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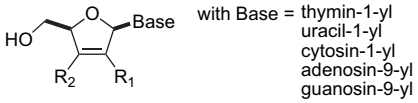
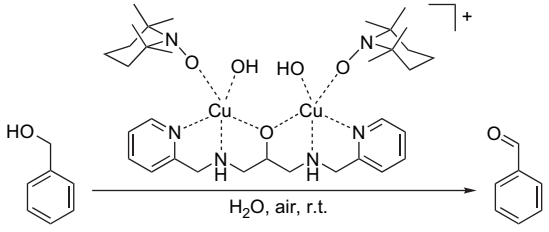
Contents

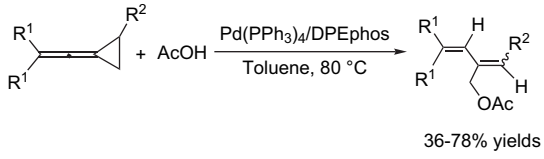
REPORT



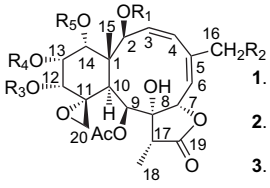
The synthesis of 2′,3′-didehydro-2′,3′-dideoxynucleosides having a branching group at either of the 2′- or 3′-positions other than a proton and branching groups at both of the 2′- and 3′-positions other than a proton is reviewed. The report contains 81 references.

ARTICLES

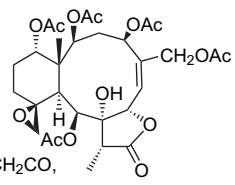




$Pd(PPh_3)_4$-catalyzed reactions of vinylidenecyclopropanes **1** with acetic acid proceeded smoothly at 80 °C in toluene to give the corresponding acetylated dienes **2** in moderate to good yields in the presence of DPEphos ligand.



1. R_1, R_3, R_4 = Ac, R_2 = Cl, R_5 = $(CH_3)_2CHCH_2CO$
2. R_1, R_4, R_5 = Ac, R_2 = Cl, R_3 = $(CH_3)_2CHCH_2CO$
3. R_1 = $(CH_3)_2CHCH_2CH_2COOCH_2CO$, R_2 = OH, R_3, R_4, R_5 = Ac
4. R_1, R_3, R_5 = Ac, R_2 = OCH_3, R_4 = $(CH_3)_2CHCH_2CO$
5. R_1, R_4 = Ac, R_2 = OCH_3, R_3, R_5 = H
6. R_1, R_4 = Ac, R_2 = OAc, R_3, R_5 = H



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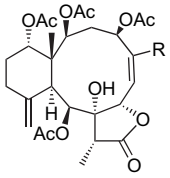
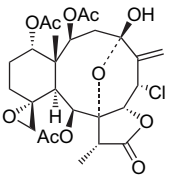


8. R = CH_2OAc
9. R = COOMe



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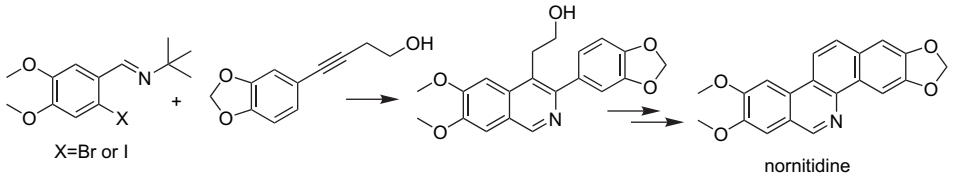
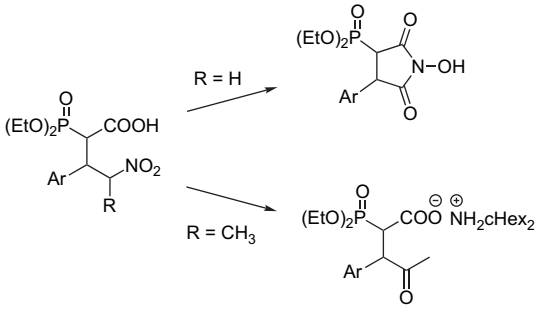
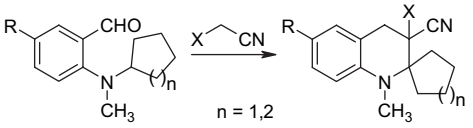
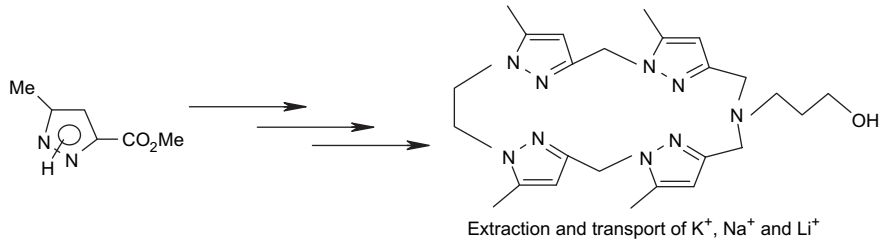
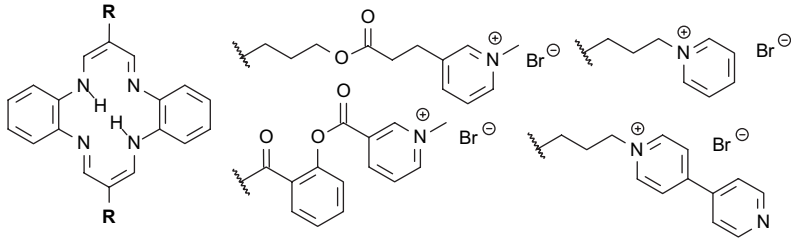
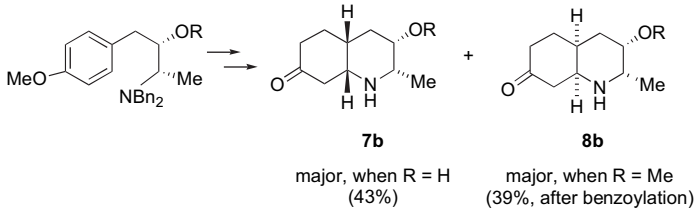


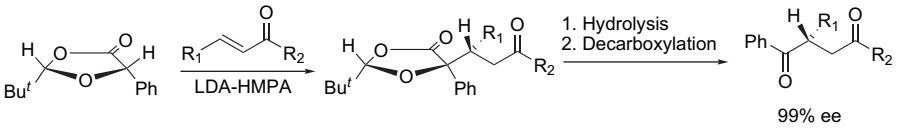


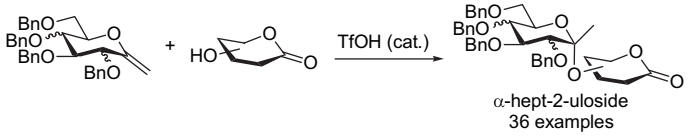


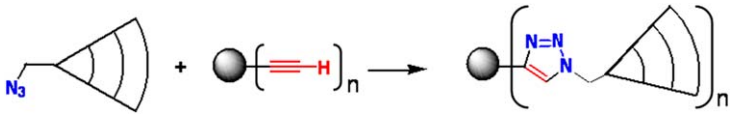




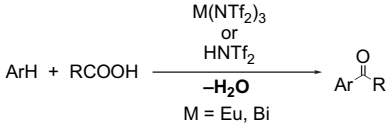


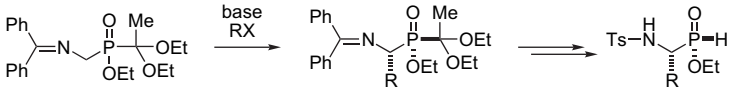


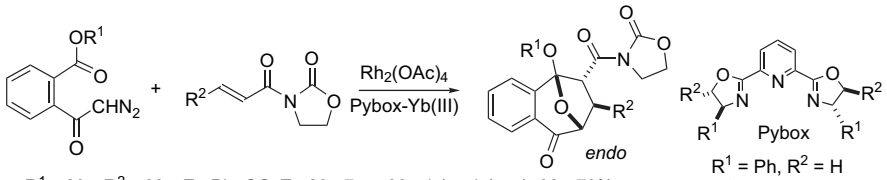




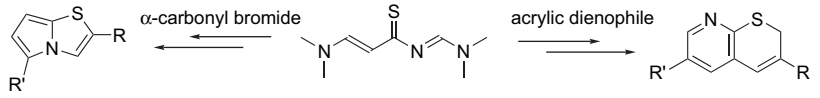
Azide-functionalized PAMAM dendrons were synthesized by the divergent method using azidopropylamine as an azide focal point and applied for the construction of symmetric PAMAM-like dendrimers containing 1,2,3-triazole rings as connectors via stitching with two multi-terminal alkynes. The stitching method was based on the click chemistry protocol, i.e., the copper-catalyzed cycloaddition reaction between an alkyne and an azide.

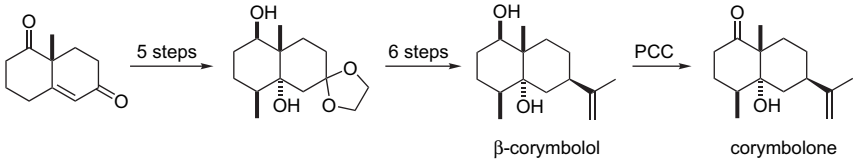


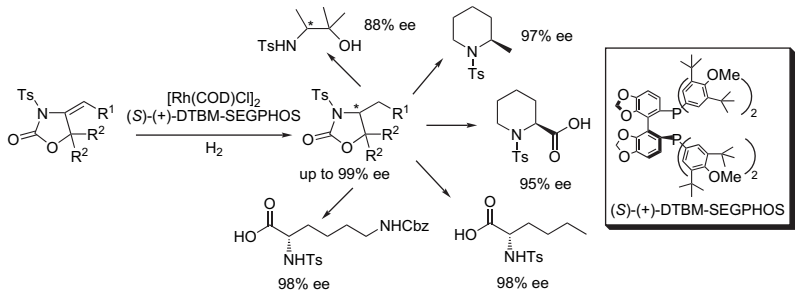


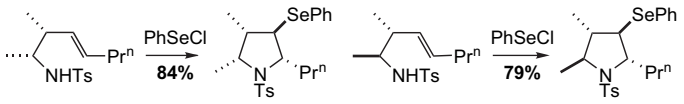


R^1 = Me, R^2 = Me, Et, Ph, CO_2Et: 93 : 7 - > 99 : 1 (*endo*/*exo*), 38 - 78% ee
R^1 = *p*-$BrC_6H_4CH_2$, R^2 = Me: > 99 : 1 (*endo*/*exo*), 96% ee

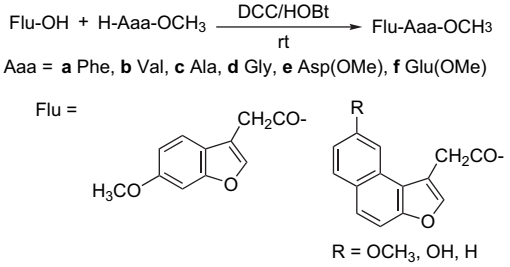


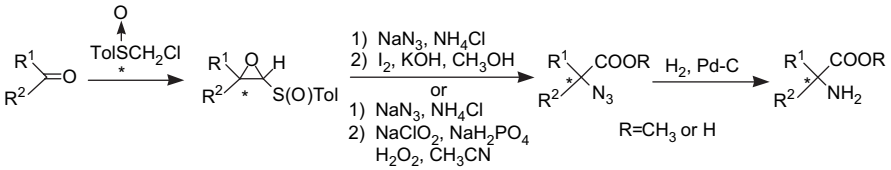


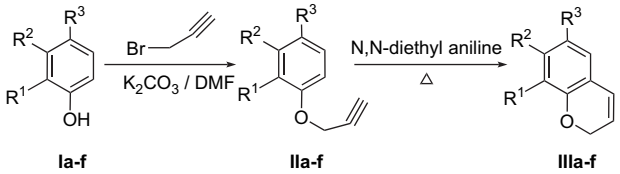


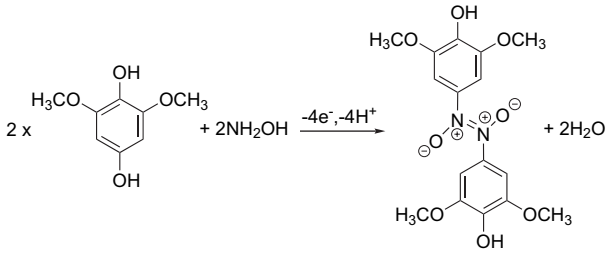


Selenocyclisations of the homoallylic sulfonamides usually proceed both very efficiently and high stereoselectively.









OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

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Synthesis of 2′,3′-didehydro-2′,3′-dideoxynucleosides having variations at either or both of the 2′- and 3′-positions

Christophe Len[a,*] and Grahame Mackenzie[b]

[a]*Synthèse et Réactivité des Substances Naturelles, UMR 6514 CNRS, Université de Poitiers, 40, Avenue du Recteur Pineau, F-86022 Poitiers Cedex, France*
[b]*Department of Chemistry, University of Hull, Hull HU6 7RX, UK*

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Contents

1. Introduction

Several nucleoside analogues have been shown to be highly effective as antiviral and antitumour agents. 2′,3′-Dideoxynucleosides (ddNs) and 2′,3′-didehydro-2′,3′-dideoxynucleosides (d4Ns), namely the nucleoside reverse transcriptase inhibitors (NRTI), form the most important class of compounds active against the human immunodeficiency virus (HIV), which causes AIDS. The NRTI approved by the US Food and Drug Administration (US FDA) for the treatment of AIDS are 3′-azido-2′,3′-dideoxythymidine (AZT, zidovudine),[1–4] 2′,3′-dideoxycytidine (ddC, zalcitabine),[5,6]

Abbreviations: ABC, (1*S*,4*R*)-4-[2-amino-6-(cyclopropylamino)-9*H*-purin-9-yl]-2-cyclopentene-1-methanol; Ac, acetyl; AD-mix, asymmetric dihydroxylation; AIBN, azobisisobutyronitrile(2,2′-azo(2-methylpropionitrile)); AIDS, acquired immunodeficiency syndrome; All, allyl; Ar, *p*-methoxyphenyl; AZT, 3′-azido-2′,3′-dideoxythymidine; bis(POC)PMPA, tenofovir disoproxil fumarate; Bn, benzyl; BSA, *N*,*O*-bis(trimethylsilyl)acetamide; Bz, benzoyl; Bu, butyl; DAST, (diethylamino)sulfur trifluoride; dba, dibenzylideneacetone; DBN, 1,5-diazabicyclo[4.3.0]non-5-ene; DBU, diazadicycloundecane; ddI, 2′,3′-dideoxyinosine; ddNs, 2′,3′-dideoxynucleosides; DEAD, diethylazodicarboxylate; DIBALH, diisobutylaluminium hydride; DMF, *N*,*N*-dimethylformamide; d4Ns, 2′,3′-didehydro-2′,3′-dideoxynucleosides; d4T, 2′,3′-didehydro-2′,3′-dideoxythymidine; ddc, 2′,3′-dideoxycytidine; DMAP, 4-dimethylaminopyridine; DMSO, dimethylsulfoxide; DMTr, dimethoxytrityl; Et, ethyl; FTC, 5-fluoro-2′,3′-dideoxy-3′-thia-β-L-cytidine; HIV, human immunodeficiency virus; HMDS, 1,1,1,3,3,3-hexamethyldisilazane; HMPA, hexamethylphosphoramide; imid, imidazol-1-yl; LTMP, lithium 2,2,6,6-tetramethylpiperidide; MCPBA, *m*-chloroperoxybenzoic acid; Me, methyl; MMTr, monomethoxytrityl; Ms, mesyl; NBS, *N*-bromosuccinimide; NMO, *N*-methylmorpholine-*N*-oxide; NMR, nuclear magnetic resonance; NRTI, nucleoside reverse transcriptase inhibitors; PCC, pyridinium chlorochromate; Ph, phenyl; Piv, pivaloyl; PTSA, *p*-toluenesulfonic acid; SAR, structure–activity relationship; TBAF, tetrabutylammonium fluoride; TBDMS, *tert*-butyldimethylsilyl; TBDPS, *tert*-butyldiphenylsilyl; 3TC, 2′,3′-dideoxy-3′-thia-β-L-cytidine; TDS, *tert*-butyldiphenylsilyl; Tf, triflate; TFA, trifluoroacetic acid; TFMTMS, trifluoromethyltrimethylsilane; TIPDS, tetraisopropyldisiloxan-1,3-diyl; TMEDA, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine; TMSOTf, trimethylsilyl triflluoromethanesulfonate; THF, tetrahydrofurane; Tr, trityl; Ts, tosyl; US FDA, US Food and Drug Administration.

* Corresponding author. Tel.: +33 5 49 36 63 89; fax: +33 5 49 45 37 02; e-mail: christophe.len@univ-poitiers.fr

0040–4020/$ - see front matter
doi:10.1016/j.tet.2006.07.050

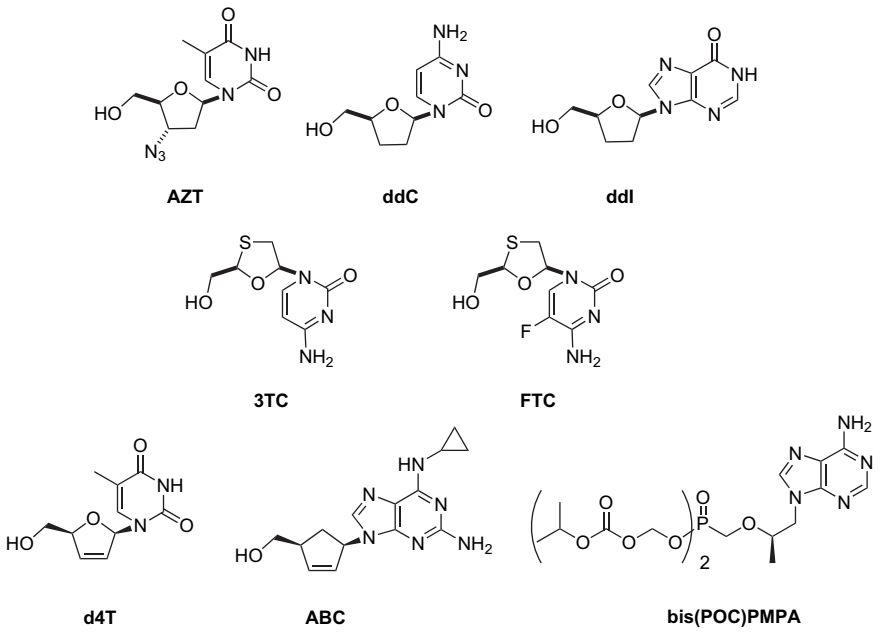


Figure 1. NRTI approved by the US FDA for the treatment of AIDS.

2′,3′-dideoxyinosine (ddI, didanosine),[7,8] 2′,3′-dideoxy-3′-thia-β-L-cytidine (3TC, lamivudine),[9,10] 5-fluoro-2′,3′-dideoxy-3′-thia-β-L-cytidine (FTC, emtricitabine),[11,12] 2′,3′-didehydro-2′,3′-dideoxythymidine (d4T, stavudine),[13,14] (1*S*,4*R*)-4-[2-amino-6-(cyclopropylamino)-9*H*-purin-9-yl]-2-cyclopentene-1-methanol (ABC, abacavir)[15–17] and bis-(POC)PMPA (tenofovir disoproxil fumarate, viread)[18,19] (Fig. 1).

The drug d4T[13,14,20–27] is a very potent and selective inhibitor of reverse transcriptase and requires anabolic activation to the 5′-triphosphate derivative by cellular kinases. Despite its approval by the US FDA, d4T shows (i) instability in acidic media due to ready glycosyl bond cleavage, which limits its usefulness as an orally bioavailable drug; (ii) side effects; and (iii) resistance arising from amino acid mutations of reverse transcriptase. In an attempt to overcome these deficiencies and provide more extensive data for a wider structure–activity relationship (SAR) to be made, a number of analogues have been synthesised with functional groups other than protons at either or both of the 2′- and 3′-positions. For the sake of clarity, this review has been arranged to describe the synthesis of 2′,3′-didehydro-2′,3′-dideoxynucleosides having (i) a branching group at either of the 2′- or 3′-positions other than a proton, and (ii) branching groups at both of the 2′- and 3′-positions other than protons. Various functionalities have been substituted at either the 2′- or 3′-position of d4Ns, which include halogeno, N_3, CF_3, CN, alkyl, alkenyl, alkynyl, aryl, thio and seleno groups. Perhaps the most sought-after targets, however, have been those possessing a fluorine atom at either of the 2′- or 3′-positions, since such substituted nucleosides are close analogues of d4T due to fluorine having a van der Waal's radius close to that of a hydrogen atom. In addition, it has been postulated that the introduction of a fluorine atom at either of the 2′- or 3′-positions of the glycone moiety could result in a stabilised glycosyl bond of d4Ns.

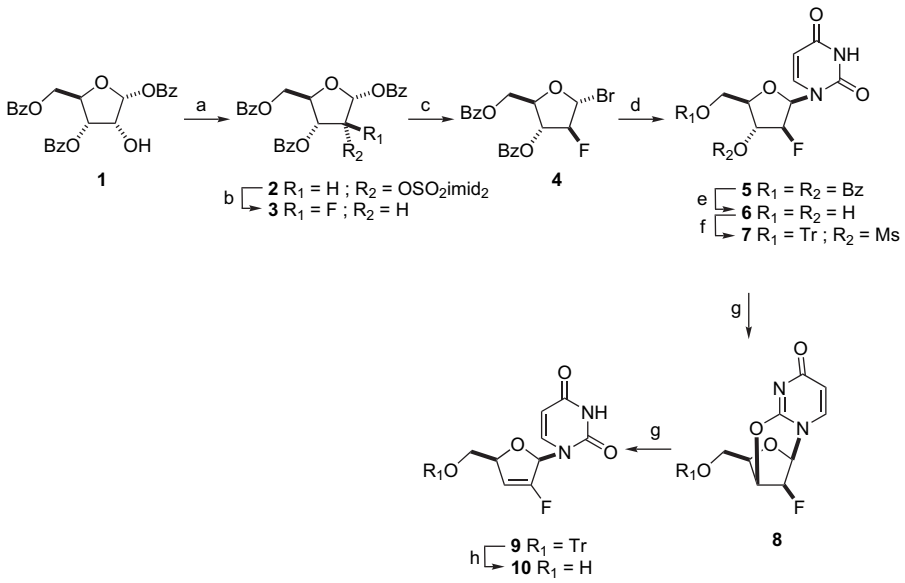
2. Synthesis of 2′- or 3′-branched 2′,3′-unsaturated nucleosides

2.1. Base-catalysed elimination

Several syntheses of 2′,3′-unsaturated nucleosides having various functional groups in either the 2′- or 3′-positions have been described, which involve base-catalysed cis- or trans-elimination. The trans-elimination can be effected with a nucleofuge (e.g., anhydro, halogen, mesyl or ester), which is either α or β to the required 2′- or 3′-branched group in the target compound. Examples of trans-eliminations in which the nucleofuge is β to either a 2′- or 3′-branched group are as follows. Martin et al. reported the synthesis of the 2′-fluoro-2′,3′-unsaturated uracil **10**[28] via the dihalogeno sugar **4**.[29] Starting from the D-ribose derivative **1**, the subsequent imidazolylsulfonate **2** was fluorinated with KHF_2 and HF to afford **3** in 63% yield, which was then converted into the dihalogeno sugar **4** in 98% yield. *N*-Glycosylation with silylated uracil gave the nucleoside **5**, which was treated with methanolic ammonia to give the fully deprotected 2′-deoxyuridine **6** in 69% yield (two steps). Treatment of **6** with trityl chloride in pyridine followed by methanesulfonyl chloride gave **7**, which, on brief treatment with aqueous sodium hydroxide, gave the anhydronucleoside **8**. With or without isolation, further treatment of **8** with sodium hydroxide gave the olefin **9**, which was deprotected with HCl in chloroform to afford the target nucleoside **10** in 35% yield (two steps) (Scheme 1).

The methodology of Horwitz et al.[30–34] has been used by different research groups to obtain **14–16** via the *O*-2,3′-anhydroxylo- derivatives **11–13** using potassium *tert*-butoxide in DMSO to deprotonate at the C-2′-position in 75–92% yields (Table 1).

Altona et al. reported the dehydrohalogenation of nucleoside analogues in basic media.[37] Starting from the D-arabinose



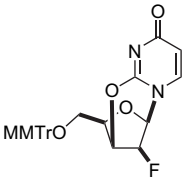
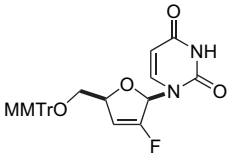
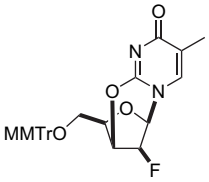
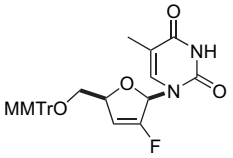
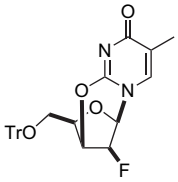
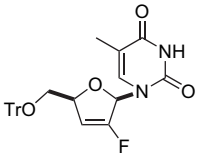
Scheme 1. Reagents and conditions: (a) NaH, $(Imid)_2SO$, DMF (85%); (b) KHF_2, butan-1,3-diol then HF, H_2O (63%); (c) HBr, AcOH, CH_2Cl_2 (98%); (d) silylated uracil, $CHCl_3$ (78%); (e) NH_3, MeOH (88%); (f) TrCl, pyridine then MsCl (86%); (g) NaOH, H_2O, EtOH (54%); (h) HCl, $CHCl_3$ (64%).

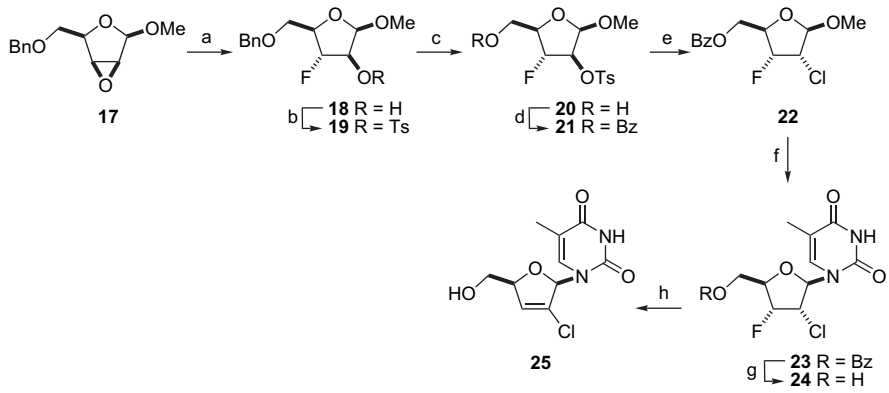
derivative **17**, treatment with KHF_2 and NaF in 1,2-ethylene glycol afforded the fluoride **18** in 31% yield.[38] Debenzylation of the tosylate **19** and subsequent benzoylation of the primary hydroxyl group in **20** provided the glycoside **21**. Replacement of the tosyloxy group of **21** by a chlorine atom using LiCl in DMSO gave the riboside **22** in 72% yield. *N*-Glycosidation of **22** with silylated thymine and subsequent deprotection of the 5′-position in **23** afforded the nucleoside **24** in 30% yield (two steps). Treatment of **24** with MeONa in methanol then gave the corresponding chloro olefin **25** in 47% yield (Scheme 2).

A similar elimination has been applied to purine nucleosides such as adenine **27** to give the target nucleoside **28** in 77% yield. It is notable that a slightly higher yield (82% vs 77%) was obtained starting from the dibenzoylated adenine derivative **26** (Scheme 3).

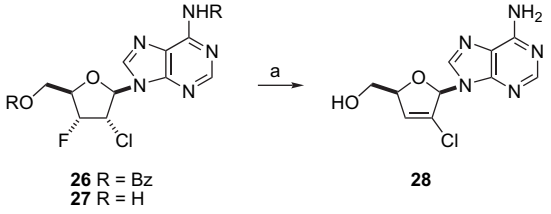
In accordance with the greater strength of the C–F bond (105.5 kcal/mol), compared to that of the C–Cl bond (78.5 kcal/mol), elimination of HCl was expected. Altona et al. suggested that a likely explanation of the HF versus HCl elimination was the conformational peculiarities of the starting nucleoside **24**. In the conformation of the D-ribofuranose ring (^{2}E: $150<P<162$), the $F_{3'}$ and $H_{2'}$ atoms are trans oriented (antiperiplanar, ap), whereas the $Cl_{2'}$ atom and $H_{1'}$ and $H_{3'}$ atoms are *gauche* arranged (synclinal, sc) (Fig. 2).

Table 1. Synthesis of 2′-fluoro nucleosides **14–16** starting from the corresponding *O*-2,3′-anhydro nucleosides **11–13**

Entry		Starting material		Olefin	Yield (%)	Refs.
1	**11**		**14**		84	35
2	**12**		**15**		75	35
3	**13**		**16**		92	36



Scheme 2. Reagents and conditions: (a) KHF_2/NaF, 1,2-ethylene glycol (31%); (b) TsCl, pyridine (89%); (c) H_2, Pd/C, EtOH (88%); (d) BzCl, pyridine (81%); (e) LiCl, DMSO (72%); (f) silylated thymine, TMSOTf, MeCN (55%); (g) NH_3, MeOH (55%); (h) MeONa, MeOH (47%).



Scheme 3. Reagents and conditions: (a) MeONa, MeOH (from **27**: 77%; from **26**: 82%).

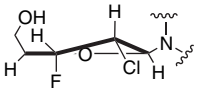
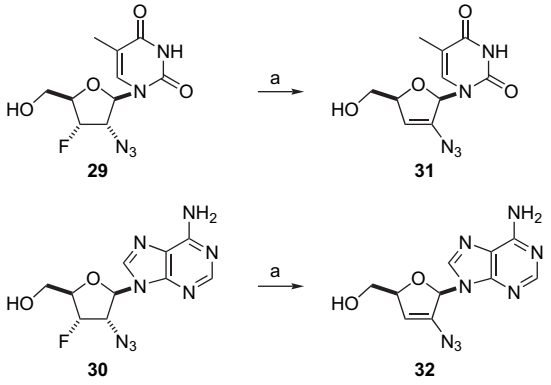


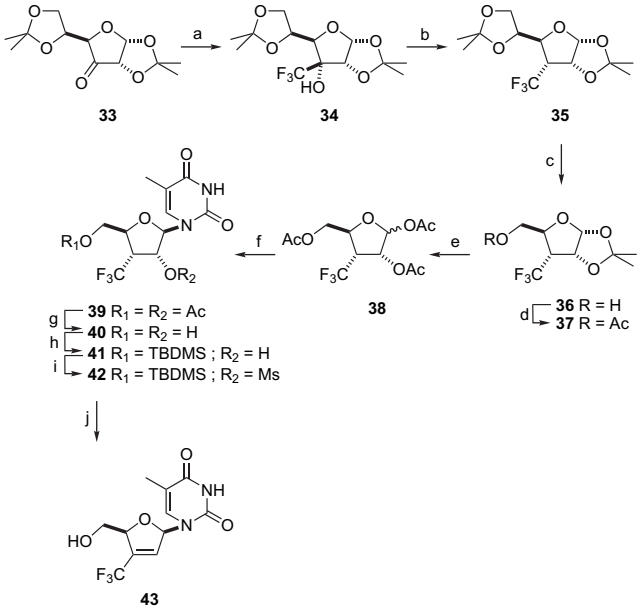
Figure 2. Conformation of the glycone moiety of the nucleoside **24**.

In accordance with the above method,[37] treatment of the nucleosides **29** and **30** afforded the vinyl azides **31** and **32** in 47% and 69% yields, respectively (Scheme 4).



Scheme 4. Reagents and conditions: (a) MeONa, MeOH (from **29**: 47%; from **30**: 69%).

Application of this strategy was described by Portella et al.[39] for the synthesis of 3′-*C*-trifluoromethyl d4T (**43**) (Scheme 5) and the d4U analogue **44** (Fig. 3). Starting from the D-glucose derivative **33**, trifluoromethylation with TFMTMS and subsequent desilylation gave the trifluoromethyl derivative **34** in 88% yield.[40] The *allo*-derivative **35** was obtained in two steps by methyloxylation and classical radical deoxygenation. Selective hydrolysis of the 5,6-ketal group on **35** followed by periodic oxidation and $NaBH_4$ reduction provided the *ribo*-derivative **36** in 68% yield (three steps). To preserve the furanose form, acetylation of the primary hydroxyl group of **36** was effected to give **37**, which, upon subsequent hydrolysis with aqueous CF_3COOH and acetylation with Ac_2O, pyridine and DMAP, yielded the two anomers **38**



Scheme 5. Reagents and conditions: (a) TFMTMS, TBAF, THF then TBAF, MeOH (88%); (b) 1. MeOCOCOCl, pyridine, CH_2Cl_2; 2. Bu_3SnH, AIBN, toluene (73%); (c) 1. H_2SO_4, MeOH, dioxane; 2. $NaIO_4$, H_2O then $NaBH_4$, H_2O, MeOH (68%); (d) Ac_2O, pyridine, CH_2Cl_2 (90%); (e) 1. CF_3COOH, H_2O; 2. Ac_2O, DMAP, pyridine (93%); (f) silylated thymine, TMSOTf, MeCN (95%); (g) MeONa, MeOH (91%); (h) TBDMSCl, DMAP, pyridine, CH_2Cl_2 (70%); (i) MsCl, pyridine, CH_2Cl_2 (100%); (j) TBAF, THF (69%).

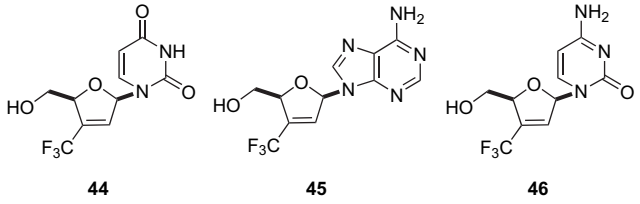
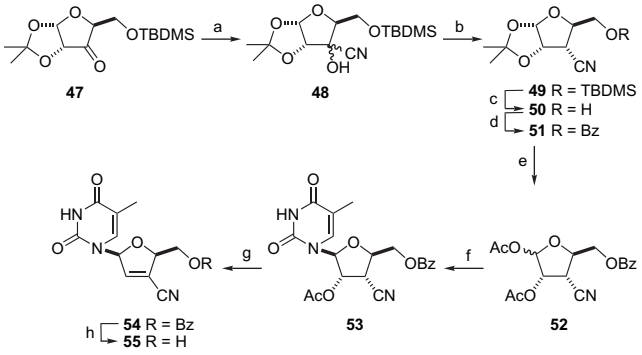


Figure 3. 3′-*C*-Trifluoromethyl nucleosides **44**–**46**.

in 84% yield (three steps). *N*-Glycosylation of the acetates **38** with silylated thymine provided the nucleoside **39**, stereospecifically, in 95% yield. After deacetylation to give **40** and selective silylation to form **41**, mesylation of **41** afforded the corresponding ester **42** in 64% yield (three steps). The elimination step was performed smoothly with TBAF, which induced desilylation and subsequent elimination leading to the target nucleoside **43** in 69% yield (Scheme 5).

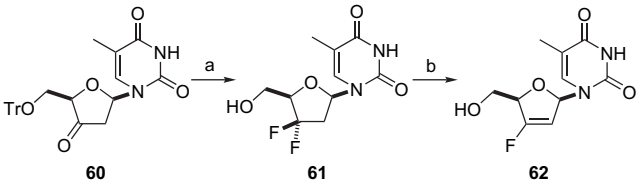
Similar eliminations were reported by Mathé et al.[41] for the synthesis of the adenosine and cytosine derivatives **45** and **46** (Fig. 3).

Chu et al. described the synthesis of different 3′-*C*-cyano-3′-deoxyribonucleosides[42] using an acetyloxy group as a nucleofuge. Treatment of the 3′-keto nucleoside **47** with NaCN in a mixture of aqueous $NaHCO_3$ and Et_2O afforded the cyanohydrin **48** as an epimeric mixture.[43] Classical Barton deoxygenation provided the 3-*C*-cyano-3-deoxy derivatives **49** and subsequent protection/deprotection steps on **50**/**51** afforded the diacetate **52** in 54% overall yield. *N*-Glycosylation with the silylated thymine afforded the nucleoside **53** stereoselectively, and this was treated with DBU and DMAP in dichloromethane to give the 2′,3′-unsaturated nucleoside **54** in 83% yield (two steps). Careful deprotection of the primary hydroxyl group afforded the target nucleoside **55** in 68% yield (Scheme 6). Introduction of uracil, cytosine, adenosine and guanosine into the diacetate **52**, followed by mild base-catalysed elimination, gave the corresponding nucleosides **56**–**59** (Fig. 4).



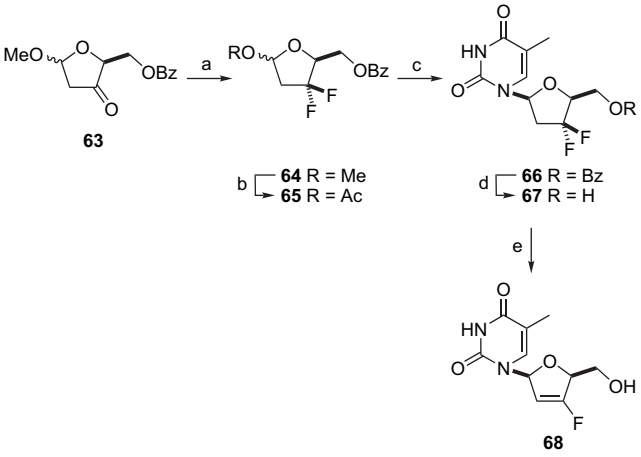
Scheme 6. Reagents and conditions: (a) Ref. 46; (b) 1. PhO(CS)Cl, DMAP, CH_2Cl_2; 2. AIBN, Bu_3SnH, toluene (68%); (c) HCl, MeOH (66%); (d) BzCl, pyridine (95%); (e) 1. TFA, H_2O; 2. Ac_2O, pyridine (90%); (f) BSA, thymine, TMSOTf, MeCN (86%); (g) DMAP, BDU, CH_2Cl_2 (96%); (h) K_2CO_3, MeOH (68%).

Examples of trans-eliminations with the nucleofuge α to either the 2′- or 3′-branched group have also been described. Herdewijn et al.[44] reported the synthesis of 3′,3′-difluoro-2′,3′-dideoxythymidine (**61**), starting from the corresponding 3′-ketothymidine **60** by treatment with DAST, similar to that described by Bergstrom.[45] Treatment of the *gem* difluoro compound **61** with sodium methoxide in anhydrous dimethylformamide yielded the target nucleoside **62** in 62% yield (Scheme 7).



Scheme 7. Reagents and conditions: (a) Ref. 45; (b) MeONa, MeOH (62%).

Chu et al. developed this type of strategy to effect a more general synthetic methodology, as exemplified by the introduction of the 3′,3′-difluoro functionality into a glycone moiety before condensation with a heterocyclic base.[46,47] Thus, treatment of the 3-keto derivative **63** with DAST afforded the 3,3-difluoro analogue **64**, which was transglycosylated to the acetate **65** in 63% overall yield. Condensation of **65** with silylated thymine in the presence of TMSOTf gave the corresponding nucleosides **66** and deprotection of the 5′-hydroxyl group followed by treatment of **67** with sodium methoxide afforded the target nucleoside **68** in 16% yield (three steps) (Scheme 8).



Scheme 8. Reagents and conditions: (a) DAST, CH_2Cl_2 (66%); (b) Ac_2O, H_2SO_4, AcOH (95%); (c) silylated thymine, TMSOTf, MeCN (53%); (d) NH_3, MeOH (55%); (e) MeONa, DMF (62%).

Application of this strategy permitted different L-2′,3′-didehydro-2′,3′-dideoxy-3′-fluoronucleosides **69**–**72** to be obtained (Fig. 5).

In order to provide compounds for an extended SAR study, Chu et al. reported the synthesis of the corresponding D-enantiomers,[48] starting from D-mannitol (**73**). After diacetalisation of **73** and oxidative cleavage, the D-glyceraldehyde

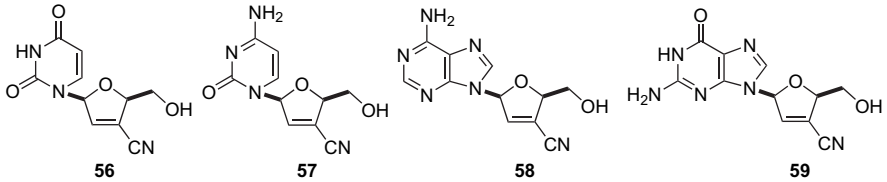


Figure 4. 3′-*C*-Cyano L-nucleosides **56**–**59**.

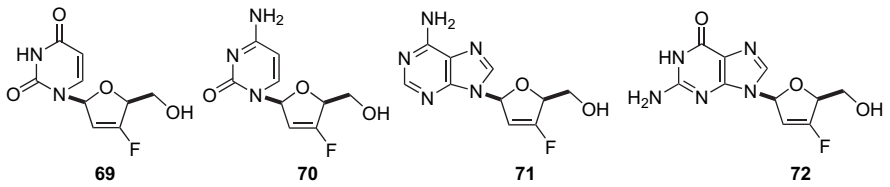
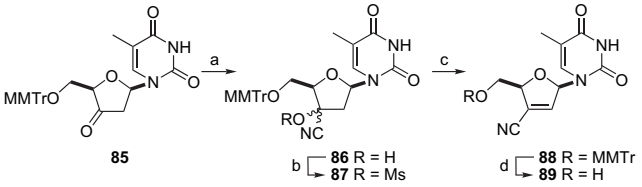


Figure 5. 3′-*C*-Fluoro L-nucleosides **69–72**.

derivative **74** was reacted with (1,3-dioxolan-2-ylmethyl)-magnesium bromide to give the alcohol **75** in 94% yield. Following Swern oxidation of **75**, the resulting ketone **76** was treated with DAST to yield the difluorinated intermediate **77** in 51% yield. Selective deprotection, benzoylation of the primary hydroxyl group in **78** and acidic treatment of **79** afforded the epimeric acetates **80** in 73% yield (four steps). These key and versatile epimeric acetates provided ready access to the D-2′,3′-didehydro-2′,3′-dideoxy-3′-fluoro-nucleosides **62** and **81–84** (Scheme 9) to complement the L-analogues **68–72**, thus providing a more systematic SAR investigation to be made.

Chattopadhyaya et al. reported the synthesis of the 3′-*C*-cyano-2′,3′-unsaturated nucleosides **89**[49] in which the 3′-keto-thymidine **85** was treated with sodium cyanide and sodium bicarbonate in an ethyl acetate–water mixture to afford the two epimers **86** in 70% yield. The unseparated epimeric nitriles **86** were treated with methylsulfonyl chloride in pyridine to afford the 3′-*C*-cyano-mesylates **87**, which underwent base-catalysed elimination using a refluxing mixture of pyridine and triethylamine to give the 2′,3′-unsaturated nucleosides **88** in 46% overall yield (three steps). Subsequent deprotection of the primary hydroxyl group gave the target nucleoside **89** in 88% yield (Scheme 10).

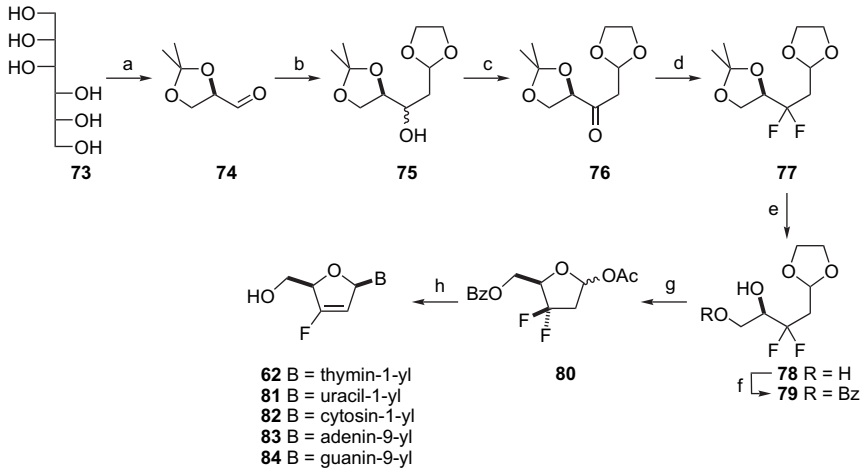
Krayesvsky et al. described the synthesis of the hydrolytically unstable nucleoside **95** starting from the ketone **90** (Scheme 11).[50] Thus, the reaction of **90** with MeMgI and MeI provided the 3-*C*-methyl derivative **91** in 83% yield with complete stereoselectivity. After benzoylation of the tertiary hydroxyl group, condensation of the resulting ester



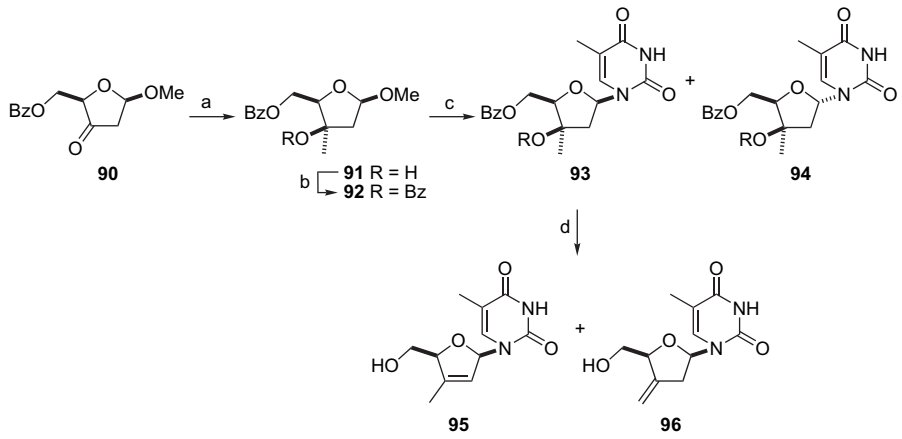
Scheme 10. Reagents and conditions: (a) NaCN, $NaHCO_3$, ethyl acetate, H_2O; (b) MsCl, pyridine; (c) Et_3N, pyridine (from **85**: 46%, three steps); (d) AcOH, H_2O (88%).

92 with silylated thymine gave both anomers **93** and **94** due to the lack of neighbouring group participation. Separation of the anomers required the deprotection of **93** and **94** to enable efficient chromatographic resolution followed by re-benzoylation. The target nucleosides, 3′-*C*-methyl derivative **95** and the 3′-*C*-methylene derivative **96**, were obtained in 34% and 11% yields, respectively, by treating the corresponding precursors **93** and **94** with thionyl chloride followed by ammonia in methanol to effect elimination and deprotection.

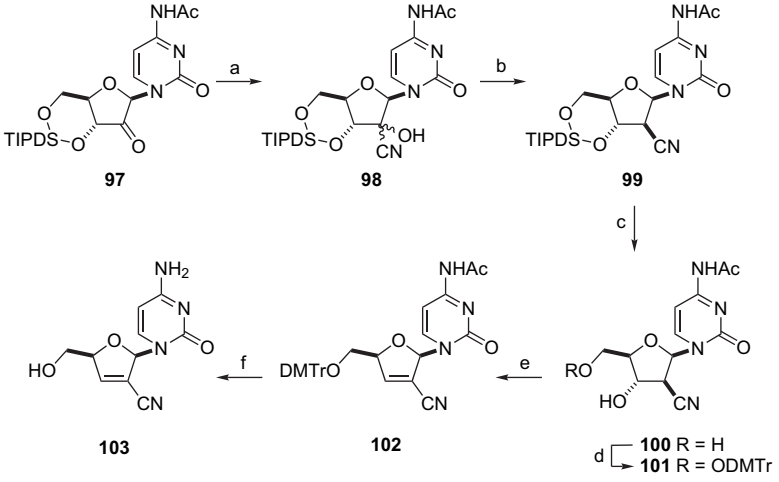
In contrast to the trans-eliminations seen in these types of nucleosides, the alternative cis-eliminations are only effected when the nucleofuge is β to either the 2′- or 3′-branched group. These are exemplified in the synthesis of the nucleoside **103**, starting from the 2′-keto nucleoside **97**. The starting material was treated with NaCN in a mixture of aqueous $NaHCO_3$ and Et_2O to afford the cyanohydrins **98** in 98% yield as an isomeric mixture (Scheme 12). This was treated, firstly, with phenyl chlorothionoformate in the presence of triethylamine and DMAP in MeCN to give the



Scheme 9. Reagents and conditions: (a) 1. acetone, H_2SO_4; 2. $NaIO_4$, H_2O; (b) (1,3-dioxolan-2-ylmethyl)magnesium bromide, THF (94%); (c) $(ClCO)_2$, Et_3N, DMSO (95%); (d) DAST, CH_2Cl_2 (51%); (e) HCl, dioxane (90%); (f) BzCl, pyridine (85%); (g) 1. HCl, MeOH; 2. Ac_2O, H_2SO_4, AcOH (95%); (h) 1. silylated heterocyclic bases, TMSOTf, MeCN; 2. NH_3, MeOH; 3. MeONa, DMF.



Scheme 11. Reagents and conditions: (a) MeMgI, MeI, Et_2O (83%); (b) BzCl, *N*-methylimidazole (54%); (c) 1. silylated thymine, TMSOTf, $C_2H_4Cl_2$; 2. MeONa, MeOH (for **93**: 34%; for **94**: 47%, two steps), (chromatographic separation of anomers); 3. BzCl, pyridine (95%); (d) 1. $SOCl_2$; 2. NH_3, MeOH (for **95**: 34%; for **96**: 11%, two steps).



Scheme 12. Reagents and conditions: (a) NaCN, H_2O, EtOH (98%); (b) 1. PhO(CS)Cl, Et_3N, DMAP, MeCN; 2. Bu_3SnH, AIBN, toluene (73%); (c) TBAF, AcOH, THF (84%); (d) DMTrCl, pyridine (83%); (e) $(Imid)_2CS$, DMF (73%); (f) 1. AcOH, H_2O (69%); 2. HCl, MeOH (66%, two steps).

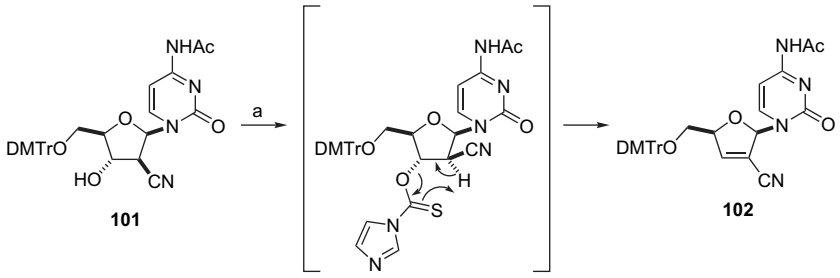
corresponding thiocarbonate, which was not purified, and, secondly, with Bu_3SnH in the presence of AIBN in toluene to effect radical deoxygenation and, as a consequence, the cyano derivative **99** in 73% yield (two steps) as the sole product, due to steric hindrance of the β face. Classical removal of the silyl protecting group of **99** afforded compound **100**, which was treated with dimethoxytrityl chloride to give the protected derivative **101** in 83% yield. Reaction of **101** with *N*,*N*′-thiocarbonyldiimidazole in DMF furnished the β-elimination product **102** in 73% yield without isolation of the carbonylimidazole ester intermediate. Detritylation and deacetylation of **102** gave the target nucleoside **103** in 66% yield (two steps).[51,52]

The cis-elimination seen in the conversion of **101** into **102** is likely to be due to intramolecular participation of the thiocarbonyl group with the 2′-proton of the thionocarbonate intermediate, as illustrated in the mechanism depicted in Scheme 13.

cis-Elimination was found to proceed more smoothly using a thionocarbonate than with either a carbonate or an ester, where more forcing conditions were required. As well as introducing the thiocarbonyl group with *N*,*N*′-thiocarbonyldiimidazole in DMF, phenyloxythiocarbonyl chloride and DMAP in acetonitrile have additionally been employed, with the subsequent thiocarbonate derivatives **104**–**106** also undergoing efficient *syn*-eliminations in the 2′- and 3′-positions to give **107**–**109** (Table 2).

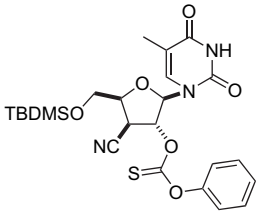
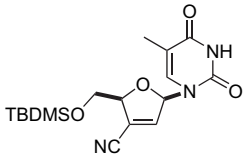
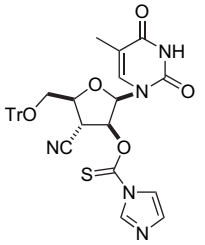
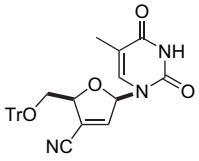
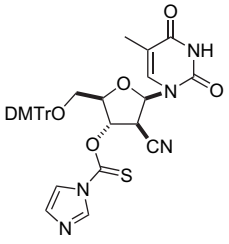
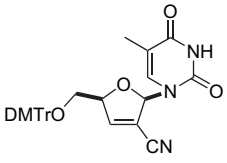
Other cis-elimination reactions have employed the methylsulfonyl group as a nucleofuge. Martin et al. described the synthesis of the 2′-fluoro nucleoside **16**[28] directly from the mesyl derivative **110**. It is notable that the corresponding *O*-2,3′-anhydro pyrimidine was not formed in the reaction. Deprotection of **16** with acid gave the 2′,3-unsaturated nucleoside **111** (Scheme 14).

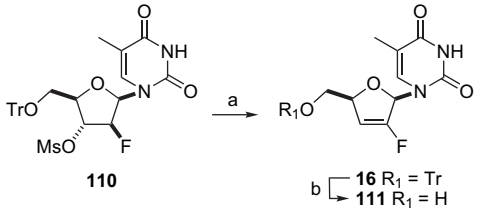
A number of routes involving a cis-elimination step have used 2′,3′-epoxides as the starting materials. Faul et al. described the synthesis of a 3′-*C*-cyano-2′,3′-unsaturated nucleoside **114**, which also makes use of a mesyl nucleofuge.[55] Reaction of the epoxide **112** with LiCN introduced the cyano group into the $C_{3'}$ position, thus giving **113**. Subsequent mesylation of the secondary hydroxyl group in the presence of triethylamine and ethyl acetate afforded the



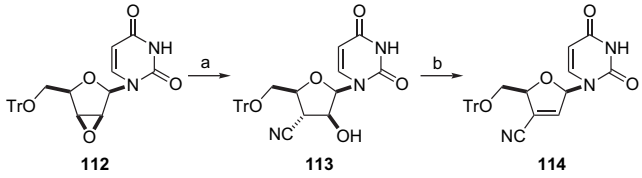
Scheme 13. Reagents and conditions: (a) $(Imid)_2CS$, DMF (73%).

Table 2. Synthesis of *C*-cyano nucleosides **107–110** from the corresponding thiocarbonyl derivatives **104–106**

Entry		Substrate		Olefin	Yield (%)	Refs.
1	**104**		**107**		80	53
2	**105**		**108**		nd	54
3	**106**		**109**		84	52



Scheme 14. Reagents and conditions: (a) NaOH, H_2O, EtOH (55%); (b) HCl, $CHCl_3$ (78%).

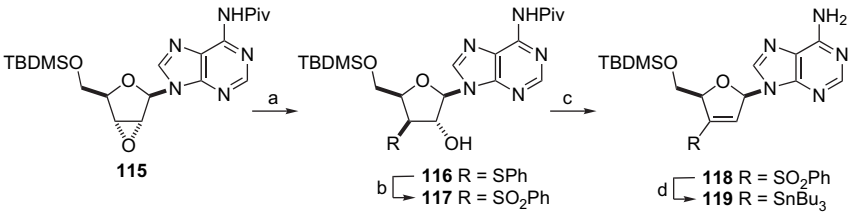


Scheme 15. Reagents and conditions: (a) LiCN, THF (68%); (b) MsCl, Et_3N, ethyl acetate (81%).

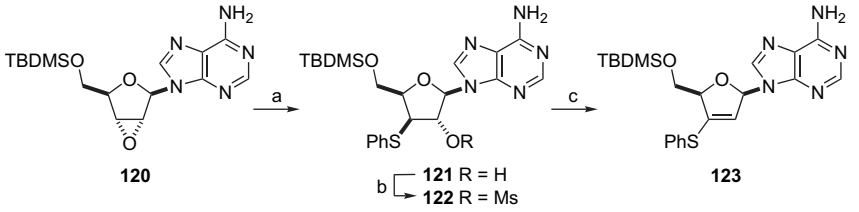
2′,3′-unsaturated nucleoside **114** in 55% overall yield (Scheme 15).

Tanaka et al. described the synthesis of 3′-*C*-stannyl-d4A (**119**) by radical-mediated desulfonylative stannylation.[56] Starting from the epoxide **115**, ring opening was followed by MCPBA oxidation of **116** to give the β-hydroxysulfone product **117** in 90% yield. Deprotection of the amino group of the aglycone and subsequent methylsulfonylation directly afforded the cis-elimination product **118** in 81% yield (two steps). Radical-mediated desulfonylative stannylation of **118** proceeded efficiently by reacting with Bu_3SnH in the presence of AIBN and triethylamine in refluxing benzene to give the 3′-*C*-stannyl nucleoside **119** in 76% yield (Scheme 16). This result was in accordance with the work described by Chattopadhyaya et al. using uracil and adenine analogues.[57]

Application of this strategy permitted the synthesis of the corresponding *C*-phenylthio derivative **123** from **120** (Scheme 17).[56] Mesylation of the nucleoside **121** gave the



Scheme 16. Reagents and conditions: (a) PhSH, MeONa (90%); (b) MCPBA, MeOH (100%); (c) 1. NH_3, MeOH; 2. $MeSO_2Cl$, DMAP, pyridine (81%); (d) Bu_3SnH, AIBN, Et_3N, benzene (76%).



Scheme 17. Reagents and conditions: (a) PhSH, MeONa (100%); (b) MsCl, DMAP, pyridine (98%); (c) DBN, MeCN (78%).

corresponding sulfonyl ester **122** in excellent yield (98%), which subsequently underwent cis-elimination with DBN in refluxing acetonitrile to afford the vinyl sulfide **123** in 78% yield. It is notable, in this example, that the acidity of the $H_{3'}$ proton was insufficient to allow spontaneous cis-elimination to take place.

Chattopadhyaya et al. reported similar work for the synthesis of the 3′-*C*-seleno derivative **127** starting from the epoxide **124** (Scheme 18).[58] Ring opening of **124** to form **125** and subsequent mesylation gave the 3′-*C*-seleno derivative **126** in 49% yield. Treatment of **126** in basic conditions afforded the cis-elimination product **127** in 92% yield. Starting from compound **127**, the oxidation with MCPBA gave the 3′-*C*-selenonyl derivative **128** in 83% and deprotection of the primary hydroxyl group of **128** in acidic conditions afforded the target nucleoside **129** in 97% yield.

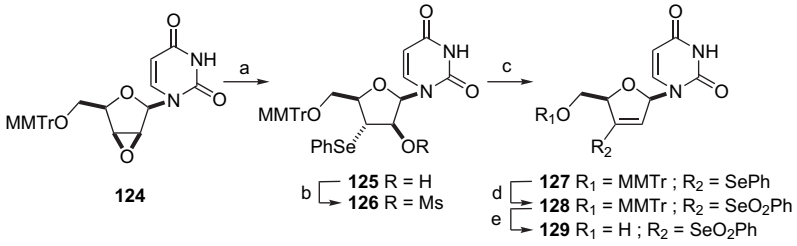
2.2. Oxidative elimination

The synthesis of 2′,3′-unsaturated nucleosides has been reported using selenoxide elimination under mild conditions. Tanaka et al. described the synthesis of 2′-*C*- and 3′-*C*-branched 2′,3′-unsaturated nucleosides via a β-hydroxyselenide intermediate **132** (Scheme 19).[59,60] Walden inversion at the 3′-position by treatment of the 3′-*O*-mesyl derivative **130** with $(PhSe)_2$ and $NaBH_4$ in refluxing THF–ethanol gave the corresponding selenide **131** in 81% yield. Conversion of compound **131** into the β-hydroxyselenide **132** was effected in almost quantitative yield by deacetylation followed by selective silylation of the primary hydroxyl group. When the nucleoside **132** was brominated in CCl_4 with $SOBr_2$ in the presence of imidazole, a mixture of β-bromoselenides **133** and **134** was obtained in 72% yield. This mixture was subjected to selenoxide elimination in CH_2Cl_2 by treatment with MCPBA to provide the corresponding bromovinyl nucleosides **135** and **136**, which were separated by column chromatography in 42% and 38% yields, respectively.

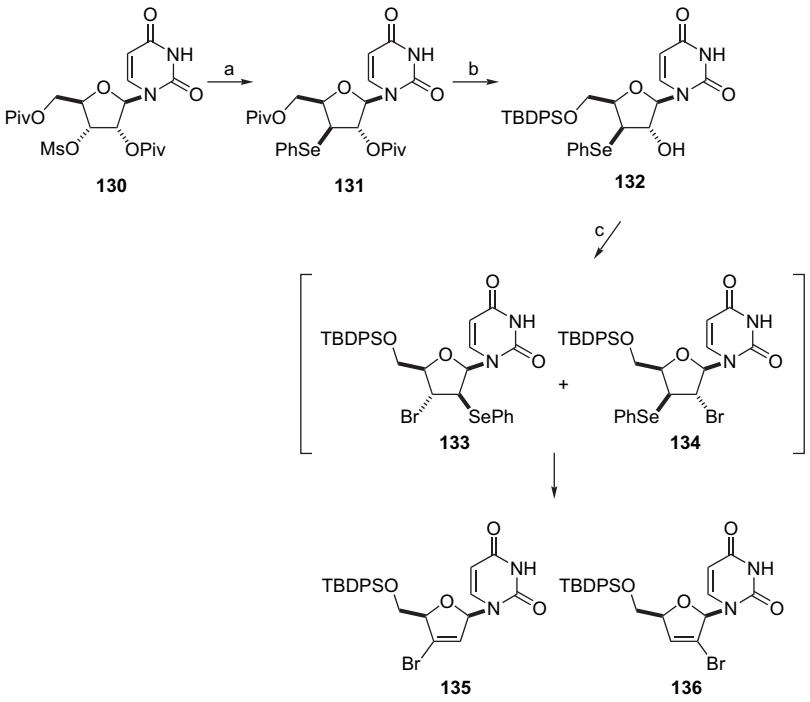
The authors proposed that the regioisomers **133** and **134** were obtained via a 2′,3′-up seleniranium intermediate, which then underwent ring opening by bromide ions at the α-face (Scheme 20).

Application of the aforementioned strategy permitted the synthesis of the adenine analogues **137** and **138** in 41% and 33% yields, respectively (Fig. 6).[60]

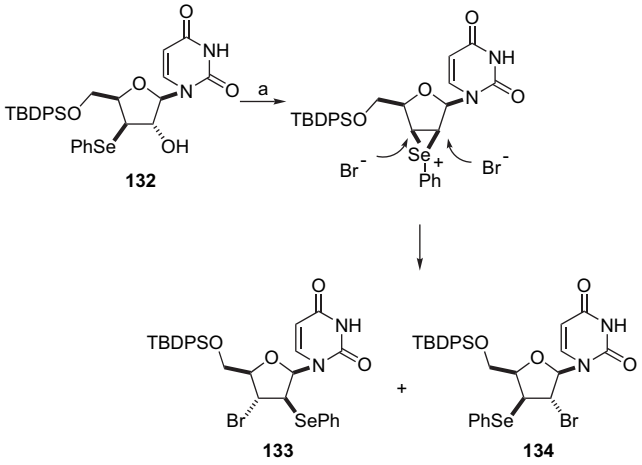
A similar cis-elimination involving selenoxide fragmentation was observed by Myasaka et al., in which the unstable enol ester **140** was detected by NMR spectroscopy, as an intermediate in the conversion of the selenide derivative **139** into the ketone **141** by reaction with MCPBA. It is notable that attempts to isolate the intermediate enol acetate **140** by chromatographic purification were unsuccessful (Scheme 21).[61]



Scheme 18. Reagents and conditions: (a) $(PhSe)_2$, $LiAlH_4$, THF (55%); (b) MsCl, pyridine (89%); (c) *t*-BuOK, DMF (92%); (d) MCPBA, MeOH (83%); (e) AcOH, H_2O (97%).



Scheme 19. Reagents and conditions: (a) $(PhSe)_2$, $NaBH_4$, THF, EtOH (81%); (b) 1. NaOH, H_2O; 2. TBDPSCl, pyridine (96%); (c) 1. imidazole, CCl_4, $SOBr_2$ (72%); 2. MCPBA, $CHCl_3$ (for **135**: 42%; for **136**: 38%).



Scheme 20. Reagents and conditions: (a) imidazole, CCl_4, $SOBr_2$.

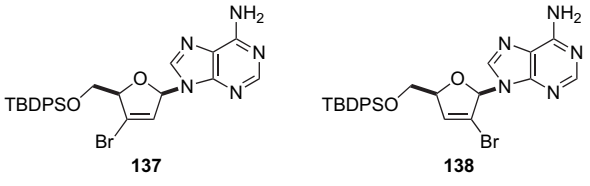


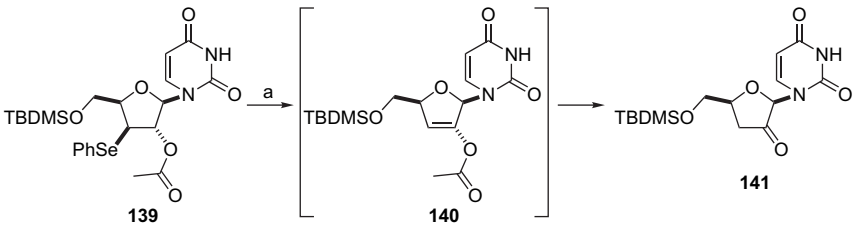
Figure 6. Bromovinyl nucleosides **137** and **138**.

Chen et al. described the synthesis of 2′-fluoro-2′,3′-dideoxy-2′,3′-didehydro-L-nucleosides using oxidative elimination of the 2′-phenylseleno intermediate **144** (Scheme 22).[62] Stereospecific introduction of the 2′-phenylseleno moiety into **142** afforded the 2′-α-phenylselenolactone **143** in 60% yield. Treatment of **143** with LiHMDS in THF followed by fluorination in the presence of $FN(SO_2Ph)_2$ provided the 2′-α-fluorinated lactone **144** in 86% yield. Subsequent oxidative elimination of the 2′-phenylseleno derivative **144** provided the 2′-fluoro-enonelactone **145** in 90% yield. Reduction of **145** with DIBALH and acylation of the resulting lactol **146** with acetic anhydride afforded an anomeric mixture of acetates **147** in 96% yield. *N*-Glycosylation of **147** with silylated thymine gave the nucleoside analogues **148** and **149** and subsequent deprotection of the primary hydroxyl group afforded the target nucleoside **150** in 38% yield and the corresponding anomer **151**. Application of this procedure for different heterocyclic bases furnished the nucleosides **152–154** (Fig. 7).

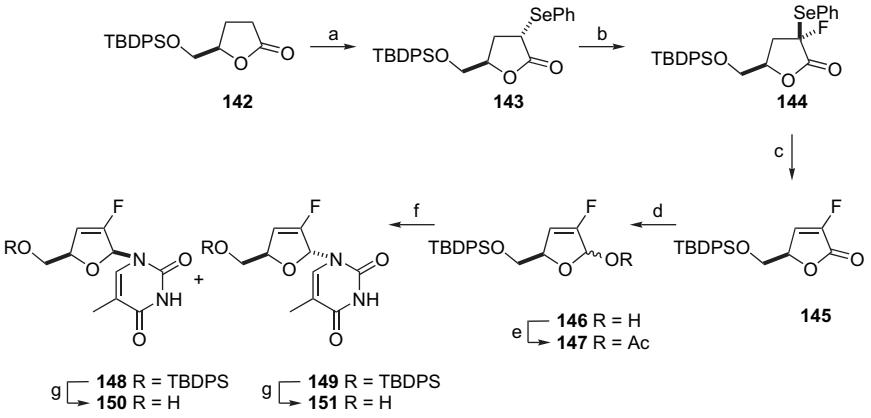
2.3. Hetero-Cope rearrangement

Different research groups have applied a hetero-Cope rearrangement of allylic nucleosides to obtain 3′-*C*-branched 2′,3′-unsaturated nucleosides. Matsuda et al. described the Wittig olefination of the 2′-keto nucleoside **155** to afford the methylidene nucleoside **156** in quantitative yield,[63] which, following desilylation to **157** and subsequent carbamoylation in the presence of 1,1′-thiocarbonyldiimidazole in DMF, afforded the 3′-imidazolylcarbonylthiomethyl derivative **158** resulting from an allylic rearrangement. Barton deoxygenation of **158** with Bu_3SnH and AIBN in toluene and subsequent deprotection of the primary hydroxyl group provided the 3′-methyl derivative **95** in 45% yield (two steps) (Scheme 23). Matsuda et al. reported in the same paper[63] that deoxygenation of the 2′-*O*-methyloxalyl ester **160** by a Barton deoxygenation afforded the *endo* olefin **159** in 91% yield. It was proposed by the authors that the allyl radical intermediate **161** was involved in the conversion of each of the nucleosides **158** and **160** into the elimination product **159** (Scheme 24).

Czernecki et al. applied the aforementioned strategy by esterifying the 3′-methylidene nucleoside **162** to give the



Scheme 21. Reagents and conditions: (a) MCPBA, CH_2Cl_2.



Scheme 22. Reagents and conditions: (a) LiHMDS, THF, PhSeBr (60%); (b) LiHMDS, $FN(SO_2Ph)_2$, THF (86%); (c) H_2O_2, pyridine (90%); (d) DIBALH, toluene (93%); (e) Ac_2O, Et_3N (96%); (f) silylated thymine, TMSOTf, MeCN (55%); (g) $Et_3N(HF)_3$, THF (69%).

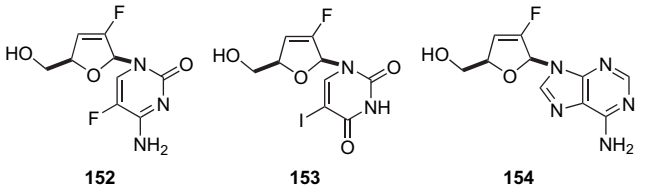
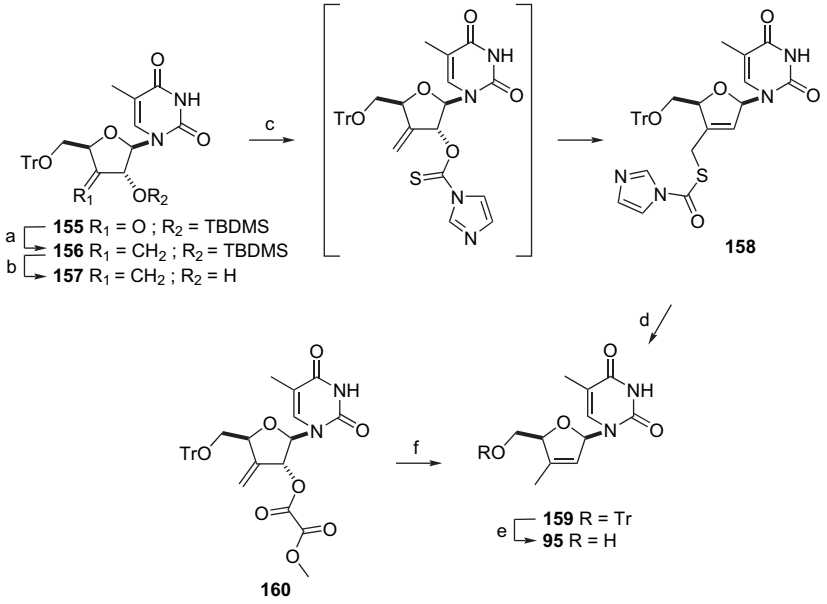


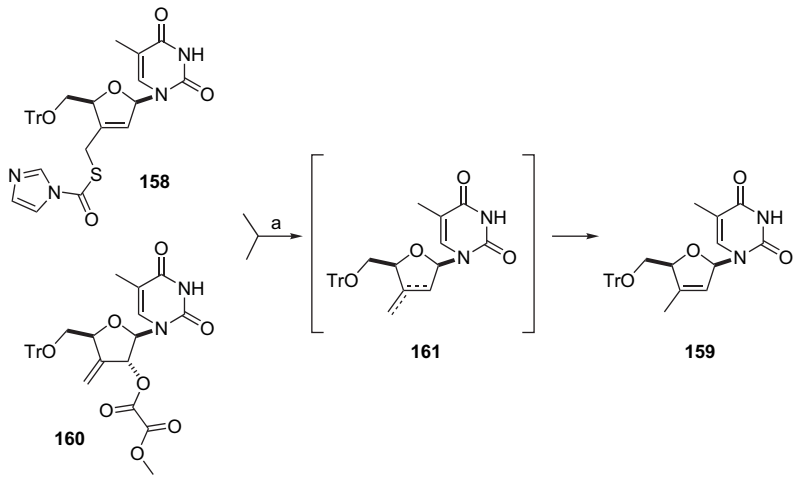
Figure 7. 2′-Fluoro L-nucleosides **152**–**154**.

phenoxythiocarbonyl allylic rearrangement product **163** in 49% yield. Barton deoxygenation to give **164** and deprotection of the primary hydroxyl group gave the target 2′,3′-unsaturated nucleoside **95** in 41% yield (Scheme 25).[64]

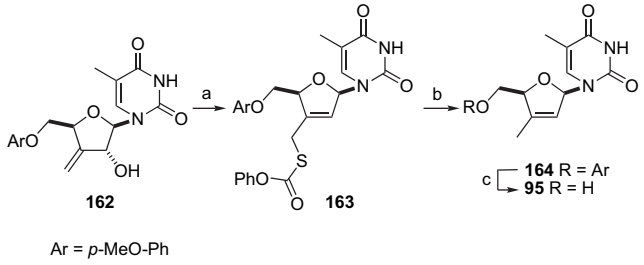
Czernecki et al. described the synthesis of various 3′-branched 2′,3′-unsaturated pyrimidine nucleosides by modification of the preceding methodology.[65] Treatment of the nucleosides **162** and **165** with triphenylphosphine in the



Scheme 23. Reagents and conditions: (a) Ph_3PMeBr, BuLi, THF (99%); (b) 1. TBAF, THF (99%); (c) $(Imid)_2CO$, DMF (84%); (d) Bu_3SnH, AIBN, toluene (83%); (e) HCOOH (54%); (f) Bu_3SnH, AIBN, toluene (91%).



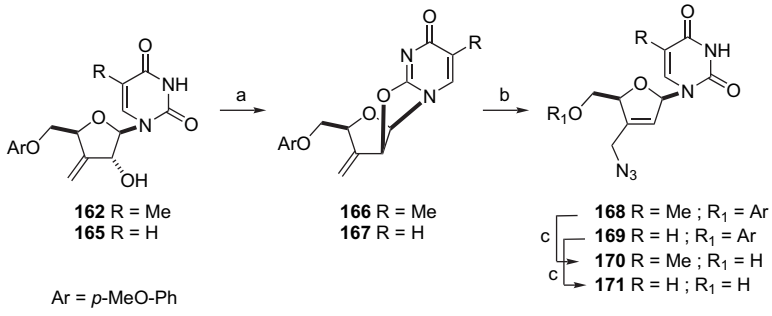
Scheme 24. Reagents and conditions: (a) Bu_3SnH, AIBN, toluene (from **158**: 83%; from **160**: 91%).



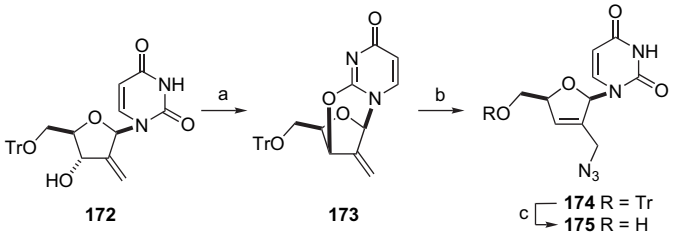
Scheme 25. Reagents and conditions: (a) PhO(CS)Cl, DMAP, pyridine (49%); (b) Bu_3SnH, AIBN, toluene (75%); (c) $(NH_4)_2Ce(NO_3)_6$, MeCN, H_2O (55%).

presence of DEAD gave the 2,2′-anhydro derivatives **166** and **167** in 70% and 94% yield, respectively. Compounds **166** and **167** were each reacted with lithium azide in dimethylformamide to give **168** and **169** resulting from allylic rearrangement and 2,2′-anhydro ring opening. Subsequent deprotection of the primary hydroxyl group by oxidation with cerium ammonium nitrate furnished the target 2′,3′-unsaturated nucleosides **170** and **171** in 43% and 16% yield, respectively (two steps) (Scheme 26).

Application of this type of chemistry enabled the authors to obtain the 2′-*C*-branched counterpart **175**.[66] Starting from the 2′-*C*-methylidene derivative **172**, an intramolecular reaction was carried out to furnish the 2,3′-anhydro nucleoside **173** in 70% yield. Heating the nucleoside **173** in the presence of lithium azide in dimethylformamide resulted in the formation of the corresponding azido derivative **174** and deprotection of the 5′-position gave the target nucleoside **175** in low yield (8%) (two steps) (Scheme 27). It is notable that the azidation of the anhydro derivative **173** to give **174** resulted in a poor yield compared with that obtained for the nucleoside **169** (12% vs 85%).



Scheme 26. Reagents and conditions: (a) PPh_3, DEAD, DMF (for **166**: 70%; for **167**: 94%); (b) LiN_3, DMF (for **168**: 94%; for **169**: 85%); (c) $(NH_4)_2Ce(NO_3)_6$, MeCN, H_2O (for **170**: 46%; for **171**: 19%).

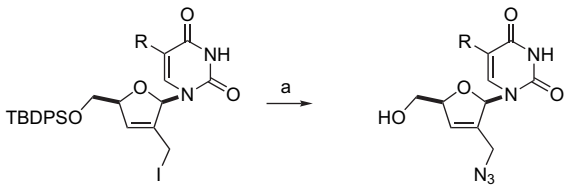


Scheme 27. Reagents and conditions: (a) PPh_3, DEAD, DMF (70%); (b) LiN_3, DMF (12%); (c) BF_3–Et_2O, Et_3SiH, MeCN (68%).

Samuelsson et al. described the synthesis of the 2′-*C*-methyl-substituted nucleosides **182** and **183** via alcohol transposition.[67] Starting from the 5′-*O*-silylated nucleosides **176** and **177**, the allylic iodides **178** and **179** were each obtained in 90% yield by reaction with chlorodiphenylphosphine in the presence of imidazole and iodine in a mixture of toluene–acetonitrile. Substitution of iodide in **178** and **179** by OAc using tetrabutylammonium acetate in methylene chloride gave **180** and **181**. Deprotection of the primary hydroxyl group in each of these compounds gave the target nucleosides **182** and **183** in 84% and 86% yield, respectively (Scheme 28).

Samuelsson et al.[67] proposed a plausible mechanism for the rearrangement obtained for the chlorodiphenylphosphine–iodine–imidazole system involved in the conversion of **177** into **179** (Scheme 29).

Using the same reagents, **178** and **179** were synthesised in a similar fashion. They were converted into the corresponding azides, which were subsequently deprotected to give the final nucleosides **184** and **175** (Scheme 30).



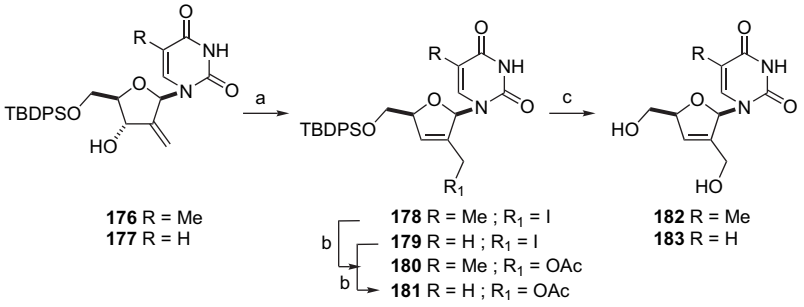
Scheme 30. Reagents and conditions: (a) 1. NaN_3, DMF; 2. TBAF, THF (for **184**: 96%; for **175**: 92%).

2.4. Cope elimination

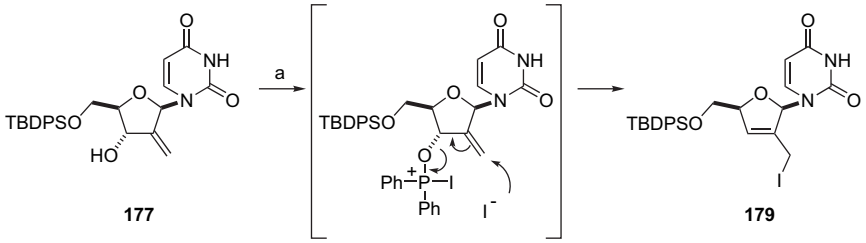
Chiacchio et al. reported a route to the 2′-*C*-methyl analogue of d4T, **195**, which employed the key steps of a 1,3-dipolar cycloaddition of a nitrone and a Cope elimination (Scheme 31).[68] The starting material, *C*-methoxycarbonyl-*C*,*N*-dimethyl nitrone (**185**), was reacted with allyl acetate to give a mixture of acetyloxymethyl derivatives **186**. Treatment of **186** with methyl triflate to give **187** and subsequent hydrogenation afforded the lactones **188** in 93% yield (three steps). Protection of the primary hydroxyl group furnished the 5′-*O*-silylated compounds **189** and **190**, which were separated by flash chromatography. Subsequent DIBALH reduction of lactone **189** proceeded with complete stereoselectivity to give, exclusively, the lactol **191** in 86% yield. After acetylation, the *N*-glycosylation of **192** with silylated thymine afforded the corresponding β-nucleoside **193**, stereoselectively, in 92% yield. Elimination of the *N*-dimethylamino group was performed according to a Cope elimination by treatment with MCPBA to form **194** followed by deprotection of the primary hydroxyl group to afford the target nucleoside **195** in 64% yield (two steps).

2.5. Other methods

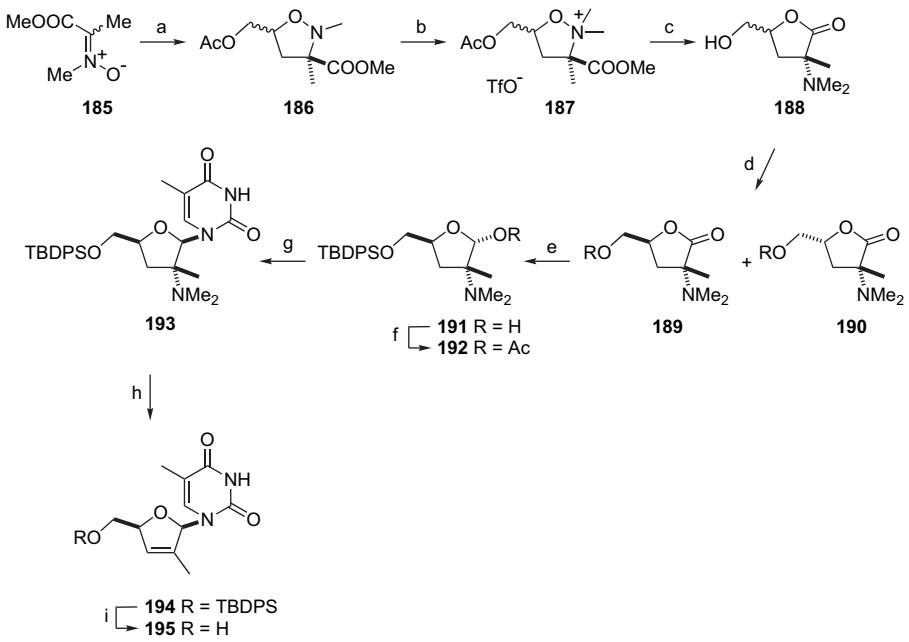
Chu et al. reported a convergent route to 2′-fluoro-2′,3′-unsaturated L-nucleosides starting from L-gulonic-γ-lactone (**196**) (Scheme 32).[69] Acetalation and cleavage of the lactone **196** afforded the L-glyceraldehyde derivative **197**, which was subjected to Horner–Emmons reaction with triethyl α-fluorophosphonoacetate and sodium bis(trimethylsilyl)amide in THF to give a mixture of olefins **198** in 98% yield. These, under acidic conditions, followed by silylation of the primary hydroxyl group, furnished the lactone **199** in 70% yield. DIBALH reduction of **199** provided the lactols **200**, which were acetylated to give the acetates **201**. *N*-Glycosylation of **201** with silylated thymine afforded the nucleoside analogues **202** and **203** and subsequent deprotection gave the target thymine analogue **150** in 26% yield (two steps) and the corresponding α-anomer **151**.



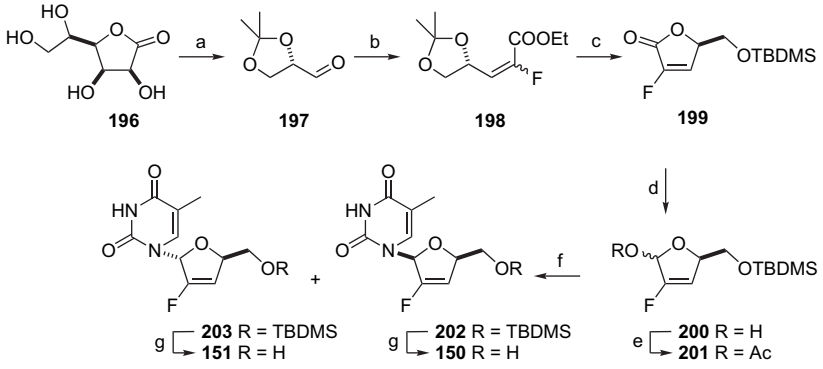
Scheme 28. Reagents and conditions: (a) Ph_2PCl, I_2, imidazole, toluene, MeCN (for **178**: 90%; for **179**: 90%); (b) $N(Bu)_4OAc$, CH_2Cl_2 (for **180**: 94%; for **181**: 96%); (c) 1. NH_3, MeOH; 2. TBAF, THF (for **182**: 84%; for **183**: 86%).



Scheme 29. Reagents and conditions: (a) Ph_2PCl, I_2, imidazole, toluene, MeCN (90%).



Scheme 31. Reagents and conditions: (a) AllylOAc (97%); (b) TfOMe, CCl_4 (100%); (c) H_2, Pd/C (96%); (d) TBDPSCl, imidazole, CH_2Cl_2 (for **189** 47%; for **190** 43%); (e) DIBALH, toluene (86%); (f) AcCl, pyridine, CH_2Cl_2 (88%); (g) silylated thymine, $SnCl_4$, CH_2Cl_2 (92%); (h) MCPBA, CH_2Cl_2 (65%); (i) TBAF, THF (99%).



Scheme 32. Reagents and conditions: (a) Ref. 70; (b) $(EtO)_2P(O)CHFCOOEt$, NaHMDS, THF (98%); (c) 1. HCl, EtOH; 2. TBDMSCl, imidazole, CH_2Cl_2 (70%); (d) DIBALH, CH_2Cl_2 (80%); (e) Ac_2O, Et_3N, CH_2Cl_2 (78%); (f) silylated thymine, TMSOTf, $C_2H_4Cl_2$ (64%); (g) TBAF, THF (for **150**: 41%; for **151**: 26%).

This type of strategy was also applied to extend the L-series of compounds, which included the uracil, cytosine, adenine and guanine derivatives **154** and **204**–**206**.[69] The alternative D-series **10** and **207**–**210** employed D-mannitol as the starting point (Fig. 8).[70]

Chu et al. described a second convergent route to 2′-fluoro-4′-ethynyl-2′,3′-unsaturated D- and L-nucleosides starting from the isopropylidene-protected D-glyceraldehyde **74**, which was converted in a four-step route into the lactol **211** (Scheme 33).[71] Wittig homologation of the lactol **211** and silylation of the secondary hydroxyl group furnished a 5:2 mixture of the *E*- and *Z*-dienes **212** and **213**, respectively, in 80% total yield, which were separated by chromatography. The *E*-isomer **212** was converted into the diol **214** in 83% yield using the classical oxidation reagents OsO_4 and NMO. Selective benzoylation of the primary hydroxyl group afforded the ester **215** and subsequent oxidation by pyridinium chlorochromate gave the α,β-unsaturated ketone **216**, which is the key intermediate in the strategy, since it is universal for routes to both the D- and L-series of nucleosides. A Grignard reaction of **216** with HCCMgBr gave a separable mixture of the two tertiary alcohols **217** and **218**, in a ratio of 3:2, respectively, with a total yield of 72%. To obtain compounds in the D-series, the TBDMS groups of one of the alcohols **217** were removed with TBAF to form **219**, followed by periodate oxidation and acetylation with acetic anhydride to give the 3-fluoro-2,3-unsaturated-4-ethynyl-D-furanose **220** in 76% yield (three steps). *N*-Glycosidation of **220** with silylated thymine afforded the nucleoside **221** in 55% yield and the corresponding anomer **222** in 18% yield. Subsequent deprotection of the primary hydroxyl group of **221** furnished the target nucleoside **223** in 91% yield.

The same strategy was applied to extending the D-series of compounds to include the cytosine and adenine derivatives **224** and **225**. The alternative L-series **226**–**228** employed the alcohol **218** obtained from the ketone branch point intermediate **216** in the strategy (Fig. 9).

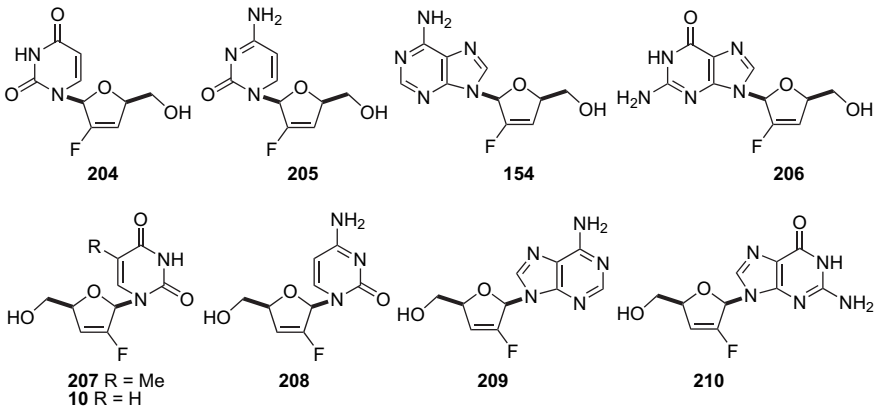
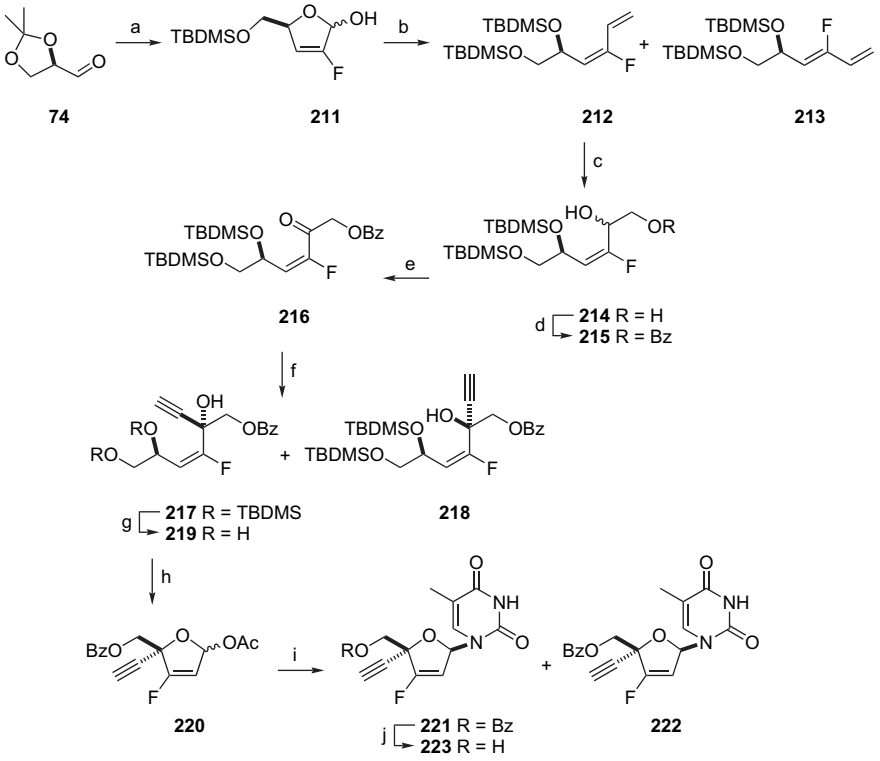


Figure 8. 2′-Fluoro nucleosides **10**, **154** and **204**–**210**.



Scheme 33. Reagents and conditions: (a) 1. $(EtO)_2P(O)CHFCOOEt$, NaHMDS, THF (98%), 2. HCl, EtOH; 3. TBDMSCl, imidazole, CH_2Cl_2 (70%); 4. DIBAHL, CH_2Cl_2 (80%); (b) 1. $MePPh_3Br$, NaH, DMSO, THF (91%); 2. TBDMSCl, imidazole, CH_2Cl_2 (87%); (c) OsO_4, NMO, acetone, H_2O (83%); (d) BzCl, pyridine (84%); (e) PCC, 4 Å molecular sieves, CH_2Cl_2 (72%); (f) HCCMgBr, THF (72%); (g) TBAF, AcOH, THF (98%); (h) 1. $NaIO_4$, EtOH, H_2O; 2. Ac_2O, pyridine (78%); (i) silylated thymine, $SnCl_4$, $C_2H_4Cl_2$ (10%); (j) NH_3, MeOH (91%).

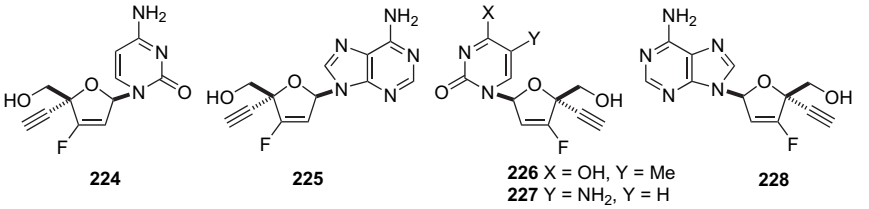
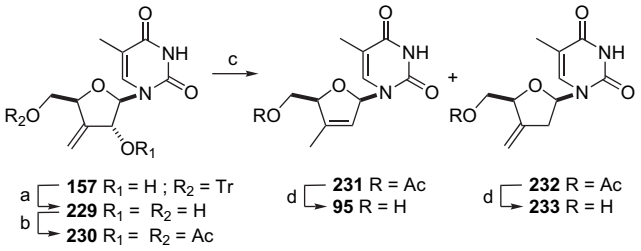


Figure 9. 4′-Ethynyl-2′-fluoro nucleosides **224**–**228**.

Allylic acetates are known to be converted into the corresponding olefins using organopalladium chemistry. Application of this methodology to nucleoside chemistry was explored by Matsuda et al.[63] Detritylation of the methylidene nucleoside **157** afforded **229**, followed by acetylation, furnished the diacetate **230** in 88% yield (two steps), which was reduced with $LiBH_4$ in the presence of PPh_3 and a catalytic amount of $(PhCN)_2PdCl_2$ in THF to give a mixture of

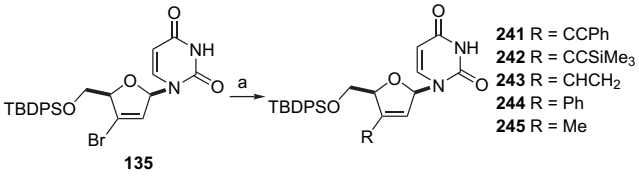
231 and **232** (3:1) in 50% yield. Classical chromatographic purification and deprotection of the primary hydroxyl group in each case gave the 3′-methyl derivative **95** and the *exo* olefin **233** in 98% and 95% yield, respectively (Scheme 34).



Scheme 34. Reagents and conditions: (a) HCOOH (97%); (b) Ac_2O, DMAP, MeCN (89%); (c) $LiBH_4$, PPh_3, $(PhCN)_2PdCl_2$ (50%); (d) MeONa, MeOH (for **95**: 98%; for **233**: 95%).

In 1993, Chattopadhyaya et al. reported evidence for nitroxide radical formation in a radical-promoted denitration reaction, as part of a study to synthesise various 3′-branched 2′,3′-unsaturated nucleosides, as exemplified by the synthesis of **240** (Scheme 35).[72] Thus, the thymidine analogue **234** was treated with *N*-methylhydroxylamine hydrochloride in pyridine to give the corresponding 3′-(*E*)-methylnitrone **235** in 52% yield. This was treated with ethyl vinyl ether and acrylonitrile to afford the 3′-spiro nucleoside **236** by 1,3-dipolar cycloaddition. Desilylation to give **237** and deoxygenation of the secondary hydroxyl group vicinal to the 3′-spiro function via **238** gave the 3′-*C*-substituted nucleoside **239**, which was deprotected to furnish the target compound **240** in 18% yield (four steps).

Various 2′- and 3′-*C*-branched 2′,3′-unsaturated nucleosides were prepared starting from 2′,3′-didehydro-2′,3′-dideoxynucleosides. Tanaka et al. described the synthesis of 2′-*C*- and 3′-*C*-branched 2′,3′-unsaturated nucleosides via palladium-catalysed cross-coupling of the bromovinyl intermediates.[59,60] The 3′-bromo derivative **135** was subjected to a Sonogashira reaction, which gave the nucleosides **241** and **242** (Scheme 35) and, in the same paper, Tanaka et al.[60] described an alternative method using organotin reagents, as coupling partners, to obtain the nucleosides **243–245** (Scheme 36).



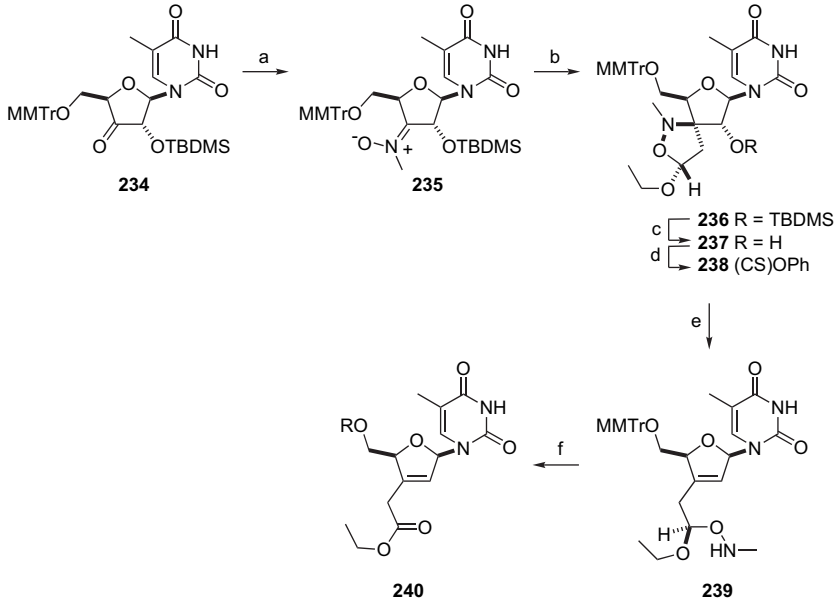
Scheme 36. Reagents and conditions: (a) For **241**: PhCCH, $(Ph_3P)_2PdCl_2$/CuI, Et_3N, DMF (68%); for **242**: Me_3SiCCH, $(Ph_3P)_2PdCl_2$/CuI, Et_3N, DMF (62%); for **243**: $Bu_3SnCHCH_2$, $(Ph_3P)_2PdCl_2$/CuI, Et_3N, DMF (37%); for **244**: Ph_4Sn, $(Ph_3P)_2PdCl_2$/CuI, dioxane (39%); for **245**: Me_4Sn, $(Ph_3P)_4Pd$, dioxane (14%).

In a similar manner, 2′-*C*- and 3′-*C*-bromovinyl nucleosides **136–138** were subjected to the Sonogashira cross-coupling reaction to afford the corresponding nucleosides **246–254** (Fig. 10).

Tanaka et al. reported the vinylic stannylation of d4T at either the 3′- or 2′-position using Bu_3SnOMe followed by TMEDA, LTMP and HMPA.[73] Thus, the 3′-*C*-stannyl derivative **255** was obtained in 60% yield. Application of organotin chemistry at the Sn–C bond of the nucleoside **255** provided access to a variety of 3′-substituted d4T analogues (**256–261**) in 73–100% yield (Scheme 37).

Using a similar procedure, Tanaka et al. reported the synthesis of various 3′-*C*-branched analogues **262–266** (Fig. 11).[56]

2′-*C*-Vinyl- and 3′-*C*-vinyl-2′,3′-unsaturated nucleosides were obtained starting from different monosaccharides. Schmalz et al. reported the synthesis of 3′-*C*-vinyl d4Ns



Scheme 35. Reagents and conditions: (a) MeNHOH, pyridine (52%); (b) ethyl vinyl ether (94%); (c) NH_4F, MeOH (93%); (d) PhO(CS)Cl, DMAP, MeCN (85%); (e) Bu_3SnH, AIBN, toluene (30%); (f) AcOH, H_2O (75%).

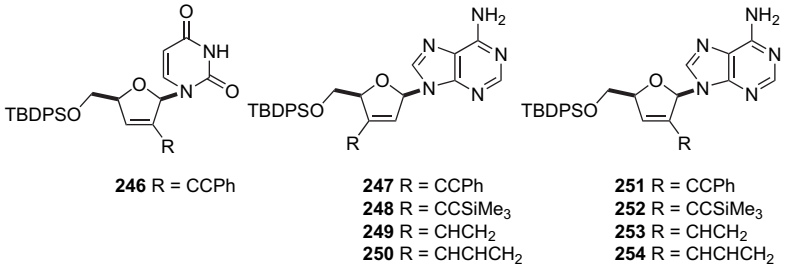
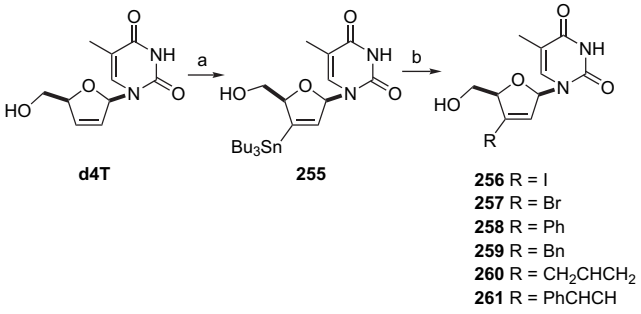


Figure 10. 2′- and 3′-*C*-Branched nucleosides **246**–**254**.



Scheme 37. Reagents and conditions: (a) 1. Bu_3SnOMe; 2. LTMP, HMPA, TMEDA, THF (60% two steps); (b) for **256**: I_2, THF (93%); for **257**: NBS, THF (100%); for **258**: PhI, $(PPh_3)_4Pd$, CuI, DMF (97%); for **259**: BnBr, $(PPh_3)_4Pd$, CuI, DMF (78%); for **260**: AllBr, $(PPh_3)_4Pd$, CuI, DMF (73%); for **261**: β-bromostyrene, $(PPh_3)_4Pd$, CuI, DMF (81%).

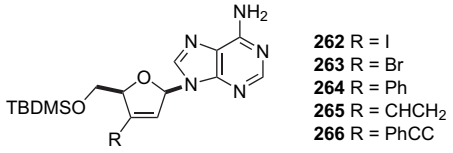


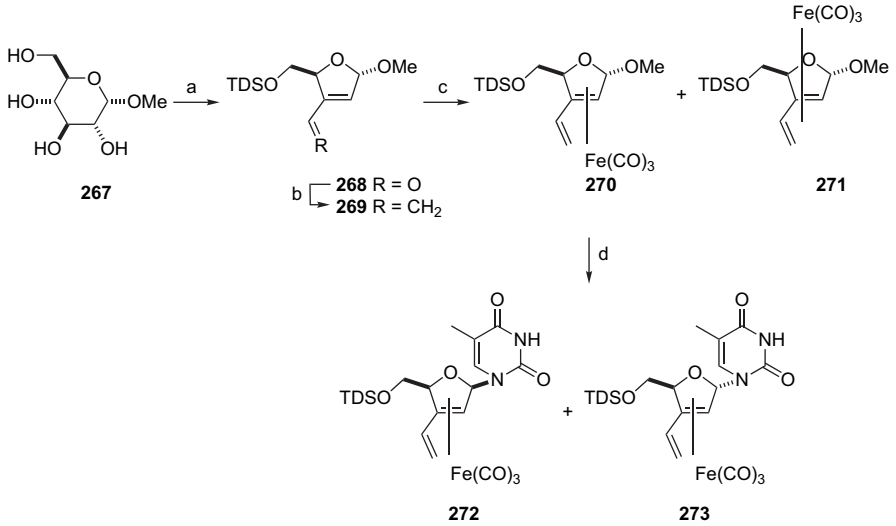
Figure 11. 3′-*C*-Branched adenosine derivatives **262**–**266**.

starting from methyl α-D-glucopyranoside (**267**)[74] in which it was first converted into the aldehyde **268** by a sequence of reactions involving selective silylation of the primary hydroxyl group, Mitsunobu epoxidation and LiBr-induced rearrangement/ring contraction. Wittig homologation of **268** and, finally, diastereoselective complexation of the diene **269** with $[Fe_2(CO)_9]$ gave a mixture of the *endo*-complexes **270** and **271** (3.3:1). The major product **270** was subjected to *N*-glycosidation using Vorbruggen chemistry to furnish the protected anomeric pair of nucleosides **272** and **273** (1.6:1) in 27% total yield (Scheme 38).

Application of this strategy also permitted the synthesis of the corresponding 3′-*C*-vinyl nucleosides **274**–**287** (Fig. 12).

Schmalz et al. reported the synthesis of 2′-*C*-vinyl-2′,3′-unsaturated nucleosides starting from D-ribonolactone (**288**).[74] After selective tritylation, the lactone **288** was converted into the enol triflate **289** in 85% yield. Then, C–C bond formation was achieved via Stille coupling using tributylvinylstannane to afford the diene **290** in 87% yield. Complexation of the 1,3-butadiene derivative **290** with $[Fe_2(CO)_9]$ gave a mixture of complexes **291** and **292**, which was readily separated by flash chromatography. Subsequent reduction of **291** with DIBAHL, acidic methanolysis and silylation furnished the corresponding diene **293** in 87% yield. Diastereoselective *N*-glycosidation provided the target β-nucleoside **294**, stereoselectively, in 22% overall yield (Scheme 39).

Application of this procedure for different heterocyclic bases afforded the nucleosides **295**–**300** (Fig. 13).



Scheme 38. Reagents and conditions: (a) 1. TDSCl, pyridine (98%); 2. DEAD, PPh_3, benzene (81%); 3. LiBr, $(Me_2N)_2CO$, toluene (68%); (b) CH_2PPh_3, THF (86%); (c) $[Fe_2(CO)_9]$, Et_2O (72%); (d) silylated thymine, $SnCl_4$, $C_2H_4Cl_2$ (82%).

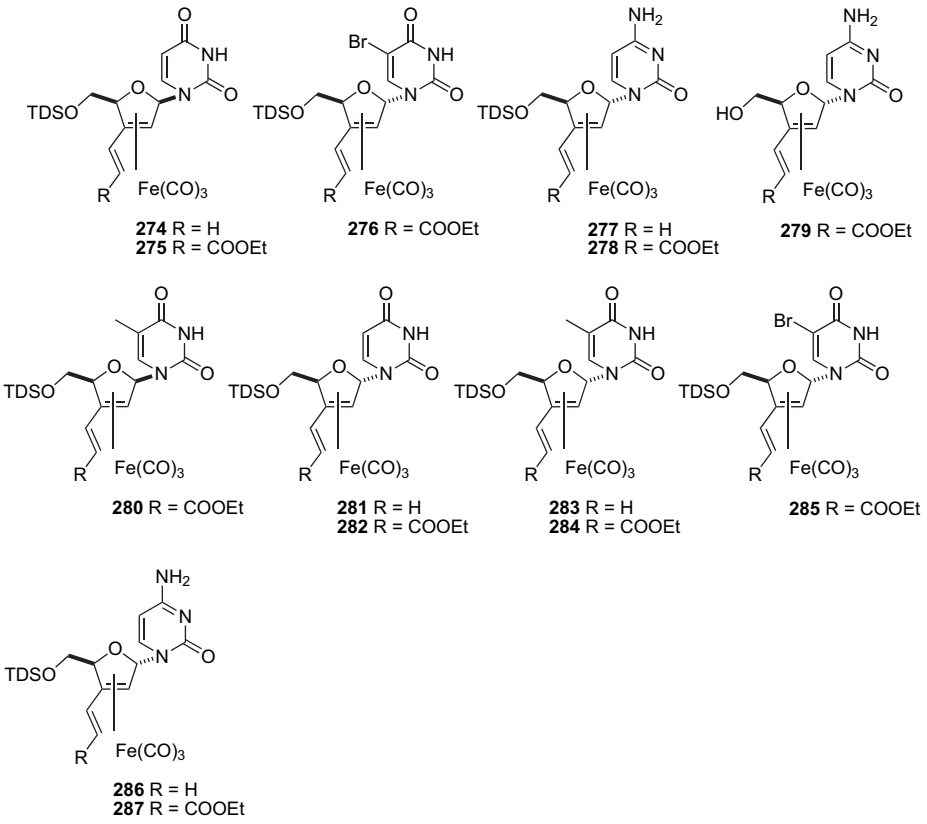
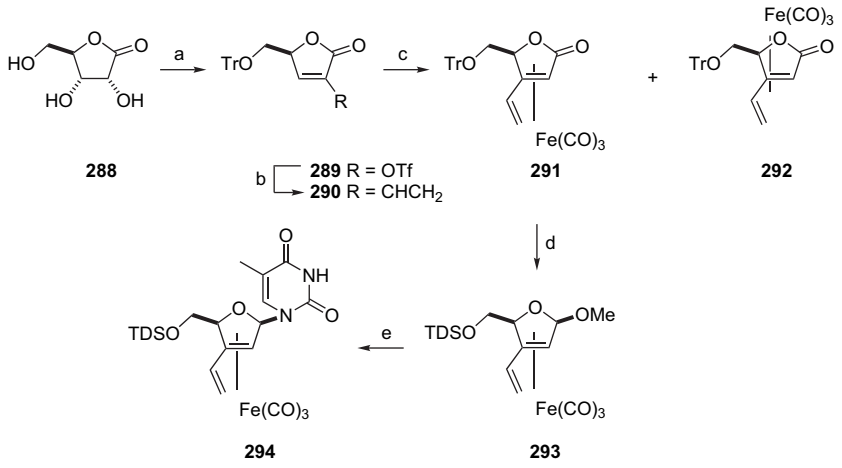


Figure 12. 3′-*C*-Vinyl nucleoside derivatives **274**–**287**.



Scheme 39. Reagents and conditions: (a) 1. TrCl, pyridine (67%); 2. Tf_2O, pyridine, CH_2Cl_2 (85%); (b) $Bu_3SnCHCH_2$, Ph_3As, $[Pd_2(dba)_3]$, LiCl, THF (87%); (c) $[Fe_2(CO)_9]$, EtOAc (69%); (d) 1. DIBAHL, toluene (92%); 2. $HC(OMe)_3$, PTSA, MeOH (99%); TDSCl, imidazole, CH_2Cl_2 (96%); (e) silylated thymine, $SnCl_4$, $C_2H_4Cl_2$ (75%).

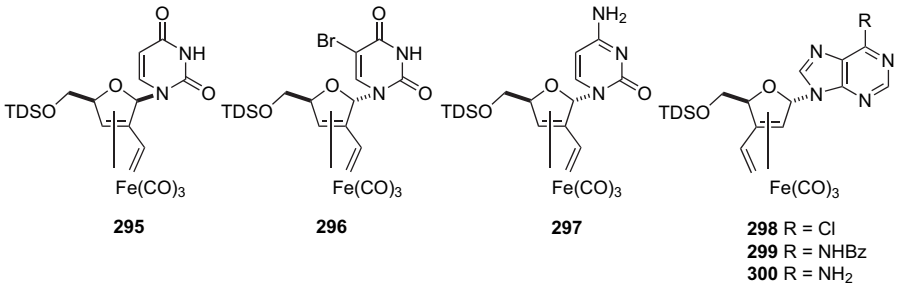


Figure 13. 2′-*C*-Vinyl nucleoside derivatives **295**–**300**.

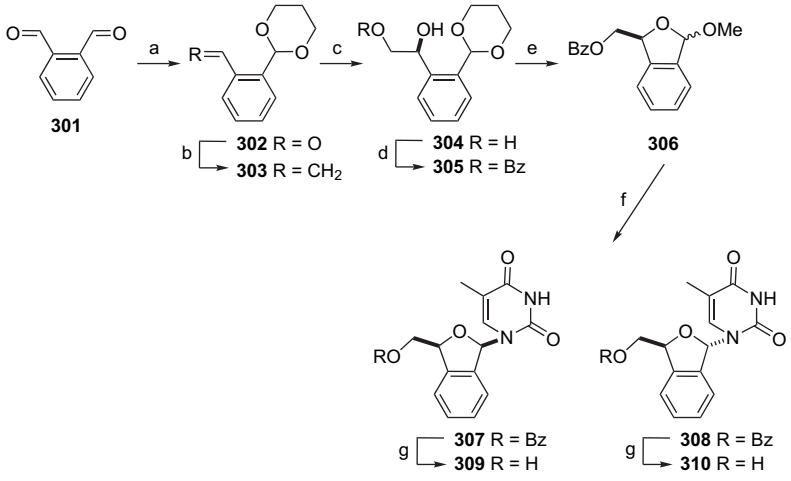
3. Synthesis of 2′- and 3′-dibranched 2′,3′-unsaturated nucleosides

Analogues of d4T having a benzo[*c*]furan core were described by Ewing et al.[75–81] The target nucleosides were first obtained as a racemic mixture[75] and, in subsequent papers, as enantiomerically pure forms.[76–81] For simplicity, only the asymmetric synthesis of benzo[*c*]furan analogues are described here. Starting from phthalaldehyde **301**, selective protection of one of the formyl groups was achieved by acetal formation to give **302**. This was followed by Wittig homologation of the remaining formyl group to give the corresponding styrene **303** in 58% yield. The ethene functional group was converted into the corresponding dihydro derivatives **304** in 85% yield (ee>99%) using the commercial Sharpless reagent, AD-mix α. After selective benzoylation of the primary hydroxyl group of **304**, the corresponding esters **305** were cyclised and methylated to afford the corresponding 1,3-dihydrobenzo[*c*]furan derivatives **306** in 82% yield (two steps), analogous to an anomeric mixture of 2′,3′-didehydro-2′,3′-dideoxyfuranosides. Both of the thymine derivatives **307** and **308** were obtained by standard Vorbruggen chemistry on **306**, due to the lack of neighbouring group participation to direct stereoselectivity. After removal of the benzoyl protection and subsequent silica gel chromatography, the target nucleosides **309** and **310** were obtained enantiomerically pure in 9% and 19% overall yield, respectively (Scheme 40).

The nucleosides **309** and **310** are analogous to 2′,3′-didehydro-2′,3′-dideoxynucleosides in the D-series. The related enantiomers analogous to L-nucleosides were synthesised using the same strategy, but employing AD-mix β. This work was further extended to provide the full set of related isomers **311**–**315**, having uracil and cytosine as heterocyclic bases, accordingly (Fig. 14). In each case, the use of the appropriate AD-mix afforded an enantiomerically pure nucleoside.[76]

4. Conclusions

A major initiative to synthesise 2′,3′-didehydro-2′,3′-dideoxynucleosides branched at the olefinic moiety has been led by attempts to discover compounds with increased activity over d4T, to provide structure–activity data and to offer a continuity of new drugs as alternatives to the previous generation to combat the rise of resistance. To date, the majority of work has been directed towards 2′,3′-didehydro-2′,3′-dideoxynucleosides having branching at either the 2′- or 3′-positions. Although most examples in this field are pyrimidine nucleosides, the corresponding purine analogues have also received some attention. Not surprisingly, however, most targets have been closely related to d4T, with the fluorine-branched analogues perhaps being the most commonly sought by a number of research groups, resulting in an interesting and diverse number of strategies having been explored.[28,29,35,36,44–48,62,69–71] The other halogens, chlorine,[37,38] bromine[56,59,60,73] and iodine,[56,73] have also received some attention along with the azide.[37,38] After fluorine as a substituent, however, the next most attractive targets have been nucleosides with a branched methyl group



Scheme 40. Reagents and conditions: (a) propan-1,3-diol, PTSA, toluene (75%); (b) Ph_3PMe, BuLi, THF (77%); (c) AD-mix α, *t*-BuOH, H_2O (85%); (d) BzCl, pyridine (89%); (e) HCl, MeOH (92%); (f) silylated thymine, TMSOTf, $C_2H_4Cl_2$ (for **307**: 23%; for **308**: 47%); (g) NH_3, MeOH (quant).

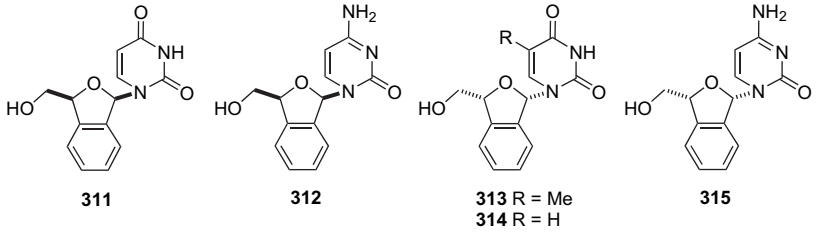


Figure 14. 2′-*C*- and 3′-*C*-Dibranched nucleosides **311**–**315** having a benzo[*c*]furan core.

or an analogous alkyl substituent[39–41,50,59,60,63,64,66–68,74] and, to a lesser extent, a nitrile group.[42,43,49,51–55] Such targets have also been obtained by diverse strategies. Other functional groups attached to the olefinic part of such nucleosides include, stannyl,[56,73] thio,[56] seleno,[58] phenyl,[73] alkynyl[56,59,60] and, to a greater extent, alkenyl.[56,59,60,73] More recently, the latter type has attracted attention in the form of $Fe(CO)_3$ complexes of 2′-*C*-vinyl- and 3′-*C*-vinyl-2′,3′-unsaturated nucleosides.[74] A novel type of 2′,3′-didehydro-2′,3′-dideoxynucleoside which is analogous to d4T, but where the unsaturation at the 2′,3′-positions is part of a benzo[*c*]furan system has been observed.[75–81] Such types of nucleoside analogues form the sole examples of 2′,3′-didehydro-2′,3′-dideoxynucleosides, which can be classified as having branching at both the 2′- and 3′-positions. Thus, routes to such compounds have required alternative approaches to those of other 2′,3′-didehydro-2′,3′-dideoxynucleoside, at least in constructing the glycone-type moiety.

Most of the strategies employed to obtain 2′,3′-didehydro-2′,3′-dideoxynucleosides branched at the olefinic group of the glycone have depended upon total rather than partial synthesis (i.e., modification of naturally occurring nucleosides). In most cases, total synthesis has involved in a convergent approach, where the glycone moiety is constructed with the required branching group in place before, or introduced after, attachment of the heterocyclic base, and where the olefinic group is formed in the final step prior to deprotection. To date, there are only a few examples[62,69,71,74,76–81] of convergent syntheses in which the final target functionalities in the 2′- and/or 3′-positions and π-character are present on the glycone precursor immediately prior to condensation to effect nucleoside formation. Classical chemistry has played a major role involving base (e.g., NaOH, *t*-BuOK, MeONa and, sometimes, DBN) catalysis to effect the elimination step and with nucleofuges such as *O*-2,3′-anhydro systems, F and OMs with the latter proving to be the most popular.[28,29,35–58] Eliminations have included those in which the leaving group is on the 2′-position and eventual branching is on the 3′-position or vice versa. An alternative popular approach has used ketonic carbonyls on either the 2′- or 3′-positions, which have facilitated both a branching group and leaving group on the same carbon, as in the example of *gem* difluoro derivatives giving fluoro-branched olefins.[44,46–48] Both base-catalysed cis- and trans-elimination reactions have proved successful. The latter have been used where the nucleofuge is substituted either α or β to the branching group, whereas the former have been limited to cases where the nucleofuge is β to the branch. cis-Eliminations have included classical-type base-catalysed eliminations, but also intramolecular base catalysis is involved with participation from a thiocarbonyl group. Base-catalysed eliminations have provided a reasonably diverse set of branching groups to include F, Cl, N_3, Me, CF_3, CN, PhS, SO_2Ph, $SnBu_3$, SePh and SeO_2Ph. Oxidative eliminations [59–62] have been used to a lesser extent in which the double bond is generated by oxidation of PhSe with MCPBA. Both total and divergent routes have been used to obtain the PhSe-substituted nucleosides. Such oxidations have, however, been limited to introducing the halogens F, Cl and Br in either the 2′- or 3′-positions of the olefinic nucleosides. The introduction of methyl or methylene groups in such nucleosides has made good use of the hetero-Cope reaction.[63–67] Although routes to nucleosides using this chemistry are multistep, the yields are quite high. Some examples have involved an efficient intramolecular addition–elimination mechanism with either oxalate or imidazole thiocarbonyl groups followed by high-yielding radical deoxygenation or desulfurisation, by Barton-type chemistry, and subsequent rearrangement of an exocyclic double bond to give a methyl group at either of the 2′- or 3′-positions. Variations which involve intermolecular introduction of a function group at the exocyclic double bond have also been successful using nucleophiles such as azide or iodide and have generated nucleosides with, e.g., CH_2N_3, CH_2OH or CH_2I, in either the 2′- or 3′-positions.[65–67] Another rearrangement has been that of an exocyclic double bond, in the form of an allylic acetate nucleoside derivative, to form the target system employing organopalladium chemistry.[59,60] Worthy of mention is an individual approach involving the construction of the glycone moiety by a 1,3-cycloaddtion reaction and eventual Cope elimination of an *N*-dimethylamino group to obtain a methyl group in the 2′-position.[68] An interesting example of how to introduce a fluoro-substituted alkene into a nucleoside has involved a Horner–Emmons reaction at an early synthetic step and eventually constructing the glycone moiety with the required functionality ready for attachment of the base.[69] This strategy has been exploited to produce a number of purine and pyrimidine 2′- and 3′-fluoro derivatives. An individual approach was to form the 3′-spiro nucleoside **236** via a 1,3-dipolar addition and ring open to form an ethoxycarbonylmethylene branch at the 3′-position.[72] A more general approach has been the direct substitution of 2′,3′-didehydro-2′,3′-dideoxynucleosides to introduce branch groups at either the 2′- or 3′-positions by coupling bromovinyl nucleosides[59,60] with organopalladium and organotin reagents or, alternatively, by forming a tertiary butyltin vinyl nucleoside and palladium-catalysed cross-coupling.[56,73] These methods have conveniently provided a variety of branch groups in the 2′- or 3′-positions including phenyl, alkyl, alkenyl, alkynyl and halogens. Additionally convenient in accessing a variety of derivatives has been the direct coupling to d4T by stannylation at the 2′-position and subsequent halogenation or palladium-assisted carbon–carbon coupling with a variety of aryl, alkyl and alkenyl groups. 2′-Alkenyl derivatives as $Fe(CO)_3$ complexes have been approached by an alternative route of constructing a 2′-*C*-vinylic glycone moiety, complexing it with $Fe(CO)_3$ and then condensing with a pyrimidine base.[74] This methodology was extended to the 3′-*C*-vinylic series with different pyrimidine bases. Finally, a series of 2′-*C*- and 3′-*C*-dibranched nucleosides with a benzo[*c*]furan core have been synthesised by a convergent route employing conventional Vorbruggen chemistry on a preformed benzo[*c*]furan system.[75–81] An interesting feature of the route to this unusual glycone system in nucleoside chemistry is the highly effective use of the stereoselective Sharpless hydroxylation to obtain compounds analogous to conventional nucleosides in the D- and L-series, accordingly.

References and notes

1. Mitsuya, H.; Weinhold, K. J.; Furman, P. A.; St Clair, M. H.; Nusinoff-Lehrman, S.; Gallo, R. C.; Bolognesi, D.; Barry, D. W.; Broder, S. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 7096–7100.

2. Herdewijn, P.; Balzarini, J.; De Clercq, E.; Pauwels, R.; Baba, M.; Broder, S.; Vanderhaeghe, H. *J. Med. Chem.* **1987**, *30*, 1270–1278.
3. Daluge, S. M.; Purifoy, D. J.; Savina, P. M.; St Clair, M. H.; Parry, N. R.; Dev, I. K.; Novak, P.; Ayers, K. M.; Reardon, J. E.; Roberts, G. B.; Fyfe, J. A.; Blum, M. R.; Averett, D. R.; Dornsife, R. E.; Domin, B. A.; Ferone, R.; Lewis, D. A.; Krenitsky, T. A. *Antimicrob. Agents Chemother.* **1994**, *38*, 1590–1603.
4. Larder, B. A.; Kemp, S. D.; Harrigan, P. R. *Science* **1995**, *269*, 696–699.
5. Mitsuya, H.; Broder, S. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 1911–1915.
6. Chu, C. K.; Schinazi, R. F.; Arnold, B. H.; Cannon, D. L.; Doboszewski, B.; Bhadti, V. B.; Gu, Z. *Biochem. Pharmacol.* **1988**, *37*, 3543–3548.
7. De Clercq, E.; Van Aerschot, A.; Herdewijn, P.; Baba, M.; Pauwels, R.; Balzarini, J. *Nucleosides Nucleotides* **1989**, *8*, 659–671.
8. Schinazi, R. F.; Sommadossi, J. P.; Saalmann, V.; Cannon, D. L.; Xie, M. Y.; Hart, G. C.; Smith, G. A.; Hahn, E. F. *Antimicrob. Agents Chemother.* **1990**, *34*, 1061–1067.
9. Coates, J. A. V.; Cammack, N.; Jenkinson, H. J.; Mutton, I. M.; Pearson, B. A.; Storer, R.; Cameron, J. M.; Penn, C. R. *Antimicrob. Agents Chemother.* **1992**, *36*, 202–205.
10. Schinazi, R. F.; Lloyd, R. M.; Nguyen, M. N.; Cannon, D. L.; Mcmillan, A.; Ilksoy, N.; Chu, C. K.; Liotta, D. C.; Bazmi, H. Z.; Mellors, J. W. *Antimicrob. Agents Chemother.* **1993**, *37*, 875–881.
11. Rousseau, F. S.; Kahn, J. O.; Thompson, M.; Mildvan, D.; Shepp, D.; Sommadossi, J. P.; Delehanty, J.; Simpson, J. N.; Wang, L. H.; Quinn, J. B.; Wakeford, C.; van der Horst, C. *J. Antimicrob. Chemother.* **2001**, *48*, 507–513.
12. Molina, J. M.; Ferchal, F.; Rancinan, C.; Raffi, F.; Rozenbaum, W.; Sereni, D.; Morlat, P.; Journot, V.; Decazes, J. M.; Chene, G. *J. Infect. Dis.* **2000**, *182*, 599–602.
13. Lin, T. S.; Schinazi, R. F.; Prusoff, W. H. *Biochem. Pharmacol.* **1987**, *36*, 2713–2718.
14. Balzarini, J.; Van Aerschot, A.; Herdewijn, P.; De Clercq, E. *Biochem. Pharmacol.* **1989**, *38*, 869–874.
15. Daluge, S. M.; Good, S. S.; Faletto, M. B.; Miller, W. H.; St Clair, M. H. *Antimicrob. Agents Chemother.* **1997**, *41*, 1082–1093.
16. Tisdale, M.; Alnadaf, T.; Cousens, D. *Antimicrob. Agents Chemother.* **1997**, *41*, 1094–1098.
17. Faletto, M. B.; Miller, W. H.; Garvey, E. P.; St Clair, M. H.; Daluge, S. M. *Antimicrob. Agents Chemother.* **1997**, *41*, 1099–1107.
18. Arimilli, M. N.; Kim, C. U.; Dougherty, J.; Mulato, A.; Oliyai, R.; Shaw, J. P.; Cundy, K. C.; Bischofberger, N. *Antiviral Chem. Chemother.* **1997**, *8*, 557–564.
19. Robbins, B. L.; Srinivas, R. V.; Kim, C.; Bischofberger, N.; Fridland, A. *Antimicrob. Agents Chemother.* **1998**, *42*, 612–617.
20. Bolon, P. J.; Wang, P.; Chu, C. K.; Gosselin, G.; Boudou, V.; Pierra, C.; Mathé, C.; Imbach, J. L.; Faraj, A.; Abdelaziz El Alaoui, M.; Sommadossi, J. P.; Balakrishna Pai, S.; Zhu, Y. L.; Lin, J. S.; Cheng, T. C.; Schinazi, R. F. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1657–1662.
21. Lin, T. S.; Luo, M. Z.; Liu, M. C.; Zhu, Y. L.; Gullen, E.; Dutschman, G. E.; Cheng, Y. C. *J. Med. Chem.* **1996**, *39*, 1757–1759.
22. Herdewijn, P.; Pauwels, R.; Baba, M.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1987**, *30*, 2131–2137.
23. Balzarini, J.; Pauwels, R.; Baba, M.; Robins, M. J.; Zou, R.; Herdewijn, P.; De Clercq, E. *Biochem. Biophys. Res. Commun.* **1987**, *145*, 269–276.
24. Shi, J.; Mcatee, J. J.; Schlueter-Wirtz, S.; Tharnisch, P.; Juodawlkis, A.; Liotta, D. C.; Schinazi, R. F. *J. Med. Chem.* **1999**, *42*, 859–867.
25. Ma, L.; Hurwitz, S. J.; Shi, J. X.; Mcatee, J. J.; Liotta, D. C.; Mcclure, H. M.; Schinazi, R. F. *Antimicrob. Agents Chemother.* **1999**, *43*, 381–384.
26. Baba, M.; Pauwels, R.; Balzarini, J.; Herdewijn, P.; De Clercq, E. *Biochem. Biophys. Res. Commun.* **1987**, *145*, 1080–1086.
27. Herdewijn, P.; Balzarini, J.; Baba, M.; Pauwels, R.; Van Aerschot, A.; Janssen, G.; De Clercq, E. *J. Med. Chem.* **1988**, *31*, 2040–2048.
28. Martin, J. A.; Busshnell, D. J.; Duncan, I. B.; Dunsdon, S. J.; Hall, M. J.; Machin, P. J.; Merrett, J. H.; Parkes, K. E. B.; Roberts, N. A.; Thomas, G. J.; Galpin, S. A. *J. Med. Chem.* **1990**, *33*, 2137–2145.
29. Tann, C. H.; Brodfueher, P. R.; Brundidge, S. P.; Sapino, C.; Howell, H. G. *J. Org. Chem.* **1985**, *50*, 3644–3647.
30. Horwitz, J. P.; Chua, J.; Da Rooge, M. A.; Noel, M. *Tetrahedron Lett.* **1964**, *38*, 2725–2727.
31. Horwitz, J. P.; Chua, J.; Klundt, I. L.; Da Rooge, M. A.; Noel, M. *J. Am. Chem. Soc.* **1964**, *86*, 1896–1897.
32. Horwitz, J. P.; Chua, J. *Synthetic Procedures in Nucleic Acid Chemistry*; Zobrach, W. W., Tipson, R. S., Eds.; Interscience: New York, NY, 1968; Vol. 1, p 344.
33. Horwitz, J. P.; Chua, J.; Da Rooge, M. A.; Noel, M.; Klundt, I. L. *J. Org. Chem.* **1966**, *31*, 205–211.
34. Horwitz, J. P.; Chua, J.; Noel, M.; Donatti, J. T. *J. Org. Chem.* **1967**, *32*, 817–818.
35. Sterzycki, R. Z.; Ghazzouli, I.; Brankovan, V.; Martin, J. C.; Mansuri, M. M. *J. Med. Chem.* **1990**, *33*, 2150–2157.
36. Huang, J. T.; Chen, L. C.; Wang, L.; Kim, M. H.; Warshaw, J. A.; Armastrong, D.; Zhu, Q. Y.; Chou, T. C.; Watanabe, K. A.; Matulic-Adamic, J.; Su, T. S.; Fox, J. J.; Polsky, B.; Baron, P. A.; Gold, J. W. M.; Hardy, W. D.; Zuckerman, E. *J. Med. Chem.* **1991**, *34*, 1640–1646.
37. Mikhailopoulo, I. A.; Pricota, T. I.; Sivets, G. G.; Altona, C. *J. Org. Chem.* **2003**, *68*, 5897–5908.
38. Mikhailopoulo, I. A.; Poopeiko, N. E.; Pricota, T. I.; Sivets, G. G.; Kvasyuk, E. I.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1991**, *34*, 2195–2202.
39. Lavaire, S.; Plantier-Royon, R.; Portella, C.; De Monte, M.; Kirn, A.; Aubertin, A. M. *Nucleosides Nucleotides* **1998**, *17*, 2267–2280.
40. Lavaire, S.; Plantier-Royon, R.; Portella, C. *J. Carbohydr. Chem.* **1996**, *15*, 361–370.
41. Jeannot, F.; Gosselin, G.; Standring, D.; Bryant, M.; Sommadossi, J. P.; Loi, A. G.; La Colla, P.; Mathé, C. *Bioorg. Med. Chem.* **2002**, *10*, 3153–3161.
42. Zhu, W.; Gumina, G.; Schinazi, R. F.; Chu, C. K. *Tetrahedron* **2003**, *59*, 6423–6431.
43. Filichev, V. V.; Brandt, M.; Pedersen, E. B. *Carbohydr. Res.* **2001**, *333*, 115–122.
44. Van Aerschot, A.; Herdewijn, P.; Balzarini, J.; Pauwels, R.; De Clercq, E. *J. Med. Chem.* **1989**, *32*, 1743–1749.
45. Bergstrom, D.; Romo, E.; Shum, P. *Nucleosides Nucleotides* **1987**, *6*, 53–61.
46. Chong, Y.; Gumina, G.; Mathew, J. S.; Schinazi, R. F.; Chu, C. K. *J. Med. Chem.* **2003**, *46*, 3245–3256.
47. Gumina, G.; Schinazi, R. F.; Chu, C. K. *Org. Lett.* **2001**, *3*, 4177–4180.

48. Zhou, W.; Gumina, G.; Chong, Y.; Wang, J.; Schinazi, R. F.; Chu, C. K. *J. Med. Chem.* **2004**, *47*, 3399–3408.
49. Wu, J. C.; Chattopadhyaya, J. *Tetrahedron* **1989**, *45*, 855–862.
50. Fedorov, I. I.; Kazmina, E. M.; Novicov, N. A.; Gurskaya, G. V.; Bochkarev, A. V.; Kasko, M. V.; Victorova, L. S.; Kukhanova, M. K.; Balzarini, J.; De Clercq, E.; Krayevski, A. A. *J. Med. Chem.* **1992**, *35*, 4567–4575.
51. Matsuda, A.; Nakajima, Y.; Azuma, A.; Tanaka, M.; Sasaki, T. *J. Med. Chem.* **1991**, *34*, 2917–2919.
52. Azuma, A.; Nakajima, Y.; Nishizono, N.; Minakawa, N.; Suzuki, M.; Hanaoka, K.; Kobayashi, T.; Tanaka, M.; Sasaki, T.; Matsuda, A. *J. Med. Chem.* **1993**, *36*, 4183–4189.
53. Calvo-Mateo, A.; Camarasa, M. J.; Diaz-Ortiz, A.; De Las Heras, F. G.; Alemany, A. *Tetrahedron* **1988**, *44*, 4895–4903.
54. Matsuda, A.; Satoh, M.; Nakashima, H.; Yamamoto, N.; Ueda, T. *Heterocycles* **1988**, *27*, 2545–2548.
55. Faul, M. M.; Huff, B. E.; Dunlap, S. E.; Frank, S. A.; Fritz, J. E.; Kaldor, S. W.; Le Tourneau, M. E.; Stazak, M. A.; Ward, J. A.; Werner, J. A.; Winneroski, L. L. *Tetrahedron* **1997**, *53*, 8085–8104.
56. Onuma, S.; Kumamoto, H.; Kawato, M.; Tanaka, H. *Tetrahedron* **2002**, *58*, 2497–2503.
57. Wu, J. C.; Pathak, T.; Tong, W.; Vial, J. M.; Remaud, G.; Chattopadhyaya, J. *Tetrahedron* **1988**, *44*, 6705–6722.
58. Wu, J. C.; Chatoopadhyaya, J. *Tetrahedron* **1989**, *45*, 4507–4522.
59. Haraguchi, K.; Itoh, Y.; Tanaka, H.; Miyasaka, T. *Tetrahedron Lett.* **1991**, *32*, 3391–3394.
60. Haraguchi, K.; Itoh, Y.; Tanaka, H.; Akita, M.; Miyasaka, T. *Tetrahedron* **1993**, *49*, 1371–1390.
61. Haraguchi, K.; Tanaka, H.; Itoh, Y.; Miyasaka, T. *Tetrahedron Lett.* **1991**, *32*, 777–780.
62. Chen, S. H.; Wang, Q.; Mao, J.; King, I.; Dutschman, G. E.; Gullen, E. A.; Cheng, Y. C.; Doyle, T. W. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1589–1594.
63. Matsuda, A.; Okajima, H.; Ueda, T. *Heterocycles* **1989**, *29*, 25–28.
64. Czernecki, S.; Ezzitouni, A.; Krausz, P. *Synthesis* **1990**, 651–653.
65. Czernecki, S.; Ezzitouni, A. *J. Org. Chem.* **1992**, *57*, 7325–7328.
66. Czernecki, S.; Ezzitouni, A. *Tetrahedron Lett.* **1993**, *34*, 315–318.
67. Ionnidis, P.; Classon, B.; Samuelsson, B.; Kvarnstrom, I. *Nucleosides Nucleotides* **1993**, *12*, 449–462.
68. Chiacchio, U.; Rescifina, A.; Iannazzo, D.; Romeo, G. *J. Org. Chem.* **1999**, *64*, 28–36.
69. Lee, K.; Choi, Y.; Gullen, E.; Schlueter-Wirtz, S.; Schinazi, R. F.; Cheng, Y. C.; Chu, C. K. *J. Med. Chem.* **1999**, *42*, 1320–1328.
70. Lee, K.; Choi, Y.; Gumina, G.; Zhou, W.; Schinazi, R. F.; Chu, C. K. *J. Med. Chem.* **2002**, *45*, 1313–1320.
71. Chen, X.; Zhou, W.; Schinazi, R. F.; Chu, C. K. *J. Org. Chem.* **2004**, *69*, 6034–6041.
72. Hossain, N.; Papchikhin, A.; Plavec, J.; Chattopahyaya, J. *Tetrahedron* **1993**, *49*, 10133–10156.
73. Kumamoto, H.; Tanaka, H. *J. Org. Chem.* **2002**, *67*, 3541–3547.
74. Schlawe, D.; Majdalani, A.; Velcicki, J.; Hebler, E.; Wieder, T.; Prokop, A.; Scmalz, H. G. *Angew. Chem., Int. Ed.* **2004**, *43*, 1731–1734.
75. Ewing, D. F.; Fahmi, N.; Len, C.; Mackenzie, G.; Ronco, G.; Villa, P.; Shaw, G. *Nucleosides Nucleotides* **1999**, *18*, 2613–2630.
76. Ewing, D. F.; Fahmi, N.; Len, C.; Mackenzie, G.; Pranzo, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3561–3565.
77. Belloli, E.; Len, C.; Mackenzie, G.; Ronco, G.; Bonte, J. P.; Vaccher, C. *J. Chromatogr., A* **2001**, *943*, 91–100.
78. Ewing, D. F.; Len, C.; Mackenzie, G.; Ronco, G.; Villa, P. *Tetrahedron: Asymmetry* **2000**, *11*, 4995–5002.
79. Sélouane, A.; Vaccher, C.; Villa, P.; Postel, D.; Len, C. *Tetrahedron: Asymmetry* **2002**, *13*, 407–413.
80. Pilard, S.; Riboul, D.; Glaçon, V.; Moitessier, N.; Chapleur, Y.; Postel, D.; Len, C. *Tetrahedron: Asymmetry* **2002**, *13*, 529–537.
81. Egron, D.; Périgaud, C.; Gosselin, G.; Aubertin, A. M.; Faraj, A.; Sélouane, A.; Postel, D.; Len, C. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4473–4475.

Biographical sketch

Christophe Len was born in L'Isle Adam (France) in 1966. He received his Ph.D. from the University of Picardie-Jules Verne (UPJV) in Amiens (France) under the supervision of Professor P. Villa in the field of carbohydrate chemistry. In 1996, he joined Doctor G. Mackenzie's group at the University of Hull (UK) as a post-doctoral fellow to work on the synthesis of nucleoside analogues. In 1997, he became Maître de Conférences at UPJV and worked on the chemistry of antiviral nucleoside analogues specialising on those with novel glycone systems. In 2003, he received his habilitation and was promoted to full Professor in 2004 at the University of Poitiers (France). His current main research interests are in the total synthesis of natural products and bioactive molecules, which include carbohydrates and nucleoside analogues having restricted conformations.

Grahame Mackenzie graduated with a B.Tech. and Ph.D. at the University of Bradford. His post graduate and post-doctoral research fellowship work were with Gordon Shaw at the University of Bradford and then with George Brown at the Sloan Kettering Cancer Research Institute, New York, USA. He took an appointment as Senior Lecturer at the University of Lincoln and then moved to the University of Hull, firstly as a Senior Lecturer and then as Reader in Bio-organic Chemistry. He has been a Visiting Professor at the University of Hokkaido Japan and CNRS Post Rouge, Director de Recherche at the Université de Lyon, France. Since 1992 he has been a Visiting Professor at the Université de Picardie, Jules Verne, Université d'Artois and Université de Limoges France. He has published some 130 papers in the fields of carbohydrate and nitrogen heterocyclic chemistry, particularly in relation to the synthesis of nucleosides and glycolipids. More recently his work has focused on the chemistry of plant spore materials and he is Scientific Director of Sporomex Ltd.

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Aerobic oxidation of primary alcohols under mild aqueous conditions promoted by a dinuclear copper(II) complex

Susanne Striegler*

Department of Chemistry and Biochemistry, 179 Chemistry Building, Auburn University, Auburn, AL 36849-5312, USA

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Abstract—A sugar-discriminating dinuclear copper(II) complex was investigated for its ability to promote aerobic oxidation of primary benzylic alcohols in the presence of TEMPO and base. The transformation of benzyl alcohol to benzaldehyde was chosen as exploratory model reaction. The constitution of the catalytically active species was deducted from isothermal titration calorimetry and kinetic experiments, and the catalytic reaction was characterized both in aqueous organic and aqueous solution. The dinuclear complex is found to selectively oxidize primary over secondary alcohols in aqueous solution at ambient temperature with a turnover rate of 9 h^{-1}. A mechanism for the catalytic cycle is proposed.

1. Introduction

Ecologically benign oxidations of alcohol groups have attracted much attention in recent years.[1–8] Catalysts for the oxidation of petrochemicals are required to have a very broad substrate scope that includes primary and secondary, aliphatic, benzylic, and allylic alcohols. On the other hand, catalysts designed for the transformation of biomolecules need to be able to selectively transform only one out of several different functional groups in the same molecule, ideally without protection of the remaining other groups. The development of a regioselective oxidation method to catalytically transform underivatized carbohydrates into hexose-6-carbaldehydes in aqueous solution is a long-term goal in this laboratory. Hexose-6-carbaldehydes are precursor compounds for unnatural carbohydrates that might evolve as new synthons for the preparation of glycosylated pharmaceuticals.[9]

Recently reported aerobic catalyst that promote oxidation of primary alcohols into aldehydes, while preventing overoxidation of this aldehyde into the corresponding carboxylic acid, use in situ prepared mixtures of Cu(II) salts and bipyridine ligands[10–13] or mononuclear Cu(I) phenanthroline complexes[14–17] in the presence of base and 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) as co-catalysts. Selectivity of mononuclear bipyridine copper(II) complexes toward oxidation of activated primary, but not secondary benzylic alcohols has been observed.[10,11] Oxidation of secondary benzylic and aliphatic alcohols into ketones is demonstrated for derivatized bipyridine copper(I) catalysts that are employed at elevated reaction temperature in the presence of excess of TEMPO.[18] The conversion of benzyl alcohol (**1**) into benzaldehyde (**2**) is usually used to establish oxidation ability of the catalyst toward primary alcohols due to the higher reactivity of the aromatic alcohols when compared to aliphatic alcohols, and the ease of detection by gas chromatographic analysis.[10–12,14–17]

A large variety of mono- and dinuclear copper(II) complexes with and without pyridine moieties in the backbone ligand were synthesized in this laboratory and investigated for their carbohydrate recognition properties.[19–22] All selected mononuclear complexes were incapable to promote oxidation of **1** into **2**, while the transformation is conveniently achieved with the dinuclear complex *N*,*N*-bis[(2-pyridylmethyl)-1,3-diaminopropan-2-olato] (μ-acetato) dicopper(II) perchlorate (Cu_2(bpdpo), **3**). Complex **3** was previously established to selectively discriminate between various carbohydrates depending on the number of hydroxyl groups of the sugar involved in coordination to **3**.[20,21] It is therefore postulated that if complex **3** is able to catalyze oxidation reactions in water, then it may be possible to use this complex for selective carbohydrate and glycoside oxidation.

To establish catalytic transformation ability of **3**, the aerobic oxidation of **1** into **2** was chosen as exploratory model study. The reaction is investigated on dependence of the concentrations of the co-catalysts TEMPO and base; the kinetic of the reaction is investigated in both aqueous organic and predominantly aqueous solutions at ambient temperature.

* Tel.: +1 334 844 6954; fax: +1 334 844 6959; e-mail: susanne.striegler@auburn.edu

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In addition, the proposed catalytically active species is characterized and a mechanism for the reaction suggested. The results obtained are discussed below.

2. Results and discussion

2.1. Composition of the dinuclear copper(II) complex in alkaline solution

Spectrophotometric titration of the backbone ligand of the sugar-discriminating dinuclear copper(II) complex *N*,*N*-bis-[(2-pyridylmethyl)-1,3-diaminopropan-2-olato] (μ-acetato) dicopper(II) perchlorate (Cu_2(bpdpo), **3**) in the presence of 2-fold molar amounts of copper(II) ions with sodium hydroxide shows that the bridging acetate anion bound in the solid state is exchanged against two hydroxyl ions and two water molecules in alkaline aqueous solution (Scheme 1).[23,24] Two species, $[Cu_2(L_{-H})(OH)]^{2+}$ (**3a**) and $[Cu_2(L_{-H})(OH)_2]^{+}$ (**3b**), are observed in equilibrium depending upon the pH of the solution (Fig. 1).[20] A mononuclear species, $[Cu(L)]^{2+}$, is present below pH 8.

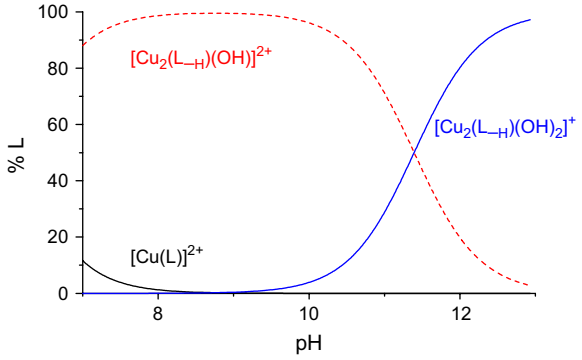


Figure 1. Distribution of species at pH 7–13 related to the binuclear copper(II) complex Cu_2(bpdpo) (**3**), calculated from measured UV–vis spectra in dependence of the pH.

2.2. Coordination of the TEMPO co-catalyst to the dinuclear copper(II) complex

Isothermal titration calorimetry was used to determine the interaction between the dinuclear copper(II) complex **3** and the TEMPO co-catalyst in aqueous alkaline acetonitrile (Fig. 2). Relating the titration data to a sequential binding model for four binding sites provide the best fit and reveal exothermic interaction of the first TEMPO molecule with one of the copper(II) centers with a rather low binding constant (K_1=320), while coordination of the second molecule of TEMPO is an endothermic process resulting in a strong TEMPO–**3**–TEMPO complex (K_2=9800). The interaction of the remaining two coordination sites of the Cu(II) core with TEMPO is exothermic, but results in weak TEMPO association only (K_3=400; K_4=14). The titration data reveal that the second molecule of TEMPO binds strongly to the dinuclear metal complex **3**, provided the first molecule of TEMPO is already weakly associated. This observation suggests that excess of TEMPO will enforce formation of a TEMPO–**3**–TEMPO complex in alkaline solution by replacement of coordinated water in **3b** (Chart 1). Further TEMPO coordination to **3b** is presumably slowed down as (a) replacement of hydroxyl ions is required, which coordinate stronger than water molecules, and (b) already coordinated TEMPO molecules provide steric hindrance to further association of TEMPO.

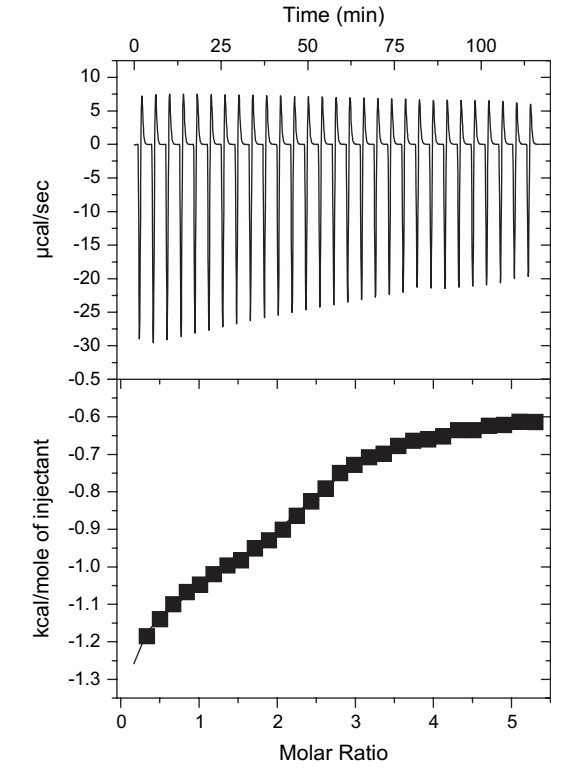
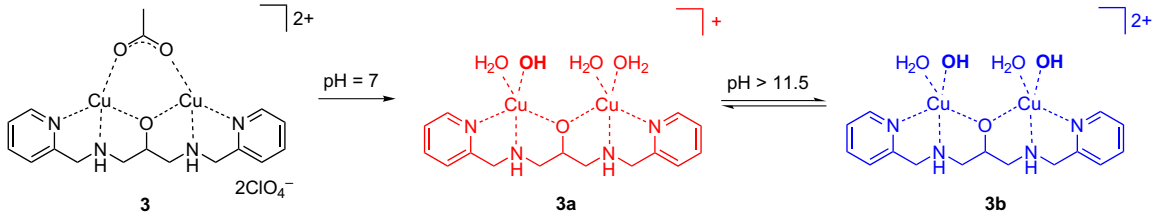


Figure 2. Isothermal titration of Cu_2(bpdpo) (**3**) with TEMPO in aqueous, alkaline acetonitrile (CH_3CN/H_2O=2/1) at 300 K. Fitting of the data was best using the sequential binding model for four sites; χ=61.5; K_1=322±28, ΔH_1=−3261±181 kcal mol^{-1}, ΔS_1=0.608 cal mol^{-1} K^{-1}; K_2=9.81E3±9.8E2, ΔH_2=877.9±192 kcal mol^{-1}, ΔS_2=21.2 cal mol^{-1} K^{-1}; K_3=393±35, ΔH_3=−1146±117 kcal mol^{-1}, ΔS_3=8.05 cal mol^{-1} K^{-1}; K_4=14.0±2.1, ΔH_4=−2.998E4±3.94E3 kcal mol^{-1}, ΔS_4=−94.6 cal mol^{-1} K^{-1}.



Scheme 1. Equilibria of the major species $[Cu_2(L_{-H})(OH)]^{2+}$ (**3a**) and $[Cu_2(L_{-H})(OH)_2]^{+}$ (**3b**) formed in alkaline water.

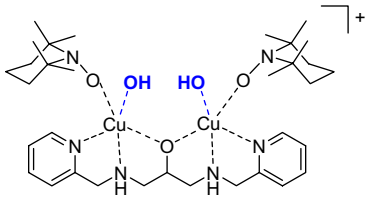
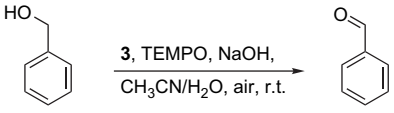


Chart 1. Suggested constitution of the catalytically active species derived from dinuclear copper(II) complex **3** and TEMPO.

2.3. Dependence of the catalytic activity of the dinuclear copper(II) complex on TEMPO and base as co-catalysts

The catalytic oxidation of benzyl alcohol **1** into benzaldehyde **2** was employed as exploratory model reaction to study the oxidation ability of **3** and was monitored by GC analysis (Scheme 2). All reactions were conducted under aerobic conditions at ambient temperature with 5 mol % of **3** with respect to the substrate concentration. Addition of TEMPO and base to a solution of **3** in presence of oxygen is required to detect any transformation, as has been established by appropriate control reactions (data not shown). Overoxidation of **2** into benzoic acid was not observed under the given conditions, which is in agreement with results for mononuclear copper(I) and copper(II) complexes reported by others earlier.[10,17]



Scheme 2. Oxidation of benzyl alcohol (**1**) into benzaldehyde (**2**) promoted by dinuclear copper(II) complex **3** in the presence of TEMPO and base.

According to the proposed structure of the dinuclear catalytically active species (Chart 1), the oxidation is expected to depend in a linear fashion on the concentration of the co-catalyst TEMPO. In order to verify this, product formation was determined by gas chromatography after withdrawing aliquots of the reaction mixture at defined time points and subsequent decomposition of the catalyst **3** with sodium sulfide (see Section 3). The molar ratios of complex **3** and TEMPO were varied in the presence of excess base (Fig. 3).

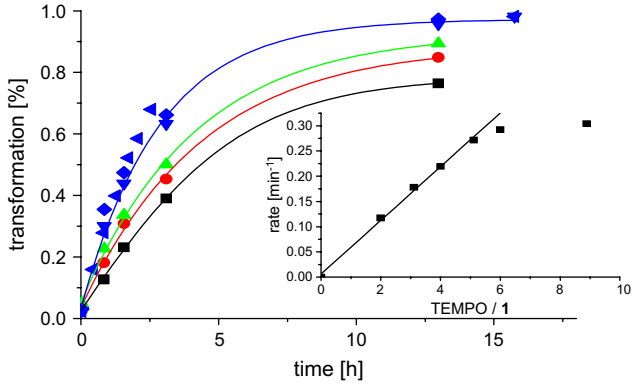


Figure 3. Oxidation of benzyl alcohol into benzaldehyde in the presence of **3** (4.5 mM) and excess base (80 mM) in CH_3CN/H_2O=2/1; the molar ratio between the copper(II) ions of **3** and TEMPO equals (a) 2:2 (■), (b) 2:3 (●), (c) 2:4 (▲), and (d) 2:5 (◀), 2:6 (▶), or 2:10 (◆). The inset shows a linear correlation between the initial rate and the TEMPO concentration for low co-catalyst concentrations.

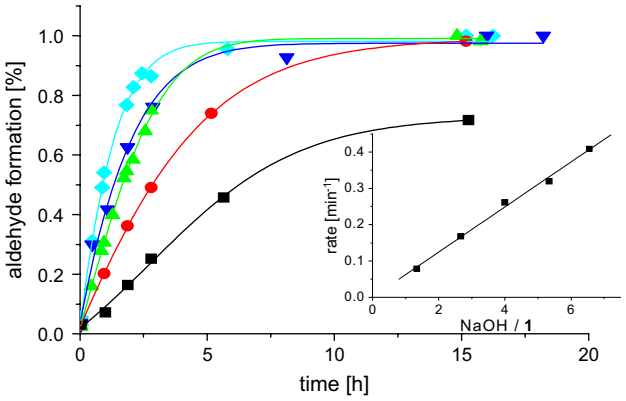


Figure 4. Oxidation of benzyl alcohol (90 mM) into benzaldehyde in the presence of **3** (4.5 mM) and excess TEMPO (18 mM) in CH_3CN/H_2O=2/1; the molar ratio between the copper(II) ions of **3** and NaOH equals (a) 2:1.3 (■), (b) 2:2.6 (●), (c) 2:4 (▲), (d) 2:5 (▼) and, (e) 2:6.7 (◆). The inset shows the linear correlation between the initial rate and the base concentration.

Increasing the TEMPO concentration by 2-fold doubles the initial rate acceleration of the oxidation, when the molar ratio between the copper(II) ions and TEMPO is kept below 2:5. Additional increase of the TEMPO concentration does not speed up the initial rate of the reaction further.

In the next experiment, the molar ratio of TEMPO to the dinuclear complex **3** was kept constant at 4:1, while the base concentration was varied. Linear dependence of the initial reaction rate of the oxidation on the base concentration is observed (Fig. 4). Using less than equimolar amounts of base compared to the amount of copper(II) ions in the metal complex core leads to incomplete substrate oxidation indicating that formation of the catalytically active species requires at least one hydroxyl ion per copper ion. Increasing the base concentration by 2-fold results in a linear increase of the initial rate of the oxidation suggesting that molar amounts of base with respect to **3** are involved in the catalytic turnover. Further, control experiments demonstrated that the reaction does not proceed in the absence of the dinuclear copper(II) complex, or if copper(II) acetate is used as a potential catalyst. The oxidation does also not proceed in pure acetonitrile indicating that water is required during the catalytic turnover.

Last, the initial rate of the aerobic oxidation of benzyl alcohol in the presence of **3** (4.5 mM), TEMPO (18 mM), and NaOH (18 mM) in aqueous organic solution (CH_3CN/H_2O=2/1) was determined (Fig. 5). The oxidation follows classical saturation kinetics and was fitted with Michaelis–Menten model for enzymatic reactions, giving a turnover rate (k_{cat}) of 0.64 min^{-1} (=38 h^{-1}) and a substrate affinity (K_m) of 340 mM. The initial rate of the reaction depends linearly on the catalyst concentration.

2.4. Selectivity for primary versus secondary benzylic alcohols, control reactions

Carbohydrates are multifunctional biomolecules containing primary and secondary alcohol groups. Protection and deprotection of hydroxyl groups that need to remain unchanged are therefore required prior to application of conventional oxidation methods. In the light of our postulate

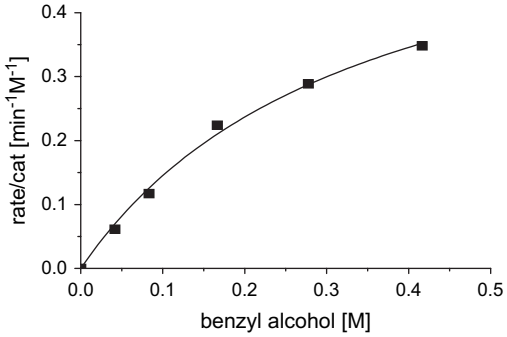


Figure 5. Initial rate plot of the aerobic oxidation of benzyl alcohol in the presence of **3** (4.5 mM), TEMPO (22 mM), and NaOH (18 mM) in aqueous acetonitrile (CH_3CN/H_2O=2/1) at ambient temperature. Initial rate data are plotted against concentrations of the substrate benzyl alcohol; k_{cat}=0.64 min^{-1} (=38 h^{-1}), K_m=340 mM.

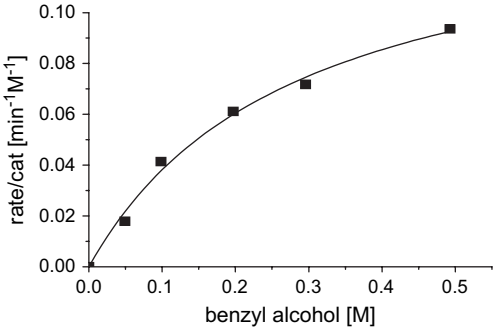


Figure 7. Initial rate plot of the aerobic oxidation of benzyl alcohol in the presence of **3** (4.5 mM) and TEMPO (22 mM) in aqueous NaOH (18 mM) containing 8% CH_3CN at ambient temperature. Initial rate data are plotted against increasing concentrations of the substrate benzyl alcohol; k_{cat}=0.15 min^{-1} (=9 h^{-1}), K_m=281 mM.

that dinuclear complex **3** may be able to selectively oxidize the primary hydroxyl group in carbohydrates, we investigated its ability to regioselectively oxidize a primary alcohol function over a secondary in a model substrate. For that purpose, we chose the oxidation of 1-phenylethanol into acetophenone under the same conditions as for the oxidation of benzyl alcohol.

The reaction was monitored by GC analysis. No evidence for oxidation of the activated secondary alcohol was found, even if the reaction was allowed to proceed for 15 h after which the oxidation of benzyl alcohol was completed (Fig. 6). This finding suggests that the hydrogen atom abstraction by TEMPO in the secondary alcohol might be hindered by the methyl group in 1-phenylethanol, i.e., the methyl group in 1-phenylethanol does not stabilize the forming TEMPOH species. In contrast, the formation of TEMPOH during benzyl alcohol oxidation can be stabilized through hydrogen bonds between TEMPOH and the aldehyde proton in benzaldehyde. A similar rationale for the observed selectivity was given by others previously.[10,11]

2.5. Oxidation in water

All experiments reported before were conducted in aqueous organic solvent (CH_3CN/H_2O=2/1). However, the most suitable reaction conditions for the transformation of biomolecules involve water as main solvent. Polar organic solvents, such as pyridine or DMF, dissolve carbohydrates, but are less attractive from both an economic and environmental viewpoint. The catalytic oxidation of benzyl alcohol into benzaldehyde was subsequently conducted in aqueous solution at pH 12.5. Due to the low solubility of TEMPO and high benzyl alcohol concentrations in water, even at alkaline pH, 8% acetonitrile are necessary in the reaction solution. The proceeding of the oxidation was monitored by GC analysis (Fig. 7).

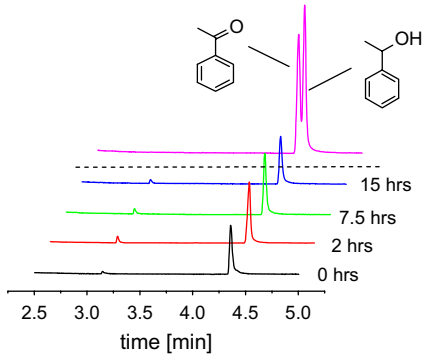


Figure 6. Gas chromatographic traces of sample aliquots of the putative catalytic oxidation of 1-phenylethanol (90 mM) into acetophenone for 0–15 h. The reaction was conducted in the presence of **3** (4.5 mM), TEMPO (18 mM), and NaOH (18 mM) in CH_3CN/H_2O=2/1 at ambient temperature; the trace in magenta refers to an equimolar mixture of commercially available 1-phenylethanol and acetophenone standards separated under the same conditions.

The oxidation follows classical saturation kinetics, and non-linear regression was applied to fit the data according to the Michaelis–Menten model, giving a turnover rate (k_{cat}) of 0.15 min^{-1} (9 h^{-1}) and a substrate affinity (K_m) of 281 mM. As the reaction does not proceed in the absence of **3** or when Cu(II) acetate is used instead of **3**, the self-promoted (k_{non}) and the potential metal ion-catalyzed oxidation of the substrate were not determined. The turnover rate of the catalytic benzyl alcohol oxidation by **3** in aqueous solution is only 4-fold slower than the same reaction in aqueous acetonitrile (see Fig. 5, k_{cat}=38 h^{-1}, K_m=340 mM).

Although our catalytic system promotes alcohol oxidation with a turnover in the same order of magnitude as the catalyst recently reported by Sheldon et al. (k_{cat}=14 h^{-1}),[10] it has several advantages for our intended purpose toward carbohydrate oxidation: (i) the system is able to work under mild, predominantly aqueous conditions, (ii) the dinuclear copper(II) complex **3** is structurally characterized in solution, (iii) the constitution of the most likely catalytically active species has been established, and (iv) complex **3** is able to differentiate between carbohydrates containing *cis*-diols and *cis*,*cis*-triols.[19–21] In the light of these results, we are encouraged to extend our investigations in further studies about the oxidation of carbohydrates.

2.6. Oxidation mechanism

Based on the determination of the catalytically active species and the observed catalytic turnover of benzyl alcohol into benzaldehyde, a mechanism for the catalytic cycle of the oxidation is proposed (Fig. 8). The dinuclear

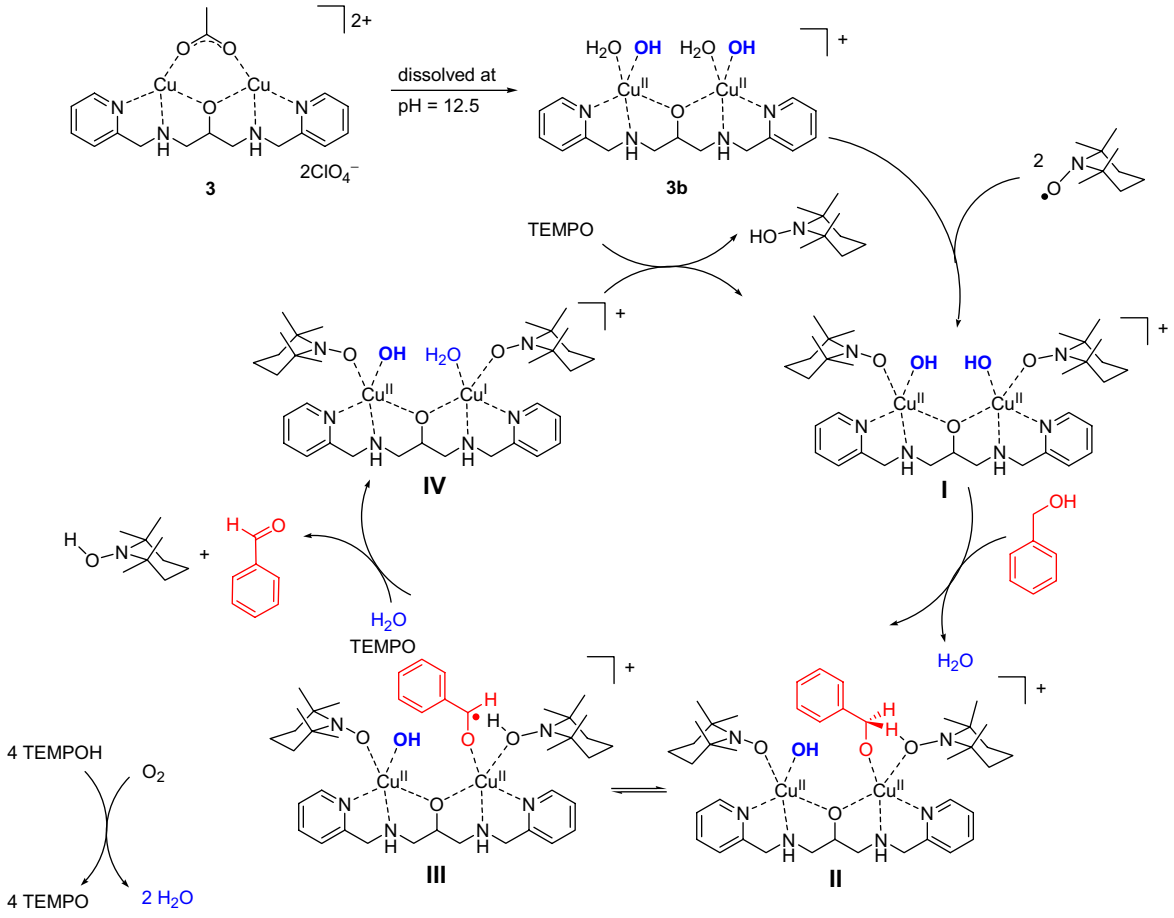


Figure 8. Proposed mechanism for the oxidation of benzyl alcohol into benzaldehyde by the dinuclear copper(II) complex **3**.

copper(II) complex **3** exchanges first the bridging acetate ion against two water molecules and two hydroxyl groups. Subsequently, TEMPO radicals replace the weakly coordinating water molecules (Fig. 8, species **I**). The substrate benzyl alcohol is then coordinated to one copper(II) center under displacement of one hydroxyl group (Fig. 8, species **II**). This is possible either by binding of the anion from the equilibrium of alcohol and alcoholate that exists in basic solution, or by deprotonation of the alcohol at the copper(II) center and release of water. Subsequent transfer of a hydrogen atom to TEMPO is followed by release of benzaldehyde under reduction of Cu(II) into Cu(I) and coordination of water (Fig. 8, species **III**). The formed TEMPOH is very likely weakly coordinated to **3** and as such easily displaced from the complex by another TEMPO radical (Fig. 8, species **IV**). Regeneration of the catalytically active species is then achieved by formal deprotonation of the coordinated water molecule by another molecule of TEMPO radical and oxidation of Cu(I) into Cu(II) (Fig. 8, species **I**). The two molecules of TEMPOH that are formed during the catalytic cycle are reoxidized by oxygen present in the reaction solution. Control experiments (data not shown) have demonstrated that in the absence of both oxygen or TEMPO no reaction is observed, indicating that oxygen is the regenerative agent for the TEMPO radical and not for the copper(II) complex **3**.

The proposed mechanism is in agreement with the finding that (a) only two molecules of TEMPO coordinate strongly to the transition metal complex (see Section 2.2), while (b) the catalytic transformation is linearly dependent on the TEMPO concentration as long as the molar ratio between **3** and TEMPO is less than 1:5. Further increase did not show a significant effect (see Fig. 3). The proposed mechanism furthermore reflects the observed linear dependence of the initial reaction rate on the hydroxide concentration (see Fig. 4).

In conclusion, a catalytic system based on a dinuclear copper(II) complex **3** has been developed that is able to oxidize primary benzylic alcohols catalytically at ambient temperature. Base and TEMPO are required as co-catalysts, water and oxygen are in addition necessary for the catalytic reaction. Our current efforts are directed toward the detailed investigation of the aerobic oxidation of unactivated aliphatic alcohols, including monosaccharides, in purely aqueous alkaline solution, utilizing the introduced system of dinuclear copper(II) complex **3** and TEMPO.

3. Experimental

3.1. General

All chemicals were purchased from Sigma–Aldrich and used without further purification. Nanopure water (18 MΩ) was used for all kinetic experiments described. The dinuclear copper complex **3** was prepared as described previously.[20,21]

3.2. Typical procedure for alcohol oxidation

Round bottom flasks (50 mL) were charged with the dinuclear copper(II) complex **3** (30 mg, 4.57 mmol) dissolved in 9 mL of alkaline aqueous acetonitrile each (CH_3CN/H_2O=2/1). The solutions turned from dark blue to yellow-green after vigorous stirring at ambient temperature for 45 min. Subsequently, 200 μL aliquots of a TEMPO stock solution in acetonitrile were added to adjust the total TEMPO concentration in the final reaction mixtures to 18 mM. The solutions were stirred for another 30 min to allow formation of the catalytically active species. Darkening of the yellow-green solutions to dark green is observed. Varying amounts of benzyl alcohol are then added to each flask via syringe, and the total volume of each solution is adjusted with the solvent mixture to a final volume of 10 mL yielding final substrate concentrations in the range from 50 to 450 mM. Sample aliquots (20 μL) of the reaction mixture were taken in 60 s intervals, diluted with 10 μL of a 1 M aqueous Na_2S solution and 100 μL acetonitrile, centrifuged to remove precipitated CuS and filtered. The supernatant was subjected to GC analysis. The same procedure was followed for the oxidation in water, except that alkaline water was used and benzyl alcohol was added as aliquots from a CH_3CN stock solution, so that the final amount of acetonitrile in water remained at 8% for all flasks.

3.3. Typical procedure for GC analysis

All oxidation experiments were monitored on a A14 gas chromatograph (Shimadzu) with AOC-20 autoinjector and flame ionization detector. Helium was used as carrier gas, a Rtx-1 capillary column (30 m×0.25 mm×0.25 μm) was used as stationary phase. Sample aliquots were treated prior to analysis as described above. GC analysis for all experiments was performed isocratic at 100 °C, 0.25 μL injection (1/100 split) at 200 °C and flame ionization detection at 220 °C. The retention of benzyl alcohol (**1**) allows baseline separation from benzaldehyde (**2**) under these conditions (R_f (**1**)=3.9 min; R_f (**2**)=3.0 min).

Acknowledgements

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References and notes

1. Sigman, M. S.; Jensen, D. R. *Acc. Chem. Res.* **2006**, *39*, 221–229.
2. Stahl, S. S. *Science* **2005**, *309*, 1824–1826.
3. Zhan, B.-Z.; Thompson, A. *Tetrahedron* **2004**, *60*, 2917–2935.
4. Stoltz, B. M. *Chem. Lett.* **2004**, *33*, 362–367.
5. Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400–3420.
6. Sheldon, R. A.; Arends, I. W. C. E. *Adv. Synth. Catal.* **2004**, *346*, 1051–1071.
7. Marko, I. E.; Giles, P. R.; Tsukazaki, M.; Chelle-Regnaut, I.; Gautier, A.; Dumeunier, R.; Philippart, F.; Doda, K.; Mutonkole, J.-L.; Brown, S. M.; Urch, C. J. *Adv. Inorg. Chem.* **2004**, *56*, 211–240.
8. Zhang, C. X.; Liang, H.-C.; Humphreys, K. J.; Karlin, K. D. Copper–dioxygen Complexes and Their Roles in Biomimetic Oxidation Reactions. In *Catalysis by Metal Complexes*; 2003; Vol. 26, pp 79–121.
9. Mazur, A. W.; Hiler, G. D. *J. Org. Chem.* **1997**, *62*, 4471–4475.
10. Gamez, P.; Arends, I.; Sheldon, R. A.; Reedijk, J. *Adv. Synth. Catal.* **2004**, *346*, 805–811.
11. Gamez, P.; Arends, I.; Reedijk, J.; Sheldon, R. A. *Chem. Commun.* **2003**, 2414–2415.
12. Jiang, N.; Ragauskas, A. J. *Org. Lett.* **2005**, *7*, 3689–3692.
13. Geisslmeir, D.; Jary, W. G.; Falk, H. *Monatsh. Chem.* **2005**, *136*, 1591–1599.
14. Marko, I. E.; Gautier, A.; Dumeunier, R. L.; Doda, K.; Philippart, F.; Brown, S. M.; Urch, C. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 1588–1591.
15. Contel, M.; Izuel, C.; Laguna, M.; Villuendas, P. R.; Alonso, P. J.; Fish, R. H. *Chem.—Eur. J.* **2003**, *9*, 4168–4178.
16. Betzemeier, B.; Cavazzini, M.; Quici, S.; Knochel, P. *Tetrahedron Lett.* **2000**, *41*, 4343–4346.
17. Marko, I. E.; Giles, P. R.; Tsukazaki, M.; Brown, S. M.; Urch, C. J. *Science* **1996**, *274*, 2044–2046.
18. Ragagnin, G.; Betzemeier, B.; Quici, S.; Knochel, P. *Tetrahedron* **2002**, *58*, 3985–3991.
19. Striegler, S.; Tewes, E. *Eur. J. Inorg. Chem.* **2002**, 487–495.
20. Striegler, S.; Dittel, M. *J. Am. Chem. Soc.* **2003**, *125*, 11518–11524.
21. Striegler, S.; Dittel, M. *Inorg. Chem.* **2005**, *44*, 2728–2733.
22. Striegler, S.; Dittel, M. *Anal. Chim. Acta* **2003**, *484*, 53–62.
23. Gampp, H.; Maeder, M.; Meyer, C. J.; Zuberbühler, A. D. *Talanta* **1986**, *33*, 943–951.
24. Binstead, R. A.; Jung, B.; Zuberbühler, A. D. *SPECFIT/32™ Global Analysis System*; Spectrum Software Associates: Marlborough, MA, USA, 2000.

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Palladium-catalyzed reactions of vinylidenecyclopropanes with acetic acid

Jian-Mei Lu and Min Shi*

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China

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Abstract—$Pd(PPh_3)_4$-catalyzed reactions of vinylidenecyclopropanes **1** with acetic acid proceeded smoothly at 80 °C in toluene to give the corresponding acetylated dienes **2** in moderate to good yields in the presence of DPEphos ligand. The plausible mechanism is proposed on the basis of the control and deuterium labeling experiments.

1. Introduction

Vinylidenecyclopropanes **1**[1] are one of the most remarkable organic compounds known. They have an allene moiety connected by a cyclopropane ring and yet they are thermally stable and reactive substances. Thermal and photochemical skeletal conversions of vinylidenecyclopropanes **1** have attracted much attention from mechanistic, theoretical, spectroscopic and synthetic viewpoints.[2,3] Vinylidenecyclopropanes **1** also undergo a variety of unique addition reactions with electrophiles to give novel products sometimes along with the formation of cyclopropane ring-opened products.[4] Previously, we reported the palladium-catalyzed isomerization of a variety of methylenecyclopropanes (MCPs), another kind of molecules having surprising stability along with a high level of strain, in acetic acid to give the corresponding 1-substituted or 1,1-disubstituted dienes in good yields.[5] However, to the best of our knowledge, there has been no report on the palladium-catalyzed reactions of vinylidenecyclopropanes **1** until now. In this context, we wish to disclose the first example of palladium-catalyzed reactions of vinylidenecyclopropanes with acetic acid to give the corresponding acetylated dienes **2** in moderate to good yields.

2. Results and discussion

As an initial examination, the reaction of vinylidenecyclopropane **1a** with acetic acid (2.0 equiv) was carried out with a variety of catalysts in toluene at 80 °C. The results are summarized in Table 1. As shown in Table 1, $Pd(PPh_3)_4$ can catalyze the reaction of vinylidenecyclopropane **1a** with acetic acid in toluene to produce **2a** in moderate yields as mixtures of *E*- and *Z*-isomers (Table 1). The structure of product **2a** was determined by ^1H and ^{13}C NMR spectroscopic data, HRMS and NOESY analytic data (Supplementary data). The NOESY of **2a** is shown in Figure 1, which clearly indicates that the major isomer has *E*-configuration. Other palladium catalysts, such as $PdCl_2(PPh_3)_2$, $Pd(OAc)_2$, $PdCl_2(dppf)$ and $Pd(dba)_2$, did not catalyze the reaction under identical conditions (Table 1, entries 5, 8–10). A variety of phosphine ligands, such as PPh_3, $AsPh_3$, tri-2-furylphosphine (TFP), bis[(2-diphenylphosphino)phenyl]ether (DPEphos), 1,4-bis(diphenylphosphino)butane (dppb) and 1,3-bis(diphenylphosphino)propane (dppp), were also examined for this reaction to improve the yield of **2a**. We found that when $Pd(PPh_3)_4$ (10 mol %) and DPEphos (40 mol %) were utilized in this reaction, **2a** can be obtained in 58% yield as mixtures of *E*- and *Z*-isomers (*E*:*Z*=6:1) (Table 1, entry 16). Using $Pd(OAc)_2$ or $Pd(dba)_2$ as a catalyst, **2a** was still obtained in lower yield even in the presence of $AsPh_3$ or DPEphos ligand (Table 1, entries 6, 11 and 12).

Using $Pd(PPh_3)_4$ (10 mol %) and DPEphos (40 mol %) as the catalyst, solvent effects were also examined upon heating or under reflux. The results are summarized in Table 1 as entries 16–20. As can be seen from these experiments, toluene is the best solvent for this reaction at 80 °C (Table 1, entries 16–20). We found that the employed amount of DPEphos slightly affected the yield of product **2a** in toluene at 80 °C (Table 1, entries 21–23). When $Pd(PPh_3)_4$ (10 mol %) and DPEphos (20 mol %) were used, **2a** was obtained in 64% yield, which is the highest yield in this reaction (Table 1, entry 22).

Keywords: Palladium catalyst; Vinylidenecyclopropanes; Acetic acid; Acetylated dienes; Deuterium labeling experiment.
* Corresponding author. Fax: +86 21 64166128; e-mail: mshi@pub.sioc.ac.cn

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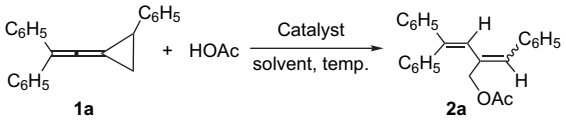
Table 1. Optimization of the reaction condition of **1a** with acetic acid



Entry[a]	Catalyst/ligand/mol %	Solvent	Temp/°C	Time/h	**2a** Yield[b]/% (*E*:*Z*)[c]
1	—	Toluene	80	48	N.R
2	$Pd(PPh_3)_4$ (10)	Toluene	80	5	44 (6:1)
3	$Pd(PPh_3)_4/PPh_3$ (10/40)	Toluene	80	6	37 (6:1)
4	$Pd(PPh_3)_4/AsPh_3$ (10/40)	Toluene	80	6	50 (6:1)
5	$Pd(OAc)_2$	Toluene	80	12	Complex
6	$Pd(OAc)_2/AsPh_3$ (10/40)	Toluene	80	18	14 (9:1)
7	$Pd(PPh_3)_4$/TFP (10/40)	Toluene	80	6	38 (6:1)
8	$PdCl_2(PPh_3)_2/PPh_3$ (10/40)	Toluene	80	20	N.R
9	$PdCl_2$(dppf)/dppf (10/20)	Toluene	80	24	N.R
10	$Pd(dba)_2$ (10)	Toluene	80	9	Complex
11	$Pd(dba)_2$/DPEphos (10/20)	Toluene	80	18	42 (8:1)
12	$Pd(OAc)_2$/DPEphos (10/20)	Toluene	80	18	36 (7:1)
13	$Pd(PPh_3)_4$/dppp (10/40)	Toluene	80	33	34 (11:1)
14	$Pd(PPh_3)_4$/dppb (10/40)	Toluene	80	33	32 (5:1)
15	$Pd(PPh_3)_4/(o\text{-}CH_3C_6H_4)_3P$ (10/40)	Toluene	80	17	36 (6:1)
16	$Pd(PPh_3)_4$/DPEphos (10/40)	Toluene	80	20	58 (6:1)
17	$Pd(PPh_3)_4$/DPEphos (10/40)	Toluene	110	11	26 (9:1)
18	$Pd(PPh_3)_4$/DPEphos (10/40)	Dioxane	100	9	10 (11:1)
19	$Pd(PPh_3)_4$/DPEphos (10/40)	CH_3CN	80	9	21 (9:1)
20	$Pd(PPh_3)_4$/DPEphos (10/40)	THF	66	33	14 (12:1)
21	$Pd(PPh_3)_4$/DPEphos (20/60)	Toluene	80	36	36 (>40:1)
22	$Pd(PPh_3)_4$/DPEphos (10/20)	Toluene	80	18	64 (7:1)
23	$Pd(PPh_3)_4$/DPEphos (10/10)	Toluene	80	12	60 (8:1)

[a] All reactions were carried out using **1a** (0.3 mmol), AcOH (0.6 mmol) and catalysts in a variety of solvents (2.0 mL).
[b] Isolated yields.
[c] Determined from ^{1}H NMR spectroscopic data and NOESY.

Under these optimized conditions, we next examined a variety of vinylidenecyclopropanes **1** with acetic acid for the reaction generality. The results are summarized in Table 2. With respect to the electron-rich and electron-poor arylvinylidenecyclopropanes **1** (R^1, R^2=aryl), they reacted with acetic acid smoothly to provide the corresponding acetylated dienes **2** in moderate to good yields (Table 2, entries 1–7). For arylvinylidenecyclopropane **1c** (R^1=C_6H_5 and R^2=*p*-ClC_6H_4), the corresponding *E*- and *Z*-isomers can be separated by silica gel chromatograph. In other cases, the corresponding *E*- and *Z*-isomers are inseparable. For alkylvinylidenecyclopropanes **1i** and **1j** (R^1=alkyl, R^2=aryl), the corresponding acetylated dienes **2i** and **2j** were also formed in 36 and 61% yields, respectively (Table 2, entries 8 and 9).

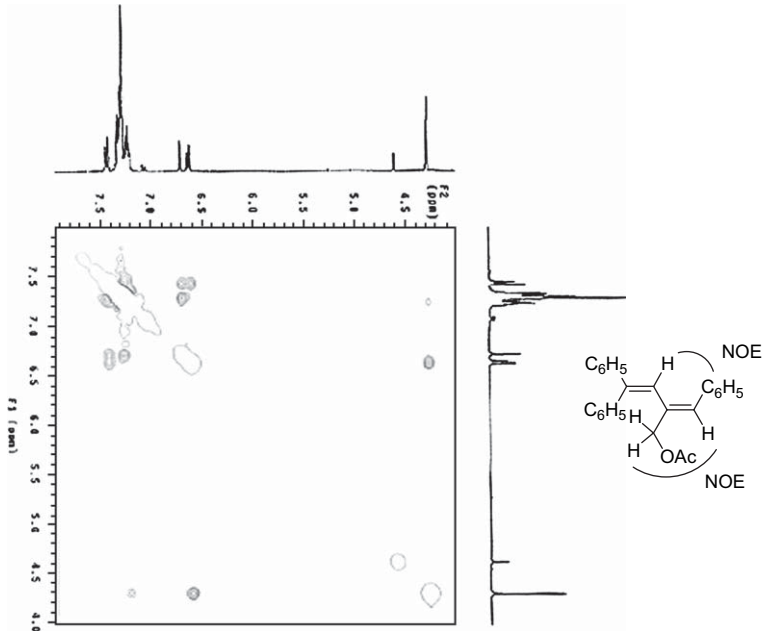
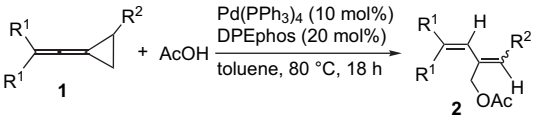


Figure 1.

Table 2. Palladium-catalyzed reactions of vinylidenecyclopropanes **1** with acetic acid in toluene

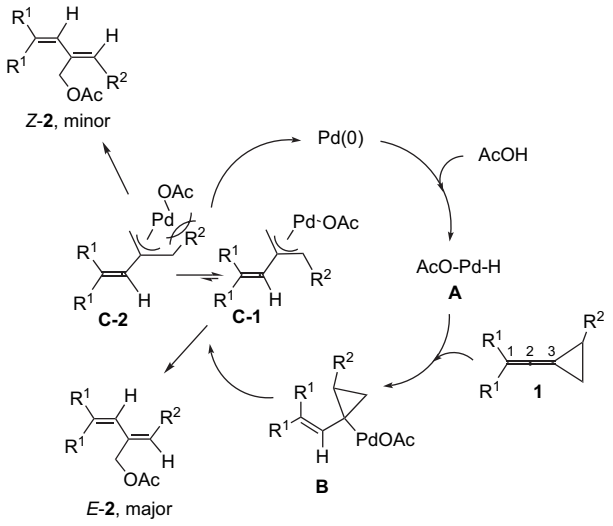


Entry[a]	**1** (R^1/R^2)	**2** Yield[b]/% (*E*:*Z*)[c]
1	**1b** (C_6H_5/*p*-MeC_6H_4)	**2b**, 67 (8:1)
2	**1c** (C_6H_5/*p*-ClC_6H_4)	**2c**, 67 (7:1)
3	**1d** (C_6H_5/*p*-$MeOC_6H_4$)	**2d**, 78 (19:1)
4	**1e** (*p*-MeC_6H_4/C_6H_5)	**2e**, 75 (8:1)
5	**1f** (*p*-FC_6H_4/C_6H_5)	**2f**, 67 (11:1)
6	**1g** (*p*-$MeOC_6H_4$/C_6H_5)	**2g**, 70 (14:1)
7	**1h** (*p*-ClC_6H_4/C_6H_5)	**2h**, 65 (8:1)
8	**1i** (^{n}Bu/C_6H_5)	**2i**, 36 (5:1)
9	**1j** (CH_3/C_6H_5)	**2j**, 61 (5:1)

[a] All reactions were carried out using **1** (0.3 mmol), AcOH (0.6 mmol), $Pd(PPh_3)_4$ (10 mol %) and DPEphos (20 mol %) in toluene (2.0 mL).
[b] Isolated yields.
[c] Determined from ^{1}H NMR spectroscopic data and NOESY.

It should be noted that for alkylvinylidenecyclopropanes **1i** and **1j**, other complicated products were also formed presumably due to the β-hydride elimination from aliphatic R^1 group. In addition, we found that vinylidenecyclopropanes **1** are labile under the reaction conditions, partially leading to the formation of **2** in moderate yields.

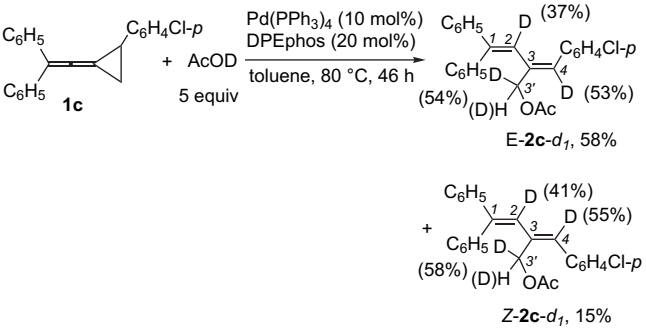
A plausible mechanism for the formation of acetylated dienes **2** is outlined in Scheme 1 on the basis of previous investigations.[5,6] The initial step is a regioselective hydropalladation of vinylidenecyclopropane **1** with hydridopalladium species **A**, generated from oxidative addition of Pd(0) with acetic acid, to afford intermediate **B**, which undergoes β-carbon elimination to give two π-allyl-palladium intermediates **C-1** and **C-2**. Intermediate **C-1** should be the major conformer because of the steric repulsion between R^2 group and palladium metal center in intermediate **C-2**. Reductive elimination of intermediates **C-1** and **C-2** gives the corresponding product **2** as mixtures of *E*- and *Z*-isomers, leading to the formation of *E*-**2** as major product from intermediate



Scheme 1. Plausible mechanism for the reactions of vinylidenecyclopropanes **1** with acetic acid in the presence of palladium(0) catalyst.

C-1, along with the regeneration of palladium(0) catalyst. Previously, Yamamoto and co-workers reported that alkynes can be allylated by carbon pronucleophiles in the presence of palladium/acetic acid catalyst via a π-allyl-palladium intermediate.[7] However, we found that no such allylation occurred in our system when malononitrile [$CH_2(CN)_2$] (2.0 equiv) and diethyl malonate [$CH_2(COOEt)_2$] (2.0 equiv) were used as the carbon pronucleophiles in the presence of $Pd(PPh_3)_4$ (10 mol %)/DPEphos (20 mol %)/AcOH (20 mol %). This result suggests that the reaction mechanism is not involved in the nucleophilic attack of AcOH to π-allyl intermediates **C-1** and **C-2** to produce **2**. In addition, it should also be noted here that when formic acid was used instead of acetic acid in this case, many unidentified products were formed.[8]

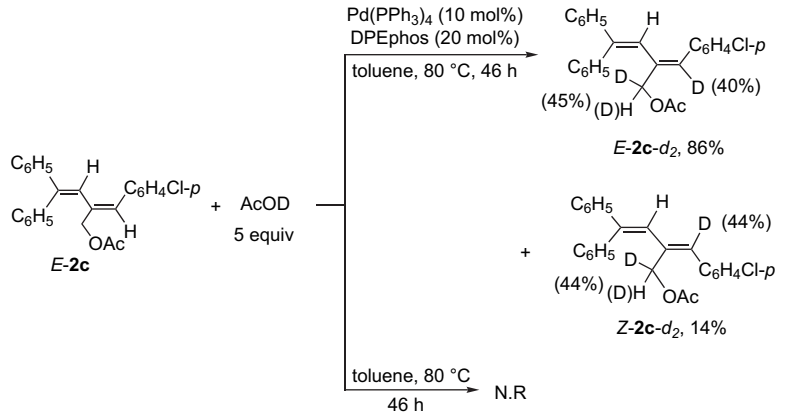
In order to clarify the mechanism of this reaction, the reaction of **1c** in deuterated acetic acid AcOD (D content 99%) was carried out under identical conditions (Scheme 2).[5] Based on the observed ^{1}H NMR spectral data, we confirmed that besides the olefinic protons at C_2 (D content: 37% in *E*-**2c**-d_1 and 41% in *Z*-**2c**-d_1), deuterium incorporation also occurred at the olefinic protons of C_4 (D content 53% in *E*-**2c**-d_1 and 55% in *Z*-**2c**-d_1) and at the allylic protons of $C_{3'}$ (D content: 54% in *E*-**2c**-d_1 and 58% in *Z*-**2c**-d_1). The 37% D content at C_2 is due to the generation of AcO–Pd–H species via β-hydride elimination during the reaction, which can initiate the same reaction to give the acetylated diene **2c** without deuterium incorporation even in AcOD (Scheme 1).[5,9]



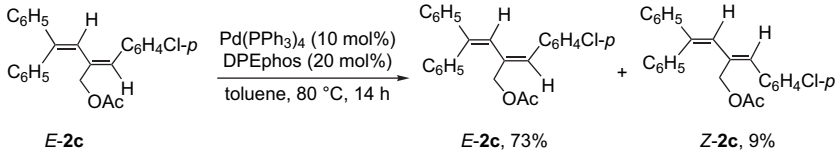
Scheme 2. Reaction of vinylidenecyclopropane **1c** with AcOD (5.0 equiv) under these optical conditions.

The control experiment confirmed that deuterium incorporation at the olefinic protons of C_4 and the allylic protons of $C_{3'}$ is derived from the scrambling of *E*-**2c** with AcOD catalyzed by Pd(0) as shown in Scheme 3 because similar D contents at C_4 and $C_{3'}$ were observed in the reaction of *E*-**2c** with AcOD in the presence of Pd(0) catalyst and no reaction occurred in the absence of Pd(0) catalyst as in the previously reported example.[5]

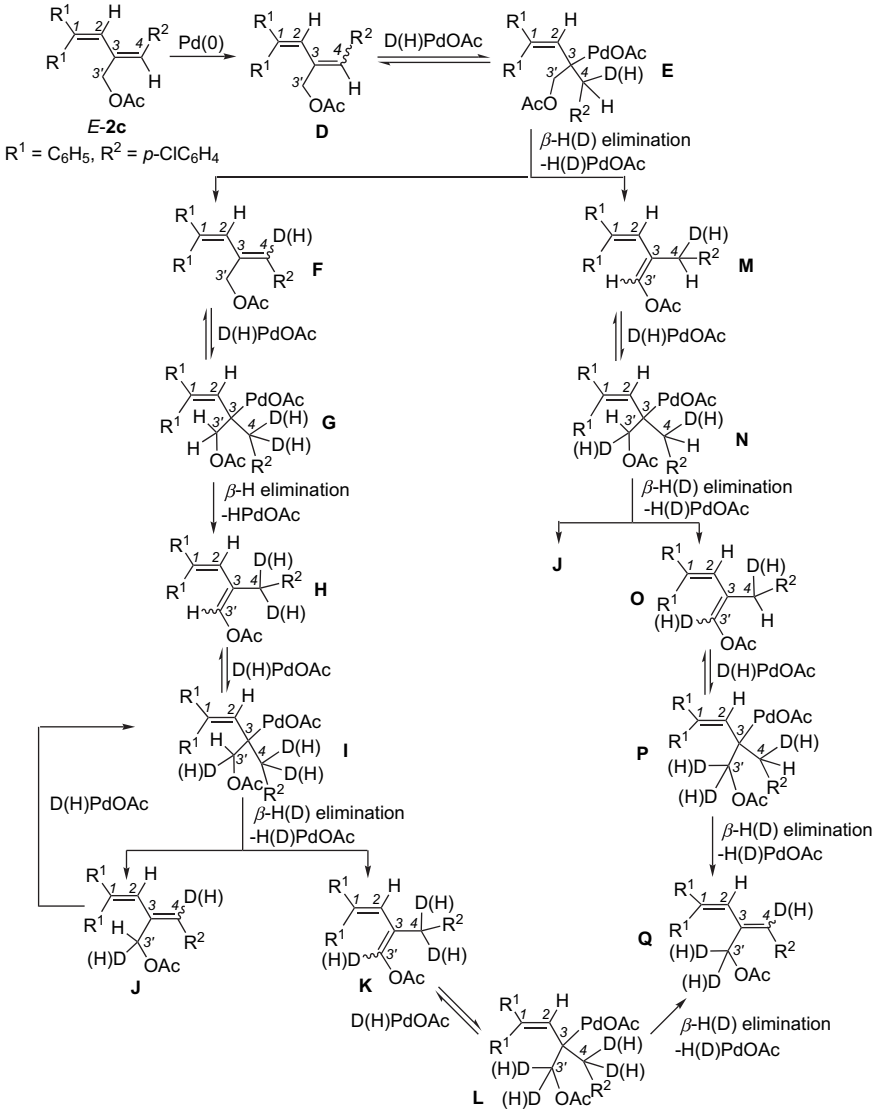
The control experiment of the transformation of *E*-**2c** to *E*- and *Z*-regioisomers in the presence of Pd(0) catalyst was also examined under the standard conditions. The result is shown in Scheme 4, which clearly indicates that *E*- and *Z*-isomerization independently takes place through the corresponding π-allyl intermediates **C-1** and **C-2** and it is not related with HOAc in the reaction system. A plausible mechanism for the formation of *E*-**2c**-d_2 and *Z*-**2c**-d_2 is shown in Scheme 5. The initial step is a palladium-catalyzed



Scheme 3. Reactions of *E*-**2c** with AcOD (5 equiv).

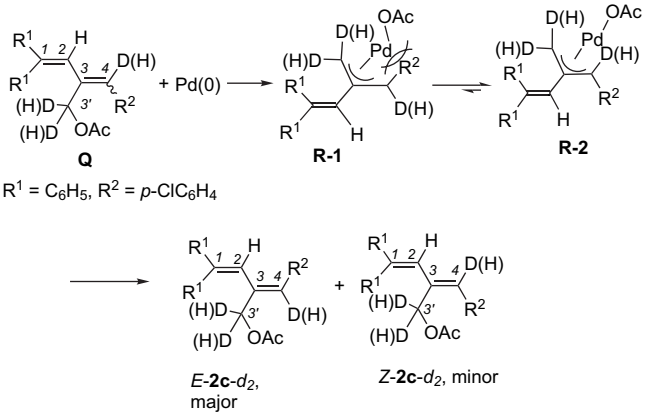


Scheme 4. Isomerization of *E*-**2c** in the presence of Pd(0).



Scheme 5. Plausible mechanism for the formation of *E*-**2c**-*d* and *Z*-**2c**-*d* in the presence of palladium(0) catalyst.

isomerization of *E*-**2c** to produce intermediate **D** as mixtures of *E*- and *Z*-isomers. Regioselective deuteropalladation or hydropalladation of **D** with deuteropalladium species or hydridopalladium species, generated from the oxidative addition of Pd(0) with deuterated acetic acid (AcOD) and β-hydride elimination during the reaction, respectively, to afford intermediate **E**.[5] Intermediate **E** undergoes β-hydride (β-H) or β-deuterium (β-D) elimination to give intermediates **F** and **M**. Intermediate **F** undergoes the same processes (deuteropalladation or hydropalladation, β-hydride or β-deuterium elimination and the repeated processes) to afford intermediates **J** and **Q** via intermediates **G**, **H**, **I**, **K** and **L**, successively. Regioselective deuteropalladation or hydropalladation of **J** regenerates intermediate **I**. From the same processes (deuteropalladation or hydropalladation, β-hydride or β-deuterium elimination and the repeated processes), intermediates **J** and **Q** would be also formed from intermediate **M** via intermediates **N**, **O** and **P**, respectively (Scheme 5). Then, palladium-catalyzed isomerization of intermediate **Q** gives the corresponding *E*-isomer as the major product because of the different steric effect between intermediates **R-1** and **R-2** as that described above (Scheme 6).



Scheme 6. Isomerization of intermediate **Q** to form *E*-**2c**-d_2 and *Z*-**2c**-d_2.

Overall, on the basis of the control and deuterium labeling experiments, the initial step of this reaction should indeed proceed through the hydropalladation of the C_1 and C_2 olefinic moieties of **1** via the hydridopalladium species as shown in Scheme 1. The repeated deuteropalladation or hydropalladation and β-hydride or β-deuterium elimination between the C_3 and C_4 olefinic moieties in **2** catalyzed by Pd(0) in AcOD caused the scrambling at C_4 protons and at the allylic protons of $C_{3'}$ as shown in Scheme 2.

3. Conclusion

We have disclosed the first example of palladium(0)-catalyzed reactions of vinylidenecyclopropanes **1** with acetic acid to give the corresponding acetylated dienes **2** under mild conditions. On the basis of the control and deuterium labeling experiments, we found that this reaction process is involved in the regioselective hydropalladation of vinylidenecyclopropanes **1** with AcO–Pd–H as shown in Scheme 1. Efforts are underway to elucidate the mechanistic details of this reaction and to disclose its scope and limitations. Work along this line is currently in progress.

4. Experimental

4.1. General methods

^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. Mass spectra were recorded by EI and MALDI methods, and HRMS was measured on Kratos Analytical Concept mass spectrometer (EI), Bruker FT mass spectrometer (ESI), and IonSpec 4.7 Tesla FTMS (MALDI). Organic solvents used were dried by standard methods when necessary. Commercially obtained reagents were used without further purification. All reactions were monitored by TLC with Yinlong GF254 silica gel coated plates. Flash column chromatography was carried out using 300–400 mesh silica gel at increased pressure.

4.2. General procedure for palladium-catalyzed reaction of vinylidenecyclopropanes with acetic acid

Under an argon atmosphere, vinylidenecyclopropanes **1** (0.3 mmol), $Pd(PPh_3)_4$ (10 mol %), DPEphos (20 mol %), toluene (2.0 mL) and acetic acid (0.6 mmol) were added into a Schlenk tube. The mixture was stirred at 80 °C for 18 h. Then the solvent was removed under reduced pressure and the residue was purified by a flash column chromatography.

4.2.1. Compound 2a. A yellow oil, (*E*-isomer): ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ 1.99 (s, 3H, CH_3), 4.29 (s, 2H, CH_2), 6.62 (s, 1H), 6.71 (d, J=1.2 Hz, 1H), 7.19–7.32 (m, 13H, Ar), 7.41–7.44 (m, 2H, Ar). (*Z*-isomer): ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ 1.99 (s, 3H, CH_3), 4.61 (s, 2H, CH_2), 6.64 (s, 2H), 7.05–7.08 (m, 2H, Ar), 7.19–7.32 (m, 13H, Ar). (*E*-isomer): ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 20.9, 66.8, 124.9, 127.5, 127.65, 127.67, 128.0, 128.1, 128.19, 128.24, 129.3, 129.7, 132.6, 133.5, 136.7, 140.1, 142.5, 144.9, 170.7. IR (CH_2Cl_2) ν 3056, 3024, 2922, 2850, 1739, 1597, 1493, 1444, 1373, 1232, 1075, 1030, 763, 699 cm^{-1}. MS (%) *m*/*z* 354 (M^+, 2), 294 (100), 293 (40), 43 (27), 352 (26), 295 (25), 203 (22), 217 (20), 91 (20). HRMS (MALDI) calcd for $C_{25}H_{22}O_2Na$: 377.1512, found: 377.1522 ($M+Na^+$).

4.2.2. Compound 2b. A yellow oil, (*E*-isomer): ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ 1.98 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 4.27 (s, 2H, CH_2), 6.60 (s, 1H), 6.72 (s, 1H), 7.09 (d, J=8.1 Hz, 2H, Ar), 7.19–7.34 (m, 12H, Ar). (*Z*-isomer): ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ 1.98 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 4.60 (s, 2H, CH_2), 6.63 (s, 1H), 6.64 (s, 1H), 6.97 (d, J=8.1 Hz, 2H, Ar), 7.19–7.34 (m, 12H, Ar). (*E*-isomer): ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 20.9, 21.2, 66.8, 125.1, 127.6, 127.90, 127.92, 128.1, 128.2, 129.0, 129.3, 129.8, 132.7, 132.8, 133.9, 137.4, 140.1, 142.5, 144.4, 170.4. IR (CH_2Cl_2) ν 3054, 3023, 2962, 2920, 2850, 1738, 1597, 1509, 1493, 1444, 1374, 1260, 1229, 1029, 868, 806, 758, 699 cm^{-1}. MS (%) *m*/*z* 368 (M^+, 1), 43 (100), 308 (43), 293 (32), 330 (33), 91 (29), 105 (29), 57 (28), 215 (19). HRMS (MALDI) calcd for $C_{26}H_{24}O_2Na$: 391.1669, found: 391.1674 ($M+Na^+$).

4.2.3. Compound 2c. A yellow oil, (*E*-isomer): ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ 2.01 (s, 3H, CH_3), 4.31 (s, 2H, CH_2), 6.53 (s, 1H), 6.62 (d, J=1.5 Hz, 1H), 7.16–7.34 (m,

14H, Ar). (*Z*-isomer): ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ 2.01 (s, 3H, CH_3), 4.57 (s, 2H, CH_2), 6.55 (s, 1H), 6.62 (d, J=0.9 Hz, 1H), 6.99 (d, J=9.0 Hz, 2H, Ar), 7.24–7.35 (m, 12H, Ar). (*E*-isomer): ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 20.9, 66.6, 124.3, 127.85, 127.93, 128.0, 128.18, 128.20, 128.4, 129.7, 130.4, 130.9, 133.1, 134.3, 135.2, 139.8, 142.3, 145.5, 170.4. (*Z*-isomer): ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 21.0, 62.1, 127.6, 127.7, 128.19, 128.24, 128.44, 128.47, 128.7, 129.9, 130.2, 133.3, 134.1, 134.7, 135.4, 140.1, 142.9, 143.9, 170.6. (*E*-isomer): IR (CH_2Cl_2) ν 3056, 3025, 2962, 2846, 1740, 1594, 1498, 1444, 1372, 1228, 1091, 1030, 1013, 868, 763, 699 cm^{-1}. (*Z*-isomer): IR (CH_2Cl_2) ν 3056, 3025, 2961, 2920, 1740, 1597, 1489, 1444, 1374, 1232, 1092, 1028, 1014, 970, 829, 807, 763, 700 cm^{-1}. (*E*-isomer): MS (%) *m*/*z* 388 (M^+, 1), 43 (100), 328 (73), 293 (62), 215 (35), 330 (25), 202 (24), 329 (23), 292 (22). (*Z*-isomer): MS (%) *m*/*z* 388 (M^+, 3), 43 (100), 293 (63), 328 (43), 215 (35), 91 (27), 57 (26), 292 (20), 202 (20). (*E*-isomer): HRMS (MALDI) calcd for $C_{25}H_{21}O_2ClNa$: 411.1122, found: 411.1140 (M+Na^+). (*Z*-isomer): HRMS (MALDI) calcd for $C_{25}H_{21}O_2ClNa$: 411.1122, found: 411.1133 (M+Na^+).

4.2.4. Compound 2d. A yellow oil, (*E*-isomer): ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ 1.97 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 4.26 (s, 2H, CH_2), 6.57 (s, 1H), 6.71 (d, J=1.5 Hz, 1H), 6.80–6.83 (m, 2H, Ar), 7.21–7.39 (m, 12H, Ar). (*Z*-isomer): ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ 1.99 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 4.60 (s, 2H, CH_2), 6.62 (s, 1H), 6.64 (s, 1H), 7.02 (d, J=8.7 Hz, 4H, Ar), 7.21–7.39 (m, 10H, Ar). (*E*-isomer): ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 20.9, 55.1, 66.9, 113.6, 125.2, 127.5, 127.8, 127.9, 128.07, 128.13, 129.4, 129.7, 130.6, 131.5, 132.5, 140.1, 142.5, 144.3, 159.0, 170.4. IR (CH_2Cl_2) ν 3056, 3026, 2932, 2836, 1738, 1605, 1509, 1444, 1374, 1252, 1176, 1032, 756, 700 cm^{-1}. MS (%) *m*/*z* 384 (M^+, 7), 43 (100), 49 (79), 57 (58), 324 (57), 51 (45), 84 (44), 105 (39), 207 (30). HRMS (MALDI) calcd for $C_{26}H_{24}O_3Na$: 407.1618, found: 407.1626 (M+Na^+).

4.2.5. Compound 2e. A yellow oil, (*E*-isomer): ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ 1.99 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 4.29 (s, 2H, CH_2), 6.60 (s, 1H), 6.65 (s, 1H), 7.08–7.30 (m, 11H, Ar), 7.44 (d, J=7.5 Hz, 2H, Ar). (*Z*-isomer): ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ 1.98 (s, 3H, CH_3), 2.35 (s, 6H, $2CH_3$), 4.60 (s, 2H, CH_2), 6.60 (s, 1H), 6.65 (s, 1H), 7.08–7.30 (m, 13H, Ar). (*E*-isomer): ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 20.9, 21.1, 21.3, 66.8, 123.9, 127.4, 127.9, 128.2, 128.8, 128.9, 129.3, 129.7, 132.1, 133.9, 136.8, 137.2, 137.5, 137.7, 139.9, 144.8, 170.5. IR (CH_2Cl_2) ν 3023, 2920, 2853, 1740, 1067, 1509, 1493, 1445, 1369, 1228, 1023, 822, 752, 700 cm^{-1}. MS (%) *m*/*z* 382 (M^+, 3), 43 (100), 322 (82), 307 (73), 215 (36), 105 (35), 91 (30), 323 (28), 229 (28). HRMS (MALDI) calcd for $C_{27}H_{26}O_2Na$: 405.1825, found: 405.1845 (M+Na^+).

4.2.6. Compound 2f. A yellow oil, (*E*-isomer): ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ 2.02 (s, 3H, CH_3), 4.36 (s, 2H, CH_2), 6.59 (s, 1H), 6.60 (s, 1H), 6.95–7.38 (m, 13H, Ar). (*Z*-isomer): ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ 2.02 (s, 3H, CH_3), 4.65 (s, 2H, CH_2), 6.55 (s, 1H), 6.59 (s, 1H), 6.95–7.38 (m, 13H, Ar). (*E*-isomer): ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 20.9, 66.8, 115.0 (d, J=11.0 Hz), 115.3 (d, J=11.8 Hz), 125.0, 127.5, 128.2, 129.1, 129.5 (d, J=8.0 Hz), 131.3 (d, J=8.1 Hz), 132.7, 133.1, 135.7 (d, J=3.9 Hz), 136.5, 138.5 (d, J=3.9 Hz), 142.9, 162.4 (d, J=246.4 Hz), 162.6 (d, J=246.8 Hz), 170.4. IR (CH_2Cl_2) ν 3050, 3019, 2919, 2850, 1740, 1600, 1508, 1446, 1371, 1275, 1226, 1158, 1095, 1029, 838, 764, 751, 698 cm^{-1}. MS (%) *m*/*z* 390 (M^+, 0.31), 49 (100), 84 (54), 51 (29), 86 (28), 43 (27), 47 (13), 127 (11), 330 (10). HRMS (MALDI) calcd for $C_{25}H_{20}O_2F_2Na$: 413.1324, found: 413.1333 (M+Na^+).

4.2.7. Compound 2g. A yellow oil, (*E*-isomer): ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ 2.00 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.32 (s, 2H, CH_2), 6.56 (s, 1H), 6.58 (s, 1H), 6.81–6.88 (m, 4H, Ar), 7.13–7.30 (m, 7H, Ar), 7.44 (d, J=7.2 Hz, 2H, Ar). (*Z*-isomer): ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ 1.99 (s, 3H, CH_3), 3.80 (s, 6H, $2OCH_3$), 4.62 (s, 2H, CH_2), 6.50 (s, 1H), 6.64 (s, 1H), 6.81–6.88 (m, 4H, Ar), 7.07–7.30 (m, 9H, Ar). (*E*-isomer): ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 20.9, 55.13, 55.19, 66.8, 113.4, 113.5, 122.8, 127.3, 128.2, 129.16, 129.19, 130.9, 131.7, 132.5, 134.0, 135.4, 136.9, 144.1, 159.30, 159.32, 170.5. IR (CH_2Cl_2) ν 3028, 3001, 2954, 2934, 2836, 1739, 1605, 1573, 1511, 1463, 1443, 1369, 1287, 1247, 1175, 1110, 1033, 974, 919, 834, 754, 738, 699 cm^{-1}. MS (%) *m*/*z* 414 (M^+, 18), 354 (100), 135 (70), 353 (42), 242 (34), 323 (29), 355 (27), 341 (27), 84 (25). HRMS (MALDI) calcd for $C_{27}H_{26}O_4Na$: 437.1723, found: 437.1724 (M+Na^+).

4.2.8. Compound 2h. A yellow oil, (*E*-isomer): ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ 2.02 (s, 3H, CH_3), 4.37 (s, 2H, CH_2), 6.63 (s, 2H), 7.07–7.36 (m, 13H, Ar). (*Z*-isomer): ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ 2.02 (s, 3H, CH_3), 4.65 (s, 2H, CH_2), 6.59 (s, 2H), 7.07–7.36 (m, 13H, Ar). (*E*-isomer): ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 20.9, 66.8, 125.9, 127.7, 128.3, 128.4, 128.6, 128.9, 129.1, 131.0, 132.9, 133.3, 133.9, 134.0, 136.5, 138.0, 140.6, 142.6, 170.4. IR (CH_2Cl_2) ν 3019, 2920, 2846, 1740, 1590, 1491, 1368, 1275, 1260, 1227, 1091, 1014, 831, 764, 750, 697 cm^{-1}. MS (%) *m*/*z* 422 (M^+, 9), 327 (100), 277 (73), 362 (62), 278 (47), 292 (46), 364 (41), 215 (40), 43 (37). HRMS (MALDI) calcd for $C_{25}H_{20}O_2Cl_2Na$: 445.0733, found: 445.0745 (M+Na^+).

4.2.9. Compound 2i. A yellow oil, (*E*-isomer): ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ 0.77 (t, J=6.6 Hz, 3H, CH_3), 0.92 (t, J=6.9 Hz, 3H, CH_3), 1.12–1.15 (m, 4H, $2CH_2$), 1.26–1.41 (m, 4H, $2CH_2$), 1.85 (t, J=7.5 Hz, 2H, CH_2), 2.07 (t, J=6.3 Hz, 2H, CH_2), 2.09 (s, 3H, CH_3), 4.65 (s, 2H), 5.74 (s, 1H), 6.48 (s, 1H), 7.15–7.34 (m, 3H, Ar), 7.41 (d, J=7.8 Hz, 2H). (*Z*-isomer): ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ 0.88–0.95 (m, 6H, $2CH_3$), 1.26–1.41 (m, 8H, $4CH_2$), 2.07–2.13 (m, 2H, CH_2), 2.09 (s, 3H, CH_3), 2.27 (t, J=7.8 Hz, 2H, CH_2), 4.74 (s, 2H, CH_2), 5.77 (s, 1H), 6.58 (s, 1H), 7.15–7.34 (m, 5H, Ar). (*E*-isomer): ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 13.9, 14.0, 21.0, 22.5, 22.8, 29.5, 29.9, 30.8, 35.8, 68.7, 120.3, 126.9, 127.9, 128.5, 128.9, 133.9, 137.1, 145.2, 170.7. (*Z*-isomer): ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 13.9, 14.0, 20.9, 22.4, 22.8, 30.3, 30.4, 30.8, 36.7, 63.6, 124.8, 127.0, 128.1, 128.3, 128.7, 132.1, 136.7, 145.2, 170.7. IR (CH_2Cl_2)

ν 3059, 3025, 2956, 2930, 2871, 1743, 1599, 1494, 1456, 1376, 1228, 1027, 966, 915, 803, 751, 696 cm^{-1}. MS (%) *m/z* 314 (M^+, 1), 91 (100), 43 (74), 155 (40), 197 (37), 41 (36), 141 (28), 115 (27), 211 (26). HRMS (EI) calcd for $C_{21}H_{30}O_2$: 314.2246, found: 314.2252.

4.2.10. Compound 2j. A yellow oil, (*E*-isomer): ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 1.44 (d, J=0.6 Hz, 3H, CH_3), 1.78 (d, J=1.2 Hz, 3H, CH_3), 2.10 (s, 3H, CH_3), 4.66 (s, 2H), 5.76 (s, 1H), 6.48 (s, 1H), 7.15–7.41 (m, 5H, Ar). (*Z*-isomer): ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 1.86 (s, 3H, CH_3), 1.87 (d, J=1.2 Hz, 3H, CH_3), 2.07 (s, 3H, CH_3), 4.74 (s, 2H, CH_2), 5.79 (d, J=1.2 Hz, 1H), 6.59 (s, 1H), 7.15–7.41 (m, 5H, Ar). (*E*-isomer): ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 19.6, 21.0, 25.7, 68.5, 120.7, 126.8, 128.0, 128.7, 128.8, 133.6, 137.1, 137.5, 170.8. (*Z*-isomer): ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 19.6, 21.0, 26.8, 63.6, 125.2, 127.1, 128.3, 128.7, 133.1, 133.6, 136.5, 136.8, 171.0. IR (CH_2Cl_2) ν 3059, 3019, 2968, 2920, 1741, 1488, 1446, 1374, 1228, 1029, 965, 920, 751, 696 cm^{-1}. MS (%) *m/z* 230 (M^+, 4), 43 (100), 155 (81), 91 (51), 170 (32), 115 (29), 129 (19), 128 (18), 77 (17). HRMS (EI) calcd for $C_{15}H_{18}O_2$: 230.1307, found: 230.1304.

4.3. General procedure for palladium-catalyzed reaction of vinylidenecyclopropane 1c with deuterated acetic acid

Under an argon atmosphere, vinylidenecyclopropane **1c** (0.3 mmol), $Pd(PPh_3)_4$ (10 mol %), DPEphos (20 mol %), toluene (2.0 mL) and deuterated acetic acid (1.5 mmol) were added into a Schlenk tube. The mixture was stirred at 80 °C for 46 h. Then the solvent was removed under reduced pressure and the residue was purified by a flash column chromatography.

Acknowledgements

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Supplementary data

^1H and ^{13}C NMR spectroscopic data and analytic data for compounds **2a–2j**. This material is available free of charge via the Internet. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.07.052.

References and notes

1. For the synthesis of vinylidenecyclopropanes, see: (a) Isagawa, K.; Mizuno, K.; Sugita, H.; Otsuji, Y. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2283–2285 and references cited therein; (b) Sasaki, T.; Eguchi, S.; Ohno, M.; Nakata, F. *J. Org. Chem.* **1976**, *41*, 2408–2411; (c) Sasaki, T.; Eguchi, S.; Ogawa, T. *J. Org. Chem.* **1974**, *39*, 1927–1930; (d) Sasaki, T.; Eguchi, S.; Ogawa, T. *Heterocycles* **1975**, *3*, 193–196; (e) Eguchi, S.; Arasaki, M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1047–1050; (f) Sugita, H.; Mizuno, K.; Mori, T.; Isagawa, K.; Otsuji, Y. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 984–986; (g) Patrick, T. B. *Tetrahedron Lett.* **1974**, *15*, 1407–1408; (h) Al-Dulayymi, J. R.; Baird, M. S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1547–1548; (i) Patrick, T. B. *J. Org. Chem.* **1977**, *42*, 3354–3356; (j) Hartzler, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 4527–4531.
2. (a) Poutsma, M. L.; Ibarbia, P. A. *J. Am. Chem. Soc.* **1971**, *93*, 440–450; (b) Smadja, W. *Chem. Rev.* **1983**, *83*, 263–320; (c) Paulson, D. R.; Crandall, J. K.; Bunnell, C. A. *J. Org. Chem.* **1970**, *35*, 3708–3714; (d) Hendrick, M. E.; Hardie, J. A.; Jones, M. *J. Org. Chem.* **1971**, *36*, 3061–3062; (e) Patrick, T. B.; Haynie, E. C.; Probst, W. J. *J. Org. Chem.* **1972**, *37*, 1553–1556; (f) Aue, D. H.; Meshishnek, M. J. *J. Am. Chem. Soc.* **1977**, *99*, 223–231; (g) Sasaki, T.; Eguchi, S.; Ogawa, T. *J. Am. Chem. Soc.* **1975**, *97*, 4413–4414; (h) Sadler, I. H.; Stewart, J. A. G. *J. Chem. Soc., Perkin Trans. 2* **1973**, *3*, 278–288; (i) Sugita, H.; Mizuno, K.; Saito, T.; Isagawa, K.; Otsuji, Y. *Tetrahedron Lett.* **1992**, *33*, 2539–2542; (j) Mizuno, K.; Sugita, H.; Kamada, T.; Otsuji, Y. *Chem. Lett.* **1994**, 449–452; (k) Akasaka, T.; Misawa, Y.; Ando, W. *Tetrahedron Lett.* **1990**, *31*, 1173–1176; (l) Mizuno, K.; Sugita, H.; Isagawa, K.; Goto, M.; Otsuji, Y. *Tetrahedron Lett.* **1993**, *34*, 5737–5738; (m) Mizuno, K.; Nire, K.; Sugita, H.; Otsuji, Y. *Tetrahedron Lett.* **1993**, *34*, 6563–6566; (n) Mizuno, K.; Sugita, H.; Hirai, T.; Maeda, H. *Chem. Lett.* **2000**, 1144–1145; (o) Mizuno, K.; Nire, K.; Sugita, H.; Maeda, H. *Tetrahedron Lett.* **2001**, *42*, 2689–2692; (p) Mizuno, K.; Maeda, H.; Sugita, H.; Nishioka, S.; Hirai, T.; Sugimoto, A. *Org. Lett.* **2001**, *3*, 581–584; (q) Mizuno, K.; Sugita, H.; Hirai, T.; Maeda, H.; Otsuji, Y.; Yasuda, M.; Hashiguchi, M.; Shima, K. *Tetrahedron Lett.* **2001**, *42*, 3363–3366; (r) Maeda, H.; Zhen, L.; Hirai, T.; Mizuno, K. *ITE Lett. Batteries, New Technol. Med.* **2002**, *3*, 485–491; (s) Sydnes, L. K. *Chem. Rev.* **2003**, *103*, 1133–1150.
3. For recent contributions from our group, see: (a) Shi, M.; Lu, J.-M. *J. Org. Chem.* **2006**, *71*, 1920–1923; (b) Shi, M.; Lu, J.-M. *Synlett* **2005**, 2352–2356; (c) Xu, G.-C.; Liu, L.-P.; Lu, J.-M. *J. Am. Chem. Soc.* **2005**, *127*, 14552–14553; (d) Shi, M.; Ma, M.; Shao, L.-X. *Tetrahedron Lett.* **2005**, *46*, 7609–7613; (e) Xu, G.-C.; Ma, M.; Liu, L.-P. *Synlett* **2005**, 1869–1872; (f) Shi, M.; Lu, J.-M.; Xu, G.-C. *Tetrahedron Lett.* **2005**, *46*, 4745–4748.
4. For the reactions of vinylidenecyclopropanes with carbenes and carbene complexes, see: (a) Crandall, J. K.; Paulson, D. R.; Bunnell, C. A. *Tetrahedron Lett.* **1969**, *48*, 4217–4220; (b) Hwu, C.-C.; Wang, F.-C.; Yeh, M.-C. P. *J. Organomet. Chem.* **1994**, *474*, 123–128; (c) Billups, W. E.; Haley, M. M.; Boese, R.; Blaser, D. *Tetrahedron* **1994**, *50*, 10693–10700; (d) Maeda, H.; Hirai, T.; Sugimoto, A.; Mizuno, K. *J. Org. Chem.* **2003**, *68*, 7700–7706; (e) Bloch, R.; Perchec, P. L.; Conia, J.-M. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 798–799; (f) Pasto, D. J.; Yang, S. H. *J. Org. Chem.* **1986**, *51*, 1676–1680; For the addition reactions of vinylidenecyclopropanes, see: (g) Pasto, D. J.; Miles, M. F. *J. Org. Chem.* **1976**, *41*, 2068–2611; (h) Pasto, D. J.; Chen, A. F.-T.; Binsch, G. *J. Am. Chem. Soc.* **1973**, *95*, 1553–1562; (i) Pasto, D. J.; Chen, A. *J. Am. Chem. Soc.* **1971**, *93*, 2562–2564; (j) Pasto, D. J.; Borchardt, J. K.; Fehlner, T. P.; Baney, H. F.; Schwartz, M. E. *J. Am. Chem. Soc.* **1976**, *98*, 526–529; (k) Pasto, D. J.; Fehlner, T. P.; Schwartz, M. E.; Baney, H. F. *J. Am. Chem. Soc.* **1976**, *98*, 530–534; (l) Pasto, D. J.; Miles, M. F. *J. Org. Chem.* **1976**, *41*,

425–432; (m) Pasto, D. J.; Chen, A. F.-T.; Cuirdaru, G.; Paquette, L. A. *J. Org. Chem.* **1973**, *38*, 1015–1026; (n) Gompper, R.; Lach, D. *Tetrahedron Lett.* **1973**, *29*, 2683–2686; (o) See Ref. 2a; (p) Gompper, R.; Lach, D. *Tetrahedron Lett.* **1973**, *29*, 2687–2690; (q) Pasto, D. J.; Wampfler, D. *Tetrahedron Lett.* **1974**, *22*, 1933–1936; (r) See Ref. 2g; (s) Pasto, D. J.; Whitmer, J. L. *J. Org. Chem.* **1980**, *45*, 1987–1990; (t) Pasto, D. J.; Brophy, J. E. *J. Org. Chem.* **1991**, *56*, 4554–4559; (u) Cairns, P. M.; Combie, L.; Pattenden, G. *Tetrahedron Lett.* **1982**, *23*, 1405–1408; (v) Crombie, L.; Maddocks, P. J.; Pattenden, G. *Tetrahedron Lett.* **1978**, *19*, 3483–3486.

5. Shi, M.; Wang, B.-Y.; Huang, J.-W. *J. Org. Chem.* **2005**, *70*, 5606–5610 and references cited therein.
6. (a) For a recent review see: Nakamura, I.; Yamamoto, Y. *Adv. Synth. Catal.* **2002**, *344*, 111–129; (b) de Meijere, A.; Brase, S. *J. Organomet. Chem.* **1999**, *576*, 88–110; (c) Itazaki, M.; Nishihara, Y.; Osakada, K. *J. Org. Chem.* **2002**, *67*, 6889–6895.
7. Patil, N. T.; Kadota, I.; Shibuya, A.; Gyong, Y. S.; Yamamoto, Y. *Adv. Synth. Catal.* **2004**, *346*, 800–804.
8. (a) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Parisi, L. M. *J. Organomet. Chem.* **2003**, *687*, 562–566; (b) Prasad, K.; Jiang, X.-L.; Slade, J. S.; Clemens, J.; Repic, O.; Blacklock, T. J. *Adv. Synth. Catal.* **2005**, *347*, 1769–1773.
9. (a) Trost, B. M.; Rise, F. *J. Am. Chem. Soc.* **1987**, *109*, 3161–3163; (b) Trost, B. M.; Schimidt, T. *J. Am. Chem. Soc.* **1988**, *110*, 2301–2303; (c) Trost, B. M.; Brieden, W.; Baringhaus, K. H. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1335–1336; (d) Al-Masum, M.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 3809–3810; (e) Kadota, I.; Shibuya, A.; Gyoung, Y.-S.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 10262–10263 and references cited therein; (f) See Ref. 7.

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Ten new antifouling briarane diterpenoids from the South China Sea gorgonian *Junceella juncea*

Shu-Hua Qi,[a,*] Si Zhang,[a] Pei-Yuan Qian,[b] Zhi-Hui Xiao[a] and Ming-Yi Li[a]

[a]*Guangdong Key Laboratory of Marine Materia Medica, South China Sea Institute of Oceanology, The Chinese Academy of Sciences, 164 West Xingang Road, Guangzhou, 510301 Guangdong, People's Republic of China*
[b]*Hong Kong University of Science and Technology/Department Biology—CML/Clearwater Bay, KLN, Hong Kong, China*

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Abstract—Ten new antifouling briarane diterpenoids, juncins R–ZI (**1–10**) were isolated from the South China Sea gorgonian coral *Junceella juncea*. The structures of these new compounds were established by extensive spectroscopic analysis, including 1D and 2D NMR data. Compounds **1–10** all showed potent antifouling activities against the larval settlement of barnacle *Balanus amphitrite* at nontoxic concentrations with EC_{50} values of 0.004, 0.34, 2.65, 1.61, 3.77, 21.06, 0.004, 0.14, 1.47, and 0.51 μg mL^{-1}. The structure–activity relationship was discussed.

1. Introduction

In the past, antifouling paints containing tributyltin (TBT), copper or organonitrogen compounds have been used to protect ship hulls. However, these substances, especially TBT, are highly toxic and persistent in the marine environment and can adversely affect nontarget organism, leading to a total ban on the production of the TBT-based coating since January 2003 and application in January 2008. The imminent prohibition of TBT-based coating means that there is a need to develop new environmentally compatible alternatives that would be equally efficient against several fouling organisms such as barnacles. In the marine environment, many sessile organisms such as gorgonians, soft corals, sponges, and seaweeds are known to elaborate chemical defense mechanisms against predation and epibiont growth. The use of natural marine products that are capable of inhibiting one or several stages of fouling on ships and other submerged structures may provide an acceptable solution from the aspect of environmental impact.

Gorgonians are a major source of unusual secondary metabolites that play important roles in protecting the colonies against grazing, feeding, and the settlement of both the adult and larval form of marine organisms such as barnacles.[1–3] Gorgonian *Junceella juncea* (Ellisellidae) belongs to the genus *Junceella* that is known to produce highly oxidized diterpenoids of the briarane class (3,8-cyclized cembranoids). In recent years, briarane-type diterpenoids continue to attract the attention of investigations because of the structural complexity and interesting biological activities, such as cytotoxicity, anti-inflammatory, antiviral, immunomodulatory activity, insect control, antifouling, biotoxin, and ichthyotoxicity.[4] Previous chemical investigations on *J. juncea* have yielded more than 20 briaranes.[5–11] During the course of our further investigation on the EtOH/CH_2Cl_2 extract of *J. juncea* by semi-preparative HPLC, 10 new briarane diterpenoids, juncins R–ZI (**1–10**) were obtained from an EtOAc soluble fraction of the EtOH/CH_2Cl_2 extract. Antifouling bioassay tests showed that the EtOAc soluble fraction led to 0% larval settlement and 10% mortality toward barnacle *Balanus amphitrite* (Cirripedia) larvae at concentration of 100.0 μg mL^{-1}, and compounds (**1–10**) all had potent antifouling activities against *B. amphitrite* larvae at nontoxic concentrations with EC_{50} values of 0.004, 0.34, 2.65, 1.61, 3.77, 21.06, 0.004, 0.14, 1.47, and 0.51 μg mL^{-1}. These EC_{50} values were lower than the standard requirement of an EC_{50} of 25 μg mL^{-1} established by the US Navy program as an efficacy level for natural antifoulants. In this paper, we report the isolation, structural elucidation, and antifouling activities of compounds **1–10**.

2. Results and discussion

The residue from the EtOH/CH_2Cl_2 extract of *J. juncea* was partitioned in H_2O and extracted with EtOAc. The EtOAc extract was chromatographed over silica gel to give 12 fractions, and then selected fractions were rechromatographed

Keywords: *Junceella juncea*; Briarane diterpenoids; Antifouling; Structure–activity relationship.
* Corresponding author. Tel.: +86 20 89023105; fax: +86 20 84458964; e-mail: shuhuaqi2001@yahoo.com

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Table 1. ^{13}C NMR spectral data of compounds **1–11**[a]

Carbon	1	2	3	4	5	6	7	8	9	10	11
1	46.5	46.5	46.4	46.5	47.5	47.4	47.5	47.5	47.9	47.1	48.3
2	74.0	74.0	75.5	74.1	75.5	75.1	72.8	72.0	72.9	72.8	75.8
3	131.8	131.8	131.4	131.2	131.7	132.5	38.1	38.2	37.4	40.5	132.5
4	128.2	128.2	128.5	128.6	128.0	127.1	69.2	69.3	67.6	97.2	128.3
5	140.1	140.1	139.6	141.6	141.2	139.3	140.1	141.9	136.8	138.0	147.0
6	125.9	125.9	122.7	122.8	123.4	123.4	123.7	122.5	139.1	55.3	121.6
7	78.5	78.5	78.8	78.9	79.1	79.2	76.4	76.4	76.7	78.6	81.8
8	81.2	81.0	81.2	81.1	81.2	81.3	80.3	83.2	82.9	81.4	82.0
9	63.7	63.7	63.8	63.9	64.2	64.2	71.4	73.3	72.2	71.7	65.7
10	32.6	32.7	32.7	32.7	30.7	30.6	39.6	42.4	43.3	40.5	31.3
11	58.4	58.3	58.3	58.4	60.4	60.3	62.3	151.0	150.7	56.2	60.4
12	73.3	72.8	73.3	73.3	76.0	75.9	23.5	25.6	29.3	24.7	76.6
13	66.5	66.4	66.6	66.3	68.1	68.2	24.5	27.6	27.6	29.7	70.0
14	73.3	73.6	73.8	73.9	76.5	77.0	73.2	70.9	74.1	73.2	77.3
15	14.2	14.4	14.4	14.4	13.7	13.6	15.1	15.2	14.4	15.5	13.8
16	44.5	44.5	63.0	72.2	73.1	63.9	65.6	65.9	166.6	117.8	63.0
17	44.0	44.0	44.1	44.2	44.3	44.3	42.2	42.4	42.7	49.9	45.6
18	6.3	6.3	6.3	6.3	6.3	6.3	6.6	6.6	6.4	7.2	7.4
19	175.0	175.0	176.9	175.3	175.6	175.7	176.4	176.4	175.4	174.2	176.9
20	49.1	49.1	48.7	48.9	48.5	48.3	58.9	113.0	112.4	51.2	47.5
CH_3COO	169.7	169.7	169.7	169.6	170.2	169.9	169.5	169.3	169.2	169.3	168.2
	169.8	169.8	170.0	169.6	170.4	170.1	170.1	169.9	169.6	169.9	170.3
	170.1	170.1	170.1	169.9	170.5	170.4	170.2	170.1	169.8	173.4	171.0
	172.3	171.8	170.1	170.2		170.5	170.7	170.7	170.5		
							170.8	170.9			
CH_3COO	20.5	20.5	20.5	20.8	21.1	20.8	20.8	20.7	20.8	20.8	20.8
	21.0	20.9	20.6	20.9	21.4	21.1	20.9	20.8	21.1	21.1	21.1
	21.3	21.1	20.7	21.3	21.5	21.3	20.9	20.9	21.2	21.8	21.4
	21.5	21.5	21.5	21.5		21.4	21.0	21.0	21.7		
							21.1	21.8			
1′	172.3	171.8	171.1	171.7							
2′	43.2	43.6	60.8	42.6							
3′	25.0	25.7	172.4	25.0							
4′	22.4	22.3	42.7	22.4							
5′	22.4	22.3	29.7	22.4							
6′			25.6								
7′, 8′			22.3								
OCH_3				53.0	53.2				53.0		

[a] All compounds were determined at 125 MHz with TMS as an internal standard, and measured in $CDCl_3$; chemical shifts are in parts per million.

on silica gel, Sephadex LH-20, and semi-preparative HPLC to yield compounds **1–10**. These compounds had a similar briarane core.

Juncin R (**1**) had a molecular formula of $C_{33}H_{43}ClO_{14}$ as deduced from its NMR spectra and ESIMS, which showed a pair of peaks at *m/z* 699/701 (3:1) $[M+H]^+$ suggesting one chlorine atom in **1**. Its IR and UV spectra indicated the presence of hydroxyls (3543 cm^{-1}), a γ-lactone (1790 cm^{-1}), esters (1750, 1739, and 1720 cm^{-1}), and a conjugated diene system (274 nm). The ^{13}C (DEPT) and ^1H NMR spectral data (Tables 1 and 2) showed signals for four acetate esters and an isovalerate ester [δ_C 172.3 (s), 43.2 (t), 25.0 (d), 22.4 (2q)], a tertiary methyl (δ_H 1.13, s), a secondary methyl (δ_H 1.13, d, J=7.0 Hz), a γ-lactone (δ_C 175.0), an exocyclic 11(20)-epoxide [δ_H 2.93, 3.60 (each br s), δ_C 49.1 (t), 58.4 (s)], a conjugated diene [δ_C 131.8 (d), 128.2 (d), 140.1 (s), 125.9 (d), δ_H 5.61 (t, J=9.8 Hz), 6.36 (d, J=10.5 Hz), 6.03 (d, J=8.6 Hz)], an exocyclic methylene [δ_C 44.2 (t), δ_H 4.58, 4.64 (each d, J=13.6 Hz)], an oxygenated quaternary carbon and six oxygenated methines. These data showed that **1** was a briarane-type diterpenoid with a 3,5(6)-conjugated diene and an exocyclic 11(20)-epoxide, similar to the structures of gemmacolide F,[12] juncenolides B–D,[8,12] juncins I–K,[9] and juncin Q (**11**), which we previously obtained from *J. juncea*.[11] Comparison of the ^1H and ^{13}C NMR spectral data of **1** with those of **11** revealed the difference between them, **1** had some additional signals for an acetate ester and an isovalerate ester, and a signal for a methylene bearing chlorine ($-CH_2Cl$)[13] [δ_C 44.2 (t), δ_H 4.58, 4.64 (each d, J=13.6 Hz)] in place of an oxymethylene ($-CH_2OH$) [δ_C 63.0(t), δ_H 4.63, 5.44 (each d, J=16.3 Hz) in **11**] at position C-16. The additional acetate and isovalerate groups were assigned to C-12 and C-14, respectively, because of HMBC correlations of H-12 with δ_C 170.1, and H-14/2′/3′ with C-1′ (δ_C 172.3) (Table 4). The skeletal structure of **1** was further deduced from the ^1H–^1H COSY and HMBC correlation data (Table 4).

According to a summary about the chemical shifts of exocyclic 11,20-epoxy groups in briarane derivatives, that while the ^{13}C NMR data for C-11 and C-20 appeared at δ_C 62–63 and 58–60 ppm, respectively, the epoxy group was β-oriented and the cyclohexane ring existed in a boat conformation; however, if the ^{13}C NMR data for C-11 and C-20 were shifted upfield and signals appeared at δ_C 55–61 and 47–52 ppm, respectively, the epoxy group was α-oriented and the cyclohexane ring had a chair conformation,[14] the stereochemistry of 11,20-epoxide [δ_C 58.4 (C-11), 49.1 (C-20)] in **1** should be α-oriented, and the cyclohexane ring was in a boat conformation. The *Z* configuration of the disubstituted double bond at C-3 was determined by the proton

Table 2. ^{1}H NMR spectral data of compounds **1–5**[a]

H	1	2	3	4	5
2	5.44 (d, 9.5)	5.51 (d, 9.5)	5.67 (d, 9.2)	5.57 (d, 9.0)	5.96 (d, 9.6)
3	5.61 (t, 9.8)	5.61 (t, 9.8)	5.63 (t, 9.5)	5.56 (t, 8.9)	5.69 (t, 10.2)
4	6.36 (d, 10.5)	6.36 (d, 10.5)	6.33 (d, 9.7)	6.28 (d, 8.1)	6.28 (d, 10.9)
6	6.03 (d, 8.6)	6.04 (d, 8.6)	5.70 (d, 8.4)	5.88 (d, 8.6)	5.84 (d, 8.0)
7	4.95 (d, 8.6)	4.96 (d, 8.6)	4.97 (d, 8.4)	5.00 (d, 8.6)	5.00 (d, 8.4)
9	4.73 (d, 4.6)	4.73 (d, 4.6)	4.74 (d, 4.1)	4.74 (d, 4.6)	4.80 (d, 4.3)
10	3.57 (d, 4.6)	3.56 (d, 4.6)	3.63 (d, 4.7)	3.61 (br s)	3.58 (d, 4.1)
12	4.88 (d, 2.6)	4.91 (d, 2.6)	4.86 (br s)	4.88 (d, 2.2)	3.59 (br s)
13	5.09 (t, 3.4)	5.08 (t, 3.4)	5.07 (br s)	5.09 (t, 3.7)	5.00 (t, 4.0)
14	5.24 (d, 3.0)	5.20 (d, 2.5)	5.20 (br s)	5.20 (t, 2.1)	3.74 (br s)
15	1.13 (s)	1.14 (s)	1.13 (s)	1.13 (s)	0.99 (s)
16	4.58, 4.64 (each d, 13.6)	4.55, 4.66 (each d, 13.6)	4.62, 5.41 (each d, 15.6)	4.23, 4.50 (each d, 14.9)	4.20, 4.30 (each d, 14.3)
17	2.30 (q, 7.0)	2.30 (q, 7.0)	2.30 (q, 7.0)	2.31 (q, 7.1)	2.33 (q, 7.0)
18	1.13 (d, 7.0)	1.13 (d, 7.0)	1.15 (d, 7.0)	1.16 (d, 7.1)	1.17 (d, 7.0)
20	2.93, 3.60 (each br s)	2.93, 3.60 (each br s)	2.92, 3.60 (each br s)	2.93, 3.60 (each br s)	2.76, 3.52 (each br s)
2-OAc	1.96 (s)	1.97 (s)		1.94 (s)	2.08 (s)
9-OAc	2.22 (s)	2.20 (s)	2.26 (s)	2.14 (s)	2.19 (s)
12-OAc	2.16 (s)		2.13 (s)	2.22 (s)	
13-OAc	1.95 (s)	1.94 (s)	1.96 (s)		2.17 (s)
14-OAc		2.07 (s)	2.10 (s)	2.06 (s)	
16-OAc					
2′	2.10 (2H, m)	2.11 (2H, m)	4.44, 4.54 (each d, 15.7)	2.09 (2H, m)	
3′	1.99 (1H, m)	1.99 (1H, m)		1.98 (1H, m)	
4′	0.97 (3H, d, 6.5)	0.97 (3H, d, 6.5)	2.29 (2H, m)	0.92 (6H, d, 6.5)	
5′	1.01 (3H, d, 6.5)	1.01 (3H, d, 6.5)	1.26 (2H, m)		
6′			2.14 (1H, m)		
7′ and 8′			0.98 (6H, 6.5)		
OCH_3				3.80 (3H, s)	3.81 (3H, s)

[a] All compounds were determined at 500 MHz, and measured in $CDCl_3$; chemical shift values δ are in parts per million, and coupling constant values J in hertz.

coupling constant (J=10.5 Hz) between the olefinic protons H-3 and H-4. The *E* configuration of the trisubstituted double bond at C-5 was demonstrated by the NOE correlation between H-6 and H-16 (as shown in Fig. 2). The relative stereochemistries of the 11 chiral centers of **1** were also deduced by the analysis of NOE correlations (Fig. 2). In the NOESY spectrum of **1**, NOE correlations between Me-15 with H-13/14/20, and H-20 with H-12 suggested that H-20, H-13, H-12, H-14, and Me-15 were all in the β-orientations; meanwhile, correlations of H-2 with H-10, H-9 with H-10, and Me-18 with H-9/10 indicated that H-2, H-9, H-10, and Me-18 were α orientated, correspondingly, correlation of H-17 with H-7 suggested the β-orientations of H-17 and H-7. Based on above observation, the relative stereochemistry of juncin R (**1**) was assigned as 1*R**, 2*S**, 3*Z*, 5*E*, 7*S**, 8*R**, 9*S**, 10*S**, 11*R**, 12*R**, 13*R**, 14*R**, and 17*R**, and its structure was proposed as shown in Figure 1.

Juncins S–ZI (**2–10**) were analogues of juncin R (**1**). Their stereostructure determinations were thus aided by comparison of their spectroscopic data with those of **1** and some known briarane-type diterpenoids. However, complete NMR studies (including HSQC, HMBC, ^{1}H–^{1}H COSY, and NOESY spectra) on each new compound were performed in order to unambiguously determine their structures and to assign all the proton and carbon resonances. HMBC, HSQC, and ^{1}H–^{1}H COSY spectra showed that compounds **1–6** and **7–10** contained similar oxygenation patterns meanwhile NOESY spectrum gave the relative stereochemistry information of chiral centers. Some key points for structure elucidations of compounds **2–10** are described below.

Juncin S (**2**) showed the same molecular formula of $C_{33}H_{43}ClO_{14}$ as compound **1**, which was deduced from the ESIMS and NMR data of **2**. There was almost no obvious difference between the ^{13}C and ^{1}H NMR spectral data of **2** and **1** (Tables 1 and 2), however, they were obtained from a same fraction by semi-preparative HPLC (Luna™ C18(2), 250×10 mm i.d., 5 ml min^{-1}) with different retention times (t_R) (20.3 min for **1**, and 17.3 min for **2**), using MeOH/H_2O (64:36) as eluent. Comparison of the HMBC spectrum of **2** with that of **1** revealed that the differences between them were the substituent positions of an isovalerate group and an acetate group. In **2**, an isovalerate group was attached to C-12 instead of C-14, and an acetate group was attached to C-14 instead of C-12. These were deduced from HMBC correlations of δ_H 4.91 (d, J=2.6 Hz, H-12), 2.11 (2H, m, H-2′) and 1.99 (1H, m, H-3′) with δ_C 171.8 (s, C-1′), and HMBC correlations of δ_H 5.20 (d, J=2.5 Hz, H-14) and 2.07 (s, 3H) with δ_C 170.1 (s). So, the structure of juncin S

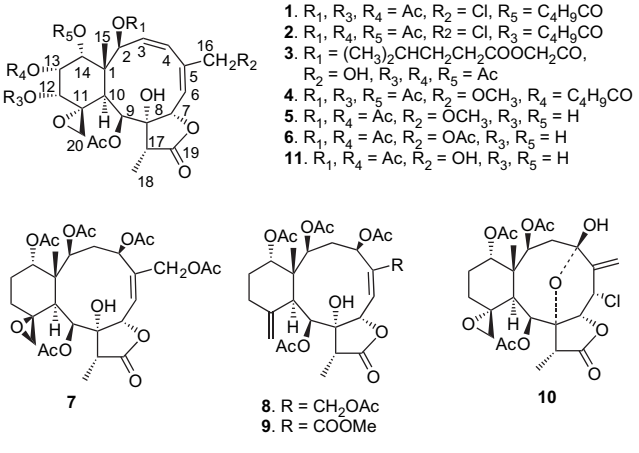

Figure 1. Structures of compounds **1–11**.

(**2**) was determined, and its relative stereochemistry was the same as that of **1**.

Juncin T (**3**) was assigned the molecular formula of $C_{36}H_{48}O_{17}$ on the basis of its ESIMS and NMR data. Comparison of overall ^1H and ^{13}C NMR spectral data (Tables 1 and 2) revealed similarities between **3** and **11**. The difference between them was the appearance of two additional ester signals in **3**. The ^{13}C (DEPT) and ^1H NMR spectral data of **3** (Tables 1 and 2) showed signals for four acetate groups assigned to C-9, C-12, C-13, and C-14 because their carbonyl carbons were correlated with the corresponding oxymethine protons in the HMBC spectrum of **3**. Other additional signals were assigned to be an $-OCOCH_2OCOCH_2CH_2CH(CH_3)_2$ unit, which was supported by the HMBC correlations of δ_H 4.44, 4.54 (each d, J=15.7 Hz, H-2′) with δ_C 171.1 (s, C-1′) and 172.4 (s, C-3′), of δ_H 2.29 (2H, m, H-4′) and 1.26 (2H, m, H-5′) with δ_C 172.4 (s, C-3′) and 25.6 (t, C-6′), and ^1H–^1H COSY spectrum showing correlations of δ_H 1.26 (2H, m, H-5′) with δ_H 2.29 (2H, m, H-4′), 2.14 (1H, m, H-6′), and δ_H 2.14 (1H, m, H-6′) with δ_H 0.98 (6H, d, J=6.5 Hz, H-7′ and 8′). NOESY spectrum proved that the relative stereochemistry of **3** was the same as that of **1**. So, the structure of juncin T (**3**) was determined as shown in Figure 1.

Juncin U (**4**) was found to have a molecular formula of $C_{34}H_{46}O_{15}$ as determined from its HRESIMS. Its ^{13}C and ^1H NMR data (Tables 1 and 2) were similar to those of **11** with the difference of some additional signals for an acetate ester, an isovalerate ester, and an oxymethyl (δ_C 53.0, q). In **4**, the ^1H and ^{13}C NMR spectra showed the existence of four acetate and one isovalerate groups which were assigned to C-2, C-9, C-12, C-14, and C-13 because their carbonyl carbons were correlated with the corresponding oxymethine protons in the HMBC spectrum. The additional oxymethyl was attached to the oxymethylene C-16 because of the HMBC correlation of δ_H 3.80 (3H, s) with δ_C 72.2 (t, C-16). On the basis of complete NMR studies, the structure of juncin U (**4**) was elucidated, and its relative stereochemistry was proved to be the same as that of **1**.

Juncin V (**5**) had a molecular formula of $C_{27}H_{36}O_{13}$ as deduced from its ESIMS and NMR data. Its ^{13}C and ^1H NMR data (Tables 1 and 2) were very similar to those of **11** with the only difference of an additional oxymethyl (δ_C 53.2, q) attached to C-16 because of the HMBC correlation of δ_H 3.81 (3H, s) with δ_C 73.1 (t, C-16). Based on complete NMR studies, the structure of juncin V (**5**) was elucidated as shown in Figure 1, and its relative stereochemistry was proved to be the same as that of **1**.

Juncin W (**6**) exhibited a molecular formula of $C_{28}H_{37}O_{14}$ as deduced from its ESIMS and NMR data. Its ^{13}C and ^1H NMR data (Tables 1 and 3) were closely similar to those of **11** with the only difference of an additional acetate group attached to the oxymethylene C-16 because of the HMBC correlations of δ_H 4.75, 5.04 (each d, J=15.6 Hz, H-16) and 2.12 (3H, s) with δ_C 170.5 (s). Based on complete NMR study, the structure of juncin W (**6**) was inferred as shown in Figure 1, and its relative stereochemistry was proved to be the same as that of **1**.

Juncin X (**7**) had a molecular formula of $C_{30}H_{40}O_{14}$ as deduced from its ESIMS and NMR data. Its ^{13}C and ^1H NMR spectral data (Tables 1 and 3) were similar to those of **6** with the obvious difference that three methylenes appeared and a C-3/4 double bond disappeared in **7**. Complete analysis of the HMBC and ^1H–^1H COSY spectral data (Table 4) showed a gross structure of **7** that was similar to

Table 3. ^1H NMR spectral data of compounds **6–10**[a]

H	6	7	8	9	10
2	5.91 (d, 10.0)	4.92 (d, 5.5)	5.24 (d, 7.2)	4.88 (d, 7.5)	5.30 (d, 7.5)
3	5.75 (t, 10.5)	1.90 (m), 2.75 (br d, 14.0)	1.81 (m), 2.80 (dd, 4.2, 14.5)	1.84 (m), 2.72 (br t, 14.5)	3.38 (dd, 7.7, 16.3), 1.59 (d, 16.3)
4	6.27 (d, 10.5)	5.01 (dd, 5.4, 12.2)	5.14 (dd, 5.6, 12.6)	5.91 (dd, 5.9, 12.2)	
6	5.69 (d, 8.6)	5.76 (d, 9.9)	5.78 (d, 10.2)	7.06 (d, 10.0)	4.90 (d, 2.4)
7	4.98 (d, 8.5)	5.53 (d, 10.0)	5.61 (d, 10.5)	5.63 (d, 10.0)	4.33 (d, 2.7)
9	4.82 (d, 4.5)	4.83 (d, 4.8)	4.82 (d, 4.8)	5.60 (d, 2.8)	5.62 (br s)
10	3.58 (d, 4.1)	3.29 (d, 2.9)	3.22 (d, 5.3)	3.29 (d, 2.4)	2.78 (br s)
12	3.61 (br s)	2.14, 2.21 (each m)	2.20 (m)	2.15 (m)	2.11, 2.04 (each m)
13	4.98 (t, 3.7)	1.93, 2.00 (each m)	1.73 (m)	1.80 (m)	2.01, 1.95 (each m)
14	3.80 (br s)	4.73 (d, 4.2)	4.73 (d, 4.6)	4.70 (br s)	5.05 (br s)
15	1.00 (s)	1.11 (1H, s)	1.11 (s)	1.03 (s)	1.22 (s)
16	4.75, 5.04 (each d, 15.6)	4.62, 5.36 (each br d, 16.3)	5.32, 4.78 (each br d, 17.3)		5.63, 5.92 (each br s)
17	2.35 (q, 7.0)	2.35 (q, 7.0)	2.48 (q, 7.0)	2.65 (q, 7.0)	2.74 (q, 7.0)
18	1.18 (d, 7.0)	1.15 (d, 7.0)	1.12 (d, 7.0)	1.20 (d, 7.0)	1.32 (d, 7.0)
20	2.76, 3.42 (each br s)	2.46 (d, 3.5), 2.80 (d, 4.0)	4.87, 4.98 (each s)	4.96, 5.0 (each s)	2.41 (d, 3.2), 2.64 (d, 2.8)
2-OAc	2.03 (s)	2.01 (s)	1.90 (s)	1.90 (s)	2.09 (s)
4-OAc		2.03 (s)	1.98 (s)	1.97 (s)	
9-OAc	2.18 (s)	2.26 (s)	2.26 (s)	2.22 (s)	2.24 (s)
12-OAc					
13-OAc	2.16 (s)				
14-OAc		2.04 (s)	2.05 (s)	2.07 (s)	2.09 (s)
16-OAc	2.12 (s)	2.13 (s)	2.13 (s)		
OCH_3				3.83 (s)	
OH					6.57 (s)

[a] All compounds were determined at 500 MHz, and measured in $CDCl_3$; chemical shift values δ are in parts per million, and coupling constant values J in hertz.

Table 4. HMBC and ^{1}H–^{1}H COSY correlation data of compounds **1**, **7**, and **10**

H	**1**		**7**		**10**	
	HMBC	^{1}H–^{1}H COSY	HMBC	^{1}H–^{1}H COSY	HMBC	^{1}H–^{1}H COSY
2	C-1, 3, 4, 10, 14, 15, Me*C*OO	H-3	C-1, 3, 4, 10, 14, 15, Me*C*OO	H-3	C-1, 3, 4, 10, 14, 15, Me*C*OO	H-3
3	C-1, 2, 5	H-2, 4	C-1, 2, 5	H-2, 4	C-1, 2, 5	H-2
4	C-2, 6	H-3	C-2, 6, Me*C*OO	H-3		
6	C-4, 5, 16	H-7	C-4, 5, 7, 16	H-7	C-5, 16	H-7
7	C-5, 6, 8, 9	H-6	C-5, 6, 8, 9	H-6	C-5, 6, 8	H-6
9	C-1, 7, 8, 10, 11, 17, Me*C*OO	H-10	C-1, 7, 8, 10, 11, 17, Me*C*OO	H-10	C-1, 7, 8, 10, 11, 17, Me*C*OO	H-10
10	C-1, 2, 8, 9, 11, 12, 14, 15, 20	H-9	C-1, 2, 8, 9, 11, 12, 14, 15, 20	H-9	C-1, 2, 8, 9, 11, 12, 14, 15, 20	H-9
12	C-11, 13, 14, Me*C*OO	H-13	C-10, 11, 13, 14	H-13	C-10, 11, 13, 14	H-13
13	C-11, 12, 14, Me*C*OO	H-12, 14	C-1, 11, 12, 14	H-12, 14	C-1, 11, 12, 14	H-12, 14
14	C-1, 1′	H-13	C-1, 2, 10, 12, 13, Me*C*OO	H-13	C-1, 2, 10, 12, 13, Me*C*OO	H-13
15	C-1, 2, 10, 14		C-1, 2, 10, 14		C-1, 2, 10, 14	
16	C-4, 5, 6		C-4, 5, 6, Me*C*OO		C-4, 5, 6	
17	C-8, 9, 18, 19	H-18	C-8, 9, 18, 19	H-18	C-8, 9, 18, 19	H-18
18	C-8, 17, 19	H-17	C-8, 17, 19	H-17	C-8, 17, 19	H-17
20	C-11, 12		C-11, 12		C-11, 12	
2′	C-1′, 3′, 4′, 5′	H-3′				
3′	C-1′, 2′, 4′, 5′	H-2′, 4′				
4′	C-2′, 3′, 5′	H-3′				
5′	C-2′, 3′, 4′	H-3′				

junceellolide I[14] and (+)-11α,20α,-epoxy-junceellolide D.[15] Comparison of the ^{1}H and ^{13}C NMR spectral data of **7** with those of (+)-11α,20α,-epoxy-junceellolide D revealed that the only difference between them is **7** had an acetoxymethylene group at C-16 instead of a methyl, which was proved by the HMBC spectrum (Table 4) showing correlations of δ_H 4.62, 5.36 (each br d, J=16.3 Hz, H-16) with δ_C 123.7 (d, C-6), 140.1 (s, C-5), and 170.7 (s).

Recently, the stereochemistry of 11,20-epoxy group in (+)-11α,20α,-epoxy-junceellolide D [δ_C 62.6 (C-11), 59.4 (C-20)] was corrected to be β-oriented.[14] Comparison of ^{13}C NMR chemical shifts of C-11 and C-20 of **7** [δ_C 62.3 (C-11), 58.9 (C-20)] with those of **1** [δ_C 58.4 (C-11), 49.1 (C-20)] and (+)-11α,20α,-epoxy-junceellolide D showed that the stereochemistry of 11,20-epoxy group in **7** should be β-oriented, leading to the configuration of cyclohexane ring in a boat form. The *E* configuration of the trisubstituted double bond at C-5 was determined by the NOE correlation between H-6 and H-16 (as shown in Fig. 2). The relative stereochemistry of the nine chiral centers of **7** was also deduced by the analysis of NOESY spectrum (Fig. 2), in which NOE correlations of H-2 with H-10/4, H-10 with H-9/20, and Me-18 with H-9/10 indicated that H-2, H-4, H-9, H-10, H-20, and Me-18 were all in the α-orientations. NOE correlations of Me-15 with H-14/17, and H-17 with H-7 suggested that H-7, 14, 17, and Me-15 were all in the β-orientations. Based on above observation, the relative stereochemistry of juncin X (**7**) was assigned as 1*R**, 2*S**, 5*E*, 7*S**, 8*R**, 9*S**, 10*S**, 11*S**, 14*S**, and 17*R**, and its structure was elucidated as shown in Figure 1.

Juncin Y (**8**) analyzed for $C_{30}H_{40}O_{13}$ by HRESIMS and ^{13}C NMR spectrometry. The ^{13}C and ^{1}H NMR spectral data of **8** were closely similar to those of **7** (Tables 1 and 3). However, the ^{13}C and ^{1}H NMR spectra of **8** showed that an exocyclic 11(20)-epoxide was converted into a double bond [δ_C 150.1 (s) and 113.0 (t), δ_H 4.87, 4.98 (each 1H, s)]. This was supported by the HMBC spectrum that showed the correlations of δ_H 4.87, 4.98 (each 1H, s) with δ_C 150.1 (s, C-11) and 42.4 (d, C-10). Based on above data and the NOESY spectrum of **8**, the relative stereochemistry of **8** was assigned as 1*R**, 2*S**, 5*E*, 7*S**, 8*R**, 9*S**, 10*S**, 14*S**, and 17*R**, and its structure was elucidated as shown in Figure 1.

Juncin Z (**9**) exhibited the molecular formula of $C_{29}H_{38}O_{13}$ as deduced from its ESIMS and NMR data. Its ^{13}C and ^{1}H NMR spectral data (Tables 3 and 1) were very similar to those of **8**. The only difference between them was that an acetoxymethylene group at C-16 was transformed into a methyl esterified carboxyl group, which was supported by the HMBC spectrum with correlations of δ_H 7.06 (d, J=10.0 Hz, H-6), 3.83 (3H, s, –OMe) with δ_C 166.6 (s, C-16). It was rare that an esterified carboxyl group was placed at C-16 in briarane-type diterpenes. Based on the 1D and 2D NMR studies, the structure of juncin Z (**9**) was elucidated, and its relative stereochemistry was assigned as 1*R**, 2*S**, 5*E*, 7*S**, 8*R**, 9*S**, 10*S**, 14*S**, and 17*R**.

Juncin ZI (**10**) exhibited a molecular ion peak at *m*/*z* 556/558 (3:1) $[M+H]^+$ in its ESIMS. Together with ^{1}H and ^{13}C NMR spectral data, a molecular formula of $C_{26}H_{33}ClO_{11}$ was established and confirmed by HRESIMS. Its ^{13}C and

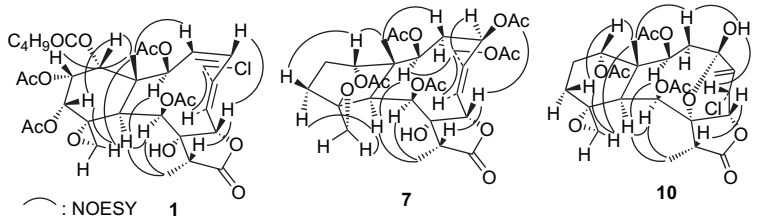

Figure 2. Key NOESY correlations for compounds **1**, **7**, and **10**.

^{1}H NMR spectral data (Tables 1 and 3) were similar to those of **7**. The main difference between them was the appearance of a characteristic quaternary hemiketal carbon (δ_C 97.4, s) and an exocyclic double bond [δ_C 138.0 (s), 117.8 (t), δ_H 5.63, 5.92 (each 1H, br s)] instead of a trisubstituted olefin in **10**. Complete analysis of the HMBC and ^{1}H–^{1}H COSY spectral data (Table 4) showed a gross structure of **10** that was similar to juncin P[11] and junceellolide A.[16] Comparison of the ^{1}H and ^{13}C NMR spectral data of **10** with those of junceellolide A revealed that the only difference between them is that a double bond was converted into an exocyclic 11(20)-epoxide [δ_C 56.2 (s) and 51.2 (t), δ_H 2.41 (1H, d, J=3.2 Hz), 2.64 (1H, d, J=2.8 Hz)] in **10**, which was supported by the HMBC spectrum with correlations of δ_H 2.41 (1H, d, J=3.2 Hz, H-20), 2.64 (1H, d, J=2.8 Hz, H-20) with δ_C 56.2 (s, C-11) and 40.5 (d, C-10).

Comparison of ^{13}C NMR chemical shifts of C-11 and C-20 of **10** with those of **1** [δ_C 58.4 (C-11), 49.1 (C-20)] showed that the stereochemistry of 11,20-epoxy group in **10** should be α-oriented, leading to the configuration of cyclohexane ring in a chair form. The relative stereochemistry of the 11 chiral centers of **10** was also deduced from its NOESY spectrum (Fig. 2). In the NOESY spectrum, NOE correlations between Me-15 with H-3β/14/20/9-OAc, and 4-OH with H-6/3β suggested that H-20, H-14, H-6, 4-OH, and Me-15 were all in the β-orientations, while NOE correlations of H-2 with H-10, H-9 with H-10, and Me-18 with H-9/10 indicated that H-2, H-9, H-10, and Me-18 were all in the α-orientations, with corresponding correlation of H-17 with H-7 suggesting the β-orientations of H-17 and H-7. On the basis of above data, the structure of juncin ZI (**10**) was elucidated, and its relative stereochemistry was determined as 1*R**, 2*S**, 4*S**, 6*S**, 7*R**, 8*R**, 9*S**, 10*S**, 11*R**, 14*S**, and 17*R**.

2.1. Antifouling activity against barnacle larvae

Antifouling bioassay tests showed that the EtOAc soluble fraction of the EtOH/CH_2Cl_2 extract of *J. juncea* led to 0% larval settlement and 10% mortality toward barnacle *B. amphitrite* larvae at concentration of 100.0 μg mL^{-1}, and compounds (**1**–**10**) had potent antifouling activities at nontoxic concentrations with EC_{50} values of 0.004, 0.34, 2.65, 1.61, 3.77, 21.06, 0.004, 0.14, 1.47, and 0.51 μg mL^{-1}. The EC_{50} values of compounds (**1**–**10**) were lower than the standard requirement of an EC_{50} of 25 μg mL^{-1} established by the US Navy program as an efficacy level for natural antifoulants, indicating that compounds **1**–**10** are potential natural nontoxic antifouling agents. Besides renillafoulins A–C,[17] this is the second time for reporting the antifouling activities of briarane-type metabolites from marine organisms.

Based on the parent molecules of renillafoulins A–C, a preliminary structure–activity relationship study suggested that the antifouling functional group was the furan ring in briarane-type diterpenoids.[18] In our study, according to above observation, the structure–activity relationship was further summarized as follows. Comparison of the antifouling activities of compounds **1**–**6**, **8**, and **9** suggested that the potency of briarane-type diterpenoids inhibiting larval settlement could be increased as the exocyclic oxymethylene C-16 (such as –CH_2OH and –CH_2OCH_3 in **3**, **4**, and **5**) was substituted by a methylene bearing chlorine (–CH_2Cl in **1** and **2**), and decreased as the exocyclic oxymethylene C-16 was esterified (–CH_2OAc in **6**) or the acetoxymethylene C-16 (–CH_2OAc in **8**) was oxygenated to be an esterified carboxyl group (–COOMe in **9**). Further comparison of the antifouling activities of compounds **1**–**6** also indicated that the chain lengths of esters at C-1, 12, 13, and 14 could affect the potency of briarane-type diterpenoids. Moreover, compound **7** was more potent than compounds **8** and **9**, which suggested that the exocyclic 11,20-epoxy group was important for the antifouling activities of briarane-type diterpenoids.

3. Experimental

3.1. General experimental procedures

Optical rotations were measured with a Horiba SEAP-300 spectropolarimeter. UV spectra were measured with a Shimadzu double-beam 210A spectrophotometer in MeOH solution. IR (KBr) spectra were obtained on a Bio-Rad FTS-135 infrared spectrophotometer. ^{1}H, ^{13}C, and 2D NMR spectra were recorded on a Bruker DRX-500 MHz NMR spectrometer with TMS as an internal standard. MS spectral data were obtained on an LCQ^{DECA} XP HPLC/MS^n spectrometer for ESIMS. Semi-preparative HPLC was carried out on ODS columns (Phenomenex, 250×10 mm i.d., 5 ml min^{-1}) with a Waters 996 photodiode array detector. Si gel (200–300 mesh) for column chromatography and GF_{254} for TLC were obtained from the Qindao Marine Chemical Factory, Qindao, People's Republic of China.

3.2. Animal material

The South China Sea gorgonian coral *J. juncea* (12 kg, wet weight) was collected in Sanya, Hainan Province, China in October 2003 and identified by Professor Zou R. L., The South China Sea Institute of Oceanology, *Academia Sinica*. A voucher specimen (No. 0310) was deposited in the South China Sea Institute of Oceanology, *Academia Sinica*, Guangzhou, China.

3.3. Extraction and isolation

The frozen specimen was extracted with EtOH/CH_2Cl_2 (2:1) three times at room temperature, and the solvent was evaporated in vacuo. The residue was partitioned in H_2O and extracted with EtOAc three times. The EtOAc extract was concentrated in vacuo to afford 85 g of residue, and then the EtOAc portion was subjected to column chromatography (CC) on silica, using petroleum ether/EtOAc (from 10:1 to 0:10) as eluent. By combining the fractions with TLC (GF_{254}) monitoring, 12 fractions were obtained. Fraction 5 was subjected to CC on silica gel, eluted with $CHCl_3$/Me_2CO (from 10:1 to 9:1) to give four sub-fractions (A–D). Sub-fraction A was subjected to CC on silica gel, eluted with $CHCl_3$/Me_2CO (10:1) to give **3** (3.2 mg); sub-fractions B–D were chromatographed over Sephadex LH-20 eluted with $CHCl_3$/MeOH (1:1) then purified with semi-preparative HPLC (Luna™ C18(2), 250×10 mm i.d., 5 ml min^{-1}), using MeOH/water (64:36) as eluent to yield **10** (retention time of 5.3 min, 5.9 mg), **8** (retention time of 8.3 min, 4.5 mg), **2** (retention time of 17.3 min, 4 mg), and **1** (retention time of 20.3 min, 11 mg) and MeOH/water (63:37) as eluent to yield

7 (retention time of 11.1 min, 6.0 mg), **9** (retention time of 12.8 min, 4.5 mg), and **4** (retention time of 15.3 min, 3.7 mg). Fraction 7 was repeatedly subjected to CC on silica gel and chromatographed over Sephadex LH-20, then purified with semi-preparative HPLC (Luna™ C18(2), 250×10 mm i.d., 5 ml min^{-1}), using MeOH/water (48:52) as eluent to yield **5** (retention time of 14.4 min, 3.2 mg) and **6** (retention time of 16.2 min, 14.5 mg).

3.3.1. Juncin R (1). White powder; $[\alpha]_D$ −36.2 (*c* 1.16, $CHCl_3$); IR (KBr) ν_{max} 3543, 1790, 1750, 1739, 1720, 1644 cm^{-1}; ^1H NMR spectral data, see Table 2; ^{13}C NMR spectral data, see Table 1; ESIMS(+) *m/z* 699 $[M+H]^+$; HRESIMS *m/z* 699.2412 $[M+H]^+$ (calcd for $C_{33}H_{44}ClO_{14}$, 699.2419).

3.3.2. Juncin S (2). White powder; $[\alpha]_D$ −32.8 (*c* 1.02, $CHCl_3$); IR (KBr) ν_{max} 3542, 1787, 1750, 1738, 1720, 1645 cm^{-1}; ^1H NMR spectral data, see Table 2; ^{13}C NMR spectral data, see Table 1; ESIMS(+) *m/z* 699 $[M+H]^+$; HRESIMS *m/z* 699.2413 $[M+H]^+$ (calcd for $C_{33}H_{44}ClO_{14}$, 699.2419).

3.3.3. Juncin T (3). White powder; $[\alpha]_D$ −14.0 (*c* 0.4, $CHCl_3$); IR (KBr) ν_{max} 3538, 1783, 1747, 1732, 1718, 1645 cm^{-1}; ^1H NMR spectral data, see Table 2; ^{13}C NMR spectral data, see Table 1; ESIMS(+) *m/z* 753 $[M+H]^+$; HRESIMS *m/z* 753.2963 $[M+H]^+$ (calcd for $C_{36}H_{49}O_{17}$, 753.2969).

3.3.4. Juncin U (4). White powder; $[\alpha]_D$ −18.9 (*c* 0.37, $CHCl_3$); IR (KBr) ν_{max} 3550, 1790, 1750, 1738, 1641 cm^{-1}; ^1H NMR spectral data, see Table 2; ^{13}C NMR spectral data, see Table 1; ESIMS(+) *m/z* 695 $[M+H]^+$; HRESIMS *m/z* 695.2908 $[M+H]^+$ (calcd for $C_{34}H_{47}O_{15}$, 695.2915).

3.3.5. Juncin V (5). White powder; $[\alpha]_D$ −13.1 (*c* 0.32, $CHCl_3$); IR (KBr) ν_{max} 3564, 3480, 1779, 1740, 1641 cm^{-1}; ^1H NMR spectral data, see Table 2; ^{13}C NMR spectral data, see Table 1; ESIMS(+) *m/z* 569 $[M+H]^+$; HRESIMS *m/z* 569.2230 $[M+H]^+$ (calcd for $C_{27}H_{37}O_{13}$, 569.2234).

3.3.6. Juncin W (6). White powder; $[\alpha]_D$ −11.7 (*c* 1.45, $CHCl_3$); IR (KBr) ν_{max} 3560, 3478, 1783, 1743, 1640 cm^{-1}; ^1H NMR spectral data, see Table 2; ^{13}C NMR spectral data, see Table 1; ESIMS(+) *m/z* 597 $[M+H]^+$; HRESIMS *m/z* 597.2178 $[M+H]^+$ (calcd for $C_{28}H_{37}O_{14}$, 597.2183).

3.3.7. Juncin X (7). White powder; $[\alpha]_D$ +21.34 (*c* 0.89, $CHCl_3$); IR (KBr) ν_{max} 3540, 1790, 1748, 1738, 1720 cm^{-1}; ^1H NMR spectral data, see Table 3; ^{13}C NMR spectral data, see Table 1; ESIMS(+) *m/z* 625 $[M+H]^+$; HRESIMS *m/z* 625.2492 $[M+H]^+$ (calcd for $C_{30}H_{41}O_{14}$, 625.2496).

3.3.8. Juncin Y (8). White powder; $[\alpha]_D$ +36 (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max} 3542, 1780, 1750, 1732, 1720 cm^{-1}; ^1H NMR spectral data, see Table 3; ^{13}C NMR spectral data, see Table 1; ESIMS(+) *m/z* 609 $[M+H]^+$; HRESIMS *m/z* 609.2541 $[M+H]^+$ (calcd for $C_{30}H_{41}O_{13}$, 609.2547).

3.3.9. Juncin Z (9). White powder; $[\alpha]_D$ +31.57 (*c* 0.95, $CHCl_3$); IR (KBr) ν_{max} 3564, 1779, 1743, 1646 cm^{-1}; ^1H NMR spectral data, see Table 3; ^{13}C NMR spectral data, see Table 1; ESIMS(+) *m/z* 595 $[M+H]^+$; HRESIMS *m/z* 595.2385 $[M+H]^+$ (calcd for $C_{29}H_{39}O_{13}$, 595.2390).

3.3.10. Juncin ZI (10). White powder; $[\alpha]_D$ +9.3 (*c* 1.29, $CHCl_3$); IR (KBr) ν_{max} 3530, 1788, 1749, 1736, 1718 cm^{-1}; ^1H NMR spectral data, see Table 3; ^{13}C NMR spectral data, see Table 1; ESIMS(+) *m/z* 557 $[M+H]^+$; HRESIMS *m/z* 557.1782 $[M+H]^+$ (calcd for $C_{26}H_{34}ClO_{11}$, 557.1789).

3.4. Larval settlement bioassays

Adults of *B. amphitrite* Darwin were collected from the intertidal zone in Hong Kong (N: 22°22′, E: 114°16′) in October 2005. After 12 h of exposure to air, several hundred adults were placed in a container filled with (FSW) (30 ppt salinity) to induce the release of larvae. Larval culture was maintained according to the method described by Thiyagarajan[19] and Harder et al.[20] Briefly, released nauplii were collected on sieves (90 μm). Larvae were reared to cyprid stage at a density of about 2 larvae mL^{-1}. When kept at 26 °C, and fed with *Isochrysis galbana*, larvae developed to the cyprid stage within six days. The culture medium was changed daily. The newly molted cyprid larvae were filtered onto a 100 μm sieve and were then washed with FSW to remove algae and detritus. Only cyprids at an age of one or two days, stored at 4 °C for two days at most, were used in the experiments.

In vitro still water larval settlement assays were performed using 24-well polystyrene plates. The tested samples were soluble in DMSO and added to autoclaved 0.22-μm filtered seawater (FSW) with different concentrations (0.05, 0.2, 1, 10, and 50 μg mL^{-1}). Twenty competent larvae were added to each well with 1 mL testing solution in four replicates, and wells containing 0.22-μm-sterile-filtered seawater (FSW) added with DMSO were served as control. The 24-well plates were incubated at 28 °C for 24 h. The effects of the tested samples activating antagonists on the larvae were determined by examining the plates with the aid of a dissecting microscope to check for: (1) attached larvae, (2) unattached larvae, and (3) dead larvae. The percentage of larval settlement was determined by counting the number of attached individuals and expressed as a proportion of the total number of larvae in the well. The EC_{50} (inhibits 50% of settlement of *B. amphitrite* larvae in comparison with the control) was the mean of three repeated experiments with different batches of larvae, and calculated by using the Probit software program.

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References and notes

1. Pawlik, J. R. *Chem. Rev.* **1993**, *93*, 1911–1922.
2. Koh, L. L.; Goh, N. K. C.; Chou, L. M.; Tan, Y. W. *J. Exp. Mar. Biol. Ecol.* **2000**, *251*, 103–115.

3. Wilsanand, V.; Wagh, A. B.; Bapuji, M. *Indian J. Mar. Sci.* **1999**, *28*, 280–284.
4. Sung, P. J.; Sheu, J. H.; Wu, S. W.; Xu, J. P. *Heterocycles* **2002**, *57*, 535–579.
5. Isaacs, S.; Carmely, S.; Kashman, Y. *J. Nat. Prod.* **1990**, *53*, 596–602.
6. Anjaneyulu, A. S. R.; Rao, N. S. K. *J. Chem. Soc., Perkin Trans. 1* **1997**, 959–962.
7. Shen, Y. C.; Lin, Y. C.; Chiang, M. Y. *J. Nat. Prod.* **2002**, *65*, 54–56.
8. Shen, Y. C.; Lin, Y. C.; Ko, C. L.; Wang, L. T. *J. Nat. Prod.* **2003**, *66*, 302–305.
9. Anjaneyulu, A. S. R.; Rao, V. L.; Sastry, V. G.; Venugopal, M. J. R. V.; Schmitz, F. J. *J. Nat. Prod.* **2003**, *66*, 507–510.
10. Sung, P. J.; Fan, T. Y.; Fang, L. S.; Sheu, J. H.; Wu, S. W.; Wang, G. H.; Lin, M. R. *Heterocycles* **2003**, *61*, 587–592.
11. Qi, S. H.; Zhang, S.; Huang, H.; Xiao, Z. H.; Huang, J. S.; Wu, J. *J. Nat. Prod.* **2004**, *67*, 1907–1910.
12. He, H. Y.; Faulkner, D. J. *Tetrahedron* **1991**, *47*, 3271–3280.
13. Rodríguez, A. D.; Ramírez, C.; Cóbar, O. M. *J. Nat. Prod.* **1996**, *59*, 15–22.
14. Sheu, J. H.; Chen, Y. P.; Hwang, T. Long.; Chiang, M. Y.; Fang, L. S.; Sung, P. J. *J. Nat. Prod.* **2006**, *69*, 269–273.
15. Shin, J.; Park, M.; Fenical, W. *Tetrahedron* **1989**, *45*, 1633–1638.
16. García, M.; Rodríguez, J.; Jiménez, C. *J. Nat. Prod.* **1999**, *62*, 257–260.
17. Keifer, P. A.; Rinehart, K. L.; Hooper, I. R. *J. Org. Chem.* **1986**, *54*, 4450–4454.
18. Clare, A. S.; Rittschof, D.; Gerhart, D. J.; Hooper, I. R.; Bonaventura, J. *Mar. Biotechnol.* **1999**, *1*, 427–436.
19. Thiyagarajan, V.; Harder, T.; Qian, P. Y. *J. Exp. Mar. Biol. Ecol.* **2003**, *287*, 223–236.
20. Harder, T.; Thiyagarajan, V.; Qian, P. Y. *Biofouling* **2001**, *17*, 211–219.

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A concise synthesis of nornitidine via nickel- or palladium-catalyzed annulation

Yu Luo,[a,b] Yuhua Mei,[a] Jianbo Zhang,[a] Wei Lu[a,*] and Jie Tang[a]

[a]*Institute of Medicinal Chemistry, Shanghai Key Laboratory of Green Chemistry and Chemical Process, Department of Chemistry, East China Normal University, Shanghai 200062, China*
[b]*Shanghai Institute of Materia Medica, SIBS, Chinese Academy of Sciences, Shanghai 201203, China*

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Abstract—A concise method to synthesize benzo[*c*]phenanthridine alkaloid, nornitidine, was developed utilizing nickel- or palladium-catalyzed iminoannulation of an internal alkyne. The advantages of this strategy included readily available starting materials, inexpensive reagents, short reaction steps, and good yields.

1. Introduction

The fully aromatized benzo[*c*]phenanthridine alkaloids, such as nitidine and fagaronine (Fig. 1), are an important group of naturally occurring alkaloids with a broad range of pharmacological activities, including anti-tumor and anti-viral activities.[1] Nitidine and other benzo[*c*]phenanthridine alkaloid analogues exhibit potent anti-tumor activity by the inhibition of DNA topoisomerase I,[2] and are considered as potential anti-tumor drugs. However, these compounds can only be isolated in very small amounts. For example, nitidine could be isolated in a yield of 0.003–0.07% from *Zanthoxylum* and *Fagara* varieties.[3] For these reasons, synthetic chemists have devoted enormous efforts to establish concise and versatile methods for the preparation of benzo[*c*]phenanthridine alkaloids and their analogues.[4] Many of the previously reported benzophenanthridine synthetic processes have shown some disadvantages such as numerous steps, low yields or poor generality. Thus, a convenient synthesis is needed for the synthesis of these compounds as well as their analogues. In this paper we report a concise synthesis of nornitidine, which is a synthetic precursor to nitidine.[5]

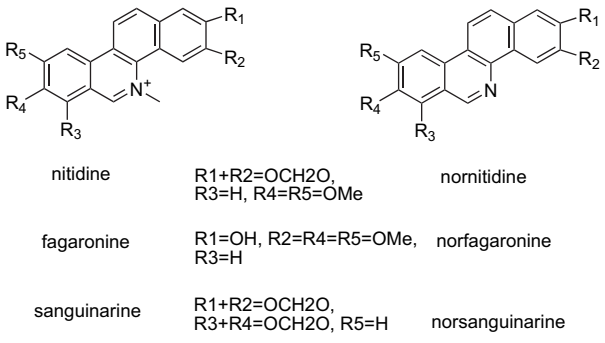
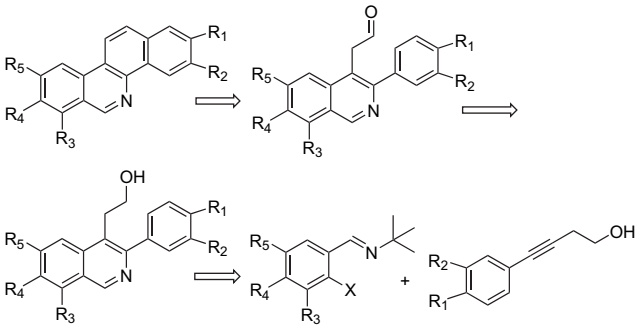


Figure 1. Structures of some benzo[*c*]phenanthridine alkaloids.

Retrosynthetic analysis indicated that the application of Larock's[6] or Cheng's[7] methodology could afford isoquinolines, which could be further transformed to benzo[*c*]phenanthridine alkaloids (Scheme 1). In this paper we report a new synthetic approach to nornitidine by nickel- and palladium-catalyzed annulation reactions. The advantages of our method include easy access to starting materials, short reaction steps, good yields and one-step reaction to construct all carbon atoms of the alkaloid.



Scheme 1. Retrosynthesis of benzo[*c*]phenanthridine alkaloids.

Keywords: Benzo[*c*]phenanthridine; Isoquinolines; Nitidine; Palladium; Nickel; Catalysis.
* Corresponding author. Fax: +86 21 62602475; e-mail: wlu@chem.ecnu.edu.cn

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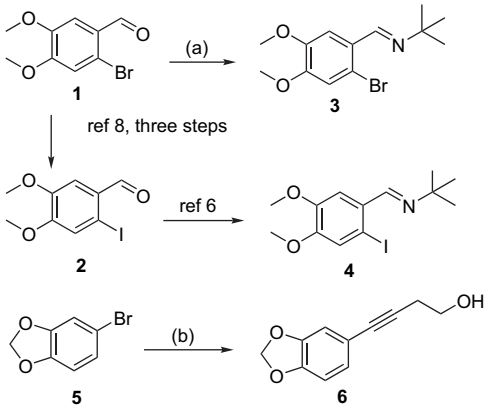
2. Results and discussion

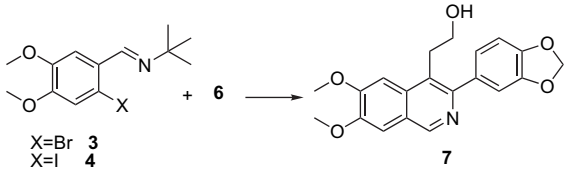
First, 2-bromobenzaldimine **3**, 2-iodobenzaldimine **4**, and alkyne **6** were prepared as outlined in Scheme 2. 2-Bromobenzaldimine **3** was prepared in a 96% yield, by treatment of the aldehyde **1** with *tert*-butylamine.[6] 2-Iodobenzaldimine **4** was synthesized from the aldehyde **2**,[6] which was prepared from **1** in three steps.[8] The internal alkyne **6** was prepared via Sonogashira reaction[9] from the commercially available bromide **5** in 80% yield.



Scheme 2. Reagents and conditions: (a) *tert*-butylamine, 96%; (b) $Pd(PPh_3)_2Cl_2$, CuI, 3-butyn-1-ol, DIPA, 80%.

Then, the annulation of 2-bromobenzaldimine **3** and 2-iodobenzaldimine **4** with the alkyne **6** was investigated (Table 1). We first chose $Pd(OAc)_2$ as the catalyst[6] and bromide **3** and iodide **4** as the substrates to synthesize iosquinoline **7**. Bromide **3** did not react with alkyne **6** (entry 1), while iodide **4** reacted with alkyne **6** to give compound **7** in a poor yield (entry 2). Optimization of this reaction, using a variety of ligands such as PPh_3, tri-*o*-tolylphosphin, *rac*-BINAP, did not improve the yield. Cyclization of bromide **3** and alkyne **6** by $NiBr_2$(dppe)/Zn[7] afforded isoquinoline **7** in a good yield, while annulation of iodide **4** and alkyne **6** gave a moderate yield. Since bromide **1** was more conveniently available than iodide **2** (Scheme 2), synthesis of isoquinoline **7** from 2-bromobenzaldimine **3** appeared to be more appealing both synthetically and economically. The NOESY spectrum of compound **7**, shown in Figure 2, indicated the correlation between H_1 and H_2. Therefore, H_3 could be assigned, which

Table 1. Catalytic annulation of bromide **3** and iodide **4** with alkyne **6**



Entry	Imine	Method[a]	Yield[b] (%)
1[b]	**3**	$Pd(OAc)_2$	—
2	**4**	$Pd(OAc)_2$	38
3	**3**	$NiBr_2$(dppe)/Zn	73
4	**4**	$NiBr_2$(dppe)/Zn	58

[a] Isolated yields.
[b] No reaction occurred.

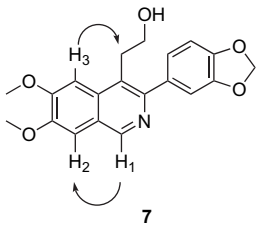
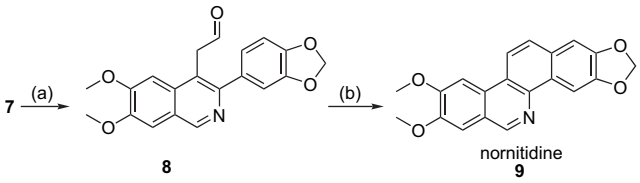


Figure 2. NOESY spectrum of isoquinoline **7**.

showed the correlation with the methylene. As expected, the regioselectivity of the annulation reaction was correct.

Subsequently, oxidation of **7** was investigated. While oxidation of compound **7** with PCC or Dess–Martin reagent gave a low yield, Swern oxidation[10] of isoquinoline **7** proceeded smoothly to afford aldehyde **8**, which was then cyclized under acidic conditions[11] to afford nornitidine **9** in a good yield, as illustrated in Scheme 3.



Scheme 3. Reagents and conditions: (a) $(COCl)_2$, DMSO, DIPEA, CH_2Cl_2, 77%; (b) AcOH, 40% HBr, 78%.

3. Conclusion

We have developed a concise synthetic method to prepare nornitidine via nickel- or palladium-catalyzed annulation in three linear steps in a good yield, using readily available starting materials and inexpensive reagents. This efficient process should allow for easy synthesis of a variety of benzo[*c*]phenanthridine alkaloids and their analogues.

4. Experimental

4.1. General

^1H, ^{13}C NMR, and NOESY spectra were recorded on Bruker DRX-500. Chemical shifts (δ, ppm) were reported for signal center, and coupling constant *J* was reported in units of hertz. High-resolution mass spectra were recorded on Finnigan MAT-95 mass spectrometer. Elemental analyses were performed on Elementar Vario EL *III*. Column chromatography was performed on 200–300 mesh silica gel. All reagents were used directly as obtained commercially, unless otherwise noted.

4.1.1. *N*-(2-Bromo-4,5-dimethoxybenzylidene)-*tert*-butylamine (3). A mixture of 2-bromo-4,5-dimethoxybenzaldehyde **1** (4.00 g, 16.3 mmol) and *tert*-butylamine (25 mL) was stirred under a nitrogen atmosphere at room temperature for 20 h. The excessive *tert*-butylamine was removed under reduced pressure, and the resulting mixture was dissolved in dichloromethane, dried (Na_2SO_4), and filtered. Removal of

the solvent afforded 4.7 g of imine **3** as a pale yellow solid (96% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.33 (s, 9H), 3.92 (s, 3H), 3.97 (s, 3H), 7.02 (s, 1H), 7.60 (s, 1H), 8.54 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=29.5, 55.6, 55.8, 57.2, 109.6, 114.5, 116.2, 127.6, 148.3, 150.9, 153.7. MS (EI): *m*/*z*=299, 301.

4.1.2. 4-(3,4-Methylenedioxyphenyl)-3-butyn-1-ol (6). A mixture of $Pd(PPh_3)_2Cl_2$ (0.71 g, 1.00 mmol), CuI (0.19 g, 1.00 mmol), bromide **5** (6.8 g, 33.8 mmol), and 3-butyn-1-ol (2.6 g, 37.2 mmol) in degassed DIPA (20 mL) was refluxed for 4 h under nitrogen atmosphere. After cooling, the reaction mixture was filtered, and the filtrate was concentrated to give a residue, which was purified by silica gel chromatography (ethyl acetate/petroleum ether = 3:1) to afford 5.1 g of compound **6** (80% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ=2.66 (t, *J*=6.3 Hz, 2H), 3.79 (t, *J*=6.3 Hz, 2H), 5.96 (s, 2H), 6.73 (d, *J*=7.8 Hz, 1H), 6.86 (d, *J*=1.5 Hz, 1H), 6.93 (dd, *J*=1.5 Hz, *J*=7.8 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=23.3, 60.6, 81.5, 84.7, 100.9, 107.9, 111.3, 116.4, 125.7, 146.9, 147.1. MS (EI): *m*/*z*=190. HRMS (EI): *m*/*z* calcd for $C_{11}H_{10}O_3$ [M^+]: 190.0630; found: 190.0632.

4.1.3. 6,7-Dimethoxy-4-(2-hydroxy-ethyl)-3-(3,4-methylenedioxyphenyl)-isoquinoline (7).

4.1.3.1. Palladium-catalyzed annulation. To a mixture of dry DMF (34 mL), $Pd(OAc)_2$ (100 mg, 0.44 mmol), Na_2CO_3 (980 mg, 9.2 mmol), and alkyne **6** (2.6 g, 13.6 mmol) under nitrogen atmosphere was added imine **4** (3.2 g, 9.2 mmol). The contents were heated in an oil bath at 100 °C for 8 h. The reaction mixture was cooled, diluted with chloroform (90 mL), which was washed with water (400 mL). The organic layer was concentrated and the residue was purified by silica gel chromatography (acetone/dichloromethane = 1:4) to afford 1.2 g of pure compound **7** (38% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ=3.32 (t, *J*=7 Hz, 2H), 3.86 (t, *J*=7 Hz, 2H), 4.05 (s, 3H), 4.07 (s, 3H), 6.01 (s, 2H), 6.89 (d, *J*=8 Hz, 1H), 6.96 (dd, *J*=8 Hz, *J*=1.2 Hz, 1H), 6.99 (d, *J*=1.2 Hz, 1H), 7.23 (s, 1H), 7.37 (s, 1H), 8.97 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=32.1, 56.0, 56.1, 62.4, 101.0, 102.3, 105.8, 108.0, 110.0, 122.9, 123.8, 123.9, 132.4, 135.2, 147.0, 147.4, 147.7, 149.9, 151.4, 153.3. MS (EI): *m*/*z*=353. HRMS (EI): *m*/*z* calcd for $C_{20}H_{19}NO_5$ [M^+]: 353.1263; found: 353.1276. Anal. Calcd for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.42; N, 3.96. Found: C, 67.51; H, 5.72; N, 4.04.

4.1.3.2. Nickel-catalyzed annulation. A flask containing $NiBr_2$(dppe) (62 mg, 0.1 mmol), zinc powder (260 mg, 4.0 mmol), and 2-bromobenzaldimine **3** (0.60 g, 2.0 mmol) was evacuated and purged with nitrogen gas three times. Freshly distilled acetonitrile containing alkyne **6** (0.50 g, 2.6 mmol) was added to the system and the reaction mixture was stirred at reflux for 2 h. The reaction mixture was cooled, filtered, and evaporated to give a residue, which was purified by silica gel chromatography (acetone/dichloromethane = 1:4) to afford 0.51 g of pure compound **7** (73% yield). When 2-iodobenzaldimine **4** was used in place of bromide **3**, 0.40 g of compound **7** was obtained (58% yield).

4.1.4. 6,7-Dimethoxy-4-(2-oxo-ethyl)-3-(3,4-methylenedioxyphenyl)-isoquinoline (8). To a cooled (−60 °C) solution of oxalyl chloride (0.21 mL, 2.2 mmol) in 7.0 mL of CH_2Cl_2 was added dropwise a solution of DMSO (0.32 mL, 4.4 mmol) in 3 mL of CH_2Cl_2, and the mixture was stirred for 15 min. Then a solution of compound **7** (0.40 g, 1.1 mmol) in 30 mL of CH_2Cl_2 was added dropwise, and the stirring was continued for 30 min. Then DIPEA (2.8 mL, 17 mmol) was added slowly. After stirring for 15 min, the mixture was allowed to reach room temperature, and quenched with water (25 mL). The organic phase was separated, dried (Na_2SO_4), and evaporated to afford a residue, which was purified by silica gel chromatography (acetone/chloroform = 1:15) to give 0.31 g of pure **8** (77% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ=4.02 (s, 3H), 4.05 (s, 3H), 4.12 (s, 2H), 6.02 (s, 2H), 6.82–6.87 (m, 2H), 6.92–6.93 (m, 2H), 7.28 (s, 1H), 9.07 (s, 1H), 9.78 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=45.0, 56.0, 101.1, 101.8, 106.0, 108.1, 110.0, 117.9, 123.1, 123.7, 132.5, 134.7, 147.4, 147.7, 149.0, 150.2, 152.4, 153.7, 199.0. MS (EI): *m*/*z*=351. HRMS (EI): *m*/*z* calcd for $C_{20}H_{17}O_5$ [M^+]: 351.1107; found: 351.1201.

4.1.5. Nornitidine (9). To a mixture of aldehyde **8** (0.13 g, 0.37 mmol) and acetic acid (3.0 mL), was added 40% hydrobromic acid (1.0 mL), and stirred at room temperature for 30 min. To the mixture was added 10% NaOH solution (30 mL), and it was extracted with CH_2Cl_2 (80 mL). The organic phase was dried and evaporated to give a residue, which was purified by silica gel chromatography (acetone/chloroform = 1:100) to give 96 mg of nornitidine (78% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ=4.10 (s, 3H), 4.17 (s, 3H), 6.13 (s, 2H), 7.28 (s, 1H), 7.41 (s, 1H), 7.84 (d, *J*=9 Hz, 1H), 7.91 (s, 1H), 8.30 (d, *J*=9 Hz, 1H), 8.73 (s, 1H), 9.26 (s, 1H). MS (EI): *m*/*z*=333. HRMS (EI): *m*/*z* calcd for $C_{20}H_{15}NO_4$ [M^+]: 333.1001; found: 333.1010.

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References and notes

1. (a) Simanek, V. *The Alkaloids*; Bross, A., Ed.; Academic: New York, NY, 1985; Vol. 26, pp 185–240; (b) Suffiness, W. M.; Gordell, G. A. *The Alkaloids*; Bross, A., Ed.; Academic: New York, NY, 1983; Vol. 25, pp 178–188.
2. Taira, Z.; Matsumoto, M.; Ishida, S.; Icikawa, T.; Sakiya, Y. *Chem. Pharm. Bull.* **1994**, *42*, 1556.
3. Cushman, M.; Cheng, L. *J. Org. Chem.* **1978**, *43*, 286.
4. Recent papers for the synthesis of benzo[*c*]phenanthridine alkaloids: (a) Clement, B.; Weide, M.; Wolschendorf, U.; Kock, I. *Angew. Chem., Int. Ed.* **2005**, *44*, 635; (b) Kock, I.; Clement, B. *Synthesis* **2005**, 1052; (c) Le, T. N.; Gang, S. G.; Cho, W.-J. *J. Org. Chem.* **2004**, *69*, 2768; (d) Le, T. N.; Gang, S. G.; Cho, W.-J. *Tetrahedron Lett.* **2004**, *45*, 2763; (e) Treus, M.; Estevez, J. C.; Castedo, L.; Estevez, R. J. *Tetrahedron Lett.* **2002**, *43*, 5323; (f) Harayama, T.; Akiyama, T.; Nakano, Y.; Shibaike, K.; Akamatsu, H.; Hori, A.; Abe, H.; Takeuchi, Y. *Synthesis* **2002**, 237; (g) Harayama,

T.; Akiyama, T.; Akamatsu, H.; Kawano, K.; Abe, H.; Takeuchi, Y. *Synthesis* **2001**, 444; (h) Harayama, T.; Akamatsu, H.; Okamura, K.; Miyagoe, T.; Akiyama, T.; Abe, H.; Takeuchi, Y. *J. Chem. Soc., Perkin Trans. 1* **2001**, 523; (i) Nakanishi, T.; Suzuki, M. *Org. Lett.* **1999**, *1*, 985; (j) Nakanishi, T.; Suzuki, M.; Mashiba, A.; Ishikawa, K.; Yokotsuka, T. *J. Org. Chem.* **1998**, *63*, 4235; (k) Green, G. R.; Mann, I. S.; Mullane, M. V.; Mckilop, A. *Tetrahedron* **1998**, *54*, 9875; (l) Treus, M.; Estevez, J. C.; Castedo, L.; Estevez, R. J. *Tetrahedron Lett.* **2000**, *41*, 6351.

5. (a) Arthur, H. R.; Ng, Y. L. *J. Chem. Soc.* **1959**, 4010; (b) Gopinath, K. W.; Govindachari, T. R.; Parthasarathy, P. C.; Viswanathan, N. *J. Chem. Soc.* **1959**, 4012.
6. (a) Roesch, K. R.; Zhang, H.; Larock, R. C. *J. Org. Chem.* **2001**, *66*, 8042; (b) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 5306.
7. Korivi, R. P.; Cheng, C.-H. *Org. Lett.* **2005**, *7*, 5179.
8. (a) Charlton, J. L.; Oleschuk, C. J.; Chee, G.-L. *J. Org. Chem.* **1996**, *61*, 3452; (b) Coltart, D. M.; Charlton, J. L. *Can. J. Chem.* **1996**, *74*, 88.
9. (a) Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46; (b) Tykwinski, R. R. *Angew. Chem., Int. Ed.* **2003**, *42*, 1566; (c) Negishi, E. I.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979.
10. Carrillo, L.; Badia, D.; Dominguez, E.; Anakabe, E.; Osante, I.; Tellitu, I.; Vicario, J. L. *J. Org. Chem.* **1999**, *64*, 1115.
11. Bradsher, C. K.; Jackson, W. J. *J. Am. Chem. Soc*. **1954**, *76*, 734.

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Spontaneous Nef reaction of 3-aryl-2-(diethoxyphosphoryl)-4-nitroalkanoic acids

Henryk Krawczyk,[a,*] Łukasz Albrecht,[a] Jakub Wojciechowski[b] and Wojciech M. Wolf[b]

[a]*Technical University (Politechnika), Institute of Organic Chemistry, Żeromskiego 116, 90-924 Łódź, Poland*
[b]*Technical University (Politechnika), Institute of General and Ecological Chemistry, Żeromskiego 116, 90-924 Łódź, Poland*

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Abstract—Spontaneous Nef reaction of primary and secondary 3-aryl-2-(diethoxyphosphoryl)-4-nitroalkanoic acids has been observed for the first time. The reaction provides a general and effective, highly diastereoselective synthesis of 3-(diethoxyphosphoryl)-1-hydroxysuccinimides and 2-(diethoxyphosphoryl)-4-oxoalkanoic acids.

1. Introduction

Acid promoted hydrolysis of primary and secondary nitroalkanes to the corresponding carbonyl compounds, commonly known as the Nef reaction, represents a synthetically important transformation.[1–3] The ability to transform a nitroalkane to an aldehyde or ketone makes the nitro group a masked carbonyl group. Considerable effort has been devoted to optimize conditions of this reaction. Within this area, we have recently demonstrated that the carboxylic acid functionality participates as an intramolecular catalyst in the Nef reaction of primary and secondary 2-(diethoxyphosphoryl)-4-nitroalkanoic acids.[4] We have found that this reaction proceeds in water in the absence of any additives. Under these conditions 2-(diethoxyphosphoryl)-4-nitrobutanoic acid underwent conversion into 3-(diethoxyphosphoryl)-1-hydroxysuccinimide, while 2-(diethoxyphosphoryl)-4-nitropentanoic and hexanoic acids afforded the corresponding 2-(diethoxyphosphoryl)-4-oxoalkanoic acids.

Intramolecular catalysis of the Nef reaction represents a conceptually new approach to the preparation of 1-hydroxysuccinimides,[5] and provides an attractive entry to 2-(diethoxyphosphoryl)-4-oxoalkanoic acids.[6–10] The latter transformation would be very valuable in the synthesis of α-diethoxyphosphoryl-γ-butyrolactones. There has been an intense activity in the application of α-diethoxyphosphoryl-γ-lactones for the preparation of their α-alkylidene derivatives by Horner–Wadsworth–Emmons olefination.[11–15] We have recently discovered that these lactones can also be successfully used as starting materials for the preparation of ethyl cyclopropanecarboxylates.[16]

The Nef reaction based on the intramolecular catalysis would significantly benefit from availability of substituted 2-(diethoxyphosphoryl)-4-nitroalkanoic acids. Recently, we have described an efficient route to (*E*)-3-aryl-2-(diethoxyphosphoryl)acrylic acids **1**.[17] In this paper we report that a variety of 3-(diethoxyphosphoryl)-1-hydroxysuccinimides **8a–e** and 2-(diethoxyphosphoryl)-4-oxopentanoic acids **9a–e** can be prepared by addition of nitromethane or nitroethane to the acids **1a–e**, and subsequent spontaneous Nef reaction of the resulting 2-(diethoxyphosphoryl)-4-nitrobutanoic acids **5a–e** and 2-(diethoxyphosphoryl)-4-nitropentanoic acids **6a–e**, respectively.

2. Results and discussion

Our initial attempts to obtain the nitroalkanoic acids **5a–e** and **6a–e** by a self-catalytic Michael addition of nitromethane and nitroethane to the dicyclohexylammonium salts of acids **1a–e** under previously reported conditions were unsuccessful.[4,17] In all cases the unreacted starting materials were recovered. The problem was eventually solved by modifying the Michael acceptor. *tert*-Butyl acrylates **2a–e** were generated by treatment of the acids **1a–e** with *tert*-butyl alcohol in the presence of magnesium sulfate and sulfuric acid (Scheme 1 and Table 1).[18] It was found that the use of the nitroalkane as both the reagent and the solvent with potassium *tert*-butoxide (50 mol %) as a catalyst gave the best results in terms of yield and purity of the products. The addition proceeded effectively at room temperature. The

Keywords: Intramolecular catalysis; Nef reaction; Michael reaction; 4-Oxoalkanoic acids; *N*-Hydroxysuccinimides.
* Corresponding author. Fax: +48 42 6365530; e-mail: henkrawc@p.lodz.pl

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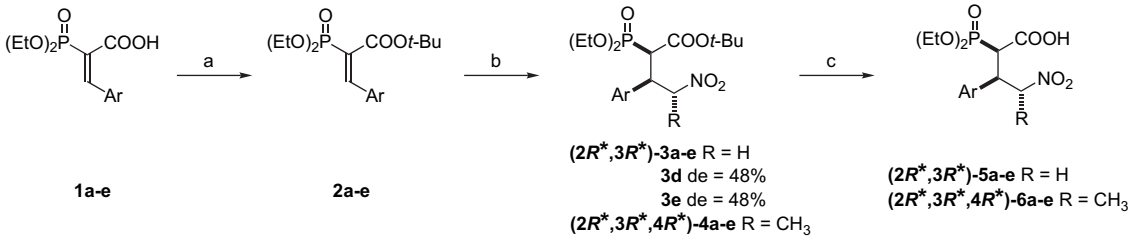
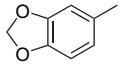


Scheme 1. Reagents and conditions: (a) $MgSO_4$ (5 equiv), H_2SO_4 (1 equiv), *t*-BuOH (4 equiv), CH_2Cl_2, rt; (b) $MeNO_2$ or $EtNO_2$, *t*-BuOK (0.5 equiv), rt; and (c) CF_3COOH–CH_2Cl_2 (1:1), rt, 24 h.

Table 1. *tert*-Butyl acrylates **2**, nitroalkanoates **3** and **4**, and nitroalkanoic acids **5** and **6** prepared

	Ar	**2**		**3** (R=H)		**4** (R=CH_3)		**5**	**6**
		Yield [%]	Reaction time [days]	Yield [%]	Reaction time [days]	Yield [%]	Reaction time [days]	(R=H) Yield [%]	(R=CH_3) Yield [%]
a	4-NO_2–C_6H_4–	82	2	90	1	70	1	90	85
b	4-Br–C_6H_4–	85	2	67	1	66	1	80	89
c	4-CH_3–C_6H_4–	88	4	80	8	49	4	89	84
d	4-CH_3O–C_6H_4–	82	4	56	24	58	5	77	92
e		91	3	73	11	51	5	94	93

yields of the products obtained from nitromethane were similar to those derived from nitroethane. However, the addition of nitromethane to the acrylates **2a–e** was much slower and was highly dependant on the particular electrophile used.

The products **3a–e** and **4a–e** were formed as mixtures of diastereoisomers. Notably, the crystalline nitroalkanoates **3a–c** and **4a–e** were isolated as single diastereoisomers. In each case, the crystalline adduct was the major diastereoisomer present in the reaction mixture. This result indicates that diastereoisomeric products undergo rapid epimerization due to acidic hydrogens at C-2 and C-4 atoms. On the contrary, the crystalline phosphonates **3d** and **3e** were isolated as inseparable mixtures of diastereoisomers, each in a 1:0.35 ratio.

The relative stereochemistry of the stereogenic centers C-2 and C-3 in the phosphonates **3a–c** and **4a–e** was assigned to be (2*R**,3*R**) on the basis of ^1H and ^{13}C NMR data. The values of coupling constants $^3J_{H2–H3}$=10.6–12.2 Hz and $^3J_{P–Cipso}$=14.5–16.4 Hz indicate that the phosphonates exist almost exclusively as a single conformers having antiplanarly oriented phenyl and phosphoryl groups as well as H-2 and H-3 atoms.[19–22]

The relative stereochemistry of the phosphonate **4a** was unequivocally determined to be (2*R**,3*R**,4*R**) by X-ray crystallographic analysis.[23] It is worth noting that the phosphonate **4a** exists in a fully extended zig–zag conformation having the phosphoryl and 4-nitrophenyl groups in antiplanar, and 4-nitrophenyl and methyl groups in gauche positions (Fig. 1). By analogy with the above results the relative configuration of the adducts **4b–e** was assigned to be (2*R**,3*R**,4*R**).

Deprotection of the *tert*-butyl alkanoates **3a–e** and **4a–e** with CF_3COOH afforded crystalline alkanoic acids **5a–e** and **6a–e**, respectively. Notably all the acids were obtained as

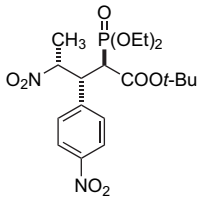
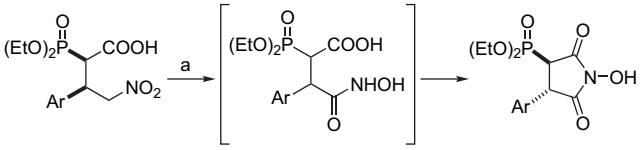


Figure 1. Conformation of the *tert*-butyl (2*R**,3*R**,4*R**)-2-diethoxyphosphoryl-4-nitro-3-(4-nitrophenyl)pentanoate (**4a**).

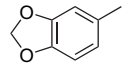
single diastereoisomers. The assignment of the relative configuration of the acids **5a–e** and **6a–e** was based on comparison of their NMR spectral data with those of the respective *tert*-butyl esters **3a–e** and **4a–e**. The acids displayed similar values of the coupling constants $^3J_{H2–H3}$ and $^3J_{P–Cipso}$ to those observed for the esters **3a–e** and **4a–c**. Thus, the relative configuration (2*R**,3*R**) and (2*R**,3*R**,4*R**) could be assigned to the acids **5a–e** and **6a–e**, respectively.

The availability of the requisite nitroalkanoic acids **5a–e** and **6a–e** allowed us to attempt their conversion into 1-hydroxysuccinimides **8a–e** and 4-oxoalkanoic acids **9a–e**, respectively, by the spontaneous Nef reaction. After much experimentation, we found that heating the 4-nitrobutanoic acids **5a–e** in boiling water for 40–70 min was optimal, and provided the desired 1-hydroxysuccinimides **8a–e** in excellent yields (Scheme 2 and Table 2). A noteworthy feature of the Nef reaction is that the formation of the *N*-hydroxysuccinamic acids **7a–e** followed by their ring closure and



Scheme 2. Reagent and condition: (a) H_2O, reflux.

Table 2. 1-Hydroxysuccinimides **8** and 4-oxoalkanoates **10** prepared

	Ar	8		10	
		Yield [%]	Reaction time [min]	Yield [%]	Reaction time [min]
a	4-NO_2–C_6H_4–	60	40	70	120
b	4-Br–C_6H_4–	67	55	56	120
c	4-CH_3–C_6H_4–	68	70	50	120
d	4-CH_3O–C_6H_4–	64	70	62	60
e		79	60	59	90

loss of water occurs with epimerization, giving 1-hydroxysuccinimides **8a–e** as thermodynamically stable trans isomers, exclusively.

Spectroscopic studies were not useful in determining the stereochemistry of imides **8a–e**. X-ray crystallographic analysis conducted on the imide **8b** revealed that the phosphoryl and aryl groups are in trans relationship and allowed us to assign the (3*R**,4*S**) relative stereochemistry to the products **8a–e** (Fig. 2). In this context it is also worth noting that the values of coupling constant $^3J_{P-H4}$=18.0–18.1 Hz observed in ^{1}H NMR spectra of **8a** and **8b** are consistent with the synperiplanar arrangement of the phosphorus and H-4 atoms. The 1-hydroxysuccinimide ring in the crystal structure of **8b** is virtually planar. Deviations from the least-squares mean plane calculated for all endocyclic non-hydrogen atoms are smaller than 0.03 Å. On the contrary to the unsubstituted *N*-hydroxysuccinimide molecule, as reported by Jones,[24] bond lengths of the equivalent endocyclic C–N and C–C bonds are practically equal [N–C3 1.379(5), N–C4 1.372(5), C2–C3 1.524(5), C1–C4 1.517(5) Å]. In the crystal, molecules are linked into centrosymmetric dimers through the hydrogen bonds between the hydroxyl and phosphoryl groups. The respective interatomic O1···O4 [1−*x*, 1−*y*, 1−*z*] distance is 2.599(5) Å. The exocyclic carbonyl bonds are quite short [C3=O2 1.203(4), C4=O3 1.197(4) Å], when compared to the standard values reported for amides and γ-lactams 1.234 and 1.235 Å, respectively[25] and are not involved in the hydrogen bonding.

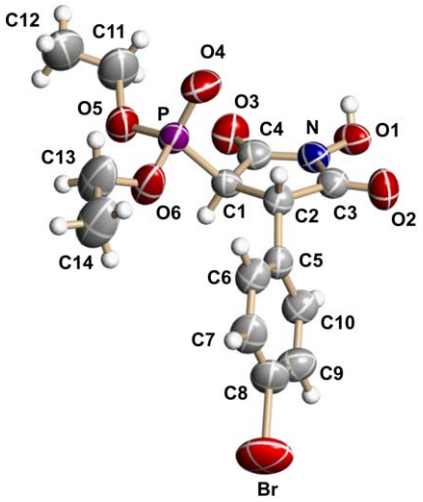
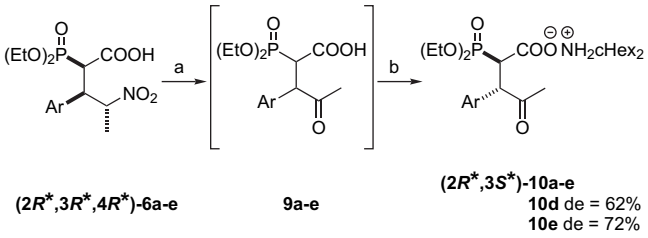


Figure 2. View of **8b** with atom numbering. Displacement ellipsoids were drawn at the 50% probability level.

Next, we focused our attention on converting 4-nitropentanoic acids **6a–e** to the target 4-oxopentanoic acids **9a–e** (Scheme 3). The Nef reaction proceeded effectively in boiling water and it was completed within 1–2 h. The 4-oxoalkanoic acids **9a–e** were then isolated as crystalline dicyclohexylammonium salts **10a–e** in good overall yields (Table 2).



Scheme 3. Reagents and conditions: (a) H_2O, reflux and (b) *c*Hex_2NH (1.1 equiv), CH_2Cl_2, rt.

The stereochemistry of products **10a–e** was similar to that observed for hydroxyimides **8a–e**. The dicyclohexylammonium alkanoates **10a–c** were formed as (2*R**,3*S**) diastereoisomers, exclusively. A notable exception is represented by the products **10d** and **10e** that are formed as mixtures of diastereoisomers of (2*R**,3*S**) and (2*R**,3*R**) in ratios 81:19 and 86:14, respectively. The assignment of the relative configuration was based on ^{1}H and ^{13}C NMR data. It is reasonable to assume that the phosphonates (2*R**,3*S**)-**10a–e** are single conformers with the phosphoryl and acyl groups ($^3J_{P-C=O}$=18.2–19.6 Hz) as well as H-2 and H-3 ($^3J_{H2-H3}$=11.3–11.8 Hz) antiplanar.

3. Conclusions

In conclusion, we have demonstrated that the Nef reaction of primary and secondary 3-aryl-2-(diethoxyphosphoryl)-4-nitroalkanoic acids is assisted by intramolecular catalysis. This reaction provides a general and an efficient methodology for the preparation of the corresponding 3-(diethoxyphosphoryl)-1-hydroxysuccinimides and 2-(diethoxyphosphoryl)-4-oxoalkanoic acids in a highly stereoselective manner.

4. Experimental

4.1. General

NMR spectra were recorded on a Bruker DPX 250 instrument at 250.13 MHz for ^{1}H and 62.9 MHz for ^{13}C and 101.3 MHz for ^{31}P NMR using tetramethylsilane as an internal and 85% H_3PO_4 as an external standard. The multiplicity of carbons was determined by DEPT experiments. IR spectra were measured on a Specord M80 (Zeiss) instrument. Elemental analyses were performed on a Perkin–Elmer PE 2400 analyzer. Melting points were determined in open capillaries and are uncorrected. Acrylic acids **1a–e** were prepared according to the literature procedure.[17]

4.2. General procedure for the preparation of *tert*-butyl (*E*)-3-aryl-2-(diethoxyphosphoryl)acrylates 2a–e

Concentrated sulfuric acid (0.98 g, 10 mmol) was added to a stirred suspension of magnesium sulfate (6.00 g, 50 mmol) in CH_2Cl_2 (40 mL) and the resulting mixture was stirred at

room temperature for 15 min. Acrylic acid **1** (10 mmol) and *tert*-butyl alcohol (2.96 g, 40 mmol) were then added. The mixture was stoppered tightly and was stirred for an appropriate period of time (shown in Table 1) at room temperature. The reaction progress was occasionally monitored with ^{31}P NMR. When the progress of the reaction was no longer observed, saturated $NaHCO_3$ solution was added (50 mL). The organic layer was separated, washed with water (2×20 mL), and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure afforded a crude product, which was purified by column chromatography (eluent: ethyl acetate/hexane 2:1).

4.2.1. *tert*-Butyl (*E*)-2-(diethoxyphosphoryl)-3-(4-nitrophenyl)acrylate (2a). 2.70 g, 82% yield, yellow oil; R_f=0.5 (ethyl acetate/hexane 2:1); IR (film): 1720, 1348, 1256, 1156 cm^{-1}; ^{31}P NMR ($CDCl_3$): δ=12.98; ^{1}H NMR ($CDCl_3$): δ=1.39 (t, 3H, $^3J_{HH}$=7.0 Hz, CH_3CH$_2$OP), 1.40 (t, 3H, $^3J_{HH}$=7.0 Hz, CH_3CH$_2$OP), 1.48 (s, 9H, C(CH_3)$_3$), 4.15–4.28 (m, 4H, 2×CH$_3$CH_2OP), 7.62 (d, 1H, $^3J_{HP}$= 23.8 Hz, ArCH=C), 7.63 (d, 2H, $^3J_{HH}$=8.8 Hz, 2×CH_{Ar}), 8.24 (d, 2H, $^3J_{HH}$=8.8 Hz, 2×CH_{Ar}). Anal. calcd for $C_{17}H_{24}NO_7P$: C, 52.99; H, 6.28; N, 3.63. Found: C, 53.11; H, 6.17; N, 3.51.

4.2.2. *tert*-Butyl (*E*)-3-(4-bromophenyl)-2-(diethoxyphosphoryl)acrylate (2b). 3.56 g, 85% yield, pale yellow oil; R_f=0.5 (ethyl acetate/hexane 2:1); IR (film): 1716, 1368, 1252, 1032 cm^{-1}; ^{31}P NMR ($CDCl_3$): δ=14.39; ^{1}H NMR ($CDCl_3$): δ=1.37 (t, 6H, $^3J_{HH}$=7.0 Hz, 2×CH_3CH$_2$OP), 1.49 (s, 9H, C(CH_3)$_3$), 4.10–4.25 (m, 4H, 2×CH$_3$CH_2OP), 7.35 (d, 2H, $^3J_{HH}$=8.8 Hz, 2×CH_{Ar}), 7.49 (d, 1H, $^3J_{HP}$= 24.0 Hz, ArCH=C), 7.51 (d, 2H, $^3J_{HH}$=8.8 Hz, 2×CH_{Ar}). Anal. calcd for $C_{17}H_{24}BrO_5P$: C, 48.70; H, 5.77. Found: C, 48.79; H, 5.65.

4.2.3. *tert*-Butyl (*E*)-2-(diethoxyphosphoryl)-3-(4-methylphenyl)acrylate (2c). 3.11 g, 88% yield, pale yellow oil; R_f=0.5 (ethyl acetate/hexane 2:1); IR (film): 1716, 1368, 1256, 1024 cm^{-1}; ^{31}P NMR ($CDCl_3$): δ=15.37; ^{1}H NMR ($CDCl_3$): δ=1.36 (t, 6H, $^3J_{HH}$=7.1 Hz, 2×CH_3CH$_2$OP), 1.50 (s, 9H, C(CH_3)$_3$), 2.36 (s, 3H, CH_3Ph), 4.13–4.20 (m, 4H, 2×CH$_3$CH_2OP), 7.17 (d, 2H, $^3J_{HH}$=8.0 Hz, 2×CH_{Ar}), 7.39 (d, 2H, $^3J_{HH}$=8.0 Hz, 2×CH_{Ar}), 7.52 (d, 1H, $^3J_{HP}$=24.5 Hz, ArCH=C). Anal. calcd for $C_{18}H_{27}O_5P$: C, 61.01; H, 7.68. Found: C, 61.12; H, 7.79.

4.2.4. *tert*-Butyl (*E*)-2-(diethoxyphosphoryl)-3-(4-methoxyphenyl)acrylate (2d). 3.03g, 82% yield, pale yellow oil; R_f=0.5 (ethyl acetate/hexane 2:1); IR (film): 1716, 1604, 1512, 1368, 1260, 1152, 1028 cm^{-1}; ^{31}P NMR ($CDCl_3$): δ=16.30; ^{1}H NMR ($CDCl_3$): δ=1.36 (t, 6H, $^3J_{HH}$=7.0 Hz, 2×CH_3CH$_2$OP), 1.52 (s, 9H, C(CH_3)$_3$), 3.84 (s, 3H, CH_3OPh), 4.08–4.22 (m, 4H, 2×CH$_3$CH_2OP), 6.88 (d, 2H, $^3J_{HH}$=8.8 Hz, 2×CH_{Ar}), 7.47 (d, 2H, $^3J_{HH}$=8.8 Hz, 2×CH_{Ar}), 7.49 (d, 1H, $^3J_{HP}$=24.5 Hz, ArCH=C). Anal. calcd for $C_{18}H_{27}O_6P$: C, 58.37; H, 7.35. Found: C, 58.28; H, 7.27.

4.2.5. *tert*-Butyl (*E*)-2-(diethoxyphosphoryl)-3-(3,4-methylenedioxyphenyl)acrylate (2e). 3.49 g, 91% yield, pale yellow oil; R_f=0.5 (ethyl acetate/hexane 2:1); IR (film): 1716, 1368, 1256, 1028 cm^{-1}; ^{31}P NMR ($CDCl_3$): δ=15.56; ^{1}H NMR ($CDCl_3$): δ=1.37 (t, 6H, $^3J_{HH}$=7.0 Hz, 2×CH_3CH$_2$OP), 1.53 (s, 9H, C(CH_3)$_3$), 4.09–4.24 (m, 4H, 2×CH$_3$CH_2OP), 6.00 (s, 2H, CH_2O$_2$Ph), 6.80 (d, 1H, $^3J_{HH}$=8.5 Hz, CH_{Ar}), 7.01 (d, 1H, $^3J_{HH}$=8.5 Hz, CH_{Ar}), 7.04 (s, 1H, CH_{Ar}), 7.43 (d, 1H, $^3J_{HP}$=24.5 Hz, ArCH=C). Anal. calcd for $C_{18}H_{25}O_7P$: C, 56.25; H, 6.56. Found: C, 56.34; H, 6.64.

4.3. General procedure for the preparation of *tert*-butyl 3-aryl-2-(diethoxyphosphoryl)-4-nitroalkanoates 3a–e and 4a–e

To a solution of a corresponding *tert*-butyl acrylate **2** (5 mmol) in nitromethane (20 mL) or nitroethane (10 mL) was added potassium *tert*-butoxide (280 mg, 2.5 mmol). The reaction mixture was left at room temperature for an appropriate period of time. The reaction progress was occasionally monitored with ^{31}P NMR. After the acrylate **2** completely reacted the solvent was evaporated and residue was taken up in CH_2Cl_2 (25 mL), washed with H_2O (2×15 mL), and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure afforded a crude product, which was purified by crystallization from diethyl ether to give pure alkanoates **3** and **4**.

4.3.1. *tert*-Butyl 2-(diethoxyphosphoryl)-4-nitro-3-(4-nitrophenyl)butanoate (3a). Crude product: ^{31}P NMR ($CDCl_3$): δ=19.02, 19.32 (0.42:1); (2*R**,3*R**)-**3a**: (2.01 g, 90% yield), white crystals, mp 164–168 °C; IR (CCl_4): 1736, 1552, 1348, 1280, 1160, 1020 cm^{-1}; ^{31}P NMR ($CDCl_3$): δ=19.32; ^{1}H NMR ($CDCl_3$): δ=1.17 (s, 9H, C(CH_3)$_3$), 1.36 (t, 3H, $^3J_{HH}$=7.0 Hz, CH_3CH$_2$OP), 1.39 (t, 3H, $^3J_{HH}$=7.0 Hz, CH_3CH$_2$OP), 3.35 (dd, 1H, $^2J_{HP}$= 20.1 Hz, $^3J_{HH}$=11.8 Hz, PCHCOO*t*-Bu), 4.18–4.30 (m, 5H, 2×CH$_3$CH_2OP, CHAr), 4.75 (dd, 1H, $^2J_{HH}$=13.5 Hz, $^3J_{HH}$=10.6 Hz, ArCHCH_AH$_B$NO$_2$), 5.27 (dd, 1H, $^2J_{HH}$=13.5 Hz, $^3J_{HH}$=4.1 Hz, ArCHCH$_A$$H_BNO_2$), 7.44 (d, 2H, $^3J_{HH}$=8.8 Hz, 2×CH_{Ar}), 8.20 (d, 2H, $^3J_{HH}$=8.8 Hz, 2×CH_{Ar}); ^{13}C NMR ($CDCl_3$): δ=16.11 (d, $^3J_{CP}$=5.4 Hz, *C*H$_3$CH$_2$OP), 16.19 (d, $^3J_{CP}$=5.2 Hz, *C*H$_3$CH$_2$OP), 27.23 (C(*C*H$_3$)$_3$), 42.22 (d, $^2J_{CP}$=3.4 Hz, Ar*C*H), 49.24 (d, $^1J_{CP}$=128.5 Hz, P*C*HCOO*t*-Bu), 63.32 (d, $^2J_{CP}$=3.0 Hz, CH$_3$*C*H$_2$OP), 63.42 (d, $^2J_{CP}$=3.9 Hz, CH$_3$*C*H$_2$OP), 77.89 (*C*H$_2$NO$_2$), 82.77 (*C*(CH$_3$)$_3$), 123.61 (*C*H$_{Ar}$), 129.27 (*C*H$_{Ar}$), 144.55 (d, $^3J_{CP}$=15.7 Hz, *C*$_{Ar}$), 146.91 (*C*$_{Ar}$), 165.07 (d, $^3J_{CP}$=6.0 Hz, PCH*C*OO*t*-Bu). Anal. calcd for $C_{18}H_{27}N_2O_9P$: C, 48.43; H, 6.10; N, 6.28. Found: C, 48.53; H, 6.18; N, 6.20.

4.3.2. *tert*-Butyl 3-(4-bromophenyl)-2-(diethoxyphosphoryl)-4-nitrobutanoate (3b). Crude product: ^{31}P NMR ($CDCl_3$): δ=19.63, 19.99 (0.38:1); (2*R**,3*R**)-**3b**: (1.61 g, 67% yield), white crystals, mp 144–146 °C; IR (CCl_4): 1736, 1552, 1276, 1240, 1224, 1160, 1060, 992, 976 cm^{-1}; ^{31}P NMR ($CDCl_3$): δ=19.99; ^{1}H NMR ($CDCl_3$): δ=1.17 (s, 9H, C(CH_3)$_3$), 1.38 (t, 3H, $^3J_{HH}$=7.0 Hz, CH_3CH$_2$OP), 1.40 (t, 3H, $^3J_{HH}$=7.0 Hz, CH_3CH$_2$OP), 3.28 (dd, 1H, $^2J_{HP}$= 19.6 Hz, $^3J_{HH}$=11.9 Hz, PCHCOO*t*-Bu), 4.01–4.15 (m, 1H, CHAr), 4.18–4.29 (m, 4H, 2×CH$_3$CH_2OP), 4.66 (dd, 1H, $^2J_{HH}$=13.2 Hz, $^3J_{HH}$=10.7 Hz, ArCHCH_AH$_B$NO$_2$), 5.20 (dd, 1H, $^2J_{HH}$=13.2 Hz, $^3J_{HH}$=4.1 Hz, ArCHCH$_A$$H_BNO_2$), 7.13 (d, 2H, $^3J_{HH}$=8.5 Hz, 2×CH_{Ar}), 7.44 (d, 2H, $^3J_{HH}$=8.5 Hz, 2×CH_{Ar}); ^{13}C NMR ($CDCl_3$): δ=16.03

(d, $^3J_{CP}$=5.8 Hz, *C*H$_3$CH$_2$OP), 16.15 (d, $^3J_{CP}$=5.6 Hz, *C*H$_3$CH$_2$OP), 27.14 (C(*C*H$_3$)$_3$), 42.03 (d, $^2J_{CP}$=3.7 Hz, Ar*C*H), 49.49 (d, $^1J_{CP}$=128.1 Hz, P*C*HCOO*t*-Bu), 63.07 (d, $^2J_{CP}$=3.2 Hz, CH$_3$*C*H$_2$OP), 63.18 (d, $^2J_{CP}$=2.4 Hz, CH$_3$*C*H$_2$OP), 78.26 (*C*H$_2$NO$_2$), 82.30 (*C*(CH$_3$)$_3$), 121.91 (*C*$_{Ar}$), 129.76 (*C*H$_{Ar}$), 131.55 (*C*H$_{Ar}$), 135.95 (d, $^3J_{CP}$=15.9 Hz, *C*$_{Ar}$), 165.18 (d, $^3J_{CP}$=7.0 Hz, PCH*C*OO*t*-Bu). Anal. calcd for $C_{18}H_{27}BrNO_7P$: C, 45.01; H, 5.67; N, 2.92. Found: C, 45.11; H, 5.71; N, 2.80.

4.3.3. *tert*-Butyl 2-(diethoxyphosphoryl)-3-(4-methylphenyl)-4-nitrobutanoate (3c). Crude product: ^{31}P NMR (CDCl$_3$): δ=20.13, 20.61 (0.39:1); (2*R**,3*R**)-**3c**: (1.66 g, 80% yield), white crystals, mp 79–81 °C; IR (CCl$_4$): 1728, 1556, 1248, 1156, 1024 cm^{-1}; ^{31}P NMR (CDCl$_3$): δ=20.61; ^{1}H NMR (CDCl$_3$): δ=1.14 (s, 9H, C(C*H*$_3$)$_3$), 1.37 (t, 3H, $^3J_{HH}$=7.0 Hz, C*H*$_3$CH$_2$OP), 1.41 (t, 3H, $^3J_{HH}$=7.0 Hz, C*H*$_3$CH$_2$OP), 2.29 (s, 3H, C*H*$_3$Ph), 3.30 (dd, 1H, $^2J_{HP}$=19.3 Hz, $^3J_{HH}$=12.0 Hz, PC*H*COO*t*-Bu), 3.98–4.09 (m, 1H, C*H*Ar), 4.17–4.31 (m, 4H, 2×CH$_3$C*H*$_2$OP), 4.66 (dd, 1H, $^2J_{HH}$=12.8 Hz, $^3J_{HH}$=10.8 Hz, ArCHC*H*$_A$H$_B$NO$_2$), 5.18 (dd, 1H, $^2J_{HH}$=12.8 Hz, $^3J_{HH}$=4.0 Hz, ArCHCH$_A$*H*$_B$NO$_2$), 7.10 (s, 4H, 4×C*H*$_{Ar}$); ^{13}C NMR (CDCl$_3$): δ=15.98 (d, $^3J_{CP}$=6.0 Hz, *C*H$_3$CH$_2$OP), 16.08 (d, $^3J_{CP}$=5.9 Hz, *C*H$_3$CH$_2$OP), 20.67 (*C*H$_3$Ph), 27.02 (C(*C*H$_3$)$_3$), 42.20 (d, $^2J_{CP}$=3.8 Hz, Ar*C*H), 49.74 (d, $^1J_{CP}$=127.6 Hz, P*C*HCOO*t*-Bu), 62.88 (d, $^2J_{CP}$=3.4 Hz, CH$_3$*C*H$_2$OP), 62.93 (d, $^2J_{CP}$=3.7 Hz, CH$_3$*C*H$_2$OP), 78.70 (*C*H$_2$NO$_2$), 81.86 (*C*(CH$_3$)$_3$), 127.76 (*C*H$_{Ar}$), 128.96 (*C*H$_{Ar}$), 133.58 (d, $^3J_{CP}$=15.8 Hz, *C*$_{Ar}$), 137.51 (*C*$_{Ar}$), 165.28 (d, $^3J_{CP}$=5.4 Hz, PCH*C*OO*t*-Bu). Anal. calcd for $C_{19}H_{30}NO_7P$: C, 54.93; H, 7.28; N, 3.37. Found: C, 54.77; H, 7.37; N, 3.26.

4.3.4. *tert*-Butyl 2-(diethoxyphosphoryl)-3-(4-methoxyphenyl)-4-nitrobutanoate (3d). 1.21 g, 56% yield, white crystals, mp 93–95 °C; IR (CCl$_4$): 1728, 1556, 1252, 1148, 1024 cm^{-1}; ^{31}P NMR (CDCl$_3$): δ=20.13, 20.55 (0.35:1); ^{1}H NMR (CDCl$_3$): δ=1.16 (s, 9H, C(C*H*$_3$)$_3$, major), 1.28 (t, 3H, $^3J_{HH}$=7.0 Hz, C*H*$_3$CH$_2$OP, minor), 1.30 (t, 3H, $^3J_{HH}$=7.0 Hz, C*H*$_3$CH$_2$OP, minor), 1.38 (t, 3H, $^3J_{HH}$=7.2 Hz, C*H*$_3$CH$_2$OP, major), 1.41 (t, 3H, $^3J_{HH}$=7.2 Hz, C*H*$_3$CH$_2$OP, major), 1.46 (s, 9H, C(C*H*$_3$)$_3$, minor), 3.23 (dd, 1H, $^2J_{HP}$=23.2 Hz, $^3J_{HH}$=6.2 Hz, PC*H*COO*t*-Bu, minor), 3.28 (dd, 1H, $^2J_{HP}$=19.2 Hz, $^3J_{HH}$=12.0 Hz, PC*H*COO*t*-Bu, major), 3.76 (s, 3H, C*H*$_3$OPh, major), 3.78 (s, 3H, C*H*$_3$OPh, minor), 3.98–4.29 (m, 5H, 2×CH$_3$C*H*$_2$OP, C*H*Ar), 4.64 (dd, 1H, $^2J_{HH}$=13.0 Hz, $^3J_{HH}$=11.0 Hz, ArCHC*H*$_A$H$_B$NO$_2$, major), 5.07 (d, 2H, $^3J_{HH}$=7.5 Hz, ArCHC*H*$_2$NO$_2$, minor), 5.18 (dd, 1H, $^2J_{HH}$=13.0 Hz, $^3J_{HH}$=4.0 Hz, ArCHCH$_A$*H*$_B$NO$_2$, major), 6.79–6.86 (m, 2H, 2×C*H*$_{Ar}$), 7.12–7.20 (m, 2H, 2×C*H*$_{Ar}$); ^{13}C NMR (CDCl$_3$): δ=15.98 (d, $^3J_{CP}$=5.4 Hz, *C*H$_3$CH$_2$OP), 16.06 (d, $^3J_{CP}$=5.6 Hz, *C*H$_3$CH$_2$OP), 27.06 (C(*C*H$_3$)$_3$, major), 27.46 (C(*C*H$_3$)$_3$, minor), 41.11 (d, $^2J_{CP}$=2.6 Hz, Ar*C*H, minor), 41.89 (d, $^2J_{CP}$=3.5 Hz, Ar*C*H, major), 49.84 (d, $^1J_{CP}$=127.4 Hz, P*C*HCOO*t*-Bu, major), 50.58 (d, $^1J_{CP}$=129.4 Hz, P*C*HCOO*t*-Bu, minor), 54.85 (*C*H$_3$OPh), 62.44 (d, $^2J_{CP}$=7.3 Hz, CH$_3$*C*H$_2$OP, minor), 62.69 (d, $^2J_{CP}$=6.9 Hz, CH$_3$*C*H$_2$OP, minor), 62.91 (d, $^2J_{CP}$=6.0 Hz, CH$_3$*C*H$_2$OP, major), 77.27 (d, $^3J_{CP}$=8.4 Hz, *C*H$_2$NO$_2$, minor), 78.75 (*C*H$_2$NO$_2$, major), 81.84 (*C*(CH$_3$)$_3$, major), 82.61 (*C*(CH$_3$)$_3$, minor), 113.69 (*C*H$_{Ar}$, major), 113.84 (*C*H$_{Ar}$, minor), 128.64 (d, $^3J_{CP}$=16.0 Hz, *C*$_{Ar}$, major), 128.68 (*C*H$_{Ar}$, minor), 129.02 (*C*H$_{Ar}$, major), 129.11 (d, $^3J_{CP}$=11.8 Hz, *C*$_{Ar}$, minor), 159.07 (*C*$_{Ar}$), 165.30 (d, $^3J_{CP}$=5.2 Hz, PCH*C*OO*t*-Bu, major), 166.33 (d, $^3J_{CP}$=4.1 Hz, PCH*C*OO*t*-Bu, minor). Anal. calcd for $C_{19}H_{30}NO_8P$: C, 52.90; H, 7.01; N, 3.25. Found: C, 52.99; H, 7.12; N, 3.36.

4.3.5. *tert*-Butyl 2-(diethoxyphosphoryl)-3-(3,4-methylenedioxyphenyl)-4-nitrobutanoate (3e). 1.62 g, 73% yield, white crystals, mp 83–86 °C; IR (CCl$_4$): 1732, 1556, 1248, 1148, 1044 cm^{-1}; ^{31}P NMR (CDCl$_3$): δ=19.97, 20.35 (0.35:1); ^{1}H NMR (CDCl$_3$): δ=1.21 (s, 9H, C(C*H*$_3$)$_3$, major), 1.30 (t, 3H, $^3J_{HH}$=7.0 Hz, C*H*$_3$CH$_2$OP, minor), 1.32 (t, 3H, $^3J_{HH}$=7.0 Hz, C*H*$_3$CH$_2$OP, minor), 1.38 (t, 3H, $^3J_{HH}$=7.2 Hz, C*H*$_3$CH$_2$OP, major), 1.41 (t, 3H, $^3J_{HH}$=7.2 Hz, C*H*$_3$CH$_2$OP, major), 1.46 (s, 9H, C(C*H*$_3$)$_3$, minor), 3.20 (dd, 1H, $^2J_{HP}$=23.2 Hz, $^3J_{HH}$=6.0 Hz, PC*H*COO*t*-Bu, minor), 3.24 (dd, 1H, $^2J_{HP}$=19.5 Hz, $^3J_{HH}$=12.0 Hz, PC*H*COO*t*-Bu, major), 3.95–4.30 (m, 5H, 2×CH$_3$C*H*$_2$OP, C*H*Ar), 4.63 (dd, 1H, $^2J_{HH}$=13.0 Hz, $^3J_{HH}$=10.8 Hz, ArCHC*H*$_A$H$_B$NO$_2$, major), 5.06 (d, 1H, $^3J_{HH}$=4.2 Hz, ArCHC*H*$_2$NO$_2$, minor), 5.09 (s, 1H, ArCHC*H*$_2$NO$_2$, minor), 5.17 (dd, 1H, $^2J_{HH}$=13.0 Hz, $^3J_{HH}$=4.0 Hz, ArCHCH$_A$*H*$_B$NO$_2$, major), 5.93 (s, 2H, C*H*$_2$O$_2$Ph, major), 5.94 (s, 2H, C*H*$_2$O$_2$Ph, minor), 6.70–6.74 (m, 3H, 3×C*H*$_{Ar}$); ^{13}C NMR (CDCl$_3$): δ=16.00 (d, $^3J_{CP}$=5.6 Hz, *C*H$_3$CH$_2$OP), 16.08 (d, $^3J_{CP}$=5.7 Hz, *C*H$_3$CH$_2$OP), 27.15 (C(*C*H$_3$)$_3$, major), 27.49 (C(*C*H$_3$)$_3$, minor), 41.55 (d, $^2J_{CP}$=3.5 Hz, Ar*C*H, minor), 42.36 (d, $^2J_{CP}$=3.3 Hz, Ar*C*H, major), 49.87 (d, $^1J_{CP}$=127.4 Hz, P*C*HCOO*t*-Bu, major), 50.58 (d, $^1J_{CP}$=129.1 Hz, P*C*HCOO*t*-Bu, minor), 62.53 (d, $^2J_{CP}$=7.0 Hz, CH$_3$*C*H$_2$OP, minor), 62.79 (d, $^2J_{CP}$=5.4 Hz, CH$_3$*C*H$_2$OP, minor), 62.92 (d, $^2J_{CP}$=3.6 Hz, CH$_3$*C*H$_2$OP, major), 63.02 (d, $^2J_{CP}$=2.3 Hz, CH$_3$*C*H$_2$OP, major), 77.16 (d, $^3J_{CP}$=8.1 Hz, *C*H$_2$NO$_2$, minor), 78.67 (*C*H$_2$NO$_2$, major), 81.97 (*C*(CH$_3$)$_3$, major), 82.76 (*C*(CH$_3$)$_3$, minor), 100.91 (CH$_2$O$_2$Ph), 107.78 (*C*H$_{Ar}$, minor), 107.99 (*C*H$_{Ar}$, major), 108.09 (*C*H$_{Ar}$), 121.05 (*C*H$_{Ar}$, minor), 121.57 (*C*H$_{Ar}$, major), 130.27 (d, $^3J_{CP}$=16.1 Hz, *C*$_{Ar}$, major), 130.98 (d, $^3J_{CP}$=11.8 Hz, *C*$_{Ar}$, minor), 147.09 (*C*$_{Ar}$), 147.51 (*C*$_{Ar}$, major), 147.68 (*C*$_{Ar}$, minor), 165.22 (d, $^2J_{CP}$=5.6 Hz, PCH*C*OO*t*-Bu, major), 166.28 (d, $^2J_{CP}$=3.8 Hz, PCH*C*OO*t*-Bu, minor). Anal. calcd for $C_{19}H_{28}NO_9P$: C, 51.24; H, 6.34; N, 3.14. Found: C, 51.33; H, 6.22; N, 3.21.

4.3.6. *tert*-Butyl 2-(diethoxyphosphoryl)-4-nitro-3-(4-nitrophenyl)pentanoate (4a). Crude product: ^{31}P NMR (CDCl$_3$): δ=19.30, 19.34, 19.96, 20.43 (1:0.31:0.28:0.62); (2*R**,3*R**,4*R**)-**4a**: (1.61 g, 70% yield), white crystals, mp 216–218 °C; IR (CCl$_4$): 1724, 1544, 1348, 1248, 1156, 1020 cm^{-1}; ^{31}P NMR (CDCl$_3$): δ=19.30; ^{1}H NMR (CDCl$_3$): δ=1.17 (s, 9H, C(C*H*$_3$)$_3$), 1.38–1.44 (m, 6H, 2×C*H*$_3$CH$_2$OP), 1.42 (d, 3H, $^3J_{HH}$=6.8 Hz, C*H*$_3$CHNO$_2$), 3.37 (dd, 1H, $^2J_{HP}$=21.0 Hz, $^3J_{HH}$=11.8 Hz, PC*H*COO*t*-Bu), 4.17–4.30 (m, 4H, 2×CH$_3$C*H*$_2$OP), 4.41 (ddd, 1H, $^3J_{HH}$=11.8, $^3J_{HP}$=8.6 Hz, $^3J_{HH}$=4.7 Hz, Ar–C*H*), 5.42 (dq, 1H, $^3J_{HH}$=6.8 Hz, $^3J_{HH}$=4.7 Hz, CH$_3$C*H*NO$_2$), 7.36 (d, 2H, $^3J_{HH}$=8.8 Hz, 2×C*H*$_{Ar}$), 8.18 (d, 2H, $^3J_{HH}$=8.8 Hz, 2×C*H*$_{Ar}$); ^{13}C NMR (CDCl$_3$): δ=12.60 (*C*H$_3$CHNO$_2$), 16.19 (2×*C*H$_3$CH$_2$OP), 27.22 (C(*C*H$_3$)$_3$), 47.06 (Ar*C*H), 48.34 (d, $^1J_{CP}$=129.5 Hz, P*C*HCOO*t*-Bu), 63.32 (d, $^2J_{CP}$=5.7 Hz, CH$_3$*C*H$_2$OP), 63.40 (d, $^2J_{CP}$=5.0 Hz, CH$_3$*C*H$_2$OP), 82.82 (d, $^3J_{CP}$=7.0 Hz, CH$_3$*C*HNO$_2$), 83.01

($C(CH_3)_3$), 123.21 (CH_{Ar}), 130.26 (CH_{Ar}), 141.98 (d, $^3J_{CP}$=14.5 Hz, C_{Ar}), 147.58 (C_{Ar}), 165.21 (PCH*C*OO*t*-Bu). Anal. calcd for $C_{19}H_{29}N_2O_9P$: C, 49.56; H, 6.35; N, 6.08. Found: C, 49.67; H, 6.47; N, 6.00.

4.3.7. *tert*-Butyl 3-(4-bromophenyl)-2-(diethoxyphosphoryl)-4-nitropentanoate (4b). Crude product: ^{31}P NMR ($CDCl_3$): δ=19.97, 20.77, 21.23 (1:0.15:0.39); (2*R**,3*R**,4*R**)-**4b**: (1.63 g, 66% yield), white crystals, mp 172–174 °C; IR (CCl_4): 1724, 1548, 1392, 1288, 1248, 1156, 1024 cm^{-1}; ^{31}P NMR ($CDCl_3$): δ=19.97; ^{1}H NMR ($CDCl_3$): δ=1.16 (s, 9H, C(CH_3)$_3$), 1.34–1.44 (m, 6H, 2×CH_3CH$_2$OP), 1.40 (d, 3H, $^3J_{HH}$=6.5 Hz, CH_3CHNO$_2$), 3.33 (dd, 1H, $^2J_{HP}$=20.5 Hz, $^3J_{HH}$=12.0 Hz, PC*H*COO*t*-Bu), 4.17–4.32 (m, 5H, 2×CH$_3$CH_2OP, Ar–C*H*), 5.34 (dq, 1H, $^3J_{HH}$=6.5 Hz, $^3J_{HH}$=4.5 Hz, CH$_3$C*H*NO$_2$), 7.02 (d, 2H, $^3J_{HH}$=8.5 Hz, 2×CH_{Ar}), 7.43 (d, 2H, $^3J_{HH}$=8.5 Hz, 2×CH_{Ar}); ^{13}C NMR ($CDCl_3$): δ=12.29 (*C*H$_3$CHNO$_2$), 16.09 (d, $^3J_{CP}$=3.4 Hz, *C*H$_3$CH$_2$OP), 16.19 (d, $^3J_{CP}$=3.3 Hz, *C*H$_3$CH$_2$OP), 27.14 (C(*C*H$_3$)$_3$), 46.79 (d, $^2J_{CP}$=3.0 Hz, Ar*C*H), 48.52 (d, $^1J_{CP}$=129.1 Hz, P*C*HCOO*t*-Bu), 63.04 (d, $^2J_{CP}$=7.3 Hz, CH$_3$*C*H$_2$OP), 63.20 (d, $^2J_{CP}$=6.4 Hz, CH$_3$*C*H$_2$OP), 82.36 (*C*(CH$_3$)$_3$), 83.10 (CH$_3$*C*HNO$_2$), 122.18 (C_{Ar}), 130.77 (CH_{Ar}), 131.25 (CH_{Ar}), 133.31 (d, $^3J_{CP}$=16.0 Hz, C_{Ar}), 165.32 (d, $^2J_{CP}$=6.3 Hz, PCH*C*OO*t*-Bu). Anal. calcd for $C_{19}H_{29}BrNO_7P$: C, 46.17; H, 5.19; N, 2.83. Found: C, 46.28; H, 5.27; N, 2.95.

4.3.8. *tert*-Butyl 2-(diethoxyphosphoryl)-3-(4-methylphenyl)-4-nitropentanoate (4c). Crude product: ^{31}P NMR ($CDCl_3$): δ=20.45, 20.63, 21.27, 21.91, (0.19:1:0.16:0.45); (2*R**,3*R**,4*R**)-**4c**: (1.05 g, 49% yield), white crystals, mp 133–135 °C; IR (CCl_4): 1732, 1552, 1392, 1368, 1252, 1160, 1028 cm^{-1}; ^{31}P NMR ($CDCl_3$): δ=20.63; ^{1}H NMR ($CDCl_3$): δ=1.12 (s, 9H, C(CH_3)$_3$), 1.35–1.44 (m, 6H, 2×CH_3CH$_2$OP), 1.41 (d, 3H, $^3J_{HH}$=6.5 Hz, CH_3CHNO$_2$), 2.29 (s, 3H, CH_3Ph), 3.36 (dd, 1H, $^2J_{HP}$=19.9 Hz, $^3J_{HH}$= 12.2 Hz, PC*H*COO*t*-Bu), 4.19–4.30 (m, 5H, 2×CH$_3$CH_2OP, Ar–C*H*), 5.32 (dq, 1H, $^3J_{HH}$=6.5 Hz, $^3J_{HH}$=4.4 Hz, CH$_3$C*H*NO$_2$), 6.98 (d, 2H, $^3J_{HH}$=8.0 Hz, 2×CH_{Ar}), 7.08 (d, 2H, $^3J_{HH}$=8.0 Hz, 2×CH_{Ar}); ^{13}C NMR ($CDCl_3$): δ= 12.11 (*C*H$_3$CHNO$_2$), 16.09 (d, $^3J_{CP}$=5.5 Hz, *C*H$_3$CH$_2$OP), 16.18 (d, $^3J_{CP}$=5.2 Hz, *C*H$_3$CH$_2$OP), 20.80 (*C*H$_3$Ph), 27.06 (C(*C*H$_3$)$_3$), 47.00 (d, $^2J_{CP}$=3.2 Hz, Ar*C*H), 48.80 (d, $^1J_{CP}$=128.7 Hz, P*C*HCOO*t*-Bu), 62.94 (d, $^2J_{CP}$=7.6 Hz, CH$_3$*C*H$_2$OP), 63.06 (d, $^2J_{CP}$=7.6 Hz, CH$_3$*C*H$_2$OP), 81.96 (*C*(CH$_3$)$_3$), 83.41 (CH$_3$*C*HNO$_2$), 128.73 (CH_{Ar}), 128.90 (CH_{Ar}), 130.95 (d, $^3J_{CP}$=15.7 Hz, C_{Ar}), 137.70 (C_{Ar}), 165.51 (d, $^2J_{CP}$=6.2 Hz, PCH*C*OO*t*-Bu). Anal. calcd for $C_{20}H_{32}NO_7P$: C, 55.94; H, 7.51; N, 3.26. Found: C, 55.77; H, 7.64; N, 3.11.

4.3.9. *tert*-Butyl 2-(diethoxyphosphoryl)-3-(4-methoxyphenyl)-4-nitropentanoate (4d). Crude product: ^{31}P NMR ($CDCl_3$): δ=20.58, 21.00, 21.54 (1:0.14:0.41); (2*R**,3*R**,4*R**)-**4d**: (1.29 g, 58% yield), white crystals, mp 138–140 °C; IR (CCl_4): 1728, 1512, 1392, 1368, 1252, 1160, 1024 cm^{-1}; ^{31}P NMR ($CDCl_3$): δ=20.58; ^{1}H NMR ($CDCl_3$): δ=1.14 (s, 9H, C(CH_3)$_3$), 1.33–1.44 (m, 9H, 2×CH_3CH$_2$OP, CH_3CHNO$_2$), 3.34 (dd, 1H, $^2J_{HP}$=20.0 Hz, $^3J_{HH}$=12.2 Hz, PC*H*COO*t*-Bu), 3.77 (s, 3H, CH_3OPh), 4.18–4.31 (m, 5H, 2×CH$_3$CH_2OP, Ar–C*H*), 5.30 (dq, 1H, $^3J_{HH}$=6.5 Hz, $^3J_{HH}$=4.2 Hz, CH$_3$C*H*NO$_2$), 6.81 (d, 2H, $^3J_{HH}$=8.8 Hz, 2×CH_{Ar}), 7.03 (d, 2H, $^3J_{HH}$=8.8 Hz, 2×CH_{Ar}); ^{13}C NMR ($CDCl_3$): δ=12.11 (*C*H$_3$CHNO$_2$), 16.09 (d, $^3J_{CP}$=4.8 Hz, *C*H$_3$CH$_2$OP), 16.17 (d, $^3J_{CP}$= 5.7 Hz, *C*H$_3$CH$_2$OP), 27.13 (C(*C*H$_3$)$_3$), 46.68 (d, $^2J_{CP}$= 3.3 Hz, Ar*C*H), 48.89 (d, $^1J_{CP}$=128.7 Hz, P*C*HCOO*t*-Bu), 54.98 (*C*H$_3$OPh), 62.94 (d, $^2J_{CP}$=7.8 Hz, CH$_3$*C*H$_2$OP), 63.06 (d, $^2J_{CP}$=7.4 Hz, CH$_3$*C*H$_2$OP), 82.00 (*C*(CH$_3$)$_3$), 83.48 (CH$_3$*C*HNO$_2$), 113.45 (CH_{Ar}), 125.95 (d, $^3J_{CP}$= 16.4 Hz, C_{Ar}), 130.14 (CH_{Ar}), 159.26 (C_{Ar}), 165.54 (d, $^2J_{CP}$=6.0 Hz, PCH*C*OO*t*-Bu). Anal. calcd for $C_{20}H_{32}NO_8P$: C, 53.93; H, 7.24; N, 3.14. Found: C, 53.77; H, 7.35; N, 3.01.

4.3.10. *tert*-Butyl 2-(diethoxyphosphoryl)-3-(3,4-methylenedioxyphenyl)-4-nitropentanoate (4e). Crude product: ^{31}P NMR ($CDCl_3$): δ=20.34, 21.04, 21.53 (1:0.14:0.39); (2*R**,3*R**,4*R**)-**4e**: (1.17 g, 51% yield), white crystals, mp 101–107 °C; IR (CCl_4): 1728, 1552, 1488, 1444, 1392, 1368, 1256, 1160, 1032 cm^{-1}; ^{31}P NMR ($CDCl_3$): δ=20.34; ^{1}H NMR ($CDCl_3$): δ=1.19 (s, 9H, C(CH_3)$_3$), 1.35–1.46 (m, 9H, 2×CH_3CH$_2$OP, CH_3CHNO$_2$), 3.29 (dd, 1H, $^2J_{HP}$=20.0 Hz, $^3J_{HH}$=12.2 Hz, PC*H*COO*t*-Bu), 4.18–4.31 (m, 5H, 2×CH$_3$CH_2OP, Ar–C*H*), 5.29 (dq, 1H, $^3J_{HH}$=6.5 Hz, $^3J_{HH}$=4.5 Hz, CH$_3$C*H*NO$_2$), 5.92–5.94 (m, 2H, CH_2O$_2$Ph), 6.57 (dd, 1H, $^3J_{HH}$=8.0 Hz, $^4J_{HH}$=1.8 Hz, CH_{Ar}), 6.62 (d, 1H, $^4J_{HH}$=1.8 Hz, CH_{Ar}), 6.72 (d, 1H, $^3J_{HH}$=8.0 Hz, CH_{Ar}); ^{13}C NMR ($CDCl_3$): δ=12.19 (*C*H$_3$CHNO$_2$), 16.11 (d, $^3J_{CP}$=5.9 Hz, *C*H$_3$CH$_2$OP), 16.19 (d, $^3J_{CP}$=4.2 Hz, *C*H$_3$CH$_2$OP), 27.21 (C(*C*H$_3$)$_3$), 47.09 (Ar*C*H), 48.89 (d, $^1J_{CP}$=128.7 Hz, P*C*HCOO*t*-Bu), 62.99 (d, $^2J_{CP}$=7.9 Hz, CH$_3$*C*H$_2$OP), 63.12 (d, $^2J_{CP}$=7.0 Hz, CH$_3$*C*H$_2$OP), 82.09 (*C*(CH$_3$)$_3$), 83.43 (CH$_3$*C*HNO$_2$), 100.98 (*C*H$_2$O$_2$Ph), 107.84 (CH_{Ar}), 109.29 (CH_{Ar}), 122.68 (CH_{Ar}), 127.63 (d, $^3J_{CP}$=16.4 Hz, C_{Ar}), 147.27 (C_{Ar}), 147.39 (C_{Ar}), 165.45 (d, $^2J_{CP}$=6.3 Hz, PCH*C*OO*t*-Bu). Anal. calcd for $C_{20}H_{30}NO_9P$: C, 52.29; H, 6.58; N, 3.05. Found: C, 52.20; H, 6.69; N, 3.17.

4.4. General procedure for the preparation of 3-aryl-2-(diethoxyphosphoryl)-4-nitroalkanoic acids 5a–e and 6a–e

To a solution of a corresponding *tert*-butyl alkanoate **3** or **4** (2.5 mmol) in CH_2Cl_2 (5 mL) was added trifluoroacetic acid (5 mL). The reaction mixture was left at room temperature for 24 h. The solvent was evaporated and residue was taken up in Et_2O (15 mL) and left to crystallize. Filtration of the crystals afforded pure alkanoic acids **5** and **6**.

4.4.1. (2*R,3*R**)-2-(Diethoxyphosphoryl)-4-nitro-3-(4-nitrophenyl)butanoic acid (5a).** 878 mg, 90% yield, white crystals, mp 149–151 °C; IR (CCl_4): 1728, 1552, 1352, 1224, 1152, 1020 cm^{-1}; ^{31}P NMR (acetone-*d*): δ=19.35; ^{1}H NMR (acetone-*d*): δ=1.21 (t, 3H, $^3J_{HH}$=7.0 Hz, CH_3CH$_2$OP), 1.22 (t, 3H, $^3J_{HH}$=7.0 Hz, CH_3CH$_2$OP), 3.64 (dd, 1H, $^2J_{HP}$=20.8 Hz, $^3J_{HH}$=11.5 Hz, PC*H*COOH), 4.04–4.25 (m, 5H, 2×CH$_3$CH_2OP, C*H*Ar), 4.93 (dd, 1H, $^2J_{HH}$=13.5 Hz, $^3J_{HH}$=11.0 Hz, ArCHCH_AH$_B$NO$_2$), 5.30 (dd, 1H, $^2J_{HH}$=13.5 Hz, $^3J_{HH}$=4.1 Hz, ArCHCH$_A$$H_BNO_2$), 7.63 (d, 2H, $^3J_{HH}$=8.8 Hz, 2×CH_{Ar}), 8.07 (d, 2H, $^3J_{HH}$=8.8 Hz, 2×CH_{Ar}); ^{13}C NMR (acetone-*d*): δ=16.50 (d, $^3J_{CP}$=5.7 Hz, *C*H$_3$CH$_2$OP), 16.57 (d, $^3J_{CP}$=3.5 Hz, *C*H$_3$CH$_2$OP), 43.50 (d, $^2J_{CP}$=3.6 Hz, Ar*C*H), 49.03 (d,

$^{1}J_{CP}$=126.8 Hz, P*C*HCOOH), 64.07 (d, $^{2}J_{CP}$=6.4 Hz, CH_3CH_2OP), 64.17 (d, $^{2}J_{CP}$=6.8 Hz, CH_3CH_2OP), 78.87 (CH_2NO_2), 124.28 (CH_{Ar}), 130.80 (CH_{Ar}), 146.57 (d, $^{3}J_{CP}$=15.5 Hz, C_{Ar}), 148.52 (C_{Ar}), 168.21 (d, $^{2}J_{CP}$=5.7 Hz, PCH*C*OOH). Anal. calcd for $C_{14}H_{19}N_2O_9P$: C, 43.08; H, 4.91; N, 7.18. Found: C, 43.20; H, 4.79; N, 7.11.

4.4.2. (2*R,3*R**)-3-(4-Bromophenyl)-2-(diethoxyphosphoryl)-4-nitrobutanoic acid (5b).** 848 mg, 80% yield, white crystals, mp 128–130 °C; IR (CCl_4): 1732, 1556, 1220, 1172, 1012, 984 cm^{-1}; ^{31}P NMR (acetone-*d*): δ=19.80; ^{1}H NMR (acetone-*d*): δ=1.34 (dt, 3H, $^{3}J_{HH}$=7.1 Hz, $^{4}J_{HP}$=0.5 Hz, CH_3CH$_2$OP), 1.35 (dt, 3H, $^{3}J_{HH}$=7.1 Hz, $^{4}J_{HP}$=0.5 Hz, CH_3CH$_2$OP), 3.66 (dd, 1H, $^{2}J_{HP}$=20.2 Hz, $^{3}J_{HH}$=11.7 Hz, PC*H*COOH), 4.04–4.28 (m, 5H, 2×CH$_3$CH_2OP, C*H*Ar), 4.94 (dd, 1H, $^{2}J_{HH}$=13.2 Hz, $^{3}J_{HH}$=11.1 Hz, ArCHCH_AH$_B$NO$_2$), 5.35 (dd, 1H, $^{2}J_{HH}$=13.2 Hz, $^{3}J_{HH}$=4.2 Hz, ArCHCH$_A$$H_BNO_2$), 7.39 (d, 2H, $^{3}J_{HH}$=8.5 Hz, 2×CH_{Ar}), 7.50 (d, 2H, $^{3}J_{HH}$=8.5 Hz, 2×CH_{Ar}); ^{13}C NMR (acetone-*d*): δ=16.55 (d, $^{3}J_{CP}$=3.5 Hz, *C*H$_3$CH$_2$OP), 16.64 (d, $^{3}J_{CP}$=3.3 Hz, *C*H$_3$CH$_2$OP), 43.43 (d, $^{2}J_{CP}$=3.9 Hz, Ar*C*H), 49.32 (d, $^{1}J_{CP}$=126.3 Hz, P*C*HCOOH), 63.94 (d, $^{2}J_{CP}$=6.0 Hz, CH$_3$*C*H$_2$OP), 64.04 (d, $^{2}J_{CP}$=6.5 Hz, CH$_3$*C*H$_2$OP), 79.31 (*C*H$_2$NO$_2$), 121.30 (C_{Ar}), 131.51 (*C*H$_{Ar}$), 132.39 (*C*H$_{Ar}$), 138.34 (d, $^{3}J_{CP}$=15.7 Hz, C_{Ar}), 168.32 (d, $^{2}J_{CP}$=5.6 Hz, PCH*C*OOH). Anal. calcd for $C_{14}H_{19}BrNO_7P$: C, 39.64; H, 4.51; N, 3.30. Found: C, 39.51; H, 4.39; N, 3.40.

4.4.3. (2*R,3*R**)-2-(Diethoxyphosphoryl)-3-(4-methylphenyl)-4-nitrobutanoic acid (5c).** 799 mg, 89% yield, white crystals, mp 112–115 °C; IR (CCl_4): 1736, 1552, 1220, 1040, 1016 cm^{-1}; ^{31}P NMR (acetone-*d*): δ=20.16; ^{1}H NMR (acetone-*d*): δ=1.34 (t, 3H, $^{3}J_{HH}$=7.1 Hz, CH_3CH$_2$OP), 1.35 (t, 3H, $^{3}J_{HH}$=7.1 Hz, CH_3CH$_2$OP), 2.26 (s, 3H, CH_3Ph), 3.60 (dd, 1H, $^{2}J_{HP}$=19.8 Hz, $^{3}J_{HH}$=11.8 Hz, PC*H*COOH), 4.03–4.26 (m, 5H, 2×CH$_3$CH_2OP, C*H*Ar), 4.89 (dd, 1H, $^{2}J_{HH}$=13.0 Hz, $^{3}J_{HH}$=11.2 Hz, ArCHCH_AH$_B$NO$_2$), 5.32 (dd, 1H, $^{2}J_{HH}$=13.0 Hz, $^{3}J_{HH}$=4.2 Hz, ArCHCH$_A$$H_BNO_2$), 7.10 (d, 2H, $^{3}J_{HH}$=7.5 Hz, 2×CH_{Ar}), 7.28 (d, 2H, $^{3}J_{HH}$=7.5 Hz, 2×CH_{Ar}); ^{13}C NMR (acetone-*d*): δ=16.41 (d, $^{3}J_{CP}$=4.1 Hz, *C*H$_3$CH$_2$OP), 16.50 (d, $^{3}J_{CP}$=4.1 Hz, *C*H$_3$CH$_2$OP), 20.96 (CH_3Ph), 43.34 (d, $^{2}J_{CP}$=4.2 Hz, Ar*C*H), 49.45 (d, $^{1}J_{CP}$=126.9 Hz, P*C*HCOOH), 64.09 (CH$_3$*C*H$_2$OP), 64.19 (d, $^{2}J_{CP}$=1.7 Hz, CH$_3$*C*H$_2$OP), 79.53 (*C*H$_2$NO$_2$), 128.99 (*C*H$_{Ar}$), 129.85 (*C*H$_{Ar}$), 135.44 (d, $^{3}J_{CP}$=16.0 Hz, C_{Ar}), 138.20 (C_{Ar}), 168.32 (d, $^{2}J_{CP}$=5.5 Hz, PCH*C*OOH). Anal. calcd for $C_{15}H_{22}NO_7P$: C, 50.14; H, 6.17; N, 3.90. Found: C, 50.25; H, 6.29; N, 3.77.

4.4.4. (2*R,3*R**)-2-(Diethoxyphosphoryl)-3-(4-methoxyphenyl)-4-nitrobutanoic acid (5d).** 722 mg, 77% yield, white crystals, mp 108–110 °C; IR (CCl_4): 1716, 1552, 1256, 1172, 1028 cm^{-1}; ^{31}P NMR (acetone-*d*): δ=20.17; ^{1}H NMR (acetone-*d*): δ=1.34 (t, 3H, $^{3}J_{HH}$=7.0 Hz, CH_3CH$_2$OP), 1.35 (t, 3H, $^{3}J_{HH}$=7.2 Hz, CH_3CH$_2$OP), 3.58 (dd, 1H, $^{2}J_{HP}$=19.8 Hz, $^{3}J_{HH}$=11.8 Hz, PC*H*COOH), 3.76 (s, 3H, CH_3OPh), 4.01–4.28 (m, 5H, 2×CH$_3$CH_2OP, C*H*Ar), 4.88 (dd, 1H, $^{2}J_{HH}$=12.8 Hz, $^{3}J_{HH}$=11.2 Hz, ArCHCH_AH$_B$NO$_2$), 5.30 (dd, 1H, $^{2}J_{HH}$=12.8 Hz, $^{3}J_{HH}$=4.5 Hz, ArCHCH$_A$$H_BNO_2$), 6.84 (d, 2H, $^{3}J_{HH}$=8.5 Hz, 2×CH_{Ar}), 7.32 (d, 2H, $^{3}J_{HH}$=8.5 Hz, 2×CH_{Ar}); ^{13}C NMR (acetone-*d*): δ=16.48 (d, $^{3}J_{CP}$=5.5 Hz, *C*H$_3$CH$_2$OP), 16.56 (d, $^{3}J_{CP}$=4.3 Hz, *C*H$_3$CH$_2$OP), 43.16 (d, $^{2}J_{CP}$=4.1 Hz, Ar*C*H), 49.64 (d, $^{1}J_{CP}$=126.0 Hz, P*C*HCOOH), 55.39 (CH_3OPh), 64.02 (d, $^{2}J_{CP}$=6.5 Hz, 2×CH$_3$*C*H$_2$OP), 79.67 (*C*H$_2$NO$_2$), 114.58 (*C*H$_{Ar}$), 130.24 (d, $^{3}J_{CP}$=12.8 Hz, C_{Ar}), 130.34 (*C*H$_{Ar}$), 160.16 (C_{Ar}), 168.39 (d, $^{2}J_{CP}$=5.4 Hz, PCH*C*OOH). Anal. calcd for $C_{15}H_{22}NO_8P$: C, 48.00; H, 5.91; N, 3.73. Found: C, 48.11; H, 5.83; N, 3.82.

4.4.5. (2*R,3*R**)-2-(Diethoxyphosphoryl)-3-(3,4-methylenedioxyphenyl)-4-nitrobutanoic acid (5e).** 914 mg, 94% yield, white crystals, mp 138–140 °C; IR (CCl_4): 1716, 1552, 1228, 1168, 1016 cm^{-1}; ^{31}P NMR (acetone-*d*): δ=20.03; ^{1}H NMR (acetone-*d*): δ=1.34 (t, 3H, $^{3}J_{HH}$=7.1 Hz, CH_3CH$_2$OP), 1.35 (t, 3H, $^{3}J_{HH}$=7.1 Hz, CH_3CH$_2$OP), 3.58 (dd, 1H, $^{2}J_{HP}$=19.8 Hz, $^{3}J_{HH}$=11.7 Hz, PC*H*COOH), 4.00–4.28 (m, 5H, 2×CH$_3$CH_2OP, C*H*Ar), 4.88 (dd, 1H, $^{2}J_{HH}$=12.8 Hz, $^{3}J_{HH}$=11.7 Hz, ArCHCH_AH$_B$NO$_2$), 5.30 (dd, 1H, $^{2}J_{HH}$=12.8 Hz, $^{3}J_{HH}$=4.3 Hz, ArCHCH$_A$$H_BNO_2$), 5.97 (s, 2H, C$H_2O_2$Ph), 6.75 (d, 1H, $^{3}J_{HH}$=8.0 Hz, CH_{Ar}), 6.85 (dd, 1H, $^{3}J_{HH}$=8.0 Hz, $^{4}J_{HH}$=1.6 Hz, CH_{Ar}), 6.99 (d, 1H, $^{4}J_{HH}$=1.6 Hz, CH_{Ar}); ^{13}C NMR (acetone-*d*): δ=16.47 (d, $^{3}J_{CP}$=4.0 Hz, *C*H$_3$CH$_2$OP), 16.55 (d, $^{3}J_{CP}$=5.5 Hz, *C*H$_3$CH$_2$OP), 43.70 (d, $^{2}J_{CP}$=3.9 Hz, Ar*C*H), 49.63 (d, $^{1}J_{CP}$=126.0 Hz, P*C*HCOOH), 64.05 (d, $^{2}J_{CP}$=6.6 Hz, 2×CH$_3$*C*H$_2$OP), 79.61 (*C*H$_2$NO$_2$), 102.13 (*C*H$_2$O$_2$Ph), 108.77 (*C*H$_{Ar}$), 109.13 (*C*H$_{Ar}$), 123.08 (*C*H$_{Ar}$), 132.19 (d, $^{3}J_{CP}$=16.4 Hz, C_{Ar}), 148.14 (C_{Ar}), 148.56 (C_{Ar}), 168.34 (d, $^{2}J_{CP}$=5.7 Hz, PCH*C*OOH). Anal. calcd for $C_{15}H_{20}NO_9P$: C, 46.28; H, 5.18; N, 3.60. Found: C, 46.41; H, 5.33; N, 3.72.

4.4.6. (2*R,3*R**,4*R**)-2-(Diethoxyphosphoryl)-4-nitro-3-(4-nitrophenyl)pentanoic acid (6a).** 859 mg, 85% yield, white crystals, mp 155–157 °C; IR (CCl_4): 1728, 1528, 1352, 1232, 1160, 1024, 664 cm^{-1}; ^{31}P NMR (acetone-*d*): δ=19.42; ^{1}H NMR (acetone-*d*): δ=1.35 (t, 3H, $^{3}J_{HH}$=7.1 Hz, CH_3CH$_2$OP), 1.35 (t, 3H, $^{3}J_{HH}$=7.1 Hz, CH_3CH$_2$OP), 1.47 (d, 3H, $^{3}J_{HH}$=6.7 Hz, CH_3CHNO$_2$), 3.88 (dd, 1H, $^{2}J_{HP}$=21.0 Hz, $^{3}J_{HH}$=12.0 Hz, PC*H*COOH), 4.17–4.29 (m, 4H, 2×CH$_3$CH_2OP), 4.47 (ddd, 1H, $^{3}J_{HH}$=12.0, $^{3}J_{HP}$=8.2 Hz, $^{3}J_{HH}$=4.3 Hz, Ar–C*H*), 5.53 (dq, 1H, $^{3}J_{HH}$=6.7 Hz, $^{3}J_{HH}$=4.3 Hz, CH$_3$C*H*NO$_2$), 7.57 (d, 2H, $^{3}J_{HH}$=8.8 Hz, 2×CH_{Ar}), 8.21 (d, 2H, $^{3}J_{HH}$=8.8 Hz, 2×CH_{Ar}); ^{13}C NMR (acetone-*d*): δ=12.96 (*C*H$_3$CHNO$_2$), 16.47 (d, $^{3}J_{CP}$=3.4 Hz, *C*H$_3$CH$_2$OP), 16.56 (d, $^{3}J_{CP}$=3.3 Hz, *C*H$_3$CH$_2$OP), 47.79 (d, $^{1}J_{CP}$=127.9 Hz, P*C*HCOOH), 48.39 (d, $^{2}J_{CP}$=3.1 Hz, Ar*C*H), 64.02 (d, $^{2}J_{CP}$=2.7 Hz, CH$_3$*C*H$_2$OP), 64.14 (CH$_3$*C*H$_2$OP), 84.35 (CH$_3$*C*HNO$_2$), 123.96 (*C*H$_{Ar}$), 131.48 (*C*H$_{Ar}$), 143.74 (d, $^{3}J_{CP}$=16.0 Hz, C_{Ar}), 148.68 (C_{Ar}), 168.36 (d, $^{2}J_{CP}$=6.0 Hz, PCH*C*OOH). Anal. calcd for $C_{15}H_{21}N_2O_9P$: C, 44.56; H, 5.24; N, 6.93. Found: C, 44.64; H, 5.32; N, 6.80.

4.4.7. (2*R,3*R**,4*R**)-3-(4-Bromophenyl)-2-(diethoxyphosphoryl)-4-nitropentanoic acid (6b).** 975 mg, 89% yield, white crystals, mp 156–158 °C; IR (CCl_4): 1736, 1552, 1224, 1164, 1024, 664 cm^{-1}; ^{31}P NMR (acetone-*d*): δ=19.86; ^{1}H NMR (acetone-*d*): δ=1.35 (t, 3H, $^{3}J_{HH}$=6.8 Hz, CH_3CH$_2$OP), 1.36 (t, 3H, $^{3}J_{HH}$=7.0 Hz, CH_3CH$_2$OP), 1.45 (d, 3H, $^{3}J_{HH}$=6.8 Hz, CH_3CHNO$_2$), 3.77 (dd, 1H, $^{2}J_{HP}$=20.5 Hz, $^{3}J_{HH}$=12.2 Hz, PC*H*COOH), 4.17–4.29 (m, 4H, 2×CH$_3$CH_2OP), 4.34 (ddd, 1H, $^{3}J_{HH}$=12.2,

$^3J_{HP}$=8.2 Hz, $^3J_{HH}$=4.2 Hz, Ar–C*H*), 5.45 (dq, 1H, $^3J_{HH}$= 6.8 Hz, $^3J_{HH}$=4.2 Hz, CH_3CHNO_2), 7.19 (d, 2H, $^3J_{HH}$= 8.5 Hz, 2×CH_{Ar}), 7.50 (d, 2H, $^3J_{HH}$=8.5 Hz, 2×CH_{Ar}); ^{13}C NMR (acetone-*d*): δ=12.66 (CH_3CHNO_2), 16.44 (d, $^3J_{CP}$=3.0 Hz, CH_3CH_2OP), 16.54 (d, $^3J_{CP}$=2.9 Hz, CH_3CH_2OP), 47.82 (d, $^1J_{CP}$=127.9 Hz, PCHCOOH), 48.07 (d, $^2J_{CP}$=3.6 Hz, ArCH), 63.97 (d, $^2J_{CP}$=7.2 Hz, CH_3CH_2OP), 64.08 (d, $^2J_{CP}$=6.5 Hz, CH_3CH_2OP), 84.32 (d, $^3J_{CP}$=1.7 Hz, CH_3CHNO_2), 122.53 (C_{Ar}), 132.05 (CH_{Ar}), 132.08 (CH_{Ar}), 135.30 (d, $^3J_{CP}$=16.4 Hz, C_{Ar}), 168.39 (d, $^2J_{CP}$=6.0 Hz, PCHCOOH). Anal. calcd for $C_{15}H_{21}BrNO_7P$: C, 41.11; H, 4.83; N, 3.20. Found: C, 41.23; H, 4.96; N, 3.30.

4.4.8. (2*R,3*R**,4*R**)-2-(Diethoxyphosphoryl)-3-(4-methylphenyl)-4-nitropentanoic acid (6c).** 783 mg, 84% yield, white crystals, mp 148–150 °C; IR (CCl_4): 1720, 1552, 1164, 1020, 664 cm^{-1}; ^{31}P NMR (acetone-*d*): δ=20.36; ^{1}H NMR (acetone-*d*): δ=1.36 (t, 3H, $^3J_{HH}$=7.0 Hz, CH_3CH_2OP), 1.37 (t, 3H, $^3J_{HH}$=7.0 Hz, CH_3CH_2OP), 1.42 (d, 3H, $^3J_{HH}$=6.6 Hz, CH_3CHNO_2), 2.27 (s, 3H, CH_3Ph), 3.72 (dd, 1H, $^2J_{HP}$=20.2 Hz, $^3J_{HH}$=12.3 Hz, PCHCOOH), 4.18–4.28 (m, 4H, 2×CH_3CH_2OP), 4.34 (ddd, 1H, $^3J_{HH}$=12.3 Hz, $^3J_{HP}$=8.4 Hz, $^3J_{HH}$=3.9 Hz, CHAr), 5.41 (dq, 1H, $^3J_{HH}$=6.6 Hz, $^3J_{HH}$=3.9 Hz, CH_3CHNO_2), 7.06 (s, 4H, 4×CH_{Ar}); ^{13}C NMR (acetone-*d*): δ=12.52 (CH_3CHNO_2), 16.45 (d, $^3J_{CP}$=3.3 Hz, CH_3CH_2OP), 16.55 (d, $^3J_{CP}$=3.2 Hz, CH_3CH_2OP), 20.95 (CH_3Ph), 48.09 (d, $^1J_{CP}$=127.4 Hz, PCHCOOH), 48.20 (d, $^2J_{CP}$=3.8 Hz, ArCH), 63.90 (d, $^2J_{CP}$=6.9 Hz, CH_3CH_2OP), 64.05 (d, $^2J_{CP}$=6.4 Hz, CH_3CH_2OP), 84.54 (CH_3CHNO_2), 129.59 (CH_{Ar}), 129.90 (CH_{Ar}), 132.71 (d, $^3J_{CP}$=16.4 Hz, C_{Ar}), 138.43 (C_{Ar}), 168.51 (d, $^2J_{CP}$=6.0 Hz, PCHCOOH). Anal. calcd for $C_{16}H_{24}NO_7P$: C, 51.47; H, 6.48; N, 3.75. Found: C, 51.59; H, 6.70; N, 3.67.

4.4.9. (2*R,3*R**,4*R**)-2-(Diethoxyphosphoryl)-3-(4-methoxyphenyl)-4-nitropentanoic acid (6d).** 892 mg, 92% yield, white crystals, mp 160–162 °C; IR (CCl_4): 1728, 1548, 1512, 1264, 1176, 1008, 960 cm^{-1}; ^{31}P NMR (acetone-*d*): δ=20.61; ^{1}H NMR (acetone-*d*): δ=1.35 (t, 3H, $^3J_{HH}$=7.0 Hz, CH_3CH_2OP), 1.36 (t, 3H, $^3J_{HH}$=7.2 Hz, CH_3CH_2OP), 1.43 (d, 3H, $^3J_{HH}$=6.8 Hz, CH_3CHNO_2), 3.70 (dd, 1H, $^2J_{HP}$=20.2 Hz, $^3J_{HH}$=10.0 Hz, PCHCOOH), 3.76 (s, 3H, CH_3OPh), 4.17–4.28 (m, 4H, 2×CH_3CH_2OP), 4.32 (ddd, 1H, $^3J_{HH}$=12.5 Hz, $^3J_{HP}$=8.2 Hz, $^3J_{HH}$=4.0 Hz, CHAr), 5.39 (dq, 1H, $^3J_{HH}$=6.8 Hz, $^3J_{HH}$=4.0 Hz, CH_3CHNO_2), 6.84 (d, 2H, $^3J_{HH}$=8.8 Hz, 2×CH_{Ar}), 7.12 (d, 2H, $^3J_{HH}$=8.8 Hz, 2×CH_{Ar}); ^{13}C NMR (acetone-*d*): δ= 12.59 (CH_3CHNO_2), 16.54 (d, $^3J_{CP}$=3.3 Hz, CH_3CH_2OP), 16.63 (d, $^3J_{CP}$=3.2 Hz, CH_3CH_2OP), 47.98 (d, $^2J_{CP}$= 3.6 Hz, ArCH), 48.32 (d, $^1J_{CP}$=127.0 Hz, PCHCOOH), 55.46 (CH_3OPh), 63.81 (d, $^2J_{CP}$=6.3 Hz, CH_3CH_2OP), 63.89 (d, $^2J_{CP}$=4.7 Hz, CH_3CH_2OP), 84.72 (CH_3CHNO_2), 114.34 (CH_{Ar}), 127.87 (d, $^3J_{CP}$=18.2 Hz, C_{Ar}), 131.19 (CH_{Ar}), 160.40 (C_{Ar}), 168.57 (d, $^2J_{CP}$=5.9 Hz, PCHCOOH). Anal. calcd for $C_{16}H_{24}NO_8P$: C, 49.36; H, 6.21; N, 3.60. Found: C, 49.49; H, 6.33; N, 3.67.

4.4.10. (2*R,3*R**,4*R**)-2-(Diethoxyphosphoryl)-3-(3,4-methylenedioxyphenyl)-4-nitropentanoic acid (6e).** 937 mg, 93% yield, white crystals, mp 163–166 °C; IR (CCl_4): 1736, 1552, 1224, 1040, 664 cm^{-1}; ^{31}P NMR (acetone-*d*): δ=20.08; ^{1}H NMR (acetone-*d*): δ=1.35 (t, 3H, $^3J_{HH}$=7.0 Hz, CH_3CH_2OP), 1.36 (t, 3H, $^3J_{HH}$=7.0 Hz, CH_3CH_2OP), 1.46 (d, 3H, $^3J_{HH}$=6.6 Hz, CH_3CHNO_2), 3.68 (dd, 1H, $^2J_{HP}$=20.4 Hz, $^3J_{HH}$=12.2 Hz, PCHCOOH), 4.17–4.29 (m, 4H, 2×CH_3CH_2OP), 4.29 (ddd, 1H, $^3J_{HH}$=12.2 Hz, $^3J_{HP}$=8.6 Hz, $^3J_{HH}$=4.2 Hz, Ar–CH), 5.40 (dq, 1H, $^3J_{HH}$=6.6 Hz, $^3J_{HH}$=4.2 Hz, CH_3CHNO_2), 5.97 (s, 2H, CH_2O_2Ph), 6.65 (dd, 1H, $^3J_{HH}$=8.1 Hz, $^4J_{HH}$=1.6 Hz, CH_{Ar}), 6.75 (d, 1H, $^3J_{HH}$=8.1 Hz, CH_{Ar}), 6.76 (d, 1H, $^4J_{HH}$=1.6 Hz, CH_{Ar}); ^{13}C NMR (acetone-*d*): δ=12.64 (CH_3CHNO_2), 16.50 (2×CH_3CH_2OP), 48.24 (d, $^1J_{CP}$=125.8 Hz, PCHCOOH), 48.31 (ArCH), 63.96 (2×CH_3CH_2OP), 84.62 (CH_3CHNO_2), 102.12 (CH_2O_2Ph), 108.59 (CH_{Ar}), 110.06 (CH_{Ar}), 123.68 (CH_{Ar}), 129.34 (d, $^3J_{CP}$=17.2 Hz, C_{Ar}), 148.28 (C_{Ar}), 156.54 (C_{Ar}), 168.44 (PCHCOOH). Anal. calcd for $C_{16}H_{22}NO_9P$: C, 47.65; H, 5.50; N, 3.47. Found: C, 47.77; H, 5.42; N, 3.56.

4.5. General procedure for the preparation of 4-aryl-3-(diethoxyphosphoryl)-1-hydroxysuccinimides 8a–e

A solution of a corresponding 4-nitrobutanoic acid **5** (1 mmol) in water (15 mL) was heated at reflux for an appropriate period of time (shown in Table 2). The resulting solution was cooled to room temperature, the solvent was evaporated and the residue was taken up in Et_2O (10 mL) and left to crystallize. Filtration of the crystals afforded pure 1-hydroxysuccinimides **8**.

4.5.1. (3*R,4*S**)-3-(Diethoxyphosphoryl)-4-(4-nitrophenyl)-1-hydroxysuccinimide (8a).** 223 mg, 60% yield, pale yellow crystals, mp 167–170 °C; IR (CCl_4): 1732, 1528, 1348, 1208, 1032 cm^{-1}; ^{31}P NMR (acetone-*d*): δ=18.97; ^{1}H NMR (acetone-*d*): δ=1.26 (t, 3H, $^3J_{HH}$=7.0 Hz, CH_3CH_2OP), 1.30 (t, 3H, $^3J_{HH}$=7.0 Hz, CH_3CH_2OP), 3.78 (dd, 1H, $^2J_{HP}$=23.0 Hz, $^3J_{HH}$=5.2 Hz, PCHC(O)N), 4.07–4.28 (m, 4H, 2×CH_3CH_2OP), 4.50 (dd, 1H, $^3J_{HP}$=18.0 Hz, $^3J_{HH}$=5.2 Hz, ArCHC(O)N), 7.77 (d, 2H, $^3J_{HH}$=8.8 Hz, 2×CH_{Ar}), 8.28 (d, 2H, $^3J_{HH}$=8.8 Hz, 2×CH_{Ar}); ^{13}C NMR (acetone-*d*): δ=16.00 (d, $^3J_{CP}$=5.8 Hz, CH_3CH_2OP), 16.09 (d, $^3J_{CP}$=5.7 Hz, CH_3CH_2OP), 44.86 (d, $^1J_{CP}$=143.5 Hz, PCHC(O)N), 45.50 (d, $^2J_{CP}$=2.5 Hz, ArCHC(O)N), 63.43 (d, $^2J_{CP}$=6.7 Hz, CH_3CH_2OP), 64.21 (d, $^2J_{CP}$=6.4 Hz, CH_3CH_2OP), 124.14 (CH_{Ar}), 130.31 (CH_{Ar}), 143.83 (d, $^3J_{CP}$=3.0 Hz, C_{Ar}), 148.14 (C_{Ar}), 166.49 (d, $^2J_{CP}$=4.4 Hz, C(O)NOH), 170.31 (d, $^3J_{CP}$= 8.4 Hz, C(O)NOH). Anal. calcd for $C_{14}H_{17}N_2O_8P$: C, 45.17; H, 4.60; N, 7.53. Found: C, 45.30; H, 4.72; N, 7.41.

4.5.2. (3*R,4*S**)-4-(4-Bromophenyl)-3-(diethoxyphosphoryl)-1-hydroxysuccinimide (8b).** 272 mg, 67% yield, pale yellow crystals, mp 149–152 °C; IR (CCl_4): 1740, 1220, 1036 cm^{-1}; ^{31}P NMR (acetone-*d*): δ=19.24; ^{1}H NMR (acetone-*d*): δ=1.26 (dt, 3H, $^3J_{HH}$=7.1 Hz, $^4J_{HP}$= 0.4 Hz, CH_3CH_2OP), 1.30 (dt, 3H, $^3J_{HH}$=7.0 Hz, $^4J_{HP}$= 0.5 Hz, CH_3CH_2OP), 3.63 (dd, 1H, $^2J_{HP}$=23.1 Hz, $^3J_{HH}$=4.8 Hz, PCHC(O)N), 4.05–4.26 (m, 4H, 2×CH_3CH_2OP), 4.27 (dd, 1H, $^3J_{HP}$=18.1 Hz, $^3J_{HH}$=4.8 Hz, ArCHC(O)N), 7.39 (d, 2H, $^3J_{HH}$=7.5 Hz, 2×CH_{Ar}), 7.59 (d, 2H, $^3J_{HH}$=7.5 Hz, 2×CH_{Ar}); ^{13}C NMR (acetone-*d*): δ= 16.45 (d, $^3J_{CP}$=5.9 Hz, CH_3CH_2OP), 16.54 (d, $^3J_{CP}$=5.7 Hz, CH_3CH_2OP), 45.53 (d, $^1J_{CP}$=142.8 Hz, PCHC(O)N), 45.73 (ArCHC(O)N), 63.87 (d, $^2J_{CP}$=6.6 Hz, CH_3CH_2OP), 64.64 (d, $^2J_{CP}$=6.4 Hz, CH_3CH_2OP), 122.44 (C_{Ar}), 131.30

(CH_{Ar}), 132.70 (CH_{Ar}), 136.55 (d, $^3J_{CP}$=3.5 Hz, C_{Ar}), 167.09 (*C*(O)NOH), 171.27 (d, $^3J_{CP}$=8.4 Hz, *C*(O)NOH). Anal. calcd for $C_{14}H_{17}BrNO_6P$: C, 41.40; H, 4.22; N, 3.45. Found: C, 41.51; H, 4.31; N, 3.30.

4.5.3. (3*R,4*S**)-3-(Diethoxyphosphoryl)-4-(4-methylphenyl)-1-hydroxysuccinimide (8c).** 232 mg, 68% yield, pale yellow crystals, mp 158–161 °C; IR (CCl_4): 1720, 1512, 1356, 1216, 1032 cm^{-1}; ^{31}P NMR (acetone-*d*): δ=18.97; ^1H NMR ($CDCl_3$): δ=1.31–141 (m, 6H, 2×CH_3CH$_2$OP), 2.35 (s, 3H, CH_3Ph), 3.51 (dd, 1H, $^2J_{HP}$=24.5 Hz, $^3J_{HH}$=4.5 Hz, PC*H*C(O)N), 4.11–4.33 (m, 5H, 2×CH$_3$CH_2OP, ArC*H*C(O)N), 7.08 (d, 2H, $^3J_{HH}$=8.0 Hz, 2×CH_{Ar}), 7.20 (d, 2H, $^3J_{HH}$=8.0 Hz, 2×CH_{Ar}); ^{13}C NMR (CH_3OD): δ=15.63 (d, $^3J_{CP}$=4.9 Hz, *C*H$_3$CH$_2$OP), 15.71 (d, $^3J_{CP}$=5.3 Hz, *C*H$_3$CH$_2$OP), 20.25 (*C*H$_3$Ph), 45.40 (d, $^1J_{CP}$=142.3 Hz, P*C*HC(O)N), 45.60 (d, $^2J_{CP}$=2.4 Hz, Ar*C*HC(O)N), 63.95 (d, $^2J_{CP}$=6.7 Hz, CH$_3$*C*H$_2$OP), 64.50 (d, $^2J_{CP}$=6.6 Hz, CH$_3$*C*H$_2$OP), 128.02 (CH_{Ar}), 129.87 (CH_{Ar}), 133.22 (d, $^3J_{CP}$=3.8 Hz, C_{Ar}), 138.52 (C_{Ar}), 167.44 (d, $^2J_{CP}$=4.4 Hz, *C*(O)NOH), 172.23 (d, $^3J_{CP}$=7.5 Hz, *C*(O)NOH). Anal. calcd for $C_{15}H_{20}NO_6P$: C, 52.79; H, 5.91; N, 4.10. Found: C, 52.71; H, 6.03; N, 3.97.

4.5.4. (3*R,4*S**)-3-(Diethoxyphosphoryl)-4-(4-methoxyphenyl)-1-hydroxysuccinimide (8d).** 228 mg, 64% yield, pale yellow crystals, mp 174–175 °C; IR (CCl_4): 1728, 1516, 1256, 1216, 1040 cm^{-1}; ^{31}P NMR (acetone-*d*): δ=19.48; ^1H NMR (acetone-*d*): δ=1.26 (dt, 3H, $^3J_{HH}$=7.2 Hz, $^4J_{HP}$=0.5 Hz, CH_3CH$_2$OP), 1.30 (dt, 3H, $^3J_{HH}$=7.0 Hz, $^4J_{HP}$=0.5 Hz, CH_3CH$_2$OP), 3.54 (dd, 1H, $^2J_{HP}$=23.2 Hz, $^3J_{HH}$=4.5 Hz, PC*H*C(O)N), 3.80 (s, 3H, CH$_3$OPh), 4.08–4.25 (m, 5H, 2×CH$_3$CH_2OP, ArC*H*C(O)N), 6.94 (d, 2H, $^3J_{HH}$=9.0 Hz, 2×CH_{Ar}), 7.30 (d, 2H, $^3J_{HH}$=9.0 Hz, 2×CH_{Ar}); ^{13}C NMR (acetone-*d*): δ=16.79 (d, $^3J_{CP}$=5.6 Hz, *C*H$_3$CH$_2$OP), 16.88 (d, $^3J_{CP}$=5.3 Hz, *C*H$_3$CH$_2$OP), 45.98 (Ar*C*HC(O)N), 46.33 (d, $^1J_{CP}$=141.5 Hz, P*C*HC(O)N), 55.90 (*C*H$_3$OPh), 64.13 (d, $^2J_{CP}$=6.7 Hz, CH$_3$*C*H$_2$OP), 64.86 (d, $^2J_{CP}$=6.4 Hz, CH$_3$*C*H$_2$OP), 115.40 (CH_{Ar}), 129.50 (C_{Ar}), 130.48 (CH_{Ar}), 160.74 (C_{Ar}), 167.64 (d, $^2J_{CP}$=4.7 Hz, *C*(O)NOH), 172.17 (d, $^3J_{CP}$=7.4 Hz, *C*(O)NOH). Anal. calcd for $C_{15}H_{20}NO_7P$: C, 50.42; H, 5.64; N, 3.92. Found: C, 50.51; H, 5.75; N, 3.82.

4.5.5. (3*R,4*S**)-3-(Diethoxyphosphoryl)-4-(3,4-methylenedioxyphenyl)-1-hydroxysuccinimide (8e).** 293 mg, 79% yield, pale yellow crystals, mp 210–211 °C; IR (CCl_4): 1724, 1504, 1256, 1220, 1032 cm^{-1}; ^{31}P NMR (acetone-*d*): δ=19.42; ^1H NMR (acetone-*d*): δ=1.26 (t, 3H, $^3J_{HH}$=7.0 Hz, CH_3CH$_2$OP), 1.30 (t, 3H, $^3J_{HH}$=7.0 Hz, CH_3CH$_2$OP), 3.55 (dd, 1H, $^2J_{HP}$=23.0 Hz, $^3J_{HH}$=4.8 Hz, PC*H*C(O)N), 4.06–4.26 (m, 5H, 2×CH$_3$CH_2OP, ArC*H*C(O)N), 6.02 (s, 2H, CH_2O$_2$Ph), 6.83–6.93 (m, 3H, 3×CH_{Ar}); ^{13}C NMR (acetone-*d*): δ=16.55 (2×*C*H$_3$CH$_2$OP), 46.04 (d, $^1J_{CP}$=143.2 Hz, P*C*HC(O)N), 46.12 (Ar*C*HC(O)N), 63.75 (CH$_3$*C*H$_2$OP), 64.86 (CH$_3$*C*H$_2$OP), 102.16 (*C*H$_2$O$_2$Ph), 109.08 (CH_{Ar}), 109.69 (CH_{Ar}), 122.77 (CH_{Ar}), 123.46 (C_{Ar}), 130.87 (C_{Ar}), 148.42 (C_{Ar}), 167.25 (d, $^2J_{CP}$=5.9 Hz, *C*(O)NOH), 171.57 (d, $^3J_{CP}$=6.9 Hz, *C*(O)NOH). Anal. calcd for $C_{15}H_{18}NO_8P$: C, 48.52; H, 4.89; N, 3.77. Found: C, 48.62; H, 5.00; N, 3.70.

4.6. General procedure for the preparation of dicyclohexylammonium 3-aryl-2-(diethoxyphosphoryl)-4-oxopentanoates 10a–e

A solution of 4-nitropentanoic acid **6** (1 mmol) in water (15 mL) was heated at reflux for an appropriate period of time (shown in Table 2). The resulting solution was cooled to room temperature and the solvent was evaporated. The residue was dissolved in CH_2Cl_2 (10 mL) and dicyclohexylamine (1 mmol, 181 mg) was added. The solvent was evaporated off and the residue was taken up in Et_2O (10 mL) and left to crystallize. Filtration of the crystals afforded pure 4-oxopentanoates **10**.

4.6.1. Dicyclohexylammonium (2*R,3*S**)-2-(diethoxyphosphoryl)-3-(4-nitrophenyl)-4-oxopentanoate (10a).** 388 mg, 70% yield, pale yellow crystals, mp 163–165 °C; IR (CCl_4): 2936, 1712, 1512, 1344, 1240, 1056, 1032, 968 cm^{-1}; ^{31}P NMR ($CDCl_3$): δ=25.56; ^1H NMR ($CDCl_3$): δ=0.97 (t, 3H, $^3J_{HH}$=7.1 Hz, CH_3CH$_2$OP), 1.11 (t, 3H, $^3J_{HH}$=7.1 Hz, CH_3CH$_2$OP), 1.16–1.38 (m, 6H, 3×CH_2(*c*Hex)), 1.40–1.90 (m, 10H, 5×CH_2(*c*Hex)), 1.98–2.35 (m, 4H, 2×CH_2(*c*Hex)), 2.13 (s, 3H, CH_3CO), 2.98–3.07 (m, 2H, 2×C*H*(*c*Hex)), 3.65 (dd, 1H, $^2J_{HP}$=20.6 Hz, $^3J_{HH}$=11.8 Hz, PC*H*COO$^-$), 3.67–4.12 (m, 4H, 2×CH$_3$CH_2OP), 4.70 (dd, 1H, $^3J_{HH}$=11.8 Hz, $^3J_{HP}$=8.5 Hz, ArC*H*), 7.54 (d, 2H, $^3J_{HH}$=8.7 Hz, 2×CH_{Ar}), 8.16 (d, 2H, $^3J_{HH}$=8.7 Hz, 2×CH_{Ar}); ^{13}C NMR ($CDCl_3$): δ=15.66 (d, $^3J_{CP}$=6.7 Hz, *C*H$_3$CH$_2$OP), 15.78 (d, $^3J_{CP}$=7.9 Hz, *C*H$_3$CH$_2$OP), 24.56 (*C*H$_2$(*c*Hex)), 24.80 (*C*H$_2$(*c*Hex)), 28.50 (*C*H$_2$(*c*Hex)), 29.34 (*C*H$_3$CO), 51.68 (d, $^1J_{CP}$=126.0 Hz, P*C*HCOO$^-$), 52.21 (Ar*C*H), 57.48 (*C*H(*c*Hex)), 60.76 (d, $^2J_{CP}$=6.8 Hz, CH$_3$*C*H$_2$OP), 61.85 (d, $^2J_{CP}$=6.2 Hz, CH$_3$*C*H$_2$OP), 123.08 (CH_{Ar}), 130.02 (CH_{Ar}), 143.80 (C_{Ar}), 146.87 (C_{Ar}), 170.10 (PCH*C*OO$^-$), 205.08 (d, $^3J_{CP}$=18.2 Hz, CH$_3$*C*O). Anal. calcd for $C_{27}H_{43}N_2O_8P$: C, 58.47; H, 7.81; N, 5.05. Found: C, 58.61; H, 7.73; N, 5.15.

4.6.2. Dicyclohexylammonium (2*R,3*S**)-3-(4-bromophenyl)-2-(diethoxyphosphoryl)-4-oxopentanoate (10b).** 329 mg, 56% yield, white crystals, mp 155–157 °C; IR (CCl_4): 2936, 1712, 1636, 1356, 1240, 1056, 1032, 968 cm^{-1}; ^{31}P NMR ($CDCl_3$): δ=26.04; ^1H NMR ($CDCl_3$): δ=0.97 (t, 3H, $^3J_{HH}$=7.0 Hz, CH_3CH$_2$OP), 1.12 (t, 3H, $^3J_{HH}$=7.0 Hz, CH_3CH$_2$OP), 1.18–1.34 (m, 6H, 3×CH_2(*c*Hex)), 1.39–1.58 (m, 4H, 2×CH_2(*c*Hex)), 1.60–1.70 (m, 2H, CH_2(*c*Hex)), 1.74–1.88 (m, 4H, 2×CH_2(*c*Hex)), 1.95–2.07 (m, 4H, 2×CH_2(*c*Hex)), 2.08 (s, 3H, CH_3CO), 2.94–3.04 (m, 2H, 2×C*H*(*c*Hex)), 3.57 (dd, 1H, $^2J_{HP}$=20.6 Hz, $^3J_{HH}$=11.8 Hz, PC*H*COO$^-$), 3.59–4.11 (m, 4H, 2×CH$_3$CH_2OP), 4.53 (dd, 1H, $^3J_{HH}$=11.8 Hz, $^3J_{HP}$=8.6 Hz, ArC*H*), 7.22 (d, 2H, $^3J_{HH}$=8.5 Hz, 2×CH_{Ar}), 7.41 (d, 2H, $^3J_{HH}$=8.5 Hz, 2×CH_{Ar}); ^{13}C NMR ($CDCl_3$): δ=15.70 (d, $^3J_{CP}$=7.3 Hz, *C*H$_3$CH$_2$OP), 15.82 (d, $^3J_{CP}$=7.7 Hz, *C*H$_3$CH$_2$OP), 24.66 (*C*H$_2$(*c*Hex)), 24.91 (*C*H$_2$(*c*Hex)), 28.59 (*C*H$_2$(*c*Hex)), 29.02 (*C*H$_3$CO), 51.53 (d, $^1J_{CP}$=127.4 Hz, P*C*HCOO$^-$), 52.51 (Ar*C*H), 57.24 (*C*H(*c*Hex)), 60.63 (d, $^2J_{CP}$=6.6 Hz, CH$_3$*C*H$_2$OP), 61.80 (d, $^2J_{CP}$=6.6 Hz, CH$_3$*C*H$_2$OP), 121.04 (C_{Ar}), 130.96 (CH_{Ar}), 131.17 (CH_{Ar}), 135.21 (C_{Ar}), 170.65 (d, $^2J_{CP}$=3.8 Hz, PCH*C*OO$^-$), 205.72 (d, $^3J_{CP}$=18.2 Hz, CH$_3$*C*O). Anal. calcd for $C_{27}H_{43}BrNO_6P$: C, 55.10; H, 7.36; N, 2.38. Found: C, 55.01; H, 7.23; N, 2.27.

4.6.3. Dicyclohexylammonium (2*R,3*S**)-2-(diethoxyphosphoryl)-3-(4-methylphenyl)-4-oxopentanoate (10c).** 261 mg, 50% yield, white crystals, mp 122–124 °C; IR (CCl_4): 2936, 1720, 1512, 1356, 1248, 1032, 968, 664 cm^{-1}; ^{31}P NMR ($CDCl_3$): δ=26.33; ^1H NMR ($CDCl_3$): δ=0.96 (t, 3H, $^3J_{HH}$=7.1 Hz, CH_3CH$_2$OP), 1.10 (t, 3H, $^3J_{HH}$=7.0 Hz, CH_3CH$_2$OP), 1.19–1.35 (m, 6H, 3×CH_2(*c*Hex)), 1.41–1.68 (m, 6H, 3×CH_2(*c*Hex)), 1.76–1.86 (m, 4H, 2×CH_2(*c*Hex)), 1.98–2.03 (m, 4H, 2×CH_2(*c*Hex)), 2.06 (s, 3H, CH_3CO), 2.30 (s, 3H, CH_3Ph), 2.95–3.04 (m, 2H, 2×C*H*(*c*Hex)), 3.62 (dd, 1H, $^2J_{HP}$=20.8 Hz, $^3J_{HH}$=11.3 Hz, PC*H*COO$^-$), 3.55–4.11 (m, 4H, 2×CH$_3$CH_2OP), 4.50 (dd, 1H, $^3J_{HH}$=11.3 Hz, $^3J_{HP}$=9.1 Hz, ArC*H*), 7.08 (d, 2H, $^3J_{HH}$=7.5 Hz, 2×CH_{Ar}), 7.22 (d, 2H, $^3J_{HH}$=7.5 Hz, 2×CH_{Ar}); ^{13}C NMR ($CDCl_3$): δ=15.60 (d, $^3J_{CP}$=6.6 Hz, *C*H$_3$CH$_2$OP), 15.75 (d, $^3J_{CP}$=7.1 Hz, *C*H$_3$CH$_2$OP), 20.71 (*C*H$_3$Ph), 24.62 (*C*H$_2$(*c*Hex)), 24.84 (*C*H$_2$(*c*Hex)), 28.56 (*C*H$_2$(*c*Hex)), 28.78 (*C*H$_3$CO), 51.40 (d, $^1J_{CP}$=127.2 Hz, P*C*HCOO$^-$), 52.19 (Ar*C*H), 57.44 (*C*H(*c*Hex)), 60.64 (d, $^2J_{CP}$=6.7 Hz, CH$_3$*C*H$_2$OP), 61.66 (d, $^2J_{CP}$=6.6 Hz, CH$_3$*C*H$_2$OP), 128.76 (*C*H$_{Ar}$), 129.10 (*C*H$_{Ar}$), 132.84 (*C*$_{Ar}$), 136.54 (*C*$_{Ar}$), 171.13 (d, $^2J_{CP}$=3.8 Hz, PCH*C*OO$^-$), 206.13 (d, $^3J_{CP}$=19.3 Hz, CH$_3$*C*O). Anal. calcd for $C_{28}H_{46}NO_6P$: C, 64.22; H, 8.85; N, 2.67. Found: C, 64.34; H, 8.96; N, 2.77.

4.6.4. Dicyclohexylammonium 2-(diethoxyphosphoryl)-3-(4-methoxyphenyl)-4-oxopentanoate (10d). 333 mg, 62% yield, white crystals, mp 136–138 °C; IR (CCl_4): 2936, 1716, 1512, 1356, 1248, 1032 cm^{-1}; ^{31}P NMR ($CDCl_3$): δ=26.30, 26.71 (81:19); (2*R**,3*S**)-**10d**: ^{31}P NMR ($CDCl_3$): δ=26.30; ^1H NMR ($CDCl_3$): δ=0.98 (t, 3H, $^3J_{HH}$=7.0 Hz, CH_3CH$_2$OP), 1.12 (t, 3H, $^3J_{HH}$=7.2 Hz, CH_3CH$_2$OP), 1.18–1.34 (m, 6H, 3×CH_2(*c*Hex)), 1.40–1.67 (m, 6H, 3×CH_2(*c*Hex)), 1.76–1.86 (m, 4H, 2×CH_2(*c*Hex)), 1.97–2.04 (m, 4H, 2×CH_2(*c*Hex)), 2.05 (s, 3H, CH_3CO), 2.91–3.04 (m, 2H, 2×C*H*(*c*Hex)), 3.60 (dd, 1H, $^2J_{HP}$=20.8 Hz, $^3J_{HH}$=11.8 Hz, PC*H*COO$^-$), 3.55–4.20 (m, 4H, 2×CH$_3$CH_2OP), 3.78 (s, 3H, CH_3OPh), 4.49 (dd, 1H, $^3J_{HH}$=11.8 Hz, $^3J_{HP}$=8.8 Hz, ArC*H*), 6.82 (d, 2H, $^3J_{HH}$=8.8 Hz, 2×CH_{Ar}), 7.24 (d, 2H, $^3J_{HH}$=8.8 Hz, 2×CH_{Ar}); ^{13}C NMR ($CDCl_3$): δ=15.75 (d, $^3J_{CP}$=5.5 Hz, *C*H$_3$CH$_2$OP), 15.84 (d, $^3J_{CP}$=6.2 Hz, *C*H$_3$CH$_2$OP), 24.65 (*C*H$_2$(*c*Hex)), 24.88 (*C*H$_2$(*c*Hex)), 28.59 (*C*H$_2$(*c*Hex)), 28.76 (*C*H$_3$CO), 51.48 (d, $^1J_{CP}$=127.3 Hz, P*C*HCOO$^-$), 52.17 (Ar*C*H), 54.97 (*C*H$_3$OPh), 57.01 (*C*H(*c*Hex)), 60.61 (d, $^2J_{CP}$=6.7 Hz, CH$_3$*C*H$_2$OP), 61.56 (d, $^2J_{CP}$=7.5 Hz, CH$_3$*C*H$_2$OP), 113.57 (*C*H$_{Ar}$), 127.98 (*C*$_{Ar}$), 130.29 (*C*H$_{Ar}$), 158.36 (*C*$_{Ar}$), 171.12 (d, $^2J_{CP}$=3.8 Hz, PCH*C*OO$^-$), 206.17 (d, $^3J_{CP}$=19.2 Hz, CH$_3$*C*O). Anal. calcd for $C_{28}H_{46}NO_7P$: C, 62.32; H, 8.59; N, 2.60. Found: C, 62.33; H, 8.70; N, 2.47.

4.6.5. Dicyclohexylammonium 2-(diethoxyphosphoryl)-3-(3,4-methylenedioxyphenyl)-4-oxopentanoate (10e). 326 mg, 59% yield, pale yellow crystals, mp 144–146 °C; IR (CCl_4): 2936, 1712, 1612, 1484, 1352, 1240, 1040, 968 cm^{-1}; ^{31}P NMR ($CDCl_3$): δ=26.36, 26.76 (86:14); (2*R**,3*S**)-**10e**: ^{31}P NMR ($CDCl_3$): δ=26.36; ^1H NMR ($CDCl_3$): δ=1.02 (t, 3H, $^3J_{HH}$=7.1 Hz, CH_3CH$_2$OP), 1.14 (t, 3H, $^3J_{HH}$=7.1 Hz, CH_3CH$_2$OP), 1.21–1.36 (m, 6H, 3×CH_2(*c*Hex)), 1.41–1.53 (m, 4H, 2×CH_2(*c*Hex)), 1.60–1.68 (m, 2H, CH_2(*c*Hex)), 1.75–1.85 (m, 4H, 2×CH_2(*c*Hex)), 1.95–2.06 (m, 4H, 2×CH_2(*c*Hex)), 2.08 (s, 3H, CH_3CO), 2.87–3.02 (m, 2H, 2×C*H*(*c*Hex)), 3.55 (dd, 1H, $^2J_{HP}$=20.6 Hz, $^3J_{HH}$=11.7 Hz, PC*H*COO$^-$), 3.64–4.13 (m, 4H, 2×CH$_3$CH_2OP), 4.47 (dd, 1H, $^3J_{HH}$=11.7 Hz, $^3J_{HP}$=8.8 Hz, ArC*H*), 5.91 (s, 2H, CH_2OPh), 6.73 (d, 1H, $^3J_{HH}$=8.0 Hz, CH_{Ar}), 6.81 (s, 1H, CH_{Ar}), 6.83 (d, 1H, $^3J_{HH}$=8.0 Hz, CH_{Ar}); ^{13}C NMR ($CDCl_3$): δ=15.61 (d, $^3J_{CP}$=3.6 Hz, *C*H$_3$CH$_2$OP), 15.71 (d, $^3J_{CP}$=4.0 Hz, *C*H$_3$CH$_2$OP), 24.51 (*C*H$_2$(*c*Hex)), 24.75 (*C*H$_2$(*c*Hex)), 28.44 (*C*H$_2$(*c*Hex)), 28.62 (*C*H$_3$CO), 51.39 (d, $^1J_{CP}$=127.2 Hz, P*C*HCOO$^-$), 52.01 (Ar*C*H), 57.21 (*C*H(*c*Hex)), 60.44 (d, $^2J_{CP}$=6.5 Hz, CH$_3$*C*H$_2$OP), 61.50 (d, $^2J_{CP}$=6.5 Hz, CH$_3$*C*H$_2$OP), 100.52 (*C*H$_2$O$_2$Ph), 107.70 (*C*H$_{Ar}$), 109.12 (*C*H$_{Ar}$), 122.72 (*C*H$_{Ar}$), 129.57 (*C*$_{Ar}$), 146.45 (*C*$_{Ar}$), 147.15 (*C*$_{Ar}$), 170.75 (d, $^2J_{CP}$=3.8 Hz, PCH*C*OO$^-$), 205.85 (d, $^3J_{CP}$=19.6 Hz, CH$_3$*C*O). Anal. calcd for $C_{28}H_{44}NO_8P$: C, 60.75; H, 8.01; N, 2.53. Found: C, 60.87; H, 8.13; N, 2.45.

4.7. X-ray single crystal structure analysis for 8b

Formula: $C_{14}H_{17}NO_6PBr$, M_w=406.20, pale yellow crystal 0.40×0.30×0.20 mm, a=8.3309(4), b=10.0423(4), c=11.7799(4) Å, α=74.941(4), β=76.686(4), γ=65.860(4)°, V=859.81(6) Å^3, ρ_{calc}=1.569 g cm^{-3}, μ=2.51 cm^{-1}, Z=2, crystal system: triclinic, space group: P-1, λ=0.71073 Å, T=293 K, ω scans, 8916 reflections collected ($\pm h$,$\pm k$,$\pm l$), $2\theta_{max}$=50°, 2932 unique reflections (R_{int}=0.021) and 2406 observed reflections [$I \geq 2\sigma(I)$], 239 refined parameters, refinement on F^2, R_{all}=0.059, $wR(F^2)$=0.145, max. and min. residual electron density ($\Delta\rho_{max}$=0.88 and $\Delta\rho_{min}$=−0.85) eÅ^{-3}—both peaks located near Br atom, X-ray data were collected with Kuma Diffraction KM4 CCD area detector diffractometer. Structure was solved by direct methods and refined by full matrix least-squares—SHELXTL.[26]

Crystallographic data (excluding structure factors) for the structure reported herein, have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 605788. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. Any request should be accompanied by a full literature citation.

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References and notes

1. Noland, W. E. *Chem. Rev.* **1955**, *55*, 137–155.
2. Pinnick, H. W. *Org. React.* **1990**, *38*, 655–791.
3. Ballini, R.; Petrini, M. *Tetrahedron* **2004**, *60*, 1017–1047.
4. Krawczyk, H.; Wolf, W. M.; Śliwiński, M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2794–2798.
5. Moonen, K.; Laureyn, I.; Stevens, C. V. *Chem. Rev.* **2004**, *104*, 6177–6215.

6. Truel, I.; Mohamed-Hachi, A.; About-Jaudet, E.; Collignon, N. *Synth. Commun.* **1997**, 1165–1172.
7. Touil, S.; Zantour, H. *Phosphorus Sulfur Silicon Relat. Elem.* **1997**, 183–190.
8. Kraus, G. A.; Choudhury, P. K. *Org. Lett.* **2002**, 2033–2034.
9. Kraus, G. A.; Choudhury, P. K. *Eur. J. Org. Chem.* **2004**, 2193–2197.
10. Błaszczyk, E.; Krawczyk, H.; Janecki, T. *Synlett* **2004**, 2685–2688.
11. Villiéras, J.; Rambaud, M. *Synthesis* **1984**, 406–408.
12. Minami, T.; Hirakawa, K.; Koyanagi, S.; Nakamura, S.; Yamaguchi, M. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2385–2390.
13. Lee, K.; Jackson, J. A.; Wiemer, D. F. *J. Org. Chem.* **1993**, *58*, 5967–5971.
14. Janecki, T.; Błaszczyk, E. *Synthesis* **2001**, 403–408.
15. Janecki, T.; Błaszczyk, E. *Tetrahedron Lett.* **2001**, *42*, 2919–2922.
16. Krawczyk, H.; Wąsek, K.; Kędzia, J. *Synlett* **2005**, 2648–2652.
17. Krawczyk, H.; Albrecht, Ł. *Synthesis* **2005**, 2887–2896.
18. Wright, S. W.; Hageman, D. L.; Wright, A. S.; McClure, L. D. *Tetrahedron Lett.* **1997**, *38*, 7345–7348.
19. Adiwidjaja, G.; Meyer, B.; Thiem, J. Z. *Naturforsch.* **1979**, 1547–1551.
20. Benezra, C. *J. Am. Chem. Soc.* **1973**, *95*, 6890–6894.
21. Bentrude, W. G.; Setzer, W. N. *Phosphorus-31 NMR Spectroscopy in Stereochemical Analysis*; Verkade, J. G., Quin, L. D., Eds.; VCH: Deerfield, 1987; Chapter 11.
22. Piotowska, D. G.; Wróblewski, A. E. *Tetrahedron* **2003**, *59*, 8405–8410.
23. Krawczyk, H.; Albrecht, Ł.; Wojciechowski, J.; Wolf, W. M. *Acta Crystallogr., Sect. E* **2006**, *62*, o2743–o2745.
24. Jones, P. G. *Acta Crystallogr., Sect. E* **2003**, *59*, o1951–o1952.
25. Allen, F. H.; Kennard, O.; Watson, D. G.; Brammer, L.; Orpen, A. G.; Taylor, R. Typical Interatomic Distances: Organic Compounds. In *International Tables for Crystallography*; Wilson, A. J. C., Ed.; Kluwer: Dordrecht, 1992; Vol. C, pp 685–705.
26. Sheldrick, G. M. *SHELXTL, Version 6.12*; Bruker AXS: Madison, Wisconsin, WI, 2001.

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A novel *tert*-amino effect based approach to 1,2,3,4-tetrahydroquinoline-2-spirocycloalkanes

Anton V. Tverdokhlebov,[a,*] Alexander P. Gorulya,[a] Andrey A. Tolmachev,[b] Alexander N. Kostyuk,[c] Alexander N. Chernega[c] and Eduard B. Rusanov[c]

[a]*Enamine Ltd, Alexandra Matrosova str. 23, 01103 Kiev, Ukraine*
[b]*Kiev National Taras Shevchenko University, Volodimirska str. 62, 01033 Kiev, Ukraine*
[c]*Institute of Organic Chemistry NAS, Murmanska str. 5, 02094 Kiev, Ukraine*

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Abstract—An interaction of 2-[cyclohexyl(methyl)amino]benzaldehydes with substituted acetonitriles X-CH_2CN (X=CN, Tos, hetaryl) was found to yield 1-methyl-1,2,3,4-tetrahydrospiro(quinoline-2,1′-cyclohexane)-3-carbonitriles. The corresponding spiroquinoline-2,1′-cyclopentane analogues were obtained similarly starting from 2-[cyclopentyl(methyl)amino]benzaldehydes. The reaction was assumed to proceed via initial Knoevenagel condensation and further ring closure of the formed adduct according to the *tert*-amino effect mechanism. The structure of the prepared compounds was confirmed unambiguously by X-ray crystallographic study.

1. Introduction

1,2,3,4-Tetrahydroquinolines have wide pharmaceutical applications.[1,2] A number of 2,2-disubstituted tetrahydroquinoline derivatives occurs in the nature. Thus, the most known are the *Streptomyces* alkaloid virantmycin[3–10] and its related compounds, the benzastatins.[11–13] Moreover a large family of 2-substituted tetrahydroquinoline alkaloids has been isolated recently from the South African plant sources.[14–19] Quinoline-2-spirocycloalkanes form separate group of 2-substituted tetrahydroquinolines. In particular, the quinoline-2-spirocyclohexanes are especially attractive since 1-azaspiro[5,5]undecane moiety is the core of the histrionicotoxines,[20,21] the potent potassium channel blockators from the frog *Dendrobates histrionicus* (Fig. 1). So, the 2-spirotetrahydroquinoline system consists of the substructures of different natural products and, therefore, elaboration of new synthetic approaches to it is the prospective task.

The most suitable method for tetrahydroquinoline-2-spirocyclohexanes preparation was developed by Kouznetsov and co-workers.[22–28] It includes electrophilic cyclization of 1-allyl-1-anilinocyclohexanes readily available from the cyclohexanone derived Schiff bases and allylmagnesium bromide. It seems to be the best approach reported to date and has been successfully applied in the preparation of various natural products analogues.[29–31] However, the method has some limitations. It only allows products unsubstituted at position 3 of the quinoline moiety to be obtained and spiroquinolines bearing electron-withdrawing groups in the benzene ring are hardly available through this approach.[23,25] A few other syntheses of spirocyclic tetrahydroquinolines were also published.[32–35] Furthermore, several approaches to 1,2-dihydroquinoline-2-spirocycloalkanes were reported[36–41] and some of these compounds were reduced into corresponding tetrahydro derivatives.[37,38]

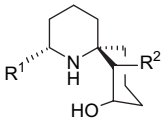

Figure 1. The histrionicotoxines. R^1 and R^2 are C_3–C_4 alkenyl.

The so-called *tert*-amino effect[†] is known as an efficient method of tetrahydroquinoline system formation (Scheme 1).[42–47] Thus, heating of compounds of type **1** in high-boiling polar solvents affords tetrahydroquinoline derivatives **2** in good yields.[42–47] The reaction is assumed to proceed via sigmatropic hydrogen 1,5-shift occurring from the canonic structure **3** and further ring closure of the bipolar intermediate

Keywords: Aldehydes; *tert*-Amino effect; Nitriles; Quinoline; Spiro compounds.
* Corresponding author. Tel./fax: +380445586553; e-mail: atver@univ.kiev.ua

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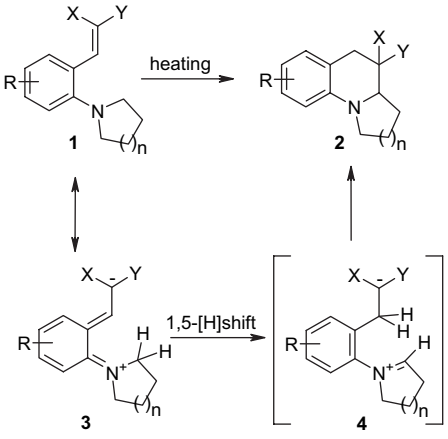
† The term was coined[48,49] to describe this type and related cyclizations.

4.[44–46] The starting materials **1** are obtained easily from the appropriate aldehydes and active methylenes X-CH_2-Y. Recently the *tert*-amino effect has been employed to prepare spirocyclic compounds using cyclic methylene components (Scheme 1, X and Y form a ring), namely the 1,3-cyclohexanedione, the Meldrum's acid, and the barbituric acid derivatives.[50–52] However, the potential of the *tert*-amino effect in the synthesis of spiro compounds is believed not to be exhausted by the use of cyclic methylenes. It seems possible to bring in a spiro-center in position 2 of tetrahydroquinoline following the scheme 1 at the expense of replacement of the pyrrolidine or piperidine moiety by other suitable amine.



Scheme 1. The *tert*-amino effect cyclization. n=1, 2. X and Y are the electron-withdrawing groups.

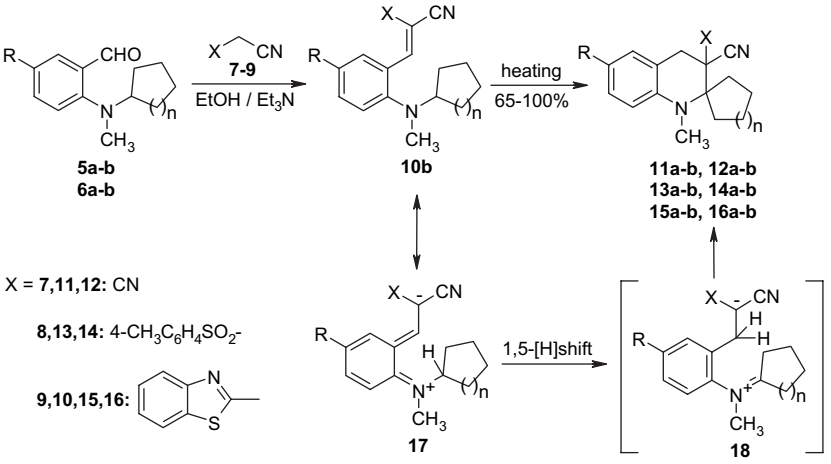
This idea was examined in the course of our research on the *tert*-amino effect[53] and spiro-heterocycles synthesis,[54,55] and the results obtained are reported herein.

2. Results and discussion

The desired aminoaldehydes **5**, **6** (Scheme 2) were prepared from 2-fluoro- and 2-chloro-5-nitrobenzaldehydes and appropriate *N*-methylcycloalkylamines. Treatment of aldehydes **5**, **6** with the nitriles **7–9** in ethanol in the presence of triethylamine was found to give the target spirocyclic quinolines **11–16** in 65–100% yields. In a single case only the reaction product appeared to be Knoevenagel adduct **10b**. Nevertheless, it was also converted into the corresponding quinoline **16b** in quantitative yield by refluxing in DMF. Apparently the derivatives **11–16** are formed according to the *tert*-amino effect mechanism (Scheme 2).[44–46] Thus, the sigmatropic hydrogen 1,5-shift occurring from the canonic structure **17** affords the bipolar intermediate **18**, which undergoes further ring closure into quinolines **11–16**. Moreover, under the conditions of Knoevenagel condensation, the cyclization of the adducts **10** turned out to be fast enough to disable their isolation, except the case of **10b**. At the same time during the previous studies[42–47,53] on the *tert*-amino effect with the same methylene compounds **7–9** and 2-pyrrolidino- or piperidinobenzaldehydes only dinitriles **2** (X=Y=CN) were obtained directly without isolation of the corresponding precursors **1**. For nitriles **8**, **9** the appropriate derivatives **1** were prepared separately and their cyclization required more drastic conditions.[53] Hence, the cycloalkyl(methyl)amino moiety is more reactive toward the *tert*-amino effect cyclization than the pyrrolidine fragment stated hitherto as the most active one.[44–46]

Within the series of compounds **11–16** the five-member derivatives (n=1) were more reactive than the six-member ones (n=2) requiring shorter reaction times and giving higher yields of the products. Furthermore, the nitro substituted compounds (R=NO_2) exhibited lower reactivity toward the cyclization than their unsubstituted analogues (R=H), whereas the nitriles **7–9** could be placed in the following reactivity order: **8**>**7**≫**9**. The latter observations are in complete agreement with the reported data.[44–46,53] Accordingly, compound **10b** is the least reactive sample and, therefore, a higher boiling solvent, DMF is needed for cyclization.

The structure of the prepared compounds **11–16** was initially deduced from ^{1}H and ^{13}C NMR spectroscopic data and then confirmed unambiguously by X-ray crystallographic study carried out for the derivative **14a** (Fig. 2). According to the



Scheme 2. Compounds **5**, **11**, **13**, **15**: n=1; compounds **6**, **10**, **12**, **14**, **16**: n=2. R=**a**: H, **b**: NO_2.

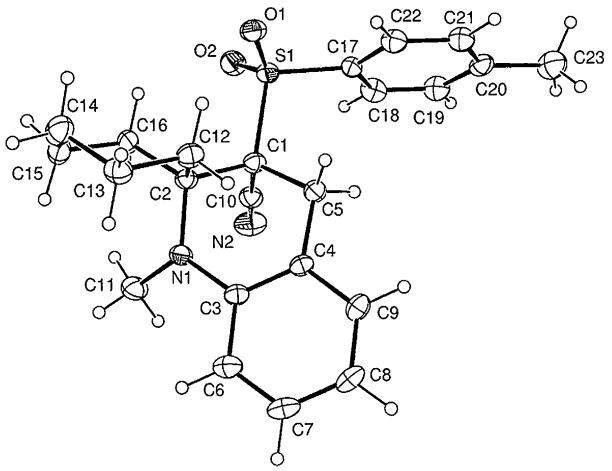


Figure 2. X-ray molecular structure of compound **14a** with the atom numbering used in the crystallographic analysis.

crystal data[‡] the cyclohexane ring adopts chair conformation. The tetrahydropyridine moiety is slightly twisted. Thus, the atoms N1, C3, C4, and C5 are almost coplanar (with precision of 0.05 Å). The atoms C2 and C1 are deviated from this plane at +0.54 Å and −0.28 Å, respectively.

To resume, the present investigation has resulted in a novel approach to 1,2,3,4-tetrahydroquinoline-2-spirocyclopentanes and -cyclohexanes. The cycloalkylamino moiety has been shown to be applicable in the *tert*-amino effect and its reactivity has been compared with that of pyrrolidine.[44–46] A spiro-center has been first generated at the expense of amine fragment during the *tert*-amino effect process. The present synthesis complements well the Kouznetsov's procedure[22–28] since it allows preparation of spiroquinolines substituted at the position 3 unavailable through the known approach.[22–28] Further research on the scope of this method for the preparation of quinolines spiro-fused with other carbo- and heterocycles of different sizes is being carried out and the results will be reported.

3. Experimental

3.1. General

N-Methylcyclopentylamine[56] and 2-benzothiazole-acetonitrile **9**[57] were prepared as reported. Other reagents were commercially available. All melting points were determined in open capillary tubes in a Thiele apparatus and were uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian UNITY*plus* 400 (400 MHz for ^{1}H and 100 MHz for ^{13}C) spectrometer in DMSO-d_6 or $CDCl_3$ solutions. Chemical shifts (δ) are given in parts per million downfield from internal Me_4Si. *J* values are in hertz. The purity of all compounds prepared was checked by ^{1}H NMR and LC/MS on an Agilent 1100 instrument.

[‡] Crystallographic data (excluding structural factors) for the structure in this paper have been deposited at the Cambridge Crystallographic Data Center as supplementary publication number CCDC 604539. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

3.1.1. Aminobenzaldehydes 5a, 6a. Powdered K_2CO_3 (3.04 g, 0.022 mol) was added to a solution of 2-fluorobenzaldehyde (2.48 g, 0.02 mol) and appropriate amine (0.022 mol) in DMF (10 mL) and the resulted mixture was refluxed with stirring for 6 h. After cooling it was poured into water (25 mL) and extracted with EtOAc (2×10 mL). The extract was washed with saturated aqueous NH_4Cl solution, dried (Na_2SO_4), and evaporated in vacuo to give crude compounds **5a**, **6a** as red oils. Further purification by chromatography on silica gel with EtOAc–hexane (1:4, v/v) mixture as eluent afforded derivatives **5a**, **6a** as yellow oils.

3.1.1.1. 2-[Cyclopentyl(methyl)amino]benzaldehyde (5a). Yield 48%. Yellow oil; ν_{max} (KBr) 2931, 2855, 1685, 1595, 1477, 1452, 1386, 1293, 1272, 1191, 1148, 1081, 1003, 942, 832, 760 cm^{-1}. δ_H 1.54–1.84 (8H, m, 4CH$_2$), 2.79 (3H, s, NCH$_3$), 3.64 (1H, m, N-CH<), 7.08 (1H, t, *J*=7.6, 5-H), 7.19 (1H, d, *J*=7.6, 3-H), 7.49 (1H, t, *J*=7.6, 4-H), 7.80 (1H, d, *J*=7.6, 6-H), 10.37 (1H, s, CHO). δ_C 23.1 (2CH$_2$), 29.3 (2CH$_2$), 38.2 (CH$_3$), 62.3 (NCH<), 111.7 (3-C), 122.9 (5-C), 131.4 (6-C), 132.2 (4-C), 134.3 (1-C), 157.1 (2-C), 197.8 (CO). Found: 76.92 C, 8.40 H, 7.04 N; $C_{13}H_{17}NO$ requires 76.81 C, 8.43 H, 6.89 N.

3.1.1.2. 2-[Cyclohexyl(methyl)amino]benzaldehyde (6a). Yield 57%. Yellow oil; ν_{max} (KBr) 2919, 2882, 1680, 1588, 1467, 1447, 1342, 1293, 1251, 1155, 1138, 1081, 991, 987, 871, 797 cm^{-1}. δ_H 1.01–1.02 (3H, m, *c*-hexyl), 1.41–1.50 (2H, m, *c*-hexyl), 1.54–1.57 (1H, m, *c*-hexyl), 1.70–1.78 (4H, m, *c*-hexyl), 2.73 (3H, s, NCH$_3$), 2.94 (1H, m, N-CH<), 6.97 (1H, t, *J*=8.4, 5-H), 7.05 (1H, d, *J*=8.4, 3-H), 7.41 (1H, t, *J*=8.4, 4-H), 7.73 (1H, d, *J*=8.4, 6-H), 10.15 (1H, s, CHO). δ_C 24.1 (CH$_2$), 25.4 (2CH$_2$), 26.8 (2CH$_2$), 42.6 (CH$_3$), 59.1 (NCH<), 115.2 (3-C), 123.7 (5-C), 133.1 (6-C), 133.6 (4-C), 136.4 (1-C), 157.3 (2-C), 198.7 (CO). Found: 77.51 C, 8.66 H, 6.35 N; $C_{14}H_{19}NO$ requires 77.38 C, 8.81 H, 6.45 N.

3.1.2. 2-Amino-5-nitrobenzaldehydes 5b, 6b. Powdered K_2CO_3 (3.04 g, 0.022 mol) was added to a solution of 2-chloro-5-nitrobenzaldehyde (3.71 g, 0.02 mol) and appropriate amine (0.022 mol) in DMF (10 mL) and the resulted mixture was refluxed with stirring for 4 h. After cooling it was poured into water (25 mL) and the solid formed was filtered and recrystallized from *i*-PrOH to yield compounds **5b**, **6b**.

3.1.2.1. 2-[Cyclopentyl(methyl)amino]-5-nitrobenzaldehyde (5b). Yield 63%. Yellow powder; mp 79 °C (from *i*-PrOH); ν_{max} (KBr) 2964, 2864, 1677, 1598, 1507, 1316, 1256, 1158, 1072, 949, 823, 748 cm^{-1}. δ_H 1.55 (2H, m, CH$_2$), 1.71 (4H, m, 2CH$_2$), 1.94 (2H, m, CH$_2$), 2.91 (3H, s, NCH$_3$), 4.14 (1H, m, N-CH<), 7.22 (1H, d, *J*=9.2, 3-H), 8.16 (1H, dd, J^3=9.2, J^4=2.4, 4-H), 8.48 (1H, d, J^4=2.4, 6-H), 9.95 (1H, s, CHO). δ_C 21.3 (2CH$_2$), 24.2 (2CH$_2$), 38.0 (CH$_3$), 63.8 (NCH<), 126.9 (2-C), 128.4 (1-C), 129.5 (4-C), 134.7 (6-C), 138.6 (5-C), 155.5 (2-C), 193.7 (CO). Found: 62.80 C, 6.56 H, 11.20 N; $C_{13}H_{16}N_2O_3$ requires 62.89 C, 6.50 H, 11.28 N.

3.1.2.2. 2-[Cyclohexyl(methyl)amino]-5-nitrobenzaldehyde (6b). Yield 78%. Yellow powder; mp 68 °C (from *i*-PrOH); ν_{max} (KBr) 2925, 2853, 1681, 1602, 1571, 1494, 1328, 1257, 1166, 1069, 1001, 955, 745 cm^{-1}. δ_H 1.17 (1H,

m, *c*-hexyl), 1.36 (2H, m, *c*-hexyl), 1.66 (3H, m, *c*-hexyl), 1.86 (4H, m, *c*-hexyl), 2.91 (3H, s, NCH_3), 3.43 (1H, m, N-CH<), 7.08 (1H, d, *J*=9.6, 3-H), 8.15 (1H, d, *J*=9.6, 4-H), 8.48 (1H, s, 6-H), 9.90 (1H, s, CHO). δ_C 21.5 (CH_2), 24.1 ($2CH_2$), 33.5 ($2CH_2$), 37.4 (CH_3), 66.5 (NCH<), 126.1 (3-C), 128.4 (4-C), 132.2 (6-C), 133.1 (1-C), 136.5 (5-C), 155.4 (2-C), 192.6 (CO). Found: 64.22 C, 6.90 H, 10.77 N; $C_{14}H_{18}N_2O_3$ requires 64.11 C, 6.92 H, 10.68 N.

3.1.3. Spiroquinoline-3,3-dicarbonitriles 11a, 12a. Triethylamine (0.1 mL, 0.7 mmol) was added to a solution of the aldehyde **5a** or **6a** (4 mmol) and malonodinitrile **7** (0.26 g, 4 mmol) in EtOH (5 mL) and the resulted mixture was refluxed for 3 h. After cooling it was diluted with water (15 mL) and a viscous oily material precipitated. The liquid was decanted and the precipitate was chromatographed on silica gel using EtOAc–hexane (1:4, v/v) mixture as eluent. Evaporation of the appropriate fraction and drying the residue in vacuo afforded compounds **11a**, **12a** as yellowish vitreous solids.

3.1.3.1. 1-Methyl-1,2,3,4-tetrahydrospiro(quinoline-2,1′-cyclopentane)-3,3-dicarbonitrile (11a). Yield 76%. Yellowish vitreous solid becoming fluid at 30–35 °C; ν_{max} (KBr) 2955, 2878, 2246, 1601, 1580, 1496, 1456, 1342, 1312, 1178, 763, 748 cm^{-1}. δ_H 1.75–2.20 (8H, m, 2′,3′,4′,5′-CH_2), 3.05 (3H, s, NCH_3), 3.54 (2H, s, 4-CH_2), 6.82 (2H, m, 6,8-H), 7.05 (1H, d, *J*=7.2, 5-H), 7.23 (1H, t, *J*=7.2, 7-H). δ_C 25.0 (3′,4′-C), 34.3 (4-C), 35.0 (2′,5′-C), 35.8 (NCH_3), 40.0 (3-C), 70.3 (2-C), 115.0 (8-C), 115.4 (CN), 115.5 (4a-C), 118.6 (6-C), 128.7 (5-C), 128.8 (7-C), 144.0 (8a-C). Found: 76.60 C, 6.74 H, 16.66 N; $C_{16}H_{17}N_3$ requires 76.46 C, 6.82 H, 16.72 N.

3.1.3.2. 1-Methyl-1,2,3,4-tetrahydrospiro(quinoline-2,1′-cyclohexane)-3,3-dicarbonitrile (12a). Yield 67%. Yellowish vitreous solid becoming fluid at 35–40 °C; ν_{max} (KBr) 2953, 2931, 2862, 2850, 2246, 1603, 1578, 1496, 1456, 1448, 1318, 1043, 767 cm^{-1}. δ_H 1.31 (1H, m, *c*-hexane), 1.53 (2H, m, *c*-hexane), 1.74 (5H, m, *c*-hexane), 2.10 (2H, m, *c*-hexane), 3.25 (3H, s, NCH_3), 3.44 (2H, s, 4-CH_2), 6.82 (1H, t, *J*=8.4, 6-H), 6.93 (1H, d, *J*=8.4, 8-H), 7.00 (1H, d, *J*=8.4, 5-H), 7.20 (1H, t, *J*=8.4, 7-H). δ_C 22.3 (3′,5′-C), 25.0 (4′-C), 31.2 (2′,6′-C), 33.3 (4-C), 38.0 (NCH_3), 40.3 (3-C), 61.4 (2-C), 116.2 (8-C), 117.6 (CN), 118.5 (4a-C), 119.5 (6-C), 128.5 (5-C), 128.9 (7-C), 145.1 (8a-C). Found: 76.76 C, 7.30 H, 15.86 N; $C_{17}H_{19}N_3$ requires 76.95 C, 7.22 H, 15.84 N.

3.1.4. Spiroquinolines 11b, 12b, 13a–b, 14a–b, 15a–b, 16a. General procedure. A solution of the aldehydes **5a–b**, **6a–b** (4 mmol), the nitriles **7–9** (4 mmol), and triethylamine (0.1 mL) in EtOH (5 mL) was heated at reflux for 3–5 h until complete disappearance of the starting aldehyde by TLC data. After cooling the precipitate formed was filtered, washed with cold *i*-PrOH, and recrystallized from an appropriate solvent to give compounds **11b**, **12b**, **13a–b**, **14a–b**, **15a–b**, **16a**.

3.1.4.1. 1-Methyl-6-nitro-1,2,3,4-tetrahydrospiro-(quinoline-2,1′-cyclopentane)-3,3-dicarbonitrile (11b). Yield 79%. Yellow powder; mp 164 °C (from EtOH); ν_{max} (KBr) 2970, 2947, 2882, 1604, 1583, 1504, 1489, 1425, 1338, 1319, 1279, 1186, 961, 937, 750 cm^{-1}. δ_H 1.88 (4H, m, *c*-pentane), 2.09 (4H, m, *c*-pentane), 3.06 (3H, s, NCH_3), 3.86 (2H, s, 4-CH_2), 6.96 (1H, d, *J*=9.2, 8-H), 8.05 (2H, m, 5,7-H). δ_C 25.6 (3′,4′-C), 33.3 (4-C), 34.0 (2′,5′-C), 36.0 (NCH_3), 40.5 (3-C), 70.9 (2-C), 113.0 (CN), 114.9 (8-C), 115.3 (4a-C), 124.7 (5-C), 124.8 (7-C), 137.3 (6-C), 148.9 (8a-C). Found: 64.70 C, 5.40 H, 18.93 N; $C_{16}H_{16}N_4O_2$ requires 64.85 C, 5.44 H, 18.91 N.

3.1.4.2. 1-Methyl-6-nitro-1,2,3,4-tetrahydrospiro-(quinoline-2,1′-cyclohexane)-3,3-dicarbonitrile (12b). Yield 75%. Yellow powder; mp 159 °C (from EtOH); ν_{max} (KBr) 2936, 2245, 1607, 1585, 1511, 1493, 1323, 1288, 1274, 1077, 958, 920, 821, 749 cm^{-1}. δ_H 1.37 (1H, m, *c*-hexane), 1.54 (2H, m, *c*-hexane), 1.81 (5H, m, *c*-hexane), 2.11 (2H, m, *c*-hexane), 3.35 (3H, s, NCH_3), 3.68 (2H, s, 4-CH_2), 7.02 (1H, d, *J*=9.2, 8-H), 8.05 (2H, m, 5,7-H). δ_C 22.3 (3′,5′-C), 24.7 (4′-C), 31.5 (2′,6′-C), 32.8 (4-C), 38.1 (NCH_3), 40.8 (3-C), 62.0 (2-C), 115.4 (8-C), 116.6 (4a-C), 117.3 (CN), 124.6 (5-C), 125.1 (7-C), 138.7 (6-C), 150.5 (8a-C). Found: 65.70 C, 5.65 H, 18.02 N; $C_{17}H_{18}N_4O_2$ requires 65.79 C, 5.85 H, 18.05 N.

3.1.4.3. 1-Methyl-3-[(4-methylphenyl)sulfonyl]-1,2,3,4-tetrahydrospiro(quinoline-2,1′-cyclopentane)-3-carbonitrile (13a). Yield 98%. White crystals; mp 92 °C (from EtOH); ν_{max} (KBr) 2956, 2928, 2865, 1594, 1492, 1456, 1327, 1300, 1150, 1084, 818, 749, 660, 577 cm^{-1}. δ_H 1.65 (1H, m, *c*-pentane), 1.82 (2H, m, *c*-pentane), 1.98 (2H, m, *c*-pentane), 2.22 (1H, m, *c*-pentane), 2.40 (3H, s, CH_3), 2.52 (2H, m, *c*-pentane), 2.96 (3H, s, NCH_3), 3.25 (1H, d, *J*=18.0, 4-H), 3.53 (1H, d, *J*=18.0, 4-H), 6.57 (1H, d, *J*=8.4, 8-H), 6.70 (1H, t, *J*=8.4, 6-H), 6.88 (1H, d, *J*=8.4, 5-H), 7.07 (1H, t, *J*=8.4, 7-H), 7.25 (2H, d, *J*=8.0, Tos), 7.73 (2H, d, *J*=8.0, Tos). δ_C 21.7 (CH_3), 23.0 (3′-C), 24.2 (4′-C), 33.7 (2′-C), 34.4 (4-C), 34.7 (5′-C), 37.4 (NCH_3), 67.1 (3-C), 70.8 (2-C), 115.1 (8-C), 117.4 (4a-C), 117.5 (CN), 118.1 (6-C), 127.7 (5-C), 128.1 (7-C), 129.3 (2,6-C_{Tos}), 130.4 (3,5-C_{Tos}), 133.5 (4-C_{Tos}), 144.5 (8a-C), 146.0 (1-C_{Tos}). Found: 69.50 C, 6.33 H, 7.50 N, 8.33 S; $C_{22}H_{24}N_2O_2S$ requires 69.44 C, 6.36 H, 7.36 N, 8.43 S.

3.1.4.4. 1-Methyl-3-[(4-methylphenyl)sulfonyl]-6-nitro-1,2,3,4-tetrahydrospiro(quinoline-2,1′-cyclopentane)-3-carbonitrile (13b). Yield 91%. Yellow crystals; mp 189–190 °C (from dioxane); ν_{max} (KBr) 2967, 1603, 1588, 1509, 1497, 1313, 1272, 1147, 810, 671, 584 cm^{-1}. δ_H 1.56 (1H, m, *c*-pentane), 1.70 (2H, m, *c*-pentane), 1.85–2.01 (3H, m, *c*-pentane), 2.30 (3H, s, CH_3), 2.37 (2H, m, *c*-pentane), 2.88 (3H, s, NCH_3), 3.70 (1H, d, *J*=18.8, 4-H), 3.80 (1H, d, *J*=18.8, 4-H), 6.55 (1H, d, J^3=9.6, 8-H), 7.27 (2H, d, *J*=8.0, Tos), 7.64 (2H, d, *J*=8.0, Tos), 7.83 (1H, dd, J^3=9.6, J^4=2.0, 7-H), 7.93 (1H, d, J^4=2.0, 5-H). δ_C 21.1 (CH_3), 22.8 (3′-C), 24.4 (4′-C), 32.9 (2′-C), 33.4 (5′-C), 34.1 (4-C), 38.1 (NCH_3), 67.9 (3-C), 70.4 (2-C), 113.3 (CN), 116.7 (4a-C), 117.2 (8-C), 123.4 (5-C), 124.3 (7-C), 129.0 (2,6-C_{Tos}), 130.2 (3,5-C_{Tos}), 132.4 (4-C_{Tos}), 137.4 (6-C), 146.5 (1-C_{Tos}), 149.2 (8a-C). Found: 62.11 C, 5.45 H, 10.03 N, 7.60 S; $C_{22}H_{23}N_3O_4S$ requires 62.10 C, 5.45 H, 9.88 N, 7.54 S.

3.1.4.5. 1-Methyl-3-[(4-methylphenyl)sulfonyl]-1,2,3,4-tetrahydrospiro(quinoline-2,1′-cyclohexane)-3-carbonitrile (14a). Yield 95%. White crystals; mp 204 °C (from

acetonitrile); ν_{max} (KBr) 2947, 2919, 2858, 1594, 1492, 1453, 1325, 1153, 1079, 756, 664, 597, 578 cm^{-1}. δ_H 1.39 (2H, m, *c*-hexane), 1.52 (1H, m, *c*-hexane), 1.64 (1H, m, *c*-hexane), 1.76 (1H, m, *c*-hexane), 1.87 (2H, m, *c*-hexane), 2.03 (1H, m, *c*-hexane), 2.40 (2H, m, *c*-hexane), 2.51 (3H, s, CH_3), 2.63 (1H, d, *J*=17.2, 4-H), 3.22 (3H, s, NCH_3), 3.37 (1H, d, *J*=17.2, 4-H), 6.70 (1H, t, *J*=7.2, 6-H), 6.85 (2H, m, 5,8-H), 7.09 (1H, t, *J*=7.2, 7-H), 7.47 (2H, d, *J*=7.6, Tos), 7.84 (2H, d, *J*=7.6, Tos). δ_C 21.7 (CH_3), 22.1 (3′-C), 22.9 (5′-C), 25.3 (4′-C), 30.5 (2′-C), 32.4 (4-C), 32.9 (6′-C), 38.2 (NCH_3), 64.7 (2-C), 67.0 (3-C), 117.8 (CN), 118.4 (8-C), 118.5 (4a-C), 119.4 (6-C), 128.2 (5-C), 128.8 (7-C), 130.5 (2,6-C_{Tos}), 130.6 (3,5-C_{Tos}), 133.4 (4-C_{Tos}), 145.5 (8a-C), 146.8 (1-C_{Tos}). Found: 70.13 C, 6.60 H, 7.22 N, 8.19 S; $C_{23}H_{26}N_2O_2S$ requires 70.02 C, 6.64 H, 7.10 N, 8.13 S.

3.1.4.6. 1-Methyl-3-[(4-methylphenyl)sulfonyl]-6-nitro-1,2,3,4-tetrahydrospiro(quinoline-2,1′-cyclohexane)-3-carbonitrile (14b). Yield 86%. Yellow crystals; mp 201 °C (from acetonitrile); ν_{max} (KBr) 2931, 1602, 1507, 1486, 1317, 1288, 1269, 1143, 1133, 919, 752, 544 cm^{-1}. δ_H 1.39 (2H, m, *c*-hexane), 1.60 (1H, m, *c*-hexane), 1.67 (1H, m, *c*-hexane), 1.80 (2H, m, *c*-hexane), 2.15 (2H, m, *c*-hexane), 2.30 (2H, m, *c*-hexane), 2.52 (3H, s, CH_3), 2.88 (1H, d, *J*=18.8, 4-H), 3.32 (3H, s, NCH_3), 3.49 (1H, d, *J*=18.8, 4-H), 6.94 (1H, d, *J*=9.2, 8-H), 7.49 (2H, d, *J*=8.0, Tos), 7.84 (2H, d, *J*=8.0, Tos), 7.90 (1H, s, 5-H), 8.00 (1H, d, *J*=9.2, 7-H). δ_C 21.7 (CH_3), 22.3 (3′-C), 22.4 (5′-C), 22.5 (2′-C), 25.0 (4′-C), 30.8 (6′-C), 32.4 (4-C), 38.4 (NCH_3), 64.4 (2-C), 67.2 (3-C), 116.4 (8-C), 117.2 (CN), 118.9 (4a-C), 124.1 (5-C), 125.0 (7-C), 130.6 (2,6-C_{Tos}), 130.7 (3,5-C_{Tos}), 133.0 (4-C_{Tos}), 138.6 (6-C), 147.1 (1-C_{Tos}), 151.2 (8a-C). Found: 62.73 C, 5.84 H, 9.50 N, 7.35 S; $C_{23}H_{25}N_3O_4S$ requires 62.85 C, 5.73 H, 9.56 N, 7.29 S.

3.1.4.7. 3-(Benzothiazol-2-yl)-1-methyl-1,2,3,4-tetrahydrospiro(quinoline-2,1′-cyclopentane)-3-carbonitrile (15a). Yield 81%. Yellowish powder; mp 121 °C (from dioxane); ν_{max} (KBr) 2954, 2915, 2872, 1600, 1578, 1496, 1483, 1454, 1432, 1339, 1312, 760, 729 cm^{-1}. δ_H 1.75 (5H, m, *c*-pentane), 2.07 (3H, m, *c*-pentane), 2.90 (3H, s, NCH_3), 3.50 (1H, d, *J*=17.2, 4-H), 3.79 (1H, d, *J*=17.2, 4-H), 6.73 (1H, t, *J*=7.2, 6-H), 6.86 (1H, d, *J*=7.2, 8-H), 7.03 (1H, d, *J*=7.2, 5-H), 7.15 (1H, t, *J*=7.2, 7-H), 7.42 (1H, t, *J*=8.0, H_X), 7.51 (1H, t, *J*=8.0, H_X), 8.01 (1H, d, *J*=8.0, H_X), 8.05 (1H, d, *J*=8.0, H_X). δ_C 24.9 (3′-C), 25.0 (4′-C), 32.9 (4-C), 34.4 (2′-C), 35.6 (5′-C), 37.3 (NCH_3), 50.3 (3-C), 69.6 (2-C), 113.9 (8-C), 117.8 (4a-C), 118.0 (6-C), 120.9 (CN), 122.1 (4-C_X), 122.9 (7-C_X), 125.7 (6-C_X), 126.4 (5-C_X), 128.1 (5-C), 128.8 (7-C), 135.5 (7a-C_X), 144.1 (8a-C), 150.7 (3a-C_X), 166.7 (2-C_X). Found: 73.60 C, 5.84 H, 11.86 N, 8.74 S; $C_{22}H_{21}N_3S$ requires 73.50 C, 5.89 H, 11.69 N, 8.92 S.

3.1.4.8. 3-(Benzothiazol-2-yl)-1-methyl-6-nitro-1,2,3,4-tetrahydrospiro(quinoline-2,1′-cyclopentane)-3-carbonitrile (15b). Yield 64%. Yellow powder; mp 146 °C (from dioxane); ν_{max} (KBr) 2932, 1604, 1584, 1505, 1494, 1335, 1313, 1262, 1182, 766 cm^{-1}. δ_H 1.55 (1H, m, *c*-pentane), 1.75 (3H, m, *c*-pentane), 1.99 (2H, m, *c*-pentane), 2.23 (2H, m, *c*-pentane), 3.05 (3H, s, NCH_3), 3.78 (1H, d, *J*=17.6, 4-H), 3.90 (1H, d, *J*=17.6, 4-H), 6.98 (1H, d, *J*=9.6, 8-H), 7.45 (1H, t, *J*=8.0, H_X), 7.54 (1H, t, *J*=8.0, H_X), 8.05 (4H, m, 2H_X, 5,7-H). δ_C 25.2 (3′-C), 25.3 (4′-C), 34.1 (NCH_3), 34.7 (2′-C), 36.3 (5′-C), 36.9 (4-C), 49.7 (3-C), 71.3 (2-C), 113.0 (CN), 117.6 (8-C), 120.0 (4a-C), 122.3 (4-C_X), 123.1 (7-C_X), 124.5 (6-C_X), 124.8 (5-C_X), 126.0 (5-C), 126.8 (7-C), 135.0 (7a-C_X), 137.4 (6-C), 149.7 (8a-C), 151.6 (3a-C_X), 165.5 (2-C_X). Found: 65.30 C, 4.90 H, 13.80 N, 7.86 S; $C_{22}H_{20}N_4O_2S$ requires 65.33 C, 4.98 H, 13.85 N, 7.93 S.

3.1.4.9. 3-(Benzothiazol-2-yl)-1-methyl-1,2,3,4-tetrahydrospiro(quinoline-2,1′-cyclohexane)-3-carbonitrile (16a). Yield 69%. Yellowish powder; mp 112 °C (from dioxane); ν_{max} (KBr) 2934, 2856, 1601, 1494, 1454, 1435, 1316, 970, 754, 730 cm^{-1}. δ_H 1.23 (1H, m, *c*-hexane), 1.50 (2H, m, *c*-hexane), 1.67 (4H, m, *c*-hexane), 1.88 (1H, m, *c*-hexane), 2.02 (1H, m, *c*-hexane), 2.18 (1H, m, *c*-hexane), 3.15 (3H, s, NCH_3), 3.53 (1H, d, *J*=17.2, 4-H), 3.64 (1H, d, *J*=17.2, 4-H), 6.76 (1H, t, *J*=7.6, 6-H), 6.88 (1H, d, *J*=7.6, 8-H), 7.03 (1H, d, *J*=7.6, 5-H), 7.17 (1H, t, *J*=7.6, 7-H), 7.38 (1H, t, *J*=8.0, H_X), 7.48 (1H, t, *J*=8.0, H_X), 7.87 (1H, d, *J*=8.0, H_X), 8.02 (1H, d, *J*=8.0, H_X). δ_C 22.5 (3′-C), 22.7 (5′-C), 25.2 (4′-C), 30.3 (2′-C), 32.4 (4-C), 36.2 (6′-C), 37.8 (NCH_3), 51.0 (3-C), 61.6 (2-C), 116.7 (8-C), 118.8 (4a-C), 119.5 (CN), 121.4 (6-C), 122.6 (7-C_X), 123.5 (4-C_X), 126.1 (5-C_X), 127.0 (6-C_X), 128.3 (5-C), 129.0 (7-C), 135.7 (7a-C_X), 145.6 (8a-C), 151.7 (3a-C_X), 167.2 (2-C_X). Found: 73.83 C, 6.25 H, 11.34 N, 8.48 S; $C_{23}H_{23}N_3S$ requires 73.96 C, 6.21 H, 11.25 N, 8.58 S.

3.1.5. 2-(Benzothiazol-2-yl)-3-{2-[cyclohexyl(methyl)-amino]-5-nitrophenyl}-2-propenenitrile (10b). Triethylamine (0.1 mL, 0.7 mmol) was added to a solution of the aldehyde **6b** (1.67 g, 4 mmol) and the nitrile **9** (0.7 g, 4 mmol) in EtOH (5 mL) and the resulted mixture was refluxed for 3 h. After cooling the precipitated solid was filtered and recrystallized from EtOH to yield compound **10b**. Yield 94%. Yellow powder; mp 179–180 °C; ν_{max} (KBr) 2933, 2222, 1601, 1583, 1493, 1328, 1313, 1278, 1172, 1076, 1003, 758 cm^{-1}. δ_H 1.13 (3H, m, *c*-hexyl), 1.54 (1H, m, *c*-hexyl), 1.65–1.78 (4H, m, *c*-hexyl), 1.90 (2H, m, *c*-hexyl), 2.94 (3H, s, NCH_3), 3.19 (1H, m, N-CH<), 7.17 (1H, d, *J*=9.2, 3′-H), 7.45 (1H, t, *J*=7.8, H_X), 7.53 (1H, t, *J*=7.8, H_X), 8.01 (2H, m, 2H_X), 8.20 (2H, m, 4′,6′-H), 8.86 (1H, s, 3-H). δ_C 23.0 (CH_2), 26.7 (2CH_2), 28.8 (2CH_2), 41.5 (CH_3), 61.6 (NCH<), 99.2 (2-C), 116.0 (2′-C), 118.6 (CN), 119.1 (1′-C), 120.9 (7-C_X), 122.4 (6′-C), 125.3 (4-C_X), 125.5 (4′-C), 129.2 (6-C_X), 129.3 (5-C_X), 136.5 (5′-C), 140.6 (7a-C_X), 152.1 (3-C), 153.7 (3′-C), 157.5 (4a-C_X), 164.6 (2-C_X). Found: 66.20 C, 5.36 H, 13.40 N, 7.69 S; $C_{23}H_{22}N_4O_2S$ requires 66.01 C, 5.30 H, 13.39 N, 7.66 S.

3.1.6. 3-(Benzothiazol-2-yl)-1-methyl-6-nitro-1,2,3,4-tetrahydrospiro(quinoline-2,1′-cyclohexane)-3-carbonitrile (16b). A solution of the compound **10b** (0.84 g, 2 mmol) in DMF (5 mL) was heated at reflux for 3 h. After cooling it was poured into water (15 mL) and the precipitate separated was filtered. Recrystallization from dioxane afforded derivative **16b**. Yield 99%. Yellow powder; mp 215–216 °C; ν_{max} (KBr) 2947, 1604, 1584, 1506, 1492, 1320, 1289, 1260, 768, 753 cm^{-1}. δ_H 1.23 (1H, m, *c*-hexane), 1.50 (2H, m,

c-hexane), 1.74 (4H, m, *c*-hexane), 1.90 (1H, m, *c*-hexane), 2.09 (1H, m, *c*-hexane), 2.19 (1H, m, *c*-hexane), 3.28 (3H, s, NCH_3), 3.64 (1H, d, J=16.8, 4-H), 3.82 (1H, d, J=16.8, 4-H), 7.00 (1H, d, J=9.2, 8-H), 7.42 (1H, t, J=8.0, H_X), 7.51 (1H, t, J=8.0, H_X), 7.92 (1H, d, J=8.0, H_X), 8.02 (2H, m, 5-H, H_X), 8.08 (1H, d, J=9.2, 7-H). δ_C 22.4 (3′-C), 22.7 (5′-C), 24.9 (4′-C), 30.4 (2′-C), 32.9 (4-C), 35.5 (6′-C), 38.4 (NCH_3), 51.0 (3-C), 62.7 (2-C), 115.8 (8-C), 119.6 (CN), 120.7 (4a-C), 122.8 (7-C_X), 123.6 (4-C_X), 124.5 (5-C), 125.3 (7-C), 126.4 (6-C_X), 127.2 (5-C_X), 135.5 (7a-C_X), 138.4 (6-C), 151.4 (8a-C), 151.7 (3a-C_X), 166.1 (2-C_X). Found: 65.84 C, 5.39 H, 13.40 N, 7.62 S; $C_{23}H_{22}N_4O_2S$ requires 66.01 C, 5.30 H, 13.39 N, 7.66 S.

References and notes

1. Katritzky, A. R.; Rachwal, S.; Rachwal, B. *Tetrahedron* **1996**, *52*, 15031–15070.
2. Kouznetsov, V.; Palma, A.; Ewert, C.; Varlamov, A. *J. Heterocycl. Chem.* **1998**, *35*, 761–785.
3. Francis, C. L.; Ward, A. D. *Aust. J. Chem.* **1994**, *47*, 2109–2117.
4. Williamson, N. M.; March, D. R.; Ward, A. D. *Tetrahedron Lett.* **1995**, *36*, 7721–7724.
5. Pearce, C. M.; Sanders, J. K. M. *J. Chem. Soc., Perkin Trans. 1* **1990**, 409–411.
6. Morimoto, Y.; Matsuda, F.; Shirahama, H. *Tetrahedron Lett.* **1990**, *31*, 6031–6034.
7. Morimoto, Y.; Matsuda, F.; Shirahama, H. *Synlett* **1991**, 201–203.
8. Hill, M. L.; Raphael, R. A. *Tetrahedron* **1990**, *46*, 4587–4594.
9. Cooper, M. A.; Francis, C. L.; Holman, J. W.; Kasum, B.; Taverner, T.; Tiekink, E. R. T.; Ward, A. D. *Aust. J. Chem.* **2000**, *53*, 123–129.
10. Steinhagen, H.; Corey, E. J. *Org. Lett.* **1999**, *1*, 823–824.
11. Michael, J. P. *Nat. Prod. Rep.* **1997**, 605–618.
12. Kim, W.-G.; Kim, J.-P.; Kim, C.-J.; Lee, K.-H.; Yoo, I.-D. *J. Antibiot.* **1996**, *49*, 20–25.
13. Kim, W.-G.; Kim, J.-P.; Yoo, I.-D. *J. Antibiot.* **1996**, *49*, 26–30.
14. Rakotoson, J. H.; Fabre, N.; Jacquemond-Collet, I.; Hannedouche, S.; Fouraste, I.; Moulis, C. *Planta Med.* **1998**, *64*, 762–763.
15. Houghton, P. J.; Woldemariam, T. Z.; Watanabe, Y.; Yates, M. *Planta Med.* **1999**, *65*, 250–254.
16. Jacquemond-Collet, I.; Hannedouche, S.; Fabre, N.; Fouraste, I.; Moulis, C. *Phytochemistry* **1999**, *51*, 1167–1169.
17. Jacquemond-Collet, I.; Bessiere, J.-M.; Hannedouche, S.; Bertrand, C.; Fouraste, I.; Moulis, C. *Phytochem. Anal.* **2001**, *12*, 312–319.
18. Jacquemond-Collet, I.; Benoit-Vical, F.; Valentin, A.; Stanislas, E.; Mallie, M.; Fouraste, I. *Planta Med.* **2002**, *68*, 68–69.
19. Nakayama, H.; Ferreira, M. E.; de Arias, A. R.; de Bilbao, N. V.; Torres, S.; Schinini, A.; Fournet, A. *Phytother. Res.* **2001**, *15*, 630–632.
20. Kotera, M. *Bull. Soc. Chim. Fr.* **1989**, 370–397.
21. Daly, J. W. *Progress in the Chemistry of Organic Natural Products*; Herz, W., Grisebach, H., Kirby, G. W., Eds.; Springer: Wien, 1982; Vol. 41, p 205.
22. Prostakov, N. S.; Kouznetsov, V. V.; Stashenko, E. E. *Khim. Geterotsikl. Soedin.* **1989**, 1514–1519; *Chem. Heterocycl. Compd. (Engl. Transl.)* **1989**, *25*, 1267–1271.
23. Kouznetsov, V. V.; Aliev, A. E.; Palma, A. R.; Varlamov, A. V.; Prostakov, N. S. *Khim. Geterotsikl. Soedin.* **1991**, 947–952; *Chem. Heterocycl. Compd. (Engl. Transl.)* **1991**, *27*, 756–761.
24. Kouznetsov, V. V.; Palma, A. R.; Fernandes, M.; Aliev, A. E.; Shevtsov, V. K.; Varlamov, A. V.; Prostakov, N. S. *Khim. Geterotsikl. Soedin.* **1991**, 1350–1353; *Chem. Heterocycl. Compd. (Engl. Transl.)* **1991**, *27*, 1080–1083.
25. Kouznetsov, V. V.; Palma, A.; Aliev, A. E.; Fernandes, M.; Prostakov, N. S.; Varlamov, A. V. *Khim. Geterotsikl. Soedin.* **1993**, 784–788; *Chem. Heterocycl. Compd. (Engl. Transl.)* **1993**, *29*, 671–675.
26. Palma, A. R.; Silva, I.; Stashenko, E.; Martinez, J. R.; Kouznetsov, V. *J. Heterocycl. Chem.* **1999**, *36*, 675–680.
27. Kouznetsov, V. V.; Zubkov, F. I.; Nikitina, E. V.; Duarte, L. D. A. *Tetrahedron Lett.* **2004**, *45*, 1981–1984.
28. Zubkov, F. I.; Nikitina, E. V.; Kouznetsov, V. V.; Duarte, L. D. A. *Eur. J. Org. Chem.* **2004**, 5064–5074.
29. Palma, A.; Carrillo, C.; Stashenko, E.; Kouznetsov, V.; Bahsas, A.; Amaro-Luis, J. *Tetrahedron Lett.* **2001**, *42*, 6247–6249.
30. Kouznetsov, V.; Zubkov, F.; Palma, A.; Restrepo, G. *Tetrahedron Lett.* **2002**, *43*, 4707–4709.
31. Palma, A.; Agredo, J. S.; Carrillo, C.; Kouznetsov, V.; Stashenko, E.; Bahsas, A.; Amaro-Luis, J. *Tetrahedron* **2002**, *58*, 8719–8727.
32. Fischer, M.; Wagner, F. *Chem. Ber.* **1969**, *102*, 3486–3494.
33. Ito, Y.; Miyata, S.; Nakatsuka, M.; Saegusa, T. *J. Am. Chem. Soc.* **1981**, *103*, 5250–5251.
34. Paudler, W. W.; Zeiler, A. G.; Goodman, M. M. *J. Heterocycl. Chem.* **1972**, *10*, 423–424.
35. Knolker, H.-J.; Boese, R.; Hartmann, K. *Tetrahedron Lett.* **1991**, *32*, 1953–1956.
36. Barmettler, P.; Hansen, H.-J. *Helv. Chim. Acta* **1990**, *73*, 1515–1573.
37. Hamann, L. G.; Higuchi, R. I.; Zhi, L.; Edwards, J. P.; Wang, X.-N.; Marschke, K. B.; Kong, J. W.; Farmer, L. J.; Jones, T. K. *J. Med. Chem.* **1998**, *41*, 623–639.
38. Dorey, G.; Lockhart, B.; Lestage, P.; Casara, P. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 935–939.
39. Walter, H.; Sauter, H.; Winkler, T. *Helv. Chim. Acta* **1992**, *75*, 1274–1280.
40. Edwards, J. P.; Ringgenberg, J. D.; Jones, T. K. *Tetrahedron Lett.* **1998**, *38*, 5139–5142.
41. Kobayashi, K.; Takabatake, H.; Kitamura, T.; Morikawa, O.; Konishi, H. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 1697–1699.
42. Verboom, W.; Reinhoudt, D. N.; Visser, R.; Harkema, S. *J. Org. Chem.* **1984**, *49*, 269–276.
43. Nijhuis, W. H. N.; Verboom, W.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1987**, *109*, 3136–3138.
44. Groenen, L. C.; Verboom, W.; Nijhuis, W. H. N.; Reinhoudt, D. N.; van Hummel, G. J.; Feil, D. *Tetrahedron* **1988**, *44*, 4637–4644.
45. Nijhuis, W. H. N.; Verboom, W.; El-Fadl, A. A.; Harkema, S.; Reinhoudt, D. N. *J. Org. Chem.* **1989**, *54*, 199–208.
46. Nijhuis, W. H. N.; Verboom, W.; El-Fadl, A. A.; van Hummel, G. J.; Reinhoudt, D. N. *J. Org. Chem.* **1989**, *54*, 209–216.
47. Kelderman, E.; Noorlander-Bunt, H. G.; Van Eerden, J.; Verboom, W.; Reinhoudt, D. N. *Recl. Trav. Chim. Pays-Bas* **1991**, *110*, 115–123.
48. Verboom, W.; Reinhoudt, D. N. *Recl. Trav. Chim. Pays-Bas* **1990**, *109*, 311–324.
49. Meth-Cohn, O.; Suschitzky, H. *Adv. Heterocycl. Chem.* **1972**, *14*, 211–278.
50. Glukhareva, T. V.; Dyachenko, E. V.; Morzherin, Yu. Yu. *Khim. Geterotsikl. Soedin.* **2002**, 1610–1611; *Chem. Heterocycl. Compd. (Engl. Transl.)* **2002**, *38*, 1426–1427.

51. Dyachenko, E. V.; Glukhareva, T. V.; Morzherin, Yu. Yu. *Khim. Geterotsikl. Soedin.* **2003**, 1737–1738; *Chem. Heterocycl. Compd. (Engl. Transl.)* **2003**, *39*, 1532–1533.
52. Dyachenko, E. V.; Glukhareva, T. V.; Nikolaenko, E. F.; Tkachev, A. V.; Morzherin, Yu. Yu. *Izv. Akad. Nauk, Ser. Khim.* **2004**, 1191–1198; *Russ. Chem. Bull.* **2004**, *53*, 1240–1247.
53. Tverdokhlebov, A. V.; Gorulya, A. P.; Tolmachev, A. A.; Kostyuk, A. N.; Chernega, A. N.; Rusanov, E. B. *Synthesis* **2005**, 2161–2170.
54. Tverdokhlebov, A. V.; Resnyanska, E. V.; Zavada, A. V.; Tolmachev, A. A.; Kostyuk, A. N.; Chernega, A. N. *Tetrahedron* **2004**, *60*, 5777–5783.
55. Tverdokhlebov, A. V.; Zavada, A. V.; Tolmachev, A. A.; Kostyuk, A. N.; Chernega, A. N.; Rusanov, E. B. *Tetrahedron* **2005**, *61*, 9618–9623.
56. Neidigh, K. A.; Avery, M. A.; Williamson, J. S.; Bhattacharyya, S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2527–2532.
57. Saito, K.; Kambe, S.; Nakano, Y.; Sakurai, A.; Midorikawa, H. *Synthesis* **1983**, 210–212.

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A new tetrapyrazolic macrocycle. Synthesis and its use in extraction and transport of K^+, Na^+ and Li^+

Smaail Radi,* Abderrahmane Yahyi, Abdelkrim Ramdani, Ismail Zidane and Brahim Hacht

Département de chimie, Faculté des Sciences, Université Med I, Oujda 60 000, Maroc

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Abstract—The synthesis of a new tetrapyrazolic macrocyclic structure with a functionalised arm is described. The complexing properties of this new compound towards alkali metal ions (K^+, Na^+, Li^+) were studied by liquid–liquid extraction and liquid membrane transport processes. The extracted and the transport cation percentage were determined by atomic absorption measurements and UV spectroscopy.

1. Introduction

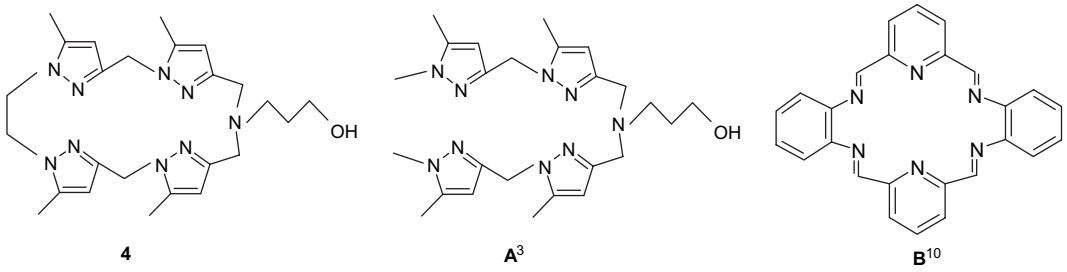
The ability of pyrazole and its derivatives to act as ligands with sp^2 hybrid nitrogen donors is evident from the large number of articles, several of them being reviews.[1,2] In our recent works, a series of acyclic pyrazole compounds containing one, two, three or four pyrazole rings were prepared and demonstrated to extract only transition metal cations[3–6] whereas macrocyclic pyrazolic compounds are expected to also form stable complexes with alkali metals.[7,8]

We now describe the synthesis of a new tetrapyrazolic macrocycle **4** (Fig. 1) containing a mobile chain with a donor heteroatom and its binding ability (extraction and transport) towards alkali metal ions. The presence of a functional mobile chain also provides this structure with the possibility of being immobilised on the surface of a solid material (organic resin or silica gel) by covalent bonding.

2. Results and discussion

Our strategy was to develop a simple and high yielding procedure, in only a few steps, to prepare the desired macrocycle compound. The result of our investigation is given below (Scheme 1). The preparation in good yield of *N*-(3-chloromethyl-5-methylpyrazolyl)-4-methylpyrazolyl methane **2** from 3(5)-carboxymethyl-5(3)-methylpyrazole **1** has been already reported[9] in the literature. The reaction of compound **2** with 3-aminopropanol in THF using sodium bicarbonate as base leads to the tetrapyrazolic structure **3** in a 70% yield. The final cyclisation step was carried out under liquid–liquid phase transfer catalysis conditions and the target macrocycle **4** was formed in a 20% yield.

Structures of all compounds were determined on the basis of the corresponding analytical and spectroscopic data.



4 **A**[3] **B**[10]

Figure 1. New tetrapyrazolic macrocycle **4** and literature compounds **A** and **B**.

Keywords: Macrocycle; Liquid–liquid extraction; Liquid membrane; Transport; Cations.
* Corresponding author. Tel.: +212 36 50 06 01; fax: +212 36 50 06 03; e-mail: radi_smaail@yahoo.fr

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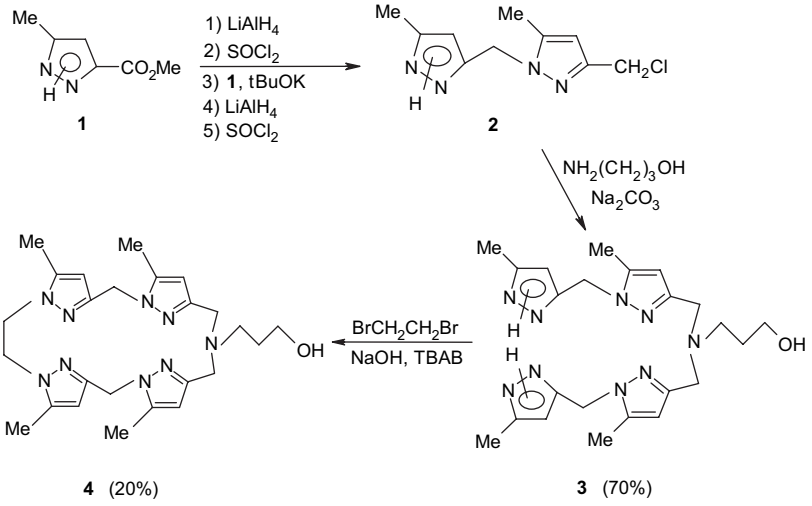

Scheme 1. Preparation steps of compound **4**.

2.1. Liquid–liquid extraction of individual cations

We used this method in order to study the relative capabilities of macrocycle **4** in extracting Li^+, Na^+ and K^+ cations. Metal picrates were extracted into the organic phase by complex formation with the macrocycle; the decrease in absorbance of the picrate in the aqueous phase was followed by UV spectroscopy. The percentage limits of extraction are given in Table 1.

Table 1. Yields of extraction of alkali metal ions

	Potassium (1.33 Å)	Sodium (0.98 Å)	Lithium (0.60 Å)
4	50	38	38
A	0	0	0
B	0	0	0

A: acyclic pyrazolic compound.[3]
B: macrocycle with pyridine-type sp^2 nitrogens.[10]

In order to show that the macrocycle does not simply protonate in the presence of metal picrates, we have determined the extracted cation percentage by atomic absorption measurements and the same results were found.

The results in Table 1 show that in analogy to our previous works[3–8] in which acyclic pyrazolic compound **A** with a weak affinity for alkali cations led to no extraction properties and pyrazolic macrocycles were expected to form stable complexes, again this new macrocycle **4** shows better extraction percentages for alkali cations.

We noticed a high affinity for all alkali metal cations, especially for potassium. This is undoubtedly related to the size of the cavity, which is possibly enlarged at the junctions between pyrazole units. The ionic radii and the flexibility of the macrocycle also enable cation binding with a possible contribution from the side arm.

The complexing power of this pyrazolic macrocycle was attributed to the existence of sp^2 lone pairs forming an electronegative internal cavity. In order to verify this, we compared a known[10] cyclic structure **B**, which possesses pyridine-type sp^2 nitrogens with an internal cavity of a comparable size, with a synthesized macrocycle **4** and it gave negative results regardless of the cation used (Li^+, Na^+ or K^+). This serves to emphasise the novel complexation properties of the macrocycle structures containing linked pyrazole groups, and indicates that the shape of the macrocyclic cavity of **4** must play an important role.

2.2. Transport of individual cations across a membrane

As an extension of the ability of this macrocycle to extract or release (according to the conditions) alkali metal cations, its role as transfer agent across a liquid membrane was studied.

These experiments were performed using the Schulman bridge method.[11] In each case there was no transfer of picrate ion across the membrane in the absence of the macrocycle.

In the presence of macrocycle, the transfer rates were calculated (from the linear part of the curve) and are given in Table 2.

Table 2. Cation transport rates ($\times 10^{-6}$ mol/h) across a liquid membrane

	Potassium (1.33 Å)	Sodium (0.98 Å)	Lithium (0.60 Å)
4	0.23	0.12	0.06

The results in Table 2 show that in analogy to the extraction yield, the potassium cation, which is well extracted (50%), has a higher rate of transport. This means that this cation, which is better extracted also is better transported, one can say that transport is determined by complex lipophilicity.

However, Li^+ and Na^+, which have identical percentage of extraction (38%), have different rates of transport. It is 0.12×10^{-6} mol/h for Na^+ and only half this for Li^+ (0.06×10^{-6} mol/h). This suggests that the stability constant of ligand–cation is higher in the case of lithium than in the case of sodium and consequently the Na^+ is more easily decomplexed in the receiving aqueous phase. We can thus say that the phenomenon of transport for these cations (Li^+ and Na^+) is simply controlled by the decomplexation step.

3. Conclusion

In conclusion, we have prepared a new tetrapyrazolic macrocycle, which has an unusual aptitude for formation of complexes with alkali cations. It has been demonstrated that this macrocycle particularly extracts and transports K^+ ions.

4. Experimental

4.1. General

All solvents and other chemicals, obtained from usual commercial sources, were of analytical grade and used without further purification. The proton NMR spectra were obtained with a Bruker AC 300 spectrometer. Elemental analyses were performed by Microanalysis Central Service (CNRS). Molecular weights were determined on a JEOL JMS DX-300 Mass Spectrometer. Picrate absorbances were measured with a Philips PU 8620 Spectrophotometer. Atomic absorption measurements were performed by Spectra Varian A.A. 400 Spectrophotometer.

4.1.1. Synthesis of 3. A mixture of compound **2**[9] (1.75 g, 7.8×10^{-3} mol), 3-aminopropanol (0.293 g, 3.9×10^{-3} mol) and sodium carbonate (4.96 g, 46.8×10^{-3} mol) in THF (100 mL) was stirred under reflux for 20 h. The mixture was then filtered, evaporated and the residue was separated on alumina using CH_2Cl_2/EtOH (90/10) as eluent to give a 70% yield of **3** as yellow oil. R_f=0.60 CH_2Cl_2/EtOH (9/1); ^{1}H NMR ($CDCl_3$) δ: 1.82 (m, 2H); 2.22 (s, 6H); 2.26 (s, 6H); 2.74 (t, 2H, J=6.2 Hz); 3.57 (s, 4H); 3.74 (m, 2H); 5.17 (s, 4H); 5.90 (s, 2H); 6.00 (s, 2H). Anal. Calcd for $C_{23}H_{33}N_9O$: C, 61.19; H, 7.31; N, 27.93. Found: C, 61.14; H, 7.40; N, 27.90; *m/z*: 451 (M^+); IR: ν(OH)=3300 cm^{-1}, ν(NH)=3140 cm^{-1}, ν(tertiary nitrogen)=1120 cm^{-1}.

4.1.2. Synthesis of macrocycle 4. To a mixture of **3** (2.12 g, 4.7×10^{-3} mol) and 1,2-dibromoethane (0.89 g, 4.7×10^{-3} mol) in toluene (500 mL) was added a concentrated solution of NaOH (2 g of NaOH in H_2O (2 mL)). The mixture was stirred under reflux for 20 h in the presence of a catalytic quantity of tetrabutyl ammonium bromide. The resulting mixture was then filtered, evaporated and separated on alumina using CH_2Cl_2/EtOH (95/5) as eluent to give a 20% yield of **4** as yellow oil. R_f=0.40 CH_2Cl_2/EtOH (9.5/0.5); ^{1}H NMR ($CDCl_3$) δ: 1.79 (m, 2H); 2.24 (s, 12H); 2.66 (t, 2H, J=6.2 Hz); 3.60 (s, 4H); 3.81 (m, 2H); 4.10 (s, 4H); 5.17 (s, 4H); 5.82 (s, 2H); 6.00 (s, 2H). Anal. Calcd for $C_{25}H_{35}N_9O$: C, 62.89; H, 7.33; N, 26.41. Found: C, 62.85; H, 7.35; N, 26.39; *m/z*: 477 (M^+); IR: ν(OH)=3250 cm^{-1}, ν(C=N)=1615 cm^{-1}, ν(C=C)=1575 cm^{-1}, ν(tertiary nitrogen)=1120 cm^{-1}.

4.2. Extraction experiments

A solution of 7×10^{-5} M of macrocycle in CH_2Cl_2 (50 mL) was stirred for 2 h with an aqueous solution (50 mL) of metal picrates 7×10^{-5} M; the complexation was followed first by measuring the picrate anion concentration in the aqueous phase by UV spectroscopy at 355 nm, second by measuring the concentration of cations in the aqueous phase by atomic absorption. The temperature remained constant during all the experiments at 25 °C and at pH 7 measured by a pH-meter. This was explained by the absence of nitrogen protons in macrocycle and by the low alkalinity and concentration of picrate ions exchanged.

4.3. Transport experiments

The apparatus used in the method of Schulman bridge[11] contains three phases. Phase I: aqueous solution (6 mL) of nitrate (10^{-1} mol/L) and alkali cation picrate (2×10^{-3} mol/L). Phase II: chloroform solution (50 mL) of the product to be studied (7×10^{-4} mol/L). Phase III: distilled water (24 mL).

References and notes

1. Trofimenko, S. *Chem. Rev.* **1972**, *72*, 497–509.
2. Trofimenko, S. *Prog. Inorg. Chem.* **1986**, *34*, 115–210.
3. Radi, S.; Ramdani, A.; Lekchiri, Y.; Morcellet, M.; Crini, G.; Morcellet, J.; Janus, L. *Eur. Polym. J.* **2000**, *36*, 1885–1892.
4. Radi, S.; Ramdani, A.; Lekchiri, Y.; Morcellet, M.; Crini, G.; Janus, L.; Bacquet, M. *New J. Chem.* **2003**, *27*, 1224–1227.
5. Malek, F.; Ramdani, A.; Radi, S. *J. Chem. Res.* **2004**, *9*, 640–641.
6. Malek, F.; Ramdani, A.; Zidane, I.; Yahyi, A.; Radi, S. *Tetrahedron* **2005**, *61*, 2995–2998.
7. Radi, S.; Ramdani, A.; Lekchiri, Y.; Morcellet, M.; Crini, G.; Morcellet, J.; Janus, L. *J. Chem. Res.* **2003**, *11*, 712–714.
8. Radi, S.; Ramdani, A.; Lekchiri, Y.; Morcellet, M.; Crini, G.; Janus, L. *Tetrahedron* **2004**, *60*, 939–942.
9. Fifani, J.; Ramdani, A.; Tarrago, G. *New J. Chem.* **1977**, *1*, 521–528.
10. Ramdani, A.; Tarrago, G. *Tetrahedron* **1981**, *37*, 991–1000.
11. Kobuke, Y.; Hanji, K.; Horiguchi, K.; Asada, M.; Nakayama, Y.; Furukawa, J. *J. Am. Chem. Soc.* **1976**, *98*, 7414–7419.

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Synthesis, crystal structures and the preliminary evaluation of the new dibenzotetraaza[14]annulene-based DNA/RNA binding agents

Dariusz Pawlica,[a] Marijana Radić Stojković,[b] Lesław Sieroń,[c] Ivo Piantanida[b] and Julita Eilmes[a,*]

[a]*Department of Chemistry, Jagiellonian University, Ingardena 3, 30-060 Kraków, Poland*
[b]*Laboratory for Supramolecular and Nucleoside Chemistry Ruđer Bošković Institute, PO Box 180, HR-10002 Zagreb, Croatia*
[c]*Institute of General and Ecological Chemistry, Technical University of Łódź, Żeromskiego 116, 90-924 Łódź, Poland*

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Abstract—A series of water-soluble dicationic dibenzotetraaza[14]annulenes have been prepared in order to examine their interactions with nucleic acids. Pendant water-solubilizing *N*-pyridinium, 4,4′-bipyridinium and *N*-methyl pyridinium moieties have been attached to the central core via linkers generated by direct N-alkylations and ester creating couplings, respectively. The crystal structures of derivatives equipped with 3-(*N*-pyridinium-1-yl)propyl and 3-(4,4′-bipyridinium-1-yl)propyl substituents have been determined. Interactions with *ct*-DNA have been studied and evidenced by means of spectrophotometric titrations with Scatchard analysis and thermal denaturation experiments.

1. Introduction

Dibenzotetraaza[14]annulenes (Fig. 1) are among the most extensively studied synthetic macrocycles.[1] The attention which has been focused on these macrocyclic compounds arose mainly from their resemblance to porphyrins, and consequently, from their relevance in bioinorganic chemistry[2] and materials science.[3] Similarly to porphyrins, they have four coplanar nitrogen donor atoms and a number of double bonds with substantial π delocalization (benzenoid rings and 1,3-diiminato fragments). Unlike porphyrins, dibenzotetraaza[14]annulenes are Hückel anti-aromatic (4*n*) and have a 14-membered inner ring as compared to the larger 16-atom inner porphyrin ring.[4] It is of importance for the potential applications of dibenzotetraaza[14]annulenes that they are relatively easy to synthesize,[5] highly reactive at the *meso* positions[6] and capable of accommodating various substituents on the phenylene rings and diimine carbons. In addition, crystallography reveals that they adopt various conformations ranging from planar to saddle shaped, depending on the ring substitution.[7] Accordingly, as ligands for transition metals and main group elements, they offer a wide variety of coordination modes and geometries.[7] Thus it appears that the structure and properties of dibenzotetraaza[14]annulenes can easily be tuned through the careful choice of peripheral substituents and inserted metal ions. They therefore seem to be very attractive for the design and synthetic elaboration of tailor-made drugs for biomedical applications.

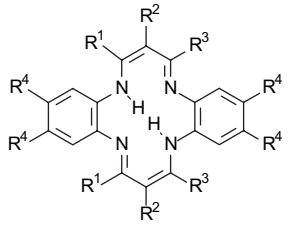

Figure 1.

In this paper we report on the preparation, structure and preliminary evaluation of novel dibenzotetraaza[14]annulene-based DNA/RNA binders. There is no data, as of yet, in the literature on the similar applications of dibenzotetraaza[14]annulenes. In contrast, porphyrins, to which they are often compared, belong to the most often and successfully explored systems in this area, capable of interacting with DNA via intercalation, minor/major groove binding[8] as well as in some cases through outside binding of self-stacked helically organized porphyrin oligomers.[9] Also other macrocycles and their metal complexes have been widely employed in studies focused on similar biomedical applications.[10]

Keywords: Dibenzotetraaza[14]annulenes; Water-solubilizing groups; Synthesis; Crystal structure; DNA binding; UV–vis titration; DNA thermal denaturation.
* Corresponding author. Tel.: +48 12 6632294; fax: +48 12 6340515; e-mail: jeilmes@chemia.uj.edu.pl

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We have chosen the β-unsubstituted macrocycles, known for their planar conformation,[11] as the central core of potential DNA intercalators/binding agents. Water-solubilizing cationic groups based on pyridinium and bipyridinium moieties have been linked to the main framework through spacers of variable lengths, flexibility and chemical characteristics. The molecules thus designed possess appropriate molecular sizes, planar chromophores and positively charged centres at the ends of the side chains linked to the *meso* positions. They are therefore expected to offer diverse modes of supramolecular interactions with nucleic acids. First of all, the central flat part of these molecules can insert and stack between base pairs of double helical DNA, in this function they can resemble porphyrin-based DNA binders. Pendant cationic residues that are important for generating water solubility provide centres of electrostatic and cation to π supramolecular interactions. They are independent, in fact, from the central planar core since the linkers are mainly aliphatic, relatively long and flexible. External electrostatic interactions between cationic moieties and anionic phosphate backbone can also be expected, as well as additional noncovalent forces generated by ester-function-containing linkers. A question arises also as to whether dibenzotetraaza[14]annulene derivatives will exhibit a tendency of self-aggregation on the nucleic acids backbone, similarly to their porphyrin analogs.[9] It seems reasonable to expect that features that make dibenzotetraaza[14]annulenes different from porphyrins (i.e., smaller coordination cavity size, anti-aromaticity and flexibility of the ring) will be of significance in modifying their interactions with nucleic acids, as compared to their porphyrin-based analogues.

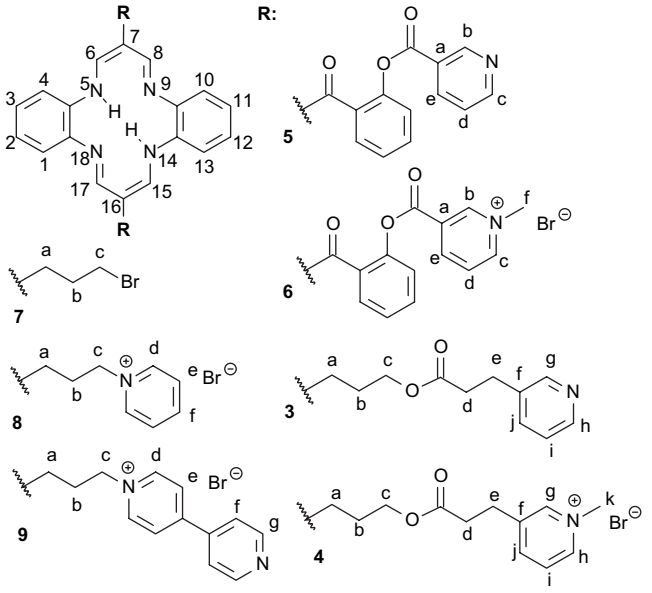


Figure 2. Potential DNA/RNA binding agents **4**, **6**, **8** and **9**, and other new derivatives of dibenzotetraaza[14]annulene.

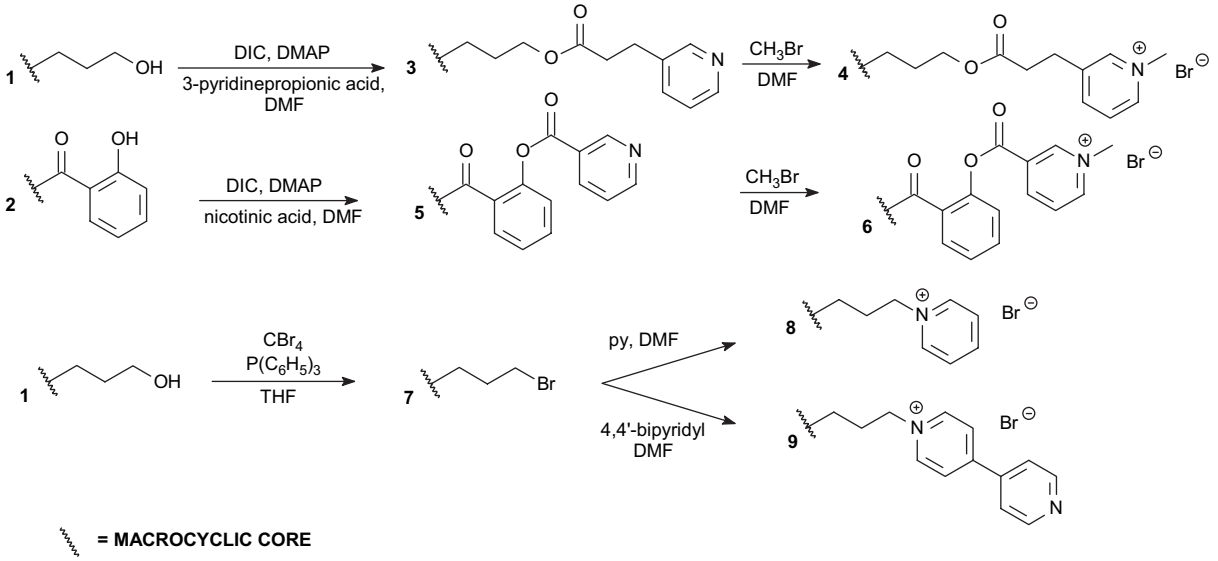
Finally, it is relevant to note that the possible metallation of these new macrocyclic ligands with various metal ions can give rise to complexes with new metal-centre-dependent properties, such as specificity in targeting DNA sites. Appropriately chosen central metal ions may allow the preparation of complexes able to selectively break DNA strands.[12]

Potential DNA/RNA binding agents **4**, **6**, **8**, **9** and other new derivatives of dibenzotetraaza[14]annulene synthesized in this work are shown in Figure 2. Scheme 1 outlines the reactions performed.

2. Results and discussion

2.1. Synthesis

To synthesize water-soluble dicationic products **4**, **6**, **8** and **9** we have used dibenzotetraaza[14]annulenes **1**[13] and **2**[14] as substrates and employed the reactivities of OH groups at their *meso* substituents. Thus, ester-linkages-creating couplings between the OH groups of **1** and COOH group of 3-pyridinepropionic acid allowed 3-hydroxypropyl of **1** to be transformed into 3-(3-pyridyl)propionyloxypropyl. Similarly, the phenolic OH groups of the substrate **2** have been esterified by means of nicotinic acid to give corresponding



Scheme 1.

(3-pyridyl)carbonyloxybenzoyl derivatives. Coupling procedures using diisopropylcarbodiimide (DIC) as a dehydrating agent[15] and dimethylaminopyridine (DMAP) as an acylation catalyst[16] were successfully employed in both cases affording products **3** and **5** in fair yields of 72% and 87%, respectively. In the next steps, **3** and **5** have been methylated by means of bromomethane giving **4** and **6** in yields of 75% and 81%, respectively.

To synthesize dicationic products **8** and **9**, substrate **1** has been transformed to **7** with the use of a PPh_3–CBr_4 mixture.[17] Bis(bromopropyl)dibenzotetraaza[14]annulene **7** was then reacted with pyridine and 4,4′-bipyridine to give **8** and **9** in reasonable yields of 63% and 71%, respectively.

All new products have been characterized by elemental analysis, ^{1}H and ^{13}C NMR, ESI-MS and IR data. ^{1}H and ^{13}C NMR signals with their assignments and other spectroscopic and analytical data are collected in Section 4.

2.2. Crystallography

The structures of compounds **8** and **9** with the atomic numbering scheme are shown in Figures 3 and 4. Crystal data and structural refinement details are given in Table 1.

Both compounds crystallize in the $P2_1/c$ space group with two molecules per unit cell. The central 14-membered ring of the macrocyclic cation of each compound has a planar conformation and lies across a centre of inversion. The macrocyclic rings are not ideally planar. The distortion from planarity is up to 0.45(2) Å for N1 atom of **8**, and 0.044(2) Å for C7 atom of **9**.

The difference in the Fourier map analysis of **8** exhibited two peaks located in the expected positions of H amine atoms that refer to the separation between the two half-proton positions and indicate the presence of two tautomeric states of a tetraaza[14]annulene ring.[11c] In the structure of **9** at 90 K, only one peak corresponding to the H amine atom was found. The aliphatic chains in both compounds adopt nearly planar extended conformations with torsion angles: C9–C10–C11–C12 of 178.0(2)° and 174.8(3)°, and C10–C11–C12–N3 of −169.7(2)° and 167.4(2)° for **8** and **9**, respectively. In the crystal structure of **9**, the bipyridinium moiety is slightly twisted, with an interplanar angle of 9.9(1)° between the two pyridine rings.

The supramolecular structure of compound **8** is defined by C–H···Br, C–H···π and π···π stacking interactions between the ions, as shown in Figure 5. The two π···π-bonded

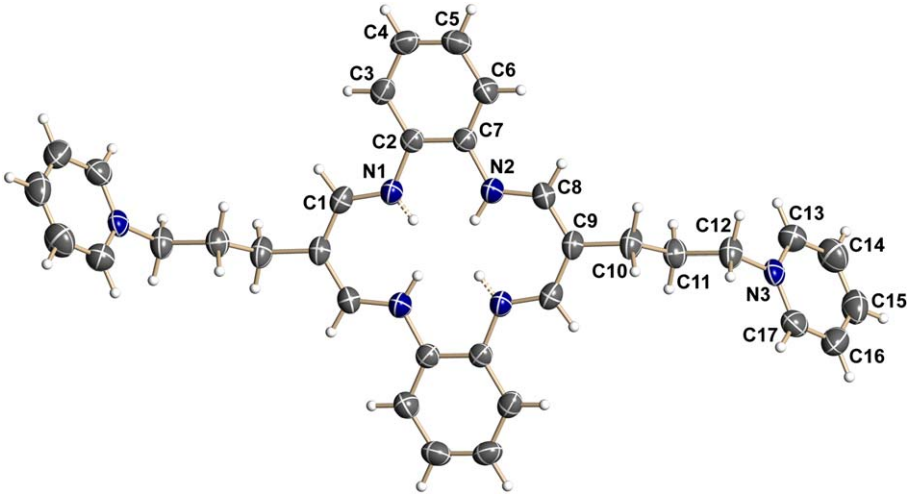


Figure 3. The structure of macrocyclic cation of **8** at 290 K, showing 50% probability displacement ellipsoids with the atom numbering scheme.

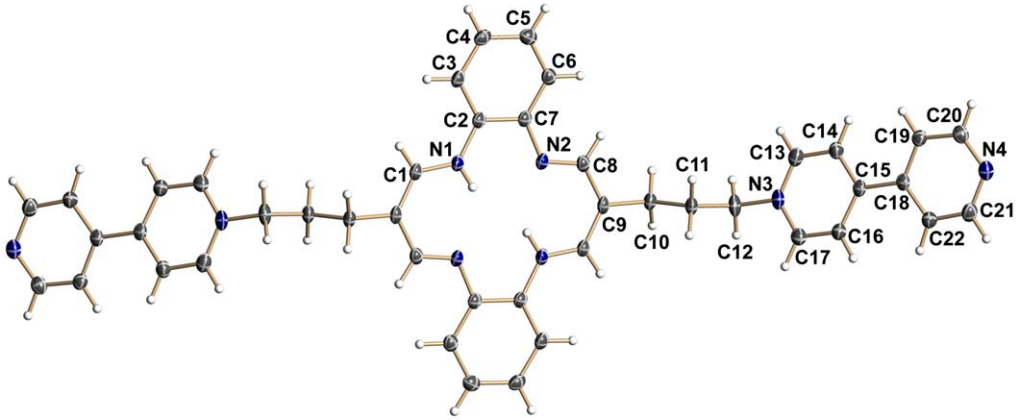


Figure 4. The structure of macrocyclic cation of **9** at 90 K, showing 50% probability displacement ellipsoids with the atom numbering scheme.

Table 1. Crystal data and structural refinement details for **8** and **9**

	8	**9**
Empirical formula	$C_{34}H_{36}N_6^{2+}\cdot 2Br^-$	$C_{44}H_{42}N_8^{2+}\cdot 4H_2O\cdot 2Br^-$
Formula weight	688.49	914.74
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/c$
a (Å)	14.0767(14)	7.6302(2)
b (Å)	8.3116(9)	18.7942(4)
c (Å)	15.4211(17)	14.8324(3)
β (°)	122.314(11)	101.1100(10)
V (Å^3), Z	524.8(3), 2	2087.16(8), 2
d_{calc} (g/cm^3)	1.500	1.456
F(000)	704	944
Temperature (K)	290	90
Radiation type, wavelength (Å)	Mo Kα, 0.71073	Cu Kα, 1.54178
Absorption coefficient (mm^{-1})	2.693	2.893
Theta range (°)	2.64–25.00	3.84–69.98
Limiting indices, h, k, l	$-16\rightarrow13$, $-9\rightarrow9$, $-16\rightarrow16$	$-8\rightarrow9$, $-22\rightarrow22$, $-17\rightarrow18$
Reflections collected	6887	22623
Independent reflections	2514	3935
Data/restraints/parameters	2514/190/0	3935/282/5
Goodness-of-fit on F^2	1.000	1.093
Final R indices [$I>2\sigma(I)$]	R=0.0315, wR^2=0.0901	R=0.0474, wR^2=0.1363
Final R indices [all data]	R=0.0402, wR^2=0.0925	R=0.0475, wR^2=0.1364
Largest diff. peak and hole ($e\cdot$Å^{-3})	0.39, −0.49	1.36, −1.20

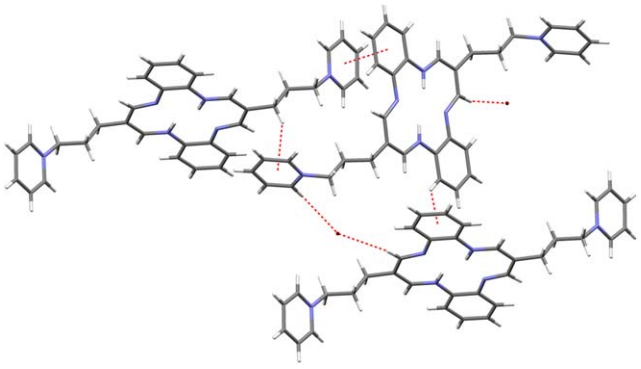


Figure 5. The intermolecular C–H···Br, C–H···π and π···π stacking interactions in **9**, shown as dashed lines.

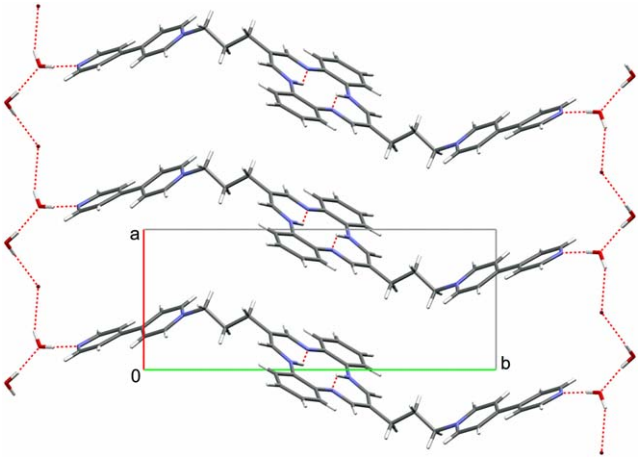


Figure 6. The one-dimensional hydrogen-bonded ladder motif in **9**, running along the *a*-axis.

benzene rings N3/C(13–17) and C(2–7) are almost fully eclipsed with a centroid–centroid distance of 3.446(2) Å. The results agree well with the recent reports showing that in the absence of strong hydrogen-bond donors, C–H···π and π···π interactions often play an important role in the supramolecular assembly of aromatic compounds.[18]

In contrast, structure **9** is stabilized mainly by a network of O–H···N, O–H···O and O–H···Br hydrogen bonds. Hydrogen bonds involving water molecules and bromide anions lead to the formation of infinite one-dimensional chains. The cation moieties link these chains via O–H···N hydrogen bonds in a supramolecular ladder motif, running along the *a*-axis, as represented in Figure 6.

The hydrogen-bond interactions observed in the structures are summarized in Table 2.

2.3. UV–vis spectroscopy, binding to *ct*-DNA

Compounds **4**, **6**, **8** and **9** are moderately soluble in pure water and somewhat less in an aqueous buffered system (in the range of $c=1\times10^{-3}$ mol dm^{-3}), probably due to the higher ionic strength. The UV–vis tests showed compounds **4**, **8** and **9** to be stable in an aqueous solution within the temperature range of 25–90 °C for at least one week, whereas the spectrum of the freshly prepared aqueous solution **6** substantially changed over the time, even in deoxygenated conditions. Since no precipitation was observed, and solution **6** was stable in the dark, the chemical decomposition of **6** was most likely taking place under UV–vis irradiation. A structure comparison of unstable **6** and stable **4**, **8** and **9** suggested that the aromatic ester bonds of **6** were decomposing. The product **6** was therefore not used in further studies. The UV–vis absorbance of buffered aqueous solutions of **4**, **8** and **9** was proportional to their concentration up to 5×10^{-5} mol dm^{-3}, indicating no significant intermolecular stacking. Absorption maxima of **4**, **8** and **9** and the corresponding molar extinction coefficients are given in Table 3.

The interactions of **4**, **8** and **9** with *ct*-DNA were examined by spectrophotometric titrations and thermal denaturation experiments, exemplified by Figures 7 and 8, respectively.

Table 2. The hydrogen-bond interactions (Å, °)

D–H···A	H···A	D···A	∠ D-H···A	Symmetry code (#)
8				
N1–H2′···N2$^{\#}$	2.12	2.758(3)	131	$-x$, $-y+1$, $-z+1$
N2–H2···N1$^{\#}$	2.11	2.758(3)	132	$-x$, $-y+1$, $-z+1$
C1–H1···Br1$^{\#}$	2.87	3.713(3)	151	$-x$, $-y+1$, $-z+1$
C13–H13···Br1$^{\#}$	2.99	3.890(2)	162	x, $-y+½$, $z-½$
C6–H6···C_g(1)$^{\#}$	3.04	3.817(3)	142	$-x$, $y-½$, $-z+½$
C10–H10B···C_g(1)$^{\#}$	2.89	3.711(3)	143	$-x+1$, $y-½$, $-z+^3/_2$
9				
N1–H1···N(2)$^{\#}$	2.11	2.788(3)	133	$-x$, $-y+1$, $-z$
O1–H01···Br1$^{\#}$	2.54	3.381(2)	177	$-x+1$, $y+½$, $-z+½$
O1–H102···O2$^{\#}$	1.87	2.699(4)	172	$x+1$, y, z
O2–H201···N4$^{\#}$	1.99	2.818(4)	170	x, $-y+½$, $z-½$
O2–H202···Br1$^{\#}$	2.53	3.310(3)	154	$-x+1$, $y+½$, $-z+½$
C10–H10A···C_g(2)$^{\#}$	2.60	3.362(3)	134	$-x+1$, $y+½$, $-z+½$

C_g(1)=N3/C13/C14/C15/C16/C17; C_g(2)=C2/C3/C4/C5/C6/C7.

Table 3. Electronic absorption maxima and corresponding molar extinction coefficients of **4**, **8** and **9**[a]

	λ_{max}/nm	$\varepsilon\times10^3$/dm^3 mol^{-1} cm^{-1}
4	265	28.6
	383	34.6
	443	11.3
	447	11.2
8	263	29.79
	379	34.88
	427	12.29
9	258	49.67
	385	25.53
	431	11.45
	448	11.62

[a] Sodium cacodylate buffer, I=0.05 mol dm^{-3}, pH=7.

Titration data were processed according to Scatchard equation.[19] The results of all experiments are collected in Table 4.

The addition of *calf thymus* (*ct*)-DNA yielded strong bathochromic and hypochromic effects in UV–vis spectra of **4** and **8** (Fig. 7, Table 4) but only very weak changes in the UV–vis spectrum of **9** (Table 4). Binding constants (log K_s) and ratios n (Table 4) calculated by Scatchard equation can be considered only as the cumulative values since deviation from the isosbestic points in UV–vis titrations can be observed (Fig. 7), which implies the co-existence of various types of complexes.

In thermal denaturation experiments, the addition of **4** and **8** stabilized the *ct*-DNA double helix, whereas the addition of **9** again did not show any measurable impact on the *ct*-DNA melting temperature. The stabilizing influence of **8** was found to be higher than that of **4**.

One could expect that, similarly to the porphyrins, dibenzotetraaza[14]annulenes **4**, **8** and **9** would base their interactions with DNA on intercalation and/or minor/major groove binding. As inferred from the experiments depicted above, only **4** and **8** exhibited pronounced interactions with the *ct*-DNA. Strong bathochromic and hypochromic changes in the UV–vis spectra of **4** and **8** pointed towards aromatic

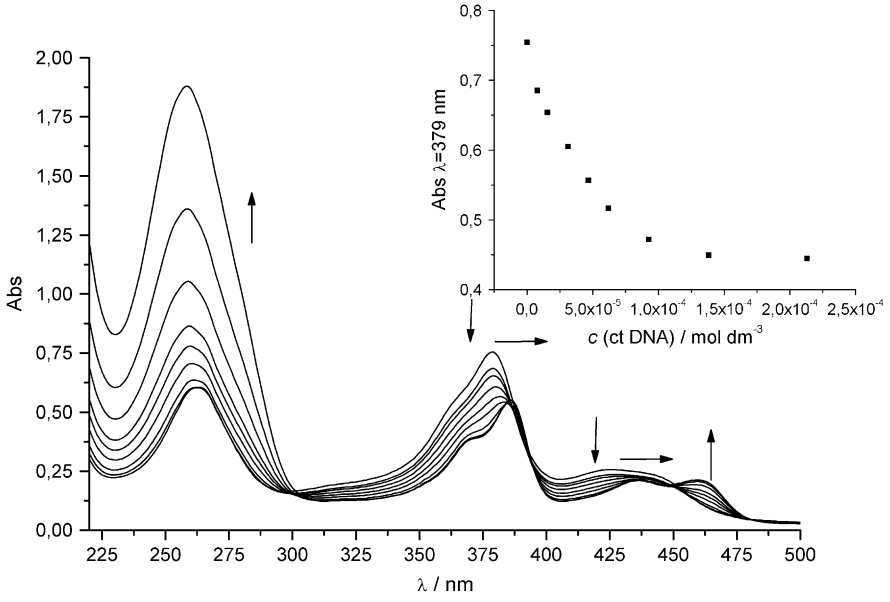


Figure 7. Changes in UV–vis spectrum of **8** (c=2.06×10^{-5} mol dm^{-3}) upon titration with *ct*-DNA and dependence of **8** absorbance at λ_{max}=379 nm on c (*ct*-DNA), at pH=7, sodium cacodylate buffer, I=0.05 mol dm^{-3}.

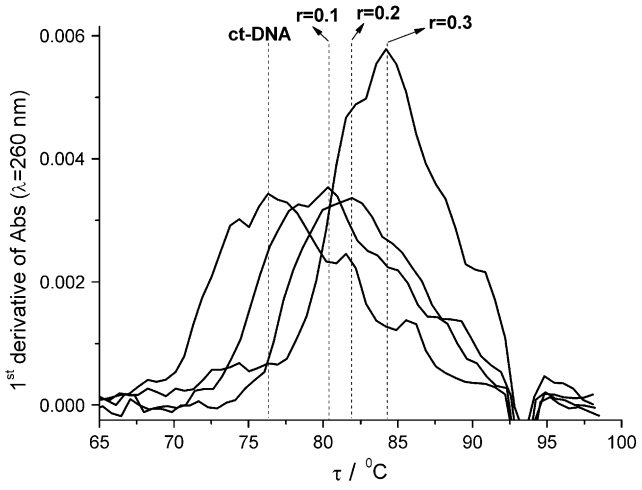


Figure 8. Thermal denaturation experiments of *ct*-DNA and **8** at pH=7.0 (sodium cacodylate, I=0.05 mol dm^{-3}), the ([**8**]/[*ct*-DNA]) ratios (r) are 0.0, 0.1, 0.2 and 0.3. For measuring conditions, see Section 4.

stacking interactions with *ct*-DNA,[20,21] which together with the thermal stabilization of the *ct*-DNA gave evidence of an intercalative mode of binding. However, systematic deviation from the isosbestic points in the UV–vis titrations of **4** and **8** as well as values of ratio n (Table 4) far too high for intercalation, indicate the simultaneous formation of various types of complexes. Therefore the binding of **4** and **8** into one of the DNA grooves and/or on the outer surface of the polynucleotide cannot be neglected.

The question arises, in turn, as to why, unlike **4** and **8**, compound **9** exhibited very weak (if any) interactions with the *ct*-DNA. A comparison of the structures suggests that differences in the binding affinities of **4** and **8**, in relation to those of **9**, depend mainly on the size, rigidity and chemical constitution of their pendant *meso* substituents. Compounds **4**, **8** and **9** have analogous dicationic structures and possess an identical dibenzotetraaza[14]annulene core but the exposure of the positive charges and the bulkiness of their substituents differ significantly. The bipyridinium-containing substituents of **9** are more rigid and bulky than those attached to **4** and **8**. It seems reasonable to suppose that intercalative and groove-binding abilities of **9** have been suppressed due to steric hindrance created by its *meso* substituents.

Table 4. Changes of **4**, **8**, **9** UV–vis spectra upon titration with *ct*-DNA, binding constants ($\log K_s$) and ratios $n_{([\text{bound compound}]/[ct\text{-DNA}])}$ calculated from the UV–vis titrations;[a] and ΔT_m values[f] (°C) of *ct*-DNA upon the addition of **4**, **8** and **9**

	[b]$\Delta\lambda_1$	[b]$\Delta\lambda_2$	[c]H/%	$\log K_s$	[d]n	[f]ΔT_m (°C)
4	+2	+8	−35	5.2	0.69	+2.1
8	+7	+9	−46	4.7	0.84	+7.2
9	0	+2	−8	[e]	[e]	0

Experimental conditions: pH=7.0 (sodium cacodylate buffer, I=0.05 mol dm^{-3}).

[a] Titration data were processed according to Scatchard equation.[19]

[b] Shift of the absorbance maximum; $\Delta\lambda=\lambda$(**4**, **8** and **9**)$-\lambda$(complex); Absorbance maxima λ_1 (**4**: λ=383 nm, **8**: λ=379 nm, **9**: λ=385 nm) λ_2=(**4**: λ=443 nm, **8**: λ=427 nm, **9**: λ=448 nm).

[c] Hypochromic effect; H=[Abs(**4**, **8**, **9**)−Abs(complex)]/Abs(**4**, **8** and **9**)×100; values Abs(complex) were calculated by Scatchard equation[19] for **4** and **8** and the last experimental values were used for the Abs(complex) of **9**.

[d] Accuracy of n±10–30%, consequently $\log K_s$ values vary in the same order of magnitude.

[e] Not possible to calculate by using Scatchard equation due to the small spectroscopic changes.

[f] Error in ΔT_m: ±0.5 °C; $r_{[\text{compound}]/[ct\text{-DNA}]}$=0.3.

It seems noteworthy to mention that the reasoning presented here agrees well with the results reported earlier for closely related analogues of the porphyrin.[21,22] Namely, for less substituted porphyrin (P2 corresponding to **4** and **8**) the increase in ΔT_m reflected the stabilization of the double helix due to the intercalation of the porphyrin moiety,[21,22] while results for more sterically congested analogues (P3 and P4 corresponding to **9**) supported an outside binding mode.[21]

It is difficult at this stage to explain why **8** and **4** differ so much in their stabilizing influence on the *ct*-DNA melting temperatures. Since structures **4** and **8** are quite similar, as well as the observed hypo- and bathochromic effects and obtained log K_s values, one could speculate that the spatial orientation of terminal groups with positive charges could be of decisive importance. A much more detailed study is needed, however, in order to support this assumption.

3. Conclusions

A new class of DNA/RNA binding agents based on the dibenzotetraaza[14]annulene backbone has been synthesized by the chemical transformations within its *meso*-substituted functional groups. The reaction sequence involved esterifications with 3-pyridinepropionic and nicotinic acids, followed by the N-alkylation of the pyridine moieties. Alternatively, the bis(bromopropyl)dibenzotetraaza[14]annulene has been synthesized from a corresponding hydroxypropyl substrate, followed by reactions with pyridine and 4,4′-bipyridine.

X-ray crystallography showed a nearly planar macrocyclic core in **8** and **9** with aliphatic chains adopting extended planar conformations. Terminal groups of the pendant *meso* moieties were found to play a significant role in the supramolecular assembly of **9** arranged in ladder-like motifs.

Spectrophotometric titrations with the use of the Scatchard analysis and the thermal denaturation experiments showed products **4** and **8** to be capable of strong interactions with *ct*-DNA. A mixed mode of binding is proposed involving intercalation and groove binding, both influenced remarkably by the bulkiness and rigidity of the pendant *meso* substituents.

The results reported here demonstrated, for the first time, that dibenzotetraaza[14]annulene derivatives may be of value in research aiming at rational drug design. Further studies of their interactions with various DNA and RNA sequences focused on the potential selectivity as well as biological activity, seem to be of considerable interest.

4. Experimental

4.1. General

Macrocyclic substrates 7,16-bis(hydroxypropyl)-5,14-dihydrodibenzo[*b*,*i*][1,4,8,11]tetraazacyclotetradecine (**1**) and

7,16-bis(2-hydroxybenzoyl)-5,14-dihydrodibenzo[*b*,*i*][1,4,8,11]tetraazacyclotetradecine (**2**) were prepared by the procedures described earlier.[13,14] Other chemicals (diisopropylcarbodiimide (DIC), 4-dimethylaminopyridine (DMAP), tetrabromomethane, bromomethane and triphenylphosphine) were purchased from commercial sources (Sigma–Aldrich, Fluka) and were used as received. Solvents were dried using standard methods and were freshly distilled before use. Elemental analyses were performed on a Euro-EA (EuroVector) microanalyzer. ^{1}H and ^{13}C NMR were run on a Bruker AMX (500 MHz) and a Mercury Varian (300 MHz) spectrometers. Chemical shifts (δ) are expressed in parts per million and *J* values in hertz. Signal multiplicities are denoted as s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). ESI mass spectra were taken on a Bruker Esquire 3000 spectrometer. The IR spectra were recorded in KBr with a Bruker IFS 48 spectrophotometer. Melting points were measured with use of a Boethius apparatus and were uncorrected.

4.2. Syntheses

4.2.1. 7,16-Bis[3-(3-pyridyl)propionyloxypropyl]-5,14-dihydrodibenzo[*b*,*i*][1,4,8,11]tetraazacyclotetradecine (3). 3-Pyridinepropionic acid (0.61 g, 4 mmol), DIC (0.65 mL, 4 mmol) and DMAP (0.1 g, 0.82 mmol) were added to a solution of **1** (0.2 g, 0.5 mmol) in dimethylformamide (50 mL). The reaction mixture was protected from moisture and stirred at room temperature for 24 h. The product was precipitated by dropwise addition of water, filtered off and dried under vacuum. Red powder, yield 0.24 g (72%), mp 148 °C. ^{1}H NMR (500 MHz; DMSO-d_6; δ ppm): 1.75 (m, 4H, H^{b}), 2.22 (t, *J*=7.2 Hz, 4H, H^{a}), 2.69 (t, *J*=7.7 Hz, 4H, H^{d}), 2.87 (t, *J*=7.7 Hz, 4H, H^{e}), 4.06 (t, *J*=6.4 Hz, 4H, H^{c}), 6.90 (dd, *J*=6.0, 2.5 Hz, 4H, H^{2,3}, H^{11,12}), 7.26 (m, 6H, H^{1,4}, H^{10,13}, H^{i}), 7.65 (d, *J*=7.8 Hz, 2H, H^{j}), 7.80 (d, *J*=5.9 Hz, 4H, =CHN), 8.39 (dd, *J*=4.7, 1.3 Hz, 2H, H^{h}), 8.45 (d, *J*=1.7 Hz, 2H, H^{g}), 13.57 (t, *J*=5.9 Hz, 2H, NH); ^{13}C NMR (125 MHz; DMSO-d_6; δ ppm): 27.25, 28.36, 30.39, 34.36 (C^{a}, C^{b}, C^{d}, C^{e}), 63.10 (C^{c}), 107.03 (C^{7,16}), 113.64, 123.21, 124.08, 135.61, 135.80, 136.69, 147.24, 147.44, 149.46 (*o*-C_6H_4, C=N, py) 171.91 (C=O); IR (KBr) ν_{max} (cm^{-1}): 3174, 3061, 3030, 2928, 1716, 1652, 1593, 1554; ESI-MS (*m*/*z*): 671.2 (M+H)$^{+}$; Anal. Calcd for $C_{40}H_{42}N_6O_4$: C, 71.62; H, 6.31; N, 12.53. Found: C, 71.20; H, 6.62; N, 12.79%.

4.2.2. 7,16-Bis[3-(*N*-methyl pyridinium-3-yl)propionyloxypropyl]-5,14-dihydrodibenzo[*b*,*i*][1,4,8,11]tetraazacyclotetradecine dibromide dihydrate (4). A solution of **3** (0.19 g, 0.15 mmol) in dimethylformamide (30 mL) was treated with liquid (cooled to −10 °C) bromomethane (5 mL). The mixture was stirred for 24 h under argon at room temperature. The solvent and excess of bromomethane were removed on a rotary evaporator. The oily residue was dissolved in methanol-*tert*-butyl methyl ether (2:5, 70 mL) and left overnight in a refrigerator. The reddish-brown crystals were collected by filtration and dried in vacuo. Yield 0.1 g (75%), mp 223 °C. ^{1}H NMR (300 MHz; DMSO-d_6; δ ppm): 1.78 (m, 4H, H^{b}), 2.27 (t, *J*=6.9 Hz, 4H, H^{a}), 2.83 (t, *J*=7.5 Hz, 4H, H^{d}), 3.05 (t, *J*=7.5 Hz, 4H, H^{e}), 4.08 (t, *J*=6.5 Hz, 4H, H^{c}), 4.31 (s, 6H, H^{k}), 6.90 (dd, *J*=6.1 Hz, *J*=3.5 Hz, 4H, H^{2,3}, H^{11,12}), 7.28 (dd, *J*=6.1, 3.5 Hz, 4H, H^{1,4}, H^{10,13}), 7.83 (d, *J*=5.9 Hz, 4H, =CHN), 8.04 (dd, *J*=6.0, 8.0 Hz, 2H, H^{i}), 8.48 (d, *J*=8.0 Hz, 2H, H^{j}), 8.85 (d, *J*=6.0 Hz, 2H, H^{h}), 9.00 (s, 2H, H^{g}), 13.58 (t, *J*=5.9 Hz, 2H, NH); ^{13}C NMR (75 MHz; DMSO-d_6; δ ppm): 26.82 (C^{e}), 28.31 (C^{a}), 30.42 (C^{b}), 33.13 (C^{d}), 47.70 (C^{k}), 63.42 (C^{c}), 107.07 (C^{7,16}), 113.74 (C^{1,4}, C^{10,13}), 124.18 (C^{2,3}, C^{11,12}), 127.03 (C^{i}), 136.68 (C^{IV}), 140.91 (C^{f}), 143.21 (C^{h}), 144.73 (C^{j}), 145.03 (C^{g}), 147.57 (C=N), 171.61 (C=O); IR (KBr) ν_{max} (cm^{-1}): 3382, 3072, 2898, 1722, 1640, 1589, 1546, 1509, 1451, 1418, 1399, 1357, 1284, 1217, 1157; ESI-MS (*m*/*z*): 350.2 ($C_{42}H_{48}N_6O_4^{2+}$/2); Anal. Calcd for $C_{42}H_{48}Br_2N_6O_4\cdot 2H_2O$: C, 56.26; H, 5.84; N, 9.37. Found: C, 56.39; H, 5.94; N: 9.35%.

4.2.3. 7,16-Bis[2-(3-pyridyl)carbonyloxybenzoyl]-5,14-dihydrodibenzo[*b*,*i*][1,4,8,11]tetraazacyclotetradecine (5). A reaction mixture was prepared containing **2** (0.2 g, 0.38 mmol), nicotinic acid (0.47 g, 3.8 mmol), DIC (0.6 mL, 3.8 mmol) and DMAP (0.1 g, 0.82 mmol) in dimethylformamide (50 mL). Further procedure was analogous to that of **3**. Orange powder, yield 0.25 g (87%), mp 263 °C. ^{1}H NMR (300 MHz; $CDCl_3$; δ ppm): 7.11 (dd, *J*=3.5, 6.1 Hz, 4H, H^{2,3}, H^{11,12}), 7.19 (dd, *J*=3.5, 6.1 Hz, 4H, H^{1,4}, H^{10,13}), 7.33–7.45 (m, 6H, *o*-C_6H_4', H^{d}), 7.54–7.63 (m, 4H, *o*-C_6H_4'), 8.31 (dt, *J*=6.2, 3.4 Hz, 2H, H^{e}), 8.53 (d, *J*=6.6 Hz, 4H, =CHN), 8.75 (dd, *J*=4.9, 1.7 Hz, 2H, H^{c}), 9.24 (dd, *J*=2.2, 0.8 Hz, 2H, H^{b}), 14.23 (t, *J*=6.6 Hz, 2H, NH); ^{13}C NMR (75 MHz; $CDCl_3$; δ ppm): 109.89 (C^{7,16}), 115.75, 123.31, 123.40, 124.99, 126.42, 126.81, 129.41, 131.27, 137.57, 147.66, 151.37, 152.78, 154.08 (*o*-C_6H_4, *o*-C_6H_4', C=N, py), 163.90 (O–C=O), 190.97 (C=O); IR (KBr) ν_{max} (cm^{-1}): 3072, 1745, 1654, 1591, 1496, 1450, 1416, 1330, 1270, 1194, 1096, 1076; ESI-MS (*m*/*z*): 739.2 (M+H)$^{+}$; Anal. Calcd for $C_{44}H_{30}N_6O_6$: C, 71.54; H, 4.09; N, 11.38. Found: C, 71.24; H, 4.14; N, 11.52%.

4.2.4. 7,16-Bis[2-(*N*-methyl pyridinium-3-yl)carbonyloxybenzoyl]-5,14-dihydrodibenzo[*b*,*i*][1,4,8,11]tetraazacyclotetradecine dibromide trihydrate (6). Prepared analogously to **4** starting from **5** (0.1 g, 0.14 mmol) and bromomethane (5 mL). Orange crystals, yield 0.1 g (81%), mp 207 °C. ^{1}H NMR (500 MHz; DMSO-d_6; δ ppm): 4.40 (s, 6H, H^{f}) 7.20 (dd, *J*=3.5, 6.1 Hz, 4H, H^{2,3}, H^{11,12}), 7.32 (dd, *J*=3.5, 6.1 Hz, 4H, H^{1,4}, H^{10,13}), 7.55 (m, 4H, *o*-C_6H_4'), 7.73 (m, 4H, *o*-C_6H_4'), 8.27 (dd, *J*=6.3, 8.0 Hz, 2H, H^{d}), 8.52 (d, *J*=6.6 Hz, 4H, =CHN), 9.02 (d, *J*=8.2 Hz, 2H, H^{e}), 9.25 (d, *J*=6.5 Hz, 2H, H^{c}), 9.68 (s, 2H, H^{b}), 14.17 (t, *J*=6.6 Hz, 2H, NH); ^{13}C NMR (75 MHz; DMSO-d_6; δ ppm): 48.20 (C^{f}), 109.33 (C^{7,16}), 115.71, 123.22, 126.84, 126.96, 127.97, 128.26, 129.68, 131.59, 131.79, 136.01, 144.92, 146.94, 147.15, 149.45, 152.69 (*o*-C_6H_4, *o*-C_6H_4', C=N, py), 160.43 (O–C=O), 189.65 (C=O); IR (KBr) ν_{max} (cm^{-1}): 3398, 3009, 2923, 1747, 1644, 1617, 1591, 1498, 1308, 1267, 1194, 1090; ESI-MS (*m*/*z*): 384.2 ($C_{46}H_{36}N_6O_4^{2+}$/2); Anal. Calcd for $C_{46}H_{36}Br_2N_6O_6\cdot 3H_2O$: C, 56.22; H, 4.31; N, 8.55. Found: C, 56.52; H, 4.14; N, 8.38%.

4.2.5. 7,16-Bis(3-bromopropyl)-5,14-dihydrodibenzo-[*b*,*i*][1,4,8,11]tetraazacyclotetradecine (7). Compound **1** (0.4 g, 1 mmol) was dissolved in warm tetrahydrofuran (250 mL). The solution was allowed to cool to room

temperature and then was treated with tetrabromomethane (1.33 g, 4 mmol) and triphenylphosphine (1.05 g, 4 mmol). The reaction mixture was stirred for 24 h at room temperature, concentrated on a rotary evaporator to half volume, transferred to a separatory funnel and diluted with chloroform (200 mL). The mixture was washed thoroughly with cold water (5×50 mL), dried over anhydrous $CaCl_2$, concentrated to a small volume and left in a refrigerator overnight. Dark-red crystalline product was collected by filtration and dried under vacuum. Yield 0.29 g (55%), mp 217 °C. ^{1}H NMR (500 MHz; DMSO-d_6; 50 °C; δ ppm): 2.16 (m, 4H, H^b), 2.49 (t, J=6.9 Hz, 4H, H^a), 3.68 (t, J=6.6 Hz, 4H, H^c), 7.03 (dd, J=6.0, 3.6 Hz, 4H, $H^{2,3}$, $H^{11,12}$), 7.38 (dd, J=6.0, 3.6 Hz, 4H, $H^{1,4}$, $H^{10,13}$), 7.95 (br s, 4H, =CHN), 13.69 (br s, 2H, NH); ^{13}C NMR (125 MHz; DMSO-d_6; 50 °C; δ ppm): 31.01, 34.54, 35.05 (C^a, C^b, C^c), 107.03 ($C^{7,16}$), 114.23 ($C^{1,4}$, $C^{10,13}$), 124.68 ($C^{2,3}$, $C^{11,12}$), 137.35 (C^{IV}), 148.06 (C=N); IR (KBr) ν_{max} (cm^{-1}): 3168, 3068, 2954, 2885, 1650, 1593, 1554, 1451, 1423, 1401, 1357, 1340, 1314, 1296, 1218, 1160; MALDI-MS (*m*/*z*): 528.08 (M^+), 530.08 $(M+2)^+$; Anal. Calcd for $C_{24}H_{26}Br_2N_4$: C, 54.36; H, 4.94; N, 10.57. Found: C, 54.58; H, 5.12; N, 10.47%.

4.2.6. 7,16-Bis[3-(*N*-pyridinium-1-yl)propyl]-5,14-dihydrodibenzo[*b*,*i*][1,4,8,11]tetraazacyclotetradecine dibromide trihydrate (8). Pyridine (5 mL) was added to a solution of **7** (0.19 g, 0.19 mmol) in dimethylformamide (50 mL). The reaction mixture was stirred at 45 °C under argon for 48 h. The solution was concentrated to a small volume and diluted with diethyl ether to precipitate the product. Deep-red crystalline product was filtered off, washed thoroughly with chloroform and dried. Yield 0.08 g (63%), mp 253 °C. Crystals suitable for X-ray measurements were grown by slow diffusion of *tert*-butyl methyl ether into the solution of **8** in methanol. ^{1}H NMR (300 MHz; DMSO-d_6; δ ppm): 2.18 (m, 4H, H^b), 2.32 (t, J=6.5 Hz, 4H, H^a), 4.68 (t, J=7.2 Hz, 4H, H^c), 6.92 (dd, J=6.1, 3.5 Hz, 4H, $H^{2,3}$, $H^{11,12}$), 7.28 (dd, J=6.1, 3.5 Hz, 4H, $H^{1,4}$, $H^{10,13}$), 7.86 (d, J=5.9 Hz, 4H, =CHN), 8.16 (dd, J=6.7, 7.8 Hz, 4H, H^e), 8.60 (t, J=7.8 Hz, 2H, H^f), 9.17 (d, J=5.6 Hz, 4H, H^d), 13.57 (t, J=6.0 Hz, 2H, NH); ^{13}C NMR (75 MHz; DMSO-d_6; δ ppm): 28.70, 32.81 (C^a, C^b), 60.43 (C^c), 106.33 ($C^{7,16}$), 113.88 ($C^{1,4}$, $C^{10,13}$), 124.19 ($C^{2,3}$, $C^{11,12}$), 127.89 (C^e), 136.68 (C^{IV}), 144.75, 145.32 (C^d, C^f), 147.62 (C=N); IR (KBr) ν_{max} (cm^{-1}): 3451, 3398, 3046, 3022, 2919, 2851, 1634, 1588, 1539, 1488, 1457, 1420, 1398, 1357, 1288, 1217, 1158, 1002; ESI-MS (*m*/*z*): 264.1 ($C_{34}H_{36}N_6^{2+}$/2); Anal. Calcd for $C_{34}H_{36}Br_2N_6\cdot 3H_2O$: C, 55.00; H, 5.70; N, 11.32. Found: C, 54.75; H, 5.66; N, 11.03% (**8** is slightly hygroscopic; the content of water depends on the sample preparation).

4.2.7. 7,16-Bis{3-[4-(4-pyridyl)*N*-pyridinium-1-yl]-propyl}-5,14-dihydrodibenzo[*b*,*i*][1,4,8,11]tetraazacyclotetradecine dibromide pentahydrate (9). 4,4′-Bipyridyl (0.6 g, 3.8 mmol) was added to a solution of **7** (0.1 g, 0.19 mmol) in dimethylformamide (50 mL) and the mixture was stirred at 45 °C under argon for 48 h. The solvent was partially removed under reduced pressure, water (50 mL) was added and the mixture was washed thoroughly with chloroform (5×50 mL). Aqueous layer was concentrated to half volume and left overnight in a refrigerator. The deep-red crystalline product was filtered off and dried in vacuo. Yield 0.11 g (71%), mp 187 °C. Crystals suitable for X-ray measurements were obtained by slow evaporation of aqueous solution of **9**. ^{1}H NMR (300 MHz; DMSO-d_6; δ ppm): 2.25 (m, 4H, H^b), 2.35 (t, J=6.9 Hz, 4H, H^a), 4.74 (t, J=6.7 Hz, 4H, H^c), 6.90 (dd, J=6.1, 3.5 Hz, 4H, $H^{2,3}$, $H^{11,12}$), 7.23 (dd, J=6.1, 3.5 Hz, 4H, $H^{1,4}$, $H^{10,13}$), 7.76 (d, J=5.9 Hz, 4H, =*CH*N), 7.95 (dd, J=1.7, 4.5 Hz, 4H, H^f), 8.59 (d, J=7.0 Hz, 4H, H^g), 8.81 (dd, J=1.7, 4.5 Hz, 4H, H^e), 9.30 (d, J=7.0 Hz, 4H, H^d), 13.42 (t, J=6.0 Hz, 2H, NH); ^{13}C NMR (75 MHz; DMSO-d_6; δ ppm): 28.92, 32.06 (C^a, C^b), 60.21 (C^c), 106.13 ($C^{7,16}$), 113.82, 121.71, 124.18, 124.95, 136.51, 140.57, 145.31, 147.33, 150.78, 152.01 (*o*-C_6H_4, C=N, bipyridyl); IR (KBr) ν_{max} (cm^{-1}): 3388, 2921, 2853, 1637, 1588, 1543, 1459, 1402, 1354, 1286, 1217, 1179, 1162; ESI-MS (*m*/*z*): 341.1 ($C_{44}H_{42}N_8^{2+}$/2); Anal. Calcd for $C_{44}H_{42}Br_2N_8\cdot 5H_2O$: C, 56.66; H, 5.62; N, 12.01. Found: C, 56.40; H, 5.40; N, 12.19% (**9** is slightly hygroscopic; the content of water depends on the sample preparation).

4.3. Crystallography

Intensity data for the crystal of **8** were collected on a KUMA KM4CCD κ-axis diffractometer equipped with monochromated Mo Kα radiation (λ=0.71073 Å) at room temperature. The data integration and numerical absorption corrections were carried out with the CrysAlis program.[23] Intensity data for the crystal of **9** were collected using a Bruker AXS Smart APEX CCD 3-circle diffractometer with MonoCap capillary and monochromated Cu Kα radiation (λ=1.54178 Å) at a temperature of 90 K. Data collection and data reduction were done with the SMART and SAINT-PLUS programs.[24] Empirical absorption corrections were carried out using the SADABS program.[25] The structures were solved by direct methods by using the SHELXS-97 program.[26] All non-hydrogen atoms were refined anisotropically by full-matrix least-squares based on F^2 using the SHELXL-97 program,[27] and the complete set of reflections. The final geometrical calculations were carried out with the PLATON program.[28] The relevant crystal data and experimental details are summarized in Table 1.

All hydrogen atoms were located from Fourier difference maps, assigned isotropic thermal parameters 1.2 times those of their parent non-H atoms (with the exception of the free refined hydrogen atoms of the water molecules), and included in the refinements as riding atoms with N–H 0.86, C_{sp}–H 0.93 and C^2_{sp}–H 0.97 Å for **8**, and with N–H 0.88, C_{sp}–H 0.95, C^2_{sp}–H 0.95 and O–H 0.84 Å for **9**.

4.4. UV–vis spectroscopy

UV–vis spectra were recorded on a Varian Cary 100 Bio spectrophotometer. The spectroscopic studies were performed in aqueous buffer solution (pH=7, sodium cacodylate buffer, I=0.05 mol dm^{-3}). Under the experimental conditions, absorbance of all studied compounds was proportional to their concentrations. Calf thymus *ct*-DNA was purchased from Aldrich, dissolved in the sodium cacodylate buffer, I=0.05 mol dm^{-3}, pH=7, additionally sonicated and filtered through a 0.45 μm filter and final concentration was determined spectroscopically as the concentration of

phosphates.[29,30] Spectroscopic titrations were performed by adding portions of polynucleotide solution to the solution of the studied compound and allowing to incubate for 90 s; the incubation time necessary for reaching thermodynamic equilibrium was checked for each compound. Titration data were processed by Scatchard equation,[19] all having satisfactory correlation coefficients (>0.999), obtained values for K_s and n are given in Table 4. Thermal melting curves for DNA and their complexes with studied compounds were determined as previously described by following the absorption change at 260 nm as a function of temperature. Absorbance of the ligands was subtracted from every curve, and the absorbance scale was normalized. The T_m values are the midpoints of the transition curves, determined from the maximum of the first derivative and checked graphically by the tangent method. ΔT_m values were calculated subtracting T_m of the free nucleic acid from T_m of the complex. Every ΔT_m value here reported was the average of at least two measurements, the error in ΔT_m is ± 0.5 °C.

5. Crystallographic data

Full details of crystallographic data for the structural analysis has been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 602969 for compound **8** and No. 603881 for compound **9**. Copies of this information can be obtained, free of charge via www.ccdc.cam.ac.uk/data_request/cif.

References and notes

1. Mountford, P. *Chem. Soc. Rev.* **1998**, *27*, 105–115 and references therein.
2. (a) Dzugan, S. J.; Busch, D. H. *Inorg. Chem.* **1990**, *29*, 2528–2532; (b) Arai, T.; Kashitani, K.; Kondo, H.; Sakaki, S. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 705–709; (c) Eilmes, J. *Polyhedron* **1992**, *11*, 581–584 and references therein.
3. (a) Drew, M. G. B.; Jutson, N. J.; Mitchell, P. C. H.; Potter, R. J.; Thompsett, D. *J. Mater. Chem.* **1992**, *2*, 817–822; (b) Lu, Y. W.; Keita, B.; Nadjo, L. *New J. Chem.* **1997**, *21*, 581–588; (c) Gupta, V. K.; Prasad, R.; Kumar, P.; Mangla, R. *Anal. Chim. Acta* **2000**, *420*, 19–27; (d) Rudolph, M.; Dautz, S.; Jäger, E. G. *J. Am. Chem. Soc.* **2000**, *122*, 10821–10830.
4. (a) Honeybourne, C. L. *Tetrahedron* **1973**, *29*, 1549–1557; (b) Ricciardi, G.; Bavoso, A.; Rosa, A.; Lelj, F.; Cizov, Y. *J. Chem. Soc., Dalton Trans.* **1995**, 2385–2389.
5. Cutler, A. R.; Alleyne, C. S.; Dolphin, D. *Inorg. Chem.* **1985**, *24*, 2276–2281 and references therein.
6. See e.g.: (a) Sakata, K.; Saitoh, Y.; Kawakami, K.; Nakamura, N.; Hashimoto, M. *Synth. React. Inorg. Met.-Org. Chem.* **1995**, *25*, 1279–1293; (b) Hardie, M. J.; Malic, N.; Nichols, P. J.; Raston, C. L. *Tetrahedron Lett.* **2001**, *42*, 8075–8079; (c) Eilmes, J.; Ptaszek, M.; Woźniak, K. *Polyhedron* **2002**, *21*, 7–17; (d) Eilmes, J.; Ptaszek, M.; Dobrzycki, Ł.; Woźniak, K. *Polyhedron* **2003**, *22*, 3299–3305.
7. Cotton, F. A.; Czuchajowska, J. *Polyhedron* **1990**, *9*, 2553–2566 and references therein.
8. See e.g.: (a) Fiel, R. J. *J. Biomol. Struct. Dyn.* **1989**, *6*, 1259–1274; (b) Marzillli, L. G. *New J. Chem.* **1990**, *14*, 409–420; (c) Armitage, B. *Chem. Rev.* **1998**, *98*, 1171–1200; (d) McMillin, D. R.; Shelton, A. H.; Bejune, S. A.; Fanwick, P. E.; Wall, R. K. *Coord. Chem. Rev.* **2005**, *249*, 1451–1459; (e) Pasternack, R. F.; Ewen, S.; Rao, A.; Meyer, A. S.; Freedman, M. A.; Collings, P. J.; Frey, S. L.; Ranen, M. C.; de Paula, J. C. *Inorg. Chim. Acta* **2001**, *317*, 59–71; (f) Johnson, D. S.; Boger, D. L.; In *Comprehensive Supramolecular Chemistry*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Vögtle, F., Eds.; Pergamon: Oxford, New York, NY, 1996; Vol. 4, Chapter 3, pp 106–107 and references therein; (g) Song, R.; Kim, Y.-S.; Lee, C. O.; Sohn, Y. S. *Tetrahedron Lett.* **2003**, *44*, 1537–1540.
9. (a) Scolaro, L. M.; Romeo, A.; Pasternack, R. F. *J. Am. Chem. Soc.* **2004**, *126*, 7178–7179; (b) Chen, X.; Liu, M. J. *Inorg. Biochem.* **2003**, *94*, 106–113 and references therein; (c) Pasternack, R. F.; Gibbs, E. J.; Collings, P. J.; dePaula, J. C.; Turzo, L. C.; Terracina, A. *J. Am. Chem. Soc.* **1998**, *120*, 5873–5878.
10. (a) Aoki, S.; Kimura, E. *Chem. Rev.* **2004**, *104*, 769–787; Liu, J.; Zhang, H.; Chen, C.; Deng, H.; Lu, T.; Ji, L. *Dalton Trans.* **2003**, 114–119.
11. (a) Weiss, M. C.; Gordon, G.; Goedken, V. L. *Inorg. Chem.* **1977**, *16*, 305–310; (b) Rihs, G.; Sigg, I.; Haas, G.; Winkler, T. *Helv. Chim. Acta* **1985**, *68*, 1933–1935; (c) Azuma, N.; Tani, H.; Ozawa, T.; Niida, H.; Tajima, K. *J. Chem. Soc., Perkin Trans. 2* **1995**, 343–348.
12. (a) Meunier, B. *Chem. Rev.* **1992**, *92*, 1411–1456; (b) Pratviel, G.; Pitié, M.; Périgaud, C.; Gosselin, G.; Bernadou, J.; Meunier, B. *J. Chem. Soc., Chem. Commun.* **1993**, 149–151; (c) Ward, B.; Skorobogaty, A.; Dabrowiak, J. C. *Biochemistry* **1986**, *25*, 7827–7833.
13. Hanke, R.; Breitmaier, E. *Chem. Ber.* **1982**, 1657–1661.
14. Sigg, I.; Haas, G.; Winkler, T. *Helv. Chim. Acta* **1982**, *65*, 275–279.
15. Bailey, P. D.; Mills, T. J.; Pettecrew, R.; Price, R. A.; In *Comprehensive Organic Group Transformation II*; Katritzky, A. R., Taylor, R. J. K., Eds.; Elsevier Pergamon: Amsterdam, 2005; Vol. 5, Chapter 5.06, p 223.
16. Buckley, B. R.; In *Comprehensive Organic Group Transformation II*; Katritzky, A. R., Taylor, R. J. K., Eds.; Elsevier Pergamon: Amsterdam, 2005; Vol. 5, Chapter 5.06, p 131.
17. (a) Katritzky, A. R.; Nowak-Wydra, B.; Marson, C. M. *Chem. Scr.* **1987**, *27*, 477–478; (b) Wagner, A.; Heitz, M.-P.; Mioskowski, C. *Tetrahedron Lett.* **1989**, *30*, 557–558.
18. (a) Desiraju, G. R.; Steiner, T. *The Weak Hydrogen Bond in Structural Chemistry and Biology*; Oxford University Press: New York, NY, 1999; (b) Umezawa, Y.; Tsuboyama, S.; Takahashi, H.; Uzawa, J.; Nishio, M. *Tetrahedron* **1999**, *55*, 10047–10056; (c) Hua, L. Z.; Ying, D. C.; Hui, L. J.; Jiang, L. Y.; Hua, M. Y.; Zeng, Y. X. *New J. Chem.* **2000**, *24*, 1057–1062.
19. (a) Scatchard, G. *Ann. N.Y. Acad. Sci.* **1949**, *51*, 660–672; (b) McGhee, J. D.; Von Hippel, P. H. *J. Mol. Biol.* **1976**, *103*, 679–684.
20. Dougherty, G.; Pilbrow, J. R. *Int. J. Biochem.* **1984**, *16*, 1179–1192.
21. Procházková, K.; Zelinger, Z.; Lang, K.; Kubát, P. *J. Phys. Org. Chem.* **2004**, *17*, 890–897.
22. Lugo-Ponce, P.; McMillin, D. R. *Coord. Chem. Rev.* **2000**, *208*, 169–191.
23. *Xcalibur CCD System, CrysAlis Software System, v. 1.171*; Oxford Diffraction, Ltd: Abingdon, England, 2006.
24. *SMART and SAINT-PLUS: Area Detector Control and Integration Software, v. 5.629 and 6.45*; Bruker Analytical X-ray Instruments: Madison, WI, 2003.
25. Sheldrick, G. M. *SADABS, Program for Area Detector Adsorption Correction, v. 2.10*; Institute for Inorganic Chemistry, University of Göttingen: Göttingen, Germany, 2003.

26. Sheldrick, G. M. *SHELXS-97, Program for solution of crystal structures*; University of Göttingen: Göttingen, Germany, 1997.
27. Sheldrick, G. M. *SHELXL-97, Program for refinement of crystal structures*; University of Göttingen: Göttingen, Germany, 1997.
28. Spek, A. L. *PLATON, A Multipurpose Crystallographic Tool*; Utrecht University: Utrecht, The Netherlands, 2005.
29. Chaires, J. B.; Dattagupta, N.; Crothers, D. M. *Biochemistry* **1982**, *21*, 3933–3940.
30. Palm, B. S.; Piantanida, I.; Žinić, M.; Schneider, H.-J. *J. Chem. Soc., Perkin Trans. 2* **2000**, 385–392.

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Synthesis of enantiopure *cis*-decahydroquinolines from homotyramines by Birch reduction and aminocyclization

Marisa Mena, Nativitat Valls, Mar Borregán and Josep Bonjoch*

Laboratori de Química Orgànica, Facultat de Farmàcia, Universitat de Barcelona, Av. Joan XXIII s/n, 08028-Barcelona, Spain

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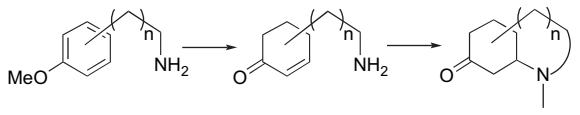
Abstract—Birch reduction of homotyramines with a *syn*-β-amino alcohol unit followed by acid treatment of formed dihydroanisole derivatives gives polysubstituted enantiopure *cis*-decahydroquinolines. The stereoselectivity of the process differs if the hydroxyl group is free or protected. The procedure allows the synthesis of 7-oxodecahydroquinolines embodying four stereogenic centres with the same relative configuration as that of lepadins F and G.

1. Introduction

The use of (ω-aminoalkyl)methoxybenzene derivatives (e.g., tyrosine and tyramine compounds) as starting materials to elaborate azabicyclic compounds through a Birch reduction followed by an intramolecular cyclization of the resulting amino-tethered cyclohexenone (Scheme 1) is well-precedented in the literature. Following this methodology, octahydroindoles,[1,2] azaspiroundecanes,[3] 6-azabicyclo-[3.2.1]octanes,[4] 2-azabicyclo[3.3.1]nonanes,[5] and decahydroquinolines[6] have been prepared, but, apart from of our work on the synthesis of enantiopure octahydroindoles,[2] all described processes lead to racemic compounds.



Scheme 1. The Birch reduction/aminocyclization process leading to azabicyclic compounds.

In this paper, we describe the synthesis of enantiopure polysubstituted decahydroquinolines from homotyramine precursors following the aforementioned Birch reduction/aminocyclization sequence.[7] The interest of this work, aside from studying the stereocontrol of the process, lies in the possible usefulness of the resulting compounds in the synthesis of lepadin alkaloids. These natural products are structurally characterized by the presence of a 2,3,5-trisubstituted cis-fused decahydroquinoline ring. The substitution pattern, which has a methyl group at C(2), a hydroxyl group, free or protected, at C(3) and a functionalized side chain at C(5), shows a variety of stereochemical arrangements.[8] Total enantioselective syntheses of lepadins A,[9] B,[9–11] C,[9] D–E[11] and H,[11] as well as a formal route to *rac*-lepadin B[12] have been reported.

We focused our attention on the synthesis of *cis*-decahydroquinolines incorporating a methyl at C(2) and a hydroxyl at C(3), with an *S* configuration at both stereogenic centres, as occurs in lepadins A, B and C. In lepadins F and G both substituents also have a cis relationship, although their absolute configuration is unknown (see Scheme 2). The strategies described for the construction of 3-hydroxy-2-methyldecahydroquinolines involve the elaboration of a polyfunctionalized piperidine followed by carbocyclic ring closure through aldol processes[9,10] or the construction of the piperidine ring from cyclohexanone derivatives either by an intramolecular enamine alkylation[11] or by using a xanthate-mediated radical cyclization.[12] In our approach, we envisaged enantiopure anisole derivatives of type **I** (R=H or Me) as potential intermediates for the aforementioned *cis*-decahydroquinolines, as they would bring about ring closure by forming the N–C(8a) bond.[13]

2. Results and discussion

2.1. Synthetic aspects

For the proposed studies of Birch reduction of homotyramines followed by an aminocyclization process to achieve *cis*-decahydroquinolines of interest in the lepadin field, α-methyl-β-aminoalcohol **I** was required. The synthesis of *syn*-α-methyl-β-amino alcohols (**II**, Scheme 3) is

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* Corresponding author. Tel.: +34 934024540; fax: +34 934024539; e-mail: josep.bonjoch@ub.edu

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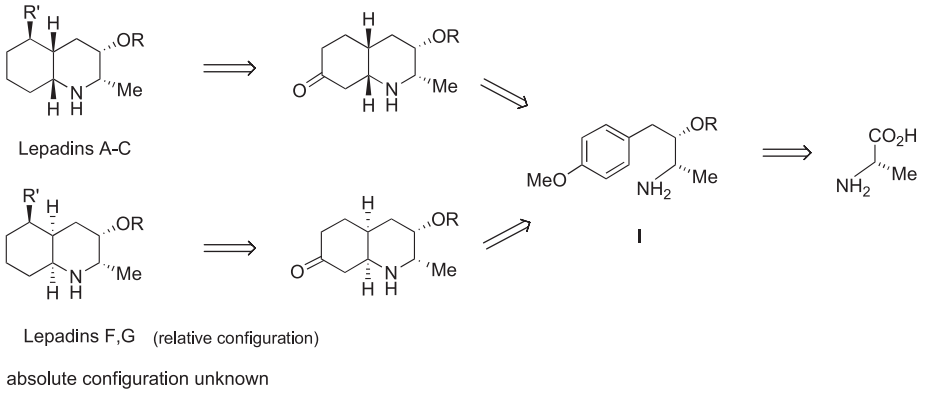
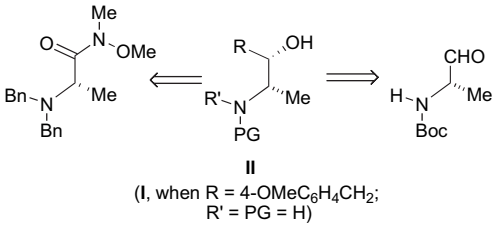
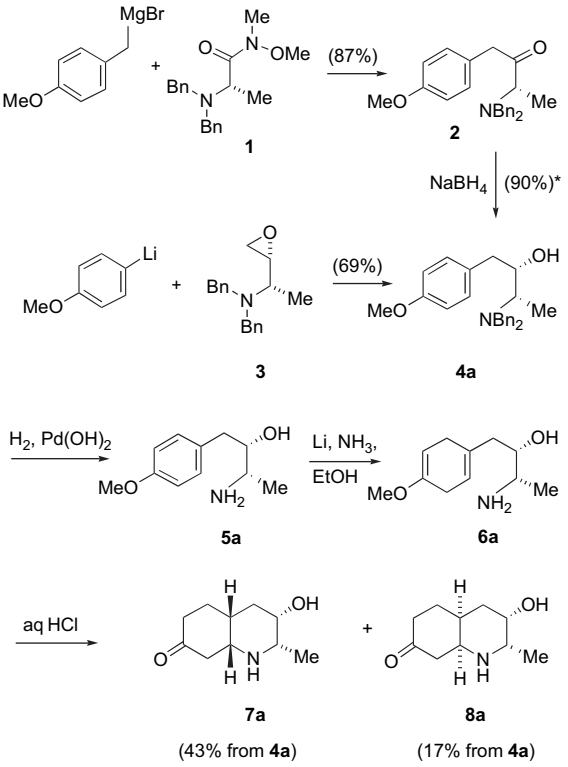


Scheme 2. Retrosynthetic approach to lepadin alkaloids.

well-precedented not only by the methodological studies of the reactivity of alanine derivatives but also by the presence of this structural motif in several natural products other than the aforementioned lepadins, such as various piperidine alkaloids[14] (i.e., carpamic acid, azimic acid, julifloridine and cassine inter alia). The most suitable procedures for *syn* amino alcohols of type **II** are the organometallic addition upon the Weinreb amide of *N*,*N*-dibenzylalanine[15] followed by hydride reduction of the resulting α-amino ketone[16] or the organometallic addition upon the *N*-Boc-alaninal.[17,18] To our knowledge, none of these versatile approaches have been used in reactions involving *p*-methoxybenzylmagnesium bromide, as was required in the present work. We decided to use the protocol involving the Weinreb amide of *N*,*N*-dibenzylalanine and, in addition, introduced a new approach based on the ring-opening of a suitable epoxide with a lithium reagent is introduced to achieve aminoalcohol **I**.



Scheme 3. Synthesis of enantiopure *syn*-α-methyl-β-amino alcohols.

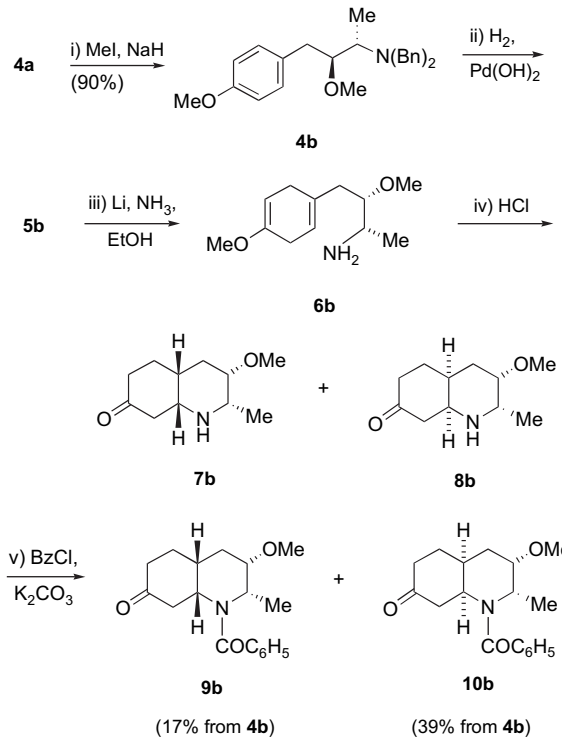


Scheme 4. Synthesis of *cis*-decahydroquinolines.

Coupling of either the *p*-methoxybenzylmagnesium bromide with Weinreb amide **1**[19,20] or the *p*-methoxyphenyllithium with the (*R*) isomer of [(*S*)-1′-(dibenzylamino)ethyl]oxirane (**3**)[21] in the presence of $BF_3 \cdot Et_2O$ (Ganem's conditions)[22,23] gave synthetic access to the required aminoalcohol **4a**, a diastereoselective reduction of the initially formed β-amino ketone **2** being necessary in the former sequence (Scheme 4, * denotes that 10% of the epimer of **4a**[24] was additionally isolated in this route, see Section 3). A loss of enantiopurity observed in this sequence (**1**→**4a**) when the coupling of the Weinreb amide **1** was carried out at 0 °C[25] and was avoided at −40 °C.

Debenzylation of **4a** gave the primary amine **5a**, which was submitted to the Birch reduction conditions (Li/NH_3) to allow the formation of dihydroanisole **6a**. This was treated with a 2 N HCl solution at 75 °C, and the decahydroquinoline ring was formed after enol ether hydrolysis, double bond isomerization and an intramolecular 1,4-addition of the amino group across the cyclohexenone intermediate. The process is stereoselective, with the exclusive formation of *cis*-isomers of the decahydroquinoline ring. Polysubstituted decahydroquinolines **7a** (43%) and **8a** (17%) were isolated in a 2.5:1 ratio and a overall yield of 60% from the sequence **4a**→**7a**+**8a**.

We then carried out the same sequence of reactions but starting from *syn*-amino ether **4b**, which was obtained by *O*-methylation of aminoalcohol **4a** (Scheme 5). In this series, the aminocyclization step starting from dihydroanisole **6b** gave a 1:2.3 mixture of decahydroquinolines **7b** and **8b**, which were only partially separated. However, when the reaction mixture was basified and treated with benzoyl chloride after aminocyclization, the corresponding amides **9b** and **10b** were isolated in 17 and 39% overall yields (four steps from **4b**).



Scheme 5.

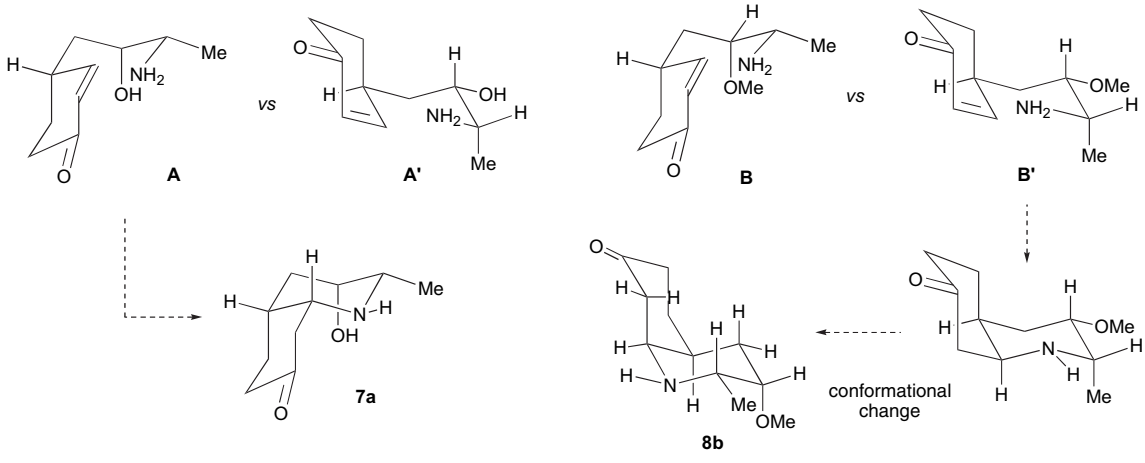
In the cyclization processes (**6**→**7**+**8**), both in series **a** (3-OH) and series **b** (3-OMe), the isolated decahydroquinolines showed a cis-fused relationship. The major compound of series **a** (i.e., **7a**) showed the same pattern of absolute configuration in its four stereocentres as lepadins A–C, while that of series **b** (i.e., **8b**) matched the relative configuration of lepadins F and G, allowing them to be considered as advanced building blocks for elaborating the aforementioned alkaloids.

The stereoselective *cis*-perhydroquinoline formation through a 6-*exo* process agreed with the stereochemical outcome observed in related cyclizations,[6] and with both the steric and electronic preferences for a pseudo axial addition of the nucleophilic species to the cyclohexenone moiety. Interestingly, the configuration of the new methine carbons (i.e., C-4a and C-8a) is controlled to some extent by the oxygenated function. Why does the decalin ring formation change diastereoselectivity if there is a free or protected hydroxyl group? Considering that the axial attack proceeds through a chair-like transition state in the hydroxyl series perhaps a hydrogen bonding favours the formation of enone **A** with respect to the epimeric enone **A′**, which could be in equilibrium by means of a tautomeric process through their corresponding dienol ether. On the contrary in series **b**, in which the hydroxyl group is protected as methyl ether, the steric factors (a 1,3-diaxial relationship between the C3–OMe and C4a–C5 bonds) prevent to some extent the formation of epimer **B**, and the formation of **B′** being favoured (Scheme 6). Thus, the ratio of *cis*-decahydroquinoline with an *S* configuration at the two new stereogenic centres formed in the aminocyclization to the diastereoisomers with a *R* configuration was higher in compounds with a methoxy rather than hydroxyl substituent.

2.2. NMR studies of decahydroquinolines 7–10 (series a and b)

The stereochemistry of the synthesized azabicyclic compounds was elucidated by 2D NMR spectra (COSY, HSQC). The N-inside (**7a** and **7b**) and N-outside (**8a** and **8b**) *cis*-decahydroquinoline isomers[26] in the amino series are clearly differentiated by two NMR features: (i) the ^{1}H NMR chemical shift of H-2, which appears more deshielded (δ 3.1) in the N-outside than in the N-inside derivatives (δ 2.8), due to the compression upon H-2 of the C8–C8a bond, which has a 1,3-cis relationship, on the N-outside derivatives; (ii) the ^{13}C NMR chemical shift of C(2) is more upfielded (∼10 ppm) in compounds with the N-outside conformation than those with the N-inside conformation; moreover the signals given by the carbon atoms at C-4, C-6 and C-8 also appear in a higher field in the N-outside derivatives.

The key evidence for the conformational elucidation of **7a** was found in the ^{1}H NMR coupling pattern for the methylene protons at C-8, which appear as dd (J=14.6, 5.4 Hz). The relative configuration for methoxy derivative **7b** is the same as that observed in **7a** and their NMR data follows the same pattern of chemical shifts (Scheme 2). The absolute configuration of **7a** was deduced by considering that: (a) the



Scheme 6.

coupling constants for H-2 (qd, J=6.6, 2 Hz) and H-3 (q, J=2.4 Hz) determined their location and hence fixed the methyl at C(2) and the hydroxyl at C(3) to an equatorial and axial disposition, respectively; (b) the multiplicity of H-8a (br s) implied an equatorial relationship with respect to the cyclohexane ring, which discarded not only a trans junction of the decaline ring but also, taking into account the preferred conformation, implied a *R* configuration for C(8a). For the major component in the methoxy series **8b**, the axial proton H-8a is strongly coupled to one adjacent axial. Hence, its resonance signal appears as a deceptively simple doublet (J=10.4 Hz) of triplets (J=4.8 Hz) centred at δ 3.43.

In summary, the twin chair conformation with the nitrogen axially substituting the carbocyclic ring is the lowest energy conformation for **7a**, whereas the twin chair conformation with the nitrogen equatorially substituting the carbocyclic ring is the lowest energy conformation for **8b** (Fig. 1).

Interestingly, the *N*-benzoyl derivatives **9a**, prepared from amine **7a** in quantitative yield, and **10b** (Fig. 2) showed a different preferred conformations to that of their precursors **7a** and **8b**, respectively, as has been observed in synthetic intermediates in lepadin synthesis[9–11] when the amino group is converted to a carbamate or amide group.

In summary, a new synthetic entry to enantiopure polysubstituted *cis*-decahydroquinolines has been reported. Since the observed stereoselectivity allows lepadin-type stereochemistries to be achieved, further studies using decahydroquinolines **9a** and **10b** as advanced synthetic intermediates are in progress with the aim of achieving lepadins A–C and F and G, respectively.

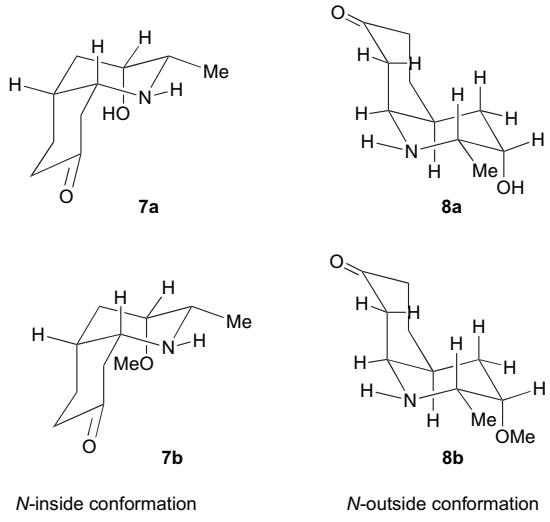


Figure 1. Preferred conformation of decahydroquinolines **7** and **8**.

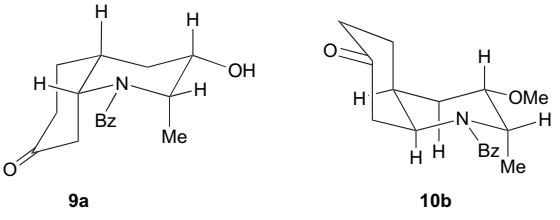


Figure 2. Preferred conformation of decahydroquinolines **9** and **10**.

3. Experimental

3.1. General

All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions. Analytical TLC was performed on SiO_2 (silica gel 60 F_{254}, Merck) or Al_2O_3 (ALOX N/UV_{254}, Polygram), and the spots were located with iodoplatinate reagent (compounds **1**–**8**) or 1% aqueous $KMnO_4$ (compounds **9** and **10**). Chromatography refers to flash chromatography and was carried out on SiO_2 (silica gel 60, SDS, 230–240 mesh ASTM) or Al_2O_3 (aluminium oxide 90, Merck). Drying of organic extracts during workup of reactions was performed over anhydrous Na_2SO_4. Optical rotations were recorded with a Perkin–Elmer 241 polarimeter. ^{1}H and ^{13}C NMR spectra were recorded with a Varian Gemini 200 or 300, or a Varian Mercury 400 instrument. Chemical shifts are reported in parts per million downfield (δ) from Me_4Si. All new compounds were determined to be >95% pure by ^{1}H NMR spectroscopy.

3.1.1. (*S*)-(*N*,*N*-Dibenzyl)amino-*N*-methoxy-*N*-methylpropionamide (1). To a solution of benzyl (*S*)-2-(*N*,*N*-dibenzylamino)propionate[27] (2.15 g, 6 mmol) and HCl·HN(OMe)Me (3.0 g, 30 mmol) in THF (90 mL) at −20 °C, ^{i}PrMgCl (30 mL of a 2 M in THF, 60 mmol) was added dropwise over a period of 30 min. The reaction mixture was stirred for 2 h at this temperature and then warmed to rt for 2.5 h. NH_4Cl (20 mL) was added and the product was extracted with CH_2Cl_2 (3×20 mL). The combined organic layer was dried and concentrated to an oil, which contained **1** and BnOH. The latter was removed under vacuum to afford compound **1** (1.94 g), which was used without further purification. The ^{1}H NMR data were identical to those previously reported.[20] R_f=0.1 (SiO_2, 9:1 hexane/EtOAc); ^{13}C NMR (50 MHz, $CDCl_3$) 14.9 (CH_3), 54.4 (CH_2), 56.1 (CH), 60.1 (CH_2), 126.8 (CH), 127.4 (CH), 127.6 (CH), 128.1 (CH), 128.3 (CH), 128.5 (CH), 139.8 (C), 173.9 (C).

3.1.2. (3*S*)-3-(*N*,*N*-Dibenzyl)amino-1-(4-methoxyphenyl)butan-2-one (2). To a solution of **1** (1.81 g, 5.8 mmol) in THF (50 mL) at −40 °C, 2-methoxybenzylmagnesium chloride 0.25 M in THF (46 mL, 11.6 mmol) was added dropwise. The reaction mixture was stirred for 2 h 30 min at −40 °C and then quenched with NH_4Cl. The organic layer was dried and concentrated to an oil, which was purified by chromatography (SiO_2, 9:1 hexane/EtOAc) to give **2** as a colourless oil (2.17 g, 87%). R_f=0.5 (SiO_2, 9:1 hexane/EtOAc); $[\alpha]_D^{25}$ −8.8 (*c* 1.0, $CHCl_3$); IR (KBr) 1715, 1611 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 1.15 (d, J=6.6 Hz, 3H), 3.47 (d, J=13.2 Hz, 2H), 3.52 (q, J=6.6 Hz, 1H), 3.72 (d, J=15.0 Hz, 1H), 3.74 (d, J=13.2 Hz, 2H), 3.76 (s, 3H), 3.88 (d, J=15.3 Hz, 1H), 6.74 (d, J=8.6 Hz, 2H), 6.84 (d, J=8.6 Hz, 2H), 7.20–7.40 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) 7.1 (CH_3), 45.3 (CH_2), 54.6 (CH_2), 55.2 (CH_3), 60.6 (CH), 113.8 (CH), 126.5 (C), 127.2 (CH), 128.4 (CH), 128.9 (CH), 130.3 (CH), 139.2 (C), 158.3 (C). Anal. Calcd for $C_{25}H_{27}NO_2$: C, 80.40; H, 7.29; N, 3.75. Found: 80.00; H, 7.29; N, 3.67.

3.1.3. (2*S*,3*S*)-3-(*N*,*N*-Dibenzyl)amino-1-(4-methoxyphenyl)butan-2-ol (4a). *Method A* (from ketone **2**): to a solution of **2** (2.15 g, 5.75 mmol) in MeOH (68 mL) at −20 °C, $NaBH_4$ (453 mg, 11.5 mmol) was added. The reaction mixture was stirred for 1 h at this temperature, and then quenched with brine (30 mL). The product was extracted with CH_2Cl_2 (3×30 mL), dried and concentrated to give a mixture of alcohols **4a** and *epi*-**4a**[24] in a 9:1 ratio according to the NMR spectrum. Purification by chromatography (SiO_2, 9:1 hexane/EtOAc) gave **4a** (1.94 g, 90%) and *epi*-**4a** (216 mg, 10%).

Compound **4a**: colourless oil. R_f=0.24 (SiO_2, 9:1 hexane/EtOAc); $[\alpha]_D^{25}$ −5.6 (*c* 1.4, $CHCl_3$); IR (KBr) 3600–3100, 1611 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 1.07 (d, *J*=6.6 Hz, 3H), 2.38 (dd, *J*=14.0, 7.8 Hz, 1H), 2.60 (dq, *J*=9.3, 6.6 Hz, 1H), 2.78 (dd, J_1=14.3, 3.0 Hz, 1H), 3.30 (d, *J*=13.5 Hz, 2H), 3.68 (m, 1H), 3.77 (s, 3H), 3.82 (d, *J*=13.5 Hz, 2H), 6.77 (d, *J*=9 Hz, 2H), 7.11 (d, *J*=9 Hz, 2H), 7.20–7.40 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) 8.3 (CH_3), 39.1 (CH_2), 53.2 (CH_2), 55.2 (CH_3), 57.7 (CH), 71.9 (CH), 113.5 (CH), 127.1 (CH), 128.4 (CH), 128.9 (CH), 130.1 (CH), 131.0 (C), 138.7 (C), 157.8 (C). Anal. Calcd for $C_{25}H_{29}NO_2 \cdot 1/2H_2O$: C, 78.12; H, 7.81; N, 3.64. Found: C, 77.84; H, 8.16; N, 3.34.

Compound *epi*-**4a**: colourless oil. R_f=0.14 (SiO_2, 9:1 hexane/EtOAc); IR (KBr) 3600–3100, 1611 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 1.17 (d, *J*=6.6 Hz, 3H), 2.30 (dd, *J*=13.8, 9.6 Hz, 1H), 2.75 (quint, *J*=6.9 Hz, 1H), 3.21 (dd, *J*=13.8, 3.0 Hz, 1H), 3.50 (*J*=13.8 Hz, 2H), 3.73–3.81 (m, 1H), 3.80 (d, *J*=14.1 Hz, 2H), 6.80 (d, *J*=9.0 Hz, 2H), 7.02 (d, *J*=9.0 Hz, 2H), 7.20–7.40 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) 8.6 (CH_3), 40.6 (CH_2), 54.7 (CH_2), 55.3 (CH_3), 57.2 (CH), 74.7 (CH), 113.9 (CH), 126.8 (CH), 128.2 (CH), 128.8 (CH), 130.2 (CH), 131.0 (C), 140.0 (C), 158.1 (C).

Method B (from epoxide **3**): to a solution of *n*-BuLi (1.6 M in hexanes, 1.05 mL, 1.68 mmol) in THF (3.5 mL) at −78 °C was added 4-bromoanisole (0.2 mL, 1.56 mmol). The reaction mixture was stirred for 90 min, treated with a solution of (2*R*)-[1′(*S*)-(dibenzylamino)ethyl]oxirane[21] (162 mg, 0.6 mmol) in THF (2 mL) and $BF_3 \cdot Et_2O$ (0.21 mL, 1.68 mmol) and continuously stirred at −78 °C for 2 h prior to being quenched with saturated NH_4Cl (4 mL) and warmed to rt. The product was extracted with CH_2Cl_2 (3×10 mL), and the organic layer was dried and concentrated to give an oil, which was purified by chromatography (SiO_2, 9:1 hexane/EtOAc) to give **4a** as a colourless oil (153 mg, 69%). The spectroscopic data and specific rotation were identical with the product obtained by *method A*.

3.1.4. (2*S*,3*S*)-*N*,*N*-Dibenzyl-3-methoxy-4-(4-methoxyphenyl)-2-butanamine (4b). To a suspension of NaH (195 mg, 4.89 mmol) in THF (2 mL) at 0 °C a solution of **4a** (1.22 g, 3.26 mmol) in THF was transferred (1 mL+1 mL). The reaction mixture was warmed over 20 min to rt and then MeI (2 mL, 32.6 mmol) was added. The reaction was sealed and stirred for 48 h. NH_4Cl was added (10 mL) and the product was extracted with CH_2Cl_2 (3×20 mL). The resulting organic layer was washed with H_2O (15 mL) and brine (15 mL), dried and concentrated to give an oil, which was purified by chromatography (SiO_2, 9:1 hexane/EtOAc) to give **4b** as a colourless oil (1.14 g, 90%). R_f=0.42 (SiO_2, 9:1 hexane/EtOAc); $[\alpha]_D^{25}$ −4.6 (*c* 1.0, $CHCl_3$); IR (KBr) 1611 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 1.13 (d, *J*=6.9 Hz, 3H), 2.74–2.88 (m, 3H), 3.13 (s, 3H), 3.22 (dt, *J*=7.2, 4.8 Hz, 1H), 3.43 (d, *J*=13.5 Hz, 2H), 3.77 (s, 3H), 4.01 (d, *J*=13.5 Hz, 2H), 6.73 (d, *J*=8.7 Hz, 2H), 6.94 (d, *J*=8.7 Hz, 2H), 7.20–7.32 (m, 6H), 7.39–7.41 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) 10.1 (CH_3), 37.4 (CH_2), 55.1 (CH), 55.2 (CH_2), 55.2 (CH_3), 59.2 (CH_3), 88.1 (CH), 113.5 (CH), 126.6 (CH), 128.1 (CH), 128.9 (CH), 130.2 (CH), 132.3 (C), 140.9 (C), 157.7 (C). Anal. Calcd for $C_{26}H_{31}NO_2$: C, 80.17; H, 8.02; N, 3.60. Found: C, 80.07; H, 8.31; N, 3.40.

3.1.5. (2*S*,3*S*)-3-Amino-1-(4-methoxyphenyl)butan-2-ol (5a). A suspension of **4a** (2.16 g, 5.75 mmol) and $Pd(OH)_2/C$ (210 mg, 20%) in EtOH (110 mL) was stirred at rt under hydrogen atmosphere overnight. The catalyst was removed by filtration through Celite and the filtrate was concentrated to give **5a** as an oil (1.12 g), which was used directly in the next step. An analytical sample was obtained by chromatography (Al_2O_3, CH_2Cl_2 saturated with NH_3). $[\alpha]_D^{25}$ −15.5 (*c* 0.7, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) 1.12 (d, *J*=6.6 Hz, 3H), 2.56 (dd, *J*=14.0, 8.6 Hz, 1H), 2.74–2.86 (m, 2H), 3.40–3.46 (m, 1H), 3.78 (s, 3H), 6.84 (d, *J*=8.7 Hz, 2H), 7.14 (d, *J*=8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) 20.5 (CH_3), 39.6 (CH_2), 50.3 (CH), 54.7 (CH_2), 55.2 (CH_3), 76.4 (CH), 113.7 (CH), 130.1 (C), 130.2 (CH), 158.0 (C).

3.1.6. (2*S*,3*S*)-3-Methoxy-4-(4-methoxyphenyl)-2-butanamine (5b). Operating as above, starting from **4b** (1.14 g, 2.92 mmol), **5b** was obtained (615 mg) as an oil, which was used directly in the next step. An analytical sample was obtained by chromatography (Al_2O_3, 98:2 CH_2Cl_2 saturated with NH_3/MeOH). $[\alpha]_D^{25}$ +8.4 (*c* 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) 1.11 (d, *J*=6.3 Hz, 3H), 2.56 (dd, *J*=14.3, 6.5 Hz, 1H), 2.90–2.81 (m, 2H), 3.07 (dt, *J*=6.6, 5.4 Hz, 1H), 3.30 (s, 3H), 3.79 (s, 3H), 6.84 (d, *J*=8.4 Hz, 2H), 7.15 (d, *J*=8.4 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) 20.1 (CH_3), 35.8 (CH_2), 49.2 (CH), 55.2 (CH_3), 58.8 (CH_3), 87.6 (CH), 113.7 (CH), 130.4 (CH), 130.8 (C), 158.0 (C).

3.1.7. (2*S*,3*S*)-3-Amino-1-(4-methoxy-2,5-dihydrophenyl)butan-2-ol (6a). To a solution of **5a** (1.12 g, 5.75 mmol) in EtOH (6 mL) at −78 °C, ammonia (46 mL) was added. Small chips of lithium (280 mg, 40 mmol) were added until the solution become a persistent deep blue for 1.5 h. The cooling bath was removed, the ammonia was allowed to evaporate overnight and the reaction mixture was evaporated. The dried extract was dissolved in brine (15 mL) and the product was extracted with CH_2Cl_2 (3×15 mL), dried with Na_2SO_4 and concentrated to give **6a** (1.112 g) as an oil, which was used directly in the next step. ^1H NMR (200 MHz, $CDCl_3$) 1.11 (d, *J*=6.3 Hz, 3H), 2.08 (dd, *J*=14.1, 9.0 Hz, 1H), 2.21 (dd, *J*=13.5, 3.3 Hz, 1H), 2.69–2.84 (m, 6H), 3.33–3.40 (m, 1H), 3.55 (s, 3H), 4.63 (m, 1H), 5.51 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 20.2 (CH_3), 29.1 (CH_2), 29.4 (CH_2), 41.6 (CH_2), 50.8 (CH), 53.7 (CH_3), 73.1 (CH), 90.2 (CH), 120.2 (CH), 132.4 (C), 152.6 (C).

3.1.8. (2*S*,3*S*)-3-Methoxy-4-(4-methoxy-2,5-dihydrophenyl)-2-butanamine (6b). Operating as above, starting from **5b** (611 mg, 2.92 mmol), **6b** was obtained (620 mg) as an oil, which was used directly in the next step. ^{1}H NMR (200 MHz, $CDCl_3$) 1.09 (d, J=6.6 Hz, 3H), 2.14–2.29 (m, 2H), 2.74–2.84 (m, 3H), 2.87–2.96 (m, 1H), 3.02–3.07 (m, 1H), 3.40 (s, 3H), 3.55 (s, 3H), 4.62 (m, 1H), 5.49 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) 20.1 (CH_3), 29.2 (CH_2), 30.0 (CH_2), 37.9 (CH_2), 49.3 (CH), 53.9 (CH_3), 58.4 (CH_3), 84.7 (CH), 90.4 (CH), 120.1 (CH), 132.6 (C), 152.9 (C).

3.1.9. Aminocyclization of 6a. A solution of **6a** (95 mg, 0.48 mmol) in 2 N HCl (1.6 mL) was stirred for 3.5 h at 70 °C. The mixture was basified with NaOH (1 N, 10 mL) and the solution was extracted with CH_2Cl_2 (4×10 mL) and $CHCl_3$/MeOH (4×10 mL), dried and concentrated to give a brown oil. Purification by chromatography (Al_2O_3, CH_2Cl_2 saturated with NH_3) gave a partially separated 2.5:1 mixture of **7a** (37 mg, 43%) and **8a** (15 mg, 17%).

3.1.9.1. (2*S*,3*S*,4a*R*,8a*R*)-3-Hydroxy-2-methyloctahydroquinolin-7-one (7a). White solid; mp 112–114 °C; R_f=0.17 (Al_2O_3, 99:1 CH_2Cl_2 saturated with NH_3/MeOH); ^{1}H NMR (400 MHz, $CDCl_3$, gCOSY) 1.11 (d, J=6.8 Hz, 3H, Me), 1.81 (ddd, J=14.8, 5.6, 3.6 Hz, H-4eq), 1.87 (dm, J=14 Hz, H-5eq), 1.95 (dt, J=14.4, 2 Hz, H-4ax), 2.05 (m, H-4a), 2.24 (dt, J=14.4, 2 Hz, H-6eq), 2.29 (dd, J=14.4, 5.6 Hz, H-8ax), 2.32 (m, H-6ax), 2.50 (qd, J=13.6, 4.8 Hz, H-5ax), 2.65 (ddd, J=14.8, 4.8, 0.8 Hz, H-8eq), 2.80 (qd, J=6.6, 2 Hz, H-2ax), 3.35 (br s, H-8a), 3.58 (q, J=2.4 Hz, H-3eq); ^{13}C NMR (100 MHz, $CDCl_3$, gHSQC) 18.1 (Me), 28.8 (C-5), 33.5 (C-4a), 36.4 (C-4), 41.6 (C-6), 47.5 (C-8), 56.8 (C-8a), 59.3 (C-2), 68.2 (C-3), 210.8 (C-7). HRMS (ESI-TOF) calcd for $C_{10}H_{18}NO_2$ (M^++1) 184.1332, found 184.1337.

3.1.9.2. (2*S*,3*S*,4a*S*,8a*S*)-3-Hydroxy-2-methyloctahydroquinolin-7-one (8a). Colourless oil; R_f=0.14 (Al_2O_3, 99:1 CH_2Cl_2 saturated with NH_3/MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) 1.10 (d, J=6.6 Hz, 3H, Me), 1.72–1.98 (m, 4H), 2.15–2.44 (m, 4H), 2.93 (t, J=12.6 Hz, H-8ax), 3.06 (qd, J=6.5, 1.8 Hz, H-2ax), 3.39 (dt, J=11.7, 4.8 Hz, H-8a), 3.76 (br s, H-3eq); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) 17.7 (Me), 28.0 (C-5), 28.1 (C-4a), 31.9 (C-4), 36.6 (C-6), 42.6 (C-8), 47.5 (C-2), 55.9 (C-8a), 68.2 (C-3), 210.9 (C-7). HRMS (ESI-TOF) calcd for $C_{10}H_{18}NO_2$ (M^++1) 184.1332, found 184.1331.

3.1.10. Aminocyclization of 6b. Following the above procedure for the aminocyclization of **6a** using methoxy derivative **6b** (225 mg, 1.07 mmol), heating at 70 °C for 3 h and purifying by chromatography (Al_2O_3, 99:1 CH_2Cl_2 saturated with NH_3/MeOH), a partially separated mixture of **7b** (36 mg, 17%) and **8b** (50 mg, 22%) was obtained.

3.1.10.1. (2*S*,3*S*,4a*R*,8a*R*)-3-Methoxy-2-methyldecahydroquinolin-7-one (7b). White solid; mp 45–47 °C; R_f=0.25 (Al_2O_3, 99:1 CH_2Cl_2 saturated with NH_3/MeOH); $[\alpha]_D^{25}$ +14.6 (*c* 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, gCOSY) 1.12 (d, J=6.8 Hz, 3H, Me), 1.62 (ddd, J=14.8, 5.6, 3.2 Hz, H-4eq), 1.74 (m, H-5eq), 2.00 (dm, J=12 Hz, H-4a), 2.13 (dt, J=14.8, 2.2 Hz, H-4ax), 2.23 (td, J=14, 6 Hz, H-6ax), 2.26 (dm, J=14.8 Hz, H-8), 2.32 (dddd, J=14, 4.8, 2.4, 2.4 Hz, H-6eq), 2.61 (dd, J=14.8, 5.6 Hz, H-8), 2.63 (qd, J=14, 4.2 Hz, H-5ax), 2.78 (qd, J=6.5, 2.4 Hz, H-2ax), 3.05 (q, J=2.7 Hz, H-3eq), 3.30 (masked, H-8a), 3.31 (s, 3H, OMe); ^{13}C NMR (100 MHz, $CDCl_3$, gHSQC) 18.1 (Me), 26.9 (C-5), 30.9 (C-4), 33.4 (C-4a), 41.4 (C-6), 47.6 (C-8), 56.3 (C-2), 56.9 (OMe), 58.7 (C-8a), 76.9 (C-3), 210.6 (C-7). HRMS (ESI-TOF) calcd for $C_{11}H_{20}NO_2$ (M^++1) 198.1489, found 198.1487.

3.1.10.2. (2*S*,3*S*,4a*S*,8a*S*)-3-Methoxy-2-methyldecahydroquinolin-7-one (8b). Colourless oil; R_f=0.19 (Al_2O_3, 99:1 CH_2Cl_2 saturated with NH_3/MeOH); ^{1}H NMR (400 MHz, $CDCl_3$, gCOSY) 1.11 (d, J=6.8 Hz, 3H, Me), 1.75–2.00 (m, 4H, H-4, H-5), 2.20–2.30 (m, 3H, H-4a, H-6), 2.39 (ddd, J=14.4, 4.4, 1.5 Hz, H-8eq), 2.62 (dd, J=14.4, 10 Hz, H-8ax), 3.13 (qd, J=6.5, 3.2 Hz, H-2ax), 3.34 (masked, H-3eq), 3.36 (s, 3H, OMe), 3.43 (ddd, J=10, 4.8, 4.8 Hz, H-8a); ^{13}C NMR (100 MHz, $CDCl_3$, gHSQC) 16.0 (Me), 27.6 (C-5), 27.8 (C-4), 29.6 (C-4a), 37.7 (C-6), 43.7 (C-8), 48.1 (C-2), 53.3 (C-8a), 56.7 (OMe), 76.4 (C-3), 210.9 (C-7). HRMS (ESI-TOF) calcd for $C_{11}H_{20}NO_2$ (M^++1) 198.1489, found 198.1487.

3.1.11. (2*S*,3*S*,4a*R*,8a*R*)-1-Benzoyl-3-hydroxy-2-methyloctahydroquinolin-7-one (9a). A solution of **7a** (12 mg, 0.07 mmol) was dissolved in THF (0.2 mL) and H_2O (0.2 mL) was added. Then, K_2CO_3 (39 mg, 0.28 mmol) and BzCl (8.4 μL, 0.074 mmol) were added. The reaction mixture was stirred for 2 h at rt, extracted with CH_2Cl_2 (4×15 mL), dried and concentrated to give a brown oil. Purification by column chromatography (Al_2O_3, from CH_2Cl_2 saturated with NH_3 to 98:2 CH_2Cl_2 saturated with NH_3/MeOH) gave **9a** (19 mg, 99%). R_f=0.44 (Al_2O_3, 98:2 CH_2Cl_2 saturated with NH_3); ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers) 1.20 and 1.30 (2br d, CH_3), 1.70–2.20 (m, 6H), 2.34 (br, 1H), 2.75 (m, 1H), 3.85–4.15 (br, 2H), 5.07 (br, 1H), 7.25–7.45 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) 14.1 and 15.7 (CH_3), 27.5 and 28.6 (C-4), 29.7 (C-5), 31.9 (C-4a), 36.2 (C-6), 49.1 (C-8), 53.4 (C-2), 55.3 (C-8a), 74.6 (C-3), 125.9, 128.8, 129.5, 136.5 (Ar), 171.6 and 172.2 (NCO), 208.0 (C-7). HRMS (ESI-TOF) calcd for $C_{17}H_{22}NO_3$ (M^++1) 288.1594, found 288.1585.

3.1.12. (2*S*,3*S*,4a*R*,8a*R*)-1-Benzoyl-3-methoxy-2-methyloctahydroquinolin-7-one (9b). Operating as above, starting from **7b** (16 mg, 0.08 mmol) and after purification by chromatography (Al_2O_3, CH_2Cl_2 saturated with NH_3), amide **9b** (24 mg, 99%) was obtained as a white solid. Mp 100–102 °C; R_f=0.52 (Al_2O_3, CH_2Cl_2 saturated with NH_3); ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers) 1.05 and 1.25 (2br d, CH_3), 1.70–2.20 (m, 6H), 2.35 (br, 1H), 2.75 (m, 1H), 3.20 and 3.40 (2s, 3H, OCH_3), 3.25–3.45 (masked, 2H), 3.95 (br, 0.5H), 4.15 (br, 0.5H), 5.0 (br, 0.5H), 5.20 (br, 0.5H), 7.20–7.65 (m, 4H, ArH), 8.20 (d, J=7.5 Hz, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) 15.0 and 16.0 (CH_3), 25.3 and 25.7 (C-4), 27.6 (C-5), 32.6 and 33.5 (C-4a), 36.0 and 36.4 (C-6), 43.6 and 45.2 (C-8), 45.4, 49.4, 51.2 and 56.2 (C-2 and C-8a), 55.6 and 56.6 (OCH_3), 77.9 and 78.4 (C-3), 125.7, 128.7, 129.4, 136.6 (Ar), 171.6 (NCO), 207.4 and 207.9 (C-7). HRMS (ESI-TOF) calcd for $C_{18}H_{24}NO_3$ (M^++1) 302.1751, found 302.1752.

3.1.13. (2*S*,3*S*,4a*R*,8a*R*)- and (2*S*,3*S*,4a*S*,8a*S*)-1-Benzoyl-3-methoxy-2-methyloctahydroquinolin-7-one (9b and 10b). A solution of **6b** (90 mg, 0.42 mmol) in 2 N HCl (2 mL) was stirred for 3 h at 75 °C. The mixture was basified with K_2CO_3 (464 mg, 3.36 mmol) and BzCl (0.06 mL, 0.5 mmol) in THF (2 mL) was added. The reaction mixture was stirred for 2 h at rt, concentrated and extracted with CH_2Cl_2 (4×20 mL). The dried organic layers were concentrated to give a brown oil, which was purified by chromatography (SiO_2, from hexane/EtOAc 7:3 to EtOAc) to give a 1:2.3 mixture of **9b** (22 mg, 17% from **4b**) and **10b** (50 mg, 39% from **4b**). For data of **9b**, see above.

Compound **10b**: colourless oil; R_f=0.14 (SiO_2, 1:1 hexane/EtOAc); $[\alpha]_D^{25}$ +16 (*c* 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, gCOSY) 1.25 (d, *J*=6.8 Hz, 3H, Me), 1.80 (m, H-5), 1.87 (m, H-4), 1.99 (dt, *J*=14, 5.2 Hz, H-4eq), 2.11 (dddd, *J*=12, 11, 9.4, 4.4 Hz, H-5ax), 2.25 (ddd, *J*=15.4, 10, 5.4 Hz, H-6ax), 2.36 (m, H-4a), 2.64 (masked, 1H, H-6), 2.59 and 2.67 (2dd, *J*=16.8, 5.6 Hz, 1H each, H-8), 3.20 (s, 3H, OMe), 3.51 (ddd, *J*=10.8, 5.4, 5.4 Hz, H-3ax), 4.12 (ddd, *J*=5.6, 5.6, 2.8 Hz, H-8a), 4.24 (quint, *J*=6.4 Hz, H-2eq), 7.40 (s, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$, gHSQC) 12.5 (Me), 26.5 (C-5), 28.5 (C-4), 33.3 (C-4a), 38.5 (C-6), 43.0 (C-8), 51.9 (C-8a), 52.8 (C-2), 56.2 (OMe), 75.0 (C-3), 126.8, 128.6, 130.0, 136.6 (Ar), 173.2 (NCO), 205.4 (C-7). HRMS (ESI-TOF) calcd for $C_{18}H_{24}NO_3$ (M^++1) 302.1751, found 302.1750.

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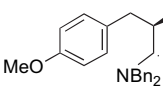
References and notes

1. (a) Ueda, N.; Tokuyama, T.; Sakan, T. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 2012–2014; (b) Bonjoch, J.; Catena, J.; Valls, N. *J. Org. Chem.* **1996**, *61*, 7106–7115.
2. (a) Bonjoch, J.; Catena, J.; Isábal, E.; López-Canet, M.; Valls, N. *Tetrahedron: Asymmetry* **1996**, *7*, 1899–1902; (b) Bonjoch, J.; Catena, J.; Terricabras, D.; Fernández, J.-C.; López-Canet, M.; Valls, N. *Tetrahedron: Asymmetry* **1997**, *8*, 3143–3151; (c) Valls, N.; López-Canet, M.; Vallribera, M.; Bonjoch, J. *Chem.—Eur. J.* **2001**, *7*, 3446–3460.
3. Venit, J. J.; DiPierro, M.; Magnus, P. *J. Org. Chem.* **1989**, *54*, 4298–4301.
4. (a) Gensler, W. J.; Gatsonis, C. D.; Ahmed, Q. A. *J. Org. Chem.* **1968**, *33*, 2968–2971; (b) Furstoss, R.; Esposito, G.; Teissier, P.; Waegell, B. *Bull. Soc. Chim. Fr.* **1974**, 2485–2494.
5. Adachi, J.; Nomura, K.; Mitsuhashi, K. *Chem. Pharm. Bull.* **1976**, *24*, 85–91.
6. (a) Momose, T.; Uchida, S.; Kinoshita, M.; Imanishi, T. *Chem. Pharm. Bull.* **1977**, *25*, 1797–1802; (b) Momose, T.; Uchida, S.; Kinoshita, M.; Imanishi, T. *Chem. Pharm. Bull.* **1978**, *26*, 620–626; (c) Liu, D.; Wikström, H. V.; Dijkstra, D.; deVries, J. B.; Venhuis, B. J. *J. Med. Chem.* **2006**, *49*, 1494–1498.
7. For studies of decahydroquinol-7-ones by this strategy in the racemic series, see Ref. 6. For other synthesis of decahydroquinoline derivatives by intramolecular aza-Michael ring closure upon cyclohexenones, see: Taber, D. F.; Joshi, P. V.; Kanai, K. *J. Org. Chem.* **2004**, *69*, 2268–2271.
8. (a) For Lepadin A, see: Steffan, B. *Tetrahedron* **1991**, *47*, 8729–8732; (b) For Lepadins B and C, see: Kubanek, J.; Williams, D. E.; de Silva, E. D.; Allen, T.; Anderson, R. J. *Tetrahedron Lett.* **1995**, *36*, 6189–6192; (c) For Lepadins D–F, see: Wright, A. D.; Goclik, E.; König, G. M.; Kaminsky, R. *J. Med. Chem.* **2002**, *45*, 3067–3072; (d) For Lepadins F–H, see: Davis, R. A.; Carroll, A. R.; Quinn, R. J. *J. Nat. Prod.* **2002**, *65*, 454–457.
9. (a) Toyooka, N.; Okumura, M.; Takahatam, H. *J. Org. Chem.* **1999**, *64*, 2182–2183; (b) Toyooka, N.; Okumura, M.; Takahatam, H.; Nemoto, H. *Tetrahedron* **1999**, *55*, 10673–10684.
10. (a) Osawa, T.; Aoyagi, S.; Kobayashi, C. *Org. Lett.* **2000**, *2*, 2955–2958; (b) Osawa, T.; Aoyagi, S.; Kobayashi, C. *J. Org. Chem.* **2001**, *66*, 3338–3347.
11. Pu, X.; Ma, D. *Angew. Chem., Int. Ed.* **2004**, *43*, 4222–4225.
12. Kalai, C.; Tate, E.; Zard, S. Z. *Chem. Commun.* **2002**, 1430–1431.
13. For a previous work in this field, see: Mena, M.; Bonjoch, J. *Tetrahedron* **2005**, *61*, 8264–8270.
14. (a) Sato, S.; Aoyagi, S.; Kibayashi, C. *Org. Lett.* **2003**, *5*, 3839–3842; (b) Cassidy, M. P.; Padwa, A. *Org. Lett.* **2004**, *6*, 4029–4031; (c) Tsai, M.-R.; Chen, B.-F.; Cheng, C.-C.; Chang, N.-C. *J. Org. Chem.* **2005**, *70*, 1780–1785; (d) Lemire, A.; Charette, A. B. *Org. Lett.* **2005**, *7*, 4029–4031.
15. For a review in the chemistry of *N*,*N*-dibenzylamino aldehydes, see: Reetz, M. T. *Chem. Rev.* **1999**, *99*, 1121–1162.
16. For the formation of *syn*-amino alcohols in the reduction of *N*,*N*-dibenzyl α-alkyl-α-amino ketones, see: Hart, S. A.; Sabat, M.; Etzkorn, F. A. *J. Org. Chem.* **1998**, *63*, 7580–7581.
17. For a review in the chemistry of *N*-protected-α-amino aldehydes, see: Gryko, D.; Chalko, J.; Jurczak, J. *Chirality* **2003**, *15*, 514–541.
18. (a) Ibuka, T.; Habashita, H.; Otaka, A.; Fujii, N.; Oguchi, Y.; Uyehara, T.; Yamamoto, Y. *J. Org. Chem.* **1991**, *56*, 4370–4382; (b) Angle, S. R.; Breitenbucher, J. G.; Arnaiz, D. O. *J. Org. Chem.* **1992**, *57*, 5947–5955; (c) Kumar, K. K.; Datta, A. *Tetrahedron* **1999**, *55*, 13899–13906; (d) Randl, S.; Blechert, S. *Tetrahedron Lett.* **2004**, *45*, 1167–1169.
19. Weinreb amide **1**, although previously reported,[20] was here reported by reaction of tribenzyl alanine with *N*,*O*-dimethylhydroxylamine using isopropylmagnesium chloride according to a protocol introduced by Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U.-H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461–5464.
20. Beaulieu, P. L.; Wernic, D. *J. Org. Chem.* **1996**, *61*, 3635–3645.
21. Barluenga, J.; Baragaña, B.; Concellón, J.-M. *J. Org. Chem.* **1995**, *60*, 6696–6699.
22. Eis, M. J.; Wrobel, J. E.; Ganem, B. *J. Am. Chem. Soc.* **1984**, *106*, 3693–3694.
23. For a precedent, in the ring-opening of epoxide **3** by an organolithium reagent in the presence of $BF_3{\cdot}Et_2O$, see Ref. 13. For the reductive alkylation of epoxide **3** with organolithium reagents, see: Concellón, J. M.; Suárez, J. R.; Del Solar, V. *Org. Lett.* **2006**, *8*, 349–351.
24.  *epi*-**4a**

25. Reetz, M. T.; Drewes, M. W.; Lennick, K.; Schmitz, A.; Holdgrün, X. *Tetrahedron: Asymmetry* **1990**, *1*, 375–378.
26. For NMR studies of decahydroquinolines, see: (a) Eliel, E. L.; Vierhapper, F. W. *J. Org. Chem.* **1976**, *41*, 199–208; (b) Vierhapper, F. W.; Eliel, E. L. *J. Org. Chem.* **1977**, *42*, 51–62; (c) Spande, T. F.; Jain, P.; Garraffo, H. M.; Pannell, L. K.; Yeh, H. J. C.; Daly, J. W.; Fukumoto, S.; Imamura, K.; Torres, J. A.; Snelling, R. R.; Jones, T. H. *J. Nat. Prod.* **1999**, *62*, 5–21; (d) Phuan, P.-W.; Kozlowski, M. C. *J. Org. Chem.* **2002**, *67*, 6339–6346.
27. (a) Reetz, M. T.; Drewes, M. W.; Schmitz, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1141–1143; (b) Reetz, M. T.; Drewes, M. W.; Schwickardi, R. *Org. Synth.* **1999**, *76*, 110–122.

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Enantioselective synthesis of 2-substituted-1,4-diketones from (*S*)-mandelic acid enolate and α,β-enones

Gonzalo Blay,[a] Isabel Fernández,[a] Belen Monje,[a] M. Carmen Muñoz,[b] José R. Pedro[a,*] and Carlos Vila[a]

[a]*Departament de Química Orgànica, Facultat de Química, Universitat de València, Dr. Moliner, 50, E-46100 Burjassot, València, Spain*
[b]*Departamento de Física Aplicada, Universidad Politécnica de Valencia, E-46071 València, Spain*

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Abstract—An approach for the synthesis of chiral non-racemic 2-substituted-1,4-diketones from (*S*)-mandelic acid and α,β-enones has been developed. The reaction of lithium enolate of the 1,3-dioxolan-4-one derived from optically active (*S*)-mandelic acid and pivalaldehyde with α,β-unsaturated carbonyl compounds proceeds readily to give the corresponding Michael adducts in good yields and with high diastereoselectivities. The addition of HMPA (3 equiv) reverses and strongly enhances the diastereoselectivity of the reaction. A change in the reaction mechanism from a lithium catalyzed to the one where catalysis has been suppressed by coordination of HMPA to lithium is proposed to explain these results. Subsequent basic hydrolysis of the 1,3-dioxolan-4-one moiety yields the corresponding α-hydroxy acids (in hemiacetal form), which after decarboxylation with oxygen in the presence of pivalaldehyde and the Co(III)Me_2opba complex as catalyst give chiral 2-substituted 1,4-dicarbonyl compounds with very high enantiomeric excesses. In this approach, (*S*)-mandelic acid acts as an umpoled chiral equivalent of the benzoyl anion.

1. Introduction

1,4-Diketones are important and valuable precursors for the synthesis of substituted cyclopentenones,[1] such as jasmones, cuparenones, and prostaglandins, and for the synthesis of five-membered heterocyclic compounds.[2] Although a variety of synthetic methods have been developed for the preparation of 1,4-diketones,[3] the most widely used approach is the Michael addition to α,β-unsaturated ketones of either unmasked acyl anions such as acyllithium[4] and acyl-transition metal complexes,[5] or, specially, of masked acyl anions and their equivalents,[6] thiazolinium salts, alkoxyvinylcuprates, cyanohydrins, nitronate anions, and anions of 1,3-dithians.

The conjugate addition reactions often result in generation of new stereocenters, and accordingly a number of new methods to construct these stereogenic centers in a diastereo- and enantioselective fashion have been developed in the last decade.[7] In fact excellent results on the asymmetric Michael addition of enolate carbon nucleophiles to α,β-unsaturated ketones leading to 1,5-dicarbonyl compounds have been reported.[8] However, the asymmetric conjugate addition of acyl anion equivalents leading to the less accessible 1,4-dicarbonyl compounds has not been studied thoroughly.[9] During the last years, we have reported the use of different mandelic acid derivatives as umpoled masked d^1-synthons for the nucleophilic benzoylation of alkyl and aryl halides to give aryl alkyl ketones[10] and nitrobenzophenones, respectively.[11] In both syntheses, the key step is the aerobic oxidative decarboxylation of an α-hydroxy acid, which is carried out with oxygen in the presence of pivalaldehyde and a Co(III) complex as catalyst. In this paper we described a highly diastereoselective addition of (*S*)-(+)-mandelic acid enolate to α,β-enones and the transformation of the resulting adducts into chiral non-racemic 2-substituted-1,4-diketones.[12] This strategy, based on the Seebach principle of self-regeneration of stereocenters,[13] formally involves the use of (*S*)-mandelic acid as a source of the benzoyl anion and also as a source of chiral information. Similar Michael additions to ethyl crotonate[14] and cyclopentenone[15] have been reported previously.

2. Results and discussion

The synthesis of enantiomerically pure 2-substituted-1,4-diketones is outlined in Scheme 1. The first step involves the conjugate addition of (*S*)-(+)-mandelic acid enolate to α,β-enones. Although the formation of the mandelic acid

* Corresponding author. Tel.: +34 963544329; fax: +34 963544328; e-mail: jose.r.pedro@uv.es

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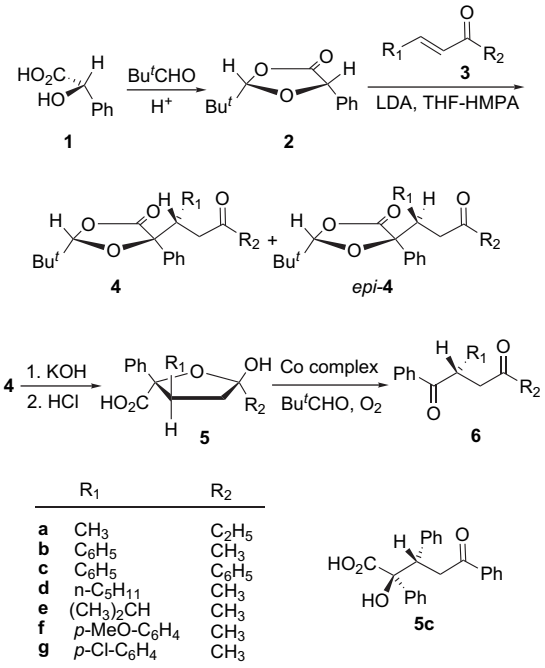
enolate leads to the loss of chirality at the stereogenic center, according to the Seebach principle of self-regeneration of stereocenters,[13] it is possible to regenerate the chiral information if (*S*)-(+)-mandelic acid (**1**) is previously transformed into (2*S*,5*S*)-*cis*-2-*tert*-butyl-5-phenyl-1,3-dioxolan-4-one (**2**) derived from pivalaldehyde.[16]



	R_1	R_2
a	CH_3	C_2H_5
b	C_6H_5	CH_3
c	C_6H_5	C_6H_5
d	n-C_5H_{11}	CH_3
e	$(CH_3)_2CH$	CH_3
f	*p*-MeO-C_6H_4	CH_3
g	*p*-Cl-C_6H_4	CH_3

Scheme 1. Synthesis of chiral non-racemic 1,4-diketones from mandelic acid.

In order to optimize the reaction conditions for the conjugate addition, we studied the reaction of 1,3-dioxolan-4-one **2** with enone **3a** (Table 1). Compound **2** was deprotonated by addition to a freshly prepared solution of LDA (1.5 equiv) in THF at −78 °C, and then enone **3a** (1 equiv) was added to the resulting enolate solution (direct addition protocol). This process provided a fair yield (49%) of a separable diastereomer mixture of **4a** and *epi*-**4a**, with moderate diastereoselectivity (**4a**:*epi*-**4a** ratio 35:65) (entry 1). In a modification of the experimental procedure we carried out the formation of enolate in the presence of the Michael acceptor since it is known that similar enolates may suffer some decomposition even at low temperatures.[17] So, LDA was added to a mixture of dioxolan-4-one **2** and enone **3a** in THF at −78 °C (inverse addition protocol). In this way, slight increases in the yield (60%) as well as in the diastereoselectivity (**4a**:*epi*-**4a** ratio 30:70) were produced (entry 2). The effect of the enolate aggregation state was also examined. In most reactions involving the participation of carbanions, the use of HMPA as an additive increases the reactivity as well as modifies the selectivity.[18] In our case, when 3 equiv of HMPA were used (entries 3 and 4) in the Michael addition of the lithium enolate of **2** to enone **3a** an improvement of the reaction yield, specially with the inverse addition protocol (85%, entry 4), together with an increase and full reversion of the diastereoselectivity were observed. Thus, only compound **4a** was obtained (de>99%). Addition of more HMPA (6 equiv) (entries 5 and 6) did neither further enhanced the yield of the reaction nor modified the diastereoselectivity, while the use of 1.5 equiv of HMPA decreased the diastereoselectivity (entry 7). The use of TMEDA[18] (entry 8) as substitutive for HMPA decreased both the yield and the diastereoselectivity. Therefore, the inverse addition protocol together with the use of HMPA (3 equiv) as additive seemed to be the optimal reaction conditions to get a good yield and a high diastereoselectivity (entry 4).

Table 1. Michael reaction of 1,3-dioxolan-4-one **2** with enone **3a**

Entry	Addition	Additive (equiv)	Yield (%)[a]	**4a**:*epi*-**4a**[b]
1	Direct	None	49	35:65
2	Inverse	None	60	30:70
3	Direct	HMPA (3)	64	97:3
4	Inverse	HMPA (3)	85	100:0
5	Direct	HMPA (6)	53	98:2
6	Inverse	HMPA (6)	82	99:1
7	Inverse	HMPA (1.5)	85	84:16
8	Inverse	TMEDA (3)	16	30:70

[a] Yields refer to isolated products.
[b] Diastereomeric ratios determined by ^{1}H NMR prior to chromatographic purification.

In order to verify the generality of the effect of HMPA as an additive in this reaction, that is, increasing of the reaction yield and specially the full reversion of the diastereoselectivity, we carried out a comparative study with two more enones (**3b** and **3c**) using the inverse addition protocol in the absence of HMPA (Table 2, entries 1, 3, and 5) and in the presence of 3 equiv of HMPA (entries 2, 4, and 6). In both cases, the results were very similar to those obtained with enone **3a**, without practically any influence of the aliphatic or aromatic nature of the substituents R_1 and R_2.

Finally the scope of the reaction using the inverse addition protocol and HMPA was studied with several different enones, bearing either aliphatic (**3d** and **3e**) or aromatic (**3f** and **3g**) substituents. In all the three cases of enones where substituents R_1 and R_2 were both aliphatic, the reaction proceeded with good yields (73–85%) and high diastereoselectivities (from 95:5 to 100:0 ratios) (entries 2, 7, and 8). In a similar way, the reaction proceeded also with good yields (76–93%) and high diastereoselectivities (from 94:6 to 99:1 ratios) with enones having R_1 aromatic and R_2 aliphatic substituents (entries 4, 9, and 10). In the case of chalcone **3c** the reaction proceeded also with good yield (70%) and full diastereoselectivity (100:0 ratio, entry 6).

Table 2. Michael reaction of 1,3-dioxolan-4-one **2** with α,β-enones **3** (inverse addition protocol)

Entry	Enone **3**	R_1	R_2	HMPA (equiv)	Yield (%)[a]	**4**:*epi*-**4**[b]
1	**3a**	CH_3	C_2H_5	0	60	30:70
2	**3a**	CH_3	C_2H_5	3	85	100:0
3	**3b**	C_6H_5	CH_3	0	34	35:65
4	**3b**	C_6H_5	CH_3	3	85	98:2
5	**3c**	C_6H_5	C_6H_5	0	58	30:70
6	**3c**	C_6H_5	C_6H_5	3	70	100:0
7	**3d**	*n*-C_5H_{11}	CH_3	3	80	95:5
8	**3e**	$(CH_3)_2CH$	CH_3	3	73	98:2
9	**3f**	*p*-$MeOC_6H_4$	CH_3	3	76	99:1
10	**3g**	*p*-ClC_6H_4	CH_3	3	93	94:6

[a] Yields refer to isolated products.
[b] Diastereomeric ratios determined by ^{1}H NMR prior to chromatographic purification.

It is important to note that under the optimized conditions (inverse addition protocol and 3 equiv of HMPA as additive) the Michael adducts were obtained practically as only one diastereomer out of the four possible ones, attending to the configuration of the two newly created stereogenic centers. The stereochemical structures of the Michael adducts **4a**–**4g** were elucidated by NOEs. These experiments showed in all of the cases the cis-relationship between the *t*-Bu group and the phenyl group from the starting 1,3-dioxolan-4-one. The absolute configuration of the newly formed quaternary carbon atom was then assigned to be *S*, upon the consideration that the absolute configuration of the carbon bearing the *t*-Bu group in **2** is *S* and it remains unaltered from **2** to **4**.[13] Furthermore, in the case of the adduct **4c** the absolute stereochemistry was unambiguously determined by single X-ray diffraction (Fig. 1).[19] According to this, the absolute configuration of the tertiary carbon atom bearing the aryl group was assigned to be *S*.

For the other adducts the assignment of the stereochemistry at the tertiary stereocenter in the side chain was established later, after hydrolysis of the 1,3-dioxolan-4-one ring and cyclization to hemiacetals **5** (see below). The configuration of this carbon was *S* in all of the cases, except in compounds **4a** and **4d** as a consequence of a change of priority when applying the Cahn–Ingold–Prelog rules. The stereochemical structures of the Michael adducts *epi*-**4a**, *epi*-**4b** and *epi*-**4c** were also elucidated by NOEs. These experiments showed again in all of the cases the cis-relationship between the *t*-Bu group and the phenyl group from the starting 1,3-dioxolan-4-one, indicating that compounds **4** and *epi*-**4** have the same configuration at the quaternary stereocenter and differ only on the stereochemistry of the tertiary stereogenic center of the side chain.

As the results in Tables 1 and 2 show, the addition of HMPA causes a dramatic change in the diastereomer distribution of the Michael products. HMPA is a highly polar aprotic solvent frequently used to accelerate organolithium reactions and, in some cases, to alter the course of the reaction. Its usefulness stems from its ability to coordinate very strongly to lithium to give separated ion pairs, in which the carbanion and lithium counterion are separated. This normally results in an increase in the nucleophilicity and reactivity of the carbanion. However, this effect is not sufficient to explain the change in the diastereomer distribution with HMPA. According to the findings by Biddle and Reich,[20] this substantial change in diastereoselectivity in the formation of the 1,4-adduct may be attributed to a change in mechanism from lithium catalyzed reaction to one where catalysis has been suppressed by the coordination of HMPA to lithium. Thus, in the absence of HMPA, the reaction is expected to proceed through an eight-membered chelated transition state (TSs C and E, Fig. 2)[21] with lithium being coordinated to the enolate and enone carbonyl oxygens with TS C being the preferred one as it minimizes any repulsion between the benzoyl group and the dioxolanone ring (Fig. 2). Addition of HMPA suppresses the lithium catalyzed mechanism and the reaction may proceed through a different, nonchelated TS D, which minimizes the *gauche* interactions between the enolate and enone substituents. Also, the lower stereoselectivity found in the absence of HMPA can be explained by a competition of these two mechanisms, chelated with contact ion pairs, and nonchelated with separated ion pairs, in low concentration but more reactive, if the reaction is governed by Curtin–Hammet kinetics.

The next step in our synthetic sequence was the cleavage of the 1,3-dioxolan-4-one moiety present in compound **4** (and also in compound *epi*-**4a** for comparison purposes), which was achieved upon basic hydrolysis with ethanolic KOH and reprotonation to give the corresponding α-hydroxy-δ-oxocarboxylic acids. Interestingly, all these compounds were obtained as cyclic hemiacetal acid **5**, and only the product resulting from the hydrolysis of **4c** was obtained as an open α-hydroxy-δ-oxocarboxylic acid **5c**. In all the cases the reaction yields were equal or higher to 90% (Table 3).

The stereochemical structures of the cyclic hemiacetal acids **5** were established by NOEs. As a representative example, irradiation in compound **5a** of the signal at δ 7.49 corresponding to the *ortho*-protons of the phenyl group enhanced the signal at δ 0.76 corresponding to the methyl group. On the other hand, irradiation in *epi*-**5a** of the signal at δ 7.70 corresponding to the *ortho*-protons of the phenyl group gave NOE with the signal at δ 2.50 corresponding to the

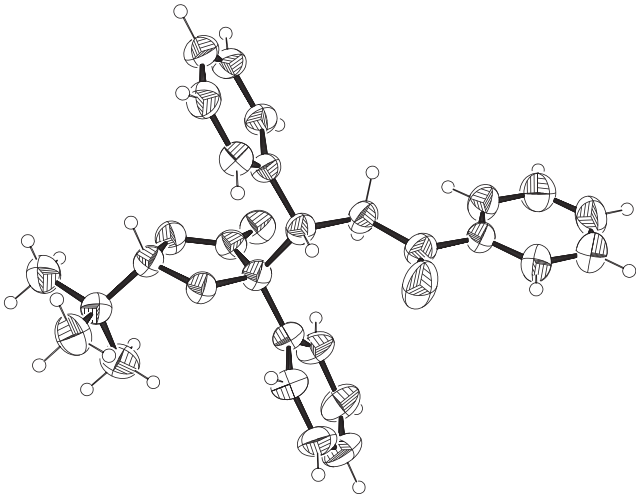


Figure 1. ORTEP drawing for compound **4c**.

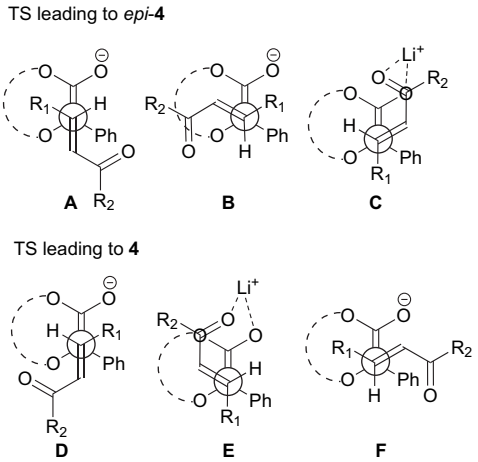


Figure 2. Possible TS for the approach of the enone to the *Re*-face of the enolate of **2**.

Table 3. Hydrolysis of the Michael adducts **4** and oxidative decarboxylation of hydroxy acids **5**

Entry	Adduct **4**	R_1	R_2	Yield **5** (%)[a,b]	Yield **6** (%)[a,c]
1	**4a**	CH_3	C_2H_5	90	75
2	*epi*-**4a**	CH_3	C_2H_5	94	78
3	**4b**	C_6H_5	CH_3	90	60
4	**4c**	C_6H_5	C_6H_5	95	82
5	**4d**	n-C_5H_{11}	CH_3	90	75
6	**4e**	$(CH_3)_2CH$	CH_3	90	82
7	**4f**	p-$MeOC_6H_4$	CH_3	90	72
8	**4g**	p-ClC_6H_4	CH_3	95	69

[a] Yields refer to isolated products.
[b] Yield from **4**.
[c] Yield from **5**.

proton on the tertiary carbon atom (Fig. 3). According to these experiments the absolute configuration of the tertiary carbon atom bearing the methyl group in the side chain was determined to be *R* in compound **5a** and *S* in compound *epi*-**5a**, upon the consideration that the absolute configuration of the quaternary carbon bearing the phenyl and carboxy groups was *S* in all the cases as explained earlier. These experiments also allowed the assignment of the absolute stereochemistry of the tertiary stereocenter of compound **4a**, that is, the *R* configuration of this stereocenter in compound **5a** was assigned to this carbon in its Michael adduct precursor **4a**. The opposite configuration *S* was therefore assigned to the adduct *epi*-**4a**.

Finally, the oxidative decarboxylation of the α-hydroxy acid moiety present in compound **5**, either in open form (**5c**) or as cyclic hemiacetal (**5a**, **5b**, **5d**–**5g**) was carried out by using a catalytic system developed in our laboratory that employs oxygen as terminal oxidant in the presence of pivalaldehyde and a catalytic amount of the Co(III)Me_2opba complex (Fig. 4).[10] Under these conditions the 1,4-diketones were obtained with fair to good yields. Much more importantly, products highly enantiomerically enriched (ee>99%) were obtained, as it was proven by ^{1}H NMR experiments using the chiral lanthanide shift reagent Eu(hfc)$_3$ under conditions previously optimized for racemic mixtures.

In summary, we have developed a strategy for the asymmetric Michael reaction of a masked benzoyl anion equivalent to α,β-enones that formally involves the use of (*S*)-mandelic acid as a source of chiral information and as a source of benzoyl anion. The preservation of the chiral information of the (*S*)-mandelic acid is based on the Seebach principle of self-regeneration of stereocenters whilst its use as an 'Umpoled' equivalent of the benzoyl anion is based on an oxidative decarboxylation of α-hydroxy acids developed in our laboratory. This strategy appears as a convenient method for the synthesis of highly enantioenriched chiral non-racemic 2-substituted-1,4-diketones.

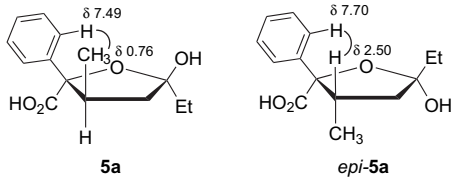


Figure 3. Significant NOE in compounds **5a** and *epi*-**5a**.

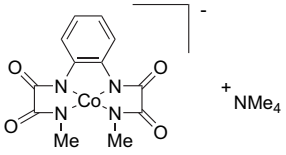


Figure 4. Co(III) *ortho*-phenylene-bis(*N*′-methyloxamidate) complex.

3. Experimental

3.1. General

All melting points are uncorrected. Column chromatography was performed on silica gel (Merck, silica gel 60, 230–400 mesh). Optical rotations were measured on a Perkin–Elmer 243 polarimeter. NMR spectra were recorded on a Bruker Advance 300 DPX spectrometer (300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR) or a Varian Unity 400 (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR) as indicated, and referenced to the residual non-deuterated solvent as internal standard. The carbon type was determined by DEPT experiments. Mass spectra were run by electron impact at 70 eV or by chemical ionization using methane as ionizing gas on a Fisons Instruments VG Autospec GC 8000 series spectrometer. (2*S*,5*S*)-*cis*-2-*tert*-Butyl-5-phenyl-1,3-dioxolan-4-one (**2**) was prepared according to the literature.[16] All new compounds were determined to be >95% pure by ^{1}H NMR spectroscopy.

3.2. General experimental procedure for the Michael reaction (inverse addition protocol)

A solution of freshly prepared LDA (1.25 mmol) in dry THF (1.3 mL) was slowly added to a solution of (2*S*,5*S*)-*cis*-2-*tert*-butyl-5-phenyl-1,3-dioxolan-4-one (**2**) (220 mg, 1 mmol) and α,β-unsaturated carbonyl compound **3** (1.25 mmol) in dry THF:HMPA (5 mL:0.53 mL) at −78 °C. The reaction was allowed to reach −40 °C and it was quenched with a saturated aqueous solution of NH_4Cl at this temperature, and extracted with diethyl ether (3×30 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated and the residue was purified by flash chromatography (silica gel, hexane:diethyl ether or hexane:dichloromethane) to afford Michael adducts **4**. Yields are included in Table 2.

3.2.1. (2*S*,5*S*,1′*R*)-2-(*tert*-Butyl)-5-(1′-methyl-3′-oxopentyl)-5-phenyl-1,3-dioxolan-4-one (4a). An oil; $[\alpha]_D^{25}$ −9 (*c* 1.1, $CHCl_3$); HRMS (EI) *m*/*z* 318.1833 (M^+, 9, $C_{19}H_{26}O_4$ requires 318.1831), 220 (62), 105 (100); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (s, 9H), 0.90 (d, *J*=7.0 Hz, 3H), 0.99 (t, *J*=7.2 Hz, 3H), 2.21 (dd, *J*=16.6, 8.9 Hz, 1H), 2.37 (dq, *J*=14.8, 7.4 Hz, 2H), 2.51 (dd, *J*=16.7, 4.3 Hz, 1H), 2.85 (m, 1H), 5.33 (s, 1H), 7.3–7.4 (m, 3H), 7.62 (dd, *J*=6.6, 1.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.6 (q), 14.5 (q), 23.3 (q), 35.2 (s), 36.6 (t), 37.5 (d), 43.9 (t), 84.1 (s), 109.5 (d), 125.8 (d), 127.9 (d), 128.0 (d), 136.2 (s), 172.6 (s), 209.1 (s).

3.2.2. (2*S*,5*S*,1′*S*)-2-(*tert*-Butyl)-5-(1′-methyl-3′-oxopentyl)-5-phenyl-1,3-dioxolan-4-one (*epi*-4a). An oil; $[\alpha]_D^{25}$

+26 (*c* 1.4, $CHCl_3$); HRMS (EI) *m/z* 318.1846 (M^+, 7.2, $C_{19}H_{26}O_4$ requires 318.1831), 220 (27.8), 105 (100); ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, *J*=7.4 Hz, 3H), 0.91 (s, 9H), 1.04 (d, *J*=6.8 Hz, 3H), 2.23 (m, 4H), 2.81 (m, 1H), 5.38 (s, 1H), 7.3–7.4 (m, 3H), 7.64 (dd, *J*=8.5, 1.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.5 (q), 15.4 (q), 23.5 (q), 35.5 (s), 36.3 (t), 39.0 (d), 42.9 (t), 84.7 (s), 110.6 (d), 125.4 (d), 128.0 (d), 128.1 (d), 137.1 (s), 173.2 (s), 209.5 (s).

3.2.3. (2*S*,5*S*,1′*S*)-2-(*tert*-Butyl)-5-(3′-oxo-1′-phenylbutyl)-5-phenyl-1,3-dioxolan-4-one (4b). An oil; $[\alpha]_D^{25}$ −75 (*c* 0.7, $CHCl_3$); HRMS (EI) *m/z* 366.1811 (M^+, 0.3, $C_{23}H_{26}O_4$ requires 366.1831), 220 (43), 147 (31), 105 (100); ^1H NMR (300 MHz, $CDCl_3$) δ 0.73 (s, 9H), 1.95 (s, 3H), 2.76 (dd, *J*=17.2, 4.1 Hz, 1H), 3.23 (dd, *J*=17.2, 10.2 Hz, 1H), 3.88 (dd, *J*=10.2, 4.3 Hz, 1H), 4.50 (s, 1H), 7.2–7.4 (m, 8H), 7.57 (dd, *J*=8.1, 2.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.2 (q), 30.6 (q), 35.0 (s), 43.6 (t), 50.4 (d), 84.7 (s), 110.1 (d), 125.7 (d), 127.7 (d), 128.1 (d), 128.2 (d), 128.3 (d), 129.3 (d), 137.2 (s), 137.6 (s), 172.3 (s), 205.3 (s).

3.2.4. (2*S*,5*S*,1′*R*)-2-(*tert*-Butyl)-5-phenyl-5-(3′-oxo-1′-phenylbutyl)-1,3-dioxolan-4-one (*epi*-4b). Mp 136–138 °C (CH_2Cl_2); $[\alpha]_D^{25}$ +69 (*c* 1.4, $CHCl_3$); HRMS (EI) *m/z* 366.1831 (M^+, 0.4, $C_{23}H_{26}O_4$ requires 366.1831), 220 (43), 105 (100); ^1H NMR (300 MHz, $CDCl_3$) δ 0.82 (s, 9H), 1.83 (s, 3H), 2.40 (dd, *J*=17.1, 4.4 Hz, 1H), 3.05 (dd, *J*=17.1, 10.6 Hz, 1H), 3.96 (dd, *J*=10.6, 4.4 Hz, 1H), 4.53 (s, 1H), 7.2–7.4 (m, 8H), 7.79 (dd, *J*=8.5, 1.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.5 (q), 30.2 (q), 35.2 (s), 42.7 (t), 49.5 (d), 85.3 (s), 110.4 (d), 125.5 (d), 128.1 (d), 128.2 (d), 128.3 (d), 128.7 (d), 129.4 (d), 137.2 (s), 137.3 (s), 172.6 (s), 205.8 (s).

3.2.5. (2*S*,5*S*,1′*S*)-2-(*tert*-Butyl)-5-(1′,3′-diphenyl-3′-oxopropyl)-5-phenyl-1,3-dioxolan-4-one (4c). Mp 116–118 °C (CH_2Cl_2:hexane); $[\alpha]_D^{25}$ −99 (*c* 1.0, $CHCl_3$); HRMS (EI) *m/z* 428.1980 (M^+, 0.3, $C_{28}H_{28}O_4$ requires 428.1988), 209 (32), 105 (100); ^1H NMR (300 MHz, $CDCl_3$) δ 0.72 (s, 9H), 3.26 (dd, *J*=17.3, 3.8 Hz, 1H), 3.84 (dd, *J*=17.3, 10.4 Hz, 1H), 4.11 (dd, *J*=10.2, 3.8 Hz, 1H), 4.45 (s, 1H), 7.2–7.6 (m, 11H), 7.64 (dd, *J*=7.7, 1.5 Hz, 2H), 7.81 (dd, *J*=8.6, 1.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.2 (q), 35.0 (s), 38.6 (t), 50.6 (d), 85.0 (s), 110.2 (d), 125.8 (d), 127.6 (d), 128.0 (d), 128.1 (d), 128.2 (d), 128.3 (d), 128.5 (d), 129.3 (d), 133.1 (d), 136.6 (s), 137.4 (s), 137.8 (s), 172.4 (s), 196.8 (s).

3.2.6. (2*S*,5*S*,1′*R*)-2-(*tert*-Butyl)-5-(1′,3′-diphenyl-3′-oxopropyl)-5-phenyl-1,3-dioxolan-4-one (*epi*-4c). Mp 168–170 °C (CH_2Cl_2); $[\alpha]_D^{25}$ +88 (*c* 0.8, $CHCl_3$); HRMS (EI) *m/z* 428.1980 (M^+, 0.5, $C_{28}H_{28}O_4$ requires 428.1988), 209 (32), 105 (100); ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (s, 9H), 2.88 (dd, *J*=17.3, 3.8 Hz, 1H), 3.70 (dd, *J*=17.3, 10.7 Hz, 1H), 4.17 (dd, *J*=10.7, 3.6 Hz, 1H), 4.59 (s, 1H), 7.2–7.5 (m, 11H), 7.69 (dd, *J*=8.6, 1.5 Hz, 2H), 7.85 (dd, *J*=8.7, 1.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.5 (q), 35.3 (s), 37.6 (t), 49.8 (d), 85.6 (s), 110.4 (d), 125.5 (d), 127.8 (d), 128.0 (d), 128.3 (d), 128.37 (d), 128.42 (d), 128.6 (d), 129.5 (d), 133.0 (d), 136.7 (s), 137.3 (s), 137.4 (s), 172.7 (s), 197.2 (s).

3.2.7. (2*S*,5*S*,1′*R*)-2-(*tert*-Butyl)-5-(1′-*n*-pentyl-3′-oxobutyl)-5-phenyl-1,3-dioxolan-4-one (4d). An oil; $[\alpha]_D^{25}$ −30 (*c* 0.5, $CHCl_3$); HRMS (EI) *m/z* 360.2286 (M^+, 5.8, $C_{22}H_{32}O_4$ requires 360.2301), 247 (14), 220 (100), 141 (20), 105 (91); ^1H NMR (300 MHz, $CDCl_3$) δ 0.84 (t, *J*=6.6 Hz, 3H), 0.87 (s, 9H), 1.20 (m, 7H), 1.81 (m, 1H), 2.12 (s, 3H), 2.18 (dd, *J*=17.1, 4.7 Hz, 1H), 2.57 (dd, *J*=17.1, 6.8 Hz, 1H), 2.85 (m, 1H), 5.30 (s, 1H), 7.36 (m, 3H), 7.66 (dd, *J*=7.7, 1.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9 (q), 22.4 (t), 23.3 (q), 27.1 (t), 29.2 (t), 30.5 (q), 31.8 (t), 34.8 (s), 41.3 (d), 42.6 (t), 83.5 (s), 108.7 (d), 126.1 (d), 127.9 (d), 128.1 (d), 135.8 (s), 172.5 (s), 206.7 (s).

3.2.8. (2*S*,5*S*,1′*S*)-2-(*tert*-Butyl)-5-(1′-isopropyl-3′-oxobutyl)-5-phenyl-1,3-dioxolan-4-one (4e). Mp 78–81 °C (CH_2Cl_2); $[\alpha]_D^{25}$ −41 (*c* 0.5, $CHCl_3$); HRMS (EI) *m/z* 332.1991 (M^+, 2.3, $C_{20}H_{28}O_4$ requires 332.1988), 221 (14), 220 (100), 219 (28); ^1H NMR (300 MHz, $CDCl_3$) δ 0.51 (d, *J*=6.8 Hz, 3H), 0.80 (d, *J*=7.0 Hz, 3H), 0.83 (s, 9H), 2.07 (m, 1H), 2.12 (s, 3H), 2.26 (dd, *J*=17.0, 4.4 Hz, 1H), 2.57 (dd, *J*=17.0, 7.1 Hz, 1H), 2.84 (ddd, *J*=7.2, 4.5, 1.9 Hz, 1H), 5.28 (s, 1H), 7.32 (m, 3H), 7.67 (dd, *J*=7.9, 1.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.1 (q), 23.1 (q), 23.3 (q), 25.8 (d), 30.2 (q), 35.0 (s), 38.3 (t), 47.6 (d), 83.7 (s), 109.4 (d), 125.8 (d), 128.0 (d), 128.1 (d), 137.0 (s), 173.0 (s), 206.7 (s).

3.2.9. (2*S*,5*S*,1′*S*)-2-(*tert*-Butyl)-5-(1′-*p*-methoxyphenyl-3′-oxobutyl)-5-phenyl-1,3-dioxolan-4-one (4f). Mp 110–111 °C (CH_2Cl_2); $[\alpha]_D^{25}$ −71 (*c* 1.5, $CHCl_3$); HRMS (EI) *m/z* 396.1946 (M^+, 0.3, $C_{24}H_{28}O_5$ requires 396.1936), 177 (100), 135 (10), 105 (16), 77 (8); ^1H NMR (300 MHz, $CDCl_3$) δ 0.73 (s, 9H), 1.94 (s, 3H), 2.71 (dd, *J*=16.8, 4.4 Hz, 1H), 3.17 (dd, *J*=16.8, 10.2 Hz, 1H), 3.77 (s, 3H), 3.83 (dd, *J*=10.2, 4.4 Hz, 1H), 4.58 (s, 1H), 6.78 (d, *J*=8 Hz, 2H), 7.12 (d, *J*=8 Hz, 1H), 7.26–7.34 (m, 3H), 7.56 (dd, *J*=8.1, 1.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.2 (q), 30.5 (q), 35.0 (s), 43.7 (t), 49.6 (d), 55.1 (q), 84.7 (s), 109.9 (d), 113.6 (d), 125.7 (d), 128.0 (d), 128.1 (d), 129.4 (s), 130.3 (d), 137.2 (s), 158.9 (s), 172.2 (s), 205.4 (s).

3.2.10. (2*S*,5*S*,1′*S*)-2-(*tert*-Butyl)-5-(1′-*p*-chlorophenyl-3′-oxobutyl)-5-phenyl-1,3-dioxolan-4-one (4g). An oil; $[\alpha]_D^{25}$ −70 (*c* 0.9, $CHCl_3$); HRMS (EI) *m/z* 400.1441 (M^+, 0.3, $C_{23}H_{25}ClO_4$ requires 400.1441), 220 (20), 181 (13), 105 (100); ^1H NMR (300 MHz, $CDCl_3$) δ 0.76 (s, 9H), 1.97 (s, 3H), 2.75 (dd, *J*=16.8, 4.2 Hz, 1H), 3.17 (dd, *J*=16.8, 10.2 Hz, 1H), 3.86 (dd, *J*=10.2, 4.2 Hz, 1H), 4.72 (s, 1H), 7.11 (d, *J*=8.7 Hz, 2H), 7.21 (d, *J*=8.7 Hz, 1H), 7.27–7.31 (m, 3H), 7.53 (dd, *J*=7.7, 1.95 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.2 (q), 30.5 (q), 35.2 (s), 43.6 (t), 49.8 (d), 84.4 (s), 110.2 (d), 125.6 (d), 128.1 (d), 128.3 (d), 128.4 (d), 130.6 (6), 133.4 (s), 136.1 (s), 136.9 (s), 172.0 (s), 204.9 (s).

3.3. General experimental procedure for the basic hydrolysis of the Michael adducts 4

The Michael adducts **4** (0.28 mmol) were treated with a 5% KOH solution in ethanol (0.63 mL, 0.56 mmol) at room temperature until complete reaction of the starting material (TLC) is achieved. The solution was poured into ice and

acidified with 1 M HCl until pH 2. The aqueous mixture was extracted with EtOAc (3×30 mL), and the organic layers were washed with brine until neutrality, dried, filtered, and concentrated under reduced pressure to give compound **5**. Yields are included in Table 3.

3.3.1. (2*S*,3*R*,5*R*)-5-Ethyl-5-hydroxy-3-methyl-2-phenyltetrahydrofuran-2-carboxylic acid (5a). An oil; $[\alpha]_D^{27}$ +89 (*c* 1.0, $CHCl_3$); HRMS (CI) *m/z* 233.1153 (M^++1−H_2O, 100, $C_{14}H_{17}O_3$ requires 233.1178), 215 (93), 188 (32); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.76 (d, *J*=6.8 Hz, 3H), 1.15 (t, *J*=7.6 Hz, 3H), 1.62 (q, *J*=6.8 Hz, 1H), 2.14 (q, *J*=7.6 Hz, 2H), 2.50 (m, 2H), 7.3–7.4 (m, 3H), 7.49 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.6 (q), 17.0 (q), 25.4 (t), 35.4 (d), 42.8 (t), 88.7 (s), 113.8 (s), 125.7 (d), 128.17 (d), 128.22 (d), 131.2 (s), 173.6 (s).

3.3.2. (2*S*,3*S*,5*S*)-5-Ethyl-5-hydroxy-3-methyl-2-phenyltetrahydrofuran-2-carboxylic acid (*epi*-5a). An oil; $[\alpha]_D^{25}$ +91 (*c* 0.8, $CHCl_3$); HRMS (EI) *m/z* 232.1090 (M^+-H_2O, 0.6, $C_{14}H_{16}O_3$ requires 232.1100), 105 (100); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (t, *J*=7.5 Hz, 3H), 1.18 (d, *J*=7.0 Hz, 3H), 1.78 (dd, *J*=12.1, 4.5 Hz, 1H), 1.86 (br s, 1H, OH), 2.11 (q, *J*=7.5 Hz, 2H), 2.41 (dd, *J*=12.4, 10.2 Hz, 1H), 2.50 (m, 1H), 7.3–7.5 (m, 3H), 7.70 (dd, *J*=8.1, 1.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.5 (q), 14.8 (q), 25.5 (t), 39.0 (d), 41.3 (t), 89.1 (s), 113.4 (s), 126.1 (d), 128.4 (d), 128.8 (d), 132.2 (s), 171.8 (s).

3.3.3. (2*S*,3*S*,5*R*)-5-Hydroxy-3-methyl-2,3-diphenyltetrahydrofuran-2-carboxylic acid (5b). An oil; $[\alpha]_D^{25}$ +104 (*c* 1.3, $CHCl_3$); HRMS (EI) *m/z* 281.1176 (M^++1−H_2O, 100, $C_{18}H_{17}O_3$ requires 281.1178), 264 (45), 263 (93), 253 (57), 236 (30), 193 (39), 176 (34), 105 (22); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.00 (s, 3H), 2.31 (dd, *J*=13.2, 4.3 Hz, 1H), 2.93 (dd, *J*=13.2, 8.6 Hz, 1H), 3.63 (dd, *J*=8.7, 4.4 Hz, 1H), 7.0–7.2 (m, 8H), 7.33 (dd, *J*=7.9, 1.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.4 (q), 46.7 (t), 47.5 (d), 90.5 (s), 111.3 (s), 126.0 (d), 127.1 (d), 127.7 (d), 127.9 (d), 128.2 (d), 128.3 (d), 130.7 (s), 139.1 (s), 173.0 (s).

3.3.4. (2*S*,3*S*)-2-Hydroxy-5-oxo-2,3,5-triphenylpentanoic acid (5c). Mp 128–130 °C (EtOAc); $[\alpha]_D^{25}$ −58 (*c* 0.7, CH_3OH); HRMS (EI) *m/z* 342.1261 (M^+-H_2O, 7, $C_{23}H_{18}O_3$ requires 342.1256), 296 (67), 105 (100); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.16 (dd, *J*=16.8, 2.5 Hz, 1H), 3.85 (dd, *J*=17.0, 11.1 Hz, 1H), 4.24 (dd, *J*=0.9, 2.5 Hz, 1H), 6.9–7.6 (m, 13H), 7.87 (d, *J*=8.0 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 41.5 (t), 48.9 (d), 81.3 (s), 126.1 (d), 126.2 (d), 126.9 (d), 127.3 (d), 127.6 (d), 128.2 (d), 129.1 (d), 130.2 (d), 133.5 (d), 137.0 (s), 140.1 (s), 142.2 (s), 176.1 (s), 198.5 (s).

3.3.5. (2*S*,3*R*,5*R*)-5-Hydroxy-5-methyl-3-*n*-pentyl-2-phenyltetrahydrofuran-2-carboxylic acid (5d). An oil; $[\alpha]_D^{25}$ +74 (*c* 1.4, $CHCl_3$); HRMS (EI) *m/z* 247.1709 (M^+-CO_2H, 3, $C_{16}H_{23}O_2$ requires 247.1698), 230 (67), 173 (85), 160 (42), 105 (100); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (t, *J*=7.2 Hz, 3H), 1.00 (m, 1H), 1.14 (m, 7H), 1.76 (dd, *J*=12.6, 3.7 Hz, 1H), 1.89 (s, 3H), 2.36 (ddt, *J*=7.8, 7.7, 3.5 Hz, 1H), 2.49 (dd, *J*=12.6, 8.0 Hz, 1H), 7.38 (tt, *J*=8.7, 1.4 Hz, 1H), 7.44 (m, 2H), 7.53 (dd, *J*=8.6, 1.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9 (q), 18.5 (q), 22.5 (t), 26.4 (t), 30.7 (t), 31.5 (t), 41.2 (d), 42.6 (t), 88.9 (s), 111.3 (s), 125.7 (d), 128.1 (d), 128.2 (d), 131.3 (s), 173.5 (s).

3.3.6. (2*S*,3*S*,5*R*)-5-Hydroxy-3-isopropyl-5-methyl-2-phenyltetrahydrofuran-2-carboxylic acid (5e). Mp 105–107 °C ($CHCl_3$); $[\alpha]_D^{25}$ +123 (*c* 0.6, $CHCl_3$); HRMS (EI) *m/z* 228.1157 (M^+-2H_2O, 0.4, $C_{15}H_{16}O_2$ requires 228.1150), 202 (42), 160 (34), 159 (100), 131 (13), 115 (17), 105 (94), 77 (60), 51 (19); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.60 (d, *J*=6.8 Hz, 3H), 0.78 (d, *J*=6.9 Hz, 3H), 1.80 (m, 1H), 1.91 (s, 3H), 1.97 (dd, *J*=12.9, 4.6 Hz, 1H), 2.29 (dd, *J*=12.9, 8.6 Hz, 1H), 2.47 (m, 1H), 7.46 (m, 3H), 7.52 (dd, *J*=8.5, 1.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.7 (q), 18.3 (q), 21.6 (q), 26.5 (d), 36.2 (t), 45.5 (d), 89.3 (s), 111.2 (s), 126.0 (d), 128.1 (d), 128.2 (d), 131.1 (s), 173.5 (s).

3.3.7. (2*S*,3*S*,5*R*)-5-Hydroxy-5-methyl-3-*p*-methoxyphenyl-2-phenyltetrahydrofuran-2-carboxylic acid (5f). An oil; $[\alpha]_D^{25}$ +124 (*c* 1.1, $CHCl_3$); HRMS (EI) *m/z* 310.1197 (M^+-H_2O, 11, $C_{19}H_{18}O_4$ requires 310.1205), 266 (5), 223 (7), 176 (100), 134 (12), 105 (80), 77 (19); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.00 (s, 3H), 2.26 (dd, *J*=13.2, 4.2 Hz, 1H), 2.92 (dd, *J*=13.2, 8.7 Hz, 1H), 3.60 (dd, *J*=8.7, 4.2 Hz, 1H), 3.67 (s, 3H), 6.62 (d, *J*=9.0 Hz, 2H), 6.99 (d, *J*=9.0 Hz, 1H), 7.11–7.22 (m, 3H), 7.33 (dd, *J*=8.1, 1.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.3 (q), 46.7 (d), 46.8 (t), 55.0 (q), 90.4 (s), 111.2 (s), 113.6 (d), 125.9 (d), 127.7 (d), 127.8 (d), 129.3 (d), 130.9 (s), 131.1 (s), 158.4 (s), 173.1 (s).

3.3.8. (2*S*,3*S*,5*R*)-3-*p*-Chlorophenyl-5-hydroxy-5-methyl-2-phenyltetrahydrofuran-2-carboxylic acid (5g). An oil; $[\alpha]_D^{25}$ +99 (*c* 1.1, $CHCl_3$); HRMS (EI) *m/z* 314.0710 (M^+-H_2O, 0.3, $C_{18}H_{15}O_3Cl$ requires 314.0709), 270 (9), 176 (42), 105 (100), 77 (26); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.00 (s, 3H), 2.24 (dd, *J*=13.5, 4.2 Hz, 1H), 2.94 (dd, *J*=13.5, 8.7 Hz, 1H), 3.61 (dd, *J*=8.7, 4.2 Hz, 1H), 7.00 (d, *J*=8.7 Hz), 7.06 (d, *J*=8.7 Hz, 1H), 7.15–7.23 (m, 3H), 7.31 (dd, *J*=7.5, 1.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.3 (q), 46.8 (t), 46.9 (d), 90.3 (s), 111.2 (s), 125. 8 (d), 127.9 (d), 128.1 (d), 128.4 (d), 129.5 (d), 130.4 (s), 132.9 (s), 137.7 (s), 172.7 (s).

3.4. General experimental procedure for the catalytic aerobic decarboxylation of compound 5

A solution of compound **5** (0.11 mmol) in 0.2 mL of acetonitrile was added to a stirred mixture of Co(III)Me_2opba complex (6.5×10^{-3} mmol) and pivalaldehyde (0.33 mmol) in 0.2 mL of acetonitrile under a dioxygen atmosphere. The mixture was stirred at room temperature until consumption of the starting material as indicated by TLC. The reaction product **6** was purified by flash column chromatography.

3.4.1. (*R*)-2-Methyl-1-phenyl-1,4-hexanedione (6a). An oil; $[\alpha]_D^{25}$ +16 (*c* 0.6, $CHCl_3$); HRMS (EI) *m/z* 204.1159 (M^+, 5, $C_{13}H_{16}O_2$ requires 204.1150), 175 (51), 105 (100); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (t, *J*=7.4 Hz, 3H), 1.16 (d, *J*=7.4 Hz, 3H), 2.47 (q, *J*=7.4 Hz, 2H), 2.54 (dd, *J*=17.9, 5.1 Hz, 1H), 3.12 (dd, *J*=17.9, 8.7 Hz, 1H), 3.97

(m, 1H), 7.45 (m, 2H), 7.53 (m, 1H), 7.96 (dd, *J*=8.4, 1.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.6 (q), 17.8 (q), 36.0 (t), 36.1 (d), 45.6 (t), 128.4 (d), 128.6 (d), 133.0 (d), 135.9 (s), 203.5 (s), 210.0 (s).

3.4.2. (*S*)-2-Methyl-1-phenyl-1,4-hexanedione (*epi*-6a). An oil; $[\alpha]_D^{25}$ −15 (*c* 1.3, $CHCl_3$); ^{1}H and ^{13}C NMR spectra identical to those of compound **6a**.

3.4.3. (*S*)-1,2-Diphenyl-1,4-pentanedione (6b). An oil; $[\alpha]_D^{25}$ +263 (*c* 1.1, $CHCl_3$). HRMS (EI) *m*/*z* 252.1155 (M^+, 7.3, $C_{17}H_{16}O_2$ requires 252.1150), 234 (2), 105 (100), 77 (24); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.19 (s, 3H), 2.76 (dd, *J*=18.1, 4.0 Hz, 1H), 3.62 (dd, *J*=17.9, 10.0 Hz, 1H), 5.11 (dd, *J*=10.2, 4.0 Hz, 1H), 7.2–7.4 (m, 7H), 7.47 (tt, *J*=6.4, 1.3 Hz, 1H), 7.96 (dd, *J*=8.7, 1.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.7 (q), 48.1 (t), 48.8 (d), 127.3 (d), 128.1 (d), 128.4 (d), 128.9 (d), 129.2 (d), 132.9 (d), 136.3 (s), 138.6 (s), 198.9 (s), 206.8 (s).

3.4.4. (*S*)-1,2,4-Triphenyl-1,4-butanedione (6c). Mp 153–155 °C (CH_2Cl_2); $[\alpha]_D^{25}$ +50 (*c* 1.1, $CHCl_3$); HRMS (EI) *m*/*z* 314.1311 (M^+, 10, $C_{22}H_{18}O_2$ requires 314.1307), 209 (12), 111 (17), 105 (100), 97 (29), 77 (31); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.31 (dd, *J*=18.1, 3.8 Hz, 1H), 4.22 (dd, *J*=18.0, 10.0 Hz, 1H), 5.33 (dd, *J*=10.0, 3.7 Hz, 1H), 7.23 (tt, *J*=7.2, 2.3 Hz, 1H), 7.3–7.5 (m, 8H), 7.49 (tt, *J*=7.4, 2.1 Hz, 1H), 7.56 (tt, *J*=7.3, 1.2 Hz, 1H), 7.99 (dd, *J*=7.1, 1.5 Hz, 2H), 8.03 (dd, *J*=7.2, 1.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.9 (t), 48.7 (d), 127.4 (d), 128.1 (d), 128.2 (d), 128.5 (d), 128.6 (d), 128.9 (d), 129.2 (d), 132.9 (d), 133.3 (d), 136.3 (s), 136.4 (s), 138.6 (s), 198.1 (s), 198.9 (s).

3.4.5. (*R*)-2-Pentyl-1-phenyl-1,4-pentanedione (6d). An oil; $[\alpha]_D^{25}$ +57 (*c* 0.5, $CHCl_3$); HRMS (EI) *m*/*z* 246.1638 (M^+, 1.2, $C_{16}H_{22}O_2$ requires 246.1620), 176 (26), 133 (15), 105 (100), 77 (77); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81 (t, *J*=6.6 Hz, 3H), 1.21 (m, 6H), 1.41 (m, 1H), 1.63 (m, 1H), 2.13 (s, 3H), 2.58 (dd, *J*=18.0, 4.1 Hz, 1H), 3.14 (dd, *J*=18.1, 9.4 Hz, 1H), 3.90 (m, 1H), 7.45 (br t, *J*=7.7 Hz, 2H), 7.54 (tt, *J*=7.1, 1.5 Hz, 1H), 7.97 (dd, *J*=8.7, 1.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9 (q), 22.4 (t), 26.8 (t), 30.1 (q), 31.7 (t), 32.3 (t), 41.3 (d), 45.1 (t), 128.4 (d), 128.6 (d), 132.9 (d), 136.8 (s), 203.4 (s), 207.4 (s).

3.4.6. (*S*)-2-Isopropyl-1-phenyl-1,4-pentanedione (6e). An oil; $[\alpha]_D^{25}$ +110 (*c* 0.7, $CHCl_3$); HRMS (EI) *m*/*z* 218.1292 (M^+, 2, $C_{14}H_{18}O_2$ requires 218.1307), 161 (17), 133 (5), 105 (100), 77 (33), 51 (9); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (d, *J*=6.8 Hz, 3H), 1.04 (d, *J*=6.9 Hz, 3H), 2.02 (m, 1H), 2.15 (s, 3H), 2.52 (dd, *J*=18.0, 3.3 Hz, 1H), 3.18 (dd, *J*=18.0, 10.5 Hz, 1H), 3.82 (ddd, *J*=10.2, 4.8, 3.3 Hz, 1H), 7.44 (dt, *J*=7.5, 1.2 Hz, 2H), 7.52 (tt, *J*=7.2, 1.5 Hz, 1H), 7.96 (dd, *J*=8.7, 1.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.5 (q), 21.2 (q), 29.7 (d), 30.1 (q), 41.1 (t), 47.0 (d), 128.4 (d), 128.5 (d), 132.7 (d), 137.4 (s), 203.1 (s), 207.7 (s).

3.4.7. (*S*)-2-*p*-Methoxyphenyl-1-phenyl-1,4-pentanedione (6f). An oil; $[\alpha]_D^{25}$ +39 (*c* 1.8, $CHCl_3$); HRMS (EI) *m*/*z* 282.1244 (M^+, 66, $C_{18}H_{18}O_3$ requires 282.1255), 264 (19), 177 (100), 135 (21), 105 (88), 91 (11), 77 (51); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.18 (s, 3H), 2.73 (dd, *J*=17.7, 4.2 Hz, 1H), 3.57 (dd, *J*=17.7, 9.9 Hz, 1H), 3.73 (s, 3H), 5.06 (dd, *J*=9.9, 4.2 Hz, 1H), 6.80 (d, *J*=8.7 Hz, 2H), 7.17 (d, *J*=8.7 Hz, 1H), 7.36 (d, *J*=7.2 Hz, 2H), 7.46 (tt, *J*=7.2, 1.5 Hz, 1H), 7.95 (dd, *J*=7.2, 1.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.0 (q), 47.8 (d), 48.0 (t), 55.1 (q), 114.5 (d), 128.4 (d), 128.8 (d), 129.1 (d), 130.4 (s), 132.8 (d), 136.2 (s), 158.7 (s), 199.9 (s), 207.0 (s).

3.4.8. (*S*)-2-*p*-Chlorophenyl-1-phenyl-1,4-pentanedione (6g). An oil; $[\alpha]_D^{25}$ +13 (*c* 0.6, $CHCl_3$); HRMS (EI) *m*/*z* 286.0760 (M^+, 4, $C_{17}H_{15}ClO_2$ requires 286.0760), 268 (1), 165 (1), 138 (3), 105 (100), 77 (25); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.19 (s, 3H), 2.74 (dd, *J*=18.0, 4.2 Hz, 1H), 3.57 (dd, *J*=18.0, 9.8 Hz, 1H), 5.09 (dd, *J*=9.8, 4.2 Hz, 1H), 7.20 (d, *J*=8.6 Hz, 2H), 7.25 (d, *J*=8.6 Hz, 1H), 7.38 (d, *J*=7.5 Hz, 2H), 7.50 (tt, *J*=7.2, 1.5 Hz, 1H), 7.93 (dd, *J*=7.5, 1.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.0 (q), 47.8 (t), 47.9 (d), 128.5 (d), 128.8 (d), 129.3 (d), 129.4 (d), 133.1 (d), 133.2 (s), 136.0 (s), 137.0 (s), 198.5 (s), 206.5 (s).

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References and notes

1. (a) Ellison, R. A. *Synthesis* **1973**, 397–412; (b) Bentley, P. H. *Chem. Soc. Rev.* **1973**, *2*, 29–48; (c) Stetter, H.; Kulhmann, H. *Synthesis* **1975**, 379–382; (d) Sum, P. E.; Weiler, L. *Can. J. Chem.* **1978**, *56*, 2301–2304; (e) Wenkert, E.; Buckwalter, B. L.; Craveiro, A. A.; Sanchez, E. L.; Sathe, S. S. *J. Am. Chem. Soc.* **1978**, *100*, 1267–1273; (f) Mussatto, M. C.; Savoia, D.; Trombini, C.; Umani-Ronchi, A. *J. Org. Chem.* **1980**, *45*, 4002–4005; (g) Wenkert, E.; Greenberg, R. S.; Ragu, M. S. *J. Org. Chem.* **1985**, *50*, 4681–4685; (h) Takahashi, K.; Aihara, T.; Ogura, K. *Chem. Lett.* **1987**, 2359–2362; (i) Pecuniso, A.; Menicagli, R. *J. Org. Chem.* **1988**, *53*, 2614–2617; (j) Fiandanese, V.; Marchese, G.; Naso, F. *Tetrahedron Lett.* **1988**, *29*, 3587–3590; (k) Bergman, R.; Nilsson, B.; Wickberg, B. *Tetrahedron Lett.* **1990**, *31*, 2783–2786; (l) Yamashita, M.; Tashika, H.; Uchida, M. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 1257–1261; (m) Tsukasa, H. *Biosci. Biotechnol. Biochem.* **1994**, *58*, 1181–1182; (n) Piancattelli, G.; D'Auria, M.; D'Onofrio, F. *Synthesis* **1994**, 867–889; (o) Galopin, C. C. *Tetrahedron Lett.* **2001**, *42*, 5589–5591; (p) Roberts, S. M.; Santoro, M. G.; Sickle, E. S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1735–1742.
2. (a) Gribble, G. W. *Comprehensive Heterocyclic Chemistry*; Katrizky, A. R., Rees, C. W., Scriven, E. F., Eds.; Pergamon: Oxford, 1996; Vol. 2, p 207; (b) Benassi, R. *Comprehensive Heterocyclic Chemistry*; Katrizky, A. R., Rees, C. W., Scriven, E. F., Eds.; Pergamon: New York, NY, 1996; Vol. 2, p 259; (c) Amarnath, V.; Anthony, D. C.; Amarnath, K.; Valentine, W. M.; Wetterau, L. A.; Graham, D. G. *J. Org. Chem.* **1991**, *56*, 6924–6931; (d) Hou, X. L.; Cheung, H. Y.;

Hon, T. U.; Kwan, P. L.; Lo, T. H.; Tong, S. Y.; Wong, H. N. C. *Tetrahedron* **1998**, *54*, 1955–2020; (e) Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2849–2866; (f) Ferreira, V. F.; de Sousa, M. C. B. V.; Cunha, A. C.; Pereira, L. O. R.; Ferreira, M. L. G. *Org. Prep. Proced. Int.* **2001**, *33*, 411–454; (g) Raghavan, S.; Anuradha, K. *Synlett* **2003**, 711–713.

3. (a) Pecunioso, A.; Menicagli, R. *J. Org. Chem.* **1988**, *53*, 2614–2617; (b) Freeman, F.; Kim, D. S. H. L.; Rodriguez, E. *J. Org. Chem.* **1992**, *57*, 1722–1727; (c) Wedler, C.; Schick, H. *Synthesis* **1992**, 543–544; (d) Katritzky, A. R.; Zhang, G. F.; Jiang, J. L. *J. Org. Chem.* **1995**, *60*, 7605–7611; (e) Huang, J.-T.; Su, T.-L.; Watanabe, K. A. *J. Org. Chem.* **1991**, *56*, 4811–4815; (f) Lu, X. Y.; Ji, J. G.; Ma, D. W.; Shen, W. *J. Org. Chem.* **1991**, *56*, 5774–5778; (g) Bergman, R.; Nilsson, R.; Wickberg, B. *Tetrahedron Lett.* **1990**, *31*, 2783–2786; (h) Matsumoto, S.; Okubo, Y.; Mikami, K. *J. Am. Chem. Soc.* **1998**, *120*, 4015–4016; (i) Yasuda, M.; Tsuji, S.; Shigeyoshi, Y.; Baba, A. *J. Am. Chem. Soc.* **2002**, *124*, 7440–7447; (j) Yuguchi, M.; Tokuda, M.; Orito, K. *J. Org. Chem.* **2004**, *69*, 908–914; (k) Song Xue, A.; Li, L.; Liu, Y.; Guo, Q. *J. Org. Chem.* **2006**, *71*, 215–218.
4. Seyferth, D.; Hui, R. C. *J. Am. Chem. Soc.* **1985**, *107*, 4551–4553.
5. (a) Cooke, M. P., Jr.; Parlman, R. M. *J. Am. Chem. Soc.* **1977**, *99*, 5222–5224; (b) Hegedus, L. S.; Perry, R. J. *J. Org. Chem.* **1985**, *50*, 4955–4960; (c) Corey, E. J.; Hegedus, L. S. *J. Am. Chem. Soc.* **1969**, *91*, 4926–4928; (d) Hermanson, J. R.; Hershberger, J. W.; Pinhas, A. R. *Organometallics* **1995**, *14*, 5426–5437; (e) Seyferth, D.; Hui, R. C. *Tetrahedron Lett.* **1986**, *27*, 1473–1476; (f) Lipshutz, B. H.; Elworthy, T. R. *Tetrahedron Lett.* **1990**, *31*, 477–480; (g) Li, N.-S.; Yu, S.; Kabalka, G. W. *Organometallics* **1998**, *17*, 3815–3818.
6. (a) Hassner, A.; Lokanatha Rai, K. M. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, p 541; (b) Stetter, H.; Kuhlmann, H. *Org. React.* **1991**, *40*, 407–496; (c) Yadav, J. S.; Anuradha, K.; Subba Reddy, B. V.; Eeshwaraiah, B. *Tetrahedron Lett.* **2003**, *44*, 8959–8962; (d) Anjaiah, S.; Chandrasekhar, S.; Grée, R. *Tetrahedron Lett.* **2004**, *45*, 569–571; (e) Mattson, A. E.; Bharadwaj, A. R.; Scheidt, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 2314–2315; (f) Johnson, J. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 1326–1328; (g) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534–541; (h) Barrett, A. G. M.; Andrew, C.; Love, A. C.; Tedeschi, L. *Org. Lett.* **2004**, *6*, 3377–3380; (i) Myers, M. C.; Bharadwaj, A. R.; Milgram, B. C.; Scheidt, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 14675–14680.
7. (a) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346–353; (b) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336–345; (c) Alexakis, A.; Benhaim, C. *Org. Lett.* **2000**, *2*, 2579–2581; (d) Chataigner, I.; Gennari, C.; Piarulli, U.; Ceccarelli, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 916–918; (e) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171–196; (f) Enders, D.; Berner, O. M.; Vignola, N.; Bats, J. W. *Chem. Commun.* **2001**, 2498–2499; (g) Hupe, E.; Knochel, P. *Angew. Chem., Int. Ed.* **2001**, *40*, 3022–3025; (h) Kacprzak, K.; Gawronski, J. *Synthesis* **2001**, 961–998; (i) Luchaco-Cullis, C. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 8192–8193; (j) List, B. *Tetrahedron* **2002**, *58*, 5573–5590; (k) Molt, O.; Schrader, T. *Synthesis* **2002**, 2633–2670; (l) Duursma, A.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2003**, *125*, 3700–3701; (m) Ma, J. A.; Cahard, D. *Angew. Chem., Int. Ed.* **2004**, *43*, 4566–4583; (n) Andrey, O.; Alexakis, A.; Tomassini, A.; Bernardinelli, G. *Adv. Synth. Catal.* **2004**, *346*, 1147–1168; (o) Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2005**, *105*, 933–971; (p) Zielinska-Błajet, M.; Kowalczyk, R.; Skarżewski, J. *Tetrahedron* **2005**, *61*, 5235–5240; (q) Evans, D. A.; Seidel, D. *J. Am. Chem. Soc.* **2005**, *127*, 9958–9959; (r) Lattanzi, A. *Tetrahedron: Asymmetry* **2006**, *17*, 837–841.
8. (a) Sibi, M.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033–8061; (b) Krause, N.; Hoffman-Röder, A. *Synthesis* **2001**, 171–196; (c) Kumagai, N.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2001**, *3*, 4251–4254; (d) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877–1894; (e) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726–3748; (f) Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481–2495; (g) Notz, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580–591; (h) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138–5175; (i) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719–724; (j) Wang, J.; Li, H.; Zu, L.; Wang, W. *Adv. Synth. Catal.* **2006**, *348*, 425–428.
9. (a) Colombo, L.; Gennari, C.; Scolastico, C. *J. Chem. Soc., Chem. Commun.* **1979**, 591–592; (b) Colombo, L.; Gennari, C.; Resnati, G.; Scolastico, C. *Synthesis* **1981**, 74–76; (c) Colombo, L.; Gennari, C.; Scolastico, C.; Guanti, G.; Narisano, E. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1278–1283; (d) Colombo, L.; Gennari, C.; Resnati, G.; Scolastico, C. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1284–1286; (e) Enders, D.; Breuer, K.; Runsink, J.; Teles, J. H. *Helv. Chim. Acta* **1996**, *79*, 1899–1902; (f) Davis, J. H.; Forrester, K. *Tetrahedron Lett.* **1999**, *40*, 1621–1622; (g) Enders, D.; Kallfass, U. *Angew. Chem., Int. Ed.* **2002**, *41*, 1743–1745; (h) Vázquez, J.; Prieto, A.; Fernández, R.; Enders, D.; Lassaletta, J. M. *Chem. Commun.* **2002**, 498–499; (i) Kerr, M. S.; de Alaniz, J. R. *J. Am. Chem. Soc.* **2002**, *124*, 10298–10299; (j) Kerr, M. S.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 8876–8877; (k) Enders, D.; Balesiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534–541; (l) Mennen, S. M.; Blank, J. T.; Tran-Dube, M. B.; Imbriglio, J. E.; Miller, S. J. *Chem. Commun.* **2005**, 195–197; (m) Vázquez, J.; Cristea, E.; Diez, E.; Lassaletta, J. M.; Prieto, A.; Fernández, R. *Tetrahedron* **2005**, *61*, 4115–4128; (n) de Alaniz, J. R.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 6284–6289; (o) Nahm, M. R.; Potnick, J. R.; White, P. S.; Johnson, J. S. *J. Am. Chem. Soc.* **2006**, *128*, 2751–2756.
10. Blay, G.; Fernández, I.; Formentin, P.; Monje, B.; Pedro, J. R.; Ruiz, R. *Tetrahedron* **2001**, *57*, 1075–1081.
11. (a) Blay, G.; Cardona, L.; Fernández, I.; Michelena, R.; Pedro, J. R.; Ramírez, T.; Ruiz, R. *Synlett* **2004**, 2325–2328; (b) Barroso, S.; Blay, G.; Cardona, L.; Fernández, I.; García, B.; Pedro, J. R. *J. Org. Chem.* **2004**, *69*, 6821–6829.
12. Preliminary results for this work have been published: Blay, G.; Fernández, I.; Monje, B.; Pedro, J. R.; Ruiz, R. *Tetrahedron Lett.* **2002**, *43*, 8463–8466.
13. Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem., Int. Ed.* **1996**, *35*, 2708–2748.
14. Aitken, R. A.; Thomas, A. W. *Synlett* **1998**, 102–103.
15. Mase, T.; Houpis, I. A.; Akao, A.; Dorziotis, L.; Emerson, K.; Hoang, T.; Iida, T.; Itoh, T.; Kamei, K.; Kato, S.; Kato, Y.; Kawasaki, M.; Lang, F.; Lee, J.; Lynch, J.; Maligres, P.; Molina, A.; Nemoto, T.; Okada, S.; Reamer, R.; Song, J. Z.; Tschaen, D.; Wada, T.; Zewge, D.; Volante, R. P.; Reider, P. J.; Tomimoto, K. *J. Org. Chem.* **2001**, *66*, 6775–6786.
16. Seebach, D.; Naef, R.; Calderari, G. *Tetrahedron* **1984**, *40*, 1313–1324.
17. Kraus, G.; Dneprovskaia, E. *Tetrahedron Lett.* **2000**, *41*, 21–24.

18. *Handbook of Reagents for Organic Synthesis. Acidic and Basic Reagents*; Reich, J. H., Rigby, J. H., Eds.; Wiley: Chichester, UK, 1999; pp 160 and 376.
19. Crystallographic data (excluding structure factors) for **4c** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 607970. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
20. (a) Biddle, M. M.; Reich, H. J. *J. Org. Chem.* **2006**, *71*, 4031–4039; (b) Sikorski, W. H.; Reich, H. J. *J. Am. Chem. Soc*. **2001**, *123*, 6527–6535; (c) Reich, H. J.; Sikorski, W. H. *J. Org. Chem.* **1999**, *64*, 14–15.
21. Oare, D. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 157–172.

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Synthesis of 1-deoxyhept-2-ulosyl-glycono-1,5-lactone utilizing α-selective O-glycosidation of 2,6-anhydro-1-deoxy-D-hept-1-enitols

Rie Namme,[a] Takashi Mitsugi,[a] Hideyo Takahashi,[a] Moto Shiro[b] and Shiro Ikegami[a,*]

[a]*School of Pharmaceutical Sciences, Teikyo University, Sagamiko, Sagamihara, Kanagawa 199-0195, Japan*
[b]*Rigaku Corporation, 3-9-12 Matsubara, Akishima, Tokyo 196-0003, Japan*

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Abstract—A series of 1-deoxy-heptulo-2-pyranosyl-glycono-1,5-lactones were synthesized utilizing completely α-selective O-glycosidation of heptenitols. Anomeric configuration of the products was confirmed by $^{3}J_{C,H}$ coupling measurement and X-ray crystal structural analysis. The benzyl-protected ketosyl saccharides were partly unstable, and glycosidic linkage was prone to cleave under the usual debenzylation conditions. To prevent this, we surveyed various additives for the Pd-catalyzed hydrogenation reaction and found that basic alumina was the most effective.

1. Introduction

Bioactive sugar chains containing ketoses such as fructose and sialic acids are abundant in nature. The sialic acid family, represented by *N*-acetylneuraminic acid (Neu5Ac), consists of oligosaccharides or glycoconjugates in the form of α-ketosides. To take a notable example, 3-deoxy-D-*manno*-oct-2-ulosonic acid is a constituent of glycolipids of Gram-negative bacteria and is α-linked to lipid A. Since sialic acids are involved in numerous biological processes, they are attractive targets for drug discovery.[1] It is also known that 1-deoxy-α-D-*gluco*-heptulose 2-phosphate, which is a 1-*C*-methyl analogue of D-glucose 1-phosphate, is a potent phosphorylase inhibitor. The interaction of heptulose 2-phosphate with enzymes has been examined thoroughly.[2] It is expected that heptulosyloligosaccharides can be utilized as a new class of bioactive oligosaccharides. In the synthetic field, therefore, stereoselective construction of ketosides[3,4] as well as artificial ones[5–8] has been enthusiastically investigated.

For the synthesis of ketosyl saccharides, several methods have been developed by our group.[6,7] We have used *exo*-glycals in the construction of artificial sugar chains and reported the O-glycosidation of heptenitols,[9–12] which are among the simplest *exo*-glycals formed by Tebbe-type methylenation[13] of glyconolactone. The acid-promoted O-glycosidation of 2,6-anhydro-1-deoxyhept-1-enitols **1a–c** (Fig. 1) with

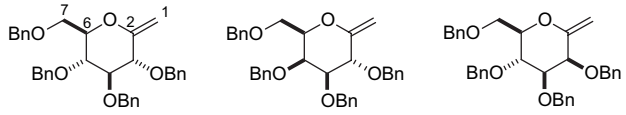
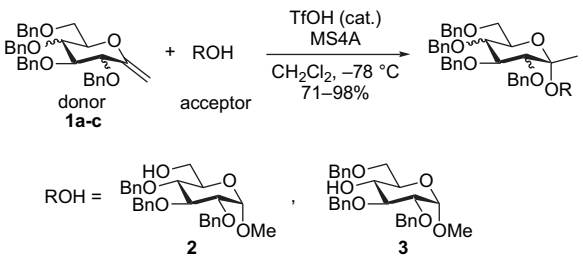


Figure 1. 2,6-Anhydro-1-deoxyhept-1-enitols as glycosyl donors.

methyl α-D-glucopyranosides **2** and **3** afforded 1-deoxyhept-2-ulosylglucosides, i.e., the 1′-*C*-methyl-substituted analogue of naturally occurring aldoside (Scheme 1). This glycosidation was promoted by various acids such as $TiCl_4$, $SnCl_4$, trimethylsilyl trifluoromethanesulfonate (TMSOTf), and trifluoromethanesulfonic acid (TfOH). The best result was achieved using TfOH as a promoter at −78 °C. As far as we have examined, the glycosidation of D-*gluco*-, D-*galacto*-, and D-*manno*-hept-1-enitols **1a–c** gave only α-ketoside, and the formation of β-ketoside was not detected. The glycosidation of peracetylated heptenitols with a 3-*O*-acetyl group also took place in an α-selective manner.



Scheme 1. Glycosidation of hept-1-enitols **1a–c**.

Keywords: Ketoside; *exo*-Glycal; Heptenitol; Heptuloside; O-Glycosidation; Basic alumina.
* Corresponding author. Tel.: +81 42 685 3730; fax: +81 42 685 3729; e-mail: somc@pharm.teikyo-u.ac.jp

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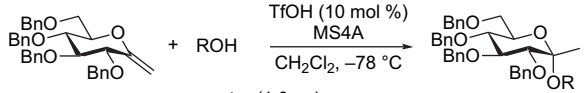
To investigate the generality of this α-selective glycosidation, we planned to examine the O-glycosidation of heptenitols using various glycosyl acceptors. We herein present a new library of hept-2-ulosylsaccharides and their X-ray crystallographic analyses.

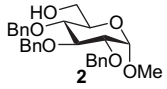
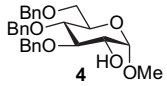
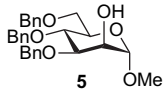
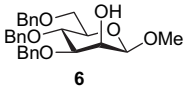
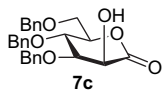
2. Results and discussion

2.1. Glycosidation of heptenitols

As the ketosyl saccharides have quaternary anomeric carbons, we suspected that the unreactive axial hydroxyl group of the pyranose might not be glycosylated efficiently. We first examined the O-glycosidation of heptenitol **1a** with pyranosides **2**, **4**, **5**, and **6** (Table 1). The reaction was performed in CH_2Cl_2 at −78 °C in the presence of 10 mol % of TfOH. After quenching the reaction with triethylamine, the solvent was removed and the residue was subjected to column chromatography to afford the desired disaccharide in pure form. In the case of the primary alcohol **2**, the corresponding disaccharide was obtained in 97% yield with α-stereoselectivity.[6a] The glucopyranoside **4**, which has an equatorial secondary hydroxyl group, showed similar reactivity (Table 1, entry 2). On the other hand, glycosidation with mannopyranosides **5** and **6**, which have axial secondary hydroxyl groups, proceeded very slowly (3 h) to give disaccharides in low yields (Table 1, entries 3 and 4). It is clear that pyranoside with an axially oriented hydroxyl group is reluctantly glycosylated. We next used the mannono-1,5-lactone **7c** as an acceptor because we were interested in its conformational and electronic differentiation from $^4C_1$ pyranoside. Surprisingly, the reaction with **7c** proceeded rapidly (15 min), and the corresponding disaccharide was obtained in 86% yield with complete α-stereoselectivity. It should be noted that the secondary alcohol **7c** reacted more rapidly than the primary alcohol **2**. The rate of this glycosidation with glycosyl acceptors increased roughly in the following order:Axial secondary OH (**5**, **6**)≪equatorial secondary OH (**4**)≈primary OH (**2**)<secondary OH on lactone ring (**7c**).

Table 1. O-Glycosidation of **1a**



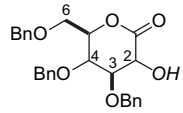
Entry	Acceptor (ROH)	Time (min)	Yield (%)
1	 **2**	60	97
2	 **4**	50	94
3	 **5**	180	34
4	 **6**	180	26
5	 **7c**	15	86

Encouraged by the promising results obtained, we attempted the synthesis of heptulosylsaccharide using glycono-1,5-lactones as the most reactive glycosyl acceptors. The use of lactones provides an additional advantage, enabling the transformation of the resulting disaccharides by methylenation,[6b,13] reduction, or alkylation to afford a wide variety of sugar-related compounds.

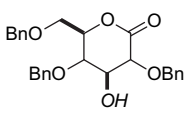
Thus, the glycosidation of a combination of heptenitols **1a–c** as glycosyl donors and sugar lactones **7–10**[14] derived from D-glucose, D-galactose, and D-mannose as acceptors (Fig. 2) was explored (Table 2).

Hydroxyl groups at C-2 in glyconolactones were smoothly glycosylated to afford heptulosyl-(2→2)-glyconolactones **11aa–cc** in high yields (Table 2, entries 1–9). As we expected, C-2-OH in mannono-1,5-lactone reacted easily with the heptenitol **1a**, **1b**, and **1c** giving the corresponding disaccharides in high yield (Table 2, entries 3, 6, 9). Similarly, C-3-OH and C-4-OH were efficiently glycosylated to afford the corresponding heptulosyl-(2→3)-glyconolactones **12** and heptulosyl-(2→4)-glyconolactones **13**, respectively (Table 2, entries 10–27). Glycosidation with C-4-OH in galactono-1,5-lactone **9b** also proceeded well and yielded the corresponding disaccharides (Table 2, entries 20, 23, 26). No remarkable differences in reactivity were observed in the glycosidation of *gluco*-, *galacto*-, and *manno*-heptenitols. In addition, it is noteworthy that all heptulosides were obtained as their respective single isomers.

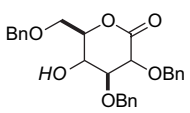
The glycosidation of **1a–c** with primary alcohols **10a–c** was performed in the same manner (Table 2, entries 28–38). In entries 33 and 35 in Table 2, disaccharides were obtained in excellent yields within 15 min. In other cases, a longer reaction time was required for the completion of glycosidation. In addition, a longer reaction time caused the decomposition of heptenitols and heptulosides (Table 2, entries 30, 31, 37).



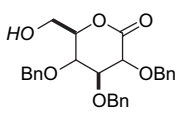
7a (Glc): 2-OH(α), 4-OBn(α)
7b (Gal): 2-OH(α), 4-OBn(β)
7c (Man): 2-OH(β), 4-OBn(α)



8a (Glc): 2-OBn(α), 4-OBn(α)
8b (Gal): 2-OBn(α), 4-OBn(β)
8c (Man): 2-OBn(β), 4-OBn(α)



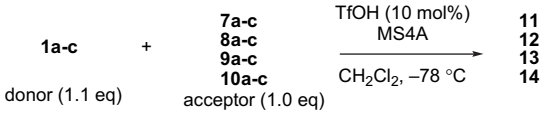
9a (Glc): 2-OBn(α), 4-OH(α)
9b (Gal): 2-OBn(α), 4-OH(β)
9c (Man): 2-OBn(β), 4-OH(α)



10a (Glc): 2-OBn(α), 4-OBn(α)
10b (Gal): 2-OBn(α), 4-OBn(β)
10c (Man): 2-OBn(β), 4-OBn(α)

Figure 2. Glycono-1,5-lactones as glycosyl acceptors.

Table 2. O-Glycosidation of **1a–c** with glycono-1,5-lactones



Entry	Donor	Acceptor	Time (min)	Product	Yield (%)
1	**1a**	**7a**	40	**11aa** Glc-(2→2)-Glc	89
2	**1a**	**7b**	30	**11ab** Glc-(2→2)-Gal	95
3	**1a**	**7c**	15	**11ac** Glc-(2→2)-Man	86
4	**1b**	**7a**	15	**11ba** Gal-(2→2)-Glc	99
5	**1b**	**7b**	17	**11bb** Gal-(2→2)-Gal	83
6	**1b**	**7c**	17	**11bc** Gal-(2→2)-Man	98
7	**1c**	**7a**	17	**11ca** Man-(2→2)-Glc	89
8	**1c**	**7b**	15	**11cb** Man-(2→2)-Gal	95
9	**1c**	**7c**	12	**11cc** Man-(2→2)-Man	89
10	**1a**	**8a**	30	**12aa** Glc-(2→3)-Glc	93
11	**1a**	**8b**	15	**12ab** Glc-(2→3)-Gal	91
12	**1a**	**8c**	20	**12ac** Glc-(2→3)-Man	81
13	**1b**	**8a**	20	**12ba** Gal-(2→3)-Glc	88
14	**1b**	**8b**	15	**12bb** Gal-(2→3)-Gal	89
15	**1b**	**8c**	30	**12bc** Gal-(2→3)-Man	77
16	**1c**	**8a**	15	**12ca** Man-(2→3)-Glc	84
17	**1c**	**8b**	15	**12cb** Man-(2→3)-Gal	88
18	**1c**	**8c**	30	**12cc** Man-(2→3)-Man	84
19	**1a**	**9a**	30	**13aa** Glc-(2→4)-Glc	99
20	**1a**	**9b**	30	**13ab** Glc-(2→4)-Gal	81
21	**1a**	**9c**	20	**13ac** Glc-(2→4)-Man	81
22	**1b**	**9a**	22	**13ba** Gal-(2→4)-Glc	94
23	**1b**	**9b**	20	**13bb** Gal-(2→4)-Gal	82
24	**1b**	**9c**	20	**13bc** Gal-(2→4)-Man	83
25	**1c**	**9a**	16	**13ca** Man-(2→4)-Glc	97
26	**1c**	**9b**	15	**13cb** Man-(2→4)-Gal	97
27	**1c**	**9c**	30	**13cc** Man-(2→4)-Man	73
28	**1a**	**10a**	50	**14aa** Glc-(2→6)-Glc	72
29[a]	**1a**	**10a**	10	**14aa** Glc-(2→6)-Glc	67
30[b]	**1a**	**10b**	210	**14ab** Glc-(2→6)-Gal	77
31	**1a**	**10c**	120	**14ac** Glc-(2→6)-Man	74
32[a]	**1a**	**10c**	15	**14ac** Glc-(2→6)-Man	82
33	**1b**	**10a**	14	**14ba** Gal-(2→6)-Glc	96
34	**1b**	**10b**	60	**14bb** Gal-(2→6)-Gal	75
35	**1b**	**10c**	10	**14bc** Gal-(2→6)-Man	97
36	**1c**	**10a**	90	**14ca** Man-(2→6)-Glc	69
37	**1c**	**10b**	60	**14cb** Man-(2→6)-Gal	70
38	**1c**	**10c**	40	**14cc** Man-(2→6)-Man	79

[a] The amount of TfOH was increased to 15 mol %.
[b] After 200 min, 5 mol % of TfOH was added.

In particular, glycosidation of *gluco*-heptenitol **1a** with galactono-1,5-lactone **10b** was quite slow, and therefore another portion of TfOH was added for the completion of the reaction (Table 2, entry 30). In entries 29 and 32 in Table 2, although the amount of TfOH was increased to 15 mol % to complete the reaction in a shorter time, yields were not increased.

It was surprising that the primary alcohols **10a–c** were unreactive in some cases. The reactivity may depend on the combination of a glycosyl donor and an acceptor. For example, glycosidation of *gluco*-heptenitol **1a** with mannonolactone **10c** required 2 h (Table 2, entry 31), but otherwise the reaction of *galacto*-heptenitol **1b** with **10c** was completed in 10 min (Table 2, entry 35). Although the reactivity varied, heptulosyl-(2→6)-glyconolactones **14aa–cc** were obtained as their respective single isomers.

We therefore achieved the synthesis of 36 examples of 1-deoxy-2-heptulopyranosyl-glycono-1,5-lactone in a combination of heptenitols **1a–c** as glycosyl donors and **7–10** as acceptors. All *gluco*-, *galacto*-, and *manno*-heptuloside products were isolated as their respective single anomeric isomers.

2.2. Determination of the configurations at anomeric position

The configurations at C-2′ anomeric position of hept-2-ulosides were determined by X-ray crystallographic analyses and NMR study.

manno-Hept-2-uloside **14cc** was obtained as colorless crystals. The X-ray crystallographic structure of **14cc** is shown in Figure 3.[15] Based on this X-ray crystallographic analysis, it was elucidated that *manno*-heptuloside possessed a $^5C_2$ chair conformation and α-anomeric configuration. Additionally, the mannonolactone part had a $B_{2,5}$ boat conformation. As only one isomer was formed in every case, it is suggested that other *manno*-heptulosides also possess the α-anomeric configuration.

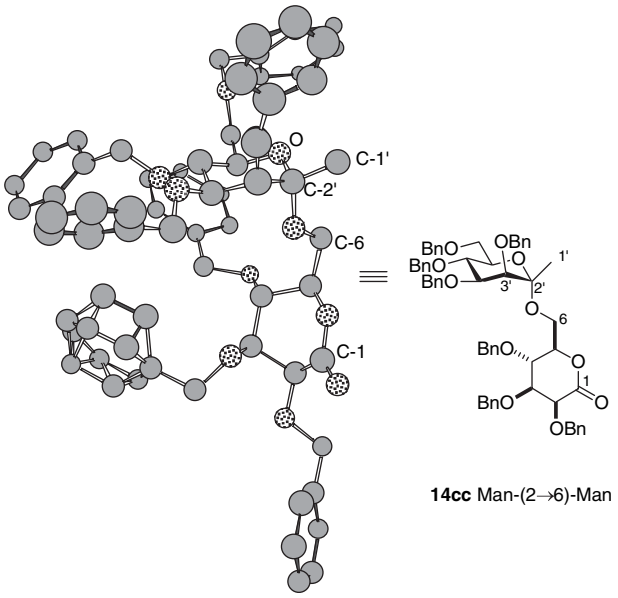
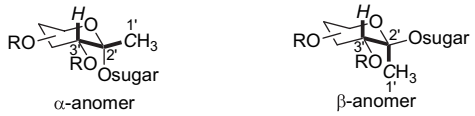


Figure 3. X-ray crystal structure of **14cc**. Hydrogen atoms are omitted for clarity.

The anomeric configuration of *gluco*- and *galacto*- heptulopyranosides was anticipated by analyzing the vicinal C–H coupling constants $^{3}J_{C,H}$ in NMR spectra.[10,16] It is known that the magnitude of $^{3}J_{C,H}$ depends on the dihedral angle between the C-1/C-2 bond and C-3/H-3 bond. As shown in Figure 4, the C-1′ exocyclic carbon and H-3′ axial proton are oriented synclinally in α-ketoside and antiperiplanarly in β-ketoside. By the measurement of the vicinal coupling constant $^{3}J_{C\text{-}1',H\text{-}3'}$ of our products, which were approximately 1.8–2.0 Hz, it is obvious that newly formed glycosidic bonds have the α-configuration. We can be fairly certain that the O-glycosidation of *gluco*-, *galacto*-, and *manno*-heptenitols gave α-glycosides.



11aa Glc-(2→2)-Glc 1.9 Hz
12ba Gal-(2→3)-Glc 2.0 Hz
13ab Glc-(2→4)-Gal 1.8 Hz
14bb Gal-(2→6)-Gal 1.9 Hz

Figure 4. Vicinal coupling constants $^{3}J_{C\text{-}1',H\text{-}3'}$.

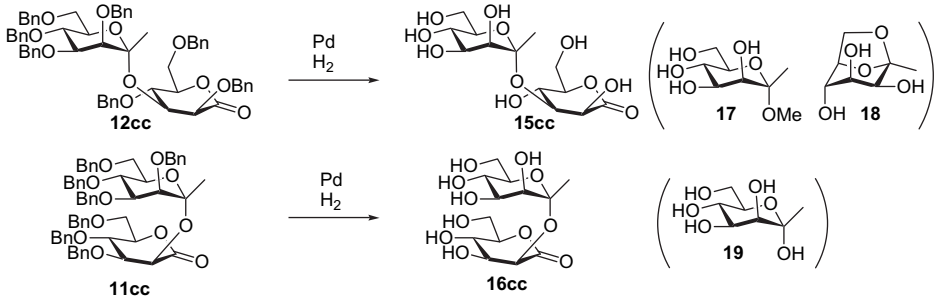
2.3. Deprotection

We then focused on the deprotection of protected hydroxyl groups. In preliminary experiments, it was found that the removal of benzyl groups by hydrogenolysis was accompanied by the cleavage of ketoside bonds. Other reactions such as Birch reduction, catalytic hydrogen transfer,[17] the use of lithium naphthalenide,[18] and oxidation[19–21] gave unsatisfactory results.

We therefore returned to the use of Pd-catalyzed hydrogenolysis. The deprotection of Man-(2→3)-Man **12cc** was examined in various solvents using Pd/C or $Pd(OH)_2/C$ as a catalyst (Table 3). When the reaction proceeded in MeOH, solvolysis occurred to afford **17** (Table 3, entry 1). Using less nucleophilic trifluoroethanol (TFE) as a solvent, intramolecular cyclization followed by cleavage of the ketoside bond gave the cyclized product **18** quantitatively (Table 3, entry 2). It was speculated that the acidity of TFE caused the cleavage of ketoside. Similarly, the use of THF as a solvent resulted in the formation of **18** (Table 3, entry 3). On the hypothesis that the formation of a hydrogen bond would prevent intramolecular nucleophilic attack of the anomeric center, hydrogenolysis was performed in mixed solvents THF/H_2O, and the desired product **15cc** was obtained in 44% yield (Table 3, entry 4).

Although the use of such mixed solvents appeared promising, unexpected solvolysis occurred in the case of Man-(2→2)-Man **11cc** (Table 3, entry 6). It was found that deprotected disaccharides vary in stability. In order to prevent solvolysis, slightly basic conditions were examined. In the presence of

Table 3. Deprotection of **11cc** and **12cc**



Entry	Substrate	Pd	Cat. (wt %)	Solvent	Time (h)	Yield (%)	Other products
1	**12cc**	Pd/C	20	MeOH	4	0	**17**
2		$Pd(OH)_2/C$	25	TFE	48	0	**18**
3		Pd/C	50	THF	9	0	**18**
4		$Pd(OH)_2/C$	20	THF/H_2O	15	44	
5[a]		$Pd(OH)_2/C$	50	THF; MeOH	70	97	
6	**11cc**	$Pd(OH)_2/C$	50	THF/H_2O	2	0	**19**
7[a]		$Pd(OH)_2/C$	50	THF; MeOH	37	65	

[a] Hydrogenation was performed in the presence of basic alumina (50 wt %).

organic or inorganic bases such as pyridine, triethylamine, sodium acetate, and potassium carbonate, hydrogenolysis did not proceed smoothly.[22] We finally found that basic alumina was effective: it prevented undesired side reactions and maintained the catalyst activity. In the presence of basic alumina, the solubility of substrates in solvent markedly affected the reaction rate. In the early stage of hydrogenolysis, the reaction proceeds much faster in THF than in MeOH or *t*-BuOH. Then, as debenzylation progresses, the solubility in THF becomes low, requiring MeOH to be added. Under these conditions, both **12cc** and **11cc** were debenzylated in satisfactory yields (Table 3, entries 5 and 7).

Thus, debenzylation of 36 heptulosides **11**–**14** was explored using catalytic hydrogenation in the presence of $Pd(OH)_2/C$ and basic alumina (Table 4). In many cases, debenzylation afforded the desired deprotected disaccharides. However, some substrates were quite unstable even under basic conditions, and deprotected disaccharides could not be isolated. Particularly, the removal of benzyl groups in heptulosyl-(2→6)-glyconolactone was difficult. It appears that deprotected heptulosides **21** are fairly unstable.[23] Although considerable effort was made, further improvement was not achieved in these cases except for Gal-(2→6)-Gal **14b**. Ultimately, the 25 disaccharides shown in Table 4 were obtained in a deprotected form.

3. Conclusion

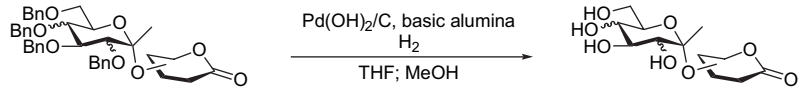
We achieved the synthesis of disaccharides, hept-2-ulosyl-glyconolactones, by acid-promoted O-glycosidation of 2,6-anhydro-1-deoxyhept-1-enitols **1a**–**c**. Under the reaction conditions described here, O-glycosidation of heptenitols **1a**–**c** proceeded with complete stereoselectivity, and each disaccharide was isolated as a single anomeric isomer. Their configurations at anomeric position were identified as α-stereochemistry by X-ray crystallography and NMR vicinal coupling constant $^3J_{C\text{-}1',H\text{-}3'}$. Although the removal of benzyl groups was problematic, we found that Pd-catalyzed hydrogenolysis in the presence of basic alumina was effective in preventing cleavage of the ketoside bonds.

4. Experimental

4.1. General methods

Melting points were measured on a YANACO Micro Melting Point Apparatus and were uncorrected. IR spectra were recorded on a Jasco FT-IR-8000 Fourier-transform infrared spectrometer. ^1H and ^{13}C NMR, and three-bond carbon–proton coupling constants $^3J_{C,H}$ were measured on a JEOL ECP 600 (600 MHz) NMR spectrometer in $CDCl_3$, CD_3OD,

Table 4. Deprotection



Entry	*O*-benzylated disaccharide	Product	Yield (%)
1	**11aa** Glc-(2→2)-Glc	**16aa** Glc-(2→2)-Glc	quant.
2	**11ab** Glc-(2→2)-Gal	**16ab** Glc-(2→2)-Gal	89
3	**11ac** Glc-(2→2)-Man	**16ac** Glc-(2→2)-Man	quant.
4	**11ba** Gal-(2→2)-Glc	**16ba** Gal-(2→2)-Glc	78
5	**11bb** Gal-(2→2)-Gal	**16bb** Gal-(2→2)-Gal	quant.
6	**11bc** Gal-(2→2)-Man	**16bc** Gal-(2→2)-Man	quant.
7	**11ca** Man-(2→2)-Glc	**16ca** Man-(2→2)-Glc	89
8	**11cb** Man-(2→2)-Gal	**16cb** Man-(2→2)-Gal	83
9	**11cc** Man-(2→2)-Man	**16cc** Man-(2→2)-Man	65
10	**12aa** Glc-(2→3)-Glc	**15aa** Glc-(2→3)-Glc	quant.
11	**12ab** Glc-(2→3)-Gal	**15ab** Glc-(2→3)-Gal	99
12	**12ba** Gal-(2→3)-Glc	**15ba** Gal-(2→3)-Glc	97
13	**12bb** Gal-(2→3)-Gal	**15bb** Gal-(2→3)-Gal	quant.
14	**12ca** Man-(2→3)-Glc	**15ca** Man-(2→3)-Glc	98
15	**12cb** Man-(2→3)-Gal	**15cb** Man-(2→3)-Gal	83
16	**12cc** Man-(2→3)-Man	**15cc** Man-(2→3)-Man	65
17	**13aa** Glc-(2→4)-Glc	**20aa** Glc-(2→4)-Glc	quant.
18	**13ab** Glc-(2→4)-Gal	**20ab** Glc-(2→4)-Gal	91
19	**13ac** Glc-(2→4)-Man	**20ac** Glc-(2→4)-Man	quant.
20	**13ba** Gal-(2→4)-Glc	**20ba** Gal-(2→4)-Glc	75
21	**13bb** Gal-(2→4)-Gal	**20bb** Gal-(2→4)-Gal	quant.
22	**13bc** Gal-(2→4)-Man	**20bc** Gal-(2→4)-Man	quant.
23	**13cb** Man-(2→4)-Gal	**20cb** Man-(2→4)-Gal	94
24	**13cc** Man-(2→4)-Man	**20cc** Man-(2→4)-Man	quant.
25	**14bb** Gal-(2→6)-Gal	**21bb** Gal-(2→6)-Gal	59

or D_2O solutions. Mass spectra (MS) and high-resolution mass spectra (HRMS) were recorded with a JEOL JMS-SX102A mass spectrometer with FAB using 3-nitrobenzyl alcohol (NBA) as the matrix. Optical rotations were measured with a Jasco DIP-370 digital polarimeter. X-ray crystallographic measurements were performed with a Rigaku RAXIS-RAPID Imaging Plate Diffractometer with graphite monochromated MoK_α radiation at 123 K. TLC was performed on precoated plates (Merck TLC Aluminum sheets silica 60 F_{254}) with detection by UV light or with phosphomolybdic acid in EtOH/H_2O followed by heating. Column chromatography was performed using SiO_2 (Silica Gel 60 N, spherical, neutral, Kanto).

4.2. General procedure 1: glycosidation of heptenitols with alcohols

To a stirred mixture of hept-1-enitol **1a** (237.0 mg, 0.44 mmol), hydroxylactone **7a** (180.0 mg, 0.40 mmol), and molecular sieves 4 Å (400.0 mg) in CH_2Cl_2 (8.0 mL) was added TfOH (3.5 μL, 0.04 mmol) at −78 °C. The reaction mixture was stirred at −78 °C and then quenched with triethylamine. After the removal of the solvent, the residue was purified by column chromatography (silica gel, neutral, hexane/ethyl acetate 3:1) to give disaccharide **11aa** (350.0 mg).[24]

4.2.1. 3,4,5,7-Tetra-*O*-benzyl-1-deoxy-α-D-*gluco*-hept-2-ulosyl-(2→2)-3,4,6-tri-*O*-benzyl-D-glucono-1,5-lactone (11aa). Colorless syrup; $[\alpha]_D^{26}$ +64.9 (*c* 1.16, $CHCl_3$); IR (neat): 3031, 2913, 2869, 1763, 1105, 1082, 1028, 1029, 739, 700 cm^{-1}; HRMS (FAB): calcd for $C_{62}H_{64}O_{11}K$ 1023.4086, found 1023.4096.

4.2.2. 3,4,5,7-Tetra-*O*-benzyl-1-deoxy-α-D-*gluco*-hept-2-ulosyl-(2→2)-3,4,6-tri-*O*-benzyl-D-galactono-1,5-lactone (11ab). Colorless needle; mp 81–83 °C; $[\alpha]_D^{25}$ +70.6 (*c* 0.5, $CHCl_3$); IR (KBr): 3031, 2913, 2869, 1761, 1497, 1455, 1362, 735, 698 cm^{-1}; HRMS (FAB): calcd for $C_{62}H_{64}O_{11}K$ 1023.4086, found 1023.4096.

4.2.3. 3,4,5,7-Tetra-*O*-benzyl-1-deoxy-α-D-*gluco*-hept-2-ulosyl-(2→2)-3,4,6-tri-*O*-benzyl-D-mannono-1,5-lactone (11ac). Colorless syrup; $[\alpha]_D^{27}$ +47.6 (*c* 1.15, $CHCl_3$); IR (neat): 3031, 2928, 2867, 1775, 1455, 1127, 1082, 1065, 1028, 737, 698 cm^{-1}; HRMS (FAB): calcd for $C_{62}H_{64}O_{11}K$ 1023.4086, found 1023.4076.

4.2.4. 3,4,5,7-Tetra-*O*-benzyl-1-deoxy-α-D-*galacto*-hept-2-ulosyl-(2→2)-3,4,6-tri-*O*-benzyl-D-glucono-1,5-lactone (11ba). Colorless syrup; $[\alpha]_D^{29}$ +59.4 (*c* 1.21, $CHCl_3$); IR (neat): 3031, 2917, 2869, 1763, 1455, 1100, 737, 700 cm^{-1}; HRMS (FAB): calcd for $C_{62}H_{64}O_{11}K$ 1023.4086, found 1023.4096.

4.2.5. 3,4,5,7-Tetra-*O*-benzyl-1-deoxy-α-D-*galacto*-hept-2-ulosyl-(2→2)-3,4,6-tri-*O*-benzyl-D-galactono-1,5-lactone (11bb). Colorless syrup; $[\alpha]_D^{26}$ +52.5 (*c* 1.05, $CHCl_3$); IR (neat): 3031, 2923, 2874, 1763, 1455, 1101, 739, 700 cm^{-1}; HRMS (FAB): calcd for $C_{62}H_{64}O_{11}K$ 1023.4086, found 1023.4084.

4.2.6. 3,4,5,7-Tetra-*O*-benzyl-1-deoxy-α-D-*galacto*-hept-2-ulosyl-(2→2)-3,4,6-tri-*O*-benzyl-D-mannono-1,5-lactone (11bc). Colorless syrup; $[\alpha]_D^{27}$ +48.9 (*c* 1.03, $CHCl_3$); IR (neat): 3031, 2915, 2867, 1775, 1455, 1096, 1059, 737, 698 cm^{-1}; HRMS (FAB): calcd for $C_{62}H_{64}O_{11}K$ 1023.4086, found 1023.4061.

4.2.7. 3,4,5,7-Tetra-*O*-benzyl-1-deoxy-α-D-*manno*-hept-2-ulosyl-(2→2)-3,4,6-tri-*O*-benzyl-D-glucono-1,5-lactone (11ca). Colorless syrup; $[\alpha]_D^{27}$ +49.1 (*c* 1.06, $CHCl_3$); IR (neat): 3031, 2911, 2869, 1763, 1455, 1098, 1078, 737, 698 cm^{-1}; HRMS (FAB): calcd for $C_{62}H_{64}O_{11}K$ 1023.4086, found 1023.4086.

4.2.8. 3,4,5,7-Tetra-*O*-benzyl-1-deoxy-α-D-*manno*-hept-2-ulosyl-(2→2)-3,4,6-tri-*O*-benzyl-D-galactono-1,5-lactone (11cb). Colorless syrup; $[\alpha]_D^{26}$ +57.7 (*c* 1.13, $CHCl_3$); IR (neat): 3031, 2915, 2867, 1758, 1455, 1096, 737, 698 cm^{-1}; HRMS (FAB): calcd for $C_{62}H_{64}O_{11}K$ 1023.4086, found 1023.4105.

4.2.9. 3,4,5,7-Tetra-*O*-benzyl-1-deoxy-α-D-*manno*-hept-2-ulosyl-(2→2)-3,4,6-tri-*O*-benzyl-D-mannono-1,5-lactone (11cc). Colorless syrup; $[\alpha]_D^{25}$ +65.5 (*c* 1.01, $CHCl_3$); IR (neat): 3031, 2923, 2867, 1777, 1455, 1073, 739, 698 cm^{-1}; HRMS (FAB): calcd for $C_{62}H_{64}O_{11}K$ 1023.4086, found 1023.4084.

4.2.10. 3,4,5,7-Tetra-*O*-benzyl-1-deoxy-α-D-*gluco*-hept-2-ulosyl-(2→3)-2,4,6-tri-*O*-benzyl-D-glucono-1,5-lactone (12aa). Colorless syrup; $[\alpha]_D^{26}$ +98.8 (*c* 1.14, $CHCl_3$); IR (neat): 3031, 2927, 2863, 1754, 1455, 1073, 737, 698 cm^{-1}; HRMS (FAB): calcd for $C_{62}H_{64}O_{11}Na$ 1007.4346, found 1007.4355.

4.2.11. 3,4,5,7-Tetra-*O*-benzyl-1-deoxy-α-D-*gluco*-hept-2-ulosyl-(2→3)-2,4,6-tri-*O*-benzyl-D-galactono-1,5-lactone (12ab). Colorless syrup; $[\alpha]_D^{30}$ +90.9 (*c* 1.04, $CHCl_3$); IR (neat): 3032, 2921, 2867, 1750, 1455, 1096, 737, 698 cm^{-1}; HRMS (FAB): calcd for $C_{62}H_{64}O_{11}K$ 1023.4086, found 1023.4075.

4.2.12. 3,4,5,7-Tetra-*O*-benzyl-1-deoxy-α-D-*gluco*-hept-2-ulosyl-(2→3)-2,4,6-tri-*O*-benzyl-D-mannono-1,5-lactone (12ac). Colorless syrup; $[\alpha]_D^{27}$ +35.3 (*c* 1.08, $CHCl_3$); IR (neat): 3031, 2924, 2869, 1765, 1455, 1125, 1088, 739, 698 cm^{-1}; HRMS (FAB): calcd for $C_{62}H_{64}O_{11}K$ 1023.4086, found 1023.4085.

4.2.13. 3,4,5,7-Tetra-*O*-benzyl-1-deoxy-α-D-*galacto*-hept-2-ulosyl-(2→3)-2,4,6-tri-*O*-benzyl-D-glucono-1,5-lactone (12ba). Colorless syrup; $[\alpha]_D^{26}$ +101.7 (*c* 1.08, $CHCl_3$); IR (neat): 3031, 2924, 2870, 1754, 1455, 1096, 1069, 737, 698 cm^{-1}; HRMS (FAB): calcd for $C_{62}H_{64}O_{11}Na$ 1007.4346, found 1007.4354.

4.2.14. 3,4,5,7-Tetra-*O*-benzyl-1-deoxy-α-D-*galacto*-hept-2-ulosyl-(2→3)-2,4,6-tri-*O*-benzyl-D-galactono-1,5-lactone (12bb). Colorless needle; mp 127–128 °C; $[\alpha]_D^{24}$ +101.0 (*c* 1.0, $CHCl_3$); IR (KBr): 3031, 2867, 1732, 1497, 1098, 735, 696 cm^{-1}; HRMS (FAB): calcd for $C_{62}H_{64}O_{11}K$ 1023.4086, found 1023.4094.

4.2.15. 3,4,5,7-Tetra-*O*-benzyl-1-deoxy-α-D-*galacto*-hept-2-ulosyl-(2→3)-2,4,6-tri-*O*-benzyl-D-mannono-1,5-lactone (12bc). Colorless syrup; $[\alpha]_D^{28}$ +44.2 (*c* 1.28, $CHCl_3$); IR (neat): 3031, 2915, 2869, 1765, 1455, 1098, 737,

698 cm^{-1}; HRMS (FAB): calcd for $C_{62}H_{64}O_{11}K$ 1023.4086, found 1023.4082.

4.2.16. 3,4,5,7-Tetra-*O*-benzyl-1-deoxy-α-D-*manno*-hept-2-ulosyl-(2→3)-2,4,6-tri-*O*-benzyl-D-glucono-1,5-lactone (12ca). Colorless syrup; $[\alpha]_D^{27}$ +68.3 (*c* 1.18, $CHCl_3$); IR (neat): 3031, 2911, 2867, 1757, 1455, 1092, 1073, 745, 702 cm^{-1}; HRMS (FAB): calcd for $C_{62}H_{64}O_{11}K$ 1023.4086, found 1023.4093.

4.2.17. 3,4,5,7-Tetra-*O*-benzyl-1-deoxy-α-D-*manno*-hept-2-ulosyl-(2→3)-2,4,6-tri-*O*-benzyl-D-galactono-1,5-lactone (12cb). Colorless syrup; $[\alpha]_D^{26}$ +77.9 (*c* 1.10, $CHCl_3$); IR (neat): 3031, 2919, 2869, 1750, 1455, 1119, 1071, 752, 735, 696 cm^{-1}; HRMS (FAB): calcd for $C_{62}H_{64}O_{11}K$ 1023.4086, found 1023.4064.

4.2.18. 3,4,5,7-Tetra-*O*-benzyl-1-deoxy-α-D-*manno*-hept-2-ulosyl-(2→3)-2,4,6-tri-*O*-benzyl-D-mannono-1,5-lactone (12cc). Colorless syrup; $[\alpha]_D^{30}$ +39.7 (*c* 1.16, $CHCl_3$); IR (neat): 3031, 2915, 2867, 1773, 1455, 1113, 739, 698 cm^{-1}; HRMS (FAB): calcd for $C_{62}H_{64}O_{11}K$ 1023.4086, found 1023.4083.

4.2.19. 3,4,5,7-Tetra-*O*-benzyl-1-deoxy-α-D-*gluco*-hept-2-ulosyl-(2→4)-2,3,6-tri-*O*-benzyl-D-glucono-1,5-lactone (13aa). Colorless syrup; $[\alpha]_D^{28}$ +47.6 (*c* 1.09, $CHCl_3$); IR (neat): 3031, 2924, 2869, 1792, 1455, 1088, 735, 698 cm^{-1}; HRMS (FAB): calcd for $C_{62}H_{64}O_{11}K$ 1007.4346, found 1007.4331.

4.2.20. 3,4,5,7-Tetra-*O*-benzyl-1-deoxy-α-D-*gluco*-hept-2-ulosyl-(2→4)-2,3,6-tri-*O*-benzyl-D-galactono-1,5-lactone (13ab). Colorless syrup; $[\alpha]_D^{27}$ +29.8 (*c* 1.13, $CHCl_3$); IR (neat): 3031, 2924, 2867, 1791, 1455, 1090, 7367, 698 cm^{-1}; HRMS (FAB): calcd for $C_{62}H_{64}O_{11}K$ 1023.4086, found 1023.4074.

4.2.21. 3,4,5,7-Tetra-*O*-benzyl-1-deoxy-α-D-*gluco*-hept-2-ulosyl-(2→4)-2,3,6-tri-*O*-benzyl-D-mannono-1,5-lactone (13ac). Colorless syrup; $[\alpha]_D^{27}$ +26.8 (*c* 1.06, $CHCl_3$); IR (neat): 3031, 2924, 2869, 1769, 750, 739, 698 cm^{-1}; HRMS (FAB): calcd for $C_{62}H_{64}O_{11}K$ 1023.4086, found 1023.4111.

4.2.22. 3,4,5,7-Tetra-*O*-benzyl-1-deoxy-α-D-*galacto*-hept-2-ulosyl-(2→4)-2,3,6-tri-*O*-benzyl-D-glucono-1,5-lactone (13ba). Colorless syrup; $[\alpha]_D^{30}$ +60.6 (*c* 0.83, $CHCl_3$); IR (neat): 3031, 2921, 2870, 1790, 1455, 1098, 737, 698 cm^{-1}; HRMS (FAB): calcd for $C_{62}H_{64}O_{11}K$ 1023.4086, found 1023.4082.

4.2.23. 3,4,5,7-Tetra-*O*-benzyl-1-deoxy-α-D-*galacto*-hept-2-ulosyl-(2→4)-2,3,6-tri-*O*-benzyl-D-galactono-1,5-lactone (13bb). Colorless syrup; $[\alpha]_D^{30}$ +27.4 (*c* 0.85, $CHCl_3$); IR (neat): 3031, 2923, 2870, 1788, 1455, 1100, 737, 698 cm^{-1}; HRMS (FAB): calcd for $C_{62}H_{64}O_{11}K$ 1023.4086, found 1023.4083.

4.2.24. 3,4,5,7-Tetra-*O*-benzyl-1-deoxy-α-D-*galacto*-hept-2-ulosyl-(2→4)-2,3,6-tri-*O*-benzyl-D-mannono-1,5-lactone (13bc). Colorless syrup; $[\alpha]_D^{27}$ +28.6 (*c* 1.02, $CHCl_3$); IR (neat): 3031, 2923, 2872, 1769, 1455, 1101, 1082, 735, 698 cm^{-1}; HRMS (FAB): calcd for $C_{62}H_{64}O_{11}K$ 1023.4086, found 1023.4081.

4.2.25. 3,4,5,7-Tetra-*O*-benzyl-1-deoxy-α-D-*manno*-hept-2-ulosyl-(2→4)-2,3,6-tri-*O*-benzyl-D-glucono-1,5-lactone (13ca). Colorless syrup; $[\alpha]_D^{27}$ +36.9 (*c* 1.06, $CHCl_3$); IR (neat): 3031, 2915, 2867, 1786, 1455, 1100, 1084, 745, 700 cm^{-1}; HRMS (FAB): calcd for $C_{62}H_{64}O_{11}K$ 1023.4086, found 1023.4087.

4.2.26. 3,4,5,7-Tetra-*O*-benzyl-1-deoxy-α-D-*manno*-hept-2-ulosyl-(2→4)-2,3,6-tri-*O*-benzyl-D-galactono-1,5-lactone (13cb). Colorless syrup; $[\alpha]_D^{27}$ −0.43 (*c* 1.07, $CHCl_3$); IR (neat): 3031, 2907, 2869, 1788, 1455, 1111, 739, 700 cm^{-1}; HRMS (FAB): calcd for $C_{62}H_{64}O_{11}K$ 1023.4086, found 1023.4074.

4.2.27. 3,4,5,7-Tetra-*O*-benzyl-1-deoxy-α-D-*manno*-hept-2-ulosyl-(2→4)-2,3,6-tri-*O*-benzyl-D-mannono-1,5-lactone (13cc). Colorless syrup; $[\alpha]_D^{30}$ +9.8 (*c* 1.05, $CHCl_3$); IR (neat): 3031, 2924, 2870, 1767, 1455, 1109, 748, 737, 698 cm^{-1}; HRMS (FAB): calcd for $C_{62}H_{64}O_{11}K$ 1023.4086, found 1023.4080.

4.2.28. 3,4,5,7-Tetra-*O*-benzyl-1-deoxy-D-*gluco*-hept-2-ulosyl-(2→6)-2,3,4-tri-*O*-benzyl-D-glucono-1,5-lactone (14aa). Colorless syrup; mp 79–81 °C; $[\alpha]_D^{25}$ +70.3 (*c* 1.00, $CHCl_3$); IR (KBr): 3031, 2867, 1759, 1455, 1123, 1071, 739, 696 cm^{-1}; HRMS (FAB): calcd for $C_{62}H_{64}O_{11}K$ 1023.4086, found 1023.4102.

4.2.29. 3,4,5,7-Tetra-*O*-benzyl-1-deoxy-D-*gluco*-hept-2-ulosyl-(2→6)-2,3,4-tri-*O*-benzyl-D-galactono-1,5-lactone (14ab). Colorless syrup; $[\alpha]_D^{25}$ +78.8 (*c* 1.17, $CHCl_3$); IR (neat): 3031, 2921, 2869, 1752, 1455, 1067, 735, 698 cm^{-1}; HRMS (FAB): calcd for $C_{62}H_{64}O_{11}Na$ 1007.4346, found 1007.4333.

4.2.30. 3,4,5,7-Tetra-*O*-benzyl-1-deoxy-D-*gluco*-hept-2-ulosyl-(2→6)-2,3,4-tri-*O*-benzyl-D-mannono-1,5-lactone (14ac). Colorless syrup; $[\alpha]_D^{29}$ +19.8 (*c* 1.07, $CHCl_3$); IR (neat): 3031, 2928, 2870, 1775, 1455, 1096, 739, 698 cm^{-1}; HRMS (FAB): calcd for $C_{62}H_{64}O_{11}K$ 1023.4088, found 1023.4066.

4.2.31. 3,4,5,7-Tetra-*O*-benzyl-1-deoxy-D-*galacto*-hept-2-ulosyl-(2→6)-2,3,4-tri-*O*-benzyl-D-glucono-1,5-lactone (14ba). Colorless syrup; $[\alpha]_D^{27}$ +66.6 (*c* 1.12, $CHCl_3$); IR (neat): 3031, 2919, 2874, 1757, 1455, 1096, 739, 698 cm^{-1}; HRMS (FAB): calcd for $C_{62}H_{64}O_{11}K$ 1023.4086, found 1023.4086.

4.2.32. 3,4,5,7-Tetra-*O*-benzyl-1-deoxy-α-D-*galacto*-hept-2-ulosyl-(2→6)-2,3,4-tri-*O*-benzyl-D-galactono-1,5-lactone (14bb). Colorless syrup; $[\alpha]_D^{27}$ +75.8 (*c* 1.19, $CHCl_3$); IR (neat): 3031, 2917, 2869, 1750, 1455, 1109, 1057, 745, 737, 745, 698 cm^{-1}; HRMS (FAB): calcd for $C_{62}H_{64}O_{11}Na$ 1007.4346, found 1007.4362.

4.2.33. 3,4,5,7-Tetra-*O*-benzyl-1-deoxy-α-D-*galacto*-hept-2-ulosyl-(2→6)-2,3,4-tri-*O*-benzyl-D-mannono-1,5-lactone (14bc). Colorless syrup; $[\alpha]_D^{26}$ +23.1 (*c* 1.14, $CHCl_3$); IR (neat): 3031, 2917, 2870, 1775, 1455, 1113, 1098, 735, 698 cm^{-1}; HRMS (FAB): calcd for $C_{62}H_{64}O_{11}K$ 1023.4086, found 1023.4099.

4.2.34. 3,4,5,7-Tetra-*O*-benzyl-1-deoxy-α-D-*manno*-hept-2-ulosyl-(2→6)-2,3,4-tri-*O*-benzyl-D-glucono-1,5-lactone (14ca). Colorless syrup; $[\alpha]_D^{27}$ +57.2 (*c* 1.32, $CHCl_3$); IR

(neat): 3031, 2921, 2867, 1757, 1455, 1094, 1078, 735, 698 cm^{-1}; HRMS (FAB): calcd for $C_{62}H_{64}O_{11}K$ 1023.4086, found 1023.4081.

4.2.35. 3,4,5,7-Tetra-*O*-benzyl-1-deoxy-α-D-*manno*-hept-2-ulosyl-(2→6)-2,3,4-tri-*O*-benzyl-D-galactono-1,5-lactone (14cb). Colorless syrup; $[\alpha]_D^{27}$ +56.8 (*c* 1.28, $CHCl_3$); IR (neat): 3031, 2921, 2869, 1750, 1455, 1104, 737, 698 cm^{-1}; HRMS (FAB): calcd for $C_{62}H_{64}O_{11}K$ 1023.4086, found 1023.4101.

4.2.36. 3,4,5,7-Tetra-*O*-benzyl-1-deoxy-α-D-*manno*-hept-2-ulosyl-(2→6)-2,3,4-tri-*O*-benzyl-D-mannono-1,5-lactone (14cc). Colorless block; mp 111 °C; $[\alpha]_D^{27}$ +22.7 (*c* 0.92, $CHCl_3$); IR (KBr): 3032, 2936, 2346, 1775, 1499, 1456, 1109, 739, 700 cm^{-1}; HRMS (FAB): calcd for $C_{62}H_{64}O_{11}K$ 1023.4086, found 1023.4168.

4.3. General procedure 2: deprotection

To a solution of **11aa** (73.0 mg, 0.07 mmol) in THF (2.5 mL) were added basic alumina (18.0 mg) and 20% $Pd(OH)_2$/C (37.0 mg) under an argon atmosphere, and the mixture was stirred under a hydrogen atmosphere (balloon) at room temperature. After 20 h, to the mixture was added MeOH (0.3 mL) and stirred for 28 h. The reaction mixture was filtered through filter paper, and the filtrate was evaporated and dried to give **16aa** (28.0 mg).

4.3.1. 1-Deoxy-D-*gluco*-hept-2-ulosyl-(2→2)-D-glucono-1,5-lactone (16aa). Colorless amorphous solid; $[\alpha]_D^{23}$ +96.2 (*c* 1.24, CH_3OH); ^1H NMR (600 MHz, CD_3OD): δ 4.61 (m, 1H), 4.52 (m, 1H), 4.48 (m, 1H), 3.99 (m, 1H), 3.86–3.58 (m, 8H), 1.53 (s, 3H, H-1′); ^{13}C NMR (150 MHz, CD_3OD): δ 176.0, 103.5, 81.5, 77.8, 75.2, 75.1, 74.0, 73.8, 71.8, 71.4, 64.4, 62.8, 23.2.

4.3.2. 1-Deoxy-α-D-*gluco*-hept-2-ulosyl-(2→2)-D-galactono-1,5-lactone (16ab). Colorless amorphous solid; $[\alpha]_D^{27}$ +60.8 (*c* 0.23, CH_3OH); ^1H NMR (600 MHz, CD_3OD): δ 4.67 (d, *J*=8.8 Hz, 1H, H-2), 4.36 (dd, *J*=8.3, 8.8 Hz, 1H), 4.15 (dd, *J*=2.2, 8.8 Hz, 1H, H-3), 3.82 (ddd, *J*=2.2, 5.8, 10.2 Hz, 1H), 3.74 (dd, *J*=2.5, 11.6 Hz, 1H), 3.70 (m, 1H), 3.58–3.52 (m, 4H), 3.23 (m, 1H), 3.09 (d, *J*=9.9 Hz, 1H, H-3′), 1.47 (s, 3H, H-1′); ^{13}C NMR (150 MHz, CD_3OD): δ 175.0, 103.3, 81.2, 78.1, 75.7, 75.1, 74.4, 73.4, 71.7, 70.3, 63.5, 62.5, 22.8.

4.3.3. 1-Deoxy-α-D-*gluco*-hept-2-ulosyl-(2→2)-D-mannono-1,5-lactone (16ac). Colorless amorphous solid; $[\alpha]_D^{24}$ +118.6 (*c* 0.5, CH_3OH); ^1H NMR (600 MHz, CD_3OD): δ 4.86 (d, *J*=2.8 Hz, 1H, H-2), 4.12 (ddd, *J*=8.3, 5.8, 2.5 Hz, 1H, H-5), 3.95 (dd, *J*=1.1, 2.8 Hz, 1H, H-3), 3.87 (ddd, *J*=9.9, 2.2, 6.6 Hz, 1H, H-6′), 3.78 (dd, *J*=9.1, 9.6 Hz, 1H, H-4′), 3.75 (dd, *J*=2.5, 12.4 Hz, 1H, H-6), 3.71 (dd, *J*=2.2, 11.8 Hz, 1H, H-7′), 3.7 (dd, *J*=1.1, 8.3 Hz, 1H, H-4), 3.64 (dd, *J*=6.6, 11.8 Hz, 1H, H-7′), 3.49 (dd, *J*=5.8, 12.4 Hz, 1H, H-6), 3.13 (dd, *J*=9.9, 9.1 Hz, 1H, H-5′), 3.11 (d, *J*=9.6 Hz, 1H, H-3′), 1.45 (s, 3H, –CH_3); ^{13}C NMR (150 MHz, CD_3OD): δ 172.5, 103.1, 82.2, 78.3, 77.2, 75.3, 74.9, 72.1, 70.8, 69.9, 63.0, 62.8, 22.7.

4.3.4. 1-Deoxy-α-D-*galacto*-hept-2-ulosyl-(2→2)-D-glucono-1,5-lactone (16ba). Colorless amorphous solid; ^1H NMR (600 MHz, CD_3OD): δ 4.52–4.47 (m, 2H), 4.39 (dd, *J*=4.7, 5.0 Hz, 1H), 3.91 (m, 1H), 3.80 (m, 2H), 3.70–3.66 (m, 2H), 3.63–3.55 (m, 3H), 3.49 (d, *J*=10.2 Hz, 1H, H-3′), 1.46 (s, 3H, H-1′).

4.3.5. 1-Deoxy-α-D-*galacto*-hept-2-ulosyl-(2→2)-D-galactono-1,5-lactone (16bb). Colorless amorphous solid; $[\alpha]_D^{28}$ +60.2 (*c* 1.01, CH_3OH); ^1H NMR (600 MHz, CD_3OD): δ 4.68 (d, *J*=8.8 Hz, 1H, H-2), 4.35 (dd, *J*=8.5, 8.5 Hz, 1H), 4.16 (dd, *J*=2.2, 8.8 Hz, 1H, H-3), 4.04 (m, 1H), 3.81 (m, 1H), 3.71–3.65 (m, 3H), 3.61–3.51 (m, 4H), 1.49 (s, 3H, H-1′); ^{13}C NMR (150 MHz, CD_3OD): δ 175.0, 103.6, 81.2, 75.7, 74.7, 73.4, 73.0, 71.7, 71.2, 70.4, 63.5, 62.9, 22.7.

4.3.6. 1-Deoxy-α-D-*galacto*-hept-2-ulosyl-(2→2)-D-mannono-1,5-lactone (16bc). Colorless amorphous solid; ^1H NMR (600 MHz, CD_3OD): δ 4.91 (d, *J*=2.5 Hz, 1H, H-2), 4.16 (ddd, *J*=8.3, 2.5, 5.8 Hz, 1H, H-5), 4.12 (ddd, *J*=1.4, 4.1, 7.7 Hz, 1H, H-6′), 4.00 (dd, *J*=2.5, 0.8 Hz, 1H, H-3), 3.95 (dd, *J*=9.9, 3.3 Hz, 1H, H-4′), 3.85 (dd, *J*=3.3, 1.4 Hz, 1H, H-5′), 3.79 (dd, *J*=2.5, 12.4 Hz, 1H, H-6), 3.75 (dd, *J*=0.8, 8.3 Hz, 1H, H-4), 3.69 (dd, *J*=5.8, 12.4 Hz, 1H, H-6), 3.67 (dd, *J*=7.7, 11.5 Hz, 1H, H-7′), 3.57 (d, *J*=9.9 Hz, 1H, H-3′), 3.56 (dd, *J*=4.1, 11.5 Hz, 1H, H-7′), 1.45 (s, 3H, H-1′); ^{13}C NMR (150 MHz, CD_3OD): δ 172.8, 103.4, 82.2, 77.3, 74.8, 74.2, 71.6, 71.6, 70.8, 69.8, 63.3, 62.8, 22.6.

4.3.7. 1-Deoxy-α-D-*manno*-hept-2-ulosyl-(2→2)-D-glucono-1,5-lactone (16ca). Colorless amorphous solid; ^1H NMR (600 MHz, CD_3OD): δ 4.46 (m, 1H), 4.38 (m, 1H), 3.90 (m, 1H), 3.77 (dd, *J*=1.7, 11.8 Hz, 1H), 3.72 (dd, *J*=3.3, 9.1 Hz, 1H, H-4′), 3.68 (dd, *J*=3.9, 11.8 Hz, 1H), 3.63–3.59 (m, 3H), 3.55 (d, *J*=3.3 Hz, 1H, H-3′), 3.51 (dd, *J*=1.9, 6.1 Hz, 1H), 3.47 (dd, *J*=9.1, 9.4 Hz, 1H, H-5′), 1.41 (s, 3H, H-1′); ^{13}C NMR (150 MHz, CD_3OD): δ 176.0, 104.6, 81.4, 76.0, 74.4, 73.8, 73.7, 72.5, 71.2, 67.9, 64.3, 63.0, 22.3.

4.3.8. 1-Deoxy-α-D-*manno*-hept-2-ulosyl-(2→2)-D-galactono-1,5-lactone (16cb). Colorless amorphous solid; ^1H NMR (600 MHz, CD_3OD): δ 4.69 (d, *J*=8.8 Hz, 1H, H-2), 4.32 (dd, *J*=8.5, 8.5 Hz, 1H, H-6), 4.14 (dd, *J*=2.5, 8.8 Hz, 1H, H-3), 3.82 (ddd, *J*=2.2, 5.8, 9.9 Hz, 1H, H-6′), 3.78 (dd, *J*=3.3, 9.6 Hz, 1H, H-4′), 3.73 (dd, *J*=2.2, 11.6 Hz, 1H, H-7′), 3.69 (m, 1H, H-5), 3.64 (d, *J*=3.3 Hz, 1H, H-3′), 3.59 (dd, *J*=5.8, 11.6 Hz, 1H, H-7′), 3.56 (m, 1H, H-4), 3.55 (dd, *J*=6.6, 8.5 Hz, 1H, H-6), 3.53 (dd, *J*=9.6, 9.9 Hz, 1H, H-5′) 1.39 (s, 3H, H-1′); ^{13}C NMR (150 MHz, CD_3OD): δ 174.8, 104.4, 81.2, 75.3, 75.1, 74.5, 73.5, 72.6, 70.3, 67.8, 63.6, 62.8, 21.9.

4.3.9. 1-Deoxy-α-D-*manno*-hept-2-ulosyl-(2→2)-D-mannono-1,5-lactone (16cc). Colorless amorphous solid; ^1H NMR (600 MHz, CD_3OD): δ 4.79 (d, *J*=4.4 Hz, 1H, H-2), 4.43 (dd, *J*=4.4, 2.8 Hz, 1H, H-3), 4.24 (dd, *J*=2.8, 9.1 Hz, 1H, H-4), 3.96 (dd, *J*=3.3, 9.6 Hz, 1H, H-4′), 3.89–3.85 (m, 2H, H-5, H-6′), 3.74 (dd, *J*=2.2, 11.6 Hz, 1H, H-7′), 3.71 (d, *J*=3.3 Hz, 1H, H-3′), 3.7 (dd, *J*=2.6, 11.6 Hz, 1H, H-6), 3.57 (dd, *J*=6.6, 11.6 Hz, 1H, H-7′), 3.56 (dd, *J*=5.2, 11.6 Hz, 1H, H-6), 3.47 (dd, *J*=9.6, 9.6 Hz, 1H, H-5′), 1.39 (s, 3H, H-1′); ^{13}C NMR (150 MHz, CD_3OD): δ 176.0,

103.9, 79.7, 75.6, 74.2, 72.5, 71.4, 70.9, 69.5, 68.1, 64.3, 63.1, 21.9.

4.3.10. 1-Deoxy-α-D-*gluco*-hept-2-ulosyl-(2→3)-D-glucono-1,5-lactone (15aa). Colorless amorphous solid; $[\alpha]_D^{28}$ +87.7 (*c* 1.02, CH_3OH); ^1H NMR (600 MHz, CD_3OD): δ 4.57 (dd, *J*=6.9, 6.9 Hz, 1H, H-3), 4.49 (d, *J*=6.9 Hz, 1H, H-2), 4.43 (dd, *J*=6.9, 8.0 Hz, 1H, H-4), 3.89 (m, 1H, H-5), 3.72–3.66 (m, 3H, H-6, H-5′, H-6′), 3.62–3.53 (m, 3H, H-6, H-4′, H-7′), 3.29 (m, 1H, H-7′), 3.14 (d, *J*=9.4 Hz, 1H, H-3′), 1.46 (s, 3H, H-1′); ^{13}C NMR (150 MHz, CD_3OD): δ 176.1, 102.9, 78.8, 77.7, 76.1, 75.3, 74.5, 72.1, 71.4, 71.2, 64.0, 62.2, 21.9.

4.3.11. 1-Deoxy-α-D-*gluco*-hept-2-ulosyl-(2→3)-D-galactono-1,5-lactone (15ab). Colorless amorphous solid; $[\alpha]_D^{25}$ +44.4 (*c* 1.02, CH_3OH); ^1H NMR (600 MHz, CD_3OD): δ 4.52–4.48 (m, 2H), 4.28 (m, 1H), 3.80 (m, 1H), 3.72–3.69 (m, 2H), 3.60–3.50 (m, 4H), 3.17 (dd, *J*=9.4, 9.6 Hz, 1H), 3.10 (dd, *J*=9.6 Hz, 1H, H-2), 1.45 (s, 3H, H-1′); ^{13}C NMR (150 MHz, CD_3OD): δ 175.9, 102.8, 80.1, 78.2, 76.0, 75.1, 75.1, 74.6, 72.1, 70.5, 63.7, 62.7, 22.1.

4.3.12. 1-Deoxy-α-D-*galacto*-hept-2-ulosyl-(2→3)-D-glucono-1,5-lactone (15ba). Colorless amorphous solid; ^1H NMR (600 MHz, CD_3OD): δ 4.58 (dd, *J*=6.9, 7.2 Hz, 1H, H-3), 4.51 (d, *J*=7.2 Hz, 1H, H-2), 4.43 (dd, *J*=6.9, 7.7 Hz, 1H, H-4), 3.95 (m, 1H), 3.87 (m, 1H, H-5), 3.82 (m, 1H), 3.68–3.65 (m, 2H), 3.63–3.52 (m, 4H), 1.46 (s, 3H, H-1′); ^{13}C NMR (150 MHz, CD_3OD): δ 176.1, 103.2, 78.7, 76.0, 74.4, 73.1, 72.1, 71.9, 71.6, 71.0, 64.0, 62.6, 21.9.

4.3.13. 1-Deoxy-D-*galacto*-hept-2-ulosyl-(2→3)-D-galactono-1,5-lactone (15bb). Colorless amorphous solid; ^1H NMR (600 MHz, CD_3OD): δ 4.53 (d, *J*=8.0 Hz, 1H, H-2), 4.48 (dd, *J*=8.0, 8.0 Hz, 1H), 4.27 (dd, *J*=2.5, 8.0 Hz, 1H, H-3), 3.93 (m, 1H), 3.79 (m, 1H, H-4), 3.71–3.69 (m, 2H), 3.66 (dd, *J*=3.0, 10.2 Hz, 1H, H-4′), 3.60–3.54 (m, 3H), 3.50 (dd, *J*=10.2 Hz, 1H, H-3′), 1.48 (s, 3H, H-1′); ^{13}C NMR (150 MHz, CD_3OD): δ 176.0, 103.1, 80.0, 76.0, 74.9, 74.5, 73.7, 71.7, 71.4, 70.6, 63.7, 63.1, 21.9.

4.3.14. 1-Deoxy-α-D-*manno*-hept-2-ulosyl-(2→3)-D-glucono-1,5-lactone (15ca). Colorless amorphous solid; $[\alpha]_D^{26}$ +59.6 (*c* 0.69, CH_3OH); ^1H NMR (600 MHz, CD_3OD): δ 4.63 (d, *J*=7.2 Hz, 1H, H-2), 4.59 (dd, *J*=6.9, 7.2 Hz, 1H, H-3), 4.53 (dd, *J*=4.4, 6.9 Hz, 1H, H-4), 3.87 (m, 1H), 3.78 (dd, *J*=3.3, 9.6 Hz, 1H, H-4′), 3.72–3.69 (m, 2H), 3.64–3.58 (m, 3H), 3.59 (d, *J*=3.3 Hz, 1H, H-3′), 3.52 (dd, *J*=9.6, 9.6 Hz, 1H, H-5′), 1.42 (s, 3H, H-1′); ^{13}C NMR (150 MHz, CD_3OD): δ 176.8, 104.1, 80.1, 76.2, 75.2, 74.7, 73.0, 72.7, 72.3, 67.9, 64.2, 62.6, 20.8.

4.3.15. 1-Deoxy-α-D-*manno*-hept-2-ulosyl-(2→3)-D-galactono-1,5-lactone (15cb). Colorless amorphous solid; $[\alpha]_D^{25}$ +7.39 (*c* 0.57, CH_3OH); ^1H NMR (600 MHz, CD_3OD): δ 4.61 (dd, *J*=7.7, 8.0 Hz, 1H, H-5′), 4.51 (d, *J*=8.0 Hz, 1H, H-2), 4.23 (dd, *J*=1.7, 8.0 Hz, 1H, H-3), 3.80 (dd, *J*=2.2, 11.3 Hz, 1H, H-6), 3.75 (dd, *J*=3.3, 9.6 Hz, 1H, H-7′), 3.67 (dd, *J*=2.2, 7.7 Hz, 1H, H-4′), 3.67 (m, 1H, H-5), 3.57–3.52 (m, 4H, H-4, H-6, H-3′, H-6′), 3.47 (dd, *J*=9.6, 9.9 Hz, 1H, H-7′), 1.44 (s, 3H, H-1′); ^{13}C NMR (150 MHz, CD_3OD): δ 175.9, 104.0, 80.0, 79.6, 75.9, 75.6, 75.0, 74.7, 72.6, 69.7, 68.0, 63.5, 20.8.

4.3.16. 1-Deoxy-α-D-*manno*-hept-2-ulosyl-(2→3)-D-mannono-1,5-lactone (15cc). Colorless amorphous solid; $[\alpha]_D^{28}$ +76.4 (*c* 0.99, CH_3OH); ^1H NMR (600 MHz, CD_3OD): δ 4.61 (dd, *J*=3.3 Hz, 1H, H-2), 4.18 (dd, *J*=3.3, 0.6 Hz, 1H, H-3), 4.15 (ddd, *J*=2.5, 5.0, 9.9 Hz, 1H, H-6′), 4.03 (ddd, *J*=2.5, 5.2, 8.0 Hz, 1H, H-5), 3.82 (m, 1H, H-4), 3.75 (dd, *J*=2.5, 12.7 Hz, 1H, H-6), 3.72 (dd, *J*=3.3, 9.6 Hz, 1H, H-4′), 3.67 (dd, *J*=2.5, 11.8 Hz, 1H, H-7′), 3.62 (dd, *J*=5.0, 12.7 Hz, 1H, H-6), 3.60 (dd, *J*=5.2, 11.8 Hz, 1H, H-7′), 3.48 (d, *J*=3.3 Hz, 1H, H-3′), 3.46 (dd, *J*=9.6, 9.9 Hz, 1H, H-5′), 1.41 (s, 3H, H-1′); ^{13}C NMR (150 MHz, CD_3OD): δ 175.0, 103.3, 82.6, 76.5, 75.2, 74.4, 72.4, 70.2, 68.8, 68.0, 62.9, 62.4, 22.4.

4.3.17. 1-Deoxy-α-D-*gluco*-hept-2-ulosyl-(2→4)-D-glucono-1,5-lactone (20aa). Colorless amorphous solid; $[\alpha]_D^{25}$ +93.0 (*c* 0.96, CH_3OH); ^1H NMR (600 MHz, D_2O): δ 4.65 (m, 1H), 4.41 (m, 1H), 4.15 (m, 1H), 3.74–3.62 (m, 5H), 3.57–3.51 (m, 2H), 3.19 (m, 1H), 3.12 (m, 1H), 1.28 (s, 3H, H-1′); ^{13}C NMR (150 MHz, D_2O): δ 178.0, 102.9, 80.1, 77.0, 74.1, 74.0, 73.8, 73.7, 73.4, 70.7, 62.3, 61.4, 21.4.

4.3.18. 1-Deoxy-α-D-*gluco*-hept-2-ulosyl-(2→4)-D-galactono-1,5-lactone (20ab). Colorless amorphous solid; $[\alpha]_D^{25}$ +135.2 (*c* 0.6, H_2O); ^1H NMR (600 MHz, D_2O): δ 4.46 (m, 2H), 4.40 (m, 1H), 4.04 (m, 1H), 3.84 (m, 1H), 3.70 (m, 1H), 3.66–3.58 (m, 3H), 3.54 (m, 1H), 3.24 (m, 1H), 3.19 (m, 1H), 1.28 (s, 3H, H-1′); ^{13}C NMR (150 MHz, D_2O): δ 177.0, 102.0, 81.0, 77.0, 74.6, 73.6, 73.3, 73.3, 71.4, 70.3, 61.0, 60.5, 21.4.

4.3.19. 1-Deoxy-α-D-*gluco*-hept-2-ulosyl-(2→4)-D-mannono-1,5-lactone (20ac). Colorless amorphous solid; $[\alpha]_D^{25}$ +135.2 (*c* 0.6, H_2O); ^1H NMR (600 MHz, D_2O): δ 4.65 (d, *J*=2.8 Hz, 1H, H-2), 4.29 (m, 1H, H-5), 4.03 (m, 1H, H-3), 3.93 (m, 1H, H-4), 3.71 (dd, *J*=2.2, 12.4 Hz, 1H, H-7′), 3.63–3.59 (m, 2H, H-6, H-6), 3.55 (dd, *J*=5.0, 12.4 Hz, 1H, H-7′), 3.46 (dd, *J*=9.4, 9.6 Hz, 1H), 3.37 (ddd, *J*=2.2, 5.0, 9.9 Hz, 1H, H-6′), 3.21 (dd, *J*=9.6, 9.6 Hz, 1H), 3.10 (d, *J*=9.9 Hz, 1H, H-3′), 1.37 (s, 3H, H-1′); ^{13}C NMR (150 MHz, D_2O): δ 175.2, 102.7, 81.3, 76.4, 73.9, 73.8, 73.4, 70.3, 70.1, 68.9, 61.9, 61.1, 22.1.

4.3.20. 1-Deoxy-α-D-*galacto*-hept-2-ulosyl-(2→4)-D-glucono-1,5-lactone (20ba). Colorless amorphous solid; ^1H NMR (600 MHz, CD_3OD): δ 4.62 (dd, *J*=4.9, 7.1 Hz, 1H, H-4), 4.24 (dd, *J*=3.6, 4.9 Hz, 1H, H-3), 4.21 (d, *J*=3.6 Hz, 1H, H-2), 4.07 (ddd, *J*=1.1, 4.1, 8.2 Hz, 1H, H-6′), 4.05 (ddd, *J*=7.1, 3.3, 3.6 Hz, 1H, H-5), 3.88 (dd, *J*=3.3, 12.7 Hz, 1H, H-6), 3.76 (dd, *J*=3.3, 1.1 Hz, 1H, H-5′), 3.67–3.64 (m, 3H, H-6, H-4′, H-7′), 3.56 (dd, *J*=4.1, 11.3 Hz, 1H, H-7′), 3.48 (d, *J*=9.9 Hz, 1H, H-3′), 1.44 (s, 3H, H-1′).

4.3.21. 1-Deoxy-α-D-*galacto*-hept-2-ulosyl-(2→4)-D-galactono-1,5-lactone (20bb). Colorless amorphous solid; ^1H NMR (600 MHz, CD_3OD): δ 4.99 (dd, *J*=2.2, 5.8 Hz, 1H, H-4), 4.33 (dd, *J*=5.8, 6.3 Hz, 1H, H-3), 4.17 (d, *J*=6.3 Hz, 1H, H-2), 3.96–3.90 (m, 2H), 3.78–3.76 (m, 2H), 3.62–3.55 (m, 4H), 3.46 (d, *J*=9.9 Hz, 1H), 1.46 (s, 3H, H-1′); ^{13}C NMR (150 MHz, CD_3OD): δ 177.1, 102.9, 83.0, 76.3, 75.4, 75.3, 73.4, 73.2, 71.3, 71.1, 62.7, 61.5, 21.6.

4.3.22. 1-Deoxy-α-D-*galacto*-hept-2-ulosyl-(2→4)-D-mannono-1,5-lactone (20bc). Colorless amorphous solid; ^{13}C NMR (150 MHz, CD_3OD): δ 174.8, 103.5, 82.9, 74.7, 74.6, 73.7, 71.6, 71.1, 70.8, 69.6, 63.2, 62.8, 22.9.

4.3.23. 1-Deoxy-α-D-*manno*-hept-2-ulosyl-(2→4)-D-galactono-1,5-lactone (20cb). Colorless amorphous solid; ^{1}H NMR (600 MHz, CD_3OD): δ 4.37 (m, 2H), 4.18 (dd, *J*=8.5, 8.5 Hz, 1H), 4.13 (m, 1H), 4.02 (dd, *J*=5.0, 11.3 Hz, 1H), 3.84–3.80 (m, 2H), 3.71–3.62 (m, 4H), 3.52 (m, 1H), 1.46 (s, 3H, H-1′); ^{13}C NMR (150 MHz, CD_3OD): δ 177.1, 102.9, 83.0, 76.3, 75.4, 75.3, 73.4, 73.2, 71.3, 71.1, 62.7, 61.5, 21.6.

4.3.24. 1-Deoxy-α-D-*manno*-hept-2-ulosyl-(2→4)-D-mannono-1,5-lactone (20cc). Colorless amorphous solid; $[\alpha]_D^{25}$ +76.8 (*c* 0.48, CH_3OH); ^{1}H NMR (600 MHz, CD_3OD): δ 4.47 (d, *J*=3.0 Hz, 1H, H-2), 4.34 (ddd, *J*=5.2, 5.5, 3.3 Hz, 1H, H-5), 4.12 (dd, *J*=2.2, 5.2 Hz, 1H, H-4), 4.01 (ddd, *J*=3.0, 2.2 Hz, 1H, H-3), 3.78 (dd, *J*=3.3, 12.4 Hz, 1H, H-6), 3.74 (dd, *J*=2.2, 11.8 Hz, 1H, H-7′), 3.73–3.69 (m, 2H, H-4′, H-6), 3.59 (dd, *J*=6.1, 11.8 Hz, 1H, H-7′), 3.54 (d, *J*=3.3 Hz, 1H, H-3′), 3.48 (dd, *J*=9.6, 9.9 Hz, 1H, H-5′), 3.39 (ddd, *J*=2.2, 6.1, 9.9 Hz, 1H, H-6′), 1.45 (s, 3H, H-1′); ^{13}C NMR (150 MHz, CD_3OD): δ 174.4, 104.4, 83.7, 76.2, 75.1, 74.8, 72.5, 70.5, 69.5, 67.9, 63.4, 63.0, 21.7.

4.3.25. 1-Deoxy-α-D-*galacto*-hept-2-ulosyl-(2→6)-D-galactono-1,5-lactone (21bb). Colorless amorphous solid; ^{1}H NMR (600 MHz, CD_3OD): δ 4.26 (d, *J*=8.8 Hz, 1H, H-2), 4.17 (dd, *J*=8.3, 8.8 Hz, 1H, H-3), 4.08 (dd, *J*=3.3, 8.3 Hz, 1H, H-4), 3.80–3.78 (m, 2H, H-5, H-5′), 3.70 (dd, *J*=3.3, 9.9 Hz, 1H, H-4′), 3.68 (m, 1H, H-6′), 3.61 (dd, *J*=6.9, 11.3 Hz, 1H), 3.58 (dd, *J*=5.5, 11.3 Hz, 1H), 3.55 (dd, *J*=5.8, 9.6 Hz, 1H), 3.51 (dd, *J*=6.3, 9.6 Hz, 1H), 3.47 (dd, *J*=9.9 Hz, 1H, H-3′), 1.34 (s, 3H, H-1′).

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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.2006.07.032.

References and notes

1. Boons, G.-J.; Demchenko, A. V. *Carbohydrate-based Drug Discovery*; Wong, C. H., Ed.; Wiley-VCH: Weinheim, 2003; Vol. 1, pp 55–102.
2. Johnson, L. N.; Hu, S.-H.; Barford, D. *Faraday Discuss.* **1992**, *93*, 131–142.
3. For recent reviews on sialylation: (a) Boons, G.-J.; Demchenko, A. V. *Chem. Rev.* **2000**, *100*, 4539–4565; (b) Hansson, J.; Oscarson, S. *Curr. Org. Chem.* **2000**, *4*, 535–564; (c) Kiefel, M. J.; Itzstein, M. *Chem. Rev.* **2002**, *102*, 471–490.
4. Krog-Jensen, C.; Oscarson, S. *J. Org. Chem.* **1998**, *63*, 1780–1784.
5. Dondoni, A. *Pure Appl. Chem.* **2000**, *72*, 1577–1588 and references cited therein.
6. (a) Li, X. L.; Ohtake, H.; Takahashi, H.; Ikegami, S. *Tetrahedron* **2001**, *57*, 4283–4295; (b) Li, X. L.; Ohtake, H.; Takahashi, H.; Ikegami, S. *Synlett* **2001**, 1885–1888; (c) Namme, R.; Mitsugi, T.; Takahashi, H.; Ikegami, S. *Tetrahedron Lett.* **2005**, *46*, 3033–3036.
7. (a) Li, X. L.; Ohtake, H.; Takahashi, H.; Ikegami, S. *Tetrahedron* **2001**, *57*, 4297–4309; (b) Li, X. L.; Takahashi, H.; Ohtake, H.; Shiro, M.; Ikegami, S. *Tetrahedron* **2001**, *57*, 8053–8066.
8. Yamanoi, T.; Oda, Y.; Yamazaki, I.; Shinbara, M.; Morimoto, K.; Matsuda, S. *Lett. Org. Chem.* **2005**, *2*, 242–246.
9. Other groups also investigated the O-glycosidation of *exo*-glycals: (a) Chang, C.-F.; Yang, W.-B.; Chang, C.-C.; Lin, C.-H. *Tetrahedron Lett.* **2002**, *43*, 6515–6519; (b) Lin, H.-C.; Yang, W.-B.; Gu, Y.-F.; Chen, C.-Y.; Wu, C.-Y.; Lin, C.-H. *Org. Lett.* **2003**, *5*, 1087–1089; (c) Colinas, P. A.; Lieberknecht, A.; Bravo, R. D. *Tetrahedron Lett.* **2002**, *43*, 9065–9068; (d) Colinas, P. A.; Ponzinibbio, A.; Lieberknecht, A.; Bravo, R. D. *Tetrahedron Lett.* **2003**, *44*, 7985–7988.
10. Enzymatic O-glycosidation of heptenitols: Schlesselmann, P.; Fritz, H.; Lehmann, J.; Uchiyama, T.; Brewer, C. F.; Hehre, E. J. *Biochemistry* **1982**, *21*, 6606–6614.
11. O-Glycosidation of heptenitols promoted by iodonium ion, see: Noort, D.; Veeneman, G. H.; Boons, G.-J. P. H.; van der Marel, G. A.; Mulder, G. J.; van Boom, J. H. *Synlett* **1990**, 205–206.
12. For reviews of *exo*-glycal chemistry, see: (a) Taillefumier, C.; Chapleur, Y. *Chem. Rev.* **2004**, *104*, 263–292; (b) Lin, C.-H.; Lin, H.-C.; Yang, W.-B. *Curr. Top. Med. Chem.* **2005**, *5*, 1431–1457.
13. (a) RajanBabu, T. V.; Reddy, G. S. *J. Org. Chem.* **1986**, *51*, 5458–5461; (b) Petasis, N. A.; Lu, S.-P. *Tetrahedron Lett.* **1995**, *36*, 2393–2396.
14. For synthetic procedures of compounds **7**–**10**, see Supplementary data.
15. CCDC 610513 contains the supplementary crystallographic data for compound **14cc**. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.
16. Tvaroska, I.; Travel, F. R. Carbon–proton coupling constants in the conformational analysis of sugar molecules. In *Advances in Carbohydrate Chemistry and Biochemistry*; Horton, D., Ed.; Academic: San Diego, CA, 1995; Vol. 51, pp 15–61.
17. Bieg, T.; Szeja, W. *Synthesis* **1985**, 76–77.
18. Liu, H.-J.; Yip, J. *Tetrahedron Lett.* **1997**, *38*, 2253–2256.
19. Schuda, P. F.; Cichowicz, M. B.; Heimann, M. R. *Tetrahedron Lett.* **1983**, *24*, 3829–3830.
20. Binkley, R. W.; Hehmann, D. G. *J. Org. Chem.* **1990**, *55*, 378–380.
21. (a) Hirama, M.; Shimizu, M. *Synth. Commun.* **1983**, *13*, 781–786; (b) Angibeaud, P.; Defaye, J.; Gadelle, A.; Utille, J.-P. *Synthesis* **1985**, 1123–1125.
22. (a) Czech, B. P.; Bartsh, R. A. *J. Org. Chem.* **1984**, *49*, 4076–4078; (b) Sajiki, H.; Hirota, K. *Tetrahedron* **1998**, *54*, 13981–13996.
23. In some cases, decomposition of debenzylated disaccharides **15**, **16**, **20**, and **21** was observed during work-up. Filtration through a celite pad caused decomposition, and therefore filter paper was used for separation of the catalyst.
24. For the peak assignments in ^{1}H and ^{13}C NMR spectra for compounds **11**–**14**, see Supplementary data.

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Convergent synthesis of PAMAM dendrimers using click chemistry of azide-functionalized PAMAM dendrons

Jae Wook Lee,[a,*] Jung Hwan Kim,[a] Byung-Ku Kim,[a] Ji Hyeon Kim,[b] Won Suk Shin[c] and Sung-Ho Jin[c]

[a]*Department of Chemistry, Dong-A University, Hadan-2-dong, Busan 604-714, Republic of Korea*
[b]*Department of Chemical and Biochemical Engineering, Dongguk University, Seoul 100-715, Republic of Korea*
[c]*Department of Chemistry Education and Center for Plastic Information System, Pusan National University, Busan 609-735, Republic of Korea*

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Abstract—Azide-functionalized PAMAM dendrons containing an azidopropylamine focal point were synthesized by the divergent method and applied for the construction of symmetric PAMAM-like dendrimers containing 1,2,3-triazole rings as connectors via stitching with two different multi-terminal alkynes. The stitching method was based on the click chemistry protocol, i.e., the copper-catalyzed cycloaddition reaction between an alkyne and an azide.

1. Introduction

Organoazides are versatile intermediates in synthetic organic chemistry, because the azide group can subsequently be converted into several other types of substituent groups.[1] Azides are among the most stable 1,3-dipoles and generally can be stored for indefinite time without significant decomposition. Since the 1,3-dipolar cycloaddition of azides with alkynes was investigated by Huisgen et al.,[2] it has been attracted much attention because of the synthetic importance of the five-membered [1,2,3]-triazole heterocycles.[3] The traditional method for producing the triazoles by cycloaddition requires elevated temperature, typically in refluxing conditions and also provides a mixture of 1,4- and 1,5-disubstituted triazoles. Over the years, several efforts to control the 1,4- versus 1,5-regioselectivity have been reported.[4] Recently the click chemistry,[5] which is the Cu(I)-catalyzed Huisgen [2+3] dipolar cycloaddition reaction between an organic azide and a terminal alkyne, has found many applications[6] in combinatorial and organic chemistries, bioconjugations, and materials science. The reaction, characterized by very high yields, mild and simple reaction conditions, excellent oxygen and water tolerance, and simple product isolations, is highly chemoselective affording only the desired 1,2,3-triazole even in the presence of a large variety of other functional groups.

Dendrimers, which are prepared by repetition of a given set of reactions using either divergent or convergent strategies, are highly branched and regular macromolecules with well-defined structures and have served as functional objects in nanotechnology and nanoscience.[7] The convergent approach to dendrimer synthesis introduced by Fréchet and co-workers revolutionized the synthetic approaches to monodisperse dendrimers.[8] The convergent methodology installs the core in the final step, enabling the incorporation of functionalities. It provides greater structural control than the divergent approach due to its relatively low number of coupling reactions at each growth step. The ability to prepare well-defined symmetrical dendrimers is the most attractive features of the convergent synthesis. By far the most widely used dendrimers prepared by convergent syntheses are the poly(benzyl ether)s, developed by Fréchet and Grayson,[8c] and the poly(arylethynyl)s developed by Moore and co-workers. On the other hand, PAMAM dendrimers are synthesized by the divergent approach. This methodology involves building the dendrimers from the core by an iterative synthetic procedure.[9] Although many methods for the convergent synthesis of various dendrimers were developed, a relatively few methods for PAMAM dendrimer have been reported in the literature.[10] Recent research emphasis seems to shift from the synthesis of novel dendrimers to their properties and potential applications, but future applications of dendrimers rely on efficient and practical synthetic procedures.[11]

Although there are several reports to synthesize triazole-mediated dendritic materials using click chemistry,[12] relatively few applications in PAMAM dendrimer synthesis

Keywords: Alkyne; Azide; Click chemistry; PAMAM dendrimers; 1,2,3-Triazoles.
* Corresponding author. Tel.: +82 51 200 7251; fax: +82 51 200 7259; e-mail: jlee@donga.ac.kr

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have been reported.[13] 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 show the characteristic behaviors. Due to our interest in developing new functional dendrimers, we became involved in exploring efficient cycloaddition reactions that provide easy accesses to dendrimers. Herein, we present the synthesis of azide-functionalized poly(amidoamine) (PAMAM) dendrons **1-Dm** and their application to the convergent synthesis of poly(amidoamine) (PAMAM) dendrimers by reacting **1-Dm** with two different multi-terminal alkynes.

2. Results and discussion

The synthetic strategy for PAMAM dendrimers is schematically shown in Figure 1. PAMAM dendrons **1-Dm** (m=1–3: generation of dendron) are synthesized by the divergent approach using azidopropylamine as an azide focal point shown in Scheme 1. Although, we have screened with several Lewis acid-catalyzed Michael addition reactions to find the efficient condition in conjugate addition of free amine,[14] we utilized a standard PAMAM synthesis eventually furnishing us with the desired ester-terminated dendrons. This methodology involves typical stepwise and iterative two-step reaction sequences, consisting of amidation of methyl ester groups with a large excess of ethylenediamine (EDA) and Michael addition of primary amines with methyl acrylate (MA) to produce methyl ester terminal groups. The reaction of azidopropylamine and 3.5 equiv of MA in methanol gave dendron **1-D1** in 86% yield. For dendron **1-D2**, dendron **1-D1** was reacted with 20 equiv of EDA in methanol and then removal of methanol and excess EDA under vacuum produced the amine-terminated dendron, which was reacted with 7 equiv of MA in methanol to afford dendron **1-D2** in 91% yield. Dendron **1-D3** was obtained from **1-D2** by the consecutive amidation and Michael addition reactions in yield of 64%. The yield of high generation dendron (**1-D3**) is lower than those of low generation dendrons (**1-D1** and **1-D2**). The somewhat lower isolation yield of the former could be due to side reaction(s) between an azide group and the acrylate added in excess.[15] The structures of the dendrons **1-Dm** were confirmed by ^{1}H and ^{13}C NMR spectroscopies, IR spectroscopy, and FAB mass spectra. In the ^{1}H NMR spectra ($CDCl_3$) shown in Figure 2, the peaks of the amide protons (NH) were found at 6.96 ppm for **1-D2**, and at 6.99 and 7.61 ppm for **1-D3**, respectively. The IR spectra show the azide (N_3) at 2098 cm^{-1} and C=O of esters at 1739 cm^{-1} for **1-D1**, azide (N_3) at 2096 cm^{-1}, C=O of esters at 1737 cm^{-1}, and C=O of amides at 1667 cm^{-1} for **1-D2**, and azide (N_3) at 2096 cm^{-1}, C=O of esters at 1735 cm^{-1}, and C=O of amides at 1652 cm^{-1} for **1-D3**. Their FAB mass spectra exhibited very good correlation with the calculated molecular masses.

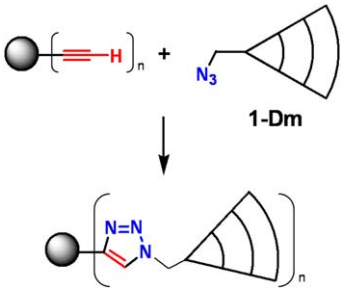


Figure 1. Synthetic strategy for PAMAM dendrimers linked by the triazole units.

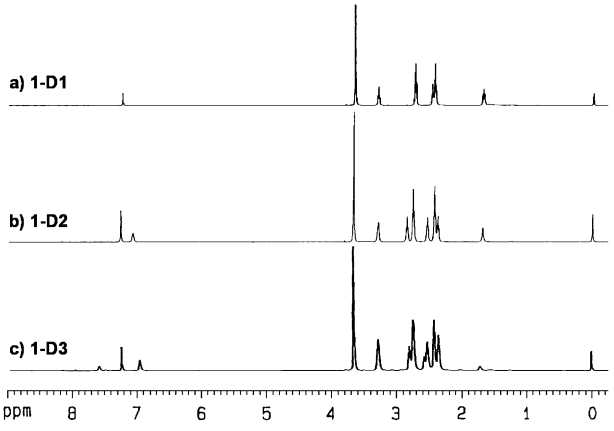
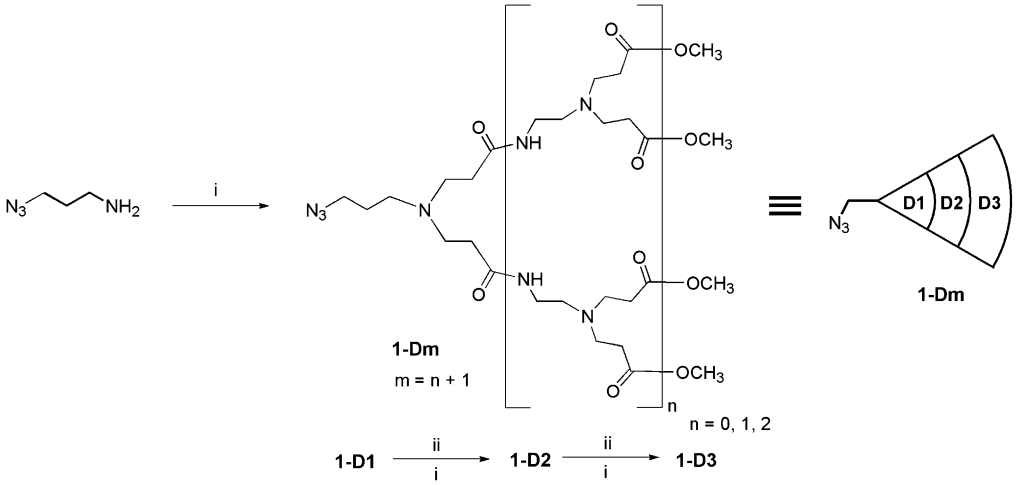
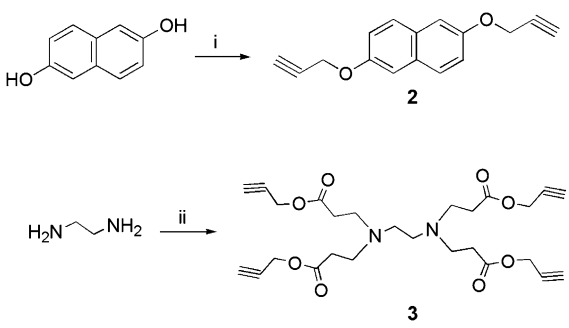


Figure 2. ^{1}H NMR spectra for dendrons (a) **1-D1**, (b) **1-D2**, and (c) **1-D3**.



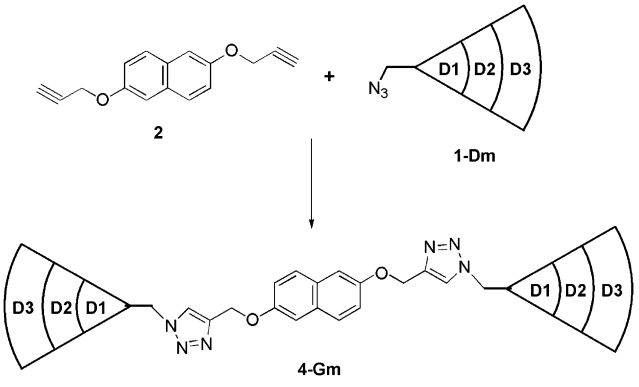
Scheme 1. Reagents and conditions: (i) methyl acrylate, MeOH, rt; (ii) ethylenediamine, MeOH, rt.

The inward growth employed by the convergent synthesis is ideally suited for the attachment of diverse core moieties. As a result, building dendrimers via the convergent approach allows for the synthesis of symmetric dendrimers and for incorporation of specific functions into the dendrimer's interior. To efficiently connect the azide focal point PAMAM dendrons with core unit(s) via the convergent approach, we intended to use the click condition using Cu(I) species.[16] 2,6-Bis-prop-2-ynyloxynaphthalene **2** and *N*,*N*,*N*′,*N*′-tetra-(prop-2-ynyloxycarbonylethyl)-1,2-diaminoethane **3**, designed to present alkyne functionalities available for dendrimer growth via click reactions with the dendrons, were synthesized readily from the bis-propargylation of 2,6-dihydroxynaphthalene with propargyl bromide in the presence of a base and Michael addition of 1,2-diaminoethane with propargyl acrylate in yields of 87 and 95%, respectively (Scheme 2). The structures of these compounds were confirmed by ^{1}H and ^{13}C NMR spectroscopies, IR spectroscopy, and FAB mass spectra. The IR spectra show the terminal ≡C–H at 3277 cm^{-1} and C≡C triple bond at 2131 cm^{-1} for compound **2** and the terminal ≡C–H at 3290 cm^{-1}, C≡C triple bond at 2128 cm^{-1}, and C═O of esters at 1739 cm^{-1} for compound **3**.



Scheme 2. Reagents and conditions: (i) propargyl bromide, K_2CO_3, DMF, rt; (ii) propargyl acrylate, CH_3CN, rt.

To test the effectiveness of the dipolar cycloaddition reactions of the bis(alkynes) core **2** and azide-dendrons **1-Dm** (Scheme 3), we have screened several conditions using various Cu(I) sources in different solvents.[6,16] We have found that the reaction conducted under the conditions of 10 mol % of $CuSO_4 \cdot 5H_2O$ with 20 mol % of sodium ascorbate in a 4:1 solvent ratio of THF to H_2O for 2.5 h at room temperature afforded the desired product **4-G1** in yield of 99%. The generation and disappearance of the mono-triazole derivative were monitored by TLC runs of the reaction mixture. Given the success in the synthesis of first generation dendrimers, we expanded this reaction to get higher generation dendrimers with 5 mol % of $CuSO_4 \cdot 5H_2O$ and 10 mol % of sodium ascorbate with respect to the alkyne in a 4:1 solvent ratio of THF to H_2O. Reactions of the core **2** with 2.1 equiv of **1-D2** and **1-D3** afforded the PAMAM dendrimers **4-G2** and **4-G3** in yields of 95 and 91%, respectively, after 4 and 6.5 h. For completion of the reaction between the dendritic azide and the alkynes, the higher generation dendron takes longer time than the lower generation dendron, which can be ascribed to the steric demand of the dendron. The symmetric PAMAM dendrimers were purified by column chromatography and the structures were confirmed by ^{1}H and ^{13}C NMR spectroscopies, IR spectroscopy, and FAB or MALDI mass spectra. From the ^{1}H NMR spectra ($CDCl_3$), the peaks of the methylene protons adjacent to the nitrogen of triazole, the triazole proton, and the methylene protons adjacent to the carbon of triazole in dendrimers **4-Gm** were found at 4.36, 7.77, and 5.27 ppm for **4-G1**, 4.39, 7.85, and 5.26 ppm for **4-G2**, and 4.41, 7.93, and 5.26 ppm for **4-G3**, respectively (Fig. 3). As the dendrimer generation increased, the peaks of the methylene protons adjacent to the nitrogen of triazole and the triazole proton shifted gradually to down-field, which may be influenced by the dendritic microenvironment effect.[17] IR data also confirmed that neither alkyne (~3277 cm^{-1}) nor azide (~2098 cm^{-1}) residues remain in the final dendrimer. Their FAB mass spectra exhibited very good correlation with the calculated molecular masses. Analysis of the dendrimers by gel-permeation chromatography (GPC) from THF eluant shows very low polydispersity values PDI=1.02 and 1.04 for **4-G1** and **4-G2**, respectively (Fig. 4). Unfortunately, GPC analysis of **4-G3** could not be performed due to their poor solubility and aggregation property in THF.



Scheme 3. Reagents and conditions: 10 mol % of $CuSO_4 \cdot 5H_2O$/20 mol % of sodium ascorbate, THF/H_2O (4:1), rt.

To probe the viability of our approach, we next turned our attention toward the construction of PAMAM dendrimers **5-Gm** with tetra(alkyne) **3** (Scheme 4). The reaction of the tetra(alkyne) **3** and 4.4 equiv of azide-dendrons **1-D1** in the presence of 0.1, 0.2, and 0.5 equiv of CuI with respect to the alkyne in THF (0.1 M) did not occur at room temperature. However, the reaction proceeded at 50 °C very efficiently to afford the desired product **5-G1** in isolated

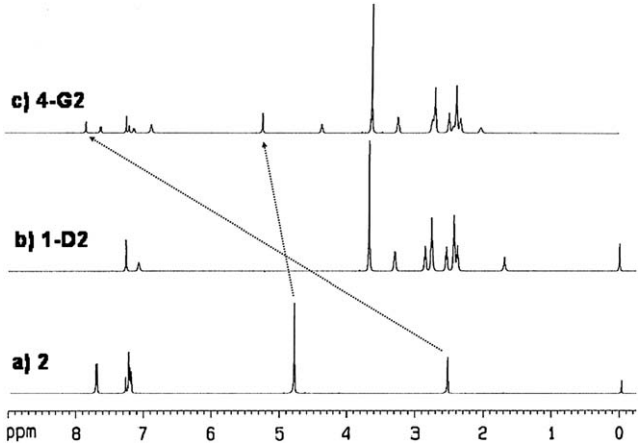


Figure 3. ^{1}H NMR spectra for (a) **2**, (b) **1-D2**, and (c) **4-G2**.

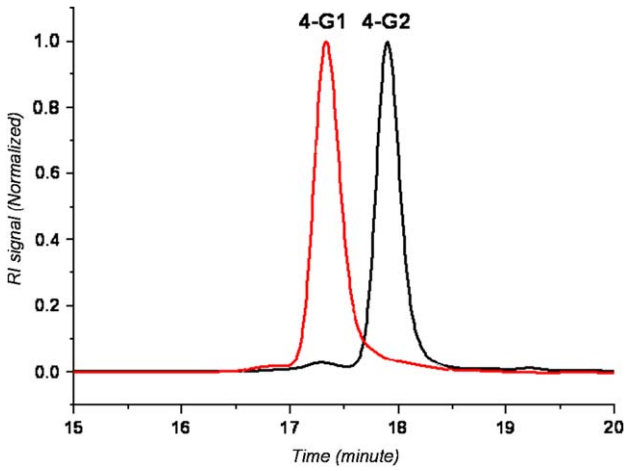
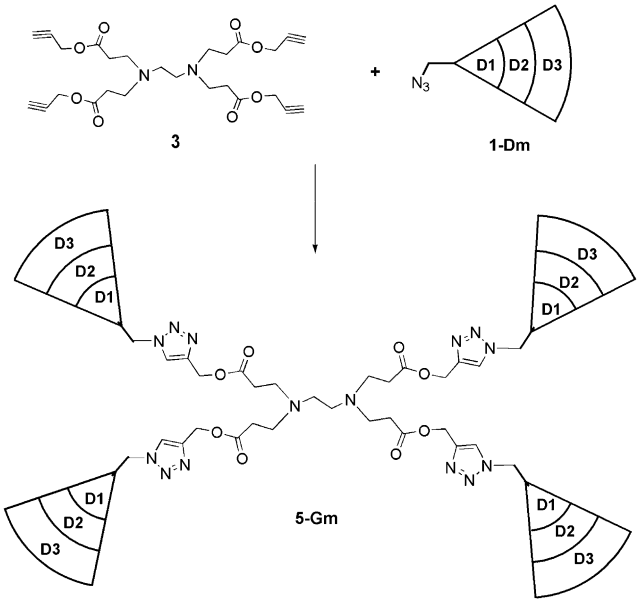


Figure 4. GPC diagrams of dendrimers **4-Gm** obtained from THF eluant.

yields of ~85% after 24 h irrespective of the amount of CuI used. We have found that the reaction conducted in 5 mol % of $CuSO_4 \cdot 5H_2O$ and 10 mol % of sodium ascorbate with respect to the alkyne in a 4:1 solvent ratio of DMF to H_2O proceeded smoothly at room temperature and finished within 24 h at 60 °C providing the desired product **5-G1** in an isolated yield of 95%. The generation and disappearance of the mono, di, and tri-triazole derivatives were monitored by TLC runs of the reaction mixture. Based on these optimizations for the synthesis of the first generation dendrimer, we fixed conditions for higher generation dendrimers. It was observed that the reactions carried out with 5 mol % of $CuSO_4 \cdot 5H_2O$ and 10 mol % of sodium ascorbate with respect to the alkyne in a 4:1 solvent ratio of DMF to H_2O at 60 °C proceeded quickly than those using CuI. Therefore, we tried to synthesize higher generation dendrimers with 5 mol % of $CuSO_4 \cdot 5H_2O$ and 10 mol % of sodium ascorbate with respect to the alkyne in a 4:1 solvent ratio of DMF to H_2O (Scheme 4). The reactions of the tetra(alkyne) **3** and 4.4 equiv of azide-dendrons **1-D2** and **1-D3** afforded the



Scheme 4. Reagents and conditions: 20 mol % of $CuSO_4 \cdot 5H_2O$/40 mol % of sodium ascorbate, DMF/H_2O (4:1), 60 °C.

PAMAM dendrimers **5-G2** and **5-G3** in yields of 69 and 56%, respectively, after 30 and 38 h, which were separated by column chromatography. The low yields, in the absence of any side product(s) as observed by TLC, could be due to significant retention of the polar dendrimer in the silica column. To improve the isolated yield of dendrimers, we decided to use the membrane dialysis. The crude product was dissolved in methanol and dialyzed (cellulose membrane with molecular weight cut-off 1000) against methanol for 1 day to provide **5-G2** and **5-G3** in yields of 90 and 84%, respectively. For completion of the reaction between the dendritic azide and the alkyne, the higher generation dendron takes longer time than the lower generation dendron, which can be differentiated by the accessibility of azide group due to the steric hindrance (bulkiness) of dendron and spatial congestion of core region. This observation led us to imagine that the reaction between the dendritic azide and the core was kinetically controlled. This result showed that the formation of triazole could be regarded as a new connector to construct the symmetric PAMAM dendrimers from dendrons.

The structures of the PAMAM dendrimers were also confirmed by ^1H and ^{13}C NMR spectroscopies, IR spectroscopy, and FAB and MALDI mass spectra. From the ^1H NMR spectra ($CDCl_3$), the peaks of the methylene protons adjacent to the nitrogen of triazole, the triazole proton, and the methylene protons adjacent to the carbon of triazole in dendrimers **5-Gm** were found at 4.35, 7.77, and 5.18 ppm for **5-G1**, 4.37, 7.79, and 5.16 ppm for **5-G2**, and 4.36, 7.71, and 5.16 ppm for **5-G3**, respectively (Fig. 5). There are no characteristic differences in their chemical shifts according to the dendrimer generations, which may have same chemical environments in the tetra-branched core system compared to the bis-branched core. The IR spectra show the disappearance of the acetylene peak at ~3290 cm^{-1} and the azide peak at ~2096 cm^{-1} in the final dendrimer (Fig. 6) while the ^1H NMR revealed no alkyne peak at around δ 2.47 ppm. Their FAB and MALDI mass spectra exhibited very good correlation with the calculated molecular masses. Analysis of the dendrimers by gel-permeation chromatography (GPC) from THF eluant shows very low polydispersity values PDI=1.02 for **5-G1**, which means no signs of products with defects that would arise from incomplete coupling (Fig. 7). Unfortunately, GPC analysis for **5-G2** and **5-G3** could not be performed due to their poor solubility and aggregation property in THF.

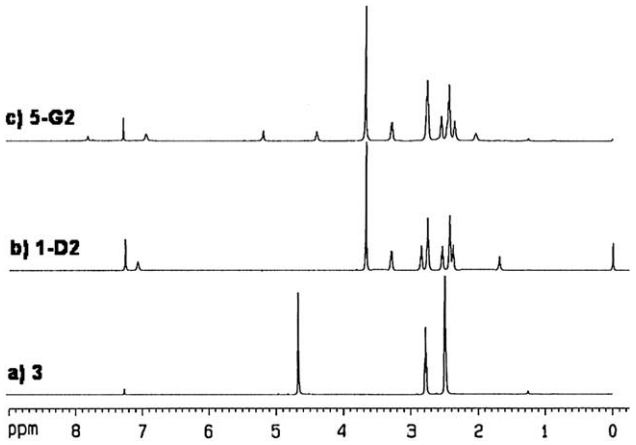


Figure 5. ^1H NMR spectra for (a) **3**, (b) **1-D2**, and (c) **5-G2**.

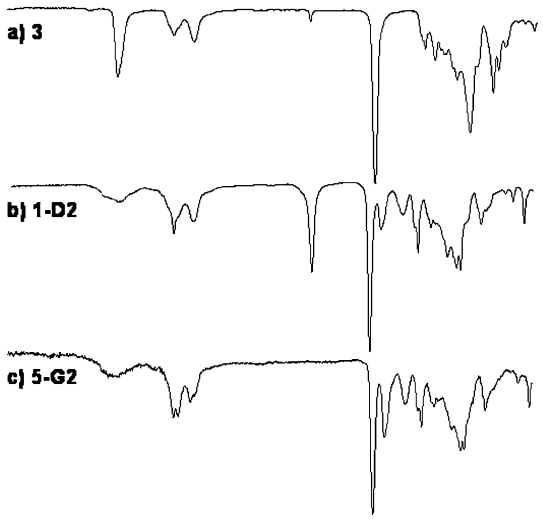


Figure 6. IR spectra for (a) **3**, (b) **1-D2**, and (c) **5-G2**.

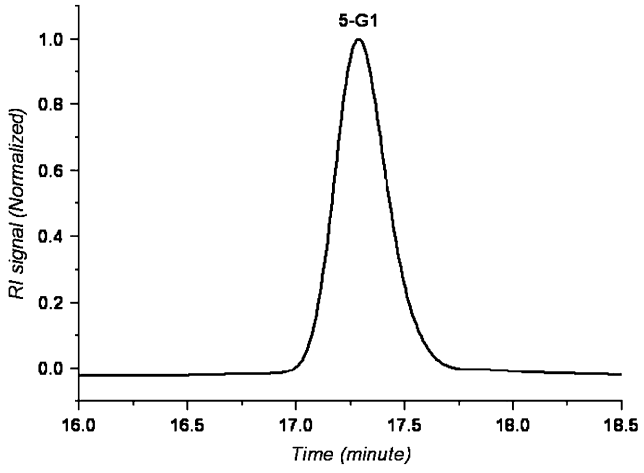


Figure 7. GPC diagrams of dendrimers **5-G1** obtained from THF eluant.

3. Conclusion

We have demonstrated that the azide-functionalized PAMAM dendrons are synthesized by the divergent approach using azidopropylamine as an azide focal point and that click reactions between the bis- or tetra-terminal alkynes and the azide-functionalized PAMAM dendrons lead to the formation of symmetric PAMAM dendrimers in high yields. This method can be applied for the fast synthesis of PAMAM-like dendrimers with different lengths (spacers) at core and may then provide an insight into designing various symmetrical dendrimers with the functional cores. We are currently working toward the synthesis of various functional dendrimers using this strategy for tailored applications.

4. Experimental

4.1. General

^{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. FAB and MALDI mass spectra were obtained from Korea Basic Science Institute (KBSI) 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.

4.2. Synthesis of azide-functionalized-PAMAM dendron 1-Dm

4.2.1. Synthesis of azide-functionalized-PAMAM dendron 1-D1. A solution of azidopropylamine (3.0 g, 30 mmol) in methanol (25 mL) was added dropwise to a stirred solution of methyl acrylate (6.5 g, 75 mmol) in methanol (25 mL) over a period of 1 h in an ice-water bath. The resulting solution was stirred for 30 min in an ice-water bath and then allowed to warm to room temperature and stirred for further 48 h. The volatiles were removed under reduced pressure using a rotary evaporator and vacuum. The residue was purified by column chromatography (EtOAc/*n*-hexane, 1:1) to afford the desired product (7.02 g, 86%). Dendron **1-D1**: a colorless oil; 86% yield; IR 2954, 2825, 2098, 1739, 1437, 1256, 1198, 1173 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.69 (quint, J=6.6 Hz, 2H), 2.44 (t, J=6.9 Hz, 4H), 2.48 (t, J=6.6 Hz, 2H), 2.74 (t, J=6.9 Hz, 4H), 3.31 (t, J=6.6 Hz, 2H), 3.67 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=173.33, 51.94, 50.95, 49.67, 49.58, 32.94, 27.06; FABMS: m/z=273 [M^++H], 202; HRMS (FAB) calcd for $C_{11}H_{20}N_4O_4$: 272.1485; found: 273.1563 [M^++H].

4.2.2. Synthesis of azide-functionalized-PAMAM dendron 1-D2. A solution of ester **1-D1** (3.8 g, 14 mmol) in methanol (100 mL) was added dropwise to a stirred solution of 1,2-diaminoethane (21 g, 0.35 mol) in methanol (100 mL) over a period of 1 h in an ice-water bath. The resulting solution was allowed to warm to room temperature and stirred for further 7 days at room temperature at which time no methyl ester was detectable by NMR spectroscopy. The solvent was removed under reduced pressure using a rotary evaporator maintaining the temperature not higher than 40 °C and then the excess 1,2-diaminoethane was removed using an azeotropic mixture of toluene and methanol (9:1). The remaining toluene was removed by azeotropic distillation using methanol and finally kept under vacuum to provide the amino-terminated product (4.55 g, 99%) as a colorless oil. A solution of the previously prepared amino-terminated product (3.15 g, 9.6 mmol) in methanol (50 mL) was added dropwise to a stirred solution of methyl acrylate (5.84 g, 67.2 mmol) in methanol (50 mL) over a period of

1 h in an ice-water bath. The resulting solution was stirred for 30 min in an ice-water bath and then allowed to warm to room temperature and stirred for further 60 h. The volatiles were removed under reduced pressure using a rotary evaporator and vacuum. The residue was purified by column chromatography (EtOAc/methanol, 10:1) to afford the desired product (5.9 g, 91%). Dendron **1-D2**: a colorless gum; 91% yield; IR 3295, 2952, 2828, 2096, 1737, 1667, 1531, 1436, 1257, 1196, 1173 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=1.70 (quint, J=6.6 Hz, 2H), 2.36 (t, J=6.57 Hz, 4H), 2.43 (t, J=6.54 Hz, 8H), 2.49–2.54 (m, 6H), 2.75 (t, J=6.51 Hz, 12H), 3.25–3.33 (m, 6H), 3.67 (s, 12H), 6.96 (br s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=173.12, 172.33, 53.08, 51.72, 50.26, 49.87, 49.46, 49.34, 37.22, 33.92, 32.79, 26.46; FABMS: m/z=674 [M^++2H], 672 [M^+]; HRMS (FAB) calcd for $C_{29}H_{52}N_8O_{10}$: 672.3806; found: 673.3885 [M^++H].

4.2.3. Synthesis of azide-functionalized-PAMAM dendron 1-D3. Dendron **1-D3** was synthesized from **1-D2** (3.5 g, 5.2 mmol) using same method as successive amidation of methyl ester groups with a large excess of ethylenediamine (EDA) and Michael addition of primary amines with methyl acrylate (MA) in yield of 64–70% and the spectroscopic data are as follows. Dendron **1-D3**: a colorless gum; 64% yield; IR 3304, 2952, 2825, 2096, 1735, 1652, 1540, 1437, 1256, 1196, 1177 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=1.71 (quint, J=6.8 Hz, 2H), 2.37 (m, 12H), 2.43 (t, J=6.5 Hz, 16H), 2.54 (t, J=5.7 Hz, 10H), 2.59 (m, 4H), 2.76 (t, J=6.5 Hz, 20H), 2.81 (t, J=6.5 Hz, 8H), 3.29 (m, 14H), 3.67 (s, 24H), 6.99 (br s, 4H), 7.61 (br s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=173.39, 172.69, 172.63, 53.27, 52.87, 51.99, 50.36, 50.19, 49.75, 49.56, 49.45, 37.87, 37.48, 34.12, 33.04, 26.64; FABMS: m/z=1474 [M^++H]; HRMS (FAB) calcd for $C_{65}H_{116}N_{16}O_{22}$: 1472.8450; found: 1473.8528 [M^++H].

4.3. Synthesis of multi(alkynes) core 2 and 3

4.3.1. Synthesis of 2,6-bis-prop-2-ynyloxynaphthalene 2. A solution of 2,6-dihydroxynaphthalene (0.25 g, 1.56 mmol) and propargyl bromide (0.52 g, 4.68 mmol) in DMF (20 mL) in the presence of K_2CO_3 (0.54 g, 3.9 mmol) was stirred at room temperature for 12 h. The reaction mixture was added to EtOAc (50 mL) and the resulting solution was washed with brine (20 mL×3). The organic phase was dried with magnesium sulfate and concentrated. The residue was purified by recrystallization (EtOAc/*n*-hexane system) and column chromatography (EtOAc/*n*-hexane, 1:4) to afford the desired product **2** (0.32 g, 87%). IR 3277, 2964, 2924, 2853, 2131, 1604, 1508, 1399, 1229, 1168, 1022 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=2.55 (t, J=2.1 Hz, 2H), 4.80 (d, J=2.1 Hz, 4H), 7.19–7.22 (m, 4H), 7.69 (d, J=8.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=154.72, 130.35, 128.92, 119.59, 108.29, 79.01, 75.99, 56.37; FABMS: m/z=236 [M^+], 197; HRMS (FAB) calcd for $C_{16}H_{12}O_2$: 236.0837; found: 237.0916 [M^++H].

4.3.2. Synthesis of *N,N,N′,N′*-tetra(prop-2-ynyloxycarbonylethyl)-1,2-diaminoethane 3. A solution of propargyl acrylate (458 mg, 4.16 mmol) in CH_3CN (5 mL) was added dropwise to a stirred solution of 1,2-diaminoethane (50 mg, 0.83 mol) in CH_3CN (5 mL) over a period of 5 min in an ice-water bath. The resulting solution was allowed to warm to room temperature and stirred for further 23 h at room temperature. The volatiles were removed under reduced pressure using a rotary evaporator and vacuum. The residue was purified by column chromatography (EtOAc/*n*-hexane, 2:3) to afford the desired product (395 mg, 95%). IR 3290, 2950, 2827, 2128, 1739, 1166, 1025 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=2.46–2.49 (m, 16H), 2.77 (t, J=6.9 Hz, 8H), 4.67 (d, J=2.3 Hz, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=172.00, 78.12, 75.40, 52.69, 52.30, 50.02, 33.01; FABMS: m/z=501 [M^++H], 403, 264, 250; HRMS (FAB) calcd for $C_{26}H_{32}N_2O_8$: 500.2159; found: 501.2237 [M^++H].

4.4. Synthesis of PAMAM-like dendrimers 4-Gm from azide-PAMAM dendrons 1-Dm and bis(alkynes) core 2

General procedure: A mixture of azido-dendrons **1-Dm** (0.21 mmol) and 2,6-bis-prop-2-ynyloxynaphthalene **2** (0.10 mmol) in THF/H_2O (4:1, 1 mL) in the presence of 10 mol % $CuSO_4 \cdot 5H_2O$ with 20 mol % sodium ascorbate was stirred at room temperature for ~7 h. 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/methanol system or methanol) to afford the desired product.

4.4.1. Compound 4-G1. Yield 99%; IR 3142, 2954, 2845, 1735, 1604, 1436, 1226, 1167, 1113 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=2.08 (m, 4H), 2.41 (m, 12H), 2.73 (m, 8H), 3.63 (s, 12H), 4.36 (t, J=6.7 Hz, 4H), 5.27 (s, 4H), 7.14 (d, J=8.8 Hz, 2H), 7.20 (d, J=1.7 Hz, 2H), 7.62 (d, J=8.8 Hz, 2H), 7.77 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=172.65, 154.83, 143.84, 129.76, 128.32, 123.28, 119.14, 107.51, 62.06, 51.59, 50.35, 49.01, 47.82, 32.85; FABMS: m/z=782 [M^++2H]; HRMS (FAB) calcd for $C_{38}H_{52}N_8O_{10}$: 780.3806; found: 781.3885 [M^++H]. PDI=1.02.

4.4.2. Compound 4-G2. Yield 93%; IR 3318, 2952, 2827, 1736, 1666, 1604, 1531, 1436, 1225, 1198, 1175 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=2.03 (m, 4H), 2.33 (m, 8H), 2.39 (t, J=6.6 Hz, 16H), 2.44 (m, 4H), 2.50 (t, J=5.8 Hz, 8H), 2.71 (t, J=6.6 Hz, 16H), 2.74 (m, 8H), 3.23–3.27 (m, 8H), 3.64 (s, 24H), 4.39 (t, J=6.8 Hz, 4H), 5.26 (s, 4H), 6.89 (br s, 4H), 7.15 (dd, J=8.8, 2.2 Hz, 2H), 7.22 (d, J=2.2 Hz, 2H), 7.64 (d, J=8.8 Hz, 2H), 7.85 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=172.87, 172.14, 154.77, 143.71, 129.63, 128.20, 123.18, 119.02, 107.22, 61.85, 52.71, 51.48, 49.70, 49.44, 49.01, 47.81, 36.96, 33.77, 32.50; FABMS: m/z=1582 [M^++2H]; HRMS (FAB) calcd for $C_{74}H_{116}N_{16}O_{22}$: 1580.8450; found: 1581.8528 [M^++H]. PDI=1.04.

4.4.3. Compound 4-G3. Yield 91%; IR 3308, 2954, 2828, 1735, 1659, 1647, 1604, 1544, 1437, 1227, 1196, 1178 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=2.05 (m, 4H), 2.35 (m, 24H), 2.41 (t, J=6.4 Hz, 32H), 2.53–2.54 (m, 20H), 2.57 (m, 8H), 2.74 (t, J=6.5 Hz, 40H), 2.78 (m, 16H), 3.27 (m, 24H), 3.66 (s, 48H), 4.41 (t, J=6.5 Hz, 4H), 5.26 (s, 4H), 7.00 (br s, 8H), 7.16 (d, J=8.8 Hz, 2H), 7.26 (d, J=2.2 Hz, 2H), 7.55 (br s, 4H), 7.66 (d, J=8.8 Hz,

2H), 7.93 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=173.45, 172.83, 172.72, 155.46, 144.27, 130.28, 128.82, 123.87, 119.63, 107.86, 62.46, 53.34, 52.97, 52.05, 50.21, 49.66, 48.56, 37.98, 37.60, 34.22, 33.11; MS (MALDI) *m/z* calcd for $C_{146}H_{244}N_{32}O_{46}$: 3181.7738; found: 3181.9377 [M^+].

4.5. Synthesis of PAMAM-like dendrimers 5-Gm from azide-PAMAM dendrons 1-Dm and tetra(alkynes) core 3

General procedure: A mixture of azido-dendrons **1-Dm** (0.05 mmol) and tetra(prop-2-ynyloxycarbonylethyl)-1,2-diaminoethane **3** (0.01 mmol) in DMF/H_2O (4:1, 0.5 mL) in the presence of 20 mol % of $CuSO_4\cdot 5H_2O$ with 40 mol % of sodium ascorbate was stirred at 60 °C for ~38 h. The reaction mixture was poured into brine (20 mL) and the resulting solution was extracted with CH_2Cl_2 (20 mL×3). The combined organic phase was dried with sodium sulfate, concentrated, and purified by column chromatography (EtOAc/methanol system or methanol). On the other hand, the membrane dialysis for **5-G2** and **5-G3** was also carried out. The crude product was dissolved in methanol and dialyzed (regenerated cellulose membrane, Spectra/Por MWCO, 1000, Spectrum Laboratories Inc., The Netherlands) against methanol for 1 day. The retentate was evaporated, and the residue was dried in a vacuum to provide **5-G2** and **5-G3** in yields of 90 and 84%, respectively.

4.5.1. Compound 5-G1. Yield 95%; IR 2953, 2923, 2849, 1735, 1661, 1536, 1437, 1252, 1199, 1176, 1049 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.03–2.07 (m, 8H), 2.40–2.44 (m, 36H), 2.71–2.75 (m, 24H), 3.66 (s, 24H), 4.35 (t, *J*=7.0 Hz, 8H), 5.18 (s, 8H), 7.77 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=172.78, 171.89, 142.25, 124.13, 57.60, 51.50, 50.23, 49.38, 48.92, 47.80, 32.22, 27.92; FABMS: *m/z*=1590 [M^++H]; HRMS (FAB) calcd for $C_{70}H_{112}N_{18}O_{24}$: 1588.8097; found: 1589.8175 [M^++H]. PDI=1.02.

4.5.2. Compound 5-G2. Yield 90%; IR 2952, 2921, 2851, 1735, 1662, 1533, 1436, 1252, 1199, 1176, 1048 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=2.01 (m, 8H), 2.32–2.36 (m, 12H), 2.41 (t, *J*=6.6 Hz, 48H), 2.51–2.52 (m, 24H), 2.73 (t, *J*=6.7 Hz, 56H), 3.25–3.30 (m, 16H), 3.65 (s, 48H), 4.37 (t, *J*=6.7 Hz, 8H), 5.16 (s, 8H), 6.93 (br s, 8H), 7.79 (s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=173.42, 172.69, 172.58, 143.03, 124.41, 58.05, 53.34, 52.60, 52.02, 50.53, 50.34, 50.17, 50.04, 49.64, 48.38, 37.57, 36.86, 34.37, 34.20, 33.09, 31.81, 28.57; HRMS (MALDI) calcd for $C_{142}H_{240}N_{34}O_{48}$: 3189.7384; found: 3191.6426 [M^+], 3214.1877 [M^++Na].

4.5.3. Compound 5-G3. Yield 84%; IR 3302, 2952, 2827, 1736, 1661, 1649, 1540, 1437, 1257, 1198, 1177, 1045 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=2.01 (m, 8H), 2.34 (m, 36H), 2.40–2.41 (m, 96H), 2.57 (m, 48H), 2.73–2.73 (m, 120H), 3.26 (m, 48H), 3.65 (s, 96H), 4.37 (m, 8H), 5.16 (s, 8H), 6.92 (br s, 16H), 7.71 (s, 4H), 7.78 (br s, 8H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=173.40, 172.78, 172.68, 172.57, 143.03, 124.40, 58.07, 53.35, 52.87, 52.57, 52.02, 50.55, 50.35, 50.16, 50.03, 49.64, 49.28, 48.38, 37.57, 34.38, 34.21, 33.40, 33.09, 32.72, 28.61; MS (MALDI) *m/z* calcd for $C_{286}H_{496}N_{66}O_{96}$: 6391.5959; found: 6415.7686 [M^++Na].

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References and notes

1. Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188.
2. (a) Huisgen, R.; Szeimies, G.; Moebius, L. *Chem. Ber.* **1967**, *100*, 2494; (b) Huisgen, R. *1,3-Dipolar Cycloaddition Chemistry*; Wiley: New York, NY, 1984; (c) Huisgen, R. *Pure Appl. Chem.* **1989**, *61*, 613.
3. (a) Katritzky, A. R.; Zhang, Y.; Singh, S. K. *Heterocycles* **2003**, *60*, 1225; (b) Wang, Z.-X.; Qin, H.-L. *Chem. Commun.* **2003**, 2450.
4. (a) Palacios, F.; Ochoa de Retana, A. M.; Pagalday, J.; Sanchez, J. M. *Org. Prep. Proced. Int.* **1995**, *27*, 603; (b) Hlasta, D. J.; Ackerman, J. H. *J. Org. Chem.* **1994**, *59*, 6184; (c) Mock, W. L.; Irra, T. A.; Wepsiec, J. P.; Adhya, M. *J. Org. Chem.* **1989**, *54*, 5302; (d) Peng, W.; Zhu, S. *Synlett* **2003**, 187.
5. Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004.
6. Bock, V. D.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J. Org. Chem.* **2006**, 51.
7. (a) Grimsdale, A. C.; Müllen, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 5592; (b) Tomalia, D. A. *Prog. Polym. Sci.* **2005**, *30*, 294.
8. (a) Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1990**, *112*, 7638; (b) Hawker, C. J.; Fréchet, J. M. J. *J. Chem. Soc., Chem. Commun.* **1990**, 1010; (c) Grayson, S. M.; Fréchet, J. M. J. *Chem. Rev.* **2001**, *101*, 3819.
9. (a) Tomalia, D. A.; Baker, H.; Dewald, J.; Hall, M.; Kallos, G.; Martin, S.; Roeck, J.; Ryder, J.; Smith, P. *Polym. J.* **1985**, *17*, 117; (b) Tomalia, D. A.; Naylor, A. M.; Goddard, W. A., III. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 138.
10. Convergent synthesis of internally branched PAMAM dendrimers has been reported: Pittelkow, M.; Christensen, J. B. *Org. Lett.* **2005**, *7*, 1295.
11. (a) Majoros, I. J.; Myc, A.; Thomas, T.; Mehta, C. B.; Baker, J. R., Jr. *Biomacromolecules* **2006**, *7*, 572; (b) Gupta, U.; Agashe, H. B.; Asthana, A.; Jain, N. K. *Biomacromolecules* **2006**, *7*, 649; (c) Duncan, R.; Izzo, L. *Adv. Drug Delivery Rev.* **2005**, *57*, 2215; (d) Ambade, A. V.; Savariar, E. N.; Thayumanavan, S. *Mol. Pharm.* **2005**, *2*, 264; (e) Venditto, V. J.; Regino, C. A. S.; Brechbiel, M. W. *Mol. Pharm.* **2005**, *2*, 302; (f) McCarthy, T. D.; Karellas, P.; Henderson, S. A.; Giannis, M.; O'Keefe, D. F.; Heery, G.; Paull, J. R. A.; Matthews, B. R.; Holan, G. *Mol. Pharm.* **2005**, *2*, 312.
12. (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) Helms, B.; Mynar, J. L.; Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **2004**, *126*, 15020; (c) Malkoch, M.; Schleicher, K.; Drockenmuller, E.; Hawker, C. J.; Russell, T. P.; Wu, P.; Fokin, V. V. *Macromolecules* **2005**, *38*, 3663; (d) Joralemon, M. J.; O'Reilly, R. K.; Matson, J. B.; Nugent, A. K.; Hawker, C. J.; Wooley, K. L. *Macromolecules* **2005**, *38*, 5436; (e) Lee, J. W.; Kim, B. K. *Bull. Korean Chem. Soc.*

2005, *26*, 658; (f) Lee, J. W.; Kim, B. K.; Jin, S. H. *Bull. Korean Chem. Soc.* **2005**, *26*, 833; (g) Lee, J. W.; Kim, B. K.; Kim, J. H.; Shin, W. S.; Jin, S. H. *Bull. Korean Chem. Soc.* **2005**, *26*, 1790; (h) Rijkers, D. T. S.; van Esse, G. W.; Merkx, R.; Brouwer, A. J.; Jacobs, H. J. F.; Pieters, R. J.; Liskamp, R. M. J. *Chem. Commun.* **2005**, 4581; (i) Mynar, J. L.; Choi, T.-L.; Yoshida, M.; Kim, V.; Hawker, C. J.; Fréchet, J. M. J. *Chem. Commun.* **2005**, 5169; (j) Wu, P.; Malkoch, M.; Hunt, J. N.; Vestberg, R.; Kaltgrad, E.; Finn, M. G.; Fokin, V. V.; Sharpless, K. B.; Hawker, C. J. *Chem. Commun.* **2005**, 5775; (k) Joosten, J. A. F.; Tholen, N. T. H.; Maate, F. A. E.; Brouwer, A. J.; van Esse, G. W.; Rijkers, D. T. S.; Liskamp, R. M. J.; Pieters, R. J. *Eur. J. Org. Chem.* **2005**, 3182; (l) Lee, J. W.; Kim, B. K. *Synthesis* **2006**, 615; (m) Lee, J. W.; Kim, J. H.; Kim, B. K.; Shin, W. S.; Jin, S. H. *Tetrahedron* **2006**, *62*, 894.

13. (a) Lee, J. W.; Kim, B. K.; Kim, H. J.; Han, S. C.; Shin, W. S.; Jin, S. H. *Macromolecules* **2006**, *39*, 2418; (b) Lee, J. W.; Kim, J. H.; Kim, B. K. *Tetrahedron Lett.* **2006**, *47*, 2683; (c) Lee, J. W.; Kim, B. K.; Kim, J. H.; Shin, W. S.; Jin, S. H. *J. Org. Chem.* **2006**, *71*, 4988.
14. (a) Wabnitz, T. C.; Spencer, J. B. *Tetrahedron Lett.* **2002**, *43*, 3891; (b) Xu, L.-W.; Xia, C.-G. *Tetrahedron Lett.* **2004**, *45*, 4507; (c) Jenner, G. *Tetrahedron Lett.* **1995**, *36*, 233; (d) Azizi, N.; Saidi, M. R. *Tetrahedron* **2004**, *60*, 383; (e) Yang, L.; Xu, L.-W.; Xia, C.-G. *Tetrahedron Lett.* **2005**, *46*, 3279; (f) Chaudhuri, M. K.; Hussain, S.; Kantamb, M. L.; Neelima, B. *Tetrahedron Lett.* **2005**, *46*, 8329; (g) Loh, T. P.; Wie, L. L. *Synlett* **1998**, 975; (h) Varala, R.; Alam, M. M.; Adapa, S. R. *Synlett* **2003**, 720; (i) Bartoli, G.; Bosco, M.; Marcantoni, E.; Petrini, M.; Sambri, L.; Torregiani, E. *J. Org. Chem.* **2001**, *66*, 9052; (j) Srivastava, N.; Banik, B. K. *J. Org. Chem.* **2003**, *68*, 2109; (k) Matsubara, S.; Yashioka, M.; Utimoto, K. *Chem. Lett.* **1994**, 827.
15. It is known that the reaction between α,β-unsaturated esters and azides gives triazolines, which can be converted to other derivatives. See: (a) Finely, K. T. *The Chemistry of Heterocyclic Compounds*; Weissberger, A., Talor, E. C., Eds.; Wiley: New York NY, 1980; pp 1–63; (b) Anderson, G. T.; Henry, J. R.; Weinreb, S. M. *J. Org. Chem.* **1991**, *56*, 6946; (c) Yadav, J. S.; Reddy, B. V. S.; Geetha, V. *Synlett* **2002**, 513.
16. (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.
17. (a) Mong, T. K.-K.; Niu, A.; Chow, H.-F.; Wu, C.; Li, L.; Chen, R. *Chem.—Eur. J.* **2001**, *7*, 686; (b) Wong, C.-H.; Chow, H.-F.; Hui, S.-K.; Sze, K.-H. *Org. Lett.* **2006**, *8*, 1811; (c) Sun, H.; Kaifer, A. E. *Org. Lett.* **2005**, *7*, 3845.

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Friedel–Crafts acylation reaction using carboxylic acids as acylating agents

Masato Kawamura, Dong-Mei Cui[†] and Shigeru Shimada[*]

National Institute of Advanced Industrial Science and Technology (AIST), Tsukuba Central 5, Tsukuba, Ibaraki 305-8565, Japan

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Abstract—Dehydrative Friedel–Crafts acylation reaction of aromatic compounds with carboxylic acids as acylating agents was investigated in the presence of Lewis acid- or Brønsted acid-catalyst. Various metal triflates and bis(trifluoromethanesulfonyl)amides showed catalytic activity at high temperature, among which $Eu(NTf_2)_3$ proved to be the most effective and efficiently catalyzed the acylation reaction of alkyl- and alkoxybenzenes with aliphatic and aromatic carboxylic acids at 250 °C. $Bi(NTf_2)_3$ was more effective than $Eu(NTf_2)_3$ at lower temperature, but proved to be hydrolyzed in the presence of a small amount of water to give $HNTf_2$ and $[Bi_6O_4(OH)_4(H_2O)_6](NTf_2)_6$. The structure of the latter compound was confirmed by a single crystal X-ray analysis. Among five Brønsted acids, HOTf, $HNTf_2$, $HCTf_3$, TsOH, and Nafion® SAC-13, $HNTf_2$ has proved to be the most efficient catalyst and more effective than $Eu(NTf_2)_3$ for the acylation of *p*-xylene with heptanoic acid at 220 °C or lower temperature. $HNTf_2$ catalyzed the acylation of anisole with carboxylic acids in high yields in refluxing toluene with azeotropic removal of water.

1. Introduction

The Friedel–Crafts acylation reaction is a useful method for the preparation of aromatic ketones and is widely used not only in laboratory scale but also in large scale in industry.[1] The most common procedure uses acid chlorides, which are usually prepared from the corresponding carboxylic acids and thionyl chloride, as acylating agents and a stoichiometric or an excess amount of $AlCl_3$ as a reaction promoter. This procedure suffers from severe corrosion and waste problems (stoichiometric amounts of SO_2 and HCl are formed as by-products and $AlCl_3$ is hydrolyzed to form a large amount of waste). Therefore, there are strong demands for a cleaner alternative that meets recent requirement for environmentally benign chemical processes.

Several new methods have been explored to overcome these disadvantages. One important direction is to substitute the stoichiometric reaction promoter by efficient catalysts, and another is to replace acid chlorides by cleaner alternatives such as acid anhydrides and esters. Recently a number of reports have described catalytic Friedel–Crafts acylation reaction using acid anhydrides as acylating agents.[2] However, the use of acid anhydrides necessarily yields 1 equiv of carboxylic acids as by-products. Methyl esters, which form methanol as a by-product, could be employed in the presence of excess amount of trifluoromethanesulfonic acid.[3] Meldrum's acids are also used as acylating agents in Lewis acid-catalyzed acylations.[4] However, the most desirable acylating agents are probably carboxylic acids, which are common precursors of acid chlorides and anhydrides, because the reaction produces water as the only by-product. Recently there are some reports on catalytic Friedel–Crafts acylation reactions using carboxylic acids as acylating agents; zeolites,[5,6] heteropoly acids and their salts,[5,7] clay,[5,8] Lewis acids,[9] and graphite/TsOH[10] have been used as catalysts.

Our approach to the catalytic Friedel–Crafts acylation reaction using carboxylic acids as acylating agents was started by using simple Lewis acid- and Brønsted acid-catalysts, since the potential of these catalysts for this reaction was not well explored at the time we started. We have reported that some Lewis acids are effective for the intramolecular Friedel–Crafts acylation of carboxylic acids to form cyclic aromatic ketones.[11] In this paper, we describe the details on the intermolecular Friedel–Crafts acylation reaction catalyzed by Lewis acid- and Brønsted acid-catalysts.[12]

* Corresponding author. Tel.: +81 29 861 6257; fax: +81 29 861 4511; e-mail: s-shimada@aist.go.jp
† Present address: College of Pharmaceutical Sciences, Zhejiang University of Technology, Hangzhou 310014, PR China.

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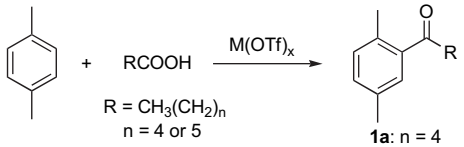
2. Results and discussion

2.1. Lewis acid-catalyzed Friedel–Crafts acylation reaction of *p*-xylene with hexanoic and heptanoic acids

The acylation of *p*-xylene with hexanoic and heptanoic acids was selected as a model reaction to examine catalytic performance of metal triflates, $M(OTf)_3$ and $M(OTf)_4$.[13] The results are summarized in Table 1. The reaction was carried out using a sealed glass tube with an excess of *p*-xylene (30–65 equiv to carboxylic acids) in an oil bath set at the temperature shown in tables. The reaction can take place at 180 °C with various Lewis acids, although the yields of desired ketone **1a** are low. At this temperature, $Sc(OTf)_3$ (Table 1, entry 1) afforded **1a** in the highest yield, 39%, among 14 metal triflates tested. $Bi(OTf)_3$, which has been utilized as a catalyst for Friedel–Crafts acylation using acid chlorides and anhydrides as acylating agents in recent years,[2d,14] also showed relatively good results under these conditions (Table 1, entry 32). As it can be seen from Table 1, considerable side reaction took place at 180 °C in many cases; for example, $Sc(OTf)_3$ afforded **1a** in 39% yield although the carboxylic acid was completely consumed (Table 1, entry 1). However, the reaction at higher temperature, 250 °C, unexpectedly proved to give the desired product in higher yields. In most cases, rare earth metal triflates gave ketone **1b** in moderate to high yields at 250 °C, among which $Yb(OTf)_3$ showed the highest performance (83% yield, Table 1, entry 24). Although $Hf(OTf)_4$ has high activity for the conversion of heptanoic acid, secondary reaction of ketone **1b** easily takes place under the reaction conditions to give uncharacterized side products and longer reaction time causes the disappearance of **1b** (Table 1, entries 28 and 29).

Table 1. Reaction of *p*-xylene with hexanoic and heptanoic acids[a]

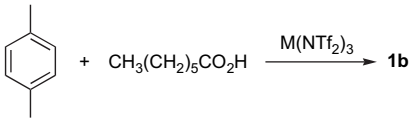


Entry	Catalyst (mol %)	*n*	Conditions	Conv. (%)[b]	Yield (%)[c]
1	$Sc(OTf)_3$ (20)	4	180 °C, 45 h	>99	39
2[d]	$Sc(OTf)_3$ (20)	5	250 °C, 12 h	>99	49
3	$Y(OTf)_3$ (20)	4	180 °C, 45 h	40	12
4	$Y(OTf)_3$ (15)	5	250 °C, 12 h	>99	65
5	$La(OTf)_3$ (15)	5	250 °C, 12 h	52	0
6	$Pr(OTf)_3$ (15)	5	250 °C, 12 h	66	23
7	$Nd(OTf)_3$ (20)	4	180 °C, 45 h	20	Trace
8	$Nd(OTf)_3$ (15)	5	250 °C, 12 h	72	29
9	$Sm(OTf)_3$ (20)	4	180 °C, 45 h	45	20
10	$Sm(OTf)_3$ (15)	5	250 °C, 12 h	97	64
11	$Eu(OTf)_3$ (20)	4	180 °C, 45 h	>99	29
12[d]	$Eu(OTf)_3$ (20)	5	250 °C, 12 h	83	52
13	$Gd(OTf)_3$ (15)	5	250 °C, 12 h	96	62
14	$Tb(OTf)_3$ (20)	4	180 °C, 45 h	21	1
15	$Dy(OTf)_3$ (20)	4	180 °C, 60 h	3	2
16[d]	$Dy(OTf)_3$ (15)	5	250 °C, 12 h	97	80
17	$Ho(OTf)_3$ (20)	4	180 °C, 45 h	30	3
18	$Ho(OTf)_3$ (15)	5	250 °C, 12 h	99	65
19	$Er(OTf)_3$ (20)	4	180 °C, 45 h	41	16
20	$Er(OTf)_3$ (15)	5	250 °C, 12 h	>99	66
21	$Tm(OTf)_3$ (20)	4	180 °C, 45 h	15	8
22	$Tm(OTf)_3$ (15)	5	250 °C, 12 h	>99	43
23	$Yb(OTf)_3$ (20)	4	180 °C, 45 h	76	14
24[d]	$Yb(OTf)_3$ (20)	5	250 °C, 12 h	>99	83
25	$Lu(OTf)_3$ (20)	4	180 °C, 45 h	51	28
26	$Lu(OTf)_3$ (15)	5	250 °C, 12 h	>99	63
27	$Hf(OTf)_4$ (20)	4	180 °C, 62 h	46	25
28[e]	$Hf(OTf)_4$ (20)	5	180 °C, 1.25 h	89	36
29[d]	$Hf(OTf)_4$ (20)	5	250 °C, 12 h	>99	0
30[d]	$Ga(OTf)_3$ (20)	5	250 °C, 12 h	94	22
31[d]	$In(OTf)_3$ (20)	5	250 °C, 12 h	>99	62
32	$Bi(OTf)_3$ (20)	4	180 °C, 45 h	75	33

[a] The ratio of *p*-xylene/carboxylic acid is 65/1 for the reaction of hexanoic acid and 50/1 for the reaction of heptanoic acid, unless otherwise noted.
[b] Conversion of carboxylic acids was determined by GC analysis using naphthalene (for hexanoic acid) or docosane (for heptanoic acid) as an internal standard.
[c] Yields are based on carboxylic acids and are determined by GC analysis using naphthalene (for hexanoic acid) or docosane (for heptanoic acid) as an internal standard.
[d] *p*-Xylene/carboxylic acid=65/1.
[e] *p*-Xylene/carboxylic acid=60/1.

Then we examined four bis(trifluoromethanesulfonyl)-amide salts, $Sc(NTf_2)_3$,[15] $Yb(NTf_2)_3$,[16] $Eu(NTf_2)_3$,[17] and $Bi(NTf_2)_3$,[18] which are stronger Lewis acids than the corresponding triflates. $Sc(NTf_2)_3$ afforded **1b** in higher yield than $Sc(OTf)_3$ (Table 2, entry 1) while $Yb(NTf_2)_3$ showed poorer results than $Yb(OTf)_3$ (Table 2, entry 2). Considering their strong Lewis acidity, $Yb(NTf_2)_3$ and $Sc(NTf_2)_3$ were expected to give more promising results. However, their strong Lewis acidity seemed to promote undesirable side reaction at the same time. The best result was obtained by using $Eu(NTf_2)_3$ to give **1b** in excellent yields (Table 2, entries 3 and 5). The yield of **1b** decreased when the amount of catalyst or *p*-xylene was reduced (Table 2, entries 6–8). Figure 1 shows the effect of temperature on the yield of **1b** in $Eu(NTf_2)_3$-catalyzed reaction. At 240 °C or higher, more than 80% of **1b** is formed after 12 h, while the yield drastically decreases at 230 °C or lower. On the other hand, $Bi(NTf_2)_3$, which is less selective than $Eu(NTf_2)_3$ at 250 °C (Table 2, entry 4), proved to be more effective than $Eu(NTf_2)_3$ at 220 °C (Table 2, entry 9). Only 1 mol % of

Table 2. Reaction of *p*-xylene with heptanoic acid[a]



Entry	$M(NTf_2)_3$ (mol %)	Temp (°C)	Time (h)	Conv. (%)[b]	Yield (%)[c]
1	$Sc(NTf_2)_3$ (15)	250	12	98	75
2	$Yb(NTf_2)_3$ (15)	250	10	>99	64
3	$Eu(NTf_2)_3$ (15)	250	12	>99	91
4	$Bi(NTf_2)_3$ (15)	250	8	>99	80
5[d]	$Eu(NTf_2)_3$ (20)	250	12	>99	96
6[e]	$Eu(NTf_2)_3$ (20)	250	12	87	75
7	$Eu(NTf_2)_3$ (10)	250	12	>99	73
8[d]	$Eu(NTf_2)_3$ (5)	260	18	51	15
9	$Bi(NTf_2)_3$ (20)	220	9	80	53
10[d]	$Bi(NTf_2)_3$ (1)	220	48	92	66

[a] The ratio of *p*-xylene/carboxylic acid is 50/1 unless otherwise noted.
[b] Conversion of the carboxylic acid was determined by GC analysis using docosane as an internal standard.
[c] Yields are based on the carboxylic acid and are determined by GC analysis using docosane as an internal standard.
[d] *p*-Xylene/carboxylic acid=65/1.
[e] *p*-Xylene/carboxylic acid=30/1.

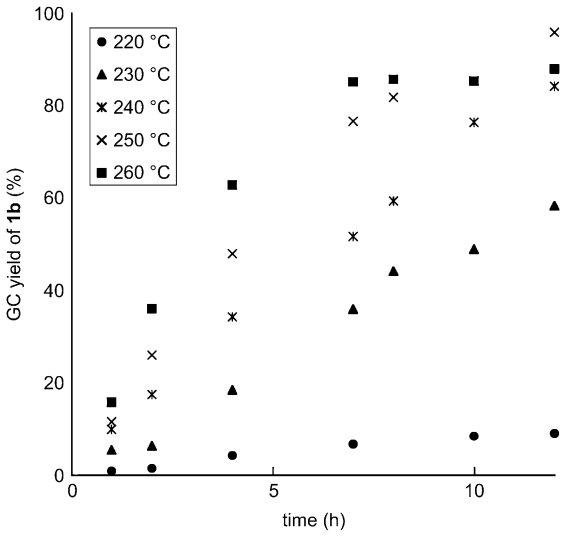
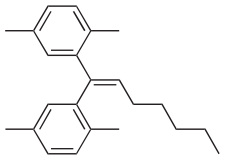


Figure 1. Temperature and time dependence of the yield of **1b** in the $Eu(NTf_2)_3$-catalyzed reaction of *p*-xylene with *n*-heptanoic acid.

$Bi(NTf_2)_3$ afforded **1b** in 66% yield after 48 h (Table 2, entry 10).

As mentioned above, considerable side reactions take place depending on the catalysts and reaction conditions. We tried to identify the structures of side products and succeeded to elucidate the structure of one of the major by-products, **2**. In the reaction of *p*-xylene with heptanoic acid using 20 mol % of $Yb(NTf_2)_3$ at 250 °C, **2** was isolated in 19% yield in addition to 51% of **1b**. The structure of **2** was confirmed by ^1H and ^{13}C NMR, IR, and HRMS spectroscopies. Compound **2** is probably derived from the dehydrative condensation of **1b** and *p*-xylene. Although other by-products were detected by TLC analysis, their structures could not be identified.

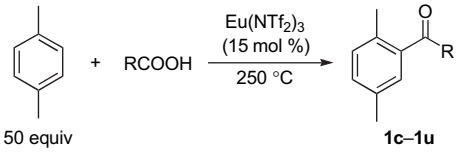


2

It is noteworthy that the acylation using aliphatic carboxylic acids is successful despite high reaction temperature because Friedel–Crafts acylation reaction of aliphatic acid chlorides with a catalytic amount of Lewis acids is often only successful for highly reactive aromatic compounds such as anisole.[19] At higher reaction temperature, side reactions of ketone products are suggested.[2d,e]

In order to clarify the scope and limitation of $Eu(NTf_2)_3$-catalyzed Friedel–Crafts acylation, reaction of *p*-xylene with various carboxylic acids (Table 3) as well as that of various aromatic compounds with aliphatic carboxylic acids (Table 4) was examined. In the reaction of *p*-xylene, straight chain carboxylic acids afforded ketones in good yields (Table 3, entries 5, 7, and 10–14) although the yields decreased to some extent in the cases of short chain carboxylic acids (Table 3, entries 1–3), whose boiling points are much lower than the reaction temperature and probably caused the decreased yields. The use of branched carboxylic acids, especially at the α-position, decreased the yields considerably (Table 3, entries 4, 6, 8, and 9), suggesting the high sensitivity of *p*-xylene to the steric hindrance around the carboxyl group. Acylation with aromatic carboxylic acids also successfully proceeded to give benzophenones (Table 3, entries 15–19).

Table 3. $Eu(NTf_2)_3$-catalyzed Friedel–Crafts acylation of *p*-xylene and anisole using various carboxylic acids

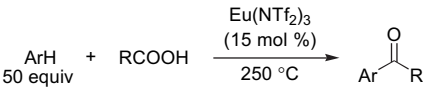


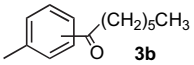
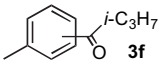
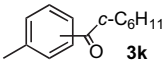
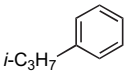
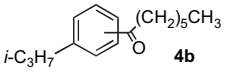
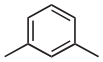
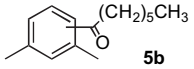
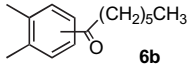
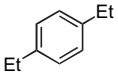
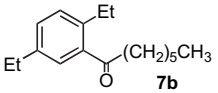
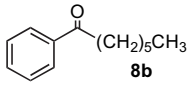
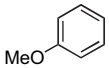
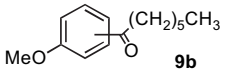
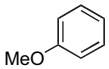
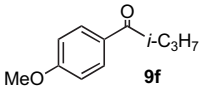
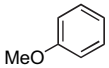
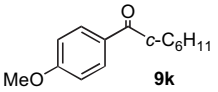
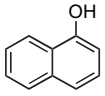
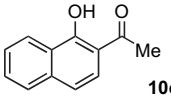
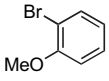
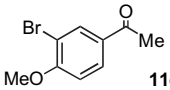
Entry	R	Time (h)	Conv. (%)[a]	Product	Yield (%)[b]
1	CH_3	8	94	**1c**	48
2	C_2H_5	8	>99	**1d**	56
3	*n*-C_3H_7	9	>99	**1e**	61
4	*i*-C_3H_7	16	91	**1f**	34
5	*n*-C_4H_9	9	98	**1g**	70
6	*i*-C_4H_9	11	>99	**1h**	55
7	*n*-C_5H_{11}	7	96	**1i**	65 (78)[c]
8	*i*-C_5H_{11}	10	>99	**1j**	61
9	*c*-C_6H_{11}	17	>99	**1k**	21
10	*n*-C_7H_{15}	12	>99	**1l**	80
11	*n*-C_8H_{17}	12	nd[d]	**1m**	86
12	*n*-C_9H_{19}	13	>99	**1n**	82
13	*n*-$C_{10}H_{21}$	13	>99	**1o**	76
14	*n*-$C_{11}H_{23}$	14	>99	**1p**	72
15	Ph	14	>99	**1q**	66
16	2-MeC_6H_4	14	>99	**1r**	59
17	4-MeC_6H_4	14	94	**1s**	76
18	2-FC_6H_4	13	>99	**1t**	76
19	4-FC_6H_4	16	60	**1u**	60

[a] Conversion of the carboxylic acid was determined by GC analysis using docosane as an internal standard.
[b] Isolated yield unless otherwise noted.
[c] The value in the parenthesis is GC yield.
[d] Not determined.

Acylation of toluene is less sensitive to the steric hindrance of carboxylic acids than that of *p*-xylene and afforded ketones in moderate to good yields with usual *p*-selectivity (Table 4, entries 1–3). Other alkylbenzenes such as cumene, *o*- and *m*-xylene, and *p*-diethylbenzene gave ketones in good yield (Table 4, entries 4–7), while benzene afforded **8b** only in 4% yield under the same reaction conditions (Table 4, entry 8). The acylation of anisole is more efficient than that of alkylbenzenes as expected and gave ketones in good yields with excellent *p*-selectivity (Table 4, entries 9–11). The reactions mentioned above were carried out by using large excess amount of aromatic compounds as reactants as well as solvents. Since chlorobenzene does not react with carboxylic acids under the present reaction conditions, it can be used as a solvent of this reaction. Acetylation of 1-naphthol was carried out using excess amount of acetic acid in chlorobenzene to give ketone **10c** in good yield (Table 4, entry 12). In the same way, 2-bromoanisole was acetylated to give **11c** as a single isomer although the yield was low (Table 4, entry 13). The reaction of 1-naphthol may proceed via naphthyl acetate (*O*-acylated product), which readily undergoes Fries rearrangement to form **10c**.[20]

Table 4. Reaction of various aromatic compounds with aliphatic carboxylic acids catalyzed by $Eu(NTf_2)_3$



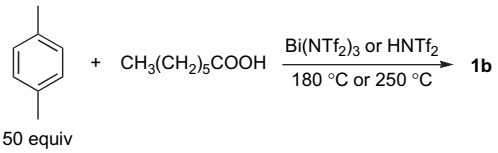
Entry	ArH	Product	Time (h)	Yield (%)[a]	Isomer ratio[b]
1		 **3b**	17	78	*o*-/*m*-/*p*-=22/5/73
2		 **3f**	24	58	(*o*-+*m*-)/*p*-=14/86
3		 **3k**	24	58	(*o*-+*m*-)/*p*-=12/88
4		 **4b**	19	71	(*o*-+*m*-)/*p*-=15/85
5		 **5b**	12	74	96/4[c,d]
6		 **6b**	12	85	88/12[e,f]
7[g]		 **7b**	12	74	
8		 **8b**	24	4	
9		 **9b**	6	87	*o*-/*p*-=<3/>97[f]
10		 **9f**	16	77	
11		 **9k**	16	80	
12[h]		 **10c**	18	83	
13[h]		 **11c**	15	11	

[a] Isolated yields.
[b] The ratio of regioisomers was determined by GC analysis unless otherwise noted.
[c] The ratio of regioisomers was determined by GC–MS analysis.
[d] 1-(2,4-Dimethylphenyl)-1-heptanone/other regioisomers.
[e] 1-(3,4-Dimethylphenyl)-1-heptanone/1-(2,3-dimethylphenyl)-1-heptanone.
[f] The ratio of regioisomers was determined by ^{1}H NMR.
[g] $Eu(NTf_2)_3$ (10 mol %) was used.
[h] Reaction was carried out in chlorobenzene using 4 equiv of AcOH.

2.2. Evaluation of catalytic activity of $Bi(NTf_2)_3$ and $HNTf_2$

We had interest in the exceptional activity of $Bi(NTf_2)_3$, only 1 mol % of which catalyzed the reaction of *p*-xylene with heptanoic acid to give **1b** in 66% yield, as mentioned above (Table 2, entry 10). Since it has been reported that $Bi(NTf_2)_3$ is hydrolyzed by water[18b] and the present reaction produces water as a by-product, it is possible that $HNTf_2$, which will be produced by the hydrolysis of $Bi(NTf_2)_3$, is working as a catalyst at least partially in $Bi(NTf_2)_3$-catalyzed reactions. Since complete hydrolysis of $Bi(NTf_2)_3$ produces 3 equiv of

Table 5. Reaction of various aromatic compounds with aliphatic carboxylic acids catalyzed by $Eu(NTf_2)_3$



Entry	Catalyst (mol %)	Temp (°C)	Time (h)	Conv. (%)[a]	Yield (%)[a]
1	$Bi(NTf_2)_3$ (1)	180	50	46	12
2	$Bi(NTf_2)_3$ (1)	220	50	85	65
3	$Bi(NTf_2)_3$ (20)	180	48	41	27
4	$Bi(NTf_2)_3$ (20)	220	9	80	53
5	$HNTf_2$ (3)	180	50	57	18
6	$HNTf_2$ (3)	220	28	97	84
7	$HNTf_2$ (60)	180	48	56	25
8	$HNTf_2$ (60)	220	9	97	78

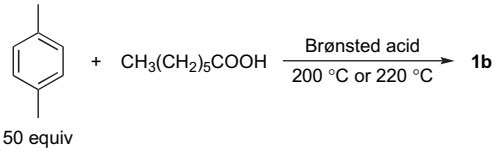
[a] The yields and the conversions were determined by GC analysis using docosane as an internal standard.

$HNTf_2$, catalytic activity of $Bi(NTf_2)_3$ was compared with that of 3 equiv of $HNTf_2$ (Table 5). At 180 °C, very similar results were obtained (Table 5, entries 1, 3, 5, and 7), while 3 equiv of $HNTf_2$ showed higher activity than $Bi(NTf_2)_3$ at 220 °C (Table 5, entries 2, 4, 6, and 8). Since we have confirmed partial hydrolysis of $Bi(NTf_2)_3$ (vide infra), the results in Table 5 probably suggest that $HNTf_2$ mainly catalyzes the reaction in $Bi(NTf_2)_3$-catalyzed dehydrative acylations, while $Bi(NTf_2)_3$ acts as a Lewis acid catalyst at the beginning stage of the reaction.

2.3. $HNTf_2$-catalyzed Friedel–Crafts acylation reaction using carboxylic acids as acylating agents

Based on the above results, we examined the catalytic activities of several Brønsted acids for the reaction of *p*-xylene with heptanoic acid (Table 6). Among five Brønsted acids tested, $HNTf_2$ showed the highest performance; 10 mol % of $HNTf_2$ at 200 or 220 °C afforded **1b** in high yields (Table 6, entries 2 and 3). HOTf is less efficient than $HNTf_2$ (Table 6, entry 5), while *p*-toluenesulfonic acid did not afford **1b** at all (Table 6, entry 4). The use of $HCTf_3$[21] and Nafion® SAC-13 afforded a complex mixture (Table 6, entries 6 and 7). In the latter case, the formation of *p*-xylene dimer (2,5,4′-trimethyldiphenylmethane) as a by-product was confirmed by GC–MS analysis of the reaction mixture.[22]

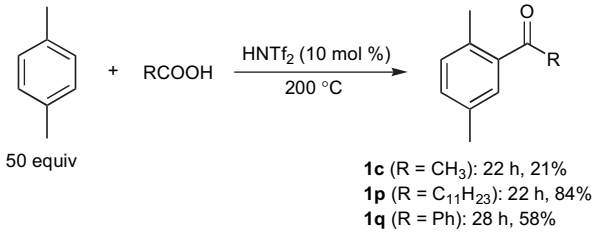
Table 6. Brønsted acid-catalyzed Friedel–Crafts acylation of *p*-xylene with heptanoic acid[a]



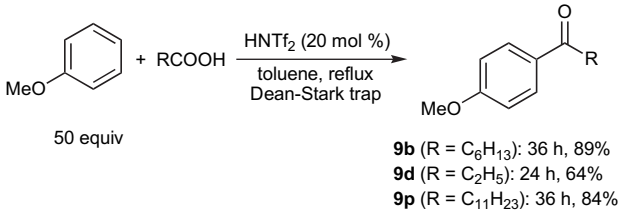
Entry	Brønsted acid (mol %)	Temp (°C)	Time (h)	Conv. (%)[a]	Yield (%)[a]
1	$HNTf_2$ (20)	220	15	>99	82
2	$HNTf_2$ (10)	220	16	98	89
3	$HNTf_2$ (10)	200	16	94	89
4	HOTs (10)	220	16	38[b]	0
5	HOTf (10)	220	24	98	70
6	$HCTf_3$ (10)	220	9	97	20
7	Nafion® SAC-13[c]	220	50	52	10

[a] Reactions were carried out in a sealed glass tube, and yields and conversions were determined by GC analysis using docosane as an internal standard unless otherwise noted.
[b] Determined by GC analysis using tetradecane as an internal standard.
[c] 20 wt %.

To evaluate the generality of $HNTf_2$-catalyzed reaction, acylation of *p*-xylene and anisole with several carboxylic acids was examined (Schemes 1 and 2). Acetylation of *p*-xylene afforded ketone **1c** in a low yield probably because the boiling point of acetic acid is much lower than the reaction temperature, while dodecanoic acid and benzoic acid gave ketones in moderate to good yields. The acylation of anisole can be conducted in refluxing toluene with azeotropic removal of water. By using 20 mol % of $HNTf_2$, acylation of anisole efficiently took place to give ketones in good yields. Acylation products of toluene were not observed at all under these conditions.



Scheme 1. $HNTf_2$-catalyzed acylation of *p*-xylene with carboxylic acids.



Scheme 2. $HNTf_2$-catalyzed acylation of anisole with carboxylic acids.

2.4. Structure of hydrolysis product of $Bi(NTf_2)_3$

Anhydrous $Bi(NTf_2)_3$ is highly moisture sensitive and fumes in air.[18b] It is reported that $Bi(NTf_2)_3$ is hydrolyzed in the presence of water,[18b] while no structural information is available on the bismuth-containing product by the hydrolysis. Therefore, we have tried the hydrolysis of $Bi(NTf_2)_3$ under various conditions and succeeded to isolate colorless single crystals of the hydrolysis product under the conditions similar to those of the catalytic acylation reaction, i.e., in *p*-xylene in the presence of n-$C_6H_{13}CO_2H$ or c-$C_6H_{11}CO_2H$ and a small amount of water.[23] The hydrolysis was attempted in the presence of 2.4, 3, and 6 equiv (to Bi) of water and gave crystals of the same hydrolysis product in all cases. The structure was identified by a single crystal X-ray analysis to be $[Bi_6O_4(OH)_4(H_2O)_6](NTf_2)_6$ **12** (Fig. 2). Similar hexanuclear $[Bi_6O_4(OH)_4]$ structures were reported for $[Bi_6O_4(OH)_4](NO_3)_6\cdot(H_2O)_n$[24] and $[Bi_6O_4(OH)_4](ClO_4)_6\cdot(H_2O)_n$.[25] Each oxygen atom of $[Bi_6O_4(OH)_4]$ units disordered in two positions with nearly equal occupancies (showed in red and yellow in Fig. 2). This disorder is understood to show the positions of oxide and hydroxide oxygen

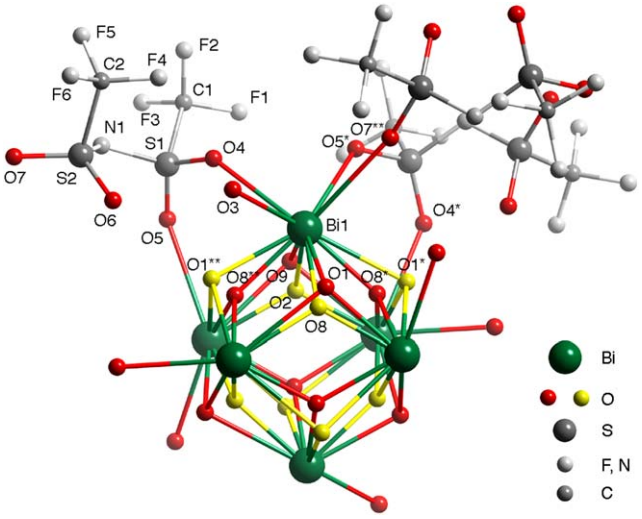


Figure 2. Structure of $[Bi_6O_4(OH)_4(H_2O)_6](NTf_2)_6$. Only NTf_2^- anions bound to the top bismuth atom are shown for clarity. Oxygen atoms in yellow are one set of disordered oxygen atoms (see text).

atoms judging from Bi–O distances, which suggest O2 and O8 (Bi–O, 2.107(12)–2.204(13) Å) are oxide oxygens and O1 and O9 (Bi–O, 2.297(14)–2.557(16) Å) are hydroxide oxygens.[24,25] Each bismuth atom is coordinated by one water molecule (disordered in two positions; only one of the disordered water oxygen (O3) is shown in Fig. 2) and three oxygen atoms of NTf_2^- anions. Bi–O distances for water molecule is 2.59(2) and 2.65(3) Å and those for NTf_2^- anions ranges from 2.693(6) to 2.909(8) Å. The bismuth atoms, therefore, eight coordinate and their geometric arrangement can be described as a distorted square antiprism. Among four oxygen atoms of each NTf_2^- anion, three are used for the coordination to bismuth atoms and one is used for the hydrogen bonding. As shown in Figure 3, each $[Bi_6O_4(OH)_4(H_2O)_6]$ unit is coordinated by 12 NTf_2^- anions, every two of which are shared between two $[Bi_6O_4(OH)_4(H_2O)_6]$ units. Therefore, each $[Bi_6O_4(OH)_4(H_2O)_6]$ unit is connected to six other $[Bi_6O_4(OH)_4(H_2O)_6]$ units to form a 3D-network structure.

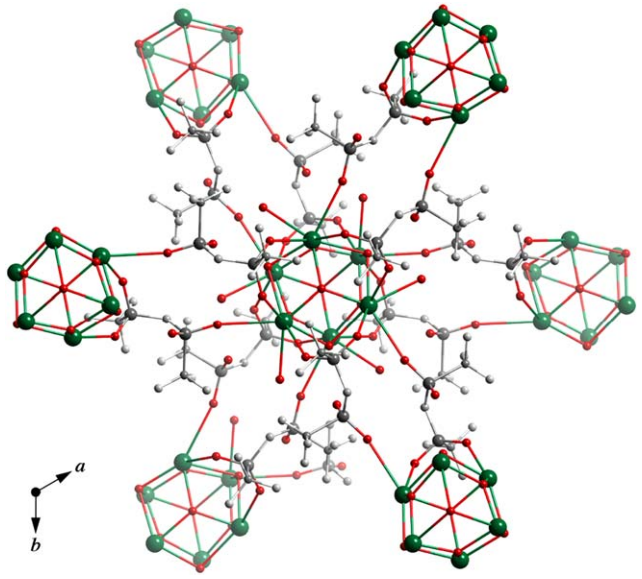


Figure 3. A view showing seven $[Bi_6O_4(OH)_4]$ units.

In order to evaluate the catalytic activity of **12**, Friedel–Crafts acylation reaction of *p*-xylene with hexanoic acid was carried out in the presence of **12** (Bi/hexanoic acid/*p*-xylene=0.2/1/65; 180 °C, 45 h). The yield of ketone (2%; 5% carboxylic acid conversion) was much lower than that (27%) obtained in the reaction carried out under the similar reaction conditions using $Bi(NTf_2)_3$ (Table 5, entry 3). This result supports our assumption that the main catalytically active species is $HNTf_2$ in the $Bi(NTf_2)_3$-catalyzed dehydrative acylations.

3. Conclusions

Dehydrative Friedel–Crafts acylation reaction of aromatic compounds with carboxylic acids as acylating agents can be catalyzed by simple Lewis acid- and Brønsted acid-catalysts. Lewis acid-catalyzed reaction of *p*-xylene with aliphatic carboxylic acids can take place at 180 °C with various metal triflates and bis(trifluoromethanesulfonyl)-amides, while higher reaction temperature generally affords desired ketones with higher selectivities. $Eu(NTf_2)_3$ shows the highest performance at 250 °C and efficiently catalyzes the acylation reaction of alkyl- and alkoxybenzenes with aliphatic and aromatic carboxylic acids. Brønsted acid-catalyst $HNTf_2$ has proved to be more efficient than $Eu(NTf_2)_3$ for the acylation of *p*-xylene with carboxylic acids at 200 °C. $HNTf_2$ catalyzes the acylation of anisole with carboxylic acids in high yields in refluxing toluene with azeotropic removal of water. These catalytic systems do not require any additives and can be applied to a wide range of carboxylic acids and aromatic compounds. Therefore, the present catalytic systems are superior to the reported counterparts in terms of simplicity and generality. These results suggest that Lewis acid- and Brønsted acid-catalysts have a great potential as catalysts for dehydrative Friedel–Crafts acylation using carboxylic acids as acylating agents.

4. Experimental

4.1. General

Reagents were purchased from Tokyo Kasei Kogyo, Junsei Chemical, Kanto Chemical, Aldrich, and Wako Pure Chemical Industries and used as received unless otherwise noted. Anisole, *m*-xylene, and cumene were distilled from CaH_2 prior to use. Preparative TLC was performed on Wakogel 60N (Wako Pure Chemical Industries). ^1H and ^{13}C NMR were recorded on a JEOL JMN-LA500 (499 MHz for ^1H, 125 MHz for ^{13}C) using $CDCl_3$ as a solvent and tetramethylsilane as an internal standard. IR spectra were measured using a JASCO FT/IR-610. GC analyses were performed on a Shimadzu GC-18A using an Ultra Alloy® FFAP capillary column (30 M×0.25 mm, Frontier Laboratories) or TC-FFAP capillary column (30 M×0.25 mm, GL Sciences Inc.). Low- and high-resolution GC–MS (EI) were measured on a Shimadzu QP-5000 spectrometer with a Shimadzu GC-17A and a DB-1 (25 M×0.32 mm, J&W Scientific), and JEOL JMS-GC MATE (BU20) spectrometer with a Hewlett

Packard HP6890 GC system and a NEUTRA BOND-1 capillary column (30 M×0.25 mm, GL Science).

4.2. A typical procedure for Friedel–Crafts acylation

A mixture of $Eu(NTf_2)_3$ (87.8 mg, 0.0885 mmol), octanoic acid (85.1 mg, 0.590 mmol), docosane (22.3 mg, an internal standard for GC analysis), and *p*-xylene (3.62 mL, 29.5 mmol) was stirred at 250 °C for 12 h with periodical monitoring of octanoic acid conversion by GC. After cooling to room temperature, water (3 mL) was added to the mixture and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (3×10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (hexane/EtOAc=27/1) to give 1-(2,5-dimethylphenyl)-1-octanone **1l** as a pale yellow oil (109 mg, 80% yield).

Characterization data for the new compounds are shown below. All new compounds except for the by-product **2** were determined to be >95% pure by ^{1}H NMR spectroscopy. ^{1}H NMR spectrum of compound **2** showed some small unidentified signals in the aliphatic region.

4.2.1. 1-(2,5-Dimethylphenyl)-3-methyl-1-butanone (1h). The title compound was obtained by the reaction of isovaleric acid (51.1 mg, 0.500 mmol) and *p*-xylene (3.06 mL, 25.0 mmol) as described in the typical procedure in 55% yield (52.4 mg) as a pale yellow oil after the purification by preparative TLC (hexane/EtOAc=28/1). ^{1}H NMR δ 0.98 (d, 6H, J=6.8 Hz), 2.25 (nonet, 1H, J=6.8 Hz), 2.35 (s, 3H), 2.43 (s, 3H), 2.75 (d, 2H, J=6.8 Hz), 7.09–7.38 (m, 3H); ^{13}C NMR δ 20.51, 20.87, 22.65, 25.07, 50.65, 128.72, 131.58, 131.68, 134.37, 134.99, 138.68, 204.87; IR (neat) ν 1686 cm^{-1}; HRMS calcd for $C_{19}H_{30}O$ [M$^+$] 190.1358, found 190.1366.

4.2.2. 1-(2,5-Dimethylphenyl)-1-undecanone (1o). The title compound was obtained by the reaction of undecanoic acid (81.5 mg, 0.437 mmol) and *p*-xylene (2.68 mL, 21.9 mmol) as described in the typical procedure in 76% yield (90.9 mg) as a colorless oil after the purification by preparative TLC (hexane/EtOAc=30/1). ^{1}H NMR δ 0.88 (t, 3H, J=7.5 Hz), 1.39–1.20 (m, 14H), 1.68 (quintet, 2H, J=7.5 Hz), 2.35 (s, 3H), 2.43 (s, 3H), 2.86 (t, 2H, J=7.5 Hz), 7.08–7.41 (m, 3H); ^{13}C NMR δ 14.08, 20.61, 20.90, 22.65, 24.39, 29.29, 29.32, 29.45, 29.48, 29.55, 31.87, 41.67, 128.73, 131.61, 131.69, 134.46, 135.02, 138.40, 205.17; IR (neat) ν 1684 cm^{-1}; HRMS calcd for $C_{19}H_{30}O$ [M$^+$] 274.2297, found 274.2298.

4.2.3. 1,1-Bis(2,5-dimethylphenyl)-1-heptene (2). A mixture of $Yb(NTf_2)_3$ (101 mg, 0.100 mmol), heptanoic acid (65.1 mg, 0.500 mmol), and *p*-xylene (3.06 mL, 25.0 mmol) was stirred at 250 °C for 12 h. After cooling to room temperature, water (3 mL) was added to the mixture and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (3×5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (hexane/EtOAc=30/1) to give **1b** (56.2 mg, 51% yield) and **2** (30.5 mg, 19% yield). Characterization data for **2**: ^{1}H NMR δ 0.85 (t, 3H, J=7.5 Hz), 1.21–1.30 (m, 4H), 1.41 (quintet, 2H, J=7.0 Hz), 2.00 (q, 2H, J=7.5 Hz), 2.10 (s, 3H), 2.24 (s, 6H), 2.29 (s, 3H), 5.70 (t, 1H, J=7.5 Hz), 6.85–6.94 (m, 3H), 6.97 (dd, 1H, J=7.5, 1.5 Hz), 7.03 (d, 1H, J=7.5 Hz), 7.05 (d, 1H, J=7.5 Hz); ^{13}C NMR δ 14.04, 19.58, 20.49, 20.96, 20.99, 22.49, 29.26, 29.60, 31.53, 127.17, 127.46, 129.92, 130.32, 130.60, 130.97, 132.26, 133.08, 133.79, 134.40, 134.65, 140.11, 140.16, 142.77; IR (neat) ν 2952, 2925, 2862, 1496, 1454, 808 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{26}O$ [M$^+$] 306.2348, found 306.2351.

4.2.4. 1-(4-Isopropylphenyl)-1-heptanone and its isomers (4b). The title compounds were obtained as a mixture of isomers (*p*-isomer:(*o*-+*m*-isomers)=85/15) by the reaction of heptanoic acid (50.8 mg, 0.390 mmol) and cumene (2.71 mL, 19.5 mmol) as described in the typical procedure in 71% yield (64.7 mg) as a pale yellow oil after the purification by preparative TLC (hexane/EtOAc=22/1). The minor isomers were only characterized by GC–MS that showed M$^+$ ion peaks and the similar fragment patterns as that of the major isomer. ^{1}H NMR (for *p*-isomer) δ 0.89 (t, 3H, J=7.2 Hz), 1.27 (d, 6H, J=7.0 Hz), 1.25–1.42 (m, 6H), 1.72 (quintet, 2H, J=7.5 Hz), 2.94 (t, 2H, J=7.5 Hz), 2.96 (septet, 1H, J=7.0 Hz), 7.31 (d, 2H, J=8.4 Hz), 7.90 (d, 2H, J=8.4 Hz); ^{13}C NMR (for *p*-isomer) δ 14.02, 22.52, 23.66, 24.45, 29.07, 31.66, 34.20, 38.52, 126.59, 128.29, 134.98, 154.27, 200.25; IR (neat) ν 1684 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{24}O$ [M$^+$] 232.1827, found 232.1820.

4.2.5. 1-(2,4-Dimethylphenyl)-1-heptanone (5b). The title compound was obtained by the reaction of heptanoic acid (75.7 mg, 0.582 mmol) and *m*-xylene (3.56 mL, 29.1 mmol) as described in the typical procedure in 74% yield (94.6 mg) as a colorless oil after the purification by preparative TLC (hexane/EtOAc=27/1). GC–MS analysis of the product showed the presence of a small amount of isomer (ca. 4% by the TIC integration). ^{1}H NMR δ 0.88 (t, 3H, J=7.0 Hz), 1.23–1.40 (m, 6H), 1.68 (quintet, 2H, J=7.5 Hz), 2.34 (s, 3H), 2.47 (s, 3H), 2.86 (t, 2H, J=7.5 Hz), 7.02–7.06 (m, 2H), 7.56 (d, 1H, J=8.5 Hz); ^{13}C NMR δ 13.97, 21.24, 21.35, 22.49, 24.52, 29.00, 31.63, 41.32, 126.16, 128.81, 132.73, 135.27, 138.31, 141.46, 204.13; IR (neat) ν 1684 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{22}O$ [M$^+$] 218.1671, found 218.1664.

4.2.6. 1-(3,4-Dimethylphenyl)-1-heptanone and 1-(2,3-dimethylphenyl)-1-heptanone (6b). The title compounds were obtained as a mixture (1-(3,4-dimethylphenyl)-1-heptanone/1-(2,3-dimethylphenyl)-1-heptanone=88/12) by the reaction of heptanoic acid (73.0 mg, 0.561 mmol) and *o*-xylene (3.42 mL, 28.0 mmol) as described in the typical procedure in 85% yield (104 mg) as a colorless oil after the purification by preparative TLC (hexane/EtOAc=20/1). ^{1}H NMR δ 0.86–0.92 (m, 3H), 1.27–1.42 (m, 6H), 1.66–1.75 (m, 2H), 2.27–2.34 (m, 6H), 2.83 (t, 0.24H, J=7.5 Hz, for the minor isomer), 2.92 (t, 1.76H, J=7.5 Hz, for the major isomer), 7.13 (t, 0.12H, J=7.5 Hz, for the minor isomer), 7.17–7.24 (m, 1H), 7.28 (d, 0.12H, J=7.5 Hz, for the minor isomer), 7.69 (dd, 0.88H, J=8.0, 2.0 Hz, for the major isomer), 7.73 (d, 0.88H, J=2.0 Hz, for the major isomer); ^{13}C NMR (for the major isomer) δ 14.39, 20.12, 20.32, 22.89,

24.90, 29.44, 32.04, 38.89, 126.17, 129.56, 130.10, 135.45, 137.18, 142.62, 200.93; IR (neat) ν 1681 cm^{-1}; HRMS calcd for $C_{15}H_{22}O$ [M^+] 218.1671, found 218.1664.

4.2.7. 1-(2,5-Diethylphenyl)-1-heptanone (7b). The title compound was obtained by the reaction of heptanoic acid (82.6 mg, 0.635 mmol) and *p*-diethylbenzene (4.94 mL, 31.8 mmol) as described in the typical procedure in 74% yield (115 mg) as a colorless oil after the purification by preparative TLC (hexane/EtOAc=20/1). ^1H NMR δ 0.89 (t, 3H, J=7.0 Hz), 1.20 (t, 3H, J=7.5 Hz), 1.24 (t, 3H, J=7.5 Hz), 1.28–1.42 (m, 6H), 1.70 (quintet, 2H, J=7.5 Hz), 2.65 (q, 2H, J=7.5 Hz), 2.76 (q, 2H, J=7.5 Hz), 2.87 (t, 2H, J=7.5 Hz), 7.18 (d, 1H, J=8.0 Hz), 7.22 (dd, 1H, J=2.0, 8.0 Hz), 7.33 (d, 1H, J=2.0 Hz); ^{13}C NMR δ 14.01, 15.51, 16.11, 22.51, 24.31, 26.43, 28.34, 28.97, 31.65, 42.19, 127.18, 130.16, 130.36, 138.85, 140.61, 141.40, 205.86; IR (neat) ν 1691 cm^{-1}; HRMS calcd for $C_{17}H_{26}O$ [M^+] 246.1984, found 246.1989.

4.3. A typical procedure for $HNTf_2$-catalyzed Friedel–Crafts acylation with azeotropic removal of H_2O

A mixture of $HNTf_2$ (141 mg, 0.500 mmol), heptanoic acid (325 mg, 2.50 mmol), anisole (13.5 g, 125 mmol), and toluene (30 mL) was refluxed for 36 h in 100 mL flask equipped with Dean–Stark apparatus. After cooling to room temperature, water was added to the mixture and the organic layer was separated. The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by preparative TLC (hexane/EtOAc=24/1) to give 1-(4-methoxyphenyl)-1-heptanone **9b** as a white solid (488 mg, 89% yield). Mp: 38–39 °C (lit.[26] mp 39–40 °C).

4.4. Hydrolysis of $Bi(NTf_2)_3$

4.4.1. Hydrolysis of $Bi(NTf_2)_3$ in *p*-xylene. $Bi(NTf_2)_3$ (105 mg, 0.10 mmol), *p*-xylene (4 mL), and carboxylic acid (heptanoic acid, 72 μL, 66 mg, 0.51 mmol or cyclohexanecarboxylic acid, 64 mg, 0.50 mmol) were mixed in a glass tube. Under these conditions, some $Bi(NTf_2)_3$ remained undissolved (the amount of $Bi(NTf_2)_3$ was too much for complete dissolution). Then 4.7, 5.4, or 10.4 μL of water was added. In some cases, the mixture was heated to reflux for a few minutes, while in other case the mixture was kept at room temperature. In all cases, colorless crystals of $[Bi_6O_4(OH)_4(H_2O)_6](NTf_2)_6$ were formed within a few days.

4.4.2. X-ray crystallography. Crystals were covered by inert oil (Paratone 8236, Exxon) and mounted on a glass fiber under cold nitrogen flow. Data were collected on a Bruker Smart Apex CCD area detector diffractometer. Crystal data, data collection, and refinement parameters for $[Bi_6O_4(OH)_4(H_2O)_6](NTf_2)_6$ are given in Table 7. Hydrogen atoms could not be located. The number of hydrogen in $[Bi_6O_4(OH)_4]$ was assumed to keep the charge balance as well as from the similar structures reported.[23,24] O3 atom was judged to be an oxygen atom of a water molecule from its position as well as the Bi–O distance. Disorder was observed for O1 (O8), O2 (O9), O3, S2, F4–F6, O6, O7, and C2 atoms (the atomic numberings refer to those in Fig. 2).

Table 7. Crystallographic data for $[Bi_6O_4(OH)_4(H_2O)_6](NTf_2)_6$

Formula	$C_{12}H_{16}Bi_6F_{36}N_6O_{38}S_{12}$
Formula weight	3174.82
Crystal size (mm)	0.14×0.13×0.11
Crystal system	Trigonal
Space group	*R*-3 (no. 148)
a (Å)	19.1789(8)
b (Å)	19.1789(8)
c (Å)	15.8377(13)
α (°)	90
β (°)	90
γ (°)	120
V (Å)	5045.1(5)
Z	3
D_{calc} (g cm^{-3})	3.135
F(000)	4344
μ(Mo Kα) (cm^{-1})	16.18
T (K)	153(2)
No. of rflns measd	7602
No. of unique rflns (R_{int})	2473
No. of variables	202
*R*1 ($I_0>2\sigma(I_0)$)	0.0319
*wR*2 (all data)	0.0859
GOF	1.05
Diff peak, hole (e$Å^{-3}$)	1.80, −1.64

5. Crystallographic data

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 608158. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

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References and notes

1. Olah, G. A. *Friedel–Crafts and Related Reactions*; Wiley-Interscience: New York, NY, 1964; Vol. III, part 1.
2. For recent examples, see: (a) Kawada, A.; Mitamura, S.; Matsuo, J.; Tsuchiya, T.; Kobayashi, S. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 2325–2333; (b) Singh, R. P.; Kamble, R. M.; Chandra, K. L.; Saravanan, P.; Singh, V. K. *Tetrahedron* **2001**, *57*, 241–247; (c) Duris, F.; Barbier-Baudry, D.; Dormond, A.; Desmurs, J. R.; Bernard, J. M. *J. Mol. Catal. A: Chem.* **2002**, *188*, 97–104; (d) Le Roux, C.; Dubac, J. *Synlett* **2002**, 181–200; (e) Prakash, G. K. S.; Yan, P.; Torok, B.; Bucsi, I.; Tanaka, M.; Olah, G. A. *Catal. Lett.* **2003**, *85*, 1–6; (f) Sheemol, V. N.; Tyagi, B.; Jasra, R. V. *J. Mol. Catal. A: Chem.* **2004**, *215*, 201–208; (g) Hardacre, C.; Katdare, S. P.; Milroy, D.; Nancarrow, P.; Rooney, D. W.; Thompson, J. M. *J. Catal.* **2004**, *227*, 44–52; (h) Nakamura, H.; Arata, K. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1893–1896; (i) Matsushita, Y.; Sugamoto, K.; Matsui, T. *Tetrahedron Lett.* **2004**, *45*, 4723–4727; (j) Earle, M. J.; Hakala, U.; Hardacre, C.; Karkkainen, J.; McAuley, B. J.; Rooney, D. W.; Seddon, K. R.; Thompson, J. M.; Wähälä, K. *Chem. Commun.* **2005**,

903–905; (k) Hao, X.; Yoshida, A.; Nishikido, J. *Tetrahedron Lett.* **2005**, *46*, 2697–2700; (l) Arai, S.; Sudo, Y.; Nishida, A. *Tetrahedron* **2005**, *61*, 4639–4642; (m) Xiao, Y.; Malhotra, S. V. *J. Organomet. Chem.* **2005**, *690*, 3609–3613; (n) Zane, F.; Melada, S.; Signoretto, M.; Pinna, F. *Appl. Catal., A* **2006**, *299*, 137–144.

3. Hwang, J. P.; Prakash, G. K. S.; Olah, G. A. *Tetrahedron* **2000**, *56*, 7199–7203.
4. (a) Fillion, E.; Fishlock, D.; Wilsily, A.; Goll, J. M. *J. Org. Chem.* **2005**, *70*, 1316–1327; (b) Fillion, E.; Fishlock, D. *J. Am. Chem. Soc*. **2005**, *127*, 13144–13145; (c) Fillion, E.; Dumas, A. M.; Kuropatwa, B. A.; Malhotra, N. R.; Sitler, T. C. *J. Org. Chem.* **2006**, *71*, 409–412.
5. For a review on solid catalysts in Friedel–Crafts acylation reactions, see: (a) Sartori, G.; Maggi, R. *Chem. Rev.* **2006**, *106*, 1077–1104.
6. (a) Chiche, B.; Finiels, A.; Gauthier, C.; Geneste, P. *J. Org. Chem.* **1986**, *51*, 2128–2130; (b) Gauthier, C.; Chiche, B.; Finiels, A.; Geneste, P. *J. Mol. Catal.* **1989**, *50*, 219–229; (c) Wang, Q. L.; Ma, Y.; Ji, X.; Yan, H.; Qiu, Q. *J. Chem. Soc., Chem. Commun.* **1995**, 2307–2308; (d) Singh, A. P.; Pandey, A. K. *J. Mol. Catal. A: Chem.* **1997**, *123*, 141–147; (e) Pandey, A. K.; Singh, A. P. *Catal. Lett.* **1997**, *44*, 129–133; (f) De Castro, C.; Primo, J.; Corma, A. *J. Mol. Catal. A: Chem.* **1998**, *134*, 215–222.
7. (a) Izumi, Y.; Ogawa, M.; Nohara, W.; Urabe, K. *Chem. Lett.* **1992**, 1987–1990; (b) Kaur, J.; Kozhevnikov, I. V. *Chem. Commun.* **2002**, 2508–2509; (c) Firouzabadi, H.; Iranpoor, N.; Nowrouzi, F. *Tetrahedron* **2004**, *60*, 10843–10850.
8. Chiche, B.; Finiels, A.; Gautheir, C.; Geneste, P. *J. Mol. Catal.* **1987**, *42*, 229–235.
9. (a) Suzuki, K.; Kitagawa, H.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3729–3734; (b) Kobayashi, S.; Moriwaki, M.; Hachiya, I. *Tetrahedron Lett.* **1996**, *37*, 4183–4186; (c) Walker, M. U.S. Patent 5,362,375, 2002; *Chem. Abstr.* **2002**, *136*, 262987; (d) Earle, M. J.; Hakala, U.; McAuley, B. J.; Nieuwenhuyzen, M.; Ramani, A.; Seddon, K. R. *Chem. Commun.* **2004**, 1368–1369.
10. Sarvari, M. H.; Sharghi, H. *Helv. Chim. Acta* **2005**, *88*, 2282–2287.
11. (a) Cui, D.-M.; Kawamura, M.; Shimada, S.; Hayashi, T.; Tanaka, M. *Tetrahedron Lett.* **2003**, *44*, 4007–4010; (b) Cui, D. M.; Zhang, C.; Kawamura, M.; Shimada, S. *Tetrahedron Lett.* **2004**, *45*, 1741–1745.
12. Preliminary results have been published. Kawamura, M.; Cui, D.-M.; Hayashi, T.; Shimada, S. *Tetrahedron Lett.* **2003**, *44*, 7175–7177.
13. For reviews on metal triflates in organic synthesis, see: (a) Steel, P. G. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2727–2751; (b) Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. W. *Chem. Rev.* **2002**, *102*, 2227–2302; (c) Gaspard, H.; Le Roux, C. *Eur. J. Org. Chem.* **2004**, 2517–2532.
14. (a) Desmurs, J. R.; Lsbrouillere, M.; Le Roux, C.; Gaspard, H.; Laporterie, A.; Dubac, J. *Tetrahedron Lett.* **1997**, *38*, 8871–8874; (b) Gmouth, S.; Yang, H.; Vaultier, M. *Org. Lett.* **2003**, *5*, 2219–2222.
15. Ishihara, K.; Kubota, M.; Yamamoto, H. *Synlett* **1996**, 265–266.
16. (a) Mikami, K.; Kotera, O.; Motoyama, Y.; Tanaka, M. *Inorg. Chem. Commun.* **1998**, *1*, 10–11; (b) Nie, J.; Xu, J.; Zhou, G. *J. Chem. Res., Synop.* **1999**, 446–447.
17. Bhatt, A. I.; May, I.; Volkovich, V. A.; Collison, D.; Helliwell, M.; Polovov, I. B.; Lewin, R. G. *Inorg. Chem.* **2005**, *44*, 4934–4940.
18. (a) Ishihara, K.; Hiraiwa, Y.; Yamamoto, H. *Synlett* **2000**, 80–82; (b) Picot, A.; Repicheta, S.; Le Roux, C.; Dubac, J.; Rouques, N. *J. Fluorine Chem.* **2002**, *116*, 129–134.
19. For successful examples for less reactive aromatic compounds, see: (a) Kobayashi, S.; Iwamoto, S. *Tetrahedron Lett.* **1998**, *39*, 4697–4700; (b) See Ref. 8.
20. The similar direct C-acylation of 1-naphthol was reported by Kobayshi and co-workers. They found that a catalytic amount of acetic acid accelerated $Sc(OTf)_3$-catalyzed Fries rearrangement of aryl acetate, and that 1-naphthol underwent direct C-acylation in the presence of $Sc(OTf)_3$ or $Hf(OTf)_4$, see Ref. 9b.
21. Waller, F. J.; Barret, A. G. M.; Braddock, D. C.; Ramprasad, D.; McKinnell, R. M.; White, A. J. P.; Williams, D. J.; Ducray, R. *J. Org. Chem.* **1999**, *64*, 2910–2913.
22. Zeolite-catalyzed dehydrative Friedel–Crafts acylation reaction also gives the *p*-xylene dimer as a by-product, see Ref. 6a.
23. We have found that this crystallization procedure was useful for the preparation of single crystals of $[Eu(NTf_2)_3(H_2O)_3]$ and $[Yb(NTf_2)_3(H_2O)_5]$. Kawamura, M.; Shimada, S., submitted for publication.
24. (a) Lazarini, F. *Cryst. Struct. Commun.* **1979**, *8*, 69–74; (b) Sundvall, B. *Acta Chem. Scand. A* **1979**, *33*, 219–224; (c) Lazarini, F. *Acta Crystallogr., Sect. B* **1979**, *35*, 448–450.
25. (a) Sundvall, B. *Acta Chem. Scand. A* **1980**, *34*, 93–98; (b) Sundvall, B. *Inorg. Chem.* **1983**, *22*, 1906–1912.
26. Pianka, M.; Edwards, J. D. *J. Chem. Soc. C* **1967**, 2281–2290.

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Diastereoselective alkylation of iminomethylenephosphinates possessing an asymmetric center at the phosphorus atom

Takehiro Yamagishi, Terumitsu Haruki and Tsutomu Yokomatsu*

School of Pharmacy, Tokyo University of Pharmacy and Life Sciences, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan

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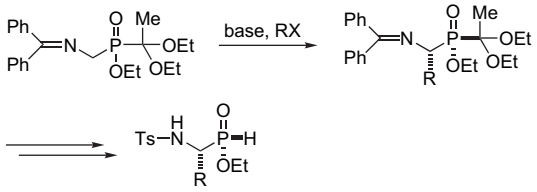
Abstract—Diastereoselective synthesis of α-aminophosphinates was achieved by alkylation of imines with a 1,1-diethoxyethylphosphinyl group. These products were readily converted into α-amino-*H*-phosphinates.

1. Introduction

α-Aminophosphinic acid derivatives are of much interest due to their usefulness both in the development of catalytic antibodies[1] and pharmacologically active substances.[2] Some peptides incorporating these molecules were shown to be effective inhibitors against aspartic acid proteases and Zn metalloproteases.[3] For the preparation of various α-aminophosphinic acid derivatives, α-amino-*H*-phosphinates have been utilized as versatile synthetic intermediates.[4] This class of compounds has previously been prepared through the addition of phosphinic acid[5] or silyl phosphonite[6] to imines. An alternative synthesis of α-amino-*H*-phosphinates involves the alkylation of iminomethylenephosphinates having a diethoxymethyl group at the phosphorus atom, followed by conversion of the diethoxymethylphosphinyl moiety to P–H group with 6 M HCl at reflux.[7] In this methodology, the alkylated products were given as a mixture of diastereomers arising from the chirality of the phosphorus atom, and the relative configuration of the major isomer as well as its stereoselectivity remained unclear. The methodology was limited by the harsh conditions necessary for the deprotection of the acetal group.[8]

During our studies on the stereoselctive synthesis of α-amino-*H*-phosphinic acid derivatives, we envisioned iminomethylenephosphinates bearing a 1,1-diethoxyethyl group instead of a diethoxymethyl group, which could be successfully employed as a substrate for the stereoselective alkylation of phosphorus-stabilized carbanions. The 1,1-diethoxyethyl group may give rise to a pronounced steric hindrance around the carbanions and could work as a good directing group for the diastereoselective alkylation of the carbanions.

In this paper, we wish to describe our experimental results on the alkylation of racemic iminomethylenephosphinates possessing a 1,1-diethoxyethyl group at the phosphorus atom. As expected, these reactions proceeded in a highly diastereoselective manner to give α-substituted α-aminophosphinates, which were readily converted to α-substituted α-amino-*H*-phosphinates under mild conditions (Scheme 1).



Scheme 1.

2. Results and discussion

The requisite starting materials **4** and **5** were prepared as shown in Scheme 2. The addition of *H*-phosphinate **1**[8] to 1,3,5-hexahydrotriazine provided benzylamine **2**, which was subjected to hydrogenolytic removal of the benzyl group giving amine **3**. Treatment of **3** with benzophenone in toluene at reflux afforded imine **4**. Following Hoppe's procedure,[9] **3** was converted to imine **5**.

First, alkylation of **4** with benzyl bromide (2 equiv) was examined in THF at −78 °C by using representative strong bases (Scheme 3). When BuLi was used as a basic reagent, the reaction was completed within 1.5 h to give a diastereomeric mixture of (R^*,R_P^*)-**6** and (S^*,R_P^*)-**6** in a 51% yield.

Keywords: α-Amino-*H*-phosphinates; Phosphorus; Alkylations; Diastereoselectivity.
* Corresponding author. Tel./fax: +81 426 76 3239; e-mail: yokomatu@ps.toyaku.ac.jp

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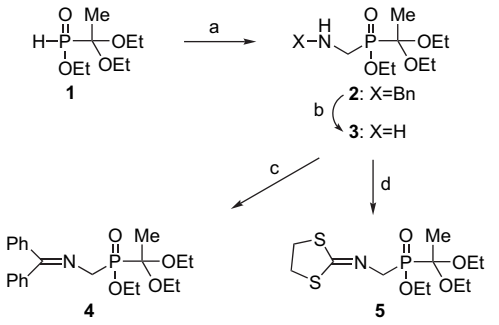
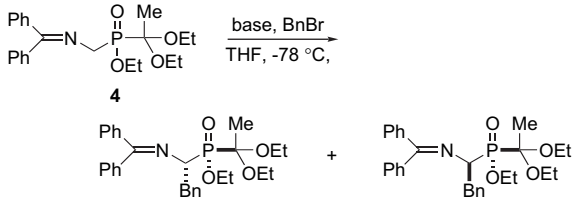


Scheme 2. Reagents and conditions: (a) 1,3,5-tribenzylhexahydrotriazine, toluene, reflux, 85%; (b) H_2, $Pd(OH)_2$–C, MeOH, 83%; (c) benzophenone, toluene, reflux, 87%; (d) CS_2, 1,2-dibromoethane, NEt_3, K_2CO_3, $CHCl_3$, reflux, 32%.

The ratio was determined to be 2.2:1 preferring (R^*,R_P^*)-**6** on the basis of ^{31}P (121 MHz) NMR analysis. Upon using LDA, the yield was significantly increased to 70% albeit the diastereoselectivity was similar to that for BuLi. While utilizing lithium 2,2,6,6-tetramethylpiperidide (LTMP) took longer reaction time (20 h) compared to the cases of BuLi and LDA (1.5 h), the diastereoselectivity was improved up to 6.9:1. KHMDS was found to be a good base for inducing a high diastereoselectivity with a modest yield. The best result was observed when the reaction was carried out with LHMDS; (R^*,R_P^*)-**6** and (S^*,R_P^*)-**6** were obtained in a 78% yield with a ratio of 10.1:1 and the individual diastereomers were isolated in a pure state by flash column chromatography on silica gel. Although the exact reason why LHMDS was the most effective among examined basic reagents remained unclear, it seems likely to be associated with steric bulk of the basic reagents.

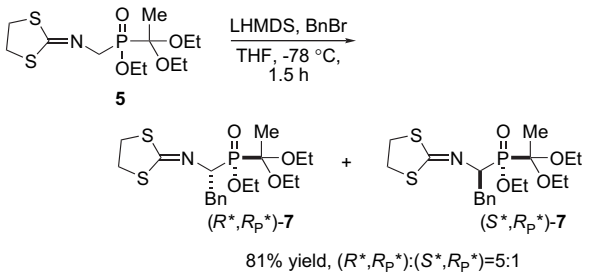


base	time (h)	yield (%)	(R^*,R_P^*):(S^*,R_P^*)
BuLi	1.5	51	2.2:1
LDA	1.5	70	3.0:1
LTMP	20	58	6.9:1
KHMDS	1.5	52	10.1:1
LHMDS	1.5	78	10.1:1

Scheme 3.

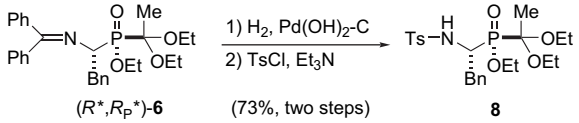
The benzylation of **5** under optimized conditions provided (R^*,R_P^*)-**7** and (S^*,R_P^*)-**7** in a 81% yield, however, (R^*,R_P^*)-selectivity (5:1) was eroded in comparison to the case of **4** (Scheme 4). This result indicated *N*-diphenylmethyleneamine derivative **4** was a relatively good substrate.

The relative stereochemistry of (R^*,R_P^*)-**6** was verified after conversion to the corresponding tosylamide **8** (Scheme 5). Hydrogenolysis of (R^*,R_P^*)-**6** in the presence of $Pd(OH)_2$–C, followed by tosylation of the resulting amine afforded **8**. The stereochemistry of **8** was confirmed by X-ray



Scheme 4.

crystallographic analysis (Fig. 1). The relative configuration of (R^*,R_P^*)-**7** was ascertained by comparison with an authentic sample prepared from (R^*,R_P^*)-**6** through exchanging the protecting group at the nitrogen atom.



Scheme 5.

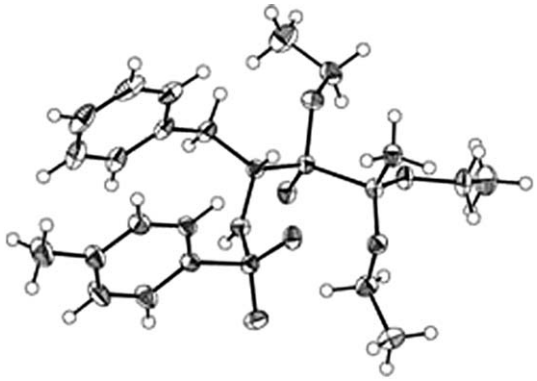
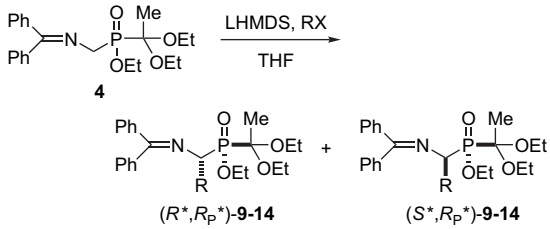


Figure 1. ORTEP drawing of the X-ray crystal structure of **8**.

The diastereoselective alkylation of **4** with several electrophiles was further examined. The results are summarized in Table 1.

Reactions with allyl bromide derivatives and iodomethane proceeded smoothly at −78 °C and were completed within 1.5 h providing (R^*,R_P^*)-**9**–**11** and (S^*,R_P^*)-**9**–**11** in good yields (entries 1–3). On the other hand, when the same conditions were applied to the less reactive alkyl halides (*n*-BuBr, *i*-PrI, *i*-BuBr), reactions were quite sluggish. However, the alkylation products ((R^*,R_P^*)-**12**–**14** and (S^*,R_P^*)-**12**–**14**) were obtained in 47–71% yields, upon warming the reaction mixture from −78 to 0 °C or at room temperature (entries 4–6). In view of diastereoselectivity, the reaction of allyl bromide gave (R^*,R_P^*)-**9** predominantly in a ratio of 7.7:1 (entry 1). The reactions of methallyl bromide and *i*-BuBr also showed good selectivity (entries 2 and 6). Unfortunately, reactions with other electrophiles (MeI, *n*-BuBr, *i*-PrI) resulted in decrease of diastereoselectivity (entries 3–5). The relative configuration of (R^*,R_P^*)-**9**–**14** was estimated analogously to (R^*,R_P^*)-**6**, whose stereochemistry was previously determined. Although a similar reaction of

Table 1. Diastereoselective alkylation of **4** with several electrophiles

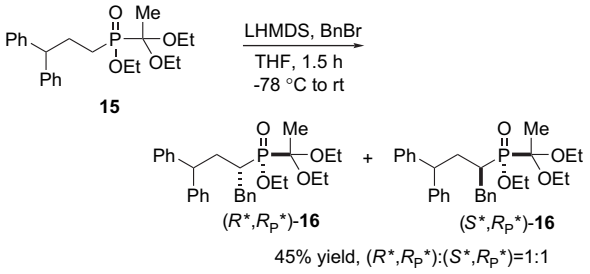


Entry	RX[a]	Temp (°C)	Time (h)	Product	Yield (%)[b]	(*R**,*R*P*): (*S**,*R*P*)[c]
1	Allyl bromide	−78	1.5	**9**	90	7.7:1
2	Methallyl bromide	−78	1	**10**	98	7.8:1
3	MeI	−78	1.5	**11**	77	4.5:1
4	*n*-BuBr	−78 to 0	24	**12**	50	4.8:1
5	*i*-PrI	−78 to 0	24	**13**	47	6.8:1
6	*i*-BuI[d]	−78 to rt	20	**14**	71	10.0:1

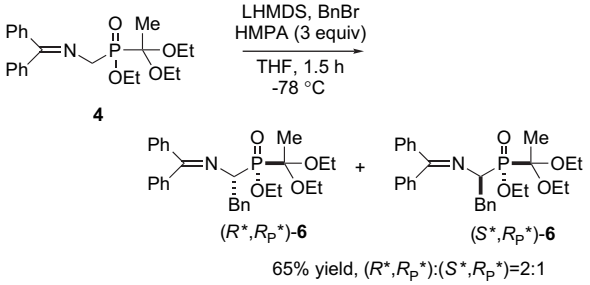
[a] Electrophiles (2 equiv) were utilized unless stated otherwise.
[b] Combined yield of (*R**,*R*P*)- and (*S**,*R*P*)-products.
[c] Determined by ^{31}P NMR (121 MHz, $CDCl_3$) analysis of crude products.
[d] *i*-BuI (5 equiv) was utilized.

4 with *p*-nitrobromobenzene was examined, formation of any S_NAr products was not detected. Thus, suitable electrophiles in this methodology were confirmed to be alkyl halide derivatives.

To probe the origin of the diastereocontrol, we performed the following experiments. The LHMDS-mediated benzylation of phosphinate **15** without a nitrogen atom, prepared from **1** and 3,3-diphenylpropyl bromide, proceeded in a nonstereoselective manner ((*R**,*R*P*)-**16**/(*S**,*R*P*)-**16**=1:1) in contrast to the reaction of **4** (Scheme 6). When the LHMDS-mediated benzylation of **4** was carried out in the presence of additive HMPA (3 equiv), the diastereoselectivity was lowered ((*R**,*R*P*)-**6**/(*S**,*R*P*)-**6**=2:1) compared to that without HMPA (Scheme 7). These results represent that the chelation



Scheme 6.



Scheme 7.

of the lithium atom to the nitrogen atom of the substrates is likely to be a significant factor for the occurrence of good (*R**,*R*P*)-selectivity.

On the basis of the above-mentioned results, the stereoselectivity in the alkylation of **4** is possibly accounted for by invoking the anion intermediate **17** bearing a planar sp^2 carbanionic carbon, wherein the lithium atom is coordinated by phosphinyl oxygen and a nitrogen atom (Fig. 2). An approach of electrophiles from the side of the 1,1-diethoxyethyl group was hindered by this bulky moiety, therefore, the access of the electrophiles occurred preferentially from the opposite side of a 1,1-diethoxyethyl group leading to (*R**,*R*P*)-products. Similar working models were proposed by Denmark and Hannesian for the asymmetric alkylation of anions derived from phosphonamidates[10] and phosphonamide,[11] respectively.

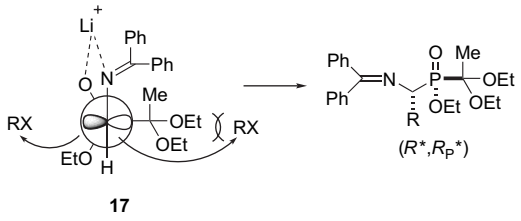
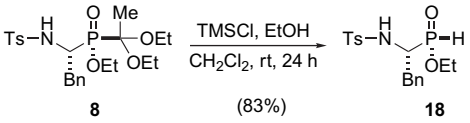


Figure 2.

Finally, the 1,1-diethoxyethyl moiety of **8** was readily removed by treatment with TMSCl and ethanol at room temperature furnishing α-amino-*H*-phosphinate **18** (Scheme 8). It is worthy to note that this deprotection step proceeded in a highly diastereoselective manner (20:1) to give **18** in good yield, while the deprotection step may be prone to epimerization at the phosphorus atom. Compound **18** was isolated in pure form by column chromatography on silica gel.



Scheme 8.

3. Conclusion

In conclusion, we have developed a method for preparing α-aminophosphinates through alkylation of iminomethylenephosphinates with 1,1-diethoxyethyl moiety. The feature of this method is a high diastereoselectivity controlled by the asymmetric center at the phosphorus atom. The protective group of the alkylated product was removed under mild conditions giving α-amino-*H*-phosphinate. Application to chiral variants is ongoing.

4. Experimental

4.1. General

All melting points were taken on a Yanagimoto micro-melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO FTIR-620. Mass spectra were

measured on a Finnigan TSQ-700 by electrospray ionization. Elemental analysis were recorded on an Elemental Vavio EL. NMR spectra were obtained on Bruker DPX400 NMR spectrometer operating at 400 MHz for ^{1}H, 100 MHz for ^{13}C, and 162 MHz for ^{31}P. ^{31}P NMR spectra were also obtained on Varian Mercury-300BB instrument operating at 121 MHz. The chemical shift data for each signal on ^{1}H NMR are given in units of δ relative to $CHCl_3$ (δ=7.26) for $CDCl_3$ solution. For ^{13}C NMR spectra, the chemical shifts in $CDCl_3$ are recorded relative to the $CDCl_3$ resonance (δ=77.0). The chemical shifts of ^{31}P are recorded relative to external 85% H_3PO_4 (δ=0) with broadband ^{1}H decoupling. Flash column chromatography was performed on 40–100 μm silica gel 60 (Kanto Chemical Co., Inc.). Column chromatography was carried out using 63–210 μm silica gel 60N (Kanto Chemical Co., Inc.). Preparative HPLC was performed on JASCO HPLC systems consisting of the following: pump, PU-986; detector, UV-975, measured at 254 nm; column, GL Sciences Inertsil PREP SIL; flow rate, 15.0 mL min^{-1}. Analytical TLC was carried out with precoated silica gel 60 F_{254} plates (Merck).

4.1.1. Ethyl (benzylamino)methyl(1,1-diethoxyethyl)-phosphinate (2). A stirred solution of **1** (22.4 g, 100 mmol) and 1,3,5-tribenzylhexahydro-1,3,5-triazine (11.79 g, 33 mmol) in toluene (165 mL) was heated to reflux for 12 h followed by cooling to room temperature and concentration under reduced pressure. The resulting residue was purified by flash column chromatography ($CHCl_3$/MeOH=1:0 to 20:1) to give **2** (27.9 g, 85%). A pale yellow oil; TLC R_f=0.36 ($CHCl_3$/MeOH=20:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.22 (5H, m), 4.30–4.19 (2H, m), 3.90 (1H, d, J=13.4 Hz), 3.86 (1H, d, J=13.4 Hz), 3.76–3.67 (4H, m), 3.08 (1H, dd, J=6.4, 14.6 Hz), 2.95 (1H, dd, J=9.8, 14.6 Hz), 1.54 (3H, d, J=11.0 Hz), 1.34 (3H, t, J=7.1 Hz), 1.19 (3H, t, J=7.1 Hz), 1.18 (3H, t, J=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 128.1, 127.9, 126.1, 101.1 (d, J_{CP}=137.2 Hz), 61.6 (d, J_{CP}=7.2 Hz), 58.0 (d, J_{CP}=4.9 Hz), 57.4 (d, J_{CP}=7.0 Hz), 54.8 (d, J_{CP}=13.1 Hz), 44.5 (d, J_{CP}=92.5 Hz), 20.3 (d, J_{CP}=11.7 Hz), 16.5 (d, J_{CP}=5.1 Hz), 15.2, 15.0; ^{31}P NMR (162 MHz, $CDCl_3$) δ 43.63; IR (neat) 3321, 1155, 1036 cm^{-1}; MS m/z 330 (MH^+). HRMS calcd for $C_{16}H_{29}NO_4P$: 330.1834 (MH^+). Found: 330.1831.

4.1.2. Ethyl aminomethyl(1,1-diethoxyethyl)phosphinate (3). To a solution of **2** (10.01 g, 30.4 mmol) in MeOH (304 mL) was added $Pd(OH)_2$–C (1.83 g) and stirred for 5 h at room temperature under a hydrogen atmosphere. The catalyst was removed by filtration through a pad of Celite and the filtrate was concentrated to give a residue. To a solution of the residue in CH_2Cl_2 (334 mL) was added Et_3N (6.9 mL, 6.7 mmol) and the mixture was stirred for 30 min at room temperature. To the mixture was added Et_2O (100 mL) and resulting crystal was removed by filtration. The filtrate was concentrated to give **3** (6.03 g, 83%). A pale yellow oil; TLC R_f=0.30 ($CHCl_3$/MeOH=20:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.28–4.19 (2H, m), 3.79–3.62 (4H, m), 3.11 (1H, dd, J=2.1, 15.7 Hz), 2.98 (1H, dd, J=7.3, 15.7 Hz), 1.53 (3H, d, J=10.9 Hz), 1.34 (3H, t, J=7.0 Hz), 1.21 (6H, t, J=7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 101.3 (d, J_{CP}=29.0 Hz), 61.6 (d, J_{CP}=7.3 Hz), 58.0 (d, J_{CP}=4.9 Hz), 57.4 (d, J_{CP}=6.6 Hz), 38.2 (d, J_{CP}=85.4 Hz), 19.7 (d, J_{CP}=11.6 Hz), 16.4 (d, J_{CP}=4.9 Hz), 15.1, 15.0; ^{31}P NMR (162 MHz, $CDCl_3$) δ 44.29; IR (neat) 3012, 1160, 1036 cm^{-1}; MS m/z 240 (MH^+). HRMS calcd for $C_9H_{23}NO_4P$: 240.1365 (MH^+). Found: 240.1360.

4.1.3. Ethyl 1,1-diethoxyethyl{[(diphenylmethylene)amino]methyl}phosphinate (4). A suspension of **3** (970 mg, 4.0 mmol) and benzophenone (810 mg, 4.0 mmol) in toluene (11 mL) was heated to reflux for 12 h with azeotropic removal of water in a Dean–Stark trap. The mixture was cooled to room temperature and concentrated to give a residue, which was purified by flash column chromatography ($CHCl_3$) to give **4** (1.42 g, 87%). A colorless oil; TLC R_f=0.26 (hexane/EtOAc=1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65–7.24 (10H, m), 4.27–4.23 (2H, m), 4.05 (1H, dd, J=14.0, 26.9 Hz), 3.98 (1H, dd, J=14.0, 26.9 Hz), 3.73–3.61 (4H, m), 1.57 (3H, d, J=11.2 Hz), 1.34 (3H, t, J=7.1 Hz), 1.14 (6H, t, J=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 135.5, 130.2, 128.5–127.9 (aromatic), 101.2 (d, J_{PC}=140.4 Hz), 62.0 (d, J_{PC}=7.3 Hz), 57.9 (d, J_{PC}=5.1 Hz), 57.7 (d, J_{PC}=6.9 Hz), 51.8 (d, J_{PC}=96.6 Hz), 20.5 (d, J_{PC}=11.8 Hz), 16.6 (d, J_{PC}=5.1 Hz), 15.3, 15.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ 42.44; IR (neat) 1620, 1158, 1036 cm^{-1}; MS m/z 404 (MH^+). HRMS calcd for $C_{22}H_{31}NO_4P$ (MH^+): 404.1991. Found: 404.1994.

4.1.4. Ethyl 1,1-diethoxyethyl[(1,3-dithiolan-2-ylideneamino)methyl]phosphinate (5). To a solution of **3** (5.00 g, 20.9 mmol) in $CHCl_3$ (42 mL) was added CS_2 (3.1 mL, 52.0 mmol) and Et_3N (11.7 mL, 83.6 mmol) and stirred for 30 min at room temperature. To the mixture was added 1,2-dibromoethane (4.5 mL, 52 mmol) and heated to reflux for 1 h. Concentration of the mixture gave a residue, which was dissolved in EtOH (25 mL). To this solution was added K_2CO_3 (2.89 g, 20.9 mmol) and heated to reflux for 4 h. The mixture was poured into H_2O and extracted with Et_2O. The combined extracts were washed with brine and dried over $MgSO_4$. Removal of the solvent gave a residue, which was purified by flash column chromatography ($CHCl_3$) to give **5** (2.30 g, 32%). A pale yellow oil; TLC R_f=0.37 ($CHCl_3$/MeOH=20:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.27 (1H, dd, J=7.1, 14.3 Hz), 4.25 (1H, dd, J=7.1, 14.3 Hz), 3.95 (1H, dd, J=10.5, 14.5 Hz), 3.91 (1H, dd, J=12.0, 14.5 Hz), 3.83–3.63 (4H, m), 3.59 (2H, t, J=6.1 Hz), 3.43 (2H, t, J=6.5 Hz), 1.57 (3H, t, J=11.2 Hz), 1.34 (3H, t, J=7.1 Hz), 1.21 (3H, t, J=7.0 Hz), 1.20 (3H, t, J=7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4 (d, J_{PC}=16.5 Hz), 100.9 (d, J_{PC}=141.2 Hz), 61.8 (d, J_{PC}=7.2 Hz), 57.8 (d, J_{PC}=5.1 Hz), 57.4 (d, J_{PC}=7.1 Hz), 56.5 (d, J_{PC}=97.2 Hz), 37.5, 34.6, 20.3 (d, J_{PC}=11.8 Hz), 16.3 (d, J_{PC}=5.0 Hz), 15.2, 15.0; ^{31}P NMR (162 MHz, $CDCl_3$) δ 40.22; IR (neat) 1595, 1157, 1037 cm^{-1}; MS m/z 342 (MH^+). HRMS calcd for $C_{12}H_{25}NO_4PS_2$ (MH^+): 342.0963. Found: 342.0948.

4.1.5. (1*R,*R*$_P$*)- and (1*S**,*R*$_P$*)-Ethyl 1,1-diethoxyethyl{1-[(diphenylmethylene)amino]-2-phenylethyl}-phosphinate ((*R**,*R*$_P$*)-6 and (*S**,*R*$_P$*)-6).** To a solution of **4** (400 mg, 1.0 mmol) in THF (4.7 mL) was added 1.0 M THF solution of LHMDS (1.5 mL, 1.5 mmol) and stirred for 30 min at the same temperature. To the mixture was added benzyl bromide (0.24 mL, 2.0 mmol) and stirred for 1.5 h at the same temperature. The mixture was diluted with satd NH_4Cl solution and extracted with Et_2O. The combined

extracts were washed with brine and dried over $MgSO_4$. Removal of the solvent gave a residue, which was purified by flash column chromatography ($CHCl_3$) to give a mixture of (*R**,*R*P*)-**6** and (*S**,*R*P*)-**6** (358 mg, 78%). Analytical samples of individual isomers were obtained upon re-purification by flash column chromatography (hexane/EtOAc=5:1 to 1:1).

(*R**,*R*P*)-**6**: A pale yellow oil; TLC R_f=0.61 (hexane/EtOAc=1:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57–6.96 (15H, m), 4.32–4.18 (2H, m), 4.04–4.00 (1H, m), 3.83–3.64 (4H, m), 3.46 (1H, ddd, *J*=1.9, 6.2, 13.3 Hz), 3.36–3.31 (1H, m), 1.66 (3H, d, *J*=11.1 Hz), 1.34 (3H, t, *J*=7.1 Hz), 1.21 (3H, t, *J*=7.0 Hz), 1.18 (3H, t, *J*=7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3, 135.4–126.1 (aromatic), 102.2 (d, J_{PC}=134.7 Hz), 65.8 (d, J_{PC}=95.3 Hz), 62.0 (d, J_{PC}=7.1 Hz), 58.0 (d, J_{PC}=6.5 Hz), 57.8 (d, J_{PC}=4.8 Hz), 36.8, 21.0 (d, J_{PC}=12.1 Hz), 16.7 (d, J_{PC}=4.9 Hz), 15.5, 15.3; ^{31}P NMR (162 MHz, $CDCl_3$) δ 42.44; IR (neat) 1620, 1155, 1034 cm^{-1}; MS *m*/*z* 494 (MH^+). HRMS calcd for $C_{29}H_{37}NO_4P$ (MH^+): 494.2460. Found: 494.2451.

(*S**,*R*P*)-**6**: A pale yellow oil; TLC R_f=0.53 (hexane/EtOAc=1:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61–6.98 (15H, m), 4.30–4.17 (2H, m), 4.08–4.06 (1H, m), 3.86–3.65 (4H, m), 3.51–3.46 (1H, m), 3.38–3.31 (1H, m), 1.43 (3H, d, *J*=10.9 Hz), 1.27 (3H, t, *J*=7.1 Hz), 1.15 (3H, t, *J*=7.0 Hz), 1.11 (3H, t, *J*=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 135.7–126.1 (aromatic), 102.1 (d, J_{PC}=136.7 Hz), 64.1 (d, J_{PC}=92.7 Hz), 62.1 (d, J_{PC}=7.5 Hz), 58.4 (d, J_{PC}=4.7 Hz), 57.5 (d, J_{PC}=7.2 Hz), 36.9, 20.6 (d, J_{PC}=11.8 Hz), 16.9 (d, J_{PC}=4.8 Hz), 15.4, 15.3; ^{31}P NMR (162 MHz, $CDCl_3$) δ 42.59; IR (neat) 1618, 1153, 1034 cm^{-1}; MS *m*/*z* 494 (MH^+). HRMS calcd for $C_{29}H_{37}NO_4P$ (MH^+): 494.2460. Found: 494.2442.

4.1.6. (1*R,*R*P*)- and (1*S**,*R*P*)-Ethyl 1,1-diethoxyethyl[1-(1,3-dithiolan-2-ylideneamino)-2-phenylethyl]phosphinate ((*R**,*R*P*)-7 and (*S**,*R*P*)-7).** These compounds were prepared from **5** (341 mg, 1.0 mmol) in an analogous manner to that for (*R**,*R*P*)-**6**. Purification of the residue by flash column chromatography ($CHCl_3$) gave a mixture of (*R**,*R*P*)-**7** and (*S**,*R*P*)-**7** (350 mg, 81%). Analytical samples of individual isomers were obtained upon re-purification by flash column chromatography (hexane/EtOAc=5:1 to 1:1).

(*R**,*R*P*)-**7**: A pale yellow oil; TLC R_f=0.38 (hexane/EtOAc=1:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.15 (5H, m), 4.32–4.25 (2H, m), 3.80–3.66 (5H, m), 3.34–3.28 (3H, m), 3.21–3.16 (3H, m), 1.60 (3H, d, *J*=11.1 Hz), 1.35 (3H, t, *J*=7.1 Hz), 1.23 (3H, t, *J*=6.9 Hz), 1.21 (3H, t, *J*=7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7 (d, J_{PC}=17.5 Hz), 138.5 (d, J_{PC}=13.6 Hz), 129.9, 127.9, 126.2, 102.1 (d, J_{PC}=135.7 Hz), 71.4 (d, J_{PC}=100.6 Hz), 62.1 (d, J_{PC}=7.4 Hz), 58.2 (d, J_{PC}=4.2 Hz), 57.6 (d, J_{PC}=7.4 Hz), 37.4, 35.8, 34.3, 20.9 (d, J_{PC}=12.0 Hz), 16.7 (d, J_{PC}=4.9 Hz), 15.6, 15.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ 40.97; IR (neat) 1591, 1153, 1039 cm^{-1}; MS *m*/*z* 432 (MH^+). HRMS calcd for $C_{19}H_{31}NO_4PS_2$ (MH^+): 432.1432. Found: 432.1408.

(*S**,*R*P*)-**7**: A pale yellow oil; TLC R_f=0.25 (hexane/EtOAc=1:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24–7.17 (5H, m), 4.35–4.26 (2H, m), 3.98–3.90 (1H, m), 3.76–3.60 (4H, m), 3.49 (1H, ddd, *J*=5.4, 11.1, 13.4 Hz), 3.34–3.15 (4H, m), 3.04 (1H, ddd, *J*=2.1, 5.4, 13.4 Hz), 1.56 (3H, d, *J*=10.9 Hz), 1.38 (3H, t, *J*=7.1 Hz), 1.22 (6H, t, *J*=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3 (d, J_{PC}=16.0 Hz), 138.5 (d, J_{PC}=14.1 Hz), 129.9, 128.0, 126.2, 101.6 (d, J_{PC}=138.5 Hz), 70.7 (d, J_{PC}=95.7 Hz), 62.3 (d, J_{PC}=7.5 Hz), 58.5 (d, J_{PC}=4.3 Hz), 57.7 (d, J_{PC}=8.0 Hz), 37.4, 35.9, 34.4, 20.9 (d, J_{PC}=11.4 Hz), 16.8 (d, J_{PC}=4.2 Hz), 15.7, 15.3; ^{31}P NMR (162 MHz, $CDCl_3$) δ 41.08; IR (neat) 1591, 1151, 1034 cm^{-1}; MS *m*/*z* 432 (MH^+). HRMS calcd for $C_{19}H_{31}NO_4PS_2$ (MH^+): 432.1432. Found: 432.1409.

4.1.7. (1*R,*R*P*)-Ethyl 1,1-diethoxyethyl(1-{[(4-methylphenyl)sulfonyl]amino}-2-phenylethyl)phosphinate (8).** To a solution of (*R**,*R**P)-**6** (360 mg, 0.72 mmol) in MeOH (7.2 mL) was added $Pd(OH)_2$–C (43.2 mg) and stirred for 40 h at room temperature under a hydrogen atmosphere. The catalyst was removed by filtration through a pad of Celite and the filtrate was concentrated to give a residue. To a solution of the residue in CH_2Cl_2 (3.2 mL) was added Et_3N (0.21 mL, 1.51 mmol) and TsCl (288 mg, 1.51 mmol) and the mixture was stirred for 2 h at room temperature. The mixture was poured into H_2O and extracted with Et_2O. The combined extracts were washed with brine and dried over $MgSO_4$. Removal of the solvent gave a residue, which was purified by flash column chromatography ($CHCl_3$) to give **8** (306 mg, 88%). Colorless plates; mp 126–132 °C; TLC R_f=0.38 ($CHCl_3$/MeOH=20:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.09 (5H, m), 5.59 (1H, dd, *J*=7.5, 7.7 Hz), 4.24–4.12 (2H, m), 4.10–4.00 (1H, m), 3.79–3.63 (4H, m), 3.22 (1H, ddd, *J*=6.3, 9.8, 14.5 Hz), 2.89 (1H, ddd, *J*=7.7, 12.0, 14.3 Hz), 2.37 (3H, s), 1.53 (3H, d, *J*=11.6 Hz), 1.25 (3H, t, *J*=7.0 Hz), 1.20 (6H, t, *J*=7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.8, 138.8, 137.5, 129.5–126.4 (aromatic), 102.9 (d, J_{PC}=141.2 Hz), 62.3 (d, J_{PC}=7.5 Hz), 58.9 (d, J_{PC}=4.5 Hz), 58.2 (d, J_{PC}=7.4 Hz), 53.1 (d, J_{PC}=87.1 Hz), 36.9, 21.4, 19.5 (d, J_{PC}=12.1 Hz), 16.3 (d, J_{PC}=5.8 Hz), 15.4, 15.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ 41.19; IR (KBr) 3117, 1332, 1156, 1034 cm^{-1}; MS *m*/*z* 484 (MH^+). Anal. Calcd for $C_{23}H_{34}NO_6PS$: C, 57.13; H, 7.09. Found: C, 57.12; H, 7.01.

4.2. Crystal data for compound 8

X-ray crystal data of **8** were collected by Mac-Science DIP Image plate diffractometer. The structure was solved by a direct method using SIR97[12] and refined with a full matrix least-squares method.[13] Molecular formula=$C_{23}H_{34}NO_6PS$, M_r=483.55, monoclinic, space group=$P2_1/C$, a=13.0570 (3) Å, b=15.2600 (3) Å, c=16.0060 (3) Å, V=2547.50 (10) Å^3, T=100 (2) K, Z=4, D_x=1.261 mg m^{-3}, (Mo Kα)=0.71073 Å, μ=0.226 mm^{-1}, R=0.0538 over 5574 independent reflections. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication numbers CCDC 600772. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.3. Preparation of various α-aminophosphinates

4.3.1. (1*R,*R*$_P$*)- and (1*S**,*R*$_P$*)-Ethyl 1,1-diethoxyethyl{1-[(diphenylmethylene)amino]but-3-enyl}phosphinate ((*R**,*R*$_P$*)-9 and (*S**,*R*$_P$*)-9).** This compound was prepared from **4** (200 mg, 0.5 mmol), 1.0 M THF solution of LHMDS (0.75 mL, 0.75 mmol) and allyl bromide (85 μL, 1.0 mmol) in an analogous manner to that for (*R**,*R*$_P$*)-**6**. Purification of the residue by flash column chromatography ($CHCl_3$) gave a mixture of (*R**,*R*$_P$*)-**9** and (*S**,*R*$_P$*)-**9** (200 mg, 90%). Analytical samples of individual isomers were obtained upon re-purification by flash column chromatography (hexane/EtOAc=5:1 to 2:1).

(*R**,*R*$_P$*)-**9**: A pale yellow oil; TLC R_f=0.34 (hexane/EtOAc=1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63–7.23 (10H, m), 5.61–5.50 (1H, m), 5.04–4.96 (2H, m), 4.31–4.17 (2H, m), 3.99 (1H, ddd, *J*=3.3, 9.7, 9.7 Hz), 3.76–3.66 (4H, m), 2.90–2.79 (2H, m), 1.59 (3H, d, *J*=11.0 Hz), 1.33 (3H, t, *J*=7.1 Hz), 1.18 (3H, t, *J*=7.1 Hz), 1.15 (3H, t, *J*=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.5, 135.9, 135.6–127.9 (aromatic), 117.2, 102.0 (d, J_{PC}=134.6 Hz), 63.3 (d, J_{PC}=96.2 Hz), 61.9 (d, J_{PC}=7.3 Hz), 57.8 (d, J_{PC}=6.6 Hz), 57.7 (d, J_{PC}=4.9 Hz), 35.1, 21.0 (d, J_{PC}=12.2 Hz), 16.7 (d, J_{PC}=4.9 Hz), 15.5, 15.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ 42.27; IR (neat) 1639, 1618, 1155, 1032 cm^{-1}; MS *m*/*z* 444 (MH^+). HRMS calcd for $C_{25}H_{35}NO_4P$ (MH^+): 444.2304. Found: 444.2281.

(*S**,*R*$_P$*)-**9**: A pale yellow oil; TLC R_f=0.28 (hexane/EtOAc=1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80–7.24 (10H, m), 5.63–5.51 (1H, m), 5.04–4.96 (2H, m), 4.32–4.18 (2H, m), 4.04–4.02 (1H, m), 3.75–3.61 (4H, m), 2.89–2.70 (2H, m), 1.38 (3H, d, *J*=11.1 Hz), 1.27 (3H, t, *J*=7.1 Hz), 1.18 (3H, t, *J*=7.0 Hz), 1.15 (3H, t, *J*=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.4 (d, J_{PC}=2.5 Hz), 136.0, 117.2, 101.8 (d, J_{PC}=136.6 Hz), 62.0 (d, J_{PC}=6.8 Hz), 61.6 (d, J_{PC}=95.2 Hz), 58.2 (d, J_{PC}=4.5 Hz), 57.3 (d, J_{PC}=7.1 Hz), 35.2 (d, J_{PC}=1.9 Hz), 20.6 (d, J_{PC}=12.0 Hz), 16.8 (d, J_{PC}=4.8 Hz), 15.4, 15.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ 42.72; IR (neat) 1635, 1618, 1155, 1032 cm^{-1}; MS *m*/*z* 444 (MH^+). HRMS calcd for $C_{25}H_{35}NO_4P$ (MH^+): 444.2304. Found: 444.2299.

4.3.2. (1*R,*R*$_P$*)- and (1*S**,*R*$_P$*)-Ethyl 1,1-diethoxyethyl{1-[(diphenylmethylene)amino]-3-methylbut-3-enyl}phosphinate ((*R**,*R*$_P$*)-10 and (*S**,*R*$_P$*)-10).** These compounds were prepared from **4** (200 mg, 0.5 mmol), 1.0 M THF solution of LHMDS (0.75 mL, 0.75 mmol), and methallyl bromide (0.1 mL, 1.0 mmol) in an analogous manner to that for (*R**,*R*$_P$*)-**6**. Purification of the residue by flash column chromatography ($CHCl_3$) gave a mixture of (*R**,*R*$_P$*)-**10** and (*S**,*R*$_P$*)-**10** (224 mg, 98%). Analytical samples of individual isomers were obtained upon re-purification by flash column chromatography (hexane/EtOAc=10:1 to 2:1).

(*R**,*R*$_P$*)-**10**: A colorless oil; TLC R_f=0.38 (hexane/EtOAc=1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63–7.26 (10H, m), 4.68 (1H, s), 4.66 (1H, s), 4.32–4.19 (2H, m), 4.09–4.02 (1H, m), 3.75–3.62 (4H, m), 2.78 (2H, t, *J*=6.9 Hz), 1.60 (3H, d, *J*=11.1 Hz), 1.39 (3H, s), 1.35 (3H, t, *J*=7.1 Hz), 1.19 (3H, t, *J*=7.1 Hz), 1.16 (3H, t, *J*=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.6 (d, J_{PC}=2.4 Hz), 135.6, 132.3–127.8 (aromatic), 114.0, 102.1 (d, J_{PC}=134.8 Hz), 61.9 (d, J_{PC}=96.2 Hz), 61.9 (d, J_{PC}=7.3 Hz), 57.8 (d, J_{PC}=6.2 Hz), 57.7 (d, J_{PC}=4.2 Hz), 38.9, 22.3, 20.9 (d, J_{PC}=12.0 Hz), 16.6 (d, J_{PC}=5.1 Hz), 15.5, 15.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ 42.75; IR (neat) 1649, 1620, 1155, 1034 cm^{-1}; MS *m*/*z* 458 (MH^+). HRMS calcd for $C_{26}H_{37}NO_4P$ (MH^+): 458.2460. Found: 458.2485.

(*S**,*R*$_P$*)-**10**: A colorless oil; TLC R_f=0.30 (hexane/EtOAc=1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67–7.21 (10H, m), 4.71 (1H, s), 4.65 (1H, s), 4.24–4.18 (2H, m), 4.12–4.08 (1H, m), 3.82–3.64 (4H, m), 2.78 (2H, t, *J*=4.0 Hz), 1.44 (3H, d, *J*=10.9 Hz), 1.37 (3H, s), 1.25 (3H, t, *J*=7.1 Hz), 1.13 (3H, t, *J*=7.1 Hz), 1.10 (3H, t, *J*=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.6, 135.9, 130.0–127.9 (aromatic), 114.2, 102.1 (d, J_{PC}=136.8 Hz), 62.0 (d, J_{PC}=7.3 Hz), 60.4 (d, J_{PC}=94.6 Hz), 58.4 (d, J_{PC}=4.6 Hz), 57.5 (d, J_{PC}=7.2 Hz), 38.9, 22.5, 20.6 (d, J_{PC}=11.7 Hz), 16.8 (d, J_{PC}=4.8 Hz), 15.4, 15.3; ^{31}P NMR (162 MHz, $CDCl_3$) δ 43.03; IR (neat) 1653, 1618, 1153, 1036 cm^{-1}; MS *m*/*z* 458 (MH^+). HRMS calcd for $C_{26}H_{37}NO_4P$ (MH^+): 458.2460. Found: 458.2443.

4.3.3. (1*R,*R*$_P$*)- and (1*S**,*R*$_P$*)-Ethyl 1,1-diethoxyethyl{1-[(diphenylmethylene)amino]ethyl}phosphinate ((*R**,*R*$_P$*)-11 and (*S**,*R*$_P$*)-11).** These compounds were prepared from **4** (200 mg, 0.5 mmol), 1.0 M THF solution of LHMDS (0.75 mL, 0.75 mmol), and methyl iodide (62 μL, 1.0 mmol) in an analogous manner to that for (*R**,*R*$_P$*)-**6**. Purification of the residue by flash column chromatography ($CHCl_3$) gave a mixture of (*R**,*R*$_P$*)-**11** and (*S**,*R*$_P$*)-**11** (161 mg, 77%). Analytical samples of individual isomers were obtained upon re-purification by preparative HPLC (EtOAc/MeOH=50:1).

(*R**,*R*$_P$*)-**11**: A colorless oil; TLC R_f=0.18 (hexane/EtOAc=1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65–7.21 (10H, m), 4.09–4.03 (2H, m), 3.95 (1H, ddd, *J*=6.8, 6.8, 13.1 Hz), 3.75–3.56 (4H, m), 1.59 (3H, d, *J*=11.0 Hz), 1.47 (3H, dd, *J*=7.0, 15.5 Hz), 1.29 (3H, t, *J*=7.0 Hz), 1.16 (3H, t, *J*=7.1 Hz), 1.14 (3H, t, *J*=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2 (d, J_{PC}=2.0 Hz), 135.7–127.7 (aromatic), 101.8 (d, J_{PC}=133.4 Hz), 61.7 (d, J_{PC}=7.2 Hz), 58.1 (d, J_{PC}=97.0 Hz), 57.5 (d, J_{PC}=4.7 Hz), 57.4 (d, J_{PC}=6.9 Hz), 20.9 (d, J_{PC}=12.0 Hz), 16.6 (d, J_{PC}=5.0 Hz), 16.1 (d, J_{PC}=4.1 Hz), 15.5, 15.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ 43.62; IR (neat) 1618, 1155, 1039 cm^{-1}; MS *m*/*z* 418 (MH^+). HRMS calcd for $C_{23}H_{33}NO_4P$ (MH^+): 418.2147. Found: 418.2150.

(*S**,*R*$_P$*)-**11**: A colorless oil; TLC R_f=0.18 (hexane/EtOAc=1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80–7.19 (10H, m), 4.31–4.24 (2H, m), 4.04 (1H, ddd, *J*=6.9, 6.9, 13.8 Hz), 3.79–3.49 (4H, m), 1.48 (3H, dd, *J*=6.9, 15.5 Hz), 1.41 (3H, d, *J*=10.8 Hz), 1.33 (3H, t, *J*=7.1 Hz), 1.12 (3H, t, *J*=7.1 Hz), 1.07 (3H, t, *J*=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2 (d, J_{PC}=2.1 Hz), 136.0–127.7 (aromatic), 101.6 (d, J_{PC}=135.7 Hz), 62.0 (d, J_{PC}=7.5 Hz), 58.1 (d, J_{PC}=4.5 Hz), 57.4 (d, J_{PC}=6.9 Hz), 56.8 (d, J_{PC}=100.0 Hz), 20.8 (d, J_{PC}=11.7 Hz), 16.8 (d, J_{PC}=4.8 Hz), 16.3 (d, J_{PC}=4.7 Hz), 15.4, 15.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ 44.09; IR (neat) 1616, 1153, 1034 cm^{-1}; MS

m/*z* 418 (MH^+). HRMS calcd for $C_{23}H_{33}NO_4P$ (MH^+): 418.2147. Found: 418.2136.

4.3.4. (1*R,*R*$_P$*)- and (1*S**,*R*$_P$*)-Ethyl 1,1-diethoxyethyl{1-[(diphenylmethylene)amino]pentyl}phosphinate ((*R**,*R*$_P$*)-12 and (*S**,*R*$_P$*)-12).** To a solution of **4** (200 mg, 0.5 mmol) in THF (2.5 mL) was added 1.0 M THF solution of LHMDS (0.75 mL, 0.75 mmol) at −78 °C and stirred for 30 min at the same temperature. To the mixture was added *n*-butyl bromide (107 μL, 1.0 mmol) and stirred for 24 h at 0 °C. The mixture was diluted with satd NH_4Cl solution and extracted with Et_2O. The combined extracts were washed with brine and dried over $MgSO_4$. Removal of the solvent gave a residue, which was purified by column chromatography (hexane/EtOAc=10:1 to 2:1) to give a mixture of (*R**,*R*$_P$*)-**12** and (*S**,*R*$_P$*)-**12** (115 mg, 50%). Analytical samples of individual isomers were obtained upon re-purification by preparative HPLC ($CHCl_3$/MeOH=50:1).

(*R**,*R*$_P$*)-**12**: A colorless oil; TLC R_f=0.38 (hexane/EtOAc=1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.24 (10H, m), 4.27–4.16 (2H, m), 3.95 (1H, ddd, *J*=2.7, 2.7, 10.2 Hz), 3.79–3.49 (4H, m), 2.17–2.03 (2H, m), 1.37 (3H, d, *J*=10.9 Hz), 1.25 (3H, t, *J*=7.1 Hz), 1.22–1.17 (2H, m), 1.14 (3H, t, *J*=7.1 Hz), 1.12 (3H, t, *J*=7.1 Hz), 1.03–0.95 (2H, m), 0.83 (3H, t, *J*=7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.9 (d, J_{PC}=2.8 Hz), 136.7–128.4 (aromatic), 102.3 (d, J_{PC}=135.4 Hz), 62.3 (d, J_{PC}=94.4 Hz), 62.3 (d, J_{PC}=7.4 Hz), 58.7 (d, J_{PC}=4.4 Hz), 57.8 (d, J_{PC}=7.1 Hz), 30.6 (d, J_{PC}=2.4 Hz), 29.6 (d, J_{PC}=13.1 Hz), 22.9, 21.0 (d, J_{PC}=12.0 Hz), 17.3 (d, J_{PC}=4.8 Hz), 15.8, 15.6, 14.3; ^{31}P NMR (162 MHz, $CDCl_3$) δ 42.77; IR (neat) 1616, 1153, 1034 cm^{-1}; MS *m*/*z* 460 (MH^+). HRMS calcd for $C_{26}H_{38}NO_4P$ (MH^+): 460.2617. Found: 460.2627.

(*S**,*R*$_P$*)-**12**: A colorless oil; TLC R_f=0.32 (hexane/EtOAc=1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.24 (10H, m), 4.25–4.16 (2H, m), 3.95 (1H, ddd, *J*=2.6, 2.6, 10.2 Hz), 3.78–3.49 (4H, m), 2.17–2.00 (2H, m), 1.37 (3H, d, *J*=10.9 Hz), 1.25 (3H, t, *J*=7.1 Hz), 1.23–1.16 (2H, m), 1.14 (3H, t, *J*=7.1 Hz), 1.08 (3H, t, *J*=7.1 Hz), 1.01–0.95 (2H, m), 0.83 (3H, t, *J*=7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.6 (d, J_{PC}=2.8 Hz), 136.1–127.9 (aromatic), 102.1 (d, J_{PC}=133.5 Hz), 63.8 (d, J_{PC}=95.8 Hz), 61.9 (d, J_{PC}=7.3 Hz), 57.8 (d, J_{PC}=6.4 Hz), 57.7 (d, J_{PC}=4.8 Hz), 30.2, 29.4 (d, J_{PC}=12.9 Hz), 22.5, 21.0 (d, J_{PC}=12.1 Hz), 16.7 (d, J_{PC}=4.9 Hz), 15.5, 15.2, 13.9; ^{31}P NMR (162 MHz, $CDCl_3$) δ 43.16; IR (neat) 1618, 1155, 1034 cm^{-1}; MS *m*/*z* 460 (MH^+). HRMS calcd for $C_{26}H_{38}NO_4P$ (MH^+): 460.2617. Found: 460.2620.

4.3.5. (1*R,*R*$_P$*)- and (1*S**,*R*$_P$*)-Ethyl 1,1-diethoxyethyl{1-[(diphenylmethylene)amino]-2-methylpropyl}phosphinate ((*R**,*R*$_P$*)-13 and (*S**,*R*$_P$*)-13).** These compounds were prepared from **4** (200 mg, 0.5 mmol), 1.0 M THF solution of LHMDS (0.75 mL, 0.75 mmol), and *iso*-propyl iodide (100 μL, 1.0 mmol) in an analogous manner to that for (*R**,*R*$_P$*)-**12**. Purification of the residue by column chromatography (hexane/EtOAc=5:1 to 1:1) gave a mixture of (*R**,*R*$_P$*)-**13** and (*S**,*R*$_P$*)-**13** (104 mg, 47%). Analytical samples of individual isomers were obtained upon re-purification by preparative HPLC ($CHCl_3$/MeOH=50:1).

(*R**,*R*$_P$*)-**13**: A colorless oil; TLC R_f=0.37 (hexane/EtOAc=1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64–7.26 (10H, m), 4.29–4.13 (2H, m), 3.82–3.60 (4H, m), 3.70 (1H, dd, *J*=3.5, 3.5 Hz), 2.64–2.54 (1H, m), 1.52 (3H, d, *J*=11.0 Hz), 1.31 (3H, t, *J*=7.1 Hz), 1.16 (3H, t, *J*=6.9 Hz), 1.14 (3H, t, *J*=7.0 Hz), 1.04 (3H, d, *J*=6.7 Hz), 0.92 (3H, d, *J*=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.9 (d, J_{PC}=2.9 Hz), 135.8–127.9 (aromatic), 102.0 (d, J_{PC}=134.0 Hz), 68.9 (d, J_{PC}=94.4 Hz), 61.6 (d, J_{PC}=7.4 Hz), 57.8 (d, J_{PC}=4.6 Hz), 57.7 (d, J_{PC}=6.9 Hz), 30.2, 21.7 (d, J_{PC}=8.9 Hz), 20.8 (d, J_{PC}=12.3 Hz), 19.4 (d, J_{PC}=6.4 Hz), 16.7 (d, J_{PC}=5.1 Hz), 15.5, 15.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ 42.63; IR (neat) 1616, 1155, 1034 cm^{-1}; MS *m*/*z* 446 (MH^+). HRMS calcd for $C_{25}H_{37}NO_4P$ (MH^+): 446.2460. Found: 446.2479.

(*S**,*R*$_P$*)-**13**: A colorless oil; TLC R_f=0.37 (hexane/EtOAc=1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.26 (10H, m), 4.25–4.16 (2H, m), 3.87 (1H, dd, *J*=3.1, 3.1 Hz), 3.78–3.50 (4H, m), 2.64–2.54 (1H, m), 1.36 (3H, d, *J*=12.8 Hz), 1.25 (3H, t, *J*=6.9 Hz), 1.24 (3H, d, *J*=6.1 Hz), 1.12 (3H, t, *J*=7.0 Hz), 1.04 (3H, t, *J*=7.1 Hz), 0.82 (3H, d, *J*=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.8 (d, J_{PC}=2.8 Hz), 136.0–127.9 (aromatic), 101.9 (d, J_{PC}=134.9 Hz), 66.2 (d, J_{PC}=93.8 Hz), 61.7 (d, J_{PC}=7.3 Hz), 58.4 (d, J_{PC}=3.9 Hz), 57.2 (d, J_{PC}=7.6 Hz), 30.3, 22.2 (d, J_{PC}=12.8 Hz), 20.6 (d, J_{PC}=12.1 Hz), 18.5 (d, J_{PC}=3.1 Hz), 16.8 (d, J_{PC}=4.9 Hz), 15.4, 15.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ 43.14; IR (neat) 1616, 1153, 1034 cm^{-1}; MS *m*/*z* 446 (MH^+). HRMS calcd for $C_{25}H_{37}NO_4P$ (MH^+): 446.2460. Found: 446.2457.

4.3.6. (1*R,*R*$_P$*)- and (1*S**,*R*$_P$*)-Ethyl 1,1-diethoxyethyl{1-[(diphenylmethylene)amino]-3-methylbutyl}phosphinate ((*R**,*R*$_P$*)-14 and (*S**,*R*$_P$*)-14).** These compounds were prepared from **4** (200 mg, 0.5 mmol), 1.0 M THF solution of LHMDS (0.75 mL, 0.75 mmol), and *iso*-butyl iodide (0.29 mL, 2.5 mmol) in an analogous manner to that for (*R**,*R*$_P$*)-**12**. Purification of the residue by flash column chromatography ($CHCl_3$) gave a mixture of (*R**,*R*$_P$*)-**14** and (*S**,*R*$_P$*)-**14** (162 mg, 71%). Analytical samples of individual isomers were obtained upon re-purification by flash column chromatography (hexane/EtOAc=5:1 to 2:1).

(*R**,*R*$_P$*)-**14**: A pale yellow oil; TLC R_f=0.33 (hexane/EtOAc=1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01–7.12 (10H, m), 4.18–4.02 (2H, m), 3.90 (1H, ddd, *J*=2.5, 9.8, 9.8 Hz), 3.60–3.44 (4H, m), 1.92–1.85 (2H, m), 1.80–1.71 (1H, m), 1.44 (3H, d, *J*=11.0 Hz), 1.20 (3H, t, *J*=7.1 Hz), 1.04 (3H, t, *J*=7.0 Hz), 0.99 (3H, t, *J*=7.1 Hz), 0.71 (3H, d, *J*=6.6 Hz), 0.38 (3H, d, *J*=6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.7, 130.0–127.9 (aromatic), 102.2 (d, J_{PC}=134.2 Hz), 62.2 (d, J_{PC}=94.9 Hz), 62.0 (d, J_{PC}=7.3 Hz), 57.8 (d, J_{PC}=6.4 Hz), 57.7 (d, J_{PC}=4.8 Hz), 39.8, 24.8 (d, J_{PC}=12.6 Hz), 23.7, 21.3, 20.6 (d, J_{PC}=12.1 Hz), 16.7 (d, J_{PC}=5.0 Hz), 15.5, 15.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ 43.15; IR (neat) 1618, 1155, 1034 cm^{-1}; MS *m*/*z* 460 (MH^+). HRMS calcd for $C_{26}H_{39}NO_4P$ (MH^+): 460.2617. Found: 460.2641.

4.3.7. Ethyl 3,3-diphenylpropyl(1,1-diethoxyethyl)phosphinate (15). To a stirred suspension of 60% NaH (420 mg,

10.5 mmol) in DMF (25 mL) was added a solution of **1** (2.19 g, 10.0 mmol) in THF (10 mL). After stirring for 1 h at 0 °C, stirring was continued for 3 h at room temperature. To the mixture was added a solution of 3,3-diphenylpropyl bromide (4.19 g, 15 mmol) in THF (15 mL) at 0 °C and stirred for 12 h at room temperature. The mixture was poured into H_2O and extracted with Et_2O. The combined extracts were washed with brine and dried over $MgSO_4$. Removal of the solvent gave a residue, which was purified by flash column chromatography ($CHCl_3$) to give **15** (2.32 g, 57%). A colorless oil; TLC R_f=0.33 (hexane/EtOAc=1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.16 (10H, m), 4.29–4.10 (2H, m), 3.93 (1H, t, J=7.9 Hz), 3.80–3.56 (4H, m), 2.52–2.34 (2H, m), 1.80–1.55 (2H, m), 1.42 (3H, d, J=11.1 Hz), 1.30 (3H, t, J=7.1 Hz), 1.17 (3H, t, J=6.8 Hz), 1.15 (3H, t, J=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9 (d, J_{PC}= 17.3 Hz), 128.4–126.2 (aromatic), 101.1 (d, J_{PC}=138.1 Hz), 61.3 (d, J_{PC}=6.7 Hz), 57.9 (d, J_{PC}=4.7 Hz), 57.4 (d, J_{PC}=7.0 Hz), 52.0 (d, J_{PC}=14.4 Hz), 26.9 (d, J_{PC}=3.9 Hz), 24.2 (d, J_{PC}=86.3 Hz), 20.4 (d, J_{PC}=12.4 Hz), 16.6 (d, J_{PC}=5.3 Hz), 15.4, 15.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ 50.09; IR (neat) 1158, 1038 cm^{-1}; MS *m/z* 405 (MH^+). HRMS calcd for $C_{23}H_{34}O_4P$ (MH^+): 405.2195. Found: 405.2181.

4.3.8. (1*R,R_P*)- and (1*S**,R_P*)-Ethyl 1-benzyl-3,3-diphenylpropyl(1,1-diethoxyethyl)phosphinate ((*R**,R_P*)-16 and (*S**,R_P*)-16).** These compounds were prepared from **15** (210 mg, 0.49 mmol), 1.0 M THF solution of LHMDS (0.74 mL, 0.74 mmol), and benzyl bromide (0.12 mL, 0.98 mmol) in an analogous manner to that for (*R**,R_P*)-**12**. Purification of the residue by flash column chromatography (hexane/EtOAc=4:1 to 1:1) gave a mixture of (*R**,R_P*)-**16** and (*S**,R_P*)-**16** (108 mg, 45%) in a ratio of 1:1. A colorless oil; TLC R_f=0.30 (hexane/EtOAc=1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–6.77 (15H, m), 4.36–4.06 (2H, m), 4.03–3.95 (0.5H, m), 3.92–3.88 (0.5H, m), 3.79–3.57 (4H, m), 3.49–3.43 (0.5H, m), 3.40–3.34 (0.5H, m), 2.83–2.57 (2H, m), 2.18–2.03 (2H, m), 1.45 (1.5H, d, J=10.9 Hz), 1.38 (1.5H, t, J=7.1 Hz), 1.37 (3H, d, J=11.3 Hz), 1.28–1.13 (7.5H, m); ^{31}P NMR (162 MHz, $CDCl_3$) δ 49.89, 48.88; IR (neat) 1153, 1035 cm^{-1}; MS *m/z* 495 (MH^+). HRMS calcd for $C_{30}H_{40}O_4P$ (MH^+): 495.2640. Found: 495.2645.

4.3.9. (1*R,R_P*)-Ethyl 1-{[(4-methylphenyl)sulfonyl]-amino}-2-phenylethylphosphinate (18).** To a solution of (*R**,R_P*)-**8** (60 mg, 0.12 mmol) in CH_2Cl_2 (0.4 mL) was added EtOH (50 μL) and TMSCl (32 μL, 0.24 mmol) at room temperature. After stirring for 2.5 h at the same temperature, the mixture was concentrated to give a residue, which was purified by flash column chromatography ($CHCl_3$/MeOH=40:1 to 20:1) to give **18** (37 mg, 83%). Colorless crystals; mp 121–124 °C; TLC R_f=0.28 ($CHCl_3$/MeOH=20:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–7.02 (9H, m), 7.12 (1H, d, J=570.7 Hz), 4.12–4.06 (2H, m), 3.74 (1H, ddd, J=5.7, 9.0, 16.5 Hz), 3.04 (1H, ddd, J=5.6, 9.5, 14.6 Hz), 2.89 (1H, ddd, J=9.3, 12.0, 14.1 Hz), 2.37 (3H, s), 1.30 (3H, t, J=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2, 137.2, 135.5, 129.6–126.4 (aromatic), 63.3 (d, J_{PC}=7.4 Hz), 53.5 (d, J_{PC}=109.3 Hz), 33.1, 21.5, 16.1 (d, J_{PC}=5.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 34.83; IR (KBr) 3087, 1331, 1161, 1043 cm^{-1}; MS *m/z* 368 (MH^+). HRMS calcd for $C_{17}H_{23}NO_4PS$ (MH^+): 368.1085. Found: 368.1080.

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References and notes

1. (a) Martin, M. T.; Angeles, T. S.; Sugasawara, R.; Aman, N. I.; Napper, A. D.; Darsley, M. J.; Sanchez, R. I.; Booth, P.; Titmas, R. C. *J. Am. Chem. Soc.* **1994**, *116*, 6508; (b) Li, T.; Janda, K. D. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2001.
2. *Aminophosphonic and Aminophosphinic Acids: Chemistry and Biological Activity*; Kukhar, V. P., Hudson, H. R., Eds.; Wiley: Chichester, UK, 2000.
3. For a review, see: Collinsová, M.; Jirácek, J. *Curr. Med. Chem.* **2000**, *7*, 629.
4. For selected examples: (a) Matziari, M.; Georgiadis, D.; Dive, V.; Yiotakis, A. *Org. Lett.* **2001**, *3*, 659; (b) Cristau, H.-J.; Coulombeeau, A.; Genevois-Borella, A.; Sanchez, F.; Pirat, J.-L. *J. Organomet. Chem.* **2002**, *643–644*, 381; (c) Liu, X.; Hu, X. E.; Tian, X.; Mazur, A.; Ebetino, F. H. *J. Organomet. Chem.* **2002**, *646*, 212.
5. Baylis, E. K.; Campbell, C. D.; Dingwall, J. G. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2845.
6. (a) Jiao, X.-Y.; Verbruggen, C.; Borloo, M.; Bollaert, W.; Groot, A. D.; Dommisse, R.; Haemers, A. *Synthesis* **1994**, 23; (b) Boyd, E. A.; Chan, W. C.; Loh, V. M., Jr. *Tetrahedron Lett.* **1996**, *37*, 1647.
7. McCleery, P. P.; Tuck, B. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1319.
8. (a) Baylis, E. K. *Tetrahedron Lett.* **1995**, *36*, 9385; (b) Froestl, W.; Mickel, S. J.; Hall, R. G.; Sprecher, G.; Strub, D.; Baumann, P. A.; Brugger, F.; Gentsch, C.; Jaekel, J.; Olpe, H.-R.; Rihs, G.; Vassout, A.; Waldmeier, P. C.; Bittiger, H. *J. Med. Chem.* **1995**, *38*, 3297.
9. Hoppe, D.; Beckmann, L. *Liebigs Ann. Chem.* **1979**, 2066.
10. (a) Denmark, S. E.; Chen, C.-T. *J. Org. Chem.* **1994**, *59*, 2922; (b) Denmark, S. E.; Chen, C.-T. *J. Am. Chem. Soc.* **1995**, *117*, 11879.
11. (a) Hanessian, S.; Bennani, Y. L.; Delome, D. *Tetrahedron Lett.* **1990**, *31*, 6461; (b) Hanessian, S.; Bennani, Y. L. *Tetrahedron Lett.* **1990**, *31*, 6465; (c) Hanessian, S.; Bennani, Y. L.; Hervé, Y. *Synlett* **1993**, 35.
12. Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G. L.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Spagna, R. *J. Appl. Crystallogr.* **1999**, *32*, 115.
13. Sheldrick, G. M. *SHELXL97, Program for the Refinement of Crystal Structures*; University of Göttingen: Göttingen, Germany, 1997.

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Asymmetric cycloaddition reactions between 2-benzopyrylium-4-olates and 3-(2-alkenoyl)-2-oxazolidinones in the presence of 2,6-bis(oxazolinyl)pyridine-lanthanoid complexes

Hiroyuki Suga,* Tomohiro Suzuki, Kei Inoue and Akikazu Kakehi

Department of Chemistry and Material Engineering, Faculty of Engineering, Shinshu University, Wakasato, Nagano 380-8553, Japan

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Abstract—Highly enantioselective (96% ee) and *endo*-selective (>99:1) cycloaddition reactions were observed between carbonyl ylides, generated from *o*-(*p*-bromobenzyloxy)carbonyl-α-diazoacetophenone, and 3-crotonoyl-2-oxazolidinone using (4*S*,5*S*)-Pybox-4,5-Ph_2-Yb$(OTf)_3$ (20 mol %) as the chiral Lewis acid catalyst. In contrast, high *exo*-selectivity (*exo*/*endo*=82:18; 96% ee, *exo*) was observed for the reaction of *o*-methoxycarbonyl-α-diazoacetophenone with 3-acryloyl-2-oxazolidinone under similar conditions as reported previously. In the case of cycloaddition reactions between 2-benzopyrylium-4-olate, generated from *o*-methoxycarbonyl-α-diazoacetophenone, and 3-cinnamoyl- or 3-[(*E*)-3-(ethoxycarbonyl)propenoyl]-2-oxazolidinones, using the same chiral Lewis acid, the reaction favored the *endo*-adduct with relatively good enantioselectivity (72 and 78% ee, respectively).

1. Introduction

The 1,3-dipolar cycloaddition reactions between 1,3-dipoles and dipolarophiles have proven to be an efficient and popular procedure in the synthesis of biologically important five-membered heterocyclic compounds, with construction of up to four stereocenters in one concerted process.[1] Accordingly, several examples of highly enantioselective chiral Lewis acid-catalyzed asymmetric cycloaddition reactions of 1,3-dipoles such as nitrones,[2] nitrile oxides,[3] nitrile imines,[4] and diazo alkanes[5] have been developed over the last decade. We have previously reported on the efficient asymmetric induction observed for cycloaddition reactions between a carbonyl ylide, generated from *o*-methoxycarbonyl-α-diazoacetophenone (**1**) via an intramolecular carbenoid–carbonyl reaction, and benzyloxyacetaldehyde derivatives, α-ketobenzyl ester derivatives, and 3-acryloyl-2-oxazolidinone, in the presence of chiral 2,6-bis(oxazolinyl)pyridine (Pybox)-rare earth metal complexes as the Lewis acid catalysts (Scheme 1).[6] From a synthetic point of view, it is valuable to investigate the scope of substrates for the asymmetric cycloadditions of carbonyl ylides[8] toward the preparation of naturally occurring optically active oxabicyclic compounds and their derivatives via tandem intramolecular carbenoid–carbonyl cyclization–cycloaddition sequence.[1a,7] Although various carbonyl dipolarophiles, which can be coordinated in bidentate fashion, have exhibited high enantioselectivities, only 3-acryloyl-2-oxazlidinone (**4a**) has been investigated as an olefinic dipolarophile. To elucidate the scope and limitations of cycloadditions that involve olefinic dipolarophiles, we undertook studies to investigate the reactions of *o*-alkoxycarbonyl-α-diazoacetophenones with 3-crotonoyl-, 3-(2-pentenoyl)-, 3-cinnamoyl-, and 3-[(*E*)-3-(ethoxycarbonyl)propenoyl]-2-oxazolidinones. In this paper, we present our findings on the highly *endo*-selective,[9] with modest to relatively good enantioselectivities, reactions between 1-methoxy-2-benzopyrylium-4-olate and the above 3-(2-alkenoyl)-2-oxazolidinones, in the presence of chiral Pybox-lanthanoid triflate complexes. In contrast, a cycloaddition that involves 3-acryloyl-2-oxazolidinone (**4a**) exhibited high *exo*-selectivity[9] with high enantioselectivity of *exo*-adduct as reported previously.[6] Moreover, high enantioselectivity along with extremely high *endo*-selectivity has been found to obtain for a reaction between *o*-(*p*-bromobenzyloxy)carbonyl-α-diazoacetophenone (**3**) and 3-crotonoyl-2-oxazolidinone using (4*S*,5*S*)-Pybox-4,5-Ph_2-Yb$(OTf)_3$ as a chiral Lewis acid catalyst.

2. Results and discussion

Previous studies have shown that, in addition to the presence of achiral Lewis acids, the ionic radius of the rare earth metal triflates can influence the diastereoselectivity of the

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* Corresponding author. Tel.: +81 26 269 5392; fax: +81 26 269 5424; e-mail: sugahio@shinshu-u.ac.jp

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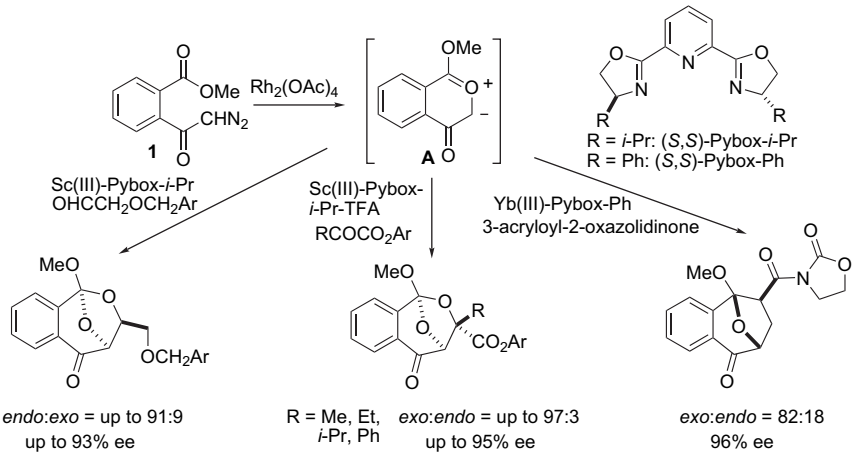


Scheme 1. Asymmetric cycloaddition reactions of 2-benzopyrylium-4-olate catalyzed by chiral Pybox-rare earth metal complexes.

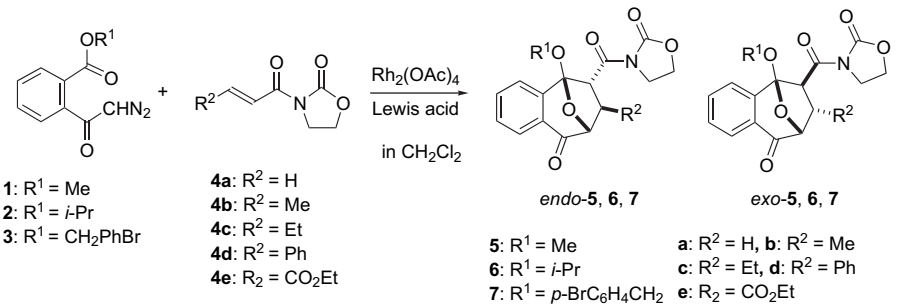
cycloaddition reaction between 1-methoxy-2-benzopyrylium-4-olate (**A**) and 3-acryloyl-2-oxazolidinone (**4a**).[10] To determine whether a similar relationship exist for 3-crotonoyl-2-oxazolidinone (**4b**),[10] the cycloaddition reaction was carried out using several rare earth metal triflates (10 mol %), which involved the slow addition (over a period of 1 h) of a solution of *o*-methoxycarbonyl-α-diazoacetophenone (**1**) to oxazolidinone **4b** (2 equiv) under $Rh_2(OAc)_4$-catalyzed conditions in CH_2Cl_2 at room temperature (Table 1, entries 4 and 5). In the case of $Yb(OTf)_3$ (10 mol %), the presence of the Lewis acid catalyst resulted in only a slight increase of the *exo*-adduct (entry 5 vs 3); significant differences in the diastereoselectivities were not observed. In contrast, the cycloaddition reaction of 3-acryloyl-2-oxazolidinone (**4a**) in the presence of $Yb(OTf)_3$ exhibited a drastic difference in the diastereoselectivities (entry 2 vs 1).[10] Extending the addition time (from 1 to 6 h) of diazocarbonyl substrate **1** slightly increased the *exo*-adduct and resulted in a practically nonstereoselective reaction (entry 6). Cycloaddition reactions using various lanthanoid triflates (entries 6–11) revealed that the diastereoselectivity of the reactions is influenced by the ionic radius of the rare earth metal, of which, under the similar conditions, $Tm(OTf)_3$ exhibited the highest *exo*-selectivity (*exo*/*endo*=63:37). The use of lanthanoid triflates with metal having larger ionic radius than that of Tm increased the amount of the *endo*-adducts (entries 8–11). In the case of $La(OTf)_3$, which has the largest ionic radius, the catalyst was moderately *endo*-selective (entry 11).

Table 1. Reactions of α-diazoacetophenone **1** with oxazolidinone **4a** or **4b** in the absence and in the presence of rare earth metal triflates[a]

Entry	R	Olefin	Lewis acid	Ionic radius (Å)[b]	Addition time (h)	Yield (%)	*endo*:*exo*[c]
1[d]	H	**4a**	None	—	1	82	80:20
2[d]	H	**4a**	$Yb(OTf)_3$	0.87	1	88	19:81
3	Me	**4b**	None	—	1	71	83:17
4	Me	**4b**	$Sc(OTf)_3$	0.75	1	33	85:15
5	Me	**4b**	$Yb(OTf)_3$	0.87	1	55	60:40
6	Me	**4b**	$Yb(OTf)_3$	0.87	6	58	48:52
7	Me	**4b**	$Tm(OTf)_3$	0.88	6	70	37:63
8	Me	**4b**	$Er(OTf)_3$	0.89	6	84	39:61
9	Me	**4b**	$Ho(OTf)_3$	0.90	6	75	46:54
10	Me	**4b**	$Eu(OTf)_3$	0.95	6	78	62:38
11	Me	**4b**	$La(OTf)_3$	1.03	6	41	70:30

[a] The reaction was carried out by adding a solution of diazo compound **1** in CH_2Cl_2 over a period of 1 or 6 h to a suspension of the Lewis acid (10 mol %), MS 4 Å, $Rh_2(OAc)_4$ (2 mol %), and oxazolidinone **4a** or **4b** (2 equiv) in CH_2Cl_2.
[b] See Ref. 11.
[c] Determined by ^1H NMR (400 MHz).
[d] Previously reported, see Ref. 10.

Next, the reaction between diazoacetophenone **1** and oxazolidinone **4b** (Scheme 2) was employed to determine the asymmetric induction using chiral Lewis acid catalysts that were prepared from various chiral Pybox ligands (Fig. 1) and rare earth metal triflates. First, the chiral $Yb(OTf)_3$ catalysts involving (*S*,*S*)-Pybox-Ph or (4*S*,5*S*)-Pybox-4,5-Ph_2 were examined under several reaction temperatures (Table 2, entries 2–5 and 11–13). The catalysts were prepared by stirring the corresponding Pybox ligands and $Yb(OTf)_3$ in THF for 2 h at room temperature, then by drying in vacuo for 1 h. The cycloaddition reactions were conducted by adding a solution of **1** in CH_2Cl_2 to a suspension of the catalyst (10 mol %) in CH_2Cl_2 over a period of 6 h. In terms of the reaction temperatures, reflux or room temperature resulted in relatively good yields (entries 2 and 3), whereas lower temperature resulted in decreased yields (entries 4 and 5). Interestingly, high *endo*-selectivity was observed in all cases, which is in contrast to the reaction without Pybox ligand (Table 1, entry 6), and also to the reaction with 3-acryloyl-2-oxazolidinone (**4a**) under similar conditions (Table 2, entry 1).[6] The difference in the diastereoselectivities of the oxazolidinones **4b** and **4a** reactions using the chiral Yb(III) catalyst can be attributed to dissimilar stabilities of the *endo*- and *exo*-products, which would also govern the character of the corresponding transition states. Although the energy differences may seem minor, simple calculations of the heats of formation by a semi-empirical PM3 method reveal that *endo*-**5b** is more stable than *exo*-**5b** by 1.38 kcal/mol, whereas *exo*-**5a** is more stable than *endo*-**5a** by 3.12 kcal/mol. The higher *endo*-selectivity of the Pybox-$Yb(OTf)_3$ catalyst is attributable to the larger chiral Yb(III) complex, relative to those of achiral lanthanoid triflates, and the increased steric repulsion between the methoxy and the coordinated oxazolidinone moieties during the transition state leads to *exo*-**5b**. The enantioselectivities of *endo*-**5b**, however, were unsatisfactory.



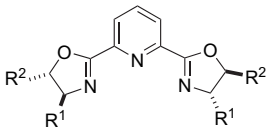
1: R^1 = Me
2: R^1 = *i*-Pr
3: R^1 = CH_2PhBr

4a: R^2 = H
4b: R^2 = Me
4c: R^2 = Et
4d: R^2 = Ph
4e: R_2 = CO_2Et

5: R^1 = Me
6: R^1 = *i*-Pr
7: R^1 = *p*-$BrC_6H_4CH_2$

a: R^2 = H, **b**: R^2 = Me
c: R^2 = Et, **d**: R^2 = Ph
e: R_2 = CO_2Et

Scheme 2. Reactions of diazoacetophenones **1**, **2**, and **3** with 2-oxazolidinone **4a**–**e**.



R^1 = Ph, R^2 = H : (*S*,*S*)-Pybox-Ph
R^1 = Ph, R^2 = Ph : (4*S*,5*S*)-Pybox-4,5-Ph_2

Figure 1. Structures of chiral Pybox ligands.

Effects of the ionic radius on the enantio- and diastereoselectivities of chiral catalysts were examined using several lanthanoid triflates (entries 6–10 and 14–18). Although high enantioselectivity was observed for the minor *exo*-adduct in several cases, especially those utilizing (4*S*,5*S*)-Pybox-4,5-Ph_2 as the chiral ligand (entries 11, 14, and 16), the enantioselectivity of the *endo*-adduct did not improved significantly. Our studies show that the enantioselectivities are somewhat affected by the ionic radius of the metal triflate, and sense of asymmetric induction was switched between Ho and Er when Pybox-Ph was used as a chiral ligand (entries 8 and 9). Improved enantioselectivity of the *endo*-adduct was obtained using the (*S*,*S*)-Pybox-Ph-$Tm(OTf)_3$ catalyst, unfortunately, the enantioselectivity was not reproducible with several runs (entry 6). In contrast to the behavior of the bare lanthanoid triflates (without the Pybox ligands), it is interesting that the ionic radius of the metal complexes did not influence the diastereoselectivity when Pybox-lanthanoid triflates were used as catalysts.

The influence of the alkoxy substituent (OR^1) of the diazo substrate (Scheme 2) on the enantio- and diastereoselectivities was investigated. Reactions using diazo substrates **2** and **3**, which contain isopropyl ester and *p*-bromobenzyl ester, respectively, were carried out in the presence of chiral catalysts that involve (*S*,*S*)-Pybox-Ph or (4*S*,5*S*)-Pybox-4,5-Ph_2 with $Yb(OTf)_3$ or $Tm(OTf)_3$ (Table 3). In the case of (4*S*,5*S*)-Pybox-4,5-Ph_2-$Yb(OTf)_3$-catalyzed reaction of diazo substrate **2** (isopropyl ester), both the yield of the adducts and the enantioselectivity of major *endo*-cycloadduct were considerably less than that of substrate **1** (methyl ester) (entry 1). The reaction of substrate **3** (*p*-bromobenzyl ester), however, was promising in terms of enantioselectivity and extremely high *endo*-selectivity. Thus, in the cases of $Yb(OTf)_3$ with chiral ligand (*S*,*S*)-Pybox-Ph or (4*S*,5*S*)-Pybox-4,5-Ph_2, the catalyzed (10 mol %) reaction afforded only *endo*-cycloadduct as the sole product with over 80% ee (entries 2 and 4). Moreover, increasing the catalyst to

Table 2. Reactions of diazoacetophenone **1** with oxazolidinone **4b** in the presence of chiral Pybox-lanthanoid complexes[a]

Entry	4	Pybox	$M(OTf)_3$	IR (Å)[b]	Temp	Yield (%)	*endo*:*exo*[c]	% ee[d] (*endo*)	% ee[d] (*exo*)
1[e]	**4a**	Ph	$Yb(OTf)_3$	0.87	−10	94	18:82	8	96
2	**4b**	Ph	$Yb(OTf)_3$	0.87	Reflux	65	97:3	30	52
3	**4b**	Ph	$Yb(OTf)_3$	0.87	rt	71	99:1	28	20
4	**4b**	Ph	$Yb(OTf)_3$	0.87	−10	18	97:3	38	52
5	**4b**	Ph	$Yb(OTf)_3$	0.87	−25	5	97:3	30	52
6	**4b**	Ph	$Tm(OTf)_3$	0.88	rt	81–68	95:5 to 93:7	74–26	10–4
7	**4b**	Ph	$Er(OTf)_3$	0.89	rt	53	96:4	18	20
8	**4b**	Ph	$Ho(OTf)_3$	0.90	rt	50	95:5	22	20
9	**4b**	Ph	$Eu(OTf)_3$	0.95	rt	88	97:3	−8	38
10	**4b**	Ph	$La(OTf)_3$	1.03	rt	34	90:10	−24	36
11	**4b**	4,5-Ph_2	$Yb(OTf)_3$	0.87	Reflux	79	97:3	50	>99
12	**4b**	4,5-Ph_2	$Yb(OTf)_3$	0.87	rt	67	92:8	40	16
13	**4b**	4,5-Ph_2	$Yb(OTf)_3$	0.87	−10	8	94:6	44	42
14	**4b**	4,5-Ph_2	$Tm(OTf)_3$	0.88	rt	50	96:4	40	>99
15	**4b**	4,5-Ph_2	$Er(OTf)_3$	0.89	rt	59	97:3	42	76
16	**4b**	4,5-Ph_2	$Ho(OTf)_3$	0.90	rt	57	96:4	52	90
17	**4b**	4,5-Ph_2	$Eu(OTf)_3$	0.95	rt	96	98:2	24	50
18	**4b**	4,5-Ph_2	$La(OTf)_3$	1.03	rt	83	90:10	8	16

[a] The reaction was carried out by adding a solution of diazo compound **1** in CH_2Cl_2 over a period of 6 h to a suspension of the chiral catalyst (10 mol %), MS 4 Å, $Rh_2(OAc)_4$ (2 mol %), and **4a** or **4b** (2 equiv) in CH_2Cl_2.
[b] See Ref. 11.
[c] Determined by ^1H NMR analysis (400 MHz).
[d] Determined by HPLC analysis (Daicel Chiralpak AD-H).
[e] Previously reported, see Ref. 6.

Table 3. Reactions of diazoacetophenones **2** or **3** with oxazolidinone **4b** in the presence of chiral Pybox-lanthanoid complexes[a]

Entry	Diazo substrate	R^1	Pybox	$M(OTf)_3$	mol %	Yield (%)	*endo*:*exo*[b]	% ee[c] (*endo*)
1	**2**	*i*-Pr	4,5-Ph_2	$Yb(OTf)_3$	10	39	89:11[d]	8
2	**3**	*p*-$BrC_6H_4CH_2$	Ph	$Yb(OTf)_3$	10	40	>99:1	84
3	**3**	*p*-$BrC_6H_4CH_2$	Ph	$Tm(OTf)_3$	10	51	>99:1	72
4	**3**	*p*-$BrC_6H_4CH_2$	4,5-Ph_2	$Yb(OTf)_3$	10	57	>99:1	81
5	**3**	*p*-$BrC_6H_4CH_2$	4,5-Ph_2	$Yb(OTf)_3$	20	60	>99:1	96
6	**3**	*p*-$BrC_6H_4CH_2$	4,5-Ph_2	$Yb(OTf)_3$	30	25	>99:1	92

[a] The reaction was carried out at room temperature by adding a solution of diazo substrate **2** or **3** in CH_2Cl_2 over a period of 6 h to a suspension of the chiral catalyst (10 mol %), MS 4 Å, $Rh_2(OAc)_4$ (2 mol %), and **4b** (2 equiv) in CH_2Cl_2.
[b] Determined by ^1H NMR analysis (400 MHz).
[c] Determined by HPLC analysis (Daicel Chiralpak IA).
[d] Calculated from yields.

20 mol % in (4*S*,5*S*)-Pybox-4,5-Ph_2-$Yb(OTf)_3$-catalyzed reaction increased the enantioselectivity to 96% ee (entry 5). Although the absolute configuration of the *endo*-adduct has yet to be determined, the enantio-facial selection is probably similar to that reported by Desimoni in the Mukaiyama–Michael reaction between 2-trimethylsilyloxyfuran and 3-crotonoyl-2-oxazolidinone, which is catalyzed by a chiral Pybox-4,5-Ph_2–$La(OTf)_3$ complex (shown as tetrahydrate by X-ray analysis).[12] According to the proposed structure of the (4*S*,5*S*)-Pybox-4,5-Ph_2-$La(OTf)_3$-3-crotonoyl-2-oxazolidinone complex, the carbonyl ylide presumably approaches from the *re*-face of 3-crotonoyl-2-oxazolidinone with *endo*-orientation.

As shown in Scheme 2, cycloadditions between 3-(2-pentenoyl)- (**4c**), 3-cinnamoyl- (**4d**), or 3-[(*E*)-3-(ethoxycarbonyl)-propenoyl]-2-oxazolidinones (**4e**) and diazoacetophenone **1** or **3**, as the diazo substrates, were carried out using (*S*,*S*)-Pybox-Ph- or (4*S*,5*S*)-Pybox-4,5-Ph_2-$Yb(OTf)_3$ as the catalyst. With the exception of the reaction between **4e** and **3**, the reactions favored the *endo*-cycloadduct, which was similar to that of **4b**. In the case of **1** and oxazolidinone **4c**, the reaction exhibited high *endo*-selectivity but moderate enantioselectivity, which did not substantially improve by increasing the catalyst load (Table 4, entries 1–3). Unfortunately, the reaction between **3** and **4c** at room temperature in the presence of (4*S*,5*S*)-Pybox-4,5-Ph_2-$Yb(OTf)_3$ (10 mol %) did not occur, presumably due to the low reactivity of **4c** as a dipolarophile. Despite the sluggish reaction of oxazolidine **4d**, which required reflux conditions (CH_2Cl_2) to drive the cycloaddition, even with **1** as a carbonyl ylide precursor, relatively good enantioselectivity with high *endo*-selectivity was obtained (entry 4). The reaction between **1** and olefinic dipolarophile **4e** afforded relatively good enantioselectivity of the *endo*-cycloadduct (entries 5–7). It is interesting to note that the diastereoselectivity improved as the catalyst was increased from 10 to 30%. Surprisingly, in contrast to the cycloaddition reactions, which have been described to this point, the reaction between diazoacetophenone **3** and oxazolidinone **4e** in the presence of (4*S*,5*S*)-Pybox-4,5-Ph_2-$Yb(OTf)_3$ (10 and 20 mol %) afforded only the opposite regioisomer with an *exo*-configuration (*exo*-**7e′**).[9] The regiochemistry of *exo*-**7e′** was determined by comparing the chemical shifts of the methine protons (H-6, H-7, and H-8) of the epoxy-bridged bicyclic ring with those of cycloadducts *endo*-**5b**, *endo*-**7b**, and *endo*-**5e** (Fig. 2). In contrast to the comparable chemical shifts of *endo*-**5b** and *endo*-**7b**, the chemical shifts of *endo*-**5e** and *exo*-**7e′** were drastically dissimilar. Coupling constants between the methine protons (H-6, H-7, and H-8) of the four cycloadducts were comparable. These ^1H NMR data suggest that *endo*-**5b** and *endo*-**7b** share the same regio- and stereochemistries, whereas *endo*-**5e** and *exo*-**7e′** have similar stereo-, but different regiochemistries. In comparison to the other cycloadducts, the upfield shift of H-6 for cycloadduct *exo*-**7e′** indicates substitution of the ethoxycarbonyl group at C-6. Furthermore, NOEs were observed between H-6 and the benzyl methylene, and between H-6 and H-8. Based on these NMR studies, *exo*-**7e′** was determined to have the opposite regiochemistry of *endo*-**5b**, *endo*-**7b**, and *endo*-**5e**. Although the switch in the regioselectivity remains unclear, it is important to note such reactions that exhibit high regio- and diastereoselectivities with moderate enantioselectivity.

Table 4. Reactions of diazoacetophenone **1** or **3** with oxazolidinone **4c**–**4e** in the presence of chiral Pybox-$Yb(OTf)_3$ complexes[a]

Entry	Diazo substrate	Oxazolidinone	Pybox	mol %	Temp (°C)	Yield (%)	*endo*:*exo*[b]	% ee[c] (*endo*)
1	1	**4c**	4,5-Ph_2	10	rt	32	>99:1	30
2	1	**4c**	4,5-Ph_2	20	rt	47	99:1	28
3	1	**4c**	4,5-Ph_2	30	rt	49	98:2	38
4	1	**4d**	Ph	10	Reflux	13	>99:1	72
5	1	**4e**	4,5-Ph_2	10	rt	54	76:24	78
6	1	**4e**	4,5-Ph_2	20	rt	51	83:17	78
7	1	**4e**	4,5-Ph_2	30	rt	55	93:7	68
8	3	**4e**	4,5-Ph_2	10	rt	15[d]	>1:99[e]	56 (*exo*)
9	3	**4e**	4,5-Ph_2	20	Reflux	15[d]	>1:99[e]	66 (*exo*)

[a] The reaction was carried out by adding a solution of diazo compound **1** or **3** in CH_2Cl_2 over a period of 6 h to a suspension of the chiral Yb catalyst (10 mol %), MS 4 Å, $Rh_2(OAc)_4$ (2 mol %), and **4c**–**4e** (2 equiv) in CH_2Cl_2.
[b] Determined by ^1H NMR analysis (400 MHz).
[c] Determined by HPLC analysis (Daicel Chiralpak IA).
[d] Regioisomer *exo*-**7e′** was obtained.
[e] Only *exo*-isomer was obtained.

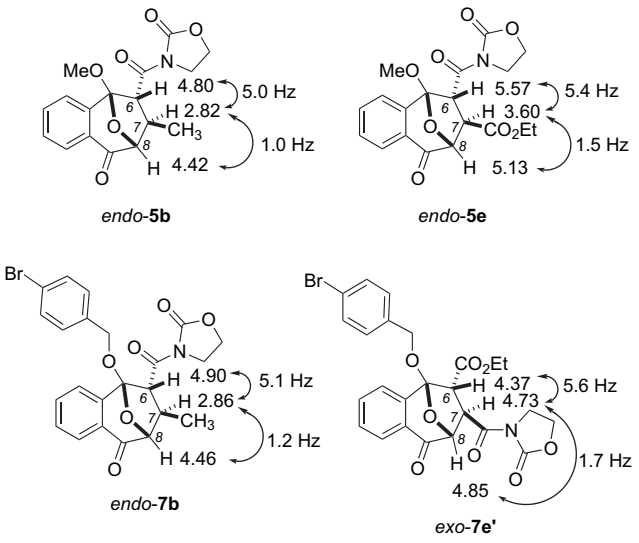


Figure 2. Regiochemistry of cycloadducts.

3. Conclusion

We have found that the cycloaddition reaction between a carbonyl ylide, which was generated from **3**, and 3-crotonoyl-2-oxazolidinone, in the presence of (4*S*,5*S*)-Pybox-4,5-Ph_2-Yb$(OTf)_3$ (20 mol %) as the chiral Lewis acid catalyst, afforded the *endo*-cycloadduct as a sole product (*endo*/*exo*=>99:1) with extremely high enantioselectivity (96% ee). In contrast, the reaction between **1**, as a carbonyl ylide precursor, and 3-acryloyl-2-oxazolidinone, under the similar conditions, exhibited *exo*-selectivity (*exo*/*endo*= 82:18). Although the cycloaddition reactions of **3** with other 3-(2-alkenoyl)-2-oxazolidinones were slow or problematic, the reaction between **1** and 3-cinnamoyl- (**4d**) or 3-[(*E*)-3-(ethoxycarbonyl)propenoyl]-2-oxazolidinones (**4e**), using the same catalyst, exhibited *endo*-selectively with relatively high enantioselectivity (72 and 78% ee, respectively). Studies to expand this methodology of enantioselective cycloaddition to other diazo substrates are currently underway.

4. Experimental

4.1. General

Melting points are uncorrected. IR spectra were obtained using an FT–IR spectrophotometer. ^{1}H NMR spectra were obtained using a 400 MHz instrument; chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (internal standard). ^{13}C NMR spectra were recorded using a 100 MHz instrument with broadband proton decoupling; chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane, with the middle resonance of $CDCl_3$ (77.0 ppm) as the internal standard. Preparative and medium-pressure column chromatography were performed using columns packed with Wakogel C-300HG. All reactions were carried out using dried glass and under an argon atmosphere.

o-Methoxycarbonyl-α-diazoacetophenone (**1**), *o*-isopropoxycarbonyl-α-diazoacetophenone (**2**) and *o*-(*p*-bromobenzyloxy)carbonyl-α-diazoacetophenone (**3**) were prepared by following procedures as described in a previous paper.[13] With the exception of rare earth metal triflates, the commercially available Lewis acids including $Rh_2(OAc)_4$ were used without further purifications. The rare earth metal triflates were individually dried in vacuo in an Schlenk tube at 200 °C for 12 h before use. Commercially available powdered 4 Å molecular sieves (MS 4 Å) were dried in vacuo at 250 °C for 12 h before use. CH_2Cl_2 was purified by distillation, first over $CaCl_2$ and then over CaH_2, under argon.

4.2. General procedures for the reactions of *o*-(alkoxycarbonyl)-α-diazoacetophenones with 3-(2-alkenoyl)-2-oxazolidinones

Typical procedures are exemplified by the asymmetric cycloaddition reaction between **3** and **4b**. To a solution of Yb$(OTf)_3$ (62.2 mg, 0.10 mmol) in THF (2 mL) was added a solution of 2,6-bis[(4*S*,5*S*)-(−)-4,5-diphenyl-2-oxazolin-2-yl]pyridine [(4*S*,5*S*)-Pybox-4,5Ph_2, 52.16 mg, 0.10 mmol] in THF (3.0 mL). After stirring the mixture for 2 h, the solvent was removed in vacuo and the resulting solid was dried in vacuo (<3 mmHg) at room temperature for 1 h. The residue was used as a catalyst without further purification. To a suspension of 3-crotonoyl-2-oxazolidinone (155.2 mg, 1.0 mmol) and 4 Å MS (0.5 g) in CH_2Cl_2 (1 mL) were added a solution of the catalyst prepared above in CH_2Cl_2 (4 mL), followed by $Rh_2(OAc)_4$ (4.4 mg, 0.01 mmol) and CH_2Cl_2 (1 mL), and finally a solution of diazoacetophenone **3** (180.1 mg, 0.5 mmol) in CH_2Cl_2 (5 mL) over a period of 6 h. After removal of 4 Å MS through filtration (Celite), the reaction mixture was further filtered through a plug of silica gel using AcOEt/hexane (1:1, 100 mL) as the eluant. After concentrating the filtrate in vacuo, the resulting residue was purified by column chromatography (AcOEt/hexane 1:4) to provide *endo*-**7b** (116.5 mg, 60%) (*endo*/*exo* >99:1 using ^{1}H NMR, 400 MHz).

4.2.1. 5-*p*-Bromobenzyloxy-7-*exo*-methyl-6-*endo*-(2-oxazolidinoyl)carbonyl-8-oxabenzo[*c*]bicyclo[3.2.1]octan-2-one (*endo*-7b). Pale yellow prisms; mp 205–206 °C; $[\alpha]_D^{25}$ −19.83 (*c* 1.00, $CHCl_3$); 96% ee estimated using chiral HPLC; IR (KBr) 637, 708, 752, 802, 839, 896, 936, 972, 1011, 1069, 1121, 1272, 1340, 1461, 1489, 1546, 1599, 1894, 2371, 2875, 2920, 2977, 2997, 3031, 3057, 3094 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.48 (3H, d, *J*=7.1 Hz), 2.86 (1H, m), 3.44–3.51, 3.80–3.89, 4.29–4.43 (4H, m), 4.46 (1H, d, *J*=1.2 Hz), 4.85 (1H, d, *J*=11.9 Hz), 4.90 (1H, d, *J*=5.1 Hz), 4.95 (1H, d, *J*=11.9 Hz), 7.28–7.36 (2H, m), 7.46–7.50 (2H, m), 7.28–7.34, 7.45–7.57, 8.03–8.08 (4H, m); ^{13}C NMR ($CDCl_3$) δ 20.7 (CH_3), 38.6 (CH), 43.3 (CH_2), 55.9 (CH), 61.9 (CH_2), 65.2 (CH_2), 87.1 (CH), 108.9 (C), 121.4 (C), 122.8 (CH), 126.7 (CH), 129.1 (CH), 129.3 (CH), 130.1 (C), 131.3 (CH), 133.3 (CH), 136.5 (C), 142.1 (C), 152.9 (C), 169.9 (C), 193.5 (C); Mass spectrometry (EI) *m*/*z* 487 (M^++2), 485 (M^+), 400, 382, 356, 332, 316, 298, 270, 254, 229, 214, 201, 187, 171, 155, 133, 117, 104, 90, 76, 63, 37, 13; HRMS (EI) calcd for $C_{23}H_{20}BrNO_6$: 485.0473 (M^+), found: 485.0498. Anal. Calcd for $C_{23}H_{20}BrNO_6$: C, 56.80; H, 4.15; N, 2.88%. Found: C, 57.15; H, 4.17; N, 2.52%.

The enantiomeric excess was determined using chiral HPLC analysis (Daicel Chiralpak IA; hexane/2-PrOH, 4:1 v/v;

UV detection, 254 nm; flow rate, 0.5 mL/min; 35 °C; t_{minor}=42.64 min, t_{major}=35.69 min).

4.2.2. 5-Methoxy-7-*exo*-methyl-6-*endo*-(2-oxazolidinoyl)-carbonyl-8-oxabenzo[*c*]bicyclo[3.2.1]octan-2-one (*endo*-5b). Colorless prisms; mp 181–183 °C; $[\alpha]_D^{25}$ +56.11 (*c* 1.00, $CHCl_3$); *endo*/*exo*=95:5; 74% ee (*endo*) estimated using chiral HPLC; IR (KBr) 708, 758, 1044, 1202, 1252, 1304, 1387, 1458, 1508, 1541, 1653, 1699, 1773, 2361, 2976 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (3H, d, *J*=7.3 Hz), 2.82 (1H, m), 3.40–3.59, 3.75–3.85, 4.30–4.42 (4H, m), 3.60 (3H, s), 4.42 (1H, d, *J*=1.0 Hz), 4.80 (1H, d, *J*=5.0 Hz), 7.2–8.0 (4H, m); ^{13}C NMR ($CDCl_3$) δ 20.6 (CH_3), 38.5 (CH), 43.3 (CH_2), 51.5 (CH_3), 55.0 (CH), 61.8 (CH_2), 86.9 (CH), 109.0 (C), 122.8 (CH), 126.6 (CH), 129.1 (CH), 129.9 (C), 133.2 (CH), 142.2 (C), 152.8 (C), 170.1 (C), 193.6 (C); Mass spectrometry (EI) *m*/*z* 331 (M^+), 299, 271, 244, 216, 187, 163, 133, 105, 69, 41, 14; HRMS (EI) calcd for $C_{17}H_{17}NO_6$: 331.1054 (M^+), found: 331.1028. Anal. Calcd for $C_{17}H_{17}NO_6$: C, 61.63; H, 5.17; N, 4.23%. Found: C, 61.70; H, 5.08; N, 4.24%.

4.2.3. 5-Methoxy-7-*endo*-methyl-6-*exo*-(2-oxazolidinoyl)-carbonyl-8-oxabenzo[*c*]bicyclo[3.2.1]octan-2-one (*exo*-5b). ^1H NMR ($CDCl_3$) δ 0.86 (3H, d, *J*=7.6 Hz), 3.39 (3H, s), 3.60–3.68 (1H, m), 4.00–4.50 (4H, m), 4.15 (1H, d, *J*=5.1 Hz), 4.87 (1H, d, *J*=8.9 Hz), 7.20–8.0 (4H, m). The minor *exo*-adduct was characterized using ^1H NMR; unfortunately, isolation of the *exo*-adduct using column chromatography was unsuccessful.

The enantiomeric excess was determined using chiral HPLC analysis (Daicel Chiralpak AD-H; hexane/2-PrOH, 4:1 v/v; UV detection, 254 nm; flow rate, 0.5 mL/min; 35 °C; t_{minor} (*endo*)=43.83 min, t_{major} (*endo*)=32.51 min, t_{minor} (*exo*)=62.68 min, t_{major} (*exo*)=18.64 min).

4.2.4. 7-*exo*-Ethyl-5-methoxy-6-*endo*-(2-oxazolidinoyl)-carbonyl-8-oxabenzo[*c*]bicyclo[3.2.1]octan-2-one (*endo*-5c). Colorless prisms; mp 122–123 °C; $[\alpha]_D^{25}$ +25.39 (*c* 1.00, $CHCl_3$); 30% ee estimated using chiral HPLC; IR (KBr) 632, 665, 782, 816, 835, 893, 918, 934, 972, 1126, 1166, 1460, 1481, 1512, 1600, 1965, 1989, 2857, 2874, 2931, 2992, 3069, 3376 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (3H, t, *J*=7.3 Hz), 1.72–1.91 (2H, m), 2.59 (1H, m), 3.50–3.60, 3.80–3.90, 4.35–4.42 (4H, m), 3.60 (3H, s), 4.50 (1H, d, *J*=1.5 Hz), 4.86 (1H, d, *J*=5.6 Hz), 7.20–8.10 (4H, m); ^{13}C NMR ($CDCl_3$) δ 12.3 (CH_3), 27.7 (CH_2), 43.3 (CH_2), 45.7 (CH), 51.6 (CH_3), 53.2 (CH), 61.8 (CH_2), 84.9 (CH), 108.6 (C), 122.9 (CH), 126.6 (CH), 129.0 (CH), 130.0 (C), 133.2 (CH), 142.1 (C), 152.9 (C), 170.1 (C), 193.7 (C); Mass spectrometry (EI) *m*/*z* 345 (M^+), 313, 284, 269, 258, 243, 226, 201, 199, 187, 176, 163, 148, 133, 105, 91, 77, 55, 38, 24, 12; HRMS (EI) calcd for $C_{18}H_{19}NO_6$: 345.1211 (M^+), found: 345.1187. Anal. Calcd for $C_{18}H_{19}NO_6$: C, 62.60; H, 5.55; N, 4.06%. Found: C, 62.87; H, 5.50; N, 4.05%.

The enantiomeric excess was determined using chiral HPLC analysis (Daicel Chiralpak IA; hexane/2-PrOH, 4:1 v/v; UV detection, 254 nm; flow rate, 0.5 mL/min; 35 °C; t_{minor}=31.44 min, t_{major}=23.88 min).

4.2.5. 7-*endo*-Ethyl-5-methoxy-6-*exo*-(2-oxazolidinoyl)-carbonyl-8-oxabenzo[*c*]bicyclo[3.2.1]octan-2-one (*exo*-5c). ^1H NMR ($CDCl_3$) δ 0.84 (3H, t, *J*=7.3 Hz), 1.23–1.40 (2H, m), 3.39 (3H, s), 3.64 (1H, m), 4.05–4.24 (4H, m), 4.26 (1H, d, *J*=5.1 Hz), 4.92 (1H, d, *J*=8.8 Hz), 7.20–8.10 (4H, m). The minor *exo*-adduct was characterized using ^1H NMR; unfortunately, isolation of the *exo*-adduct using column chromatography was unsuccessful.

4.2.6. 5-Methoxy-6-*endo*-(2-oxazolidinoyl)carbonyl-7-*exo*-phenyl-8-oxabenzo[*c*]bicyclo[3.2.1]octan-2-one (*endo*-5d). Colorless prisms; mp 210–212 °C; $[\alpha]_D^{25}$ +30.35 (*c* 1.00, $CHCl_3$); 72% ee estimated using chiral HPLC; IR (KBr) 638, 674, 706, 785, 837, 986, 1051, 1077, 1113, 1150, 1161, 1223, 1257, 1299, 1317, 1359, 1388, 1459, 1475, 1520, 1602, 1700, 1780, 2995, 3029, 3060 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.69 (3H, s), 3.90 (1H, dd, *J*=1.7, 6.1 Hz), 4.80 (1H, d, *J*=1.7 Hz), 3.52–3.60, 3.78–3.88, 4.32–4.38 (4H, m), 5.34 (1H, d, *J*=6.1 Hz), 7.32–7.43 (5H, m), 7.26–7.30, 7.50–7.62, 8.08–8.11 (4H, m); ^{13}C NMR ($CDCl_3$) δ 43.6 (CH_2), 48.2 (CH), 53.7 (CH_3), 55.8 (CH), 62.0 (CH_2), 85.6 (CH), 108.6 (C), 124.8 (CH), 126.5 (CH), 127.5 (CH), 128.0 (CH), 128.5 (CH), 129.2 (CH), 131.1 (C), 134.1 (CH), 134.7 (C), 142.7 (C), 153.4 (C), 169.8 (C), 192.7 (C); Mass (EI) *m*/*z* 393 (M^+), 361, 335, 317, 306, 278, 247, 235, 218, 187, 176, 163, 148, 133, 115, 103, 91, 77, 55, 38, 24, 13; HRMS (EI) calcd for $C_{22}H_{19}NO_6$: 393.1211 (M^+), found: 393.1187. Anal. Calcd for $C_{22}H_{19}NO_6$: C, 67.17; H, 4.87; N, 3.56%. Found: C, 67.40; H, 4.80; N, 3.40%.

The enantiomeric excess was determined using chiral HPLC analysis (Daicel Chiralpak IA; hexane/2-PrOH, 4:1 v/v; UV detector, 254 nm; flow rate, 0.5 mL/min; 35 °C; t_{minor}=46.98 min, t_{major}=25.86 min).

4.2.7. 7-*exo*-Ethoxycarbonyl-5-methoxy-6-*endo*-(2-oxazolidinoyl)carbonyl-8-oxabenzo[*c*]bicyclo[3.2.1]octan-2-one (*endo*-5e). Colorless prisms; mp 179 °C; $[\alpha]_D^{25}$ +20.67 (*c* 0.80, $CHCl_3$); 78% ee estimated on the basis of chiral HPLC; IR (KBr) 654, 707, 769, 825, 867, 943, 1019, 1051, 1107, 1158, 1244, 1369, 1474, 1600, 1787, 2920, 2958 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (3H, t, *J*=7.1 Hz), 3.60 (1H, dd, *J*=1.5, 5.4 Hz), 3.65 (3H, s), 3.34–3.48, 3.79–3.90, 4.34–4.44 (4H, m), 4.22–4.33 (2H, m), 5.13 (1H, dd, *J*=1.5, 0.49 Hz), 5.57 (1H, d, *J*=5.4 Hz), 7.35–7.38, 7.46–7.61, 8.01–8.05 (4H, m); ^{13}C NMR ($CDCl_3$) δ 14.2 (CH_3), 43.0 (CH_2), 48.1 (CH), 50.2 (CH), 51.6 (CH_3), 61.9 (CH_2), 62.1 (CH_2), 82.2 (CH), 108.6 (C), 122.7 (CH), 126.8 (CH), 129.3 (CH), 129.5 (C), 133.5 (CH), 141.9 (C), 152.5 (C), 169.0 (C), 170.5 (C), 192.1 (C); Mass spectrometry (EI) *m*/*z* 389 (M^+), 357, 343, 329, 316, 302, 284, 271, 257, 243, 229, 215, 201, 199, 187, 176, 163, 148, 133, 115, 104, 92, 77, 63, 50, 38, 24, 13; HRMS (EI) calcd for $C_{19}H_{19}NO_8$: 389.1109 (M^+), found: 389.1078. Anal. Calcd for $C_{19}H_{19}NO_8$: C, 58.61; H, 4.92; N, 3.60%. Found: C, 58.63; H, 4.85; N, 3.65%.

The enantiomeric excess was determined using chiral HPLC analysis (Daicel Chiralpak IA; hexane/2-PrOH, 4:1 v/v; UV detection, 254 nm; flow rate, 0.5 mL/min; 35 °C; t_{minor}=42.16 min, t_{major}=35.76 min).

4.2.8. 7-*endo*-Ethoxycarbonyl-5-methoxy-6-*exo*-(2-oxazolidinoyl)carbonyl-8-oxabenzo[*c*]bicyclo[3.2.1]octan-2-one (*exo*-5e). ^{1}H NMR ($CDCl_3$) δ 1.15 (3H, t, J=7.2 Hz), 3.40 (3H, s), 3.99–4.53 (6H, m), 4.54 (1H, dd, J=5.2, 9.2 Hz), 4.99 (1H, d, J=5.2 Hz), 5.14 (1H, d, J=9.2 Hz), 7.47–7.70 (3H, m), 7.96–7.98 (1H, m). The minor *exo*-adduct was characterized using ^{1}H NMR; unfortunately, isolation of the *exo*-adduct using column chromatography was unsuccessful.

4.2.9. 5-Isopropoxy-7-*exo*-methyl-6-*endo*-(2-oxazolidinoyl)carbonyl-8-oxabenzo[*c*]bicyclo[3.2.1]octan-2-one (*endo*-6b). Colorless prisms; mp 178 °C; $[\alpha]_D^{25}$ +7.24 (*c* 1.00, $CHCl_3$); 8% ee estimated on the basis of chiral HPLC; IR (KBr) 634, 708, 751, 807, 846, 899, 921, 953, 970, 1004, 1031, 1048, 1114, 1165, 1219, 1246, 1269, 1296, 1337, 1385, 1463, 1511, 1540, 1563, 1600, 1683, 2371, 2876, 2931, 2973, 2996 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.29 (3H, d, J=6.1 Hz), 1.32 (3H, d, J=6.4 Hz), 1.44 (3H, d, J=7.1 Hz), 2.66 (1H, m), 3.56–3.65, 3.81–3.91, 4.16–4.27, 4.32–4.38 (4H, m), 4.41 (1H, m), 4.39 (1H, d, J=1.7 Hz), 4.82 (1H, d, J=5.9 Hz), 7.28–7.33, 7.44–7.50, 7.50–7.58, 7.98–8.07 (4H, m); ^{13}C NMR ($CDCl_3$) δ 20.4 (CH_3), 24.2 (CH_3), 24.5 (CH_3), 39.0 (CH), 43.3 (CH_2), 57.0 (CH), 61.8 (CH_2), 68.9 (CH), 87.0 (CH), 109.8 (C), 123.5 (CH), 126.5 (CH), 128.9 (CH), 130.0 (C), 133.0 (CH), 143.2 (C), 152.8 (C), 170.4 (C), 193.8 (C); Mass spectrometry (EI) *m/z* 359 (M^+), 299, 272, 260, 245, 229, 213, 201, 185, 173, 156, 145, 129, 114, 104, 88, 69, 50, 39, 24, 13; HRMS (EI) calcd for $C_{19}H_{21}NO_6$: 359.1368 (M^+), found: 359.1362. Anal. Calcd for $C_{19}H_{21}NO_6$: C, 63.50; H, 5.89; N, 3.74%. Found: C, 63.68; H, 5.87; N, 3.74%.

The enantiomeric excess was determined using chiral HPLC analysis (Daicel Chiralpak IA; hexane/2-PrOH, 4:1 v/v; UV detection, 254 nm; flow rate, 0.5 mL/min; 35 °C; t_{minor}=27.32min, t_{major}=20.12 min).

4.2.10. 5-Isopropoxy-7-*endo*-methyl-6-*exo*-(2-oxazolidinoyl)carbonyl-8-oxabenzo[*c*]bicyclo[3.2.1]octan-2-one (*exo*-6b). Colorless prisms; mp 174–175 °C; $[\alpha]_D^{25}$ +6.10 (*c* 0.25, $CHCl_3$); 1% ee estimated on the basis of chiral HPLC; IR (KBr) 633, 709, 749, 803, 890, 920, 949, 974, 1002, 1032, 1048, 1114, 1170, 1223, 1246, 1274, 1295, 1333, 1391, 1440, 1523, 1545, 1571, 1611, 1673, 2351, 2865, 2902, 2973, 2996 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.84 (3H, d, J=7.3 Hz), 1.18 (3H, d, J=2.7 Hz), 1.19 (3H, d, J=2.9 Hz), 3.65 (1H, m), 3.99 (1H, m), 4.06–4.17 (2H, m), 4.21 (1H, d, J=4.9 Hz), 4.39–4.51 (2H, m), 4.85 (1H, d, J=9.0 Hz), 7.44–7.51, 7.60–7.68, 7.98–8.02 (4H, m); ^{13}C NMR ($CDCl_3$) δ 15.3 (CH_3), 24.0 (CH_3), 24.6 (CH_3), 35.1 (CH), 43.3 (CH_2), 58.0 (CH), 62.0 (CH_2), 69.5 (CH), 84.7 (CH), 108.4 (C), 124.7 (CH), 126.2 (CH), 128.8 (CH), 130.2 (C), 133.9 (CH), 145.2 (C), 153.5 (C), 170.2 (C), 194.1 (C); Mass spectrometry (EI) *m/z* 359 (M^+), 316, 300, 272, 260, 245, 229, 212, 201, 185, 173, 156, 145, 127, 115, 105, 88, 68, 57, 47, 35, 24, 13; HRMS (EI) calcd for $C_{19}H_{21}NO_6$: 359.1368 (M^+), found: 359.1352.

The enantiomeric excess was determined using chiral HPLC analysis (Daicel Chiralpak IA; hexane/2-PrOH, 4:1 v/v; UV detection, 254 nm; flow rate, 0.5 mL/min; 35 °C; t_{minor}=17.89 min, t_{major}=12.79 min).

4.2.11. 5-*p*-Bromobenzyloxy-6-*endo*-ethoxycarbonyl-7-*exo*-(2-oxazolidinoyl)carbonyl-8-oxabenzo[*c*]bicyclo[3.2.1]octan-2-one (*exo*-7e′). Colorless solid; mp 43–45 °C; $[\alpha]_D^{25}$ −34.77 (*c* 1.00, $CHCl_3$); 56% ee estimated using chiral HPLC; IR (KBr) 624, 986, 1015, 1042, 1071, 1109, 1215, 1298, 1368, 1387, 1460, 1480, 1489, 1601, 1709, 1732, 1788, 2340, 2361, 2402, 2926, 3021, 3393 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.05 (3H, t, J=7.1 Hz), 3.75–3.93 (2H, m), 4.04–4.18 (2H, m), 4.37 (1H, d, J=5.6 Hz), 4.41–4.53 (2H, m), 4.73 (1H, dd, J=5.6, 1.7 Hz), 4.85 (1H, d, J=1.7 Hz), 4.86 (1H, d, J=12.2 Hz), 4.96 (1H, d, J=12.2 Hz), 7.43–7.53 (4H, m), 7.32–7.38, 7.54–7.60, 7.99–8.11 (4H, m); ^{13}C NMR ($CDCl_3$) δ 14.0 (CH_3), 43.1 (CH_2), 46.6 (CH), 52.5 (CH), 61.5 (CH_2), 62.3 (CH_2), 65.7 (CH_2), 82.6 (CH), 107.9 (C), 121.5 (C), 124.3 (CH), 127.2 (CH), 129.0 (CH), 129.2 (C), 129.5 (CH), 131.4 (CH), 133.6 (CH), 136.3 (C), 141.4 (C), 152.6 (C), 168.0 (C), 170.5 (C), 190.1 (C); Mass spectrometry (EI) *m/z* 545 (M^++2), 543 (M^+), 501, 340, 315, 287, 272, 242, 215, 186, 171, 149, 133, 104, 90, 63, 40, 24; HRMS (EI) calcd for $C_{25}H_{22}BrNO_8$: 543.0528 (M^+), found: 543.0495. Satisfactory elemental analysis was not obtained because only a small amount of product was obtained.

The enantiomeric excess was determined using chiral HPLC analysis (Daicel Chiralpak IA; hexane/2-PrOH, 4:1 v/v; UV detection, 254 nm; flow rate, 0.5 mL/min; 35 °C; t_{minor}=115.87 min, t_{major}=154.54 min).

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References and notes

1. For recent reviews, see: (a) *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; Wiley: Hoboken, NJ, 2003; (b) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863; (c) *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 5, Chapter 3.
2. For representative examples, see: (a) Gothelf, K. V.; Thomsen, I.; Jørgensen, K. A. *J. Am. Chem. Soc.* **1996**, *118*, 59; (b) Kobayashi, S.; Kawamura, M. *J. Am. Chem. Soc.* **1998**, *120*, 5840; (c) Kanemasa, S.; Oderaotoshi, Y.; Tanaka, J.; Wada, E. *J. Am. Chem. Soc.* **1998**, *120*, 12355; (d) Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1998**, *63*, 5483; (e) Kobayashi, S.; Kawamura, M. *Tetrahedron Lett.* **1999**, *40*, 3213; (f) Desimoni, G.; Faita, G.; Mortoni, A.; Righetti, P. *Tetrahedron Lett.* **1999**, *40*, 2001; (g) Iwasa, S.; Tsushima, S.; Shimada, T.; Nishiyama, H. *Tetrahedron Lett.* **2001**, *42*, 6715; (h) Iwasa, S.; Tsushima, S.; Shimada, T.; Nishiyama, H. *Tetrahedron* **2002**, *58*, 227; (i) Gothelf, K. V.; Jørgensen, K. A. *J. Org. Chem.* **1994**, *59*, 5687; (j) Jensen, K. B.; Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1997**, *62*, 2471; (k) Hori, K.; Kodama, H.; Ohta, T.; Furukawa, I. *J. Org. Chem.* **1999**, *64*, 5017; (l) Heckel, A.; Seebach, D. *Chem.—Eur. J.* **2002**, *8*, 560; (m) Suga, H.;

Kakehi, A.; Ito, S.; Sugimoto, H. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 327; (n) Sibi, M. P.; Ma, Z.; Jasperse, C. P. *J. Am. Chem. Soc.* **2004**, *126*, 718; (o) Suga, H.; Nakajima, T.; Itoh, K.; Kakehi, A. *Org. Lett.* **2005**, *7*, 1431; For reactions with α,β-unsaturated aldehydes, see: (p) Viton, F.; Bernardinelli, G.; Kündig, E. P. *J. Am. Chem. Soc.* **2002**, *124*, 4968; (q) Mita, T.; Ohtsuki, N.; Ikeno, T.; Yamada, T. *Org. Lett.* **2002**, *4*, 2457; (r) Shirahase, M.; Kamenasa, S.; Oderaotoshi, Y. *Org. Lett.* **2004**, *6*, 675; (s) Carmona, D.; Lamata, M. P.; Viguri, F.; Rodriguez, R.; Oro, L. A.; Balana, A. I.; Lahoz, F. J.; Tejero, T.; Merino, P.; Franco, S.; Montesa, I. *J. Am. Chem. Soc.* **2004**, *126*, 2716; (t) Kano, T.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 11926.

3. Sibi, M. P.; Itoh, K.; Jasperse, C. P. *J. Am. Chem. Soc.* **2004**, *126*, 5366.
4. Sibi, M. P.; Stanley, L. M.; Jasperse, C. P. *J. Am. Chem. Soc.* **2005**, *127*, 8276.
5. Kanemasa, S.; Kanai, T. *J. Am. Chem. Soc.* **2000**, *122*, 10710.
6. (a) Suga, H.; Inoue, K.; Inoue, S.; Kakehi, A. *J. Am. Chem. Soc.* **2002**, *124*, 14836; (b) Suga, H.; Inoue, K.; Inoue, S.; Kakehi, A.; Shiro, M. *J. Org. Chem.* **2005**, *70*, 47.
7. For reviews, see: (a) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223; (b) Padwa, A.; Hornbuckle, S. F. *Chem. Rev.* **1991**, *91*, 263.
8. For examples of catalytic asymmetric cycloadditions of carbonyl ylides using chiral Rh catalyst, see: (a) Hodgson, D. M.; Stupple, P. A.; Johnstone, C. *Tetrahedron Lett.* **1997**, *38*, 6471; (b) Hodgson, D. M.; Stupple, P. A.; Johnstone, C. *Chem. Commun.* **1999**, 2185; (c) Kitagaki, S.; Anada, M.; Kataoka, O.; Matsuno, K.; Umeda, C.; Watanabe, N.; Hashimoto, S. *J. Am. Chem. Soc.* **1999**, *121*, 1417; (d) Kitagaki, S.; Yasugahira, M.; Anada, M.; Nakajima, M.; Hashimoto, S. *Tetrahedron Lett.* **2000**, *41*, 5931.
9. The *endo*-adduct is defined as the product in which the more important substituent is on the opposite side of the epoxy bridge, whereas the *exo*-adduct indicates the product in which the more important substituent is on the same side as the epoxy bridge.
10. Inoue, K.; Suga, H.; Inoue, S.; Sato, H.; Kakehi, A. *Synthesis* **2003**, 1413.
11. Shannon, R. D. *Acta Crystallogr.* **1976**, *A32*, 751.
12. (a) Desimoni, G.; Faita, G.; Quadrelli. *Chem. Rev.* **2003**, *103*, 3119; (b) Desimoni, G.; Faita, G.; Filippone, S.; Mella, M.; Zampori, M. G.; Zema, M. *Tetrahedron* **2001**, *57*, 10203.
13. (a) Suga, H.; Kakehi, A.; Ito, S.; Inoue, K.; Ishida, H.; Ibata, T. *Org. Lett.* **2000**, *2*, 3145; (b) Suga, H.; Kakehi, A.; Ito, S.; Inoue, K.; Ishida, H.; Ibata, T. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 1115; (c) Ueda, K.; Ibata, T.; Takebayashi, M. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 2779; (d) Ibata, T.; Toyoda, J.; Sawada, M.; Takai, Y.; Tanaka, T. *Tetrahedron Lett.* **1988**, *29*, 317.

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Unsymmetrical polyheteropolyene: a versatile building block for the preparation of pyrrolo[2,1-*b*]thiazoles and 2*H*-thiopyrano[2,3-*b*]pyridines

Cyrille Landreau, Pascal Janvier, Karine Julienne, Jean Claude Meslin and David Deniaud*

Laboratoire de Synthèse Organique, UMR CNRS 6513, FR CNRS 2465, UFR des Sciences et des Techniques, 2, rue de la Houssinière, BP 92208, 44322 Nantes Cedex 3, France

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Abstract—The synthesis of two classes of bisheterocyclic compounds, pyrrolothiazoles and thiopyranopyridines, is reported. The 4-dimethylamino-2-dimethylaminomethylenamino-1-thiabuta-1,3-diene **1** is used like a useful building block for the chemoselective synthesis of these heterocycles. Indeed, synthon **1** can react as thiazabutadiene or thiabutadiene form to afford either five- or six-membered ring monocyclic azadienes, themselves being precursors to the bicyclic structures. Semi-empirical calculations were undertaken to explain this efficient chemoselectivity.

1. Introduction

Pyrrolo[2,1-*b*]thiazoles and especially 2*H*-thiopyrano[2,3-*b*]pyridines are unusual ring systems, which may be of interest from a biological aspect. Since the first synthesis of the former was reported,[1] only few other preparations have sporadically been proposed,[2] despite di- and tetrahydroderivatives having attracted attention as potentially antineoplastic[3] or hypoglycemic agents,[4] or as modulators of dopaminergic neurotransmission in CNS in vivo[5] and as γ-lactam analogues of the penems.[6] To the best of our knowledge, few reports deal with the construction of 2*H*-thiopyrano[2,3-*b*]pyridines.[7] In the latest report, oxime ethers of these compounds were shown to display antihypertensive properties,[7c,d] and spirohydantoin derivatives were tested for their ability to inhibit aldose reductase.[7e]

In the course of our continued endeavour to expand the use of heterodienes in heterocyclic synthesis,[8] we describe herein a novel and simple methodology to access both of these heterocycles, using relatively low cost reactants. Moreover, this method involves a convenient common polyheteropolyenic precursor, namely the 4-dimethylamino-2-dimethylaminomethylenamino-1-thiabuta-1,3-diene **1**, constituted of a 1-thiabutadienic chain fused to a 1-thia-3-azabutadienic moiety and appropriately substituted with good leaving, strong electron-releasing groups. Using a similar methodology, we recently described a novel route to thiazolopyrimidines or imidazothiazines involving a double annulation reaction from an equivalent symmetrical polyheteropolyenic precursor.[9]

The use of such synthons has already been investigated by Liebscher and co-workers.[10] Their work, however, was restricted to the preparation of monocycles. As for us, our firm intention was to build bicyclic structures with an efficient chemoselectivity, in one or two steps, starting from a similar substrate and using various reagents.

2. Results and discussion

2.1. Synthesis of pyrrolo[2,1-*b*]thiazoles

The starting polyheteropolyenic precursor **1** was obtained in two steps in good yield by sulfhydration of 3-dimethylaminoacrylonitrile followed by condensation with *N*,*N*-dimethylformamide dimethylacetal. This 4-dimethylamino-2-dimethylaminomethylenamino-1-thiabuta-1,3-diene **1** was isolated as a mixture of stereoisomers and was used without further purification. This synthon can react as a thiazadiene or as an azadiene form for the first cyclization to give the heterocyclic compound.

With the aim of investigating the reactivity of the compound **1**, it was first subjected to alkylation with methyl bromoacetate and 2,4′-dibromoacetophenone (Scheme 1, Table 1).

Keywords: Cycloaddition; Bisheterocycles; Azadiene; Thiazadiene.
* Corresponding author. Tel.: +33 2 51 12 54 06; fax: +33 2 51 12 54 02; e-mail: david.deniaud@univ-nantes.fr

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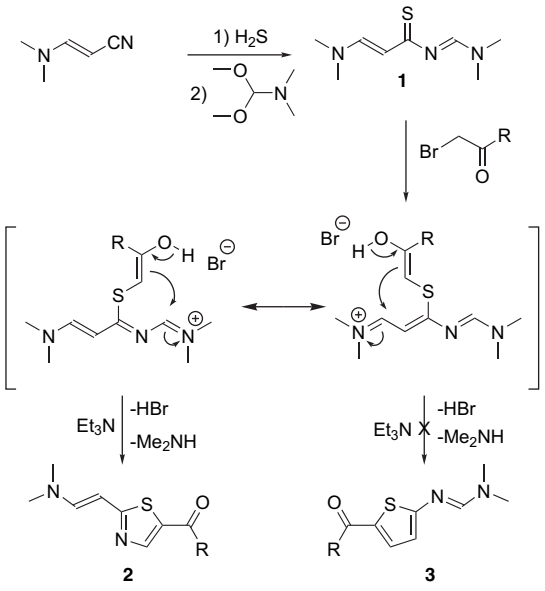
Treatment with triethylamine induced the expected intramolecular cyclization of the resulting *S*-alkylated salt by condensation of the enol with the amidinium moiety. The following spontaneous loss of dimethylamine provided good yields of thiazole derivatives **2** as the exclusive products, whereas the concurrent formation of thiophenes **3** might also have been expected as previously demonstrated by our group.[11] The proof of the thiazole structure, and therefore the total chemoselectivity, was given by the ^{1}H NMR spectra where we observed the loss of dimethylamino group and the presence of characteristic singlets.



Scheme 1. Synthesis of **2** and **3**.

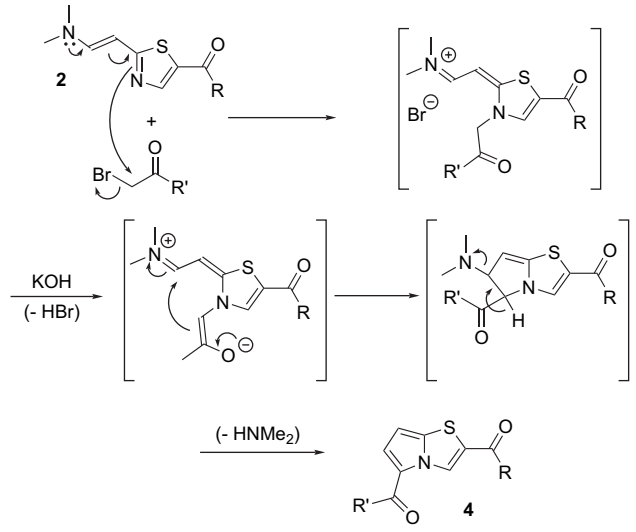
Table 1. Yields of compounds **2a,b**

Compounds	R	Yield (%)
2a	OCH_3	81
2b	*p*-BrC_6H_4	81

The isolated compounds **2**, which have now a 1-azadiene chain, were then allowed to react with another α-carbonyl bromide (Scheme 2, Table 2). The resulting *N*-alkylated salts were cyclized in situ by addition of KOH leading to pyrrolo[2,1-*b*]thiazoles **4**, by loss of dimethylamine, in modest to good yields. This result is somewhat surprising since Stanovnik and co-workers have failed to fuse a pyrrole to a similar dihydrothiazolium salt.[12]

2.2. Synthesis of 2*H*-thiopyrano[2,3-*b*]pyridines

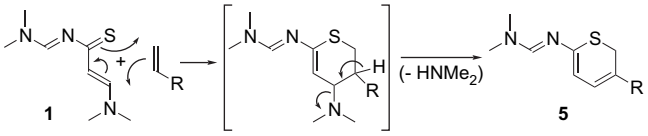
We continued our investigations by exposing polyheteropolyene **1** to acrylic dienophiles (Scheme 3, Table 3). The expected [4+2] cycloaddition occurred with faultless chemoselectivity to give, after deamination, the corresponding 2*H*-thiopyrane derivatives **5** without trace of 1,3-thiazines. This result corroborates previous related studies in which the 1-thiabuta-1,3-dienic chain was noticed to be significantly more reactive towards Diels–Alder reactions than the 1-thia-3-aza-1,3-butadienic derivative.[13]



Scheme 2. Reactions of compounds **2a,b** with α-carbonyl bromides.

Table 2. Yields of compounds **4a–f**

Compounds	R	R′	Yield (%)
4a	OCH_3	C_6H_5	77
4b	OCH_3	*p*-BrC_6H_4	85
4c	*p*-BrC_6H_4	OCH_3	70
4d	*p*-BrC_6H_4	OC_2H_5	67
4e	*p*-BrC_6H_4	*p*-ClC_6H_4	72
4f	*p*-BrC_6H_4	*p*-$NO_2C_6H_4$	55



Scheme 3. Reaction of polyheteropolyene **1** with acrylic dienophiles.

Table 3. Yields of compounds **5a–c**

Compounds	R	Yield (%)
5a	CN	61
5b	$COCH_3$	78
5c	$COOCH_3$	82

In order to understand this behaviour we have calculated the frontier molecular orbital (FMO) energies and MO coefficients by semi-empirical calculations.[14] For the polyheteropolyene **1** the electronic differences between C4 (N–*C*═C) and C9 (N–*C*═N) are not significant. It should be also noted that the HOMO-1 should be considered as the heterodiene HOMO because only that frontier orbital possesses the adequate coefficients and symmetry (vide infra) to react in a normal hetero-Diels–Alder cycloaddition. Both methods used by us (AM1[15] and PM3[16]) indicate a significant larger HOMO P_z coefficient for C4 than for C9 (Table 4), independent of the stereochemistry of the double bonds, in agreement with the experimental results.

Although acrylic dienophiles were always used in large excess, the reactivity of the generated 2-aza-1,3-dienic heterocycle **5** was low enough to ensure nearly complete

Table 4. Calculated AM1 MO coefficients for compound **1**

Eigenvalue HOMO	−8.17 eV
MO coefficient	
P_z C9 (N–*C*═N)	−0.09
P_z S	0.62
P_z C4 (N–*C*═C)	−0.24

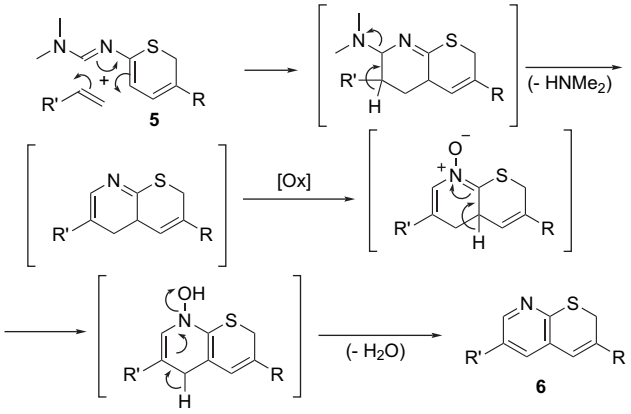
consumption of the starting material before double condensation could occur.

Subsequent [4+2] cycloadditions between the isolated 2*H*-thiopyranes **5**, bearing a 2-azadienic chain, and other dienophiles were performed using higher temperatures and longer reaction times, providing 2*H*-thiopyrano[2,3-*b*]pyridines **6** in modest to good yields (Table 5, method A: in two steps from **1**). Although the mechanistic details of the cyclization remain unknown, we suggest the loss of dimethylamine to lead to a 4a,5-dihydro-2*H*-thiopyrano[2,3-*b*]pyridine, which would then rearrange to the more stable unsaturated final product (Scheme 4). Oxidation probably occurred during the work-up procedure to give an intermediate *N*-oxide, itself undergoing a [1,4]-proton shift followed by dehydration. Furthermore, such rearrangements are precedented in the pyridinic series.[17]

Table 5. Yields of compounds **6a–f**

Compounds	R	R′	Yield (%)
6a	$COOCH_3$	CN	45[a]
6b	$COCH_3$	$COOCH_3$	54[a]
6c	$COOCH_3$	$COCH_3$	75[a]
6d	$COCH_3$	$COCH_3$	94[b]
6e	CN	CN	53[b]
6f	$COOCH_3$	$COOCH_3$	71[b]

[a] Compounds obtained by method A from **5**.
[b] Compounds obtained by method B from **1**.



Scheme 4. Synthesis of compounds **6**.

An attractive feature of this process is that 2*H*-thiopyrano[2,3-*b*]pyridines **6** could also be obtained directly from compound **1** in better overall yields (Table 5, method B: in one step from **1**). In this case, much harsher reaction conditions than for monocondensation were naturally required, and substituents R and R′ on the resulting heterocycle were identical. It is worth pointing out the excellent result obtained by this path with methyl vinyl ketone under relatively mild conditions.

In addition, the use of further reactants has been investigated in a view to extend the usefulness of our methodology. However, against all expectations, refluxing a solution of **2** in pure methyl vinyl ketone, conditions that might have provided a 5*H*-thiazolo[3,2-*a*]pyridine, resulted in none of the desired cycloadduct. Again, despite our attempts, neither ketenes nor sulfenes could undergo a successful cycloaddition with **1**, **2** or **5**. In most cases, starting material together with degraded products was recovered.

3. Conclusion

Thus we have demonstrated the 4-dimethylamino-2-dimethylaminomethylenamino-1-thiabuta-1,3-diene **1** to be a convenient precursor for the preparation of both pyrrolo[2,1-*b*]thiazoles **4** and 2*H*-thiopyrano[2,3-*b*]pyridines **6**, although some yields need to be optimized. We have shown that we have a faultless chemoselective control between the azadiene and thiadiene forms. We believe synthons of this type to be particularly applicable to solid-phase synthesis and combinatorial chemistry. Some of these possibilities are being examined in our laboratory, and these results will be published in due course.

4. Experimental

4.1. General comments

All reagents were purchased either from Acros Organics or Aldrich. Elemental analyses were performed by the C.N.R.S. Analysis Laboratory (Vernaison). Column chromatographies were conducted on silica gel 60 (40–63 μm), available from E. Merck. Thin layer chromatographies were performed on 0.5 mm×20 cm×20 cm E. Merck silica gel plates (60 F-254). Melting points were measured using a Reichert microscope. ^{13}C and ^{1}H NMR spectra were recorded at room temperature using a BRUKER AC 200 at 50 and 200 MHz, respectively. Chemical shifts (δ) are given in parts per million downfield from tetramethylsilane as internal standard. Mass spectra were determined with a Hewlett–Packard 5989 spectrometer. IR spectra were obtained using a BRUKER Vector 22 spectrometer. All chemicals were of reagent grade and used without further purification. THF was freshly distilled from Na/benzophenone, while CH_2Cl_2 was distilled over CaH_2. All reactions were carried in an Ar atmosphere.

4.1.1. 4-Dimethylamino-2-dimethylaminomethylenamino-1-thiabuta-1,3-diene (1).[18] To a suspension of 2-amino-4-dimethylamino-1-thiabuta-1,3-diene (10 mmol) in CH_2Cl_2 (20 mL) was added *N*,*N*-dimethylformamide dimethyl acetal (11 mmol). The mixture was refluxed for 3 h. After removal of the solvent, the residue was diluted with CH_2Cl_2 (5 mL) and compound **2** was precipitated by addition of Et_2O (80 mL) and collected by filtration as ochre crystals (yield: 92%). Mp: 170 °C. IR (KBr): 1587, 1419, 1344, 1324, 1255, 1245, 1083 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.96 (br s, 6H), 3.14 (s, 3H), 3.17 (s, 3H), 5.94 (d, 1H,

J=12.0 Hz), 8.25 (d, 1H, J=12.0 Hz), 8.90 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 35.4, 37.3, 40.8, 44.8, 107.8, 158.8, 166.2, 206.4. MS *m/z*: 185 (100, M^+), 152 (39), 114 (43), 98 (20), 82 (39). Anal. calcd for $C_8H_{15}N_3S$: C, 51.86; H, 8.16; N, 22.68. Found: C, 51.99; H, 8.25; N, 22.47.

4.2. General procedure for the preparation of 2-(2-dimethylaminovinyl)thiazoles (2)

A solution of thiazadiene **1** (2 mmol) and methyl bromoacetate (2.1 mmol, for **2a**) or 2,4′-dibromoacetophenone (2.1 mmol, for **2b**) in CH_2Cl_2 (10 mL) was stirred at rt for 15 h (for **2a**) or 2 h (for **2b**). After addition of triethylamine (4.2 mmol), stirring was continued for 4 h. The solvent was then removed, and the residue was diluted with CH_2Cl_2 and chromatographed (using as eluent CH_2Cl_2/EtOAc 3/2 for **2a**, 9/1 for **2b**). Compounds **2** were crystallized from hexane/Et_2O (for **2a**) or Et_2O (for **2b**).

4.2.1. 2-(2-Dimethylaminovinyl)-5-methoxycarbonylthiazole (2a). Violet crystals (yield: 81%). Mp: 104 °C. IR (KBr): 1691, 1623, 1388, 1244, 1211, 1088 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 2.90 (s, 3H), 3.31 (s, 3H), 4.13 (s, 3H), 5.45 (d, 1H, J=12.8 Hz), 8.00 (d, 1H, J=12.8 Hz), 8.38 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 34.1, 38.3, 51.8, 89.5, 119.2, 148.0, 149.2, 161.7, 175.5. MS *m/z*: 212 (94, M^+), 197 (13), 180 (45), 170 (33), 152 (100), 138 (25). Anal. calcd for $C_9H_{12}N_2O_2S$: C, 50.93; H, 5.70; N, 13.20. Found: C, 50.80; H, 5.85; N, 13.42.

4.2.2. 5-*p*-Bromobenzoyl-2-(2-dimethylaminovinyl)thiazole (2b). Ochre crystals (yield: 81%). Mp: 163 °C. IR (KBr): 1626, 1602, 1437, 1380, 1315, 1262, 1214, 1107, 1008 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.99 (s, 6H), 5.45 (d, 1H, J=12.8 Hz), 7.58 (d, 1H, J=12.8 Hz), 7.59–7.72 (m, 4H), 7.88 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 40.8 (2C), 90.9, 126.7, 129.4 (2C), 131.8 (2C), 132.0, 137.6, 148.0, 151.1, 177.6, 185.5. MS *m/z*: 338/336 (79/78, M^+), 296/294 (18/19), 185/183 (40/38), 153 (100). Anal. calcd for $C_{14}H_{13}BrN_2OS$: C, 49.86; H, 3.89; N, 8.31. Found: C, 50.01; H, 4.10; N, 8.38.

4.3. General procedure for the preparation of pyrrolo[2,1-*b*]thiazoles (4)

A solution of 2-(2-dimethylaminovinyl)thiazole **2** (1 mmol) and α-carbonyl bromide (1.2 mmol of phenacyl bromide for **4a**, 2,4′-dibromoacetophenone for **4b**, 2-bromo-4′-chloroacetophenone for **4e**, 2-bromo-4′-nitroacetophenone for **4f**, 2 mmol of methyl acetate for **4c**, ethyl acetate for **4d**) in THF (10 mL) was heated for 24 h at 70 °C. After cooling to rt, the solvent was removed and the residue was diluted (20 mL) with MeOH (for **4a–c**) or EtOH (for **4d–f**). Powdered KOH (2 mmol) was added and the reaction mixture was further stirred for 24 h at rt and concentrated by rotary evaporation. The residue was then chromatographed using as eluent CH_2Cl_2. Compounds **4** were crystallized from Et_2O.

4.3.1. 5-Benzoyl-2-methoxycarbonylpyrrolo[2,1-*b*]thiazole (4a). Yellow crystals (yield: 77%). IR (KBr): 3134, 1707, 1616, 1564, 1443, 1427, 1385, 1301, 1191, 1090, 886, 746, 720 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.96 (s, 3H), 6.42 (dd, 1H, J=4.4 Hz, J=0.6 Hz), 7.27 (d, 1H, J=4.4 Hz), 7.44–7.87 (m, 5H), 9.43 (d, 1H, J=0.6 Hz). ^{13}C NMR ($CDCl_3$) δ 52.8, 101.1, 123.2, 124.8, 128.0, 128.4 (2C), 128.9 (2C), 129.9, 131.6, 139.0, 141.5, 161.9, 183.0. MS *m/z*: 285 (100, M^+), 257 (16), 208 (38), 180 (14). Anal. calcd for $C_{15}H_{11}NO_3S$: C, 63.15; H, 3.89; N, 4.91. Found: C, 62.99; H, 3.83; N, 4.96.

4.3.2. 5-*p*-Bromobenzoyl-2-methoxycarbonylpyrrolo[2,1-*b*]thiazole (4b). Yellow crystals (yield: 85%). Mp: 146 °C. IR (KBr): 1724, 1610, 1568, 1425, 1406, 1396, 1260, 1091, 885, 740 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.96 (s, 3H), 6.43 (dd, 1H, J=4.4 Hz, J=0.6 Hz), 7.23 (d, 1H, J=4.4 Hz), 7.60–7.74 (m, 4H), 9.39 (d, 1H, J=0.6 Hz). ^{13}C NMR ($CDCl_3$) δ 52.9, 101.4, 123.4, 124.4, 126.4, 127.8, 129.7, 130.4 (2C), 131.7 (2C), 137.7, 141.8, 161.8, 181.6. MS *m/z*: 365/363 (100/98, M^+), 337/335 (9/9), 256 (17), 208 (47). Anal. calcd for $C_{15}H_{10}BrNO_3S$: C, 49.47; H, 2.77; N, 3.85. Found: C, 49.46; H, 2.85; N, 3.76.

4.3.3. 2-*p*-Bromobenzoyl-5-methoxycarbonylpyrrolo[2,1-*b*]thiazole (4c). Yellow crystals (yield: 70%). Mp: 201 °C. ^{1}H NMR ($CDCl_3$) δ 3.88 (s, 3H), 6.38 (dd, 1H, J=4.4 Hz, J=0.6 Hz), 7.37 (d, 1H, J=4.4 Hz), 7.66–7.79 (m, 4H), 8.83 (d, 1H, J=0.6 Hz). ^{13}C NMR ($CDCl_3$) δ 51.6, 100.8, 116.4, 124.6, 128.1, 129.9, 130.3 (2C), 132.4 (2C), 133.0, 136.0, 138.8, 160.9, 186.7. MS *m/z*: 365/363 (100/95, M^+), 334/332 (35/35), 307/305 (24/22), 185/183 (14/14). Anal. calcd for $C_{15}H_{10}BrNO_3S$: C, 49.47; H, 2.77; N, 3.85. Found: C, 49.41; H, 2.64; N, 3.74.

4.3.4. 2-*p*-Bromobenzoyl-5-ethoxycarbonylpyrrolo[2,1-*b*]thiazole (4d). Yellow crystals (yield: 67%). Mp: 122 °C. IR (KBr): 1693, 1638, 1523, 1419, 1306, 1213, 1178, 1122, 1109, 742. ^{1}H NMR ($CDCl_3$) δ 1.38 (t, 3H, J=7.2 Hz), 4.34 (q, 2H, J=7.2 Hz), 6.36 (dd, 1H, J=4.4 Hz, J=0.6 Hz), 7.36 (d, 1H, J=4.4 Hz), 7.65–7.78 (m, 4H), 8.83 (d, 1H, J=0.6 Hz). ^{13}C NMR ($CDCl_3$) δ 14.5, 60.4, 100.6, 116.6, 124.4, 127.9, 129.8, 130.2 (2C), 132.2 (2C), 132.7, 135.9, 138.5, 160.4, 186.4. MS *m/z*: 379/377 (100/95, M^+), 351/349 (44/39), 307/305 (45/46), 185/183 (40/36). Anal. calcd for $C_{16}H_{12}BrNO_3S$: C, 50.81; H, 3.20; N, 3.70. Found: C, 50.73; H, 3.25; N, 3.79.

4.3.5. 2-*p*-Bromobenzoyl-5-*p*-chlorobenzoylpyrrolo[2,1-*b*]thiazole (4e). Yellow crystals (yield: 72%). Mp: 203 °C. IR (KBr): 1628, 1613, 1587, 1565, 1431, 1403, 1387, 1296, 1176, 1088, 999, 885, 838, 739 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 6.48 (dd, 1H, J=4.4 Hz, J=0.6 Hz), 7.29 (d, 1H, J=4.4 Hz), 7.46–7.82 (m, 8H), 9.26 (d, 1H, J=0.6 Hz). ^{13}C NMR ($CDCl_3$) δ 101.9, 124.8, 128.4, 128.7, 128.9 (2C), 130.3 (2C), 130.4 (2C), 131.0, 132.5 (2C), 133.8, 135.8, 137.1, 138.2, 142.2, 181.8, 186.6. MS *m/z*: 447/445/443 (29/100/77, M^+), 331 (24), 185/183 (27/26). Anal. calcd for $C_{20}H_{11}BrClNO_2S$: C, 54.01; H, 2.49; N, 3.15. Found: C, 53.86; H, 2.62; N, 3.06.

4.3.6. 2-*p*-Bromobenzoyl-5-*p*-nitrobenzoylpyrrolo[2,1-*b*]thiazole (4f). Orange crystals (yield: 55%). Mp: 247 °C. IR (KBr): 1626, 1619, 1587, 1522, 1429, 1398, 1347, 1292, 1177, 848, 742 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 6.53 (dd, 1H, J=4.4 Hz, J=0.6 Hz), 7.27 (d, 1H, J=4.4 Hz), 7.70–8.39 (m, 8H), 9.27 (d, 1H, J=0.6 Hz). ^{13}C NMR ($CDCl_3$) δ 102.5, 123.9 (2C), 124.5, 128.6, 129.1, 129.8 (2C), 130.4

(2C), 130.7, 132.5 (2C), 134.4, 135.7, 143.4, 144.3, 180.6, 183.7. MS *m/z*: 456/454 (100/99, M^+), 426/424 (36/30), 334/332 (33/31), 185/183 (76/75), 157/155 (49/51). Anal. calcd for $C_{20}H_{11}BrN_2O_4S$: C, 52.76; H, 2.44; N, 6.15. Found: C, 52.57; H, 2.60; N, 6.32.

4.4. General procedure for the preparation of *N*,*N*-dimethyl-*N*′-(6*H*-thiopyran-2-yl)formamidines (5)

A solution of thiazadiene **1** (2 mmol) in pure acrylonitrile (5 mL, for **5a**) or in a mixture of another dienophile (1 mL of methyl vinyl ketone for **5b**, 4 mL of methyl acrylate for **5c**) and CH_2Cl_2 (5 mL) was stirred for 16 h at 80 °C (for **5a**), at 40 °C (for **5b**) or at 50 °C (for **5c**). After cooling to rt, the mixture was concentrated and purified by chromatography (CH_2Cl_2/EtOAc 7/3 for **5a**,**b**, 9/1 for **5c**) and crystallization from Et_2O/hexane 1/1 (for **5b**) or hexane (for **5c**). Compound **5a** was isolated as an oil.

4.4.1. *N*′-(5-Cyano-6*H*-thiopyran-2-yl)-*N*,*N*-dimethylformamidine (5a). Red oil (yield: 61%). Hygroscopic. R_f=0.3 (EtOAc). ^{1}H NMR ($CDCl_3$) δ 3.14 (s, 3H), 3.15 (s, 3H), 3.53 (s, 2H), 6.14 (d, 1H, *J*=7.2 Hz), 6.89 (d, 1H, *J*=7.2 Hz), 7.80 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 27.7, 35.9, 41.5, 88.1, 109.1, 119.9, 142.4, 152.1, 155.7. MS *m/z*: 193 (28, M^+), 160 (16), 84 (68), 66 (63), 43 (100).

4.4.2. *N*′-(5-Acetyl-6*H*-thiopyran-2-yl)-*N*,*N*-dimethylformamidine (5b). Orange crystals (yield: 78%). Mp: 118 °C. IR (KBr): 1635, 1619, 1496, 1472, 1360, 1289, 1227, 1110 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.34 (s, 3H), 3.06 (s, 3H), 3.09 (s, 3H), 3.74 (s, 2H), 6.04 (d, 1H, *J*=7.2 Hz), 7.20 (d, 1H, *J*=7.2 Hz), 7.83 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 24.9 (2C), 35.1, 40.8, 109.2, 118.9, 139.5, 155.9, 156.8, 195.2. MS *m/z*: 210 (11, M^+), 167 (100). Anal. calcd for $C_{10}H_{14}N_2OS$: C, 57.12; H, 6.71; N, 13.32. Found: C, 57.01; H, 6.97; N, 13.45.

4.4.3. *N*′-(5-Methoxycarbonyl-6*H*-thiopyran-2-yl)-*N*,*N*-dimethylformamidine (5c). Orange crystals (yield: 82%). Mp: 95 °C. IR (KBr): 1665, 1621, 1503, 1443, 1353, 1288, 1266, 1229, 1194, 1163, 1107, 1084 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.05 (s, 3H), 3.08 (s, 3H), 3.72 (s, 2H), 3.76 (s, 3H), 6.03 (d, 1H, *J*=7.2 Hz), 7.31 (d, 1H, *J*=7.2 Hz), 7.81 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 26.2, 35.1, 40.9, 51.6, 109.3 (2C), 138.5, 154.6, 155.9, 166.8. MS *m/z*: 226 (100, M^+), 211 (59), 193 (39), 167 (77). Anal. calcd for $C_{10}H_{14}N_2O_2S$: C, 53.08; H, 6.24; N, 12.38. Found: C, 53.25; H, 6.44; N, 12.17.

4.5. General procedure for the preparation of 2*H*-thiopyrano[2,3-*b*]pyridines (6)

Method A: A solution of *N*,*N*-dimethyl-*N*′-(6*H*-thiopyran-2-yl)formamidine **5** (1 mmol) in a dienophile (5 mL) was heated at 70 °C for 24 h (for **6b**, **e**, **f**) or two days (for **6c**). After cooling to rt and removal of the solvent, the residue was diluted with CH_2Cl_2. Compounds **6** were isolated by chromatography (CH_2Cl_2 for **6e**, CH_2Cl_2/EtOAc 9/1 for **6b**, **c**, 5/1 for **6f**) followed by crystallization from Et_2O.

Method B: A solution of thiazadiene **1** (1 mmol) in a dienophile (5 mL) was heated at 70 °C for two days (for **6d**) or six days (for **6a**, **g**). After cooling to rt, the mixture was concentrated under reduced pressure. The resulting residue was chromatographed (CH_2Cl_2 for **6g**, CH_2Cl_2/EtOAc 9/1 for **6a**, 5/1 for **6d**). Then compounds **6** were crystallized from Et_2O.

4.5.1. 6-Cyano-3-methoxycarbonyl-2*H*-thiopyrano[2,3-*b*]pyridine (6a). Yellow crystals (yield: 45%). Mp: 134 °C. IR (KBr): 2234, 1717, 1584, 1426, 1390, 1256, 1228, 1115 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.88 (s, 3H), 4.02 (d, 2H, *J*=0.9 Hz), 7.43 (t, 1H, *J*=0.9 Hz), 7.61 (d, 1H, *J*=2.1 Hz), 8.52 (t, 1H, *J*=2.1 Hz). ^{13}C NMR ($CDCl_3$) δ 25.5, 52.9, 106.1, 116.1, 125.2, 127.0, 133.9, 138.5, 152.1, 164.1, 165.2. MS *m/z*: 232 (37, M^+), 217 (100), 173 (46). Anal. calcd for $C_{11}H_8N_2O_2S$: C, 56.89; H, 3.47; N, 12.06. Found: C, 56.76; H, 3.39; N, 11.83.

4.5.2. 3-Acetyl-6-methoxycarbonyl-2*H*-thiopyrano[2,3-*b*]pyridine (6b). Yellow crystals (yield: 54%). Mp: 148 °C. IR (KBr): 1726, 1669, 1588, 1427, 1389, 1313, 1237, 1214, 1139, 766 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.50 (s, 3H), 3.95 (s, 3H), 3.96 (d, 2H, *J*=0.9 Hz), 7.35 (t, 1H, *J*=0.9 Hz), 8.05 (d, 1H, *J*=2.1 Hz), 8.91 (t, 1H, *J*=2.1 Hz). ^{13}C NMR ($CDCl_3$) δ 24.4, 25.6, 52.6, 123.1, 126.7, 132.2, 135.5, 137.5, 151.4, 164.6, 165.3, 196.2. MS *m/z*: 249 (82, M^+), 206 (100), 147 (18). Anal. calcd for $C_{12}H_{11}NO_3S$: C, 57.82; H, 4.45; N, 5.62. Found: C, 57.69; H, 4.61; N, 5.64.

4.5.3. 6-Acetyl-3-methoxycarbonyl-2*H*-thiopyrano[2,3-*b*]pyridine (6c). Yellow crystals (yield: 75%). Mp: 173 °C. IR (KBr): 1720, 1684, 1647, 1581, 1391, 1309, 1253, 1223, 1196, 1135, 1061, 991, 731 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.59 (s, 3H), 3.87 (s, 3H), 4.00 (d, 2H, *J*=0.9 Hz), 7.51 (t, 1H, *J*=0.9 Hz), 7.93 (d, 1H, *J*=2.1 Hz), 8.82 (t, 1H, *J*=2.1 Hz). ^{13}C NMR ($CDCl_3$) δ 25.6, 26.6, 52.7, 124.2, 126.8, 129.7, 135.3, 135.7, 150.3, 164.1, 165.6, 195.5. MS *m/z*: 249 (42, M^+), 234 (100), 190 (37). Anal. calcd for $C_{12}H_{11}NO_3S$: C, 57.82; H, 4.45; N, 5.62. Found: C, 57.79; H, 4.48; N, 5.69.

4.5.4. 3,6-Diacetyl-2*H*-thiopyrano[2,3-*b*]pyridine (6d). Yellow crystals (yield: 94%). Mp: 205 °C. IR (KBr): 1689, 1665, 1620, 1577, 1383, 1303, 1216, 1130, 932 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.50 (s, 3H), 2.61 (s, 3H), 3.97 (d, 2H, *J*=0.9 Hz, SC*H*$_2$), 7.36 (t, 1H, *J*=0.9 Hz), 7.99 (d, 1H, *J*=2.1 Hz), 8.84 (t, 1H, *J*=2.1 Hz). ^{13}C NMR ($CDCl_3$) δ 24.5, 25.6, 26.7, 126.9, 129.6, 132.4, 135.6, 135.9, 150.6, 164.9, 195.5, 196.2. MS *m/z*: 233 (79, M^+), 218 (14), 190 (100), 147 (22). Anal. calcd for $C_{12}H_{11}NO_2S$: C, 61.78; H, 4.75; N, 6.00. Found: C, 61.66; H, 4.96; N, 6.17.

4.5.5. 3,6-Dicyano-2*H*-thiopyrano[2,3-*b*]pyridine (6e). Ochre crystals (yield: 53%). Mp: 180 °C. IR (KBr): 2234, 1627, 1583, 1421, 1388, 1128, 927, 747 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 4.11 (d, 2H, *J*=0.9 Hz), 7.49 (t, 1H, *J*=0.9 Hz), 8.13 (d, 1H, *J*=2.1 Hz), 8.75 (d, 1H, *J*=2.1 Hz). ^{13}C NMR (DMSO-d_6) δ 26.0, 105.6, 105.9, 116.5, 117.6, 126.0, 139.3, 139.7, 152.8, 161.9. MS *m/z*: 199 (91, M^+), 198 (100). Anal. calcd for $C_{10}H_5N_3S$: C, 60.29; H, 2.53; N, 21.09. Found: C, 60.45; H, 2.38; N, 21.23.

4.5.6. 3,6-Bis(methoxycarbonyl)-2*H*-thiopyrano[2,3-*b*]pyridine (6f). Yellow crystals (yield: 71%). Mp: 150 °C.

IR (KBr): 1726, 1646, 1584, 1441, 1396, 1311, 1243, 1210, 1142, 766 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.87 (s, 3H), 3.94 (s, 3H), 4.00 (d, 2H, J=0.9 Hz), 7.50 (t, 1H, J=0.9 Hz), 7.99 (d, 1H, J=2.1 Hz), 8.88 (t, 1H, J=2.1 Hz). ^{13}C NMR ($CDCl_3$) δ 25.6, 52.6, 52.7, 123.1, 124.1, 126.6, 135.3, 137.2, 151.1, 163.8, 165.3, 165.6. MS *m/z*: 265 (31, M^+), 250 (100), 206 (38), 147 (22), 146 (22). Anal. calcd for $C_{12}H_{11}NO_4S$: C, 54.33; H, 4.18; N, 5.28. Found: C, 54.52; H, 4.35; N, 5.45.

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References and notes

1. Kongo, H.; Nagasawa, F. *J. Pharm. Soc. Japan* **1937**, *57*, 1050.
2. (a) Pyl, T.; Dinse, H.-D.; Sietz, O. *Justus Liebigs Ann. Chem.* **1964**, *676*, 141; (b) Molloy, B. B.; Reid, D. H.; Skelton, F. S. *J. Chem. Soc.* **1965**, 65; (c) McKenzie, S.; Molloy, B. B.; Reid, D. H. *J. Chem. Soc. C* **1966**, 1908; (d) Ceder, O.; Beijer, B. *Tetrahedron* **1972**, *28*, 4341; (e) Gewald, K.; Hain, U.; Hartung, P. *Monatsh. Chem.* **1981**, *112*, 1393; (f) Kojima, H.; Yamamoto, K.; Kinoshita, Y.; Inoue, H. *J. Heterocycl. Chem.* **1992**, *29*, 1473; (g) Hoh-Gyu, H.; Kee Dal, N.; Heduck, M. *Heterocycles* **2002**, *57*, 1697; (h) Kel'in, A. V.; Sromek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074; (i) Tverdokhlebov, A. V.; Andrushko, A. P.; Resnyanska, E. V.; Tolmachev, A. A. *Synthesis* **2004**, *14*, 2317.
3. Lalezari, I.; Schwartz, E. L. *J. Med. Chem.* **1988**, *31*, 1427.
4. Aicher, T. D.; Balkan, B.; Bell, P. A.; Brand, L. J.; Cheon, S. H.; Deems, R. O.; Fell, J. B.; Fillers, W. S.; Fraser, J. D.; Gao, J.; Knorr, D. C.; Kahle, G. G.; Leone, C. L.; Nadelson, J.; Simpson, R.; Smith, H. C. *J. Med. Chem.* **1998**, *41*, 4556.
5. Tverdokhlebov, A. V.; Resnyanska, E. V.; Tolmachev, A. A.; Andrushko, A. P. *Synthesis* **2003**, *17*, 2632.
6. (a) Baldwin, J. E.; Lee, E. *Tetrahedron* **1986**, *42*, 6551; (b) Baldwin, J. E.; Lowe, C.; Schofield, C. J.; Lee, E. *Tetrahedron Lett.* **1986**, *27*, 3461; (c) Jephcote, V. J.; John, D. I.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2195; (d) Boyd, D. B.; Elzey, T. K.; Hatfield, L. D.; Kinnick, M. D.; Morin, J. M., Jr. *Tetrahedron Lett.* **1986**, *27*, 3453; (e) Maki, Y.; Sako, M.; Kurahashi, N.; Hirota, K. *J. Chem. Soc., Chem. Commun.* **1988**, 110.
7. (a) Becher, J.; Dreier, C.; Frandsen, E. G.; Wengel, A. S. *Tetrahedron* **1978**, *34*, 989; (b) Christensen, M. C.; Becher, J. *J. Heterocycl. Chem.* **1981**, *18*, 1357; (c) Ferrarini, P. L.; Mori, C.; Badawneh, M.; Calderone, V.; Greco, R.; Manera, C.; Martinelli, A.; Nieri, P.; Saccomanni, G. *Eur. J. Med. Chem.* **2000**, *35*, 815; (d) Saccomanni, G.; Badawneh, M.; Adinolfi, B.; Calderone, V.; Cavallini, T.; Ferrarini, P. L.; Greco, R.; Manera, C.; Testai, L. *Bioorg. Med. Chem.* **2003**, *11*, 4921; (e) Da Settimo, F.; Primofiore, G.; La Motta, C.; Salerno, S.; Novellino, E.; Greco, G.; Lavecchia, A.; Laneri, S.; Boldrini, E. *Bioorg. Med. Chem.* **2005**, *13*, 491.
8. (a) Charrier, J.-D.; Landreau, C.; Deniaud, D.; Reliquet, A.; Reliquet, F.; Meslin, J. C. *Tetrahedron* **2001**, *57*, 4195; (b) Landreau, C.; Deniaud, D.; Evain, M.; Reliquet, A.; Meslin, J. C. *J. Chem. Soc., Perkin Trans. 1* **2002**, 741; (c) Landreau, C.; Deniaud, D.; Evain, M.; Reliquet, A.; Meslin, J. C. *Synthesis* **2002**, *3*, 403; (d) Pearson, M. S. M.; Robin, A.; Bourgougnon, N.; Meslin, J. C.; Deniaud, D. *J. Org. Chem.* **2003**, *68*, 8583; (e) Robin, A.; Julienne, K.; Meslin, J. C.; Deniaud, D. *Tetrahedron Lett.* **2004**, *45*, 9557; (f) Robin, A.; Julienne, K.; Meslin, J. C.; Deniaud, D. *Eur. J. Org. Chem.* **2006**, *3*, 634.
9. (a) Landreau, C.; Deniaud, D.; Reliquet, A.; Meslin, J. C. *Eur. J. Org. Chem.* **2003**, *3*, 421; (b) Landreau, C.; Deniaud, D.; Meslin, J. C. *J. Org. Chem.* **2003**, *68*, 4912.
10. (a) Pätzel, M.; Liebscher, J. *Synthesis* **1993**, 951; (b) Knoll, A.; Liebscher, J. *Synthesis* **1987**, 949; (c) Knoll, A.; Liebscher, J. *J. Prakt. Chem.* **1985**, *327*, 455.
11. Robin, A.; Meslin, J. C.; Deniaud, D. *Synthesis* **2004**, *10*, 1633.
12. Jukić, L.; Čopar, A.; Malešič, M.; Krbavčič, A.; Svete, J.; Stanovnik, B. *J. Heterocycl. Chem.* **1999**, *36*, 1147.
13. Marchand, A.; Pradère, J. P.; Guingant, A. *Tetrahedron Lett.* **1997**, *38*, 1033.
14. Stewart, J. J. P. *MOPAC 2000*; Fujitsu Limited: Tokyo, Japan, 1999.
15. Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.
16. Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209.
17. (a) Morel, G.; Marchand, E.; Pradère, J. P.; Toupet, L.; Sinbandhit, S. *Tetrahedron* **1996**, *52*, 10095; (b) Nomura, Y.; Takeuchi, Y.; Tomoda, S.; Ito, M. M. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2779.
18. Blake, A. J.; McNab, H.; Murray, M. E.-A. *J. Chem. Soc., Perkin Trans. 1* **1989**, 589.

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Total syntheses of the sesquiterpenes β-corymbolol and corymbolone

Helena M. C. Ferraz,* Antonio J. C. Souza,† Beatriz S. M. Tenius and Graziela G. Bianco

Instituto de Química, Universidade de São Paulo, CP 26.077, 05513-970 São Paulo, SP, Brazil

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This paper is dedicated to Professor Nicola Petragnani, for his invaluable contribution to the development of the Brazilian Organic Synthesis

Abstract—The first total synthesis of racemic corymbolone, an eudesmane sesquiterpene isolated from *Cyperus* species used in traditional medicine to treat many diseases, is reported. In the developed sequence, the immediate precursor of corymbolone is the diol β-corymbolol, an epimer at C_1 of the natural α-corymbolol. Thus, starting from the readily available Wieland–Miescher Ketone, the title compounds were achieved in 11 and 12 steps, respectively, in ca. 3% overall yield.

1. Introduction

Corymbolone (**1**) is a sesquiterpenic keto-alcohol first isolated in 1985, in South America, from the rhizomes of *Cyperus corymbosus* Rottboll.[1] Some years later, corymbolone was isolated in Cameroon, from *Cyperus articulatus* L., along with another eudesmane sesquiterpene, the diol α-corymbolol (**2a**).[2] Since 1994, *C. articulatus* L. and *C. corymbosus* Rottb. are treated as synonymous.[3] This cyperaceae is a tropical sedge widely distributed in southern and western Africa, where it is known as 'mandassi',[2] as well as in the Amazonian region, where it is called 'piripiri'.[4] The crude drug prepared from the rhizomes of this plant has been used in traditional medicine as contraceptive[5,6] and for treating many other diseases.[7,8]

Both corymbolone and corymbolol (Fig. 1) bear an axial hydroxyl group at the C_5 position, which is not an usual feature of the eudesmane sesquiterpenes.

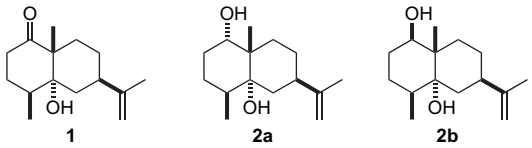
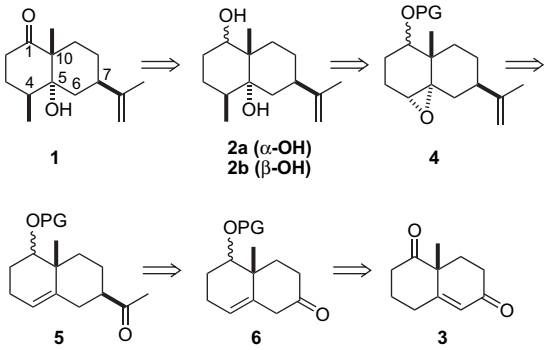


Figure 1. Corymbolone (**1**), α-corymbolol (**2a**) and β-corymbolol (**2b**).

The reported biological activity and the rare presence of an angular hydroxyl group, as well as the lack in the literature of any described synthesis of these compounds, stimulated us to investigate some approaches for their total synthesis. Thus, starting from the readily available Wieland–Miescher Ketone (**3**), we designed the retrosynthetic analysis depicted in Scheme 1.



Scheme 1. Retrosynthetic approach for **1** and **2**.

The functionalization of the A ring of **1** involves a nucleophilic opening of the α-epoxide **4**, by means of an adequate organometallic reagent, followed by oxidation of the secondary hydroxyl group of **2a** or **2b**. Since it is well known that the S_N2-type opening of cyclohexyl oxiranes is a trans-diaxial process, it can be foreseen that the organometallic reagent would attack the less substituted center (C_4) of **4** from the β-face. Therefore, the stereoselective α-epoxidation of **5** is a requirement to ensure the correct introduction of the axial methyl and hydroxyl groups at C_4

Keywords: Corymbolone; Corymbolol; Eudesmane sesquiterpenes; *Cyperaceae* species.
* Corresponding author. Tel./fax: +55 11 3091 3851; e-mail: hmferraz@iq.usp.br
† Present address: Centro de Ciências da Saúde–UNISANTOS–Santos–SP.

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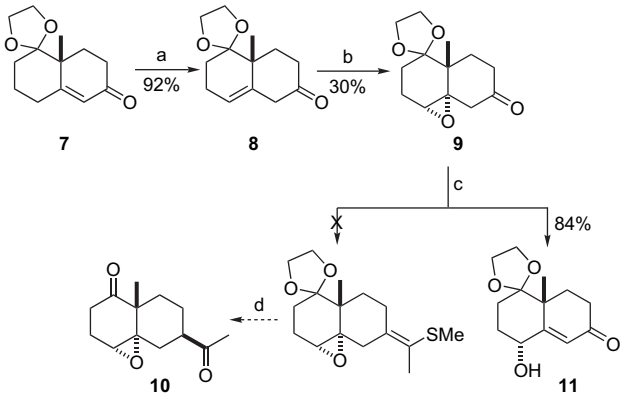
and C_5, respectively. A preferential epoxidation from the α-face could be expected, due to the steric hindrance offered by the C_{10} β-methyl group.

Concerning the B ring, the retrosynthetic analysis suggests that the isopropenyl unit could be introduced by homologation of the carbonyl group of **6**, followed by an olefination reaction of the resulting acetyl group present in **5** (or in some synthetic equivalent).

Finally, the migration of the double bond from the C_5–C_6 to the C_4–C_5 position, in an appropriate stage of the synthesis, would complete the retrosynthetic approach. The experimental results further described confirm the feasibility of the proposed sequence.

2. Results and discussion

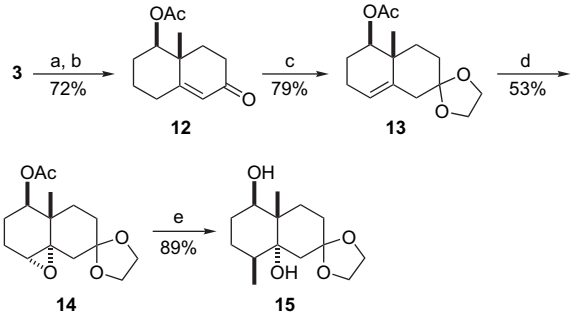
In a previous paper,[9] we presented the results of our attempts to promote the stereoselective α-epoxidation of the β,γ-unsaturated ketone **8**, obtained by deconjugation of **7**. By this first proposed protocol, the resulting product **9** would be submitted to a Horner–Emmons olefination, followed by hydrolysis, to furnish the advanced intermediate **10**. However, this sequence could not be achieved, since the desired epoxide **9** was obtained in very low yield (30%), accompanied by the reconjugated ketone **7** as the major product. Moreover, the epoxide **9** showed to be very unstable, even at 0 °C, and when submitted to the olefination reaction gave exclusively the allylic alcohol **11**, in 84% yield (Scheme 2). The formation of this alcohol can be rationalized on the basis of a deprotonation at C_6, with subsequent opening of the epoxide ring.



Scheme 2. Reagents and conditions: (a) i: *t*-BuOK/*t*-BuOH, 1 h, rt; ii: NaH_2PO_4 0.3 M; (b) *m*-CPBA, CH_2Cl_2, 2 h, rt; (c) $(EtO)_2P(O)CHCH_3(SMe)$, THF, 4 h, −78 °C and (d) H_3O^+.[9]

In view of these disappointing results, we formulated a second synthetic approach,[10] where none of the intermediates has acidic protons at C_6, for circumventing the undesirable reactions mentioned above. The envisaged key-intermediate of the new sequence was the α-epoxide **14**, which could be obtained from the ketone **3** (Scheme 3).

Thus, the acetate **12** was easily obtained by reduction[11] and acetylation[12] of **3**. The deconjugative ketalization of **12** was undertaken by treatment with ethylene glycol in the presence of *p*-TSA, leading to **13**[12] as a white crystalline solid.



Scheme 3. Reagents and conditions: (a) $NaBH_4$, EtOH, 0 °C, 92%; (b) Ac_2O, py, DMAP, rt, 78%; (c) ethylene glycol, *p*-TSA, PhH, 12 h, reflux; (d) *m*-CPBA, CH_2Cl_2, 3 h, rt and (e) MeMgI, CuI, Et_2O, 8 h, rt.[10]

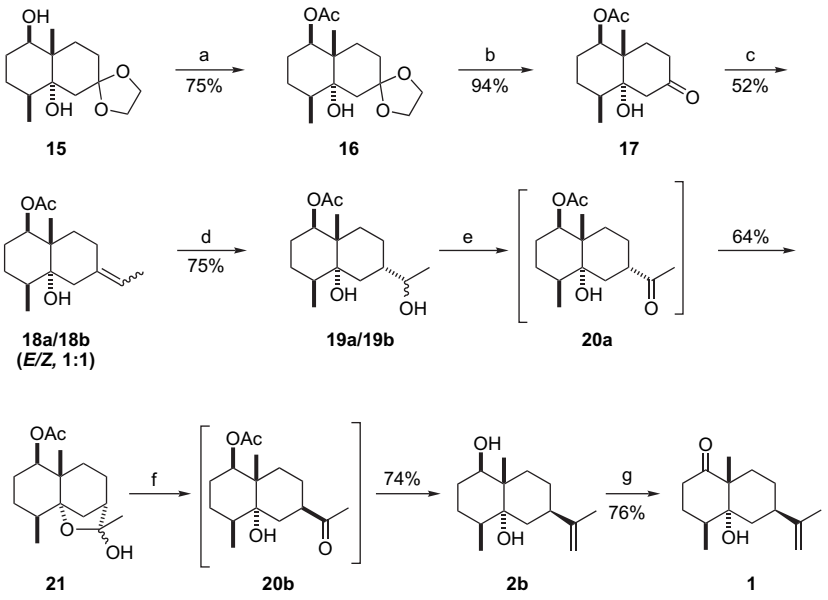
It must be noted that some years after the publication of the above mentioned results,[10] the same sequence of reactions (from **3** to **13**) was employed by Danishefsky et al. in the total syntheses of baccatin III and taxol.[13]

The epoxidation of **13** was performed by classical conditions (*m*-CPBA in dichloromethane), giving a diastereomeric mixture (ca. 7:3, by ^1H NMR analysis) of the epoxides, which were separated by silica column chromatography into the pure α-isomer **14** (53%) and the corresponding β-isomer (19%). The correct structure of **14** was determined by NMR spectroscopy, and confirmed by X-ray analysis.[14]

Although a greater ratio of the desired α-epoxide had been expected a priori, the lower assessed α/β ratio can be probably attributed to a competitive hindrance between the C_{10} β-methyl group and the α-oxygen of the ketal group at C_7. Other epoxidizing reagents (DMD and TBHPMo) were then tried, not only on the intermediate **13**, but also on other related substrates.[15] The results thus obtained were more unfavourable, since the major isomers were always the β-epoxides. We have then decided to pursuit the synthetic route using the earlier protocol (*m*-CPBA-promoted epoxidation of **13**), in spite of the moderate yield of **14**.

The trans-diaxial opening of the epoxide **14** was best performed employing methylmagnesium iodide in the presence of 10% of cuprous iodide, although with loss of the protecting group at C_1. Eventually, the presence of the copper salt should preserve the chemoselectivity towards the epoxide ring, therefore avoiding the attack to the acetyl group. Nevertheless, a great excess of the Grignard reagent was required to achieve good results in the epoxide opening, since 2 equiv were consumed by the acetate group, giving the diol **15** as final product. At this point, the synthetic problems concerning the construction of the ring A of the target molecule were solved.

The introduction of the isopropenyl unit at C_7, as stated in the retrosynthetic analysis, would be possible following a sequence of reactions already employed by Heathcock et al.,[12] and by de Groot et al.,[16] in their syntheses of other eudesmane sesquiterpenes. The approach consists in a Wittig reaction at the C_7 carbonyl group, followed by hydroboration of the C_7–C_{11} double bond, oxidation of the hydroxyl group at C_{11} and, finally, another olefination of the resulting methyl ketone.



Scheme 4. Reagents and conditions: (a) Ac_2O, Et_3N, DMAP, 72 h, rt; (b) AcOH, 20 min, 65°C; (c) $Ph_3P{=}CHCH_3$, DMSO, 15 min, rt; (d) i: $BH_3{\cdot}THF$, 21 h, rt; ii: NaOH 3 N, H_2O_2, 15 min, rt; (e) PCC, AcONa, CH_2Cl_2, 3 h, rt; (f) $Ph_3P{=}CH_2$, DMSO, 7 h, 50°C and (g) PCC, CH_2Cl_2, 3 h, rt.

The complete sequence from **15** to **1**, and hence to **2b**, was accomplished with success, as summarized in Scheme 4.

Since the first step in the construction of the ring B would be a Wittig olefination of the regenerated carbonyl group at C_7, the protection of both the hydroxyl groups in **15** seemed to be a requirement. We attempted at first the diacetylation of **15**, by treatment with Ac_2O/Et_3N under DMAP catalysis. Unfortunately, several experiments employing these conditions, as well as changing Et_3N for pyridine, and running the reaction at different times and temperatures, furnished exclusively the monoacetylated derivative **16**. Attempts to protect the C_5 hydroxyl group of **16** with different alkoxy groups were also fruitless.

In view of this somewhat surprising stability of **15** and **16** towards both acidic and basic media, we decided to disregard the protection of the tertiary alcohol and to submit the ketone **17** directly to the Wittig reaction. It must be pointed out that a successful Wittig reaction in a hydroxylated substrate has already been reported.[16] In a first set of experiments, **17** was treated with excess (ranging from 2 to 5 equiv) of ethylidene triphenylphosphorane in ethyl ether, at room temperature, furnishing the desired olefin **18** as a mixture of *E* and *Z* isomers, in poor yields. The main product of these reactions was the α,β-unsaturated ketone formed by dehydration of **17**. Under these conditions, the best yield of **18** was 29%.

Assuming that the low yield of **18** could be due not only to the concurrence of the elimination reaction, but also to the low solubility of **17** in ethyl ether, a set of experiments was performed using DMSO as the solvent (where the substrate is more soluble) and the corresponding lithium dimsyl as the base. Under these conditions, and using 2 equiv of the phosphonium salt, the desired olefin **18** was obtained in a considerably increased yield. A rigorous control of the reaction time showed to be necessary, the best result (52% yield) being achieved after 15 min at room temperature. Although quite modest, this yield can be considered acceptable, since it was recompensed by accomplishing the conversion of **17** into **18** in a single step, avoiding the protection (and subsequent deprotection) of the hydroxyl group at C_5.

The regioselective hydroboration of **18** gave mainly, as expected, the anti-Markovnikov product **19** (75% yield, after silica column chromatography), together with minor amounts of its regioisomer. The stereoselectivity of the reaction was remarkably high, with the hydroxyalkyl substituent at C_7 assuming exclusively the undesired α-axial position. Probably, this high stereoselectivity is due to the steric hindrance offered by the axial hydroxyl group at C_5.

Considering the relative configurations of corymbolone and α-corymbolol, an essential requirement for pursuing the synthesis would be the axial to equatorial inversion of the hydroxyalkyl substituent at C_7. An obvious attempt involves the oxidation of **19**, expecting that the produced methyl ketone (**20a**) would assume the thermodynamically more stable equatorial position (**20b**). Nevertheless, the oxidation of **19**, using PCC in the presence of AcONa, led directly to the lactol **21**, instead of the expected methyl ketone.

Fortunately, the desired epimerization of C_7 was successfully achieved by submitting the lactol **21** to a Wittig reaction with methylene triphenylphosphorane. The highly basic medium of the reaction promoted the opening of the hemiketal **21**, followed by equilibration to **20b**, which was then converted irreversibly into the olefinic product. The conditions employed—warming at 50 °C—also promoted the deprotection of the hydroxyl group at C_1, in contrast to that observed in the olefination of **17**, performed at room temperature.

Therefore, to our delight, β-corymbolol (**2b**) was obtained in a single step from the lactol **21**, in 74% yield. Finally, the oxidation of **2b** to corymbolone (**1**) was performed in 76% yield, by treatment with PCC.

In summary, the first total syntheses of racemic β-corymbolol and corymbolone was accomplished in 11 and 12 steps, respectively, from the commercially available Wieland–Miescher Ketone (**3**). As the enantiomerically pure ketone **3** can be easily prepared,[17,18] the approach herein reported could be adapted for the chiral synthesis of the title compounds. Since α-corymbolol (**2a**) was already obtained by reduction of corymbolone,[2] our sequence also represents a racemic formal synthesis of this natural product.

3. Experimental

3.1. General

Melting points (Kofler hot-stage) are uncorrected. ^{1}H NMR spectra were recorded at 200 MHz on a Bruker AC-200 spectrometer, in $CDCl_3$, using TMS as an internal standard. ^{13}C NMR spectra were recorded at 50.3 MHz on a Bruker AC-200 spectrometer. IR spectra were measured on a Perkin–Elmer 1750 or Nicolet 510 FT-IR Spectrometer. Mass spectra were measured with a Finnigan MAT (ITD) 800. The intermediates **12–15** were prepared as previously described.[10]

3.2. 1β-Acetoxy-5α-hydroxy-4β,10β-dimethyl-7,7-ethylenodioxy-decalin (16)

To a solution of the alcohol **15** (0.15 g, 0.59 mmol) in Et_3N (5 mL) was added Ac_2O (1 mL), followed by DMAP (some crystals) at room temperature. After stirring for 72 h the reaction mixture was diluted with MeOH (10 mL). The mixture was concentrated under reduced pressure and the residue was quenched with diluted HCl and extracted with AcOEt. The organic layer was washed with satd aq $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography ($CHCl_3$/AcOEt, 7:3 as eluent), to give **16** as an oil, which decomposes partially to the corresponding ketone **17**, and therefore was used without further purification (75%; 0.13 g, 0.44 mmol). ^{1}H NMR δ 5.06 (dd, J 7.8, 6.1 Hz, 1H), 4.27 (s, 1H), 3.93–3.79 (m, 4H), 2.05 (d, J 14.0 Hz, 1H), 1.90 (s, 3H), 2.22–1.15 (m, 10H), 0.99 (s, 3H), 0.89 (s, 3H); ^{13}C NMR δ 170.4, 109.6, 76.9, 76.8, 64.1, 63.7, 41.1, 39.2, 38.8, 31.2, 30.4, 25.8, 22.6, 21.0, 16.2, 16.0; IR (film) ν_{max}: 3431, 2931, 1730, 1247, 986 cm^{-1}.

3.3. 1β-Acetoxy-4β,10β-dimethyl-5α-hydroxy-octal-7-one (17)

A solution of **16** (0.53 g, 1.8 mmol) in AcOH (5 mL) was stirred at 65 °C for 20 min, and then cooled to 10 °C, when a satd solution of $NaHCO_3$ was added. After extraction with AcOEt, the organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexanes/AcOEt, 7:3 as eluent), affording **17** (94%; 0.42 g, 1.7 mmol) as white crystals. Mp 184–185 °C; ^{1}H NMR δ 5.12 (dd, J 8.0, 6.3 Hz, 1H), 2.90 (d, J 14.7 Hz, 1H), 2.85–1.32 (m, 11H), 2.00 (s, 3H), 1.27 (s, 3H), 1.06 (d, J 7.6 Hz, 3H); ^{13}C NMR δ 211.9, 170.6, 80.5, 76.8, 50.0, 40.9, 40.6, 37.5, 33.9, 25.8, 22.6, 21.1, 17.2, 16.0; IR (film) ν_{max}: 3405, 2935, 1726, 1699, 1256 cm^{-1}; MS (EI) m/z (%) 254 ($M^{\bullet+}$, 2), 109 (100); Anal. Calcd for $C_{14}H_{22}O_4$: C=66.12%, H=8.72%; Found: C=66.51%, H=9.05%.

3.4. *E*- and *Z*-1β-Acetoxy-4β,10β-dimethyl-5α-hydroxy-7-ethylidene decalin (18a/18b)

n-BuLi (1.7 M in hexane; 2.1 mL, 3.5 mmol) was added to anhydrous DMSO (20 mL), under N_2 atmosphere. After stirring for 30 min, ethyl triphenylphosphonium bromide (1.6 g; 4.3 mmol) was added and the mixture was stirred for 1 h at room temperature. A solution of **17** (0.40 g; 1.6 mmol) in anhydrous DMSO (10 mL) was added, the mixture was stirred for 15 min at room temperature and then poured into H_2O (100 mL). After extraction with AcOEt, the organic layer was washed with satd NaCl solution, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was chromatographed on silica gel (hexanes/AcOEt, 9:1 as eluent) to give a 1:1 mixture of **18a/18b** (52%; 0.22 g, 0.83 mmol). ^{1}H NMR δ 5.50 (q, J 6.6 Hz, 1/2H), 5.23 (q, J 6.7 Hz, 1/2H), 5.08 (dd, J 10.4, 5.7 Hz, 1H), 2.90–1.20 (m, 15H), 2.00 (s, 3H), 1.16 (s, 3H), 1.06 (d, J 8.1 Hz, 3/2H), 1.02 (d, J 8.2 Hz, 3/2H); ^{13}C NMR δ 170.8, 135.7/135.5, 121.9/121.7, 77.4, 76.8/76.4, 43.6, 42.2, 39.2/39.1, 35.7/35.3, 34.9/31.3, 26.4, 22.9/22.8, 21.2, 16.6/16.5, 16.1/15.8, 12.9/12.6; IR (film) ν_{max}: 3509, 2959, 2931, 1714, 1263 cm^{-1}; MS (EI) m/z (%) 266 ($M^{\bullet+}$, 2), 124 (100); Anal. Calcd for $C_{16}H_{26}O_3$: C=72.14%, H=9.84%; Found: C=71.71%, H=9.53%.

3.5. 1β-Acetoxy-4β,10β-dimethyl-5α-hydroxy-7α-(1′-hydroxy)-ethyl decalin (19a and 19b)

A solution of $BH_3\cdot THF$ (1.0 M; 2.9 mL, 2.9 mmol) was slowly added to a solution of **18** (0.19 g, 0.71 mmol) in anhydrous THF (15 mL) at 0 °C, under N_2. The mixture was stirred for 21 h at room temperature and then for 1 h at reflux. The reaction mixture was cooled to 0 °C, and a mixture of NaOH 3 M (2 mL) and H_2O_2 30% (1.8 mL) was added. After stirring for 15 h at room temperature, the mixture was stirred for 1 h under reflux and then was allowed to reach room temperature, when brine was added. The layers were separated and the aqueous phase was then extracted with CH_2Cl_2. The combined organic phases were concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexanes/AcOEt, 7:3 as eluent), to give a 1:1 mixture of the diastereoisomeric diols **19a** and **19b** (75%; 0.15 g, 0.53 mmol). Analytical samples were obtained by further purification. **19a**: ^{1}H NMR δ 5.10 (dd, J 10.4, 5.8 Hz, 1H), 4.54 (br s, 2H), 3.90 (q, J 6.4 Hz, 1H), 2.40 (dd, J 14.7, 7.9 Hz, 1H), 2.31–1.58 (m, 11H), 1.99 (s, 3H), 1.19 (d, J 6.4 Hz, 3H), 1.08 (s, 3H), 1.04 (d, J 7.7 Hz, 3H); ^{13}C NMR δ 171.0, 77.3, 75.8, 73.6, 41.0, 39.6, 38.1, 37.1, 31.5, 26.2, 22.8, 22.7, 21.2, 17.7, 17.2, 16.4; IR (film) ν_{max}: 3367, 2931, 1714, 1248, 1083 cm^{-1}.

19b: ^{1}H NMR δ 5.10 (dd, J 10.9, 5.4 Hz, 1H), 3.98 (q, J 6.1 Hz, 1H), 3.41 (br s, 2H), 2.29–1.29 (m, 12H), 2.00 (s, 3H), 1.17 (d, J 6.2 Hz, 3H), 1.09 (s, 3H), 1.03 (d, J 7.6 Hz, 3H); ^{13}C NMR δ 171.0, 77.1, 75.6, 70.9, 41.3, 39.8, 38.3, 30.5, 30.2, 26.2, 23.6, 22.8, 22.5, 21.2, 17.1, 16.3; IR (film) ν_{max}: 3156, 2971, 2959, 1729, 1248 cm^{-1}.

Anal. Calcd for $C_{16}H_{28}O_4$: C=67.57%, H=9.92%; Found: 67.30%, H=10.13%.

3.6. 5-7(1′)-Hemiacetal of 1β-acetoxy-4β,10β-dimethyl-5α-hydroxy-7α-(1′-oxo-1′-methyl)-decalin (21)

To a solution of **19a/19b** (0.080 g, 0.28 mmol) in CH_2Cl_2 (10 mL), was added PCC (0.16 g, 0.74 mmol), followed by anhydrous NaOAc (0.018 mg, 0.22 mmol). After stirring for 3 h at room temperature, the reaction mixture was quenched with water and diluted with CH_2Cl_2. The organic layer was washed with $NaHCO_3$ (5%) and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was chromatographed on silica gel (hexanes/AcOEt, 7:3 as eluent), to give **21** (64%; 0.051 g, 0.18 mmol). This product showed to be very unstable and was employed in the next step without any purification. ^{1}H NMR δ 4.92 (dd, *J* 9.2, 6.7 Hz, 1H), 2.18–1.19 (m, 13H), 2.01 (s, 3H), 1.50 (s, 3H), 1.11 (s, 3H), 1.03 (d, *J* 7.5 Hz, 3H); ^{13}C NMR δ 170.8, 104.7, 90.8, 79.8, 44.9, 42.4, 39.4, 36.0, 33.8, 27.0, 23.5, 22.4, 22.3, 21.2, 17.4, 16.7.

3.7. Octahydro-4β,8aβ-dimethyl-6β-(1-methylethenyl)-1β,4aα-(2*H*)-naphthalenediol; corymbolol (2b)[2]

To anhydrous DMSO (20 mL) under N_2, *n*-BuLi (2.5 M in hexane; 0.92 mL, 2.3 mmol) was added. After stirring for 30 min, methyl triphenylphosphonium bromide (0.82 g; 2.3 mmol) was added and the mixture was stirred for 1 h. A solution of **21** (0.13 g; 0.46 mmol) in anhydrous DMSO (5 mL) was added and the mixture was stirred for 7 h at 50 °C. After this period the reaction mixture was quenched with water (50 mL) and extracted with AcOEt, the organic layer was washed with satd NaCl solution, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was chromatographed on silica gel (hexanes/AcOEt, 7:3 as eluent), to give **2b** as an oil (74%; 0.081 g, 0.34 mmol). ^{1}H NMR δ 4.73 (s, 2H), 3.89 (dd, *J* 10.5, 5.9 Hz, 1H), 2.48–1.19 (m, 14H), 1.75 (s, 3H), 1.04 (d, *J* 7.2 Hz, 3H), 1.02 (s, 3H); ^{13}C NMR δ 150.2, 108.5, 77.4, 74.1, 41.7, 41.1, 39.6, 38.3, 33.2, 26.7, 26.3, 25.9, 21.0, 16.7, 15.5; IR (film) ν_{max}: 3422, 2941, 2867, 1456, 1011 cm^{-1}; MS (EI) *m*/*z* (%) 220 ([M−H_2O]$^{\bullet+}$, 2), 109 (100).

3.8. Octahydro-4aα-hydroxy-4β,8aβ-dimethyl-6β-(1-methylethenyl)-1(2*H*)-naphthalenone; corymbolone (1)[1]

To a solution of **2b** (0.040 g, 0.17 mmol) in CH_2Cl_2 (10 mL), PCC (0.11 g, 0.51 mmol) was added. After stirring for 3 h at room temperature, the reaction mixture was quenched with water and diluted with CH_2Cl_2. The organic layer was washed with $NaHCO_3$ (5%) and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was chromatographed on silica gel (hexanes/AcOEt, 7:3 as eluent), to give **1** as an oil (76%; 0.031 g, 0.13 mmol). ^{1}H NMR δ 4.74 (s, 2H), 2.72–2.60 (m, 1H), 2.48–2.33 (m, 3H), 1.96–1.32 (m, 9H), 1.75 (s, 3H), 1.24 (s, 3H), 1.19 (d, *J* 7.5 Hz, 3H); ^{13}C NMR δ 215.8, 149.5, 108.9, 78.6, 51.2, 40.5, 39.3, 37.2, 34.2, 30.1, 27.9, 25.4, 21.1, 20.4, 17.7; IR (film) ν_{max}: 3430, 2959, 2927, 2859, 1692 cm^{-1}; MS (EI) *m*/*z* (%) 236 (M$^{\bullet+}$, 10), 109 (100).

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References and notes

1. Garbarino, J. A.; Gambaro, V.; Chamy, M. C. *J. Nat. Prod.* **1985**, *48*, 323.
2. Nyasse, B.; Tih, R. G.; Sondengam, B. L.; Martin, M. T.; Bodo, B. *Phytochemistry* **1988**, *27*, 179.
3. Gordon-Gray, K. D.; Ward, C. J.; Edwards, T. J. *S. Afr. J. Bot.* **2006**, *72*, 147 and references cited therein.
4. Zoghbi, M. G. B.; Andrade, E. H. A.; Oliveira, J.; Carreira, L. M. M.; Guilhon, G. M. S. P. *J. Essent. Oil Res.* **2006**, Jan/Feb.
5. Maxwell, N. *Americas*; Organization of American States: Washington, DC, 1977; Vol. 29, portuguese version, p 2.
6. Garbarino, J. A.; Chamy, M. C.; Gambaro, V. *Phytochemistry* **1985**, *24*, 2726.
7. Ngo Bum, E.; Lingenhoehl, K.; Rakotonirina, A.; Olpe, H.-R.; Schmutz, M.; Rakotonirina, S. *J. Ethnopharmacol.* **2004**, *95*, 303.
8. Duarte, M. C. T.; Figueira, G. M.; Sartoratto, A.; Rehder, V. L. G.; Delarmelina, C. *J. Ethnopharmacol.* **2005**, *97*, 305.
9. Ferraz, H. M. C.; Tenius, B. S. M. *An. Acad. Bras. Cienc.* **1989**, *61*, 147.
10. Souza, A. J. C.; Ferraz, H. M. C.; Tenius, B. S. M. *Quim. Nova* **1993**, *16*, 105.
11. Boyce, C. B. C.; Whitehurst, J. S. *J. Chem. Soc.* **1960**, 2680.
12. Heathcock, C. H.; Ratcliffe, R. *J. Am. Chem. Soc.* **1971**, *93*, 1746.
13. Danishefsky, S. J.; Masters, J. J.; Young, W. B.; Link, J. T.; Snyder, L. B.; Magee, T. V.; Jung, D. K.; Isaacs, R. C. A.; Bornmann, W. G.; Alaimo, C. A.; Coburn, C. A.; Di Grandi, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 2843.
14. Castellano, E. E.; Zukerman-Schpector, J.; Ferraz, H. M. C.; Souza, A. J. C.; Tenius, B. S. M. *Acta Crystallogr.* **1992**, *C48*, 2080.
15. Ferraz, H. M. C.; Muzzi, R. M.; Vieira, T. O.; Viertler, H. *Tetrahedron Lett.* **2000**, *41*, 5021.
16. Kesselmans, R. P. W.; Wijnberg, J. B. P. A.; Minnaard, A. J.; Walinga, R. E.; de Groot, A. *J. Org. Chem.* **1991**, *56*, 7237.
17. Fuhshuku, K.; Funa, N.; Akeboshi, T.; Ohta, H.; Hosomi, H.; Ohba, S.; Sugai, T. *J. Org. Chem.* **2000**, *65*, 129 and references cited therein.
18. Kasai, Y.; Shimanuki, K.; Kuwahara, S.; Watanabe, M.; Harada, N. *Chirality* **2006**, *18*, 177.

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Highly enantioselective hydrogenation of exocyclic double bond of *N*-tosyloxazolidinones catalyzed by a neutral rhodium complex and its synthetic applications

Zengming Shen, Xiyan Lu* and Aiwen Lei

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China

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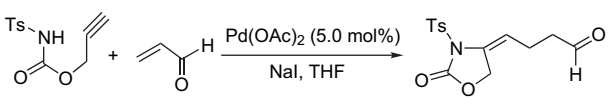
Abstract—A highly enantioselective synthesis of optically active *N*-tosyl-4-alkyl-1,3-oxazolidin-2-ones based on the asymmetric hydrogenation of the trisubstituted exocyclic double bond of *N*-tosyl-4-alkylidene-1,3-oxazolidin-2-ones under the catalysis of neutral $[Rh(COD)Cl]_2$ (COD=1,5-cyclooctadiene) and (*S*)-(+)-DTBM-SEGPHOS was developed. The utility of this highly enantioselective reaction was exemplified by the synthesis of optically active amino acids, amino alcohols, and piperidine derivatives.

1. Introduction

Amino acids,[1] amino alcohols,[2] and piperidine derivatives[3] are compounds of immense interest in nature and importance for the pharmaceutical industry. In addition to their biological importance, they are widely used as catalysts or chiral ligands in many organic or transition-metal catalyzed transformations.[2–5] Thus to develop a synthetic method of experimental simplicity and high generality for these amino acids, amino alcohols, and piperidine derivatives is a challenge for organic chemists.

In our previous work, *N*-tosyloxazolidinones with a trisubstituted exocyclic double bond were conveniently synthesized under the catalysis of the Pd(II) species (Scheme 1).[6] The asymmetric hydrogenation of the trisubstituted exocyclic double bond will afford homochiral *N*-tosyl-4-alkyl-1,3-oxazolidin-2-ones, which can be used as the intermediates for the synthesis of homochiral amino acids, amino alcohols, and piperidine derivatives.



Scheme 1. Synthesis of *N*-tosyl-4-alkylidene-1,3-oxazolidin-2-ones.

However, the asymmetric hydrogenation of the trisubstituted exocyclic double bond of *N*-tosyl-4-alkylidene-1,3-oxazolidin-2-ones has not been reported in the literatures.[7–11] Dixneuf reported the enantioselective hydrogenation of *N*-acyl-4-methylene-1,3-oxazolidin-2-ones catalyzed by a chiral BINAP–Ru complex with 99% ee,[10] but the exocyclic double bond in their substrates is disubstituted, not trisubstituted, and the substituent on the nitrogen atom is an acyl group rather than a tosyl group. Herein, we wish to report the enantioselective hydrogenation of the trisubstituted exocyclic double bond of *N*-tosyloxazolidinones to the optically active *N*-tosyl-4-alkyl-1,3-oxazolidin-2-ones with high enantioselectivity and its application for synthesizing the optically active amino acids, amino alcohols, and piperidine derivatives.

2. Results and discussion

Initially, *N*-tosyloxazolidinone (**1**) was used as the substrate for the asymmetric hydrogenation. Nearly no reaction occurred using chiral BINAP–Ru(II) complexes as the catalyst (Table 1, entries 1–3). Using the cationic $[Rh(COD)_2]OTf$ and (*S*)-BINAP as the catalyst, the hydrogenation of compound **1** only afforded unexpected product **3** (Table 1, entries 4 and 5) in which not only the exocyclic double bond was hydrogenated, but also the acetal group was transformed to an ether with the cleavage of one of the ethoxy groups. Similar phenomena were observed using the cationic $[Rh(COD)_2]BF_4$ and (*R*)-(−)-DTBM-SEGPHOS (Table 1, entry 11). This implied that the cationic Rh catalysts exhibited higher catalytic activities for hydrogenation, but gave

Keywords: Enantioselective hydrogenation; Exocyclic double bonds; *N*-Tosyloxazolidinones; Rhodium complex.
* Corresponding author. Tel.: +86 21 54925158; fax: +86 21 64166128; e-mail: xylu@mail.sioc.ac.cn

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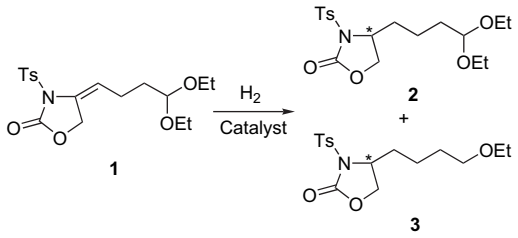
Table 1. Hydrogenation of *N*-tosyl-4-alkylidene-1,3-oxazolidin-2-ones catalyzed by different metal complexes[a]



Entry	Metal species	Solvent	Yield(%)[b]/ee(%)[c]	
			2	**3**
1[d]	[RuCl((*S*)-BINAP)(PhH)]Cl	EtOH	4/58	—
2[d]	$[NH_2Et_2][\{RuCl((S)\text{-BINAP})\}_2(\mu\text{-}Cl)_3]$	CH_2Cl_2	—	—
3[d]	$[NH_2Et_2][\{RuCl((S)\text{-BINAP})\}_2(\mu\text{-}Cl)_3]$	EtOH	—	—
4[e]	$[Rh(COD)_2]OTf$	CH_2Cl_2	—	35/20
5[e]	$[Rh(COD)_2]OTf$	Toluene	—	29/12
6[f]	$[Rh(COD)Cl]_2$	EtOH	47/16	—
7[f]	$[Rh(COD)Cl]_2$	CH_2Cl_2	40/43	—
8[g]	$[Rh(COD)Cl]_2$	CH_2Cl_2	90/43	—
9[g]	$[Rh(COD)Cl]_2$	Toluene	92/29	—
10[g]	$[Ir(COD)Cl]_2$	CH_2Cl_2	67/30	—
11[e]	$[Rh(COD)_2]BF_4$	CH_2Cl_2	—	40/5

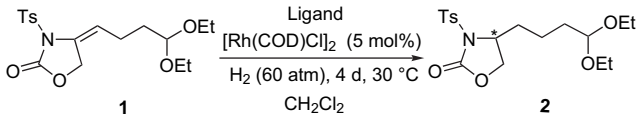
[a] Using (*S*)-BINAP (entries 4–10) and (*R*)-(−)-DTBM-SEGPHOS[13] (entry 11) as ligand.
[b] Isolated yield.
[c] ee values were determined by HPLC.
[d] Conditions: H_2 (100 atm), 50 °C, 2 days, substrate/catalyst=33/1 (entry 1), substrate/catalyst=50/1 (entries 2 and 3).
[e] Conditions: H_2 (60 atm), 30 °C, 4 days, substrate/catalysts/ligand=10/0.96/1.
[f] Conditions: H_2 (30 atm), 30 °C, 2.6 days, substrate/metal species/ligand=20/1/2.2.
[g] Conditions: H_2 (60 atm), 30 °C, 4 days, substrate/metal species/ligand=20/1/2.2.

low ee values.[12] Fortunately, the hydrogenation of compound **1** using the catalyst generated in situ from neutral $[Rh(COD)Cl]_2$ and (*S*)-BINAP gave the expected product **2** in medium yield (Table 1, entries 6 and 7). When the pressure of hydrogen was increased to 60 atm and the reaction time was prolonged to 4 days, the yield was increased to 90% in CH_2Cl_2 and 92% in toluene (Table 1, entries 8 and 9). The ee value was higher in CH_2Cl_2 (43% ee) (Table 1, entry 8). A similar result was obtained using the combination of neutral $[Ir(COD)Cl]_2$ and (*S*)-BINAP (Table 1, entry 10).

Different chiral ligands were tried for screening to improve the enantioselectivity of product **2** using $[Rh(COD)Cl]_2$ as the catalyst precursor under the typical conditions of H_2 (60 atm) at 30 °C in CH_2Cl_2 for 4 days. The use of (−)-DIOP,[14] (*S*,*S*)-BPPM,[15] (*R*, S_P)-**4**,[16] and (*S*)-**5**[17] as ligands gave low yields and ee values (Table 2, entries 1–4). Using (*R*)-tol-BINAP, (*S*)-H_8-BINAP,[18] and (*S*)-SEGPHOS[13] as ligands, the yields were excellent but with medium ee values (Table 2, entries 5–7). Fortunately, excellent enantioselectivity (93% ee) was observed for the combination of $[Rh(COD)Cl]_2$ and (*R*)-(−)-DTBM-SEGPHOS,[13] which exhibits higher steric hindrance and electron-rich properties, but the yield was still not satisfactory (Table 2, entry 8; Scheme 2).

Finally, nearly quantitative yield (99%) and high enantioselectivity (92% ee) were obtained when toluene was used

Table 2. Asymmetric hydrogenation of *N*-tosyloxazolidinone with different chiral ligands[a]



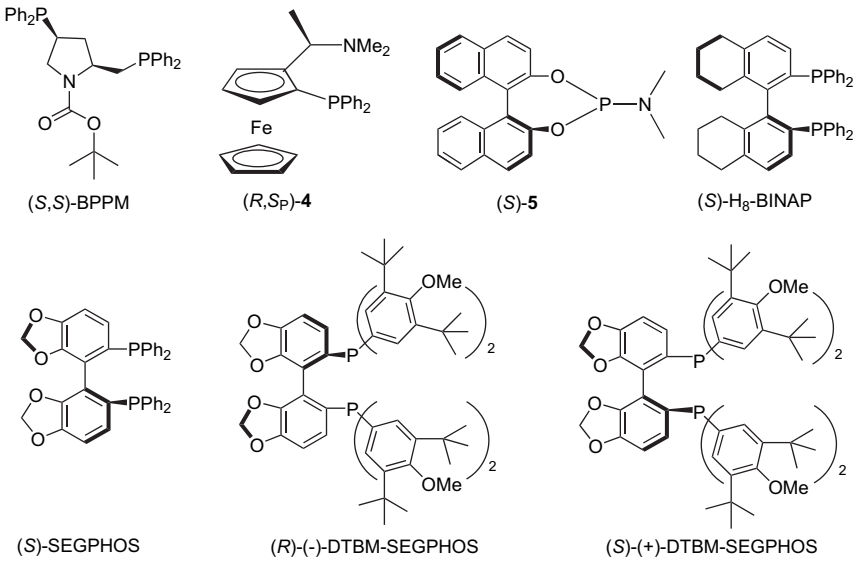
Entry	Ligand	Yield (%)[b]	ee (%)[c]
1	(−)-DIOP	47	7 (+)
2	(*S*,*S*)-BPPM	9	—
3	(*R*, S_P)-**4**	9	16 (−)
4[d]	(*S*)-**5**	Trace	—
5	(*R*)-Tol-BINAP	86	47 (−)
6[e]	(*S*)-H_8-BINAP	91	42 (+)
7[e]	(*S*)-SEGPHOS	99	53 (+)
8[e]	(*R*)-(−)-DTBM-SEGPHOS	52	93 (−)

[a] Reactions were carried out in dry and oxygen-free CH_2Cl_2 with substrate (0.013 M)/metal species/ligand=20/1/2.2 at 30 °C under 60 atm hydrogen pressure during 4 days.
[b] Isolated yield.
[c] ee values were determined by HPLC. The sign of optical rotation was shown in the parenthesis.
[d] Substrate (0.013 M)/metal species/ligand=20/1/4.2.
[e] Substrate (0.1 mmol, 0.026 M).

as the solvent instead of CH_2Cl_2 (Table 3, entry 1). When the amount of catalyst was decreased to 0.5 mol %, excellent enantioselectivity (97% ee) was achieved (Table 3, entry 2).

With this good result in hand, the asymmetric hydrogenation of different kinds of exocyclic double bonds was tried (Table 4). Most of the substrates gave high yield,[19] but the enantioselectivity of the reaction appeared relatively sensitive to the structure of the substrates. (1) Compounds **1** and **6a** gave the highest enantioselectivity. The terminal olefin in (*E*)-**6a** or the acetal group in **1** is possible to coordinate with the metal atom of the catalyst, making the asymmetric hydrogenation of (*E*)-**6a** and **1** more efficient (Table 3, entry 2; Table 4, entry 1). (2) The configuration of exocyclic double bond showed an important effect on the enantioselectivity of the asymmetric hydrogenation (Table 4, entries 1–3, compare (*E*)-**6a**, (*E*)-**6b**, and (*Z*)-**6c**). (3) The bulkiness of the neighboring group of the exocyclic double bond could also influence the enantioselectivity (Table 4, compare entries 4–6). *N*-Acyl-4-methylene-1,3-oxazolidin-2-one (**6f**) could be hydrogenated under our reaction conditions with excellent yield and satisfactory enantioselectivity (Table 4, entry 7).

The result of the high enantioselectivity of the hydrogenation of the exocyclic double bonds encouraged us to use the homochiral oxazolidinones as a synthon for synthesizing optically active compounds. Lysine is considered as an indispensable amino acid for growth of animals.[20] While several methods for synthesizing L-lysine have been reported,[21] a convenient method with high efficiency is still a challenge especially a method for the synthesis of both enantiomers by simply changing the configuration of the chiral ligand. Thus, natural lysine derivative was selected as the first target as shown in Scheme 3. According to our previous work,[6] 4-alkylidene-*N*-tosyloxazolidinone (**10**) can be selectively prepared from compound **9** and acrolein by a Pd(II) catalyzed reaction. Subsequent treatment of **10** with triethyl orthoformate in the presence of a catalytic amount of *p*-toluenesulfonic acid (PTSA) led to *N*-tosyloxazolidinone (**1**) in 88% yield. The enantioselective hydrogenation of



Scheme 2. Chiral ligands for asymmetric hydrogenation.

Table 3. Asymmetric hydrogenation of **1** leading to **2**[a]

Entry	[Rh(COD)Cl]$_2$ (mol %)	(*R*)-(−)-DTBM-SEGPHOS (mol %)	Yield (%)[b]	ee (%)[c]
1[d]	5	10	99	92
2[e]	0.5	1.0	100	97

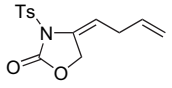
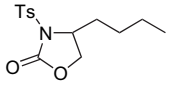
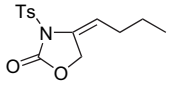
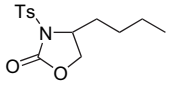
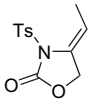
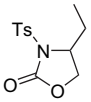
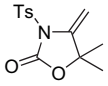
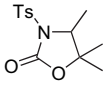
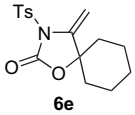
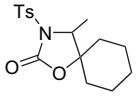
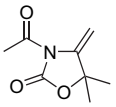
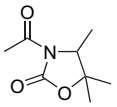
[a] Conditions: H_2 (60 atm), toluene, 30 °C, 4 days.
[b] Isolated yield.
[c] ee values were determined by HPLC.
[d] Substrate (0.1 mmol, 0.026 M).
[e] Substrate (14.4 mmol, 0.13 M).

compound **1**, using (*S*)-(+)-DTBM-SEGPHOS as ligand, gave chiral saturated *N*-tosyloxazolidinone (**2**) in quantitative yield with 97% ee. The lysine derivative **14** was finally achieved by further transformations. Compound **14** was characterized as the L-lysine derivative by comparison with the natural lysine derivative.[21d] The enantiomeric excess of compound **14** was measured by converting **14** to its methyl ester **15** (98% ee). The D-lysine derivative was also obtained by a similar route with 99% ee, when (*R*)-(−)-DTBM-SEGPHOS was used as the ligand in the hydrogenation reaction.

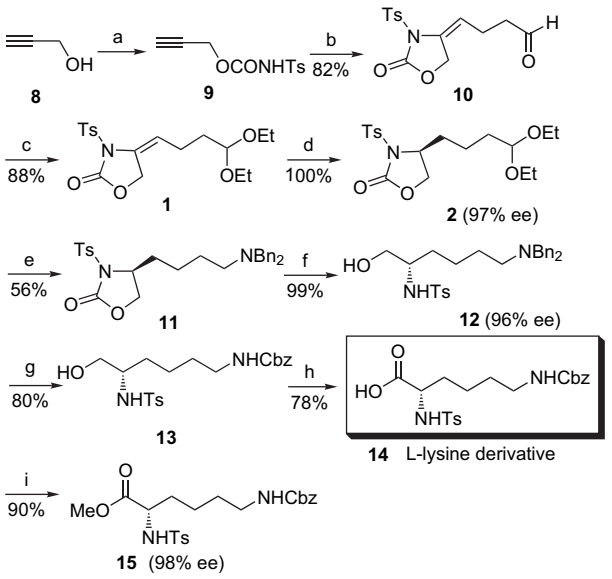
Similarly, the method was extended to the synthesis of natural L-norleucine derivative as shown in Scheme 4. The asymmetric hydrogenation of compound **6a** with (*S*)-(+)-DTBM-SEGPHOS as ligand was the key reaction and gave compound **7a** in quantitative yield with 99% ee. It was converted to the L-norleucine derivative **17** by further transformations. The absolute configuration and enantiomeric excess of compound **17** were determined by its methyl ester **18** (98% ee).[22]

The development of methods for the asymmetric synthesis of piperidines remains an area of considerable interest due to the presence of this heterocyclic ring in a large number of biologically important compounds.[3] Using chiral *N*-tosyloxazolidinone (**2**) (97% ee), the *N*-tosyl-L-pipecolic acid (**22**) and *N*-tosyl-(*R*)-α-pipecoline (**25**) could be easily synthesized as shown in Scheme 5. The absolute configuration and ee value of **22** were determined after esterification[23]

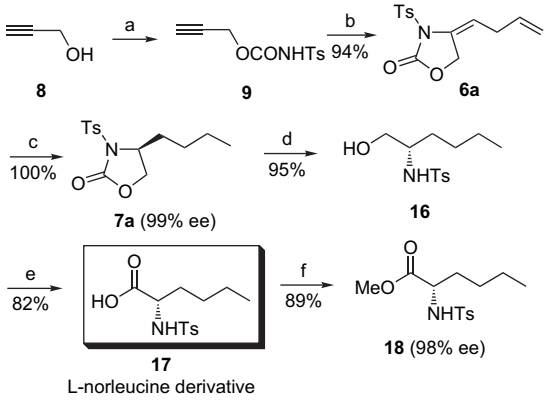
Table 4. Asymmetric hydrogenation of exocyclic double bonds[a]

Entry	Substrate	Product	Yield (%)[b]	ee (%)[c]
1	 **6a**	 **7a**	100	99 (+)
2	 **6b**	 **7a**	100	92 (+)
3	 **6c**	 **7c**	97	27 (−)
4	 **6d**	 **7d**	96	87 (−)
5	 **6e**	 **7e**	100	81 (−)
6	 **6f**	 **7f**	97	39 (+)
7	 **6g**	 **7g**	96	80 (−)

[a] Reaction conditions: substrate (0.26 mmol, 0.13 M), [Rh(COD)Cl]$_2$ (0.5 mol %), (*S*)-(+)-DTBM-SEGPHOS (1 mol %), H_2 (60 atm), toluene, 30 °C, 4 days.
[b] Isolated yield.
[c] ee values were determined by HPLC and the sign of optical rotation was shown in the parenthesis.



Scheme 3. Synthesis of natural L-lysine derivative **14**. (a) TsNCO, THF; (b) $Pd(OAc)_2$, LiBr, acrolein; (c) *p*-TsOH·H_2O, $HC(OEt)_3$; (d) $[Rh(COD)Cl]_2$ (0.5 mol %), (*S*)-(+)-DTBM-SEGPHOS (1 mol %), toluene, H_2 (60 atm), 30 °C, 4 days; (e) (i) THF/HCl (2 N) (3/1); (ii) Et_3N; (iii) Bn_2NH, $NaBH_3CN$; (f) LiOH·H_2O, THF/H_2O (3/1); (g) (i) $Pd(OH)_2$/C (20%), MeOH, H_2 (1 atm); (ii) Cbz-Cl, K_2CO_3, THF/H_2O; (h) Jones' reagent, acetone; (i) MeOH, *p*-TsOH (cat.), benzene, reflux.



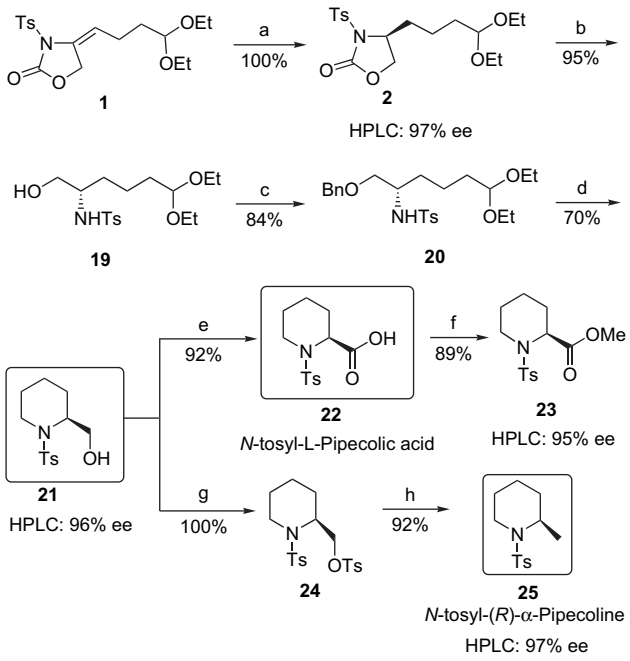
Scheme 4. Synthesis of natural L-norleucine derivative **17**. (a) TsNCO, THF; (b) $Pd(OAc)_2$, LiBr, Et_3N, 3-bromo-propene; (c) $[Rh(COD)Cl]_2$ (0.5 mol %), (*S*)-(+)-DTBM-SEGPHOS (1 mol %), toluene, H_2 (60 atm), 30 °C, 4 days; (d) LiOH·H_2O, THF/H_2O (3/1); (e) Jones' reagent, acetone; (f) MeOH, *p*-TsOH (cat.), benzene, reflux.

and the absolute configuration of **25** (97% ee) was determined by comparison with the literature.[24]

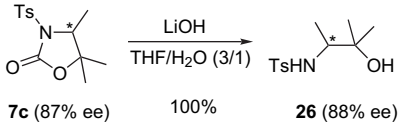
Homochiral oxazolidinones could be also converted to homochiral *N*-tosylamino alcohols in quantitative yield with retention of configuration by hydrolysis under basic condition, for example, **12**, **16**, **19**, and **26** (Scheme 6), which could be used as chiral ligands or their precursors.[2,5]

3. Conclusion

The asymmetric hydrogenation of the trisubstituted or disubstituted exocyclic double bond of *N*-tosyloxazolidinones was achieved under the catalysis of neutral $[Rh(COD)Cl]_2$ and (*S*)-(+)-DTBM-SEGPHOS with nearly quantitative yield and high enantioselectivity. This method provided a novel way to prepare chiral *N*-tosyloxazolidinones with high enantiomeric excess. The advantage and the utility of this reaction were exemplified by the synthesis of the amino acids, amino alcohols, and piperidine derivatives.



Scheme 5. Synthesis of natural piperidine derivatives. (a) $[Rh(COD)Cl]_2$ (0.5 mol %), (*S*)-(+)-DTBM-SEGPHOS (1 mol %), toluene, H_2 (60 atm), 30 °C, 4 days; (b) LiOH·H_2O, THF/H_2O (3/1); (c) NaH, BnBr, THF, −40 °C to 0 °C; (d) (i) *p*-TsOH, MeOH; (ii) Pd/C (10%), H_2 (1 atm), EtOH, rt; (e) Jones' reagent, acetone; (f) MeOH, *p*-TsOH (cat.), benzene, reflux; (g) TsCl, Et_3N, DMAP (cat.), CH_2Cl_2, rt; (h) $LiAlH_4$, Et_2O, reflux.



Scheme 6. Synthesis of *N*-tosylamino alcohols.

4. Experimental

4.1. General

NMR spectra were recorded on a Varian Mercury Vx 300 spectrometer. Infrared spectra were obtained on a Bio-Rad FTS-185 machine. Mass spectra were recorded on Agilent 5973 or Agilent 1100 machine. The optical rotation was measured on a Perkin–Elmer 341 polarimeter and the enantiomeric excesses were determined after separation of the enantiomers by HPLC on a Perkin–Elmer (785A, 200 IC Pump) or Waters (515 Pump, 2487 λ Dual Absorbance Detector) instrument. Elemental analyses were carried out on Elementar Vario EL instruments. All solvents were dried and distilled before use according to the standard methods. All melting points were uncorrected.

4.2. Synthesis of *N*-tosyl-4-alkylidene-1,3-oxazolidin-2-ones

4.2.1. (*E*)-*N*-Tosyl-4-(4′,4′-diethoxybutylidene)-1,3-oxazolidin-2-one (1). To a solution of **10**[6] (3.26 g, 20 mmol) in ethanol (70 mL) was added triethyl orthoformate (3 g, 20 mmol). The mixture was stirred over night in the presence of a catalytic amount of *p*-toluenesulfonic acid (274 mg, 1.4 mmol) at room temperature. After addition of saturated $NaHCO_3$ solution (30 mL), the reaction mixture was extracted with ethyl acetate (3×30 mL). The combined organic extracts were dried (anhydrous sodium sulfate), filtered, and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate=6/1 (v/v)) to give white solid **1** in 88% yield, mp 76–77 °C (recrystallization from petroleum ether/dichloromethane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (t, J=7.2 Hz, 6H), 1.74–1.78 (m, 2H), 1.97–1.99 (m, 2H), 2.46 (s, 3H), 3.42–3.59 (m, 2H), 3.59–3.69 (m, 2H), 4.47 (t, J=5.4 Hz, 1H), 4.81–4.82 (m, 2H), 5.93 (tt, J=8.1, 3.0 Hz, 1H), 7.36 (d, J=7.8 Hz, 2H), 7.93 (d, J=7.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.24, 21.66, 22.11, 32.66, 61.06, 65.65, 101.57, 106.79, 127.96, 127.99, 129.79, 134.25, 146.01, 151.90; IR (KBr): ν 2970, 2929, 1805, 1789, 1694, 1598, 1368, 1166, 1062 cm^{-1}; EIMS *m*/*z*: 337 ([M−OEt]$^+$), 266, 228, 182, 155, 154, 138, 129, 103, 91, 85. Anal. Calcd for $C_{18}H_{25}NO_6S$: C, 56.38; H, 6.57; N, 3.65. Found: C, 56.17; H, 6.68; N, 3.47.

4.2.2. (*E*)-*N*-Tosyl-4-(but-3′-enylidene)-1,3-oxazolidin-2-one (6a). To a solution of *p*-toluenesulfonyl isocyanate (3.1 mL, 20.4 mmol) in THF (255 mL) was added propargyl alcohol (1 mL, 17 mmol) under nitrogen. After the mixture was stirred for 1 h at room temperature, triethylamine (2.35 mL, 17 mmol) was added to the mixture. A solution of allyl bromide (14.7 mL, 170 mmol), LiBr (3.0 g, 34 mol), and $Pd(OAc)_2$ (5 mol %, 190.4 mg) in THF (85 mL) was added to the mixture over 4 h at room temperature and stirred at the same temperature for additional 4.5 h. The solvent was evaporated and the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate=4/1 (v/v)) to give white solid **6a** in 94% yield, mp 84–86 °C (recrystallization from petroleum ether/ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.46 (s, 3H), 2.67 (dd, J=6.9, 6.9 Hz, 2H), 4.79 (s, 2H), 5.05 (d, J=13.5 Hz, 2H), 5.72–5.85 (m, 1H), 5.97–6.04 (m, 1H), 7.35 (d, J=8.1 Hz, 2H), 7.93 (d, J=8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.7, 30.6, 65.5, 104.6, 115.8, 128.0, 129.0, 129.8, 134.2, 134.4, 146.1, 151.8; IR (KBr): ν 2900, 1805, 1790, 1693, 1596, 1383, 1354, 1194, 1181, 1063, 678, 543 cm^{-1}; ESIMS *m*/*z*: 294 (M+H$^+$), 311 (M+NH$_4^+$). HRMS Calcd for $C_{14}H_{15}NO_4S$: 293.0722. Found: 293.0714.

4.2.3. (*E*)-*N*-Tosyl-4-butylidene-1,3-oxazolidin-2-one (6b). To a solution of **6a** (500 mg, 1.7 mmol) in EtOH (87 mL) was added Pd/C (5%, 32 mg). The mixture was stirred under H_2 (1 atm) for 3 h at room temperature. The solvent was evaporated and the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate=50/1 to 20/1 (v/v)) to give white solid **6b** in 59% yield, mp 84–85 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, J=7.5 Hz, 3H), 1.41–1.53 (m, 2H), 1.84–1.92 (m, 2H), 2.46 (s, 3H), 4.78–4.80 (m, 2H), 5.90–5.97 (m, 1H), 7.36 (d, J=8.7 Hz, 2H), 7.93 (d, J=8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.6, 21.7, 22.4, 28.9, 65.7, 107.8, 127.6, 128.0, 129.8, 134.3, 146.0, 152.0; IR (KBr): ν 2964, 1803, 1679, 1594, 1366, 1180 cm^{-1}; ESIMS *m*/*z*: 296 (M+H$^+$). HRMS Calcd for [$C_{14}H_{17}NO_4S$+Na$^+$]: 318.0776. Found: 318.0766.

4.2.4. Compounds 6c,[25] 6d,[25] 6e,[26] 6f,[25] and 6g.[10a] The above compounds were synthesized according to the literature procedure.

4.3. Typical procedure for the enantioselective hydrogenation of exocyclic double bonds of oxazolidinones

4.3.1. (*S*)-*N*-Tosyl-4-(4′,4′-diethoxybutyl)-1,3-oxazolidin-2-one (2). In a nitrogen-filled glove box, $[Rh(COD)Cl]_2$[27] (0.5 mol %, 1.3 mg) and (*S*)-(+)-DTBM-SEGPHOS[13] (1 mol %, 6.1 mg) dissolved in dry and oxygen-free toluene (4 mL) were stirred for 30 min at room temperature in a glass tube. Compound **1** (200 mg, 0.52 mmol) was added to the mixture. The glass tube was transferred to a stainless steel autoclave in the glove box. After the autoclave was displaced with hydrogen three times, it was pressurized with hydrogen (60 atm) and stirred at 30 °C for 4 days. The solvent was evaporated and the residue was purified by means of column chromatography over silica gel (petroleum ether/ethyl acetate=6/1 to 4/1 (v/v)) to give colorless oil (*S*)-**2** in 100% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (t, J=7.2 Hz, 3H), 1.20 (t, J=7.0 Hz, 3H), 1.22–1.45 (m, 2H), 1.51–1.72 (m, 2H), 1.75–1.90 (m, 1H), 1.90–2.07 (m, 1H), 2.45 (s, 3H), 3.40–3.57 (m, 2H), 3.57–3.70 (m, 2H), 4.08 (dd, J=9.0, 3.3 Hz, 1H), 4.37–5.00 (m, 3H), 7.35 (d, J=8.1 Hz, 2H), 7.95 (d, J=8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.2, 18.7, 21.6, 33.0, 33.3, 57.0, 61.2, 61.4, 67.3, 102.3, 128.2, 129.6, 134.9, 145.4, 152.1; IR (film): ν 2976, 2875, 1785, 1597, 1372, 1173, 666 cm^{-1}; EIMS *m*/*z*: 385 (M$^+$), 340, 184, 155, 140, 103, 91, 85, 75, 47. HRMS Calcd for $C_{16}H_{22}NO_5S$ ([M−OEt]$^+$): 340.1288. Found: 340.1240; HPLC analysis: 97% ee (DAICEL CHIRALCEL AD-H, eluent, hexane/2-propanol=90/10, flow rate 0.6 mL min^{-1}, detection 225 nm light), t_R of major-isomer 20.86 min and that of minor-isomer 27.88 min; $[\alpha]_D^{20}$ +44.5 (*c* 1.12, $CHCl_3$).

4.3.2. *N*-Tosyl-4-(4′-ethoxybutyl)-1,3-oxazolidin-2-one (3). Oil (yield: 40%) (Table 1, entry 11). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (t, J=7.2 Hz, 3H), 1.23–1.46 (m, 2H), 1.47–1.68 (m, 2H), 1.75–1.89 (m, 1H), 1.90–2.05 (m, 1H), 2.45 (s, 3H), 3.35–3.40 (m, 2H), 3.45 (q, J=7.2 Hz, 2H), 4.08 (dd, J=8.7, 3.3 Hz, 1H), 4.37 (dd, J=8.4, 8.4 Hz, 1H), 4.44–4.52 (m, 1H), 7.35 (d, J=8.4 Hz, 2H), 7.95 (d, J=8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.2, 20.5, 21.7, 29.3, 33.4, 57.2, 66.2, 67.5, 69.9, 128.4, 129.7, 135.1, 145.5, 152.2; IR (film): ν 1786, 1597, 1371, 1173, 666 cm^{-1}; EIMS *m*/*z*: 342 (M+H$^+$), 186, 155, 142, 140, 108, 91, 65, 59. Anal. Calcd for $C_{16}H_{23}NO_5S$: C, 56.29; H, 6.79; N, 4.10. Found: C, 56.34; H, 6.92; N, 3.96; HPLC analysis: 5% ee (DAICEL CHIRALCEL AD-H, eluent, hexane/2-propanol=90/10, flow rate 0.6 mL min^{-1}, detection 225 nm light), t_R of major-isomer 13.37 min and that of minor-isomer 16.39 min.

4.3.3. (+)-*N*-Tosyl-4-butyl-1,3-oxazolidin-2-one (7a). White solid (yield: 99%), mp 100–101 °C. ^{1}H NMR

(300 MHz, $CDCl_3$) δ 0.87 (t, J=7.5 Hz, 3H), 1.10–1.38 (m, 4H), 1.80–1.95 (m, 2H), 2.45 (s, 3H), 4.06 (dd, J=3.3, 8.4 Hz, 1H), 4.37 (dd, J=8.4, 8.4 Hz, 1H), 4.45–4.48 (m, 1H), 7.35 (d, J=8.1 Hz, 2H), 7.96 (d, J=8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 21.6, 22.2, 25.4, 33.2, 57.2, 67.5, 128.2, 129.6, 135.0, 145.4, 152.2; IR (KBr): ν 2962, 2927, 2854, 1778, 1596, 1486, 1395, 1363, 1174, 1148, 1091, 820, 667, 608, 547 cm^{-1}; ESIMS m/z: 298 ($M+H^+$), 315 ($M+NH_4^+$). Anal. Calcd for $C_{14}H_{19}NO_4S$: C, 56.55; H, 6.44; N, 4.71. Found: C, 56.30; H, 6.37; N, 4.99; HPLC analysis: 99% ee (DAICEL CHIRALCEL OJ, eluent, hexane/2-propanol=70/30, flow rate 0.7 mL min^{-1}, detection 230 nm light), t_R of minor-isomer 19.13 min and that of major-isomer 26.79 min; $[\alpha]_D^{20}$ +54.9 (c 1.03, $CHCl_3$).

4.3.4. (−)-*N*-Tosyl-4-ethyl-1,3-oxazolidin-2-one (7c). White solid (yield: 97%), mp 87–89 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J=7.2 Hz, 3H), 1.82–2.01 (m, 2H), 2.45 (s, 3H), 4.08 (dd, J=3.3, 8.7 Hz, 1H), 4.38 (dd, J=8.7, 8.7 Hz, 1H), 4.43–4.50 (m, 1H), 7.35 (d, J=8.4 Hz, 2H), 7.96 (d, J=8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.5, 21.6, 26.4, 57.9, 67.0, 128.3, 129.7, 135.0, 145.5, 152.3; IR (KBr): ν 1766, 1597, 1373, 1175, 1111, 815, 664, 545 cm^{-1}; ESIMS m/z: 270 ($M+H^+$), 287 ($M+NH_4^+$). Anal. Calcd for $C_{12}H_{15}NO_4S$: C, 53.52; H, 5.61; N, 5.20. Found: C, 53.72; H, 5.60; N, 5.15; HPLC analysis: 27% ee (DAICEL CHIRALPAK AD-H, eluent, hexane/2-propanol=90/10, flow rate 0.8 mL min^{-1}, detection 230 nm light), t_R of major-isomer 21.71 min and that of minor-isomer 32.54 min; $[\alpha]_D^{20}$ −10.7 (c 1.01, $CHCl_3$).

4.3.5. (−)-*N*-Tosyl-4,5,5-trimethyl-1,3-oxazolidin-2-one (7d). White solid (yield: 96%), mp 99–102 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (d, J=4.8 Hz, 3H), 1.40 (s, 3H), 1.42 (s, 3H), 2.45 (s, 3H), 4.14 (q, J=4.8 Hz, 1H), 7.35 (d, J=8.4 Hz, 2H), 7.95 (d, J=8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.4, 21.4, 21.6, 27.4, 62.2, 82.3, 128.1, 129.6, 135.1, 145.3, 151.1; IR (KBr): ν 1774, 1596, 1359, 1330, 1278, 1171, 1160, 1131, 1089, 818, 728, 663, 581, 549 cm^{-1}; ESIMS m/z: 284 ($M+H^+$), 301 ($M+NH_4^+$). Anal. Calcd for $C_{13}H_{17}NO_4S$: C, 55.11; H, 6.05; N, 4.94. Found: C, 55.28; H, 6.05; N, 4.90; HPLC analysis: 87% ee (DAICEL CHIRALPAK AD-H, eluent, hexane/2-propanol=90/10, flow rate 0.8 mL min^{-1}, detection 230 nm light), t_R of minor-isomer 12.04 min and that of major-isomer 13.38 min; $[\alpha]_D^{20}$ −25.7 (c 1.11, $CHCl_3$).

4.3.6. (−)-*N*-Tosyl-4-methyl-1-oxa-3-aza-spiro[4,5]-decan-2-one (7e). White solid (yield: 100%), mp 85–87 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (d, J=6.6 Hz, 3H), 1.26–1.82 (m, 10H), 2.45 (s, 3H), 4.14 (q, J=6.6 Hz, 1H), 7.34 (d, J=8.4 Hz, 2H), 7.95 (d, J=8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.7, 21.6, 21.8, 22.0, 24.7, 30.4, 36.1, 61.6, 83.5, 128.2, 129.7, 135.3, 145.2, 151.1; IR (KBr): ν 1768, 1598, 1370, 1359, 1174, 1124, 1029, 603, 548 cm^{-1}; ESIMS m/z: 324 ($M+H^+$), 341 ($M+NH_4^+$). Anal. Calcd for $C_{16}H_{21}NO_4S$: C, 59.42; H, 6.52; N, 4.33. Found: C, 59.67; H, 6.74; N, 4.13; HPLC analysis: 81% ee (DAICEL CHIRALCEL OJ-H, eluent, hexane/2-propanol=90/10, flow rate 0.8 mL min^{-1}, detection 230 nm light), t_R of major-isomer 18.71 min and that of minor-isomer 23.04 min; $[\alpha]_D^{20}$ −27.4 (c 1.0, $CHCl_3$).

4.3.7. (+)-*N*-Tosyl-4-methyl-1,3-oxazolidin-2-one (7f). White solid (yield: 97%), mp 94–97 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53 (d, J=6.3 Hz, 3H), 2.45 (s, 3H), 3.93 (dd, J=8.4, 3.6 Hz, 1H), 4.43 (dd, J=8.4, 8.4 Hz, 1H), 4.53–4.60 (m, 1H), 7.36 (d, J=8.4 Hz, 2H), 7.94 (d, J=8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.5, 21.6, 53.5, 69.5, 128.3, 129.7, 135.0, 145.5, 152.0; IR (KBr): ν 1783, 1596, 1363, 1170, 664, 546 cm^{-1}; ESIMS m/z: 256 ($M+H^+$), 273 ($M+NH_4^+$). Anal. Calcd for $C_{11}H_{13}NO_4S$: C, 51.75; H, 5.13; N, 5.49. Found: C, 51.96; H, 5.19; N, 5.33; HPLC analysis: 39% ee (DAICEL CHIRALPAK AD-H, eluent, hexane/2-propanol=90/10, flow rate 0.8 mL min^{-1}, detection 230 nm light), t_R of minor-isomer 18.13 min and that of major-isomer 23.21 min; $[\alpha]_D^{20}$ +14.7 (c 1.04, $CHCl_3$).

4.3.8. (−)-*N*-Acetyl-4,5,5-trimethyl-1,3-oxazolidin-2-one (7g). White solid (yield: 96%), mp 39–40 °C (lit.[10a] mp 42 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (d, J=6.5 Hz, 3H), 1.41 (s, 3H), 1.43 (s, 3H), 2.52 (s, 3H), 4.17 (q, J=6.5 Hz, 1H); IR (KBr): ν 1762, 1702 cm^{-1}; ESIMS m/z: 171, 127, 114, 101, 84, 70, 59, 43, 39; HPLC analysis: 80% ee (DAICEL CHIRALCEL OJ-H, eluent, hexane/2-propanol=90/10, flow rate 0.8 mL min^{-1}, detection 200 nm light), t_R of major-isomer 9.04 min and that of minor-isomer 10.13 min; $[\alpha]_D^{20}$ −51.4 (c 0.54, EtOH).

4.4. Synthesis of L-lysine

4.4.1. (*S*)-*N*-Tosyl-4-((4′-dibenzylamino)butyl)-1,3-oxazolidin-2-one (11). To a solution of THF (31 mL) and 2 N HCl (7.6 mL) was added (*S*)-**2** (2.52 g, 6.6 mmol) at room temperature and the mixture was stirred for 30 min at room temperature. After triethylamine (2.4 mL, 17.2 mmol) was introduced via a syringe and stirred for 5 min at 0 °C, dibenzylamine (1.3 mL, 6.6 mmol) was added to the mixture and the reaction mixture was stirred for 10 min at 0 °C. Then, sodium cyanoborohydride (411.3 mg, 6.6 mmol) was added in one portion at 0 °C. The reaction mixture was stirred for 8 h at room temperature and then poured into 2 N HCl (pH=2) at 0 °C. Concentrated NaOH solution was added to the mixture at 0 °C to make the solution basic (pH=12). Then, saturated NaCl solution (30 mL) was added and the reaction mixture was extracted with ethyl acetate (3×30 mL). The combined organic extracts were washed with brine (30 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate/Et_3N=80/10/1 to 100/20/1 (v/v/v)) to give white solid (*S*)-**11** in 56% yield, mp 88–90 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20–1.30 (m, 2H), 1.42–1.50 (m, 2H), 1.63–1.79 (m, 2H), 2.35 (t, J=6.9 Hz, 2H), 2.41 (s, 3H), 3.48 (d, J=13.5 Hz, 2H), 3.53 (d, J=13.5 Hz, 2H), 3.95 (dd, J=8.4, 3.3 Hz, 1H), 4.31 (dd, J=8.4, 8.4 Hz, 1H), 4.38–4.41 (m, 1H), 7.21–7.34 (m, 12H), 7.90 (d, J=8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8, 21.5, 26.5, 33.0, 52.6, 57.0, 58.2, 67.3, 126.7, 128.08, 128.13, 128.6, 129.6, 134.9, 139.6, 145.3, 152.1; IR (KBr): ν 2943, 2799, 1786, 1598, 1494, 1390, 1174, 1091, 911, 666 cm^{-1}; EIMS m/z: 492 (M^+), 210, 181, 155, 91, 65, 43. Anal. Calcd for $C_{28}H_{32}N_2O_4S$: C, 68.27; H, 6.55; N, 5.69. Found: C, 68.01; H, 6.53; N, 5.58; $[\alpha]_D^{20}$ +38.4 (c 1.01, $CHCl_3$).

4.4.2. (2*S*)-6-Dibenzylamino-2-tosylaminohexanol (12). To a solution of (*S*)-**11** (1.7 g, 3.5 mmol) in THF (48 mL)

and water (16 mL) was added lithium hydroxide (308.7 mg, 7.3 mmol) at room temperature. The mixture was stirred for 9 h. After addition of saturated NH_4Cl solution (30 mL), the reaction mixture was extracted with ethyl acetate (3×30 mL). The combined organic extracts were washed with brine (2×20 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate=2/1 (v/v)) to give colorless oil (*S*)-**12** in 99% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00–1.35 (m, 6H), 1.87–1.93 (br, 1H), 2.27 (t, *J*=6.9 Hz, 2H), 2.39 (s, 3H), 3.11–3.20 (m, 1H), 3.37–3.57 (m, 6H), 4.52 (d, *J*=8.4 Hz, 1H), 7.23–7.33 (m, 12H), 7.74 (d, *J*=8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 22.9, 26.5, 31.3, 52.6, 55.6, 58.3, 64.8, 126.8, 127.1, 128.2, 128.8, 129.7, 137.5, 139.8, 143.5; IR (film): ν 3502, 3282, 2941, 2798, 1600, 1495, 1453, 1029 cm^{-1}; EIMS *m*/*z*: 466 (M^+), 435, 375, 311, 210, 181, 155, 91, 65. HRMS Calcd for $C_{27}H_{34}N_2O_3S$: 466.2290. Found: 466.2319; HPLC analysis: 96% ee (KROMASIL DMB, eluent, hexane/2-propanol=95/5, flow rate 1 mL min^{-1}, detection 230 nm light), t_R of major-isomer 18.46 min and that of minor-isomer 20.04 min; $[\alpha]_D^{20}$ −3.1 (*c* 1.15, $CHCl_3$).

4.4.3. (2*S*)-2-Tosylamino-6-benzyloxycarbonylaminohexanol (13). To a solution of (*S*)-**12** (1.6 g, 3.3 mmol) in methanol (155 mL) was added $Pd(OH)_2$/C (20%, 1.1 g). The mixture was stirred for 8.5 h under hydrogen (1 atm) at room temperature. The solution was filtered and the filtrate was evaporated under reduced pressure to afford a crude product, which was dissolved in THF (63 mL) and water (47 mL) containing potassium carbonate (1.36 g, 9.9 mmol). Cbz-Cl (0.7 mL, 5.0 mmol) was added to the mixture via a syringe over 15 min period at 0 °C and stirred over night at room temperature. After the addition of brine (30 mL), the reaction mixture was extracted with ethyl acetate (3×30 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate) to give white solid (*S*)-**13** in 80% yield, mp 88–90 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06–1.53 (m, 6H), 2.43 (s, 3H), 2.49 (t, *J*=6.0 Hz, 1H), 3.08 (dt, *J*=6.3, 6.3 Hz, 2H), 3.19–3.30 (m, 1H), 3.45–3.48 (m, 2H), 4.81–4.83 (br, 1H), 5.10 (s, 2H), 5.22 (d, *J*=7.8 Hz, 1H), 7.26–7.37 (m, 7H), 7.75 (d, *J*=8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.48, 21.69, 29.43, 30.67, 39.96, 55.28, 64.42, 66.73, 127.02, 128.07, 128.12, 128.50, 129.65, 136.40, 137.61, 143.44, 156.78; IR (KBr): ν 3522, 3349, 3275, 2939, 1685, 1546, 1164, 1087, 686, 570 cm^{-1}; ESIMS *m*/*z*: 421 ($M+H^+$). Anal. Calcd for $C_{21}H_{28}N_2O_5S$: C, 59.98; H, 6.71; N, 6.66. Found: C, 59.97; H, 7.00; N, 6.66; $[\alpha]_D^{20}$ +9.2 (*c* 0.85, $CHCl_3$).

4.4.4. *N*-Tosyl-*N*′-benzyloxycarbonyl-L-lysine (14). To a solution of Jones' reagent (2.69 M, 14.7 mL) in acetone (27 mL) was added a solution of (*S*)-**13** (673 mg, 1.6 mmol) in acetone (15 mL) via a dropping funnel over 30 min at 0 °C and the resulting mixture was stirred for 8 h at room temperature. After the addition of isopropanol (10 mL), the solvent was evaporated under reduced pressure and the brine (30 mL) was added. The aqueous solution was extracted with ethyl acetate (3×30 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate=3/1 to 1/2 (v/v)) to give white solid (*S*)-**14** in 78% yield, mp 120–121 °C (recrystallization from benzene) (lit.[21] mp 121–122 °C (benzene)). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.10–1.30 (m, 4H), 1.42–1.60 (m, 2H), 2.35 (s, 3H), 2.82–2.87 (m, 2H), 3.55–3.60 (m, 1H), 4.99 (s, 2H), 7.20–7.24 (m, 1H), 7.30–7.40 (m, 6H), 7.63 (d, *J*=8.1 Hz, 2H); IR (KBr): ν 3381, 3265, 2862, 1740, 1653, 1456, 566 cm^{-1}; ESIMS *m*/*z*: 435 ($M+H^+$), 452 ($M+NH_4^+$). Anal. Calcd for $C_{21}H_{26}N_2O_6S$: C, 58.05; H, 6.03; N, 6.45. Found: C, 58.04; H, 6.09; N, 6.29; $[\alpha]_D^{20}$ +13.0 (*c* 2.32, MeOH) (recrystallization from benzene) (lit.[21] $[\alpha]_D^{23}$ +13.5 (*c* 2.2, MeOH)).

4.4.5. *N*-Tosyl-*N*′-benzyloxycarbonyl-L-lysine methyl ester (15). Compound (*S*)-**14** (recrystallization from benzene) (150 mg, 0.35 mmol) was dissolved in methanol (1.5 mL) containing *p*-toluenesulfonic acid (15 mg). The solution was slowly distilled during 6 h; more methanol–benzene being added as required. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate. The solution was washed successively with 10% aqueous sodium hydrogen carbonate, water, dried, and evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel (petroleum ether/ethyl acetate=2/1 (v/v)) to give white solid (*S*)-**15** in 90% yield, mp 76–78 °C (recrystallization from petroleum ether/ethyl acetate) (lit.[28] mp 80–81 °C (recrystallization from benzene/light petroleum)). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25–1.50 (m, 4H), 1.61–1.75 (m, 2H), 2.41 (s, 3H), 3.15 (dt, *J*=6.3, 6.3 Hz, 2H), 3.48 (s, 3H), 3.85–3.92 (m, 1H), 4.70–4.80 (br, 1H), 5.10 (s, 2H), 5.48 (d, *J*=8.4 Hz, 1H), 7.26–7.37 (m, 7H), 7.70 (d, *J*=8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 21.9, 29.0, 32.5, 40.4, 52.3, 55.4, 66.5, 127.1, 127.96, 127.99, 128.4, 129.5, 136.5, 143.6, 156.4, 172.0; IR (KBr): ν 3350, 3271, 2951, 2859, 1739, 1687, 1546 cm^{-1}; ESIMS *m*/*z*: 449 ($M+H^+$), 466 ($M+NH_4^+$); HPLC analysis: 98% ee (DAICEL CHIRALPAK AD-H, eluent, hexane/2-propanol=83/17, flow rate 0.7 mL min^{-1}, detection 225 nm light), t_R of minor-isomer 56.88 min and that of major-isomer 66.29 min; $[\alpha]_D^{20}$ +19.7 (*c* 4.59, $CHCl_3$).

4.5. Synthesis of L-norleucine

4.5.1. (*S*)-2-(Tosylamino)hexanol (16). Compound **16** was synthesized from **7a** similar to the synthesis of (*S*)-**12**. Compound (*S*)-**16**: white solid (yield: 95%), mp 81–83 °C (recrystallization from petroleum ether/ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.75 (t, *J*=6.6 Hz, 3H), 0.95–1.20 (m, 4H), 1.25–2.03 (m, 2H), 2.32 (t, *J*=5.7 Hz, 1H), 2.43 (s, 3H), 3.21–3.23 (m, 1H), 3.46–3.60 (m, 2H), 4.97 (d, *J*=7.5 Hz, 1H), 7.31 (d, *J*=8.1 Hz, 2H), 7.78 (d, *J*=8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 21.4, 22.2, 27.6, 31.2, 55.6, 64.7, 127.1, 129.6, 137.6, 143.4; IR (KBr): ν 3560, 3501, 3278, 2957, 2931, 1599, 1425, 1335, 1163, 1152, 1087, 1055, 674, 554 cm^{-1}; ESIMS *m*/*z*: 272 ($M+H^+$), 289 ($M+NH_4^+$). Anal. Calcd for $C_{13}H_{21}NO_3S$: C, 57.54; H, 7.80; N, 5.16. Found: C, 57.57; H, 7.61; N, 5.11; $[\alpha]_D^{20}$ −19.9 (*c* 1.1, MeOH).

4.5.2. *N*-Tosyl-L-norleucine (17). Compound **17** was synthesized from **16** similar to the synthesis of (*S*)-**14**. Compound (*S*)-**17**: white solid (yield: 82%), mp 113–115 °C

(recrystallization from benzene). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (t, J=7.2 Hz, 3H), 1.22–1.31 (m, 4H), 1.58–1.78 (m, 2H), 2.41 (s, 3H), 3.89–3.96 (m, 1H), 4.00–4.72 (br, 1H), 5.13 (d, J=9.3 Hz, 1H), 7.27 (d, J=8.1 Hz, 2H), 7.72 (d, J=8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.6, 21.4, 21.9, 26.8, 32.6, 55.3, 127.1, 129.6, 136.5, 143.8, 177.0; IR (KBr): ν 3246, 2950, 2870, 1716, 1415, 1324, 1170, 1094, 811, 689, 574 cm^{-1}; ESIMS m/z: 286 (M+H$^+$), 303 (M+NH$_4^+$). Anal. Calcd for $C_{13}H_{19}NO_4S$: C, 54.72; H, 6.71; N, 4.91. Found: C, 54.86; H, 6.57; N, 4.86; $[\alpha]_D^{20}$ +6.7 (c 1.96, MeOH).

4.5.3. Methyl (L)-2-(tosylamino)hexanoate (18). Compound **18** was synthesized similar to the synthesis of (*S*)-**15**. Compound (*S*)-**18**: white solid (yield: 89%), mp 46–48 °C (recrystallization from petroleum ether/ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, J=7.2 Hz, 3H), 1.22–1.34 (m, 4H), 1.57–1.75 (m, 2H), 2.42 (s, 3H), 3.49 (s, 3H), 3.87–3.94 (m, 1H), 5.07 (d, J=9.0 Hz, 1H), 7.30 (d, J=8.1 Hz, 2H), 7.73 (d, J=8.1 Hz, 2H); IR (KBr): ν 3268, 2958, 2858, 1743, 1598, 1459, 1345, 1166, 1089, 819, 671, 574, 556 cm^{-1}; ESIMS m/z: 300 (M+H$^+$), 317 (M+NH$_4^+$); HPLC analysis: 98% ee (DAICEL CHIRALCEL OD, eluent, hexane/2-propanol = 95/5, flow rate 0.7 mL min^{-1}, detection 225 nm light), t_R of minor-isomer 22.87 min and that of major-isomer 26.13 min; $[\alpha]_D^{20}$ −11 (c 2.01, EtOH) (lit.[22] $[\alpha]_D^{20}$ −12 (c 2.0, EtOH)).

4.6. Synthesis of *N*-tosyl-L-pipecolic acid and *N*-tosyl-(*R*)-α-pipecoline

4.6.1. (2*S*)-2-Tosylamino-6,6-diethoxyhexanol (19). Compound **19** was synthesized from (*S*)-**2** similar to (*S*)-**12**. Compound (*S*)-**19**: oil (yield: 95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (t, J=6.9 Hz, 6H), 1.21–1.49 (m, 6H), 2.36 (t, J=5.7 Hz, 1H), 2.43 (s, 3H), 3.21–3.25 (m, 1H), 3.25–3.61 (m, 6H), 4.33 (t, J=6.0 Hz, 1H), 5.07 (d, J=7.8 Hz, 1H), 7.31 (d, J=8.1 Hz, 2H), 7.77 (d, J=8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.2, 20.7, 21.4, 31.1, 33.0, 55.4, 60.9, 61.0, 64.3, 102.4, 126.9, 129.5, 137.6, 143.2; IR (KBr): ν 3471, 3284, 2976, 2931, 2879, 1599, 1326, 1160 cm^{-1}; EIMS m/z: 282 ([M−CH$_2$OH–C$_2$H$_5$OH]$^+$), 268, 238, 155, 103, 91, 85, 57, 47, 41. HRMS Calcd for $C_{16}H_{26}NO_4S$ ([M−HOCH$_2$]$^+$): 328.1582. Found: 328.1565; $[\alpha]_D^{20}$ −5.3 (c 0.85, EtOH).

4.6.2. (*S*)-2-Tosylamino-6,6-diethoxyhexanol benzyl ether (20). Sodium hydride (293.8 mg of 60% dispersion in mineral oil, 7.34 mmol) was added to a stirred solution of (*S*)-**19** (1.28 g, 3.6 mmol) in dry THF (6 mL) at −40 °C and the mixture was stirred for 30 min with warming to 0 °C. To the above mixture at 0 °C was added dropwise benzyl bromide (0.44 mL, 3.6 mmol) and the mixture was stirred for 2 h. The reaction was quenched with saturated NH_4Cl solution (15 mL) and stirred for 10 min at 0 °C. The mixture was extracted with EtOAc and the extract was washed with brine twice and dried over $MgSO_4$. Concentration under reduced pressure gave a residue, which was purified by chromatography on silica gel (petroleum ether/ethyl acetate) to give colorless oil (*S*)-**20** (84%, 1.34 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.182 (t, J=7.5 Hz, 3H), 1.184 (t, J=7.2 Hz, 3H), 1.25–1.40 (m, 2H), 1.47–1.60 (m, 4H), 2.41 (s, 3H), 3.19–3.23 (m, 1H), 3.29–3.35 (m, 2H), 3.35–3.52 (m, 2H), 3.57–3.63 (m, 2H), 4.34 (s, 2H), 4.37 (t, J=5.4 Hz, 1H), 4.78 (d, J=8.1 Hz, 1H), 7.19–7.34 (m, 7H), 7.70 (d, J=8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.2, 20.6, 21.3, 32.1, 33.1, 53.3, 60.9, 71.0, 72.9, 102.5, 126.8, 127.4, 127.5, 128.1, 129.3, 137.6, 137.9, 142.9; IR (KBr): ν 3280, 2976, 2871, 1599, 1455, 1332, 1162, 1093, 666 cm^{-1}; EIMS m/z: 358 ([M−CH$_3$C$_6$H$_4$]$^+$), 282, 248, 202, 155, 103, 91, 85, 57, 47. Anal. Calcd for $C_{24}H_{35}NO_5S$: C, 64.11; H, 7.85; N, 3.12. Found: C, 64.19; H, 8.07; N, 3.06; $[\alpha]_D^{20}$ −12.1 (c 1.5, EtOH).

4.6.3. (*S*)-*N*-Tosyl-2-hydroxymethylpiperidine (21). To a solution of (*S*)-**20** (1.3 g, 2.9 mmol) in THF (23 mL) was added *p*-toluenesulfonic acid (1.1 g, 5.8 mmol). The mixture was stirred for 32 h at room temperature. The reaction was quenched with saturated $NaHCO_3$ solution (30 mL) and stirred for 10 min at 0 °C. The mixture was extracted with EtOAc and the extract was washed twice with brine and dried over $MgSO_4$. Concentration under reduced pressure gave a residue, which was hydrogenated (H_2, 1 atm) in dry EtOH (80 mL) under the catalysis of Pd/C (10%) (40%, 2.12 g) for 2.5 days at room temperature. The reaction mixture was filtrated. The filtrate was concentrated under reduced pressure and then purified by chromatography on silica gel (petroleum ether/ethyl acetate=4/1 to 2/1 (v/v)) to give colorless oil (*S*)-**21** (70%, 545 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24–1.66 (m, 6H), 2.00–2.05 (m, 1H), 2.43 (s, 3H), 3.10 (dt, J=2.7, 13.8 Hz, 1H), 3.54–3.60 (m, 1H), 3.79–3.90 (m, 2H), 3.99–4.00 (m, 1H), 7.30 (d, J=8.1 Hz, 2H), 7.75 (d, J=8.1 Hz, 2H); IR (KBr): ν 3520, 2942, 1598, 1447, 1328, 1156, 1094, 658, 549 cm^{-1}; EIMS m/z: 270 (M+H)$^+$, 238, 155, 91, 65, 55; HPLC analysis: 97% ee (DAICEL CHIRALCEL OJ-H, eluent, hexane/2-propanol=80/20, flow rate 0.8 mL min^{-1}, detection 230 nm light), t_R of minor-isomer 9.18 min and that of major-isomer 9.99 min; $[\alpha]_D^{20}$ −45.0 (c 0.27, EtOH).

4.6.4. *N*-Tosyl-L-pipecolic acid (22). This compound was synthesized from (*S*)-**21** similar to (*S*)-**14**. Compound (*S*)-**22**: oil (yield: 92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24–1.53 (m, 2H), 1.61–1.81 (m, 3H), 2.13–2.18 (m, 1H), 2.42 (s, 3H), 3.20 (dt, J=2.7, 12.3 Hz, 1H), 3.72–3.76 (m, 1H), 4.76 (d, J=4.5 Hz, 1H), 6.80–7.30 (br, 1H), 7.28 (d, J=8.1 Hz, 2H), 7.69 (d, J=8.1 Hz, 2H); IR (KBr): ν 2964, 2949, 2882, 2861, 1714, 1361, 1336, 1160 cm^{-1}; ESIMS m/z: 284 (M+H$^+$), 301 (M+NH$_4^+$); $[\alpha]_D^{20}$ −24.3 (c 1.0, EtOH).

4.6.5. Methyl *N*-tosyl-L-pipecolate (23). This compound was synthesized similar to (*S*)-**15**. Compound (*S*)-**23**: oil (yield: 89%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23–1.52 (m, 2H), 1.61–1.70 (m, 3H), 2.08–2.13 (m, 1H), 2.42 (s, 3H), 3.20 (dt, J=2.4, 12.0 Hz, 1H), 3.54 (s, 3H), 3.73–3.78 (m, 1H), 4.74 (d, J=5.1 Hz, 1H), 7.27 (d, J=8.4 Hz, 2H), 7.66 (d, J=8.4 Hz, 2H); IR (KBr): ν 2949, 1731, 1596, 1338, 1154, 943, 586 cm^{-1}; EIMS m/z: 297 (M$^+$), 239, 155, 142, 139, 91, 82, 65, 55, 41; HPLC analysis: 95% ee (DAICEL CHIRALPAK AD-H, eluent, hexane/2-propanol=100/0.01, flow rate 0.7 mL min^{-1}, detection 254 nm light), t_R of major-isomer 37.79 min and that of minor-isomer 40.71 min; $[\alpha]_D^{20}$ −40.5 (c 0.65, MeOH) (lit.[23] $[\alpha]_D^{20}$ −37.2 (c 0.62, MeOH)).

4.6.6. (*S*)-*N*-Tosyl-*O*-tosyl-2-hydroxymethylpiperidine[29] (24). Alcohol **21** (299 mg, 1.1 mmol) was added to a solution of triethylamine (0.76 mL, 5.5 mmol) and DMAP (16 mg) in CH_2Cl_2 (60 mL). Then the toluene-*p*-sulfonyl chloride (419.5 mg, 2.2 mmol) dissolved in CH_2Cl_2 (20 mL) was added dropwise to the mixture under ice-water cooling during 1 h. After the resulting mixture was stirred at ambient temperature overnight, it was diluted with CH_2Cl_2 (20 mL), washed with water (10 mL) and brine (10 mL), then dried and evaporated. The residue was subjected to column chromatography on silica gel (petroleum ether/ethyl acetate=4/1 (v/v)) to give oil (*S*)-**24** in 87% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22–1.52 (m, 5H), 1.72 (m, 1H), 2.42 (s, 3H), 2.47 (s, 3H), 2.83 (t, J=14.4 Hz, 1H), 3.70 (m, 1H), 4.00–4.13 (m, 2H), 4.24–4.27 (m, 1H), 7.26 (d, J=7.6 Hz, 2H), 7.35 (d, J=8.1 Hz, 2H), 7.67 (d, J=7.6 Hz, 2H), 7.75 (d, J=8.1 Hz, 2H); IR (KBr): ν 2947, 2868, 1598, 1363, 1191, 1178, 1095, 977, 816, 553 cm^{-1}; ESIMS *m*/*z*: 424 (M+H$^+$), 441 (M+NH$_4^+$); $[\alpha]_D^{20}$ −54.63 (*c* 1.2, EtOH) (lit.[29] $[\alpha]_D^{23}$ +55 (*c* 0.8, EtOH)).

4.6.7. *N*-Tosyl-(*R*)-α-pipecoline[24] (25). An ether (3 mL) solution of (*S*)-**24** was added to a suspension of $LiAlH_4$ (8.4 mg, 0.22 mmol) in Et_2O (3 mL) at 0 °C. The reaction mixture was stirred at room temperature for 10 min and then refluxed for 24 h after hydrolysis by successive addition of 0.3 mL of water, 0.3 mL of 15% NaOH, and 0.9 mL of water, the precipitate formed was filtered off. The filtrate was washed with aqueous $NaHCO_3$ and saturated NaCl and dried over sodium sulfate. The solvent was removed in vacuo. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate=5/1 (v/v)) to give white solid (*R*)-**25** in 92% yield, mp 61–62 °C (recrystallization from petroleum ether/ethyl acetate) (lit.[24] mp 68–70 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (d, J=7.2 Hz, 3H), 1.25–1.61 (m, 6H), 2.42 (s, 3H), 2.97 (dt, J_1=1.6, J_2=12.6 Hz, 1H), 3.70 (dd, J_1=3.5, J_2=12.6 Hz, 1H), 4.21–4.26 (m, 1H), 7.27 (d, J=8.1 Hz, 2H), 7.70 (d, J=8.1 Hz, 2H); IR (KBr): ν 2925, 1597, 1328, 1164, 1093, 822, 600 cm^{-1}; EIMS *m*/*z*: 253 (M$^+$), 238, 239, 155, 91, 65, 56, 55, 41; HPLC analysis: 97% ee (DAICEL CHIRALCEL OJ-H, eluent, hexane/2-propanol=98/2, flow rate 0.7 mL min^{-1}, detection 230 nm light), t_R of minor-isomer 22.71 min and that of major-isomer 28.29 min; $[\alpha]_D^{20}$ −39.3 (*c* 0.85, EtOH) (lit.[24] $[\alpha]_D^{20}$ +41.0 (*c* 0.98, EtOH)).

4.7. Synthesis of optically active amino alcohol derivatives

4.7.1. (+)-*N*-Tosyl-2-methyl-3-aminobutan-2-ol (26). This compound was synthesized from **7c** similar to (*S*)-**12**. Compound (+)-**26**: white solid (quantitative yield), mp 83–85 °C (recrystallization from petroleum ether/ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (d, J=6.9 Hz, 3H), 1.15 (s, 3H), 1.17 (s, 3H), 1.86 (s, 1H), 2.43 (s, 3H), 3.17 (dq, J=8.1, 6.9 Hz, 1H), 4.67 (d, J=8.1 Hz, 1H), 7.31 (d, J=8.4 Hz, 2H), 7.77 (d, J=8.4 Hz, 2H); IR (KBr): ν 3495, 3288, 2989, 1597, 1334, 1153, 1085, 666, 543 cm^{-1}; ESIMS (ESI) *m*/*z*: 258 (M+H$^+$), 275 (M+NH$_4^+$); HPLC analysis: 88% ee (DAICEL CHIRALPAK AD, eluent, hexane/2-propanol=70/30, flow rate 0.7 mL min^{-1}, detection 230 nm light), t_R of minor-isomer 23.21 min and that of major-isomer 31.63 min; $[\alpha]_D^{20}$ +34.3 (*c* 0.54, MeOH).

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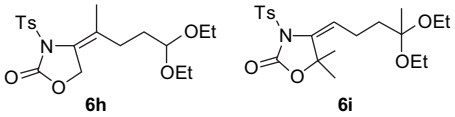
References and notes

1. (a) For a review on synthetic methods of α-amino acids, see: Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539; (b) Williams, R. H. *Synthesis of Optically Active α-Amino Acids*; Pergamon: New York, NY, 1989; (c) Schollkopf, U. *Top. Curr. Chem.* **1983**, *109*, 65; (d) Wagner, I.; Musso, H. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 816.
2. Bergmeier, S. C. *Tetrahedron* **2000**, *56*, 2561.
3. For reviews, see: (a) Laschat, S.; Dickner, T. *Synthesis* **2000**, *13*, 1781; (b) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701; (c) Baliah, V.; Jeyraman, R.; Chandrasekaran, L. *Chem. Rev.* **1983**, *83*, 379; (d) Bates, R. W.; Sa-Ei, L. *Tetrahedron* **2002**, *58*, 5957; (e) Notz, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580.
4. Coppola, D. M.; Schuster, H. F. *Asymmetric Synthesis: Construction of Chiral Molecules Using Amino Acids*; Wiley: New York, NY, 1987.
5. (a) Xu, Z.; Wang, R.; Xu, J.; Da, C.; Yan, W.; Chen, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5747; (b) Xu, Z.; Chen, C.; Xu, J.; Miao, M.; Yan, W.; Wang, R. *Org. Lett.* **2004**, *6*, 1193.
6. Lei, A.; Lu, X. *Org. Lett.* **2000**, *2*, 2699.
7. Ohta, T.; Miyake, T.; Seido, N.; Kumobayashi, H.; Takaya, H. *J. Org. Chem.* **1995**, *60*, 357.
8. Yue, T. Y.; Nugent, W. A. *J. Am. Chem. Soc.* **2002**, *124*, 13692.
9. Gendre, P. L.; Braun, T.; Bruneau, C.; Dixneuf, P. H. *J. Org. Chem.* **1996**, *61*, 8453.
10. (a) Gendre, P. L.; Thominot, P.; Bruneau, C.; Dixneuf, P. H. *J. Org. Chem.* **1998**, *63*, 1806; (b) Gendre, P. L.; Jérôme, F.; Bruneau, C.; Dixneuf, P. H. *Chem. Commun.* **1998**, 533.
11. Chung, J. Y.; Zhao, D.; Hughes, D. L.; McNamara, J. M.; Grabowski, E. J.; Reider, P. J. *Tetrahedron Lett.* **1995**, *36*, 7379.
12. The similar phenomena for the asymmetric hydrogenation of geraniol and nerol were reported by Noyori and co-workers. Inoue, S.-I.; Osada, M.; Koyano, K.; Takaya, H.; Noyori, R. *Chem. Lett.* **1985**, 1007.
13. Saito, T.; Yokozawa, T.; Ishizaki, T.; Moroi, T.; Sayo, N.; Miura, T.; Kumobayashi, H. *Adv. Synth. Catal.* **2001**, *343*, 264.
14. Kagan, H. B.; Dang, T.-P. *J. Am. Chem. Soc.* **1972**, *94*, 6429.
15. Baker, G. L.; Fritschel, S. J.; Stille, J. R.; Stille, J. K. *J. Org. Chem.* **1981**, *46*, 2954.
16. Hayashi, T.; Mise, T.; Fukushima, M.; Kagotani, M.; Nagashima, N.; Hamada, Y.; Matsumoto, A.; Kawakami, S.; Konishi, M.; Yamamoto, K.; Kumada, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1138.
17. Arnold, L. A.; Imbos, R.; Mandoli, A.; de Vries, A. H. M.; Naasz, R.; Feringa, B. L. *Tetrahedron* **2000**, *56*, 2865.
18. Zhang, X.; Mashima, K.; Koyano, K.; Sayo, N.; Kumobayashi, H.; Akutogawa, S.; Takaya, H. *Tetrahedron Lett.* **1991**, *32*, 7283.

19. It should be pointed out that **6h** and **6i** were not hydrogenated under the typical conditions (Table 4).



6h **6i**

20. (a) Greenstein, J. P.; Winitz, M. *Chemistry of the Amino Acids*; Wiley: New York, NY, 1961; (b) Friedman, M. *Absorption and Utilization of Amino Acids*; CRC: Boca Raton, FL, 1989.
21. (a) Klabunovskii, E. I.; Karpeiskaya, E. I.; Levitina, E. S.; Godunova, L. F.; Kaigorodova, L. N. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1985**, 2157; (b) Fasth, K.-J.; Hörnfeldt, K.; Lángström, B. *Acta Chem. Scand.* **1995**, *49*, 301; (c) Siebum, A. H. G.; Tsang, R. K. F.; van der Steen, R.; Raap, J.; Lugtenburg, J. *Eur. J. Org. Chem.* **2004**, 4391; (d) Kjer, A.; Larsen, P. O. *Acta Chem. Scand.* **1961**, *15*, 750.
22. The absolute configuration of compound **18** was also assigned as L, namely *S* by comparison with the optical rotation of literature: (a) Bajgrowicz, J. A.; Hallaoui, A. E.; Jacquier, R.; Pigière, C.; Viallefont, P. *Tetrahedron* **1985**, *41*, 1833; (b) Bajgrowicz, J. A.; Hallaoui, A. E.; Jacquier, R.; Pigière, C.; Viallefont, P. *Tetrahedron Lett.* **1984**, *25*, 2759.
23. The absolute configuration of compound **23** ($[\alpha]_D^{20}$ −40.5 (*c* 0.65, MeOH)) was assigned as L, namely *S* by comparison with the optical rotation of literature (lit. $[\alpha]_D^{23}$ −37.2 (*c* 0.62, MeOH)): Iwata, M.; Kuzuhara, H. *Chem. Lett.* **1985**, 1941.
24. The absolute configuration of compound **25** ($[\alpha]_D^{20}$ −39.3 (*c* 0.85, EtOH)) was assigned *R* by comparison with the optical rotation of literature (lit. $[\alpha]_D^{20}$ +41.0 (*c* 0.98, EtOH)): Ripperger, H.; Schreiber, K. *Tetrahedron* **1965**, *21*, 1485.
25. Tamaru, Y.; Kimura, M.; Tanaka, S.; Kure, S.; Yoshida, Z. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2838.
26. Kimura, M.; Kure, S.; Yoshida, Z.; Tanaka, S.; Fugami, K.; Tamaru, Y. *Tetrahedron Lett.* **1990**, *31*, 4887.
27. Giordano, G.; Crabtree, R. H. *Inorg. Synth.* **1979**, *19*, 218.
28. (a) Barrass, B. C.; Elmove, D. T. *J. Chem. Soc.* **1957**, 4830; (b) Irving, C. C.; Gutmann, H. R. *J. Org. Chem.* **1959**, *24*, 1979.
29. Knight, D. W.; Lewis, N.; Share, A. C.; Haigh, D. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3673.

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Selenocyclisations of homoallylic sulfonamides: stereoselective methods for the elaboration of substituted pyrrolidines, pyrrolines and derivatives

Andrew D. Jones,[a] Adele L. Redfern,[a] David W. Knight,[a,*] Ian R. Morgan[a] and Andrew C. Williams[b]

[a]*Centre for Heterocyclic Synthesis, School of Chemistry, Cardiff University, Park Place, Cardiff CF10 3AT, UK*
[b]*Eli Lilly and Co. Ltd, The Lilly Research Centre, Erl Wood Manor, Windlesham, Surrey GU20 6PH, UK*

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Abstract—Selenocyclisations of the homoallylic sulfonamides [e.g., **26**, **28** and **30**] using phenylselanyl halides lead exclusively to β-selanyl-pyrrolidines [e.g., **27**, **29** and **31**] by an overall 5-*endo-trig* pathway, but with considerable variations in the stereochemical outcome, depending upon the substituents and the precise conditions used. Subsequent oxidative eliminations lead smoothly to the corresponding 3-pyrrolines and thence to poly-hydroxylated pyrrolidines.

1. Introduction

The introduction of a phenylselanyl group into a molecule can serve a number of synthetic purposes, although, most often, subsequent oxidation to the corresponding selenoxide and thermal [2,3]-elimination involving a proton β-to the heteroatom leading to alkene formation is its immediate fate.[1,2] Less often, a phenylselanyl group can serve as a radical precursor or assist in the stabilisation of a carbanion. There are a number of methods available for the introduction of selanyl groups, many of which have been applied to the synthesis of selanyl-pyrrolidines **1**, perhaps the simplest being the direct addition of a selanyl halide to a 2,5-dihydropyrrole, the resulting β-halo selanides **2** being useful as synthetic intermediates for subsequent ring formation, amongst other applications (Fig. 1).[3]

Similar additions to 2,3-dihydropyrroles in the presence of amines or inorganic azides result in synthetically useful α-amino-[4] and α-azido-selanides **3**, respectively, as a result of interception of the presumed cyclic phenylselanonium ion by the nitrogen nucleophile, probably directed by the ring nitrogen (Fig. 1).[5]

A much more common strategy for the introduction of a phenylselanyl group into such *N*-heterocycles is the trapping of an enolate derived from a five-membered lactam [cf. **4**] or pyrrolidine carboxylate, with a phenylselanyl halide.[6] Such an addition is most commonly followed by oxidative elimination,[7] a reaction which can sometimes pose unexpected problems[8] but which thereby leads to an α,β-unsaturated carbonyl system primed, amongst other transformations, for Michael additions. Rather than elimination, such phenylselanyl groups [cf. **5**] can also serve as precursors to carbon-centred radicals **6**.[9] Another very common strategy for the introduction of a phenylselanyl group into a pyrrolidine is by S_N2 attack of a selenium nucleophile on an activated β-hydroxy-pyrrolidine **7** leading to derivatives **8** (Fig. 1).[10] A somewhat less common but elegant procedure for the formation of β-selanyl-pyrroles involves [1,3]-dipolar cycloadditions between azomethine ylides and phenylselanylethene [phenyl(vinyl)selane].[11]

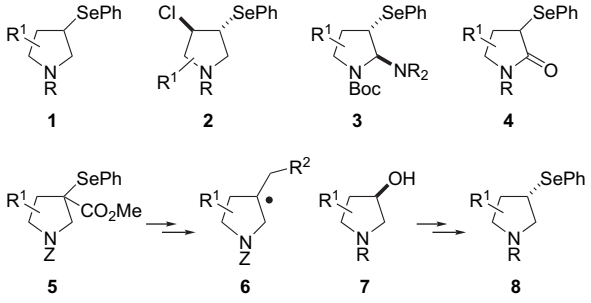

Figure 1. Various types of β-selanyl-pyrrolidines.

Inevitably perhaps, selenocyclisations have been applied to the elaboration of selanyl-pyrrolidines. In early examples,[12] an electrophilic selenium species generated from diphenyl diselenide using ammonium persulfate (peroxydisulfate)

* Corresponding author. E-mail: knightdw@cf.ac.uk

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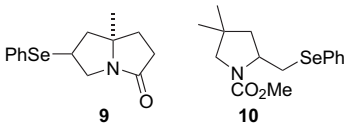


Figure 2. Pyrrolidines from 5-*endo* and 5-*exo* selenocyclisations.

was used to induce a 5-*endo-trig* cyclisation leading to the pyrrolizidinone **9** from the corresponding γ-allyl lactam. Prior to this, Clive had shown that 5-*exo* selanyl-cyclisations of *N*-alkenyl carbamates were viable and gave good yields of the pyrrolidines **10** (Fig. 2).[13]

Using more conventional conditions (phenylselanyl halides and a mild base, Na_2CO_3), it was subsequently found that homoallylic benzylamines **11** underwent both 4-*exo* and 5-*endo* cyclisation modes to give high yields but of mixtures of azetidines **12** and pyrrolidines **13**. The ratio of products depended strongly upon the substituents (alkyl or aryl), solvents (acetonitrile or dichloromethane) and the selanyl halide employed for the cyclisation (Cl or Br) (Fig. 3).[14] Pyrrolidines **13** were especially favoured by a combination of phenylselanyl bromide in dichloromethane, but other patterns were more difficult to discern. Related cyclisations can also be carried out asymmetrically: the 5-*endo* mode seems effective only in examples having a distal phenyl group [**14** and **16**] but with such precursors, diastereoisomer ratios in excess of 9:1 can be obtained in the products [**15** and **17**, respectively] using an enantiopure arylselanyl triflate [Ar*SeOTf].[15]

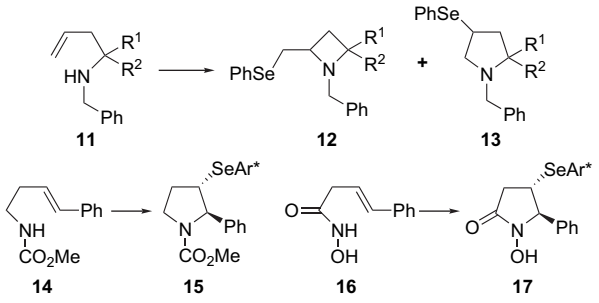
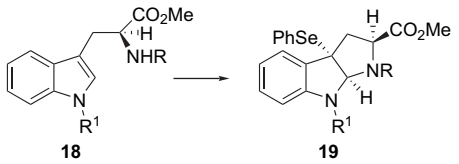


Figure 3. Pyrrolidines from 5-*endo* selenocyclisations.

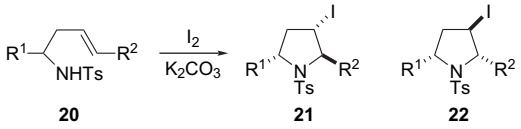
Imine analogues corresponding to the benzylamines **11** also undergo similar selenocyclisations to give exclusively β-selanyl-pyrrolidines, following borohydride reduction of the resulting iminium species, but with little stereoselectivity.[16] Related cyclisations are also known, which give five-membered ring products from selenocyclisations of *O*-allylic hydroxamic acids, hydroxylamines and hydrazines.[17]

A final and rather spectacular example involves 5-*endo-trig* cyclisation of tryptophan derivatives **18** to give the benzopyrrolizidines **19**, serving both to block the usual chemistry of the indole residue as well as providing other opportunities for further functionalisation (Scheme 1).[18]



Scheme 1. Benzopyrrolizidines from 5-*endo* selenocyclisations of tryptophanes.

It was against this background that we wondered if related 5-*endo-trig* selenocyclisations of *N*-tosylsulfonyl homoallylic amines **20** might provide a useful approach to β-selanyl-pyrrolidines and especially if it would be possible to control both the regiochemistry and the stereoselectivity of such projected cyclisations. This was far from certain, in view of the foregoing observations of the lack of regiocontrol in selenium-induced cyclisations of the allylic benzylamines **11**[14] and of the very limited success of related cyclisations when applied to homoallylic carbamates (Fig. 3). Further, our own studies on related iodocyclisations of the sulfonamides **20** had revealed sensitivity to isomerisation under acidic conditions. Thus, while exposure of sulfonamides **20** to iodine in the presence of potassium carbonate led very largely to the 2,5-*trans* isomers **21**, in the absence of base, the corresponding 2,5-*cis* isomers **22** were obtained, usually exclusively (Scheme 2).[19] Additional experiments pointed to an acid-catalysed ring opening and re-closure towards the more thermodynamically stable *cis* isomers **22** as being responsible. It was therefore quite uncertain at the outset how such substrates would respond to selenocyclisation.



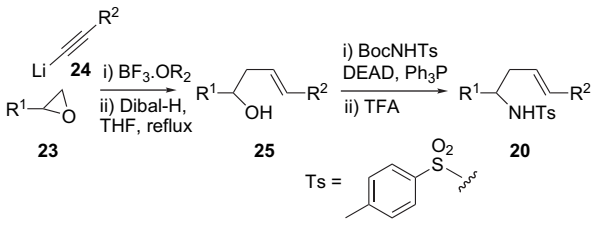
Scheme 2. 5-*endo* Iodocyclisations of homoallylic sulfonamides.

A further motivation of our investigations of such a selenium-mediated process was the finding that elimination of the elements of hydrogen iodide from the iodo-pyrrolidines **21** or **22** failed to give acceptable yields of the anticipated pyrrolines; we expected that the corresponding selanyl-pyrrolidines would be much more amenable to such eliminations, given that their formation could be controlled. The general principle of overall 5-*endo-trig* electrophile-driven cyclisation is now well established as a useful and often highly stereoselective method for the synthesis of five-membered saturated heterocycles.[20] An additional attraction of this type of heterocyclic synthesis is that ring formation is accompanied by the incorporation of a potentially useful functional group. Herein, we report in full on our initial studies of such cyclisations.[21]

2. Results and discussion

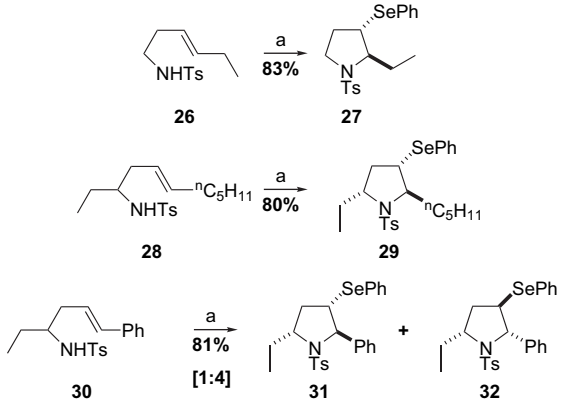
We first chose to examine the prospects for 5-*endo-trig* selenocyclisations of both alkyl and aryl substituted homoallylic sulfonamides **20**. These were all synthesised[19] by the addition of an acetylide **24** to a monosubstituted epoxide **23** in the presence of boron trifluoride etherate[22] or, better, the corresponding tetrahydrofuran complex,[23] followed by reduction using either lithium aluminium hydride or Dibal-H in hot tetrahydrofuran (Scheme 3). The necessary sulfonamide group was then introduced into the resulting homoallylic alcohols **25** by Mitsunobu reaction with *N*-Boc tosylamide [BocNHTs], a procedure introduced by the Weinreb group.[24] Deprotection using trifluoroacetic acid completed the sequence.

Guided by the early results of Clive,[13] we were delighted to find that the simplest substrate **26** was converted smoothly



Scheme 3. Precursor synthesis.

into a single pyrrolidine, assumed to be the 2,3-*trans* diastereoisomer **27** (see below), in excellent yield by brief exposure to phenylselanyl chloride in dichloromethane at low temperature (−78 °C) (Scheme 4). Similarly, the more highly substituted precursor **28** gave essentially a single product **29** under the same conditions, contaminated with what appeared to be traces of other pyrrolidine diastereoisomers, according to ^{1}H NMR spectroscopy.

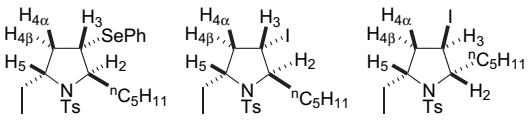


Scheme 4. Reagents and conditions: PhSeCl (1.1 equiv), CH_2Cl_2, −78 °C, <1 h.

Unfortunately, under the same relatively straightforward conditions, the related styryl derivative **30** gave a mixture of the trisubstituted pyrrolidines **31** and **32**, but still in good yield. In contrast to similar cyclisations of the homoallylic benzylamines **11** (Fig. 3), we did not detect any azetidine formation.

The stereochemistries of the present [**27**, **29**, **31** and **32**] and subsequent β-selenopyrrolidines were determined principally by comparisons between their proton coupling constants and those displayed by the corresponding β-iodopyrrolidines. Structural assignments in the latter cases have been firmly established by both NOE experiments and X-ray crystallographic analysis.[19] An exception was the very first example (**27**), in which overlapping resonances prevented such comparisons, although these data did allow a definite assignment of a pyrrolidine rather than an azetidine structure to this product. Hence, the *trans*-stereochemistry is based largely on the assumption of trans addition of the amine and selenium groups across the alkene, for which there seems to be few if any exceptions and certainly none in the present reactions. The other comparative *J* values are set out in Figure 4.

Similar comparisons between the 2-phenyl-3-seleno and 2-phenyl-3-iodo-pyrrolidines [**31**, **32** and **35**, **36**, respectively]



	29	**33**	**34**
$J_{2,3}$	1.4	1.7	3.4
$J_{3,4\alpha}$	7.5	6.6	5.7
$J_{3,4\beta}$	1.9	2.2	3.5
$J_{4\alpha,5}$	8.7	8.8	7.5
$J_{4\beta,5}$	3.3	3.2	6.8
$J_{2,1'\text{-}CH_2}$	10.1, 2.9	10.3, 3.3	9.1, 3.6
$J_{5,1'\text{-}CH_2}$	11.3, 3.3	11.3, 3.1	8.0, 4.2

Figure 4. Comparative coupling constants in hertz for β-seleno- and β-iodo-pyrrolidines.

gave much the same support for the stereochemical assignments (Fig. 5).

These data are also consistent with those shown in Figure 4, and hence it appeared that such stereochemical assignments were on a sound basis. Further, these were also in accord with a likely initial chair-like transition state conformation **37** controlled by an equatorial positioning of the substituents 'R' attached to the sp^3 carbon (Fig. 6).

Consonant with these assignments and with the conformation **37** were the outcomes of similar selenocyclisations of the more substituted homoallylic sulfonamides **38** and **40**.[19] Each proceeded smoothly under the same conditions to give only the diastereoisomers **39** and **41**, respectively (Scheme 5).

	31 R = SePh	**35** R = I	**32** R = SePh	**36** R = I
$J_{2,3}$	2.1	2.3	5.9	4.9
$J_{3,4\alpha}$	7.6	8.7	7.6	6.2
$J_{3,4\beta}$	2.5	2.4	5.6	6.2
$J_{4\alpha,5}$	6.4	6.7	4.8	6.2
$J_{4\beta,5}$	2.5	3.0	5.2	6.2

Figure 5. Comparative coupling constants in hertz for 2-phenyl-pyrrolidines.

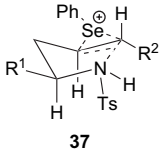
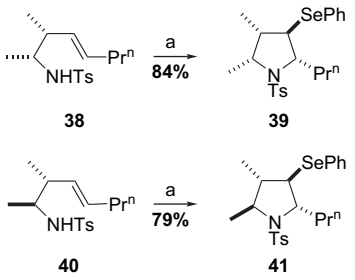


Figure 6. Possible chair-like conformation leading to the initial 2,5-*trans*-pyrrolidines.



Scheme 5. Reagents and conditions: PhSeCl (1.1 equiv), CH_2Cl_2, −78 °C, <1 h.

Once again, initial structural assignments were made on the basis of comparisons between these products and the corresponding iodo-pyrrolidines **42** and **43**, respectively (Fig. 7).[19]

The close correspondence between the two pairs of coupling constants strongly supports these assignments, as do the likely transition state conformations, which are extrapolations of the simpler proposal **37** (Fig. 6). In the first example where the product **39** has the selanyl group positioned trans to the other three substituents, one of the methyl substituents must be positioned axially, given the intermediacy of such a chair-like conformation. The preference is therefore clearly in favour of that conformation **44** in which the methyl group adjacent to the selenonium ion is placed in an equatorial position (Fig. 8). By contrast, the conformation **45** leading to the 'all-trans' product **41** has all substituents positioned equatorially, thereby removing any realistic element of choice regarding other possible conformations. These two assignments were also supported by subsequent elimination reactions described in Figure 8.

We then returned to the problem of the non-stereoselective cyclisation of the phenyl derivative **30** (Scheme 4). On the assumption that this might be due to acid-catalysed isomerisation of some kind, most probably by ring opening and

	39 R = SePh	42 R = I	41 R = SePh	43 R = I
$J_{2,3}$	8.3	8.7	5.3	6.3
$J_{3,4}$	11.4	11.6	8.7	9.2
$J_{4,5}$	7.2	7.2	8.3	9.4
$J_{2,1'\text{-}CH_2}$	4.6, 5.1	3.6, 6.2	4.2, 7.6	7.6, 4.1

Figure 7. Comparative coupling constants for 4,5-dimethylpyrrolidines.

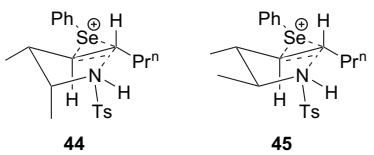
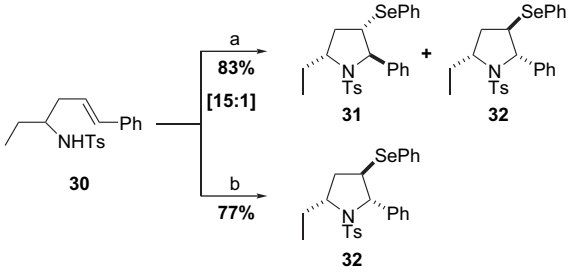


Figure 8. Possible chair-like conformations leading to 4,5-dimethylpyrrolidines **39** and **41**.

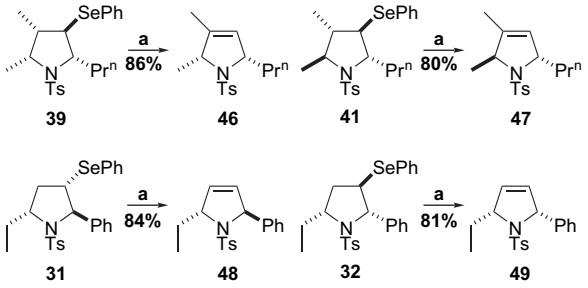
re-closure as in the case of the related iodo-pyrrolidines (Scheme 2),[19] we felt that the generation of free hydrogen chloride during the cyclisation might be responsible. The cyclisation was therefore repeated but in the presence of an equivalent of anhydrous potassium carbonate (Scheme 6). This resulted in a distinct increase in the proportion of the 2,5-*trans* isomer **31** formed, lending weight to our supposition that acid-catalysed isomerisation was taking place.



Scheme 6. Reagents and conditions: (a) PhSeCl (1.1 equiv), K_2CO_3 (1 equiv), water (trace), CH_2Cl_2, −78 °C, < 1 h; (b) **30** (0.14 mmol), PhSeCl (1.1 equiv), CH_2Cl_2, −78 °C then add 10 M HCl (one drop), 0.5 h.

The best result was obtained when a small amount of water was also added, presumably to facilitate reaction between the base and the acid generated as the cyclisation proceeded. This 15:1 ratio in favour of the 2,5-*trans* isomer **31** then suggested that if additional acid were to be added, then isomerisation ought to be encouraged. This turned out to be the case: when a drop of concentrated hydrochloric acid was added at the outset, only the 2,5-*cis* isomer **32** was isolated, confirming our supposition that this is the thermodynamic isomer, formed via the initial kinetic product **31**.

To both show one synthetic utility of these selanyl-pyrrolidines and also to provide further evidence for the assigned stereochemistries, we next examined the viability of oxidative elimination reactions. As shown in Scheme 7, these all proceeded smoothly under very simple conditions.[7,25]



Scheme 7. (a) H_2O_2 (30%), THF, 20 °C, 1 h.

In the cases of 4,5-dimethylpyrrolidines **39** and **41**, each possesses a 3,4-*trans* substitution pattern and hence the derived selenoxides **50** are perfectly set up to undergo *syn* eliminations to give the observed products **46** and **47**, respectively (Fig. 9). By contrast, the corresponding iodo-pyrrolidines **42** and **43**[19] failed to give more than traces of the 3-pyrrolines **46** and **47** under conditions (DBU, hot toluene[19,26]), which delivered good yields of this product type from iodo-pyrrolidines having no substituents in the 4-position. While the presence of the β-methyl group might contribute to this, presumably the major reason for this failure is the *syn*-disposition of the 4-proton and the 3-iodo atoms.

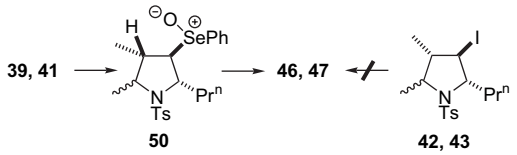
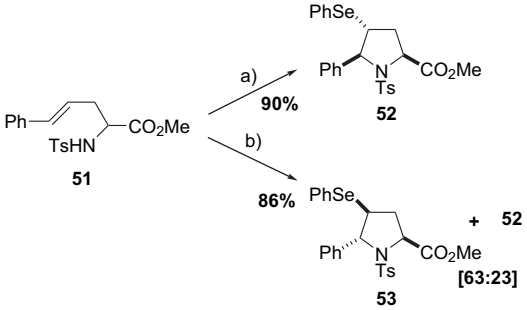


Figure 9. Eliminations from β-selanyl- and β-iodo-pyrrolidines.

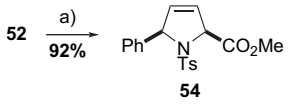
As expected, both 2-phenyl-pyrrolidines **31** and **32** underwent smooth elimination to give excellent yields of the corresponding pyrrolines **48** and **49** (Scheme 7). In both cases, no isomerisation was observed and both displayed spectroscopic and analytical data, which correlated exactly with the same products derived from the corresponding iodopyrrolidines **35** and **36** (Fig. 5).[19]

With the aim of demonstrating further the utility of this chemistry, we felt that examples with more reactive functional groups, which would subsequently be available for further manipulation, ought to be tested. In view of the foregoing results, we also chose to restrict this investigation to the seemingly more awkward aryl substituted alkenes. Hence, the cinnamyl glycinate **51** was chosen as the first test substrate; this was readily prepared from cinnamyl bromide and the enolate of *N*-benzylidene glycinate using the excellent Stork procedure,[27] followed by exchange of the protecting group.[19] When subjected to 'thermodynamic' conditions (Scheme 4), once again mixtures of the 2,5-*cis* and *trans* selanyl-pyrrolidines were obtained. Even at ambient temperature, when using phenylselanyl chloride in the absence of base, gross mixtures of diastereoisomers were obtained; for example, prolonged reaction in dichloromethane led to a 3:1 mixture but to a more useful 9:1 mixture in favour of the 2,5-*cis* isomer in acetonitrile. It was only when we used phenylselanyl bromide in dichloromethane for an extended period at ambient temperature that only the 2,5-*cis* isomer **52** was isolated (Scheme 8). Much of the same result could also be obtained using acetonitrile as solvent.



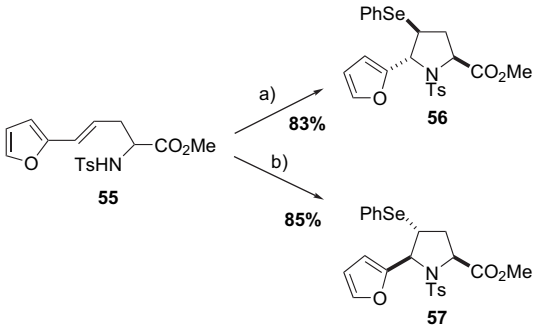
Scheme 8. (a) PhSeBr, CH_2Cl_2, 20 °C, 72 h; (b) PhSeCl, K_2CO_3, −78 to 20 °C.

Many attempts to obtain the 2,5-*trans* isomer **53** as essentially the sole product failed or were not repeatable with certainty. Two of the better results are detailed in Section 3; this particular cyclisation turned out to be the most capricious of all those studied and results, in terms of stereochemistry, were very often completely irreproducible. The relative stereochemistries of the two products **52** and **53** were again assigned on the basis of comparisons of coupling constants, both with the foregoing selanyl-pyrrolidines and with related iodo-pyrrolidines.[28] In the case of the 2,5-*cis* isomer **52**, subsequent oxidative elimination of the selenium group proceeded uneventfully to give an excellent yield of the 3-pyrroline **54** (Scheme 9).



Scheme 9. (a) H_2O_2 (30%), THF, 20 °C, 1 h.

We then turned to cyclisations of the related 2-furyl derivative **55**. In this case, we identified three additional features. Firstly, the furan residue would very likely be sensitive to the acidic conditions generated during cyclisations conducted in the absence of base. Secondly, if conditions could be found that gave single diastereoisomers, then the furan ring could subsequently be oxidatively cleaved to give the corresponding carboxylate group, thereby enabling further homologation of the initial product(s). Finally, an additional beneficial feature of the furan should be as a facilitating group for the cyclisations; our previous studies on iodocyclisations of similar substrates having 2-furyl substituents had suggested that the furyl oxygen actively participates in the cyclisations.[29] In view of the first concern, we first examined cyclisations under basic conditions and were pleased to find that exposure of the substrate **55** to phenylselanyl chloride at low temperature in tetrahydrofuran containing 1.5 equiv of potassium carbonate gave an excellent yield of the hoped-for 2,5-*trans* diastereoisomer **56**, as essentially a single product (Scheme 10). Rather surprisingly, however, when the same reaction was carried out at ambient temperature, but in acetonitrile, only the corresponding 2,5-*cis* isomer **57** was obtained, again in excellent yield. Once again, the stereochemistries were assigned on the basis of comparisons with the foregoing data.

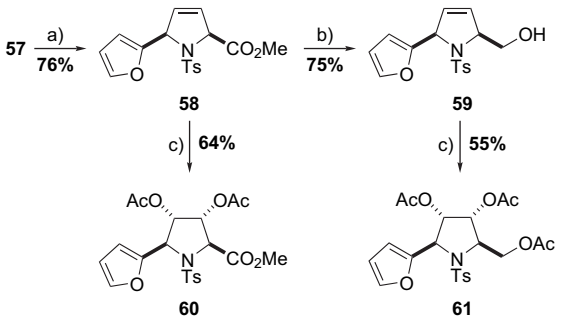


Scheme 10. (a) PhSeCl, THF, K_2CO_3 (1.5 equiv), −78 °C, 2 h; (b) PhSeCl, MeCN, K_2CO_3 (1.5 equiv), 20 °C, 2 h.

This somewhat surprising result probably reflects the anticipated participation by the furyl oxygen. Even with this effect,[29] the stereochemical outcome of the low temperature cyclisation leading to the 2,5-*trans* isomer **56** is again consistent with the intermediacy of a chair-like transition state conformation (Figs. 6 and 8). An explanation for the formation of the 2,5-*cis* isomer **57** is not so obvious, beyond it being the thermodynamically more stable isomer, which is formed at higher temperature.

We have briefly exemplified some of the synthetic potential of these selanyl-pyrrolidines using the 2,5-*cis*-2-furyl isomer **57** (Scheme 11). Oxidative elimination once again occurred

uneventfully to provide an excellent return of the expected 3-pyrroline **58**, which was subsequently smoothly reduced to the corresponding 3-pyrroline methanol **59** using Dibal-H.



Scheme 11. (a) H_2O_2 (30%), THF, 20 °C, 2 h; (b) Dibal-H, toluene, 0 °C, 3 h; (c) OsO_4 in *t*-BuOH, aqueous acetone, 20 °C, 16 h then evaporate solvents and add Ac_2O and dry pyridine, 20 °C, 20 h.

Osmylation of both pyrrolines in aqueous acetone followed by per-acetylation (to facilitate isolation) was essentially completely stereoselective and gave reasonable yields of the two fully functionalised pyrrolidines **60** and **61**, which should serve as useful precursors to a wide range of polyhydroxylated pyrrolidines and derived bicyclic systems.

In conclusion, this type of overall 5-*endo-trig* selenocyclisation has clear potential for the rapid assembly of pyrrolidines, pyrrolines and derived structures in a controlled and stereoselective manner. However, exceptions to this may occur in a few substrates having aryl substituents at the distal end of the alkene group, when stereochemistry can be more difficult to control.

3. Experimental

3.1. General

NMR spectra were recorded using a Bruker WM or DPX spectrometers, operating at 250 or 400 MHz for ^{1}H NMR spectra and at 67.5 or 100.6 MHz for ^{13}C NMR spectra, respectively. Unless stated otherwise, NMR spectra were measured using dilute solutions in deuteriochloroform. All NMR measurements were carried out at 30 °C and chemical shifts are reported as parts per million on the delta scale downfield from tetramethylsilane (TMS: δ=0.00) or relative to the resonances of $CDCl_3$ (δ=7.27 ppm in proton spectra and δ=77.0 ppm for the central line of the triplet in carbon spectra). Coupling constants (*J*) are reported in hertz. Infrared spectra were recorded as thin films for liquids and as Nujol mulls for solids, using a Perkin–Elmer 1600 series FTIR spectrophotometer and sodium chloride plates. Low-resolution mass spectra were obtained using a VG Platform II Quadrupole spectrometer operating in the electron impact (EI; 70 eV) or atmospheric pressure chemical ionisation (ApcI) modes, as stated. High-resolution mass spectrometric data were obtained from the EPSRC Mass Spectrometry Service, University College, Swansea, using the ionisation modes specified. All mass spectroscopic data involving selanides were compared against selenium-80. Melting points were determined using a Kofler hot stage apparatus and are uncorrected. Elemental analyses were obtained using a Perkin–Elmer 240C Elemental Microanalyser.

All reactions were conducted in oven-dried apparatus under an atmosphere of dry nitrogen unless otherwise stated. All organic solutions from aqueous work-ups were dried by brief exposure to dried magnesium sulfate, followed by gravity filtration. The resulting dried solutions were evaporated using a Büchi rotary evaporator under water aspirator pressure and at ambient temperature unless otherwise stated. Column chromatography was carried out using Merck Silica Gel 60 (230–400 mesh). TLC analyses were carried out using Merck silica gel 60 F_{254} pre-coated, aluminium-backed plates, which were visualised using ultraviolet light or potassium permanganate or ammonium molybdenate sprays.

Ether refers to diethyl ether and petrol to the fraction boiling at 60–80 °C unless stated otherwise.

All starting materials were synthesised as described in full in Ref. 19.

3.2. Selenocyclisations: general procedure A

A stirred solution of the cyclisation precursor (1 mmol) in dry dichloromethane (5 ml) was cooled to −78 °C and solid phenylselanyl chloride (1.1 mmol) added portionwise. Stirring was continued at this temperature until cyclisation was complete, typically after 0.5–1 h, according to TLC analysis. The solvent was evaporated and the residue purified by column chromatography.

3.2.1. (2*RS*,3*SR*)-2-Ethyl-3-(phenylselanyl)-1-tosylpyrrolidine 27. (*E*)-Homoallylic tosylamide **26** (20 mg, 0.08 mmol) was cyclised according to general procedure A to leave an orange oil, which was purified by column chromatography (dichloromethane) to give the *title compound* **27** (30 mg, 83%) as a clear, colourless oil, R_f 0.78 (dichloromethane); ν_{max}(film)/cm^{-1} 2950, 2930, 2867, 1586, 1452; δ_H (400 MHz, $CDCl_3$) 0.86 (3H, t, *J*=7.5 Hz, 2′-Me), 1.61 (1H, ddq, *J*=13.9, 8.8, 7.5 Hz, 1′-H_a), 1.73 (1H, dddd, *J*=13.4, 6.5, 3.1, 2.9 Hz, 4-H_a), 1.89 (1H, dqd, *J*=13.9, 7.5, 3.6 Hz, 1′-H_b), 2.24 (1H, dddd, *J*=13.4, 9.6, 7.6, 6.2 Hz, 4-H_b), 2.47 (3H, s, Ar-Me), 3.37 (1H, ddd, *J*=9.6, 9.6, 6.5 Hz, 5-H_a), 3.46–3.58 (3H, m, 2-H, 3-H, 5-H_b), 7.24–7.36 (7H, m), 7.73 (2H, d, *J*=8.3 Hz, 2×ArH); δ_C (100 MHz, $CDCl_3$) 10.0 (2′-Me), 21.6 (Ar-Me), 29.5 (1′-CH_2), 30.6 (4-CH_2), 44.1 (3-CH), 47.8 (5-CH_2), 67.8 (2-CH), 127.9 (ArCH), 128.0 (ArCH), 129.1 (ArCH), 129.6 (ArCH), 131.5 (ArC), 133.6 (ArC), 134.7 (ArCH), 143.2 (ArC); *m/z* (FAB) 410 (M^++1, 66%), 380 (48), 252 (97), 184 (100), 155 (76), 91 (79), 69 (54). Found: M^++1, 410.0697. $C_{19}H_{24}NO_2SSe$ requires: M, 410.0693.

3.2.2. (2*RS*,3*SR*,5*RS*)-5-Ethyl-2-pentyl-3-phenylselanyl-1-tosylpyrrolidine 29. (*E*)-Homoallylic tosylamide **28** (100 mg, 0.4 mmol) in dichloromethane (2 ml) was subjected to the general cyclisation conditions A to give an orange oil, which was purified by column chromatography (dichloromethane) to give the *title compound* **29** (102 mg, 80%) as a pale yellow oil, R_f 0.53 (dichloromethane); ν_{max}(film)/cm^{-1} 3050, 2940, 2870, 1590, 1465; δ_H (250 MHz, $CDCl_3$) 0.92 (3H, t, *J*=6.9 Hz, 5′-Me), 0.98 (3H, t, *J*=7.2 Hz,

2″-Me), 1.01–1.49 (10H, m), 2.00 (1H, ddd, *J*=14.2, 3.3, 1.9 Hz, 4-H_a), 2.45 (3H, s, Ar-Me), 2.59 (1H, ddd, *J*=14.2, 8.7, 7.5 Hz, 4-H_b), 3.59 (1H, ddd, *J*=7.5, 1.9, 1.4 Hz, 3-H), 3.78 (1H, dddd, *J*=11.3, 8.7, 3.3, 3.3 Hz, 5-H), 3.93 (1H, ddd, *J*=10.1, 2.9, 1.4 Hz, 2-H), 7.28–7.50 (7H, m), 7.80 (2H, d, *J*=8.3 Hz, 2×ArH); δ_C (67.8 MHz, $CDCl_3$) 10.0 (Me), 14.1 (Me), 21.6 (Ar-Me), 22.5 (CH_2), 25.7 (CH_2), 27.3 (CH_2), 31.1 (CH_2), 31.3 (CH_2), 34.6 (4-CH_2), 43.7 (3-CH), 61.6 (5-CH), 69.5 (2-CH), 126.9 (ArCH), 127.9 (ArCH), 128.0 (ArC), 129.2 (ArCH), 129.7 (ArCH), 134.7 (Ar-CH), 142.9 (ArC), 143.5 (ArC); *m/z* (FAB) 478 (M^++1, 16%), 322 (30), 212 (100), 155 (35), 91 (43). Found: M^++1, 480.1480. $C_{24}H_{34}NO_2SSe$ requires: M, 480.1475.

3.2.3. (2*RS*,3*SR*,4*RS*,5*SR*)-4,5-Dimethyl-3-phenylselanyl-2-propyl-1-tosylpyrrolidine 39. Using general procedure A, (2*SR*, 3*SR*)-(*E*)-homoallylic tosylamide **38** (20 mg, 0.07 mmol) was cyclised to afford the *title compound* **39** (30 mg, 84%), following column chromatography (dichloromethane), as a pale yellow oil, R_f 0.56 (dichloromethane); ν_{max}(film)/cm^{-1} 2966, 2931, 2868, 1475, 1342; δ_H (250 MHz, $CDCl_3$) 0.96 (3H, t, *J*=7.2 Hz, 3′-Me), 1.01 (3H, d, *J*=6.9 Hz, 4-Me), 1.14 (3H, d, *J*=6.9 Hz, 5-Me), 1.29–1.42 (1H, m, 4-H), 1.49–1.65 (2H, m, 2′-CH_2), 1.88–2.01 (2H, m, 1′-CH_2), 2.42 (3H, s, Ar-Me), 2.81 (1H, dd, *J*=11.4, 8.3 Hz, 3-H), 3.46 (1H, ddd, *J*=8.3, 5.1, 4.6 Hz, 2-H), 3.72 (1H, dq, *J*=7.2, 6.9 Hz, 5-H), 7.11–7.62 (9H, m); δ_C (67.8 MHz, $CDCl_3$) 12.8 (3′-Me), 14.2 (4-Me), 17.2 (2′-CH_2), 17.6 (5-Me), 21.5 (Ar-Me), 35.2 (1′-CH_2), 40.8 (4-CH), 49.6 (3-CH), 56.1 (5-CH), 65.7 (2-CH), 127.7 (ArC), 129.0 (ArCH), 129.2 (ArCH), 129.6 (ArCH), 131.5 (ArCH), 134.4 (ArC), 136.7 (ArCH), 142.8 (ArC); *m/z* (FAB) 451 (M^+, 69%), 408 (45), 198 (100), 155 (58), 91 (84), 77 (18), 68 (23). Found: M^+, 451.1086. $C_{22}H_{29}NO_2SSe$ requires: M, 451.1084.

3.2.4. (2*RS*,3*SR*,4*RS*,5*RS*)-4,5-Dimethyl-3-phenylselanyl-2-propyl-1-tosylpyrrolidine 41. Using general procedure A, (2*RS*, 3*SR*)-(*E*)-homoallylic tosylamide **40** (20 mg, 0.07 mmol) was cyclised to afford the *title compound* **41** (28 mg, 84%), following column chromatography (dichloromethane), as a pale yellow oil, R_f 0.58 (dichloromethane); ν_{max}(film)/cm^{-1} 2966, 2931, 2868, 1590, 1475, 1342; δ_H (250 MHz, $CDCl_3$) 0.88 (3H, t, *J*=7.2 Hz, 3′-Me), 1.04 (3H, d, *J*=6.5 Hz, 4-Me), 1.11 (3H, d, *J*=6.6 Hz, 5-Me), 1.17–1.98 (5H, m), 2.43 (3H, s, Ar-Me), 2.88 (1H, dd, *J*=8.7, 5.3 Hz, 3-H), 3.28 (1H, dq, *J*=8.3, 6.6 Hz, 5-H), 4.11 (1H, ddd, *J*=7.6, 5.3, 4.2 Hz, 2-H), 7.13–7.62 (9H, m); δ_C (67.8 MHz, $CDCl_3$) 14.0 (3′-Me), 16.6 (4-Me), 17.1 (5-Me), 18.1 (2′-CH_2), 21.5 (Ar-Me), 37.2 (1′-CH_2), 48.1 (4-CH), 50.9 (3-CH), 62.3 (5-CH), 68.0 (2-CH), 126.8 (ArCH), 128.5 (ArCH), 129.2 (ArCH), 129.3 (ArC), 131.5 (ArCH), 136.3 (ArCH), 140.5 (ArC), 142.5 (ArC); *m/z* (FAB) 451 (M^+, 35%), 408 (45), 198 (100), 155 (59), 91 (84), 77 (18), 68 (24). Found: M^+, 451.1110. $C_{22}H_{29}NO_2SSe$ requires: M, 451.1084.

3.2.5. (2*SR*,3*RS*,5*SR*)-5-Ethyl-2-phenyl-3-phenylselanyl-1-tosylpyrrolidine 31. A stirred mixture of (*E*)-homoallylic tosylamide **30** (0.28 g, 0.86 mmol), anhydrous potassium carbonate (0.12 g, 0.86 mmol) and water (10 μl) in dichloromethane (5 ml) was maintained at −78 °C for 20 min before the portionwise addition of phenylselanyl chloride (0.18 g, 0.94 mmol). After a further 0.5 h, the cooling bath was removed and the mixture allowed to warm to ambient temperature, then the solvents were largely evaporated. The residue was separated by column chromatography (dichloromethane) to give the 2,5-*trans* isomer **31** (0.32 g, 83%) as a yellow oil, R_f 0.28 (hexane–EtOAc, 10:1); ν_{max}(film)/cm^{-1} 3030, 2960, 2930, 2880, 1590, 1455, 1340; δ_H (250 MHz, $CDCl_3$) 0.87 (3H, t, *J*=7.6 Hz, 2′-Me), 1.66–1.83 (2H, m, 1′-CH_2), 2.04 (1H, ddd, *J*=12.8, 2.5, 2.5 Hz, 4-H_b), 2.36 (3H, s, Ar-Me), 2.63 (1H, ddd, *J*=12.8, 7.6, 6.4 Hz, 4-H_a), 3.61 (1H, ddd, *J*=7.6, 2.5, 2.1 Hz, 3-H), 4.07–4.11 (1H, m, 5-H), 5.03 (1H, d, *J*=2.1 Hz, 2-H), 7.14–7.34 (12H, m), 7.59 (2H, d, *J*=8.2 Hz, 2×ArH); δ_C (67.8 MHz, $CDCl_3$) 11.3 (2′-Me), 21.1 (Ar-Me), 28.0 (1′-CH_2), 33.8 (4-CH_2), 48.1 (3-CH), 63.4 (5-CH), 72.4 (2-CH), 126.4 (ArCH), 126.9 (ArCH), 127.5 (ArCH), 128.4 (ArCH), 129.0 (ArCH), 129.9 (ArCH), 134.6 (ArCH), 134.8 (ArC), 135.3 (ArCH), 139.5 (ArC), 141.7 (ArC), 142.6 (ArC). Found (EI): M^+, 485.0927. $C_{25}H_{27}NO_2SSe$ requires: M, 485.0928.

The sample was contaminated with ca. 6% of the corresponding 2,5-*cis* isomer **32** (following compound).

3.2.6. (2*RS*,3*SR*,5*SR*)-5-Ethyl-2-phenyl-3-phenylselanyl-1-tosylpyrrolidine 32. To a stirred solution of (*E*)-homoallylic tosylamide **30** (50 mg, 0.14 mmol) in dichloromethane (1 ml) maintained at −78 °C was added phenylselanyl chloride (30 mg, 0.15 mmol). After 5 min at this temperature, one drop of 10 M hydrochloric acid was added. After a further 0.5 h, the cooling bath was removed and the mixture allowed to warm to ambient temperature, then the solvents were largely evaporated. The residue was separated by column chromatography (dichloromethane) to give the 2,5-*cis* isomer **32** (61 mg, 77%) as a yellow oil, R_f 0.28 (hexanes–EtOAc, 9:1); ν_{max}(film)/cm^{-1} 3025, 2950, 2925, 2877, 1590, 1455, 1340; δ_H (250 MHz, $CDCl_3$) 0.99 (3H, t, *J*=7.4 Hz, 2′-Me), 1.61–1.71 (2H, m, 1′-CH_2), 2.02 (1H, ddd, *J*=13.2, 5.6, 5.2 Hz, 4-H_a), 2.23 (1H, ddd, *J*=13.2, 7.6, 4.8 Hz, 4-H_b), 2.44 (3H, s, Ar-Me), 3.47 (1H, ddd, *J*=7.6, 5.9, 5.6 Hz, 3-H), 3.79–3.83 (1H, m, 5-H), 4.58 (1H, d, *J*=5.9 Hz, 2-H), 7.18–7.36 (12H, m), 7.62 (2H, d, *J*=8.3 Hz, 2×ArH); δ_C (67.8 MHz, $CDCl_3$) 10.9 (2′-Me), 21.5 (Ar-Me), 29.4 (1′-CH_2), 36.7 (4-CH_2), 47.9 (3-CH), 62.6 (5-CH), 70.6 (2-CH), 126.4 (ArCH), 126.6 (ArCH), 127.5 (ArCH), 127.6 (ArCH), 127.8 (ArCH), 128.1 (ArCH), 128.3 (ArCH), 129.1 (ArC), 129.5 (ArCH), 134.8 (ArC), 141.3 (ArC), 143.1 (ArC). Found: M^+, 485.0930.

3.3. Oxidative elimination of phenylselanyl group: general procedure B

To a stirred solution of a phenylselanyl pyrrolidine (1 mmol) in tetrahydrofuran (1 ml) was added aqueous hydrogen peroxide (30%, 0.2 ml) and the resulting solution stirred at ambient temperature for 1 h. The bulk of the solvent was evaporated, the residue dissolved in dichloromethane (2 ml) and the resulting solution washed with water (3×1 ml) then dried, filtered through a short plug of silica gel and evaporated to leave essentially pure pyrroline.

3.3.1. (2*RS*,5*SR*)-4,5-Dimethyl-2-propyl-1-tosyl-3-pyrroline 46. Oxidation of 4,5-*syn*-dimethyl pyrrolidine **39** (20 mg) gave the 2,5-*cis*-pyrroline **46** (11 mg, 86%) as

a colourless viscous oil, R_f 0.67 (dichloromethane); ν_{max} (film)/cm^{-1} 3060, 2950, 1580, 1420, 1340; δ_H (250 MHz, $CDCl_3$) 0.93 (3H, t, J=7.3 Hz, 3′-Me), 1.39 (3H, d, J=6.5 Hz, 5-Me), 1.57 (3H, d, J=0.8 Hz, 4-Me), 1.26–1.78 (4H, m, 1′-, 2-CH_2), 2.42 (3H, s, Ar-Me), 4.24–4.29 (1H, m, 2-H), 4.40 (1H, qd, J=6.5, 0.8 Hz, 5-H), 5.15–5.17 (1H, m, 3-H), 7.28 (2H, d, J=8.3 Hz, 2×ArH), 7.69 (2H, d, J=8.3 Hz, 2×ArH); δ_C (100 MHz, $CDCl_3$) 13.5 (3′-Me), 14.1 (4-Me), 18.4 (2′-CH_2), 21.4 (Ar-Me), 22.1 (5-Me), 39.9 (1′-CH_2), 65.6 (5-CH), 66.9 (2-CH), 122.6 (ArCH), 127.6 (4-C), 127.7 (3-CH), 129.6 (ArCH), 138.6 (ArC), 143.2 (ArC); m/z (ES) 294 (M^++1, 100%), 145 (22), 104 (21), 102 (18), 83 (23), 60 (69). Found: M^++1, 294.1528. $C_{16}H_{24}NO_2S$ requires: M, 294.1532.

3.3.2. (2*RS*,5*RS*)-4,5-Dimethyl-2-propyl-1-tosyl-3-pyrroline 47. Oxidation of 4,5-*anti*-dimethyl pyrrolidine **41** (20 mg) gave 2,5-*trans*-pyrroline **47** (10 mg, 80%) as a colourless viscous oil, R_f 0.65 (dichloromethane); ν_{max}(film)/cm^{-1} 3060, 2950, 1580, 1420, 1340; δ_H (250 MHz, $CDCl_3$) 0.85 (3H, t, J=7.3 Hz, 3′-Me), 1.35 (3H, d, J=6.4 Hz, 5-Me), 1.65 (3H, s, 4-Me), 1.11–1.91 (4H, m, 1′-, 2-CH_2), 2.41 (3H, s, Ar-Me), 4.36–4.43 (1H, m, 5-H), 4.48–4.56 (1H, m, 2-H), 5.26–5.27 (1H, m, 3-H), 7.28 (2H, d, J=8.3 Hz, 2×ArH), 7.73 (2H, d, J=8.3 Hz, 2×ArH); δ_C (100 MHz, $CDCl_3$) 14.0 (3′-Me), 17.7 (4-Me), 19.2 (2′-CH_2), 19.4 (5-Me), 21.4 (Ar-Me), 36.9 (1′-CH_2), 65.7 (5-CH), 66.5 (2-CH), 122.7 (ArCH), 126.8 (3-CH), 129.3 (ArCH), 134.3 (ArC), 138.2 (ArC); m/z (ES) 294 (M^++1, 100%), 198 (7), 153 (10), 102 (18), (23). Found: M^++1, 294.1529. $C_{16}H_{24}NO_2S$ requires: M, 294.1532.

3.3.3. (2*SR*,5*RS*)-5-Ethyl-2-phenyl-1-tosyl-3-pyrroline 48. Following general procedure B, oxidation of phenylselanyl pyrrolidine **31** (20 mg) gave 2,5-*trans*-pyrroline **48** (10 mg, 84%) as a colourless, viscous oil, R_f 0.48 (dichloromethane); ν_{max}(film)/cm^{-1} 3050, 2950, 1590, 1430, 1340; δ_H (270 MHz, $CDCl_3$) 0.88 (3H, t, J=7.2 Hz, 2′-Me), 1.85–2.14 (2H, m, 1′-CH_2), 2.23 (3H, s, Ar-Me), 4.57–4.69 (1H, m, 5-H), 5.50 (1H, app. ddd, J=5.3, 2.0, 1.9 Hz, 2-H), 5.58 (1H, ddd, J=6.3, 2.0, 1.8 Hz, 4-H), 5.69 (1H, ddd, J=6.3, 1.9, 1.6 Hz, 3-H), 6.83–7.19 (9H, m); δ_C (67.5 MHz, $CDCl_3$) 8.0 (2′-Me), 21.3 (Ar-Me), 28.4 (1′-CH_2), 67.7 (5-CH), 71.6 (2-CH), 126.4 (ArCH), 127.8 (ArCH), 127.9 (ArCH), 128.7 (ArCH), 128.9 (4-CH), 129.0 (3-CH), 129.9 (ArCH), 137.7 (ArC), 138.1 (ArC), 141.8 (ArC); m/z (ES) 328 (M^++1, 100%), 245 (8), 157 (9), 102 (9). Found: M^++1, 328.1372. $C_{19}H_{22}NO_2S$ requires: M, 328.1376.

3.3.4. (2*SR*,5*SR*)-5-Ethyl-2-phenyl-1-tosyl-3-pyrroline 49. Following general procedure B, oxidation of phenylselanyl pyrrolidine **32** (20 mg) gave 2,5-*cis*-pyrroline **49** (10 mg, 81%) as a colourless viscous oil, R_f 0.47 (dichloromethane); ν_{max}(film)/cm^{-1} 3050, 2950, 1590, 1430, 1340; δ_H (270 MHz, $CDCl_3$) 0.90 (3H, t, J=7.6 Hz, 2′-Me), 1.53–1.99 (2H, m, 1′-CH_2), 2.33 (3H, s, Ar-Me), 4.38–4.46 (1H, m, 5-H), 5.40 (1H, app. ddd, J=2.0, 2.0, 2.0 Hz, 2-H), 5.56 (1H, ddd, J=6.3, 2.0, 1.9 Hz, 4-H), 5.68 (1H, ddd, J=6.3, 2.0, 1.9 Hz, 3-H), 7.15–7.32 (7H, m), 7.56 (2H, d, J=8.2 Hz, 2×ArH); δ_C (67.5 MHz, $CDCl_3$) 10.6 (2′-Me), 21.9 (Ar-Me), 30.8 (1′-CH_2), 69.8 (5-CH), 71.1 (2-CH), 127.7 (ArCH), 128.0 (ArCH), 128.3 (ArCH), 128.8 (ArCH), 129.1 (4-CH), 129.7 (3-CH), 130.0 (ArCH), 135.7 (ArC), 141.3 (ArC), 143.8 (ArC); m/z (ES) 328 (M^++1, 100%), 245 (7), 157 (9), 102 (11). Found: M^++1, 328.1371. $C_{19}H_{22}NO_2S$ requires: M, 328.1376.

3.4. Pyrrolidine carboxylate formation and derivatives

3.4.1. Methyl (2*SR*,4*RS*,5*SR*)-5-phenyl-4-phenylselanyl-1-tosylpyrrolidine-2-carboxylate 52. To a stirred solution of cinnamyl tosylamide **51** (0.22 g, 0.60 mmol) in dry dichloromethane (5 ml) at ambient temperature was added phenylselanyl bromide (0.285 g, 1.21 mmol) in one portion and the resulting solution stirred for 72 h then filtered through silica, eluted first with toluene to remove excess selanyl bromide. Further elution with dichloromethane provided the product, which was crystallised from toluene–hexane to give 2,5-*cis*-pyrrolidine carboxylate **52** (0.279 g, 90%) as colourless crystals, mp 128–130 °C; $\nu_{max}(CHCl_3)$/cm^{-1} 2950, 2910, 1740, 1450; δ_H (400 MHz, DMSO-d_6) 1.89 (1H, app. dt, J=13.2, 7.5 Hz, 3-H_a), 2.36 (1H, app. dt, J=ca. 13.2, 5.9 Hz, 3-H_b), 2.43 (3H, s, Ar-Me), 3.63 (1H, app. q, J=ca. 6.3 Hz, 4-H), 3.77 (3H, s, OMe), 4.34 (1H, d, J=5.4 Hz, 5-H), 4.47 (1H, dd, J=7.5, 6.2 Hz, 2-H), 7.26–7.38 (8H, m), 7.40 (2H, d, J=8.2 Hz), 7.49 (2H, d, J=7.4 Hz), 7.59 (2H, d, J=8.2 Hz); δ_C (100 MHz, DMSO-d_6) 21.6 (Ar-Me), 35.6 (3-CH_2), 47.8 (4-CH), 53.0 (OMe), 61.5 (5(2)-CH), 69.9 (2(5)-CH), 126.8 (ArC), 127.5 (2×ArCH), 128.0 (2×ArCH), 128.6 (2×ArCH), 128.9 (ArCH), 129.9 (2×ArCH), 130.4 (2×ArCH), 133.7 (ArC), 135.5 (2×ArCH), 141.1 (ArC), 144.5 (ArC), 172.3 (C=O) [one ArCH obscured]; m/z (APCI) 516 (M^++1, 100%). Found: M^++1, 516.0750. $C_{25}H_{26}NO_4SSe$ requires: M, 516.0748.

3.4.2. Methyl (2*SR*,4*SR*,5*RS*)-5-phenyl-4-phenylselanyl-1-tosylpyrrolidine-2-carboxylate 53. Most experiments resulted in the formation of mixtures (see Section 2). In one of the more reproducible cyclisations, to a stirred solution of cinnamyl tosylamide **51** (0.205 g, 0.57 mmol) in dry dichloromethane (4 ml) maintained at −78 °C and containing anhydrous potassium carbonate (0.087 g, 0.63 mmol) was added phenylselanyl chloride (0.12 g, 0.63 mmol) in one portion and the resulting solution stirred for1 h at this temperature then allowed to warm to ambient temperature. The bulk of the solvent was removed and the residue separated as described above for the 2,5-*cis* isomer to give 2,5-*trans*-pyrrolidine carboxylate **53** containing 23% of the 2,5-*cis* isomer **52** (0.252 g, 86%) as an oil. The 2,5-*trans* isomer **53** showed δ_H (400 MHz, DMSO-d_6) 2.16 (1H, app. dt, J=14.2, 3.5 Hz, 3-H_a), 2.32 (3H, s, Ar-Me), 3.09 (1H, app. dt, J=14.2, 8.6 Hz, 3-H_b), 3.67–3.71 (1H, obscured m, contains J=4.7 Hz, 4-H), 3.69 (3H, s, OMe), 4.79 (1H, d, J=4.7 Hz, 5-H), 4.88 (1H, dd, J=8.6, 3.5 Hz, 2-H), 6.91 (2H, d, J=7.3 Hz, 2×ArH), 7.03 (2H, t, J=7.7 Hz, 2×ArH), 7.12 (2H, dd, J=8.2, 6.9 Hz, 2×ArH), 7.17 (2H, t, J=8.2 Hz, 2×ArH), 7.26–7.32 (4H, m), 7.39 (2H, dd, J=6.9, 1.3 Hz, 2×ArH); δ_C (100 MHz, DMSO-d_6) 21.4 (Ar-Me), 36.7 (3-CH_2), 48.1 (4-CH), 52.6 (OMe), 62.3 (5(2)-CH), 70.8 (2(5)-CH), 127.1 (2×ArCH), 128.1 (2×ArCH), 128.4 (2×ArCH), 129.3 (2×ArCH), 129.8 (2×ArCH), 130.1 (ArCH), 133.7 (ArC), 134.3 (2×ArCH), 139.2 (ArC), 142.9 (ArC), 172.8 (C=O) [one ArCH and one ArC obscured]; m/z (APCI) 516 (M^++1, 100%).

Alternatively, cinnamyl tosylamide **51** (0.217 g, 0.604 mmol) and anhydrous potassium carbonate (0.21 g,

1.5 mmol) were stirred together in dry acetonitrile (1 ml) at −78 °C then phenylselanyl chloride (0.21 g, 1.1 mmol) was added portionwise. After 1 h at this temperature, the mixture was stirred for 16 h without further cooling. Dichloromethane (10 ml) was then added, the mixture filtered and the filtrate evaporated. Analysis of the residue by proton NMR showed a 2,5-*trans*/*cis* ratio of 88:12 [**53**:**52**]. The weight of the otherwise clean product indicated a combined yield of 87%.

3.4.3. Methyl (2*SR*,5*RS*)-5-phenyl-1-tosyl-3-pyrroline-2-carboxylate 54. Oxidation of 2,5-*cis*-5-phenyl carboxylate **52** (0.17 g, 0.33 mmol) according to general procedure B gave 2,5-*cis*-pyrroline carboxylate **54** (0.11 g, 92%) as a colourless solid, mp 119–121 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 3025, 2952, 1758, 1597, 1494, 1455, 1352, 1165, 1092; δ_H (400 MHz, $CDCl_3$) 2.33 (3H, s, Ar-Me), 3.77 (3H, s, OMe), 5.36–5.39 (1H, m, 5-H), 5.57–5.60 (1H, m, 2-H), 5.73–5.79 (2H, m, 3-, 4-H), 7.10 (2H, d, J=8.2 Hz, 2×ArH), 7.18–7.24 (3H, m), 7.35 (2H, dd, J=ca. 7.5, 1.8 Hz, 2×*o*-ArH), 7.53 (2H, d, J=8.2 Hz, 2×ArH); δ_C (100 MHz, $CDCl_3$) 21.5 (ArMe), 52.7 (OMe), 68.5 (3(4)-CH), 71.0 (4(3)-CH), 123.0 (CH), 127.6 (2×ArCH), 127.8 (CH), 127.9 (2×ArCH), 128.4 (2×s ArCH), 129.2 (2×ArCH), 133.1 (CH), 135.6 (ArC), 139.2 (ArC), 143.5 (ArC), 170.3 (C=O); *m*/*z* (ES) 358 (M^++1, 100%), 298 (38), 203 (31). Found: M^++1, 358.1109. $C_{19}H_{20}NO_4S$ requires: M, 358.1113.

3.4.4. Methyl (2*RS*,4*RS*,5*SR*)-5-(furan-2-yl)-4-phenylselanyl-1-tosylpyrrolidine-2-carboxylate 56. Tosylamide **55** (0.35 g, 1.0 mmol) and anhydrous potassium carbonate (0.21 g, 1.5 mmol) were stirred together in dry tetrahydrofuran (1 ml) at −78 °C and phenylselanyl chloride (0.21 g, 1.1 mmol) in tetrahydrofuran (1 ml) was added dropwise. After stirring for 2 h at this temperature, the bulk of the solvent was evaporated and the residue separated by column chromatography (hexanes–EtOAc, 6:1) to give 2,5-*trans*-pyrrolidine-2-carboxylate **56** (0.42 g, 83%) as a colourless solid, mp 89–92 °C (hexane–ether); $\nu_{max}(CHCl_3)/cm^{-1}$ 2963, 2922, 1748, 1438, 1159, 1098; δ_H (400 MHz, $CDCl_3$) 2.31 (1H, ddd, J=13.8, 4.3, 4.3 Hz, 3-H_a), 2.37 (3H, s, Ar-Me), 3.01 (1H, ddd, J=13.8, 8.7, 8.7 Hz, 3-H_b), 3.72–3.76 (1H, m, 4-H), 3.84 (3H, s, OMe), 4.57 (1H, dd, J=8.7, 4.3 Hz, 2-H), 5.05 (1H, d, J=4.8 Hz, 5-H), 6.18 (1H, dd, J=3.1, 1.9 Hz, 4′-H), 6.26 (1H, d, J=3.1 Hz, 3′-H), 6.85 (1H, d, J=1.9 Hz, 5′-H), 7.10–7.35 (9H, m); δ_C (100 MHz, $CDCl_3$) 22.0 (ArMe), 37.5 (3-CH_2), 45.0 (4-CH), 53.5 (OMe), 61.0 (2-CH), 63.0 (5-CH), 111.5 (4′-CH), 113.0 (3′-CH), 127.8 (ArCH), 128.3 (ArCH), 130.1 (ArCH), 130.3 (ArCH), 134.8 (ArC), 135.0 (ArCH), 135.1 (ArC), 143.0 (ArC), 152.0 (ArC), 171.5 (C=O); *m*/*z* (EI) 505 (M^+, 7%), 350 (7), 192 (9), 155 (16), 134 (16), 92 (100). Found: M^+, 505.0462. $C_{23}H_{23}NO_5SSe$ requires: M, 505.0462.

3.4.5. Methyl (2*RS*,4*SR*,5*RS*)-5-(furan-2-yl)-4-phenylselanyl-1-tosylpyrrolidine-2-carboxylate 57. Tosylamide **55** (0.35 g, 1.0 mmol) and anhydrous potassium carbonate (0.21 g, 1.5 mmol) were stirred together in dry acetonitrile (1 ml) at ambient temperature and phenylselanyl chloride (0.21 g, 1.1 mmol) was added portionwise. After stirring for 2 h at this temperature, the bulk of the solvent was evaporated and the residue separated by column chromatography (hexanes–EtOAc, 6:1) to give 2,5-*cis*-pyrrolidine-2-carboxylate **57** (0.43 g, 85%) as a colourless crystalline solid, mp 98–99 °C (hexane–ether); $\nu_{max}(CHCl_3)/cm^{-1}$ 2952, 1756, 1598, 1438, 1355, 1290, 1203, 1161, 1095, 1023; δ_H (400 MHz, $CDCl_3$) 2.17 (1H, ddd, J=13.2, 7.4, 5.1 Hz, 3-H_a), 2.35 (3H, s, Ar-Me), 2.50 (1H, ddd, J=13.2, 7.4, 6.0 Hz, 3-H_b), 3.78 (3H, s, OMe), 3.83–3.87 (1H, m, 4-H), 4.61 (1H, dd, J=7.4, 7.4 Hz, 2-H), 4.82 (1H, d, J=3.9 Hz, 5-H), 6.25 (1H, dd, J=3.2, 1.9 Hz, 4′-H), 6.51 (1H, d, J=ca. 3.2 Hz, 3′-H), 7.25–7.40 (8H, m), 7.64 (2H, d, J=8.2 Hz, 2×ArH); δ_C (100 MHz, $CDCl_3$) 21.5 (ArMe), 35.6 (3-CH_2), 43.8 (4-CH), 52.5 (OMe), 60.6 (2-CH), 63.7 (5-CH), 109.3 (4′-CH), 110.4 (3′-CH), 127.4 (ArCH), 127.8 (ArCH), 128.1 (ArCH), 129.2 (ArCH), 129.4 (ArCH), 134.5 (ArC), 135.1 (ArC), 142.2 (5′-CH), 143.8 (ArC), 151.9 (ArC), 171.9 (C=O); *m*/*z* (EI) 505 (M^+, 32%), 446 (15), 275 (21), 192 (95), 166 (59), 155 (86), 133 (100), 106 (70), 90 (87). Found: M^+, 505.0462. $C_{23}H_{23}NO_5SSe$ requires: M, 505.0462. Anal. Calcd for $C_{23}H_{23}NO_5SSe$: C, 54.76; H, 4.60; N, 2.78. Found: C, 54.88; H, 4.74; N, 3.02%.

3.4.6. Methyl (2*RS*,5*SR*)-5-(furan-2-yl)-1-tosyl-3-pyrroline-2-carboxylate 58. To a stirred solution of 2,5-*cis*-selanyl-pyrrolidine **57** (0.40 g, 0.79 mmol) in tetrahydrofuran (5 ml) was added aqueous hydrogen peroxide (30%, 0.2 ml, 2.5 equiv). After 2 h at ambient temperature, the bulk of the solvent was evaporated and the residue dissolved in dichloromethane (10 ml) and water (10 ml). The separated organic solution was washed with water (2×10 ml) then dried and evaporated. Column chromatography of the residue (hexanes–EtOAc, 4:1) gave 2,5-*cis*-pyrroline **58** (0.21 g, 76%) as a colourless crystalline solid, mp 129–131 °C (hexanes–ether); $\nu_{max}(CHCl_3)/cm^{-1}$ 2955, 1760, 1598, 1434, 1351, 1166; δ_H (400 MHz, $CDCl_3$) 2.44 (3H, s, Ar-Me), 3.79 (3H, s, OMe), 5.39 (1H, dd, J=4.5, 2.2 Hz, 2-H), 5.77 (1H, dd, J=4.0, 2.0 Hz, 5-H), 5.89–6.01 (2H, m, 3-, 4-H), 6.28 (1H, dd, J=3.2, 1.8 Hz, 4′-H), 6.30 (1H, d, J=3.2 Hz, 3′-H), 7.25 (2H, d, J=8.2 Hz, 2×ArH), 7.33 (1H, app. br s, 5′-H), 7.71 (2H, d, J=8.2 Hz, 2×ArH); δ_C (100 MHz, $CDCl_3$) 21.6 (ArMe), 52.7 (OMe), 63.8 (5-CH), 67.9 (2-CH), 108.6 (3′-CH), 110.5 (4′-CH), 124.9 (3(4)-CH), 127.7 (2×ArCH), 129.3 (2×ArCH), 129.7 (4(3)-CH), 135.9 (ArC), 142.5 (5′-CH), 143.6 (ArC), 151.8 (ArC), 170.0 (C=O); *m*/*z* (EI) 347 (M^+, 2%), 288 (100), 192 (34), 155 (90), 132 (84), 104 (74), 77 (49), 65 (85). Found: M^+, 347.0828. $C_{17}H_{17}NO_5S$ requires: M, 347.0827. Anal. Calcd for $C_{17}H_{17}NO_5S$: C, 58.78; H, 4.93; N, 4.03. Found: C, 58.93; H, 4.79; N, 4.36%.

3.4.7. Methyl (2*RS*,5*RS*)-5-(furan-2-yl)-1-tosyl-3-pyrroline-2-methanol 59. The foregoing ester **58** (0.15 g, 0.43 mmol) was stirred in dry toluene (1 ml), cooled in an ice bath for 10 min before the dropwise addition of diisobutylaluminium hydride in toluene (0.6 ml of a 1.5 M solution, 0.91 mmol). The resulting mixture was stirred for 3 h then quenched by the careful addition of methanol (0.2 ml) followed by 2 M hydrochloric acid (2 ml). The resulting mixture was filtered, the solids washed with toluene and the filtrate separated into organic and aqueous layers. The latter was extracted with ether (3×5 ml) and the extracts combined with the organic layer from the original filtrate. The resulting

organic solution was dried, filtered and evaporated. Column chromatography of the residue (hexanes–EtOAc, 2:1) separated the pyrroline-methanol **59** (0.10 g, 75%) as a colourless oil, ν_{max}(film)/cm^{-1} 3450; δ_H (400 MHz, $CDCl_3$) 2.36 (3H, s, Ar-Me), 3.66 (1H, dd, J=11.6, 3.1 Hz, 1′-H_a), 3.77 (1H, dd, J=11.6, 3.1 Hz, 1′-H_b), 4.54–4.57 (1H, m, 2-H), 5.51 (1H, d, J=1.7 Hz, 5-H), 5.63–5.67 (2H, m, 3-, 4-H), 6.24–6.28 (2H, m, 3′-, 4′-H), 7.23 (2H, d, J=8.2 Hz, 2×ArH), 7.34 (1H, app. br s, 5′-H), 7.67 (2H, d, J=8.2 Hz, 2×ArH); δ_C (100 MHz, $CDCl_3$) 21.5 (ArMe), 58.2 (2-CH), 64.2 (5-CH), 65.3 (1′-CH_2), 108.0 (3′-CH), 110.0 (4′-CH), 127.4 (CH), 127.7 (CH), 127.9 (CH), 129.8 (CH) 134.5 (C), 142.6 (5′-CH), 144.0 (C), 152.6 (C). m/z (APCI) found: M^++1 (100%), 320.0959. $C_{16}H_{18}NO_4S$ requires: M, 320.0957.

3.4.8. Methyl (2*SR*,3*RS*,4*SR*,5*SR*)-3,4-diacetyloxy-5-(furan-2-yl)-1-tosylpyrrolidine-2-carboxylate 60. Pyrroline-2-carboxylate **58** (0.10 g, 0.29 mmol) was stirred in aqueous acetone (1:5; 2 ml) containing *N*-methylmorpholine-*N*-oxide (0.071 g, 0.60 mmol) at ambient temperature and osmium tetroxide (0.15 ml of a 5% solution in *t*-BuOH, 0.03 mmol) was added and the resulting solution stirred for 16 h then concentrated. The residue was dissolved in dry pyridine (2 ml) and acetic anhydride (0.06 ml, 0.60 mmol) was added. After a further 20 h at ambient temperature, 2 M hydrochloric acid (5 ml) was added and the resulting mixture extracted with dichloromethane (3×10 ml). The combined extracts were washed with brine (10 ml) then dried and evaporated. Column chromatography of the residue (hexanes–EtOAc, 6:1) separated the diacetate **60** (0.085 g, 64%) as an oil, ν_{max}(film)/cm^{-1} 2950, 1748, 1598, 1440, 1352, 1164, 1120, 1090; δ_H (400 MHz, $CDCl_3$) 1.78 (3H, s, OAc), 2.01 (3H, s, OAc), 2.42 (3H, s, Ar-Me), 3.81 (3H, s, OMe), 4.37 (1H, d, J=6.7 Hz, 2-H), 4.86 (1H, d, J=3.0 Hz, 5-H), 5.40 (1H, dd, J=3.6, 3.6 Hz, 4-H), 5.54 (1H, dd, J=6.7, 3.6 Hz, 5-H), 6.29 (1H, dd, J=3.2, 1.9 Hz, 4′-H), 6.55 (1H, d, J=3.2 Hz, 3′-H), 7.31 (2H, d, J=8.2 Hz, 2×ArH), 7.34 (1H, app. br s, 5′-H), 7.70 (2H, d, J=8.2 Hz, 2×ArH); δ_C (100 MHz, $CDCl_3$) 20.3 (Me), 20.4 (Me), 21.6 (ArMe), 53.1 (OMe), 60.6 (5-CH), 62.6 (2-CH), 72.6 (3-CH), 73.1 (4-CH), 110.1 (3′-CH), 110.7 (4′-CH), 128.0 (CH), 129.6 (CH), 134.2 (C), 143.1 (5′-CH), 144.1 (C), 149.1 (C), 169.2 (C═O), 169.3 (C═O), 169.8 (C═O); m/z (APCI) found: M^++1 (100%), 466.1174. $C_{21}H_{24}NO_9S$ requires: M, 466.1172.

3.4.9. (2*SR*,3*RS*,4*SR*,5*SR*)-2-Acetyloxymethyl-3,4-diacetyloxy-5-(furan-2-yl)-1-tosylpyrrolidine 61. Pyrroline-2-methanol **59** (50 mg, 0.157 mmol) was stirred in aqueous acetone (1:5, 2 ml) containing *N*-methylmorpholine-*N*-oxide (39 mg, 0.33 mmol) at ambient temperature and osmium tetroxide (80 μl of a 5% solution in *t*-BuOH, 0.015 mmol) was added and the resulting solution stirred for 16 h then concentrated. The residue was dissolved in dry pyridine (2 ml) and acetic anhydride (33 μl, 0.60 mmol) was added. After a further 20 h at ambient temperature, 2 M hydrochloric acid (5 ml) was added and the resulting mixture extracted with dichloromethane (3×10 ml). The combined extracts were washed with brine (10 ml) then dried and evaporated. Column chromatography of the residue (hexanes–EtOAc, 6:1) separated the triacetate **61** (40 mg, 55%) as a colourless solid, mp 76–78 °C (hexane–ether), ν_{max}(film)/cm^{-1} 2950, 1756, 1360, 1212, 1167; δ_H (400 MHz, $CDCl_3$) 1.78 (3H, s, OAc), 1.94 (3H, s, OAc), 2.06 (3H, s, OAc), 2.45 (3H, s, Ar-Me), 3.81–4.22 (1H, m, 2-H), 4.37 (1H, dd, J=11.8, 8.5 Hz, CH_aH$_b$OAc), 4.46 (1H, dd, J=11.8, 5.6 Hz, CH$_a$$H_b$OAc), 4.78 (1H, d, J=4.7 Hz, 5-H), 5.38 (1H, dd, J=4.7, 4.7 Hz, 3-H), 5.48 (1H, dd, J=4.7, 4.7 Hz, 4-H), 6.33 (1H, dd, J=3.3, 1.5 Hz, 4′-H), 6.42 (1H, d, J=3.3 Hz, 3′-H), 7.30 (2H, d, J=8.2 Hz, 2×ArH), 7.31 (1H, d, J=1.5 Hz, 5′-H), 7.80 (2H, d, J=8.2 Hz, 2×ArH); δ_C (100 MHz, $CDCl_3$) 20.2 (Me), 20.6 (Me), 21.4 (Me), 21.6 (ArMe), 59.9 (5-CH), 60.9 (2-CH), 63.4 (CH_2OAc), 71.7 (3-CH), 73.2 (4-CH), 119.6 (3′-CH), 110.5 (4′-CH), 127.9 (CH), 129.5 (CH), 134.3 (C), 142.9 (5′-CH), 143.9 (C), 149.5 (C), 169.2 (C═O), 169.3 (C═O), 170.3 (C═O); m/z (APCI) found: M^++1 (100%), 480.1329. $C_{22}H_{26}NO_9S$ requires: M, 480.1328.

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References and notes

1. Nicolaou, K. C.; Petasis, N. A. *Selenium in Natural Product Synthesis*; CIS: Philadelphia, PA, 1984; Paulmier, C. *Selenium Reagents and Intermediates in Organic Synthesis*; Pergamon: Oxford, 1986; Liotta, D. *Organoselenium Chemistry*; Wiley Interscience: New York, NY, 1987.
2. Wirth, T. *Tetrahedron* **1999**, *55*, 1; Tiecco, M. Electrophilic Selenium, Selenocyclisations. In *Organoselenium Synthesis: Modern Developments in Organic Synthesis*; Wirth, T., Ed.; Topics in Current Chemistry; Springer: Heidelberg, 2000; p 7; Wirth, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 3740.
3. For recent examples, see: Lescop, C.; Mévellec, L.; Huet, F. *J. Org. Chem.* **2001**, *66*, 4187; Davies, H. M. L.; Cao, G. *Tetrahedron Lett.* **1998**, *39*, 5943.
4. See for example: Beach, J. W.; Kim, H. O.; Jeong, L. S.; Nampalli, S.; Islam, Q.; Ahn, S. K.; Babu, J. R.; Chu, C. K. *J. Org. Chem.* **1992**, *57*, 3887; Díaz, Y.; El-Laghdach, A.; Matheu, M. I.; Castillón, S. *J. Org. Chem.* **1997**, *62*, 1501; Kassou, M.; Castillón, S. *J. Org. Chem.* **1997**, *62*, 3696; Costenaro, E. R.; Fontoura, L. A. M.; Oliveira, D. F.; Correia, C. R. D. *Tetrahedron Lett.* **2001**, *42*, 1599.
5. Tingoli, M.; Tiecco, M.; Testaferri, L.; Andrenacci, R.; Balducci, R. *J. Org. Chem.* **1993**, *58*, 6097.
6. Danishefsky, S.; Regan, J.; Doehner, R. *J. Org. Chem.* **1981**, *46*, 5255; Baldwin, J. E.; Moloney, M. G.; Shim, S. B. *Tetrahedron Lett.* **1991**, *32*, 1379; Niwa, H.; Miyachi, Y.; Okamoto, O.; Uosaki, Y.; Kuroda, A.; Ishiwata, H.; Yamada, K. *Tetrahedron* **1992**, *48*, 393; Li, B.; Smith, M. B. *Synth. Commun.* **1995**, *25*, 1265; Bailey, J. H.; Cherry, D. T.; Crapnell, K. M.; Moloney, M. G.; Shim, S. B. *Tetrahedron* **1997**, *53*, 11731 and references cited therein.
7. Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.
8. Herdeis, C.; Kelm, B. *Tetrahedron* **2003**, *59*, 217.
9. Murphy, J. A.; Tripoli, R.; Khan, T. A.; Mali, U. W. *Org. Lett.* **2005**, *7*, 3287 and reference cited therein.

10. See, for example, Rüeger, H.; Benn, M. H. *Can. J. Chem.* **1982**, *60*, 2918; Tsai, Y.-M.; Ke, B.-W.; Yang, C.-T.; Lin, C.-H. *Tetrahedron Lett.* **1992**, *33*, 7895; Baldwin, J. E.; Field, R. A.; Lawrence, C. C.; Lee, V.; Robinson, J. K.; Schofield, C. J. *Tetrahedron Lett.* **1994**, *35*, 4649; Mater, S. C.; Ramanjulu, J.; Vera, M. D.; Pfizenmayer, A. J.; Joullié, M. M. *J. Org. Chem.* **1994**, *59*, 5192; Lin, C.-C.; Shimazaki, M.; Heck, M.-P.; Aoki, S.; Wang, R.; Kimura, T.; Ritzen, H.; Takayama, S.; Wu, S.-H.; Weitz-Schmidt, G.; Wong, C.-H. *J. Am. Chem. Soc.* **1996**, *118*, 6826; Robinson, J. K.; Lee, V.; Claridge, T. D. W.; Baldwin, J. E.; Schofield, C. J. *Tetrahedron* **1998**, *54*, 981; Greenwood, E. S.; Hitchcock, P. B.; Parsons, P. J. *Tetrahedron* **2003**, *59*, 3307; Curtis, K. L.; Fawcett, J.; Handa, S. *Tetrahedron Lett.* **2005**, *46*, 5297.
11. Pearson, W. H.; Szura, D. P.; Postich, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 1329; Mans, D. M.; Pearson, W. H. *J. Org. Chem.* **2004**, *69*, 6419.
12. Burgess, L. E.; Meyers, A. I. *J. Am. Chem. Soc.* **1991**, *113*, 9858; For cyclisations which favour a 6-*exo* pathway over 5-*endo* processes in alkenyl carbamates, see: Toshimitsu, A.; Terao, K.; Uemura, S. *J. Org. Chem.* **1986**, *51*, 1724.
13. Clive, D. L.; Farina, V.; Singh, A.; Wong, C. K.; Kiel, W. A.; Menchen, S. M. *J. Org. Chem.* **1980**, *45*, 2120; Clive, D. J.; Wong, C. K.; Kiel, W. A.; Menchen, S. M. *J. Chem. Soc., Chem. Commun.* **1978**, 379; For similar cyclisations but using *N*-phenylselenosuccinimide, see: Nicolaou, K. C.; Claremon, D. A.; Barnette, W. E.; Seitz, S. P. *J. Am. Chem. Soc.* **1979**, *101*, 3704; Webb, R. R.; Danishefsky, S. *Tetrahedron Lett.* **1983**, *24*, 1357; Tiecco, M.; Testaferri, L.; Tingoli, M.; Bartoli, D.; Balducci, R. *J. Org. Chem.* **1990**, *55*, 429; For an elegant combination of selenocyclisation followed by *N*-alkylation to establish the pyrrolizidine system in mitomycin, see: Danishefsky, S.; Berman, E. M.; Ciufolini, M.; Etheredge, S. J.; Segmuller, B. E. *J. Am. Chem. Soc.* **1985**, *107*, 3891; See also: Back, T. G.; Dyer, B. P.; Nan, S. *Tetrahedron* **1999**, *55*, 3191 (carbamate cyclisations); Toshimitsu, A.; Terao, K.; Uemura, S. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1837 (*N*-alkenyl imidate cyclisations).
14. Berthe, B.; Outurquin, F.; Paulmier, C. *Tetrahedron Lett.* **1997**, *38*, 1393.
15. Tiecco, M.; Testaferri, L.; Marini, F.; Sternativo, S.; Bagnoli, L.; Santi, C.; Temperini, A. *Tetrahedron: Asymmetry* **2001**, *12*, 1493; See also: Déziel, R.; Malenfant, E. *J. Org. Chem.* **1995**, *60*, 4660; Takada, H.; Nishibayashi, Y.; Uemura, S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1511; Fragale, G.; Wirth, T. *Eur. J. Org. Chem.* **1998**, 1361.
16. Boelens, M.; DeKimpe, N. *J. Chem. Soc., Chem. Commun.* **1993**, 916; De Smaele, D.; De Kimpe, N. *J. Chem. Soc., Chem. Commun.* **1995**, 2029.
17. Tiecco, M.; Testaferri, L.; Tingoli, M.; Bagnoli, L. *J. Chem. Soc., Chem. Commun.* **1995**, 235; Tiecco, M.; Testaferri, L.; Tingoli, M.; Marini, F. *J. Chem. Soc., Chem. Commun.* **1995**, 237; Tiecco, M.; Testaferri, L.; Marini, F. *Tetrahedron* **1996**, *52*, 11841; Tiecco, M.; Testaferri, L.; Tingoli, M.; Bagnoli, L.; Marini, F.; Santi, C.; Temperini, A. *Gazz. Chim. Ital.* **1996**, *126*, 635; Tiecco, M.; Testaferri, L.; Tingoli, M.; Santi, C. *Tetrahedron Lett.* **1995**, *36*, 163; Tiecco, M.; Testaferri, L.; Tingoli, M.; Bagnoli, L.; Santi, C. *Tetrahedron* **1995**, *51*, 1277; Tiecco, M.; Testaferri, L.; Marini, F.; Sternativo, S.; Santi, C.; Bagnoli, L.; Temperini, A. *Tetrahedron: Asymmetry* **2001**, *12*, 3053.
18. Crich, D.; Huang, X. *J. Org. Chem.* **1999**, *64*, 7218 and references therein; For applications, see: Marsden, S. P.; Depew, K. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1994**, *116*, 11143; Depew, K. M.; Marsden, S. P.; Zatorska, D.; Zatorski, A.; Bornmann, W. G.; Danishefsky, S. D. *J. Am. Chem. Soc.* **1999**, *121*, 11963; Ley, S. V.; Cleator, E.; Hewitt, P. R. *Org. Biomol. Chem.* **2003**, *1*, 3492; Hewitt, P. R.; Cleator, E.; Ley, S. V. *Org. Biomol. Chem.* **2004**, *2*, 2415; For the generation of oxygen analogues, see: Sunazuka, T.; Shirahata, T.; Tsuchiya, S.; Hirose, T.; Mori, R.; Harigaya, Y.; Kuwajima, I.; Ōmura, S. *Org. Lett.* **2005**, *7*, 941.
19. Jones, A. D.; Knight, D. W.; Hibbs, D. E. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1182.
20. For a review, see: Knight, D. W. *Prog. Heterocycl. Chem.* **2002**, *14*, 19.
21. For a preliminary report of some of these results, see: Jones, A. D.; Knight, D. W.; Redfern, A. L.; Gilmore, J. *Tetrahedron Lett.* **1999**, *40*, 3267.
22. Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 361.
23. Evans, A. B.; Knight, D. W. *Tetrahedron Lett.* **2001**, *42*, 6947.
24. Henry, J. R.; Marcin, L. R.; McIntosh, M. C.; Scola, P. M.; Harris, G. D.; Weinreb, S. M. *Tetrahedron Lett.* **1989**, *30*, 5709.
25. Raederstorff, D.; Shu, A. Y. L.; Thompson, J. E.; Djerassi, C. *J. Org. Chem.* **1987**, *52*, 2337.
26. Williams, D. R.; White, F. W. *J. Org. Chem.* **1987**, *52*, 5067.
27. Stork, G.; Leong, A. Y. M.; Touzin, A.-M. *J. Org. Chem.* **1976**, *41*, 3491.
28. Knight, D. W.; Redfern, A. L.; Gilmore, J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2874.
29. Knight, D. W.; Redfern, A. L.; Gilmore, J. *Tetrahedron Lett.* **1998**, *39*, 8909.

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Carboxylic fused furans for amino acid fluorescent labelling

Ana M. Piloto, Andrea S. C. Fonseca, Susana P. G. Costa and M. Sameiro T. Gonçalves*

Centro de Química, Universidade do Minho, Campus de Gualtar, P-4710-057 Braga, Portugal

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Abstract—Four carboxylic fused furans are presented as new fluorescent labels for the amino and hydroxyl functions of organic molecules. Various representative L-amino acids were chosen as models, labelled at their N-terminus and also at their side-chain. Fluorescent derivatives were obtained in high yields, and their absorption and emission properties were studied.

1. Introduction

In order to enhance the sensitivity of analytical methodologies, the interest in fluorescent derivatisation has been steadily growing in recent years, as fluorescence is far more sensitive than common UV techniques. The development of novel fluorescent derivatisation reagents and their subsequent evaluation with model compounds has broad application in biology and biochemistry, to investigate the structure and dynamics of living systems.[1,2]

Amino acids are the building blocks in biological systems like proteins, enzymes and many other molecules with biological activity. The understanding of their physiological role is of utmost importance, given that a number of disorders are directly associated with the presence or lack of particular amino acids, and there is a practical interest in their detection in areas such as clinical chemistry.[3–5]

As most amino acids are poor UV-absorbing, fluorescence derivatisation is often employed for their determination. Although, a large number of fluorescent tagging reagents have been developed through the years, which cover the UV/vis spectrum and are specifically reactive towards different functional groups,[6–10] there is only scarce information on the application of benzofurans and naphthofurans in this field.[11,12]

Arene ring-fused furans are found in various naturally occurring compounds and a number of their natural and synthetic derivatives are associated with diverse biological and pharmacological activities.[13–16] Regarding arenofurans, benzofurans have been the subject of more extensive studies for the development of efficient routes for their synthesis.[17,18] Compared to benzofurans, synthetic methods for the preparation of naphthofurans have been less reported.[19,20] The most applied synthetic protocol reported is the intramolecular aldol-type condensation via dehydrative cyclisation of properly substituted aromatic *o*-alkoxycarbonyl compounds[16] or α-aryloxycarbonyl compounds.[21]

Following our interest in developing new chomophores and to extend our preliminary results,[22–24] we decided to investigate the application of fused furans in derivatisation reactions with biomolecules. We now present a study involving two systems, namely benzofuran and naphthofuran, bearing different substituents and representative amino acids of different character as models.

The main purpose of our work is to present a label for amino acids that have no (or low) intrinsic fluorescence or that are not easily detectable by ultraviolet absorption, thus excluding tryptophan and tyrosine. Regarding phenylalanine, the least UV-absorbing and fluorescent of the three aromatic amino acids, there is a practical interest in its tagging in order to enhance its properties.

Evaluation of the fluorescence properties was carried out for all labelled amino acids in ethanol and the influence of solvent polarity in emission was measured for one of the derivatives.

2. Results and discussion

Fluorophores **1** and **2a–c** were obtained by an alkaline ring contraction of the corresponding oxobenzopyran **3** and

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* Corresponding author. Tel.: +351 253 604386; fax: +351 253 678983; e-mail: msameiro@quimica.uminho.pt

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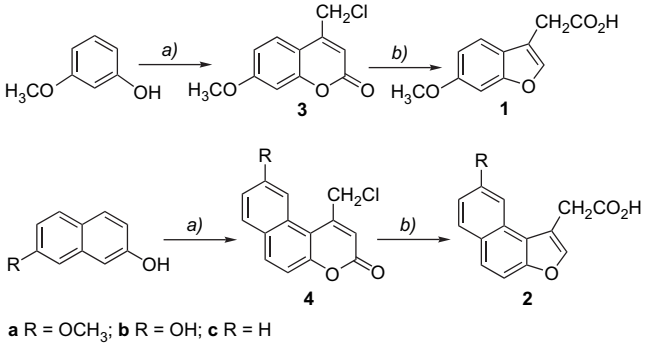
oxobenzo[*f*]benzopyran **4a–c**, respectively. The precursors 1-chloromethyl-6-methoxy-3-oxo-3*H*-benzopyran (**3**) and 1-chloromethyl-3-oxo-3*H*-benzo[*f*]benzopyrans (**4a–c**) were prepared through a Pechmann reaction of 3-methoxyphenol or 2-naphthol and its derivatives with ethyl 4-chloroacetoacetate by a known procedure,[25] in good yields (71–92%). Heating to 80 °C compounds **3** or **4a–c** in aqueous 2 M sodium hydroxide solution yielded the 2-(5-methoxybenzofuran-1-yl)ethanoic acid, Bfm-OH (**1**) (92%) or 2-(naphtho[2,1-*b*]furan-1-yl)ethanoic acids (**2a–c**) (94–98%) (Scheme 1, Table 1).



Scheme 1. Synthesis of fluorescent heterocycles **1–4**. Reagents and conditions: (a) $ClCH_2COCH_2CO_2Et$, aq H_2SO_4 70%, rt; (b) aq 2 M NaOH, 80 °C.

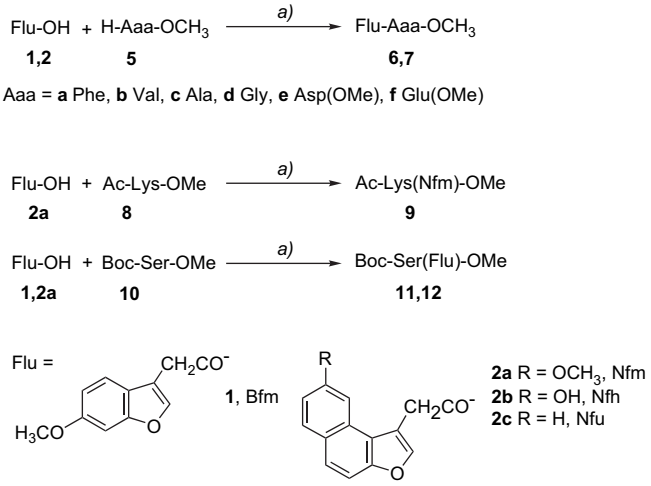
In the IR spectra of precursors **3** and **4a–c**, a strong band between 1739 and 1689 cm^{-1} confirmed the presence of the carbonyl group of the heterocycle. The ^1H NMR spectra showed the characteristic signal of proton 2 (H-2) of the pyran ring at δ 6.48 ppm (**3**) and 6.62–6.76 ppm (**4a–c**), in addition to the expected signals of the fused rings, and the chloromethylene group at δ between 4.98 and 5.30 ppm. In the ^{13}C NMR spectra of these compounds, relevant signals for the heterocycle were visible from δ 150.87 to 152.27 ppm (C-1), 112.00 to 117.37 ppm (C-2) and 159.38 to 160.02 ppm (C-3). The protons corresponding to the chloromethylene group appeared between δ 41.34 and 46.17 ppm.

For the target compounds **1** and **2a–c**, strong stretching vibration bands for the carboxyl group were present at 3550–3103 cm^{-1} and 1703–1715 cm^{-1}. In the ^1H NMR spectra, the singlet corresponding to proton H-2 of the furan ring at δ 7.75–8.01 ppm, as well as a broad signal for the carboxyl OH at high δ (12.40 to 12.60 ppm) were visible. ^{13}C NMR data confirmed the heterocyclic ring contraction by showing the signals corresponding to carbons 1 and 2 (C-1 and C-2) at δ 113.83–115.94 ppm and δ 142.31–143.64 ppm, respectively. Signals between 171.97 and 172.62 ppm were assigned to the carboxyl group.

Table 1. Synthesis of fluorescent heterocycles **1–4**

	Compound	Yield (%)	Mp (°C)
1	Bfm-OH	92	124.6–126.0
2a	Nfm-OH	98	176.8–178.9
2b	Nfh-OH	96	167.8–169.0
2c	Nfu-OH	94	171.4–173.0
3	Opm-Cl	79	199.5–200.8
4a	Obm-Cl	83	179.2–180.7
4b	Obh-Cl	92	250.0–250.7
4c	Obb-Cl	71	179.5–182.7

The carboxylic heterocyclic labels **1** and **2a** were linked to the α-amine group of L-phenylalanine and L-valine methyl esters (**5a** and **5b**), by coupling with the aid of *N*,*N*′-dicyclohexylcarbodiimide (DCC) assisted by 1-hydroxybenzotriazole (HOBt) under standard conditions. After purification by chromatography on silica gel, the corresponding acetyl derivatives **6a**,**b** and **7a**,**b** were obtained (Scheme 2, Table 2, entries 1–4).



Scheme 2. Synthesis of labelled amino acid derivatives **6**, **7**, **9**, **11** and **12**. Reagents and conditions: (a) DCC, HOBt, DMF, rt.

By comparison of fluorescence data obtained for these derivatives, which will be discussed later, it was concluded that the naphthofuran derivatives are more interesting than their benzofuran counterparts for labelling applications. The extension of its structure (incorporating to the molecule one more aromatic ring) resulted in an expected increase in the quantum yield of fluorescence (Φ_F). Two other naphthofuran derivatives, **2b**,**c**, were used in the reaction with model valine methyl ester, under the same reaction conditions. The resulting fluorogenic derivatives **7c**,**d** (Scheme 2, Table 2, entries 5 and 6) differ from **7a** in the substituent attached at position 8 of the naphthofuran moiety (OH and H, respectively). Their fluorescence properties were inferior to those

Table 2. Synthesis of labelled amino acid derivatives **6**, **7**, **9**, **11** and **12**

Entry	Label	Amino acid	Product		Yield (%)	Mp (°C)
1	**1**	**5a**	**6a**	Bfm-Phe-OMe	87	128.9–130.6
2	**1**	**5b**	**6b**	Bfm-Val-OMe	71	Oil
3	**2a**	**5a**	**7a**	Nfm-Phe-OMe	72	146.3–148.4
4	**2a**	**5b**	**7b**	Nfm-Val-OMe	89	159.0–161.0
5	**2b**	**5b**	**7c**	Nfh-Val-OMe	57	145.3–145.9
6	**2c**	**5b**	**7d**	Nfu-Val-OMe	83	141.5–143.0
7	**2a**	**5c**	**7e**	Nfm-Ala-OMe	90	190.1–192.0
8	**2a**	**5d**	**7f**	Nfm-Gly-OMe	95	171.9–174.0
9	**2a**	**5e**	**7g**	Nfm-Asp(OMe)-OMe	98	136.8–137.7
10	**2a**	**5f**	**7h**	Nfm-Glu(OMe)-OMe	98	166.3–169.0
11	**2a**	**8**	**9**	Ac-Lys(Nfm)-OMe	71	185.7–186.9
12	**1**	**10**	**11**	Boc-Ser(Bfm)-OMe	65	Oil
13	**2a**	**10**	**12**	Boc-Ser(Nfm)-OMe	54	Oil

of the 8-methoxy derivative and as a result, reaction of compound **2a** with the α-amine group of a set of representative L-amino acid methyl esters, namely alanine, glycine and aspartic and glutamic acids (protected at their carboxyl side-chain as methyl esters) was carried out in the same conditions (Scheme 2, Table 2, entries 7–10).

In addition to labelling amino acids at their N-terminus, the alternative acylation at a lysine ω-amine group was also investigated. Thus, the methyl ester of *N*-acetyl-lysine (**8**) was reacted with **2a** under the conditions reported above, to give the expected fluorescent derivative **9** (Scheme 2, Table 2, entry 11). Another approach for side-chain labelling was undertaken by reacting *N-tert*-butyloxycarbonylserine methyl ester **10** with compounds **1** and **2a** to give the corresponding fluorescent ester derivatives **11** and **12** (Scheme 2, Table 2, entries 12 and 13).

All labelled amino acids (**6**, **7**, **9**, **11** and **12**) were obtained as solid materials (except **6b**, **11** and **12**, which were oils) in yields ranging from 54 to 98% (Table 2) and were characterised by elemental analyses or high-resolution mass spectrometry, NMR (^{1}H and ^{13}C), IR and UV/vis spectroscopies.

The IR spectra of labelled compounds showed bands due to stretching vibrations of the carbonyl group from 1658 to 1628 cm^{-1} (amide linkage) and from 1761 to 1707 cm^{-1} (ester group). ^{1}H NMR spectra showed signals of the amino acid residues, such as a singlet for the methyl ester (δ 3.45–3.94 ppm), a multiplet for the α-CH (δ 4.35–4.90 ppm, except for **7f**, which was a doublet at 3.97 ppm) and a doublet for α-NH (δ 5.18–6.69 ppm), in addition to the protons of the heterocyclic moiety. In ^{13}C NMR, signals of amide type carbonyl were found from δ 169.34 to 171.01 ppm and of the ester type occurred from δ 170.04 to 172.86 ppm.

Electronic absorption and emission spectra of 10^{-6} M solutions of compounds **1**, **2**, **6**, **7**, **9**, **11** and **12** in degassed absolute ethanol were measured, absorption and emission maxima, and Φ_F are also reported (Table 3). The quantum yields were calculated using 9,10-diphenylanthracene as standard (Φ_F=0.95 in ethanol).[26] For the relative quantum yields' determination, 9,10-diphenylanthracene was excited at the wavelengths of maximum absorption found for each one of the compounds to be tested.

The longest wavelength absorption maximum of all compounds was located between 285–301 nm. Compound **2a** absorbs and emits at longer wavelength, when compared to **1**, the bathochromic shifts being 13 and 34 nm, respectively. The fluorescence quantum yield for **2a** (0.20) was 10 times higher than for **1** (0.02). When these two labels were linked to phenylalanine and valine methyl esters, the same trend was observed, the Φ_F for compounds **6a**–**b** being about 0.07 and for compounds **7a**–**b** higher than 0.3 (Table 3, entries 5–8). Having in mind that our purpose was to obtain a heterocycle for labelling applications, which required a significant Φ_F, we decided to use the naphthofuran moiety in the following studies.

In order to access the influence of substituents at this heterocycle, absorption spectra in ethanol of compounds **2b**,**c** and **7c**,**d** showed that the insertion of more electron donating substituents at position 8 shifted bathochromically the absorption maximum by 5–8 nm (compare entries 2–4 and 8–10). In the emission spectra, a bathochromic shift is observed when comparing compounds **7b**–**d** (21–25 nm).

The Φ_F was also affected by the substituent, as naphthofurans **2a**,**b** had higher Φ_F than the unsubstituted **2c**. We expected that the substitution with an electron-donor would result in an increase in fluorescence intensity and Φ_F, as it was observed for the OMe substituent. However, in the case of OH substituent we observed that the values were similar to that of the unsubstituted derivative probably due to the presence of H-bonds to the solvent (Table 3, entries 3, 4 and 9, 10).

Taking these results into consideration, we studied the properties of the derivatives resulting from the reaction of **2a** with other representative amino acids. The resulting labelled amino acids (**7a**,**b**,**e**–**h**, **9** and **12**) exhibit moderate to good fluorescence quantum yields ($0.13<\Phi<0.44$) and the Stokes' shifts are about 50 nm. There appears to be some influence from the amino acid residue on Φ_F, since labelled acidic (**7g** and **7h**) and polar uncharged (**12**) residues have lower

Table 3. UV and fluorescence data for compounds **1**, **2**, **6**, **7**, **9**, **11** and **12**

Entry		Compound	UV λ_{max} (nm)	Fluorescence		Stokes' shift (nm)
				λ_{em} (nm)	Φ_F	
1	**1**	Bfm-OH	285	315	0.020±0.003	30
2	**2a**	Nfm-OH	298	349	0.20±0.01	51
3	**2b**	Nfh-OH	301	349	0.062±0.003	48
4	**2c**	Nfu-OH	293	340	0.076±0.008	47
5	**6a**	Bfm-Phe-OMe	288	315	0.064±0.007	27
6	**6b**	Bfm-Val-OMe	288	315	0.070±0.006	27
7	**7a**	Nfm-Phe-OMe	298	349	0.32±0.02	52
8	**7b**	Nfm-Val-OMe	298	346	0.37±0.03	49
9	**7c**	Nfh-Val-OMe	300	350	0.10±0.01	50
10	**7d**	Nfu-Val-OMe	292	325	0.13±0.01	33
11	**7e**	Nfm-Ala-OMe	298	349	0.24±0.02	49
12	**7f**	Nfm-Gly-OMe	297	343	0.24±0.01	46
13	**7g**	Nfm-Asp(OMe)-OMe	298	346	0.14±0.01	48
14	**7h**	Nfm-Glu(OMe)-OMe	298	347	0.14±0.02	49
15	**9**	Ac-Lys(Nfm)-OMe	297	347	0.44±0.03	50
16	**11**	Boc-Ser(Bfm)-OMe	287	314	0.064±0.007	27
17	**12**	Boc-Ser(Nfm)-OMe	298	349	0.13±0.01	51

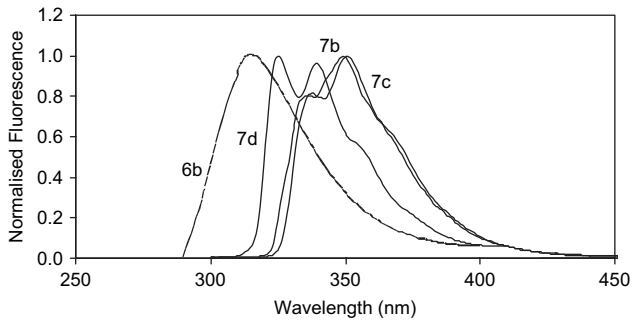


Figure 1. Normalised fluorescence spectra of valine labelled with different fluorophores **6b** and **7b–d**.

Φ_F than the free label **2a**, probably due to the possibility of occurrence of H-bonds between the label and the acidic or polar side chains. For all other derivatives the linkage is done through an amide bond and there are no extra effects from the side chains. The higher electron donating character of N and its resonance effect through the amide bond result in higher Φ_F when compared to the free label.

These results showed that 2-(8-methoxynaphtho[2,1-*b*]-furan-1-yl)ethanoic acid, Nfm-OH (**2a**) was a suitable fluorophore for the considered amino acids.

In Figure 1, the fluorescence spectra of valine labelled with different fluorophores (**6b**, **7b**, **7c** and **7d**) are shown.

In order to further elucidate the solvent interaction, absorption and emission spectra of model compound **7a**, Nfm-Phe-OMe, were measured in 10 other solvents of different polarity and proton donor ability, such as *n*-hexane, diethyl ether, toluene, 1,4-dioxane, ethyl acetate, methanol, acetonitrile, dichloromethane (DCM), *N*,*N*-dimethylformamide (DMF) and dimethyl sulfoxide (DMSO). The wavelengths of maximum absorption and emission and Φ_F for this compound are listed in Table 4.

From the results, it can be seen that the polarity of the solvent does not influence significantly the position of the band of absorption and emission; the wavelengths of maximum absorption and emission range from 296 to 299 nm and from 343 to 351 nm, respectively. However, a more significant influence of the character of the solvent on Φ_F was observed. Concerning the Φ_F obtained in the various solvents, higher values seem to be associated with aprotic solvents, either apolar or polar, such as 1,4-dioxane, DMF or diethyl ether, the highest being 0.57 (1,4-dioxane). In protic solvents like ethanol and methanol, quantum yields were slightly lower (0.32 and 0.33, respectively), which may be related with the high ability for H-bond donating/electron density acceptance power displayed by these solvents, which could affect the conjugation on the heterocyclic moiety. For the chlorinated solvent, the Φ_F value was analogous to that of the protic solvents.

Table 4. UV and fluorescence data for compound **7a** in different solvents

Entry	Solvent	UV λ_{max} (nm)	Fluorescence		Stokes' shift (nm)
			λ_{max} (nm)	Φ_F	
1	*n*-Hexane	296	343	0.29±0.02	47
2	Diethyl ether	297	345	0.45±0.03	48
3	Ethanol	298	346	0.32±0.02	48
4	Toluene	298	346	0.50±0.03	48
5	1,4-Dioxane	297	348	0.57±0.04	51
6	Ethyl acetate	297	346	0.36±0.03	49
7	Methanol	297	347	0.33±0.03	50
8	Acetonitrile	297	348	0.40±0.03	51
9	DCM	299	347	0.30±0.04	48
10	DMF	299	350	0.55±0.03	51
11	DMSO	299	351	0.36±0.04	52

With the aim of testing the possibility of using these fluorophores as labels in peptide chemistry, stability tests, such as hydrogenation catalysed by Pd/C, acidolysis (6 M HCl, trifluoroacetic acid, TFA), aminolysis with 2-(*N*,*N*-diethylamino)ethylamine (DEAEA)[27] and reduction with metals (Mg/MeOH),[28] were carried out. Fluorescent valine methyl ester, Nfm-Val-OMe (**7b**), used as model, was treated under similar conditions to those usually required for cleavage of protecting groups during peptide synthesis.[29] In these conditions, the compound showed good stability, being recovered in yields from 95 to 100% (Pd/C, HCl, TFA and Mg) and 85% (DEAEA), as it was confirmed by ^{1}H NMR. Treatment with base (aqueous 1 M NaOH) was also performed, resulting in quantitative cleavage of the ester function, without affecting the label. All labelled compounds were also stable to prolonged storage at room temperature.

3. Conclusions

A series of carboxylic fused furans were synthesised in excellent yields by a simple procedure from the corresponding oxobenzopyrans. These heterocycles were used in the derivatisation of representative L-amino acids of different character, such as nonpolar aliphatic (valine and alanine) or aromatic (phenylalanine), basic (lysine), polar uncharged (glycine and serine) and acidic (aspartic and glutamic acids) amino acids. From the study of the absorption and emission properties, carried out for all labelled residues, we concluded that the 2-(8-methoxynaphtho[2,1-*b*]furan-1-yl)-ethanoic acid (**2a**) was the most interesting fluorophore.

Considering the high yields of the synthesis and derivatisation reactions as well as the fluorescence properties and also the stability to different deprotection conditions, usually used in peptide synthesis, naphthofurans seem to be promising for fluorescent labelling purposes.

4. Experimental

4.1. General

All melting points were uncorrected and were measured on a Gallenkamp melting point apparatus. TLC analyses were carried out on 0.25 mm thick precoated silica plates (Merck Fertigplatten Kieselgel 60F_{254}) and spots were visualised under UV light. Chromatography on silica gel was carried out on Merck Kieselgel (230–240 mesh). IR spectra were determined on a Perkin–Elmer FTIR-1600 using KBr discs or Nujol. UV/vis spectra were run on a Hitachi U-2000 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian 300

spectrometer in $CDCl_3$ or DMSO-d_6 at 300 MHz at 25 °C. All chemical shifts are given in parts per million using δ_H Me_4Si=0 ppm as reference and J values are given in hertz. ^{13}C NMR spectra were run in the same instrument at 75.4 MHz using the solvent peak as internal reference. Assignments were made by comparison of chemical shifts, peak multiplicities and J values, and were supported by spin decoupling-double resonance and bidimensional heteronuclear correlation HMBC and HMQC techniques. Mass spectrometric analyses were performed at the C.A.C.T.I.—Unidad de Espectrometria de Masas of the University of Vigo, Spain, on a Hewlett–Packard 5989 A spectrometer for low-resolution spectra and a VG Autospec M spectrometer for high-resolution mass spectra. Elemental analyses were carried out on a Leco CHNS 932 instrument. Fluorescence spectra were collected using a Spex Fluorolog 1680 Spectrometer.

4.1.1. 2-(5-Methoxybenzofuran-1-yl)ethanoic acid, Bfm-OH (1). A suspension of compound **3** (0.500 g, 2.23×10^{-3} mol) in aqueous 2 M sodium hydroxide solution (10 mL) was stirred for 16 h at 80 °C. After cooling, the reaction mixture was acidified with aqueous 6 M hydrochloric acid solution until pH=5–6. The mixture was extracted with ethyl acetate (3×20 mL), the organic extracts were combined, dried with magnesium sulfate and evaporated under vacuum in a rotary evaporator to yield compound **1** as a off-white solid (0.422 g, 92%). Mp=124.6–126.0 °C. TLC (chloroform/methanol, 95:5): R_f 0.30. ^1H NMR (DMSO-d_6, 300 MHz): δ=3.63 (s, 2H, CH_2), 3.78 (s, 3H, OCH_3), 6.87 (dd, J=2.4 and 8.7 Hz, 1H, H-6), 7.15 (d, J=2.4 Hz, 1H, H-4), 7.44 (d, J=8.7 Hz, 1H, H-7), 7.75 (s, 1H, H-2), 12.15 (br s, 1H, OH). ^{13}C NMR (DMSO-d_6, 75.4 MHz): δ_C=29.07 (CH_2), 55.59 (OCH_3), 95.94 (C-4), 111.54 (C-6), 113.83 (C-1), 120.30 (C-7), 120.98 (C-7a), 142.31 (C-2), 155.58 (C-3a), 157.72 (C-5), 171.97 (CO_2H). IR (KBr 1%, cm^{-1}): ν=3424, 3051, 3017, 2908, 2836, 1708, 1627, 1595, 1490, 1441, 1401, 1292, 1233, 1143, 1120, 1075, 1023, 935, 805. UV/vis (ethanol, nm): λ_{max} (ε)=285 (1828 $M^{-1}\,cm^{-1}$). HRMS (EI): calcd for $C_{11}H_{10}O_4$ [M^+]: 206.0579; found: 206.0578.

4.1.2. 2-(8-Methoxynaphtho[2,1-*b*]furan-1-yl)ethanoic acid, Nfm-OH (2a). Starting with Obm-Cl (**4a**) (0.232 g, 8.44×10^{-4} mol) and following the same procedure described above for Bfm-OH (**1**), followed by recrystallisation from ethyl acetate/*n*-hexane, compound **2a** was obtained as a brown solid (0.212 g, 98%). Mp=176.8–178.9 °C. TLC (chloroform/methanol, 9.8:0.2): R_f 0.51. ^1H NMR (DMSO-d_6, 300 MHz): δ=3.90 (s, 3H, OCH_3), 4.04 (s, 2H, CH_2), 7.14 (dd, J=9.0 and 2.5 Hz, 1H, H-7), 7.56 (s, 1H, H-9), 7.58 (d, J=9.0 Hz, 1H, H-4), 7.75 (d, J=9.0 Hz, 1H, H-5), 7.93 (d, J=9.0 Hz, 1H, H-6), 7.96 (s, 1H, H-2), 12.60 (br s, 1H, OH). ^{13}C NMR (DMSO-d_6, 75.4 MHz): δ_C=31.03 (CH_2), 55.06 (OCH_3), 102.99 (C-9), 110.09 (C-4), 115.74 (C-1), 115.87 (C-7), 120.52 (C-3b), 125.21 (C-5a), 125.45 (C-5), 129.13 (C-5b), 130.41 (C-6), 143.20 (C-2), 153.22 (C-3a), 157.78 (C-8), 172.62 (CO_2H). IR (KBr 1%, cm^{-1}): ν=3442, 3103, 3016, 2966, 2922, 1703, 1627, 1602, 1523, 1468, 1409, 1383, 1358, 1281, 1259, 1232, 1201, 1179, 1135, 1120, 1107, 1040, 1023, 947, 876, 838, 833. UV/vis (ethanol, nm): λ_{max} (ε)=298 (8436 $M^{-1}\,cm^{-1}$). Anal. Calcd for $C_{15}H_{12}O_4$ (256.25): C 70.30, H 4.72; found: C 70.48, H 4.81.

4.1.3. 2-(8-Hydroxynaphtho[2,1-*b*]furan-1-yl)ethanoic acid, Nfh-OH (2b). Starting with Obh-Cl (**4b**) (0.205 g, 7.86×10^{-4} mol) and following the same procedure described above for Bfm-OH (**1**), compound **2b** was obtained as a brown solid (0.183 g, 96%). Mp=167.8–169.0 °C. TLC (chloroform/methanol, 5:2): R_f 0.36. ^1H NMR (DMSO-d_6, 300 MHz): δ=3.97 (s, 2H, CH_2), 7.05 (dd, J=8.7 and 2.4 Hz, 1H, H-7), 7.44 (d, J=2.4 Hz, 1H, H-9), 7.49 (d, J=8.7 Hz, 1H, H-4), 7.67 (d, J=9.0 Hz, 1H, H-5), 7.85 (d, J=9.0 Hz, 1H, H-6), 7.91 (s, 1H, H-2), 9.84 (s, 1H, OH), 12.57 (br s, 1H, CO_2H). ^{13}C NMR (DMSO-d_6, 75.4 MHz): δ_C=30.75 (CH_2), 105.71 (C-9), 109.25 (C-4), 115.62 (C-1), 116.07 (C-7), 119.91 (C-3b), 124.49 (C-5a), 125.60 (C-5), 129.64 (C-5b), 130.44 (C-6), 142.79 (C-2), 153.11 (C-3a), 156.04 (C-8), 172.13 (CO_2H). IR (KBr 1%, cm^{-1}): ν=3365, 3107, 2926, 2860, 1715, 1636, 1533, 1471, 1419, 1388, 1360, 1334, 1286, 1259, 1239, 1193, 1173, 1107, 1033, 883, 860, 833. UV/vis (ethanol, nm): λ_{max} (ε)=301 (7970 $M^{-1}\,cm^{-1}$). HRMS (EI) calcd for $C_{14}H_{10}O_4$ [M^+]: 242.0579; found: 242.0586.

4.1.4. 2-(Naphtho[2,1-*b*]furan-1-yl)ethanoic acid, Nfu-OH (2c). Starting with Obh-Cl (**4c**) (0.207 g, 8.46×10^{-4} mol) and following the same procedure described above for Bfm-OH (**1**), compound **2c** was obtained as a brownish solid, which was recrystallised from ethyl acetate/*n*-hexane. Compound **2c** was obtained as a beige solid (0.180 g, 94%). Mp=171.4–173.0 °C. TLC (chloroform/methanol, 5.8:0.2): R_f 0.28. ^1H NMR (DMSO-d_6, 300 MHz): δ=4.04 (s, 2H, CH_2), 7.51 (dt, J=8.0 and 1.2 Hz, 1H, H-8), 7.60 (dt, J=8.0 and 1.2 Hz, 1H, H-7), 7.77 (d, J=9.0 Hz, 1H, H-4), 7.84 (d, J=9.0 Hz, 1H, H-5), 8.01 (s, 1H, H-2), 8.04 (br d, J=8.1 Hz, 1H, H-9), 8.18 (br d, J=8.1 Hz, 1H, H-6), 12.60 (br s, 1H, OH). ^{13}C NMR (DMSO-d_6, 75.4 MHz): δ_C=31.08 (CH_2), 112.74 (C-4), 115.94 (C-1), 121.18 (C-3b), 123.14 (C-6), 124.44 (C-8), 125.67 (C-5), 126.49 (C-7), 127.96 (C-5a), 129.01 (C-9), 130.36 (C-5b), 143.64 (C-2), 152.69 (C-3a), 172.50 (CO_2H). IR (KBr 1%, cm^{-1}): ν=3550–3000, 2900, 1707, 1623, 1583, 1524, 1413, 1387, 1323, 1286, 1232, 1197, 1177, 1158, 1120, 1110, 1024, 992, 949, 939, 857, 830. UV/vis (ethanol, nm): λ_{max} (ε)=293 (7442 $M^{-1}\,cm^{-1}$). HRMS (EI) calcd for $C_{14}H_{10}O_3$ [M^+]: 226.0630; found: 226.0634.

4.1.5. 1-Chloromethyl-6-methoxy-3-oxo-3*H*-benzopyran, Opm-Cl (3). To a solution of 3-methoxyphenol (1.1 mL, 1.0×10^{-2} mol) in 70% aqueous sulfuric acid (10 mL), ethyl 4-chloroacetoacetate (2.02 mL, 1.5×10^{-2} mol) was added and stirred at room temperature for 78 h. The reaction mixture was poured into ice water and stirred for 2 h to give a fine violet precipitate. The solid was collected by filtration, washed with cold water and dried in a vacuum oven. Purification by dry chromatography on silica gel using chloroform/*n*-hexane, 2:1 as eluent gave compound **3** as a white solid (1.77 g, 79%). Mp=199.5–200.8 °C. TLC (chloroform): R_f 0.65. ^1H NMR (DMSO-d_6, 300 MHz): δ=3.85 (s, 3H, OCH_3), 4.98 (s, 2H, CH_2), 6.48 (s, 1H, H-2), 6.98–7.03 (m, 2H, H-5 and H-7), 7.75 (d, J=8.4 Hz, 1H, H-8). ^{13}C NMR (DMSO-d_6, 75.4 MHz): δ_C=41.34 (CH_2), 56.00 (OCH_3), 101.06 (C-5), 110.44 (C-8a), 112.00 (C-2), 112.35 (C-7), 126.38 (C-8), 150.87 (C-1), 155.26 (C-4a), 160.02 (C-3), 162.61 (C-6). IR (KBr 1%, cm^{-1}): ν=3070,

3023, 2853, 1725, 1623, 1611, 1558. UV/vis (ethanol, nm): λ_{max} (ε)=325 (14125 $M^{-1}\,cm^{-1}$). HRMS (EI) calcd for $C_{11}H_9O_3^{35}Cl$ [M^+]: 224.0240; found: 224.0251; calcd for $C_{11}H_9O_3^{37}Cl$ [M^+]: 226.0194; found: 226.0202.

4.1.6. 1-Chloromethyl-9-methoxy-3-oxo-3*H*-benzo[*f*]-benzopyran, Obm-Cl (4a). Starting with 7-methoxy-2-naphthol (0.348 g, 2.0×10^{-3} mol) and following the same procedure as described above for the preparation of compound **3**, using ethyl acetate/*n*-hexane 3:7, as the chromatography eluent, followed by recrystallisation from ethyl acetate/*n*-hexane, compound **4a** was obtained as an off-white solid (0.456 g, 83%). Mp=179.2–180.7 °C. TLC (ethyl acetate/*n*-hexane, 3:4): R_f 0.58. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=4.02 (s, 3H, OCH_3), 4.98 (s, 2H, CH_2), 6.62 (s, 1H, H-2), 7.24 (dd, J=9.0 and 2.4 Hz, 1H, H-8), 7.31 (d, J=9.0 Hz, 1H, H-5), 7.79–7.90 (m, 2H, H-10 and H-7), 7.92 (d, J=9.0 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ_C=45.60 (CH_2), 55.55 (OCH_3), 105.71 (C-10), 111.80 (C-4b), 115.11 (C-5), 117.02 (C-8), 117.24 (C-2), 126.29 (C-6a), 130.23 (C-6b), 131.15 (C-7), 133.93 (C-6), 150.96 (C-1), 155.76 (C-4a), 159.69 (C-9), 159.99 (C-3). IR (KBr 1%, cm^{-1}): ν=3068, 1739, 1626, 1585, 1548, 1521, 1445, 1430, 1346, 1286, 1242, 1218, 1168, 1148, 1054, 1021, 912, 899, 863, 837, 734. UV/vis (ethanol, nm): λ_{max} (ε)=354 (12826 $M^{-1}\,cm^{-1}$). Anal. Calcd for $C_{15}H_{11}O_3Cl$ (274.70): C 65.58, H 4.04; found C 65.50, H 4.21.

4.1.7. 1-Chloromethyl-9-hydroxy-3-oxo-3*H*-benzo[*f*]benzopyran, Obh-Cl (4b). Starting with 2,7-dihydroxynaphthalene (0.320 g, 2.0×10^{-3} mol) and following the same procedure described above for compound **3**, using ethyl acetate/*n*-hexane 3:7, as the chromatography eluent, compound **4b** was obtained as beige solid (0.482 g, 92%). Mp=250.0–250.7 °C. TLC (chloroform/methanol 5.8:0.2): R_f 0.35. ^{1}H NMR (DMSO-d_6, 300 MHz): δ=5.30 (s, 2H, CH_2), 6.76 (s, 1H, H-2), 7.16 (dd, J=8.7 and 2.1 Hz, 1H, H-8), 7.32 (d, J=8.7 Hz, 1H, H-5), 7.81 (d, J=2.1 Hz, 1H, H-10), 7.92 (d, J=9.0 Hz, 1H, H-7), 8.09 (d, J=9.0 Hz, 1H, H-6), 10.21 (s, 1H, OH). ^{13}C NMR (DMSO-d_6, 75.4 MHz): δ_C=46.17 (CH_2), 108.66 (C-10), 110.67 (C-4b), 113.90 (C-5), 115.77 (C-2), 117.25 (C-8), 125.22 (C-6a), 130.31 (C-6b), 131.33 (C-7), 134.35 (C-6), 152.27 (C-1), 155.35 (C-4a), 157.80 (C-9), 159.38 (C-3). IR (KBr 1%, cm^{-1}): ν=3287, 2930, 1689, 1624, 1597, 1542, 1467, 1438, 1406, 1363, 1306, 1256, 1234, 1218, 1195, 1138, 1044, 1001, 968, 850, 840, 773, 731, 702. UV/vis (ethanol, nm): λ_{max} (ε)=361 (12190 $M^{-1}\,cm^{-1}$). HRMS (EI) calcd for $C_{14}H_9O_3^{35}Cl$ [M^+]: 260.0240; found: 260.0246; calcd for $C_{14}H_9O_3^{37}Cl$ [M^+]: 262.0211; found: 262.0206.

4.1.8. 1-Chloromethyl-3-oxo-3*H*-benzo[*f*]benzopyran, Obb-Cl (4c). Starting with 2-naphthol (1.0 g, 6.98×10^{-3} mol) and following the same procedure described above for compound **3**, using ethyl acetate/*n*-hexane 3:7, as the chromatography eluent, followed by recrystallisation from ethyl acetate/*n*-hexane gave compound **4c** as a yellow solid (1.22 g, 71%). Mp=179.5–182.7 °C. TLC (ethyl acetate/*n*-hexane, 2:8): R_f 0.36. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=5.09 (s, 2H, CH_2), 6.76 (s, 1H, 2-H), 7.52 (d, J=8.7 Hz, 1H, 5-H), 7.61 (dt, J=7.6 and 1.0 Hz, 1H, 8-H), 7.72 (dt, J=7.6 and 1.5 Hz, 1H, H-9), 7.96 (dd, J=8.1 and 1.2 Hz, 1H, 7-H), 8.04 (d, J=9.0 Hz, 1H, 6-H), 8.49 (br d, J=9.0 Hz, 1H, 10-H). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ_C=45.79 (CH_2), 112.50 (C-4b), 117.37 (C-2), 117.78 (C-5), 124.90 (C-10), 125.80 (C-8), 128.51 (C-9), 128.75 (C-6b), 129.88 (C-7), 131.29 (C-6a), 134.33 (C-6), 151.22 (C-1), 155.10 (C-4a), 159.97 (C-3). IR (KBr 1%, cm^{-1}): ν=3550, 3070, 1716, 1693, 1588, 1550, 1520, 1457, 1433, 1416, 1345, 1323, 1285, 1254, 1212, 1166, 1144, 1124, 1013, 1002, 918, 877, 862, 828. UV/vis (ethanol, nm): λ_{max} (ε)=(11,449 $M^{-1}\,cm^{-1}$). HRMS (EI): calcd for $C_{14}H_9O_2^{35}Cl$ [M^+]: 244.0291; found: 244.0290; calcd for $C_{14}H_9O_2^{37}Cl$ [M^+]: 246.0262; found: 246.0267.

4.2. General method for the synthesis of fluorescent-labelled L-amino acids 6, 7, 9, 11 and 12

Carboxylic compounds (**1**, **2**) were reacted with an amino acid methyl ester (2 equiv) in DMF by a standard DCC/HOBt coupling.[29] After evaporation of the solvent and chromatography on silica gel, the required acetyl derivatives (**6**, **7**, **9**, **11** and **12**) were obtained.

4.2.1. *N*-[(5-Methoxybenzofuran-1-yl)ethanoyl]phenylalanine methyl ester, Bfm-Phe-OMe (6a). The product of the reaction of Bfm-OH (**1**) (0.105 g; 5.1×10^{-4} mol) with phenylalanine methyl ester hydrochloride (**5a**) was chromatographed using chloroform as the eluent to give compound **6a** as a yellow solid (0.162 g, 87%). Mp=128.9–130.6 °C. TLC (chloroform): R_f 0.28. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.97–3.05 (m, 2H, β-CH_2 Phe), 3.60 (s, 2H, CH_2), 3.70 (s, 3H, OCH_3 Phe), 3.88 (s, 3H, OCH_3), 4.80–4.90 (m, 1H, α-H Phe), 6.00 (d, J=7.5 Hz, 1H, α-NH Phe), 6.80–6.84 (m, 2×Ar-H, 2H, Phe), 6.88 (dd, J=2.4 and 8.4 Hz, 1H, H-6), 7.04 (d, J=2.1 Hz, 1H, H-4), 7.10–7.18 (m, 3×Ar-H, 3H, Phe), 7.33 (d, J=8.7 Hz, 1H, H-7), 7.43 (s, 1H, H-2). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ_C=31.60 (CH_2), 37.50 (β-CH_2 Phe), 52.32 (OCH_3 Phe), 52.87 (α-CH Phe), 55.71 (OCH_3), 96.07 (C-4), 112.05 (C-6), 113.36 (C-3a), 119.75 (C-7), 120.45 (C-7a), 127.04 (C-4 Phe), 128.46 (C-3 and C-5 Phe), 128.93 (C-2 and C-6 Phe), 135.32 (C-1 Phe), 142.18 (C-2), 156.43 (C-1), 158.41 (C-5), 169.34 (CONH), 171.68 (CO_2CH_3). IR (KBr 1%, cm^{-1}): ν=3289, 3064, 3030, 3008, 2956, 2930, 1750, 1659, 1629, 1602, 1587, 1544, 1494, 1455. UV/vis (ethanol, nm): λ_{max} (ε)=288 (4717 $M^{-1}\,cm^{-1}$). HRMS (EI): calcd for $C_{21}H_{21}NO_5$ [M^+]: 367.1420; found: 367.1402.

4.2.2. *N*-[(5-Methoxybenzofuran-1-yl)ethanoyl]valine methyl ester, Bfm-Val-OMe (6b). The product of the reaction of Bfm-OH (**1**) (0.103 g, 5.0×10^{-4} mol) with valine methyl ester hydrochloride (**5b**) was chromatographed using chloroform as the eluent to give compound **6b** as a yellow oil (0.113 g, 71%). TLC (chloroform): R_f 0.27. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=0.73 (d, J=6.9 Hz, 3H, γ-CH_3 Val), 0.84 (d, J=6.9 Hz, 3H, γ-CH_3 Val), 2.00–2.08 (m, 1H, β-CH Val), 3.66 (s, 3H, OCH_3 Val), 3.77 (s, 2H, CH_2), 3.86 (s, 3H, OCH_3), 4.52–4.59 (m, 1H, α-CH Val), 6.11 (d, J=8.1 Hz, 1H, α-NH Val), 6.91 (dd, J=2.1 and 8.7 Hz, 1H, H-6), 7.03 (d, J=2.4 Hz, 1H, H-4), 7.43 (d, J=8.7 Hz, 1H, H-7), 7.56 (s, 1H, H-2). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ_C=17.62 (γ-CH_3 Val), 18.88 (γ-CH_3 Val), 31.09 (β-CH Val), 31.79 (CH_2), 52.31 (OCH_3 Val), 55.70 (OCH_3), 57.10 (α-C Val), 96.12 (C-4), 112.06 (C-6),

113.59 (C-3a), 119.76 (C-7), 120.47 (C-7a), 142.22 (C-2), 156.51 (C-1), 158.45 (C-5), 169.64 (CONH), 172.21 (CO_2CH_3). IR (KBr 1%, cm^{-1}): ν=3290, 1685, 1641. UV/vis (ethanol, nm): λ_{max} (ε)=288 (4888 $M^{-1}\,cm^{-1}$). HRMS (EI) calcd for $C_{17}H_{21}NO_5$ [M^+]: 319.1420; found: 319.1426.

4.2.3. *N*-[(8-Methoxynaphtho[2,1-*b*]furan-1-yl)ethanoyl]phenylalanine methyl ester, Nfm-Phe-OMe (7a). The product of the reaction of Nfm-OH (**2a**) (0.095 g, 3.71×10^{-4} mol) with phenylalanine methyl ester hydrochloride (**5a**) was chromatographed using ethyl acetate/*n*-hexane 4:6, as the eluent to give compound **7a** as a white solid (0.111 g, 72%). Mp=146.3–148.4 °C. TLC (ethyl acetate/*n*-hexane, 4:6): R_f 0.38. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.80–2.96 (m, 2H, β-CH_2 Phe), 3.57 (s, 3H, OCH_3 Phe), 3.93 (s, 3H, OCH_3), 3.96 (s, 2H, CH_2), 4.80–4.90 (m, 1H, α-CH Phe), 6.05 (d, J=8.1 Hz, 1H, α-NH Phe), 6.47 (br d, J=7.5 Hz, 2H, H-2 and H-6 Phe), 6.79 (br t, J=7.5 Hz, 2H, H-3 and H-5 Phe), 6.96 (br t, J=7.5 Hz, 1H, H-4 Phe), 7.14 (dd, J=9.0 and 2.1 Hz, 1H, H-7), 7.48 (d, J=2.1 Hz, 1H, H-9), 7.52 (d, J=9.0 Hz, 1H, H-4), 7.62 (s, 1H, H-2), 7.73 (d, J=9.0 Hz, 1H, H-5), 7.85 (d, J=9.0 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ_C=33.97 (CH_2), 37.57 (β-CH_2 Phe), 52.15 (OCH_3 Phe), 52.87 (α-CH Phe), 55.56 (OCH_3), 102.32 (C-9), 109.99 (C-4), 115.04 (C-1), 116.77 (C-7), 120.00 (C-3b), 125.63 (C-5a), 126.26 (C-5), 126.85 (C-4 Phe), 128.13 (C-3 and C-5 Phe), 128.52 (C-2 and C-6 Phe), 129.41 (C-5b), 130.37 (C-6), 134.90 (C-1 Phe), 142.66 (C-2), 154.44 (C-3a), 158.65 (C-8), 169.75 (CONH), 171.38 (CO_2CH_3). IR (KBr 1%, cm^{-1}): ν=3284, 2958, 2927, 2852, 1750, 1662, 1625, 1543, 1524, 1468, 1431, 1362, 1262, 1224, 1199, 1174, 1099, 1017, 823, 792. UV/vis (ethanol, nm): λ_{max} (ε)=298 (8261 $M^{-1}\,cm^{-1}$). HRMS (EI) calcd for $C_{25}H_{23}NO_5$ [M^+]: 417.1576; found: 417.1588.

4.2.4. *N*-[(8-Methoxynaphtho[2,1-*b*]furan-1-yl)ethanoyl]valine methyl ester, Nfm-Val-OMe (7b). The product of the reaction of Nfm-OH (**2a**) (0.095 g, 3.71×10^{-4} mol) with valine methyl ester hydrochloride (**5b**) was chromatographed using chloroform/*n*-hexane 9:1, as the eluent to give compound **7b** as a brown solid (0.122 g, 89%). Mp=159.0–161.0 °C. TLC (ethyl acetate/*n*-hexane, 4:6): R_f 0.48. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=0.54 (d, J=6.9 Hz, 3H, γ-CH_3 Val), 0.63 (3H, d, J=6.9 Hz, γ-CH_3 Val), 1.85–2.00 (m, 1H, β-CH Val), 3.48 (s, 3H, OCH_3 Val), 4.02 (s, 3H, OCH_3), 4.03 (s, 2H, CH_2), 4.46–4.56 (m, 1H, α-CH Val), 6.11 (d, J=8.4 Hz, 1H, α-NH Val), 7.13 (dd, J=9.0 and 2.4 Hz, 1H, H-7), 7.50 (s, 1H, H-9), 7.52 (d, J=9.0 Hz, 1H, H-4), 7.70 (d, J=8.7 Hz, 1H, H-5), 7.74 (s, 1H, H-2), 7.84 (d, J=9.0 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ_C=17.47 (γ-CH_3 Val), 18.55 (γ-CH_3 Val), 30.91 (β-CH Val), 34.05 (CH_2), 51.84 (OCH_3 Val), 55.49 (OCH_3), 57.27 (α-CH Val), 102.43 (C-9), 110.00 (C-4), 115.23 (C-1), 116.55 (C-7), 119.87 (C-3b), 125.54 (C-5a), 126.24 (C-5), 129.30 (C-5b), 130.34 (C-6), 142.65 (C-2), 155.45 (C-3a), 158.49 (C-8), 170.00 (CONH), 171.77 (CO_2CH_3). IR (KBr 1%, cm^{-1}): ν=3442, 3295, 3116, 3078, 2998, 2964, 1739, 1658, 1630, 1603, 1545, 1525, 1474, 1432, 1410, 1383, 1358, 1290, 1232, 1202, 1183, 1120, 1038, 1027, 832. UV/vis (ethanol, nm): λ_{max} (ε)=298 (10,196 $M^{-1}\,cm^{-1}$). HRMS (EI) calcd for $C_{21}H_{23}NO_5$ [M^+]: 369.1576; found: 369.1560.

4.2.5. *N*-[(8-Hydroxynaphtho[2,1-*b*]furan-1-yl)ethanoyl]valine methyl ester, Nfh-Val-OMe (7c). The product of the reaction of Nfh-OH (**2b**) (0.090 g, 3.71×10^{-4} mol) with valine methyl ester hydrochloride (**5b**) was chromatographed using ethyl acetate/*n*-hexane 3:7, as the eluent to give compound (**7c**) as a brown solid (0.075 g, 57%). Mp=145.3–145.9 °C. TLC (ethyl acetate/*n*-hexane, 1:1): R_f 0.65. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=0.62 (d, J=6.9 Hz, 3H, γ-CH_3 Val), 0.74 (d, J=6.9 Hz, 3H, γ-CH_3 Val), 2.00–2.10 (m, 1H, β-CH Val), 3.57 (s, 3H, OCH_3 Val), 4.04 (s, 2H, CH_2), 4.52–4.62 (m, 1H, α-CH Val), 6.45 (d, J=8.7 Hz, 1H, α-NH Val), 7.13 (dd, J=8.7 and 2.4 Hz, 1H, H-7), 7.47 (d, J=8.7 Hz, 1H, H-4), 7.54 (d, J=2.4 Hz, 1H, H-9), 7.66 (d, 1H, J=9.0 Hz, H-5), 7.69 (s, 1H, H-2), 7.82 (d, J=8.7 Hz, 1H, H-6), 8.16 (br s, 1H, OH). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ_C=17.43 (γ-CH_3 Val), 18.71 (γ-CH_3 Val), 30.73 (β-CH Val), 33.56 (CH_2), 52.27 (OCH_3 Val), 57.57 (α-CH Val), 105.78 (C-9), 109.72 (C-4), 114.68 (C-1), 116.20 (C-7), 119.36 (C-3b), 125.29 (C-5a), 126.32 (C-5), 129.21 (C-5b), 130.79 (C-6), 142.74 (C-2), 154.39 (C-3a), 155.67 (C-8), 171.01 (CONH), 172.53 (CO_2CH_3). IR (KBr 1%, cm^{-1}): ν=3427, 3313, 2961, 2929, 1723, 1658, 1629, 1537, 1468, 1441, 1410, 1387, 1289, 1261, 1219, 1195, 1155, 1136, 1120, 1102, 1032, 994, 847, 834. UV/vis (ethanol, nm): λ_{max} (ε)=300 (17650 $M^{-1}\,cm^{-1}$). HRMS (EI) calcd for $C_{20}H_{21}NO_5$ [M^+]: 355.1420; found: 355.1416.

4.2.6. *N*-[(Naphtho[2,1-*b*]furan-1-yl)ethanoyl]valine methyl ester, Nfu-Val-OMe (7d). The product of the reaction of Nfu-OH (**2c**) (0.090 g, 3.71×10^{-4} mol) with valine methyl ester hydrochloride (**5b**) was chromatographed using chloroform/*n*-hexane 9:1, as the eluent to give compound (**7d**) as a yellow solid (0.104 g, 83%). Mp=141.5–143.0 °C. TLC (ethyl acetate/*n*-hexane, 1:1): R_f 0.85. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=0.56 (d, J=6.9 Hz, 3H, γ-CH_3 Val), 0.66 (d, J=6.9 Hz, 3H, γ-CH_3 Val), 1.89–2.01 (m, 1H, β-CH Val), 3.51 (s, 3H, OCH_3 Val), 4.03 (s, 2H, CH_2), 4.5–4.60 (m, 1H, α-CH Val), 6.24 (d, J=9.0 Hz, 1H, α-NH Val), 7.45 (dt, J=7.2 and 1.0 Hz, 1H, H-8), 7.57 (dt, J=7.2 and 1.2 Hz, 1H, H-7), 7.65 (d, J=9.0 Hz, 1H, H-4), 7.75 (d, J=9.0 Hz, 1H, H-5), 7.76 (s, 1H, H-2), 7.95 (d, J=8.7 Hz, 1H, H-9), 8.16 (d, J=8.4 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ_C=17.4 (γ-CH_3 Val), 18.6 (γ-CH_3 Val), 31.0 (β-CH Val), 33.8 (CH_2), 51.9 (OCH_3), 57.2 (α-CH Val), 112.6 (C-4), 115.3 (C-1), 120.5 (C-3b), 123.0 (C-6), 124.5 (C-8), 126.3 (C-5), 126.7 (C-7), 128.04 (C-5a), 129.0 (C-9), 130.7 (C-5b), 143.1 (C-2), 153.8 (C-3a), 169.8 (CONH), 171.9 (CO_2CH_3). IR (KBr 1%, cm^{-1}): ν=3290, 3279, 2960, 2929, 2852, 1809, 1742, 1658, 1651, 1584, 1538, 1464, 1437, 1388, 1372, 1312, 1266, 1205, 1151, 1107, 1022, 990, 931, 857, 804. UV/vis (ethanol, nm): λ_{max} (ε)=292 (1758 $M^{-1}\,cm^{-1}$). HRMS (EI) calcd for $C_{20}H_{21}NO_4$ [M^+]: 339.1471; found: 339.1471.

4.2.7. *N*-[(8-Methoxynaphtho[2,1-*b*]furan-1-yl)ethanoyl]-alanine methyl ester, Nfm-Ala-OMe (7e). The product of the reaction of Nfm-OH (**2a**) (0.104, 4.06×10^{-4} mol) with alanine methyl ester hydrochloride (**5c**) (0.054 g, 3.90×10^{-4} mol) was chromatographed using ethyl acetate/*n*-hexane 3:7, as the eluent to give compound **7e** as a white solid (0.125 g, 90%). Mp=190.1–192.0 °C. TLC (ethyl acetate/*n*-hexane, 4:6): R_f 0.32. ^{1}H NMR ($CDCl_3$, 300 MHz):

δ=1.20 (d, J=7.2 Hz, 3H, β-CH_3 Ala), 3.50 (s, 3H, OCH_3 Ala), 3.95 (s, 3H, OCH_3), 3.99 (s, 2H, CH_2), 4.50–4.65 (m, 1H, α-CH Ala), 6.22 (d, J=7.5 Hz, 1H, α-NH Ala), 7.14 (dd, J=9.0 and 2.7 Hz, 1H, H-7), 7.52 (d, J=9.0 Hz, 2H, H-9 and H-4), 7.66 (d, J=9.0 Hz, 1H, H-5), 7.72 (s, 1H, H-2), 7.84 (d, J=9.0 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ_C=18.00 (β-CH_3 Ala), 33.90 (CH_2), 48.08 (α-CH Ala), 52.16 (OCH_3 Ala), 55.49 (OCH_3), 102.42 (C-9), 110.02 (C-4), 115.09 (C-1), 116.55 (C-7), 119.97 (C-3b), 125.55 (C-5a), 126.19 (C-5), 129.33 (C-5b), 130.32 (C-6), 142.66 (C-2), 154.41 (C-3a), 158.48 (C-8), 169.71 (CONH), 172.74 (CO_2CH_3). IR (KBr 1%, cm^{-1}): ν=3435, 3299, 2961, 2926, 1741, 1654, 1630, 1601, 1543, 1475, 1454, 1407, 1384, 1359, 1261, 1232, 1201, 1185, 1154, 1021, 829, 802. UV/vis (ethanol, nm): λ_{max} (ε)=298 (6456 $M^{-1}\,cm^{-1}$). HRMS (EI) calcd for $C_{19}H_{19}NO_5$ [M^+]: 341.1263; found: 341.1265.

4.2.8. *N*-[(8-Methoxynaphtho[2,1-*b*]furan-1-yl)ethanoyl]glycine methyl ester, Nfm-Gly-OMe (7f). The product of the reaction of Nfm-OH (**2a**) (0.177 g, 6.91×10^{-4} mol) with glycine methyl ester hydrochloride (**5d**) was chromatographed using ethyl acetate/*n*-hexane 3:7, as the eluent to give compound **7f** as a white solid (0.215 g, 95%). Mp=171.9–174.0 °C. TLC (ethyl acetate/*n*-hexane, 7:3): R_f 0.46. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=3.57 (s, 3H, OCH_3 Gly), 3.96 (s, 3H, OCH_3), 3.97 (d, J=4.5 Hz, 2H, CH_2 Gly), 4.04 (s, 2H, CH_2), 6.18 (br s, 1H, α-NH Gly), 7.15 (dd, J=9.0 and 2.4 Hz, 1H, H-7), 7.50–7.55 (m, 2H, H-4 and H-9), 7.70 (d, J=8.7 Hz, 1H, H-5), 7.74 (s, 1H, H-2), 7.85 (d, J=9.0 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ_C=33.74 (CH_2), 41.27 (CH_2 Gly), 52.12 (OCH_3 Gly), 55.51 (OCH_3), 102.37 (C-9), 110.01 (C-4), 115.01 (C-1), 116.61 (C-7), 119.96 (C-3b), 125.53 (C-5a), 126.23 (C-5), 129.33 (C-5b), 130.34 (C-6), 142.75 (C-2), 154.40 (C-3a), 158.55 (C-8), 169.73 (CONH), 170.45 (CO_2CH_3). IR (Nujol, cm^{-1}): ν=3280, 2954, 2924, 2854, 1741, 1652, 1628, 1556, 1522, 1463, 1435, 1413, 1377, 1272, 1259, 1247, 1228, 1197, 1176, 826. UV/vis (ethanol, nm): λ_{max} (ε)=297 (7965 $M^{-1}\,cm^{-1}$). HRMS (EI) calcd for $C_{18}H_{17}NO_5$ [M^+]: 327.1107; found: 327.1100.

4.2.9. *N*-[(8-Methoxynaphtho[2,1-*b*]furan-1-yl)ethanoyl]-aspartic acid dimethyl ester, Nfm-Asp(OMe)-OMe (7g). The product of the reaction of Nfm-OH (**2a**) (0.10 g, 3.90×10^{-4}) with aspartic acid dimethyl ester hydrochloride (**5e**) (0.193 g, 9.75×10^{-4} mol) was chromatographed using ethyl acetate/*n*-hexane 4:6, as the eluent to give compound **7g** as a white solid (0.153 g; 98%). Mp=136.8–137.7 °C. TLC (ethyl acetate/*n*-hexane, 6:4): R_f 0.46. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.60–2.70 (m, 1H, β-CH Asp), 2.80–2.90 (m, 1H, β-CH Asp), 3.15 (s, 3H, OCH_3 Asp, side-chain), 3.49 (s, 3H, OCH_3 Asp, main chain), 3.95 (s, 3H, OCH_3), 4.00 (s, 2H, CH_2), 4.78–4.87 (m, 1H, α-CH Asp), 6.69 (d, J=7.5 Hz, 1H, α-NH Asp), 7.13 (dd, J=2.40 and 8.9 Hz, 1H, H-7), 7.45 (d, J=2.4 Hz, 1H, H-9), 7.50 (d, J=9.0 Hz, 1H, H-4), 7.66 (d, J=8.7 Hz, 1H, H-5), 7.72 (s, 1H, H-2), 7.82 (d, J=9.0 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ_C=33.86 (CH_2), 35.60 (β-CH_2 Asp), 48.45 (α-CH Asp), 51.49 (OCH_3 Asp, side-chain), 52.50 (OCH_3 Asp, main chain), 55.48 (OCH_3), 102.34 (C-9), 110.12 (C-4), 114.91 (C-1), 116.47 (C-7), 119.90 (C-3b), 125.51 (C-5a), 126.06 (C-5), 129.30 (C-5b), 130.28 (C-6), 142.75 (C-2), 154.43 (C-3a), 158.45 (C-8), 170.00 (CONH), 170.58 (CO_2CH_3 Asp, main chain), 170.70 (CO_2CH_3 Asp, side-chain). IR (KBr 1%, cm^{-1}): ν=3333, 2954, 2924, 2854, 1739, 1648, 1627, 1598, 1519, 1463, 1436, 1400, 1378, 1304, 1228, 1200, 1178, 1120, 1107, 1060, 1040, 1024. UV/vis (ethanol, nm): λ_{max} (ε)=298 (7856 $M^{-1}\,cm^{-1}$). HRMS (EI) calcd for $C_{21}H_{21}NO_7$ [M^+]: 399.1318; found: 399.1319.

4.2.10. *N*-[(8-Methoxynaphtho[2,1-*b*]furan-1-yl)ethanoyl]glutamic acid dimethyl ester, Nfm-Glu(OMe)-OMe (7h). The product of the reaction of Nfm-OH (**2a**) (0.10 g, 3.90×10^{-4} mol) with glutamic acid dimethyl ester hydrochloride (**5f**) was chromatographed using ethyl acetate/*n*-hexane 2:8, as the eluent to give compound **7h** as a white solid (0.160 g, 98%). Mp=166.3–169.0 °C. TLC (ethyl acetate/*n*-hexane, 7:3): R_f 0.48. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.60–1.80 (m, 2H, β-CH_2 Glu), 1.82–2.00 (m, 2H, γ-CH_2 Glu), 3.49 (s, 3H, OCH_3 Glu), 3.50 (s, 3H, OCH_3 Glu), 3.94 (s, 3H, OCH_3), 3.99 (s, 2H, CH_2), 4.52–4.64 (m, 1H, α-CH Glu), 6.42 (d, J=7.8 Hz, 1H, α-NH Glu), 7.12 (dd, J=8.9 and 2.4 Hz, 1H, H-7), 7.44–7.55 (m, 2H, H-9 and H-4), 7.65–7.75 (m, 2H, H-5 and H-2), 7.82 (d, J=9.0 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ_C=26.63 (β-CH_2 Glu), 29.34 (γ-CH_2 Glu), 33.93 (CH_2), 51.58 (OCH_3 Glu, main chain), 51.72 (α-CH Glu), 52.23 (OCH_3 Glu, side-chain), 55.46 (OCH_3), 102.28 (C-9), 110.02 (C-4), 115.00 (C-1), 116.52 (C-7), 119.94 (C-3b), 125.53 (C-5a), 126.19 (C-5), 129.28 (C-5b), 130.35 (C-6), 142.74 (C-2), 154.43 (C-3a), 158.55 (C-8), 170.31 (CONH), 171.61 (CO_2CH_3 Glu, main chain), 172.86 (CO_2CH_3 Glu, side-chain). IR (Nujol, cm^{-1}): ν=3311, 2954, 2925, 2854, 1761, 1715, 1651, 1628, 1531, 1463, 1377, 1271, 1230, 1177, 1134, 1120, 1035, 1018, 829. UV/vis (ethanol, nm): λ_{max} (ε)=298 (6716 $M^{-1}\,cm^{-1}$). HRMS (EI) calcd for $C_{22}H_{23}NO_7$ [M^+]: 413.1475; found: 413.1476.

4.2.11. *N*-Acetyl-ω-[(8-methoxynaphtho[2,1-*b*]furan-1-yl)ethanoyl]lysine methyl ester, Ac-Lys(Nfm)-OMe (9). The product of the reaction of Nfm-OH (**2a**) (0.10 g, 3.90×10^{-4} mol) with *N*-acetyl-lysine methyl ester hydrochloride (**8**) was chromatographed using ethyl acetate/*n*-hexane 3:7, as the eluent to give compound **9** as a white solid (0.122 g, 71%). Mp=185.7–186.9 °C. TLC (chloroform/methanol, 5.8:0.2): R_f 0.46. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=0.95–1.15 (m, 2H, γ-CH_2 Lys), 1.20–1.50 (m, 4H, β-CH_2 Lys and δ-CH_2 Lys), 1.97 (s, 3H, CH_3 Ac), 3.00–3.60 (m, 2H, ε-CH_2 Lys), 3.69 (s, 3H, OCH_3 Lys), 3.96 (s, 5H, OCH_3 and CH_2), 4.35–4.45 (m, 1H, α-CH Lys), 5.82 (t, J=6.0 Hz, 1H, NH Lys, side-chain), 5.95 (d, J=7.8 Hz, 1H, α-NH Lys), 7.15 (dd, J=9.0 and 2.4 Hz, 1H, H-7), 7.49 (d, J=2.4 Hz, 1H, H-9), 7.52 (d, J=9.0 Hz, 1H, H-4), 7.70 (s, 1H, H-2), 7.72 (d, J=9.0 Hz, 1H, H-5), 7.85 (d, J=9.0 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ_C=22.23 (γ-CH_2 Lys), 23.00 (CH_3 Ac), 28.84 (β-CH_2 Lys), 31.65 (δ-CH_2 Lys), 33.97 (CH_2), 39.07 (ε-CH_2 Lys), 51.73 (α-CH Lys), 52.28 (OCH_3 Lys), 55.57 (OCH_3), 102.50 (C-9), 110.05 (C-4), 115.36 (C-1), 116.55 (C-7), 119.98 (C-3b), 125.52 (C-5a), 126.25 (C-5), 129.32 (C-5b), 130.40 (C-6), 142.72 (C-2), 154.41 (C-3a), 158.58 (C-8), 169.90 (CONH Ac), 170.32 (CONH), 172.84 (CO_2CH_3). IR (KBr 1%, cm^{-1}): ν=3289, 3077, 2951,

2931, 2859, 1748, 1651, 1633, 1601, 1550, 1525, 1474, 1464, 1454, 1434, 1415, 1375, 1359, 1290, 1258, 1231, 1200, 1180, 1146, 830. UV/vis (ethanol, nm): λ_{max} (ε)=297 (5333 $M^{-1}\,cm^{-1}$). HRMS (EI) calcd for $C_{24}H_{28}N_2O_6$ [M^+]: 440.1947; found: 440.1948.

4.2.12. *N*-*tert*-Butyloxycarbonyl-*O*-[(5-methoxybenzofuran-1-yl)ethanoyl]serine methyl ester, Boc-Ser(Bfm)-OMe (11). The product of the reaction of Bfm-OH (**1**) (0.087 g, 4.22×10^{-4} mol) with *N*-*tert*-butyloxycarbonylserine methyl ester (**10**) was chromatographed using chloroform as the eluent to give compound **11** as a brown oil (0.111 g, 65%). TLC (chloroform): R_f 0.23. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.43 (s, 9H, C(CH_3)$_3$), 3.63–3.67 (m, 5H, CH_2 and OCH_3), 3.70 (s, 3H, OCH_3 Ser), 3.83 (s, 3H, OCH_3), 4.35–4.53 (m, 2H, β-CH_2 Ser), 4.54–4.57 (m, 1H, α-CH Ser), 5.25 (d, J=7.5 Hz, 1H, α-NH Ser), 6.89 (dd, J=2.4 and 8.4 Hz, 1H, H-6), 6.99 (d, J=2.4 Hz, 1H, H-4), 7.39 (d, J=8.4 Hz, 1H, H-7), 7.50 (s, 1H, H-2). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ_C=28.16 (C(*C*H_3)$_3$), 29.47 (CH_2), 64.68 (β-CH_2 Ser), 52.59 (OCH_3 Ser), 52.74 (α-CH Ser), 55.60 (OCH_3), 80.25 (*C*(CH_3)$_3$), 95.94 (C-4), 111.83 (C-6), 112.45 (C-3a), 119.62 (C-7), 120.71 (C-7a), 141.87 (C-2), 155.02 (*C*O_2C(CH_3)$_3$), 156.13 (C-3a), 158.15 (C-5), 170.04 (*C*O_2CH_3), 171.10 (CH_2*C*O_2). IR (KBr 1%, cm^{-1}): ν=3293, 3044, 3030, 3000, 2946, 1752, 1733, 1660, 1629, 1612, 1597, 1554, 1498, 1450. UV/vis (ethanol, nm): λ_{max} (ε)=287 (5427 $M^{-1}\,cm^{-1}$).

4.2.13. *N*-*tert*-Butyloxycarbonyl-*O*-[(8-methoxynaphtho[2,1-*b*]furan-1-yl)ethanoyl]serine methyl ester, Boc-Ser(Nfm)-OMe (12). The product of the reaction of Nfm-OH (**2a**) (0.095 g, 3.71×10^{-4} mol) with *N*-*tert*-butyloxycarbonylserine methyl ester (**10**) methyl ester hydrochloride was chromatographed using ethyl acetate/*n*-hexane 2:8, as the eluent to give compound **12** as an off-white oil (0.092 g, 54%). TLC (ethyl acetate/*n*-hexane, 4:6): R_f 0.47. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.42 (s, 9H, C(CH_3)$_3$), 3.45 (s, 3H, OCH_3 Ser), 3.99 (s, 3H, OCH_3), 4.07 (s, 2H, CH_2), 4.40–4.48 (m, 2H, β-CH_2 Ser), 4.50–4.60 (m, 1H, α-CH Ser), 5.18 (d, J=7.5 Hz, 1H, α-NH Ser), 7.16 (dd, J=8.9 and 2.7 Hz, 1H, H-7), 7.51 (d, J=9.0 Hz, 1H, H-4), 7.58 (d, J=2.7 Hz, 1H, H-9), 7.67 (d, J=9.0 Hz, 1H, H-5), 7.69 (s, 1H, H-2), 7.86 (d, J=9.0 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ_C=28.20 (C(*C*H_3)$_3$), 31.73 (CH_2), 52.42 (OCH_3 Ser), 52.78 (α-CH Ser), 55.42 (OCH_3), 65.06 (β-CH_2 Ser), 80.31 (*C*(CH_3)$_3$), 103.08 (C-9), 110.22 (C-4), 114.23 (C-1), 115.65 (C-7), 120.15 (C-3b), 125.70 (C-5a), 125.77 (C-5), 129.36 (C-5b), 130.51 (C-6), 142.45 (C-2), 153.99 (C-3a), 155.07 (*C*O_2C(CH_3)$_3$), 158.27 (C-8), 169.73 (*C*O_2CH_3), 170.43 (CH_2*C*O_2). IR (KBr 1%, cm^{-1}): ν=3376, 2977, 2839, 1745, 1720, 1707, 1629, 1598, 1519, 1505, 1474, 1436, 1367, 1232, 1161, 1121, 1060, 1022, 950, 876, 830. UV/vis (ethanol, nm): λ_{max} (ε)=298 (12705 $M^{-1}\,cm^{-1}$). HRMS (EI) calcd for $C_{24}H_{27}NO_8$ [M^+]: 457.1737; found: 457.1736.

4.3. Stability tests with Nfm-Phe-OMe (7a)

4.3.1. Catalytic hydrogenation. A suspension of Nfm-Phe-OMe (**7a**) (4.0×10^{-2} g, 9.58×10^{-5} mol) in methanol (1.0 mL) and 1,4-cyclohexadiene (9.6×10^{-2} mL, 2.58×10^{-4} mol) was mixed with 10% palladium on charcoal catalyst (0.014 g) and refluxed for 7 h with stirring. The catalyst was filtered off and washed with methanol; the combined liquids were then evaporated under reduced pressure affording the compound as a white solid (3.8×10^{-2} g, 95%). ^{1}H NMR was well compared with the starting material.

4.3.2. Acidolysis with hydrochloric acid. To the fully protected amino acid Nfm-Phe-OMe (**7a**) (2.01×10^{-2} g, 4.36×10^{-5} mol) was added 6 M HCl (0.20 mL) under rapid stirring over 1 h. Evaporation under reduced pressure gave a white solid (2.01×10^{-2} g, 100%). ^{1}H NMR confirmed the structure of the compound.

4.3.3. Acidolysis with trifluoroacetic acid. To the fully protected amino acid Nfm-Phe-OMe (**7a**) (2.2×10^{-2} g, 5.27×10^{-5} mol) was added 0.74 mL of trifluoroacetic acid under rapid stirring over 5 h. Evaporation under reduced pressure gave a white solid (2.2×10^{-2} g, 100%). ^{1}H NMR confirmed the structure of the compound.

4.3.4. Aminolysis. A solution of Nfm-Phe-OMe (**7a**) (2.0×10^{-2} g, 4.79×10^{-5} mol) in dry acetonitrile was treated with DEAEA (4.1×10^{-2} mL, 2.87×10^{-4} mol) for 27 h according to the procedure of Grehn et al.[27] The product was purified by flash chromatography, using chloroform/*n*-hexane 6:1, as the eluent, to give the compound as an oily solid (1.7×10^{-2} g, 85%). ^{1}H NMR was well compared with the starting material.

4.3.5. Reduction with Mg/MeOH. To a solution of Nfm-Phe-OMe (**7a**) (2.0×10^{-2} g, 4.33×10^{-5} mol) in dry methanol (2 mL) magnesium powder (1.0×10^{-2} g, 4.11×10^{-5} mol) was added and the resulting mixture was sonicated for 2.30 h, at room temperature. More magnesium was added (3.2×10^{-2} g, 1.32×10^{-5} mol), in small portions (1.0×10^{-2} g each) and the resulting mixture was sonicated for another 7 h. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (4 mL) and extracted with ethyl acetate. The organic layer was dried with $MgSO_4$, concentrated to dryness to give an off-white oil (1.9×10^{-2} g, 95%). ^{1}H NMR was well compared with the starting material.

4.3.6. Alkaline hydrolysis. To the fully protected amino acid Nfm-Phe-OMe (**7a**) (2.0×10^{-2} g, 4.79×10^{-5} mol) in 1,4-dioxane (2 mL), 1 M NaOH (7.2×10^{-2} mL, 7.19×10^{-5} mol) was added at low temperature. The solution was stirred at 0 °C for 5 h and acidified to pH 3 with 1 M $KHSO_4$. After extraction with ethyl acetate and evaporation of the solvent, Nfm-Phe-OH (**13**) was obtained as an orange solid (0.019 g, 100%). Mp=191.0–193.0 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.80–2.90 (m, 2H, β-CH_2 Phe), 3.87 (s, 3H, OCH_3), 3.95 (s, 2H, CH_2), 4.80–4.90 (m, 1H, α-CH Phe), 6.12 (d, J=7.8 Hz, 1H, α-NH Phe), 6.48 (d, J=6.9 Hz, 2H, H-2 and H-6 Phe), 6.73 (t, J=7.5 Hz, 2H, H-3 and H-5 Phe), 6.91 (t, J=7.5 Hz, 1H, H-4 Phe), 7.13 (dd, J=9.3 and 2.4 Hz, 1H, H-7), 7.41 (d, J=2.4 Hz, 1H, H-9), 7.52 (d, J=9.0 Hz, 1H, H-4), 7.58 (s, 1H, H-2), 7.72 (d, J=8.7 Hz, 1H, H-5), 7.85 (d, J=9.0 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ_C=33.72 (CH_2), 36.92 (β-CH_2 Phe), 52.91 (α-CH Phe), 55.51 (OCH_3), 102.20 (C-9), 109.99 (C-4), 114.63 (C-1), 116.80 (C-7), 119.84 (C-3b),

125.67 (C-5a), 126.36 (C-5), 126.98 (C-4 Phe), 128.19 (C-3 and C-5 Phe), 128.56 (C-2 and C-6 Phe), 129.34 (C-5b), 130.44 (C-6), 134.53 (C-1), 142.83 (C-2), 154.47 (C-3a), 158.67 (C-8), 170.88 (CONH), 174.16 (CO_2H). IR (Nujol, cm^{-1}): ν=3399, 3383, 2954, 2923, 2854, 2586, 1731, 1626, 1538, 1522, 1497, 1463, 1455, 1431, 1418, 1378, 1357, 1259, 1228, 1208, 1178, 1122, 1103, 1084, 1037, 1016, 831. HRMS (EI) calcd for $C_{24}H_{21}NO_5$ [M^+]: 403.1420; found: 403.1432.

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References and notes

1. Ivancia-Jelecki, J.; Baricevic, M.; Santak, M.; Forcia, D. *Anal. Biochem.* **2006**, *349*, 277.
2. Liu, Y.; Xu, Y.; Qian, X.; Liu, J.; Shen, L.; Li, J.; Zhang, Y. *Bioorg. Med. Chem.* **2006**, *14*, 2935.
3. Ros-Lis, J. V.; Garcia, B.; Jiménez, D.; Martínez-Mánez, R.; Sancenón, F.; Soto, J.; Gonzalvo, F.; Valldecabres, M. C. *J. Am. Chem. Soc.* **2004**, *126*, 4064.
4. Li, X.; Ma, H.; Dong, S.; Duan, X.; Liang, S. *Talanta* **2004**, *62*, 367.
5. Brendan, W. B.; Steven, R. W.; Robert, T. K. *Anal. Chem.* **2000**, *72*, 865.
6. Zhu, Q.; Li, D. B.; Uttamchandani, M.; Yao, S. Q. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1033.
7. Inoue, H.; Fukunaga, K.; Munemura, S.; Tsuruta, Y. *Anal. Biochem.* **2005**, *339*, 191.
8. Kuroda, N.; Sugihara, S.; Sugihara, Y.; Wada, M.; Kishikawa, N.; Ohba, Y.; Nakashima, K. *J. Chromatogr., A* **2005**, *1066*, 119.
9. Cao, L.-W.; Wang, H.; Li, J.-S.; Zhang, H.-S. *J. Chromatogr., A* **2005**, *1063*, 143.
10. Hirano, J.; Hamase, K.; Fukuda, H.; Tomita, T.; Zaitsu, K. *J. Chromatogr., A* **2004**, *1059*, 225.
11. Haj-Yehia, A. I.; Benet, L. Z. *J. Chromatogr., B* **1995**, *666*, 45.
12. Abdul-Aziz, M.; Auping, J. V.; Meador, M. A. *J. Org. Chem.* **1995**, *60*, 1303.
13. Ishiguro, K.; Ohira, Y.; Oku, H. *J. Nat. Prod.* **1998**, *61*, 1126.
14. Zubaidha, P. K.; Chavan, S. P.; Racherla, U. S.; Ayyangar, N. R. *Tetrahedron* **1991**, *47*, 5759.
15. Hofnung, M.; Quillardet, P.; Michel, V.; Touati, E. *Res. Microbiol.* **2002**, 427.
16. Lee, K.-H.; Huang, B.-R. *Eur. J. Med. Chem.* **2002**, *37*, 333.
17. del Carmen Cruz, M.; Tamariz, J. *Tetrahedron Lett.* **2004**, *45*, 2377.
18. Xie, X.; Chen, B.; Lu, J.; Han, J.; She, X.; Pan, X. *Tetrahedron Lett.* **2004**, *45*, 6235.
19. Yavari, I.; Anary-Abbasinejad, M.; Alizadeh, A. *Tetrahedron Lett.* **2002**, *43*, 4503.
20. Hagiwara, H.; Sato, K.; Nishino, D.; Hoshi, T.; Suzuki, T.; Ando, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2946.
21. Meshram, H. M.; Sekhar, K. C.; Ganesh, Y. S. S.; Yadav, J. S. *Synlett* **2000**, 1273.
22. Frade, V. H. J.; Gonçalves, M. S. T.; Moura, J. C. V. P. *Tetrahedron Lett.* **2005**, *46*, 4949.
23. Costa, S. P. G.; Batista, R. M. F.; Cardoso, P.; Belsley, M.; Raposo, M. M. M. *Eur. J. Org. Chem.*, in press. doi:10.1002/ejoc.200600059.
24. Piloto, A. M.; Costa, S. P. G.; Gonçalves, M. S. T. *Tetrahedron Lett.* **2005**, *46*, 4757.
25. Furuta, T.; Wang, S. S.-H.; Dantzker, J. L.; Dore, T. M.; Bybee, W. J.; Callaway, E. M.; Denk, W.; Tsien, R. Y. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 1193.
26. Morris, J. V.; Mahaney, M. A.; Huber, J. R. *J. Phys. Chem.* **1976**, *80*, 969.
27. Grehn, L.; Gunnarson, K.; Ragnarsson, U. *Acta Chem. Scand., Ser. B* **1987**, *41*, 18.
28. Maia, H. L. S.; Monteiro, L. S.; Sebastião, J. *Eur. J. Org. Chem.* **2001**, 1967.
29. Bodanszky, M.; Bodanszky, A. *The Practice of Peptide Synthesis*; Springer: Berlin, 1984.

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A synthesis of optically active α-quaternary α-amino acids and esters by assembling three components, ketones, (*R*)-chloromethyl *p*-tolyl sulfoxide, and sodium azide, via sulfinyloxiranes

Tsuyoshi Satoh,* Mizue Hirano, Akio Kuroiwa and Youhei Kaneko

Department of Chemistry, Faculty of Science, Tokyo University of Science, Ichigaya-funagawara-machi 12, Shinjuku-ku, Tokyo 162-0826, Japan

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Abstract—Treatment of lithium α-sulfinyl carbanion of chloromethyl *p*-tolyl sulfoxides with ketones at low temperature afforded adducts in almost quantitative yields, which were exposed to *t*-BuOK to give sulfinyloxiranes in high yields. The sulfinyloxirane was reacted with benzylamine to give α-amino aldehyde, which was oxidized with iodine in methanol to afford α-amino carboxylic ester in moderate yield. The sulfinyloxiranes were treated with sodium azide to afford α-azido aldehydes in good yields. Oxidation with $NaClO_2$ followed by catalytic hydrogenation of the azido group of the α-azido aldehydes gave α-quaternary α-amino acids in good overall yields. The oxidation of the azido aldehydes with iodine in methanol in the presence of KOH followed by the catalytic hydrogenation resulted in α-quaternary α-amino acid methyl esters in good yields. When these reactions were carried out starting from unsymmetrical ketones and optically pure (*R*)-chloromethyl *p*-tolyl sulfoxide, a new method for a synthesis of optically active α-quaternary α-amino acids and esters in good overall yields was realized.

1. Introduction

Optically active α,α-disubstituted (α-quaternary) α-amino acids and their derivatives, including cyclic α-amino acids with the α-carbon embedded in the ring, have recently received considerable attention. α-Quaternary α-amino acids, in some case, are found as antibiotics, for example, lactacystin.[1] Very interestingly, α-methylisoleucine, α-methylalloisoleucine, and α-methylnorvaline have been found as meteoritic α-amino acids form the Murchison meteorite.[2]

Cyclic α-quaternary α-amino acids are also quite interesting compounds. For instance, 1-aminocyclopropane carboxylic acid is known to be the biosynthetic precursor of the plant hormone, ethylene.[3] 1-Aminocyclopentane-1,3-dicarboxylic acid acts as a metabotropic glutamate receptor (mGluR) agonist.[4] Recently, α-quaternary α-amino acids and cyclic α-amino acids are used in controlling peptide secondary structures.[5] Synthesis of α-quaternary α-amino acids[6] and cyclic α-amino acids[7] are actively investigated recently because of the importance of these compounds in molecular biology and synthetic organic chemistry as mentioned above.

We have also been interested in the synthesis of α-amino acids, including optically active α-quaternary α-amino acids and their derivatives, and cyclic α-amino acids.[8] In continuation of our investigation concerning the development of new synthetic methods for α-amino acids, we recently realized a new method for synthesis of α-quaternary α-amino acids and cyclic α-amino acids **5** from ketones **1**, chloromethyl *p*-tolyl sulfoxide **2**, and nitrogen nucleophiles (benzylamine or sodium azide). The key reaction is the nucleophilic opening of sulfinyloxiranes **3** with the nitrogen nucleophiles to afford aldehydes **4**. This method was developed into an asymmetric synthesis by using unsymmetrical ketones with optically active (*R*)-chloromethyl *p*-tolyl sulfoxide **2** (Scheme 1).[9]

2. Results and discussion

2.1. Synthesis of α-quaternary α-amino acid methyl ester from a sulfinyloxirane with benzylamine as a nitrogen nucleophile

We previously reported a method for synthesizing α-amino ketones and α-amino aldehydes by nucleophilic opening of sulfinyloxiranes with several amines.[10] Based on these experiences, at first, a synthesis of cyclic α-amino acid was investigated starting from cyclopentadecanone (Scheme 2).

Keywords: α-Amino acid; α-Quaternary α-amino acid; Cyclic α-amino acid; Sulfinyloxirane; Asymmetric synthesis.
* Corresponding author. Tel.: +3 5228 8272; fax: +3 5261 4631; e-mail: tsatoh@ch.kagu.tus.ac.jp

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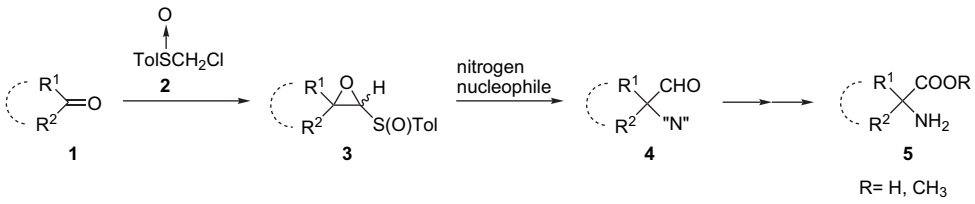
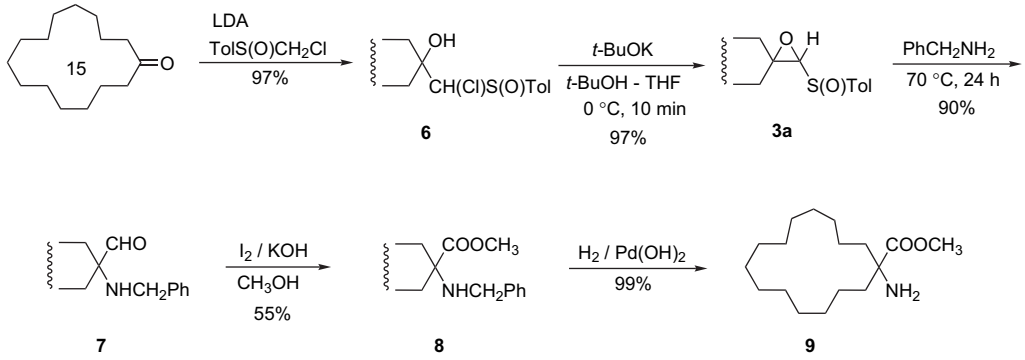


Scheme 1.



Scheme 2.

Lithium α-sulfinyl carbanion of chloromethyl *p*-tolyl sulfoxide at −78 °C was treated with cyclopentadecanone to give the adduct **6** in almost quantitative yield.[11] Treatment of **6** with 1.3 equiv of *t*-BuOK in a mixture of *t*-BuOH and THF at 0 °C resulted in the formation of sulfinyloxirane **3a** in 97% yield as crystals.[12] The sulfinyloxirane **3a** was warmed at 70 °C in 9 equiv of benzylamine without a solvent for 24 h to give cleanly the desired α-amino aldehyde **7** as crystals in 90% yield.

Next, we tried to oxidize the aldehyde group in **7** to a carboxylic acid or an ester group in the presence of amino group in the molecule, which is recognized to be rather difficult. After some examinations of the oxidation, a somewhat old-fashioned oxidation using iodine, reported by Inch,[13] was found to be successful. Thus, aldehyde **7** was treated with a solution of KOH and iodine in methanol at room temperature for 20 min to give the desired methyl ester **8** in 55% yield. However, the oxidation was found to be sensitive to the reaction conditions and the yield of **8** was variable and reproducibility was low. Finally, the benzyl group on the nitrogen of the ester **8** was removed under hydrogenolysis conditions using $Pd(OH)_2$ as a catalyst to afford cyclic α-amino acid methyl ester **9** in quantitative yield.

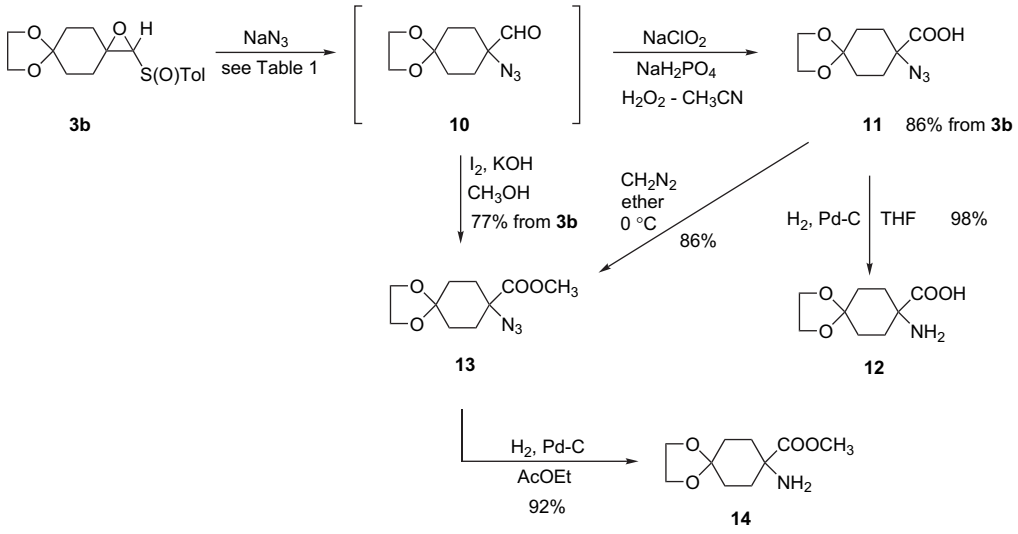
2.2. Synthesis of α-quaternary α-amino acids and methyl esters by the nucleophilic ring-opening of the sulfinyloxiranes with azido anion as a nitrogen nucleophile

As mentioned above, because of the oxidation of the aldehyde group in the presence of an amino group in the same molecule was found to be difficult, we next planned to use the azido anion as the nitrogen nucleophile expecting formation of azido aldehydes. We used sulfinyloxirane **3b**, synthesized from 1,4-cyclohexanedione mono ethylene ketal in the same way as described above, as a representative substrate of the investigation (Scheme 3).

At first, we started to find the reaction conditions concerning the ring-opening of sulfinyloxirane **3b** with sodium azide and the results of the investigation are summarized in Table 1. Initially, sulfinyloxirane **3b** was treated with NaN_3 (3 equiv) in DMSO at the concentration of 0.1 mol/L at 65 °C (entry 1). The starting material disappeared after 43 h and the desired azido aldehyde **10** was obtained; however, purification of **10** was found to be rather difficult and it appeared that **10** was somewhat unstable. The crude **10**, without further purification, was oxidized with $NaClO_2$ in the presence of H_2O_2 in acetonitrile[14] to afford the azido carboxylic acid **11** in 65% overall yield from **3b** (Table 1, entry 1).

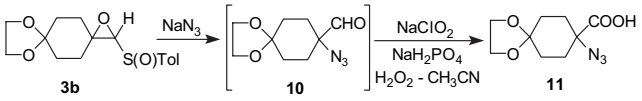
Improvement of the yield of **11** was studied (entries 2–6). The reaction time could be reduced by addition of 15-crown-5 in the reaction mixture; however, the yield was not improved (entry 2). Using higher concentration of the reaction mixture gave a worse result (entry 3). Using lower concentration of the reaction mixture showed no effect (entry 4). Finally, we changed the conditions of this reaction from an aprotic solvent to a protic solvent reported by Caron and Sharpless[15] and Crotti and co-workers[16] (entries 5 and 6). A solution of **3b** with NaN_3 (3 equiv) in methanol in the presence of water and ammonium chloride was refluxed for 16 h and the product **10** was oxidized to give **11** in much higher yield (82%). The best yield of **11** was obtained when 5 equiv of NaN_3 was used (entry 6).

Hydrogenation of the azido group in **11** was successfully carried out in THF with 10% Pd–C to give the desired cyclic quaternary α-amino acid **12** in quantitative yield (Scheme 3). In the case of a synthesis of α-amino acid ester directly from sulfinyloxirane **3b**, the crude azido aldehyde **10** was oxidized with iodine in methanol in the same way as described above for the synthesis of **8** (see Scheme 2). This reaction worked to afford the desired azido methyl ester **13** in 77% overall yield from **3b**. The same azido methyl ester **13** was



Scheme 3.

Table 1. Reaction of sulfinyloxirane **3b** with NaN_3 followed by oxidation of the resultant azido aldehyde **10** with $NaClO_2$



Entry	NaN_3/ equiv	Solvent	Concentration (mol/L)	Conditions	Yield of **11**[a]/%
1	3	DMSO	0.1	65 °C, 43 h	65
2	3[b]	DMSO	0.1	60 °C, 34 h	61
3	3	DMSO	0.5	65 °C, 36 h	24
4	3	DMSO	0.05	65 °C, 43 h	61
5	3	MeOH–H_2O (8:1)[c]	0.1	Reflux, 16 h	82
6	5	MeOH–H_2O (8:1)[c]	0.1	Reflux, 12 h	86

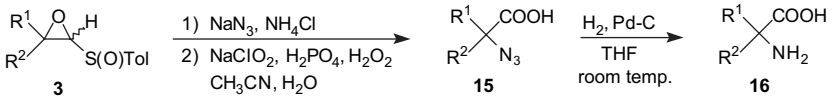
[a] Two-step overall yield from **3b**.
[b] 15-Crown-5 of 3.6 equiv was added.
[c] In the presence of NH_4Cl.

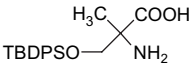
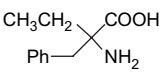
obtained from the azido carboxylic acid **11** by ester formation with diazomethane in 86% yield. Finally, the azido methyl ester **13** was catalytically reduced in ethyl acetate with Pd–C as a catalyst to give the desired cyclic quaternary α-amino acid methyl ester **14** in high yield.

In order to know the generality of this method for synthesis of α-quaternary α-amino acids and esters, we carried out the reactions using other ketones and the results are summarized in Tables 2 and 3. Table 2 shows the synthesis of α-quaternary α-amino acids, **16a** and **16b**, starting from *tert*-butyldiphenylsilyloxy-2-propanone and 1-phenyl-2-butanone, respectively. Sulfinyloxiranes **3c** and **3d** were synthesized from the ketones in quantitative yields. Ring-opening of the sulfinyloxiranes with NaN_3 followed by oxidation of the resultant aldehyde to azido carboxylic acids **15a** and **15b** proceeded quite smoothly. Finally, reduction of the azido group took place without any problem to afford the desired α-quaternary α-amino acids (**16a** and **16b**) in quantitative yields. It is worth noting that **16a** is an α-methylserine derivative and **16b** is an α-ethylphenylalanine. Asymmetric synthesis of these amino acids is discussed later (vide infra).

The results for the synthesis of α-quaternary α-amino acid methyl esters, including cyclic congeners, are summarized in Table 3. Starting from cyclobutanone, cyclodecanone, and cyclododecanone, the desired cyclic α-quaternary α-amino acid methyl esters were synthesized in good overall

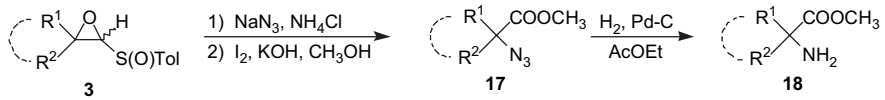
Table 2. Synthesis of α-quaternary α-amino acids **16** from sulfinyloxiranes **3** via α-azido carboxylic acids **15**

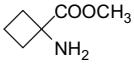
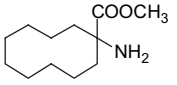
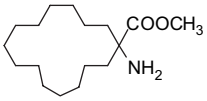
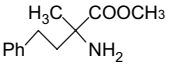
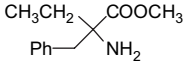


Entry	**3**				**15**		**16**		
		R^1	R^2	Yield/%[a]		Yield/%[b]			Yield/%
1	**3c**	CH_3	$TBDPSOCH_2$	98[c]	**15a**	94	**16a**		99
2	**3d**	CH_3CH_2	$PhCH_2$	98[d]	**15b**	87	**16b**		99

[a] Two-step overall yield from ketone.
[b] Two-step overall yield from **3**.
[c] A mixture of two diastereomers (70:30).
[d] A mixture of two diastereomers (65:35).

Table 3. Synthesis of α-quaternary α-amino acid methyl esters **18** from sulfinyloxiranes **3**



Entry	3				17		18	
		R^1	R^2	Yield/%[a]		Yield/%[b]		Yield/%
1	**3e**	$-(CH_2)_3-$		92	**17a**	55	**18a** 	98
2	**3f**	$-(CH_2)_9-$		80	**17b**	72	**18b** 	95
3	**3a**	$-(CH_2)_{14}-$		94	**17c**	75	**9** 	95
4	**3g**	CH_3	$PhCH_2CH_2$	90[c]	**17d**	67	**18c** 	99
5	**3d**	CH_3CH_2	$PhCH_2$	98[d]	**17e**	90	**18d** 	97

[a] Two-step overall yield from ketone.
[b] Two-step overall yield from **3**.
[c] A mixture of two diastereomers (59:41).
[d] A mixture of two diastereomers (65:35).

yield (entries 1–3). In the case of **3e**, the reaction of NaN_3 followed by oxidation with iodine gave moderate yield of azido ester **17a** (entry 1). The reactions starting from 4-phenyl-2-butanone and 1-phenyl-2-butanone gave **18c** and α-ethylphenylalanine methyl ester **18d**, respectively, in good overall yields (entries 4 and 5).

From the results described above, we concluded that the procedure mentioned above is highly applicable to many different kinds of ketones and a variety of α-quaternary α-amino acids and methyl esters could be synthesized.

2.3. Asymmetric synthesis of α-quaternary α-amino acids and methyl esters including cyclic congeners by using optically pure (*R*)-chloromethyl *p*-tolyl sulfoxide

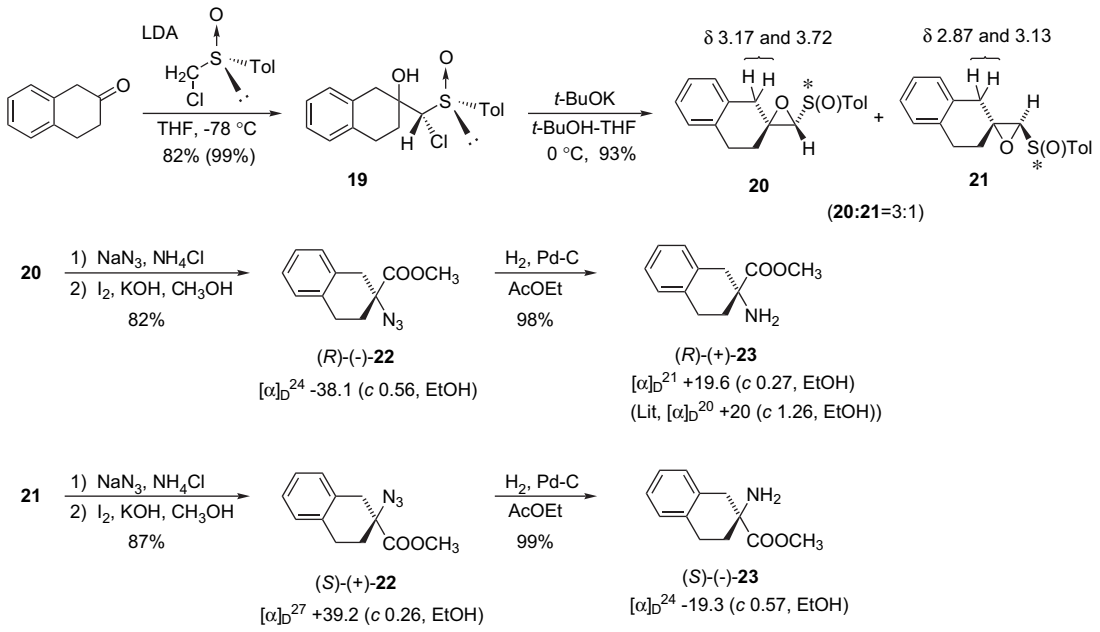
As a further development of this investigation, we next planned the asymmetric synthesis of α-quaternary α-amino acids and methyl esters including cyclic congeners by using optically pure (*R*)-chloromethyl *p*-tolyl sulfoxide. An asymmetric synthesis of methyl 2-aminotetraline-2-carboxylate, α-ethylphenylalanine and its methyl ester, and α-methylserine methyl ester is discussed below.

Asymmetric synthesis of both enantiomers of methyl 2-aminotetraline-2-carboxylate from β-tetralone is shown in Scheme 4. Lithium α-sulfinyl carbanion generated from optically pure (*R*)-chloromethyl *p*-tolyl sulfoxide[10b] with LDA at −78 °C was treated with β-tetralone to give the adduct **19** as a mixture of two diastereomers in 82% yield (99% yield calculated from the consumed sulfoxide).[17] Without separation, the mixture was treated with *t*-BuOK in a mixture of *t*-BuOH–THF at 0 °C to afford a 3:1 mixture of sulfinyloxiranes **20** and **21**. These sulfinyloxiranes were easily separated by silica gel column chromatography. The enantiomeric excess of **20** and **21** was determined to be over 99% by HPLC using CHIRALPAK AD as a chiral stationary column.

The absolute configuration of sulfinyloxiranes **20** and **21** could easily be determined as shown in Scheme 4. Thus, as we already reported, the addition reaction of the lithium α-sulfinyl carbanion of (*R*)-chloromethyl *p*-tolyl sulfoxide to carbonyl carbon was proved to induce *R* configuration at the carbon bearing the chlorine atom.[10b] The whole stereochemistry of the sulfinyloxiranes **20** and **21** was easily determined from the ^1H NMR spectrum. As shown in Scheme 4, the chemical shift of the benzylic hydrogens of the main product **20** was markedly lowered compared with those of **21**, which indicates that the benzylic carbon and the sulfinyl group of **20** should be cis.[10b]

The main product **20** was treated with NaN_3 in the same way as described above and the resulting azido aldehyde was oxidized with I_2 in methanol to give the desired azido methyl ester (*R*)-(−)-**22** in 82% overall yield from **20**. The enantiomeric excess of (*R*)-(−)-**22** was determined to be over 99% by HPLC using CHIRALCEL OD as a chiral stationary column. Finally, the catalytic hydrogenation of (*R*)-(−)-**22** with Pd–C/H_2 in ethyl acetate gave the expected (*R*)-(+)-methyl 2-aminotetraline-2-carboxylate (*R*)-(+)-**23** in a quantitative yield. All the spectral data and the specific rotations were highly consistent with the reported value.[18] The minor sulfinyloxirane **21** was treated with NaN_3 followed by I_2 in methanol to give the enantiomer of the azido methyl ester (*S*)-(+)-**22** in 87% yield. Finally, the catalytic hydrogenation of (*S*)-(+)-**22** gave (*S*)-(−)-**23** in a quantitative yield.

In continuation of the asymmetric synthesis of α-quaternary α-amino acids and their derivatives, an asymmetric synthesis

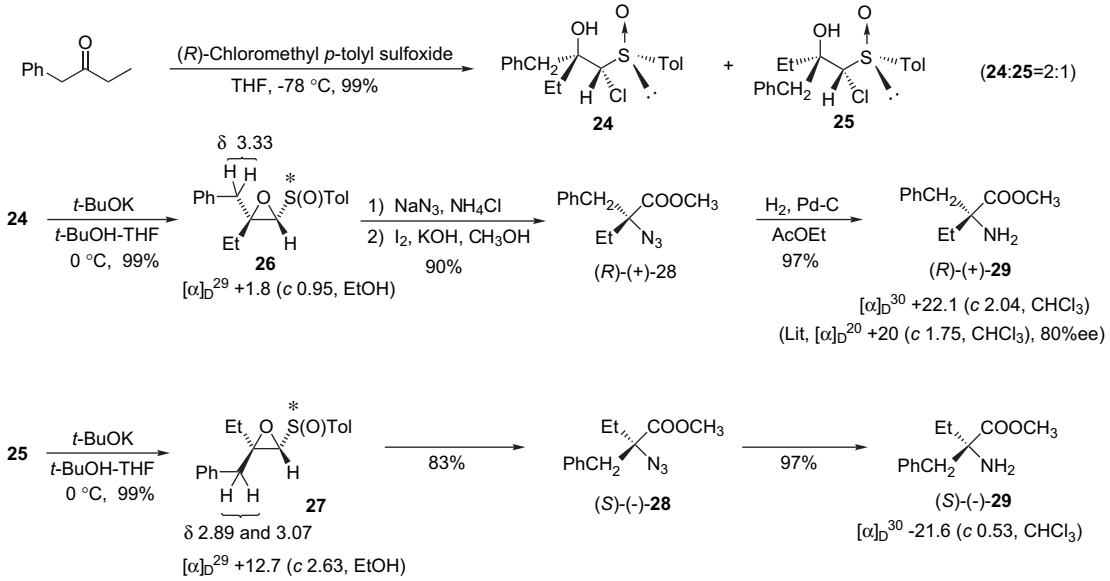


Scheme 4. Asymmetric synthesis of both enantiomers of methyl 2-aminotetraline-2-carboxylate **23** from β-tetralone and (*R*)-chloromethyl *p*-tolyl sulfoxide.

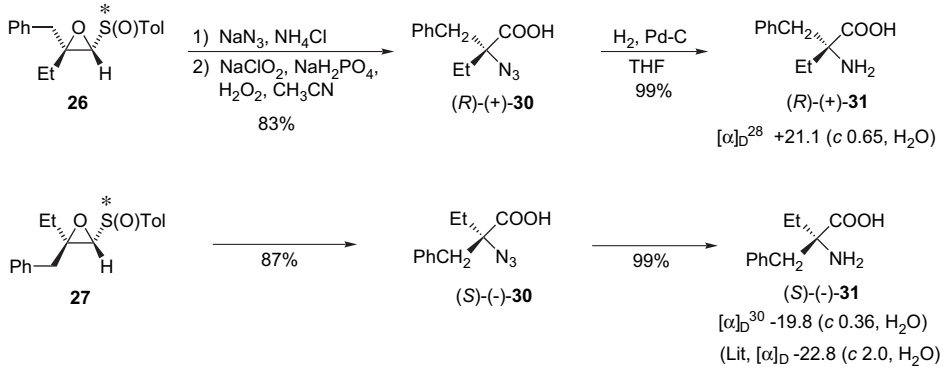
of both enantiomers of α-ethylphenylalanine methyl ester **29** and α-ethylphenylalanine **31** was investigated from 1-phenyl-2-butanone as shown in Schemes 5 and 6. At first, lithium α-carbanion of (*R*)-chloromethyl *p*-tolyl sulfoxide was reacted with 1-phenyl-2-butanone to give adducts **24** and **25** in quantitative yield. In this case, the ratio of the main product **24** and minor product **25** was 2:1. These adducts were separated by silica gel column chromatography and both were treated with *t*-BuOK to afford sulfinyloxiranes **26** and **27**, respectively, in quantitative yields.

The absolute structure of sulfinyloxiranes **26** and **27** was determined by the chemical shift of their ^{1}H NMR, as mentioned above, as shown in Scheme 5. The optical purity was determined to be over 99% by using HPLC with chiral column (CHIRALCEL OD). The main sulfinyloxirane **26** was treated with NaN_3 followed by iodine in methanol to give azido methyl ester (*R*)-**28** in 90% overall yield. Finally, the azido group in (*R*)-**28** was hydrogenated in ethyl acetate with Pd–C as a catalyst to give (*R*)-α-ethylphenylalanine methyl ester (*R*)-(+)-**29** in quantitative yield. All the spectral data and the specific rotations were highly consistent with the reported value.[19] In the same way, the minor sulfinyloxirane **27** gave (*S*)-α-ethylphenylalanine methyl ester (*S*)-(−)-**29** in good overall yield through azido methyl ester (*S*)-**28**.

Synthesis of α-amino acid itself, not its ester, is also quite important. We investigated the synthesis of both enantiomers of α-ethylphenylalanine **31** from the optically active



Scheme 5. Asymmetric synthesis of both enantiomers of α-ethylphenylalanine methyl ester **29** from 1-phenyl-2-butanone and (*R*)-chloromethyl *p*-tolyl sulfoxide.

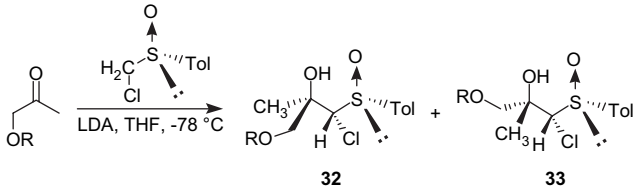


Scheme 6. Asymmetric synthesis of both enantiomers of α-ethylphenylalanine **31** from sulfinyloxiranes **26** and **27.**

sulfinyloxiranes **26** and **27** (Scheme 6). The main sulfinyloxirane **26** was treated with NaN_3 and the resultant azido aldehyde was oxidized with $NaClO_2$ to afford azido carboxylic acid (*R*)-(+)-**30** in 83% overall yield. The purified (*R*)-**30** was hydrogenated in THF with Pd–C as a catalyst to give the desired amino acid (*R*)-(+)-**31** in quantitative yield. Starting from the sulfinyloxirane **27** the enantiomer of α-ethylphenylalanine (*S*)-(−)-**31** was obtained in high overall yield and all the spectral data and the specific rotations were consistent with the reported value.[20] Purification of the α-amino acid **31** was performed as follows: After the hydrogenation, the catalyst was filtered off and the solvent was evaporated. The residue was dissolved in a small amount of water and the cloud was removed by passing the solution slowly through a pad of Celite. Water was evaporated and the residual crystals were recrystallized from methanol.

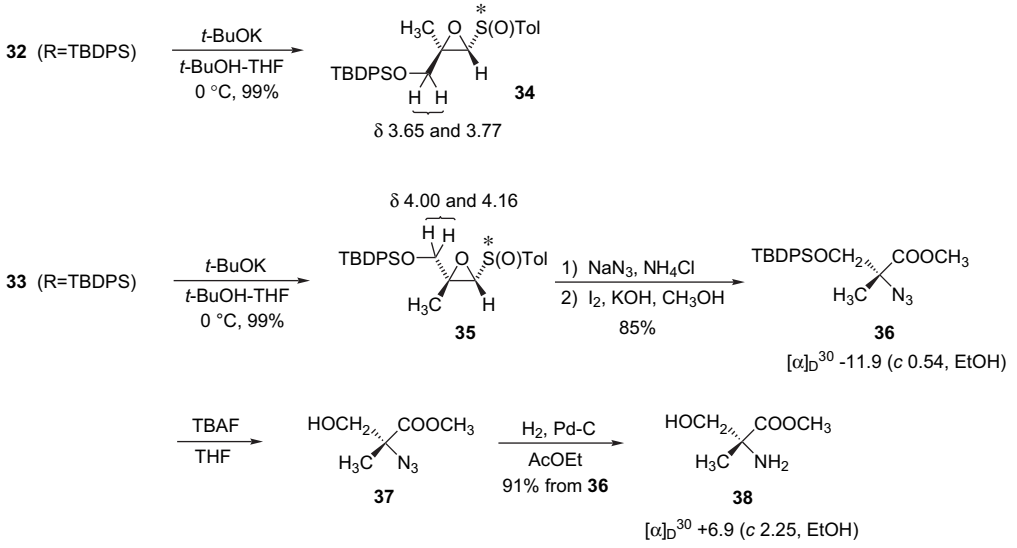
Finally, asymmetric synthesis of the serine derivative, (*R*)-α-methylserine methyl ester **38**, was investigated starting from hydroxyacetone (Scheme 7 and Table 4). First, diastereoselectivity of the addition reaction of lithium carbanion of chloromethyl *p*-tolyl sulfoxide with hydroxyacetone and its derivatives was studied and the results are summarized in Table 4.

Table 4. Diastereoselective addition of chloromethyl *p*-tolyl sulfoxide to *O*-protected acetols



Entry	R	LDA (equiv)	**32**:**33**	Yield/%
1	H	2.5	1:1	82
2	THP	1.2	1:1.5	99
3	TBDMS	1.5	1:2.0	94
4	TBDPS	1.5	1:2.3	99

The addition reaction of lithium α-sulfinyl carbanion of chloromethyl *p*-tolyl sulfoxide with hydroxyacetone itself gave adducts **32** and **33** in good yields; however, no diastereoselectivity was observed (entry 1). We synthesized *O*-protected hydroxyacetones and performed the addition reaction and found that the most bulky protecting group (TBDPS) showed the highest diastereoselectivity (entry 4).



Scheme 7. Asymmetric synthesis of (*R*)-α-methylserine methyl ester **38** from the main adduct of TBDPS-protected acetol and (*R*)-chloromethyl *p*-tolyl sulfoxide.

A synthesis of methylserine methyl ester **38** was investigated starting from this main adduct (R=TBDPS).

First, the minor adduct **32** and the main adduct **33** were converted to sulfinyloxiranes **34** and **35**, respectively, and the stereochemistry of these compounds was determined from ^{1}H NMR as mentioned above. Sulfinyloxirane **35** was treated with NaN_3 followed by iodine to give azido methyl ester **36** in good yield. The silyl protecting group of **36** was removed with TBAF to give the alcohol **37**, which was reduced with Pd–C as a catalyst in ethyl acetate to afford the desired α-methylserine methyl ester **38** in 91% overall yield from **36**.

In conclusion, a new method for the synthesis of α-quaternary α-amino acids and their methyl esters was realized starting from unsymmetrical ketones and chloromethyl *p*-tolyl sulfoxides through sulfinyloxiranes in good overall yields in relatively short steps. Asymmetric synthesis of α-quaternary α-amino acids and their methyl esters was also developed by using optically active chloromethyl *p*-tolyl sulfoxide. The absolute stereochemistry of the sulfinyloxiranes, at the same time absolute configuration of the amino acids or their esters, was easily determined from ^{1}H NMR of the optically active sulfinyloxiranes, which is one of the most striking characteristics of this method.

3. Experimental

3.1. General

All melting points are uncorrected. ^{1}H NMR spectra were measured in a $CDCl_3$ solution with JEOL JNM-LA 500 spectrometer. Electron-impact mass spectra (MS) were obtained at 70 eV by direct insertion. Silica gel 60 (Merck) containing 0.5% fluorescence reagent 254 and a quartz column were used for column chromatography and the products having UV absorption were detected by UV irradiation. In experiments requiring a dry solvent and reagent, benzylamine, DMSO, DMF, and acetonitrile were distilled from CaH_2 and THF was distilled from diphenylketyl. Methanol, *t*-BuOH, and ethyl acetate were distilled before use.

3.1.1. 2′-(*p*-Tolylsulfinyl)spiro[cyclopentadecane-1,1′-oxirane] (3a). This sulfinyloxirane was synthesized from cyclopendadecanone and chloromethyl *p*-tolyl sulfoxide through the adduct **6**[10] in almost quantitative yield in a similar way as described before.[11] Colorless crystals; mp 71–72 °C (AcOEt–hexane). IR (KBr) 2928, 2848, 1464, 1444, 1086, 1049 (SO), 810, 756 cm^{-1}; ^{1}H NMR δ 1.33–1.74 (26H, m), 1.87–1.93 (1H, m), 2.02–2.08 (1H, m), 2.42 (3H, s), 3.62 (1H, s), 7.35, 7.58 (each 2H, d, *J*=8.0 Hz). MS *m*/*z* (%) 236 (M$^+$, 32), 140 (100), 139 (24), 91 (45), 81 (33). Calcd for $C_{23}H_{36}O_2S$: M, 376.2436. Found: *m*/*z* 376.2432. Anal. Calcd for $C_{23}H_{36}O_2S$: C, 73.35; H, 9.64; S, 8.51. Found: C, 73.35; H, 9.59; S, 8.54.

3.1.2. 1-(Benzylamino)cyclopentadecanecarbaldehyde (7). A solution of **3a** (414 mg; 1.1 mmol) in dry benzylamine (1.08 mL; 9.9 mmol) was warmed at 70 °C for 24 h. The benzylamine was evaporated under vacuum to give a residue, which was purified by silica gel column chromatography to give **7** (340 mg; 90%) as colorless crystals; mp 56.5–58 °C (EtOH–H_2O). IR (KBr) 3322 (NH), 2923, 2857, 2787, 2696, 1709 (CO), 1455, 694 cm^{-1}; ^{1}H NMR δ 1.21–1.63 (29H, m), 3.55 (2H, s), 7.24–7.34 (5H, m), 9.39 (1H, s). MS *m*/*z* (%) 343 (M$^+$, 1), 272 (15), 202 (11), 146 (50), 133 (8), 91 (100). Calcd for $C_{23}H_{37}NO$: M, 343.2873. Found: *m*/*z* 343.2878. Anal. Calcd for $C_{23}H_{37}NO$: C, 80.41; H, 10.86; N, 4.08. Found: C, 80.42; H, 10.80; N, 4.23.

3.1.3. Methyl 1-(benzylamino)cyclopentadecanecarboxylate (8). A solution of KOH (80 mg; 1.43 mmol) in methanol (2 mL) was added to a solution of iodine (155 mg; 0.61 mmol) in 2 mL of methanol at room temperature with stirring. After 10 min, the solution was added dropwise to a solution of the aldehyde **7** (30 mg; 0.087 mmol) in methanol. The reaction mixture was stirred at room temperature for 20 min. The reaction was quenched by adding satd aq $Na_2S_2O_3$ and the whole was extracted with $CHCl_3$. The extract was washed with satd aq NH_4Cl and dried over $MgSO_4$. The product was purified by silica gel column chromatography to give **8** (17.8 mg; 55%) as colorless needles; mp 106–107.5 °C (EtOH–hexane). IR (KBr) 3338 (NH), 2928, 2855, 1716 (CO), 1459, 1218, 701 cm^{-1}; ^{1}H NMR δ 1.20–1.40 (25H, m), 1.57–1.65 (2H, m), 1.73–1.79 (2H, m), 3.51 (2H, s), 3.73 (3H, s), 7.22–7.32 (5H, m). MS *m*/*z* (%) 373 (M$^+$, 0.5), 315 (23), 314 (100), 91 (27). Calcd for $C_{24}H_{39}NO_2$: M, 373.2981. Found: *m*/*z* 373.2964. Anal. Calcd for $C_{24}H_{39}NO_2$: C, 77.16; H, 10.52; N, 3.75. Found: C, 77.32; H, 10.52; N, 3.94.

3.1.4. Methyl 1-aminocyclopentadecanecarboxylate (9). Palladium hydroxide (20 wt % Pd on carbon; 18 mg) was added to a solution of **8** (17.5 mg) in ethyl acetate (0.5 mL) and the reaction mixture was stirred at room temperature under hydrogen atmosphere for 12 h. The catalyst was filtered off and the solvent was evaporated to give a residue, which was purified by short silica gel column to afford **9** (13.1 mg; 99%) as a colorless oil; IR (neat) 3381(NH), 3314 (NH), 2929, 2857, 1732 (CO), 1460, 1222 cm^{-1}; ^{1}H NMR δ 1.25–1.37 (26H, m), 1.53–1.59 (2H, m), 1.69–1.75 (2H, m), 3.71 (3H, s). MS *m*/*z* (%) 283 (M$^+$, trace), 268 (2), 225 (16), 224 (100). Calcd for $C_{17}H_{33}NO_2$: M, 283.2511. Found: *m*/*z* 283.2504.

3.1.5. 2″-(*p*-Tolylsulfinyl)dispiro[1,3-dioxolane-2,1′-cyclohexane-4′,1″-oxirane] (3b). Colorless crystals; mp 88–89 °C (AcOEt–hexane). IR (KBr) 2964, 2891, 1092, 1031 (SO), 931 cm^{-1}; ^{1}H NMR δ 1.56–1.64 (1H, m), 1.79–2.12 (6H, m), 2.31–2.37 (1H, m), 2.43 (3H, s), 3.73 (1H, s), 3.96–4.02 (4H, m), 7.37, 7.60 (each 2H, d, *J*=8.0 Hz). MS *m*/*z* (%) 308 (M$^+$, 0.8), 169 (100), 140 (36), 125 (26), 99 (76), 86 (50). Calcd for $C_{16}H_{20}O_4S$: M, 308.1082. Found: *m*/*z* 308.1084. Anal. Calcd for $C_{16}H_{20}O_4S$: C, 62.31; H, 6.54; S, 10.40. Found: C, 62.32; H, 6.52; S, 10.40.

3.1.6. 2-(*tert*-Butyldiphenylsilanyloxy)methyl-2-methyl-3-(*p*-tolylsulfinyl)oxirane (3c). Less polar isomer (*Z*)-**3c**: Colorless crystals; mp 122.0–123.0 °C (AcOEt–hexane). IR (KBr) 3050, 2932, 2858, 1493, 1472, 1428, 1112, 1048 (SO), 811, 743, 702 cm^{-1}; ^{1}H NMR δ 1.12 (9H, s), 1.53 (3H, s), 2.40 (3H, s), 3.71 (1H, s), 4.00 (1H, d, *J*=11.6 Hz), 4.16 (1H, d, *J*=11.6 Hz), 7.32 (2H, d, *J*=7.9 Hz), 7.40–7.49 (8H, m), 7.71–7.75 (4H, m). MS *m*/*z* (%) 464

(M^+, trace), 407 (20), 268 (24), 267 (100), 243 (18), 239 (20), 199 (61), 197 (33), 140 (37), 135 (64), 129 (28), 91 (20). Calcd for $C_{27}H_{32}O_3SSi$: M, 464.1841. Found: *m/z* 464.1844. Anal. Calcd for $C_{27}H_{32}O_3SSi$: C, 69.79; H, 6.94; S, 6.90. Found: C, 69.54; H, 6.93; S, 7.15.

More polar isomer (*E*)-**3c**: Colorless oil; IR (neat) 2931, 2859, 1493, 1472, 1428, 1113, 1088, 1048 (SO), 703 cm^{-1}; ^1H NMR δ 1.01 (9H, s), 1.72 (3H, s), 2.43 (3H, s), 3.65 (1H, d, *J*=11.9 Hz), 3.77 (1H, d, *J*=11.9 Hz), 3.90 (1H, s), 7.35–7.38 (6H, m), 7.40–7.43 (2H, m), 7.59–7.64 (6H, m). MS *m/z* (%) 464 (M^+, trace), 268 (24), 267 (100), 239 (20), 199 (57), 197 (32), 183 (22), 139 (38), 135 (66), 129 (31), 91 (22). Calcd for $C_{27}H_{32}O_3SSi$: M, 464.1841. Found: *m/z* 464.1836.

3.1.7. 2-Benzyl-2-ethyl-3-(*p*-tolylsulfinyl)oxirane (3d). Less polar isomer (*Z*)-**3d**: Colorless oil; IR (neat) 3029, 2973, 2939, 1598, 1495, 1455, 1401, 1085, 1045 (SO), 1016, 704 cm^{-1}; ^1H NMR δ 0.87 (3H, t, *J*=7.9 Hz), 1.53 (1H, sextet, *J*=7.4 Hz), 1.61 (1H, sextet, *J*=7.4 Hz), 2.45 (3H, s), 3.33 (2H, s), 3.78 (1H, s), 7.25–7.31 (1H, m), 7.34–7.41 (6H, m), 7.64 (2H, d, *J*=8.3 Hz). MS *m/z* (%) 300 (M^+, trace), 161 (25), 140 (34), 139 (15), 92 (20), 91 (100). Calcd for $C_{18}H_{20}O_2S$: M, 300.1184. Found: *m/z* 300.1186.

More polar isomer (*E*)-**3d**: Colorless crystals; mp 77.5–78.5 °C (AcOEt–hexane). IR (KBr) 3029, 2972, 2925, 1598, 1495, 1454, 1085, 1049 (SO), 703 cm^{-1}; ^1H NMR δ 1.23 (3H, t, *J*=7.6 Hz), 1.86 (1H, sextet, *J*=7.1 Hz), 2.01 (1H, sextet, *J*=7.1 Hz), 2.42 (3H, s), 2.89 (1H, d, *J*=14.7 Hz), 3.07 (1H, d, *J*=14.7 Hz), 3.67 (1H, s), 7.18–7.31 (5H, m), 7.35 (2H, d, *J*=8.3 Hz), 7.57 (2H, d, *J*=8.3 Hz). Anal. Calcd for $C_{18}H_{20}O_2S$: C, 71.97; H, 6.71; S, 10.67. Found: C, 72.02; H, 6.69; S, 10.68.

3.1.8. 2′-(*p*-Tolylsulfinyl)spiro[cyclobutane-1,1′-oxirane] (3e). Colorless oil; IR (neat) 2942, 1493, 1416, 1086, 1051 (SO), 815 cm^{-1}; ^1H NMR δ 1.97–2.04 (2H, m), 2.41–2.47 (1H, m), 2.43 (3H, s), 2.55–2.62 (1H, m), 2.66–2.72 (1H, m), 2.84–2.90 (1H, m), 3.77 (1H, s), 7.36, 7.59 (each 2H, d, *J*=8.2 Hz). MS *m/z* (%) 222 (M^+, 0.3), 206 (2), 140 (43), 139 (45), 123 (16), 92 (57), 91 (42), 83 (100). Calcd for $C_{12}H_{14}O_2S$: M, 222.0714. Found: *m/z* 222.0712.

3.1.9. 2′-(*p*-Tolylsulfinyl)spiro[cyclodecane-1,1′-oxirane] (3f). Colorless crystals; mp 61.5–62.5 °C (AcOEt–hexane). IR (KBr) 2936, 2906, 1483, 1085, 1045 (SO), 809 cm^{-1}; ^1H NMR δ 1.55–1.93 (16H, m), 2.00–2.10 (1H, m), 2.17–2.31 (1H, m), 2.42 (3H, s), 3.63 (1H, s), 7.35, 7.58 (each 2H, d, *J*=8.1 Hz). MS (FAB) *m/z* (%) 307 ($[M+H]^+$, 55), 289 (10), 167 (100), 154 (51), 149 (52), 141 (63), 140 (51), 81 (39). Calcd for $C_{18}H_{27}O_2S$: [M+H] 307.1732. Found: *m/z* 307.1737. Anal. Calcd for $C_{18}H_{27}O_2S$: C, 70.55; H, 8.55; S, 10.46. Found: C, 70.54; H, 8.57; S, 10.45.

3.1.10. 2-Methyl-2-(2-phenylethyl)-3-(*p*-tolylsulfinyl)-oxirane (3g). Less polar isomer (*Z*)-**3g**: Colorless oil; IR (neat) 3005, 1599, 1494, 1455, 1381, 1218, 1086, 1040 (SO), 1016, 771 cm^{-1}; ^1H NMR δ 1.46 (3H, s), 2.21–2.35 (2H, m), 2.42 (3H, s), 2.85–2.91 (1H, m), 2.98–3.04 (1H, m), 3.70 (1H, s), 7.21–7.28 (3H, m), 7.32 (2H, d, *J*=7.3 Hz), 7.36 (2H, d, *J*=8.0 Hz), 7.58 (2H, d, *J*=8.0 Hz). MS *m/z* (%) 300 (M^+, trace), 140 (20), 92 (19), 91 (100). Calcd for $C_{18}H_{20}O_2S$: M, 300.1184. Found: *m/z* 300.1185.

More polar isomer (*E*)-**3g**: Colorless oil; IR (neat) 3027, 2927, 1599, 1495, 1455, 1395, 1208, 1087, 1047 (SO), 1016, 701 cm^{-1}; ^1H NMR δ 1.76 (3H, s), 1.94 (2H, t, *J*=8.3 Hz), 2.42 (3H, s), 2.68–2.72 (2H, m), 3.71 (1H, s), 7.12–7.15 (2H, m), 7.17–7.20 (1H, m), 7.24–7.29 (2H, m), 7.36 (2H, d, *J*=8.0 Hz), 7.60 (2H, d, *J*=8.0 Hz). MS *m/z* (%) 300 (M^+, trace), 140 (28), 92 (18), 91 (100). Calcd for $C_{18}H_{20}O_2S$: M, 300.1184. Found: *m/z* 300.1192.

3.1.11. 8-Azido-1,4-dioxaspiro[4,5]decane-8-carboxylic acid (11). A solution of **3b** (20.1 mg; 0.065 mmol) in methanol (0.56 mL) and water (0.07 mL) was heated with NaN_3 (21.2 mg; 0.33 mmol) in the presence of NH_4Cl (7.7 mg; 0.15 mmol) for 12 h under reflux. The reaction mixture was diluted with water, and the whole was extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and the solvent was evaporated under vacuum to afford the azido aldehyde **10**. Without further purification, $NaClO_2$ (74.3 mg; 0.82 mmol) was added to a solution of azido aldehyde **10** in acetonitrile (0.13 mL), NaH_2PO_4 (95.3 mg) in water and 35% H_2O_2 (71 mg; 0.65 mmol). The reaction mixture was stirred at room temperature for 16 h. A small amount of Na_2SO_3 was added to destroy the unreacted $NaClO_2$ and H_2O_2 at 0 °C. Acidification with 10% aqueous HCl afforded **11** (12.7 mg; 86% from **3b**) as colorless prisms; mp 60–62 °C (AcOEt–hexane). IR (KBr) 2935, 2890, 2111 (N_3), 1719 (CO), 1265, 1152, 1106, 954 cm^{-1}; ^1H NMR δ 1.70–1.73 (2H, m), 1.83 (2H, ddd, *J*=13.0, 12.8, 4.0 Hz), 1.96 (2H, d, *J*=13.8 Hz), 2.17 (2H, ddd, *J*=13.3, 13.1, 4.0 Hz), 3.94–4.00 (4H, m). MS *m/z* (%) 227 (M^+, trace), 185 (2), 155 (3), 126 (46), 99 (100), 82 (25). Anal. Calcd for $C_9H_{13}N_3O_4$: C, 47.57; H, 5.77; N, 18.49. Found: C, 47.62; H, 5.79; N, 18.04.

3.1.12. 8-Amino-1,4-dioxaspiro[4,5]decane-8-carboxylic acid (12). Palladium carbon 10% (54 mg) was added to a solution of **11** (54 mg; 0.24 mmol) in THF (2.4 mL). The reaction mixture was stirred at room temperature for 13 h under hydrogen atmosphere. The catalyst was filtered off and the solvent was evaporated under vacuum to afford **12** (47 mg; 98%) as colorless crystals; dec 193 °C. IR (KBr) 2954, 2931, 2883, 2598, 1616 (CO), 1560, 1400, 1333, 1273, 1129, 1095, 880 cm^{-1}; ^1H NMR (D_2O) δ 1.61 (2H, t, *J*=11.0 Hz), 1.69–1.81 (4H, m), 2.05–2.10 (2H, m), 3.89 (4H, s). MS (FAB) *m/z* (%) 202 ($[M+H]^+$, 43), 185 (92), 154 (49), 138 (23), 137 (52), 136 (31), 93 (100). Calcd for $C_9H_{16}NO_4$: M, 202.1079. Found: *m/z* 202.1081.

3.1.13. Methyl 8-Azido-1,4-dioxaspiro[4,5]decane-8-carboxylate (13). CH_2N_2 in Et_2O was added dropwise to a solution of **11** (37.5 mg; 0.17 mmol) in Et_2O at 0 °C until the light yellow color of excess CH_2N_2 appeared. The reaction mixture was stirred for 10 min. After concentration, the residue was purified by silica gel flash chromatography to give **13** (34.1 mg; 86%) as a colorless oil. IR (neat) 2959, 2935, 2884, 2109 (N_3), 1739 (CO), 1440, 1277, 1249, 1151, 1105, 938 cm^{-1}; ^1H NMR δ 1.66–1.70 (2H, m), 1.82 (2H, ddd, *J*=12.9, 12.7, 4.0 Hz), 1.89–1.95 (2H, m), 2.13 (2H,

ddd, J=13.2, 13.0, 4.0 Hz), 3.80 (3H, s), 3.92–3.99 (4H, m). MS m/z (%) 241 (M^+, trace), 126 (61), 99 (100), 82 (25).

3.1.14. Direct oxidation of 3b to 13 using iodine in methanol. A solution of **3b** (20 mg; 0.065 mmol) in methanol (0.58 mL) and water (0.072 mL) was heated under reflux with NaN_3 (21.1 mg; 0.33 mmol) in the presence of NH_4Cl (7.6 mg; 0.14 mmol) for 11 h. The reaction mixture was diluted with water, and the whole was extracted with $CHCl_3$. The solution was dried over $MgSO_4$ and the solvent was evaporated under vacuum to afford the azido aldehyde **10**. A solution of iodine (115 mg; 0.45 mmol) and a 4% (w/w) solution of potassium hydroxide (59.2 mg; 0.91 mmol) in methanol (1.4 g) was stirred at room temperature for 10 min. This solution was added dropwise to a solution of the azido aldehyde **10** in methanol (1 mL). The reaction mixture was stirred at room temperature for 20 min. The reaction was quenched by satd aq $Na_2S_2O_3$. The whole was extracted with $CHCl_3$ and the organic layer was washed with brine, and dried over $MgSO_4$. After concentration, the residue was purified by silica gel flash chromatography to give **13** (12.1 mg; 77% from **3b**) as a colorless oil.

3.1.15. Methyl 8-amino-1,4-dioxaspiro[4,5]decane-8-carboxylate (14). Colorless oil; IR (neat) 3376 (NH), 3310 (NH), 2953, 2885, 1729 (CO), 1440, 1241, 1108 cm^{-1}; ^1H NMR δ 1.55–1.69 (6H, m), 1.83–1.95 (2H, m), 2.05–2.16 (2H, m), 3.72 (3H, s), 3.95 (4H, s). MS m/z (%) 215 (M^+, 3), 187 (8), 168 (12), 156 (100), 99 (31), 94 (45), 86 (33). Calcd for $C_{10}H_{17}NO_4$: M, 215.1158. Found: m/z 215.1156.

3.1.16. 2-Azido-3-(*tert*-butyldiphenylsilanyloxy)-2-methylpropionic acid (15a). Colorless amorphous; IR (KBr) 3072, 2933, 2860, 2651, 2103 (N_3), 1719 (CO), 1428, 1259, 1113, 824, 702 cm^{-1}; ^1H NMR δ 1.05 (9H, s), 1.36 (1H, s), 3.80 (1H, d, J=10.4 Hz), 3.98 (1H, d, J=10.4 Hz), 7.39–7.44 (6H, m), 7.66–7.70 (4H, m). MS (FAB) m/z (%) 429 ($[M+H+Na_2]^+$, 30), 428 (100), 406 ($[M+H+Na]^+$, 30), 301 (30), 199 (21), 197 (20), 135 (43), 123 (68). Calcd for $C_{20}H_{25}N_3O_3SiNa$: M, 406.1563. Found: m/z 406.1559.

3.1.17. 2-Azido-2-benzylbutyric acid (15b). Yellow amorphous; IR (neat) 2977, 2109 (N_3), 1714 (CO), 1454, 1260, 701 cm^{-1}; ^1H NMR δ 1.03 (3H, t, J=7.5 Hz), 1.76–1.85 (1H, m), 1.97–2.05 (1H, m), 3.04 (1H, d, J=14.0 Hz), 3.22 (1H, d, J=14.0 Hz), 7.24–7.34 (5H, m). MS m/z (%) 219 (M^+, 1), 147 (12), 92 (50), 91 (100). Calcd for $C_{11}H_{13}N_3O_2$: M, 219.1007. Found: m/z 219.1009.

3.1.18. 2-Amino-3-(*tert*-butyldiphenylsilanyloxy)-2-methylpropionic acid (16a). Colorless crystals; dec 195 °C (MeOH). IR (KBr) 3049, 2931, 2857, 1645 (CO), 1589, 1509, 1428, 1400, 1362, 1113, 1088, 701 cm^{-1}; ^1H NMR (CD_3OD) δ 1.08 (9H, s), 1.39 (3H, s), 3.68 (1H, d, J=10.7 Hz), 4.00, (1H, d, J=10.7 Hz), 7.34–7.47 (6H, m), 7.65–7.72 (4H, m). MS (FAB) m/z (%) 358 ($[M+H]^+$, 100), 234 (36), 199 (20), 174 (37), 135 (30). Calcd for $C_{20}H_{28}NO_3Si$: 358.1838. Found: m/z 358.1834.

3.1.19. 2-Amino-2-benzylbutyric acid (16b). Colorless crystals; dec 218 °C (MeOH). IR (KBr) 3411, 2970, 1619 (CO), 1522, 1497, 1397, 703 cm^{-1}; ^1H NMR (CD_3OD) δ 1.00 (3H, t, J=7.6 Hz), 1.68–1.72 (1H, m), 2.01–2.05 (1H, m), 2.95 (1H, d, J=14.1 Hz), 3.27 (1H, d, J=14.1 Hz), 7.24–7.35 (5H, m). MS (FAB) m/z (%) 194 ($[M+H]^+$, 100), 154 (22), 148 (31), 137 (18), 93 (18). Calcd for $C_{11}H_{16}NO_2$: 194.1181. Found: m/z 194.1181.

3.1.20. Methyl 1-azidocyclobutanecarboxylate (17a). Colorless oil; IR (neat) 2957, 2108 (N_3), 1739 (CO), 1250, 1138 cm^{-1}; ^1H NMR δ 1.96–2.11 (2H, m), 2.25–2.31 (2H, m), 2.58–2.64 (2H, m), 3.82 (3H, s).

3.1.21. Methyl 1-azidocyclodecanecarboxylate (17b). Colorless oil; IR (neat) 2927, 2106 (N_3), 1743 (CO), 1251, 1202 cm^{-1}; ^1H NMR δ 1.45–1.66 (14H, m), 1.84–2.04 (4H, m), 3.81 (3H, s).

3.1.22. Methyl 1-azidocyclopentadecanecarboxylate (17c). Colorless oil; IR (neat) 2930, 2858, 2107 (N_3), 1743 (CO), 1460, 1255 cm^{-1}; ^1H NMR δ 1.24–1.42 (24H, m), 1.66–1.73 (2H, m), 1.82–1.88 (2H, m), 3.79 (3H, s).

3.1.23. Methyl 2-azido-2-methyl-4-phenylbutyrate (17d). Colorless oil; IR (neat) 3028, 2955, 2105 (N_3), 1741 (CO), 1604, 1498, 1457, 1380, 1251, 1174, 1113, 1068, 700 cm^{-1}; ^1H NMR δ 1.55 (3H, s), 1.93–1.99 (1H, m), 2.10–2.16 (1H, m), 2.53–2.59 (1H, m), 2.69–2.75 (1H, m), 3.76 (3H, m), 7.16–7.21 (3H, m), 7.26–7.30 (2H, m). MS (FAB) m/z (%) 234 ($[M+H]^+$, 3), 197 (54), 149 (30), 135 (100), 105 (40), 91 (51). Calcd for $C_{12}H_{16}N_3O_2$: 234.1243. Found: m/z 234.1243.

3.1.24. Methyl 2-azido-2-benzylbutyrate (17e). Colorless oil; IR (neat) 3032, 2976, 2954, 2106 (N_3), 1739 (CO), 1497, 1456, 1243, 1199, 1122, 1003, 701 cm^{-1}; ^1H NMR δ 0.97 (3H, t, J=7.3 Hz), 1.75 (1H, sextet, J=7.0 Hz), 1.92 (1H, sextet, J=7.0 Hz), 3.01 (1H, d, J=14.1 Hz), 3.16 (1H, d, J=14.1 Hz), 3.76 (3H, s), 7.20 (2H, d, J=7.6 Hz), 7.24–7.32 (3H, m). MS m/z (%) 233 (M^+, trace), 145 (10), 91 (100). Calcd for $C_{12}H_{15}N_3O_2$: M, 233.1164. Found: m/z 233.1166.

3.1.25. Methyl 1-aminocyclobutanecarboxylate (18a). Colorless oil; IR (neat) 3370 (NH), 2927, 2856, 1733 (CO), 1275, 1122 cm^{-1}; ^1H NMR δ 1.91–2.04 (4H, m), 2.53–2.58 (2H, m), 3.76 (3H, s). MS (FAB) m/z (%) 130 ($[M+H]^+$, 13), 93 (100), 75 (52). Calcd for $C_6H_{12}NO_2$: 130.0868. Found: m/z 130.0865.

3.1.26. Methyl 1-aminocyclodecanecarboxylate (18b). Colorless oil; IR (neat) 3377 (NH), 2925, 1732 (CO), 1196 cm^{-1}; ^1H NMR δ 1.47–1.75 (18H, m), 1.85–1.91 (2H, m), 3.70 (3H, s). MS (FAB) m/z (%) 214 ($[M+H]^+$, 34), 185 (25), 154 (100), 137 (83), 136 (86), 107 (29), 93 (53), 89 (23). Calcd for $C_{12}H_{24}NO_2$: 214.1808. Found: m/z 214.1814.

3.1.27. Methyl 2-amino-2-methyl-4-phenylbutyrate (18c). Colorless oil; IR (neat) 3377 (NH), 3311 (NH), 3027, 2926, 2856, 1731 (CO), 1603, 1497, 1454, 1199, 1117, 700 cm^{-1}; ^1H NMR δ 1.38 (3H, s), 1.77 (2H, s), 1.86–1.92 (1H, m), 2.01–2.07 (1H, m), 2.49–2.55 (1H, m), 2.63–2.69 (1H, m), 3.71 (3H, s), 7.16–7.20 (3H, m), 7.27 (2H, d, J=6.7 Hz). MS m/z (%) 207 (M^+, 3), 149 (11), 148

(100), 102 (21), 91 (67). Calcd for $C_{12}H_{17}NO_2$: M, 207.1260. Found: *m/z* 207.1262.

3.1.28. Methyl 2-amino-2-benzylbutyrate (18d). Colorless oil; IR (neat) 3379 (NH), 3316 (NH), 3030, 2967, 1732 (CO), 1604, 1495, 1455, 1196, 1117, 997, 757, 703 cm^{-1}; ^1H NMR δ 0.89 (3H, t, J=7.7 Hz), 1.59–1.66 (3H, m), 1.95 (1H, sextet, J=7.7 Hz), 2.76 (1H, d, J=13.1 Hz), 3.17 (1H, d, J=13.1 Hz), 3.70 (3H, s), 7.13 (2H, d, J=6.7 Hz), 7.20–7.30 (3H, m). MS (FAB) *m/z* (%) 208 ($[M+H]^+$, 100), 149 (18), 148 (60), 116 (26), 91 (38). Calcd for $C_{12}H_{18}NO_2$: 208.1337. Found: *m/z* 208.1337.

3.1.29. (2*S*,3*R*,*R*s)-(+)-2-Tetralin-2-yl-3-(*p*-tolylsulfinyl)oxirane (20). Colorless crystals; mp 78–79.5 °C (AcOEt–hexane). IR (KBr) 2925, 1495, 1086, 1046 (SO), 750 cm^{-1}; ^1H NMR δ 1.69–1.74 (1H, m), 2.18 (1H, ddd, J=13.5, 10.6, 5.5 Hz), 2.43 (3H, s), 2.87–2.95 (1H, m), 2.96–3.05 (1H, m), 3.17 (1H, d, J=18.0 Hz), 3.72 (1H, d, J=18.0 Hz), 3.86 (1H, s), 7.13–7.21 (4H, m), 7.37 (2H, d, J=8.0 Hz), 7.62 (2H, d, J=8.0 Hz). $[\alpha]_D^{24}$ +61.8 (*c* 0.40, $CHCl_3$). Racemic-**20**: Colorless prisms; mp 104–105 °C (AcOEt–hexane). MS *m/z* (%) 298 (M^+, trace), 154 (48), 129 (100), 128 (47), 91 (39). Calcd for $C_{18}H_{18}O_2S$: M, 298.1028. Found: *m/z* 298.1034. Anal. Calcd for $C_{18}H_{18}O_2S$: C, 72.45; H, 6.08; S, 10.75. Found: C, 72.35; H, 6.00; S, 10.67.

3.1.30. (2*R*,3*R*,*R*s)-(−)-2-Tetralin-2-yl-3-(*p*-tolylsulfinyl)oxirane (21). Colorless crystals; mp 81.5–83.5 °C (AcOEt–hexane). IR (KBr) 2925, 1495, 1455, 1086, 1048 (SO), 754 cm^{-1}; ^1H NMR δ 2.28–2.33 (1H, m), 2.39–2.47 (1H, m), 2.44 (3H, s), 2.87 (1H, d, J=17.4 Hz), 3.07–3.17 (2H, m), 3.13 (1H, d, J=17.4 Hz), 3.88 (1H, s), 7.02 (1H, d, J=6.7 Hz), 7.12–7.20 (3H, m), 7.38, 7.62 (each 2H, d, J=8.6 Hz). $[\alpha]_D^{23}$ −60.7 (*c* 0.47, $CHCl_3$). Racemic-**21**: Colorless crystals; mp 133–135 °C (AcOEt–hexane). MS *m/z* (%) 298 (M^+, trace), 158 (48), 140 (23), 129 (100), 91 (41). Calcd for $C_{18}H_{18}O_2S$: M, 298.1027. Found: *m/z* 298.1027. Anal. Calcd for $C_{18}H_{18}O_2S$: C, 72.45; H, 6.08; S, 10.75. Found: C, 72.45; H, 6.09; S, 10.79.

3.1.31. (*R*)-(−)-Methyl 2-azidotetraline-2-carboxylate (22). Colorless oil; $[\alpha]_D^{24}$ −38.1 (*c* 0.56, EtOH). IR (neat) 3022, 2954, 2108 (N_3), 1743 (CO), 1455, 1435, 1282, 1256 cm^{-1}; ^1H NMR δ 2.17–2.20 (2H, m), 2.87 (1H, dt, J=17.4, 4.9 Hz), 2.95–3.04 (1H, m), 3.00 (1H, d, J=16.8 Hz), 3.31 (1H, d, J=16.8 Hz), 3.84 (3H, s), 7.08–7.17 (4H, m). MS *m/z* (%) 231 (M^+, trace), 188 (25), 144 (100), 129 (31), 117 (73), 115 (25). Calcd for $C_{12}H_{13}N_3O_2$: M, 231.1008. Found: *m/z* 231.1008. (*S*)-(+)-**22**: Colorless oil; $[\alpha]_D^{26}$ +39.2 (*c* 0.26, EtOH).

3.1.32. (*R*)-(+)-Methyl 2-aminotetraline-2-carboxylate (23). Colorless oil; $[\alpha]_D^{21}$ +19.6 (*c* 0.27, EtOH). IR (neat) 3375 (NH), 3302 (NH), 2950, 2848, 1731 (CO), 1215 cm^{-1}; ^1H NMR δ 1.87–1.94 (1H, m), 2.13–2.20 (1H, m), 2.75 (1H, d, J=16.5 Hz), 2.83 (1H, dt, J=17.1, 5.5 Hz), 3.00 (1H, ddd, J=17.1, 10.1, 6.1 Hz), 3.30 (1H, d, J=16.5 Hz), 3.74 (3H, s), 7.06–7.14 (4H, m). MS *m/z* (%) 205 (M^+, 12), 146 (100), 129 (43), 128 (12), 104 (15). Calcd for $C_{12}H_{15}NO_2$: M, 205.1103. Found: *m/z* 205.1103. (*S*)-(−)-**23**: Colorless oil; $[\alpha]_D^{24}$ −19.3 (*c* 0.57, EtOH).

3.1.33. (1*R*,2*S*,*R*s)-(−)-2-Benzyl-1-chloro-1-(*p*-tolylsulfinyl)-2-butanol (24). Colorless oil; $[\alpha]_D^{30}$ −131.9 (*c* 0.53, EtOH). Racemic-**24**: Colorless crystals; mp 161–162 °C (AcOEt–hexane). IR (KBr) 3368, 2964, 1495, 1454, 1086, 1045 (SO), 1032, 701 cm^{-1}; ^1H NMR δ 1.06 (3H, t, J=7.3 Hz), 1.78 (1H, sextet, J=7.4 Hz), 2.02 (1H, sextet, J=7.4 Hz), 2.41 (3H, s), 2.52 (1H, s), 3.19 (1H, d, J=14.1 Hz), 3.26 (1H, d, J=14.1 Hz), 4.31 (1H, s), 7.27–7.37 (9H, m). Anal. Calcd for $C_{18}H_{21}ClO_2S$: C, 64.18; H, 6.28; Cl, 10.52; S, 9.52. Found: C, 64.18; H, 6.23; Cl, 10.45; S, 9.50.

3.1.34. (1*R*,2*R*,*R*s)-(−)-2-Benzyl-1-chloro-1-(*p*-tolylsulfinyl)-2-butanol (25). Colorless crystals; $[\alpha]_D^{30}$ −50.8 (*c* 0.53, EtOH). Racemic-**25**: Colorless crystals; mp 120.5–121.5 °C (AcOEt–hexane); IR (KBr) 3324, 2970, 1456, 1084, 1042 (SO), 1017, 703 cm^{-1}; ^1H NMR δ 1.06 (3H, t, J=7.6 Hz), 1.90 (1H, sextet, J=7.3 Hz), 1.99 (1H, sextet, J=7.3 Hz), 2.41 (3H, s), 2.61 (1H, s), 3.09 (1H, d, J=14.0 Hz), 3.26 (1H, d, J=14.0 Hz), 4.22 (1H, s), 7.24–7.34 (7H, m), 7.40 (2H, d, J=8.0 Hz). Anal. Calcd for $C_{18}H_{21}ClO_2S$: C, 64.18; H, 6.28; Cl, 10.52; S, 9.52. Found: C, 63.89; H, 6.24; Cl, 10.36; S, 9.42.

3.1.35. (2*S*,3*R*,*R*s)-(+)-2-Benzyl-2-ethyl-3-(*p*-tolylsulfinyl)oxirane (26). Colorless oil; $[\alpha]_D^{29}$ +1.8 (*c* 0.95, EtOH). Spectral data see (*Z*)-**3d**.

3.1.36. (2*R*,3*R*,*R*)-(+)-2-Benzyl-2-ethyl-3-(*p*-tolylsulfinyl)oxirane (27). Colorless crystals; mp 82–83 °C (AcOEt–hexane); $[\alpha]_D^{29}$ +12.7 (*c* 2.63, EtOH). Spectral data see (*E*)-**3d**.

3.1.37. (*R*)-(+)-Methyl 2-azido-2-benzylbutyrate (28). Colorless oil; $[\alpha]_D^{30}$ +41.8 (*c* 1.52, EtOH). Spectral data see **17e**.

3.1.38. (*S*)-(−)-Methyl 2-azido-2-benzylbutyrate (28). Colorless oil; $[\alpha]_D^{29}$ −40.8 (*c* 1.03, EtOH). Spectral data see **17e**.

3.1.39. (*R*)-(+)-Methyl 2-amino-2-benzylbutyrate (29). Colorless oil; $[\alpha]_D^{30}$ +22.1 (*c* 2.04, $CHCl_3$). Spectral data see **18d**.

3.1.40. (*S*)-(−)-Methyl 2-amino-2-benzylbutyrate (29). Colorless oil; $[\alpha]_D^{30}$ −21.6 (*c* 0.53, $CHCl_3$). Spectral data see **18d**.

3.1.41. (*R*)-(+)-2-Azido-2-benzylbutyric acid (30). Colorless oil; $[\alpha]_D^{29}$ +38.9 (*c* 0.99, EtOH). Spectral data see **15b**.

3.1.42. (*S*)-(−)-2-Azido-2-benzylbutyric acid (30). Colorless oil; $[\alpha]_D^{27}$ −43.4 (*c* 0.43, EtOH). Spectral data see **15b**.

3.1.43. (*R*)-(+)-2-Amino-2-benzylbutyric acid (31). Colorless oil; $[\alpha]_D^{30}$ +21.1 (*c* 0.65, H_2O). Spectral data see **16b**.

3.1.44. (*S*)-(−)-2-Amino-2-benzylbutyric acid (31). Colorless oil; $[\alpha]_D^{30}$ −19.8 (*c* 0.36, H_2O). Spectral data see **16b**.

3.1.45. (1*R*,2*R*,*R*s)-(−)-3-(*tert*-Butyldiphenylsilanyloxy)-1-chloro-2-methyl-1-(*p*-tolylsulfinyl)-2-propanol (32). Colorless oil; $[\alpha]_D^{31}$ −124.2 (*c* 0.66, EtOH). IR (neat) 3369,

3072, 2932, 2859, 1494, 1472, 1392, 1217, 1087 (SO) cm^{-1}; ^1H NMR δ 1.07 (9H, s), 1.42 (3H, s), 2.44 (3H, s), 3.30 (1H, s), 3.70 (1H, d, J=10.4 Hz), 3.86 (1H, d, J=10.4 Hz), 4.60 (1H, s), 7.34–7.50 (10H, m), 7.59–7.65 (4H, m). MS m/z (%) 499 (M^+, trace), 445 (33), 444 (23), 443 (75), 199 (75), 198 (28), 139 (100), 135 (47), 91 (21). Calcd for $C_{27}H_{32}O_3ClSSi$: M, 499.1530. Found: m/z 499.1535.

3.1.46. (1*R*,2*S*,*R*s)-(−)-3-(*tert*-Butyldiphenylsilanyloxy)-1-chloro-2-methyl-1-(*p*-tolylsulfinyl)-2-propanol (33). Colorless oil; $[\alpha]_D^{31}$ −91.5 (c 1.29, EtOH). IR (neat) 3401, 3011, 2932, 2859, 1494, 1472, 1463, 1428, 1217, 1088 (SO), 760 cm^{-1}; ^1H NMR δ 1.10 (9H, s), 1.57 (3H, s), 2.44 (3H, s), 3.15 (1H, s), 3.80 (1H, d, J=10.4 Hz), 3.92 (1H, d, J=10.4 Hz), 4.68 (1H, s), 7.34 (2H, d, J=8.0 Hz), 7.36–7.49 (8H, m), 7.65–7.71 (4H, m). MS m/z (%) 499 (M^+, trace), 445 (32), 444 (22), 443 (74), 199 (75), 197 (27), 139 (100), 135 (47), 91 (20). Calcd for $C_{27}H_{32}O_3ClSSi$: M, 499.1530. Found: m/z 499.1521.

3.1.47. (2*R*,3*R*,*R*s)-(−)-34. Colorless oil; $[\alpha]_D^{30}$ −22.8 (c 1.16, EtOH). Spectral data see (*E*)-**3c**.

3.1.48. (2*S*,3*R*,*R*s)-(+)-35. Colorless crystals, mp 80–81 °C (AcOEt–hexane); $[\alpha]_D^{30}$ +30.3 (c 2.51, EtOH). Spectral data see (*Z*)-**3c**.

3.1.49. (*R*)-(−)-Methyl 2-azido-3-(*tert*-butyldiphenylsilanyloxy)-2-methylpropionate (36). Colorless oil; $[\alpha]_D^{27}$ −11.9 (c 0.54, EtOH). IR (neat) 2933, 2859, 2106 (N_3), 1745 (CO), 1473, 1460, 1428, 1299, 1236, 1113, 825, 702 cm^{-1}; ^1H NMR δ 1.04 (9H, s), 1.32 (3H, s), 3.76 (1H, d, J=10.0 Hz), 3.79 (3H, s), 3.94 (1H, d, J=10.0 Hz), 7.38–7.47 (6H, m), 7.64–7.68 (4H, m). MS (FAB) m/z (%) 398 ([M+H]$^+$, 1), 340 (100), 320 (59), 213 (75), 197 (24), 135 (42). Calcd for $C_{21}H_{28}O_3N_3Si$: M, 398.1900. Found: m/z 398.1894.

3.1.50. (*R*)-(+)-Methyl 2-amino-3-hydroxy-2-methylpropionate (38). Colorless oil; $[\alpha]_D^{30}$ +6.9 (c 2.25, EtOH); IR (neat) 3366 (NH), 2957, 1732 (CO), 1651, 1460, 1235, 1139, 1054 cm^{-1}; ^1H NMR δ 1.29 (3H, s), 2.45 (3H, s, NH_2, OH), 3.46 (1H, d, J=10.7 Hz), 3.75 (3H, s), 3.78 (1H, d, J=10.7 Hz). MS (FAB) m/z (%) 134 ([M+H]$^+$, 100), 74 (25), 57 (14), 55 (12). Calcd for $C_5H_{12}O_3N$: M, 134.0818. Found: m/z 134.0818.

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References and notes

1. Fenteany, G.; Standaert, R. F.; Lane, W. S.; Choi, S.; Corey, E. J.; Schreiber, S. L. *Science* **1995**, *268*, 726.
2. Cronin, J. R.; Pizzarello, S. *Science* **1997**, *275*, 951.
3. Zhou, J.; Rocklin, A. M.; Lipscomb, J. D.; Que, L., Jr.; Solomon, E. I. *J. Am. Chem. Soc.* **2002**, *124*, 4602.
4. Knopfel, T.; Kuhn, R.; Allgeier, H. *J. Med. Chem.* **1995**, *38*, 1417.
5. (a) Tanaka, M. *J. Synth. Org. Chem. Jpn.* **2002**, *60*, 125; (b) Tanaka, M.; Demizu, Y.; Doi, M.; Kurihara, M.; Suemune, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 5360; (c) Oba, M.; Tanaka, M.; Takano, Y.; Suemune, H. *Tetrahedron* **2005**, *61*, 593; (d) Tanaka, M.; Anan, K.; Demizu, Y.; Kurihara, M.; Doi, M.; Suemune, H. *J. Am. Chem. Soc.* **2005**, *127*, 11570 and the reference cited therein.
6. Some recent reviews and papers concerning α-quaternary α-amino acids: (a) Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517; (b) Sano, S.; Nagao, Y. *J. Synth. Org. Chem. Jpn.* **2000**, *58*, 756; (c) Ma, D.; Ding, K. *Org. Lett.* **2000**, *2*, 2515; (d) Tanaka, M.; Oba, M.; Tamai, K.; Suemune, H. *J. Org. Chem.* **2001**, *66*, 2667; (e) Ooi, T.; Takeuchi, M.; Ohara, D.; Maruoka, K. *Synlett* **2001**, 1185; (f) Grogner, H. *Chem. Rev.* **2003**, *103*, 2795; (g) Belokon, Y. N.; Bhave, D.; D'Addario, D.; Groaz, E.; North, M.; Tagliazucca, V. *Tetrahedron* **2004**, *60*, 1849; (h) Ooi, T.; Uematsu, Y.; Maruoka, K. *Tetrahedron Lett.* **2004**, *45*, 1675; (i) Kato, N.; Suzuki, M.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2004**, *45*, 3147.
7. Some recent reviews and papers concerning cyclic α-quaternary α-amino acids: (a) Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645; (b) Czombos, J.; Aelterman, W.; Tkachev, A.; Martins, J. C.; Tourwe, D.; Peter, A.; Toth, G.; Fulop, F.; Kimpe, N. D. *J. Org. Chem.* **2000**, *65*, 5469; (c) Kabalka, G. W.; Das, B. C.; Das, S. *Tetrahedron Lett.* **2001**, *42*, 7145; (d) Park, K.-H.; Kurth, M. J. *Tetrahedron* **2002**, *58*, 8629; (e) Bradley, D. M.; Mapitse, R.; Thomson, N. M.; Hayes, C. J. *J. Org. Chem.* **2002**, *67*, 7613; (f) Volk, F.-J.; Wagner, M.; Frahm, A. W. *Tetrahedron: Asymmetry* **2003**, *14*, 497; (g) Truong, M.; Lecornue, F.; Fadel, A. *Tetrahedron: Asymmetry* **2003**, *14*, 1063; (h) Kotha, S. *Acc. Chem. Res.* **2003**, *36*, 342; (i) Andrei, M.; Undheim, K. *Tetrahedron: Asymmetry* **2004**, *15*, 53; (j) Meyer, U.; Breitling, E.; Bisel, P.; Frahm, A. W. *Tetrahedron: Asymmetry* **2004**, *15*, 2029; (k) Kabalka, G. W.; Yao, M.-L. *J. Org. Chem.* **2004**, *69*, 8286; (l) Ung, A. T.; Pyne, S. G.; Batenburg-Nguyen, U.; Davis, A. S.; Sherif, A.; Bischoff, F.; Lesage, S. J. *Tetrahedron* **2005**, *61*, 1803; (m) Avenoza, A.; Busto, J. H.; Canal, N.; Peregrina, J. M.; Perez-Fernandez, M. *Org. Lett.* **2005**, *7*, 3597; (n) Suri, J. T.; Steiner, D. D.; Barbas, C. F., III. *Org. Lett.* **2005**, *7*, 3885.
8. (a) Satoh, T.; Ozawa, M.; Takano, K.; Kudo, M. *Tetrahedron Lett.* **1998**, *39*, 2345; (b) Satoh, T.; Ozawa, M.; Takano, K.; Chyouma, T.; Okawa, A. *Tetrahedron* **2000**, *56*, 4415; (c) Satoh, T.; Fukuda, Y. *Tetrahedron* **2003**, *59*, 9803; (d) Ota, H.; Chyouma, T.; Iso, S.; Satoh, T. *Tetrahedron Lett.* **2004**, *45*, 3903; (e) Satoh, T.; Osawa, A.; Kondo, A. *Tetrahedron Lett.* **2004**, *45*, 6703; (f) Satoh, T.; Miura, M.; Sakai, K.; Yokoyama, Y. *Tetrahedron* **2006**, *62*, 4253.
9. Preliminary results of this study were reported as a communication: Satoh, T.; Hirano, M.; Kuroiwa, A. *Tetrahedron Lett.* **2005**, *46*, 2659.
10. (a) Satoh, T.; Kaneko, Y.; Sakata, K.; Yamakawa, K. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 457; (b) Satoh, T.; Oohara, T.; Ueda, Y.; Yamakawa, K. *J. Org. Chem.* **1989**, *54*, 3130; (c) Satoh, T.; Yamakawa, K. *Synlett* **1992**, 455.
11. Satoh, T.; Takano, K.; Ota, H.; Someya, H.; Matsuda, K.; Koyama, M. *Tetrahedron* **1998**, *54*, 5557.
12. Satoh, T.; Taguchi, D.; Kurabayashi, A.; Kanoto, M. *Tetrahedron* **2002**, *58*, 4217.
13. Inch, T. D.; Ley, R. V.; Rich, P. *J. Chem. Soc. C* **1968**, 1693.

14. Dalcanale, E.; Montanari, F. *J. Org. Chem.* **1986**, *51*, 567.
15. Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1560.
16. Chini, M.; Crotti, P.; Macchia, F. *Tetrahedron Lett.* **1990**, *31*, 5641.
17. One equivalent of (*R*)-chloromethyl *p*-tolyl sulfoxide was reacted with 1.4 equiv of β-tetralone. The yield was calculated based on the sulfoxide.
18. Solladie-Cavallo, A.; Martin-Cabrejas, L. M.; Caravatti, G.; Lang, M. *Tetrahedron: Asymmetry* **2001**, *12*, 967.
19. Belokon, Y. N.; Bhave, D.; D'Addario, D.; Groaz, E.; North, M.; Tagliazucca, V. *Tetrahedron* **2004**, *60*, 1849.
20. Kruizinga, W. H.; Bolster, J.; Kellogg, R. M.; Kamphuis, J.; Boesten, W. H. J.; Meijer, E. M.; Schoemaker, H. E. *J. Org. Chem.* **1988**, *53*, 1826.

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Intramolecular electrophilic hydroarylation via Claisen rearrangement: synthesis of chromenes, heterothiochromenes and heterodihydrothiochromenes

Rajesh S. Kenny, Uday C. Mashelkar,* Deepak M. Rane and Dinesh K. Bezawada

Organic Research Laboratory, Patkar–Varde College of Science, Goregaon (W), Mumbai 400062, India

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Abstract—We have designed and synthesized several basic and novel fused ring heterocycles by intramolecular hydroarylation with an efficiency and scope to develop intermediates of potential value. This method demonstrated consistent performance with arene–ene and arene–yne substrates of diverse structural features, including propargyl ethers, allyl thioethers, and propargyl thioethers resulting in 6-*endo* products.

1. Introduction

Chromene and thiochromene analogs of the HIV-1 protease inhibitor, Ritonavir, have been prepared and are under clinical trials (Fig. 1).[1,2] Some of the patents report chromene and thiochromene as modulators of the estrogen receptors.[3,4] The addition of an aromatic ring to alkenes or alkynes to form C–C bonds via C–H functionalization provides efficient and atom-economic synthetic methods. This C–C bond formation forms the basis for the synthesis of a large number of heterocycles. These seemingly simple points lead to consequences of significant importance in both the strategy and design of simple organic molecules. Intramolecular hydroarylation, a formal addition of arene C–H bonds across multiple bonds, provides a direct route to valuable organic compounds such as annulated arenes, heterocycles, and carbocycles. In contrast to the Heck reaction, a hydroarylation approach eliminates the requirement of a halogen (or triflate) substituent, which is also a feature of other routes. These alternative routes include arene metallation–Heck type addition,[5] multiple bond activation–electrophilic substitution,[6] and metal-catalyzed Claisen rearrangement.[7,8a,b] The compatibility of $Pt(IV)Cl_4$ and $Ru(III)Cl_3$ on the cyclization of alkyne substrates, specifically propargyl–aryl ethers and alkene–aryl ethers, by multiple bond activation–electrophilic substitution have been studied.[9a,b] Cyclization via Claisen rearrangement carried out under harsh conditions is also described (Scheme 1).[9a] The thermal rearrangement of phenol **D** at 240 °C resulted into **E** and **F** in a 7:3 ratio. In contrast, substrate **D** in the presence of 2 mol % of $PtCl_4$ in dioxane at ambient temperature afforded **E** in 59% yield, whereas isomer **F** was not detected in the crude reaction mixture. Many more studies with regard to the development of catalysts for the hydroarylation reaction of alkynes and olefins have been reported.[10–19]

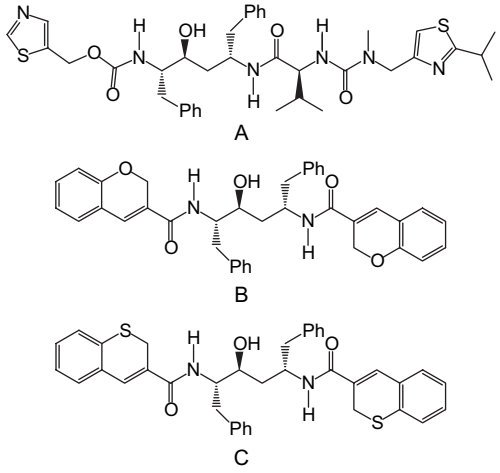

Figure 1. A is the HIV-1 protease inhibitor Ritonavir, B and C are chromene and thiochromene analogs of Ritonavir.

Keywords: Hydroarylation; Claisen rearrangement; Pyran; Thiopyran; Dihydrothiopyran; Chromene.
* Corresponding author. Tel.: +91 22 28721875; fax: +91 22 28744755; e-mail: ucmashelkar@yahoo.com

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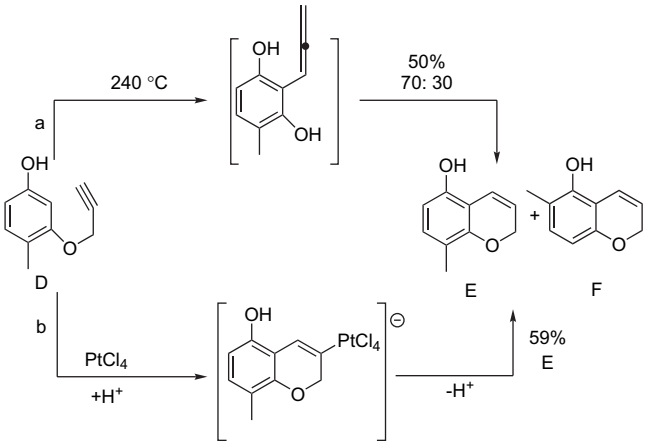
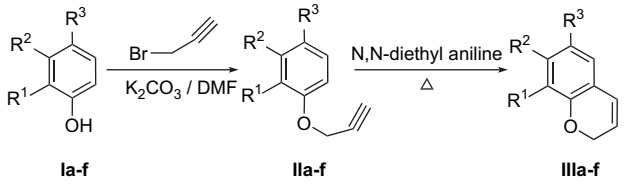


Scheme 1. Conditions: (a) 240 °C, diethyleneglycol; (b) 2 mol % $PtCl_4$, dioxane, rt.

2. Results and discussion

Initially we became interested in the possibility of making simple moieties, which could be the basic framework for various active ingredients of unexplored physiological and pharmaceutical interest. For the synthesis of the desired molecules, various phenols were reacted with propargyl bromides in the presence of base to synthesize propargyl–aryl ethers. The heteroaromatic compounds were first treated with *n*-butyllithium and sulfur to give the thiolate salt formed in situ, these were then reacted with propargyl and alkenyl bromides to give propargyl and alkenyl thioethers. Propargyl ethers underwent cyclization to give the desired products when heated in *N*,*N*-diethylaniline as solvent and base, whereas the alkenyl thioethers underwent cyclization by heating in *N*,*N*-dimethylformamide. For the cyclization of propargyl thioethers either *N*,*N*-diethylaniline or *N*,*N*-dimethylformamide is used. The yields obtained are much higher following our method of synthesis than those reported when the cyclizations were carried out using transition metal salts.[9a,b] In our first attempt we have synthesized some fused ring heterocycles from various phenol derivatives as depicted in Scheme 2. The hydroxyl derivatives **Ia–f** were reacted with propargyl bromide in the presence of potassium carbonate to give the propargyl–aryl ethers **IIa–f**. The resulting intermediates **IIa–f** were then heated in *N*,*N*-diethylaniline



Ia, IIa, IIIa:- R^1 = Ph, R^2 = R^3 = H
Ib, IIb, IIIb:- R^2 = Ph, R^1 = R^3 = H
Ic, IIc, IIIc:- R^3 = Ph, R^1 = R^2 = H
Id, IId, IIId:- R^3 = 4-BrPh, R^1 = R^2 = H
Ie, IIe, IIIe:- R^1-R^2 =  R^3 = H
If, IIf, IIIf :- R^1-R^2 =  R^3 = H

Scheme 2.

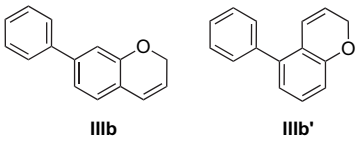
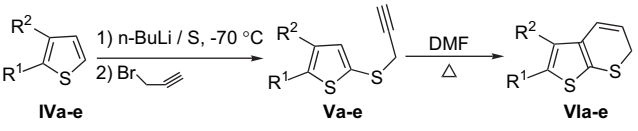


Figure 2.

at 220 °C and underwent rearrangement to give the fused ring pyran derivatives **IIIa–f**. It is possible that one of the propargyl ethers (e.g., 1-phenyl-3-(2-propynyloxy)benzene **IIb**) could upon cyclization give rise to either chromene **IIIb** and/or **IIIb′** (Fig. 2), however, under our reaction conditions only formation of chromene **IIIb** was ever observed.

With the establishment of an exciting lead, we were prepared to determine the efficacy of synthesizing thiopyran and dihydrothiopyran derivatives by following the route depicted in Schemes 3 and 4. Thiophenes **IVa–f** were reacted with *n*-butyllithium and sulfur at −70 °C to give the thiolate salts, which were then reacted in situ with propargyl bromide and α-(bromomethyl)-acrylic acid[21] to give 2-propynylsulfanyl thiophenes **Va–e** and 2-acryloylsulfanyl thiophenes **VIIa–e**, respectively. The conversion of the intermediates to the final thiopyrans **VIa–e** and dihydrothiopyrans **VIIIa–e** was achieved by heating at 145 °C in DMF for 45 min. 5,6-Dihydro-4*H*-thieno[2,3-*b*]thiopyran-5-carboxylic acid **VIIIa** has been reported as a starting material for the synthesis of presynaptic dopamine receptors.[20]



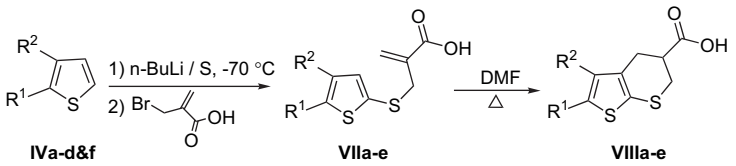
IVa, Va, VIa:- R^1 = R^2 = H. **IVb, Vb, VIb**:- R^1 = Me, R^2 = H.
IVc, Vc, VIc:- R^1 = Et, R^2 = H. **IVd, Vd, VId**:- R^1 = n-Pr, R^2 = H.
IVe, Ve, VIe:- R^1-R^2 = Benzo.

Scheme 3.

After successfully synthesizing the thiophene fused ring thiopyran and dihydrothiopyran we diverted our research interest to the synthesis of dibenzofuran and dibenzothiophene derivatives as depicted in Scheme 5. Dibenzofuran and dibenzothiophene were reacted with *n*-butyllithium resulting in mono-lithium salts,[22] which were then treated with sulfur at lower temperatures to give the *S*-lithium salts. These were then reacted with bromides at the same temperature to give the intermediate thioethers **Xa**,**b** and **XIIa**,**b**. The intermediate thioethers were then heated in *N*,*N*-diethylaniline or *N*,*N*-dimethylformamide to give the cyclized products **XIa**,**b** and **XIIIa**,**b** as depicted in Scheme 5.

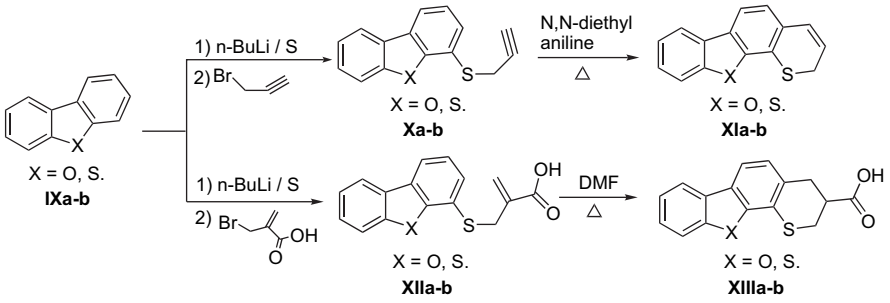
3. Conclusions

We have synthesized a large number of novel heterocyclic systems by means of Claisen rearrangement methodology. The systems developed can give access to a large number of compounds for biological testing.



IVa, VIIa, VIIIa:- $R^1 = R^2 = H$. **IVb, VIIb, VIIIb**:- R^1 = Me, R^2 = H.
IVc, VIIc, VIIIc:- R^1 = Et, R^2 = H. **IVd, VIId, VIIId**:- R^1 = n-Pr, R^2 = H.
IVf, VIIe, VIIIe:- R^1 = CN, R^2 = H.

Scheme 4.



Scheme 5.

4. Experimental

4.1. General

The 2-, 3- and 4-phenylphenols **Ia–c** and 4-bromo-4-hydroxy biphenyl **Id** required for the synthesis were purchased. 4-Hydroxydibenzofuran **Ie** and 4-hydroxydibenzothiophene **If** were synthesized according to the method reported in the literature.[22a–c] Thiophenes **IVa–f** required for the synthesis were purchased. Melting points are uncorrected, measured on a Büchi apparatus. Infrared spectra were recorded on a FTIR Perkin–Elmer spectrometer. ^{1}H NMR spectra were recorded using a 300 MHz Varien (Mercury Vx) SWBB Multinuclear Probe with tetramethylsilane (TMS) as the internal standard. Mass spectra were recorded on a MDS Sciex API 3000 LCMS.

4.2. General method for the synthesis of 2-propynyloxy aryl derivatives IIa–f. Procedure A

4.2.1. 1-Phenyl-2-(2-propynyloxy)benzene IIa. Propargyl bromide (0.40 g, 3.33 mmol) was added to a mixture of 2-phenylphenol (0.51 g, 3.0 mmol) and K_2CO_3 (0.48 g, 3.5 mmol) in dry DMF (10 mL) and stirred at room temperature for 2 h under a nitrogen atmosphere. DMF was then removed under reduced pressure and the residue dissolved in 50 mL of ethyl acetate. The organic layer was washed with water (2×25 mL), dried over sodium sulfate and concentrated under reduced pressure to give pure 1-phenyl-2-(2-propynyloxy)benzene **IIa** (0.625 g, 100%) as a gummy oil; [Found: C, 86.30; H, 5.93. $C_{15}H_{12}O$ requires: C, 86.51; H, 5.81]; IR (neat): 3289, 3061, 1503, 1480, 1434, 1266, 1210, 1123, 1023, and 1009 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.54 (t, J 2.4 Hz, 1H), 4.66 (d, J 2.4 Hz, 2H), 7.04–7.14 (m, 2H), 7.28–7.42 (m, 5H), 7.50–7.54 (m, 2H).

4.2.2. 1-Phenyl-3-(2-propynyloxy)benzene IIb. Compound **IIb** was prepared from 3-phenylphenol **Ib** (0.51 g, 3.0 mmol) in an analogous manner to that for the preparation of **IIa** as a colorless oil (0.625 g, 100%); [Found: C, 86.33; H, 5.90. $C_{15}H_{12}O$ requires: C, 86.51; H, 5.81]; IR (neat): 3303, 3015, 1597, 1573, 1478, 1422, 1295, 1215, 1197, and 1035 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.54 (t, J 2.4 Hz, 1H), 4.75 (d, J 2.4 Hz, 2H), 6.95 (dd, J 3.2 Hz, 1H), 7.20–7.24 (m, 2H), 7.32–7.46 (m, 4H), 7.52–7.59 (m, 2H).

4.2.3. 1-Phenyl-4-(2-propynyloxy)benzene IIc. Compound **IIc** was prepared from 4-phenylphenol **Ic** (0.51 g, 3.0 mmol) in an analogous manner to that for the preparation of **IIa** as a white solid (0.59 g, 95%), mp=75–78 °C; [Found: C, 86.42; H, 5.69. $C_{15}H_{12}O$ requires: C, 86.51; H, 5.81]; IR (KBr): 3275, 3303, 1603, 1584, 1519, 1486, 1287, 1237, 1118, and 1027 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 3.59 (t, J 2.4 Hz, 1H), 4.83 (d, J 2.4 Hz, 2H), 7.04–7.08 (m, 2H), 7.29(t, J 2.4 Hz, 1H), 7.41 (d, J 7.2 Hz, 2H), 7.41 (d, J 8.4 Hz, 4H).

4.2.4. 1-(4-Bromophenyl)-4-(2-propynyloxy)benzene IId. Compound **IId** was prepared from 4-(4-bromophenyl)phenol **Id** (0.75 g, 3.0 mmol) in an analogous manner to that for the preparation of **IIa** as a white solid (0.82 g, 97%), mp=93–95 °C; [Found: C, 62.65; H, 3.99; Br, 27.62. $C_{15}H_{11}BrO$ requires: C, 62.74; H, 3.86; Br, 27.83]; IR (KBr): 3282, 2915, 1602, 1580, 1518, 1480, 1376, 1283, 1240, 1076, 1027, 817, and 805 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.55 (t, J 2.4 Hz, 1H), 4.75 (d, J 2.4 Hz, 2H), 7.06 (d, J 7.8 Hz, 2H), 7.42 (d, J 7.8 Hz, 2H), 7.50–7.58 (m, 4H).

4.2.5. 4-(2-Propynyloxy)dibenzo[*b*,*d*]furan IIe. Compound **IIe** was prepared from 4-hydroxydibenzo[*b*,*d*]furan

IIe (0.55 g, 3.0 mmol) in an analogous manner to that for the preparation of **IIa**, and the crude semisolid obtained was purified by column chromatography (stationary phase: silica gel 60–120, mobile phase: 10% ethyl acetate in hexane) as a white solid (0.62 g, 93%), mp=32–34 °C; [Found: C, 81.30; H, 4.66. $C_{15}H_{10}O_2$ requires: C, 81.07; H, 4.54]; IR (KBr): 3293, 2923, 1583, 1451, 1310, 1191, 1092, 1022, and 932 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.63 (t, *J* 2.4, 2.4 Hz, 1H), 5.05 (d, *J* 2.4 Hz, 2H), 7.20 (d, *J* 7.2 Hz, 1H), 7.33 (t, *J* 7.8, 7.8 Hz, 1H), 7.40 (t, *J* 6.9, 6.9 Hz, 1H), 7.52 (t, *J* 6.9, 6.9 Hz, 1H), 7.66 (dd, *J* 1.0, 1.0 Hz, 1H), 7.70 (d, *J* 7.2, 1H), 8.00 (dd, *J* 1.0, 1.0 Hz, 1H).

4.2.6. 4-(2-Propynyloxy)dibenzo[*b*,*d*]thiophene IIf. Compound **IIf** was prepared from 4-hydroxydibenzo[*b*,*d*]thiophene **IIf** (0.60 g, 3.0 mmol) in an analogous manner to that for the preparation of **IIa**, and the crude semisolid obtained was purified by column chromatography (stationary phase: silica gel 60–120, mobile phase: 10% ethyl acetate in hexane) as a white solid (0.60 g, 84%), mp=109–110 °C; [Found: C, 75.79; H, 4.11; S, 13.58. $C_{15}H_{10}OS$ requires: C, 75.60; H, 4.23; S, 13.45]; IR (KBr): 3305, 1568, 1445, 1321, 1271, 1233, 1107, 1061, 1010, and 927 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.55 (t, *J* 2.4 Hz, 1H), 4.91 (d, *J* 2.4 Hz, 2H), 7.05 (d, *J* 7.5 Hz, 1H), 7.38–7.46 (m, 3H), 7.85 (dd, *J* 0.9, 0.9 Hz, 1H), 7.86 (d, *J* 7.5 Hz, 1H), 8.10 (d, *J* 7.5 Hz, 1H).

4.3. General method for the synthesis of chromene derivatives IIIa–f. Procedure B

4.3.1. 8-Phenyl-2*H*-chromene IIIa. 1-Phenyl-2-(2-propynyloxy)benzene **IIa** (0.370 g, 1.78 mmol) was taken up in *N*,*N*-diethylaniline (20 mL) and stirred at a temperature of 230–240 °C for 18 h under a nitrogen atmosphere. It was then cooled to room temperature and diluted with ethyl acetate (50 mL), washed three times with 50 mL of 2 N aq HCl, and then two times with 25 mL of brine. The organic layer was dried over sodium sulfate and concentrated under reduced pressure to give crude **IIIa**. The crude compound was purified by column chromatography (stationary phase: silica gel 60–120, mobile phase: 15% chloroform in hexane) to give 8-phenyl-2*H*-chromene **IIIa** (0.10 g, 27%) as a white gummy semisolid; [Found: C, 86.41; H, 5.70. $C_{15}H_{12}O$ requires: C, 86.51; H, 5.81]; IR (neat): 2918, 1461, 1429, 1212, 1110, 1070, and 1035 cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.80 (dd, *J* 2.1, 2.1 Hz, 2H), 5.82 (dt, *J* 3.6, 2.4 Hz, 1H), 6.48 (d, *J* 9.5 Hz, 1H), 6.90–6.98 (m, 2H), 7.17 (dd, *J* 2.4, 2.4 Hz, 1H), 7.29 (d, *J* 7.4 Hz, 1H), 7.38–7.43 (m, 2H), 7.53 (d, *J* 8.0 Hz, 2H). MS (EI) *m*/*z* 207.2 (M^{-1}).

4.3.2. 7-Phenyl-2*H*-chromene IIIb. Compound **IIIb** was prepared from 1-phenyl-3-(2-propynyloxy)benzene **IIb** (0.370 g, 1.78 mmol) in an analogous manner to that for the preparation of **IIIa**, and the crude product obtained was purified by column chromatography (stationary phase: silica gel 60–120, mobile phase: 5% chloroform in hexane) as a gummy oil (0.11 g, 30%); [Found: C, 86.66; H, 5.99. $C_{15}H_{12}O$ requires: C, 86.51; H, 5.81]; IR (neat): 2189, 1596, 1463, 1435, 1237, 1200, 1116, and 1018 cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.79 (dd, *J* 2.1, 2.1 Hz, 2H), 5.77 (dt, *J* 3.0, 2.2 Hz, 1H), 6.43 (d, *J* 9.5 Hz, 1H), 6.83 (d, *J* 8.1 Hz, 1H), 6.89 (d, *J* 8.0 Hz, 1H), 7.16 (t, *J* 7.5, 7.5 Hz, 1H), 7.33–7.45 (m, 5H). MS (EI) *m*/*z* 207.2 (M^{-1}).

4.3.3. 6-Phenyl-2*H*-chromene IIIc. Compound **IIIc** was prepared from 1-phenyl-4-(2-propynyloxy)benzene **IIc** (0.370 g, 1.78 mmol) in an analogous manner to that for the preparation of **IIIa**, and the crude product obtained was purified by column chromatography (stationary phase: silica gel 60–120, mobile phase: 15% chloroform in hexane) as a white solid (0.20 g, 55%); mp=78–80 °C; [Found: C, 86.69; H, 5.65. $C_{15}H_{12}O$ requires: C, 86.51; H, 5.81]; IR (KBr): 3050, 2832, 1480, 1452, 1231, 1184, 1135, 1047, 1016, 891, and 836 cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.85 (dd, *J* 1.8, 1.8 Hz, 2H), 5.80 (dt, *J* 3.5, 2.4 Hz, 1H), 6.46 (d, *J* 9.6 Hz, 1H), 6.82 (d, *J* 8.4 Hz, 1H), 7.17 (d, *J* 8.0 Hz, 1H), 7.24–7.28 (m, 2H), 7.39 (t, *J* 7.4, 7.4 Hz, 2H), 7.50 (d, *J* 8.0 Hz, 2H). MS (EI) *m*/*z* 207.4 (M^{-1}).

4.3.4. 6-(4-Bromophenyl)-2*H*-chromene IIId. Compound **IIId** was prepared from 1-(4-bromophenyl)-4-(2-propynyloxy)benzene **IId** (0.43 g, 1.5 mmol) in an analogous manner to that for the preparation of **IIIa**, and the crude product obtained was purified by column chromatography (stationary phase: silica gel 60–120, mobile phase: 5% chloroform in hexane) as a white solid (0.27 g, 63%); mp=107–110 °C; [Found: C, 62.83; H, 3.69; Br, 27.70. $C_{15}H_{11}BrO$ requires: C, 62.74; H, 3.86; Br, 27.83]; IR (KBr): 3282, 2915, 1602, 1518, 1480, 1376, 1283, 1240, 1196, and 1076 cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.87 (dd, *J* 1.8, 1.8 Hz, 2H), 5.82 (dt, *J* 3.6, 2.4 Hz, 1H), 6.49 (d, *J* 9.0 Hz, 1H), 6.80 (d, *J* 8.0 Hz, 1H), 7.25–7.28 (m, 2H), 7.35–7.41 (m, 2H), 7.48–7.55 (d, *J* 8.0 Hz, 2H). MS (EI) *m*/*z* 287.0 (M^+).

4.3.5. 2*H*-Benzo[4,5]furo[3,2-*h*]chromene IIIe. Compound **IIIe** was prepared from 4-(2-propynyloxy)dibenzo[*b*,*d*]furan **IIe** (0.45 g, 2.0 mmol) in an analogous manner to that for the preparation of **IIIa**, and the crude product obtained was purified by column chromatography (stationary phase: silica gel 60–120, mobile phase: 2% ethyl acetate in hexane) as a pale yellow solid (0.29 g, 65%); mp=68–70 °C; [Found: C, 80.90; H, 4.38. $C_{15}H_{10}O_2$ requires: C, 81.07; H, 4.54]; IR (KBr): 2921, 1497, 1427, 1306, 1228, 1191, 1665, 1012, and 930 cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.03 (dd, *J* 2.1, 2.1 Hz, 2H), 5.82 (dt, *J* 3.2, 2.0 Hz, 1H), 6.56 (d, *J* 9.0 Hz, 1H), 6.95 (d, *J* 7.8 Hz, 1H), 7.31 (t, *J* 5.9, 5.9 Hz, 1H), 7.43–7.46 (m, 2H), 7.56 (d, *J* 7.8 Hz, 1H), 7.87 (d, *J* 7.8 Hz, 1H). MS (EI) *m*/*z* 223.3 (M^{+1}).

4.3.6. 2*H*-Benzo[4,5]thieno[3,2-*h*]chromene IIIf. Compound **IIIf** was prepared from 4-(2-propynyloxy)dibenzo[*b*,*d*]thiophene **IIf** (0.475 g, 2.0 mmol) in an analogous manner to that for the preparation of **IIIa**, and the crude product obtained was purified by column chromatography (stationary phase: silica gel 60–120, mobile phase: 2% ethyl acetate in hexane) as a white solid (0.33 g, 70%); mp=88–90 °C; [Found: C, 75.42; H, 4.05; S, 13.29. $C_{15}H_{10}OS$ requires: C, 75.60; H, 4.23; S, 13.45]; IR (KBr): 2923, 1553, 1483, 1406, 1249, 1202, 1131, 1063, 1016, and 813 cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.30 (dd, *J* 2.1, 2.1 Hz, 2H), 5.78 (dt, *J* 3.6, 2.3 Hz, 1H), 6.52 (d, *J* 9.2 Hz, 1H), 7.05 (d, *J* 7.8 Hz, 1H), 7.37–7.42 (m, 2H), 7.64 (d, *J* 7.8 Hz, 1H), 7.82 (d, *J* 8.0 Hz, 1H), 8.05 (d, *J* 8.0 Hz, 1H). MS (EI) *m*/*z* 238.9 (M^{+1}).

4.4. General method for the synthesis of 2-(2-propynylsulfanyl)thiophene and benzothiophene derivatives Va–f. Procedure C

4.4.1. 2-(2-Propynylsulfanyl)thiophene Va. A solution of *n*-butyllithium (13.34 cm^3 of 15% in *n*-hexane, 31.25 mmol) was added to a solution of thiophene **IVa** (2.0 g, 23.8 mmol) in dry THF (20 mL) at −70 °C for a period of 10 min and stirred at −70 to −60 °C for 30 min under a nitrogen atmosphere. Granular sulfur (0.76 g, 23.8 mmol) was added in one portion and then the reaction mixture was stirred at −70 to −60 °C for another 30 min. A cold solution of propargyl bromide (3.11 g, 26.2 mmol) dissolved in dry THF (10 mL) was added so as to maintain the temperature between −70 and −60 °C. After the addition was complete the temperature was gradually raised to −30 °C over a period of 1 h. Reaction was quenched with 2 N cold dilute HCl solution. The mixture was extracted with ethyl acetate (2×100 mL) and the combined organic layers were washed with water (2×100 mL), saturated sodium bicarbonate (100 mL) followed by brine solution (100 mL) and dried over sodium sulfate. This organic layer was concentrated to give the crude product, which was purified by column chromatography (stationary phase: silica gel 60–120, mobile phase: 10% ethyl acetate in hexane) to give 2-(2-propynylsulfanyl)thiophene **Va** (1.8 g, 49%) as a viscous oil; [Found: C, 54.73; H, 4.03; S, 41.79. $C_7H_6S_2$ requires: C, 54.51; H, 3.92; S, 41.57]; IR (neat): 3292, 2919, 1594, 1438, 1226, 1213, 953, and 798 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.28 (t, *J* 2.4, 2.4 Hz, 1H), 3.46 (d, *J* 2.4 Hz, 2H), 7.00 (dd, *J* 1.8, 1.8 Hz, 1H), 7.25 (dd, *J* 0.9, 0.9 Hz, 1H), 7.49 (dd, *J* 0.9, 0.9 Hz, 1H).

4.4.2. 2-Methyl-5-(2-propynylsulfanyl)thiophene Vb. Compound **Vb** was prepared from 2-methylthiophene **IVb** (2.35 g, 23.8 mmol) in an analogous manner to that for the preparation of **Va**, and the crude product obtained was purified by column chromatography (stationary phase: silica gel 60–120, mobile phase: 10% chloroform in hexane) as a viscous oil (2.1 g, 53%); [Found: C, 57.33; H, 4.62; S, 38.33. $C_8H_8S_2$ requires: C, 57.10; H, 4.79; S, 38.11]; IR (neat): 3309, 3018, 1439, 1215, 1161, 1068, and 953 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.27 (t, *J* 2.4, 2.4 Hz, 1H), 2.45 (s, 3H), 3.41 (d, *J* 3.0 Hz, 2H), 6.64 (d, *J* 4.2 Hz, 1H), 7.05 (d, *J* 4.2 Hz, 1H).

4.4.3. 2-Ethyl-5-(2-propynylsulfanyl)thiophene Vc. Compound **Vc** was prepared from 2-ethylthiophene **IVc** (2.67 g, 23.8 mmol) in an analogous manner to that for the preparation of **Va**, and the crude product obtained was purified by column chromatography (stationary phase: silica gel 60–120, mobile phase: 10% chloroform in hexane) as a viscous oil (2.3 g, 54%); [Found: C, 59.15; H, 5.64; S, 35.42. $C_9H_{10}S_2$ requires: C, 59.30; H, 5.53; S, 35.18]; IR (neat): 3293, 2968, 1456, 1439, 1226, 1073, 981, and 805 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.28 (t, *J* 7.2, 7.2 Hz, 3H), 2.28 (t, *J* 2.4, 2.4 Hz, 1H), 2.82 (q, *J* 7.5, 6.8, 7.5 Hz, 2H), 3.43 (d, *J* 3.0 Hz, 2H), 6.68 (d, *J* 4.0 Hz, 1H), 7.08 (d, *J* 4.0 Hz, 1H).

4.4.4. 2-Propyl-5-(2-propynylsulfanyl)thiophene Vd. Compound **Vd** was prepared from 2-propylthiophene **IVd** (3.0 g, 23.8 mmol) in an analogous manner to that for the preparation of **Va**, and the crude product obtained was purified by column chromatography (stationary phase: silica gel 60–120, mobile phase: 10% chloroform in hexane) as a viscous oil (3.87 g, 83%); [Found: C, 61.38; H, 6.03; S, 32.45. $C_{10}H_{12}S_2$ requires: C, 61.18; H, 6.16; S, 32.66]; IR (neat): 3294, 2960, 1455, 1437, 1226, 977, and 801 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.97 (t, *J* 7.2, 7.2 Hz, 3H), 1.68 (sextet, *J* 2.3 Hz, 2H), 2.18 (t, *J* 2.4, 2.4 Hz, 1H), 2.74 (t, *J* 7.8, 7.8 Hz, 2H), 3.43 (d, *J* 2.9 Hz, 2H), 6.66 (d, *J* 3.6 Hz, 1H), 7.07 (d, *J* 3.6 Hz, 1H).

4.4.5. 2-(2-Propynylsulfanyl)benzo[*b*]thiophene Ve. Compound **Ve** was prepared from benzo[*b*]thiophene **IVe** (3.2 g, 23.8 mmol) in an analogous manner to that for the preparation of **Va**, and the crude product obtained was purified by column chromatography (stationary phase: silica gel 60–120, mobile phase: 10% chloroform in hexane) as a viscous oil (3.88 g, 80%); [Found: C, 64.46; H, 3.87; S, 31.15. $C_{11}H_8S_2$ requires: C, 64.67; H, 3.95; S, 31.39]; IR (neat): 3306, 2923, 1423, 1215, 1156, 1081, 972, and 831 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.30 (t, *J* 3.0, 3.0 Hz, 1H), 3.60 (d, *J* 2.4 Hz, 2H), 7.30–7.35 (m, 2H), 7.45 (s, 1H), 7.70–7.76 (m, 2H).

4.5. General method for the synthesis of 6*H*-thieno[1,3-*b*]thiopyran and 2*H*-benzo[4,5]thieno[2,3-*b*]thiopyran derivatives VIa–e. Procedure D

4.5.1. 6*H*-Thieno[1,3-*b*]thiopyran VIa. 2-(2-Propynylsulfanyl)thiophene **Va** (0.2 g, 1.29 mmol) was taken up in dry *N*,*N*-dimethylformamide (5 mL) and stirred at 150 °C for 30 min under a nitrogen atmosphere. Then *N*,*N*-dimethylformamide was evaporated under reduced pressure and the residue was dissolved in ethyl acetate (50 mL). The ethyl acetate layer was washed with water (2×25 mL), followed by brine (25 mL). The organic layer was dried over sodium sulfate and concentrated to give the crude compound as an oil. This crude compound was purified by column chromatography (stationary phase: silica gel 60–120, mobile phase: 10% ethyl acetate in hexane) to give 6*H*-thieno[1,3-*b*]thiopyran **VIa** (140 mg, 70%) as a viscous oil; [Found: C, 54.39; H, 3.78; S, 41.75. $C_7H_6S_2$ requires: C, 54.51; H, 3.92; S, 41.57]; IR (neat): 3037, 2878, 1613, 1406, 1207, 1042, and 874 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.48 (dd, *J* 1.5, 1.5 Hz, 2H), 5.71 (dt, *J* 3.6, 2.4 Hz, 1H), 6.50 (d, *J* 7.4 Hz, 1H), 6.85 (d, *J* 5.4 Hz, 1H), 7.00 (d, *J* 5.4 Hz, 1H). MS (EI) *m*/*z* 153.3 (M^{-1}).

4.5.2. 2-Methyl-6*H*-thieno[1,3-*b*]thiopyran VIb. Compound **VIb** was prepared from 2-methyl-5-(2-propynylsulfanyl)thiophene **Vb** (0.34 g, 2.0 mmol) in an analogous manner to that for the preparation of **VIa**, and the crude product obtained was purified by column chromatography (stationary phase: silica gel 60–120, mobile phase: 10% chloroform in hexane) as a viscous oil (0.235 g, 70%); [Found: C, 56.88; H, 4.65; S, 37.85. $C_8H_8S_2$ requires: C, 57.10; H, 4.79; S, 38.11]; IR (neat): 2918, 1436, 1378, 1196, 1120, 1062, and 962 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.41 (s, 3H), 3.45 (dd, *J* 1.5, 1.5 Hz, 2H), 5.66 (dt, *J* 3.4, 2.4 Hz, 1H), 6.40 (d, *J* 7.4 Hz, 1H), 6.53 (s, 1H). MS (EI) *m*/*z* 167.0 (M^{-1}).

4.5.3. 2-Ethyl-6*H*-thieno[1,3-*b*]thiopyran VIc. Compound **VIc** was prepared from 2-ethyl-5-(2-propynylsulfanyl)thiophene **Vc** (0.36 g, 2.0 mmol) in an analogous manner to

that for the preparation of **VIa**, and the crude product obtained was purified by column chromatography (stationary phase: silica gel 60–120, mobile phase: 10% chloroform in hexane) as a viscous oil (0.27 g, 75%); [Found: C, 59.06; H, 5.45; S, 35.01. $C_9H_{10}S_2$ requires: C, 59.30; H, 5.53; S, 35.18]; IR (neat): 2969, 1450, 1414, 1215, 1185, 1065, and 836 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.34 (t, *J* 7.5, 7.5 Hz, 3H), 2.28 (q, *J* 7.5, 6.5, 7.5 Hz, 2H), 3.53 (dd, *J* 1.5, 1.5 Hz, 2H), 5.74 (dt, *J* 3.6, 2.2 Hz, 1H), 6.48 (d, *J* 7.4 Hz, 1H), 6.63 (s, 1H). MS (EI) *m*/*z* 181.3 (M^{-1}).

4.5.4. 2-Propyl-6*H*-thieno[1,3-*b*]thiopyran VId. Compound **VId** was prepared from 2-propyl-5-(2-propynylsulfanyl)thiophene **Vd** (0.39 g, 2.0 mmol) in an analogous manner to that for the preparation of **VIa**, and the crude product obtained was purified by column chromatography (stationary phase: silica gel 60–120, mobile phase: 10% chloroform in hexane) as a viscous oil (0.3 g, 75%); [Found: C, 61.36; H, 6.25; S, 32.90. $C_{10}H_{12}S_2$ requires: C, 61.18; H, 6.16; S, 32.66]; IR (neat): 2917, 1441, 1314, 1212, 1131, 964, and 912 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.96 (t, *J* 7.2, 7.2 Hz, 3H), 1.65 (sextet, *J* 3.0 Hz, 2H), 2.68 (t, *J* 7.8, 7.8 Hz, 2H), 3.46 (dd, *J* 1.4, 1.4 Hz, 2H), 5.67 (dt, *J* 3.6, 2.4 Hz, 1H), 6.41 (d, *J* 8.0 Hz, 1H), 6.54 (s, 1H). MS (EI) *m*/*z* 195.1 (M^{-1}).

4.5.5. 2*H*-Benzo[4,5]thieno[2,3-*b*]thiopyran VIe. Compound **VIe** was prepared from 2-(2-propynylsulfanyl)-benzo[*b*]thiophene **Ve** (0.41 g, 2.0 mmol) in an analogous manner to that for the preparation of **VIa**, and the crude product obtained was purified by column chromatography (stationary phase: silica gel 60–120, mobile phase: 10% chloroform in hexane) as a white solid (0.3 g, 75%); mp=88–90 °C; [Found: C, 64.49; H, 4.08; S, 31.55. $C_{11}H_8S_2$ requires: C, 64.67; H, 3.95; S, 31.39]; IR (KBr): 2880, 1457, 1420, 1312, 1247, 1133, 1092, and 1014 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.58 (dd, *J* 1.8, 1.8 Hz, 2H), 5.81 (dt, *J* 3.6, 2.5 Hz, 1H), 6.75 (d, *J* 8.0 Hz, 1H), 7.24 (t, *J* 6.6, 6.6 Hz, 1H), 7.32 (t, *J* 6.6, 6.6 Hz, 1H), 7.69 (d, *J* 7.8 Hz, 1H), 7.79 (d, *J* 7.8 Hz, 1H), MS (EI) *m*/*z* 203.3 (M^{-1}).

4.6. General method for the synthesis of 2-(2-thienyl sulfanylmethyl)acrylic acid derivatives VIIa–e

The 2-(2-thienyl sulfanylmethyl)acrylic acid derivatives **VIIa–e** were synthesized following the general procedure C from thiophenes **IVa–d** and **IVf**, α-(bromomethyl)acrylic, acid and sulfur in the presence of *n*-butyllithium as base.

4.6.1. 2-(2-Thienyl sulfanylmethyl)acrylic acid VIIa.[20] A solution of *n*-butyllithium (13.34 cm^3 of 15% in *n*-hexane, 31.25 mmol) was added to a solution of thiophene **IVa** (2.0 g, 23.8 mmol) in dry THF (20 mL) at −78 °C for a period of 10 min and stirred at −78 °C for 30 min under a nitrogen atmosphere. Granular sulfur (0.762 g, 23.8 mmol) was added in one portion and then the reaction mixture was stirred at −78 °C for another 30 min. A cold solution of α-(bromomethyl)acrylic acid (4.32 g, 26.2 mmol) dissolved in a solution of sodium hydroxide (2.2 g, 55 mmol) in water (20 mL) is then added slowly while maintaining the temperature at −78 °C. After the addition is complete the temperature is gradually raised to −30 °C over a period of 1 h. Then the reaction was quenched with 2 N cold dilute HCl solution till pH was acidic. The mixture was extracted with ethyl acetate (2×100 mL) and the combined organic layers were washed with water (2×50 mL) and dried over sodium sulfate. This organic layer was concentrated to give the crude product, which was purified by column chromatography (stationary phase: silica gel 60–120, mobile phase: 2% methanol in chloroform) as a white solid (3.42 g, 72%); mp=84–86 °C; [Found: C, 47.76; H, 4.18; S, 32.27. $C_8H_8O_2S_2$ requires: C, 47.98; H, 4.03; S, 32.02]; IR (neat): 3031, 2629, 1685, 1622, 1443, 1402, and 1231 cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.59 (s, 2H), 5.88 (s, 1H), 6.24 (s, 1H), 6.95 (t, *J* 4.5, 4.5 Hz, 1H), 7.08 (d, *J* 4.2 Hz, 1H), 7.34 (d, *J* 5.1 Hz, 1H).

4.6.2. 2-(5-Methyl-2-thienyl sulfanylmethyl)acrylic acid VIIb. Compound **VIIb** was prepared from 2-methylthiophene **IVb** (2.35 g, 23.8 mmol) in an analogous manner to that for the preparation of **VIIa**, and the crude product obtained was purified by column chromatography (stationary phase: silica gel 60–120, mobile phase: 2% methanol in chloroform) as a white solid (3.56 g, 70%); mp=157–160 °C; [Found: C, 50.23; H, 4.55; S, 29.70. $C_9H_{10}O_2S_2$ requires: C, 50.44; H, 4.70; S, 29.92]; IR (KBr): 2632, 1687, 1622, 1445, 1408, and 1232 cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.44 (s, 3H), 3.54 (s, 2H), 5.38 (s, 1H), 6.24 (s, 1H), 6.60 (d, *J* 4.8 Hz, 1H), 6.87 (d, *J* 4.2 Hz, 1H).

4.6.3. 2-(5-Ethyl-2-thienyl sulfanylmethyl)acrylic acid VIIc. Compound **VIIc** was prepared from 2-ethylthiophene **IVc** (2.67 g, 23.8 mmol) in an analogous manner to that for the preparation of **VIIa**, and the crude product obtained was purified by column chromatography (stationary phase: silica gel 60–120, mobile phase: 2% methanol in chloroform) as a white solid (3.8 g, 70%); mp=67–68 °C; [Found: C, 52.84; H, 5.45; S, 28.27. $C_{10}H_{12}O_2S_2$ requires: C, 52.60; H, 5.30; S, 28.09]; IR (KBr): 2965, 2629, 1691, 1622, 1440, 1323, 1218, and 926 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.28 (t, *J* 7.5, 7.5 Hz, 3H), 2.80 (q, *J* 7.5, 6.6, 7.5 Hz, 2H), 3.55 (s, 2H), 5.39 (s, 1H), 6.24 (s, 1H), 6.63 (d, *J* 3.6 Hz, 1H), 6.90 (d, *J* 3.6 Hz, 1H).

4.6.4. 2-(5-Propyl-2-thienyl sulfanylmethyl)acrylic acid VIId. Compound **VIId** was prepared from 2-propylthiophene **IVd** (3.0 g, 23.8 mmol) in an analogous manner to that for the preparation of **VIIa**, and the crude product obtained was purified by column chromatography (stationary phase: silica gel 60–120, mobile phase: 2% methanol in chloroform) as a white solid (3.45 g, 60%); mp=61–62 °C; [Found: C, 54.32; H, 5.68; S, 26.34. $C_{11}H_{14}O_2S_2$ requires: C, 54.51; H, 5.82; S, 26.46]; IR (KBr): 2958, 2629, 1693, 1622, 1441, 1325, and 1230 cm^{-1}. ^1H NMR (DMSO-d_6): δ 0.97 (t, *J* 7.5, 7.5 Hz, 3H), 1.68 (sextet, *J* 2.9 Hz, 2H), 2.74 (t, *J* 7.2, 7.2 Hz, 2H), 3.56 (s, 2H), 5.38 (s, 1H), 6.24 (s, 1H), 6.64 (d, *J* 2.7 Hz, 1H), 6.91 (d, *J* 3.6 Hz, 1H).

4.6.5. 2-(5-Cyano-2-thienyl sulfanylmethyl)acrylic acid VIIe. Compound **VIIe** was prepared from 2-cyanothiophene **IVf** (2.6 g, 23.8 mmol) in an analogous manner to that for the preparation of **VIIa**, and the crude product obtained was purified by column chromatography (stationary phase: silica gel 60–120, mobile phase: 2% methanol in chloroform) as a white solid (2.73 g, 51%); mp=94–96 °C; [Found: C, 47.76; H, 3.27; N, 6.02; S, 28.65. $C_9H_7NO_2S_2$ requires: C,

47.98; H, 3.13; N, 6.22; S, 28.46]; IR (KBr): 2880, 2522, 2222,1687, 1622, 1440, 1417, 1311, and 1215 cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.70 (s, 2H), 5.56 (s, 1H), 6.32 (s, 1H), 7.04 (d, *J* 3.9 Hz, 1H), 7.24 (d, *J* 4.2 Hz, 1H).

4.7. General method for the synthesis of 5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-5-carboxylic acid derivatives VIIIa–e

5,6-Dihydro-4*H*-thieno[2,3-*b*]thiopyran-5-carboxylic acids **VIIIa–e** were synthesized following the general procedure D by heating 2-(2-thienyl sulfanylmethyl)acrylic acids **VIIa–e** in *N*,*N*-dimethylformamide at 135 °C for 45 min.

4.7.1. 5,6-Dihydro-4*H*-thieno[2,3-*b*]thiopyran-5-carboxylic acid VIIIa.[20] Compound **VIIIa** was prepared from 2-(2-thienyl sulfanylmethyl)acrylic acid **VIIIa** (0.80 g, 4.0 mmol) in an analogous manner to that for the preparation of **VIa**, and the crude product obtained was purified by column chromatography (stationary phase: silica gel 60–120, mobile phase: 3% methanol in chloroform) as a white solid (0.73 g, 91%); mp=130–132 °C; [Found: C, 48.17; H, 4.15; S, 31.80. $C_8H_8O_2S_2$ requires: C, 47.98; H, 4.03; S, 32.02]; IR (KBr): 2892, 2601, 1699, 1336, and 1213 cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.90–3.29 (m, 5H), 6.76 (d, *J* 4.9 Hz, 1H), 7.03 (d, *J* 5.1 Hz, 1H). MS (EI) *m*/*z* 199.0 (M^{-1}).

4.7.2. 2-Methyl-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-5-carboxylic acid VIIIb. Compound **VIIIb** was prepared from 2-(5-methyl-2-thienyl sulfanylmethyl)acrylic acid **VIIb** (0.85 g, 4.0 mmol) in an analogous manner to that for the preparation of **VIa**, and the crude product obtained was purified by column chromatography (stationary phase: silica gel 60–120, mobile phase: 3% methanol in chloroform) as a white solid (0.77 g, 90%); mp=126–128 °C; [Found: C, 50.65; H, 4.89; S, 30.13. $C_9H_{10}O_2S_2$ requires: C, 50.44; H, 4.70; S, 29.92]; IR (KBr): 2889, 2611, 1695, 1330, 1225, and 1109 cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.37 (s, 3H), 2.80–3.03 (m, 2H), 3.13–3.25 (m, 3H), 6.41 (s, 1H). MS (EI) *m*/*z* 213.0 (M^{-1}).

4.7.3. 2-Ethyl-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-5-carboxylic acid VIIIc. Compound **VIIIc** was prepared from 2-(5-ethyl-2-thienyl sulfanylmethyl)acrylic acid **VIIc** (0.91 g, 4.0 mmol) in an analogous manner to that for the preparation of **VIa**, and the crude product obtained was purified by column chromatography (stationary phase: silica gel 60–120, mobile phase: 3% methanol in chloroform) as a white solid (0.77 g, 85%); mp=141–143 °C; [Found: C, 52.33; H, 5.05; S, 28.32. $C_{10}H_{12}O_2S_2$ requires: C, 52.60; H, 5.30; S, 28.09]; IR (KBr): 2971, 1698, 1418, 1287, 1209, and 1022 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.25 (t, *J* 7.5, 7.5 Hz, 3H), 2.72 (q, *J* 7.1, 6.2, 7.1 Hz, 2H), 2.79–3.02 (m, 2H), 3.07–3.25 (m, 3H), 6.44 (s, 1H). MS (EI) *m*/*z* 227.1 (M^{-1}).

4.7.4. 2-Propyl-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-5-carboxylic acid VIIId. Compound **VIIId** was prepared from 2-(5-propyl-2-thienyl sulfanylmethyl)acrylic acid **VIId** (0.97 g, 4.0 mmol) in an analogous manner to that for the preparation of **VIa**, and the crude product obtained was purified by column chromatography (stationary phase: silica gel 60–120, mobile phase: 3% methanol in chloroform) as a white solid (0.83 g, 86%); mp=96–98 °C; [Found: C, 54.27; H, 5.97; S, 26.20. $C_{11}H_{14}O_2S_2$ requires: C, 54.51; H, 5.82; S, 26.46]; IR (KBr): 2876, 1705, 1413, 1269, 1205, and 1022 cm^{-1}. ^1H NMR (DMSO-d_6): δ 0.95 (t, *J* 7.5, 7.5 Hz, 3H), 1.62 (sextet, *J* 3.0 Hz, 2H), 2.65 (t, *J* 7.5, 7.5 Hz, 2H), 2.86–3.02 (m, 2H), 3.05–3.23 (m, 3H), 6.43 (s, 1H). MS (EI) *m*/*z* 241.1 (M^{-1}).

4.7.5. 2-Cyano-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-5-carboxylic acid VIIIe. Compound **VIIId** was prepared from 2-(5-cyano-2-thienyl sulfanylmethyl)acrylic acid **VIIe** (0.97 g, 4.0 mmol) in an analogous manner to that for the preparation of **VIa**, and the crude product obtained was purified by column chromatography (stationary phase: silica gel 60–120, mobile phase: 3% methanol in chloroform) as a white solid (0.85 g, 88%); mp=169–171 °C; [Found: C, 48.10; H, 3.00; N, 6.45; S, 28.27. $C_9H_7NO_2S_2$ requires: C, 47.98; H, 3.13; N, 6.22; S, 28.46]; IR (KBr): 2919, 2213, 1695, 1409, 1279, and 1211 cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.90–3.10 (m, 2H), 3.17–3.36 (m, 3H), 7.28 (s, 1H). MS (EI) *m*/*z* 224.0 (M^{-1}).

4.8. Synthesis of propynyl and acryloyl thioethers of dibenzo[*b*,*d*]furan and dibenzo[*b*,*d*]thiophene Xa,b, XIIa,b

4.8.1. 4-(2-Propynylsulfanyl)dibenzo[*b*,*d*]furan Xa. A solution of *n*-butyllithium (4.2 mL of 15% in *n*-hexane, 9.84 mmol) was added to a stirred solution of dibenzofuran (1.5 g, 8.93 mmol) in dry THF (15 mL) at −40 °C over a period of 10 min then stirred at room temperature for 2 h under a nitrogen atmosphere. Reaction was cooled to −40 °C, sulfur (0.286 g, 8.93 mmol) was added and stirring maintained at −40 to −30 °C for 30 min. Then propargyl bromide (1.07 g, 8.99 mmol) was added at the same temperature. The temperature of the reaction was raised to room temperature and stirred for another 30 min. The reaction mixture was slowly quenched with water and extracted with ethyl acetate (2×50 mL). The combined organic layer was washed with water (50 mL) and finally with brine (50 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure to give crude product, which was purified by column chromatography (stationary phase: silica gel 60–120, mobile phase: 30% chloroform in hexane) to give a white solid (0.51 g, 24%); mp 45–46 °C; [Found: C, 75.38; H, 4.15; S, 13.67. $C_{15}H_{10}OS$ requires: C, 75.60; H, 4.23; S, 13.45]; IR (KBr): 3275, 2955, 1432, 1375, and 1030 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.17 (t, *J* 2.7, 2.7 Hz, 1H), 3.81 (d, *J* 2.4 Hz, 2H), 7.30–7.38 (m, 2H), 7.46 (t, *J* 6.6, 6.6 Hz, 1H), 7.58–7.64 (m, 2H), 7.85–7.95 (m, 2H).

4.8.2. 4-(2-Propynylsulfanyl)dibenzo[*b*,*d*]thiophene Xb. Compound **Xb** was prepared from dibenzothiophene (1.64 g, 8.93 mmol) in an analogous manner to that for the preparation of **Xa**, and the crude product obtained was purified by column chromatography (stationary phase: silica gel 60–120, mobile phase: 5% ethyl acetate in hexane) as a pale yellow solid (0.68 g, 30%); mp=64–65 °C; [Found: C, 70.69; H, 3.91; S, 25.39. $C_{15}H_{10}S_2$ requires: C, 70.83; H, 3.96; S, 25.21]; IR (KBr): 3283, 2946, 1438, 1384, and 1034 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.21 (t, *J* 2.4, 2.4 Hz, 1H), 3.73 (d, *J* 3.0 Hz, 2H), 7.44–7.50 (m, 3H), 7.46 (d, *J* 7.6 Hz, 1H), 7.87–7.90 (m, 1H), 8.10–8.15 (m, 2H).

4.8.3. 2-Dibenzo[*b*,*d*]furan-4-ylsulfanylmethylacrylic acid XIIa. A solution of *n*-butyllithium (4.2 mL of 15% in *n*-hexane, 9.84 mmol) was added to a stirred solution of dibenzofuran (1.5 g, 8.93 mmol) in dry THF (15 mL) at −40 °C over a period of 10 min and stirred at room temperature for 2 h under a nitrogen atmosphere. Reaction was cooled to −40 °C, sulfur (0.286 g, 8.93 mmol) was added and stirring maintained at −40 to −30 °C for 30 min. Then a solution of α-(bromomethyl)acrylic acid (0.73 g, 4.47 mmol) in THF (5 mL) and NaOH (0.35 g, 8.95 mmol) in water (5 mL) was added simultaneously over 10 min at the same temperature. The temperature was raised to room temperature and stirred for 30 min. Water (50 mL) was added to the reaction mixture and extracted with ethyl acetate (50 mL). The aqueous layer was acidified with 2 N aq HCl solution, extracted with chloroform (3×50 mL). The combined organic layer was washed with brine (50 mL), dried over sodium sulfate and concentrated to give crude product, which was purified by column chromatography (stationary phase: silica gel 60–120, mobile phase: 3% methanol in chloroform) to give a white solid (0.46 g, 18%); mp=149–150 °C; [Found: C, 67.48; H, 4.41; S, 11.06. $C_{16}H_{12}O_3S$ requires: C, 67.59; H, 4.25; S, 11.28]; IR (KBr): 2914, 2522, 1698, 1621, 1437, and 1218 cm^{-1}. ^1H NMR (DMSO-d_6): δ 4.00 (s, 2H), 5.45 (s, 1H), 6.00 (s, 1H), 7.38–7.60 (m, 4H), 7.78 (d, *J* 7.8 Hz, 1H), 8.05 (d, *J* 7.8 Hz, 1H), 8.16 (d, *J* 7.8 Hz, 1H) 12.80 (hump, 1H).

4.8.4. 2-Dibenzo[*b*,*d*]thiophene-4-ylsulfanylmethylacrylic acid XIIb. Compound **XIIb** was prepared from dibenzothiophene (1.0 g, 5.43 mmol) in an analogous manner to that for the preparation of **XIIa**, and the crude product obtained was purified by column chromatography (stationary phase: silica gel 60–120, mobile phase: 2% methanol in chloroform) as a white solid (0.41 g, 25%); mp=162–165 °C; [Found: C, 63.72; H, 4.21; S, 21.45. $C_{16}H_{12}O_2S_2$ requires: C, 63.97; H, 4.03; S, 21.35]; IR (KBr): 2916, 1696, 1438, 1309, and 1213 cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.94 (s, 2H), 5.48 (d, *J* 0.9 Hz, 1H), 5.94 (d, *J* 1.2 Hz, 1H), 7.51–7.60 (m, 4H), 8.06 (d, *J* 7.5 Hz, 1H), 8.30 (d, *J* 8.7 Hz, 1H), 8.35 (d, *J* 7.8 Hz, 1H), 12.80 (hump, 1H).

4.8.5. 2*H*-Benzo[*b*]thiochromeno[7,8-*d*]furan XIa. Compound **XIa** is synthesized following the procedure B by heating 4-(2-propynylsulfanyl)dibenzo[*b*,*d*]furan **Xa** (0.95 g, 4.0 mmol) in *N*,*N*-diethylaniline at 220 °C for 8 h under nitrogen atmosphere. The crude product obtained was purified by column chromatography (stationary phase: silica gel 60–120, mobile phase: 15% chloroform in hexane) as a white solid (0.52 g, 55%); mp=95–97 °C; [Found: C, 75.88; H, 4.13; S, 13.64. $C_{15}H_{10}OS$ requires: C, 75.60; H, 4.23; S, 13.45]; IR (KBr): 2884, 1450, 1407, 1201, 1185, and 1019 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.55 (dd, *J* 1.5, 1.5 Hz, 2H), 5.97 (q, *J* 5.4, 4.2, 5.4 Hz, 1H), 6.65 (d, *J* 10.5 Hz, 1H), 7.05 (d, *J* 7.8 Hz, 1H), 7.31 (t, *J* 6.6, 6.6 Hz, 1H), 7.43 (t, *J* 7.3, 7.3 Hz, 1H), 7.68 (d, *J* 9.3 Hz, 1H), 7.71 (d, *J* 7.8 Hz, 1H), 7.86 (d, *J* 8.1 Hz, 1H). MS (EI) *m*/*z* 237.3 (M^{-1}).

4.8.6. 2*H*-Benzo[*b*]thiochromeno[7,8-*d*]thiophene XIb. Compound **XIb** was prepared from 4-(2-propynylsulfanyl)-dibenzo[*b*,*d*]thiophene **Xb** (0.95 g, 4.0 mmol) in an analogous manner to that for the preparation of **XIa**, and the crude product obtained was purified by column chromatography (stationary phase: silica gel 60–120, mobile phase: 15% chloroform in hexane) as a gummy oil (1.0 g, 70%); [Found: C, 70.93; H, 3.84; S, 25.38. $C_{15}H_{10}S_2$ requires: C, 70.83; H, 3.96; S, 25.21]; IR (neat): 3033, 1446, 1366, 1115, 1038, and 832 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.62 (dd, *J* 1.5, 1.5 Hz, 2H), 6.01 (q, *J* 5.5, 4.0, 5.5 Hz, 1H), 6.66 (dt, *J* 3.5, 2.6 Hz, 1H), 7.18 (d, *J* 7.8 Hz, 1H), 7.43–7.46 (m, 2H), 7.85–7.89 (m, 2H), 9.10 (d, *J* 8.8 Hz, 1H). MS (EI) *m*/*z* 253.2 (M^{-1}).

4.8.7. 3,4-Dihydro-2*H*-benzo[*b*]thiochromeno[7,8-*d*]-furan-3-carboxylic acid XIIIa. Compound **XIIIa** is synthesized following the procedure D by heating 2-dibenzo[*b*,*d*]furan-4-ylsulfanylmethylacrylic acid **XIIa** (1.1 g, 4.0 mmol) in *N*,*N*-dimethylformamide at 150 °C for 5 h under a nitrogen atmosphere. The crude product obtained was purified by column chromatography (stationary phase: silica gel 60–120, mobile phase: 2% methanol in chloroform) as a white solid (0.72 g, 65%); mp=253–254 °C; [Found: C, 67.75; H, 4.13; S, 11.40. $C_{16}H_{12}O_3S$ requires: C, 67.59; H, 4.25; S, 11.28]; IR (KBr): 2885, 2603, 1694, 1409, 1192, 1152, and 938 cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.28–3.74 (m, 5H), 7.21 (d, *J* 7.8 Hz, 1H), 7.39 (t, *J* 7.2, 7.2 Hz, 1H), 7.50 (t, *J* 7.2, 7.2 Hz, 1H), 7.76 (t, *J* 8.1, 8.1 Hz, 2H), 8.09 (d, *J* 7.5 Hz, 1H), 12.75 (hump, 1H). MS (EI) *m*/*z* 283.1 (M^{-1}).

4.8.8. 3,4-Dihydro-2*H*-benzo[4,5]thieno[3,2-*h*]thiochromene-3-carboxylic acid XIIIb. Compound **XIIIb** was prepared from 2-dibenzo[*b*,*d*]thiophene-4-ylsulfanylmethylacrylic acid **XIIb** (1.2 g, 4.0 mmol) in an analogous manner to that for the preparation of **XIIIa**, and the crude product obtained was purified by column chromatography (stationary phase: silica gel 60–120, mobile phase: 2% methanol in chloroform) as a white solid (0.888 g, 74%); mp=254–256 °C; [Found: C, 64.17; H, 3.97; S, 21.56. $C_{16}H_{12}O_2S_2$ requires: C, 63.97; H, 4.03; S, 21.35]; IR (KBr): 2888, 1697, 1406, 1271, and 1192 cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.09–3.45 (m, 5H), 7.33 (d, *J* 8.4 Hz, 1H), 7.51 (m, 2H), 8.03 (d, *J* 7.8 Hz, 2H), 8.13 (d, *J* 7.8 Hz, 1H), 12.75 (hump, 1H). MS (EI) *m*/*z* 299.1 (M^{-1}).

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References and notes

1. Kaye, P. T.; Musa, M. A.; Nchinda, A. T.; Nocanda, X. W. *Synth. Commun.* **2004**, *34*, 2575.
2. Kaye, P. T. *S. Afr. J. Chem.* **2004**, *57*, 545.
3. Kaltenbach, R. F.; Robinson, S. P.; Trainor, G. L. U.S. Patent 2005/0267183 A1, December 1, 2005.
4. Zhang, X.; Sui, Z. U.S. Patent 2006/0020018 A1, January 26, 2006.
5. (a) Kakiuchi, F.; Yamauchi, M.; Chatani, N.; Murai, S. *Chem. Lett.* **1996**, *25*, 111; (b) Thalji, R. K.; Ahrendt, K. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 9692; (c) Boele, M. D. K.; van Strijdonck, G. P. F.; de Vries,

A. H. M.; Kamer, P. C. J.; de Vries, J. G.; Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2002**, *124*, 1586; (d) Baran, P. S.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 7904.
6. Chatani, N.; Inoue, H.; Ikeda, T.; Murai, S. *J. Org. Chem.* **2000**, *65*, 4913.
7. Koch-Pomeranz, U.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta* **1973**, *56*, 2981.
8. (a) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1996**, *118*, 6305; (b) Larock, R. C.; Dotty, M. J.; Tian, Q.; Zenner, J. M. *J. Org. Chem.* **1997**, *62*, 7536.
9. (a) Pastine, S. J.; Youn, S. W.; Sames, D. *Tetrahedron* **2003**, *59*, 8859; (b) Pastine, S. J.; Youn, S. W.; Sames, D. *Org. Lett.* **2004**, *6*, 581.
10. Jia, C.; Piao, D.; Oyamada, J.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, *287*, 1992.
11. Jia, C.; Lu, W.; Oyamada, J.; Kitamura, T.; Matsuda, K.; Irie, M.; Fujiwara, Y. *J. Am. Chem. Soc.* **2000**, *122*, 7252.
12. Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633.
13. Viciu, M. S.; Stevens, E. D.; Petersen, J. L.; Nolan, S. P. *Organometallics* **2004**, *23*, 3752.
14. Trost, B. M.; Toste, F. D.; Greenman, K. *J. Am. Chem. Soc.* **2003**, *125*, 4518.
15. Boele, M. D. K.; van Strijdonck, G. P. F.; de Vries, A. H. M.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2002**, *124*, 1586.
16. Song, C. E.; Jung, D.-U.; Choung, S. Y.; Roh, E. J.; Lee, S.-g. *Angew. Chem., Int. Ed.* **2004**, *43*, 6183.
17. Reetz, M. T.; Sommer, K. *Eur. J. Org. Chem.* **2003**, *18*, 3485.
18. Matsumoto, T.; Taube, D. J.; Periana, R. A.; Taube, H.; Yoshida, H. *J. Am. Chem. Soc.* **2000**, *122*, 7414.
19. Shi, Z.; He, C. *J. Org. Chem.* **2004**, *69*, 3669.
20. Hutchison, A. J.; Verona, N. J. U.S. Patent 4,816,474, March 28, 1989.
21. Ramarajan, K.; Ramalingam, K.; O'Donnell, D. J.; Berlin, K. D. *Org. Synth. VII* **1990**, 210.
22. (a) Gilmen, H.; Young, R. V. *J. Am. Chem. Soc.* **1935**, *57*, 1121; (b) Nishioka, M.; Castle, R. N.; Lee, M. L. *J. Heterocycl. Chem.* **1985**, *22*, 215; (c) Oliveira, M. M.; Moustrou, C.; Carvalho, L. M.; Silva, J. A. C.; Samat, A.; Guglielmetti, R.; Dubest, R.; Aubard, J.; Oliveira-Campos, A. M. F. *Tetrahedron* **2002**, *58*, 1709.

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4,4′-Dihydroxy-3,3′,5,5′-tetramethoxyazodioxybenzene: an unexpected dimer formed during hydroxylamine extractions of wheat flour

R. E. Asenstorfer* and D. J. Mares

School of Agriculture and Wine, The University of Adelaide, Waite Campus, PMB 1, Glen Osmond, SA 5064, Australia

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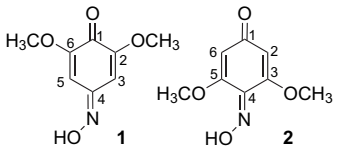
Abstract—Neutral hydroxylamine extracts of wheat contained a product that was colourless at pH<5 (λ_{max} 340 nm) and yellow at pH>9 (λ_{max} 400 nm). ESI-MS showed a major ion *m/z* 184.0 and a possible parent ion *m/z* 367.2 (MH^+) suggesting that the product resulted from the reaction of 2,6-dimethoxy-*p*-quinone with hydroxylamine. However, mass spectral and other spectroscopic data indicated that the compound was neither of the 2,6-dimethoxy-*p*-quinone oximes. A product with identical absorbance, mass spectrum, electrophoretic mobility and HPLC retention time as the pigment from hydroxylamine extracts of flour was observed amongst the reaction products of hydroxylamine and 1,4-dihydroxy-2,6-dimethoxybenzene. The structure of this product was identified by NMR, 2D NMR and IR as 4,4′-dihydroxy-3,3′,5,5′-tetramethoxyazodioxybenzene.

1. Introduction

Yellow alkaline noodles (YAN) made from wheat flour, alkaline salts such as sodium and potassium carbonate and water, are an important part of the diet in many countries of eastern and south-eastern Asia.[1] A preliminary study by Mares et al.[2] indicated that the colour of alkaline noodles was due partly to xanthophylls and partly to compounds that could be extracted with aqueous solvents. These latter compounds, in contrast to the xanthophylls, were essentially colourless at neutral or acid pH, but turned yellow at higher pH. An efficient method for the quantification of these water-soluble pigments using hydroxylamine extraction has been recently reported.[3] Together with flavone-*C*-glycosides, another unknown pigment was identified as a possible contributor to the colour of YAN.[3] This pigment was relatively unstable, colourless at pH<5 (λ_{max} 340 nm) and yellow at pH>9 (λ_{max} 400 nm). Electrospray mass spectrum yielded a major ion *m/z* 184.0 but with a possible parent ion *m/z* 367.2 (MH^+).

If the ion-mass of 184 was an MH^+ ion, it could arise from a low molecular weight oxime formed by condensation of hydroxylamine with either an aldehyde or ketone. One possible carbonyl candidate, which forms an oxime with a mass of 183, was 2,6-dimethoxy-*p*-quinone. 2,6-Dimethoxy-*p*-quinone can be isolated from wheat germ fermented with baker's yeast.[4,5] This compound forms two oxime isomers, 2,6-dimethoxy-1,4-benzoquinone-4-oxime (**1**) and 3,5-dimethoxy-1,4-benzoquinone-4-oxime (**2**). These isomers were synthesised and their properties compared with those of the flour product.



2. Results and discussion

The two oxime isomers of 2,6-dimethoxy-*p*-quinone (**1**, **2**) were synthesised and shown to have similar mass spectra with major ions (**1**) *m/z* (relative intensity) 367.0 ($2M+H^+$, 0.10), 184.0 ($M+H^+$, 0.25), 170.2 (0.10), 167.2 (0.11), 166.0 (0.68), 155.2 (0.19), 152.0 (base peak), 151.0 (0.81), 140.2 (0.25), 112.0 (0.67), 111.2 (0.26) and (**2**) *m/z* (relative intensity) 367.0 ($2M+H^+$, 0.07), 184.0 ($M+H^+$, 0.20), 170.0 (0.08), 167.2 (0.36), 166.2 (0.80), 152.0 (base peak), 151.0 (0.70), 140.0 (0.09), 112.0 (0.17), 111.0 (0.26). The mass spectra were more complex than expected and resulted from the formation of cluster ions during the ionisation process. In contrast, a relatively simple mass spectrum was obtained for the product obtained from flour, which showed major ions at

Keywords: Wheat flour; Hydroxylamine; Hydroquinone; Oxime dimer.
* Corresponding author. Tel.: +61 8 8303 7480; fax: +61 8 8303 7109; e-mail: robert.asenstorfer@adelaide.edu.au

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m/z (relative intensity) 367.2 ($M+H^+$, 0.25), 184.0 (base peak), 156.1 (0.37), 154.0 (0.47), 139.1 (0.26), 124.1 (0.08). These differences in fragmentation patterns, as well as differences in absorbance spectra and HPLC retention times, indicated that the structure of the flour product was neither (**1**) nor (**2**). The considerably larger intensity of the mass at *m/z* 367 and simpler fragmentation pattern of the flour product compared with the oxime isomers suggested this product was a dimer of 2,6-dimethoxy-*p*-quinone mono-oxime.

1-Hydroxy-2,6-dimethoxy-nitrosobenzene is a tautomeric analogue of 2,6-dimethoxy-*p*-quinone oxime. Many nitrosobenzenes dimerise under increasing concentration,[6] low temperature[7] or in the presence of organic solvents[8] to give azodioxybenzenes. Nitrosobenzene trans-dimers have a diagnostic, very strong IR band at 1253–1299 cm^{-1} due to the aromatic $\nu N^+–O^-$ frequency,[6,9] which is sensitive to the molecular environment.[10,11] Aromatic cis-dimers give two active NO stretching bands at 1389–1397 cm^{-1} and 1409 cm^{-1}. The synthetic dimeric species had a strong band at 1316 cm^{-1}, which is consistent with the trans-form of a nitroso dimer (Table 1). Another major band associated with the dimer was at 952 cm^{-1}. This band[12] has been attributed to $\nu N^+–O^-$ in compounds with aliphatic $\nu N^+–O^-$. None of the dimers described by Luttke[9] contained this band and is quite specific for the compound under investigation.

The IR OH stretching frequency (3300 cm^{-1}) of the dimer is strong while the band for both oxime monomers is either weak or missing. A strong OH stretching band indicates that the nitroso tautomer predominates over the oxime tautomer. Both oxime monomers show a medium band at approximately 1345 cm^{-1} due to $\nu N{=}O$ stretching,[6] which is absent in the dimer.

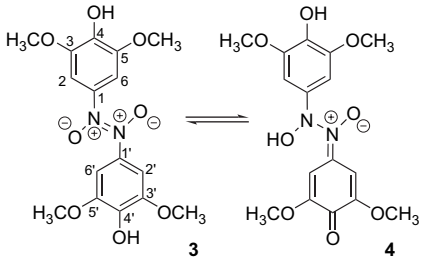
In organic solvents, such as chloroform and dichloromethane, *C*-nitrosobenzene compounds exist in monomer–dimer equilibria, with the cis-dimers being preferred over the trans-dimers, irrespective of the nature of the solid-state dimer structure.[8] However, the dimer was relatively unstable in chloroform and dichloromethane, but was stable in DMSO and water. No monomer–dimer equilibrium was observed in DMSO during the NMR experiments. The stability of dimer (**3**) and lack of monomer–dimer equilibrium are consistent with the hydroxyl groups acting as a strong electron withdrawing substituent.[6,19]

Table 1. Major peaks identified in the infrared spectra of 2,6-dimethoxy-1,4-benzoquinone-4-oxime (**1**), 3,5-dimethoxy-1,4-benzoquinone-4-oxime (**2**) and the dimer, 4,4′-dihydroxy-3,3′,5,5′-tetramethoxyazodioxybenzene (**3**)

1	2	3	ν
—	3300w	3268vs	OH
1626vs	1630vs	1644vs	C=O
1571vs	1575vs	1581vs	C=N
1452s	1454s	1455m	OH bending
1344m	1348m	—	N=O stretch
—	—	1316vs	Aryl $N^+–O^-$
1246s	1249s	1249s	=C-O-CH_3
1122vs	1125vs	1113vs	Aryl C–N stretch
1051vs	1052vs	1051s	=C-O-CH_3
—	—	952vs	$N^+–O^-$
860m	858m	852s	N–O bending
702s	704s	702m	

The aromatic protons of the dimer show a substantially higher δ (6.51 and 6.80 ppm) when compared with 2,6-dimethoxy-1,4-benzoquinone-4-oxime (**1**) (5.61 ppm) and 3,5-dimethoxy-1,4-benzoquinone-4-oxime (**2**) (doublet, 5.60 and 5.63 ppm) but lower δs than literature values for either unsubstituted or C-4 substituted cis-dimers (7.11–7.4 ppm) and trans-dimers (7.69–7.89 ppm) of nitrosobenzenes.[7] There is a significant difference ($\Delta\delta$ 0.29 ppm) between the aromatic protons of the dimer indicating the effect of shielding/deshielding. In contrast, no difference was recorded in the shifts for the 2 and 6 protons for the aromatic protons in dichloromethane and chloroform of either *cis*- or *trans*-nitroso dimers.[7]

It can be determined whether an isomer is either cis or trans in solution because the shielding/deshielding of aromatic protons in *cis*-$N_2O_2C_6H_{5-n}X_n$ is virtually negligible, whereas the shielding in the *trans*-$N_2O_2C_6H_{5-n}X_n$ is substantial.[7,13] Moreover, the aromatic proton signals for the cis-dimer should be shifted to the right compared to both the monomer and the trans-dimer. While shielding/deshielding was observed for the dimer, suggesting a trans-isomer, the aromatic proton signals were observed to be shifted to the left compared to the monomer, but shifted to the right compared to either *cis*- or *trans*-4-substituted nitrosobenzene dimers.[7] The higher δ values of the aromatic protons of our dimer were consistent with the formation of the azodioxybenzene compound (**3**). The hydroxyl group allows the contribution of the quinonoid canonical state and thus the aromatic protons were observed at lower δ values than other 4-substituted nitrosobenzenes. The double bond nature of the C–N bond and the possibility of formation of the tautomer (**4**) suggest that the energy barrier between cis and trans may not be great and the dimer may exist as both cis and trans in solution.



3 **4**

The ^{13}C NMR C1 shift of the dimer (δ 148.0) was in the range characterised by aromatic azodioxy dimers (δ 139–146) and is substantially less than the nitroso monomers (δ 162–176).[14] However, the C1 shifts of the two oximes (δ 137–138) are also substantially lower than the nitroso monomers and similar to the dimer. The exceptionally strong π-electron acceptor nature of the N=O substituent produces a strong deshielding effect causing C1 shifts to higher δ values, while the N_2O_2 and N–OH substituents have only a moderate effect.

The solvent used for NMR investigation is important. ^{13}C NMR data obtained in $CDCl_3$ or CD_2Cl_2 for nitrosobenzene monomers for the C3 and C5 and C2 and C6 carbons are

identical.[14–16] In DMSO, however, nitrosophenol monomers show differences between the C3 and C5, and the C2 and C6 carbons.[17] The position of the nitroso-oxime group in 3,5-dimethoxy-1,4-benzoquinone-4-oxime provides a larger difference between the ^{13}C shifts of quaternary carbons (C3 and C5) than the aromatic CH carbons (C2 and C6) suggesting the rotation around the C–N bond is restricted and *syn–anti* isomerism is slow.[18] However, 2,6-dimethoxy-1,4-benzoquinone-4-oxime has a broad peak at 102.4 ppm for the aromatic CH carbons (C3 and C5) suggesting the *syn–anti* isomerism is rapid and splitting is minimised.

Similar to the nitrosobenzene monomers, ^{13}C NMR studies of azodioxybenzenes[14–16] in $CDCl_3$ and CD_2Cl_2 also show no difference in the ^{13}C chemical shifts between either the C2 and C6 or the C3 and C5 carbons. However, in solid-state ^{13}C NMR, *trans*-4,4′-dichloro-azodioxybenzene $(4\text{-}ClC_6H_4NO)_2$ showed a distinction between the C2 and C6 signals ($\Delta\delta$=4.1).[8] This was thought to arise from the locked nature of the phenyl rings in the solid state and the chemical shift represents the shielding anisotropy of the azodioxy group. Similarly, the dimer (**3/4**) exhibited large differences in the ^{13}C shifts between the C3 and C5 carbons as well as the C2 and C6 carbons when measured in DMSO. The larger difference in shifts for the aromatic CH carbons (C2/C2′ and C6/C6′) compared with the quaternary carbons (C3/C3′ and C5/C5′) suggests that the azodioxy moiety is attached proximal to the aromatic CH carbons. gHMQC assignments together with differences in shifts due to shielding/deshielding magnetic anisotropy allowed the assignment of all carbons (Table 2; Fig. 1).

Table 2. Proton, carbon and gHMBC correlations of NMR of the dimer, 4,4′-dihydroxy-3,3′,5,5′-tetramethoxyazodioxybenzene (**3**)

Carbon number	^{13}C δ	^{1}H δ	gHMBC
1	148.0	—	H2[a] (2[b]), H6[a] (2)
2	94.5	6.5 (d)	H6 (3), methyl[a] (4)
3	151.9	—	H6 (4), methyl (3)
4	185.2	—	H2 (3), H6 (3)
5	153.6	—	H2 (4), methyl (3)
6	108.6	6.8 (d)	H2 (3), methyl[a] (4)
Methyl	55.5, 55.6	3.71, 3.73	—

[a] Weak association.
[b] Number in brackets refers to 2-, 3-, or 4-bond correlations.

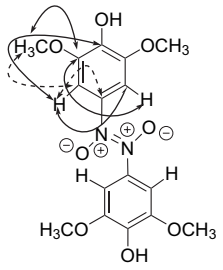
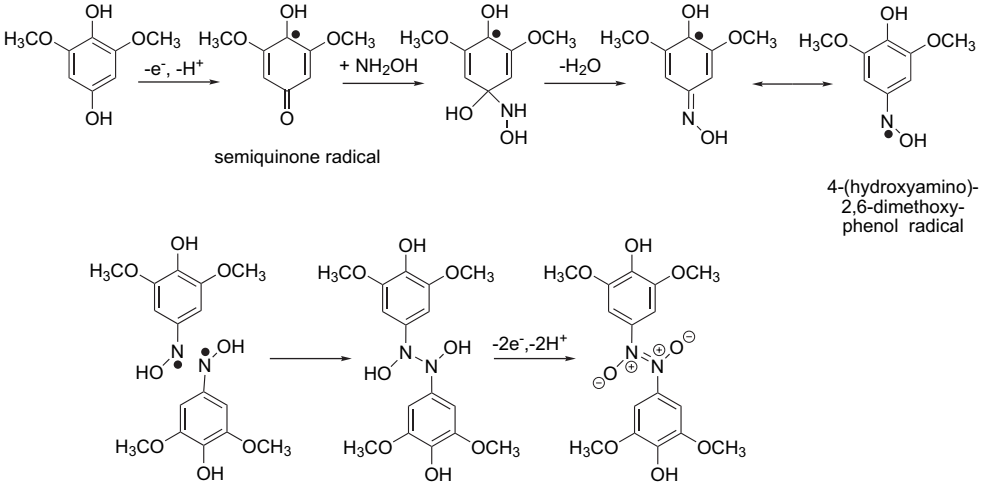


Figure 1. Correlations observed in the gHMBC spectrum of 4,4′-dihydroxy-3,3′,5,5′-tetramethoxyazodioxybenzene (**3**).

Additional evidence for the structure of the dimer arises from the absorbance spectral data. The molar extinction coefficients of the unionised oximes and the dimer are identical, while the π–π* UV band of the dimer shows a bathochromic shift of 40 nm compared with the oxime monomers due to a lengthening of the chromophore. In comparison, the π-levels of nitrosomesitylene (1,3,5-trimethyl-2-nitrosobenzene) are not changed by dimerisation[6] and there is no effect on either λ_{max} or extinction coefficient of the UV bands. The C–N bond of nitrosomesitylene has single bond character, and the nitroso group is not co-planar with the benzene moiety and is well insulated from the benzene ring in both monomer and dimer. Unlike the nitrosomesitylene dimer, the N^+–O^- group in the dimer is contiguous with the benzene moiety and the C–N bond shows some double bond character.

As most azodioxybenzenes are formed from their nitroso monomers and in the absence of strong intramolecular hydrogen bonding, 4-hydroxy species occur principally as oximes[20] and thus dimerisation is unlikely,[9] another mechanism is required for the formation of dimer (**3**). A related compound, 4,4′-dihydroxy-3,3′-dimethyldiphenyl-*N*,*N*′-dihydroxyhydrazine, detected by mass spectrometry in photographic effluent,[20] can be synthesised by reacting 2-methyl-*p*-benzoquinone with hydroxylamine in a reductive solution containing sulfite and carbonate. Therefore, a possible reaction mechanism for the synthesis of dimer (**3**) is suggested (Scheme 1). A partial oxidation of 1,4-dihydroxy-2,6-dimethoxybenzene to create 2,6-dimethoxysemiquinone is necessary prior to reaction with hydroxylamine.



Scheme 1. Suggested mechanism for the synthesis of 4,4′-dihydroxy-3,3′,5,5′-tetramethoxyazodioxybenzene (**3**).

In wheat, however, it is postulated that, 1,4-dihydroxy-2,6-dimethoxybenzene occurs as a glycoside even though this glycoside has never been isolated.[21,22] Is possible that during the deglycosylation process, 2,6-dimethoxysemiquinone radical is released, which then reacts with hydroxylamine.

3. Experimental methods

3.1. LC–mass spectrometry

The sample (5 μL) was loaded onto an HPLC column (Spherisorb S5 ODS2, 250×1 mm, Waters Corporation). The separation was performed with solvent A (5% formic acid) and solvent B (5% formic acid, 80% acetonitrile) by using a gradient system: 10–35% of solvent B in 35 min, kept constant at 35% for 5 min and then 35–95% solvent B in a further 20 min, at a flow rate of 25 μL/min. The HPLC column was connected to a UV–vis detector (HP1100, Hewlett–Packard) monitoring at 280 and 340 nm, followed by a mass spectrometer with an ion spray ion source (API-300, PE Sciex, Thornhill, Ontario, Canada). The mass spectrometer was operated in positive ion mode and was scanned from *m/z* 250 to 1000 in 1.88 s. Ion spray and orifice potentials were set at 5.5 kV and 30 V, respectively. Curtain and nebuliser gases were nitrogen and air, respectively. All mass spectral data were processed using Bio-Multiview software (version 1.2ß3, PE Sciex).

3.2. IR, NMR and melting points

Infrared spectra were collected using a Perkin–Elmer (Shelton, CT, USA) Spectrum 1 Fourier Transform Infrared (FTIR) instrument equipped with a diffuse reflectance sampling accessory. The data were exported to GRAMS/AI (Thermoelectron Corporation, Woburn, MA, USA) for processing. NMR spectra were acquired on a Varian Inova-600 NMR spectrometer, at an ^{1}H frequency of 600 MHz and ^{13}C frequency of 150 MHz. All NMR experiments were acquired at 25 °C. All spectra were processed on a Sun Microsystems Ultra Sparc 1/170 workstation using VNMR software (version 6.1A). Melting points were obtained on a hot stage microscope (C. Reichert Optische Werke A.G., Vienna, Austria).

3.3. HPLC

Separation of compounds was performed using a Hewlett–Packard HPLC 1100 instrument using a 250×4 mm analytical column (Merck, Darmstadt, Germany) packed with spherical LiChrospher 100 RP-18 (5 μm), fitted with a 4×4 mm guard column using the same packing material. Separation was carried out with solvent A (1% formic acid) and solvent B (1% formic acid, 4% acetonitrile, 95% methanol) by a gradient system elution program: 0–3 min, isocratic 10% B; 3–8 min, gradient 10–24% B; 8–11 min, isocratic 24% B; 11–18 min, gradient 24–34% B; 18–28 min, gradient 34–44% B; 28–35 min, gradient 44–65% B; 35–40 min, gradient 65–95% B; 40–55 min, isocratic 95% B; 55–60 min. A flow rate of 0.65 mL/min, detection at 340 and 280 nm and temperature set at 30 °C were used.

3.4. HVPE

The electrophoretogram, consisting of chromatography paper (Chr. 1; Whatman, England) soaked in the appropriate buffer was placed over a glass rod to minimise surface contact between two wells containing buffer of a gel electrophoresis unit (Model 715; Betheseda Research Laboratories, Gaithersburg, MD, USA). A voltage gradient of 7.5 V/cm was used. The buffers employed were borate (0.05 mol/L; pH 10.0) and citrate (0.05 mol/L; pH 7.0) and formic/acetic (0.75/1.04 mol/L; pH 1.76).

3.5. Extraction of the flour product

For direct comparison, flour (200 g) was extracted with 1 L 0.1 M hydroxylamine hydrochloride for 2 h. This was filtered and 100 mL of the filtrate was extracted with 3×100 mL dichloromethane. The dichloromethane was evaporated and the residue dissolved in DMSO for MS-analysis. Found: ES-MS, *m/z* (relative intensity) 367.2 ($M+H^+$, 0.21), 184.1 (base peak), 156.1 (0.42), 154.0 (0.26), 139.1 (0.41) and 124.0 (0.15); HPLC retention time was 21.4 min; absorbances (aq) λ_{max} 340 nm at pH 2.5 and λ_{max} 400 nm at pH 10.

3.5.1. Synthesis of 2,6-dimethoxy-1,4-benzoquinone-4-oxime (1). The *title compound* **1** (2,6-dimethoxy-4-oximino-2,5-cyclohexadienone-1) was synthesised from 2,6-dimethoxy-1,4-benzoquinone and hydroxylamine according to Bolker and Kung.[23] Found: pale yellow plates; mp 214–215 °C dec (lit[23] mp 218.8 °C dec); ES-MS, *m/z* (relative intensity) 367.0 ($2M+H^+$, 0.07), 184.0 ($M+H^+$, 0.20), 170.0 (0.08), 167.2 (0.36), 166.2 (0.80), 152.0 (base peak), 151.0 (0.70), 140.0 (0.09), 112.0 (0.17), 111.0 (0.26); HPLC retention time was 19.1 min; absorbances (aq) λ_{max} 300 nm (ε=16,000), 395 nm (ε=1200) at pH 2.5 and λ_{max} 353 nm (ε=25,300) at pH 10; δ_H (600 MHz DMSO-d_6) 3.71 (6H, s, OC*H*$_3$), 5.61 (2H, s, H2 and H6); δ_C (150.9 MHz DMSO-d_6) 56.1 (OCH$_3$), 102.4 br (C3 or C5), 137.7 (C4), 185.6 (*C*1), quaternary carbons (*C*2 and *C*6) were not observed; ν_{max} (KCl) 3233w, 3176w, 3064 (br), 2943w, 2750s (br), 2644w, 2366w, 2247w, 2174w, 2100w, 1844w, 1744w, 1626vs (C=O), 1571vs (C=N), 1452s (C–O stretch), 1430m, 1403m, 1344w, 1321w, 1246s (C–O stretch), 1228s, 1192m, 1122vs (aryl C–N stretch), 1051vs (N–OH), 1019w, 986w, 930m, 908m, 860s, 810m, 795m, 702s.

3.5.2. Synthesis of 3,5-dimethoxy-1,4-benzoquinone-4-oxime (2). The *title compound* **2** was prepared by nitrosodemethylation of 1,3,5-trimethoxybenzene (Sigma–Aldrich) according to Shpinel et al.[24] Found: pale yellow needles; mp 166–167 °C commenced sublimation, 216–217 °C dec (lit[17] mp 223–224 °C); ES-MS, *m/z* (relative intensity) 367.0 ($2M+H^+$, 0.10), 184.0 ($M+H^+$, 0.25), 170.2 (0.10), 167.2 (0.11), 166.0 (0.68), 155.2 (0.19), 152.0 (base peak), 151.0 (0.81), 140.2 (0.25), 112.0 (0.67), 111.2 (0.26); HPLC retention time was 25.4 min; λ_{max} (aq) 298 nm (ε=18,000), 395 nm (ε=1400) at pH 2.5, 353 nm (ε=29,500) at pH 10.0; δ_H (600 MHz DMSO-d_6) 3.72 (3H, s, OC*H*$_3$), 3.74 (3H, s, OC*H*$_3$), 5.60 (1H, s, *H*2), 5.63 (1H, s, *H*6); δ_C (150.9 MHz DMSO-d_6) 56.1 (O*C*H$_3$), 56.2 (O*C*H$_3$), 102.1 (*C*2 or *C*6), 103.3 (*C*2 or *C*6), 137.5 (*C*4), 157.6 (*C*3 or *C*5), 161.1 (*C*3 or *C*5), 185.6 (*C*1), in general agreement

with Maleski;[17] ν_{max} (KCl) 3236w, 3182w, 3062, 2951w, 2811w, 2800s (br), 2650w, 2249w, 2102w, 1851w, 1749w, 1630vs (C═O), 1575vs (C═N), 1465w, 1454vs (C–O stretch), 1442, 1431, 1409s, 1348w, 1249vs (C–O stretch), 1230s, 1194, 1125vs (aryl C–N stretch), 1066w, 1052vs (N–OH), 1019w, 988w, 934, 911, 858s, 809, 796, 704s.

3.5.3. Reaction of 1,4-dihydroxy-2,6-dimethoxybenzene with hydroxylamine (synthesis of 4,4′-dihydroxy-3,3′,5,5′-tetramethoxyazodioxybenzene 3). Approximately 10 mg of 1,4-dihydroxy-2,6-dimethoxybenzene and 20 mg hydroxylamine hydrochloride were added to 2 mL of water and adjusted to pH 7. This mixture was allowed to react for 16 h at 45 °C. The solution was extracted with dichloromethane. KCl was added and the dichloromethane was carefully evaporated under reduced pressure. Found: pale brown plates; mp 110–111 °C commenced sublimation (yellow needles), 183–184 °C dec; ES-MS, *m/z* (relative intensity): 367.2 ($M+H^+$, 0.25), 184.0 (base peak), 156.1 (0.37), 154.0 (0.47), 139.1 (0.26), 124.1 (0.08); λ_{max} (aq) 340 nm (ε=16,000) at pH 2.5, 400 nm (ε=17,000) at pH 10.0 (note this was estimated using HPLC and NMR data by comparing the concentration and absorbance of 2,6-dimethoxy-1,4-benzoquinone-4-oxime with the synthetic product); HPLC retention time was 21.4 min; δ_H (600 MHz DMSO-d_6) 3.71 (6H, s, OCH_3), 3.74 (6H, s, OCH_3), 6.51 (2H, d, *J* 2.1 Hz, *H*2 and *H*2′), 6.80 (2H, d, *J* 2.1 Hz, *H*6 and *H*6′); δ_C (150.9 MHz DMSO-d_6) 55.5 (OCH_3), 55.6 (OCH_3), 94.5 (*C*2, *C*2′), 108.6 (*C*6, *C*6′), 148.0 (*C*1, *C*1′), 151.9 (*C*3, *C*3′), 153.6 (*C*5, *C*5′), 175.0 (*C*4, *C*4′); ν_{max} (KCl) 3268vs (br, OH), 3092, 2965w, 2942, 2837, 2650w, 1644vs (C═O), 1581vs (C═N), 1455m (C–O stretch), 1417w, 1407, 1316vs (N^+–O^-), 1249vs (C–O stretch), 1219s, 1192w, 1181w, 1113vs (aryl C–N stretch), 1051, 1014, 952s (N^+–O^-), 907, 852s, 797, 733, 702.

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References and notes

1. Hou, G.; Kruk, M. *AIB Technical Bulletin* **1998**, *20*, 1–10.
2. Mares, D. J.; Wang, Y.; Cassidy, C. A., Cereals 97. *Proceedings of the 47th Cereal Chemistry Conference*; RACI: Melbourne, Australia, 1997; pp 114–117.
3. Asenstorfer, R. E.; Wang, Y.; Mares, D. J. *J. Cereal Sci.* **2006**, *43*, 108–119.
4. Vuataz, L. *Helv. Chim. Acta* **1950**, *3*, 433–443.
5. Cosgrove, D. J.; Daniels, D. G. H.; Whitehead, J. K.; Goulden, J. D. S. *J. Chem. Soc.* **1952**, 4821–4823.
6. Nakamoto, K.; Rundle, R. E. *J. Chem. Soc.* **1956**, *78*, 1113–1118.
7. Fletcher, D. A.; Gowenlock, B. G.; Orrell, K. G. *J. Chem. Soc., Perkin Trans. 2* **1997**, 2201–2205.
8. Fletcher, D. A.; Gowenlock, B. G.; Orrell, K. G. *J. Chem. Soc., Perkin Trans. 2* **1998**, 797–803.
9. Lüttke, W. *Z. Electrochem.* **1957**, *61*, 976–986.
10. Katritzky, A. R.; Ambler, A. P. *Physical Methods in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic: New York, NY; London, 1963; Vol. 2, pp 283–285.
11. Shindo, H. *Chem. Pharm. Bull.* **1958**, *6*, 117–129.
12. Mathis-Noël, R.; Wolf, R.; Gallais, F. *Compt. Rend. Acad. Sci.* **1956**, *242*, 1873–1876.
13. Azoulay, M.; Fischer, E. *J. Chem. Soc., Perkin Trans. 2* **1982**, 637–642.
14. Gowenlock, B. G.; Cameron, M.; Boyd, A. S. F.; Al-Tahou, B. M.; McKenna, P. *Can. J. Chem.* **1994**, *72*, 514–518.
15. Fletcher, D. A.; Gowenlock, B. G.; Orrell, K. G.; Apperley, D. C.; Hursthouse, M. B.; Malik, K. M. A. *J. Chem. Res. (S)* **1999**, 202–203.
16. Fletcher, D. A.; Gowenlock, B. G.; Orrell, K. G.; Apperley, D. C.; Hursthouse, M. B.; Malik, K. M. A. *J. Chem. Res. (M)* **1999**, 1115–1134.
17. Maleski, R. *Synth. Commun.* **1995**, *25*, 2327–2335.
18. Norris, R. K.; Sternhell, S. *Tetrahedron Lett.* **1967**, *8*, 97–101.
19. Cox, R. H.; Hamada, M. *Org. Magn. Reson.* **1979**, *12*, 322–325.
20. Lunar, L.; Rubio, S.; Pérez-Bendito, D.; Jiménez, C. *Rapid Commun. Mass Spectrom.* **2002**, *16*, 1622–1630.
21. Bungenberg de Jong, H. L.; Klaar, W. J.; Vliegenthart, J. A. *Nature* **1953**, *172*, 402–403.
22. Bouvier, E.; Horváth, C. *Acta Biochim. Biophys. Hung.* **1987**, *22*, 215–228.
23. Bolker, H. I.; Kung, F. L. *Can. J. Chem.* **1969**, *47*, 2109–2115.
24. Shpinel, Y. I.; Klimova, I. V.; Belyev, E. Y. *Zh. Obshch. Khim.* **1991**, *27*, 1493–1497.

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Corrigendum

Corrigendum to "Reactions of bis(tetrazole)phenylenes. Surprising formation of vinyl compounds from alkyl halides" [Tetrahedron 61 (2005) 7002]

A. Fleming, F. Kelleher, M. F. Mahon, J. McGinley* and V. Prajapati

Department of Chemistry, National University of Ireland – Maynooth, Maynooth, Co Kildare, Ireland

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In paragraph three of the results and discussion section, the sentence 'No obvious reason was apparent for the difference between these results and those published previously by Butler and Fleming.[9]' should be deleted as at no point in the work of Butler and Fleming did they use 1,2-dibromoethane. Therefore, the sentence was in error.

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* Corresponding author. Tel.: +353 1 708 4615; fax: +353 1 708 3815; e-mail: john.mcginley@nuim.ie

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