, $J=5.3$ Hz, OCH_2), 4.25 (t, 4H, $J=5.0$ Hz, OCH_2), 3.99 (br, 4H, $O\mathit{CH}_2CH=$), 3.87 (m, 8H, OCH_2), 3.67 (s, 4H, OCH_2). ^{13}C NMR ($CDCl_3$) (*E* isomer): δ 163.3, 156.6, 148.0, 132.9, 133.2, 129.2, 128.7, 123.8, 123.1, 121.9, 121.6, 121.5, 113.7, 112.1, 71.0, 70.6, 69.6, 69.0, 68.3, 67.9. ^{1}H NMR ($CDCl_3$) (*Z* isomer): δ 10.31 (s, 2H, NH), 8.58 (d, 2H, $J=7.2$ Hz), 8.28 (dd, 2H, $J=8.0$, 1.6 Hz), 7.48 (t, 2H, *C*), 7.15 (t, 2H, $J=7.6$ Hz), 7.10–7.02 (m, 6H), 6.95 (m, 2H), 5.55 (t, 2H, $J=4.0$ Hz, CH=), 4.41 (t, 4H, $J=5.3$ Hz, OCH_2), 4.26 (t, 4H, $J=4.8$ Hz, OCH_2), 4.08 (d, 4H, $J=4.0$ Hz, $O\mathit{CH}_2CH=$), 3.87 (m, 8H, OCH_2), 3.67 (s, 4H, OCH_2). ^{13}C NMR ($CDCl_3$) (*Z* isomer): δ 163.3, 156.6, 147.9, 133.0, 133.2, 129.3, 128.7, 123.8, 123.0, 121.9, 121.7, 121.6, 113.7, 112.1, 70.6, 69.7, 69.1, 68.4, 68.1, 66.8. Anal. Calcd for $C_{40}H_{44}N_2O_{10}$ (712.8): C 67.40; H 6.22; N 3.93. Found: C 67.55; H 6.49; N 3.98.

3.1.11.11. Compound 3e. (*E* and *Z*): Yield 139 mg (98%), colorless crystals (EtOH), mp 114–115 °C, purified using column chromatography with eluent DCM/pet. ether (40–60)/EtOAc, $R_f=0.7$ [DCM/pet. ether (40–60)/EtOAc 6:4:2]. LCMS; $m/z=701$ (M+1). IR: 3350, 2934, 2872, 1659, 1599, 1534, 1454, 1293, 1230, 1121, 1023, 751. ^{1}H NMR ($CDCl_3$) (*E* isomer): δ 10.51 (s, 2H, NH), 8.59 (d, 2H, $J=8.0$ Hz), 8.36 (d, 2H, $J=7.6$ Hz), 7.55 (m, 4H), 7.32 (m, 2H), 7.20 (t, 2H, $J=7.5$ Hz), 7.04 (d, 2H, $J=8.3$ Hz), 6.95 (t, 2H, $J=7.8$ Hz), 6.90 (d, 2H, $J=8.3$ Hz), 6.72 (t, 2H, $J=7.8$ Hz), 5.57 (s, 2H, CH=), 5.48 (s, 4H, OCH_2Ar), 4.08 (m, 4H, OCH_2), 3.82 (br, 4H, $O\mathit{CH}_2CH=$), 3.59 (m, 4H, OCH_2). ^{1}H NMR ($CDCl_3$) (*Z* isomer): δ 10.47 (s, 2H, NH), 8.59 (d, 2H, $J=8.0$ Hz), 8.36 (d, 2H, $J=7.6$ Hz), 7.55 (m, 4H), 7.36 (m, 2H), 7.20 (t, 2H, $J=7.5$ Hz), 7.00 (d, 2H, $J=8.2$ Hz), 6.95 (t, 2H, $J=7.8$ Hz), 6.90 (d, 2H, $J=8.3$ Hz), 6.84 (t, 2H, $J=7.5$ Hz), 5.48 (t, 2H, $J=4.0$ Hz, CH=), 5.43 (s, 4H, OCH_2Ar), 4.08 (m, 4H, OCH_2), 3.89 (d, 4H, $J=4.0$ Hz, $O\mathit{CH}_2CH=$), 3.59 (m, 4H, OCH_2). Anal. Calcd for $C_{42}H_{40}N_2O_8$ (700.8): C 71.99; H 5.75; N 4.00. Found: C 71.86; H 5.65; N 3.98.

3.1.11.12. Compound 4. (*E* and *Z*): Yield 84 mg (96%), colorless crystals (EtOH), mp 203–204 °C. LCMS; $m/z=441$ (M+1). IR: 3367, 3073, 3018, 2919, 2850, 1650, 1601, 1533, 1482, 1450, 1298, 1241, 1117, 910, 738. ^{1}H NMR ($CDCl_3$) (*E* isomer): δ 8.37 (br, 2H, NH), 8.25 (dd, 2H, $J=7.6$, 1.3 Hz), 7.44 (m, 2H), 7.12 (t, 2H, $J=7.3$ Hz), 6.97 (d, 2H, $J=8.2$ Hz), 5.95 (br, 2H, CH=), 4.30 (m, 4H, OCH_2), 4.10 (br, 4H, $OCH_2CH=$), 3.88 (m, 4H, OCH_2), 3.67

(m, 4H, NCH$_2$). ^{13}C NMR (CDCl$_3$) (*E* isomer): δ 165.2, 156.5, 132.5, 132.4, 128.7, 122.6, 121.9, 113.2, 71.0, 68.6, 67.9, 39.1. ^{1}H NMR (CDCl$_3$) (*Z* isomer): δ 8.37 (s, 2H, NH), 8.19 (dd, 2H, *J*=7.8, 1.4 Hz), 7.43 (m, 2H), 7.11 (t, 2H, *J*=7.3 Hz), 6.94 (d, 2H, *J*=8.2 Hz), 5.80 (t, 2H, *J*=3.9 Hz, CH=), 4.27 (m, 4H, OCH$_2$), 4.18 (d, 2H, *J*=3.9 Hz, OCH$_2$CH=), 3.88 (m, 4H, OCH$_2$), 3.62 (m, 4H, NCH$_2$). ^{13}C NMR (CDCl$_3$) (*Z* isomer): δ 165.3, 156.6, 132.4, 132.3, 128.3, 122.5, 121.7, 11.8, 68.7, 68.1, 67.0, 39.2. Anal. Calcd for $C_{24}H_{28}N_2O_6$ (440.5): C 65.44; H 6.41; N 6.36. Found: C 65.33; H 6.39; N 6.54.

3.1.11.13. Compound 5. (*E* and *Z*): Yield 57 mg (60%), colorless crystals (CH$_2$Cl$_2$), mp 208–209 °C, purified using column chromatography with eluent DCM/pet. ether (40–60)/EtOAc, R_f=0.3 [DCM/pet. ether (40–60)/EtOAc 6:4:2]. 2:1. LCMS; *m*/*z*=489 (M+1). IR: 3303, 3072, 3007, 2931, 2863, 1664, 1600, 1536, 1475, 1454, 1303, 1233, 1162, 1124, 1099, 1047, 756. ^{1}H NMR (CDCl$_3$) (*E* isomer): δ 9.73 (s, 2H, NH), 8.00 (dd, 2H, *J*=7.7, 1.3 Hz), 7.81 (m, 2H), 7.43 (dt, 2H, *J*=7.2, 1.7 Hz), 7.28 (m, 2H), 7.11 (t, 2H, *J*=7.7 Hz), 6.97 (d, 2H, *J*=8.3 Hz), 5.47 (s, 2H, CH=), 4.24 (t, 4H, *J*=4.2 Hz, OCH$_2$), 3.92 (m, 4H, O*CH$_2$*CH=), 3.71 (t, 4H, *J*=4.32 Hz, OCH$_2$). ^{13}C NMR (CDCl$_3$) (*E* isomer): δ 164.8, 156.5, 132.6, 131.4, 131.2, 129.6, 125.9, 125.1, 121.6, 113.1, 71.0, 69.2, 67.2. ^{1}H NMR (CDCl$_3$) (*Z* isomer): δ 9.81 (s, 2H, NH), 8.11 (dd, 2H, *J*=7.9, 1.5 Hz), 7.99 (m, 2H), 7.43 (dt, 2H, *J*=7.2, 1.7 Hz), 7.28 (m, 2H), 7.11 (t, 2H, *J*=7.7 Hz), 6.97 (d, 2H, *J*=8.3 Hz), 5.32 (t, 2H, *J*=5.3 Hz, CH=), 4.11 (t, 4H, *J*=4.3 Hz, CH$_2$), 3.96 (d, 4H, *J*=5.3 Hz, O*CH$_2$*CH=), 3.66 (t, 4H, *J*=4.3 Hz, OCH$_2$). ^{13}C NMR (CDCl$_3$) (*Z* isomer): δ 164.1, 156.3, 132.8, 132.2, 129.0, 125.7, 124.9, 123.9, 121.9, 113.6, 69.0, 67.7, 66.0. Anal. Calcd for $C_{28}H_{28}N_2O_6$ (488.6): C 68.84; H 5.78; N 5.73. Found: C 67.22; H 5.87; N 5.85.

3.1.11.14. Compound 6a. (*E* and *Z*): Yield 846 mg (92%), colorless crystals (EtOH), mp 203–204 °C. LCMS; *m*/*z*=461 (M+1). IR: 3393, 3066, 1674, 1599, 1537, 1502, 1488, 1453, 1387, 1335, 1292, 1248, 1204, 1189, 1125, 1044, 961, 752. ^{1}H NMR (CDCl$_3$) (*E* isomer): 8.98 (s, 2H, NH), 8.42 (dd, 2H, *J*=7.9, 1.3 Hz), 7.12 (dt, 2H, *J*=8.0, 1.5 Hz), 7.06 (m, 6H), 6.93 (d, 2H, *J*=7.4 Hz), 6.14 (s, 2H, CH=), 4.71 (s, 4H, OCH$_2$CO), 4.57 (s, 4H, O*CH$_2$*CH=). ^{13}C NMR (CDCl$_3$) (*E* isomer): δ: 166.5, 147.9, 147.3, 127.0, 126.9, 124.6, 123.5, 121.6, 120.6, 115.5, 111.5, 70.2, 68.1. ^{1}H NMR (CDCl$_3$) (*Z* isomer): δ 9.07 (s, 2H, NH), 8.42 (dd, 2H, *J*=7.9, 1.3 Hz), 7.06 (m, 8H), 6.93 (d, 2H, *J*=7.4 Hz), 5.94 (t, 2H, *J*=4.1 Hz, CH=), 4.69 (s, 4H, OCH$_2$CO), 4.65 (d, 4H, *J*=4.1 Hz, O*CH$_2$*CH=). Anal. Calcd for $C_{26}H_{24}N_2O_6$ (460.5): C 67.82; H 5.25; N 6.08. Found: C 67.53; H 5.37; N 6.13.

3.1.11.15. Compound 6b. (*E*): Yield 80 mg (73%), colorless crystals, mp 160–161 °C, purified using column chromatography with eluent DCM/pet. ether (40–60), R_f= 0.3 [DCM/pet. ether (40–60)/EtOAc 2:1:1]. LCMS; *m*/*z*= 549 (M+1). IR: 3577, 3391, 2922, 2846, 1689, 1600, 1533, 1499, 1454, 1254, 1117, 1048, 750. ^{1}H NMR (CDCl$_3$) (*E* isomer): δ 9.26 (s, 2H, NH), 8.42 (dd, 2H, *J*=8.0, 1.5 Hz), 7.17–7.02 (m, 10H), 6.93 (d, 2H, *J*=8.0 Hz), 5.81 (s, 2H, CH=), 4.76 (s, 4H, OCH$_2$CO), 4.25 (m, 4H, OCH$_2$CH$_2$), 3.98 (br, 4H, O*CH$_2$*CH=), 3.78 (m, 4H, OCH$_2$CH$_2$). ^{13}C NMR (CDCl$_3$) (*E* isomer): δ 166.5, 148.5, 147.5, 129.1, 127.4, 124.4, 123.8, 121.7, 120.3, 117.6, 112.2, 71.2, 70.5, 69.0, 68.3. Anal. Calcd For $C_{30}H_{32}N_2O_8$ (548.6): C 65.68; H 5.88; N 5.11. Found: C 65.92; H 6.02; N 4.99.

3.1.11.16. Compound 7a. (*E* and *Z*): Yield 116 mg (91%), colorless crystals (EtOH/CHCl$_3$), mp 271–272 °C. LCMS; *m*/*z*=637 (M+1). IR: 3392, 3059, 2919, 1687, 1599, 1534, 1456, 1253, 1213, 1054, 1044, 966, 749. ^{1}H NMR (CDCl$_3$) (*E* isomer): δ 8.37 (s, 2H, NH), 7.94 (d, 2H, *J*=8.9 Hz), 7.90 (dd, 2H, *J*=8.0, 1.6 Hz), 7.74 (m, 2H), 7.48 (d, 2H, *J*=8.9 Hz), 7.29 (m, 4H), 7.19 (m, 2H), 7.05 (dt, 2H, *J*=7.9, 1.6 Hz), 6.94 (dt, 2H, *J*=7.8, 1.1 Hz), 6.82 (dd, 2H, *J*=8.2, 1.2 Hz), 5.98 (t, 2H, *J*=2.2 Hz, CH=), 4.61 (d, 2H, *J*=15.4 Hz, OCH$_2$CO), 4.43 (d, 4H, *J*=2.2 Hz, *CH$_2$*CH=), 4.37 (d, 2H, *J*=15.4 Hz, OCH$_2$CO). ^{13}C NMR (CDCl$_3$) (*E* isomer): δ 166.3, 153.9, 147.6, 133.6, 130.5, 130.4, 128.0, 127.2, 127.1, 126.2, 125.1, 125.0, 124.6, 121.6, 121.2 (2C), 117.7, 111.3, 71.6, 67.9. ^{1}H NMR (CDCl$_3$) (*Z* isomer): δ 8.70 (s, 2H, NH), 8.09 (dd, 2H, *J*=7.9, 1.8 Hz), 8.00 (d, 2H, *J*=8.8 Hz), 7.74 (m, 2H), 7.49 (d, 2H, *J*=8.8 Hz), 7.41 (t, 2H, *J*=7.6 Hz), 7.29 (m, 2H), 7.19 (m, 2H), 7.13 (d, 2H, *J*=8.6 Hz), 6.98 (dt, 2H, *J*=7.8, 1.5 Hz), 6.82 (dd, 2H, *J*=8.2, 1.2 Hz), 5.47 (t, 2H, *J*=4 Hz, CH=), 4.52 (d, 2H, *J*=15.9 Hz, OCH$_2$CO), 4.49 (d, 4H, *J*=4 Hz, *CH$_2$*CH=), 4.40 (d, 2H, *J*=15.9 Hz, OCH$_2$CO). ^{13}C NMR (CDCl$_3$) (*Z* isomer): δ 166.8, 153.2, 147.8, 133.9, 130.4, 130.1, 128.4, 128.2, 127.1, 127.0, 125.5, 124.8, 124.7, 121.9, 121.5, 120.1, 115.8, 112.9, 69.8, 64.9. Anal. Calcd for $C_{40}H_{32}N_2O_6$ (636.7): C 75.46; H 5.07; N 4.40. Found: C 75.64; H 5.02; N 4.45.

3.1.11.17. Compound 7b. (*E* and *Z*): Yield 140 mg (97%), colorless crystals (EtOH), mp 212–213 °C. LCMS; *m*/*z*=725 (M+1). IR: 3397, 2922, 1707, 1686, 1535, 1456, 1362, 1255, 1219, 1117, 912, 753. ^{1}H NMR (CDCl$_3$) (*E* isomer): δ 8.73 (s, 2H, NH), 8.17 (dd, 2H, *J*=7.8, 1.6 Hz), 8.00 (d, 2H, *J*=8.9 Hz), 7.88 (d, 2H, *J*=8.2 Hz), 7.47 (d, 2H, *J*=8.9 Hz), 7.37 (dt, 2H, *J*=8.1, 1.1 Hz), 7.27 (dt, 2H, *J*=7.1, 1.2 Hz), 7.16 (d, 2H, *J*=8.4 Hz), 7.03 (dt, 2H, *J*=7.8, 1.6 Hz), 6.96 (dt, 2H, *J*=7.8, 1.2 Hz), 6.84 (dd, 2H, *J*=8.1, 1.3 Hz), 5.33 (t, 2H, *J*=2.8 Hz, CH=), 4.65 (d, 2H, *J*=15.6 Hz, OCH$_2$CO), 4.33 (d, 2H, *J*=15.6 Hz, OCH$_2$CO), 4.00 (m, 4H, OCH$_2$CH$_2$), 3.60 (dd, 2H, *J*=12.2, 2.8 Hz, O*CH$_2$*CH=), 3.51 (m, 2H, OCH$_2$CH$_2$), 3.40 (dd, 2H, *J*=12.2, 2.8 Hz, O*CH$_2$*CH=), 3.24 (m, 2H, OCH$_2$CH$_2$). ^{13}C NMR (CDCl$_3$) (*E* isomer): δ 166.9, 153.8, 147.8, 133.8, 130.5, 130.3, 128.9, 128.1, 127.3, 127.1, 125.5, 124.7, 124.3, 121.6, 120.9, 120.5, 117.2, 112.6, 68.3, 69.2, 71.0, 71.1. ^{1}H NMR (CDCl$_3$) (*Z* isomer): δ 8.64 (s, 2H, NH), 8.13 (dd, 2H, *J*=8.0, 1.6 Hz), 8.01 (d, 2H, *J*=8.9 Hz), 7.85 (d, 2H, *J*=8.2 Hz), 7.49 (d, 2H, *J*=8.9 Hz), 7.38 (dt, 2H, *J*=8.1, 1.1 Hz), 7.27 (dt, 2H, *J*=6.8, 1.2 Hz), 7.16 (d, 2H, *J*=8.4 Hz), 7.03 (dt, 2H, *J*=7.8, 1.6 Hz), 6.96 (dt, 2H, *J*=7.8, 1.2 Hz), 6.82 (dd, 2H, *J*=8.1, 1.3 Hz), 5.43 (t, 2H, *J*=3.5 Hz, CH=), 4.63 (d, 2H, *J*=15.6 Hz, OCH$_2$CO), 4.45 (d, 2H, *J*=15.6 Hz, OCH$_2$CO), 4.00 (m, 4H, OCH$_2$CH$_2$), 3.67 (dd, 2H, *J*=12.2, 3.5 Hz, O*CH$_2$*CH=), 3.53 (dd, 2H, *J*=12.2, 3.5 Hz, O*CH$_2$*CH=), 3.51 (m, 2H, OCH$_2$CH$_2$), 3.24 (m, 2H, OCH$_2$CH$_2$).^{13}C NMR (CDCl$_3$) (*Z* isomer): δ 166.6, 153.8, 147.8, 133.7, 130.3, 130.0, 128.9, 128.1, 127.1, 126.8, 125.3, 124.8, 124.6, 121.4, 121.3, 120.6, 116.9, 112.0, 70.9, 69.0, 68.0, 66.9. Anal. Calcd for $C_{44}H_{40}N_2O_8$ (724.8): C 72.91; H, 5.56; N, 3.86. Found: C 71.97; H 5.49; N 4.05.

3.1.11.18. Compound 8a. (*E* and *Z*): Yield 130 mg (100%), colorless crystals (EtOH), mp 205 °C. LCMS; *m*/*z* = 651 (M + 1). IR: 3396, 3351, 3070, 2938, 2867, 1691, 1649, 1601, 1535, 1484, 1454, 1374, 1292, 1249, 1206, 1161, 1116, 1043, 754. ^{1}H NMR (CDCl$_3$) (*E* isomer): δ 9.10 (s, 2H, NH), 8.65 (s, 2H, NH), 8.36 (dd, 2H, *J* = 8.2, 1.7 Hz), 8.03 (d, 2H, *J* = 7.6 Hz), 7.30 (m, 2H), 7.03 (m, 4H), 6.93 (d, 2H, *J* = 8.3 Hz), 6.88–6.75 (m, 4H), 5.60 (s, 2H, CH=), 4.94 (s, 4H, OCH$_2$CO), 4.21 (s, 4H, O*CH*$_2$CH=), 3.72 (s, 4H, CH$_2$N). ^{13}C NMR (CDCl$_3$) (*E* isomer): δ 165.9, 165.6, 155.2, 147.5, 133.1, 132.4, 127.3, 124.7, 122.2, 121.5, 120.4, 112.1, 111.9, 68.5, 68.3, 41.4. ^{1}H NMR (CDCl$_3$) (*Z* isomer): δ 8.89 (s, 2H, NH), 8.73 (s, 2H, NH), 8.44 (m, 2H), 8.08 (d, 2H, *J* = 8.3 Hz), 7.33 (m, 2H), 7.03 (m, 4H), 6.89–6.77 (m, 2H), 6.66 (m, 2H), 5.75 (t, 2H, *J* = 3.4 Hz, CH=), 4.94 (s, 4H, OCH$_2$CO), 4.24 (d, 4H, *J* = 3.4 Hz, O*CH*$_2$CH=), 3.84 (s, 4H, CH$_2$N). ^{13}C NMR (CDCl$_3$) (*Z* isomer): δ 165.9, 165.6, 155.2, 146.8, 133.1, 132.4, 127.3, 124.7, 122.2, 121.5, 120.4, 112.1, 111.9, 68.5, 68.3, 41.4. Anal. Calcd for $C_{36}H_{34}N_4O_8$ (650.7): C 66.45; H 5.27; N 8.61. Found: C 66.19; H 5.45; N 8.34.

3.1.11.19. Compound 8b. (*E* and *Z*): Yield 118 mg (80%), colorless crystals [EtOAc/pet. ether (40–60)], mp 174–175 °C. LCMS; *m*/*z* = 739 (M + 1). IR: 3397, 3353, 2931, 2872, 1687, 1642, 1602, 1539, 1484, 1454, 1299, 1255, 1208, 1162, 1118, 1045, 909, 732, 649. ^{1}H NMR (CDCl$_3$) (*E* isomer): δ 8.71 (s, 2H, NH), 8.60 (s, 2H, NH), 8.28 (dd, 2H, *J* = 7.7, 1.2 Hz), 8.04 (d, 2H, *J* = 7.7 Hz), 7.28 (t, 2H, *J* = 7.7 Hz), 7.10–6.80 (m, 10H), 5.74 (s, 2H, CH=), 4.83 (s, 4H, OC*H*$_2$CO), 4.13 (m, 4H, OCH$_2$), 3.89 (s, 4H, O*CH*$_2$CH=), 3.82 (m, 4H, OCH$_2$CH$_2$), 3.50 (s, 4H, OCH$_2$N). ^{13}C NMR (CDCl$_3$) (*E* isomer): δ 166.2, 164.9, 155.5, 147.3, 132.8, 132.0, 128.7 (2C), 127.5, 124.5, 122.3, 122.0, 120.8, 113.1, 112.5, 70.9, 68.7, 68.6, 68.5, 40.5. ^{1}H NMR (CDCl$_3$) (*Z* isomer): δ 8.83 (s, 2H, NH), 8.51 (s, 2H, NH), 8.28 (dd, 2H, *J* = 7.7, 1.2 Hz), 8.04 (d, 2H, *J* = 7.7 Hz), 7.35 (t, 2H, *J* = 8.4 Hz), 7.10–6.80 (m, 10H), 5.52 (t, 2H, *J* = 4.2 Hz, CH=), 4.85 (s, 4H, O*CH*$_2$CO), 4.13 (m, 8H, OCH$_2$CH$_2$, O*CH*$_2$CH=), 3.82 (m, 4H, OCH$_2$CH$_2$), 3.50 (m, 4H, OCH$_2$N). ^{13}C NMR (CDCl$_3$) (*Z* isomer): δ 166.1, 166.0, 155.7, 147.7, 132.9, 132.1, 129.1, 128.7 (2C), 124.8, 122.5, 122.3, 120.9, 113.1, 112.5, 69.3, 69.0, 68.4, 66.7, 40.8. Anal. Calcd for $C_{40}H_{42}N_4O_{10}$ (738.8): C 65.03; H 5.73; N 7.58. Found: C 65.45; H 5.54; N 8.37.

3.1.11.20. Compound 9a. (*E* and *Z*): Yield 65 mg (75%), colorless crystals [EtOAc/pet. ether (40–60)], mp 192 °C. LCMS; *m*/*z* = 431 (M + 1). IR: 3398, 1690, 1662, 1599, 1531, 1483, 1455, 1329, 1294, 1254, 1235, 1043, 1002, 966, 750. ^{1}H NMR (CDCl$_3$) (*E*): δ 9.80 (s, 1H, NH), 8.88 (s, 1H, NH), 8.49 (m, 1H), 8.29 (m, 2H), 7.53 (dt, 1H, *J* = 7.8, 1.2 Hz), 7.18 (t, 1H, *J* = 7.6 Hz), 7.10–7.04 (m, 5H), 6.96 (m, 1H), 6.90 (dd, 1H, *J* = 7.8, 1.0 Hz), 6.47 (m, 1H, CH=), 6.17 (m, 1H, CH=), 4.77 (br, 2H, O*CH*$_2$CH=), 4.76 (s, 2H, OCH$_2$CO), 4.60 (br, 2H, O*CH*$_2$CH=). ^{1}H NMR (CDCl$_3$) (*Z*): δ 9.80 (s, 1H, NH), 9.00 (s, 1H, NH), 8.40 (m, 2H), 8.23 (m, 1H), 7.50 (t, 1H, *J* = 7.8 Hz), 7.18–7.04 (m, 6H), 6.96 (m, 2H), 6.45 (t, 2H, *J* = 5.3 Hz, CH=), 4.89 (d, 2H, *J* = 5.3 Hz, O*CH*$_2$CH=), 4.71 (s, 2H, OCH$_2$CO), 4.62 (d, 2H, *J* = 5.3 Hz, O*CH*$_2$CH=). Anal. Calcd for $C_{25}H_{22}N_2O_5$ (430.5): C 69.76; H 5.15; N 6.51. Found: C 60.86; H 5.18; N 6.55.

3.1.11.21. Compound 9b. (*E* and *Z*): Yield 78 mg (82%), colorless crystals (EtOH/CHCl$_3$), mp 215–216 °C. LCMS; *m*/*z* = 475 (M + 1). IR: 3342, 2919, 1667, 1599, 1533, 1482, 1455, 1294, 1229, 1120, 1092, 1007, 911, 746. ^{1}H NMR (CDCl$_3$): (*E* isomer): 10.55 (s, 1H, NH), 9.04 (s, 1H, NH), 8.63 (dd, 1H, *J* = 8.6, 0.9 Hz), 8.35 (m, 2H), 7.52 (t, 1H, *J* = 7.4 Hz), 7.19–6.96 (m, 8H), 6.21 (m, 1H, CH=), 5.97 (m, 1H, CH=), 4.78 (s, 2H, O*CH*$_2$CH=), 4.66 (s, 2H, OCH$_2$CO), 4.24 (br, 2H, OCH$_2$CH$_2$), 4.02 (s, 2H, O*CH*$_2$CH=), 3.67 (br, 2H, OCH$_2$CH$_2$). ^{1}H NMR (CDCl$_3$) (*Z* isomer): δ 10.55 (s, 1H, NH), 8.82 (s, 1H, NH), 8.73 (d, 1H, *J* = 7.8 Hz), 8.38 (m, 2H), 7.52 (t, 1H, *J* = 7.3 Hz), 7.19–6.96 (m, 7H), 6.87 (d, 1H, *J* = 7.7 Hz), 5.97 (m, 2H, CH=), 4.87 (d, 2H, *J* = 5.6 Hz, O*CH*$_2$CH=), 4.80 (s, 2H, OCH$_2$CO), 4.26 (d, 2H, *J* = 5.6 Hz, O*CH*$_2$CH=), 4.08 (br, 2H, OCH$_2$CH$_2$), 3.66 (br, 2H, OCH$_2$CH$_2$). Anal. Calcd for $C_{27}H_{26}N_2O_6$ (474.5): C 68.34; H 5.52; N 5.90. Found: C 67.41; H 5.40; N 6.06.

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References and notes

1. (a) For reviews see (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450. (b) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012–3043. (c) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371–388. (d) Yet, L. *Chem. Rev.* **2000**, *100*, 2963–3007. (e) Martin, S. F.; Deiter, A. *Chem. Rev.* **2004**, *104*, 2199–2238.
2. Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446–552, and references therein.
3. Xu, Z.; Johannes, C. W.; Salman, S. S.; Hoyveda, A. H. *J. Am. Chem. Soc.* **1996**, *118*, 10926–10927.
4. Clark, J. S.; Kettle, J. G. *Tetrahedron Lett.* **1997**, *38*, 123–126.
5. Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 3942–3943.
6. (a) König, B.; Horn, C. *Synlett* **1996**, 1013–1014. (b) Marsella, M. J.; Maynard, H. D.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **1997**, *36*, 1101–1103. (c) Maynard, H. D.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 4137–4140. (d) Delgado, M.; Martin, J. D. *Tetrahedron Lett.* **1997**, *38*, 8387–8390. (e) Noels, A. F.; Demonceau, A. *J. Phys. Org. Chem.* **1998**, *11*, 602–609.
7. Miller, S. J.; Blackwell, H. E.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 9606–9614.
8. Meng, D. S.; Su, D.-S.; Balog, A.; Bertinato, P.; Sorenson, E. J.; Danishefsky, S. J.; Zheng, Y.-H.; Chou, T.-C.; He, L.; Horwitz, S. *J. Am. Chem. Soc.* **1997**, *119*, 2733–2734.
9. Nicolau, K. C.; He, Y.; Vourloumis, D.; Vallberg, H.; Yang, Z. *Angew. Chem., Int. Ed.* **1996**, *35*, 2399–2401.

10. Fürstner, A.; Langemann, K. *Synthesis* **1997**, 792–803.
11. Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956.
12. Ivin, K. *J. Mol. Catal. A: Chem.* **1998**, *133*, 29–40.
13. (a) Chambron, J.-C.; Collin, J.-P.; Heitz, V.; Jouvenot, D.; Kern, J.-M.; Mobian, P.; Pomeranc, D.; Sauvage, J.-P. *Eur. J. Org. Chem.* **2004**, 1627–1638. (b) Arico, F.; Mobian, P.; Kern, J.-M.; Sauvage, J.-P. *Org. Lett.* **2003**, *5*, 1887–1890. (c) Collin, J.-P.; Laemmel, A.-C.; Sauvage, J.-P. *New. J. Chem.* **2001**, *25*, 22–24.
14. Kidd, T. J.; Leigh, D. A.; Wilson, A. J. *J. Am. Chem. Soc.* **1999**, *121*, 1599–1600.
15. (a) Pinho e Melo, T. M. V. D.; Soares, M. I. L.; Rocha Gonsalves, A. M. d'A.; Paixao, J. A.; Beja, A. M.; Silva, M. R.; Alte de Veiga, L.; Passoa, J. C. *J. Org. Chem.* **2002**, *67*, 4045–4054. (b) Beckwith, A. L. J.; Bowry, V. W. *J. Org. Chem.* **1988**, *53*, 1632–1641.
16. (a) Ibrahim, Y. A.; Behbehani, H.; Ibrahim, M. R. *Tetrahedron Lett.* **2002**, *43*, 4207–4210. (b) Behbehani, H.; Ibrahim, M. R.; Ibrahim, Y. A. *Tetrahedron Lett.* **2002**, *43*, 6421–6426. (c) Ibrahim, Y. A.; Behbehani, H.; Ibrahim, M. R.; Abrar, N. M. *Tetrahedron Lett.* **2002**, *43*, 6971–6974. (d) Ibrahim, Y. A.; Behbehani, H.; Ibrahim, M. R.; Malhas, R. N. *Tetrahedron* **2003**, *59*, 7273–7282. (e) Ibrahim, Y. A.; Behbehani, H.; Khalil, N. S. *Tetrahedron* **2004**, *60*, 8429–8436.
17. Perez, M. A.; Bermejo, J. M. *J. Org. Chem.* **1993**, *58*, 2628–2630.
18. (a) Ibrahim, Y. A.; Elwahy, A. H. M.; Abbas, A. A. *Tetrahedron* **1994**, *50*, 11489–11498 and references cited therein. (b) Elwahy, A. H. M.; Abbas, A. A.; Ibrahim, Y. A. *J. Chem. Res. (S)* **1998**, 184–185. Elwahy, A. H. M.; Abbas, A. A.; Ibrahim, Y. A. *J. Chem. Res. (M)* **1998**, 901–914.
19. Ibrahim, Y. A.; Elwahy, A. H. M. *Synthesis* **1993**, 503–508.

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A one-pot access to cycloalkano[1,2-*a*]indoles through an intramolecular alkyl migration reaction in indolylborates

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Abstract—A novel one-pot protocol for the preparation of cycloalkano[1,2-*a*]indoles by way of an intramolecular alkyl migration reaction in cyclic indolylborates is described. NaOMe was found to act as a successful trialkylboryl-protecting group against to the lithiation at the C2 of the indole ring. Treatment of cyclic indolylborates with electrophiles produced cycloalkano-[1,2-*a*]indoles.

1. Introduction

The rich chemistry of organoboron compounds has provided fertile ground for the development of pivotal synthetic methodologies.[1] While an inter- or intramolecular alkyl migration from boron to carbon in organoboron compounds has been well recognized as a valuable synthetic tool for regioselective and stereospecific bond formation,[2] its use for intramolecular cyclization has been scarcely known.[3] In our continuing program to develop trialkyl(1*H*-indol-2-yl)borate as a versatile synthetic intermediate for the construction of indole derivatives,[4] an intramolecular alkyl migration from boron to the C2 of the indole ring in indolylborates has also been proven to be successful, leading to 2,3-disubstituted indoles in a one-pot treatment. Hence, we have become interested in the unprecedented use of the alkyl migration process in indolylborates, and previously reported a novel one-pot protocol for the preparation of carbazole derivatives based on the intramolecular 1,2-alkyl migration reaction in indolylborates, in which π-allyl palladium complexes were adopted as successful intramolecular electrophiles.[5]

As the core structure of [*a*]-annelated indole is present in a number of biologically active indole derivatives such as mitomycin and vincamine, the development of methods for the construction of [*a*]-annelated indole nuclei has been the subject of a number of reports.[6] We have set about the development of a novel one-pot access to [*a*]-annelated indoles by the use of the 1,2-alkyl migration process in indolylborate (**6**).[7]

2. Results and discussion

As shown in Scheme 1, we initially envisioned that alkyl migration triggered by intermolecular attack of electrophile (H_2O) on the C-3 of the indole ring in cyclic indolylborate (**6**) might provide the cyclization product (**8**) after oxidation of **7**, in which implementation of the synthetic plan first required an adequate protocol for the in situ generation of **6**. Our initial expectation to form **6** via 2-lithioindole (**A**) involved straightforward lithiation of the starting indole (**1**), followed by treatment with dialkylboranes, but all attempted experiments have met with failure. Alternatively, we anticipated that if 2-lithioindole (**5**) is available by the lithiation at the C-2 of the indole ring of alkylborane (**2**), the following spontaneous cyclization might possibly provide cyclic indolylborate (**6**).

Initially, we attempted the lithiation with *tert*-BuLi at the C-2 of the indole ring in alkylboranes (**2**), readily generated by treatment of indole (**1a**) with 9-borabicyclo[3.3.1]nonane (9-BBN) in THF at room temperature. However, an oxidative work-up of the reaction mixture allowed only the isolation of alcohol (**10a**) in 40% yield, which possibly involved the formation of tetraalkylborate (**B**) from the predominant interaction between the trialkylboryl group of **2** and *tert*-BuLi. With this in mind, we needed a feasible trialkylboryl-protecting group that would persist until the lithiation at the C2 of **2** was complete, and after that, would

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Keywords: Cyclic indolylborate; Hydroboration; Intramolecular alkyl migration; [*a*]-Annelated indoles.

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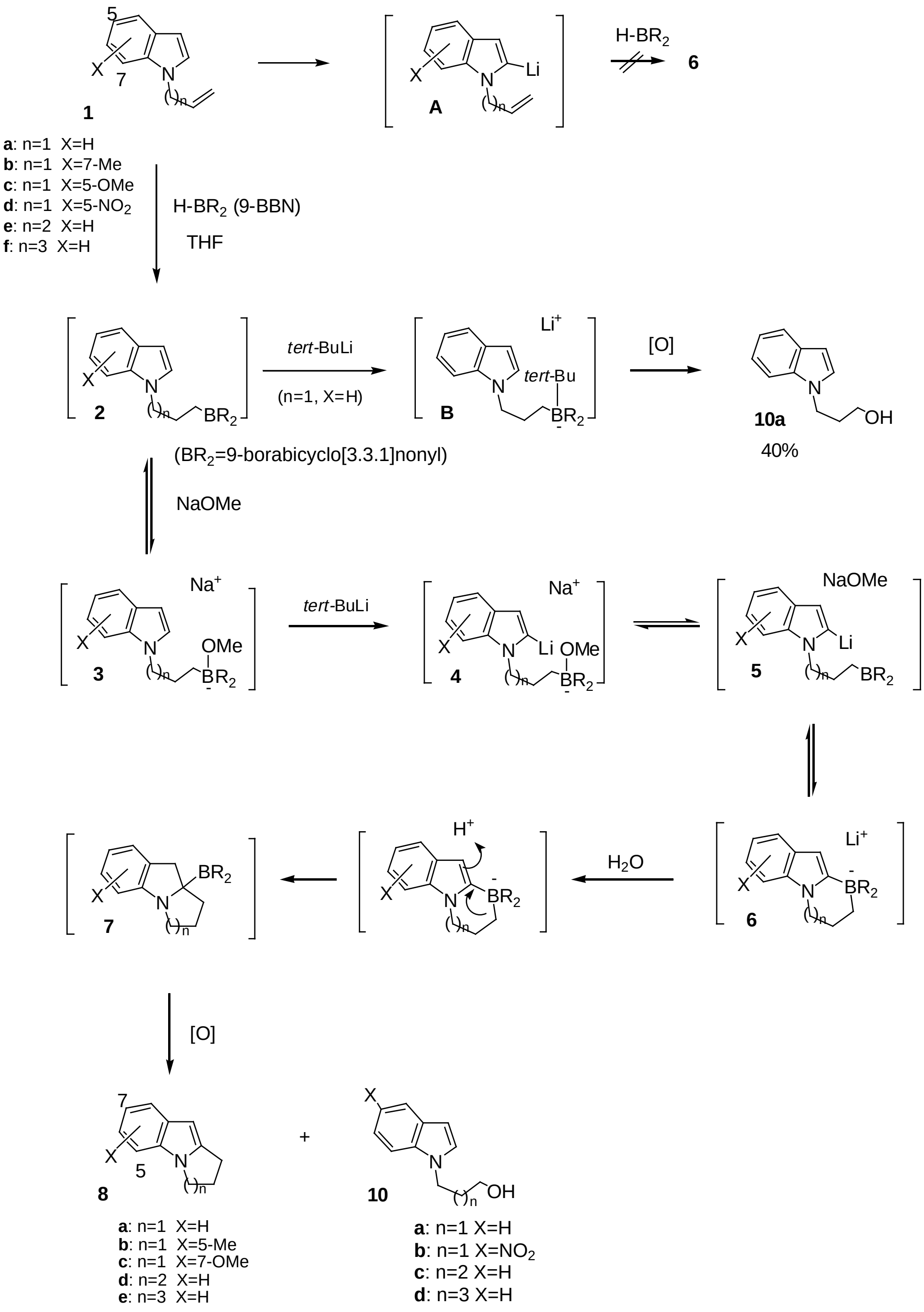


Scheme 1.

be removed to restore the trialkylboryl group. We were pleased to find that the presence of NaOMe provided marked protection against the lithiation of **2** by the formation of methoxyborate (**3**), and the following work-up of the reaction mixture with H_2O_2 in NaOH solution afforded **8**, accompanied by a small amount of **10**. The reaction outcome can be interpreted as follows: (1) hydroboration of **1** with 9-BBN produces alkylborane (**2**). (2) Treatment of **2** with NaOMe forms methoxyborate (**3**). (3) Subsequent lithiation of **3** with *tert*-BuLi generates 2-lithioindole (**4**), which is accompanied by spontaneous formation of indolylborate (**6**) via elimination of the methoxide anion (**4** to **5**). (4) Intramolecular 1,2-alkyl migration in **6** provides [*a*]-annelated indole (**8**) after oxidation of **7**. Alcohols (**10**) were possibly produced by way of oxidation of **5** or **B**.

As summarized in Table 1, the use of NaOMe (1.1 equiv), *tert*-BuLi (2.2 equiv) and TMEDA (2.2 equiv) in THF was adequate to effect the one-pot transformation of **1a** to **8a**, and the conditions were applied to further investigations. Hydroboration of **5d** brought about **6** ($n=1$, $X=5\text{-}NO_2$) in situ, which was subsequently subjected to the reaction. However, the desired cyclization product was not obtained in this transformation and only alcohol (**10b**) was isolated from the complex reaction mixtures.

Table 1. One-pot preparation of **8** from **1**[a]

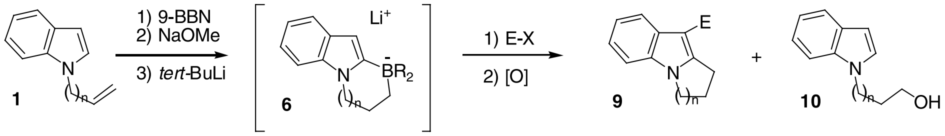
1	NaOMe (equiv)	*tert*-BuLi (equiv)	TMEDA (equiv)	Yield (%) of **8**	Yield (%) of **10**
$n=1$ X=H	—	2.2	2.2	**8a** (16)	**10a** (20)
$n=1$ X=H	1.1	2.2	2.2	**8a** (62)	—
$n=1$ X=H	2.2	2.2	2.2	**8a** (22)	**10a** (10)
$n=1$ X=H	1.1	1.1	2.2	**8a** (14)	**10a** (22)
$n=1$ X=H	1.1	3.0	2.2	**8a** (47)	**10a** (7)
$n=1$ X=H	1.1	2.2	—	**8a** (40)	**10a** (10)
$n=1$ X=H	1.1	2.2	1.1	**8a** (50)	**10a** (5)
$n=1$ X=7-Me	1.1	2.2	2.2	**8b** (53)	—
$n=1$ X=5-OMe	1.1	2.2	2.2	**8c** (60)	—
$n=1$ X=5-NO_2	1.1	2.2	2.2	—	**10b** (40)
$n=1$ X=H	1.1	2.2	2.2	**8d** (60)	**10c** (5)
$n=1$ X=H	1.1	2.2	2.2	**8e** (42)	**10d** (8)

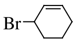
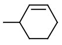
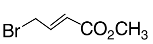
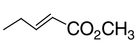
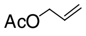
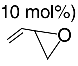
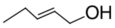
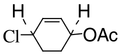
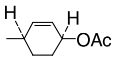
[a] Yield (%) of **8** and **10** based on **1**.

Treatment of **6** (X=H) with various electrophiles such as alkyl halides and π-allyl palladium complexes similarly produced [*a*]-annelated indoles (**9**), which allowed the introduction of various functional groups at the C3 of the indole ring (Table 2). On the reaction of indolylborate (**6**; $n=2$, X=H) with 3-bromocyclohexene, borinate (**9k**) was isolated as stable crystals in 35% yield after oxidation of the reaction mixture, which was in contrast to the formation of **9j** and **9l** from the reaction of **6** ($n=1,3$, X=H). Longer oxidation time and use of increased amount of H_2O_2 did not effect the production of **9k**. As there are examples of the successful use of diphenyliodonium ion as an electrophile toward the enolate anion,[8] the diphenyliodonium ion was also expected to be suitable for the promotion of the alkyl migration in **6**. The reaction of **6** (X=H, $n=1$) with diphenyliodonium chloride in THF under the same conditions afforded furanylindole (**9t**) in 30% yield as the only isolable product. This is probably due to the alkyl migration in **6** ($n=1$, X=H) caused by the electrophilic attack of the furanium ion (**C**) arising from the rapid oxidation of THF by diphenyliodonium ion[9] (Scheme 2).

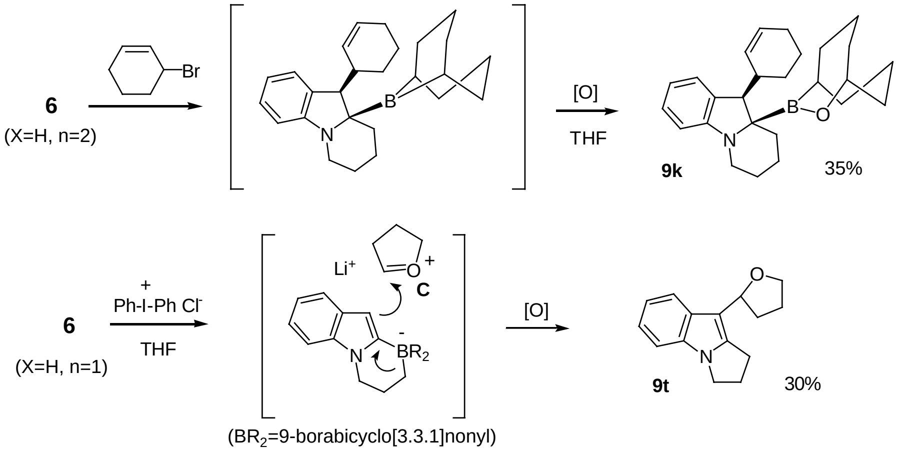
The alkyl migration reaction in indolylborates (**12**), derived from indoles (**11**) having a substituent at the olefinic carbon, was next examined. Indole (**11a**) was successfully

Table 2. One-pot preparation of **9** from **1** (X=H)[a]



E–X	E	*n*	Yield (%) of **9**	Yield (%) of **10**
CH_3–I	–CH_3	1	**9a** (55)	**10a** (10)
		2	**9b** (40)	**10c** (12)
		3	**9c** (30)	**10d** (22)
I–CH_2CN	–CH_2CN	1	**9d** (59)	**10a** (10)
		2	**9e** (40)	**10c** (10)
		3	**9f** (30)	**10d** (15)
Br–$CH_2CH{=}CH_2$	–$CH_2CH{=}CH_2$	1	**9g** (30)	**10a** (10)
		2	**9h** (30)	**10c** (15)
		3	**9i** (20)	**10d** (20)
		1	**9j** (42)	**10a** (10)
		2	—[b]	—
		3	**9l** (20)	**10d** (20)
		1	**9m** (55)	**10a** (10)
		2	**9n** (50)	**10c** (10)
		3	**9o** (39)	**10d** (10)
 $PdCl_2(PPh_3)_2$ (10 mol%)	–$CH_2CH{=}CH_2$	1	**9a** (60)	**10a** (10)
		2	**9b** (55)	**10c** (10)
		3	**9c** (26)	**10d** (15)
 $PdCl_2(PPh_3)_2$ (10 mol%)		1	**9p** (58)	**10a** (10)
		2	**9q** (50)	**10c** (15)
		3	**9i** (40)	**10d** (20)
 $PdCl_2(PPh_3)_2$ (10 mol%)		1	**9s** (42)	**10a** (10)

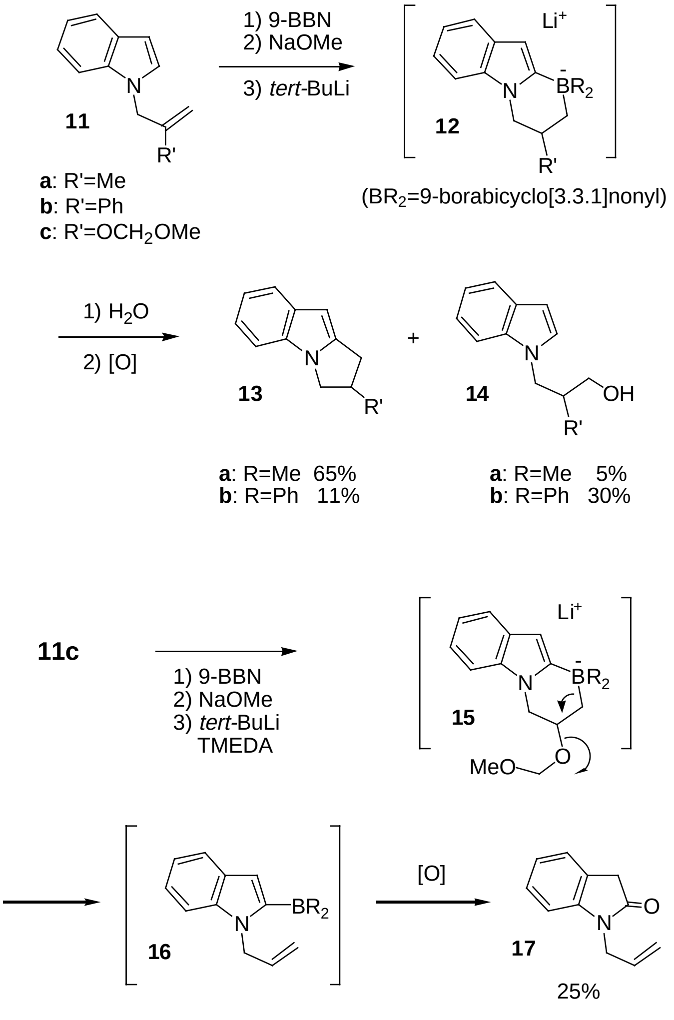
[a] Yield (%) of **9** and **10** based on **1**.
[b] Compound **9k** was isolated.



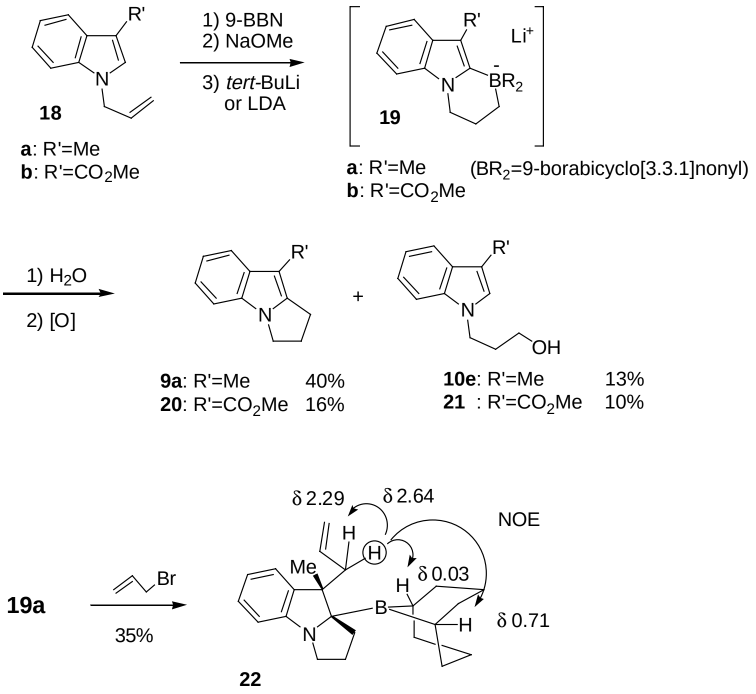
Scheme 2.

transformed to **13a** via **12** (R = Me). Otherwise, hydroboration of **11b** became much more sluggish, requiring forced reaction conditions (reflux for 2 h), and the following steps were less effective in giving **13b** in low yield, accompanied by a substantial amount of alcohol (**14b**). When indole (**11c**) bearing an alkoxy group was subjected to the alkyl migration reaction, 1-allyl-2-oxyindole (**17**) was isolated without the expected cyclization product. The rapid elimination of the alkoxy group from borate (**15**) predominantly took place to generate **16**, and the subsequent oxidation gave rise to **17**, as shown in Scheme 3.

Aqueous treatment of **19**, derived from indoles (**18**) bearing a substituent at the C-3 of the indole ring, affordrd [*a*]-annelated indoles (**9a**, **20**) and alcohols (**10e**, **21**), respectively (Scheme 4). In the case of **18b**, LDA was employed for the



Scheme 3.



Scheme 4.

lithiation at the C-2 of the indole ring in order to generate indolylborate (**19b**). Otherwise, simply treating **19a** with allyl bromide and the following work-up of the reaction mixture without a conventional oxidation allowed the isolation of alkylborane (**22**) in 35% yield as stable crystals. The reaction proceeded through the electrophilic attack of allyl bromide at the C-3 of the indole ring in **19a** with simultaneous alkyl migration in an *anti* manner[5] to produce **22**, whose structure was confirmed based on NOE experiments.

In summary, we have demonstrated a new one-pot access to cycloalkano[1,2-*a*]indoles (**9**) by way of the unprecedented use of an intramolecular alkyl migration process in indolylborate (**6**). Further extension of the protocol for the preparation of indole alkaloid is under way.

3. Experimental

3.1. General

Melting points were recorded on a Yamato MP21 and are uncorrected. MS and high-resolution MS spectra were recorded on a Micromass AutoSpec 3100 mass spectrometer. IR spectra were measured on a Hitachi Model 270-30 spectrometer. The NMR experiments were performed with a JEOL JNM-LA300 or JNM-ECA500 spectrometer, and chemical shifts are expressed in ppm (δ) with TMS as an internal reference. Medium pressure liquid chromatography (MPLC) was performed on silica gel (Silica Gel 60N, Kanto Chemical Co., Ltd).

3.2. General procedure for the preparation of 8

To a solution of **1** (2 mmol) in THF (10 mL), 9-BBN (0.5 M solution in THF, 2.2 mmol) was added at room temperature under an argon atmosphere, and the mixture was stirred for 1.5 h. Sodium methoxide (2.2 mmol) was added to the mixture, and after stirring for 30 min, TMEDA (4.4 mmol) and *tert*-BuLi (1.5 M solution in pentane, 4.4 mmol) were added to the mixture at −20 °C. After stirring for 2 h, the mixture was gradually raised to room temperature, and stirred for 4 h. To the reaction mixture, 20% NaOH (10 mL) and 30% H_2O_2 (2 mL) were added under ice-cooling and the whole was stirred for 30 min. The mixture was diluted with ethyl acetate (100 mL), washed with brine, and dried over $MgSO_4$. The solvent was removed, and the residue was separated by MPLC to give **8** (with hexane/AcOEt = 100:1) and **10** (with hexane/AcOEt = 1:1).

3.2.1. 2,3-Dihydro-1*H*-pyrrolo[1,2-*a*]indole (8a). Mp 77–78 °C (lit.[10] 78–79 °C). ^{1}H NMR ($CDCl_3$) δ: 2.59 (tt, 2H, $J=6.8$, 7.3 Hz), 3.00 (t, 2H, $J=7.3$ Hz), 4.04 (t, 2H, $J=6.8$ Hz), 6.15 (s, 1H), 7.03 (dt, 1H, $J=1.4$, 7.1 Hz), 7.10 (dt, 1H, $J=1.4$, 7.1 Hz), 7.22 (d, 1H, $J=7.1$ Hz), 7.53 (d, 1H, $J=7.1$ Hz). ^{13}C NMR ($CDCl_3$) δ: 24.1, 27.7, 43.4, 92.1, 109.3, 119.9, 120.1, 132.5, 133.2, 144.5. MS *m*/*z*: 157 (M^+).

3.2.2. 5-Methyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole (8b). Mp 90–91 °C (hexane). ^{1}H NMR ($CDCl_3$) δ: 2.64 (s, 3H), 2.55–2.65 (m, 2H), 2.94 (t, 2H, $J=7.4$ Hz), 4.36 (t, 2H, $J=6.8$ Hz), 6.11 (s, 1H), 6.81 (d, 1H, $J=7.9$ Hz), 6.91 (t, 1H, $J=7.9$ Hz), 7.34 (d, 1H, $J=7.9$ Hz). ^{13}C NMR ($CDCl_3$) δ: 17.9, 23.7, 27.9, 46.5, 92.6, 118.1, 119.3, 120.2, 121.7, 132.3, 133.4, 144.7. MS *m*/*z*: 171 (M^+). Anal. Calcd for $C_{12}H_{13}N$: C, 84.17; H, 7.65; N, 8.18. Found: C, 84.38; H, 7.55; N, 8.24.

3.2.3. 7-Methoxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole (8c). Mp 85–87 °C (lit.[11] 84–85 °C). ^{1}H NMR ($CDCl_3$) δ: 2.50–2.60 (m, 2H), 2.97 (t, 2H, $J=7.8$ Hz), 3.83 (s, 3H), 3.98 (t, 2H, *J* = 7.0 Hz), 6.08 (s, 1H), 6.77 (d, 1H, *J* = 7.8 Hz), 7.02 (br s, 1H), 7.09 (d, 1H, *J* = 7.8 Hz). ^{13}C NMR (CDCl$_3$) δ: 24.4, 27.7, 43.7, 55.9, 92.0, 102.6, 109.9, 128.1, 133.6, 145.3, 153.9. MS *m*/*z*: 187 (M$^+$).

3.2.4. 6,7,8,9-Tetrahydropyrido[1,2-*a*]indole (8d). Mp 58–59 °C (lit.[12] 57–58 °C). ^{1}H NMR (CDCl$_3$) δ: 1.80–1.95 (m, 2H), 2.00–2.15 (m, 2H), 2.97 (t, 2H, *J* = 6.3 Hz), 3.00 (t, 2H, *J* = 7.3 Hz), 4.04 (t, 2H, *J* = 6.4 Hz), 6.14 (s, 1H), 7.06 (dt, 1H, *J* = 1.5, 7.8 Hz), 7.13 (dt, 1H, *J* = 1.5, 7.8 Hz), 7.26 (d, 1H, *J* = 7.8 Hz), 7.52 (d, 1H, *J* = 7.8 Hz). ^{13}C NMR (CDCl$_3$) δ: 21.1, 23.3, 24.1, 42.1, 97.3, 108.4, 119.4, 119.9, 128.1, 136.1, 137.0. MS *m*/*z*: 171 (M$^+$).

3.2.5. 7,8,9,10-Tetrahydro-6*H*-azepino[1,2-*a*]indole (8e). Mp 86–85 °C (lit.[12] 83–85 °C). ^{1}H NMR (CDCl$_3$) δ: 2.59 (tt, 2H, *J* = 6.8, 7.3 Hz), 3.00 (t, 2H, *J* = 7.3 Hz), 4.04 (t, 2H, *J* = 6.8 Hz), 6.15 (s, 1H), 7.03 (dt, 1H, *J* = 1.4, 7.1 Hz), 7.10 (dt, 1H, *J* = 1.4, 7.1 Hz), 7.22 (d, 1H, *J* = 7.1 Hz), 7.53 (d, 1H, *J* = 7.1 Hz). ^{13}C NMR (CDCl$_3$) δ: 8.1, 28.6, 29.4, 31.0, 44.5, 98.9, 108.5, 118.8, 119.7, 120.2, 127.7, 136.8, 143.2. MS *m*/*z*: 185 (M$^+$).

3.3. General procedure for the preparation of 9

To a solution of **1** (2 mmol) in THF (10 mL), 9-BBN (0.5 M solution in THF, 2.2 mmol) was added at room temperature under an argon atmosphere, and the mixture was stirred for 1.5 h. Sodium methoxide (2.2 mmol) was added to the mixture, and after stirring for 30 min, TMEDA (4.4 mmol) and *tert*-BuLi (1.5 M solution in pentane, 4.4 mmol) were added to the mixture at −20 °C. After stirring for 2 h, the mixture was gradually raised to room temperature, and stirred for 4 h. Then, electrophile (5 mmol) was added, and the whole was stirred overnight (in the cases of alkyl halides) or heated under reflux for 3 h (in the cases of π-allyl palladium complexes). To the reaction mixture, 20% NaOH (10 mL) and 30% H$_2$O$_2$ (2 mL) were added under ice-cooling and the whole was stirred for 30 min. The mixture was diluted with ethyl acetate (100 mL), washed with brine, and dried over MgSO$_4$. The solvent was removed, and the residue was separated by MPLC to give **9** (with hexane/AcOEt = 100:1–10:1) and **10** (with hexane/AcOEt = 1:1).

3.3.1. 9-Methyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole (9a). Mp 50–51 °C (lit.[13] 48–49 °C). ^{1}H NMR (CDCl$_3$) δ: 2.24 (s, 3H), 2.52 (m, 2H), 2.88 (t, 2H, *J* = 7.3 Hz), 3.95 (t, 2H, *J* = 6.9 Hz), 7.00–7.12 (m, 2H), 7.15 (d, 1H, *J* = 7.8 Hz), 7.45 (d, 1H, *J* = 7.3 Hz). ^{13}C NMR (CDCl$_3$) δ: 8.8, 22.7, 27.5, 43.3, 100.4, 108.7, 118.1, 119.8, 133.0, 132.4, 141.1. MS *m*/*z*: 171 (M$^+$).

3.3.2. 5-Methyl-6,7,8,9-tetrahydropyrido[1,2-*a*]indole (9b). ^{1}H NMR (CDCl$_3$) δ: 1.88–1.94 (m, 2H), 2.04–2.10 (m, 2H), 2.24 (s, 3H), 2.90 (t, 2H, *J* = 6.3 Hz), 4.03 (t, 2H, *J* = 6.3 Hz), 7.11 (t, 1H, *J* = 7.8 Hz), 7.17 (t, 1H, *J* = 8.0 Hz), 7.25 (d, 1H, *J* = 8.0 Hz), 7.52 (d, 1H, *J* = 8.1 Hz). ^{13}C NMR (CDCl$_3$) δ: 8.2, 21.4, 22.5, 23.7, 42.4, 104.8, 108.4, 117.8, 119.0, 120.2, 128.6, 133.0, 136.0. HR-MS *m*/*z*: Calcd for C$_{13}$H$_{15}$N: 185.1204. Found: 185.1192.

3.3.3. 11-Methyl-7,8,9,10-tetrahydro-6*H*-azepino[1,2-*a*]-indole (9c). Mp 88–89 °C (hexane). ^{1}H NMR (CDCl$_3$) δ: 1.67–1.78 (m, 4H), 1.81–1.88 (m, 2H), 2.25 (s, 3H), 2.86 (t, 2H, *J* = 5.8 Hz), 4.13 (t, 2H, *J* = 5.2 Hz), 7.04 (t, 1H, *J* = 7.8 Hz), 7.13 (t, 1H, *J* = 7.8 Hz), 7.23 (d, 1H, *J* = 8.0 Hz), 7.48 (d, 1H, *J* = 8.0 Hz). ^{13}C NMR (CDCl$_3$) δ: 8.8, 25.5, 28.0, 29.8, 31.3, 44.6, 105.5, 108.2, 118.3, 120.4, 128.3, 135.8, 139.1. MS *m*/*z*: 199 (M$^+$). Anal. Calcd for C$_{14}$H$_{17}$N: C, 84.37; H, 8.60; N, 7.03. Found: C, 84.42; H, 8.77; N, 7.01.

3.3.4. 9-Allyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole (9d). IR (neat): 1660, 1640, 1610 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ: 2.55 (tt, 2H, *J* = 7.2, 7.3 Hz), 2.92 (t, 2H, *J* = 7.3 Hz), 3.45 (d, 2H, *J* = 5.6 Hz), 3.99 (t, 2H, *J* = 7.2 Hz), 5.00 (dd, 1H, *J* = 1.5, 10.0 Hz), 5.10 (dd, 1H, *J* = 1.7, 17.0 Hz), 6.02 (ddt, 1H, *J* = 17.0, 10.0, 5.6 Hz), 7.03 (dd, 1H, *J* = 7.8, 7.9 Hz), 7.09 (dd, 1H, *J* = 7.8, 7.9 Hz), 7.18 (d, 1H, *J* = 7.8 Hz), 7.49 (d, 1H, *J* = 7.9 Hz). ^{13}C NMR (CDCl$_3$) δ: 23.1, 27.6, 29.3, 43.3, 102.9, 109.1, 114.3, 118.4, 118.5, 119.9, 132.3, 132.4, 137.4, 141.5. HR-MS *m*/*z*: Calcd for C$_{14}$H$_{15}$N: 197.1203. Found: 197.1220.

3.3.5. 10-Allyl-6,7,8,9-tetrahydropyrido[1,2-*a*]indole (9e). ^{1}H NMR (CDCl$_3$) δ: 1.88–1.94 (m, 2H), 2.05–2.11 (m, 2H), 2.89 (t, 2H, *J* = 6.3 Hz), 3.47 (d, 2H, *J* = 6.3 Hz), 4.04 (t, 2H, *J* = 6.3 Hz), 5.01 (dd, 1H, *J* = 1.0, 10.1 Hz), 5.09 (dd, 1H, *J* = 1.0, 17.1 Hz), 5.99 (tdd, 1H, *J* = 6.3, 10.1, 17.1 Hz), 7.09 (t, 1H, *J* = 7.8 Hz), 7.15 (t, 1H, *J* = 7.8 Hz), 7.26 (d, 1H, *J* = 7.8 Hz), 7.54 (d, 1H, *J* = 8.0 Hz). ^{13}C NMR (CDCl$_3$) δ: 21.2, 22.5, 23.5, 28.5, 42.4, 107.0, 108.5, 114.2, 118.0, 119.1, 120.2, 127.9, 133.5, 136.0, 137.5. HR-MS *m*/*z*: Calcd for C$_{15}$H$_{17}$N: 211.1361. Found: 211.1353.

3.3.6. 11-Allyl-7,8,9,10-tetrahydro-6*H*-azepino[1,2-*a*]-indole (9f). ^{1}H NMR (CDCl$_3$) δ: 1.67–1.73 (m, 2H), 1.73–1.79 (m, 2H), 1.81–1.87 (m, 2H), 2.85 (t, 2H, *J* = 5.2 Hz), 3.48 (td, 2H, *J* = 1.7, 6.3 Hz), 4.15 (t, 2H, *J* = 5.8 Hz), 4.96 (qd, 1H, *J* = 1.5, 11.4 Hz), 5.03 (qd, 1H, *J* = 1.5, 17.2 Hz), 5.96 (tdd, 1H, *J* = 6.3, 11.4, 17.2 Hz), 7.03 (t, 1H, *J* = 7.8 Hz), 7.13 (dt, 1H, *J* = 1.5, 7.8 Hz), 7.25 (d, 1H, *J* = 8.0 Hz), 7.50 (d, 1H, *J* = 8.0 Hz). ^{13}C NMR (CDCl$_3$) δ: 25.5, 27.9, 28.8, 29.6, 31.2, 44.6, 107.7, 108.4, 114.1, 118.4, 118.5, 120.5, 127.6, 135.8, 138.1, 139.6. HR-MS *m*/*z*: Calcd for C$_{16}$H$_{19}$N: 225.1517. Found: 225.1526.

3.3.7. 2,3-Dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-ylaceto-nitrile (9g). Mp 99–100 °C (hexane). IR (CHCl$_3$): 2430 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ: 2.55–2.65 (m, 2H), 3.03 (t, 2H, *J* = 7.3 Hz), 3.73 (s, 2H), 4.00 (t, 2H, *J* = 6.8 Hz), 7.11 (dt, 1H, *J* = 1.0, 7.8 Hz), 7.15 (dt, 1H, *J* = 1.0, 7.8 Hz), 7.21 (d, 1H, *J* = 7.8 Hz), 7.46 (d, 1H, *J* = 7.8 Hz). ^{13}C NMR (CDCl$_3$) δ: 13.5, 23.1, 27.5, 43.7, 93.4, 109.6, 117.5, 118.1, 119.3, 120.9, 130.9, 132.3, 142.5. MS *m*/*z*: 196 (M$^+$). Anal. Calcd for C$_{13}$H$_{12}$N$_2$: C, 79.56; H, 6.16; N, 14.27. Found: C, 79.58; H, 6.25; N, 14.26.

3.3.8. 6,7,8,9-Tetrahydropyrido[1,2-*a*]indol-10-ylaceto-nitrile (9h). Mp 102–103 °C (hexane). IR (CHCl$_3$): 2428 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ: 1.91–1.97 (m, 2H), 2.06–2.12 (m, 2H), 2.94 (t, 2H, *J* = 6.3 Hz), 3.74 (s, 3H), 4.04 (t, 2H, *J* = 6.3 Hz), 7.16 (t, 1H, *J* = 7.8 Hz), 7.19 (t, 1H, *J* = 7.8 Hz), 7.28 (d, 1H, *J* = 8.0 Hz), 7.55 (d, 1H, *J* = 8.0 Hz). ^{13}C NMR (CDCl$_3$) δ: 12.7, 20.7, 22.3, 23.1, 42.3, 97.5, 108.9, 117.1, 118.2, 120.1, 121.1, 126.6, 134.6, 135.9.

MS *m/z*: 210 (M^+). Anal. Calcd for $C_{14}H_{14}N_2$: C, 79.97; H, 6.71; N, 13.32. Found: C, 79.74; H, 6.74; N, 13.20.

3.3.9. 7,8,9,10-Tetrahydro-6*H*-azepino[1,2-*a*]indol-11-ylacetonitrile (9i). Mp 102–103 °C (hexane). IR ($CHCl_3$): 2430 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.73–1.80 (m, 4H), 1.85–1.90 (m, 2H), 2.90 (t, 2H, $J=5.1$ Hz), 3.78 (s, 3H), 4.17 (t, 2H, $J=5.1$ Hz), 7.13 (t, 1H, $J=7.8$ Hz), 7.20 (dt, 1H, $J=1.5$, 7.8 Hz), 7.28 (d, 1H, $J=8.0$ Hz), 7.55 (d, 1H, $J=8.0$ Hz). ^{13}C NMR ($CDCl_3$) δ: 13.1, 25.6, 27.4, 29.3, 31.0, 44.8, 98.6, 108.9, 117.6, 118.5, 119.5, 121.4, 126.4, 135.8, 140.6. MS *m/z*: 224 (M^+). Anal. Calcd for $C_{15}H_{16}N_2$: C, 80.32; H, 7.19; N, 12.49. Found: C, 80.22; H, 7.33; N, 12.35.

3.3.10. 9-Cyclohex-2-en-1-yl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole (9j). Mp 53–54 °C (hexane). ^1H NMR ($CDCl_3$) δ: 1.62–1.71 (m, 1H), 1.72–1.83 (m, 2H9), 1.96–2.04 (m, 1H), 2.08–2.14 (m, 2H), 2.52–2.60 (m, 2H), 2.91–3.03 (m, 2H), 3.66–3.71 (m, 1H), 4.01 (t, 2H, $J=7.0$ Hz), 5.83 (s, 1H), 7.01 (t, 1H, $J=7.8$ Hz), 7.09 (t, 1H, $J=7.8$ Hz), 7.20 (d, 1H, $J=8.0$ Hz), 7.55 (d, 1H, $J=8.0$ Hz). ^{13}C NMR ($CDCl_3$) δ: 21.5, 24.1, 25.2, 27.7, 30.6, 32.7, 43.1, 109.1, 109.5, 118.2, 118.7, 119.9, 127.0, 131.0, 131.6, 132.3, 140.9. MS *m/z*: 237 (M^+). Anal. Calcd for $C_{17}H_{19}N+1/10H_2O$: C, 85.38; H, 8.09; N, 5.85. Found: C, 85.30; H, 8.22; N, 5.90.

3.3.11. *rel*-(9a*R*,10*S*)-10-Cyclohex-2-en-1-yl-9a-(9-oxa-10-borabicyclo[3.3.2]dec-10-yl)-6,7,8,9,9a,10-hexahydropyrido[1,2-*a*]indole (9k). Mp 209–210 °C (hexane/AcOEt). ^1H NMR ($CDCl_3$) δ: 0.74–0.83 (m, 1H), 1.30–2.10 (m, 24H), 2.40 (dd, 1H, $J=2.8$, 5.1 Hz), 2.91 (d, 1H, $J=2.8$ Hz), 3.51 (dt, 1H, $J=2.8$, 13.4 Hz), 3.60 (d, 1H, $J=13.4$ Hz), 4.80–4.86 (m, 1H), 5.63 (d, 1H, $J=10.3$ Hz), 5.72 (td, 1H, $J=1.8$, 10.3 Hz), 6.48 (d, 1H, $J=7.5$ Hz), 6.54 (t, 1H, $J=7.5$ Hz), 6.99 (d, 1H, $J=6.9$ Hz), 7.05 (t, 1H, $J=8.0$ Hz). ^{13}C NMR ($CDCl_3$) δ: 21.1, 21.6, 22.1, 22.6, 23.6, 24.7, 24.8, 26.9, 27.1, 31.4, 33.9, 40.2, 43.9, 56.9, 67.6, 74.3, 108.2, 116.2, 126.2, 127.3, 128.7, 130.8, 131.8, 152.8. MS *m/z*: 388, 389 (M^+). Anal. Calcd for $C_{26}H_{36}BNO+1/4H_2O$: C, 79.28; H, 9.34; N, 3.55. Found: C, 79.03; H, 9.35; N, 3.53.

3.3.12. 11-Cyclohex-2-en-1-yl-7,8,9,10-tetrahydro-6*H*-azepino[1,2-*a*]indole (9l). Mp 94–95 °C (hexane). ^1H NMR ($CDCl_3$) δ: 1.62–1.94 (m, 10H), 2.09–2.25 (m, 2H), 2.83–2.93 (m, 2H), 3.63–3.70 (m, 1H), 4.09–4.19 (m, 2H), 5.79 (d, 1H, $J=10.3$ Hz), 5.85 (td, 1H, $J=2.3$, 9.7 Hz), 6.99 (t, 1H, $J=8.0$ Hz), 7.10 (t, 1H, $J=8.0$ Hz), 7.24 (d, 1H, $J=8.4$ Hz), 7.63 (d, 1H, $J=7.8$ Hz). ^{13}C NMR ($CDCl_3$) δ: 23.0, 25.2, 25.4, 28.2, 29.5, 31.2, 31.7, 33.7, 44.4, 108.4, 114.0, 118.1, 119.4, 120.2, 126.9, 127.0, 132.5, 135.8, 139.0. MS *m/z*: 265 (M^+). Anal. Calcd for $C_{19}H_{23}N+1/10H_2O$: C, 85.40; H, 8.75; N, 5.24. Found: 85.24; H, 8.72; N, 5.16.

3.3.13. Methyl (2*E*)-4-(2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)but-2-enoate (9m). IR ($CHCl_3$): 1710, 1648 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.50–2.65 (m, 2H), 2.92 (t, 2H, $J=7.5$ Hz), 3.60 (d, 2H, $J=6.3$ Hz), 3.69 (s, 3H), 4.04 (t, 2H, $J=6.8$ Hz), 5.84 (td, 1H, $J=1.8$, 15.4 Hz), 7.05 (t, 1H, $J=7.8$ Hz), 7.10–7.19 (m, 2H), 7.21 (d, 1H, $J=8.0$ Hz), 7.43 (d, 1H, $J=8.0$ Hz). ^{13}C NMR ($CDCl_3$) δ: 23.3, 27.8, 27.9, 43.7, 51.4, 100.9, 109.5, 118.3, 118.9, 120.4, 120.9, 132.1, 132.6, 142.2, 148.1, 167.3. MS *m/z*: Calcd for $C_{16}H_{17}NO_2$: 255.1259. Found: 255.1258.

3.3.14. Methyl (2*E*)-4-(6,7,8,9-tetrahydropyrido[1,2-*a*]indol-10-yl)-but-2-enoate (9n). Mp 84–85 °C (hexane). IR ($CHCl_3$): 1710, 1654 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.87–1.93 (m, 2H), 2.03–2.11 (m, 2H), 2.83 (t, 2H, $J=6.3$ Hz), 3.57 (dd, 2H, $J=1.7$, 6.3 Hz), 3.67 (s, 3H), 4.03 (t, 2H, $J=6.3$ Hz), 5.78 (td, 1H, $J=1.7$, 15.5 Hz), 7.08 (t, 1H, $J=7.8$ Hz), 7.14 (t, 1H, $J=7.8$ Hz), 7.25 (d, 1H, $J=8.0$ Hz), 7.43 (d, 1H, $J=8.0$ Hz). ^{13}C NMR ($CDCl_3$) δ: 21.1, 22.4, 23.4, 26.9, 42.3, 51.4, 104.8, 108.6, 117.7, 119.4, 120.5, 120.6, 127.6, 134.0, 136.0, 148.0, 167.3. MS *m/z*: 269 (M^+). Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.80; H, 7.11; N, 5.20. Found: C, 75.71; H, 6.93; N, 5.11.

3.3.15. Methyl (2*E*)-4-(7,8,9,10-tetrahydro-6*H*-azepino[1,2-*a*]indol-11-yl)but-2-enoate (9o). IR ($CHCl_3$): 1708 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.66–1.72 (m, 2H), 1.74–1.80 (m, 2H), 1.83–1.90 (m, 2H), 2.82 (t, 2H, $J=5.2$ Hz), 3.61 (dd, 2H, $J=1.7$, 6.3 Hz), 3.67 (s, 3H), 4.16 (t, 2H, $J=4.6$ Hz), 5.75 (dt, 1H, $J=1.7$, 15.5 Hz), 7.05 (t, 1H, $J=8.0$ Hz), 7.11 (dt, 1H, $J=6.3$, 15.5 Hz), 7.17 (t, 1H, $J=8.0$ Hz), 7.25 (d, 1H, $J=8.0$ Hz), 7.42 (d, 1H, $J=7.8$ Hz). ^{13}C NMR ($CDCl_3$) δ: 25.6, 27.3, 27.9, 29.5, 31.2, 42.0, 51.4, 105.6, 108.6, 118.1, 118.8, 120.7, 120.8, 127.4, 136.0, 140.2, 148.7, 167.4. MS *m/z*: Calcd for $C_{18}H_{21}NO_2$: 283.1572. Found: 283.1570.

3.3.16. (2*E*)-4-(2,3-Dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)but-2-en-1-ol (9p). IR ($CHCl_3$): 3612 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.55–2.65 (m, 2H), 2.93 (t, 2H, $J=7.5$ Hz), 3.46 (d, 2H, $J=6.9$ Hz), 4.03 (t, 2H, $J=6.8$ Hz), 4.09 (br s, 2H), 5.71–5.78 (m, 1H), 5.90 (ttd, 1H, $J=1.2$, 6.3, 15.5 Hz), 7.03 (dt, 1H, $J=1.0$, 7.8 Hz), 7.10 (dt, 1H, $J=1.0$, 7.8 Hz), 7.20 (d, 1H, $J=8.0$ Hz), 7.48 (d, 1H, $J=8.0$ Hz). ^{13}C NMR ($CDCl_3$) δ: 23.3, 27.7, 43.4, 63.4, 103.1, 109.2, 118.5, 120.3, 129.0, 131.6, 132.2, 132.5, 141.5. HR-MS *m/z*: Calcd for $C_{15}H_{17}NO$: 227.1310. Found: 227.1305.

3.3.17. (2*E*)-4-(6,7,8,9-Tetrahydro-1*H*-pyrido[1,2-*a*]indol-10-yl)but-2-en-1-ol (9q). IR ($CHCl_3$): 3612 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.86–1.93 (m, 2H), 2.03–2.10 (m, 2H), 2.87 (t, 2H, $J=6.9$ Hz), 3.44 (d, 2H, $J=6.3$ Hz), 4.03 (t, 2H, $J=6.3$ Hz), 4.07 (br s, 2H), 5.65–5.74 (m, 1H), 5.80–5.88 (m, 1H), 7.07 (t, 1H, $J=8.0$ Hz), 7.13 (t, 1H, $J=8.0$ Hz), 7.24 (d, 1H, $J=8.0$ Hz), 7.44 (d, 1H, $J=7.8$ Hz). ^{13}C NMR ($CDCl_3$) δ: 21.2, 22.5, 23.5, 26.9, 63.8, 107.1, 108.6, 117.9, 119.2, 120.3, 127.8, 128.8, 131.9, 133.4, 136.0. HR-MS *m/z*: Calcd for $C_{16}H_{19}NO$: 241.1466. Found: 241.1466.

3.3.18. (2*E*)-4-(7,8,9,10-Tetrahydro-6*H*-azepino[1,2-*a*]indol-11-yl)but-2-en-1-ol (9r). IR ($CHCl_3$): 3612 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.65–1.91 (m, 6H), 2.85 (t, 2H, $J=5.7$ Hz), 3.48 (d, 2H, $J=5.7$ Hz), 4.06 (d, 2H, $J=6.3$ Hz), 4.15 (t, 2H, $J=4.6$ Hz), 5.64–5.71 (m, 1H), 5.84 (td, 1H, $J=5.7$, 15.1 Hz), 7.04 (t, 1H, $J=7.8$ Hz), 7.14 (t, 1H, $J=7.8$ Hz), 7.25 (d, 1H, $J=8.0$ Hz), 7.49 (d, 1H, $J=8.0$ Hz). ^{13}C NMR ($CDCl_3$) δ: 25.6, 27.2, 28.0, 29.6, 31.2, 44.6, 63.6, 107.9, 108.5, 118.4, 118.6, 120.6, 127.5, 128.7, 132.5, 135.9, 139.6. HR-MS *m/z*: Calcd for $C_{17}H_{12}NO$: 255.1623. Found: 255.1612.

3.3.19. *rel*-(1*R*,4*S*)-4-(2,3-Dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)cyclohex-2-en-1-yl acetate (9s). Mp 101–02 °C (hexane/AcOEt). IR ($CHCl_3$): 1720 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.86–1.94 (m, 1H), 1.94–2.00 (m, 1H), 2.09 (s, 3H), 2.55–2.65 (m, 2H), 2.99 (t, 2H, $J=7.3$ Hz), 3.60–3.66 (m, 2H), 4.02 (t, 2H, $J=7.3$ Hz), 5.30–5.36 (m, 1H), 5.88 (ddd, 1H, $J=2.4$, 4.0, 10.0 Hz), 6.10 (dd, 1H, $J=2.4$, 10.0 Hz), 7.04 (t, 1H, $J=7.8$ Hz), 7.11 (t, 1H, $J=7.8$ Hz), 7.21 (d, 1H, $J=8.0$ Hz), 7.54 (d, 1H, $J=8.0$ Hz). ^{13}C NMR ($CDCl_3$) δ: 21.4, 24.2, 26.2, 27.4, 27.8, 32.9, 43.2, 67.5, 107.9, 109.3, 118.5, 118.6, 120.2, 125.1, 131.5, 132.5, 136.8, 141.1, 170.8. MS *m*/*z*: 295 (M$^+$). Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.02; H, 7.12; N, 4.49.

3.3.20. 9-(Tetrahydrofuran-2-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole (9t). Mp 72–73 °C (hexane/AcOEt). ^{1}H NMR ($CDCl_3$) δ: 2.00–2.20 (m, 3H), 2.22–2.30 (m, 1H), 2.56–2.62 (m, 2H), 2.99–3.11 (m, 2H), 3.88–3.94 (m, 1H), 4.02 (t, 2H, $J=6.9$ Hz), 4.06–4.12 (m, 1H), 5.16 (t, 1H, $J=7.4$ Hz), 7.05 (t, 1H, $J=8.0$ Hz), 7.11 (t, 1H, $J=8.0$ Hz), 7.20 (d, 1H, $J=8.0$ Hz), 7.59 (d, 1H, $J=8.0$ Hz). ^{13}C NMR ($CDCl_3$) δ: 24.2, 26.6, 27.4, 43.5, 68.0, 75.4, 106.7, 109.5, 119.0, 119.4, 120.4, 131.1, 132.9, 141.8. MS *m*/*z*: 227 (M$^+$). Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.05; H, 7.68; N, 5.99.

3.3.21. 3-(1*H*-Indol-1-yl)propan-1-ol (10a). IR ($CHCl_3$): 3616 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.56 (br s, 1H), 2.03–2.10 (m, 2H), 3.58 (t, 2H, $J=5.7$ Hz), 4.28 (t, 2H, $J=6.8$ Hz), 6.51 (d, 1H, $J=2.9$ Hz), 7.09–7.15 (m, 2H), 7.22 (t, 1H, $J=7.8$ Hz), 7.39 (d, 1H, $J=8.0$ Hz), 7.64 (d, 1H, $J=8.0$ Hz). ^{13}C NMR ($CDCl_3$) δ: 32.7, 42.7, 59.6, 101.2, 109.4, 119.4, 121.1, 121.5, 128.0, 128.7, 136.1. HR-MS *m*/*z*: Calcd for $C_{11}H_{13}NO$: 175.0997. Found: 175.0982.

3.3.22. 3-(5-Nitro-1*H*-indol-1-yl)propan-1-ol (10b). Mp 85 °C (hexane/AcOEt). IR ($CHCl_3$): 3628 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.57 (br s, 1H), 2.03–2.12 (m, 2H), 3.61 (t, 2H, $J=6.3$ Hz), 4.34 (t, 2H, $J=6.9$ Hz), 6.68 (d, 1H, $J=2.3$ Hz), 7.28 (d, 1H, $J=2.3$ Hz), 7.41 (d, 1H, $J=9.0$ Hz), 8.10 (dd, 1H, $J=1.7$, 8.6 Hz), 8.58 (d, 1H, $J=1.7$ Hz). ^{13}C NMR ($CDCl_3$) δ: 32.6, 43.1, 59.0, 104.1, 109.3, 117.3, 118.3, 127.7, 131.2, 139.0, 141.6. MS *m*/*z*: 220 (M$^+$). Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.76; H, 5.51; N, 12.89.

3.3.23. 4-(1*H*-Indol-1-yl)butan-1-ol (10c). IR ($CHCl_3$): 3624 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.50–1.55 (m, 2H), 1.68 (br s, 1H), 1.87–1.94 (m, 2H), 3.59 (t, 2H, $J=6.3$ Hz), 4.15 (t, 2H, $J=6.8$ Hz), 6.55 (d, 2H, $J=2.9$ Hz), 7.09–7.14 (m, 2H), 7.22 (t, 1H, $J=8.0$ Hz), 7.36 (d, 1H, $J=8.0$ Hz), 7.64 (d, 1H, $J=7.8$ Hz). ^{13}C NMR ($CDCl_3$) δ: 26.8, 30.1, 46.2, 62.3, 101.1, 109.5, 119.4, 121.1, 121.5, 127.9, 128.7, 136.0. HR-MS *m*/*z*: Calcd for $C_{12}H_{15}NO$: 189.1154. Found: 189.1166.

3.3.24. 5-(1*H*-Indol-1-yl)pentan-1-ol (10d). IR ($CHCl_3$): 3620 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.35–1.40 (m, 2H), 1.53–1.60 (m, 2H), 1.83–1.90 (m, 2H), 3.60 (t, 2H, $J=6.3$ Hz), 4.13 (t, 2H, $J=6.8$ Hz), 6.49 (d, 1H, $J=2.9$ Hz), 7.08–7.12 (m, 2H), 7.21 (t, 1H, $J=8.0$ Hz), 7.34 (d, 1H, $J=8.0$ Hz), 7.63 (d, 1H, $J=7.8$ Hz). ^{13}C NMR ($CDCl_3$) δ: 23.4, 30.2, 32.4, 46.4, 62.7, 101.0, 109.4, 119.3, 121.1, 121.4, 127.9, 128.7, 136.0. HR-MS *m*/*z*: Calcd for $C_{13}H_{17}NO$: 203.1310. Found: 203.1295.

3.4. General procedure for the preparation of 13, 14 and 17

The reaction using **11** was carried out according to the procedure for the prepatation of **8**. Hydroboration of **11b** with 9-BBN was effected under reflux for 2 h.

3.4.1. 2-Methyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole (13a). Mp 58–59 °C (hexane/AcOEt). ^{1}H NMR ($CDCl_3$) δ: 1.29 (d, 3H, $J=6.9$ Hz), 2.63 (dd, 1H, $J=6.9$, 15.9 Hz), 3.04–3.14 (m, 1H), 3.19 (dd, 1H, $J=8.0$, 15.9 Hz), 3.62 (dd, 1H, $J=6.3$, 9.7 Hz), 4.22 (dd, 1H, $J=7.4$, 9.7 Hz), 6.15 (s, 1H), 7.05 (dt, 1H, $J=1.0$, 7.8 Hz), 7.11 (td, 1H, $J=1.0$, 7.8 Hz), 7.21 (d, 1H, 8.0 Hz), 7.54 (d, 1H, $J=8.0$ Hz). ^{13}C NMR ($CDCl_3$) δ: 19.7, 33.0, 37.3, 50.9, 92.6, 109.3, 119.1, 120.2, 120.3, 132.8, 132.9, 144.2. MS *m*/*z*: 171 (M$^+$). Anal. Calcd for $C_{12}H_{13}N$: C, 84.17; H, 7.65; N, 8.18. Found: C, 84.15; H, 7.64; N, 8.16.

3.4.2. 2-Phenyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole (13b). ^{1}H NMR ($CDCl_3$) δ: 3.17 (dd, 1H, $J=7.5$, 15.9 Hz), 3.50 (dd, 1H, $J=8.0$, 15.9 Hz), 4.09 (dd, 1H, $J=6.8$, 9.9 Hz), 4.15–4.22 (m, 1H), 4.51 (dd, 1H, $J=8.1$, 9.9 Hz), 6.27 (s, 1H), 7.13 (t, 1H, $J=7.8$ Hz), 7.18 (t, 1H, $J=7.8$ Hz), 7.26–7.33 (m, 4H), 7.35–7.40 (m, 2H), 7.63 (d, 1H, $J=8.0$ Hz). ^{13}C NMR ($CDCl_3$) δ: 33.3, 47.9, 51.1, 93.0, 109.5, 119.4, 120.5, 120.6, 127.1, 127.2, 129.0, 132.9, 133.2, 142.9, 143.6. HR-MS *m*/*z*: Calcd for $C_{17}H_{15}N$: 233.1204. Found: 233.1210.

3.4.3. 3-(1*H*-Indol-1-yl)-2-methylpropan-1-ol (14a). IR ($CHCl_3$): 3624 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 0.97 (d, 3H, $J=6.9$ Hz), 1.37 (br s, 1H), 2.20–2.29 (m, 1H), 3.49 (d, 2H, $J=4.0$ Hz), 3.99 (dd, 1H, $J=6.9$, 14.3 Hz), 4.24 (dd, 1H, $J=6.9$, 14.3 Hz), 7.17–7.12 (m, 2H), 7.20 (t, 1H, $J=8.0$ Hz), 7.38 (d, 1H, $J=8.0$ Hz), 7.63 (d, 1H, $J=8.0$ Hz). ^{13}C NMR ($CDCl_3$) δ: 15.0, 36.9, 49.0, 65.1, 101.2, 109.6, 119.3, 121.0, 121.5, 128.6, 136.4. HR-MS *m*/*z*: Calcd for $C_{12}H_{15}NO$: 189.1154. Found: 189.1153.

3.4.4. 3-(1*H*-Indol-1-yl)-2-phenylindole (14b). IR ($CHCl_3$): 3624 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.42 (br s, 1H), 3.31–3.38 (m, 1H), 3.78 (br s, 2H), 4.33 (dd, 1H, $J=6.9$, 14.4 Hz), 4.59 (dd, 1H, $J=8.0$, 14.4 Hz), 6.42 (d, 1H, $J=3.5$ Hz), 6.92 (d, 1H, $J=3.5$ Hz), 7.10 (t, 1H, $J=7.8$ Hz), 7.18–7.23 (m, 3H), 7.25–7.31 (m, 1H), 7.31–7.39 (m, 3H), 7.62 (d, 1H, $J=8.0$ Hz). ^{13}C NMR ($CDCl_3$) δ: 48.3, 48.7, 64.1, 101.3, 109.5, 119.5, 121.1, 121.6, 127.5, 128.1, 128.5, 128.7, 129.0, 136.2, 139.9. HR-MS *m*/*z*: Calcd for $C_{17}H_{17}NO$: 251.1301. Found: 231.1304.

3.4.5. 1-Allyl-1,3-dihydro-2*H*-indol-2-one (17). IR (neat): 1708 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 3.55 (s, 2H), 4.34 (dt, 2H, $J=5.1$, 1.5 Hz), 5.21 (dd, 1H, $J=1.0$, 10.3 Hz), 5.23 (dd, 1H, $J=1.0$, 17.1 Hz), 5.84 (tdd, 1H, $J=5.1$, 10.3, 17.1 Hz), 6.81 (d, 1H, $J=7.8$ Hz), 7.02 (dt, 1H, $J=1.0$, 7.8 Hz), 7.23 (t, 1H, $J=7.8$ Hz), 7.24 (d, 1H, $J=8.0$ Hz). ^{13}C NMR ($CDCl_3$) δ: 35.7, 42.2, 108.9, 117.5, 122.3, 124.3, 124.4, 127.7, 131.4, 144.3, 174.7. HR-MS *m/z*: Calcd for $C_{11}H_{11}NO$: 173.0840. Found: 173.0822.

3.5. Procedure for the preparation of 9a, 20, 10e and 21 from 18

Conversion of **18a** to **9a** (40%) and **10a** (13%) was carried out according to the procedure for the preparation of **8**.

Reaction using **18b** was effected as follows: to a solution of **18b** (430 mg, 2 mmol) in THF (10 mL), 9-BBN (0.5 M solution in THF, 2.2 mmol) was added at room temperature under an argon atmosphere, and the mixture was stirred for 1.5 h. Sodium methoxide (118 mg, 2.2 mmol) was added to the mixture, and after stirring for 30 min, LDA (4.4 mmol) was added to the mixture at −78 °C. After stirring for 1 h, the mixture was gradually raised to room temperature, and stirred for 4 h. To the reaction mixture, 20% NaOH (10 mL) and 30% H_2O_2 (2 mL) were added under ice-cooling and the whole was stirred for 30 min. The mixture was diluted with ethyl acetate (100 mL), washed with brine, and dried over $MgSO_4$. The solvent was removed, and the residue was separated by MPLC to give **20** (69 mg, 16%) (with hexane/AcOEt = 50:1) and **21** (47 mg, 10%) (with hexane/AcOEt = 1:1).

3.5.1. 3-(1*H*-3-Methylindol-1-yl)propan-1-ol (10e). IR ($CHCl_3$): 3624 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 2.01–2.07 (m, 2H), 2.32 (s, 3H), 3.58–3.63 (m, 2H), 4.21 (t, 2H, $J=6.3$ Hz), 6.88 (s, 1H), 7.09 (t, 1H, $J=7.8$ Hz), 7.19 (t, 1H, $J=7.8$ Hz), 7.33 (d, 1H, $J=8.0$ Hz), 7.56 (d, 1H, $J=8.0$ Hz). ^{13}C NMR ($CDCl_3$) δ: 9.6, 32.8, 42.3, 59.7, 109.1, 110.4, 118.6, 119.1, 121.4, 125.6, 128.8, 136.4. HR-MS *m/z*: Calcd for $C_{12}H_{15}NO$: 189.1154. Found: 189.1142.

3.5.2. Methyl 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylate (20). Mp 92–93 °C (hexane). IR (neat): 1686 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 2.61–2.70 (m, 2H), 3.29 (t, 2H, $J=7.5$ Hz), 3.89 (s, 3H), 4.11 (t, 2H, $J=5.8$ Hz), 7.18–7.28 (m, 3H), 8.09 (d, 1H, $J=8.0$ Hz). ^{13}C NMR ($CDCl_3$) δ: 26.2, 26.7, 44.5, 50.8, 99.5, 109.9, 121.5, 121.7, 121.8, 130.9, 132.7, 152.9, 166.0. HR-MS *m/z*: 215 (M^{+}). Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: 72.53; H, 6.11; N, 6.46.

3.5.3. Methyl 1-(3-hydroxypropyl)-1*H*-indole-3-carboxylate (21). IR (neat): 1690 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.65 (br s, 1H), 2.03–2.11 (m, 2H), 3.60 (t, 2H, $J=5.8$ Hz), 3.90 (s, 3H), 4.32 (t, 2H, $J=6.3$ Hz), 7.25–7.29 (m, 2H), 7.39–7.42 (m, 1H), 8.15–8.19 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 32.1, 43.2, 51.1, 59.0, 107.1, 110.0, 121.8, 121.9, 122.8, 126.7, 134.6, 136.6, 165.7. HR-MS *m/z*: $C_{13}H_{15}NO_3$: 233.1051. Found: 233.1042.

3.5.4. *rel*-(9*R*,9a*S*)-9-Allyl-9a-(9-borabicyclo[3.3.1]non-9-yl)-9-methyl-2,3,9,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]-indole (22). To a solution of **18a** (342 mg, 2 mmol) in THF (10 mL), 9-BBN (0.5 M solution in THF, 2.2 mmol) was added at room temperature under an argon atmosphere, and the mixture was stirred for 1.5 h. Sodium methoxide (118 mg, 2.2 mmol) was added to the mixture, and after stirring for 30 min, TMEDA (0.6 mL, 4.4 mmol) and *tert*-BuLi (1.5 M solution in pentane, 4.4 mmol) were added to the mixture at −20 °C. After stirring for 2 h, the mixture was gradually raised to room temperature, and stirred for 4 h. To the reaction mixture, allyl bromide (605 mg, 5 mmol) was added and the mixture was stirred at room temperature overnight. The mixture was diluted with ethyl acetate (100 mL), washed with brine, and dried over $MgSO_4$. The solvent was removed, and the residue was separated by MPLC (hexane/AcOEt = 100:1) to give **22** (232 mg, 35%).

Mp 127–128 °C (hexane/AcOEt). ^{1}H NMR ($CDCl_3$) δ: 0.03 (br s, 1H), 0.71 (br s, 1H), 1.22 (s, 3H), 1.15–1.35 (m, 1H), 1.38–1.88 (m, 13H), 2.03 (dd, 1H, $J=7.4$, 12.6 Hz), 2.10–2.20 (m, 1H), 2.29 (dd, 1H, $J=9.7$, 13.2 Hz), 2.64 (td, 1H, $J=2.3$, 13.2 Hz), 3.06 (dt, 1H, $J=6.8$, 11.4 Hz), 3.35 (t, 1H, $J=9.7$ Hz), 5.12 (d, 1H, $J=10.1$ Hz), 5.16 (d, 1H, $J=17.2$ Hz), 5.96 (dtd, 1H, $J=4.6$, 10.1, 17.2 Hz), 6.98 (dd, 1H, $J=1.7$, 8.3 Hz), 7.05 (dd, 1H, $J=1.7$, 7.8 Hz), 7.10–7.17 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 21.0, 23.4, 24.1, 26.6, 26.8, 31.6, 31.9, 32.7, 33.7, 43.1, 48.7, 52.1, 117.2, 117.9, 123.1, 125.7, 126.8, 136.7, 146.6, 148.2. MS *m/z*: 332, 333 (M^{+}). Anal. Calcd for $C_{23}H_{32}BN$: C, 82.87; H, 9.67; N, 4.20. Found: C, 82.74; H, 9.77; N, 4.16.

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References and notes

1. (a) Brown, H. C. *Organic Synthesis via Boranes*; Wiley: New York, 1975. (b) Vaultier, M.; Carboni, B. Boron. In Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Comprehensive Organometallic Chemistry II; Pergamon Press: London, 1995; Vol. 11, pp 191–276. (c) Suzuki, A.; Brown, H. C.; Organic Synthesis via Boranes, Suzuki Coupling; Aldrich Chemical: Milwaukee, 2003; Vol. 3.
2. (a) Brown, H. C. The rich chemistry of vinylic organoboranes. In *Organic Synthesis Today and Tomorrow*; Trost, B. M., Hutchinson, C. R., Eds.; Pergamon, 1980; pp 121–137. (b) Negishi, E.; Idacavage, M. J. *Org. React.* **1985**, *33*, 1–246.
3. (a) Hawthrone, M. F. *J. Am. Chem. Soc.* **1960**, *82*, 1886–1888. (b) Binger, P.; Koster, R. *Tetrahedron Lett.* **1961**, 156–160. (c) Brown, H. C.; Rhodes, S. P. *J. Am. Chem. Soc.* **1969**, *91*, 4306–4308. (d) Merrill, R. E.; Allen, J. L.; Abramovitch, A.; Negishi, E. *Tetrahedron Lett.* **1977**, 1019–1022.
4. Ishikura, M. *Curr. Org. Chem.* **2002**, *6*, 507–521.
5. Ishikura, M.; Kato, H. *Tetrahedron* **2002**, *58*, 9827–9838.
6. (a) Verboom, W.; Reinhoudt, D. N. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 199–213. (b) Kozikowski, A. P.; Ma, D. *Tetrahedron Lett.* **1991**, *28*, 3317–3320. (c) Ziegler, F. E.; Jeroncic, L. O. *J. Org. Chem.* **1991**, *56*, 3479–3486. (d) Markgraf, J. H.; Snyder, S. A.; Vosburg, D. A. *Tetrahedron Lett.* **1998**, *39*, 1111–1112. (e) Esmaeili, A. A.; Kheybari, H. *J. Chem. Res., Synop.* **2002**, 456–466. (f) Colandrea, V. J.; Rajaraman, S.; Jimenez, L. S. *Org. Lett.* **2003**, *5*, 785–787. (g) Katritzky, A. R.; Verma, A. K.; He, H. Y.; Chandra, R.

J. Org. Chem. **2003**, *68*, 4938–4940. (h) Vigushin, D. M.; Brooke, G.; Willows, D.; Coobes, R. C.; Moody, C. J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3661–3663. (i) Coleman, R. S.; Felpin, F. X.; Chen, W. *J. Org. Chem.* **2004**, *69*, 7309–7316. (j) Sechi, M.; Mura, A.; Sannia, L.; Orecchioni, M.; Paglietti, G. *ARKIVOC* **2004**, 97–106.

7. Ishikura, M.; Terashima, M. *Tetrahedron Lett.* **1992**, *33*, 6849–6852.
8. (a) Chen, K.; Koser, G. F. *J. Org. Chem.* **1991**, *56*, 5764. (b) Gao, P.; Portoghese, P. S. *J. Org. Chem.* **1995**, *60*, 2276.
9. Moriaty, R. M.; Prakash, O. *Org. React.* **2001**, *57*, 327–415.
10. Schweizer, E. E.; Light, K. N. *J. Org. Chem.* **1966**, *31*, 870–872.
11. Yamada, Y.; Yanagi, H.; Okada, H. *Agric. Biol. Chem.* **1974**, *38*, 381–386.
12. Bit, R. A.; Davis, P. D.; Hill, C. H.; Keech, E.; Vesey, D. R. *Tetrahedron* **1991**, *47*, 4645–4664.
13. Bailey, A. S.; Scott, P. W.; Vandrevala, M. H. *J. Chem. Soc., Perkin Trans. 1* **1980**, 97–101.

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Asymmetric Diels–Alder reactions with hydrogen bonding heterogeneous catalysts and mechanistic studies on the reversal of enantioselectivity

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Abstract—Chiral bis(oxazoline) complexes of Cu(II), Zn(II) and Mg(II) have been immobilized on silica support via hydrogen-bonding interactions. Up to 93% ee is obtained in the Diels–Alder reaction between 3-((*E*)-2-butenoyl)-1,3-oxazolin-2-one and cyclopentadiene at room temperature with the heterogeneous bis(oxazoline) complexes, and the catalysts can be recycled without losing enantioselectivity. Experimental and theoretical studies show that the reversal of the absolute product configuration upon immobilization of the PhBOX-Cu(II) catalyst is triggered by the anion dissociation from Cu(II) onto the surface of the support.

1. Introduction

Enantioselective reactions catalyzed by chiral Lewis acid complexes are of great importance for the production of enantiopure pharmaceuticals and chemicals.[1] Among various chiral Lewis acid catalysts, those containing the chiral bis(oxazoline) (BOX) ligands have shown many applications in the last decade or so.[1,2] Particularly, excellent enantioselectivities have been obtained in DA reactions using this type of the complexes.[2,3] However, relatively large amounts of the chiral catalysts (1–10 mol%) are generally required, which makes recovery and recycling of the catalyst necessary. A number of strategies have therefore been designed and employed to immobilize and recycle the complexes of BOX ligands;[4] these include covalent bonding to organic polymers and inorganic supports,[5,6] non-covalent immobilization by the interaction between cationic BOX-based metal complexes and anionic supports,[7,8] and the use of solvents of special properties such as ionic liquids.[9] Non-covalent immobilization is usually a convenient and also an industrially relevant method.[10] However, few examples of non-covalently immobilized BOX systems have been reported or known to be effective for the DA reactions at present. Mayoral et al. exchanged the BOX-M(II) (M = Cu, Mg, Zn) complexes onto laponite clays and nafion–silica nanocomposites for a benchmark DA reaction; but the ee was low ($\leq 11\%$).[8a] Hutchings et al. exchanged zeolite and mesoporous materials (MCM-41, Al-SBA-15, MSU-2) with $Cu(OAc)_2$ to obtain Cu(II)-exchanged materials, then modified the exchanged materials with chiral BOX ligands for a hetero-DA reaction. The resulting PhBOX-CuH-zeolite Y catalyst gave a higher enantioselectivity (41% ee) compared to the homogeneous analogue (20% ee) although the activity was relatively low.[8b] More recently, the immobilization of homogeneous catalysts by hydrogen bonding has been reported.[11] Parallel to our research in immobilizing BOX complexes by hydrogen bonding for the DA reactions, Klein Gebbink and co-workers reported the same strategy for similar reactions.[12] A surprising observation from these studies is that the configuration of the product changed on going from the homogeneous to the heterogeneous system. This is of both fundamental and practical significance, as it indicates that immobilization alters the active catalytic species, and both enantiomers of a product may be accessible by choosing a suitable support. However, the origin of the

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Keywords: Configuration; Diels-Alder reactions; Heterogeneous catalysis; Hydrogen bonding; Lewis acids.

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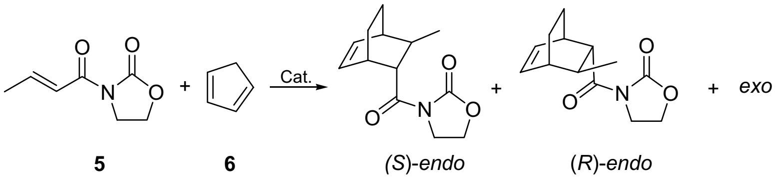
observed reversal is not yet clear, although it may be attributed to the interactions of the immobilized complexes with support surface.[8b,12] Herein we describe our results of the DA reaction of dienophile **5** with diene **6** using hydrogen bond-immobilized BOX-M(II) catalysts [Eq. 1] and the insight we gained both experimentally and computationally into the reversal of product configuration.

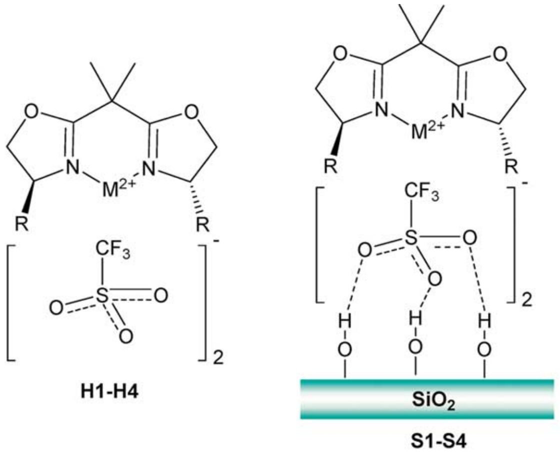


(1)

2. Results and discussion

2.1. Preparation and characterization of the catalysts

The homogeneous catalysts **H1–H4** were prepared in dichloromethane using metal triflates and 1 equiv of a BOX ligand. The corresponding supported catalysts **S1–S4** were prepared by the adsorption of complexes **H1–H4** to the surface of the silica (Fig. 1). The loading of the metal in the resulting heterogeneous catalysts is 1.0–1.1 wt% for copper and zinc, but only 0.03 wt% for magnesium. Anhydrous dichloromethane was used as the solvent for the preparation of the heterogeneous catalysts because of its dissolubility for BOX catalysts and aprotic nature (protic solvents would interfere with the adsorption).[13] Before the adsorption, the support was heated at 300 °C in order to remove the physisorbed water, which would otherwise complicate the interpretation of the results (vide infra).



Homogeneous catalysts	Corresponding supported catalysts
H1: M = Cu, R = *t*Bu	**S1**
H2: M = Cu, R = Ph	**S2**
H3: M = Zn, R = Ph	**S3**
H4: M = Mg, R = Ph	**S4**

Figure 1. The precatalysts BOX-M(II) **H1–H4** and their immobilization by hydrogen-bonding interaction.

The immobilization of the homogeneous catalysts **H1–H4** onto silica was assumed to derive from hydrogen bonding interactions between the triflate anions and surface silanol groups (Fig. 1). Direct evidence for the hydrogen bonding is obtained from IR studies. Before adsorption, the support displays a sharp peak at 3740 cm^{-1}, which can be ascribed to the stretching frequency of isolated silanols (Fig. 2a).[14] Upon adsorption of the homogeneous catalysts, the intensity of this IR band decreases considerably and only a shoulder at 3651 cm^{-1} is observed. In addition, the bending vibration of the Si–O in silanols characterized by the band at 975 cm^{-1} is red shifted to 946 cm^{-1} and becomes broad (Fig. 2b).[14] Pimentel et al. showed that hydrogen bonding results in red-shifts in the –OH stretching vibration frequency and the half-width of the band is broadened.[13] This has been confirmed by others.[11a,15] Support for the integrity of the BOX structures in **S1–S4** comes from the IR spectra (Fig. 3).

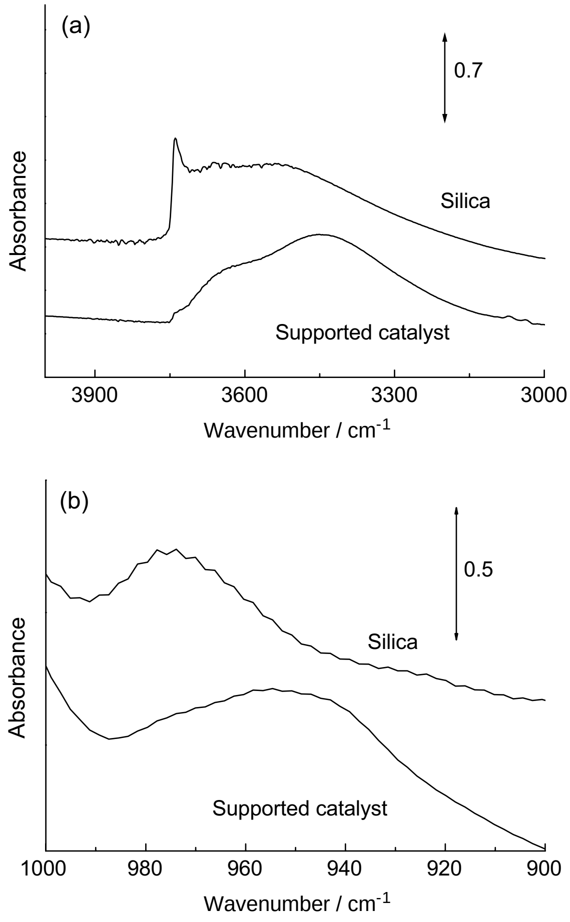


Figure 2. FTIR spectra of the stretching and the bending frequencies of the hydroxyl groups on silica before and after the immobilization of **H2**: (a) the stretching frequencies of the hydroxyl groups; (b) the bending frequencies of the hydroxyl groups.

A rather intense band at ~1630 cm^{-1} is observed, which corresponds to the C═N bond stretching and is similar to that of the homogeneous complexes (~1633 cm^{-1}). We can therefore conclude that upon adsorption of the triflates complexes **H1**–**H4** to silica, hydrogen-bonding interactions take place between silanols and sulfonate oxygen atoms, and the BOX-M(II) cations are immobilized primarily via ionic interaction.

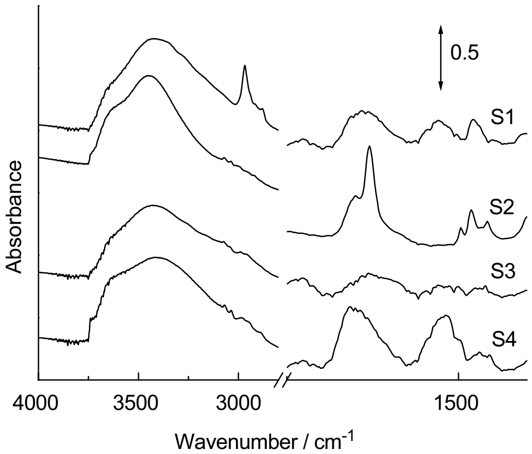


Figure 3. FTIR spectra of the supported catalysts: *t*BuBOX-Cu(II)-SiO$_2$ (**S1**), PhBOX-Cu(II)-SiO$_2$ (**S2**), PhBOX-Zn(II)-SiO$_2$ (**S3**), and PhBOX-Mg(II)-SiO$_2$ (**S4**).

2.2. Homogeneous versus heterogeneous DA reactions

For homogeneous DA reactions, better enantioselectivities are usually obtained at lower temperatures. However, practical applications of heterogeneous catalysts often need relatively high temperatures. With this in mind, the frequently used homogeneous catalysts **H1** and **H2** were initially immobilized for the DA reaction of dienophile **5** with diene **6** at room temperature [Eq. 1]. Table 1 summarizes the results obtained with **S1**, and for comparison those obtained with **H1** in homogeneous reactions are also included. As we can see, the supported catalyst displays a lower activity and enantioselectivity compared to the homogeneous analogue in dichloromethane (entries 1 and 2). This is at least partially due to leaching of copper cations into the solution, which contained 79.8 ppm copper at the time when the reaction was terminated. Nevertheless, the percentage of leaching was only 0.8%. A homogeneous experiment was carried out in which 0.8% amount of the catalyst was added and no more than 15% of conversion was observed, indicating a heterogeneous process. In contrast, an excellent enantioselectivity and enhanced activity were observed with **S1** when the less polar toluene was used as the solvent (entries 3 and 4) in which the copper leaching is reduced to 4.9 ppm. The introduction of additional substrate to the filtrate before separating the product resulted in no obvious reaction, indicating that the DA reaction we observed is heterogeneous. However, a decreased activity was observed when the heterogeneous catalyst was reused (entries 5 and 6). Based on a study by Evans et al., who showed that the hydration of **H1** brought about a detrimental effect on its activity and 3 Å molecular sieves proved effective in reactivating the catalyst,[3c] we deduced that the activity decrease could arise from the effects of moisture or copper leaching in the subsequent reactions. 3 Å molecular sieves were therefore added to the heterogeneous system and we were delighted to find that **S1** could be reused. After 3 runs, the enantioselectivity remained unchanged, although the activity decreased slightly (entries 7–9). The *endo*/*exo* ratios of **H1** and **S1** are comparable in both solvents.

The phenyl-substituted BOX ligand is known to be less enantioselective in Cu(II) catalyzed DA reactions than its *t*Bu analogue. This is also true with **S2**, as seen from Table 2. However, **S2** provides higher enantioselectivities than **H2** in all three solvents examined (Table 2, entries 1–4). This might be attributed to geometric constrains imposed on the PhBOX-Cu(II) catalyst by the silica surface.[8b,11b,c] It may also arise from the reaction occurring at the liquid–solid interface, as the enantioselectivities of related reactions are known to be solvent-dependent.[3c,16] The lower ee values observed with **H2** in toluene (3%) and ether (6%) may be also resulted from the lower solubility of the complex in the two solvents. In the case of **S1**, better enantioselectivity is obtained when toluene is used as the solvent in the heterogeneous catalysis (Table 2, entry 4). In contrast to **S1**, the phenyl-substituted **S2** affords product with the configuration opposite to that obtained with its counterpart **H2**. This is interesting, as it suggests that the DA reaction with **S2** is a heterogeneous process and more importantly, the active catalytic species are different on going from the homogeneous solution to the solid surface (vide infra).

Table 1. Homogeneous versus heterogeneous DA reactions catalyzed by the catalysts **H1** and **S1**, respectively[a]

Entry	Catalyst	Solvent	Time (h)	Conv. (%)[b]	*endo*/*exo*[c]	ee (%)[c]	Config.[d]
1	**H1**	CH$_2$Cl$_2$	8	>97[e]	89:11	90	*S*
2	**S1**	CH$_2$Cl$_2$	8	43	89:11	85	*S*
3	**H1**	Toluene	8	70	92:8	88	*S*
4	**S1**	Toluene	8	83	91:9	93	*S*
5	**S1** (1st)	Toluene	22	98	89:11	91	*S*
6	**S1** (2nd)	Toluene	22	76	92:8	92	*S*
7[f]	**S1** (1st)	Toluene	22	98	90:10	91	*S*
8[f]	**S1** (2nd)	Toluene	22	92	92:8	91	*S*
9[f]	**S1** (3rd)	Toluene	22	83	90:10	91	*S*

[a] Reactions were performed at room temperature with the ratio of catalyst/substrate = 1/10.

[b] The conversion was determined by ^{1}H NMR (400 MHz).

[c] The *endo*/*exo* ratio and the ee value of the *endo* isomer were analyzed by chiral HPLC.

[d] The configuration of the product was confirmed by comparing with the literature.[3c]

[e] There was no peak of the substrate in the ^{1}H NMR spectrum.

[f] The reaction was carried out in the presence of 3 Å molecular sieves.

Table 2. Homogeneous versus heterogeneous DA reactions catalyzed by the catalysts **H2** and **S2**, respectively[a]

Entry	Catalyst	Solvent	Conv. (%)	*endo*/*exo*	ee (%)	Config.
1	**H2**	CH_2Cl_2	100	89:11	15	*S*
2	**S2**	CH_2Cl_2	100	83:17	31	*R*
3	**S2**	Et_2O	100	90:10	21	*R*
4	**S2** (1st)	Toluene	100	83:17	42	*R*
5	**S2** (2nd)	Toluene	100	82:18	46	*R*
6	**S2** (3rd)	Toluene	98	84:16	40	*R*
7	**S2**[b]	Toluene	100	79:21	21	*R*
8	**S2**[c]	Toluene	100	83:17	36	*R*

[a] The reaction time was 22 h under the conditions the same as those given in Table 1.
[b] The silica support was calcinated at 550 °C for 4 h.
[c] The silica was firstly calcinated at 550 °C for 4 h, then refluxed in 1 M HNO_3 for 2 h and finally washed with deionized water until neutrality.

We also attempted the reuse of **S2**. Following the first run of the DA reaction in toluene, the catalyst was firstly recovered by centrifugation and then dried for the next run. However, the activity and enantioselectivity of the catalyst decreased significantly. We have tried to improve reaction by working-up under an argon atmosphere. No significant change in selectivity is found when **S2** is reused this way in toluene (Table 2, entries 4–6).

Previous results show that covering the free silanol groups on the silica increases the enantioselectivity in the DA reaction,[17] revealing the importance of the support effect. In our studies, different results are obtained. The silica involved was calcinated at 300 °C for 3 h to remove the physisorbed water. However, when the silica was calcinated at 550 °C for 4 h (corresponding to partial dehydroxylation thus less silanol groups),[14] a significant decrease in ee was observed (Table 2, entries 4 and 7). Interestingly, when the silica calcinated at 550 °C was refluxed with 1 M HNO_3 for 2 h and washed with deionized water until neutral, the resulting catalyst gave an significant improved ee value (Table 2, entry 8). By treating with the HNO_3 for 2 h, the dehydroxylated surface of silica would be partially rehydroxylated and the silanol groups regenerated,[14] and hence the ee was improved again (Table 2, entries 7 and 8). These observations suggest that the change of the silanol groups on the surface of the support can influence the enantioselectivity. This is not surprising, as the closely related DA reaction of ethyl glyoxylate with 1,3-cyclohexdiene catalyzed by **H2** has given ees depending on solvent dielectric constants.[16a] The calcination of the support alters the density of surface silanol groups and so may affect their interaction with or the 'solvation' of the BOX complex.

2.3. Mechanistic studies on the reversal of enantioselectivity

Being interested in the observed reversal of the enantioselectivity (Table 2), we decided to undertake further studies. As aforementioned, the recent reports from the groups of Hutchings and Klein Gebbink have revealed similar observations.[8b,12] However the cause for this reversal at the molecular level is still to be delineated. Such reversals in product configuration have also been noted in related homogeneous DA reactions on going from (*S*)-*t*BuBOX-Cu(II) to (*S*)-PhBOX-Cu(II) complexes.[3d,18a,19] This was a result from the BOX-Cu(II)-dienophile complexes adopting a square planar vs. a tetrahedral geometry or from π-stabilization involving the PhBOX ligand. More recently, Jørgensen has demonstrated that, a number of factors such as solvents with different dielectric constants, may have subtle influence on the geometries of the BOX-Cu(II)-dienophile intermediates.[16a]

For homogeneous asymmetric DA reactions, solvents, counterions and additives, for example, achiral ancillary ligands and molecular sieves, often influence the enantioface selection.[16a,18,20a,21] The asymmetric induction with BOX-M(II) catalysts is also dependent on the coordination geometry of the metal center,[3c,18,20] with square planar and octahedral coordination favoring α-*Si* face addition while the tetrahedral arrangement favoring α-*Re* face reaction (Fig. 4). A distorted square pyramidal geometry is expected to give the same face selection as a square planar or octahedral species.

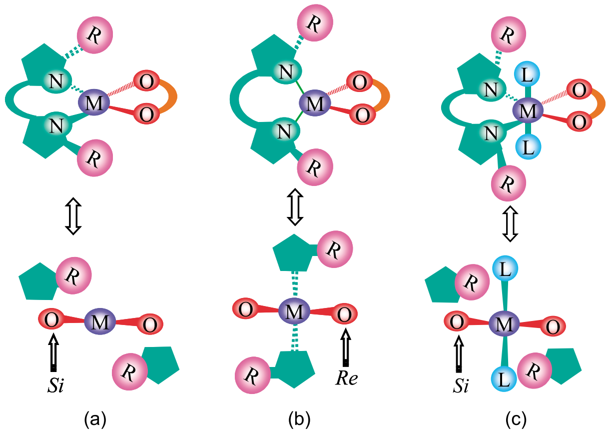


Figure 4. Effect of the BOX-M(II)-dienophile geometries on asymmetric induction: (a) planar, (b) tetrahedral, and (c) octahedral. M: metal, R: substituted group on the ring of BOX, L: coordinated anions or molecules.

Bearing solvent effects in mind, we first examined the reaction of the dienophile **5** with the diene **6** in solvents with diverse dielectric constants. As seen from Table 3, there is

Table 3. Homogeneous DA reactions catalyzed by the catalyst **H2** in different solvents at room temperature[a]

Entry	Solvent	Dielectric constant[22]	ee (%)	Config.
1	Et_2O	4.27	6	*S*
2	THF	7.52	21	*S*
3	CH_2Cl_2	8.93	15	*S*
4	MeOH	33.00	40	*S*
5	MeCN	36.64	35	*S*
6	$MeNO_2$	37.27	24	*S*

[a] The reaction time was 22 h under the conditions the same as those given in Table 1.

a correlation between the ees and the dielectric constants. Higher dielectric constants generally favor higher ees. Unlike the reaction of ethyl glyoxylate with 1,3-cyclohexadiene,[16a] there was no reversal in the product configuration. This indicates that the reversal we observed with **H2** and **S2** is less likely to be attributed solely to the change in the solvating media on going from homogeneous solution to solid surface. Because IR measurements of **S2** indicate the presence of hydrogen bondings between the triflate anions and surface silanol groups, we suggest that the reversal could simply be resulted from the dissociation of the triflate ions from Cu(II) to the surface. This hypothesis implies that the triflate is coordinated to the PhBOX-Cu(II) complexes in homogeneous reactions. However, whilst there is evidence of one triflate coordination to Cu(II) at the solid state as well as suggestion of the association of triflate with Cu(II) in catalysis,[3c,23] the literature has generally assumed that the PhBOX-Cu(II)-dienophile intermediates adopt a distorted square planar configuration with OTf^- playing little role.

To shed more light on the hypothesis that the reversal we observed resulting from the dissociation of OTf^- from the PhBOX-Cu(II) catalyst, we investigated the DA reaction catalyzed by the analogous BOX-Zn(II) and BOX-Mg(II) complexes derived from the corresponding triflates. In the absence of a coordinating ligand or counterion, the BOX-M(II)-dienophile (M = Zn, Mg) intermediates assume a tetrahedral geometry because of the lack of crystal field stabilization.[20] However, the homogeneous DA reactions catalyzed by the triflate complexes of BOX-Zn(II) and BOX-Mg(II) are consistent with OTf^- coordination, forming octahedral BOX-M(II)-dienophile intermediates.[18,20a] Thus, if immobilization leads to the removal of OTf^- from BOX-M(II) onto the surface, the heterogeneous BOX-M(II) catalysts would furnish products of opposite configuration. Table 4 summarizes the results we obtained with the catalysts **H3**, **H4** and the corresponding immobilized catalysts **S3** and **S4**. It is interesting to find that the immobilization of **H3** and **H4** did result in the reversal of enantioselectivity, providing strong support for our hypothesis above that the reversal in product configuration between **H2** and **S2** is a result of OTf^- dissociation from Cu(II) due to hydrogen bonding with the surface silanols. The lower activity observed with **S4** is due to the lower loading of magnesium in comparison with that of zinc (0.03 vs 1.0 wt%).

Table 4. Comparison of the immobilized catalysts **S3** and **S4** with the homogeneous analogues **H3** and **H4** for the DA reactions, respectively[a]

Entry	Catalyst	Solvent	Conv. (%)	*endo*/*exo*	ee (%)	Config.
1	**H3**	CH_2Cl_2	>97	89:11	22	*S*
2	**S3**	CH_2Cl_2	95	85:15	24	*R*
3	**H4**	CH_2Cl_2	95	75:15	60	*S*
4	**S4**	CH_2Cl_2	46	85:15	30	*R*

[a] The reaction time was 22 h under the conditions the same as those given in Table 1.

If anion coordination and dissociation is the cause for the product configuration reversal on going from **H2–H4** to **S2–S4**, a similar reversal is also expected when the triflate counterion of **H2–H4** is replaced with a non- or much less-coordinating anion. This is indeed the case with the PhBOX-Zn(II) and PhBOX-Mg(II) catalysts, as shown in Table 5. Thus, whilst the DA reaction catalyzed by **H3** affords the *S endo* adduct with 22% ee (entry 1) which is consistent with a octahedral Zn(II) with axial triflate coordination, the product obtained by the (*S*)-PhBOX-Zn$(SbF_6)_2$ complex has the *R* absolute configuration with 64% ee (entry 2). In the latter case, the SbF_6^- counterion is believed to be fully dissociated, giving rise to a tetrahedral Zn(II).[20c] Likewise, with less coordinating perchlorate ion, (*R*)-PhBOX-Mg(II) furnished the product with configuration opposite to that observed with the triflate complex (Table 5, entries 3 and 4).[18]

In the case of the (*S*)-*t*BuBOX catalyst **H1**, the *S endo* enantiomer is always obtained regardless of the counterion, for example, SbF_6^- (non-coordinating) or OTf^- (coordinating).[3c] Thus, on the basis of the above analysis, the catalyst **S1**, in which OTf^- dissociates due to hydrogen bonding, should give the same (*S*) *endo* enantiomer as the homogeneous **H1** does. The results obtained are fully in accordance with this prediction (Table 1, entries 1 and 2).

Applying the same argument to the (*S*)-PhBOX-Cu(II) complex, we were surprised to find that replacing the coordinating OTf^- anion with SbF_6^- and ClO_4^- did not result in the expected configuration reversal and in the case of (*S*)-PhBOX-Cu$(SbF_6)_2$, a *racemic* product was obtained (Table 5, entries 5, 6 and 8). The results obtained with (*S*)-PhBOX-Cu$(ClO_4)_2$ could be accounted for perchlorate coordination, leading to a square pyramidal or octahedral Cu(II) species and hence an adduct with *S* configuration. Although the 21-electron octahedral Cu(II) species not expected to be stable, there are a number of 5- and 6-coordinated Cu(II) complexes involving coordinated

Table 5. The DA reactions of dienophile **5** with diene **6** catalyzed by BOX-M(II) catalysts[a]

Entry	Catalyst	Time (h)	Conv. (%)	*endo*/*exo*	ee (%)	Config.
1	(*S*)-PhBOX-Zn$(OTf)_2$	22	>97	89:11	22	*S*
2[b]	(*S*)-PhBOX-Zn$(SbF_6)_2$	8	100	86:14	64	*R*
3[c]	(*R*)-PhBOX-Mg$(OTf)_2$	48	94	81:19	84	*R*
4[c]	(*R*)-PhBOX-Mg$(ClO_4)_2$	48	100	85:15	28	*S*
5	(*S*)-PhBOX-Cu$(OTf)_2$	22	100	89:11	15	*S*
6	(*S*)-PhBOX-Cu$(SbF_6)_2$	9	100	88:12	*racemic*	
7	(*S*)-PhBOX-Cu$(SbF_6)_2$ + 2 equiv H_2O	9	100	86:14	10	*S*
8	(*S*)-PhBOX-Cu$(ClO_4)_2$	2	100	86:14	28	*S*

[a] The reactions were run in CH_2Cl_2 with other conditions the same as those given in Table 1.

[b] The results were reported by Evans et al.[3c]

[c] The reactions were performed at −15 °C and were reported by Desimoni et al.[18c]

perchlorate ions.[24] However this does not explain the loss of enantioface discrimination with (*S*)-PhBOX-Cu$(SbF_6)_2$.

Enlightened by the work of Jørgensen and co-workers,[16a] and aiming to gain further insight into the observations made above and particularly into the configuration reversal encountered with **S2**, we undertook HF (Hartree–Fork) modeling of the cationic BOX-M(II)-**5** intermediates. For simplicity, the influence of the counter ions or the silanols was not considered during the calculation. The *t*BuBOX-Cu(II)-**5** and PhBOX-Zn(II)-**5** are believed to prefer square planar and tetrahedral geometry, respectively, as aforementioned. Figure 5 shows the total energies of the two cations alongside that of PhBOX-Cu(II)-**5** against the dihedral angle θ. As clearly seen, the Zn(II)-dienophile intermediate is indeed highly in favor of a tetrahedral geometry with the most stable configuration at $\theta = 80$. The energy cost on going to the perfect square planar coordination is 12.4 kcal mol^{-1} and to the tetrahedral arrangement is only 0.4 kcal mol^{-1}. In contrast, the most stable configuration for *t*BuBOX-Cu(II)-**5** is found at $\theta = 39°$, and it is significantly less energy-costly to change to the perfect square planar than to the tetrahedral geometry, 4.7 versus 9.3 kcal mol^{-1}. Thus the results from modeling confirm the speculations aforementioned, that is, the dienophile intermediate of *t*BuBOX-Cu(II) preferring square planar, and that of PhBOX-Zn(II) preferring tetrahedral in the absence of coordinating anions.

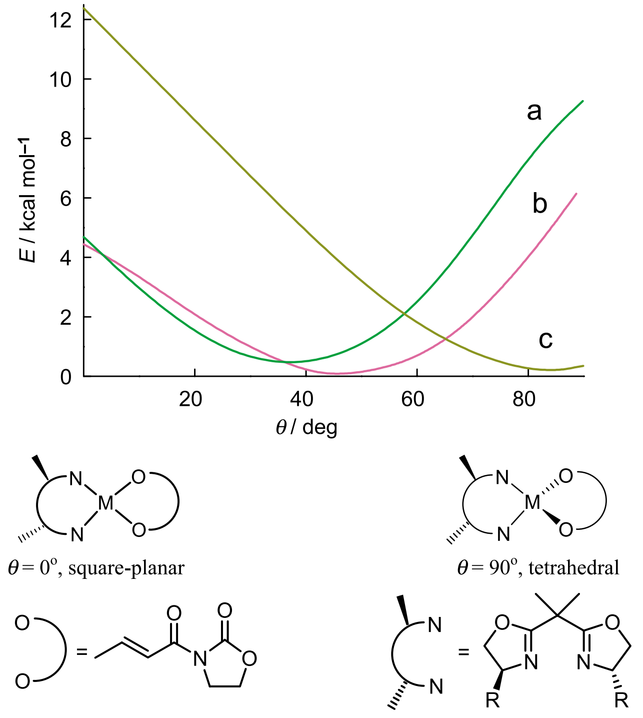


Figure 5. Calculated intermediate energies: (a) *t*BuBOX-Cu(II)-dienophile, (b) PhBOX-Cu(II)-dienophile, and (c) PhBOX-Zn(II)-dienophile. The dihedral angel θ refers to the angle between the plane of N–M–N and that of O–M–O.

Unlike those two intermediates, (*S*)-PhBOX-Cu(II)-**5** has the most stable configuration at $\theta = 46°$, right in the middle of a square planar and tetrahedral arrangement. More interestingly, the energy difference between going from the most stable state to the extreme planar and tetrahedral geometry is small, only about 1.7 kcal mol^{-1}. The energy needed for changing the dihedral angle from 46 to 80°, the most stable configuration for the tetrahedral PhBOX-Zn(II)-**5** which yields the *R endo* adduct, is 3.9 kcal mol^{-1}. This is only 0.5 kcal mol^{-1} difference from that required for a change to the square planar geometry. Such a small energy difference makes us believe that (*S*)-PhBOX-Cu(II)-**5** is flexible in configuration and is involved in a dynamic equilibrium between planar and tetrahedral geometries. This explains why the cyclization leads to a *racemic* product when the anion is non-coordinating and points to the enantioselection observed with the triflate salt of PhBOX-Cu(II) in the homogeneous DA reaction being a result of OTf^- coordination to the PhBOX-Cu(II)-dienophile species. When 2 equiv H_2O was added to the reaction catalyzed by the SbF_6^- salt, the *S endo* adduct was obtained albeit with a low 10% ee (Table 5, entry 7). This is consistent with water coordination, forming square pyramidal or octahedral Cu(II) intermediates and hence giving rise to the addition at the α-*Si* face of **5**. This may also explain the effect of support on the ees discussed earlier (Table 2, entries 7 and 8).

In the case of **S2**, in which evidence suggests that the OTf^- is dissociated, the DA reaction of **5** with cyclopentadiene **6** furnished the *R endo* adduct in 42% ee in toluene (Table 2, entry 4) instead of a *racemic* product as expected. This could be due to weak interactions between the surface Lewis acidic groups and the oxazolidinone ring oxygen of the substrate, and/or restrictions imposed by the surface on the conformations adoptable by the two phenyl rings. The formation of the *R* adduct is less likely to be purely a 'solvent' effect for an interfacial reaction, as solvents of widely different polarity did lead to the same face selection, although Jørgensen et al. found that face selection in the DA reaction of ethyl glyoxylate and 1,3-cyclohexadiene could be altered by solvents of different dielectric properties.[16a]

3. Conclusions

A series of the silica-supported heterogeneous BOX-M(II) catalysts have been successfully prepared for the DA reaction of 3-((*E*)-2-butenoyl)-1,3-oxazolin-2-one and cyclopentadiene at room temperature. The supported BOX-Cu(II) catalysts show enhanced enantioselectivities in toluene compared to their homogeneous counterparts, and it can be recycled without losing enantioselectivity. Spectroscopic evidence suggests that the immobilization of the homogeneous catalysts results from the hydrogen-bonding interactions between the triflate counterions and the surface silanol groups. Thus, as also shown by others,[11,12] hydrogen bonding can provide a simple way for the immobilization of homogeneous catalysts, which requires neither modification of the catalysts nor functionalization of the surface.

One of the most interesting observations of this study is the reversal in product configuration when the homogeneous catalyst (*S*)-PhBOX-Cu$(OTf)_2$ is immobilized. Both the experimental results and theoretical calculations indicate that the triflate counterion coordinates to Cu(II) in homogeneous reactions and the configuration reversal upon immobilization is triggered by the dissociation of the anion from the metal cation due to hydrogen-bonding interactions with the surface silanols. Since a geometric change is highly feasible of the PhBOX-Cu(II)-dienophile intermediate towards either square planar or tetrahedral configuration and a conformational rearrangement of the phenyl rings of BOX is not expected to be energy-costly, the face selection and hence the enantioselectivity can be subtly affected by a number of factors such as the surface Lewis acidic and basic groups and the restrictions imposed by the surface morphology on the conformations adoptable by the BOX ligands.

4. Experimental

4.1. General

The ^{1}H NMR spectra were recorded on a 400 MHz spectrometer with $CDCl_3$ as the solvent. Elemental analyses were carried out on an inductively coupled plasma emission spectrometer (ICP-AES). FTIR spectra of the catalysts (4000–400 cm^{-1}) were recorded on a Thermo Nicolet Impact 470 FTIR spectrometer. Self-supporting wafers of 1.3 cm were placed in an IR cell with CaF_2 windows. The wafers were purged at 60 °C for 2 h under a controlled nitrogen atmosphere with a flow rate of 60 ml min^{-1}. The spectra were obtained by scans of 64 with a resolution of 4 cm^{-1}. Theoretical calculations were performed using the Gaussian 03 program package and were carried out at the HF (Hartree–Fork) Level with 3-21G* basis set for C, O, N, H and Lanl2dz basis set for Cu and Zn. All the optimized models were based on the known crystal structures.[3c,16a] The solvent was not included in the calculation model.

4.1.1. Preparation of the heterogeneous catalysts. A BOX-M$(OTf)_2$ complex was dissolved in dichloromethane (0.28 mmol, ∼0.03 M), and the resulting solution was filtered onto the pretreated silica (530 mg) under an argon atmosphere. The suspension was stirred for 3 h at room temperature, filtered, washed with dichloromethane several times and dried in vacuum to remove the solvent.

4.1.2. Heterogeneous DA reactions. An appropriate solution of dienophile **5** (0.23 mmol, 0.23 M) was added to a supported BOX-M(II) catalyst (metal content: 0.023 mmol), and the suspension was stirred for 15 min. 12 equiv of cyclopentadiene (2.8 mmol, 182 mg) was then added. After a certain period of time the reaction was stopped, and the catalyst was separated by filtration, thoroughly washed with the same solvent and then used for the subsequent reactions. The product was isolated by filtration through silica. The conversion was determined by ^{1}H NMR. The *endo*/*exo* ratio and ee value of the *endo* isomer were analyzed by chiral HPLC [Chiralcel-OD column with hexane/ethanol (98/2) as the eluant]. The configuration of the products was confirmed by comparing with the literature.[3c]

4.1.3. Homogeneous DA reactions. An appropriate solution of dienophile **5** (0.4 mmol, ∼0.23 M) was added to a solution of BOX-M(II) catalyst (0.04 mmol, ∼0.03 M). The mixture was stirred at room temperature for 15 min, and then 12 equiv of cyclopentadiene (4.8 mmol, 317 mg) was added. After a certain period of time, the reaction was stopped and the product was isolated by filtration through silica. The conversion, *endo*/*exo* ratio and ee of the *endo* isomer were determined as described above.

4.2. Materials

2,2′-Isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] (*t*Bu-BOX) and (*S*)-2,2′-isopropylidenebis(4-phenyl-2-oxazoline) (PhBOX) were purchased from Aldrich. $Cu(OTf)_2$, $Zn(OTf)_2$ and $Mg(OTf)_2$ were purchased from Fluka. Amorphous silica (pore diameter: 9.7 nm, BET: 390 $m^2\ g^{-1}$) was commercially obtained. 3-((*E*)-2-Butenoyl)-1,3-oxazolin-2-one and the homogeneous BOX-M(II) catalysts were prepared following the literature procedures.[3b,25] Commercially available compounds were used without further purification. Solvents were dried according to standard procedures. Amorphous silica was ground, washed with 1 M HNO_3 and then with distilled water to neutrality, and dried in vacuum at 80 °C. Before use, the silica was treated in air at 300 °C for 3 h to remove the physisorbed water.

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References and notes

1. (a) *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: Weinheim, 2000. (b) *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jørgensen, K. A., Eds.; Wiley-VCH: Weinheim, 2001.
2. For reviews, (a) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1–45. (b) Jørgensen, K. A.; Johannsen, M.; Yao, S.; Audrain, H.; Thorhauge, J. *Acc. Chem. Res.* **1999**, *32*, 605–613. (c) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325–335.
3. (a) Corey, E. J.; Imai, N.; Zhang, H.-Y. *J. Am. Chem. Soc.* **1991**, *113*, 728–729. (b) Evans, D. A.; Murry, J. A.; von Matt, P.; Norcross, R. D.; Miller, S. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 798–800. (c) Evans, D. A.; Miller, S. J.; Lectka, T.; von Matt, P. *J. Am. Chem. Soc.* **1999**, *121*, 7559–7573. (d) Evans, D. A.; Johnson, J. S.; Olhava, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1635–1649.
4. For a review, Rechavi, D.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 3467–3494.
5. For examples, (a) Fernández, M. J.; Fraile, J. M.; García, J. I.; Mayoral, J. A.; Burguete, M. I.; García-Verdugo, E.; Luis, S. V.; Harmer, M. A. *Top. Catal.* **2000**, *13*, 303–309. (b) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Pitillo, M. *J. Org. Chem.* **2001**, *66*, 3160–3166. (c) Díez-Barra, E.; Fraile, J. M.; Carcía, J. I.; García-Verdugo, E.; Herrerías, C. I.; Luis, S. V.; Mayoral, J. A.; Sánchez-Verdú, P.; Tolosa, J. *Tetrahedron: Asymmetry* **2003**, *14*, 773–778.
6. For examples, (a) Corma, A.; García, H.; Moussaif, A.; Sabater, M. J.; Zniber, R.; Redouane, A. *Chem. Commun.*

2002, 1058–1059. (b) Rechavi, D.; Lemaire, M. *Org. Lett.* **2001**, *3*, 2493–2496. (c) Park, J. K.; Kim, S.-W.; Hyeon, T.; Kim, B. M. *Tetrahedron: Asymmetry* **2001**, *12*, 2931–2935.

7. (a) Fraile, J. M.; García, J. I.; Mayroal, J. A.; Tarnai, T. *Tetrahedron: Asymmetry* **1997**, *8*, 2089–2092. (b) Langham, C.; Piaggio, P.; Bethell, D.; Lee, D. F.; McMorn, P.; Bulman Page, P. C.; Willock, D. J.; Sly, C.; Hancock, F. E.; King, F.; Hutchings, G. J. *Chem. Commun.* **1998**, 1601–1602. (c) Caplan, N. A.; Hancock, F. E.; Bulman Page, P. C.; Hutchings, G. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 1685–1688.
8. (a) Fraile, J. M.; García, J. I.; Harmer, M. A.; Herrerías, C. I.; Mayoral, J. A. *J. Mol. Catal.* **2001**, *165*, 211–218. (b) Wan, Y.; McMorn, P.; Hancock, F. E.; Hutchings, G. J. *Catal. Lett.* **2003**, *91*, 145–148.
9. (a) Fraile, J. M.; García, J. I.; Herrerías, C. I.; Mayoral, J. A.; Carrié, D.; Vaultier, M. *Tetrahedron: Asymmetry* **2001**, *12*, 1891–1894. (b) Meracz, I.; Oh, T. *Tetrahedron Lett.* **2003**, *44*, 6465–6468.
10. *Chem. Eng. News: Sci. Technol.* **2004**, *82*, 37–41 and references therein.
11. (a) Bianchin, C.; Burnaby, D. G.; Evans, J.; Frediani, P.; Meli, A.; Oberhauser, W.; Psaro, R.; Sordelli, L.; Vizza, F. *J. Am. Chem. Soc.* **1999**, *121*, 5961–5971. (b) de Rege, F. M.; Morita, D. K.; Ott, K. C.; Tumas, W.; Broene, R. D. *Chem. Commun.* **2000**, 1797–1798. (c) Raja, R.; Thomas, J. M.; Jones, M. D.; Johnson, B. F. G.; Vaughan, D. E. W. *J. Am. Chem. Soc.* **2003**, *125*, 14982–14983.
12. O'Leary, P.; Krosveld, N. P.; De Jong, K. P.; van Koten, G.; Klein Gebbink, R. J. M. *Tetrahedron Lett.* **2004**, *45*, 3177–3180.
13. *The Hydrogen Bond*; Pimentel, C. C., McLellan, A. L., Eds.; 1960, 70. San Francisco and London.
14. Vansant, E. F., Van Der Voort, P., Vrancken, K. C., Eds.; *Characterization and Chemical Modification of the Silica Surface*; Elsevier: Amsterdam, 1995; Vol. 93, p 59.
15. (a) Crowell, J. E.; Beebe, T. P.; Yates, J. T., Jr. *J. Chem. Phys.* **1987**, *87*, 3668–3674. (b) Ballinger, T. H.; Yates, J. T. *J. Phys. Chem.* **1992**, *96*, 1417–1423. (c) Mawhinney, D. B.; Rossin, J. A.; Gerhart, K.; Yates, J. T., Jr. *Langmuir* **1999**, *15*, 4789–4795. (d) Panayotov, D.; Yates, J. T., Jr. *J. Phys. Chem. B* **2003**, *107*, 10560–10564.
16. (a) Thorhauge, J.; Roberson, M.; Hazell, R. G.; Jørgensen, K. A. *Chem. Eur. J.* **2002**, *8*, 1888–1898. (b) Johannsen, M.; Jørgensen, K. A. *Tetrahedron* **1996**, *52*, 7321–7328.
17. Rechavi, D.; Lemaire, M. *J. Mol. Catal. A: Chem.* **2002**, *182–183*, 239–247.
18. (a) Desimoni, G.; Faita, G.; Righetti, P. *Tetrahedron Lett.* **1996**, *37*, 3027–3030. (b) Desimoni, G.; Faita, G.; Invernizzi, A. G.; Righetti, P. *Tetrahedron* **1997**, *53*, 7671–7688. (c) Carbone, P.; Desimoni, G.; Faita, G.; Filippone, S.; Righetti, P. *Tetrahedron* **1998**, *54*, 6099–6110.
19. (a) Johannsen, M.; Jørgensen, K. A. *J. Org. Chem.* **1995**, *60*, 5757–5762. (b) Gathergood, N.; Zhuang, W.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 12517–12522. (c) Evans, D. A.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T.; Tregay, S. W. *J. Am. Chem. Soc.* **1998**, *120*, 5824–5825. (d) Evans, D. A.; Johnson, J. S.; Burgey, C. S.; Campos, K. R. *Tetrahedron Lett.* **1999**, *40*, 2879–2882.
20. (a) Takacs, J. M.; Lawson, E. C.; Reno, M. J.; Youngman, M. A.; Quincy, D. A. *Tetrahedron: Asymmetry* **1997**, *8*, 3073–3078. (b) Corey, E. J.; Ishihara, K. *Tetrahedron Lett.* **1992**, *33*, 6807–6810. (c) Evans, D. A.; Kozlowski, M. C.; Tedrow, J. S. *Tetrahedron Lett.* **1996**, *37*, 7481–7484.
21. Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1998**, *63*, 5483–5488.
22. *Handbook of Chemistry and Physics*; Lide, D. R., Ed.; CRC: New York, 1999; Chapter 6, p 148.
23. Evans, D. A.; Olhava, E. J.; Johnson, J. S.; Janey, J. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 3372–3375.
24. Gowda, N. M. N.; Naikar, S. B.; Reddy, G. K. N. *Adv. Inorg. Chem. Radiochem.* **1984**, *28*, 255–299.
25. Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238–1256.