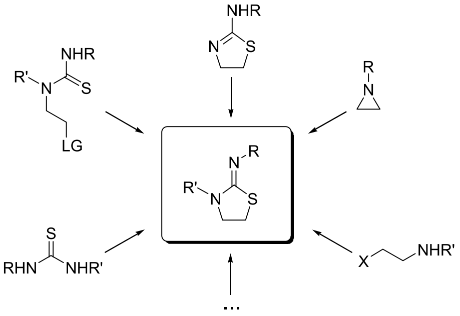
ELSEVIER

Tetrahedron

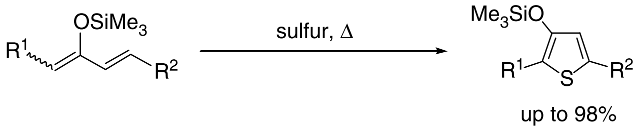
Tetrahedron Vol. 62, No. 4, 2006

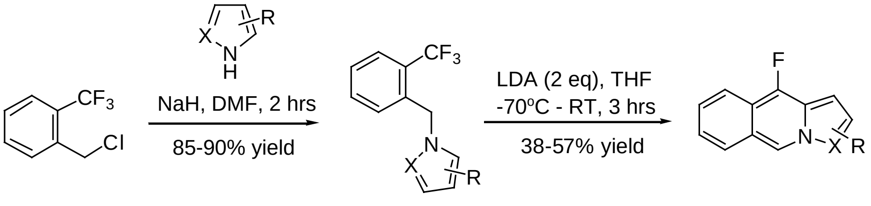
Contents

REPORT



ARTICLES

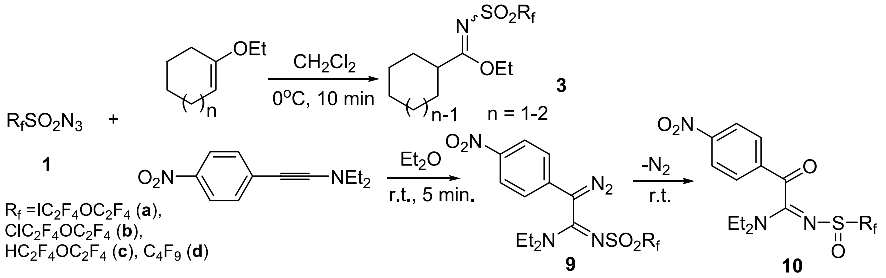




Study on the reactions of fluoroalkanesulfonyl azides with cycloalkenyl ether and aryl ynamines

pp 549–555

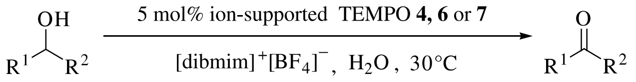
Ping He and Shizheng Zhu*



Clean and selective oxidation of alcohols catalyzed by ion-supported TEMPO in water

pp 556–562

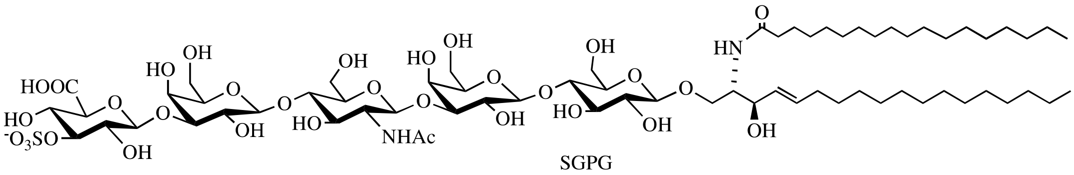
Weixing Qian, Erlei Jin, Weiliang Bao* and Yongmin Zhang



Synthetic sulfated glucuronosyl paragloboside (SGPG) and its use for the detection of autoimmune peripheral neuropathies

pp 563–577

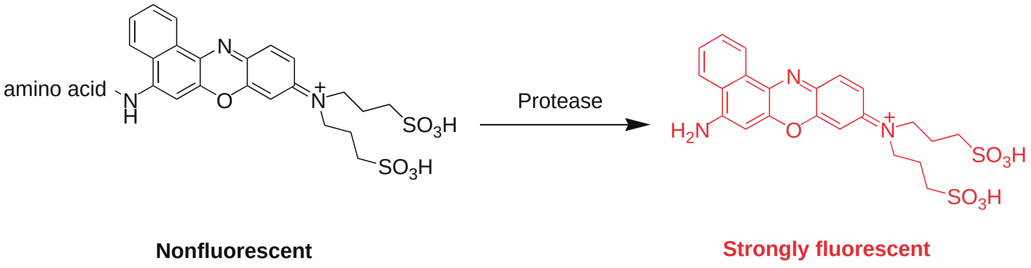
Reynald Chevalier, Benoît Colsch, Carlos Afonso, Nicole Baumann, Jean-Claude Tabet and Jean-Maurice Mallet*



Development of water-soluble far-red fluorogenic dyes for enzyme sensing

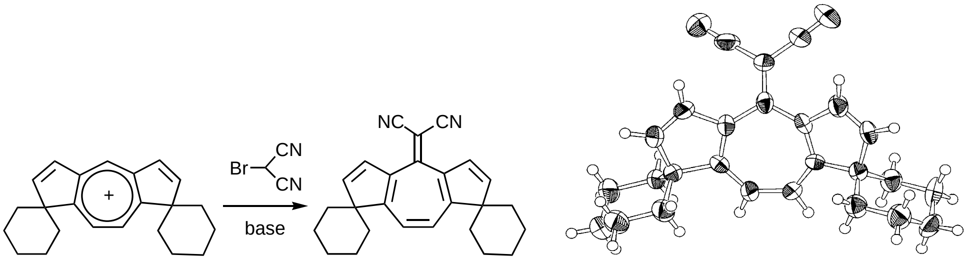
pp 578–585

Nan-hui Ho, Ralph Weissleder and Ching-Hsuan Tung*



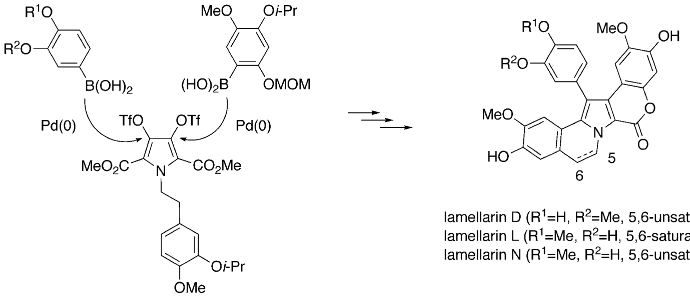
Synthesis, properties and molecular structure of a novel dicyanoheptafulvene derivative, 4′-dicyanomethylidenedispiro[cyclohexane-1, 1′-(1′,4′,7′-trihydrocyclopenta[*f*]azulene)-7′,1″-cyclohexane] **pp 586–593**

Nguyen Chung Thanh, Ryuta Miyatake, Hitoshi Kainuma, Shigeyasu Kuroda and Mitsunori Oda*



Total synthesis of lamellarins D, L, and N **pp 594–604**

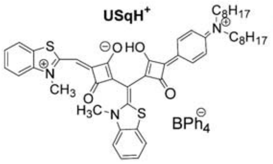
Naotaka Fujikawa, Takeshi Ohta, Tomohiro Yamaguchi, Tsutomu Fukuda,
Fumito Ishibashi and Masatomo Iwao*

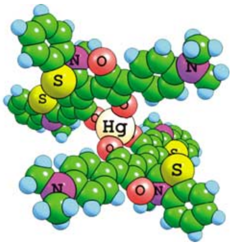


lamellarin D (R^1=H, R^2=Me, 5,6-unsaturated)
lamellarin L (R^1=Me, R^2=H, 5,6-saturated)
lamellarin N (R^1=Me, R^2=H, 5,6-unsaturated)

A squaraine-based chemosensor for Hg^{2+} and Pb^{2+} **pp 605–610**

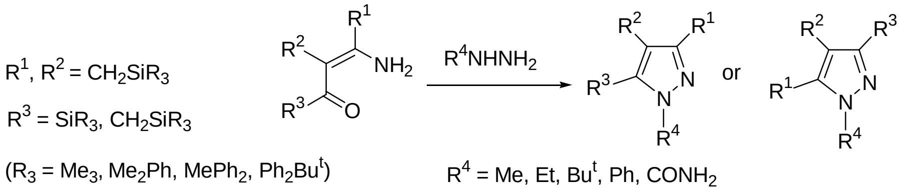
M. C. Basheer, S. Alex, K. George Thomas, Cherumuttathu H. Suresh and S. Das*





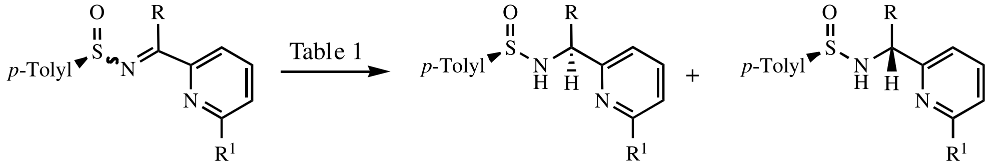
Silylated β-enaminones as precursors in the regioselective synthesis of silyl pyrazoles **pp 611–618**

Mariola Calle, Luis A. Calvo, Alfonso González-Ortega and Ana M. González-Nogal*



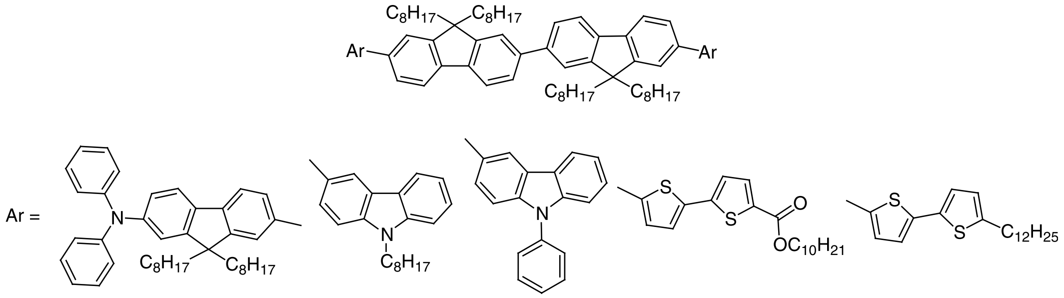
Diastereoselective reduction of enantiopure *N*-*p*-toluenesulfinyl ketimines derived from pyridyl ketones **pp 619–626**

Giorgio Chelucci,* Salvatore Baldino and Simona Chessa



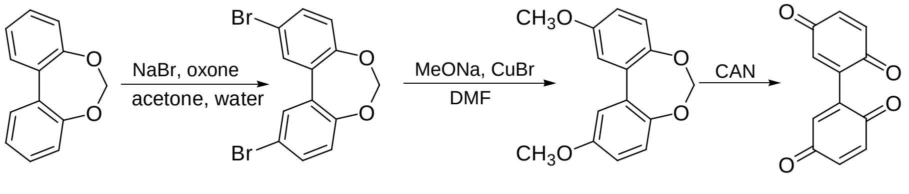
Novel bifluorene based conjugated systems: synthesis and properties **pp 627–634**

Roberto Grisorio, Antonio Dell'Aquila, Giuseppe Romanazzi, Gian Paolo Suranna, Piero Mastrorilli, Pynalisa Cosma, Domenico Acierno, Eugenio Amendola, Giuseppe Ciccarella and Cosimo Francesco Nobile*



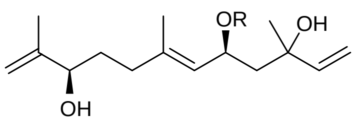
Regioselective halogenation of biphenyls for preparation of valuable polyhydroxylated biphenyls and diquinones **pp 635–639**

Paolo Bovicelli,* Roberto Antonioletti, Antonella Onori, Giovanna Delogu,* Davide Fabbri and Maria Antonietta Dettori



Amarantholidols and amarantholidosides: new nerolidol derivatives from the weed *Amaranthus retroflexus* **pp 640–646**

Brigida D'Abrosca, Paolo De Maria, Marina DellaGreca, Antonio Fiorentino,* Annunziata Golino, Angelina Izzo and Pietro Monaco

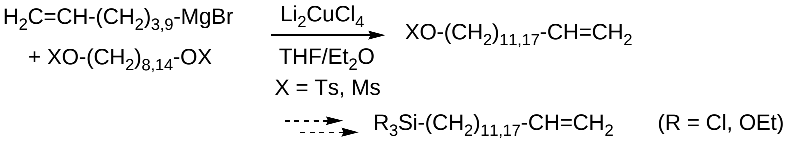


4 R = Glc
6 R = H

Synthesis of model long-chain ω-alkenyltrichlorosilanes and triethoxysilanes for the formation of self-assembled monolayers

pp 647–651

Thanh Binh Nguyen, Anne-Sophie Castanet,* Thi-Huu Nguyen, Kim Phi Phung Nguyen,
Jean-François Bardeau, Alain Gibaud and Jacques Mortier*

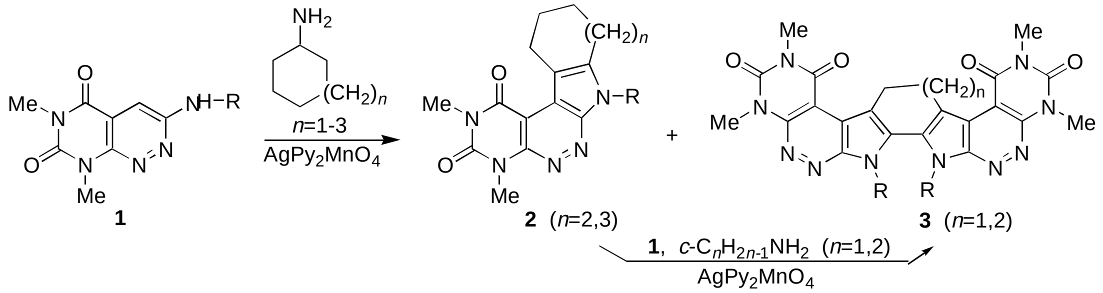


$$\begin{array}{c} H_2C{=}CH\text{-}(CH_2)_{3,9}\text{-}MgBr \\ +\ XO\text{-}(CH_2)_{8,14}\text{-}OX \end{array} \xrightarrow[\substack{THF/Et_2O \\ X = Ts,\ Ms}]{Li_2CuCl_4} XO\text{-}(CH_2)_{11,17}\text{-}CH{=}CH_2 \dashrightarrow R_3Si\text{-}(CH_2)_{11,17}\text{-}CH{=}CH_2 \quad (R = Cl, OEt)$$

Cycloalkano[1″,2″:4,5;4″,3″:4′,5′]bis(pyrrolo[2,3-*c*]pyrimido[5,4-*e*]pyridazines): synthesis, structure and mechanism of their formation

pp 652–661

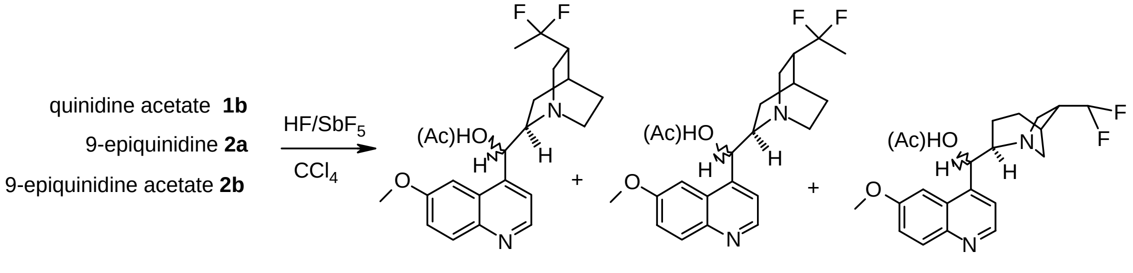
Olga V. Serduke, Anna V. Gulevskaya,* Alexander F. Pozharskii, Zoya A. Starikova and Irina A. Profatilova



Reaction of quinidine acetate, epiquinidine and its acetate in superacid: formation of *gem*-difluoro derivatives with or without rearrangement

pp 662–671

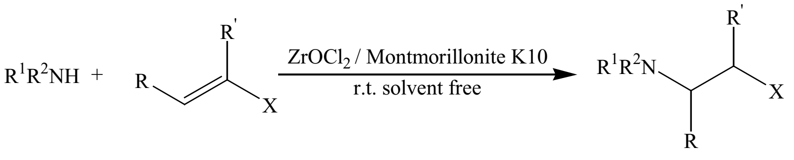
Sébastien Debarge, Bruno Violeau, Marie-Paule Jouannetaud,* Jean-Claude Jacquesy* and Alain Cousson



ZrOCl$_2$·8H$_2$O on montmorillonite K10 accelerated conjugate addition of amines to α,β-unsaturated alkenes under solvent-free conditions

pp 672–677

Mohammed M. Hashemi,* Bagher Eftekhari-Sis, Amir Abdollahifar and Behzad Khalili



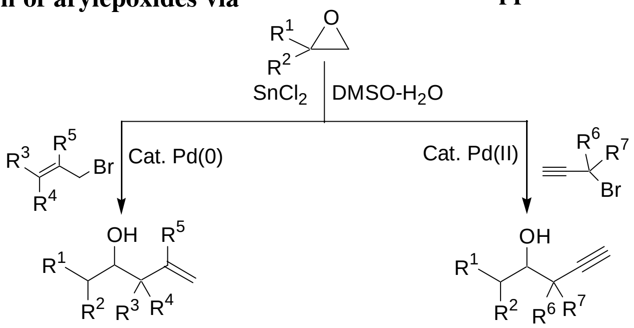
R = H, Me, Ph;   R' = H, Me;   X = COOMe, CN, COMe, CONH$_2$

Highly efficient water promoted allylation and propargylation of arylepoxides via rearrangement-carbonyl addition

pp 678–683

Ujjal Kanti Roy and Sujit Roy*

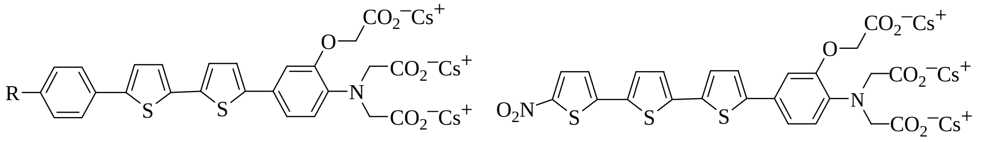
Nucleophilic reactivity of organotin is greatly enhanced by controlled addition of water to give homoallyl and homopropargyl alcohols via tandem epoxide rearrangement-carbonyl addition.



Palladium catalyzed synthesis of Ca^{2+} indicators with aryl bithiophene and terthiophene fluorophores

pp 684–690

Noël Boens, Nesibe Avcıbaşı, Subhendu S. Samanta, Amuri Kilonda, Georges J. Hoornaert and Erik Van der Eycken*

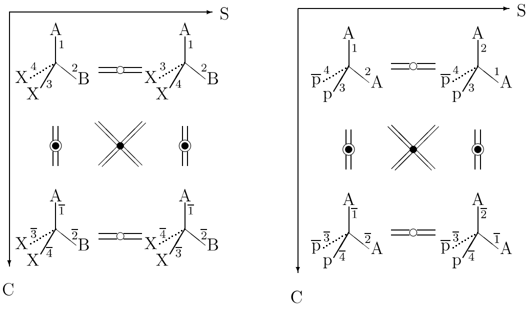


R = H, F, OMe, NO$_2$

Complete settlement of long-standing confusion on the term ‘prochirality’ in stereochemistry. Proposal of pro-*RS*-stereogenicity and integrated treatment with prochirality

pp 691–705

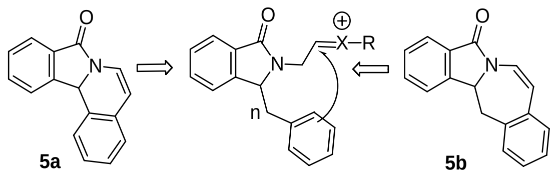
Shinsaku Fujita



Oxidized isoquinolinoisoindolinone and benzazepinoisoindolinone alkaloids cores by convergent cyclisation processes: π-aromatic attack of thionium and oxonium species

pp 706–715

Till Bousquet, Jean-François Fleury, Adam Daïch* and Pierre Netchitaïlo



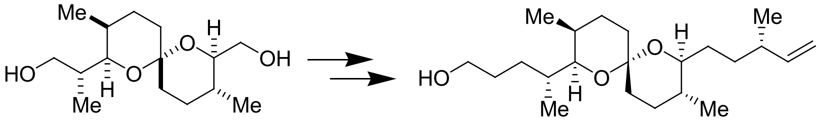
5a **5b**

X=O,S; n=0,1

Oxidized isoquinolinoisoindolinone and benzazepinoisoindolinone alkaloids cores were synthesized efficiently by using π-cationic cyclisation of thionium and oxonium cations.

Synthetic study of tautomycin. Part 2: Synthesis of Ichihara's fragment based on regioselective enzymatic acetylation of complex molecule **pp 716–725**

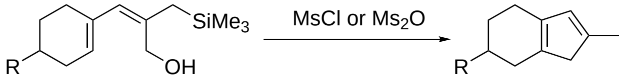
Yusuke Ishii, Shinji Nagumo,* Takayuki Arai, Masami Akuzawa, Norio Kawahara and Hiroyuki Akita



Enzymatic acetylation of complex spiroketal diol proceeded with high regioselectivity.

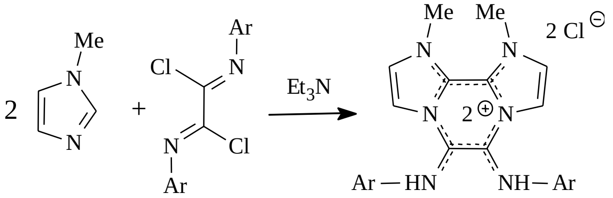
Self-cyclization of (*E*)-2-(trimethylsilylmethyl)pentadienol derivative. Synthesis of bicyclo[4.3.0] nonane ring systems **pp 726–730**

Chiaki Kuroda,* Masatoshi Okada, Shinya Shinozaki and Hideyuki Suzuki



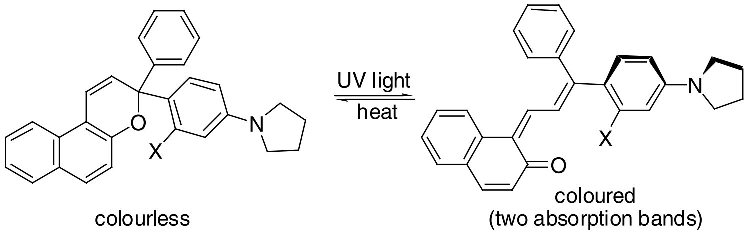
Synthesis of new bridged biimidazoles by an acylation–dimerization sequence **pp 731–736**

Thomas Welzel, Rainer Beckert,* Reinald Fischer, Sven Rau,* Dirk Walther and Helmar Görls



The synthesis and electronic absorption spectra of 3-phenyl-3(4-pyrrolidino-2-substituted phenyl)-3*H*-naphtho[2,1-*b*]pyrans: further exploration of the *ortho* substituent effect **pp 737–745**

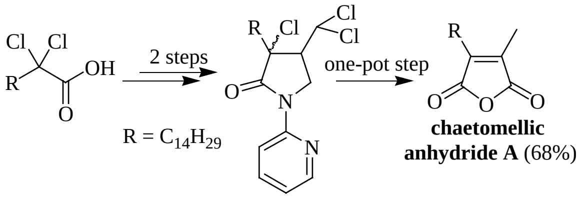
Christopher D. Gabbutt, B. Mark Heron* and Alicia C. Instone



A short approach to chaetomellic anhydride A from 2,2-dichloropalmitic acid: elucidation of the mechanism governing the functional rearrangement of the chlorinated pyrrolidin-2-one intermediate

pp 746–757

Franco Bellesia, Chiara Danieli, Laurent De Buyck, Roberta Galeazzi, Franco Ghelfi,* Adele Mucci, Mario Orena, Ugo M. Pagnoni, Andrew F. Parsons and Fabrizio Roncaglia

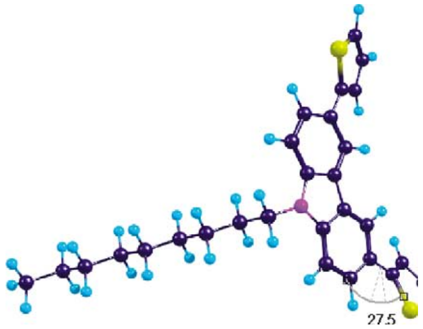


Development in synthesis and electrochemical properties of thienyl derivatives of carbazole

pp 758–764

Joanna Cabaj, Krzysztof Idzik, Jadwiga Sołoducho* and Antoni Chyla

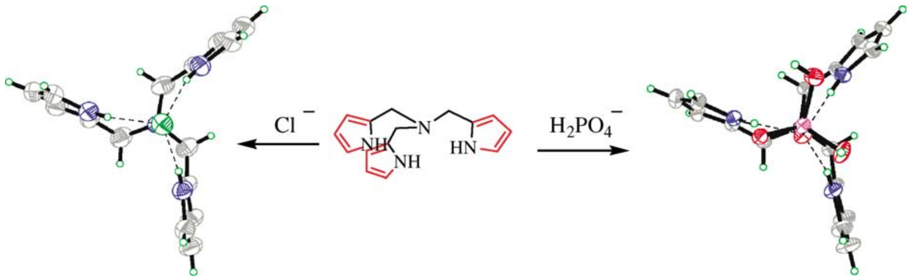
The synthesis and electrochemical properties of a series of carbazole derivatives is reported. Stille type methodology provides a simple and convenient route to obtain the title compounds, which could find application for example in sensoric and active materials.



A new tripodal anion receptor with selective binding for $H_2PO_4^-$ and F^- ions

pp 765–770

Zhenming Yin, Yanhua Zhang, Jiaqi He and Jin-Pei Cheng*



OTHER CONTENTS

*Corresponding author
ⓘ$^+$ Supplementary data available via ScienceDirect

Indexed/Abstracted in: AGRICOLA, Beilstein, BIOSIS Previews, CAB Abstracts, Chemical Abstracts. Current Contents: Life Sciences, Current Contents: Physical, Chemical and Earth Sciences, Current Contents Search, Derwent Drug File, Ei Compendex, EMBASE/Excerpta Medica, Medline, PASCAL, Research Alert, Science Citation Index, SciSearch

ELSEVIER

ISSN 0040-4020

Available online at www.sciencedirect.com
SCIENCE DIRECT®
ELSEVIER
Tetrahedron 62 (2006) 513–535
Tetrahedron

Tetrahedron report number 746

Synthetic approaches towards 2-iminothiazolidines: an overview

Matthias D'hooghe and Norbert De Kimpe*

Department of Organic Chemistry, Faculty of Bioscience Engineering, Ghent University, Coupure Links 653, B-9000 Ghent, Belgium

Received 31 August 2005

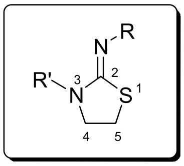
Available online 8 November 2005

Contents

---

1. Introduction

The synthesis of 2-iminothiazolidines has been studied intensively in the past, especially because of the diverse biological activities ascribed to many representatives of this class of compounds. Consequently, a large variety of synthetic protocols towards functionalized 2-iminothiazolidines and related compounds has been reported in the literature. The first reports were published more then a century ago, but also today chemists endeavour to create new and improved entries into these versatile compounds. In this review, a comprehensive overview of the different synthetic methodologies leading to 2-iminothiazolidines **1** will be discussed (Fig. 1). The chemistry of bicyclic and polycyclic derivatives will not be dealt with, as well as the synthesis of thiazolidines bearing an sp^2 carbon atom at position 4 and/or 5 (e.g., oxothiazolidines). Additionally, the preparation of 2-imino-4-thiazolines falls outside the scope of this review. The cited references are limited to journal publications, while syntheses which have been patented are not included. The general numbering of the heterocyclic ring of 2-iminothiazolidines will be sustained throughout this review, as depicted in Figure 1.



1

Figure 1.

2. Biological relevance of 2-iminothiazolidines

The 2-iminothiazolidine moiety is present in a large variety of physiologically active compounds with applications varying from medicinal to agricultural use. A few selected examples of biologically active iminothiazolidines, chosen from an impressive list, are depicted in Figure 2.

2-Iminothiazolidines applicable in medicine are, for example, 2-(tetrahydronaphthalen-1-yl)iminothiazolidine

---

Keywords: 2-Iminothiazolidines; Cyclization; *N*-(Hydroxyalkyl)thiourea derivatives; 2-Amino-2-thiazolines; Aziridines.

* Corresponding author. Tel.: +32 9 2645951; fax: +32 9 2646243; e-mail: norbert.dekimpe@UGent.be

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.09.028

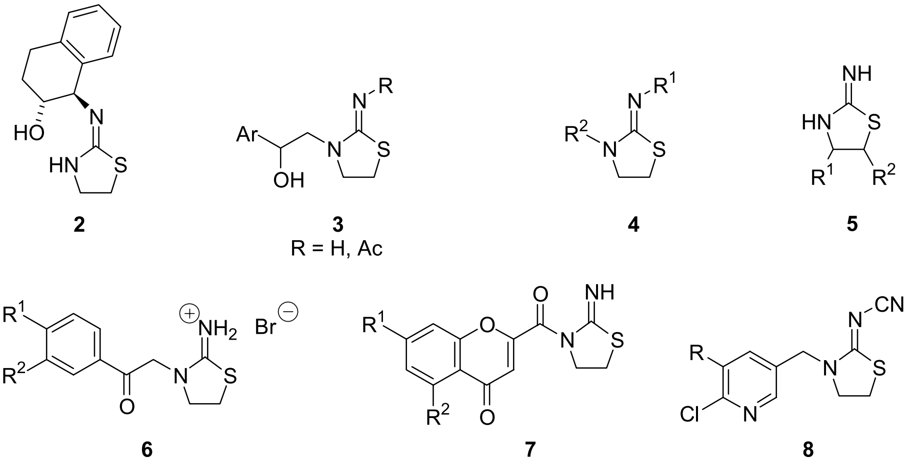
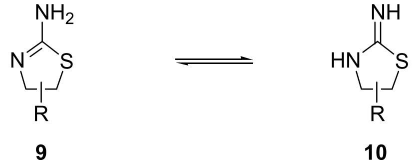


Figure 2.

2, which exhibits a pronounced antidepressant activity,[1] and β-(hydroxyethyl)thiazolidines **3**, which are effective antihypertensives.[2] Other classes of thiazolidines have a distinct influence on enzyme activity, such as 3-methylthiazolidine **4** ($R^1=H$, $R^2=Me$), a potent inhibitor of indole–ethylamine *N*-methyltransferase,[3] 2-(arylimino)thiazolidines **4** ($R^1=$ aryl), stimulators of adenylate cyclase,[4] and 4,5-dialkyl-substituted thiazolidines **5**, which have been reported as inhibitors of nitric oxide synthase.[5] Other therapeutically useful thiazolidines are, for example, 3-substituted thiazolidines **6** and **7**, featuring radioprotective properties against γ-radiation.[6] 3-Substituted 2-(cyanoimino)thiazolidines, such as thiazolidine **8**, can be used in agriculture due to their neonicotinoid insecticidal activity,[7] with thiacloprid (**8**: R=H) as a commercially available insecticide released by Bayer in 2001.[8] Furthermore, 2-iminothiazolidine-4-carboxylic acid has been reported to produce hippocampal lesions in mice,[9] and 2-iminothiazolidine-4-carboxyl peptides, formed by cleavage of modified cysteinyl residues, can be mapped to the sequence in order to locate cysteine residues in proteins.[10] Many other biological activities of 2-iminothiazolidines have been reported, including trehalase inhibition,[11] anti-inflammatory,[12] anodyne,[13] antitumor[14] and anti-Alzheimer activity,[15] which illustrate the great potential of new derivatives containing a 2-iminothiazolidine moiety and the importance of new synthetic pathways leading to these structural entities.

3. 2-Amino-2-thiazoline–2-iminothiazolidine tautomeric equilibrium

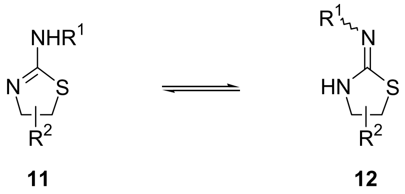
2-Amino-2-thiazolines **9** are basically capable of existing in two tautomeric forms, namely the 2-imino form **10** with an exocyclic double bond and the 2-amino form **9** possessing an endocyclic double bond (Scheme 1).



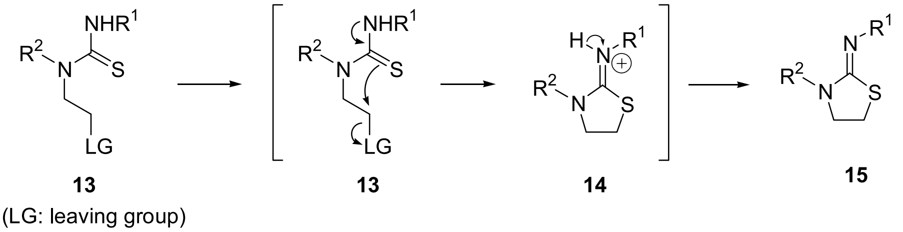
Scheme 1.

The problem of isomerism has raised some controversy in the early literature. The pioneers, Gabriel and Colman, described the reaction product of 1-phenyl-2-chloroethylamine and potassium thiocyanate as 2-imino-5-phenylthiazolidine,[16] followed by Mousseron et al. for the analogous reaction with 2-chlorocyclohexylamine,[17] whereas Wohl and Headley argued that the more stable 2-aminothiazolines **9** should always prevail.[18] The latter statement was based on IR data obtained for different derivatives, showing a very strong C=N absorption at 1640 cm^{-1}, which is characteristic for an endocyclic C=N. Furthermore, the absence of an amide II band between 1500 and 1575 cm^{-1} confirmed the assumption that the 2-amino form **9** is the predominant, if not the exclusive, form present. These conclusions were consolidated by Blum et al. using ^1H NMR spectroscopy, since the singlet, integrating exactly for two protons, disappeared by deuterium oxide addition, and also by IR spectroscopy, based on the presence of the typical NH_2 bands at 3420–3430 and 1590–1600 cm^{-1}.[19]

Whereas the 2-amino-2-thiazoline tautomer **9** predominates for *N*,*N*′-unsubstituted derivatives, thiazolidines with a substituent R^1 on the exocyclic nitrogen tend to appear as the 2-iminothiazolidine isomer **12** ($R^2=H$, Scheme 2) rather than **11**. For 2-substituted 2-iminothiazolidines **12**, *E*/*Z*-isomerism is possible across the imino double bond. Based on semi-empirical calculations, the *Z*-isomer predominates for 2-(methylimino)thiazolidine ($\Delta E=1.47$ kcal/mol), whereas, for 2-(phenylimino)thiazolidine, the *E*-isomer appears to be the most stable, although, in this case, the energy difference between both isomers is rather low ($\Delta E=0.2$ kcal/mol).[20] Except for those two derivatives, the subject of *E*/*Z*-isomerism of 2-substituted 2-iminothiazolidines has not been addressed in the literature.



Scheme 2.



Scheme 3.

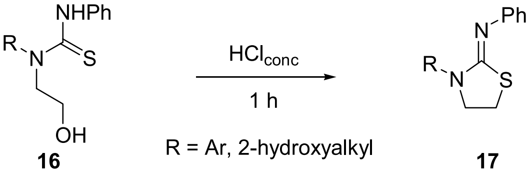
4. Syntheses of 2-iminothiazolidines

The majority of the syntheses leading to 2-iminothiazolidines reported in the literature can be divided into five different categories, each category based on a different synthetic approach. These protocols will be discussed in the following paragraphs.

4.1. Intramolecular cyclocondensation of *N*-(hydroxyalkyl)thiourea derivatives

The most frequently explored entry to 2-iminothiazolidines comprises the intramolecular cyclization of *N*-(hydroxyalkyl)thiourea derivatives using a variety of reagents and reaction conditions. These reactions are essentially based on a nitrogen-assisted nucleophilic attack of the sulfur atom of the substrate **13** (ambident nucleophile) upon expulsion of the leaving group. The resulting iminium species **14** is subsequently neutralized by loss of a proton (Scheme 3).

A convenient way to induce cyclization of *N*-(hydroxyalkyl) thioureas is based on the use of an acidic environment.[21] Thioureas **16** have been cyclized to thiazolidines **17** in the presence of concentrated HCl (Scheme 4).[22]



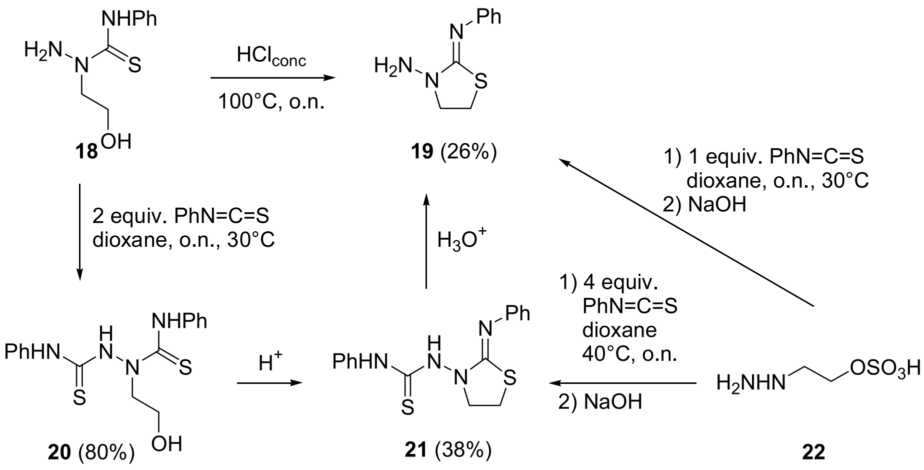
Scheme 4.

A more detailed investigation concerning the acid-catalyzed cyclization was performed by Rabinowitz et al. using *N*-amino-*N*-(hydroxyalkyl)thioureas as substrates.[23] *N*-(2-hydroxyethyl)-*N*-aminothiourea **18** was cyclized to the 3-aminothiazolidine **19** using concentrated hydrogen chloride or, alternatively, this substrate (**18**) was functionalized upon treatment with two equivalents of phenyl isothiocyanate in dioxane, affording hydrazinoethanol **20** (Scheme 5). The latter thiourea derivative **20** was cyclized in aqueous acidic medium yielding 3-aminothiazolidine **19** via thiazolidine **21**. 3-Aminothiazolidine **19** was also prepared from sulfate **22**, either directly upon treatment with 1 equiv of phenyl isothiocyanate followed by basic treatment, or via thiazolidine **21** by reaction with 4 equiv of phenyl isothiocyanate followed by acidic hydrolysis (Scheme 5, o.n. = overnight).

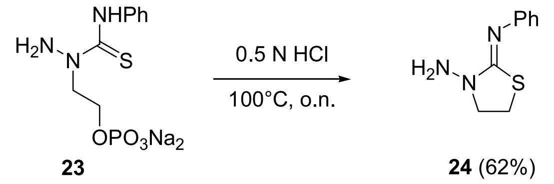
Analogously, cyclization of the thiocarbamoylated hydrazinoethyl phosphate **23**, prepared from hydrazinoethylphosphoric acid in the presence of dilute hydrogen chloride, afforded 3-aminothiazolidine **24** in 62% yield (Scheme 6).[24]

The above-mentioned acid-catalyzed cyclization method was also proven to be applicable for substrates bearing other functional groups. This was shown by the synthesis of 2-iminothiazolidines **26** containing a β-alanine moiety by means of acid-catalyzed ring closure of thiourea derivatives **25** with concentrated HCl (Scheme 7).[25] No mention was made of the detection of sideproducts, which would result from addition reactions across the amide moiety.

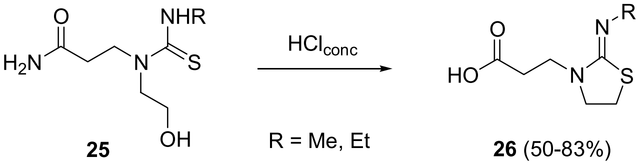
The thiourea derivatives **27**, closely related to thioureas **25**, also underwent intramolecular cyclization towards



Scheme 5.

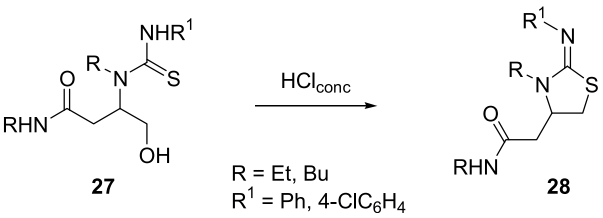


Scheme 6.



Scheme 7.

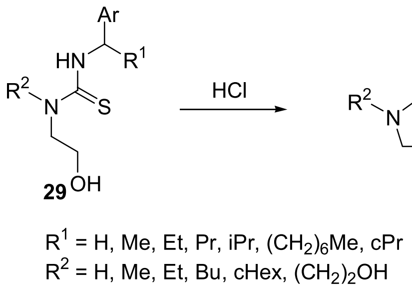
iminothiazolidines **28** upon treatment with concentrated hydrogen chloride, without the formation of undesired side-products (Scheme 8).[26]



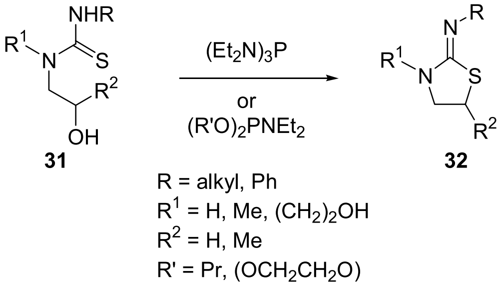
Scheme 8.

In general, the acid-catalyzed cyclisation of hydroxyalkylthiourea derivatives has been applied for the synthesis of a large variety of 2-iminothiazolidines with different substituents. *N*,*N*′,*N*′-substituted thioureas **29** have been cyclized using hydrogen chloride (Scheme 9), and the resulting 2-iminothiazolidines **30** have been used for structure–activity relationship tests, some of them showing significant diuretic and saluretic activity.[27]

An alternative for the acid-catalyzed cyclization of *N*-(β-hydroxyalkyl)thioureas was presented by Mizrakh et al.[28] These authors reported the conversion of (β-hydroxyalkyl)thioureas **31** in the presence of tri(diethylamino)phosphine or other phosphines into 5-substituted thiazolidines **32** (Scheme 10).



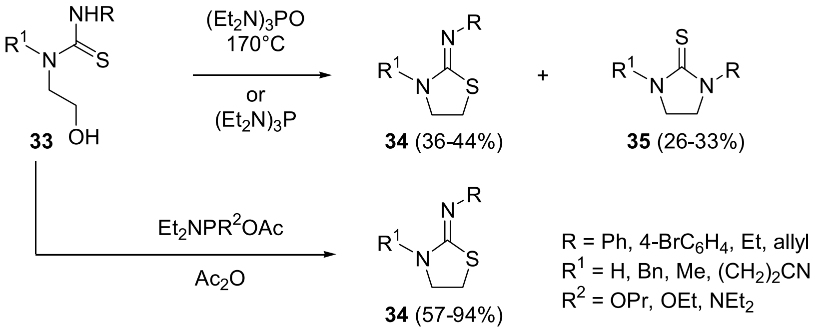
Scheme 9.



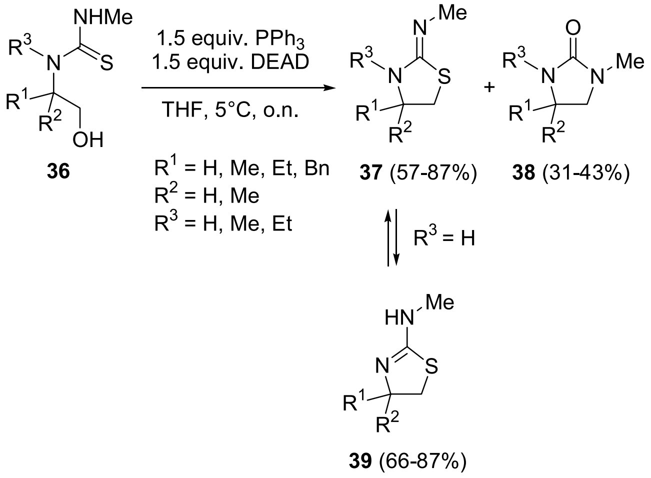
Scheme 10.

Further elaboration of this methodology involved treatment of (2-hydroxyethyl)thioureas **33** with tri(diethylamino)phosphine oxide at 170 °C or with tri(diethylamino)phosphine and resulted in mixtures of 2-imino-thiazolidines **34** and imidazolidine-2-thiones **35** (Scheme 11), whereas the reaction of the same substrates with phosphines Et_2NPR^2OAc ($R^2=$ OPr, OEt or Et_2N) in acetic acid anhydride furnished exclusively 2-iminothiazolidines **34** in good yields (Scheme 11).[29]

In recent years, two other approaches for the intramolecular cyclization of *N*-(2-hydroxyalkyl)thioureas have been developed by Kim and coworkers. The first approach involves the application of Mitsunobu reaction conditions, that is, 1.5 equiv of triphenylphosphine and 1.5 equiv of diethyl azodicarboxylate (DEAD) in THF, furnishing mixtures with 2-iminothiazolidines **37** as the major reaction products (when $R^3 \neq H$, 57–69%), besides imidazolidine-2-thiones **38** in minor quantities (31–43%). 2-Aminothiazolines **39** were isolated as the sole reaction products for derivatives **36** with $R^3=H$ (Scheme 12).[30]



Scheme 11.



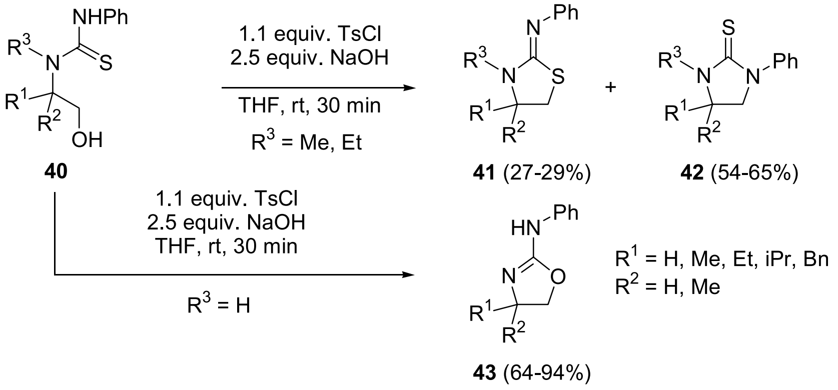
Scheme 12.

As discussed in Section 3, the 2-iminothiazolidine tautomer **37** should predominate over the thiazoline **39** when $R^3 = H$, based on semi-empirical calculations for exocyclic *N*-methyl-substituted thiazolidine without substituents on the heterocyclic ring ($R^1 = R^2 = H$).[20] Of course, the results obtained from semi-empirical calculations for 2-(methylimino)thiazolidine cannot be generalized for all thiazolidines bearing an exocyclic *N*-methyl substituent, and the presence of other substituents (such as R^1 and R^2) might have an influence on the tautomeric equilibrium. The authors did not, however, discuss the possibility of isomerism, and they described their isolated compounds as 2-methylaminothiazolines **39**, instead of 2-iminothiazolidines **37** (when $R^3 = H$).

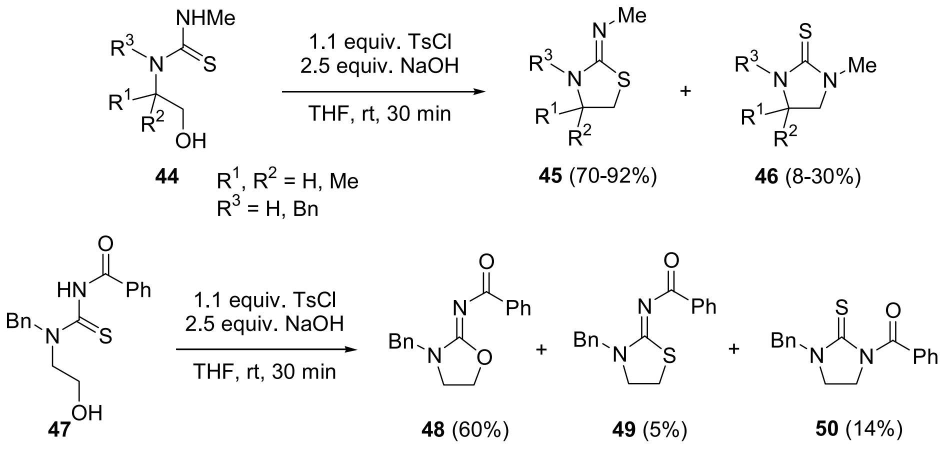
The second approach reported by this group comprises the transformation of the hydroxyl group into a tosyloxy group in a basic environment, creating a good leaving group in the δ-position of the nucleophilic thione moiety. Treatment of the *N*-phenyl thioureas **40** with 1.1 equiv of tosyl chloride in the presence of 2.5 equiv of sodium hydroxide in THF resulted in mixtures of 2-iminothiazolidines **41** as the minor constituents (27–29%) and imidazolidine-2-thiones **42** as the major compounds (Scheme 13).[31] The ratio of *S*- versus *N*-cyclization can be shifted in favor of the *S*-cyclized 2-iminothiazolidines **41** (40–72%) by changing the base from NaOH to Et_3N.[32] For thioureas **40** with $R^3 = H$, 2-phenylamino-2-oxazolines **43** were formed exclusively and in high yields through *O*-cyclization (Scheme 13). Obviously, this approach is only beneficial when 2-amino-2-oxazolines are contemplated as the target compounds.

Similar observations were reported when potassium *tert*-butoxide was used instead of sodium hydroxide, and, again, mixtures of iminothiazolidines **41** and imidazolidine-2-thiones **42** were obtained.[33]

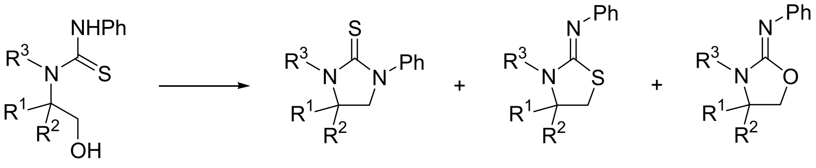
Treatment of *N*-methyl-substituted thioureas **44** with 1.1 equiv of tosyl chloride and 2.5 equiv of sodium



Scheme 13.

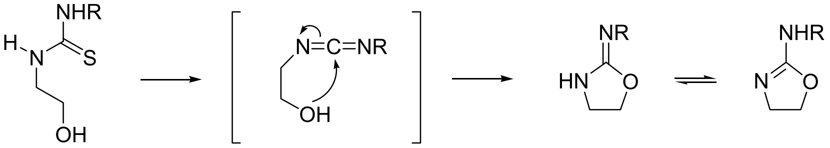


Scheme 14.



51 **52** **53** **54**

Scheme 15.



55 **56** **57** **58**

Scheme 16.

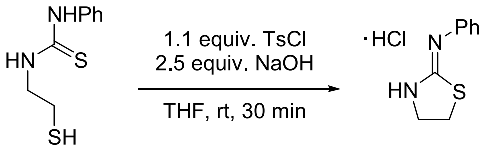
hydroxide in THF, however, afforded mixtures with 2-iminothiazolidines **45** as the major constituents and imidazolidine-2-thiones **46** as the minor compounds, in contrast with the results obtained for *N*-phenyl-substituted thioureas **40**, although similar reaction conditions were applied (Scheme 14). Cyclization of *N*-benzoyl thiourea **47** resulted in a three-component reaction mixture in which oxazolidine **48** was formed as the major compound (60%), besides minor amounts of 2-iminothiazolidine **49** and imidazolidine-2-thione **50** (Scheme 14).[34]

Finally, Kim et al. compared the cyclization of different *N*-phenyl-*N*′-(2-hydroxyalkyl)thioureas **51** utilizing Mitsunobu conditions on the one hand and the TsCl/NaOH system on the other hand (Scheme 15). Application of Mitsunobu conditions, that is, triphenylphosphine and diisopropyl azodicarboxylate in THF, afforded mixtures with the *N*-cyclized imidazolidine-2-thiones **52** as the major constituents (51–95%), whereas the *S*-cyclized thiazolidines **53** (5–32%) and *O*-cyclized oxazolidines **54** (0–17%) were formed as the minor reaction products. When the TsCl/NaOH system was used, oxazolidines **54** (in fact, the tautomeric oxazolines) were formed exclusively (with R^1 and R^2 = H or alkyl) for substrates **51** with R^3 = H, although no oxazolidines **54** were isolated when R^3 = alkyl (R^1 = R^2 = H). In the latter case, mainly imidazolidine-2-thiones **52** were formed (57–70%), besides iminothiazolidines **53** (30–43%).[35]

The authors premise that the ratio of *O*-, *N*- and *S*-cyclized products is dependent on the acidity of the thiourea moiety and the steric hindrance around the sulfur atom. Substrates with a more acidic thiourea moiety (PhCONH > PhNH > MeNH) and a less-hindered sulfur atom (*N*-unsubstituted > *N*-substituted) tend to undergo *O*-cyclization rather than *N*- and *S*-cyclization towards 2-oxazoline derivatives via initial *S*-tosylation.

The formation of oxazolines **58** from thiourea **55** using the TsCl/NaOH system can be rationalized considering the formation of a carbodiimide intermediate **56** after *S*-tosylation and elimination of TosSH, followed by intramolecular attack of the nucleophilic oxygen (Scheme 16). Indeed, literature precedents show that the thiourea sulfur reacts very fast with sulfonyl chlorides, yielding carbodiimides in the presence of a base.[36]

Based on these results, Heinelt et al. explored the possibilities of the TsCl/NaOH system for the synthesis of a variety of heterocyclic compounds using different thiourea derivatives. For example, the ring closure of thiol **59** using the TsCl/NaOH methodology afforded the thiazolidine **60**, probably via the formation of an intermediate carbodiimide which undergoes intramolecular attack of the thiol moiety (Scheme 17), in analogy with the oxazolidine formation mechanism depicted in Scheme 16.[37]



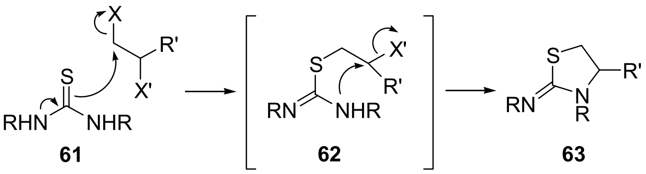
59 **60** (32%)

Scheme 17.

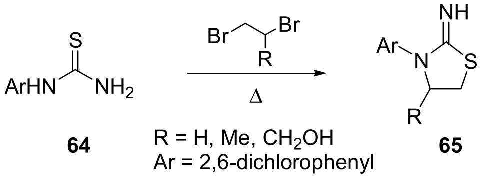
In conclusion, the intramolecular cyclization of *N*-(2-hydroxyalkyl)thioureas towards 2-iminothiazolidines has been studied intensively using a variety of conditions and reagents. Ring closure triggered by acid or by means of phosphines affords straightforward approaches towards 2-iminothiazolidines, although the yields are rather moderate to good. The TsCl/NaOH system as well as the application of Mitsunobu conditions are much less attractive when the selective synthesis of 2-iminothiazolidines is contemplated, since competition with *N*- and *O*-cyclization results in mixtures of thiazolidines, oxazolidines and imidazolidines.

4.2. Condensation of thiourea derivatives with 1,2-dihaloalkanes

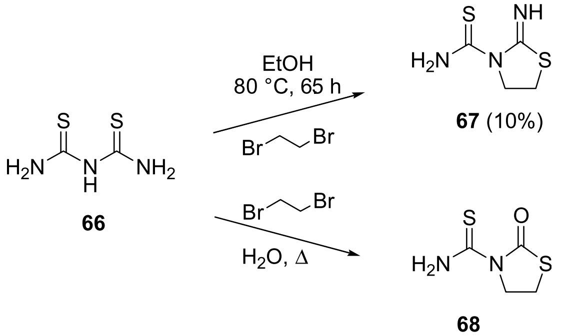
Treatment of a thiourea derivative **61** with a haloalkane affords the corresponding *S*-alkylated isothiuronium substitution product **62**, which can undergo intramolecular cyclization towards a thiazolidine ring **63** if an additional electrophilic carbon atom, such as a halogenated carbon atom, is present in the δ-position of the amino moiety (Scheme 18).



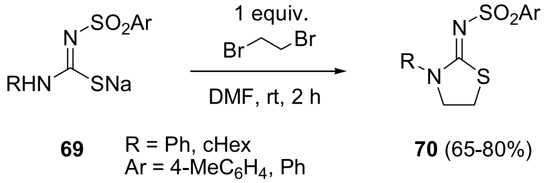
Scheme 18.



Scheme 19.



Scheme 20.



Scheme 21.

4-Substituted 2-iminothiazolidines **65** have been synthesized by the reaction of *N*-arylthioureas **64** with 1,2-dibromoalkanes (Scheme 19),[38] based on the preceding reports of Erlenmeyer et al. and Bradsher et al.[39] An analogous reaction was performed using *N*-acylthioureas and 1,2-dibromoethane, resulting in 2-(acylimino)thiazolidines.[40]

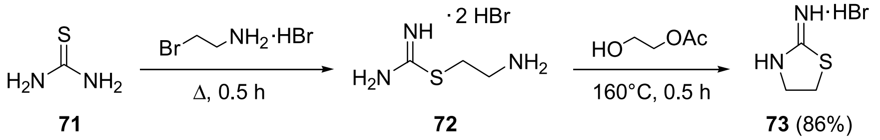
A similar reactivity was observed with dithiobiuret **66** upon treatment with 1,2-dibromoethane, although the yield was very low. After refluxing in ethanol for 6.5 h, 2-iminothiazolidine **67** was isolated from the reaction mixture, whereas reflux in water resulted only in the corresponding 2-oxo derivative **68** (Scheme 20).[41]

2-(Arenesulfonylimino)thiazolidines **70** have been prepared by alkylation of the sodium salts of thiourea derivatives **69** with 1,2-dibromoethane in DMF at room temperature for 2 h (Scheme 21).[42]

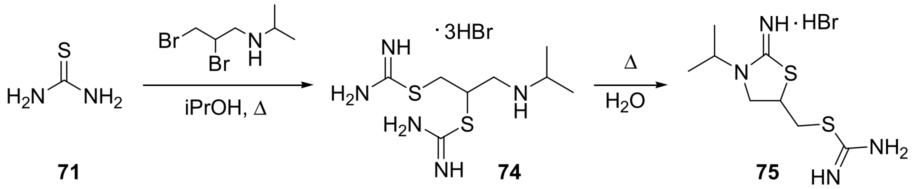
In a close relationship to the above-mentioned examples, Schoberl and Hansen described the reaction between thiourea **71** and 1-amino-2-bromoethane hydrobromide, furnishing the corresponding *S*-substitution product **72**. Heating of the latter compound (**72**) in monoacetyl ethylene glycol at 160 °C for 30 min afforded the iminothiazolidine hydrobromide **73** in 86% yield (Scheme 22).[43] Based on the semi-empirical calculations discussed in Section 3, the isolated product was probably the corresponding 2-aminothiazoline hydrobromide tautomer.[20]

The synthesis of 2-iminothiazolidine **75** proceeds via a slightly different pathway. Reaction of the thiourea **71** with *N*-isopropyl-2,3-dibromopropylamine afforded the corresponding monosubstituted 2-bromopropane intermediate [instead of the cyclized 2-imino-4-(isopropylaminomethyl)thiazolidine], which was subsequently reacted with an additional amount of thiourea to yield the disubstituted propylamine **74**. Heating of the latter propylamine (**74**) in water under reflux resulted in the thiazolidine **75** (Scheme 23).[44]

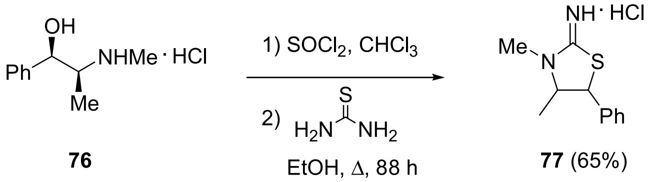
In 1961, the conversion of ephedrine hydrochloride **76** into the thiazolidine **77** was described after reaction with 2 equiv of thiourea in refluxing ethanol for 88 h (Scheme 24), although no cyclization was intended at that time.[45] It was suggested that the intermediate isothiuronium salt had



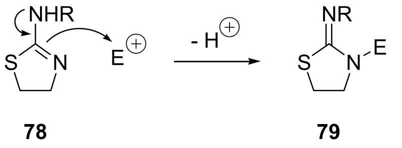
Scheme 22.



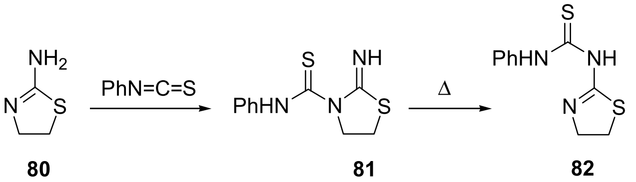
Scheme 23.



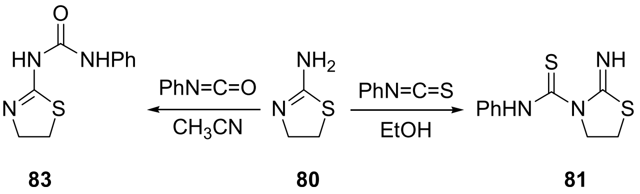
Scheme 24.



Scheme 25.



Scheme 26.



Scheme 27.

expelled ammonium chloride upon intramolecular cyclization. No details were given regarding the stereochemistry of the starting material and the stereochemical outcome of this reaction, although it can be expected that the relative stereochemistry of the ephedrine starting product **76** is conserved throughout the reaction.

Although condensation of thioureas with 1,2-dihaloalkanes or similar substrates essentially constitutes a simple procedure for the preparation of 2-iminothiazolidines, the synthetic applicability appears to be rather limited, as can be seen from the small number of papers in this area and the low yields reported.

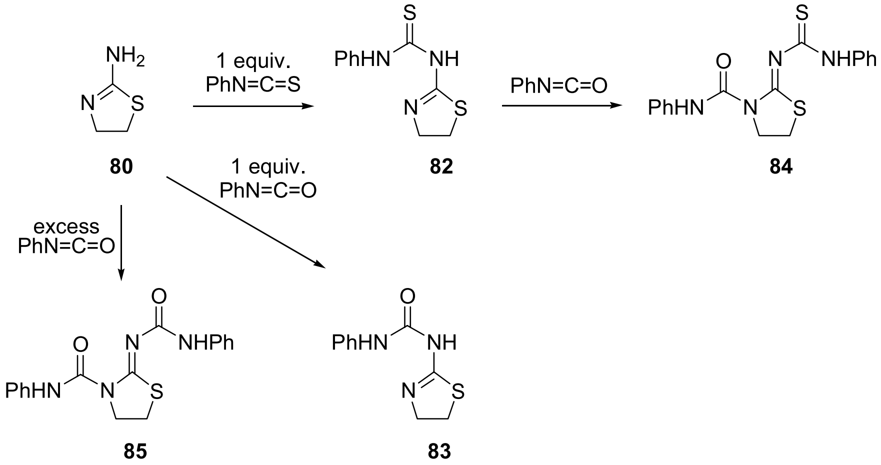
4.3. Reaction of 2-amino-2-thiazolines with electrophiles

2-Amino-2-thiazolines are good nucleophiles for the synthesis of 2-iminothiazolidines via different substitution or addition reactions. The question of regioselective functionalization of both nitrogen atoms has been the subject of reasonable controversy in the literature over the years. At present, it has been accepted that the endo regiospecificity appears to be a general and unifying rule for 2-amino-2-thiazolines bearing two non-equivalent amidine-type nitrogen atoms, which enables selective functionalization at the 3-position, that is, **78**→**79** (Scheme 25).[20]

2-Amino-2-thiazolines can be easily prepared in good yields, usually by the reaction of a 2-haloethyl isothiocyanate with an amine, although many other routes have been described. The discussion of the synthetic protocols towards 2-aminothiazolines, however, falls outside the scope of this review.

The most commonly evaluated electrophiles for the functionalization of 2-aminothiazolines are heterocumulenes such as isocyanates and isothiocyanates. In 1928, it was reported that the addition of 2-aminothiazoline **80** to phenyl isothiocyanate resulted in thiazolidine **81**, which rearranged into thiazoline **82** upon heating (Scheme 26).[46]

Reinvestigations of this research by other groups, however, gave irreproducible and often contradictory results.[47] In one of these reports, Klayman and Maul described a different reactivity of 2-aminothiazoline **80** towards phenyl isocyanate on the one hand and phenyl isothiocyanate on the other hand. The former reaction (with phenyl isocyanate) resulted in the substituted thiazoline **83**, while the latter reaction with phenyl isothiocyanate gave rise to the 2-iminothiazolidine **81** (Scheme 27). These observations were confirmed by a labelling experiment for the synthesis

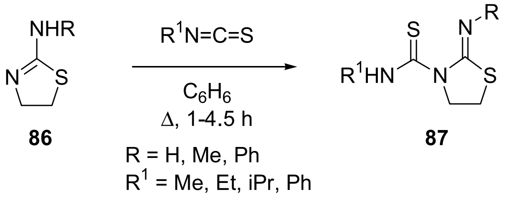


Scheme 28.

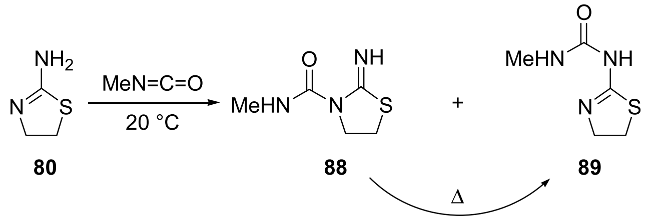
of compound **83**, and by an alternative procedure for the synthesis of compound **81**.[47c]

In another paper, the same group investigated the use of an equimolar amount of the electrophile, which resulted in the mono-adducts **82** and **83**, whereas the use of an excess of phenyl isocyanate afforded the iminothiazolidine **85**. Treatment of thiazoline **82** with phenyl isocyanate furnished the thiazolidine **84** (Scheme 28).[47d]

Yamamoto et al. have also described the transformation of thiazolines **86** into 3-(thiocarbamoyl)thiazolidines **87** upon reaction with different isothiocyanates (Scheme 29) and into 3-(carbamoyl)thiazolidine **88** from the addition of methyl isocyanate. The latter compound (**88**) isomerized to 2-aminothiazoline **89** upon heating (Scheme 30).[48]



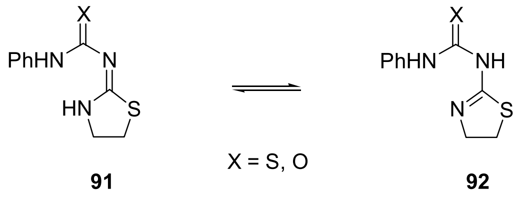
Scheme 29.



Scheme 30.

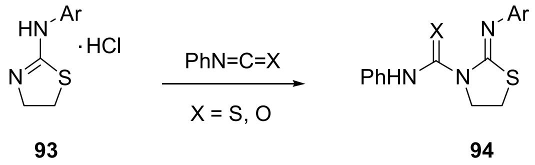
An in-depth investigation of the reactivity of 2-aminothiazoline **80** towards iso(thio)cyanates by Rasmussen et al. supplied the unambiguous evidence for the mechanism behind the formation of iminothiazolidines **90**.[49] In an earlier report, Klayman et al. concluded that phenyl isocyanate had reacted only with the exocyclic amino group of thiazoline **80**,[47c] contradictory to the findings of Fromm and Kapeller-Adler in 1928 (Scheme 26).[46] The experiments of Rasmussen et al., however, finally settled the issue and confirmed that the reaction of thiazolines **80** with iso(thio)cyanates exclusively occurs at the endocyclic nitrogen to produce thiazolidines **90** (kinetic control). The latter adducts (**90**) may undergo intramolecular rearrangement and/or dissociation to reactants and recombination at the exocyclic nitrogen to form the thermodynamically more stable thiazolidines **91** (Scheme 31), consolidating the initial work of Fromm and Kapeller-Adler.

Additionally, for thiazolidines **91**, a tautomeric 2-thiazoline isomer **92** is possible (Scheme 32). X-ray crystallography of thiazolidine **91** (X=S) could not distinguish between the two tautomers *exo*-**91** and *endo*-**92** because the bond lengths were similar.[50] Furthermore, semi-empirical calculations for thiazolidine *exo*-**91** and its thiazoline isomer *endo*-**92** (X=O) revealed that the difference in relative stability of both tautomers is very small ($\Delta E = 0.16$ kcal/mol between the *E-s-cis* conformer of *exo*-**91** and the *s*-trans–*s*-trans conformer of *endo*-**92**),[20] which might indicate a dynamic equilibrium between both isomers.



Scheme 32.

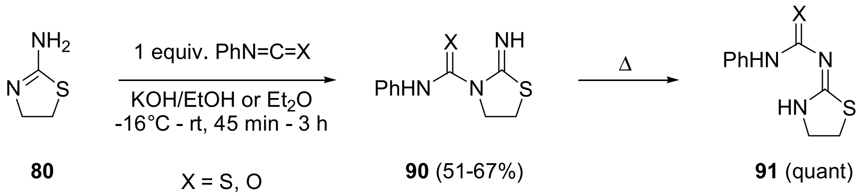
A similar reactivity was observed for 2-(*N*-arylamino) thiazolines **93**, yielding 2-aryliminothiazolidines **94** upon treatment with iso(thio)cyanates (Scheme 33). These structures were unequivocally assigned by X-ray analysis. No *endo-N–exo-N′* rearrangement of thiazolidines **94** was observed upon heating.[51]



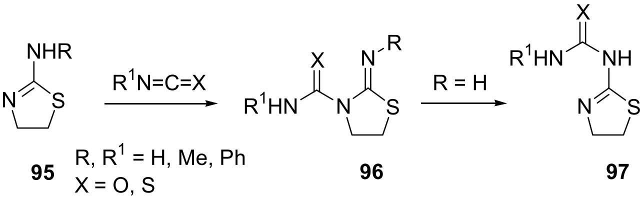
Scheme 33.

Detailed chemical and computational studies by Palacios et al. on the regioselectivity, the adduct rearrangement and the mechanistic pathway regarding the reactivity of *N*-substituted thiazolines **95** towards iso(thio)cyanates supported the endo regiospecificity and the tendency of thiazolidines **96** (R=H) to rearrange into thiazolines **97** (Scheme 34).[20] Semi-empirical calculations revealed that the endo adducts are the kinetically favored products, and that the isocyanate adducts are more stable than those of the isothiocyanates.

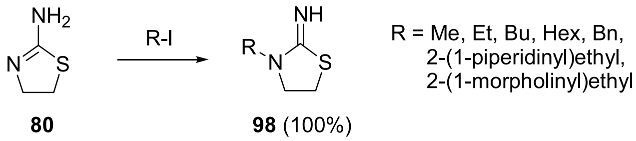
Besides iso(thio)cyanates, other electrophiles have also been evaluated for the functionalization of thiazolines. The alkylation of 2-aminothiazoline **80** with iodoalkanes



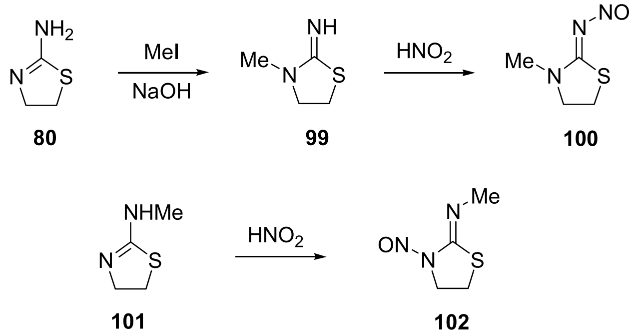
Scheme 31.



Scheme 34.



Scheme 35.



Scheme 36.

furnished the 3-alkyl-2-iminothiazolidines **98** in quantitative yields (Scheme 35).[52] 2-Aryl- and 2-alkylamino-5-methylthiazolines have also been treated with alkyl iodides to give the corresponding alkylation products.[53]

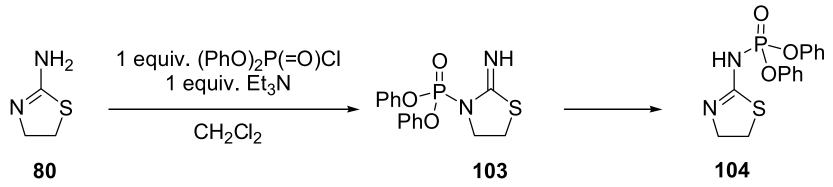
Methylation of thiazoline **80** with iodomethane to form **99** and its subsequent reaction with nitrous acid furnished 2-nitrosoimino-3-methylthiazolidine **100** (Scheme 36). When 2-(methylamino)thiazoline **101** was treated with nitrous acid, 2-methylimino-3-nitrosothiazolidine **102** was isolated (Scheme 36). These experiments acknowledged the *endo* regiospecificity of 2-aminothiazolines upon treatment with electrophiles, resulting in 3-substituted 2-iminothiazolidines.[54]

Endocyclic substitution products **103** were also formed in a phosphorylation reaction of 2-aminothiazoline **80**. The reaction of thiazoline **80** with diphenyl chlorophosphate at −10 °C resulted in the 3-substituted thiazolidine **103** (60%) besides the thiazoline **104** (8.5%), whereas no thiazolidine **103** was obtained when the same reaction was performed at room temperature. In the latter case, only thiazoline **104** was isolated (28%), besides the corresponding diacylated compound (26%), indicating a 1,3-rearrangment of the originally formed *endo*-adduct (Scheme 37). Furthermore, the alkylation of 2-amino-2-thiazoline **80** with different α-brominated Michael acceptors gave rise to bicyclic 2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazoles.[55]

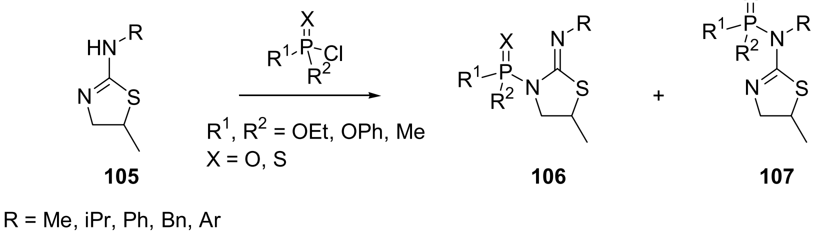
With the experimental results presented in this report, a considerable amount of confusion in the literature was cleared up, and the preliminary reports on the phosphorylation of 2-amino-2-thiazolines were corrected, since it had previously been presumed that *exo* as well as *endo* substitution took place, depending on the conditions.

As an example, the phosphorylation of 5-methylthiazolines **105** had been reported to afford mixtures of the thiazolidines **106** and the isomeric thiazolines **107**, depending on the reaction conditions and the nature of the R substituent (Scheme 38).[56] In a similar report, the thiophosphorylation of 2-aminothiazoline **80** followed by functionalization with different chlorides furnished the 3-substituted 2-(thiophosphorylimino)thiazolidines **108** (Scheme 39).[57]

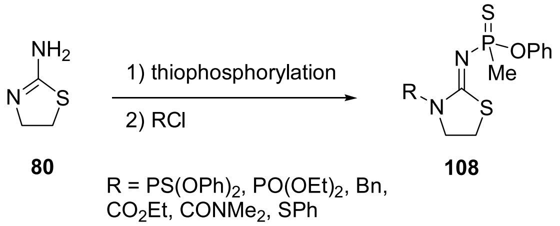
Other acylating reagents such as acid chlorides have also been employed for the functionalization of thiazolines. Treatment of 2-aminothiazoline **80** with 4-nitrobenzoyl chloride afforded the diacylated thiazolidine **109**, which was subsequently reduced by Zn and NH_4Cl in ethanol to give the monoacylated thiazolidine **110** (Scheme 40).[58]



Scheme 37.



Scheme 38.

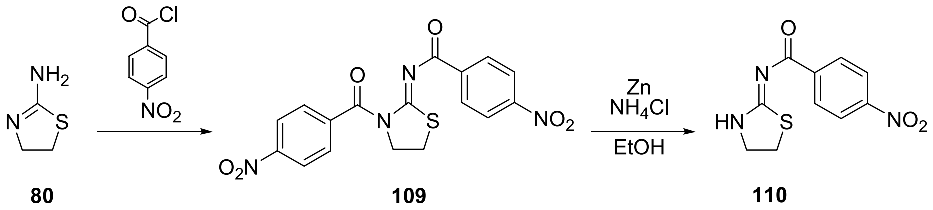


80 **108**

Scheme 39.

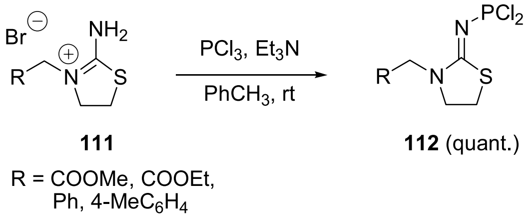
In an alternative approach, 3-alkyl-2-aminothiazolinium bromides **111** have been used as substrates for the synthesis of dichlorophosphines **112** upon reaction with 1 equiv of PCl_3 and 2 equiv of Et_3N in toluene (Scheme 41).[59] These thiazolidines **112** were further functionalized using MeOH, *i*PrSH or Me_2SO_4.

Furthermore, carbamoylation of 2-aminothiazolines with diethoxythiophosphoryl isocyanate has been realized, resulting in tautomeric mixtures of functionalized thiazolidines and thiazolines, the latter compounds probably being formed after rearrangment of the initial *endo*-adducts.[60] Condensation of 1-methyl-2-methanesulfonyl-5-nitroimidazole with the sodium salt of 2-iminothiazolidine resulted in the corresponding 3-substituted thiazolidine.[61]



80 **109** **110**

Scheme 40.



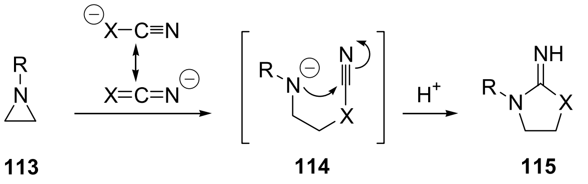
111 **112** (quant.)

Scheme 41.

In conclusion, 2-aminothiazolines can be easily transformed into 3-functionalized 2-iminothiazolidines upon treatment with different electrophiles, the construction of the heterocyclic moiety being performed in an earlier stage of the synthesis.

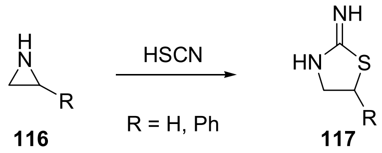
4.4. Ring expansion of aziridines

Small-ring heterocycles are prone to undergo nucleophilic ring-opening reactions, which makes them attractive substrates in organic synthesis. Ring expansion of aziridines **113** towards five-membered heterocycles has been studied extensively in the literature and appears to be a powerful method for the construction of thiazolidines. Generally, either cycloaddition reactions with heterocumulenes such as isothiocyanates or nucleophilic interactions with the ambident nucleophile thiocyanate have been described. These reactions usually proceed through the formation of a ring-opened intermediate **114** prone to intramolecular ring closure, affording the five-membered heterocycles **115** (Scheme 42).



113 **114** **115**

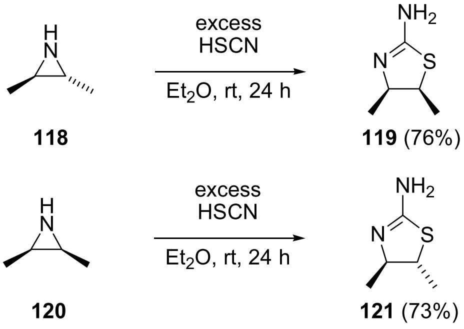
Scheme 42.



116 **117**

Scheme 43.

One of the first reports on the ring expansion of aziridines **116** involved treatment with thiocyanic acid furnishing the thiazolidines **117** (Scheme 43).[16] The compounds **117** obtained in this reaction were, in fact, the tautomeric 2-aminothiazolines, as has been proven in later studies (see Section 3).

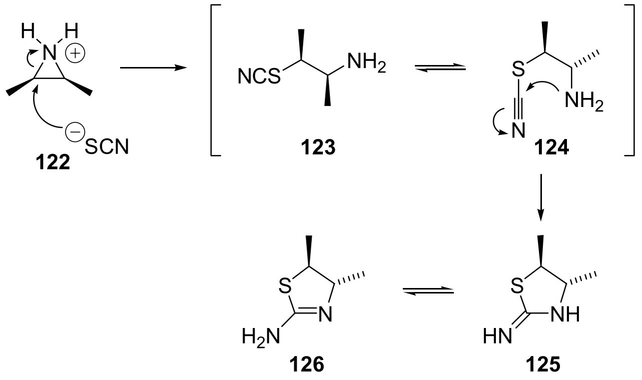


118 **119** (76%)

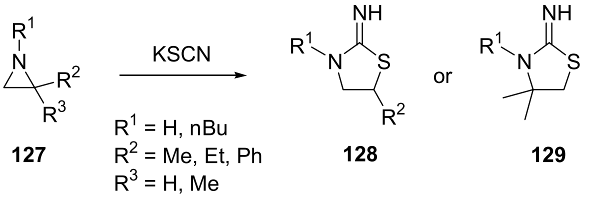
120 **121** (73%)

Scheme 44.

Further investigation of the ring expansion of aziridines with thiocyanic acid revealed that *trans*-2,3-dimethylaziridine **118** gave rise to *cis*-4,5-dimethylthiazolidine **119**, whereas *cis*-2,3-dimethylaziridine **120** was transformed into *trans*-4,5-dimethylthiazolidine **121**, upon treatment with an excess of HSCN in diethyl ether (Scheme 44).[18] These



Scheme 45.



Scheme 46.

observations were rationalized by considering a nucleophilic attack of the thiocyanate anion on the aziridinium intermediate **122**, followed by rotation around the C–C bond in the resulting 2-aminothiocyanate **123** to enable intramolecular cyclization of intermediate **124** towards thiazoline **126** (Scheme 45). In this way, *cis*-2,3-disubstituted aziridines are transformed into *trans*-4,5-disubstituted thiazolidines, while *trans*-2,3-disubstituted aziridines undergo ring expansion to *cis*-4,5-disubstituted thiazolidines.

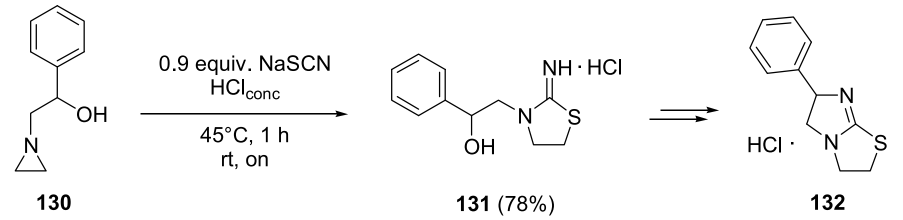
Instead of thiocyanic acid, the corresponding metal salts KSCN and NaSCN can also be used to induce ring expansion of aziridines towards thiazolidines. Earley et al. investigated the mechanism and kinetics of the addition of potassium thiocyanate to 2-substituted aziridines **127**.[62] They observed the formation of 5-substituted thiazolidines **128** when mono-substituted aziridines **127** were used, due to attack of the thiocyanate ion at the secondary carbon atom of the aziridine moiety (Scheme 46). The opposite regioselectivity was, however, observed when 2,2-dimethylaziridine was used, probably due to steric hindrance, resulting in 4,4-disubstituted thiazolidines **129** (Scheme 46).

The acid-catalyzed ring opening of aziridine **130** with sodium thiocyanate in the presence of concentrated hydrogen chloride resulted in the formation of 3-(2-hydroxyethyl)thiazolidine **131**, which was used as a substrate for the synthesis of the broad-spectrum anthelmintic, 6-phenyl-2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazole hydrochloride **132** (Scheme 47).[63] Analogous reactions were performed using the same substrate **130** with thiourea or thiocyanic acid, also yielding thiazolidine **131**.[64]

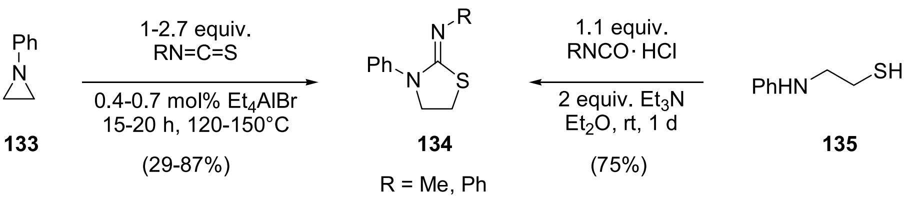
A frequently explored methodology comprises the reaction of an aziridine with an alkyl or aryl isothiocyanate using different reaction conditions and a variety of catalysts. Usually, these transformations appear to be very straightforward and efficient, which make them attractive methods for the directed synthesis of thiazolidines.

3-Phenylthiazolidines **134** were prepared from 1-phenylaziridine **133** upon treatment with isothiocyanates in the presence of a catalytic amount of Et_4AlBr (Scheme 48).[65] The same authors also described an alternative approach towards these thiazolidines **134** starting from the aminothiol **135** in reaction with the appropriate isocyanate (Scheme 48). Similarly, 1-arylaziridines have been converted into 3-aryl-2-(phenylimino)thiazolidines upon treatment with phenyl isothiocyanate in the presence of Et_4NBr.[66]

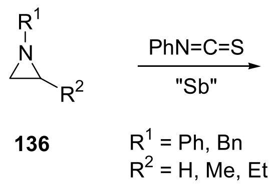
Furthermore, many metal-catalyzed ring enlargements of aziridines have been described. 5-Alkyl-substituted thiazolidines **137** have been prepared from 2-alkylaziridines **136** in a regioselective cycloaddition reaction with phenyl isothiocyanate in the presence of catalytic amounts of organoantimony(V) halides such as Ph_4SbI, Ph_4SbBr, Ph_3SbBr_2 and Ph_3SbCl_2 (designated as 'Sb' in Scheme 49).[67]



Scheme 47.

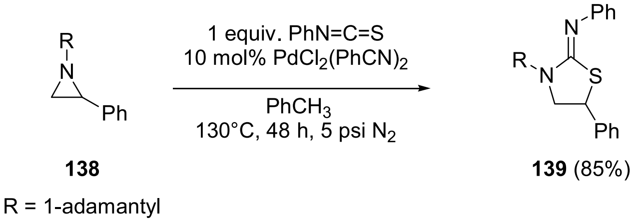


Scheme 48.



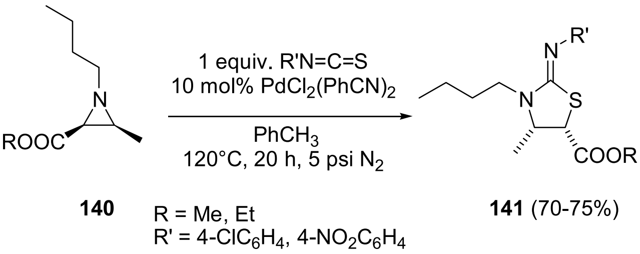
Scheme 49.

Palladium-catalyzed ring expansions of aziridines have also been evaluated. Alper et al. described the ring enlargement of 2-phenylaziridine **138** upon reaction with phenyl isothiocyanate in the presence of bis(benzonitrile)palladium dichloride, providing the thiazolidine **139** in 85% yield (Scheme 50).[68]



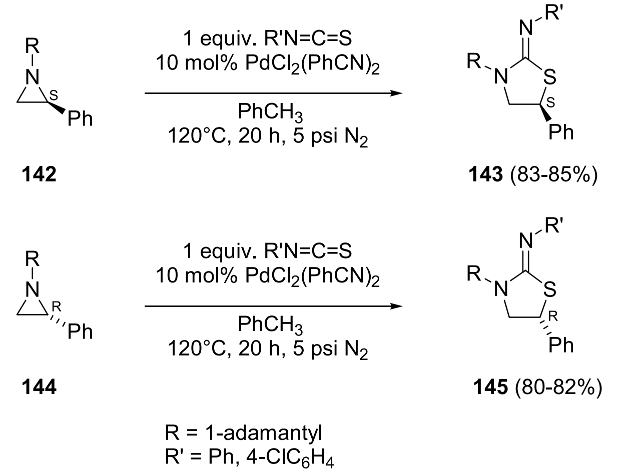
Scheme 50.

The enantiospecific version of this palladium-catalyzed cycloaddition reaction was elaborated by the same authors, using the conditions described above. First, the regio- and stereospecificity of this cycloaddition was demonstrated using *cis*-aziridine **140** in reaction with isothiocyanates, affording *cis*-thiazolidines **141** in good yield (Scheme 51). Furthermore, the enantiospecificity of the palladium-catalyzed cycloaddition was unequivocally demonstrated starting from the optically pure 2-phenylaziridines **142** and **144**, prepared from the corresponding commercially available 2-phenyloxiranes, resulting in the chiral 2-iminothiazolidines **143** and **145** after reaction with different isothiocyanates (Scheme 52).[69] Consequently, the relative, as well as the absolute, stereochemistry is conserved throughout this cycloaddition reaction.



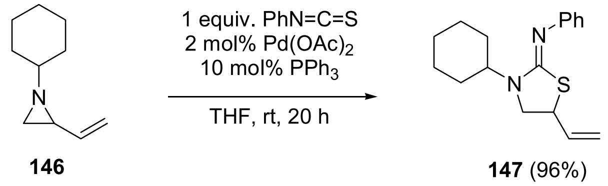
Scheme 51.

A modified version of this methodology comprises the transformation of 1-cyclohexyl-2-vinylaziridine **146** into 2-imino-5-vinylthiazolidine **147** upon treatment with phenyl isothiocyanate in the presence of 2 mol% of $Pd(OAc)_2$ and 10 mol% of triphenylphosphine in THF in an excellent yield (Scheme 53).[70] The benefit of this $Pd(OAc)_2$-catalyzed approach involves the mild reaction conditions (room temperature, 20 h), as compared to the $PdCl_2(PhCN)_2$-catalyzed cycloaddition (120 °C, 20 h, Schemes 51 and 52).



Scheme 52.

Based on the preliminary work of Markov et al.,[71] a methodology has been described for the synthesis of 2-phenylimino-3-arenesulfonylthiazolidines **149** starting from 1-arenesulfonyl-2-phenylaziridines **148** in reaction with phenyl isothiocyanate, catalyzed by lithium iodide (Scheme 54).[72] The same substrates **148** were also transformed into 2-iminothiazolidines **150** by means of sodium thiocyanate with tetrabutylammonium hydrogen sulfate as a phase-transfer catalyst (Scheme 54).[73]

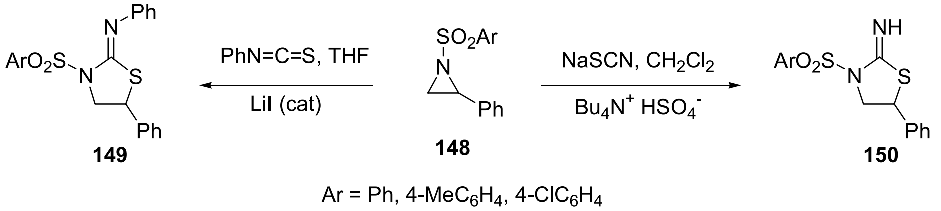


Scheme 53.

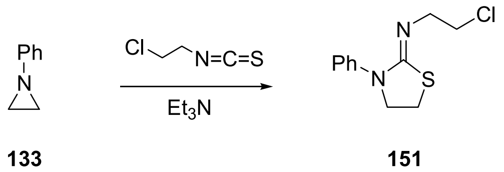
Similarly, *N*-arenesulfonylaziridines were converted into 3-arenesulfonylthiazolidines by reaction with isothiocyanates in the presence of sodium iodide instead of lithium iodide in 66–100% yield.[74]

One example of the introduction of a haloalkyl moiety on the exocyclic imino nitrogen has been published, in which the interaction of 1-phenylaziridine **133** with 2-chloroethyl isothiocyanate afforded 3-phenylthiazolidine **151** in the presence of Et_3N (Scheme 55).[75]

A new and selective approach towards 4-substituted thiazolidines has been developed very recently and comprises the intramolecular cyclization of 2-(thiocyanomethyl)aziridines **152**, prepared from the corresponding 2-(bromomethyl)aziridines upon treatment with 2 equiv of potassium thiocyanate in DMF, in the presence of a catalytic amount of titanium(IV) chloride in CH_2Cl_2. In this way, the quite labile 2-iminothiazolidines **153** were obtained in high yields and high purity. When the same reaction was carried out in the presence of 2.5 equiv of an acid chloride, the



Scheme 54.



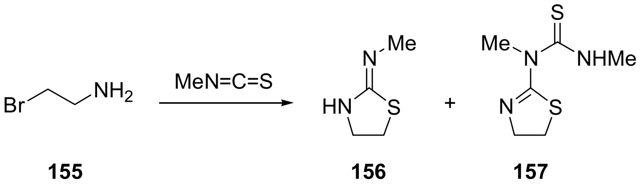
Scheme 55.

highly stable thiazolidines **154** were isolated. The acyl group in these 2-(*N*-acylimino)thiazolidines **154** could be easily removed upon treatment with potassium carbonate in methanol, affording the 2-iminothiazolidines **153**. These latter compounds (**153**) were transformed back into the stable 2-(acylimino)thiazolidines **154** by treatment with 1.2 equiv of an acyl chloride in the presence of an equimolar amount of Et_3N (Scheme 56).[76] The possibility to interconvert thiazolidines **153** into **154** and vice versa enables a long-time preservation without the loss of purity and an easy access to the desired 2-iminothiazolidines **153** whenever required. One example of an analogous 4-halomethyl-2-iminothiazolidine has already been reported, prepared by iodocyclization of the appropriate allylic thiourea using I_2 in dichloromethane.[77] The presence of a halomethyl substituent allows further elaboration towards different 4-substituted thiazolidines.

Aziridines are multifunctional substrates suitable for the synthesis of a large variety of cyclic and acyclic compounds. The ring expansion of aziridines to 2-iminothiazolidines has been proven to be a simple and efficient method for the construction of these heterocycles, mostly via interaction with isothiocyanates or thiocyanates.

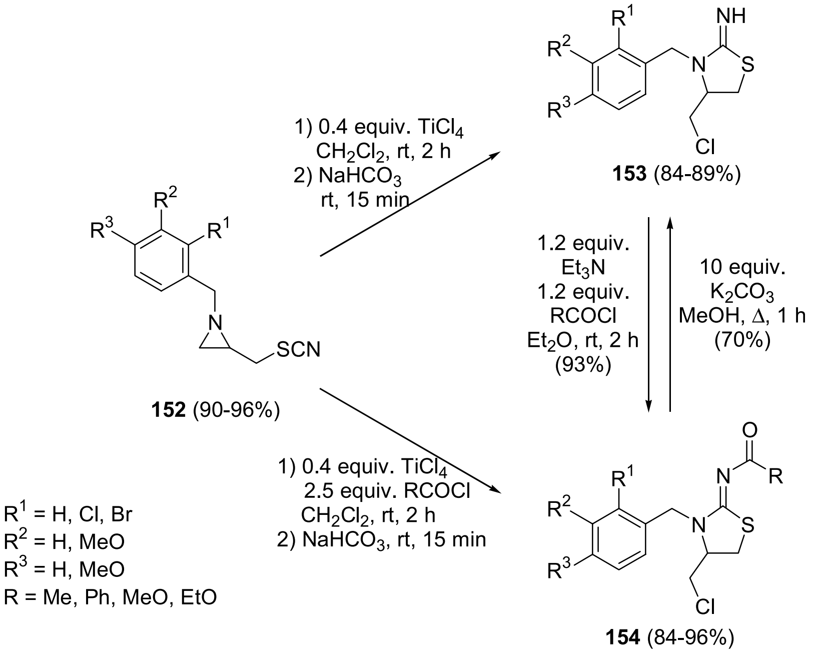
4.5. Reaction of β-haloamines with isothiocyanates and thiocyanates

The first report concerning the reaction of a β-haloamine with an isothiocyanate dates back from 1889, describing the formation of the thiazolidine **156** as the major product and thiazoline **157** as a byproduct from the reaction of 2-bromoethylamine **155** and methyl isothiocyanate (Scheme 57).[78]

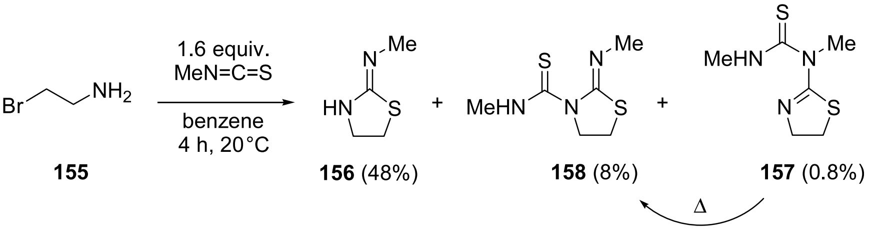


Scheme 57.

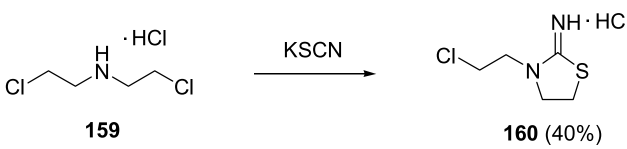
More than a century later, this 'Gabriel' reaction of 2-bromoethylamine **155** with methyl isothiocyanate was repeated under mild conditions and resulted in a mixture of 2-(methylimino)thiazolidine **156** as the major



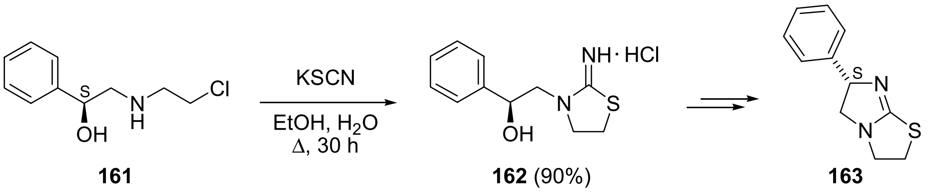
Scheme 56.



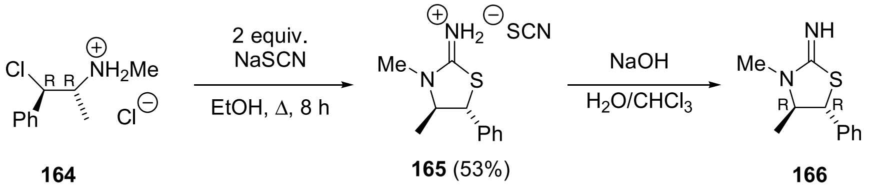
Scheme 58.



Scheme 59.



Scheme 60.



Scheme 61.

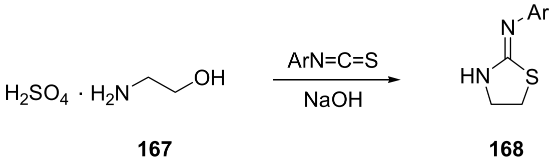
product (48%), together with two kinds of byproducts, 3-(*N*-methylthiocarbamoyl)-2-methyliminothiazolidine **158** (8% after chromatography) and *N*,*N*′-dimethyl-*N*-(2-thiazolin-2-yl)thiourea **157** (0.8% after chromatography).[79] Thermal isomerization of **157** to **158** was observed when the isolated thiazoline **157** was heated under reflux for 5 h in benzene (Scheme 58). The structures of the byproducts were confirmed by X-ray crystallography. The formation of the thiazolidine **158** as a sideproduct in this reaction had also been suggested by Yamamoto et al., based on spectroscopic analysis.[46f]

Several similar, or slightly modified, analogues of this condensation reaction have subsequently been described, either using thiocyanate salts or alkyl or aryl isothiocyanates as reagents. Evaporation of an aqueous solution of di(2-chloroethyl)amine hydrochloride **159** and potassium thiocyanate yielded the hydrochloride salt of 2-iminothiazolidine **160** in 40% yield (Scheme 59).[48] Di(2-chloroethyl)amine has also been treated with different isothiocyanates, resulting in 3-(2-chloroethyl)thiazolidines.[80]

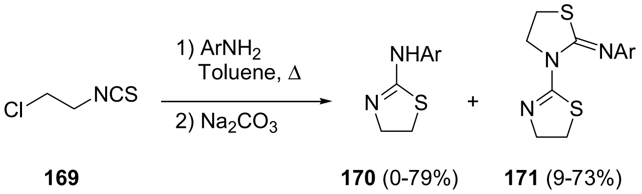
Enantiomerically pure aminoalcohol **161**, prepared from the corresponding ketone upon hydrogenation using a chiral rhodium catalyst, was treated with potassium thiocyanate to afford the chiral thiazolidine **162** (Scheme 60).[81] This compound can be used as a substrate for the synthesis of (*S*)-(−)-levamisole **163**.

The optically active 2-iminium thiazolidine **165** was prepared from the ephedrine derivative **164** upon treatment with 2 equiv of sodium thiocyanate in ethanol. This salt (**165**) was subsequently neutralized by sodium hydroxide in water/chloroform to give the enantiomerically pure 2-iminothiazolidine **166**, conserving the relative and absolute stereochemistry throughout the reaction (Scheme 61).[82] The 2-iminothiazolidine **166** was further used for the synthesis of optically active borathiazolidines and their *N*-borane adducts.

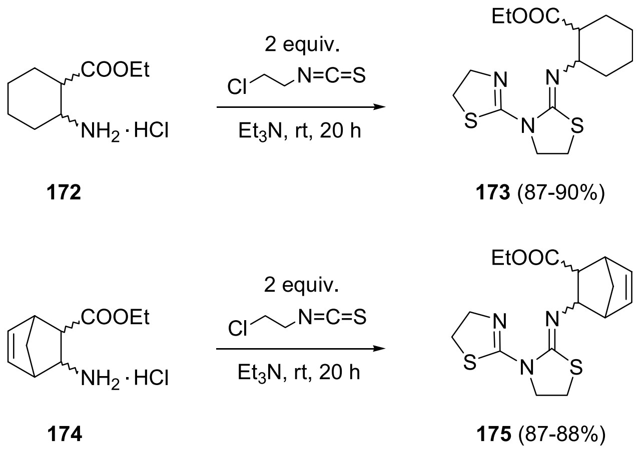
2-(Arylimino)thiazolidines **168** have been synthesized by cyclizing ethanolamine hydrogen sulfate salt **167** with aryl isothiocyanates in the presence of sodium hydroxide (Scheme 62).[4] The activity for stimulating adenylate cyclase (prepared from ventral nerve cords of the American cockroach *Periplaneta americana L.*) of these 2-(arylimino)thiazolidines was examined, showing that a certain degree of bulkiness and hydrophobicity at the 2- and



Scheme 62.



Scheme 63.



Scheme 64.

6-position on the phenyl ring were favorable for activating the adenylate cyclase.

An alternative approach comprises the reaction of a β-haloalkyl isothiocyanate with an amine instead of coupling a β-haloamine with an isothiocyanate. The reaction of 2-chloroethyl isothiocyanates **169** with aromatic amines has been studied, giving rise to mixtures of thiazolines **170** and **171** (Scheme 63).[83] Depending on the nature of the aromatic moiety, either thiazolines **170** predominated (for methylphenyl and halophenyl derivatives), or thiazolines **171** were mainly formed (for pyridine derivatives).

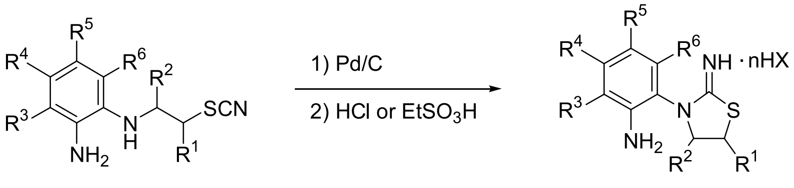
In the same way, the β-aminoesters (hydrochlorides) **172** and **174** were converted into the *cis*- and *trans*-thiazolidines **173** and **175** in excellent yields upon treatment with 2 equiv of 2-chloroethyl isothiocyanate in ethanol after 20 h at room temperature (Scheme 64).[84]

A variety of 3-arylthiazolidines **177** has been synthesized starting from *N*-(2-thiocyanatoethyl)-2-phenylenediamines **176** using Pd/C in dioxane, MeOH or CH_2Cl_2–MeOH (1/1), followed by treatment with a strong acid such as HCl or $EtSO_3H$ (Scheme 65). Some of the thiazolidines **177** are highly active antidepressants of low toxicity.[85]

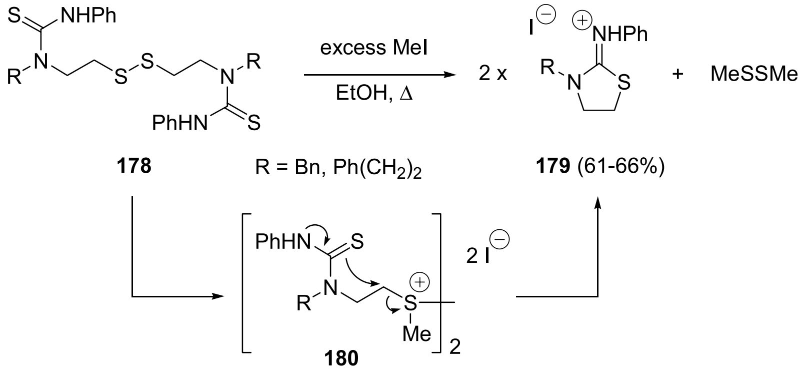
4.6. Miscellaneous

Besides the synthetic protocols discussed in the preceding paragraphs, some other interesting approaches towards 2-iminothiazolidines have been developed. In this section, all methods different from those mentioned above have been summarized.

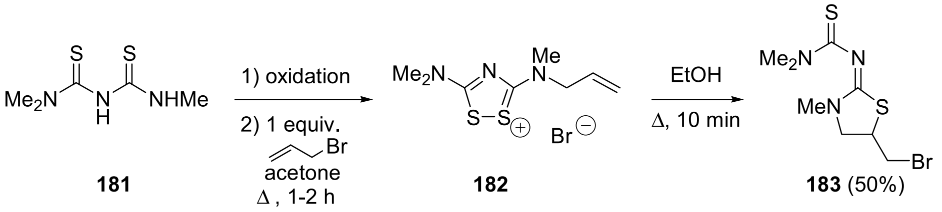
1-(2-Dithiobis)ethyl-3-phenyl-bis-thioureas **178** have been transformed into 2-iminothiazolidines **179** in good yields by treatment with an excess of iodomethane in refluxing ethanol upon expulsion of dimethyl disulfide (Scheme 66).[86] A mechanism was proposed involving methylation at the disulfide linkage, followed by intramolecular cyclization of the resulting intermediates **180** towards thiazolidines **179** (Scheme 66). The starting materials **178** were prepared by bubbling air through the appropriate *N*-monosubstituted 2-mercaptoethylamine in refluxing ethanol for three days, followed by reaction with 2 equiv of phenyl isothiocyanate.



Scheme 65.



Scheme 66.

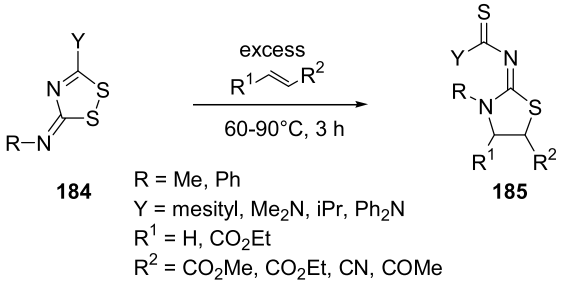


Scheme 67.

Oliver and DeMilo have developed an interesting approach towards the 5-(bromomethyl)thiazolidine **183** through rearrangement of a dithiazolium salt **182** upon heating for 10 min in ethanol (Scheme 67). The requisite dithiazolium salt **182** was prepared starting from the dithiobiuret derivative **181** via an oxidation and an alkylation step.[87] This approach is one of the few examples (along with thiazolidine **147** in Scheme 53) leading to a versatile building block **183** suitable for the synthesis of a variety of 5-substituted thiazolidines, due to the presence of the bromomethyl unit.

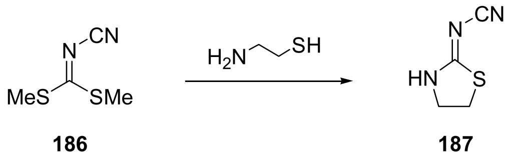
Furthermore, some thiazolidines with an ester or a nitrile substituent at the 5-position have been synthesized, for example, 3-iminodithiazoles **184** have been transformed into a variety of substituted thiazolidines **185** upon thermal cycloaddition reactions with olefins (Scheme 68).[88] When maleic acid or fumaric acid was used as the olefin, the double-bond geometry was transferred towards the end products **185**, resulting in a cis-stereochemistry starting from maleic acid and a trans-stereochemistry starting from fumaric acid.

Many synthetic efforts have been devoted to the synthesis of 2-(cyanoimino)thiazolidines, due to the versatile applications of these compounds as reagents or as biologically relevant target compounds. 2-(*N*-Cyanoimino)thiazolidines comprise a characteristic functional ring system, which can be easily derivatized at the 3-position. This substitution pattern has an influence on the reactivity and, hence, the applicability of 2-(cyanoimino)thiazolidines. 3-Acyl-2-(*N*-cyanoimino)thiazolidines are excellent acylation reagents for amines, alcohols and thiols,[89] while 3-phenylsulfenyl-2-(*N*-cyanoimino)thiazolidine can act as a sulfenylation reagent for amines and thiols.[90]



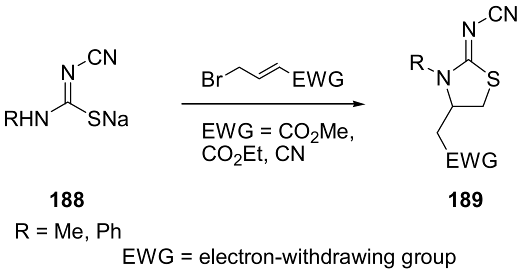
Scheme 68.

The 2-(*N*-cyanoimino)thiazolidine moiety is usually prepared according to the procedure of Neidlein and Reuter,[91] and is then further functionalized at the 3-position. This procedure involves the reaction of dimethyl cyanodithioimidocarbonate **186** with 2-aminoethanethiol, affording 2-(*N*-cyanoimino)thiazolidine **187** in a very easy and efficient way (Scheme 69).



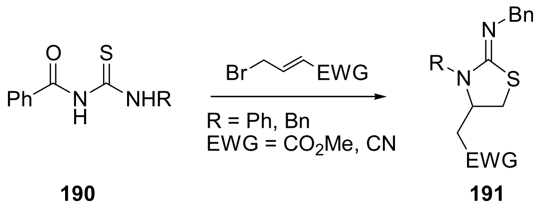
Scheme 69.

Another entry into 2-(cyanoimino)thiazolidines comprises the reaction of the sodium salts of cyanothioureas **188** with derivatives of γ-bromocrotonic acid, affording the 4-substituted 2-(cyanoimino)thiazolidines **189** (Scheme 70).[92]



Scheme 70.

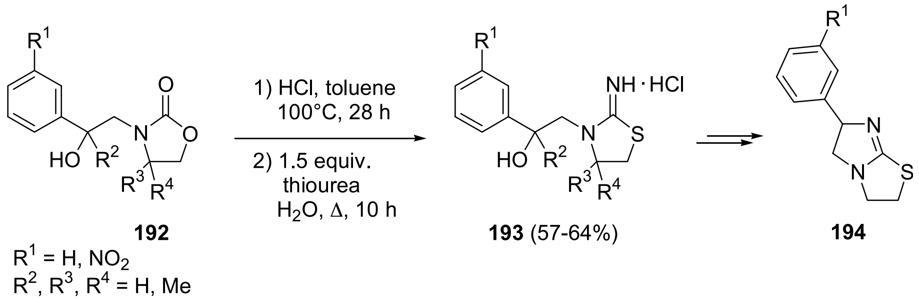
The same author also described the reaction of benzoylthioureas **190** with derivatives of γ-bromocrotonic acid, resulting in 2-(benzylimino)thiazolidines **191** (Scheme 71).[93]



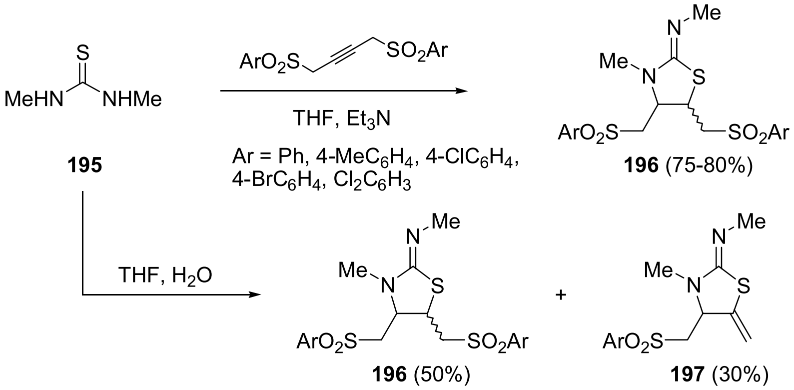
Scheme 71.

The pronounced physiological activities of 2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazoles has incited may chemists to develop new entries towards these targets, mostly via an intermediate 3-(2-hydroxyethyl)thiazolidine. These intermediates can be prepared by ring expansion of an aziridine (Scheme 47) or by reaction of an aminoalcohol with a thiocyanate (Scheme 60).

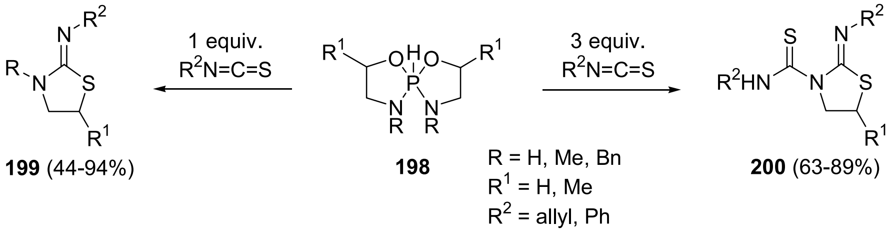
Dockx et al. have developed a method for the conversion of



Scheme 72.



Scheme 73.



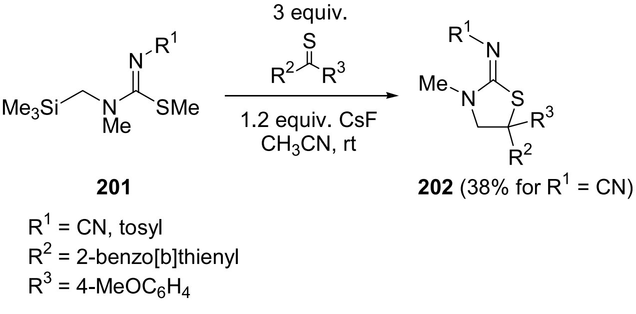
Scheme 74.

2-oxazolidinones **192** into 3-(2-hydroxyethyl)thiazolidines **193**, utilizing hydrogen chloride bubbled through a solution of **192** in toluene, followed by reflux with 1.5 equiv of thiourea in water (Scheme 72).[94] The thiazolidines **193** were further transformed into tetramisole **194** ($R^1=H$) and nitramisole **194** ($R^1=NO_2$), compounds with pronounced anthelmintic activity.

Besides the hitherto-described methodologies, some other techniques for the synthesis of 4- and/or 5-substituted thiazolidines have been reported in the literature, such as 1, 2-addition reactions onto an alkyne or the use of 1,6-dioxa-4,9-diaza-5-phosphaspiro[4.4]nonanes and silylated thiourea derivatives as starting materials.

Intramolecular 1,2-addition of *N*,*N*′-dimethylthiourea **195** across the triple bond of 1,4-diarylsulfonyl-2-butynes under mild base catalysis at ambient conditions in THF has been reported to furnish thiazolidines **196** in good yields (Scheme 73). When the reactions were performed in aqueous THF, mixtures of thiazolidines **196** and methylenethiazolidines **197** were obtained (Scheme 73).[95] No mentioned was made of the relative stereochemistry of the thiazolidines **196**, although the authors referred to earlier work in which the stereoselective addition of arene thiols across the triple bond of 1,4-diarylsulfonyl-2-butynes had been described.[96]

The reaction of 1,6-dioxa-4,9-diaza-5-phosphaspiro[4.4] nonanes **198** with alkyl and aryl isothiocyanates afforded the thiazolidines **199** and **200**, depending on the amount of reagent used (Scheme 74).[97] 2-Aryliminothiazolidines have

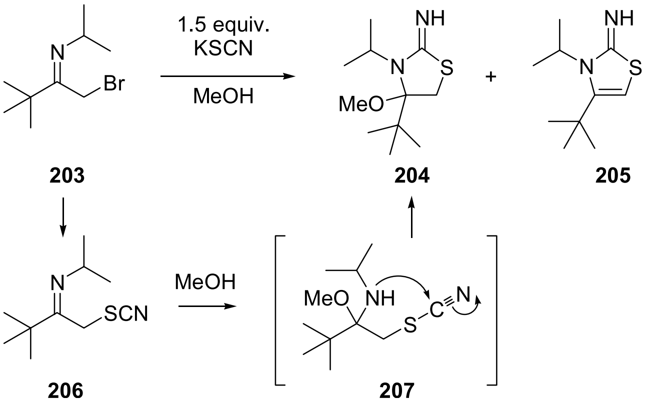


Scheme 75.

already been prepared from the reaction of β-aminoethyl phosphites and aryl isothiocyanates.[98]

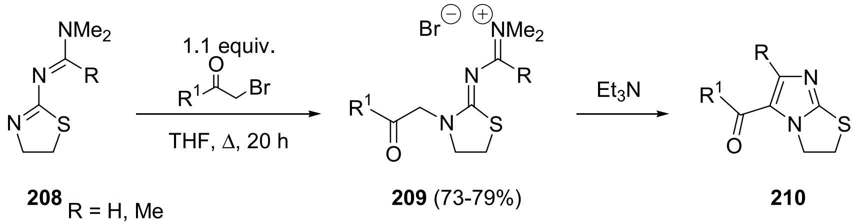
The silylated thiourea derivatives **201** can be used to provide synthetic equivalents of iminoazomethine ylides, since treatment of these compounds (**201**) with cesium fluoride in the presence of a reactive heterodipolarophile such as a thione afforded the 1,3-dipolar cycloadducts **202** via 1,3-elimination of (methylthio)trimethylsilane, although the yield is rather low (Scheme 75).[99]

α-Halomethyl ketimines, synthesized by condensation of the appropriate α-halomethyl ketone with primary amines in the presence of titanium(IV) chloride, constitute a convenient source of a 2-oxoalkyl unit.[100] Treatment of α-bromomethyl ketimine **203** with 1.5 equiv of potassium thiocyanate in methanol resulted in a mixture of the 2-iminothiazolidine **204** and thiazoline **205**. The formation of the 4-methoxythiazolidine **204** in this reaction can be rationalized considering a nucleophilic attack of methanol across the imino group of thiocyanomethyl ketimine **206**, followed by intramolecular addition to give **207** (Scheme 76).[101] The ratio of thiazoline **205** versus thiazolidine **204** changed from 40:60 over 75:25–90:10 upon gradually increasing the reaction temperature and the reaction time.



Scheme 76.

The analogous α-halomethyl ketones have been used for the alkylation of N'-(4,5-dihydrothiazol-2-yl)-N,N-dimethylamidines **208**, resulting in the formation of the amidinium salts **209** (Scheme 77).[102] These iminium salts **209** were subsequently treated with Et_3N to induce intramolecular cyclization followed by elimination of dimethylamine, furnishing the imidazo[2,1-*b*]thiazoles **210** as biologically relevant heterocyclic targets.



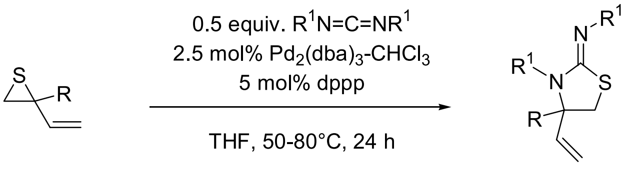
208 R = H, Me
R^1 = 4-BrC_6H_4, 4-ClC_6H_4, 4-MeC_6H_4

209 (73-79%)

210

Scheme 77.

Although the ring expansion of aziridines towards thiazolidines has been studied intensively, only one report describing the ring enlargement of thiiranes with the appropriate heterocumulene has been published. This regioselective transformation requires 5 mol% of $Pd_2(dba)_3 \cdot CHCl_3$ and 10 mol% of a bidentate phosphine ligand, dppp [1,3-bis-(diphenylphosphino)propane], for the complete conversion of the selected carbodiimide and thiirane **211** into the 4-vinylthiazolidines **212** (Scheme 78).[103] The use of different chiral ligands allowed asymmetric cycloaddition reactions, resulting in ee's varying from 17 to 68%.



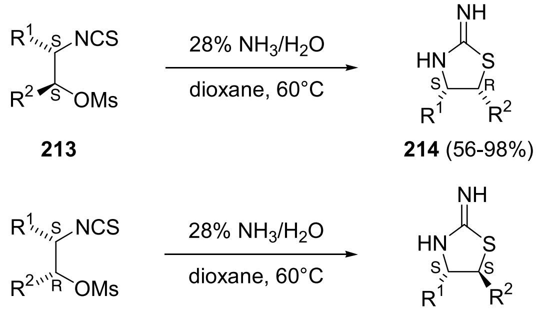
211

212 (43-97%)

R = H, Me
R^1 = 4-ClC_6H_4, 4-BrC_6H_4, 2-ClC_6H_4, 4-$NO_2C_6H_4$

Scheme 78.

Enantiomerically pure 4,5-dialkylthiazolidines **214** and **216** have been synthesized from β-(mesyloxy)isothiocyanates **213** and **215** upon treatment with aqueous ammonia in dioxane (Scheme 79).[104] The appropriate isothiocyanates **213** and **215** were prepared from the α-amino acids or β-aminoalcohols in a straightforward manner. 4,5-Dialkyl-



213

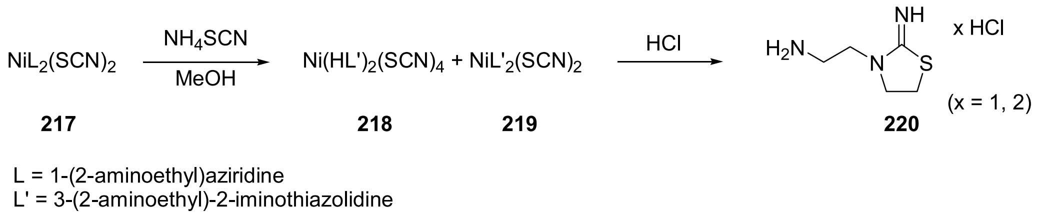
214 (56-98%)

215

216 (45-95%)

R^1 = Me, Et, nPr, nBu, nHex, nHep
R^2 = Me, Et

Scheme 79.



Scheme 80.

2-iminothiazolidines are known as potent inducible nitric oxide synthase inhibitors, which makes them potential drugs for the treatment of different inflammatory diseases.[5] Taking into account the studies of Blum et al.,[19] the reported thiazolidines **214** and **216** should occur as the tautomeric 2-amino-2-thiazolines, although the issue of isomerism was not mentioned in this reference.

Other, less common, fields have also been explored, such as, for example, the intrasphere synthesis of 3-(2-aminoethyl)-2-iminothiazolidine **220** by the reaction of bis[1-(2-aminoethyl)ethylenimine]nickel(II) thiocyanates **217** with ammonium thiocyanate, followed by demetalation of the complexes **218** and **219**, thus formed, by HCl (Scheme 80).[105]

5. Conclusions

At present, a large variety of syntheses towards 2-iminothiazolidines is available, mostly based on one of five major synthetic protocols. Depending on the substitution pattern being aimed at, different methodologies can be applied to introduce substituents at the 2-, 3-, 4- and 5-positions of the heterocyclic core. The challenge for prospective research in this area involves optimization of known methods on the one hand, and the development of new beneficial approaches on the other hand. High regio- and stereoselectivity should be the goal, as well as the development of straightforward approaches without the formation of undesired sideproducts.

Acknowledgements

The authors are indebted to the Fund for Scientific Research-Flanders (Belgium) (F. W. O.-Vlaanderen) and Ghent University (GOA project) for financial support.

References and notes

1. Shukla, U. P.; Singh, R.; Khanna, J. M.; Saxene, A. K.; Singh, H. K.; Sur, R. N.; Dhawan, B. N.; Anand, N. *Coll. Czech. Chem. Commun.* **1992**, *57*, 415.
2. Xie, M.; Zhong, A.; Zhang, X. *Yaoxue Xuebao* **1983**, *18*, 147.
3. Rokach, J.; Girard, Y.; Hamel, P.; Reader, G.; Rooney, C. S.; Mandel, L. R.; Cragoe, E. J., Jr.; Zacchei, A. G. *J. Med. Chem.* **1980**, *23*, 773.
4. Hirashima, A.; Tarui, H.; Eto, M. *Biosci. Biotechnol. Biochem.* **1994**, *58*, 1206.
5. (a) Ueda, S.; Terauchi, H.; Yano, A.; Matsumoto, M.; Kubo, T.; Kyoya, Y.; Suzuki, K.; Ido, M.; Kawasaki, M. *Bioorg. Med. Chem.* **2004**, *12*, 4101. (b) Shankaran, K.; Donnelly, K. L.; Shah, S. K.; Guthikonda, R. N.; MacCoss, M.; Humes, J. L.; Pacholok, S. G.; Grant, S. K.; Kelly, T. M.; Wong, K. K. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4539.
6. (a) Hosseinimehr, S. J.; Shafiee, A.; Mozdarani, H.; Akhlagpour, S. *J. Radiat. Res.* **2001**, *42*, 401. (b) Hosseinimehr, S. J.; Shafiee, A.; Mozdarani, H.; Akhlagpour, S.; Froughizadeh, M. *J. Radiat. Res.* **2002**, *43*, 293.
7. (a) Zhang, A.; Kayser, H.; Maienfisch, P.; Casida, J. E. *J. Neurochem.* **2000**, *75*, 1294. (b) Maienfisch, P.; Haettenschwiler, J.; Rindlisbacher, A.; Decock, A.; Wellmann, H.; Kayser, H. *Chimia* **2003**, *57*, 710.
8. Jeschke, P.; Moriya, K.; Lantzsch, R.; Seifert, H.; Lindner, W.; Jelich, K.; Gohrt, A.; Beck, M. E.; Etzel, W. *Pflanzenschutz-Nachrichten Bayer* **2001**, *54*, 147; *Chem. Abstr.* **2002**, *136*, 274776.
9. (a) Bitner, R. S.; Kanthasamy, A.; Isom, G. *Neurotoxicology* **1995**, *16*, 115. (b) Bitner, R. S.; Yim, G. K. W.; Isom, G. E. *Neurotoxicology* **1997**, *18*, 191.
10. Wu, J.; Gage, D. A.; Watson, J. T. *Anal. Biochem.* **1996**, *235*, 161.
11. Liu, C.; Xu, X.; Li, Z.; Chen, W.; Huang, Q.; Qian, X. *J. Fluorine Chem.* **2005**, *126*, 53.
12. Takagi, M.; Ishimitsu, K.; Nishibe, T. PCT Int. Appl. WO 0172723 A1, 02/11/2001; *Chem. Abstr.* **2001**, *135*, 288773.
13. Latli, B.; Casida, J. E. U.S. 6303638 B1, 16/10/2001; *Chem. Abstr.* **2001**, *135*, 303904.
14. Zubova, O. V.; Fedoseev, V. M.; Silaev, A. B. *Voprosy Onkologii* **1964**, *10*, 26; *Chem. Abstr.* **1964**, *61*, 50560.
15. Zubova, O. V.; Fedoseev, V. M.; Silaev, A. B. *Voprosy Onkologii* **1964**, *10*, 26; *Chem. Abstr.* **1964**, *61*, 50560.
16. Gabriel, S.; Colman, J. *Chem. Ber.* **1914**, *47*, 1866.
17. (a) Mousseron, M.; Winternitz, F.; Dennilaueler, R. *C.R. Acad. Sci.* **1954**, *239*, 278. (b) Winternitz, F.; Mousseron, M.; Dennilaueler, R. *Bull. Soc. Chim. France* **1956**, *382*, 1228.
18. Wohl, R. A.; Headley, D. F. *J. Org. Chem.* **1972**, *37*, 4401.
19. Weitzberg, M.; Aizenshtat, Z.; Blum, J. *J. Heterocycl. Chem.* **1984**, *21*, 1597.
20. Avalos, M.; Babiano, R.; Cintas, P.; Chavero, M. M.; Higes, F. J.; Jiménez, J. L.; Palacios, J. C.; Silvero, G. *J. Org. Chem.* **2000**, *65*, 8882.
21. Douglass, I. B.; Dains, F. B. *J. Am. Chem. Soc.* **1934**, *56*, 719.
22. Cherbuliez, E.; Willhalm, B.; Jaccard, S.; Rabinowitz, J. *Helv. Chim. Acta* **1967**, *50*, 2563.
23. Rabinowitz, J.; Chang, S.; Hayes, J. M.; Woeller, F. *J. Org. Chem.* **1969**, *34*, 372.
24. Rabinowitz, J.; Chang, S.; Capurro, N. *Helv. Chim. Acta* **1969**, *52*, 250.
25. Mizrakh, L. I.; Polonskaya, L. Y.; Vasil'ev, A. M.; Karpunina, L. B. *Zh. Obshch. Chem.* **1993**, *63*, 704; *Chem. Abstr.* **1994**, *120*, 8508.
26. Tyukhteneva, Z. I.; Badovskaya, L. A.; Kozlovskaya, I. N.;

Muzychenko, G. F. *Khimi. Geterotsikl. Soedin*. **1985**, 1629; *Chem. Abstr.* **1986**, *105*, 114951.

27. Reiter, J.; Toldy, L.; Schafer, I.; Szondy, E.; Borsy, J.; Lukovits, I. *Eur. J. Med. Chem.* **1980**, *15*, 41.
28. Mizrakh, L. I.; Polonskaya, L. Y.; Gvozdetskii, A. N.; Ivanova, T. M.; Vasil'ev, A. M.; Karpunina, L. B. *Zh. Obshch. Chem*. **1988**, *58*, 2246; *Chem. Abstr*. **1989**, *111*, 23460.
29. (a) Mizrakh, L. I.; Polonskaya, L. Y.; Gvozdetskii, A. N.; Ivanova, T. M.; Vasil'ev, A. M.; Karpunina, L. B. *Zh. Obshch. Chem*. **1992**, *62*, 1498; *Chem. Abstr.* **1993**, *118*, 124432. (b) Mizrakh, L. I.; Polonskaya, L. Y.; Gvozdetskii, A. N.; Berdyugin, V. V.; Vasil'ev, A. M.; Ivanova, T. M. *Zh. Obshch. Chem*. **1989**, *59*, 1195; *Chem. Abstr.* **1990**, *112*, 55701.
30. Kim, T. H.; Cha, M.-H. *Tetrahedron Lett.* **1999**, *40*, 3125.
31. Kim, T. H.; Min, J. K.; Lee, G.-J. *Tetrahedron Lett.* **2001**, *42*, 2413.
32. Kim, T. H.; Min, J. K.; Lee, G.-J. *Tetrahedron Lett.* **1999**, *40*, 8201.
33. Lee, N.; Cha, M.-H.; Kim, T. H. *J. Korean Chem. Soc.* **2001**, *45*, 96.
34. Kim, T. H.; Lee, N.; Lee, G.-J.; Kim, J. N. *Tetrahedron* **2001**, *57*, 7137.
35. Lee, G.-J.; Kim, J. N.; Kim, T. H. *Bull. Korean Chem. Soc.* **2002**, *23*, 19.
36. Fell, J. B.; Coppola, G. M. *Synth. Commun.* **1995**, *25*, 43.
37. Heinelt, U.; Schultheis, D.; Jäger, S.; Lindenmaier, M.; Pollex, A.; Beckmann, H. S. G. *Tetrahedron* **2004**, *60*, 9883.
38. Toldy, L.; Sohár, P. *Tetrahedron Lett.* **1970**, *2*, 181.
39. (a) Erlenmeyer, H.; Schulthess, H.; Bloch, H. *Helv. Chim. Acta* **1947**, *30*, 1336. (b) Bradsher, C. K.; Brown, F. C.; Sinclair, E. F. *J. Am. Chem. Soc.* **1956**, *78*, 6189.
40. Richter, M.; Richter, W. *Z. Chem.* **1988**, *28*, 437; *Chem. Abstr.* **1989**, *111*, 57603.
41. Yamamoto, Y.; Yoda, R.; Kouda, S. *Kyoritsu Yakka Daigaku Kenkyu Nenpo* **1973**, *18*, 46; *Chem. Abstr.* **1974**, *81*, 120524.
42. Rudorf, W.-D.; Cleve, D. *Sulfur Lett.* **2002**, *25*, 105.
43. Schoberl, A.; Hansen, G. *Chem. Ber.* **1958**, *91*, 1239.
44. Fedoseev, V. M.; Churilin, V. S. Vestn. *Mosk. Univ. Ser. II, Khimiya* **1971**, *12*, 227; *Chem. Abstr.* **1971**, *75*, 48046.
45. McCarthy, W. C.; Ho, B.-T. *J. Org. Chem.* **1961**, *26*, 4110.
46. Fromm, E.; Kapeller-Adler, R. *Justus Liebigs Ann. Chem.* **1928**, *467*, 240.
47. (a) Cherbuliez, E.; Baehler, B.; Jaccard, S.; Jindra, H.; Weber, G.; Wyss, G.; Rabinowitz, E. *Helv. Chim. Acta* **1966**, *49*, 807. (b) Cherbuliez, E.; Baehler, B.; Espejo, O.; Jaccard, S.; Jindra, H.; Rabinowitz, E. *Helv. Chim. Acta* **1966**, *49*, 2408. (c) Klayman, D. L.; Maul, J. J.; Milne, G. W. A. *Tetrahedron Lett.* **1967**, *8*, 281. (d) Klayman, D. L.; Maul, J. J.; Milne, G. W. A. *J. Heterocycl. Chem.* **1968**, *5*, 517. (e) Klayman, D. L.; Milne, G. W. A. *Tetrahedron* **1969**, *25*, 191. (f) Yamamoto, Y.; Yoda, R.; Matsumura, M. *Chem. Pharm. Bull.* **1975**, *23*, 2134. (g) Klayman, D. L.; Woods, T. S. *J. Org. Chem.* **1974**, *39*, 1819. (h) Klayman, D. L.; Woods, T. S. *J. Org. Chem.* **2000**, *1975*, 40. (i) Yamamoto, Y.; Yoda, R.; Sekine, K. *Kyoritsu Yakka Daigaku Kenkyu Nenpo* **1976**, *21*, 48; *Chem. Abstr.* **1976**, *87*, 135517. (j) Yamamoto, Y.; Yoda, R.; Koguchi, K. *Kyoritsu Yakka Daigaku Kenkyu Nenpo* **1978**, *23*, 38; *Chem. Abstr.* **1979**, *91*, 211309. (k) Karady, S.; Amato, J. S.; Dortmund, D.; Patchett, A.; Reamer, R.; Tull, R.; Weinstock, L. *Heterocycles* **1979**, *12*, 1199.
48. (a) Yamamoto, Y.; Yoda, R. *Kyoritsu Yakka Daigaku Kenkyu Nenpo* **1973**, *18*, 53; *Chem. Abstr.* **1974**, *81*, 136039. (b) Yamamoto, Y.; Yoda, R.; Sekine, K., Kyoritsu Yakka Daigaku Kenkyu Nenpo 1976, 21, 48; *Chem. Abstr.* **1977**, *87*, 135171.
49. Rasmussen, C. R.; Villani, F. J., Jr.; Mutter, M. S.; Griffin, E. A. *J. Org. Chem.* **1986**, *51*, 1910.
50. Flippen, J. L.; Karle, I. L. *J. Phys. Chem.* **1970**, *74*, 769.
51. Avalos, M.; Babiano, R.; Cintas, P.; Jiménez, J. L.; Palacios, J. C.; Valencia, C. *Heterocycles* **1993**, *35*, 1237.
52. Kuz'mina, K. K.; Ostroumova, N. G.; Markova, Y. V.; Shchukina, M. N. *Zh. Obshch. Chem.* **1962**, *32*, 3215; *Chem. Abstr.* **1963**, *58*, 66452.
53. Tsoi, L. A.; Cholpankulova, S. T.; Ryskieva, G. K.; Salimbaeva, A. D. *Khimi. Geterotsikl. Soedin*. **1981**, 917; *Chem. Abstr.* **1981**, *95*, 187137.
54. King, L. C.; Stern, E. W. *J. Org. Chem.* **1965**, *30*, 3222.
55. Kaugars, G.; Martin, S. E.; Nelson, S. J.; Watt, W. *Heterocycles* **1994**, *38*, 2593.
56. Negrebetskii, V. V.; Vorob'eva, N. N.; Razvodovskaya, L. V.; Bogel'fer, L. Y.; Ivanchenko, V. I.; Grapov, A. F.; Mel'nikov, N. N. *Zh. Obshch. Chem.* **1986**, *56*, 1764; *Chem. Abstr.* **1987**, *107*, 217715.
57. Razvodovskaya, L. V.; Vorob'eva, N. N.; Grapov, A. F.; Mel'nikov, N. N. *Zh. Obshch. Chem.* **1990**, *60*, 1764; *Chem. Abstr.* **1991**, *114*, 62201.
58. El-Kerdawy, M. M.; Hasanein, M. K.; Osman, A. N. *Egypt. J. Chem*. **1975**, *18*, 13; *Chem. Abstr.* **1977**, *87*, 5851.
59. Bansal, R. K.; Sharma, D. C.; Mahnot, R. *Tetrahedron Lett.* **1991**, *32*, 6433.
60. Negrebetskii, V. V.; Vorob'eva, N. N.; Razvodovskaya, L. V.; Grapov, A. F.; Mel'nikov, N. N. *Zh. Obshch. Chem.* **1987**, *57*, 2310; *Chem. Abstr.* **1988**, *109*, 231140.
61. Arya, V. P.; Nagarajan, K.; Shenoy, S. J. *Indian J. Chem.* **1982**, 941.
62. Earley, J. E.; O'Rourke, O. E.; Clapp, L. B.; Edwards, J. O.; Lawes, B. C. *J. Am. Chem. Soc.* **1958**, *80*, 3458.
63. Spicer, L. D.; Bullock, M. W.; Garber, M.; Groth, W.; Hand, J. J.; Long, D. W.; Sawyer, J. L.; Wayne, R. S. *J. Org. Chem.* **1968**, *33*, 1350.
64. Baklien, A.; Leeding, M. V.; Kolm, J. *Aust. J. Chem.* **1968**, *21*, 1557.
65. Sineokov, A. P.; Gladysheva, V. N.; Etlis, V. S. *Khimi. Geterotsikl. Soedin*. **1968**, 567; *Chem. Abstr.* **1968**, *69*, 96538.
66. Sineokov, A. P.; Gladysheva, F. N.; Etlis, V. S. *Khimi. Geterotsikl. Soedin*. **1970**, 611; *Chem. Abstr.* **1970**, *73*, 66351.
67. Nomura, R.; Nakano, T.; Nishio, Y.; Ogawa, S.; Ninagawa, A.; Matsuda, H. *Chem. Ber.* **1989**, *122*, 2407.
68. Baeg, J.-O.; Alper, H. *J. Am. Chem. Soc.* **1994**, *116*, 1220.
69. Baeg, J.-O.; Bensimon, C.; Alper, H. *J. Am. Chem. Soc.* **1995**, *117*, 4700.
70. Butler, D. C. D.; Inman, G. A.; Alper, H. *J. Org. Chem.* **2000**, *65*, 5887.
71. Markov, V. I.; Danileiko, D. A.; Doroshenko, V. A. *Ukr. Khim. Zh.* **1987**, *53*, 195; *Chem. Abstr.* **1988**, *108*, 37717.
72. Nadir, U. K.; Joshi, S. *Indian J. Chem.* **2003**, *42B*, 1760.
73. Nadir, U. K.; Joshi, S. *Indain J. Chem.* **2003**, *42B*, 1531.
74. Markov, V. I.; Danileiko, D. A. *Zh. Organi. Khim*. **1974**, *10*, 1262; *Chem. Abstr.* **1974**, *81*, 105381.
75. Sineokov, A. P.; Kutyreva, V. S. *Khimi. Geterotsikl. Soedin*. **1971**, 1651; *Chem. Abstr.* **1972**, *77*, 5396.

76. D'hooghe, M.; Waterinckx, A.; De Kimpe, N. *J. Org. Chem.* **2005**, *70*, 227.
77. Creeke, P. I.; Mellor, J. M. *Tetrahedron Lett.* **1989**, *33*, 4435.
78. Gabriel, S. *Ber.* **1889**, *22*, 1139.
79. Sakae, M.; Katsurada, M.; Watanabe, M.; Yoneda, F.; Nishigaki, S.; Ishida, T. *J. Heterocycl. Chem.* **1997**, *34*, 157.
80. Dorn, H.; Welfle, H. *Chem. Ber.* **1967**, *100*, 3246.
81. Takeda, H.; Tachinami, T.; Aburatani, M.; Takahashi, H.; Morimoto, T.; Achiwa, K. *Tetrahedron Lett.* **1989**, *30*, 363.
82. Cruz, A.; Macías-Mendoza, D.; Barragan-Rodríguez, E.; Tlahuext, H.; Nöth, H.; Contreras, R. *Tetrahedron: Asymmetry* **1997**, *8*, 3903.
83. Outcalt, R. J. *J. Heterocycl. Chem.* **1987**, *24*, 1425.
84. Huber, I.; Szabó, A.; Fülöp, F.; Bernáth, G.; Sohár, P. *Tetrahedron* **1992**, *23*, 4949.
85. Hornyák, G.; Bertha, F.; Zauer, K.; Lempert, K.; Feller, A.; Pjeczka, E. *Tetrahedron* **1990**, *46*, 2009.
86. Salerni, O. L.; Morrison, J. I.; Budde, W. L.; Stanley, C. W. *Tetrahedron Lett.* **1968**, *51*, 5307.
87. Oliver, J. E.; DeMilo, A. B. *J. Org. Chem.* **1974**, *15*, 2225.
88. Goerdeler, J.; Linden, H. W. *Tetrahedron Lett.* **1975**, *39*, 3387.
89. Iwata, C.; Watanabe, M.; Okamoto, S.; Fujimoto, M.; Sakae, M.; Katsurada, M.; Imanishi, T. *Heterocycles* **1988**, *27*, 323.
90. Tanaka, T.; Azuma, T.; Fang, X.; Uchida, S.; Iwata, C.; Ishida, T.; In, Y.; Maezaki, N. *Synlett* **2000**, 32.
91. Neidlein, R.; Reuter, H. *Arch. Pharm.* **1972**, *305*, 731.
92. Wobig, D. *Justus Liebigs Ann. Chem.* **1978**, 1118.
93. Wobig, D. *Liebigs Ann. Chem.* **1992**, 415.
94. Dockx, J. J. C.; De Knaep, A. G. M.; Albert, R. W. H. *Synthesis* **1982**, 511.
95. (a) Thyagarajan, B. S.; Glowienka, N.; Simon, J. A. *Phosphorus, Sulfur Silicon Relat. Elem.* **1988**, *39*, 11. (b) Thyagarajan, B. S.; Simon, J. A. *Synth. Commun.* **1988**, *18*, 197.
96. (a) Thyagarajan, B. S.; Wood, B. F., Jr.; Glowienka, J. A.; Delgado, P. *Phosphorus and Sulfur* **1985**, *25*, 1. (b) Thyagarajan, B. S.; Wood, B. F., Jr.; Glowienka, J. A. *Phosphorus and Sulfur* **1986**, *26*, 275.
97. Mizrakh, L. I.; Polonskaya, L. Y.; Gvozdetskii, A. N.; Vasil'ev, A. M. *Zh. Obshch. Chem.* **1986**, *56*, 73; *Chem. Abstr.* **1986**, *105*, 191000.
98. Mitsunobo, O.; Ohashi, T.; Mukaiyama, T. *Bull. Chem. Soc. Japan* **1966**, *39*, 708.
99. (a) Tominaga, Y.; Ogata, K.; Kohra, S.; Hojo, M.; Hosomi, A. *Tetrahedron Lett.* **1991**, *32*, 5987. (b) Tominaga, Y.; Ogata, K.; Ueda, H.; Kohra, S.; Hosomi, A. *Chem. Pharm. Bull.* **1995**, *43*, 1425.
100. (a) De Kimpe, N.; Schamp, N. *Org. Prep. Proced. Int.* **1979**, *11*, 115. (b) De Kimpe, N.; Verhé, R.; De Buyck, L.; Moens, L.; Schamp, N. *Synthesis* **1982**, 43. (c) De Kimpe, N.; Verhé, R. In *The Chemistry of α-Haloketones, α-Haloaldehydes and α-Haloimines*; Patai, S., Rappoport, Z., Eds.; Wiley: Chichester, 1988. (d) De Kimpe, N.; De Cock, W.; Stevens, C. *Tetrahedron* **1992**, *48*, 2739.
101. De Kimpe, N.; De Cock, W.; Keppens, M.; De Smaele, D.; Mészáros, A. *J. Heterocycl. Chem.* **1996**, *33*, 1179.
102. Landreau, C.; Deniaud, D.; Reliquet, A.; Meslin, J. C. *Synthesis* **2001**, 2015.
103. Larksarp, C.; Sellier, O.; Alper, H. *J. Org. Chem.* **2001**, *66*, 3502.
104. Ueda, S.; Terauchi, H.; Yano, A.; Matsumoto, M.; Kubo, T.; Kyoya, Y.; Suzuki, K.; Ido, M.; Kawasaki, M. *Bioorg. Med. Chem.* **2004**, *12*, 4101.
105. Ukraintsev, V. B.; Yakovlev, S. V.; Kukushkin, Y. N. *Zh. Obshch. Chem.* **1985**, *55*, 2572; *Chem. Abstr.* **1987**, *107*, 50714.

Biographical sketch

Matthias D'hooghe was born in Kortrijk, Belgium, in 1978. He received his master's diploma in bioscience engineering—chemistry from Ghent University, Ghent, Belgium, in 2001, where he carried out research under the guidance of Prof. N. De Kimpe, studying new entries towards 1-azabicyclo[*m.n.*0]alkanes. Subsequently, he enrolled in a PhD program at the Department of Organic Chemistry, Faculty of Bioscience Engineering, Ghent University. Currently, he is in the fifth year of the PhD program, and his main interests include synthesis and reactivity of aziridines. He is the author of 12 publications in international peer-reviewed journals.

Norbert De Kimpe obtained the diploma of chemical agricultural engineer in 1971, the PhD degree in 1975, and the habilitation degree in 1985, all from Ghent University, Ghent (Belgium). He performed postdoctoral research work at the University of Massachusetts, Harbor Campus, at Boston (USA) (1979) and at the Centre National de Recherche Scientifique (CNRS) in Thiais, Paris (France) (1983), where he worked on unstable nitrogen-substituted sulfenyl derivatives and electron-deficient carbenium ions, respectively. He made his scientific career at the Belgian National Fund for Scientific Research, where he went through all stages up to the position of Research Director. During this career, he was affiliated with the Department of Organic Chemistry, Faculty of Agricultural and Applied Biological Sciences at Ghent University, where he took up teaching positions since 1987. He is now professor in organic chemistry at the latter institution. He was a guest professor at the Centre Universitaire de Recherche sur la Pharmacopée et la Médecine Traditionelle in Butare (Rwanda, Central Africa), and at the Universities of Perpignan (France), Helsinki (Finland), Leuven (Belgium), Siena (Italy), Barcelona (Spain), Sofia (Bulgaria), Buenos Aires (Argentina), and Pretoria (South Africa). He was awarded the degree of Doctor honoris causa from the Russian Academy of Sciences in Novosibirsk (Russia) in 1998. He is the author of 378 articles in international peer-reviewed journals. His research interests include (1) the synthesis of heterocyclic compounds, with focus on agrochemicals, pharmaceuticals, and natural products, (2) flavor chemistry, and (3) the bioassay-guided isolation of physiologically active natural products from medicinal plants.

Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron 62 (2006) 537–542

Tetrahedron

A facile [4+1] type synthetic route to thiophenes from dienol silyl ethers and elemental sulfur

Yukihiro Kasano,[a] Aoi Okada,[a] Daisuke Hiratsuka,[a] Yoji Oderaotoshi,[a]
Satoshi Minakata[a] and Mitsuo Komatsu[a,b,c,*]

[a]*Department of Applied Chemistry, Graduate School of Engineering, Osaka University, Yamadaoka 2-1, Suita, Osaka 565-0871, Japan*
[b]*Center for Atomic and Molecular Technologies, Graduate School of Engineering, Osaka University, Yamadaoka 2-1, Suita, Osaka 565-0871, Japan*
[c]*Research Center for Environmental Preservation, Osaka University, Yamadaoka 2-4, Suita, Osaka 565-0871, Japan*

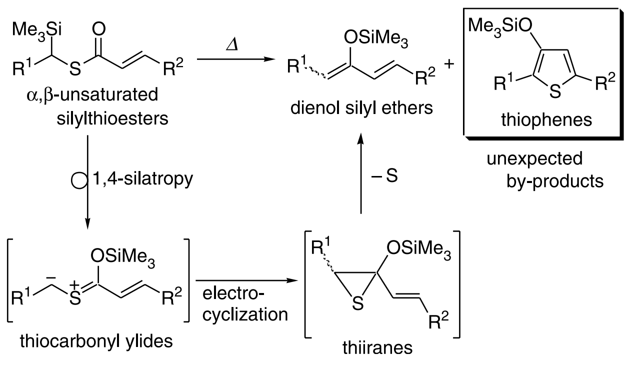
Received 13 September 2005; revised 13 October 2005; accepted 13 October 2005

Abstract—A facile method for the synthesis of thiophene derivatives via the reaction of readily accessible dienol silyl ethers with elemental sulfur is described. Dienol silyl ethers and elemental sulfur, when heated at 180 °C in the presence of MS4A, provided 3-siloxythiophene derivatives in yields up to 98%. In this reaction, thiophene derivatives might be formed through 1,2-dithiines and eight-membered cyclic tetrasulfides.

1. Introduction

The thiophene ring structure is widespread in nature and many of these compounds are biologically active.[1] Thiophene derivatives are also widely utilized as functional materials in dyes, liquid crystals and as components of organic conducting polymers.[1] Because of their significance, heterocycles are important target molecules from a synthetic point of view, and a number of methods for their preparation have been reported to date.[1] Although the Gewald, Hinsberg and Paal syntheses are well-known procedures for the construction of the ring, new or improved methodologies have been developed more recently.[1] Among these procedures, [4+1] type ring formation from 4-carbon units and elemental sulfur should be practical because of the low cost sources and, in fact, one of these reactions is used in the commercial production of thiophenes.[2] While the thermal reaction of dienes with elemental sulfur is a simple approach to thiophene synthesis,[3] a high reaction temperature is required (300–420 °C), and the efficiency is also low (up to 51%).

We previously reported on efficient methods of generation of nitrogen-centered 1,3-dipoles, azomethine ylides and azomethine imines, via an intramolecular 1,2- or 1,4-silatropic shift and their cycloaddition reactions.[4] By applying the 1,4-silatropic protocol to the generation of thiocarbonyl ylides, we developed a convenient route for the preparation of enol and dienol silyl ethers from readily accessible starting materials, as shown in Scheme 1 for the case of dienol silyl ethers.[5] These reactions proceed via the generation of thiocarbonyl ylides by the thermal 1,4-silatropy of *S*-α-silyl thioesters and electrocyclization of the thiocarbonyl ylides to give thiiranes followed by sulfur extrusion under completely neutral conditions without the need for any catalyst or additive. In these reactions, thiophene derivatives were also obtained as minor products.



Scheme 1. A convenient route to dienol silyl ethers via thiocarbonyl ylides.

Keywords: Thiophene; Dienol silyl ether; Elemental sulfur.

* Corresponding author. Tel.: +81 6 6879 7400; fax: +81 6 6879 7402; e-mail: komatsu@chem.eng.osaka-u.ac.jp

doi:10.1016/j.tet.2005.10.024

In preliminary experiments, the precursors of the thiophenes were found to be the dienol silyl ethers and elemental sulfur generated in situ. This fact stimulated us to develop a new method for the synthesis of siloxythiophenes. The desired siloxythiophenes should be equivalent to hydroxythiophenes, which have been prepared only with difficulty by low yielding and/or multi-step procedures especially for simple 3-hydroxythiophenes.[6]

From these points of view, we present the full details of an efficient and convenient approach to siloxythiophenes from dienol silyl ethers and elemental sulfur as the S_1 unit via a [4+1] type reaction.

2. Results and discussion

As mentioned in the introduction, to clarify the mechanism of generation of thiophene derivatives, the time course for the reaction of silylmethylthioester **1a** was monitored by ^{1}H NMR (Fig. 1). The thermal reaction of **1a** for 1.5 h provided a mixture of **2a** (82%) and **3a** (9%), which led to a mixture of **2a** (6%) and **3a** (55%) upon continued heating under the same conditions for 80 h. Thus, the formation of the thiophene **3a** must have been related to the consumption of the dienol silyl ether **2a**. Since sulfur might be generated in situ in this reaction, as shown in Scheme 1, it appears that the dienol silyl ether was consumed by a reaction with sulfur.

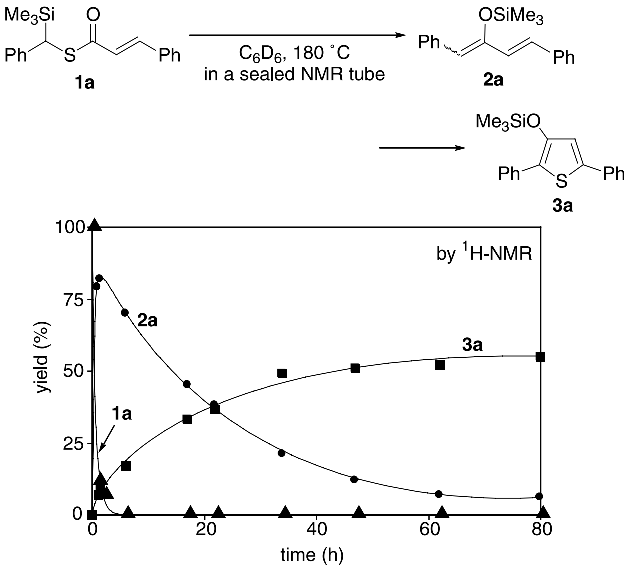
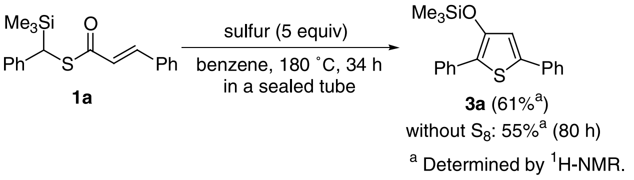


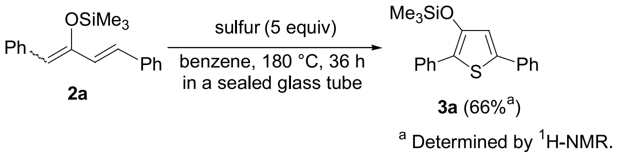
Figure 1. A time course for the reaction of α,β-unsaturated thioester **1a**.

To verify the reaction pathway proposed above, an additional experiment was carried out (Eq. 1). As shown in Figure 1, the thermal treatment of thioester **1a** at 180 °C for 80 h led to the formation of thiophene **3a** in 55% yield. In the presence of elemental sulfur (5 equiv), the reaction proceeded at an increased rate and gave a higher yield of product (61%).



(1)

Based on the above results, a solution of dienol silyl ether **2a** and 5 equiv of elemental sulfur in benzene was heated at 180 °C for 36 h in a sealed glass tube (Eq. 2) to give thiophene **3a** in 66% yield. These results verify that a dienol silyl ether is a precursor of a thiophene.



(2)

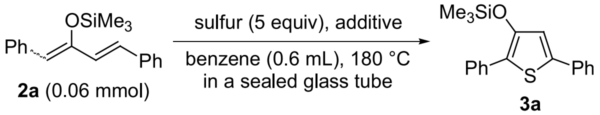
To improve the efficiency of the reaction, the effect of additives was examined (Table 1). Although triethylamine and tri-*n*-butylphosphine are well known activators of elemental sulfur,[7] the use of these reagents had no effect on the results (entries 2 and 3). Lewis acids were also ineffective because of their tendency to cause the polymerization of dienol silyl ether **2a** (entries 4, 5, 6 and 7). Interestingly, when molecular sieves 4Å (MS4A) were employed as an additive, the desired thiophene was obtained in almost quantitative yield (entry 8). To clarify the effect of MS4A, reactions using other porous inorganic materials and dehydrating agents were examined. Porous inorganic materials, such as zeolite, silica gel and alumina (entries 9, 10 and 11) and a dehydrating agent, sodium sulfate (entry 12) were ineffective except for potassium carbonate, which gave a quantitative yield (entry 13). Even when the reaction was carried out without these additives, the hydrolysis of starting dienol silyl ether did not occur, suggesting that MS4A does not function as a dehydrating reagent. Since the presence of potassium carbonate requires a longer reaction time than that with MS4A, the following experiments were carried out using MS4A as an additive.

Reactions of dienol silyl ethers **2b–e** with elemental sulfur in the presence of MS4A were carried out (Table 2). The starting dienol silyl ether **2b**, in which the substituent R^1 is a methyl group, was efficiently converted to the corresponding thiophene (entry 1). Thiophene derivative **3c** possessing no substituent at the 2-position was also obtained in good yield from dienol silyl ether **2c** (entry 2). Dialkyl substituted dienol silyl ether **2d** having no aromatic substituent reacted to give 2,5-dialkyl substituted thiophene **3d** (entry 3). Although improvements in the efficiency are needed, 2,5-unsubstituted thiophene **3e** was synthesized from the unsubstituted dienol silyl ether **2e** (entry 4). The low yield might be because of the condensation polymerization of **2e**.

The present method was applicable to other types of dienol silyl ethers.

Thermal reaction of 2,3-bis(trimethylsilyloxy)-1,3-butadiene **2f** with elemental sulfur gave 3,4-

Table 1. Effect of additives on the formation of thiophene **3a** from dienol silyl ether **2a** and elemental sulfur

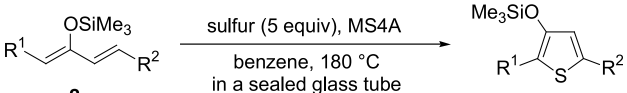


2a (0.06 mmol) **3a**

Entry	Additive		Time (h)	Yield (%)[a]
1	None		36	66
2	Et_3N	(1 equiv)	40	27[b]
3	n-Bu_3P	(1 equiv)	40	54
4	$BF_3 \cdot OEt_2$	(1 equiv)	6	0
5	AgOTf	(1 equiv)	1	0
6	$Mg(OTf)_2$	(1 equiv)	24	28
7	$Zn(OTf)_2$	(1 equiv)	18	20
8	MS4A	(10 mg)	48	98 (87)[c]
9	Zeolite[d]	(10 mg)	84	57
10	Silica gel[e]	(10 mg)	40	66
11	Alumina[f]	(10 mg)	63	37
12	Na_2SO_4	(1 equiv)	39	40
13	K_2CO_3	(1 equiv)	90	98

[a] Determined by ^{1}H NMR.
[b] Dienol silyl ether **2a** (37%) was recovered.
[c] Isolated yield. 2,5-Diphenyl-3-hydroxythiophene was also obtained in 8% yield as a result of hydrolysis of **3a** on work up.
[d] Zeolite A-4 from Wako Pure Chem. Ind.
[e] Silica gel 60 from Merck Co.
[f] Aluminium oxide 90 active basic from Merck Co.

Table 2. Reactions of dienol silyl ethers with elemental sulfur

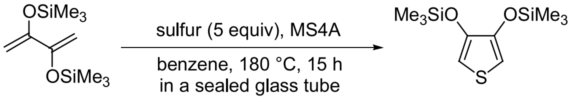


2 **3**

Entry	Dienol silyl ether	R^1	R^2	Time (h)	Thiophene	Yield (%)[a]
1	**2b**	Me	Ph	10	**3b**	80 (82)
2	**2c**	H	Ph	10	**3c**	77 (76)
3	**2d**	Me	Me	20	**3d**	44 (51)
4	**2e**	H	H	10	**3e**	14 (15)

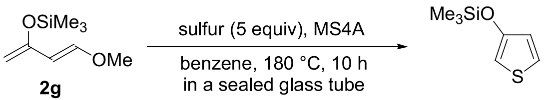
[a] Isolated yield. ^{1}H NMR yields before purification are presented in the parenthesis.

bis(trimethylsilyloxy)thiophene **3f** in 29% yield (Eq. 3).



2f **3f** 29% (3)

Since Danishefsky's diene **2g** should be a good candidate for synthesis of a functionalized thiophene, the reaction of **2g** with elemental sulfur was carried out, unexpectedly affording 5-unsubstituted thiophene **3e** in 51% yield (Eq. 4). Although the reaction mechanism is unclear at present, Danishefsky's diene is a better starting material rather than **2e** for the formation of 2,5-unsubstituted thiophene **3e**.

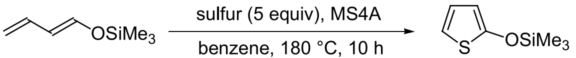


2g **3e** 45% (51%[a])

[a] Determined by ^{1}H-NMR.

(4)

To expand the utility of the system, a 1,3-butadiene having trimethylsiloxy group at 1-position was evaluated in the reaction. 1-Trimethylsilyloxy-1,3-butadiene **2h** was found to function as a starting dienol silyl ether to afford 2-siloxythiophene **3h** (Eq. 5).



2h **3h** 12% (15%[a])

[a] Determined by ^{1}H-NMR.

(5)

These results present the potential for applying this reaction to synthesis of a variety of thiophene derivatives.

While no by-products were observed in the synthesis of thiophene from dienol silyl ethers except for **2e**, 1,2-dithiine **4e** (5%) and the eight-membered cyclic tetrasulfide **5e** (2%) were obtained after 10 h in the case of the reaction of dienol silyl ether **2e**. To clarify the route of formation of the thiophene derivative, the reaction of **2e** with sulfur was followed by ^{1}H NMR and the time course is illustrated in Figure 2. Even after the complete consumption of dienol silyl ether **2e**, the amount of thiophene **3e** increased with the decrease in the amounts of **4e** and **5e**. Thus, it is conceivable that the cyclic polysulfides could be precursors of the thiophene derivative in this reaction. In practice, examples of the formation of thiophene derivatives from 1,2-dithiine have been reported.[8]

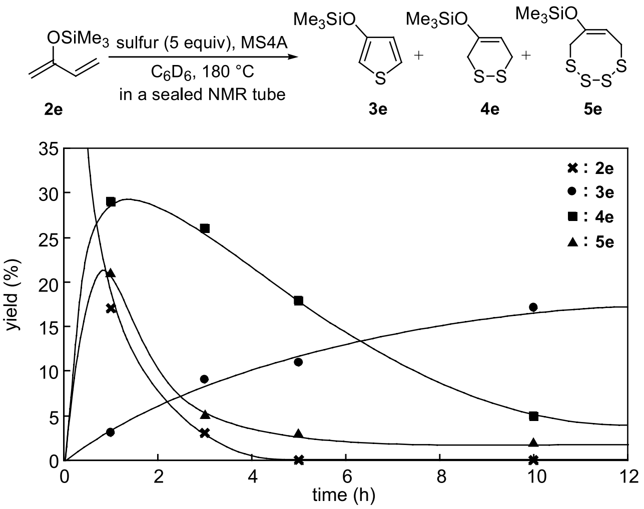
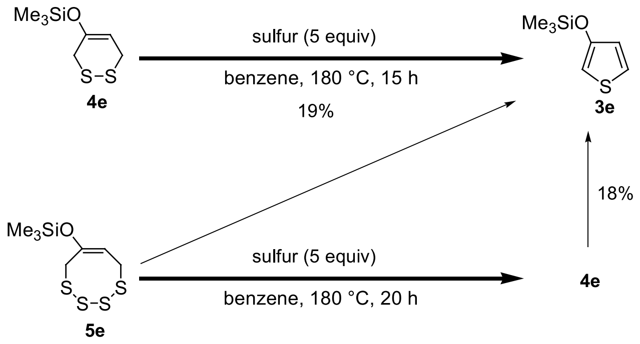


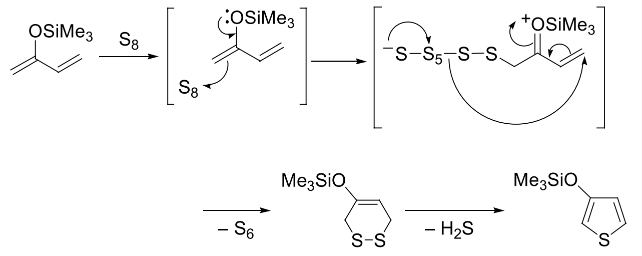
Figure 2. Time course for the reaction of dienol silyl ether **2e** with elemental sulfur.

To confirm that thiophene derivative **3e** was formed via **4e** and **5e**, these compounds were treated under the same conditions as were used for the formation of thiophene from **2e**, respectively (Scheme 2). As a result, the reaction of 1,2-dithiine **4e** gave thiophene derivative **3e** in 19%. In the case of **5e**, **4e** was also formed in situ and was gradually converted to the thiophene derivative. These results suggest that dienol silyl ether **2e** was initially converted to a mixture of cyclic polysulfides **4e** and **5e**, which were then altered to thiophene derivative **3e**. Examples of an equilibrium between 1,2-dithiines and cyclic tetrasulfides have been reported,[9] a fact that also supports the proposed reaction pathway.



Scheme 2. Thermal treatment of **4e** and **5e** leading to thiophene **3e**.

A plausible path for the formation of a thiophene derivative from a dienol silyl ether and elemental sulfur is proposed on the basis of the above results (Scheme 3). A nucleophilic attack on elemental sulfur by the carbon of the 1-position of the dienol silyl ether occurs, and the S_8 ring is opened. The elimination of S_6 followed by an attack of sulfur at the β-position of the generated carboxonium group gives the 1,2-dithiine skeleton. The elimination of hydrogen sulfide from the 1,2-dithiine then gives the thiophene derivative. Indeed, the generation of hydrogen sulfide was confirmed by using $CuSO_4$ test paper. Based on this fact, it is presumed that the effect of MS4A or potassium carbonate is to act as a scavenger of hydrogen sulfide.



Scheme 3. Plausible reaction mechanism for the generation of a thiophene derivative from a dienol silyl ether and elemental sulfur.

3. Conclusions

A convenient route to 3-siloxythiophene derivatives from readily accessible dienol silyl ethers and elemental sulfur is described. The presence of MS4A improved the efficiency of the reaction, providing thiophene derivatives in up to 98% yield. Furthermore, the isolation of a 1,2-dithiine derivative and an eight-membered cyclic tetrasulfide and a study of the reaction profile suggest that the reaction proceeds via these intermediates to form the thiophene derivatives. Further studies in this area are currently underway in our laboratory.

4. Experimental

4.1. General experimental methods

IR spectra were obtained on a Jasco FT/IR-410 infrared spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a JEOL FT NMR JNM EX 270 spectrometer (^1H NMR, 270 MHz; ^{13}C NMR, 68 MHz). Chemical shifts are reported in parts per million (δ), relative to internal TMS at 0.00 for ^1H NMR and chloroform at 77.0 for ^{13}C NMR. Mass spectra were obtained with a Shimadzu Model GC–MS-QP5000 spectrometer. High-resolution mass spectral data were obtained on a JEOL DX-303 mass spectrometer. All reactions were performed under an atmosphere of argon. Organic solvents were dried and distilled prior to use. Column chromatography was performed using silica gel 60, spherical, neutrality (Nacalai Tesque), which was dried at 140 °C under reduced pressure for 3 h prior to use. Because of high moisture sensitivity, high-resolution mass spectral (HRMS) data are given for the products instead of elemental analyses.

4.2. Synthesis of starting dienol silyl ethers

Starting dienol silyl ethers **2b**,[10] **2c**[11] and **2d**[10] were prepared according to the published procedures except for dienol silyl ether **2a**.[5]

4.2.1. 1,4-Diphenyl-2-(trimethylsilyloxy)-1,3-butadiene (2a). *trans*-1,4-Dipehnyl-but-3-en-2-one[12] (267 mg, 1.20 mmol), DBU (237 mg, 1.56 mmol) and trimethylsilyl chloride (156 mg, 1.40 mmol) were placed in a 20 mL round bottom flask and was refluxed in CH_2Cl_2 (4 mL) for 12 h. After being cooled to room temperature, hexane (20 mL) was added to the reaction mixture and washed twice with saturated aqueous Na_2CO_3 (10 mL). The organic layer was dried over $MgSO_4$, and filtered. Removal of the solvent and purification by rapid column chromatography on dried neutral silicagel afforded dienol silyl ether **2a** as a pale yellow oil. Yield: 248 mg (84%). (1*Z*,3*E*)-**2a**/(1*E*,3*E*)-**2a**=96/ 4. (1*Z*,3*E*)-**2a**: ^{1}H NMR ($CDCl_3$) δ 7.57 (br d, 2H, $J=7.3$ Hz, *o*-aromatic H), 7.44 (br d, 2H, $J=7.3$ Hz, *o*-aromatic H), 7.37–7.14 (m, 6H, aromatic H), 6.82 (d, 1H, $J=15.8$ Hz, vinyl H-4), 6.72 (d, 1H, $J=15.8$ Hz, vinyl H-3), 5.90 (s, 1H, vinyl H-1), 0.15 [s, 9H, $Si(CH_3)_3$]; ^{13}C NMR ($CDCl_3$) δ 149.8, 136.8, 136.3, 128.9, 128.8, 128.6, 128.0, 127.8, 127.5, 126.5, 126.2, 115.4, 0.9; MS (EI) *m/z* (relative intensity): 294 (M^+, 15), 203 (21), 131 (96), 73 (Me_3Si^+, 100); HRMS (EI) calcd for $C_{19}H_{20}OSi$ (M^+) 294.1440, found 294.1424. Key spectra of the minor compound (1*E*,3*E*)-**2a** obtained from the mixture of **2a**: ^{1}H NMR (C_6D_6) δ 6.23 (s, 1H, vinyl H-1), 0.28 [s, 9H, $Si(CH_3)_3$]. Only distinct signals are listed.

4.3. General procedure for the reaction of dienol silyl ether with elemental sulfur

Molecular sieves 4Å (50.0 mg) were placed in a 10 mL glass tube, which was flame-dried under reduced pressure. Elemental sulfur (48.1 mg, 1.50 mmol), dienol silyl ether **2** (0.300 mmol) and benzene (3 mL) were added to the tube and the solution was freeze-dried twice. The glass tube was then sealed and the mixture was heated at 180 °C until the amount of thiophene derivative reached a constant value. Reactions were monitored by ^{1}H NMR using benzene-d_6 as a solvent in one-fifth scale of the procedure described above with mesitylene as an internal standard. The yields of thiophene derivatives **3** listed in Tables 1 and 2 were determined by ^{1}H NMR of the crude reaction mixture based on the added mesitylene. The reaction mixture was concentrated in vacuo and the residue was purified by column chromatography on dried neutral silica gel, to afford thiophene **3**. Cyclic polysulfides **4e** and **5e** were also produced in the reaction of dienol silyl ether **2e**. Thiophenes **3a**,[5] **3e**[13], **3h**[14] and 2,5-diphenyl-3-hydroxythiophene[5] are known compounds.

4.3.1. 2-Methyl-5-phenyl-3-(trimethylsilyloxy)thiophene (3b). IR (neat) 2958, 1568, 1502, 1252 and 847 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.51 (d, 2H, $J=7.3$ Hz, *o*-aromatic H at thiphene-C5), 7.35 (dd, 2H, $J=7.3$ Hz, *m*-aromatic H), 7.25 (d, 1H, $J=7.3$ Hz, *p*-aromatic H), 6.82 (s, 1H, 4-position in thiophene), 2.27 (s, 3H, Me), 0.28 [s, 9H, $Si(CH_3)_3$]; ^{13}C NMR ($CDCl_3$) δ 148.1, 136.9, 134.5, 128.7, 126.9, 124.7, 118.6, 117.8, 11.3, 0.35; MS (EI) *m/z* (relative intensity): 262 (M^+, 54), 247 (M^+-Me, 15), 173 (10), 73 (Me_3Si^+, 100), 59 (96); HRMS (EI) calcd for $C_{10}H_{18}OSSi$ (M^+) 262.0848, found 262.0846.

4.3.2. 2-Phenyl-4-(trimethylsilyloxy)thiophene (3c). IR (neat) 2962, 1552, 1497 and 847 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.56 (d, 2H, $J=7.3$ Hz, *o*-aromatic H at thiphene-C2), 7.37 (dd, 2H, $J=7.3$ Hz, *m*-aromatic H), 7.29 (d, 1H, $J=7.3$ Hz, *p*-aromatic H), 6.93 (d, 1H, $J=1.6$ Hz, 3-position in thiophene), 6.32 (d, 1H, $J=1.6$ Hz, 5-position in thiophene), 0.30 [s, 9H, $Si(CH_3)_3$]; ^{13}C NMR ($CDCl_3$) δ 152.4, 141.8, 134.3, 128.7, 127.4, 125.1, 118.3, 104.1, 0.13; MS (EI) *m/z* (relative intensity): 248 (M^+, 100), 233 (M^+-Me, 46), 205 (30), 173 (7), 115 (14), 73 (Me_3Si^+, 17); HRMS (EI) calcd for $C_{13}H_{16}OSSi$ (M^+), 248.0691, found 248.0706.

4.3.3. 2,5-Dimethyl-3-(trimethylsilyloxy)thiophene (3d). IR (neat) 2962, 1578, 1254 and 845 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.26 (s, 1H, 4-position in thiophene), 2.34 (s, 3H, Me), 2.17 (s, 3H, Me), 0.22 [s, 9H, $Si(CH_3)_3$]; ^{13}C NMR ($CDCl_3$) δ 146.7, 133.0, 120.1, 115.6, 15.8, 10.8, 0.17; MS (EI) *m/z* (relative intensity): 200 (M^+, 100), 185 (M^+-Me, 52), 111 (19), 73 (Me_3Si^+, 44); HRMS (EI) calcd for $C_9H_{16}OSSi$ (M^+), 200.0691, found 200.0699.

4.3.4. 3,4-Bis(trimethylsilyloxy)thiophene (3f). IR (neat) 2960, 1493, 1254 and 845 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.26 (s, 2H, 2- and 5-position in thiophene), 0.26 [s, 18H, $Si(CH_3)_3$]; ^{13}C NMR ($CDCl_3$) δ 144.4, 103.0, 0.18; MS (EI) *m/z* (relative intensity): 260 (M^+, 43), 245 (M^+-Me, 14), 73 (Me_3Si^+, 100); HRMS (EI) calcd for $C_{10}H_{20}O_2SSi_2$ (M^+), 260.0723 found 260.0748.

4.3.5. 4-Trimethylsilyloxy-3*H*,6*H*-1,2-dithiine (4e). ^{1}H NMR (C_6D_6, 270 MHz) δ 5.02–4.98 (tt, $J=4.6$, 1.4 Hz, 1H, C=CH), 3.07–3.02 (m, 4H, C=CH–CH_2 and CH_2–C=CH), 0.09 [s, 9H, $Si(CH_3)_3$]; ^{13}C NMR (C_6D_6, 68 MHz) δ 149.7, 104.9, 33.3, 31.5, 0.90; MS (EI) *m/z* (%) 206 (M^+, 87), 143 (23), 142 (M^+-2S, 68), 127 (100), 85 (18), 75 (54), 73 (Me_3Si^+, 54); HRMS (EI) *m/z* calcd for $C_7H_{14}OS_2Si$ 206.0255, found 206.0253.

4.3.6. 1,2,3,4-Tetrathia-6-trimethylsilyloxy-6-cyclooctene (5e). ^{1}H NMR (C_6D_6, 270 MHz) δ 4.61 (t, $J=9.0$ Hz, 1H, C=CH), 3.07 (s, 2H, CH_2–C=CH), 2.97 (d, $J=9.0$ Hz, 2H, C=CH–CH_2), 0.21 [s, 9H, $Si(CH_3)_3$]; ^{13}C NMR (C_6D_6, 68 MHz) δ 154.2, 103.8, 41.0, 35.6, 0.66; MS (EI) *m/z* (%) 270 (M^+, 16), 206 (M^+-2S, 100), 173 (21), 159 (16), 142 (M^+-4S, 59), 127 (58), 75 (39), 73 (Me_3Si^+, 40); HRMS (EI) *m/z* calcd for $C_7H_{14}OS_4Si$ 269.9697, found 269.9698.

Acknowledgements

The work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan. One of the authors (Y.K.) expresses his special thanks for the 21st century center of excellence (21COE) program, 'Creation of Integrated EcoChemistry of Osaka University'.

References and notes

1. Russell, R. K.; Press, J. B. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. W. F.,

Padwa, A., Eds.; Pergamon: New York, 1996; Vol. 2, pp 679–729.

2. Coffman, D. D. U.S. Patent 2,410,401, Oct 29, 1946.
3. Shepard, A. F.; Henne, A. L.; Midgley, T., Jr. *J. Am. Chem. Soc.* **1934**, *56*, 1355–1356.
4. For azomethine ylides, see: (a) Komatsu, M.; Ohno, M.; Tsuno, S.; Ohshiro, Y. *Chem. Lett.* **1990**, 575–576. (b) Ohno, M.; Komatsu, M.; Miyata, H.; Ohshiro, Y. *Tetrahedron Lett.* **1991**, *32*, 5813–5816. (c) Iyoda, M.; Sultana, F.; Komatsu, M. *Chem. Lett.* **1995**, 1133–1134. (d) Komatsu, M.; Kasano, Y.; Yamaoka, S.; Minakata, S. *Synthesis* **2003**, 1398–1402. (e) Washizuka, K.-I.; Minakata, S.; Ryu, I.; Komatsu, M. *Tetrahedron* **1999**, *55*, 12969–12976. For azomethine imines, see: (f) Washizuka, K.-I.; Nagai, K.; Minakata, S.; Ryu, I.; Komatsu, M. *Tetrahedron Lett.* **1999**, *40*, 8849–8853. (g) Washizuka, K.-I.; Nagai, K.; Minakata, S.; Ryu, I.; Komatsu, M. *Tetrahedron Lett.* **2000**, *41*, 691–695.
5. Choi, J.; Imai, E.; Mihara, M.; Oderaotoshi, Y.; Minakata, S.; Komatsu, M. *J. Org. Chem.* **2003**, *68*, 6164–6171.
6. Gronowitz, G.; Hornfeldt, A.-B. In *Thiophene and its Derivatives*; Gronowitz, S., Ed.; Wiley-Interscienece: New York, 1986; Part 3, Chapter 1.
7. Bartlett, P. D.; Cox, E. F.; Davis, R. E. *J. Am. Chem. Soc.* **1961**, *83*, 103–109.
8. Cignarella, G.; Cordella, G. *Tetrahedron Lett.* **1973**, 1871–1872.
9. Rys, A. Z.; Harpp, D. N. *Tetrahedron Lett.* **1997**, *38*, 4931–4934.
10. Kanemasa, S.; Kumegawa, M.; Wada, E.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2990–3004.
11. Yokokawa, F.; Asano, T.; Shioiri, T. *Org. Lett.* **2000**, *2*, 4169–4172.
12. Fleming, I.; Pearce, A. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2485–2489.
13. Camici, L.; Dembech, P.; Ricci, A.; Seconi, G.; Taddei, M. *Tetrahedron* **1988**, *44*, 4197–4206.
14. Fiorenza, M.; Reginato, G.; Ricci, A.; Taddei, M. *J. Org. Chem.* **1984**, *49*, 551–553.

Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron 62 (2006) 543–548

Tetrahedron

A convenient procedure for the synthesis of fused fluoro isoquinolines

Alexander S. Kiselyov*

Small Molecule Drug Discovery, Chemical Diversity, 11558 Sorrento Valley Rd, Suite 5; San Diego, CA 92121, USA

Received 10 August 2005; revised 27 September 2005; accepted 12 October 2005

Abstract—A base-promoted conversion of *ortho*-trifluoromethyl benzyl derivatives of NH-heterocycles into a respective fluorinated isoquinolines (38–57% isolated yields) is reported. The reaction is general for the benzylated derivatives of the electron-rich NH-heterocycles and the respective derivatives of pyrazole. The outcome of the reaction could be explained by an intermediate formation of a highly reactive quinone methide species.

1. Introduction

The anionically activated trifluoromethyl group has attracted considerable interest due to its synthetic utility. A wide variety of aromatic, heteroaromatic, and aliphatic compounds could be accessed from the commercially available substrates containing CF_3 functionality that is conjugated with the ionizable NH or CH group.[1] These include syntheses of 2-(substituted 1-alkenyl) anilines (i),[2] 2-substituted benzothiazoles and benzoxazoles (ii),[3] 4(5)-dihydro-1*H*-imidazole (iii),[4] triazines (iv),[5] and isoxazoles,[5] 1,3-disubstituted naphthalenes (v),[6] 2,4-di- or 2,3,4-tri-substituted quinolines (vi),[7] 7-(substituted amino)-5,6-dihydrobenz[*c*]acridines (vii),[8] aza-analogues of tacrine[9] (viii), fluoronaphthalenes (ix),[10] 4-fluoroquinolines and fluoroolefins (x),[11] and 4-fluoroquinolones (xi).[12] A solid support synthesis of fluorinated aromatics using this protocol has been reported.[10] Representative examples of the chemistry of anionically activated CF_3 group are summarized in Scheme 1. It has been suggested that all of the above transformations proceed via the initial abstraction of the acidic proton from the XH moiety, followed by elimination of F^-, to afford the quinone methide intermediate **QM** (Scheme 1). The subsequent reaction of this intermediate with various nucleophiles may lead to the observed array of products.

2. Results and discussion

In our attempt to further expand the synthetic potential of the anionically activated CF_3 group, we studied the reaction of *N*-benzylated heterocycles **2a–j**, easily available from the respective NH-heterocycles and *ortho*-trifluoromethyl benzyl chloride, with LDA (Scheme 2). Under the optimized reaction conditions, the reaction afforded fused fluoro isoquinolines in good isolated yields (38–57%). Notably, this introduction of fluorine substituent into isoquinoline ring system from the respective CF_3 derivatives is unprecedented.

We studied the effect of both (i) nature of base as well as (ii) the ratio of substrate **2**: base on the reaction outcome. Freshly prepared LDA was found to be the optimal base for the conversion. NaH and Li-piperidide afforded somewhat lower yields (by ca. 10–20%), as found for the conversions of **2a**, **2d**, and **2g** to a respective derivatives **3** of the targeted isoquinolines. Application of the Grignard reagents (MeMgBr and EtMgBr) as bases resulted in a complex reaction mixtures including extensive formation of high-molecular weight products. The yields of **3** in these cases did not exceed 15%. No reaction was observed with *t*BuOK and EtONa in THF and EtOH, respectively. The optimal ratio of **2**: base (LDA) for the reaction was found to be 2.5. Lower ratios (<2 equiv) resulted in incomplete conversions of **2**, namely unreacted starting material was isolated from the reaction mixtures. Higher ratios did not affect the reaction yields. Structures of **3** were further confirmed by NOE experiments for the selected compounds.[13]

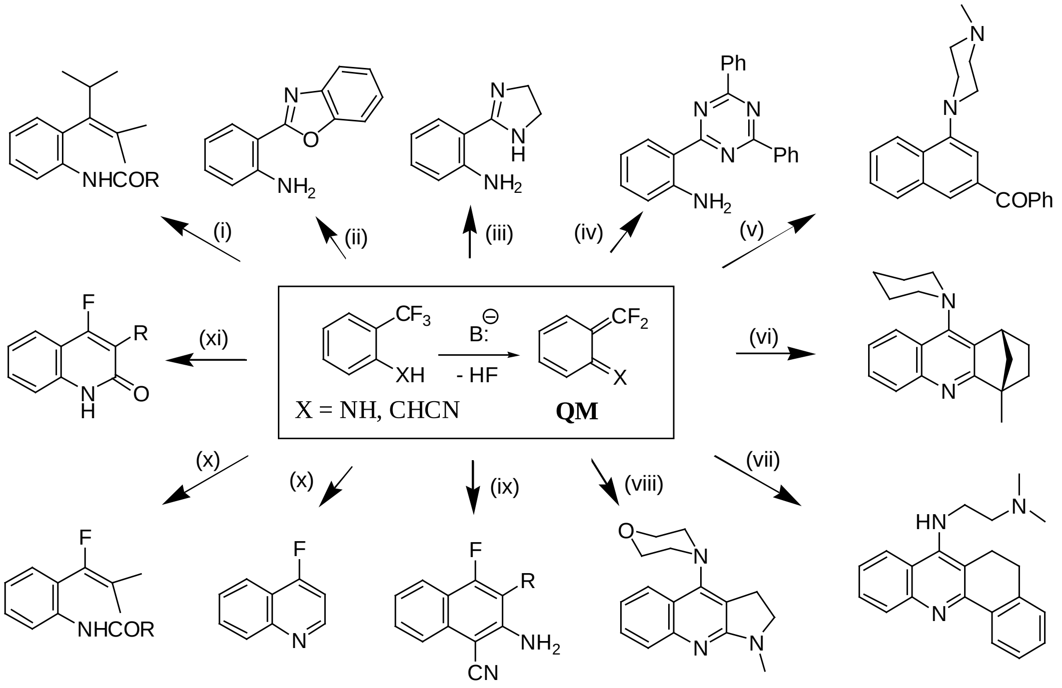
The outcome of the reported reaction could be explained by an initial abstraction of the acidic methylene proton from

---

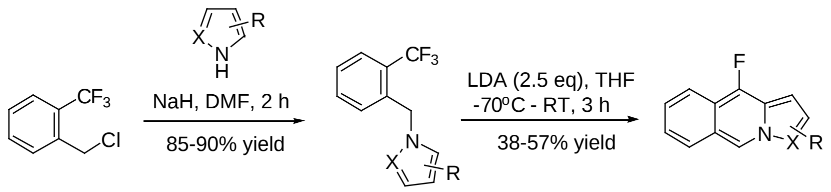
Keywords: Fluorine and compounds; Condensations; Quinone methide; Isoquinolines; Anionically activated trifluoromethyl group.

* Tel.: +1 858 794 4860; fax: +1 858 794 4931; e-mail: ask@chemdiv.com

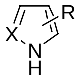
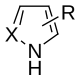
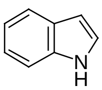
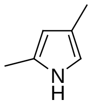
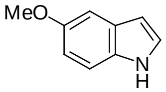
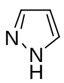
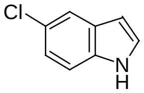
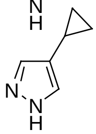
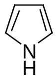
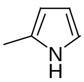
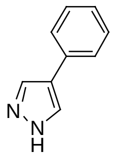
0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.10.025



Scheme 1.

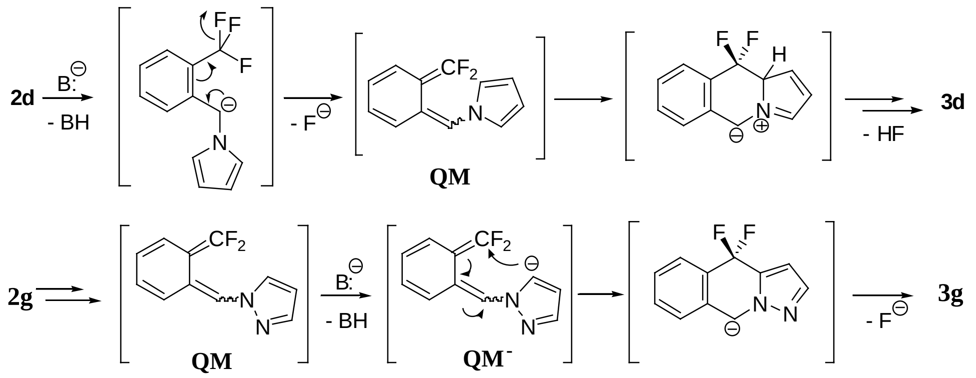


1 **2a-i** **3a-i**

Heterocycle 	Yield of 2a-i[a], %	Yield of 3a-i[a], %	Heterocycle 	Yield of 2a-i[a], %	Yield of 3a-i[a], %
a 	86	44	**f** 	89	48
b 	85	43	**g** 	90	51
c 	88	52	**h** 	87	44
d 	87	38			
e 	89	39	**i** 	86	57

[a]Yields refer to isolated analytically pure materials

Scheme 2.



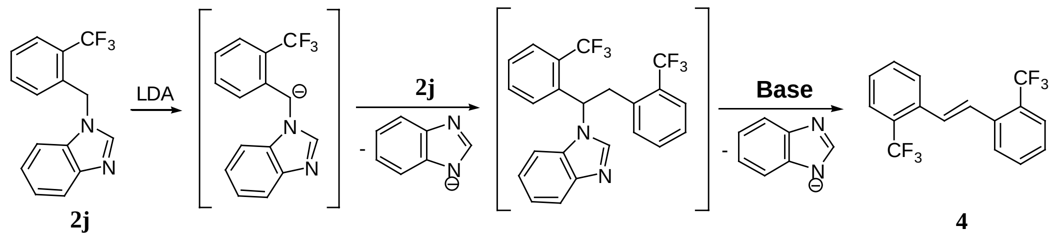
Scheme 3.

the CH_2 group of the *N*-benzylated heterocycle (Scheme 3). This intermediate undergoes conversion to quinone methide **QM** by elimination of F^-. The highly reactive species **QM** are likely to cyclize to afford, after elimination of another HF molecule and aromatization, the observed fluorinated isoquinoline **3d**. Alternatively, second equivalent of LDA could further abstract acidic C5 proton from the intermediate **QM**, as shown for the pyrazole derivative, to yield anionic species **QM**$^-$. These undergo intramolecular cyclization and elimination of F^- to yield **3g**.

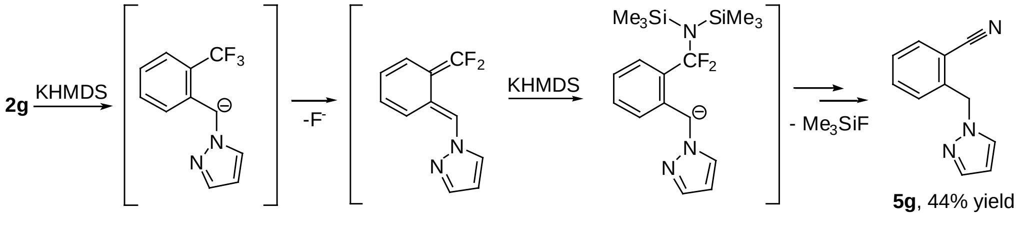
The postulated intermediacy of the quinone methide intermediate **QM** is in agreement with the lack of formation of the respective derivatives **3** in an attempted reaction of *ortho*-trifluoromethyl benzylated derivatives of 2,5-dimethylpyrrole and 5-methylpyrazole with LDA. The targeted analogues of **3** were not detected in the crude mixtures by ^{19}F NMR. Instead, both reactions resulted in complex mixtures of products, none of them major (LC MS analysis). Furthermore, attempts to convert benzimidazole derivative **2j** into a respective fluoro isoquinoline were unsuccessful under a variety of experimental conditions. The main product isolated from the reaction mixture was **4** (50–60% yields) presumably resulting from the S_N2 reaction of the respective anion with **2j** followed by the elimination of benzimidazole moiety as shown at Scheme 4. Varying amounts of **4** (5–15%) were detected in all reaction mixtures.

Notably, reaction of **2g** with potassium hexamethyl disilazide (KHMDS) under the experimental conditions described above yielded the nitrile **5g** as a major product (44% isolated yield), instead of the anticipated fluoro isoquinoline **3g**. Possible mechanism for this conversion is summarized below (Scheme 5).

In summary, we discovered a base-promoted conversion of *ortho*-trifluoromethyl benzyl derivatives of NH-heterocycles into a respective fluorinated isoquinolines (38–57% isolated yields). The reaction is general for the benzylated derivatives of the electron-rich NH-heterocycles and the respective derivatives of pyrazole. Similar reaction for the benzimidazole derivative yields a product of dimerization, instead of the expected fluoro isoquinoline. The outcome of the reaction could be explained by an intermediate formation of a highly reactive quinone methide species.



Scheme 4.



Scheme 5.

3. Experimental

All NMR spectra recorded on a Bruker 400 MHz instrument in DMSO-d_6, chemical shifts reported in ppm. MS analyses (ESI mode) were performed on a Perkin Elmer API 165 instrument. Melting points were measured with a Büchi 535 melting point apparatus. Elemental analyses were performed by Atlantic Microlab Inc, Norcrosss, GA. HPLC analyses were performed on a Beckman Gold Analytic 126 apparatus with a diode array detector model 168 at the wavelengths of 220 and 254 nm. The column employed was a YMC Pak ProC18 column, 50 mm × 4.6 mm. The solvent system was MeCN–H_2O (start: 20/80; finish: 100:0; 3 min runs; 0.1% TFA added), with a flow rate of 3 mL/min.

3.1. A typical protocol for the synthesis of 2a–j

A suspension of 60% NaH (2.5 mmol) was washed with dry hexanes and transferred via cannula to a vigorously stirred dry DMF (5 mL) under Ar. A solution of NH-heterocycle (2 mmol) in the same solvent was added at 0 °C (ice bath) and the resulting mixture was stirred for additional 15 min. A solution of *ortho*-trifluoromethyl benzyl chloride (2 mmol in 5 mL of DMF) was added at 0 °C (ice bath), the mixture was stirred for 2 h, diluted with aq NH_4Cl (25 mL) and extracted with EtOAc (2 × 15 mL). The organic phase was washed with saturated $NaHCO_3$, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The resulting solid residue was purified by flash chromatography (silica, eluent hexanes/EtOAc, 2:1) to yield the respective *N*-benzylated heterocycles **2a**–**j** in 85–90% isolated yields.

3.2. Analytical data for 2a–j

3.2.1. 1-(2-(Trifluoromethyl)benzyl)-1*H*-indole (2a). Yield 86%, oil; ^{1}H NMR δ: 5.05 (s, 2H), 6.55 (d, J=7.6 Hz, 1H), 6.85 (d, J=7.6 Hz, 1H), 6.98 (m, 1H), 7.05 (m, 1H), 7.09 (d, J=8.4 Hz, 1H), 7.12 (m, 1H), 7.18 (m, 1H), 7.28 (d, J=8.4 Hz, 1H), 7.36 (d, J=8.0 Hz, 1H), 7.62 (d, J=7.6 Hz, 1H); ^{13}C NMR: 51.9, 101.8, 111.3, 118.2, 119.1, 119.8, 122.3, 125.4, 125.7, 127.4, 128.3, 129.0, 129.3, 131.7, 133.5, 137.1; ESI MS: (M+1) 276, (M−1) 274; HR ESI MS: Exact mass calcd for $C_{16}H_{12}F_3N$ 275.0922, found: 275.0917. Elemental analysis, calcd for $C_{16}H_{12}F_3N$: C, 69.81; H, 4.39; N, 5.09. Found: C, 69.66; H, 4.47; N, 4.89.

3.2.2. 1-(2-(Trifluoromethyl)benzyl)-5-methoxy-1*H*-indole (3b). Yield 85%, oil; ^{1}H NMR δ: 3.66 (s, 3H), 5.01 (s, 2H), 6.38 (d, J=7.2 Hz, 1H), 6.55 (d, J=6.4 Hz, 1H), 6.91 (d, J=7.2 Hz, 1H), 6.98 (d, J=8.0 Hz, 1H), 7.03 (m, 1H), 7.08 (s, 1H), 7.11 (m, 1H), 7.26 (d, J=6.4 Hz, 1H), 7.38 (d, J=8.0 Hz, 1H); ^{13}C NMR: 52.1, 56.2, 101.9, 102.4, 109.0, 113.2, 117.4, 125.4, 125.8, 127.6, 128.7, 129.1, 129.5, 129.7, 131.9, 133.2, 155.9; ESI MS: (M+1) 306, (M−1) 304; HR ESI MS: Exact mass calcd for $C_{17}H_{14}F_3NO$ 305.1027, found: 305.1023. Elemental analysis, calcd for $C_{17}H_{14}F_3NO$: C, 66.88; H, 4.62; N, 4.59. Found: C, 66.71; H, 4.45; N, 4.37.

3.2.3. 1-(2-(Trifluoromethyl)benzyl)-5-chloro-1*H*-indole (2c). Yield 88%, oil; ^{1}H NMR δ: 5.08 (s, 2H), 6.45 (d, J=7.2 Hz, 1H), 6.88 (d, J=7.2 Hz, 1H), 7.02 (d, J=8.0 Hz, 1H), 7.09 (m, 1H), 7.15 (d, J=7.6 Hz, 1H), 7.27 (d, J=7.6 Hz, 1H), 7.26 (d, J=6.4 Hz, 1H), 7.42 (d, J=8.0 Hz, 1H), 7.63 (s, 1H); ^{13}C NMR: 52.2, 102.3, 113.1, 117.4, 118.8, 120.9, 124.7, 125.9, 126.7, 127.2, 128.0, 129.2, 129.6, 131.7, 133.3, 134.5; ESI MS: (M+1) 311, (M−1) 309; HR ESI MS: Exact mass calcd for $C_{16}H_{11}ClF_3N$ 309.0532, found: 309.0526. Elemental analysis, calcd for $C_{16}H_{11}ClF_3N$: C, 62.05; H, 3.58; N, 4.52. Found: C, 61.88; H, 3.44; N, 4.36.

3.2.4. 1-(2-(Trifluoromethyl)benzyl)-1*H*-pyrrole (2d). Yield 87%, oil; ^{1}H NMR δ: 4.99 (s, 2H), 5.98 (dd, J_1=8.0 Hz, J_2=4.0 Hz, 2H), 6.64 (d, J=4.0 Hz, 2H), 6.87 (d, J=8.0 Hz, 1H), 6.97 (m, 1H), 7.13 (m, 1H), 7.35 (d, J=8.0 Hz, 1H); ^{13}C NMR: δ 49.7, 106.8, 117.5, 123.0, 124.8, 125.7, 127.6, 130.1, 131.6, 133.2; ESI MS: (M+1) 226, (M−1) 224; HR ESI MS: Exact mass calcd for $C_{12}H_{10}F_3N$ 225.0765, found: 225.0761. Elemental analysis, calcd for $C_{12}H_{10}F_3N$: C, 64.00; H, 4.48; N, 6.22. Found: C, 63.75; H, 4.31; N, 6.03.

3.2.5. 1-(2-(Trifluoromethyl)benzyl)-2-methyl-1*H*-pyrrole (2e). Yield 89%, oil; 2.05 (s, 3H), 5.02 (s, 2H), 5.72 (d, J=6.8 Hz, 1H), 6.01 (dd, J_1=6.8 Hz, J_2=4.4 Hz, 1H), 6.28 (d, J=4.4 Hz, 1H), 7.02 (d, J=8.0 Hz, 1H), 7.05 (m, 1H), 7.19 (m, 1H), 7.39 (d, J=8.0 Hz, 1H); ^{13}C NMR: δ 10.8, 46.8, 105.9, 107.8, 117.4, 121.7, 124.7, 125.9, 128.1, 128.3, 129.0, 131.6, 133.5; ESI MS: (M+1) 240, (M−1) 238; HR ESI MS: Exact mass calcd for $C_{13}H_{12}F_3N$ 239.0922, found: 239.0917. Elemental analysis, calcd for $C_{13}H_{12}F_3N$: C, 65.27; H, 5.06; N, 5.85. Found: 65.04; H, 4.89; N, 5.62.

3.2.6. 1-(2-(Trifluoromethyl)benzyl)-2,4-dimethyl-1*H*-pyrrole (2f). Yield 89%, oil; ^{1}H NMR δ: 1.99 (s, 3H), 2.18 (s, 3H), 4.89 (s, 2H), 5.57 (s, 1H), 5.88 (s, 1H), 6.89 (d, J=7.6 Hz, 1H), 6.98 (m, 1H), 7.11 (m, 1H), 7.35 (d, J=8.0 Hz, 1H); ^{13}C NMR: δ 11.5, 19.6, 45.1, 108.7, 113.6, 117.3, 120.4, 124.5, 125.7, 128.2, 128.7, 129.3, 131.9, 133.0; ESI MS: (M+1) 254, (M−1) 252; HR ESI MS: Exact mass calcd for $C_{14}H_{14}F_3N$ 253.1078, found: 253.1072.

3.2.7. 1-(2-(Trifluoromethyl)benzyl)-1*H*-pyrazole (2g). Yield 90%, oil; ^{1}H NMR δ: 5.04 (s, 2H), 6.54 (dd, J_1=8.0 Hz, 1H, J_2=6.8 Hz, 1H), 7.02 (d, J=8.0 Hz, 1H), 7.05 (m, 1H), 7.19 (m, 1H), 7.31 (d, J=6.8 Hz, 1H), 7.41 (d, J=8.0 Hz, 1H), 7.55 (d, J=8.0 Hz, 1H); ^{13}C NMR: δ 51.6, 104.3, 117.5, 124.6, 125.8, 127.7, 129.1, 129.6, 132.1, 133.4, 140.2; ESI MS: (M+1) 227, (M−1) 225; HR ESI MS: Exact mass calcd for $C_{11}H_9F_3N_2$ 226.0718, found: 226.0712. Elemental analysis, calcd for $C_{11}H_9F_3N_2$: C, 58.41; H, 4.01; N, 12.38. Found: C, 58.26; H, 3.82; N, 12.12.

3.2.8. 1-(2-(Trifluoromethyl)benzyl)-4-cyclopropyl-1*H*-pyrazole (2h). Yield 87%, oil; ^{1}H NMR δ: 0.35–0.65 (m, 4H), 1.46 (m, 1H), 4.89 (s, 2H), 6.88 (d, J=7.6 Hz, 1H), 6.96 (m, 1H), 7.09 (m, 1H), 7.21 (s, 1H), 7.26 (s, 1H), 7.37 (d, J=8.0 Hz, 1H); ^{13}C NMR: δ 7.9, 8.3, 117.6, 124.8, 125.1, 125.7, 127.5, 129.6, 131.7, 132.8, 133.0, 133.7, 138.4; ESI MS: (M+1) 267, (M−1) 265; HR ESI MS: Exact mass calcd for $C_{14}H_{13}F_3N_2$ 266.1031, found: 266.1026. Elemental analysis, calcd for $C_{14}H_{13}F_3N_2$: C, 63.15; H, 4.92; N, 10.52. Found: C, 62.96; H, 4.75; N, 10.34.

3.2.9. 1-(2-(Trifluoromethyl)benzyl)-4-phenyl-1*H*-pyrazole (2i). Yield 86%, mp 134–135 °C; ^{1}H NMR δ: 4.95 (s, 2H), 6.95 (d, $J = 8.0$ Hz, 1H), 7.02 (m, 1H), 7.12 (m, 1H), 7.19 (m, 1H), 7.25–7.33 (m, 3H), 7.51 (d, $J = 8.0$ Hz, 2H), 8.06 (s, 1H), 8.22 (s, 1H); ^{13}C NMR: δ 53.7, 117.6, 124.9, 125.6, 126.4, 127.4, 127.8, 128.1, 128.5, 129.2, 129.8, 131.6, 132.3, 133.4, 137.1; ESI MS: (M + 1) 303, (M − 1) 301; HR ESI MS: Exact mass calcd for $C_{17}H_{13}F_3N_2$ 302.1031, found: 302.1027. Elemental analysis, calcd for $C_{17}H_{13}F_3N_2$: C, 67.54; H, 4.33; N, 9.27. Found: C, 67.36; H, 4.19; N, 9.13.

3.2.10. 1-(2-(Trifluoromethyl)benzyl)-1*H*-benzo[*d*]-imidazole (2j). Yield 87%, mp 122–123 °C; ^{1}H NMR δ: 5.05 (s, 2H), 6.92 (d, $J = 8.0$ Hz, 1H), 7.04 (m, 1H), 7.14 (m, 1H), 7.22–7.25 (m, 2H), 7.41 (d, $J = 8.0$ Hz, 1H), 7.62 (d, $J = 8.4$ Hz, 1H), 7.76 (d, $J = 8.4$ Hz, 1H), 8.12 (s, 1H); ^{13}C NMR δ: 49.8, 114.6, 115.1, 117.4, 122.3, 122.8, 124.8, 125.7, 127.0, 129.1, 131.8, 133.4, 133.8, 138.5, 144.2; ESI MS: (M + 1) 277, (M − 1) 275; HR ESI MS: Exact mass calcd for $C_{15}H_{11}F_3N_2$ 276.0874, found: 276.0868.

3.3. A typical protocol for the synthesis of 3a–i

A solution of the respective *N*-benzylated heterocycle **2a**–**j** (1 mmol) in 5 mL of dry THF was added to a vigorously stirred solution of freshly prepared LDA (2.5 mmol, diisopropyl amine and *n*-BuLi (2.5 M solution in hexanes)) in the same solvent (20 mL) at −70 °C (dry ice bath) under Ar. The resulting pale yellow mixture was slowly brought to rt (2 h) and stirred for additional 1 h. At this time, the TLC of the reaction mixtures (hexanes/ether, 4:1) indicated presence of highly fluorescent non-polar product and the complete consumption of the starting material. The reaction mixture was quenched with NH_4Cl (15 mL) and extracted with 2 × 20 mL of Et_2O. The organic layer was washed with saturated $NaHCO_3$ (20 mL), dried over anhydrous Na_2SO_4, concentrated and purified by flash chromatography (Silica, hexanes/ether, 5:1) to yield analytically pure fused fluoro isoquinolines **3a**–**i**.

3.4. Analytical data for 3a–i

3.4.1. 11-Fluoroindolo[1,2-*b*]isoquinoline (3a). Yield 44%, mp 184–185 °C; ^{1}H NMR δ: 6.33 (s, 1H), 7.02 (m, 1H), 7.09 (m, 1H), 7.35 (d, $J = 8.4$ Hz, 1H), 7.51 (m, 1H), 7.55 (d, $J = 8.0$ Hz, 1H), 7.61 (m, 1H), 7.74 (d, $J = 7.6$ Hz, 1H), 7.88 (d, $J = 8.0$ Hz, 1H), 9.01 (s, 1H); ^{19}F NMR: −112.7; ^{13}C NMR: 99.8, 112.2, 113.5, 118.8, 119.6, 120.0, 120.5, 122.4, 125.9, 126.7, 128.1, 128.9, 130.8, 131.1, 149.0, 151.6; ESI MS: (M + 1) 236, (M − 1) 234; HR ESI MS: Exact mass calcd for $C_{16}H_{10}FN$ 235.0797, found: 235.0788. Elemental analysis, calcd for $C_{16}H_{10}FN$: C, 81.69; H, 4.28; N, 5.95. Found: C, 81.55; H, 4.19; N, 5.84.

3.4.2. 11-Fluoro-2-methoxyindolo[1,2-*b*]isoquinoline (3b). Yield 43%, mp 214–216 °C; ^{1}H NMR δ: 3.65 (s, 3H), 6.23 (s, 1H), 6.49 (d, $J = 7.6$ Hz, 1H), 6.95 (s, 1H), 7.33 (d, $J = 7.6$ Hz, 1H), 7.44 (m, 1H), 7.54 (m, 1H), 7.69 (d, $J = 8.4$ Hz, 1H), 7.83 (d, $J = 8.4$ Hz, 1H), 8.85 (s, 1H); ^{19}F NMR: −112.2; ^{13}C NMR: 56.1, 99.1, 101.8, 110.2, 111.5, 113.2, 119.0, 119.9, 126.1, 126.4, 128.2, 128.5, 130.4, 131.3, 148.2, 150.8, 155.37; ESI MS (M + 1) 266, (M − 1) 264; HR ESI MS: Exact mass calcd for $C_{17}H_{12}FNO$ 265.0903, found: 265.0896. Elemental analysis, calcd for $C_{17}H_{12}FNO$: C, 76.97; H, 4.56; N, 5.28. Found: C, 76.82; H, 4.10; N, 5.12.

3.4.3. 2-Chloro-11-fluoroindolo[1,2-*b*]isoquinoline (3c). Yield 52%, mp 236–238 °C; ^{1}H NMR δ: 6.25 (s, 1H), 6.98 (d, $J = 7.6$ Hz, 1H), 7.32 (d, $J = 7.6$ Hz, 1H), 7.44 (m, 1H), 7.51 (s, 1H), 7.55 (m, 1H), 7.66 (d, $J = 8.4$ Hz, 1H), 7.84 (d, $J = 8.4$ Hz, 1H), 8.89 (s, 1H); ^{19}F NMR: −112.9; ^{13}C NMR: 99.3, 112.2, 114.0, 118.6, 119.5, 120.1, 120.9, 125.6, 126.0, 126.7, 127.4, 128.3, 130.7, 131.2, 148.2, 152.2; ESI MS: (M + 1) 271, (M − 1) 269; HR ESI MS: Exact mass calcd for $C_{16}H_9ClFN$ 269.0408, found: 269.0402. Elemental analysis, calcd for $C_{16}H_9ClFN$: C, 71.25; H, 3.36; N, 5.19. Found: C, 71.37; H, 3.52; N, 5.02.

3.4.4. 10-Fluoropyrrolo[1,2-*b*]isoquinoline (3d). Yield 38%, mp 156–157 °C; ^{1}H NMR δ: 6.22 (d, $J = 6.8$ Hz, 1H), 6.61 (m, 1H), 7.10 (d, $J = 7.0$ Hz, 1H), 7.42 (m, 1H), 7.50 (m, 1H), 7.62 (d, $J = 8.0$ Hz, 1H), 7.77 (d, $J = 8.0$ Hz, 1H), 8.81 (s, 1H); ^{19}F NMR: −111.5; ^{13}C NMR: 105.2, 112.6, 114.3, 119.4, 126.1, 126.5, 127.8, 128.3, 130.5, 131.1, 147.6, 150.9; ESI MS: (M + 1) 186, (M − 1) 184; HR ESI MS: Exact mass calcd for $C_{12}H_8FN$ 185.0641, found: 185.0633. Elemental analysis, calcd for $C_{12}H_8FN$: C, 77.82; H, 4.35; N, 7.56. Found: C, 77.95; H, 4.51; N, 7.41.

3.4.5. 10-Fluoro-3-methylpyrrolo[1,2-*b*]isoquinoline (3e). Yield 39%, mp 137–138 °C; ^{1}H NMR δ: 2.16 (s, 3H), 6.08 (d, $J = 6.4$ Hz, 1H), 6.42 (d, $J = 6.4$ Hz, 1H), 7.50 (m, 1H), 7.53 (m, 1H), 7.75 (d, $J = 8.4$ Hz, 1H), 7.89 (d, $J = 8.4$ Hz, 1H), 8.83 (s, 1H); ^{19}F NMR: −112.1; ^{13}C NMR: 17.0, 106.1, 114.6, 120.1, 125.4, 126.1, 126.7, 128.2, 128.9, 130.5, 131.7, 149.1, 152.0; ESI MS: (M + 1) 200, (M − 1) 198; HR ESI MS: Exact mass calcd for $C_{13}H_{10}FN$ 199.0797, found: 199.0788. Elemental analysis, calcd for $C_{13}H_{10}FN$: C, 78.37; H, 5.06; N, 7.03. Found: C, 78.48; H, 5.24; N, 6.81.

3.4.6. 10-Fluoro-1,3-dimethylpyrrolo[1,2-*b*]isoquinoline (3f). Yield 48%, mp 151–152 °C; ^{1}H NMR δ: 1.99 (s, 3H), 2.21 (s, 3H), 6.05 (s, 1H), 7.39 (m, 1H), 7.46 (m, 1H), 7.65 (d, $J = 8.0$ Hz, 1H), 7.73 (d, $J = 8.0$ Hz, 1H), 8.82 (s, 1H); ^{19}F NMR: −112.1; ^{13}C NMR: 15.9, 16.4, 108.8, 117.9, 119.3, 125.6, 125.9, 126.5, 127.6, 128.0, 130.3, 131.1, 147.6, 151.2; ESI MS: (M + 1) 214, (M − 1) 212; HR ESI MS: Exact mass calcd for $C_{14}H_{12}FN$ 213.0954, found: 213.0942. Elemental analysis, calcd for $C_{14}H_{12}FN$: C, 78.85; H, 5.67; N, 6.57. Found: C, 78.66; H, 5.81; N, 6.33.

3.4.7. 4-Fluoro-pyrazolo[1,5-*b*]isoquinoline (3g). Yield 51%, mp 165–166 °C; ^{1}H NMR δ: 6.32 (d, $J = 8.8$ Hz, 1H), 7.47 (m, 1H), 7.61 (m, 1H), 7.73 (d, $J = 8.4$ Hz, 1H), 7.82 (d, $J = 8.8$ Hz, 1H), 7.90 (d, $J = 8.4$ Hz, 1H), 8.99 (s, 1H); ^{19}F NMR: −113.7; ^{13}C NMR: 97.5, 119.5, 125.8, 126.7, 128.3, 129.1, 130.4, 131.9, 135.0, 149.3, 152.2; ESI MS: (M + 1) 187, (M − 1) 185; HR ESI MS: Exact mass calcd for $C_{11}H_7FN_2$ 186.0593, found: 186.0584. Elemental analysis, calcd for $C_{11}H_7FN_2$: C, 70.96; H, 3.79; N, 15.05. Found: C, 70.73; H, 3.86; N, 14.87.

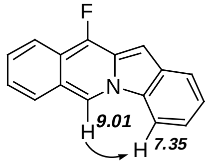
3.4.8. 3-Cyclopropyl-4-fluoro-pyrazolo[1,5-*b*]isoquinoline (3h). Yield 44%, mp 203–205 °C; ^{1}H NMR δ: 0.4–0.65 (m, 4H), 1.45 (m, 1H), 7.51 (m, 1H), 7.58 (m, 1H), 7.66 (s, 1H), 7.72 (d, $J=8.4$ Hz, 1H), 7.88 (d, $J=8.4$ Hz, 1H), 8.90 (s, 1H); ^{19}F NMR: -113.2; ^{13}C NMR: 6.3, 8.9, 114.9, 119.7, 125.9, 126.7, 128.3, 127.5, 130.8, 131.1, 132.5, 148.0, 152.0; ESI MS: (M+1) 227, (M−1) 225; HR ESI MS: Exact mass calcd for $C_{14}H_{11}FN_2$ 226.0906, found: 226.0894. Elemental analysis, calcd for $C_{14}H_{11}FN_2$: C, 74.32; H, 4.90; N, 12.38. Found: C, 74.21; H, 4.78; N, 12.22.

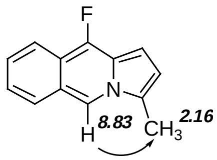
3.4.9. 4-Fluoro-3-phenyl-pyrazolo[1,5-*b*]isoquinoline (3i). Yield 57%, mp 236–238 °C; ^{1}H NMR δ: 7.18 (m, 1H), 7.28 (m, 2H), 7.50–7.55 (m, 3H), 7.58 (m, 1H), 7.69 (d, $J=8.4$ Hz, 1H), 7.88 (d, $J=8.4$ Hz, 1H), 8.70 (s, 1H), 8.94 (s, 1H); ^{19}F NMR: -113.8; ^{13}C NMR: 119.2, 125.0, 125.9, 126.7, 127.4, 128.2, 128.4, 128.7, 129.2, 130.6, 130.9, 131.3, 136.2, 147.8, 152.3; ESI MS: (M+1) 263, (M−1) 261; HR ESI MS: Exact mass calcd for $C_{17}H_{11}FN_2$ 262.0906, found: 262.0888. Elemental analysis, calcd for $C_{17}H_{11}FN_2$: C, 77.85; H, 4.23; N, 10.68. Found: C, 77.64; H, 4.12; N, 10.52.

3.4.10. Synthesis of 2-((1*H*-pyrazol-1-yl)methyl)benzonitrile (5g). A solution of KHMDS in toluene (2.5 mmol) was added to a vigorously stirred solution of **2g** (1 mmol) in dry degassed THF at −78 °C (acetone/dry ice bath). The resulting pale yellow mixture was stirred at this temperature for an additional 30 min, slowly brought up to 0 °C (2 h) and stirred at 0 °C for an additional 1 h, until LC MS of the reaction mixture revealed the absence of a starting material. The resulting dark red homogenous solution was concentrated in vacuo at rt, and the residue was partitioned between EtOAc (20 mL) and 10% aq NH_4Cl. Aqueous phase was extracted with an addl 10 mL of EtOAc, the organic phases were combined, dried over Na_2SO_4, concentrated and purified by flash-chromatography (hexanes/Et_2O, 1:1) over Silica to yield analytically pure **5g** in 44% yield, mp 131–132 °C; ^{1}H NMR δ: 5.02 (s, 2H), 6.38 (dd, $J_1=7.6$ Hz, $J_2=6.4$ Hz, 1H), 7.21–7.24 (m, 2H), 7.32 (d, $J=7.6$ Hz, 1H), 7.40 (d, $J=8.0$ Hz, 1H), 7.45 (m, 1H), 7.56 (d, $J=6.4$ Hz, 1H); ESI MS: (M+1) 184, (M−1) 182; HR ESI MS: Exact mass calcd for $C_{11}H_9N_3$ 183.0796, found: 183.0791.

References and notes

1. (a) Kiselyov, A. S.; Strekowski, L. *Org. Prep. Proced. Int.* **1996**, *28*, 289–318 and references cited therein. (b) Strekowski, L.; Kiselyov, A. S. *Trends Heterocycl. Chem.* **1993**, 73–82.
2. Hojjat, M.; Kiselyov, A. S.; Strekowski, L. *Synth. Commun.* **1994**, *24*, 267–272.
3. Kiselyov, A. S.; Hojjat, M.; Van Aken, K.; Strekowski, L. *Heterocycles* **1994**, *37*, 775–782.
4. Wydra, R. L.; Patterson, S. E.; Strekowski, L. *J. Heterocycl. Chem.* **1990**, *27*, 803–805.
5. Strekowski, L.; Lin, S.-Y.; Nguyen, J.; Redmore, N. P.; Mason, J. C.; Kiselyov, A. S. *Heterocycl. Commun.* **1995**, *1*, 331–334.
6. Strekowski, L.; Wydra, R. L.; Kiselyov, A. S.; Baird, J. H.; Burritt, A.; Coxon, J. M. *Synth. Commun.* **1994**, *24*, 257–266.
7. (a) Strekowski, L.; Patterson, S. E.; Janda, L.; Wydra, R. L.; Harden, D. B.; Lipowska, M.; Cegla, M. T. *J. Org. Chem.* **1992**, *57*, 196–201. (b) Strekowski, L.; Wydra, R. L.; Cegla, M. T.; Czarny, A.; Harden, D. B.; Patterson, S. E.; Battiste, M. A.; Coxon, J. M. *J. Org. Chem.* **1990**, *55*, 4777–4779. (c) Janda, L.; Nguyen, J.; Patterson, S. E.; Strekowski, L. *J. Heterocycl. Chem.* **1992**, *29*, 1753–1756.
8. Strekowski, L.; Wydra, R.; Harden, D. B.; Honkan, V. A. *Heterocycles* **1990**, *31*, 1565–1569.
9. Smith, L.; Kiselyov, A. S. *Tetrahedron Lett.* **1999**, *40*, 5643–5646.
10. (a) Kiselyov, A. S. *Tetrahedron* **2001**, *57*, 5321–5326. (b) Kiselyov, A. S. *Tetrahedron Lett.* **2001**, *42*, 3053–3056. (c) Kiselyov, A. S.; Strekowski, L. *Tetrahedron Lett.* **1994**, *35*, 7597–7600.
11. Strekowski, L.; Kiselyov, A. S.; Hojjat, M. *J. Org. Chem.* **1994**, *59*, 5886–5890.
12. Kiselyov, A. S.; Piatnitski, E. L.; Doody, J. *Org. Lett.* **2004**, *6*, 4061–4063.
13. Regiochemistry of substitution was further confirmed by NOE experiments:





.

Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron

Tetrahedron 62 (2006) 549–555

Study on the reactions of fluoroalkanesulfonyl azides with cycloalkenyl ether and aryl ynamines

Ping He[a] and Shizheng Zhu[a,b,*]

[a]*Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China*
[b]*School of Chemistry and Environment, South China Normal University, Guangzhou 510631, China*

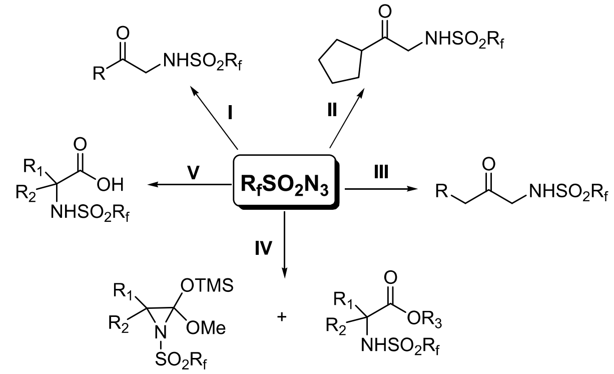
Received 18 August 2005; revised 9 October 2005; accepted 11 October 2005

Abstract—The reactions of fluoroalkanesulfonyl azides **1** with some electron-rich compounds have been studied in detail. Cycloalkenyl vinyl ethers reacted with **1** readily at 0 °C to give the corresponding ring-contraction *N*-fluoroalkanesulfonyl amidine analogues **3**. In contrast, aryl ynamine generated in situ reacted with **1** affording fluorinated α-diazoamidines **9**, which were decomposed slowly at room temperature to form [1-diethylamino-2-(4-nitro-phenyl)-2-oxo-eth-(*Z*)-ylidene]-fluoroalkanesulfinyl imine **10** with elimination of nitrogen gas. Possible mechanisms for these reactions were proposed.

1. Introduction

Organic azides are versatile starting materials for the synthesis of a variety of nitrogen-containing compounds. The azido group can react with both nucleophilic and electrophilic reagents and can be used in 1,3-dipolar cycloaddition reactions. For example, Semenov[1] once studied the reaction of arylsulfonyl azides with 2-methoxy-1-phenyl-1-butene affording methyl *N*-arylsulfony-2-phenylbutyrimidates and *N*-(2-methoxy-1-phenyl-1-butenyl) arenesulfonamides, which were formed by decomposition of the unstable triazoline intermediates followed by the elimination of N_2 and the migration of hydrogen or ethyl group. Meanwhile they also reported the reactions of arylsulfonyl azides with cycloalkenyl ether and the expected ring-contraction products were obtained. It was noteworthy that all reactions were carried out under heating (∼80 °C) conditions.

It has been well documented that the replacement of a hydrogen atom by a fluorine atom or a fluoroalkyl group in an organic molecule may profoundly influence its physical and biological properties.[2] Fluoroalkanesulfonyl azides **1** are more reactive than other nonfluorinated organic azides due to the strong electron-withdrawing property of the R_fSO_2 group. Since 1992 we have systematically studied their reactions with electron-rich olefins such as silyl enol ethers,[3] acyclic and cyclic vinyl ethers,[4] enamines etc.[5] Among them, the reactions of **1** and sily enol ethers afforded a novel approach to the formation of *N*-sulfonyl protected α-amino ketones, α-amino acids and β-amino-α-keto esters, respectively, (Scheme 1). Although various substrates containing enamine structure such as indole, carbazole and tetrakis(dimethylamino)ethylene (TDAE) were studied extensively, however, ynamine was still investigated rarely due to its relative difficult preparation and its easily hydrolysis. During our continued studying on the fluoroalkanesulfonyl azides **1**, we found that they reacted



Reagents and conditions: (**I**) Silyl enol ethers, 0 °C; (**II**) Cyclic silyl enol ethers, 0 °C; (**III**) RCH=CHOTMS, 0 °C; (**IV**) Silyl ketene acetals, 0 °C; (**V**) Disilyl ketene acetals, 0 °C.

Scheme 1.

Keywords: Fluoroalkanesulfonyl azides; Cycloalkenyl ether; Ynamine; 1,3-Dipolar cycloaddition; Triazolines.

* Corresponding author. Tel.: +86 21 54925184; fax: +86 21 64166128; e-mail: zhusz@mail.sioc.ac.cn

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.10.023

smoothly at 0 °C or room temperature with cycloalkenyl ethers and in situ generated ynamine. Herein we report these results and discuss the reaction mechanisms.

2. Results and discussion

In our previous work on $R_fSO_2N_3$ **1**, we found that the reactions of acyclic and cyclic vinyl ethers gave two different products. In the case of acyclic vinyl ether it afforded the stable cycloproducts 1-fluoroalkanesulfonyl 1,2,3-triazolines.[4b] However, the reaction of **1** with dihydropyran did not give the corresponding *N*-fluoroalkanesulfonyl azilidines but *N*-fluoroalkanesulfonyl-tetrahydropyranon-2-imines.[4a] Similar to vinyl ether and dihydropyran, cycloalkenyl ether **2**, derived from cycloketone, containing an electron-rich double bond, reacted smoothly with **1** at 0 °C, this reaction finished within 10 min (monitored by TLC).

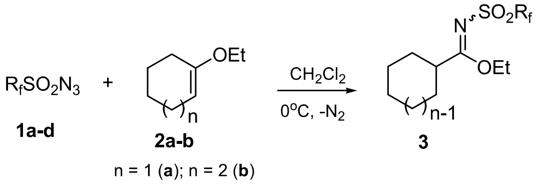
To a solution of cyclohexenyl ether **2a** in anhydrous CH_2Cl_2 was added slowly 1.33 equimolar amount of fluoroalkanesulfonyl azides **1a** at 0 °C, the nitrogen gas was released immediately. TLC analysis showed that the vinyl ether **2a** disappeared within 10 min and only one product was formed. According to the spectra data, the product was easily determined as an expected ring-contraction *N*-fluoroalkanesulfonyl amidine analogue **3aa**. The MS spectrum of **3aa** showed its quasi-molecular ion peak at *m*/*z* 548. A fragmental ion observed at *m*/*z* 69 indicated a cyclopentyl group should be involved in the molecular structure. Meanwhile a typical strong absorption at 1582 cm^{-1} in IR spectrum confirmed the existence of C=N functional group. By comparison of the ^1H NMR spectra of **2a** and **3aa**, it was observed that in **3aa** the two signals of ethoxy group (EtO) were shifted to lower field and a new multiple peak appeared at δ 3.49 ppm, which could be assigned to the CH linking cyclopentyl to other groups in the molecule. Combined with the elemental analysis result **3aa** was identified as 1-cyclopentyl-1-ethoxyl-*N*-fluoroalkanesulfonyl imine. Under the same reaction conditions other azides **1b–d** reacted with equimolar amount of **2a–b** gave the similar results. All these results were summarized in Table 1 (Scheme 2).

It was found in Table 1 that all the reactions finished within 10 min and the ring size of the cycloalkenyl ether had some influenced on the yields of **3**. In the case of the larger ring substrate cycloheptenyl ether **2b**, the relative lower yields were always obtained compared with that of cyclohexenyl ether **2a**, which might be due to the effect of the size of the ring in the ring-contraction process during the formation of **3**. According to previous studies and the above results, the possible mechanism for the formation of **3** was proposed (Scheme 3).

Table 1. Reaction results of fluoroalkanesulfonyl azides with cycloalkenyl ethers

Entry	Azides	Vinyl ether	Time (min)	Product	Yields[a]
1	**1a**	**2a**	10	**3aa**	71
2	**1b**	**2a**	10	**3ba**	70
3	**1c**	**2a**	10	**3ca**	61
4	**1d**	**2a**	10	**3da**	58
5	**1a**	**2b**	10	**3ab**	42
6	**1b**	**2b**	10	**3bb**	57
7	**1c**	**2b**	10	**3cb**	55
8	**1d**	**2b**	10	**3db**	53

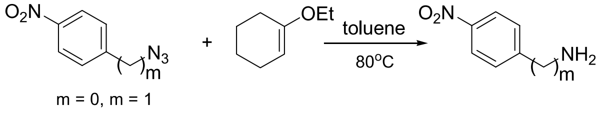
[a] Isolated yields.



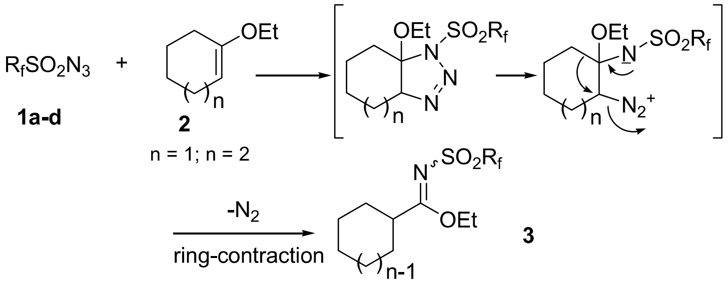
Scheme 2.

The reactions of fluoroalkanesulfonyl azides **1** with the six- and seven-membered cycloalkenyl ether **2a** (**2b**) afforded the ring-contraction products **3**, then how about the five-membered cyclopentenyl ether **2c**? Due to the larger tension of four-membered compound are very labile, the formation of ring-contraction product in the case of **2c** is impossible. Literature[6] reported that under heating the reaction of TsN_3 with **2c** in acetone could afford 1,2-disubstituted cyclopentene derivatives in high yield. However, under the similar reaction conditions (0 °C, 10 min), whatever solvents (CH_2Cl_2, Et_2O, CH_3CN, acetone) were used in the reaction of azide **1** and **2c**, the fluoroalkanesulfonyl amine $R_fSO_2NH_2$ was obtained as the major product (determined by the following ^{19}F NMR). In addition, another product, which had unsaturated bond (determined by $KMnO_4$ solution) and no fluorine atom (determined by ^{19}F NMR) was also isolated by the column chromatography, but due to its low boiling point it was removed completely when dried by oil pump.

During our investigation on the fluoroalkanesulfonyl azide **1**, we noticed that the similar reactions of electron-rich aryl azide **4** with **2** were studied rarely. Then our focus was turned to the reaction of aryl azides. It was found that no reaction occurred when 4-nitro-phenylazide **4a** reacted with cyclohexenyl ether **2a** at room temperature even it was prolonged to 12 h (monitored by TLC). Then heating the reaction up to 80 °C in toluene within 48 h, TLC analysis showed that the azide **4a** was not consumed completely and a new product was formed. After general work-up and recycling the unreacted **4a**, the new product, obtained in 86% yield, was identified as the corresponding 4-nitrophenylamine.[7] The same phenomena were also observed in the reaction of the 4-nitro-benzylazide with **2a**, the corresponding 4-nitro-benzylamine was also isolated.

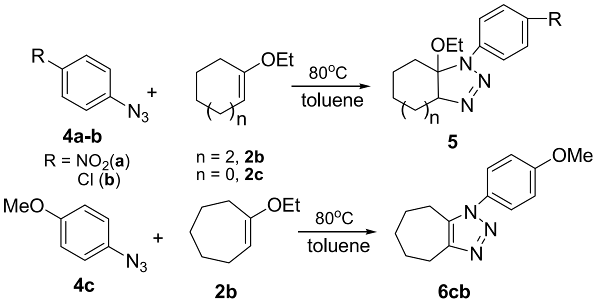


However, under the same reaction condition when mixing 4-nitro-phenylazide **4a** with cycloheptenyl ether **2b** the regiospecific [3+2] cycloadduct **5ab** was isolated successfully. This was further confirmed by the results of the reaction of **4a** and cyclopentenyl ether **2c**, the spectra data of cycloadduct **5ac** were consistence with the



Scheme 3.

literature.[8] Then other aryl azides **4b–c** were also applied to this reaction protocol (Scheme 4) and the results were listed in Table 2.



Scheme 4.

Table 2. Reaction results of aryl azides with cycloalkenyl ethers

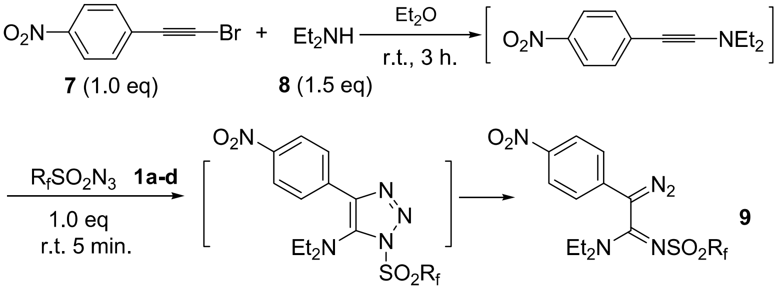
Entry	Azides (R=)	Vinyl ethers	Time (h)	Products	Yields[a]
1	R=NO_2 **4a**	**2b**	48	**5ab**	83
2	R=NO_2 **4a**	**2c**	48	**5ac**	77
3	R=Cl **4b**	**2b**	24	**5bb**	36
4	R=CH_3O **4c**	**2b**	48	**6cb**	40

[a] Based on the real azides participated in the reaction.

As seen in Table 2, the substituent R in aryl azides **4** had significant impact on the product and the isolated yields. During the same reaction time (48 h), the aryl azide with electron-rich substituent could react faster than that with electron-withdrawing one. Thus, a further elimination of one EtOH occurred and polysubstituted triazole **6cb** in stead of the corresponding **5cb** was obtained (Table 2, entry 1, 4). Meanwhile, the aryl azide with electron-withdrawing substitutent had higher isolated yields. When R=NO_2 the yield was 83%; however, when R=Cl the yield was decreased to 36% (Table 2, entry 1, 3).

In addition, the reactions of fluoroalkanesulfonyl azides **1** with ynamine were also studied. Considered the ynamine's easily hydrolysis, the 1,3-dipolar addition of fluoroalkanesulfonyl azide **1a** to *N*,*N*-diethylamino-*p*-nitrophenylacetylene generated in situ from 4-nitro-phenylacetylene bromide **7** and diethylamine **8** in anhydrous ether at room temperature was first investigated. No nitrogen gas was released and the reaction was finished in 5 min (monitored by TLC). The reaction mixture was directly purified by chromatography to afford the pure product *N*-[2-diazo-1-diethylamino-2-(4-nitro-phenyl)-eth-(*E*)-ylidene]-fluoroalkanesulfonyl imine **9a** in 75% yield (Scheme 5). A strong absorption at 2080 cm^{-1} in IR spectrum was observed, which was the typical absorption of $C=N^+=N^-$. Other azides **1**(**b–d**) reacted with arylacetylene bromide and diethyl amine gave similar α-diazoamidines in moderate yields. All these results were summarized in Table 3.

It was noteworthy that the α-diazoamidines **9** were unstable when kept at room temperature within 1–2 days and



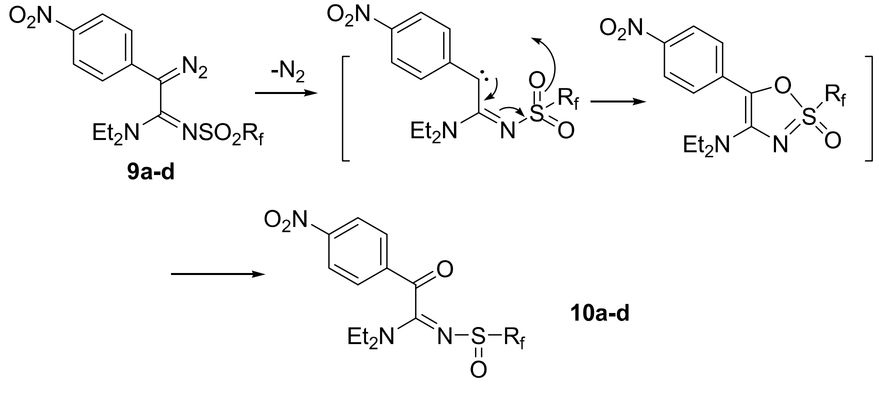
Scheme 5.

Table 3. Reaction results of fluoroalkanesulfonyl azides with arylynamine[a]

Entry	Azides	Arylacetylene bromide	Amine	Products	Yields (%)[b]
1	**1a**	**7**	**8**	**9a**	75
2	**1b**	**7**	**8**	**9b**	68
3	**1c**	**7**	**8**	**9c**	65
4	**1d**	**7**	**8**	**9d**	84

[a] Arylynamine was generated from **7** (1.0 equiv) and **8** (1.5 equiv).

[b] Isolated yields based on azides.



Scheme 6.

decomposed gradually and converted into a new product **10** completely when it was exposed for a certain time. By comparison of the spectra data of **9** and **10**, it was found that in IR spectrum the strong absorption of diazo group (2080 cm^{-1}) was disappeared and a new strong absorption was observed at 1694 cm^{-1}, which might be attributed to the existence of conjugated carbonyl structure in **10**. The total numbers of hydrogen and fluorine atoms were retained as indicated in ^1H and ^{19}F NMR spectra, however, the chemical shifts and peak shapes of all protons in **10** had obvious changes, especially the chemical shift of fluorine signal attached to the sulfonyl (SO_2CF_2) changed from -116.7 to -125.6 ppm ($\Delta\delta$: $\sim$9 ppm), which maybe resulted from the participation of sulfonyl group for the formation of product **10**. Other spectra data (MS, IR) and elemental analysis results substantiated the deduction and the possible mechanism was also proposed (Scheme 6).

3. Conclusions

In summary, the reactions of fluoroalkanesulfonyl azides **1** with cycloalkenyl ether and ynamine were studied in detail. A ring-contraction *N*-fluoroalkanesulfonyl amidine analogues **3** were obtained when **1** was reacted with cycloalkenyl vinyl ethers at 0 °C. On the other hand, in the case of aryl ynamine with **1** afforded fluorinated α-diazoamidines **9**, which were decomposed gradually at room temperature to form [1-diethylamino-2-(4-nitro-phenyl)-2-oxo-eth-(*Z*)-ylidene]-fluoroalkanesulfinyl imine **10**. Further chemical transformations of the fluorinated products are under way in our laboratory.

4. Experimental

Melting points were measured in Temp-Melt apparatus and were uncorrected. ^1H and ^{19}F NMR spectra were recorded in $CDCl_3$ (unless mentioned in text), Bruker AM-300 instruments with Me_4Si and $CFCl_3$ (with upfield negative) as the internal and external standards, respectively. IR spectra were obtained with a Nicolet AV-360 spectrophotometer. Lower resolution mass spectrum or high-resolution mass spectra (HRMS) were obtained on a Finnigan GC–MS 4021 or a Finnigan MAT-8430 instrument using the electron impact ionization technique (70 eV), respectively. Elemental analyses were performed by this Institute. All solvents were purified before use. Fluoroalkanesulfonyl azides **1**, cycloalkenyl ether **2** and arylacetylene bromide were prepared according to literature.[9–11]

4.1. General procedure for the reaction of fluoroalkanesulfonyl azides with cycloalkenyl ether

To a 10 mL round-bottom flask containing 1-ethoxycyclohexene **2a** (189 mg, 1.5 mmol) in 2 mL anhydrous CH_2Cl_2 was added slowly fluoroalkanesulfonyl azides **1a** (0.898 g, 2.0 mmol) at room temperature within 2 min. Then the mixture was continuously stirred at room temperature within 10 min until TLC analysis shown the reaction finished. The solvent was evaporated and the residue was purified on a silica column using petroleum ether–ether (50/1 v:v) as the eluant to give pure product **3aa** as a colorless oil (580 mg, 71%).

4.1.1. 1-Cyclopentyl-1-ethoxy-meth-(*Z*)-ylidene-(5′-iodo-3′-oxa-octafluoropentyl)-sulfonyl imine (3aa). Colorless oil. ^1H NMR ($CDCl_3$, 300 MHz): δ 4.29 (2H, q, $J=7.2$ Hz), 3.53–3.43 (1H, m), 2.14–2.03 (2H, m), 1.86–1.59 (6H, m), 1.36 (3H, t, $J=7.2$ Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ -65.3 (2F, t, $J=6.1$ Hz, ICF_2), -81.4 (2F, t, $J=12.8$ Hz, CF_2O), -85.9 (2F, m, OCF_2), -117.8 (2F, s, CF_2S). IR (KBr) cm^{-1}: 2970, 2878, 1582, 1326, 1292, 1188, 1145, 914. MS: *m*/*z* (%) 548 ($M^+ + 1$, 25), 478 ($M^+ - C_5H_9$, 8), 227 ($IC_2F_4^+$, 5), 96 ($M^+ + 1 - R_fSO_2$–OEt, 100), 69 ($C_5H_9^+$, 65). Anal. Calcd for $C_{12}H_{14}F_8INO_4S$: C, 26.34; H, 2.58; N, 2.56%. Found: C, 26.47; H, 2.92; N, 2.59%.

4.1.2. 1-Cyclopentyl-1-ethoxy-meth-(*Z*)-ylidene-(5′-chloro-3′-oxa-octafluoropentyl)-sulfonyl imine (3ba). Colorless oil. ^1H NMR ($CDCl_3$, 300 MHz): δ 4.29 (2H, q, $J=7.2$ Hz), 3.54–3.47 (1H, m), 2.14–2.05 (2H, m), 1.84–1.63 (6H, m), 1.35 (3H, t, $J=7.2$ Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ -74.2 (2F, s, $ClCF_2$), -81.5 (2F, t, $J=12.8$ Hz, CF_2O), -87.2 (2F, t, $J=12.8$ Hz, OCF_2), -117.9 (2F, s, CF_2S). IR (KBr) cm^{-1}: 2970, 2867, 1584, 1361, 1307, 1174, 1143, 970. MS: *m*/*z* (%) 457/455 (M^+, 2/6), 416/414 ($M^+ - C_3H_5$, 23/60), 388/386 ($M^+ - C_5H_9$, 38/100), 96 ($M^+ + 1 - R_fSO_2$–OEt, 87), 69 ($C_5H_9^+$, 59). Anal. Calcd for $C_{12}H_{14}ClF_8NO_4S$: C, 31.63; H, 3.10; N, 3.07%. Found: C, 31.71; H, 3.12; N, 3.38%.

4.1.3. 1-Cyclopentyl-1-ethoxy-meth-(*Z*)-ylidene-(1′,1′,2′,2′,4′,4′,5′,5′-octafluoro-3′-oxa-pentyl)-sulfonyl imine

(3ca). Colorless oil. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 5.87 (1H, tt, $J=3.0$, 52.8 Hz), 4.29 (2H, q, $J=7.2$ Hz), 3.52–3.48 (1H, m), 2.14–2.05 (2H, m), 1.86–1.61 (6H, m), 1.35 (3H, t, $J=7.2$ Hz). ^{19}F NMR (CDCl$_3$, 282 MHz): δ -81.2 (2F, t, $J=13.1$ Hz, CF$_2$O), -89.0 (2F, m, OCF$_2$), -118.0 (2F, s, CF$_2$S), -137.9 (2F, d, $J=52.7$ Hz, HCF$_2$). IR (KBr) cm^{-1}: 2968, 2879, 1583, 1359, 1326, 1144, 1010, 907. MS: *m/z* (%) 421 (M$^+$, 1), 380 (M$^+$ $-$C$_3$H$_5$, 8), 352 (M$^+$ $-$C$_5$H$_9$, 18), 96 (M$^+$ $+1-$R$_f$SO$_2$–EtO, 100), 69 (C$_5$H$_9^+$, 54). Anal. Calcd for C$_{12}$H$_{15}$F$_8$NO$_4$S: C, 34.21; H, 3.59; N, 3.32%. Found: C, 34.32; H, 3.59; N, 3.27%.

4.1.4. 1-Cyclopentyl-1-ethoxy-meth-(*Z*)-ylidene-perfluorobutylsulfonyl imine (3da). Colorless oil. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 4.30 (2H, q, $J=7.2$ Hz), 3.53–3.48 (1H, m), 2.12–2.06 (2H, m), 1.85–1.64 (6H, m), 1.36 (3H, t, $J=7.2$ Hz). ^{19}F NMR (CDCl$_3$, 282 MHz): δ -81.2 (3F, t, $J=8.5$ Hz, CF$_3$), -114.4 (2F, t, $J=13.8$ Hz, CF$_2$), -121.3 (2F, t, $J=4.8$ Hz, CF$_2$S), -126.5 (2F, t, $J=14.1$ Hz, CF$_2$). IR (KBr) cm^{-1}: 2967, 2878, 1583, 1360, 1237, 1140, 1012. MS: *m/z* (%) 382 (M$^+$ $-$C$_3$H$_5$, 12), 354 (M$^+$ $-$C$_5$H$_9$, 25), 96 (M$^+$ $+1-$R$_f$SO$_2$–EtO, 100), 69 (C$_5$H$_9^+$, 93). Anal. Calcd for C$_{12}$H$_{14}$F$_9$NO$_3$S: C, 34.05; H, 3.33; N, 3.31%. Found: C, 34.14; H, 3.36; N, 3.31%.

4.1.5. 1-Cyclohexyl-1-ethoxy-meth-(*Z*)-ylidene-(5′-iodo-3′-oxa-octafluoropentyl)-sulfonyl imine (3ab). Colorless oil. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 4.29 (2H, q, $J=7.2$ Hz), 3.16–3.09 (1H, m), 2.01–1.42 (8H, m), 1.36 (3H, t, $J=7.2$ Hz), 1.32–1.20 (2H, m). ^{19}F NMR (CDCl$_3$, 282 MHz): δ -65.1 (2F, t, $J=5.8$ Hz, ICF$_2$), -81.3 (2F, t, $J=13.3$ Hz, CF$_2$O), -85.7 (2F, m, OCF$_2$), -117.5 (2F, s, CF$_2$S). IR (KBr) cm^{-1}: 2938, 2861, 1584, 1332, 1292, 1186, 1146, 915. MS: *m/z* (%) 561 (M$^+$, 1), 478 (M$^+$ $-$C$_6$H$_{11}$, 3), 227 (IC$_2$F$_4^+$, 8), 110 (M$^+$ $+1-$R$_f$SO$_2$–OEt, 100), 83 (C$_6$H$_{11}^+$, 65). Anal. Calcd for C$_{13}$H$_{16}$F$_8$INO$_4$S: C, 27.82; H, 2.87; N, 2.50%. Found: C, 27.89; H, 2.93; N, 2.46%.

4.1.6. 1-Cyclohexyl-1-ethoxy-meth-(*Z*)-ylidene-(5′-chloro-3′-oxa-octafluoropentyl)-sulfonyl imine (3bb). Colorless oil. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 4.28 (2H, q, $J=7.2$ Hz), 3.16–3.07 (1H, m), 2.01–1.40 (8H, m), 1.36 (3H, t, $J=7.2$ Hz), 1.32–1.19 (2H, m). ^{19}F NMR (CDCl$_3$, 282 MHz): δ -74.1 (2F, s, ClCF$_2$), -81.3 (2F, t, $J=13.7$ Hz, CF$_2$O), -87.1 (2F, t, $J=12.6$ Hz, OCF$_2$), -117.6 (2F, s, CF$_2$S). IR (KBr) cm^{-1}: 2939, 2862, 1585, 1360, 1305, 1187, 1142, 977. MS: *m/z* (%) 471/469 (M$^+$, 0.6/1.6), 388/386 (M$^+$ $-$C$_6$H$_{11}$, 2/5), 110 (M$^+$ $+1-$R$_f$SO$_2$–OEt, 100), 83 (C$_6$H$_{11}^+$, 71). Anal. Calcd for C$_{13}$H$_{16}$ClF$_8$NO$_4$S: C, 33.24; H, 3.43; N, 2.98%. Found: C, 33.23; H, 3.43; N, 2.90%.

4.1.7. 1-Cyclohexyl-1-ethoxy-meth-(*Z*)-ylidene-(1′,1′,2′,2′,4′,4′,5′,5′-octafluoro-3′-oxa-pentyl)-sulfonyl imine (3cb). Colorless oil. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 5.87 (1H, tt, $J=3.0$, 52.5 Hz), 4.29 (2H, q, $J=7.2$ Hz), 3.17–3.07 (1H, m), 2.01–1.40 (8H, m), 1.36 (3H, t, $J=7.2$ Hz), 1.32–1.20 (2H, m). ^{19}F NMR (CDCl$_3$, 282 MHz): δ -80.9 (2F, t, $J=12.8$ Hz, CF$_2$O), -88.8 (2F, m, OCF$_2$), -117.7 (2F, s, CF$_2$S), -137.66 (2F, d, $J=52.5$ Hz, HCF$_2$). IR (KBr) cm^{-1}: 2939, 2862, 1585, 1358, 1329, 1187, 1009. MS: *m/z* (%) 435 (M$^+$, 1), 352 (M$^+$ $-$C$_6$H$_{11}$, 4), 110 (M$^+$ $+1-$R$_f$SO$_2$–EtO, 100), 83 (C$_6$H$_{11}^+$, 70). Anal. Calcd for C$_{13}$H$_{17}$F$_8$NO$_4$S: C, 35.87; H, 3.94; N, 3.22%. Found: C, 36.06; H, 3.93; N, 3.23%.

4.1.8. 1-Cyclohexyl-1-ethoxy-meth-(*Z*)-ylidene-perfluorobutylsulfonyl imine (3db). Colorless oil. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 4.29 (2H, q, $J=7.2$ Hz), 3.17–3.07 (1H, m), 2.02–1.42 (8H, m), 1.36 (3H, t, $J=7.2$ Hz), 1.33–1.20 (2H, m). ^{19}F NMR (CDCl$_3$, 282 MHz): δ -81.0 (3F, t, $J=10.0$ Hz, CF$_3$), –114.1 (2F, t, $J=15.1$ Hz, CF$_2$), –121.1 (2F, m, CF$_2$S), –126.2 (2F, m, CF$_2$). IR (KBr) cm^{-1}: 2939, 2862, 1584, 1359, 1238, 1140, 1012. MS: *m/z* (%) 437 (M$^+$, 2), 354 (M$^+$ $-$C$_6$H$_{11}$, 4), 110 (M$^+$ $+1-$R$_f$SO$_2$–EtO, 100), 83 (C$_6$H$_{11}^+$, 78). Anal. Calcd for C$_{13}$H$_{16}$F$_9$NO$_3$S: C, 35.70; H, 3.69; N, 3.20%. Found: C, 35.74; H, 3.79; N, 3.55%.

4.2. General procedure for the reaction of aryl azides with cycloalkenyl ether

To a 10 mL round-bottom flask containing 1-ethoxy-cycloheptene **2b** (227 mg, 1.62 mmol) in 2 mL anhydrous toluene was added 4-nitro phenyl azides **4a** (0.246 g, 1.5 mmol) at room temperature under N$_2$. Then the mixture was continuously stirred and heated to 80 °C. After 48 h TLC analysis showed the azide **4a** was not consumed completely. The solvent was evaporated and the residue was chromatographed on a silica column using petroleum ether–ether (20/3 v:v) as eluant to give pure product **5ab** as a yellowish solid (253 mg, 83%). Meanwhile, 80 mg of 4-nitro-phenyl azides **4a** was recycled.

4.2.1. 8a-Ethoxy-1-(4-nitro-phenyl)-1,3a,4,5,6,7,8,8a-octahydro-cycloheptatriazole (5ab). Yellowish solid. Mp 128–130 °C. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 8.25 (2H, dd, $J=9.0$, 1.5 Hz, AA′BB′), 7.65 (2H, dd, $J=9.6$, 1.5 Hz, AA′BB′), 4.62 (1H, t, $J=5.4$ Hz), 3.19–3.14 (1H, m), 2.93–2.88 (1H, m), 2.44–1.21 (10H, m), 1.16 (3H, t, $J=7.2$ Hz). IR (KBr) cm^{-1}: 2940, 2859, 1593, 1516, 1493, 1338, 1045, 860. MS: *m/z* (%) 275 (M$^+$ $-$Et, 5), 259 (M$^+$ $-$EtO, 5), 193 (M$^+$ $-$C$_2$H$_4$–C$_6$H$_{11}$, 47), 137 (M$^+$ $-$EtO–C$_6$H$_4$NO$_2$, 12), 83 (C$_6$H$_{11}^+$, 93), 55 (C$_4$H$_7^+$, 100). Anal. Calcd for C$_{15}$H$_{20}$N$_4$O$_3$: C, 59.21; H, 6.58; N, 18.42%. Found: C, 59.18; H, 6.78; N, 18.15%.

4.2.2. 1-(4-Chloro-phenyl)-8a-ethoxy-1,3a,4,5,6,7,8,8a-octahydro-cycloheptatriazole (5bb). Colorless oil. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.46–7.27 (4H, m), 4.50 (1H, t, $J=5.1$ Hz), 3.17–3.11 (1H, m), 2.99–2.93 (1H, m), 2.52–1.23 (10H, m), 1.17 (3H, t, $J=6.9$ Hz). IR (KBr) cm^{-1}: 2930, 2856, 1597, 1491, 1455, 1346, 1065, 1039, 829. MS: *m/z* (%) 295/293 (M$^+$, 1/3), 238/236 (M$^+$ $-$C$_4$H$_9$, 3/9), 182 (M$^+$ $-$C$_6$H$_4$Cl, 25), 113/111 (ClC$_6$H$_4^+$, 51), 55 (C$_4$H$_7^+$, 100). HRMS (MALDI/DHB) for [M+OH]$^+$: C$_{15}$H$_{21}$ClN$_3$O$_2$ Calcd 310.1326. Found: 310.1317.

4.2.3. 1-(4-Methoxy-phenyl)-1,4,5,6,7,8-hexahydro-cycloheptatriazole (6cb). Yellowish solid. Mp 104–106 °C. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.32 (2H, dd, $J=9.0$, 2.1 Hz, AA′BB′), 7.02 (2H, dd, $J=9.0$, 2.4 Hz, AA′BB′), 3.87 (3H, s), 2.96 (2H, t, $J=6.0$ Hz), 2.69 (2H, t, $J=5.7$ Hz), 1.87–1.67 (6H, m). IR (KBr) cm^{-1}: 2927, 2844, 1515, 1457, 1252, 1233, 1176, 1032, 841. MS: *m/z* (%) 243 (M$^+$, 11), 214 (M$^+$ $-$C$_2$H$_5$, 89), 200 (M$^+$ $-$C$_3$H$_7$, 100). Anal. Calcd for $C_{14}H_{17}N_3O$: C, 69.14; H, 7.00; N, 17.28%. Found: C, 69.18; H, 7.02; N, 17.08%.

4.3. General procedure for the reaction of fluoroalkanesulfonyl azides with in situ generated ynamine

At room temperature, to a 10 mL round-bottom flask containing 1-bromo-2-(4-nitro-phenyl)ethyne **7** (100 mg, 0.44 mmol) in 3 mL anhydrous diethyl ether was added slowly diethyl amine **8** (0.07 mL, 0.66 mmol). Then the mixture was continuously stirred at room temperature. TLC analysis showed the reaction finished within 3 h. Then fluoroalkanesulfonyl azides **1d** (143 mg, 0.44 mmol) was added dropwise to the reaction system. The original yellowish color turned to carmine immediately. TLC analysis showed that azide **1** was disappeared within 5 min. The solvent was evaporated and the residue was chromatographed on a silica column using petroleum ether–ether (1/1 v:v) as the eluant to give pure diazo product **9d** as a yellowish solid (203 mg, 85%).

4.3.1. [2-Diazo-1-diethylamino-2-(4-nitro-phenyl)-eth-(*Z*)-ylidene]-(5′-iodo-3′-oxa-octafluoropentyl)-sulfonyl imine (9a). Yellowish solid. Mp 78–80 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.28 (2H, d, $J=7.2$ Hz), 7.10 (2H, d, $J=7.2$ Hz), 3.62–3.49 (4H, m), 1.31–1.21 (6H, m). ^{19}F NMR ($CDCl_3$, 282 MHz): δ -65.2 (CF_2, t, $J=6.1$ Hz), -81.5 (CF_2, t, $J=11.7$ Hz), -85.8 (CF_2, t, $J=12.8$ Hz), -116.7 (CF_2, s). IR (KBr) cm^{-1}: 2978, 2080, 1593, 1549, 1440, 1340, 1172, 1145. MS: *m/z* (%) 640 (MH^+-N_2, 1), 296 ($M^+-N_2-R_f$, 32), 163 ($O_2NC_6H_4CH{=}N_2^+$, 100). HRMS (+ESI) for $[M+Na]^+$: $C_{16}H_{14}F_8IN_5O_5SNa$ Calcd 689.9530. Found: 689.9524.

4.3.2. [2-Diazo-1-diethylamino-2-(4-nitro-phenyl)-eth-(*Z*)-ylidene]-(5′-chloro-3′-oxa-octafluoropentyl)-sulfonyl imine (9b). Yellowish solid. Mp 58–60 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.27 (2H, d, $J=7.2$ Hz), 7.09 (2H, d, $J=7.2$ Hz), 3.63–3.40 (4H, m), 1.37–1.20 (6H, m). ^{19}F NMR ($CDCl_3$, 282 MHz): δ -74.1 (CF_2, s), -81.5 (CF_2, t, $J=12.8$ Hz), -87.2 (CF_2, t, $J=12.0$ Hz), -116.8 (CF_2, s). IR (KBr) cm^{-1}: 2988, 2945, 2082, 1562, 1533, 1449, 1349, 1308, 1176, 1137. MS: *m/z* (%) 550/548 (MH^+-N_2, 2/5), 296 ($M^+-N_2-R_f$, 93), 163 ($O_2NC_6H_4CH{=}N_2^+$, 100). Anal. Calcd for $C_{16}H_{14}ClF_8N_5O_5S$: C, 33.37; H, 2.45; N, 12.16%. Found: C, 33.66; H, 2.56; N, 11.81%.

4.3.3. [2-Diazo-1-diethylamino-2-(4-nitro-phenyl)-eth-(*Z*)-ylidene]-(1′,1′,2′,2′,4′,4′,5′,5′-octafluoro-3′-oxa-pentyl)-sulfonyl imine (9c). Yellowish solid. Mp 54–56 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.24 (2H, d, $J=8.7$ Hz), 7.08 (2H, d, $J=8.7$ Hz), 5.85 (1H, tt, $J=3.0$, 52.5 Hz), 3.64–3.47 (4H, m), 1.42–1.18 (6H, m). ^{19}F NMR ($CDCl_3$, 282 MHz): δ -81.0 (CF_2, t, $J=12.7$ Hz), -88.9 (CF_2, m), -116.8 (CF_2, s), -137.7 (CF_2, d, $J=52.5$ Hz). IR (KBr) cm^{-1}: 2989, 2945, 2081, 1594, 1557, 1442, 1342, 1136. MS: *m/z* (%) 514 (MH^+-N_2, 5), 296 ($M^+-N_2-R_f$, 100), 163 ($O_2NC_6H_4CH{=}N_2^+$, 61). HRMS (+ESI) for $[M+Na]^+$: $C_{16}H_{15}F_8N_5O_5SNa$ Calcd 564.0564. Found: 564.0561.

4.3.4. [2-Diazo-1-diethylamino-2-(4-nitro-phenyl)-eth-(*Z*)-ylidene]-perfluorobutyl-sulfonyl imine (9d). Yellowish solid. Mp 90–92 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.28 (2H, d, $J=9.0$ Hz), 7.10 (2H, d, $J=9.0$ Hz), 3.69–3.57 (4H, m), 1.42–1.20 (6H, m). ^{19}F NMR ($CDCl_3$, 282 MHz): δ -81.0 (CF_3, t, $J=9.3$ Hz), -113.2 (CF_2, t, $J=13.5$ Hz), -121.2 (CF_2, t, $J=6.3$ Hz), -126.2 (CF_2, m). IR (KBr) cm^{-1}: 2988, 2081, 1557, 1441, 1343, 1235, 1138. MS: *m/z* (%) 516 (MH^+-N_2, 5), 296 ($M^+-N_2-R_f$, 76), 163 ($O_2NC_6H_4CH{=}N_2^+$, 90), 150 (100). Anal. Calcd for $C_{16}H_{14}F_9N_5O_4S$: C, 35.37; H, 2.60; N, 12.89%. Found: C, 35.43; H, 2.66; N, 12.99%.

4.4. General procedure for the decomposition reactions of α-diazoamidines 9

At room temperature α-diazoamidines **9** decomposed slowly within 4–7 days accompanying release N_2. Finally the diazo compound **9** converted completely into one new kind of fluoroalkanesulfinyl imine **10**.

4.4.1. [1-Diethylamino-2-(4-nitro-phenyl)-2-oxo-eth-(*Z*)-ylidene]-(5′-iodo-3′-oxa-octafluoropentyl)-sulfinyl imine (10a). Yellowish oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.40 (2H, d, $J=8.7$ Hz), 8.07 (2H, d, $J=9.0$ Hz), 3.69 (2H, br), 3.19 (2H, q, $J=6.9$ Hz), 1.36 (3H, t, $J=7.2$ Hz), 1.15 (3H, t, $J=6.9$ Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ -65.4 (CF_2, t, $J=5.6$ Hz), -81.9 (CF_2, t, $J=11.7$ Hz), -86.0 (CF_2, m), -125.6 (CF_2, m). IR (KBr) cm^{-1}: 2978, 2919, 1694, 1558, 1523, 1346, 1292, 1187, 1134. MS: *m/z* (%) 640 (MH^+, 1), 296 (M^+-R_f, 100), 150 ($O_2NC_6H_4CO^+$, 56). HRMS (+ESI) for $[M+Na]^+$: $C_{16}H_{14}F_8IN_3O_5SNa$ Calcd 661.9469. Found: 661.9466.

4.4.2. [1-Diethylamino-2-(4-nitro-phenyl)-2-oxo-eth-(*Z*)-ylidene]-(5′-chloro-3′-oxa-octafluoropentyl)-sulfinyl imine (10b). Yellowish oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.40 (2H, d, $J=9.0$ Hz), 8.08 (2H, d, $J=9.0$ Hz), 3.67 (2H, br), 3.20 (2H, q, $J=7.2$ Hz), 1.38 (3H, t, $J=7.2$ Hz), 1.21 (3H, t, $J=7.2$ Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ -74.2 (CF_2, s), -81.9 (CF_2, m), -87.2 (CF_2, m), -125.6 (CF_2, m). IR (KBr) cm^{-1}: 2989, 1697, 1560, 1533, 1349, 1307, 1225, 1133, 977. MS (+ESI): *m/z* (%) 548($[M+H]^+$, 100). HRMS (+ESI) for $[M+Na]^+$: $C_{16}H_{14}ClF_8N_3O_5SNa$ Calcd 570.0113. Found: 570.0110.

4.4.3. [1-Diethylamino-2-(4-nitro-phenyl)-2-oxo-eth-(*Z*)-ylidene]-(1′,1′,2′,2′,4′,4′,5′,5′-octafluoro-3′-oxa-pentyl)-sulfinyl imine (10c). Yellowish oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.39 (2H, d, $J=9.0$ Hz), 8.06 (2H, d, $J=8.4$ Hz), 5.88 (1H, tt, $J=3.0$, 52.5 Hz), 3.68 (2H, br), 3.18 (2H, q, $J=6.9$ Hz), 1.34 (3H, t, $J=7.2$ Hz), 1.13 (3H, t, $J=7.2$ Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ -81.2 (CF_2, s), -88.8 (CF_2, m), -125.9 (CF_2, m), -137.8 (CF_2, d, $J=53.6$ Hz). IR (KBr) cm^{-1}: 2989, 2945, 1695, 1563, 1533, 1441, 1349, 1284, 1139. MS: *m/z* (%) 296 (M^+-R_f, 100), 150 ($O_2NC_6H_4CO^+$, 96). HRMS (+ESI) for $[M+Na]^+$: $C_{16}H_{15}F_8N_3O_5SNa$ Calcd 536.0503. Found: 536.0500.

4.4.4. [1-Diethylamino-2-(4-nitro-phenyl)-2-oxo-eth-(*Z*)-ylidene]-perfluorobutyl-sulfinyl imine (10d). Yellowish solid. Mp 74–76 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.41 (2H, d, $J=7.2$ Hz), 8.07 (2H, d, $J=8.7$ Hz), 3.68 (2H, br), 3.20 (2H, q, $J=6.9$ Hz), 1.36 (3H, t, $J=7.2$ Hz), 1.15 (3H, t, $J=7.2$ Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ -81.2 (CF_3, m), -122.2 (CF_2, s), -122.4 (CF_2, s), -126.6 (CF_2, m).

IR (KBr) cm^{-1}: 2987, 2944, 1696, 1560, 1441, 1349, 1228, 1211, 1139. MS: *m/z* (%) 516 (MH$^+$, 3), 296 (M$^+$ − R$_f$, 100), 150 ($O_2NC_6H_4CO^+$, 79). Anal. Calcd for $C_{16}H_{14}F_9N_3O_4S$: C, 37.29; H, 2.74; N, 8.15%. Found: C, 37.65; H, 3.11; N, 8.15%.

Acknowledgements

This work is supported by the National Science Foundation of China (Nos. 20372077 and 20472106).

References and notes

1. Semenov, V. P. *Russ. J. Org. Chem.* **1994**, *30*, 216–221.
2. (a) Welch, J. T. Selective Fluorination Organic and Bioorganic Chemistry In *ACS Symposium Series*; American Chemical Society, 456: Washington, DC, 1991. (b) Ramachandran, P. V. *Asymmetric Fluoro-organic Chemistry: Synthesis, Applications, and Future Directions*; American Chemical Society 746: Washington, DC, 2000.
3. (a) Xu, Y.; Zhu, S. Z. *Tetrahedron* **2001**, *57*, 669–674. (b) Xu, Y.; Zhu, S. Z. *Tetrahedron* **2001**, *57*, 3909–3913. (c) Xu, Y.; Zhu, S. Z. *Synthesis* **2001**, *5*, 690–692. (d) Zhu, S. Z.; Jin, G. F.; Xu, Y. *Tetrahedron* **2003**, *59*, 4389–4394.
4. (a) Zhu, S. Z.; Jin, G. F.; Zhao, J. W. *J. Fluorine Chem.* **2003**, *120*, 65–69. (b) Zhu, S. Z.; He, P.; Zhao, J. W.; Cai, X. *J. Fluorine Chem.* **2004**, *125*, 445–450.
5. (a) Xu, Y.; Wang, Y. L.; Zhu, S. Z. *J. Fluorine Chem.* **2000**, *104*, 195–200. (b) He, P.; Zhu, S. Z. *J. Fluorine Chem.* **2004**, *125*, 1529–1536. (c) He, P.; Zhu, S. Z. *J. Fluorine Chem.* **2005**, *126*, 825–830.
6. (a) Semenov, V. P.; Ogloblin, K. A. *Zh. Org. Khim.* **1987**, *23*, 898–899. (b) Semenov, V. P.; Ogloblin, K. A. *Zh. Org. Khim.* **1988**, *24*, 2389–2397.
7. Blixt, O.; Norberg, T. *J. Carbohydr. Chem.* **1997**, *16*, 143–154.
8. Huisgen, R.; Mobius, L.; Szeimies, G. *Chem. Ber.* **1965**, *98*, 1138–1152.
9. Zhu, S. Z. *Tetrahedron Lett.* **1992**, *33*, 6503–6504.
10. Tietze, L. F.; Eicher, T. *Reactions and Syntheses in the Organic Chemistry Laboratory*; University Science Books: Mill Valley, California, 1989; pp 204–205.
11. (a) Huh, D. H.; Jeong, J. S.; Lee, H. B.; Ryu, H.; Kim, Y. G. *Tetrahedron* **2002**, *58*, 9925–9932. (b) Lin, S. T.; Lee, C. C.; Liang, D. W. *Tetrahedron* **2000**, *56*, 9619–9623.

ELSEVIER

Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron 62 (2006) 556–562

Tetrahedron

Clean and selective oxidation of alcohols catalyzed by ion-supported TEMPO in water

Weixing Qian, Erlei Jin, Weiliang Bao* and Yongmin Zhang

Department of Chemistry, Xi Xi Campus, Zhejiang University, Hangzhou, Zhejiang 310028, People's Republic of China

Received 25 March 2005; revised 9 October 2005; accepted 11 October 2005

Abstract—Three different types of ion-supported TEMPO catalysts are synthesized and their catalytic activity in the chemoselective oxidation of alcohols is investigated. These new catalysts show high catalytic activity in water and can be reused for the next run by extraction of products. Recycling experiments exhibit that ion-supported TEMPO can be reused up to five times without loss of catalytic activity. This system offers a very clean, convenient, environmentally benign method for the selective oxidation of alcohols.

1. Introduction

Chemoselective oxidation of alcohols to carbonyl compounds is an important reaction in organic synthesis and many methods for this transformation have been documented in the literature in view of its importance.[1] Recently the use of metal-free catalysts for selective oxidation of organic compounds is attracting more and more attention because these metal-free catalysts are beneficial from both economic and environmental viewpoints. Moreover, they are readily able to tether to a support covalently and obviate the problem of metal leaching.[2] In the area of metal-free catalytic alcohol oxidations stable free nitroxyl radicals, such as 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), play an increasingly important role in organic synthesis.[3] Usually, efficient methods for the transformation of alcohols to carbonyl compounds or carboxylic acids under mild conditions include the use of 1 mol% of TEMPO as a catalyst and a stoichiometric amount of a terminal oxidant. Many different terminal oxidants have been developed in this reaction including sodium hypochlorite,[4] [bis(acetoxy)iodo]benzene,[5] *m*-CPBA,[6] sodium bromite,[7] trichloroisocyanuric acid,[8] oxone,[9] iodine[10] and oxygen in combination with CuCl[11] or $NaNO_2$.[12] Although these oxidants are successful for efficient alcohol oxidation, separation of the TEMPO from products needs tedious workup procedures. To simplify the product isolation and catalyst recovery the use of polymer-supported catalysts seems alternative. Various polymer-supported TEMPO or its derivatives have been synthesized either based on inorganic[13] or organic supports.[4a,b,14] This polymer-supported TEMPO, however, in some cases will result in decreasing activity or extending reaction time after recycling.[4a,15]

In the last decade ionic liquids have attracted considerable attention as an alternative reaction medium, which represents interesting properties such as high thermal stability, negligible vapor pressure, high loading capacity and easy recyclability. Various chemical reactions can be performed in ionic liquids.[16] One of the attractive features of ionic liquids in organic synthesis is that the structures with the cationic or anionic components can be modified according to requirement, so that they can be adapted to special applications. Recently, increasing attention has been focused on the use of ionic liquids as a means of immobilizing catalysts, facilitating products separation and providing an alternative to recycle the catalysts, and several publications that present their potential in catalysis have been demonstrated.[17] More recently, a TEMPO-derived task-specific ionic liquid for oxidation of alcohols by the Anelli protocol has been described.[18] In this paper, we wish to report three different types of ion-supported TEMPO catalysts for the oxidation of alcohols by an ion-supported hypervalent iodine reagent 1-(4-diacetoxyiodobenzyl)-3-methyl imidazolium tetrafluoroborate[19] $[\text{dibmin}]^+[BF_4]^-$ in water and examine their catalytic activity in different cases.

2. Results and discussion

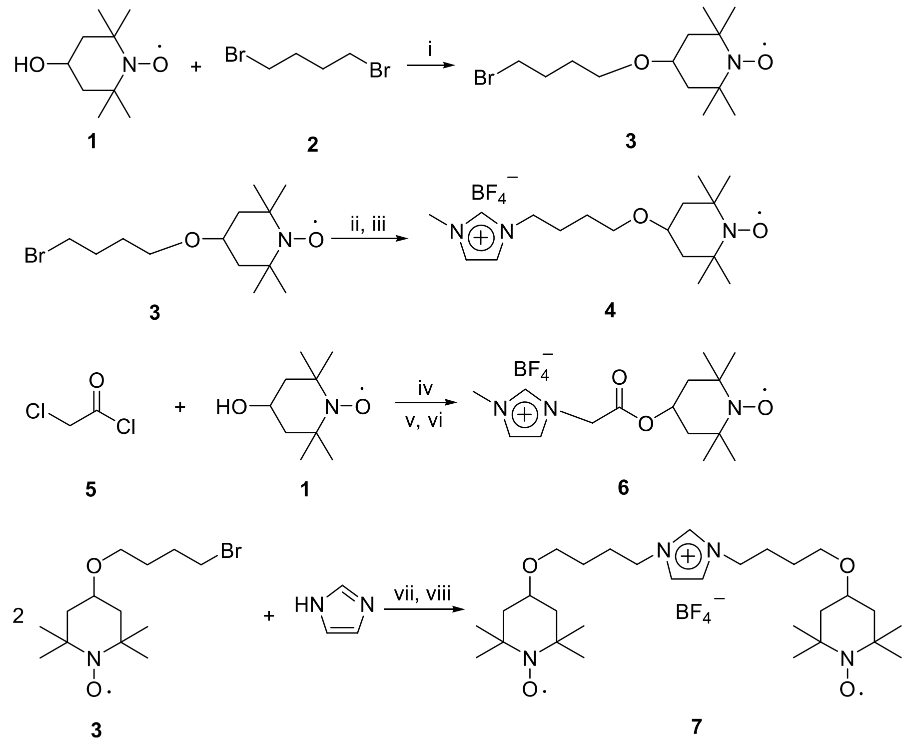
The route for the synthesis of ion-supported TEMPO catalysts was depicted in Scheme 1. Starting from the commercially available 4-hydroxyl-TEMPO (**1**), reaction

---

Keywords: Alcohols; Oxidation; Ion-supported TEMPO; Catalysis; Hypervalent iodine reagent.

* Corresponding author. Tel./fax: +86 571 88911554; e-mail: wlbao@css.zju.edu.cn

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.10.022

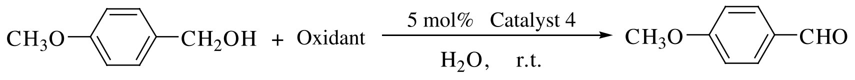


Scheme 1. Synthesis of ion-supported catalysts **4**, **6**, and **7**. Reaction conditions: (i) 1.0 equiv NaH, 1.5 equiv 1,4-dibromobutane, acetone, rt, 25%; (ii) 1.1 equiv 1-methylimidazole, CH_3CN, 60 °C, 97%; (iii) 1.5 equiv $NaBF_4$, acetone, refluxing, 86%; (iv) 1.1 equiv 2-chloroacetyl chloride, 1.1 equiv pyridine, CH_2Cl_2, 5 °C to rt, 80%; (v) 1.1 equiv 1-methylimidazole, CH_3CN, 60 °C, 98%; (vi) 1.5 equiv $NaBF_4$, acetone, refluxing, 85%; (vii) 1.1 equiv imidazole, 1.1 equiv K_2CO_3, acetone, rt; (viii) 1.1 equiv $NaBF_4$, 82%.

with 1,4-dibromobutane (**2**) as a linker in acetone afforded 4-(2,2,6,6-tetramethyl-1-oxyl-4-piperidoxyl)butyl bromide (**3**) in 25% yield.[20] Quaternization of 1-methylimidazole with **3** and subsequent anion exchange with $NaBF_4$ gave the desired ion-supported TEMPO catalyst (**4**) in 97 and 86% yields, respectively. To raise the yield in the first step, catalyst (**6**) was synthesized with chloroacetyl chloride (**5**) as a linker instead of 1,4-dibromobutane **2** and the yield reached to 80%. The rest steps were analogous to the catalyst **4**. As to symmetrical catalyst (**7**), we wanted to make imidazolium cation have higher loading capacity, reaction of imidazole with 2 equiv bromide **3** in the presence of K_2CO_3 and subsequent metathesis with $NaBF_4$ in one pot afforded the ion-supported diradical **7** in good yield, which was purified by silica gel chromatography. These ion-supported catalysts are insoluble in low polar organic solvents such as ethers or hexanes but are soluble in CH_2Cl_2 and highly soluble in water and ionic liquids. They are ideal candidates for aqueous homogeneous catalysis.

After three ion-supported TEMPO catalysts were obtained, the catalyst **4** was chosen as a candidate to investigate its catalytic activity in combination with various terminal oxidants in water.[21] Table 1 listed the results. The ion-supported TEMPO catalyst **4** proved to be an effective one for the selective oxidation of 4-methoxylbenzyl alcohol except for oxidant peracetic acid, giving 4-methoxylbenzyl aldehyde in good to excellent yields and short reaction times under mild conditions (a 1:1.2 ratio of alcohol/oxidant). It showed similar catalytic activity to that of free TEMPO (Table 1, entry 6). Using $PhI(OAc)_2$ as a terminal oxidant, the reaction did not work well because of poor solubility of $PhI(OAc)_2$ in water. Both I_2 and NaOCl showed effective oxidants. The reaction proceeded fast and gave excellent yields. However, in the case of I_2, a slight

Table 1. Oxidation of 4-methoxybenzyl alcohol catalyzed by an ion-supported TEMPO **4** in water



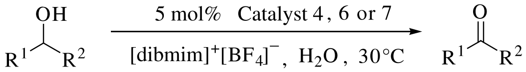
Entry	Oxidant	Time (min)	Yield (%)[a]
1	CH_3CO_3H	600	25
2	$PhI(OAc)_2$	120	70
3	I_2	40	98
4	NaOCl	3	96
5	$[dibmim]^+[BF_4]^-$	6	98
6	$[dibmim]^+[BF_4]^-$	6	97[b]

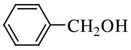
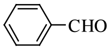
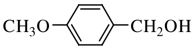
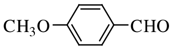
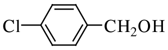
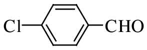
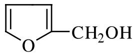
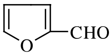
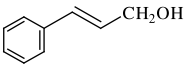
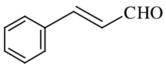
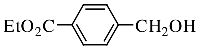
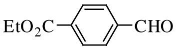
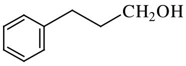
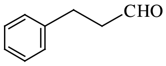
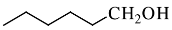
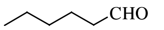
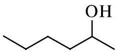
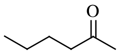
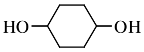
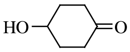
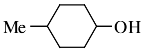
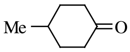
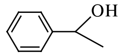
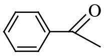
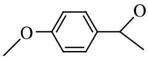
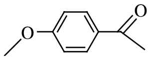
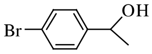
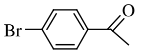
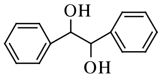
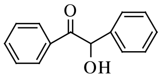
[a] Isolated yields after chromatographic purification unless otherwise noted.
[b] Free TEMPO was used as a catalyst.

excess of I_2 would contaminate the products, and in the TEMPO-bleach protocol introduced by Anelli et al. CH_2Cl_2 usually was used as a biphasic system[4c] and chlorinated byproducts could be formed.[9] After screening several terminal oxidants listed in Table 1, we found $[dibmin]^+[BF_4]^-$ to be suitable for the reaction conducted in water, which based on the following reasons: (a) readily dissolving in water due to its ion-type structure; (b) acting as a role of phase transfer catalyst (PTC) to some extent to facilitate substrate dissolving in water; (c) most part of the oxidant, which was reduced easily precipitated out from water and recovered by filtration after the products extracted by Et_2O (the oxidant can be reoxidized by peracetic acid). The ion-supported TEMPO catalyst **4** remained in filtrate, which could be reused for next run after reloading the substrates and the oxidant $[dibmin]^+[BF_4]^-$.

Next, we examined the oxidation of a variety of primary and secondary alcohols in the presence of 5 mol% of ion-supported TEMPO (**4**, **6** or **7**) catalysts employing 1.2 mol equiv of $[dibmin]^+[BF_4]^-$ as a terminal oxidant. Under these conditions, of all most alcohols were quantitatively oxidized to carbonyl compounds within 330 min in good to excellent yields (Table 2). Benzylic primary alcohols (Table 2, entries 1–4 and 6) gave excellent yields of the corresponding aldehydes in very short reaction times (6–40 min) without any noticeable overoxidation to the carboxylic acids. This methodology is mild and compatible with several functional groups other than the hydroxyl group. For example, the ester linkage of ethyl 4-(hydroxymethyl)benzoate (Table 2, entry 6) remained intact. Cinnamyl alcohol (Table 2, entry 5) was oxidized to the corresponding aldehyde in 97% yield and no double-bond addition product was found. For the oxidation of benzylic secondary alcohols (Table 2, entries 12–15), the reaction afforded excellent yields but required 15–120 min for completion. The oxidation was relatively slow for the aliphatic primary and secondary alcohols (Table 2, entries 7–11), but the good yields could be obtained by extending reaction times. Notably, from the results, as expected, obtained in experiment, the catalytic activity for the catalyst **4** is the same as that for catalyst **6** (Table 2, entries 2, 5 and 13). The symmetric catalyst **7** gives the same yields as catalyst **4** or **6** in almost half reaction times and exhibits catalytic activities two times greater than catalyst **4** or **6** alone under similar conditions (Table 2, entries 5, 7–9 and 11), which implies this ion-supported catalyst with higher loading capacity would be more economic and potential in organic synthesis.

Table 2. Oxidation of alcohols catalyzed by ion-supported TEMPO catalysts (**4**, **6** or **7**) using $[dibmim]^+[BF_4]^-$ as terminal oxidant in water



Entry	Substrate	Product	Catalyst	Time (min)	Yield (%)[a]
1			**4**	6	97[b]
2			**4**	6	98
			6	6	98
3			**4**	15	97
4			**4**	10	97[b]
5			**4**	60	98
			6	60	97
			7	20	98
6			**4**	40	90
7			**4**	240	86
			7	90	85
8			**4**	240	95[b]
			7	120	93
9			**4**	330	85[b]
			7	180	88
10			**4**	300	86
11			**4**	300	80
			7	120	78
12			**4**	120	90[b]
13			**4**	30	99
			6	30	98
14			**4**	30	98
15			**4**	15	99

[a] Isolated yields after chromatographic purification unless otherwise noted.

[b] Yields were determined by GC.

To examine whether the catalytic activity of ion-supported TEMPO **6** decreases in recycling we compared it with the catalyst **4** under the same conditions described above using 4-methoxybenzyl alcohol as a substrate. The results are listed in Table 3. It was found that almost constant yields were obtained in five subsequent runs for both catalysts. No induction period was observed upon recycling of catalysts **4** and **6**.[4a] It suggested that the ester linkage of catalyst **6** probably was stable in reaction processes.

Table 3. Recyclability of ion-supported TEMPO catalysts **4** and **6** in the oxidation of 4-methoxylbenzyl alcohol

Catalyst	Cycle (yield %)[a]				
	1	2	3	4	5
4	98	97	96	98	97
6	98	96	98	97	94

[a] Reaction time 7 min.

3. Conclusion

In conclusion, we have successfully developed three ion-supported TEMPO catalysts and examined their catalytic activities. These low molecular weight catalysts displayed the same selectivities and activities as those of free TEMPO. The symmetric catalyst **7** noticeably increased the rate of oxidation of alcohols. Their combination with an ion-supported oxidant $[\text{dibmin}]^+[BF_4]^-$ afforded an easy workup and environmentally benign catalyst system for mild and selective oxidation of primary and secondary alcohols to carbonyl compounds. Both catalysts and oxidant could be recovered and recycled, and almost no waste was produced.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were determined in $CDCl_3$ or DMSO-d_6 on a Bruker 400 MHz spectrometer with TMS as the internal standard. IR spectra were recorded on a Bruker Vector-22 infrared spectrometer. C, H, N were analyzed on a Carlo Erba 1110 elemental analyzer. GC–MS analyses were performed on a Hewlett-Packard 5973 instrument (column: HP-5 30 m × 0.25 mm × 0.25 mm). All melting points were uncorrected. The columns were handpacked with silica gel H60 (∼400). Reactions were carried out under atmosphere.

4.2. Synthesis of catalysts (4, 6, and 7)

The bromide, chloride, and tetrafluoroborate salts of ion-supported TEMPO were prepared by modification of published literature procedures.[22]

4.2.1. 4-(2,2,6,6-Tetramethyl-1-oxyl-4-piperidoxyl)butyl bromide. To a solution of 4-hydroxy-TEMPO (2.58 g, 0.015 mol) in anhydrous acetone (25 mL) was added NaH (0.6 g, 0.015 mol) and the resulting slurry stirred for 10 min at room temperature. 1,4-Dibromobutane (4.86 g, 0.0225 mol) was then added and stirred for 3 h at room temperature. The acetone was removed under reduced pressure and water (30 mL) was added to dissolve the solid. The aqueous layer was then extracted with methylene chloride (15 mL × 3). The combined organic extracts were dried over Na_2SO_4 and concentrated under vacuum to a small volume. The resulting concentrated solution was separated by flash chromatography (10:1, petroleum/ethyl acetate) to obtain red oil 1.15 g (25%); ^{1}H NMR ($CDCl_3$, ppm): $\delta = 1.17$ (s, 6H), 1.23 (s, 6H), 1.47 (t, ^3J(H,H) = 11.6 Hz, 2H), 1.68–1.73 (m, 2H), 1.90–1.96 (m, 4H), 3.42–3.47 (m, 4H), 3.50–3.57 (m, 1H); ^{13}C NMR ($CDCl_3$, ppm): $\delta = 20.8$, 28.6, 29.7, 31.7, 33.8, 44.4, 59.7, 67.0, 70.4; IR (KBr): $\nu = 2973$, 2937, 1459, 1376, 1363, 1245, 1177, 1104 cm^{-1}; MS (ESI): m/z (%): 306 (23.0) [M^+], 308 (21.6) [$M^+ + 2$], 135 (93.2) [$C_4H_8Br^+$], 137 (92.1) [$C_4H_8Br^+ + 2$], 55 (100.0) [$C_4H_7^+$]. Anal. Calcd for $C_{13}H_{25}BrNO_2$: C 50.82, H 8.20, N 4.56. Found: C 50.82, H 8.25, N 4.19.

4.2.2. 1-Methyl-3-(4-(2,2,6,6-tetramethyl-1-oxyl-4-piperidoxyl)butyl)imidazolium bromide. Under stirring, 0.922 g (3 mmol) of 4-(2,2,6,6-tetramethyl-1-oxyl-4-piperidoxyl)butyl bromide was slowly added to a solution of 0.295 g (3.6 mmol) of 1-methylimidazole in 1 mL of acetonitrile. The mixture was stirred for 6 h at 60 °C. After cooling to room temperature, 5 mL ether was added to the mixture causing precipitation of 1-methyl-3-(4-(2,2,6,6-tetramethyl-1-oxyl-4-piperidoxyl)butyl)imidazolium bromide as a red solid. This solid was recovered by filtration and washed with ether twice. The yield was 1.13 g (97%). Mp: 71–73 °C; ^{1}H NMR (DMSO-d_6, ppm): $\delta = 1.03$ (s, 6H), 1.07 (s, 6H), 1.22–1.24 (m, 2H), 1.42–1.47 (m, 2H), 1.78–1.82 (m, 4H), 3.40 (t, ^3J(H,H) = 6.4 Hz, 2H), 3.49–3.54 (m, 1H), 3.86 (s, 3H), 4.19 (t, ^3J(H,H) = 7.2 Hz, 2H), 7.74 (s, 1H), 7.80 (s, 1H), 9.19 (s, 1H); ^{13}C NMR (DMSO-d_6, ppm): $\delta = 20.9$, 26.6, 27.1, 32.8, 36.2, 45.0, 49.0, 58.3, 66.8, 70.4, 122.6, 124.0, 136.9; IR (KBr): $\nu = 3087$, 2974, 2938, 1632, 1572, 1463, 1363, 1171, 1097 cm^{-1}; MS (ESI): m/z (%): 309 (8.5) [$M^+ - Br^-$], 124 (100.0) [$C_9H_{16}^+$], 123 (66.4) [$C_7H_{15}^+$], 81 (59.8) [$C_4H_5N_2^+$], 55 (65.8) [$C_3H_5N^+$], 42 (53.6) [$C_2H_4N^+$]. Anal. Calcd for $C_{17}H_{31}BrN_3O_2$: C 52.44, H 8.03, N 10.79. Found: C 52.09, H 8.09, N 10.98.

4.2.3. 1-Methyl-3-(4-(2,2,6,6-tetramethyl-1-oxyl-4-piperidoxyl)butyl)imidazolium tetrafluoroborate. The 1-methyl-3-(4-(2,2,6,6-tetramethyl-1-oxyl-4-piperidoxyl)-butyl)imidazolium bromide obtained above 1.17 g (3 mmol) was added to a suspension of $NaBF_4$ (0.495 g, 4.5 mmol) in acetone (5 mL). The mixture was then stirred under the refluxing for 72 h. The sodium bromide precipitate was removed by filtration and the filtrate concentrated by rotary evaporation. The yield was 1.02 g (86%), red viscous oil; ^{1}H NMR (DMSO-d_6, ppm): $\delta = 1.05$ (s, 6H), 1.08 (s, 6H), 1.25 (t, ^3J(H,H) = 10.8 Hz, 2H), 1.43–1.47 (m, 2H), 1.81–1.87 (m, 4H), 3.41 (t, ^3J(H,H) = 6.4 Hz, 2H), 3.50–3.55 (m, 1H), 3.85 (s, 3H), 4.18 (t, ^3J(H,H) = 7.2 Hz, 2H), 7.68 (s, 1H), 7.74 (s, 1H), 9.06 (s, 1H); ^{13}C NMR (DMSO-d_6, ppm): $\delta = 20.8$, 26.6, 27.1, 32.7, 36.1, 44.9, 49.1, 58.5, 66.9, 70.3, 122.6, 124.0, 136.9; IR (KBr): $\nu = 3159$, 2937, 2938, 1575, 1465, 1364, 1170, 1060 cm^{-1}; MS (ESI): m/z (%): 309 (1.0) [$M^+ - BF_4^-$], 137 (78.2) [$C_8H_{13}N_2^+$], 83 (100.0) [$C_4H_7N_2^+$], 55 (70.2) [$C_3H_5N^+$], 42 (99.0) [$C_2H_4N^+$].

Anal. Calcd for $C_{17}H_{31}BF_4N_3O_2$: C 51.53, H 7.89, N 10.60. Found: C 51.15, H 7.96, N 10.62.

4.2.4. 1,3-Bis(4-(2,2,6,6-tetramethyl-1-oxyl-4-piperidoxyl)butyl)imidazolium tetrafluoroborate. To a suspension of 0.245 g (3.6 mmol) of imidazole and 0.7 g potassium carbonate in acetone (10 mL) was added 1.84 g (6 mmol) of 4-(2,2,6,6-tetramethyl-1-oxyl-4-piperidoxyl)butyl bromide, and the mixture was stirred under the refluxing for 48 h. And then 0.396 g (3.6 mmol) $NaBF_4$ was added to the mixture to continue stirring for 72 h. The sodium bromide precipitate was removed by filtration and the filtrate concentrated by rotary evaporation. The yield was 1.50 g (82%), red viscous oil; ^{1}H NMR (DMSO-d_6, ppm): $\delta=1.04$ (s, 12H), 1.07 (s, 12H), 1.22–1.26 (m, 4H), 1.37–1.42 (m, 4H), 1.70–1.76 (m, 4H), 1.82–1.86 (m, 4H), 3.37 (t, ^3J(H,H) = 6.4 Hz, 4H), 3.48–3.52 (m, 2H), 3.96 (t, ^3J(H,H) = 7.2 Hz, 4H), 7.61 (s, 2H), 8.96 (s, 1H); ^{13}C NMR (DMSO-d_6, ppm): $\delta=20.9$, 27.0, 28.1, 30.0, 32.5, 32.8, 45.0, 46.2, 56.2, 58.3, 67.0, 68.9, 70.3, 119.6, 129.1, 137.6; IR (KBr): $\nu=2973$, 2935, 2871, 1510, 1464, 1363, 1147, 1108 cm^{-1}; MS (ESI): *m/z* (%): 141 (43.2) [$C_9H_{19}N^+$], 124 (100.0) [$C_9H_{16}^+$]. Anal. Calcd for $C_{29}H_{53}BF_4N_4O_4$: C 57.24, H 8.78, N 9.21. Found: C 56.95, H 8.96, N 9.52.

4.2.5. 2,2,6,6-Tetramethyl-1-oxyl-4-piperidinyl 2-chloroacetate. To a solution of 4.3 g (0.025 mol) 4-hydroxy-TEMPO and 3.11 g (0.0275 mol) 2-chloroacetyl chloride in dichloromethane (30 mL) was slowly added 2.18 g (0.0275 mol) of pyridine under cooling, and the mixture was standing over night. The precipitate was removed by filtration and the filtrate was washed with water (30 mL), 10% $NaHCO_3$, then 2 mol dilute HCl and finally water (30 mL). The solution was dried over Na_2SO_4 and concentrated under vacuum to give red solid 4.98 g (80%). Mp: 49–51 °C; ^{1}H NMR ($CDCl_3$, ppm): $\delta=1.22$ (s, 6H), 1.25 (s, 6H), 1.68 (t, ^3J(H,H) = 11.6 Hz, 2H), 1.94–1.98 (m, 2H), 4.02 (s, 2H), 5.11–5.16 (m, 1H); ^{13}C NMR ($CDCl_3$, ppm): $\delta=20.4$, 31.8, 41.0, 43.5, 59.2, 69.1, 166.8; IR (KBr): $\nu=2978$, 2954, 1753, 1464, 1319, 1177, 1136 cm^{-1}; MS (ESI): *m/z* (%): 248 (14.5) [M$^+$], 250 (5.2) [M$^+$ + 2], 124 (53.9) [$C_9H_{16}^+$], 109 (100), 41 (82.3). Anal. Calcd for $C_{11}H_{19}ClNO_3$: C 53.12, H 7.70, N 5.63. Found: C 52.99, H 7.73, N 5.54.

4.2.6. 1-Methyl-3-(2-oxo-2-(2,2,6,6-tetramethyl-1-oxyl-4-piperidoxyl)ethyl)imidazolium chloride. (This procedure is similar to the preparation of bromide above). Mp: 225–227 °C; ^{1}H NMR (DMSO-d_6, ppm): $\delta=1.08$ (s, 6H), 1.11 (s, 6H), 1.51 (t, ^3J(H,H) = 11.6 Hz, 2H), 1.88–1.94 (m, 2H), 3.92 (s, 3H), 5.02–5.07 (m, 1H), 5.28 (s, 2H), 7.77 (s, 2H), 9.22 (s, 1H); ^{13}C NMR (DMSO-d_6, ppm): $\delta=20.7$, 32.5, 36.3, 43.8, 49.9, 58.4, 69.3, 123.7, 124.1, 138.1, 166.9; IR (KBr): $\nu=2977$, 1747, 1633, 1464, 1223, 1177 cm^{-1}; MS (ESI): *m/z* (%): 124 (34.3) [$C_6H_8N_2O^+$], 82 (100.0) [$C_4H_6N_2^+$], 56 (85.1) [$C_2H_4N_2^+$], 55 (91.2) [$C_4H_7^+$], 42 (84.2) [$C_2H_4N^+$]. Anal. Calcd for $C_{15}H_{25}ClN_3O_3$: C 54.46, H 7.62, N 12.70. Found: C 54.44, H 7.75, N 12.61.

4.2.7. 1-Methyl-3-(2-oxo-2-(2,2,6,6-tetramethyl-1-oxyl-4-piperidoxyl)ethyl)imidazolium tetrafluoroborate. (This procedure is similar to the preparation of tetrafluoroborate above). Red oil; ^{1}H NMR (DMSO-d_6, ppm): $\delta=1.15$ (s, 6H), 1.24 (s, 6H), 1.53 (t, ^3J(H,H) = 11.2 Hz, 2H), 1.90–1.94 (m, 2H), 3.90 (s, 3H), 5.02–5.08 (m, 1H), 5.21 (s, 2H), 7.71 (s, 2H), 9.05 (s, 1H); ^{13}C NMR (DMSO-d_6, ppm): $\delta=20.7$, 32.3, 36.3, 43.6, 49.9, 58.6, 69.3, 1237, 124.1, 138.1, 166.8; IR (KBr): $\nu=2978$, 2940, 1753, 1580, 1467, 1225, 1179, 1061 cm^{-1}; MS (ESI): *m/z* (%): 98 (68.2) [$C_5H_8NO^+$], 82 (46.2) [$C_4H_6N_2^+$], 55 (94.3) [$C_4H_7^+$], 41 (100.0) [$C_2H_3N^+$]. Anal. Calcd for $C_{15}H_{25}BF_4N_3O_3$: C 47.14, H 6.59, N 10.99. Found: C 46.86, H 6.76, N 10.63.

4.3. General procedure for alcohol oxidations

[dibmim]$^+$[BF_4]$^-$ (353 mg, 0.6 mmol) was added to a solution of alcohol (0.5 mmol) in 1.5 g of water containing 5% mmol of ion-supported TEMPO. The reaction mixture was stirred at 30 °C for a given time. The mixture was extracted with ether (3×8 mL) and concentrated under reduced pressure. The filtrate could be reused for next run after the oxidant in reduced form was removed by filtration. The product was purified by flash column chromatography using petroleum ether and Et_2O as eluent. All products were commercially available and identified by comparison of the isolated products with authentic samples.

4.3.1. Benzaldehyde. Oil; ^{1}H NMR ($CDCl_3$, ppm): $\delta=$ 7.52–7.56 (m, 2H; Ar-H), 7.62–7.65 (m, 1H; Ar-H), 7.88–7.90 (m, 2H; Ar-H), 10.03 (s, 1H; CHO); IR (neat): $\nu=1703$ cm^{-1} (C=O); MS (70 eV): *m/z* (%): 106 (100) [M$^+$], 105 (94) [M$^+$ − H], 77 (92) [$C_6H_5^+$].

4.3.2. 4-Methoxybenzaldehyde. Oil; ^{1}H NMR ($CDCl_3$, ppm): $\delta=3.90$ (s, 3H; CH_3), 7.01 (d, ^3J(H,H) = 7.6 Hz, 2H; Ar-H), 7.85 (d, ^3J(H,H) = 7.6 Hz, 2H; Ar-H), 9.89 (s, 1H; CHO); IR (neat): $\nu=1685$ cm^{-1} (C=O); MS (70 eV): *m/z* (%): 136 (76) [M$^+$], 135 (100) [M$^+$ − H].

4.3.3. 4-Chlorobenzaldehyde. Mp: 46–47 °C; ^{1}H NMR ($CDCl_3$, ppm): $\delta=7.53$ (d, ^3J(H,H) = 8.4 Hz, 2H; Ar-H), 7.83 (d, ^3J(H,H) = 8.4 Hz, 2H; Ar-H), 9.99 (s, 1H; CHO); IR (KBr): $\nu=1702$ cm^{-1} (C=O); MS (70 eV): *m/z* (%): 139 (100) [M$^+$], 141 (33) [M$^+$ + 2].

4.3.4. Furaldehyde. Oil; ^{1}H NMR ($CDCl_3$, ppm): $\delta=$ 6.61–6.63 (m, 1H), 7.27–7.30 (m, 1H), 7.70–7.71 (m, 1H), 9.67 (s, 1H; CHO); IR (neat): $\nu=1675$ cm^{-1} (C=O); MS (70 eV): *m/z* (%): 96 (100) [M$^+$], 95 (94) [M$^+$ − H], 39 (58) [$C_3H_3^+$].

4.3.5. Cinnamaldehyde. Oil; ^{1}H NMR ($CDCl_3$, ppm): $\delta=$ 6.73 (dd, ^3J(H,H) = 8.0, 15.6 Hz, 1H; CH), 7.44–7.45 (m, 3H; Ar-H), 7.49 (d, ^3J(H,H) = 15.6 Hz, 1H; CH), 7.56–7.58 (m, 2H; Ar-H), 9.71 (d, ^3J(H,H) = 8.0 Hz, 1H; CH); IR (neat): $\nu=1679$ cm^{-1} (C=O); MS (70 eV): *m/z* (%): 132 (73) [M$^+$], 131 (100) [M$^+$ − H], 103 (56) [$C_8H_7^+$].

4.3.6. Ethyl 4-formylbenzoate. Mp: 156–158 °C; ^{1}H NMR ($CDCl_3$, ppm): $\delta=1.43$ (t, ^3J(H,H) = 6.4 Hz, 3H; CH_3), 4.42 (q, ^3J(H,H) = 6.4 Hz, 2H; CH_2), 7.96 (d, ^3J(H,H) = 8.4 Hz, 2H; Ar-H), 8.21 (d, ^3J(H,H) = 8.4 Hz, 2H; Ar-H), 10.11 (s, 1H; CHO); IR (KBr): $\nu=3058$, 2981, 2924, 1711, 1274, 1102, 733 cm^{-1}; MS (70 eV): *m/z* (%): 178 (3.3) [M$^+$], 149 (100) [$C_9H_9O_2^+$].

4.3.7. 3-Phenylpropanal. Oil; ^{1}H NMR ($CDCl_3$, ppm): $\delta = 2.77$ (t, ^3J(H,H) = 7.2 Hz, 2H; CH_2), 2.95 (t, ^3J(H,H) = 7.2 Hz, 2H; CH_2), 7.18–7.22 (m, 3H; Ar-H), 7.27–7.31 (m, 2H; Ar-H), 9.80 (s, 1H; CHO); IR (film): $\nu = 3029$, 2928, 2826, 1726, 1497, 1454, 747, 701 cm^{-1}; MS (70 eV): *m/z* (%): 134 (58.0) [M^+], 92 (75.3) [$C_7H_8^+$], 91 (100.0) [$C_7H_7^+$].

4.3.8. Hexanal. Oil; ^{1}H NMR ($CDCl_3$, ppm): $\delta = 0.93$ (t, ^3J(H,H) = 7.2 Hz, 3H; CH_3), 1.27–1.36 (m, 4H; CH_2), 1.51–1.58 (m, 2H; CH_2), 2.42 (t, ^3J(H,H) = 7.2 Hz, 2H; CH_2), 9.77 (s, 1H; CHO); IR (film): $\nu = 2960$, 2932, 1718, 1460 cm^{-1}; MS (70 eV): *m/z* (%): 56 (82.1) [$C_4H_8^+$], 44 (100.0) [$C_2H_4O^+$].

4.3.9. Hexan-2-one. Oil; ^{1}H NMR ($CDCl_3$, ppm): $\delta = 0.91$ (t, ^3J(H,H) = 7.2 Hz, 3H; CH_3), 1.27–1.36 (m, 2H; CH_2), 1.52–1.60 (m, 2H; CH_2), 2.14 (s, 3H; CH_3), 2.43 (t, ^3J(H,H) = 7.2 Hz, 2H; CH_2); IR (film): $\nu = 2962$, 2936, 1718, 1360, 1169 cm^{-1}; MS (70 eV): *m/z* (%): 100 (7.8) [M^+], 58 (49.1) [$C_4H_{10}^+$], 43 (100.0) [$C_2H_3O^+$].

4.3.10. 4-Hydroxycyclohexanone. Oil; ^{1}H NMR ($CDCl_3$, ppm): $\delta = 1.95$–2.01 (m, 2H), 2.03–2.08 (m, 2H), 2.28–2.37 (m, 2H), 2.58–2.65 (m, 2H), 3.80 (s, 1H), 4.19–4.23 (m, 1H); IR (KBr): $\nu = 3386$ (OH), 1707 cm^{-1} (C=O); MS (70 eV): *m/z* (%): 114 (90.0) [M^+], 57 (78.4) [$C_3H_5O^+$], 55 (100.0) [$C_3H_3O^+$].

4.3.11. 4-Methylcyclohexanone. ^{1}H NMR ($CDCl_3$, ppm): $\delta = 1.02$ (d, ^3J(H,H) = 6.8 Hz, 3H; CH_3), 1.37–1.48 (m, 2H), 1.86–1.94 (m, 1H; CH), 1.98–2.02 (m, 2H), 2.34–2.38 (m, 4H); IR (neat): $\nu = 1714$ cm^{-1} (C=O); MS (70 eV): *m/z* (%): 112 (43) [M^+], 55 (100) [$C_3H_3O^+$].

4.3.12. Acetophenone. ^{1}H NMR ($CDCl_3$, ppm): $\delta = 2.59$ (s, 3H; CH_3), 7.43–7.47 (m, 2H; Ar-H), 7.54–7.57 (m, 1H; Ar-H), 7.95 (d, ^3J(H,H) = 8.8 Hz, 2H; Ar-H); IR (neat): $\nu = 1686$ cm^{-1} (C=O); MS *m/z* 120 (M^+). MS (70 eV): *m/z* (%): 120 (25) [M^+], 105 (100) [$C_7H_5O^+$], 77 (73) [$C_6H_5^+$].

4.3.13. 4-Methoxyacetophenone. Mp: 37–39°C; ^{1}H NMR ($CDCl_3$, ppm): $\delta = 2.56$ (s, 3H; CH_3), 3.87 (s, 3H; CH_3), 6.94 (d, ^3J(H,H) = 8.4 Hz, 2H; Ar-H), 7.94 (d, ^3J(H,H) = 8.4 Hz, 2H; Ar-H); IR (KBr): $\nu = 1677$ cm^{-1} (C=O); MS *m/z* 150 (M^+). MS (70 eV): *m/z* (%): 150 (29) [M^+], 135 (100) [$C_8H_7O_2^+$].

4.3.14. 4-Bromoacetophone. Mp: 50–51°C; ^{1}H NMR ($CDCl_3$, ppm): $\delta = 2.59$ (s, 3H), 7.61 (d, ^3J(H,H) = 8.4 Hz, 2H; Ar-H), 7.82 (d, ^3J(H,H) = 8.4 Hz, 2H; Ar-H); IR (KBr): $\nu = 1676$ cm^{-1} (C=O); MS *m/z* 198 (M^+), 200 (M+2). MS (70 eV): *m/z* (%): 198 (29) [M^+], 200 (27) [$M^+ + 2$], 183 (99) [$C_7H_4OBr^+$], 185 (100) [$C_7H_4OBr^+$].

4.3.15. 2-Hydroxy-1,2-diphenylethanone. Mp: 132–134 °C; ^{1}H NMR ($CDCl_3$, ppm): $\delta = 4.56$ (d, ^3J(H,H) = 6.0 Hz, 1H; OH), 5.96 (d, ^3J(H,H) = 6.0 Hz, 1H; CH), 7.27–7.34 (m, 5H; Ar-H), 7.38–7.42 (m, 2H; Ar-H), 7.50–7.54 (m, 1H; Ar-H), 7.91–7.93 (m, 2H; Ar-H); IR (KBr): $\nu = 3417$ (OH), 1680 cm^{-1} (C=O); MS (70 eV): *m/z* (%): 212 (3) [M^+], 105 (100) [$C_7H_5O^+$].

Acknowledgements

This work was financially supported by the Natural Science Foundation of China (No. 20225309).

References and notes

1. (a) Choudhary, V. R.; Chaudhari, P. A.; Narkhede, V. S. *Catal. Commun.* **2003**, *4*, 171–175. (b) Smith, M. B.; March, J. *March's Advanced Organic Chemistry: Reaction, Mechanism, and Structure*, 5th ed.; Wiley-Interscience: New York, 2001. (c) Larock, R. C. *Comprehensive Organic Transformations*, 2nd ed.; Wiley-VCH: New York, 1999. (d) Muzart, J. *Chem. Rev.* **1992**, *92*, 113–140.
2. Adam, W.; Saha-Moller, C. R.; Ganeshpure, P. A. *Chem. Rev.* **2001**, *101*, 3499.
3. De Nooy, A. E. J.; Besemer, A. C.; Van Bekkum, H. *Synthesis* **1996**, 1153–1175.
4. (a) Ferreira, P.; Phillips, E.; Rippon, D.; Tsang, S. C.; Hayes, W. *J. Org. Chem.* **2004**, *69*, 6851–6859. (b) Pozzi, G.; Cavazzini, M.; Quici, S.; Benaglia, M.; Dell'Anna, G. *Org. Lett.* **2004**, *6*, 441–443. (c) Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559–2562. (d) Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1989**, *54*, 2970–2972.
5. De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974–6977.
6. Cella, J. A.; Kelley, J. A.; Kenehan, E. F. *J. Org. Chem.* **1975**, *40*, 1860–1862.
7. Inokuchi, T.; Matsumoto, S.; Nishiyama, T.; Torii, S. *J. Org. Chem.* **1990**, *55*, 462–466.
8. (a) Jenny, C. -J.; Lohri, B.; Schlageter, M.; Eur. Pat. Appl. EP 775,684, 1997; U.S. Patent 5,821,374, 1998. (b) De Luca, L.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* **2001**, *3*, 3041–3043. (c) De Luca, L.; Giacomelli, G.; Masala, S.; Porcheddu, A. *J. Org. Chem.* **2003**, *68*, 4999–5001.
9. Bolm, C.; Magnus, A. S.; Hildebrand, J. P. *Org. Lett.* **2000**, *2*, 1173–1175.
10. Miller, R. A.; Hoerrner, R. S. *Org. Lett.* **2003**, *5*, 285–287.
11. (a) Wu, X.; Ma, L.; Ding, M.; Gao, L. *Chem. Lett.* **2005**, *34*, 312–313. (b) Semmelhack, M. F.; Schmid, C. R.; Cortes, D. A.; Chou, C. S. *J. Am. Chem. Soc.* **1984**, *106*, 3374–3376.
12. Liu, R.; Liang, X.; Dong, C.; Hu, X. *J. Am. Chem Soc.* **2004**, *126*, 4112–4113.
13. (a) Fey, T.; Fischer, H.; Bachmann, S.; Albert, K.; Bolm, C. *J. Org. Chem.* **2001**, *66*, 8154–8159. (b) Bolm, C.; Fey, T. *Chem. Commun.* **1999**, 1795–1796. (c) Heeres, A.; van Doren, H. A.; Gotlieb, K. F.; Bleeker, I. P. *Carbohydr. Res.* **1997**, *299*, 221–227. (d) Tsubokawa, N.; Kimoto, T.; Endo, T. *J. Mol. Catal. A: Chem.* **1995**, *101*, 45–50.
14. (a) Pozzi, G.; Cavazzini, M.; Quici, S.; Benaglia, M.; Dell'Anna, G. *Org. Lett.* **2004**, *6*, 441–443. (b) Ferreire, P.; Phillips, E.; Rippon, D.; Tsang, S. C.; Hayes, W. *J. Org. Chem.* **2004**, *69*, 6851–6859. (c) Tanyeli, C.; Gümüs, A. *Tetrahedron Lett.* **2003**, *44*, 1639–1642. (d) Dijksman, A.; Arends, I. W. C. E.; Sheldon, R. A. *Chem. Commun.* **2000**, 271–272.
15. Miyazawa, T.; Endo, T. *J. Polym. Sci., Polym. Chem. Ed.* **1985**, *23*, 2487.
16. (a) Welton, T. *Chem. Rev.* **1999**, *99*, 2071–2084. (b) Wasserscheid, P.; Keim, W. *Angew. Chem., Int. Ed.* **2000**, *39*, 3772–3789. (c) Wilkes, J. S. *Green Chem.* **2002**, *4*, 73–80.

(d) Wasserscheid, P.; Welton, T. In *Ionic Liquids in Synthesis*; Wiley-VCH, Weinheim: Germany, 2003. (e) Earle, M. J.; Katdare, S. P.; Seddon, K. R. *Org. Lett.* **2004**, *6*, 707–710.

17. (a) Zhao, D.; Fei, Z.; Geldbach, T. J.; Scopelliti, R.; Dyson, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 15876–15882. (b) Geldbach, T. J.; Dyson, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 8114–8115. (c) Song, C. E. *Chem. Commun.* **2004**, 1033–1034. (d) Audic, N.; Clavier, H.; Mauduit, M.; Guillemin, J. C. *J. Am. Chem. Soc.* **2003**, *125*, 9246–9249. (e) Brnger, R. P. J.; Silva, S. M.; Kamer, P. C.; van Leeuwen, P. W. N. M. *Chem. Commun.* **2002**, 3044–3045. (f) Dupont, J.; de Souza, R. F.; Suarez, P. A. Z. *Chem. Rev.* **2002**, *102*, 3667–3692.
18. Wu, X.; Ma, L.; Ding, M.; Gao, L. *Synlett* **2005**, *4*, 607–610.
19. Qian, W.; Jin, E.; Bao, W.; Zhang, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 952–955.
20. Using DMF or DMSO as a solvent, the yield was below 10%. We employed 1-bromo-2-chloroethane and 1,3-dibromopropane as a linker, but we could not obtain the desired product because of serious elimination reaction.
21. Organic reactions conducted in aqueous media may offer advantages over those occurring in organic solvents due to low cost, no toxicity, easy separation and environmental benign. (a) In *Organic Synthesis in Water*; Blackie Academic: London, 1998. (b) In *Organic Reactions in Aqueous Media*; Wiley: New York, 1997.
22. (a) Wilkes, J. S.; Zaworotko, M. J. *Chem. Commun.* **1992**, 965–967. (b) Holbrey, J. D.; Seddon, K. R. *J. Chem. Soc., Dalton Trans.* **1999**, 2133–2139.

Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron

Tetrahedron 62 (2006) 563–577

Synthetic sulfated glucuronosyl paragloboside (SGPG) and its use for the detection of autoimmune peripheral neuropathies

Reynald Chevalier,[a] Benoît Colsch,[b,c] Carlos Afonso,[c] Nicole Baumann,[b]
Jean-Claude Tabet[c] and Jean-Maurice Mallet[a,*]

[a] *Ecole Normale Supérieure, UMR CNRS 8642, 24, rue Lhomond, 75231 Paris cedex 05, France*
[b] *Laboratoire de Neurochimie, UMR INSERM 711, Hôpital de la Salpêtrière, 47 bd de l'hôpital, 75651 Paris cedex 13, France*
[c] *Université Pierre et Marie Curie, UMR CNRS 7613, 4 Place Jussieu, 75252 Paris cedex 05, France*

Received 10 August 2005; revised 6 October 2005; accepted 10 October 2005

Abstract—The sulfated glucuronosyl paragloboside SO_4-3-GlcA(β1-3)Gal-(β1-4)GlcNAc(β1-3)Gal-(β1-4)Glcβ(1-1′)Cer (SGPG) is a specific constituent of the peripheral nervous system involved in human dysimmune neuropathies. Although it is highly immunogenic in human pathology, it is not a major constituent of peripheral nerve in humans. Pure SGPG is very difficult to obtain from natural sources, but is needed for the design of efficient and reproducible immunoassays. We describe a new chemical synthesis of this important glycolipid with a stearic tail, including its complete characterization by mass spectrometry and its use in the detection of autoimmune neuropathies.

1. Introduction

Sphingoglycolipids are constituents of cellular structures of the peripheral nervous system (PNS) and the central nervous system (CNS). Several autoimmune neuropathies can be characterized, not only on clinical and electrophysiological grounds, but also on immunochemical grounds, related to the nature of the antigen recognized by antiglycolipid antibodies. The sulfated glucuronosyl paragloboside SO_4-3-GlcA(β1-3)Gal-(β1-4)GlcNAc-(β1-3)Gal-(β1-4)Glcβ(1-1′)Cer (SGPG) is a specific constituent of the peripheral nervous system. The terminal trisaccharide sequence of the SGPG (glucuronosyl sulfate-galactosyl *N*-acetylglucosaminyl) is the HNK-1 epitope, common to the SGPG lipid, and its derivatives with two lactosaminyl residues (Fig. 1), and to several adhesion molecules and myelin proteins, among which is P0, the major protein of PNS, and MAG (myelin-associated glycoprotein).[1] Clinico-biological studies in neuropathies have been performed, mainly to search for anti MAG/SGPG antibodies (reviewed in Ref. 2). Interestingly, the predominantly sensory demyelinating neuropathies with monoclonal immunoglobulins of the M type (IgMs) have antiMAG/SGPG activities, whereas axonal neuropathies, predominantly motor, or some cases of motor neuron diseases[3] with monoclonal IgMs present only anti SGPG activity.[4] Thus, there is a broad spectrum of dysimmune neuropathies characterized by anti SGPG antibodies and this has therapeutic consequences.

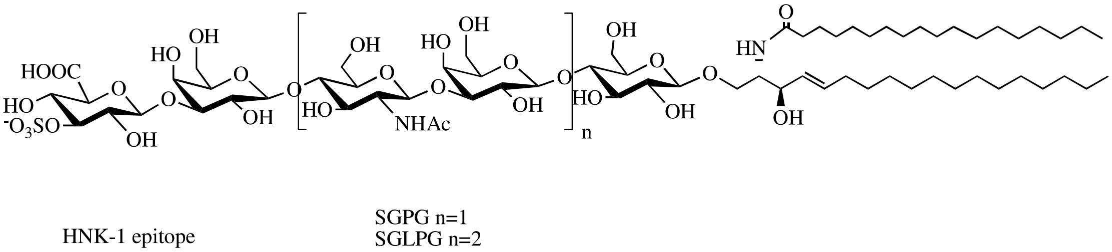
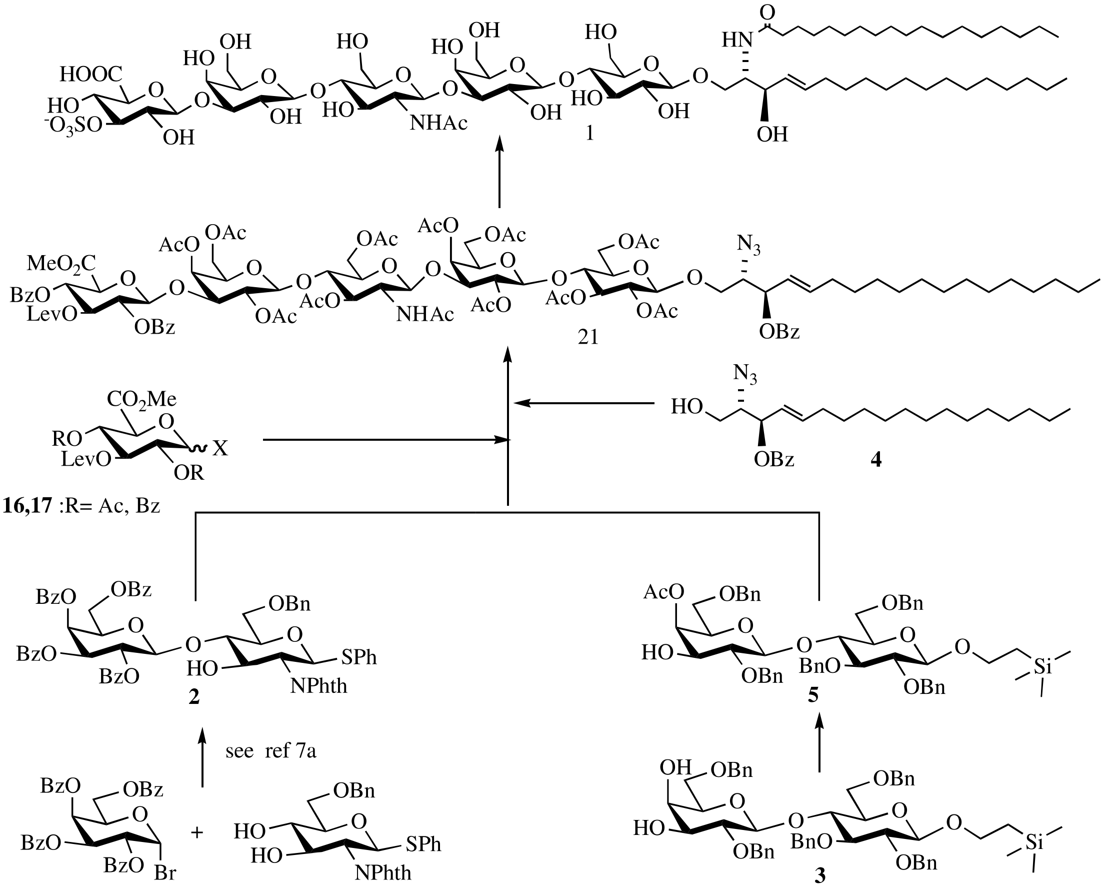


Figure 1.

Keywords: SGPG; Sphingoglycolipid; Chemical synthesis; Peripheral nervous system; Neuropathy; Electrospray mass spectrometry.

* Corresponding author. Tel.: +33 1 44323337; fax: +33 1 44323397; e-mail: Jean-Maurice.Mallet@eas.fr;
URL: http://www.chimie.ens.fr/glycoscience/

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.10.021



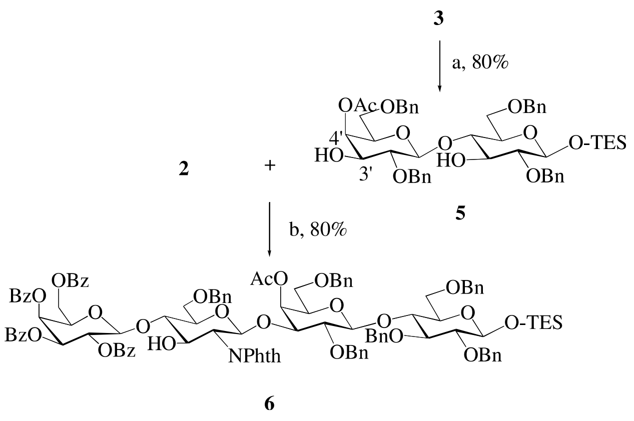
Scheme 1. Retrosynthetic analysis.

SGPG is not commercially available. Furthermore, although it is highly immunogenic in human pathology, it is not a major constituent of peripheral nerve in humans and is only a minor constituent of PNS of several animal species.[5] Thus, its purification remains a hard task. For this reason, it appears important for clinical purposes to synthesize this glycolipid.[6] In this paper, we describe a new chemical synthesis of this important glycolipid with a stearic tail, including its complete spectroscopic characterization and its use in immunodetections.

2. Chemical synthesis

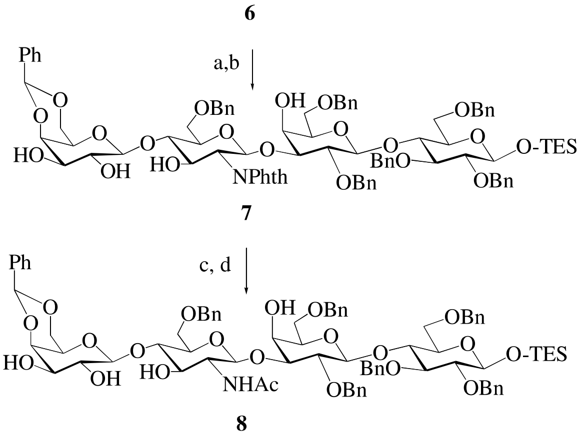
The 1 + 2 + 2 synthesis proposed (Scheme 1) is based upon our previous synthetic work[7] on lacto glycolipids. All the glycosidic linkages are 1,2 *trans*, this stereochemistry was easily assured by the use of a participating group at C2 of each glycosyl donors (acetate, benzoate and phthalimido (Phth)). The main difficulty was the expected 'placidness' of the two deactivated glycosyl donors: the acylated glucuronic unit (**16**, **17**) and the acetylated pentasaccharide imidate **20**. Three of the four key intermediates have been prepared previously: the lactose unit **3**,[8] the lactosamine unit **2**[7a] and the azidosphingosine **4**[9] and have been prepared according to a literature procedure.

We tried first the glycosylation between **2** and **3** using NIS, TfOH as a promoter in dichloromethane. The hydroxyl group at position 3 was expected to be the more reactive of the two hydroxyl groups. In contrast to previous results obtained using a Lewis X trisaccharide donor,[7a,b] a mixture of two regioisomers (the expected 3-regioisomer (55%) and its 4-regioisomer (30%)) has been obtained. In order to avoid this side reaction, we decided then to protect the position 4 of **3** by acetylation using the Lemieux method[10] yielding **5** (95%) (Scheme 2). The acetate position was checked in ^{1}H NMR (H-4′: 5.4 ppm ($J_{4,3} = 3.1$ Hz) and H-3′: 3.6 ppm). The glycosylation between **2** and **5** gave, uneventfully, rise to the formation of **6** (80%) (Scheme 2). The β-stereochemistry of the newly formed glycosidic bond was checked by ^{1}H NMR ($J_{1,2} = 8.5$ Hz).



Scheme 2. Reagents: (a) $MeC(OEt)_3$, CSA then AcOH 80%, 81%; (b) NIS, TfOH, CH_2Cl_2, −30 °C, 80%.

This tetrasaccharide **6** was transformed in four steps into a glycosyl acceptor **8**, ready to react with a glucuronosyl donor (Scheme 3). The hydroxyl group at position 3 of Gal IV is usually the more reactive of the four hydroxyl group present in **8**.



Scheme 3. Reagents: (a) MeONa/MeOH, CH_2Cl_2, 88%; (b) $PhCH(OMe)_2$, CSA, CH_3CN, 82%, (c) N_2H_4, EtOH, 80 °C, (d) Ac_2O, MeOH, 81% (two steps).

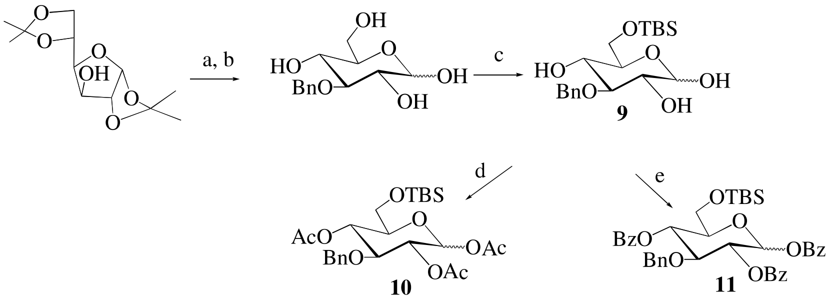
Two glucuronosyl donors have been synthesized (Schemes 4 and 5). They have a levulinoyl group at C3. This cetoester, selectively removed in presence of acetate or benzoate, is a classical and reliable choice in sulfated glycosaminoglycan chemical synthesis.[11] We introduced first a levulinate group at C3 of diacetone D-glucose and then tried without success to remove the two isopropylidene groups using hot aqueous AcOH. We moved then to a more stable temporary group, the benzyl ether. Thus, 3-*O*-benzyl glucose[12] was prepared in two steps from diacetone glucose, then silylated by terbutyldimethylsilyl chloride in pyridine[13] followed by one-pot acylation with Ac_2O to give **10** (or with BzCl to give **11**) (Scheme 4).

Jones oxidation, followed by methylation, afforded the two methyl 3-*O*-benzyl uronates in good yields. Exchange of benzyl to levulinate was at this stage uneventful. The acylated products **14** and **15** have been then transformed into glucuronosyl bromides **16** and **17** in good yield using HBr in acetic acid (Scheme 5).

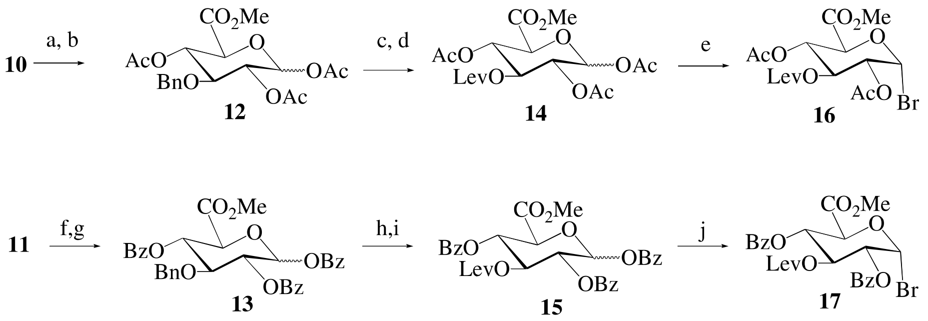
The [**8**+**16**] condensation in dichloromethane promoted by silver triflate or with Ag_2CO_3/I_2[14] at room temperature failed to give any pentasaccharide. However, the benzoylated bromide **17** (2 equiv) finally gave the pentasaccharide **18** in an acceptable yield of 50% (72% based on recovered **8**) (Scheme 6). We tried to improve this step using analogous benzoylated thiophenyl glycosides and trichloroacetimidate, without any success.

The pentasaccharide **18** was then transformed into a glycosyl donor in four steps (Scheme 7): first removal of the benzylidene and benzyl groups (H_2, Pd/C) followed by acetylation to give **19**. The regioselectivity of the last glycosylation was easily checked by NMR (H-3 Gal IV $\delta = 3.8$ ppm). The trimethylsilylethyl protecting group was then removed and the α imidate **20** was prepared using trichloroacetonitrile and DBU as a base.

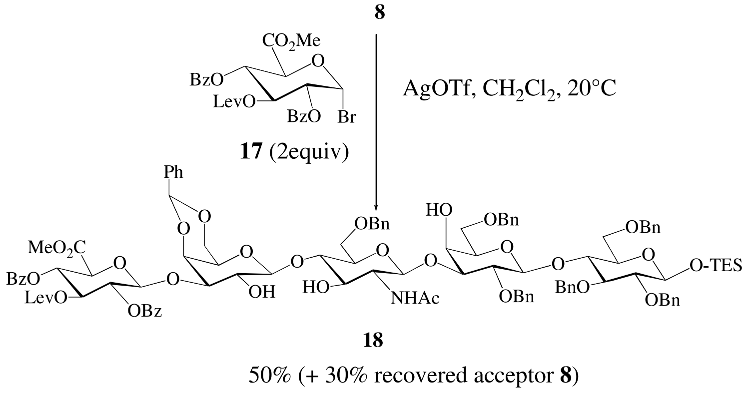
Coupling with **4** gave the glycoconjugate **21** with a good yield (75%) (Scheme 8). Compound **21** was then easily converted into **1** in a few steps (Scheme 9): reduction of azide with PPh_3[15] in aqueous THF at 50 °C, introduction of



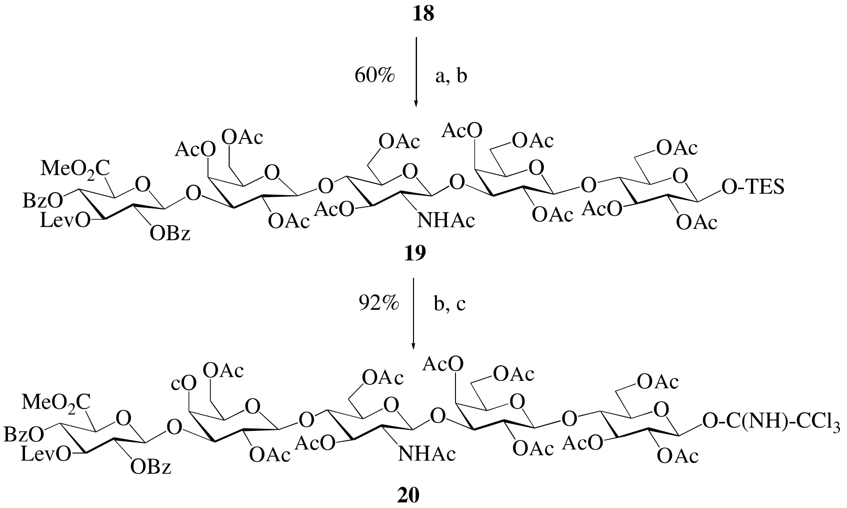
Scheme 4. Reagents: (a) BnBr, NaH, DMF; (b) H_2O, IR 120 (H^+), 85% (two steps); (c) TBS-Cl, Pyr., (d) Ac_2O, Pyr., 88% (two steps); (e) BzCl, Pyr. 90% (two steps).



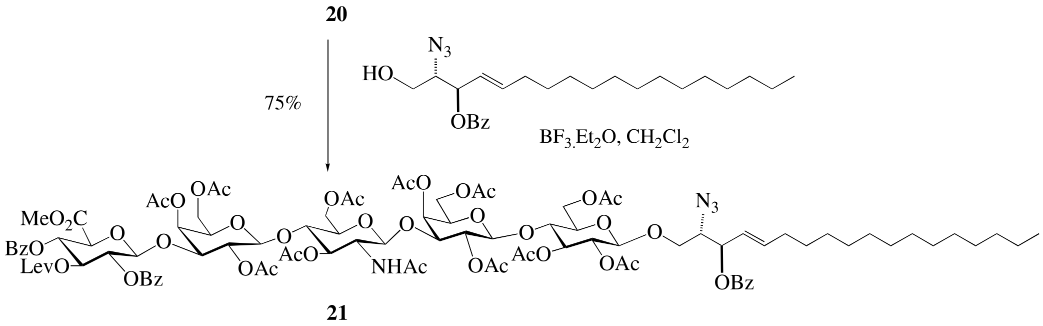
Scheme 5. Reagents (a) CrO_3, H_2SO_4, acetone; (b) MeI, $KHCO_3$, DMF 65% (two steps); (c) H_2, Pd/C, MeOH; (d) Lev_2O, Pyr., 82% (two steps); (e) HBr, AcOH, CH_2Cl_2, 90%; (f) CrO_3, H_2SO_4, acetone; (g) MeI, $KHCO_3$, DMF 68% (two steps); (h) H_2, Pd/C, MeOH; (i) Lev_2O, Pyr., 80% (two steps); (j) HBr, AcOH, CH_2Cl_2, 70%.



Scheme 6.



Scheme 7. Reagents: (a) H_2, Pd/C, MeOH; (b) Ac_2O, Pyr.; (c) CF_3COOH, CH_2Cl_2, 0–20 °C; (d) Cl_3CCN, DBU, CH_2Cl_2.

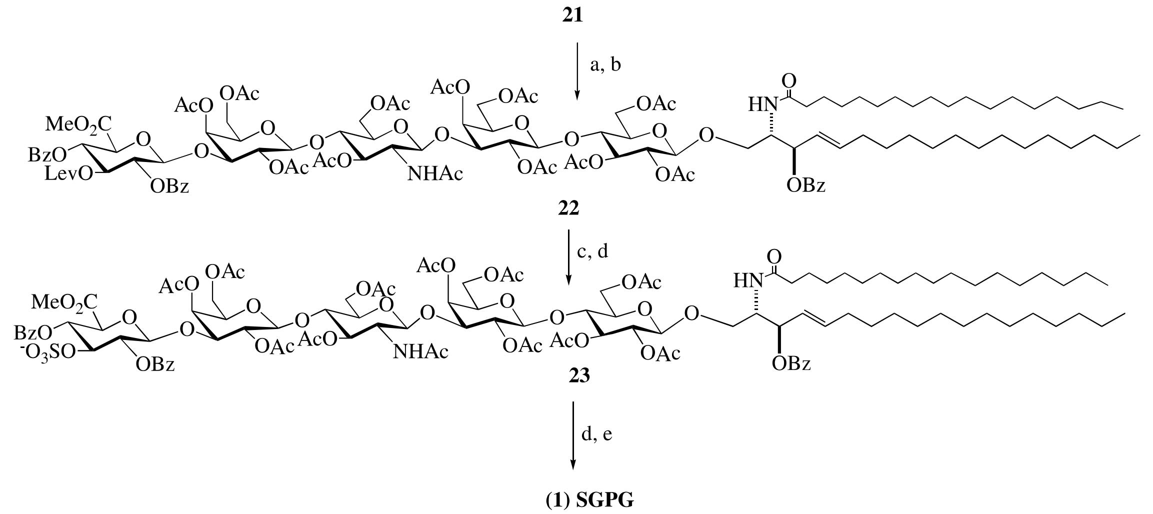


Scheme 8.

stearic acid, with DCC as a coupling agent; removal of levulinate with hydrazine monoacetate, and sulfatation of the free hydroxyl group with $SO_3 \cdot NMe_3$ in DMF at 50 °C. Final deprotection was done in two steps, that is, saponification of the methyl ester with lithium hydroxide, followed by an treatment with MeONa/MeOH/THF. This two steps sequence limits the β elimination. The ^1H NMR spectrum in DMSO-d_6 (see Fig. 2 for ethylenic and anomeric proton signals) was found in accordance with reported spectrum for natural SGPG.[6b]

3. Mass characterisation of synthetic SGPG

The negative ion ESI mass spectrum of the synthetic SGPG (Fig. 3a), recorded using the negative ion mode, displayed various singly charged ions at *m/z* 1510.1 and *m/z* 1532.1 and doubly-charged ions at *m/z* 754.5, that correspond to the, $[M-H]^-$, $[M-2H+Na]^-$ and $[M-2H]^{2-}$ quasi-molecular species, respectively. From this mass spectrum, it appears that the molecular weight of the synthetic compound was 1511.1 u consistent with the expected



Scheme 9. Reagent: (a) PPh_3, THF, H_2O, 50 °C; (b) DCC, stearic acid, CH_2Cl_2, 78% (two steps); (c) $N_2H_5 \cdot AcO$, EtOH, 81%; (d) $(Me)_3N–SO_3$, DMF, 50 °C, 80%; (e) LiOH, THF, H_2O, 0 °C; (f) MeONa, MeOH, THF, 90% (two steps).

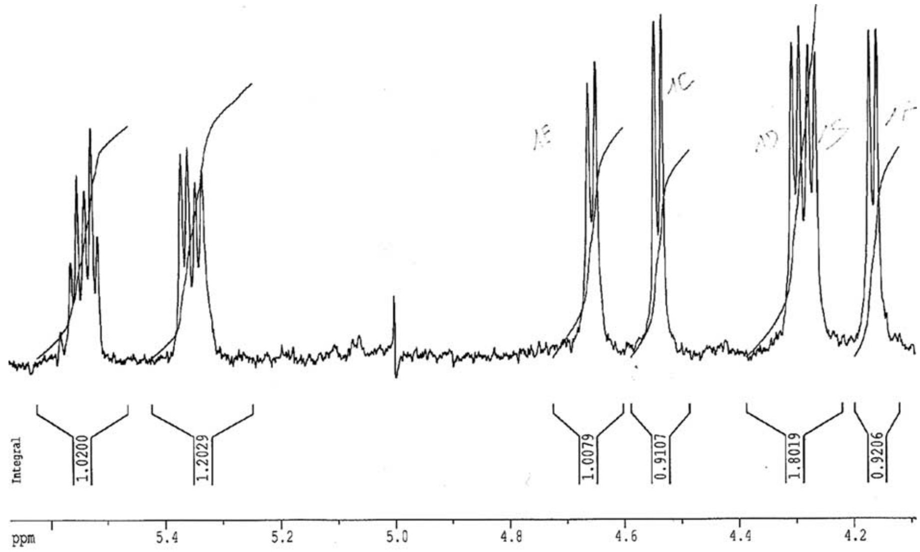


Figure 2. ^{1}H NMR selected data (DMSO-d_6, 400 MHz): ethylenic and anomeric protons.

monoisotopic peak as well as with to the natural isotopic cluster distribution, which is superimposable on the calculated cluster distribution (Fig. 3a). Furthermore, prompt fragmentations are limited since only ions at *m*/*z* 1492.1 (i.e., loss of water) and *m*/*z* 357.0 raised up to 10% of base peak (i.e., at *m*/*z* 1532.1), under these ESI source conditions. These quasi-molecular species being sufficiently abundant they can be studied by MS/MS under low energy collision excitation (CID processes).

Firstly, the collision excitation of the deprotonated molecule (*m*/*z* 1510.1) shows this precursor ion was very stable since only two product ions are displayed at *m*/*z* 1430.1 (100%) and *m*/*z* 1334.1 (5%) in the CID spectrum (not reported herein). These ions are promoted from the deprotonated molecule carrying out the negative charge at the sulfate site (the larger acidic group in gas phase) by releasing the SO_3 neutral (i.e., 80 u) and the desulfated glucuronic terminal unit, respectively. The latter loss is generated by sulfate migration form the C3 position of terminal residue likely to hydroxyl of the neighbouring glucosidic unit (study in progress) yielding a terminal sulfated glucose in the *m*/*z* 1334.1 production. This behaviour makes ambiguity on the sulfate group location.

In order to obtain more information on the sequence (except for the sulfate position), in situ consecutive ion excitations (called ‘tickle excitation’) were applied: (i) to the first generation product *m*/*z* 1430.1 ion and (ii) in second step, to the second generation product *m*/*z* 1412.2 ion (formed by water release from the previous precursor of the first generation). The recorded CID spectrum (Fig. 3b) displays a series of the losses of 158 u (glucuronic unit having lost an OH group), 162 u (glucosidic unit), 203 u (GlcNAc residue) produced either by consecutive fragmentations or directly by competitive cleavages in the ion trap cell. These different neutral losses give rise to the formation of the following ions at *m*/*z* 1412.3, *m*/*z* 1254.2, *m*/*z* 1092.1, *m*/*z* 889.9, *m*/*z* 726.7, and *m*/*z* 564.6 corresponding to the Y_i series (without significant presence of the complementary B_j series)

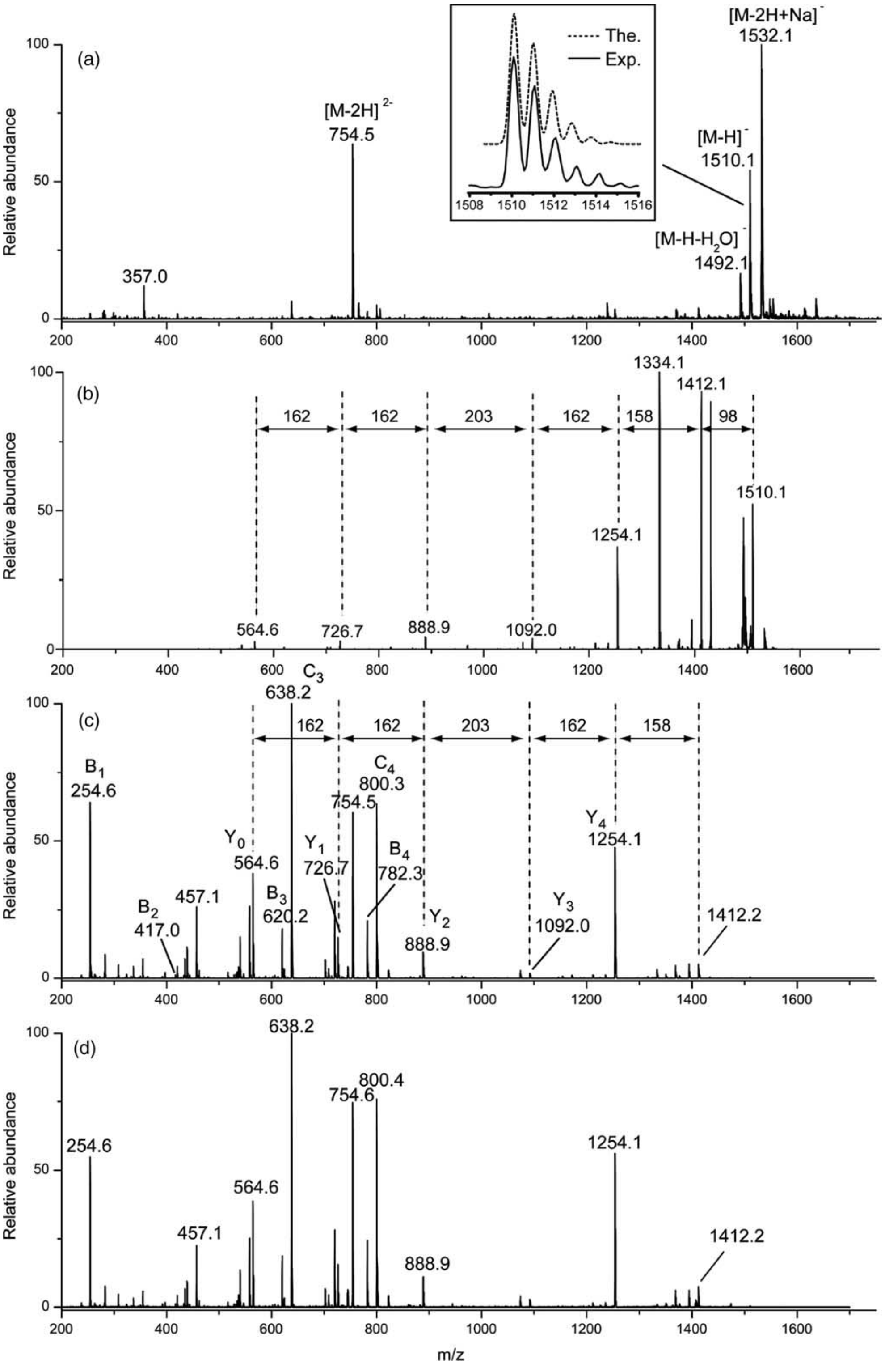


Figure 3. Negative ion ESI mass spectrum of synthetic-SGPG (a) and MS^2 experiments under CID conditions of singly-deprotonated (b) and doubly-deprotonated $[M-2H]^{2-}$ synthetic SGPG (*m/z* 754.5) (c) in comparison with CID spectrum of the doubly deprotonated natural SGPG recorded in same experimental conditions (d).

according to Domon and Costello's nomenclature.[16] They are produced after the SO_3 release by charge promoted competitive cleavages of sugar linkages and the charge is retained at the ceramide moiety. This orientation can be expected assuming that the charge location occurs at the ceramide amide group because of its particular gas phase acidity relative to other acidic sites. This observed series of product ions is consistent with the proposed sequence without assuring the sulfate position on glucuronic acid moiety.

Evidence of its location as well as the total sequence in one scanning has been achieved from the collision excitation of the doubly-deprotonated $[M-2H]^{2-}$ molecule (*m/z* 754.5).

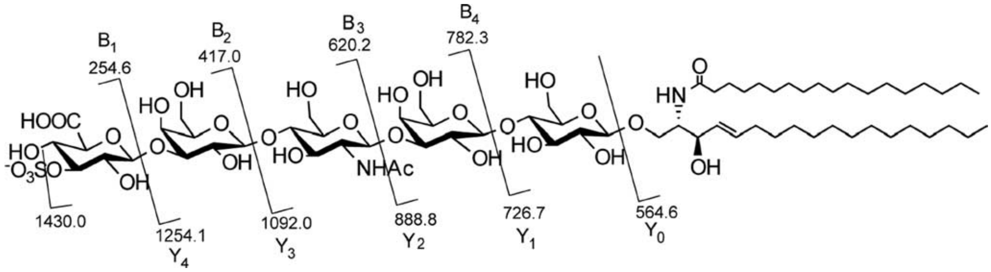


Figure 4. Main complementary product ions of the deprotonated synthetic-SGPG (C18:0; d18:1) according to Domon and Costello's nomenclature. These cleavages are observed from the doubly charged SGPG.

The CID spectrum of this precursor ion (Fig. 3c) displays different series of singly-charged product ions. These series are complementary and are noted as Y_i and B_i (Fig. 4). Interestingly, two abundant complementary product ions (more than 50% of base peak at *m/z* 638.2) appear at *m/z* 1254.1 to *m/z* 254.6 (Fig. 3c) corresponding to the Y_4 and B_1 ions (Fig. 4) give immediately the evidence on the sulfate location on the terminal glucuronidic residue. Other B_j/Y_i couples of complementary product ions are too observed at *m/z* 417.0 /*m/z* 1092.0, *m/z* 620.2/*m/z* 888.9, *m/z* 782.3/*m/z* 726.7, which confirm the SGPG whole sequence as well as the presence of sulfate on glucuronidic unit. In addition to the previous series is accompanied by other ions such as the C_4, C_3, and C_2 product ions corresponding to *m/z* 800.3, *m/z* 638.2, *m/z* 435.3, respectively, (Fig. 4). However, the complementary product Z_i ions are not observed, which indicates that they decompose into low *m/z* fragment ions beyond the product ion *m/z* ratio range (the parent ion *m/z* values must be four times lower than that of its product ions). This value is related to the low mass cut-off fixed automatically by the software of the mass spectrometer. Furthermore, from all the product B_j and C_j ions, a 80 u neutral loss is released systematically (Table 1).

Table 1. Observed consecutive loss of SO_3 (80 u) from each product B_j and C_j ions generated from the precursor doubly-deprotonated $[M-2H]^{2-}$ molecule

Series of ions	$i=4$	$i=3$	$i=2$
B_j	782.3→702.3	620.2→540.2	416.8→336.8
C_j	800.3→720.3	638.2→558.2	435.0→354.9

Finally, to obtain a definitive confidence in our interpretation, the same MS/MS experiment was performed from doubly-deprotonated natural SGPG (Fig. 3). The recorded fingerprints represented by their respective CID spectra were superimposable. Furthermore, even the peaks characterized by very weak abundances are present with similar relative abundances, which confirms the proposed SGPG structure.

4. Immunology

Elisa measurements have been done on 96-well micro plates according to the established procedure for antiglycolipid antibody Elisa[17] with two minor modifications: 100 ng of SGPG were coated per well (instead of 200 ng of glycolipid), and the enzymatic reaction was quenched 3 M HCl (instead of 3 M H_2SO_4).

We compared the sera of 49 patients with predominantly sensory peripheral neuropathies associated with the presence of a monoclonal IgM. We were able, with this synthetic SGPG (**1**), to clearly classify them into two groups: 24 had anti SGPG antibodies, 25 were completely negative (that is under the detection level). Anti SGPG antibodies titers of the 24 positives patient are shown in Figure 5 and confirm the relation between SGPG and the neuropathy, which is important for therapeutic purpose.[18] The titers were extremely variable and no correlation can be clearly established with the total amount of monoclonal IgM.

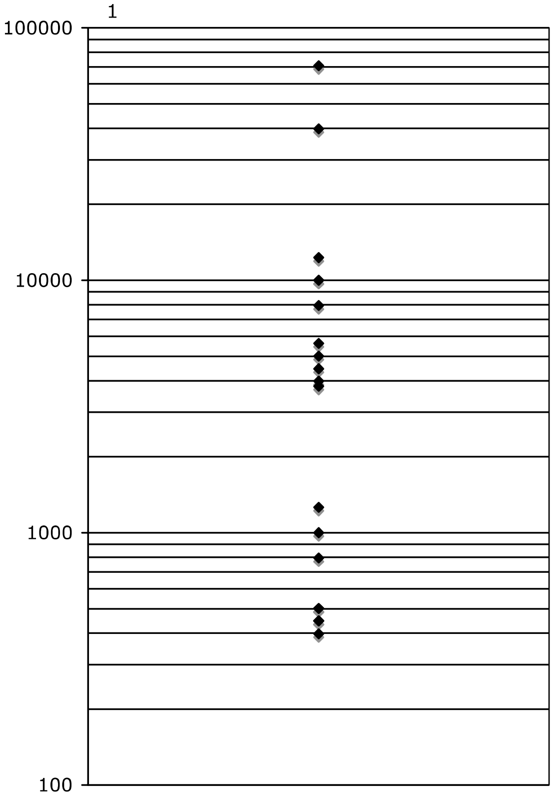


Figure 5. Anti SGPG antibodies titers, in predominantly sensory demyelinating neuropathy with monoclonal IgM. Negative sera are not shown.

This technique is much more sensitive (up to 1000 fold) than the previously used one using crude nerve extracts purified and immunodetected on a thin-layer chromatography plate.[19] For instance, patients under 1000 in Figure 5 were not diagnosed with this technique. This improved technique is now in use in routine analysis in Salpétrière hospital for diagnosis of neuropathies.

5. Conclusion

The synthetic product, although containing a single fatty acid, has the same specificity for IgM SGPG antibodies as the natural product (data not shown). The ELISA test that we have set up for clinical purposes is considerably more sensitive than immunodetection on thin-layer chromatography, and thus will allow the detection of dysimmune neuropathies, which were undiagnosed in the past. This may have therapeutic consequences, as treatments are becoming more and more specific and designed to lower antibody concentration or to interfere with immunopathogenic mechanisms. It may be that the use of solid-phase immunoadsorbents containing a reactive oligosaccharide, will permit a more selective therapy for antibody-mediated neuropathies. Synthesis of ganglioside epitopes for oligosaccharide specific immunoadsorption therapy has been suggested for the Guillain–Barré syndrome, with the aim of removing auto-antibodies either by using soluble blocking ligands administered systematically or as immunoaffinity ligands for use as extracorporeal immunoadsorbents.[20,21] This type of approach could be used for other antigens such as SGPG.

6. Experimental

6.1. General procedures

All compounds were homogeneous by TLC analysis and had spectral properties consistent with their assigned structures. Melting points were determined in capillary tubes in a Büchi 510 apparatus, and are uncorrected. Optical rotations were measured with a Perkin-Elmer Model 241 digital polarimeter at 22±3 °C. Compound purity was checked by TLC on Silica gel 60 F_{254} (E. Merck) with detection by charring with sulfuric acid. Column chromatography was performed on Silica gel 60 (E. Merck). ^{1}H NMR spectra were recorded with Brüker AM 250, AM 400 instruments. Elemental analyses were performed by Service d'Analyse de Université Pierre et Marie Curie. Chemical ionization and FAB mass spectrometry were recorded with Jeol MS700: CI (gas: ammonia); FAB (matrix: NBA, NaI). MALDI-TOF mass spectra were recorded with PerSpective Biosystems Voyager Elite (Framingham, MA, USA) equipped with a nitrogen laser (337 nm) using a 2,5-dihydroxybenzoic acid (2,5-DHB) matrix.

6.2. Mass spectrometry procedure

SGPG was analyzed by using an electrospray ionization (ESI)-ion-trap mass spectrometer[22] (Esquire 3000, Bruker) (Bremen, Germany). The source conditions were as follow: capillary high voltage 3500 V, capillary exit −50 V, skimmer 1 −20 V. The ion analysis occurred within a scan rate of 13,000 Th/s using a mass/charge ratio range of 3000 Th by using analytical scan mode through resonant ion ejection to the non-linear field at $\beta_z = 2/3$. The injection low mass cut off (LMCO) was 70 Th. Negative ion mode detection was used. The automated ion charge control (ICC) was set to 10,000 in order to avoid space charge effect. Sequential MS^n experiments were performed under resonant excitation conditions from precursor ion selected by application of broadband frequency excitation with a notch allowed a m/z ratio selection window of 2 Th. In the case of MS^n application (with $n > 2$), when chosen precursor ion was characterized by a too low abundance, it was directly excited by application of resonant frequency without to use the ion selection step. The LMCO used during the collision induced dissociation (CID) experiments (related to the excitation at particular β_z value) was set to 27% of the mass to charge ratio of the precursor ion.

6.2.1. 2-(Trimethylsilyl)ethyl (2,6-di-*O*-benzyl-4-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (5). To a stirred solution of **3** (9 g, 10 mmol) in triethyl orthoacetate (30 mL) was added, at room temperature, CSA (200 mg). After 30 min, aqueous acetic acid 80% (26 mL) was added dropwise. The mixture was stirred (15 min) and evaporated in vacuum. The residue was purified by flash chromatography (eluent, 20% EtOAc in cyclohexane) to afford **5** (9.3 g, 95%) as a colourless oil. $[\alpha]_D$ −10 (c 1 in chloroform); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43–7.30 (m, 25H, arom.), 5.40 (dd, 1H, $J_{4-3} = 3.4$ Hz, $J_{4-5} = 0.6$ Hz, H-4B), 5.03 (d, 1H, $J_{gem} = 10.5$ Hz, CHPh), 4.97 (d, 1H, $J_{gem} = 11.0$ Hz, CHPh), 4.87 (d, 1H, $J_{gem} = 11.4$ Hz, CHPh), 4.82 (d, 1H, $J_{gem} = 10.5$ Hz, CHPh), 4.79 (d, 1H, $J_{gem} = 11.0$ Hz, CHPh), 4.73 (d, 1H, $J_{gem} = 11.4$ Hz, CHPh), 4.65 (d, 1H, $J_{gem} = 12.0$ Hz, CHPh), 4.53 (d, 1H, $J_{1-2} = 7.7$ Hz, H-1B), 4.51 (d, 1H, $J_{gem} = 12.0$ Hz, CHPh), 4.49 (d, 1H, $J_{gem} = 12.0$ Hz, CHPh), 4.45 (d, 1H, $J_{1-2} = 7.7$ Hz, H-1A), 4.29 (d, 1H, $J_{gem} = 12.0$ Hz, CHPh), 4.11–4.08 (m, 1H, O–C*H*–$CH_2Si(CH_3)_3$), 4.04 (dd, 1H, $J_{4-3} = 9.0$ Hz, $J_{4-5} = 9.5$ Hz, H-4A), 3.97–3.80 (m, 2H, H-6A), 3.72–3.67 (m, 1H, H-3B), 3.69–3.65 (m, 1H, O–C*H*–$CH_2Si(CH_3)_3$), 3.63 (t, 1H, $J_{3-2} = 9.0$ Hz, H-3A), 3.57 (dt, 1H, $J_{5-6} = 6.6$ Hz, H-5B), 3.48–3.43 (m, 3H, H-2B, H-2A and H-5A), 3.38 (d, 2H, H-6B), 2.40 (d, 1H, $J_{OH-3} = 2.4$ Hz, OH), 2.09 (s, 3H, O–C=O–CH_3), 1.10 (m, 2H, O–CH_2–C*H*$_2$Si$(CH_3)_3$), 0.09 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (100 MHz): δ 170.9 (O–*C*=O–CH_3), 139.0, 138.7, 138.2, 138.1 and 137.9 (5C arom.), 128.4–127.3 (25CH arom.), 103.1 (C-1A), 102.3 (C-1B), 82.7 (C-3A), 81.8 (C-2B), 80.0 (C-2A), 76.5 (C-4A), 75.2 (CH_2Ph), 75.0 (C-5A), 74.9 (CH_2Ph), 74.9 (CH_2Ph), 73.3 (CH_2Ph), 73.1 (CH_2Ph), 72.4 (C-3B), 71.9 (C-5B), 69.5 (C-4B), 68.2 (C-6A), 67.4 (O–*C*H$_2$–CH_2Si–), 67.1 (C-6B), 20.8 (–O–C=O–*C*H$_3$), 18.4 (O–CH_2–*C*H$_2$Si–), −1.4 (Si(*C*H$_3$)$_3$); MS m/z (CI, NH_3): 952.7 $(M+NH_4)^+$; Anal. Calcd for $C_{54}H_{66}O_{12}Si$ (935.204): C 69.35, H 7.11; found C 69.30, H 7.17.

6.2.2. 2-(Trimethylsilyl)ethyl(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-(1→4)-(6-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-(1→3)-(4-*O*-acetyl-2,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (6). To a stirred mixture of **2** (6.64 g, 6.2 mmol), **5** (5.8 g, 6.2 mmol) and MS-4 Å (15 g) in anhydrous CH_2Cl_2 (150 mL) were successively added, at −30 °C and under argon, NIS (2.8 g, 12.4 mmol) and TfOH (0.165 mL, 1.86 mmol). The mixture was stirred for 30 min at −30 °C, neutralized by saturated sodium hydrogencarbonate and filtered through Celite. The filtrate was washed with saturated sodium thiosulfate, brine, dried ($MgSO_4$) and evaporated in vacuum. The residue was purified by flash chromatography (eluent gradient, 20% EtOAc in cyclohexane) and precipitated (EtOAc/hexanes) to afford **6** (9.4 g, 80%) as a white powder. $[\alpha]_D$ +48 (*c* 1 in chloroform); mp: 153–154 °C (EtOAc/hexanes); ^1H NMR (400 MHz, $CD_3C{=}OCD_3$): δ 8.24–7.15 (m, 54H, arom.), 6.21 (dd, 1H, $J_{4-3}=2.8$ Hz, $J_{4-5}=0.7$ Hz, H-4D), 6.03 (m, 2H, H-2D and H-3D), 5.65 (de, 1H, $J_{4-3}=3, 6$ Hz, H-4B), 5.59 (d, 1H, $J_{1-2}=8.5$ Hz, H-1C), 5.57 (d, 1H, $J_{1-2}=7.0$ Hz, H-1D), 5.10 (d, 1H, $J_{gem}=10.7$ Hz, CHPh), 5.00 (d, 1H, $J_{gem}=11.5$ Hz, CHPh), 5.00–4.90 (m, 1H, H-5D), 4.90 (dd, 1H, $J_{6b-6a}=11.5$ Hz, $J_{6b-5}=4.0$ Hz, H-6Db), 4.87 (d, 1H, $J_{OH-3C}=2.1$ Hz, OH), 4.85 (d, 1H, $J_{gem}=11.5$ Hz, CHPh), 4.76 (d, 1H, $J_{gem}=10.7$ Hz, CHPh), 4.79–4.73 (m, 1H, H-3C), 4.63 (d, 1H, $J_{gem}=12.2$ Hz, CHPh), 4.59 (d, 1H, $J_{gem}=12.2$ Hz, CHPh), 4.58 (d, 1H, $J_{1-2}=7.8$ Hz, H-1B), 4.57 (d, 1H, $J_{gem}=12.4$ Hz, CHPh), 4.58–4.53 (m, 1H, H-6Da), 4.53 (d, 1H, $J_{gem}=12.2$ Hz, CHPh), 4.50 (d, 1H, $J_{1-2}=7.7$ Hz, H-1A), 4.40 (d, 2H, $J_{gem}=12.2$ Hz, 2CHPh), 4.38 (d, 1H, $J_{gem}=12.2$ Hz, CHPh), 4.35 (d, 1H, $J_{gem}=12.4$ Hz, CHPh), 4.28 (dd, 1H, $J_{2-3}=10.8$ Hz, H-2C), 4.12–4.06 (m, 2H, O–C*H*–CH_2Si– and H-4C), 4.04 (dd, 1H, $J_{4-3}=9.2$ Hz, $J_{4-5}=9.8$ Hz, H-4A), 3.95 (dd, 1H, $J_{3-2}=9.6$ Hz, H-3B), 3.83–3.79 (m, 1H, H-5C), 3.77–3.70 (m, 5H, H-5B, H-6C, H-6Ab and O–C*H*–CH_2Si), 3.60–3.56 (m, 3H, H-3A, H-6Bb and H-6Aa), 3.50 (dd, 1H, H-2B), 3.46 (dd, 1H, $J_{6a-6b}=10.3$ Hz, $J_{6a-5}=6.6$ Hz, H-6Ba), 3.39 (ddd, 1H, $J_{5-6a}=3.5$ Hz, $J_{5-6b}=1.5$ Hz, H-5A), 3.30 (dd, 1H, $J_{2-3}=9.2$ Hz, H-2A), 2.14 (s, 3H, O–C=O–C*H_3*), 1.15–1.12 (m, 2H, O–CH_2–C*H_2*Si), 0.15 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (100 MHz): δ 169.4, 168.9, 168.4, 164.7, 164.5, 164.0 and 163.9 (5O–*C*=O–CH_3/Ph and 2C=O Phth), 138.7, 138.5, 138.2, 138.0, 137.7, 137.6, 2×130.5, 128.5, 128.4 and 128.0 (11C arom.), 128.8–126.0 (54CH arom.), 101.9 (C-1A), 100.8 (C-1B), 100.7 (C-1D), 97.9 (C-1C), 81.6 (C-3A), 81.4 (C-4C), 81.1 (C-2A), 78.2 (C-2B), 77.8 (C-3B), 74.7 (C-4A), 73.9 (CH_2Ph), 73.6 (C-5A), 73.4 (CH_2Ph), 73.3 (C-5C), 73.3 (CH_2Ph), 72.1 (CH_2Ph), 72.0 (C-5B), 71.8 (CH_2Ph), 71.7 (CH_2Ph), 71.1 (C-5D), 70.9 (C-3D), 69.6 (C-4B), 69.0 (C-2D), 68.3 (C-3C), 67.9 (C-4D), 67.8, 67.4, 66.9 and 61.9 (4C-6), 65.5 (O–*C*H_2–CH_2Si–), 55.7 (C-2C), 19.2 (–O–C=O–*C*H_3), 17.1 (O–CH_2–*C*H_2Si–), −3.0 ($Si(CH_3)_3$); MS *m*/*z* (CI, NH_3): 1912.9 $(M+NH_4)^+$. Anal. Calcd for $C_{109}H_{111}NO_{27}Si$ (1895.17): C 69.08, H 5.90, N 0.74; found C 68.98, H 5.92, N 0.71.

6.2.3. 2-(Trimethylsilyl)ethyl (4,6-*O*-benzylidene-β-D-galactopyranosyl)-(1→4)-(6-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-(1→3)-(2,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (7). Sodium (40 mg, 0.02 M) was added by portions to a stirred solution of **6** (7.11 g, 3.75 mmol) in MeOH/CH_2Cl_2 (80 mL/40 mL). The mixture was stirred for 2 h, neutralized by Amberlite-IR 120 (H^+), filtered and evaporated in vacuum. The residue was purified by flash chromatography (eluent, 10% MeOH in DCM) to afford a white powder (4.98 g, 92%), which was directly engaged in the next step. Benzaldehyde dimethylacetal (1.04 mL, 6.93 mmol) and *p*TsOH (190 mg, 1 mmol) were added to a stirred solution of the previous powder in CH_3CN (100 mL). The mixture was stirred at room temperature (15 min), neutralized by solid K_2CO_3, filtered through Celite and evaporated in vacuum. The residue was purified by flash chromatography (eluent, 65% EtOAc in cyclohexane) to afford **7** (4.8 g, 91%) as a white powder. $[\alpha]_D$ −18 (*c* 1 in chloroform); mp: 95–96 °C (EtOAc/cyclohexane); ^1H NMR (400 MHz, $CDCl_3$): δ 7.43–7.20 (m, 39H, arom.), 5.51 (d, 1H, $J_{1-2}=8.4$ Hz, H-1C), 5.47 (s, 1H, benzylidène), 1.08–1.04 (m, 2H, O–CH_2–C*H_2*Si), 0.06 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (100 MHz): δ 168.2, 167.9 (2C=O Phth), 139.0, 138.7, 138.4, 138.3, 138.2, 137.7, 137.2 and 131.1 (8C arom.), 133.8–126.2 (CH arom.), 103.6, 102.9, 101.9, 101.1 and 98.7 (benzylidène, C-1A, C-1B, C1-C and C1-D); MS *m*/*z* (CI, NH_3): 1541 $(M+NH_4)^+$. Anal. Calcd for $C_{86}H_{97}NO_{22}Si$ (1524.80): C 67.74, H 6.41, N 0.92; found C 67.62, H 6.52, N 0.93.

6.2.4. 2-(Trimethylsilyl)ethyl (4,6-*O*-benzylidene-β-D-galactopyranosyl)-(1→4)-(2-acetamido-6-*O*-benzyl-2-deoxy-β-D-glucopyranosyl)-(1→3)-(2,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (8). $NH_2NH_2 \cdot H_2O$ (45 mL) and H_2O (25 mL) were added to a stirred solution of **7** (4.8 g, 3.15 mmol) in ethanol (200 mL). The mixture was stirred overnight under reflux and then evaporated in vacuum. The residue was diluted in a mixture of DCM–MeOH (v/v = 1/1, 20 mL). The precipitate was filtered and acetic anhydride (5 mL, excess) was added to the filtrate at room temperature. After 2 h, solvents were evaporated in vacuum. The residue was purified by flash chromatography (eluent, 5% MeOH in DCM) and precipitated in a mixture of EtOAc/hexanes to afford **8** (3.74 g, 83%) as a white powder. $[\alpha]_D$ −11 (*c* 1 in chloroform); mp: 98–102 °C (EtOAc/hexanes); ^1H NMR (400 MHz, C_6D_6/CD_3OD: 1:1): δ 7.80–7.40 (m, 35H, arom.), 5.59 (s, 1H, benzylidene), 5.43 (d, 1H, $J_{gem}=10.7$ Hz, CHPh), 5.17 (d, 1H, $J_{gem}=11.3$ Hz, CHPh), 5.03 (s, 2H, CH_2Ph), 5.00 (d, 1H, $J_{gem}=10.7$ Hz, CHPh), 4.98 (d, 1H, $J_{gem}=11.3$ Hz, CHPh), 4.92 (d, 1H, $J_{1-2}=8.4$ Hz, H-1C), 4.81 (d, 1H, $J_{1-2}=8.8$ Hz, H-1B), 4.80 (d, 1H, $J_{gem}=11.8$ Hz, CHPh), 4.77 (d, 1H, $J_{gem}=11.8$ Hz, CHPh), 4.67 (2d, 2H, $J_{gem}=12.0$ Hz, 2CHPh), 4.60 (d, 1H, $J_{1-2}=7.8$ Hz, H-1D), 4.56 (d, 1H, $J_{1-2}=7.8$ Hz, H-1A), 4.50 (d, 1H, $J_{gem}=12.0$ Hz, CHPh), 4.49 (d, 1H, $J_{gem}=12.0$ Hz, CHPh), 4.47 (de, 1H, $J_{4-3}=3.3$ Hz, H-4B), 4.32 (t, 1H, $J_{4-3}=J_{4-5}=9.8$ Hz, H-4A), 4.30 (dd, 1H, $J_{2-3}=10.0$ Hz, H-2C), 4.26–4.14 (m, 4H, H-6Db, –O–C*H*–CH_2–Si and H-6C), 4.13 (de, 1H, $J_{4-3}=3.7$ Hz, H-4D), 4.07–4.02 (m, 4H, H-2D, H-2B, H-6Bb and H-6Ab), 4.02 (t, 1H, $J_{3-4}=10.0$ Hz, H-3C), 3.96 (t, 1H, $J_{4-5}=10.0$ Hz, H-4C), 3.94–3.89 (m, 2H, H-6Da and H-6Ba), 3.86 (dd, 1H, $J_{3-2}=9.3$ Hz, H-3B), 3.86–3.78 (m, 5H, H-5C, H-3A, H-5B, H-6Aa and –O–C*H*–CH_2–Si), 3.77 (dd, 1H, $J_{3-2}=9.9$ Hz, H-3D), 3.65 (dd, 1H, $J_{2-3}=9.1$ Hz, H-2A), 3.50–3.48 (m, 1H, H-5A), 3.30 (se, 1H, H-5D), 1.96 (S, 3H, –NH–C=O–C*H_3*), 1.23–1.16 (m, 2H, O–CH_2–CH_2–Si), 0.18 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (100 MHz): δ 173.7 (–NH–*C*=O–CH_3), 140.6, 140.4, 140.2, 139.9, 139.6, 139.6 and 139.3 (7C arom.), 129.9–127.4 (35CH arom.), 105.0 (C-1D), 104.3 (C-1A), 104.0 (C-1C), 103.7 (C-1B), 102.0 (benzylidène), 84.0 (C-3A), 83.9 (C-3B), 83.2 (C-2A), 81.4 (C-4C), 80.2 (C-2B), 77.6 (C-4A), 76.9 (C-4D), 76.4 (CH_2Ph), 76.2 (C-5A), 76.0 (CH_2Ph), 75.9 (CH_2Ph), 75.6 (C-5C), 75.0 (C-5B), 74.6 (CH_2Ph), 74.5 (CH_2Ph), 74.1 (CH_2Ph), 73.6

(C-3D), 73.5 (C-3C), 71.9 (C-2D), 70.5 (C-6B), 70.1 (C-4B), 69.9 (C-6C), 69.9 (C-6D), 69.3 (C-6A), 68.2 (O–CH$_2$–CH$_2$–Si–), 68.0 (C-5D), 57.0 (C-2C), 23.3 (–NH–C=O–CH$_3$), 19.4 (O–CH$_2$–CH$_2$–Si–), −0.8 (Si(CH$_3$)$_3$); MS *m/z* (CI): 1436.8 MH$^+$. Anal. Calcd for $C_{80}H_{97}NO_{21}Si$ (1436.7): C 66.87, H 6.80, N 0.97; found C 66.57, H 6.81, N 0.98.

6.2.5. 1,2,4-Tri-*O*-acetyl-3-*O*-benzyl-6-*O*-*tert*-butyldimethylsilyl-(α/β)-D-glucopyranose (10α/β).

Sodium hydride (9.2 g, 230 mmol, 60% in mineral oil) was added to a stirred solution of diacetone glucose (30 g, 115 mmol) in anhydrous DMF (300 mL) and benzyl bromide (27.4 mL, 230 mmol) at 0 °C. The mixture was stirred at room temperature for 3 h, cooled to 0 °C and anhydrous methanol (10 mL) was added dropwise. The solvent was removed in vacuum and the resulting residue was partitioned between Et_2O and water. The organic layer was dried ($MgSO_4$), filtered and evaporated in vacuum. Amberlite-IR 120 (H$^+$) (60 g) was added to a suspension of the previous residue in H_2O (300 mL). After 15 h under reflux, the mixture was filtered and evaporated in vacuum. The crude compound was purified by precipitation (acetone/cyclohexane) to afford **9** (24.2 g, 85%) as a white powder. TBSCl (6.42 g, 42.58 mmol) was added to a stirred solution of **9** (10.95 g, 40.55 mmol) in pyridine (100 mL) at 0 °C under argon. The mixture was immediately warmed to room temperature and stirred for 2 h. Then acetic anhydride (37 mL, 365 mmol) was added dropwise to the mixture. After one night at room temperature, solvent was removed in vacuum. The residue was diluted with DCM, washed successively with HCl (1 M), saturated sodium hydrogencarbonate, brine, dried ($MgSO_4$) and evaporated in vacuum. The residue was purified by flash chromatography (eluent, 15% EtOAc in cyclohexane) to afford a mixture of **10**α/β ($\alpha/\beta=1/1$, 18.61 g, 90%) as a white powder.

Compound **10**β. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.37–7.28 (m, 5H, arom.), 5.70 (d, 1H, $J_{1-2}=8.2$ Hz, H-1), 5.16 (dd, 1H, $J_{2-3}=9.3$ Hz, H-2), 5.13 (t, 1H, $J_{4-3}=J_{4-5}=9.5$ Hz, H-4), 4.65 (s, 2H, CH$_2$Ph), 3.78 (t, 1H, H-3), 3.60 (ddd, 1H, $J_{5-6a}=2.9$ Hz, $J_{5-6b}=5.2$ Hz, H-5), 3.75–3.65 (m, 2H, H-6), 2.10, 2.01 and 2.00 (3s, 9H, 3–O–C=O–CH$_3$), 0.90 (s, 9H, SiC(CH$_3$)$_3$), 0.00 (2s, 6H, Si(CH$_3$)$_2$).

Compound **10**α. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.37–7.28 (m, 5H, arom.), 6.35 (d, 1H, $J_{1-2}=3.7$ Hz, H-1), 5.15 (t, 1H, $J_{4-3}=J_{4-5}=10.0$ Hz, H-4), 5.06 (dd, 1H, $J_{2-3}=10.0$ Hz, H-2), 4.68 (d, 1H, $J_{gem}=11.8$ Hz, CHPh), 4.65 (d, 1H, $J_{gem}=11.8$ Hz, CHPh), 4.00 (t, 1H, H-3), 3.90 (ddd, 1H, $J_{5-6a}=2.7$ Hz, $J_{5-6b}=4.1$ Hz, H-5), 3.75–3.65 (m, 2H, H-6), 2.20, 2.03 and 2.00 (3s, 9H, 3–O–C=O–CH$_3$), 0.90 (s, 9H, SiC(CH$_3$)$_3$), −0.03 (2s, 6H, Si(CH$_3$)$_2$).

MS *m/z* (CI, NH$_3$): 528 (M+NH$_4$)$^+$. Anal. Calcd for $C_{40}H_{44}O_9Si$ (510.23): C 58.80, H 7.50; found C 58.63, H 7.52.

6.2.6. 1,2,4-Tri-*O*-benzoyl-3-*O*-benzyl-6-*O*-*tert*-butyldimethylsilyl-(α/β)-D-glucopyranose (11α/β).

Sodium hydride (9.2 g, 230 mmol, 60% in mineral oil) was added to a stirred solution of diacetone glucose (30 g, 115 mmol) in anhydrous DMF (300 mL) and benzyl bromide (27.4 mL, 230 mmol) at 0 °C. The mixture was stirred at room temperature for 3 h, cooled to 0 °C and anhydrous methanol (10 mL) was added dropwise. The solvent was removed in vacuum and the resulting residue was partitioned between Et_2O and water. The organic layer was dried ($MgSO_4$), filtered and evaporated in vacuum. Amberlite-IR 120 (H$^+$) (60 g) was added to a suspension of the previous residue in H_2O (300 mL). After one night under reflux, the mixture was filtered and evaporated in vacuum. The crude compound was purified by precipitation (acetone/cyclohexane) to afford **9** (24.2 g, 85%) as a white powder. TBDMSCl (6.42 g, 42.58 mmol) was added to a stirred solution of **9** (10.95 g, 40.55 mmol) in pyridine (100 mL) at 0 °C under argon. The mixture was immediately warmed to room temperature and stirred for 2 h. Then benzoyl chloride (27.86 mL, 240 mmol) was added dropwise to the mixture. After one night at room temperature, solvent was removed in vacuum. The residue was diluted with DCM, washed successively with HCl (1 M), saturated sodium hydrogencarbonate, brine, dried ($MgSO_4$) and evaporated in vacuum. The residue was purified by flash chromatography (eluent, 20% EtOAc in cyclohexane) to afford a mixture of **11**α/β ($\alpha/\beta=1/3$, 25.4 g, 90%) as a white powder. A small amount of this mixture was selectively recrystallized from hexanes and gave pure **11**β as a white powder.

Compound **11**β. $[\alpha]_D$ −31 (*c* 1 in chloroform); mp: 129–130 °C (hexanes); ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.08–7.04 (m, 20H, arom.), 6.17 (d, 1H, $J_{1-2}=7.8$ Hz, H-1), 5.71 (dd, 1H, $J_{2-3}=8.8$ Hz, H-2), 5.58 (t, 1H, $J_{4-3}=J_{4-5}=8.8$ Hz, H-4), 4.68 (d, 1H, $J_{gem}=11.5$ Hz, CHPh), 4.64 (d, 1H, $J_{gem}=11.5$ Hz, CHPh), 4.20 (t, 1H, H-3), 3.98 (ddd, 1H, $J_{5-6a}=3.2$ Hz, $J_{5-6b}=5.3$ Hz, H-5), 3.91 (dd, 1H, $J_{6b-6a}=11.4$ Hz, H-6b), 3.82 (dd, 1H, H-6a), 0.85 (s, 9H, SiC(CH$_3$)$_3$), −0.02 and −0.01 (2s, 6H, Si(CH$_3$)$_2$); ^{13}C NMR (100 MHz): δ 164.9, 164.9 and 164.8 (3O–C=O), 137.1, 129.5, 129.3 and 128.7 (4C arom.), 133.6–127.6 (20CH arom.), 92.5 (C-1), 79.3 (C-3), 76.0 (C-5), 73.9 (CH$_2$Ph), 72.1 (C-2), 70.4 (C-4), 62.7 (C-6), 25.7 (SiC(CH$_3$)$_3$), 18.2 (SiC(CH$_3$)$_3$), −5.5 (SiCH$_3$), −5.4 (SiCH$_3$); MS *m/z* (CI, NH$_3$): 714.4 (M+NH$_4$)$^+$. Anal. Calcd for $C_{40}H_{44}O_9Si$ (696.87): C 68.94, H 6.36; found C 68.98, H 6.38.

Compound **11**α. ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.08–7.04 (m, 20H, arom.), 6.80 (d, 1H, $J_{1-2}=3.7$ Hz, H-1), 5.62 (t, 1H, $J_{4-3}=J_{4-5}=9.7$ Hz, H-4), 5.56 (dd, 1H, $J_{2-3}=9.7$ Hz, H-2), 4.72 (d, 1H, $J_{gem}=11.4$ Hz, CHPh), 4.64 (d, 1H, $J_{gem}=11.5$ Hz, CHPh), 4.50 (t, 1H, H-3), 4.28–4.23 (m, 1H, H-5), 3.85–3.82 (m, 2H, H-6), 0.83 (s, 9H, SiC(CH$_3$)$_3$), −0.03 (2s, 6H, Si(CH$_3$)$_2$).

6.2.7. Methyl 1,2,4-tri-*O*-acetyl-3-*O*-benzyl-(α/β)-D-glucopyranosuronate (12α/β).

A solution of the Jones reagent (44.9 mL of H_2SO_4 (3.5 M) and 9.7 g of CrO_3) was dropwise added to a stirred solution of **10**α/β (12.5 g, 24.5 mmol) in acetone (100 mL) at 0 °C. This mixture was immediately warmed to room temperature, stirred for 5 h and then diluted with CH_2Cl_2 and H_2O. The aqueous layer was extracted three times with CH_2Cl_2 and the combined extracts were dried ($MgSO_4$), filtered and the solvent was removed in vacuum. The residue was dissolved in DMF (100 mL) and stirred at room temperature. CH_3I

(8.2 mL, 122.5 mmol) and $KHCO_3$ (15.3 g, 147 mmol) were added to the mixture. After one night of stirring, the suspension was filtered through Celite, the filtrate was diluted with H_2O, extracted three times with Et_2O, dried ($MgSO_4$) and evaporated in vacuum. The residue was purified by flash chromatography (eluent, 20% EtOAc in cyclohexane) to afford a mixture of **12**α/β ($\alpha/\beta=1/1$, 6.75 g, 65%) as a white powder.

Compound **12**β. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47–7.17 (m, 5H, arom.), 5.63 (d, 1H, $J_{1-2}=7.5$ Hz, H-1), 5.17 (dd, 1H, $J_{4-3}=9.0$ Hz, $J_{4-5}=9.4$ Hz, H-4), 5.10 (dd, 1H, $J_{2-3}=8.9$ Hz, H-2), 4.64 (d, 1H, $J_{gem}=12.0$ Hz, CHPh), 4.58 (d, 1H, $J_{gem}=12.0$ Hz, CHPh), 4.00 (d, 1H, H-5), 3.73 (t, 1H, H-3), 3.65 (s, 3H, $-CO_2CH_3$), 1.94 and 2×1.93 (2s, 9H, 3 $-O-C{=}O-CH_3$).

Compound **12**α. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47–7.17 (m, 5H, arom.), 6.32 (d, 1H, $J_{1-2}=3.6$ Hz, H-1), 5.18 (dd, 1H, $J_{4-3}=9.4$ Hz, $J_{4-5}=9.9$ Hz, H-4), 5.02 (dd, 1H, $J_{2-3}=9.4$ Hz, H-2), 4.58 (s, 2H, CH_2Ph), 4.26 (d, 1H, H-5), 3.93 (t, 1H, H-3), 3.64 (s, 3H, $-CO_2CH_3$), 2.09, 2.03 and 1.91 (3s, 9H, 3 $-O-C{=}O-CH_3$); MS *m/z* (CI, NH_3): 442 $(M+NH_4)^+$; l. Calcd for $C_{20}H_{24}O_{10}$ (424.407): C 56.60, H 5.70; found C 56.52, H 5.72.

6.2.8. Methyl 1,2,4-tri-*O*-benzoyl-3-*O*-benzyl-(α/β)-D-glucopyranosuronate (13α/β). Oxidation and esterification of **11**α/β (12.33 g, 17.70 mmol), as described for **12**α/β, yielded **13**α/β (7.35 g, 68%) as a white powder.

Compound **13**β. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08–7.16 (m, 20H, arom.), 6.29 (d, 1H, $J_{1-2}=6.2$ Hz, H-1), 5.86 (t, 1H, $J_{4-3}=J_{4-5}=7.4$ Hz, H-4), 5.70 (dd, 1H, $J_{2-3}=7.4$ Hz, H-2), 4.82 (d, 1H, $J_{gem}=11.4$ Hz, CHPh), 4.76 (d, 1H, $J_{gem}=11.4$ Hz, CHPh), 4.57 (d, 1H, H-5), 4.29 (t, 1H, H-3), 3.55 (s, 3H, $-CO_2CH_3$); ^{13}C NMR (100 MHz): δ 167.6, 165.2, 164.9, and164.6 (4O–C=O), 136.9, 2×129.0 and 128.9 (4C arom.), 136.9–127.8 (20CH arom.), 91.5 (C-1), 76.5 (C-3), 73.9 (CH_2Ph), 73.1 (C-5), 70.6 (C-2), 70.0 (C-4), 52.8 ($-CO_2CH_3$).

Compound **13**α. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08–7.16 (m, 20H, arom.), 6.87 (d, 1H, $J_{1-2}=3.5$ Hz, H-1), 5.86 (dd, 1H, $J_{4-3}=9.0$ Hz, $J_{4-5}=9.3$ Hz, H-4), 5.70 (dd, 1H, $J_{2-3}=9.1$ Hz, H-2), 4.78 (s, 2H, CH_2Ph), 4.70 (d, 1H, H-5), 4.29 (t, 1H, H-3), 3.71 (s, 3H, $-CO_2CH_3$); ^{13}C NMR (100 MHz): δ 167.6, 165.2, 165.1 and 164.0 (4O–C=O), 136.9, 2×129.0 and 128.9 (4C arom.), 136.9–127.8 (20CH arom.), 89.8 (C-1), 75.6 (C-3), 74.6 (CH_2Ph), 71.5 (C-5), 71.0 (C-2), 70.9 (C-4), 52.9 ($-CO_2CH_3$); MS *m/z* (CI, NH_3): 628.1 $(M+NH_4)^+$. Anal. Calcd for $C_{35}H_{30}O_{10}$ (610.62): C 68.84, H 4.95; found C 68.76, H 4.91.

6.2.9. Methyl 1,2,4-tri-*O*-acetyl-3-*O*-levulinyl-(α/β)-D-glucopyranosuronate (14α/β). A solution of **12**α/β (3 g, 7.07 mmol) in MeOH (10 mL) and EtOAc (10 mL) was hydrogenated in the presence of 10% Pd/C (100 mg) for 1 h at room temperature, filtered through Celite and concentrated. The residue was dissolved in pyridine (20 mL) and stirred at room temperature. Levulinic anhydride (5.25 g, 21.21 mmol) was added and the mixture was stirred overnight. Solvent was removed in vacuum. The residue was diluted with DCM, washed with HCl (1 M), saturated sodium hydrogen carbonate and brine. The organic layer was dried ($MgSO_4$), filtered and evaporated in vacuum. The residue was purified by flash chromatography (eluent, 20% EtOAc in cyclohexane) to afford a mixture of **14**α/β (2.44 g, 82%) as a white powder.

Compound **14**β. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.77 (d, 1H, $J_{1-2}=7.9$ Hz, H-1), 5.35 (t, 1H, $J_{3-2}=J_{3-4}=9.4$ Hz, H-3), 5.24 (t, 1H, $J_{4-5}=9.7$ Hz, H-4), 5.17 (dd, 1H, H-2), 4.20 (d, 1H, H-5), 3.76 (s, 3H, $-CO_2CH_3$), 2.75 and 2.51 (m, 4H, $CH_3C{=}O-CH_2-CH_2-$), 2.17, 2.13, 2.09 and 2.08 (4s, 12H, 3 $-C{=}O-CH_3$ and $CH_3C{=}O-CH_2$).

Compound **14**α. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.40 (d, 1H, $J_{1-2}=3.7$ Hz, H-1), 5.57 (t, 1H, $J_{3-2}=J_{3-4}=9.9$ Hz, H-3), 5.24 (t, 1H, $J_{4-5}=9.7$ Hz, H-4), 5.16 (dd, 1H, H-2), 4.40 (d, 1H, H-5), 3.77 (s, 3H, $-CO_2CH_3$), 2.75 and 2.51 (m, 4H, $CH_3C{=}O-CH_2-CH_2-$), 2.20, 2.18, 2.10 and 2.07 (4s, 12H, 3 $-C{=}O-CH_3$ and $CH_3C{=}O-CH_2$); MS *m/z* (CI, NH_3): 450 $(M+NH_4)^+$. Anal. Calcd for $C_{18}H_{24}O_{12}$ (432.38): C 50.00, H 5.59; found C 49.91, H 5.61.

6.2.10. Methyl 1,2,4-tri-*O*-benzoyl-3-*O*-levulinyl-(α/β)-D-glucopyranosuronate (15α/β). Hydrogenation and protection with levulinic anhydride of **15**α/β (2.96 g, 4.85 mmol), as described for **15**α/β, yielded **15**α/β (2.4 g, 80%) as a white powder. A small amount of this mixture was selectively crystallized from Et_2O and gave pure **15**β as a white powder.

Compound **15**β. $[\alpha]_D$ −9 (*c* 1 in chloroform); mp: 153–155 °C (Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10–7.43 (m, 15H, arom.), 6.26 (d, 1H, $J_{1-2}=7.5$ Hz, H-1), 5.84 (t, 1H, $J_{3-2}=J_{3-4}=8.9$ Hz, H-3), 5.72 (dd, 1H, H-2), 5.67 (t, 1H, $J_{4-5}=9.0$ Hz, H-4), 4.54 (d, 1H, H-5), 3.66 (s, 3H, $-CO_2CH_3$), 2.58 and 2.47 (2t, 4H, $CH_3C{=}O-CH_2-CH_2-$), 1.97 (s, 3H, $CH_3C{=}O-CH_2$); ^{13}C NMR (100 MHz): δ 205.3 (C=O), 171.6, 166.9, 165.2, 164.9 and 164.4 (5O–C=O), 2×128.7 and 128.2 (3C arom.), 133.9–128.5 (15CH arom.), 92.1 (C-1), 73.2 (C-5), 71.1 (C-3), 70.0 (C-2), 69.4 (C-4), 52.9 ($-CO_2CH_3$), 37.7 and 27.9 ($CH_3C{=}O-CH_2-CH_2-$), 29.3 ($CH_3C{=}O-CH_2$); MS *m/z* (CI, NH_3): 636.3 $(M+NH_4)^+$. Anal. Calcd for $C_{33}H_{30}O_{12}$ (618.59): C 64.07, H 4.88; found C 63.98, H 4.90.

Compound **15**α. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10–7.40 (m, 15H, arom.), 6.85 (d, 1H, $J_{1-2}=3.7$ Hz, H-1), 6.06 (t, 1H, $J_{3-2}=J_{3-4}=10.0$ Hz, H-3), 5.59 (t, 1H, $J_{4-5}=10.0$ Hz, H-4), 5.23 (dd, 1H, H-2), 4.66 (d, 1H, H-5), 3.67 (s, 3H, $-CO_2CH_3$), 2.53 and 2.42 (2t, 4H, $CH_3C{=}O-CH_2-CH_2-$), 1.92 (s, 3H, $CH_3C{=}O-CH_2$); ^{13}C NMR (100 MHz): δ 205.3 (C=O), 171.8, 167.2, 165.2, 165.1 and 164.0 (5O–C=O), 2×128.7 and 128.2 (3C arom.), 133.9–128.5 (15CH arom.), 89.6 (C-1), 70.8 (C-5), 2×69.7 (C-2 and C-4), 69.2 (C-3), 53.0 ($-CO_2CH_3$), 37.7 and 27.9 ($CH_3C{=}O-CH_2-CH_2-$), 29.3 ($CH_3C{=}O-CH_2$).

6.2.11. Methyl 2,4-di-*O*-acetyl-1-bromo-1-deoxy-3-*O*-levulinyl-α-D-glucopyranosyluronate (16). Hydrobromic acid 33% in AcOH (9 mL, excess) was added to a stirred solution of **14**α/β (1.4 g, 3.23 mmol) in CH_2Cl_2 (8 mL) at room temperature. The mixture was stirred for 2 h and neutralized with saturated sodium hydrogencarbonate. The organic layer was washed with H_2O, dried ($MgSO_4$), filtered and evaporated in vacuum. The residue was purified by flash chromatography (eluent, 25% EtOAc in cyclohexane) to afford **16** (1.31 g, 90%) as a white unstable foam; ^1H NMR (400 MHz, $CDCl_3$): δ 6.54 (d, 1H, $J_{1-2}=4.0$ Hz, H-1), 5.57 (t, 1H, $J_{3-2}=J_{3-4}=10.0$ Hz, H-3), 5.17 (dd, 1H, $J_{4-5}=10.3$ Hz, H-4), 4.80 (dd, 1H, H-2), 4.50 (d, 1H, H-5), 3.70 (s, 3H, $-CO_2CH_3$), 2.70 and 2.45 (m, 4H, $CH_3C{=}O{-}CH_2{-}CH_2{-}$), 2.09, 2.06 and 2.03 (3s, 9H, 3 $-C{=}O{-}CH_3$ and $CH_3C{=}O{-}CH_2$).

6.2.12. Methyl 2,4-di-*O*-benzoyl-1-bromo-1-deoxy-3-*O*-levulinyl-α-D-glucopyranosyluronate (17). Bromination of **15**α/β (2.3 g, 3.72 mmol), as described for **14**α/β, yielded **17** (1.7 g, 80%) as a white unstable foam; ^1H NMR (400 MHz, $CDCl_3$): δ 8.00–7.40 (m, 10H, arom.), 6.77 (d, 1H, $J_{1-2}=4.0$ Hz, H-1), 5.94 (t, 1H, $J_{3-2}=J_{3-4}=9.8$ Hz, H-3), 5.48 (dd, 1H, $J_{4-5}=10.2$ Hz, H-4), 5.12 (dd, 1H, H-2), 4.70 (d, 1H, H-5), 3.61 (s, 3H, $-CO_2CH_3$), 2.46 and 2.35 (2t, 4H, $CH_3C{=}O{-}CH_2{-}CH_2{-}$), 1.85 (s, 3H, $CH_3C{=}O{-}CH_2$); ^{13}C NMR (100 MHz): δ 205.2 (C=O), 171.6, 166.7, 165.2 and 165.1 (4O–C=O), 133.9 and 133.7 (2C arom.), 129.9–128.2 (10CH arom.), 85.5 (C-1), 72.2 (C-5), 70.6 (C-2), 69.2 (C-3), 68.6 (C-4), 52.9 ($-CO_2CH_3$), 37.7 and 27.9 ($CH_3C{=}O{-}CH_2{-}CH_2{-}$), 29.3 ($CH_3C{=}O{-}CH_2$).

6.2.13. 2-(Trimethylsilyl)ethyl(methyl 2,4-di-*O*-benzoyl-3-*O*-levulinyl-β-D-glucopyranosyluronate)-(1→3)-(4,6-*O*-benzylidene-β-D-galactopyranosyl)-(1→4)-(2-acetamido-6-*O*-benzyl-2-deoxy-β-D-glucopyranosyl)-(1→3)-(2,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (18). To a stirred mixture of **8** (1.8 g, 1.25 mmol), **17** (0.73 g, 1.25 mmol) and MS-4 Å (2.5 g) in anhydrous CH_2Cl_2 (15 mL) was added, at 0 °C and under argon, AgOTf (0.386 g, 1.5 mmol). After 1 h at 0 °C, one more equivalent of **17** and 1.2 equiv of AgOTf were added to the mixture, which was stirred for 2 h at room temperature, neutralized by Et_3N and filtered through Celite. The filtrate was successively washed with saturated sodium thiosulfate, brine, dried ($MgSO_4$) and evaporated in vacuum. The residue was purified by flash chromatography (eluent gradient, 2% MeOH in DCM) to afford first **18** (1.2 g, 50%) as a white powder and then **8** (0.54 g, 30%). $[\alpha]_D$ +2 (*c* 0.15 in chloroform); mp: 183–185 °C (DCM/MeOH); ^1H NMR (400 MHz, $CDCl_3$): δ 8.03–7.25 (m, 45H, arom.), 5.68 (t, 1H, $J_{3-2}=J_{3-4}=9.5$ Hz, H-3E), 5.60 (t, 1H, $J_{4-5}=9.5$ Hz, H-4E), 5.48 (s, 1H, benzylidène), 5.43 (dd, 1H, $J_{2-1}=7.4$ Hz, H-2E), 5.42 (d, 1H, H-1E), 5.12 (m, 1H, N*H*Ac), 5.03 (d, 1H, $J_{gem}=10.7$ Hz, CHPh), 4.93 (d, 1H, $J_{gem}=11.1$ Hz, CHPh), 4.90 (d, 1H, $J_{gem}=12.4$ Hz, CHPh), 4.78 (d, 1H, $J_{gem}=10.7$ Hz, CHPh), 4.76 (d, 1H, $J_{gem}=11.1$ Hz, CHPh), 4.74 (d, 1H, $J_{1-2}=7.8$ Hz, H-1C), 4.62 (d, 1H, $J_{gem}=12.4$ Hz, CHPh), 4.61 (d, 1H, $J_{gem}=12.1$ Hz, CHPh), 4.55 (d, 1H, $J_{gem}=12.0$ Hz, CHPh), 4.50 (d, 1H, $J_{gem}=12.0$ Hz, CHPh), 4.48 (d, 1H, $J_{1-2}=8.0$ Hz, H-1B), 4.47 (d, 1H, $J_{gem}=11.8$ Hz, CHPh), 4.43 (d, 1H, $J_{gem}=12.1$ Hz, CHPh), 4.38 (d, 1H, $J_{1-2}=7.9$ Hz, H-1A), 4.36 (d, 1H, $J_{1-2}=7.8$ Hz, H-1D), 4.35 (d, 1H, $J_{gem}=11.8$ Hz, CHPh), 4.31 (d, 1H, H-5E), 4.30 (d, 1H, $J_{4-3}=3.3$ Hz, H-4D), 4.22 (de, 1H, $J_{6b-6a}=12.1$ Hz, H-6Db), 4.06 (de, 1H, $J_{4-3}=3.6$ Hz, H-4B), 4.04–4.01 (m, 1H, H-6Da), 4.01–3.99 (m, 1H, $-CH{-}CH_2Si$), 3.98 (t, 1H, $J_{4-3}=J_{4-5}=9.1$ Hz, H-4A), 3.88 (dd, 1H, $J_{2-3}=9.9$ Hz, H-2D), 3.87–3.84 (m, 1H, H-6Bb), 3.81 (dd, 1H, H-3D), 3.78–3.74 (m, 3H, H-6A and H-6Ba), 3.70 (t, 1H, $J_{4-3}=J_{4-5}=10.0$ Hz, H-4C), 3.68 (s, 3H, CO_2CH_3), 3.67–3.62 (m, 2H, H-2C and H-2B), 3.62–3.58 (m, 1H, $-CH{-}CH_2Si$), 3.72 (t, 1H, $J_{3-2}=9.1$ Hz, H-3A), 3.58–3.52 (m, 3H, H-3C, H-3B and H-5B), 3.53–3.50 (m, 2H, H-6C), 3.49–3.44 (m, 2H, H-5D and H-5C), 3.42 (dd, 1H, H-2A), 3.40–3.37 (m, 1H, H-5A), 2.53 and 2.42 (2t, 4H, $J_{CH_2-CH_2}=6.7$ Hz, $CH_3C{=}O{-}CH_2{-}CH_2{-}$), 1.90 (s, 3H, $CH_3C{=}O{-}CH_2$), 1.59 (s, 3H, NH*Ac*), 1.06 (m, 2H, $-CH_2{-}CH_2Si$), 0.05 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (100 MHz): δ 206.0 (C=O), 172.0, 171.4, 167.8, 165.7 and 165.5 (3O–C=O, C=O–O and NHC=O), 139.5, 139.3, 139.2, 138.8, 138.7, 138.2, 138.0, 129.7 and 129.1 (9C arom.), 134.5–126.5 (45CH arom.), 103.9 (C-1D), 103.5 (C-1A), 102.8 (C-1B), 101.8 (C-1C), 100.8 (CH, benzylidene), 100.7 (C-1E), 83.2, 2×82.3, 81.5, 79.8, 78.7, 77.0, 75.7, 75.5, 74.1, 73.4, 73.2, 72.8, 72.2, 72.1, 70.2, 69.8, 68.5, 67.3 and 56.8 (20 CH cycle), 75.8, 75.3, 74.9, 2×73.8 and 73.7 (6CH_2Ph), 69.8, 2×69.0 and 68.7 (4C-6), 67.7 ($-CH_2{-}CH_2Si$), 53.3 ($-CO_2CH_3$), 38.2 and 28.4 ($CH_3C{=}O{-}CH_2{-}CH_2{-}$), 29.7 ($CH_3C{=}O{-}CH_2$), 23.4 ($NH{-}C{=}O{-}CH_3$), 18.8 ($-CH_2{-}CH_2Si$), −1.0 ($Si(CH_3)_3$); MS *m/z* (FAB): 1955 $(M+Na)^+$. Anal. Calcd for $C_{106}H_{121}NO_{31}Si$ (1933.21): C 65.85, H 6.30, N 0.72; found C 65.80, H 6.31, N 0.69.

6.2.14. 2-(Trimethylsilyl)ethyl (methyl 2,4-di-*O*-benzoyl-3-*O*-levulinyl-β-D-glucopyranosyluronate)-(1→3)-(2,4,6-tri-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-(2-acetamido-3,6-di-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-(1→3)-(2,4,6-tri-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-acetyl-β-D-glucopyranoside (19). A solution of **18** (1.2 g, 0.620 mmol) in MeOH (20 mL) was hydrogenated in the presence of 10% Pd/C (200 mg) for 5 h at room temperature, filtered through Celite and concentrated. The residue was acetylated with acetic anhydride (15 mL)-pyridine (30 mL) for 20 h at room temperature. Solvent was then removed in vacuum. The residue was diluted with DCM, washed with HCl (1 M), saturated sodium hydrogencarbonate and brine. The organic layer was dried ($MgSO_4$), filtered and evaporated in vacuum. The residue was purified by flash chromatography (eluent, 2.5% MeOH in DCM) to afford **19** (0.70 g, 60%) as a white powder. $[\alpha]_D$ +6 (*c* 0.4 in chloroform); mp: 168–172 °C (DCM/MeOH); ^1H NMR (400 MHz, $CDCl_3$): δ 8.00–7.47 (m, 10H, arom.), 5.62 (dd, 1H, $J_{3-2}=8.5$ Hz, $J_{3-4}=9.2$ Hz, H-3E), 5.54 (dd, 1H, $J_{4-5}=9.7$ Hz, H-4E), 5.50 (d, 1H, $J_{4-3}=3.1$ Hz, H-4D or B), 5.40 (d, 1H, $J_{NHAc-2}=8.8$ Hz, N*H*Ac), 5.30 (d, 1H, $J_{4-3}=3.4$ Hz, H-4D or B), 5.26 (dd, 1H, $J_{2-1}=7.3$ Hz, H-2E), 5.18 (t, 1H, $J_{3-2}=J_{3-4}=9.3$ Hz, H-3A), 5.09 (t, 1H, $J_{3-2}=J_{3-4}=9.3$ Hz, H-3C), 5.07 (dd, 1H, $J_{2-3}=10.5$ Hz, $J_{2-1}=8.0$ Hz, H-2D or B), 5.00 (dd, 1H, $J_{2-3}=9.2$ Hz, $J_{2-1}=8.0$ Hz, H-2D or B), 4.90 (dd, 1H, $J_{2-1}=8.0$ Hz, H-2A), 4.87 (d, 1H, H-1E), 4.68 (de, 1H, $J_{6b-6a}=10.5$ Hz, H-6Cb), 4.59 (d, 1H, $J_{1-2}=7.7$ Hz, H-1C), 4.49 (d, 1H, H-1A), 4.46 (de, 1H, $J_{6b-6a}=11.9$ Hz, H-6Ab), 4.40 (d, 1H, H-1D or B), 4.35 (d, 1H, H-1D or B), 4.24 (d, 1H, H-5E), 4.16–4.11 (m, 2H, H-6Aa and H-6Db or H-6Bb), 4.07–4.05 (m, 2H, H-6Db or H-6Bb and H-6Da or H-6Ba), 4.03–3.99 (m, 1H, H-6Da or H-6Ba), 3.99–3.95 (m, 1H, $-CH{-}CH_2Si$), 3.96–3.94 (m, 1H, H-6Ca), 3.90 (dd, 1H, H-3D or B), 3.82 (t, 1H, $J_{5-6}=6.5$ Hz, H-5D or B), 3.78 (t, 1H, $J_{5-6}=6.5$ Hz, H-5D or B), 3.78–3.71 (m, 3H, H-4C, H-4A and H-3D or H-3B), 3.73 (s, 3H, CO_2CH_3), 3.65–3.63 (m, 1H, H-5A), 3.59 (dd, 1H, H-2C), 3.56–3.54 (m, 1H, –*C*H–CH_2Si), 3.46–3.43 (m, 1H, H-5C), 2.49 and 2.37 (2t, 4H, $J_{CH_2-CH_2}=6.7$ Hz, CH_3–C=O–C*H*$_2$–C*H*2–), 2.19–1.91 (12s, 36H, 11 –O–C=O–CH_3 and C*H*$_3$C=O–CH_2), 1.68 (s, 3H, NH*Ac*), 1.00–0.90 (m, 2H, –CH_2–C*H*$_2$Si), 0.03 (s, 9H, Si$(CH_3)_3$); ^{13}C NMR (100 MHz): δ 205.3 (C=O), 171.6, 170.5, 170.5, 2×170.4, 170.3, 170.1, 169.8, 2×169.7, 169.5, 168.8, 168.3, 166.7, 164.9 and 164.5 (15O–C=O), 129.0 and 128.8 (2C arom.), 133.5–128.4 (10CH arom.), 100.7 (C-1D or B), 100.6 (C-1E and C-1D or B), 100.4 (C-1C), 99.9 (C-1A), 76.8 (C-3D or B), 75.8 (C-4A), 75.7 (C-3D or B), 75.0 (C-4C), 72.7 (C-5E and C-3A), 72.6 (C-5C), 72.5 (C-5A), 71.6 (C-3C and C-2A), 71.5 (C-3E), 71.4 (C-2E), 71.1 (C-5D or B), 71.0 (C-5D or B), 70.9 (C-2D or B), 70.5 (C-2D or B), 69.5 (C-4E), 68.7 (C-4D or B), 68.1 (C-4D or B), 67.4 (–*C*H$_2$–CH_2Si), 62.2 (C-6A), 61.7 and 61.5 (C-6D and C-6B), 60.4 (C-6C), 54.4 (C-2C), 52.8 (–CO_2*C*H$_3$), 37.6 and 27.9 (CH_3C=O–*C*H$_2$–*C*H$_2$–), 29.2 (*C*H$_3$C=O–CH_2), 23.0–20.1 (11 –O–C=O–*C*H$_3$ and 1 NH–C=O–*C*H$_3$), 17.8 (–CH_2–*C*H$_2$Si), −1.5 (Si$(CH_3)_3$); MS *m/z* (CI, NH_3): 1783.0 $(M+NH_4)^+$. Anal. Calcd for $C_{79}H_{103}NO_{42}Si.1H_2O$: C 53.16, H 5.93, N 0.78; found C 52.73, H 5.93, N 0.61.

6.2.15. (Methyl 2,4-di-*O*-benzoyl-3-*O*-levulinyl-β-D-glucopyranosyluronate)-(1→3)-(2,4,6-tri-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-(2-acetamido-3,6-di-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-(1→3)-(2,4,6-tri-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl) trichloroacetimidate (20). To a stirred solution of **19** (500 mg, 0.283 mmol) in CH_2Cl_2 (15 mL) was added, at 0 °C, trifluoroacetic acid (2.4 mL, 31.3 mmol). After 4 h at room temperature, 1 mL of trifluoroacetic acid was added. The mixture, after stirring for 3 h, was diluted with CH_2Cl_2, neutralized with saturated sodium hydrogencarbonate. The organic layer was dried ($MgSO_4$), filtered and evaporated in vacuum. The residue was dissolved in anhydrous CH_2Cl_2 (7 mL) and stirred at 0 °C under argon. Trichloroacetonitrile (0.426 mL, 4.25 mmol) and DBU (9 μL, 0.056 mmol) were successively added and, after stirring for 30 min, the mixture was directly purified by flash chromatography (eluent, 4% MeOH in DCM) to afford **20** (476 mg, 92%) as a white unstable foam; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60 (s, 1H, –O–C=NH–CCl_3), 6.45 (d, 1H, $J_{1-2}=3.7$ Hz, H-1A).

6.2.16. (Methyl 2,4-di-*O*-benzoyl-3-*O*-levulinyl-β-D-glucopyranosyluronate)-(1→3)-(2,4,6-tri-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-(2-acetamido-3,6-di-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-(1→3)-(2,4,6-tri-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-acetyl-β-D-glucopyranosyl)-(1→1)-(2*S*,3*R*,4*E*)-2-azido-3-*O*-benzoyl-4-octadecene-1,3-diol (21). To a stirred mixture of **20** (300 mg, 0.165 mmol), acceptor (2*S*,3*R*,4*E*)-2-azido-3-*O*-benzoyl-4-octadecene-1,3-diol (180 mg, 0.414 mmol) and MS-4 Å (500 mg) in anhydrous CH_2Cl_2 (5 mL) was added, at 0 °C and under argon, $BF_3\cdot Et_2O$ (0.063 mL, 0.495 mmol). After stirring for 3 h at 0 °C, the mixture was neutralized with saturated sodium hydrogencarbonate and filtered through Celite. The organic layer was washed with brine, dried ($MgSO_4$), filtered and evaporated in vacuum. The residue was purified by flash chromatography (eluent, 2% MeOH in DCM) to afford **21** (258 mg, 75%) as a white foam. $[\alpha]_D$ −10 (*c* 0.5 in chloroform); mp: 114.5–115 °C (DCM/MeOH); IR (film): C–N_3 2109.3 cm^{-1}; C=O 1758.5 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08–7.46 (m, 15H, arom.), 5.95 (dt, 1H, $J_{5-4}=15.0$ Hz, $J_{5-CH_2}=6.7$ Hz, H-5 sphingosine), 5.63 (dd, 1H, $J_{3-2}=9.1$ Hz, $J_{3-4}=9.5$ Hz, H-3E), 5.63–5.61 (m, 1H, H-3 sphingosine), 5.61–5.60 (m, 1H, H-4 sphingosine), 5.54 (dd, 1H, $J_{4-5}=9.7$ Hz, H-4E), 5.50 (de, 1H, $J_{4-3}=3.4$ Hz, H-4D or B), 5.38 (d, 1H, $J_{NHAc-2}=8.7$ Hz, N*H*Ac), 5.30 (d, 1H, $J_{4-3}=3.8$ Hz, H-4D or B), 5.27 (dd, 1H, $J_{2-1}=7.3$ Hz, H-2E), 5.18 (t, 1H, $J_{3-2}=J_{3-4}=9.2$ Hz, H-3A), 5.09 (dd, 1H, $J_{3-2}=10.0$ Hz, $J_{3-4}=9.3$ Hz, H-3C), 5.07 (dd, 1H, $J_{2-3}=10.0$ Hz, $J_{2-1}=8.0$ Hz, H-2D or B), 5.00 (dd, 1H, $J_{2-3}=10.0$ Hz, $J_{2-1}=8.0$ Hz, H-2D or B), 4.90 (dd, 1H, $J_{2-1}=7.8$ Hz, H-2A), 4.87 (d, 1H, H-1E), 4.69 (dd, 1H, $J_{6b-6a}=12.0$ Hz, $J_{6b-5}=2.2$ Hz, H-6Cb), 4.59 (d, 1H, $J_{1-2}=7.6$ Hz, H-1C), 4.53 (d, 1H, H-1A), 4.46 (dd, 1H, $J_{6b-6a}=11.3$ Hz, $J_{6b-5}=1.6$ Hz, H-6Ab), 4.40 (d, 1H, H-1D or B), 4.36 (d, 1H, H-1D or B), 4.25 (d, 1H, H-5E), 4.13 (dd, 1H, $J_{6b-6a}=11.5$ Hz, $J_{6b-5}=6.2$ Hz, H-6Bb), 4.09–3.99 (m, 4H, H-6Aa, H-6D and H-6Ba), 3.98–3.94 (m, 1H, H-2 sphingosine), 3.92 (dd, 1H, $J_{6a-5}=4.0$ Hz, H-6Ca), 3.90 (dd, 1H, H-3D or H-3B), 3.91–3.86 (m, 1H, H-1b sphingosine), 3.83–3.76 (m, 2H, H-5D and H-5B), 3.79–3.73 (m, 3H, H-4C, H-4A and H-3D or H-3B), 3.73 (s, 3H, CO_2CH_3), 3.64–3.57 (m, 3H, H-5A, H-2C and H-1a sphingosine), 3.44 (dt, 1H, $J_{5-4}=9.3$ Hz, H-5C), 2.50 and 2.37 (2t, 4H, $J_{CH_2-CH_2}=6.4$ Hz, CH_3–C=O–C*H*$_2$–C*H*$_2$–), 2.19–1.91 (12s, 36H, 11 –O–C=O–CH_3 and C*H*$_3$C=O–CH_2), 1.70 (s, 3H, NH*Ac*), 1.47–1.21 (m, 24H, CH_2 sphingosine), 0.91 (t, 3H, $J_{CH_3-CH_2}=7.0$ Hz, CH_3 sphingosine); ^{13}C NMR (100 MHz): δ 205.3 (C=O), 171.6, 170.6, 170.5, 2×170.4, 170.3, 170.2, 2×169.8, 169.7, 169.5, 168.8, 168.4, 166.7, 165.0, 164.9 and 164.5 (17O–C=O), 129.8, 129.0 and 128.7 (3C arom.), 133.5–128.4 (15CH arom.), 100.7 (C-1D and C-1B), 100.6 (C-1E), 100.4 (C-1C), 100.3 (C-1A), 76.8 (C-3D or C-3B), 75.7 (C-4A or C-4C), 75.6 (C-4C or C-4A), 75.0 (C-3D or C-3B), 74.6 (C-3 sphingosine), 72.7 (C-5E and C-5A), 72.6 (C-5C), 72.5 (C-3A), 71.6 (C-2D or C-2B), 71.5 (C-2A), 71.4 (C-3E), 71.3 (C-2E), 71.2 (C-5D or C-5B), 71.0 (C-5D or C-5B), 70.9 (C-2D or C-2B), 70.5 (C-3C), 69.5 (C-4E), 68.7 (C-4D or C-4B), 68.3 (C-1 sphingosine), 68.1 (C-4D or C-4B), 63.4 (C-2 sphingosine), 61.9 (C-6A), 61.7 and 61.5 (C-6D and C-6B), 60.4 (C-6C), 54.4 (C-2C), 52.8 (–CO_2*C*H$_3$), 37.6 and 27.8 (CH_3C=O–*C*H$_2$–*C*H$_2$–), 29.2 (*C*H$_3$C=O–CH_2), 32.9, 31.8, 29.6–28.6 and 22.6 (CH_2 sphingosine), 23.0–20.1 (11 –O–C=O–*C*H$_3$ and 1 NH–C=O–*C*H$_3$), 14.0 (CH_3 sphingosine); MS *m/z* (FAB): 2099.8 $(M+Na)^+$. Anal. Calcd for $C_{99}H_{128}N_4O_{44}$ (2078.159): C 57.21, H 6.20, N 2.69; found C 56.73, H 6.20, N 2.47.

6.2.17. (Methyl 2,4-di-*O*-benzoyl-3-*O*-levulinyl-β-D-glucopyranosyluronate)-(1→3)-(2,4,6-tri-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-(2-acetamido-3,6-di-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-(1→3)-(2,4,6-tri-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-acetyl-β-D-glucopyranosyl)-(1→1)-(2*S*,3*R*,4*E*)-2-octadecanamido-3-*O*-benzoyl-4-octadecene-1,3-diol (22). Compound **21** (165 mg, 79.4 μmol) and PPh_3 (62.4 mg, 238.2 μmol) were dissolved in a mixture of THF/H_2O (3 mL/0.6 mL) and stirred overnight at 50 °C. Solvents were evaporated in vacuum. The residue was purified by flash chromatography to afford a foam, which was directly engaged in the next step. To a stirred solution of this foam in CH_2Cl_2 (4 mL) were successively added stearic acid (42 mg, 198.5 μmol) and DCC (45 mg, 158.8 μmol) at room temperature. After stirring overnight, solvent was evaporated in vacuum. The residue was purified by flash chromatography (eluent, 3% MeOH in CH_2Cl_2) to afford **22** (143 mg, 78%) as a white foam. $[\alpha]_D$ +12 (*c* 0.26 in chloroform); mp: 172.5–173 °C (DCM/MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00–7.45 (m, 15H, arom.), 5.89 (dt, 1H, $J_{5-4}=15.0$ Hz, $J_{5-CH_2}=6.8$ Hz, H-5 ceramide), 5.76 (d, 1H, $J_{NH-2}=9.3$ Hz, NH ceramide), 5.63 (t, 1H, $J_{3-4}=J_{3-2}=9.4$ Hz, H-3E), 5.58–5.55 (m, 1H, H-3 ceramide), 5.55 (t, 1H, $J_{4-5}=9.5$ Hz, H-4E), 5.50 (d, 1H, $J_{4-3}=3.4$ Hz, H-4D or H-4B), 5.52–5.47 (m, 1H, H-4 ceramide), 5.35 (d, 1H, $J_{NHAc-2}=8.7$ Hz, N*H*Ac), 5.30 (d, 1H, $J_{4-3}=3.4$ Hz, H-4D or H-4B), 5.26 (dd, 1H, $J_{2-1}=7.3$ Hz, H-2E), 5.18 (t, 1H, $J_{3-2}=J_{3-4}=9.5$ Hz, H-3A), 5.08 (dd, 1H, $J_{2-3}=10.2$ Hz, $J_{2-1}=8.0$ Hz, H-2D or H-2B), 5.08 (t, 1H, $J_{3-2}=J_{3-4}=9.2$ Hz, H-3C), 5.00 (dd, 1H, $J_{2-3}=10.0$ Hz, $J_{2-1}=8.1$ Hz, H-2D or H-2B), 4.90 (dd, 1H, $J_{2-3}=9.5$ Hz, $J_{2-1}=7.8$ Hz, H-2A), 4.88 (d, 1H, H-1E), 4.69 (dd, 1H, $J_{6b-6a}=10.7$ Hz, $J_{6b-5}=3.2$ Hz, H-6Cb), 4.57 (d, 1H, $J_{1-2}=7.8$ Hz, H-1C), 4.55–4.46 (m, 1H, H-2 ceramide), 4.46 (d, 1H, H-1A), 4.40 (d, 1H, H-1D or H-1B), 4.33 (de, 1H, $J_{6b-6a}=11.8$ Hz, H-6Ab), 4.32 (d, 1H, H-1D or H-1B), 4.24 (d, 1H, H-5E), 4.13 and 4.00 (2dd, 2H, $J_{6b-6a}=11.5$ Hz, $J_{6b-5}=J_{6a-5}=6.2$ Hz, H-6D or H-6B), 4.07–4.05 (m, 2H, H-6D or H-6B), 4.05–4.02 (m, 1H, H-1b ceramide), 3.98 (dd, 1H, $J_{6a-5}=3.4$ Hz, H-6Aa), 3.92 (dd, 1H, $J_{6a-5}=3.2$ Hz, H-6Ca), 3.90 (dd, 1H, H-3D or H-3B), 3.82 (t, 1H, $J_{5-6}=6.2$ Hz, H-5D or H-5B), 3.78–3.76 (m, 1H, H-5D or H-5B), 3.76–3.70 (m, 3H, H-4C, H-4A and H-3D or H-3B), 3.73 (s, 3H, CO_2CH_3), 3.68–3.62 (m, 1H, H-1a ceramide), 3.62–3.60 (m, 1H, H-2C), 3.61–3.58 (m, 1H, H-5A), 3.44 (dt, 1H, $J_{5-4}=9.2$ Hz, H-5C), 2.50 and 2.37 (2t, 4H, $J_{CH_2-CH_2}=7.0$ Hz, CH_3–C=O–*C*H_2–*C*H_2–), 2.19–1.91 (12s, 36H, 11 –O–C=O–CH_3 and *C*H_3C=O–CH_2), 1.70 (s, 3H, NH*Ac*), 1.70–1.68 and 1.29–1.25 (m, 56H, CH_2 ceramide), 0.91 (2t, 6H, $J_{CH_3-CH_2}=7.0$ Hz, CH_3 ceramide); ^{13}C NMR (100 MHz): δ 205.3 (C=O), 172.6, 171.6, 170.6, 170.5, 2×170.4, 170.3, 170.2, 2×169.8, 169.7, 169.6, 168.8, 168.4, 166.7, 165.1, 164.9 and 164.6 (17O–C=O and 1 N–C=O), 137.6 (C-5 ceramide), 133.5–128.4 (15CH arom.), 130.2, 129.1 and 128.8 (3C arom.), 124.6 (C-4 ceramide), 100.7 (C-1D or C-1B), 100.6 (C-1E and C-1D or C-1B), 100.4 (C-1C), 100.2 (C-1A), 76.8 (C-3D or C-3B), 75.7 (C-4A), 75.6 (C-4C), 75.0 (C-3D or C-3B), 73.9 (C-3 ceramide), 72.7 (C-5E), 72.6 (C-5A), 72.5 (C-5C), 72.2 (C-3A), 2×71.6 (C-2D or C-2B and C-2A), 71.5 (C-3E), 71.4 (C-2E), 71.2 and 71.0 (C-5D and C-5B), 70.9 (C-2D or C-2B), 70.5 (C-3C), 69.5 (C-4E), 68.7 (C-4D or C-4B), 68.1 (C-4D or C-4B), 67.3 (C-1 ceramide), 61.9 (C-6A), 61.7 and 61.5 (C-6D and C-6B), 60.4 (C-6C), 54.4 (C-2C), 52.8 (–CO_2*C*H_3), 50.5 (C-2 ceramide), 37.6 and 27.9 (CH_3C=O–*C*H_2–*C*H_2–), 23.0–20.1 (11 –O–C=O–*C*H_3 and 1 NH–C=O–*C*H_3 and *C*H_3C=O–), 36.8, 33.3, 31.9, 29.7–28.9, 25.7 and 22.6 (CH_2 ceramide), 14.1 (CH_3 ceramide); MS *m/z* (FAB): 2340.0 $(M+Na)^+$. Anal. Calcd for $C_{117}H_{164}N_2O_{45}$ (2318.15): C 60.61, H 7.12, N 1.20; found C 60.68, H 7.31, N 1.11.

6.2.18. (Methyl 2,4-di-*O*-benzoyl-3-*O*-sulfo-β-D-glucopyranosyluronate)-(1→3)-(2,4,6-tri-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-(2-acetamido-3,6-di-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-(1→3)-(2,4,6-tri-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-acetyl-β-D-glucopyranosyl)-(1→1)-(2*S*,3*R*,4*E*)-2-octadecanamido-3-*O*-benzoyl-4-octadecene-1,3-diol sodium salt (23). Hydrazine monoacetate (20 mg, 215 μmol) was added to a stirred solution of **22** (100 mg, 43 μmol) in EtOH (4 mL) at room temperature. After stirring for 1 h, the mixture was neutralized with saturated sodium hydrogen carbonate, washed with brine, dried ($MgSO_4$), filtered and evaporated in vacuum. The residue was purified by flash chromatography (eluent, 2% MeOH in DCM) to afford the 3-OH compound (77 mg, 81%) as a white foam. ^{1}H RMN (400 MHz, $CDCl_3$): δ 4.15–4.1 (m, 1H, H-3E). $SO_3.Me_3N$ (72 mg, 520.5 μmol) was added to a stirred solution of the previous foam (77 mg, 34.7 μmol) in DMF (3 mL). The mixture was stirred at 40 °C for 20 h. MeOH (0.2 mL) and CH_2Cl_2 (0.2 mL) were added, and the solution was applied to a column of Sephadex LH-20 with 1:1 DCM/MeOH eluent. Glycolipid containing fractions were concentrated. Column chromatography (MeOH) of the residue on Dowex-50*2 (Na^+) resin gave **23** (65 mg, 81%) as an amorphous powder. $[\alpha]_D$ +10 (*c* 0.2 in chloroform); ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$): δ 7.70–7.05 (m, 15H, arom.), 5.50 (dt, 1H, $J_{5-4}=13.4$ Hz, $J_{5-CH_2}=6.8$ Hz, H-5 ceramide), 5.18–5.12 (m, 1H, H-3 ceramide), 5.10 (d, 1H, $J_{4-3}=3.4$ Hz, H-4D or H-4B), 5.12–5.07 (m, 1H, H-4 ceramide), 5.00 (t, 1H, $J_{4-3}=J_{4-5}=9.7$ Hz, H-4E), 4.94 (d, 1H, $J_{4-3}=3.5$ Hz, H-4D or H-4B), 4.84 (dd, 1H, $J_{2-1}=7.8$ Hz, $J_{2-3}=9.7$ Hz, H-2E), 4.74 (t, 1H, $J_{3-2}=J_{3-4}=9.4$ Hz, H-3A), 4.70 (dd, 1H, $J_{3-2}=9.3$ Hz, $J_{3-4}=9.5$ Hz, H-3C), 4.61 (t, 1H, H-3E), 4.59 (dd, 1H, $J_{2-3}=9.5$ Hz, $J_{2-1}=8.0$ Hz, H-2D or H-2B), 4.58 (d, 1H, H-1E), 4.52 (dd, 1H, $J_{2-3}=9.9$ Hz, $J_{2-1}=8.0$ Hz, H-2D or H-2B), 4.37 (dd, 1H, $J_{2-1}=8.0$ Hz, H-2A), 4.24 (d, 1H, $J_{1-2}=8.2$ Hz, H-1C), 4.08 (de, 1H, $J_{6b-6a}=9.7$ Hz, H-6Cb), 4.17 (d, 1H, H-1A), 4.09–4.04 (m, 1H, H-2 ceramide), 4.06 (d, 1H, H-1D or H-1B), 4.00 (d, 1H, H-1D or H-1B), 3.83 (d, 1H, $J_{6b-6a}=10.0$ Hz, H-6Ab), 3.83 (d, 1H, H-5E), 3.73–3.55 (m, 7H, H-6Aa, H-5D, H-5B, H-6D and H-6B), 3.63 (dd, 1H, H-3D or H-3B), 3.58–3.55 (m, 1H, H-1b ceramide), 3.54–3.50 (m, 1H, H-6Ca), 3.39 (dd, 1H, H-3D or H-3B), 3.38 (t, 1H, H-5D or H-5B), 3.22 (t, 1H, $J_{4-5}=9.5$ Hz, H-4C), 3.28–3.25 (m, 1H, H-1a ceramide), 3.27 (s, 3H, CO_2CH_3), 3.25–3.22 (m, 1H, H-5A), 3.10 (dd, 1H, H-2C), 2.99 (dt, 1H, H-5C), 1.75–1.58 (11s, 33H, –O–C=O–CH_3), 1.50 (s, 3H, NH*Ac*), 1.82–1.70 and 0.94–0.87 (m, 56H, CH_2 ceramide), 0.49 (2t, 6H, $J_{CH_3-CH_2}=7.1$ Hz, CH_3 ceramide); ^{13}C NMR (100 MHz): δ 174.0, 171.2, 170.4, 2×170.3, 170.2, 170.0, 169.9, 169.7, 169.5, 169.4, 168.8, 168.7, 167.2, 165.3 and 2×164.9 (16O–C=O and 1 N–C=O), 132.4 (C-5 ceramide), 132.2–127.3 (15CH arom.), 129.5, 129.2 and 128.8 (3C arom.), 123.5 (C-4 ceramide), 100.0 (C-1D and C-1B), 99.8 (C-1E), 99.7 (C-1C), 99.3 (C-1A), 76.9, 76.4, 75.9, 2×75.0, 73.4, 72.2, 72, 71.7, 71.6, 71.5, 71.4, 71.0, 70.3, 70.2, 69.9, 69.8, 69.7, 68.8 and 68.1 (19 CH cycle and C-3 ceramide), 66.7 (C-1 ceramide), 61.9 (C-6C), 61.3 and 61.0 (C-6D and C-6B), 60.2 (C-6A), 53.9 (C-2C), 51.6 (–CO_2*C*H_3), 50.2 (C-2 ceramide), 35.5, 31.5, 31.1, 28.9–28.1, 25.3 and 21.8 (CH_2 ceramide), 21.3–18.9 (11 –O–C=O–*C*H_3 and 1 NH–C=O–*C*H_3), 12.8 (CH_3 ceramide). MS *m/z* (FAB):

2307.9 MH^+. Anal. Calcd for $C_{112}H_{157}N_2NaO_{46}S$ (2308.5): C 57.92, H 6.81, N 1.21; found C 59.13, H 6.96, N 1.10.

6.2.19. (3-*O*-Sulfo-β-D-glucopyranosyluronic acid)-(1→3)-(β-D-galactopyranosyl)-(1→4)-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-(1→3)-(β-D-galactopyranosyl)-(1→4)-(β-D-glucopyranosyl)-(1→1)-(2*S*,3*R*,4*E*)-2-octadecanamido-3-*O*-benzoyl-4-octadecene-1,3-diol disodium salt (1). To a stirred solution of **23** (60 mg, 26 μmol) in a mixture of THF/H_2O (3.8 mL/0.2 mL) was added at 0 °C a solution of 1.25 N LiOH (0.26 mL, 1040 μmol). The mixture was stirred 3 h between 0 and 5 °C. Solvents were evaporated in vacuum. The residue was dissolved in a mixture of THF/MeOH (2 mL/2 mL) and sodium (cat., 0.15 M) was added at 0 °C. The solution was stirred for 3 h at room temperature and purified on a column of Sephadex LH-20 with $CHCl_3/MeOH/H_2O = 6:4:0.8$ to afford SGPG (35 mg, 90%) as a white foam; ^1H NMR (600 MHz, $CD_3S{=}OCD_3$): δ 5.54 (dt, 1H, $J_{5-4} = 15.2$ Hz, $J_{5-CH_2} = 6.7$ Hz, H-5 ceramide), 5.35 (dd, 1H, $J_{4-5} = 15.2$ Hz, $J_{4-3} = 7.1$ Hz, H-4 ceramide), 4.65, 4.54, 4.30, 4.27 and 4.16 (5d, 5H, 5H-1), 3.99 (t, 1H, $J_{3-2} = J_{3-4} = 9.0$ Hz, H-3E), 1.82 (s, 3H, NH*Ac*), 0.85 (t, 6H, $J_{CH_3-CH_2} = 7.1$ Hz, CH_3 ceramide); MS (MALDI-TOF): Calcd $(M+Na)^+ = 1532.74$; found = 1532.7; Calcd $(M-H+2Na)^+ = 1510.76$; found = 1510.7.

Acknowledgements

The authors thank Prof. Jacques Aubry (Nantes) for initiating this project.

References and notes

1. Voshol, H.; Van Zuylen, C. W. E. M.; Orberger, G.; Vliegenhart, J. F. G.; Schachner, M. *J. Biol. Chem.* **1996**, *271*, 22957–22960.
2. Baumann, N. *Clin. Rev. Allergy Immunol.* **2000**, *19*, 31–40.
3. Rowland, L. P.; Sherman, W. L.; Hays, A. P.; Lange, D. J.; Latov, N.; Trojaborg, W.; Younger, D. S. *Neurology* **1995**, *45*, 827–829.
4. Chassande, B.; Léger, J. M.; Ben-Younes-Chennoufi, A.; Bengoufa, D.; Maisonobe, T.; Bouche, P.; Baumann, N. *Muscle Nerve* **1998**, *21*, 55–62.
5. Ilyas, A. A.; Dalakas, M. C.; Brady, R. O.; Quarles, R. H. *Brain Res.* **1986**, *385*, 1–9.
6. Two other chemical synthesis of SGPG have been reported: (a) Nakano, T.; Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1990**, *31*, 1597–1600. (b) Nakano, T.; Ito, Y.; Ogawa, T. *Carbohydr. Res.* **1993**, *243*, 43–69. (c) Isogai, Y.; Ishida, H.; Kiso, M.; Hasegawa, A. *J. Carbohydr. Chem.* **1996**, *15*, 1119–1137.
7. For previous works on lactosaminyl and lewis X glycolipids: (a) Zhang, Y.; Esnault, J.; Mallet, J.-M.; Sinaÿ, P. *J. Carbohydr. Chem.* **1999**, *18*, 419–427. (b) Brégant, S.; Zhang, Y.; Mallet, J.-M.; Brodzki, A.; Sinaÿ, P. *Glycoconjugate J.* **1999**, *16*, 757–765. (c) Esnault, J.; Mallet, J.-M.; Zhang, Y.; Sinaÿ, P.; Le Bouar, T.; Pincet, F.; Perez, E. *Eur. J. Org. Chem.* **2001**, 253–260. (d) Gourier, C.; Pincet, F.; Perez, E.; Zhang, Y.; Mallet, J.-M.; Zhu, Z.; Sinay, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 1683–1687.
8. Jansson, K.; Ahfors, S.; Frejd, T.; Kihlberg, J.; Magnusson, G. *J. Org. Chem.* **1988**, *53*, 5629–5647.
9. Schmidt, R. R.; Zimmermann, P. *Tetrahedron Lett.* **1986**, *27*, 481–484.
10. Lemieux, R. U.; Driguez, H. *J. Am. Chem. Soc.* **1975**, *97*, 4069–4075.
11. Tabeur, C.; Mallet, J.-M.; Bonot, F.; Herbert, J.-M.; Petitou, M.; Sinaÿ, P. *Bioorg. Med. Chem.* **1999**, *7*, 2003–2012.
12. (a) Koeppem, B. H. *Carbohydr. Res.* **1972**, *24*, 154–158. (b) Charon, D.; Szabo, L. *J. Chem. Soc., Perkin. Trans. 1* **1980**, 1971–1977. (c) Takeo, K.; Kitamura, S.; Murata, Y. *Carbohydr. Res.* **1992**, *224*, 111–122.
13. Hajko, J.; Borbas, A.; Liptàk, A. *Carbohydr. Res.* **1991**, *216*, 413–420.
14. Zsiska, M.; Meyer, B. *Carbohydr. Res.* **1991**, *215*, 279–292.
15. (a) Brimacombe, J. S. *Methods Carbohydr. Chem.* **1972**, *VI*, 376. (b) Garegg, P.; Maron, L. *Acta Chem. Scand.* **1979**, *B33*, 39–41.
16. Domon, B.; Costello, C. E. *Glycoconjugate J.* **1988**, *5*, 397–409.
17. Willison, H. J.; Veitch, J.; Swan, A. V.; Baumann, N.; Comi, G.; Gregson, N. A.; Illa, I.; Zielasek, J.; Hughes, R. A. *Eur. J. Neurol.* **1999**, 71–77.
18. Renaud, S.; Gregor, M.; Fuhr, P.; Lorenz, D.; Deuschl, G.; Gratwohl, A.; Steck, A. J. *Muscle Nerve* **2003**, *27*, 611–615.
19. Ariga, T.; Kohriyama, T.; Freddo, L.; Latov, N.; Saito, M.; Kon, K.; Ando, S.; Suzuki, M.; Hemling, M. E.; Rinehart, K. L.; Kusunoki, S.; Yu, R. K. *J. Biol. Chem.* **1987**, *262*, 848–853.
20. Willison, H. J.; Townson, K.; Veitch, J.; Boffey, J.; Isaacs, N.; Andersen, S. M.; Zhang, P.; Ling, C. C.; Bundle, D. R. *Brain* **2004**, *127*, 680–691.
21. Andersen, S. M.; Ling, C. C.; Zhang, P.; Townson, K.; Willison, H. J.; Bundle, D. R. *Org. Biomol. Chem.* **2004**, *2*, 1199–1212.
22. Fenn, J. B.; Mann, M.; Meng, C. K.; Wong, S. F.; Whitehouse, C. M. *Science* **1989**, *246*, 64–71.

Available online at www.sciencedirect.com

ELSEVIER

Tetrahedron 62 (2006) 578–585

Tetrahedron

Development of water-soluble far-red fluorogenic dyes for enzyme sensing

Nan-hui Ho, Ralph Weissleder and Ching-Hsuan Tung*

Center of Molecular Imaging Research, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA 02129, USA

Received 2 March 2005; revised 5 October 2005; accepted 10 October 2005

Abstract—A series of Nile Blue analogs, 5-amino-9-dialkylamino benzo[*a*]phenoxazine dyes, **7**–**9**, were prepared by condensation of *N*-alkyl or *N*-sulfo-propyl 4-arylazo-substituted 3-hydroxyaniline with 4-arylazo-substituted 1-naphthlamines or 8-amino-2-naphthalene-sulfonic acid in the presence of perchloric acid. These fluorochromes have excitation and emission maxima near 640 and 680 nm, respectively. The fluorescence intensity in aqueous solution increases as additional sulfonate groups are added to the benzo[*a*]phenoxazine core. Compound **7**, which has two sulfonate groups, is ten-times brighter than Nile Blue. Fluorogenic substrates containing this hydrophilic far-red dye were synthesized and applied to detect enzymatic activities of two model proteases, trypsin and leucine aminopeptidase. Given their excellent fluorogenic property, these novel far-red dyes should be useful for enzyme sensing in biological assays.

1. Introduction

Fluorogenic substrates using 7-amino-4-methylcoumarin (AMC) as a reporter are the most popular probes used in proteolytic assays today.[1,2] Typically, AMC is attached to the C-terminus of a peptide sequence that is specific for a targeted protease. The amide linkage between the peptide chain and AMC results in a dramatic blue shift of both absorption and emission. Due to this unique property, when the excitation wavelength was set for free AMC, the intact probes emit almost no fluorescence unless the AMC group is released. Although AMC-based probes are in widespread use, low emission wavelength (430 nm) of AMC has restricted their uses to cell free assays to avoid interference with background autofluorescence from intact cells and tissues.

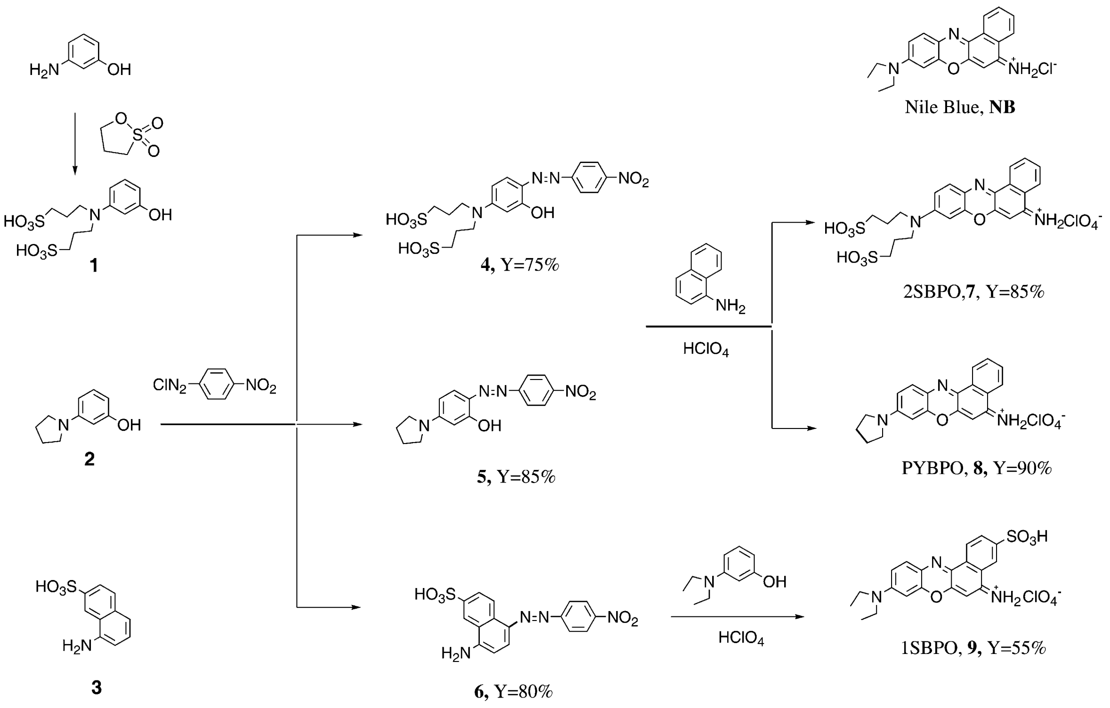
Recently, rhodamine-based fluorogenic substrates with emission maxima near 520 nm have been reported for cellular studies.[3–5] Similar to the AMC probes, peptides are linked to the rhodamine analogs by amide linkages through their C-termini. However, these rhodamine analogs contain two amino groups requiring two amino acids or peptides to react with a single fluorophore. The requirement that both peptide chains need to be cleaved from the core fluorophore further limits the linear dynamic range. Thus, there is a need for the development of fluorogenic dyes that have photochemical stability, long wavelength excitation and emission maxima, and are water-soluble for cellular as well as, potentially, for in vivo applications.

In searching industrial dyes, we found that benzo[*a*]-phenoxazines (BPO), which were utilized for dyeing fibers and paper, could potentially be converted into fluorogenic substrates. As a result of their compact and rigid structures compared to that of cyanine dyes, BPO have better photochemical stability. The relatively high molar absorbance, strong fluorescence into the deep red region (650–730 nm) and modest Stokes shifts (20–60 nm) indicate the potential utility of these dyes as fluorophores for biological applications. Indeed it had previously been demonstrated that the reaction of the primary amino group on BPO with a carboxylic acid resulted in a dramatic reduction in fluorescence intensity.[6] This is a desirable property for creating fluorogenic enzyme probes. Unfortunately, the low solubility of BPO and its tendency to aggregate in aqueous environments have limited its biological applications. We hypothesized that BPO analogs with increased sulfonation would have higher water solubility,[7] improved biocompatibility and potentially higher fluorescence output. In the present report, we detail the synthesis, characterization, and preliminary biological studies of such a new class of hydrophilic BPO-based far-red fluorogenic probes (Scheme 1). This type of probe should have potential use for in vivo sensing and imaging of proteases.[8]

Keywords: Fluorogenic; Fluorescent probe; Water-soluble; Nile Blue; Protease; Leucine aminopeptidase.

* Corresponding author. Tel.: +1 617 726 5779; fax: +1 617 726 5708; e-mail: tung@helix.mgh.harvard.edu

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.10.020



Scheme 1. Synthetic scheme of **7**–**9** and structure of Nile Blue.

2. Results and discussion

2.1. Synthesis of benzo[*a*]phenoxazine dyes

BPO dyes, such as Nile Blue (NB) and Nile Blue 2B, are generally prepared by reacting the appropriate nitrosoanilines with 1-naphthylamines or 2-naphthol in ethanol in the presence of hydrochloric acid.[9–11] However, those procedures are not suited for the synthesis of sulfonated benzo[*a*]phenoxazines. Cyclization using sulfonated nitrosoanilines or 1-naphthlamines as building blocks is not very effective. Sulfonation after cyclization is also not desirable because multiple substitutions at several aryl positions produce mixtures, which must then be separated. A recent literature report demonstrated that the bridged benzo[*a*]phenoxazinium salts could be synthesized by heating arylazo-substituted aminophenols or naphthamines with the appropriate 1-naphthylamine or aminophenol in DMF in the presence of perchloric acid.[12] We found that this method is well-suited for transforming sulfonated arylazo-substituted aminophenols into sulfonated benzo[*a*]phenoxazines (Scheme 1).

Compound **8**, which has no sulfonate group, was synthesized initially. Replacement of the 9-diethylamino group of Nile Blue with the *N*-(di-3-sulfonyl-propyl)amino group generates **7**. Compound **9** was designed to incorporate sulfonyl groups substituted on the aromatic ring (Scheme 1). The sulfonated aminophenol **1** was obtained by reaction of 3-aminophenol with propane sultone. The arylazo compounds **4**–**6** were prepared by treating the corresponding *N*-substituted aminophenols **1**–**3** with an aryl diazonium salt. Three desired dyes **7**–**9** were obtained from the corresponding arylazo compounds **4**–**6**. For compound **8**, the ring system was readily formed in 5 min; however, prolonged heating was necessary for ring condensation of **7** and **9**. During the condensation reactions, the temperature was maintained below 160 °C because product decomposition was observed at higher temperature.

2.2. Absorption and fluorescence properties

For biological applications, high fluorescence quantum yield in water is essential. It is known that π-stacking of xanthene dyes by van der Waal's forces or hydrophobic interactions causes serious fluorescence quenching in aqueous solution.[13–15] BPO type dyes, such as NB and cresyl violet readily form sandwich-like H-aggregate type of dimers or even higher aggregates in aqueous solution. H-aggregated dimers are known to be nonfluorescent due to

Table 1. Absorption and fluorescence properties of BPO dyes

Dyes	λ_{max}[a] (nm)		Extinction coefficient ($(M\ cm)^{-1}$)[a]	FWHM (nm)		Relative quantum yield[b]
	Ex	Em		H_2O	CH_3OH	
Nile Blue	635	675	4000	115	76	0.01[c]
PYBPO **8**	643	678	8000	89	77	0.03
1SBPO **9**	637	677	11,000	93	70	0.03
2SBPO **7**	633	675	36,000	86	65	0.10

[a] 1×10^{-5} M in PBS.

[b] The fluorescence intensities in water were measured from the emission curve using 'area' function of the fluorometer.

[c] Ref. 22.

the forbidden nature of transition between the lowest excited singlet and ground states.[16] To improve the fluorescence properties and to reduce the tendency of the dyes to aggregate in aqueous media, the hydrophobic ethyl group at the 9-amino position of NB were replaced with alkylsulfonate groups as in 2SBPO **7**. A similar effect is observed when a sulfonate group is introduced at one of the aryl position of the dye as in 1SBPO **9**.

The absorption and fluorescence maxima, relative fluorescence intensities and extinction coefficients for compounds **7**–**9** are summarized in Table 1. The 'parent dye', NB, is included for comparison. In general, modifications at the 9-amino and C-3 positions of the BPO have little effect on the absorption and emission maxima. PYBPO **8** shows a slightly red shifted absorption maximum at 643 nm when a pyrrolidinyl group was introduced at the 9-amino position. For dyes **7**–**9**, the absorption maximum are pH independent in the range of 4–8 and the Stokes' shifts are approximately 40 nm. The extinction coefficients of **7**–**9** in aqueous solution vary between 8000 and 36,000 $(\mathrm{M\,cm})^{-1}$. For 2SBPO **7**, a nine-fold improvement over NB, which has a very low ε value around 4000 $(\mathrm{M\,cm})^{-1}$ in aqueous solution, was achieved. The higher extinction coefficient of 2SBPO **7**, in comparison to 1SBPO **9** and PYBPO **8**, may be caused by the increased water-solubility.

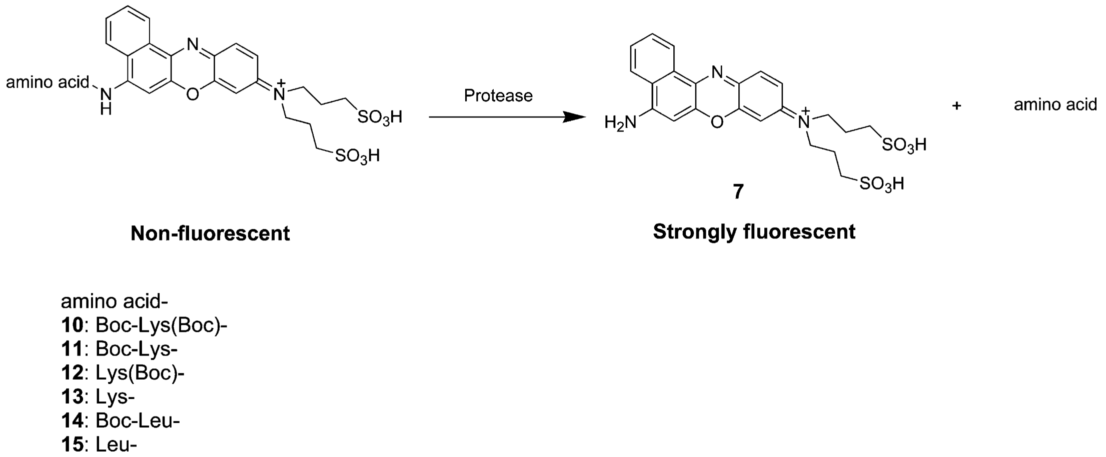
It has been previously reported that in weak acidic to basic condition, NB exists as the blue cation HNB^+ (absorbance maximum at 640 nm), and a dimer $(\mathrm{HNB})_2^{2+}$ (absorbance maximum at 600 nm).[17] Because of the close proximity of the absorption bands of the monomer and dimer, the full width at half-maximum (FWHM) values in water were used to access the equilibrium between monomer and dimer semi-quantitatively.[18,19] In methanol, sharp absorption bands near 640 nm with FWHM values ranging from 65 to 76 nm were observed for all the dyes, indicative of nonaggregated systems. In water, FWHM values for compounds **7**–**9** and NB ranged from 86 to 115 nm. The 86 nm FWHM value of **7** indicates a reduced tendency to dimerize in comparison to other dyes in aqueous solution.

Comparison of relative fluorescence emission intensities of the dyes reveal that modification with sulfonyl groups dramatically increases the fluorescence intensity in aqueous solution (Table 1). As expected, addition of sulfonate groups also increases water solubility and reduces the tendency of aggregate formation, thus resulting in a shift in the monomer–dimer equilibrium. With the increase of monomer fraction in water, the relative fluorescence intensities increase. The relative fluorescence intensity of 1SBPO **9** in water is three-fold higher than that of NB. Modification with two sulfonate groups increases the relative fluorescence intensity by a factor of 10 for 2SBPO **7**. Surprisingly, PYBPO **8** exhibits similar emission property to 1SBPO **9**. The increase in fluorescence intensity of PYBPO versus NB is likely due to its less aggregated nature. In aqueous solution, the 89 nm FWHM value of PYBPO shows less dimerization in comparison to NB (115 nm).

2.3. Water-soluble BPO-based fluorogenic substrates

Due to its superior fluorescence properties in aqueous buffer, 2SBPO **7** was chosen for subsequent preparation of fluorogenic substrates (**10**–**15**, Scheme 2). Various amino acid residues activated in situ by HATU were coupled to **7** using collidine as base. The coupling reactions were normally completed in 1–2 h at room temperature with 95–100% conversion as determined by TLC. As expected, all amino acid-2SBPO conjugates were very soluble in water and gave only low fluorescence signals.

To demonstrate the general applicability of the water-soluble BPO-based fluorogenic protease sensors, the fluorogenic substrate, Lys-2SBPO **13**, was initially synthesized for digestion with trypsin. The conjugate showed a nearly 10-fold reduction in fluorescence intensity. However, the substrate was found to be only stable at low pH. When pH > 5, spontaneous hydrolysis was observed. In order to investigate whether the spontaneous hydrolysis of 2SBPO-based substrates depends on the nature of the amino groups on the amino acid residues, we conjugated **7** to lysine with and without the Boc protected amino groups. Overall, four analogs, Boc-Lys(Boc)-2SBPO **10**, Boc-Lys-2SBPO **11**, Lys(Boc)-2SBPO **12** and Lys-2SBPO **13**, were prepared (Scheme 2). The stabilities of these conjugates in



Scheme 2. Structures of fluorogenic enzyme substrates **10**–**15**.

aqueous solution were then examined over the pH range of 4–8. Free 2SBPO **7** was included in this study as a control to verify that the fluorescence intensity of free **7** is not significantly affected within the tested pH range. Lys-2SBPO **13** and Lys(Boc)-2SBPO **12**, without protecting the α-amino groups, were found to be stable at pH 4 and 5, but not at higher pH (Fig. 1A). At pH > 5, compared to pH 4 and 5, there was approximately a three-fold difference in fluorescence intensity indicating spontaneous hydrolysis of the substrates. Importantly, when the α-amino group was blocked with a Boc group, the fluorescence intensities of Boc-Lys-2SBPO **11** and Boc-Lys(Boc)-2SBPO **10** were unchanged for at least 3 h over the pH range investigated. The experimental evidence indicates that the free α-amino residues of amino acids have a catalytic effect on the hydrolysis of the amide bond.

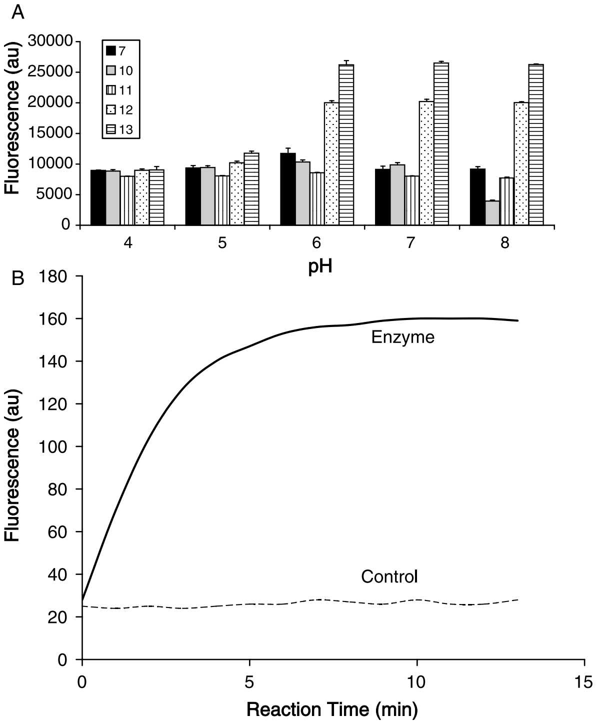


Figure 1. Effects of pH on the stabilities of the fluorogenic substrates containing lysine residues and trypsin proteolysis assays. (A) 2SBPO **7**, Boc-Lys(Boc)-2SBPO **10**, Boc-Lys-2SBPO **11**, Lys(Boc)-2SBPO **12** and Lys-2SBPO **13** (1 μM) incubated in 0.1 M buffers (pH 4.0–8.0) at room temperature for 3 h ($n = 3$). The fluorescence intensities are normalized. (B) Fluorescence assay for the hydrolysis of Boc-Lys-2SBPO **11** (4 μM) with trypsin (6 u) in 0.1 M sodium phosphate buffer (pH 7.4). The fluorescence excitation and emission were 610 and 670 nm, respectively.

The fluorogenic substrate, Boc-Lys-2SBPO **11**, was then assayed with its target protease, trypsin. Figure 1B showed the time course for the enzyme catalyzed hydrolysis at pH 7.4. After adding trypsin to the substrate solution, a strong fluorescent signal generated at 670 nm indicated catalytic cleavage of the amide bond and release of highly fluorescent free **7**. A seven-fold increase in fluorescence intensity was observed in comparison to the control reaction without trypsin.

2.4. Leucine aminopeptidase

Two BPO-based fluorogenic substrates, Boc-Leu-2SBPO **14** and Leu-2SBPO **15**, were also synthesized as model substrates to detect leucine aminopeptidase (aminopeptidase M, AP-M). AP-M is a cytosolic exopeptidase and catalyzes the hydrolysis of amino acids from the amino terminus of polypeptide chains.[20] Similar pH effects on the stabilities of leucine containing substrates were observed. At pH > 5, increase in fluorescence signal from **15** is attributable to the spontaneous hydrolysis, whereas Boc-Leu-2SBPO **14** remained stable between pH 4 and 8 (Fig. 2A). Upon incubating **14** with AP-M at neutral pH, an increase in fluorescence emission was observed (Fig. 2B). In contrast, without AP-M, the fluorescence intensity remained unchanged.

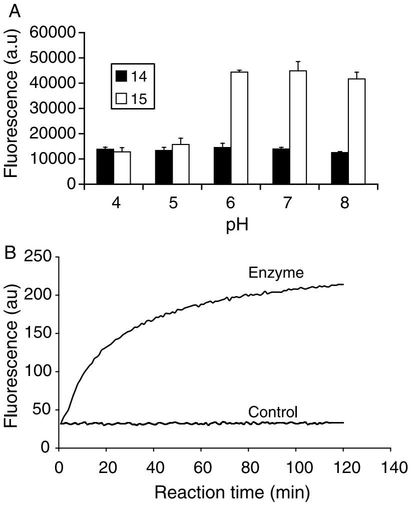


Figure 2. The effects of pH on the stabilities of Boc-Leu-2SBPO **14** and Leu-2SBPO **15** (3 h) (A) and leucine aminopeptidase proteolysis assay (B). The fluorescence assay of hydrolysis of Boc-Leu-2SBPO **14** (4 μM) with leucine aminopeptidase (0.7 u) in 0.1 M HEPES (pH 7.0) containing 5 mM $MgCl_2$ and 0.1% bovine serum albumin. The fluorescence excitation and emission were 610 and 670 nm, respectively.

The kinetic parameters for the hydrolysis of **14** with AP-M are listed in Table 2. The kinetic parameters of Leu-7-amido-4-methyl-coumarin (Leu-AMC), bis-Leu-rhodamine-110 (Bis-$(Leu)_2$-Rhod) and Leu-rhodamine-110 (Leu-Rhod110-NH_2) from the literature[4] are included in the table for comparison. Under the conditions used, the K_m values show that **14** binds more effectively to AP-M than coumarin- and rhodamine- based protease substrates. The V_{max} value for **14** is significantly higher than those of the previously reported fluorogenic substrates. The linearity of the fluorescence enhancement versus incubation time

Table 2. Kinetic parameters of the leucine aminopeptidase fluorogenic substrates

Substrates	K_m (μM)	V_{max} (nM/min)
Leu-AMC[a]	39.6 ± 3.6	4.3 ± 0.1
Bis-$(Leu)_2$-Rhod110[a]	23.6 ± 3.3	3.7 ± 0.2
Leu-Rhod110-NH_2[a]	5.6 ± 1.2	2.9 ± 0.2
Boc-Leu-2SBPO **14**[b]	2.8 ± 0.23	34 ± 0.7

[a] Ref. 4.

[b] 0.1 M HEPES, pH = 7.0, 5 mM $MgCl_2$ and 0.1% bovine serum albumin.

(for more than 10 min) is satisfactory (Fig. 2B). The high water solubility of the 2SBPO-based substrates allowed the assays to be performed without using any organic solvent as co-solvent, whereas the AMC and rhodamine-based substrates require 1–3% dimethyl sulfoxide (DMSO) as co-solvent.[4,21]

3. Conclusions

We have developed a highly efficient synthetic strategy for incorporation of sulfonate groups on the BPO moiety. This methodology allows for the production of water-soluble BPO derivatives in high yield. The mono-functional 2SBPO has excellent fluorogenic properties and is highly fluorescent in aqueous solution. The 2SBPO containing substrates have several advantages: (1) Kinetic determination of enzymatic process can be performed in aqueous solution without organic solvent. (2) Since the fluorescent spectra of the dyes are not sensitive to pH, the dyes are functional over a broad pH range. (3) Unlike coumarin and rhodamine, water-soluble BPO fluoresces beyond 650 nm in the far-red region and a better signal-to-noise ratio can be obtained. This system shows promise for in vivo enzyme imaging applications. (4) Up to a seven-fold change in fluorescence intensity can be obtained. Finally, the novel fluorogenic sensors could be used for in vivo sensing typically necessitating measurements in the far-red and near-infrared ranges.

4. Material and methods

3-Pyrrolidin-1-yl-phenol was purchased from ChemOvation (West Sussex, UK). Aminopeptidase-M (AP-M, EC 3.4.11.2) (porcine kidney, microsomal) was purchased from Sigma-Aldrich (St. Louis, MO) and Roche (Indianapolis, IN). Trypsin (porcine pancreas) and other reagents were obtained from Sigma-Aldrich and used without further purification. NMR spectra were recorded on either a Varian (Palo Alto, CA) XL-200 or an Inova-400 instrument for the ^{1}H–^{1}H 2D COSY and[13] spectra. Absorbance spectra were measured on a Varian Cary 50 Bio spectrophotometer. Fluorescence spectra were carried out on either a F-4500 (Hitachi, Danbury, CT) or a Fluorolog-3 (JOBIN YVON-SPEX, Edison, NJ) fluorophotometer. Kinetic parameters were determined on a TECAN (Salzburg, Austria) Genios Pro fluorescence micro plate reader. Electrospray mass spectra were obtained on a Platform LCT mass spectrometer (Micromass, Beverly, MA) and MALDI mass spectra were measured on a Voyager liner mass spectrometer (Applied Biosystems; Framingham, MA). The HR MALDI mass spectra were acquired on a Voyager-DE STR mass spectrometer (Applied Biosystems).

4.1. Chemical synthesis

4.1.1. 3-(3-Sulfo-propyl)aminophenol. To a solution of 3-aminophenol (5.0 g, 4.5 mmol) in 5 mL of *n*-butanol was added 1,3-propane sultone (0.56 g, 4.6 mmol), and the resulting mixture was refluxed with stirring for 30 min during which a gray precipitate was formed. The reaction mixture was stirred continuously at room temperature overnight. The precipitate was filtered and washed with cold methanol giving a gray solid (0.8 g, 80%). ^{1}H NMR (DMSO-d_6): δ 1.94 (quintet, 2H, *J* = 6.6 Hz, $\mathrm{NCH_2C}H_2\mathrm{CH_2SO_3H}$), 2.62 (t, 2H, *J* = 6.6 Hz, $\mathrm{NCH_2CH_2C}H_2\mathrm{SO_3H}$), 3.36 (t, 2H, *J* = 6.6 Hz, $\mathrm{NC}H_2\mathrm{CH_2CH_2SO_3H}$), 6.80 (m, 3H, H2, H4, H6), 7.24 (t, 1H, *J* = 7.5 Hz, H5). MS (MALDI-TOF) calcd for $C_9H_{14}NO_4S$ $(M+1)^+$: 232.27, found 231.30.

4.1.2. 3,3′-[(3-Hydroxyphenyl)amino]bis-1-propanesulfonic acid (1). A solution of 3-(3-sulfo-propyl)aminophenol (1 g, 4.3 mmol) and 1,3-propane sultone (0.54 g, 4.4 mmol) in 5 mL of DMF was heated to 130 °C for 2 h with stirring. After cooling, *t*-butyl ethyl ether was added to precipitate the dark oily product. The crude product was purified on a 35 cc Sap-Pak C_{18} cartridge (Waters, Milford, MA) eluting with water followed by 15% acetonitrile in water. The solvent was removed to give an orange-red crystalline solid (1.48 g, 95%). ^{1}H NMR (DMSO-d_6): δ 1.88 (m, 4H, $\mathrm{NCH_2C}H_2\mathrm{CH_2SO_3H}$), 2.50 (m, 4H, $\mathrm{NCH_2CH_2C}H_2\mathrm{SO_3H}$), 3.64 (m, 4H, $\mathrm{NC}H_2\mathrm{CH_2CH_2SO_3H}$), 6.20 (s, 1H, ar), 6.57, (d, 1H, *J* = 9.2 Hz, ar), 7.55 (d, 1H, *J* = 9.2 Hz, ar), 7.86 (d, 1H, *J* = 9.2 Hz, ar), 8.29 (d, 1H, *J* = 9.2 Hz, ar). MS (MALDI-TOF) calcd for $C_{12}H_{19}NO_7S_2$ $(M+1)^+$: 354.41, found 353.19.

4.1.3. 5-(Di-3-sulfonyl-propylamino)-2-(4-nitro-phenylazo)phenol (4). A solution of 4-nitroaniline (0.1 g, 0.80 mmol) was dissolved in a mixture of 0.5 mL of concentrated hydrochloric acid and 0.5 mL of water. The reaction flask was cooled in an ice-bath and sodium nitrite (55 mg, 0.80 mmol) dissolved in 100 μL of water was added slowly. The reaction mixture was stirred at 0 °C for an additional 20 min. At the end of the reaction, the solution turned orange. Then a solution of **1** (247 mg, 0.7 mmol) in 0.2 mL of methanol was added to the reaction flask. The reaction mixture was stirred for 30 min at room temperature. The red precipitate was filtered and washed with cold ethanol. The crude product was purified on a 35 cc Sep-Pak C_{18} cartridge eluting with water followed by 5% acetonitrile in water to yield **4** as a red solid (264 mg, 75%). ^{1}H NMR (DMSO-d_6): δ 1.88 (m, 4H, $\mathrm{NCH_2C}H_2\mathrm{CH_2SO_3H}$), 2.51 (m, 4H, $\mathrm{NC}H_2\mathrm{CH_2CH_2SO_3H}$), 3.64 (m, 4H, $\mathrm{NCH_2CH_2C}H_2\mathrm{SO_3H}$), 6.20 (s, 1H, ar), 6.57 (d, 1H, *J* = 9.2 Hz, ar), 7.55 (d, 1H, *J* = 9.2 Hz, ar), 7.86 (d, 1H, *J* = 9.2 Hz, ar), 8.29 (d, 1H, *J* = 9.2 Hz, ar). MS (MALDI-TOF) calcd for $C_{18}H_{23}N_4O_9S_2$ $(M+1)^+$: 503.52, found 503.10.

4.1.4. 2-(4-Nitro-phenylazo)-5-pyrrolidin-1-yl-phenol (5) and 8-amino-5-(4-nitro-phenylazo)-2-naphthalenesulfonic acid (6). Compounds **5** and **6** were synthesized using the same procedure as **4**, except 3-pyrrolidin-1-yl-phenol (**2**) and 8-amino-naphthalene-2-sulfonic acid (**3**) were used, respectively.

Compound **5**. The crude product was recrystallized in hot *n*-butanol. After drying, **5** (190 mg, 85%) was obtained as a purple solid. ^{1}H NMR (DMSO-d_6): δ 2.00 (m, 4H, $-\mathrm{C}H_2\mathrm{CH_2N}-$), 3.50 (m, 4H, $-\mathrm{CH_2C}H_2\mathrm{N}-$,), 5.86 (s, 1H, ar), 6.53 (d, 1H, *J* = 9.2 Hz, ar), 7.41 (d, 1H, *J* = 9.1 Hz, ar), 7.81 (d, 1H, *J* = 8.8 Hz, ar), 8.28 (d, 1H, *J* = 8.8 Hz, ar); MS (MALDI-TOF) calcd for $C_{16}H_{17}N_4O_3$ $(M+1)^+$: 313.33, found 313.8.

Compound **6**. The crude red solid was purified on a 35 cc Sep-Pak C_{18} cartridge eluted with a stepwise gradient, starting with water followed by 10% acetonitrile and then 20% acetonitrile in water. Pure **6** was obtained as red solid with typical yield of 80–90%. ^{1}H NMR (DMSO-d_6): δ 6.80 (d, 1H, $J=8.8$ Hz, H-7), 7.88 (d, 1H, $J=8.8$ Hz, H-6), 8.23 (m, 3H, ar), 8.36 (d, 2H, $J=8.8$ Hz, ar), 8.49 (s, 1H, H-1), 8.84 (d, 1H, $J=8.8$ Hz, H-3). MS (MALDI-TOF) calcd for $C_{16}H_{14}N_4O_5S$ $(M+1)^+$: 373.37, found 373.08.

4.1.5. 9-Di-3-sulfonyl-propylaminobenzo[*a*]phenoxazonium perchlorate (2SBPO, 7). A mixture of 5-(di-3-sulfonyl-propylamino)-2-(4-nitro-phenylazo)phenol **4** (86 mg, 0.17 mmol), 1-aminonaphthalene (27 mg, 0.19 mmol) and 3 mL of DMF containing perchloric acid (0.1 mL, 70%) was heated to 155–160 °C for 15 min with stirring. The color of the reaction mixture changed from brown to deep blue. The reaction was monitored by silica gel TLC (methanol/ethyl acetate, 4:5). After cooling, diethyl ether was added to precipitate the product. The crude perchlorate salt was purified on a 35 cc Sap-Pak C_{18} cartridge eluting with 10% acetonitrile in water (88 mg, 85%). ^{1}H NMR (DMSO-d_6): δ 1.80–2.00 (m, 4H, $NCH_2CH_2CH_2SO_3H$) 2.52–2.58 (m, 4H, $NCH_2CH_2CH_2SO_3H$), 3.70–3.80 (m, 4H, $NCH_2CH_2CH_2SO_3H$), 6.80 (s, 1H, H6), 7.10 (s, 1H, H8), 7.36 (d, 1H, $J=8.8$ Hz, H10), 7.72 (d, 1H, $J=8.8$ Hz, H11), 7.80–8.0 (m, 2H, H2, H3), 8.42 (d, 1H, $J=9.1$ Hz, H4), 8.74 (d, 1H, $J=8.4$ Hz, H1). Peak assignment was made using a combination of ^{1}H–^{1}H 2D COSY and 1D proton NMR spectra. ^{13}C NMR (400 MHz, D_2O): δ 159.35, 153.64, 149.07, 145.82, 136.73, 132.45, 131.35, 129.70, 128.82, 127.93, 122.69, 122.40, 120.85, 114.79, 96.25, 95.81, 49.94, 47.96, 22.57. HRMS (MALDI-TOF, negative-ion mode) calcd for $C_{22}H_{23}N_3O_7S_2$ $(M-2)^-$: 504.0899, found 504.093.

4.1.6. 9-Pyrrolidin-aminobenzo[*a*]phenoxazonium perchlorate (PYBPO, 8). To a solution of 2-(4-nitro-phenylazo)-5-pyrrolidin-1-yl-phenol **5** (100 mg, 0.32 mmol) in 3 mL of DMF containing perchloric acid (0.1 mL, 70%) was added 1-aminonaphthalene (50.4 mg, 0.35 mmol). The reaction mixture was refluxed for 5 min and the color of the mixture changed from brown to an intense blue. The progress of the reaction was followed by silica gel TLC with ethyl acetate/methanol (9:1). After cooling, the crude product was precipitated with diethyl ether. The precipitated salt was dissolved in a small amount of DMF and precipitated again from diethyl ether. The crude dye was purified on a 35 cc Sap-Pak C_{18} cartridge eluting with water followed by acetonitrile/water mixture going from 5 to 10% acetonitrile. The solvent was removed to yield **8** as a blue solid (120 mg, 90%). ^{1}H NMR (DMSO-d_6): δ 2.04 (m, 4H, $-CH_2CH_2N-$,), 3.58 (m, 4H, $-CH_2CH_2N-$,), 6.86 (s, 2H, ar), 7.13 (d, 1H, $J=9.6$ Hz, ar), 7.84–8.10 (m, 3H, ar), 8.46 (d, 1H, $J=8.2$ Hz, ar), 8.81 (d, 1H, $J=7.2$ Hz, ar). HRMS (ES+/TOF): calcd for $C_{20}H_{19}N_3O$ M^+: 316.1444, found 316.1447.

4.1.7. 3-Sulfonyl-9-diethylaminobenzo[*a*]phenoxazonium perchlorate (1SBPO, 9). A solution of **6** (0.1 g, 0.27 mmol) and 3-(diethylamino)phenol (0.5 g, 0.3 mmol) in 3 mL of DMF containing perchloric acid (0.1 mL, 70%) was heated to 150 °C for 25 min. The solution turned to deep blue. Upon cooling, the crude product was precipitated with ether. The product was purified on a 35 cc Sap-Pak C_{18} cartridge eluting with 20% acetonitrile in water. After removing of the solvent, **9** was obtained as a blue solid (90 mg, 55%). ^{1}H NMR (DMSO-d_6): δ 8.76–8.79 (m, 3H, H_2, H_4), 8.18 (d, 1H, $J=8.0$ Hz, H_1), 7.86 (d, 1H, $J=9.3$ Hz, H11), 7.25 (d, 1H, $J=10.5$ Hz, H10), 7.0 (s, 1H, H8), 6.85 (s, 1H, H6), 3.30 (q, 4H, $J=6.0$ Hz, CH_3CH_2N-), 1.21 (t, 6H, $J=6.0$ Hz, CH3CH2N–). HRMS (ES+/TOF): calcd for $C_{20}H_{21}N_3O_4S$ $(M)^+$: 398.1169, found 398.1168.

4.1.8. 5-*N*-α,ε-Di-*t*-butoxycarbonyl-L-lysinylamino-9-di-3-sulfonyl-propylaminobenzo[*a*]phenoxazonium perchlorate (Boc-Lys(Boc)-2SBPO, 10). To a stirred solution of (Boc)-Lys(Boc)-OH (23 mg, 0.066 mmol) in DMF (1 mL) was added 2SBPO (20 mg, 0.033 mmol), *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium PF6 (HATU) (25 mg, 0.066 mmol) and 2,4,6-collidine (43 μL, 0.33 mmol). The solution was stirred at room temperature for 2 h. The reaction was monitored by silica gel TLC. The crude product was precipitated with ether and purified on a 35 cc C_{18} cartridge (Waters) eluting with 30% acetonitrile in water to give **10** as a blue solid (25 mg, 93%). ^{1}H NMR (DMSO-d_6): δ 1.1—1.42 (m, 22H, $OC(CH_3)_3$ and CH_2), 1.60–1.82 (br s, 2H, CH_2), 1.85–2.15 (m, 4H, $NCH_2CH_2CH_2SO_3H$) 2.45–2.65 (m, 4H, $NCH_2CH_2CH_2SO_3H$), 2.90 (br s, 2H, NCH_2), 4.00–4.20 (m, 4H, $NCH_2CH_2CH_2SO_3H$), 4.40–4.60 (m, 1H, COCHN), 6.80 (s, 1H, H6), 7.35 (s, 1H, H8), 7.60 (br s, 1H, H10), 7.85–8.15 (m, 3H, H2, H3, H11), 8.45–8.65 (m, 2H, H1, H4), 8.85 (br s, 1H, NH), 10.7 (br s, 1H, NH). R_f (MeOH/AcOEt, 2:1) 0.22; MS (MALDI-TOF), calcd for $C_{38}H_{53}N_5O_{12}S_2$ $(M+1)^+$: 835.98, found: 836.06.

4.1.9. 5-*N*-α-*t*-Butoxycarbonyl-L-lysinylamino-9-di-3-sulfonyl-propylaminobenzo[*a*]phenoxazonium perchlorate (Boc-Lys-2SBPO, 11). Boc-Lys-2SBPO was obtained from Boc-Lys(Fmoc)-2SBPO by removing the fluorenylmethoxycarbonyl (Fmoc) protecting group. Boc-Lys(Fmoc)-2SBPO was synthesized using the same procedure as described for Boc-Lys(Boc)-2SBPO. Boc-Lys(Fmoc)-2SBPO was dissolved in 20% piperidine in DMF. After removing the Fmoc protecting group, the crude product was precipitated with diethyl ether and purified on a 35 cc Sap-Pak C_{18} cartridge eluting with 20% acetonitrile in water to give **11** (20 mg, 82%) as a blue solid. ^{1}H NMR (DMSO-d_6): δ 0.86 (m, 9H, $OC(CH_3)_3$), 1.30–1.50 (m, 4H, CH_2), 1.70–2.00 (m, 6H, $NCH_2CH_2CH_2SO_3H$ and CH_2), 2.95 (br s, 2H, NCH_2), 4.40 (br s, 1H, COCHN), 5.38 (br s, 1H, ar), 6.35 (s, 1H, H8), 6.44 (d, $J=8.8$ Hz, 1H, H10), 7.20 (d, $J=8.4$ Hz, 1H, H11), 7.30–7.51 (m, 3H, ar), 8.23 (br s, 1H, ar), the signals for $NCH_2CH_2CH_2SO_3H$ and $NCH_2CH_2CH_2SO_3H$ were not detected due to overlap with solvent peaks. MS (MALDI-TOF), calcd for $C_{33}H_{45}N_5O_{10}S_2Na$ $(M+Na)^+$757.86, found: 757.19.

4.1.10. 5-*N*-ε-*t*-Butoxycarbonyl-L-lysinylamino-9-di-3-sulfonyl-propylaminobenzo[*a*]phenoxazonium perchlorate (Lys(Boc)-2SBPO, 12). Lys(Boc)-2SBPO was obtained by the same procedure as described for Boc-Lys(Boc)-2SBPO, but using Fmoc-Lys(Boc)-OH (31 mg, 0.066 mmol) and 2SBPO (20 mg, 0.033 mmol). Fmoc-Lys(Boc)-2SBPO was dissolved in 20% piperidine in DMF. After 15 min, diethyl ether was added and the precipitate was filtered off. The crude product was purified on a 35 cc C_{18} cartridge (Waters) eluting with 20% acetonitrile in water to give **12** (18 mg, 75%) as blue solid. ^{1}H NMR (DMSO-d_6): δ 1.2–1.50 (m, 13H, $OC(CH_3)_3$ and CH_2), 1.6–2.2 (m, 6H, $NCH_2CH_2CH_2SO_3H$ and CH_2) 2.4–2.65 (m, 4H, $NCH_2CH_2CH_2SO_3H$), 2.95 (br s, 2H, NCH_2), 4.0–4.2 (m, 4H, $NCH_2CH_2CH_2SO_3H$), 4.8 (br s, 1H, COCHN), 6.50 (br s, 1H, NH), 6.80 (s, 1H, H6), 7.4–7.8 (br s, 1H, H8), 7.80–8.20 (m, 3H, H3, H11, H10), 8.40–8.6 (m, 2H, H1, H2, H4), 9.0 (br s, 1H, NH), 10.8 (br s, 1H, NH). MS (MALDI-TOF), calcd for $C_{33}H_{45}N_5O_{10}S_2$ $(M+1)^+$735.87, found: 736.14.

4.1.11. 5-L-Lysinylamino-9-di-3-sulfonyl-propylamino-benzo[*a*]phenoxazonium perchlorate (Lys-2SBPO, 13). Lys-2SBPO was obtained from Boc-Lys(Boc)-2SBPO. Boc-Lys(Boc)-2SBPO (25 mg, 0.03 mmol) was dissolved in TFA (1 mL). After 15 min, diethyl ether was added and the precipitate was filtered off. The crude product was purified on a 35 cc Sap-pak C_{18} cartridge eluting with 10% acetonitrile in water to give **13** (16 mg, 85%) as a blue solid. ^{1}H NMR (DMSO-d_6) δ 1.40–1.80 (m, 6H, CH_2), 1.85–2.15 (m, 6H, $NCH_2CH_2CH_2SO_3H$) 2.40–2.65 (m, 4H, $NCH_2CH_2CH_2SO_3H$), 2.8 (br s, 2H, NCH_2), 4.00–4.20 (m, 4H, $NCH_2CH_2CH_2SO_3H$), 7.40–8.50 (m, 8H, ar), 9.0 (br s, 1H, NH), the signals for NC*H*COOH were not detected due to overlapping with solvent peaks. MS (MALDI-TOF), calcd for $C_{28}H_{37}N_5O_8S_2$ $(M+1)^+$: 635.75, found: 636.13.

4.1.12. 5-*N*-*t*-Butoxycarbonyl-L-leucinylamino-9-di-3-sulfonyl-propylaminobenzo[*a*]phenoxazonium perchlorate (Boc-Leu-2SBPO, 14). Boc-Leu-2SBPO was obtained by the same procedure as described for Boc-Lys(Boc)-2SBPO from Boc-Leu-OH (15 mg, 0.066 mmol) and 2SBPO (20 mg, 0.033 mmol). The crude product was purified on a 35 cc Sap-Pak C_{18} cartridge eluting with 25% acetonitrile in water to give **14** (16 mg, 78%) as blue solid. ^{1}H NMR (DMSO-d_6): δ 0.98 (d, 6H, $J=5.5$ Hz, CH_3), 1.41 (s, 9H, $OC(CH_3)_3$), 1.6–1.8 (m, 3H, $CH(CH_3)$ and CH_2), 1.90–2.15 (m, 6H, $NCH_2CH_2CH_2SO_3H$ and CH_2) 2.4–2.65 (m, 4H, $NCH_2CH_2CH_2SO_3H$), 4.0–4.2 (m, 4H, $NCH_2CH_2CH_2SO_3H$), 4.4–4.6 (m, 1H, COCHN), 6.50 (br s, 1H, NH), 7.08 (s, 1H, H6), 7.4–7.8 (br s, 1H, H8), 7.80–8.20 (m, 3H, H3, H11, H10), 8.40–8.6 (m, 3H, H1, H2, H4), 9.0 (br s, 1H, NH), 10.8 (br s, 1H, NH). MS (MALDI-TOF), calcd for $C_{33}H_{44}N_4O_{10}S_2$ $(M+1)^+$: 720.88, found 720.75.

4.1.13. 5-L-Leucinylamino-9-di-3-sulfonyl-propylamino-benzo[*a*]phenoxazonium perchlorate (Leu-2SBPO, 15). Leu-2SBPO was obtained from Boc-Leu-2SBPO by removing the Boc protecting group. Boc-Leu-2SBPO (20 mg, 0.024 mmol) was dissolved in TFA (1 mL). After 15 min, diethyl ether was added and the precipitate was filtered off. The crude product was purified on a 35 cc Sap-pak C_{18} cartridge eluting with 20% acetonitrile in water to give **15** (16 mg, 0.92) as a blue solid. ^{1}H NMR (DMSO-d_6): δ 1.01 (d, 6H, $J=5.5$ Hz, CH_3), 1.65–1.85 (m, 3H, $CH(CH_3)$ and CH_2), 1.85–2.15 (m, 6H, $NCH_2CH_2CH_2SO_3H$ and CH_2) 2.40–2.65 (m, 4H, $NCH_2CH_2CH_2SO_3H$), 4.00–4.20 (m, 4H, $NCH_2CH_2CH_2SO_3H$), 7.08 (s, 1H, H6), 7.40–7.80 (br s, 1H, H8), 7.80–8.20 (m, 3H, H3, H11, H10), 8.40–8.60 (m, 2H, H1, H2, H4), 7.40–8.50 (m, 8H, ar), 9.00 (br s, 1H, N*H*), the signals for H_2NCHCO were not detected due to overlapping with solvent peaks. MS (MALDI-TOF), calcd for $C_{28}H_{36}N_4O_8S_2$ $(M+1)^+$620.76, Found: 620.27.

4.2. Optical properties of compounds 7–9

The excitation spectra (emission at 675 nm) and emission spectra (excitation at 635 nm) of benzo[*a*]phenoxazine dyes were determined in phosphate buffer, pH 7.4. at the concentration of 1×10^{-5} M. The extinction coefficients were also determined in phosphate buffer. The fluorescence intensities in water were measured from the emission curve using 'area' function of the fluorometer. Relative fluorescence quantum yields were obtained by using Nile Blue chloride as a reference.

4.3. pH Dependent stability of compounds 10–15

Stock solutions of compounds 2SBPO **7** and **10–15** were prepared in water at a concentration of 1×10^{-4} M. The stock solutions were then added to 0.1 M pH 4.0 (citrate–phosphate), pH 5.0 (citrate–phosphate), pH 6.0 (citrate–phosphate), pH 7.4 (PBS) and pH 8.0 (phosphate–borate) buffer. The final concentration of the solutions was 1×10^{-6} M. The fluorescence emission at 670 nm was measured with excitation at 610 nm using a plate reader at $t=0$ and 3 h.

4.4. Proteolysis of Boc-Lys-2SBPO by trypsin

A solution of trypsin (10 μL, 6 unit) was added to Boc-Lys-2SBPO (200 μL, 4 μM) in 0.1 M sodium phosphate buffer (pH 7.4) at 25 °C, and the increase in fluorescence emission at 670 nm was measured using a plate reader with excitation at 610 nm. The same conditions were applied to the control sample solution without adding trypsin.

4.5. Proteolysis of Boc-Leu-2SBPO by leucine aminopeptidase

To assess the kinetic parameters for the leucine aminopeptidase-catalyzed hydrolysis of Boc-Leu-2SBPO, aliquots of Boc-Leu-2SBPO were prepared with concentrations ranging from 1.0 to 16.6 μM in 0.1 M HEPES buffer (pH = 7.0) containing 5 mM $MgCl_2$ and 0.1% bovine serum albumin. The reactions were monitored using a fluorescence plate reader with excitation and emission at 610 and 670 nm, respectively. The total volumes of the reactions were 0.2 mL. The reactions were initiated by the addition a 5 μL (0.7 U) aliquot of aminopeptidase M stock solution. The initial velocities of the reactions were determined by the initial fluorescence intensities extracted with average values ($n=3$). The kinetic parameters for the substrate were obtained using the direct linear plot of the Eisenthal and Cornish-Bowden equation. Initial velocity measurements were converted from relative fluorescence unit (AU/min) to nM product formed/min by using a standard curve with authentic fluorophore and the same buffer conditions and wavelength settings ($n=3$).

Acknowledgements

This research was supported in part by NIH P50-CA86355, RO1 CA99385 and R21 CA114149. We thank Dr. Poguang Wang for the HRMS analysis.

References and notes

1. Zimmerman, M.; Ashe, B.; Yurewicz, E. C.; Patel, G. *Anal. Biochem.* **1977**, *78*, 47–51.
2. Harris, J. L.; Backes, B. J.; Leonetti, F.; Mahrus, S.; Ellman, J. A.; Craik, C. S. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 7754–7759.
3. McGrath, W. J.; Abola, A. P.; Toledo, D. L.; Brown, M. T.; Mangel, W. F. *Virology* **1996**, *217*, 131–138.
4. Grant, S. K.; Sklar, J. G.; Cummings, R. T. *J. Biomol. Screen.* **2002**, *7*, 531–540.
5. Zhang, H. Z.; Kasibhatla, S.; Guastella, J.; Tseng, B.; Drewe, J.; Cai, S. X. *Bioconjugate Chem.* **2003**, *14*, 458–463.
6. Sadayappan, R. V.; Karnes, H. T. *J. Pharm. Biomed. Anal.* **1996**, *15*, 83–89.
7. Yan, X.; Yuan, P. M., PCT Int. Appl., WO 2001083621, 2001.
8. Tung, C. H. *Biopolymers* **2004**, *76*, 391–403.
9. Crossley, M. L.; Dreisbach, P. F.; Hofmann, C. M.; Parker, R. P. *J. Am. Chem. Soc.* **1952**, *74*, 573–578.
10. Crossley, M. L.; Turner, R. J.; Hofmann, C. M.; Dreisbach, P. F.; Parker, R. P. *J. Am. Chem. Soc.* **1952**, *74*, 578–584.
11. Crossley, M. L.; Hofmann, C. M.; Dreisbach, P. F. *J. Am. Chem. Soc.* **1952**, *74*, 584–586.
12. Kanitz, A.; Hartmann, H. *Eur. J. Org. Chem.* **1999**, 923–930.
13. Selwyn, J. E.; Steinfeld, J. I. *J. Phys. Chem.* **1972**, *76*, 762–773.
14. Valdes-Aguilera, O.; Neckers, D. C. *Acc. Chem. Res.* **1989**, *22*, 171–177.
15. Rabinowitch, E.; Epstein, L. F. *J. Am. Chem. Soc.* **1941**, *63*, 69–78.
16. Herkstroeter, W. G.; Martic, P. A.; Farid, S. *J. Am. Chem. Soc.* **1990**, *112*, 3583–3589.
17. Savic, M.; Savic, J. *Glasnik Hemicara i Tehnologa Bosne i Hercegovine* **1968**, *16*, 55–68.
18. Chowdhury, A.; Wachsmann-Hogiu, S.; Bangal, P. R.; Raheem, I.; Peteanu, L. A. *J. Phys. Chem. B* **2001**, *105*, 12196–12201.
19. Struganova, I. A.; Hazell, M.; Gaitor, J.; McNally-Carr, D.; Zivanovic, S. *J. Phys. Chem. A* **2003**, *107*, 2650–2656.
20. Delange, R. J.; Smith, E. L. In *The Enzymes*; Boyer, P. D., Ed.; Academic: New York, 1970; pp 81–103.
21. Sun, S.; Albright, C. F.; Fish, B. H.; George, H. J.; Selling, B. H.; Hollis, G. F.; Wynn, R. *Protein Expr. Purif.* **2002**, *24*, 274–281.
22. Oliveira, H. P.; Camargo, A. J.; Macedo, L. G.; Gehlen, M. H.; da Silva, A. B. *Spectrochim. Acta A Mol. Biomol. Spectrosc.* **2002**, *58*, 3103–3111.

Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron 62 (2006) 586–593

Tetrahedron

Synthesis, properties and molecular structure of a novel dicyanoheptafulvene derivative, 4′-dicyanomethylidenedispiro[cyclohexane-1, 1′-(1′,4′,7′-trihydrocyclopenta[*f*]azulene)-7′,1″-cyclohexane]

Nguyen Chung Thanh,[a] Ryuta Miyatake,[a] Hitoshi Kainuma,[a]
Shigeyasu Kuroda[a] and Mitsunori Oda[b,*]

[a]*Department of Applied Chemistry, Faculty of Engineering, Toyama University, Gofuku 3190, Toyama 930-8555, Japan*
[b]*Department of Chemistry, Faculty of Science, Shinshu University, Asahi 3-1-1, Matsumoto, Nagano 390-8621, Japan*

Received 24 August 2005; accepted 6 October 2005

Abstract—A novel dicyanoheptafulvene **9** annulated by two spiro[4,5]deca-1,3-dienes was synthesized by the reaction of dispirocyclopentaazulenium cation **8** with bromomalononitrile. Although **9** was found to have a nonplanar heptafulvene structure by its X-ray crystallographic analysis, it is still capable of π-conjugation and thus shows appreciable contribution of the dipolar resonance form **9B** based on its spectroscopic data. The degree of the contribution was further evaluated for various dicyanoheptafulvenes in terms of the partial sum of atomic charges of the dicyanomethylene group in the calculated structures besides the interplanar angles of the heptafulvene part and the length of the exocyclic double bond in the crystal structures.

1. Introduction

Heptafulvene (**1**) having a typical cross-conjugated system belongs to a non-alternant hydrocarbon and appears red in color because of it relatively narrow HOMO–LUMO gap.[1] For more than four decades since its first synthesis continuous attention is still drawn not only to the ground and excited state structures[2] and its derivatives towards understanding their stability in respect to aromaticity but also to their application to colorants and optical materials.[3] While **1** shows a polyolefinic nature and is reactive,[1] 8,8-dicyanoheptafulvene (**2**) is relatively stable[4] and reluctant to electrophilic substitution and cycloaddition reactions.[5] The planar structure of **2**, revealed by X-ray crystallographic analysis,[6] and its large dipole moment (7.49 D)[7] indicate a significant contribution of the resonance form **2B**. On the other hand, 8,8-dicycano-2,6-dimethylheptafulvene (**3**)[8] shows smaller dipole moment than the value expected by regarding its seven-membered ring as a planar and regular heptagonal, and its X-ray analysis[9] revealed that **3** has a boat form like 1,3,5-cycloheptatriene[10] due to steric hindrance between the methyl and cyano groups. Feasibility of the dipolar contribution of dicyanoheptafulvenes should be dependent on its molecular planarity and also on the relative thermodynamic stability of the tropylium cation part in the polar canonical form; that is, it is expected that a dicyanoheptafulvene derivative with the more stable cationic part in the form shows the more significant dipolar contribution. Although there have been known many tropylium cation derivatives more stable than the parent tropylium ion **4**, only a few of the corresponding dicycanoheptafulvene derivatives have appeared in the literature. Mori and Takeshita et al. synthesized dithiin-annulated dicyanoheptafulvenes, **5** and **6**, from the tropylium cation **7**, and clarified their crystal structures;[11,12] the heptafulvene **5** has a nonplanar structure and **6** has a nearly planar structure. While **6** shows almost the same degree of contribution of the polar canonical form to that of **2**, **5** indicates diminished contribution compared with those of **2** and **6** based on the spectroscopic data (Chart 1).

In the meantime, we have recently reported a new, highly stable hydrocarbon cation, dispiro[cyclohexane-1,1′-(1′,7′-dihydrocyclopenta[*f*]azulenium)-7′,1″-cyclohexane] ion (**8**),[13] whose pK_R+ value (13.2) is greater by 9.3 pK_R+ unit than that of the tropylium cation **4**.[14] Thus, 4′-dicyanomethylidenedispiro[cyclohexane-1, 1′-(1′, 4′, 7′-trihydrocyclopenta-[*f*]azulene)-7′,1″-cyclohexane] (**9**)

Keywords: Heptafulvene; Carbenium ions; Cyclopenta[*f*]azulenes; Density functional calculation; X-ray crystal structures.

* Corresponding author. Tel./fax: +81 263 37 3343;
e-mail: mituoda@shinshu-u.ac.jp

doi:10.1016/j.tet.2005.10.015

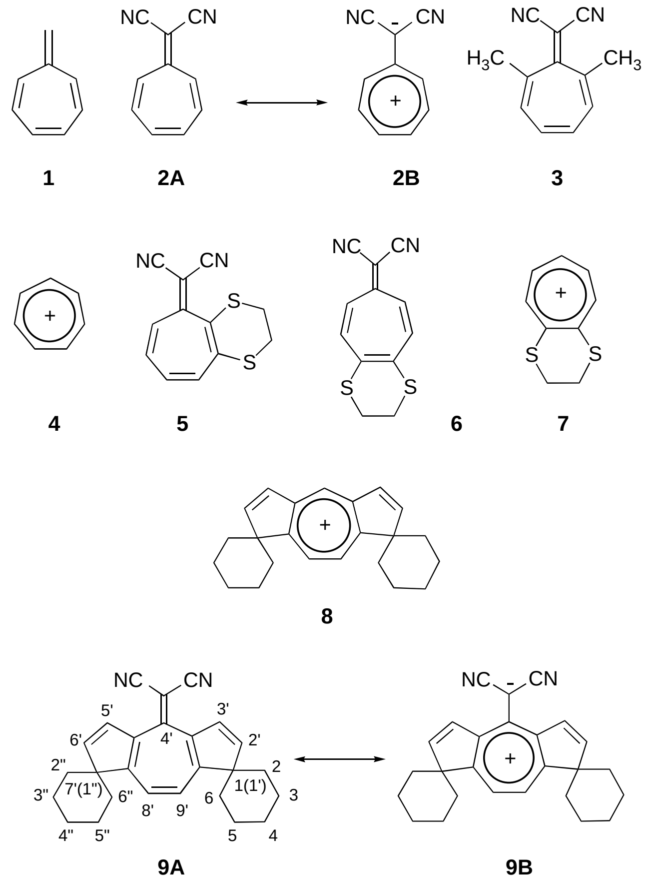


Chart 1.

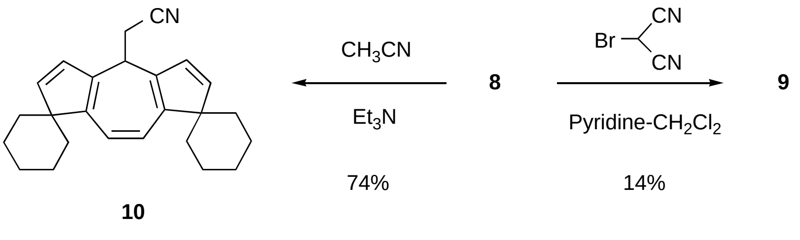
derived from carbocation **8** is expected to indicate great contribution of the resonance form **9B**. Herein we describe the synthesis, spectroscopic properties and molecular structure of **9**, which indicate that compound **9** is a unique example of 8,8-dicyanoheptafulvene derivatives having appreciable contribution of its dipolar resonance form despite its nonplanar structure. We also discuss the degree of the contribution for various 8,8-dicyanoheptafulvenes based on their structural features both in the crystal and calculated structures.

2. Results and discussion

2.1. Synthesis and spectroscopic properties of 9

The reaction of **8** in acetonitrile in the presence of triethylamine as a base gave the acetonitrile adduct **10** in 74% yield. This result encouraged us to synthesize the desired dicyanoheptafulvene **9** from **8** by the Mori–Takeshita method, which is a procedure for preparing **2** directly from a tropylium salt.[15] The reaction of **8** with bromomalononitrile in the presence of pyridine as a base in dichloromethane gave **9** as orange-red microcrystals in 14% yield, accompanied with some unidentified minor products (Scheme 1). Under similar conditions with other bases, such as triethylamine or DBU, the yield of **9** was less than 6%.

The structure of **9** was fully characterized by spectroscopic and elemental analyses. The assignments of proton signals of **9** in the ^{1}H NMR spectrum, summarized in Figure 1 with those of **8** and the corresponding hydrocarbon **11**, were based on the relationships in H–H COSY and DFNOE experiments (Fig. 2). The average proton chemical shift ($\delta_{av}=7.18$ ppm in $CDCl_3$, $\delta_{av}=7.35$ ppm in DMSO-d_6) of the olefinic protons of **9** was found to be close to the middle value between those of **11** ($\delta_{av}=6.48$ ppm in $CDCl_3$) and **8** ($\delta_{av}=8.26$ ppm in $CDCl_3$). The δ_{av} value of **9** shows downfield shift of 0.17 ppm in the aprotic dipolar solvent of DMSO-d_6 compared with that in $CDCl_3$. It is noteworthy that the field shift by solvent polarity also changes the signal line-up of the hydrogens at the $2'(6')$ and $3'(5')$ positions in the spectra; that is, while in $CDCl_3$ the $2'(6')$ hydrogen in **9** resonates at higher field than the $3'(5')$ hydrogen similarly to the case of **11**, in DMSO-d_6 the $2'(6')$ hydrogen resonates at lower field than the $3'(5')$ hydrogen similarly to the case of **8**. These results clearly show that contribution of the resonance form **9B** enhances in a polar solvent. The aliphatic methylene protons at the 2 (6, $2''$, and $6''$) position in NMR shift to down field in the series **11**→**9**→**8**, indicating that the anisotropic deshielding effect of the seven-membered ring part ascends in this order. Under the acidic conditions with a mixture of CF_3CO_2D and DMSO-d_6, the protonated species **12** was observed in the ^{1}H NMR spectrum and **9** was recovered quantitatively by alkaline work-up (Scheme 2). In the ^{13}C NMR spectra, the cyano-substituted carbon atom of **2**, **6** and **9** resonates at δ 70.1, 68.7 and 68.9 ppm, respectively, (Table 1). The high-field shift of the carbon can be explained by a shielding effect of the anion charge localized at the dicyanomethylene group in the polar canonical form. On the other hand, the carbon of dimethyl derivative **3** appears at relatively lower field of δ 81.6 ppm and that of **5** at δ 80.1 ppm. From these NMR spectroscopic data, it is strongly suggested that contribution of the resonance form **9B** is very important in **9**. Particularly, comparison of the ^{13}C chemical shifts between **9** and **2** indicates that **9** has a large degree of the contribution the same as **2** and **6** have. Furthermore, the IR spectra of these dicyanoheptafulvenes show characteristic features. The stretching frequency (ν_{CN}) of dicyanoheptafulvenes is well-known to be denotive of the resonance contribution. The frequency data of **2**, **3**, **5**, **6** and **9** are



Scheme 1.

11

9

8

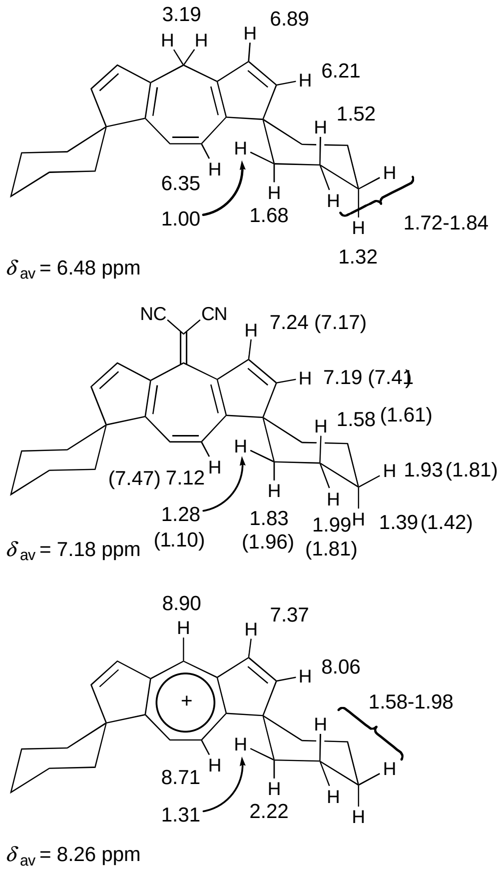


Figure 1. Proton chemical shifts (δ in ppm) of **8**, **9**, and **11** in $CDCl_3$. δ_{av} is an average shift of the olefinic protons. The values given in parentheses are obtained in DMSO-d_6.

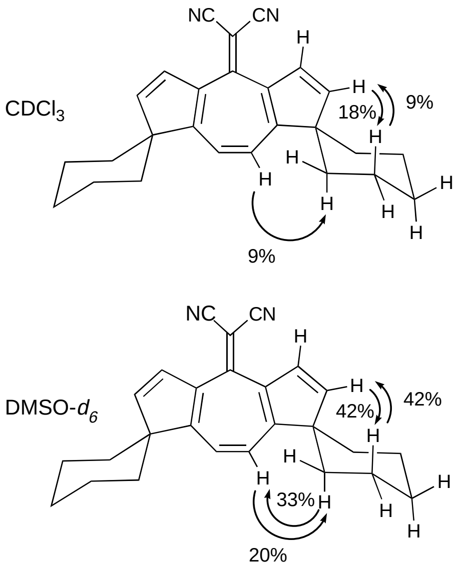
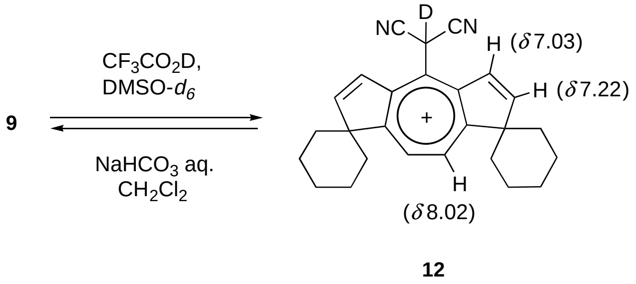


Figure 2. Result of NOE experiments in different solvents.

shown in Table 1, clearly indicating that a similar degree of the conjugation through the cyano group is occupied in **2**, **5**, **6** and **9** except **3**. Based on these spectroscopic data, as a whole the same degree of the singnificant dipolar contribution is shown for **2**, **6** and **9**, the dimished contribution for **6**, and the fairly reduced contribution for **2**.



Scheme 2.

Table 1. Selected ^{13}C NMR, IR data and exocyclic C–C double bond lengths of the dicyanoheptafulvenes **2**, **3**, **5**, **6**, and **9**

	^{13}C NMR (δ)[a]	IR (ν_{CN} cm^{-1})	C=C (Å)
2	70.1	2205[b,c] (2196[d])	1.422
3	81.6	2223[b] (2225[e])	1.361
5	80.1	2204[d]	1.389
6	68.7	2202[d]	1.395
9	68.9	2207[b]	1.385

[a] Chemical shift of the carbon atom substituted by the cyano groups.
[b] Our data obtained with an FT-IR instrument.
[c] Taken from Ref. 6.
[d] Taken from Ref. 16.
[e] Taken from Ref. 8.

2.2. X-ray crystallographic analysis of 9

The crystal structure of **9** was elucidated by X-ray crystallographic analysis. Single crystals of **9** were obtained by recrystallization from a mixture of ether and dichloromethane. An ORTEP drawing and the crystal packing of **9** are shown in Figure 3. There are two independent molecules of **9** in the unit cell with a slight difference in the bond lengths and angles, and both structures are asymmetric. The structures show cyclohexane rings with a chair conformation and the seven-membered ring with a boat conformation. Selected bond lengths of the two structures and their averages are listed in Table 2. The length of the exocyclic C–C double bond is characteristic for heptafulvenes; the longer bond is estimated to have the greater contribution of the dipolar resonance form. The average bond length between the 4′ and dicyanomethylene carbon atoms for **9** is 1.385 Å which is close to those of **5** and **6** and in the middle of those of **2** and **3** (Table 1). Interplanar angles between the least square planes in the heptafulvene part of **9** are summarized with those of **2**, **3**, **5**, and **6** in Table 3. While **2** is completely planar and **6** a nearly planar structure, the heptafulvene parts of **3**, **5** and **9** are nonplanar. The angles α and β increase in the order of **9**, **5** and **3**. Among them the value of 45.3° for angle β in **3** is noteworthy and this extraordinary bending around this C1 position must cause interference of the π-conjugation. On the other hand, the degree of the bendings in **5** and **9** are not serious as seen in **3** and, therefore, these compounds are still capable of π-conjugation. We also assume that thermodynamic stability of the cationic part of **9B** may play an important role for π-conjugation for **9**. Since **9** has appreciable contribution of the dipolar form based on spectroscopic data, it is now not too much to state that dicycanoheptafulvene tolerates the bending for π-conjugation to some extent.

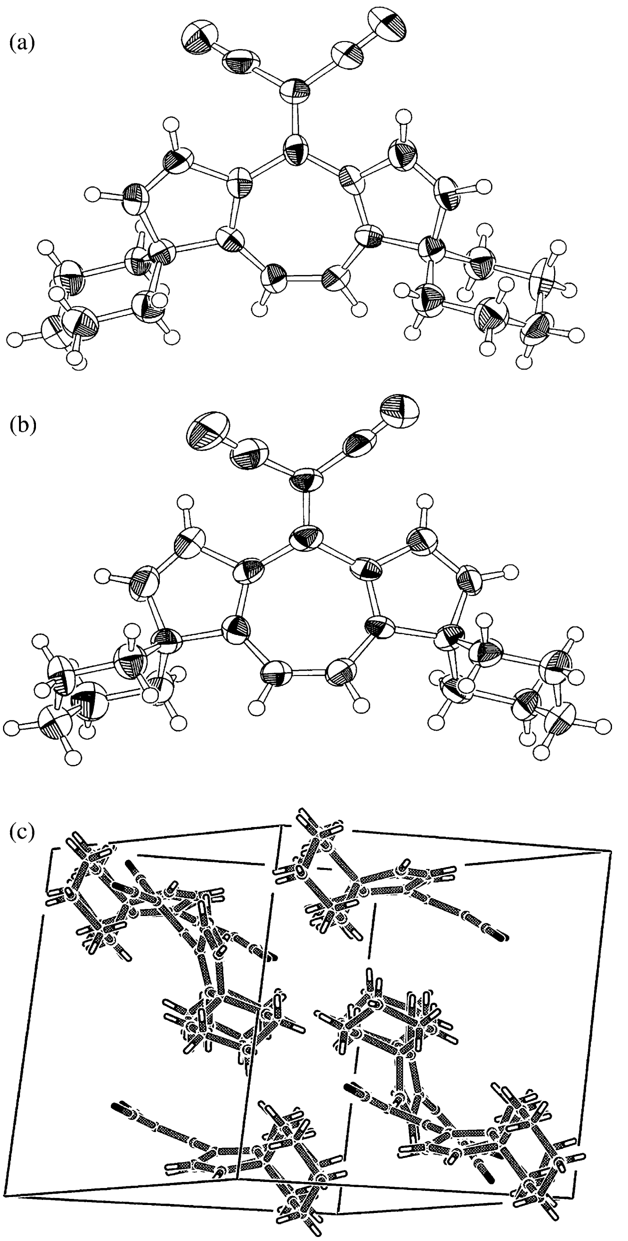


Figure 3. ORTEP drawings of the two independent molecules of **9**, (a) and (b), and its crystal packing (c).

2.3. Density functional calculations of various dicyanoheptafulvenes

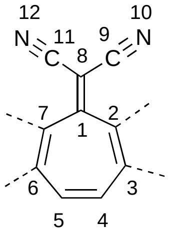
We have further studied the structural features of dicyanoheptafulvene derivatives by density functional calculations. Optimized structures at the MB3LYP/6-31G (d) level of theory using the Mulliken program (ver. 2.0.0, IBM Inc.) were obtained for **2**, **3**, **5**, **6**, and **9** (Fig. 4). The gross calculated structures except that of **5** were similar to the corresponding crystal structures. The crystal structure of **5** has the dithiin ring of a chair conformation and one of the sulfur atoms close to the dicyanomethylene moiety aligns the moiety. However, we could not obtain such a conformer as a minimum by this level of calculations but one with a boat conformation of the dithiin ring and the sulfur atom directed to the other side. The interplanar angles of the calculated structures are listed in Table 3. Bond lengths of the calculated structures of **4**, **6** and **9** show good accordance with those of the crystal structures, respectively. The lengths of the dicyanoheptafulvene part of the calculated structure for **9** are listed in Table 2. The difference between the calculated and crystal structures is less than 0.036 Å. The large difference is observed at the molecular edge distant from the seven-membered ring and the difference is less than 0.012 Å in the middle part of the compound, implying that molecular distortion in the crystal structure is forced by packing. Also the differences for **3** and **6** are less than 0.031 and 0.039 Å, respectively. On the other hand, the difference for **2** is not small. Particularly, the bond length of C(4)–C(5) in the crystal structure is unusually short. As attention was previously drawn by Shimanouchi et al.,[9] the packing of **2** in the crystal is very tight and intermolecular interaction is significantly important. Thus, comparison between the crystal structure of **2** with others must be carefully made (Table 4).

In order to evaluate the degree of contribution of the dipolar resonance form diagonostically, a partial sum of atomic charges of the dicyanomethylene group for **2**, **3**, **5**, **6** and **9** was obtained from Mulliken's net atomic charge data of the optimized structures, which are listed in Table 5. Although there are some differences between calculated and crystal structures for **2** and **5**, the sum value increases in the order of $\mathbf{3}<\mathbf{5}<\mathbf{2}\sim\mathbf{9}\sim\mathbf{6}$, which is in good conformity to the degree of the dipolar contribution based on spectroscopic data. The border between the slightly reduced and fairly reduced contributions seems to lie between the sum values of −0.35 and −0.31 and the border between the significant and slightly reduced contributions between the sum values of −0.41 and −0.35. We cannot evaluate the degree quantitatively so far, mainly because there is no scale of experimental data, which indicates zero and 100% contributions. However, the partial sum of charges obtained simply by molecular orbital calculations shows some guide line in this respect, as we have shown herein.

3. Summary

In summary, we have synthesized a new derivative of 8,8-dicyanoheptafulvene **9** annulated by two spiro[4,5]deca-1,3-dienes and elucidated its spectroscopic properties and crystal structure. Although **9** has a nonplanar heptafulvene part, a significant degree of contribution of the dipolar resonance form **9B** was suggested by spectroscopic data. The interplanar angles of the heptafulvene part in **9** are not serious as seen in **3**. Besides this structural feature the stability of the cationic part of the dipolar form in **9B** may play an important role for the contribution. It is not too much to state that 8,8-dicyanoheptafulvene is able to tolerate its bending to a certain extent for sustaining the dipolar contribution. In other words, we have demonstrated that evaluation of the contribution for dicyanoheptafulvenes cannot be made simply by their planarity. We have also pointed out a guide line for evalution of the degree of contribution of the dipolar resonance form; comparison of the partial sum of the dicyanomethylene part, which can be obtained by molecular orbital calculations, indicates its tendancy.

Table 2. Bond lengths of crystal and calculated structures, the average of the dicyanoheptafulvene part in the two independent crystal structures of **9** and difference between crystal and calculated structures



Bond[a]	Length (Å)				
	Crystal structure			Calculated Structure	Δ (Å)
	Structure (1)	Structure (2)	Average		
C(1)–C(8)	1.39(1)	1.38(1)	1.385	1.397	0.012
C(8)–C(9)	1.43(1)	1.41(1)	1.42	1.428	0.008
C(8)–C(11)	1.42(1)	1.45(1)	1.435	1.428	−0.007
C(9)–N(10)	1.14(1)	1.14(1)	1.14	1.166	0.024
C(11)–N(12)	1.13(1)	1.13(1)	1.13	1.166	0.036
C(1)–C(2)	1.45(1)	1.47(1)	1.46	1.458	0.002
C(2)–C(3)	1.396(10)	1.378(10)	1.387	1.395	0.008
C(3)–C(4)	1.405(10)	1.407(10)	1.406	1.414	0.008
C(4)–C(5)	1.370(10)	1.37(1)	1.37	1.376	0.006
C(5)–C(6)	1.418(10)	1.41(1)	1.414	1.414	0
C(6)–C(7)	1.380(10)	1.38(1)	1.38	1.395	0.015
C(7)–C(1)	1.45(1)	1.45(1)	1.45	1.458	0.008

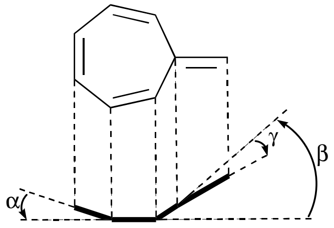
[a] For numbering, see the structure above.

4. Experimental

4.1. General

Melting points were measured on a Yanaco MP-3 and are uncorrected. IR spectra were recorded on a Perkin-Elmer Spectrum RX I spectrometer. UV spectra were measured on a Shimadzu UV-1600 spectrometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 Hz) were recorded with tetramethylsilane as an internal standard on a JEOL α400. Mass spectra were measured on a JEOL GC-Mate mass spectrometers. The perchlorate salt of **8** was prepared by our reported way.[12] Column chromatography was done with active neutral alumina (200 mesh) purchased from Wako, Inc. The density functional calculations were conducted by using the Mulliken (ver. 2.0.0, IBM Co.) on an IBM RS6000/397 computer. The MB3LYP (Mulliken's Meccke3LYP) functional in Mulliken uses the locl correlation function of Perdew and Wang[16] instead of the Vosko, Wilk, and Nusair functional,[17] and is very similar to Becke3LYP density by Stephenes et al.[18]

Table 3. Interplanar angles (in degree) of the heptafulvene part of crystal and calculated structures of **2**, **3**, **5**, **6**, and **9**



Compound	α	β	γ
2	0[a] (0)[b]	0[a] (0)	0[a] (0)
3	20.1[a] (19.5)	45.3[a] (45.5)	4.0[a] (4.8)
5	17.8[c] (14.6)	31.5[c] (26.7)	5.4[c] (7.5)
6	1.2[c] (1.1)	1.7[c] (2.1)	0.4[c] (0)
9	14.6[d] (14.6)	29.3[d] (31.6)	2.1[d] (5.8)

[a] Taken from Refs. 6 and 9.

[b] The values in parentheses are obtained from calculated structures.

[c] Obtained from their crystal data.

[d] The average between the two independent molecules in the crystal.

4.1.1. Dispiro[cyclohexane-1,1′-(4-cyanomethyl-1′,7′-dihydrocyclopenta[*f*]azulene)-7′,1″-cyclohexane] (10).

A solution of 40.3 mg (0.100 mmol) of the cation **8** in 5 ml of dry acetonitrile at 0 °C was added dropwise 46 μl (0.30 mmol) of triethylamine. After being stirred at the same temperature for 24 h, the reaction mixture was poured into 50 ml of water and was extracted with chloroform (20 ml×3). The combined organic layer was washed with brine and dried with anhydrous $MgSO_4$. After evaporation of the solvent, the residual dark brown oil was purified by chromatography (toluene as eluent) to give 25.4 mg (74% yield) of **10** as a pale yellow oil. ^{1}H NMR ($CDCl_3$) $\delta=$ 1.23–1.84 (m, 20H), 2.36 (d, $J=7.3$ Hz, 2H), 4.05 (t, $J=$ 7.3 Hz, 1H), 6.24 (d, $J=5.6$ Hz, 2H), 6.36 (s, 2H), 6.36 (d, $J=$ 5.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) $\delta=25.2$, 26.0, 29.7, 31.2, 32.5, 35.6, 44.9, 57.3, 115.1, 121.6, 133.1, 136.5, 143.5, 148.2. IR (liq. film) ν (cm^{-1}) 1926s, 2249w, 1712m, 1449m, 1270m, 737w; MS (70 eV) m/z (rel intensity) 323 (M^+, 0.1), 317 (9), 303 (100), 191 (10), 167 (9); UV λ_{max} (CH_2Cl_2) 231sh nm (log $\varepsilon=4.21$), 248 (4.23), 289sh (3.80), 318 (3.68), 364 (3.71). Found: 343.22999. Calcd for $C_{25}H_{29}N$: M, 343.23161.

4.1.2. Dispiro[cyclohexane-1,1′-(4-dicyanomethylidene-1′,7′-dihydrocyclopenta[*f*]azulene)-7′,1″-cyclohexane] (9).

A solution of 80.5 mg (0.200 mmol) of the cation **8**

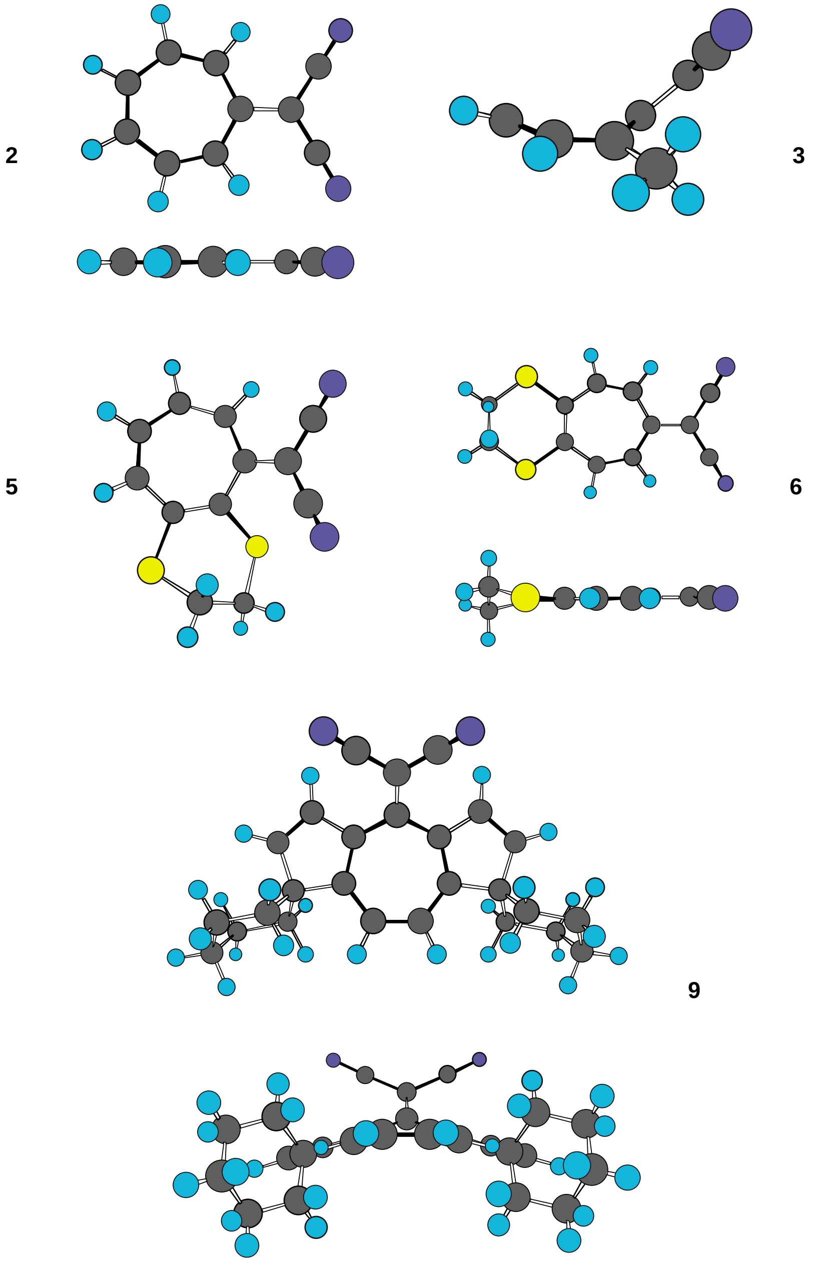


Figure 4. Calculated structures (Chem 3D output) of **2**, **3**, **5**, **6**, and **9**.

Table 4. Bond lengths (Å) of crystal and calculated structures and their difference for **2**, **3**, and **6**

Bond[a]	**2**			**3**			**6**		
	Crystal structure	Calculated structure	Δ	Crystal structure	Calculated structure	Δ	Crystal structure	Calculated structure	Δ
C(1)–C(8)	1.422	1.403	−0.018	1.361	1.380	0.019	1.392	1.402	0.010
C(8)–C(9)	1.450	1.425	−0.025	1.413	1.432	0.019	1.419	1.425	0.006
C(8)–C(11)	1.450	1.425	−0.025	1.420	1.432	0.012	1.425	1.425	0
C(9)–N(10)	1.125	1.166	0.041	1.134	1.165	0.031	1.138	1.166	0.024
C(11)–N(12)	1.125	1.166	0.041	1.140	1.165	0.025	1.127	1.166	0.039
C(1)–C(2)	1.425	1.447	0.022	1.460	1.478	0.018	1.437	1.442	0.002
C(2)–C(3)	1.353	1.366	0.013	1.350	1.367	0.017	1.348	1.365	0.017
C(3)–C(4)	1.448	1.432	−0.016	1.410	1.431	0.021	1.406	1.440	0.034
C(4)–C(5)	1.311	1.365	0.054	1.338	1.357	0.019	1.396	1.385	−0.009
C(5)–C(6)	1.448	1.432	−0.016	1.420	1.431	0.011	1.411	1.439	0.028
C(6)–C(7)	1.353	1.366	0.013	1.342	1.367	0.025	1.360	1.365	0.005
C(7)–C(1)	1.448	1.447	−0.001	1.470	1.478	0.008	1.422	1.442	0.020

[a] The numbering is the same as shown in Table 2.

Table 5. Partial sum of atomic charges of the dicyanomethylene part in the calculated structures of **2**, **3**, **5**, **6**, and **9**

	Atom[a]	Atomic charge	Partial sum		Atom[a]	Atomic charge	Partial sum
2	C(8)	0.023269	−0.410417	**3**	C(8)	0.070521	−0.313099
	C(9)	0.279301			C(9)	0.302540	
	C(11)	0.279432			C(11)	0.302355	
	N(10)	−0.496191			N(10)	−0.494300	
	N(12)	−0.496228			N(12)	−0.494215	
5	C(8)	0.048997	−0.350007	**6**	C(8)	0.019467	−0.417878
	C(9)	0.278396			C(9)	0.278624	
	C(11)	0.312643			C(11)	0.278560	
	N(10)	−0.494300			N(10)	−0.497310	
	N(12)	−0.494215			N(12)	−0.497219	
9	C(8)	0.037115	−0.416074				
	C(9)	0.276615					
	C(11)	0.276637					
	N(10)	−0.503196					
	N(12)	−0.503245					

[a] The numbering is the same as shown in Table 2.

and 43.5 mg (0.300 mmol) of bromomalononitrile[14] in 5 ml of dichloromethane at room temperature under nitrogen atmosphere was added 66 μl (0.80 mmol) of pyridine. After being stirred for 3 h, the reaction mixture was poured into 50 ml of a 1 M HCl solution and was extracted with dichloromethane (30 ml × 3). The combined organic layer was washed with brine and dried with anhydrous $MgSO_4$. After evaporation of the solvent, the residual dark red oil was purified by chromatography (benzene as eluent) to give 10.2 mg (14% yield) of **9** as orange red microcrystals. Mp = 181–182 °C. ^1H NMR ($CDCl_3$) $\delta = 1.28$ (dm, $J = 13.2$ Hz, 4H), 1.39 (qt, $J = 13.2$, 3.3 Hz, 2H), 1.58 (qt, $J = 13.2$, 3.3 Hz, 4H), 1.83 (td, $J = 13.2$, 3.3 Hz, 4H), 1.93 (dm, $J = 13.2$ Hz, 2H), 1.99 (dm, $J = 13.2$ Hz, 4H), 7.12 (s, 2H), 7.19 (d, $J = 5.6$ Hz, 2H), 7.24 (d, $J = 5.6$ Hz, 2H); ^{13}C NMR ($CDCl_3$) $\delta = 24.7$, 25.7, 32.8, 59.8, 68.9, 116.8, 127.4, 116.8, 127.4, 130.4, 138.8, 146.5, 157.0, 159.9. IR (liq. film) ν (cm^{-1}) 2922s, 2851m, 2207w, 1465m, 1119w, 1040w, 771w; MS (70 eV) *m/z* (rel intensity) 366 (M^+, 100), 310 (9), 254 (7); UV λ_{max} (CH_2Cl_2) 223 nm ($\log \varepsilon = 3.93$), 249 (3.66), 292 (4.00), 347sh (3.24), 453 (3.93). HRMS Found: 366.21024. Calcd For for $C_{26}H_{26}N_2$: 366.20959. Found: C, 85.04; H, 7.25; N, 7.63%. Calcd for $C_{26}H_{26}N_2$: C, 85.21; H, 7.15; N, 7.64%.

4.2. X-ray structural analysis of 9

Orange prismatic crystals of **9** were obtained by recrystallization from a mixture of ether and dichloromethane. One of them having approximate dimensions of 0.50 × 0.30 × 0.50 mm was mounted on a glass fiber. All measurements were made on a Rigaku AFC7R diffractometer with graphite monochromated Mo Kα radiation and a rotating anode generator. Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using the setting angles of 25 carefully centered reflections in the range $22.01 < 2\theta < 24.43°$, corresponded to a primitive monoclinic cell with dimensions: $a = 13.727(4)$ Å, $b = 14.675(5)$ Å, $c = 12.333(4)$ Å, $\alpha = 113.19(2)°$, $\beta = 91.04(3)°$, $\gamma = 65.24(2)°$, $V = 2041(1)$ Å^3. For $Z = 4$ and formular weight = 366.50, the calculated density is 1.19 g cm^{-3}. Based on a statistical analysis of intensity distribution and the successful solution and refinement of the structure, the space group was uniquely determined to be $P\bar{1}$ (# 2). The data were collected at a temperature of 23 ± 1 °C using the $\omega - 2\theta$ scan technique to a maximum 2θ value of 60.0°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.27° with a take-off angle of 6.0°. Scans of $(1.26 + 0.30 \tan \theta)°$ were made at speeds of 32.0°/min (in ω). The weak reflections ($I < 10.0\sigma(I)$) were rescanned (maximum of five scans) and the counts were accumulated to ensure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background couting time was 2:1. The diameter of the incident beam collimetor was 0.5 mm and the crystal to detecter distance was 235 mm. The computer-controlled slits were set to 3.0 mm (horizontal) and 3.0 mm (vertical). Of the 12,370 reflections, which were collected, 11,907 were unique ($R_{int} = 0.025$). The intensities of three representative reflections were measured after every 150 reflections. No decay correction was applied. The linear absorption coefficient, μ, for Mo Kα radiation is 0.7 cm^{-1}. An empirical absorption correction based on azimuthal scans of several reflections was applied, which resulted in transmission factors ranging from 0.88 to 1.00. The structure was solved by direct methods and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement was based on 1818 observed reflections ($I > 3.00\sigma(I)$) and 505 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of: $R = 0.051$, $Rw = 0.061$, and $R1 = 0.051$ for $I > 3.0\sigma(I)$ data. The standard deviation of an observation of unit weight was 1.38. The weighting scheme was based on counting statistics and included a factor ($p = 0.050$) to downweight the intense reflections. Plots of $\Sigma w(|Fo| - |Fc|)^2$ versus $|Fo|$, reflection order in data collection, $\sin \theta/\lambda$ and various classses of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.23 and -0.17 e^- Å^{-3}, respectively. Tables of fractional atomic coordinates, thermal parameters, bond lengths and angles have been deposited at the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, United Kingdom (CCDC 273181).

Acknowledgements

We thank Mr. Takuya Uchiyama at Toyama University for preliminary calculations of heptafulvene derivatives. The present work was supported by a Grant-in-Aid for Scientific Research (No. 13640528) from the Ministry of Education, Sports, Culture, Science and Technology, Japan.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.10.015. Cartecian coordinates, total energies, dipole moments and net atomic charges of optimized geometries of **2**, **3**, **5**, **6** and **9** at the Mulliken's B3LYP/6-31G(d) level of theory are available.

References and notes

1. Doering, W. v. E.; Woley, D. W. *Tetrahedron* **1960**, *11*, 183–198. Schenk, W. K.; Kyburz, R.; Neuenschwander, M. *Helv. Chim. Acta* **1975**, *58*, 1099–1119. Li, X.; Neuenschwander, M. *Helv. Chim. Acta* **2000**, *83*, 562–570.
2. For recent theoretical studies of heptafulvenes, see following; Moellerstedt, H.; Piqueras, M. C.; Crespo, R.; Ottosson, H. *J. Am. Chem. Soc.* **2004**, *126*, 13938–13939. Najafian, K.; Schleyer, P. v. R.; Tidwell, T. T. *Org. Biomol. Chem.* **2003**, *1*, 3410–3417. Stepien, B. T.; Krygowski, T. M.; Cryanski, M. K. *J. Phys. Org. Chem.* **2003**, *16*, 426–430. Fabian, J.; Diaz, L. A.; Seifert, G.; Niehaus, T. *THEOCHEM* **2002**, *594*, 41–53. Kovacevic, B.; Liebman, J. F.; Maksic, Z. B. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1544–1548. Havenith, R. W. A.; Fowler, P. W.; Steiner, E. *J. Chem. Soc., Perkin Trans. 2* **2002**, 502–507. Steien, B. T.; Cyranski, M. K.; Krygowski, T. M. *Chem. Phys. Lett.* **2002**, *350*, 537–542. Hinchliffe, A.; Machado, H. J. S. *Int. J. Mol. Sci.* **2000**, *1*, 39–48.
3. Otani, H.; Mizuguchi, J. *Chem. Lett.* **1999**, 389–390. Mizuguchi, J.; Suzuki, T.; Matsumoto, S.; Otani, H. *J. Phys. Chem. B* **1999**, *103*, 426–430. Yumura, K.; Otani, H.; Mizuguchi, J. *Dyes Pigm.* **1998**, *38*, 227–242. For photochromism of the vinylogous compounds, see also following; Waela, V. D.; Schmidhammer, U.; Mrozek, T.; Daub, J.; Riedle, E. *J. Am. Chem. Soc.* **2002**, *124*, 2438–2439. Mrozek, T.; Görner, H. J.; Daub, J. *Chem. Commun.* **1999**, 1487–1488. Spretzer, H.; Daub, J. *Chem. Eur. J.* **1996**, *2*, 1150–1158. Daub, J.; Salbech, J.; Knöchel, T.; Fischer, C.; Kunkely, H.; Rapp, K. M. *Angew. Chem., Int. Ed. Engl.* **1989**, *122*, 1494–1495. Gierisch, S.; Bauer, W.; Burgemeister, T.; Daub, J. *Chem. Ber.* **1989**, *122*, 2341–2349.
4. Nozoe, T.; Mukai, T.; Osaka, K.; Shishido, N. *Bull. Chem. Soc. Jpn.* **1961**, *34*, 1384–1390.
5. Nair, V.; Abhilash, K. G.; Zeimer, B. *Tetrahedron Lett.* **2005**, *46*, 2307–2309. Nair, V.; Anikumar, G. *Synlett* **1998**, 950–957. Kikuchi, K.; Maki, Y.; Nomata, E.; Tada, K. *Chem. Lett.* **1978**, 677–680. Oda, M.; Funamizu, M.; Kitahara, Y. *Chem. Ind. (London)* **1969**, 75. Oda, M.; Tani, H.; Kitahara, Y. *Chem. Commun.* **1969**, 739.
6. Shimanouchi, H.; Ashida, T.; Sasada, Y.; Murata, I.; Kitahara, Y. *Bull. Chem. Soc. Jpn.* **1965**, *38*, 1230. Shimanouchi, H.; Ashida, T.; Sasada, Y.; Murata, I.; Kitahara, Y. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 2322–2331.
7. Yamakawa, M.; Watanabe, H.; Mukai, T.; Nozoe, T.; Kubo, M. *J. Am. Chem. Soc.* **1960**, *82*, 5665–5667.
8. Oda, M.; Funamizu, M.; Kitahara, Y. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 2386–2387.
9. Shimanouchi, H.; Sasada, Y.; Kabuto, C.; Kitahara, Y. *Tetrahedron Lett.* **1968**, 5053–5054. Shimanouchi, H.; Sasada, Y.; Kabuto, C.; Kitahara, Y. *Acta Crystallogr., Sect. B* **1974**, *30*, 1267–1277.
10. Taetteberg, M. *J. Am. Chem. Soc.* **1964**, *86*, 4265–4270. Butcher, S. S. *J. Chem. Phys.* **1965**, *42*, 1833–1836. Davis, R. E.; Tulinsky, A. *J. Am. Chem. Soc.* **1966**, *88*, 4583–4588. Stegemann, J.; Lindner, H. J. *Acta Crystallogr., Sect. B.* **1979**, *35*, 2161–2165.
11. Reduction potential study of tropylium cations shows that of the (1,2-ethylenedithia)tropylium cation has greater stability than the tropylium cation; Yamashita, Y.; Hagiya, K.; Saito, G.; Mukai, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 271–279.
12. Mori, A.; Kubo, K.; Takeshita, H. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3742–3746. Kubo, K.; Mori, A.; Takeshita, H.; Tsuzuki, H. *Acta Crystallogr., Sect. C* **1994**, *50*, 604–606.
13. Oda, M.; Kainuma, H.; Miyatake, R.; Kuroda, S. *Tetrahedron Lett.* **2002**, *43*, 3485–3488. Oda, M.; Kainuma, H.; Uchiyama, T.; Miyatake, R.; Kuroda, S. *Tetrahedron* **2003**, *59*, 2831–2841.
14. Komatsu, K.; Takeuchi, K.; Arima, M.; Waki, Y.; Shirai, S.; Okamoto, K. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3257–3261.
15. Takeshita, H.; Mori, A.; Kubo, K. *Org. Synth.* **1998**, *75*, 210–214.
16. Perdew, J. P.; Wang, Y. *Phys. Rev. B* **1992**, *45*, 13244–13249.
17. Vosko, S. H.; Wilk, L.; Nusair, M. *Can. J. Phys.* **1980**, *58*, 1200–1211.
18. Stephens, P. J.; Devlin, F. J.; Chabolowski, C. F.; Frisch *J. Phys. Chem.* **1994**, *98*, 11623–11627.

Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron

Tetrahedron 62 (2006) 678–683

Highly efficient water promoted allylation and propargylation of arylepoxides via rearrangement-carbonyl addition

Ujjal Kanti Roy and Sujit Roy*

Organometallics and Catalysis Laboratory, Chemistry Department, Indian Institute of Technology, Kharagpur 721302, India

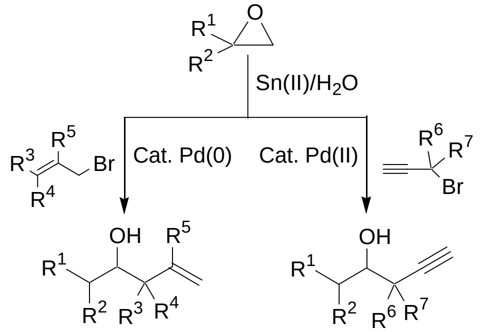
Received 1 July 2005; revised 21 September 2005; accepted 6 October 2005

Abstract—A simple and highly efficient one-pot procedure for allylation and propargylation of arylepoxides has been developed. A combination of $SnCl_2$ and catalytic Pd(0) or Pd(II) promotes the reaction of organic halides and epoxides in DMSO with controlled water addition, leading to the regioselective formation of the corresponding homoallyl and homopropargyl alcohols in good yields.

1. Introduction

The addition of allyl, propargyl or allenylstannanes to organic electrophiles like aldehydes, imines, and epoxides is a well-known tool for carbon–carbon bond formation in organic chemistry.[1] Epoxides are one of the most useful and versatile substrates in organic synthesis due to their high reactivity. A number of methods have been reported for the cleavage of epoxides with various nucleophiles. On the other hand, only a few methods are known for the allylation and propargylation of epoxides.[2–4] Except for a few, the methods suffer from a lack of efficiency and simplicity. Therefore, the development of simple and novel reagents, which are more efficient and provide convenient procedures with improved yields still remains a challenge for synthetic organic chemists.

Along with others, we have been exploring a bimetallic strategy to generate allyl and propargyl organometallic reagents.[5] The strategy involves oxidative addition of an organic halide (RX) across catalytic d^8/d^{10} metal [M], followed by redox-transmetallation of R-[M]-X to tin(II) to generate R-Sn(IV) in situ. Successful delineation of the strategy for carbonyl allylation and propargylation prompted us to investigate the nucleophilic addition of organotin(IV) to an epoxide. Previously we reported that under strictly anhydrous condition, lithium hydroxide could promote such reactivity. However, a major synthetic limitation was the use of stoichiometric excess (3 equiv with respect to Sn^{II}) of lithium hydroxide, along with $Sn(OTf)_2$ as the second additive.[6] Remarkably, we now find that the reactivity of organotin towards epoxides can be tuned simply by the controlled addition of water in DMSO leading to homoallyl and homopropargyl alcohols via epoxide rearrangement-carbonyl addition reaction, and present our findings in this report (Scheme 1).



Scheme 1. Tandem epoxide rearrangement and allylation/propargylation.

2. Results and discussion

2.1. Effect of water and catalyst

Reaction of styrene oxide **2a** and 3-bromopropene **1a** in the presence of anhydrous stannous chloride and catalytic $Pd_2(dba)_3 \cdot CHCl_3$ in DMSO at 60 °C led to the formation of 1-phenyl-pent-4-en-2-ol **3a** in 39% yield (Table 1, entry 4). The yield of **3a** was negligible for reactions in DCM, and THF, while in DMF it was 33%. On the other hand, reaction in the absence of catalyst afforded majorly 1-phenyl-ethane-1,2-diol **6**, along with unreacted epoxide **2a** and epoxide rearrangement product, phenylacetaldehyde **7** (entry 5).

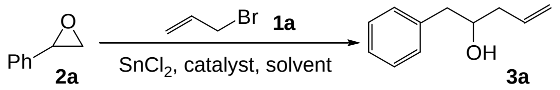
Keywords: Allylation; Propargylation; Organotin; Palladium; Aqueous promotion.

---

* Corresponding author. Tel.: +91 3222 283338; fax: +91 3222 282252; e-mail: sroy@chem.iitkgp.ernet.in

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.10.005

Table 1. Reaction of styrene epoxide with allyl bromide: effect of water[a]



#	Solvent	Water (μl)	Temperature (°C)	Yield (%)
1	DCM	—	40	Trace
2	THF	—	60	Trace
3	DMF	—	60	33
4	DMSO	—	60	39
5[b]	DMSO	—	60	Trace[c]
6	DMSO	70	60	73
7	DCM	70	40	Trace
8	THF	70	60	Trace
9	DMF	70	60	55

[a] Condition: styrene oxide 0.5 mmol, $SnCl_2$ 1 mmol, allyl bromide 1.5 mmol, $Pd_2dba_3\cdot CHCl_3$ 0.01 mmol, solvent 3 ml, 11 h.

[b] Without catalyst.

[c] Major products $PhCH(OH)CH_2OH$ **6** and $PhCH_2CHO$ **7**.

Remarkably, the addition of a controlled amount of water (~3 equiv) in DMSO dramatically increased the yield of **3a** to 73% (entry 6). Note that such dramatic enhancement is not observed for other organic-aqueous combinations (entries 7–9).

The effect of water on the yield of homoallyl alcohol **3a** and diol **6** was further scrutinised carefully for reactions conducted with 2 mmol of $SnCl_2$. As shown in Figure 1, upon slow addition of water the yield of **3a** slowly increases and reaches a maximum near 6–8 mmol, after which it decreases sharply. On the other hand, the yield of diol **6** remains below 20% until 6–8 mmol of water is added; beyond which it rises very rapidly. From data points for any two successive addition of water, one finds that the yield difference in case of **3a** does not correlate linearly with that of **6**. The above observations highlight the critical role of water in enhancing the nucleophilic addition reaction rate.

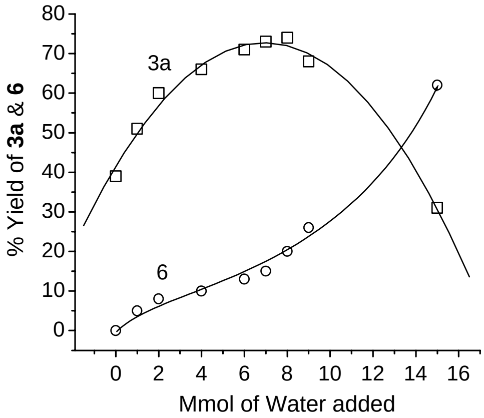
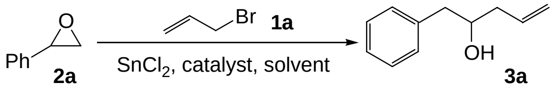


Figure 1. Effect of water on epoxide allylation. Homoallyl alcohol **3a** (□), diol **6** (○). Condition: styrene oxide **2a** 1 mmol, $SnCl_2$ 2 mmol, allyl bromide 3 mmol, Pd_2dba_3 2 mol%, DMSO 3 ml, 60 °C, 11 h.

Our findings on the role of water corroborates many recent reports on the increased reactivity of in situ or ex situ generated organometallic nucleophiles in aqueous or aqueous-organic medium.[7,8] It is now well established that the reagent combination of Pd(0/II)/$SnCl_2$/allyl bromide generates allyltrihalostannane.[9] That a stoichiometric 3 equiv of water with respect to tin is needed in our case suggests that a likely active species is $RSn(OH)_3$.[7c] This suggestion is close in line with the one proposed by Li et al. for the arylation of aldehydes.[8] It is presumed that by virtue of its coordinating ability DMSO could further stabilize the hydroxytin(IV) intermediate.[10]

Screening of catalysts at 2% loading (Table 2) indicates that among the metal complexes, $Pd_2dba_3\cdot CHCl_3$ and $NiCl_2(PPh_3)_2$ cause >60% product formation, while among the metal salts $Pd(OAc)_2$ and $Ni(OAc)_2\cdot 4H_2O$ are superior to others. The best condition is shown as in entry 15.

Table 2. Reaction of styrene epoxide with allyl bromide: effect of catalyst[a]

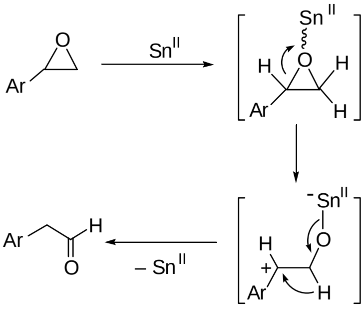


#	Catalyst	mol (%)	Time (h)	Yield (%)
1	None	—	24	Trace
2	CuCl	30	24	27
3	$CuCl_2,2H_2O$	30	24	33
4	$Cu(OAc)_2\cdot H_2O$	2	11	47
5	$Ni(OAc)_2\cdot 4H_2O$	2	11	55
6	$NiCl_2(PPh_3)_2$	2	11	64
7	$PtCl_2(PPh_3)_2$	2	11	50
8	$Pd(dba)_2$	2	11	43
9	$Pd(PPh_3)_4$	2	11	49
10	$PdCl_2(PPh_3)_2$	2	11	54
11	$PdCl_2(MeCN)_2$	2	11	55
12	$PdCl_2$(Phen)	2	11	59
13	$Pd(OAc)_2$	2	11	60
15	$Pd_2dba_3\cdot CHCl_3$	2	11	73

[a] Condition: styrene oxide 0.5 mmol, anhydrous $SnCl_2$ 1 mmol, allyl bromide 1.5 mmol, DMSO 3 ml, H_2O 70 μl, 60 °C.

2.2. Epoxide rearrangement-carbonyl allylation

The formation of homoallyl alcohol **3a** suggests that the reaction pathway does not involve direct allylation of the epoxide, instead is a case of allylation of a benzylic aldehyde. Lewis acid catalyzed rearrangement of epoxides to benzylic aldehydes is well documented.[11] Control experiments with styrene oxide confirmed that under our reaction conditions, such rearrangement is promoted by tin(II) in DMSO, but not the transition metal partner. Thus, reaction of **2a** (0.5 mmol) with $SnCl_2$ (0.3 mmol) in DMSO resulted in rapid rearrangement within 30 min leading to the formation of phenylacetaldehyde **7** (84%). Under similar conditions, but with $Pd_2dba_3\cdot CHCl_3$ the yield of phenylacetaldehyde **7** was negligible even after 6 h. Therefore, the epoxide rearrangement is viewed as a typical Lewis acid catalyzed pathway involving Sn^{II} (Scheme 2).[12]

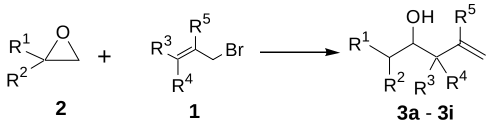


Scheme 2. Sn^{II} assisted rearrangement of arylepoxide.

2.3. Generality of the method: allylation of arylepoxide

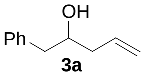
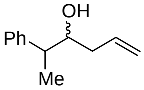
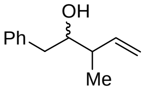
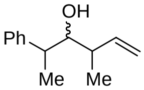
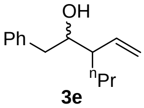
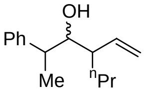
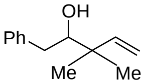
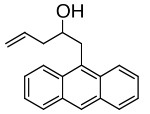
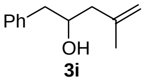
The generality of the reaction was further tested for the allylation of epoxides (Table 3). Reaction of styrene epoxide **2a** with allyl bromides **1a**–**1e** afforded exclusively the γ-regioselective products **3a**, **3c**, **3e**, **3g**, and **3i** in 65–75% yields (entries 1, 3, 5, 7, 9). To test if steric crowding is tolerated, α-methylstyrene epoxide **2b** was reacted with allyl bromides **1a**, **1b**, and **1c** to afford the corresponding homoallyl alcohols **3b**, **3d**, and **3f** in 70–82% yield (entries 2, 4, 6). Furthermore, 1-(9-anthryl)-ethylene oxide **2c** reacted smoothly with allyl bromide **1a** giving rise to the allylation product **3h** in 83% yield (entry 8). For reactions with 3-substituted allyl bromides, the *syn*/*anti* diastereoselectivity in the product varied from case to case (entries 2–6). In comparison to the very good allylation reactivity of arylepoxides, attempted reactions with aliphatic epoxides provided complicated mixtures. Thus, reactions of cyclohexene oxide and **1a** even at lower temperature gave rise to a number of intractable products.

Table 3. Epoxide rearrangement-allylation[a]



2a: R^1=Ph, R^2=H
2b: R^1=Ph, R^2=Me
2c: R^1=Anthryl, R^2=H

1a: R^3=H, R^4=H, R^5=H
1b: R^3=Me, R^4=H, R^5=H
1c: R^3=^{n}Pr, R^4=H, R^5=H
1d: R^3=Me, R^4=Me, R^5=H
1e: R^3=H, R^4=H, R^5=Me

#	Bromide	Epoxide	Product	Time (h)	Yield (%)	*syn*/*anti*[b]
1	**1a**	**2a**	 **3a**	11	73	—
2	**1a**	**2b**	 **3b**	13	80	63/37
3	**1b**	**2a**	 **3c**	13	71	40/60
4	**1b**	**2b**	 **3d**	13	82	80/20
5	**1c**	**2a**	 **3e**	14	67	66/34
6	**1c**	**2b**	 **3f**	13	70	70/30
7	**1d**	**2a**	 **3g**	12	75	—
8	**1a**	**2c**	 **3h**	14	83	—
9	**1e**	**2a**	 **3i**	13	35	—

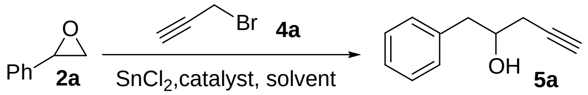
[a] Condition: epoxide 0.5 mmol, $SnCl_2$ 1 mmol, allyl bromide 1.5 mmol, $Pd_2dba_3 \cdot CHCl_3$ 0.01 mmol, DMSO–H_2O (3 ml–70 μl), 60 °C.

[b] Based on NMR.

2.4. Generality of the method: propargylation of arylepoxide

The scope of the reaction was successfully extended to the propargylation of epoxides. In the presence of catalytic $Pd(OAc)_2$, the model reaction of 3-bromo-prop-1-yne **4a** and styrene oxide **2a** yielded 68% of 1-phenyl-pent-4-yn-2-ol **5a** (Table 4, entry 4). In comparison, other catalysts showed poor efficiency. Complete absence of isomeric allenyl alcohol suggests that under the reaction conditions, metallotropic rearrangement between the propargyltin and allenyltin is completely arrested.[5f] The generality of the method was further tested for the reaction of styrene oxide **2a**, α-methyl styrene oxide **2b** and 1-(9-anthryl)-ethylene oxide **2c** with propargyl bromides **2a**–**2c** affording moderate to good yields of the corresponding homopropargyl alcohols **5a**–**5e** (Table 5).

Table 4. Reaction of styrene epoxide with propargyl bromide: effect of catalyst[a]



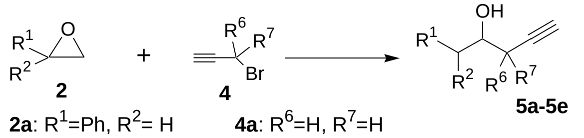
#	Catalyst	mol%	Yield (%)
1	None	—	Trace
2	$NiCl_2(PPh_3)_2$	2	31
3	$Ni(OAc)_2 \cdot 4H_2O$	4	26
4	$Pd(OAc)_2$	2	68
5	$PtCl_2(PPh_3)_2$	2	59
6	$PdCl_2(Phen)$	2	52
7	$Pd(PPh_3)_4$	2	31
8	$Pd(dba)_2$	2	28
9	$Pd_2dba_3 \cdot CHCl_3$	2	2

[a] Condition: styrene oxide 0.5 mmol, $SnCl_2$ 1 mmol, propargyl bromide 1.5 mmol, catalyst 0.01 mmol, DMSO–H_2O (3 ml–70 μl), rt, 20 h.

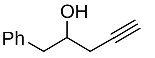
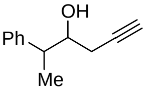
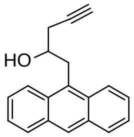
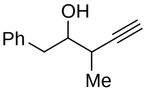
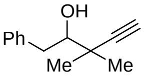
2.5. Comments on plausible mechanism

Whilst a detailed mechanism of the present reaction must await further studies, some of the plausible bond forming steps are enumerated below (Scheme 3, where R = allyl or propargyl). The suggestions are based on previous studies[7–11] and observations described in previous sections. In early stages of the reaction formation of organotrihalostannane R-$SnXCl_2$ **I** is postulated by a well-known redox trans-metallation pathway involving oxidative addition of organic halide RX across palladium, insertion of tin(II) halide, followed by reductive elimination.[9] The profound involvement of water enables us to suggest the formation of a

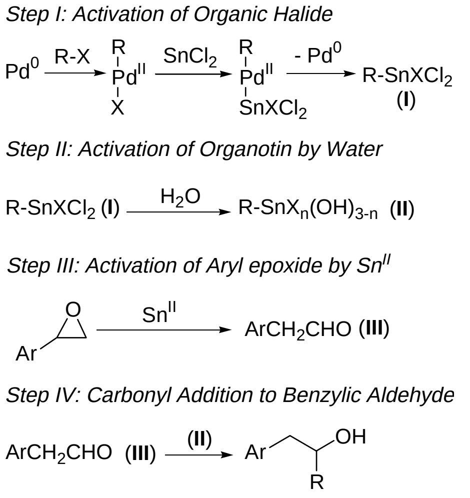
Table 5. Epoxide rearrangement-propargylation[a]



2a: R^1=Ph, R^2= H **4a**: R^6=H, R^7=H
2b: R^1=Ph, R^2=Me **4b**: R^6=Me, R^7=H
2c: R^1=Anthryl, R^2=H **4c**: R^7=Me, R^7=Me

#	Bromide	Epoxide	Product	Time (h)	Yield (%)	*syn*/ *anti*[b]
1	**4a**	**2a**	 **5a**	18	61	—
2	**4a**	**2b**	 **5b**	22	43	65/35
3	**4a**	**2c**	 **5c**	15	92	—
4	**4b**	**2a**	 **5d**	14	71	40/60
5	**4c**	**2a**	 **5e**	16	48	—

[a] Condition: epoxide 0.5 mmol, $SnCl_2$ 1 mmol, propargyl bromide 1.5 mmol, $Pd(OAc)_2$ 0.01 mmol, solvent DMSO–H_2O (3 ml–70 µl), rt.
[b] Based on NMR.



Scheme 3. Plausible mechanism for epoxide rearrangement and carbonyl addition of reactive organotin.

more reactive organotin intermediate $RSnX_n(OH)_{3\text{-}n}$ **II** in solution.[7,8] Under the reaction conditions, simultaneous rearrangement of the arylepoxide to the benzylic aldehyde **III** occurs (vide Scheme 2).[12] The final step of the reaction would involve a carbonyl addition via S_E2' attack of organotin intermediate **II** to aldehyde **III** to furnish the end-organic product.

3. Conclusion

In summary, we have demonstrated a facile allylation and propargylation of arylepoxides to afford the corresponding homoallyl and homopropargyl alcohols with a two carbon extension. The reaction is promoted simply by the addition of a limited amount of water to generate a reactive organotin species. The end-organic product arises from simultaneous epoxide rearrangement and carbonyl addition, the latter being 100% γ-regioselective, and devoid of allenyl-isomers (in case of propargylation). All of the above features are expected to add to the synthetic utility of the present reaction. Further work is warranted to understand the mechanistic details of the reaction.

4. Experimental

4.1. General comments

^1H (200 MHz) NMR spectra were recorded on a BRUKER-AC 200 spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (deuterochloroform: δ 7.27 ppm). Data are reported as follows: chemical shifts, multiplicity (s= singlet; d=doublet; t=triplet; q=quartet; br=broad; m=multiplet), coupling constant (Hz). ^{13}C (54.6 MHz) NMR spectra were recorded on a BRUKER-AC 200 MHz spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (deuterochloroform: δ 77.0 ppm). ESI mass spectra were recorded on a Waters LCT mass spectrometer. Elemental analyses were carried out using a CHNS/O Analyzer Perkin Elmer 2400 Series II instrument. IR spectra were taken on a Thermo Nicolet FTIR Spectrometer (NEXUS-870). Melting points were determined on an Electrothermal 9100 melting point apparatus and are uncorrected.

4.2. General procedure

The procedure given below was followed in all cases. All products showed satisfactory spectral and analytical data.

4.3. Allylation of epoxides

$Pd_2dba_3\cdot CHCl_3$ (10 mg, 0.01 mmol) was added to a solution of allyl bromide (1.5 mmol) in a DMSO–H_2O solvent mixture (3 ml–70 µl) and was allowed to stir for 5 min at a bath temperature of 60 °C. Anhydrous $SnCl_2$ (190 mg, 1 mmol) was added and the reaction stirred for 6 h. Finally, epoxide (0.5 mmol) was added and the reaction was monitored by TLC. After completion, the reaction was quenched by adding water and ammonium fluoride. The mixture was extracted into ethylacetate. The combined organic layer was washed with water (4×50 ml), brine and dried over anhydrous $MgSO_4$. Solvent removal under reduced pressure followed by column chromatography over silica gel 60–120 (eluent, 2% EtOAc in hexane) afforded the desired allylated product.

4.3.1. 1-Phenylpent-4-en-2-ol (3a).[13,7k,3c] Using the general procedure (as in Section 4.3) but with 3-bromo-propene **1a** (181 mg, 1.5 mmol) and styrene epoxide **2a** (60 mg, 0.5 mmol) afforded the title compound **3a** (59 mg, 73%) as a light yellow oily liquid.

4.3.2. 2-Phenylhex-5-en-3-ol (3b).[3c] Using the general procedure (as in Section 4.3) but with 3-bromo-propene **1a** (181 mg, 1.5 mmol) and α-methylstyrene epoxide **2b** (67 mg, 0.5 mmol) afforded the title compound **3b** (70 mg, 80%) as a light yellow oily liquid.

4.3.3. 3-Methyl-1-phenylpent-4-en-2-ol (3c).[14] Using the general procedure (as in Section 4.3) but with 1-bromo-but-2-ene **1b** (202 mg, 1.5 mmol) and styrene epoxide **2a** (60 mg, 0.5 mmol) afforded the title compound **3c** (63 mg, 71%) as a light yellow oily liquid.

4.3.4. 4-Methyl-2-phenylhex-5-en-3-ol (3d).[14b,15] Using the general procedure (as in Section 4.3) but with 1-bromo-but-2-ene **1b** (202 mg, 1.5 mmol) and α-methylstyrene epoxide **2b** (67 mg, 0.5 mmol) afforded the title compound **3d** (78 mg, 82%) as a light yellow oily liquid.

4.3.5. 1-Phenyl-3-propylpent-4-en-2-ol (3e).[5c,5e] Using the general procedure (as in Section 4.3) but with 1-bromo-hex-2-ene **1c** (245 mg, 1.5 mmol) and styrene epoxide **2a** (60 mg, 0.5 mmol) afforded the title compound **3c** (68 mg, 67%) as a light yellow oily liquid.

4.3.6. 2-Phenyl-4-propylhex-5-en-3-ol (3f). Using the general procedure (as in Section 4.3) but with 1-bromo-hex-2-ene **1c** (245 mg, 1.5 mmol) and α-methylstyrene epoxide **2b** (67 mg, 0.5 mmol) gave the title compound **3f** (76 mg, 70%) as a yellow viscous liquid, *syn*:*anti* 70:30; IR (neat) 3450, 3020, 2958, 2928, 2871, 1495, 1454, 1261, 1070, 1031, 914,743,700 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.75–0.95 (3H, m, $CH_2CH_2CH_3$), 1.15–1.47 (7H, m, $CH_2CH_2CH_3+PhCHMe$), 1.75 (1H, br s, O*H*), 1.96–2.06 (1H, m, $CH_2{=}CH{-}CH$), 2.81–2.88 (1H, m, Ph-C*H*), 3.58–3.71 (1H, m, C*H*–OH), 4.92–5.21 (2H, m, $CH_2{=}CH$), 5.61–5.71 (1H, m, $CH_2{=}CH$), 7.16–7.34 (5H, m, *Ph*). ^{13}C NMR ($CDCl_3$): δ [13.94, 14.01] (*anti*+*syn*), 17.19, [20.16, 20.32] (*anti*+*syn*), [33.6, 34.33] (*anti*+*syn*), 43.24, 47.31, 77.84, 117.63, 126.19, 127.72, [128.37, 128.45] (*anti*+*syn*), 138.05, 145.02. ESI-MS: for $C_{15}H_{22}O$ [M], $[M-OH]^+=201.16$. Anal. ($C_{15}H_{22}O$) Calcd, C: 82.52, H: 10.16; found, C: 82.58, H: 10.19.

4.3.7. 3,3-Dimethyl-1-phenylpent-4-en-2-ol (3g).[16] Using the general procedure (as in Section 4.3) but with 1-bromo-3-methyl-but-2-ene **1d** (224 mg, 1.5 mmol), and styrene epoxide **2a** (60 mg, 0.5 mmol) afforded the title compound **3g** (71 mg, 75%) as a light yellow oily liquid.

4.3.8. 1-Anthrylpent-4-en-2-ol (3h). Using the general procedure (Section 4.3) but with 3-bromo-propene **1a** (181 mg, 1.5 mmol) and 1-(9-anthryl)-ethylene oxide **2c** (110 g, 0.5 mmol) afforded the title compound **3h** (109 mg, 83%) as yellow solid, mp 90–92 °C; IR (KBr) 3396, 2963, 1262, 1098, 1019, 800 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.72 (1H, br s, O*H*), 2.42–2.48 (2H, m, $CH_2{=}CH{-}CH_2$), 3.79–3.83 (2H, m, anthryl-CH_2), 4.12–4.15 (1H, m, C*H*–OH), 5.16–5.26 (2H, m, $CH_2{=}CH$), 5.84–5.93 (1H, m, $CH_2{=}CH$), 7.42–7.56 (4H, m, aromatic), 7.97–8.02 (2H, m, aromatic), 8.28–8.36 (3H, m, aromatic). ^{13}C NMR ($CDCl_3$): δ 34.74, 41.93, 72.18, 118.40, 124.64, 124.89, 125.71, 126.57, 129.17, 130.53, 130.62, 131.52, 134.74. ESI-MS: for $C_{19}H_{18}O$ [M], $[M+H]^+=263.14$, $[M-OH]^+=245.13$. Anal. ($C_{19}H_{18}O$) Calcd, C: 86.99, H: 6.92; found, C: 86.92, H: 6.76.

4.3.9. 4-Methyl-1-phenylpent-4-en-2-ol (3i).[5a,16] Using the general procedure (as in Section 4.3) but with 3-bromo-2-methyl-propene **1e** (203 mg, 1.5 mmol) and styrene epoxide **2a** (60 mg, 0.5 mmol) afforded the title compound **3i** (31 mg, 35%) as a light yellow oily liquid.

4.4. Propargylation of epoxide

$Pd(OAc)_2$ (3 mg, 0.01 mmol) was added to a solution of propargyl bromide (1.5 mmol) in a DMSO–H_2O solvent mixture (3 ml–70 μl) and was allowed to stir for 5 min at rt. Anhydrous $SnCl_2$ (190 mg, 1 mmol) was added and the reaction stirred for 6 h. Finally epoxide (0.5 mmol) was added and the reaction was monitored by TLC. After completion, the reaction was quenched by adding water and ammonium fluoride. The mixture was extracted into ethylacetate. The combined organic layer was washed with water (4×50 ml), brine and dried over anhydrous $MgSO_4$. Solvent removal under reduced pressure followed by column chromatography over silica gel 60–120 (eluent, 2% EtOAc in hexane) afforded the desired propargylated product.

4.4.1. 1-Phenyl-pent-4-yn-2-ol (5a).[16] Using the general procedure (as in Section 4.4) but with 3-bromo-propyne **4a** (179 mg, 1.5 mmol), and styrene epoxide **2a** (60 mg, 0.5 mmol) afforded the title compound **5a** (49 mg, 61%) as a light yellow oily liquid.

4.4.2. 2-Phenyl-hex-5-yn-3-ol (5b).[6] Using the general procedure (as in Section 4.4) but with 3-bromo-propyne **4a** (179 mg, 1.5 mmol) and α-methylstyrene epoxide **2b** (67 mg, 0.5 mmol) afforded the title compound **5b** (38 mg, 43%) as a light yellow oily liquid.

4.4.3. 1-Anthryl-pent-4-yn-2-ol (5c). Using the general procedure (as in Section 4.4) but with 3-bromo-propyne **4a** (179 mg, 1.5 mmol) and 1-(9-anthryl)-ethylene oxide **2c** (110 mg, 0.5 mmol) gave the title compound **5c** (120 mg, 92%) as a yellow solid, mp 84–87 °C (dec); IR (KBr) 3442, 3295, 2925, 1670, 1653, 1600, 1457, 1317, 1261, 1074, 1025, 734, 700, 668 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.85 (1H, br s, O*H*), 2.21–2.23 (1H, t, $J=2.6$ Hz, acetylenic), 2.54–2.58 (2H, m), 3.91–3.99 (2H, m), 4.28–4.31 (1H, m), 7.44–7.59 (4H, m, aromatic), 8.00–8.05 (2H, m, aromatic), 8.34–8.41 (3H, m, aromatic). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 27.06, 34.16, 71.25, 71.30, 80.81, 124.47, 124.96, 125.91, 127.28, 129.23, 129.86, 130.57, 131.54. ESI-MS: for $C_{19}H_{16}O$ [M], $[M+H]^+=261.12$, $[M-OH]^+=243.12$. Anal. ($C_{19}H_{16}O$) Calcd, C: 87.66, H: 6.19; found, C: 87.75, H: 6.21.

4.4.4. 3-Methyl-1-phenyl-pent-4-yn-2-ol(5d).[16] Using the general procedure (as in Section 4.4) but with 3-bromo-but-1-yne **4b** (200 mg, 1.5 mmol) and styrene epoxide **2a** (60 mg, 0.5 mmol) afforded the title compound **5d** (62 mg, 71%) as a light yellow oily liquid.

4.4.5. 3,3-Dimethyl-1-phenyl-pent-4-yn-2-ol (5e).[5b,6] Using the general procedure (as in Section 4.4) but with 3-bromo-3-methyl-but-1-yne **4c** (220 mg, 1.5 mmol) and styrene epoxide **2a** (60 mg, 0.5 mmol) afforded the title compound **5e** (45 mg, 48%) as a light yellow oily liquid.

Acknowledgements

We thank CSIR for financial support. Research fellowship to U.K.R. (UGC-SRF) is acknowledged.

Supplementary data

Supplementary data associated with this article can be found, in the online version at doi: 10.1016/j.tet.2005.10.005

References and notes

1. Recent reviews: (a) Marshall, J. A. *Chem. Rev.* **2000**, *100*, 3163–3185. (b) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763–2793.
2. (a) Naruta, Y.; Maruyama, K. *Chem. Lett.* **1987**, 963–966. (b) Imai, T.; Nishida, S. *J. Org. Chem.* **1990**, *55*, 4849–4852. (c) Overman, L. E.; Renhowe, P. A. *J. Org. Chem.* **1994**, *59*, 4138–4142. (d) Likhar, P. R.; Kumar, M. P.; Bandyopadhyay, A. K. *Tetrahedron Lett.* **2002**, *43*, 3333–3335. (e) Yadav, J. S.; Reddy, B. V. S.; Satheesh, G. *Tetrahedron Lett.* **2003**, *44*, 6501–6504.
3. (a) Deng, D. L.; Lu, Z. H. *Chin. Chem. Lett.* **1993**, *4*, 857–858. (b) Deng, D. L.; Lu, Z. H. *Youji Huaxue* **1995**, *15*, 95–99. (c) Jiang, N.; Hu, Q.; Reid, C. S.; Lu, Y.; Li, C. J. *Chem. Commun.* **2003**, 2318–2319.
4. (a) Oh, B. K.; Cha, J. H.; Cho, Y. S.; Choi, K. I.; Koh, H. Y.; Chang, M. H.; Pae, A. N. *Tetrahedron Lett.* **2003**, *44*, 2911–2913. (b) Hojo, M.; Harada, H.; Ito, H.; Hosomi, A. *Chem. Commun.* **1997**, 2077–2078.
5. (a) Kundu, A.; Prabhakar, M.; Vairamani, M.; Roy, S. *Organometallics* **1997**, *16*, 4796–4799. (b) Kundu, A.; Prabhakar, M.; Vairamani, M.; Roy, S. *Organometallics* **1999**, *18*, 2782–2785. (c) Sinha, P.; Roy, S. *Chem. Commun.* **2001**, 1798–1799. (d) Banerjee, M.; Roy, S. *Chem. Commun.* **2003**, 534–535. (e) Sinha, P.; Roy, S. *Organometallics* **2004**, *23*, 67–71. (f) Banerjee, M.; Roy, S. *Org. Lett.* **2004**, *13*, 2137–2140.
6. Banerjee, M.; Roy, U. K.; Sinha, P.; Roy, S. *J. Organomet. Chem.* **2005**, *690*, 1422–1428.
7. Representative examples on enhancement of nucleophilic reactivity of organostannanes by water, please see: (a) Boldrini, G. P.; Lodi, L.; Tagliavini, E.; Tarasco, C.; Trombini, C.; Umani-Ronchi, A. *J. Org. Chem.* **1987**, *52*, 5447–5452. (b) Kanagawa, Y.; Nishiyama, Y.; Ishii, Y. *J. Org. Chem.* **1992**, *57*, 6988–6991. (c) Takahara, J. P.; Masuyama, Y.; Kurusu, Y. *J. Am. Chem. Soc.* **1992**, *114*, 2577–2586. (d) Yanagiswa, A.; Inoue, H.; Morodome, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 10356–10357. (e) Li, X.-R.; Loh, T.-P. *Tetrahedron: Asymmetry* **1996**, *7*, 1535–1538. (f) Houllemare, D.; Outurquin, F.; Paulmier, C. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1629–1632. (g) Okano, T.; Kiji, J.; Doi, T. *Chem. Lett.* **1998**, 5–6. (h) Chan, T. H.; Yang, Y.; Li, C. J. *J. Org. Chem.* **1999**, *64*, 4452–4455. (i) Ito, A.; Kishida, M.; Kurusu, Y.; Masuyama, Y. *J. Org. Chem.* **2000**, *65*, 494–498. (j) Shibata, I.; Yoshimura, N.; Yabu, M.; Baba, A. *Eur. J. Org. Chem.* **2001**, 3207–3211. (k) Tan, X.-H.; Shen, B.; Deng, W.; Zhao, H.; Liu, L.; Guo, Q.-X. *Org. Lett.* **2003**, *5*, 1833–1835.
8. Huang, T.; Meng, Y.; Venkatraman, S.; Wang, D.; Li, C. J. *J. Am. Chem. Soc.* **2001**, *123*, 7451–7452.
9. Thoonen, S.; Deelman, B.-J.; Koten, G. v. *Tetrahedron* **2003**, *59*, 10261–10268.
10. For interaction between polar coordinating solvent and Sn(IV) species please see: Satchell, D. P. N.; Satchell, R. S. *Chem. Rev.* **1969**, *69*, 251–278 and references therein.
11. For examples of arylepoxide rearrangement, please see: (a) Kulasegaram, S.; Kulawiec, R. J. *J. Org. Chem.* **1994**, *59*, 7195–7196. (b) Lemini, C.; Ordonez, J.; Perez-Flores, J.; Cruz-Almanza, R. *Synth. Commun.* **1995**, *25*, 2695–2702. (c) Picions, J.; Mahmood, S. J.; Gill, A.; Hilliard, M.; Hossain, M. M. *Tetrahedron Lett.* **1998**, *39*, 2681–2684. (d) Ranu, B. C.; Jana, U. *J. Org. Chem.* **1998**, *63*, 8212–8216. (e) Vankar, Y. D.; Chaudhuri, N. C.; Singh, S. P. *Synth. Commun.* **1986**, *16*, 1621–1626. (f) Suda, K.; Kikkawa, T.; Nakajima, S.-i.; Takanami, T. *J. Am. Chem. Soc.* **2004**, *126*, 9554–9555.
12. The possibility of epoxide rearrangement by $RSnCl_3$ cannot be ruled out. For $SnCl_4$ mediated epoxide rearrangement, see: Kita, Y.; Matsuda, S.; Inoguchi, R.; Ganesh, J. K.; Fujioka, H. *Tetrahedron Lett.* **2005**, *46*, 89–91.
13. Masalov, N.; Feng, W.; Cha, J. K. *Org. Lett.* **2004**, *6*, 2365–2368.
14. (a) Collins, S.; Kuntz, B. A.; Hong, Y. *J. Org. Chem.* **1989**, *54*, 4154–4158. (b) Collins, S.; Dean, W. P.; Ward, D. G. *Organometallics* **1988**, *7*, 2289–2293.
15. Hirashita, T.; Kambe, S.; Tsuji, H.; Omori, H.; Araki, S. *J. Org. Chem.* **2004**, *69*, 5054–5059.
16. McCluskey, A.; Muderawan, I. W.; Muntari; Young, D. J. *J. Org. Chem.* **2001**, *66*, 7811–7817.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
ELSEVIER
Tetrahedron
Tetrahedron 62 (2006) 684–690

Palladium catalyzed synthesis of Ca^{2+} indicators with aryl bithiophene and terthiophene fluorophores

Noël Boens, Nesibe Avcıbaşı,[†] Subhendu S. Samanta, Amuri Kilonda, Georges J. Hoornaert and Erik Van der Eycken*

Department of Chemistry, Katholieke Universiteit Leuven, Celestijnenlaan 200F, 3001 Heverlee, Belgium

Received 27 June 2005; revised 5 October 2005; accepted 5 October 2005

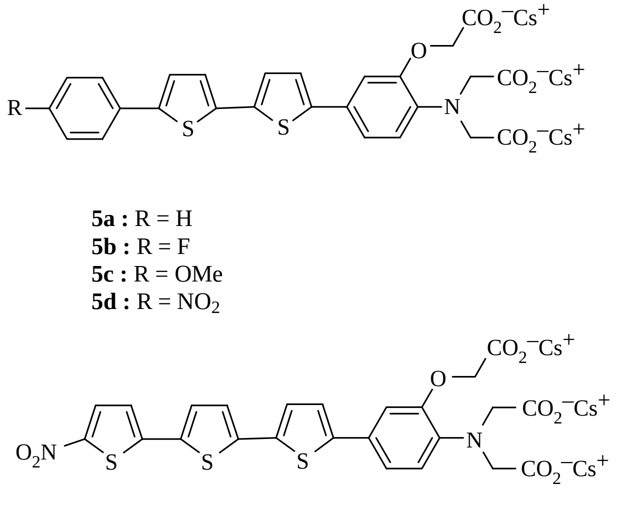
Abstract—Five new fluorescent indicators for Ca^{2+} were synthesized using the Stille reaction. They all consist of the tricarboxylate chelator APTRA (*o*-aminophenol-*N*,*N*,*O*-triacetic acid) linked to a (substituted) bithiophene or terthiophene fluorophore. The dissociation constants K_d measured via fluorimetric titrations at 21 °C in 100 mM KCl buffered solution, pH 7.05, for the Ca^{2+} complexes with the new probes are in the range between 10 and 40 μM.

1. Introduction

Fluorescence spectroscopy and microscopy continue to be attractive methods for sensing and imaging (changes of) ion concentrations. Fluorescent chemosensors that show a spectral response upon binding of Ca^{2+} are mostly derivatives of the Ca^{2+} chelators APTRA (*o*-aminophenol-*N*,*N*,*O*-triacetic acid),[1] and BAPTA [1,2-bis(*o*-aminophenoxy)ethane-*N*,*N*,*N*′,*N*′-tetraacetic acid].[2]

The selection of a Ca^{2+} chelator depends on the Ca^{2+} concentration one intends to measure. The ground-state dissociation constant (K_d) of the formed Ca^{2+} complex must be well-matched with the Ca^{2+} concentration range of interest. High affinity Ca^{2+} probes, based on the tetracarboxylate Ca^{2+} ligand BAPTA,[2] become fully bound to Ca^{2+} at concentrations around and above 1 μM. Since the fluorescence response of these Ca^{2+} indicators becomes saturated at these high Ca^{2+} concentrations, a series of indicators using the tricarboxylate chelator APTRA[1] with low affinity for Ca^{2+} (K_d for the Ca^{2+}–APTRA complex is around 30 μM) has been developed.[3–5] APTRA-based indicators are appropriate for measuring elevated intracellular Ca^{2+} levels[6] and for Ca^{2+} concentration measurements in the lumen of stores,[7] because they can detect Ca^{2+} levels between 1 and 100 μM.

In this paper, we describe the synthesis of five new fluorescent low-affinity Ca^{2+} indicators **5a–d** and **9** with, respectively, bithiophene and terthiophene moieties linked to APTRA (see Fig. 1). Additionally, we also report their fluorescence emission and excitation spectra and investigate their Ca^{2+} binding properties in buffered aqueous solution via fluorimetric titrations.



5a : R = H
5b : R = F
5c : R = OMe
5d : R = NO_2

9

Figure 1. Chemical structures of the new Ca^{2+} indicators.

Keywords: Fluorescent indicator; Thiophene; Stille reaction; Ca^{2+}.

* Corresponding author. Tel.: +32 16 327406; fax: +32 16 327990; e-mail: erik.vandereycken@chem.kuleuven.be

[†] On leave from the Department of Chemistry, Faculty of Science, Ege University, 35100 Bornova, Izmir, Turkey.

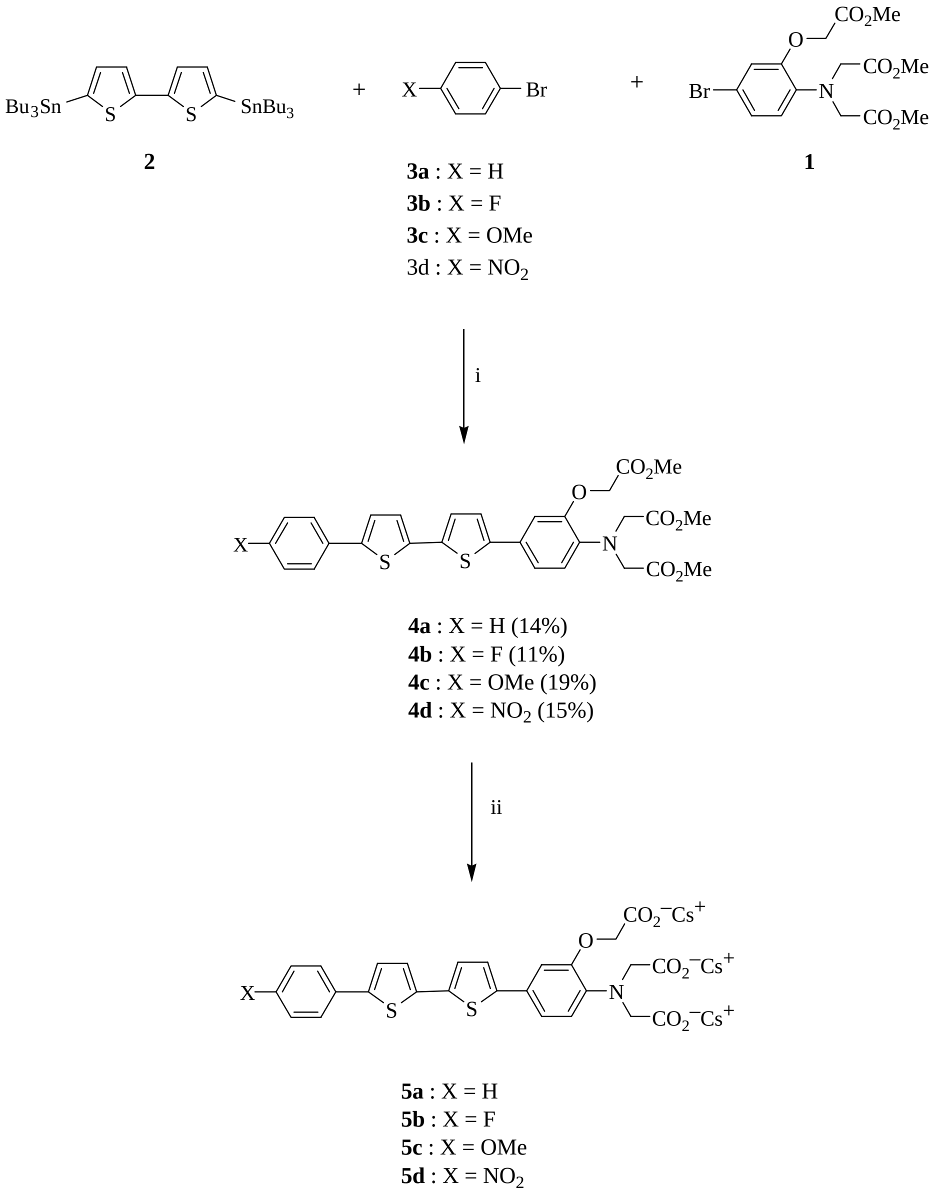
doi:10.1016/j.tet.2005.10.002

2. Results and discussion

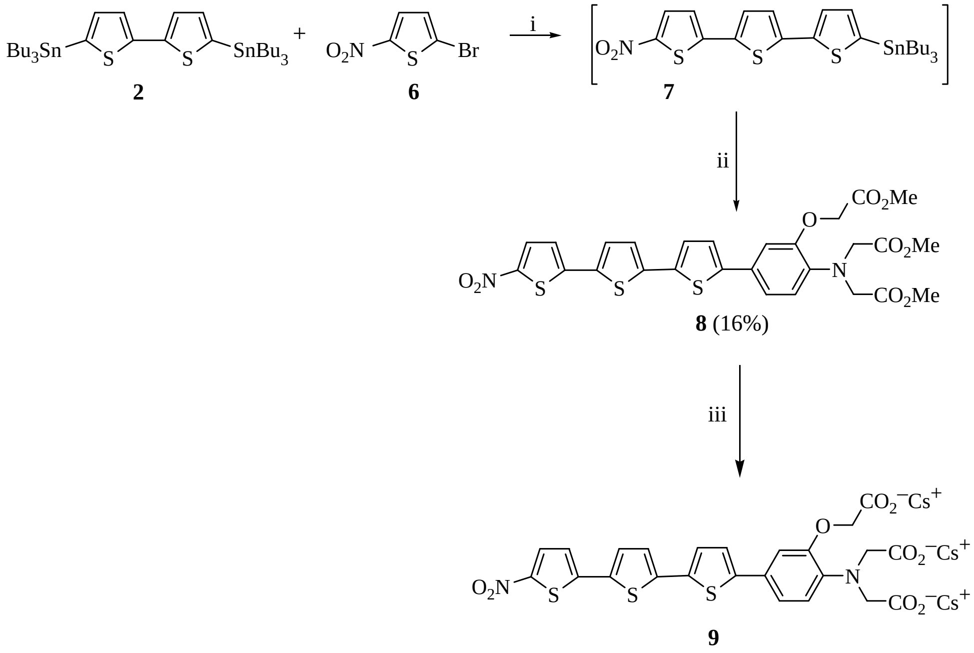
The bithiophene containing indicators **5a–d** are synthesized via a palladium catalyzed coupling reaction between 2,2′-bithiene-5,5′-diylbis(tributylstannane) **2**, an appropriately *p*-substituted bromobenzene **3a–d** and dimethyl 2,2′-([4-bromo-2-(2-methoxy-2-oxoethoxy)phenyl]imino-(diacetate (bromo-APTRA trimethylester, **1**), followed by saponification of the esters **4a–d** (Scheme 1). The terthiophene derivative **9** is similarly synthesized via a palladium catalyzed coupling of 2-bromo-5-nitrothiophene **6** and 2,2′-bithiene-5,5′-diylbis(tributylstannane) **2**, followed by a palladium catalyzed reaction between the intermediately formed compound **7** and **1** (Scheme 2). Saponification yields the functional indicator **9**. The ionophore containing bromo-APTRA trimethylester **1** was synthesized in high yield according to our improved procedure.[8]

2.1. Synthesis of the bithiophene compounds 4a–d

The procedure involves a one-pot reaction. The 2,2′-bithiene-5,5′-diylbis(tributylstannane) **2**,[9] a suitable *p*-substituted bromobenzene **3**, dimethyl 2,2′-{[4-bromo-2-(2-methoxy-2-oxoethoxy)phenyl]imino}diacetate **1** and a catalytic amount of tetrakis(triphenylphosphine)palladium(0) [Pd(PPh$_3$)$_4$] were heated in toluene. This one-pot procedure gives compounds **4a–d** in yields ranging from 11 to 19% (Scheme 1), together with an array of inseparable unidentified side compounds. When the reaction was performed as a two-step procedure (vide infra), via coupling of the 2,2′-bithiene-5,5′-diylbis(tributylstannane) **2** with the *p*-substituted bromobenzene **3**, followed by reaction of the crude intermediate stannane with dimethyl 2,2′-{[4-bromo-2-(2-methoxy-2-oxoethoxy)phenyl]imino}diacetate **1**, the yield did not improve.



Scheme 1. Synthesis of **5a–d**. Reagents and conditions: (i) 5 mol% Pd(PPh$_3$)$_4$, toluene, 80 °C, 3 h; then 120 °C, 2 h; (ii) CsOH, MeOH, reflux, overnight.



Scheme 2. Synthesis of **9**. Reagents and conditions: (i) 5 mol% Pd(PPh$_3$)$_4$, toluene, 80 °C, 3 h; (ii) **1**, 5 mol% Pd(PPh$_3$)$_4$, toluene, 120 °C, 2 h; (iii) CsOH, MeOH, reflux, overnight.

2.2. Synthesis of the terthiophene compound 8

The procedure starts by reacting 2,2′-bithiene-5,5′-diylbis-(tributylstannane) **2**[9] with 2-bromo-5-nitrothiophene **6**[10] catalyzed by tetrakis(triphenyl-phosphine)palladium(0) in toluene at 80 °C (Scheme 2). The resulting stannane **7** is not isolated and is directly reacted with dimethyl 2,2′-{[4-bromo-2-(2-methoxy-2-oxoethoxy)phenyl]imino}-diacetate **1** upon catalysis with Pd(PPh$_3$)$_4$ in toluene at 120 °C. Compound **8** is isolated in 16% yield, from a complex mixture of inseparable side compounds, after a laborious purification by column chromatography and HPLC separation. Performing the procedure as a one-pot reaction gave unsatisfactory results.

Several attempts to synthesize **8** following different strategies were unsuccessful. The commercially available 2,2′-bithiophene could be coupled in 67% yield with 2-bromo-5-nitrothiophene under Stille conditions catalyzed by Pd(PPh$_3$)$_4$, after preparation of the corresponding zincate upon consecutive treatment with LDA and ZnCl$_2$ at −10 °C. The tributyltin derivative of the resulting 5-nitro-[2,2′,5′,2″]terthiophene, necessary for the Stille coupling with bromo-APTRA trimethylester **1**, could not be formed upon deprotonation of this compound with BuLi or LDA and reaction with Bu$_3$SnCl. 5-Nitro-[2,2′,5′,2″]terthiophene was then brominated using NBS in chloroform affording 5-bromo-5″-nitro-2,2′,5′,2″-terthiophene in 72% yield. We did not succeed in preparing the required tributyltin derivative, neither upon reaction with the in situ generated anion and Bu$_3$SnCl nor with (Bu$_3$Sn)$_2$/Pd(PPh$_3$)$_4$. Direct reaction of 5″-bromo-5-nitro-[2,2′,5′,2″]terthiophene with the in situ generated boronate of **1** (upon reaction with bis(pinacolata)diborone) did not work. Procedures starting from the 5,5′-dibromo-2,2′-bithiophene upon palladium catalyzed reaction with the in situ generated zincates of 2-bromo-5-nitrothiophene and **1** were not successful either.

2.3. Hydrolysis of the APTRA ester derivatives

To perform the Ca^{2+} binding studies in aqueous solution, the esters must be transformed into their corresponding water-soluble alkali salts, because only the salts (not the esters!) are able to bind Ca^{2+}. The methyl esters **4a–d** and **8** were readily transformed in situ into the respective tricaesium salts **5a–d** and **9** by saponification with a large excess of caesium hydroxide in refluxing methanol[11] (Schemes 1 and 2) and were used as such for the fluorescence measurements. Comparison of the UV absorption and fluorescence excitation and emission spectra of the esters in methanol and the resulting caesium salts in water indicates that the fluorophore structure remains unchanged.

2.4. Fluorescence excitation and emission spectra

The spectroscopic measurements were done on solutions that mimic the intracellular environment of mammalian cells. The solutions contained 100 mM KCl and 10 mM MOPS (3-[*N*-morpholino]propanesulfonic acid) as pH buffer, and were adjusted to pH 7.05 with KOH or HCl. The free Ca^{2+} concentrations in the solutions were adjusted with Ca^{2+}–nitrilotriacetic acid buffers, as described by Fabiato and Fabiato.[12] Free Ca^{2+} concentrations were computed with the CHELATOR program developed by Schoenmakers et al.[13] The indicator concentrations were in the order of a few μM, yielding an absorbance per cm optical path length of approximately 0.1 at the absorption maximum.

The absorption, excitation and emission properties of the new indicators **5a–d** and **9** are summarized in Table 1. The absorption maxima are all in the near UV. The molar absorption coefficients $\varepsilon_{\max}$ at the wavelength of maximum absorption are in the range $(10–30)\times 10^3\ \mathrm{M}^{-1}\ \mathrm{cm}^{-1}$. Binding of Ca^{2+} shifts the absorption maxima to shorter

Table 1. Spectroscopic properties and fluorescence quantum yields of the indicators **5a–d** and **9** in free and Ca^{2+} bound form, determined at 21 °C in solutions containing 10 mM MOPS and 100 mM KCl, pH 7.05

Compound	Absorption ε_{max}		Excitation λ_{max} (nm)		Emission λ_{max} (nm)		ϕ_f			
	Free	Bound	Free	Bound	Free	Bound	λ_{ex}(nm)	Ref	Free	Bound
5a	27,910	20,600	385	359	572	sh 454	360	QS[a]	0.25	0.06
					sh 432	sh 432	345	QS[a]	0.34	0.08
5b	[b]	[b]	384	369	574	548	375	QS[a]	0.11	0.06
					sh 437	sh 437	360	QS[a]	0.10	0.05
					sh 455	sh 455				
5c	11,000	10,000	385	343	551	496	365	QS[a]	0.26	0.02
5d	17,200	13,100	389	325	554	506	425	Ay[c]	5×10^{-4}	4×10^{-5}
							435	Ay[c]	3×10^{-4}	4×10^{-5}
9	7540	6860	370	364	549	447	390	AY[c]	6×10^{-3}	5×10^{-3}
	9340	6210					410	AY[c]	4×10^{-3}	3×10^{-3}
							440	AY[c]	3×10^{-3}	2×10^{-3}

[a] Quinine bisulfate in 0.1 N H_2SO_4.

[b] Not determined because of insufficient solubility.

[c] Acridine yellow in MeOH.

wavelengths. Similar effects are observed in the excitation spectra (Fig. 2). The fluorescence intensity decreases upon binding Ca^{2+} (as illustrated in Fig. 2) are indicative of a lower fluorescence quantum yield of the Ca^{2+} bound form compared to the free form. The fluorescence quantum yield values ϕ_f are compiled in Table 1. The nitro group makes **5d** and **9** practically non-fluorescent.

2.5. Ca^{2+} binding properties

We used fluorescence spectroscopy to study the Ca^{2+} binding properties of the synthesized indicators, by monitoring the changes in their fluorescence excitation and/or emission spectra that accompany Ca^{2+} binding (from 0 to 0.83 mM free Ca^{2+}). The ground-state dissociation constants K_d of the complexes between Ca^{2+} and the probes **5a–d** and **9** were estimated in buffered aqueous solution (pH 7.05) by fluorimetric titration. Nonlinear fitting of Eq. 1[4] to the steady-state fluorescence data F as a function of $[Ca^{2+}]$ yields values of K_d, the fluorescence signals F_{min} and F_{max} at minimal and maximal $[Ca^{2+}]$, respectively, (corresponding to the free and Ca^{2+} bound forms of the probe, respectively), and n (the number of calcium ions bound per probe). Eq. 1 assumes that the absorbance of the sample is small (<0.1) and that the Ca^{2+} complex formation in the excited

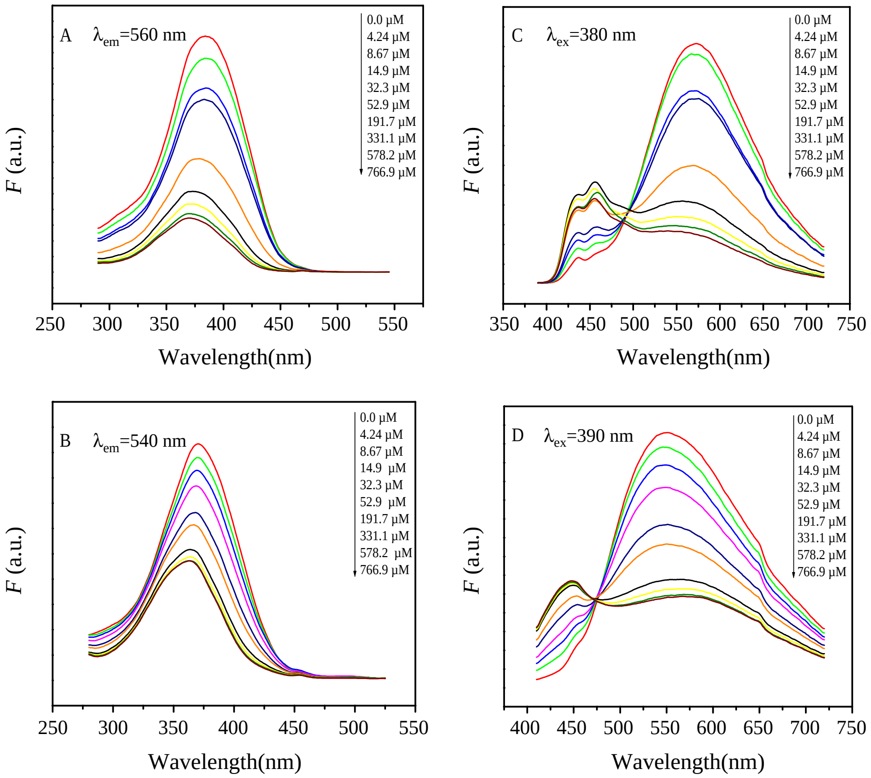


Figure 2. Fluorescence excitation spectra of **5b** (A) and **9** (B) in buffered solutions as a function of free $[Ca^{2+}]$. Corresponding fluorescence emission spectra of **5b** (C) and **9** (D) as a function of free $[Ca^{2+}]$. All spectra were recorded at 21 °C using solutions containing 100 mM KCl and 10 mM MOPS, pH 7.05.

state is negligible.[4]

$$F = \frac{[\mathrm{Ca}^{2+}]^n F_{\max} + K_\mathrm{d} F_{\min}}{K_\mathrm{d} + [\mathrm{Ca}^{2+}]^n} \qquad (1)$$

Fitting Eq. 1 to the steady-state fluorescence data F of **5a–d** with n, K_d, $F_{\min}$, and $F_{\max}$ as freely adjustable parameters always gave values of n close to 1, indicating that one calcium ion is bound per fluorescent indicator **5a–d**. Therefore, n was kept fixed at 1 in the final fittings of Eq. 1 to the fluorescence excitation or emission spectral data of **5a–d**. For the terthiophene indicator **9**, the best fits were obtained with n somewhat higher than 1. Two illustrative examples of the best least-squares fitting of Eq. 1 to the fluorimetric titration data as a function of free [Ca^{2+}] are shown in Figure 3.

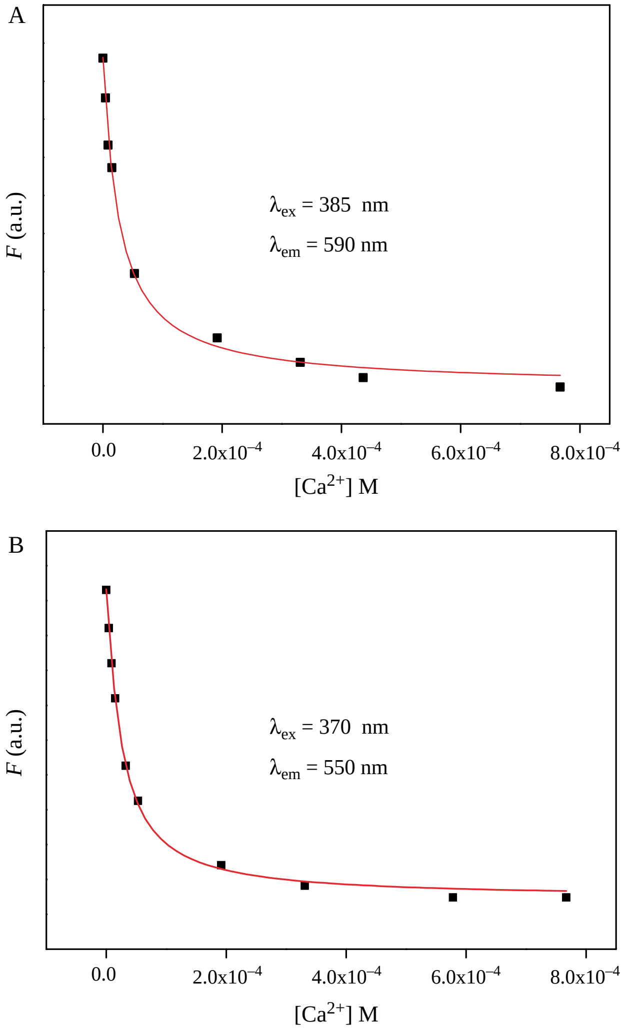


Figure 3. Estimation of K_d (and n) for the Ca^{2+} complexes with **5b** (A) and **9** (B) using fluorimetric excitation titration data [according to Eq. 1]. Data were obtained from experiments performed at 21 °C and pH 7.05.

The estimated K_d values are in the range of elevated intracellular [Ca^{2+}]. The average K_d values at 21 °C in 100 mM KCl, pH 7.05, computed from the best K_d estimates for the Ca^{2+} complexes with the indicators **5a**, **5b**, **5c** and **5d** are 16, 20, 11 and 36 μM, respectively. For the Ca^{2+} complex with **9**, the best fits were consistently obtained when n was freely adjustable. The average $K_\mathrm{d}(\mathrm{Ca}^{2+})$ value equals 7 ± 3 μM with $n = 1.11 \pm 0.07$.

The measured $K_\mathrm{d}(\mathrm{Ca}^{2+})$ values of the commercially available indicators mag-fura-2, mag-fura-5 and mag-indo-1 are 25, 28 and 35 μM,[3] respectively. The arylthiophene-APTRA probe Thio-H[4] has a $K_\mathrm{d}(\mathrm{Ca}^{2+})$ value of 45 μM, while for dioxopyrrolopyrrole probes[5] $K_\mathrm{d}(\mathrm{Ca}^{2+})$ values in the 10–20 μM range have been reported.

3. Conclusions

Five new fluorescent indicators **5a–d** and **9** with low affinity for Ca^{2+} (Fig. 1) based on bithiophene or terthiophene moieties linked to APTRA have been synthesized via a convergent route in which the key step is a palladium catalyzed coupling reaction. The indicators **5a–c** have reasonable fluorescence quantum yields, which decrease upon Ca^{2+} binding. The nitro group, however, makes **5d** and **9** practically non-fluorescent. The dissociation constants for Ca^{2+} are in the 10–40 μM range. The excitation and emission maxima of the free forms of the indicators shift to shorter wavelengths upon Ca^{2+} binding.

4. Experimental

4.1. Materials and methods

Melting points were taken using a Reichert-Jung Thermovar apparatus or an Electrothermal 9200 digital melting point apparatus, and are uncorrected. Infrared spectra were recorded on a Perkin Elmer 1720 Fourier Transform Spectrometer and a Perkin Elmer 297 grating IR spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker WM 250, a Bruker Avance 300, or a Bruker AMX 400. They were taken using $\mathrm{CDCl_3}$ as solvent; the ^{1}H and ^{13}C chemical shifts are reported in ppm relative to tetramethylsilane or the deuterated solvent as an internal reference. Mass spectra were run on a Kratos MS50TC and a Kratos Mach III data system. The ion source temperature was 150–250 °C, as required. High-resolution EI-mass spectra were performed with a resolution of 10,000. The low-resolution spectra were taken with a HP5989A MS instrument. For the chromatography, analytical TLC plates [Alugram SIL G/UV$_{254}$ and 70–230 mesh silicagel (Merck)] were used. The absorption measurements were performed on a Perkin Elmer Lambda 6 UV/vis spectrophotometer. Up to six indicator concentrations were used for the determination of the molar absorption coefficients, ε, of each indicator. Corrected steady-state excitation and emission spectra were recorded on a SPEX Fluorolog-3. Fluorescence quantum yields of the free and bound forms of indicators were determined using acridine yellow in methanol and quinine bisulfate in 0.1 N sulfuric acid as references. The fluorescence quantum yields of these references were taken to be 0.57 for acridine yellow in methanol,[14] and 0.50 in 0.1 N sulfuric acid for quinine bisulfate.[15] The buffered (pH 7.05) solutions of the uncomplexed form of the indicators all contained 100 mM KCl and 10 mM MOPS. In addition, **5a** and **5c** contained 10 mM nitrilotriacetic acid, whereas the **5b**, **5d** and **9** solutions contained 6.5 mM nitrilotriacetic acid. The indicator concentration was chosen so that the absorbance at the excitation wavelength never exceeded 0.1. All aqueous solutions were prepared with Milli-Q water. All measurements were done at 21 °C.

4.2. Synthesis

4.2.1. General procedure for the synthesis of the bithiophene compounds 4a–d. Dry toluene (20 mL) was added by a syringe to a mixture of 2,2′-bithiene-5, 5′-diylbis(tributylstannane) **2** (1.3 mmol), the corresponding aryl bromide **3a–d** (1.3 mmol), dimethyl 2,2′-{[4-bromo-2-(2-methoxy-2-oxoethoxy)phenyl]imino}-diacetate **1** (1.3 mmol), and $Pd(PPh_3)_4$ (0.065 mmol) under nitrogen atmosphere. The resulting mixture was first stirred at 80 °C for 3 h, and then at 120 °C for 2 h. The precipitate was filtered off and washed with dichloromethane. The solvent was evaporated and the residue was subjected to column chromatography using 40% ethyl acetate in hexane as eluent, followed by HPLC using the same eluent to get analytically pure compounds **4a–d** as solids (in 11–19% yield), after recrystallisation from a mixture of ethyl acetate and hexane. For TLC analysis, compounds **4a–d** have R_f values of 0.2–0.3 (EtOAc/hexane: 40:60).

4.2.1.1. Dimethyl 2,2′-{[2-(2-methoxy-2-oxoethoxy)-4-(5′-phenyl-2,2′-bithien-5-yl)phenyl]imino}diacetate 4a. The title compound was prepared in 14% yield as crystals. Mp 125–126 °C; IR ν_{max}^{KBr} (cm^{-1}) 3075, 3000, 2951, 2917, 1733, 1604, 1495, 1428, 1269, 1219, 1186, 1060, 1010, 960, 851, 801, 760; ^{1}H NMR δ 7.60 (d, J=7.32 Hz, 2H), 7.38 (t, J=7.30 Hz, 2H), 7.30–7.08 (m, 6H), 7.04 (d, J=1.83 Hz, 1H), 6.89 (d, J=8.42 Hz, 1H), 4.72 (s, 2H), 4.23 (s, 4H), 3.81 (s, 3H), 3.74 (s, 6H); ^{13}C NMR δ 171.5 (2× COO), 169.1 (COO), 149.6 (C), 142.9 (C), 142.7 (C), 139.2 (C), 136.7 (C), 136.0 (C), 134.0 (C), 128.9 (2×CH), 128.45 (C), 127.5 (CH), 125.6 (2×CH), 124.4 (CH), 124.3 (CH), 123.8 (CH), 123.1 (CH), 120.2 (CH), 119.9 (CH), 112.5 (CH); 66.3 (CH_2O), 53.6 (2×CH_2N), 52.2 (CH_3O), 51.8 (2×CH_3O); HRMS calcd for $C_{29}H_{27}NO_7S_2$ [$M^{+\cdot}$] 565.1229, found 565.1218.

4.2.1.2. Dimethyl 2,2′-{[4-[5′-(4-fluorophenyl)-2,2′-bithien-5-yl]-2-(2-methoxy-2-oxoethoxy)phenyl]imino}-diacetate 4b. The title compound was synthesized in 11% yield as crystals. Mp 115 °C; IR ν_{max}^{KBr} (cm^{-1}) 3076, 3011, 2953, 1739, 1437, 1178, 1067, 1010, 838, 795; ^{1}H NMR δ 7.57 (m, 2H), 7.38–7.04 (m, 8H), 6.89 (d, J=9.36 Hz, 1H), 4.72 (s, 2H), 4.23 (s, 4H), 3.81 (s, 3H), 3.74 (s, 6H); ^{13}C NMR δ 171.5 (2×COO), 169.1 (COO), 162.3 (C), 149.6 (C), 142.7 (C), 141.7 (C), 139.2 (C), 136.7 (C), 135.8 (C), 130.3 (C), 128.5 (C), 127.2 (2×CH), 124.4 (CH), 124.3 (CH), 123.7 (CH), 123.6 (CH), 120.2 (CH), 119.9 (CH), 115.9 (2×CH), 112.4 (CH), 66.3 (CH_2O), 53.5 (2×CH_2N), 52.2 (CH_3O), 51.8 (2×CH_3O); HRMS calcd for $C_{29}H_{26}NO_7S_2F$ [$M^{+\cdot}$] 583.1135, found 583.1143.

4.2.1.3. Dimethyl 2,2′-{[4-[5′-(4-methoxyphenyl)-2,2′-bithien-5-yl]-2-(2-methoxy-2-oxoethoxy)phenyl]imino}-diacetate 4c. The title compound was synthesized in 19% yield as crystals. Mp 127–128 °C; IR ν_{max}^{KBr} (cm^{-1}) 2955, 1746, 1603, 1500, 1440, 1249, 1175, 1072, 1026, 830, 794; ^{1}H NMR δ 7.51 (d, J=8.79 Hz, 2H), 7.17 (dd, J=8.43 Hz, 1.83, 1H), 7.08 (m, 4H), 7.03 (d, J=2.19 Hz, 1H), 6.89 (t, J=8.40, 7.32 Hz, 3H), 4.71 (s, 2H), 4.23 (s, 4H), 3.83 (s, 3H), 3.81 (s, 3H), 3.73 (s, 6H); ^{13}C NMR δ 171.5 (2× COO), 169.1 (COO), 159.3 (C), 149.6 (C), 143.0 (C), 142.4 (C), 139.1 (C), 136.2 (C), 135.7 (C), 128.6 (C), 126.9 (C), 126.8 (2×CH), 124.3 (CH), 124.1 (CH), 123.0 (CH), 122.7 (CH), 120.1 (CH), 119.9 (CH), 114.3 (2×CH), 112.4 (CH), 66.3 (CH_2O), 55.3 (OCH_3), 53.5 (2×CH_2N), 52.2 (CH_3O), 51.8 (2×CH_3O); HRMS calcd for $C_{30}H_{29}NO_8S_2$ [$M^{+\cdot}$] 595.1335, found 590.1320.

4.2.1.4. Dimethyl 2,2′-{[2-(2methoxy-2-oxoethoxy)-4-[5′-(4-nitrophenyl)-2,2′-bithien-5-yl]phenyl]imino}di-acetate 4d. The title compound was prepared in 15% yield as crystals. Mp 151–152 °C; IR ν_{max}^{KBr} (cm^{-1}) 2954, 1747, 1595, 1514, 1448, 1337, 1278, 1210, 1176, 1067, 1008, 848, 793; ^{1}H NMR δ 8.22 (d, J=8.79 Hz, 2H, C_6H_4), 7.69 (d, J=8.79 Hz, 2H, C_6H_4), 7.38 (d, J=4 Hz, 1H, C_4H_2S), 7.17 (m, 3H, 2×C_4H_2S, C_6H_3), 7.10 (d, J=4 Hz, 1H, C_4H_2S), 7.04 (d, J=1.83 Hz, 1H, C_6H_3), 6.89 (d, J=8.43 Hz, 1H, C_6H_3), 4.72 (s, 2H, $O\mathit{CH}_2CO_2CH_3$), 4.24 (s, 4H, $N(\mathit{CH}_2CO_2CH_3)_2$), 3.81 (s, 3H, $OCH_2CO_2\mathit{CH}_3$), 3.74 (s, 6H, $N(CH_2CO_2\mathit{CH}_3)_2$); ^{13}C NMR δ 171.5 (2× $N(CH_2\mathit{C}OOCH_3)_2$), 169.1 ($OCH_2\mathit{C}OOCH_3$), 149.6, 139.5, 128.1, 120.3, 119.8, 112.5 (C_6H_3), 146.4, 140.1, 2×125.4, 2×124.4, (C_6H_4), 143.8, 139.8, 139.4, 135.0, 126.5, 125.3, 124.6, 123.2 (2×C_4H_2S), 66.3 ($O\mathit{C}H_2COOCH_3$), 53.5 (2×$N(\mathit{C}H_2COOCH_3)_2$), 52.2 ($OCH_2COO\mathit{C}H_3$), 51.8 (2×$N(CH_2COO\mathit{C}H_3)_2$); HRMS calcd for $C_{29}H_{26}N_2O_9S_2$ [$M^{+\cdot}$] 610.1080, found 610.1079.

4.2.2. The terthiophene compound dimethyl 2,2′-{[2-(2-methoxy-2-oxoethoxy)-4-(5″-nitro-2,2′;5′2″-terthien-5-yl-)phenyl]imino}diacetate 8. Dry toluene (15 mL) was added by a syringe to a mixture of 2,2′-bithiene-5, 5′-diylbis(tributylstannane) **2** (0.745 g, 1 mmol), 2-bromo-5-nitrothiophene **6** (0.208 g, 1 mmol), and $Pd(PPh_3)_4$ (0.058 g, 0.05 mmol) under nitrogen atmosphere. The resulting mixture was stirred at 80 °C for 3 h. After cooling to room temperature, dimethyl 2,2′-{[4-bromo-2-(2-methoxy-2-oxoethoxy)phenyl]imino}diacetate **1** (0.404 g, 1 mmol) was added and the resulting mixture was further heated at 120 °C for 2 h. The precipitate was filtered off and washed with dichloromethane. The solvent was evaporated and the residue was subjected to column chromatography using 40% ethyl acetate in hexane as eluent, followed by HPLC using the same eluent to get analytically pure compound **8** (0.099 g, 16% yield) as a solid (needles), after recrystallisation from a mixture of ethyl acetate and hexane.

Mp 144–145 °C; IR ν_{max}^{KBr} (cm^{-1}) 2956, 1746, 1604, 1504, 1430, 1325, 1210, 1178, 1076, 1010, 794; ^{1}H NMR (300 MHz) δ 7.85 (d, J=4 Hz, 1H, C_4H_2S), 7.27 (d, J=5.77 Hz, 1H, C_4H_2S), 7.18 (m, 2H, C_4H_2S), 7.11 (m, 2H, C_4H_2S), 7.06 (m, 2H, C_6H_3), 6.89 (d, J=8.41 Hz, 1H, C_6H_3), 4.72 (s, 2H, $O\mathit{CH}_2CO_2CH_3$), 4.24 (s, 4H, $N(\mathit{CH}_2CO_2CH_3)_2$), 3.81 (s, 3H, $OCH_2CO_2\mathit{CH}_3$), 3.74 (s, 6H, $N(CH_2CO_2\mathit{CH}_3)_2$); ^{13}C NMR (75 MHz) δ 171.5 (2×$N(CH_2\mathit{C}OOCH_3)_2$), 169.1 ($OCH_2\mathit{C}OOCH_3$), 149.6 ($C_4H_2S$ C–NO_2), 149.0 (C_6H_3 C–O), 144.9 (C_6H_3 C–N), 144.3 (C), 140.2 (C), 139.6 (C), 134.5 (C), 133.0 (C), 129.8 (C), 128.0 (CH), 127.5 (CH), 125.7 (CH), 124.4 (CH), 123.3 (CH), 122.1 (CH), 120.4 (CH), 119.8 (CH), 112.6 (CH)

($3\times C_4H_2S$ and C_6H_3), 66.3 (O*C*H_2COOCH_3), 53.5 ($2\times N(CH_2COOCH_3)_2$), 52.2 (OCH_2COOCH_3), 51.8 ($2\times N(CH_2COOCH_3)_2$); HRMS calcd for $C_{27}H_{24}N_2O_9S_3$ [$M^{+\cdot}$] 616.0644, found 616.0666.

4.2.3. Hydrolysis of the APTRA ester derivatives. The Cs salts were prepared in situ from compounds **4a–d** and **8** according to a published procedure.[11] A solution of the methyl ester (approximately 10^{-5} mol) and anhydrous CsOH (approximately 10^{-4} mol) in methanol (3 mL) was refluxed overnight. After evaporation of the methanol, the product was dissolved in water (100 mL) and used for the fluorescence measurements.

Acknowledgements

N.A. wishes to thank Professor Dr. S. Icli for his support. A.K. and S.S.S. are grateful to the DWTC (Belgium) for a postdoctoral fellowship. The authors are grateful to the University Research Fund of the K.U. Leuven for IDO-grant IDO/00/001 and to the FWO for grant G.0320.00. The DWTC through IAP-V-03 is thanked for continuing support.

References and notes

1. Otten, P. A.; London, R. E.; Levy, L. A. *Bioconjugate Chem.* **2001**, *12*, 76–83.
2. Tsien, R. Y. *Biochemistry* **1980**, *19*, 2396–2404.
3. Haugland, R. P. *The Handbook. A Guide to Fluorescent Probes and Research Labeling Technologies*, 10th ed.; Molecular Probes: Eugene (Oregon), 2005.
4. Cielen, E.; Stobiecka, A.; Tahri, A.; Hoornaert, G. J.; De Schryver, F. C.; Gallay, J.; Vincent, M.; Boens, N. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1197–1206.
5. Avcibaşi, N.; Smet, M.; Metten, B.; Dehaen, W.; De Schryver, F. C.; Bultynck, G.; Callewaert, G.; De Smedt, H.; Missiaen, L.; Boens, N. *Int. J. Photoenergy* **2004**, *6*, 159–167.
6. (a) Parker, I.; Choi, J.; Yao, Y. *Cell Calcium* **1996**, *20*, 105–121. (b) Eilers, J.; Callewaert, G.; Armstrong, C.; Konnerth, A. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 10272–10276. (c) Rajdev, S.; Reynolds, I. *J. Neurosci. Lett.* **1993**, *162*, 149–152. (d) Konishi, M.; Hollingworth, S.; Harkins, A. B.; Baylor, S. M. *J. Gen. Physiol.* **1991**, *97*, 271–301. (e) Zhao, M.; Hollingworth, S.; Baylor, S. M. *Biophys. J.* **1996**, *70*, 896–916.
7. (a) Hirose, K.; Iino, M. *Nature* **1994**, *372*, 791–794. (b) van de Put, F. H.; De Pont, J. J.; Willems, P. H. *J. Biol. Chem.* **1994**, *269*, 12438–12443. (c) Sugiyama, T.; Goldman, W. F. *Am. J. Physiol. Cell Physiol.* **1995**, *269*, C698–C705. (d) Golovina, V. A.; Blaustein, M. P. *Science* **1997**, *275*, 1643–1648.
8. Metten, B.; Smet, M.; Boens, N.; Dehaen, W. *Synthesis* **2005**, 1838–1844.
9. Miller, L. L.; Yu, Y. *J. Org. Chem.* **1995**, *60*, 6813–6819.
10. Babasinian, V. S. *J. Am. Chem. Soc.* **1935**, *57*, 1763–1764.
11. Grynkiewicz, G.; Poenie, M.; Tsien, R. Y. *J. Biol. Chem.* **1985**, *260*, 3440–3450.
12. Fabiato, A.; Fabiato, F. *J. Physiol. (Paris)* **1979**, *75*, 463–505.
13. Schoenmakers, T. J. M.; Visser, G. J.; Flik, G.; Theuvenet, A. P. R. *Bio Techniques* **1992**, *12*, 870–872 see also pp 874, 876, 878–879.
14. Olmsted, J. *J. Phys. Chem.* **1979**, *83*, 2581–2584.
15. Dawson, W. R.; Windsor, M. W. *J. Phys. Chem.* **1968**, *72*, 3251.

Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron 62 (2006) 691–705

Tetrahedron

Complete settlement of long-standing confusion on the term 'prochirality' in stereochemistry. Proposal of pro-*RS*-stereogenicity and integrated treatment with prochirality

Shinsaku Fujita*

Department of Chemistry and Materials Technology, Kyoto Institute of Technology, Matsugasaki, Sakyoku, Kyoto 606-8585, Japan

Received 29 August 2005; accepted 4 October 2005

Abstract—Long-standing confusion on the term 'prochirality' in stereochemistry has been analyzed by a critical review on the definitions described in the IUPAC recommendations 1996 (*Pure Appl. Chem.*, **1996**, 68, 2193). Thereby, the confusion has been clarified to come from the fact that the scope and limitations of the terms 'enantiotopic', 'diastereotopic', and 'stereoheterotopic' are not so fully specified to discriminate between prochirality and prostereogenicity. Entangled situations due to the confusion have been avoided by abstracting the concept of pro-*RS*-stereogenicity from the conventional 'prostereogenicity' on the same line as the concept of *RS*-stereogenicity was separated from the conventional 'stereogenicity' (S. Fujita, *J. Org. Chem.*, **2004**, 69, 3158). This abstraction, which has been based on stereoisograms and *RS*-stereoisomeric groups, has provided us with a systematic approach for investigating the relationship between the prochirality and the pro-*RS*-stereogenicity. Thus, the prochirality and the pro-*RS*-stereogenicity can be discussed in terms of a common theoretical framework, that is, coset representations of *RS*-stereoisomeric groups, where the conventional terms on topicities are replaced by unambiguous terms on sphericities (homospheric, enantiospheric, and hemispheric) and *RS*-tropicities (*RS*-homotropic, *RS*-enantiotropic, and *RS*-hemitropic). Moreover, the pro-*RS*-stereogenicity defined in the present paper has been correlated to the capability of designating *pro-R*/*pro-S* descriptors without any ambiguity. Thereby, the long-standing confusion on the term 'prochirality' has been settled completely.

1. Introduction

The term 'prochirality' was proposed to specify (non)-equivalency of ligands[1] in accord with the term 'chirality' used in the original version of the CIP system.[2] Although the term 'chirality' was replaced by the term 'stereogenicity' in the revised CIP system[3] and although the usage of 'prochirality' with reference to prostereoisomerism was suggested to be altogether abondoned,[4] the term 'prochirality' has still been used even in cases that should be specified by the term 'prostereogenicity' or 'prostereoisomerism'. In fact, the term 'prochirality' is used in different, sometimes contradictory ways, as the IUPAC Recommendations 1996 on 'Basic Terminology of Stereochemistry' has pointed out.[5] Even in textbooks on stereochemistry,[6–8] one cannot find a common and convincing view on how the terms 'prochiral' and 'prostereogenic' are different.

In the present article, we will propose a novel approach to use the term 'prochirality' purely geometrically on the same line as the term 'chirality' is used in such a purely geometrical fashion as different from the term 'stereogenicity'. For this purpose, the concept of pro-*RS*-stereogenicity will be proposed to deepen discussions on stereochemical equivalency, where the concepts of holantimers and stereoisograms proposed for discussing stereoisomerism[9] will be extended and applied to intramolecular stereochemistry. This approach will provide a consistent way to settle the entangled situations between 'prochirality' and 'prostereogenic' (or 'prostereoisomerism') as well as to give a more systematic foundation to descriptors *pro-R*/*pro-S*.

2. Backgrounds and problem setting

2.1. Prochirality versus prostereogenicity

Rule P91.1.1.1.1 of the IUPAC Provisional Recommendations 2004 describes 'At least one stereogenic unit must be present in every enantiomer; however, conversely, the presence of stereogenic units does not require the corresponding molecular entity to be chiral.'[10] Thus the state-of-the-art terminology conceptually differentiates the term 'stereogenicity' from the term 'chirality' but gives

---

Keywords: Prochirality; Pro-*RS*-stereogenicity; Chirality; Stereogenicity; Stereoisogram.
E-mail address: fujitas@chem.kit.ac.jp
* *URL*: http://imt.chem.kit.ac.jp/fujita/fujitas/fujita.html

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.10.016

no convincing descriptions about how the two terms are different or overlapped. The unsettled discrimination between the two terms leaves such derived terms as ‘prochirality’ and ‘prostereogenicity’ (‘prostereoisomerism’) still suspended in more entangled situations. Among the four ways which the IUPAC Recommendations 1996 listed as different, sometimes contradictory ways in the usage of the term ‘prochirality’,[5] a representative definition is cited below:

> The term prochiral also applied to a tetrahedral atom of an achiral or chiral molecule, which is bonded to two stereoheterotopic groups.
>
> **Case 1**. For example, the prochiral molecule CH_3CH_2OH can be converted into the chiral molecule CH_3CHDOH by isotopic replacement of one of the two enantiotopic hydrogen atoms of the methylene group. The carbon atom of the methylene group is called prochiral.
>
> **Case 2**. The prochiral molecule $HOCH(CH_2COOH)_2$ can be converted into a chiral product by esterification of one of the two enantiotopic CH_2COOH groups. The carbon atom of the CHOH group is called prochiral.
>
> **Case 3**. The chiral molecule $CH_3CHOHCH_2CH_3$ can be converted into one of the diastereoisomers of $CH_3CHOHCHDCH_3$ by the isotopic replacement of one of the two *diastereotopic* hydrogen atoms of the methylene group. The carbon atom of the methylene group is called prochiral.
>
> The stereoheterotopic groups in these cases may be described as *pro-R* or *pro-S*. Reference to the two stereoheterotopic groups as prochiral, although common, is strongly discouraged. See *chirality center*. [Itemized and Underlined by the author.]

In order to avoid confusion, the prochirality connoting all of Cases 1–3 is referred to as ‘prochirality (IUPAC)’ or simply ‘prochirality(I)’, which is linked with the ‘stereoheterotopicity’ described above.

Case 3 uses the term ‘diastereomers’ in connection with the term ‘diastereotopic’. Because diastereomers are defined as stereoisomers that are not enantiomers, the term ‘diastereomers’ connotes various kinds of stereoisomers (e.g., straight-chained stereoisomers such as sugars, *cis–trans* isomers of alkenes or cycloalkanes (or heteroanalogs)). It follows that the term *diastereotopic* connotes various kinds of stereoheterotopic relationships other than enantiotopic relationships. Hence, it is necessary to develop a logical framework for classifying such diastereotopic relationships into theoretically meaningful subsets in order to provide stereochemistry with a more systematic format.

2.2. Enantiotopicity, diastereotopicity, and stereoheterotopicity

The ‘prochirality(I)’ is concerned with the capability of describing *pro-R* or *pro-S*. This is called here *pro-R*/*pro-S-discriminability*. For the sake of consistent terminology, a single criterion for determining the *pro-R*/*pro-S*-discriminability should be established. As found easily by the inspection of Cases 1–3, this has been ascribed to ‘stereoheterotopicity’ according to IUPAC recommendations 1996. However, it must be clarified whether or not the stereoheterotopicity of Cases 1 and 2 (i.e., ‘enantiotopicity’) is the same as the term *enantiotopicity* which is defined geometrically as follows:

Definition 1. The term *enantiotopic* is referred to constitutionally identical atoms or groups in molecules which are related by symmetry elements of the second kind only (mirror plane, inversion center or rotation-reflection axis).[5]

If the stereoheterotopicity of Case 2 (i.e., ‘enantiotopicity’) were the same as the term *enantiotopicity* of Definition 1, the IUPAC recommendation 1996 would involve an inconsistency shown in Figure 1.

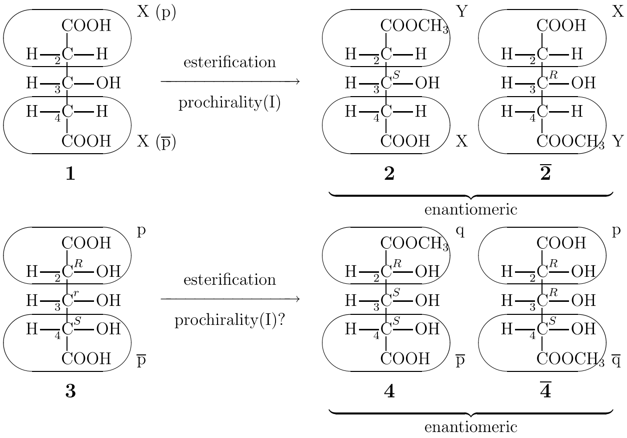


Figure 1. Conversions of achiral molecules into enantiomers: 3-hydroxyglutaric acid (**1**) and a *meso*-2,3,4-trihydroxyglutaric acid (**3**).

(1) The two ligands CH_2COOH of $HOCH(CH_2COOH)_2$ (**1**) described in Case 2 are enantiotopic according to Definition 1. Because the stereoheterotopicity of Case 2 (i.e., ‘enantiotopicity’) is regarded as the same as the term *enantiotopicity* of Definition 1, the central atom of **1** is concluded to be prochiral(I) according to the IUPAC recommendations 1996. The achiral **1** is literally (or geometrically) prochiral so as to generate enantiomers (i.e., **2** and/or $\overline{\mathbf{2}}$) under chiral environments (e.g., the action of a chiral reagent as a hypothetical esterification agent), as shown in Figure 1.

(2) On the other hand, the *R*-CH(OH)COOH ligand (p) and the *S*-CH(OH)COOH ligand ($\overline{\mathrm{p}}$) in **3** are enantiotopic in terms of Definition 1. As found easily, the achiral **3** generates enantiomers (i.e., **4** and/or $\overline{\mathbf{4}}$) under chiral environments (e.g., the action of a chiral reagent as a hypothetical esterification agent). Because the reaction of **1** producing the enantiomers (**2** and/or $\overline{\mathbf{2}}$) is correlated to the prochirality(I) of **1**, the same type of reaction of **3** producing the enantiomers (**4** and/or $\overline{\mathbf{4}}$) should be referred to as prochiral(I) so long as the stereoheterotopicity of Case 2 (i.e., ‘enantiotopicity’) is regarded as the same as the term *enantiotopicity* of Definition 1.

(3) On the contrary to the conclusion described in the preceding paragraph, **3** is presumed not to be prochiral(I), because **3** is stereogenic, as designated by the *r*-configuration of the 3-carbon atom. As a result, a ‘prochiral(I)’ carbon in **3** (cf. the underlined sentences

in the IUPAC recommendations 1996) would be concluded to be a 'stereogenic' carbon.

It follows that the stereoheterotopicity of Case 2 (i.e., 'enantiotopicity') disregards the enantiotopicity in **3**, which stems from the geometrical definition (Definition 1). In other words, the 'enantiotopicity' due to the stereoheterotopicity of Case 2 is different from the term *enantiotopicity* of Definition 1.

Obviously, the IUPAC recommendations 1996 have avoided the difficulty shown in Figure 1 by adding the word may in the expression 'The stereoheterotopic groups in these cases may be described as *pro-R* or *pro-S*.' Thereby, the case of **3** is apparently excluded as an exceptional one. However, the inconsistency that the stereoheterotopicity of Case 2 (i.e., 'enantiotopicity') is different from the term *enantiotopicity* of Definition 1 still remains unsolved.

Another way to avoid the difficulty shown in Figure 1 is to change the definition of the term *enantiotopic* as follows:

Definition 2. Enantiotopic ligands (p. 1198 of Ref. 6): Homomorphic ligands in constitutionally equivalent locations that are related by a symmetry plane (or center or alternating axis of symmetry) but not by a (simple) symmetry axis. Replacement of one or the other enantiotopic ligand by a new ligand produces enantiomers. See also heterotopic.

Compare the expression 'constitutionally identical atoms or groups' in Definition 1 with the expression 'homomorphic ligands in constitutionally equivalent locations' in Definition 2. Because the term 'homomorphic ligands' (p 1200 of Ref. 6) is defined as ligands that are structurally (including configurationally) identical when detached, the *R*-CH(OH)COOH ligand (p) and the *S*-CH(OH)COOH ligand ($\bar{p}$) in **3** are concluded not to be enantiotopic (nor diastereotopic) in terms of Definition 2. Thus, the case of **3** shown in Figure 1 is excluded by equalizing Definition 2 to the stereoheterotopicity of Case 2 (i.e., 'enantiotopicity'). However, Definition 2 is inconsistent to the fact that the reactions of **1** and **3** shown in Figure 1 belong to the same category.

Moreover, the settlement by adopting Definition 2 has an essential drawback. Compare the pair of two carboxyl groups in **1** with the pair of two carboxyl groups in **3**. Each pair is regarded as enantiotopic even in terms of Definition 2 (of course in terms of Definition 1). It follows that, by the change of viewpoints, the adoption of Definition 2 results in the same inconsistency as described for Definition 1.

As found in the preceding discussions, the stereoheterotopicity of Cases 1 and 2 (i.e., 'enantiotopicity') as a single criterion for determining *pro-R*/*pro-S*-discriminability is different from the term *enantiotopicity* of Definition 1. Thus, the unconscious and erroneous equalization of the stereoheterotopicity of Cases 1 and 2 (i.e., 'enantiotopicity') to the term *enantiotopicity* of Definition 1 is found to be a source of confusion concerning 'prochirality(I)'.

Even without the counter examples shown in Figure 1, the use of the word may in the IUPAC recommendations 1996 means that the term 'stereoheterotopic groups' (i.e., 'enantiotopic groups' for Cases 1 and 2 or 'diastereotopic groups' for Case 3) implies the presence of two types, that is, *pro-R*/*pro-S*-discriminable ones and *pro-R*/*pro-S*-undiscriminable ones. However, no concrete methods are described to differentiate them. In other words, there is no explicit criterion for determining whether given stereoheterotopic groups are differentiated or not by the *pro-R*/*pro-S*-descriptors.

2.3. Symmetry operations versus permutations

In the preceding discussions, we have followed the conventional terminology of stereochemistry, which is descriptive in nature. This way has provided us with some sense of frustration, because the conventional terminology has been based on a multiple accumulation of definition terms, which tends to suffer from verbal transmutation, as pointed out by Mislow.[11] The above-described equalization of the stereoheterotopicity of Cases 1 and 2 (i.e., 'enantiotopicity') to the term enantiotopicity of Definition 1 and the change of Definition 1 into Definition 2 are typical examples of such verbal transmutation.

To proceed to further discussions, a more systematic approach is necessary, where such inner structures as chirality/achirality of ligands is properly taken into consideration. This means that symmetry operations such as rotoreflections (improper rotations) are strictly differentiated from permutabilities. According to this guideline, we shall reexamine the examples shown in Figure 1 with adding related examples.

Let us represent the hydroxyl group (OH), the hydrogen atom, and the two carboxylmethyl ligands on the central atom of **1** by the symbols A, B, and X, respectively, in order to extend the cases shown in Figure 1 into general cases. Thereby, the formula **1** is converted into a simplified formula (**5**), as shown in the top row of Figure 2. On the same line, the formula **6** is obtained from **2** by placing p=*R*-CH(OH)COOH and $\bar{p}$=*S*-CH(OH)COOH, as shown in the second row of Figure 2. The molecule of Case 3 is represented as **8** by placing A=OH, placing p=*R*-CH(OH)CH_3 ($\bar{p}$=*S*-CH(OH)CH_3), and X=H, as shown in the third row of Figure 2.

The effect of inner structures, that is, chirality/achirality of ligands, can be demonstrated by comparing a permutation $\tilde{\sigma}_{d(2)}$ ($\sim$(1)(2)(3 4)) with a rotoreflection $\sigma_{d(2)}$ ($\sim$(1)(2)(3 4)). The difference between $\tilde{\sigma}_{d(2)}$ and $\sigma_{d(2)}$ is illustrated by taking **5** and **6** as examples:

(1) The permutation $\tilde{\sigma}_{d(2)}$ ($\sim$(1)(2)(3 4)) is referred to as an *RS-skeletal permutation* because it contains no rotoreflections of ligands. This operation is represented by the symbol (○).
   (a) The two Xs detached from positions 3 and 4 are interchanged by the operation of $\tilde{\sigma}_{d(2)}$ so that **5** is converted into itself.
   (b) The same permutation $\tilde{\sigma}_{d(2)}$ ($\sim$(1)(2)(3 4)) converts **6** into **7**, where the two molecules **6** and **7** are conventionally regarded as diastereomers.

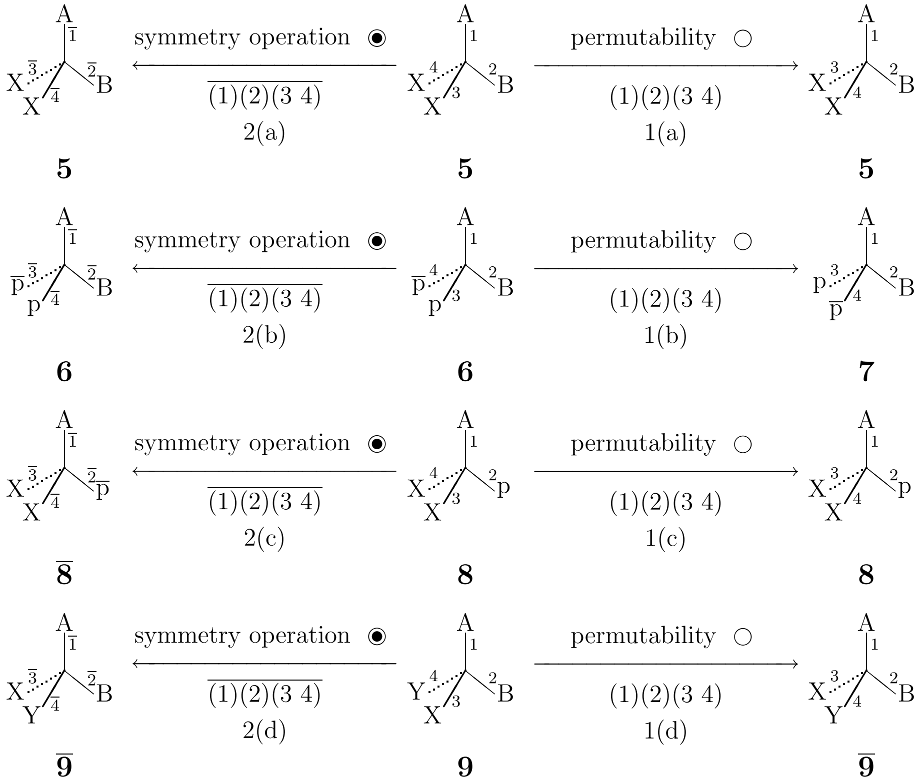


Figure 2. Symmetry operations versus permutations.

   (c) The same permutation $\tilde{\sigma}_{d(2)}$ ($\sim$(1)(2)(3 4)) converts **8** into itself, where the two Xs detached from positions 3 and 4 are interchanged by the operation of $\tilde{\sigma}_{d(2)}$.
   (d) The same permutation $\tilde{\sigma}_{d(2)}$ ($\sim$(1)(2)(3 4)) converts **9** into its enantiomer $\bar{\mathbf{9}}$, where the X and the Y detached from positions 3 and 4 are interchanged by the operation of $\tilde{\sigma}_{d(2)}$.

(2) The rotoreflection $\sigma_{d(2)}$ ($\sim\overline{(1)(2)(3\ 4)}$) contains alternation of ligand chirality. The overline of the symbol $\overline{(1)(2)(3\ 4)}$ represents that each chiral ligand in isolation is converted into its enantiomeric one in isolation (i.e., an inner rotoreflection). This operation is symbolized as (◉), where the open circle (○) represents the permutation of the tetrahedral skeleton and the solid circle (●) represents the inner rotoreflection of the ligands.
   (a) By operating the rotoreflection $\sigma_{d(2)}$ ($\sim\overline{(1)(2)(3\ 4)}$) onto the molecule (**5**), we obtain the corresponding mirror image ($\bar{\mathbf{5}}$) that is superposable onto the original molecule (**5**). In this case, however, the effect of inner rotoreflections is concealed because the ligands in **5** are all achiral in isolation. Thus, the rotoreflection $\sigma_{d(2)}$ converts A, B, and X into the corresponding mirror images $\bar{A}$, $\bar{B}$, and $\bar{X}$, where the pair of A/$\bar{A}$ (or B/$\bar{B}$, or X/$\bar{X}$) is conceptually differentiated but is equalized as being $A=\bar{A}$, $B=\bar{B}$, or $X=\bar{X}$ because of their achiralities.
   (b) By operating the rotoreflection $\sigma_{d(2)}$ ($\sim\overline{(1)(2)(3\ 4)}$) onto the molecule (**6**), we can obtain the corresponding mirror image ($\bar{\mathbf{6}}$) that is superposable onto the original molecule (**6**).
   (c) By operating the rotoreflection $\sigma_{d(2)}$ ($\sim\overline{(1)(2)(3\ 4)}$) onto the molecule (**8**), we can obtain the corresponding mirror-image molecule ($\bar{\mathbf{8}}$) that is enantiomeric to the original molecule (**8**).
   (d) The rotoreflection $\sigma_{d(2)}$ ($\sim\overline{(1)(2)(3\ 4)}$) converts the molecule (**9**) into its enantiomer ($\bar{\mathbf{9}}$), where we place $A=\bar{A}$, $B=\bar{B}$, $X=\bar{X}$, and $Y=\bar{Y}$ because of their achiralities.

By the analyses described above, the stereoheterotopicity of Case 3 (i.e., 'diastereotopicity') comes from the skeletal permutation process 1(c), where the corresponding operation $\tilde{\sigma}_{d(2)}$ ($\sim$(1)(2)(3 4)) is not related to Definition 1. If one pursues a single criterion for *pro-R*/*pro-S* descriptors, one should select the skeletal permutation process 1(a) for the stereoheterotopicity of Cases 1 and 2 because both the processes 1(a) and 1(c) belong to skeletal permutation processes. The conventional terminology has selected a way in which it regards the skeletal permutation process 1(a) as 'enantiotopic' because the geometrical process 2(a) and the skeletal permutation process 1(a) occasionally give the same effect as shown in the top row of Figure 2. In other words, the inconsistency for the 'stereoheterotopicity' of the IUPAC recommendations 1996 stems from the unconscious equalization of the rotoreflection $\sigma_{d(2)}$ ($\sim\overline{(1)(2)(3\ 4)}$) to the *RS*-skeletal permutation $\tilde{\sigma}_{d(2)}$ ($\sim$(1)(2)(3 4)) in terms of the occasional results of the process 2(a) and the process 1(a) (the top row of Fig. 2).

The unconscious equalization can be alternatively explained as follows. The conventional term 'stereoheterotopicity' can be expressed as a mixed operation of '$\sigma_{d(2)}+\tilde{\sigma}_{d(2)}+$ other operations', although the effective operation for the *pro-R*/*pro-S*-nomenclature is $\tilde{\sigma}_{d(2)}$. From the mixed operation, the operation $\sigma_{d(2)}$ is presumed to be adopted—even though $\tilde{\sigma}_{d(2)}$ is actually operated—in the first step for determining the enantiotopicity of Cases 1 and 2; and then the operation $\sigma_{d(2)}$ is switched to $\tilde{\sigma}_{d(2)}$ in the next step for comparing Cases 1 and 2 with Case 3. By the use of the term 'stereoheterotopicity', one is unconsciously forced to disregard whether $\sigma_{d(2)}$ or $\tilde{\sigma}_{d(2)}$ is selected from the mixed operation ('$\sigma_{d(2)} + \tilde{\sigma}_{d(2)} +$ other operations') in the first step for referring to the enantiotopicity of Cases 1 and 2. Thus, the mixing-up of $\sigma_{d(2)}$ and $\tilde{\sigma}_{d(2)}$ is concealed by the coinage of the term 'stereoheterotopicity'.

A similar equalization appears between the process 2(d) and the process 1(d), because these processes convert the molecule **9** into the same enantiomer ($\bar{\mathbf{9}}$), as shown in the bottom row of Figure 2. In the conventional stereochemistry, this equalization causes confusion concerning pseudo-asymmetry, as pointed out in a recent paper.[12] It should be noted that the ligands A, B, X, and Y are converted conceptually into self-enantiomeric ligands, that is, $\bar{\mathrm{A}}$, $\bar{\mathrm{B}}$, $\bar{\mathrm{X}}$, and $\bar{\mathrm{Y}}$ in the process 2(d). After this conceptual alteration of (a)chirality, we place $\mathrm{A} = \bar{\mathrm{A}}$, $\mathrm{B} = \bar{\mathrm{B}}$, $\mathrm{X} = \bar{\mathrm{X}}$, and $\mathrm{Y} = \bar{\mathrm{Y}}$ to characterize the process 2(d). This feature is compared with the different feature of the process 1(d), which is not accompanied with such conceptual chirality alteration of ligands. The different features result in special effects of the process 2(b) and the process 1(b) for the ligand set, A, B, p, and $\bar{\mathrm{p}}$. Thus, the difference between the process 2(b) and the process 1(b) is ascribed to the pseudoasymmetry of the molecule **6**.

The analyses on the examples listed in Figure 2 show that the discrimination between symmetry operations (e.g., $\sigma_{d(2)}$) and permutations (e.g., $\tilde{\sigma}_{d(2)}$) is a key to revise the 'prochirality(I)' into a more logical format. The construction of such a more logical format is the task we shall pursue in the next section.

3. *RS*-Stereoisomerism

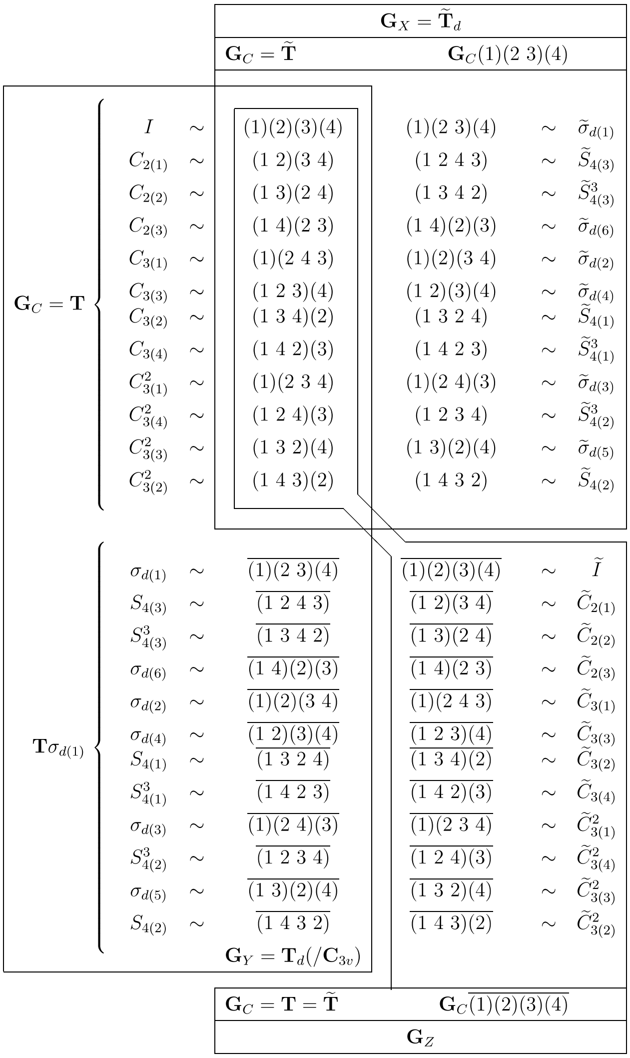
3.1. *RS*-Stereoisomeric groups

As discussed in the preceding section, symmetry operations (e.g., $\sigma_{d(2)}$) and permutations (e.g., $\tilde{\sigma}_{d(2)}$) should be discriminated and then integrated in order to comprehend stereochemistry. For this purpose, such permutations should be restricted to *RS*-skeletal permutations (see below) so as to give necessary and sufficient pieces of information for discussing prochirality and prostereogenicity (strictly speaking, pro-*RS*-stereogenicity). Thereby, *RS*-stereoisomeric groups are constructed, as exemplified by a tetrahedral skeleton of T_d-symmetry (Fig. 3).[13]

The four positions of a tetrahedral skeleton is numbered sequentially as shown in Figure 2 (e.g., **5**). From a geometrical point of view, the tetrahedral skeleton belongs to the point group T_d so that the four positions construct an orbit (equivalence class) that is governed by the coset representation (CR) represented by the symbol $T_d(/C_{3v})$. The CR is regarded as a permutation representation with ligand-chirality alternation (e.g., $\sigma_{d(1)} \sim \overline{(1)(2\;3)(4)}$, $\sigma_{d(2)} \sim \overline{(1)(2)(3\;4)}$, etc.). The CR $T_d(/C_{3v})$ can be regarded as a permutation group ($\mathbf{G}_Y$):

$$\mathbf{G}_Y = \mathbf{G}_C + \mathbf{G}_C\sigma_{d(1)}, \tag{1}$$

where each operation contained in $\mathbf{G}_C$ is called proper rotation or simply rotation and each operation contained in $\mathbf{G}_C\sigma_{d(1)}$ is called improper rotation or simply rotoreflection. For the sake of convenience, the correspondence between each operation of T_d and its permutation is shown in Figure 3, where the symbols of the operations of T_d are adopted in accord with those reported in an educational article.[14] Because any operation can be selected as a representative, the coset $\mathbf{G}_C\sigma_{d(1)}$ $(= T\sigma_{d(1)})$ can be represented by $\mathbf{G}_C\sigma_{d(2)}$ $(= T\sigma_{d(2)})$ and so on.



		$\mathbf{G}_X = \tilde{\mathbf{T}}_d$		
		$\mathbf{G}_C = \tilde{\mathbf{T}}$	$\mathbf{G}_C(1)(2\;3)(4)$	
$\mathbf{G}_C = \mathbf{T}$	$I \sim$	$(1)(2)(3)(4)$	$(1)(2\;3)(4)$	$\sim \tilde{\sigma}_{d(1)}$
	$C_{2(1)} \sim$	$(1\;2)(3\;4)$	$(1\;2\;4\;3)$	$\sim \tilde{S}_{4(3)}$
	$C_{2(2)} \sim$	$(1\;3)(2\;4)$	$(1\;3\;4\;2)$	$\sim \tilde{S}^3_{4(3)}$
	$C_{2(3)} \sim$	$(1\;4)(2\;3)$	$(1\;4)(2)(3)$	$\sim \tilde{\sigma}_{d(6)}$
	$C_{3(1)} \sim$	$(1)(2\;4\;3)$	$(1)(2)(3\;4)$	$\sim \tilde{\sigma}_{d(2)}$
	$C_{3(3)} \sim$	$(1\;2\;3)(4)$	$(1\;2)(3)(4)$	$\sim \tilde{\sigma}_{d(4)}$
	$C_{3(2)} \sim$	$(1\;3\;4)(2)$	$(1\;3\;2\;4)$	$\sim \tilde{S}_{4(1)}$
	$C_{3(4)} \sim$	$(1\;4\;2)(3)$	$(1\;4\;2\;3)$	$\sim \tilde{S}^3_{4(1)}$
	$C^2_{3(1)} \sim$	$(1)(2\;3\;4)$	$(1)(2\;4)(3)$	$\sim \tilde{\sigma}_{d(3)}$
	$C^2_{3(4)} \sim$	$(1\;2\;4)(3)$	$(1\;2\;3\;4)$	$\sim \tilde{S}^3_{4(2)}$
	$C^2_{3(3)} \sim$	$(1\;3\;2)(4)$	$(1\;3)(2)(4)$	$\sim \tilde{\sigma}_{d(5)}$
	$C^2_{3(2)} \sim$	$(1\;4\;3)(2)$	$(1\;4\;3\;2)$	$\sim \tilde{S}_{4(2)}$
$\mathbf{T}\sigma_{d(1)}$	$\sigma_{d(1)} \sim$	$\overline{(1)(2\;3)(4)}$	$\overline{(1)(2)(3)(4)}$	$\sim \tilde{I}$
	$S_{4(3)} \sim$	$\overline{(1\;2\;4\;3)}$	$\overline{(1\;2)(3\;4)}$	$\sim \tilde{C}_{2(1)}$
	$S^3_{4(3)} \sim$	$\overline{(1\;3\;4\;2)}$	$\overline{(1\;3)(2\;4)}$	$\sim \tilde{C}_{2(2)}$
	$\sigma_{d(6)} \sim$	$\overline{(1\;4)(2)(3)}$	$\overline{(1\;4)(2\;3)}$	$\sim \tilde{C}_{2(3)}$
	$\sigma_{d(2)} \sim$	$\overline{(1)(2)(3\;4)}$	$\overline{(1)(2\;4\;3)}$	$\sim \tilde{C}_{3(1)}$
	$\sigma_{d(4)} \sim$	$\overline{(1\;2)(3)(4)}$	$\overline{(1\;2\;3)(4)}$	$\sim \tilde{C}_{3(3)}$
	$S_{4(1)} \sim$	$\overline{(1\;3\;2\;4)}$	$\overline{(1\;3\;4)(2)}$	$\sim \tilde{C}_{3(2)}$
	$S^3_{4(1)} \sim$	$\overline{(1\;4\;2\;3)}$	$\overline{(1\;4\;2)(3)}$	$\sim \tilde{C}_{3(4)}$
	$\sigma_{d(3)} \sim$	$\overline{(1)(2\;4)(3)}$	$\overline{(1)(2\;3\;4)}$	$\sim \tilde{C}^2_{3(1)}$
	$S^3_{4(2)} \sim$	$\overline{(1\;2\;3\;4)}$	$\overline{(1\;2\;4)(3)}$	$\sim \tilde{C}^2_{3(4)}$
	$\sigma_{d(5)} \sim$	$\overline{(1\;3)(2)(4)}$	$\overline{(1\;3\;2)(4)}$	$\sim \tilde{C}^2_{3(3)}$
	$S_{4(2)} \sim$	$\overline{(1\;4\;3\;2)}$	$\overline{(1\;4\;3)(2)}$	$\sim \tilde{C}^2_{3(2)}$
		$\mathbf{G}_Y = \mathbf{T}_d(/\mathbf{C}_{3v})$		
		$\mathbf{G}_C = \mathbf{T} = \tilde{\mathbf{T}}$	$\mathbf{G}_C\overline{(1)(2)(3)(4)}$	
		$\mathbf{G}_Z$		

Figure 3. *RS*-Stereoisomeric group for a tetraheral skeleton, the subgroups of which corresponds to the symmetries of tetrahedral molecules derived from the tetrahedral skeleton.[13]

From the permutational point of view, the tetrahedral skeleton belongs to the symmetric group of degree 4, that is, $\mathbf{S}^{[4]}$ $(= \mathbf{G}_X)$, which is represented as follows:

$$\mathbf{G}_X = \mathbf{G}_C + \mathbf{G}_C\tilde{\sigma}_{d(1)}, \tag{2}$$

where each operation contained in the coset $\mathbf{G}_C\tilde{\sigma}_{d(1)}$ is called *RS*-skeletal permutation. Note that any member of the coset, for example, $\tilde{\sigma}_{d(1)}$ $(\sim (1)(2\;3)(4))$, $\tilde{\sigma}_{d(2)}$ $(\sim (1)(2)(3\;4))$, etc., can be selected as the representative of the coset. Such symbols with a tilde for representing permutations without ligand-chirality alternation (e.g., $\tilde{\sigma}_{d(1)}$, $\tilde{\sigma}_{d(2)}$, etc.) correspond to those for representing rotoreflections of T_d with ligand-chirality alternation (e.g., $\sigma_{d(1)} \sim \overline{(1)(2\ 3)(4)}$, $\sigma_{d(2)} \sim \overline{(1)(2)(3\ 4)}$, etc.).

To integrate $\mathbf{G}_Y$ and $\mathbf{G}_X$, an additional group $\mathbf{G}_Z$ is necessary as follows:

$$\mathbf{G}_Z = \mathbf{G}_C + \mathbf{G}_C\tilde{I}, \tag{3}$$

where we place $\tilde{I} \sim \overline{(1)(2)(3)(4)}$ and each operation contained in $\mathbf{G}_C\tilde{I}$ is called ligand inversion. Such symbols as $\tilde{I}$ $(=\overline{(1)(2)(3)(4)})$ correspond to those of $\mathbf{T}$ with no ligand-chirality alternation (e.g., $I \sim (1)(2)(3)(4)$).

From the three groups represented by Eqs. 1–3, we can construct a combined set as follows:

$$\mathbf{G} = \mathbf{G}_Y \cup \mathbf{G}_X \cup \mathbf{G}_Z = \mathbf{G}_C + \mathbf{G}_C\sigma_{d(1)} + \mathbf{G}_C\tilde{\sigma}_{d(1)} + \mathbf{G}_C\tilde{I}, \tag{4}$$

which is a group that contains $\mathbf{G}_C$ as a normal subgroup. Eq. 4 is regarded as a coset decomposition of the group $\mathbf{G}$ by the normal subgroup $\mathbf{G}_C$. The operations of $\mathbf{G}$ are shown in Figure 3, where the operations of the coset $\mathbf{G}_C$ $(=\mathbf{G}_C I)$ appear in the left-upper quarter, those of the coset $\mathbf{G}_C\sigma_{d(1)}$ appear in the left-lower quarter, those of the coset $\mathbf{G}_C\tilde{\sigma}_{d(1)}$ appear in the right-upper quarter, and those of the coset $\mathbf{G}_C\tilde{I}$ appear in the right-lower quarter.

3.2. Enantiomers, *RS*-diastereomers, and holantimers

As found easily, a starting molecule is converted by every operations of $\mathbf{G}_C$ (rotations) into a homomer, which is here defined as an identical molecule if the numbering of the positions is disregarded. It should be noted that the set of the homomers corresponding to $\mathbf{G}_C$ represents a single molecule. It follows that the following three types of stereoisomers (stereoisomeric relationships) and the corresponding attributes can be formulated in terms of the cosets appearing in Eq. 4.[9]

(1) *Enantiomers— chirality/achirality*. The molecule generated from the starting molecule by $\sigma_{d(1)}$ is converted into a homomer, that is, an identical molecule by every operation of the coset $\mathbf{G}_C\sigma_{d(1)}$ (i.e., rotoreflections). Thus, the coset $\mathbf{G}_C\sigma_{d(1)}$ corresponds to a single molecule, which is called the enantiomer of the original molecule corresponding to the coset $\mathbf{G}_C$. The relationship between the starting molecule and the enantiomer is referred to as being enantiomeric. More strictly speaking, the enantiomeric relationship is described by the group $\mathbf{G}_Y$ (the point group T_d) or either one of its subgroups. An attribute of a molecule capable of generating the enantiomer is called chirality. The term achirality is used to refer to being self-enantiomeric, where a starting molecule is superposable to its mirror image (its enantiomeric molecule). The usage of the term 'enantiomeric' in self-enantiomeric (achiral) cases is necessary to a systematic treatment of chiral and achiral cases in terms of a common theoretical framework.[15] This usage causes no confusion because of the proposal of stereoisograms described below.

(2) *RS-Diastereomers— RS-stereogenicity/RS-astereogenicity*. Similarly, the coset $\mathbf{G}_C\tilde{\sigma}_{d(1)}$ (i.e., *RS*-skeletal permutations) corresponds to a single molecule, which is called the *RS*-diastereomer of the starting molecule. The relationship between the starting molecule and the *RS*-diastereomer is referred to as being *RS*-diastereomeric. More strictly speaking, the *RS*-diastereomeric relationship is described by the group $\mathbf{G}_X$ (the symmetric group $\mathbf{S}^{[4]}$) or either one of its subgroups. An attribute of a molecule capable of generating the *RS*-diastereomer is called *RS*-stereogenicity. The term *RS*-astereogenicity is used to refer to being self-*RS*-diastereomeric, where a starting molecule is superposable with its *RS*-diastereomeric molecule.

(3) *Holantimers— sclerality/asclerality*. Further, the coset $\mathbf{G}_C\tilde{I}$ (i.e., ligand inversions) corresponds to a single molecule, which is called the holantimer of the starting molecule. The relationship between the starting molecule and the holantimer is referred to as being holantimeric. More strictly speaking, the holantimeric relationship is described by the group $\mathbf{G}_Z$ or either one of its subgroups. An attribute of a molecule capable of generating the holantimer is called sclerality. The term asclerality is used to refer to being self-holantimeric, where a starting molecule is superposable with its holantimeric molecule.

As found easily, a representative of each coset, for example, $I \sim (1)(2)(3)(4) \in \mathbf{G}_C$ (for the original molecule), $\sigma_{d(1)} \sim \overline{(1)(2\ \ 3)(4)} \in \mathbf{G}_C\sigma_{d(1)}$ (for its enantiomer), $\tilde{\sigma}_{d(1)} \sim (1)\times(2\ 3)(4) \in \mathbf{G}_C\tilde{\sigma}_{d(1)}$ (for its *RS*-diastereomer), and $\tilde{I} \sim \overline{(1)(2)(3)(4)} \in \mathbf{G}_C\tilde{I}$ (for its holantimer), can be used to generate the relevant stereoisomers without using all the operations of $\mathbf{G}$. Other sets of representatives can be selected to generate the relevant stereoisomers.

In the conventional terminology, diastereomers are defined as stereoisomers other than enantiomers. In place of the conventional dichotomy between enantiomers and diastereomers, the present approach specifies the terms enantiomeric, *RS*-diastereomeric, and holantimeric distinctly by means of three subgroups ($\mathbf{G}_Y$, $\mathbf{G}_X$, and $\mathbf{G}_Z$) of the *RS*-stereoisomeric group ($\mathbf{G}$), which in turn corresponds to the term *RS-stereoisomeric*. It should be emphasized that the term *RS*-stereoisomers represents a theoretically meaningful subset of conventional stereoisomers.

3.3. Stereoisograms of five types

The *RS*-stereoisomers defined as above are aligned so as to give a stereoisogram.[9] For example, the stereoisogram shown in Figure 4 is obtained for the molecule **9** from the data shown in Figure 2. The stereoisogram is characterized as Type I by means of the modes of three relationships: vertical double-headed arrows with the symbol ◉ (enantiomeric pairs), horizontal double-headed arrows with the symbol ○ (*RS*-diastereomeric pairs), and diagonal equality symbols with the symbol ● (self-holantimeric, i.e., homomeric for the holantimeric relationship). Thus, each stereoisogram of Type I represents a chiral/*RS*-stereogenic/ascleral molecule.

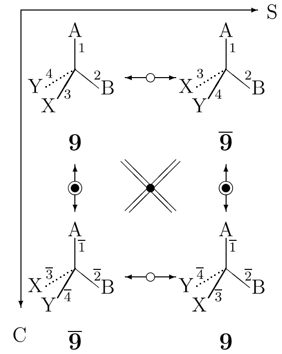


Figure 4. Stereoisogram of Type I. Each one-membered orbit ({A}, {B}, {X}, or {Y}) is governed by a coset representation (CR) which is characterized by the symbol $\mathbf{G}_{\mathrm{I}}(/\mathbf{G}_{\mathrm{I}})$) or a CR type $\frac{[-,-,a]}{[-,-,a]}$. For the symbols, see Table 1.

Tetrahedral molecules with various substitution patterns are examined and categorized into five types in terms of stereoisograms, as shown in Figure 5.[9] In terms of the three attributes, stereoisograms are classified into five types, that is, Type I (chiral/*RS*-stereogenic/ascleral [−,−,*a*]), Type II (chiral/*RS*-astereogenic/scleral [−,*a*,−]), Type III (chiral/*RS*-stereogenic/scleral [−,−,−]), Type IV (achiral/*RS*-astereogenic/ascleral [*a*,*a*,*a*]), and Type V (achiral/*RS*-stereogenic/scleral [*a*,−,−]). For the sake of convenience, symbols such as [−,−,*a*] are used to show the three attributes in the order of chirality/achirality, *RS*-stereogenicity/*RS*-astereogenicity, and sclerality/asclerality. Note that the letter '*a*' represents achirality, *RS*-astereogenicity, or asclerality, while the letter '−' represents chirality, *RS*-stereogenicity, or sclerality.

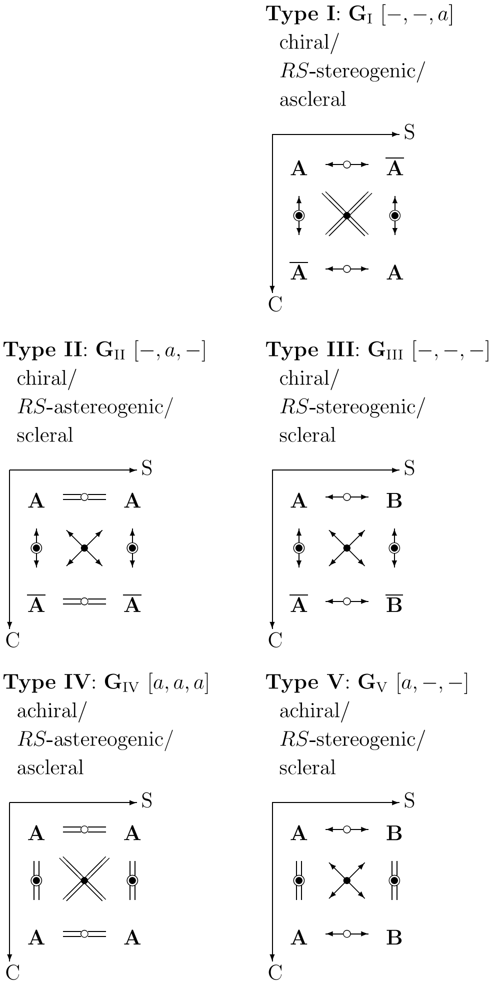


Figure 5. Stereoisograms of five types.[12] The symbols **A** and $\bar{\mathbf{A}}$ (or **B** and $\bar{\mathbf{B}}$) represent a pair of enantiomers. The symbols $\mathbf{G}_{\mathrm{I}}$, $\mathbf{G}_{\mathrm{II}}$, $\mathbf{G}_{\mathrm{III}}$, $\mathbf{G}_{\mathrm{IV}}$, and $\mathbf{G}_{\mathrm{V}}$ represent the corresponding subgroups of **G**.

It should be noted that a set of *RS*-stereoisomers characterized by a stereoisogram is an equivalence class (or an orbit) under the corresponding *RS*-stereoisomeric group.[16] Thereby, Types I to V for determining stereoisograms are also used to determine molecular types. This topic is the subject of the next subsection.

3.4. Subgroups of *RS*-stereoisomeric groups

The term *RS*-stereoisomers proposed as a theoretically meaningful subset of the conventional term 'stereoisomers' are further classified into enantiomers, *RS*-diastereomers, and holantimers in terms of stereoisograms.[9] The three relationships (enantiomeric, *RS*-diastereomeric, and holantimeric) correspond to three attributes of a molecule, that is, chirality (achirality), *RS*-stereogenicity (*RS*-astereogenicity), and sclerality (asclerality). The combination of the three attributes results in five types of molecules characterized by stereoisograms of Types I to V. Because the existence of at most five types (Types I–V) has been proved generally,[17] the relationship between chirality and *RS*-stereogenicity has been fully clarified. As a result, what is to be compared with the concept of chirality is concluded to be *RS*-stereogenicity (and/or sclerality), but not the conventional stereogenicity.

Each molecule of Type I, II, III, IV, or V is characterized by a subgroup of the corresponding *RS*-stereoisomeric group.[13] As for tetrahedral molecules, let us represent such subgroups of **G** (Fig. 3) by the symbols as follows: $\mathbf{G}_{\mathrm{I}}$, $\mathbf{G}_{\mathrm{II}}$, $\mathbf{G}_{\mathrm{III}}$, $\mathbf{G}_{\mathrm{IV}}$, and $\mathbf{G}_{\mathrm{V}}$. For example, because the molecule **9** corresponding to the stereoisogram of Type I (Fig. 4) is fixed (or stabilized in mathematical terminology) by the operations I and $\tilde{I}$, it belongs to the subgroup $\mathbf{G}_9$:

$$\mathbf{G}_9 = \{I, \tilde{I}\} = \{(1)(2)(3)(4), \overline{(1)(2)(3)(4)}\}, \tag{5}$$

which is a special case of a subgroup of Type I (i.e., $\mathbf{G}_{\mathrm{I}}$). It should be noted that the molecule **9** is usually regarded as an asymmetric molecule belonging to the point group $\mathbf{C}_1$ ($=\{I\}$) in terms of the conventional stereochemistry. Thus, the concept of stereoisograms allows us to find a concealed symmetry shown by $\mathbf{G}_9$ (Eq. 5).

In general, the subgroups of five types, that is, $\mathbf{G}_{\mathrm{I}}$ to $\mathbf{G}_{\mathrm{V}}$, are characterized as follows:

(1) A subgroup represented by $\mathbf{G}_{\mathrm{I}}$ that corresponds to a stereoisogram of Type I ([−,−,*a*]) contains operations selected from the cosets $\mathbf{G}_{\mathrm{C}}$ and $\mathbf{G}_{C}\tilde{I}$ (cf. Eq. 3 and Fig. 3). In other words, the subgroup $\mathbf{G}_{\mathrm{I}}$ is an ascleral subgroup of $\mathbf{G}_{Z}$. In this context, the group $\mathbf{G}_{Z}$ can be regarded as the maximal subgroup of Type I ($\mathbf{G}_{\mathrm{I}}$) within the group **G**.

(2) Such a subgroup $\mathbf{G}_{\mathrm{II}}$ as corresponding to a stereoisogram of Type II ([−,*a*−]) contains operations selected

from the cosets $\mathbf{G}_C$ and $\mathbf{G}_C\tilde{\sigma}_{d(1)}$ (cf. Eq. 2 and Fig. 3). In other words, the subgroup $\mathbf{G}_{\mathrm{II}}$ is an *RS*-astereogenic subgroup of $\mathbf{G}_X$. Thus, the group $\mathbf{G}_X$ can be regarded as the maximal subgroup of Type II ($\mathbf{G}_{\mathrm{II}}$) within the group $\mathbf{G}$.

(3) Such a subgroup $\mathbf{G}_{\mathrm{III}}$ as corresponding to a stereoisogram of Type III ($[-,-,-]$) contains operations selected from the coset $\mathbf{G}_C$. In other words, the subgroup $\mathbf{G}_{\mathrm{III}}$ is a (chiral/*RS*-stereogenic/scleral) subgroup of $\mathbf{G}_C$. Thus, the group $\mathbf{G}_C$ can be regarded as the maximal subgroup of Type III ($\mathbf{G}_{\mathrm{III}}$) within the group $\mathbf{G}$.

(4) Such a subgroup $\mathbf{G}_{\mathrm{IV}}$ as corresponding to a stereoisogram of Type IV ($[a,a,a]$) contains operations selected from the cosets $\mathbf{G}_C$, $\mathbf{G}_C\sigma_{d(1)}$, $\mathbf{G}_C\tilde{\sigma}_{d(1)}$, and $\mathbf{G}_C\tilde{I}$ (cf. Eq. 4 and Fig. 3). In other words, the subgroup $\mathbf{G}_{\mathrm{IV}}$ is an achiral/*RS*-astereogenic/ascleral subgroup of $\mathbf{G}$. Thus, the group $\mathbf{G}$ can be regarded as the maximal subgroup of Type IV ($\mathbf{G}_{\mathrm{IV}}$) within the group $\mathbf{G}$ itself.

(5) Such a subgroup $\mathbf{G}_{\mathrm{V}}$ as corresponding to a stereoisogram of Type V ($[a,-,-]$) contains operations selected from the cosets $\mathbf{G}_C$ and $\mathbf{G}_C\sigma_{d(1)}$ (cf. Eq. 1 and Fig. 3). In other words, the subgroup $\mathbf{G}_{\mathrm{V}}$ is an achiral subgroup of $\mathbf{G}_Y$. Thus, the group $\mathbf{G}_Y$ can be regarded as the maximal subgroup of Type V ($\mathbf{G}_{\mathrm{V}}$) within the group $\mathbf{G}$.

4. Intramolecular stereochemistry

4.1. Local symmetries and global symmetries

Fujita has proposed the concept of sphericity (the terms homospheric, enantiospheric, and hemispheric), which is regarded as an attribute of an orbit (an equivalence classes) governed by a coset representation (CR).[18,19] The definition of prochirality according to Fujita's USCI approach is an attribute of a molecule having at least one enantiospheric orbit. A more intuitive approach to judge sphericity has been reported.[20] On the other hand, permutabilities have been discussed so as to propose the concept of tropicity, which is regarded as an attribute of an orbit of another type.[21] To gain a deeper insight to stereochemistry, the concept of tropicity shall be restricted into a theoretically meaningful subconcept, that is, *RS*-tropicity. Thereafter, the concepts of sphericity and *RS*-tropicity shall be integrated by taking account of chirality and *RS*-stereogenicity. The concept of sphericity based on a CR $\mathbf{G}(/\mathbf{H})$ is characterized by comparing the chirality/achirality of the point group $\mathbf{G}$ (global symmetry) with the chirality/achirality of the subgroup $\mathbf{H}$ (local symmetry).[18,19] This methodology is extended to deal with *RS*-stereoisomeric groups discussed in the present paper.

Let the symbol $\mathbf{G}_\alpha$ represent the global symmetry of a molecule (α=I, II, III, IV, or V). The ligands of the molecule are divided into orbits (equivalence classes). Let any ligand in such an orbit be fixed (stabilized) by a subgroup $\mathbf{H}_\beta$ (β=I, II, III, IV, or V), which is the local symmetry of the orbit. Then, the orbit is governed by the CR $\mathbf{G}_\alpha(/\mathbf{H}_\beta)$. The size of the orbit is equal to the degree of the CR, that is, $|\mathbf{G}_\alpha|/|\mathbf{H}_\beta|$, where the symbols $|\mathbf{G}_\alpha|$ and $|\mathbf{H}_\beta|$ represent the orders of $\mathbf{G}_\alpha$ and $\mathbf{H}_\beta$, respectively. Possible modes for the combination of $\mathbf{G}_\alpha$ with $\mathbf{H}_\beta$ are listed in Table 1.

For example, each ligand (A, B, X, or Y) of **9** shown in Figure 4 constructs a one-membered orbit under the action of the group $\mathbf{G}_9$. The operations I and $\tilde{I}$ fix the ligand A (or B, or X, or Y) of **9**, so that the stabilizer (i.e., the local symmetry) of the one-membered orbit containing A is determined to be $\mathbf{G}_9$ shown in Eq. 5. Hence the orbit is governed by the CR $\mathbf{G}_9(/\mathbf{G}_9)$ as a special case of $\mathbf{G}_{\mathrm{I}}(/\mathbf{H}_{\mathrm{I}})$. The degree of the CR, that is, $|\mathbf{G}_9|/|\mathbf{G}_9|=1$, is in agreement with the size (i.e., 1) of each orbit. For the sake of convenience (cf. Table 1), the type of the CR is represented by a CR type $[-,-,a]/[-,-,a]$ or $\frac{[-,-,a]}{[-,-,a]}$, where the first set of a numerator and a denominator (i.e., $-/-$) is called 'chiral part', the second set of a numerator and a denominator (i.e., $-/-$) is called '*RS*-stereogenic part', and the third set of a numerator and a denominator (i.e., a/a) is called 'scleral part'.

To apply the concepts of sphericity[18,19] and tropicity[21] to CRs for *RS*-stereoisomeric groups, each CR type (e.g., $[-,-,a]/[-,-,a]$ or $\frac{[-,-,a]}{[-,-,a]}$) is interpreted in terms of the criteria shown in Table 2. Note that the original term tropicity[21] is restricted into the term *RS*-tropicity. Thereby, the terms 'prochiral' and 'pro-*RS*-stereogenic' are defined as attributes of molecules with respect to relevant orbits:

(1) Prochirality is ascribed to the presence of at least one enantiospheric orbit contained in a molecule. Thereby, the molecule is prochiral with respect to the enantiospheric orbit(s).

Table 1. CRs and CR types for *RS*-stereoisomeric groups

	RS-Astereogenic			*RS*-Stereogenic		
	Type	CR	CR type	Type	CR	CR type
Chiral				Type I	$\mathbf{G}_{\mathrm{I}}(/\mathbf{H}_{\mathrm{I}})$	$\frac{[-,-,a]}{[-,-,a]}$
					$\mathbf{G}_{\mathrm{I}}(/\mathbf{H}_{\mathrm{III}})$	$\frac{[-,-,a]}{[-,-,-]}$
	Type II	$\mathbf{G}_{\mathrm{II}}(/\mathbf{H}_{\mathrm{II}})$	$\frac{[-,a,-]}{[-,a,-]}$	Type III	$\mathbf{G}_{\mathrm{III}}(/\mathbf{H}_{\mathrm{III}})$	$\frac{[-,-,-]}{[-,-,-]}$
		$\mathbf{G}_{\mathrm{II}}(/\mathbf{H}_{\mathrm{III}})$	$\frac{[-,a,-]}{[-,-,-]}$			
Achiral	Type IV	$\mathbf{G}_{\mathrm{IV}}(/\mathbf{H}_{\mathrm{IV}})$	$\frac{[a,a,a]}{[a,a,a]}$	Type V	$\mathbf{G}_{\mathrm{V}}(/\mathbf{H}_{\mathrm{III}})$	$\frac{[a,-,-]}{[-,-,-]}$
		$\mathbf{G}_{\mathrm{IV}}(/\mathbf{H}_{\mathrm{II}})$	$\frac{[a,a,a]}{[-,a,-]}$		$\mathbf{G}_{\mathrm{V}}(/\mathbf{H}_{\mathrm{III}})$	$\frac{[a,-,-]}{[-,-,-]}$
		$\mathbf{G}_{\mathrm{IV}}(/\mathbf{H}_{\mathrm{I}})$	$\frac{[a,a,a]}{[-,-,a]}$			
		$\mathbf{G}_{\mathrm{IV}}(/\mathbf{H}_{\mathrm{V}})$	$\frac{[a,a,a]}{[a,-,-]}$			

Table 2. Criteria for determining sphericity and *RS*-tropicity

Prochiral or not		Pro-*RS*-stereogenic or not	
Chiral part	Sphericity	*RS*-Stereogenic part	*RS*-Tropicity
a/*a*	Homospheric	*a*/*a*	*RS*-homotropic
a/−	Enantiospheric	*a*/−	*RS*-enantiotropic
−/−	Hemispheric	−/−	*RS*-hemitropic

(2) Pro-*RS*-stereogenicity is ascribed to the presence of at least one *RS*-enantiotropic orbit. Thereby, the molecule is pro-*RS*-stereogenic with respect to the *RS*-enantiotropic orbit(s).

It should be noted that an orbit governed by a CR is characterized by a CR type, which is in turn factorized into two distinct kinds of attributes, that is, sphericity and *RS*-tropicity. This means that 'enantiosphericity' and '*RS*-enantiotropicity', for example, can appear concurrently as attributes of an orbit. Logically, one more kind of attribute for sclerality can be defined but cannot be utilized as useful descriptors at present.

According to the criteria shown in Table 2, each orbit ({A}, {B}, {X}, or {Y}) characterized by a CR type $\frac{[-,-,a]}{[-,-,a]}$ in **9** is concluded to be hemispheric and *RS*-hemitropic. It follows that **9** is not prochiral nor pro-*RS*-stereogenic with respect to each of the one-membered orbits.

Because the operations I and $\tilde{C}_{2(1)}$ fix the molecule **10** shown in Figure 6, the molecule **10** belongs to the subgroup $\mathbf{G}_{10}$:

$$\mathbf{G}_{10} = \{I, \tilde{C}_{2(1)}\} = \{(1)(2)(3)(4), \overline{(1\ 2)(3\ 4)}\}, \tag{6}$$

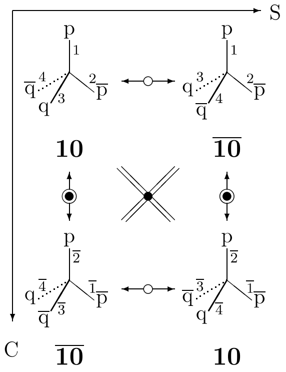


Figure 6. Stereoisogram of Type I. Each two-membered orbit ({p, $\bar{\text{p}}$} or {q, $\bar{\text{q}}$}) is governed by a coset representation (CR) which is characterized by the symbol $\mathbf{G}_{\text{I}}$(/$\mathbf{G}_{\text{III}}$) or a CR type $\frac{[-,-,a]}{[-,-,-]}$.

which is determined as the global symmetry of the molecule (as a special case of $\mathbf{G}_{\text{I}}$). Thereby, the ligands in **10** are divided into two orbits, that is, {p, $\bar{\text{p}}$} and {q, $\bar{\text{q}}$}, under the action of $\mathbf{G}_{10}$. The ligand p (or $\bar{\text{p}}$) of the former orbit {p, $\bar{\text{p}}$} (Fig. 6) is fixed only by I, so that the stabilizer (i.e., the local symmetry) of the two-membered orbit {p, $\bar{\text{p}}$} is determined to be $\mathbf{H}_{10_{\text{p}}}$ as follows:

$$\mathbf{H}_{10_{\text{p}}} = \{I\} = \{(1)(2)(3)(4)\}. \tag{7}$$

Hence, the two-membered orbit is governed by the coset representation $\mathbf{G}_{10}$(/$\mathbf{H}_{10_{\text{p}}}$) as a special case of $\mathbf{G}_{\text{I}}$(/$\mathbf{H}_{\text{III}}$), which is represented as [−,−,*a*]/[−,−,−]. This holds true for the latter orbit of {q, $\bar{\text{q}}$}. According to the criteria shown in Table 2, each orbit ({p, $\bar{\text{p}}$} or {q, $\bar{\text{q}}$}) characterized by the CR type $\frac{[-,-,a]}{[-,-,-]}$ in **10** is concluded to be hemispheric and *RS*-hemitropic. It follows that **10** is not prochiral nor pro-*RS*-stereogenic with respect to each of the two-membered orbits.

The conclusions for **9** and **10** are in agreement with the fact that Type I molecules are already characterized as chiral and *RS*-stereogenic (cf. Fig. 5).

4.2. Pro-*RS*-stereogenicity

The molecule **8** shown in Figure 2 is characterized by the stereoisogram of Type II shown in Figure 7. This molecule belongs to the group $\mathbf{G}_8$:

$$\mathbf{G}_8 = \mathbf{G}_{11} = \{I, \tilde{\sigma}_{d(2)}\} = \{(1)(2)(3)(4), (1)(2)(3\ 4)\}. \tag{8}$$

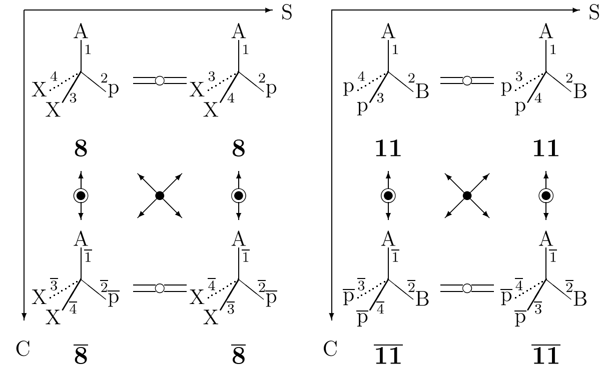


Figure 7. Stereoisograms of Type II containing pro-*RS*-stereogenicity.

Thereby, the four ligands are divided into three orbits, that is, {A}, {p}, and {X, X}. Because the ligand A (or p) of the orbit {A} (or {p}) is fixed by I and $\tilde{\sigma}_{d(2)}$, the local symmetry of the orbit is determined to be $\mathbf{G}_8$. Hence, the one-membered orbit {A} (or {p}) is governed by the CR $\mathbf{G}_8$ (/$\mathbf{G}_8$), which is characterized as a special case of $\mathbf{G}_{\text{II}}$(/$\mathbf{H}_{\text{II}}$). In terms of the CR type $\frac{[-,a,-]}{[-,a,-]}$ corresponding to $\mathbf{G}_{\text{II}}$(/$\mathbf{H}_{\text{II}}$), the *RS*-stereogenic part *a*/*a* (i.e., global *RS*-astereogenicity/local *RS*-astereogenicity) shows that the one-membered orbit {A} (or {p}) is *RS*-homotropic.

On the other hand, the ligand X of the orbit {X, X} is fixed by I, the local symmetry of the orbit is determined to be $\mathbf{H}_{8\text{X}}$ as follows:

$$\mathbf{H}_{8\text{X}} = \mathbf{H}_{11\text{p}} = \{I\} = \{(1)(2)(3)(4)\}. \tag{9}$$

Hence, the two-membered orbit {X,X} is governed by the CR $\mathbf{G}_8$(/$\mathbf{H}_{8\text{X}}$), which is characterized as a special case of $\mathbf{G}_{\text{II}}$(/$\mathbf{H}_{\text{III}}$). In terms of the corresponding CR type $\frac{[-,a,-]}{[-,-,-]}$, the *RS*-stereogenic part *a*/− (i.e., global *RS*-astereogenicity/local *RS*-stereogenicity) shows that the two-membered orbit {X, X} of **8** is *RS*-enantiotropic. Hence, **8** is concluded to be pro-*RS*-stereogenic with respect to the orbit {X, X}.

On the same line, the molecule **11** belongs to $\mathbf{G}_{11}$ (Eq. 8), which corresponds to a Type-II stereoisogram, as shown in the right of Figure 7. The four ligands are divided into three orbits, that is, {A}, {B}, {p, p}. The one-membered orbit {A} (or {B}) is governed by the CR $\mathbf{G}_{11}(/\mathbf{G}_{11})$, which is characterized as a special case of $\mathbf{G}_{\mathrm{II}}(/\mathbf{H}_{\mathrm{II}})$. In terms of the corresponding CR type $\frac{[-,a,-]}{[-,a,-]}$, the *RS*-stereogenic part *a*/*a* (i.e., global *RS*-astereogenicity/local *RS*-astereogenicity) indicates that the one-membered orbit {A} (or {B}) is *RS*-homotropic.

On the other hand, because the local symmetry of the orbit {p, p} is determined to be $\mathbf{H}_{11\mathrm{p}}$ (Eq. 9), the orbit is governed by the CR $\mathbf{G}_{11}(/\mathbf{H}_{11\mathrm{p}})$, which is characterized as a special case of $\mathbf{G}_{\mathrm{II}}(/\mathbf{H}_{\mathrm{III}})$. The *RS*-stereogenic part *a*/− (i.e., global *RS*-astereogenicity/local *RS*-stereogenicity) appearing in the corresponding CR type $\frac{[-,a,-]}{[-,-,-]}$ shows that the two-membered orbit {p, p} of **11** is *RS*-enantiotropic. Hence, **11** is concluded to be pro-*RS*-stereogenic with respect to the orbit {p, p}.

Among the molecules of Type II listed in Figure 7 of Ref. 9, the molecules with $\mathrm{A^2pq}$, $\mathrm{Ap^2\bar{p}}$, $\mathrm{Ap^2q}$, $\mathrm{p^2\bar{p}q}$, $\mathrm{p^2\bar{q}q}$, and $\mathrm{p^2qr}$ have orbits of $\mathbf{G}_{\mathrm{II}}(/\mathbf{H}_{\mathrm{III}})$ ($\frac{[-,a,-]}{[-,-,-]}$). They are concluded to be pro-*RS*-stereogenic with respect to the relevant two-membered orbits.

Figure 8 shows stereoisograms of Type II without Pro-*RS*-stereogenicity. By referring to the operations listed in Figure 3, the molecule **12** shown in Figure 8 is determined to belong to the group $\mathbf{G}_{12}$:

$$\mathbf{G}_{12} = \mathbf{G}_{13} = \{I, C_{2(1)}, \tilde{\sigma}_{d(2)}, \tilde{\sigma}_{d(4)}\}$$
$$= \{(1)(2)(3)(4), (1\;2)(3\;4), (1)(2)(3\;4), (1\;2)(3)(4)\}, \tag{10}$$

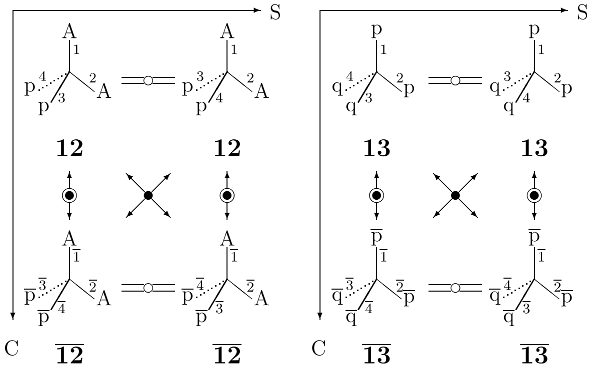


Figure 8. Stereoisograms of Type II without Pro-*RS*-stereogenicity.

which is a subgroup of $\mathbf{G}_X$ (Eq. 2). Thereby, the four ligands are divided into two orbits, that is, {A, A} and {p, p}. The local symmetry of the orbit {A, A} is determined to be $\mathbf{H}_{12\mathrm{A}}$ as follows:

$$\mathbf{H}_{12\mathrm{A}} = \{(1)(2)(3)(4), (1)(2)(3\;4)\}. \tag{11}$$

Hence, the two-membered orbit {A, A} is governed by the CR $\mathbf{G}_{12}(/\mathbf{H}_{12\mathrm{A}})$, which is characterized as a special case of $\mathbf{G}_{\mathrm{II}}(/\mathbf{H}_{\mathrm{II}})$. The *RS*-stereogenic part *a*/*a* (i.e., global *RS*-astereogenicity/local *RS*-astereogenicity) appearing in the corresponding CR type $\frac{[-,a,-]}{[-,a,-]}$ shows that the two-membered orbit {A, A} of **12** is *RS*-homotropic. Hence, **12** is concluded not to be pro-*RS*-stereogenic with respect to the orbit {A, A}.

The local symmetry of the orbit {p, p} of **12** is determined to be $\mathbf{H}_{12\mathrm{p}}$:

$$\mathbf{H}_{12\mathrm{p}} = \{(1)(2)(3)(4), (1\;2)(3)(4)\}, \tag{12}$$

which is conjugate to $\mathbf{H}_{12\mathrm{A}}$ (Eq. 11). Because the group $\mathbf{H}_{12\mathrm{p}}$ is a special case of $\mathbf{H}_{\mathrm{II}}$, the two-membered orbit {p, p} of **12** is *RS*-homotropic. Hence, **12** is also concluded not to be pro-*RS*-stereogenic with respect to the orbit {p, p}.

On the same line, the molecule **13** shown in Figure 8 is found to belong to the group $\mathbf{G}_{13}$ shown in Eq. 10. The two orbits, that is, {p, p} and {q, q}, can be concluded to be *RS*-homotropic by the same procedure as above. Hence, the orbits are concluded not to be pro-*RS*-stereogenic.

Among the molecules of Type II listed in Figure 7 of Ref. 9 the molecules with $\mathrm{p^4}$, $\mathrm{A^3p}$, $\mathrm{Ap^3}$, $\mathrm{p^3q}$, and $\mathrm{p^3\bar{p}}$ in addition to those listed in Figure 8 have orbits of $\mathbf{G}_{\mathrm{II}}(/\mathbf{H}_{\mathrm{II}})$ ($\frac{[-,a,-]}{[-,a,-]}$) and no orbits of $\mathbf{G}_{\mathrm{II}}(/\mathbf{H}_{\mathrm{III}})$ ($\frac{[-,a,-]}{[-,-,-]}$). They are concluded not to be pro-*RS*-stereogenic.

4.3. Prochirality

The molecule **6** shown in Figure 2 is characterized by the stereoisogram of Type V shown in Figure 9. This molecule belongs to the group $\mathbf{G}_6$:

$$\mathbf{G}_6 = \{I, \sigma_{d(2)}\} = \{(1)(2)(3)(4), \overline{(1)(2)(3\;4)}\}, \tag{13}$$

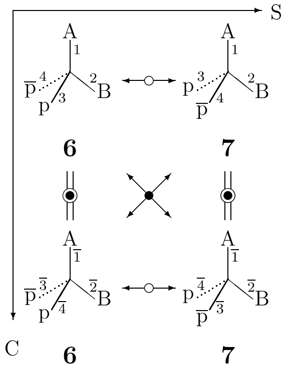


Figure 9. Stereoisogram of Type V containing prochirality.

which is isomorphic to the group shown in Eq. 8 but different in ligand-chirality alternation. Thereby, the four ligands are divided into three orbits, that is, {A}, {B}, {p, p̄}. Because the ligand A (or B) of the orbit {A} (or {B}) is fixed by I and $\sigma_{d(2)}$, the local symmetry of the orbit is determined to be $\mathbf{G}_6$. Hence, the one-membered orbit {A} (or {B}) is governed by the CR $\mathbf{G}_6(/\mathbf{G}_6)$, which is characterized as a special case of $\mathbf{G}_{\mathrm{V}}(/\mathbf{H}_{\mathrm{V}})$. The CR is represented by the CR type $\frac{[a,-,-]}{[a,-,-]}$. The chiral part *a*/*a* (i.e., global achiral/local achiral) appearing in the CR type $\frac{[a,-,-]}{[a,-,-]}$ shows that the one-membered orbit {A} (or {B}) is homospheric.

On the other hand, the ligand p (or p̄) of the orbit {p, p̄} is fixed by *I*, the local symmetry of the orbit is determined to be $\mathbf{H}_{6\mathrm{p},\bar{\mathrm{p}}}$ as follows:

$$\mathrm{H}_{6\mathrm{p},\bar{\mathrm{p}}} = \{I\} = \{(1)(2)(3)(4)\}. \tag{14}$$

Hence, the two-membered orbit {p, p̄} is governed by the CR $\mathbf{G}_6(/\mathbf{H}_{6\mathrm{p},\bar{\mathrm{p}}})$, which is characterized as a special case of $\mathbf{G}_{\mathrm{V}}(/\mathbf{H}_{\mathrm{III}})$. In terms of the corresponding CR type $\frac{[a,-,-]}{[-,-,-]}$, the chiral part *a*/− (i.e., global achiral/local chiral) shows that the two-membered orbit {p, p̄} of **6** is enantiospheric. Hence, **6** is concluded to be prochiral with respect to the orbit {p, p̄}.

4.4. Pro-*RS*-stereogenicity and prochirality

Figure 10 shows stereoisograms of Type IV containing pro-*RS*-stereogenicity superposed to prochirality. By referring to the operations listed in Figure 3, the molecule **5** shown in Figure 10 is found to belong to the group $\mathbf{G}_5$:

$$\mathbf{G}_5 = \{I, \sigma_{d(2)}, \tilde{\sigma}_{d(2)}, \tilde{I}\}$$
$$= \{(1)(2)(3)(4), \overline{(1)(2)(3\ 4)}, (1)(2)(3\ 4), \overline{(1)(2)(3)(4)}\}, \tag{15}$$

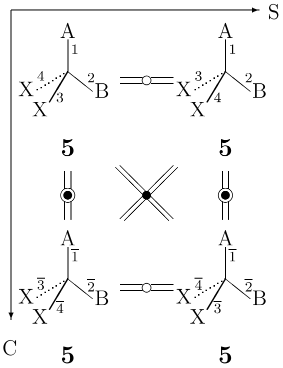


Figure 10. Stereoisogram of Type IV containing pro-*RS*-stereogenicity superposed to prochirality (for the orbit {X, X}).

which is a Type IV-subgroup of **G** (Eq. 4). Thereby, the four ligands are divided into three orbits, that is, {A}, {B} and {X, X}. Because the local symmetry of the orbit {A} (or {B}) is determined to be $\mathbf{H}_{5\mathrm{A}}$ (=$\mathbf{G}_5$) the one-membered orbit is governed by the CR $\mathbf{G}_5(/\mathbf{H}_{5\mathrm{A}})$, which is characterized as a special case of $\mathbf{G}_{\mathrm{IV}}(/\mathbf{H}_{\mathrm{IV}})$. In terms of the corresponding CR type $\frac{[a,a,a]}{[a,a,a]}$, the chiral part *a*/*a* (i.e., global achirality/local achirality) and the *RS*-stereogenic part *a*/*a* (i.e., global *RS*-astereogenicity/local *RS*-astereogenicity) show that the one-membered orbit is homospheric and *RS*-homotropic. Hence, **5** is concluded not to be prochiral and not to be pro-*RS*-stereogenic with respect to the orbit {A} (or {B}).

The local symmetry of the two-membered orbit {X, X}, on the other hand, is determined to be $\mathbf{H}_{5\mathrm{X}}$ as follows:

$$\mathbf{H}_{5\mathrm{X}} = \{(1)(2)(3)(4), \overline{(1)(2)(3)(4)}\}. \tag{16}$$

Hence, the two-membered orbit {X, X} is governed by the CR $\mathbf{G}_5(/\mathbf{H}_{5\mathrm{X}})$. This is characterized as a special case of $\mathbf{G}_{\mathrm{IV}}(/\mathbf{H}_{\mathrm{I}})$, which is represented by the CR type $\frac{[a,a,a]}{[-,-,a]}$. In terms of the CR type, the chiral part *a*/− (i.e., global achirality/local chirality) shows that the two-membered orbit {X, X} of **5** is enantiospheric. Hence, **5** is concluded to be prochiral with respect to the orbit {X, X}. At the same time, the *RS*-stereogenic part *a*/− (i.e., global *RS*-astereogenicity/local *RS*-stereogenicity) appearing in the CR type shows that the two-membered orbit {X, X} is *RS*-enantiotropic. Hence, **5** is concluded to be pro-*RS*-stereogenic with respect to the orbit {X, X}. In summary, **5** is both prochiral and *RS*-prostereogenic with respect to the two-membered orbit {X, X}.

Figure 11 shows stereoisograms of Type IV containing pro-*RS*-stereogenicity and prochirality in a separate fashion. By referring to the operations listed in Figure 3, the molecule **14** shown in Figure 11 is found to belong to the group $\mathbf{G}_{14}$:

$$\mathbf{G}_{14} = \{I, \sigma_{d(2)}, \tilde{\sigma}_{d(4)}, \tilde{C}_{2(1)}\}$$
$$= \{(1)(2)(3)(4), \overline{(1)(2)(3\ 4)}, (1\ 2)(3)(4), \overline{(1\ 2)(3\ 4)}\}, \tag{17}$$

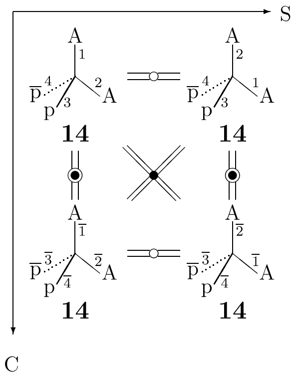


Figure 11. Stereoisogram of Type IV containing pro-*RS*-stereogenicity (for the orbit {A, A}) and prochirality (for the orbit {p,p̄}) distinctly.

which is a Type-IV subgroup of **G** (Eq. 4). Thereby, the four ligands are divided into two orbits, that is, {A, A} and {p, p̄}.

The local symmetry of the two-membered orbit {A, A} is determined to be $\mathbf{H}_{14\mathrm{A}}$ as follows:

$$\mathbf{H}_{14\mathrm{A}} = \{(1)(2)(3)(4), \overline{(1)(2)(3\ \ 4)}\}. \tag{18}$$

Hence, the two-membered orbit {A, A} is governed by the CR $\mathbf{G}_{14}(/\mathbf{H}_{14\mathrm{A}})$, which is characterized as a special case of $\mathbf{G}_{\mathrm{IV}}(/\mathbf{H}_{\mathrm{V}})$. In terms of the corresponding CR type $\frac{[a,a,a]}{[a,-,-]}$, the chiral part *a*/*a* (i.e., global achirality/local achirality) shows that the two-membered orbit {A, A} of **14** is homospheric. The *RS*-stereogenic part *a*/− in the CR type [*a*,*a*,*a*]/[*a*,-,-] (i.e., global *RS*-astereogenicity/local *RS*-stereogenicity) shows that the two-membered orbit {A, A} of **14** is *RS*-enantiotropic. Hence, **14** is concluded to be pro-*RS*-stereogenic with respect to the orbit {A, A}.

On the other hand, the local symmetry of the two-membered orbit $\{\mathrm{p}, \bar{\mathrm{p}}\}$ of **14** is determined to be $\mathbf{H}_{14\mathrm{p},\bar{\mathrm{p}}}$ as follows:

$$\mathbf{H}_{14\mathrm{p},\bar{\mathrm{p}}} = \{(1)(2)(3)(4), (1\ 2)(3)(4)\}. \tag{19}$$

Hence, the two-membered orbit $\{\mathrm{p}, \bar{\mathrm{p}}\}$ is governed by the CR $\mathbf{G}_{14}(/\mathbf{H}_{14\mathrm{p},\bar{\mathrm{p}}})$. This is characterized as a special case of $\mathbf{G}_{\mathrm{IV}}(/\mathbf{H}_{\mathrm{II}})$, which is represented by the CR type $\frac{[a,a,a]}{[-,a,-]}$. In terms of the CR, the chiral part $a/-$ (i.e., global achirality/local chirality) shows that the two-membered orbit $\{\mathrm{p}, \bar{\mathrm{p}}\}$ of **14** is enantiospheric. Hence, **14** is concluded to be prochiral with respect to the orbit $\{\mathrm{p}, \bar{\mathrm{p}}\}$. At the same time, the *RS*-stereogenic part a/a (i.e., global *RS*-astereogenicity/local *RS*-astereogenicity) appearing in the CR type $\frac{[a,a,a]}{[-,a,-]}$ shows that the two-membered orbit $\{\mathrm{p}, \bar{\mathrm{p}}\}$ is *RS*-homotropic. Hence, **14** is concluded not to be pro-*RS*-stereogenic with respect to the orbit $\{\mathrm{p}, \bar{p}\}$.

In summary, **14** in Figure 11 is pro-*RS*-stereogenic with respect to the orbit {A, A} and prochiral with respect to the orbit $\{\mathrm{p}, \bar{\mathrm{p}}\}$. Thus, **14** contains pro-*RS*-stereogenicity and prochirality in a separate fashion. The result of **14** shows that the combination of the term ‘prochirality(I)’ with the *proR*/*proS*-discriminability of the two As turns out to be misdirected and that the pro-*RS*-stereogenicity of the orbit {A, A} is the very thing for explaining the *proR*/*proS*-discriminability. Moreover, the prochirality of **14** in the purely geometrical sense turns out to come from the enantiospheric nature of the orbit $\{\mathrm{p}, \bar{\mathrm{p}}\}$.

Figure 12 shows stereoisograms of Type IV containing prochirality, which is ascribed to a four-membered orbit of $\{\mathrm{p}, \mathrm{p}, \bar{\mathrm{p}}, \bar{\mathrm{p}}\}$. By referring to the operations listed in Figure 3, the molecule **15** shown in Figure 12 is found to belong to the group $\mathbf{G}_{15}$:

$$\begin{aligned}\mathbf{G}_{15} &= \{I, C_{2(1)}, S_{4(1)}, S^{4}_{4(1)}; \tilde{\sigma}_{d(2)}, \tilde{\sigma}_{d(4)}, \tilde{C}_{2(2)}, \tilde{C}_{2(3)}\} \\ &= \{(1)(2)(3)(4), (1\ 2)(3\ 4), \overline{(1\ 3\ 2\ 4)}, \overline{(1\ 4\ 2\ 3)}; \\ &\qquad (1)(2)(3\ 4), (1\ 2)(3)(4), \overline{(1\ 3)(2\ 4)}, \overline{(1\ 4)(2\ 3)}\},\end{aligned} \tag{20}$$

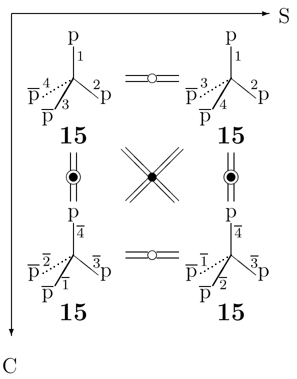


Figure 12. Stereoisogram of Type IV containing a four-membered prochiral orbit.

which is a Type-IV subgroup of **G** (Eq. 4). Thereby, the four ligands construct a four-membered orbit, that is, $\{\mathrm{p}, \mathrm{p}, \bar{\mathrm{p}}, \bar{\mathrm{p}}\}$.

The local symmetry of the four-membered orbit is determined to be $\mathbf{H}_{15\mathrm{p},\bar{\mathrm{p}}}$ as follows:

$$\mathbf{H}_{15\mathrm{p},\bar{\mathrm{p}}} = \{(1)(2)(3)(4), (1)(2)(3\ 4)\}. \tag{21}$$

Hence, the four-membered orbit is governed by the CR $\mathbf{G}_{15}(/\mathbf{H}_{15\mathrm{p},\bar{\mathrm{p}}})$, which is characterized as a special case of $\mathbf{G}_{\mathrm{IV}}(/\mathbf{H}_{\mathrm{II}})$. The CR is represented by the CR type $\frac{[a,a,a]}{[-,a,-]}$. Because the orders of the relevant groups are $|\mathbf{G}_{15}| = 8$ and $|\mathbf{H}_{15\mathrm{p},\bar{\mathrm{p}}}| = 2$, the degree of the CR is calculated as being $|\mathbf{G}_{15}|/|\mathbf{H}_{15\mathrm{p},\bar{\mathrm{p}}}| = 8/2 = 4$, which is equal to the size of the orbit. In terms of the CR type $\frac{[a,a,a]}{[-,a,-]}$, the chiral part $a/-$ (i.e., global achirality/local chirality) shows that the four-membered orbit $\{\mathrm{p}, \mathrm{p}, \bar{\mathrm{p}}, \bar{\mathrm{p}}\}$ of **15** is enantiospheric. Hence, **15** is concluded to be prochiral with respect to the four-membered orbit. The *RS*-stereogenic part a/a in the CR type $\frac{[a,a,a]}{[-,a,-]}$ (i.e., global *RS*-astereogenicity/local *RS*-astereogenicity) shows that the four-membered orbit is *RS*-homotropic. Hence, **15** is concluded not to be pro-*RS*-stereogenic with respect to the orbit.

Among the molecules of Type IV listed in Figure 7 of Ref. 9 the molecules with the formula A^4, A^3B, and A^2B^2 have orbits of $\mathbf{G}_{\mathrm{IV}}(/\mathbf{H}_{\mathrm{IV}})$ ($\frac{[a,a,a]}{[a,a,a]}$) and no orbits of other types. The two- or more-membered orbits appearing in these molecules are homospheric and *RS*-homotropic so that the molecules are not prochiral nor pro-*RS*-stereogenic.

5. Coset representations of *RS*-stereoisomeric groups

As discussed in the preceding subsections, coset representations (CRs) of *RS*-stereoisomeric groups are important to judge prochirality and pro-*RS*-stereogenicity. Appropriate subgroups of the group **G** shown in Figure 3 describe the symmetries of tetrahedral molecules. The subgroups ascribed to the tetrahedral molecules are classified into five types in terms of stereoisograms, $\mathbf{G}_{\mathrm{I}}$, $\mathbf{G}_{\mathrm{II}}$, $\mathbf{G}_{\mathrm{III}}$, $\mathbf{G}_{\mathrm{IV}}$, and $\mathbf{G}_{\mathrm{V}}$. A set of ligands constructs an orbit governed by a CR collected in Table 3, which is characterized in terms of the criteria listed in Table 2.

As shown in Table 3, there are three CR types for exhibiting *RS*-enantiotropicity, that is, $\mathbf{G}_{\mathrm{II}}(/\mathbf{H}_{\mathrm{III}})$ ($\frac{[a,a,a]}{[-,-,a]}$), $\mathbf{G}_{\mathrm{IV}}(/\mathbf{H}_{\mathrm{I}})$ ($\frac{[a,a,a]}{[-,-,a]}$), and $\mathbf{G}_{\mathrm{IV}}(/\mathbf{G}_{\mathrm{V}})$ ($\frac{[a,a,a]}{[a,-,-]}$). Note that the *RS*-stereogenic parts of these CR types are all equal to $a/-$. Thus, they are pro-*RS*-stereogenic (cf. Table 2), where their global symmetries (Types II and IV) are *RS*-astereogenic. The presence of pro-*RS*-stereogenicity in an *RS*-astereogenic molecule is consistent with the meaning of the prefix ‘pro’.

On the other hand, there are three CR types for exhibiting enantiosphericity, that is, $\mathbf{G}_{\mathrm{IV}}(/\mathbf{H}_{\mathrm{II}})$ ($\frac{[a,a,a]}{[-,a,-]}$), $\mathbf{G}_{\mathrm{IV}}(/\mathbf{H}_{\mathrm{I}})$ ($\frac{[a,a,a]}{[-,-,a]}$), and $\mathbf{G}_{\mathrm{V}}(/\mathbf{H}_{\mathrm{III}})$ ($\frac{[a,-,-]}{[-,-,-]}$). Note that the chiral parts of these CR types are all equal to $a/-$. Thus, they are prochiral (cf. Table 2), where their global symmetries (Types IV and V) are achiral. The presence of prochirality in an achiral molecule is consistent with the meaning of the prefix ‘pro’.

Logically speaking, one finds another possible case characterized by the CR $\mathbf{G}_{\mathrm{IV}}(/\mathbf{H}_{\mathrm{III}})$ and the corresponding CR type $\frac{[a,a,a]}{[-,-,-]}$. Such a case remains as a conjecture, that is, it may not be allowed chemically because of the degree of the CR.

Table 3. CRs of *RS*-stereoisomeric groups for examining prochirality and pro-*RS*-stereogenicity

Molecule	CR	CR type	Sphericity[a] *RS*-tropicity[b]	Prochirality and/or pro-*RS*-stereogenicity	Examples
Type I	$\mathbf{G}_{\mathrm{I}}(/\mathbf{H}_{\mathrm{I}})$	$\frac{[-,-,a]}{[-,-,a]}$	Hemispheric *RS*-hemitropic		Figure 4
	$\mathbf{G}_{\mathrm{I}}(/\mathbf{H}_{\mathrm{III}})$	$\frac{[-,-,a]}{[-,-,-]}$	Hemispheric *RS*-hemitropic		Figure 6
Type II	$\mathbf{G}_{\mathrm{II}}(/\mathbf{H}_{\mathrm{II}})$	$\frac{[-,a,-]}{[-,a,-]}$	Hemispheric *RS*-homotropic		Figure 8
	$\mathbf{G}_{\mathrm{II}}(/\mathbf{H}_{\mathrm{III}})$	$\frac{[-,a,-]}{[-,-,-]}$	Hemispheric $\underline{\textit{RS}\text{-enantiotropic}}$	pro-*RS*-stereogenic	Figure 7
Type III	$\mathbf{G}_{\mathrm{III}}(/\mathbf{H}_{\mathrm{III}})$	$\frac{[-,-,-]}{[-,-,-]}$	Hemispheric *RS*-hemitropic		
Type IV	$\mathbf{G}_{\mathrm{IV}}(/\mathbf{H}_{\mathrm{IV}})$	$\frac{[a,a,a]}{[a,a,a]}$	Homospheric *RS*-homotropic		Figure 10
	$\mathbf{G}_{\mathrm{IV}}(/\mathbf{H}_{\mathrm{II}})$	$\frac{[a,a,a]}{[-,a,-]}$	$\underline{\text{Enantiospheric}}$ *RS*-homotropic	Prochiral	Figures 11 and 12
	$\mathbf{G}_{\mathrm{IV}}(/\mathbf{H}_{\mathrm{I}})$	$\frac{[a,a,a]}{[-,-,a]}$	$\underline{\text{Enantiospheric }\textit{RS}\text{-enantiotropic}}$	Prochiral and pro-*RS*-stereogenic	Figure 10
	$\mathbf{G}_{\mathrm{IV}}(/\mathbf{H}_{\mathrm{V}})$	$\frac{[a,a,a]}{[a,-,-]}$	Homospheric $\underline{\textit{RS}\text{-enantiotropic}}$	pro-*RS*-stereogenic	Figure 11
Type V	$\mathbf{G}_{\mathrm{V}}(/\mathbf{H}_{\mathrm{V}})$	$\frac{[a,-,-]}{[a,-,-]}$	Homospheric *RS*-hemitropic		Figure 9
	$\mathbf{G}_{\mathrm{V}}(/\mathbf{H}_{\mathrm{III}})$	$\frac{[a,-,-]}{[-,-,-]}$	$\underline{\text{Enantiospheric}}$ *RS*-hemitropic	Prochiral	Figure 9

[a] An underlined attribute corresponds to the term prochirality.

[b] An underlined attribute corresponds to the term pro-*RS*-stereogenicity.

6. Discussions on the conventional terminology

6.1. The *pro-R*/*pro-S* descriptors

As clarified by the present analyses, the confusion on the term 'prochirality' (e.g., the prochirality(I)) started from the misalliance that the term 'prochirality' was correlated to the *pro-R*/*pro-S* descriptors,[1] although the same term was alternatively ascribed to 'enantiotopicity' from a purely geometrical viewpoint (e.g., Definition 1).[5] The misleading start stemmed from the unfortunate selection of the molecule **5** as a representative of the 'prochiral(I)' cases for the *pro-R*/*pro-S* descriptors. Because the orbit {X, X} of **5** is characterized by the CR $\mathbf{G}_{\mathrm{IV}}(/\mathbf{H}_{\mathrm{I}})$ and the CR type $\frac{[a,a,a]}{[-,-,a]}$, the orbit is enantiospheric/*RS*-enantiotropic and consequently the molecule **5** is prochiral/pro-*RS*-stereogenic with respect to the orbit. The concurrent appearance of prochirality and pro-*RS*-stereogenicity for the orbit {X, X} of **5** cannot be formulated by the conventional terminology.

As a result of the present analyses, the *pro-R*/*pro-S* descriptors should be correlated to pro-*RS*-stereogenicity, which is specified by *RS*-enantiotropicity. Even in the case of **5**, the descriptor *pro-R* or *pro-S* is ascribed to the pro-*RS*-stereogenicity, not to the prochirality. Thereby, the *RS*-enantiotropicity (not the conventional enantiotopicity) gives a common theoretical standpoint for the *pro-R*/*pro-S*-discriminability in Cases 1 and 2 and in Case 3 of the IUPAC recommendations 1996.

It should be emphasized again that the source of the 'prochirality confusion' is ascribed to the orbit governed by $\mathbf{G}_{\mathrm{IV}}(/\mathbf{H}_{\mathrm{I}})$ ($\frac{[a,a,a]}{[-,-,a]}$), where the global symmetry (i.e., $\mathbf{G}_{\mathrm{IV}}$) is achiral/*RS*-astereogenic while the local symmetry is chiral/*RS*-stereogenic. Cases 1–3 and related cases are summarized in the words of the present terminology as follows:

(1) Because the two-membered orbit {X, X} of **5** shown in Figure 2 is governed by the CR $\mathbf{G}_{\mathrm{IV}}(/\mathbf{H}_{\mathrm{I}})$ or the CR type $\frac{[a,a,a]}{[-,-,a]}$ (cf. Fig. 10), the orbit is enantiospheric and *RS*-enantiotropic so that **5** is both prochiral and pro-*RS*-stereogenic with respect to the orbit {X, X}.

Cases 1 and 2 of the IUPAC recommendations 1996 which correspond to **5** disregards the concurrent occurrence of the prochirality and the pro-*RS*-stereogenicity.

(2) Because the two-membered orbit {X, X} of **8** shown in Figure 2 is governed by the CR $\mathbf{G}_{\mathrm{II}}(/\mathbf{H}_{\mathrm{III}})$ or the CR type $\frac{[-,a,-]}{[-,-,-]}$ (cf. the right of Fig. 7), the orbit is hemispheric and *RS*-enantiotropic. Hence, **8** is not prochiral but pro-*RS*-stereogenic with respect to the orbit {X, X}.

Case 3 of the IUPAC recommendations 1996 which corresponds to **8** of Figure 2 confuses pro-RS-stereogenicity with prochirality despite of the absence of the latter.

(3) Because the two-membered orbit {A, A} of **14** shown in Figure 11 is governed by the CR $\mathbf{G}_{\mathrm{IV}}(/\mathbf{H}_{\mathrm{V}})$ or the CR type $\frac{[a,a,a]}{[a,-,-]}$, the orbit is homospheric and *RS*-enantiotropic so that the molecule **14** is not prochiral but pro-*RS*-stereogenic with respect to the orbit {A, A}.

Although the IUPAC recommendations 1996 is silent about this case, Case 3 may cover this case if the expression 'the chiral molecule' is changed to connote achiral molecules as well as chiral molecules. This ad-hoc change results in the mixing-up between a Type-II molecule (**8**) and a Type-IV molecule (**14**). In contrast, the present conclusion on **14** is based on the CR $\mathbf{G}_{\mathrm{IV}}(/\mathbf{H}_{\mathrm{V}})$ or the CR type $\frac{[a,a,a]}{[a,-,-]}$.

(4) On the other hand, **14** contains another two-membered orbit {p, $\bar{\mathrm{p}}$}, which is governed by the CR $\mathbf{G}_{\mathrm{IV}}(/\mathbf{H}_{\mathrm{II}})$ or the CR type $\frac{[a,a,a]}{[-,a,-]}$. Hence, the orbit {p, $\bar{\mathrm{p}}$} is enantiospheric and *RS*-homotropic so that **14** is prochiral but not pro-*RS*-stereogenic with respect to the orbit {p, $\bar{\mathrm{p}}$}.

The IUPAC recommendation 1996 is silent about the prochiral nature of **14** with respect to the orbit {p, $\bar{\mathrm{p}}$}.

(5) Because the two-membered orbit {p, $\bar{\mathrm{p}}$} of **6** shown in Figure 2 is governed by the CR $\mathbf{G}_{\mathrm{V}}(/\mathbf{H}_{\mathrm{III}})$ or the CR type $\frac{[a,-,-]}{[-,-,-]}$ (cf. Fig. 9), the orbit is enantiospheric and

RS-hemitropic so that **6** is prochiral and not pro-*RS*-stereogenic with respect to the orbit $\{p, \bar{p}\}$.

The IUPAC recommendation 1996 is also silent about the prochiral nature of **6** with respect to the orbit $\{p, \bar{p}\}$.

6.2. Enantiotopicity versus enantiosphericity/enantiotropicity

As clarified by the present analyses, the conventional term 'enantiotopic' has suffered from verbal transmutation, for example, from Definition 1 to Definition 2. Moreover, the term 'enantiotopic' has been misleadingly used to test the *pro-R*/*pro-S*-discriminability, that is, the capability of being named by the *pro-R*/*pro-S*-descriptors (cf. Cases 1 and 2 of the IUPAC 1996 recommendations).

Because the confusion on the term 'prochirality' comes from the misleading usage of the term 'enantiotopic', a quick remedy is to use the term 'enantiotopic' only in the original meaning (Definition 1) and to use the term 'prochiral' only in a geometrical meaning. If this remedy is adopted, the *pro-R*/*pro-S*-discriminability loses its criterion, especially, in determining Cases 1 and 2. If the term 'stereoheterotopic' is used in place of the term 'enantiotopic', the criterion of the *pro-R*/*pro-S*-discriminability becomes confused with those of other stereochemical naming systems (e.g., *E*/*Z*-descriptors). Note that, as diastereomers (i.e., stereoisomers other than enantiomers) contain several classes of stereoisomers that require distinct naming systems, the term 'diastereotopic' connotes several relationships in addition to those corresponding to the *pro-R*/*pro-S*-discriminability.

It is emphasized here that the term 'enantiotopic' represents a relationship between two objects even if it is used in the geometrical meaning (Definition 1). If the number of objects to be considered is larger than two, every pair of two objects in a molecule must be multiply compared to comprehend the whole symmetrical features of the molecule. This way is, obviously, unsuitable to a systematic treatment with a mathematical basis, for example, combinatorial enumeration of stereoisomers.[19]

The more thorough remedy proposed here is to adopt the terms that are defined as attributes of an equivalence class (orbit). Thus, we adopt the term enantiospheric to test the prochirality of an orbit as well as the term *RS*-enantiotropic to test the pro-*RS*-stereogenicity of an orbit. The latter term determines the *pro-R*/*pro-S*-discriminability of the orbit. Moreover, the attributes of two kinds are integrated to be ascribed to a CR type on the basis of the CR that governs the orbit.

Such sphericity terms (homospheric, enantiospheric, and hemispheric) as extended here by means of a CR type (or a CR of an *RS*-stereoisomeric group) is consistent to the original ones that have been defined by the CR of a point group.[18,20] Note the point group is a subgroup of the *RS*-stereoisomeric group (cf. $\mathbf{G}_Y$ and $\mathbf{G}$ shown in Fig. 3). As a result, the sphericity terms extended here are capable of deriving the conventional term 'enantiotopic' (Definition 1) according to the procedure reported in previous articles.[20,22] On the other hand, such *RS*-tropicity terms (*RS*-homotropic, *RS*-enantiotropic, and *RS*-hemitropic) as defined here by means of the same CR type (or the same CR of the *RS*-stereoisomeric group) is equivalent to the one that can be alternatively defined by the CR of the permutation group $\mathbf{G}_X$. Although stereogenicity/astereogenicity as global/local permutation-group symmetry has been discussed in a recent paper,[21] a rational restriction within *RS*-stereogenicity/*RS*-astereogenicity is necessary to provide the foundation of *pro-R*/*pro-S*-discriminability, as described in the present paper. Because the *RS*-tropicity terms defined here are capable of dealing with the *pro-R*/*pro-S*-discriminability (via pro-*RS*-stereogenicity) and of excluding other types of diastereoisomerisms, they are more discriminative than the conventional term 'diastereotopic'.

6.3. 'Prochiral(I) atoms'

According to the IUPAC recommendations 1996, reference to the two stereoheterotopic groups as prochiral(I) is strongly discouraged while reference to a central carbon atom as prochiral(I) is recommended.

From the present standpoint, however, a more strict description on the reference is required. Any orbit of ligands is governed by the coset representation $\mathbf{G}_\alpha(/\mathbf{H}_\beta)$ ($\alpha,\beta=$I, II, III, IV, or V), which is characterized by a CR type or separately by sphericity and *RS*-tropicity (cf. Table 2). Because pro-*RS*-stereogenicity is determined by the *RS*-tropicity, the pro-*RS*-stereogenicity (in place of prochirality(I)) is ascribed to the $\mathbf{G}_\alpha(/\mathbf{H}_\beta)$-orbit. Hence, if a molecule is referred to as pro-*RS*-stereogenic, the relevant orbit should be specified. See **14** in Figure 11, where the orbit {A, A} gives pro-*RS*-stereogenicity and the other orbit $\{p, \bar{p}\}$ gives prochirality. See also **5** in Figure 10, where the orbit {X, X} gives prochirality as well as pro-*RS*-stereogenicity.

When the $\mathbf{G}_\alpha(/\mathbf{H}_\beta)$-orbit is taken into consideration, the corresponding central atom is governed by $\mathbf{G}_\alpha(/\mathbf{G}_\alpha)$-orbit. Note that the local symmetry $\mathbf{H}_\beta$ of the orbit is a subgroup of the local symmetry $\mathbf{G}_\alpha$ of the central atom. If such a condition as found in the local symmetries is satisfied, such a central atom is permissible to be referred to as pro-*RS*-stereogenic. Even in this case, the relevant $\mathbf{G}_\alpha(/\mathbf{H}_\beta)$-orbit should be specified.

7. Conclusions

The present systematic approach based on stereoisograms and *RS*-stereoisomeric groups has terminated such long--standing confusion on prochirality(I) as described in the IUPAC recommendations 1996.

An *RS*-stereoisomeric group for characterizing a molecule is categorized into either one of the five types $\mathbf{G}_\alpha$ ($\alpha=$I, II, III, IV, or V) by means of stereoisograms. Then, an orbit of ligands in the molecule is governed by the coset representation (CR) $\mathbf{G}_\alpha(/\mathbf{H}_\beta)$ ($\alpha,\beta=$I, II, III, IV, or V), which is characterized by a CR type or separately by sphericity and *RS*-tropicity.

Among the CRs, the following three CR types exhibit *RS*-enantiotropicity: $\mathbf{G}_{\mathrm{II}}(/\mathbf{H}_{\mathrm{III}})$ (the CR type: $\frac{[-,a,-]}{[-,-,-]}$), $\mathbf{G}_{\mathrm{IV}}(/\mathbf{H}_{\mathrm{I}})$ (the CR type $\frac{[a,a,a]}{[-,-,a]}$), and $\mathbf{G}_{\mathrm{IV}}(/\mathbf{H}_{\mathrm{V}})$ (the CR type: $\frac{[a,a,a]}{[a,-,-]}$), where the *RS*-stereogenic (the second) parts of these CR types are all equal to $a/-$. The molecules are pro-*RS*-stereogenic with respect to the relevant orbits, where the global symmetries (Types II and IV) are *RS*-astereogenic and the local symmetries (Types I, III, and V) are *RS*-stereogenic.

On the other hand, the following three CR types exhibit enantiosphericity: $\mathbf{G}_{\mathrm{IV}}(/\mathbf{H}_{\mathrm{II}})$ (the CR type: $\frac{[a,a,a]}{[-,a,-]}$), $\mathbf{G}_{\mathrm{IV}}(/\mathbf{H}_{\mathrm{I}})$ (the CR type: $\frac{[a,a,a]}{[-,-,a]}$), and $\mathbf{G}_{\mathrm{V}}(/\mathbf{H}_{\mathrm{III}})$ (the CR type: $\frac{[a,-,-]}{[-,-,-]}$), where the chiral (the first) parts of these CR types are all equal to $a/-$. The molecules are prochiral with respect to the relevant orbits, where the global symmetries (Types IV and V) are achiral and the local symmetries (Types I, II, and III) are chiral.

The long-standing confusion on prochirality(I) is concluded to stem from an unfortunate selection of the case $\mathbf{G}_{\mathrm{IV}}(/\mathbf{H}_{\mathrm{I}})$ (e.g., **5**) as a representative of prochiral(I) cases for determining *pro-R*/*pro-S*-discriminability, that is, the capability of designating *pro-R*/*pro-S*-descriptors. Occasionally and unfortunately, the $\mathbf{G}_{\mathrm{IV}}(/\mathbf{H}_{\mathrm{I}})$-orbit is enantiospheric (leading to prochirality) and, at the same time, *RS*-enantiotropic (leading to pro-*RS*-stereogenicity), as indicated by the CR type ($\frac{[a,a,a]}{[-,-,a]}$).

The pro-*RS*-stereogenicity defined in the present paper is correlated to the *pro-R*/*pro-S*-discriminability without any ambiguity, so that it is clearly discriminated from the prochirality defined geometrically. Moreover, the pro-*RS*-stereogenicity and the prochirality can be discussed in terms of a common theoretical framework, that is, coset representations of *RS*-stereoisomeric groups and the corresponding CR types.

References and notes

1. Hanson, K. R. *J. Am. Chem. Soc.* **1966**, *88*, 2731–2742.
2. Prelog, V. *Science* **1976**, *193*, 17–24.
3. Prelog, V.; Helmchen, G. *Angew. Chem., Int. Ed. Eng.* **1982**, *21*, 567–583.
4. Mislow, K.; Siegel, J. *J. Am. Chem. Soc.* **1984**, *106*, 3319–3328.
5. IUPAC Recommendations 1996 *Pure Appl. Chem.* **1996**, *68*, 2193–2222.
6. Eliel, E.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994.
7. Buxton, S. R.; Roberts, S. M. *Guide to Organic Stereochemistry*; Addison Wesley Longman: New York, 1996.
8. North, N. *Principles and Applications of Stereochemistry*; Stanley Thornes: Cheltenham, 1998.
9. Fujita, S. *J. Org. Chem.* **2004**, *69*, 3158–3165.
10. IUPAC Chemical Nomenclature and Structure Representation Division Provisional Recommendations. Nomenclature of Organic Chemistry **2004**, http://www.iupac.org/reports/provisional/abstract04/favre_310305.html.
11. Mislow, K. *Chirality* **2002**, *14*, 126–134.
12. Fujita, S. *Tetrahedron* **2004**, *60*, 11629–11638.
13. Fujita, S. *J. Math. Chem.* **2004**, *35*, 265–287.
14. Fujita, S. *J. Chem. Educ.* **1986**, *63*, 744–746.
15. The terms 'chiral' and 'achiral' are defined as attributes of a molecule in a balanced fashion. On the same line as the term 'enantiomeric' is defined to represent a relationship between two chiral molecules, the term 'self-enantiomeric' is convenient to represents a hypothetical relationship between an achiral molecule and its superposable mirror image.
16. In the convensional terminology, the term 'stereoisomers' is based on the relationship between a reference molecule and a comparison molecule. This means that such an achiral molecule as **5** selected as a reference has no comparison molecule. It is not so easy to show a criteria for judging the non-existence of such a comparison molecule if one obeys the conventional terminology. The term 'stereoisomers' lacks specification as equivalence classes (orbits) whereas the term '*RS*-stereoisomers' represents a set of four molecules appearing in a stereoisogram, which expresses an orbit of relevant molecules.
17. Fujita, S. *MATCH Commun. Math. Comput. Chem.* **2005**, *54*, 39–52.
18. Fujita, S. *J. Am. Chem. Soc.* **1990**, *112*, 3390–3397.
19. Fujita, S. *Symmetry and Combinatorial Enumeration in Chemistry*; Springer: Berlin, 1991.
20. Fujita, S. *J. Org. Chem.* **2002**, *67*, 6055–6063.
21. Fujita, S. *J. Math. Chem.* **2003**, *33*, 113–143.
22. Fujita, S. *J. Comput. Chem. Jpn.* **2004**, *3*, 113–120.

Tetrahedron 62 (2006) 706–715

Tetrahedron

Oxidized isoquinolinoisoindolinone and benzazepinoisoindolinone alkaloids cores by convergent cyclisation processes: π-aromatic attack of thionium and oxonium species

Till Bousquet, Jean-François Fleury, Adam Daïch* and Pierre Netchitaïlo

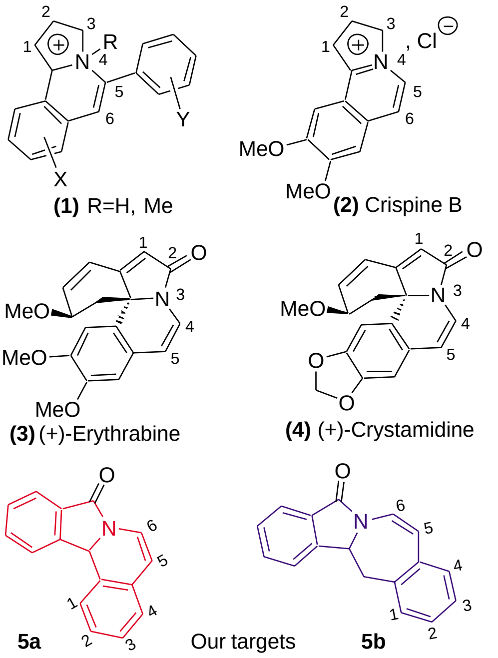
Laboratoire de chimie, URCOM, EA 3221, UFR des Sciences & Techniques de l'Université du Havre, B.P: 540,
25 rue Philippe Lebon, F-76058 Le Havre Cedex, France

Received 2 September 2005; revised 30 September 2005; accepted 3 October 2005

Abstract—An efficient methodology for synthesis of isoindoloisoquinoline **5a** and isoindolobenzazepine **5b** in oxidized forms as tetracyclic alkaloids cores are reported from *N*-bromoethylphthalimide (**6**) or phthalic anhydride and 2-phenylthioethylamine (**8**) in a five- or six-step sequence, respectively, in overall very good yields. The key step of this methodology is based on an intramolecular π-cationic cyclization of the thionium ion species. Alternatively, another four-step route was explored and based in an ultimate step on the cyclodehydration of an aldehyde functionality, which used as intermediate in the latest strategy, via the oxonium ion cation.

1. Introduction

The pyrrolo[2,1-*a*]isoquinoline skeleton is a structural motif common to a large and diverse family of natural products, which shown a remarkable array of biological activity.[1] The latter includes for example the so popular marine lamellarins,[2] erythrina[3] and aporhoedane[4] (including protoberberines) families, which produced a plethora of structures with profound important properties. In contrary, pyrrolo[2,1-*a*]isoquinoline motif with an olefinic moiety at α and β positions of the nitrogen atom of the isoquinoline nucleus (Scheme 1), as respectively, in iminium salts (**1**),[5] crispine B (**2**),[6] (+)-erythrabine (**3**)[7] and (+)-crystamidine (**4**)[8] are few explored. Some of unnatural compounds of type **1** are patented and have been reported to possess antidepressant activity.[5] Crispine B (**2**) is one of alkaloid products isolated from extracts of *Carduus crispus L.* which have been used in Chinese folk medicine for the treatment of cold, stomachache and rheumatism. The further screening of this compound for its inhibitory effect on the growth of some human-cancer lines in vitro by the SRB method showed that this product have significant cytotoxic activity.[6] Elsewhere, other study have reveled the existence of (+)-erythrabine (**3**) and (+)-crystamidine (**4**) together in nature, which were thought for long time to be artifacts.[7] While structures **3** and **4** as the sole erythrina alkaloids products with double bond at C_4–C_5 linkage, have not showed at this time any biological properties, they are useful intermediates



Scheme 1. Selected examples of clinical important natural and non natural pyrrolo[2,1-*a*]isoquinolines (**1**–**4**) and our targets **5a**,**b**.

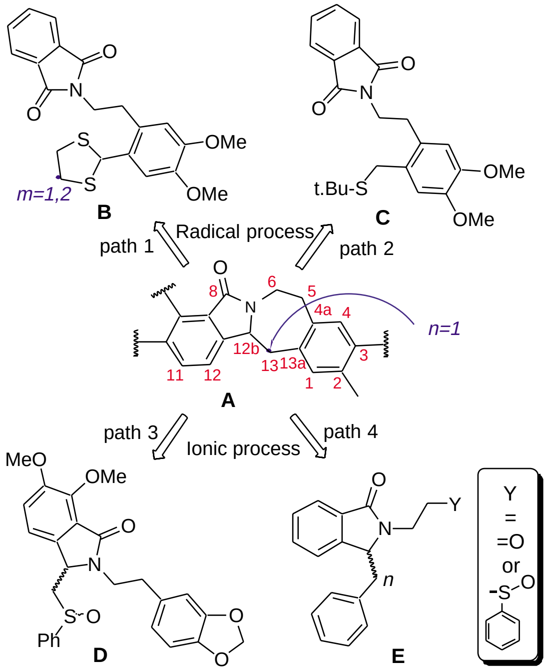
Keywords: Isoindole; Isoquinoline; Benzazepine; Thionium ion; Oxonium ion; *N*-Acyliminium ion; Cyclization; α-Amidoalkylation; Pummerer; Alkaloid.

* Corresponding author. Tel.: +33 2 32 74 44 03; fax: +33 2 32 74 43 91; e-mail: adam.daich@univ-lehavre.fr

0040–4020/$ - see front matter © 2005 Published by Elsevier Ltd.
doi:10.1016/j.tet.2005.10.017

in organic synthetic chemistry, especially in the elaboration of other erythrina alkaloids products exemplified by erysotrine,[9] 8-oxoerythrinine,[10] and both of enantiomers of 3-demethoxyerythratidinone.[11] Furthermore, the azepinic homologues of the oxidized pyrrolo[2,1-*a*]isoquinoline have been reported to constitute a valuable platform to access easily homoerythrinan alkaloids as 2,7-dihydrohomoerysotrine and 3-epischelhammericine.[12]

Most of the hitherto reported syntheses of these type of compounds rely on a small number of strategies; the sulfur chemistry constitute an important one of them and in this case the ring closure was executed by radical or ionic process as shown in Scheme 2. In fact, if we consider the formation of the azepine ring system as in aporhoedanes (protoberberines), erythrinan, and homoerythrinan alkaloids for examples, the radical approaches have relied on the generation of the C_{12b}–C_{13} bond from appropriate imide-thioacetal **B** (path 1)[13] or imide-thioether **C** (path 2)[14] by photocyclization followed by deketalisation or oxidative formation with $Pb(OAc)_4$, respectively. In the ionic process, the sulfur-directed 5-exo selective aryl radical cyclization onto an enamide functionality using the tandem Bu_3SnH/AIBN followed by the Pummerer type-cyclization was also operated. During these processes, the ring closure involves the formation of the C_{13}–C_{13a} bond via the π-cyclization of the thionium ion generated from the sulfoxide **D** in acid conditions (path 3).[15]



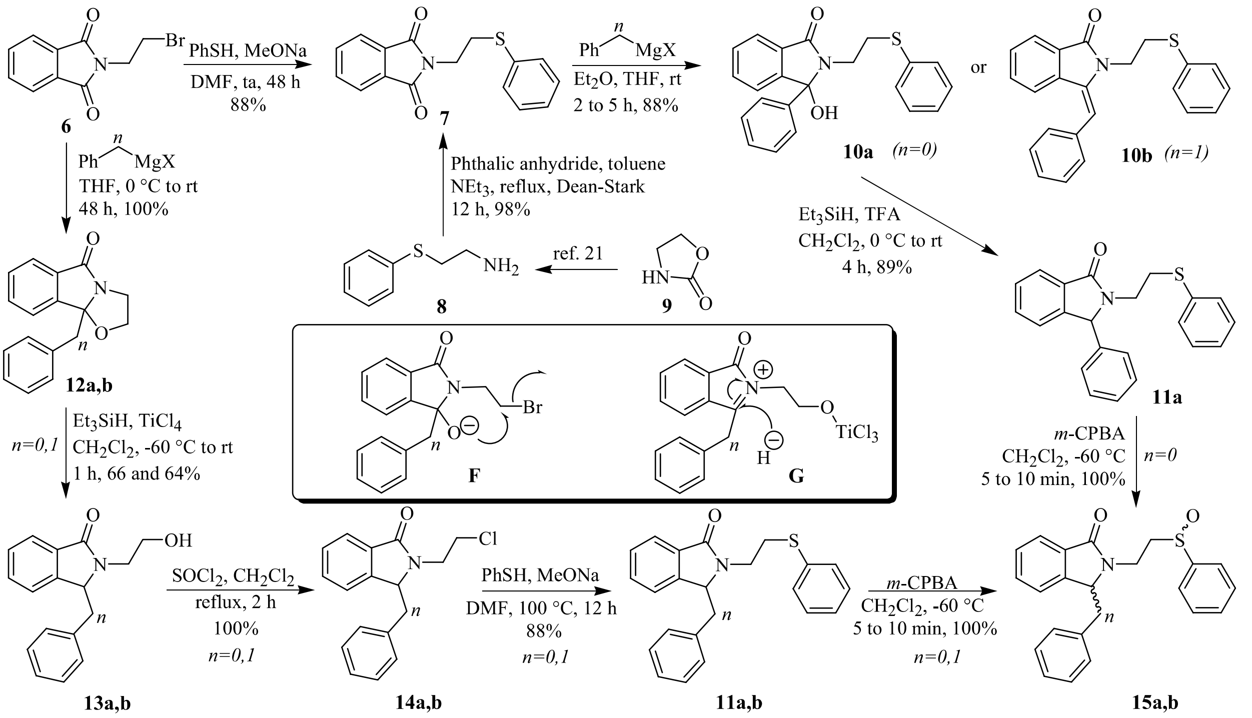
Scheme 2. Retrosynthetic scheme leading to isoindoloisoquinoline (**5a**, $n=0$) and related isoindolobenzazepine (**5b**, $n=1$).

2. Results and discussion

In our laboratory we are interested in the development of synthetic methodologies towards original aza-heterocyclic systems containing isoindole, isoquinoline and/or benzazepine moieties with promising pharmaceutical activities. In this sense, we have recently explored the utility of *N*-phenylthioalkylimides as remarkable synthons for the synthesis of various aza-fused [1,3]thiazines,[16,17] [1,3]thiazepines,[17] [1,3]thiazocinones in racemic,[17,18] or chiral[18] forms as well as isoindolo[2,1-*b*]isoquinolines alkaloids cores and their corresponding thio-bridged systems.[19] These compounds are obtained by the tandem thiocyclization/π-cationic cyclization of *N*-acyliminium ion in acidic conditions,[16,17] α-amidoalkylation/Friedel-Crafts type-cyclization[18] and finally Pummerer reaction/*N*-acyliminium ion cyclization.[19] In all these methodology, the phenylthio group was incorporated in the final structure except during the formation of the isoindolo[2,1-*b*]isoquinoline alkaloid core in which the phenylthio group was eliminated in an ultimate stage by reduction.[19]

In our search for new synthetic applications for *N*-phenylthioalkylimides, we wish to report herein our finding in this area by using the *N*-acyliminium ion chemistry in combination with the Pummerer cyclization. So with the above considerations in hand, we speculated that the oxidized tetracyclic alkaloids frameworks **5a**,**b** might conceivably be constructed by formation of the C_{4a}–C_5 bond through electrophilic cyclization of the sulfoxide derivatives **E** (path 4 in Scheme 2). Interestingly, the Pummerer reaction seemed to be particularly well adapted for driving this plan since the cyclized Pummerer product which bear a phenylthio group at exocyclic position on the C_5 (Scheme 2) could produce efficaciously in concise manner saturated tetracyclic alkaloids cores or oxidized tetracyclic systems **5a**,**b** as in Scheme 1 by C-S linkage reduction or oxidative thiophenol elimination, respectively.

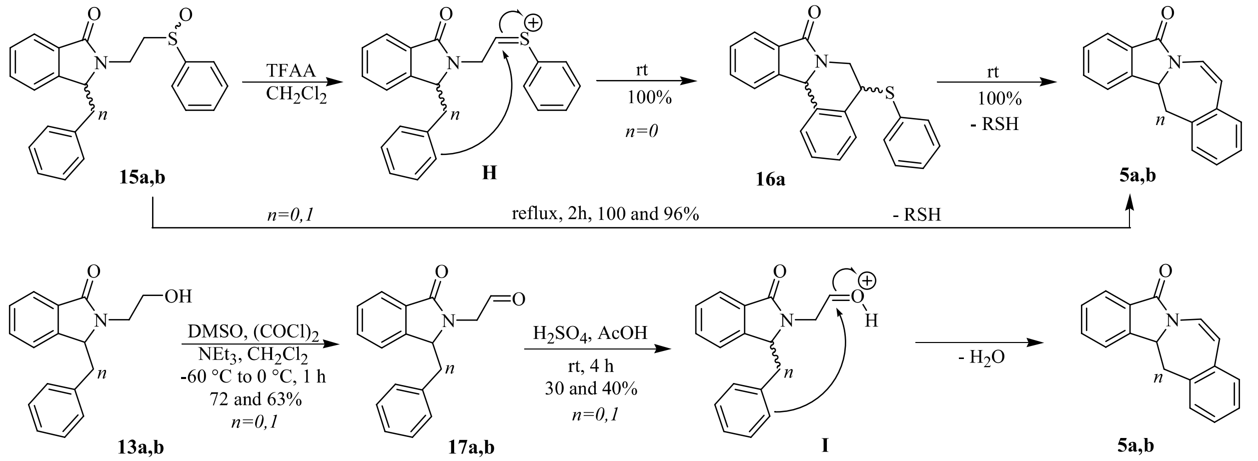
As a starting point of our study, the *N*-phenylthioethyl-α-phenyl(or benzyl)lactam derivatives **11a**,**b**, as sulfoxides precursors, constitutes a valuable target molecules (Scheme 3). We expected to obtain these products in a three-step sequence from the commercially available *N*-bromoethylphthalimide (**6**). So the halide (**6**) was *S*-alkylated with slight excess (1.2 equiv) of thiophenol in alkaline medium in 88% yield.[17,20] This product was also obtained in high yield of 98% in an alternative pathway from phthalic anhydride and the known 2-phenylthioethylamine[21] by the thermal amino-anhydride condensation in refluxing toluene in the presence of a catalytic amount of dry triethylamine under azeotropic removal of water.[22] Regioselective carbophilic addition onto the resulted phthalimide derivative **7** was performed with a large excess of Grignard reagents (RMgX with RX = PhBr and BnCl) in analogy to our precedent reports (i.e., RMgX, Et_2O, THF, room temperature, 2–5 h)[16] and afforded α-phenyl-α-hydroxylactam **10a** in 88% yield. In the case of the use of benzylmagnesium chloride, however, the changes operated in the experimental part notably in the work-up procedure (acidic or neutral conditions), no traces of α-benzyl-α-hydroxylactam were detected in the reaction mixture but only the enamidone **10b** as the consequence of the dehydration reaction of the latter α-hydroxylactam was isolated in good yield (96%). Because of the apparition of a stereogenic centre adjacent to the nitrogen atom, the ^1H NMR spectra of α-phenyl-α-hydroxylactam **10a** showed the magnetically non-equivalence of the methylene protons (–N–CH_2–) of the phenylthioethyl group, which appears as a classical AB system. Finally, the expected



Scheme 3. Sequential pathways leading to 2,3-dihydro-2-(2-phenylsulfanylethyl)-3-phenylisoindol-1-one (**15a**) and 3-benzyl-2-(2-phenylsulfanylethyl)-2,3-dihydroisoindol-1-one (**15b**) as thionium ions precursors.

N-phenylthioethyl-α-phenyllactam derivative **11a** was obtained in an ultimate stage from α-phenyl-α-hydroxy-lactam **10a** by removing the hydroxyl function with 2 equiv of triethylsilane and a large excess of TFA as hydride and proton sources, respectively. After 4 h of the reaction at room temperature, the excepted α-phenyllactam derivative **11a** was isolated in good yield (89%). Finally, the Pummerer thionium ion precursor **15a** was reached easily in quantitative yield by *m*-CPBA oxidation of **11a** in dry dichloromethane at −60 °C. The latter was isolated as uncoloured oil as a mixture of inseparable two diasteromers in 54/46 ratio. In addition, to avoid the formation of the non expected sulfone derivative, 1 equiv of *m*-CPBA and few minutes of reaction were necessary (in general only 5–10 min).

Because of this strategy was not general (all tentative to accede α-benzyllactam derivative **11b** have failed), our attention was turned to explore another approach starting again from *N*-bromoethylphthalimide (**6**). The choice of this sequence was based on two considerations: first, the oxazole ring in the oxazoloisoindolone tricyclic system might give the isoindolone ring equipped with alcohol function and aryl or aralkyl group at suitable positions, respectively. Second, the oxazoloisoindolone tricyclic system might limitated the proportion of the enamidone function, which could be formed after the ring cleavage according to the Meyers reports.[23] Thus, treatment of halide **6** with 1.2 equiv of Grignard reagents (RMgX with RX = PhBr and BnCl) in analogy to the procedure described above in dry THF over 48 h gave the tricyclic oxazoloisoindolones **12a**[24] and **12b** in quantitative yields. The formation of these products resulted from the regioselective carbophilic addition of RMgX onto one carbonyl group of the imide function followed by an intramolecular nucleophilic substitution of the bromine atom with oxygen anion as shown in the intermediate **F** (Scheme 3). These oxazoloisoindolones **12a** and **12b** were then converted easily to the *N*-hydroxy-alcohol derivatives **13a**,**b** by triethylsilane reduction as described above for **11a** in 66 and 64% yields, respectively. In these cases, the reaction occurred at −60 °C in dry dichloromethane and in the presence of $TiCl_4$ as catalyst instead of TFA used above during the transformation of **10a** into **11a**. Herein, $TiCl_4$ coordinates efficaciously the oxygen atom of the oxazole ring in **12a**,**b** inducing the formation of the *N*-acyliminium intermediate **G** (Scheme 3), which easily reduced by the hydride anion. Interestingly, the reaction proceeded cleanly and in the case of the reductive-cleavage of **12b** ($n=1$), no traces of the byproduct as *N*-hydroxy-ethyl-3-benzylidene were isolated. The above alcohol derivatives **13a**,**b** were treated with 1.5 equiv of thionyl chloride under reflux of dichloromethane for 2 h and the resulting halide **14a**,**b**, obtained in quantitative yields, were *S*-alkylated in accordance with the procedure described above for the synthesis of *N*-(2-phenylthioethyl)phthalimide (**7**) to give after chromatography purification (using SiO_2 column with a mixture of cyclohexane–AcOEt (4/1) as eluent) *N*-(2-phenylthioethyl)isoindolone derivatives **11a**,**b** in 88% yield in both cases. The reaction was slower then the one used for the production of the imide **7**. Consequently, the heat at 100 °C for 12 h was necessary for complete transformation of halides **14a**,**b** into corresponding sulfides **11a**,**b**. The requisite sulfoxides **15a**,**b** were then obtained by using same procedure reported above for oxidation of **11a** into **15a**. The latter **15a** and its benzyl isomer **15b** were isolated after short reaction times, which in general do not exceed 10 min, in quantitative yield for each case. Furthermore, these sulfoxides were isolated as a mixture of two diastereomers in comparable ratio of about 55/45.



Scheme 4. The π-cationic cyclization of sulfoxides **15a**,**b** and corresponding formyl derivatives **17a**,**b** into isoindolinones **5a**,**b** under acidic conditions.

Taking into account that sulfoxides similar to **15a**,**b** (see also intermediate **D** in Scheme 2) have been reported in the literature to constitute excellent precursors for the Pummerer type-cyclization,[19,26] the sulfoxide **15a** obtained above as a model substrate was subjected to TFAA at room temperature under Pummerer conditions (Scheme 4). The expected cyclization was readily induced by the intermediary of the thionium species **H**; and after 30 min of reaction, 5,12*b*-dihydro-5-phenylthioisoindolo[1,2-*a*]isoquinolin-8(6*H*)-one (**16a**) was formed as a mixture of two diastereomers in 56/44 ratio (*cis* and *trans* isomers). The purification of the product by short column chromatography gives pure **16a** as uncoloured oil in quantitative yield. Similarly, cyclization of sulfoxide **15b** was also occurred under identical conditions (quantitative yield) and, interestingly, furnished directly the benzazepine product 12*b*,13-tetrahydrobenzo[4,5]azepino[2,1-*a*]isoindol-8-one (**5b**) via the intermediacy of the expected and 'non-isolated' 5-phenylthio-5,6,12*b*,13-tetrahydrobenzo-[4,5]azepino[2,1-*a*]isoindol-8-one (**16b**) followed by spontaneous lost of thiophenol. In order to isolate the cyclized sulfure **16b**, other cyclization protocols, notably under lower temperature, diluted solution, other solvent, etc…, have failed in all cases. Furthermore, this product **5b** and its isoquinoline derivative **5a** were also obtained in one-step procedure by heating **15a**,**b** and TFAA on refluxing dichloromethane for 2 h in 100 and 96% yields, respectively. In addition, exposition of neat sulfure **16a** at laboratory atmosphere or in dichloromethane for 3 h at room temperature produces quantitatively the oxidized product **5a**.

In an alternative pathway, compounds **5a** and **5b** could be obtained in two-steps starting from the more accessible *N*-hydroxyethylisoindolinones **13a** and **13b** (Scheme 4). This strategy commences with the oxidation of alcohols **13a**,**b** into corresponding acetaldehydes **17a**,**b**. The Swern reaction conducted at −60 to 0 °C for 1 h in dichloromethane seemed to be more practical since this protocol delivered straightforwardly, cleanly and with appreciable yields (72 and 63%, respectively) the expected *N*-isoindol-2-ylacetaldehydes **17a** ($n=0$) and **17b** ($n=1$), candidates for the final cyclization step (Scheme 4). In the case of *N*-isoindol-2-ylacetaldehyde possessing an benzyl appendage **17b** ($n=1$), no traces of *N*-phthalimidin-2-ylethanol and/or *N*-phthalimidin-2-ylacetaldehyde as by products were observed even when the temperature was raised (up to room temperature) and the reaction time prolonged (up to 2 h).

Taking into account that Brönsted acid (HCO_2H, AcOH, H_2SO_4 and PTSA)[27,28] or Lewis acid ($ZnCl_2$ and $BF_3\cdot Et_2O$)[28a] are reported to induce cyclization of appropriate amidoacetals to tetrahydroisoquinolines[27] and isoindolobenzazepines,[28] we then proceeded to apply this method to the synthesis of dihydroisoquinoline **5a** and oxidized benzazepine **5b** directly from acetaldehydes **17a** and **17b**. Among all attempts used for cyclization of acetaldehydes **17a**,**b** into our targets **5a**,**b**, the tandem AcOH/H_2SO_4 in 1/2 ratio constitutes the best cyclodehydration combination for achieving this reaction with, however, low yields (30 and 40%, respectively). In this process, the oxidized alkaloids cores **5a**,**b** were formed via the intermediacy of the oxonium cation **I** followed by the dehydration of the tricyclic secondary alcohol obtained by the Friedel-Crafts reaction.

The structure elucidation of the cyclized products **5a**,**b** as well as all compounds intermediates was based on their spectroscopic data (IR, ^1H NMR and ^{13}C NMR including NOE difference and DEPT experiments) as well as their microanalyses.

The ^1H NMR analyses indicated that in the isoindolones structures **5a** and **5b**, the angular protons appear as singlet at $\delta=5.86$ ppm for **5a** and a doublet of doublet at $\delta=5.08$ ppm for **5b** with coupling constant of $J=7.0$, 3.1 Hz characteristics of an AMX system. These latter absorb downfield compared to the same protons of their acetaldehydes congeners **17a** ($\delta=5.65$ ppm) and **17b** ($\delta=4.96$ ppm), respectively. The same profile was also observed for these protons in comparison to the ones of their sulfoxides precursors, with however, a big difference on the chemical shift values which are $\Delta\delta=+0.44$ ppm and $\Delta\delta=+0.39$ ppm in favour of the cyclized products **5a** and **5b**, to the detriment of the sulfoxides **15a** and **15b**. Interestingly, when the comparison was done with minor form of **15a** and **15b**, respectively, only a little difference ($\delta=5.73$ ppm for **15a** and $\delta=5.01$ ppm for **15b** in their minor forms) was observed. Especially diagnostic was also the appearance of one olefinic proton with coupling constant of $J=7.8$ Hz for **5a** and $J=14.1$ Hz for **5b** at $\delta=6.20$ and 6.10 ppm, respectively. These latter appear as a doublet in each case characteristic of an AB system and constitutes ultimately the consequence of the intramolecular cyclization of **15a**,**b** into **5a**,**b**.

Furthermore, the key feature in the ^{13}C NMR spectra of **5a** and **5b**, was the appearance of fifteen signals in the aromatic regions. One of these disappears in the corresponding DEPT program spectra in comparison to spectra of their precursors **15a**,**b** or **17a**,**b** as the consequence of the π-cationic cyclization process.

Finally, these observations are in agreement with the fact that C_{4a}–C_5 and C_5–C_6 bonds, formed during the tandem π-cyclization/elimination process, have the same effect on the absorbance of the $C_{12b}H$ angular and the olefinic C_5H and C_6H protons absorbance as well as the C_5, C_6 and C_{12b} carbon signals. These results are also in agreement with previous reports dealing on analogous compounds.[28]

3. Conclusion

In summary, we have shown that imide **7** could generate in two-steps α-phenyllactam **11a** by successive Grignard carbophilic addition and α-hydroxylactam triethylsilane reduction mediated by an *N*-acyliminium cation. Because of the benzyl equivalent of α-phenyllactam **11a** could not obtained by this procedure, another approach using the bicyclic lactams chemistry in a four-step sequence was used successfully. In these conditions, α-substituted isoindolones **11a** and **11b** were isolated in an overall good yield from the readily available *N*-(2-bromoethyl)phthalimide (**6**) by the tandem Grignard addition/S_N2 *O*-cyclisation → oxazoline cleavage → alcohol chlorination and finally the nucleophilic chloride displacement with phenylthio anion. In the last step, the *m*-CPBA oxidation of **11a** and **11b** lead to the expected thionium ion precursors **15a** and **15b** cleanly, in very short times, and in quantitative yields.

Treatment of the latter sulfoxides **15a**,**b** under Pummerer conditions produced efficiently in high yields the cyclized isoindoloisoquinoline derivative **16a** while corresponding benzazepine component **16b** was instable and cyclized directly into the requisite tricyclic product **5b**. Taking advantage from this behavior, the alkaloids cores **5a** and **5b**, were then obtained in comparable high yields in a one-pot procedure from corresponding sulfoxides **15a**,**b** when the Pummerer-type cyclization was operated under refluxing dichloromethane. Alternatively, these targets **15a**,**b** were also obtained, with however, lower yields, from the formyl intermediates **17a**,**b** under acid influence. During this transformation the reaction involves an initial arylation of oxonium ion, followed by spontaneous water elimination. This, is resulted from the likely and unstable secondary alcohol adduct as the resulting product of the ring closure into isoindolones fused to isoquinoline ring **5a** and benzazepine ring **5b**.

4. Experimental

4.1. General

All melting points were measured on a Boetius micro hot-stage and are uncorrected. The infrared spectra of solids (potassium bromide) and liquids (neat) were recorded on a Perkin Elmer FT-IR paragon 1000 spectrometer. The ^1H and ^{13}C NMR spectra were recorded on a Bruker 300 (300 MHz) instrument in deuteriochloroform unless other indicated solvent and chemical shifts (δ) are expressed in ppm relative to TMS as internal standard. Ascending thin-layer chromatography was performed on precoated plates of silica gel 60 F 254 (Merck) and the spots visualized using an ultraviolet lamp or iodine vapour. Mass spectral measurements were recorded on a AEI MS 902 S spectrophotometer. The elemental analyses were carried out by the microanalysis laboratory of INSA, F-76130 Mont-Saint-Aignan, France.

4.1.1. *N*-(2-Phenylthioethyl)phthalimide (7). *Method A*. To a stirred solution, under an atmosphere of dry argon, of thiophenol (1.32 g, 12 mmol) in 15 mL of dry DMF was added (65 mg, 12 mmol) of sodium methoxide. After stirring for 40 min at room temperature, *N*-bromoethylphthalimide (**6**, 2.52 g, 10 mmol) was added slowly dropwise over a period of 5 min. The mixture was then allowed to react at the ambient temperature for 48 h (monitored by TLC using CH_2Cl_2/cyclohexane as eluent) and hydrolysed by crushed ice. The solution was filtered off and the solid was recrystallized from dry ethanol to give the expected imide **7**. In the case of the solid is not formed, the solution was extracted three times with diethyl ether, the organic layer was dried over $MgSO_4$ and concentrated in vacuo. The oily residue was passed through short Celite column and recrystallized in the second time from dry ethanol to give the above imide **7** in 88% yield. *Method B*. A mixture of 2-phenylthioethylamine (**8**, 1.53 g, 10 mmol), phthalic anhydride (1.48 g, 10 mmol) and two drops of dry triethylamine in toluene (50 mL) was refluxed with a Dean–Stark apparatus for 12 h. After cooling, the reaction mixture was concentrated under reduced pressure. The residue was dissolved into CH_2Cl_2 (50 mL), washed with 5% HCl solution then with a 10% $NaHCO_3$ solution and then with water. The organic layer was dried over $MgSO_4$, concentrated under reduced pressure, and recrystallization of the residue from dry ethanol gave the desired imide **7** in 98% yield; mp = 69 °C (lit.[17], isolated as oil in 69% yield); IR (KBr) $\tilde{\upsilon}_{max}=1712\ cm^{-1}$ (C═O); ^1H NMR ($CDCl_3$, 300 MHz) δ 3.19 (t, 2H, $J=7.0$ Hz, C–CH_2–S), 3.90 (t, 2H, $J=7.0$ Hz, N–CH_2–C), 7.19–7.23 (m, 2H, aromatic), 7.36–7.41 (m, 3H, aromatic), 7.64–7.71 (m, 2H, phthalimide), 7.74–7.82 (m, 2H, phthalimide); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 31.6, 37.5, 123.3, 126.4, 129.1, 129.6, 132.0, 134.1, 134.9, 168.2; MS (EI): $m/z=283$ [M^+]. Anal. Calcd for $C_{16}H_{13}NO_2S$ (283.35): C, 67.82; H, 4.62; N, 4.94. Found. C, 67.78, H, 4.42, N, 4.78.

4.2. General procedure for Grignard addition onto *N*-(2-phenylthioethyl)phthalimide (7)

To a well stirred and cold solution of imide (**7**, 2.83 g, 10 mmol) under dry nitrogen atmosphere in a mixture of anhydrous diethyl ether and anhydrous THF (40 mL) was added slowly in dropwise, over a period of 30 min, a 0.5 M solution of Grignard reagent (phenylmagnesium bromide or benzylmagnesium chloride (15 mmol)) in dry THF. After 2–5 h of reaction at room temperature, the reaction was hydrolysed under stirring with water (40 mL) then with 0.5 M NH_4Cl solution (40 mL), and the solution was passed through Celite. After separation, the organic layer was washed with water, brine, dried over $MgSO_4$ and concentrated under reduced pressure. Recrystallization of the reaction residue from a dry ethanol give α-hydroxylactam **10a** or enamidone **10b** in yields of 88 and 96%, respectively.

4.2.1. 3-Hydroxy-3-phenyl-2-(2-phenylthioethyl)-2,3-dihydroisoindol-1(2*H*)-one (10a). This product was isolated as white prisms in 88% yield and melted at 150 °C; IR (KBr) $\tilde{\upsilon}_{max}=3313$ (OH), 1684 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.61–2.79 (m, 1H, CH_2–CH_2), 2.94–3.12 (m, 2H, CH_2–CH_2), 3.44–3.64 (m, 1H, CH_2–CH_2), 4.48 (s broad, 1H, OH), 7.02–8.39 (m, 13H, aromatic), 7.59–8.68 (m, 1H, aromatic); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 30.7, 39.1, 122.9, 123.4, 126.0, 126.1, 126.3, 128.5, 128.7, 128.8, 129.1, 129.7, 130.1, 133.1, 135.2, 138.4, 149.9, 168.2; MS (EI): $m/z=361$ [M^+]. Anal. Calcd for $C_{22}H_{19}NO_2S$ (361.11): C, 73.10; H, 5.30; N, 3.88. Found. C, 73.00; H, 5.12; N, 3.63.

4.2.2. (*E*)-3-Benzylidene-1,2-dihydro-2-(phenylthioethyl)-1*H*-isoindol-1-one (10b). This product was isolated as a yellow oil in 88% yield after chromatograph on silica gel column using a mixture of diethyl acetate–hexane (3/7) as eluent; IR (neat) $\tilde{\upsilon}_{max}=3019$ and 2976 (CH), 1700 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.28 (dd, 2H, $J=7.5$, 7.1 Hz, CH_2–CH_2), 4.13 (dd, 2H, $J=7.5$, 7.1 Hz, CH_2–CH_2), 6.41 (s, 1H, CH=C), 7.16–7.23 (m, 1H, aromatic), 7.27–7.35 (m, 4H, aromatic), 7.38–7.46 (m, 6H, aromatic), 7.48–7.53 (m, 2H, aromatic), 7.78 (d, 1H, $J=8.4$ Hz, aromatic); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 31.6, 39.4, 110.3, 123.3, 123.4, 126.7, 128.0, 128.8, 129.3, 129.5, 129.7, 129.9, 129.7, 130.3, 131.8, 135.1, 135.2, 135.3, 136.1, 166.7; MS (EI): $m/z=357$ [M^+]. Anal. Calcd for $C_{23}H_{19}NOS$ (357.12): C, 77.28; H, 5.36; N, 3.92. Found. C, 77.04; H, 5.12; N, 3.87.

4.2.3. 2,3-Dihydro-3-phenyl-2-(2-phenylthioethyl)-isoindol-1-one (11a). To a solution of 3-hydroxy-3-phenyl-2-(2-phenylthioethyl)-2,3-isoindol-1-one (**10a**, 1.80 g, 5 mmol) in 30 mL of dry dichloromethane, was added on stirring and cooling at 0 °C dropwise 5 mL of TFA. After 5 min of reaction, triethylsilane (1.53 mL, 10 mmol) dissolved in 10 mL of anhydrous dichloromethane was added slowly over a period of 5 min. After 4 h of the reaction at room temperature, the solvent was evaporated under reduced pressure. The oily residue was diluted with 30 mL of dichloromethane and 30 mL of saturated sodium hydrogenocarbonate solution. The organic layer was separated, washed twice with water, brine, dried over $MgSO_4$ and concentrated under reduced pressure. Recrystallization of the reaction residue from a dry ethanol give α-phenyllactam **11a** in 89% yield as white crystals; mp=120 °C; IR (KBr) $\tilde{\upsilon}_{max}=3009$ and 2985 (CH), 1684 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.97–3.05 (m, 1H, CH_2–CH_2), 3.10–3.31 (m, 2H, CH_2–CH_2), 3.93–4.07 (m, 1H, CH_2–CH_2), 5.52 (s, 1H, CH), 7.04–7.33 (m, 11H, aromatic), 7.42–7.46 (m, 2H, aromatic), 7.82–7.95 (m, 1H, aromatic); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 31.5, 40.2, 65.6, 123.2, 123.6, 126.1, 127.8, 128.5, 128.9, 129.1, 129.2, 131.4, 132.0, 135.3, 136.9, 146.4, 168.9; MS (EI): $m/z=345$ [M^+]. Anal. Calcd for $C_{22}H_{19}NOS$ (345.46): C, 76.49; H, 5.54; N, 4.05. Found. C, 76.21; H, 5.38; N, 3.79.

4.3. General procedure for Grignard addition onto *N*-(2-bromoethyl)phthalimide (6)

To a well stirred and cold solution (0 °C) of halide (**6**, 6 g, 22.5 mmol) under dry argon atmosphere in anhydrous THF (150 mL) was added slowly in dropwise, over a period of 30 min, a 0.5 M solution of Grignard reagent (phenylmagnesium bromide or benzylmagnesium chloride (1.2 equiv, 27 mmol)) in dry THF. After 48 h of reaction at room temperature, the reaction mixture was hydrolysed under stirring with cold water (100 mL) then passed through a short column of Celite. After separation, the organic layer was washed with water, brine, dried over $MgSO_4$ and concentrated under reduced pressure. Recrystallization of the reaction residue from a dry ethanol or cyclohexane/diethyl ether gave oxazoline derivatives **12a** or **12b** in quantitative yield.

4.3.1. 2,3-Dihydro-9*b*-phenyloxazolo[2,3-*a*]isoindol-5-(9*bH*)-one (12a). This product was isolated as yellow-white solid in quantitative yield and melted at 146 °C (lit.[24], 148–150 °C); IR (KBr) $\tilde{\upsilon}_{max}=3012$ and 2995 (CH), 1689 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.19–3.35 (m, 1H, CH_2–CH_2), 4.06–4.20 (m, 2H, CH_2–CH_2), 4.32–4.44 (m, 1H, CH_2–CH_2), 7.21–7.65 (m, 8H, aromatic), 7.75–7.88 (m, 1H, aromatic); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 41.6, 70.3, 100.5, 123.6, 123.7, 124.4, 125.8, 125.9, 128.9, 129.0, 130.2, 131.2, 133.6, 138.0; MS (EI): $m/z=251$ [M^+]. Anal. Calcd for $C_{16}H_{13}NO_2$ (251.09): C, 76.48; H, 5.21; N, 5.57. Found. C, 76.22; H, 5.06; N, 5.39.

4.3.2. 9*b*-Benzyl-2,3-dihydrooxazolo[2,3-*a*]isoindol-5-(9*bH*)-one (12b). This product was isolated as yellow solid in quantitative yield and melted at 53 °C (decomposition); IR (KBr) $\tilde{\upsilon}_{max}=3021$ and 2987 (CH), 1710 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.72–2.92 (m, 1H, CH_2–CH_2), 3.16 (d, 1H, $J=14.0$ Hz, CH_2–C), 3.38 (d, 1H, $J=14.0$ Hz, CH_2–C), 3.85–4.05 (m, 3H, CH_2–CH_2), 7.20–7.36 (m, 5H, aromatic), 7.44–7.62 (m, 3H, aromatic), 7.69–7.72 (m, 1H, aromatic); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 43.0, 43.2, 69.9, 100.6, 122.7, 124.2, 127.0, 128.1, 130.1, 130.7, 133.1, 135.2, 138.1, 147.1, 173.9; MS (EI): $m/z=265$ [M^+]. Anal. Calcd for $C_{17}H_{15}NO_2$ (265.31): C, 76.96; H, 5.70; N, 5.28. Found. C, 76.79; H, 5.54; N, 5.11.

4.4. General procedure for cleavage-reduction of oxazoloisoindolones (12a,b)

To a cold (−60 °C) and stirred solution of oxazoloisoindolone (**12a**) or (**12b**) (10 mmol) in 40 mL of dry dichloromethane, was added dropwise (15 mL, 15 mmol) of 1.0 M $TiCl_4$ solution in dry THF. After 10 min of reaction under stirring, triethylsilane (4.58 mL, 30 mmol) dissolved in 10 mL of anhydrous dichloromethane was added slowly by syringe over a period of 2 min. The reaction mixture was allowed to reach gradually room temperature during 30 min and allowed to react again for an additional 30 min. After addition of 30 mL saturated NH_4Cl solution and 30 mL of dichloromethane, the organic layer was separated, washed twice with water, brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the reaction residue by flash chromatography on silica gel column using a mixture of cyclohexane–AcOEt (1/1) as eluent give the expected alcohol derivative (**13a**) or (**13b**) in 66 and 64% yields, respectively.

4.4.1. 2-(2-Hydroxyethyl)-2,3-dihydro-3-phenylisoindol-1-one (13a). This product was isolated as a white solid in 66% yield and melted at 99 °C (methanol/water) (lit.[25], 110–112 °C); IR (KBr) $\tilde{\upsilon}_{max}=3401$ (OH), 3009 and 2986 (CH), 1702 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.98–3.11 (m, 1H, CH_2–CH_2), 3.63–3.85 (m, 2H, CH_2–CH_2), 3.87–3.97 (m, 1H, CH_2–CH_2), 4.41 (s broad, 1H, OH), 5.67 (s, 1H, CH), 7.09–7.79 (m, 9H, aromatic); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 44.3, 61.7, 66.2, 123.2, 123.6, 127.8, 128.5, 128.9, 129.3, 131.2, 132.1, 136.8, 146.6, 170.2; MS (EI): $m/z=235$ $[M^+-H_2O]$. Anal. Calcd for $C_{16}H_{15}NO_2$ (253.11): C, 75.87; H, 5.97; N, 5.53. Found. C, 75.63; H, 5.81; N, 5.34.

4.4.2. 3-Benzyl-2-(2-hydroxyethyl)-2,3-dihydroisoindol-1-one (13b). This product was isolated as an uncolourless oil in 64% yield; IR (neat) $\tilde{\upsilon}_{max}=3397$ (OH), 3015 and 2990 (CH), 1673 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.86 (dd, 1H, $J=14.1$, 7.8 Hz, CH_2–CH), 3.37–3.57 (m, 2H, CH_2–CH_2), 3.86 (t, 2H, $J=5.5$ Hz, CH_2–CH_2), 3.95–4.07 (m, 1H, CH_2–CH_2), 4.91 (dd, 1H, $J=7.8$, 4.7 Hz, CH–CH_2), 6.85–6.94 (m, 1H, aromatic), 7.02–7.12 (m, 2H, aromatic), 7.23–7.27 (m, 3H, aromatic), 7.35–7.47 (m, 2H, aromatic), 7.71–7.79 (m, 1H, aromatic); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 38.5, 44.6, 62.0, 62.3, 123.0, 123.6, 127.2, 128.3, 128.6, 129.6, 131.3, 131.8, 135.9, 145.3, 169.9; MS (EI): $m/z=249$ $[M^+-H_2O]$. Anal. Calcd for $C_{17}H_{17}NO_2$ (267.32): C, 76.38; H, 6.41; N, 5.24. Found. C, 76.06; H, 6.21; N, 5.06.

4.5. General procedure for chlorination of alcohols (13a,b)

To a stirred solution of 5 mmol of alcohol **13a** or **13b** in 40 mL of dry dichloromethane under argon atmosphere was added slowly 1.5 equiv of freshly distilled thionyl chloride (0.56 mL, 0.89 g, 7.5 mmol) and the mixture was allowed to react at reflux for 2 h. After cooling and concentration under vacuo, the oily residue was diluted with dry dichloromethane and treated with charcoal. The concentration of the solution under reduced pressure give suitable aliphatic halide **14a** or **14b** in quantitative yield.

4.5.1. 2-(2-Chloroethyl)-2,3-dihydro-3-phenylisoindol-1-one (14a). This product was isolated as an orange oil in quantitative yield; IR (neat) $\tilde{\upsilon}_{max}=3012$ and 2988 (CH), 1689 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.16–3.30 (m, 1H, CH_2–CH_2), 3.51–3.62 (m, 1H, CH_2–CH_2), 3.71–3.83 (m, 1H, CH_2–CH_2), 4.14–4.27 (m, 1H, CH_2–CH_2), 5.72 (s, 1H, CH), 7.10–7.96 (m, 9H, aromatic); MS (EI): $m/z=271$ $[M^+]$. Anal. Calcd for $C_{16}H_{14}ClNO$ (271.74): C, 70.72; H, 5.19; N, 5.15. Found. C, 70.39; H, 5.01; N, 4.92.

4.5.2. 3-Benzyl-2-(2-chloroethyl)-2,3-dihydroisoindol-1-one (14b). This product was isolated as an uncolourless oil in quantitative yield; IR (neat) $\tilde{\upsilon}_{max}=3021$ and 2979 (CH), 1685 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.97 (dd, 1H, $J=14.1$, 7.8 Hz, CH_2–CH), 3.38–3.60 (m, 2H, CH_2–CH_2 and CH_2–CH), 3.68–3.89 (m, 2H, CH_2–CH_2), 4.31–4.44 (dt, 1H, $J=5.5$, 4.7 Hz, CH_2–CH_2), 5.06 (dd, 1H, $J=7.8$, 4.7 Hz, CH–CH_2), 6.91–6.99 (m, 1H, aromatic), 7.02–7.14 (m, 2H, aromatic), 7.19–7.34 (m, 3H, aromatic), 7.36–7.50 (m, 2H, aromatic), 7.75–7.84 (m, 1H, aromatic); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 38.5, 42.5, 42.6, 61.6, 123.1, 123.7, 127.2, 128.4, 128.7, 129.5, 131.4, 131.6, 135.7, 145.2, 168.8; MS (EI): $m/z=285$ $[M^+]$. Anal. Calcd for $C_{17}H_{16}ClNO$ (285.77): C, 71.45; H, 5.64; N, 4.90. Found. C, 71.20; H, 5.36; N, 4.61.

4.6. General procedure for *S*-alkylation of *N*-chloroethylisoindolones (14a,b)

The procedure is identical to that used for synthesis of *N*-(2-phenylthioethyl)phthalimide (**7**). After 12 h of reaction at 100 °C, the reaction mixture was cold and diluted with water (30 mL) and diethyl ether (30 mL). The organic layer was separated, washed twice with water, brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the reaction residue by flash chromatography on silica gel column using a mixture of cyclohexane–AcOEt (4/1) as eluent gave the expected sulfure (**11a**) or (**11b**) in 88% yield in both cases.

4.6.1. 2,3-Dihydro-3-phenyl-2-(2-phenylthioethyl)isoindol-1-one (11a). The characteristics of this component, obtained in 88% yield, are identical to that reported above in Section 4.2.3

4.6.2. 3-Benzyl-2,3-dihydro-2-(2-phenylthioethyl)-isoindol-1-one (11b). This product was not isolated in pure form (impurities do not exceed 5%). The product obtained as an orange oil in 88% yield (determined by GC–MS coupling) was used in the next without other purification; IR (neat) $\tilde{\upsilon}_{max}=3017$ and 2988 (CH), 1694 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.75 (dd, 1H, $J=13.3$, 7.8 Hz, CH_2–CH), 3.15–3.50 (m, 4H, CH_2–CH_2 and CH_2–CH), 4.15–4.28 (m, 1H, CH_2–CH_2), 4.87 (dd, 1H, $J=7.8$, 4.7 Hz, CH_2–CH), 6.85–6.91 (m, 3H, aromatic), 7.08–7.29 (m, 6H, aromatic), 7.31–7.47 (m, 4H, aromatic), 7.71–7.80 (m, 1H, aromatic); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.9, 31.8, 38.4, 61.2, 122.9, 123.5, 126.3, 127.1, 128.2, 128.5, 128.7, 129.1, 129.4, 131.1, 131.9, 135.2, 135.7, 145.0, 168.5; MS (EI): $m/z=359$ $[M^+]$. Anal. Calcd for $C_{23}H_{21}NOS$ (359.49): C, 76. 85; H, 5.89; N, 3.90. Found. C, 76.55; H, 5.63; N, 3.68.

4.7. General procedure for oxidation of *N*-phenylthioethylisoindolone derivatives (11a,b)

To a solution of sulfides **11a**,**b** (1 mmol) in 10 mL of dry dichloromethane was added in one portion under vigorous stirring at −60 °C a solution of *m*-CPBA (0.18 g, 1 mmol) in dry dichloromethane (10 mL). After 2–5 min of reaction at this temperature and an additional 5 min at room temperature, the mixture was alkalinised with a saturated solution of $NaHCO_3$ (15 mL). The organic layer after separation, was dried over $MgSO_4$, concentrated under reduced pressure, and the residue was passed through short silica gel column using a mixture of cyclohexane–AcOEt (1/2) as eluent to give the expected cyclic sulfoxides **15a** or **15b** as inseparable two diastereosomers in quantitative yield.

4.7.1. 2,3-Dihydro-2-(2-phenylsulfanylethyl)-3-phenylisoindol-1-one (15a). This product was isolated as a mixture of two diastereomers (54/46) as a white solid in quantitative yield; IR (KBr) $\tilde{\upsilon}_{max}=3009$ and 2986 (CH), 1698 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.83–2.94 (m, 2×1H, CH_2–CH_2, mixture), 3.07–3.51 (m, 2×2H, CH_2–CH_2, mixture), 3.91–4.18 (m, 2×1H, CH_2–CH_2, mixture), 5.42 (s, 1H, CH of minor isomer), 5.73 (s, 1H, CH of major isomer), 7.08–7.18 (m, 2×2H, aromatic, mixture), 7.21–7.62 (m, 2×11H, aromatic, mixture), 7.76–7.92 (m, 2×1H, aromatic, mixture); MS (EI): $m/z=361$ [M^+]. Anal. Calcd for $C_{22}H_{19}NO_2S$ (361.11): C, 73.10; H, 5.30; N, 3.88. Found. C, 73.04; H, 5.11; N, 3.65.

4.7.2. 3-Benzyl-2-(2-phenylsulfanylethyl)-2,3-dihydroisoindol-1-one (15b). This product was isolated as a mixture of two diastereomers (55/45) as a white solid in quantitative yield; IR (KBr) $\tilde{\upsilon}_{max}=3012$ and 2990 (CH), 1693 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.79–2.92 (m, 1H, CH_2–CH of major isomer), 2.96–3.08 (m, 1H, CH_2–CH of minor isomer), 3.22–3.53 (m, 2×3H, CH_2–CH_2 and CH_2–CH, mixture), 3.68–3.89 (m, 2×1H, CH_2–CH, mixture), 4.11–4.31 (m, 2×1H, CH_2–CH_2, mixture), 4.69 (dd, 1H, $J=8.6$, 4.7 Hz, CH of minor isomer), 5.01 (dd, 1H, $J=7.8$, 4.6 Hz, CH of major isomer), 6.80–7.12 (m, 2×2H, aromatic, mixture), 7.16–7.89 (m, 2×12H, aromatic, mixture); MS (EI): $m/z=375$ [M^+]. Anal. Calcd for $C_{23}H_{21}NO_2S$ (375.13): C, 73.57; H, 5.64; N, 3.73. Found. C, 73.36; H, 5.49; N, 3.61.

4.8. General procedure for Swern oxidation of *N*-hydroxyethylisoindolone derivatives (13a,b)

To a mixture of oxalyl chloride (1.01 mL, 11.83 mmol, 3.15 equiv) in 15 mL of anhydrous dichloromethane and cooled at −60 °C was added dropwise dry DMSO (1.33 m, 18.78 mmol, 5 equiv) and the mixture stirred at −60 °C for 15 min. A solution of *N*-hydroxyethylisoindolone derivatives (**13a**,**b**, 3.75 mmol, 1 equiv) in 30 mL of anhydrous dichloromethane was then added slowly and the resulting solution stirred at same temperature for 1 h, at which time triethylamine (2.80 mL, 19.9 mmol, 5.3 equiv) was added and the reaction mixture was allowed to warm to 0 °C. After hydrolysis with saturated sodium hydrogenocarbonate solution, the solution was then concentrated under reduced pressure. The residue was redissolved in dichloromethane, washed twice with water, brine, dried over Na_2SO_4, and concentrated to dryness in vacuo. Purification of the reaction residue by flash chromatography on silica gel column using a mixture of cyclohexane–AcOEt (2/3) as eluent give the expected formyl derivative (**17a**) or (**17b**) in acceptable yield.

4.8.1. (1,3-Dihydro-1-oxo-3-phenylisoindol-2-yl)acetaldehyde (17a). This product was isolated as an uncolourless oil in 72% yield; IR (neat) $\tilde{\upsilon}_{max}=3010$ and 2987 (CH), 1684 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.75 (d, 1H, $J=18.7$ Hz, CH_2), 4.71 (d, 1H, $J=18.7$ Hz, CH_2), 5.65 (s, 1H, CH), 7.07–7.19 (m, 3H, aromatic), 7.25–7.51 (m, 5H, aromatic), 7.87–7.91 (m, 1H, aromatic), 9.52 (s, 1H, CH=O); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 50.4, 65.2, 123.3, 123.8, 127.7, 128.5, 129.1, 129.3, 130.6, 132.3, 136.1, 146.5, 169.0, 196.9; MS (EI): $m/z=251$ [M^+]. Anal. Calcd for $C_{16}H_{13}NO_2$ (251.09): C, 76.48; H, 5.21; N, 5.57. Found. C, 76.29; H, 5.11; N, 5.39.

4.8.2. (3-Benzyl-1,3-dihydro-1-oxoisoindol-2-yl)acetaldehyde (17b). This product was isolated as an uncolourless oil in 63% yield; IR (neat) $\tilde{\upsilon}_{max}=3014$ and 2992 (CH), 1698 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.97 (dd, 1H, $J=14.1$, 7.0 Hz, CH_2–CH), 3.14 (dd, 1H, $J=14.1$, 6.3 Hz, CH_2–CH), 3.99 (d, 1H, $J=19.6$ Hz, CH_2), 4.62 (d, 1H, $J=19.6$ Hz, CH_2), 4.96 (dd, 1H, $J=7.0$, 6.3 Hz, CH–CH_2), 7.03–7.10 (m, 3H, aromatic), 7.12–7.55 (m, 5H, aromatic), 7.78–7.83 (m, 1H, aromatic), 9.52 (s, 1H, CH=O); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 39.1, 51.3, 61.4, 122.9, 123.8, 127.3, 128.4, 128.7, 129.3, 131.1, 131.7, 135.9, 145.4, 169.0, 196.9; MS (EI): $m/z=265$ [M^+]. Anal. Calcd for $C_{17}H_{15}NO_2$ (265.11): C, 76.96; H, 5.70; N, 5.28. Found. C, 76.78; H, 5.43; N, 5.12.

4.9. General procedure for cyclodeshydratation of aldehydes 17a,b or Pummerer type-cyclization of sulfoxides 15a,b into cyclic isoindolone 5a,b

Method A: Cyclocondensation. To a stirred and cold solution of aldehydes (**17a**,**b**, 2 mmol) in 15 mL of glacial acetic acid was added dropwise concentrated sulphuric acid (96–98%, 30 mL). The mixture was stirred at room temperature for 4 h and neutralised carefully on cooling with addition dropwise of 30% ammonia solution. After extraction with dichloromethane and separation, the organic layer was washed with water, brine, dried over $MgSO_4$, and concentrated to dryness in vacuo. Purification of the reaction residue by flash chromatography on silica gel column using a mixture of cyclohexane–AcOEt (4/1) as eluent gave the expected cyclic product (**5a**) or (**5b**) in 30% and 40% yields. *Method B: Pummerer cyclization*. To a stirred solution of sulfoxides (**15a**,**b**, 2.77 mmol) in 45 mL of dry dichloromethane was added dropwise TFAA (6 mL, 42.6 mmol). After 2 h of reaction at reflux, the reaction mixture was washed successively with saturated sodium hydrogenocarbonate solution and brine. The organic layer was dried over $MgSO_4$, concentrated under reduced pressure, and the residue was passed through short silica gel column using a mixture of cyclohexane–AcOEt (4/1) as eluent to give the expected cyclic product (**5a**) or (**5b**) in 100 and 96% yields, respectively.

4.9.1. Isoindolo[1,2-*a*]isoquinolin-8(12*bH*)-one (5a). This product was isolated as an orange solid in yields indicated above; mp=122 °C (ethanol/diethyl ether); IR (KBr) $\tilde{\upsilon}_{max}=3009$ (CH), 1703 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.86 (s, 1H, CH), 6.20 (d, 1H, $J=7.8$ Hz, CH=CH), 7.16–7.31 (m, 4H, aromatic), 7.52–7.71 (m, 3H, aromatic), 7.90 (dd, 2H, $J=6.3$, 7.8 Hz CH=CH+aromatic); ^{13}C NMR

($CDCl_3$, 75 MHz) δ 57.8, 123.4, 123.9, 124.2, 124.6, 125.6, 126.9, 128.5, 128.6, 128.7, 129.2, 129.3, 132.1, 132.5, 134.5, 172.1; MS (EI): *m*/*z* = 233 [M^+]. Anal. Calcd for $C_{16}H_{11}NO$ (233.08): C, 82.38; H, 4.75; N, 6.00. Found. C, 82.21; H, 4.66; N, 5.86.

4.9.2. 12*b*,13-Dihydrobenzo[4,5]azepino[2,1-*a*]isoind-ol-8-one (5b). This product was isolated as a white-yellow solid in yields indicated above; mp = 110 °C (ethanol); IR (KBr) $\tilde{\upsilon}_{max}$ = 3012 (CH), 1701 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.05 (dd, 1H, *J* = 14.1, 7.0 Hz, CH_2–CH), 3.51 (dd, 1H, *J* = 14.1, 3.1 Hz, CH_2–CH), 5.08 (dd, 1H, *J* = 7.0, 3.1 Hz, CH–CH_2), 6.10 (d, 1H, *J* = 14.1 Hz, CH=CH), 6.88–6.93 (m, 2H, aromatic), 7.05–7.52 (m, 6H, CH=CH + aromatic), 7.74 (d, 1H, *J* = 7.0 Hz, aromatic); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 42.0, 60.6, 109.9, 121.4, 122.4, 124.3, 127.0, 127.4, 129.0, 129.9, 130.8, 131.2, 133.0, 135.4, 135.9, 144.4, 165.8; MS (EI): *m*/*z* = 247 [M^+]. Anal. Calcd for $C_{17}H_{13}NO$ (247.10): C, 82.38; H, 4.75; N, 6.00. Found. C, 82.21; H, 4.66; N, 5.86.

4.9.3. (*cis* and *trans*)-5,12*b*-Dihydro-5-phenylthioiso-indolo[1,2-*a*]isoquinolin-8(6*H*)-one (16a). Following a procedure similar to that described above for the preparation of cyclic isoindolines **5a**,**b**, the sulfide **16a** as the Pummerer type-cyclization intermediate was isolated when the reaction was performed at room temperature for 30 min. After a similar work-up as above, this product, **16a**, was obtained as a mixture of two diastereomers in 56/44 ratio as uncolourless oil in quantitative yield; IR (neat) $\tilde{\upsilon}_{max}$ = 3016 and 2983 (CH), 1704 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.18 (dd, 1H, *J* = 14.1, 9.4 Hz, CH_2–CHS, major isomer), 3.32 (dd, 1H, *J* = 14.1, 5.5 Hz, CH_2–CHS, minor isomer), 4.31 (dd, 1H, *J* = 14.1, 3.9 Hz, CH_2–CHS, major isomer), 4.44 (dd, 1H, *J* = 14.1, 5.5 Hz, CH_2–CHS, minor isomer), 4.48 (s, 1H, CH, major isomer), 5.67 (s, 1H, CH, minor isomer), 6.33 (dd, 1H, *J* = 9.4, 3.9 Hz, SCH–CH_2, major isomer), 6.47 (d, 1H, *J* = 5.5 Hz, SCH–CH_2, minor isomer), 6.97–7.41 (m, 2×13H, aromatic, mixture), 7.83–7.96 (m, 2×1H, aromatic, mixture); MS (EI): *m*/*z* = 233 [$M^+ - PhSH$].

Acknowledgements

The authors are grateful for many helpful comments and fruitful discussions throughout the course of this work with Professor Bernard Decroix. The authors also thank the Scientific Council of University of Le Havre, France, for their support of this research program.

References and notes

1. (a) Boekelheide, V. *Alkaloids* **1960**, *7*, 201. (b) Hill, R. K. *Alkaloids* **1967**, *9*, 483.
2. (a) Bowden, B. F., Studies in Natural Products Chemistry. In *Bioact. Nat. Pro. (Part D)* **2000**, *23*, 233. (b) Urban, S.; Hickford, S. J. H.; Blunt, J. W.; Munro, M. H. G. *Curr. Org. Chem.* **2000**, *4*, 765. (c) Reddy, M. V. R.; Rao, M. R.; Rhodes, D.; Hansen, M. S. T.; Rubins, K.; Bushman, F. D.; Venkateswarlu, Y.; Faulkner, D. J. *J. Med. Chem.* **1999**, *42*, 1901. (d) Chawla, A. S.; Kapoor, V. K. In Pelletier, S. W., Ed.; Alkaloids: Chemical and Biological Prospectives; 1995, 86.
3. (a) Schultes, R. E.; Raffauf, D. *The Healing Forest. Medicinal and Toxic Plants of the Northwest Amazonia*; R. F. Dioscorides, 1990; See also the references cited therein. (b) Amer, M. E.; Shamma, M.; Freyer, A. J. *J. Nat. Prod.* **1991**, *54*, 329 and references cited therein. (c) Dyke, S. F.; Quessy, S. N. In Rodrigo, R. G. A., Ed.; The Alkaloids; Academic: New York, 1981; Vol. 18.
4. (a) Shamma, M. In *The Protoberberines and Retro-Protoberberines*; Blomquist, A. T., Wasserman, H., Eds.; The Isoquinoline Alkaloids: Chemistry and Pharmacology; Academic: New York, 1972; Vol. 25, p 268. (b) Shamma, M.; Moniot, J. *Isoquinoline Alkaloids Research*; Plenum: New York, 1978. (c) Shamma, M.; Rahimizadeh, M. *J. Nat. Prod.* **1986**, *49*, 398. (d) Bentley, K. W. The Berberines and Tetrahydroberberines. In Ravindranath, B., Ed.; The Isoquinoline Alkaloids: Chemistry and Pharmacology; Harwood Academic: Bangalore, 1988; Vol. 1, p 219.
5. (a) Sorgi, K. L.; Maryanoff, C. A.; McComsey, D. F.; Graden, D. W.; Maryanoff, B. E. *J. Am. Chem. Soc.* **1990**, *112*, 3567. (b) Maryanoff, B. E.; McComsey, D. F.; Mutter, M. S.; Sorgi, K. L.; Maryanoff, C. A. *Tetrahedron Lett.* **1988**, *29*, 5073.
6. (a) Zhang, Q.; Tu, G.; Zhao, Y.; Cheng, T. *Tetrahedron* **2002**, *58*, 6795. (b) Knölker, H.-J.; Agarwal, S. *Tetrahedron Lett.* **2005**, *46*, 1173.
7. (a) Juma, B. F.; Majinda, R. R. T. *Phytochemistry* **2004**, *65*, 1397. (b) See also Ref. 3b.
8. Ito, K.; Haruna, M.; Jinno, Y.; Furukawa, H. *Chem. Pharm. Bull.* **1976**, *24*, 52.
9. Tsuda, Y.; Hosoi, S.; Nakai, A.; Ohshima, T.; Sakai, Y.; Kiuchi, F. *J. Chem. Soc., Chem. Commun.* **1984**, 1216.
10. Jousse, C.; Desmaële, D. *Eur. J. Org. Chem.* **1999**, 909.
11. (a) Allin, S. M.; James, S. L.; Elsegood, M. R. J.; Martin, W. P. *J. Org. Chem.* **2002**, *67*, 9464. (b) Allin, S. M.; Streetley, G. B.; Slater, M.; James, S. L.; Martin, W. P. *Tetrahedron Lett.* **2004**, *45*, 5493.
12. Toda, J.; Niimura, Y.; Sano, T.; Tsuda, Y. *Heterocycles* **1998**, *48*, 1599 and the references cited therein.
13. Kessar, S. V.; Singh, T.; Vohra, R. *Tetrahedron Lett.* **1987**, *28*, 5323.
14. Mazzocchi, P. H.; King, C. R.; Ammon, H. L. *Tetrahedron Lett.* **1987**, *28*, 2473.
15. (a) Ishibashi, H.; Kawanami, H.; Iriyama, H.; Ikeda, M. *Tetrahedron Lett.* **1995**, *36*, 6733. (b) Ishibashi, H.; Kawanami, H.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 6817.
16. Hucher, N.; Decroix, B.; Daïch, A. *J. Org. Chem.* **2001**, *66*, 4695.
17. Hucher, N.; Pesquet, A.; Netchitaïlo, P.; Daïch, A. *Eur. J. Org. Chem.* **2005**, 2758.
18. Cul, A.; Daïch, A.; Decroix, B.; Sanz, G.; Van Hijfte, L. *Heterocycles* **2004**, *64*, 33.
19. Hucher, N.; Daïch, A.; Decroix, B. *Org. Lett.* **2000**, *2*, 1201.
20. Sazaki, K. *Biol. Pharm. Bull.* **1995**, *18*, 1228.
21. Ishibashi, H.; Uegaki, M.; Sakai, M.; Takeda, Y. *Tetrahedron* **2001**, *57*, 2115.
22. Cul, A.; Daïch, A.; Decroix, B.; Sanz, G.; Van Hijfte, L. *Tetrahedron* **2004**, *60*, 11029.
23. (a) Meyers, A. I.; Romo, D. *Tetrahedron* **1991**, *47*, 9503. (b) Meyers, A. I.; Groaning, M. D. *Tetrahedron* **2000**, *56*, 9843.

24. Mertens, P.; Zilch, H.; Konig, B.; Schafer, W.; Poll, T.; Kampe, W.; Seidel, H.; Leser, U.; Leinert, H. *J. Med. Chem.* **1993**, *36*, 2526.
25. Aeberli, P.; Houlihan, W. J. *J. Org. Chem.* **1969**, *34*, 165.
26. (a) Garofalo, A.; Campiani, G.; Nacci, V.; Fiorini, I. *Heterocycles* **1992**, *34*, 51. (b) Saitoh, T.; Ichikawa, T.; Horiguchi, Y.; Toda, J.; Sano, T. *Chem. Pharm. Bull.* **2001**, *49*, 979. (c) Horiguchi, Y.; Sonobe, A.; Saitoh, T.; Toda, J.; Sano, T. *Chem. Pharm. Bull.* **2001**, *49*, 1132. (d) Horiguchi, Y.; Saitoh, T.; Terakado, S.; Honda, K.; Kimura, T.; Toda, J.; Sano, T. *Heterocycles* **2001**, *54*, 967 and references cited therein.
27. Elliot, R.; Hewgill, F.; McDonald, E.; McKenna, P. *Tetrahedron Lett.* **1980**, 4633.
28. (a) Napolitano, E.; Spinelli, G.; Fiaschi, R.; Marsili, A. *J. Chem. Soc., Perkin Trans. 1* **1986**, 785. (b) See for example, the following reference, Couture, A.; Deniau, E.; Grandclaudon, P.; Hoarau, C. *Tetrahedron* **2000**, *56*, 1491.

Available online at www.sciencedirect.com
SCIENCE DIRECT®

Tetrahedron 62 (2006) 716–725

Tetrahedron

Synthetic study of tautomycin. Part 2: Synthesis of Ichihara's fragment based on regioselective enzymatic acetylation of complex molecule

Yusuke Ishii,[a] Shinji Nagumo,[b,*] Takayuki Arai,[c] Masami Akuzawa,[a]
Norio Kawahara[a] and Hiroyuki Akita[c]

[a]*Hokkaido College of Pharmacy, Katuraoka 7-1, Otaru 047-02, Japan*
[b]*Department of Applied Chemistry, Kogakuin University, Nishi-shinjuku 1-24-2, Shinjuku, Tokyo 163-8677, Japan*
[c]*School of Pharmaceutical Science, Toho University, Miyama 2-2-1, Funabashi, Chiba 274-8510, Japan*

Received 31 May 2005; accepted 3 October 2005

Abstract—Formal synthesis of tautomycin, which inhibits type 1 and type 2A protein phosphatases, was achieved. Spiroketal diol **21** was synthesized from alcohol **2** or **11**. The regioselective enzymatic acetylation of **21** with the lipase 'Amano PS' gave monoacetate **23** in 90% yield, which was converted into Ichihara's intermediate **31** based on Julia coupling and Wittig homologation.

1. Introduction

Tautomycin was isolated by Isono et al. from a culture of *Streptomyces spiroverticillatus*.[1] The structure contains spiroketal and maleic anhydride moieties and 13 chiral centers. The absolute configuration of the compound was determined by spectroscopic analysis of chemical degradation products and conformational calculations.[2] Tautomycin is a representative tumor promoter and specifically inhibits type 1 and type 2A protein phosphatases.[3] Total syntheses have been achieved by several groups.[4] The structural complexity and unique biological activity stimulated us to carry out a synthetic study of tautomycin on the basis of the original strategy. We herein report the formal synthesis of tautomycin based on regioselective enzymatic protection of a spiroketal compound with two primary hydroxy groups.[5]

1.1. Synthetic strategy

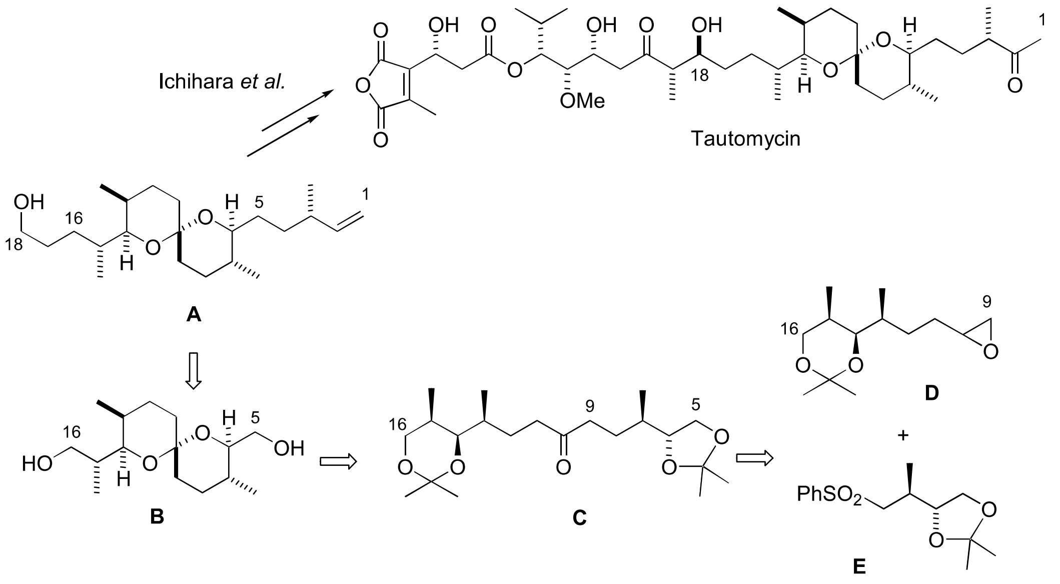
Scheme 1 shows our retrosynthesis. We chose compound **A**, which is a synthetic intermediate of tautomycin reported by Ichihara et al. as a target molecule.[4a] This molecule should be obtainable by successive installation of two kinds of alkyl chains to compound **B** corresponding to segment C5–C16. This plan requires selective functionalization between different primary hydroxy groups at the C5 and C16 positions of **B**. Enzymatic esterification with lipase was expected to be an efficient approach for controlling the regiochemistry, since lipase exhibited potential molecular recognition in many cases of chiral resolution of racemic alcohols.[6] Although regioselective enzymatic esterification has been reported, most of them are examples for limited types of substrates.[7] Selective acetylation between different primary hydroxy groups in a highly complex molecule had not been reported when we started this study. Compound **B** should be stereoselectively prepared by transacetalization of ketone **C** with five stereocenters. Compound **C** can be retrosynthetically divided into segment C9–C16 **D** and sulfone **E**, which would be easily prepared from (+)-malic acid.[8]

1.2. Synthesis of segment C9–C16

We previously reported highly enantioselective esterification of *meso*-diol **1** with lipase from *Porcine pancreas* 'PPL' (Scheme 2).[9] At first, we therefore selected (−)-**2** as a starting material for our synthesis of segment C9–C16. Sulfinylation of (−)-**2** (95% ee) with PhSSPh and Bu_3P[10] followed by oxidation of the sulfur atom with MCPBA gave sulfone **4** in excellent yield. Removal of acetyl and benzyl groups in **4** and the subsequent acetalization provided **7** efficiently. Treatment of **7** with *tert*-BuLi and allyl bromide afforded the alkylated product **8** in 82% yield.

Keywords: Tautomycin; Regioselective; Enzymatic acetylation.
* Corresponding author. Tel.: +81 3 3340 2683; fax: +81 3 3340 0147; e-mail: bt13071@ns.kogakuin.ac.jp

0040–4020/$ - see front matter © 2005 Published by Elsevier Ltd.
doi:10.1016/j.tet.2005.10.013



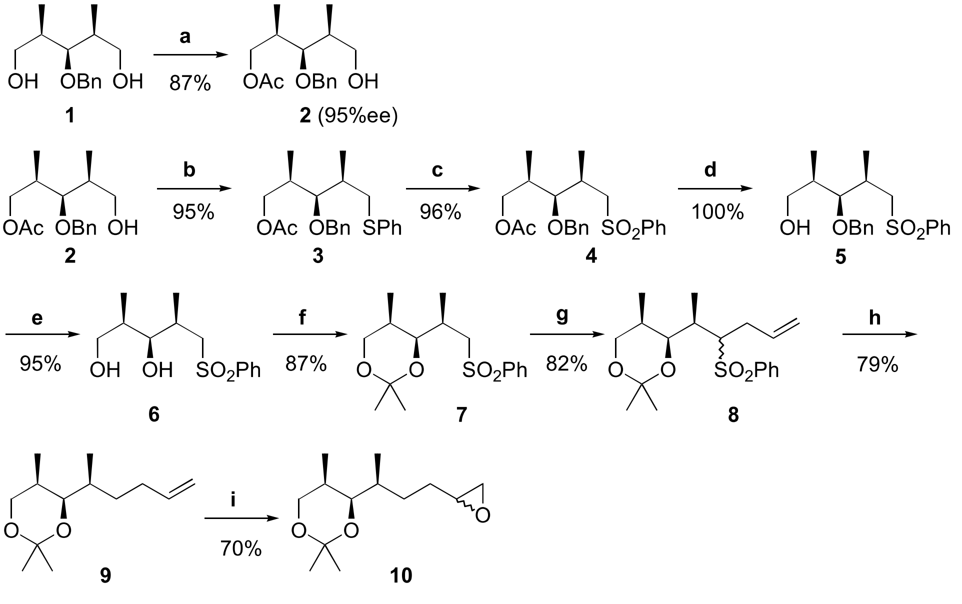
Scheme 1.

Desulfurization[11] of **8** with Na(Hg) resulted in the formation of **9** corresponding to segment C9–C16 of tautomycin. Treatment of **9** with MCPBA gave epoxide **10** as an epimeric mixture.

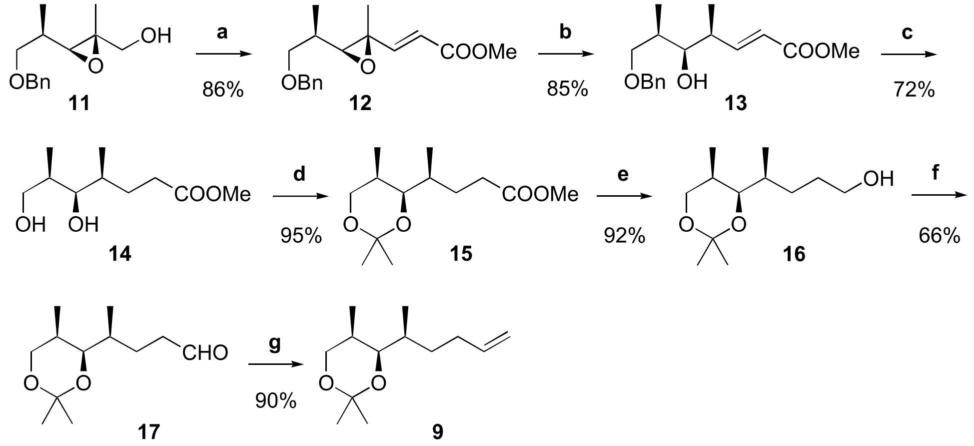
We also developed an alternative route for the synthesis of optically active **9** based on palladium-catalyzed hydrogenolysis of vinyloxirane with HCOOH (Scheme 3).[12] Epoxyalcohol **11**, which was synthesized according to Meyers's method,[13] was converted into vinyloxirane **12** by oxidation and subsequent Wittig homologation. Reductive C–O bond cleavage of **12** with HCOOH in the presence of $Pd(dba)_2$ afforded alcohol **13** along with a small amount of inseparable stereo isomer. The ratio was found to be ca. 7:1 based on the ^1H NMR spectroscopic data. Catalytic hydrogenation of **13** with $Pd(OH)_2$–C gave diol **14**, which could be separated from a small amount of isomer by column chromatography with silica gel. Diol **14** was coverted into **15** upon treatment with 2,2-dimethoxypropane in the presence of $TsOH \cdot H_2O$. Reduction of **15** with $LiAlH_4$ followed by TPAP oxidation produced aldehyde **17**, which was finally converted into **9** by Wittig homologation.

1.3. Synthesis of spiroketaldiol corresponding to segment C5–C16 and enzymatic regioselective acetylation of the diol

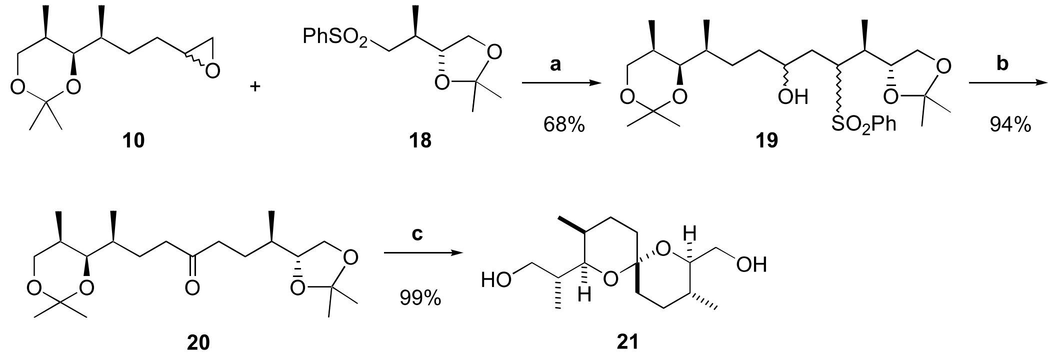
Next, coupling of the segment C5–C8 and the segment C9–C16 was carried out (Scheme 4). Without separation, **10** was subjected to the coupling with an anion generated from **18**. $BF_3 \cdot Et_2O$ was essential for the smooth conversion to give the hydroxysulfone **19** in 68% yield.[4h,14] Treatment of **19** with Na(Hg) followed by Swern oxidation afforded ketone **20** corresponding to the segment C5–C16.



Scheme 2. (a) Lipase PPL, vinyl acetate, 33 °C, 2 day; (b) PhSSPh, *n*-Bu_3P, pyridine; (c) MCPBA, CH_2Cl_2; (d) K_2CO_3, MeOH (e) H_2, $Pd(OH)_2$–C, MeOH; (f) $(MeO)_2CMe_2$, 10-camphorsulfonic acid, benzene; (g) allyl bromide, *tert*-BuLi, THF; (h) 5% Na(Hg), MeOH, reflux; (i) MCPBA, CH_2Cl_2.



Scheme 3. (a) (i) Dess–Martin oxidn (ii) $Ph_3P{=}CHCOOMe$, DMSO; (b) Pd(dba), Ph_3P, HCOOH, Et_3N, dioxane; (c) H_2, $Pd(OH)_2$–C, MeOH; (d) $(MeO)_2CMe_2$, $TsOH \cdot H_2O$; (e) DIBAL-H, toluene, −78 °C; (f) TPAP, NMO, CH_2Cl_2; (g) $Ph_3PMe^+ \cdot Br^-$, n-BuLi, THF.



Scheme 4. (a) *tert*-BuLi, $BF_3 \cdot Et_2O$, THF; (b) (i) 5% Na(Hg), MeOH, reflux (ii) TPAP, NMO, CH_2Cl_2; (c) 10-camphorsulfonic acid, MeOH.

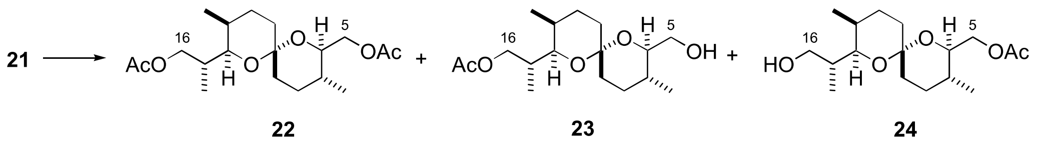
Transformation of **20** into the spiroketal **21** proceeded stereoselectively upon treament with camphorsulfonic acid in MeOH to give **21** in 99% yield. The structure of **21** was assigned on the basis of spectroscopic data. The stereochemistry of the newly introduced asymmetric center at the C10 position was determined by observed NOEs between C6–H and C14–H or C15–Me proton.

The most important issue in our synthetic study of tautomycin is enzymatic differentiation of two primary hydroxy groups in **21**. Based on the results of a screening experiment, the lipase 'Amano PS' from *Pseudomonas* sp. was selected as a catalyst of regioselective acetylation of **21**. The enzyme preferentially accelerated the acetylation of a hydroxy group at the C16 position to provide **23** in 90% yield (Table 1). On the other hand, chemical acetylation of **21** with an equivalent of acetic anhydride in pyridine did not show a satisfactory selectivity. The structure of **23** was assigned on the basis of spectroscopic data. A decoupling experiment of the ^{1}H NMR spectrum showed a correlation between two protons at the C16 position (δ 4.06, dd, $J=11.0$, 4.2 Hz: δ 3.86, dd, $J=11.0$, 6.4 Hz) and C15–H.

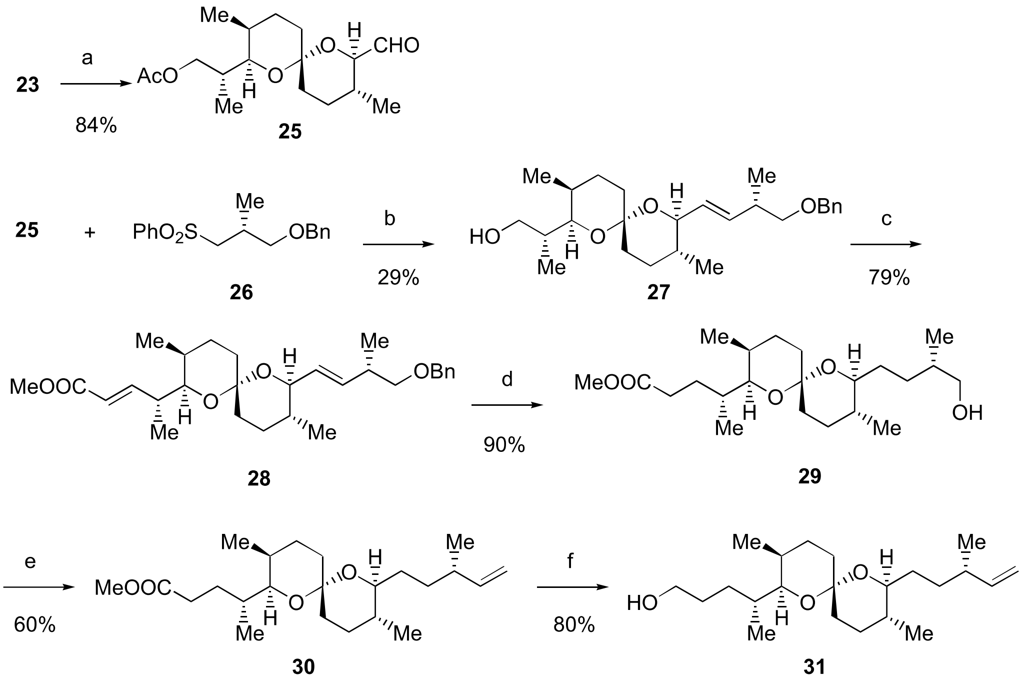
1.4. Conversion of 24 into 31 corresponding to C1–C18 of tautomycin

Finally, the conversion of monoacetate **23** into Ichihara's intermediate of tautomycin was attempted through Julia coupling[15] and Wittig homologation (Scheme 5). Oxidation of **23** with Dess–Martin periodinane gave the aldehyde **25**, which was coupled with the sulfone **26** upon treatment with n-BuLi at −50 °C to afford β-hydroxysulfone. After acetylation of the crude β-hydroxysulfone, reductive elimination of the acetylated product accompanied deprotection of the terminal acetyl group to give **27**. Dess–Martin oxidation of **27** followed by Wittig

Table 1.



	22 (%)	23 (%)	24 (%)	21 (Recovered) (%)
Amano PS, vinyl acetate	5	90	2	3
Ac_2O, pyridine	11	36	16	31



Scheme 5. (a) Dess–Martin oxidn; (b) (i) *n*-BuLi, THF, −50 °C (ii) Ac_2O, DMAP, pyridine (iii) 5% Na(Hg), MeOH, 50 °C; (c) (i) Dess–Martin oxidn (ii) $Ph_3P{=}CHCOOMe$, CH_2Cl_2 (d) H_2, $Pd(OH)_2$–C,MeOH; (e) (i) Dess–Martin oxidn (ii) $Ph_3PMe^+\cdot Br^-$, *n*-BuLi, THF, 0 °C; (f) $LiAlH_4$, THF, 0 °C.

homologation provided α,β-unsaturated ester **28**, which was converted into **29** in high yield upon treatment with $Pd(OH)_2$–C under H_2. Dess–Martin oxidation of **29** followed by treatment with $Ph_3P{=}CH_2$ gave the terminal alkene **30**. Finally, reduction of **30** with $LiAlH_4$ afforded alcohol **31**, whose spectroscopic data were identical with those reported by Ichihara et al.

2. Conclusion

In conclusion, we achieved the formal synthesis of tautomycin based on regioselective enzymatic acetylation of spiroketal diol **21**. Compound **21** was prepared from optically active monoacetate **2** (12 steps, 16.5% overall yield). The intermediate **10** in the synthetic route of **21** was alternatively made based on pallaium-catalyzed hydrogenolysis of vinyloxirane with HCOOH. Regioselective enzymatic acetylation of **21** with the lipase 'Amano PS' proceeded with high selectivity to give the desired monoacetate **23** in 90% yield. An efficient molecular recognition by using the lipase 'Amano PS' would be applicable to the differentiation of complex compounds having plural primary alcohols. Finally, conversion of **23** into Ichihara's intermediate **31** based on Julia coupling and Wittig homologation was achieved.

3. Experimental

3.1. General methods

The melting points were determined on a Yanaco micro melting point apparatus and were uncorrected. Optical rotations were measured on a JASCO DIP-370. IR spectra were recorded on a JASCO A-3, JASCO IRA-102 or a JASCO FT-IR-7000 spectrometer. NMR spectra were recorded on a JEOL GX-270, a JEOL EX-400, or a JEOL AL-400 spectrometer using tetramethylsilane as an internal standard. Chemical shifts are given in ppm. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; br, broad. MS spectra were measured on a Hitachi M-2000 (EI-MS, SIMS), a JEOL JMA-DX303 or a JEOL JMA-DA5000 (FAB-MS) instrument. Column chromatography was carried out on Merck's Silica gel 60 (70–230 mesh ASTM).

3.1.1. (2*R*,3*S*,4*R*)-3-Benzyloxy-2,4-dimethyl-5-(phenylthio)pentyl acetate (3). To a mixture of **2** (19.2 g, 68.6 mmol), diphenyl disulfide (19.4 g, 89.0 mmol) and pyridine (100 ml) was added tri-*n*-butylphosphine (28 ml, 113 mmol) at room temperature. The mixture was stirred for 30 h at room temperature, then quenched with brine and extracted with Et_2O. The organic layer was washed with 2 N HCl and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with hexane–AcOEt (19/1) to give **3** (24.3 g, 65.3 mmol, 95%) as a colorless oil: $[\alpha]_D^{25}$ +9.1 (*c* 1.38, $CHCl_3$); IR (neat) 1740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.15 (10H, m), 4.57 (2H, s), 4.00–3.91 (2H, m), 3.55 (1H, t, *J*=4.9 Hz), 3.05 (1H, dd, *J*=12.7, 6.4 Hz), 2.80 (1H, dd, *J*=12.7, 7.3 Hz), 2.14–1.97 (2H, m), 2.01 (3H, s), 1.11 (3H, d, *J*=6.8 Hz), 1.01 (3H, d, *J*=6.8 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 171.0, 138.6, 136.7, 129.3, 128.9, 128.3, 127.5, 127.5, 126.0, 81.6, 74.6, 67.1, 38.4, 35.7, 35.4, 20.9, 15.0, 12.9; FAB-MS *m*/*z* 373 (M^+ +1). Anal. Calcd for $C_{22}H_{28}O_3S$: C, 70.93; H, 7.58. Found: C, 70.64; H, 7.69.

3.1.2. (2*R*,3*S*,4*R*)-3-Benzyloxy-2,4-dimethyl-5-(phenylsulfonyl)pentyl acetate (4). To a solution of **3** (1.09 g, 2.93 mmol) in CH_2Cl_2 (15 ml) was added MCPBA (70% purity, 2.20 g, 8.92 mmol) at 0 °C. The mixture was stirred at room temperature for 24 h, then quenched with 10% aqueous Na_2SO_3 and extracted with CH_2Cl_2. The extract was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with hexane–AcOEt (4/1) to give **5** (1.14 g, 2.82 mmol, 96%) as as a colorless oil: $[\alpha]_D^{24}$ −27.3 (*c* 1.37, $CHCl_3$); IR (neat) 1740 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.88 (2H, d, *J*=7.3 Hz), 7.64 (1H, t, *J*=7.3 Hz), 7.54 (2H, t, *J*=7.9 Hz), 7.37–7.22 (5H, m), 4.47 (2H, s), 4.01–3.87 (2H, m), 3.52 (1H, t, *J*=4.9 Hz), 3.34 (1H, dd, *J*=14.2, 3.9 Hz), 2.90 (1H, dd, *J*=14.2, 7.8 Hz), 2.58–2.44 (1H, m), 2.13–1.98 (1H, m), 2.03 (3H, s), 1.11 (3H, d, *J*=6.8 Hz), 0.93 (3H, d, *J*=6.8 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 170.9, 139.8, 138.2, 133.6, 129.3, 128.4, 127.9, 127.7, 127.6, 80.7, 73.3, 67.0, 59.3, 34.6, 30.7, 20.9, 15.6, 12.6; FAB-MS *m/z* 405 (M$^+$+1). Anal. Calcd for $C_{22}H_{28}O_5S$: C, 65.32; H, 6.98. Found: C, 64.98; H, 7.18.

3.1.3. (2*R*,3*S*,4*R*)-3-Benzyloxy-2,4-dimethyl-5-phenylsulfonyl-1-pentanol (5). To a solution of **4** (1.14 g, 2.82 mmol) in methanol (10 ml) was added K_2CO_3 (0.800 g, 5.80 mmol) at room temperature. After being stirred for 30 min, the mixture was poured into brine. The mixture was extracted with Et_2O. The extract was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with hexane–AcOEt (2/1) to give **5** (1.02 g, 2.82 mmol, 100%) as a colorless oil: $[\alpha]_D^{23}$ −22.2 (*c* 1.07, $CHCl_3$); IR (neat) 3527 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.92–7.83 (2H, m), 7.68–7.49 (3H, m), 7.38–7.22 (5H, m), 4.47 (2H, s), 3.61 (1H, t, *J*=4.6 Hz), 3.53 (2H, d, *J*=5.9 Hz), 3.34 (1H, dd, *J*=14.2, 4.0 Hz), 2.92 (1H, dd, *J*=14.2, 8.2 Hz), 2.57 (1H, m), 1.98–1.78 (2H, m), 1.12 (3H, d, *J*=6.9 Hz), 0.91 (3H, d, *J*=6.9 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 139.8, 138.2, 133.6, 129.3, 128.4, 127.9, 127.7, 81.4, 73.0, 66.2, 59.5, 37.1, 30.4, 15.8, 12.2; FAB-MS *m/z* 363 (M$^+$+1). Anal. Calcd for $C_{20}H_{26}O_4S$: C, 66.27; H, 7.23. Found: C, 65.99; H, 7.35.

3.1.4. (2*R*,3*S*,4*R*)-2,4-Dimethyl-5-(phenylsulfonyl)pentane-1,3-diol (6). A mixture of **5** (19.4 g, 53.6 mmol), 20% $Pd(OH)_2$–C (1.00 g) and methanol (150 ml) was stirred under H_2 atmosphere at room temperature for 2 h. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with hexane–AcOEt (1/2) to give **6** (13.9 g, 51.1 mmol, 95%) as a colorless oil: $[\alpha]_D^{24}$ −5.5 (*c* 1.09, $CHCl_3$); IR (neat) 3464 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (2H, d, *J*=7.3 Hz), 7.66 (1H, t, *J*=7.3 Hz), 7.58 (2H, t, *J*=7.3 Hz), 3.73 (1H, t, *J*=4.9 Hz), 3.61 (2H, d, *J*=4.9 Hz), 3.32 (1H, dd, *J*=14.4, 4.9 Hz), 2.96 (1H, dd, *J*=14.4, 7.3 Hz), 2.46–2.32 (3H, m), 1.76 (1H, m), 1.08 (3H, d, *J*=6.8 Hz), 0.93 (3H, d, *J*=6.8 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 139.8, 133.7, 129.3, 127.8, 75.0, 66.2, 59.9, 37.3, 31.8, 14.7, 11.8; FAB-MS *m/z* 273 (M$^+$+1). Anal. Calcd for $C_{13}H_{20}O_4S$: C, 57.32; H, 7.40. Found: C, 57.09; H, 7.72.

3.1.5. (2*R*,3*S*,4*R*)-1,3-Isopropylidenedioxy-2,4-dimethyl-5-(phenylsulfonyl)pentane (7). To a solution of **6** (11.8 g, 43.4 mmol) and 2,2-dimethoxypropane (25 ml) in benzene (100 ml) was added 10-camphorsulfonic acid (1.00 g, 4.31 mmol) at room temperature. The mixture was stirred at room temperature for 24 h, then quenched with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The extract was dried over $MgSO_4$ and concentrated under reduced pressure to give **7** (11.8 g, 37.8 mmol, 87%) as a white crystal: mp 64–65 °C; $[\alpha]_D^{24}$ −23.0 (*c* 1.30, $CHCl_3$); IR (neat) 2990 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (2H, d, *J*=7.3 Hz), 7.67 (1H, t, *J*=7.3 Hz), 7.58 (2H, t, *J*=7.3 Hz), 4.00 (1H, dd, *J*=11.7, 2.9 Hz), 3.60 (1H, dd, *J*=8.8, 2.4 Hz), 3.54 (1H, dd, *J*=11.7, 1.5 Hz), 3.16 (1H, dd, *J*=14.2, 2.0 Hz), 2.83 (1H, dd, *J*=14.2, 9.8 Hz), 2.06 (1H, m), 1.47 (1H, m), 1.36 (3H, s), 1.34 (3H, s), 1.13 (3H, d, *J*=6.4 Hz), 0.83 (3H, d, *J*=6.8 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 139.7, 133.7, 129.3, 128.0, 99.0, 74.0, 66.9, 58.2, 31.1, 29.9, 29.5, 18.9, 16.2, 10.4; FAB-MS *m/z* 313 (M$^+$+1). Anal. Calcd for $C_{16}H_{24}O_4S$: C, 61.51; H, 7.74. Found: C, 61.71; H, 7.96.

3.1.6. (5*R*,6*S*,7*R*)-6,8-Isopropylidenedioxy-5,7-dimethyl-4-phenylsulfonyl-1-octene (8). To a solution of *tert*-BuLi (1.7 M in pentane, 6.0 ml, 10.2 mmol) in THF (10 ml) was added dropwise **7** (2.07 g, 6.63 mmol) in THF (10 ml) at −78 °C under an argon atmosphere. The reaction mixture was stirred at −78 °C for 1 h and then −20 °C for 15 min. After the mixture was recooled to −78 °C, allyl bromide (1.20 g, 9.92 mmol) in THF (5 ml) was added dropwise. After being stirred at −78 °C for 30 min, the mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The extract was dried over $MgSO_4$ and concentrated under reduced pressure to give **8** (1.92 g, 5.45 mmol, 82%) as a colorless oil: $[\alpha]_D^{20}$ +13.1 (*c* 1.31, $CHCl_3$); IR (neat) 2988 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90–7.85 (2H, m), 7.69–7.65 (1H, m), 7.60–7.55 (2H, m), 5.70–5.61 (0.5H, m), 5.53–5.42 (0.5H, m), 5.11–5.03 (2H, m), 4.45 (0.5H, dd, *J*=9.8, 2.4 Hz), 4.17 (0.5H, dd, *J*=11.7, 2.4 Hz), 3.95 (0.5H, dd, *J*=11.7, 2.4 Hz), 3.71 (0.5H, dd, *J*=9.8, 2.4 Hz), 3.61 (0.5H, dd, *J*=11.7, 1.5 Hz), 3.52 (0.5H, dd, *J*=11.7, 1.5 Hz), 3.05–2.99 (1H, m), 2.80 (0.5H, dt, *J*=15.1, 5.9 Hz), 2.58–2.39 (2H, m), 2.34–2.27 (0.5H, m), 2.10–2.00 (0.5H, m), 1.80–1.75 (0.5H, m), 1.46 (1.5H, s), 1.39 (1.5H, s), 1.34 (3H, s), 1.26 (1.5H, d, *J*=7.3 Hz), 1.06 (1.5H, d, *J*=6.8 Hz), 0.99 (1.5H, d, *J*=6.8 Hz), 0.80 (1.5H, d, *J*=6.8 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 139.9, 138.4, 135.2, 133.8, 133.7, 129.3, 128.9, 128.4, 119.3, 117.7, 99.0, 73.6, 73.0, 67.1, 66.7, 63.7, 35.7, 33.3, 32.1, 30.1, 29.8, 29.7, 29.5, 28.3, 19.2, 18.8, 11.1, 10.7, 10.5, 9.7; FAB-MS *m/z* 353 (M$^+$+1). Anal. Calcd for $C_{19}H_{28}O_4S$: C, 64.74; H, 8.01. Found: C, 64.51; H, 8.28.

3.1.7. (5*S*,6*S*,7*R*)-6,8-Isopropylidenedioxy-5,7-dimethyl-1-octene (9). A solution of **8** (6.02 g, 17.1 mmol) and 5% Na(Hg) (12.0 g) in methanol (60 ml) was refluxed for 4 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The extract was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with hexane–AcOEt (19/1) to give **9** (2.86 g, 13.5 mmol, 79%) as a colorless oil: $[\alpha]_D^{20}$ −13.6

(c 1.49, $CHCl_3$); IR (neat) 2935 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.80 (1H, ddt, $J=16.8$, 10.2, 6.9 Hz), 5.02 (1H, dd, $J=16.8$, 1.5 Hz), 4.95 (1H, dd, $J=10.2$, 1.5 Hz), 4.06 (1H, dd, $J=11.7$, 2.9 Hz), 3.59 (1H, dd, $J=11.7$, 2.0 Hz), 3.48 (1H, dd, $J=9.8$, 2.4 Hz), 2.25–2.09 (1H, m), 2.08–1.92 (1H, m), 1.65–1.40 (2H, m), 1.41 (3H, s), 1.40 (3H, s), 1.04 (3H, d, $J=6.9$ Hz), 1.03–0.94 (2H, m), 0.92 (3H, d, $J=6.3$ Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 138.5, 114.5, 98.5, 76.0, 67.1, 33.5, 30.6, 30.1, 29.8, 29.7, 18.9, 15.4, 10.4; FAB-MS m/z 213 ($M^+ + 1$). Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.53; H, 11.39. Found: C, 73.81; H, 11.79.

3.1.8. (5*S*,6*S*,7*R*)-1,2-Epoxy-6,8-isopropylidenedioxy-5,7-dimethyloctane (10). According to the preparation of **4**, **9** (3.01 g, 14.2 mmol) was converted into **10** (2.27 g, 9.96 mmol, 70%) as a colorless oil: $[\alpha]_D^{20}$ -9.4 (c 1.04, $CHCl_3$); IR (neat) 3048, 1199 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.07 (1H, dd, $J=11.5$, 2.4 Hz), 3.60 (1H, dd, $J=11.5$, 1.8 Hz), 3.48 (1H, dd, $J=9.7$, 2.4 Hz), 2.90 (1H, m), 2.76 (1H, m), 2.48 (1H, m), 1.71–1.35 (11H, m), 1.16–0.98 (4H, m), 0.93 (3H, d, $J=6.6$ Hz), 0.92 (3H, d, $J=6.4$ Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 98.4, 75.7, 66.8, 52.2, 51.9, 47.0, 46.6, 33.8, 33.6, 29.7, 29.6, 29.5, 29.4, 29.1, 27.0, 26.7, 18.7, 15.34, 15.31, 10.31, 10.28; EI-MS m/z 213 ($M^+ - CH_3$), 197, 171, 129; HR-MS m/z 213.1491 (Calcd for $C_{12}H_{21}O_3$: 213.1491).

3.1.9. Methyl (2*E*,4*S*,5*S*,6*R*)-7-benzyloxy-4,5-epoxy-4,6-dimethyl-2-heptenoate (12). To a solution of **11**[17] (1.21 g, 5.13 mmol) in CH_2Cl_2 (30 ml) was added Dess–Martin periodinane (3.26 g, 7.07 mmol) at room temperature. The mixture was stirred at room temperature for 40 min, then quenched with 1 N NaOH solution and extracted with Et_2O. The extract was dried over $MgSO_4$ and concentrated under reduced pressure to give crude aldehyde compound, which was dissolved in DMSO (15 ml). To the solution was added methyl (triphenylphosphoraniliden)acetate (2.57 g, 7.70 mmol) at room temperature under an argon atmosphere. The mixture was stirred at room temperature for 30 min, then quenched with H_2O and extracted with Et_2O. The extract was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with hexane–AcOEt (100/3) to give **12** (1.28 g, 4.41 mmol, 86%) as a colorless oil: $[\alpha]_D^{20}$ $+4.0$ (c 1.21, $CHCl_3$); IR (neat) 1725, 1657 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.37–7.24 (5H, m), 6.77 (1H, d, $J=15.8$ Hz), 6.00 (1H, d, $J=15.8$ Hz), 4.47 (2H, s), 3.75 (3H, s), 3.45 (1H, dd, $J=9.2$, 4.9 Hz), 3.33 (1H, dd, $J=9.2$, 8.2 Hz), 2.65 (1H, d, $J=9.2$ Hz), 1.93–1.75 (1H, m), 1.43 (3H, s), 1.10 (3H, d, $J=6.6$ Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 166.5, 150.3, 138.2, 128.3, 127.5, 127.3, 120.8, 73.1, 72.5, 69.5, 59.5, 51.6, 33.8, 15.9, 14.4; EI-MS m/z 290 (M^+), 259, 169; HR-MS m/z 290.1500 (Calcd for $C_{17}H_{22}O_4$: 290.1517).

3.1.10. Methyl (2*E*,4*S*,5*R*,6*R*)-7-benzyloxy-4,6-dimethyl-5-hydroxy-2-heptenoate (13). To a solution of tris-(dibenzylideneacetone)dipalladium(0)–chloroform adduct (66 mg, 0.064 mmol) in THF (3 ml) was added HCOOH (0.106 ml, 2.81 mmol), triethylamine (0.178 ml, 1.28 mmol) and triphenylphosphine (16.8 mg, 0.064 mmol) at room temperature under an argon atmosphere. After being stirred for 5 min, a solution of **12** (186 mg, 0.641 mmol) in THF (3 ml) was added to the reaction mixture. After being stirred for 4 h, the reaction mixture was filtered. The filtrate was concentrated under reduced pressure extracted with Et_2O. The extract was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with hexane–AcOEt (19/1) to give **13** (160 mg, 0.548 mmol, 85%) as a colorless oil. Compound **13** contained small amounts of any stereo isomer (ca. 7:1): $[\alpha]_D^{20}$ -19.6 (c 1.35, $CHCl_3$); IR (neat) 3508, 1723, 1655 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.40–7.23 (5H, m), 6.80 (1H, dd, $J=15.8$, 9.2 Hz), 5.85 (1H, d, $J=15.8$ Hz), 4.53 (1H, d, $J=11.9$ Hz), 4.47 (1H, d, $J=11.9$ Hz), 3.72 (3H, s), 3.65 (1H, d, $J=8.9$ Hz), 3.56 (1H, dd, $J=8.9$, 4.0 Hz), 3.50 (1H, dd, $J=8.9$, 5.0 Hz), 2.83 (1H, br), 2.55–2.37 (1H, m), 1.87–1.73 (1H, m), 1.15 (3H, d, $J=6.6$ Hz), 0.96 (3H, d, $J=6.9$ Hz). For minor isomer, 7.04 (1/7H, dd, $J=15.6$, 8.4 Hz), 5.88 (1/7H, dd, $J=15.6$, 1.0 Hz), 1.01 (3/7H, d, $J=6.8$ Hz), 0.98 (3/7H, $J=7.1$ Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 167.0, 151.0, 137.8, 128.4, 127.7, 127.5, 120.8, 76.8, 75.5, 73.5, 51.5, 40.8, 35.9, 16.7, 9.7; SIMS m/z 293 ($M^+ + 1$); HR-MS m/z 293.1780 (Calcd for $C_{17}H_{25}O_4$: 293.1751).

3.1.11. Methyl (4*S*,5*R*,6*R*)-5,7-dihydroxy-4,6-dimethylheptanoate (14). According to the preparation of **6**, **13** (286 mg, 0.979 mmol) was converted into **14** (144 mg, 0.706 mmol, 72%) as a colorless oil: $[\alpha]_D^{20}$ -19.4 (c 1.25, $CHCl_3$); IR (neat) 3402, 1734 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.69 (2H, dd, $J=4.6$, 1.3 Hz), 3.67 (3H, s), 3.51 (1H, dd, $J=7.6$, 3.6 Hz), 2.52 (2H, br), 2.41 (1H, ddd, $J=15.8$, 8.9, 5.9), 2.31 (1H, ddd, $J=15.8$, 8.6, 6.9 Hz), 1.94–1.71 (1H, m), 1.70–1.54 (1H, m), 1.45–1.30 (1H, m), 0.98 (3H, d, $J=6.6$ Hz), 0.97 (3H, d, $J=6.9$ Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 174.3, 77.2, 67.4, 51.6, 36.6, 35.5, 31.4, 28.0, 14.8, 10.0; SIMS m/z 205 ($M^+ + 1$); HR-MS m/z 205.1431 (Calcd for $C_{10}H_{21}O_4$: 205.1439).

3.1.12. Methyl (4*S*,5*R*,6*R*)-5,7-isopropylidenedioxy-4,6-dimethylheptanoate (15). According to the preparation of **7**, **14** (15.5 mg, 0.0760 mmol) was converted into **15** (17.6 mg, 0.0721 mmol, 95%) as a colorless oil: $[\alpha]_D^{20}$ -15.0 (c 1.68, $CHCl_3$); IR (neat) 1742 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.06 (1H, dd, $J=11.5$, 2.6 Hz), 3.67 (3H, s), 3.60 (1H, dd, $J=11.5$, 1.6 Hz), 3.47 (1H, dd, $J=8.6$, 2.3 Hz), 2.48–2.22 (2H, m), 1.86–1.71 (1H, m), 1.67–1.45 (2H, m), 1.41 (3H, s), 1.39 (3H, s), 1.28–1.11 (1H, m), 1.07 (3H, d, $J=6.9$ Hz), 0.92 (3H, d, $J=6.3$ Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 174.1, 98.7, 75.9, 67.1, 51.6, 33.8, 31.3, 29.9, 29.7, 26.7, 26.1, 19.0, 15.3, 10.4; EI-MS m/z 229 ($M^+ - CH_3$); HR-MS m/z 229.1442 (Calcd for $C_{12}H_{21}O_4$: 229.1439).

3.1.13. (4*S*,5*R*,6*R*)-5,7-Isopropylidenedioxy-4,6-dimethyl-1-heptanol (16). To a solution of **15** (133 mg, 0.545 mmol) in toluene (3 ml) was added dropwise diisobutylaluminium hydride (DIBAH, 1.0 M toluene sol., 1.36 ml, 1.36 mmol) at −78 °C under an argon atmosphere. The mixture was stirred at −78 °C for 20 min and then quenched with a small amount of H_2O. The precipitate was removed by filtration.

The filtrate was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with hexane–AcOEt (4/1) to give **16** (108 mg, 0.500 mmol, 92%) as a colorless oil: $[\alpha]_D^{20}$ −10.8 (*c* 0.83, $CHCl_3$); IR (neat) 3410 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.06 (1H, dd, *J*=11.5, 3.0 Hz), 3.72–3.55 (3H, m), 3.48 (1H, dd, *J*=9.9, 2.3 Hz), 1.78–1.30 (7H, m), 1.41 (3H, s), 1.40 (3H, s), 1.35 (3H, d, *J*=6.9 Hz), 1.10–0.90 (1H, m), 0.93 (3H, d, *J*=6.3 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 98.7, 76.1, 67.2, 63.1, 33.9, 29.9, 29.7, 29.6, 26.9, 19.0, 15.7, 10.5; EI-MS *m/z* 201 (M^+ −CH_3); HR-MS *m/z* 201.1501 (Calcd for $C_{11}H_{21}O_3$: 201.1489).

3.1.14. (4*S*,5*R*,6*R*)-5,7-Isopropylidenedioxy-4,6-dimethylheptanal (17). To a solution of **16** (43.0 mg, 0.199 mmol) in CH_2Cl_2 (3 ml) was added *N*-methylmorpholine *N*-oxide (NMO, 35 mg, 0.299 mmol) and tetrapropylammonium perruthenate (TPAP, trace) at 0 °C under an argon atmosphere. After being stirred for 1.5 h, the reaction mixture was diluted with ether and filtered through a Celite pad. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with hexane–AcOEt (1/1) to give **17** (28.0 mg, 0.131 mmol, 66%) as a colorless oil: $[\alpha]_D^{20}$ −13.9 (*c* 0.59, $CHCl_3$); IR (neat) 1723 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 9.80 (1H, t, *J*=1.6 Hz), 4.07 (1H, dd, *J*=11.5, 2.6 Hz), 3.60 (1H, dd, *J*=11.5, 1.6 Hz), 3.48 (1H, dd, *J*=9.6, 2.3 Hz), 2.61–2.35 (2H, m), 1.85–1.70 (1H, m), 1.67–1.45 (2H, m), 1.41 (3H, s), 1.40 (3H, s), 1.25–1.10 (1H, m), 1.07 (3H, d, *J*=6.9 Hz), 0.92 (3H, d, *J*=6.3 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 202.2, 98.7, 75.9, 67.1, 41.2, 33.8, 29.9, 29.7, 23.0, 19.0, 15.4, 10.5; EI-MS *m/z* 199 (M^+ −CH_3); HR-MS *m/z* 199.1346 (Calcd for $C_{11}H_{19}O_3$: 199.1333).

3.1.15. Conversion of 17 into 9. To a suspension of methyltriphenylphosphonium bromide (356 mg, 0.997 mmol) in THF (2 ml) was added dropwise *n*-BuLi (1.56 M in toluene, 0.617 ml, 0.963 mmol) at 0 °C under an argon atmosphere. After being stirred for 10 min, a solution of **17** (71.0 mg, 0.332 mmol) in THF (2 ml) was added to the mixture at −20 °C. After being stirred for 1 h at −20 °C, the reaction mixture was quenched with H_2O at 0 °C and extracted with Et_2O. The extract was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with hexane–AcOEt (9/1) to give **9** (63.7 mg, 0.300 mmol, 90%) as a colorless oil.

3.1.16. (2*R*,3*S*)-1,2-Isopropylidenedioxy-3-methyl-4-(phenylsulfonyl)butane (18). According to the preparation of **3**, (2*R*,3*R*)-(−)-erythro-3-methylbutane-1,2,4-triol 1, 2-acetonide[12] (1.1 g, 6.88 mmol) was converted into thiophenylated compound (971 mg, 3.85 mmol, 56%) as a colorless oil: $[\alpha]_D^{22}$ +23.4 (*c* 1.05, $CHCl_3$); IR (neat) 2988 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.39–7.33 (2H, m), 7.30–7.22 (2H, m), 7.18–7.10 (1H, m), 4.03 (1H, dd, *J*=7.6, 6.9 Hz), 3.93 (1H, dt, *J*=7.6, 6.9 Hz), 3.61 (1H, t, *J*=7.6 Hz), 3.37 (1H, dd, *J*=13.0, 3.6 Hz), 2.68 (1H, dd, *J*=13.0, 9.2 Hz), 1.97–1.80 (1H, m), 1.39 (3H, s), 1.34 (3H, m), 0.99 (3H, d, *J*=6.6 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 136.9, 128.8, 128.7, 125.6, 109.0, 79.2, 67.9, 37.3, 37.1, 26.6, 25.6, 15.1; EI-MS *m/z* 252 (M^+), 237; HR-MS *m/z* 252.1174 (Calcd for $C_{14}H_{20}O_2S_1$: 252.1183). According to the preparation of **4**, this thiophenylated compound (980 mg, 3.89 mmol) was converted into **18** (733 mg, 2.85 mmol, 66%) as a colorless oil: $[\alpha]_D^{22}$ +16.4 (*c* 1.00, $CHCl_3$); IR (neat) 2988, 1307, 1149 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (2H, dt, *J*=7.6, 2.0 Hz), 7.65 (1H, tt, *J*=7.6, 2.0 Hz), 7.57 (2H, t, *J*=7.6 Hz), 4.02 (1H, dd, *J*=8.3, 6.0 Hz), 3.82 (1H, q, *J*=6.0 Hz), 3.60 (1H, dd, *J*=8.3, 6.0 Hz), 3.49 (1H, dd, *J*=14.0, 2.0 Hz), 2.90 (1H, dd, *J*=14.0, 9.8 Hz), 2.21–2.09 (1H, m), 1.27 (3H, s), 1.23 (3H, s), 1.13 (3H, d, *J*=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.9, 133.6, 129.3, 127.9, 109.3, 78.7, 67.6, 58.6, 33.1, 26.4, 25.2, 16.5; EI-MS *m/z* 269 (M^+ −Me), 101; HR-MS *m/z* 269.0875 (Calcd for $C_{13}H_{17}O_4S_1$: 269.0847).

3.1.17. (2*R*,3*R*,9*S*,10*R*,11*R*)-1,2:10,12-Diisopropylidenedioxy-3,9,11-trimethyl-6-dodecanone (20). To a solution of *tert*-BuLi (1.7 M in pentane, 0.30 ml, 0.510 mmol) in THF (1.6 ml) was added dropwise a solution of **18** (77.9 mg, 0.274 mmol) in THF (0.5 ml) at −78 °C under an argon atmosphere. After being stirred for 1 h, a solution of **10** (60.5 mg, 0.265 mmol) in THF (0.5 ml) and boron trifluoride etherate ($BF_3 \cdot Et_2O$, 0.1 ml, 0.380 mmol) was added to this solution. After being stirred at −78 °C for 30 min, the mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The extract was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with hexane–AcOEt (2/1) to give **19** (92.3 mg, 0.180 mmol, 68%) as a colorless oil: $[\alpha]_D^{22}$ −6.2 (*c* 0.93, $CHCl_3$); IR (neat) 3506 cm^{-1}; SIMS *m/z* 513 (M^+ +1); HR-MS *m/z* 513.2893 (Calcd for $C_{27}H_{45}O_7S$: 513.2883). Anal. Calcd for $C_{27}H_{44}O_7S$: C, 62.93; H, 8.93. Found: C, 63.25; H, 8.65. A solution of **19** (555 mg, 1.08 mmol) and 5% Na(Hg) (4.7 g) in methanol (18 ml) was refluxed for 1.5 h. The reaction mixture was quenched with H_2O and extracted with Et_2O. The extract was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with hexane–AcOEt (2/1) to give alcohol (397 mg) as a colorless oil. To a solution of this alcohol in CH_2Cl_2 (8 ml) was added NMO (188 mg, 1.61 mmol) and TPAP (19 mg, 0. 054 mg) at 0 °C under an argon atmosphere. After being stirred for 1.5 h, the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel eluted with Et_2O to give **20** (375 mg, 1.01 mmol, 94%) as a colorless oil: $[\alpha]_D^{19}$ −15.9 (*c* 1.39, $CHCl_3$); IR (neat) 1714 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.06 (1H, dd, *J*=11.2, 2.4 Hz), 4.00 (1H, dd, *J*=7.8, 6.4 Hz), 3.82 (1H, dd, *J*=13.7, 7.3 Hz), 3.62–3.54 (2H, m), 3.46 (1H, dd, *J*=9.8, 2.4 Hz), 2.59–2.33 (4H, m), 1.91–1.81 (1H, m), 1.77–1.67 (1H, m), 1.66–1.32 (4H, m), 1.40 (3H, s), 1.39 (6H, s), 1.34 (3H, s), 1.19–1.07 (1H, m), 1.06 (3H, d, *J*=6.8 Hz), 0.90 (3H, d, *J*=6.4 Hz), 0.83 (3H, d, *J*=6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.8, 108.8, 98.6, 80.2, 76.0, 67.8, 67.1, 40.5, 39.8, 36.2, 33.8, 29.9, 29.8, 27.7, 26.7, 25.6, 24.8, 19.0, 15.5, 15.3, 10.5; SIMS *m/z* 371 (M^+ +1); HR-MS *m/z* 371.2811 (Calcd for $C_{21}H_{39}O_5$: 371.2795). Anal. Calcd for $C_{21}H_{38}O_5$: C, 68.07; H, 10.34. Found: C, 68.29; H, 10.95.

3.1.18. (2*R*,3*R*,6*R*,8*R*,8(1*R*),9*S*)-2-Hydroxymethyl-8-(2-hydroxy-1-methylethyl)-3,9-dimethyl-1,7-dioxaspiro[5.5]-undecane (21). To a solution of **20** (334 mg, 0.903 mmol) in methanol (3 ml) was added CSA (20 mg, 0.0862 mmol) at room temperature. The mixture was stirred for 1 h, then quenched with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The extract was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with hexane–AcOEt (1/1) to give **21** (244 mg, 0.897 mmol, 99%) as a colorless oil: $[\alpha]_D^{19}$ -66.1 (*c* 1.03, $CHCl_3$); IR (neat) 3379 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.74 (1H, d, $J=$ 10.6 Hz), 3.64 (1H, dd, $J=10.9$, 4.3 Hz), 3.58–3.43 (3H, m), 3.35 (1H, ddd, $J=9.9$, 6.9, 3.0 Hz), 2.20–1.97 (2H, m), 1.88–1.73 (2H, m), 1.72–1.37 (9H, m), 1.09 (3H, d, $J=$ 6.8 Hz), 0.96 (3H, d, $J=7.3$ Hz), 0.85 (3H, d, $J=6.4$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 95.9, 75.1, 72.4, 64.7, 64.0, 37.5, 36.0, 30.9, 29.9, 28.1, 27.7, 26.7, 17.4, 14.3, 11.4; SIMS *m*/*z* 273 ($M^+ + 1$); HR-MS *m*/*z* 273.2082 (Calcd for $C_{15}H_{29}O_4$: 273.2064). Anal. Calcd for $C_{15}H_{28}O_4$: C, 66.14; H, 10.36. Found: C, 65.76; H, 11.02.

3.1.19. (2*R*,3*R*,6*R*,8*R*,8(1*R*),9*S*)-2-Acetoxymethyl-8-2-acetoxy-1-methylethyl)-3,9-dimethyl-1,7-dioxaspiro-[5.5]undecane (22), (2*R*,3*S*,3(1*R*),6*R*,8*R*,9*R*)-2-(2-acetoxy-1-methylethyl)-8-hydroxymethyl-3,9-dimethyl-1,7-dioxaspiro[5.5]undecane (23) and (2*R*,3*R*,6*R*,8*R*,8(1*R*),9*S*)-2-acetoxymethyl-8-(2-hydroxy-1-methylethyl)-3,9-dimethyl-1,7-dioxaspiro[5.5]undecane (24). A mixture of spirodiol **1** (94.6 mg, 0.348 mmol), lipase Amano PS (100 mg) and vinylacetate (20 ml) was incubated at 33 °C for 39 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with hexane–AcOEt (9/1 → 1/1) to give **22** (6.0 mg, 0.017 mmol, 5%), **23** (98.0 mg, 0.312 mmol, 90%), **24** (2.0 mg, 0.0064 mmol, 2%) and **21** (3.0 mg, 0.011 mmol, 3%) as colorless oils. **22**: $[\alpha]_D^{22}$ -54.3 (*c* 1.06, $CHCl_3$); IR (neat) 1742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.22 (1H, dd, $J=11.7$, 2.4 Hz), 4.12 (1H, dd, $J=11.7$, 6.8 Hz), 4.06 (1H, dd, $J=11.2$, 4.4 Hz), 3.85 (1H, dd, $J=11.2$, 6.3 Hz), 3.49–3.43 (2H, m), 2.08 (3H, s), 2.06 (3H, s), 2.10–1.99 (1H, m), 1.98–1.86 (1H, m), 1.81–1.71 (1H, m), 1.70–1.36 (8H, m), 1.07 (3H, d, $J=6.3$ Hz), 0.94 (3H, d, $J=6.8$ Hz), 0.88 (3H, d, $J=6.3$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 171.0, 95.9, 73.0, 72.7, 66.3, 65.5, 35.7, 34.7, 31.2, 29.7, 28.1, 27.9, 26.5, 21.0, 20.9, 17.6, 14.9, 11.0; SIMS *m*/*z* 357 ($M^+ + 1$); HR-MS *m*/*z* 357.2262 (Calcd for $C_{19}H_{33}O_6$: 357.2275). **23**: $[\alpha]_D^{22}$ -68.9 (*c* 0.99, $CHCl_3$); IR (neat) 3480, 1741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.06 (1H, dd, $J=11.0$, 4.2 Hz), 3.86 (1H, dd, $J=11.0$, 6.2 Hz), 3.73 (1H, br d, $J=10.7$ Hz), 3.59–3.52 (1H, m), 3.45 (1H, dd, $J=$ 10.1, 2.4 Hz), 3.34 (1H, ddd, $J=10.1$, 6.8, 2.9 Hz), 2.06 (3H, s), 2.06–1.89 (2H, m), 1.82–1.73 (1H, m), 1.70–1.39 (9H, m), 1.08 (3H, d, $J=6.6$ Hz), 0.95 (3H, d, $J=7.0$ Hz), 0.85 (3H, d, $J=6.4$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 95.9, 75.0, 72.7, 66.1, 64.0, 36.0, 34.8, 30.8, 29.8, 28.1, 27.6, 26.6, 20.9, 17.4, 14.8, 11.1; SIMS *m*/*z* 315 ($M^+ + 1$); HR-MS *m*/*z* 315.2170 (Calcd for $C_{17}H_{31}O_5$: 315.2170). Anal. Calcd for $C_{17}H_{30}O_5$: C, 64.94; H, 9.62. Found: C, 64.99; H, 10.15. **24**: $[\alpha]_D^{22}$ -64.3 (*c* 1.36, $CHCl_3$); IR (neat) 3422, 1734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.25 (1H, dd, $J=11.2$, 2.4 Hz), 4.09 (1H, dd, $J=11.2$, 6.8 Hz), 3.64 (1H, dd, $J=10.7$, 3.9 Hz), 3.57–3.44 (3H, m), 2.13–2.00 (1H, m), 2.08 (3H, s), 1.87–1.20 (11H, m), 1.08 (3H, d, $J=6.3$ Hz), 0.95 (3H, d, $J=6.8$ Hz), 0.88 (3H, d, $J=6.3$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2 (s), 96.0 (s), 72.8 (d), 72.4 (d), 65.6 (t), 64.9 (t), 37.4 (d), 35.6 (t), 31.4 (d), 29.8 (t), 28.1 (d), 28.0 (t), 26.7 (t), 20.9 (q), 17.5 (q), 14.3 (q), 11.3 (q); SIMS *m*/*z* 315 ($M^+ + 1$); HR-MS *m*/*z* 315.2167 (Calcd for $C_{17}H_{31}O_5$: 315.2170).

3.1.20. (2*R*,2(1*R*),3*S*,6*R*,8*R*,9*R*)-2-(2-Acetoxy-1-methylethyl)-8-formyl-3,9-dimethyl-1,7-dioxaspiro [5.5]-undecane (25). To a solution of **23** (95.0 mg, 0.303 mmol) in CH_2Cl_2 (2 ml) was added Dess–Martin periodinane (193 mg, 0.455 mmol) at 0 °C under an argon atmosphere. The mixture was stirred at 0 °C for 1 h, then quenched with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The extract was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with hexane–AcOEt (9/1) to give **25** (80.0 mg, 0.256 mmol, 84%) as a colorless oil: $[\alpha]_D^{22}$ -45.6 (*c* 1.22, $CHCl_3$); IR (neat) 1742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.58 (1H, d, $J=2.4$ Hz), 4.05 (1H, dd, $J=11.2$, 4.4 Hz), 3.85 (1H, dd, $J=11.2$, 6.3 Hz), 3.59 (1H, d, $J=10.0$ Hz), 3.42 (1H, d, $J=$ 10.0 Hz), 2.06 (3H, s), 2.02–1.37 (11H, m), 1.07 (3H, d, $J=$ 6.8 Hz), 0.95 (6H, d, $J=6.8$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.3, 171.2, 95.8, 79.4, 73.1, 66.0, 35.3, 34.7, 30.1, 29.5, 28.0, 27.3, 26.3, 20.9, 16.6, 14.8, 11.0; SIMS *m*/*z* 313 ($M^+ + 1$); HR-MS *m*/*z* 313.2013 (Calcd for $C_{17}H_{29}O_5$: 312.2013).

3.1.21. (2*R*)-1-Benzyloxy-2-methyl-3-phenylsulfonyl-propane (26). According to the preparation of **3**, (*S*)-(−)-3-benzyloxy-2-methylpropanol[17] (231 mg, 1.28 mmol) was converted into the thiophenylated compound (334 mg, 1.23 mmol, 96%) as a colorless oil: $[\alpha]_D^{22}$ $+10.3$ (*c* 1.07, $CHCl_3$); IR (neat) 2962 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.22 (9H, m), 7.14 (1H, tt, $J=7.3$, 2.0 Hz), 4.47 (2H, s), 3.46–3.38 (2H, m), 3.15 (1H, dd, $J=13.2$, 6.0 Hz), 2.79 (1H, dd, $J=13.2$, 7.3 Hz), 2.07 (1H, octet, $J=6.8$ Hz), 1.06 (3H, d, $J=6.8$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 137.2, 128.82, 128.80, 128.3, 127.5, 125.6, 74.0, 73.0, 37.5, 33.8, 16.8; EI-MS *m*/*z* 272 (M^+); HR-MS *m*/*z* 272.1238 (Calcd for $C_{17}H_{20}O_1S_1$: 272.1234). According to the preparation of **4**, this thiophenylated compound (300 mg, 1.10 mmol) was converted into **26** (317 mg, 1.04 mmol, 95%) as a colorless oil: $[\alpha]_D^{22}$ -4.6 (*c* 1.09, $CHCl_3$); IR (neat) 1586, 1305 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94–7.89 (2H, m), 7.64 (1H, tt, $J=7.3$, 1.5 Hz), 7.55 (2H, t, $J=6.8$ Hz), 7.36–7.23 (5H, m), 4.43 (1H, d, $J=12.2$ Hz), 4.40 (1H, d, $J=12.2$ Hz), 3.45–3.38 (2H, m), 3.31(1H, dd, $J=9.3$, 6.0 Hz), 2.93 (1H, dd, $J=14.2$, 7.8 Hz), 2.46–2.33 (1H, m), 1.12 (3H, d, $J=6.8$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.1, 138.1, 133.5, 129.2, 128.4, 127.8, 127.6, 127.5, 73.5, 72.9, 59.3, 29.4, 17.2; EI-MS *m*/*z* 304 (M^+); HR-MS *m*/*z* 304.1105 (Calcd for $C_{17}H_{20}O_3S_1$: 304.1132).

3.1.22. (2*R*,2(3*S*),3*R*,6*R*,8*R*,8(1*R*),9*S*)-2-(4-Benzyloxy-3-methyl-1-butenyl)-8-(2-hydroxy-1-methylethyl)-3,9-dimethyl-1,7-dioxaspiro[5.5]undecane (27). To a solution of **26** (112 mg, 0.368 mmol) in THF (1.7 μl) was added dropwise *n*-BuLi (1.58 M in hexane, 0.442 mmol, 280 μl) at −50 °C. After being stirred for 15 min, a solution of **25** (76.5 mg, 0.245 mmol) in THF (400 μl) was slowly added to the reaction mixture. The mixture was stirred for 30 min, then quenched with saturated aqueous NH_4Cl and extracted with ethylacetate. The extract was dried over $MgSO_4$ and concentrated to give crude β-hydroxysulfone as a mixture of four diastereomers. To a solution of the β-hydroxysulfone in pyridine (3 μl) were added 4-dimethylaminopyridine (0.170 mmol, 21 mg) and acetic anhydride (0.681 mmol, 64 μl) at room temperature. The mixture was stirred for 1 h, then quenched with H_2O and extracted with ethylacetate. The combined organic layers were washed with 2 N aqueous HCl and saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated to give crude β-acetoxysulfone. To a solution of this β-acetooxysulfone in methanol (4 ml) was added sodium–mercury amalgam (5% Na–Hg, 656 mg, 2.94 mmol) at room temperature. After being stirred for 1 h at 50 °C, the reaction mixture was quenched with H_2O at room temperature and extracted with ethylacetate. The extract was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with hexane–AcOEt (9/1) to give **27** (29.1 mg, 0.0700 mmol, 29% from **25**) as a colorless oil: $[\alpha]_D^{22}$ −30.0 (*c* 1.25, $CHCl_3$); IR (neat) 3470, 1715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.27 (5H, m), 5.58 (1H, dd, J=15.1, 6.8 Hz), 5.44 (1H, ddd, J=15.1, 7.8, 1.0 Hz), 4.51 (2H, s), 3.65 (1H, dd, J=10.2, 4.4 Hz), 3.61 (1H, dd, J=10.2, 7.8 Hz), 3.51 (1H, dd, J=10.0, 2.4 Hz), 3.45 (1H, dd, J=10.0, 6.3 Hz), 3.40 (1H, dd, J=9.3, 6.8 Hz), 3.32 (1H, dd, J=9.3, 6.8 Hz), 2.53 (1H, heptet, J=6.8 Hz), 2.08 (1H, tt, J=13.1, 4.4 Hz), 1.88–1.72 (2H, m), 1.71–1.22 (9H, m), 1.12 (3H, d, J=6.8 Hz), 1.06 (3H, d, J=6.3 Hz), 0.95 (3H, d, J=6.8 Hz), 0.77 (3H, d, J=6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 136.1, 129.8, 128.3, 127.5, 127.4, 96.0, 76.7, 75.4, 72.9, 72.6, 65.0, 37.6, 36.7, 36.0, 34.7, 30.1, 28.2, 27.8, 26.6, 18.1, 17.0, 14.5, 11.4; SIMS *m*/*z* 417 (M^++1); HR-MS *m*/*z* 417.2997 (Calcd for $C_{26}H_{41}O_4$: 417.3003).

3.1.23. (2*R*,2(3*S*),3*R*,6*R*,8*R*,8(1*R*),9*S*)-2-(4-Benzyloxy-3-methyl-1-butenyl)-8-(3-methoxycarbonyl-1-methyl-2-propenyl)-3,9-dimethyl-1,7-dioxaspiro[5.5]undecane (28). According to the preparation of **25**, **27** (26.0 mg, 0.0625 mmol) was converted into the corresponding aldehyde (24.0 mg, 0.0580 mmol, 93%) as a colorless oil: $[\alpha]_D^{22}$ −58.8 (*c* 1.02, $CHCl_3$); IR (neat) 1725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.67 (1H, d, J=2.9 Hz), 7.36–7.24 (5H, m), 5.57 (1H, dd, J=15.1, 6.8 Hz), 5.44 (1H, dd, J=15.1, 7.8 Hz), 4.51 (2H, s), 3.83 (1H, dd, J=9.8, 2.4 Hz), 3.56 (1H, dd, J=9.8, 7.8 Hz), 3.40 (1H, dd, J=9.3, 6.8 Hz), 3.32 (1H, dd, J=9.3, 6.8 Hz), 2.66–2.47 (2H, m), 2.11 (1H, tt, J=13.2, 4.4 Hz), 1.83–1.73 (1H, m), 1.71–1.27 (8H, m), 1.20 (3H, d, J=6.8 Hz), 1.07 (3H, d, J=6.8 Hz), 0.96 (3H, d, J=6.8 Hz), 0.78 (3H, d, J=6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.5, 138.6, 136.2, 129.7, 128.3, 127.5, 127.4, 96.2, 76.7, 75.3, 72.9, 70.9, 49.3, 36.8, 35.8, 34.7, 30.0, 29.0, 27.6, 26.3, 18.0, 17.0, 11.6, 11.5; SIMS *m*/*z* 415 (M^++1); HR-MS *m*/*z* 415.2856 (Calcd for $C_{26}H_{39}O_4$: 415.2846). To a solution of the aldehyde compound (23.2 mg, 0.0560 mmol) in CH_2Cl_2 (0.350 ml) was added methyl (triphenylphosphoraniliden)acetate (56 mg, 0.168 mmol) at 0 °C under an argon atmosphere. The mixture was stirred at room temperature for 3 h, then quenched with H_2O and extracted with Et_2O. The extract was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with hexane–AcOEt (9/1) to give **28** (22.3 mg, 0.0474 mmol, 85%) as a colorless oil: $[\alpha]_D^{22}$ −54.6 (*c* 0.74, $CHCl_3$); IR (neat) 1727 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.22 (5H, m), 6.80 (1H, dd, J=15.8, 9.2 Hz), 5.89 (1H, dd, J=15.8, 0.7 Hz), 5.56 (1H, dd, J=15.8, 6.6 Hz), 5.43 (1H, dd, J=15.8, 7.6 Hz), 4.52 (2H, s), 3.73 (3H, s), 3.58 (1H, dd, J=10.0, 7.6 Hz), 3.45 (1H, dd, J=10.0, 2.0 Hz), 3.41 (1H, dd, J=9.2, 6.6 Hz), 3.32 (1H, dd, J=9.2, 7.2 Hz), 2.62–2.38 (2H, m), 2.04 (1H, tt, J=13.2, 4.3 Hz), 1.70–1.24 (9H, m), 1.17 (3H, d, J=6.3 Hz), 1.08 (3H, d, J=6.9 Hz), 0.90 (3H, d, J=6.9 Hz), 0.77 (3H, d, J=6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 150.7, 138.7, 136.2, 129.8, 128.3, 127.53, 127.45, 120.9, 96.2, 76.8, 75.3, 73.8, 73.0, 51.5, 39.6, 36.8, 35.9, 34.7, 30.0, 28.7, 27.7, 26.4, 18.1, 17.7, 17.1, 10.8; SIMS *m*/*z* 471 (M^++1); HR-MS *m*/*z* 471.3102 (Calcd for $C_{29}H_{43}O_5$: 471.3108).

3.1.24. (2*S*,2(3*S*),3*R*,6*R*,8*R*,8(1*R*),9*S*)-2-(4-Hydroxy-3-methylbutyl)-8-(3-methoxycarbonyl-1-methylpropyl)-3,9-dimethyl-1,7-dioxaspiro[5.5]undecane (29). According to the preparation of **6**, **28** (12.3 mg, 0.0262 mmol) was converted into **29** (9.4 mg, 0.024 mmol, 90%) as a colorless oil: $[\alpha]_D^{22}$ −70.8 (*c* 0.37, $CHCl_3$); IR (neat) 3468, 1744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.67 (3H, s), 3.51 (1H, dd, J=10.7, 6.3 Hz), 3.46 (1H, dd, J=10.7, 6.3 Hz), 3.30 (1H, dd, J=10.3, 2.4 Hz), 3.22–3.15 (1H, m), 2.44–2.25 (2H, m), 2.09–1.97 (1H, m), 1.89–1.74 (2H, m), 1.72–1.24 (16H, m), 1.00 (3H, d, J=6.8 Hz), 0.93 (3H, d, J=6.3 Hz), 0.90 (3H, d, J=6.8 Hz), 0.82 (3H, d, J=6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 95.8, 74.6, 74.5, 68.2, 51.6, 36.1, 35.7, 34.9, 34.0, 31.0, 30.2, 30.0, 28.9, 28.1, 27.5, 26.9, 26.7, 18.1, 16.5, 16.0, 10.8; SIMS *m*/*z* 385 (M^++1); HR-MS *m*/*z* 385.2981 (Calcd for $C_{22}H_{41}O_5$: 385.2952).

3.1.25. (2*R*,2(1*R*),3*S*,6*R*,8*S*,8(3*S*),9*R*)-2-(3-Methoxycarbonyl-1-methylpropyl)-8-(3-methyl-4-pentenyl)-3,9-dimethyl-1,7-dioxaspiro[5.5]undecane (30). To a solution of **29** (3.7 mg, 0.0096 mmol) in CH_2Cl_2 (74 μl) was added Dess–Martin periodinane (6.1 mg, 0.016 mmol) and $NaHCO_3$ (8.1 mg, 0.096 mmol) at 0 °C. The mixture was stirred at room temperature for 2 h, then quenched with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The extract was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with hexane–AcOEt (6/1) to give aldehyde compound (3.2 mg) as a colorless oil. To a suspension of methyltriphenylphosphonium bromide (9.0 mg, 0.025 mmol) in THF (90 μl) was added potassium *t*-butoxide (2.6 mg, 0.024 mmol) at 0 °C under an argon atmosphere. After being stirred for 30 min, a solution of the aldehyde compound (9.7 mg) in THF (30 μl) was added to the mixture at 0 °C. After 2 h, the reaction mixture was quenched with H_2O at 0 °C and extracted with ethylacetate. The extract was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with hexane–AcOEt (20/1) to give **30** (2.3 mg, 0.0061 mmol, 60%) as a colorless oil: $[\alpha]_D^{22}$ −62.7 (*c* 0.15, $CHCl_3$); IR (neat) 1744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.72 (1H, ddd, J=17.6, 10.3, 7.3 Hz), 5.00–4.89 (2H, m), 3.67 (3H, s), 3.28 (1H, dd, J=9.8, 2.4 Hz), 3.14 (1H, t, J=9.8 Hz), 2.40 (1H, ddd, J=15.6, 9.8, 5.4 Hz), 2.29 (1H, ddd, J=15.6, 9.8, 7.3 Hz), 2.18–1.98 (2H, m), 1.89–1.76 (2H, m), 1.71–1.35 (9H, m), 1.34–1.18 (5H, m), 1.01 (3H, d, J=6.8 Hz), 1.00 (3H, d, J=6.3 Hz), 0.91 (3H, d, J=6.8 Hz), 0.81 (3H, d, J=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 145.0, 112.4, 95.6, 74.7, 74.6, 51.5, 37.9, 36.1, 35.0, 34.1, 32.9, 31.2, 30.9, 30.2, 28.2, 27.6, 27.0, 26.7, 20.1, 18.0, 16.1, 10.8; SIMS *m/z* 381 (M^++1); HR-MS *m/z* 381.3015 (Calcd for $C_{23}H_{41}O_4$: 381.3003).

3.1.26. (2*S*,2(1*R*),3*S*,6*R*,8*S*,8(3*S*),9*R*)-2-(4-Hydroxy-1-methylbutyl)-8-(3-methyl-4-pentenyl)-3,9-dimethyl-1,7-dioxaspiro[5.5]undecane (31). To a solution of **30** (2.0 mg, 0.0053 mmol) in THF (30 μl) was added $LiAlH_4$ (0.4 mg) at 0 °C. The mixture was stirred at 0 °C for 10 min, then quenched with a small amount of H_2O. The precipitate was removed by filtration. The filtrate was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with hexane–AcOEt (4/1) to give **31** (1.6 mg, 0.0045 mmol, 80%) as a colorless oil: $[\alpha]_D^{22}$ −60.0 (*c* 0.16, $CHCl_3$); IR (neat) 3350 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.72 (1H, ddd, J=17.5, 10.2, 7.6 Hz), 4.96 (1H, d, J=17.5 Hz), 4.91 (1H, d, J=10.2 Hz), 3.72–3.57 (2H, br), 3.30 (1H, dd, J=10.2, 2.3 Hz), 3.16 (1H, t, J=9.0 Hz), 2.19–1.95 (2H, m), 1.90–1.77 (1H, m), 1.74–1.16 (18H, m), 1.02 (3H, d, J=6.3 Hz), 1.00 (3H, d, J=6.9 Hz), 0.90 (3H, d, J=6.9 Hz), 0.82 (3H, d, J=6.6 Hz); [Ichihara's data: δ 5.73 (1H, ddd, J=17.2, 9.9, 7.3 Hz), 4.96 (1H, dt, J=17.2, 1.6 Hz), 4.92 (1H, dd, J=9.9, 1.6 Hz), 3.65 (2H, td, J=6.6, 2.6 Hz), 3.30 (1H, dd, J=10.3, 2.3 Hz), 3.16 (1H, td, J=9.0, 1.6 Hz), 2.17–1.97 (2H, m), 1.85 (1H, m), 1.73–1.20 (17H, m), 1.02 (3H, d, J=5.9 Hz), 1.00 (3H, d, J=6.6 Hz), 0.90 (3H, d, J=6.9 Hz), 0.82 (3H, d, J=6.6 Hz)]; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 145.0, 112.3, 95.6, 74.74, 74.67, 63.3, 37.9, 36.1, 35.1, 34.3, 32.9, 30.9, 30.3, 29.5, 28.3, 27.8, 27.5, 26.7, 20.1, 18.1, 16.5, 10.9; SIMS *m/z* 353 (M^++1); HR-MS *m/z* 353.3064 (Calcd for $C_{22}H_{41}O_3$: 353.3054).

Acknowledgements

A Grant-in Aid for Encouragement of Young Scientists (10771254 to S.N.) from the Ministry of Education, Science and Culture of Japan is gratefully acknowledged. We are also grateful to the Akiyama Foundation (to S.N.) for its support to this project. We also thank Dr. Yoshihiko Hirose (Amano Pharmaceutical Co., Ltd) for the generous gift of Amano PS.

References and notes

1. Cheng, X.-C.; Kihara, T.; Kusakabe, H.; Magae, J.; Kobayashi, Y.; Fang, R.-P.; Ni, Z.-F.; Shen, Y.-C.; Ko, K.; Yamaguchi, I.; Isono, K. *J. Antibiot.* **1987**, *40*, 907.
2. (a) Ubukata, M.; Cheng, X.-C.; Isono, K. *J. Chem. Soc., Chem. Commun.* **1990**, 244. (b) Cheng, X.-C.; Ubukata, M.; Isono, K. *J. Antibiot.* **1990**, *43*, 809. (c) Ubukata, M.; Cheng, X.-C.; Isobe, M.; Isono, K. *J. Chem. Soc., Perkin Trans. 1* **1993**, 617.
3. Magae, J.; Osada, H.; Cheng, X.-C.; Isono, K. *J. Antibiot.* **1992**, *45*, 252.
4. For total syntheses, see: (a) Oikawa, H.; Oikawa, M.; Ueno, T.; Ichihara, A. *Tetrahedron Lett.* **1994**, *35*, 4809. (b) Oikawa, M.; Ueno, T.; Oikawa, H.; Ichihara, A. *J. Org. Chem.* **1995**, *60*, 5048. (c) Ichikawa, Y.; Tsuboi, K.; Jiang, Y.; Naganawa, A.; Isobe, M. *Tetrahedron Lett.* **1995**, *36*, 7101. (d) Shimizu, S.; Nakamura, S.; Nakada, M.; Shibasaki, M. *Tetrahedron* **1996**, *52*, 13363. (e) Sheppeck, J.; Liu, W.; Chamberlin, R. *J. Org. Chem.* **1997**, *62*, 387. (f) Tsuboi, K.; Ichikawa, Y.; Naganawa, A.; Isobe, M.; Ubukata, M.; Isono, K. *Tetrahedron* **1997**, *53*, 5083. (g) Jiang, Y.; Ichikawa, Y.; Isobe, M. *Tetrahedron* **1997**, *53*, 5103. (h) Tsuboi, K.; Ichikawa, Y.; Jiang, Y.; Naganawa, A.; Isobe, M. *Tetrahedron* **1997**, *53*, 5123. For formal synthesis, see: (i) Marshall, J. A.; Yanik, M. M. *J. Org. Chem.* **2001**, *66*, 1373. For synthetic studies, see: (j) Oikawa, M.; Oikawa, H.; Ichihara, A. *Tetrahedron Lett.* **1993**, *34*, 4797. (k) Nakamura, S.; Shibasaki, M. *Tetrahedron Lett.* **1994**, *35*, 4145. (l) Ueno, T.; Oikawa, M.; Oikawa, H.; Ichihara, A. *Biosci. Biotechnol. Biochem.* **1995**, *59*, 2104. (m) Maurer, K. W.; Armstrong, R. W. *J. Org. Chem.* **1996**, *61*, 3106.
5. A part of this work has been reported: Nagumo, S.; Arai, T.; Akita, H. *Tetrahedron Lett.* **1997**, *38*, 5165.
6. Wong, C.-H.; Whitesides, G. M. *Enzymes in Synthetic Organic Chemistry*; Pergamon: Oxford, 1994.
7. (a) Palmer, D. C.; Terradas, F. *Tetrahedron Lett.* **1994**, *35*, 1673. (b) Morimoto, T.; Murakami, N.; Nagata, A.; Sakakibara, J. *Chem. Pharm. Bull.* **1994**, *42*, 751. (c) Danieli, B.; Luisetti, M.; Riva, S.; Bertinotti, A.; Ragg, E.; Scaglioni, L.; Bombaredelli, E. *J. Org. Chem.* **1995**, *60*, 3637.
8. Mori, K.; Iwasawa, H. *Tetrahedron* **1980**, *36*, 87.
9. Nagumo, S.; Arai, T.; Akita, H. *Chem. Pharm. Bull.,* **1996**, *44*, 1391.
10. Mitsunobu, O. *Synthesis* **1981**, 1.
11. Dabby, R. E.; Kenyson, J.; Mason, R. F. *J. Chem. Soc.* **1952**, 4881.
12. (a) Nagasawa, K.; Shimizu, I.; Nakata, T. *Tetrahedron Lett.* **1996**, *37*, 6881. (b) Oshima, M.; Yamazaki, H.; Shimizu, I.; Nisar, M.; Tsuji, J. *J. Am. Chem. Soc.* **1989**, *111*, 6280.
13. Meyers, A. I.; Babiak, K. A.; Campbell, C. A.; Comins, D. L.; Fleming, M. P.; Henning, R.; Heuschmann, M.; Hudspeth, J. P.; Kane, J. M. *J. Am. Chem. Soc.* **1983**, *105*, 5015.
14. (a) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391. (b) Eis, M. J.; Wrobel, J. E.; Ganem, B. *J. Am. Chem. Soc.* **1984**, *106*, 3693.
15. Julia, M.; Paris, J.-M. *Tetrahedron Lett.* **1973**, 4833.

ELSEVIER

Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron 62 (2006) 726–730

Tetrahedron

Self-cyclization of (*E*)-2-(trimethylsilylmethyl)pentadienol derivative. Synthesis of bicyclo[4.3.0]nonane ring systems

Chiaki Kuroda,[a,*] Masatoshi Okada,[a] Shinya Shinozaki[a] and Hideyuki Suzuki[b]

[a]*Department of Chemistry, Rikkyo University, Nishi-Ikebukuro, Toshima-ku, Tokyo 171-8501, Japan*
[b]*Research Foundation of Itsuu Laboratory, Tamagawa, Setagaya-ku, Tokyo 158-0094, Japan*

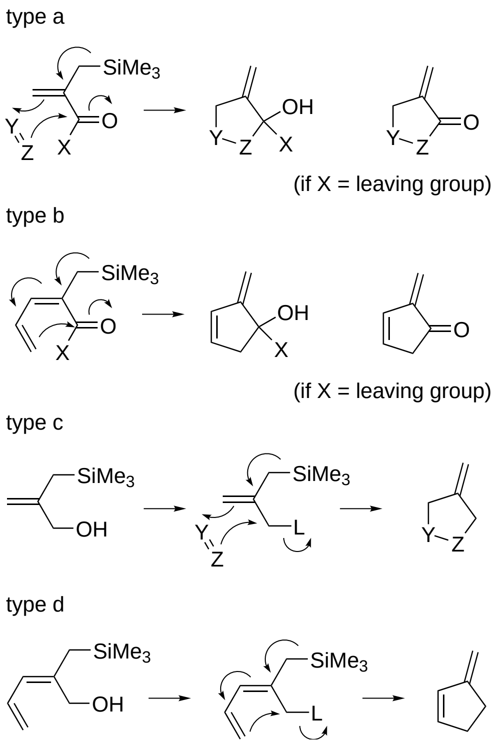
Received 28 July 2005; accepted 30 September 2005

Abstract—Utility and limitation of the title reaction was studied. When (*E*)-3-(4-*t*-butyl- and 4-phenylcyclohex-1-en-1-yl)-2-(trimethylsilylmethyl)prop-2-en-1-ols were treated with Ms_2O or MsCl, 3-*t*-butyl- and 3-phenyl-8-methylbicyclo[4.3.0]nona-1(6),7-dienes were obtained, respectively. The corresponding (*Z*)-isomer afforded a complex mixture, among which an elimination product was detected. (*E*)-4-(4-*t*-Butylcyclohexylidene)-2-(trimethylsilylmethyl)but-2-en-1-ol afforded only elimination product.

1. Introduction

α,β-Unsaturated carbonyl compounds substituted by trimethylsilylmethyl group at the α-position are unique building blocks in organic synthesis since the β-carbon reacts as an allylsilane[1] but not as an unsaturated carbonyl. Therefore, this moiety acts as a carbon 1,3-dipole based on the nucleophilicity of the β-carbon and the electrophilicity of the carbonyl carbon.[2] This enables to synthesize odd-membered ring compounds[3] via a reaction with the appropriate double-bond compound (Scheme 1, type a). We previously prepared several five-membered ring compounds such as γ-lactones[4] or cyclopentanes[5] via this type of reaction.[6] Further conjugated compounds, that is, α,β,γ,δ-unsaturated carbonyl compounds having α-trimethylsilylmethyl group cyclize themselves to a five-membered ring since the δ-carbon is nucleophilic and reacts with carbonyl carbon (Scheme 1, type b). As an example of this type of reaction, we recently described synthesis of bicyclo[4.3.0]nonane and spiro[4.5]decane carbon skeletons (vide infra).[7]

On the other hand, β-(hydroxymethyl)allylsilane also acts as a carbon-1,3-dipole after conversion of the hydroxy group into an appropriate leaving group. The expected product is a five-membered ring after reaction with a double-bond compound (Scheme 1, type c). This type of reaction was developed by Trost's group and is well documented in review articles.[8] The related [3+4] cycloaddition reaction (homo-Diels–Alder type of reaction) utilizing this unit as the dienophile has also been established.[9] We recently reported a five-carbon ring expansion reaction by replacing



Scheme 1.

Keywords: Bicyclo[4.3.0]nonane; Allylsilane; Pentadienol; Cyclization.

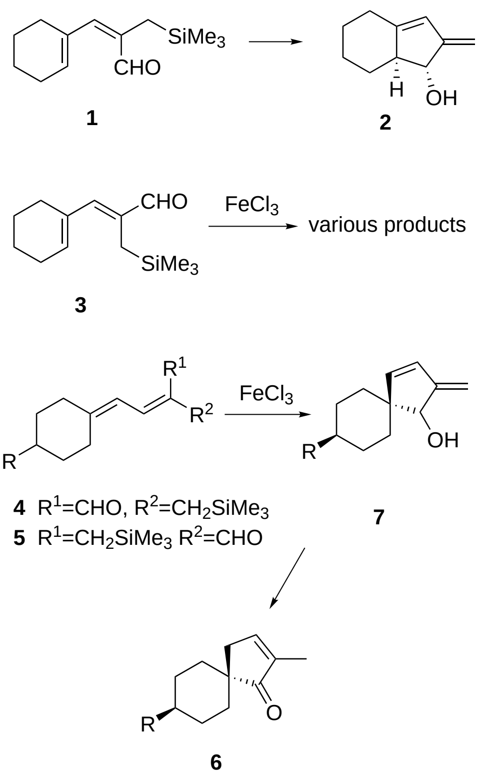
* Corresponding author. Tel.: +81 3 3985 2396; fax: +81 3 3985 2396; e-mail: chkkuroda@grp.rikkyo.ne.jp

doi:10.1016/j.tet.2005.09.146

the C=C double bond of the Cope rearrangement with a β-(hydroxymethyl)allylsilane unit (homo-Cope type of reaction).[10]

Further conjugation to β-(hydroxymethyl)allylsilane provides the fourth type of substrate (Scheme 1, type d). Although this type of reaction is an analogue of the 'type b', a problem is expected. Namely, it is for a simple elimination to occur as a competitive reaction, giving a triene if the double bond has some substituents, while this type of elimination reaction is not expected for the 'type b' reaction. The aim of the present study is to clarify the utility and the limitation of this type of reaction.

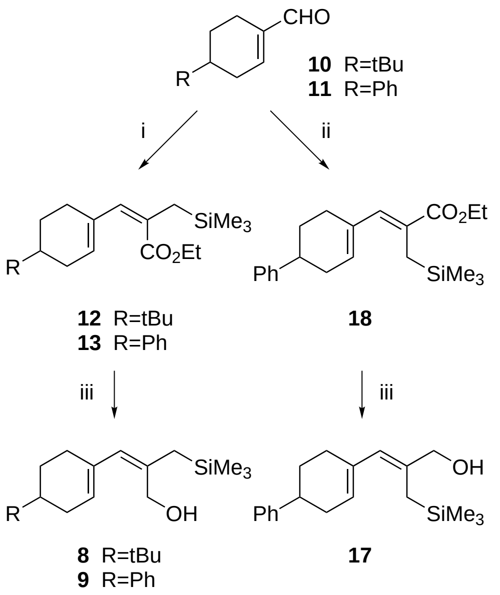
We planned to study the cyclization of 'type d' on the basis of our previous study of the 'type b' reaction,[7a] the outline of which is shown in Scheme 2. In these reactions, the geometry of the cyclization precursor was an important factor for the synthesis of bicyclo[4.3.0]nonane. Namely, (*E*)-precursor **1** cyclized to give the expected product **2** in good yield, while (*Z*)-precursor **3** afforded only a complex mixture. In contrast, in the synthesis of the spiro[4.5]decane carbon framework, both (*E*)- (**4**) and (*Z*)-dienes (**5**) ultimately afforded the same compound **6**, which is the isomerization product of **7**. Here we report that bicyclo[4.3.0]nonane can be synthesized from (*E*)-2-(trimethylsilylmethyl)pentadienol, as in the case of pentadienal, however, spiro[4.5]decane was not obtained.



Scheme 2.

2. Results and discussion

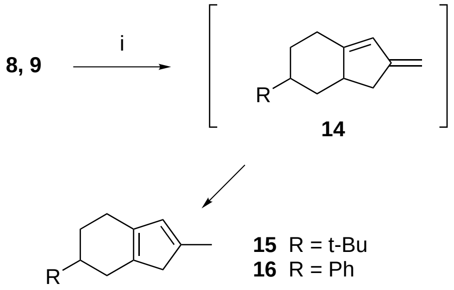
Following the fact that (*E*)-2-(trimethylsilylmethyl)pentadienal **1** cyclized immediately,[7a] we first studied the cyclization of the 3-cyclohexenyl-2-(trimethylsilylmethyl)prop-2-en-1-ol derivative expecting that the cyclization would occur faster than elimination. Since the expected cyclization product is a hydrocarbon, we chose the *t*-butyl- or phenyl-substituted compounds **8** and **9** as the substrates in order to reduce handling problem due to volatility. Compounds **8**[7a] and **9** were synthesized from 4-*t*-butylcyclohex-1-enecarbaldehyde (**10**) and 4-phenylcyclohex-1-enecarbaldehyde (**11**), respectively, via the (*E*)-selective Horner–Wadsworth–Emmons (HWE) reactions[11] followed by DIBAL-H reduction of the ester **12** and **13** (Scheme 3). Compound **11** was prepared from 4-phenylcyclohex-2-en-1-one[12] (see Section 3), which was prepared from 4-phenylcyclohexanone by a standard method.



Scheme 3. Reagents and conditions: (i) $(PhO)_2P(O)CH(CO_2Et)CH_2SiMe_3$, NaH, THF, rt; (ii) $(EtO)_2P(O)CH(CO_2Et)CH_2SiMe_3$, NaH, THF, rt; (iii) DIBAL-H, CH_2CH_2, −60 °C.

The 'type d self-cyclization reaction' was then studied. Firstly, following our previous report on the five-carbon ring expansion reaction,[10] **8** was treated with Tf_2O in CH_2Cl_2 at −60 °C in the presence of 2,6-lutidine, however, only a complex product mixture was obtained. Some other bases such as Na_2CO_3, LDA, and BuLi were used instead of 2,6-lutidine but no cyclization product was obtained. Conversion of the hydroxy group into halogen was also tried using halogenation reagents such as PPh_3/CBr_4,[13] but without success.

Then, **8** was converted to its mesylate, which is a less reactive leaving group than triflate. When **8** was treated with Ms_2O in CH_2Cl_2 and pyridine at room temperature, the reaction proceeded within 10 min. The product was not the mesylate but a bicyclic hydrocarbon formed by the 'type d' cyclization reaction (85% yield) (Scheme 4). The product was found not to be the originally expected compound **14** (R = *t*-Bu), but **15**, as characterized from the NMR spectra. Namely, although four olefinic carbons were observed in the ^{13}C NMR, the terminal olefin protons expected for **14** were not found in the ^{1}H NMR, but instead of them, only one alkene proton was

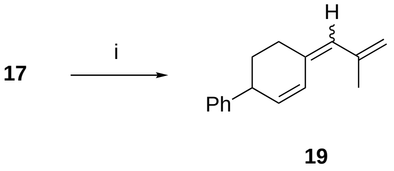


Scheme 4. Reagents and conditions: (i) Ms_2O (for **8**) or MsCl (for **9**), pyridine, CH_2Cl_2, 0 °C.

found at δ 5.90 (br s) together with a pair of methylene protons (δ 2.70 and 2.79) and a methyl group. It is easily expected that **15** is the isomerization product of **14**.

The same reaction was also carried out using **9** as the substrate. The expected product **16** was obtained in only 28% yield via an analogous Ms_2O treatment as above. However, when MsCl was used as the reagent, **16** was afforded in 53% yield, although a longer reaction time (17 h) was required.

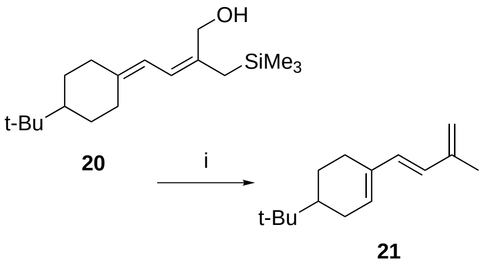
Since the geometry of the allylsilane is considered to be an important factor,[7a] the reaction of the (*Z*)-precursor was also studied using **17** as the substrate, which was prepared via a (*Z*)-selective HWE reaction (**11** to **18**)[14] followed by DIBAL-H reduction (Scheme 3). When **17** was treated with MsCl or Ms_2O in pyridine/CH_2Cl_2, only a complex mixture was afforded among which the presence of triene **19** was detected from ^1H NMR spectrum of the reaction mixture (Scheme 5). The geometry of the double-bond in **19** was not determined. Since C-1 and C-5 of the penta-2,4-dien-1-ol unit in **17** are too distant to cyclize, the result indicates that the *Z* to *E* isomerization did not occur, while such an isomerization process occurred partly for the corresponding aldehyde **3**.[7]



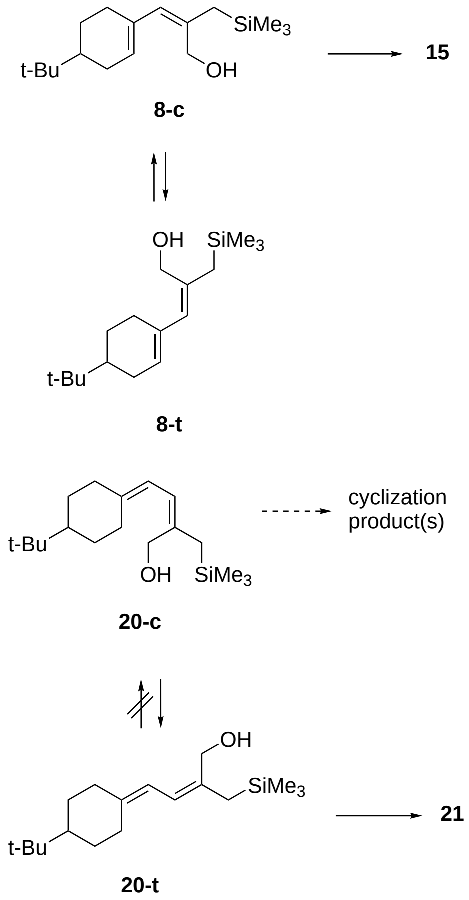
Scheme 5. Reagents and conditions: (i) MsCl, pyridine, CH_2Cl_2, 0 °C.

Cyclization of 4-cyclohexylidene-2-(trimethylsilylmethyl)but-2-en-1-ol derivative to the spiro[4.5]decane type of compound was also studied. The substrate **20** was synthesized in accordance with the previously reported procedure.[7] When this compound was treated with Ms_2O and pyridine in CH_2Cl_2, triene **21** was afforded in 77% yield (Scheme 6), together with a small amount of its (*Z*)-isomer. The (*E*)-geometry of **21** was determined from the *J*-value (16.0 Hz) of the olefinic protons. Both compounds **21** and **19** are considered to be the products of simple elimination of mesylate followed by protodesilylation.

The difference in results between **8** and **20** indicates that the substitution pattern of the 2-(trimethylsilylmethyl)pentadienol is an important factor. Namely, C-1 and C-5 of pentadienol are close to each other for **8** (and **9**) but far for **20**. For **8**, steric congestion of both s-cis (Scheme 7, conformer **8-c**) and s-trans (**8-t**) conformers are almost equal, while s-cis conformer (**20-c**) is highly congested and only s-trans conformer (**20-t**) can be considered for **20**. Also, mesylation is hindered for **20-c** by both the trimethylsilyl group and cyclohexane ring.



Scheme 6. Reagents and conditions: (i) Ms_2O, pyridine, CH_2Cl_2, 0 °C.



Scheme 7.

In conclusion, the utility and limitation of the self-cyclization reaction of 2-(trimethylsilylmethyl)pentadienol in the synthesis of five-memberd ring was revealed. Cyclization of 4,5-disubstituted (*E*)-2-(trimethylsilylmethyl)pentadienol occurred predominantly over the elimination reaction, and was shown to be useful in the synthesis of bicyclo[4.3.0]nonane compounds. In contrast, the elimination reaction giving triene occurred from both 4,5-disubstituted (*Z*)-2-(trimethylsilylmethyl)pentadienol and 5,5-disubstituted (*E*)-2-(trimethylsilylmethyl)pentadienol. This suggests that both the geometry of the double-bond and the position of the substituents are important factors for the self-cyclization reaction.

3. Experimental

3.1. General procedure

IR spectra were recorded on a Jasco FT/IR-230 spectrometer. Both ^{1}H and ^{13}C NMR spectra were measured on a Jeol GSX-400 (400 MHz for ^{1}H; 100 MHz for ^{13}C) spectrometer. Chemical shifts were reported on the δ scale (ppm) with solvent ($CHCl_3=7.26$) as an internal standard, unless otherwise noted. The signal of the solvent ($CDCl_3=77.0$) was used as a standard for ^{13}C NMR spectra. Both low-resolution mass spectra (MS) and high-resolution mass spectra (HRMS) were obtained on a Jeol SX-102A, CMATE II, or Shimadzu GCMS-QP5050 mass spectrometer with the EI method. Analytical TLC was done on precoated TLC plates (Kieselgel 60 F254, layer thickness 0.2 mm). Wakogel C-200 or florisil (100–200 mesh) was used for column chromatography. Anhydrous Na_2SO_4 or $MgSO_4$ was used for drying the extracted organic layers. For dry solvent, THF was distilled from $LiAlH_4$, and CH_2Cl_2 was distilled from CaH_2. All new compounds were determined to be >95% pure by ^{1}H and ^{13}C NMR, unless otherwise noted.

3.2. Preparation of the substrates

3.2.1. 4-Phenylcyclohex-1-enecarbaldehyde (11). To a stirred solution of LDA, prepared from iPr$_2$NH (0.90 cm^3, 5.93 mmol) and BuLi (2.0 cm^3, 3.08 mmol, 1.54 M solution in hexane) in dry THF (3 cm^3) was added a solution of $Ph_2P(O)CH_2OMe$ (730 mg, 2.11 mmol) in THF (13 cm^3) at −60 °C under Ar. A solution of 4-phenylcyclohex-2-en-1-one (255 mg, 1.48 mmol) in THF (6 cm^3) was added, and the mixture was stirred with slow warming to room temperature. After confirming the reaction on TLC, an aqueous solution of HCl (2 M) was added, and the mixture was heated to 80–90 °C for 20 h. This was cooled to room temperature again, $NaHCO_3$ aq. was added, and the product was extracted with Et_2O and dried. Evaporation of the solvent followed by silica gel (15 g) column chromatography using hexane–Et_2O (9/1) as eluent yielded **11** (168.9 mg, 61%) as an oil; IR (neat) 2927, 1682, 1643, 1163, 758, and 700 cm^{-1}; ^{1}H NMR ($CDCl_3$, $Me_4Si=0.00$) $\delta=1.66$–1.78 (1H, m), 2.00–2.08 (1H, m), 2.16–2.28 (1H, m), 2.38–2.55 (2H, m), 2.60–2.70 (1H, m), 2.80–2.90 (1H, m), 6.85–6.89 (1H, m, C=CH), 7.19–7.34 (5H, m, Ph), and 9.48 (1H, s, CHO); ^{13}C NMR ($CDCl_3$) $\delta=21.79$, 28.60, 34.29, 39.68, 126.38, 126.67 (2C), 128.49 (2C), 141.24, 145.45, 150.35, and 193.76; MS *m/z* 186 (M$^+$, 11%), 115 (6), 104 (100), 95 (28), 78 (14), and 51 (13); HRMS [Found: *m/z* 186.1074 (M$^+$). Calcd for $C_{13}H_{14}O$: 186.1045].

3.3. (*E*)-Selective HWE reaction

See our previous paper for the procedure and spectral data of **12**.[7a] By the same procedure, **13** (29.5 mg, 77%) was synthesized from **11** (21.0 mg).

3.3.1. (*E*)-Ethyl 3-(4-phenylcyclohex-1-en-1-yl)-2-(trimethylsilylmethyl)prop-2-enoate (13). An oil; IR (neat) 2952, 1720, 1248, 1217, and 852 cm^{-1}; ^{1}H NMR ($CDCl_3$) $\delta=0.10$ (9H, s, $SiMe_3$), 1.33 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 1.71–2.48 (8H, m), 2.77–2.87 (1H, m), 4.21 (AB, each q, $J=7.1$ Hz, OCH_2CH_3), 5.76 (1H, br, $C{=}CHC_{ring}$), 5.93 (1H, br s, $CH{=}CCO_2Et$), and 7.18–7.37 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) $\delta=-1.67$ (3C), 14.01, 25.63, 27.44, 29.72, 33.98, 39.59, 60.21, 125.91, 126.64 (2C), 127.74, 128.23 (2C), 129.20, 132.87, 134.93, 146.64, and 170.56; MS *m/z* 342 (M$^+$, 4%), 297 (3), 223 (11), 195 (6), 117 (14), 91 (31), and 73 (100); HRMS [Found: *m/z* 342.2064 (M$^+$). Calcd for $C_{21}H_{30}O_2Si$: 342.2015].

3.4. (*Z*)-Selective HWE reaction

See our previous paper for the procedure.[7a] Compound **18** (90%) was prepared from **11** but was not characterized at this stage and was subjected to the next reduction step (**18** to **17**) without purification.

3.5. Reduction

See our previous paper for the procedure and the spectral data of **8**. By the same procedure, **13** and **18** afforded **9** (100%) and **17** (90%), respectively.

3.5.1. (*E*)-3-(4-Phenylcyclohex-1-en-1-yl)-2-(trimethylsilylmethyl)prop-2-en-1-ol (9). An oil; IR (neat) 3338, 2927, 1246, 1018, 852, 756, and 698 cm^{-1}; ^{1}H NMR ($CDCl_3$) $\delta=0.07$ (9H, s, $SiMe_3$), 1.65–2.45 (9H, m), 2.75–2.84 (1H, m), 4.20 (1H, d, $J=12.0$ Hz, CHHOH), 4.29 (1H, d, $J=12.0$ Hz, CHHOH), 5.56 (1H, br, $C{=}CHC_{ring}$), 5.60 (1H, br s, $CH{=}CCH_2OH$), and 7.18–7.34 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) $\delta=-1.31$ (3C), 24.93, 29.84, 30.02, 33.74, 39.71, 62.34, 124.85, 125.93, 126.73 (2C), 128.13, 128.27 (2C), 134.72, 137.47, and 146.82; MS *m/z* 300 (M$^+$, 8%), 271 (55), 210 (7), 195 (7), 181 (8), 167 (7), 155 (7), 117 (17), 91 (48), and 73 (100); HRMS [Found: *m/z* 300.1922 (M$^+$). Calcd for $C_{19}H_{28}OSi$: 300.1910].

3.5.2. (*Z*)-3-(4-Phenylcyclohex-1-en-1-yl)-2-(trimethylsilylmethyl)prop-2-en-1-ol (17). An oil; IR (neat) 3390, 1726, 1452, and 852 cm^{-1}; ^{1}H NMR ($CDCl_3$) $\delta=0.07$ (9H, s, $SiMe_3$), 1.73–2.48 (9H, m), 2.75–2.84 (1H, m), 4.20 (2H, s, CH_2OH), 5.73 (1H, br, $C{=}CHC_{ring}$), 5.78 (1H, br s, $CH{=}CCH_2OH$), and 7.18–7.34 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) $\delta=-0.56$ (3C), 19.84, 29.88, 30.02, 33.79, 39.72, 69.34, 124.69, 125.53, 125.98, 126.84 (2C), 128.34 (2C), 135.01, 137.28, and 146.95; MS *m/z* 300 (M$^+$, 2%), 271 (1), 210 (13), 195 (10), 181 (10), 167 (10), 155 (9), 117 (30), 106 (42), 91 (74), and 73 (100); HRMS [Found: *m/z* 300.1927 (M$^+$). Calcd for $C_{19}H_{28}OSi$: 300.1910].

3.6. Cyclization reaction

In a 10 cm^3 round bottomed flask, a solution of **8** (27.4 mg, 0.094 mmol) in dry CH_2Cl_2 (3 cm^3, freshly distilled from CaH_2) was prepared, and to this solution was added successively pyridine (0.055 cm^3) and methanesulfonic anhydride (70.8 mg, 0.40 mmol) at 0 °C with stirring. $CaCl_2$ drying tube was attached, and the stirring was continued for 10 min. Water was added, and the product was extracted with Et_2O followed by drying and evaporation. The resultant residue was chromatographed on florisil (1 g) using pentane as eluent to afford **15** (15.1 mg, 85%).

Similarly, **9** (6.7 mg, 0.022 mmol) afforded **16** (2.5 mg, 53%) by treatment with methanesulfonic chloride (0.007 cm^3) instead of methanesulfonic anhydride in pyridine (0.015 cm^3) and CH_2Cl_2 (3 cm^3).

3.6.1. 3-*t*-Butyl-8-methylbicyclo[4.3.0]nona-1(6),7-diene (15). An oil; IR (neat) 2924, 1645, 1468, 1365, 1265, and 741 cm^{-1}; ^1H NMR ($CDCl_3$) $\delta=0.90$ (9H, s, *t*-Bu), 1.17–1.40 (2H, m), 1.85–2.34 (5H, m), 2.01 (3H, s, Me), 2.70 (1H, dd, $J=3.5$, 22 Hz), 2.79 (1H, br d, $J=22$ Hz), and 5.90 (1H, br s); ^{13}C NMR ($CDCl_3$) $\delta=24.6$, 25.5, 26.8, 27.4 (3C), 29.7, 32.4, 45.3, 46.9, 128.9, 137.0, 138.0, and 141.9; MS *m/z* 190 (M^+, 21%), 175 (3), 133 (34), 106 (100), 91 (84), and 41 (44); HRMS [Found: *m/z* 190.1691 (M^+). Calcd for $C_{14}H_{22}$: 190.1722].

3.6.2. 8-Methyl-3-phenylbicyclo[4.3.0]nona-1(6),7-dien (16). An oil; IR (neat) 2925, 1452, 1377, 750, and 698 cm^{-1}; ^1H NMR ($CDCl_3$) $\delta=1.77$–2.06 (2H, m), 2.04 (3H, s, Me), 2.35–2.60 (4H, m), 2.77 (1H, br d, $J=22.7$ Hz, C*H*H in cyclopentadiene), 2.84 (1H, br d, $J=22.7$ Hz, CH*H* in cyclopentadiene), 2.84–2.92 (1H, m), 5.95 (1H, s, CH=C), and 7.18–7.34 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) $\delta=16.18$, 24.86, 30.47, 33.63, 41.27, 46.64, 125.94, 126.95 (2C), 128.32 (2C), 128.84, 136.12, 137.98, 142.20, and 147.31; MS *m/z* 210 (M^+, 22%), 106 (100), and 91 (90); HRMS [Found: *m/z* 210.1375 (M^+). Calcd for $C_{16}H_{18}$: 210.1409].

3.7. Treatment of 17 and 20 with Ms_2O or MsCl

Compound **20** was treated with Ms_2O, and **17** was treated with MsCl following the cyclization of the corresponding (*E*)-isomers. Compound **17** afforded only a complex mixture, while **20** (32.0 mg, 0.09 mmol) afforded **21** (17.1 mg, 77%) after florisil column chromatography using pentane as eluent.

3.7.1. 6-(2-Methylprop-2-enylidene)-3-phenylcyclohex-1-ene (19). This compound could not be isolated in the pure form. The following data were assigned from a complex mixture of hydrocarbon products. ^1H NMR ($CDCl_3$) $\delta=1.92$ (3H, s, Me), 3.54 (1H, br, CHPh), 4.89 (1H, s, C=C*H*H), 5.02 (1H, s, C=CH*H*), 5.80 (1H, s, CH_2=C–C*H*=C), 5.86 (1H, dd, $J=2.5$, 9.4 Hz, C*H*=CH), 6.24 (1H, dd, $J=1.3$, 9.4 Hz, CH=C*H*), and 7.19–7.34 (5H, m, Ph); MS *m/z* 210 (M^+, 18%), 195 (9), 167 (14), 106 (100), and 91 (76).

3.7.2. 4-*t*-Butyl-1-(3-methylbuta-1,3-dienyl)cyclohex-1-ene (21). An oil; IR (neat) 2956, 1620, 1468, 1363, and 958 cm^{-1}; ^1H NMR ($C_6D_6=7.15$) $\delta=0.80$ (9H, s, *t*-Bu), 1.02–1.20 (2H, m), 1.68–2.07 (4H, m), 1.86 (3H, s, Me), 2.27–2.35 (1H, m), 4.99 (1H, br s), 5.08 (1H, br s), 5.72–5.79 (1H, m), 6.38 (1H, d, $J=16.0$ Hz), and 6.41 (1H, d, $J=16.0$ Hz); ^{13}C NMR ($C_6D_6=128.0$) $\delta=18.8$, 24.1, 26.2, 27.2 (3C), 27.9, 32.1, 44.4, 115.8, 130.6, 132.6, 135.9, and 142.7 (one carbon was not identified because of overlapping with the solvent signal); MS *m/z* 204 (M^+, 13%), 189 (2), 147 (11), 133 (14), 119 (17), 105 (88), 91 (44), 57 (100), and 41 (93); HRMS [Found: *m/z* 204.1870 (M^+). Calcd for $C_{15}H_{24}$: 204.1878].

Acknowledgements

The authors wish to thank Professor E. Horn of Rikkyo University for help in the writing of this article. The financial support was partly obtained from Frontier Project of Rikkyo University.

References and notes

1. For review on the reaction of allylsilane, (a) Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063–2192. (b) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207–2293. (c) Hosomi, A. *Acc. Chem. Res.* **1988**, *21*, 200–206.
2. (a) Kuroda, C.; Suzuki, H. *Curr. Org. Chem.* **2003**, *7*, 115–131. (b) Kuroda, C. *Recent Res. Devel. Pure Appl. Chem.* **1998**, *2*, 189–198.
3. For review on the synthesis of carbocycles, see, (a) Ho, T.-L. *Carbocycle Construction in Terpene Synthesis*; VCH: New York, 1988. (b) Thebtaranonth, C.; Thebtaranonth, Y. *Cyclization Reactions*; CRC: Boca Raton, 1994.
4. For examples, (a) Kuroda, C.; Ito, K. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2297–2303. (b) Kuroda, C.; Kobayashi, K.; Koito, A.; Anzai, S. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 1947–1961. (c) Kuroda, C.; Inoue, S.; Takemura, R.; Satoh, J. Y. *J. Chem. Soc., Perkin Trans. 1* **1994**, 521–526.
5. Kuroda, C.; Nogami, H.; Ohnishi, Y.; Kimura, Y.; Satoh, J. Y. *Tetrahedron* **1997**, *53*, 839–858.
6. For related studies reported from our laboratory: (a) Kuroda, C.; Kasahara, T.; Akiyama, K.; Amemiya, T.; Kunishima, T.; Kimura, Y. *Tetrahedron* **2002**, *58*, 4493–4504. (b) Kuroda, C.; Koshio, H.; Koito, A.; Sumiya, H.; Musase, A.; Hirono, Y. *Tetrahedron* **2000**, *56*, 6441–6455. (c) Kuroda, C.; Murase, A.; Suzuki, H.; Endo, T.; Anzai, S. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1639–1647.
7. (a) Kuroda, C.; Honda, S.; Nagura, Y.; Koshio, H.; Shibue, T.; Takeshita, T. *Tetrahedron* **2004**, *60*, 319–331. (b) Kuroda, C.; Koshio, H. *Chem. Lett.* **2000**, 962–963.
8. (a) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1–20. (b) Chan, D. M. T. In *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jørgensen, K. A., Eds.; Wiley: Weinheim, 2002; pp 57–84.
9. (a) Giguere, R. J.; Duncun, S. M.; Bean, J. M.; Purvis, L. *Tetrahedron Lett.* **1988**, *29*, 6071–6074. (b) Hoffmann, H. M. R.; Eggert, U.; Gibbels, U.; Giesel, K.; Koch, O.; Lies, R.; Rabe, J. *Tetrahedron* **1988**, *44*, 3899–3917. (c) Hoffmann, H. M. R.; Henning, R. *Helv. Chim. Acta* **1983**, *66*, 828–841.
10. (a) Suzuki, H.; Monda, A.; Kuroda, C. *Tetrahedron Lett.* **2001**, *42*, 1915–1917. (b) Suzuki, H.; Kuroda, C. *Tetrahedron* **2003**, *59*, 3157–3174.
11. Suzuki, H.; Kuroda, C. *J. Chem. Res. (S)* **2003**, 310–312.
12. (a) Booker-Milburn, K. I.; Thompson, D. F. *Tetrahedron* **1995**, *51*, 12955–12962. (b) Nakatani, K.; Takada, K.; Isoe, S. *J. Org. Chem.* **1995**, *60*, 2466–2473.
13. Axelrod, E. H.; Milne, G. M.; van Tamelen, E. E. *J. Am. Chem. Soc.* **1970**, *92*, 2139–2141.
14. Henning, R.; Hoffmann, H. M. R. *Tetrahedron Lett.* **1982**, *23*, 2305–2308.

Tetrahedron 62 (2006) 731–736

Tetrahedron

Synthesis of new bridged biimidazoles by an acylation–dimerization sequence

Thomas Welzel,[a] Rainer Beckert,[a,*] Reinald Fischer,[b] Sven Rau,[b,*]
Dirk Walther[b] and Helmar Görls[b]

[a]*Institute of Organic and Macromolecular Chemistry, Friedrich Schiller University, Humboldtstr. 10, D-07743 Jena, Germany*
[b]*Institute of Inorganic and Analytical Chemistry, Friedrich Schiller University, August-Bebelstr. 2, D-07743 Jena, Germany*

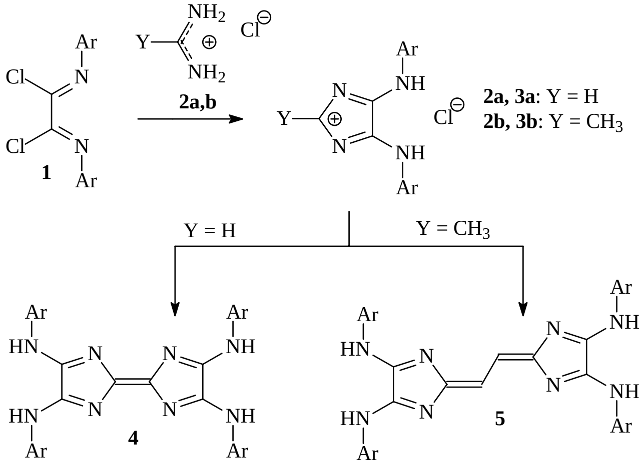
Received 17 August 2005; revised 23 September 2005; accepted 29 September 2005

Abstract—*N*-Methylimidazole reacts with bis-imidoylchlorides derived from oxalic acid and yields new bis-cationic tricyclic systems of type of diimidazo[1,2-*a*:2′,1′-*c*]pyrazines. Under identical conditions, 1,2-dimethylimidazole has been transformed into pyrrolo[1,2-*a*]imidazoles. 2,2′-Biimidazole itself can be cyclized with bis-imidoylchlorides thus yielding a new heterotricycle, which possesses two different 1,4-diaza-1,3-diene substructures.

1. Introduction

In the recent past, 2,2′-biimidazoles have gained increasing importance for the preparation of metal complexes, artificial receptors, two-step redox systems and supramolecular architectures.[1] In addition, bridged derivatives of biimidazole and their benzologues have often been applied in order to study the formation and dimerization of nucleophilic carbenes.[2] The most commonly used approach to generate highly substituted derivatives of 2,2′-biimidazole was followed transition metal mediated homocoupling strategy. Due to its low solubility, 2,2′-biimidazole itself ‘glycosine of Debus’ can be transformed to produce material soluble in organic solvents, which then allows further functionalization.[3] However, a wider application of 2,2′-biimidazole is restricted due to low yields, which can only be obtained in costly and time consuming synthesis.

Bis-imidoylchlorides derived from oxalic acid **1** are distinguished by their well defined electrophilicity, which lies between typical acyl chlorides and reactive alkyl halides. Because of this fact, selective cyclization reactions are possible, which often initiate cascade reactions (Scheme 1). For example, cyclization reactions of formamidine **2a** and acetamidine **2b** lead to five-membered ring systems **3a**,**b** in which the H atoms in 2-position and at the 2-methyl group exhibit an increased acidity. Consequently, a rapid sequence of reactions, finally leads to the formation of stable tetraazafulvalenes **4**[4] or fulvadienes of type **5**.[5] As part of our ongoing studies in the area of cascade reactions using cycloamidines we report our findings on cylization reactions of bis-electrophilic building blocks **1** with easily accessible imidazoles.



Scheme 1. The cyclization reaction of bis-imidoylchlorides **1** with formamidine and acetamidine.

2. Results and discussion

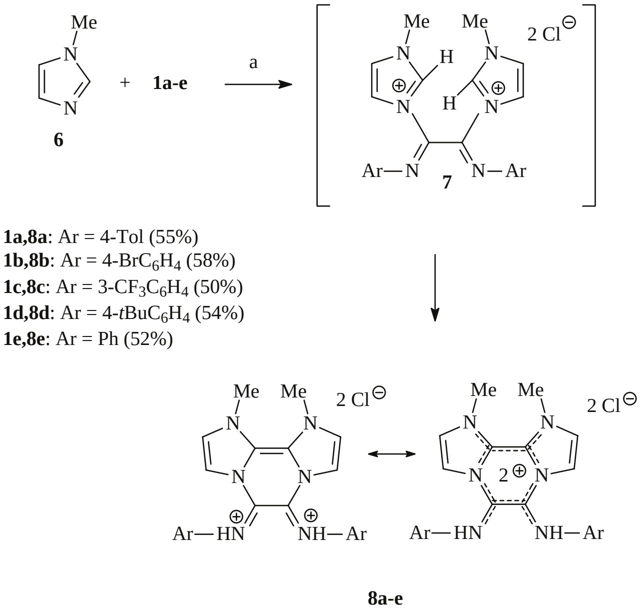
We studied the acylation of *N*-methylimidazole **6** because it represents a cyclic amidine with bielectrophiles **1** in order to

---

Keywords: Imidazoles; 2,2′-Biimidazoles; Bis-imidoylchlorides; Cascade reaction.

* Corresponding authors. Tel.: +49 3641 948230; fax: +49 3641 948212 (R. B.); Tel.: +49 3641 948113; fax: +49 3641 948102 (S. R.); e-mail addresses: C6bera@uni-jena.de; Sven.rau@uni-jena.de

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.09.141



1a,8a: Ar = 4-Tol (55%)
1b,8b: Ar = 4-BrC_6H_4 (58%)
1c,8c: Ar = 3-$CF_3C_6H_4$ (50%)
1d,8d: Ar = 4-*t*BuC_6H_4 (54%)
1e,8e: Ar = Ph (52%)

Scheme 2. (a) Toluene, triethylamine, 95 °C, 12 h.

achieve bis-azolium salts of type **7** (Scheme 2). Even upon a brief heating period from mixtures containing **1** and **6** in toluene, yellow salts precipitated and were isolated. Elemental analysis and mass spectra indicated the molecular composition of a bis-imidazolium salt of type **7**.

However, when the same reaction was carried out in the presence of triethylamine, a product was obtained in moderate yield whereby the ^{1}H NMR data was not in accordance with structure **7**. The aliphatic region showed one singlet at 2.34 ppm (6H) for tolyl CH_3 groups and another at 4.79 ppm (6H) for *N*-Me, which is shifted for about 1.3 ppm downfield compared to the starting material **6**. In the aromatic region, the compound displayed two well resolved double doublets for the tolyl substructure as well as for the 4-/5-H of imidazole. Both imidazole H-atoms are shifted downfield of about 1.5 ppm. The main evidence for another structure, however, was that no signal for the hydrogen in 2-position could be detected. From this data we conjectured that most likely a C–C-bond formation in derivative **8** occurred (Scheme 2). Single-crystal X-ray analysis allowed an unambigous structural assignment of this compound, as shown in Figure 1. The X-ray data of **8a** unequivocally demonstrates its molecular structure of a bridged bis-imidazolium salt, hence ruling out a higher-membered cyclooligomeric compound. Very interestingly both NH functions are involved in hydrogen bonding to a chloride anion. The 1,4-diaza-1,3-dien-substructure in **1**[6] was converted into an endiamide structure with a shortening of the C–C bond from 1.50 to 1.35 Å and an extension of the C–N bond from 1.24 to 1.38 Å. The length of the newly formed C–C bond in the bis-amidinium structure between the imidazole rings lies with 1.42 Å between a double and a single bond. The positive charges are therefore delocalised over several bonds including the pyrazine ring thus forming an almost planar tricycle. The synthesis of unsubstituted diimidazo[1,2-*a*:2′,1′-*c*]pyrazine has already been reported,[7] however, in a four-step protocol giving an overall yield of only 34%.

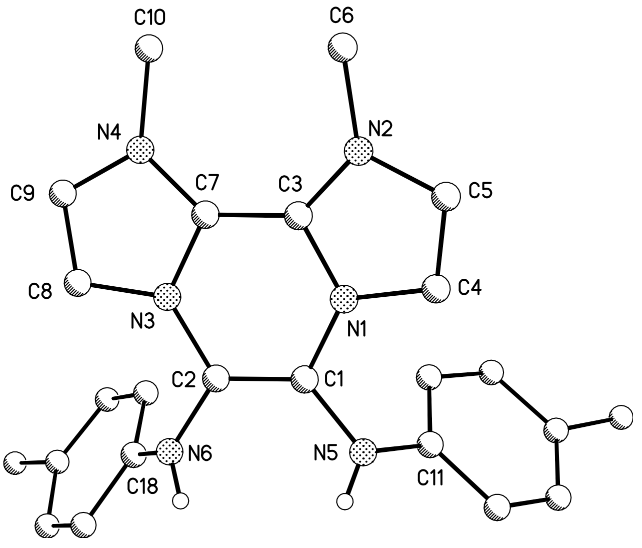
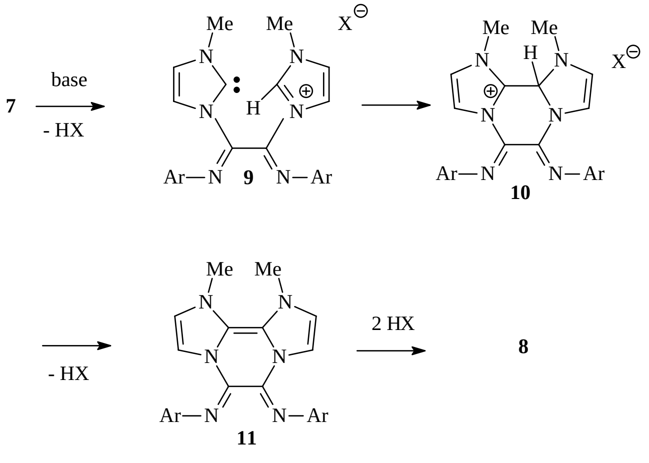
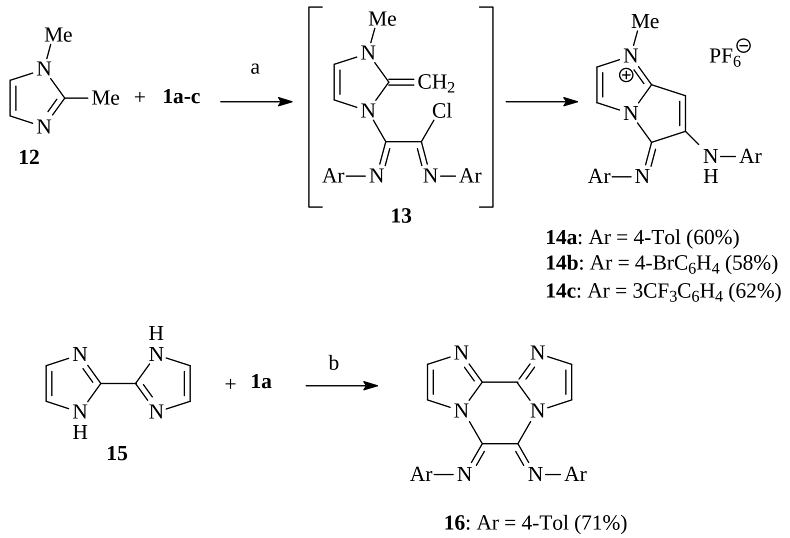


Figure 1. Molecular structure and atomic numbering for derivative **8a**.

Obviously, the coupling of both imidazoles in 2,2′-position is the result of a cascade reaction, which involves intramolecular redox steps. We propose the following mechanism (Scheme 3): the base triethylamine deprotonates the primarily formed **7** at one of the acidic 2-positions to give **9**. This nucleophilic carbene immediately adds the close amidinium system under formation of a single bond to yield **10**. The fast addition reaction has recently been reported[8] to be characteristic for such types of carbenes. Then a further deprotonation step leads to the dimer **11**, which also can be regarded as bridged electron-rich olefin. These olefins display a pattern of reactivity, which is unusual. They are generally air-sensitive and can be oxidized to provide stable radical cations and even dications.[9] In this case, however, the 1,4-diaza-1,3-diene substructure in **11** acts as an electron-accepting substructure. Most likely, an intramolecular electron transfer finally leads to the delocalized dication in **8**. Further support of this pathway is provided regarding that similar oxalamidines can easily be reduced by two consecutive electron transfer steps to yield tetraaminoethenes.[10] According to the best of our knowledge, the tricycle in derivative **8** represents the first system in which an electron-rich olefin combines with an



Scheme 3. Proposed mechanism for the formation of biimidazolium salts of type **8**.



Scheme 4. (a) Toluene, triethylamine, rt, 4 h, then aqueous NH_4PF_6; (b) THF, *n*-butyllithium, argon atmosphere, −20 °C→rt.

electron-accepting 1,4-diazadiene. The protonation of both exocyclic nitrogen atoms realizes the optimal charge distribution in **8** (Scheme 3) which can be compared with the dications of Schwesingers vinamidine bases.[11]

In the course of further experiments other azoles were tested with respect to cascade reactions. Whereas thiazole and benzothiazole only gave tar-like materials, benzimidazole could be recovered unreacted under the same reaction conditions.

1,2-Dimethylimidazole **12** reacted with **1a–c** in the presence of triethylamine to give red crystalline compounds (Scheme 4). The structure of a cationic pyrrolo[1,2-*a*] imidazole **14a** could be determined by HRMS and multidimensional NMR. On the other hand, employing a large excess of triethylamine gave the neutral form of **14**, which showed decomposition during work-up. Obviously, in the first step an activation of the 2-methyl group by acylation at the ring nitrogen took place followed by its deprotonation leading to intermediate **13**. This cyclic ketene-*N*,*N*-acetal is suspected to possess a large charge density at the β-carbon,[12] which then undergoes the final cyclization reaction with the imidoylchloride still present in structure **14**.

We also studied cyclization reactions of 2,2′-biimidazole **15** with **1**. Treatment of the dianion of **15** (generated by addition of 2 equiv of *n*-BuLi to 2,2′-biimidazole at −20 °C) with **1a** gives in good yield the new tricycle derivative **16** (Scheme 4). Elemental analysis and MS data confirm the structure of 1:1 cyclization product. In its ^{1}H NMR spectrum the characteristic *E*/*Z*-interconversion of both aryl residues is visible by broad signals of arylic protons at room temperature. The X-ray analysis of the orange crystals of **16** was possible and the result is shown in Figure 2. The 1,4-diaza-1,3-dien-substructure is retained in

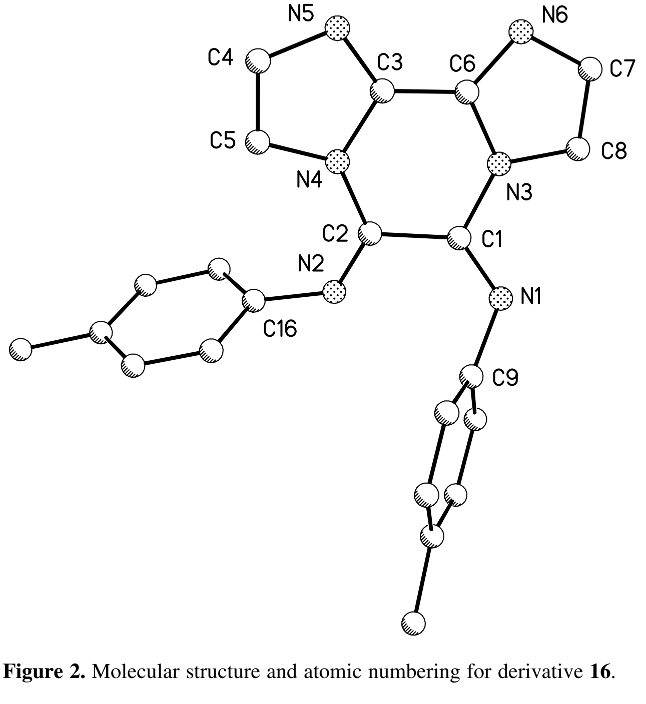


Figure 2. Molecular structure and atomic numbering for derivative **16**.

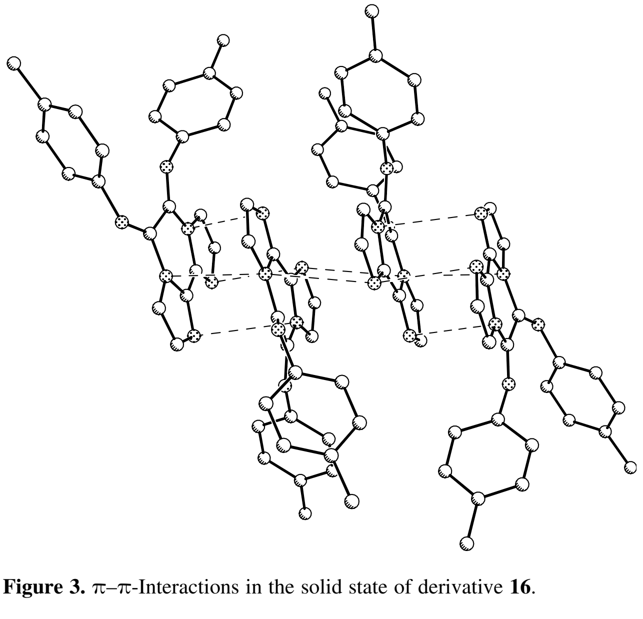


Figure 3. π–π-Interactions in the solid state of derivative **16**.

this molecule as shown by the lengths of the C–C bond with 1.51 Å and of the C–N double bond with 1.27 Å. In contrast to the bis-cationic molecule of **7**, the neutral system of **16** is not involved in H-bonding. Due to its planarity, the new tricycle **16** is capable of aggregation in the solid state via π–π interactions (Fig. 3).

The heterotricycle **16** can also be regarded as a new chelat ligand, which possesses two different 1,4-diazadiene substructures. Thus, we also synthesized complexes with catalytically relevant metals; their structures and applications will be the subject of a forthcoming paper.

3. Experimental

3.1. General

All reactions were monitored by TLC, carried out on 0.25 mm Merck silicia gel plates (60F254) using UV light. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker DRX 400 or Bruker AC 250 spectrometer. Melting points are measured with a Galen TM 3 apparatus and are uncorrected. UV/vis spectra were recorded on a Perkin-Elmer Lambda 19 spectrophotometer. MS spectra were taken from measurements on a Finnigan MAT SAQ 710 mass spectrometer. Elemental analyses were carried out in-house with an automatic analyzer LECO CHNS 932.

The bis-imidoylchlorides (**1a**–**d**)[6] were synthesized according to literature. Other reagents were commercially available and were used without further purification. All solvents were of reagent grade and were dried and distilled before use.

3.2. Crystal structure determination

The intensity data for the compound was collected on a Nonius KappaCCD diffractometer, using graphite-monochromated Mo K$_\alpha$ radiation. Data were corrected for Lorentz and polarization effects, but not for absorption.[13,14]

The structures were solved by direct methods (SHELXS[15]) and refined by full-matrix least squares techniques against Fo^2 (SHELXL-97[16]). The hydrogen atoms for the amine-groups N5 and N6 of **8a** were located by difference Fourier synthesis and refined isotropically. All other hydrogen atoms were included at calculated positions with fixed thermal parameters. All non-hydrogen atoms were refined anisotropically.[16] XP (SIEMENS Analytical X-ray Instruments, Inc.) was used for structure representations.

Crystal Data for **8a**.[17] $C_{24}H_{26}Cl_2N_6$, Mr = 469.41 g mol^{-1}, yellow prism, size 0.03×0.03×0.02 mm^3, orthorhombic, space group $Pna2_1$, a = 10.1730(3), b = 19.4414(7), c = 11.6071(2) Å, V = 2295.62(11) Å^3, T = 20 °C, Z = 4, ρ_{calcd} = 1.358 g cm^{-3}, μ (Mo K$_\alpha$) = 3.08 cm^{-1}, F(000) = 984, 15,570 reflections in h(−13/12), k(−25/20), l(−15/14), measured in the range 2.04° ≤ Θ ≤ 27.48°, completeness $\Theta_{\max}$ = 99.6%, 5109 independent reflections, R_{int} = 0.043, 4437 reflections with $F_o > 4\sigma(F_o)$, 298 parameters, 1 restraints, $R1_{\text{obs}}$ = 0.042, wR^2_{obs} = 0.112, $R1_{\text{all}}$ = 0.051, wR^2_{all} = 0.118, GOOF = 1.022, Flack-parameter 0.41(5) (inversion twin), largest difference peak and hole: 0.321/−0.259 e Å^{-3}.

Crystal Data for **16**.[17] $C_{22}H_{18}N_6$, Mr = 366.42 g mol^{-1}, red-orange prism, size 0.06×0.06×0.05 mm^3, monoclinic, space group $C2/c$, a = 32.0951(8), b = 9.3313(4), c = 12.8590(5) Å, β = 104.807(2)°, V = 3723.2(2) Å^3, T = −90 °C, Z = 8, ρ_{calcd} = 1.307 g cm^{-3}, μ (Mo K$_\alpha$) = 0.82 cm^{-1}, F(000) = 1536, 12,875 reflections in h(−40/41), k(−11/12), l(−16/16), measured in the range 2.28° ≤ Θ ≤ 27.48°, completeness $\Theta_{\max}$ = 99.6%, 4257 independent reflections, R_{int} = 0.033, 3228 reflections with $F_o > 4\sigma(F_o)$, 253 parameters, 0 restraints, $R1_{\text{obs}}$ = 0.047, wR^2_{obs} = 0.119, $R1_{\text{all}}$ = 0.066, wR^2_{all} = 0.133, GOOF = 1.002, largest difference peak and hole: 0.290/−0.228 e Å^{-3}.

3.3. General procedure for the syntheses of heterotricycles (8a–8e)

N-Methylimidazole **6** (2.64 g, 32 mmol) and triethylamine (3.50 g, 34.6 mmol) were added to a solution of the appropriate bis-imidoylchloride **1** (16 mmol) in 100 mL of dry toluene and the resulting solution was kept at 95 °C for 12 h. After cooling to room temperature a precipitate was formed, which was separated by a Büchner funnel. The resulting crude product was recrystallized from methanol to yield yellow crystals. In order to achieve a better solubility (NMR, elemental analyses) the dichlorides were in some cases converted into the dihexafluorophosphates.

3.3.1. 1,10-Dimethyl-*N*,*N*′-di-4-tolyl-diimidazolium[1,2-*a*:2′,1′-*c*]pyrazine-5,6-diamine-dichloride (8a). Yield: 4.10 g (55%), mp 244 °C (decomp.); ^{1}H NMR (400 MHz, D$_2$O): δ 2.34 (s, 6H), 4.79 (s, 6H), 6.65–7.13 (m, 8H), 8.19 (d, J = 2.0 Hz, 2H), 8.32 (d, J = 2.0 Hz, 2H); ^{13}C NMR (100 MHz, D$_2$O): δ 19.79, 41.33, 116.53, 116.98, 122.26, 125.73, 129.97, 130.77, 132.47, 137.97; MS (ESI in methanol, only the mass of cation could be observed): m/e(%): 397.4 (M−1)$^+$(10), 199.2 (M)$^{2+}$(10), 163.2 (100); IR (ATR): 3442 cm^{-1} ($\nu_{\text{N–H}}$); UV/vis (H$_2$O) $\lambda_{\max}$ (log ε): 229 nm (4.5), 288 (4.2). Anal. Calcd for $C_{24}H_{26}Cl_2N_6$: C, 61.41; H, 5.58; N, 17.90. Found: C, 61.54; H, 5.71; N, 17.63.

3.3.2. 1,10-Dimethyl-*N*,*N*′-bis(4-bromophenyl)-diimidazolium[1,2-*a*:2′,1′-*c*]pyrazine-5,6-diaminedichloride (8b). Yield: 5.21 g (58%), mp 217 °C (decomp.); ^{1}H NMR (250 MHz, D$_2$O): δ 4.61 (s, 6H), 6.36–7.20 (m, 8H), 8.25 (d, J = 2.0 Hz, 2H), 8.47 (d, J = 2.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO, hexafluorophosphate): δ 41.06, 112.97, 117.06, 118.14, 121.42, 126.76, 130.52, 132.01, 140.95; MS (DEI, only the mass of cation could be observed): m/e(%): 512 (M–CH$_3$)$^+$(10), 161 (10); IR (ATR): 3460 cm^{-1} ($\nu_{\text{N–H}}$); UV/vis (H$_2$O) $\lambda_{\max}$ (log ε): 230 nm (4.4), 293 (4.4). Anal. Calcd for $C_{22}H_{20}\,Br_2F_{12}N_6P_2$: C, 32.30; H, 2.46; N, 10.27. Found: C, 31.92; H, 2.46; N, 10.34.

3.3.3. 1,10-Dimethyl-*N*,*N*′-bis(3-trifluoromethylphenyl)-diimidazolium[1,2-*a*:2′,1′-*c*]-pyrazine-5,6-diamine-dichloride (8c). Yield: 4.63 g (50%), mp 190 °C (decomp.); ^{1}H NMR (250 MHz, D$_2$O): δ 4.61 (s, 6H), 6.61–7.30 (m, 8H), 8.27 (d, J = 2.1 Hz, 2H), 8.50 (d, J = 2.1 Hz, 2H); ^{13}C NMR (62 MHz, D$_2$O): δ 41.23, 116.53, 116.98, 122.26, 125.73, 129.97, 130.77, 132.47, 137.9; MS (DEI, only the mass of cation could be observed): *m*/*e*(%): 490 $(M–CH_3)^+$(100); IR (ATR): 3382 cm^{-1} ($\nu_{N–H}$); UV/vis (H_2O) λ_{max} (log ε): 215 nm (3.9), 291 (3.9). Anal. Calcd for $C_{24}H_{20}F_{18}N_6P_2$: C, 36.20; H, 2.53; N, 10.55. Found: C, 36.18; H, 2.34; N, 10.45.

3.3.4. 1,10-Dimethyl-*N*,*N*′-bis(4-*tert*-butylphenyl)-diimidazolium[1,2-*a*:2′,1′-*c*]pyrazine-5,6-diaminedichloride (8d). Yield: 4.82 g (54%), mp 241 °C (decomp.); ^{1}H NMR (250 MHz, D_2O): δ 1.18 (s, 18H), 4.59 (s, 6H), 6.31–7.08 (m, 8H), 8.22 (d, $J=2.1$ Hz, 2H), 8.44 (d, $J=2.1$ Hz, 2H); ^{13}C NMR (100 MHz, DMSO, hexafluorophosphate): δ 31.72, 34.25, 41.00, 115.92, 116.99, 121.59, 125.95, 126.67, 130.44, 138.99, 143.96; MS (ESI in methanol, only the mass of cation could be observed): *m*/*e*(%): 481.4 $(M-1)^+$(80), 241.2 $(M)^{2+}$(100); IR (ATR): 3325 cm^{-1} ($\nu_{N–H}$); UV/vis (H_2O) λ_{max} (log ε): 230 nm (4.4), 295 (4.4). Anal. Calcd for $C_{30}H_{38}F_{12}N_6P_2$: C, 46.64; H, 4.96; N, 10.88. Found: C, 46.46; H, 4.96; N, 10.64.

3.3.5. 1,10-Dimethyl-*N*,*N*′-diphenyl-diimidazolium[1,2-*a*:2′,1′-*c*]pyrazine-5,6-diamine-dichloride (8e). Yield: 3.76 g (52%), mp 183 °C (decomp.); ^{1}H NMR (400 MHz, DMSO): δ 4.64 (s, 6H), 6.71–7.18 (m, 10H), 8.34 (d, $J=2.0$ Hz, 2H), 8.61 (d, $J=2.0$ Hz, 2H), 9.87 (s, 2H); ^{13}C NMR (100 MHz, DMSO): δ 41.04, 116.28, 116.96, 122.03, 127.42, 129.21, 129.39, 130.09, 141.93; MS (ESI in methanol, only the mass of cation could be observed): *m*/*e*(%): 369.2 $(M-1)^+$(40), 185.1 $(M)^{2+}$(100); IR (ATR) 3421 cm^{-1} ($\nu_{N–H}$); UV/vis (H_2O) λ_{max} (log ε): 227 nm (4.3), 288 (4.3). Anal. Calcd for $C_{22}H_{22}F_{12}N_6P_2$: C, 40.01; H, 3.36; N, 12.73. Found: C, 40.95; H, 3.49; N, 12.18.

3.4. General procedure for synthesis of pyrrolo[1,2-*a*] imidazoliumhexafluorophosphates (14a–c)

1,2-Dimethylimidazole **12** (0.50 g, 5.2 mmol), 5.2 mmol of the appropriate bis-imidoylchloride **1** and triethylamine (0.50 g, 5.2 mmol) were dissolved in 50 mL of dry toluene and stirred at room temperature for 4 h. The mixture was filtered off and the red crude product was dissolved in water. A saturated aqueous solution of ammoniumhexafluorophosphate was added until the precipitation was completed. The precipitate was separated by a Büchner funnel and dried in vacuo.

3.4.1. 1-Methyl-5-(4-tolylimino)-6-(4-tolylamino)-1*H*-pyrrolo[1,2-*a*]imidazoliumhexafluorophosphate (14a). Yield: 1.50 g (60%), red crystals, mp 209 °C (decomp.); ^{1}H NMR (400 MHz, DMSO): δ 2.30 (s, 3H), 2.35 (s, 3H), 3.66 (s, 3H), 6.12 (d, $J=2.3$ Hz, 1H), 6.51 (s, 1H), 7.08 (d, $J=2.3$ Hz, 1H), 7.12–7.41 (m, 8H), 10.35 (s, 1H); ^{13}C NMR (100 MHz, DMSO): δ 20.42, 20.59, 33.80, 81.53, 115.16, 119.16, 120.41, 124.56, 129.79, 130.37, 133.81, 136.00, 136.29, 140.66, 141.94, 146.92, 158.18; MS (ESI in methanol, chloride, only the mass of cation could be observed): *m*/*e*(%): 329.2 $(M)^+$(100); HRMS: calcd. for $C_{21}H_{21}N_4$: 329.176621630, found: 329.176960000; IR (ATR): 3342 cm^{-1} ($\nu_{N–H}$); UV/vis ($CHCl_3$) λ_{max} (log ε): 406 nm (3.7), 504 (3.9). Anal. Calcd for $C_{21}H_{21}F_6N_4P$: C, 53.17; H, 4.46; N, 11.81. Found: C, 52.99; H, 4.36; N, 11.79.

3.4.2. 1-Methyl-5-(4-bromophenylimino)-6-(4-bromophenylamino)-1*H*-pyrrolo[1,2-*a*]imidazoliumhexafluorophosphate (14b). Yield: 1.82 g (58%), red crystals, mp 200 °C (decomp.); ^{1}H NMR (400 MHz, DMSO): δ 3.68 (s, 3H), 6.33 (d, $J=2.3$ Hz, 1H), 6.61 (s, 1H), 7.15 (d, $J=2.3$ Hz, 1H), 7.18–7.75 (m, 8H), 10.34 (s, 1H); ^{13}C NMR (100 MHz, DMSO): δ 34.42, 83.84, 116.32, 116.88, 119.70, 121.90, 122.76, 125.46, 132.73, 133.46, 138.75, 141.50, 144.09, 146.85, 158.39; MS (DCI with water, chloride, only the mass of cation could be observed): *m*/*e*(%): 457 $(M)^+$(100); IR (ATR): 3325 cm^{-1} ($\nu_{N–H}$); UV/vis ($CHCl_3$) λ_{max} (log ε): 400 nm (3.6), 501 (3.8). Anal. Calcd for $C_{19}H_{15}Br_2F_6N_4P$: C, 37.77; H, 2.50; N, 9.27. Found: C, 38.08; H, 2.38; N, 9.08.

3.4.3. 1-Methyl-5-(3-trifluoromethylphenylimino)-6-(3-trifluoromethylphenylamino)-1*H*-pyrrolo[1,2-*a*]imidazoliumhexafluorophosphate (14c). Yield: 1.90 g (62%), red crystals, mp 95 °C (decomp.); ^{1}H NMR (250 MHz, DMSO): δ 3.70 (s, 3H), 6.22 (d, $J=2.3$ Hz, 1H), 6.74 (s, 1H), 7.17 (d, $J=2.3$ Hz, 1H), 7.52–7.83 (m, 8H), 10.46 (s, 1H); ^{13}C NMR (62 MHz, DMSO): δ 34.03, 84.40, 115.70, 115.88, 116.81, 120.58, 121.52, 123.18, 123.28, 125.23, 125.95, 130.38, 130.45, 130.79, 130.89, 131.40, 139.67, 141.55, 145.01, 146.02, 157.74; MS (ESI in methanol, chloride, only the mass of cation could be observed): *m*/*e* (%): 437.2 $(M)^+$(100); IR (ATR): 3332 cm^{-1} ($\nu_{N–H}$); UV/vis ($CHCl_3$) λ_{max} (log ε): 363 nm (3.4), 494 (3.7). Anal. Calcd for $C_{21}H_{15}F_{12}N_4P$: C, 43.31; H, 2.60; N, 9.92. Found: C, 43.03; H, 2.50; N, 9.57.

3.4.4. 5,6-Bis(4-tolylimino)-*N*,*N*′-diimidazo-[1,2-*a*:2′,1′-*c*]pyrazine (16). To a cooled (−20 °C) suspension of 2,2′-biimidazole **15** (0.20 g, 1.5 mmol) in 40 mL of dry THF 2 equiv of *n*-butyllithium (0.1 M solution, *n*-hexane) were added by means of a syringe under argon. Then a solution of **1a** (0.45 g, 1.5 mmol) in dry THF was added slowly and the solution was allowed to warm up to room temperature under stirring for 20 h. The solvent was evaporated in vacuo and the resulting crude product was purified by column chromatography (SiO_2, toluene/ethylacetate 1:1) to give orange crystals. Yield: 0.4 g (71%), mp 192 °C (decomp.); ^{1}H NMR (400 MHz, D_2O): δ 2.32 (s, 6H), 6.30–7.12 (m, 12H); MS (DEI): *m*/*e*(%): 367 $(M)^+$(60), 351 (100); IR (ATR): 3172 cm^{-1} ($\nu_{N–H}$); UV/vis ($CHCl_3$) λ_{max} (log ε): 248 nm (4.4), 289 (3.8). Anal. Calcd for $C_{22}H_{18}N_6$: C, 72.11; H, 4.95; N, 22.94. Found: C, 71.82; H, 5.22; N, 22.30.

Acknowledgements

This work was supported by Deutsche Forschungsgemeinschaft (DFG), SFB 436.

References and notes

1. (a) Nonell, S.; Borrell, J.; Borros, S.; Colominas, C.; Rey, O.; Rubio, N.; Sanchez-Garcia, D.; Teixido, J. *Eur. J. Org. Chem.* **2003**, *9*, 1635–1640. (b) Allen, W.; Fowler, C.; Lynch, V.; Sessler, J. *Chem. Eur. J.* **2001**, *7*, 721–729. (c) Causey, C. P.;

Allen, W. *J. Org. Chem.* **2002**, *67*, 5963–5968. (d) Jena, S.; Rath, N.; Dash, K. C. *Indian J. Chem., Sect. A* **1999**, 350–354. (e) Goulle, V.; Thummel, R. P. *Inorg. Chem.* **1990**, *29*, 1767–1772. (f) Ames, J. R.; Houghtaling, M. A.; Terrian, D. L.; Mitchell, T. P. *Can. J. Chem.* **1997**, *75*, 28–36.

2. (a) Shi, Z.; Thummel, R. P. *Tetrahedron Lett.* **1995**, *36*, 2741–2744. (b) Thummel, R. P.; Goulle, V.; Chen, B. *J. Org. Chem.* **1989**, *54*, 3057–3061. (c) Herrmann, W. A.; Elison, M.; Fischer, J.; Köcher, C.; Artus, G. R. *Chem. Eur. J.* **1996**, *2*, 772–780. (d) Taton, T. A.; Chen, P. *Angew. Chem.* **1996**, *108*, 1098–1100.
3. (a) Mathews, D. P.; Whitten, J. P.; McCarthy, J. R. *J. Heterocycl. Chem.* **1987**, *24*, 689–692. (b) Mathews, D. P.; Whitten, J. P.; McCarthy, J. R. *J. Org. Chem.* **1986**, *51*, 1891–1894.
4. Käpplinger, C.; Beckert, R.; Günther, W.; Görls, H. *Liebigs Ann. Recl.* **1997**, *3*, 617–622.
5. (a) Brandenburg, J.; Käpplinger, C.; Beckert, R. *Synthesis* **1996**, *11*, 1302–1304. (b) Müller, D.; Beckert, R.; Weston, J.; Görls, H. *Eur. J. Org. Chem.* **2001**, *23*, 4551–4555.
6. Lindauer, D.; Beckert, R.; Döring, M.; Fehling, P.; Görls, H. *J. Prakt. Chem.* **1995**, *337*, 143–152.
7. Melloni, P.; Fasar-Bassini, D.; Dradi, E.; Confalonieri, C. *J. Heterocycl. Chem.* **1974**, *11*, 731–735.
8. Alder, R. W.; Blake, M. E.; Chaker, L.; Harvey, J. M.; Paolini, F.; Schütz, J. *Angew. Chem.* **2004**, *116*, 6020–6036.
9. Lemal, M. D. In *The Chemistry of the Amino Group*; Patai, S., Ed.; Wiley: London, 1968; pp 701–748. Haug, E.; Kantlehner, W. 4th ed.; Methoden Org. Chem. (Houben-Weyl); Thieme: Stuttgart, 1993; Vol. E15; pp 2898–2904.
10. (a) Wenzel, M.; Lindauer, D.; Beckert, R.; Boese, R.; Anders, E. *Chem. Ber.* **1996**, *128*, 39–44. (b) Wenzel, M.; Beckert, R.; Günther, W.; Görls, H. *Eur. J. Org. Chem.* **1998**, *9*, 1803–1810.
11. (a) Schwesinger, R. *Angew. Chem.* **1987**, *99*, 1209–1210. (b) Schwesinger, R.; Mißfeldt, M.; Peters, K.; von Schnering, H. G. *Angew. Chem.* **1987**, *99*, 1210–1212.
12. (a) Gruseck, A.; Heuschmann, M. *Chem. Ber.* **1987**, *120*, 2053–2064. (b) Kuhn, N.; Bohnen, H.; Kreutzberg, J.; Bläser, D.; Boese, R. *J. Chem. Soc., Chem. Commun.* **1993**, *14*, 1136–1137. (c) Quast, H.; Ach, M.; Kindermann, M. K.; Rademacher, P.; Schindler, M. *Chem. Ber.* **1993**, *126*, 503–516.
13. Nonius B. V. *COLLECT*, Data Collection Software; Netherlands, 1998.
14. Otwinowski, Z.; Minor, W. Processing of X-Ray Diffraction Data Collected in Oscillation Mode. In *Methods in Enzymology*; Carter, C. W., Sweet, R. M., Eds.; Macromolecular Crystallography, Part A; Academic: London, 1997.
15. Sheldrick, G. M. *Acta Crystallogr., Sect. A* **1990**, *46*, 467–473.
16. Sheldrick, G. M. *SHELXL-97*; University of Göttingen, Germany, 1997.
17. CCDC 280199 (**8a**) and 280200 (**16**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk).

Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron 62 (2006) 737–745

Tetrahedron

The synthesis and electronic absorption spectra of 3-phenyl-3(4-pyrrolidino-2-substituted phenyl)-3*H*-naphtho[2,1-*b*]pyrans: further exploration of the *ortho* substituent effect

Christopher D. Gabbutt, B. Mark Heron* and Alicia C. Instone

Department of Colour and Polymer Chemistry, The University of Leeds, Leeds LS2 9JT, UK

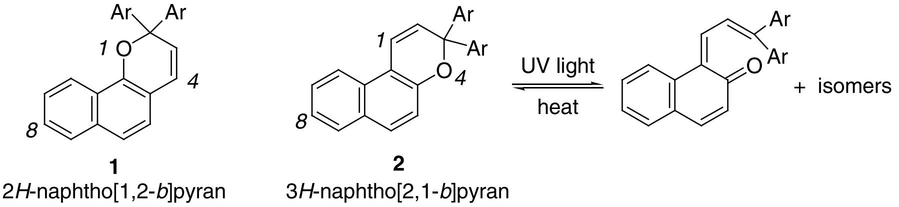
Received 21 July 2005; revised 16 September 2005; accepted 29 September 2005

Abstract—Introduction of a substituent into a sterically demanding 2-position of a 3-(4-pyrrolidinophenyl) ring of a 3,3-diaryl-3*H*-naphtho[2,1-*b*]pyran results in the generation of an additional short wavelength absorption band leading to organic photochromes that appear as dull shades of orange and red.

1. Introduction

The electrocyclic ring-opening–ring-closing sequence of the isomeric diaryl substituted naphthopyrans **1** and **2** (Scheme 1) with the accompanying colour change has rendered these compounds invaluable to the ophthalmic photochromic sun and contact lens industries.[1] Other applications of photochromic naphthopyrans, for example, in fuel[2] and security markers,[3] as UV light intensity indicators[4] and as hair dyes[5] have been documented.

Optimising the photochromic response of these T-type[6] naphthopyrans has attracted significant academic[7] and industrial attention.[1] Perhaps the simplest and most significant means to achieve control of the hue and persistence of the ring-opened isomer of the naphthopyran system is through the manipulation of substituents located on the geminal diaryl unit.[8] The intensification of the photo-generated colour of **2** has been accomplished through the introduction of a group into at least one of the *ortho* positions of one of the aryl groups attached to 3-C, for example, **3**.[9] This phenomenon has been attributed to a steric effect in which the *ortho* substituent hinders the thermal ring closure of the photo-generated coloured species to the colourless pyran form; a feature that has recently been correlated to the size of the introduced group in **4**.[10] The net result of this steric effect is a photostationary state in which there is an appreciable concentration of the ring-opened form, which is manifest in an intensification of the developed colour. Further manipulation of the photochromism of naphthopyrans has been accomplished through steric interactions between a terminal pyrrolidine donor function and neighbouring substituents, for example, **5**. In this instance, as the magnitude of these steric interactions increase λ_{max} is shifted hypsochromically until a maximum interaction is observed with **5**, X = Br.[11]

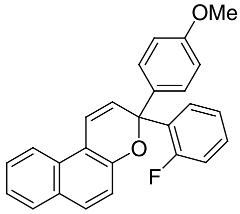


Scheme 1.

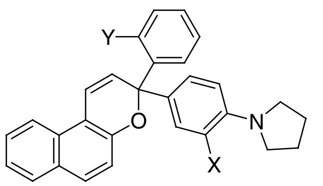
Keywords: Naphthopyrans; Photochromism; Steric effects; Dual absorption bands; Synthesis.

* Corresponding author. Tel.: +44 113 3432925; fax: +44 113 3432947; e-mail: b.m.heron@leeds.ac.uk

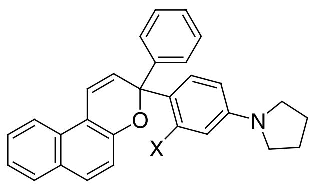
0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.09.143



3



4 X = H, Y = halogen, Me, MeO
5 Y = H, X = halogen, Me, MeO



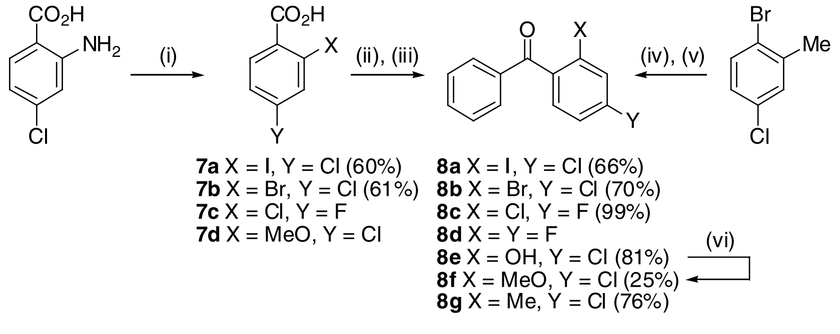
6

We were interested in exploring novel naphthopyrans of type **6** in which the influence of alternating the nature of X, located in a sterically demanding position in the main electron donating aryl moiety, upon the photochromic response could be investigated.[12]

2. Results and discussion

In order to synthesise **6** we required access to a range of 2-substituted 4-pyrrolidinobenzophenones. Thus, the dihalogenobenzoic acids **7a**,**b** were accessed by diazonium salt chemistry from 4-chloroanthranilic acid.[13] Conversion to the acid chlorides and a subsequent Friedel-Crafts reaction with benzene afforded the benzophenones **8a**,**b** (Scheme 2). 2-Chloro-4-fluorobenzophenone **8c** was obtained in a similar manner from 2-chloro-4-fluorobenzoic acid. Using this Friedel-Crafts protocol with 4-chloro-2-methoxybenzoic acid resulted in concomitant demethylation and benzoylation[14] to give 4-chloro-2-hydroxybenzophenone **8e**. *O*-Methylation of **8e** was only accomplished in low yield using excess MeI and powdered KOH in DMSO to afford the 2-methoxybenzophenone **8f**. 4-Chloro-2-methybenzophenone was accessed in 76% yield by the action of the Grignard reagent derived from 2-bromo-5-chlorotoluene on the Weinreb amide,[11,15] *N*-methoxy-*N*-methylbenzamide.

We have previously employed the nucleophilic substitution of an activated halogen atom from benzophenones to afford aminosubstituted benzophenones.[11,16] However, the present benzophenones, **8a–d**, contain two halogen atoms that are activated towards nucleophilic displacement. Heating **8d** in an excess of pyrrolidine resulted in the formation of 2,4-dipyrrolidinobenzophenone **9** (72%) and 4-fluoro-2-pyrrolidinobenzophenone **10a** (17%) which were separated by column chromatography. None of the desired benzophenone **11d** was isolated from the crude product. It is likely that the initial reaction involves preferential displacement of the 4-fluorine atom of **8d** to afford 2-fluoro-4-pyrrolidinobenzophenone **11d** together with a smaller amount of **10a** as a consequence of the simultaneous but less favoured displacement of the 2-fluorine atom. However, under prolonged heating, the 2-fluorine atom of **11d**, although electronically deactivated towards displacement due to the 4-pyrrolidine substituent diminishing the electron withdrawing influence of the C═O group, is still sufficiently activated towards displacement leading to **9**. Displacement of the 4-fluorine atom from **10a** is less likely since the steric interaction between the 2-pyrrolidine unit and the C═O group result in rotation of the C═O unit out of conjugation with the fluorophenyl ring, which renders the F atom inactive towards displacement. A modified version of this protocol was next investigated in which 1 equiv of pyrrolidine was employed with added K_2CO_3 base (Method 1). Termination of the reaction after ~1 h gave a product from which **10a** (28%) and the desired **11d** (37%) were isolated by column chromatography. Repeating this protocol with benzophenones **8a–c** provided access to the desired 2-substituted 4-pyrrolidinobenzophenones though in each case their formation was accompanied by varying amounts of the 2-pyrrolidino substituted benzophenone **10a** or **10b** and **9** (Scheme 3). The conversion of benzophenones **8f**,**g** to **11f**,**g**, respectively, was particularly sluggish requiring 4 days heating in the presence of DMSO to effect even a mediocre yield of the products (Method 2). Interestingly the formation of **11f** was accompanied by some of the demethylated compound **11e** (19%).

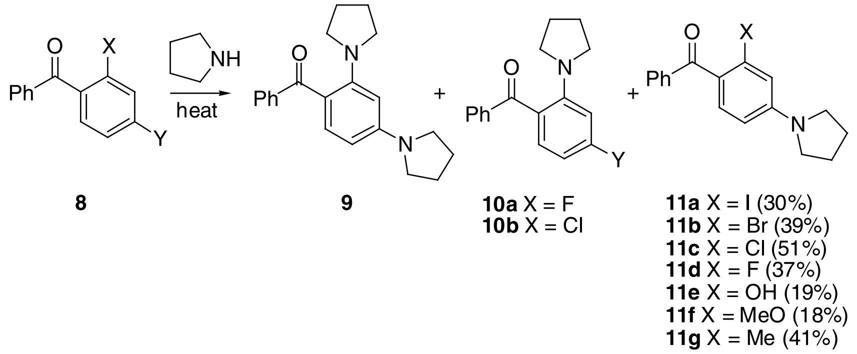


7a X = I, Y = Cl (60%)
7b X = Br, Y = Cl (61%)
7c X = Cl, Y = F
7d X = MeO, Y = Cl

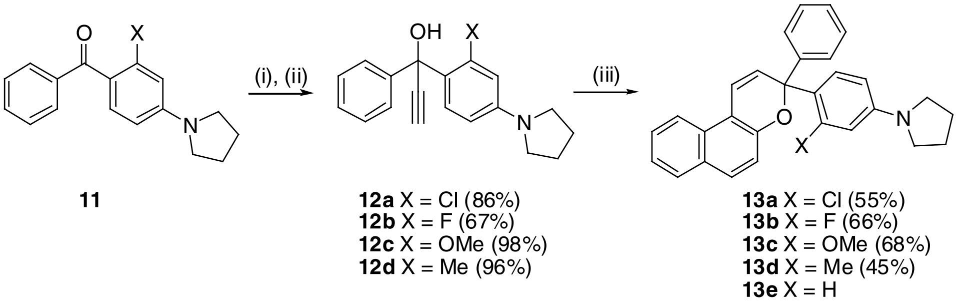
8a X = I, Y = Cl (66%)
8b X = Br, Y = Cl (70%)
8c X = Cl, Y = F (99%)
8d X = Y = F
8e X = OH, Y = Cl (81%)
8f X = MeO, Y = Cl (25%)
8g X = Me, Y = Cl (76%)

Reagents: (i) c.HCl, $NaNO_2$, H_2O, 0 °C then either CuBr or KI and heat; (ii) $SOCl_2$, heat; (iii) $AlCl_3$, PhH, heat; (iv) Mg, anhyd. Et_2O, heat; (v) *N*-methoxy-*N*-methylbenzamide, anhyd. Et_2O, heat then aq. HCl; (vi) excess MeI, KOH, DMSO, 40 °C

Scheme 2.



Scheme 3.



Reagents: (i) LiTMSA, anhyd. THF, 0 °C - RT; (ii) KOH, MeOH then AcOH;
(iii) 2-naphthol, acidic alumina, PhMe, reflux

Scheme 4.

The majority of the benzophenones **11** were efficiently transformed into the prop-2-yn-1-ols **12a–d** on reaction with an excess of lithium trimethylsilylacetylide, which was derived from *n*-butyllithium and trimethylsilylacetylene. Removal of the TMS group from the initial adduct was accomplished in the same flask by addition of methanolic KOH (2 equiv). Yields for this conversion were typically high (67–98%) (Scheme 4).[10,11,17] Somewhat surprisingly the reaction of both **11a** and **11b** failed to give any of the propynols and instead multicomponent mixtures were formed. Attempts to isolate the trimethylsilyl intermediates were also unsuccessful.

The most versatile and efficient route to 3,3-diaryl-3*H*-naphtho[2,1-*b*]pyrans relies upon the one pot, acid-catalysed reaction of a 2-naphthol with a 1,1-diarylprop-2-yn-1-ol; a transformation that was developed from an original naphthopyran synthesis reported by Iwae and Ide in 1962.[18] Heating the propynols **12** with 2-naphthol in toluene in the presence of acidic alumina gave the naphthopyrans **13a–d** in 45–68% yield (Scheme 4).

The ^{1}H NMR spectra of **13a**,**c**,**d** displayed a doublet at ~δ 6.3 with a coupling constant of 10 Hz characteristic of 2-H in 3*H*-naphtho[2,1-*b*]pyrans.[11,17,19] The doublet for 1-H was obscured by the aromatic protons, however, 2D ^{1}H–^{1}H COSY experiments revealed that 3-H resonated at ~δ 7.3. The fluorine substituted compound **13b**, afforded a double doublet at δ 6.30 for 2-H with $J=10.0$, 3.6 Hz (Fig. 1).

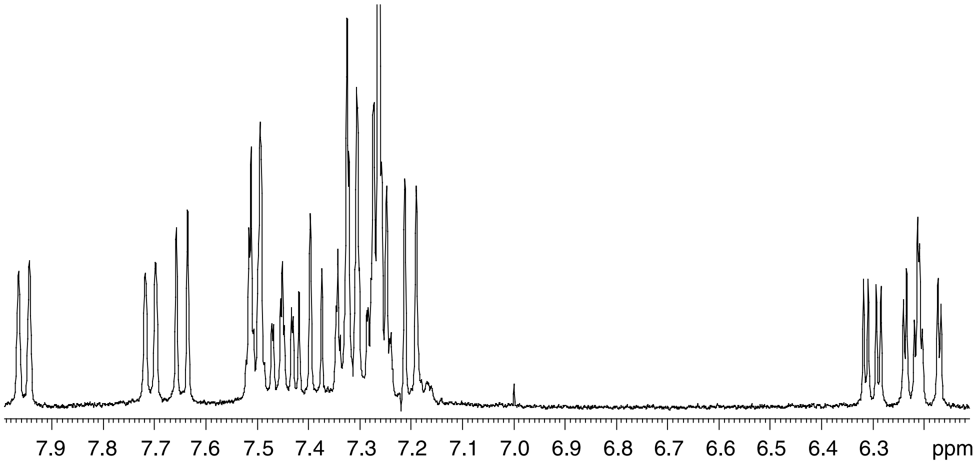
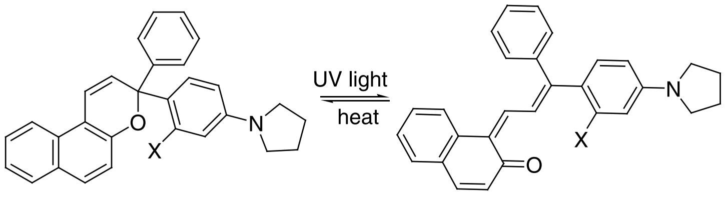


Figure 1. ^{1}H NMR spectrum (6–8 ppm) of Naphthopyran **13b**.

Table 1. Spectroscopic data for naphthopyrans **13**



13

Entry	X	λ_{max} (nm)		$t_{1/2}$ (s)
13a	Cl	403	480	44
13b	F	394	501	21
13c	OMe	399	519	73
13d	Me	410	507	104
13e	H	538		5

This additional coupling is due to long range coupling of the proximal fluorine atom to 2-H.[10]

The spectroscopic data (Table 1) and selected spectra (Fig. 2) obtained for toluene solutions of the naphthopyrans (**13a–e**) merit some comment. The most striking feature of these spectra is the appearance of two absorption maxima of approximately equal intensity (for **13a**,**d**) in the visible region; a short wavelength band at ca. 400 nm and the expected longer wavelength band at ca. 500 nm. This feature is most unusual and to our knowledge provides the first example of an unsymmetrically substituted 3*H*-naphtho[2,1-*b*]pyran displaying such absorption characteristics.[20] Symmetrical 3,3-bis(4-dialkylaminophenyl)-3*H*-naphtho[2,1-*b*]pyrans, for example, 3,3-bis(4-dimethylaminophenyl)-3*H*-naphtho[2,1-*b*]pyran (λ_{max} 446 and 560 nm in PhMe solution), exhibit two absorption bands in the visible region but typically, the short wavelength band is present as a much less intense band or shoulder.[21] Additionally, the overall lifetime of the photo-generated species derived from these symmetrically substituted compounds is very short with $t_{1/2}$ typically less than 1 s, which renders these compounds ineffective as materials for ophthalmic lens applications.

If we first consider the data for **13b** X = F, and compare this with the data for the parent compound **13e** X = H, which displays a single absorption band with λ_{max} 538 nm ($t_{1/2}$ = 5 s) it can be seen that the incorporation of the *ortho* X group has induced a hypsochromic shift in λ_{max} of the long wavelength band. This shift in λ_{max} is due to the twisting of the pyrrolidinophenyl unit out of plane with the remainder of the conjugated system and hence reducing the donor properties of this unit as a result of less efficient π overlap, which leads to the observed hypsochromic shift. One further consequence of the pyrrolidinophenyl unit twisting is that the remaining phenyl ring may now adopt a more planar arrangement thus increasing its donor potential, which we believe results in a bathochromic shift and intensification of a band from the UV region into the yellow end of the visible spectrum at 394 nm. The larger chlorine atom in compound **13a** results in the pyrrolidinophenyl unit twisting further out of plane, which leads to a greater hypsochromic shift in the long wavelength band of 21 nm compared to **13b**, and a

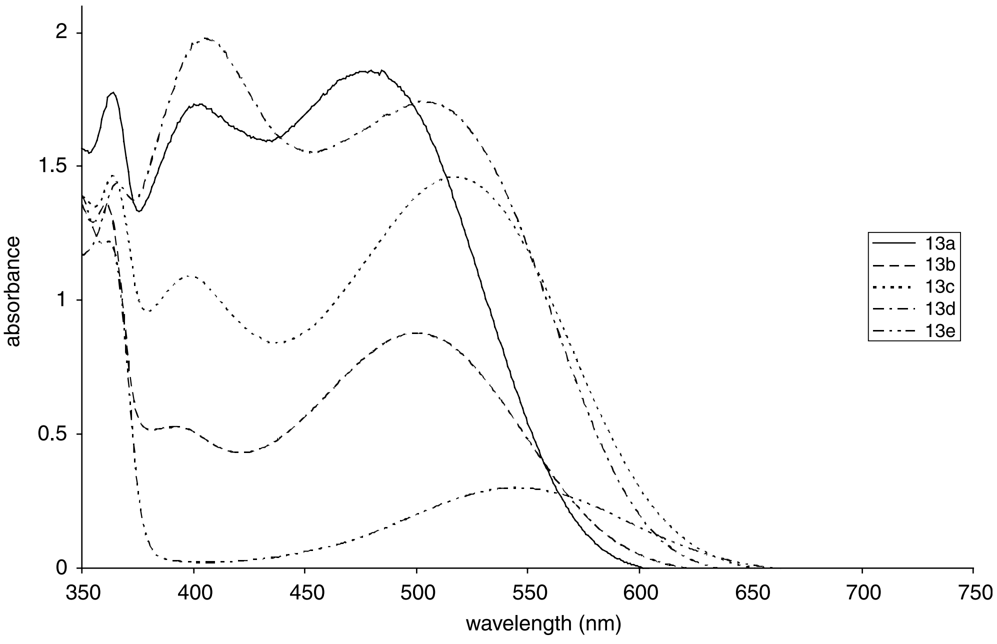


Figure 2. UV–visible spectra for toluene solutions of Naphthopyrans **13** after UV irradiation.

10 nm bathochromic shift in the shorter wavelength band to 403 nm relative to that of **13b**.

It is immediately apparent that the spectroscopic data for the methoxy **13c** and methyl **13d** substituted naphthopyrans are at odds with the trend suggested for **13a** and **13b**. Available data[10,11,22] would suggest that a methyl group is similar in its spatial requirements to a chlorine atom but has markedly different electronic properties. It may be that for **13d** the effect of the reduced conjugation induced by twisting is countered by the donor properties of the methyl group leading to a bathochromic shift in λ_{max} to 507 nm. However, this inductive electron donation cannot easily be aligned with the accompanying bathochromic shift in the short wavelength band to 410 nm. The long wavelength band for **13c** appears at 519 nm, which would support the influence of the *ortho* donor group increasing conjugation, however, the short wavelength band appears at 399 nm midway for the series of **13**. Clearly there is some subtle interplay between the two aryl rings of the naphthopyrans **13c** and **13d**, which bear electron donating *ortho* substituents.

The half-life data presented in Table 1 of the coloured ring-opened forms relates to the time taken for the intensity of the long wavelength absorption band under steady state conditions to fade to half its original value upon cessation of irradiation. The half-life of **13b** is 21 s, which is in accord with our earlier results since fluorine is the smallest group and thus induces less steric hindrance during the ring-closing process.[10] As expected the chloro compound **13a** has a longer half-life of 44 s, due to the increased steric effects associated with its larger size. The methyl compound **13d** has an unusually long half-life, 104 s, compared to that of the chloro compound, even though it is of a similar size.[22] The methoxy compound **13c** with a half-life of 73 s, falls between that determined for **13d** and **13b** and is in agreement with data for previous comparisons between the *o*-tolyl and *o*-methoxyphenyl C-3 substituted naphthopyrans.[10]

In summary, the introduction of a group into one of the C-3 aryl groups *ortho* to the point of attachment of the group to the pyran ring and *meta* to a strong electron donor group induces a dramatic change in the appearance of the visible spectrum of the photo-generated dye from a single absorption band to two bands of approximately equal intensity when the *ortho* group is spatially demanding (**13**, X=Cl, Me). The appearance of the spectrum has been rationalised by considering steric interactions between the two aryl rings and the remainder of the chromophore. The ability to manipulate the appearance of the visible spectrum may be of value in the design of new neutral shades of naphthopyrans, which presently rely upon either amino substituted 2*H*-naphtho[1,2-*b*]pyrans[23] or heterocyclic fused benzo- and naphtho- pyrans.[24]

3. Experimental

3.1. General

Melting points were determined in capillary tubes and are uncorrected. Visible spectra were recorded for ca. 3×10^{-5} mol dm^{-3} solutions in spectroscopic grade toluene in 10 mm quartz cells at 21 °C using an Analytik Jena Specord S100 diode array spectrophotometer. Samples were irradiated to a steady state of absorbance using a Spectroline 8 W lamp (365 nm). Infrared spectra were recorded on a Perkin-Elmer 882 spectrophotometer in KBr discs unless otherwise specified. NMR spectra were recorded on a Bruker Avance 400 MHz instrument for solutions in $CDCl_3$; *J* values are given in Hz. Flash chromatography separations were performed on chromatography silica (40–60 μm particle size distribution) as supplied by Fluorochem Ltd.

3.2. Preparation of 2-substituted-4-chlorobenzoic acids

A solution sodium nitrite (7.05 g, 102 mmol) in water (15 mL) was added slowly to a cold (0 °C) stirred solution of 2-amino-4-chlorobenzoic acid (17.16 g, 100 mmol) in water (250 mL) and concd HCl (75 mL). On completion of the addition the solution was stirred for 5 min and then a solution of the appropriate halide (102 mmol) in water (25 mL) was added. The cooling bath was removed and the mixture stirred for a further 5 min before carefully heating the suspension to 90 °C for 10 min. The mixture was cooled to room temperature and the precipitated solid collected and washed with water (3×50 mL). The crude product was recrystallised from ethanol and water. The following acids were prepared in this way:

3.2.1. 4-Chloro-2-iodobenzoic acid 7a. From potassium iodide as a light brown powder (16.9 g, 60%), mp 160–163 °C (lit. mp 165–166 °C[25]), δ_H 3.49 (1H, br s, OH), 7.63 (1H, dd, *J*=8.4, 2.1 Hz, 5-H), 7.80 (1H, d, *J*=8.3 Hz, 6-H), 8.14 (1H, d, *J*=2.1 Hz, 3-H).

3.2.2. 2-Bromo-4-chlorobenzoic acid 7b. From copper(I) bromide as a light brown powder (14.4 g, 61%), mp 154–156 °C (lit. mp 155 °C[26]), δ_H 3.84 (1H, br s, OH), 7.46 (1H, dd, *J*=8.3, 2.1 Hz, 5-H), 7.65 (1H, d, *J*=2.0 Hz, 3-H), 7.76 (1H, d, *J*=8.4 Hz, 6-H).

3.3. Preparation of 2-substituted-4-halogeno-benzophenones

The 2-substituted-4-halogenobenzoic acid **7** (26 mmol), thionyl chloride (4.40 mL, 60 mmol) and one drop of *N*,*N*-dimethylformamide were heated under reflux for 2 h. The excess thionyl chloride was removed from the cooled reaction mixture and the remaining acid chloride was dissolved in benzene (116 mL, 1.3 mol). Aluminium chloride (3.87 g, 29 mmol) was added portion-wise over ca. 10 min to this solution and the resulting suspension was refluxed for ca. 1 h. The reaction mixture was poured onto ice (300 g) and concd HCl (50 mL). The organic layer was separated and the aqueous layer extracted with ethyl acetate (3×100 mL). The combined organic phases were washed with 5% aqueous NaOH solution (50 mL), water (3×50 mL) and dried (anhyd Na_2SO_4). Removal of the solvent gave the crude benzophenones that were recrystallised from hexane and ethyl acetate. The following benzophenones were obtained by this protocol:

3.3.1. 4-Chloro-2-iodobenzophenone 8a. From 4-chloro-2-iodobenzoic acid as pale brown microcrystals (5.9 g, 66%), mp 60–62 °C, ν_{max} 1676, 1594, 1572 cm^{-1}, δ_H 7.23 (1H, d, J=8.3 Hz, 6-H), 7.42 (1H, dd, J=8.2, 2.0 Hz, 5-H), 7.48 (2H, m, 3′,5′-H), 7.62 (1H, m, 4′-H), 7.78 (2H, m, 2′,6′-H), 7.94 (1H, d, J=1.9 Hz, 3-H). (Found: C, 45.6; H, 2.2; $C_{13}H_8ClIO$ requires C, 45.6; H, 2.4%).

3.3.2. 2-Bromo-4-chlorobenzophenone 8b. From 2-bromo-4-chlorobenzoic acid as a colourless viscous oil (5.4 g, 70%), bp 155 °C at 0.4 mmHg (lit. bp 220 °C at 14 mmHg[26]), δ_H 7.33 (1H, m, Ar-H), 7.46 (4H, m, Ar-H), 7.59 (1H, m, Ar-H), 7.78 (2H, m, Ar-H).

3.3.3. 2-Chloro-4-fluorobenzophenone 8c. From 2-chloro-4-fluorobenzoic acid as colourless microcrystals (6.0 g, 99%), mp 40–42 °C (lit. mp 45–47 °C[27]), δ_H 7.09 (1H, m, 5-H), 7.21 (1H, dd, J=8.5, 2.4 Hz, 3-H), 7.40 (1H, dd, J=8.5, 5.9 Hz, 6-H), 7.47 (2H, m, 3′,5′-H), 7.60 (1H, m, 4′-H), 7.79 (2H, m, 2′,6′-H).

3.3.4. 4-Chloro-2-hydroxybenzophenone 8e. From 4-chloro-2-methoxybenzoic acid as cream microcrystals (4.9 g, 81%), mp 70–71 °C (lit. mp 74.5 °C[28]), δ_H 6.86 (1H, dd, J=8.6, 2.0 Hz, 5-H), 7.10 (1H, d, J=2.0 Hz, 3-H), 7.53 (3H, m, 6-H, 3′,5′-H), 7.61 (1H, m, 4′-H), 7.66 (2H, m, 2′,6′-H), 12.20 (1H, s, OH).

3.4. Preparation of 4-chloro-2-methoxybenzophenone

Methyl iodide (4.66 mL, 74.8 mmol) was added to a stirred solution of 4-chloro-2-hydroxybenzophenone **8e** (8.70 g, 37.4 mmol) and finely ground potassium hydroxide (2.30 g, 41.1 mmol) in anhyd dimethylsulfoxide (40 mL). The mixture was maintained at 40 °C and after 4 h further methyl iodine (4.66 mL, 74.8 mmol) was added to the mixture. After heating for 14 h at 40 °C a further quantity of methyl iodide (4.66 mL, 74.8 mmol) was added and the mixture stirred at 40 °C for a further 3 h. The solution was poured into water (300 mL), the organic layer was separated and the aqueous layer extracted with ethyl acetate (3× 100 mL). The organic phases were combined, washed with brine (5×50 mL), water (100 mL), dried (anhyd Na_2SO_4) and evaporated. The title compound **8f** was obtained after column chromatography using 10% ethyl acetate in hexane as colourless microcrystals (2.3 g, 25%), mp 91–93 °C, ν_{max} 1651, 1588, 1567 cm^{-1}, δ_H 3.72 (3H, s, OCH_3), 6.98 (1H, d, J=1.7 Hz, 3-H), 7.04 (1H, dd, J=8.1, 1.8 Hz, 5-H), 7.31 (1H, d, J=8.1 Hz, 6-H), 7.43 (2H, m, 3′,5′-H), 7.56 (1H, m, 4′-H), 7.78 (2H, m, 2′,6′-H), δ_C 56.3, 112.6, 121.1, 127.6, 128.7, 130.2, 131.1, 133.6, 137.9, 138.0, 158.5, 195.7. (Found: C, 67.9; H, 4.5; $C_{14}H_{11}ClO_2$ requires C, 68.2; H, 4.5%).

3.5. Preparation of 4-chloro-2-methylbenzophenone

A solution of 2-bromo-5-chlorotoluene (13.3 mL, 100 mmol) in anhyd diethyl ether (40 mL) was added drop wise to magnesium turnings (2.55 g, 105 mmol) in anhyd diethyl ether (40 mL). After ca. ⅓ of the solution of 4-bromo-2-chloroanisole had been added one crystal of iodine was added and the mixture stirred. Upon initiation of the reaction mixture the remaining solution of 2-bromo-5-chlorotoluene was added at such a rate so as to maintain a steady reflux. On completion of the addition the suspension was refluxed for a further 1 h and then cooled to room temperature. A solution of *N*-methoxy-*N*-methylbenzamide (10.2 mL, 67 mmol) in anhyd diethyl ether (20 mL) was added drop wise via syringe to this solution of the Grignard reagent so as to maintain a constant reflux. On completion of the addition the mixture was refluxed for a further 2 h and then left to stand overnight at room temperature. The mixture was poured onto ice (~200 g) and aqueous HCl (100 mL, 2 M) and the organic layers separated. The aqueous layer was extracted with ethyl acetate (3× 100 mL) and the combined organic phases were washed with water (3×50 mL), dried (anhyd Na_2SO_4) and evaporated to afford the crude product. Elution from silica using 40% ethyl acetate in hexane as the eluent gave 4-chloro-2-methylbenzophenone **8g** as a yellow oil (11.7 g, 76%) bp 135 °C at 0.4 mmHg (lit. bp 150–155 °C at 0.5 mmHg[29]), δ_H 2.32 (3H, s, CH_3), 7.25 (3H, m, Ar-H), 7.46 (2H, m, 3′, 5′-H), 7.59 (1H, m, 4′-H), 7.77 (2H, m, 2′, 6′-H).

3.6. Attempted preparation of 2-fluoro-4-pyrrolidinobenzophenone

2,4-Difluorobenzophenone **8d** (5.02 g, 23 mmol) was dissolved in pyrrolidine (11.7 mL, 140 mmol) and stirred at room temperature for 10 min and then heated under reflux until TLC examination of the reaction mixture indicated that no further changes were apparent (~5 h). The cooled mixture was poured into water (300 mL) and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (3×100 mL) and the combined organic phases were washed with water (6×50 mL), dried (anhyd Na_2SO_4) and evaporated to afford the crude product. Purification was effected by elution from silica with 30% EtOAc in hexane to afford two fractions

Fraction 1. 4-Fluoro-2-pyrrolidinobenzophenone **10a** as yellow microcrystals (1.05 g, 17%), mp 74–75 °C, ν_{max} 1646, 1614, 1577 cm^{-1}, δ_H 1.91 (4H, m, $(CH_2)_2$), 3.12 (4H, m, $N(CH_2)_2$), 6.37 (1H, m, 5-H), 6.50 (1H, dd, J=12.8, 2.4 Hz, 3-H), 7.24 (1H, m, 6-H), 7.47 (2H, m, 5′,3′-H), 7.57 (1H, m, 4′-H), 7.91 (2H, m, 2′,6′-H). (Found: C, 76.0; H, 6.1; N, 5.2; $C_{17}H_{16}NOF$ requires C, 75.8; H, 6.0; N, 5.2%).

Fraction 2. 2,4-Dipyrrolidinobenzophenone **9** as yellow microcrystals (5.3 g, 72%), mp 142–145 °C, ν_{max} 1624, 1602, 1575 cm^{-1}, δ_H 1.89 (4H, m, $(CH_2)_2$), 2.01 (4H, m, $(CH_2)_2$), 3.21 (4H, m, $N(CH_2)_2$), 3.35 (4H, m, $N(CH_2)_2$), 5.85 (1H, d, J=2.0 Hz, 3-H), 5.93 (1H, dd, J=8.7, 2.1 Hz, 5-H), 7.24 (1H, d, J=8.6 Hz, 6-H), 7.42 (2H, m, 5′,3′-H), 7.49 (1H, m, 4′-H), 7.87 (1H, m, 2′,6′-H). (Found: C, 78.9; H, 7.7; N, 8.7; $C_{21}H_{24}N_2O$ requires C, 78.7; H, 7.6; N, 8.7%).

3.7. Preparation of 2-substituted 4-pyrrolidinobenzophenones (Method 1)

The halogenobenzophenone **8** (23 mmol) was dissolved in pyrrolidine (1.92 mL, 23 mmol) containing potassium carbonate (0.32 g, 23 mmol) and stirred at room temperature for 10 min and then heated under reflux until TLC examination of the reaction mixture indicated that formation of 2,4-dipyrrolidinobenzophenone commenced (~1 h).

The cooled mixture was poured into water (100 mL) and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (3×100 mL) and the combined organic phases were washed with water (6×50 mL), dried (anhyd Na_2SO_4) and evaporated to afford the crude product. Purification was effected by elution from silica with 30% EtOAc in hexane. The following benzophenones were prepared in this manner:

3.7.1. 2-Iodo-4-pyrrolidinobenzophenone 11a.

From 4-chloro-2-iodobenzophenone **8a**, elution from silica gave three fractions. *Fraction 1*. 2-Iodo-4-pyrrolidinobenzophenone **11a** as yellow microcrystals (2.60 g, 30%), mp 117–120 °C, ν_{max} 1642, 1593 cm^{-1}, δ_H 1.90 (4H, m, $(CH_2)_2$), 3.12 (4H, m, $N(CH_2)_2$), 6.64 (1H, dd, $J=8.3$, 1.9 Hz, 5-H), 6.81 (1H, d, $J=1.9$ Hz, 3-H), 7.17 (1H, d, $J=8.3$ Hz, 6-H), 7.47 (2H, m, 3′,5′-H), 7.56 (1H, m, 4′-H), 7.91 (2H, m, 2′,6′-H), δ_C 26.3, 51.7, 114.1, 115.1, 122.8, 128.8, 130.8, 133.0, 133.2, 137.9, 138.5, 149.1, 196.2. (Found: C, 54.0; H, 4.3; N, 3.8; $C_{17}H_{16}NOI$ requires C, 54.1; H, 4.2; N, 3.7%).

Fraction 2. 4-Chloro-2-pyrrolidinobenzophenone **10b** (0.26 g, 4%), δ_H 2.05 (4H, m, $(CH_2)_2$), 3.36 (4H, m, $N(CH_2)_2$), 6.42 (1H, dd, $J=8.7$ Hz, 2.3, 5-H), 6.57 (1H, d, $J=2.4$ Hz, 3-H), 7.36 (1H, d, $J=8.6$ Hz, 6-H), 7.43 (2H, m, 3′,5′-H), 7.54 (1H, m, 4′-H), 7.78 (2H, m, 2′,6′-H).

Fraction 3. 2,4-Dipyrrolidinobenzophenone **9** (0.29 g, 4%).

3.7.2. 2-Bromo-4-pyrrolidinobenzophenone 11b.

From 2-bromo-4-chlorobenzophenone **8b**, elution from silica gave two fractions. *Fraction 1*. 2-Bromo-4-pyrrolidinobenzophenone **11b** as yellow microcrystals (2.95 g, 39%), mp 117–120 °C, ν_{max} 1642, 1593 cm^{-1}, δ_H 1.90 (4H, m, $(CH_2)_2$), 3.12 (4H, m, $N(CH_2)_2$), 6.64 (1H, dd, $J=8.3$, 1.9 Hz, 5-H), 6.81 (1H, d, $J=1.9$ Hz, 3-H), 7.17 (1H, d, $J=8.3$ Hz, 6-H), 7.46 (2H, m, 5′,3′-H), 7.56 (1H, m, 4′-H), 7.91 (2H, m, 2′,6′-H), δ_C 25.8, 51.3, 113.6, 114.7, 122.3, 127.3, 128.3, 130.4, 132.6, 132.8, 137.5, 138.1, 148.7, 195.8. (Found: C, 61.7; H, 5.3; N, 4.6; $C_{17}H_{16}NOBr$ requires C, 61.8; H, 4.9; N, 4.2%).

Fraction 2. 4-Chloro-2-pyrrolidinobenzophenone **10b** (0.33 g, 5%).

3.7.3. 2-Chloro-4-pyrrolidinobenzophenone 11c.

From 2-chloro-4-fluorobenzophenone **8c**, elution from silica gave three fractions. *Fraction 1*. 2-Chloro-4-pyrrolidinobenzophenone **11c** as yellow microcrystals (3.35 g, 51%), mp 95–98 °C, ν_{max} 1650, 1591 cm^{-1}, δ_H 2.04 (4H, m, $(CH_2)_2$), 3.33 (4H, m, $N(CH_2)_2$), 6.41 (1H, dd, $J=8.6$, 2.4 Hz, 5-H), 6.56 (1H, d, $J=2.4$ Hz, 3-H), 7.35 (1H, d, $J=8.6$ Hz, 6-H), 7.43 (2H, m, 5′,3′-H), 7.52 (1H, m, 4′-H), 7.77 (2H, m, 2′,6′-H), δ_C 25.8, 48.0, 109.4, 113.2, 124.2, 128.6, 130.4, 132.7, 133.5, 135.0, 139.2, 150.4, 195.2. (Found: C, 71.3; H, 5.7; N, 4.9; $C_{17}H_{16}NOCl$ requires C, 71.5; H, 5.6; N, 4.9%).

Fraction 2. 4-Fluoro-2-pyrrolidinobenzophenone **10a** (60 mg, 1%).

Fraction 3. 2,4-Dipyrrolidinobenzophenone **9** (0.37 g, 5%).

3.7.4. 2-Fluoro-4-pyrrolidinobenzophenone 11d.

From 2,4-difluorobenzophenone **8d**, elution from silica gave two fractions. *Fraction 1*. 2-Fluoro-4-pyrrolidinobenzophenone **11d** as yellow microcrystals (2.3 g, 37%), mp 86–90 °C, ν_{max} 1645, 1609, 1579 cm^{-1}, δ_H 2.06 (4H, m, $(CH_2)_2$), 3.36 (4H, m, $N(CH_2)_2$), 6.18 (1H, dd, $J=14.0$, 2.3 Hz, 3-H), 6.35 (1H, dd, $J=8.8$, 2.3 Hz, 5-H), 7.44 (2H, m, 5′,3′-H), 7.53 (1H, m, 4′-H), 7.58 (1H, d, $J=8.6$ Hz, 6-H), 7.60 (2H, m, 2′,6′-H), δ_C 25.4, 47.7, 97.9 (d, $J=26.9$ Hz), 107.3 (d, $J=1.3$ Hz), 113.2 (d, $J=12.5$ Hz), 128.0, 129.2 (d, $J=1.6$ Hz), 131.8, 133.5 (d, $J=4.5$ Hz), 139.9, 152.1 (d, $J=12.3$ Hz), 161.9, 164.4, 192.7. (Found: C, 75.3; H, 6.2; N, 5.4; $C_{17}H_{16}NOF$ requires C, 75.8; H, 6.0; N, 5.2%).

Fraction 2. 4-Fluoro-2-pyrrolidinobenzophenone **10a** as yellow microcrystals (1.7 g, 28%).

3.8. Preparation of 2-substituted 4-pyrrolidinobenzophenones (Method 2)

The halogenobenzophenone **8** (23 mmol) was dissolved in a mixture of pyrrolidine (5.85 mL, 70 mmol) and anhyd DMSO (30 mL) and stirred at room temperature for 10 min and then heated under reflux until TLC examination of the reaction mixture indicated that no further changes were apparent (∼4 days). The cooled mixture was poured into water (300 mL) and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (3×100 mL) and the combined organic phases were washed with water (6×50 mL), dried (anhyd Na_2SO_4) and evaporated to afford the crude product. Purification was effected by elution from silica with 30% EtOAc in hexane. The following benzophenones were prepared in this manner:

3.8.1. 2-Methoxy-4-pyrrolidinobenzophenone 11f.

From 4-chloro-2-methoxybenzophenone **8f**, elution from silica gave two fractions. *Fraction 1*. 2-Methoxy-4-pyrrolidinobenzophenone **11f** as yellow microcrystals (1.16 g, 18%), mp 83–85 °C, ν_{max} 1630, 1592 cm^{-1}, δ_H 2.02 (4H, m, $(CH_2)_2$), 3.35 (4H, m, $N(CH_2)_2$), 3.69 (3H, s, OCH_3), 6.01 (1H, d, $J=2.0$ Hz, 3-H), 6.14 (1H, dd, $J=8.6$, 2.1 Hz, 5-H), 7.39 (2H, m, 6-H, Ar-H), 7.46 (2H, m, Ar-H), 7.70 (2H, m, 2′,6′-H), δ_C 25.9, 48.1, 55.7, 94.7, 104.0, 115.9, 128.1, 129.8, 131.6, 134.4, 141.0, 152.2, 161.3, 195.5. (Found: C, 76.7; H, 6.9; N, 4.9; $C_{18}H_{19}NO_2$ requires C, 76.8; H, 6.8; N, 5.0%).

Fraction 2. 2-Hydroxy-4-pyrrolidinobenzophenone **11e** as green microcrystals (1.17 g, 19%), mp 55–58 °C, ν_{max} 3435, 1628, 1549, 1522 cm^{-1}, δ_H 2.02 (4H, m, $(CH_2)_2$), 3.38 (4H, m, $N(CH_2)_2$), 6.05 (2H, m, 3,5-H), 7.38 (1H, d, $J=8.6$ Hz, 6-H), 7.48 (3H, m, Ar-H), 7.61 (2H, m, 2′,6′-H), 13.04 (1H, s, OH), δ_C 25.3, 47.6, 97.8, 104.3, 109.2, 128.1, 128.7, 130.7, 135.4, 139.0, 153.4, 166.0, 198.1. (Found: C, 76.0; H, 6.1; N, 4.9; $C_{17}H_{17}NO_2$ requires C, 76.4; H, 6.4; N, 5.2%).

3.8.2. 2-Methyl-4-pyrrolidinobenzophenone 11g.

From 4-chloro-2-methylbenzophenone **8g**. As yellow microcrystals (2.5 g, 41%), mp 65–67 °C, ν_{max} 1631, 1608, 1577 cm^{-1}, δ_H 2.02 (4H, m, $(CH_2)_2$), 2.53 (3H, s, CH_3), 3.35 (4H, m, $N(CH_2)_2$), 6.31 (1H, dd, $J=8.6$, 2.3 Hz, 5-H), 6.42 (1H, d, $J=2.2$ Hz, 3-H), 7.33 (1H, d, $J=8.6$ Hz, 6-H), 7.42 (2H, m, 5′,3′-H), 7.49 (1H, m, 4′-H), 7.71 (2H, m, 2′,6′-H), δ_C 22.4, 25.9, 47.9, 107.8, 114.6, 124.7, 128.4, 130.2, 131.5, 131.8, 134.8, 140.9, 142.5, 150.1, 197.5. (Found: C, 81.4; H, 7.3; N, 5.2; $C_{18}H_{19}NO$ requires C, 81.5; H, 7.2; N, 5.3%).

3.9. Preparation of prop-2-yn-1-ols

n-Butyllithium (1.6 M in hexanes) (9.4 mL, 15 mmol) was added slowly via syringe to a cold (−10 °C), stirred solution of trimethylsilylacetylene (2.12 mL, 15 mmol) in anhyd tetrahydrofuran (60 mL) under nitrogen atmosphere. On completion of the addition (ca. 5 min) the cold solution was allowed to stir for 1 h. The pyrrolidinobenzophenone **11** (12 mmol) was added in a single portion and the mixture stirred until TLC examination of the reaction mixture indicated that none of the benzophenone remained (ca. 3 h). The reaction mixture was re-cooled to 0 °C and a solution of methanolic potassium hydroxide from potassium hydroxide (1.74 g, 31 mmol) in methanol (20 mL) was added in a single portion. The cooling bath was then removed and the mixture warmed to room temperature, after ca. 15 min TLC examination indicated that deprotection was complete. The mixture was acidified to pH ~7 using glacial acetic acid and then poured into water (500 mL). The organic layer was separated and the aqueous layer extracted with ethyl acetate (3×100 mL). The organic phases were combined, washed with water (3×50 mL) and dried (anhyd Na_2SO_4). Removal of the solvent gave the prop-2-yn-1-ol, which was recrystallised from hexane and ethyl acetate. The following alkynols were obtained in this way:

3.9.1. 1-(2-Chloro-4-pyrrolidinophenyl)-1-phenylprop-2-yn-1-ol 12a. From 2-chloro-4-pyrrolidinobenzophenone **11c** as a brown powder (3.2 g, 86%), mp 70–73 °C, ν_{max} 3285, 1607 cm^{-1}, δ_H 1.84 (4H, m, $(CH_2)_2$), 2.72 (1H, s, alkynic-H), 3.11 (4H, m, $N(CH_2)_2$), 3.42 (1H, br s, OH), 6.30 (1H, dd, $J=8.8$, 2.5 Hz, 5-H), 6.38 (1H, d, $J=2.5$ Hz, 3-H), 7.17 (3H, m, Ar-H), 7.40 (2H, m, 2′,6′-H), 7.54 (1H, d, $J=8.7$ Hz, 6-H). (Found: C, 73.0; H, 5.7; N, 4.5; $C_{19}H_{18}NOCl$ requires C, 73.2; H, 5.8; N, 4.5%).

3.9.2. 1-(2-Fluoro-4-pyrrolidinophenyl)-1-phenylprop-2-yn-1-ol 12b. From 2-fluoro-4-pyrrolidinobenzophenone **11d** as a pale brown powder (2.4 g, 67%), mp 76–80 °C, ν_{max} 3278, 1624 cm^{-1}, δ_H 1.99 (4H, m, $(CH_2)_2$), 2.84 (1H, s, alkynic-H), 2.90 (1H, br s, OH), 3.24 (4H, m, $N(CH_2)_2$), 6.19 (1H, dd, $J=14.7$, 2.4 Hz, 3-H), 6.27 (1H, dd, $J=8.7$, 2.4 Hz, 5-H), 7.31 (4H, m, Ar-H), 7.59 (2H, m, 2′,6′-H). (Found: C, 76.9; H, 6.0; N, 4.7; $C_{19}H_{18}NOF$ requires C, 77.2; H, 6.1; N, 4.7%).

3.9.3. 1-(2-Methoxy-4-pyrrolidinophenyl)-1-phenylprop-2-yn-1-ol 12c. From 2-methoxy-4-pyrrolidinobenzophenone **11f** as a pale brown powder (3.6 g, 98%), mp 75–78 °C, ν_{max} 3286, 1613 cm^{-1}, δ_H 1.99 (4H, m, $(CH_2)_2$), 2.78 (1H, s, alkynic-H), 3.28 (4H, m, $N(CH_2)_2$), 3.76 (3H, s, OCH_3), 4.91 (1H, br s, OH), 6.08 (1H, m, 3,5-H), 7.09 (1H, d, $J=8.4$ Hz, 6-H), 7.29 (3H, m, Ar-H), 7.56 (2H, m, 2′,6′-H). (Found: C, 78.2; H, 6.5; N, 4.3; $C_{20}H_{21}NO_2$ requires C, 78.2; H, 6.9; N, 4.6%).

3.9.4. 1-(2-Methyl-4-pyrrolidinophenyl)-1-phenylprop-2-yn-1-ol 12d. From 3-methyl-4-pyrrolidinobenzophenone **11g** as a pale brown gum (3.3 g, 96%), ν_{max} 3247, 1604 cm^{-1}, δ_H 1.82 (4H, m, $(CH_2)_2$), 1.91 (3H, s, CH_3), 2.64 (1H, br s, OH), 2.70 (1H, s, alkynic-H), 3.13 (4H, m, $N(CH_2)_2$), 6.19 (1H, d, $J=2.4$ Hz, 3-H), 6.27 (1H, dd, $J=8.6$, 2.4 Hz, 5-H), 7.13 (3H, m, Ar-H), 7.37 (2H, m, 2′,6′-H), 7.59 (1H, d, $J=8.6$ Hz, 6-H). Satisfactory elemental analysis could not be obtained for this compound.

3.10. Preparation of 3,3-diaryl-3*H*-naphtho[2,1-*b*]pyrans

A stirred solution of 2-naphthol (0.48 g, 3.3 mmol) and the prop-2-yn-1-ol **12** (3.3 mmol) in toluene (40 mL) was warmed to 50 °C. Acidic alumina (2.5 g) was added and the mixture was refluxed until TLC examination indicated that none of the prop-2-yn-1-ol remained (ca. 1.5 h). The mixture was cooled to ~50 °C, filtered and the alumina was washed with hot toluene (2×20 mL). Removal of the toluene from the combined washings and filtrate gave a gum that was eluted from silica (40% ethyl acetate in hexane) to afford the naphthopyran. The following naphthopyrans were obtained using this protocol:

3.10.1. 3-(2-Chloro-4-pyrrolidinophenyl)-3-phenyl-3*H*-naphtho[2,1-*b*]pyran 13a. From 1-(2-chloro-4-pyrrolidinophenyl)-1-phenylprop-2-yn-1-ol as pale pink microcrystals (0.79 g, 55%), mp 170–173 °C, ν_{max} 1607 cm^{-1}, δ_H 1.91 (4H, m, $(CH_2)_2$), 3.17 (4H, m, $N(CH_2)_2$), 6.31 (1H, dd, $J=8.8$, 2.6 Hz, Ar-H), 6.37 (1H, d, $J=10.0$ Hz, 2-H), 6.51 (1H, d, $J=2.5$ Hz, Ar-H), 7.19 (1H, d, $J=8.8$ Hz, 5-H), 7.27 (5H, m, Ar-H, 1-H), 7.44 (3H, m, Ar-H), 7.51 (1H, d, $J=8.8$ Hz, Ar-H), 7.62 (1H, d, $J=8.8$ Hz, 6-H), 7.68 (1H, d, $J=8.4$ Hz, 7-H), 7.94 (1H, d, $J=8.5$ Hz, 10-H). (Found: $[M+H]^+$437.1536; C, 79.1; H, 5.6; N, 3.2; $C_{29}H_{24}NOCl$ requires $[M+H]^+$437.1540; C, 79.5; H, 5.5; N, 3.2%).

3.10.2. 3-(2-Fluoro-4-pyrrolidinophenyl)-3-phenyl-3*H*-naphtho[2,1-*b*]pyran 13b. From 1-(2-fluoro-4-pyrrolidinophenyl)-1-phenylprop-2-yn-1-ol as light brown microcrystals (0.92 g, 66%), mp 179–182 °C, ν_{max} 1624 cm^{-1}, δ_H 1.96 (4H, m, $(CH_2)_2$), 3.21 (4H, m, $N(CH_2)_2$), 6.21 (2H, dd, $J=25.1$, 2.4 Hz, Ar-H and m, Ar-H), 6.30 (1H, dd, $J=10.0$, 3.6 Hz, 2-H), 7.19 (1H, d, $J=8.8$ Hz, 5-H), 7.26 (2H, m, Ar-H), 7.32 (3H, m, Ar-H, 1-H), 7.39 (1H, m, Ar-H), 7.44 (1H, m, Ar-H), 7.50 (2H, m, Ar-H), 7.64 (1H, d, $J=8.8$ Hz, 6-H), 7.71 (1H, d, $J=8.5$ Hz, 7-H), 7.96 (1H, d, $J=8.8$ Hz, 10-H). (Found: $[M+H]^+$422.1921; C, 82.5; H, 5.8; N, 3.3; $C_{29}H_{24}NOF$ requires $[M+H]^+$422.1920; C, 82.6; H, 5.7; N, 3.3%).

3.10.3. 3-(2-Methoxy-4-pyrrolidinophenyl)-3-phenyl-3*H*-naphtho[2,1-*b*]pyran 13c. From 1-(2-methoxy-4-pyrrolidinophenyl)-1-phenylprop-2-yn-1-ol as pale pink microcrystals (0.97 g, 68%), mp 153–155 °C, ν_{max} 1614 cm^{-1}, δ_H 1.95 (4H, m, $(CH_2)_2$), 3.25 (4H, m, $N(CH_2)_2$), 3.56 (3H, s, OCH_3), 6.07 (1H, d, $J=2.1$ Hz, Ar-H), 6.11 (1H, dd, $J=8.5$, 2.3 Hz, Ar-H), 6.45 (1H, d, $J=10.2$ Hz, 2-H), 7.21 (3H, m, Ar-H, 5-H), 7.25 (3H, m, Ar-H, 1-H), 7.42 (1H, m, Ar-H), 7.47 (3H, m, Ar-H), 7.61 (1H, d, $J=8.8$ Hz, 6-H), 7.68 (1H, d, $J=8.6$ Hz, 7-H), 7.93 (1H, d, $J=8.5$ Hz, 10-H). (Found: $[M+H]^+$434.2110; C, 82.9;

H, 6.4; N, 3.1; $C_{30}H_{27}NO_2$ requires $[M+H]^+$434.2110; C, 83.1; H, 6.3; N, 3.2%).

3.10.4. 3-(2-Methyl-4-pyrrolidinophenyl)-3-phenyl-3*H*-naphtho[2,1-*b*]pyran 13d. From 1-(2-methyl-4-pyrrolidinophenyl)-1-phenylprop-2-yn-1-ol as pale pink microcrystals (0.62 g, 45%), mp 170–172 °C, ν_{max} 1608 cm^{-1}, δ_H 1.92 (4H, m, $(CH_2)_2$), 2.23 (3H, s, CH_3), 3.22 (4H, m, $N(CH_2)_2$), 6.08 (1H, d, $J=9.9$ Hz, 2-H), 6.25 (1H, dd, $J=8.6$, 2.6 Hz, Ar-H), 6.35 (1H, d, $J=2.4$ Hz, Ar-H), 7.15 (1H, d, $J=8.8$ Hz, 5-H), 7.24 (2H, m, Ar-H), 7.30 (4H, m, Ar-H, 1-H), 7.46 (3H, m, Ar-H), 7.61 (1H, d, $J=8.8$ Hz, 6-H), 7.68 (1H, d, $J=8.8$ Hz, 7-H), 7.94 (1H, d, $J=8.4$ Hz, 10-H). (Found: $[M+H]^+$418.2169; C, 86.1; H, 6.5; N, 3.3; $C_{30}H_{27}NO$ requires $[M+H]^+$418.2165; C, 86.3; H, 6.5; N, 3.4%).

Acknowledgements

We thank the EPSRC for the provision of a mass spectrometry service, University of Wales (Swansea). The University of Leeds is thanked for a research scholarship to A.C.I. and James Robinson Ltd, (Huddersfield) for additional funding.

References and notes

1. Mann, C.; Melzig, M.; Weigand, U. PCT WO 03/080595 A1, 2003. Chan, Y. -P.; Breyne, O.; Jean, P. PCT WO 01/36424 A2, 2001. Lin, J.; Van Gemert, B. PCT WO 99/31082, 1999. Clarke, D. A.; Heron, B. M.; Gabbutt, C. D.; Hepworth, J. D.; Partington, S. M.; Corns, S. N. PCT WO 98/42693 A1, 1998. Rickwood, M.; Smith, K. E.; Gabbutt, C. D.; Hepworth, J. D. PCT WO 94/22850, 1994. Garrity, N. E. U.S. Patent No. 6,174,464 B1, 2002. Momoda, J.; Matsuoka, S.; Nagou, H. U.S. Patent No. 6,525,194 B2, 2003.
2. McCallien, D. W. J.; Bezer, M. GB Patent No. 2344599, 2000.
3. Camus, M. Eur. Patent No. 488902, 1992. McDonald, L. J.; Ames, C. J.; Thomas, D. W.; Colgan, D. C. PCT WO 02/02319 A1, 2002.
4. Forest, S. E.; Krummen, M. S.; Yelton, J. A. PCT WO 02/03949 A2, 2002.
5. McManus, M., Federer, B. U.S. Patent No. 0,122,780 A1, 2002.
6. Compounds undergoing a thermally driven ring closure reaction are said to exhibit T-type photochromism; Bouas-Laurent, H.; Dürr, H. *Pure Appl. Chem.* **2001**, *73*, 639.
7. Frigoli, M.; Moustrou, C.; Samat, A.; Guglielmetti, R. *Eur. J. Org. Chem.* **2003**, 2799. Salvador, M. A.; Coelho, P. J.; Burrows, H. D.; Oliveira, M. M.; Carvalho, L. M. *Helv. Chim. Acta* **2004**, *87*, 1400. Gentili, P. L.; Romani, A.; Becker, R. S.; Favaro, G. *Chem. Phys.* **2005**, *309*, 167. Delbaere, S.; Micheau, J. -C.; Vermeersch, G. *J. Org. Chem.* **2003**, *68*, 8968. Gabbutt, C. D.; Heron, B. M.; Thomas, D. A.; Light, M. E.; Hursthouse, M. B. *Tetrahedron Lett.* **2004**, *45*, 6151. Ahmed, S. A.; Sallenave, X.; Fages, F.; Mieden-Gundert, G.; Müller, W. M.; Müller, U.; Vögtle, F.; Pozzo, J.-L. *Langmuir* **2002**, *18*, 7096.
8. Van Gemert, B. In *Organic Photochromic and Thermochromic Compounds*; Crano, J. C., Guglielmetti, R. J., Eds.; Main Photochromic Families; Plenum: New York, 1998; Vol. 1, p 113. Hepworth, J. D.; Gabbutt, C. D.; Heron, B. M. In *Colour Science '98*; Griffiths, J., Ed.; Dye and Pigment Chemistry; University of Leeds: Leeds, 1999; Vol. 1, p 161.
9. Van Gemert, B.; Bergomi, M. P. U.S. Patent No. 5,066,818, 1991.
10. Gabbutt, C. D.; Heron, B. M.; Instone, A. C. *Heterocycles* **2003**, *60*, 843.
11. Gabbutt, C. D.; Heron, B. M.; Instone, A. C.; Horton, P. N.; Hursthouse, M. B. *Tetrahedron* **2005**, *61*, 463.
12. Preliminary communication of our results as an invited lecture at the 10th International Conference on Dyes, Pigments and Functional Dyes, Colorchem '04, Czech Republic, May 2004.
13. Hodgson, H. H. *Chem. Rev.* **1947**, *40*, 251. Zollinger, H. *Angew. Chem.* **1978**, *90*, 151. Nonhebel, D. C. *J. Chem. Soc. (Special Publication)* **1970**, 409.
14. Rizzi, G. P. *Synth. Commun.* **1983**, *13*, 1173.
15. Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.
16. Gabbutt, C. D.; Heron, B. M.; McCreary, J. C.; Thomas, D. A. *J. Chem. Res. S* **2002**, 69.
17. Gabbutt, C. D.; Hepworth, J. D.; Heron, B. M.; Partington, S. M.; Thomas, D. A. *Dyes and Pigments* **2001**, *49*, 65. Gabbutt, C. D.; Gelbrich, T.; Hepworth, J. D.; Heron, B. M.; Hursthouse, M. B.; Partington, S. M. *Dyes and Pigments* **2002**, *54*, 79.
18. Iwai, I.; Ide, J. *Chem. Pharm. Bull.* **1962**, *10*, 926.
19. Barberis, C.; Campredon, M.; Lokshin, V.; Giusti, G.; Faure, R. *Magn. Reson. Chem.* **1995**, *33*, 977. Delbaere, S.; Teral, Y.; Bochu, C.; Campredon, M.; Vermeersch, G. *Magn. Reson. Chem.* **1999**, *37*, 159.
20. Clarke, D. A.; Heron, B. M.; Gabbutt, C. D.; Hepworth, J. D.; Partington, S. M.; Corns, S. N. PCT WO 98/45281 A1, 1998.
21. Gabbutt, C. D.; Hepworth, J. D.; Heron, B. M. Unpublished results. See also: Harié, G.; Samat, A.; Guglielmetti, R.; De Keukeleire, D.; Saeyens, W.; Van Parys, I. *Tetrahedron Lett.* **1997**, *38*, 3075 for an example of symmetrically substituted 3*H*-naphtho[2,1-*b*]pyrans with multiple absorption bands.
22. Collings, P. J.; Hird, M. *Introduction to Liquid Crystals: Chemistry and Physics*; Taylor Francis: London, 1997; p 70. Hatano, Y. In *Chemistry and Applications of Leuco Dyes*; Muthyala, R., Ed.; Plenum: New York, 1997; p 176.
23. Clarke, D. A.; Heron, B. M.; Gabbutt, C. D.; Hepworth, J. D.; Partington, S. M.; Corns, S. N. PCT WO 00/18755 A1, 2000.
24. Rickwood, M., Hepworth, J. D., Gabbutt, C. D., PCT WO 95/05382 A1, 1995. Guglielmetti. R., Pozzo, J. L., Samat, A. U.S. Patent No. 5,527,911 A, 1996.
25. Pelz, K.; Ernest, I.; Alderova, E.; Metysova, J.; Protiva, M. *Collect. Czech. Chem. Commun.* **1968**, *33*, 1852.
26. Cam-Van, N. T.; Diep, B. K.; Buu-Hoi, N. P. *Tetrahedron* **1964**, *20*, 2195.
27. Zhang, C.; Wang, Z. Y. *Macromolecules* **1993**, *26*, 2234.
28. Perrot, C.; Cerutti, E. *Bull. Soc. Chim. Fr.* **1974**, 2225.
29. Aeberli, P.; Eden, P.; Gogerty, J. G.; Houlihan, W. J.; Penberthy, C. *J. Med. Chem.* **1975**, *18*, 177.

Available online at www.sciencedirect.com
SCIENCE DIRECT®

Tetrahedron 62 (2006) 746–757

Tetrahedron

A short approach to chaetomellic anhydride A from 2,2-dichloropalmitic acid: elucidation of the mechanism governing the functional rearrangement of the chlorinated pyrrolidin-2-one intermediate

Franco Bellesia,[a] Chiara Danieli,[a] Laurent De Buyck,[b] Roberta Galeazzi,[c] Franco Ghelfi,[a,*] Adele Mucci,[a] Mario Orena,[c] Ugo M. Pagnoni,[a] Andrew F. Parsons[d] and Fabrizio Roncaglia[a]

[a] *Dipartimento di Chimica, Università degli Studi di Modena e Reggio Emilia, Via Campi 183, I-41100 Modena, Italy*
[b] *Department of Organic Chemistry, Faculty of Biosciences Engineering, Ghent University, Coupure Links 653, B-9000 Ghent, Belgium*
[c] *Dipartimento di Scienze dei Materiali e della Terra, Università Politecnica delle Marche, Via Brecce Bianche, I-60131 Ancona, Italy*
[d] *Department of Chemistry, University of York, Heslington, York, YO10 5DD, UK*

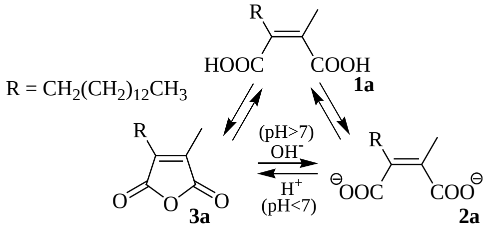
Received 20 June 2005; revised 26 September 2005; accepted 29 September 2005

Abstract—Chaetomellic anhydride A was efficiently attained in three steps, starting from 2,2-dichloropalmitic acid and 2-(3-chloro-2-propenylamino)pyridine. Atom transfer radical cyclisation selectively formed the cis-stereoisomer of the trichloropyrrolidin-2-one, which underwent a stereospecific functional rearrangement to form a substituted maleimide. The choice of 2-pyridyl, as 'cyclisation auxiliary' in the atom transfer radical cyclisation step, proved beneficial for hydrolysis of the maleimide to form the desired anhydride.

---

1. Introduction

The screening of natural products to find new anticancer agents for use in the chemotherapeutic intervention of human tumors having mutated ras genes, has led to the evaluation of various microbial fermentation extracts.[1] From this intense screening work, carried out by a research group at Merck, chaetomellic dicarboxylic acids, isolated from the coelomycete *Chaetomella Acutiseta*, have been shown to have promising activities. Of these compounds, chaetomellic acid A (**1a**) (Scheme 1) proved to be the most active substance, inhibiting recombinant human FPTase with a IC_{50} value of 55 nM (Scheme 1).[1,2]



Scheme 1.

Chaetomellic dicarboxylic acids have a high propensity to cyclize and **1a** was, in fact, isolated as chaetomellic anhydride A (**3a**). The cyclic form, however, is unstable under mild basic conditions (pH = 7.5) and is readily hydrolysed to the dicarboxylate anion **2a**, which, apparently, is the biologically active component (Scheme 1).[1] FPTase activity of the diacid anion of **1** is noncompetitive towards the acceptor peptide Ras but is highly competitive with respect to farnesyl pyrophosphate (FPP). This may be explained by the structural similarity between dicarboxylate anion **2a** and FPP, since both possess a hydrophilic head group bound to a hydrophobic tail (Fig. 1). The maleate unit aligns well with the corresponding diphosphate moiety, since the negatively charged oxygen atoms can achieve a spacing within 0.1 Å,[3] while the flexible nature of the aliphatic chain permits it to fill the same space as the hydrophobic end of FPP upon binding to the enzyme.[1] Recently, in an effort to characterize the FPP binding site of rubber transferase, and to identify if species-specific differences exist for this enzyme, Vederas showed that **1** is able to inhibit, in vitro, rubber biosynthesis promoted by rubber transferase from *Hevea Brasiliensis*.[4] More recently

---

Keywords: Halocompound; Pyrrolidinone; Radical reaction; Rearrangement.

* Corresponding author. Fax: +39 059 373543; e-mail: ghelfi.franco@unimore.it

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.09.140

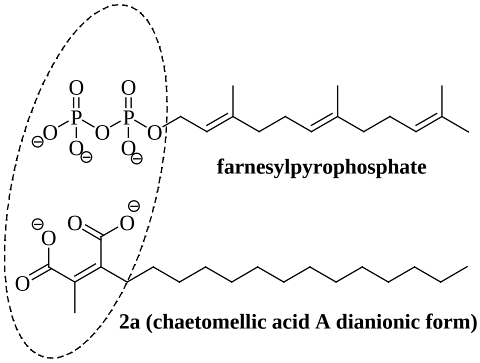


Figure 1. Structural similarity between the dianionic form of chaetomellic acid A (**2a**) and farnesyl pyrophosphate.

the same author found that **1** was also able to reduce the activity of the penicillin-binding protein **1b** (PBP1b), albeit with modest potency.[5]

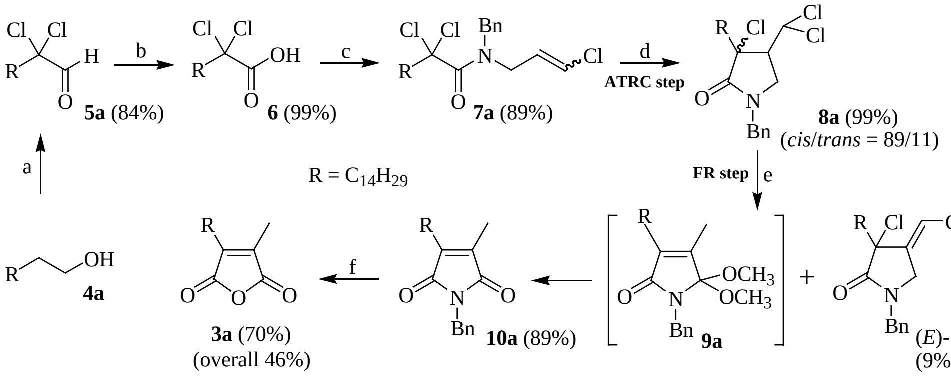
Because of its potent inhibitory activity, chaetomellic acid A has been the subject of considerable synthetic efforts. So far, nine different routes have been devised for the preparation of this interesting product.[2,6–15] In general, the synthesis of anhydride **3a** has been targeted since this compound is more easy to manipulate/isolate than diacid **1a**. The synthetic strategies investigated can be grouped into two general categories: (i) alkylation of maleic precursors[6–11,15,16] and (ii) assembly of the pivotal 1,4-dicarbonyl group.[2,12–14] In spite of the variety of employed methods, all of the reported procedures suffer from one or more of the following disadvantages: (i) low yields, (ii) costly reagents, (iii) unstable precursors and/or reactants, (iv) harmful solvents, (v) or unwieldy protocols. As a result, these procedures are not well-suited for large scale production, as evidenced by the high price of **1a**, which is sold by ICN or Calbio Chem at ca. 18,000 €/g.

Recently, our group has disclosed an original and robust route to chaetomellic anhydride A (**3a**) (Scheme 2).[17] Attractive features of the new strategy are: (i) an inexpensive starting material, 2,2-dichloropalmitic (**6**) acid, is easily prepared in two steps from the parent aliphatic alcohol (**4a**), (ii) inexpensive reagents are used, (iii) a halogen atom transfer radical cyclisation (ATRC) is used to efficiently construct the trichlorinated 2-pyrrolidinone **8a**,[18] (iv) an elegant functional rearrangement (FR) of **8a** to a maleimide (**9a**) is employed,[19] (v) the target molecule is prepared in only four steps, (vi) the approach is efficient (an overall yield of 55% from **6**, and 46% from **4a**) and (vii) the synthesis involves simple experimental procedures. Furthermore this route is versatile, as illustrated by the preparation of structural analogues of **3a** such as the chaetomellic anhydride **C** and roccellic acid (a lichens metabolite).[20]

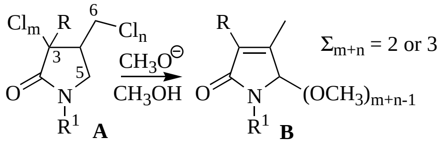
Notwithstanding the long list of advantages of this approach, there still remain a couple of aspects that need to be improved and/or explained, if we want to increase the appeal of the strategy for large scale production of **3a**.

The first aspect that needs improvement concerns the synthetic approach to **3a**. In our previous work, the conversion of the intermediate acetal **9a** to chaetomellic anhydride A (**3a**) is achieved by acid hydrolysis to **10a**, followed, according to Argade's protocol,[9] by a basic hydrolysis, and finally, reaction under acid conditions gives anhydride **3a**. These series of operations are time-consuming and the conditions for the basic hydrolysis (KOH/**10a**, 21 mol/mol, and solvent/**10a**, 28 L/mol) are not compatible with large-scale preparations.

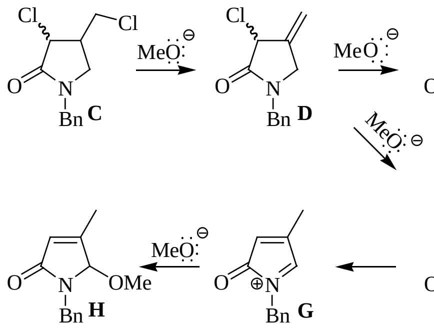
The second aspect concerns the reaction mechanism for the FR of **8a**. The isolation of a moderate amount of (*E*)-**11a**, the *exo*-dehydrohalogenated pyrrolidin-2-one by-produced during the FR reaction of **8a** to **9a/10a** (Scheme 2), and the evidence that this compound cannot be regarded as an intermediate in the formation of **9a/10a** cast some doubts on the reaction mechanism we formerly proposed to rationalise the FR.[19] The FR of 4-methyl-pyrrolidin-2-ones **A** chlorinated at the C(3) and C(6) positions (these are easily prepared by ATRC of the parent *N*-(3-chloro-2-propenyl)-α-perchloroamides) is a quite general reaction and takes place when **A** is treated with a solution of alkaline methoxide in methanol under mild conditions. In practice two or three of the C–Cl groups at the C(3) and C(6) positions of **A** are replaced by a double bond between carbons C(3) and C(4), and one or two methoxy groups at C(5) (Scheme 3). All transformations from **A** to **B** start with a concerted hydro-halo-elimination (E2) and loss of C(4)–H by either an *endo-* or an *exo*-path is possible. The preferred pathway proceeds by the more stable *anti*-periplanar



Scheme 2. (a) Cl_2, DMF–HCl, $CHCl_3$, 70 °C, 3 h; (b) Br_2, NaOH, CH_2Cl_2/H_2O, 1.5 h; (c) (1) $(COCl)_2$, CH_2Cl_2, DMF, 23 °C, 2 h, (2) *N*-benzyl-3-Cl-2-propenylamine, Py, 23 °C, 1 h; (d) CuCl–TMEDA, CH_3CN/CH_2Cl_2, argon, 60 °C, 20 h; (e) (1) Na^0, CH_3OH/ether, 25 °C, 20 h, (2) H^+/H_2O; (f) (1) KOH, CH_3OH/THF, reflux, 2 h, (2) H^+/H_2O.



Scheme 3.



Scheme 4.

conformation.[19] The mechanism, we issued for the illustrative case of the dichloro γ-lactam **C**, is outlined in Scheme 4. After initial formation of the *exo*-methylene intermediate **D**, the double bond was expected to shift inside the ring affording the 4-pyrrolin-2-one **F**, directly or via the formation of Δ^3 intermediate **E**. However, the isomerisation of (*E*)-**11a** was not observed and so the mechanism needs to be further investigated.

Herein, we report that the effectiveness of the FR is linked to the geometry of the starting 4-methyl-pyrrolidin-2-one, since the *exo* C=C bond can only move into conjugation if a hydrogen atom is present at C(3). As a consequence, the higher is the percentage of the cis stereoisomer, which can afford the pivotal 3-pyrrolin-2-one intermediate, the higher the expected yield of the rearranged product. In this work, we describe the use of 2-pyridyl group as a cyclisation auxiliary in the ATRC step, which allowed the final sequence of hydrolyses to be condensed to just a single operation that is linked to the FR in a one-pot reaction. In this way the efficiency of the overall process was substantially improved.

2. Results and discussion

To reduce the number of steps required to convert the intermediate acetal **9a** into the target anhydride **3a**, and develop a method attractive for scale up, we investigated two strategies. In the first instance, we sought to establish acidic conditions that performed the transformation in a straightforward manner, while we also looked at the use of an alternative cyclisation auxiliary that made **9a** and **10a** more susceptible to hydrolysis. Also, since the chlorinated pyrrolidin-2-one **8a** is isolated as a mixture of cis and trans isomers, we sought to elucidate the origin of the side product **11a** and thereby understand the mechanism of the FR. To do this it appeared necessary to isolate the cis and trans isomers for a separate study of their behaviour towards methoxide ion.

Foreseeable problems, including the difficulty in separating *cis*-**8a** and *trans*-**8a**,[17] steered us to use a molecule with a smaller skeleton than **3a**, as a model substrate. For this we choose dimethyl maleic anhydride **3b**, which is a very useful building-block in organic synthesis.[21] This substance, also known as pyrocinchonic anhydride, represents the most simple archetype for chaetomellic anhydride A (**3a**), the long *n*-tetradecylic aliphatic chain on the carbon C(3) in **3a** being here replaced by a methyl group (Fig. 2).

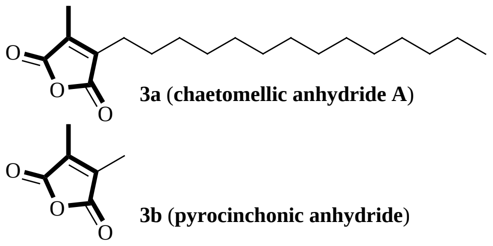
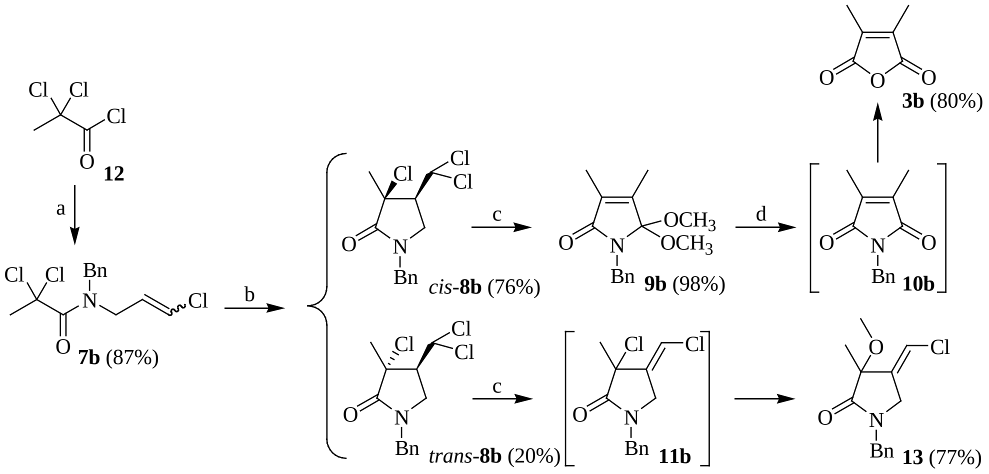


Figure 2. Pyrocinchonic anhydride (**3b**) as a simple archetype for chaetomellic anhydride A (**3a**).

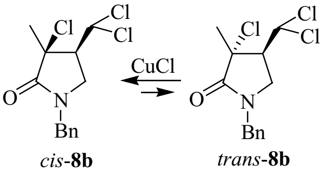
Following the synthetic path developed for the synthesis of **3a** (Scheme 2), 2,2-dichloropropanoyl chloride (**12**) was treated with *N*-benzyl-3-chloro-2-propenylamine to afford amide **7b** in good yield (Scheme 5). Then **7b** was efficiently



Scheme 5. (a) *N*-benzyl-3-Cl-2-propenylamine, Py, rt, 5 h; (b) CuCl–TMEDA, CH$_3$CN, argon, rt, 20 h; (c) Na^0, CH$_3$OH, 25 °C, 20 h; (d) CH$_3$SO$_3$H/CH$_3$COOH (1/1), 140 °C, 20 h.

cyclised, using CuCl/*N*,*N*,*N*′,*N*′-tetramethylenediamine (TMEDA) in acetonitrile (AN) at room temperature, to provide the trichlorinated pyrrolidin-2-one **8b** (96%) as a 79:21 mixture of cis-/trans- isomers.

As previously reported,[22–26] the stereogenic centre at C-3 of an 3-alkyl-3-chloro-4-chloroalkyl-γ-lactams is configurationally labile during the ATRC of the parent *N*-allyl α-perchloroamide. This is due to a reversible radical generation at the C(3) centre,[†] promoted by the redox catalyst (Scheme 6).[24,26] Consequently, the stereochemistry of products is directed by thermodynamic factors and the isomer that predominates has the largest appendages at C(3) and C(4) on the opposite sides of the ring, that is, in this example, the *cis*-**8b** isomer predominates (datum also confirmed by computational calculations). Since C(3) epimerization is a gradual process, a higher temperature and a longer reaction time generally improve the selectivity for the cis isomer. In fact when the ATRC of **7b** was carried out at 60 °C, rather than at room temperature, pyrrolidin-2-one **8b** was isolated in the same yield, but with a significantly higher cis-/trans-ratio of 89:11 (compared to 80:20).

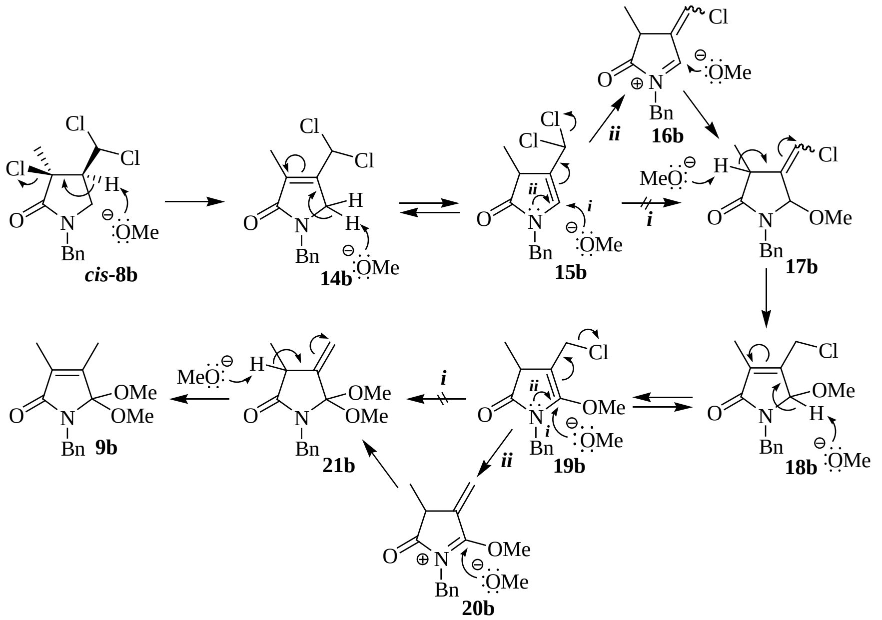


Scheme 6.

In contrast to what was observed for **8a**, we were pleased to see that *cis*-**8b** and *trans*-**8b** were separable by flash chromatography. To get an insight into the FR mechanism, the two compounds were subjected to the FR using methoxide in methanol, following the previously reported protocol (Scheme 5).[19] The major isomer *cis*-**8b** gave almost a quantitative yield (98%) of *N*-benzyl-5, 5-dimethoxy-3,4-dimethyl-3-pyrrolin-2-one (**9b**).

On the contrary, when *trans*-**8b** was reacted with the methoxide ion in methanol, the main product (77%) isolated was (*E*)-*N*-benzyl-4-chloromethylen-3-methoxy-3-methyl-2-pyrrolidinone (**13**), a compound with a similar structure to (*E*)-**11a**, which was obtained as a byproduct from the FR of **8a**. Evidently, due to the relatively low steric crowding around the C(3)–Cl group, the conceivable intermediate (*E*)-**11b** underwent facile methoxy-de-halogenation. This behaviour was confirmed by quenching the reaction of *trans*-**8b** after 1 h; this gave (*E*)-**11b**, as the second main product in the reaction mixture, after **13**. A small amount of **9b** was also observed in the attempted FR of *trans*-**8b**, but it was consistent with the small quantity of the *cis*-**8b** contaminating the starting material. These results definitely prove that the efficiency of the FR depends on the diastereoisomeric ratio of the chlorinated pyrrolidin-2-ones, and is consistent with the results obtained for the FR of **8a**[17] (Scheme 2) or equivalent adducts.[20]

In a previous work, we established that the FR starts with a bimolecular hydro-halo-elimination.[19] Hence, the more easily the required *anti*-periplanar conformation is achieved the more favourably the resulting E2 elimination will be. Accordingly, *cis*-**8b** follows the *endo*-dehydrochlorination path to give the 3-pyrrolin-2-one **14b** (Scheme 7), whereas *trans*-**8b** is forced to dehydrohalogenate in the alternative *exo*-direction to afford the 4-alkyliden-pyrrolidin-2-one (*E*)-**11b** (Scheme 5).



Scheme 7.

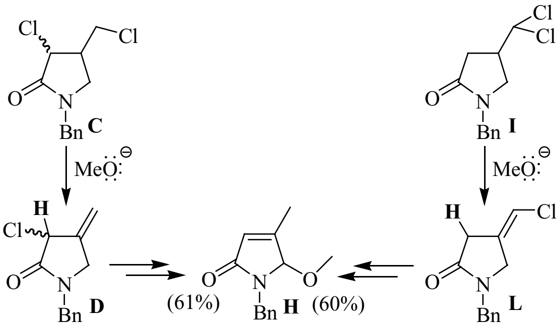
[†] The configurational change through a nucleophilic attack was firmly ruled out by the quantitative recovery of *cis*-**8b** after treatment with LiCl/TMEDA or $CuCl_2$/TMEDA under the same conditions of the ATRC of **7b**.

For compounds **14b** and (*E*)-**11b** the C=C bond lies in a different position. When the C=C bond is in conjugation with the C=O bond, the electron-withdrawing effect of the carbonyl group increases the acidity of vinylogous C(5)–H hydrogen atom.[27,28] This helps migration of the C=C bond from the α,β-position (Scheme 7, adduct **14b**) to the β,γ-position (Scheme 7, adduct **15b**), a clear example of tautomeric equilibrium where the conjugated form is thermodynamically favoured.[28,29] This property is well known and has been extensively used to prepare silyloxypyrroles from α,β-unsaturated γ-lactams,[27,30,31] and also in the manipulation of the (CO)–C=C–CH moiety in open chain compounds.[32–37]

The shift in the position of the C=C bond in **17b** triggers the subsequent substitution of one of the two *exo* chlorines by a C=C *exo*/Δ^3 base catalyzed transposition leading to compound **18b** (Scheme 7). Related reactions involving consecutive prototropic and anionotropic changes have been reported,[38,39] including the transformation of a trialkyl-γ-chloroallylammonium salt into the corresponding trialkyl-α-ethoxyallylammonium salt by reaction with sodium ethoxide, described by Ingold and Rothstein back in 1928.[39] The conversion of **15b** to **17b** is likely to occur by a stepwise mechanism involving the N-1 lone pair and the participation of the acylimmonium cation intermediate **16b** (Scheme 7, path ii).[37] Analogous steps are reasonably implicated along the way from **18b** to acetal **9b**. The alternative direct transformation by a S_N2' substitution (Scheme 7, path i)[40,41] appears doubtful since the nucleophilic substitution of allylic intermediate (*E*)-**11b** proceeded without rearrangement (Scheme 5).

Good evidence for the stepwise mechanism was obtained by analysing the reaction mixture after a short reaction time (2 min). This allowed the detection and separation of the proposed intermediate **18b**. The isolation of **18b** suggests that the Δ^3/Δ^4 transposition of **18b** to **19b** is the slowest step in the rearrangement.

The proposed shift of the *exo* C=C bond (to move inside the ring) was erroneously formulated following experimental evidence which showed that *N*-benzyl-3-chloro-4-chloromethyl-2-pyrrolidinone (**C**) and *N*-benzyl-4-dichloromethyl-2-pyrrolidinone (**I**), two substrates that react by an initial *exo*-elimination, both rearrange in high yield to give *N*-benzyl-4-methyl-3-pyrrolin-2-one (**H**) (Scheme 8).[19] In the light of our current observations, these two examples appear to be exceptional, presumably because both have an acidic α hydrogen at C(3), which allows the *exo* C=C bond to move in to conjugation for the early intermediates **D** and **L** (Scheme 8). In contrast, for adducts analogous to **11b**, the lack of C(3)–H bonds and the insufficient acidity of the C(5)–H proton precludes the transposition.



Scheme 8.

In summary, the configuration of the starting α,γ-halogenated 2-pyrrolidinones influences the FR. For an effective FR the configuration of the precursor should permit an *endo*-elimination. If, however, the reaction is forced to proceed by *exo*-elimination then (for a successful FR) the precursor must have a hydrogen atom at C(3).

Following our studies on the mechanism of the FR, we tackled the problem of the one-pot hydrolysis of **9b** to form anhydride **3b**. The process requires two sequential hydrolyses: the first hydrolysis forms maleimide **10b** from acetal **9b** and the second forms anhydride **3b** from **10b** (Scheme 5). To arrive at a one-pot process we needed a suitable acid that promoted both hydrolyses and initial results using methanesulfonic acid (MSA) are collected in Table 1.

Hydrolysis of **10b** to form **3b** is possible using MSA in acetic acid (Table 1, entries 4–9) but not in aqueous media,

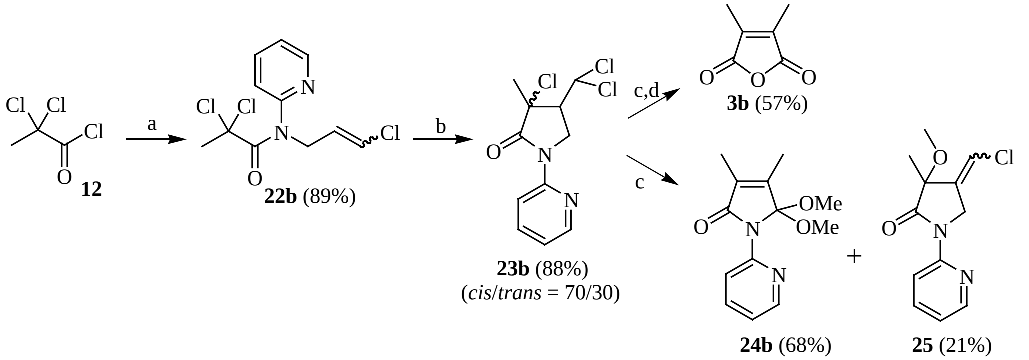
Table 1. Solvolysis of the *N*-benzyl-5,5-dimethoxy-3,4-dimethyl-3-pyrrolin-2-one **9b**[a]

Item	Promoter (mL)	Solvent (mL)	*T* (°C)	*t* (h)	Conversion (%)[b]	**10b** (%)[b]	**3b** (%)[b]
1	MSA (0.08)[c]	H_2O (1.2)	100	4	100	100	0
2	MSA (0. 45)	H_2O (1.7)	100	4	100	100	0
3	MSA (0. 45)	H_2O (1.7)	140	4	100	100	0
4	MSA (0.26)	AcOH (1)	100	4	100	95	4
5	MSA (0.26)	AcOH (1)	120	20	100	86	14
6	MSA (0.5)	AcOH (0.5)	100	40	100	53	47
7	MSA (0.5)	AcOH (0.5)	120	20	100	35	65
8	MSA (0.5)	AcOH (0.5)	140	20	100	0	100 (79)[d]
9[e]	MSA (0.65)	AcOH (0.65)	140	20	100	5	95
10	MSA (1.0)	—	25	100	100	100	0
11	H_2SO_4 (0.5)	AcOH (0.5)	120	20	100	0[f]	Traces[f]
12	NaOH (2.5)[c]	H_2O (0.5)	120	3	0	0	0

[a] Substrate 1 mmol.
[b] GC values.
[c] Values in mmol.
[d] Determined on isolated material.
[e] Solvolysis performed directly on the crude product from the FR of *cis*-**8b** after solvent evaporation.
[f] Extensive formation of black resinous material.

presumably because **10b** is more soluble in acetic acid than in water (Table 1, entries 1–3). The complete conversion of **10b** in to **3b** required 0.5 mL of MSA per mmol of **10b**, together with heating at 140 °C for 20 h (Table 1, entry 8). Unfortunately, when the crude FR product (obtained after reaction solvent evaporation) from *cis*-**8b** was reacted under these conditions, some maleimide **10b** remained (Table 1, entry 9). Also, reaction of **10b** with MSA at room temperature, or the use of H_2SO_4 in place of MSA, or the use of basic conditions were ineffective (Table 1, entries 10–12).

As our studies on the solvolysis of *N*-benzylmaleimide **10b** were not completely satisfactory, we searched for an auxiliary more suited to removal by hydrolysis. In this respect, we were helped by the work of Baumann[42] who discovered an elegant way to prepare dimethylmaleic anhydride by dimerization of maleic anhydride using 2-aminopyridine. Interestingly, the last step in the synthesis involved acid hydrolysis of *N*-(2-pyridyl)-3,4-dimethylmaleimide.[42] This strategy was used by Argade for the preparation of chaetomellic anhydride A from 2-bromopalmitoyl chloride—the final step in the synthesis involved hydrolysis of a *N*-(2-pyridyl)maleimide derivative.[13,14]

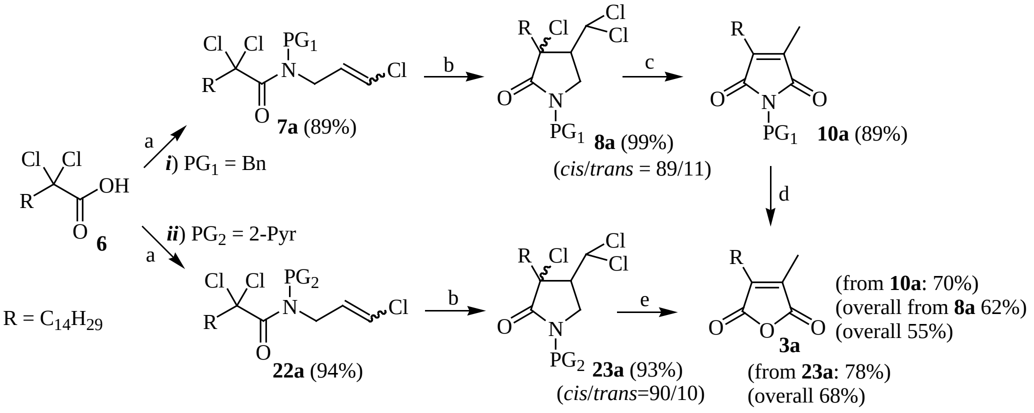


Scheme 9. (a) 2-(3-chloro-2-propenylamino)pyridine, Py, argon, 35 °C, 20 h; (b) CuCl–TMEDA, CH_3CN, Argon, rt, 20 h; (c) Na^0, CH_3OH, 25 °C, 20 h; (d) H_2SO_4 4 N, 110 °C, 1 h.

The apparent vulnerability of *N*-(2-pyridyl)maleimides to acid conditions spurred us to investigate the ATRC and FR reactions of a precursor with a 2-pyridyl auxiliary (Scheme 9). *N*-(3-Chloro-2-propenyl)-*N*-(2-pyridyl)-2,2-dichloropropanamide (**22b**) was easily prepared, in excellent yield (89%), by a metathesis reaction between **12** and 2-(3-chloro-2-propenylamino)pyridine. An ATRC reaction of **22b** (under similar conditions to amide **7b**) afforded the halogenated pyrrolidin-2-one (**23b**) as a mixture of cis-/trans- isomers (70:30) in an excellent yield (88%). The FR of *cis*-**23b**/*trans*-**23b** was accomplished using the same conditions as for **8b**. As expected, along with the desired acetal **24b**, isolated in a respectable yield of 68%, we also recovered a moderate amount (21%) of the *exo*-dehydrohalogenated pyrrolidin-2-one (*E*)-**25**.

In order to develop a one-pot hydrolysis reaction, we investigated the reaction of crude product **24b** (isolated by solvent evaporation of the FR reaction mixture) with the acid conditions reported by Baumann (H_2SO_4 4 N 1 mL/mmol of substrate, heating at 110 °C) (Scheme 9). The reaction was completed in just one hour and pyrocinchonic anhydride was recovered in a satisfactory yield of 57%. If one takes into account that only the *cis*-**23b** component can rearrange, the yield of pyrocinchonic anhydride increases to 81%.

When compared with the one-pot transformation of *N*-benzyl lactam *cis*-**8b** to **3b** (Scheme 5), the parallel



Scheme 10. (a) (1) $(COCl)_2$, CH_2Cl_2, DMF, 23 °C, 2 h, (2) *N*-benzyl-3-Cl-2-propenylamine (path ***i***) or 2-(3-chloro-2-propenylamino)pyridine (path ***ii***), Py, 23 °C, 1 h; (b) CuCl–TMEDA, CH_3CN, argon, 60 °C, 20 h; (c) (1) Na^0, CH_3OH/ether, 25 °C, 20 h, (2) H^+/H_2O; (d) (1) KOH, CH_3OH/THF, reflux, 2 h, (2) H^+/H_2O; (e) (1) Na^0, CH_3OH/ether, 25 °C, 20 h, (2) H_2SO_4 4 N, 110 °C, 2 h.

one-pot conversion of the *N*-(2-pyridyl) lactam **23b** to the same anhydride (Scheme 9) has some advantages including: (i) a lower reaction temperature, (ii) total conversion of precursor and (iii) a simplified purification procedure because byproduct **25** remains in the acidic aqueous phase.

The good result using the new one-pot hydrolysis method spurred us to apply this method to the synthesis of chaetomellic anhydride A. Thus, the *N*-(3-chloro-2-propenyl)-*N*-(2-pyridyl)-2,2-dichlorohexadecanamide **22a** was prepared and cyclised to give to **23a** (as an inseparable pair of cis-/trans- isomers in a ratio of 90:10) adhering to standard protocols (Scheme 10, path ***ii***). Both products were delivered in high yields. It is noted that, owing to the polar nature of the 2-pyridyl substituent, **22a** was completely soluble in acetonitrile, so the ATRC step did not require dilution with a less polar cosolvent (e.g., CH_2Cl_2) as was required for the *N*-benzyl amide **7a** (Scheme 2).[17] The ensuing FR of **23a** was accomplished using sodium in methanol (at 25 °C), after which the solvent was removed under vacuum and the residue dissolved in 4 N H_2SO_4. The solution was then heated to 110 °C to give, after 2 h, the target anhydride **3a** in a respectable 78% yield. No effort was spent to recover the side product derived from *exo*-elimination. The overall yield of chaetomellic anhydride A (**3a**) using this three step approach was 68% (Scheme 10, path ***ii***), which is significantly higher than the 55% yield observed with the previously reported four step process (Scheme 10, path ***i***). The increased efficiency is due to the increased effectiveness of the one-pot conversion of **23a** to **3a** (78%) compared to the stepwise conversion of **8a** to **3a** (overall 62% yield).

3. Computational investigation

In order to investigate the major thermodynamic stability of *cis*-**8b** with respect to *trans*-**8b**, a complete, extensive unconstrained conformational analysis of both isomers was performed by using AMBER* force field[43] and the Monte Carlo[44] conformational search (MC/EM) varying all the degrees of freedom including H_2O as implicit solvent that was chosen in order to simulate the polarity of the solution media (methanol). All the conformers within the energy gap of 6.0 kcal/mol were kept and subsequently only those which lie below 3.6 kcal/mol were fully analysed. Within this energy gap, 11 conformers were observed for compound *cis*-**8b**, and 12 conformers for *trans*-**8b**. Then the lowest energy conformation for both diastereomers was optimized at ab initio level by using the density functional method B3LYP/6-31G* and it resulted that *cis*-**8b** is 4.5 kcal/mol more stable than *trans*-**8b**. Thus, the reaction path leading to the chaetomellic anhydride (Scheme 5) is the most relevant one, the preferential formation of the major isomer *cis*-**8b** being explained by its thermodynamic stability.

It is worth mentioning that a similar trend was observed when the conformational analysis was carried out with the corresponding cis- and trans-compounds having at C-3 a C12 chain in place of the methyl, since the cis-isomer resulted again more stable than the trans-one. However, in this case a large number of low energy conformations were found for both diastereomers, and the energy difference among the two lowest ones resulted to be only 0.2 kcal/mol.

4. Conclusion

Chaetomellic anhydride A has been efficiently obtained in just three steps, starting from 2,2-dichloropalmitic acid and 2-(3-chloro-2-propenylamino)pyridine. The choice of 2-pyridyl, as ‘cyclisation auxiliary’[45] in the ATRC step, allowed the FR to be combined with the final hydrolysis step in a straightforward one-pot reaction. We have also succeeded in unravelling the FR mechanism. The FR, which is promoted by bases in protic solvents, is observed for a variety of polyhalogenated pyrrolidin-2-ones issued by ATRC of *N*-allyl-α-perchloroamides.[17,19,20] We have discovered that for an effective FR the configuration of the starting α,γ-halogenated 2-pyrrolidinones is critical and should be arranged in such a way that initial *endo*-elimination is possible. However, even for those substrates forced to undergo *exo*-eliminations, provided that at least one hydrogen atom is present at C(3), the FR can proceed.

The procedure, here reported, can also be fruitfully used for a short laboratory scale preparation of the versatile building-block pyrocinchonic anhydride. Computational investigations to confirm the proposed pathway and studies of the exact role of the 2-pyridyl substituent on the hydrolysis reaction are in progress and will be reported in due course.

5. Experimental

5.1. General

Reagents and solvents were standard grade commercial products, purchased from Aldrich, Acros, Fluka or RdH, and used without further purification, except acetonitrile and CH_2Cl_2 that were dried over three batches of 3 Å sieves (5% w/v, 12 h). The silica gel used for flash chromatography was Silica Gel 60 Merck (0.040–0.063 mm). *N*-Benzyl-3-chloro-2-propenylamine (as a 58/42 mixture of *E*/*Z* isomers) was prepared by *N*-alkylation of benzylamine with 1,3-dichloro-2-propene, following the procedure of Shipman.[46] 2,2-Dichloropalmitic (**6**)[17] acid and 2,2-dichloropropanoyl chloride (**11**)[25] were prepared according given procedures. ^1H NMR, IR and MS spectra were recorded on Bruker DPX 200 and Bruker Avance400, Perkin Elmer 1600 Series FTIR, and HP 5890 GC-HP 5989A MS instruments, respectively. The structural assignment of compounds **8b**, **13**, **18b**, **23a**, **23b** and **25** was determined by homonuclear Nuclear Overhauser Enhancement and heteronuclear H,C inverse-detection NMR correlation techniques. The direct and long-range H,C correlations on **13**, **18b** and **25** allowed us to unambiguously establish their regiochemistry, whereas NOESY experiments enabled the configuration of the double bond in **13** and **25**, and the relative stereochemistry at the C(3) and C(4) carbons in **8b**, **23a** and **23b**, to be determined.

5.2. Computational details

Molecular mechanics calculations were performed on SGI IRIX 6.5 Octane2 workstations using the implementation of

Amber all-atom force field (AMBER*) within the framework of Macromodel version 5.5.[47] The solvent effect was included by the implicit water GB/SA solvation model of Still et al.[48] The torsional space of each molecule was randomly varied with the usage-directed Monte Carlo conformational search of Chang-Guida-Still. For each search, at least 1000 starting structures for each variable torsion angle was generated and minimized until the gradient was less than 0.05 kJ/(Å mol). The cyclic moieties containing the amide bonds were also included into the search. Duplicate conformations and those with an energy in excess of 6 kcal/mol above the global minimum were discarded.

All DFT calculations were carried out using the standard tools available in the Gaussian 98 package,[49] with the DFT/B3LYP functional (i.e., Becke's three parameter hybrid functional with the Lee-Yang-Parr correlation functional)[50] and the 6-31G(d) basis set.

5.3. Preparation of 2-(3-chloro-2-propenylamino) pyridine

2-Aminopyridine (11.29 g, 120 mmol) was weighed in a Schlenk tube fitted with a perforable septum (blocked by a screw cap) and a stirring bar. Next, toluene (30 mL) and 1,3-dichloropropene (mixture of *E*/*Z* isomers, 5.55 mL, 60 mmol) were added under argon. The solution, under vigorous stirring, was heated at 100 °C. After 20 h, the reaction mixture was diluted with H_2O (30 mL) and petroleum ether (bp 40–60 °C; 30 mL). The organic layer was separated, whereas the aqueous phase was extracted with a 1/1 solution of toluene/petroleum ether (20 mL). The organic extracts were collected and concentrated under vacuum. The crude product was recovered (6.59 g, 65%) as a pale yellow liquid, which did not require further purification; bp 119–121 °C (0.6 mmHg). [Found: C, 57.0; H, 5.4; N, 16.7. $C_8H_9ClN_2$ requires C, 56.98; H, 5.38; N, 16.61]; ^1H NMR ($CDCl_3$, 200 MHz): δ trans isomer 3.96 (2H, dt, J=1.2, 5.9 Hz, NHCH_2), 4.7 (1H, br s, NH); 6.05 (1H, dt, J=13.8, 5.8 Hz, NHCH$_2$CH), 6.22 (1H, dt, J=13.8, 1.3 Hz, CHCl), 6.38 (1H, dt, J=8.4, 0.9 Hz, C(3)H), 6.60 (1H, ddd, J=7.3, 5.0, 0.9 Hz, C(5)H), 7.42 (1H, ddd, J=8.4, 7.3, 2.0 Hz, C(4)H), 8.09 (1H, ddd, J=5.0, 2.0, 0.9 Hz, C(6)H); cis isomer 4.13 (2H, dt, J=1.7, 6.1 Hz, NHCH_2), 4.8 (1H, br s, NH); 5.94 (1H, dt, J=7.5, 6.1 Hz, NHCH$_2$CH), 6.17 (1H, dt, J=7.5, 1.7 Hz, CHCl), 6.40 (1H, dt, J=8.4, 0.9 Hz, C(3)H), 6.60 (1H, ddd, J=7.3, 5.0, 0.9 Hz, C(5) H), 7.43 (1H, ddd, J=8.4, 7.3, 2.0 Hz, C(4)H), 8.09 (1H, ddd, J=5.0, 2.0, 0.9 Hz, C(6)H); *m*/*z* (EI): 168 (28%, M^+), 133 (100), 119 (40), 116 (10), 107 (12), 79 (22), 78 (30).

5.4. Preparation of *N*-benzyl-*N*-(3-chloro-2-propenyl)-2,2-dichloropropanamide (7b)

In a double-necked rounded bottom flask (100 mL), fitted with a dropping funnel and a reflux condenser, closed on the top with a $CaCl_2$ tube, CH_2Cl_2 (15.0 mL), *N*-benzyl-3-chloro-2-propenylamine (mixture of *E*/*Z* stereoisomers, 1.82 g, 10 mmol) and pyridine (1.0 mL, 12 mmol) were introduced. A CH_2Cl_2 (5 mL) solution of 2,2-dichloropropanoyl chloride (**12**) (1.61 g, 10 mmol) was then carefully added to the stirred solution cooled in a ice-bath (15 min). Next, the bath was removed and the reaction mixture left at room temperature, while stirring. After 20 h, the mixture was washed in sequence with HCl 2.5% w/v (2×15 mL) and NaOH 2.5% w/v (20 mL). The organic phase was then separated and concentrated. Flash-chromatography of the crude product on silica gel, using petroleum ether (bp 40–60 °C)–diethyl ether (9.5/0.5) as eluent, afforded 2.67 g of **7b** (87%), as a mixture of *E*/*Z* stereoisomers; pale yellow oil. [Found: C, 50.9; H, 4.6; N, 4.6. $C_{13}H_{14}Cl_3NO$ requires C, 50.92; H, 4.60; N, 4.57]; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.40 (3H, s, Cl$_2$CCH_3), 3.7–5.1 (4H, br m, CH_2NCH_2), 5.7–6.3 (2H, br m, CH=CH), 7.2–7.4 (5H, br s, Ar(H)); IR (film): 1660 (C=O) cm^{-1}; *m*/*z* (EI): 305 (3%, M^+), 270 (17), 230 (22), 91 (100).

5.5. Cyclisation of *N*-benzyl-*N*-(3-chloro-2-propenyl)-2,2-dichloropropanamide (7b)

CuCl (40 mg, 0.4 mmol) and the 2,2-dichloro-amide **7b** (1.23 g, 4 mmol) were weighted in a Schlenk tube fitted with a perforable septum (blocked by a screw cap) and a magnetic stirrer bar. Dry acetonitrile (4 mL) and TMEDA (121 μL, 0.8 mmol) were then added under argon. The mixture was stirred at room temperature and after 20 h diluted with HCl_{aq} 5% w/v (5 mL) and extracted with CH_2Cl_2 (3×6 mL). The combined organic layers were concentrated and the crude product was purified by flash chromatography on silica gel, eluting with a petroleum ether (bp 40–60 °C)–diethyl ether gradient (from 10/0 to 5/5). This gave the pyrrolidinones *cis*-**8b** (0.94 g, 76%), as a white crystalline solid, and *trans*-**8b** (0.24 g, 20%), as a yellow oil. The isomers could also be separated by crystallization from diethyl ether.

5.5.1. cis-N-Benzyl-3-chloro-4-dichloromethyl-3-methyl-2-pyrrolidinone (*cis*-8b). Mp 103–104 °C. [Found: C, 50.8; H, 4.6; N, 4.5. $C_{13}H_{14}Cl_3NO$ requires C, 50.92; H, 4.60; N, 4.57]; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.97 (3H, s, C(3) CH_3), 2.90 (1H, dt, J=7.3, 9.3 Hz, C(4)H), 3.08 (1H, dd, J=10.2, 9.2 Hz, C(5)H), 3.38 (1H, dd, J=10.2, 7.2 Hz, C(5)H), 4.38 (1H, d, J=14.7 Hz, N(1)CHAr), 4.66 (1H, d, J=14.7 Hz, N(1)CHAr), 5.98 (1H, d, J=9.4 Hz, C(4)CH), 7.20–7.40 (5H, m, CHAr); ^1H NMR (CD_3OD, 400 MHz): δ 1.92 (3H, s, C(3)CH_3), 3.15 (2H, m, C(4)H, C(5)H), 3.49 (1H, m, C(5)H), 4.34 (1H, d, J=14.8 Hz, N(1)CHAr), 4.71 (1H, d, J=14.8 Hz, N(1)CHAr), 6.20 (1H, m, C(4)CH), 7.24–7.40 (5H, m, CHAr); ^{13}C NMR (CD_3OD, 400 MHz): δ 26.30 (CH$_3$), 47.80 (NCH$_2$), 48.65 (NCH$_2$), 55.47 (C(4)), 69.94 (C(3)), 73.06 (C(4)CH), 129.05 (*Ar*), 129.11 (*Ar*), 129.95 (*Ar*), 136.61 (*Ar*), 172.63 (C=O); IR (KBr): 1707 (C=O) cm^{-1}; *m*/*z* (EI): 305 (3%, M^+), 270 (100), 187 (17), 186 (33), 91 (100).

5.5.2. trans-N-Benzyl-3-chloro-4-dichloromethyl-3-methyl-2-pyrrolidinone (*trans*-8b). [Found: C, 50.8; H, 4.6; N, 4.5. $C_{13}H_{14}Cl_3NO$ requires C, 50.92; H, 4.60; N, 4.57]; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.82 (3H, s, C(3)CH_3), 3.30 (2H, m, C(4)H, C(5)H), 3.62 (1H, m, C(5)H), 4.38 (1H, d, J=14.7 Hz, N(1)CHAr), 4.68 (1H, d, J=14.7 Hz, N(1)CHAr), 5.89 (1H, d, J=4.6 Hz, C(4)CH), 7.24–7.40 (5H, m, CHAr); ^1H NMR (CD_3OD, 400 MHz): δ 1.77 (3H, s, CH_3C(3)), 3.37 (2H, m, HC(4), HC(5)), 3.65

(1H, m, *H*C(5)), 4.47 (1H, d, *J*=14.6 Hz, N(1)C*H*Ar), 4.57 (1H, d, *J*=14.6 Hz, N(1)C*H*Ar), 6.33 (1H, d, *J*=5.3 Hz, C(4)C*H*), 7.27–7.40 (5H, m, C*H*Ar); ^{13}C NMR (CD$_3$OD, 400 MHz): *δ* 21.34 (*C*H$_3$), 46.98 (N*C*H$_2$), 48.02 (N*C*H$_2$), 56.34 (*C*(4)), 69.16 (*C*(3)), 72.60 (C(4)*C*H), 129.10 (*Ar*), 129.41 (*Ar*), 129.90 (*Ar*), 136.52 (*Ar*), 172.90 (*C*=O); IR (film): 1709 (C=O) cm^{-1}; *m*/*z* (EI): 305 (3%, M$^+$), 270 (100), 187 (17), 186 (33), 91 (100).

5.6. Rearrangement of *cis*-*N*-benzyl-3-chloro-4-dichloromethyl-3-methyl-2-pyrrolidinone (*cis*-8b)

In a Schlenk tube, fitted with a perforable septum blocked by a screw cap, ethyl ether/CH$_3$OH 2:1 (3 mL) and *cis*-**8b** (0.61 g, 2 mmol) were added. The solution was thermostated at 25 °C. Apart, in a second Schlenk tube, Na^0 (0.184 g, 8 mmol) was carefully dissolved in CH$_3$OH (3 mL), and when the effervescence ceased, the alkaline solution was thermostated at 25 °C, after which it was poured into the first Schlenk tube. The reaction mixture was stirred for 20 h. Then it was diluted with water (2 mL) and extracted with CH$_2$Cl$_2$ (3×5 mL). The combined organic layers were collected and concentrated. Flash-chromatography of the crude product on silica gel, using a petroleum ether (bp 40–60 °C)/diethyl ether gradient (from 10/0 to 5/5) as eluent, afforded *N*-benzyl-5,5-dimethoxy-3,4-dimethyl-3-pyrrolin-2-one (**9b**) (0.514 g, 98%), as a pale yellow microcrystalline solid. Mp 63–64 °C. [Found: C, 68.7; H, 7.3; N, 5.4. C$_{15}$H$_{19}$NO$_3$ requires C, 68.94; H, 7.33; N, 5.36]; ^{1}H NMR (CDCl$_3$, 400 MHz): *δ* 1.77 (3H, q, *J*=1.2 Hz, C(4)C*H*$_3$), 1.90 (3H, q, *J*=1.3 Hz, C(3)C*H*$_3$), 2.78 (6H, s, OC*H*$_3$), 4.37 (2H, s, NC*H*$_2$Ar), 7.27–7.40 (5H, m, C*H*Ar), ^{13}C NMR (CDCl$_3$, 400 MHz): *δ* 8.02 (C(3)*C*H$_3$), 9.07 (C(4)*C*H$_3$), 41.40 (*C*H$_2$), 50.51 (O*C*H$_3$), 112.73 (*C*(5)), 127.17 (*C*(4′)Ar), 128.09 (*C*(3′)Ar, *C*(5′)Ar), 129.34 (*C*(2′)Ar, *C*(6′)Ar), 132.70 (*C*(3)), 137.39 (*C*(1′)Ar), 144.06 (*C*(4)), 170.13 (*C*=O); IR (KBr): 1712 (C=O) cm^{-1}; *m*/*z* (EI): 262 (8%, M$^+$+1), 261 (43), 231 (12), 230 (45), 214 (24), 202 (15), 156 (13), 141 (38), 91 (100).

Following the previous procedure but carrying out the work up after 2 min at 25 °C we succeeded in isolating the *N*-benzyl-4-chloromethyl-3-methyl-5-methoxy-3-pyrrolin-2-one (**18b**) (as the main product in the reaction mixture), as a colourless oil. [Found: C, 63.1; H, 6.1; N, 5.3. C$_{14}$H$_{16}$ClNO$_2$ requires C, 63.28; H, 6.07; N, 5.27]; ^{1}H NMR (CDCl$_3$, 400 MHz): *δ* 2.01 (3H, t, *J*=1.1 Hz, C(3)C*H*$_3$), 3.02 (3H, s, OC*H*$_3$), 4.18 (1H, d, *J*=14.8 Hz, NC*H*Ar), 4.19 (1H, dq, *J*=12.0, 1.1 Hz, C*H*Cl), 4.33 (1H, d, *J*=12.0 Hz, C*H*Cl), 4.98 (1H, d, *J*=14.8 Hz, NC*H*Ar), 5.31 (1H, q, *J*=1.1 Hz, *H*C(5)), 7.20–7.40 (5H, m, C*H*Ar); ^{13}C NMR (400 MHz, CDCl$_3$): 8.92 (*C*H$_3$), 35.18 (*C*H$_2$Cl), 43.62 (N*C*H$_2$), 50.48 (O*C*H$_3$), 86.0 (*C*(5)), 127.62 (*Ar*), 128.44 (*Ar*), 128.70 (*Ar*), 136.16 (*C*(3)), 136.81 (*Ar*), 143.55 (*C*(4)) 169.58 (*C*=O); IR (film) 1695 (C=O) cm^{-1}; *m*/*z* (EI): 265 (31%, M$^+$), 250 (3), 235 (14), 234 (18), 233 (22), 230 (44), 200 (10), 170 (12), 91 (100).

5.7. Rearrangement of *trans*-*N*-benzyl-3-chloro-4-dichloromethyl-3-methyl-2-pyrrolidinone (*trans*-8b)

Following the procedure for the rearrangement of *cis*-**8b**, *trans*-**8b** (0.61 g, 2 mmol) gave (*E*)-*N*-benzyl-4-chloromethylen-3-methoxy-3-methyl-2-pyrrolidinone (**13**) (0.41 g, 77%), as a colourless oil. [Found: C, 63.1; H, 6.1; N, 5.3. C$_{14}$H$_{16}$ClNO$_2$ requires C, 63.28; H, 6.07; N, 5.27]; ^{1}H NMR (CDCl$_3$, 400 MHz): *δ* 1.48 (3H, s, C(3)C*H*$_3$), 3.17 (3H, s, OC*H*$_3$), 3.82 (1H, dd, *J*=15.3, 2.7 Hz, C(5)*H*$_2$), 3.92 (1H, dd, *J*=15.3, 2.7 Hz, C(5)*H*$_2$), 4.53 (1H, d, *J*=14.6 Hz, NC*H*$_2$Ar), 4.61 (1H, d, *J*=14.6 Hz, NC*H*$_2$Ar), 6.30 (1H, t, *J*=2.7 Hz, C=C*H*Cl), 7.20–7.40 (5H, m, Ar*H*); ^{13}C NMR (CDCl$_3$, 400 MHz): *δ* 24.80 (C(3)*C*H$_3$), 46.51 (*C*H$_2$Ar), 46.98 (*C*(5)), 52.38 (O*C*H$_3$), 80.14 (*C*(3)), 116.48 (C=*C*HCl), 127.78 (*C*Ar), 127.96 (*C*Ar), 128.70 (*C*Ar), 135.08 (*C*Ar), 136.26 (*C*(4)), 171.95 (*C*=O); IR (film): 1707 (C=O) cm^{-1}; *m*/*z* (EI): 265 (1%, M$^+$), 235 (24), 230 (96), 229 (38), 214 (6), 174 (7), 132 (38), 97 (100), 91 (63).

Following the previous procedure but carrying out the work up after 1 h at 25 °C we succeeded in isolating a small amount of (*E*)-*N*-benzyl-4-chloromethyl-3-methoxy-3-methyl-2-pyrrolidinone (**11b**) (as the second main product in the reaction mixture after **13**), as a colourless oil. [Found: C, 58.0; H, 4.9; N, 5.2. C$_{13}$H$_{13}$Cl$_2$NO requires C, 57.80; H, 4.85; N, 5.18]; ^{1}H NMR (CDCl$_3$, 200 MHz): *δ* 1.89 (3H, s, C(3)C*H*$_3$), 3.90 (1H, dd, *J*=14.9, 2.5 Hz, C(5)*H*$_2$), 4.00 (1H, dd, *J*=14.9, 2.5 Hz, C(5)*H*$_2$), 4.48 (1H, d, *J*=14.7 Hz, NC*H*$_2$Ar), 4.69 (1H, d, *J*=14.7 Hz, NC*H*$_2$Ar), 6.54 (1H, t, *J*=2.5 Hz, C=C*H*Cl), 7.23–7.42 (5H, m, Ar*H*); IR (film) 1715 (C=O) cm^{-1}; *m*/*z* (EI): 269 (10%, M$^+$), 234 (100), 125 (17), 91 (83), 65 (23).

5.8. Hydrolysis of *N*-benzyl-5,5-dimethoxy-3,4-dimethyl-3-pyrrolin-2-one (9b)

In a Schlenk tube, were added acetal **9b** (0.52 g, 1 mmol), acetic acid (0.5 mL) and methanesulfonic acid (0.5 mL). The mixture, under vigorous stirring, was heated to 140 °C for 20 h, after which time it was diluted with H$_2$O (4 mL) and then extracted with CH$_2$Cl$_2$ (3×4 mL). The combined organic layers were concentrated under vacuum. Flash chromatography of the crude product on silica gel, using a petroleum ether (bp 40–60 °C)–ethyl acetate gradient (from 10/0 to 8.5/1.5) as eluent, gave 3,4-dimethylmaleic anhydride (**3b**) (0.10 g, 79%), as a pale brown microcristalline solid. Mp 92–94 °C. The MS spectrum is consistent with that of an authentical sample purchased from Aldrich.

5.9. Preparation of *N*-(3-chloro-2-propenyl)-*N*-(2-pyridyl)-2,2-dichloropropanamide (22b)

In a double-necked round bottom flask (100 mL), fitted with a dropping funnel and a reflux condenser, closed on the top with a CaCl$_2$ tube, CH$_2$Cl$_2$ (20 mL), 2-(3-chloro-2-propenylamino)pyridine (mixture of *E*/*Z* stereoisomers, 4.22 g, 25 mmol) and pyridine (2.43 mL, 30 mmol) were introduced. A CH$_2$Cl$_2$ (5 mL) solution of 2,2-dichloropropanoyl chloride (**12**) (4.84 g, 30 mmol) was then carefully added to the stirred solution cooled in a ice-bath (15 min). Next, the bath was removed and the reaction mixture left at room temperature, under stirring. After 20 h, the mixture was diluted with brine–H$_2$O (10 mL/20 mL) and basified with NaOH (pellets). Then diethyl ether (40 mL) was added. The organic phase was separated while the aqueous layer was further washed with diethyl ether–CH$_2$Cl$_2$ (1/1, 3× 20 mL). The combined organic extracts were finally concentrated under reduced pressure. Flash chromatography of the crude product on silica gel, using a petroleum ether (bp 40–60 °C)–diethyl ether gradient (from 10/0 to 7/3) as eluent, gave amide **22b** (6.53 g, 89%, mixture of two *E*/*Z* stereoisomers) as a pale yellow oil. [Found: C, 45.1; H, 3.7; N, 9.4. $C_{11}H_{11}Cl_3N_2O$ requires C, 45.00; H, 3.78; N, 9.54]; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.35 (3H, s, *trans* CCl_2CH_3), 4.78 (2H, d, $J=5.8$ Hz, *trans* $C{=}CCH_2N$), 4.94 (2H, dd, $J=6.1$, 1.5 Hz, *cis* $C{=}CCH_2N$), 5.91–6.14 (2H, m, *cis*+*trans* $HC{=}CH$), 7.26 (1H, ddd, $J=7.3$, 4.9, 1.1 Hz, C(5′)Ar*H*), 7.41 (1H, dt, $J=8.4$, 1.1 Hz, C(3′)Ar*H*), 7.76 (1H, ddd, $J=8.4$, 7.3, 2.0 Hz, C(4′)Ar*H*), 8.54 (1H, ddd, $J=4.9$, 2.0, 1.1 Hz, C(6′)Ar*H*); IR (film): 1670 (C=O) cm^{-1}; *m*/*z* (EI): 292 (13%, M$^+$), 257 (68), 167 (42), 131 (100), 78 (30), 75 (33).

5.10. Cyclisation of *N*-(3-chloro-2-propenyl)-*N*-(2-pyridyl)-2,2-dichloropropanamide (22b)

CuCl (99 mg, 1 mmol) and the 2,2-dichloroamide **22b** (2.94 g, 10 mmol) were weighed in a Schlenk tube fitted with a perforable septum (blocked by a screw cap) and a magnetic stirrer bar. Dry acetonitrile (10 mL) and TMEDA (302 μL, 2 mmol) were then added under argon. The mixture was stirred at room temperature and after 20 h diluted with $NaOH_{aq}$ (0.3% w/v, 20 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were concentrated and the crude product was purified by flash chromatography on silica gel, eluting with petroleum ether (bp 40–60 °C)–diethyl ether gradient (from 10/0 to 8/2). This gave the pyrrolidinones *cis*-**23b** (1.82 g, 62%), as a pale orange crystalline solid, and *trans*-**23b** (0.76 g, 26%), as an orange solid.

5.10.1. cis-N-(2-Pyridyl)-3-chloro-4-dichloromethyl-3-methyl-2-pyrrolidinone (*cis*-23b). Mp 112–114 °C. [Found: C, 45.1; H, 3.8; N, 9.5. $C_{11}H_{11}Cl_3N_2O$ requires C, 45.00; H, 3.78; N, 9.54]; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.02 (3H, s. C(3)C*H*$_3$), 3.02 (1H, dt, $J=9.8$, 7.4 Hz, C(4)*H*), 3.73 (1H, dd, $J=12.0$, 9.9 Hz, C(5)*H*), 4.54 (1H, dd, $J=12.0$, 7.4 Hz, C(5)*H*), 6.11 (1H, d, $J=9.7$ Hz, C(4)C*H*Cl$_2$), 7.12 (1H, ddd, $J=7.3$, 5.0, 1.2 Hz, C(5′)Ar*H*), 7.74 (1H, ddd, $J=8.5$, 7.3, 2.1 Hz, C(4′)Ar*H*), 8.37 (1H, dt, $J=8.5$, 1.0 Hz, C(3′)Ar*H*), 8.39 (1H, ddd, $J=5.0$, 2.1, 0.9 Hz, C(6′)Ar*H*); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 25.87 (C(3)*C*H$_3$), 47.33 (*C*(5)), 53.93 (*C*(4)), 69.66 (*C*(3)), 71.36 (C(4)*C*HCl$_2$), 115.09 (*C*(3′)Ar), 120.65 (*C*(5′)Ar), 138.05 (*C*(4′)Ar), 147.77 (*C*(6′)Ar), 150.70 (*C*(2′)Ar), 169.66 (*C*=O); IR (KBr): 1706 (C=O) cm^{-1}; *m*/*z* (EI): 292 (8%, M$^+$), 257 (5), 209 (23), 173 (100), 145 (23).

5.10.2. trans-N-(2-Pyridyl)-3-chloro-4-dichloromethyl-3-methyl-2-pyrrolidinone (*trans*-23b). Mp 104–105 °C. [Found: C, 45.1; H, 3.8; N, 9.5. $C_{11}H_{11}Cl_3N_2O$ requires C, 45.00; H, 3.78; N, 9.54]; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.89 (3H, s. C(3)C*H*$_3$), 3.41 (1H, dt, $J=7.4$, 4.3 Hz, C(4)*H*), 4.32 (1H, dd, $J=12.3$, 4.1 Hz, C(5)*H*), 4.43 (1H, dd, $J=12.3$, 7.4 Hz, C(5)*H*), 5.99 (1H, d, $J=4.4$ Hz, C(4)C*H*Cl$_2$), 7.12 (1H, ddd, $J=7.3$, 4.8, 1.2 Hz, C(5′)Ar*H*), 7.74 (1H, ddd, $J=8.5$, 7.3, 2.1 Hz, C(4′)Ar*H*), 8.39 (1H, dt, $J=8.5$, 1.0 Hz, C(3′)Ar*H*), 8.41 (1H, ddd, $J=4.8$, 2.1, 0.9 Hz, C(6′)Ar*H*); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 21.19 (C(3)*C*H$_3$), 45.51 (*C*(5)), 54.00 (*C*(4)), 68.45 (*C*(3)), 70.82 (C(4)*C*HCl$_2$), 114.97 (*C*(3′)Ar), 120.51 (*C*(5′)Ar), 137.98 (*C*(4′)Ar), 147.77 (*C*(6′)Ar), 150.83 (*C*(2′)Ar), 169.72 (*C*=O); IR (KBr): 1717 (C=O) cm^{-1}; *m*/*z* (EI): 292 (8%, M$^+$), 257 (5), 209 (23), 173 (100), 145 (23).

5.11. Rearrangement of *N*-(2-pyridyl)-3-chloro-4-dichloromethyl-3-methyl-2-pyrrolidinone (23b)

Following the procedure for the rearrangement of *cis*-**8b**, **23b** (mixture 71/29 of cis/trans stereoisomers, 0.59 g, 2 mmol) gave the 3-pyrrolin-2-one **24b** (0.34 g, 68%), as a pale brown solid, and the lactam **25** (0.11 g, 21%), as a yellow oil.

5.11.1. N-(2-Pyridyl)-5,5-dimethoxy-3,4-dimethyl-3-pyrrolin-2-one (24b). Mp 70-72 °C. [Found: C, 63.1; H, 6.5; N, 11.2. $C_{13}H_{16}N_2O_3$ requires C, 62.89; H, 6.50; N, 11.28]; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.87 (3H, q, $J=1.2$ Hz, C(4)C*H*$_3$), 1.96 (3H, q, $J=1.2$ Hz, C(3)C*H*$_3$), 3.14 (6H, s, C(5)OC*H*$_3$), 7.11 (1H, ddd, $J=7.3$, 5.0, 1.2 Hz, C(5′)Ar*H*), 7.64 (1H, dt, $J=8.5$, 1.0 Hz, C(3′)Ar*H*), 7.71 (1H, ddd, $J=8.5$, 7.3, 2.1 Hz, C(4′)Ar*H*), 8.54 (1H, ddd, $J=5.0$, 2.1, 1.2 Hz, C(6′)Ar*H*); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 8.19 (C(3)*C*H$_3$), 9.25 (C(4)*C*H$_3$), 51.09 (O*C*H$_3$), 113.93 (*C*(5)), 117.05 (*C*(3′)Ar), 120.57 (*C*(5′)Ar), 132.37 (*C*(3)), 137.69 (*C*(4′)Ar), 145.46 (*C*(4)), 148.90 (*C*(6′)Ar), 149.57 (*C*(2′)Ar), 169.16 (*C*=O); IR (KBr): 1713 (C=O) cm^{-1}; *m*/*z* (EI): 248 (1%, M$^+$), 233 (5), 217 (39), 203 (100), 135(12), 78 (23).

5.11.2. (E)-N-(2-Pyridyl)-4-chloromethylen-3-methoxy-3-methyl-2-pyrrolidinone (25). [Found: C, 57.1; H, 5.2; N, 11.0. $C_{12}H_{13}ClN_2O_2$ requires C, 57.04; H, 5.19; N, 11.09]; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.56 (3H, s, C(3)C*H*$_3$), 3.26 (3H, s, C(3)OC*H*$_3$), 4.63 (1H, dd, $J=17.0$, 2.8 Hz, C(5)*H*), 4.81 (1H, dd, $J=17.0$, 2.6 Hz, C(5)*H*), 6.39 (1H, t, $J=2.7$ Hz, C=C*H*Cl), 7.12 (1H, ddd, $J=7.3$, 5.0, 0.9 Hz, C(5′)Ar*H*), 7.75 (1H, ddd, $J=8.5$, 7.3, 2.1 Hz, C(4′)Ar*H*), 8.42 (1H, ddd, $J=5.0$, 2.1, 0.9 Hz, C(6′)Ar*H*), 8.53 (1H, dt, $J=8.5$, 1.0 Hz, C(3′)Ar*H*); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 25.37 (C(3)*C*H$_3$), 47.72 (*C*(5)), 52.83 (O*C*H$_3$), 81.71 (*C*(3)), 115.16 (*C*(3′)Ar), 116.83 (C=*C*HCl), 120.45 (*C*(5′)Ar), 135.53 (*C*(4)=CHCl), 137.96 (*C*(4′)Ar), 147.73 (*C*(6′)Ar), 150.75 (*C*(2′)Ar), 172.35 (*C*=O); IR (film): 1723 (C=O) cm^{-1}; *m*/*z* (EI): 252 (19%, M$^+$), 222 (19), 217 (43), 216 (32), 189 (9), 185 (10), 173 (18), 157 (15), 132 (32), 97 (100), 78 (31).

5.12. One-pot preparation of 3,4-dimethylmaleic anhydride (3b)

Pyrrolidin-2-one **24b** (a 71/29 mixture of cis/trans stereoisomers, 1.18 g, 4 mmol) was first rearranged following the procedure described for the rearrangement of *cis*-**8b**. After the 20 h period at 25 °C, the solvent was removed under vacuum and the residue treated with H_2SO_4 4 N (4 mL). The resulting mixture was then heated at 110 °C for 1 h, after which time it was extracted with CH_2Cl_2 (3×3 mL). The combined organic layers were concentrated under vacuum, giving anhydride **3b** (0.29 g, 57%).

5.13. Preparation of *N*-(3-chloro-2-propenyl)-*N*-(2-pyridyl)-2,2-dichlorohexadecanamide (22a)

2,2-Dichlorohexadecanoic acid (**6**) (6.51 g, 20 mmol) was weighed in a Schlenk tube fitted with a perforable septum (blocked by a screw cap) and a $CaCl_2$ tube on the side arm. Next, dry CH_2Cl_2 (10.5 mL) was added under argon. The solution was thermostated at 23 °C, and while stirring, DMF (33 μL) and $(COCl)_2$ (2.64 mL, 40 mmol) were injected using a syringe. The side arm stopcock was opened to vent out any gases (CO, CO_2 and HCl) produced during the reaction. After 2 h, solvent and excess oxalyl chloride were removed under reduced pressure. The crude acyl chloride was diluted with dry CH_2Cl_2 (10 mL), then the solution, thermostated at 23 °C, was treated with a solution of pyridine (3.49 mL, 40 mmol) and 2-(3-chloro-2-propenylamino)pyridine (mixture of *E*/*Z* stereoisomers, 7.60 g, 45 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred for 2 h and then washed with NaOH 1 M (2× 20 mL). Next, the organic phase was recovered and concentrated. Flash chromatography of the crude product on silica gel, using a petroleum ether (bp 40–60 °C)–diethyl ether gradient (from 10/0 to 9/1) as eluent, gave amide **22a** (8.95 g, 94%, mixture of two *E*/*Z* stereoisomers), as a yellow oil. [Found: C, 60.7; H, 7.7; N, 5.9. $C_{24}H_{37}Cl_3N_2O$ requires C, 60.57; H, 7.84; N, 5.89]; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.89 (3H, t, $J=6.5$ Hz, $CH_2CH_2CH_3$), 1.27 (22H, br s, $(CH_2)_n$), 1.62 (2H, qn, $J=7.1$ Hz, CCl_2CH_2-CH_2), 2.49 (2H, m, CCl_2CH_2) 4.70 (1H, d, $J=5.8$ Hz, *trans* $C{=}CCH_2N$), 4.87 (1H, dd, $J=6.2$, 1.4 Hz, *cis* $C{=}CCH_2N$), 5.93–6.16 (2H, m, *cis*+*trans* $HC{=}CH$), 7.25 (1H, ddd, $J=7.3$, 4.9, 1.1 Hz, C(5′)Ar*H*), 7.41 (1H, dt, $J=8.4$, 1.1 Hz, C(3′)Ar*H*), 7.76 (1H, ddd, $J=8.4$, 7.3, 2.0 Hz, C(4′)Ar*H*), 8.54 (1H, ddd, $J=4.9$, 2.0, 1.1 Hz, C(6′)Ar*H*); IR (film): 1669 (C=O) cm^{-1}; *m*/*z* (EI): 475 (11%, $M^+ + 1$), 439 (100), 403 (25), 257 (38), 195 (47), 167 (72), 131 (94), 75 (43).

5.14. Cyclisation of *N*-(3-chloro-2-propenyl)-*N*-(2-pyridyl)-2,2-dichlorohexadecanamide (22a)

CuCl (99 mg, 1 mmol) and **22a** (4.76 g, 10 mmol) were weighed into a Schlenk tube fitted with a perforable septum (blocked by a screw cap). Dry acetonitrile (10 mL) and TMEDA (302 μL, 2 mmol) were then added, under argon. The mixture was stirred at 60 °C and after 20 h the mixture was diluted with $NaOH_{aq}$ 0.3% w/v (20 mL) and extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were concentrated and the crude product was purified by flash chromatography on silica gel, eluting with petroleum ether (bp 40–60 °C)–ethyl acetate gradient (from 10/0 to 9.4/0.6). This gave the pyrrolidinone **23a** (4.43 g, 93%), as an 90/10 (^1H NMR spectrum) mixture of inseparable *cis*-/*trans*-diastereoisomers; pale yellow oil. [Found: C, 60.7; H, 7.9; N, 5.9. $C_{24}H_{37}Cl_3N_2O$ requires C, 60.57; H, 7.84; N, 5.89]; ^1H NMR ($CDCl_3$, 400 MHz): *cis* diastereoisomer (90%) δ 0.89 (3H, t, $J=6.5$ Hz, $CH_2CH_2CH_3$), 1.10–1.60 (24H, br m, $C(3)CH_2(CH_2)_{12}CH_3$), 2.40 (2H, m, $C(3)CH_2$), 3.23 (1H, dt, $J=7.5$, 9.3 Hz, C(4)*H*), 3.73 (1H, dd, $J=9.4$, 11.6 Hz, C(5)*H*), 4.50 (1H, dd, $J=7.5$, 11.6 Hz, C(5)*H*), 6.10 (1H, d, $J=9.3$ Hz, $CHCl_2$), 7.09 (1H, ddd, $J=7.4$, 4.9, 1.0 Hz, C(5′)Ar*H*), 7.70 (1H, ddd, $J=8.4$, 7.4, 1.9 Hz, C(4′)Ar*H*), 8.37 (2H, m, C(3′)Ar*H*, C(6′)Ar*H*), ^{13}C NMR ($CDCl_3$, 400 MHz): δ 14.07 (CH_3), 22.63 (CH_3CH_2), 25.52 ($C(3)CH_2CH_2$), 29.17, 29.30, 29.40, 29.44, 29.52, 29.59 ($(CH_2)_9$), 31.86 ($CH_3CH_2CH_2$), 37.14 ($C(3)CH_2$), 47.00 (*C*(5)), 48.37 (*C*(4)), 71.60 ($CHCl_2$), 73.26 (*C*(3)), 114.99 (*C*(3′)Ar), 120.48 (*C*(5′)Ar), 137.87 (*C*(4′)Ar), 147.64 (*C*(6′)Ar), 150.68 (*C*(2′)Ar), 168.95 (*C*=O); ^1H NMR ($CDCl_3$, 400 MHz): *trans* diastereoisomer (10%) δ 0.89 (3H, t, $J=6.5$ Hz, $CH_2CH_2CH_3$), 1.10–1.60 (24H, br m, $C(3)CH_2(CH_2)_{12}CH_3$), 2.40 (2H, m, $C(3)CH_2$), 3.34 (1H, dt, $J=4.2$, 5.5 Hz, C(4)*H*), 4.37 (2H, d, $J=5.5$ Hz, $C(5)H_2$), 5.98 (1H, $J=4.2$ Hz, $CHCl_2$), 7.09 (1H, ddd, $J=7.4$, 4.9, 1.0 Hz, C(5′)Ar*H*), 7.70 (1H, ddd, $J=8.4$, 7.4, 1.9 Hz, C(4′)Ar*H*), 8.37 (2H, m, C(3′)Ar*H*, C(6′)Ar*H*), ^{13}C NMR ($CDCl_3$, 400 MHz): δ 14.07 (CH_3), 22.63 (CH_3CH_2), 24.42 ($C(3)CH_2CH_2CH_2$), 29.17, 29.30, 29.40, 29.44, 29.52, 29.59 ($(CH_2)_9$), 31.66 ($CH_3CH_2CH_2$), 32.95 ($C(3)CH_2$), 45.37 (*C*(5)), 53.34 (*C*(4)), 70.51 ($CHCl_2$), 72.66 (*C*(3)), 114.81 (*C*(3′)Ar), 120.26 (*C*(5′)Ar), 137.87 (*C*(4′)Ar), 147.64 (*C*(6′)Ar), 150.68 (*C*(2′)Ar), 169.04 (*C*=O); IR (film) 1726 (C=O) cm^{-1}; *m*/*z* (EI): 475 (2%, $M+H^+$), 439 (39), 369 (18), 355 (53), 280 (25), 278 (26), 195 (100).

5.15. One-pot preparation of 3-tetradecyl-4-methylmaleic anhydride (chaetomellic anhydride A) (3a)

In a Schlenk tube, fitted with a perforable septum blocked by a screw cap, ethyl ether/CH_3OH 1:1 (1.6 mL) and **23a** (0.48 g, 1 mmol) were added. The solution was thermostated at 25 °C. In a second Schlenk tube, Na^0 (92 mg, 4 mmol) was carefully dissolved in CH_3OH (1.5 mL), and when the effervescence ceased, the alkaline solution was thermostated at 25 °C, after which it was poured into the first Schlenk tube. The reaction mixture was stirred for 20 h. Next, in the same Schlenk tube, was added H_2SO_4 (4 N, 0.25 mL), the solvent removed under vacuum and the residue treated with H_2SO_4 (4 N, 0.75 mL) and water (0.25 mL). The mixture was then heated at 110 °C for 2 h (under a current of argon to remove CH_3OH released from hydrolysis of **23a**), after which time it was diluted with H_2O (2 mL) and extracted with CH_2Cl_2 (3×3 mL) and the combined organic layers concentrated under reduced pressure. Flash chromatography of the crude product on silica gel, using a petroleum ether (bp 40–60 °C)–ethyl acetate gradient (from 10/0 to 9/1), gave **3a** (0.24 g, 78%),[1] as a pale yellow oil. [Found: 73.86; H, 10.52. $C_{19}H_{32}O_3$ requires C, 73.98; H, 10.46]; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.88 (3H, t, $J=6.7$ Hz, $CH_2CH_2CH_2CH_3$), 1.25 (22H, br s, $CH_2(CH_2)_9CH_2$), 1.57 (2H, m, $C(3)CH_2CH_2$), 2.07 (3H, s, $C(4)CH_3$), 2.45 (2H, t, $J=7.6$ Hz, $C(3)CH_2$); IR (film): 1766 (C=O) cm^{-1}; *m*/*z* (EI): 308 (5, M^+), 290 (15), 280 (4), 263 (7), 235 (8), 150 (33), 126 (100), 43 (45).

Acknowledgements

We thank the Ministero della Università e della Ricerca Scientifica e Tecnologica (MURST) for financial assistance, and the Fondazione Cassa di Risparmio di Modena for the financial support given for the acquisition of the Bruker Avance400 Spectrometer.

References and notes

1. Singh, S. B.; Zink, D. L.; Liesch, J. M.; Goetz, M. A.; Jenkins, R. G.; Nallin-Omstead, M.; Silverman, K. C.; Bills, G. F.; Mosley, R. T.; Gibbs, J. B.; Albers-Schonberg, G.; Lingham, R. B. *Tetrahedron* **1993**, *49*, 5917–5926.
2. Singh, S. B.; Jayasuriya, H.; Silverman, K. C.; Bonfiglio, C. A.; Williamson, J. M.; Lingham, R. B. *Bioorg. Med. Chem.* **2000**, *8*, 571–580.
3. Scholte, A. A.; Eubanks, L. M.; Poulter, C. D.; Vederas, J. C. *Bioorg. Med. Chem.* **2004**, *12*, 763–770.
4. Mau, C. J. D.; Garneau, S.; Scholte, A. A.; Van Fleet, J. E.; Vederas, J. C.; Cornish, K. *Eur. J. Biochem.* **2003**, *270*, 3939–3945.
5. Garneau, S.; Qiao, L.; Chen, L.; Walker, S.; Vederas, J. C. *Bioorg. Med. Chem.* **2004**, *12*, 6473–6494.
6. Kar, A.; Argade, N. P. *J. Org. Chem.* **2002**, *67*, 7131–7134.
7. Deshpande, A. M.; Natu, A. A.; Argade, N. P. *J. Org. Chem.* **1998**, *63*, 9557–9558.
8. Slade, R. M.; Branchaud, B. P. *J. Org. Chem.* **1998**, *63*, 3544–3549.
9. Desai, S. B.; Argade, N. P. *J. Org. Chem.* **1997**, *62*, 4862–4863.
10. Poigny, S.; Guyot, M.; Samadi, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2175–2177.
11. Ratemi, E. S.; Dolence, J. M.; Poulter, C. D.; Vederas, J. C. *J. Org. Chem.* **1996**, *61*, 6296–6301.
12. Kates, M. J.; Schauble, J. H. *J. Org. Chem.* **1996**, *61*, 4164–4167.
13. Argade, N. P.; Naik, R. H. *Bioorg. Med. Chem.* **1996**, *4*, 881–883.
14. Argade, N. P.; Naik, R. H. Indian Patent IN 184694; *Chem. Abstr*. **2004**, *141*, 260541.
15. Slade, R. M.; Branchaud, B. P. *Tetrahedron Lett.* **1994**, *35*, 4071–4072.
16. Singh, S. B. *Tetrahedron Lett.* **1993**, *34*, 6521–6524.
17. De Buyck, L.; Cagnoli, R.; Ghelfi, F.; Merighi, G.; Mucci, A.; Pagnoni, U. M.; Parsons, A. F. *Synthesis* **2004**, 1680–1686.
18. Clark, A. J. *Chem. Soc. Rev.* **2002**, *31*, 1–11.
19. Ghelfi, F.; Stevens, C.; Laureyn, I.; Van Meenen, E.; Rogge, T. M.; De Buyck, L.; Nikitin, K. V.; Grandi, R.; Libertini, M. C.; Pagnoni, U. M.; Schenetti, L. *Tetrahedron* **2003**, *59*, 1147–1157.
20. De Buyck, L.; Danieli, C.; Ghelfi, F.; Pagnoni, U. M.; Parsons, A. F.; Pattarozzi, M.; Roncaglia, F. *Tetrahedron* **2005**, *60*, 2871–2877.
21. Mangaleswaran, S.; Argade, N. P. *Synthesis* **2002**, 865–868.
22. Benedetti, M.; Forti, L.; Ghelfi, F.; Pagnoni, U. M.; Ronzoni, R. *Tetrahedron* **1997**, *53*, 14031–14042.
23. Bellesia, F.; Forti, L.; Ghelfi, F.; Ghirardini, G.; Libertini, E.; Pagnoni, U. M.; Pinetti, A.; Prochilo, N. *Synth. Commun.* **1999**, *29*, 3739–3748.
24. Iwamatsu, S.; Kondo, H.; Matsubara, K.; Nagashima, H. *Tetrahedron* **1999**, *55*, 1687–1706.
25. Ghelfi, F.; Bellesia, F.; Forti, L.; Ghirardini, G.; Grandi, R.; Libertini, E.; Montemaggi, M. C.; Pagnoni, U. M.; Pinetti, A.; De Buyck, L.; Parsons, A. F. *Tetrahedron* **1999**, *55*, 5839–5852.
26. Slough, G. A. *Tetrahedron Lett.* **1993**, *34*, 6825–6828.
27. Planas, L.; Viret, J. P.; Royer, J. *J. Org. Chem.* **2004**, *69*, 3087–3092.
28. Baker, J. T.; Sifniades, S. *J. Org. Chem.* **1979**, *44*, 2798–2800.
29. Schmidlin, T.; Tamm, C. *Helv. Chim. Acta* **1980**, *63*, 121–131.
30. Dudot, B.; Micouin, L.; Baussanne, I.; Royer, J. *Synthesis* **1999**, 688–694.
31. Ciavatta, M. L.; Villani, G.; Trivellone, E.; Cimino, G. *Tetrahedron Lett.* **1995**, *36*, 8673–8676.
32. Cardillo, G.; Fabbroni, S.; Gentilucci, L.; Perciaccante, R.; Tolomelli, A. *Tetrahedron: Asymmetry* **2005**, *15*, 593–601.
33. Kim, S.; Lim, C. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 5378–5380.
34. Domingo, L. R.; Gil, S.; Parra, M.; Sáez, J. A.; Torres, M. *Tetrahedron* **2003**, *59*, 6233–6239.
35. Nesmeyanov, A. N.; Freidlina, R. K.; Zarharkin, L. I. *Quart. Rev.* **1956**, *10*, 330–370.
36. Cason, J.; Allinger, N. L.; Sumrell, G. *J. Org. Chem.* **1953**, *18*, 850–856.
37. Owen, L. N.; Sultanbawa, M. U. S. *J. Chem. Soc.* **1949**, 3105–3109.
38. Owen, L. N.; Sultanbawa, M. U. S. *J. Chem. Soc.* **1949**, 3089–3098.
39. Ingold, K. J.; Rothstein, E. *J. Chem. Soc.* **1929**, 8–14.
40. Smith, M. B.; March, J. *March's Advanced Organic Chemistry*; Wiley: New York, 2001; pp 421–423.
41. Kormos, B. L.; Cramer, C. J. *J. Org. Chem.* **2003**, *68*, 6375–6386.
42. Baumann, M. E.; Bosshard, H.; Breitenstein, W.; Rihs, G.; Winkler, T. *Helv. Chim. Acta* **1984**, *67*, 1897–1905.
43. Weiner, S. J.; Kollman, P. A.; Nguyen, D. T.; Case, D. A. *J. Comput. Chem.* **1986**, *4*, 230–252.
44. Chang, G.; Guida, W. C.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 4379–4386.
45. Cagnoli, R.; Ghelfi, F.; Pagnoni, U. M.; Parsons, A. F.; Schenetti, L. *Tetrahedron* **2003**, *59*, 9951–9960.
46. Ince, J.; Ross, T. M.; Shipman, M.; Slawin, A. M. Z. *Tetrahedron* **1996**, *52*, 7037–7044.
47. Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caulfield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440–467.
48. Still, W. C.; Tempczyk, A.; Hawley, R. C.; Hendrickson, T. *J. Am. Chem. Soc.* **1990**, *12*, 6127–6129.
49. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millan, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Patersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malik, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzales, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. *Gaussian 98*, Revision A.9; Gaussian Inc.: Pittsburgh, PA, 1998.
50. Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652.

Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron 62 (2006) 758–764

Tetrahedron

Development in synthesis and electrochemical properties of thienyl derivatives of carbazole

Joanna Cabaj,[a] Krzysztof Idzik,[a] Jadwiga Sołoducho[a,*] and Antoni Chyla[b]

[a]Institute of Organic Chemistry, Biochemistry and Biotechnology, Wrocław, University of Technology,
50-370 Wrocław, Wybrzeże Wyspiańskiego 27, Poland
[b]Institute of Physical and Theoretical Chemistry, Wroclaw, University of Technology, 50-370 Wrocław, Wybrzeże Wyspiańskiego 27, Poland

Received 10 March 2005; revised 12 September 2005; accepted 29 September 2005

Abstract—A convenient and higher yielding synthetic route to *N*-alkyl-bis(thiophene)- and *N*-alkyl-bis(ethylenedioxythiophene) carbazole derivatives is reported and their aggregation, and electrochemical properties are characterized. The key step in the synthesis of this group of compounds has been the Stille-type coupling reaction between the *N*-alkyldibromocarbazole and tin derivatives of thiophene or ethylenedioxythiophene, as the best way for preparation of conjugated *N*-alkylcarbazole derivatives. For this group of compounds we also present an electrochemical polymerization effect.

1. Introduction

Since their discovery, conjugated monomers and their polymers attract continuing interest as a result of their suitability in a broad range of applications, such as batteries,[1] electroluminescent devices, field-effect transistors and photovoltaics.

The need for sensitive and highly specific chemical sensors is of growing importance in both the monitoring and control of human exposure to chemicals present in environment and medical technology. As a result of this great hopes and expectations are associated with sensors based on organic materials. The manufacture of high quality ultrathin, anisotropic organic films by means of the Langmuir–Blodgett (LB) technique is finding important practical application in many fields including sensorics, electrooptics and electronic devices as well as biomimetic systems.[1–7]

Carbazole is a well-known hole-transporting and electroluminescent unit. Polymers containing carbazole moieties either in the main or side chains have attracted much attention because of their unique properties, which allow for various photonic applications (photoconductivity, electroluminescence, and photorefraction).[8,9]

In this paper, supplementing our previous publications, we report on the synthesis of novel amphiphilic, monomeric derivatives of 2-thiophene- and 2-(3,4-ethylenedioxythiophene)carbazole, and their aggregation properties in LB films.[10–12] In many photonic applications like photon funnels or energy transfer controllers[13] the concentration of chromophore is essential as well as the knowledge of the LB film architecture. We undertook the study of formation of single and two-component Langmuir and LB films of synthesized alkylheteroaromatic molecules. Particular attention has been paid to the films containing alkylheteroaromatic compounds mixed with polyoctadecylthiophene (PODT), docosanoic acid (DA) and 22-tricosenoic acid (TA), which are low molecular mass amphiphilic molecules facilitating the deposition (DFs—Deposition Facilitators). PODT was prepared by the typical chemical oxidative polymerisation with $FeCl_3$, DA and TA (Aldrich) were carefully recrystallised from chloroform.

Since the Langmuir–Blodgett technique allows the controlled, layer-by-layer deposition of ordered molecular films on solid substrates, the films constructed by means of this method are expected to be components for potential applications in sensorics, photonics or photoelectronics.[14]

Advantages in the processability of chemically polymerized soluble thiophene derivatives, have been recognized by a number of researchers in this field. But chemical polymerization enables the deposition of films on substrates by a variety of methods, for example the Langmuir–Blodgett technique. In this case electrochemical deposition of polymer on platinum or ITO plates were used. The photophysical properties of the thin film of monomers

---

Keywords: Electrochemical properties; Thienyl derivative; Carbazole.

* Corresponding author. Tel.: +48 71 320 24 27; fax: +48 71 328 40 64; e-mail: jadwiga.soloducho@pwr.wroc.pl

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.09.142

and polymers and their electrochemical properties were then investigated.

2. Results and discussion

2.1. Synthesis of bis(2-thiophene)- and bis(2-(3,4-ethylenedioxythiophene))carbazoles

Based of our previous work,[15] we found that the Stille procedure is a convenient method for the preparation of another group of carbazole derivatives with aggregation properties. One of them, *N*-nonyl-3,6-bis(2-thiophene)carbazole (TPC, **3c**) was patented because of its gave aggregation and electrochemical properties.[16]

Scheme 1 illustrates the synthetic routes for the novel *N*-alkyl-3,6-bis(2-thiophene)- or -(2-(3,4-ethylenedioxythiophene))carbazoles. These compounds were synthesized by a two-step procedure. *N*-alkylcarbazole (**1**)[17] was successfully brominated using *N*-bromosuccinimide (NBS), to give the dibromo compound **2**. A Stille-type coupling reaction was employed to obtain 3,6-bis (2-thiophene)-*N*-alkylcarbazole (**3**) from 2-trimethyltinthiophene (Scheme 1) and 3,6-dibromo-*N*-alkyl-carbazole (**2**). A similar procedure was used to synthesize the 2-(3,4-ethylenedioxythiophene) derivatives of *N*-alkylcarbazoles (**4**). Compound **4** was achieved with a high yield (90%) using this method.

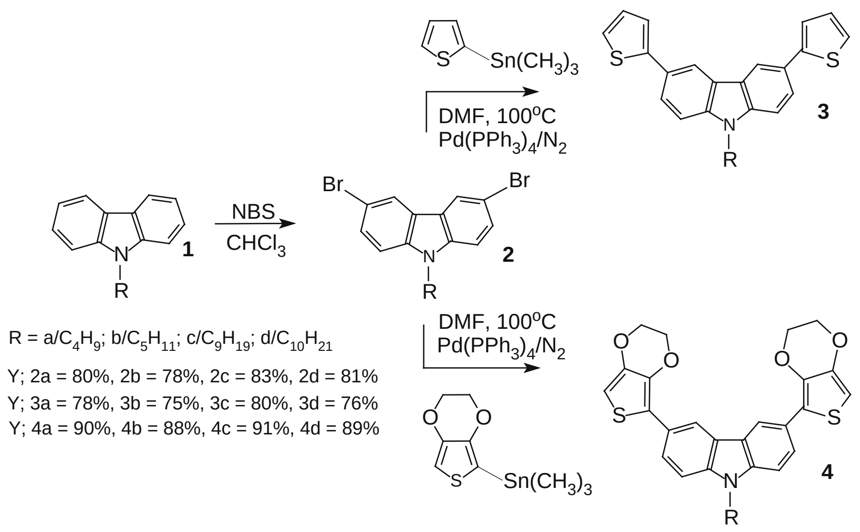
The structures of the synthesized compounds were confirmed by ^{1}H and ^{13}C NMR, and elemental analysis.

2.2. Langmuir films

The molecular structures of the components for the binary systems of interest are shown in Figure 1.

To obtain Langmuir films, the synthesized compounds (Scheme 1): *N*-butyl-3,6-bis(2-thiophene)carbazole (**3a**), *N*-butyl-3,6-bis(2-(3,4-ethylenedioxythiophene)carbazole (**4a**), *N*-amyl-3,6-bis(2-thiophene)carbazole (**3b**), *N*-amyl-3,6-bis(2-(3,4-ethylenedioxythiophene)carbazole (**4b**), *N*-nonyl-3,6-bis(2-thiophene)carbazole (**3c**), *N*-decyl-3,6-bis(2-thiophene)carbazole (**3d**), *N*-decyl-3,6-bis(2-(3,4-ethylenedioxythiophene)carbazole (**4d**), were dissolved in chloroform (Aldrich, HPLC grade). Concentrations of solutions were maintained at ca. 1 mg/ml.

The films of desired composition were formed by dropwise spreading of *N*-alkylcarbazole derivatives solutions, with or without DFs (docosanoic acid, tricosenoic acid and



Scheme 1.

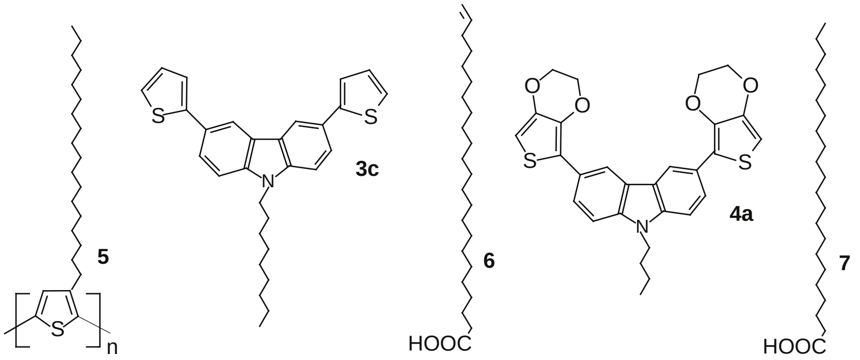


Figure 1. The binary system components: **3c**, *N*-nonyl-3,6-bis(2-thiophene)carbazole (TPC); **4a**, *N*-butyl-3,6-bis(2 (3,4-ethylenedioxythiophene) carbazole (DTPC); **5**, *PODT*; **6**, *TA*; **7**, *DA*.

polyoctadecylthiophene) on high purity water at 295 K. The binary systems were mixed to obtain resulting molar compositions of the deposition mixture of 2:1, 1:1 and 1:2. The electrical conductivity of this quartz double distilled, deionized water was lower than 10^{-5} S/m. The π–A isotherms were measured by means of a commercial LB trough (KSV, System 5000), using a Pt hydrophilic Wilhelmy plate. The compression rates used in our experiments ranged between 5 and 100 mm/min, depending on the rigidity of the films. From the measured π–A isotherms of all synthesized derivatives of *N*-alkylcarbazole it was clear that the derivatives with an even number of C atoms in alkyl chains do not form stable Langmuir films.[18] Therefore *N*-nonyl-3,6-bis(2-thiophene)carbazole (TPC)—the derivative with odd number of C atoms in the alkyl chains was chosen for further experiments. Properties of the other derivatives are still under investigation. Figure 3 shows the π–A isotherms of the investigated binary systems of TPC. For comparison the π–A isotherm of pure TPC is shown in Figure 2. Although pure TPC forms good Langmuir films their LB films are not very stable because the transfer occurs under a relatively low surface pressure. The surface pressure π is generally considered to be equal to the reduction of the pure liquid surface tension by the film, i.e. $\pi = \sigma_0 - \sigma$, where σ_0 is the surface tension of the pure liquid and σ is the tension of the film covered surface.

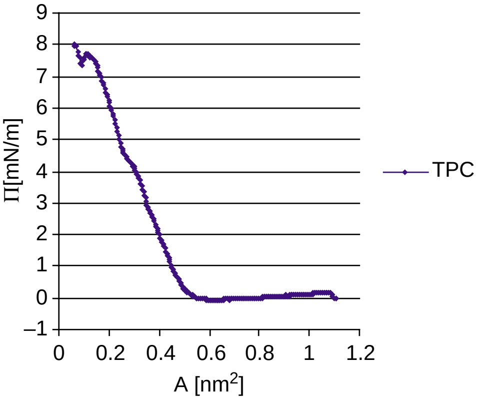


Figure 2. π–A Isotherm of TPC.

Comparison of π–A isotherms of Figure 3 shows that when using binary films, one can obtain much higher surface pressures and therefore closer packing, and PODT facilitates this process the most effectively. This is caused by synergy between the structures of TPC and PODT.

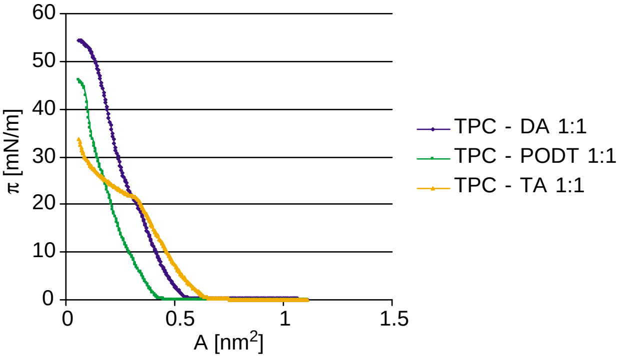


Figure 3. π–A Isotherms of TPC–DA, TPC–PODT, TPC–TA complexes.

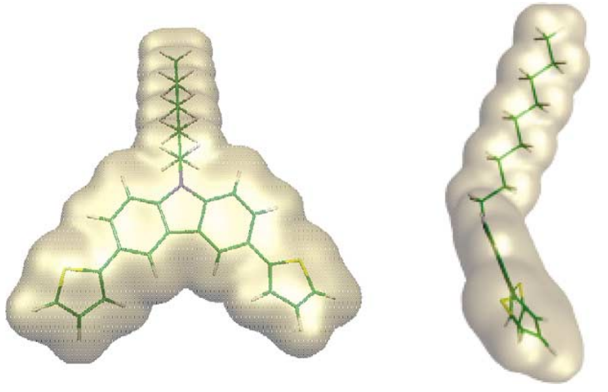


Figure 4. The computer-generated models of TPC.

In Figure 4 a computer-generated (optimization structure-AM1, *Gaussian*03, Molekel) model of the TPC molecule is presented. If the average plane of all aromatic rings (hydrophilic part of molecule) was laid flat on the water, the aliphatic chain would be elevated by 35°. In such an arrangement calculated area per molecule equals ca. 1.1 nm^2, which is also confirmed by π–A isotherm.

During compression, molecules can slip each under the other forming a ‘spoon like’ stacking and in close packed phase (liquid condensed) both calculated and measured, from π–A isotherm, the area per molecule amounts to ca. 0.4 nm^2. In Figure 5 we propose LB film structures for the binary systems of interest. Tricosenoic and docosanoic acids, the model amphiphiles can also be effectively used for creation of binary systems of interest.

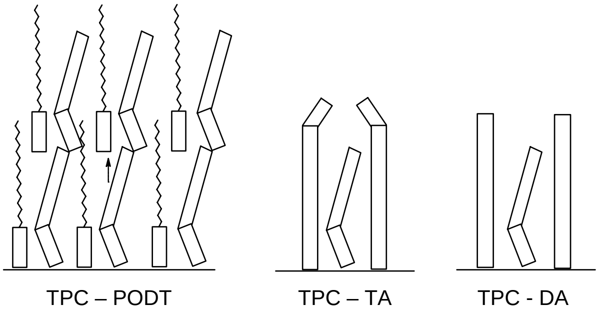


Figure 5. LB films structures of measured binary systems.

In our case the deposited LB films are complete and of high quality, as confirmed by additivity of UV–vis spectra (Fig. 6).

Contrary to TPC, DTPC does not form any stable Langmuir films, neither alone nor in binary systems. In solution it forms dimers, as confirmed by 2D photoluminescence spectra. The 2D photoluminescence spectrum together with excitation and emission spectra are shown in Figure 7.

In the excitation spectrum of DTPC (Fig. 7) one can observe two strong, specific regions, a monomer region (ca. 330 nm), and one corresponding to the dimer (ca. 400 nm). In the emission spectrum, the monomer region is at a characteristic wavelength at ca. 380 nm whereas the second region (470 nm) is covered by the absorbance of the dimer.

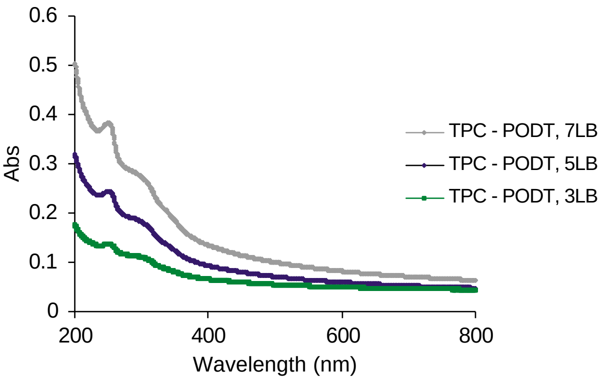


Figure 6. UV–vis spectra of binary complex's (TPC–PODT) LB films.

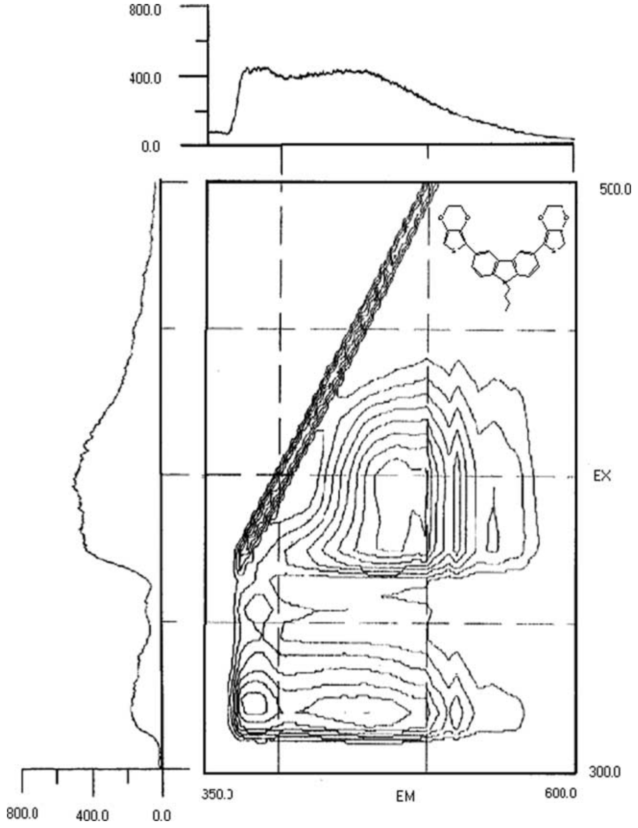


Figure 7. 2D Photoluminescence spectrum of DTPC.

2.3. Electrochemical characterization of PTPC

To enable a comparison of the conductivity of LB films in different binary systems, electrochemically deposited poly(*N*-nonyl-3,6-bis(thiophene)carbazole) (PTPC) films were generated. The electrochemical synthesis of PTPC was carried out by the galvanostatic method on both platinum and ITO-coated glass substrates.

At Figure 8 is shown the repeated potential scan polymerization for TPC in 0.1 M tetrabuthylammonium perchlorate/acetonitrile. The polymerization begins at an $E_{\text{onset,m}}$ of 0.09 V with an $E_{\text{p,m}}$ at 0.15 V. Carbazoles electropolymerize at much lower potential and relative rapidly compared to the single-ring monomers such as pyrrole, or EDOT.

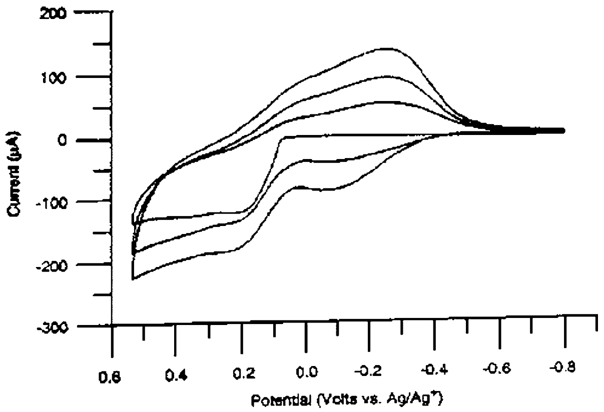


Figure 8. Repeating potential scanning polymerization of 0.01 mol TPC in 0.1 M tetrabutylammonium perchlorate/acetonitrile (TBAP/CH_3CN) at a scan rate of 100 mV/s.

The preferred method of polymer synthesis for optimum film formation was the application of potential near 1.4 V in an electrolyte solution of $(Bu)_4N(BF_4)$ 0.2 M/acetonitrile. The deposition of PTPC was found to proceed rapidly and the synthesis of thick PTPC films was not complicated and we were able to obtain homogenous and stable electroconductive polymer ($\sigma = 6.25 \times 10^{-8}$ S/cm).

Figure 9 shows the conductivity dependence as a current–voltage plot, which is linear over the range of film thickness.

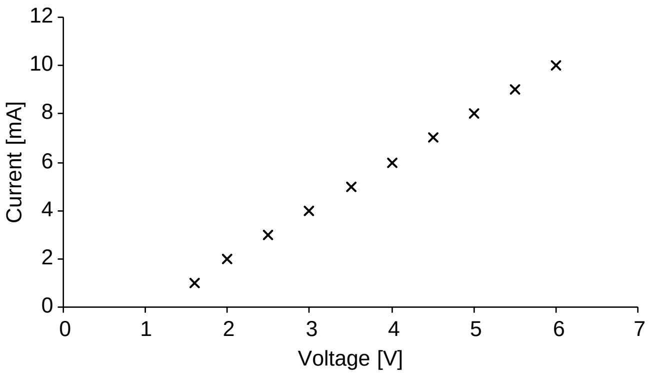


Figure 9. Current–voltage characteristic of electropolymer PTPC.

In our case we were only able to measure the spectroelectrochemistry of an electrochemically prepared film of PTPC (Fig. 10). The absorption spectra of solutions of PTPC were not obtained, due to the insoluble nature of the polymer.

The absorbance spectrum of the thin PTPC layer suggests a ground state electronic structure with minimal interchain aggregation in the condensed state.[19]

The dark PTPC polymer is illustrated by the photograph in Figure 11.

From our previous experience and theoretical calculations[20] we can say that the structure of TPC should be almost planar, whereas the dihedral angle between the central ring (carbazole) and lateral one (thiophene) is 27.5° (Fig. 12).

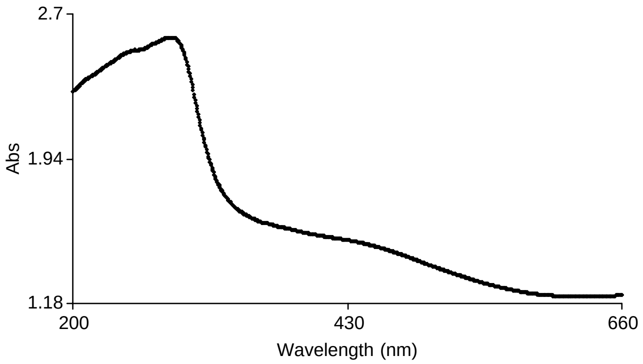


Figure 10. The UV–vis spectrum of electropolymer PTPC film.

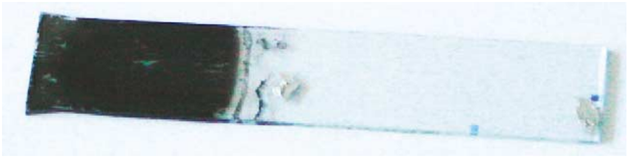


Figure 11. PTPC polymer films electrochemical deposited on ITO glass after electrical measurements.

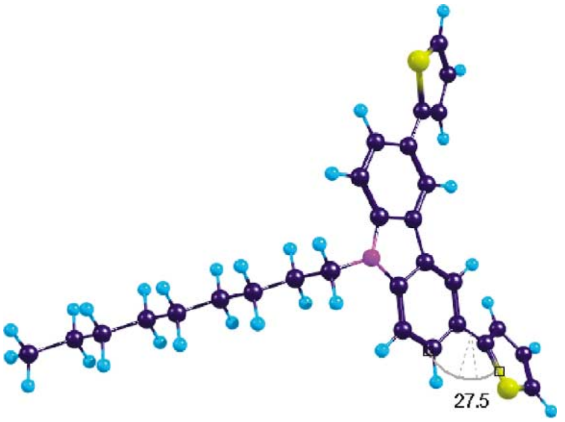


Figure 12. Fully optimized geometries (AM1 level of theory) of *N*-nonyl-3,6-bis(2-thiophene)carbazole, TPC.

3. Conclusions

A series of *N*-alkylcarbazole derivatives have been synthesized using the Stille condensation reaction. This methodology provides a convenient route to obtain the title compounds, which could find applications for example in sensoric and active materials.[21] Carbazole derivatives mixed with substances facilitating film building gave stable and good quality Langmuir and Langmuir–Blodgett films of desired composition. We examined the electroconductivity of LB films built with TPC monomer in a binary system. The electrical properties of a thin polymer film of PTPC, obtained by electrochemical polymerization, were determined.

4. Experimental

4.1. General

Melting points are uncorrected. All NMR spectra were acquired a Brucker VXR-300 at 300 (^{1}H) and 75 (^{13}C) MHz in $CDCl_3$ using TMS as internal standard. Column chromatography was carried out on Merck Kiesel silica gel 60. Dry DMF was used immediately after distilling from a solution containing benzophenone-sodium. Other starting materials, reagents and solvents were used as received from suppliers.

The purity of the products was checked by thin layer chromatography, and their molecular structures were confirmed by ^{1}H NMR and ^{13}C NMR spectroscopy as well as by elemental analysis and UV–vis spectroscopy.

4.2. Synthesis

4.2.1. Compound a. *The procedure for preparation of N-alkylcarbazoles* (**1a**–**1d**). *N*-Alkylation of aromatic compounds involving nitrogen heterocycles such as carbazole with alkyl halide in presence of based solution and benzyl triethyl ammonium chloride (BTEAC) as phase-transfer catalyst readily proceeded under mild conditions, starting from 1 g of carbazole.[17]

Selected data for **1c**. $Y=81\%$ (1.41 g), mp 23–24 °C, ^{1}H NMR ($CDCl_3$) δ 8.10 (d, $J=7.8$ Hz, 2H, arom. H), 7.49–7.37 (m, 4H, arom. H), 7.25–7.19 (m, 2H, arom. H), 4.27 (t, $J=7.2$ Hz, 2H, CH_2), 1.84 (q, $J=7.2$ Hz, 2H, CH_2), 1.46–1.24 (m, 12H, CH_2), 0.87 (t, $J=7.2$ Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ 140.4, 140.0, 125.7, 123.0, 120.5, 118.8, 108.8, 43.1, 32.0, 29.6, 29.6, 29.4, 29.3, 29.1, 27.4, 22.8, 14.4. For $C_{21}H_{27}N$ calcd C, 85.95; H, 9.27; N, 4.77, found; C, 85.70, H, 9.05, N, 4.67.

4.2.2. Compound b. *The procedure for preparation of N-alkyl-3,6-dibromocarbazole* (**2a**–**2d**). *N*-Alkylcarbazoles were converted to dibromocarbazole derivatives in presence of NBS in anhydrous chloroform, starting from 1 g of **1a**–**1d**.[17] *Selected data for* **2b**. $Y=78\%$ (1.30 g), mp 72 °C, ^{1}H NMR ($CDCl_3$) δ 8.04 (s, 2H, arom. H), 7.47 (d, $J=9.1$ Hz, 2H, arom. H), 7.16 (d, $J=10.1$ Hz, 2H, arom. H), 4.15 (t, $J=7.2$ Hz, 2H, CH_2), 1.75 (q, $J=7.2$ Hz, 2H, CH_2), 1.30–1.20 (m, 4H, CH_2), 0.79 (t, $J=6.8$ Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ 139.3, 129.0, 123.4, 123.3, 111.9, 110.4, 43.3, 29.3, 28.6, 22.5, 13.9. For $C_{17}H_{19}N$ calcd C, 86.02; H, 6.80; N, 5.90, found; C, 85.9; H, 6.75; N, 5.79.

Compound **2c**. $Y=83\%$ (1.28 g), mp 46–47 °C, ^{1}H NMR ($CDCl_3$) δ 8.06 (s, 2H, arom. H), 7.48 (d, $J=6.7$ Hz, 2H,arom. H) 7.19 (d, $J=8.6$ Hz, 2H, arom. H), 4.15 (t, $J=7.2$ Hz, 2H, CH_2), 1.76 (q $J=7.1$ Hz, 2H, CH_2), 1.25–1.17 (m, 12H, arom. H), 0.82 (t, $J=6.5$ Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ 139.3, 129.0, 123.4, 123.2, 111.9, 110,4, 43.3, 31.8, 29.4, 29.3, 29.2, 28.7, 27.2, 22.6, 14.1. For $C_{21}H_{25}NBr_2$ calcd C, 55.89; H, 5.58; N, 3.10, found; C, 55.76; H, 5.48; N, 3.00.

Compound **2d**. $Y=81\%$ (1.23 g), mp 54–56 °C, ^{1}H NMR ($CDCl_3$) δ 8.14 (s, 2H, arom. H), 7.56 (d, $J=6.7$ Hz, 2H, arom. H), 7.27 (d, $J=8.7$ Hz, arom. H), 4.45 (t, $J=7.0$ Hz, 2H, CH_2), 1.81 (q, $J=7.1$ Hz, 2H, CH_2), 1.35–1.19 (m, 14H, CH_2), 0.91 (t, $J=6.8$ Hz, 3H, CH_3). ^{13}C NMR δ 140.5, 125.6, 122.9, 120.4, 118.8, 108.7, 43.1, 31.9, 29.6, 29.6, 29.4, 29.0, 27.4, 22.8, 14.3. For $C_{22}H_{27}NBr_2$ calcd C, 56.78; H, 5.85; N, 3.015, found; C, 56.70; H, 5.75; N, 2.95.

4.2.3. Compound c. *The procedure for preparation of N-alkyl-3,6-(2-thiophene)carbazoles* (**3a–3d**). Monomers were synthesized according to our previous method[15] by a coupling reaction of *N*-alkyl-2,7-dibromocarbazoles (**2a–2d**) with 2-trimethyltin-thiophene, starting from 1 g of **2a–2d**. *Selected data for* **3a**. $Y=78\%$ (0.79 g), mp 110 °C, ^{1}H NMR ($CDCl_3$) δ 8.35 (d, $J=7.1$ Hz, 2H, arom. H), 7.75 (d, $J=10.3$ Hz, 2H, thioph. H), 7.41–7.37 (m, 4H, arom, H), 7.27 (d, $J=7.2$ Hz, 2H, thioph. H), 7.13 (d, $J=6.4$ Hz, 2H, thioph. H), 4.30 (t, $J=7.2$ Hz, 2H, CH_2), 1.90–1.66 (m, 2H, CH_2), 1.64–1.32 (m, 4H, CH_2), 0.95 (t, $J=7.3$ Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ 140.4, 125.5, 122.8, 120.3, 118.6, 108.6, 42.7, 31.1. 20.5, 13.8. For $C_{24}H_{21}NS_2$ calcd C, 74.38; H, 5.46; N, 3.61; found C, 74.60; H, 5.68; N, 3.20.

Compound **3b**. $Y=75\%$ (0.76 g), mp 63 °C, ^{1}H NMR ($CDCl_3$) δ 8.05 (s, 2H, arom. H), 7.49 (d, $J=6.8$ Hz, 2H, arom. H), 7.31–7.29 (m, 2H, arom. H), 7.19–7.16 (m, 4H, arom. H), 7.09–7.07 (m, 2H, arom.H), 4.13 (t, $J=7.2$ Hz, 2H, CH_2), 1.75 (q, $J=7.4$ Hz, 2H, CH_2), 1.46–1.22 (m, 4H, CH_2), 0.82 (t, $J=6.9$ Hz, 3H, CH_3). ^{13}C NMR, ($CDCl_3$) δ 139.3, 129.0, 126.9, 125.2, 123.5, 123.3, 111.9, 110.4, 43.3, 29.4, 28.6, 22.5, 13.9. For $C_{25}H_{23}NS_2$ calcd C, 74.80; H, 5.77; N, 3.49; found C, 74.40; H, 5.20; N, 3.30.

Compound **3c**. $Y=80\%$ (0.81 g), mp 193–195 °C, ^{1}H NMR ($CDCl_3$) δ 8.05 (s, 2H, arom. H), 7.47 (d, $J=6.8$ Hz, 2H, arom. H), 7.32–7.29 (m, 2H, arom. H), 7.17 (d, $J=8.7$ Hz, 2H, arom. H), 7.09–7.07 (m, 2H, arom. H), 4.13 (t, $J=7.2$ Hz, 2H, CH_2), 1.75 (q $J=7.1$ Hz, 2H, CH_2), 1.25–1.19 (m, 12H, CH_2), 0.81 (t, $J=6.8$ Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ 139.3, 126.9, 125.1, 123.5, 123.3, 111.9, 110.4, 43.4, 31.9, 29.5, 29.3, 28.8, 27.2, 22.7, 14.1. For $C_{29}H_{31}NS_2$ calcd C, 76.13; H, 6.83; N, 3.06; found C, 75.90; H, 6.50; N, 2.88.

Compound **3d**. $Y=76\%$ (0.77 g), mp 189–191 °C, ^{1}H NMR ($CDCl_3$) δ 8.05 (s, 2H, arom. H), 7.48 (d, $J=6.8$ Hz, 2H, arom. H), 7.32–7.29 (, 2H, arom. H), 7.18 (d, $J=8.7$ Hz, 2H, arom. H), 7.09–7.07 (m, 2H, arom. H), 4.13 (t, $J=7.2$ Hz, 2H, CH_2), 1.75 (q, $J=7.1$ Hz, 2H, CH_2), 1.25–1.16 (m, 14H, CH_2), 0.84 (t, $J=6.8$ Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ 139.3, 129.0, 126.9, 125.1, 123.4, 123.3, 111.9, 110.4, 43.4, 31.9, 29.5, 29.3, 29.2, 28.8, 27.2, 22.6, 14.1. For $C_{30}H_{33}NS_2$ calcd C, 76.41; H, 7.05; N, 2.97; found C, 76.35; H, 6.95; N, 2.70.

4.2.4. Compound d. *The preparation of N-alkyl-3,6-(2-(3,4-ethylenedioxythiophene))carbazoles* (**4a–4b**). These compounds were successfully synthesized according to our method reported for preparation of 3,4-ethylenedioxythiophene derivatives of tetrazines, starting from 1 g of **2a–2d**.[15]

Compound **4a**. $Y=90\%$ (1.19 g), oil, ^{1}H NMR ($CDCl_3$) δ 8.02 (s, 2H, arom. H), 7.46 (d, $J=6.7$ Hz, 2H, arom. H), 7.17 (d, $J=8.7$ Hz, 2H, arom. H), 6.26 (s, 2H, arom. H), 4.12 (t, $J=7.2$ Hz, 10H, CH_2), 1.72 (q, $J=7.4$ Hz, 2H, CH_2), 1.27 (sec., $J=7.5$ Hz, 2H, CH_2), 0.87 (t, $J=7.3$ Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ 141.8, 139.3, 129.0, 123.4, 123.2, 111.9, 110.6, 110.4, 99.7, 64.7, 43.0, 31.0, 20.5, 13.9. For $C_{28}H_{25}NS_2O_4$ calcd C, 66.77; H, 5.00; N, 2.78, found C, 66.20; H, 4.60; N, 2.70.

Compound **4b**. $Y=88\%$ (1.15 g), mp 68–70 °C, ^{1}H NMR ($CDCl_3$) δ 8.02 (s, 2H, arom. H), 7.46 (d, $J=6.7$ Hz, 2H, arom. H), 7.15 (d, $J=8.7$ Hz, 2H, arom. H), 6.3 (s, 2H, arom. H), 4.13 (m, 10H, CH_2), 1.73 (q, $J=7.2$ Hz, 2H, CH_2), 1.28–1.21 (m, 4H, CH_2), 0.81 (t, $J=6.8$ Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ 141.8, 139.3, 129.0, 123.4, 123.2, 111.9, 110.4, 99.7, 64.7, 43.3, 29.4, 28.6, 22.5, 13.9. For $C_{29}H_{27}NS_2O_4$ calcd C, 67.23; H, 5.26; N, 2.71 found C, 66.89; H, 4.66; N, 2.67.

Compound **4c**. $Y=91\%$ (1.16 g), oil, ^{1}H NMR ($CDCl_3$) δ 8.04 (s, 2H, arom, H), 7.46 (d, $J=6.8$ Hz, 2H, arom. H), 7.16 (d, $J=8.7$ Hz, 2H, arom. H), 6.25 (s, 2H, arom. H), 4.12 (t, $J=7.2$ Hz, 10H, CH_2), 1.73 (t, $J=7.0$ Hz, 2H, CH_2), 1.24–1.17 (m, 14H, CH_2), 0.81 (t, $J=6.8$ Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ 141.8, 139.3, 129.0, 123.5, 123.2, 111.9, 110.4, 99.7, 64.7, 43.4, 31.8, 29.4, 29.3, 29.2, 28.8, 27.2, 22.6, 14.1. For $C_{33}H_{35}NS_2O_4$ calcd C, 69.08; H, 6.15; N, 2.44 found C, 68.70; H, 5.73; N, 2.04.

Compound **4d**. $Y=89\%$ (1.12 g), mp 55 °C, ^{1}H NMR ($CDCl_3$) δ 8.05 (s, 2H, arom. H), 7.47 (d, $J=6.8$ Hz, 2H, arom. H), 7.18 (d, $J=8.7$ Hz, 2H, arom. H), 6.26 (s, 2H, arom. H), 4.13 (t, $J=7.2$ Hz, 2H, CH_2), 1.74 (q, $J=7.1$ Hz, 2H, CH_2), 1.24–1.16 (m, 14H, CH_2), 0.81 (t, $J=6.8$ Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ 141.8, 139.3, 129.0, 1253.5, 123.3, 111.9, 110.4, 99.7, 64.7, 43.4, 31.9, 29.5, 29.4, 29.3, 29.2, 28.8, 27.2, 26.7, 14.1. For $C_{34}H_{37}NS_2O_4$ calcd C, 69.49; H, 6.35; N, 2.38; found, C, 69.30; H, 6.20; N, 2.27.

4.3. Oxidative polymerization

Monomer TPC was electrochemically polymerized using repeated potential scan polymerization with a standard three-electrode. Electropolymerization of TPC was carried on in 0.1 M tetrabuthylammonium perchlorate/acetonitrile at a scan rate of 100 mV/s.

4.4. Electrochemical polymerization

Polymer electrochemistry was carried out on a standard model galvanostat employing a platinum disk working electrode or ITO (area = 1.55 cm^2) disk working electrode, and a platinum plate counter electrode. Spectroelectrochemistry experiments were carried out on a Cary 100 Bio Varian UV–vis spectrophotometer. Polymer films were deposited onto ITO-coated glass plates (9.8×50.0×0.5 mm, 20 Ω/square, Delta Technologies). Insoluble polymers were cast onto ITO or platinum plates (10×70×0.2 mm) from dry acetonitrile.

Acknowledgements

Financial support from the Polish Science Foundation (KBN, Grant No. PBZ-KBN-098/T09/2003) is gratefully acknowledged.

References and notes

1. Nguyen, V. C.; Potje-Kamloth, K. *Thin Solid Films* **1999**, *338*, 142–148.
2. Cabala, R.; Meister, V.; Potje-Kamloth, K. *J. Chem. Soc., Faraday Trans.* **1997**, *93*, 131–137.

3. Selampinar, F.; Toppare, L.; Akbulut, U.; Yalcin, T.; Süzer, S. *Synth. Met.* **1995**, *68*, 109–116.
4. Toppare, L.; Akbulut, U.; Yalçin, T.; Süzer, S. *Synth. Met.* **1995**, *68*, 109–116.
5. Brook, T. E.; Narayanaswamy, R. *Sensors Actuators B* **1998**, *51*, 77–83.
6. Swager, T. M. *Acc. Chem. Res.,* **1998**, *31*, 201–207.
7. Iraqi, A.; Wataru, I. *Chem. Mater.* **2004**, *16*, 442–448.
8. Sanda, F.; Nakai, T.; Kobayashi, N.; Masuda, K. *Macromolecules* **2004**, *37*, 2703–2708.
9. Mello, S. V.; Dynarowicz-Łętka, P.; Dhanabalan, A.; Bianchi, R. F.; Onmori, R.; Janssen, R. A. J.; Oliveira, O. N., Jr. *Colloid. Surf. A* **2002**, *198–200*, 45–51.
10. Chyla, A.; Kucharski, S.; Janik, R.; Sworakowski, J.; Bieńkowski, M. *Thin Solid Films* **1996**, *284–285*, 496–499.
11. Chyla, A.; Lewandowska, A.; Sołoducho, J.; Górecka-Drzazga, A.; Szablewski, M. *IEEE. Trans. DEI* **2001**, *8*, 559–565.
12. Niski, H.; Kohno, H.; Kano, T. *Bull. Chem. Soc.* **1981**, *54*, 1897–1898.
13. *Langmuir–Blodgett Films*; Roberts, G. G., Ed.; Plenum Press: New York, 1990.
14. Bard, A. J. *Integrated Chemical Systems. A Chemical Approach to Nanotechnology*; Wiley: New York, 1994.
15. Sołoducho, J.; Doskocz, J.; Cabaj. Roszak, S. *Tetrahedron* **2003**, *59*, 4761–4766.
16. Sołoducho, J.; Cabaj, J.; Chyla, A. *Pol. Pat.* **2004**, *P369*, 384.
17. Sotzing, G. A.; Reddinger, J. L.; Katritzky, A. R.; Sołoducho, J.; Musgrave, R.; Reynolds, J. R.; Steel, P. J. *Chem. Mater.* **1997**, *9*, 1578–1587.
18. Jarvis, N. L. *J. Phys. Chem.,* **1965**, *69*, 1789.
19. Chama, M.; Myles, D. J. T.; Hicks, R. G. *Chem. Mater.* **2005**, *17*, 2672–2678.
20. Sołoducho, J.; Roszak, S.; Chyla, A. *New J. Chem.* **2001**, *25*, 1175–1181.
21. Chevrot, C.; Henri, T. *Synth. Met.* **2001**, *118*, 157–166.

Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron 62 (2006) 765–770

Tetrahedron

A new tripodal anion receptor with selective binding for $H_2PO_4^-$ and F^- ions

Zhenming Yin,[a,b] Yanhua Zhang,[a] Jiaqi He[a] and Jin-Pei Cheng[a,*]

[a]*Department of Chemistry, State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, China*
[b]*College of Chemistry and Life Science, Tianjin Normal University, Tianjin 300074, China*

Received 30 June 2005; revised 13 September 2005; accepted 16 September 2005

Abstract—The anions binding properties of the pyrrole-based tripodal anion receptor **1** were studied by X-ray crystallography, ^{1}H NMR, and ESI-MS. It revealed that this new tripodal receptor has a preference for binding $H_2PO_4^-$ and F^- ions.

1. Introduction

Anion complexation of synthetic host molecules has become an important theme in supramolecular chemistry because of the amazing impact of anions in many chemical and biological processes.[1] Among the various synthetic hosts, trigonal receptors based on the prototype of tri(2-aminoethyl)amine have been of special interest for their preorganized C_3-symmetry anion-binding geometry. A number of acyclic anion receptors of this type have been designed by attaching various functional groups, and some have indeed shown very good binding ability.[2] On the other hand, it has been found in other cases that pyrrole could serve as an effective anion binding moiety by virtue of its hydrogen bond-donating property.[3] For examples, calixpyrrole,[4] dipyrrolequinoxaline,[5] dipyrrolemethane,[6] and pyrrolic amide[7] are all found to be good anion receptors. This triggered us to examine if tri(2-pyrrolylmethyl)amine (**1**), the recently reported synthetic analog of tri(2-aminoethyl)amine,[8] could show a similar anion binding behavior. In the present work, by using X-ray crystal analysis, we found that the neutral receptor **1** could bind chloride ion and dihydrogen phosphate in an effective C_3-symmetry cone-like topology solely by hydrogen bonds. In addition, the protonated **1** can bind sulfate ion by both hydrogen bonds and electrostatic interaction in the solid state. The ^{1}H NMR study revealed that the tripodal receptor **1** had a selectivity for $H_2PO_4^-$ and F^- ions in DMSO solution.

2. Results and discussion

2.1. X-ray crystallographic studies

In the case of $\mathbf{1}\cdot Cl^-$ complex, X-ray crystal analysis showed that molecule **1** was C_3-symmetrical and adopted a cone-like conformation so as to allow the three pyrrole-NHs to associate with the chloride through hydrogen bonds (Fig. 1). The nitrogen-to-Cl^- distances from the three pyrrole moieties were 3.217, 3.222, and 3.268 Å, respectively, which were slightly shorter than those in the chloride complex of calix[4]pyrrole[4a] and implied that **1** might have a better anion binding ability than calix[4]pyrrole. The distance of chloride to the apical tertiary nitrogen atom was 3.747 Å.

Colorless crystals of $\mathbf{1}\cdot F^-$ complex were obtained by a similar procedure to $\mathbf{1}\cdot Cl^-$ complex. ^{1}H NMR study confirmed that **1** formed a 1:1 complex with fluoride ion. However, the quality of the crystal was not good enough to allow its structure to be solved.

Molecule **1** was also C_3-symmetrical and adopted a cone-like conformation in the crystal of $\mathbf{1}\cdot H_2PO_4^-$ complex (Fig. 2). However, only one oxygen atom of the dihydrogen phosphate was found associated with the three pyrrole-NHs through hydrogen bonds. The nitrogen-to-oxygen distances from the three pyrrole moieties were 2.843, 2.858, and 2.910 Å, respectively. The distance of the bonded oxygen atom to the apical tertiary nitrogen atom was 3.348 Å. Mediated by the hydrogen bonds between the other oxygen atom and two hydroxyl groups of dihydrogen phosphate, four $\mathbf{1}\cdot H_2PO_4^-$ complexes were self-assembled into a supramolecular tetramer (Fig. 3). This phenomenon is

---

Keywords: Tri(2-pyrrolylmethyl)amine; Anions binding; X-ray crystallographic structure.

* Corresponding author. Tel.: +86 22 23499174; fax: +86 10 68514074; e-mail: jpcheng@nankai.edu.cn

0040–4020/$ - see front matter © 2005 Published by Elsevier Ltd.
doi:10.1016/j.tet.2005.09.066

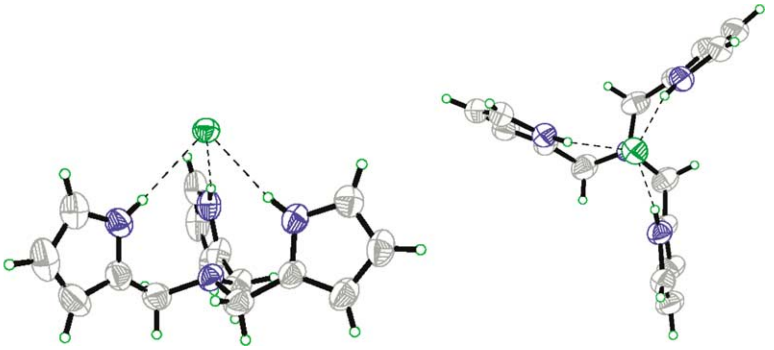


Figure 1. Side view (left) and top view (right) of the X-ray structure of **1**$\cdot$Cl$^-$ complex ([*n*-Bu]$_4$N$^+$ counter-ions were omitted for clarity).

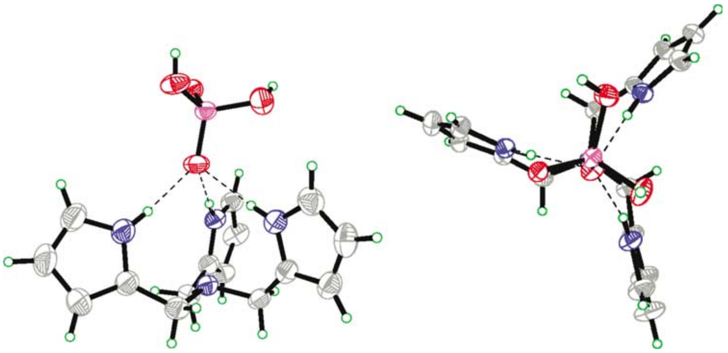


Figure 2. Side view (left) and top view (right) of the X-ray structure of **1**$\cdot$H$_2$PO$_4^-$ complex ([*n*-Bu]$_4$N$^+$ counter-ions were omitted for clarity).

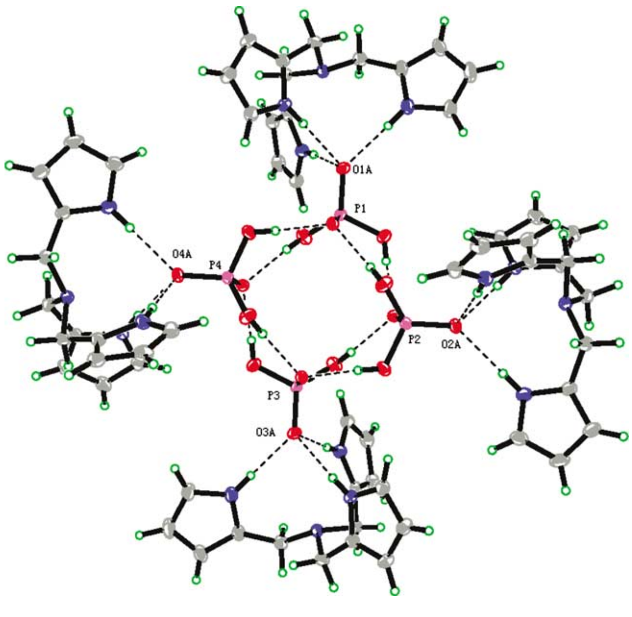


Figure 3. Supramolecular tetramer of **1**$\cdot$H$_2$PO$_4^-$ complex formed via O$\cdots$H–O hydrogen bonds ([*n*-Bu]$_4$N$^+$ counter-ions were omitted for clarity).

consistent with the fact that dihydrogen phosphate aggregate in solution via hydrogen bonds at higher concentration and similar to the recent observation for crystal structure of urea–(H$_2$PO$_4^-$)$_2$ complex.[9] In the tetramer, each **1**$\cdot$H$_2$PO$_4^-$ complex simultaneously accepted two and donated two O$\cdots$H–O hydrogen bonds (2.608 Å, 175.74° and 2.673 Å, 165.68°). These hydrogen bonds caused the crystal of **1**$\cdot$H$_2$PO$_4^-$ complex had a different crystal system with **1**$\cdot$Cl$^-$ complex.

In the crystal of **1**H$^+$$\cdot$SO$_4^{2-}$ complex, the oxygen atom of the sulfate was found to be much closer to the apical nitrogen (2.644 Å), which suggested that the apical nitrogen should be protonated. This may be supported by previous observations of the protonated apical nitrogen in anion binding of some tri(2-aminoethyl)amine receptors.[2d,10] In the crystal of **1**$\cdot$H$_2$PO$_4^-$ complex, the apical nitrogen was not protonated, probably due to lower acidity of H$_2$PO$_4^-$ in comparison with that of HSO$_4^-$.[11]

It was observed that the C_3-symmetric conformation of **1** was somewhat destroyed either by associating with the large size sulfate ion or by protonation of the apical tertiary nitrogen. It was shown that the two pyrrole NHs and the apical NH pointed to the same direction to form a claw-shaped cleft with the sulfate bonded in (Fig. 4). Two pyrrole nitrogen-to-oxygen distances were 2.804 and 2.806 Å, respectively. The third pyrrole NH pointed to a reverse direction and bonded the second sulfate as assisted by methylene C–H. The nitrogen-to-oxygen distance was 2.764 Å and carbon-to-oxygen distance 3.288 Å. The C–Hs that participated in binding anions were probably assisted by the adjacent cationic center. The cationic hosts and divalent anions were alternated each other and assembled into a one-dimensional pillar through hydrogen bonds (Fig. 4).

2.2. NMR studies

^{1}H NMR study of anion recognition of **1** was conducted in DMSO solution because of the poor solubility of [*n*-Bu]$_4$NHSO$_4$ in other solvents. Only one signal of pyrrole NH was observed, suggesting that the conformation of **1** in

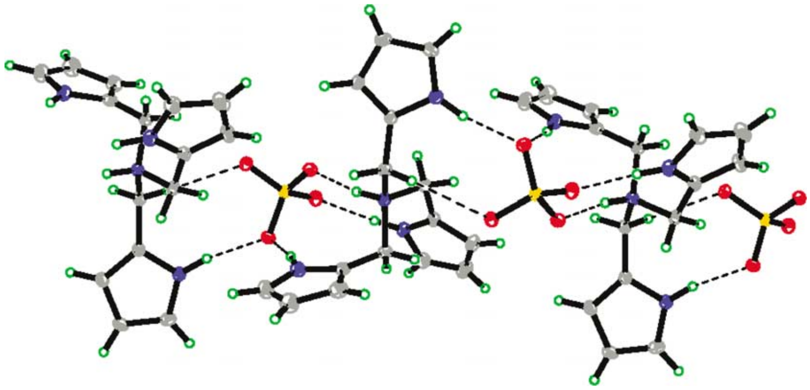


Figure 4. Side view of the assembled pillar of $\mathbf{1}H^+ \cdot SO_4^{2-}$ complex ($[n\text{-Bu}]_4N^+$ counter-ions were omitted for clarity).

solution should be symmetrical. Addition of the tetrabutylammonium salts ($[n\text{-Bu}]_4N^+A^-$; $A^- = F^-$, Cl^-, $H_2PO_4^-$, HSO_4^-) into the DMSO solution of **1** led to downfield shifts of the N–H resonance, which indicated the participation of pyrrole NH in binding anions by hydrogen bonding interactions. Although other tripodal receptors were reported to have selectivity for tetrahedron oxoanions,[2] in the present case of **1**, the largest chemical shift was found in its association with fluoride ion (Fig. 5). Upon addition of fluoride, the NH signal was shifted downfield significantly and the peak was broadened. After 2 equiv of fluoride were added, the exact position of the signal was almost unable to be ascertained. In the case of $H_2PO_4^-$, the pyrrole NH signal was also shifted downfield significantly, but with less extent than did fluoride (Fig. 5). On the other hand, addition of chloride or HSO_4^- caused only a small downfield shift of the NH signals. The possibility that the large ^1H NMR change occurring upon the addition of $H_2PO_4^-$ and F^- arises from their higher negative charge and better hydrogen bond acceptor properties with respect to HSO_4^- and Cl^-.[12] The X-ray crystallographic studies revealed that **1** had a higher preorganization ability than protonated **1**, which might be the reason why **1** had a selective binding for $H_2PO_4^-$ with respect to HSO_4^-. According to the shift patterns of the pyrrole NH, the complexes of **1** with anions should follow a 1:1 type binding model.[13] The association constants were deducted accordingly and summarized in Table 1. It clearly showed that the anion receptor **1** had higher selectivities for $H_2PO_4^-$ and F^-.

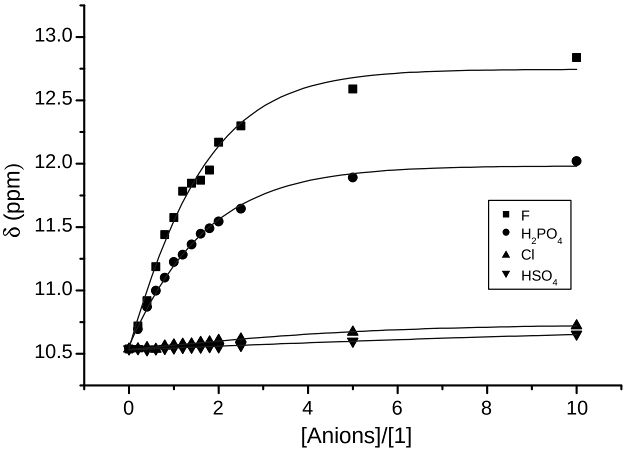
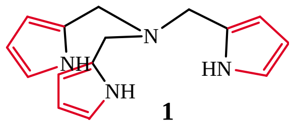


Figure 5. ^1H NMR titration curves of **1** with $[n\text{-Bu}]_4N^+$ salts of F^-, Cl^-, $H_2PO_4^-$, and HSO_4^-.

Table 1. Association constants (K_a) of **1** with anions in DMSO



1

Anions	K_a (M^{-1})
F^-	187
$H_2PO_4^-$	240
Cl^-	29
HSO_4^-	<10

The negative ion mode electrospray ionization mass spectrometry (ESI-MS) is particularly useful for determining the stoichiometry of anion complexes[14] and was, therefore, performed for the complexes of **1**. The molecular peak attributed to the $\mathbf{1} \cdot F^-$ complex ($m/z = 273.5$; Fig. 6) was observed, which confirmed the conclusion from the ^1H NMR study.

3. Conclusion

In summary, we herein described the anions recognition of a tripodal pyrrole receptor **1**, which displayed a binding preference to $H_2PO_4^-$ and F^- ions in comparison with other anions tested. The solid structure of $\mathbf{1} \cdot Cl^-$, $\mathbf{1} \cdot H_2PO_4^-$, and $\mathbf{1}H^+ \cdot SO_4^{2-}$ complexes were characterized by X-ray crystallography. It was found that the neutral receptor **1** could bind chloride ion and dihydrogen phosphate in an effective C_3-symmetry cone-like topology exclusively by hydrogen bonds. To the best of our knowledge, compound **1** is the first pyrrole-based acyclic tripodal anions receptor.[15]

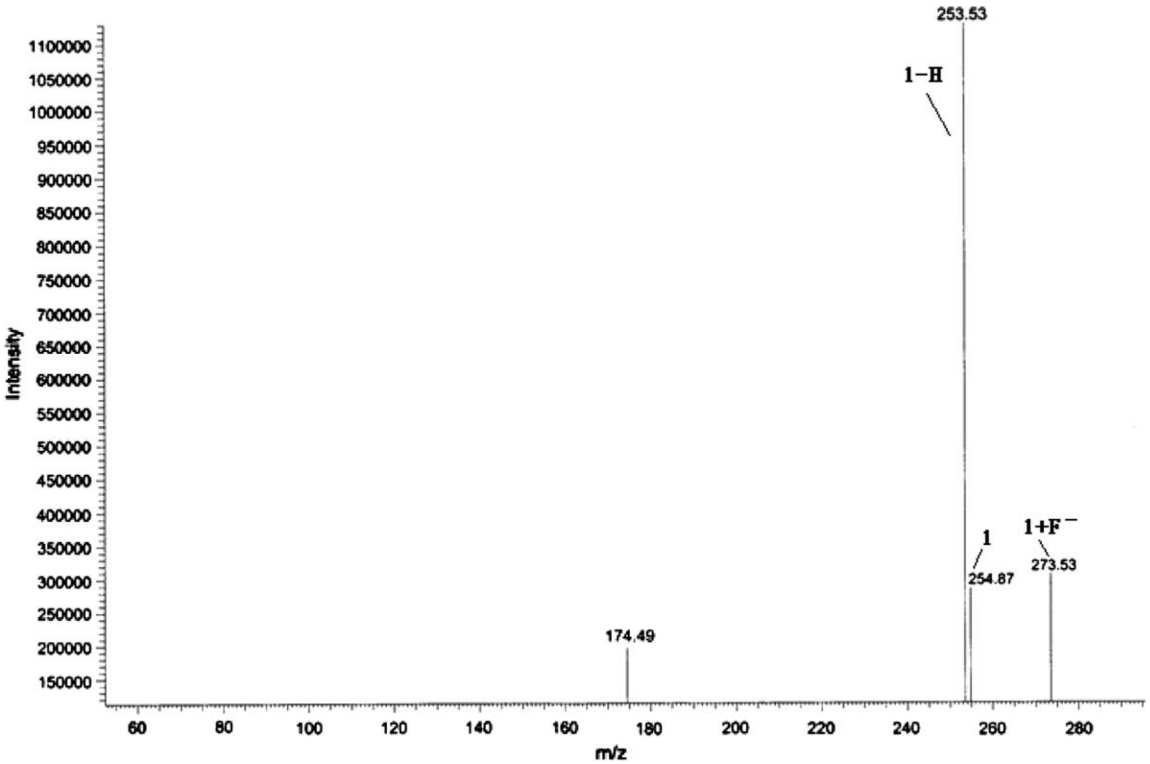


Figure 6. Negative ion mode ESI-MS of 1:1 mixture of **1** and $[n\text{-Bu}]_4N\cdot F$ in $CHCl_3$ solution.

4. Experimental

4.1. General

^1H NMR spectra were recorded in DMSO-d_6, with TMS as the internal standard, on a BRUKER AC-P300 MHz spectrometer. Mass spectra were recorded on a AEIMS-50/PS 30 mass spectrometer. Pyrrole was distilled under reduced pressure prior to use. All other commercially available reagents were used without further purification.

4.2. Synthesis

The receptor of **1** was synthesized with a modified literature procedure.[8] pyrrole (18 g), 37% formaldehyde aqueous solution (20 mL), NH_4Cl (4.78 g), ethanol (60 mL) and water (20 mL) were mixed in a 250 mL flask. The mixture was stirred at 40 °C for 1 h. Then, it was poured into 200 mL of water and extracted with ethyl acetate (30×3). The combined organic phase was dried over Na_2SO_4. The volatiles were removed by rotary evaporation. The residue was recrystallized from CH_2Cl_2 to give **1** as a white powder (11 g, yield 48%). Mp 137–138 °C (lit.[8] mp 137–138 °C). ^1H NMR ($CDCl_3$, 300 MHz); δ 3.60 (s, 6H, –CH_2–), 6.09 (s, 3H, 3-C_4H_3N), 6.17–6.18 (m, 3H, 4-C_4H_3N), 6.74–6.75 (m, 3H, 5-C_4H_3N), 8.22 (s, 3H, NH).

4.3. X-ray crystallography

The $\mathbf{1}\cdot Cl^-$ complex was prepared by dissolving equal amounts of n-Bu_4NCl (24 mg) and **1** (22 mg) in a 2:1 (v/v) ethyl acetate and petroleum ether solution, followed by slow evaporation. The crystals of $\mathbf{1}H^+\cdot SO_4^{2-}$ and $\mathbf{1}\cdot H_2PO_4^-$ complexes were prepared slightly differently. First, equal amounts of anions (as $[n\text{-Bu}]_4N^+$ salt)(29 mg) and **1** (22 mg) were dissolved into 0.5 mL methanol, then 5 mL ethyl acetate was added. Slow evaporation of the solvents provided colorless crystals.

The diffraction data were measured on a BRUKER SMART 1000 CCD diffractometer with Mo Kα radiation (λ= 0.71073 Å) by ϖ scan mode at 293(2) K. All data were corrected by semi-empirical method using SADABS program. The program SAINT[16] was used for integration of the diffraction profiles. The structure was solved by the direct methods using SHELXS program of the SHELXL-97 package and refined with SHELXL.[17] The final refinement was performed by full matrix least-squares methods with anisotropic thermal parameters for all non-hydrogen atoms on F^2. The hydrogen atoms of **1** were placed in the geometrically calculated positions. All hydrogen atoms were included in the final refinement in the riding model approximation with displacement parameters derived from the parent atoms to which they were bonded. Crystallographic data and refinement parameters of the three crystals were summarized in Table 2.

4.4. Binding titration

The ^1H NMR spectra were recorded on a BRUKER AC-P300 instrument. In a typical anion titration experiment,[18] aliquots of an anion (tetrabutylammonium fluoride, chloride, dihydrogen phosphate or hydrogen sulfate, 0.5 M DMSO-d_6 solution) were added to a 0.5 mL 5 mM solution of receptor **1**. Thirteen aliquots were added corresponding to 0, 0.2, 0.4, 0.6, 0.8, 1, 1.2, 1.4, 1.6, 1.8, 2, 2.5, 5, and 10 equiv of anion. The chemical shift of the pyrrole proton on the receptor was monitored as it moved downfield upon addition of anion. The association constants, K_a, was calculated by non-linear least-square

Table 2. X-ray crystallographic data for complexes $\mathbf{1}\cdot\mathrm{Cl}^-$, $\mathbf{1}\cdot\mathrm{H_2PO_4^-}$ and $\mathbf{1}\mathrm{H}^+\cdot\mathrm{SO_4^{2-}}$

	$\mathbf{1}\cdot\mathrm{Cl}^-$	$\mathbf{1}\cdot\mathrm{H_2PO_4^-}$	$\mathbf{1}\mathrm{H}^+\cdot\mathrm{SO_4^{2-}}$
CCDC number	269157	275964	269158
Empirical formula	$C_{31}H_{54}ClN_5$	$C_{31}H_{56}N_5O_4P$	$C_{22}H_{20}N_6O_7$
Formula weight	532.24	593.78	593.86
Crystal system	Monoclinic	Tetragonal	Orthorhombic
Space group	$P2_1/n$	I-4	$P2_12_12_1$
a (Å)	14.066(2)	18.0091(16)	13.3926(13)
b (Å)	16.202(3)	18.0091(16)	14.0190(14)
c (Å)	14.798(2)	22.173(4)	18.6205(18)
α (°)	90	90	90
β (°)	95.955(3)	90	90
γ (°)	90	90	90
V (Å^3)	3354.3(9)	7191.4(16)	3496.0(6)
Z	4	8	4
D_{calcd} (g/cm^3)	1.054	1.097	1.128
μ (mm^{-1})	0.139	0.115	0.132
Total reflections	18048	19713	19055
Unique reflections	5918	6348	6159
R_1/wR_2 [$I>2\sigma(I)$]	0.0513/0.1183	0.0388/0.0966	0.0371/0.1108
R_1/wR_2 (all data)	0.1524/0.1440	0.0571/0.1073	0.0458/0.1182
GoF on F^2	0.998	1.016	1.060

analysis using the equation

$$\Delta\delta = \frac{\Delta\delta_{\max}}{2[\mathrm{H}]_0}\left\{\frac{1}{K} + [\mathrm{A}]_0 + [\mathrm{H}]_0 - \sqrt{\left(\frac{1}{K} + [\mathrm{A}]_0 + [\mathrm{H}]_0\right)^2 - 4[\mathrm{A}]_0[\mathrm{H}]_0}\right\},$$

where A is anions and H is the receptor **1**.[13]

Acknowledgements

This project was supported by the Major State Basic Research Development Program of China (Grant no. G2000078100) and the Natural Science Foundation of China (NSFC no. 20072020). Z. M. Y would also like to acknowledge the financial support from Tianjin Normal University.

References and notes

1. (a) Bianchi, A.; Bowman-James, K.; Garcia-Espana, E. *Supramolecular Chemistry of Anions*; Wiley-VCH: New York, 1997. (b) Beer, P. D.; Gale, P. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 486–516.
2. (a) Valiyaveettil, S. J.; Engbersen, F. J.; Verboon, W.; Renhoudt, D. N. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 900–902. (b) Beer, P. D.; Chen, Z.; Goulden, A. J.; Graydon, A.; Stokes, S. E.; Wear, T. *J. Chem. Soc., Chem. Commun.* **1993**, 1834–1836. (c) Bazzicalupi, C.; Bencini, A.; Berni, E.; Bianchi, A.; Ciattini, S.; Giorgi, C.; Maoggi, S.; Paoletti, P.; Valtancoli, B. *J. Org. Chem.* **2002**, *67*, 9107–9110. (d) Xie, H.; Yi, S.; Yang, X.; Wu, S. *New J. Chem.* **1999**, *23*, 1105–1110.
3. Sessler, J. L.; Camiplo, S.; Gale, P. A. *Coord. Chem. Rev.* **2003**, *240*, 17–55.
4. (a) Gale, P. A.; Sessler, J. L.; Kral, V.; Lynch, V. *J. Am. Chem. Soc.* **1996**, *118*, 5140–5141. (b) Gale, P. A.; Sessler, J. L.; Kral, V. *Chem. Commun.* **1998**, 1–8. (c) Gale, P. A.; Anzenbacher, P., Jr.; Sessler, J. L. *Coord. Chem. Rev.* **2001**, *222*, 57–102.
5. (a) Black, C. B.; Andrioletti, B.; Try, A. C.; Ruiperez, C.; Sessler, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 10438–10439. (b) Aldakov, D.; Anzenbacher, P., Jr. *J. Am. Chem. Soc.* **2004**, *126*, 4752–4753. (c) Pohl, R.; Aldakov, D.; Kubat, P.; Jursikova, K.; Marquez, M.; Anzenbcher, P., Jr. *Chem. Commun.* **2004**, 1282–1283.
6. (a) Drubi Vega, I. El.; Gale, P. A.; Hursthouse, M. B.; Light, M. E. *Org. Biomol. Chem.* **2004**, *2*, 2935–2941. (b) Coskun, A.; Akkaya, E. U. *Tetrahedron Lett.* **2004**, *45*, 4947–4949.
7. (a) Schmuck, C. *Chem. Commun.* **1999**, 843–844. (b) Gale, P. A.; Camiolo, S.; Tizzard, G. J.; Chapman, C. P.; Light, M. E.; Coles, S. J.; Hursthouse, M. B. *J. Org. Chem.* **2001**, *66*, 7849–7853. (c) Yin, Z.; Li, Z.; Yu, A.; He, J.; Cheng, J.-P. *Tetrahedron Lett.* **2004**, *45*, 6803–6806.
8. Shi, Y.; Cao, C.; Odom, A. L. *Inorg. Chem.* **2004**, *43*, 275–281.
9. (a) Flatt, L. S.; Lynch, V.; Anslyn, E. V. *Tetrahedron Lett.* **1992**, *33*, 2785–2788. (b) Amendola, V.; Boiocchi, M.; Esteban-Gomez, D.; Fabbrizzi, L.; Monzani, E. *Org. Biomol. Chem.* **2005**, *3*, 2632–2639.
10. Kang, S. O.; Llinares, J. M.; Powell, D.; Bowman-James, K. *J. Am. Chem. Soc.* **2003**, *125*, 10152–10153.
11. Kondo, S.; Hiraoka, Y.; Kurumatani, N.; Yano, Y. *Chem. Commun.* **2005**, 1720–1722.
12. Boiocchi, M.; Boca, L. D.; Gomez, D. E.; Fabbrizzi, L.; Licchelli, M.; Monzani, E. *J. Am. Chem. Soc.* **2004**, *126*, 16507–16514.
13. Lu, G.-Y.; Hu, H.-W. *Sci. China Ser. B* **1996**, *39*, 398–405.
14. (a) Kavallieratos, K.; Sachleben, R. A.; Van Berkel, G. J.; Moyer, B. A. *Chem. Commun.* **2000**, 187–188. (b) Szumna, A.; Jurczak, J. *Eur. J. Org. Chem.* **2001**, 4031–4039. (c) Burns, B. H.;

Calderon-Kawasaki, K.; Kularatne, S. *J. Org. Chem.* **2005**, *70*, 2803–2807.

15. The anion binding properties of a cryptand-like calixpyrrole with C_3-symmetry have been previously reported. See: Bucher, C.; Zimmerman, R. S.; Lynch, V.; Sessler, J. L. *J. Am. Chem. Soc.* **2001**, *123*, 9716–9717.
16. *Bruker AXS*; SAINT Software Reference Manual: Madison, WI, 1998.
17. Sheldrick, G. M. *SHELXTL NT: Program for Solution and Refinement of Crystal Structures*, version 5.1; University of Göttingen: Göttingen, Germany, 1997.
18. Evans, A. J.; Matthews, S. E.; Cowley, A. R.; Beer, P. D. *Dalton Trans.* **2003**, 4644–4650.

TETRAHEDRON

EXECUTIVE BOARD OF EDITORS FOR TETRAHEDRON PUBLICATIONS

Chairman: **Professor B. Ganem**
Editor Emeritus: **Professor H. H. Wasserman**

Professor D. L. Boger, The Scripps Research Institute, La Jolla, CA, USA

Professor S. G. Davies, University of Oxford, Oxford, UK

Professor B. Ganem, Cornell University, Ithaca, NY, USA

Professor L. Ghosez, Laboratoire de Chimie Organique de Synthèse,
Université Catholique de Louvain, B-1348 Louvain-la-Neuve, Belgium
Fax: 32 10 47 29 44; e-mail: vanlierde@chim.ucl.ac.be

Professor Lin Guo-Qiang, Shanghai Institute of Organic Chemistry,
Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032,
China
Fax: 86 21 641 66263; e-mail: tetrahed@pub.sioc.ac.cn
(Senior Referees, Professor T.-Y. Luh, Professor S.-M. Ma and
Professor H. N. C. Wong)

Professor S. F. Martin, Chemistry and Biochemistry Department,
The University of Texas, 1 University Station A5300,
Austin, TX 78712-0165, USA
Fax: 1 512 471 4180; e-mail: tet@mail.utexas.edu

Professor W. B. Motherwell, Department of Chemistry, University
College London, 20 Gordon Street, London, WC1H 0AJ, UK
Fax: 44 20 7679 7524; e-mail: w.b.motherwell@ucl.ac.uk

Professor G. H. Posner, Department of Chemistry, Johns Hopkins
University, Baltimore, MD 21218, USA
Fax: 1 410 516 8420; e-mail: ghp@jhu.edu

Professor M. Shibasaki, The University of Tokyo, Japan

Professor T. Shioiri, Graduate School of Environmental & Human Sciences
Meijo University, Shiogamaguchi, Tempaku, Nagoya 468-8502, Japan
Fax: 81 52 832 1555; e-mail: tetra@ccmfs.meijo-u.ac.jp

Professor R. J. K. Taylor, Department of Chemistry, University of York,
Heslington, York, YO10 5DD, UK
Fax: 44 1904 434523; e-mail: tet@york.ac.uk
(Associate Editors, Dr. P. A. O'Brien, Dr. D. K. Smith and
Dr. I. J. S. Fairlamb)

Professor E. J. Thomas, University of Manchester, UK
(Associate Editor, Professor J. A. Joule)

Professor H. Waldmann, Max-Planck-Institut für Molekular Physiology,
Dortmund, Germany

Professor H. H. Wasserman, Yale University, New Haven, CT, USA

Professor C.-H. Wong, The Scripps Research Institute, La Jolla, CA, USA

Professor J. Wood, Yale University, New Haven, CT, USA

Professor Y. Yamamoto, Tohoku University, Sendai, Japan
(Associate Editor, Professor M. Hirama)

Professor S. Z. Zard, Laboratoire de Synthèse Organique, Ecole
Polytechnique, F-91128 Palaiseau Cedex, France
(Associate Editor, Dr. B. Sire)

Editors of the Tetrahedron Organic Chemistry Series: **Professor J.-E. Bäckvall,** University of Stockholm, Sweden
Professor Sir J. E. Baldwin, FRS, Dyson Perrins Laboratory, Oxford, UK
Professor R. M. Williams, Colorado State University, Fort Collins, USA

BOARD OF CONSULTING EDITORS

A. Alexakis, University of Geneva, Switzerland
J.-E. Bäckvall, University of Stockholm, Sweden
V. Balzani, University of Bologna, Italy
M. Banwell, Australian National University, Canberra, Australia
A. G. M. Barrett, Imperial College, London, UK
C. Bolm, RWTH Aachen, Germany
E. M. Carreira, ETH, Zürich, Switzerland
G. W. Coates, Cornell University, Ithaca, NY, USA
D. Corey, University of Texas Southwestern Medical Center, Dallas, TX, USA
E. J. Corey, Harvard University, Cambridge, MA, USA
J. Cossy, ESPCI, Paris, France
D. P. Curran, University of Pittsburgh, PA, USA
S. J. Danishefsky, Columbia University, New York, NY, USA
A. Dondoni, University of Ferrara, Italy
D. A. Evans, Harvard University, Cambridge, MA, USA
P. A. Evans, Indiana University, Bloomington, IN, USA
S. Florio, University of Bari, Italy
G. C. Fu, MIT, Cambridge, MA, USA
N. Fusetani, University of Tokyo, Japan
S. Ikegami, Teikyo University, Kanagawa, Japan
T. Katsuki, Kyushu University, Fukuoka, Japan
Y. Kishi, Harvard University, Cambridge, MA, USA
P. Knochel, Ludwigs-Maximilians-University, Munich, Germany
P. Kocienski, University of Leeds, UK
Y. Langlois, Université de Paris-Sud, Orsay, France
E. Lee, Seoul National University Seoul, Korea
S. V. Ley, University of Cambridge, UK
B. H. Lipshutz, University of California, Santa Barbara, CA, USA
X.-Y. Lu, Shanghai Institute of Organic Chemistry, China
D. MacMillan, California Institute of Technology, Pasadena, CA, USA
P. D. Magnus, University of Texas at Austin, TX, USA
L. N. Mander, Australian National University, Canberra, Australia
G. Mehta, Indian Institute of Science, Bangalore, India
G. Molander, University of Pennsylvania, Philadelphia, PA, USA
J. Moore, University of Illinois at Urbana-Champaign, IL, USA
T. Mukaiyama, Kitasato Institute, Tokyo, Japan
K. C. Nicolaou, Scripps Research Institute, La Jolla, CA, USA
R. Noyori, Nagoya University, Japan
S. Omura, Kitasato Institute, Tokyo, Japan
G. Ourisson, Centre National de la Recherche Scientifique, Strasbourg, France
L. E. Overman, University of California, Irvine, CA, USA
I. Paterson, University of Cambridge, UK
G. Pattenden, University of Nottingham, UK
S. Roberts, University of Manchester, UK
S. L. Schreiber, Harvard University, Cambridge, MA, USA
V. Snieckus, Queen's University, Kingston, Canada
Y. Thebtaranonth, Mahidol University, Bangkok, Thailand
K. Tomioka, Kyoto University, Japan
J. D. Wuest, University of Montreal, Canada
H. Yamamoto, University of Chicago, IL, USA
M. Yus, University of Alicante, Spain

Tetrahedron
Instructions to contributors

Please follow these instructions carefully to ensure that the review and publication of your paper are as swift and efficient as possible. These notes may be copied freely.

Tetrahedron seeks to publish experimental or theoretical research results of outstanding significance and timeliness in the field of Organic Chemistry, Bioorganic Chemistry and related disciplines. Publications may be in the form of Articles, Reports, or Symposia-in-Print.

The contents of papers are the sole responsibility of the authors, and publication shall not imply the concurrence of the Editors or Publisher.

ARTICLES should describe original research in organic chemistry of high quality and timeliness. Because of restrictions on the size of the journal, priority will be given to those contributions describing scientific work having as broad appeal as possible to the diverse readership. We ask referees to help in the selection of articles which have this breadth and suggest that papers covering narrower aspects of the field be sent to journals specializing in those areas. It is strongly recommended that articles be written in English.

REPORTS are specially commissioned reviews of research results of topical importance. Such articles, published only in English, are commissioned in appropriate fields by the Editors of Tetrahedron Reports.

SYMPOSIA-IN-PRINT comprise collections of original research papers (including experimental sections) covering timely areas of organic chemistry. Topics for forthcoming Symposia are announced in the journal from time to time. A Guest Editor will invite authors active in the field to submit papers which are then reviewed and processed for publication by the Guest Editor under the usual refereeing system. Opportunity is also provided for other active investigators to submit contributions. These Symposia are published in English.

Journal policy

The language of submission is English, but articles in French or German will be considered. Papers are submitted on the understanding that the subject matter has not been previously published and is not being submitted elsewhere. Authors must accept full responsibility for the factual accuracy of the data presented and should obtain any authorization necessary for publication. All papers are sent to referees who advise the Editor on the matter of acceptance in accordance with the high standards required. Referees' names are not disclosed, but their views are forwarded by the Editor to the authors for consideration. Authors are **strongly** encouraged to suggest the names and addresses of suitable referees.

Journal conventions

Nomenclature: Authors will find the following reference books and websites useful for recommended nomenclature. It is the responsibility of the author to provide correct chemical nomenclature.

IUPAC Nomenclature of Organic Chemistry; Rigaudy, J.; Klesney, S. P., Eds; Pergamon: Oxford, 1979.

A Guide to IUPAC Nomenclature of Organic Compounds (Recommendations 1993); Panico, R.; Powell, W. H.; Richer, J. C., Eds; Blackwell Publishing: Oxford, 1993.

http://www.acdlabs.com/iupac/nomenclature

http://www.chem.qmul.ac.uk/iupac/

X-ray crystallographic data: Prior to submission of the manuscript, the author should deposit crystallographic data for organic and metal-organic structures with the Cambridge Crystallographic Data Centre. The data, without structure factors, should be sent by e-mail to: deposit@ccdc.cam.ac.uk, as an ASCII file, preferably in the CIF format. Hard copy data should be sent to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. A checklist of data items for deposition can be obtained from the CCDC Home Page on the World Wide Web (http://www.ccdc.cam.ac.uk/) or by e-mail to: fileserv@ccdc.cam. ac.uk, with the one-line message, sendme checklist. The data will be acknowledged, within three working days, with one CCDC deposition number per structure deposited. These numbers should be included with the following standard text in the manuscript: Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC ... Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk]. Deposited data may be accessed by the journal and checked as part of the refereeing process. If data are revised prior to publication, a replacement file should be sent to CCDC.

Instructions regarding GenBank/DNA Sequence Linking: Many Elsevier journals cite 'gene accession numbers' in their running text and footnotes. Gene accession numbers refer to genes or DNA sequences about which further information can be found in the database at the National Center for Biotechnical Information (NCBI) at the National Library of Medicine. Elsevier authors wishing to enable other scientists to use the accession numbers cited in their papers via links to these sources, should type this information in the following manner:

For each and every accession number cited in an article, authors should type the accession number in **bold, underlined text**. Letters in the accession number should always be capitalised. (See Example 1 below). This combination of letters and format will enable Elsevier's typesetters to recognize the relevant texts as accession numbers and add the required link to GenBank's sequences.

Example 1: 'GenBank accession nos. **AI631510**, **AI631511**, **AI632198**, and **BF223228**), a B-cell tumor from a chronic lymphatic leukemia (GenBank accession no. **BE675048**), and a T-cell lymphoma (GenBank accession no. **AA361117**)'.

Authors are encouraged to check accession numbers used very carefully. **An error in a letter or number can result in a dead link**. In the final version of the ***printed*** **article**, the accession number text will not appear bold or underlined (see Example 2 below).

Example 2: 'GenBank accession nos. AI631510, AI631511, AI632198, and BF223228, a B-cell tumor from a chronic lymphatic leukemia (GenBank accession no. BE675048), and a T-cell lymphoma (GenBank accession no. AA361117)'.

In the final version of the ***electronic*** **copy**, the accession number text will be linked to the appropriate source in the NCBI databases enabling readers to go directly to that source from the article.

Experimental: Authors should be as concise as possible in experimental descriptions. The Experimental section must contain all the information necessary to guarantee reproducibility. An introductory paragraph containing information concerning solvents, sources of less common starting materials, special equipment, etc. should be provided. The procedures should be written in the past tense and include the weight, mmol, volume, etc. in brackets after the names of the substances or solvents. General reaction conditions should be given only once. The title of an experiment should include the chemical name and compound number of the product prepared: subsequently, these compounds should be identified by their number. Details of the work up procedure must be included. An experimental procedure is not normally required for known compounds prepared by a literature procedure; in such cases, the reference will suffice. For known compounds prepared by a novel procedure, comparative data together with the literature reference are required (e.g. m.p. and published m.p. with a reference to the latter).

Characterization of new compounds: All new compounds should be fully characterized with relevant physical and spectroscopic data, normally including compound description, m.p./b.p. if appropriate, IR, NMR, MS and $[\alpha]_D$ values for enantiopure compounds. In addition, microanalyses should be included whenever possible (normally $\pm 0.4\%$). Under appropriate circumstances, and at the Editor's discretion, high resolution mass data (normally to ± 5 ppm) may serve in lieu of microanalyses; in this case a statement must be included regarding the purity of the products and how this was determined [e.g. all new compounds were determined to be >95% pure by HPLC (or GLC or ^{1}H NMR spectroscopy)].

For compound libraries prepared by combinatorial methods, a significant number of diverse examples must be fully characterized (normally half of the members for libraries up to 40 compounds, 20 representative examples for bigger libraries). Resin-bound intermediates do not have to be fully characterized if acceptable characterization of released products is provided

Supplementary material: Elsevier accepts electronic supplementary material to support and enhance your scientific research. Supplementary files offer the author additional possibilities to publish supporting applications, movies, animation sequences, high-resolution images, background datasets, sound clips and more. Supplementary files supplied will be published online alongside the electronic version of your article in Elsevier web products, including ScienceDirect: http://www.sciencedirect.com.

In order to ensure that your submitted material is directly usable, please ensure that data is provided in one of our recommended file formats. Supplementary data must be saved in files separate from those for the manuscript and figures, and all file names must be supplied. Supplementary files should either be referred to from within the text of your manuscript in the same way as for figures and tables, or their presence be indicated by adding a paragraph entitled "Supplementary Data" at the end of the manuscript, detailing which data is supplied. In addition, authors should also provide a concise and descriptive caption for each file.

When supplying supplementary material, authors must state whether data files are either i) for online publication or ii) to be used as an aid for the refereeing of the paper only. All supplementary data will be subject to peer-review. For more detailed instructions please visit Elsevier's Author Gateway at http://authors.elsevier.com, and click on Artwork instructions, then Multimedia files.

Manuscript preparation

General requirements: Manuscripts should be printed on one side of the page only, using black type on good quality white paper. Pages must be numbered. The corresponding author's full mailing address, plus phone and fax numbers and e-mail address should be included. The manuscript should be compiled in the following order: Title, Authors, Affiliations, Abstract, Keywords, Introduction, Results, Discussion, Conclusion, Experimental, References, Captions, Tables, Figures, Schemes.

Graphical Abstracts: Authors must supply a graphical abstract at the time the paper is first submitted. The abstract should summarise the contents of the paper in a concise, pictorial form designed to capture the attention of a wide readership and for compilation of databases. Carefully drawn chemical structures are desired that serve to illustrate the theme of the paper. Authors may also provide appropriate text, not exceeding 50 words.

The content of the graphical abstract will be typeset and should be kept within an area of 5cm by 17cm. Authors must supply the graphical abstract on disk as well as in printed form, or if using online submission include the graphical abstract in the main article file and then attach the graphic separately.

For examples of graphical abstracts, please consult a recent issue of the journal or visit the journal page on ScienceDirect at: http://www.sciencedirect.com/science/journal/00404020 and click 'Sample Issue Online'.

Title: The title should be brief, specific and rich in informative words; it should not contain any literature references or compound numbers.

Authors and affiliations: Where possible, supply given names, middle initials and family names for complete identification. Use superscript lowercase letters to indicate different addresses, which should be as detailed as possible, and must include the country name. The corresponding author should be indicated with an asterisk, and contact details (fax, e-mail) should be placed in a footnote. There should be only one corresponding author. Information relating to other authors (e.g. present addresses) should be placed in footnotes indicated by the appropriate symbols (see below).

Abstract: Authors must include a short abstract of approximately four to six lines that states briefly the purpose of the research, the principal results and major conclusions. References and compound numbers should not be mentioned in the abstract unless full details are given.

Text: Text should be subdivided in the simplest possible way consistent with clarity. Headings should reflect the relative importance of the sections. Ensure that all tables, figures and schemes are cited in the text in numerical order. The preferred position for chemical structures should be indicated. Trade names should have an initial capital letter, and trademark protection should be acknowledged in the standard fashion, using the superscripted characters $^{\text{TM}}$ and $^{®}$ for trademarks and registered trademarks respectively (although not for words which have entered common usage, e.g. pyrex). All measurements and data should be given in SI units where possible, or other internationally accepted units. Abbreviations should be used consistently throughout the text, and all nonstandard abbreviations should be defined on first usage. Authors are requested to draw attention to hazardous materials or procedures by adding the word **CAUTION** followed by a brief descriptive phrase and literature references if appropriate. The experimental information should be as concise as possible, while containing all the information necessary to guarantee reproducibility.

References: In the text, references should be indicated by superscript Arabic numerals which run consecutively through the paper and appear after any punctuation; ensure that all references are cited in the text and vice versa. The reference list should preferably contain only literature references; other information (e.g. experimental details) should be placed either within the body of the text, or as a footnote to the text. Preferably, each reference should contain only one literature citation. Authors are expected to check the original source reference for accuracy. Journal[1] titles should be abbreviated according to American Chemical Society guidelines (*The ACS Style Guide*; Dodd, J. S., Ed.: American Chemical Society: Washington, DC, 1997). Inclusive pagination is strongly recommended. Book references[2,3] should cite author(s), chapter title (if applicable), editor(s), book title, edition/volume, publisher name, publisher location, date and pages. Examples, including a thesis citation,[4] are shown below.

1. Barton, D. H. R.; Yadav-Bhatnagar, N.; Finet, J.-P.; Khamsi, J. *Tetrahedron Lett.* **1987,** *28,* 3111–3114.

2. Katritzky, A. R. *Handbook of Organic Chemistry*; Pergamon: Oxford, 1985; pp 53–86.
3. Smith, D. H.; Masinter, L. M.; Sridharan, N. S. In *Heuristic DENDRAL: Analysis of Molecular Structure*; Wipke, W. T.; Heller, S. R.; Feldmann, R. J.; Hyde, E., Eds. Computer representation and manipulation of chemical information. John Wiley: New York, 1974; pp 287–298.
4. Cato, S. J. Ph.D. Thesis, University of Florida, 1987.

Footnotes: Footnotes should appear at the bottom of the appropriate page and be indicated by the following symbols: *, †, ‡, §, ¶, ‖.

Tables

All tables should be cited in the text, and numbered in order of appearance with Arabic numerals. All table columns should have a brief explanatory heading and where appropriate, units of measurement. *Vertical lines should not be used.* Footnotes to tables should be typed below the table, each on a separate line, and should be referred to by superscript letters.

Artwork

Figures, schemes and equations must be cited in the text and numbered in order of appearance with Arabic numerals; other graphics should be placed at a particular position in the text but not specifically referenced. All graphics (including chemical structures) must be supplied camera-ready, for reproduction at single or double column width (83 mm or 176 mm, respectively). Please ensure that all illustrations within a paper are consistent in type and quality. Captions should not be included as part of the graphic; instead all captions should be supplied at the end of the text. All graphics must be labelled with the figure or scheme number, and the corresponding author's name.

If graphics are created using ChemDraw the preferred settings are: font 10 pt Helvetica, chain angle 120°, bond spacing 18% of length, fixed length 14.4 pt (0.508 cm), bold width 2.0 pt (0.071 cm), line width 0.6 pt (0.021 cm), margin width 1.6 pt (0.056 cm), and hash spacing 2.5 pt (0.088 cm). Compound numbers should be in bold face.

Computer-generated illustrations, halftones and line/tones should also be provided where possible. The following points should be taken into consideration when preparing electronic graphic files: Tagged Image File Format (TIFF) or Encapsulated PostScript (EPS) files are preferred. Suggested packages for line graphics are ChemDraw, Adobe Illustrator (version 3.0 or above), Freehand and Corel Draw. Graphics created in WordPerfect and Word generally have too low a resolution for our requirements. Files of scanned line graphics can be accepted at a minimum resolution of 1000 dpi, for scanned halftones, 300 dpi, and scanned line/tones, 500 dpi. Colour should be scanned at 300 dpi (500 dpi for colour line/tones).

For detailed instructions on the preparation of electronic artwork, consult Elsevier's Author Gateway at http://authors.elsevier.com

Graphics: Since we cannot guarantee the usability of graphic files, hard copies of all illustrations must accompany the accepted printout of the manuscript in all cases.

Colour: Colour figures may be printed in the journal at no charge to the author, provided that the Editor considers the colour necessary to convey scientific information. Colour figures should be supplied in hard copy format ready for reproduction.

Colour figures should be clearly marked as being intended for colour reproduction on the Web and in print or to be reproduced in colour on the Web and in black-and-white in print.

If only colour on the web is required, black-and-white versions of the figures should also be supplied for printing purposes.

Copyright guidelines

Upon acceptance of an article, Authors will be asked to transfer copyright (for more information on copyright see http://authors.elsevier.com). This transfer will ensure the widest possible dissemination of information. A letter will be sent to the corresponding Author confirming receipt of the manuscript. A form facilitating transfer of copyright will be provided.

If excerpts from other copyrighted works are included, the Author(s) must obtain written permission from the copyright owners and credit the source(s) in the article. Elsevier has preprinted forms for use by Authors in these cases: contact Elsevier's Rights Department, Oxford, UK: phone (+44) 1865 843830, fax (+44) 1865 853333, e-mail: permissions@elsevier.com. Requests may also be completed on-line via the Elsevier homepage (http://www.elsevier.com/locate/permissions).

Online submission of manuscripts

Tetrahedron manuscripts can be submitted using the TetSubmit online submission and review environment. Authors are required to go to the website and upload their article and its associated artwork. Authors are asked to ensure that their files only have one file extension (e.g., .doc). A PDF file is generated and the reviewing process is carried out using the PDF. All correspondence between editor and author is performed by e-mail. Authors are, however, legally obliged to sign and return a physical transfer of copyright form by conventional mail.

To submit your paper online, please go to: http://www.tetsubmit.com

Templates are provided in order to allow authors to view their paper in a style close to the final printed form. Their use is optional. All manuscripts will be fully typeset from the author's electronic files. It should be noted that due to defined typesetting standards and the complex requirements of electronic publishing, the Publisher will not always be able to exactly match the layout the author has submitted. In particular, in the finished journal article, figures and tables are usually placed at the top or bottom of pages. The template is only intended to be used in assisting with the preparation and submission of manuscripts.

It should be noted that the use of the journal template is not a requirement and its adoption will neither speed nor delay publication. Elsevier can handle most major word processing packages and in general most formatting applied by authors for style and layout is replaced when the article is being typeset.

These templates contain a large number of macros. To ensure successful PDF conversion in TetSubmit, it is important that the author saves a new document based on the template, rather than saving the template itself. To use the template, the author should save the final document as a Word file with a '.doc' extension (rather than the '.dot' extension).

Please ensure that the graphical abstract is included as page 1 of your manuscript when submitting online.

For detailed instructions on the preparation of electronic artwork, consult Elsevier's Author Gateway at http://authors.elsevier.com

Mail submission of manuscripts

The original and three copies of the manuscript, including the graphical abstract should be sent to the appropriate Regional Editor (see below). Authors must also include a brief statement justifying acceptance. To achieve rapid publication authors are encouraged to fax or preferably e-mail their first submission to the Editor at the time that they mail the manuscript; the date of submission will be taken as the date of e-mail. The corresponding author's full mailing address, plus phone and fax numbers and e-mail address should be supplied to aid rapid communication. Papers sent to the wrong Regional Editor will be forwarded (causing delay) to the appropriate Editor as determined by the *permanent address* of the corresponding author.

Disk submission: When a manuscript has been accepted for publication by the editorial office, authors are requested to also supply their paper (and graphical abstract) in electronic format on disk. Please give full details of operating system, programs used, number of files sent, and information contained in each file. It is important that the file on disk and the accepted printout are identical.

Text: We can accept most word-processing formats (but prefer Microsoft Word: IBM or Macintosh). Most formatting codes will be removed or replaced on processing your article so there is no need for you to use excessive layout styling. In addition, do not use options such as automatic word breaking, justified layout, double columns, automatic paragraph numbering (especially for numbered references) or EndNote. However, do use bold face, italic, subscripts, superscripts, etc. Do not embed the figures into the text file.

Editorial offices

(1) **Contributions from Austria, Belgium, France, Germany, Portugal, Spain and Switzerland,** Professor L. Ghosez, Laboratoire de Chimie Organique de Synthèse, Université Catholique de Louvain, Place L. Pasteur 1, B-1348 Louvain-la-Neuve, Belgium. **Fax: +32 10 47 29 44; e-mail: vanlierde@chim.ucl.ac.be**

(2) **China,** Professor Lin Guo-Qiang, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, China (manuscripts from Taiwan may be sent to Professor Lin, or to the usual Editor in Japan, at the choice of the authors). **Fax: +86 21 641 66263; e-mail: tetrahed@pub.sioc.ac.cn**

(3) **Japan and South Korea,** Professor T. Shioiri, Graduate School of Environmental & Human Sciences, Meijo University, Shiogamaguchi, Tempaku, Nagoya 468-8502, Japan. **Fax: +81 52 832 1555; e-mail: tetra@ccmfs.meijo-u.ac.jp**

(4) **The Americas,** Professor S. F. Martin, Chemistry and Biochemistry Department, The University of Texas, 1 University Station A5300, Austin, TX 78712-0165, USA. **Fax: +800 435 6857; e-mail: tet@mail.utexas.edu**

(5) **All regions other than those specified under (1)–(4) above,** Professor R. J. K. Taylor, Department of Chemistry, University of York, Heslington, York YO10 5DD, UK. **Fax: +44 1904 434523; e-mail: tet@york.ac.uk**

Tetrahedron Symposia-in-Print: To the Guest Editor as announced for the particular symposium.

Tetrahedron Reports:
The Americas, Professor G. H. Posner, Department of Chemistry, Johns Hopkins University, Baltimore, MD 21218, USA. **Fax: +1 410 516 8420; e-mail: ghp@jhu.edu**
Other locations, Professor W. B. Motherwell, Department of Chemistry, University College London, 20 Gordon Street, London, WC1H 0AJ, UK. **Fax: +44 20 7679 7524; e-mail: w.b.motherwell@ucl.ac.uk**

Proofs

Proofs will be despatched via e-mail or fax and should be returned to the publisher with corrections as quickly as possible, normally within 48 hours of receipt.

Offprints

The corresponding author will be sent 25 free offprints. Additional offprints can be ordered when the paper is accepted. Correspondence regarding offprints should be directed to: Global Author Support, Elsevier Ireland Ltd, Elsevier House, Brookvale Plaza, East Park, Shannon, Co. Clare, Ireland; e-mail: authorsupport@elsevier.com

Page charges

None.

Author benefits

Contributors to Elsevier journals are entitled to a 30% discount on all Elsevier books.

Other enquiries

Visit Elsevier's Author Gateway (http://authors.elsevier.com) for the facility to track accepted articles and set up e-mail alerts to inform you of when an article's status has changed. The Author Gateway also provides detailed artwork guidelines, copyright information, frequently asked questions and more.

Contact details for questions arising after acceptance of an article, especially those relating to proofs, are provided after registration of an article for publication.