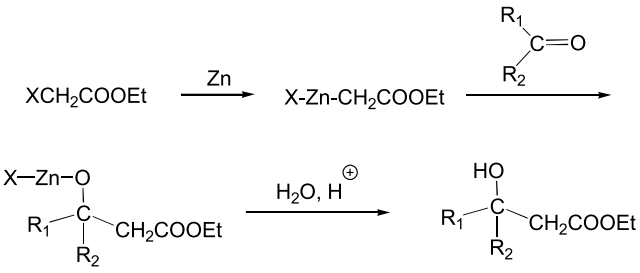
ELSEVIER

Tetrahedron

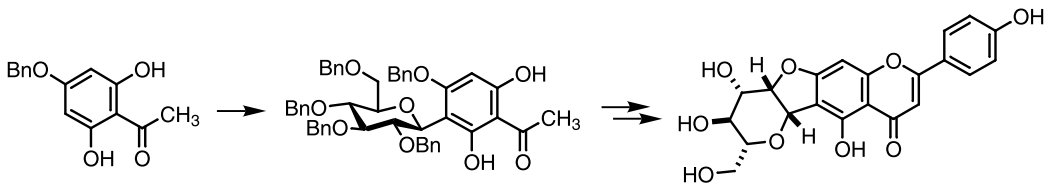
Tetrahedron Vol. 60, No. 42, 2004

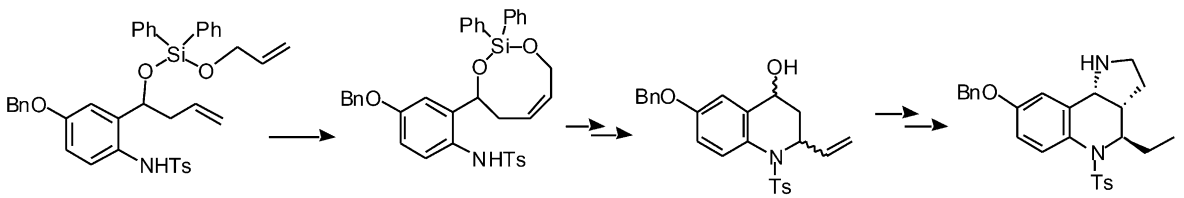
Contents

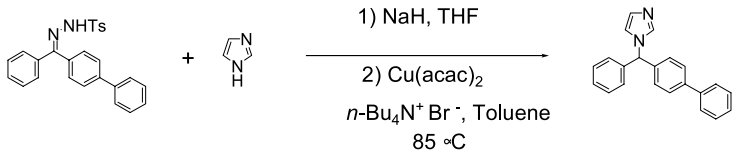
REPORT

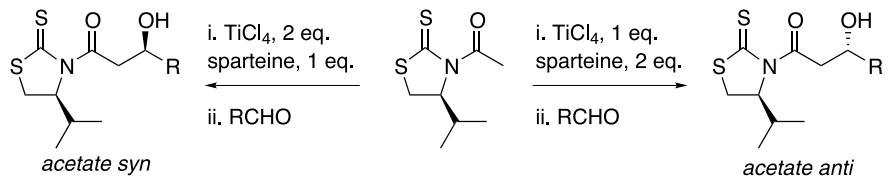


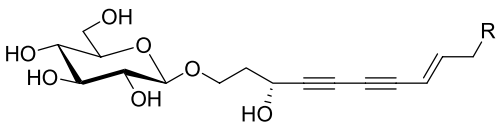
ARTICLES

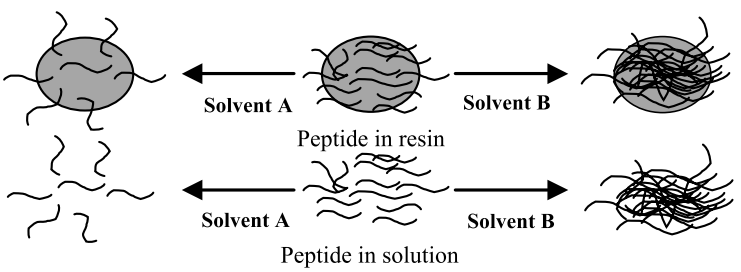


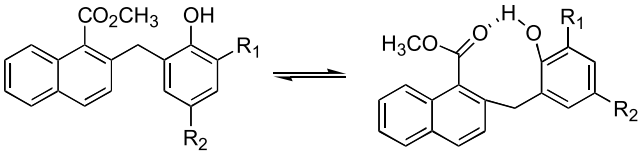




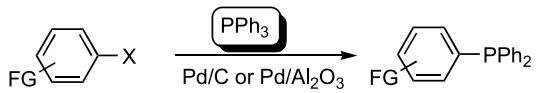




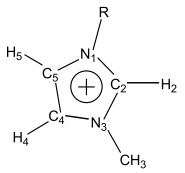




The enthalpy of nine-membered intramolecular hydrogen bonding between carbonyl groups and phenolic hydroxyl groups of 2-arylmethylphenols was related to the electron-withdrawing ability of the substituents on the phenol and the basicity of the carbonyl group. The entropy loss was dependent on the rotation freedom of the phenol group.

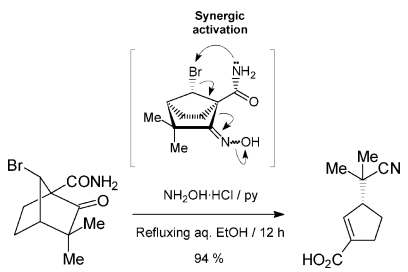


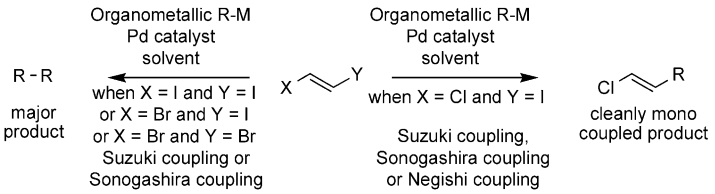
X = Cl, Br, OTf, ONf; FG = COMe, CHO, COOMe, CN, OMe, Cl, py

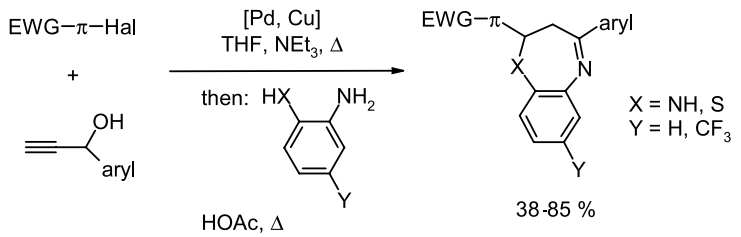


R: C_2H_5 (**1**), C_3H_7 (**2**), C_4H_9 (**3**), C_5H_{11} (**4**), C_6H_{13} (**5**), C_7H_{15} (**6**), C_8H_{17}(**7**)

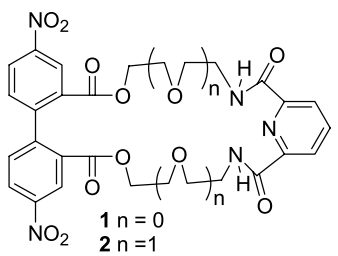
X^-: Br^- (**a**), BF_4^- (**b**), PF_6^- (**c**)

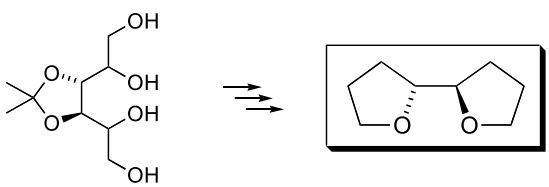




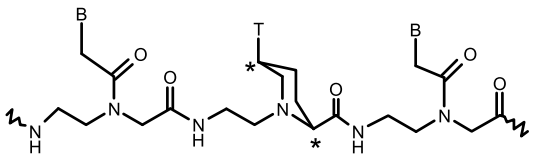


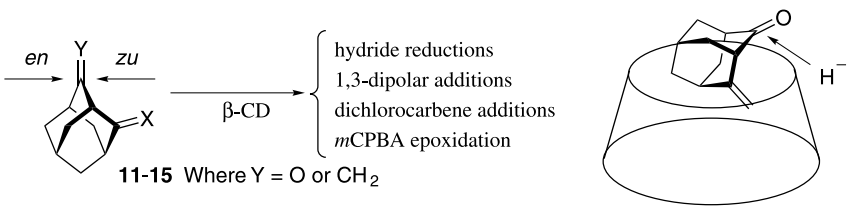
Ligands **1** and **2** are able to act as colorimetric sensor selective for fluoride anion. The colour seems to be developed after deprotonation reaction of the amide groups through an intermolecular charge transfer process. X-ray diffraction studies of ligand **2** has also included.

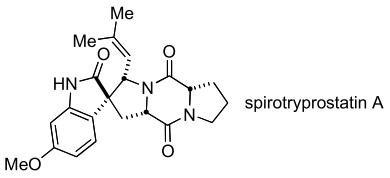


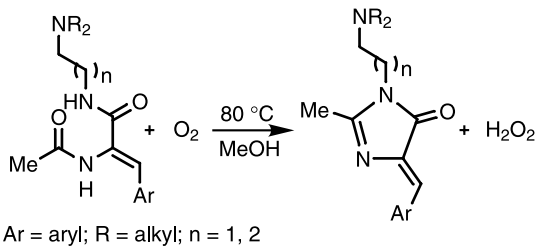


Evaluation of bis-THF as chiral ligand for R-Li in four different ractions









OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

SCIENCE DIRECT™

Full text of this journal is available, on-line from **ScienceDirect**. Visit **www.sciencedirect.com** for more information.

CONTENTS Direct

This journal is part of **ContentsDirect**, the ***free*** alerting service which sends tables of contents by e-mail for Elsevier books and journals. You can register for **ContentsDirect** online at: **http://contentsdirect.elsevier.com**

Indexed/Abstracted in: AGRICOLA, Beilstein, BIOSIS Previews, CAB Abstracts, Chemical Abstracts, Chemical Engineering and Biotechnology Abstracts, Current Biotechnology 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
Tetrahedron
ELSEVIER
Tetrahedron 60 (2004) 9325–9374

Tetrahedron report number 692

The Reformatsky reaction in organic synthesis. Recent advances

Rogelio Ocampo[a] and William R. Dolbier, Jr.[b,*]

[a]*Departamento de Química, Universidad de Caldas, A.A. 275, Manizales, Colombia*
[b]*Department of Chemistry, University of Florida, Gainesville, FL 32611-7200, USA*

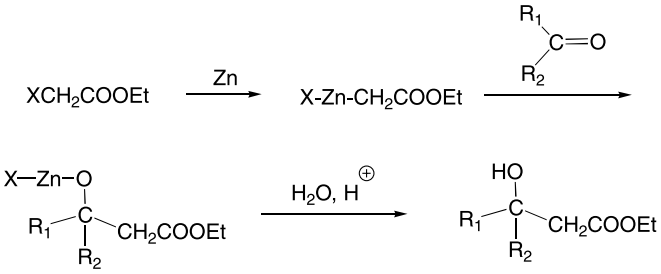
Received 2 June 2004

Available online 27 August 2004

Contents

Keywords: Reformatsky reaction; Organic synthesis; Organozinc reagent.
* Corresponding author. Tel.: +57-352-392-0591; fax: +57-352-846-1962; e-mail: wrd@chem.ufl.edu

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.07.018



Scheme 1. X = halogen; R_1 and R_2 = H, alkyl, aryl.

1. Introduction

The classical form of the well-known Reformatsky reaction, introduced for the first time in 1887,[1] consists of the zinc-induced formation of β-hydroxyalkanoates from ethyl α-haloacetates in a reaction with aldehydes or ketones (Scheme 1).

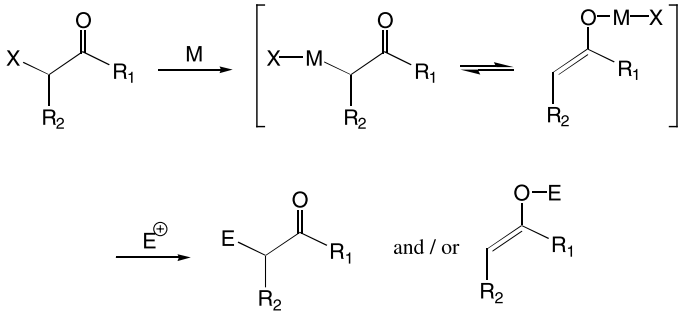
The reaction was ultimately found to be applicable to alkyl 2-haloalkanoates in general as well as to 'remote' (3-, 4-, 5- or higher) haloalkanoates. The scope of the Reformatsky reaction was also extended beyond the use of aldehydes or ketones as electrophiles. In addition, a number of other metals and catalysts[2] were found to promote the role analogous to that of zinc. These facts called for a broader, more comprehensive definition, and therefore, as stated in a previous review,[3] "Reformatsky reactions are defined as those resulting from metal insertions into carbon–halogen bonds activated by carbonyl-, carbonyl-derived or carbonyl-related groups in vicinal or vinylogous positions with practically all kinds of electrophiles". In a general sense, the Reformatsky reaction can be taken as subsuming all enolate formations by oxidative addition of a metal or a low-valent metal salt or complex into a carbon–halogen bond (or carbon–leaving group bond) activated by a vicinal carbonyl-derived group, followed by a reaction of the enolates thus formed with an appropriate electrophile (Scheme 2).[4,5] However, an aqueous metal-free electrochemical Reformatsky reaction, presumably proceeding via a radical mechanism, was reported recently.[6]

Several recent reviews have appeared, focusing on the structure and nature of the organozinc reagent (spectroscopically and theoretically),[3,7] substitution of zinc by other metals,[2,3] zinc activation,[3,4b] experimental protocols,[3–5] different precursors and electrophiles,[3] and reactions and applications in organic synthesis.[3,4,8]

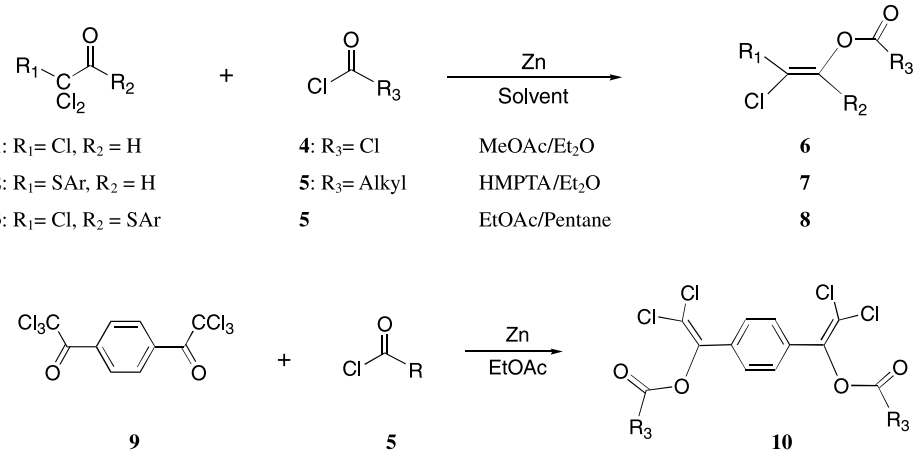
Reformatsky reactions have been recognized as among the most useful methods for the formation of carbon–carbon bonds, becoming a valuable tool in modern organic synthesis with a broad applicability and great versatility in numerous inter- and intramolecular reactions involving a great variety of electrophiles. As such, this methodology is considered a useful alternative to base-induced aldol reactions or, at the least, an important complement to other enolate reactions. A retro-Reformatsky reaction was recently reported and was used as one of the steps in the synthesis of heterocyclic enamines.[9]

One of the advantages of the Reformatsky reaction is that the reaction proceeds under neutral conditions, in contrast to the aldol reaction which, in general, requires a base to generate the enolate or an acid to activate the electrophile. Very important is the fact that in classical Reformatsky reactions no *O*-products are obtained, and even reagents with strong affinities for oxygen such as TMS–Cl afford only C-silylated products in most of the cases. Thus, the site of the reaction is strictly determined by the site of the halogen substituent, although some few exceptions to this rule are known (Scheme 3).[10–12]

Chloral **1** and other polyhalogenated carbonyl compounds react with phosgene **4** in the presence of zinc dust to afford 2,2-dihalovinyl chloroformate **6** clearly via an *O*-enolate reaction with the phosgene acting as the electrophile.[10]



Scheme 2.



1: R_1= Cl, R_2 = H **4**: R_3= Cl **6**
2: R_1= SAr, R_2 = H **5**: R_3= Alkyl **7**
3: R_1= Cl, R_2 = SAr **5** **8**

9 **5** **10**

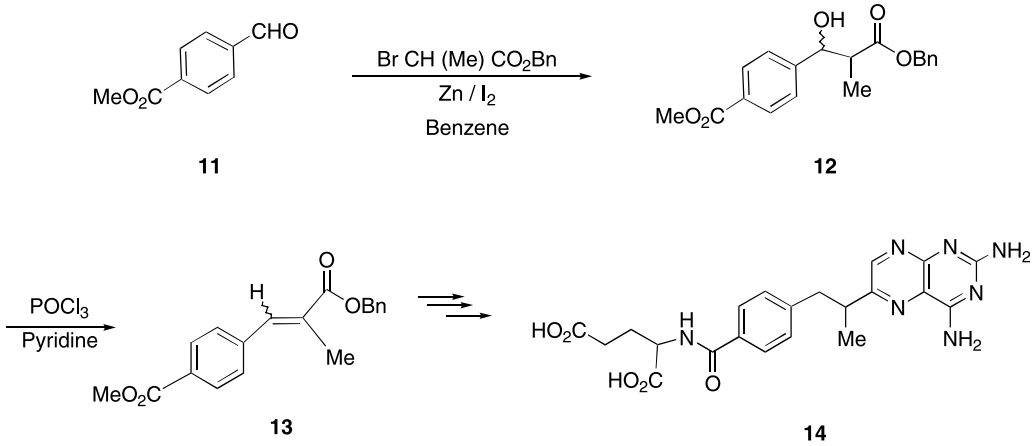
Scheme 3.

Likewise, *O*-enolate attack of polyhalogenated compounds **2**, **3** and **9** on acyl chlorides **5** in Reformatsky reactions led to vinyl compounds **7**, **8** and **10** (Scheme 3).[11,12]

However, several disadvantages of Reformatsky reactions have been recognized in the past. A problem encountered in many reactions is the unselective dehydration of the aldols initially formed, but this problem has been overcome either by substantially lowering the reaction temperature or by using silylated starting materials. Perhaps, the most serious limitation attributed to Reformatsky reactions has been the lower yields and stereoselectivities associated with them in comparison to those of aldol reactions.[13] It is well known that base-induced aldolizations are readily stereocontrolled, and the low stereoselectivities associated with Reformatsky reactions have discouraged synthetic chemists from using them, particularly if asymmetric targets were desired. This perception has often limited the synthetic applications of the Reformatsky reaction, it being used largely for those syntheses that involve subsequent elimination or oxidation steps on the product aldol, as for example in the synthesis of (−)-oudemansins.[14] Also, the Reformatsky condensation of benzyl α-bromopropionate with methyl 4-formylbenzoate **11** is conducted without stereochemical concerns because it is followed by dehydration of the diastereomeric products **12**, to afford the respective α,β-unsaturated ester **13**, which was used to prepare antifolate 9-alkyl-10-deazaminopterins **14** (Scheme 4).[15] Similarly, β-substituted acrylates RCH=$CHCO_2Et$ (R=Ar, Cyhex, 3-Py) were synthesized via the reaction of the respective aldehydes with ethyl bromoacetate by way of one-pot Reformatsky/dehydration processes prompted by HMPT and zinc.[16]

In the total synthesis of (+)-10,10-difluorothromboxane A_2, synthesis of the key aldehyde intermediate **18** was accomplished in 14 steps. Diastereoselectivity was high in all but the Reformatsky step with aldehyde **15** (Scheme 5).[17] However, both epimers, **16** and **17**, obtained in this reaction could be converted efficiently to key aldehyde **18**. This is a good example of how a non-diastereoselective Reformatsky reaction was able to be useful in a stereo directed synthesis.

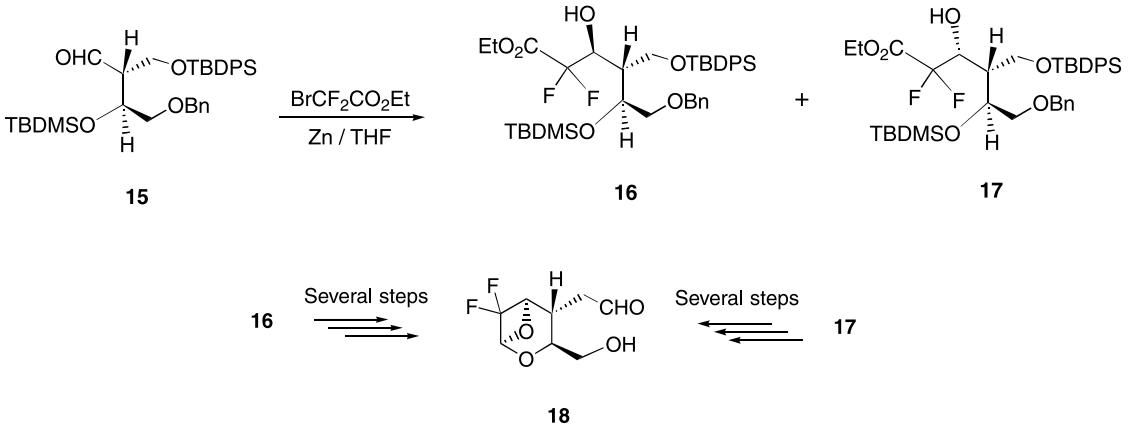
Sometimes the diastereomeric mixture resulting from Reformatsky reactions can be resolved by conventional chromatographic techniques, so that the subsequent synthetic steps can be performed on the specific diastereomer.[18] However, such syntheses are obviously not convenient enough to have broad application.



11 **12**

13 **14**

Scheme 4.



Scheme 5.

Stereoselectivity in Reformatsky reactions has become a challenge of interest during the past decade, and a lot of recent progress has been made in this area. As will be illustrated later, there are now a number of examples of highly diastereo- and enantioselective Reformatsky reactions, deriving from the use of chiral ligands, thus circumventing the limitation mentioned above and rescuing the modern synthetic potential of this methodology. Therefore, the Reformatsky reaction is now suited for applications to the synthesis of complex target molecules, including being very applicable to intramolecular aldol processes, even when medium sized rings are desired. It is the intent of this review to summarize the most recent progress in the use of Reformatsky reactions in organic synthesis, including the latest developments in diastereo- and enantioselective reactions.

2. Metals or derivatives and catalysts for Reformatsky reactions

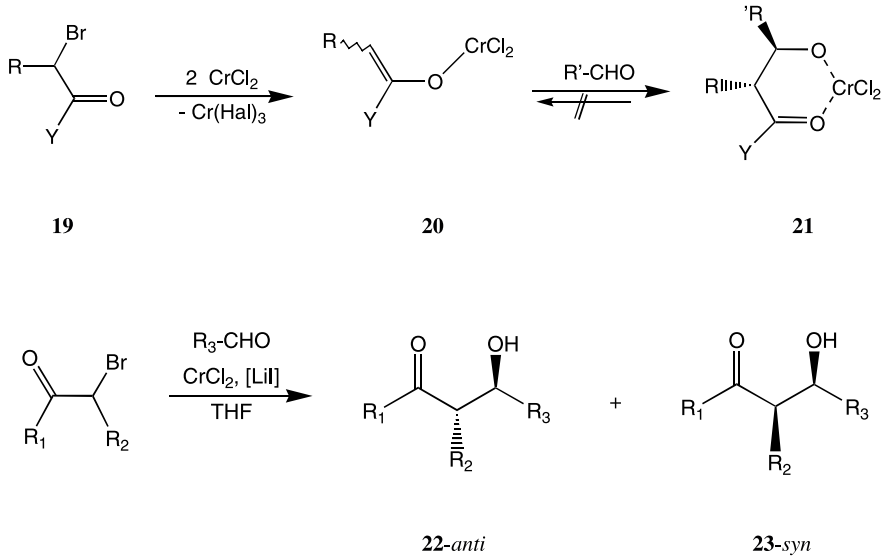
2.1. Zinc metal activation and catalysts

Previous reviews[3,5,8] have summarized the most common methods of metal activation, which function to either remove the deactivating zinc oxide layer from the metal surface or to achieve a fine distribution of the metal. Such methods generally use procedures that involve simple washing of the zinc (in the form of dust, foil, pellets or turnings),[3,8] depassivating procedures employing reagents such as iodine,[8,19] chlorotrimethylsilane,[20] iodine-chlorotrimethylsilane,[21] 1,2-dibromoethane,[8,22] copper (I) halides,[3,8,23] mercuric halide,[3,8,24] or molecular sieves.[23e,f] Improved classical and non-classic Reformatsky reactions have been accomplished by the use of special types of activated zinc, which include the use of zinc–copper,[25] zinc–silver[23,26] or zinc/silver–graphite couples.[27] Good results have also been reported by using reduction-based activation of zinc halides in solution. Examples of this latter category are the so-called Rieke zinc™ (zinc chloride reduced by potassium),[28] or zinc chloride reduced by lithium with ultrasonic irradiation,[29] lithium naphthalenide[30] or sodium.[31] A new protocol of zinc chloride or tin (II) chloride reduction by sodium in liquid ammonia has been reported[32] for the synthesis of β-hydroxyesters, homoallylic and homopropargylic alcohols, with yields ranging from 61 to 96%. The activity of the resulting metal is lower than the corresponding Rieke-zinc™, but remarkably safe and short-time procedures and low cost render this approach particularly attractive for larger-scale applications.

In addition to the different zinc activation protocols available, it is also possible to use diethyl zinc[33,34] or some additives in combination with zinc,[3] for instance tantalum (prepared readily from tantalum(V) chloride and activated zinc)[35] or binuclear complexes (for example the vanadium complex $[V_2Cl_3(hmpa)_6][ZnCl_3(hmpa)]$).[36] This vanadium binuclear complex proved to be useful for other carbon–carbon formations as well. A combination of Zn/Et_2AlCl/AgOAc has been used as a modification for Reformatsky reactions of bromodifluoroacetate.[37] Cp_2TiCl_2 is reported to be a very special catalyst for zinc-mediated Reformatsky reactions of bromoacetate with 1-cyano-1-phenylsulfonyl alkenes[38] and alkyl 4-bromocrotonates with 1,1-dicyanoalkenes.[39] Although the catalytic role of Cp_2TiCl_2 is not well understood yet, strong evidence has been presented in favor of an SET mechanism in the course of Reformatsky reagent formation. Also Hg_2Cl_2,[40] triethyl boron,[41–44] cerium (III) salts,[3,45–47] disodium telluride,[3] titanium(II) chloride/copper,[48] titanium (IV) chloride,[42,49] (*o*-tolyl)$_3$P/$TiCl_4$,[50] titanium tetra iodide,[51] titanocene (III) chloride,[52] trialkylantimony/iodine, tributyl(phenyl)stannyllithium and diethyl aluminum chloride[53] are recognized examples of additives or inductors for Reformatsky reactions. In the presence of trimethylsilyl triflate, the 1,4-addition of a Reformatsky reagent on carbonyls α,β-unsaturated was observed.[54] A benzotriazole-mediated Reformatsky reaction has emerged as an interesting alternative for use with fluorinated precursors,[55,56] as well as with non-fluorinated analogs.[57]

2.2. Metals or derivatives other than zinc

There are a number of well-documented reports of Reformatsky-type reactions that use metals, metal salts, or



Scheme 6. Yields: 44–88%; ratio **22/23**: up to 0:100.

complexes other than zinc. A number of these variants have permitted interesting improvements, particularly in terms of some degree of stereocontrol. The chromium-Reformatsky reaction,[58] the SmI_2-promoted Reformatsky reaction (Kagan reagent),[59] and the indium-mediated Reformatsky reactions[60] (among several others) deserve special comment.

2.2.1. The chromium-Reformatsky reaction.[58] α-Haloketones, esters, nitriles and other Reformatsky substrates (e.g., **19**) readily react with chromium (II) salts, usually chromium dichloride, in the presence of carbonyl compounds via the intermediates **20** and **21** to give the corresponding aldol compounds **22** and **23** (Scheme 6), whereas crotonates react with high regioselectivity to yield α-products.[61]

These reactions usually proceed in THF, DMF or acetonitrile, with 2-haloketones and vinylogous compounds being the most reactive substrates, whereas esters (especially acetates) are much less reactive. Under the usual conditions alkyl, alkenyl and aryl halides are not useful substrates for the chromium-Reformatsky reaction. Unreactive electrophiles in intermolecular reactions include alkyl, alkenyl and aryl halides, esters, amides, imides, imines, immonium salts and α-halocarbonyl compounds; usually unreactive (<5%) are nitriles, Michael acceptors, allyl and benzyl halides, sulfoxides and others. Aldehydes are preferred more than 50–100 times over methyl ketones, and even more so over higher ketones (>200:1) which thus can be used as solvent.

A significant diastereoselectivity is an important feature of the chromium Reformatsky reaction, usually favoring the *syn* products **23** when aldehydes are used as electrophiles, particularly if large α′-residues are used, and this will be explained in Section 4.4.[61–64] However, by making use of chiral auxiliaries, excellent diastereomeric excess of *anti* products **22** has been possible.[65,66] Yields are often higher through LiI addition and by switching from THF to acetonitrile solvent.[58,67] The nature and bulkiness of the aldehyde seems to have little influence on the reactions and most yields are in 80–98% range.[67] Even aldehydes prone to self-condensation (i.e., phenylacetaldehyde) react cleanly, while the reaction with ketones yields the kinetic cross aldol products with one or two new quaternary centers. The reaction does not require special activation of the reagent and proceeds at room temperature and is suitable for microscale preparations.[61] The chromium (II) Reformatsky reaction was recently used as a key step in the synthesis of fragments and the complete carbon backbone of the novel diterpenoid tonantzitlolone.[68]

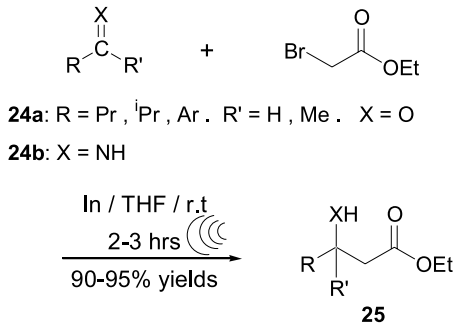
2.2.2. The samarium diiodide-promoted Reformatsky reaction (Kagan reagent). The one-electron reducing agent, samarium diiodide, has shown a remarkable versatility in promoting numerous synthetic transformations.[59] Because of its moderate oxidation potential and high oxophilicity, this divalent lanthanide reagent displays in general functional group selectivity in the reduction step and leads to the formation of products with high diastereoselectivities. Starting with α-bromoesters alone in THF, the reaction conditions can be controlled in such a way that a Reformatsky-type self-condensation takes place affording β-ketoesters,[69] or by further reduction it leads to β-hydroxyesters. $Sm(OTf)_2$ has proved to be reactive as well to promote Reformatsky-type reactions using α-haloesters or Peterson-type reactions using halides containing a silyl group.[70] The samarium diiodide-promoted Reformatsky reaction has been used extensively and efficiently to promote intramolecular Reformatsky reactions leading to medium- and large-sized carbocycles. Also, much of the progress on stereo control in Reformatsky-type reactions has been performed via the use of SmI_2, particularly for diastereoselective cyclizations. Section 4.3 illustrates several examples of SmI_2-cyclizations and other

intramolecular Reformatsky reactions, whereas Section 4.4 will discuss the stereochemical aspects of SmI_2-promoted Reformatsky reactions.

Samarium diiodide or metallic samarium can also be used in combination with other metals. For example, moderate to good yields of β-hydroxy ketones can be obtained from the reaction of α-bromoacetophenone with aldehydes in THF–H_2O under mild and neutral conditions in the presence of cadmium(II) chloride–metallic samarium[71] or bismuth (III) chloride–metallic samarium.[72]

Lanthanide salts other than samarium derived ones, in combination with lithium benzenetellurolate (PhTeLi) demonstrated good effectiveness for promotion of Reformatsky reactions to afford moderate yields and diastereoselectivity of β-hydroxyesters. Lanthanide chloride or lanthanide trifluoromethanesulfonates,[73] or $CeCl_3$[74] have been used for this purpose, the reaction proceeding with the latter reagents smoothly under mild conditions to give 47–95% yields of β-hydroxy esters. Such reagents were particularly efficient when sterically hindered and enolizable ketones were used. Mischmetall, an alloy of the light lanthanides, has been introduced recently for several kinds of organic procedures including Reformatsky-type reactions.[75]

2.2.3. The indium-mediated Reformatsky reaction. Indium has emerged as an interesting alternative with respect to Reformatsky reactions. Organoindium reagents have been used in a variety of transformations,[60,76,77] including allylations, Reformatsky reactions and cyclopropanations, some with a significant degree of diastereoselectivity when using external chiral aminoalcohols such as cinchonine or chinchonidine.[78] The sonochemical Reformatsky reaction of aldehydes or ketones **24a** with ethyl α-bromoesters in the presence of indium affords β-hydroxyesters **25** in good to excellent yields under mild conditions (Eq. 1).[79,80]



(1)

Interesting advantages of the Reformatsky-type reactions using indium derive from the fact that (i) the organoindium reagent is not reduced by hydroxyl groups (so, the reaction might be conducted in aqueous media),[81] and (ii) the reaction of aldehyde/ketone mixtures proceeds chemoselectively with exclusive addition to the aldehyde.[79] The analogous indium-mediated reaction of α-haloesters with imines **24b** instead of aldehydes produces 3,4-disubstituted β-lactams **26**.[82] A highly stereoselective synthesis of 4-octulose derivatives was recently reported via a key indium-mediated Reformatsky reaction using bromoacetonitrile.[83]

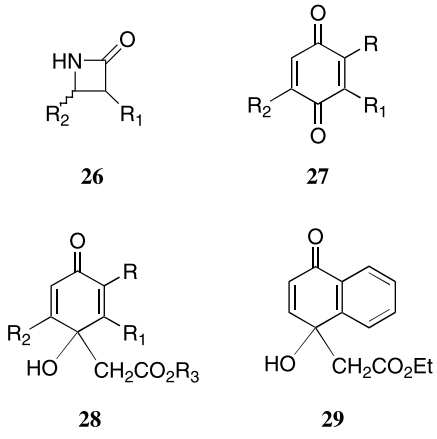


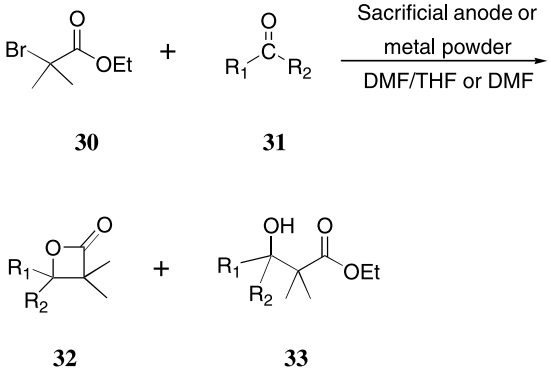
Table 1. Comparison of results from classical and electrochemically supported Reformatsky reactions induced by indium or zinc

Substrate **31**		Reformatsky reaction conditions and results					
R_1	R_2	Indium			Zinc		
		Method	Yield(%) **32**+**33**	Ratio **32/33**	Method	Yield(%) **32**+**33**	Ratio **32/33**
Me	Me	Anode	36	7:93	Anode	35	0:100
		Powder	59	19:81	Powder	43	0:100
Et	Et	Anode	61	>99:1	Anode	72	46:54
		Powder	88	100:0	Powder	75	12:88
$-(CH_2)_5-$		Anode	84	95:5	Anode	76	2:98
		Powder	83	77:23	Powder	96	0:100
Et	Ph	Anode	46	>99:1	Anode	89	100:0
		Powder	72	94:6	Powder	67	36:64
n-Pr	Ph	Anode	56	99:1	Anode	88	100:0
		Powder	76	97:3	Powder	95	62:38
n-Bu	Ph	Anode	38	>99:1	Anode	85	99:1
		Powder	78	99:1	Powder	53	96:4
Et	H	Anode	37	0:100	Anode		
n-Bu	H	Anode	50	0:100	Anode		
Ph	H	Anode	93	0:100	Anode		

See Ref. 85.

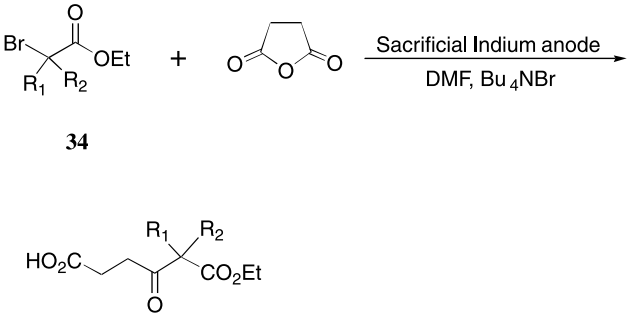
Application of the indium-mediated Reformatsky reaction has been extended to *p*-quinones **27** [R=R$_1$=H, R$_2$=H, Me, MeO] with methyl and ethyl iodoacetate giving good yields of *p*-quinols **28** under mild conditions.[84] In this manner, naturally occurring quinol esters such as jacaranone **29** are conveniently prepared in a one-pot synthesis.

Indium-promoted, electrochemically-supported Reformatsky reactions of α-bromoalkanoates **30** (typically ethyl α-bromoisobutyrate) with ketones and aldehydes **31** produce di-, tri- and tetra-substituted β-lactones **32**[85] and negligible amounts of the respective β-hydroxy adducts **33** (Eq. 2 and Table 1). With few exceptions, the yield of β-lactones is significantly lower if zinc is used instead of indium.[85]



(2)

In a similar fashion, the use of zinc, tin, aluminum, indium and iron as sacrificial anodes in an electrochemically assisted Reformatsky reaction of ethyl 2-bromoalkanoates **34** with succinic anhydride produces in all cases the expected 1-ethyl 3-oxohexanedioates **35** in good to moderate yields (Eq. 3).[86] A recent report establishes that the iron-mediated electrochemical Reformatsky reaction of α-chloroesters with carbonyl compounds efficiently produces β-hydroxyesters, and the reaction is also applicable for the generation of β-hydroxy ketones or nitriles.[87]

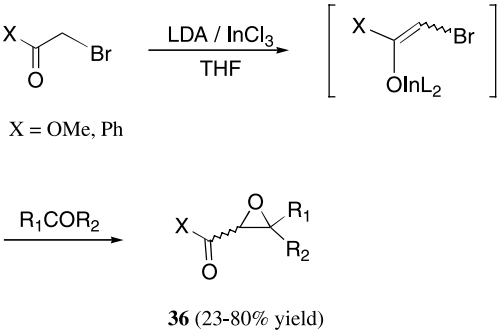


35a: R$_1$=R$_2$=Me, 80% yield

35b: R$_1$=Et; R$_2$=H, 74% yield

(3)

Indium trichloride has been used instead of metallic indium in Reformatsky-type reactions on enamines, and the reaction may be accelerated by addition of acetic acid, although reported yields are only moderate.[88] Reformatsky- and Darzens-type reactions of indium give rise to epoxy esters **36** in 23–80% yields with selectivities of 52:48 to 82:18 for the *trans*-epoxide stereo isomers (Eq. 4).[89]



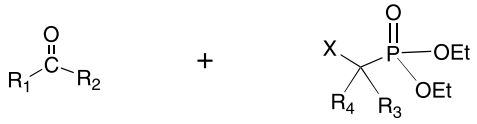
36 (23-80% yield)

(4)

2.2.4. Reformatsky-type reactions involving other metals. Reformatsky-type reactions are possible with a lot of metals other than zinc or in combination with it. The electro reductive coupling of α-chloro esters or α-chloro nitriles with carbonyl compounds by means of a sacrificial zinc anode and a nickel catalyst has been reported.[90] This method has also been applied to fluorinated Reformatsky reagents generated from methyl chlorodifluoroacetate.[91]

At least one example is known of the use of aluminum metal in combination with bismuth (III) chloride to promote a Reformatsky reaction.[92] Moreover, use of low-valent metals for Reformatsky-type reactions has provided interesting alternatives. For example, the use of scandium (III) triflate in the presence of triphenylphosphine,[93] metal gallium,[94] or germanium metal[95] to promote Reformatsky reactions has been reported. In the latter case, germanium metal was prepared in situ by reduction of germanium (II) iodide with potassium metal, these reactions being achieved with high stereocontrol (see Section 4.4).

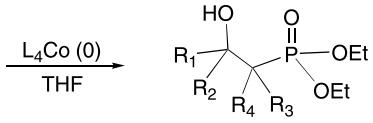
Cobalt is also being used extensively. Low-valent complexes of cobalt and phosphorus donor ligands (phosphines and phosphinites) proved to be efficient mediators in Reformatsky-type reactions.[96] This method was used in Reformatsky-type additions of α-halophosphonates **37** to carbonyl compounds **31** to yield β-hydroxyphosphonates **38** (Eq. 5)[97] and in additions of α-halocarbonyls **39** to (*R*)-2,3-*O*-cyclohexylidenegliceraldehyde **40** to afford diastereomeric α-hydroxycarbonyls **41** with acceptable *anti* diastereoselectivity (Eq. 6).[98]



31 **37**

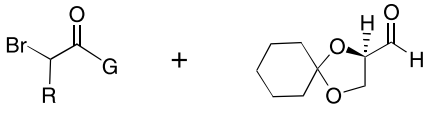
R_1, R_2 = H, alkyl, aryl R_3, R_4 = H, F; X = Cl, Br, I

(5)



38

L = Me_3P Yields: 22-81%



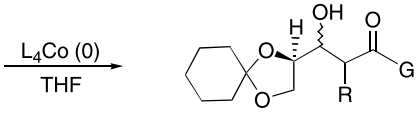
39 **40**

R = H, CH:CH_2

G = alkyl, aryl, OMe

R,G = CH_2CH_2OC:O

(6)



41

L = Me_3P, Ph_3P Yields= 50-90%

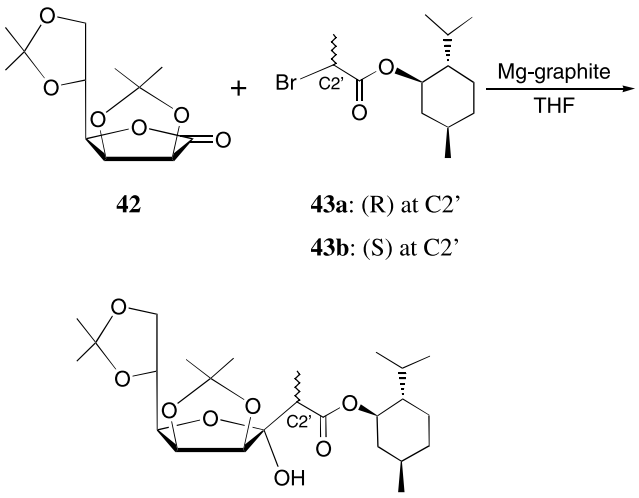
3,4-*anti* / 3,4-*syn* = 67:33 to 98:2

2,3-*anti* / 2,3-*syn* = 57:43 to 78:22

Cobalt–phosphine complex directed Reformatsky methodology can be applied stereospecifically[99,100] by using chiral auxiliaries, as will be discussed in Section 4.4.

A mild and efficient Reformatsky-type reaction promoted by diethyl zinc with catalytic amounts of $RhCl(PPh_3)_3$ has been reported to be useful for both inter- and intramolecular condensations,[101] even when using imines as electrophiles.[102]

On the other hand, synthetic highly active metal–graphite surface compounds (for instance magnesium) have been utilized,[103] with the method being applied to the stereoselective synthesis of α-substituted ulosonic acid derivatives **44** via Reformatsky reactions of chiral precursors **43** with aldonolactones **42** (Eq. 7).[104] This approach to ulosonic acids represents an alternative method to the SmI_2-promoted approach.[105]



42 **43a**: (R) at C2'

43b: (S) at C2'

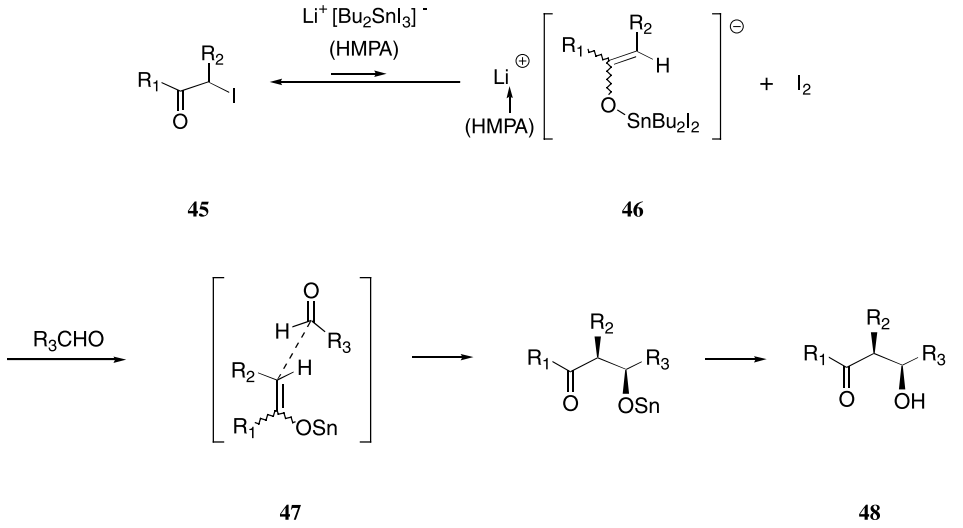
44

70-86% yields. Ratio (R)/(S) at C2' = 60:40

(7)

Reformatsky-type reactions are also possible with calcium reagents by using calcium atom–THF co-condensates[106] or manganese.[107,108] Although manganese is a relatively abundant metal and has stronger potential reduction than zinc, it has rarely been utilized in organic synthesis, with a thin but tightly bound oxide layer on its surface being mainly responsible for its low reactivity. The metal-oxide coating is effectively removed by treatment with Me_3SiCl.[109,110] Manganese metal (activated by Me_3SiCl and $PbCl_2$ or Et_2AlCl) proved to be a very efficient Reformatsky mediator.[107] The effect of lead on manganese is opposite to its effect on zinc where a catalytic amount of lead deactivates the metal.[109] Another method of activation of manganese was introduced recently,[111] consisting of the generation of manganese metal in situ, starting from Li_2MnCl_4 (derived from $MnCl_2$ and LiCl) and magnesium turnings (pretreated with 1,2-dibromoethane).[111] This method was used for a manganese-mediated reaction of α-haloesters (X=Cl, Br, I) with aldehydes, affording the expected β-hydroxy esters in good yield (78–94%) but with very low stereoselectivity.

Tin metal,[32,86] tin (II) chloride,[112] tin (II) triflate,[113] or tin complexes[114,115] promote Reformatsky reactions efficiently. For example, the combination of hexabutyldistannane ($Bu_3SnSnBu_3$) with dibutyldiiodotin (Bu_2SnI_2) is an effective reagent for Reformatsky-type reactions.[114] In its reaction with aldehydes, aldol-type products were obtained in 90% yields with a 54:46 ratio of *erythro*- and *threo* adducts. Even greater diastereoselectivity was obtained in Reformatsky-type reactions promoted by a tin iodide ate complex $Li^+[n\text{-}Bu_2SnI_3]$ **46** generated from equimolar amounts of Bu_2SnI_2 and LiI in THF/HMPA (Scheme 7).[115] This complex promotes the reaction of α-iodoketones **45** with aldehydes to afford good to excellent yields of the expected products **48** with a diastereoselectivity of up 95:5



Scheme 7.

in favor of the *syn* isomers, which is explained in terms of a transition state **47**.

Typical procedure.[115] To a THF (1 mL) solution of *n*-Bu_2SnI_2 (0.95 g, 2 mmol) and LiI (0.266 g, 2 mmol) was added HMPA (0.360 g, 2 mmol) at 6 °C (bath temperature), and the solution was stirred for 5 min. To the solution was added α-iodopropiophenone (0.520 g, 2 mmol) and benzaldehyde (0.106 g, 1 mmol). The solution was stirred at 6 °C for 12 h. MeOH (3 mL) was added to quench the reaction and volatiles were removed under reduced pressure. Work-up on the crude product by column chromatography (eluting with hexanes/ethyl acetate 1:1) completed the process.

Other complexes are also able to promote Reformatsky-type reactions. For example, the $Fe(CO)_5$-promoted reaction of α-bromocarboxylates with aldehydes and ketones has been reported,[116] and experimental conditions may be controlled to induce ketone: O addition instead of C:C addition if desired.[117] It is also reported that a tetrakis(triphenylphosphine) Pd(0) complex may function as a catalyst for coupling vinyl iodides[118] or aryl iodides[119] with Reformatsky reagents.

A Reformatsky-type aldol reaction of α-chloroketones with aldehydes has been achieved recently, using reactive barium as a low-valent metal,[120] and it was considered very effective for obtaining β-hydroxy ketones.

3. Non-conventional reaction conditions

A Reformatsky reaction is run typically at temperatures ranging from room temperature to the boiling point of the solvent in which the reaction is carried out. However, there are numerous reports of Reformatsky reactions (as with a lot of other organic reactions) run under non-conventional reaction conditions involving ultrasound, high pressure and microwave heating.[121] Solvent-free reactions[122] or aqueous reactions[123] offer obvious advantages which come from avoiding the need for flammable or anhydrous solvents, while mitigating environmental and economic concerns. Under these conditions, reactive functional groups, such as hydroxyl and carboxylic acid can be tolerated in a substrate without the need for time-consuming protection-deprotection schemes. The non-solvent reaction has some additional advantage because solvent removal by distillation is also not necessary. Reformatsky and Luche reactions were found to proceed efficiently in the absence of solvent[124] by mixing aldehyde or ketone with bromo-compound and Zn–NH_4Cl and by keeping the mixture at room temperature for 1–4 h. Dry medium reaction under microwave irradiation was applied to an alkali metal fluoride-mediated silyl-Reformatsky reaction.[125] Solid-phase methods have been applied also to Reformatsky reactions and other derivatizations involving C60/C70 fullerenes,[126,127] and to the synthesis of α,α-difluoro-β-aminoacids via the benzotriazole-mediated Reformatsky reaction with resin-bounded amino acids, aldehydes and the α,α-difluoro Reformatsky reagent.[56] Recently, solid-phase chemical synthesis of phosphonoacetate and thiophophonoacetate oligodeoxynucleotides was accomplished.[128]

Reformatsky reactions of α-bromoesters and carbonyl compounds, via a radical chain mechanism, can be carried out in concentrated aqueous salt solutions using catalytic amounts of benzoyl peroxide or peracids without any co-solvent,[6,129] with preparative yields being comparable to those of the traditional procedure. Similarly, aqueous medium zinc-mediated Reformatsky reactions of aliphatic aldehydes have been performed successfully by the addition of $BF_3 \cdot OEt_2$ and benzoyl peroxide.[43] Aqueous samarium/$CdCl_2$-,[71] $BiCl_3$/Sm-,[72] $BiCl_3$/Al-,[92] and indium-mediated[81] Reformatsky reactions have been already mentioned.

The Reformatsky reaction of α-bromoesters with carbonyl compounds, with reproducible yields of β-hydroxyesters (10–92%) are also possible using a mild and effective method of electrochemical zinc activation, based on the cathodic reduction of a catalytic amount of zinc bromide in acetonitrile.[130] The method is also applicable to the coupling of α-bromoesters with anhydrides. Reformatsky reactions may also be assisted electrochemically,[86] using zinc, tin, aluminum, indium,[85] iron[87] and nickel[90,131] as sacrificial anodes. The amount of current consumed for the dissolution of 1 equiv of anode metal strongly depends on the kind of metal. Whereas Al and Fe require 1 faraday per equivalent, Sn demands only 0.9 faraday per equivalent, and Zn and In require an even smaller amount of current. It is assumed that in the case of the last three metals, the electrochemical Reformatsky reaction is overlapped by a current-independent normal Reformatsky reaction, in which the anode acts as activated metal.[86] The electrosynthesis of various β-hydroxy esters, β-hydroxy nitriles, and 2,3-epoxy esters was successfully achieved under extremely mild conditions with a zinc/nickel combination.[90] The mechanism involved reduction of a Ni(II) complex to a Ni(0) complex, oxidative addition to the α-chloro ester to the Ni(0) complex, and a Zn(II)/Ni(II) exchange, leading to an organozinc Reformatsky reagent.

As already mentioned, ultrasound has become a valuable tool to promote a number of reactions[121] and large-scale Reformatsky reactions may be efficiently conducted in special reactors equipped with an ultrasound generator.[132,133] The reaction under HIU is found to be concentration dependent, and is particularly useful for substrates with increasing steric demands.[134] It has been recently used for the synthesis of β-amino esters and β-lactams.[135] In some cases, it is possible to exert some degree of stereo control, as in the case of the 73:27 *threo*/*erythro* ratio obtained (67% yield) in the ultrasound-promoted Reformatsky-type reaction of trifluoroacetaldehyde with ethyl α-bromopropionate in the presence of Zn.[136] Ultrasound was also a key tool in the stereoselective Reformatsky reaction (e.e.>98%) of tricarbonyl (η^6-arene)chromium (0) complexes, which afford β-amino esters and β-lactams[137] (stereochemistry associated to Reformatsky reactions will be discussed in Section 4.4).

Chiral induction and ultrasound acceleration on Reformatsky reactions have been performed using both non-fluorinated[19] and fluorinated α-bromo precursors.[138–140] Ultrasound turned out to be an interesting alternative for the generation and storage of the organozinc derived from ethyl bromodifluoroacetate.[140] This is pretty important, specifically for the reaction with NO_2 bearing carbonyl compounds, which require a previous preparation of the organozinc. Several additional reports are known on sonochemically assisted Reformatsky reactions[141] and particularly indium-mediated ones.[79,80] The production of highly reactive Zn powder by simultaneous electrochemical and ultrasound assistance appears to be especially important in medium- or large-scale processes involving Reformatsky reactions, Barbier allylation, alkyne reduction, reductive dehalogenation and 4-nitrophenyl ester cleavage.[142] The results show that Zn powders produced sono-electrochemically are highly reactive.

3.1. Supported metal-induced Reformatsky reactions

'High-surface' alkali metals can be conveniently prepared via deposition of corresponding metals on various supports such as NaCl, polyethylene, polypropylene and cross-linked polystyrene from their solutions in liquid ammonia. Alkali metals deposited on polymeric supports can be stored as stable suspensions in inert solvents, and addition of the suspension of supported alkali metal to a solution of zinc chloride gave an active zinc on polymeric support. This form of zinc is as active as zinc prepared by potassium graphite[28] or lithium suspension reduction.[29] Polyethylene supported activated zinc was used for Barbier reactions and for the Reformatsky reaction of α-bromoesters and carbonyl compounds, producing β-hydroxyesters in excellent yields.[143] This method offers considerable benefits: the metal surface is highly developed so its activity is high, the reaction proceeds selectively and the handling of reagents in such form as well as the separation of the reaction products from the support is a facile operation. Under these conditions, the reactions turned out to be equally efficient from α-chloro esters and α-bromo esters.

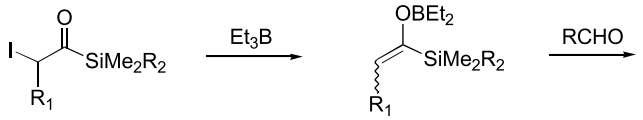
4. Reformatsky reactions involving non-fluorinated substrates

This section deals with application of the classical Reformatsky and Reformatsky-type reactions to a number of synthetic procedures involving non-fluorinated substrates. A lot of progress has been made in this field, particularly with regard to (a) the extension of the reaction to unconventional electrophiles and precursors, (b) the development of alternative methods that provided significant improvements in yields or stereocontrol, shortening of reaction times, simplification of work-up procedures, and (c) the development of multi-step syntheses involving Reformatsky reactions.

4.1. Precursors of Reformatsky reagents

The most familiar version of the Reformatsky reaction consists of the in situ generation of an organozinc intermediate derived from α-halocarbonyl compounds, α-haloesters, α-halothioesters, α-halonitriles, α-haloamides, α-haloimides, α-halo anhydrides,[144] α-halolactones or α-halophosphonates.[3,48,50,93,95,97,98] By treatment with activated zinc or other metals, these substrates generate carbon nucleophiles that add to a large number of electrophiles. Typically these reactions take place in polar solvents, particularly THF, DME, acetonitrile, dioxane, DMF, DMSO, HMPT or mixtures of such solvents.[3] Examples are also known of Reformatsky reactions being carried out in halogenated solvents, such as CH_2Cl_2.[42,48,50,93,95,145–148]

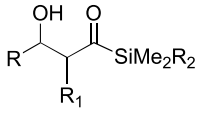
α-Haloacylsilanes **49** (X=Cl, Br, I) react with aldehydes in the presence of triethylboron with moderate to good diastereoselectivity, usually favoring the *erythro* isomer **51** (Eq. 8).[41]



49a **50**

R^1 = H, Me, n-C_6H_{13} ; R^2 = Me, *t*-Bu, Ph

R = Me, Ph, *t*-Bu, PhCH:CH



51

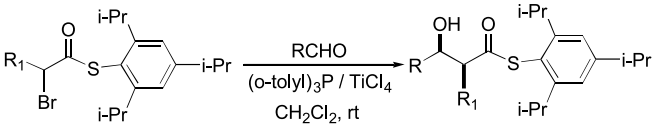
Yields: 32-79%

erythro/threo ratio: 6:94 to 96:4

(8)

The so-called Tischenko reaction[149] sometimes accompanies the Reformatsky reaction of benzaldehyde with acylsilanes **49** affording 1,3-diol monoester **56** via the Cannizaro-like intermediates **52** through **55** (Scheme 8).[41]

Aryl α-hydroxythioesters **58** have been prepared from aldehydes and α-bromothioesters **57** in the presence of a (*o*-tolyl)$_3$P/$TiCl_4$ combination (Eq. 9),[50] with high yields and good *syn*/*anti* stereoselectivity (up to 95:5).

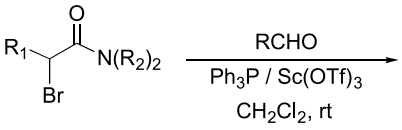


57 **58**

Yields: up to 93%. S*yn*/*anti* ratios up to 98:2

(9)

As expected, the larger the sulfenyl group in the thioester, the greater the diastereoselectivity obtained. The same observation holds for the Reformatsky reaction of α-bromoamides **59** with aldehydes in the presence of triphenylphosphine/scandium (III) trifluoromethanesulfonate (Eq. 10)[93] or triphenylphosphine/germanium tetrachloride combinations,[95] which gives rise to α-hydroxyamides **60** with *syn*/*anti* ratios of up to 98:2[93] or up to 99:1.[95]

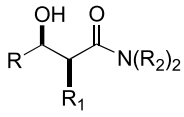


59a, R^2 = Ph

59b, R^2R^2 = $(CH_2)_5$

59c, R^2R^2 = $(COOCH_2CH_2)$

(10)

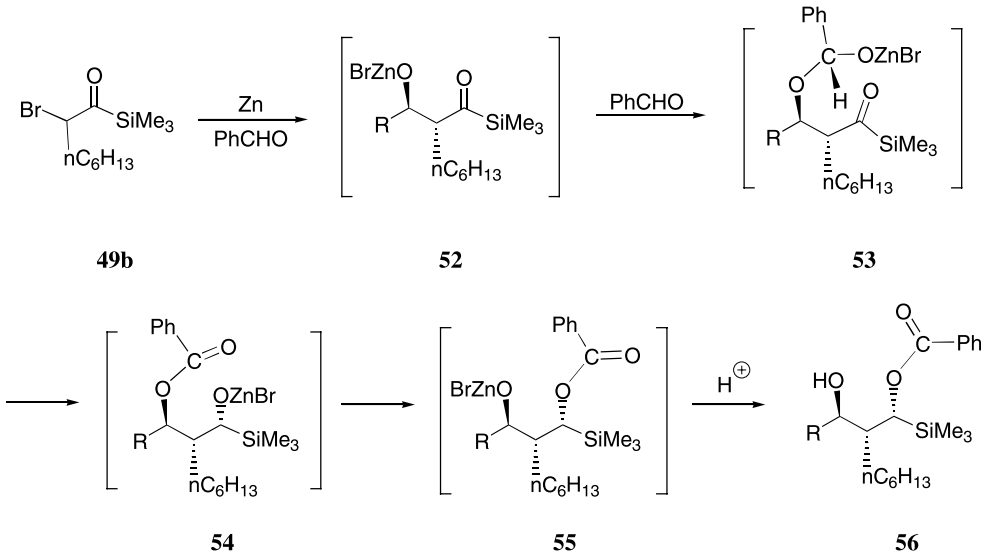


60

Yields: up to 93%. *Syn*/*anti* ratios up to 98:2

In addition to the above-mentioned examples, Table 2 contains other selected examples of classical intermolecular Reformatsky reactions affording β-hydroxy-derivatives or the respective dehydrated products.

On the other hand, in the presence of zinc, α-bromomalonates **62** react with *N*-arylpyrrolidine-2-thiones **61** to give the respective α,β-unsaturated derivatives **63** (Eq. 11). This unprecedented Reformatsky reaction has been used for the synthesis of tricyclic analogues **64** of quinolone antibacterial agents.[159]



49b **52** **53**

54 **55** **56**

Scheme 8.

Table 2. Selected examples of classical Reformatsky reactions

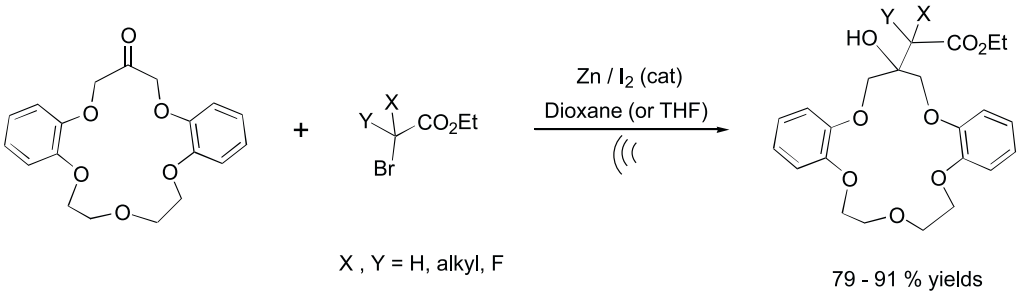
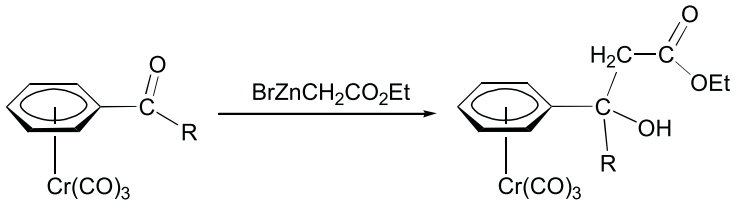
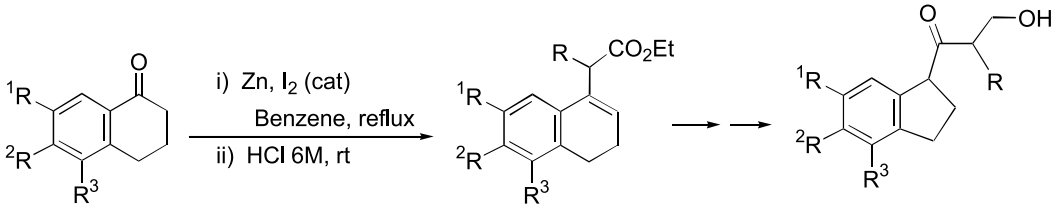
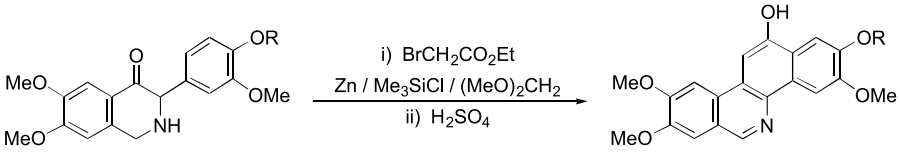
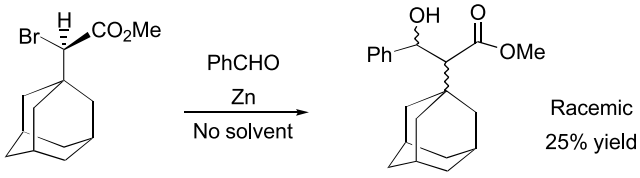
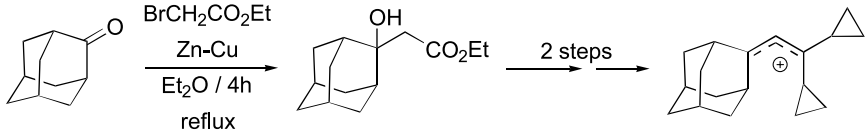
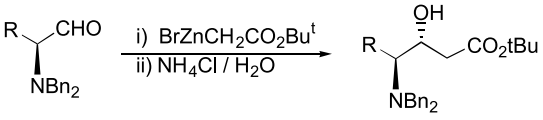
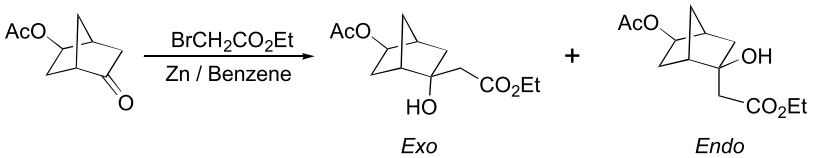
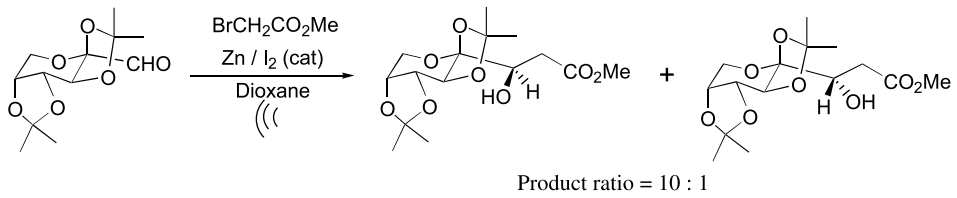
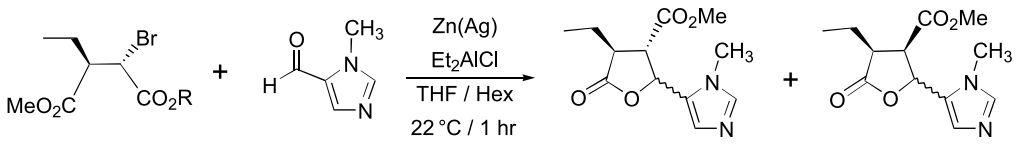
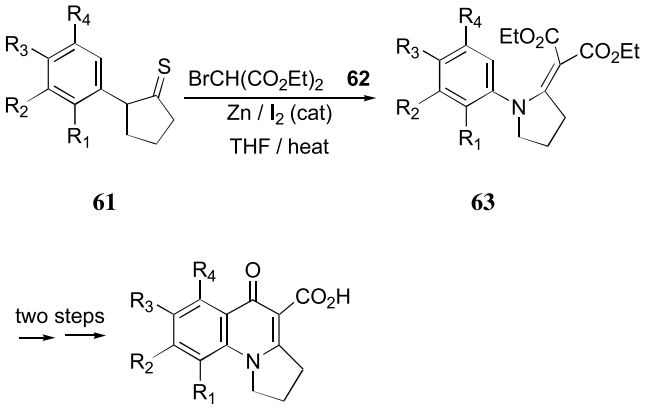
Entry	Reactions	Refs.
1		141
2	 Analog reactions performed on formyl and acetyl derivatives of $(\eta^5\text{-}C_5H_5)Mn(CO)_3$ and $(\eta^5\text{-}C_5H_5)Re(CO)_3$	150
3		151
4		152
5		153
6		154
7	 Yields= 30-87%; *anti*:*syn* ratio= 62:38 to 80:20	155
8	 *Exo*:*endo* ratio = 57:43	156

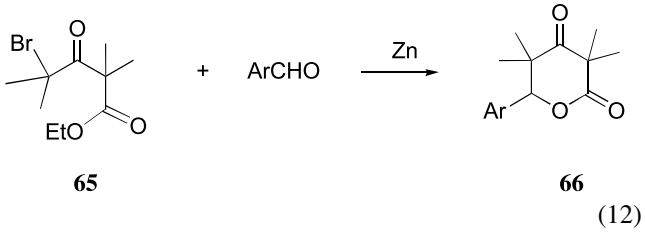
Table 2 (*continued*)

Entry	Reactions	Refs.
9	 Product ratio = 10 : 1	157
10	 Combined yield = 94% ; Product ratio = 91:9	158

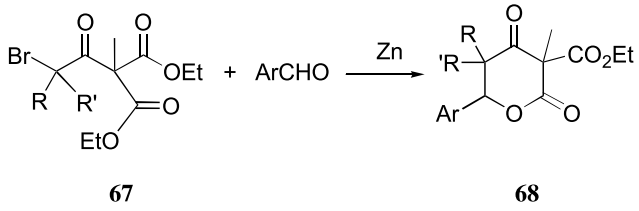


(11)

γ-Bromoderivatives of β-ketoesters or malonates have also been used as substrates for Reformatsky reactions with aldehydes, producing δ-lactones that result from ring closure of the respective adducts. In this manner, 6-aryl substituted tetrahydro-3,3,5,5-tetramethyl-2,4-pyrandiones **66** or 6-substituted 3-alkoxycarbonyl-3,5,5-trimethyl-2,3,5,6-tetrahydropyran-2,4-diones **68** have been synthesized, starting from aromatic aldehydes and alkyl 4-bromo-2,2,4-trimethyl-3-oxopentanoates **65** (Eq. 12)[160] or dialkyl 2-methyl-2-(2-bromoacyl)malonates **67**,[161] respectively (Eq. 13).

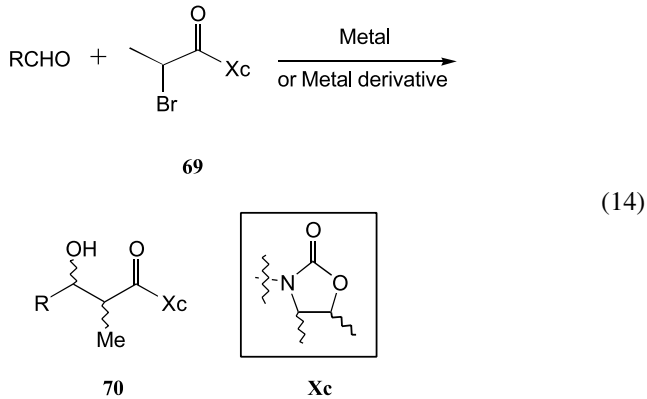


(12)

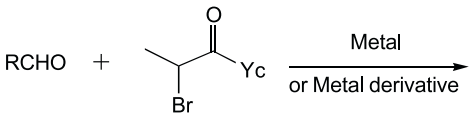


(13)

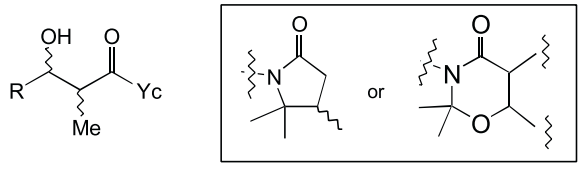
4.1.1. α-Bromoamides as precursors. Straightforward Reformatsky reactions of α-bromoamides with carbonyl compounds give the expected β-hydroxyamides. There have been some interesting developments on Reformatsky reactions of α-bromoacyl-derived oxazilidones **69** (Eq. 14)[65,66,73,74,93,95,99,162–166] or α-bromoacyl-derived oxazinones **71** (Eq. 15)[167–170] as special classes of α-bromoamides to be added to carbonyl compounds.



(14)



71

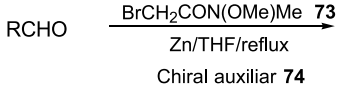


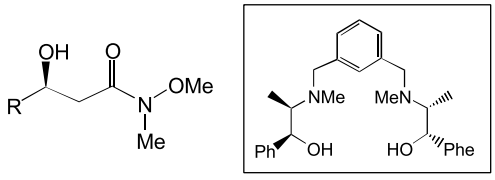
72 **Yc**

(15)

Introduction of chiral auxiliaries based on these amide moieties has been the key to significant improvements in terms of stereocontrol of the Reformatsky reactions induced by zinc,[162–164,167,168] chromium,[65,66] SmI_2 or other lanthanides,[73,74,166] germanium-[95] or cobalt.[99] Stereochemical aspects of the Reformatsky reactions of fluorinated precursors, making use of chiral auxiliaries, will be discussed in Section 5.1.

Chiral β-hydroxy Weinreb amides **75** are obtained in a similar fashion by the Reformatsky reaction of α-bromo Weinreb amides **73** with carbonyls in the presence of chiral β-aminoalcohols **74** as auxiliaries (Eq. 16)[171] (more details on asymmetric approaches are included in Section 4.4).

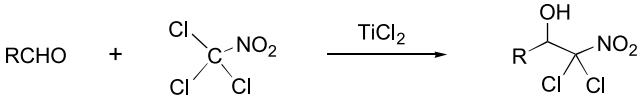




75 Chiral auxiliar **74**

(16)

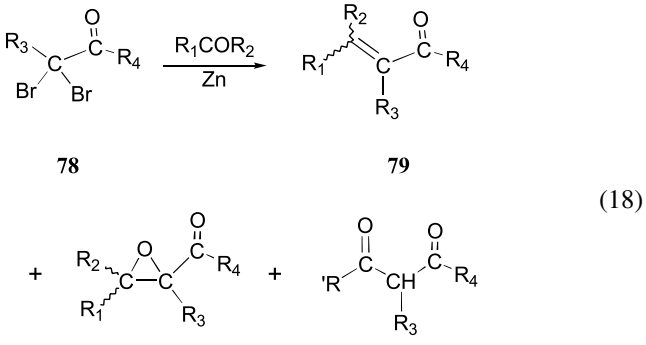
4.1.2. Polyhaloprecursors. In a Reformatsky-like reaction, trichloronitromethane **76** adds to aldehydes in the presence of tin(II) chloride to yield α,α-dichloro-α-nitroalcohols **77** (Eq. 17), with aliphatic aldehydes affording higher yields than aromatic aldehydes.[112]



76 **77**

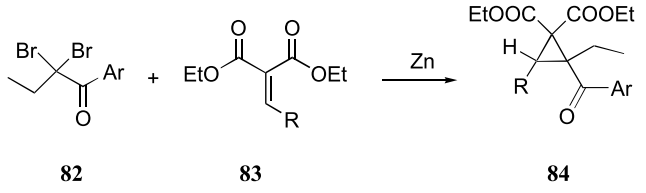
(17)

Zn-mediated reactions of α,α-dibromo ketones **78** with carbonyl compounds, depending on the starting reagents, the nature of the solvent, and the reaction conditions, give rise to α,β-unsaturated ketones **79**, α,β-epoxyketones **80** or α-alkyl-β-diketones **81** (or mixtures of such products) (Eq. 18).[172] However, 1-aryl-2,2-dibromobutane-1-ones **82** react with zinc and α-arylmethylidene-, or α-alkylidene-malonates **83** via a Reformatsky reaction followed by an internal malonic alkylation to give the respective cyclopropane-1,1-dicarboxylates **84**, which are formed mainly as *Z* isomers (Eq. 19).[173]



78 **79** **80** **81**

(18)

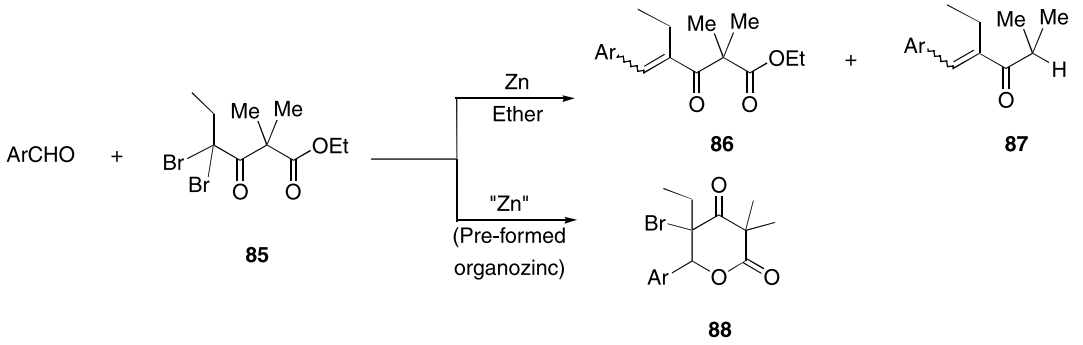


82 **83** **84**

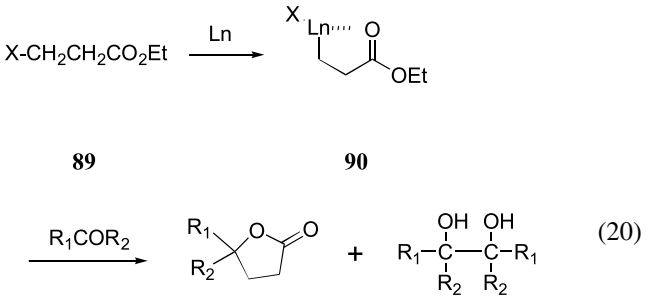
(19)

Reaction of γ,γ-dibromo-β-ketoesters (e.g., ethyl 4,4-dibromo-2,2-dimethyl-3-oxohexanoate) **85** with Zn and aromatic aldehydes, depending on the specific reaction conditions, affords the reduced non-halogenated α,β-unsaturated ester **86**, the respective decarboxylated ketone **87** or a mono-halogenated δ-lactone **88** (i.e., a pyrandione derivative) (Scheme 9).[174] This kind of reaction sometimes is prone to giving rearrangement products.

4.1.3. 'Remote' Reformatsky precursors. β-Metal enolates, commonly known as homoenolates, may be involved in Reformatsky like reactions as nucleophiles. Generation of homoenolates has been accomplished by several methods,[175] those being preferable that use a direct reaction from 3-halo carbonyl compounds and a metal. Zinc ester homoenolates, readily prepared in benzene–DMF or dimethylacetamide from ethyl 3-iodopropanoate by means of a zinc–copper couple, can be added to carbonyl compounds.[175] An improved procedure achieves the direct preparation of lanthanoid ester homoenolates **90** from 3-haloesters **89** and lanthanoid metals (La, Ce, Nd, Sm), and in turn **90** is added to carbonyl compounds without the need of additives or catalysts. In this manner, γ-lactones **91** have been prepared in good yields under mild conditions, even at room temperature (Eq. 20).[176] Pinacol derivatives **92** are often side products, which are generated by reaction with the carbonyl substrate.[176] As high as 63% yield of a pinacol **92** derived from acetophenone may be obtained as the only product if acetophenone is added to the homoenolate ester **90** previously prepared from the 3-iodoester **89** with Sm.[176]



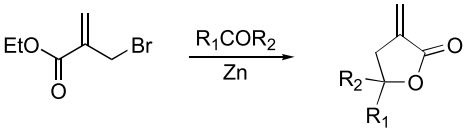
Scheme 9.



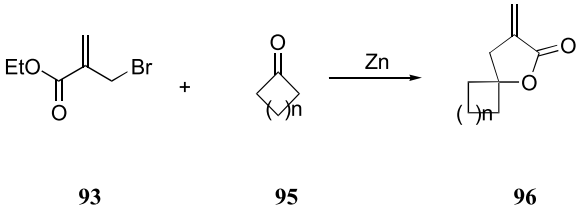
(20)

Combined % yields of (**91** + **92**) = 63-93%;
product ratio **91**/**92** = 66:34 to 93:7

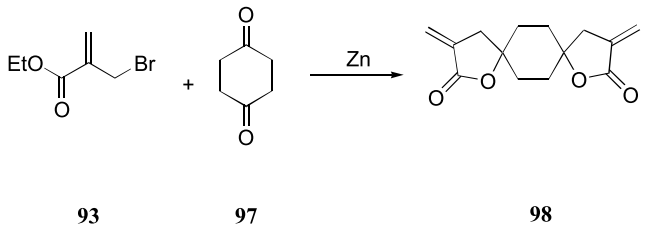
4.1.4. α-(Bromomethyl)acrylates as precursors. The Dreiding–Schmidt reaction[177] consists of the Zn-induced Reformatsky-like additions of α-(bromomethyl)acrylates **93** to carbonyl compounds followed by subsequent ring closure to form α-methylidene-γ-butyrolactones **94** (Eq. 21).[177] Although cyclic ketones **95** straightforwardly give rise to spiro derivatives such as **96** (Eq. 22),[177] it has been reported that piperidone does not generate the anticipated spiro α-methylene-γ-butyrolactones.[178] When starting from dicarbonyl compounds (for instance **97**), several spiro moieties like **98** may be formed in the same molecule (Eq. 23).[177]



(21)

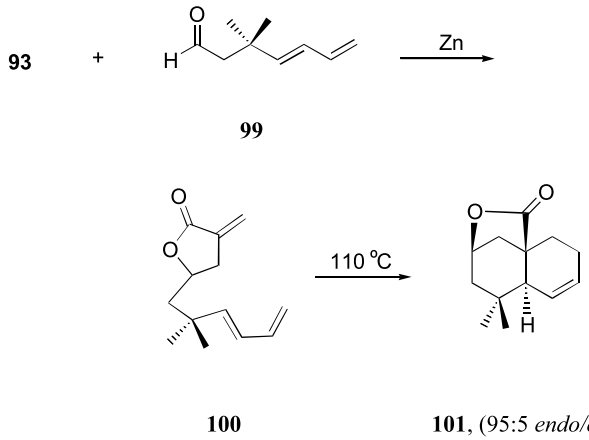


(22)

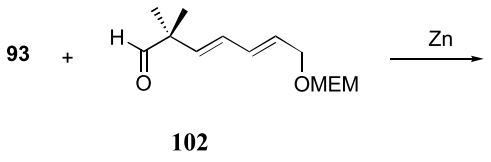


(23)

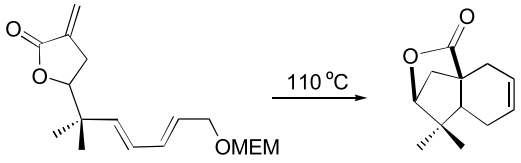
The preparation of α-methylene-γ-butyrolactones has been reviewed separately,[179] and additional comments and selected examples have been included in another recent review on Reformatsky reactions.[3] Recent developments in applying this methodology have used dienals **99** to generate α-methylene-γ-butyrolactones **100** bearing a dienyl side chain,[180] useful substrates for preparing tricyclic cycloadducts **101** via a Diels–Alder reaction (Eq. 24),[181] or the analogous tricyclic adducts **104** and **107** (Eqs. 25 and 26).[180] It has been observed that the size of the tether connecting the α-methylene-γ-butyrolactone moiety and the diene system defines the size of the resulting ring (Eqs. 24–26). It is also important to mention that highly functionalized tethers or use of a furan ring as diene system prevent the intramolecular Diels–Alder pathway. Also, sometimes the product is not the α-methylene-γ-butyrolactone moiety itself but the respective β-hydroxy adduct, which can be cyclized very easily with NaH.[180]



(24)

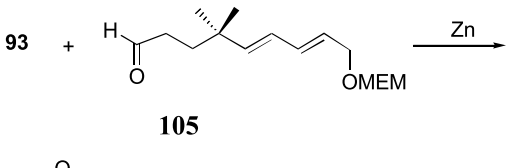


102

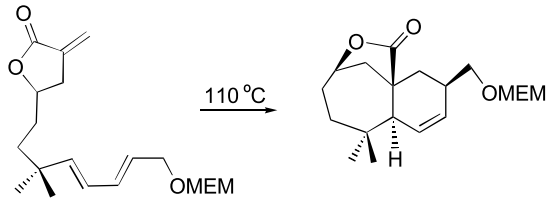


103 **104**, (3:97 *endo/exo*)

(25)



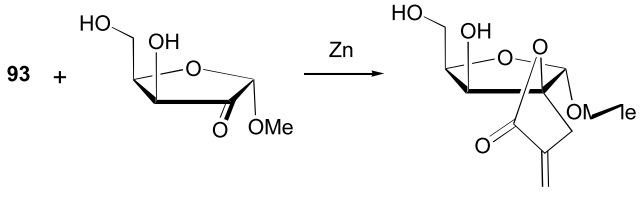
105



106 **107**, (53:47 *endo/exo*)

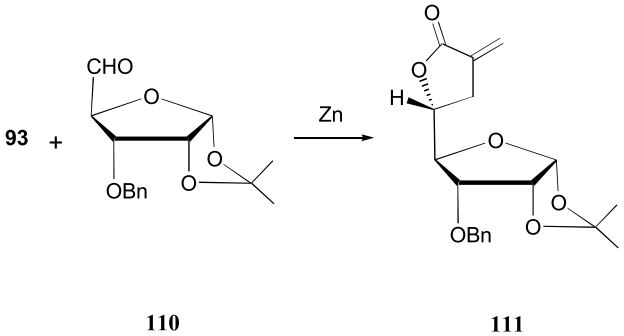
(26)

This use of α-(bromomethyl)acrylates for the generation of α-methylene-γ-butyrolactones has been extended to the preparation of sugar derivatives[182,183] such as the antifungal active compounds **109** and **111**, starting from their respective carbonyl precursors **108** and **110** (Eqs. 27 and 28).[182]



108 **109**

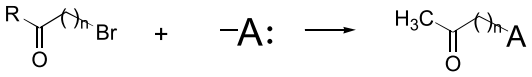
(27)



110 **111**

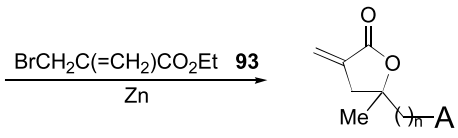
(28)

Moreover, this methodology has been exploited by attaching addends **A**, **113**, for example pyrimidine-[184] or purine-derived nucleic acid bases,[185] γ-aryloxy- (with aryl groups such as phenyl-derivatives, biphenyl, coumarin, flavone, xanthone, carbazole, dibenzofuran or quinolinone moieties),[186,187] or steroidal residues[188] to the tail of ketones before the Drieding–Schmidt reaction is performed with the respective carbonyl derivatives **114** (Eq. 29). The resulting products **115** are useful for different kinds of biological activities, such as antifungal, antitumor, antiplatelet, antiviral agents or vasorelaxing molecules.



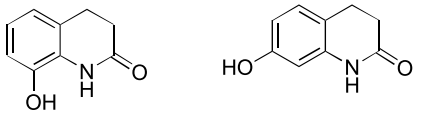
112, n= 1, 2 **113** **114**

(29)

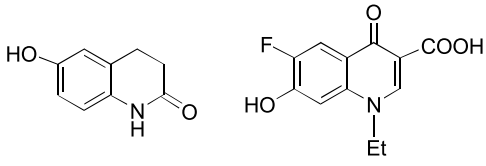


115

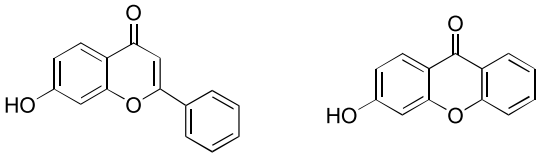
113a **113b**



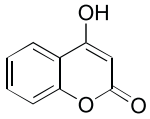
113c **113d**



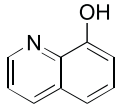
113e **113f**



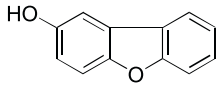
113g **113h**



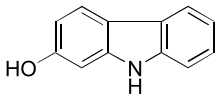
113i



113j

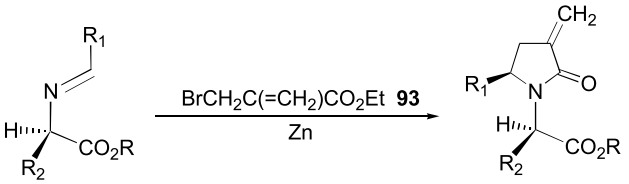


113k



113 l

The Dreiding–Schmidt reaction, when applied to α-iminoeiminoesters **116**, furnishes analogous α-methylene-γ-butyrolactams **117** with stereoselectivities as high as 100% e.e. (Eq. 30).[189]



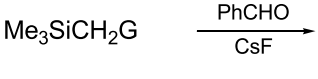
116 **117**

(30)

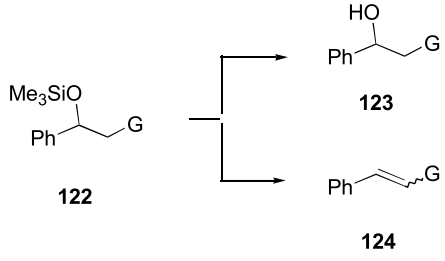
4.1.5. 4-Bromocrotonates and related precursors. It can be considered that precursors bearing halogen atoms in γ-position of α,β-unsaturated esters, with Zn, give rise to ambidentate organozinc intermediates which are able to be added to carbonyls (or to other electrophiles) either by γ- or α- attack (Scheme 10).

However, in practice several examples demonstrate that Reformatsky reagents derived from 4-bromocrotonates and 3-bromomethylcrotonates add to electrophiles regioselectively through the γ-carbon (see later),[98,190–193] and some bromomethyl-substituted heteroaromatic compounds behave like 4-bromocronates.[194] The analogous α,β-unsaturated-γ-haloesters [for example 2-(2-chloroalkylidene)-malonates **118**], on quenching with electrophiles, give products **119** or **120** of either α- or γ-attack. respectively (Scheme 10).[195]

4.1.6. Precursors with leaving groups other than halogen atoms. Several substrates bearing leaving groups other than halogens may undergo reaction in a Reformatsky-like fashion, giving rise to β-hydroxy functionalized compounds. In these cases zinc or other metals needs to be replaced by salts or analogous agents to promote the reaction. For example α-trimethylsilyl- acetic or phosphonic compounds of the form Me_3SiCH_2G (G=CN, CO_2Et, $P(O)(OEt)_2$) **121** condense with aromatic aldehydes in the presence of fluorides (KF, CsF, Bu_4NF) unsupported or supported,[125,196] under microwave irradiation in heterogeneous dry media. The silyl-Reformatsky reaction leads to the O-silylated adduct **122**, which can either be subsequently hydrolyzed to give desilylated derivatives **123** or dehydrated to give the respective alkenes **124** (Eq. 31).[125,197] Syntheses of α-methylene-γ-lactones are available by this method,[198] which represents an alternative approach to the Dreiding–Schmidt reaction.[177–180]



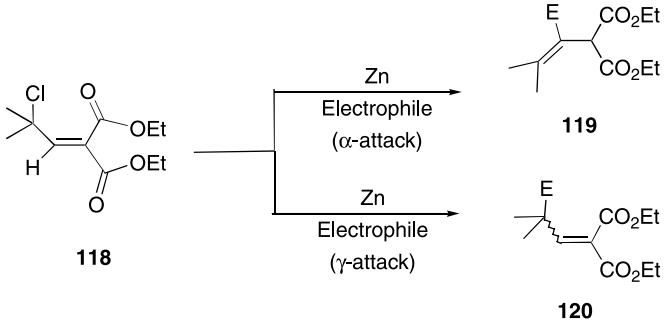
121a, G = CN
121b, G = CO_2Et
121c, G = $P(O)OEt_2$



122 **123** **124**

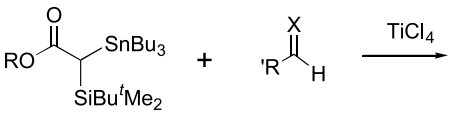
(31)

Similar reactions utilize α-silyl-α-stannylacetic derivatives **125** and aldehydes or aldimines **126** in the presence of $TiCl_4$[199] to diastereoselectively produce *syn* products **127** (Eq. 32), or zinc-induced Reformatsky-Peterson reactions of $Me_3SiCHClCN$ **128** with carbonyls to produce alkenenitriles **129** (Eq. 33).[200]

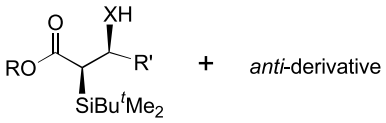


118 **119** **120**

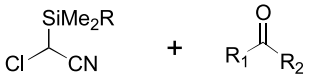
Scheme 10.



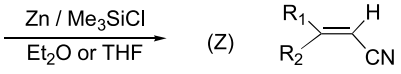
125 **126**, X = O or N-Bn (32)



127



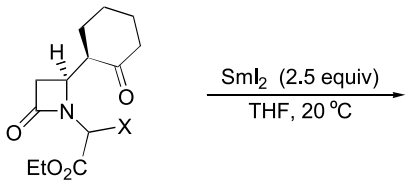
128



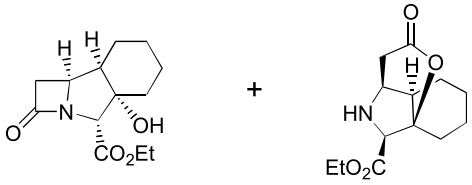
129, 65-99% yields (33)

Z/E ratio: 58:42 to 100:0

In addition, precursors **130** bearing benzoyloxy,[201] or S-Pyr[202] groups may act as leaving groups in intramolecular SmI_2-mediated Reformatsky-type reactions to afford the respective products **131** (Eq. 34), although reaction conditions may be controlled to favor rather the rearranged products **132**. SmI_2-promoted intramolecular Reformatsky reactions will be mentioned in Section 4.3.



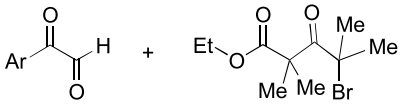
130, X = OBz or S-Pyr (34)



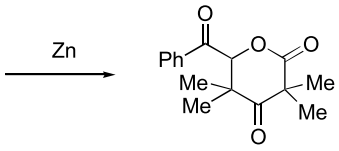
131 **132**

4.2. Electrophiles

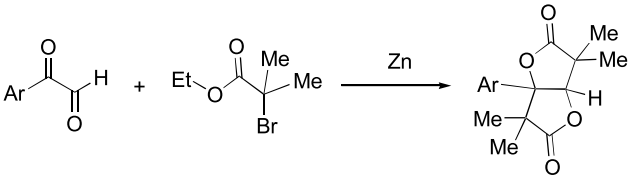
4.2.1. 'Classical' electrophiles. It is well recognized[3,4,8] that Reformatsky reagents act as nucleophiles with a number of electrophiles including aldehydes, ketones, nitriles, phosphonates, amides and imides, affording the expected β-hydroxy- or α,β-unsaturated products. If key functional groups are appropriately located, adducts may spontaneously close up to γ-lactones,[158] or δ-lactones.[203] Also, specific precursors give rise to monocyclic pyran-2,4-diones, for example, **135** (Eq. 35),[160,174,204] dilactones, for example, **137** (Eq. 36),[205] and pyran-2,4-diones bearing spiro moieties, for example, **139**, **141** and **143** (Eqs. 37–39).[161,206–208]



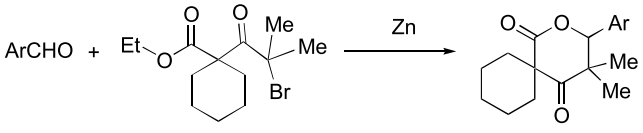
133 **134** (35)



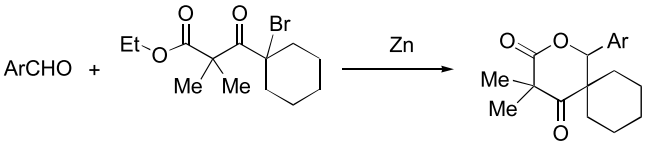
135



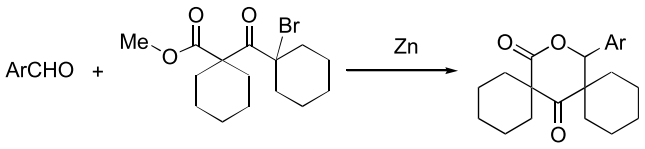
133 **136** **137** (36)



138 **139** (37)



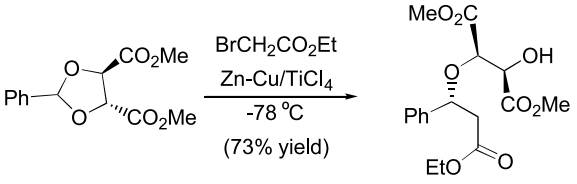
140 **141** (38)



142 **143**

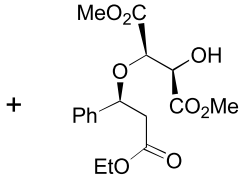
(39)

In the presence of Lewis acids such as $TiCl_4$ or $BF_3 \cdot Et_2O$, acetals may release an alkoxy group upon reaction with organozinc Reformatsky reagents providing 50–90% yields of β-alkoxyesters with variable levels of *erythro/threo* diastereoselectiviy. Up to 84% e.e. is reported for reactions starting from chiral acetals.[42] Thus, chiral six-membered- and five-membered-cyclic acetals (e.g., **144** and **147**) are opened by Reformatsky reagents (Eqs. 40 and 41).[42]

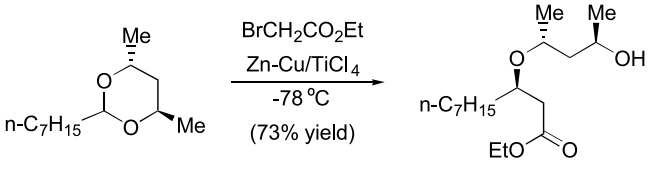


144 **145**

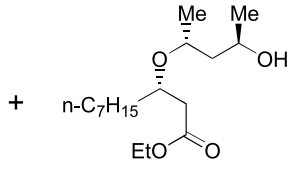
(40)



146



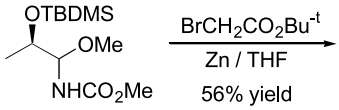
147 **148**



149

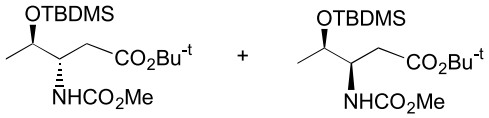
(41)

Likewise, a methoxy group present at the α-position in *N*-methoxycarbonyls (e.g., **150**) may be displaced by Reformatsky reagents or other organozinc compounds through a probable imine-mediated mechanism to furnish β-(*N*-methoxycarbonyl)aminoesters **151** with high *anti* diastereoselectivity, which can then be converted to β-amino esters (Eq. 42).[209]



150

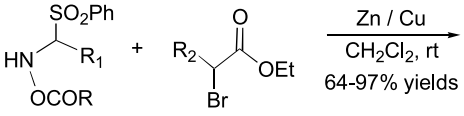
(42)



***Anti*-151** ***Syn*-151**

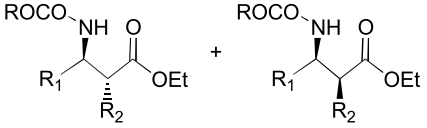
Ratio *anti/syn* = 9:1

Displacement of a leaving group from the structurally related N-protected amidoalkylphenyl sulfones **152** can be effected by zinc-based Reformatsky reagents. The reaction has become an alternative entry to β-amino esters (e.g., **153**) with variable stereoselectivity (Eq. 43).[193] As such, α-amidoalkylphenyl sulfones are considered to be imine equivalents. The analogous reaction of **152** with 4-methyl-crotonates gives rise to a mixture of **154** and **155** resulting from α- and γ-attack, respectively, with a modest regio-selectivity (Eq. 44).[193]



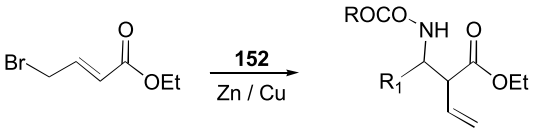
152

(43)



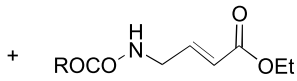
***Anti*-153** ***Syn*-153**

Ratio *anti/syn* = 8:92 to 40:60



154

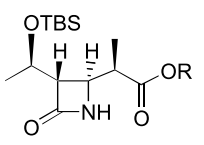
(44)



155

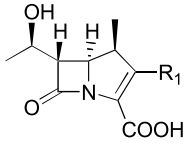
Ratio **155**/**154** = 49:51 to 30:70

Table 3 summarizes some additional examples of Reformatsky reactions that make use of acetal-, *N*-acetal-derived, or structurally related substrates, such as 2-acetoxytetrahydrofuran (or 2-acetoxytetrahydropyran) derivatives (entry 1),[49] 4-acetoxy-2-azetidinones (entry 2),[163,164,167–170,191] cyclic tertiary 2,2-bis(alkoxy)amines and 2-alkoxyimmonium ions bearing an acetal moiety (entries 3 and 4),[194] oxazolidines (entry 5),[145,210] and oxazinanes (entry 6).[211] The reaction shown in entry 2 is reported to be a crucial step in the synthesis of key intermediates (e.g., **156**) to 1β-carbapenems (e.g., **157**),[163,164,167–170,191] while the reactions of entries 3 and 4 have been used for the synthesis of antimalarial quinoline-4-methanols such as **158**.[194]



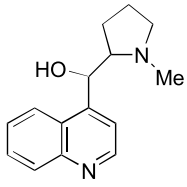
R= Bn, H, Me

156



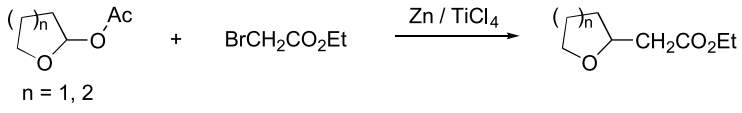
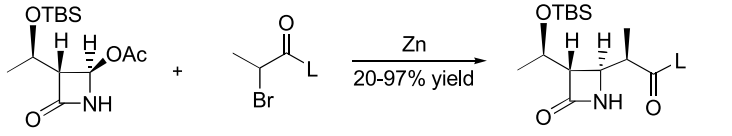
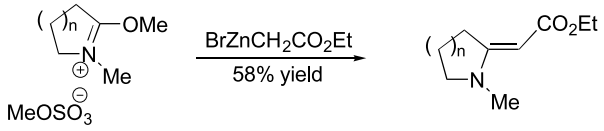
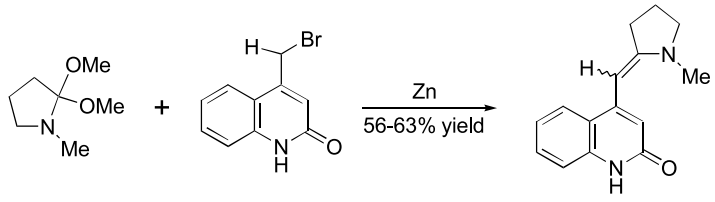
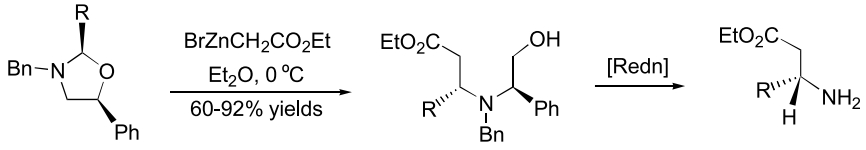
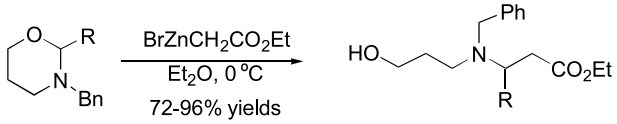
R_1= $SCH_2C(NH)NMe_2$

157

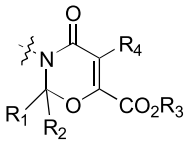


158

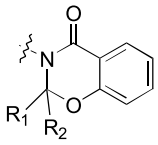
Table 3. Selected examples of Reformatsky reactions involving acetal-related substrates

Entry	Reactions	Refs.
1	 n = 1, 2	49
2[a]	 89-98% diastereoselectivity	163, 164, 167–169, 191
3		194
4		194
5		145, 210
6		211

[a] In entry 2, the following groups hold for L.

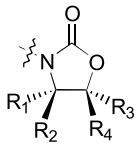


,



,

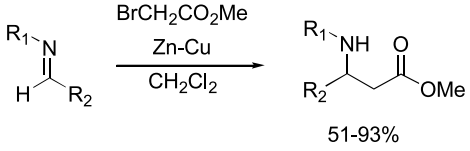
R_1 = Me, Bu, Bn, 4-furan
R_2 = Me, Bn
R_3 = Me, Et
R_4 = Ar
R_1R_2 = $(CH_2)_5$



R_1 = H, Me, ^{i}Pr, Bu, Bn
R_2 = H, Me, Bu, Bn
R_3 = H, Me
R_4 = H, Me
R_3R_4 = $(CH_2)_5$

On the other hand, α-oxoketene dithioacetals **159** leads to phenol derivatives **160** under classical Reformatsky conditions by using an excess of the organozinc precursor (Scheme 11).[212] The reaction can be used for the synthesis of substituted ethyl 3-hydroxy-5-(methylthio)stilbenecarboxylates **161** and for the synthesis of 4-, and 4,5-disubstituted 6-(methylthio)pyran-2-ones **162** in moderate to good yields.

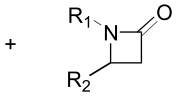
4.2.2. 'Non-classical' electrophiles. A previous review[3] briefly mentioned some Reformatsky reactions involving 'uncommon electrophiles', such as azomethines, nitriles, acyl chlorides, anhydrides, lactones, esters, orthoformates, oxiranes, azirines, aminals, nitrones, alkynes and inorganic acid chlorides. Also, as illustrated in Eqs. 45–48, Reformatsky reagents add to imines and related compounds, for example, **163** and **166** (Eqs. 45–48), in the same fashion as they do with aldehydes, affording β-amino carbonyl derivatives such as β-amino esters (like **164**) or β-lactams **165**, with β-amino esters being preferred especially when an *ortho*-substituent is present in an arylamine-derived imine (Eqs. 45 and 46).[102,137,148,193,199,213–215]



163 **164**

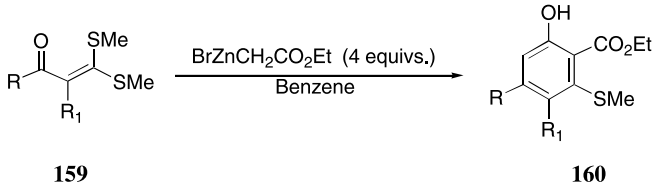
51-93%

(45)

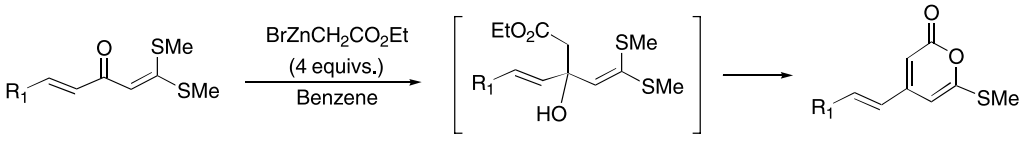


165

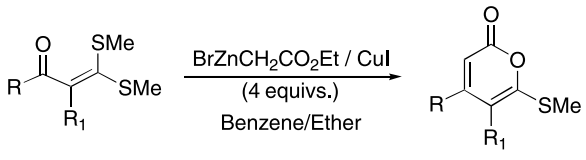
0-22% (Typically 0%)



159 **160**

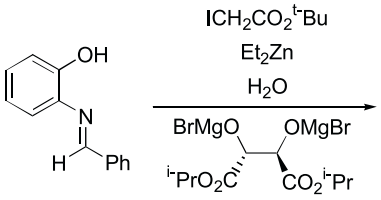


159a **161**

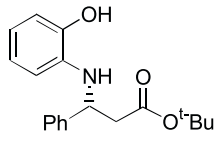


159 **162**

Scheme 11.



163a (46)

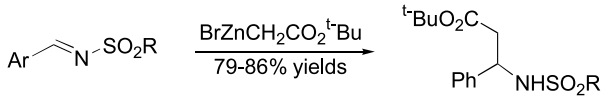


164a (12-83% yield, 0-93% ee)

163b **164b**

OR* derived from:		
	(-)-Menthol	20% ee
	(-)-Isopinocampheol	40% ee
	(+)-Isomenthol	50% ee
	(-)-*trans*-2-phenylcyclohexanol	98% ee
	(-)-8-Phenylmenthol	98% ee

(47)

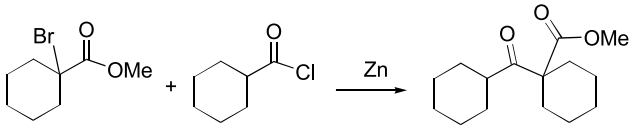


166 **167**

(48)

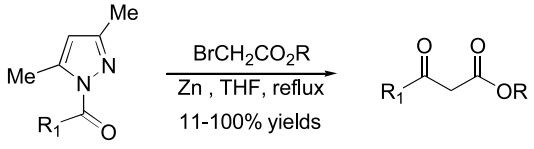
Sulfenamides **163a** (where R_1 = SPh) exhibit quite similar behavior and they also afford β-amino esters upon reaction with Reformatsky reagents.[216] Ordinary imines also condense with Reformatsky reagents in the presence of (1-trimethylsilyl)-benzotriazole, affording good yields of the corresponding β-amino esters.[57] The Reformatsky reaction with imines is commonly known as the Gilman-Speeter reaction,[217] and by further deprotection methods, the products may be readily converted to β-aminoacids. It was already mentioned (Eq. 30) that imines may be converted to α-methylene-γ-lactams by condensation with Reformatsky reagents derived from 2-(bromomethyl)acrylates via a Dreiding–Schmidt-type reaction.[189] Reformatsky reactions of imines involving fluorinated precursors and electrophiles will be mentioned in Section 5.

It is well recognized that leaving groups from acyl derivatives and related compounds are prone to be replaced also by Reformatsky reagents affording β-ketoesters, β-keto-related compounds or their respective enols. A number of examples of straightforward Reformatsky reactions involving acyl chlorides,[208,218,219] anhydrides,[86,220] lactones,[221] and amides bearing potential leaving groups[222–225] are reported, and some selected examples are shown in Eq. 49–53. Eq. 49 represents the first step for the preparation of some pyran-2,4-diones targets containing spiro systems, (e.g., **143** in Eq. 39),[208] and the reaction depicted in Eq. 53 was recently used for the synthesis of heterocyclic enamines via the ring transformation reaction of γ-lactones **177**.[221] Some intramolecular Reformatsky reactions produce a Dieckman-like product or its enol, for example, **176** (Eq. 52), and this kind of Reformatsky–Claisen path which results from the good leaving ability of the pyrrole group is reported to be more efficient than the analogous Dieckman reaction.[222] As expected, oxazilidine- or oxazinane-based amides (e.g., **173**) react with Reformatsky reagents to afford β-ketoesters **174** (Eq. 51),[225] and the same observation is true for amides (e.g., **171**) bearing good leaving groups (Eq. 50).[225b]



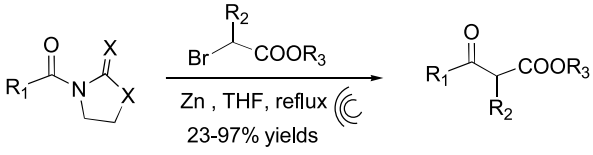
168 **169** **170**

(49)



171 **172**

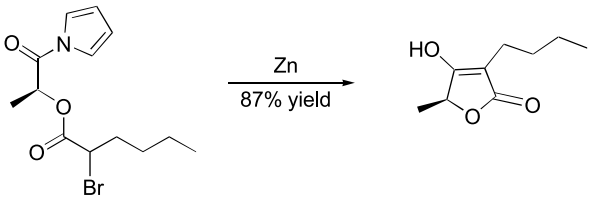
(50)



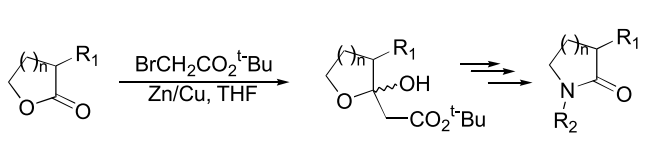
173 **174**

With X being: O, S

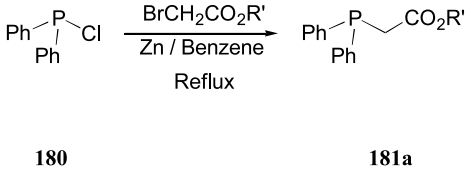
(51)



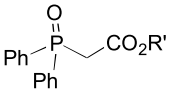
175 176 (52)



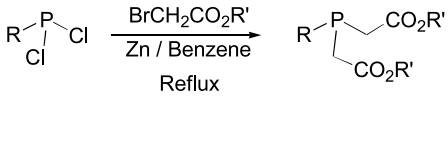
177 178 179 (53)



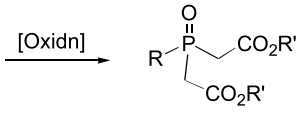
180 181a (54)



181b



182 183a (55)

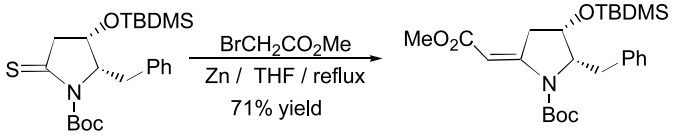
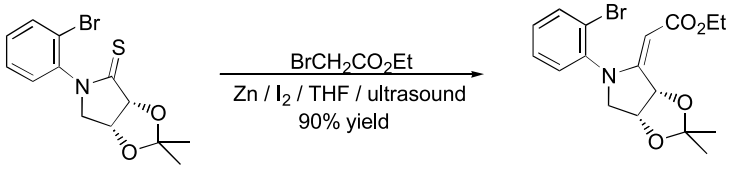
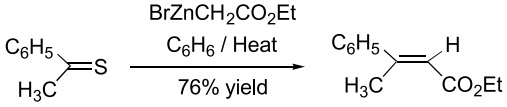
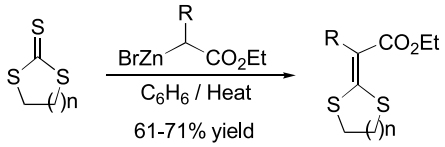
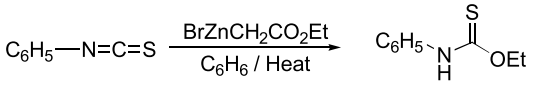


183b

Reformatsky reactions with electrophiles that are analogous to acyl chlorides involve chlorophosphines (e.g., **180**) or dichlorophosphines (e.g., **182**). They react with alkyl bromoacetates in the presence of Zn to form (alkoxycarbonylmethyl)phosphines **181a** (Eq. 54) or bis-(alkoxycarbonylmethyl)phosphines **183a** (Eq. 55), which can be converted to the respective oxides **181b** or **183b** by oxidation.[226]

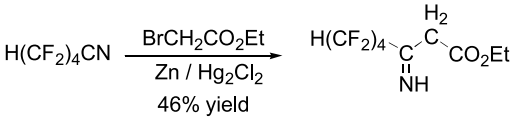
Reformatsky reactions involving thiocarbonyl compounds, particularly γ-thioalactams[159,225,227,228] usually give rise to the respective elimination products. Organozinc reagents are shown to undergo facile C–C bond formation on trithiocarbonates, xanthates, thione and dithioesters through

Table 4. Selected examples of Reformatsky reactions involving thiocarbonyl derived substrates

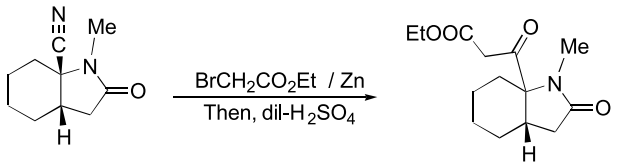
Entry	Reactions	Refs.
1		227
2		228
3		229
4		229
5		229

carbophilic addition yielding products formed by elimination of either sulfur or an alkylthio group.[229] A list of selected examples appear in Table 4. As seen in entry 5, a rare Reformatsky reaction involving phenylisothiocyanate produces ethyl *N*-phenylthiocarbamate, probably through a ketene elimination on the intermediate Reformatsky adduct.[229]

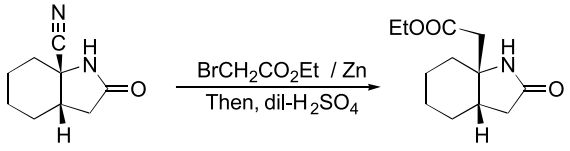
Reformatsky reactions with nitriles as electrophiles, commonly known as the Blaise reaction,[230] give rise to β-imino ester intermediates (e.g., **185**), which afford β-ketoesters (e.g., **187**) or the respective enols after hydrolytic work-up (Eqs. 56 and 57). If desired, the cyano group may be removed during the course of the Reformatsky reaction (Eqs. 58 and 59).[231,232] Removal of the nitrile group starting from tertiary β-amino nitriles represents a very facile access to functionalized amines when a β-amino ester synthon is required.[232]



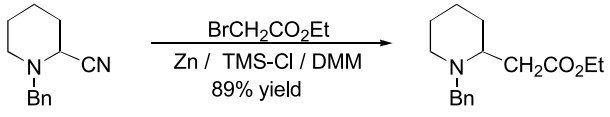
184 **185** (56)



186 **187** (57)

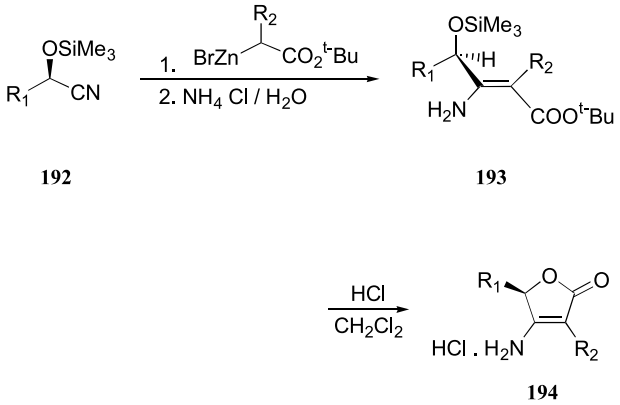


188 **189** (58)

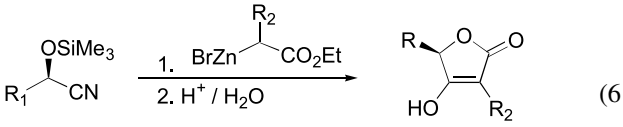


190 **191** (59)

The Blaise reaction on chiral (*R*)-*O*-silyl-protected cyanohydrins **192** starting from *tert*-butyl bromoesters gave good yields (54–83%) of the corresponding *tert*-butyl (*R*)-3-amino-4-trimethylsilyloxy-2-alkenoates **193** without racemization (e.e. up to 95%), which were then cyclized to the corresponding α,β-unsaturated β-amino-γ-hydroxybutyrolactones **194** in the presence of HCl (Eq. 60).[147] When starting from ethyl bromoesters the Blaise reaction gave rise to the analogous α,β-unsaturated β-hydroxy-γ-butyrolactones **195** (Eq. 61).[233,234] Tetronic acids prepared this way have interest as pharmaceuticals and agrochemicals, and they may be synthesized on a large scale.



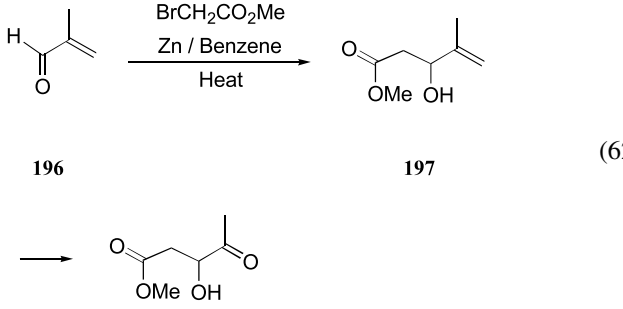
192 **193** **194** (60)



192 **195** (61)

N,N-Disubstituted α-aminonitriles are reactive with activated halides under Reformatsky conditions in the presence of zinc and 10 mol% of acetic acid, and the reaction is used as a key step for the synthesis of tertiary homoallylamines and α-amino esters.[235]

4.2.3. Michael or Michael-type acceptors. There is not a reliable way to predict the regiochemistry (1,2- or 1,4-) during the addition of Reformatsky reagents to α,β-unsaturated carbonyls. In fact, there are some examples of classical carbonyl attack (1,2-addition),[212,236–238] particularly on α,β-unsaturated aldehydes (for instance see Eq. 62),[236,239,240] whereas some other examples illustrate conjugate additions (such as that of Eq. 63).[54,173,241]



196 **197** (62)

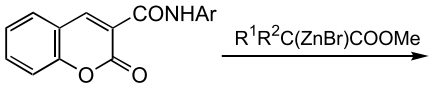
198 **199** (63)

A clear 1,2-addition pathway with methacrolein **196**

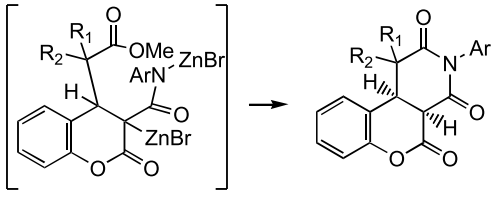
(Eq. 62) can be exploited as a 'masked ketone' in such a way that further cleavage of the double bond generates the carbonyl group, instead of using methyl glyoxal as the starting material. This method was efficiently used as the key step for the synthesis of 4-acetoxy-1-oxazetidin-2-ones.[236]

Sometimes a minor structural modification on the substrate induces the regiochemistry to switch. For example, the 1,2-Reformatsky addition with 3-arylmethylene-4,5-dihydrofuran-2(3*H*)-ones is reported versus 1,4-addition to 4-arylmethylene-3-methyl-isoxazol-5(4*H*)-ones.[242] However, there is some suggestion that bulky Reformatsky reagents tend to undergo conjugate additions, especially if the reaction is carried out on α,β-unsaturated ketones in the presence of trimethylsilyl triflate in THF at −78 °C.[54] This trend was observed in reactions with 2-cyclopenten-1-one, 2-cyclohexan-1-one and carvone.

Heterocyclization of *N*-arylamides **200** of 2-oxochromen-3-carboxylic acids via a conjugate Reformatsky reaction with conventional reagents has led to 4α-10β-dihydro-1*H*-chromeno[3,4-*c*]pyridine-2,4,5-triones **201** after hydrolysis (Eq. 64).[243]

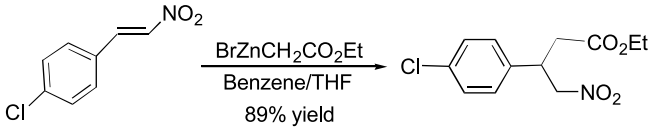


200

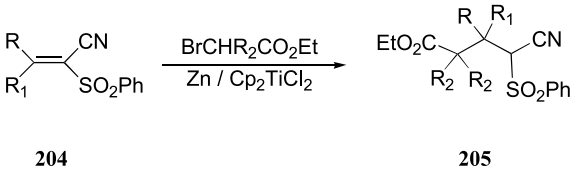


201 (64)

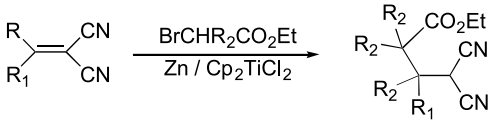
Michael-type addition of Reformatsky reagents has been observed on electron-deficient alkenes, for example α-nitrostyrenes **202** (Eq. 65),[244] 1-cyano-1-phenylsulfonyl alkenes **204** (Eq. 66),[38] and 1,1-dicyanoalkenes **206** (Eqs. 67 and 68).[39] The reactions with 1-cyano-1-phenylsulfonyl alkenes or 1,1-dicyanoalkenes require catalytic amounts of Cp_2TiCl_2, and the reaction gives rise to γ-functionalized esters in each case. Conjugate addition of Reformatsky reagents to 1,3-diaza-1,3-butadienes **209** is also possible, and such reaction results in the formation of dihydropyrimidinones **210** via a spontaneous ring closure of the respective adduct (Eq. 69).[245]



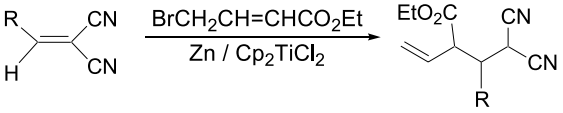
202 **203** (65)



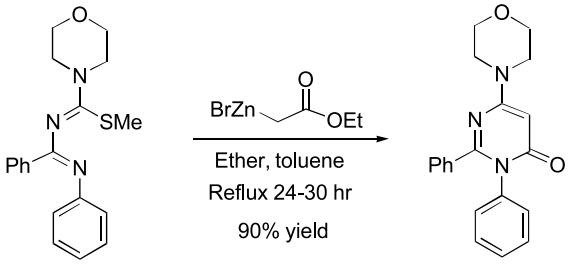
204 **205** (66)



206 **207** (67)

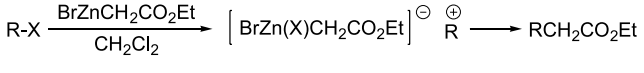


206 **208** (68)



209 **210** (69)

4.2.4. Carbon electrophiles other than carbonyl or related groups. In addition to the electrophiles already mentioned as active substrates for Reformatsky reactions, very reactive alkyl halides may substitute halogen for Reformatsky reagents. Thus, treatment of diphenylchloromethane **211** with $BrZnCH_2CO_2Et$ in CH_2Cl_2 gives rise to the respective substitution product ethyl 3,3-diphenylpropionate **213** in 96% yield, probably mediated by a ionic pair **212** (Eq. 70).[146] Similar behavior is exhibited by 1-bromoadamantane and 1-phenylethyl chlorides, so that this is a useful method to produce α-substituted ethyl acetates in good yields (69–96%).



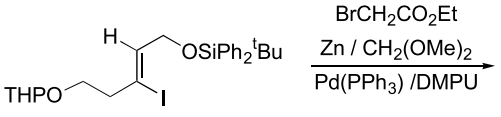
R = Ph_2CH, $PhCH(CH_3)$, Ad ; X = Cl, Br. 69-96% yields

211 **212** **213** (70)

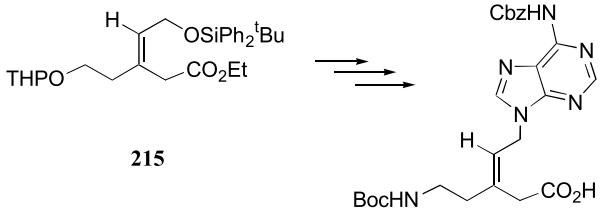
C60 and C70 fullerenes are also prone to add organozinc reagents including not only the classic Reformatsky reagents, but also those which derive from α-bromoketones, allyl bromide, benzyl bromide, α-bromoacetonitrile and 1-iodobutane, to form the respective mono-alkylated derivatives along with minor by-products including the

1,4-disubstituted ones.[126,127] Typically the reactions are carried out in the absence of any solvent.

On the other hand, vinyl and aryl iodides (e.g., **214**) couple with Reformatsky reagents in the presence of palladium (0) catalysts (Eq. 71),[118,119] and the reaction has been used as the key step for the synthesis of the Boc-protected *Z*- and *E*-olefinic peptide nucleic acid analogues (*Z*-OPA and *E*-OPA) monomer **216** containing the base thymine.[118]



214

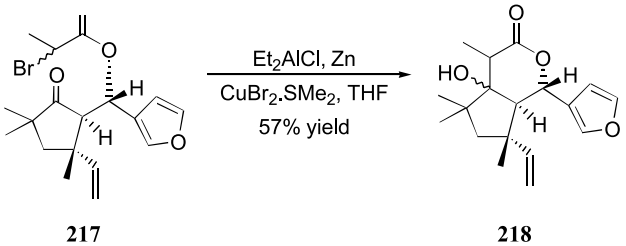


215 **216**

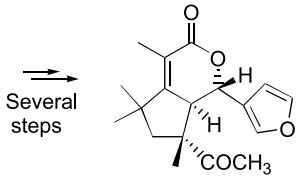
(71)

4.3. Intramolecular Reformatsky reactions

Zn/Et_2AlCl-mediated or Rieke-zinc-promoted intramolecular Reformatsky reactions are well known procedures, and several examples have been presented in a previous review.[3] Key steps for the synthesis of the BCD framework of Richardianidins **219** (Eq. 72),[53] C(16),C(18)-*epi*-cytochalasin D **222** (Eq. 73),[246] and the daphniphyllum alkaloids framework **225**[247] make use of this methodology.

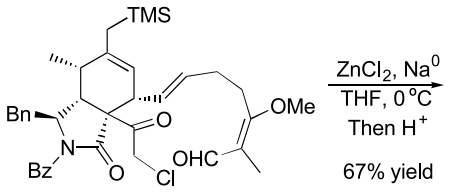


217 **218**

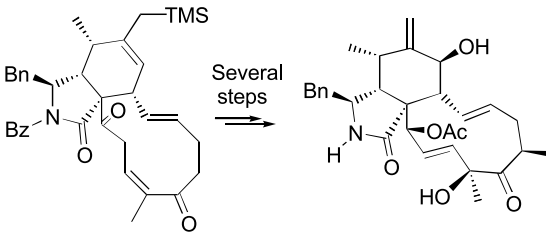


219

(72)

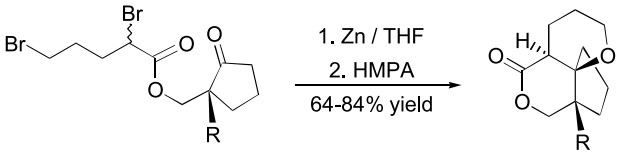


220

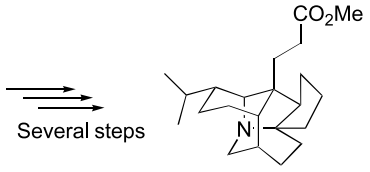


221 **222**

(73)



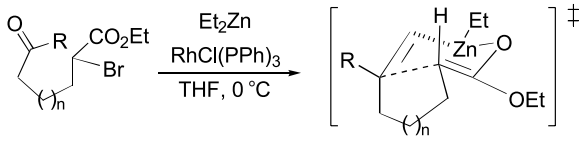
223 **224**



225, *racemic*

(74)

$RhCl(PPh_3)_3/Et_2Zn$ couple has proved to be an efficient agent for both inter- and intramolecular Reformatsky reactions with some degree of stereocontrol favoring *cis* isomers (e.g., **228**). Such stereoselectivity is enhanced when the intramolecular reaction leads to five-membered rings (Eq. 75),[101] and this effect has been attributed to a sterically and electronically more favored rigid conformation of transition state **227** when $n=1$.

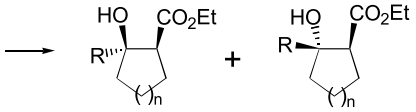


226a : R = H , n = 1 **227**

226b : R = Me , n = 1

226c : R = H , n = 2

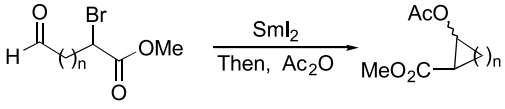
226d : R = Me , n = 2



228a (63% yield)	**229a** (5% yield)
228b (59% yield)	**229b** (5% yield)
228c (41% yield)	**229c** (33% yield)
228d (65% yield)	**229d** (26% yield)

(75)

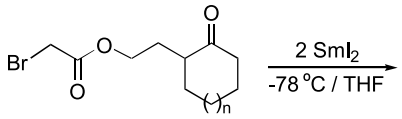
As briefly mentioned on a previous review[3] and also in Section 2.2.2, samarium diiodide[59] is among the most exploited agents for intramolecular Reformatsky-type reactions, especially because of the observed high yields and stereocontrol. For instance, acetoxycarbonyl precursors **230** (*n* being equal to 6, 7, 9, 12, or 13) were converted to the respective eight-membered to 15-membered cyclic β-acetoxyesters **231**, with yields ranging from 63 to 82% (Eq. 76).[248]



230 **231**

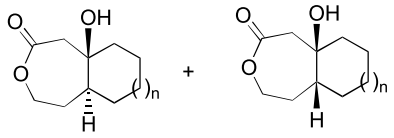
(76)

Identical chemistry occurs for α-bromoesters with compounds such as **232** which bear a properly placed carbonyl group for the generation of five-, six- and larger-membered rings, a particularly useful reaction for the generation of stereo-defined lactones with fused rings. Diastereomeric ratios **233/234** of up 200:1 have been observed (Eqs. 77 and 78).[249] This kind of closure was used for the synthesis of (2*R*,4*R*)-supellapyrone, the sex pheromone of the brown-banded cockroach *supella longipalpa*.[250]

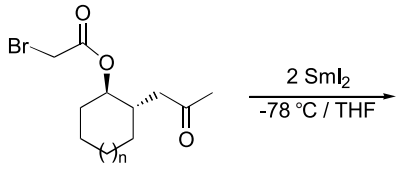


232a

(77)

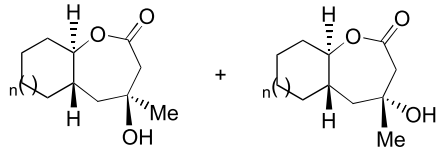


233a **234a**



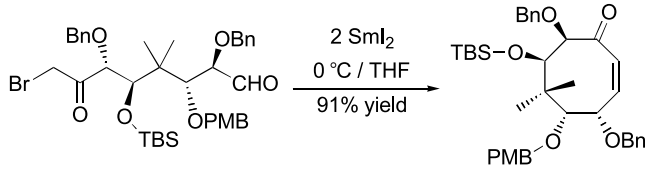
232b

(78)



233b **234b**

This methodology has been applied also to the asymmetric synthesis of **235**, which is a fully functionalized B ring system of taxol (Eq. 79).[251]

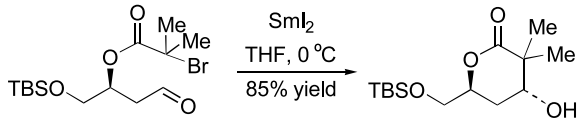
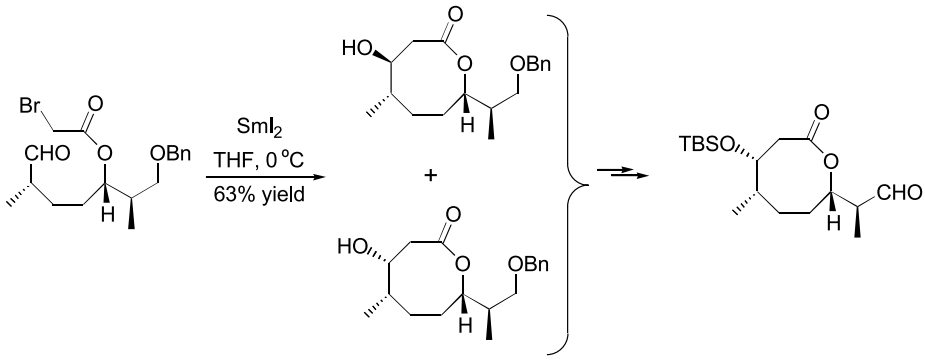
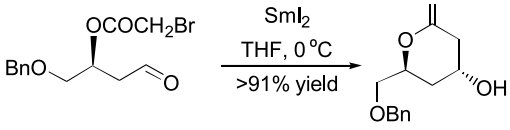
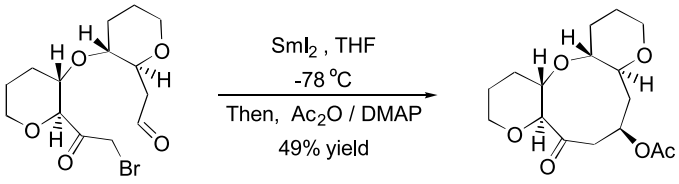
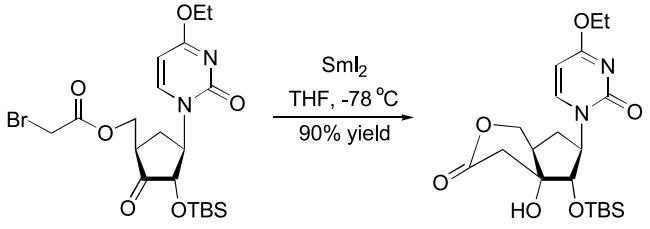


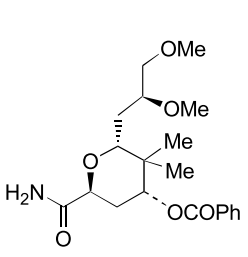
232c **235**

(79)

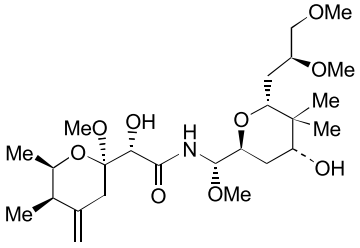
Selected examples of practical applications of intramolecular SmI_2-promoted Reformatsky reactions to synthesis are listed in Table 5. The reaction shown in entry 1 constitutes the key step to the synthesis of (+)-benzoylpedamide **236**, which is a synthetic intermediate in the preparation of the potent insect toxin pederin **237**,[252] while the synthesis of the bioactive (−)-octalactin A **238** is mediated by reaction illustrated in entry 2.[253] The reaction in entry 3 is useful for the synthesis of (+)-compactin lactone, a potent competitive inhibitor of the HMG–CoA,[254] and the reaction of entry 4 involves the crucial step in the approach to the F–M ring framework of ciguatoxine (CTX1B) **239** or model compounds,[255] while entry 5 illustrates a carbon–carbon bond forming reaction in nucleoside chemistry.[256]

Table 5. Examples of synthetic applications of SmI_2-promoted intramolecular Reformatsky reactions

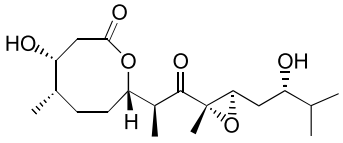
Entry	Reactions	Ref.
1		252
2		253
3		254
4		255
5		256



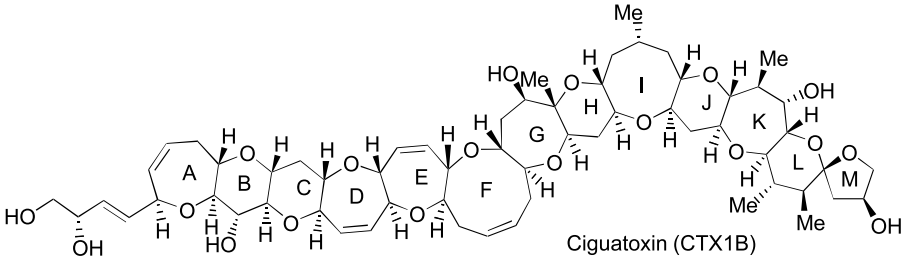
236



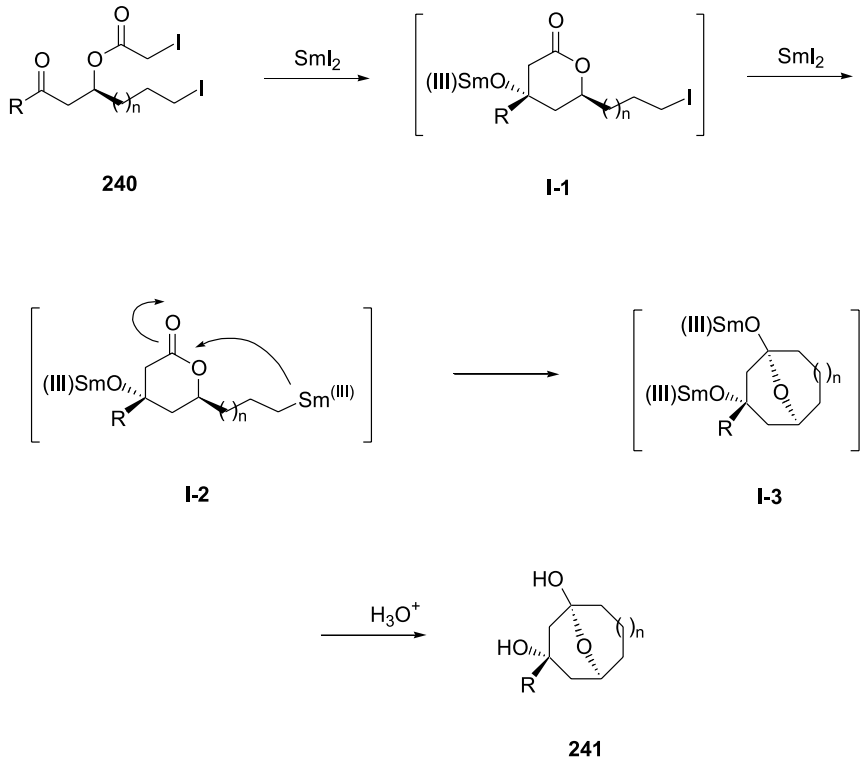
237



238



239



Scheme 12.

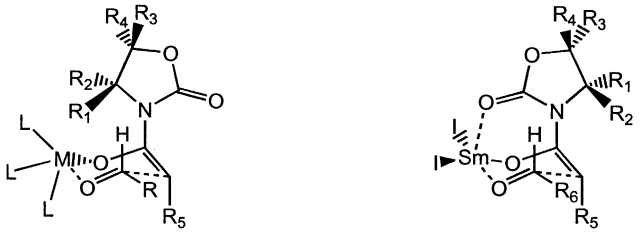
A similar SmI_2-promoted intramolecular Reformatsky reaction constitutes the key step in the synthesis of the novel inhibitor of cholesterol biosynthesis, (−)decarestrictine,[257] and of (−)-borrelidin.[258]

Samarium(II) iodide is also used to access eight- and nine-membered carbocycles, for example, **241**, via a domino reaction, comprised of a Reformatsky reaction from **240** to form intermediate **I-1**, which is followed by an internal nucleophilic acyl substitution reaction that is undergone by intermediate **I-2** (Scheme 12).[259] This method represents a general and efficient approach to

Table 6. Examples of stereoselectivity accomplished by using chiral auxiliaries attached to precursors

Entry	Chiral precursor	E^+	Reformatsky agent	Reaction conditions	Products	Yield (%)	Stereo selectivity[a]	Refs.
1	**242a**	**245**	Zn	THF, 0 °C 30 min	**249a**+**250a**	99	91:9[b]	163
2	**242b**	**245**	Zn	cf. entry 1	**249b**+**250b**	91	90:10[b]	163
3	**242c**	**245**	Zn	cf. entry 1	**249c**+**250c**	99	90:10[b]	163, 164
4	**242c**	PhCHO	Zn	cf. entry 1	**251**+**252**	98	98:2[b]	162
5	**242d**	**246**	$CrCl_2$/LiI (cat)	THF, rt, 5 h	**253**+**254**	63	8:92	65
6	**242d**	^{i}-PrCHO	$CrCl_2$/LiI (cat)	cf. entry 5	**255**+**256**	91	4:96	65, 66
7	**242b**	^{i}-PrCHO	$CrCl_2$/LiI (cat)	THF, 20 °C	**257**+**258**	88	5:95[b]/(98:2)[c]	65, 66
8	**242e**	PhCHO	GeI_2/K	THF, rt, 18 h	**259**+**260**	94	99:1[b]/(99:1)[c]	95
9	**242e**	**247**	$Co[P(Ph)_3]_4$	THF, −0 °C 2 h	**261**	70	>96% d.e.	99
10	**242f**	^{t}-BuCHO	SmI_2	THF, −78 °C, 0.5 h	**262**	87	>99% d.e	166
11	**242g**	**248**	SmI_2	THF, −78 °C, 1 h	**263**+**264**	94	96:4	260
12	**243a**	**245**	Zn	THF, reflux, 20 min	**265a**+**266a**	87	98:2[b]	168
13	**243b**	**245**	Zn	cf. entry 12	**265b**+**266b**	76	99.6:0.4[b]	168
14	**243c**	**245**	Zn	cf. entry 12	**265c**+**266c**	85	98:2[b]	169a
15	**244a**	**163b**	Zn/I_2	Sonication, rt 48 h	**267a**	45	98% d.e	214
16	**244b**	**163b**	Zn/I_2	cf. entry 15	**267b**	55	98% d.e	214

[a] Ratios of products in the respective order.
[b] Ratios (2,3-*syn*/*anti*) in entries 1–4, 7–8 and 12. Ratios of isomers α/β in entries 12, 13 and 14.
[c] Diastereomeric ratio (i.e., *R*/*S* in respect of carbon α) in parenthesis.



(a) (b)

Figure 1. (a) Transition state according to the Zimmerman–Traxler model.[61,64,95,99] (b) Transition state according to Nerz–Stormes–Thornton model.[166,262]

a variety of highly functionalized, stereo-defined carbocycles.

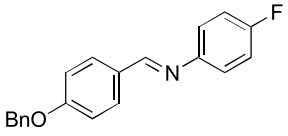
SmI_2-promoted cyclization reactions involving substrates containing benzoyloxy or S-pyridyl moieties as leaving groups, which lead to fused bicyclic or tricyclic (β-lactams, have already been mentioned (Eq. 34).[201]

4.4. Advances in stereochemical aspects

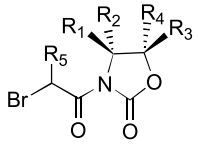
The chromium-,[58,61–67] SmI_2-,[59,166,201,202,249–259,260–263] scandium-,[93] germanium-,[95] indium-,[78] cobalt-,[98–100] rhodium-,[101] and tin-[48–52,115,199,200] versions of the Reformatsky reaction, combined with introduction of chiral or stereo inductor auxiliaries into the precursors have rescued the Reformatsky methodology as a synthetic tool even for asymmetric targets. Some brief mention was made on this matter in Section 2.2, Eqs. 6, 8–10, 14–16, 32, 34, 40–43, 46, 47, 72, 73 and 77–79, and Schemes 6–8 and 12.

4.4.1. Chiral or stereo inductor auxiliaries. Some degree of diastereoselectivity and enantiofacial differentiation has been made possible through the use of halo precursors bearing chiral or stereo inductor auxiliaries attached in the form of esters or amides (e.g., **242** through **244**). These chiral moieties derive mainly from alcohols such as menthol and related compounds,[214,264] oxazolidines,[163,164,166] and oxazinanes.[167–169] A relevant equation appear in Table 3 (entry 2). In addition, Table 6 lists some selected examples of the best stereoselectivities attained by these methods. As seen in Table 6, *syn* products are regularly favored, and this *syn* preference is explained in terms of an enantiofacial *re* differentiation which is probably derived from a chair-like, six-membered transition state, according to the Zimmerman-Traxler,[61,64,95,99] or Nerz-Stormes-Thornton models (Fig. 1).[166,262] The chromium Reformatsky reactions favor *anti* products when starting from α-bromo amides or α-bromo esters (entries 5–7), but the opposite trend is observed when the reaction is carried out using α-halo ketones.[65,66]

Further functional group conversions or removal of the chiral auxiliary makes possible the synthesis of asymmetric targets. For instance, products **249** and **265**, prepared according to conditions specified in entries 1–3 and 12–14, have been appropriately converted to 1β-methylcarbapenems.[163–169,191] Also, products **256**, **258**, **262** or **267**, which were readily prepared as illustrated in entries 6, 7, 10, 15 and 16, may be hydrolyzed to afford the respective β-hydroxyacids with high enantiomeric excesses,[166,264] and products **267** may be converted to the respective β-lactams with up to 99% e.e., a key procedure in preparing 3-substitued azetidin-2-ones, which exhibit cholesterol

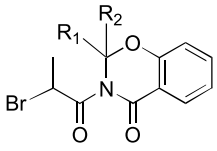


163b

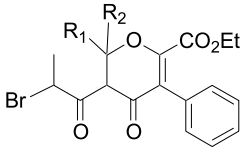


242

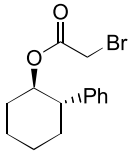
a: $R_1 = {}^{i}Pr$, $R_2 = R_3 = R_4 = H$, $R_5 = Me$
b: $R_1 = Bn$, $R_2 = R_3 = R_4 = H$, $R_5 = Me$
c: $R_1 = R_2 = {}^{n}Bu$, $R_3R_4 = (CH_2)_5$, $R_5 = Me$
d: $R_1 = Bn$, $R_2 = R_3 = R_4 = R_5 = H$
e: $R_1 = H$, $R_2 = Ph$, $R_3 = H$, $R_4 = Ph$, $R_5 = Me$
f: $R_1 = {}^{i}Pr$, $R_2 = R_3 = R_4 = R_5 = H$
g: $R_1 = H$, $R_2 = Bn$, $R_3 = R_4 = R_5 = H$



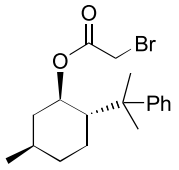
243a: $R_1 = R_2 = {}^{n}Bu$
243b: $R_1 = R_2 = Bn$



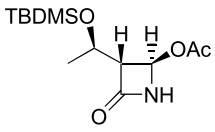
243c: $R_1R_2 = (CH_2)_5$



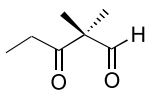
244a



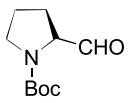
244b



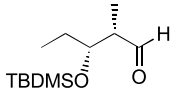
245



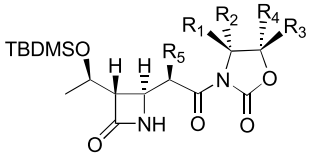
246



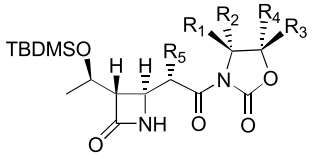
247



248

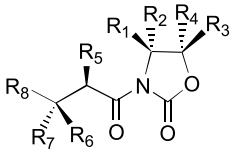


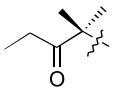
249



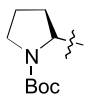
250

a: R_1 = ^{i}Pr , R_2 = R_3 = R_4 = H , R_5 = Me
b: R_1 = Bn , R_2 = R_3 = R_4 = H , R_5 = Me
c: R_1 = R_2 = ^{n}Bu , R_3R_4 = $(CH_2)_5$, R_5 = Me
d: R_1 = Bn , R_2 = R_3 = R_4 = R_5 = H
e: R_1 = H , R_2 = Ph , R_3 = H , R_4 = Ph , R_5 = Me
f: R_1 = ^{i}Pr , R_2 = R_3 = R_4 = R_5 = H
g: R_1 = H , R_2 = Bn , R_3 = R_4 = R_5 = H

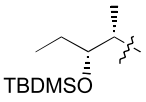




R_8 moiety for **253** and **254**



R_8 moiety for **261**



R_8 moiety for **263** and **264**

251 (2,3-*syn*), R_1=R_2= ^{n}Bu, R_3R_4= $(CH_2)_5$, R_5= Me, R_6= OH, R_7= H, R_8= Ph

252 (2,3-*anti*), R_1=R_2= ^{n}Bu, R_3R_4= $(CH_2)_5$, R_6= H, R_7= OH, R_8= Ph

253 R_1= Bn, R_2=R_3=R_4=R_5= H, R_6= OH, R_7= H

254 R_1= Bn, R_2=R_3=R_4=R_5= H, R_6= H, R_7= OH

255 R_1= Bn, R_2=R_3=R_4= H, R_5= Me, R_6= OH, R_7= H, R_8= ^{i}Pr

256 R_1= Bn, R_2=R_3=R_4= H, R_5= Me, R_6= H, R_7= OH, R_8= ^{i}Pr

257 (2,3-*syn*), R_1= Bn, R_2=R_3=R_4= H, R_5= Me, R_6= OH, R_7= H, R_8= ^{i}Pr

258 (2,3-*anti*), R_1= Bn, R_2=R_3=R_4= H, R_5= Me, R_6= H, R_7= OH, R_8= ^{i}Pr

259 (2,3-*syn*), R_1= H, R_2= Ph, R_3= H, R_4= Ph, R_5= Me, R_6= OH, R_7= H, R_8= Ph

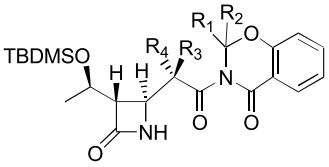
260 (2,3-*anti*), R_1= H, R_2= Ph, R_3= H, R_4= Ph, R_5= Me, R_6= H, R_7= OH, R_8= Ph

261 (2,3-*syn*), R_1= H, R_2= Ph, R_3= H, R_4= Ph, R_5= Me, R_6= OH, R_7= H

262 R_1= ^{i}Pr, R_2=R_3=R_4=R_5= H, R_6 and R_7= OH and H; configuration at C3 not determined, R_8= ^{t}Bu

263 R_1= H, R_2= Bn, R_3=R_4=R_5= H, R_6= H, R_7= OH

264 R_1= H, R_2= Bn, R_3=R_4=R_5= H, R_6= OH, R_7= H

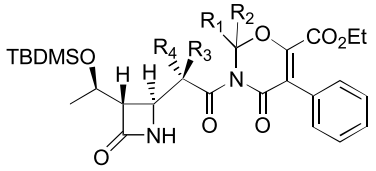


265a R_1=R_2= ^{n}Bu, R_3= H, R_4= Me (α-isomer)

265b R_1=R_2= Bn, R_3= H, R_4= Me (α-isomer)

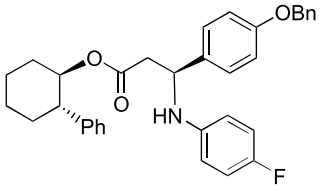
266a R_1=R_2= ^{n}Bu, R_3= Me, R_4= H (β-isomer)

266b R_1=R_2= Bn, R_3= Me, R_4= H (β-isomer)

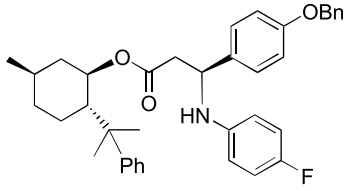


265c R_1R_2= $(CH_2)_5$, R_3= H, R_4= Me (α-isomer)

266c R_1=R_2= $(CH_2)_5$, R_3= Me, R_4= H (β-isomer)



267a

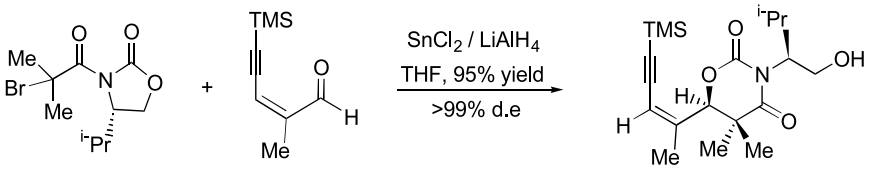


267b

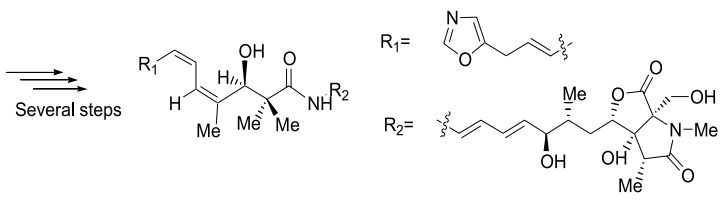
absorption inhibitory activity.[214] Products **259**, which resulted from the germanium Reformatsky reactions (entry 8), have been converted to the respective methyl esters with optical purities >99%,[95] whereas the adduct **261**, which resulted from the cobalt-phosphine Reformatsky approach (entry 9), was stereospecifically converted to the dolastatin 10 unit dolaproine (Dap) useful as a human anticancer agent.[99] Similar conversions from products **254** of chromium Reformatsky reactions (entry 5) were used for the synthesis of fragment A of epothilons, macrocyclic lactones with taxol-like mitose inhibition profile.[65] An efficient, related synthetic route was developed to prepare substituted δ-lactones in enantiopure forms which are potentially useful for biosynthetic studies with genetically engineered modular polyketide synthase (PKS). The method involves hydrolysis of products **263** that were prepared by SmI_2-promoted Reformatsky reactions starting from the enantiomeric (*S*)-4-benzyloxazolidinone (entry 11 in Table 6).[260]

On the other hand, a Sn(II)-enolate asymmetric Reformatsky-type condensation of an acyloxazolidinone **268** to Me_3Si–(acetylene)–CH=C(Me)CHO **269**, producing adduct **270**, is involved as the key step in the convergent enantioselective total synthesis of the antitumor antibiotic neooxazolomycin **271** (Eq. 80).[265]

Further deprotection of the products **273** of highly stereocontrolled Reformatsky reactions, makes possible the synthesis of all four diastereomers of β-hydroxy-α-amino acids **274**, starting from a chiral serine aldehyde **272** via a variety of carbonyl addition reactions including the Reformatsky reaction (Eq. 81).[266] The method readily allows for stereospecific incorporation of both C and H isotopes in amino acid side chains, and a similar procedure has been reported with the analogous fluorinated Reformatsky reaction in the synthesis of L-4,4-difluoroglutamic acid involving an analogous N-protected derivative of L-serine (see later).[267]

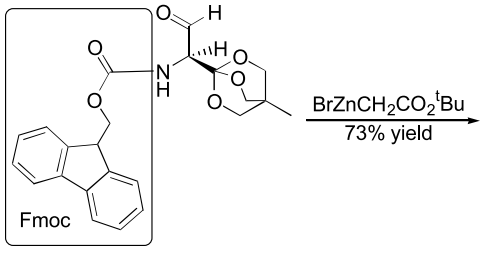


268 **269** **270**

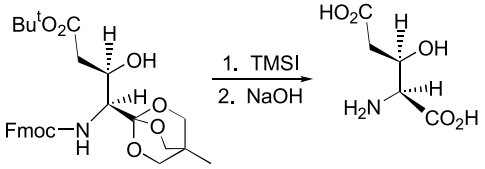


271

(80)



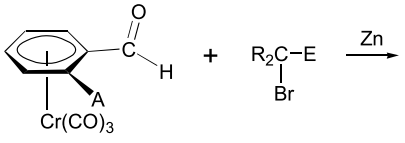
272



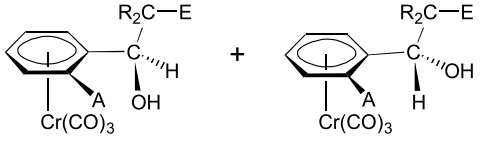
273, (2S,3R), ratio *threo/erythro* 92:8 **274**, (2S,3R), 98% ee

(81)

Cp-based complexes exert some diastereo control. For example, it was reported recently that titanocene (III)-promoted Reformatsky reactions occur with *anti* diastereoselectivity.[52] Tricarbonyl (η^6-arene)chromium (0) (e.g., **275**) and ferrocene-based related complexes may function as chiral auxiliaries, (Eqs. 82 and 83),[33,137,268] giving products with high enantiomeric excesses, in such a way that it is possible to correlate the absolute configuration of the obtained products with the configuration of the starting tricarbonylchromium complexed chiral substrates. Also, a highly stereoselective synthesis (e.e.>98%) of a mixture of β-amino esters **279** and β-lactams **280** was accomplished using enantiomerically pure tricarbonyl (η^6-benzaldimine)-chromium complexes **278** in a Reformatsky-type reaction promoted by ultrasound (Eq. 83).[137]



275

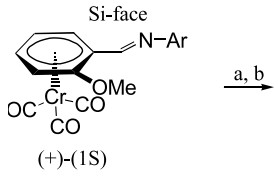


276 (major) **277** (minor)

62-88% combined yield. %d.e ranging from= 2-100%

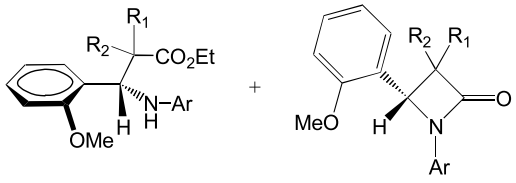
With E= CO_2Me, $CO_2{}^tBu$, CO_2Et, CN. R= H, Me. A= Me, OMe

(82)



(+)-(1S)

278



(83)

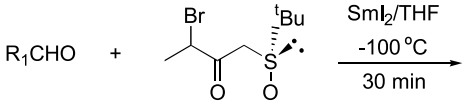
279 **280**

70-94% combined yield; ee of **279** and **280** up to 98%

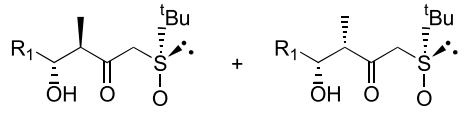
With R1= H, Me. R2= H, Me. Ar= Ph, p-(MeO)Ph

Conditions: (a) $R_1R_2C(Br)CO_2Et$/Zn/dioxane, 20–25 °C, ultrasound. (b) CH_2Cl_2, *hv*, air (for decomplexation).

A recent development on diastereoselective Reformatsky reactions involving chiral α-bromo-α′-sulfinyl ketones **281** and linear aldehydes in the presence of SmI_2 gives rise to the respective adducts (**282**+**283**) with of up to 98% *syn* diastereomeric excess (Eq. 84).[263] Further reduction of the Reformatsky adducts furnishes *anti* and *syn*-2-methyl-1,3-diols moieties in excellent yields and diastereoselectivities. Related chiral sulfinylimines have been used in Reformatsky reactions of fluorinated precursors (see Section 5).[269,270]



281

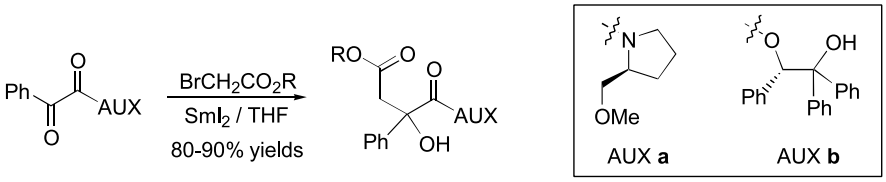


(84)

282 **283**

Yields: 55–87%. *Syn*/*anti* ratios: 45:55 to 98:2. Ratios **282**/**283**: 80:20 to 96:4.

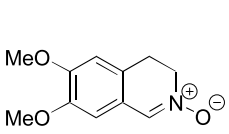
SmI_2-induced Reformatsky reactions of chiral diols- or chiral (2*S*)-methoxymethylpyrrolidine-based α-ketoesters/amides **284** afforded the corresponding adducts **285** with 80–90% yields and 60–89% diastereomeric excess (Eq. 85).[261]



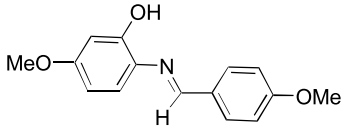
284a **285a** (R= Me, 72% d.e; R= ^{t}Bu, 89% d.e)

284b **285b** (R= Me, 60% d.e)

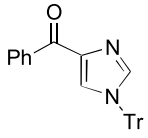
Table 7. Selected examples of the best enantioselectivities accomplished by adding chiral auxiliaries



286

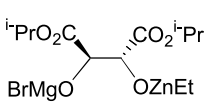


287

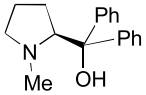


288

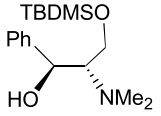
Entry	Precursor	E^{+}	Reformatsky agent	Reaction conditions	Chiral auxiliary	Product	Yield (%)	e.e. (%)	Ref.
1	$ICH_2CO_2CEt_3$	**286**	Et_2Zn	CH_2Cl_2, 0 °C, 2 h	**289**	**297**	99	86	34
2	$ICH_2CO_2^tBu$	**287**	Et_2Zn	CH_2Cl_2, 0 °C, 12 h	**289**	**298**	58	96	213
3	$BrCH_2CO_2^tBu$	PhCHO	Zn–Cu	THF, 0 °C	**290**	**299a**	91	75	274
4	$BrCH_2CO_2^tBu$	PhCHO	Zn	THF, 0 °C, 15–20 h	**291**	**299a**	100	65	276
5	$BrCH_2CO_2^tBu$	PhCHO	Zn–Cu	THF, reflux, 5 h	**292**	**299b**	57	64	272b
6	$BrCH_2CO_2^{i2}Bu$	PhAc	Zn–Cu	THF, Tol, −13 °C, 25 h	**293**	**300**	65	74	277
7	$BrCH_2CO_2^tBu$	PhCHO	Zn	THF, 0 °C, 24 h	**294**	**299a**	90	62	273
8	$BrCH_2CO_2^tBu$	**288**	Zn	THF, Pyr, −40 °C, 4 h	**295**	**301**	>99	97	279
9	$BrCH_2CO_2Et$	PhCHO	Zn/TMSCl	THF, 50 °C, 20 min	**296**	**299a**	49	34	280



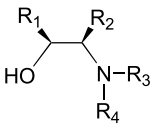
289



290

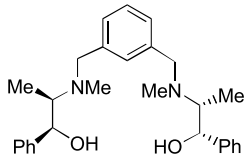


291



292, R_1=R_2= Ph, R_3= Bn, R_4= Me

293, R_1= Ph, R_2= Me, R_3=R_4= allyl

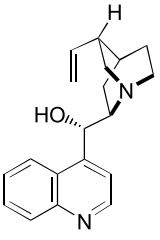


294

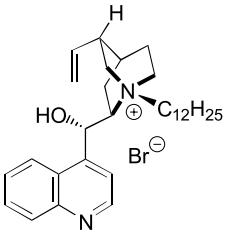
4.4.2. Chiral auxiliaries as additives. From catalytic to stoichiometric amounts of chiral auxiliaries such as carbohydrates,[271] amino alcohols (ephedrines and *N*-alkylephedrines),[171,272–278] cinchonine and cinchona alkaloids,[78,279] chiral micelles,[280] chiral α-imino esters,[189] α-amino acid esters and peptide derivatives[281] may be added as ligands to a reaction mixture, in order to exert some extent of stereocontrol. In some specific cases, good enantiomeric excesses have been obtained, as listed in Table 7. Entries 1 and 2 illustrate the use of chiral tartrate derivatives **289** as chiral auxiliaries, particularly for the asymmetric addition of Reformatsky-type reagents to isoquinoline *N*-oxide derivatives **286** and imines **287**,[34,213] whereas entries 3–7 demonstrate the use of chiral aminoalcohols or derivatives **290**-**294**.[273–276] However, the best results are observed when cinchona alkaloids **295** are used as chiral ligands (entry 8), although in this particular case the high enantioselectivity is attributed to the enantiofacial discrimination which results from chelation with the sp^2-nitrogen adjacent to the reactive carbonyl center.[279] Quaternary salts **296** deriving from cinchonines bearing long chains, as chiral micelles, create a chiral environment for asymmetric Reformatsky reactions, affording moderate enantiomeric excesses (entry 9).[280] Similarly, micelles deriving from chiral amino alcohols of the form **290**-**294** exert a related behavior.[280] Chiral β-(*N*-arylamino)esters **298** from entry 2 may be easily converted to the respective chiral β-amino esters by simple deprotection procedures.[213]

4.5. Synthetic applications

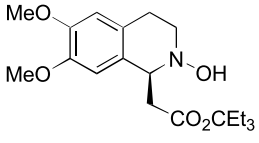
A number of examples have been mentioned throughout this review dealing with important synthetic targets which can be synthesized via multistep procedures involving the Reformatsky methodology as at least one of the key steps. Several of those targets are molecules with some biomedical potential, or synthetic intermediates for their preparation, which include for instance 9-alkyl-10-deazaminopterins,[15] richardianidins,[53] epothylons,[65] tonantzitlolone,[68] dolaproine,[99] nucleoside- and nucleotide derivatives,[128,256] a monomer for a polymer analog of a nucleic acid,[118] (+)-pilocarpine,[158] 1β-carbapenems,[163–169,191] peptides (with projection to peptide libraries),[202] cadinanolide,[198] a tetracyclic model for the aziridinomitosenes,[228] (+)-pederin,[252] α-, and β-amino acids and their respective esters and β-lactams,[57] (−)-octalactin,[253] (+)-compactin lactone,[254] ciguatoxine (CTX1B) or model compounds,[255] (−)-decarestrictine,[257] (−)-borrelidin,[258] neooxazolomycin,[265] trienomycin,[282] bremazocine,[283] the cytotoxic macrolide 15-*epi*-haterumalide NA,[284] 4-octulose derivatives,[83] 8-azapsoralens and other coumarin-derived products,[203,285] quinol esters such as jacaranone,[84] quinoline 4-methanols,[194] tetronic acids,[233,234] ulosonic acids,[104,105] analogues of quinolone antibacterial agents,[159] C-glycosyl derivatives,[286] phenolic derivatives (with aryl groups such as phenyl-derivatives, biphenyl, coumarin, flavone, xanthone, carbazole, dibenzofuran or quinolinone



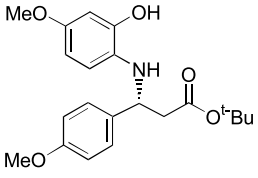
295



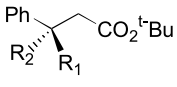
296



297



298

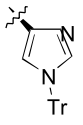


299a, R_1=H, R_2= OH

299b, R_1=OH, R_2= H

300, R_1= Me, R_2= OH

301, R_2= OH



R_1 for **301**

As may be anticipated, the quality of the results in terms of the stereocontrol is affected by the ratio of the chiral ligand with respect to the starting materials.

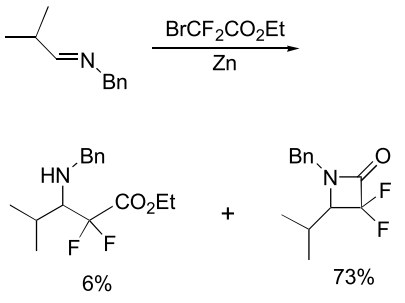
moieties),[186,187] steroidal residues,[188] taxoid rings,[251] *epi*-cytochalasin D,[246] daphniphyllum alkaloids,[247] supellapyrone (a pheromone),[250] agrochemicals,[233,234] 3-hydroxycitronellic

acid,[287] (±)-heritol as insecticide,[288] (±)-nimbidiol and (±)-nimbiol,[289] 3,4-diphenylbutanoic acids with antifungal activity,[290] (*Z*)- and (*E*)-4-amino-2-(trifluoromethyl)-2-butenoic acids as potential mechanism-based inactivators of γ-aminobutyric acid aminotransferase (GABA-AT),[291] liposidomycin-B (nucleoside antibiotic),[292] (+)-castanospermine,[293] equine metabolites of anabolic steroids,[294] fuscol (a marine diterpene with potential as anti-inflamatory),[295] a vitamin A analogue[296] of pyrimidine-,[184] purine-derived nucleic acid bases,[185] and other targets with medicinal or broad biological interest.[112,297–302] Some such targets are associated as agents that are presumably or certainly bioactive as antitumoral, antiviral, antifungal, antibiotic, antimalarial, vasorelaxing molecules, metabolic inhibitors of cholesterol biosynthesis or antifolates, pesticides, pheromones, etc.

Additional miscellaneous examples which can be mentioned include: enantioselective synthesis of indane acetic derivatives,[303] γ-amino-β-hydroxyacids,[155] formation of highly oxidized terpenes derived from abietic acid,[304] and other terpenoids,[305] butenolides such as (±)-mintlactone,[306] synthetic approaches to homochiral bicyclo-[5.2.1]decanes based on D-camphor,[307] synthesis of a stable neutral hydrocarbon radical 2,5,8-tri-*tert*-butylphenalenyl,[308] adamantyl derivatives for generation of carbocations,[154] cyclopentenones,[309] quinoline derivatives,[310] tetrahydrofuran units and five-membered ring lactones fused to hexopyranosides,[311] 3-arylidene and 3-cyclohexylidene benzofuran-2(3*H*)-ones,[312] superferrocenophane,[313] and targets for applications in cosmetics.[314]

5. Recent reports of Reformatsky reactions involving fluorinated substrates

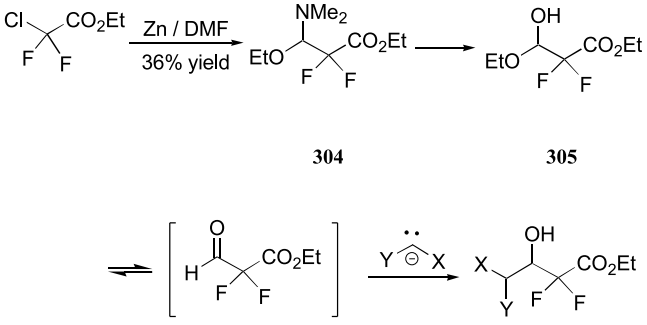
The subject of Reformatsky reactions of fluorine-containing precursors and substrates has been recently reviewed.[315] Classical reactions analogous to those of non-fluorinated systems lead to the synthesis of α,α-difluoro-β-hydroexyesters and α,α-difluoro-β-hydroxyketones, and the replacement of carbonyl compounds for imines[269,270,316,317] produces the anticipated α,α-difluoro-β-amino esters, for example, **302**, or their respective α,α-difluoro-β-lactams, for example, **303** (Eq. 86).[317] The Reformatsky reaction of fluorinated precursors with imines was carried out recently using rhodium catalysis, and it was used for the synthesis of functionalized (*Z*)-fluoroalkene-type dipeptide isosteres.[318] *N*-(α-aminoalkyl)benzotriazoles derived from aldehydes behave as imine equivalents, and as such they condense with monofluorinated Reformatsky reagents to afford the expected α-fluoro-β-amino esters.[55] The benzotriazole methodology with $BrZnCF_2CO_2Et$ has been also applied under solid-phase conditions for the preparation of α,α-difluoro-β-amino acids on a solid support (MBHA linked amines).[56] The carboxyl function gives access to a large range of possible transformations making these derivatives a useful tool for the generation of large libraries of fluorinated compounds including peptides, β-peptides and peptidomimetics.



(86)

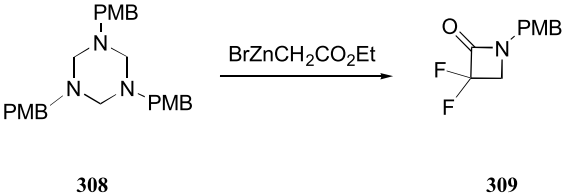
302, 6% yield **303**, 73% yield

DMF can also work as electrophile with the zinc-based Reformatsky agent derived from ethyl chlorodifluoroacetate, thus giving a Vilsmeier-type N–O acetal product **304**, convertible into the respective ethyl hemiacetal **305**, which is chemically equivalent to a difluoromalonaldehydic derivative **306**. This latter product condenses with active methylene compounds via aldol-like reactions (Eq. 87),[319] and the procedure is useful for the synthesis of diverse functionalized α,α-difluorinated esters and amides.



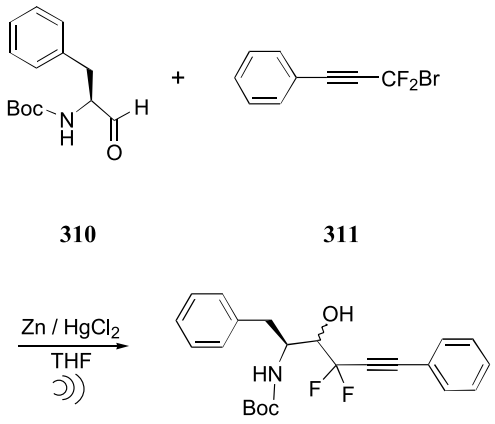
(87)

It is expected that N–O acetals or related substrates condense with fluorinated Reformatsky reagents, and specifically with 1,3-oxazolidines, which upon reaction generate laterally functionalized fluorine-containing β-lactams (see Section 5.1).[320] Similarly, ethyl bromodifluoroacetate condenses with N,N′,N″-trisubstituted hexahydro-1,3,5-triazines, for example, **308** (Schiff base trimer) under Reformatsky conditions, which is a useful route toward N-protected 3,3-difluoroazetidin-2-ones **309** (Eq. 88).[321]



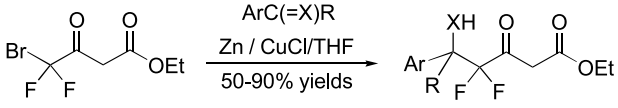
(88)

Chlorodifluoro- and bromodifluoroacetylene derivatives (e.g., **311**) have been used in Reformatsky-like reactions as well (Eq. 89).[322] The product **312** of this Reformatsky-like reaction has been used for the synthesis of a key intermediate of potent proteinase inhibitors.[322]



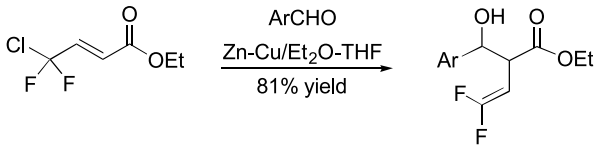
310 311 312 (89)

In the presence of zinc and cuprous chloride, straightforward reaction of 4-halo-4,4-difluoroacetoacetate **313** with aromatic aldehydes or aryl ketones[323] (or their respective imines[324]) under mild conditions gives good to excellent yields of the corresponding δ-hydroxyl-γ,γ-difluoro-β-keto esters or their related δ-amino-γ,γ-difluoro-β-ketoesters **314** (Eq. 90).[323,324]

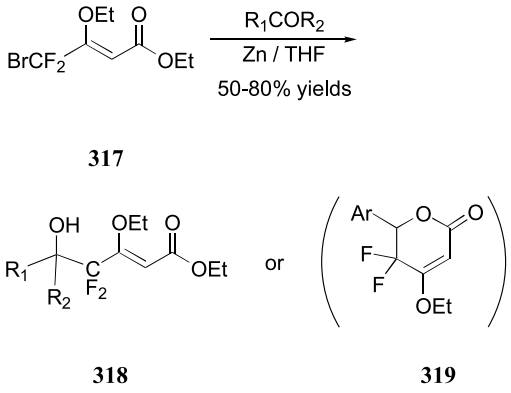


313 Being X= O, NH 314 (90)

Analogous to how 4-bromocrotonates behave in Reformatsky reactions, 4-bromo- or 4-chloro-4,4-difluorocrotonates **315** react either in the α-regiochemical mode or by γ-attack, giving rise to α-substituted 4,4-difluoro-3-butenoates (e.g., **316**, Eq. 91)[325] or γ substituted 4,4-difluoro-2-butenoates (e.g., **318**, Eq. 92), respectively.[326] In the latter case, the expected α,β-unsaturated γ,γ-difluoropyran-2-one **319** was formed starting from aromatic aldehydes with prolonged reaction times.



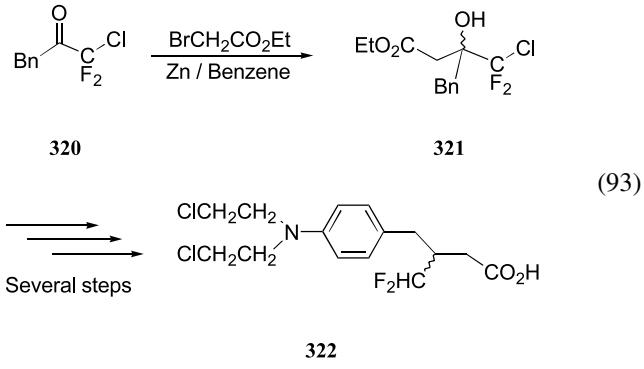
315 316 (91)



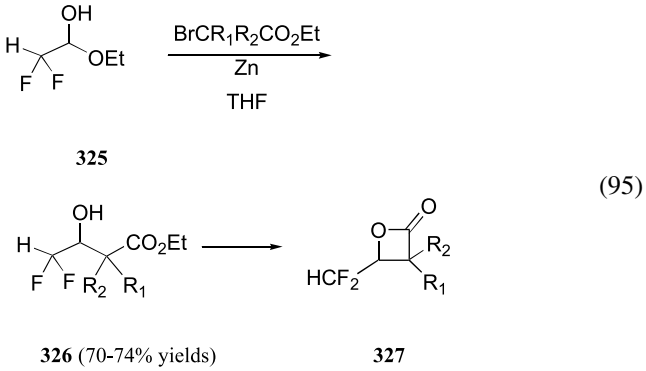
(92)

The reaction of ethyl bromodifluoroacetate with Michael acceptors in the presence of copper powder has been studied recently, and the method has been used for the synthesis of 4,4-difluoro-α-tocopherol.[327]

In general, it is recognized that chlorodifluorocompounds releases chlorine in Reformatsky reactions very much slower than do the analogous bromo- or iodo-compounds, but the chloro-derived precursors are cheaper. Some reports encourage usage of chlorodifluoro- precursors, introducing little experimental variants that allow the reactions to proceed favorably to products. Representative examples of slight experimental modifications include the catalysis of nickel under electrochemical conditions,[91] the use of couples such as Zn/CuCl or Zn/AgOAc,[328] or the combination Zn/AgOAc/Et_2AlCl,[37] and the indium-mediated Reformatsky reactions starting from 2,2-difluoro-2-halo-1-furan-2-ylethanones,[81] the latter case being useful for the synthesis of α,α-difluoro-β-hydroxy ketones in binary aqueous media. As already mentioned, ultrasound is an additional important tool in Reformatsky reactions of both non-fluorinated[19,79,80,141] and fluorinated[138–140] precursors, and it is indispensable with NO_2 bearing aldehydes or ketones which require prior generation of the organozinc $BrZnCF_2CO_2Et$, which is only stable when generated under ultrasonicating conditions.[140] Lanthanide salts have been used successfully, and such is the case for the SmI_2-induced reaction of chloro- and bromodifluoroacetates with aldehydes, giving rise to the expected classical α,α-difluoro-β-hydroxyesters in good yields.[329] SmI_2 has also been used with perfluorinated Reformatsky and related nucleophilic intermediates.[330] Alternatively, by using catalytic amounts of lanthanide salts (e.g., cerium trichloride) Reformatsky methodology starting from chloro- and bromodifluoroacetates[45] and from ethyl chlorofluoroacetate,[46] or ethyl bromofluoroacetate[47] has become recognized as an efficient and simple procedure. However, the relative inertness of the chlorodifluoro moiety becomes an advantage if additions of Reformatsky reagents to chlorodifluoroketones are desired. For instance, the key step for the preparation of chlorambucil derivatives **322**, involves a Reformatsky reaction with the chlorodifluoroketone **320**, providing the adduct **321** with the CF_2Cl moiety remaining unchanged (Eq. 93).[331]

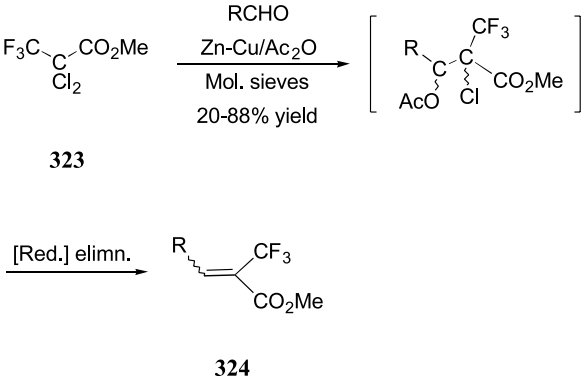


(93)

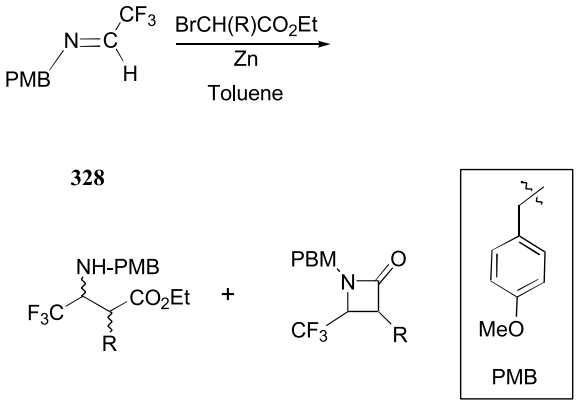


(95)

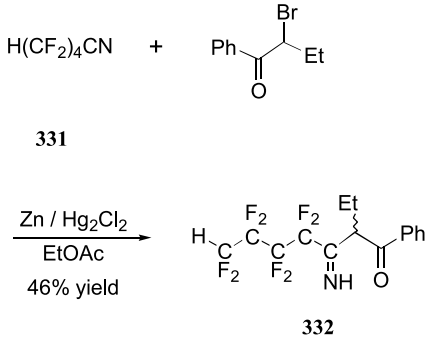
One-pot Reformatsky reaction/acylation/reductive elimination starting from the readily available $CF_3CCl_2CO_2Me$ **323** with aldehydes constitutes a general synthetic scheme for the preparation of mixtures (*E*/*Z*) of α-(trifluoromethyl)-α,β-unsaturated carboxylates **324**, mostly in favor of the *Z* isomers with selectivities ranging from 53:47 to 66:34, useful as fluorine-containing building blocks (Eq. 94).[332]



(94)



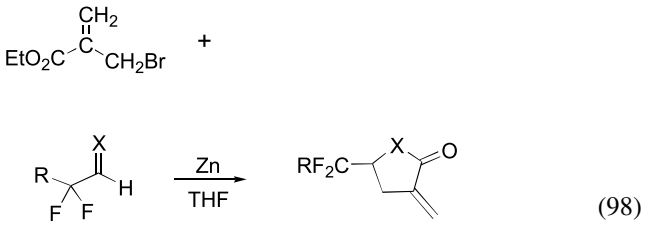
(96)



(97)

On the other hand, Eqs. 95–97 illustrate common reactions of non-fluorinated Reformatsky reagents with fluorinated electrophiles, giving rise to the anticipated products. Eq. 95 deals with the reaction of a classical Reformatsky reagent with a fluorinated hemiacetal **325** to afford γ,γ-difluoro-β-hydroxyesters **326**, with low *threo*/*erythro* selectivity,[333] and Eq. 96 shows a typical Reformatsky reaction with a fluorinated imine **328**, which affords a mixture of the β-amino esters **329** and the respective β-lactams **330**, with the β-lactams being preferred over the β-amino esters.[334] β-Lactones **327** bearing a lateral difluoro moiety can be obtained from **326** by standard procedures. The Reformatsky reaction of a fluorinated nitrile **331** gives a 46% yield of the rare tautomeric form **332**, stable at temperatures of up 145 °C (Eq. 97).[40]

The version of the Dreiding–Schmidt reaction[177–180] of methyl 2-(bromomethyl)acrylate applied to difluoro- or trifluoroacetaldehyde **333a–b** (or their acetals) gives rise, respectively, to the expected γ-difluoromethyl-α-methylene-γ-butyrolactones **334a**[335] or γ-trifluoromethyl-α-methylene-γ-butyrolactones **334b** (Eq. 98),[336] potent in vitro antitumor compounds, even stronger than 5-fluorouracil. Analogous reaction of methyl 2-(bromomethyl)-acrylate with difluoro-, or trifluoroethanimine **333c–d** generates the respective γ-difluoromethyl-α-methylene-γ-butyrolactams **334c–d** (Eq. 98).[335]



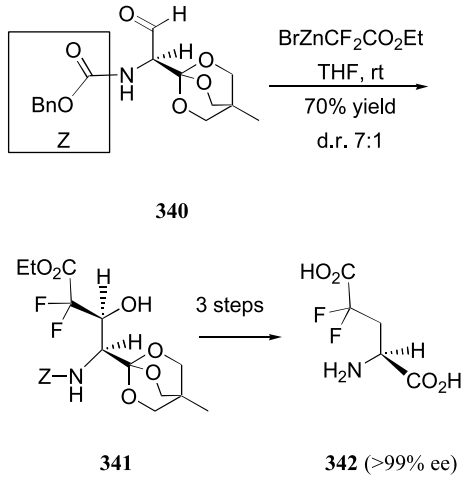
(98)

333a, R= H, X= O **334a**, R= H, X= O
333b, R= F, X= O **334b**, R= F, X= O
333c, R= H, X= NH **334c**, R= H, X= NH
333d, R= F, X= NH **334d**, R= F, X= NH

Domino Reformatsky-Wittig reactions of 4-bromocrotonates with perfluorinated ketophosphonium salts **335** afford either perfluoroalkylated 1,4-alkadienes **337** resulting from α-attack, or 5-(perfluoroalkyl)-substituted 2,5-alkadienes **339** corresponding to γ-attack (Scheme 13).[337,338] Regioselectivities of up 100% in favor of the γ-product **339** are reported.

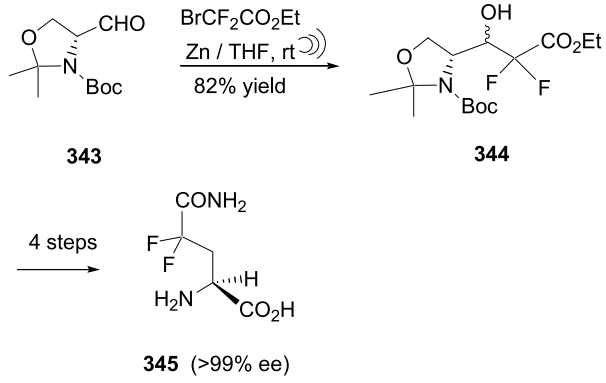
5.1. Advances in stereochemical aspects

Stereochemical control on the Reformatsky reaction of aldehydes and bromodifluoroacetate was briefly mentioned in a short review on asymmetric fluoroalkylations.[339] Some stereoselective developments with fluorinated substrates make use of enzymatic resolution techniques of racemic products using lipase MY from *Candida cylindracea*[340] or lipase PS or Novozym 435.[341] Asymmetric induction of catalytic Cp_2TiCl_2 in Reformatsky reactions of chiral electrophiles, particularly derived from carbohydrates, with bromo- and iododifluoroacetate with diastereoselectivities of up 95:5 is also reported.[342–344] Significant progress has been made on diastereo- and enantioselective Reformatsky reactions of fluorinated precursors, taking advantage of some of the methodologies described in Section 4.4 involving chiral precursors or electrophiles, or chiral auxiliaries as additives. For instance, chiral N-protected aldehyde **340**, chemically deriving from L-serine, was used a the key synthetic intermediate for the enantioselective preparation of L-4,4-diluoroglutamic acid **342**, with the crucial step being the 7:1 diastereoselective Reformatsky reaction of $BrCF_2CO_2Et$ to afford **341** (Eq. 99), and the whole sequence was amenable to a large-scale preparation of the enantiopure difluorinated amino acid **342**.[267]



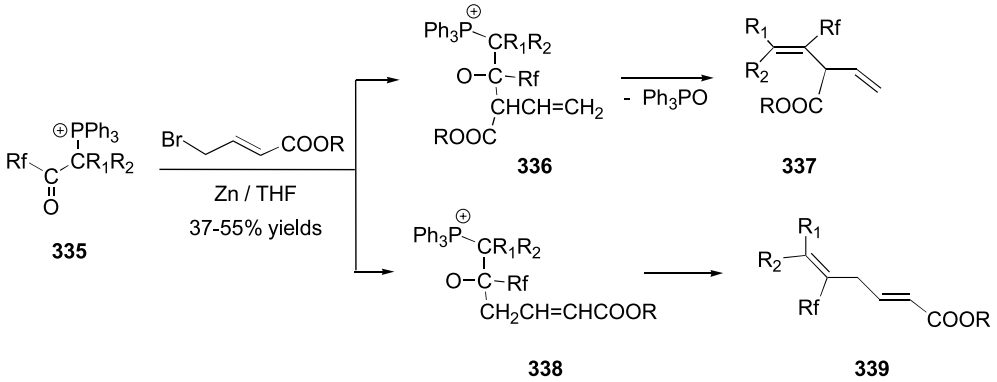
(99)

A similar synthetic strategy was applied to the preparation of the structurally related L-4,4-difluoroglutamine **345**, starting in this case from (*R*)-Garner's aldehyde **343**, which bears a chiral oxazolidine moiety (Eq. 100).[345]

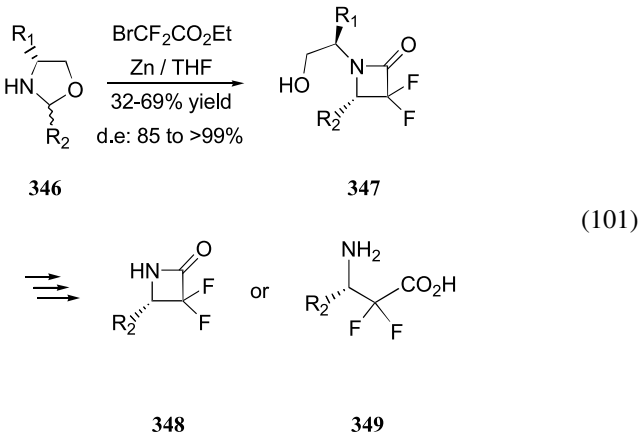


(100)

Chiral oxazolidines (e.g., **346**) function themselves as electrophiles with the bromodifluoro Reformatsky reagent, and this reaction is used to stereoselectively generate *N*-alkyl functionalized α,α-difluoro-β-amino acids **347**, which may be converted either to β-lactams **348** or to the respective α,α-difluoro-β-amino acids **349** (Eq. 101).[320]



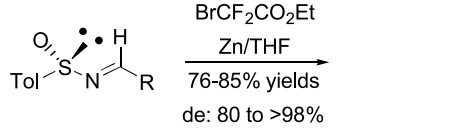
Scheme 13.



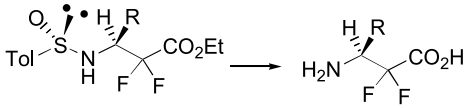
346 347 348 349 (101)

Chiral α,α-difluoro-β-amino acids, obtained in this manner, were used recently for the synthesis of difluorinated pseudopeptides.[346]

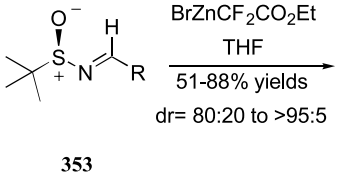
Enantiopure sulfinylimines (e.g., **350** and **353**) have become very promising imine equivalents[269,270] for use in carrying out stereocontrolled Reformatsky reactions from fluorinated precursors, affording the respective β-[*N*-(alkylsulfinyl)-amino]-α,α-difluoro-esters (**351** and **354**). The highest diastereomeric ratios are obtained with bulky aryl or cycloalkyl R groups,[270] and stereodefined products can be clearly anticipated. (*Ss*)-sulfinimines **350** generate (*Ss*,3*S*) diastereomers **351** (Eq. 102),[269] while the respective (*Rs*,3*R*) diastereomers **354** result from the (*Rs*) starting sulfinimines **353** (Eq. 103).[270]



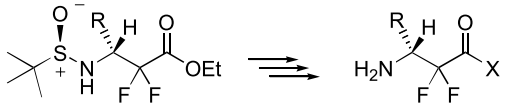
350



351 352 (102)



353 (103)



354 355

Diastereoselectivity exhibited by the bromodifluoro- Reformatsky reactions with chiral sulfinimines[269,270] has been explained in terms of the Ellman and Davis transition state models depicted in Figure 2,[347] which account for the predictable addition to the *Re* face of the (*Ss*)-sulfinimine (Fig. 2a) or to the *Si* face of the (*Rs*)-sulfinimine (Fig. 2b and c).

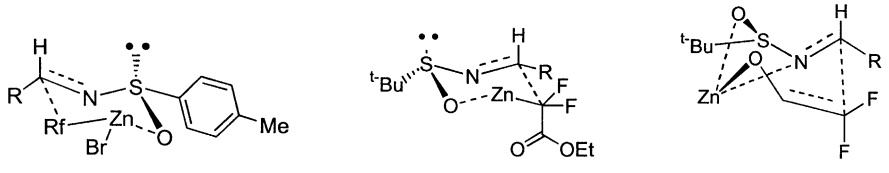
Further transformations of these Reformatsky products give rise to the respective α,α-difluoro-β-aminoacids **352** and **355**, or β-branched α,α-difluoro-β-amino esters useful for solid-phase peptide synthesis, and enantiomeric excesses even greater than 99% are reported.[269,270]

Chiral carbinols or amino alcohols such as ephedrine-[139] or *N*-methylephedrine derivates[348] of the form **292**, **293** and **294** are similarly effective chiral auxiliaries for enantioselective Reformatsky reactions of the bromodifluoro-Reformatsky reaction, leading to enantiomeric excesses similar to those which have been observed with the non-fluorinated version (as described in Table 7).

5.2. Recent applications in synthesis

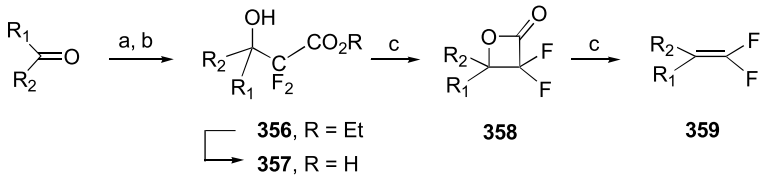
Several examples of syntheses of diverse fluorinated targets have been already mentioned in the previous sections, and in addition, some other examples deserve mention. For example, the classical route of carbonyl compounds to olefins was modified to generate 1,1-difluoroolefins **359** via the bromodifluoro- Reformatsky adducts **356** and their respective acids **357** (Scheme 14).[349,350] By this procedure α,α-difluoro-β-lactones **358** were systematically formed and isolated, and they were then thermally decarboxylated to afford 1,1-difluoroalkenes **359**.

A related methodology has made possible the generation of α-fluoro-β-hydroxyacids **361** and **365** via the non-aqueous alkaline hydrolysis of the respective diastereomeric α-fluoro-β-hydroxyesters **360** and **364** obtained from the



(a) (b) (c)

Figure 2.



Scheme 14. (a) $BrCF_2CO_2Et$, $Zn/CeCl_3$, THF, rt; (b) NaOH, rt, 12 h, then HCl; (c) $PhSO_2Cl/Pyr/CHCl_3$, 0 °C; (d) Heat.

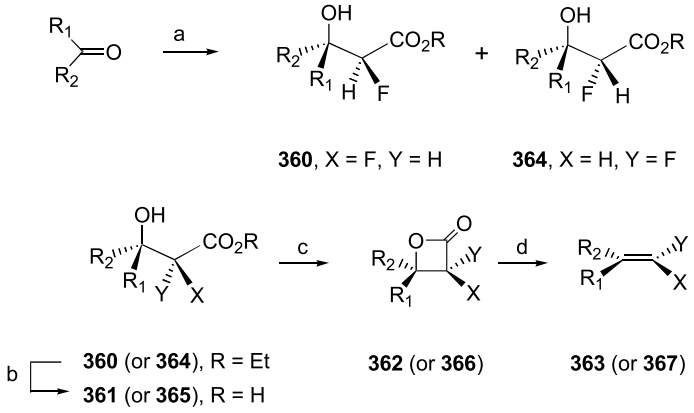
$CeCl_3$-catalyzed Reformatsky reaction.[47] Some of these α-fluoro-β-hydroxyacids could be converted to the novel α-fluoro-β-lactones **362** and **366**,[351] which are promising synthetic intermediates for the stereospecific generation of (*E*)- or (*Z*)-1-fluoroolefins **363** and **367** (Scheme 15).

Other significant synthetic applications involving fluorinated systems include the synthesis of (+)-10,10-difluorothromboxane A_2,[17] and other diverse synthons for medicinal chemistry targets,[270] the new quinoline antibacterial agent DQ-113 from ethyl bromofluoroacetate,[352] 3,3-difluoro-L-homocystein,[316] optically pure α,α-difluoro-β-amino acids,[320] a potential inhibitor of human thrombin,[353] a key intermediate of potent proteinase inhibitors,[322] chlorambucil derivatives,[331] (*S*)-β,β-difluoromalic acid,[340] nucleoside derivatives for antiviral assays,[342–344] alkyl fluorides,[354] cyclopentane derivatives containing a CF_2CO_2Et group,[355] (*Z*)-2-fluoroacrylate thioesters and other desired fluoroacrylates,[356] antitumoral compounds such as γ-difluoromethyl- and γ-difluoromethyl-α-methylene-γ-butyrolactones,[335,357] 14,14-difluoro-4-demethoxydaunorubicin,[358] enzyme inhibitors (for instance interleukin-1β converting enzyme (ICE),[359] a leucinal-derived hapten synthesized to elicit catalytic antibodies,[360] renin,[361,362] human leukocyte elastase[363] or aspartate transcarbamoylase,[219] β-*gem*-difluoromethylene C-glycosides,[334,364] vitamin D3 analogues,[365,366] or antagonists,[367] N-substituted dibenzoxazepines (analgesic PGE2 antagonists),[368] and, in general, biologically active compounds with CF_2 units as isopolar and isosteric replacement sites for ether oxygen.[318,369]

6. Concluding remarks

As seen throughout this review, much progress has been made on the asymmetric version of Reformatsky reactions, involving both fluorinated and non-fluorinated Reformatsky reagents. This significant progress has rescued Reformatsky methodology so that it is now even more useful than before for modern organic synthesis. When condensations are needed in planning organic synthesis, there are several factors which make the Reformatsky reaction a choice worth considering. Among those special factors which deserve emphasis are: (i) easy predictable C–C addition without C–O bond formations (with very few exceptions), (ii) demanding of neutral conditions (in contrast to the strong alkaline medium required for aldol condensations), (iii) smoothness of the Reformatsky reagents (in comparison to Grignard reagents), and (iii) the possibility of good levels of stereoselectivity, as described in the latest developments. We have seen that syntheses of a number of natural products very often involve key steps consisting of classical Reformatsky reactions or Reformatsky-type procedures, including cases where diastereomeric or enantiomeric control is desired. Much progress has also been made on the use of diastereoselective intramolecular Reformatsky reactions in assembling rings of varied sizes.

However, there has only been limited progress in developing alternative procedures with the goal of replacing organic solvents. Although there are some few reports on aqueous medium or non-solvent Reformatsky reactions, the quest for



For **360** through **363**, X= F, Y= H. For **364** through **367**, X= H, Y= F

Scheme 15. (a) $BrCHFCO_2Et$, $Zn/CeCl_3$, THF, rt; (b) NaOH/abs. EtOH, 0 °C, 2 h, then HCl; (c) $MePhSO_2Cl/DMAP/CHCl_3$, −50 °C; (d) Heat.

green chemistry is expected to lead to safer and more efficient procedures in the future, including those that produce less waste.

References and notes

1. Reformatsky, S. *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 1210.
2. Orsini, F.; Sello, G. *Curr. Org. Synth.* **2004**, *1*, 111–135.
3. Fürstner, A. *Synthesis* **1989**, 571–590.
4. (a) Fürstner, A. In *Encyclopedia of Reagents for Organic Synthesis*. Paquette, L. A., Ed.; Wiley: New York, 1995; pp 2402–2408. (b) Fürstner, A. In *Organozinc Reagents*. Knochel, P., Jones, P., Eds.; University Press: Oxford, 1999; pp 287–305. (c) Rathke, M. W.; Weipert, P. In *Comprehensive Organic Synthesis*. Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, pp 277–299. (d) Rathke, M. W. In *Organic Reactions*. John Wiley and Sons: New York, 1975; Vol. 22, Chapter 2, pp 30–59.
5. Zinc-induced Reformatsky reactions should be considered only a small subdivision of organozinc chemistry. (a). For documentation on organozinc chemistry, see: *Organozine Reagents*. Knochel, P., Jones, P., Eds.; University Press: Oxford, 1999; 354 p(b) For a review on transition metal catalyzed reactions of organozinc reagents, see:Erdik, E. *Tetrahedron* **1992**, *48*, 9577–9648.
6. Areias, M. C. C.; Bieber, L. W.; Navarro, M.; Diniz, F. B. *J. Electroanal. Chem.* **2003**, *558*, 125–130.
7. (a) Horner, W.; Bertagnolli, H. *J. Organomet. Chem.* **2002**, *649*, 128–135. (b) Ertel, T. S.; Horner, W.; Abraham, I.; Bertagnolli, H. *J. Phys. IV* **1997**, *7*, 947–948.
8. For older reviews, see: (a) Shriner, R. L. *Org. React.* **1942**, *1*, 1. (b) Rathke, M. W. *Org. React.* **1975**, *22*, 423–460. (c) Gaudemar, M. *Organomet. Chem. Rev., Sect. A*, **1972**, *8*, 183–233. (d) Nützel, K. *Houben-Weyl*, Vol. XIII/2a, Georg Thieme: Stuttgart, 1973, p 805. (e) Diaper, D. G. M.; Kuksis, A. *Chem. Rev.* **1959**, *59*, 89. (f) Brossi, M.; Kaenel, H. R. *Schweiz. Lab.-Z*, **1984**, *41*, 55–57. (g) Vul'fson, N. S.; Vinograd. L. K. *Reactions and Research Methods for Organic Compounds Reformatsky Reaction*, Vol. 17; Khimiya: Moscow, 1967.
9. Zhao, M.-X.; Wang, M.-X.; Yu, C.-Y.; Huang, Z.-T.; Fleet, G. W. *J. Org. Chem.* **2004**, *69*, 997–1000.
10. Bowman, M. P.; Senet, J. P. G.; Malfroot, T.; Olofson, R. A. *J. Org. Chem.* **1990**, *55*, 5982–5986.
11. Shchepin, V. V.; Russkikh, N. Y.; Desyatkov, D. A. *Zh. Org. Khim.* **1993**, *29*, 2316–2317.
12. (a) Shchepin, V. V.; Chuprikova, T. Y.; Petukhova, I. Y. *Zh. Org. Khim.* **1991**, *27*, 1796–1797. (b) Shchepin, V. V.; Efremov, D. I.; Desyatkov, D. A. *Zh. Org. Khim.* **1993**, *29*, 410–411.
13. For a review on some aspects on the stereochemistry of the Reformatsky reactions, see: Guette, J. P. In *Organomettaliques Fonct. Ambidents, Recl. Commun., Colloq. Fr.-Bulg.*; Blagoev, B., Gaudemar-Bardone, F., Mladenova, M., Eds., 1980. Acad. Bulg. Sci., Inst. Chim. Org.: Sofia, pp 123–129.
14. Akita, H.; Chen, S.-Y.; Nagumo, S. *Tetrahedron: Asymmetry* **1994**, *5*, 1207–1210.
15. DeGraw, J. I.; Christie, P. H.; Kisliuk, R. L.; Gaumont, Y.; Sirotnak, F. M. *J. Med. Chem.* **1990**, *33*, 212–215.
16. Khan, R. H.; Rastogi, R. C. *Indian J. Chem. Sect. B* **1992**, *31B*, 276.
17. Witkowski, S.; Rao, Y. K.; Premchandran, R. H.; Halushka, P. V.; Fried, J. *J. Am. Chem. Soc.* **1992**, *114*, 8464–8472.
18. Gomes Constantino, M.; Gonzaga de Oliveira Matias, L.; da Silva, G. V. J.; Gomes Heleno, V. C.; Gambardella, M. T. D. P. *Synth. Commun.* **1997**, *27*, 4285–4295.
19. Izquierdo, I.; Plaza, M. T.; Robles, R.; Mota, A. J.; Franco, F. *Tetrahedron: Asymmetry* **2001**, *12*, 2749–2754.
20. (a) Gawronski, J. K. *Tetrahedron Lett.* **1984**, *25*, 2605. (b) Picotin, G.; Miginiac, P. *J. Org. Chem.* **1987**, *52*, 4796. (c) Stephen, C. J. *Tetrahedron Lett.* **1992**, *33*, 6193–6196.
21. Guertler, S.; Ruf, S.; Johner, M.; Otto, H. H. *Pharmazie* **1996**, *51*, 811–815.
22. Gaudemar, M. *Tetrahedron Lett.* **1983**, *24*, 2749.
23. (a) Kuwajima, I.; Nakamura, E.; Hashimoto, K. *Org. Synth.* **1983**, *61*, 122. (b) Stocker, G. E.; Hoffmann, W. F.; Alberts, A. W.; Cragoe, E. J.; Peana, A. A.; Gilfillan, J. L.; Huff, J. W.; Novello, F. C.; Prugh, J. D.; Smith, R. L.; Willard, A. K. *J. Med. Chem.* **1985**, *28*, 347. (c) Maruoka, K.; Hashimoto, S.; Kitagawa, Y.; Yamamoto, H.; Nozaki, H. *Bull. Chem. Soc. Jpn* **1980**, *53*, 3301. (d) Maruoka, K.; Hashimoto, S.; Kitagawa, Y.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 7705. (e) Kuroboshi, M.; Ishihara, T. *Tetrahedron Lett.* **1987**, *28*, 6481. (f) Ishihara, T.; Kuroboshi, M. *Chem. Lett.* **1987**, 1145.
24. (a) Bellasoued, M.; Arous-Chtara, R.; Gaudemar, M. *J. Organomet. Chem.* **1982**, *231*, 185. (b) Lucas, M.; Guetté, J. P. *J. Chem. Res. (S)* **1978**, 214. (c) Bellasoued, M.; Gaudemar, M. *J. Organomet. Chem.* **1975**, *93*, 9. (d) Gaudemar-Bardone, F.; Gaudemar, M.; Mladenova, M. *Synthesis* **1987**, 1130. (e) Bogavac, M.; Arsenijevic, L.; Arsenijevic, V. *Bull. Soc. Chim. Fr.* **1980**, *II*, 145.
25. Santaniello, E.; Manzocchi, A. *Synthesis* **1977**, 698.
26. Slougui, N.; Rousseau, G. *Synth. Commun.* **1987**, *17*, 1.
27. (a) Csuk, R.; Fürstner, A.; Weidmann, H. *J. Chem. Soc., Chem. Commun.* **1986**, 775. (b) Csuk, R.; Glaenzer, B. I. *J. Carbohydr. Chem.* **1990**, *9*, 797–807.
28. Rieke, R. D.; Li, P. T. J.; Burns, T. P.; Uhm, S. T. *J. Org. Chem.* **1981**, *46*, 4323.
29. Boudjouk, P.; Thompson, D. P.; Ohrbom, W. H.; Han, B. H. *Organometallics* **1986**, *5*, 1257.
30. Rieke, R. D.; Uhm, S. J. *Synthesis* **1975**, 452.
31. Arnold, R. T.; Kulenovic, S. T. *Synth. Commun.* **1977**, *7*, 223.
32. Makosza, M.; Grela, K.; Fabianowski, W. *Tetrahedron* **1996**, *52*, 9575–9580.
33. Malfait, S.; Pélinski, L.; Brocard, J. *Tetrahedron: Asymmetry* **1998**, *9*, 2595–2610.
34. Ukaji, Y.; Yoshida, Y.; Inomata, K. *Tetrahedron: Asymmetry* **2000**, *11*, 733–736.
35. Aoyagi, Y.; Tanaka, W.; Ohta, A. *J. Chem. Soc., Chem. Commun.* **1994**, 1225–1226.
36. Kataoka, Y.; Makihira, I.; Yamagata, T.; Tani, K. *Organometallics* **1997**, *16*, 4788–4795.
37. Curran, T. T. *J. Org. Chem.* **1993**, *58*, 6360–6363.
38. Zhao, Z.; Ding, Y.; Zhao, G. *Synth. Commun.* **2001**, *31*, 2089–2096.
39. Ding, Y.; Zhao, Z.; Zhow, C. *Tetrahedron* **1997**, *53*, 2899–2906.
40. Fylyakova, V. I.; Saitkulova, F. G.; Pashkevich, K. I. *Izv. Akad. Nauk. Ser. Khim.* **1992**, 1228–1229.
41. Horiuchi, Y.; Taniguchi, M.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1995**, *36*, 5353–5356.

42. Basile, T.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *Synthesis* **1990**, 305–311.
43. Chattopadhyay, A.; Salaskar, A. *Synthesis* **2000**, 561–564.
44. Nozaki, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn* **1991**, *64*, 403–409.
45. Shen, Y.; Qi, M. *J. Fluorine Chem.* **1994**, *67*, 229–232.
46. Shen, Y.; Qi, M. *J. Chem. Res. (S)* **1993**, 222–223.
47. Ocampo, R.; Dolbier, W. R.; Abboud, K. A.; Zuluaga, F. *J. Org. Chem.* **2002**, *67*, 72–78.
48. (a) Kagayama, A.; Igarashi, K.; Shiina, I.; Mukaiyama, T. *Bull. Chem. Soc. Jpn* **2000**, *73*, 2579–2585. (b) Mukaiyama, T.; Kagayama, A.; Igarashi, K.; Shiina, I. *Chem. Lett.* **1999**, 1157–1158.
49. Hayashi, M.; Sugiyama, M.; Toba, T.; Oguni, N. *J. Chem. Soc., Chem. Commun.* **1990**, 767–768.
50. Hashimoto, Y.; Kikuchi, S. *Chem. Lett.* **2002**, 126–127.
51. Shimizu, M.; Kobayashi, F.; Hayakawa, R. *Tetrahedron* **2001**, *57*, 9591–9595.
52. (a) Parrish, J. D.; Shelton, D. R.; Little, R. D. *Org. Lett.* **2003**, *5*, 3615–3617. (b) Parrish, J. D.; Shelton, D. R.; Park, Y. S.; Little, R. D. *Proc. Electrochem. Soc.* **2003**, *2003–12*, 161–164.
53. Sánchez, M.; Bermejo, F. *Tetrahedron Lett.* **1997**, *38*, 5057–5060.
54. Kim, S.; Han, W. S.; Lee, J. M. *Bull. Kor. Chem. Soc.* **1992**, *13*, 466–467.
55. Katritzky, A. R.; Nichols, D. A.; Qi, M. *Tetrahedron Lett.* **1998**, *39*, 7063–7066.
56. (a) Vidal, A.; Nefzi, A.; Houghten, R. A. *J. Org. Chem.* **2001**, *66*, 8268–8272.Vidal, A.; Nefzi, A.; Houghten, R. A. Abstr. Pap., 223rd ACS National Meeting, 2002, ORGN-234 and FLUO-008.
57. Katritzky, A. R.; Hong, Q.; Yang, Z. *J. Org. Chem.* **1995**, *60*, 3405–3408. (b) Strah, S.; Katritzky, A. R.; Belyakov, S. A. *Abstr. Pap.-Am. Chem. Soc.* 1998, 215th ORGN-191.
58. For a recent review on chromium (II) and chromium (III)-mediated organic synthesis, included the chromium-Reformatsky reaction, see: (a) Fürstner, A. *Chem. Rev.* **1999**, *99*, 991–1045. (b) Wessjohann, L. A.; Scheid, G. *Synthesis* **1999**, *1*, 1–36.
59. For reviews on the application of SmI_2 in organic synthesis, see: (a) Krief, A.; Laval, A.-M. *Chem. Rev.* **1999**, *99*, 745. (b) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307. (c) Molander, G. A.; Harris, C. R. *Tetrahedron* **1998**, *54*, 3321. (d) Skrydstrup, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 345. (e) Molander, G. A. In *Organic Reactions*; Paquette, L. A., Ed. John Wiley: New York, 1994, Vol. 46, p 211. (f) Imamoto, T. Lanthanides in Organic Synthesis; Academic Press: London, 1994. (g) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29. (h) Curran, D. P.; Fevig, T. L.; Jaspersen, C. P.; Totleben, M. L. *Synlett* **1992**, 943. (i) Inanaga, J. *Trends Org. Chem.* **1990**, *1*, 23–30.
60. For reviews on indium in organic synthesis, see: (a) Podlech, J.; Maier, T. C. *Synthesis* **2003**, 633. (b) Cintas, P. *Synlett* **1995**, 1087.
61. (a) Wessjohann, L. A.; Wild, H. *Synthesis* **1997**, 512–514. (b) Wessjohann, L. A.; Wild, H. *Synlett* **1997**, *6*, 731–733.
62. Buse, C. T.; Heathcock, C. H. *Tetrahedron Lett.* **1978**, *19*, 1685.
63. Mainz, J.; Arrieta, A.; Lopez, X.; Ugalde, J. M.; Cossio, F. P.; Lecea, B. *Tetrahedron Lett.* **1993**, *34*, 6111–6114.
64. Wessjohann, L. A.; Wild, H. *Synlett* **1997**, 731.
65. Gabriel, T.; Wessjohann, L. A. *Tetrahedron Lett.* **1997**, *38*, 1363–1366.
66. Gabriel, T.; Wessjohann, L. A. *Tetrahedron Lett.* **1997**, *38*, 4387–4388.
67. Wessjohann, L. A.; Gabriel, T. *J. Org. Chem.* **1997**, *62*, 3772–3774.
68. Wittenberg, R.; Beier, C.; Drager, G.; Jas, G.; Jasper, C.; Monenschein, H.; Kirschning, A. *Tetrahedron Lett.* **2004**, *45*, 4457–4460.
69. Park, H. S.; Lee, I. S.; Kim, Y. H. *Tetrahedron Lett.* **1995**, *36*, 1673–1674.
70. Fukuzawa, S.; Mutoh, K.; Tsuchimoto, T.; Hiyama, T. *J. Org. Chem.* **1996**, *61*, 5400–5405.
71. Xu, X. L.; Lu, P.; Zhang, Y.-M. *Chin. Chem. Lett.* **1999**, *10*, 729–730.
72. Zhang, J.-M.; Zhang, Y.-M. *Chin. J. Chem.* **2002**, *20*, 111–113.
73. Hirano, K.; Fukuzawa, S. *Kidorui* **1998**, *32*, 312–313.
74. Fukuzawa, S.; Hirai, K. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1963–1965.
75. Lannou, M. I.; Helion, F.; Namy, J.-L. *Tetrahedron* **2003**, *59*, 10551–10565.
76. Chauhan, K. K.; Frost, C. G.; Waite, D. C. Abstr. Pap.-220th ACS Meeting, 2000, ORGN-114.
77. Wang, Z.; Hammond, G. B. *J. Org. Chem.* **2000**, *65*, 6547.
78. Johar, P. S.; Araki, S.; Butsugan, Y. *J. Chem. Soc., Perkin Trans. 1* **1992**, 711–713.
79. Bang, K.; Lee, K.; Park, Y. K.; Lee, P. H. *Bull. Kor. Chem. Soc.* **2002**, *23*, 1272–1276.
80. Lee, P. H.; Bang, K.; Lee, K.; Sung, S.-Y.; Chang, S. *Synth. Commun.* **2001**, *31*, 3781–3789.
81. Chung, W. J.; Higashiya, S.; Welch, J. T. *J. Fluorine Chem.* **2001**, *112*, 343–347.
82. Banik, B. K.; Ghatak, A.; Becker, F. F. Abstr. Pap., 223rd ACS National Meeting, 2002, ORGN-308.
83. Izquierdo, I.; Plaza, M. T.; Tamayo, J. A.; Mota, A. J. *Synthesis* **2004**, 1083–1087.
84. Araki, S.; Katsumura, N.; Kawasaki, K.; Butsugan, Y. *J. Chem. Soc., Perkin Trans. 1* **1991**, 499–500.
85. (a) Schick, H.; Ludwig, R.; Schwarz, K.-H.; Kleiner, K.; Kunath, A. *J. Org. Chem.* **1994**, *59*, 3161–3164. (b) Schick, H.; Ludwig, R.; Kleiner, K.; Kunath, A. *Tetrahedron* **1995**, *51*, 2939–2946.
86. (a) Schwarz, K.-H.; Kleiner, K.; Ludwig, R.; Schick, H. *J. Org. Chem.* **1992**, *57*, 4013–4015. (b) Schwarz, K.-H.; Kleiner, K.; Ludwig, R.; Schick, H. *Chem. Ber.* **1993**, *126*, 1247–1249.
87. Durandetti, M.; Meignein, C.; Perichon, J. *Org. Lett.* **2003**, *5*, 317–320.
88. Tussa, L.; Lebreton, C.; Mosset, P. *Chem.-A Eur. J.* **1997**, *3*, 1064–1070.
89. Hirashita, T.; Kinoshita, K.; Yamamura, H.; Kawai, M.; Araki, S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 825–828.
90. Conan, A.; Sibille, S.; Perichon, J. *J. Org. Chem.* **1991**, *56*, 2018–2024.
91. Mcharek, S.; Sibille, S.; Nedelec, J. Y.; Perichon, J. *J. Organomet. Chem.* **1991**, *401*, 211–215.
92. Shen, Z.; Zhang, J.; Zou, H.; Yang, M. *Tetrahedron Lett.* **1997**, *38*, 2733–2736.
93. Kagoshima, H.; Hashimoto, Y.; Saigo, K. *Tetrahedron Lett.* **1998**, *39*, 8465–8466.
94. Han, Y.; Chi, Z.-F.; Huang, Y. Z. *Chin. Chem. Lett.* **1996**, *7*, 713–716.

95. (a) Kagoshima, H.; Hashimoto, Y.; Oguro, D.; Saigo, K. *J. Org. Chem.* **1998**, *63*, 691–697. (b) Kagoshima, H.; Hashimoto, Y.; Oguro, D.; Kutsuna, T.; Saigo, K. *Tetrahedron Lett.* **1998**, *39*, 1203–1206.
96. (a) Orsini, F.; Pelizzoni, T.; Pulici, M.; Vallarino, L. M. *J. Org. Chem.* **1994**, *59*, 1–3. (b) Orsini, F. *J. Org. Chem.* **1997**, *62*, 1159. (c) Orsini, F.; Pulici, M. In *Trends in Organometallic Chemistry*, Research Trends Ed., Trivandrum: India, 1994; Vol. 1, pp 625–667. (d) Orsini, F.; Pulici, M.; Vallarino, L. M. *J. Organomet. Chem.* **1995**, *495*, C1–C5.
97. Orsini, F. *Tetrahedron Lett.* **1998**, *39*, 1425–1428.
98. Orsini, F.; Leccioli, C. *Tetrahedron: Asymmetry* **1997**, *8*, 4011–4019.
99. Pettit, G. R.; Grealish, M. P. *J. Org. Chem.* **2001**, *66*, 8640–8642.
100. Duffield, J. J.; Pettit, G. R. *J. Nat. Prod.* **2001**, *64*, 472–479.
101. (a) Kanai, K.; Wakabayashi, H.; Honda, T. *Org. Lett.* **2000**, *2*, 2549–2551. (b) Marshall, J. A. *Chemtracts* **2000**, *13*, 705–707.
102. Honda, T.; Wakabayashi, H.; Kanai, K. *Chem. Pharm. Bull.* **2002**, *50*, 307–308.
103. Review: Csuk, R.; Glänzer, B. I.; Fürstner, A. *Adv. Organomet. Chem.* **1988**, *28*, 85–137.
104. Csuk, R.; Schröeder, C.; Krieger, C. *Tetrahedron* **1997**, *53*, 12947–12960.
105. Hanessian, S.; Girard, C. *Synlett* **1994**, 865–867.
106. Yokoyama, Y.; Tsuchikawa, T.; Hiramatsu, M.; Mochida, K. *Main Group Metal Chem.* **2000**, *23*, 691–693.
107. Takai, K.; Ueda, T.; Hayashi, T.; Moriwake, T. *Tetrahedron Lett.* **1996**, *37*, 7049–7052.
108. Suh, Y.-S.; Rieke, R. D. *Tetrahedron Lett.* **2004**, *45*, 1807–1809.
109. Takai, K.; Kakiuchi, T.; Utimoto, K. *J. Org. Chem.* **1994**, *59*, 2671–2673.
110. (a) Fürstner, A.; Hupperts, A. *J. Am. Chem. Soc.* **1995**, *117*, 4468–4475. (b) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390–2392. (c) Gaudemar, M. *Bull. Soc. Chim. Fr.* **1962**, 974–987.
111. Kakiya, H.; Nishimae, S.; Shinokubo, H.; Oshima, K. *Tetrahedron* **2001**, *57*, 8807–8815.
112. Demir, A. S.; Tanyeli, C.; Mahasneh, A. S.; Aksoy, H. *Synthesis* **1994**, 155–157.
113. Davies, S. G.; Edwards, A. J.; Evans, G. B.; Mortlock, A. A. *Tetrahedron* **1994**, *50*, 6621–6642.
114. Shibata, I.; Yamaguchi, T.; Baba, A.; Matsuda, H. *Chem. Lett.* **1993**, 97–100.
115. Shibata, I.; Suwa, T.; Sakakibara, H.; Baba, A. *Org. Lett.* **2002**, *4*, 301–303.
116. (a) Kuznetsov, N. Y.; Khrustalev, V. N.; Terentiev, A. B.; Belokon, Y. N. A. N. *Russ. Chem. Bull.* **2001**, *50*, 548–550. (b) Terent'ev, A. B.; Vasil'eva, T. T.; Kuz'mina, N. A.; Chakhovskaya, O. V.; Brodsky, E. S.; Belokon', Y. N. *Russ. Chem. Bull.* **2000**, *49*, 722–723. (c) Terent'ev, A. B.; Vasil'eva, T. T.; Kuz'mina, N. A.; Mysov, E. I.; Ikonnikov, N. S.; Kuznetsov, N. Y.; Belokon', Y. N. *Russ. Chem. Bull.* **1999**, *48*, 1121–1127.
117. Terentiev, A. B.; Vasilieva, T. T.; Kuzmina, N. A.; Mysov, E. I.; Kuznetzov, N. Y.; Belokon, Y. N. *J. Chem. Res. (S)* **1998**, 306 [*J. Chem. Res.* (*M*) **1998**, 1281–9].
118. (a) Roberts, C. D.; Schutz, R.; Leumann, C. J. *Synlett* **1999**, *6*, 819–821. (b) Cantin, M.; Schutz, R.; Leumann, C. J. *Tetrahedron Lett.* **1997**, *38*, 4211–4214.
119. De Vos, E.; Esmans, E. L.; Alderweireldt, F. C.; Balzarini, J.; De Clercq, E. *J. Heterocycl. Chem.* **1993**, *30*, 1245–1252.
120. Yanagisawa, A.; Takahashi, H.; Arai, T. *Chem. Commun.* **2004**, 580–581.
121. For a review on non-conventional reaction conditions (ultrasound, high pressure and microwave heating) in organic synthesis, see: Giguere, R. J. *Org. Synth.: Theory Appl.* **1989**, *1*, 103–172.
122. For a review on solvent-free reactions, see: Tanaka, K.; Toda, F. *Chem. Rev.* **2000**, *100*, 1025–1074.
123. For a review on water medium, see: Li, C. J. *Chem. Rev.* **1993**, *93*, 2023.
124. (a) Gholap, A. R.; Chavan, A. P. *J. Chem. Res. (S)* **2003**, 374–376. (b) Tanaka, K.; Kishigami, S.; Toda, F. *J. Org. Chem.* **1991**, *56*, 4333–4334.
125. (a) Latouche, R.; Texier-Boullet, F.; Hamelin, J. *Bull. Soc. Chim. Fr.* **1993**, *130*, 535–546. (b) Latouche, R.; Texier--Boullet, F.; Hamelin, J. *Tetrahedron Lett.* **1991**, *32*, 1179–1182.
126. Wang, G.-W.; Murata, Y.; Komatsu, K.; Wan, T. S. M. *Chem. Commun.* **1996**, 2059–2060.
127. Wang, Z.; Meier, M. S. Abstr. Pap.-223rd ACS Meeting 2002, ORGN-134.
128. Dellinger, D. J.; Sheehan, D. M.; Christensen, N. K.; Lindberg, J. G.; Caruthers, M. H. *J. Am. Chem. Soc.* **2003**, *125*, 940–950.
129. Bieber, L. W.; Malvestiti, I.; Storch, C. *J. Org. Chem.* **1997**, *62*, 9061–9064.
130. Rollin, Y.; Gebehenne, C.; Derien, S.; Dunach, E.; Perichon, J. *J. Organomet. Chem.* **1993**, *461*, 9–13.
131. Adrian, J. C.; Snapper, M. L. *J. Org. Chem.* **2003**, *68*, 2143–2150.
132. Hilgers, G.; Hess, J. Ger. Offen. German Patent: DE 90-4016076 9900518, 1991, 6 pp.
133. Lim, C. L.; Han, B. H. *J. Kor. Chem. Soc.* **1991**, *35*, 762–764.
134. (a) Ross, N. A.; Bartsch, R. A. *J. Org. Chem.* **2003**, *68*, 360–366. (b) Ross, N. A.; Bartsch, R. A.; Marchand, A. P. *ARKIVOC* **2003**, 27–30.
135. Ross, N. A.; MacGregor, R. R.; Bartsch, R. A. *Tetrahedron* **2004**, *60*, 2035–2041.
136. Kitazume, T. *Ultrasonics* **1990**, *28*, 322–325.
137. Baldoli, C.; Del Buttero, P.; Licandro, E.; Papagni, A. *Tetrahedron* **1996**, *52*, 4849–4856.
138. Coe, P. L.; Löhr, M.; Rochin, C. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2803–2812.
139. Andrés, J. M.; Martinez, M. A.; Pedrosa, R.; Perez-Encabo, A. *Synthesis* **1996**, 1070–1072.
140. Altenburger, J. M.; Schirlin, D. *Tetrahedron Lett.* **1991**, *32*, 7255–7258.
141. (a) Ross, N. A.; Bartsch, R. A. *J. Heterocycl. Chem.* **2001**, *38*, 1255–1258. (b) Ross, N. A.; Bartsch, R. A. Abstr. Pap.-Am. Chem. Soc. 2002, 224th ORGN-888.
142. Durant, A.; Delplancke, J. L.; Libert, V.; Reisse, J. *Eur. J. Org. Chem.* **1999**, 2845–2851.
143. Makosza, M.; Nieczypor, P.; Grela, K. *Tetrahedron* **1998**, *54*, 10827–10836.
144. Mylari, B. L.; Zembrowki, W. J. *J. Org. Chem.* **1991**, *56*, 2587–2589.
145. Andrés, C.; González, A.; Pedrosa, R.; Perez-Encabo, A. *Tetrahedron Lett.* **1992**, *33*, 2895–2898.
146. Bott, K. *Tetrahedron Lett.* **1994**, *35*, 555–556.
147. Syed, J.; Forster, S.; Effenberger, F. *Tetrahedron: Asymmetry* **1998**, *9*, 805–815.

148. Adrian, J. C.; Barkin, J. L.; Hassib, L. *Tetrahedron Lett.* **1999**, *34*, 2457–2460.
149. Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447–6449.
150. Bitterwolf, T. E.; Dai, X. *J. Organomet. Chem.* **1992**, *440*, 103–112.
151. Ferraz, H. M. C.; Silva, L. F. *Tetrahedron* **2001**, *57*, 9939–9949.
152. Olugbade, T. A.; Waigh, R. D.; Mackay, S. P. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2657–2660.
153. Krasuts'kii, P. O.; Semenova, I. G.; Voitsits'ka, O. D.; Simurova, N. V. *Ukr. Khim. Zh.* **1997**, *63*, 107–110.
154. Olah, G. A.; Reddy, V. P.; Casanova, J.; Prakash, G. K. *J. Org. Chem.* **1992**, *57*, 6431–6434.
155. Andrés, J. M.; Pedrosa, R.; Pérez, A.; Pérez-Encabo, A. *Tetrahedron* **2001**, *57*, 8521–8530.
156. Yates, P.; Kaldas, M. *Can. J. Chem.* **1992**, *70*, 1492–1505.
157. Izquierdo, I.; Plaza, M. T.; Robles, R.; Mota, A. *Tetrahedron: Asymmetry* **1997**, *8*, 2597–2606.
158. Dener, J. M.; Zhang, L. H.; Rapoport, H. *J. Org. Chem.* **1993**, *58*, 1159–1166.
159. (a) Michael, J. P.; de Koning, C. B.; Stanbury, T. V. *Tetrahedron Lett.* **1996**, *37*, 9403–9406. (b) Michael, J. P.; Hosken, G. D.; Howard, A. S. *Tetrahedron* **1988**, *44*, 3025–3026. (c) Michael, J. P.; de Koning, C. B.; Hosken, G. D.; Stanbury, T. V. *Tetrahedron* **2001**, *57*, 9635–9648.
160. Shchepin, V. V.; Gladkova, G. E. *Zh. Org. Khim.* **1995**, *31*, 1094.
161. Shchepin, V. V.; Fatukhova, Y. K.; Kirillov, N. T.; Russkikh, N. Y.; Litvinov, D. N. *Russ. J. Org. Chem.* **2000**, *36*, 1120–1123.
162. Ito, Y.; Terashima, S. *Tetrahedron* **1991**, *47*, 2821–2834.
163. Ito, Y.; Sasaki, A.; Tamoto, K.; Sunagawa, M.; Terashima, S. *Tetrahedron* **1991**, *47*, 2801–2820.
164. Kobayashi, Y.; Ito, Y.; Terashima, S. *Tetrahedron* **1992**, *48*, 55–66.
165. Mori, M.; Oida, S. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2389–2392.
166. (a) Fukuzawa, S.; Matsuzawa, H.; Yoshimitsu, S. *J. Org. Chem.* **2000**, *65*, 1702–1706. (b) Fukuzawa, S.; Tatsuzawa, M.; Hirano, K. *Tetrahedron Lett.* **1998**, *39*, 6899–6900.
167. Seki, M.; Kondo, K.; Iwasaki, T. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2851–2856.
168. (a) Kondo, K.; Seki, M.; Kuroda, T.; Yamanaka, T.; Iwasaki, T. *J. Org. Chem.* **1995**, *60*, 1096–1097. (b) Kondo, K.; Seki, M.; Kuroda, T.; Yamanaka, T.; Iwasaki, T. *J. Org. Chem.* **1997**, *62*, 2877–2884.
169. (a) Pyun, D. K.; Jeong, W. J.; Jung, H. J.; Kim, J. H.; Lee, J. S.; Lee, C. H.; Kim, B. J. *Synlett* **2001**, 1950–1952. (b) Jeong, W. J.; Pyun, D. K.; Jung, H. J.; Kim, J. H.; Lee, C. H.; Kim, B. J. Abstr. Pap.-Am. Chem. Soc. 2001, 221st ORGN-555.
170. Lu, X.; Xu, Z.; Yang, G.; Fan, R. *Org. Proc. Res. Dev.* **2001**, *5*, 186–188.
171. Andrés, J. M.; Pedrosa, R.; Perez-Encabo, A. *Tetrahedron* **2000**, *56*, 1217–1223.
172. Shchepin, V. V.; Gladkova, G. E.; Russkikh, N. Y. *Zh. Org. Khim.* **1992**, *28*, 1156–1162.
173. Shchepin, V. V.; Tryastsin, A. A.; Shchepin, R. V.; Kalyuzhnyi, M. M.; Lewis, S. B. *Russ. J. Org. Chem.* **2001**, *37*, 1596–1599.
174. Shchepin, V. V.; Gladkova, G. E. *Zh. Org. Khim.* **1993**, *29*, 474–479.
175. For reviews, see: (a) Werstiuk, N. H. *Tetrahedron* **1982**, *39*, 205. (b) Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 932.
176. Fukuzawa, S.; Sumimoto, N.; Fujinami, T.; Sakai, S. *J. Org. Chem.* **1990**, *55*, 1628–1631.
177. (a) Oler, E.; Reininger, K.; Schmidt, U. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 457. (b) Löfler, A.; Pratt, D.; Pucknat, J.; Gelbard, G.; Dreiding, A. S. *Chimia* **1969**, *23*, 413.
178. Ikramuddeen, T. M.; Chandrasekara, N.; Ramarajan, K.; Garrison, G. L.; Berlin, K. *Indian J. Chem. Sect. B* **1994**, *33B*, 362–364.
179. For reviews on the synthesis of α-methylene-γ-butyrolactones: (a) Hoffmann, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 94. (b) Grieco, P. A. *Synthesis* **1975**, 67. (c) Petragnani, N.; Feraz, H. M. C.; Silva, G. V. J. *Synthesis* **1986**, 157.
180. Richter, F.; Bauer, M.; Perez, C.; Maichle-Möessmer, C.; Maier, M. E. *J. Org. Chem.* **2002**, *67*, 2474–2480.
181. Maier, M. E.; Pérez, C. *Synlett* **1998**, 159–160.
182. Rauter, A. P.; Ferreira, M. J.; Font, J.; Virgili, A.; Figueredo, M.; Figueiredo, J. A.; Ismael, M. I.; Canda, T. L. *J. Carbohydr. Chem.* **1995**, *14*, 929–948.
183. Rauter, A. P.; Figueiredo, J.; Ismael, M.; Canda, T.; Font, J.; Figueredo, M. *Tetrahedron: Asymmetry* **2001**, *12*, 1131–1146.
184. (a) Kim, J. C.; Kim, J.-A.; Kim, Si.-H.; Park, J. I.; Kim, Se.-H.; Choi, S.-K.; Park, W.-W. *Arch. Pharm. Res.* **1996**, *19*, 235–239. (b) Kim, J. C.; Kim, J.-A.; Park, J. I.; Kim, S.-H.; Kim, S.-H.; Choi, S.-K.; Park, W.-W. *Arch. Pharm. Res.* **1997**, *20*, 253–258. (c) Huang, B.-R.; Lee, K.-H.; Tseng, T.-L.; Wang, H.-M.; Chen, C.-F.; Tzeng, C.-C. *Gaox. Yix. Kex. Zaz.* **1993**, *9*, 707–711. (d) Huang, B.-R.; Lee, K.-H.; Hwang, L. C.; Han, C. H.; Chen, Y. L.; Tzeng, C. C.; Chen, C. F. *Zhong. Yaox. Zaz.* **1991**, *43*, 447–455.
185. Kim, J. C.; Kim, S.-H.; Kim, J.-A.; Choi, S.-K.; Park, W.-W. *Arch. Pharm. Res.* **1998**, *21*, 458–464.
186. (a) Tzeng, C.-C.; Lee, K.-H.; Wang, T.-C.; Han, C.-H.; Chen, Y.-L. *Pharm. Res.* **2000**, *17*, 715–719. (b) Tzeng, C.-C.; Chen, I.-L.; Chen, Y.-L.; Wang, T.-C.; Chang, Y.-L.; Teng, C.-M. *Helv. Chim. Acta* **2000**, *83*, 349–358. (c) Hsu, S.-L.; Chen, Y.-L.; Tzeng, C.-C.; Fang, K.-C.; Sheu, J.-Y. *Helv. Chim. Acta* **2001**, *84*, 874–879. (d) Chen, Y.-L.; Chen, I.-L.; Tzeng, C.-C.; Wang, T.-C. *Helv. Chim. Acta* **2000**, *83*, 989–994. (e) Wang, T.-C.; Chen, Y.-L.; Tzeng, C.-C.; Liou, S.-S.; Tzeng, W.-F.; Chang, Y.-L.; Teng, C.-M. *Helv. Chim. Acta* **1998**, *81*, 1038–1047. (f) Tzeng, C.-C.; Zhao, Y.-L.; Chen, Y.-L.; Liou, S.-S.; Wang, T.-C.; Chang, Y.-L.; Teng, C.-M. *Helv. Chim. Acta* **1997**, *80*, 2337–2344. (g) Tzeng, C.-C.; Chen, Y.-L.; Wang, C.-J.; Wang, T.-C.; Chang, Y.-L.; Teng, C.-M. *Helv. Chim. Acta* **1997**, *80*, 1161–1168. (h) Wang, T.-C.; Chen, Y.-L.; Tzeng, C.-C.; Liou, S.-S.; Chang, Y.-L.; Teng, C.-M. *Helv. Chim. Acta* **1996**, *79*, 1620–1626. (i) Chen, Y.-L.; Wang, T.-C.; Lee, H.-H.; Tzeng, C.-C.; Chang, Y.-L.; Teng, C.-M. *Helv. Chim. Acta* **1996**, *79*, 651–657. (j) Chen, Y.-L.; Wang, T.-C.; Fang, K.-C.; Chang, N.-C.; Tzeng, C.-C. *Heterocycles* **1999**, *50*, 453–462.
187. Wang, T.-C.; Zhao, Y.-L.; Kuo, D.-H. *Eur. J. Med. Chem.* **2001**, *36*, 909–914.
188. Sawant, M. S.; Katoch, R.; Trivedi, G. K.; Desai, U. R. *J. Chem. Soc., Perkin Trans. 1* **1998**, 843–846.
189. Dembélé, Y. A.; Belaud, C.; Hitchcock, P.; Villiéras, J. *Tetrahedron: Asymmetry* **1992**, *3*, 351–354.

190. Yamamoto, H.; Oritani, T.; Yamashita, K. *Agric. Biol. Chem.* **1990**, *54*, 1923–1929.
191. Mastalerz, H.; Menard, M. *J. Org. Chem.* **1994**, *59*, 3223–3226.
192. Sakai, K.; Takahashi, K.; Nukano, T. *Tetrahedron* **1992**, *48*, 8229–8238.
193. Mecozzi, T.; Petrini, M. *Tetrahedron Lett.* **2000**, *41*, 2709–2712.
194. Jain, S.; Jain, R.; Singh, J.; Anand, N. *Tetrahedron Lett.* **1994**, *35*, 2951–2954.
195. Shchepin, V. V.; Rodygin, A. S.; Balandina, M. I. *Zh. Org. Khim.* **1991**, *27*, 2035–2039.
196. Csuk, R.; Glaenzer, B. I. *J. Carbohydr. Chem.* **1990**, *9*, 809–822.
197. Fürstner, A.; Kollegger, G.; Weidmann, H. *J. Organomet. Chem.* **1991**, *414*, 295–305.
198. Kuroda, C.; Ito, K. *Bull. Chem. Soc. Jpn* **1996**, *69*, 2297–2303.
199. (a) Akai, S.; Tsuzuki, Y.; Matsuda, S.; Kitagaki, S.; Kita, Y. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2813–2820. (b) Akai, S.; Tsuzuki, Y.; Matsuda, S.; Kitagaki, S.; Kita, Y. *Synlett* **1991**, 911–912.
200. (a) Palomo, C.; Aizpurua, J. M.; Concepcion Lopez, M.; Aurrekoetxea, N. *Tetrahedron Lett.* **1990**, *31*, 2205–2208. (b) Palomo, C.; Aizpurua, J. M.; Aurrekoetxea, N. *Tetrahedron Lett.* **1990**, *31*, 2209–2210.
201. Jacobsen, M. F.; Turks, M.; Hazell, R.; Skrydstrup, T. *J. Org. Chem.* **2002**, *67*, 2411–2417.
202. Ricci, M.; Blakskjr, P.; Skrydstrup, T. *J. Am. Chem. Soc.* **2000**, *122*, 12413–12421.
203. Dutta, L. N.; Bhattacharyya, M.; Sarkar, A. K. *Can. J. Chem.* **1995**, *73*, 1556–1562.
204. Shchepin, V. V.; Korzun, A. E.; Sazhneva, Y. K.; Nedugov, A. N. *Chem. Heterocycl. Compd.* **2001**, *37*, 374–375.
205. (a) Shchepin, V. V.; Fotin, D. V.; Nedugov, A. N.; Fotin, V. V. *Russ. J. Org. Chem.* **2002**, *38*, 256–258. (b) Shchepin, V. V.; Fotin, D. V.; Nedugov, A. N.; Fotin, V. V.; Vakhrin, M. I. *Chem. Heterocycl. Compd.* **2001**, *37*, 650.
206. Shchepin, V. V.; Kirillov, N. F. *Chem. Heterocycl. Compd.* **2000**, *36*, 1110–1111.
207. Kirillov, N. F.; Shchepin, V. V. *Russ. J. Org. Chem.* **2001**, *37*, 811–813.
208. Kirillov, N. F.; Shchepin, V. V. *Russ. J. Org. Chem.* **2001**, *37*, 1223–1224.
209. Kise, N.; Yamazaki, H.; Mabuchi, T.; Shono, T. *Tetrahedron Lett.* **1994**, *35*, 1561–1564.
210. Nishiyama, T.; Kishi, H.; Kitano, K.; Yamada, F. *Bull. Chem. Soc. Jpn* **1994**, *67*, 1765–1768.
211. Alberola, A.; Álvarez, M. A.; Andrés, C.; González, A.; Pedrosa, R. *Synthesis* **1990**, 1057–1058.
212. Datta, A.; Ila, H.; Junjappa, H. *J. Org. Chem.* **1990**, *55*, 5589–5594.
213. Ukaji, Y.; Takenaka, S.; Horita, Y.; Inomata, K. *Chem. Lett.* **2001**, 254–255.
214. Shankar, B. B.; Kirkup, M. P.; McCombie, S. W.; Clader, J. W.; Ganguly, A. K. *Tetrahedron Lett.* **1996**, *37*, 4095–4098.
215. Robinson, A. J.; Wyatt, P. B. *Tetrahedron* **1993**, *49*, 11329–11340.
216. Lee, J.-H.; Lee, Y.-Y.; Goo, Y.-M.; Kim, K. *Bull. Kor. Chem. Soc.* **1993**, *14*, 172–174.
217. Hart, D. J.; HA, D.-C. *Chem. Rev.* **1989**, *89*, 1447.
218. Fotin, V. V.; Shchepin, V. V.; Fotin, D. V.; Vakhrin, M. I. *Russ. J. Org. Chem.* **1999**, *35*, 1278–1281.
219. Lindell, S. D.; Turner, R. M. *Tetrahedron Lett.* **1990**, *31*, 5381–5384.
220. Schick, H.; Ludwig, R. *Synthesis* **1992**, 369–370.
221. Wang, M.-X.; Liu, Y.; Gao, H.-Y.; Zhang, Y.; Yu, C.-Y.; Huang, Z.-T.; Fleet, G. W. J. *J. Org. Chem.* **2003**, *68*, 3281–3286.
222. Brandaenge, S.; Holmgren, E.; Leijonmarck, H.; Rodríguez, B. *Acta Chem. Scand.* **1995**, *49*, 922–928.
223. Yassin, F. A.; El-Farargy, A. F.; El-Mobayed, M. M.; El-Kady, M. Y.; Abd El-Maksoud, M. R. *J. Chem. Soc. Pakist.* **1991**, *13*, 267–272.
224. El-Safty, M. A.; El-Bahaei, S. A.; Yassin, F. A. *Afinidad* **1992**, *49*, 131–134.
225. (a) Kashima, C.; Huang, X. C.; Harada, Y.; Hosomi, A. *J. Org. Chem.* **1993**, *58*, 793–794. (b) Kashima, C.; Kita, I.; Takahashi, K.; Hosomi, A. *J. Heterocycl. Chem.* **1995**, *32*, 723–725.
226. (a) Kielbasinski, P.; Mikolajczyk, M. *Synthesis* **1995**, 144–146. (b) Fagadar-Cosma, E.; Fagadar-Cosma, G. *Rev. Roum. Chim.* **2003**, *48*, 211–217.
227. Lee, H. K.; Kim, J.; Pak, C. S. *Tetrahedron Lett.* **1999**, *40*, 2173–2174.
228. Michael, J. P.; de Koning, C. B.; Petersen, R. L.; Stanbury, T. V. *Tetrahedron Lett.* **2001**, *42*, 7513–7516.
229. Chandrasekharam, M.; Bhat, L.; Ila, H.; Junjappa, H. *Tetrahedron Lett.* **1993**, *34*, 6439–6442.
230. Hannick, S. M.; Kishi, Y. J. *J. Org. Chem.* **1983**, *48*, 3833–3835.
231. Mohri, K.; Yoshida, Y.; Mataga, S.; Hisatsune, Y.; Isobe, K.; Tsuda, Y. *Heterocycles* **1997**, *45*, 2405–2412.
232. Dartiguelongue, C.; Payan, S.; Duval, O.; Gomès, L. M.; Waigh, R. *Bull. Soc. Chim. Fr.* **1997**, *134*, 769–772.
233. Duffield, J. J.; Regan, A. C. *Tetrahedron: Asymmetry* **1996**, *7*, 663–666.
234. Poechlauer, P.; Hartmann, M.; Mayrhofer, H. Abstr. Pap.-Am. Chem. Soc. 2001, 221st ORGN-507.
235. Bernardi, L.; Bonini, B. F.; Capito, E.; Dessole, G.; Fochi, M.; Comes-Franchini, M.; Ricci, A. *Synlett* **2003**, 1778–1782.
236. Sheppard, A.; Miller, M. J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2519–2525.
237. Akhmetvaleev, R. R.; Imaeva, L. R.; Belogaeva, T. A.; Baikova, I. P.; Miftakhov, M. S. *Russ. J. Org. Chem.* **1999**, *35*, 242–245.
238. Lavallee, J. F.; Spino, C.; Ruel, R.; Hogan, K. T.; Deslongchamps, P. *Can. J. Chem.* **1992**, *70*, 1406–1426.
239. (a) Ruel, R.; Deslongchamps, P. *Tetrahedron Lett.* **1990**, *31*, 3961–3964. (b) Ruel, R.; Deslongchamps, P. *Can. J. Chem.* **1992**, *70*, 1939–1949.
240. Zegelman, L.; Hassner, A.; Mendel, Z.; Dunkelblum, E. *Tetrahedron Lett.* **1993**, *34*, 5641–5644.
241. Dyer, J.; Keeling, S.; Moloney, M. G. *Tetrahedron Lett.* **1996**, *37*, 4573–4576.
242. Batra, S.; De, D.; Seth, M.; Bhaduri, A. P. *J. Chem. Res. (S)* **1993**, 202 [*J. Chem. Res.* (*M*) **1993**, 1228].
243. (a) Shchepin, V. V.; Fotin, D. V. *Chem. Heterocycl. Compd.* **2002**, *38*, 1430–1431. (b) Shchepin, V. V.; Fotin, D. V.; Shurov, S. N. *Russ. J. Org. Chem.* **2003**, *39*, 1231–1233.
244. Menicagli, R.; Samaritani, S. *Tetrahedron* **1996**, *52*, 1425–1432.

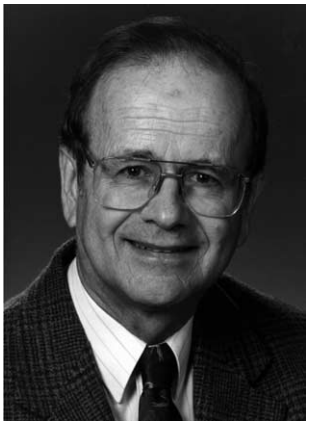
245. Mazumdar, S. N.; Mahajan, M. P. *Tetrahedron Lett.* **1990**, *31*, 4215–4218.
246. Vedejs, E.; Duncan, S. M. *J. Org. Chem.* **2000**, *65*, 6073–6081.
247. Heathcock, C. H.; Ruggeri, R. B.; McClure, K. F. *J. Org. Chem.* **1992**, *57*, 2585–2594.
248. Inanaga, J.; Yokoyama, Y.; Handa, Y.; Yamaguchi, M. *Tetrahedron Lett.* **1991**, *32*, 6371–6374.
249. Molander, G. A.; Etter, J. B.; Harring, L. S.; Thorel, P. J. *J. Am. Chem. Soc.* **1991**, *113*, 8036–8045.
250. Fujita, K.; Mori, K. *Eur. J. Org. Chem.* **2001**, 493–502.
251. Shiina, I.; Uoto, K.; Mori, N.; Kosugi, T.; Mukaiyama, T. *Chem. Lett.* **1995**, 181–182.
252. Takemura, T.; Nishii, Y.; Takahashi, S.; Kobayashi, J.; Nakata, T. *Tetrahedron* **2002**, *58*, 6359–6365.
253. Inoue, S.; Iwabuchi, Y.; Irie, H.; Hatakeyama, S. *Synlett* **1998**, 735–736.
254. Reddy, P. P.; Yen, K.-F.; Uang, B.-J. *J. Org. Chem.* **2002**, *67*, 1034–1035.
255. (a) Inoue, M.; Sasaki, M.; Tachibana, K. *J. Org. Chem.* **1999**, *64*, 9416–9429. (b) Inoue, M.; Sasaki, M.; Tachibana, K. *Tetrahedron* **1999**, *55*, 10949–10970. (c) Inoue, M.; Sasaki, M.; Tachibana, K. *Tetrahedron Lett.* **1997**, *38*, 1611–1614.
256. Ichikawa, S.; Minakawa, N.; Shuto, S.; Tanaka, M.; Sasaki, T.; Matsuda, A. Nucl. Acids Symp. Ser. 1996, 35 (33th Symposium on Nucleic Acids Chemistry, 1996), 13–14. (b) Ichikawa, S.; Shuto, S.; Minakawa, N.; Matsuda, A. *J. Org. Chem.* **1997**, *62*, 1368–1375.
257. Yamada, S.; Tanaka, A.; Oritani, T. *Biosci. Biotech. Biochem.* **1995**, *59*, 1657–1660.
258. Nagamitsu, T.; Tacano, D.; Fukuda, T.; Otoguro, K.; Kuwajima, I.; Harigaya, Y.; Omura, S. *Org. Lett.* **2004**, *6*, 1865–1867.
259. Molander, G. A.; Brown, G. A.; Storch de Gracia, I. *J. Org. Chem.* **2002**, *67*, 3459–3463.
260. Kim, S.-J.; Kang, H.-Y.; Sherman, D. H. *Synthesis* **2001**, 1790–1793.
261. Fukuzawa, S.; Miura, M.; Matsuzawa, H. *Tetrahedron Lett.* **2001**, *42*, 4167–4169.
262. Nerz-Stormes, M.; Thornton, E. R. *J. Org. Chem.* **1991**, *56*, 2489.
263. Obringer, M.; Colobert, F.; Neugnot, B.; Solladié, G. *Org. Lett.* **2003**, *5*, 629–632.
264. Basavaiah, D.; Bharathi, T. K. *Tetrahedron Lett.* **1991**, *32*, 3417–3420.
265. Kende, A. S.; Kawamura, K.; DeVita, R. J. *J. Am. Chem. Soc.* **1990**, *112*, 4070–4072.
266. Blaskovich, M. A.; Lajoie, G. A. *J. Am. Chem. Soc.* **1993**, *115*, 5021–5030.
267. Ding, Y.; Wang, J.; Abboud, K. A.; Xu, Y.; Dolbier, W. R.; Richards, N. G. J. *J. Org. Chem.* **2001**, *66*, 6381–6388.
268. Brocard, J.; Mahmoudi, M.; Pelinski, L.; Maciejewski, L. *Tetrahedron* **1990**, *46*, 6995–7002.
269. (a) Sorochinsky, A.; Voloshin, N.; Markovsky, A.; Belik, M.; Yasuda, N.; Uekusa, H.; Ono, T.; Berbasov, D. O.; Soloshonok, V. A. *J. Org. Chem.* **2003**, *68*, 7448–7454. (b) Soloshonok, V. A.; Ohkura, H.; Sorochinsky, A.; Voloshin, N.; Markovsky, A.; Belik, M.; Yamazaki, T. *Tetrahedron Lett.* **2002**, *43*, 5445–5448. (c) Sorochinsky, A.; Berbasov, D. O.; Soloshonok, V. A. Abstr. Pap.-Am. Chem. Soc. 2003, 226th. ORGN-530.
270. Staas, D. D.; Savage, K. L.; Homnick, C. F.; Tsou, N. N.; Ball, R. G. *J. Org. Chem.* **2002**, *67*, 8276–8279.
271. Ribeiro, C. M. R.; Santos, E. S.; Jardim, A. H. O.; Maia, M. P.; da Silva, F. C.; Moreira, A. P. D.; Ferreira, V. F. *Tetrahedron: Asymmetry* **2002**, *13*, 1703–1706.
272. (a) Mi, A.; Wang, Z.; Zhang, J.; Jiang, Y. *Synth. Commun.* **1997**, *27*, 1469–1473. (b) Mi, A.; Wang, Z.; Chen, Z.; Jiang, Y. *Tetrahedron: Asymmetry* **1995**, *6*, 2641–2642.
273. Andrés, J. M.; Martin, Y.; Pedrosa, R.; Perez-Encabo, A. *Tetrahedron* **1997**, *53*, 3787–3794.
274. Soai, K.; Kawase, Y. *Tetrahedron: Asymmetry* **1991**, *2*, 781–784.
275. Pini, D.; Uccello-Barretta, G.; Mastantuono, A.; Salvadori, P. *Tetrahedron* **1997**, *53*, 6065–6072.
276. (a) Pini, D.; Mastantuono, A.; Salvadori, P. *Tetrahedron: Asymmetry* **1994**, *5*, 1875–1876. (b) Mastantuono, A.; Pini, D.; Rolfini, C.; Salvadori, P. *Chirality* **1995**, *7*, 499–504.
277. Soai, K.; Oshio, A.; Saito, T. *J. Chem. Soc., Chem. Commun.* **1993**, 811–812.
278. Seki, K.; Tatuzawa, M.; Fukuzawa, S. *Kidorui* **1997**, *30*, 282–283.
279. (a) Ojida, A.; Yamano, T.; Taya, N.; Tasaka, A. *Org. Lett.* **2002**, *4*, 3051–3054. (b) Park, D. H.; Choi, H. J.; Lee, S.-G. *J. Kor. Chem. Soc.* **2003**, *47*, 597–600.
280. Zhang, Y.; Wu, W. *Tetrahedron: Asymmetry* **1997**, *8*, 3575–3578.
281. (a) Wang, Z. Y.; Shen, J.; Jiang, C. S.; You, T. P. *Chin. Chem. Lett.* **2000**, *11*, 659–662. (b) Jiang, C.; Li, D.; Cheng, Q.; Ke, Y.; You, T. *Huaxue Tongbao* **2001**, 637–640.
282. Yadav, J. S.; Praveen Kumar, T. K.; Maniyan, P. P. *Tetrahedron Lett.* **1993**, *34*, 2969–2972.
283. Greiner, E.; Folk, J. E.; Jacobson, A. E.; Rice, K. C. *Bioorg. Med. Chem.* **2004**, *12*, 233–238.
284. Kigoshi, H.; Kita, M.; Ogawa, S.; Itoh, M.; Uemura, D. *Org. Lett.* **2003**, *5*, 957–960.
285. VanSickle, A. P.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 895–901.
286. Orsini, F.; Pelizzoni, F. *Carbohydr. Res.* **1993**, *243*, 183–189.
287. Fkyerat, A.; Burki, N.; Tabacchi, R. *Tetrahedron: Asymmetry* **1996**, *7*, 2023–2028.
288. Zubaidha, P. K.; Chavan, S. P.; Racherla, U. S.; Ayyangar, N. R. *Tetrahedron* **1991**, *47*, 5759–5768.
289. Karpha, T. K.; Ghosal, M.; Mukherjee, D. *Indian J. Chem. Sect. B.* **1990**, 301–303.
290. Lee, S. H.; Lee, S.-G.; Song, C. E.; Kim, I. O.; Chung, B. Y. *Kor. J. Med. Chem.* **1997**, *7*, 34–40.
291. Johnson, T. R.; Silverman, R. B. *Bioorg. Med. Chem.* **1999**, *7*, 1625–1636.
292. Kalyanakumar, R.; Chadha, M. S.; Chattopadhyay, A.; Mamdapur, V. R. *Indian J. Chem. Sect. B.* **1996**, *35B*, 356–358.
293. Grassberger, V.; Berger, A.; Dax, K.; Fechter, M.; Gradnig, G.; Stuetz, A. E. *Liebigs Ann. Chem.* **1993**, 379–380.
294. McKinney, A. R.; Ridley, D. D. *Aust. J. Chem.* **2001**, *54*, 757–761.
295. Iwashima, M.; Nagaoka, H.; Kobayashi, K.; Yamada, Y. *Tetrahedron Lett.* **1992**, *33*, 81–82.
296. Vaezi, M. F.; Alam, M.; Sani, B. P.; Rogers, T. S.; Simpson-Herren, L.; Wille, J. J.; Hill, D. L.; Doran, T. I.; Brouillette, W. J.; Muccio, D. D. *J. Med. Chem.* **1994**, *37*, 4499–4507.
297. Cheng, C. Y.; Wu, S. C.; Hsin, L. W.; Tam, S. W. *J. Med. Chem.* **1992**, *35*, 2243–2247.
298. Lu, Q.; Duan, W. H.; Cai, J. C. *Chin. Chem. Lett.* **2002**, *13*, 113–114.

299. Kurosawa, T.; Fujiwara, M.; Nakano, H.; Sato, M.; Yoshimura, T.; Murai, T. *Steroids* **2001**, *66*, 499–504.
300. Yuan, W.; Munoz, B.; Wong, C.-H.; Haeggstroem, J. Z.; Wetterholm, A.; Samuelsson, B. *J. Med. Chem.* **1993**, *36*, 211–220.
301. McPherson, D. W.; DeHaven-Hudkins, D. L.; Callahan, A. P.; Knapp, F. F. *J. Med. Chem.* **1993**, *36*, 848–854.
302. Adamczyk, M.; Johnson, D. D.; Reddy, R. E. *Bioconjugate Chem.* **1998**, *9*, 403–408.
303. Zhang, M.; Zhu, L.; Ma, X. *Tetrahedron: Asymmetry* **2003**, *14*, 3447–3453.
304. (a) Presser, A.; Potschger, I.; Haslinger, E.; Hufner, A. *Monatsh. Chem.* **2002**, *133*, 231–239. (b) Presser, A.; Haslinger, E.; Weis, R.; Huefner, A. *Monatsh. Chem.* **1998**, *129*, 921–930.
305. Cambie, R. C.; Moratti, S. C.; Rutledge, P. S.; Weston, R. J.; Woodgate, P. D. *Aust. J. Chem.* **1990**, *43*, 1151–1162.
306. Chavan, S. P.; Zubaidha, P. K.; Ayyangar, N. R. *Tetrahedron Lett.* **1992**, *33*, 4605–4608.
307. Vostrikov, N. S.; Abutkov, A. V.; Spirikhin, L. V.; Fatykhov, A. A.; Miftahov, M. S. *Russ. Chem. Bull.* **2001**, *50*, 654–658.
308. Goto, K.; Kubo, T.; Yamamoto, K.; Nakasuji, K.; Sato, K.; Shiomi, D.; Takui, T.; Kubota, M.; Kobayashi, T.; Yakusi, K.; Ouyang, J. *J. Am. Chem. Soc.* **1999**, *121*, 1619–1620.
309. Ceccherelli, P.; Curini, M.; Marcotullio, M. C.; Rosati, O. *J. Org. Chem.* **1990**, *55*, 311–315.
310. Atkins, R. J.; Breen, G. F.; Crawford, L. P.; Grinter, T. J.; Harris, M. A.; Hayes, J. F.; Moores, C. J.; Saunders, R. N.; Share, A. C.; Walsgrove, T. C.; Wicks, C. *Org. Proc. Res. Dev.* **1997**, *1*, 185–197.
311. Rauter, A. P.; Oliveira, O.; Canda, T.; Leroi, E.; Ferreira, H.; Ferreira, M. J.; Ascenso, J. A. *J. Carbohydr. Chem.* **2002**, *21*, 257–273.
312. Balakumar, A.; Janardhanam, S.; Rajagopalan, K. *Indian J. Chem. Sect. B* **1993**, *32B*, 313–317.
313. Hisatome, M.; Watanabe, J.; Kawajiri, Y.; Yamakawa, K.; Iitaka, Y. *Organometallics* **1990**, *9*, 497–503.
314. Obara, R.; Wawrzenczyk, C. *J. Cosmet. Sci.* **1998**, *49*, 299–308.
315. For a review on fluorinated organozinc reagents in general, see: Davis, C. R.; Burton, D. J. In *Organozinc Reagents*; Knochel, P., Jones, P., Eds.; University Press: Oxford, 1999, p 57–76.
316. Baldwin, J. E.; Lynch, G. P.; Schofield, C. J. *Tetrahedron* **1992**, *48*, 9085–9100.
317. Angelastro, M. R.; Bey, P.; Mehdi, S.; Peet, N. P. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1235–1238.
318. Otaka, A.; Watanabe, J.; Yukimasa, A.; Sasaki, Y.; Watanabe, H.; Kinoshita, T.; Oishi, S.; Tamamura, H.; Fujii, N. *J. Org. Chem.* **2004**, *69*, 1634–1645.
319. (a) Tsukamoto, T.; Kitazume, T. *J. Chem. Soc., Chem. Commun.* **1992**, 540–541. (b) Tsukamoto, T.; Kitazume, T. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1177–1181.
320. Marcotte, S.; Pannecoucke, X.; Feasson, C.; Quirion, J.-C. *J. Org. Chem.* **1999**, *64*, 8461–8464.
321. Lacroix, S.; Cheguillaume, A.; Gerard, S.; Marchand-brynaert, J. *Synthesis* **2003**, 2483–2486.
322. (a) Sham, H. L.; Betebenner, D. A.; Wideburg, N. E.; Kempf, D. J.; Plattner, J. J.; Norbeck, D. W. *J. Fluorine Chem.* **1995**, *73*, 221–224. (b) Sham, H. L.; Betebenner, D. A. *J. Chem. Soc., Chem. Commun.* **1991**, 1134–1135.
323. Wang, Y.; Zhu, S. *Tetrahedron Lett.* **2001**, *42*, 5741–5744.
324. Wang, Y.; Zhu, S. *Synthesis* **2002**, 1813–1818.
325. Tsukamoto, T.; Kitazume, T. *Synlett* **1992**, 977–979.
326. Hu, Q.-S.; Hu, C.-M. *J. Fluorine Chem.* **1997**, *83*, 87–88.
327. Kumadaki, I. Abstr. Pap.-226th ACS Meeting 2003, FLUO-010.
328. Kuroboshi, M.; Ishihara, T. *Bull. Chem. Soc. Jpn* **1990**, *63*, 428–437.
329. Yoshida, M.; Suzuki, D.; Iyoda, M. *Synth. Commun.* **1996**, *26*, 2523–2529.
330. Yoshida, M.; Suzuki, D.; Iyoda, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 643–648.
331. (a) Coe, P. L.; Markou, M.; Tatlow, J. C. *J. Fluorine Chem.* **1997**, *84*, 113–118. (b) Coe, P. L.; Markou, M.; Tatlow, J. C. *J. Fluorine Chem.* **1998**, *89*, 183–188.
332. Allmendinger, T.; Lang, R. W. *Tetrahedron Lett.* **1991**, *32*, 339–340.
333. Kaneko, S.; Yamazaki, T.; Kitazume, T. *J. Org. Chem.* **1993**, *58*, 2302–2312.
334. Gong, Y.; Kato, K. *J. Fluorine Chem.* **2001**, *111*, 77–80.
335. Murata, K.; Kaneko, S.; Kitazume, T. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2685–2688.
336. Watanabe, S.; Sakai, Y.; Kitazume, T.; Yamazaki, T. *J. Fluorine Chem.* **1994**, *68*, 59–61.
337. Shen, Y.; Xiang, Y. *J. Fluorine Chem.* **1991**, *51*, 349–355.
338. Shen, Y.; Gao, S.; Xiang, Y. *J. Fluorine Chem.* **1993**, *63*, 151–155.
339. Iseki, K. In *Enantiocontrolled Synthesis of Fluoro-Organic Compounds: Stereochemical Challenges and Biomedical Targets*; Soloshonok, V. A., Ed.; John Wiley & Sons, Ltd., 1999, chapter 2, pages 33–62.
340. Tsukamoto, T.; Yoshiyama, T.; Kitazume, T. *Tetrahedron: Asymmetry* **1991**, *2*, 759–762.
341. Watanabe, S.; Fujita, T.; Sakamoto, M.; Takeda, H.; Kitazume, T.; Yamazaki, T. *J. Fluorine Chem.* **1997**, *82*, 1–7.
342. Matsumura, Y.; Fujii, H.; Nakayama, T.; Morizawa, Y.; Yasuda, A. *J. Fluorine Chem.* **1992**, *57*, 203–207.
343. Kotra, L. P.; Xiang, Y.; Newton, M. G.; Schinazi, R. F.; Cheng, Y.-C.; Chu, C. K. *J. Med. Chem.* **1997**, *40*, 3635–3644.
344. Kotra, L. P.; Newton, M. G.; Chu, C. K. *Carbohydr. Res.* **1998**, *306*, 69–80.
345. Meffre, P.; Dave, R. H.; Leroy, J.; Badet, B. *Tetrahedron Lett.* **2001**, *42*, 8625–8627.
346. Gouge, V.; Jubault, P.; Quirino, J.-C. *Tetrahedron Lett.* **2004**, *45*, 773–776.
347. (a) Cogan, D. A.; Liu, G.; Ellman, J. A. *Tetrahedron* **1999**, *55*, 8883–8904. (b) Davis, F. A.; Reddy, R. T.; Reddy, R. E. *J. Org. Chem.* **1992**, *57*, 6387–6389.
348. Braun, M.; Vonderhagen, A.; Waldmueller, D. *Liebigs Ann.* **1995**, 1447–1450.
349. (a) Dolbier, W. R.; Ocampo, R.; Paredes, R. *J. Org. Chem.* **1995**, *60*, 5372–5373. (b) Ocampo, R.; Dolbier, W. R.; Paredes, R. *J. Fluorine Chem.* **1998**, *88*, 41–50.
350. Ocampo, R.; Dolbier, W. R.; Bartberger, M. D.; Paredes, R. *J. Org. Chem.* **1997**, *62*, 109–114.
351. Ocampo, R.; Dolbier, W. R.; Zuluaga, F. *Coll. Czech. Chem. Commun.* **2002**, *67*, 1325–1334.
352. Inagaki, H.; Sugita, K.; Miyauchi, R. N.; Miyauchi, S.; Takeda, T.; Itoh, M.; Takahashi, H.; Takemura, M. *ARKIVOC* **2003**, 112–117.
353. Altenburger, J. M.; Schirlin, D. *Tetrahedron Lett.* **1991**, *32*, 7255–7258.
354. Takeuchi, Y.; Kanada, A.; Kawahara, S.; Koizumi, T. *J. Org. Chem.* **1993**, *58*, 3483–3485.

355. Morikawa, T.; Uejima, M.; Kobayashi, Y.; Taguchi, T. *J. Fluorine Chem.* **1993**, *65*, 79–89.
356. Pirrung, M. C.; Rowley, E. G.; Holmes, C. P. *J. Org. Chem.* **1993**, *58*, 5683–5689.
357. Fukuda, H.; Kitazume, T. *Heterocycles* **1997**, *46*, 275–285.
358. Matsuda, F.; Matsumoto, T.; Ohsaki, M.; Terashima, S. *Bull. Chem. Soc. Jpn* **1991**, *64*, 2983–2989.
359. Robinson, R. P.; Donahue, K. M. *J. Org. Chem.* **1992**, *57*, 7309–7314.
360. Shen, R.; Priebe, C.; Patel, C.; Rubo, L.; Su, T.; Kahn, M.; Sugasawara, R. *Tetrahedron Lett.* **1992**, *33*, 3417–3420.
361. Doherty, A. M.; Kaltenbronn, J. S.; Hudspeth, J. P.; Repine, J. T.; Roark, W. H.; Sircar, I.; Tinney, F. J.; Connolly, C. J.; Hodges, J. C.; et al *J. Med. Chem.* **1991**, *34*, 1258–1271.
362. Doherty, A. M.; Sircar, I.; Kornberg, B. E.; Quin, J.; Winters, R. T.; Kaltenbronn, J. S.; Taylor, M. D.; Batley, B. L.; Rapundalo, S. R.; et al *J. Med. Chem.* **1992**, *35*, 2–14.
363. Skiles, J. W.; Miao, C.; Sorcek, R.; Jacober, S.; Mui, P. W.; Chow, G.; Weldon, S. M.; Possanza, G.; Skoog, M.; et al *J. Med. Chem.* **1992**, *35*, 4795–4808.
364. Marcotte, S.; D'Hooge, F.; Ramadas, S.; Feasson, C.; Pannecoucke, X.; Quirion, J.-C. *Tetrahedron Lett.* **2001**, *42*, 5879–5882.
365. Konno, K.; Ojima, K.; Hayashi, T.; Takayama, H. *Chem. Pharm. Bull.* **1992**, *40*, 1120–1124.
366. Gill, H. S.; Londowski, J. M.; Corradino, R. A.; Zinsmeister, A. R.; Kumar, R. *J. Med. Chem.* **1990**, *33*, 480–490.
367. Saito, N.; Matsunaga, T.; Fujishima, T.; Anzai, M.; Saito, H.; Takenouchi, K.; Miura, D.; Ishizuka, S.; Takayama, H.; Kittaka, A. *Org. Biomol. Chem.* **2003**, *1*, 4396–4402.
368. Hallinan, E. A.; Hagen, T. J.; Husa, R. K.; Tsymbalov, S.; Rao, S. N.; vanHoeck, J. P.; Rafferty, M. F.; Stapelfeld, A.; Savage, M. A.; Reichman, M. *J. Med. Chem.* **1993**, *36*, 3293–3299.
369. Fukuda, H.; Kitazume, T. *J. Fluorine Chem.* **1995**, *74*, 171–176.

Biographical sketch

Rogelio Ocampo was born on July 9, 1962 in Marquetalia, Caldas (Colombia). He performed undergraduate studies of Education in Biology and Chemistry at Universidad de Caldas in Manizales (Colombia) where he obtained his degree in 1984. His graduated studies were performed at Universidad del Valle in Cali (Colombia) from where he obtained the MSc degree (1990) and PhD degree (1997). He received his doctoral training as a visitor scholar (partially granted by COLCIENCIAS) at University of Florida (1994–1996) from Professors William R. Dolbier, Jr. and Rodrigo Paredes (Universidad del Valle). His doctoral dissertation was graded *Cum Laude*, and he was awarded with the Colombian IV Prize of Chemistry (second place) in 2001. After his PhD degree he was back to Universidad de Caldas, where he is at present Professor of Organic Chemistry. His current interest is focused on synthesis and physical organic chemistry of fluorinated β-lactones and related compounds, working in collaborative projects of Universidad de Caldas-Universidad del Valle-University of Florida. At present, he is member of the research group *SIMERQO* granted by COLCIENCIAS (Colombia).



William R. Dolbier, Jr. Bill Dolbier is currently the Col. Allen R. and Margaret G. Crow Professor of Chemistry at the University of Florida. He received his BS in Chemistry from Stetson University in 1961 and obtained his PhD in organic chemistry from Cornell University in 1965, working with Mel Goldstein. After one and a half years of postdoctoral work with Bill Doering at Yale, he joined the faculty at UF in 1966, where he has been ever since, serving as Chairman from 1983 to 1988. Bill's research interests continue to be physical organic in nature, and he maintains long-term interests in thermal homolytic reactions, pericyclic reactions, and free radical reactivity. Since 1975, his efforts have mainly focused on the study of molecules containing fluorine. In recent years, his efforts have increasingly been devoted to development of new synthetic methods in organofluorine chemistry. Bill received the ACS award for Creative Work in Fluorine Chemistry in 2000, and is currently a member of the Executive Committee of the Fluorine Division of the ACS. When not immersed in such activities, Bill's main interests continue to be his wife, Jing, son, Stephen, three grandchildren, and a little handball.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 60 (2004) 9375–9379
Tetrahedron

Concise total synthesis of flavone *C*-glycoside having potent anti-inflammatory activity

Takumi Furuta, Tomoyuki Kimura, Sachiko Kondo, Hisashi Mihara, Toshiyuki Wakimoto, Haruo Nukaya, Kuniro Tsuji and Kiyoshi Tanaka*

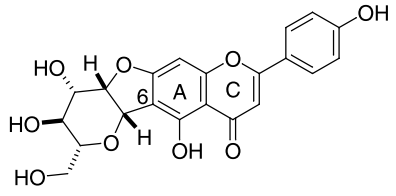
School of Pharmaceutical Sciences, University of Shizuoka, 52-1 Yada, Shizuoka 422-8526, Japan

Received 18 June 2004; revised 6 August 2004; accepted 9 August 2004

Abstract—The total synthesis of anti-inflammatory active flavone *C*-glycoside isolated from oolong tea extract is achieved. Introducing a *C*-glucosyl moiety to an aryl system and constructing a fused tetracyclic ring characteristic to this natural product were conducted based on the *O*-to-*C* rearrangement of sugar moiety and the successive intramolecular Mitsunobu reaction, respectively. This concise and efficient synthetic pathway is applicable to the large-scale synthesis of target flavone and for constructing a large library of related compounds.
© 2004 Elsevier Ltd. All rights reserved.

1. Introduction

Naturally-occurring aryl *C*-glycosides[1] exhibit interesting biological activities. Especially, *C*-glycosyl flavonoids show a variety of bioactivities such as antiviral,[2] cytotoxic,[3] and DNA binding[4] activities. Recently, a novel, anti-inflammatory active flavone *C*-glycoside **1**, which connects a mannose sugar moiety at the 6-position of a flavone skeleton, has been isolated as minor constituent of oolong tea extract.[5] The activity of **1** is exceptionally significant and evaluation based on the suppression of contact hypersensitivity in mice induced by the treatment of 2,4-dinitrofluorobenzene indicates that **1** is ~1000 times stronger than the conventionally used anti-inflammatory drug, dexamethasone. On the other hand, this flavone is structurally characterized by the fused tetracyclic ring system composed of a mannosyl moiety, A, and C rings of flavone framework. The intriguing biological activity, unique structural features, and limited natural sources promoted us to undertake a synthetic study of this flavone. The first total synthesis of **1** was accomplished recently by Nakatsuka and co-workers.[6] Herein, concise and efficient total synthesis of **1** based on *O*-to-*C* rearrangement[7] and intramolecular Mitsunobu reaction[8] for the *C*-glycoside formation and the construction of its tetracyclic ring system, respectively, is described (Fig. 1).



1

Figure 1. Anti-inflammatory active flavone *C*-glycoside.

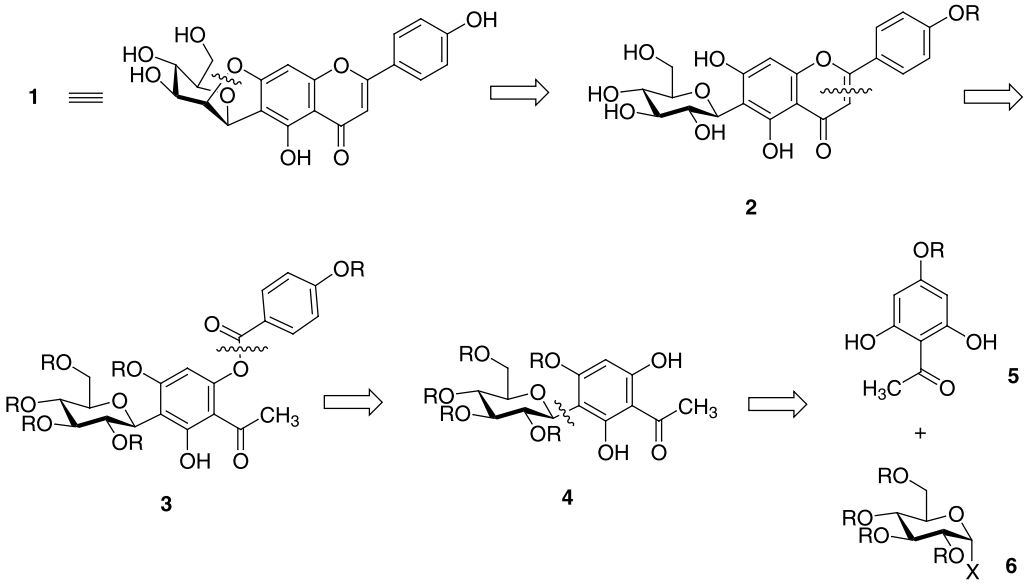
2. Results and discussion

Scheme 1 depicts the retrosynthetic pathway for compound **1**, where the fused tetracyclic ring system may be feasibly constructed by the regioselective intramolecular Mitsunobu reaction between the 2-position of the glucosyl moiety and the phenolic hydroxyl group of isovitexin derivative **2**. Mono-acylated aryl *C*-glycoside **3**, which can be prepared from **4**, was selected as a precursor for forming the flavone ring. The *C*-glycosidic linkage of **4** can be formed by an *O*-to-*C* rearrangement using acetophenone derivative **5** and the glycosyl donor **6** in the presence of Lewis acid catalyst.

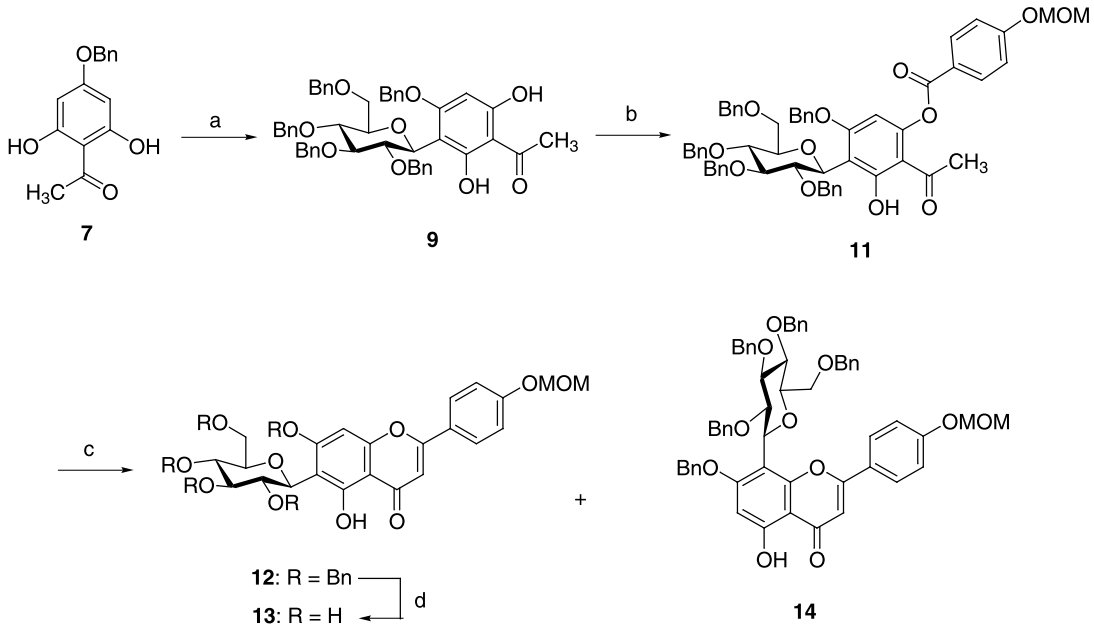
According to the retrosynthetic pathway, the benzyl protected *C*-glucoside **9** was selected as a key intermediate (Scheme 2). Schmidt and co-workers prepared compound **9** via a four-step synthetic manipulation, including the *O*-to-*C* rearrangement of the corresponding α-*O*-glucoside, which was prepared by *O*-glucosidation using a TBS-protected acetophenone derivative followed by deprotection–protection sequence.[9]

Keywords: Flavone *C*-glycoside; *O*-to-*C* rearrangement; Mitsunobu reaction; Anti-inflammatory activity.
* Corresponding author. Tel.: +81-54-264-5746; fax: +81-54-264-5745; e-mail: tanakaki@u-shizuoka-ken.ac.jp

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.08.015



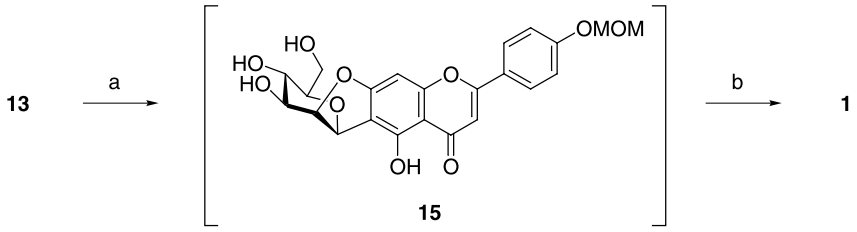
Scheme 1. Retrosynthetic analysis of **1**.



Scheme 2. Synthesis of isovitexin and vitexin derivatives. Reagents and conditions: (a) *O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl) trichloroacetimidate (**8**), TMSOTf, CH_2Cl_2, 0 °C to rt, 69%; (b) 4-(methoxymethoxy)benzoic acid (**10**), DCC, DMAP, CH_2Cl_2, rt, 82%; (c) K_2CO_3, pyridine, reflux, 1 h, **12** (17%), **14** (15%); (d) $Pd(OH)_2$, H_2, EtOH, 35 °C, 95%.

We envisaged that **9** could be directly formed from monobenzyl protected acetophenone derivative **7**,[10] which is readily available from phloroglucinol on the gram scale, as a starting glycosyl acceptor. Using improvements from previous preparations, the direct synthesis of **9** from **7** was attempted. As expected, glycosylation of **7** with *O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)trichloroacetimidate (**8**)[11] in the presence of catalytic amounts of TMSOTf[12] gave the desired β-configured **9** via *O*-to-*C* rearrangement in 69% yield. Subsequent condensation of **9** with 4-(methoxymethoxy)benzoic acid (**10**)[13] selectively afforded monoacylated derivative **11**. The appearance of two sets of peaks in the ^1H and ^{13}C NMR spectra, which both agree with the structure of **11**, suggests that **11** exists as a rotational isomer at ambient temperature on the NMR time-scale.

Although the many synthetic flavonoid studies are reported, reliable and mild reaction conditions for C ring formation are not readily available. Both of the following synthetic methods, (i) Baker–Venkataraman rearrangement-successive acid catalyzed cyclization,[9] and (ii) chalcone formation-oxidative cyclization using I_2[14] or another oxidant,[15] have been widely used for this purpose. However, both cyclizations often require strongly acidic or basic conditions to obtain the desired flavones in satisfactory chemical yields. We decided to apply the cyclization conditions,[16]



Scheme 3. Completion of the synthesis of the target flavone. Reagents and conditions: (a) 1,1′-azobis(*N*,*N*-dimethylformamide), Bu_3P, THF, 50 °C; (b) 4 N HCl–dioxane, MeOH, rt, 32% (two steps).

which were previously employed for preparing flavonol derivatives. Thus, upon refluxing a pyridine solution of **11** in the presence of K_2CO_3, both the isovitexin-type flavone **12** and vitexin-type derivative **14** were obtained as separable mixture in 17 and 15% yields, respectively. The formation of both isomeric flavones indicated that the C ring construction occurred via Baker–Venkataraman rearrangement of the acyl group and successive cyclization under these reaction conditions.

Removing the benzyl protecting groups of **12** by hydrogenation with Pearlman's catalyst in EtOH provided **13** in excellent yield.

Next, we turned our attention to constructing the tetracyclic ring system that corresponds to the left part of the molecule. Intramolecular cyclization of **13** under modified Mitsunobu conditions[8b,c] in THF followed by the removal of the MOM protecting group by treating with 4 N HCl–dioxane in MeOH to yield target flavone **1** in 32% for two steps without generation of another flavone isomers (Scheme 3). It is noteworthy that flavone **15** was synthesized as a dominant product in the first step even in the presence of reactive primary and phenolic hydroxyl groups in substrate **13**.

3. Conclusion

In summary, the total synthesis of compound **1** was accomplished by combining *C*-glycoside formation, flavone ring construction, and intramolecular Mitsunobu reaction as key steps. This concise and efficient synthetic protocol, which consists of six steps from known acetophenone derivative **7** in 3% overall yield, could be employed not only for large-scale synthesis of target flavone, but also for preparing related derivatives that would be useful for studying structure–activity relationship. Synthetic efforts for preparing a series of flavone derivatives based on this synthetic pathway and evaluating their biological activities are currently under investigation in our laboratory.

4. Experimental

4.1. General

Melting points are uncorrected. Optical rotations were measured on a JASCO P-1030 polarimeter. ^1H and ^{13}C NMR spectra were obtained on JEOL ECA-500 at 500 and 125 MHz, respectively, with chemical shifts being reported as δ ppm from tetramethylsilane as an internal standard. IR spectra were recorded on a JASCO WS/IR-8000. The mass spectra were measured on a JEOL MStation JMS-700 spectrometer. THF was distilled from sodium benzophenone ketyl, CH_2Cl_2, MeOH and pyridine were from calcium hydride, magnesium and NaOH, respectively. Unless otherwise noted, all reactions were run under an argon atmosphere. All extractive organic solutions were dried over anhydrous $MgSO_4$, filtered and then concentrated under reduced pressure. Column chromatography was carried out with silica gel 60N spherical (63–210 mesh, KANTO CHEMICAL) or Sephadex LH-20 (Amersham Biosciences).

4.1.1. *O*-to-*C* Rearrangement to 4-benzyloxy-2,6-dihydroxy-3-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-acetophenone (9). To a mixture of 4-benzyloxy-2,6-dihydroxyacetophenone (**7**)[10] (1.4 g, 5.4 mmol) and *O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)trichloroacetimidate (**8**)[11] (3.7 g, 5.4 mmol) in CH_2Cl_2 (40 mL) was added TMSOTf (97 μL, 0.54 mmol) at 0 °C. After being stirred at room temperature for 18 h, the mixture was added H_2O at 0 °C and the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 and the combined organic layer was washed with brine, dried and evaporated to give a residue, which was purified by column chromatography (SiO_2, toluene–EtOAc=9/1) to afford **9**[9] (2.9 g, 69%) as a colorless oil.

4.1.2. 4-Benzyloxy-2-hydroxy-6-(4-methoxymethoxybenzoyloxy)-3-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-acetophenone (11). A mixture of **9** (509 mg, 0.65 mmol), 4-(methoxymethoxy)benzoic acid (**10**)[13](117 mg, 0.65 mmol), DCC (161 mg, 0.78 mmol) and DMAP (8.0 mg, 65 μmol) in CH_2Cl_2 (15 mL) was stirred at room temperature for 12 h. After the addition of H_2O, the mixture was extracted with CH_2Cl_2. The organic layer was washed with brine, dried and evaporated to give a residue. The residue was purified by column chromatography (SiO_2, toluene–EtOAc=10/1) to afford **11** (504 mg, 82%) as a colorless oil.

$[\alpha]_D^{20}=-12.1$ (*c* 1.3, $CHCl_3$); ^1H NMR (C_6D_6, rotamers): δ 14.48, 13.59 (s, 1H, OH), 8.03 (d, 2H, J=8.5 Hz, Ar), 7.40–7.00 (m, 25H, Bn), 6.91 (d, 2H, J=8.5 Hz, Ar), 6.20, 6.10 (s, 1H, Ar), 5.57, 5.31 (d, 1H, J=9.4 Hz, sugar H-1), 5.00–4.20 (m, 10H, Bn), 4.72, 4.65 (dd, 1H, J=9.4, 10 Hz, sugar H-2), 4.65 (s, 2H, MOM), 4.02, 3.98 (t, 1H, J=8.8 Hz, sugar H-4), 3.88, 3.80 (dd, 1H, J=8.8, 10 Hz, sugar H-3), 3.76, 3.64 (m, 1H, sugar H-6), 3.58, 3.49 (m, 1H, sugar H-5), 2.97 (s, 3H, MOM), 2.22, 2.18 (s, 3H, Ac); ^{13}C NMR (C_6D_6, rotamers): δ 201.8, 201.4 (Ac), 164.8, 164.4 (Ar), 163.7, 162.2 (Ar), 162.2 (Ar), 162.1 (Ar), 154.0, 153.3 (Ar),

139.7–139.1 (Bn), 132.4 (Ar), 130.0–125.0 (Bn), 116.2 (Ar), 112.9, 112.4 (Ar), 110.9, 109.3 (Ar), 100.3, 100.1 (Ar), 93.8 (MOM), 88.1, 87.9 (sugar C-3), 80.1, 79.8 (sugar C-5), 79.2, 78.9 (sugar C-2), 75.2, 75.1 (sugar C-4), 74.7, 74.6 (sugar C-1), 75.0–70.0 (Bn), 69.2, 69.4 (sugar C-6), 55.6 (MOM), 31.7, 31.5 (Ac); IR ($CHCl_3$): 3011, 1738, 1607, 1283, 1244; MS (FAB) *m/z* 945 $(M+H)^+$; HRMS calcd for $C_{58}H_{57}O_{12}$ $(M+H)^+$ 945.3850, found 945.3846.

4.2. Flavone ring formation to isovitexin and vitexin derivatives

A mixture of **11** (693 mg, 0.74 mmol), K_2CO_3 (507 mg, 3.7 mmol) and MS 4 Å (70 mg) in pyridine (148 mL) was stirred under reflux for 1 h. After concentration of the reaction mixture, the residue was diluted with EtOAc and washed with saturated $CuSO_4$. The organic layer was washed with brine, dried and evaporated to give a residue. The residue was purified by column chromatography (SiO_2, toluene–EtOAc=20/1) to afford the less polar fraction containing vitexin derivative **14** and the pure isovitexin derivative **12** (115 mg, 17%) as a polar fraction. Further purification of the less polar fraction by preparative HPLC (YMC-pack ODS-A S-5 SH-343-5, CH_3CN, 6 mL/min, t_R=20.7 min) gave vitexin derivative **14** (100 mg, 15%).

4.2.1. 7-Benzyloxy-5-hydroxy-2-(4-methoxymethoxyphenyl)-6-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-4*H*-1-benzopyran-4-one (isovitexin derivative) (12). Pale yellow oil; $[\alpha]_D^{20}=-18.0$ (*c* 1.2, $CHCl_3$); ^1H NMR (C_6D_6, rotamers): δ 14.34, 14.27 (s, 1H, OH), 7.53–6.80 (m, 25H, Bn), 7.32 (m, 2H, Ar), 6.91 (m, 2H, Ar), 6.36, 6.34 (s, 1H, Ar), 6.14, 6.06 (s, 1H, Ar), 5.55, 5.38 (d, 1H, J=9.5 Hz, sugar H-1), 5.05, 4.63 (t, 1H, J=9.5 Hz, sugar H-2), 5.00–4.40 (m, 10H, Bn), 4.65 (s, 2H, MOM), 4.06, 4.04 (t, 1H, J=9.2 Hz, sugar H-4), 3.90, 3.87 (m, 1H, sugar H-3), 3.85, 3.76, 3.72, 3.64 (m, 2H, sugar H-6), 3.67, 3.57 (m, 1H, sugar H-5), 3.02 (s, 3H, MOM); ^{13}C NMR (C_6D_6, rotamers): δ 182.5 (C=O), 163.8, 162.2 (Ar), 163.0 (Ar), 161.7, 161.0 (Ar), 160.2 (Ar), 157.7, 157.6 (Ar), 130.0–127.0 (Bn), 128.5 (Ar), 125.5 (Ar), 116.4 (Ar), 110.9, 110.6 (Ar), 105.8 (Ar) 106.0, 105.5 (Ar), 93.5 (MOM), 91.7, 91.0 (Ar), 87.5 (sugar C-3), 80.5 (sugar C-5), 79.3, 78.9 (sugar C-2), 78.7 (sugar C-4), 75.2–73.5 (Bn), 73.2, 73.0 (sugar C-1), 69.2 (sugar C-6), 56.2 (MOM); IR ($CHCl_3$): 3011, 2930, 2866, 1655, 1609, 1454, 1348; MS (FAB) *m/z* 927 $(M+H)^+$; HRMS calcd for $C_{58}H_{55}O_{11}$ $(M+H)^+$ 927.3745, found 927.3782.

4.2.2. 7-Benzyloxy-5-hydroxy-2-(4-methoxymethoxyphenyl)-8-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-4*H*-1-benzopyran-4-one (vitexin derivative) (14). Pale yellow oil; $[\alpha]_D^{20}=-20.5$ (*c* 1.2, $CHCl_3$); ^1H NMR (C_6D_6): δ 14.02 (s, 1H, OH), 7.70–6.50 (m, 25H, Bn), 7.91 (d, 2H, J=9.2 Hz, Ar), 7.06 (m, 2H, Ar), 6.36 (s, 1H, Ar), 6.35 (s, 1H, Ar), 5.33 (d, 1H, J=9.9 Hz, sugar H-1), 5.00–4.00 (m, 10H, Bn), 4.68 (s, 2H, MOM), 4.34 (m, 1H, sugar H-2), 4.19 (m, 1H, sugar H-4), 3.83 (t, 1H, J=8.8 Hz, sugar H-3), 3.71 (dd, 1H, J=3.5, 10.7 Hz, sugar H-6a), 3.52 (dd, 1H, J=1.2, 10.7 Hz, sugar H-6b), 3.40 (d, 1H, J=9.9 Hz, sugar H-5), 2.99 (s, 3H, MOM); ^{13}C NMR (C_6D_6): δ 182.8 (C=O), 163.8 (Ar), 163.3 (Ar), 162.5 (Ar), 160.4 (Ar), 155.9 (Ar), 140.0–125.0 (Bn), 129.6 (Ar), 125.2 (Ar), 117.7 (Ar), 106.1 (Ar) 105.5 (Ar), 93.9 (MOM), 96.4 (Ar), 88.5 (sugar C-3), 79.9 (sugar C-5), 78.6 (sugar C-4), 78.5 (sugar C-2), 80.0–70.0 (Bn), 75.5 (sugar C-1), 68.8 (sugar C-6), 55.5 (MOM); IR ($CHCl_3$): 3011, 2934, 2870, 1653, 1607, 1589, 1431, 1360; MS (FAB) *m/z* 927 $(M+H)^+$; HRMS calcd for $C_{58}H_{55}O_{11}$ $(M+H)^+$ 927.3745, found 927.3740.

4.2.3. 6-(β-D-Glucopyranosyl)-5,7-dihydroxy-2-(4-methoxymethoxyphenyl)-4*H*-1-benzopyran-4-one (13). A mixture of **12** (10 mg, 11 μmol) and $Pd(OH)_2$ (2.0 mg) in EtOH (3.0 mL) was stirred at 35 °C for 1 h under hydrogen. After concentration of the reaction mixture, the residue was purified by column chromatography (SiO_2, $CHCl_3$–MeOH=5/1) to afford **13** (5.0 mg, 95%).

Mp 175–177 °C; yellow needles (from acetone–H_2O); $[\alpha]_D^{20}=+28.0$ (*c* 0.25, MeOH); ^1H NMR (acetone-d_6+D_2O): δ 8.00 (d, J=8.6 Hz, 2H), 7.20 (d, J=8.6 Hz, 2H), 6.69 (s, 1H), 6.54 (s, 1H), 5.30 (s, 2H), 4.94 (d, J=9.8 Hz, 1H), 3.9–3.7 (m, 3H), 3.7–3.3 (m, 3H), 3.45 (s, 3H); ^{13}C NMR (acetone-d_6+D_2O): δ 183.0, 164.3, 163.8, 161.0, 160.7, 157.7, 128.7, 124.9, 117.1, 108.5, 104.8, 104.5, 95.3, 94.6, 81.6, 79.0, 75.0, 72.9, 70.4, 61.5, 56.1; IR (Nujol): 3380, 1653, 1634, 1609, 1574, 1244, 1154, 984; MS (FAB) *m/z* 477 $(M+H)^+$; HRMS calcd for $C_{23}H_{25}O_{11}$ $(M+H)^+$ 477.1397, found 477.1353.

4.2.4. Transformation to target flavone 1. To a mixture of **13** (16 mg, 34 μmol), 1,1′-azobis(*N*,*N*-dimethylformamide) (12 mg, 68 μmol) in THF (2.0 mL) was added *n*-Bu_3P (17 μL, 68 μmol) at 0 °C. After stirring at 50 °C for 24 h, the mixture was concentrated and the residue was subjected to column chromatography (SiO_2, $CHCl_3$–MeOH=50/1) to afford the mixture (14.6 mg) containing compound **15**. Part of the mixture (6.7 mg) was dissolved in MeOH (1.0 mL) and treated with 4 N HCl–dioxane (0.2 mL). After stirring at room temperature for 30 min, the reaction mixture was evaporated to give a residue containing the target flavone **1**. The chemical yield (32%) of **1** from **13** was obtained from the HPLC quantification (YMC-pack ODS R-ODS-5A, MeOH–H_2O=1/1, 0.3 mL/min, t_R=37.0 min).

Under the same Mitsunobu conditions started from **13** (19 mg, 40 μmol) and subsequent deprotection by 4 N HCl–dioxane gave **1** (3.3 mg, 20%) after purification by column chromatography (Sephadex LH-20, MeOH). The synthetic **1** was identical with the authentic sample in terms of the ^1H and ^{13}C NMR spectroscopic data[5] as well as the retention time in HPLC analysis.

Mp 229–232 °C; yellow needles (from MeOH); $[\alpha]_D^{20}=-174.5$ (*c* 0.17, MeOH); IR (Nujol): 3345, 1672, 1626, 1611, 1574, 1561, 1252, 1086; MS (FAB) *m/z* 415 $(M+H)^+$; HRMS calcd for $C_{21}H_{19}O_9$ $(M+H)^+$ 415.1029, found 415.1032.

References and notes

1. (a) Postema, M. H. D. *Tetrahedron* **1992**, *48*, 8545. (b) Postema, M. H. D. *C-Glycoside Synthesis*; CRC: London,

1995. (c) Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides*; Pergamon: Tarrytown, NY, 1995.
2. Nagai, T.; Miyaichi, Y.; Tomimori, T.; Suzuki, Y.; Yamada, H. *Chem. Pharm. Bull.* **1990**, *38*, 1329.
3. Hirobe, C.; Qiao, Z.-S.; Takeya, K.; Itokawa, H. *Phytochemistry* **1997**, *46*, 521.
4. Carte, B. K.; Carr, S.; DeBrosse, C.; Hemling, M. E.; MacKenzie, L.; Offen, P.; Berry, D. E. *Tetrahedron* **1991**, *47*, 1815.
5. Ishikura, Y.; Tsuji, K.; Nukaya, H. *Jpn. Kokai Tokkyo Koho* **2002**, 194828.
6. The compound **1** was synthesized by 14 steps from the commercially available glucal derivative in 0.2% overall yield: Nakatsuka, T.; Tomimori, Y.; Fukuda, Y.; Nukaya, H. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3201.
7. For examples, see: (a) Matsumoto, T.; Katsuki, M.; Suzuki, K. *Tetrahedron Lett.* **1988**, *29*, 6935. (b) Matsumoto, T.; Katsuki, M.; Jona, H.; Suzuki, K. *J. Am. Chem. Soc.* **1991**, *113*, 6982. (c) Kumazawa, T.; Ohki, K.; Ishida, M.; Sato, S.; Onodera, J.; Matsuba, S. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1379. (d) Herzner, H.; Palmacci, E. R.; Seeberger, P. H. *Org. Lett.* **2002**, *4*, 2965. (e) Kanai, A.; Kamino, T.; Kuramochi, K.; Kobayashi, S. *Org. Lett.* **2003**, *5*, 2837.
8. (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Tsunoda, T.; Otsuka, J.; Yamamiya, Y.; Itô, S. *Chem. Lett.* **1994**, 539. (c) Tsunoda, T.; Yamamiya, Y.; Kawamura, Y.; Itô, S. *Tetrahedron Lett.* **1995**, *36*, 2529.
9. Mahling, J.-A.; Jung, K.-H.; Schmidt, R. R. *Liebigs Ann.* **1995**, 461.
10. Cairns, H. *Tetrahedron* **1972**, *28*, 359.
11. Schmidt, R. R.; Stumpp, M. *Liebigs Ann. Chem.* **1983**, 1249.
12. Mahling, J.-A.; Schmidt, R. R. *Synthesis* **1993**, 325.
13. Inouye, M.; Chiba, J.; Nakazumi, H. *J. Org. Chem.* **1999**, *64*, 8170.
14. (a) Pinto, D. C. G. A.; Silva, A. M. S.; Cavaleiro, J. A. S. *Tetrahedron Lett.* **1994**, *35*, 9459. (b) Kumazawa, T.; Minatogawa, T.; Matsuba, S.; Sato, S.; Onodera, J. *Carbohydr. Res.* **2000**, *329*, 507.
15. Litkei, G.; Gulácsi, K.; Antus, S.; Blaskó, G. *Liebigs Ann.* **1995**, 1711.
16. (a) Lynch, H. M.; O'Toole, T. M.; Wheeler, T. S. *J. Chem. Soc.* **1952**, 2063. (b) Tanaka, H.; Stohlmeyer, M. M.; Wandless, T. J.; Taylor, L. P. *Tetrahedron Lett.* **2000**, *41*, 9735.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 60 (2004) 9381–9390

Synthetic studies on bradykinin antagonist martinellines: construction of a pyrrolo[3,2-*c*]quinoline skeleton using silicon-tether RCM reaction and allylic amination

Osamu Hara,[a,*] Kazuhiko Sugimoto[b] and Yasumasa Hamada[b,*]

[a]*Faculty of Pharmacy, Meijo University, 150 Yagotoyama, Tempaku-ku, Nagoya 460-8503, Japan*
[b]*Graduate School of Pharmaceutical Sciences, Chiba University, Yayoi-cho, Inage-ku, Chiba 263-8522, Japan*

Received 16 June 2004; revised 6 August 2004; accepted 9 August 2004

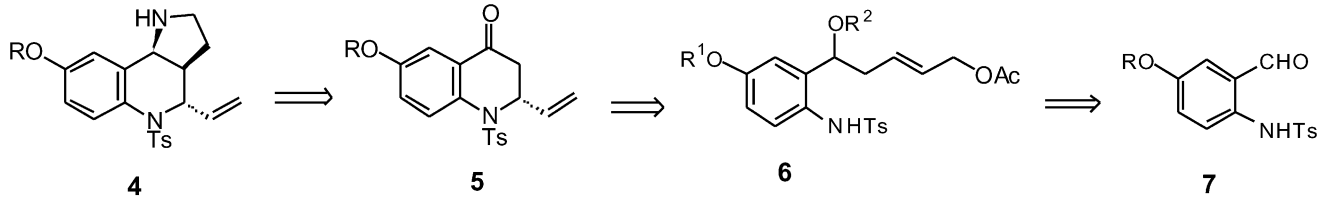
Abstract—The pyrrolo[3,2-*c*]quinoline consisting of a core structure of martinellines, the first naturally occurring heterocycle, was prepared through silicon-tether ring-closing metathesis reaction and intramolecular allylic amination as key steps.
© 2004 Elsevier Ltd. All rights reserved.

1. Introduction

Heterocycles constitute the core structures of numerous biologically active natural products and have occupied a very important position as lead compounds of medicines. Recently, we have been interested in the unique structure and biological activities of martinelline (**1**) and martinellic acid (**2**), novel bradykinin antagonists, isolated from *Martinella equitosensis* by Witherup et al. in 1995.[1] Especially, the pyrrolo[3,2-*c*]quinoline ring (**3**), which is the structural nucleus of the martinellines and the first naturally occurring ring, has attracted wide attention as a synthetic target. Many research groups have reported not only the synthesis of the core heterocycle but also the synthesis of martinellines.[2,3] We have already demonstrated an asymmetric construction of the tetrahydroquinoline skeleton via asymmetric allylic substitution reaction using our developed chiral ligand, 9-PBN.[4,5] We describe here a new method for construction of the pyrroloquinoline skeleton using the allylic substitution reaction and silicon-tether ring-closing metathesis (RCM) reaction as key reactions. As shown in Scheme 1, pyrroloquinoline **4** would be constructed from tetrahydroquinolinone **5**, which could be synthesized from allyl acetate **6** by using the intramolecular cyclization developed by us (Fig. 1).

2. Results and discussion

In the synthesis of the tetrahydroquinoline ring, we first attempted the preparation of the substrate **6** by introduction of the C_4 unit to aldehyde **7** using methyl 4-bromocrotonate or crotyl reagents. The regioselective introduction using metal reagents with the allyl unit proved difficult. For example, the vinylogous Reformatsky reaction of aldehyde **7b** with methyl 4-bromocrotonate in the presence of zinc and iodine non-regioselectively proceeded to produce an equal mixture of regioisomers **9** and **10**.[4] Alkylation using the crotyl metal type reagent occurred not at the desired α position but at the undesired γ position of the crotyl unit via



Scheme 1.

Keywords: Pyrrolo[3,2-*c*]quinoline; Silicon-tether ring-closing metathesis; Intramolecular allylic amination; Martinelline; Cross-metathesis.
* Corresponding authors. Tel./fax: +81-43-2902987; e-mail: hamada@p.chiba-u.ac.jp

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.08.014

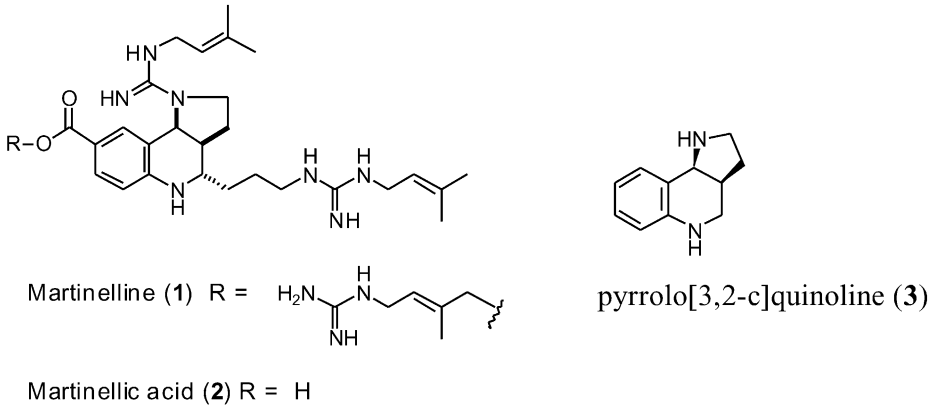
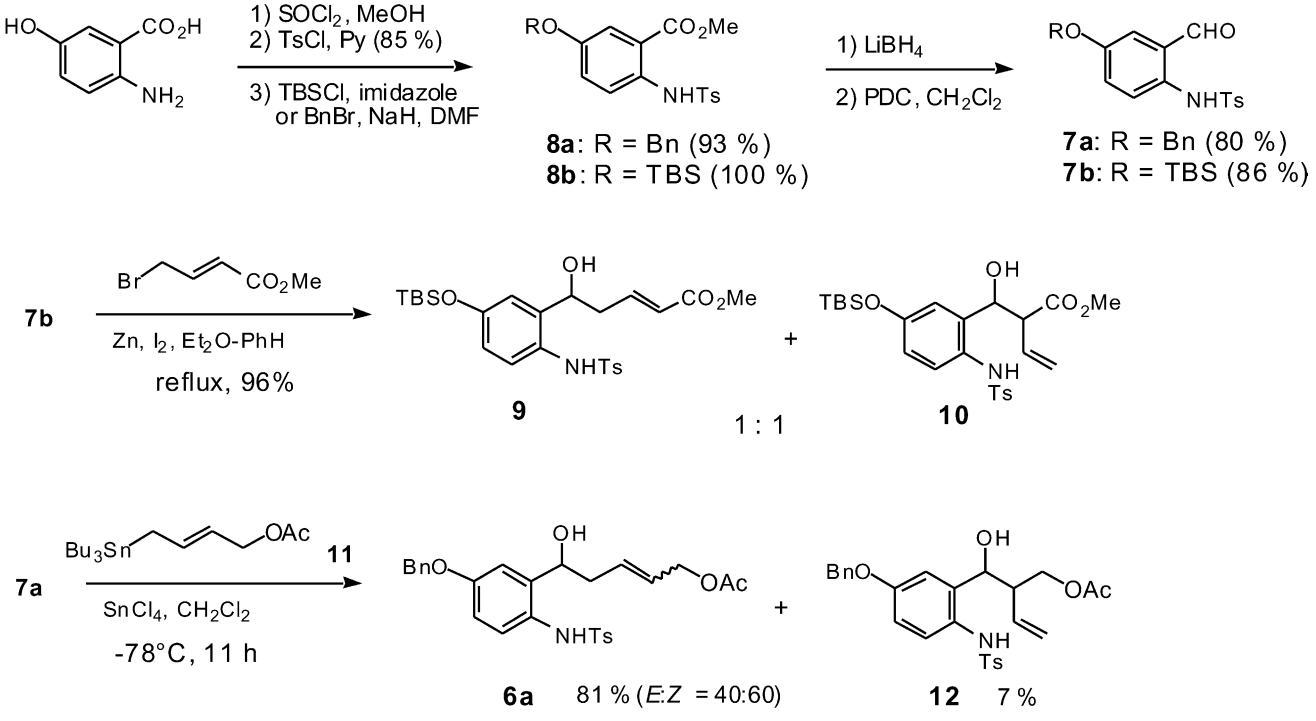


Figure 1.

$S_N 2'$ reaction. Although it appeared difficult to change the regioselectivity from γ to α position, this problem was partly solved by use of the Thomas procedure.[6] Acetoxycrotylstannane **11** was pretreated with stannic chloride in methylene chloride at −78 °C for 5 min and then aldehyde **7a** was added. The reaction proceeded regioselectively to afford an *E*/*Z* mixture of α-product **6a** in 81% yield with a small amount of γ-product **12** (Scheme 2). However, we did not pursue this approach since preparation of the starting stannane **11** was difficult for large-scale production. Recently, olefin metathesis reaction has become a powerful tool for construction of an olefin unit, and has been successfully used for synthesis of many biologically active substances so far. We thought that the olefin metathesis reaction would be able to produce the precursor **6** without contamination of the regioisomer using a cross-metathesis reaction[7] or a RCM reaction[8] (Fig. 2).

First, the cross-metathesis reaction was examined between homoallylic alcohol **13** and allylic acetate. The aldehyde **7** prepared from readily available 5-hydroxyanthranilaldehyde was converted to homoallyl alcohol **13** by reaction with allyl Grignard reagent. The cross-metathesis reactions between the olefin **13** and the donor olefins, allyl acetate and crotyl acetate, are summarized in Table 1. The mixture of olefin **13c** and allyl acetate was treated with 10 mol% of Grubbs reagent **16** to afford cross product **6c** in 15% yield (run 3). The thus-obtained compound **6c** was a mixture of *E* and *Z* olefins in the ratio of 4:1–6:1 (run 3). Since an attempt using an increasing amount of the catalyst and the allyl acetate failed to improve the chemical yield, crotyl acetate was used in place of the allyl acetate. The reaction was similarly carried out in the presence of 10 mol% of the catalyst and 5 equiv of crotyl acetate to give the desired compound in 28% yield (run 4). In this case the substrate disappeared on tlc and a large amount of a side product with the dimeric structure of **13c** generated in 57% yield. An attempt to prevent the production of this dimeric product



Scheme 2.

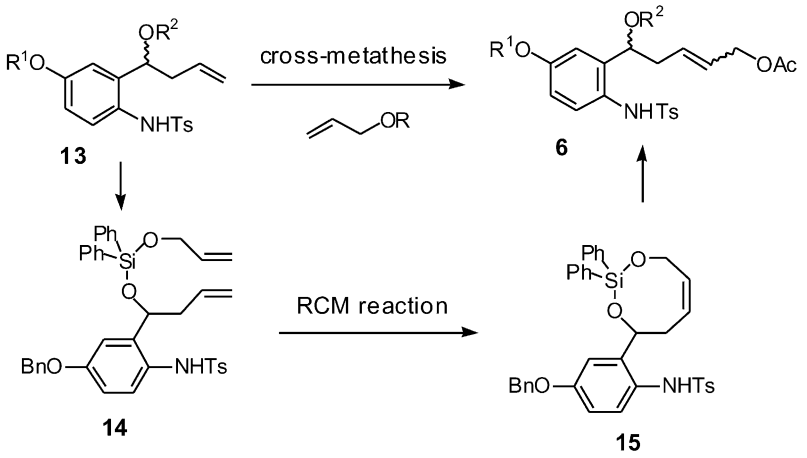
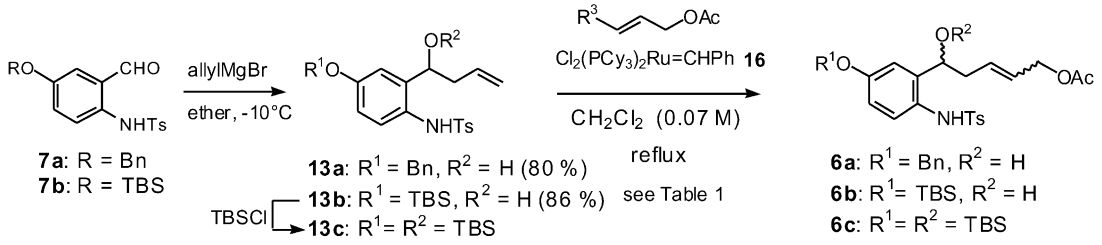


Figure 2.

failed. Next, the influence of the protecting group at the benzylic alcohol was examined because the adjacent functional groups of olefin are known to often prevent the catalytic cycle of olefin metathesis reaction by strong coordination to the ruthenium atom as a ligand. The olefin **13b** bearing a free hydroxy group was reacted with the allylic acetate in the presence of the Grubbs catalyst and the improvement of chemical yield to 42% was observed without recovery of **13b** (run 2). The change of the protecting group on the aromatic ring had no effect on the chemical yield (run 1). As the cross-metathesis gave us unsatisfactory results, we decided to carry out the chain extension of **13** by the RCM reaction. The RCM reaction has been used for the formation of a variety of cyclic compounds including not only macrocyclic compounds but also medium-ring ones. For the silicon-tether RCM reaction,[9] we needed a substrate with the allyl silyl moiety at the benzylic position. The new silicon compound was prepared from commercially available dichlorodiphenylsilane. Dichlorodiphenylsilane was treated with allyl alcohol in the presence of triethylamine in methylene chloride at room temperature to give the desired allyloxychlorodiphenylsilane **17** in 87% yield after distillation under reduced pressure. This compound, however, was very sensitive to moisture and therefore was immediately used for next reaction. Introduction of the silane residue to the hydroxyl group was performed under the general condition. The silane **17** was easily reacted with alcohol **13a** in methylene chloride at room temperature for 5 min to give the precursor **14** for the RCM reaction in 97% yield. The RCM reaction of **14** was carried out with 5 mol% of Grubbs reagent **16** in 0.07 M solution to form the cyclic silyl ether **15** with the eight-membered ring in 40% yield. As the starting material was completely consumed in this reaction, we thought that this low yield might be due to polymerization of the substrate. When the concentration of **14** was diluted to 0.01 M solution, the reaction smoothly took place at reflux for 5 h to afford the desired product **15** in 86% yield. Removal of the silicon-tether from **15** with tetra*n*-butylammonium fluoride (TBAF) gave diol **18** in 84% yield. Acid-catalyzed acetylation of **18** with acetic anhydride furnished allyl acetate **6d** (Scheme 3).

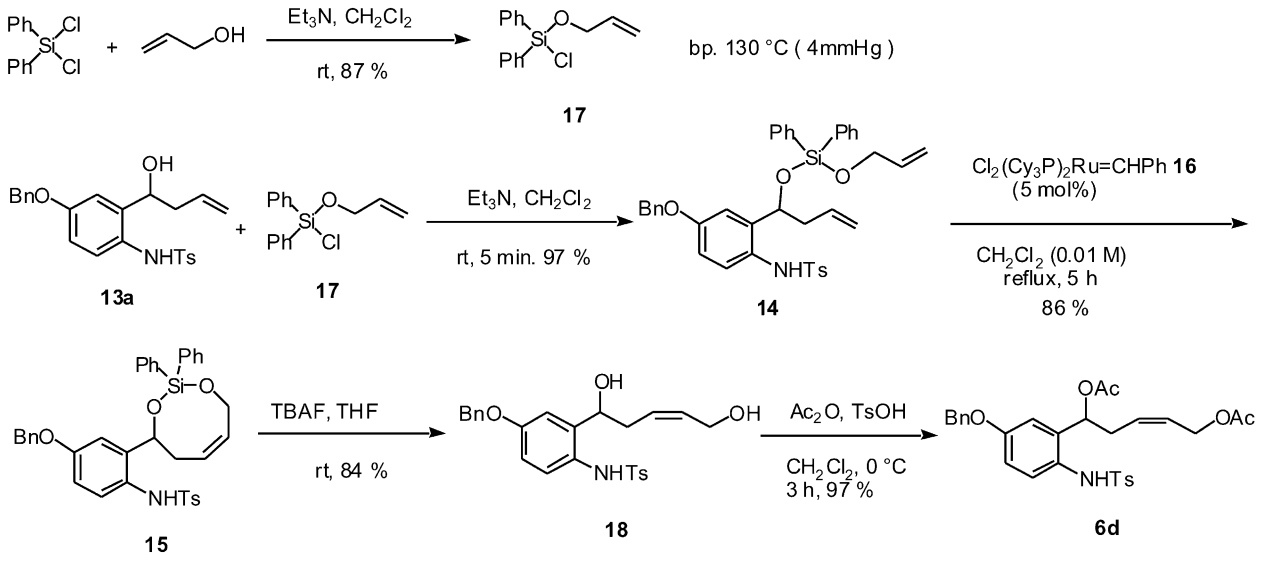
With the substrates for cyclization in hand, we next investigated intramolecular allylic substitution reaction of **6** for construction of the tetrahydroquinoline ring (Table 2). The allyl ester **6c** bearing a hinder TBS group and *E* geometry on the side chain was treated with bis(benzylidene)

Table 1. Cross-metathesis reaction between homoallylic alcohol **13** and allyl acetate



Run	Compounds	R^3	Ru (mol%)	Time (h)	Yield[a]
1	**13a**	H	10	44	38% (56%)
2	**13b**	H	10	23	42%
3	**13c**	H	10	45	15% (85%)
4	**13c**	CH_3	10	20	28%

[a] The product was obtained as a mixture of *E* and *Z* olefins in a ratio of 4:1–6:1. The parentheses are yields based on consumed starting material.

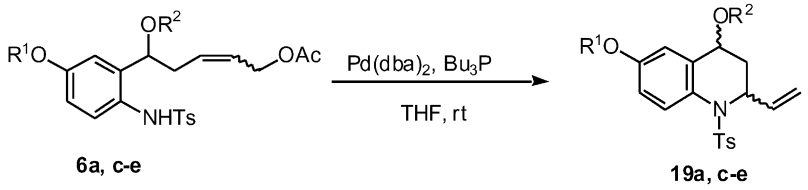


Scheme 3.

palladium ($Pd(dba)_2$) and tri*n*-butylphosphine (Bu_3P) in THF at room temperature to obtain the desired tetrahydroquinoline **19c** with *cis* relationship as a single product in 92% yield (run 1). Even if a mixture of *E* and *Z* olefins was used in this reaction, the reaction proceeded in a similar manner to afford the 2,4-*cis* product in excellent yield (run 2). The relative stereochemistry of **19c** was judged by the coupling constant of the ^1H NMR spectrum. The values of the coupling constants between the C-3 axial proton and the adjacent protons are 11.4 and 11.8 Hz, which show that both the C-4 proton and the C-2 proton are placed on the pseudo-axial position. On the other hand, compounds **6a** and **6d** bearing hydroxyl and acetoxy groups at the benzylic position gave a mixture of *cis* and *trans* diastereomers, respectively, under similar conditions. The observed outcome shows that the hydroxyl and acetoxy substituents adjacent to the π-allyl palladium complex affect the stereoselectivity of the cyclization. With this satisfactory result, the asymmetric cyclization of **6c** using (−)-9-PBN in place of Bu_3P was carried out in the presence of lithium acetate and bis(trimethylsilyl) acetamide (BSA). The reaction somewhat sluggishly proceeded in a reagent-controlled manner and provided a mixture of *cis*-**19c** and *trans*-**19c** with 60%ee each in the ratio of 68:32 (run 3).

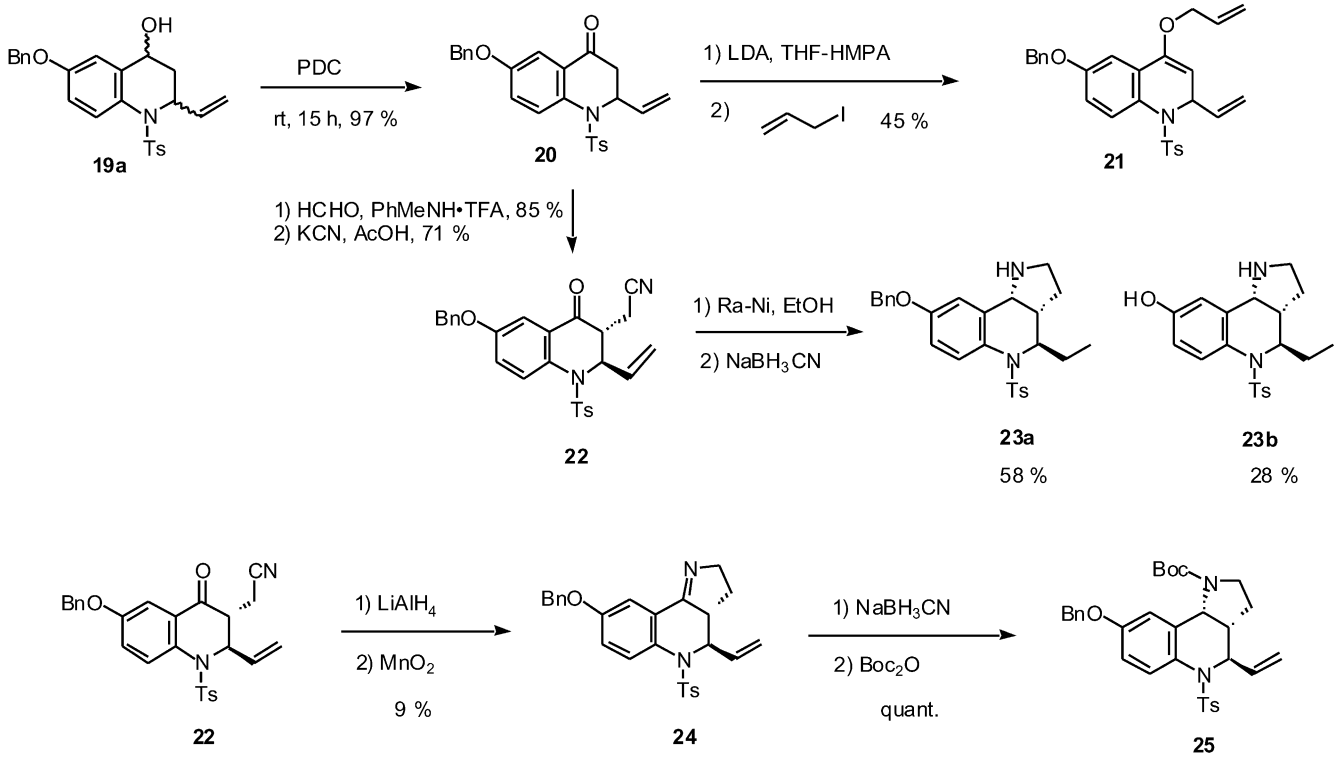
With the tetrahydroquinoline available in large quantities, we then focused our attention on introduction of the pyrrole ring. First, the α-alkylation of tetrahydroquinolone **20** was extensively investigated (Scheme 4). However, we were unable to obtain the corresponding *C*-alkylated product except *O*-alkylated product **21** which was produced by *O*-alkylation of the lithium enolate derived from **20** and lithium diisopropylamide (LDA). After many efforts we found a two-step approach including the Mannich reaction and 1,4-conjugate addition. Tetrahydroquinolone **20** was treated with paraformaldehyde in the presence of *N*-methylaniline trifluoroacetate (TFA·PhNHMe) at reflux for 33 h to provide the *exo*-methylene product in 85% yield. For the introduction of the C_1 unit, 1,4-conjugate addition of the

Table 2. Preparation of tetrahydroquinolines using palladium-catalyzed cyclization



Run	Compound	R^1	R^2	Geometry	Time (h)	Yield (%)	Ratio of *cis*:*trans*
1	**6c**	TBS	TBS	*E* only	20	92	Only *cis*
2	**6c**	TBS	TBS	Mixture of *E* and *Z*			Only *cis*
3[a]	**6c**	TBS	TBS	*E* only	35	42	68:32
4[b]	**6a**	Bn	H	Mixture of *E* and *Z*	17	96	3:1
5	**6d**	Bn	Ac	*Z* only	44	96	3:1
6	**6e**	Bn	*E* only	*E* only	16	96	Only *cis*

[a] This reaction was carried out with the combination of $Pd(dba)_2$ and (−)-9-PBN in the presence of LiOAc ans BSA.
[b] This reaction was carried out in the presence of AcOH.



Scheme 4.

nitrile group was examined. The 1,4-conjugate addition reaction cleanly proceeded by the treatment of potassium cyanide (KCN) in the presence of acetic acid at room temperature to afford *trans* 2,3-disubstituted tetrahydroquinolone **22** as the sole product in 71% yield.

For the construction of pyrroloquinoline, the reduction of nitrile of **22** with lithium aluminum hydride followed by oxidation of benzylic alcohol with manganese dioxide gave an imino product in only poor yield. The resulting imine was reduced with sodium cyanoborohydride ($NaBH_3CN$) at room temperature and then treatment with di-*t*-butyl dicarbonate (Boc_2O) gave pyrroloquinoline **25** in quantitative yield (Scheme 4). As conversion of the nitrile to the corresponding amine was disappointing, the catalytic hydrogenation was employed for the improvement of yields. Among Rh/Al_2O_3, PtO_2, and Raney Ni selected as catalysts for the hydrogenation, Raney Ni gave the best result. Finally, the synthesis of pyrroloquinoline was achieved in a two-step manner: (1) the reduction of nitrile with Raney Ni under hydrogen atmosphere and (2) reduction of the resulting cyclic imine with $NaBH_3CN$. Pyrroloquinoline **23a** and its deprotected product **23b** were obtained in 58 and 28% yields, respectively. The relative stereochemistry of pyrroloquinoline showed the C_{3-4} *cis* relationship, which was confirmed by the NOE experiment.

3. Conclusion

In summary we have established a new access to pyrroloquinolines bearing the martinelline core structure using key reactions, allylic substitution reaction catalyzed by palladium and silicon-tether RCM reaction. Further investigation directed towards total synthesis of martinellines is underway in our laboratories.

4. Experimental

4.1. General

Melting points were measured with a SIBATA NEL-270 melting point apparatus. Infrared spectra were recorded on a JASCO FT/IR-230 Fourier transform infrared spectrophotometer. Optical rotations were measured on a JASCO DIOP-14 polarimeter. ^1H NMR spectra were recorded on a JEOL JNM-GSX 400A (400 MHz), JNM GSX500A (500 MHz), or JNM ECP400 (400 MHz) spectrometer. Chemical shifts are recorded in ppm from tetramethylsilane or chloroform as the internal standard. Analytical thin layer chromatography was performed on Merck Art. 5715, Kieselgel 60F254/0.25 mm thickness plates. Mass spectra were obtained on a JEOL HX-110A spectrometer. Column chromatography was performed with silica gel BW-820MH (Fuji Davision Co.). Solvents for reaction were reagent grade and distilled from the indicated drying agent: tetrahydrofuran (THF), benzene: sodium/benzophenone ketyl; diethyl ether (Et_2O): lithium aluminum hydride ($LiAlH_4$); acetonitrile, dichloromethane (CH_2Cl_2), diisopropylamine, dimethylformamide (DMF), *n*-hexane, toluene, dichloroethane ($C_2H_4Cl_2$): calcium hydride; methanol (MeOH): iodine/magnesium. Dimethylsulfoxide (DMSO) was dried over 4 Å molecular sieves. All other commercially available reagents were used as received.

4.2. Methyl 2-amino-5-hydroxybenzoate

To a stirred solution of precooled (−15 °C) methanol (300 mL) was added dropwise thionyl chloride (26 mL, 204 mmol) over 20 min at the temperature maintaining at below −10 °C and the mixture was stirred at −10 °C for 20 min. 5-Hydroxyanthranilic acid (9 g, 58 mmol) was added to the mixture. The reaction mixture was stirred at room temperature for 2 days and heated to reflux for 4 h. After cooling, the reaction mixture was concentrated in vacuo and the residue was treated with saturated aqueous sodium hydrogen carbonate. The whole was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over magnesium sulfate, and concentrated in vacuo to give methyl 2-amino-5-hydroxybenzoate (8.6 g, 88%) as dark violet crystals: mp 160–162 °C; IR ν_{max}^{KBr} 3380, 3300, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.86 (3H, s), 6.60 (1H, d, J=8.8 Hz), 6.89 (1H, dd, J=8.8, 2.9 Hz), 7.33 (1H, d, J=2.9 Hz). The solids were used for the next reaction without further purification.

4.2.1. Methyl 5-hydroxy-2-(4-methylbenzenesulfonylamino)benzoate. To a stirred solution of the crude methyl 2-amino-5-hydroxybenzoate (8.6 g, 51.4 mmol) in pyridine (40 mL) at 0 °C was added *p*-toluenesulfonyl chloride (TsCl, 10.3 g, 54 mmol) and the reaction mixture was stirred at room temperature for 5 h. The excess TsCl was destroyed by addition of water (2 mL) and stirred for 30 min. The reaction mixture was diluted with ethyl acetate and washed with 1 N HCl, water, and saturated brine. The organic layer was dried over magnesium sulfate and concentrated in vacuo to give methyl 5-hydroxy-2-(toluenesulfonylamino)benzoate (16 g, 97%) as dark crystals which were used for next reaction without purification. The analytical sample was obtained by purification using column chromatography (silica gel, *n*-hexane/ethyl acetate=2/1) to give brown solids: mp 106–113 °C; IR ν_{max}^{KBr} 3394, 1693, 1405 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.46 (3H, s), 3.86 (3H, s), 4.79 (1H, brs), 7.17–7.71 (7H, m), 9.95 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 52.4, 116.9, 118.4, 121.8, 122.8, 127.2, 129.4, 133.1, 135.9, 143.7, 151.7, 167.5. MS: *m/z* 321 (M^+). HRMS Calcd for $C_{15}H_{15}NO_5S$: 321.0671 (M^+). Found: 321.0684.

4.2.2. Methyl 5-benzyloxy-2-(4-methylbenzenesulfonylamino)benzoate (8a). To a stirred suspension of NaH (60% oil dispersion, 5.22 g, 131 mmol) in DMF (300 mL) at −20 °C was added methyl 5-hydroxy-2-(toluenesulfonylamino)benzoate (20.0 g, 62.2 mmol) and the reaction mixture was stirred at −20 °C for 30 min under argon atmosphere. Benzyl bromide (8.1 mL, 68.4 mmol) was added dropwise to the reaction mixture at 0 °C and the reaction mixture was stirred for 15 h. The reaction mixture was queuched with H_2O at 0 °C and extracted with ethyl acetate /*n*-hexane (8/1). The organic layer was washed with water and saturated brine, dried over sodium sulfate, and concentrated in vacuo. The residue was crystallized from ethyl acetate/*n*-hexane to give the title compound **8a** (23.9 g, 93.3%) as colorless solids: mp 94–96 °C; IR ν_{max}^{KBr} 3160, 1685, 1505, 1288, 1163 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.36 (3H, s), 3.81 (3H, s), 5.00 (2H, s), 7.11 (1H, dd, J=2.9, 9.0 Hz), 7.18 (2H, d, J=8.5 Hz), 7.33–7.38 (5H, m), 7.44 (1H, d, J=2.7 Hz), 7.62 (1H, s), 7.65 (2H, d, J=9.5 Hz), 10.0 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 52.4, 70.4, 115.9, 118.0, 121.6, 122.4, 127.2, 127.5, 128.1, 129.4, 133.6, 136.2, 143.6, 154.5, 167.6. Anal. Calcd for $C_{22}H_{21}NO_5S$: C, 64.22; H, 5.14; N, 3.40. Found: C, 64.11; H, 4.99; N, 3.28.

4.2.3. *N*-(4-Benzyloxy-2-hydroxymethylphenyl)-4-methylbenzenesulfonamide. To a stirred suspension of $LiBH_4$ (1.447 g, 66.4 mmol) in THF (30 mL) at 0 °C was added dropwise a solution of **8a** (18.13 g, 44 mmol) in THF (50 mL) over 20 min and the reaction mixture was heated to reflux for 20 h. The reaction mixture was cooled to room temperature, poured into ice-10% citric acid, and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was crystallized from ethyl acetate/*n*-hexane to give the title compound (17.12 g, quant.) as colorless solids: mp 102–104 °C; IR ν_{max}^{KBr} 3423, 3091, 1499, 1028 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.40 (3H, s), 4.30 (2H, s), 5.02 (2H, s), 6.80 (1H, d, J=2.8 Hz), 6.83 (1H, dd, J=3.1, 8.55 Hz), 7.16 (1H, d, J=8.6 Hz), 7.22 (2H, d, J=8.2 Hz), 7.30–7.39 (5H, m), 7.58 (2H, d, J=8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 63.2, 70.2, 114.7, 115.6, 127.1, 127.3, 127.4, 128.1, 128.2, 128.6, 129.5, 136.0, 136.5, 136.6, 143.7, 157.6. MS: *m/z* 383 (M^+). HRMS Calcd for $C_{21}H_{21}NO_4S$: 383.1193 (M^+). Found: 383.1188.

4.2.4. *N*-(4-Benzyloxy-2-formylphenyl)-4-methylbenzenesulfonamide (7a). To a stirred solution of *N*-(4-benzyloxy-2-hydroxymethylphenyl)-4-methylbenzenesulfonamide (2 g, 5.21 mmol) in CH_2Cl_2 (25 mL) at room temperature was added pyridinium dichromate (2.35 g, 6.25 mmol) under argon atomsphere and the reaction mixture was stirred at room temperature for 3 h. Magnesium sulfate was added to the reaction mixture and the insoluble material was filtered through silica gel. The filtrate was concentrated in vacuo. The residue was crystallized from ethyl acetate/*n*-hexane to give aldehyde **7a** (1.58 g, 80%) as yellow solids: mp 121–123 °C; IR ν_{max}^{KBr} 3151, 1661, 1497, 1388, 1151 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.35 (3H, s), 5.04 (2H, s), 7.11 (1H, d, J=3.2 Hz), 7.16 (1H, dd, J=3.2, 9.0 Hz), 7.20 (2H, d, J=8.5 Hz), 7.28–7.39 (5H, m), 7.67 (1H, d, J=9.0 Hz), 7.68 (2H, d, J=8.3 Hz), 9.72 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21..5, 70.6, 20.5, 120.8, 122.9, 123.3, 127.1, 127.4, 128.3, 128.7, 129.6, 133.1, 136.0, 136.3, 143.9, 154.7, 194.4. MS: *m/z* 381 (M^+). Anal. Calcd for $C_{21}H_{19}NO_4S$: C, 66.12; H, 5.02; N, 3.67. Found: C, 65.97; H, 4.90; N, 3.55.

4.2.5. 5-[5-(*tert*-Butyldimethylsiloxy)-2-(4-methylbenzenesulfonylamino)phenyl]-5-hydroxypent-2-enoic acid methyl ester (9) and 2-{[5-(*tert*-butyldimethylsiloxy)-2-(4-methylbenzenesulfonylamino)-phenyl]-hydroxymethyl}but-3-enoic acid methyl ester (10). A mixture of **7b** (4.31 g, 10.7 mmol), methyl 3-bromocrotonate (0.6 mL), and activated zinc (1.89 g, 28.9 mmol) in ether (5 mL) and benzene (5 mL) was heated nearly to the boiling point under argon atmosphere. Iodine (254 mg, 1.07 mmol) was added. After a few minute the exothermic reaction began and an additional methyl 3-bromocrotonate (2.8 mL) was slowly added. The reaction mixture was heated to reflux for 3.5 h during which time additional activated zincs (450 mg) were added three times in every 1 h. The completion of the

reaction was judged according to tlc analysis. The mixture was cooled to 23 °C and diluted with ethyl acetate (300 mL) and the partly insoluble product was dissolved by addition of acetic acid. The clear solution was decanted for removal of an excess of zinc metal, washed with water, saturated sodium hydrogen carbonate, water, and saturated brine, and dried over magnesium sulfate. Filtration of the mixture followed by concentration of the filtrate gave the crude product (6.48 g) which was purified by column chromatography (silica gel, *n*-hexane/ethyl acetate=2/1) to give γ-product **9** (2.60 g, 48.3%) as yellow crystals together with α-product **10** (2.55 g, 47.3%) as a slightly yellow oil. **9**: mp 72–75 °C; IR ν_{max}^{neat} 3410, 3136, 1716 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.15 (6H, s), 0.95 (9H, s), 2.39 (3H, s), 2.37 (3H, s), 2.32–2.38 (1H, m), 2.46–2.52 (1H, m), 3.71 (3H, s), 4.83 (1H, td, J=7.0, 2.2 Hz), 5.72 (1H, d, J=15.7 Hz), 6.63–6.68 (2H, m), 6.76 (1H, dt, J=15.7, 7.1 Hz), 7.00 (1H, d, J=8.5 Hz), 7.23 (1H, d, J=8.2 Hz), 7.30 (1H, s), 7.59 (1H, d, J=8.2 Hz); ^{13}C NMR (100 MH, $CDCl_3$) δ −4.5, 18.2, 21.5, 25.6, 39.4, 51.5, 70.6, 119.0, 120.0, 127.3, 127.7, 129.6, 136.4, 137.9, 143.9, 166.5. HRMS Calcd for $C_{24}H_{25}NO_4S$: 505.1954 (M^+). Found: 505.1965. **10**: IR ν_{max}^{neat} 3462, 3273, 2954, 1734 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.14 (6H, s), 0.94 (9H, s), 1.66 (1H, brs), 2.38 (3H, s), 3.33–3.34 (1H, m), 4.69 (1H, d, J=17.1 Hz), 4.83 (1H, d, J=8.1 Hz), 4.94 (1H, d, J=10.3 Hz), 5.33–5.39 (1H, m), 6.52 (1H, d, J=2.9 Hz), 6.66 (1H, dd, J=8.8, 2.92 Hz), 7.18 (1H, d, J=8.8 Hz), 7.23 (2H, d, J=8.1 Hz), 7.66 (2H, d, J=8.1 Hz). HRMS Calcd for $C_{24}H_{25}NO_4S$: 505.1954 (M^+). Found: 505.1958.

4.2.6. *N*-[4-Benzyloxy-2-(1-hydroxybut-3-enyl)phenyl]-4-methylbenzenesulfonamide (13a). To a stirred solution of allylmagnesiumbromide (72.7 mL, 43.6 mmol, 0.6 M) in ether at −20 °C was added dropwise a solution of **7a** (7.922 g, 20.8 mmol) in ether (80 mL) in THF (80 mL) under argon atomsphere and the reaction mixture was stirred at −10 °C for 2 h. The reaction mixture was quenched with saturated NH_4Cl at 0 °C and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane/ethyl acetate=2/1) to give the title compound **13a** (8.76 g, 100%) as a colorless oil: IR ν_{max}^{neat} 3464, 2922, 1499, 1159 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.19–2.30 (2H, m), 2.37 (3H, s), 2.71 (1H, d, J=2.9 Hz), 4.61–4.64 (1H, m), 4.99 (2H, s), 4.99 (1H, dd, J=1.5, 17.1 Hz), 5.05 (1H, d, J=10.1 Hz), 5.55–5.63 (2H, m), 6.77 (1H, dd, J=3.1, 11.0 Hz), 7.78 (1H, s), 7.17 (1H, d, J=9.1 Hz), 7.21 (2H, d, J=7.9 Hz), 7.30–7.36 (5H, m), 7.37 (2H, d, J=6.7 Hz), 7.59 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 41.1, 70.2, 71.4, 114.0, 114.2, 118.8, 125.9, 127.2, 127.4, 127.8, 128.0, 128.5, 129.5, 133.8, 136.5, 136.7, 137.0, 143.6, 156.6. MS: m/z 423 (M^+). HRMS Calcd for $C_{24}H_{25}NO_4S$: 423.1504 (M^+). Found: 423.1476.

4.2.7. 5-[5-Benzyloxy-2-(4-methylbenzenesulfonylamino) phenyl]-5-hydroxypent-2-enyl acetate (6a). A stirred solution of **13a** (1.284 g, 3 mmol) and allylacetate (1.6 mL, 14.8 mmol) in CH_2Cl_2 (40 mL) was degassed by three freeze-thaw cycles under argon atmosphere. Grubbs reagent **16** (271 mg, 0.315 mmol) was added to the reaction mixture at room temperature and the reaction mixture was degassed again by three freeze-thaw cycles. The reaction mixture was heated to reflux for 44 h. The reaction mixture was quenched with 1 M HCl and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane/ethyl acetate=3/2 to 1/1) to give the title compound **6a** (577 mg, 38%, E/Z=6:1) as a dark oil and the starting material (726 mg, 56%) as a yellow oil. **6a**: IR ν_{max}^{neat} 2929, 3482, 3255, 3031, 2925, 1733, 1498, 1236, 1159 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.04 (3H, s), 2.17–2.24 (1H, m), 2.33–2.36 (1H, m), 2.39 (3H, s), 2.71 (1H, s), 4.46 (2H, d, J=5.2 Hz), 4.76 (1H, t, J=6.9 Hz), 5.00 (2H, s), 5.47–5.60 (2H, m), 6.75 (1H, dd, J=2.9, 8.9 Hz), 6.83 (1H, d, J=3.0 Hz), 7.03 (1H, d, J=8.9 Hz), 7.31–7.36 (5H, m), 7.37 (2H, d, J=6.7 Hz), 7.48 (1H, s), 7.60 (2H, d, J=8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 21.5, 39.8, 64.7, 70.2, 71.1, 113.8, 114.4, 126.5, 127.3, 127.4, 127.5, 127.7, 128.1, 128.6, 129.6, 130.8, 136.5, 136.7, 138.4, 143.7, 157.0. MS: m/z 495 (M^+). HRMS Calcd for $C_{27}H_{29}NO_6S$: 495.1716 (M^+). Found: 495.1703.

4.2.8. Allyloxychlorodiphenylsilane (17). To a stirred solution of dichlorodiphenylsilane (8.3 mL, 39.9 mmol) in CH_2Cl_2 (200 mL) at 0 °C was added Et_3N (6.6 mL, 47.5 mmol) and allyl alcohol (2.6 mL, 38.2 mmol) and the reaction mixture was stirred at room temperature. After 24 h, the reaction mixture was concentrated in vacuo. The residue was distilled under reduced pressure to give allyloxychlorodiphenylsilane **17** (7.826 g, 87.0%) as a colorless oil: bp 130 °C (4 mmHg); IR ν_{max}^{neat} 3071, 2864, 1646, 1590, 1428, 1125 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.33 (1H, d, J=4.9 Hz), 4.39 (1H, d, J=4.9 Hz), 5.13 (1H, t, J=10.5 Hz), 5.32 (1H, d, J=15.3 Hz), 5.92–5.99 (1H, m), 7.34–7.72 (10H, m).

4.2.9. *N*-[4-Benzyloxy-2-(1-(allyloxydiphenylsilyloxy)-but-3-enyl)phenyl]-4-methylbenzenesulfonamide (14). To a stirred solution of **13a** (989 mg, 2.35 mmol) and Et_3N (0.68 mL, 4.90 mmol) in CH_2Cl_2 (10 mL) at room temperature was added dropwise allyloxychlorodiphenylsilane (1.267 g, 4.61 mol) in CH_2Cl_2 (2 mL) under argon atmosphere and the reaction mixture was stirred at room temperature. After 5 min, the reaction mixture was quenched with saturated sodium hydrogen carbonate and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane/ethyl acetate=6/1 to 2/1) to give the title compound **14** (1.505 g, 97.4%) as a yellow oil: IR ν_{max}^{neat} 3277, 3070, 2919, 1500, 1428, 1161, 1125 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24–1.52 (1H, m), 2.28–2.36 (1H, m), 2.33 (3H, s), 3.94–3.96 (2H, m), 4.68 (1H, t, J=6.9 Hz), 4.71 (1H, d, J=12.5 Hz), 4.83 (1H, d, J=9.5 Hz), 4.92 (2H, s), 5.05 (1H, d, J=9.9 Hz), 5.19 (1H, d, J=17.0 Hz), 5.21–5.32 (1H, m), 5.72–5.83 (1H, m), 6.52 (1H, d, J=2.9 Hz), 6.78 (1H, dd, J=2.7, 8.8 Hz), 7.12 (2H, d, J=8.05 Hz), 7.30–7.64 (17H, m), 7.81 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 41.7, 64.0, 70.1, 74.6, 114.4, 114.7, 114.8, 117.6, 124.2, 127.0, 127.4, 127.8, 127.8, 127.9, 128.0, 128.5, 129.5, 130.2, 130.4, 130.6, 130.7, 133.7, 134.3, 134.8, 134.9, 135.9, 137.0,

143.4, 155.6. MS: *m/z* 661 (M^+). HRMS Calcd for $C_{39}H_{39}NO_5SSi$: 661.2318 (M^+). Found: 661.2338.

4.2.10. *N*-[4-Benzyloxy-2-(2,2-diphenyl-5,8-dihydro-4*H*-[1,3,2]dioxasilocin-4-yl)phenyl]-4-methylbenzenesulfonamide (15). A stirred solution of **14** (39 mg, 0.059 mmol) in CH_2Cl_2 (5.8 mL) was degassed by three freeze-thaw cycles under argon atmosphere and Grubbs reagent **16** (2.4 mg, 0.0029 mmol) was added to the reaction mixture at room temperature. The reaction mixture was degassed again by three freeze-thaw cycles and heated to reflux. After 5 h, the reaction mixture was queuched with 1 M HCl, and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane/ethyl acetate=3/1) to give **15** (32 mg, 85.7%) as a yellow oil: IR ν_{max}^{neat} 3273, 1497, 1160, 1125 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.34 (3H, s), 2.53–2.58 (1H, m), 2.66–2.73 (1H, m), 4.47 (1H, dd, J=4.4, 14.9 Hz), 4.58 (1H, dd, J=5.6, 14.6 Hz), 4.83 (1H, dd, J=3.2, 7.3 Hz), 4.88 (2H, s), 5.50 (1H, dd, J=8.5, 19.3 Hz), 5.88 (1H, dt, J=5.6, 11.2 Hz), 6.70 (1H, d, J=2.7 Hz), 6.74 (1H, dd, J=2.7, 8.8 Hz), 7.13 (2H, d, J=8.3 Hz), 7.20–7.66 (17H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 34.7, 61.5, 70.1, 73.2, 113.5, 114.1, 125.0, 127.1, 127.4, 127.6, 127.7, 127.7, 127.9, 128.0, 128.5, 129.4, 130.2, 130.5, 132.6, 134.3, 134.4, 134.5, 134.7, 136.6, 136.7, 136.9, 143.4, 156.2. MS: *m/z* 633 (M^+). HRMS Calcd for $C_{37}H_{35}NO_5Si$: 633.2006 (M^+). Found: 633.1992.

4.2.11. (*Z*)-1,5-Diacetoxy-5-[5-benzyloxy-2-(4-methylbenzenesulfonylamino)phenyl]-2-pentene (6d). To a stirred solution of **15** (709 mg, 1.11 mmol) in THF (7.4 mL) at room temperature was added dropwise TBAF (2.6 mL, 2.6 mmol) under argon atmosphere and the reaction mixture was stirred at room temperature for 5 h. The reaction mixture was quenched with 1 M potassium hydrogen sulfate, and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane/ethyl acetate=1/2) to give **18** (427 mg, 84.3%) as a dark oil which was used for the next reaction without further purification.

To a stirred solution of the above diol **18** (335 mg, 0.74 mmol) and *p*-toluenesulfonic acid (295 mg, 1.55 mmol) in methylene chloride (5 mL) at 0 °C was added dropwise acetic anhydride (0.20 mL, 2.13 mmol) and the reaction mixture was stirred at 0 °C for 3 h. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane/ethyl acetate=2/1) to give **6d** (385 mg, 97%) as a yellow oil: IR ν_{max}^{neat} 3255, 2923, 1735, 1498, 1236, 1162 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.83–1.87 (1H, m), 1.95 (3H, s), 2.06 (3H, s), 2.38 (3H, s), 2.67 (1H, dt, J=8.1, 14.8 Hz), 4.55 (2H, d, J=7.1 Hz), 5.03 (2H, s), 5.07–5.14 (1H, m), 5.29 (1H, dd, J=4.4, 9.5 Hz), 5.54 (1H, dt, J=6.8, 10.9 Hz), 6.92 (1H, d, J=2.9 Hz), 7.23 (1H, d, J=8.1 Hz), 7.29 (2H, dd, J=1.2, 7.8 Hz), 7.32–7.43 (7H, m), 7.61 (1H, s), 7.61 (2H, d, J=8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 20.9, 21.4, 32.2, 60.1, 70.2, 70.4, 113.8, 115.4, 126.7, 127.1, 127.5, 128.1, 128.6, 128.8, 129.2, 129.6, 135.5, 136.3, 137.0, 143.5, 157.6, 170.8, 171.4. MS: *m/z* 537 (M^+). HRMS Calcd for $C_{37}H_{35}NO_5Si$: 537.1821 (M^+). Found: 537.1803.

4.2.12. 6-Benzyloxy-1-(4-methylbenzenesulfonyl)-2-vinyl-1,2,3,4-tetrahydroquinolin-4-ol (19a). To a stirred solution of $Pd(dba)_2$ (197 mg, 0.34 mmol) in THF (35 mL) was added tri*n*-buthylphosphine (0.17 mL, 0.68 mmol) at 0 °C under argon atmosphere and the reaction mixture was degassed by three freeze-thaw cycles and stirred at 0 °C for 30 min. Allyl acetate **6a** (1.706 g, 3.4 mmol) in THF (10 mL) and AcOH (0.21 mL, 3.7 mmol) were added to the reaction mixture at 0 °C. The reaction mixture was degassed again by three freeze-thaw cycles, warmed to room temperature, and stirred for 17 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane/ethyl acetate=3/2) to give cyclized product **19a** (1.428 g, 95.7%, *cis*/*trans*=3:1) as a colorless oil. Major product: IR ν_{max}^{neat} 3504, 3032, 1606, 1487 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.60 (1H, dt, J=8.0, 16.0 Hz), 2.14 (1H, ddd, J=4.7, 7.0, 13.3 Hz), 2.37 (3H, s), 3.64–3.76 (1H, m), 4.76–4.81 (1H, m), 5.11 (2H, ABq, J=11.6 Hz), 5.12 (1H, d, J=10.5 Hz), 5.32 (1H, dq, J=1.1, 17.0 Hz), 5.87 (1H, ddd. J=4.8, 10.4, 17.0 Hz), 6.93 (1H, d, J=3.0, 8.9 Hz), 6.98 (1H, d, J=2.2 Hz), 7.15 (2H, d, J=7.9 Hz), 7.33–7.44 (7H, m), 7.66 (1H, d, J=8.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 38.8, 55.3, 64.7, 70.2, 76.7, 77.0, 77.3, 110.9, 114.4, 115.5, 126.7, 127.0, 127.5, 128.0, 128.5, 129.6, 135.8, 136.7, 138.0, 138.1, 143.7, 157.0. MS: *m/z* 435 (M^+). HRMS Calcd for $C_{25}H_{25}O_4NS$: 435.1504. Found: 435.1490.

4.2.13. 4,6-(Di-*tert*-butyldimethylsiloxy)-1-(4-methylbenzenesulfonyl)-2-vinyl-1,2,3,4-tetrahydroquinoline (19c). To a stirred solution of $Pd(dba)_2$ (1 mg, 0.0018 mmol) in THF (1 mL) was added tri*n*-buthylphosphine (0.7 μL, 0.0036 mmol) at −15 °C under argon atmosphere and the reaction mixture was degassed by three freeze-thaw cycles and stirred at −15 °C for 30 min. **6c** (22.2 mg, 0.035 mmol) in THF (1 mL) was added to the reaction mixture at −15 °C. The reaction mixture was degassed again by three freeze-thaw cycles, warmed to room temperature, and stirred for 12 h. After the reaction was completed, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane/ethyl acetate=12/1) to give **19c** (18.5 mg, 92%) as yellow crystals: mp 78–80 °C; IR ν_{max}^{neat} 3448, 2952, 1485 cm^{-1}; ^1H NMR ($CDCl_3$) δ −0.16 (6H, s), 0.19 (6H, s), 0.84 (9H, s), 0.98 (9H, s), 1.42 (1H, dt, J=11.4, 11.8 Hz), 2.19 (1H, ddd, J=4.3, 8.0, 12.5 Hz), 2.37 (3H, s), 3.19 (1H, dd, J=11.6, 4.3 Hz), 4.56–4.62 (1H, m), 5.14 (1H, dd, J=11.5, 1.0 Hz), 5.35 (1H, dd, J=1.0, 17.1 Hz), 5.83–5.88 (1H, m), 6.73 (1H, d, J=2.7 Hz), 6.76 (1H, dd, J=2.7, 8.5 Hz), 7.15 (2H, d, J=8.0 Hz), 7.31 (2H, d, J=8.0 Hz), 7.33–7.44 (2H, m), 7.51 (1H, d, J=8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.4, −4.5, −4.4, 18.0, 18.3, 21.5, 25.6, 25.7, 41.3, 56.1, 65.5, 114.5, 114.8, 119.1, 126.6, 127.0,

129.5, 135.7, 138.6, 141.5, 143.5, 154.3. MS (FAB): *m/z* 575 ($M+H^+$). Anal. Calcd for $C_{30}H_{47}NO_4SSi_2$: C, 62.78; H, 8.25; N, 2.44. Found: C, 62.49; H, 8.38; N, 2.33.

4.2.14. 6-Benzyloxy-4-(*tert*-butyldimethylsiloxy)-1-(4-methylbenzenesulfonyl)-2-vinyl-1,2,3,4-tetrahydroquinoline (19e). To a stirred solution of $Pd(dba)_2$ (127 mg, 0.22 mmol) in THF(15 mL) was added tri*n*-buthylphosphine (0.11 mL, 0.44 mmol) at 0 °C under argon atmosphere and the reaction mixture was degassed by three freeze-thaw cycles and stirred at 0 °C for 30 min. **6e** (1.357 g 2.22 mmol) in THF (7 mL) was added to the reaction mixture at 0 °C. The reaction mixture was degassed again by three freeze-thaw cycles, warmed to room temperature, and stirred for 16 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane/ethyl acetate=10/1 to 3/1) to give the title compound **19e** (1.169 g, 95.6%) as a yellow oil: IR ν_{max} 2952, 2927, 2856, 1486, 1353, 1159 cm^{-1}; ^1H NMR ($CDCl_3$) δ −0.009 (6H, s), 0.838 (9H, s), 1.43 (1H, dt, J=11.5, 12.9 Hz), 2.19 (1H, ddd, J=4.2, 8.1, 12.4 Hz), 2.36 (3H, s), 3.25 (1H, dd, J=3.9, 11.2 Hz), 4.57–4.63 (1H, m), 5.06 (2H,s), 5.12 (1H, d, J=10.2 Hz), 5.34 (1H, d, J=17.1 Hz), 5.85 (1H, ddd, J=5.4, 10.2, 16.8 Hz), 6.86 (1H, d, J=2.9 Hz), 6.91 (1H, dd, J=2.63, 8.53 Hz), 7.16 (2H, d, J=7.8 Hz), 7.31–7.49 (7H, m), 7.56 (1H, d, J=8.78 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.46, −5.41, 17.9, 21.3, 25.5, 41.1, 55.8, 65.5, 69.9, 108.9, 113.7, 114.7, 126.1, 126.8, 127.3, 127.8, 128.2, 128.2, 128.4, 128.8, 129.4, 135.6, 136.7, 138.4, 141.4, 143.4, 157.2. MS: *m/z* 549 (M^+). HRMS Calcd for $C_{31}H_{39}NO_4SSi$: 549.2369 (M^+). Found: 549.2359.

4.2.15. 6-Benzyloxy-1-(4-methylbenzenesulfonyl)-2-vinyl-2,3-dihydro-1*H*-quinolin-4-one (20). To a stirred solution of **19a** (64 mg, 0.15 mmol) in CH_2Cl_2 (1 mL) at room temperature was added pyridinium dichromate (66.3 mg, 0.176 mmol) under argon atmosphere and the reaction mixture was stirred at room temperature. After 15 h, magnesium sulfate was added to the reaction mixture and the insoluble material was filtered through silica gel. The filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane/ethyl acetate=3/1) to give quinolone **20** (62 mg, 97.3%) as brown solids: mp 92–96 °C; IR ν_{max}^{KBr} 3032, 1691, 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.37–2.43 (1H, m), 2.39 (3H, s), 2.53 (1H, dd, J=1.8, 17.9 Hz), 5.06 (2H, s), 5.13 (1H, ddd, J=2.2, 6.8 Hz), 5.16 (1H, d, J=2.0 Hz), 5.26–5.29 (1H, m), 5.78 (1H, dd, J=4.2, 10.7, 17.3 Hz), 7.82 (1H, d, J=9.0 Hz), 7.21–7.52 (11H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 391, 56.8, 70.3, 76.7, 77.0, 77.3, 110.1, 118.4, 123.1, 126.7, 126.9, 127.5, 127.9, 128.1, 128.5, 130.0, 133.5, 135.3, 136.1, 136.4, 144.4, 156.5, 191.8. MS: *m/z* 434 (M^+). HRMS Calcd for $C_{25}H_{24}O_4NS$: 434.1426. Found: 434.1434.

4.2.16. 6-Benzyloxy-3-methylene-1-(4-methylbenzenesulfonyl)-2-vinyl-2,3-dihydro-1*H*-quinolin-4-one. To a stirred mixture of paraformaldehyde (7 mg, 0.23 mmol) and *N*-methylaniline trifluoroacetate (TFA·PhNHMe, 19 mg, 0.086 mmol) in 1,4-dioxane (0.5 mL) at room temperature was added **20** (25 mg, 0.057 mmol) in 1,4-dioxane (0.5 mL) under argon atmosphere and the reaction mixture was stirred at reflux for 8 h. A second portion of paraformaldehyde (5.5 mg, 0.18 mmol) and TFA·PhNHMe (38 mg, 0.17 mmol) was added again to the reaction mixture. After stirring the mixture for 25 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane/ethyl acetate=6/1) to give the title compound (21.7 mg, 84.7%) as yellow solids; mp 104–106 °C; IR ν_{max}^{KBr} 3088, 3032, 2924, 1680, 1602, 1485, 1166 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.33 (3H, s), 5.03 (1H, dd, J=2.2, 17.3 Hz), 5.08 (2H, ABq), 5.12 (1H, dd, J=2.2, 10.5 Hz), 5.33 (1H, s), 5.68 (1H, br), 5.85 (1H, ddd, J=3.4, 10.3, 17.3 Hz), 6.11 (1H, s), 7.07 (2H, d, J=8.0 Hz), 7.24 (2H, d, J=8.3 Hz), 7.25 (1H, dd, J=3.1, 8.8 Hz), 7.35–7.44 (6H, m), 7.74 (1H, d, J=9.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 62.4, 70.3, 110.9, 118.6, 122.8, 125.5, 127.6, 127.8, 128.2, 128.6, 129.0, 129.4, 129.7, 133.3, 134.2, 136.1, 136.2, 138.6, 144.2, 157.5, 181.6. MS: *m/z* 445 (M^+). HRMS Calcd for $C_{26}H_{24}NO_4S$: 446.1426 ($M+H^+$). Found: 446.1416.

4.2.17. [6-Benzyloxy-4-oxo-1-(4-methylbenzenesulfonyl)-2-vinyl-1,2,3,4-tetrahydroquinolin-3-yl]acetonitrile (22). To a stirred solution of 6-benzyloxy-3-methylene-1-(4-methylbenzenesulfonyl)-2-vinyl-2,3-dihydro-1H-quinolin-4-one (147 mg, 0.34 mmol) in ethanol (10 mL) at room temperature was added KCN (43.8 mg, 0.673 mmol) in water (0.4 mL) and acetic acid (0.026 mL, 0.47 mmol). After stirring the reaction mixture at room temperature for 7 h, the reaction mixture was concentrated in vacuo. The residue was diluted with ethyl acetate, washed with water and saturated brine, dried over sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane/ethyl acetate=7/2) to give **22** (110 mg, 70.5%) as a brown oil: IR ν_{max}^{neat} 2924, 2250, 1690, 1488, 1164 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.17 (1H, dd, J=10.7, 17.4 Hz), 2.42 (3H, s), 2.70 (1H, ddd, J=4.2, 10.0, 16.5 Hz), 2.97 (1H, dd, J=4.39, 17.3 Hz), 5.03 (1H, dd, J=2.7, 10.2 Hz), 5.07 (2H, s), 5.30–5.36 (2H, m), 5.54–5.62 (1H, m), 7.30 (2H, d, J=8.3 Hz), 7.34–7.48 (7H, m), 7.65 (2H, d, J=8.31 Hz), 7.84 (1H, d, J=9.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.7, 21.5, 44.7, 61.6, 70.3, 110.5, 117.1, 123.0, 123.9, 124.6, 126.8, 127.0, 127.5, 128.2, 128.3, 128.6, 130.3, 133.7, 135.9, 136.5, 144.8, 156.3, 190.3. MS: *m/z* 472 (M^+). HRMS Calcd for $C_{27}H_{24}N_2O_4S$: 472.1457 (M^+). Found: 472.1447.

4.2.18. 8-Benzyloxy-4-ethyl-5-(4-methylbenzenesulfonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline (23a) and 8-hydroxy-4-ethyl-5-(4-methylbenzenesulfonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline (23b). To a stirred solution of **22** (9 mg, 0.019 mmol) in ethanol (2 mL) at room temperature was added Raney Ni (300 mg) and the reaction mixture was stirred under hydrogen atmosphere. After 48 h, the reaction mixture was filtered through celite and concentrated in vacuo to afford the crude cyclic imine (11 mg). The crude imine was dissolved in MeOH (2 mL) and sodium cyanoborohydride (3 mg, 0.048 mmol) was added at room temperature under

argon atmosphere. The reaction mixture was acidified to pH 4 with 2 N HCl. After stirring the mixture for 3 h, the reaction mixture was concentrated in vacuo, quenched with 0.1 N KOH, and extracted with ether. The organic layer was washed with water and saturated brine, dried over sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, $CHCl_3$/MeOH=20/1 containing 1% triethylamine) to give pyrroloquinoline **23a** (5 mg, 56.7%) as a colorless oil and debenzylated pyrroloquinoline **23b** (2 mg, 28.2%) as a colorless oil. **23a**: IR ν_{max}^{neat} 2926, 1491, 1162 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88–0.96 (3H, m), 1.25–1.31 (1H, m), 1.37–1.47 (1H, m), 1.85–1.88 (1H, m), 2.33–2.41 (1H, m), 2.37 (3H, s), 2.75 (1H, dt, J=5.3, 10.7 Hz), 2.95–3.04 (1H, m), 3.29 (1H, d, J=8.1 Hz), 4.24–4.30 (1H, m), 5.04 (2H, s), 6.92 (1H, dd, J=2.4, 8.8 Hz), 7.06 (1H, br), 7.15 (2H, d, J=9.0 Hz), 7.31–7.46 (6H, m), 7.62 (2H, d, J=9.0 Hz). MS: m/z 462 (M^+). HRMS (FAB, NBA) Calcd for $C_{27}H_{30}N_2O_3S$: 463.2065 ($M+H^+$). Found: 463.2070. **23b**: ^1H NMR ($CDCl_3$) δ 0.81–0.94 (3H, m). 1.25–1.35 (1H, m), 1.45–1.53 (1H, m), 1.70–1.80 (1H, m), 1.95–2.04 (1H, m), 2.37 (3H, s), 2.91–3.01 (1H, m), 3.13–3.20 (1H, m), 3.66 (1H, d, J=8.5 Hz), 4.21–4.24 (1H, m), 6.79 (1H, dd, J=2.7, 9.0 Hz), 7.10 (1H, br), 7.14 (2H, d, J=8.1 Hz), 7.38 (2H, d, J=8.3 Hz), 7.55 (1H, d, J=8.8 Hz). MS: m/z 372 (M^+). HRMS (FBA, NBA) Calcd for $C_{20}H_{25}N_2O_3S$: 373.1586 ($M+H^+$). Found: 373.1594.

Acknowledgements

This work was financially supported in part by a Grant-in-Aid for Scientific Research (C) from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

References and notes

1. Witherup, K. M.; Ransom, R. W.; Graham, A. C.; Bernard, A. M.; Salvature, M. J.; Lumma, W. C.; Anderson, P. S.; Pitzewberger, S. M.; Verga, S. L. *J. Am. Chem. Soc.* **1995**, *117*, 6682–6685.
2. (a) Ma, D.; Xia, C.; Jiang, J.; Zhang, J. *Org. Lett.* **2001**, *3*, 2189. (b) Hadden, M.; Nieuwenhuyzen, M.; Osborne, D.; Stevenson, P. J.; Thompson, N. *Tetrahedron Lett.* **2001**, *42*, 6417. (c) Snider, B. B.; Ahn, Y.; O'Hare, S. M. *Org. Lett.* **2001**, *3*, 4217. (d) Powell, D. A.; Batey, R. A. *Org. Lett.* **2002**, *4*, 2913–2916. (e) Xia, C.; Heng, L.; Ma, D. *Tetrahedron Lett.* **2002**, *43*, 9405–9409. (f) Ma, D.; Xia, C.; Jiang, J.; Zhang, J.; Tang, W. *J. Org. Chem.* **2003**, *68*, 442–451.
3. (a) Ho, T. C. T.; Jones, K. *Tetrahedron* **1997**, *53*, 8287–8294. (b) Gurjar, M. K.; Pal, S.; Rama Rao, A. V. *Heterocycles* **1997**, *45*, 231–234. (c) Kim, S. S.; Cheon, H. G.; Kang, S. K.; Yum, E. K.; Choi, J. K. *Heterocycles* **1998**, *48*, 221–226. (d) Hadden, M.; Stevenson, P. J. *Tetrahedron Lett.* **1999**, *40*, 1215–1218. (e) Batey, R. A.; Simoncic, P. D.; Lin, D.; Smyj, R. P.; Lough, A. J. *Chem. Commun.* **1999**, 651–652. (f) Lovely, C. J.; Mahmud, H. *Tetrahedron Lett.* **1999**, *40*, 2079–2082. (g) Snider, B. B.; Ahn, Y.; Foxman, B. M. *Tetrahedron Lett.* **1999**, *40*, 3339–3342. (h) Frank, K. E.; Aube, J. *J. Org. Chem.* **2000**, *65*, 655–666. (i) Nieman, J. A.; Ennis, M. D. *Org. Lett.* **2000**, *2*, 1395–1397. (j) Nyerges, M.; Fejes, I.; Toke, L. *Tetrahedron Lett.* **2000**, *41*, 7951–7954. (k) Mahmud, H.; Lovely, C. J.; Dias, H. V. R. *Tetrahedron* **2001**, *57*, 4095–4105. (l) Hadden, M.; Nieuwenhuyzen, M.; Potts, D.; Stevenson, P. J.; Thompson, N. *Tetrahedron* **2001**, *57*, 5615–5624. (m) Hadden, M.; Nieuwenhuyzen, M.; Osborne, D.; Stevenson, P. J.; Thompson, N. *Tetrahedron Lett.* **2001**, *42*, 6417–6419. (n) Batey, R. A.; Powell, D. A. *Chem. Commun.* **2001**, 2362–2363. (o) He, Y.; Mahmud, H.; Wayland, B. R.; Dias, H. V. R.; Lovely, C. J. *Tetrahedron Lett.* **2002**, *43*, 1171–1174. (p) Malassene, R.; Sanchez-Bajo, L.; Toupet, L.; Hurvois, J.; Moinet, C. *Synlett* **2002**, 1500–1504. (q) Nyerges, M.; Fejes, I.; Toke, L. *Synthesis* **2002**, 1823–1828.
4. Hamada, Y.; Kunimune, I.; Hara, O. *Heterocycles* **2002**, *56*, 97–100.
5. (a) Hamada, Y.; Seto, N.; Ohmori, H.; Hatano, K. *Tetrahedron Lett.* **1996**, *37*, 7565–7568. (b) Hamada, Y.; Seto, N.; Takayanagi, Y.; Nakano, T.; Hara, O. *Tetrahedron Lett.* **1999**, *40*, 7791–7794.
6. (a) McNeill, A. H.; Thomas, E. J. *Tetrahedron Lett.* **1990**, *31*, 6239. (b) Mortlock, S. V.; Thomas, E. J. *Tetrahedron Lett.* **1988**, *29*, 2479–2482.
7. (a) Cannon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900–1923. (b) Joelle, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 2826–2830.
8. (a) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 5426–5427. (b) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 7324–7325.
9. Hoye, T. R.; Promo, M. A. *Tetrahedron Lett.* **1999**, *40*, 1429–1432.
10. Gillard, J. W.; Fortin, R.; Morton, H. E.; Yoakim, C.; Quesnelle, C. A.; Daignault, S.; Guindon, Y. *J. Org. Chem.* **1988**, *53*, 2602–2608.
11. (a) Gras, J. *Org. Synth.* **1982**, *60*, 88–91. (b) Gras, J. *Tetrahedron Lett.* **1978**, *24*, 2111–2114.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 60 (2004) 9391–9396

Copper carbenoid mediated *N*-alkylation of imidazoles and its use in a novel synthesis of bifonazole

Erick Cuevas-Yañez,[a,*] Juan Manuel Serrano,[a] Gloria Huerta,[a] Joseph M. Muchowski[b] and Raymundo Cruz-Almanza[a,†]

[a]*Instituto de Química,UNAM. Circuito Exterior, Ciudad Universitaria, Coyoacán 04510 Mexico, D.F., Mexico*
[b]*Chemistry, Roche Palo Alto, 3431 Hillview Avenue, Palo Alto, CA 94304-1320, USA*

Received 10 June 2004; revised 5 August 2004; accepted 5 August 2004

Available online 3 September 2004

Abstract—1*H*-Imidazoles are readily *N*-alkylated by a $Cu(acac)_2$ mediated reaction with α-diazocarbonyl compounds or with diazoalkanes generated in situ from the corresponding *p*-toluensulfonyl hydrazones. The antifungal agent bifonazole was prepared by the latter method.
© 2004 Elsevier Ltd. All rights reserved.

1. Introduction

Whereas the reactions of α-diazocarbonyl derived carbenoids with monoheteroatomic aromatic systems including for example, furans,[1] pyrroles,[2] thiophenes,[3] indoles,[4] and benzofurans,[5] have been studied in some detail, those with diheteroatomic aromatic systems have been less frequently examined. One instance of an intermolecular reaction of a rhodium α-ketocarbenoid with an isoxazole has been reported,[6] and Pellicciari, et al. have described the *N*-alkylation of imidazoles and benzimidazoles with α-diazocarbonyl compounds through the copper–bronze catalyzed[7] or the photolytically generated α-ketocarbenoids.[8]

Given the frequent occurrence of the imidazole moiety in compounds of medicinal importance, especially in many broad spectrum antifungal agents,[9] we decided to take another look at the carbenoid mediated *N*-alkylation reactions of imidazoles. The ultimate intention of this study was to attempt to use such methodology to prepare some of the more common imidazole containing antifungal agents, for example, bifonazole, for which several syntheses have already been reported.[10]

Our intitial studies, which were carried out on ethyl diazoacetate and imidazole using catalytic rhodium(II) acetate[11] under various conditions, consistently failed to provide any *N*-alkylated imidazole, even though the diazo compound was consumed. In contrast, copper(II) acetylacetonate, which has been utilized to generate ammonium ylides from α-diazocarbonyl compounds,[12,13] immediately showed promise.

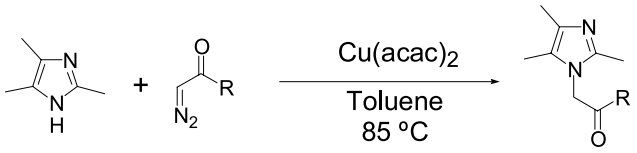
After some experimentation, the following protocol was found to be particularly effective for the generation of ethyl *N*-imidazole acetate **1**. A toluene solution of ethyl diazoacetate (1.2 equiv) was added dropwise (1 h) to a mixture of imidazole and $Cu(acac)_2$ (10 mol%) in toluene at 85 °C. The mixture was heated to reflux for 1 h, the solvent was removed in vacuo, and following chromatographic purification on silica gel, the *N*-alkylated imidazole **1** was obtained in 60% yield. In the same way, imidazole, substituted imidazoles, and benzimidazole, all were readily *N*-akylated, not only with ethyl diazoacetate, but with various α-diazoketones as well (Table 1). The noteworthy features of this process are its generality, and the economy in the use of both reagents.

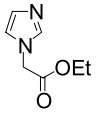
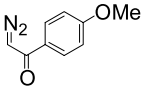
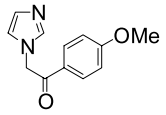
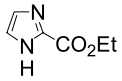
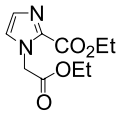
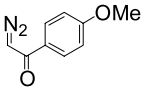
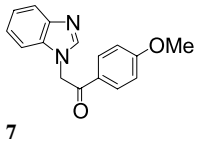
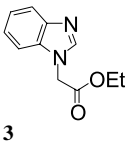
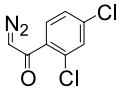
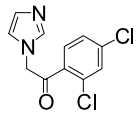
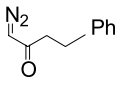
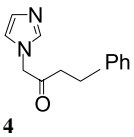
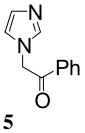
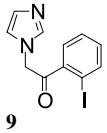
The combination of in situ generation of diazoalkanes, from aldehyde or ketone *p*-toluenesulfonylhydrazones, with transition metal catalyzed processes, has recently been successfully utilized by several groups of investigators.[14] We have devised an adaptation of these procedures to the synthesis of *N*-alkylimidazoles (see Scheme 1). Thus, tetrahydrofuran solutions of various *p*-toluenesulfonylhydrazones were converted into the sodium salts with sodium hydride, and then tetra-*n*-butylammonium bromide (0.125 equiv), imidazole (1 equiv), $Cu(acac)_2$, and toluene (to allow for a 15 mL/mmol solution of the diazo compound) were added, and the mixture was stirred at 85 °C for 24 h. In this way, imidazole, substituted

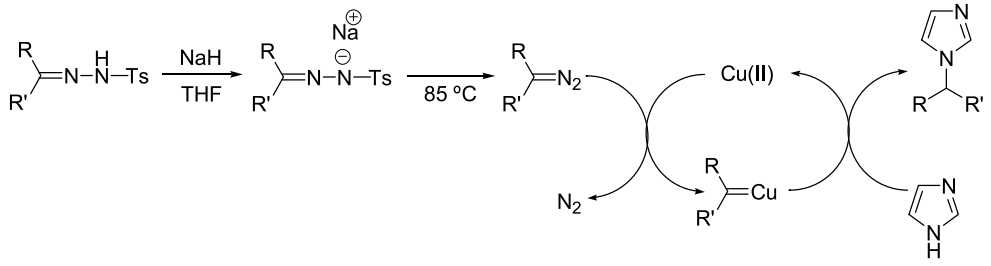
Keywords: Copper; Carbenoid; Imidazole; Bifonazole.
* Corresponding author. Tel.: +52-56-22-44-08; fax: +52-56-16-22-17; e-mail: erick.cuevas@correo.unam.mx
† Deceased. October 2003.

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.08.009

Table 1. *N*-alkylation products from α-diazo compounds, copper(II) acetylacetonate and diverse imidazoles



Imidazole	Diazo-compound	Product	Yield (%)	Imidazole	Diazocompound	Product	Yield (%)
		 **1**	71			 **6**	58
		 **2**	78			 **7**	78
		 **3**	55			 **8**	46
		 **4**	45				
		 **5**	40			 **9**	42



Scheme 1. General representation of imidazole alkylation with copper carbenoids derived from *p*-toluenesulfonylhydrazone salts.

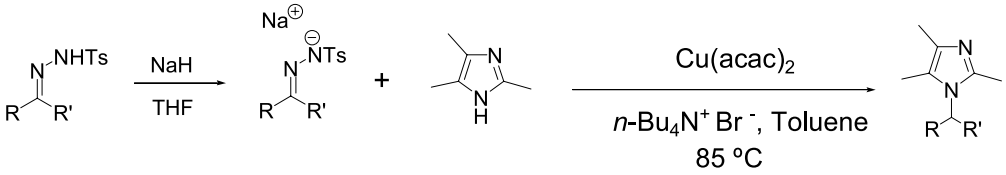
imidazoles, and benzimidazole were *N*-alkylated with mono- and diaryldiazomethanes, and diazocyclohexane (50–80% yields; Table 2). The antifungal agent Bifonazole **22** was also prepared in this manner (52% yield).

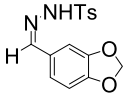
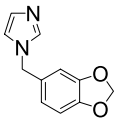
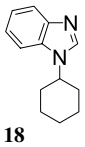
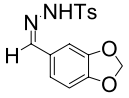
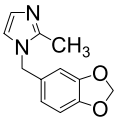
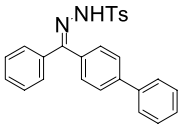
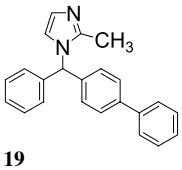
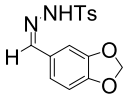
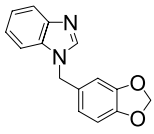
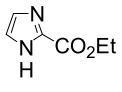
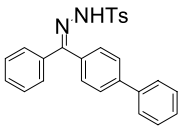
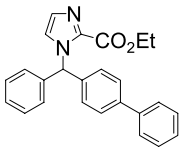
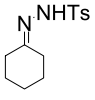
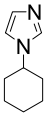
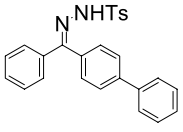
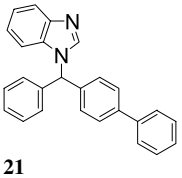
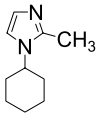
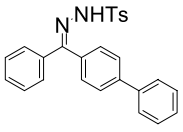
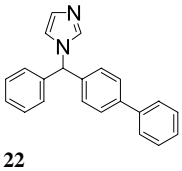
In summary, imidazoles, and benzimidazole are readily *N*-alkylated by a copper(acac)$_2$ catalyzed reaction with α-diazocarbonyl compounds or by diazoalkanes generated in situ from aldehyde or ketone *p*-touenesulfonylhydrazones. The latter one-pot procedure eliminates the need to isolate these potentially hazardous diazoalkanes. Both of the above processes make many *N*-substituted imidazoles easily available, and they represent a clearly viable alternative routes to the usual method of generation of these substances by alkylation of the imidazolyl anions with alkyl halides.

2. Experimental

The starting materials were purchased from Aldrich Chemical Co. and were used without further purification. Diazoketones were prepared from the corresponding acid

Table 2. *N*-alkylation products from *p*-toluenesulfonylhydrazones, copper(II) cetylacetonate and diverse imidazoles



Imidazole	Tosythydrazone	Product	Yield (%)	Imidazole	Tosythydrazone	Product	Yield (%)
			65				58
	10	**13**				**18**	
			75				64
	14				**12**	**19**	
			80				67
	15					**20**	
			55				76
	11	**16**				**21**	
			50				52
	17					**22**	

chlorides and excess ethereal diazomethane[15] or from carboxylic acids with triphenylphosphine, NBS and excess ethereal diazomethane.[16] Solvents were distilled before use; ether and tetrahydrofuran (THF) were dried over sodium using benzophenone as indicator. Diazomethane was prepared from *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (Diazald®) using a minimun amount of water and ethanol as cosolvent, and dried over KOH pellets before use. Silica gel (230–400 mesh) and neutral alumina were purchased from Merck. Silica plates of 0.20 mm thickness were used for thin layer chromatography. Melting points were determined with a Fisher–Johns melting point apparatus and they are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded using a Varian Gemini 200, the chemical shifts (δ) are given in ppm relative to TMS as internal standard (0.00). For analytical purposes the mass spectra were recorded on a JEOL JMS-5X 10217 in the EI mode, 70 eV, 200 °C via direct inlet probe. Only the molecular and parent ions (*m*/*z*) are reported. IR spectra were recorded on a Nicolet Magna 55-X FT instrument.

2.1. Insertion of α-diazoketones to imidazoles

Typical procedure. To a solution of imidazole (1 mmol) and $Cu(acac)_2$ (0.026 g, 0.1 mmol) in toluene (5 mL) at 85 °C under a nitrogen atmosphere was added a solution of diazoketone (1.2 mmol) in toluene (8 mL) via syringe pump over 1 h and the mixture was heated at 85 °C for additional 2 h. The mixture was allowed to cool to room temperature. The solvent was removed in vacuo and the product was purified by column chromatography (Al_2O_3 activity III, hexane/AcOEt 9:1).

2.1.1. Imidazol-1-yl acetic acid ethyl ester (1). Colorless oil[17] (71%). IR (film, cm^{-1}) 2979, 1745, 1507; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.29 (t, 3H), 4.24 (q, 2H), 4.70 (s, 2H),

6.96 (d, 1H), 7.10 (d, 1H), 7.52 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.1, 48.0, 62.3, 119.1, 129.4, 137.3, 167.3; MS [EI+] *m/z* (RI%): 154 $[M]^+$ (65), 81 $[M-CO_2Et]^+$ (100).

2.1.2. 1-Ethoxycarbonylmethylimidazole-2-carboxylic acid ethyl ester (2). Colorless oil (68%). IR (film, cm^{-1}) 2975, 1747, 1713; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.14 (t, 3H), 1.28 (t, 3H), 4.25 (q, 2H), 4.39 (q, 2H), 5.13 (s, 2H), 7.07 (d, 1H), 7.22 (d, 1H,); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.1, 14.4, 49.8, 59.2, 61.6, 115.0, 126.6, 142.7, 160.6, 167.3; MS [EI+] *m/z* (RI%): 226 $[M]^+$ (46), 82 $[M-C_6H_8O_4]^+$ (100); HRMS (FAB^+): for $C_{10}H_{15}N_2O_4$ calcd 227.1032, found 227.1039.

2.1.3. Benzoimidazol-1-yl acetic acid ethyl ester (3). White solid (55%), mp 61–62 °C (lit. 61–63 °C).[18] IR (film, cm^{-1}) 2977, 1743; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 1.21 (t, 3H), 4.17 (q, 2H), 5.25 (s, 2H), 7.25 (m, 2H), 7.6 (m, 2H), 8.21 (s, 1H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 14.1, 45.8, 61.8, 110.4, 119.6, 121.6, 122.4, 143.5, 144.6, 168.5; MS [EI+] *m/z* (RI%): 204 $[M]^+$ (27), 131 $[M-CO_2Et]^+$ (100).

2.1.4. 1-Imidazol-1-yl-4-phenylbutan-2-one (4). Colorless oil (45%). IR ($CHCl_3$, cm^{-1}) 2966, 1738; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 2.81 (s, 4H), 5.01 (s, 2H), 6.89 (s, 1H), 7.05 (s, 1H), 7.24 (m, 5H), 7.50 (s, 1H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 28.5, 54.6, 120.6, 125.9, 128.1, 128.3, 138.0, 140.8, 203.8; MS [FAB+] *m/z* (RI%): 215 $[M+1]^+$ (100); HRMS (FAB^+): for $C_{13}H_{15}N_2O$ calcd 215.1184, found 215.1189.

2.1.5. 2-Imidazol-1-yl-1-phenylethanone (5). White solid (40%), mp 118 °C (lit. 117–118 °C).[19] IR ($CHCl_3$, cm^{-1}) 2962, 1707; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 5.74 (s, 2H), 6.92 (s, 1H), 7.12 (s, 1H), 7.54 (m, 5H), 8.04 (s, 1H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 52.5, 120.8, 127.95, 128.9, 133.9, 134.4, 138.4, 193.5; MS [EI+] *m/z* (RI%): 186 $[M]^+$ (22), 105 $[C_6H_5CO]^+$ (100).

2.1.6. 2-Imidazol-1-yl-1-(4-methoxyphenyl)ethanone (6). (58%), mp 120–121 °C. IR ($CHCl_3$, cm^{-1}) 2968, 1697; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 3.90 (s, 3H), 5.44 (s, 2H), 6.84 (d, 1H), 7.0 (d, 2H), 7.20 (d, 1H), 7.58 (s, 1H), 7.97 (d, 2H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 51.7, 55.1, 113.3, 113.7, 126.7, 129.8, 163.8, 189.8; MS [FAB+] *m/z* (RI%): 217 $[M+1]^+$ (100); HRMS (FAB^+): for $C_{12}H_{13}N_2O_2$ calcd 217.0977, found 217.0981.

2.1.7. 2-Benzimidazol-1-yl-1-(4-methoxyphenyl)ethanone (7). White solid (78%), mp 133–135 °C. IR ($CHCl_3$, cm^{-1}) 2970, 1696; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 3.91 (s, 3H), 5.95 (s, 2H), 7.14 (d, 2H), 7.21 (m, 2H), 7.49 (m, 1H), 7.68 (m, 1H), 8.09 (d, 2H), 8.17 (s, 1H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 50.3, 55.6, 110.4, 114.1, 119.2, 121.3, 122.1, 127.3, 130.46, 134.5, 143.1, 144.9, 163.7, 191.5; MS [FAB+] *m/z* (RI%): 267 $[M+1]^+$ (75); HRMS (FAB^+): for $C_{16}H_{15}N_2O_2$ calcd 267.1134, found 267.1139.

2.1.8. 1-(2,4-Dichlorophenyl)-2-imidazol-1-ylethanone (8). White solid (46%), mp 169–170 °C. IR ($CHCl_3$, cm^{-1}) 2929, 1715; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 5.03 (s, 2H), 6.92 (s, 1H), 7.04 (s, 1H), 7.30 (m, 1H), 7.43 (m, 1H), 7.49 (s, 1H), 7.78 (m, 1H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 58.3, 122.6, 125.9, 126.9, 129.2, 131.4, 135.3, 139.6, 139.8, 194.7; MS [FAB+] *m/z* (RI%): 255 $[M+1]^+$ (15); HRMS (FAB^+): for $C_{11}H_9Cl_2N_2O$ calcd 255.0092, found 255.0998.

2.1.9. 2-Imidazol-1-yl-1-(2-iodophenyl)ethanone (9). White solid (42%), mp 142–143 °C. IR (film, cm^{-1}) 2961, 1687; ^{1}H NMR (DMSO-d_6, 200 MHz) 5.56 (s,2H), 7.32 (m, 2H), 7.57 (m, 2H), 7.84 (m, 2H), 8.03 (m, 1H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 54.1, 92.6, 128.3, 128.9, 131.3, 133.0, 138.6, 138.8, 140.2, 140.7, 197.5; MS [FAB+] *m/z* (RI%): 313 $[M+1]^+$ (100); HRMS (FAB^+): for $C_{11}H_{10}IN_2O$ calcd 312.9838, found 312.9841.

2.2. Preparation of *p*-toluenesulfonylhydrazones

Typical procedure. A solution of the *p*-toluenesulfonhydrazide (4.46 g, 24 mmol) and the appropriate carbonyl compound (20 mmol) in Me OH (50 mL) and 10% HCl (0.1 mL) was heated at reflux for 24 h. The reaction mixture was cooled to room temperature, the final product was filtered and purified by crystallization.

2.2.1. *p*-Toluenesulfonylhydrazone of benzo[1,3]dioxole-5-carbaldehyde (10). White solid (95%), mp 143–145 °C. IR (film, cm^{-1}) 3195, 2989, 1597, 1163; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.37 (s, 3H), 5.95 (s, 2H), 6.69 (m, 1H), 6.89 (m, 1H), 7.15, (m, 1H), 7.29 (d, 2H), 7.70 (s, 1H), 7.86 (d, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.5, 101.4, 105.6, 108.0, 123.7, 127.7, 127.8, 129.6, 135.2, 144.0, 148.0, 148.1, 149.6; MS [EI+] *m/z* (RI%): 318 $[M]^+$ (40), 91 $[C_6H_4CH_3]^+$ (100); HRMS (FAB^+): for $C_{15}H_{15}N_2O_4S$ calcd 319.0753, found 319.0755.

2.2.2. *p*-Toluenesulfonylhydrazone of -cyclohexanone (11). White solid (97%), mp 161–162 °C (lit. 156 °C).[20] IR ($CHCl_3$, cm^{-1}) 3302, 2942, 1639, 1162; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.57 (m, 2H),1.77 (m, 4H), 2.22 (m, 4H), 2.42 (s, 3H), 7.31 (d, 2H), 7.85 (d, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.5, 25.2, 25.6, 26.6, 26.6, 35.1, 128.0, 129.4, 135.4, 143.7, 163.2; MS [FAB+] *m/z* (RI%): 267 $[M+1]^+$ (100); HRMS (FAB^+): for $C_{13}H_{19}N_2O_2S$ calcd 267.1167, found 267.1163.

2.2.3. *p*-Toluenesulfonylhydrazone of biphenyl-4-yl-phenyl methanone (12). White solid (89%), mp 158–160 °C. IR ($CHCl_3$, cm^{-1}) 3276, 2926, 1599, 1164; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.42 (s, 3H), 7.13–7.24 (m, 2H), 7.32–7.72 (m, 14H), 7.86–7.88 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.5, 126.8, 126.9, 127.1, 127.6, 127.7, 127.8, 127.9, 128.2, 128.3, 128.8, 128.9, 129.6, 129.8, 130.1, 131.0, 135.3, 135.5, 136.4, 139.8, 140.1, 142,5, 143.0, 144.1, 153.9, 154.0; MS [FAB+] *m/z* (RI%): 427 $[M+1]^+$ (100); HRMS (FAB^+): for $C_{26}H_{23}N_2O_2S$ calcd 427.1480, found 427.1469.

2.3. Insertion of in situ generated diazoalkanes to imidazoles

Typical procedure. To a suspension of 60% NaH (0.063 g, 2.64 mmol) in THF (20 mL) was added the *p*-toluenesulfonylhydrazone (2.2 mmol). The mixture was stirred at

room temperature under a nitrogen atmosphere for 1 h and the solvent was removed in vacuo. Toluene (25 mL) was added and the suspension was treated successively with tetrabutylammonium bromide (0.080 g, 25 mmol), $Cu(acac)_2$ (0.052 g, 0.2 mmol) and the appropriate imidazole (2 mmol). The mixture was heated at 85 °C under a nitrogen atmosphere for 36 h. Then, the reaction mixture was allowed to cool to room temperature. The solvent was removed in vacuo and the product was purified by column chromatography (SiO_2, hexane/AcOEt 8:2).

2.3.1. 1-Benzo[1,3]dioxol-5-ylmethylimidazole (13). White solid (65%), mp 194–195 °C (lit. 198 °C).[21] IR (film, cm^{-1}) 2909, 1604; ^1H NMR ($CDCl_3$, 200 MHz) δ 5.14 (s, 2H), 6.08 (s, 2H), 6.84 (m, 1H), 7.07 (s, 1H), 7.20 (m, 1H), 7.25 (s, 1H), 7.44, (m, 1H), 7.59 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 51.5, 102.0, 106.8, 108.3, 119.3, 125.4, 128.6, 131.8, 137.8, 148.0, 148.3; MS [FAB+] *m/z* (RI%): 203 $[M+1]^+$ (50).

2.3.2. 1-Benzo[1,3]dioxol-5-ylmethyl-2-methylimidazole (14). White solid (75%), mp 200 °C (dec). IR (film, cm^{-1}) 2911, 1604; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.41 (s, 3H), 5.14 (s, 2H), 6.07 (s, 2H), 6.84 (m, 1H), 7.05 (s, 1H), 7.17 (m, 1H), 7.25 (s, 1H), 7.45, (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 23.8, 52.0, 102.0, 106.9, 108.2, 123.4, 125.4, 128.5, 131.8, 134.2, 148.6, 153.0; MS [FAB+] *m/z* (RI%): 217 $[M+1]^+$ (70); HRMS (FAB^+): for $C_{12}H_{13}N_2O_2$ calcd 217.0977, found 217.0974.

2.3.3. 1-Benzo[1,3]dioxol-5-ylmethylbenzimidazole (15). White solid (80%), mp 180–181 °C. IR (film, cm^{-1}) 2917, 1602; ^1H NMR ($CDCl_3$, 200 MHz) δ 5.09 (s, 2H), 5.99 (s, 2H), 6.94 (m, 1H), 7.20–7.34 (m, 3H), 7.45, (m, 1H), 7.53 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 47.9, 101.2, 106.8, 108.3, 110.8, 121.5, 124.6, 125.2, 128.5, 129.5, 131.8, 135.0, 144.6, 147.7.0, 148.0; MS [FAB+] *m/z* (RI%): 253 $[M+1]^+$ (30); HRMS (FAB^+): for $C_{15}H_{13}N_2O_2S$ calcd 253.0977, found 253.0978.

2.3.4. 1-Cyclohexylimidazole (16). Colorless oil (55%). IR (film, cm^{-1}) 2934, 2863; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.59 (m, 2H), 1.74 (m, 4H), 1.86 (m, 4H), 3.66 (m, 1H), 6.99 (s, 1H), 7.12 (s, 1H), 7.56 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.4, 24.8, 24.8, 26.9, 26.9, 35.1, 51.4, 120.0, 129.9, 137.6; MS [EI+] *m/z* (RI%): 150 $[M]^+$ (65), 67 $[M-C_6H_{11}]^+$ (100); HRMS (FAB^+): for $C_9H_{15}N_2$ calcd 151.1235, found 151.1238.

2.3.5. 1-Cyclohexyl-2-methylimidazole (17). White solid (50%), mp 66–68 °C. IR (film, cm^{-1}) 2936, 2862; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.55 (m, 2H), 1.72 (m, 4H), 1.85 (m, 4H), 2.40 (s, 3H), 3.63 (m, 1H), 6.97 (d, 1H), 7.10 (d, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.3, 21.8, 25.1, 25.1, 26.6, 26.6, 50.8, 119.4, 128.8, 136.2; MS [EI+] *m/z* (RI%): 164 $[M]^+$ (30), 81 $[M-C_6H_{11}]^+$ (100); HRMS (FAB^+): for $C_{10}H_{17}N_2$ calcd 165.1392, found 165.1391.

2.3.6. 1-Cyclohexylbenzimidazole (18). White solid (58%), mp 74–75 °C. IR (film, cm^{-1}) 2934, 2863; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.49 (m, 2H), 1.65 (m, 4H), 1.78 (m, 4H), 2.33 (s, 3H), 3.62 (m, 1H), 7.21 (m, 2H), 7.50 (m, 1H), 7.68 (m, 1H), 8.18 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.9, 25.3, 25.3, 26.5, 26.5, 50.8, 125.4, 125.6, 127.3, 128.0, 128.8, 136.2, 142.5; MS [EI+] *m/z* (RI%): 200 $[M]^+$ (40), 117 $[M-C_6H_{11}]^+$ (100); HRMS (FAB^+): for $C_{13}H_{17}N_2$ calcd 201.1392, found 201.1396.

2.3.7. 1-(Biphenyl-4-ylphenylmethyl)-2-methylimidazole (19). White solid (64%), mp 143–145 °C. IR (film, cm^{-1}) 3038, 2935; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.46 (s, 3H), 4.94 (s, 1H), 7.15–7.52 (m, 16H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.8, 58.5, 109.5, 126. 4, 126.6, 126.7, 126.8, 127.0, 127.8, 128.5, 128.6, 128.8, 129.8, 130.2, 138.3, 139.2, 139.3, 140.7, 156.2; MS [FAB+] *m/z* (RI%): 325 $[M+1]^+$ (10); HRMS (FAB^+): for $C_{23}H_{21}N_2$ calcd 325.1705, found 325.1700.

2.3.8. 1-(Biphenyl-4-ylphenylmethyl)imidazole-2-carboxylic acid ethyl ester (20). White solid (64%), mp 33–34 °C. IR (film, cm^{-1}) 2981, 1710; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.34 (t, 3H), 4.33 (q, 2H), 5.20 (s, 1H), 6.91 (d, 1H), 7.08–7.17 (m, 5H), 7.29–7.42 (m, 6H), 7.52–7.56 8m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.9, 61.2, 64.0, 124.0, 126.7, 127.1, 127.3, 127.9, 128.3, 128.5, 129.0, 136.4, 137.9, 138.9, 139.9, 140.7, 158.7; MS [FAB+] *m/z* (RI%): 383 $[M+1]^+$ (30); HRMS (FAB^+): for $C_{25}H_{23}N_2O_2$ calcd 383.1760, found 383.1750.

2.3.9. 1-(Biphenyl-4-ylphenylmethyl)benzimidazole (21). White solid (76%), mp 199–200 °C. IR (film, cm^{-1}) 3036, 2968; ^1H NMR ($CDCl_3$, 200 MHz) δ 5.23 (s, 1H), 6.77 (s, 1H), 7.17–7.57 (m, 17H), 7.86 (d, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 63.2, 120.2, 122.4, 122.9, 126.8, 126.9, 127.1, 127.2, 127.5, 127.7, 127.7, 127.8, 128.1, 128.2, 128.5, 128.6, 128.7, 128.8, 128.9, 129.1, 129.2, 129.8, 130.2, 136.8, 137.8, 139.9, 141.2, 142.4, 143.8; MS [FAB+] *m/z* (RI%): 361 $[M+1]^+$ (40); HRMS (FAB^+): for $C_{26}H_{21}N_2$ calcd 361.1705, found 361.1706.

2.3.10. Bifonazole, 1-(biphenyl-4-ylphenylmethyl)imidazole (22). White solid (52%), mp 140–141 °C. IR (film, cm^{-1}) 3028, 2924; ^1H NMR ($CDCl_3$, 200 MHz) δ 5.29 (s, 1H), 6.93 (s, 1H), 7.13–7.60 (m, 16H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 52.3, 126. 4, 126.6, 126.7, 126.8, 127.0, 127.8, 128.5, 128.6, 128.8, 129.8, 130.2, 138.3, 139.2, 139.3, 140.7, 156.2; MS [FAB+] *m/z* (RI%): 311 $[M+1]^+$ (10); HRMS (FAB^+): for $C_{22}H_{18}N_2$ calcd 311.1548, found 311.1550.

Acknowledgements

Financial support from CONACyT (no. 37312-E) is gratefully acknowledged. The authors would like to thank E. García, R. Patiño, A. Peña, E. Huerta, N. Zavala, J. Pérez and L. Velasco for the technical support.

References and notes

1. (a) Wenkert, E.; Guo, M.; Lavilla, R.; Porter, B.; Ramachandran, K.; Sheu, J. H. *J. Org. Chem.* **1990**, *55*, 6203. (b) Wenkert, E.; Decorzant, R.; Naf, F. *Helv. Chim. Acta*

1989, *72*, 756. (c) Wenkert, E.; Guo, M.; Pizzo, F.; Ramachandran, K. *Helv. Chim. Acta* **1987**, *70*, 1429.
2. (a) Jefford, C. W.; Wang, J. B. *Tetrahedron Lett.* **1993**, *34*, 3119. (b) Jefford, C. W.; Tang, Q.; Zaslona, A. *J. Am. Chem. Soc.* **1991**, *113*, 3513. (c) Jefford, C. W.; tang, Q.; Zaslona, A. *Helv. Chim. Acta* **1989**, *72*, 1749. (d) Jefford, C. W.; Kubota, T.; Zaslona, A. *Helv. Chim. Acta* **1986**, *69*, 2048.
3. (a) Yong, K.; Salim, M.; Carpeta, A. *J. Org. Chem.* **1998**, *63*, 9828. (b) Trammer, G. K.; Capretta, A. *Tetrahedron* **1998**, *54*, 15499. (c) Frampton, C. S.; Pole, D. L.; Yong, K.; Capretta, A. *Tetrahedron Lett.* **1997**, *38*, 5081. (d) Stortlor, H.; Skramstad, J.; Nordenson, S. *J. Chem. Soc., Chem Commun.* **1984**, 208.
4. (a) Gibe, R.; Kerr, M. A. *J. Org. Chem.* **2002**, *67*, 6247. (b) Muthusamy, S.; Gunanathan, C.; Arulananda, S.; Suresh, E.; Dastidar, P. *J. Chem. Soc., Chem. Commun.* **2002**, 824. (c) Salim, M.; Capretta, A. *Tetrahedron* **2000**, *56*, 8063. (d) Matsumoto, M.; Watanabe, N.; Kobayashi, H. *Heterocycles* **1987**, *26*, 1479.
5. (a) Padwa, A.; Wisnieff, T. J.; Walsh, E. J. *J. Org. Chem.* **1986**, *51*, 5036. (b) Padwa, A.; Wisnieff, T. J.; Walsh, E. J. *J. Org. Chem.* **1989**, *54*, 299.
6. Padwa, A.; Dean, D. C.; Osterhout, M. H.; Precedo, L.; Semones, M. A. *J. Org. Chem.* **1994**, *59*, 5347.
7. (a) Pellicciari, R.; Curini, M.; Spagnoli, N.; Ceccherelli, P. *Synthesis* **1981**, 629. (b) Pellicciari, R.; Curini, M.; Spagnoli, N. *Archiv. Pharm.* **1984**, *317*, 38.
8. Pellicciari, R.; Benedetto, D. S.; Santucci, S. *Tetrahedron Lett.* **1984**, *25*, 3103.
9. Polak, A. *Progress in Drug Research*; Jucker, E., Ed.; Birkhauser: Basel, 1997; Vol. 49, pp 219–318.
10. (a) Botta, M.; Corelli, F.; Gasparrini, F.; Messina, F.; Mugnaini, C. *J. Org. Chem.* **2000**, *65*, 4736. (b) Jones, C. D.; Winter, M. A.; Hirsch, K. S.; Stamm, N.; Taylor, H.; M, .; Holden, H. E.; Davenport, J. D.; Krumkalns, E. V.; Suhr, R. G. *J. Med. Chem.* **1990**, *33*, 416. (c) Corelli, F.; Summa, V.; Brogi, A.; Monteagudo, E.; Botta, M. *J. Org. Chem.* **2008**, *1995*, 60.
11. West, F. G.; Naidu, B. N. *J. Am. Chem. Soc.* **1993**, *115*, 1177.
12. Heath, P.; Roberts, E.; Sweeney, J. B.; Wessel, H. P.; Workman, J. A. *J. Org. Chem.* **2003**, *68*, 4083–4086.
13. Vanecko, J. A.; West, F. G. *Org. Lett.* **2002**, *4*, 2813–2816.
14. (a) Aggarwal, V. K.; Alonso, E.; Bae, I.; Hynd, G.; Lydon, K. M.; Palmer, M. J.; Patel, M.; Porcelloni, M.; Richardson, J.; Stenson, R. A.; Studley, J. R.; Vasse, J. L.; Winn, C. L. *J. Am. Chem. Soc.* **2003**, *125*, 10926. (b) Aggarwal, V. K.; Fulton, J. R.; Sheldon, C. G.; Vicente, J. *J. Am. Chem. Soc.* **2003**, *125*, 6034. (c) Aggarwal, V. K.; Alonso, E.; Hynd, G.; Lydon, K. M.; Palmer, M. J.; Porcelloni, M.; Studley, J. R. *Angew. Chem., Int. Ed.* **2001**, *40*, 1430. (d) Cheung, W. H.; Zheng, S. L.; Yu, W. Y.; Zhou, G. C.; Che, C. M. *Org. Lett.* **2003**, *5*, 2535.
15. (a) Bridson, J. N.; Hooz, J.; *Organic Syntheses Collect. Vol. VI*; Wiley: New York, 1988 p 386. (b) Scott, L. T.; Sumpter, C. A.; *Organic Syntheses Collect. Vol. VIII* p 196.
16. Cuevas-Yañez, E.; García, M. A.; de la Mora, M. A.; Muchowski, J. M.; Cruz-Almanza, R. *Tetrahedron Lett.* **2003**, *44*, 4815.
17. Fournari, P.; De Cointet, P.; Laviron, E. *Bull. Soc. Chim. Fr.* **1968**, 2438.
18. Pilarski, B. *Liebigs Ann. Chem.* **1983**, 1078.
19. Godefroi, E. F.; Heeres, J.; Van Custen, J.; Janssen, P. A. J. *J. Med. Chem.* **1969**, *12*, 784.
20. Keana, J. F. W.; Dolata, D. P.; Ollerenshaw, J. *J. Org. Chem.* **1973**, *38*, 3815.
21. Baggaley, K. H.; Heald, M.; Hindley, R. M.; Morgan, B.; Tee, J. L.; Green, J. *J. Med. Chem.* **1975**, *18*, 833.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 60 (2004) 9397–9403

Stereoselective aldol additions of titanium enolates of *N*-acetyl-4-isopropyl-thiazolidinethione

Mathis B. Hodge and Horacio F. Olivo*

Division of Medicinal and Natural Products Chemistry, College of Pharmacy, The University of Iowa, Iowa City, IA 52242, USA

Received 30 April 2004; revised 4 August 2004; accepted 5 August 2004

Available online 27 August 2004

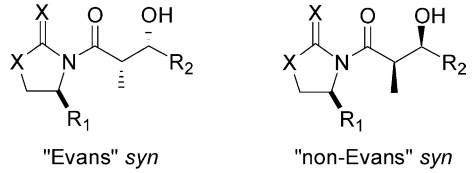
Abstract—The addition of chlorotitanium enolates of *N*-acetyl isopropyl thiazolidine-2-thione to aldehydes was investigated. The stereoselectivity of the aldol products was controlled by the number of equivalents of base added. The *syn* aldol product was obtained preferentially when 2 equiv of Lewis acid and 1 equiv of base were employed. The *anti* aldol product was obtained preferentially when 1 equiv of Lewis acid and 2 equiv of base were employed for unsaturated aldehydes. Unexpected results were found with hindered aldehydes when 2 equiv of base were employed.
© 2004 Elsevier Ltd. All rights reserved.

1. Introduction

The aldol addition reaction is of paramount importance for the synthesis of polyketides and other families of natural products.[1] Powerful chiral auxiliaries for asymmetric aldol reactions have been developed in the last twenty-five years.[2] In particular, oxazolidinones developed by Evans, are valuable chiral auxiliaries for the syntheses of aldol products. Depending on reaction conditions, the 'Evans' *syn* and 'non-Evans' *syn* aldol products can be obtained.[3] However, poor diastereomeric ratios are observed for the acetate aldol reaction using chiral oxazolidinones.[4] Several methodologies have been investigated attempting to overcome this limitation. Studies have shown that addition of a temporary auxiliary group on the *alpha* carbon improves the diastereomeric excess. Unfortunately, this sequence solution adds additional steps to the synthetic route.[5] Efforts have also been directed at other potential methodologies (Scheme 1).

Excellent stereoselectivities have been observed for chiral auxiliary-based acetate aldol reaction using 1,3-oxazolidine-2-thiones and 1,3-thiazolidine-2-thiones.[6,7] Interestingly, thiazolidinethione chiral auxiliaries have also proved to have several advantages over its oxazolidinone analogs, e.g. they can be directly reduced to aldehydes, easily removed, and displaced by some nucleophiles.[8] However, highly stereoselective acetate aldol reactions employ either expensive metals or starting materials. Fujita–Nagao's chiral auxiliary, 4-alkyl thiazolidinethione, has been used successfully to obtain the acetate *syn* aldol product[9] when using tin(II) triflate as the Lewis acid.[6] In addition, a highly hindered oxazolidinethione derived from methyl valinate was used to obtain highly diastereoselective acetate *syn* product using titanium(IV) chloride, sparteine and *N*-methylpyrrolidinone.[10] Recently, a procedure to obtain the acetate *anti* aldol product with high diastereoselectivity has been reported.[11] In this procedure, a thiazolidinethione chiral auxiliary was prepared from *tert*-leucine and dichlorophenylborane was used as the Lewis acid. Although excellent diastereoselectivities have been achieved with these sulfur chiral auxiliaries, expensive starting materials and reagents are required. Herein, we report our investigations in the acetate aldol reaction using less expensive reagents and chiral auxiliaries (Scheme 2).

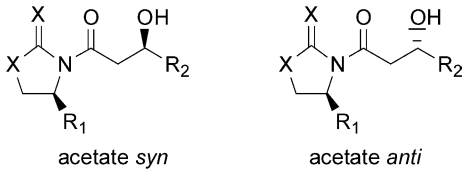
The Fujita–Nagao chiral auxiliary has been elegantly reintroduced by Crimmins.[8] Inexpensive reagents can be employed on the stereoselective aldol condensation of *N*-propionyl oxazolidinethiones and thiazolidinethiones. Interestingly, using the same chiral auxiliary, the 'Evans' *syn* or 'non-Evans' *syn* stereochemistry of the aldol product can be controlled by the nature and amount of Lewis acid and base employed. Based on these results, we decided to



Scheme 1.

Keywords: Aldol additions; Thiazolidinethiones; Chiral auxiliaries.
* Corresponding author. Tel.: +1-319-335-8849; fax: +1-319-335-8766; e-mail: horacio-olivo@uiowa.edu

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.08.008



Scheme 2.

explore the synthetic utility of these conditions in the acetate aldol addition employing thiazolidinethiones.

2. Discussion and results

A highly coordinated Lewis acid transition state is formed when *N*-acyl thiazolidinethione is treated with one or 2 equiv of titanium(IV) chloride and 1 equiv of (−)-sparteine, followed by addition of an aldehyde.[8] A mixture with a high diastereomeric ratio of aldol acetate products was obtained using these conditions, Table 1.[12] The mixture of diastereomeric products was easily separated by silica gel column chromatography. The major product was the more polar *syn* aldol diastereomer. Good to modest yields and high diastereomeric ratios were obtained when using unsaturated aldehydes (entries 1–3) and also with *p*-bromobenzaldehyde and pivalaldehyde (entries 5 and 6). Less diastereoselectivity was obtained with saturated aldehydes (entries 7–9). The major *p*-bromobenzaldehyde aldol product was studied by X-ray crystallographic analysis to confirm its relative and absolute stereochemistry, Fig. 1.[13] The *syn* aldol product **5** showed characteristic ^{1}H NMR chemical shift signals for the *alpha*-protons at 3.8 ppm (dd, $J=17.6$, 2.7 Hz) for the less shielded proton and at 3.50 ppm (dd, $J=17.6$, 9.4 Hz) for the more shielded proton. The minor less polar *anti* product showed chemical shift signals for the *alpha*-protons at 3.79 (dd, $J=17.5$, 9.5 Hz) and 3.53 (dd, $J=17.5$, 3.1 Hz). These *alpha*-proton signals and coupling constants were useful to assign the stereochemistry of the aldol carbon of other products.

Following investigations from the Crimmins' group,[8] addition of *N*-propionate thiazolidinethione to aldehydes using 1 equiv of titanium(IV) chloride and 2 equiv of base generates an open transition state where the thiocarbonyl of the chiral auxiliary is not coordinated to the metal. According to this transition state, the major diastereomeric product is expected to be the *anti* aldol product. Applying this protocol, aldol acetate additions gave preferentially the *anti* products for unsaturated aldehydes (entries 1, 3 and 4), Table 2.[12] Contrary to our expectations, a high diastereomeric ratio favoring the *syn* products was observed for benzaldehyde and pivalaldehyde (entries 5 and 7). Interestingly, switching the Lewis acid to dichlorophenylborane,[11] the diastereomeric ratio for pivalaldehyde was completely reversed (entry 8). Also, the *anti* product was observed exclusively for the addition to cinnamaldehyde when using the boron acid (entry 2). Aldol reactions with saturated aldehydes showed only a slight preference for the *anti* product (entries 10 and 11). The diastereomeric ratio was improved when the thiazolidinethione derived from phenylalanine was employed (entry 12) (Fig. 2).

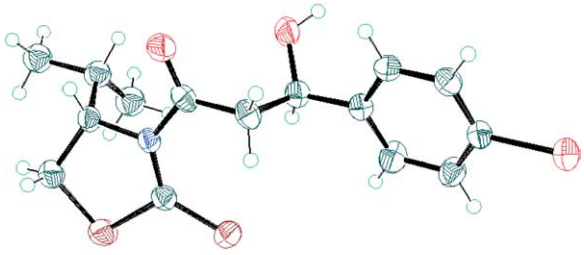
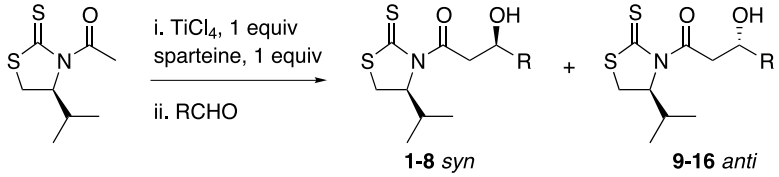


Figure 1. X-ray analysis of *syn* aldol product **5** (ORTEP drawing).

3. Conclusions

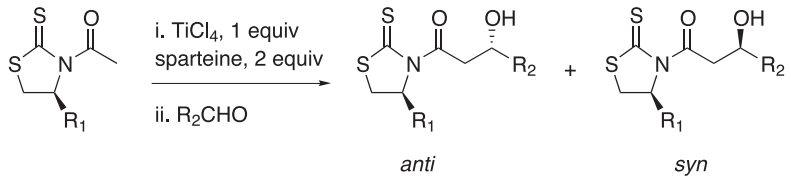
In summary, we have investigated the acetate aldol addition using inexpensive titanium(IV) chloride, sparteine and chiral thiazolidinethione derived from valine. The *syn* acetate aldol product was obtained in high diastereomeric ratio when using 2 equiv of Lewis acid and 1 equiv of base. The *anti* acetate aldol product was obtained preferentially when 1 equiv of Lewis acid and 2 equiv of base were employed for unsaturated aldehydes. In the case of hindered aldehydes, dichlorophenylborane was required to obtain the *anti* product. Further exploration of this phenomena is currently underway. The ease of separation of these

Table 1. Acetate *syn* aldol addition products



Entry	Aldehyde, R-CHO	Ratio *syn*/*anti*	Yield (%)
1	*t*-CH=CH–C_6H_5	92:8 (**1**:**10**)	73
2	–CH=$C(CH_3)_2$	91:9 (**2**:**11**)	60
3	–CH=CH–CH=CH–Br	96:4 (**3**:**12**)	94
4	–C_6H_5	85:15 (**4**:**13**)	69
5	*p*-C_6H_5-Br	95:5 (**5**:**14**)	50
6	–$C(CH_3)_3$	100:0 (**6**:**15**)	70
7	–$CH(C_6H_5)_2$	70:30 (**7**:**16**)	87
8	–CH_2CH_3	83:17 (**8**:**17**)	63
9	–$CH_2CH_2C_6H_5$	86:14 (**9**:**18**)	52

Table 2. Acetate *anti* aldol addition products



Entry	Aldehyde, R-CHO	Auxiliary	Lewis Acid	Ratio anti:syn	Yield (%)
1	*t*-CH=CH–C_6H_5	R_1=i-Pr	$TiCl_4$	82:18 (**10**:**1**)	73
2	*t*-CH=CH–C_6H_5	R_1=i-Pr	$PhBCl_2$	100:0 (**10:1**)	61
3	–CH=$C(CH_3)_2$	R_1=i-Pr	$TiCl_4$	74:26 (**11**:**2**)	60
4	–CH=CH_2	R_1=i-Pr	$TiCl_4$	73:27 (**19**:**20**)	65
5	–C_6H_5	R_1=i-Pr	$TiCl_4$	7:93 (**13**:**4**)	69
6	*p*-C_6H_4-Br	R_1=i-Pr	$TiCl_4$	37:63 (**14**:**5**)	50
7	–$C(CH_3)_3$	R_1=i-Pr	$TiCl_4$	0:100 (**15**:**6**)	70
8	–$C(CH_3)_3$	R_1=i-Pr	$PhBCl_2$	100:0 (**15**:**6**)	54
9	–$CH(C_6H_5)_2$	R_1=i-Pr	$TiCl_4$	40:60 (**16**:**7**)	99
10	–CH_2CH_3	R_1=i-Pr	$TiCl_4$	67:33 (**17**:**8**)	63
11	–$CH_2CH_2C_6H_5$	R_1=i-Pr	$TiCl_4$	64:36 (**18**:**9**)	52
12	–$CH_2CH_2C_6H_5$	R_1=Bn	$TiCl_4$	86:14 (**21**:**22**)	81

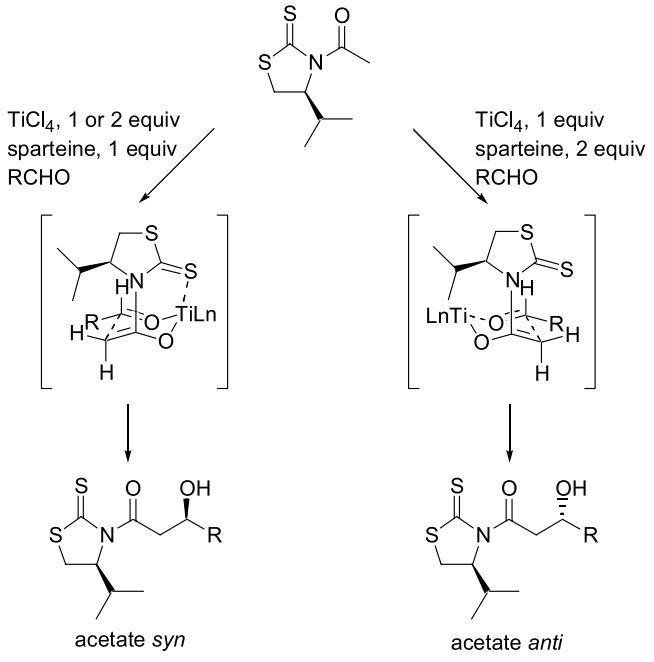


Figure 2. Suggested transition states for the titanium mediated acetate aldol reactions.

diastereomers and their advantages over their oxygen analogs make these sulfur chiral auxiliaries practical in synthesis of natural products.

4. Experimental

4.1. General procedures

General procedure. A solution of *N*-acetyl (4*S*)-isopropylthiazolidinethione (203 mg, 1.0 mmol) in freshly distilled dichloromethane (10 mL) at 0 °C, was treated dropwise with a solution of $TiCl_4$ (1.0 mL, 1 M solution in CH_2Cl_2, 1.0 mmol) under nitrogen atmosphere. The solution was stirred for 5 min and then cooled to −40 °C. A solution of (−)-sparteine (470 mg, 2.0 mmol) in dichloromethane (3 mL) was added via cannula. The reaction mixture was cooled to −78 °C and stirring continued for 35 min. A solution of aldehyde (hydrocinnamaldehyde, 135 mg, 1.0 mmoL) in dichloromethane (3 mL) was transferred via cannula to the reaction mixture, which was then stirred for 15 min at −78 °C. The reaction was quenched with the addition of 1 mL of a half-saturated NH_4Cl solution while stirring. Reaction mixture was warmed to rt and diluted with dichloromethane (20 mL) and washed with 50 mL of a half-saturated NH_4Cl solution. The organic layer was extracted with CH_2Cl_2 (2×20 mL), dried over anhydrous Na_2SO_4, filtered through cotton, and concentrated. Separation of the two diastereomers was carried out by flash column chromatography using silica gel (3×15 cm) eluting with petroleum ether/EtOAc (75:25).

4.1.1. 1-[(4*S*)-*tert*-Isopropyl-2-thioxo-thazolidine-3-yl]-(3*R*)-hydroxy-5-phenyl-pent-4-en-1-one (1). R_f 0.36 (7:3, petroleum ether/ethyl acetate); $[\alpha]_D$=+351.7 (*c* 1.0, $CHCl_3$); IR 3445, 3024, 2965, 1689, 1468, 1363 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.45 (2H, m), 7.37 (2H, m), 7.30 (1H, m), 6.73 (1H, dd, *J*=16.0, 1.1 Hz), 6.33 (1H, dd, *J*=16.0, 5.9 Hz), 5.22 (1H, m), 4.92 (1H, m), 3.79 (1H, dd, *J*=17.5, 3.1 Hz), 3.56 (1H, *J*=11.5, 8.0 Hz), 3.49 (1H, dd, *J*=17.5, 8.7 Hz), 3.08 (1H, dd, *J*=11.5, 1.0 Hz), 2.85 (1H, bs), 2.43 (1H, sext, *J*=6.7 Hz), 1.12 (3H, d, *J*=6.8 Hz), 1.05 (3H, d, *J*=6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 203.2 (C), 172.5 (C), 136.6 (C), 130.7 (CH), 130.1 (CH), 128.7 (2CH), 127.9 (CH), 126.7 (2CH), 71.6 (CH), 68.9 (CH), 45.5 (CH_2), 31.0 (CH), 30.8 (CH_2), 19.2 (CH_3), 18.0 (CH_3). ES HRMS *m*/*z* $(M+Na)^+$ calcd 358.0911, obs 358.0925.

4.1.2. 1-[(4*S*)-*tert*-Isopropyl-2-thioxo-thazolidine-3-yl]-(3*R*)-hydroxy-5-methyl-hex-4-en-1-one (2). R_f 0.45 (3:2, petroleum ether/ethyl acetate); $[\alpha]_D$=+431.4 (*c* 1.0, $CHCl_3$); IR 3437, 2967, 2932, 1689, 1468, 1256, 1161 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.25 (1H, d, quint, *J*=8.6, 1.3 Hz), 5.16 (1H, td, *J*=7.0, 1.1 Hz), 4.90 (1H, td, *J*=8.8, 3.0 Hz), 3.54 (1H, dd, *J*=17.7, 3.0 Hz), 3.53 (1H, dd,

J=11.5, 8.0 Hz), 3.31 (1H, dd, J=17.7, 8.9 Hz), 3.04 (1H, dd, J=11.5, 1.0 Hz), 2.65 (1H, bs), 2.38 (1H, sext, J=6.7 Hz), 1.74 (3H, d, J=1.3 Hz), 1.72 (3H, d, J=1.3 Hz), 1.08 (3H, d, J=6.9 Hz), 0.99 (3H, d, J=6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 203.1 (C), 172.9 (C), 136.2 (C), 125.7 (CH), 71.6 (CH) 65.3 (CH), 45.8 (CH_2), 31.0 (CH), 30.8 (CH_2), 25.9 (CH_3), 19.2 (CH_3), 18.5 (CH_3), 17.9 (CH_3). ES HRMS m/z $(M-H_2O)^+$ calcd 270.0986, obs 270.0985.

4.1.3. 1-[(4*S*)-*tert*-Isopropyl-2-thioxo-thazolidine-3-yl]-(3*R*)-hydroxy-7-bromo-hepta-4,6-diene-1-one (3). R_f 0.32 (7:3, petroleum ether/ethyl acetate); $[\alpha]_D$=+292.2 (c 1.0, $CHCl_3$); IR 3437, 3058, 1690, 1470, 1168 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.72 (1H, dd, J=13.3, 11.0 Hz), 6.35 (1H, d, J=13.3 Hz), 6.26 (1H, ddd, J=15.3, 11.0, 1.2 Hz), 5.80 (1H, dd, J=15.3, 5.6 Hz), 5.17 (1H, t, J=6.8 Hz), 4.70 (1H, m), 3.69 (1H, dd, J=17.8, 3.1 Hz), 3.53 (1H, dd, J=11.5, 7.9 Hz), 3.29 (1H, dd, J=17.6, 8.6 Hz), 3.05 (1H, d, J=11.5 Hz), 2.97 (1H, bs), 2.36 (1H, sext., J=6.8 Hz), 1.07 (3H, d, J=6.7 Hz), 0.99 (3H, d, J=6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 203.0 (C), 172.2 (C), 136.6 (CH), 134.6 (CH), 127.8 (CH), 109.5 (CH), 71.3 (CH), 67.9 (CH), 45.0 (CH_2), 31.0 (CH), 30.7 (CH_2), 19.0 (CH_3), 17.8 (CH_3).

4.1.4. 1-[(4*S*)-4-Isopropyl-2-thioxo-thiazolidine-3-yl]-(3*R*)-hydroxy-4-phenyl-propanone (4). R_f 0.45 (3:2, petroleum ether/ethyl acetate); $[\alpha]_D$=+386.7 (c 1.0, $CHCl_3$); IR 3476, 2965, 1682, 1042 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.45–7.37 (4H, m), 7.32 (1H, m), 5.30 (1H, dd, J=9.3, 2.8 Hz), 5.16 (1H, t, J=7.0 Hz), 3.82 (1H, ddd, J=17.5, 2.7, 0.8 Hz), 3.63 (1H, dd, J=17.5, 9.3 Hz), 3.51 (1H, ddd, J=11.6, 8.0, 0.6 Hz), 3.22 (1H, t, J=3.2 Hz), 3.05 (1H, d, J=11.6 Hz), 2.40 (1H, sext, J=6.7 Hz), 1.10 (3H, d, J=6.8 Hz), 1.02 (3H, d, J=6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 203.1 (C), 172.7 (C), 142.6 (C), 128.7 (2CH), 127.9 (CH), 125.9 (2CH), 71.6 (CH), 70.3 (CH), 47.0 (CH_2), 31.0 (CH), 30.9 (CH_2), 19.2 (CH_3), 18.0 (CH_3). ES HRMS m/z $(M+Na)^+$ calcd 332.0755, obs 332.0754.

4.1.5. 1-[(4*S*)-*tert*-Isopropyl-2-thioxo-thazolidine-3-yl]-(3*R*)-hydroxy-4-(*p*-bromophenyl)-propan-1-one (5). R_f 0.40 (3:2, petroleum ether/ethyl acetate); $[\alpha]_D$=+317.7 (c 1.0, $CHCl_3$); mp 100–102 °C; IR 3468, 2955, 1686, 1359, 1300, 1243, 1219, 1157, 1008 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.50 (2H, d, J=8.5 Hz), 7.29 (2H, d, J=8.5 Hz), 5.27 (1H, dd, J=9.4, 2.7 Hz), 5.16 (1H, dd, J=7.6, 6.6 Hz), 3.82 (1H, dd, J=17.6, 2.7 Hz), 3.51 (1H, ddd, J=11.5, 7.8, 1.5 Hz), 3.50 (1H, ddd, J=17.6, 9.4 Hz), 3.05 (1H, dd, J=11.5, 1.1 Hz), 2.73 (1H, bs), 2.38 (1H, sext, J=6.7 Hz), 1.08 (3H, d, J=6.8 Hz), 1.00 (3H, d, J=7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 203.1 (C), 172.3 (C), 141.5 (C), 131.6 (2CH), 127.6 (2CH), 121.5 (C), 71.5 (CH), 69.6 (CH), 46.8 (CH_2), 30.9 and 30.7 (CH and CH_2), 19.1 (CH_3), 17.8 (CH_3). ES HRMS m/z $(M-H_2O+H)^+$ calcd 369.9935, obs 369.9930.

4.1.6. 1-[(4*S*)-*tert*-Isopropyl-2-thioxo-thazolidine-3-yl]-(3*R*)-hydroxy-4,4-dimethyl-pentan-1-one (6). R_f 0.42 (7:3, petroleum ether/ethyl acetate); $[\alpha]_D$=+454.5 (c 1.0, $CHCl_3$); IR 3524, 2961, 1686, 1161 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.16 (1H, t, J=7.0 Hz), 3.83 (1H, ddd, J=10.4, 3.9, 1.8 Hz), 3.62 (1H, dd, J=17.7, 2.0 Hz), 3.53 (1H, dd, J=11.4, 8.0 Hz), 3.15 (1H, dd, J=17.7, 10.5 Hz), 3.03 (1H, dd, J=11.5, 1.0 Hz), 2.67 (1H, J=3.8 Hz), 2.38 (1H, sext, J=6.8 Hz), 1.08 (3H, d, J=6.8 Hz), 0.99 (3H, d, J=7.0 Hz), 0.95 (9H, s); ^{13}C NMR ($CDCl_3$) δ 203.4 (C), 174.2 (C), 75.4 (CH), 71.7 (CH), 41.2 (CH_2), 34.7 (C), 31.1 (CH), 30.8 (CH_2), 26.0 ($3CH_3$), 19.3 (CH_3), 18.0 (CH_3).

4.1.7. 1-[(4*S*)-*tert*-Isopropyl-2-thioxo-thazolidine-3-yl]-(3*S*)-hydroxy-4,4-diphenyl-butan-1-one (7). R_f 0.30 (7:3, petroleum ether/ethyl acetate); $[\alpha]_D$=+271.0 (c 1.0, $CHCl_3$); IR 3548, 3022, 2965, 1688, 1457, 1163 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.15 (10H, m), 5.10 (1H, t, J=6.7 Hz), 4.96 (1H, td, J=9.0, 2.4 Hz), 4.00 (1H, d, J=8.7 Hz), 3.48 (1H, dd, J=11.4, 7.9 Hz), 3.45 (1H, dd, J=17.6, 2.6 Hz), 3.29 (1H, dd, J=17.6, 9.2 Hz), 2.99 (1H, dd, J=11.4, 1.0 Hz), 2.67 (1H, bs), 2.33 (1H, sext, J=6.7 Hz), 1.02 (3H, d, J=6.7 Hz), 0.94 (3H, d, J=6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 203.0 (C), 172.8 (C), 141.9 (C), 141.2 (C), 128.9 (2CH), 128.8 (2CH), 128.7 (2CH), 128.4 (2CH), 126.8 (2CH), 71.6 (CH), 70.4 (CH), 57.6 (CH), 44.2 (CH_2), 31.0 (CH_3), 30.7 (CH_2), 19.2 (CH_3), 17.9 (CH_3). ES HRMS m/z $(M+H)^+$ calcd 400.1405, obs 400.1413.

4.1.8. 1-[(4*S*)-*tert*-Isopropyl-2-thioxo-thazolidine-3-yl]-(3*R*)-hydroxy-pentan-1-one (8). R_f 0.42 (3:2, petroleum ether/ethyl acetate); $[\alpha]_D$=+470.1 (c 1.0, $CHCl_3$); IR 3456, 2964, 2876, 1689, 1466, 1165, 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.17 (1H, t, J=6.8 Hz), 4.07 (1H, m), 3.65 (1H, dd, J=17.8, 2.3 Hz), 3.53 (1H, dd, J=11.5, 7.8 Hz), 3.12 (1H, dd, J=17.8, 9.5 Hz), 3.04 (1H, d, J=11.5 Hz), 2.69 (1H, bs), 2.37 (1H, sext, J=6.8 Hz), 1.68–1.47 (2H, m), 1.07 (3H, d, J=6.8 Hz), 0.99 (3H, d, J=6.7 Hz), 0.98 (3H, t, J=7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 203.2 (C), 173.4 (C), 71.5 (CH), 69.4 (CH), 45.2 (CH_2), 31.0 (CH), 30.7 (CH_2), 29.4 (CH_2), 19.2 (CH_3), 18.0 (CH_3), 10.1 (CH_3).

4.1.9. 1-[(4*S*)-*tert*-Isopropyl-2-thioxo-thazolidine-3-yl]-(3*R*)-hydroxy-5-phenyl-pentan-1-one (9). R_f 0.42 (3:2, petroleum ether/ethyl acetate); $[\alpha]_D$=+321.7 (c 1.0, $CHCl_3$); IR 3519, 3023, 2961, 1686, 1153 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.38–7.17 (5H, m), 5.17 (1H, m), 4.15 (1H, m), 3.67 (1H, dd, J=17.8, 2.5 Hz), 3.53 (1H, dd, J=11.5, 8.0 Hz), 3.18 (1H, dd, J=17.8, 9.2 Hz), 3.04 (1H, dd, J=11.5, 1.0 Hz), 2.97–2.68 (3H, m), 2.37 (1H, sext, J=6.7 Hz), 1.98–1.75 (2H, m), 1.08 (3H, d, J=6.8 Hz), 0.99 (3H, d, J=7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 203.1 (C), 173.1 (C), 141.8 (C), 128.5 (2CH), 128.4 (2CH), 125.9 (CH), 71.4 (CH), 67.2 (CH), 45.6 (CH_2), 37.9 (CH_2), 31.8 (CH_2), 30.9 (CH), 30.6 (CH_2), 19.1 (CH_3), 17.8 (CH_3). ES HRMS m/z $(M+Na)^+$ calcd 360.1068, obs 360.1060.

4.1.10. 1-[(4*S*)-*tert*-Isopropyl-2-thioxo-thazolidine-3-yl]-(3*S*)-hydroxy-5-phenyl-pent-4-en-1-one (10). R_f 0.48 (7:3, petroleum ether/ethyl acetate); $[\alpha]_D$=+301.5 (c 1.0, $CHCl_3$); IR 3458, 3014, 2966, 1686, 1165 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.39 (2H, m), 7.32 (2H, m), 7.24 (1H, m), 6.67 (1H, d, J=15.8 Hz), 6.27 (1H, dd, J=15.8, 5.9 Hz), 5.19 (1H, m), 4.78 (1H, m), 3.73 (1H, dd, J=17.4, 8.8 Hz), 3.52 (1H, J=11.5, 8.0 Hz), 3.48 (1H, dd, J=17.4, 3.5 Hz), 3.34 (1H, bs), 3.04 (1H, dd, J=11.5, 1.0 Hz), 2.37 (1H, sext, J=6.7 Hz), 1.07 (3H, d, J=6.8 Hz), 0.99 (3H, d, J=6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 203.2 (C), 172.9 (C), 136.7 (C), 130.9 (CH), 130.2 (CH), 128.7 (2CH), 127.9 (CH), 126.7 (2CH), 71.6 (CH), 69.4 (CH), 45.3 (CH_2), 30.9 (CH), 30.8 (CH_2),

19.3 (CH_3), 18.0 (CH_3). ES HRMS *m/z* $(M+Na)^+$ calcd 358.0911, obs 358.0925.

4.1.11. 1-[(4*S*)-*tert*-Isopropyl-2-thioxo-thazolidine-3-yl]-(3*S*)-hydroxy-5-methyl-hex-4-en-1-one (11). R_f 0.53 (3:2, petroleum ether/ethyl acetate); $[\alpha]_D=+257.3$ (*c* 1.0, $CHCl_3$); IR 3436, 2966, 2875, 1686, 1468, 1157 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.25 (1H, d, quint, $J=8.7$, 1.4 Hz), 5.18 (1H, td, $J=7.2$, 1.0 Hz), 4.81 (1H, td, $J=8.8$, 3.4 Hz), 3.57 (1H, dd, $J=17.4$, 8.8 Hz), 3.53 (1H, dd, $J=11.5$, 8.0 Hz), 3.31 (1H, dd, $J=17.4$, 3.4 Hz), 3.13 (1H, bs), 3.05 (1H, dd, $J=11.5$, 0.8 Hz), 2.37 (1H, sext, $J=6.7$ Hz), 1.73 (3H, d, $J=1.2$ Hz), 1.70 (3H, d, $J=1.2$ Hz), 1.07 (3H, d, $J=6.8$ Hz), 0.99 (3H, d, $J=7.0$ Hz); ^{13}C NMR ($CDCl_3$) δ 203.1 (C), 173.4 (C), 136.1 (C), 125.9 (CH), 71.5 (CH) 65.6 (CH), 45.6 (CH_2), 30.9 (CH), 30.7 (CH_2), 25.9 (CH_3), 19.3 (CH_3), 18.5 (CH_3), 17.9 (CH_3). ES HRMS *m/z* $(M-H_2O+H)^+$ calcd 270.0992, obs 270.0986.

4.1.12. 1-[(4*S*)-*tert*-Isopropyl-2-thioxo-thazolidine-3-yl]-(3*S*)-hydroxy-7-bromo-hepta-4,6-diene-1-one (12). R_f 0.42 (7:3, petroleum ether/ethyl acetate); $[\alpha]_D=+312.8$ (*c* 1.0, $CHCl_3$); IR 3436, 2965, 2874, 1685, 1468, 1163, 979 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.74 (1H, dd, $J=13.5$, 10.9 Hz), 6.38 (1H, d, $J=13.5$ Hz), 6.28 (1H, dd, $J=15.2$, 10.9 Hz), 5.82 (1H, dd, $J=15.2$, 5.5 Hz), 5.21 (1H, m), 4.65 (1H, m), 3.66 (1H, dd, $J=17.4$, 8.9 Hz), 3.56 (1H, dd, $J=11.6$, 8.0 Hz), 3.41 (1H, dd, $J=17.46$, 3.3 Hz), 3.08 (1H, d, $J=11.5$ Hz), 2.66 (1H, bs), 2.38 (1H, sext., $J=6.9$ Hz), 1.10 (3H, d, $J=6.8$ Hz), 1.01 (3H, d, $J=7.0$ Hz); ^{13}C NMR ($CDCl_3$) δ 203.2 (C), 172.8 (C), 136.8 (CH), 134.9 (CH), 128.1 (CH), 109.7 (CH), 71.5 (CH), 68.5 (CH), 44.9 (CH_2), 30.9 (CH), 30.8 (CH_2), 19.3 (CH_3), 18.0 (CH_3).

4.1.13. 1-[(4*S*)-4-Isopropyl-2-thioxo-thiazolidine-3-yl]-(3*S*)-hydroxy-4-phenyl-propanone (13). R_f 0.23 (4:1, petroleum ether/ethyl acetate); $[\alpha]_D=+279.2$ (*c* 1.0, $CHCl_3$); mp 88–95 C; IR 3494, 2965, 1689, 1279, 1164 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.41–7.26 (4H, m), 5.17 (2H, m), 3.84 (1H, dd, $J=17.4$, 9.5 Hz), 3.58 (1H, dd, $J=17.4$, 3.1 Hz), 3.58 (1H, m), 3.49 (1H, dd, $J=11.5$, 8.0 Hz), 3.03 (1H, dd, $J=11.5$, 1.0 Hz), 2.36 (1H, sext, $J=6.8$ Hz), 1.06 (3H, d, $J=6.9$ Hz), 0.99 (3H, d, $J=6.9$ Hz); ^{13}C NMR ($CDCl_3$) δ 203.2 (C), 173.1 (C), 142.6 (C), 128.7 (2CH), 127.9 (CH), 126.1 (2CH), 71.6 (CH), 70.9 (CH), 46.9 (CH_2), 30.9 (CH), 30.8 (CH_2), 19.2 (CH_3), 18.0 (CH_3). ES HRMS *m/z* $(M-H_2O+H)^+$ calcd 292.0830, obs 292.0824.

4.1.14. 1-[(4*S*)-*tert*-Isopropyl-2-thioxo-thazolidine-3-yl]-(3*S*)-hydroxy-4-(*p*-bromophenyl)-propan-1-one (14). R_f 0.53 (3:2, petroleum ether/ethyl acetate); $[\alpha]_D=+236.4$ (*c* 1.0, $CHCl_3$); mp 103–105 °C; IR 3415, 2964, 1698, 1343, 1156 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.48 (2H, d, $J=8.5$ Hz), 7.27 (2H, d, $J=8.5$ Hz), 5.18 (1H, t, $J=7.0$ Hz), 5.11 (1H, dt, $J=9.5$, 3.4 Hz), 3.79 (1H, dd, $J=17.5$, 9.5 Hz), 3.68 (1H, d, $J=3.6$ Hz), 3.53 (1H, dd, $J=17.5$, 3.1 Hz), 3.51 (1H, dd, $J=11.6$, 8.0 Hz), 3.05 (1H, d, $J=11.6$ Hz), 2.35 (1H, sext, $J=6.8$ Hz), 1.06 (3H, d, $J=6.8$ Hz), 0.99 (3H, d, $J=6.9$ Hz); ^{13}C NMR ($CDCl_3$) δ 203.3 (C), 172.9 (C), 141.6 (C), 131.8 (2CH), 127.8 (2CH), 121.7 (C), 71.5 (CH), 70.2 (CH), 46.8 (CH_2), 30.9 (CH), 30.8 (CH_2), 19.2 (CH_3), 18.0 (CH_3). ES HRMS *m/z* $(M-H_2O+H)^+$ calcd 369.9935, obs 369.9932.

4.1.15. 1-[(4*S*)-*tert*-Isopropyl-2-thioxo-thazolidine-3-yl]-(3*S*)-hydroxy-4,4-dimethyl-pentan-1-one (15). R_f 0.59 (7:3, petroleum ether/ethyl acetate); $[\alpha]_D=+302.3$ (*c* 1.0, $CHCl_3$); IR 3539, 2961, 1686, 1158, 757 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.20 (1H, t, $J=6.9$ Hz), 3.72 (1H, ddd, $J=10.5$, 4.8, 2.0 Hz), 3.53 (1H, dd, $J=16.7$, 10.5 Hz), 3.52 (1H, dd, $J=11.5$, 8.0 Hz), 3.31 (1H, dd, $J=16.7$, 2.0 Hz), 3.21 (1H, d, $J=4.9$ Hz), 3.04 (1H, dd, $J=11.5$, 1.1 Hz), 2.37 (1H, sext, $J=6.8$ Hz), 1.07 (3H, d, $J=6.7$ Hz), 0.99 (3H, d, $J=6.7$ Hz), 0.93 (9H, s); ^{13}C NMR ($CDCl_3$) δ 203.6 (C), 174.6 (C), 76.4 (CH), 71.7 (CH), 40.5 (CH_2), 34.9 (C), 30.9 (CH), 30.7 (CH_2), 26.0 ($3CH_3$), 19.3 (CH_3), 18.0 (CH_3). ES HRMS *m/z* $(M-H_2O+H)^+$ calcd 272.1143, obs 272.1151.

4.1.16. 1-[(4*S*)-*tert*-Isopropyl-2-thioxo-thazolidine-3-yl]-(3*R*)-hydroxy-4,4-diphenyl-butan-1-one (16). R_f 0.30 (8:2, petroleum ether/ethyl acetate); $[\alpha]_D=+191.9$ (*c* 1.0, $CHCl_3$); IR 3567, 3018, 2968, 1684, 1362, 1217, 1161 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45–7.11 (10H, m), 5.08 (1H, t, $J=7.1$ Hz), 4.87 (1H, m), 4.02 (1H, d, $J=8.7$ Hz), 3.61 (1H, dd, $J=17.2$, 9.4 Hz), 3.36 (1H, dd, $J=11.5$, 8.0 Hz), 3.24 (1H, dd, $J=17.2$, 2.8 Hz), 3.10 (1H, d, $J=4.0$ Hz), 2.92 (1H, dd, $J=11.5$, 1.0 Hz), 2.30 (1H, sext, $J=6.6$ Hz), 1.00 (3H, d, $J=6.7$ Hz), 0.93 (3H, d, $J=6.9$ Hz); ^{13}C NMR ($CDCl_3$) δ 203.1 (C), 173.1 (C), 141.9 (C), 141.2 (C), 128.9 (2CH), 128.8 (2CH), 128.6 (2CH), 128.5 (2CH), 126.9 (CH), 126.8 (CH), 71.5 (CH), 70.8 (CH), 57.9 (CH), 43.9 (CH_2), 30.8 (CH_3), 30.5 (CH_2), 19.2 (CH_3), 17.8 (CH_3).

4.1.17. 1-[(4*S*)-*tert*-Isopropyl-2-thioxo-thazolidine-3-yl]-(3*S*)-hydroxy-pentan-1-one (17). R_f 0.42 (7:3, petroleum ether/ethyl acetate); $[\alpha]_D=+313.3$ (*c* 1.0, $CHCl_3$); IR 3441, 2964, 2876, 1685, 1466, 1164 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.19 (1H, ddd, $J=7.7$, 6.3, 1.1 Hz), 3.97 (1H, m), 3.53 (1H, dd, $J=11.5$, 7.9 Hz), 3.46 (1H, dd, $J=17.5$, 9.1 Hz), 3.34 (1H, dd, $J=17.4$, 3.0 Hz), 3.25 (1H, bs), 3.05 (1H, d, $J=11.5$ Hz), 2.37 (1H, sext, $J=6.8$ Hz), 1.67–1.49 (2H, m), 1.07 (3H, d, $J=6.8$ Hz), 0.99 (3H, d, $J=6.8$ Hz), 0.98 (3H, t, $J=7.6$ Hz); ^{13}C NMR ($CDCl_3$) δ 203.3 (C), 173.9 (C), 71.5 (CH), 69.9 (CH), 44.8 (CH_2), 30.9 (CH_2), 30.7 (CH), 29.6 (CH_2), 19.2 (CH_3), 17.8 (CH_3), 10.0 (CH_3). ES HRMS *m/z* $(M-H_2O+H)^+$ calcd 244.0830, obs 244.0822.

4.1.18. 1-[(4*S*)-*tert*-Isopropyl-2-thioxo-thazolidine-3-yl]-(3*S*)-hydroxy-5-phenyl-pentan-1-one (18). R_f 0.44 (7:3, petroleum ether/ethyl acetate); $[\alpha]_D=+197.6$ (*c* 1.0, $CHCl_3$); IR 3437, 3025, 2962, 1686, 1167 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33–7.17 (5H, m), 5.18 (1H, m), 4.06 (1H, m), 3.53 (1H, dd, $J=17.8$, 9.4 Hz), 3.52 (1H, dd, $J=11.6$, 8.0 Hz), 3.33 (1H, dd, $J=17.6$, 2.7 Hz), 3.05 (1H, dd, $J=11.6$, 1.0 Hz), 2.90–2.68 (2H, m), 2.37 (1H, sext, $J=6.7$ Hz), 2.22 (1H, bs), 1.99–1.73 (2H, m), 1.08 (3H, d, $J=6.7$ Hz), 0.99 (3H, d, $J=6.9$ Hz); ^{13}C NMR ($CDCl_3$) δ 203.2 (C), 173.7 (C), 141.9 (C), 128.6 (2CH), 128.4 (2CH), 125.9 (CH), 71.4 (CH), 67.7 (CH), 45.3 (CH_2), 38.2 (CH_2), 31.8 (CH_2), 30.8 (CH), 30.7 (CH_2), 19.2 (CH_3), 17.9 (CH_3).

4.1.19. 1-[(4*S*)-*tert*-Isopropyl-2-thioxo-thazolidine-3-yl]-(3*S*)-hydroxy-pent-4-en-1-one (19). R_f 0.33 (7:3, petroleum ether/ethyl acetate); $[\alpha]_D=+354.1$ (*c* 1.0, $CHCl_3$); IR 3436, 2965, 1685, 1364, 1167 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.94 (1H, ddd, $J=17.2$, 10.5,

5.4 Hz), 5.34 (1H, dt, $J=17.2$, 1.5 Hz), 5.19 (1H, m), 5.16 (1H, m), 4.60 (1H, m), 3.64 (1H, dd, $J=17.4$, 8.9 Hz), 3.54 (1H, dd, $J=11.6$, 6.6 Hz), 3.40 (1H, dd, $J=17.4$, 3.4 Hz), 3.06 (1H, dd, $J=11.6$, 1.1 Hz), 2.83 (1H, bs), 2.37 (1H, m), 1.08 (3H, d, $J=6.8$ Hz), 0.99 (3H, d, $J=7.0$ Hz); ^{13}C NMR ($CDCl_3$) δ 203.2 (C), 173.0 (C), 138.9 (CH), 115.6 (CH_2), 71.5 (CH), 69.4 (CH), 45.0 (CH_2), 30.9 (CH), 30.8 (CH_2), 19.2 (CH_3), 18.0 (CH_3).

4.1.20. 1-[(4*S*)-*tert*-Isopropyl-2-thioxo-thazolidine-3-yl]-(3*R*)-hydroxy-pent-4-en-1-one (20). R_f 0.27 (7:3, petroleum ether/ethyl acetate); $[\alpha]_D=+340.7$ (*c* 1.0, $CHCl_3$); IR 3442, 2964, 1691, 1363, 1168 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.93 (1H, ddd, $J=17.3$, 10.5, 5.3 Hz), 5.33 (1H, dt, $J=17.3$, 1.5 Hz), 5.17 (1H, m), 5.14 (1H, m), 4.67 (1H, m), 3.65 (1H, dd, $J=17.7$, 3.0 Hz), 3.54 (1H, dd, $J=11.6$, 8.0 Hz), 3.31 (1H, dd, $J=17.7$, 8.8 Hz), 3.04 (1H, dd, $J=11.6$, 1.0 Hz), 2.79 (1H, bs), 2.37 (1H, m), 1.07 (3H, d, $J=6.8$ Hz), 0.99 (3H, d, $J=7.0$ Hz); ^{13}C NMR ($CDCl_3$) δ 203.1 (C), 172.5 (C), 138.9 (CH), 115.4 (CH_2), 71.5 (CH), 68.9 (CH), 45.2 (CH_2), 30.9 (CH), 30.8 (CH_2), 19.2 (CH_3), 17.9 (CH_3).

4.1.21. 1-[(4*S*)-Benzyl-2-thioxo-thazolidine-3-yl]-(3*R*)-hydroxy-5-phenyl-pentan-1-one (21). R_f 0.48 (7:3, petroleum ether/ethyl acetate); $[\alpha]_D=+138.5$ (*c* 1.0, $CHCl_3$); IR 3547, 3026, 2927, 1685, 1165 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.47–7.02 (10H, m), 5.39 (1H, m), 4.06 (1H, m), 3.51 (1H, dd, $J=17.5$, 9.1 Hz), 3.38 (1H, dd, $J=11.4$, 7.2 Hz), 3.31 (1H, dd, $J=17.5$, 2.4 Hz), 3.24 (1H, d, $J=3.0$ Hz), 3.21 (1H, dd, $J=13.5$, 4.1 Hz), 3.03 (1H, dd, $J=13.2$, 10.4 Hz), 2.89 (1H, d, $J=11.6$ Hz), 2.88–2.68 (2H, m), 1.98–1.72 (2H, m); ^{13}C NMR ($CDCl_3$) δ 201.6 (C), 173.8 (C), 141.9 (C), 136.5 (C), 129.6 (2CH), 129.1 (2CH), 128.7 (2CH), 128.5 (2CH), 127.4 (CH), 126.0 (CH), 68.3 (CH), 67.7 (CH), 45.7 (CH_2), 38.3 (CH_2), 37.0 (CH_2), 32.2 (CH), 31.8 (CH_2). ES HRMS *m/z* $(M+H)^+$ calcd 386.1248, obs 386.1242.

4.1.22. 1-[(4*S*)-Benzyl-2-thioxo-thazolidine-3-yl]-(3*S*)-hydroxy-5-phenyl-pentan-1-one (22). R_f 0.35 (7:3, petroleum ether/ethyl acetate); $[\alpha]_D=+190.6$ (*c* 1.0, $CHCl_3$); IR 3554, 3025, 2927, 1689, 1162 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.36–7.16 (10H, m), 5.38 (1H, m), 4.15 (1H, m), 3.67 (1H, dd, $J=17.8$, 2.3 Hz), 3.38 (1H, dd, $J=11.6$, 7.2 Hz), 3.20 (1H, dd, $J=13.1$, 4.1 Hz), 3.16 (1H, dd, $J=17.8$, 9.4 Hz), 3.03 (1H, dd, $J=13.1$, 10.3 Hz), 2.88 (1H, d, $J=11.6$ Hz), 2.85–2.67 (3H, m), 1.98–1.74 (2H, m); ^{13}C NMR ($CDCl_3$) δ 201.5 (C), 173.3 (C), 141.9 (C), 136.5 (C), 129.6 (2CH), 129.1 (2CH), 128.6 (2CH), 128.5 (2CH), 127.5 (CH), 126.0 (CH), 68.4 (CH), 67.2 (CH), 46.1 (CH_2), 38.0 (CH_2), 37.0 (CH_2), 32.2 (CH), 32.0 (CH_2). ES HRMS *m/z* $(M+Na)^+$ calcd 408.1068, obs 408.1087.

Acknowledgements

Financial support for our programs by the NIH (HD041948) and NSF (CHE-0111292) is acknowledged with thanks. We thank Dr. Dale Swenson (UI, Chemistry Department) for obtaining the X-ray crystallographic analysis of compound 5. We are indebted to Dr. Blake Watkins (University of Mississippi) for obtaining all the HRMS.

References and notes

1. (a) Mukaiyama, T. *Org. React.* **1982**, *28*, 203–331. (b) Heathcock, C. H. *Comp. Org. Synth.* **1991**, *2*, 181–238. (c) Kim, B. M.; et al. *Comp. Org. Synth.* **1991**, *2*, 239–275. (d) Franklin, A. S.; Paterson, I. *Contemp. Org. Synth.* **1994**, *1*, 317–338. (e) Evans, D. A.; Takacs, J. M.; McGee, L. R.; Ennis, M. D.; Mathre, D. J.; Bartroli, J. *Pure Appl. Chem.* **1981**, *53*, 1109–1127. (f) Palomo, C.; Oiarbide, M.; Garcia, J. M. *Chem. Eur. J.* **2002**, *8*, 36–44. (g) Alcaide, B.; Almendros, P. *Eur. J. Org. Chem.* **2002**, 1595–1601. (h) Machajewski, T. D.; Wong, C. H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352–1374. (i) Cowden, C. J.; Paterson, I. *Org. React.* **1997**, *51*, 1–200.
2. (a) Walker, M. A.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 5747–5750. (b) Hsiao, C.; Liu, L.; Miller, M. J. *J. Org. Chem.* **1987**, *52*, 2201–2206. (c) Oppolzer, W.; Blagg, J.; Rodriguez, I.; Walther, E. *J. Am. Chem. Soc.* **1990**, *112*, 2767–2772. (d) Arya, P.; Qin, H. *Tetrahedron* **2000**, *56*, 917–947.
3. (a) Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 23–32. (b) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpí, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047–1049. (c) Ager, D. J.; Prakash, I.; Schaad, D. R. *Aldrichimica Acta* **1997**, *30*, 3–12. (d) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835–876. (e) Sibi, M. P. *Aldrichimica Acta* **1999**, *32*, 93–103. More recently, the 'non-Evans' *anti* aldol product was obtained using catalytic amounts of metal: (f) Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2002**, *124*, 392–393. (g) Evans, D. A.; Downey, C. W.; Shaw, J. T.; Tedrow, J. S. *Org. Lett.* **2002**, *4*, 1127–1130.
4. Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129.
5. The acetate problem: (a) Evans, D. A.; Sjogren, E. B.; Weber, A. E.; Conn, R. E. *Tetrahedron Lett.* **1987**, *28*, 39–42. (b) Hsiao, C.-N.; Liu, L.; Miller, M. J. *J. Org. Chem.* **1987**, *52*, 2201–2206. (c) Chen, C.; Crich, D. *Tetrahedron Lett.* **1992**, *33*, 1945–1948. (d) Curtis, N. R.; Holmes, A. B.; Looney, M. G.; Pearson, N. D.; Slim, G. C. *Tetrahedron Lett.* **1991**, *32*, 537–540. (e) Gabriel, T.; Wessjohann, L. *Tetrahedron Lett.* **1997**, *38*, 4387–4388. (f) Wang, Y.-C.; Su, D.-W.; Lin, C.-M.; Tseng, H.-L.; Li, C.-L.; Yan, T.-H. *Tetrahedron Lett.* **1999**, *40*, 3577–3580. (g) Pilli, R. A.; Riatto, V. B.; Vencato, I. *Org. Lett.* **2000**, *2*, 53–56.
6. (a) Nagao, Y.; Hagiwara, Y.; Kumagai, T.; Ochiai, M.; Inoue, T.; Hashimoto, K.; Fujita, E. *J. Org. Chem.* **1986**, *51*, 2391–2393. (b) Nagao, Y.; Yamada, S.; Kumagai, T.; Ochiai, M.; Fujita, E. *J. Chem. Soc., Chem. Commun.* **1985**, 1418–1419. (c) González, A.; Aiguadé, J.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **1996**, *37*, 8949–8952. (d) Romero-Ortega, M.; Colby, D. A.; Olivo, H. F. *Tetrahedron Lett.* **2002**, *43*, 6439–6441.
7. For a review on the application of oxazolidinethiones and thiazolidinethiones in organic synthesis see: Velázquez, F.; Olivo, H. F. *Curr. Org. Chem.* **2002**, *6*, 303–340.
8. (a) Smith, T. E.; Djang, M.; Velander, A. J.; Downey, C. W.; Carroll, K. A.; van Alphen, S. *Org. Lett.* **2004**, *6*, 2317–2320. (b) Crimmins, M. T.; Siliphaivanh, P. *Org. Lett.* **2003**, *5*, 4641–4644. (c) Larrosa, I.; Romea, P.; Urpi, F.; Balsells, D.; Vilarrasa, J.; Font-Bardia, M.; Solans, X. *Org. Lett.* **2002**, *4*, 4651–4654. (d) Cosp, A.; Romea, P.; Talavera, P.; Urpí, F.; Vilarrasa, J.; Font-Bardia, M.; Solans, X. *Org. Lett.* **2001**, *3*, 615–617. (e) Crimmins, M. T.; Chaudhary, K. *Org. Lett.* **2000**, *2*, 775–777.

(f) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894–902. (g) Crimmins, M. T.; King, B. W.; Tabet, E. A. *J. Am. Chem. Soc.* **1997**, *119*, 7883–7884.
9. We refer to the acetate *syn* aldol product when the alcohol and the alkyl group on the auxiliary are on the same side and acetate *anti* aldol product when they are on opposite sides.
10. Guz, N. R.; Phillips, A. J. *Org. Lett.* **2002**, *4*, 2253–2256.
11. Zhang, Y.; Phillips, A. J.; Sammakia, T. *Org. Lett.* **2004**, *6*, 23–25.
12. See Section 4 for a general procedure.
13. CCDC 235049 contains the supplementary crystallographic data for compound (−)-**5**. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223-336033.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 60 (2004) 9405–9415
Tetrahedron

Total synthesis of bidensyneosides A_2 and C: remarkable protecting group effects in glycosylation

Benjamin W. Gung* and Ryan M. Fox†

Department of Chemistry and Biochemistry, Miami University, Oxford, OH 45056, USA

Received 12 May 2004; revised 3 August 2004; accepted 5 August 2004

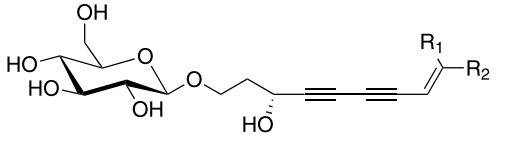
Available online 8 September 2004

Abstract—Bidensyneosides are a group of five recently identified polyacetylenic glucosides from *Bidens parviflora* WILLD, a traditional Chinese medicinal plant that contains rich bioactive natural products. It was shown that bidensyneosides inhibited both histamine release and nitric oxide production. The synthesis of bidensyneoside A2 (**2**) and C (**4**) as well as 3-deoxybidensyneoside C (**5**) are described. These syntheses establish a synthetic entry to the bidensyneosides and confirm the stereochemistry at C3. Furthermore, a remarkable protecting group effect on orthoester formation was observed during the glycosylation reaction.
© 2004 Elsevier Ltd. All rights reserved.

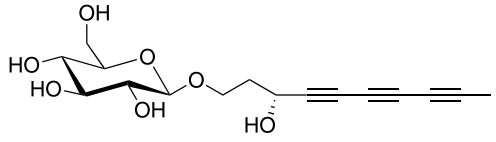
1. Introduction

Bidensyneosides are a group of five new polyacetylenic glucosides (see Fig. 1) isolated from the traditional Chinese medicinal plant *Bidens parviflora* WILLD,[1] which contains rich bioactive natural products.[2] It was shown that bidensyneosides inhibit both histamine release and nitric oxide production.[1] The structures of bidensyneosides have been assigned based on spectroscopic analysis, physicochemical properties and application of the Mosher ester method. Assays have been performed to identify the biological activity of bidensyneosides, but no attempt at their synthesis has been reported.

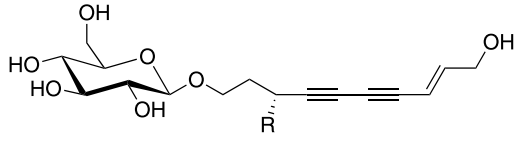
The bidensyneosides are glucosides with a 10-carbon polyacetylenic side chain. These five natural products differ from one another primarily in the oxidation degree of this side chain. In the most potent antiallergic agent, bidensyneoside C (**4**), the side chain contains hydroxyl groups at C3 and C10 while bidensyneosides A1, A2, and B lack a C10 hydroxyl group. Here we describe initial synthetic efforts in the polyacetylenyl glucoside area, which lead to the first total synthesis of bidensyneoside A_2 (**2**) and C (**4**) as well as 3-deoxybidensyneoside C (**5**). These syntheses establish a synthetic entry to the bidensyneosides, and furthermore, confirm the stereochemistry at C3.



1 Bidensyneoside A1 $R_1 = H$, $R_2 = CH_3$
2 Bidensyneoside A2 $R_1 = CH_3$, $R_2 = H$



3 Bidensyneoside B



4 R = OH, Bidensyneoside C
5 R = H, 3'-deoxybidensyneoside C

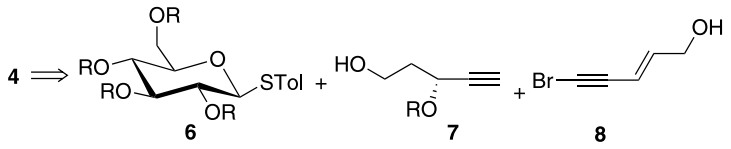
Figure 1. Structures of bidensyneosides from *Bidens parviflora* WILLD.

Since the bidensyneosides differ among themselves mainly in the aglycon side chain, the development of a strategy allowing for the convergent assembly of different side chain analogs was of importance in our synthetic planning. The consideration of a mild glycosylation step, which would allow the attachment of functionalized side chain, led to the retrosynthetic intermediates **6**, **7**, and **8** (Scheme 1).

We chose thioglucosides as the glycosylation donors because it is known that these donors are stable, and they

Keywords: Total synthesis; Natural product; Bidensyneosides; Glycosylation; Protecting group effect.
* Corresponding author. Tel.: +1-513-529-2825; fax: +1-513-529-5715; e-mail: gungbw@muohio.edu
† Beckman predoctoral scholarship recipient.

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.08.012



Scheme 1.

couple with a variety of acceptors under mild conditions.[3,4] The endiyne side chain was envisioned to arise from a copper-catalyzed coupling of intermediates **7** and **8**, and the chiral acetylenic diol **7** was envisaged to arise from an enzymatic resolution of a racemate, which could be prepared from a 3-alkoxy propanal and ethynylmagnesium bromide. The enzymatic resolution of acetylenic alcohols has been studied[5,6] and should provide both enantiomers, thereby allowing verification of the C3 stereochemistry.

2. Results and discussion

2.1. Preparation of 3-deoxybidensyneoside C 5

As a preliminary study, we first carried out the glycosylation reaction between glucose pentacetate and 4-pentyn-1-ol in the presence of $BF_3 \cdot OEt_2$.[7] The desired product **10** was obtained in 30% yield (Scheme 2).

The low yield of the desired product **10** is possibly due to anchimerically-assisted deglycosylation, as reported for 4-pentenyl glucosides.[8] For the preparation of compound **5**, nevertheless, we could easily prepare enough material to continue with the synthesis. Bromo enyne **11** was prepared from commercially available (*E*)-2-penten-4-yn-1-ol via (1) hydroxyl protection as the *t*-butyldimethylsilyl (TBS) ether,[9] and (2) bromination with NBS in the presence of $AgNO_3$.[10] The coupling of bromo alkyne **11** and glucoside **10** was carried out under Cadiot–Chodkiewicz conditions.[11] The copper-promoted coupling reaction, which was carried out in a mixture of $EtNH_2$ and MeOH, proceeded concurrently with the removal of acetate groups by $EtNH_2$, leading to the polar glucoside **12** in 31% yield. Attempted coupling with the unprotected bromo enyne **8** resulted in loss of product during work-up due to difficulties in separating the extremely polar **5** from solvent. The problem was alleviated by using a TBS ether protecting group. Diyne **12** could be extracted from the aqueous solution and purified on a silica gel column. Removal of the TBS protecting group was achieved in THF with the HF·pyridine complex. To avoid the loss of the product, the work-up consisted of adding solid $NaHCO_3$ and evaporating the solvent to a slurry, which was transferred to a silica gel column and eluted with a mixed solvent system (MeOH/$CHCl_3$, 10:90) giving 51% of **5** as a white solid.

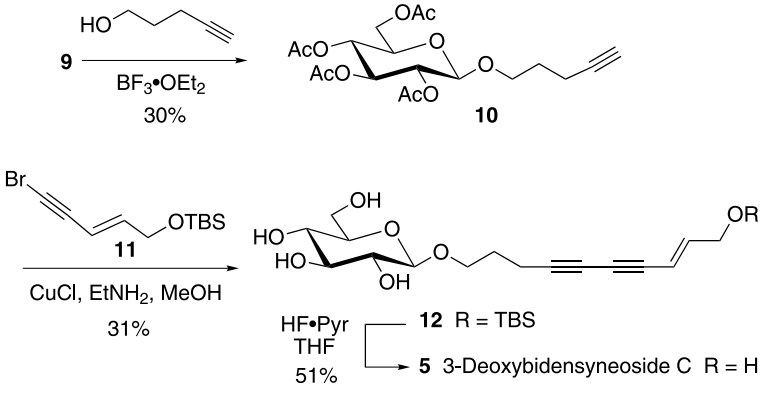
The synthetic sample gave identical ^1H and ^{13}C NMR spectra as the reported natural product.[1] Five UV absorptions were reported for 3-deoxybidensyneoside C (328, 283, 267, 252, and 239 nm),[1] but we observed only four (282, 266, 252, and 240 nm). Considering reported UV spectra for other endiynes and those reported for the other four bidensyneosides,[1] we believe that the 328 nm absorption is spurious.

2.2. Synthesis of bidensyneoside C 4

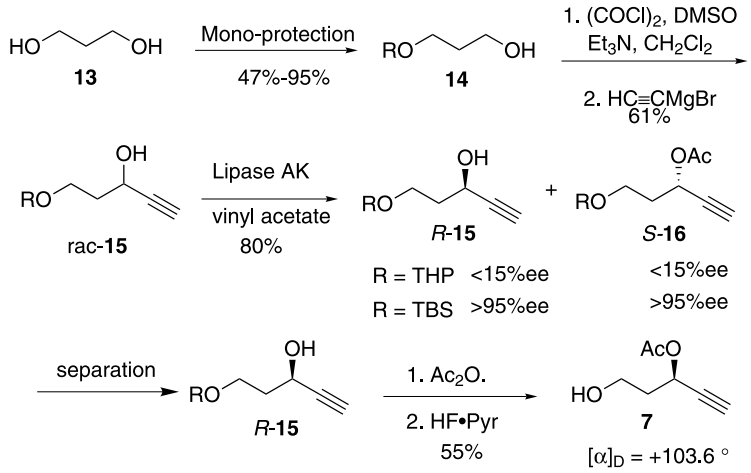
The stereo center on the side chain of this substance was introduced by using a convenient enzymatic resolution approach (Scheme 3). The THP and TBS protected aldehyde **14** were prepared from 1,3-propanediol (**13**).

Oxidation of **14** under the conditions of Swern[12] and in situ addition of ethynylmagnesium bromide to the resulting aldehyde afforded the racemic propargyl alcohol **15** in 61% yield.[13] The current preparation of **15** employs less expensive reagents and requires fewer steps than a previous reported procedure.[14]

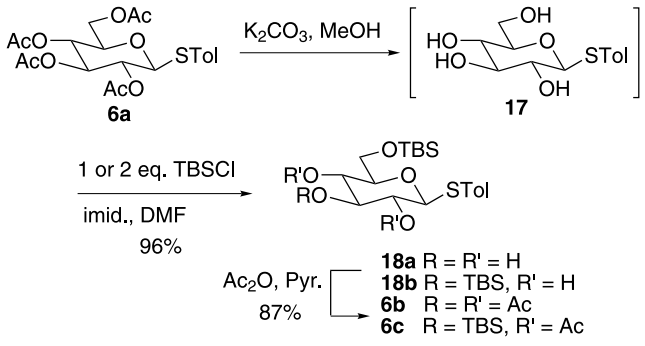
The hydroxyl protecting group at C1 of *rac*-**15** has a profound influence on the lipase-mediated kinetic resolution. The TBS ether group, unlike the THP, provides the steric bulk required for an efficient resolution and material of greater than 95% ee was obtained when this ether was treated with Amano lipase AK (from *pseudomonas* sp) in the presence of vinyl acetate in hexanes.[5,6] The progress of the enzymatic resolution was monitored carefully by ^1H NMR spectroscopy and the reaction was terminated after 50% of *rac*-**15** was consumed. After separation of the



Scheme 2.



Scheme 3.

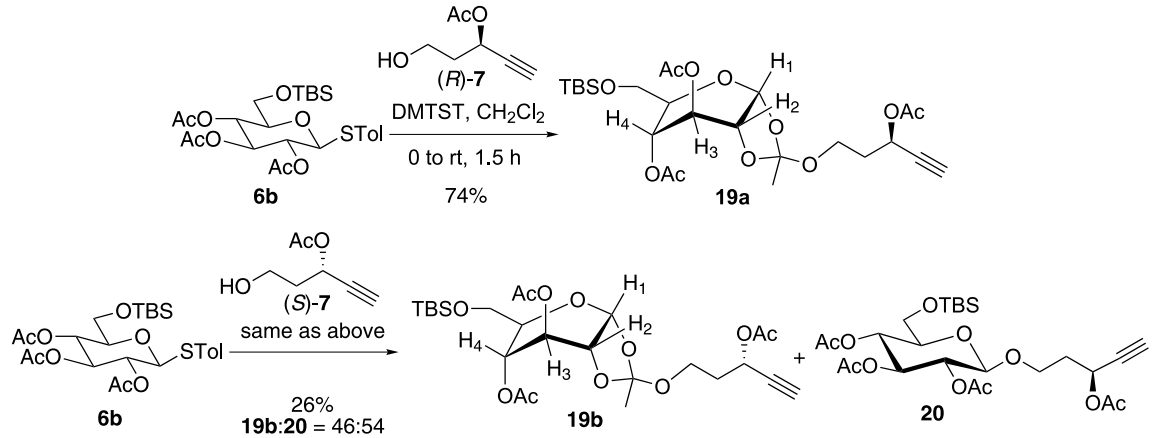


Scheme 4.

alcohol *R*-**15** from the acetate **16** by column chromatography, both enantiomers were obtained in high optical purity as confirmed by the ^{1}H NMR spectra of their *O*-methyl mandelic esters.[15] No diastereomeric isomer was detectable by 500 MHz ^{1}H NMR analysis. The final two steps in the preparation of the side chain involved the acylation of the secondary OH group in *R*-**15** and the removal of the TBS ether with HF·pyridine complex to afford the optically pure alcohol (*R*)-**7**.

The thioglucoside **6a** with four acetate groups was 'disarmed' or inert in the presence of the promoter dimethyl(methylthio) sulfonium triflate (DMTST).[16] Although DMTST is less active than other thiophiles, such as NIS/TfOH, it does not produce a nucleophile as a byproduct.[4] We thus decided to increase the reactivity of the glucoside donor by replacing some of the acetate protecting groups with TBS ethers. Thioglucoside **6a** was deacetylated with K_2CO_3 in MeOH (Scheme 4) and the crude tetraol **17** was treated with either 1 or 2 equiv of TBSCl and imidazole in DMF. This led to the selective formation of either the 6-TBS ether **18a** or the 3,6-di TBS ether **18b**, respectively. Bidensyneosides have the β-configuration at the anomeric carbon. A C2-acetate group is necessary to provide neighboring group assistance for control of stereochemistry in glycosylation.[17] Therefore, the free hydroxyl groups of **18a** and **18b** were acetylated. According to a study by Wong, replacing a C6 acetate group with TBS increases the glycosyl donor reactivity by a factor of 3–5×.[18]

When thioglucoside donor **6b** and (*R*)-**7** were allowed to react in the presence of DMTST for 1 h at room temperature, we were surprised to isolate the orthoester **19a** in 74% yield, rather than the normal anomeric coupling product (Scheme 5). The structure of **19a** was determined by a battery of NMR spectroscopy methods, including ^{1}H, ^{13}C, DEPT ^{13}C, and 2D COSY and HMBC spectra. We expected to see four carbonyl groups in the ^{13}C NMR spectrum, but saw only three and one unexpected peak at 121 ppm



Scheme 5.

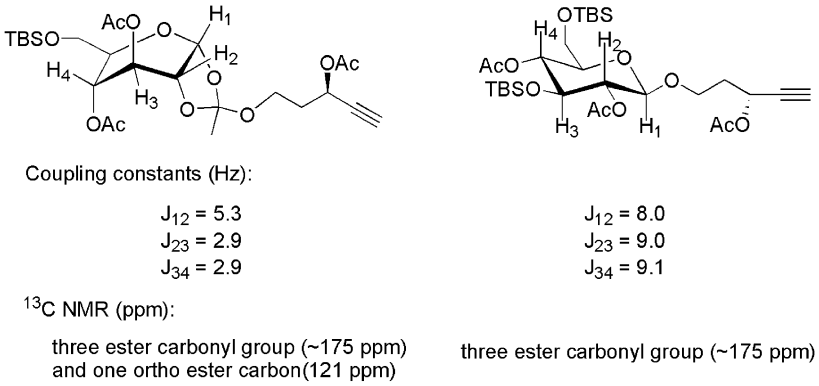


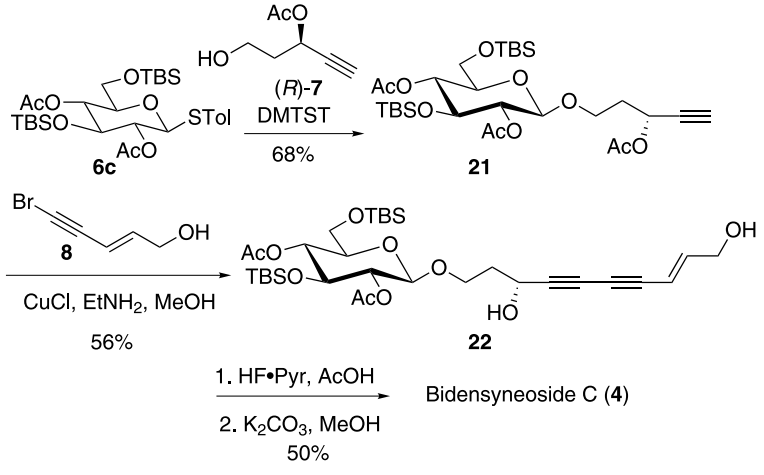
Figure 2. Comparison of the NMR data of **19a** and **21**.

indicating an orthoester. The normal glycosylation products have a chair conformation with large vicent coupling constants. The small coupling constants between H2 and H3 (J_{23}=2.9 Hz) and between H3 and H4 (J_{34}=2.9 Hz) is consistent with a twist boat or 'skew' conformation for **19a**, Figure 2, due to the constraint imposed by the bicyclic structure. Previous studies of carbohydrates containing orthoesters suggested a similar conformation.[19,20]

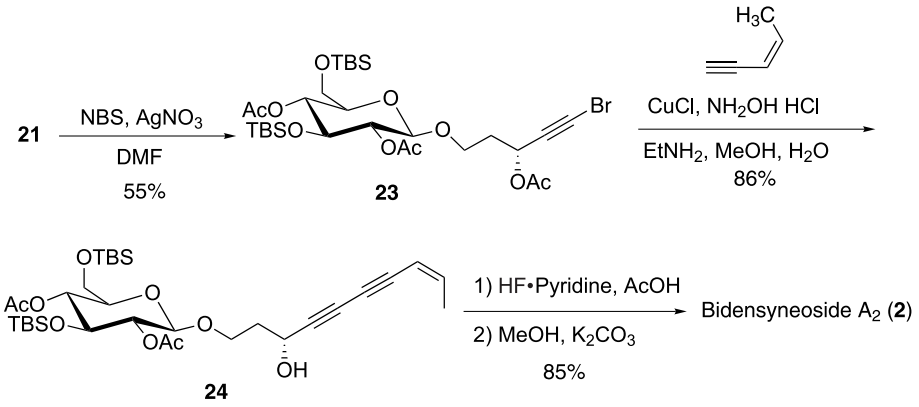
The exclusive formation of the orthoester **19a** was reproducible from **6b** and (*R*)-**7**. When the *S*-enantiomer of **7** was used as the acceptor, the normal glycosylation product **20** was also isolated in addition to the orthoester, but the yield of the reaction was only 26%. The difference between *R*- and *S*-**7** appears to be an effect of matching and mismatching pairs with regard to the glucoside donor **6b**. Therefore, we decided to use the more reactive donor **6c** to couple with alcohol **7** even though it should be possible to transform orthoester **19a** to the diastereomer of **20** under acidic conditions.[20]

The reaction was instantaneous when glucosyl donor **6c** was allowed to react with the chiral alcohol *R*-**7** in the presence of DMTST (Scheme 6). Within 5 min at 0 °C, TLC analysis indicated no starting material remaining and the glycosylation product **21** was isolated in 68% yield with no orthoester formation. The dramatic difference in glycosylation results observed between donor **6b** and **6c** originates from a single protecting group at C3. Although the formation of orthoesters is quite common in glycosylation reactions, we believe this is the first time that a single hydroxyl protecting group has been shown to effectively alter the outcome of the glycosylation reaction. Currently we believe this difference is related to the relative stability of the glycosylation intermediate, the oxycarbenium ion. It appears that donor **6b** with a C3 acetate group produces a less stable oxycarbenium ion and requires neighboring group stabilization and thus the formation of the orthoester. Donor **6c** with a TBS ether group should yield a more stable oxycarbenium ion which then reacts directly with the acceptor. An alternative explanation is that both reactions proceed through the initial formation of the orthoester, which rearranges more rapidly in the case of **6c** to the glycoside.[22]

The copper promoted coupling reaction (Cadiot–Chokwicz reaction) between the terminal alkyne **21** and the bromo alkyne **8** was carried out under the conditions discussed earlier (Scheme 2). This reaction furnished bidensyneoside C in its protected form. Interestingly, only the C3 acetate group was removed during the reaction; the two acetate groups on the glucose ring remained intact. Apparently the steric bulk of the TBS ethers in **21** prevents $EtNH_2$ from attacking these esters. Removal of the protecting groups was undertaken in the sequence shown in Scheme 6. If the acetates were removed first, it was difficult to isolate the



Scheme 6.



Scheme 7.

final product after removal of the TBS ethers. The spectroscopic data of the synthetic sample are consistent with that reported for the natural product.

2.3. Synthesis of bidensyneoside A_2 2

With the key intermediate **21** in hand, we were eager to expand our synthetic route to other members of the bidensyneosides. The commercial availability of (*Z*)-3-penten-1-yne prompted us to prepare bidensyneoside A2 (**2**) as a test for our methodology. It turns out that the more practical route for compound **2** is to prepare bromoalkyne **23** because of the volatility of (*Z*)-3-penten-1-yne (Scheme 7).

In the bromination reaction of the terminal alkyne **21**, the preferred solvent was DMF, instead of acetone, to minimize the breakage of the glycosydic bond. The copper-catalyzed coupling of bromoalkyne **23** with (*Z*)-3-penten-1-yne proceeded smoothly to produce the protected bidensyneoside A2 in 86% yield. This is consistent with our recent observation that a propargylic oxygen substitution in the bromoalkyne enhances the rate of the copper-catalyzed cross coupling reaction to produce conjugated diynes.[21] Without a propargylic oxygen substitution, homocoupling of the bromoalkyne sometimes dominates. The removal of the TBS ether and the acetate protecting group was performed in that order affording compound **2** in 85% yield for two steps. The synthetic sample was identified by spectroscopic methods and the results are consistent with the reported natural product.

3. Conclusions

The total synthesis of bidensyneoside A_2 (**2**) and C (**4**) was achieved in 7 linear steps starting from glucose pentacetate in ~14% overall yield and 3-deoxybidensyneoside C (**5**) in three steps and 4.7% overall yield. These syntheses represent the first synthetic entry to the bidensyneosides and confirm the stereochemistry at C3 of bidensyneoside C. Glycoside formation was found to be highly dependent on the nature of the protecting groups on the glucose. Exclusive formation of the normal glycosylation product or the orthoester was observed, respectively, depending on the characteristic of the protecting group at C3 of the glucoside. The electron-withdrawing acetate group led to the formation of the orthoester while an electron-releasing TBS group led to the normal glycosylation product. Based on this study, a change of protecting groups effectively alters the outcome of the glycosylation reaction. In accord with our recent observation, a propargylic oxygen substitution in the bromoalkyne enhances the copper-catalyzed cross coupling reaction to produce conjugated diynes.

4. Experimental

4.1. General

All reactions were carried out under an atmosphere of nitrogen in oven-dried glassware with magnetic stirring. Reagents were purchased from commercial sources, and used directly without further purification. Methylene chloride was dried over P_2O_5 and freshly distilled before use. Purification of reaction products was carried out by flash chromatography using silica gel 40–63 μm (230–400 mesh), unless otherwise stated. Reactions were monitored by ^{1}H NMR and/or thin-layer chromatography. Visualization was accomplished with UV light, staining with 5% $KMnO_4$ solution followed by heating or with *p*-anisaldehyde (200 ml of 95% EtOH, 10 ml of H_2SO_4, and 10 ml of *p*-anisaldehyde). Chemical shifts are recorded in ppm (δ) using tetramethylsilane (H, C) as the internal reference. Data are reported as: (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; integration; coupling constant(s) in Hz). Optical rotations were measured using Autopol III. Melting points were measured with a Gallenkamp melting point apparatus. Infrared spectra were recorded on a Perkin Elmer 1600 series FTIR. High-resolution mass spectra were recorded at Ohio State University. Lipase AK from *pseudomonas* sp[5,6] was purchased from Amano Enzyme Inc. All new compounds were determined to be >95% pure by ^{1}H NMR spectroscopy.

4.1.1. 4-Pentynyl *tetra*-acetyl-β-D-glucopyranoside (10). A solution of glucose penta-acetate **9** (1.95 g, 5.0 mmol) in CH_2Cl_2 (10 ml) was stirred with $BF_3 \cdot Et_2O$ (5.5 mmol) at room temperature for 1 h. Next, 4-pentyne-1-ol (0.63 g, 7.5 mmol) was added and the mixture was stirred for 4 h. After consumption of the starting material, the mixture was cooled to 0 °C and stirred with saturated aq. $NaHCO_3$ for 30 min. The resulting mixture was extracted three times with diethyl ether. Then the combined extracts were washed

with water, brine and dried over $MgSO_4$. The resulting solution was filtered, concentrated and purified over silica gel. (50% EtOAc/hexanes) giving a yellow syrup (632 mg, 30%).

$[\alpha]_D = 10.60$ (MeOH, $c = 6.6$), ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.67 (2H, m), 1.87 (1H, t, $J = 2.6$ Hz), 1.91–1.99 (12H, 4 s), 2.16 (2H, dt, $J = 7.1$, 2.6 Hz), 3.56 (2H, m), 3.87 (1H, dt, $J = 9.7$, 5.4 Hz), 4.00 (1H, m), 4.18 (1H, dd, $J = 12.3$, 4.6 Hz), 4.42 (d, 1H, $J = 7.9$ Hz), 4.89 (1H, t, $J = 9.3$ Hz), 4.99 (1H, t, $J = 9.6$ Hz), 5.23 (1H, t, $J = 9.4$ Hz), ^{13}C NMR (50 MHz, $CDCl_3$): δ 51.11 (CH_2), 20.97–21.10 (CH_3), 28.53 (CH_2), 62.28 (CH_2), 68.70 (CH_2), 68.75 (CH), 69.27, 71.62 (CH), 72.10 (CH), 73.11 (CH), 83.73, 101.37 (CH), 169.74, 169.78, 170.63, 171.03. IR: ν cm^{-1} 3282, 2117, 1755. HRMS: calcd for $C_{19}H_{26}O_{10}$+Na, 437.1424, found M+Na, 437.1446.

4.1.2. Silane, (1,1-dimethylethyl)dimethyl[5-bromo-(2*E*)-2-penten-4-ynyloxy] (11). To a suspension of NBS (541 mg, 3.04 mmol) and the TBS ether of 2-penten-4-yn-1-ol (510 mg, 2.6 mmol), in 20 ml acetone was added $AgNO_3$ (44 mg, 0.26 mmol). The mixture was stirred for 1 h, and then it was diluted with 50 ml Et_2O and 50 ml $NaHCO_3$. The solution was extracted three times with Et_2O and the combined organic layers were dried over $MgSO_4$. The product was purified over silica Gel (2% EtOAc/hexanes) giving a yellow oil (411 mg, 58%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.05 (6H, s), 0.86 (9H), 4.17 (2H, ddd, $J = 14.1$, 4.9, 2.2 Hz), 5.70 (1H, dt, $J = 15.8$, 2.2 Hz), 6.23 (1H, dt, $J = 15.7$, 4.1 Hz), ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.98 (CH_3), 18.73, 26.25 (CH_3), 49.53, 63.06 (CH_2), 78.84, 108.55 (CH), 144.52 (CH). IR: ν cm^{-1} 3400, 3039, 2167, 1638, 1133.

4.1.3. [10-*tert*-Butyldimethylsilyloxy-8-decen-4,6-diynyl]-β-D-glucopyranoside (12). To a 10 ml flask equipped with a stirring bar under an atmosphere of nitrogen was added $NH_2OH{\cdot}HCl$ (24 mg, 0.34 mmol), methanol (1 ml), compound **10** (200 mg, 0.48 mmol) and 70% aq $EtNH_2$ solution (1 ml). The mixture was cooled to 0 °C and CuCl (2.4 mg, 0.024 mmol) was added followed by slow addition of compound **11** (146 mg, 0.53 mmol). The reaction was stirred for 30 min, and then allowed to warm to room temperature. A KCN/NH_4Cl solution (prepared from 5 g of KCN and 20 g of NH_4Cl in 300 ml of H_2O)[11] was added to the reaction flask. The resulting mixture was then extracted seven times with EtOAc. The combined extracts were concentrated, and purified over silica gel (10% MeOH/$CHCl_3$) giving a yellow oil (66 mg, 31%).

$[\alpha]_D = -7.7$ (MeOH, $c = 0.9$), ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.10 (2×CH_3, s), 0.94 (3×CH_3, s), 1.85 (2H, m), 2.50 (2H, t, $J = 7.1$ Hz), 3.18 (1H, t, $J = 8.6$ Hz), 3.28 (2H, m), 3.37 (1H, m), 3.66 (2H, m), 3.88 (1H, dd, $J = 11.7$, 1.8 Hz), 3.97 (1H, dt, $J = 10.0$, 6.1 Hz), 4.24 (3H, dd, $J = 4.5$, 2.9 Hz, and d, $J = 7.4$ Hz), 5.78 (1H, d, $J = 15.7$ Hz), 6.34 (1H, dt, $J = 15.7$, 4.2 Hz), ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.31 (CH_3), 16.82 (CH_2), 19.16, 26.31 (CH_3), 29.81 (CH_2), 62.74 (CH_2), 63.85 (CH_2), 66.17, 69.21 (CH_2), 71.62 (CH), 74.06, 75.11 (CH), 75.33, 77.91 (CH), 78.05 (CH), 84.30, 104.46 (CH), 108.46 (CH), 146.81 (CH). IR: ν cm^{-1} 3402, 2930, 1654, 1077. HRMS: calcd for $C_{22}H_{36}O_7Si$+Na, 463.2128, found M+Na: 463.2155.

4.1.4. 3-Deoxybidensyneoside B (5). To a solution of 24 mg (0.055 mmol) **12** in 4 ml THF and at 0 °C was added 55 μl HF·pyridine. After the addition, the mixture was allowed to warm to room temperature and stirred for an additional 16 h. To the mixture was added solid $NaHCO_3$ and the solvent was evaporated to ~1 ml. The solution was directly purified over silica gel (30% MeOH/$CHCl_3$) giving a white solid (mp 158–161 °C, 9.5 mg, 51%).

$[\alpha]_D = -15.2$ (MeOH, $c = 0.14$), ^{1}H NMR (500 MHz, Methanol-d_4): δ 1.86 (2H, m), 2.50 (2H, $J = 7.12$ Hz), 3.19 (1H, dd, $J = 9.1$, 7.8 Hz), 3.29 (2H, m), 3.36 (1H, t, $J = 8.8$ Hz), 3.66(1H, dt, $J = 10.0$, 6.2 Hz), 3.69, (1H, dd, $J = 11.8$, 5.4 Hz), 3.88 (1H, dd, 11.8, 2.1 Hz), 3.98 (1H, dt, $J = 10.0$, 6.1 Hz), 4.14 (2H, dd, $J = 4.8$, 2.1 Hz), 4.27 (1H, d, $J = 7.8$ Hz), 5.78 (1H, d, $J = 15.9$ Hz), 6.36 (1H, dt, $J = 15.9$, 4.8 Hz), ^{13}C NMR (75 MHz, Methanol-d_4): δ 16.82 (CH_2), 29.81 (CH_2), 62.69 (CH_2), 62.75 (CH_2), 66.13 (C), 69.21 (CH_2), 71.64 (CH), 74.06, 75.13 (CH), 75.24, 77.93 (CH), 78.07 (CH), 84.33, 104.45 (CH), 109.13 (CH), 147.07 (CH). IR: ν cm^{-1} 3213, 2228, 2140, 1627, 1159, 1030, 1009, UV/Vis: $\lambda_{(max)}$nm: 282, 266, 252, 240. HRMS: Calculated $C_{16}H_{22}O_7$+Na = 349.1263, found $C_{16}H_{22}O_7$+Na = 349.1252.

4.1.5. (+)-3*R*-5-*tert*-butyldimethylsilyloxy-1-pentyn-3-ol (*R*-15). A solution of racemic **15** (2.62 g, 12.19 mmol) in 100 ml of hexanes was added 3 g of molecular sieves (4 Å) and vinyl acetate (6.29 g, 73.17 mmol). Next, lipase AK from *pseudomonas* sp[5,6] (2.62 g) was added and the mixture was stirred at room temperature. When ^{1}H NMR analysis indicated that the ratio of acylated alcohol to free alcohol was approximately 1:1 the mixture was filtered over a pad of Celite, washed with hexanes and purified over silica gel (15% EtOAc/hexanes) giving a yellow oil (1.06 g, 40.5%, (*R*)-**15** and a light yellow oil (1.25 g, 40%, (*S*)-**16**.

(*R*)-**15**: $[\alpha]_D = +14.8$ ($CHCl_3$, $c = 8.25$), (*S*)-**16**: $[\alpha]_D = -51.4$ (MeOH, $c = 1.52$), ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.06 (3H), 0.07 (3H), 0.88 (9H), 1.90 (2H, m), 2.44 (1H, d, $J = 2.1$ Hz), 3.55 (1H, d, $J = 6.2$ Hz), 3.84 (1H, m), 4.03 (1H, m), 4.60 (1H, m), ^{13}C NMR (200 MHz, $CDCl_3$): δ −5.14 (CH_3), 18.5, 26.25 (CH_3), 38.67 (CH_2), 61.51 (CH_2), 62.28 (CH), 73.25, 84.79. IR: ν cm^{-1} 3437, 3033, 2111, 1654. HRMS: calcd for $C_{11}H_{22}O_2Si$+Na, 237.1287, found M+Na, 237.1290.

4.1.6. (+)-3*R*-3-Acetoxy-1-*tert*-butyldimethylsilyl-4-pentyn-1-ol (*R*)-(+)-16. To a solution of *R*-**15** (1.06 g, 4.86 mmol) in 5 ml pyridine was added DMAP (5 mg) and a solution of acetic anhydride (0.74 ml, 7.40 mmol) in 3 ml of pyridine. The mixture was heated to 60 °C and stirred for 4 h.[19] After TLC analysis indicated the completion of the reaction, the solution was diluted with 2 N HCl (5 ml) and a 50:50 Et_2O/hexanes solution (5 ml). The mixture was extracted three times with a mixture of Et_2O/hexanes and the combined organic extracts were washed three times with water, and once with brine. The organic layer was dried over Na_2SO_4. The solvents were removed under reduced pressure

and the residue was purified over silica gel (15% EtOAc/hexanes) giving a light yellow oil (1.08 g, 85%).

$[\alpha]_D = +55.3$ (MeOH, $c=1.25$), ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.00 (6H, s), 0.84 (9H, s), 1.95 (2H, m), 2.03 (3H, s), 2.41 (1H, d, $J=2.1$ Hz), 3.69 (2H, m), 5.43 (1H, dt, $J=2.1$, 6.9 Hz), ^{13}C NMR (50 MHz, $CDCl_3$): δ −5.08 (CH_3), 18.64, 21.34 (CH_3), 26.26 (CH_3), 37.95 (CH_2), 58.93 (CH_2), 61.40 (CH), 73.99, 81.58, 170.13. IR: ν cm^{-1} 3447, 3311, 2123, 1747, 1231. HRMS: calcd for $C_{13}H_{24}O_3Si$+Na, 279.1392, found M+Na, 279.1389.

4.1.7. (+)-3(*R*)-3-Acetoxy-4-pentyn-1-ol (*R*)-(+)-7. To a solution of (*R*)-**16** (689 mg, 2.68 mmol) in 40 ml THF was added at 0 °C HF·pyridine complex (2.68 ml) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 18 h. After completion, the solution was diluted with Et_2O, and washed with $NaHCO_3$, brine, and dried over Na_2SO_4. The solution was concentrated and purified over silica gel (50% EtOAc/hexanes) giving a clear oil (320 mg, 84%).

$[\alpha]_D = +103.6$ (MeOH, $c=2.70$), ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.00 (2H, m), 2.05 (3H, s), 2.32 (1H, s), 2.47 (1H, d, $J=2.1$ Hz), 3.69 (2H, m), 5.49 (1H, dt, $J=2.1$, 6.7 Hz), ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.36 (CH_3), 37.86 (CH_2), 58.68 (CH_2), 61.70 (CH), 74.56, 81.18, 170.67. IR: ν cm^{-1} 3479, 3303, 2118, 1752, 1631. HRMS: calcd for $C_7H_{10}O_3$+Na, 165.0528, Found M+Na, 165.0536, Deprotection of (*S*)-(−)-**16** gave (*S*)-(−)-**7** with $[\alpha]_D = -96.6$ (MeOH, $c=40$).

4.1.8. *p*-Tolyl 6-*O*-(*tert*-butyldimethylsilyl)-1-thio-β-D-glucopyranoside (18a). To a dry 25 ml round bottom flask was added *p*-tolyl-2,3,4,6-*terta*-acetyl-1-thio-β-D-glucopyranoside (**6a**, 0.66 g, 1.45 mmol), 14 ml MeOH, and K_2CO_3 (10 mg, 0.072 mmol). The reaction was stirred at room temperature for 2 h at which point the methanol was removed by vacuum and the white residue was subject to high vacuum overnight. The mass of the flask indicated complete removal of the acetates and methanol. Then, the residue was dissolved in DMF (5 ml) and TBSCl was added (285 mg, 1.89 mmol) at 0 °C. Next, imidazole (130 mg, 1.90 mmol) was added in three portions over 10 min. The solution was stirred at room temperature for 1.5 h, and then diluted with 5 ml of 0.5 N HCl. The resulting mixture was extracted three times with Et_2O, and then the combined organic extracts were washed with $NaHCO_3$, brine and dried over $MgSO_4$. After removing the solvents under reduced pressure, the residue was purified over silica gel (70% EtOAc/hexanes) giving a clear syrup (203 mg, 35%).

$[\alpha]_D = -36.1$ (MeOH, $c=1.14$), ^{1}H NMR (200 MHz, Methanol-d_4): δ 0.10 (3H, s), 0.11 (3H, s), 0.95 (9H, s), 2.33 (3H, s), 3.18–3.34 (4H, m), 3.79 (1H, dt, $J=11.3$, 2.3 Hz), 3.98 (1H, d, $J=11.0$ Hz), 4.54 (1H, d, $J=9.6$ Hz), 7.12 (2H, d, $J=8.1$ Hz), 7.48 (2H, d, $J=8.2$ Hz), ^{13}C NMR (50 MHz, Methanol-d_4): δ −5.87 (CH_3), −5.81 (CH_3), 18.35, 20.34 (CH_3), 25.62 (CH_3), 63.30 (CH_2), 70.13 (CH), 72.70 (CH), 78.74 (CH), 81.22 (CH), 88.62 (CH), 129.56 (CH), 130.47, 132.46 (CH), 137.51. IR: ν cm^{-1} 3392, 2928, 1641, 1493, 1071. HRMS: calcd for $C_{19}H_{32}O_5SSi$+Na, 423.1637, Found M+Na: 423.1639.

4.1.9. *p*-Tolyl 3,6-*O*-bis(*tert*-butyldimethylsilyl)-1-thio-β-D-glucopyranoside (18b). To a dry 250 ml round bottom flask was added *p*-tolyl-2,3,4,6-terta-acetyl-1-thio-β-D-glucopyranoside (**6b**) (12.31 g, 26.72 mmol), 200 ml MeOH, and K_2CO_3 (184 mg, 1.34 mmol). The reaction was stirred at room temperature for 2 h at which point the methanol was removed by vacuum and the white residue was subject to high vacuum overnight. The mass of the flask indicated complete removal of ethyl acetate and methanol after 10 h. Then, the residue was dissolved in 67 ml of DMF and TBSCl was added (8.46 g, 56.1 mmol) at 0 °C. Next, imidazole (4.36 g, 64.12 mmol) was added in three portions over 10 min. The solution was stirred at room temperature for 5 h, and diluted with 25 ml of 0.5 N HCl. The resulting mixture was extracted three times with Et_2O, and the combined organic extracts were washed with aq. $NaHCO_3$, brine and dried over $MgSO_4$. After removing the solvents under reduced pressure, the residue was purified over silica gel (50% EtOAc/hexanes) giving a syrup (6.23 g, 50%).

$[\alpha]_D = -33.6$ ($CHCl_3$, $c=3.62$), ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.08 (3H, s), 0.12 (3H, s), 0.89 (18H, s), 2.31 (3H, s), 3.13–3.54 (4H, m), 3.85 (2H, d, $J=4.5$ Hz), 4.44 (1H, d, $J=9.6$ Hz), 7.08 (2H, d, $J=7.9$ Hz), 7.42 (2H, d, $J=8.0$ Hz), ^{13}C NMR (50 MHz, $CDCl_3$): δ −4.95 (CH_3), −4.14 (CH_3), −3.95 (CH_3), 18.75 (C), 18.80, 21.60 (CH_3), 26.32 (CH_3), 26.39 (CH_3), 64.61 (CH_2), 72.61 (CH), 72.76 (CH), 79.35 (CH), 79.79 (CH), 89.10 (CH), 128.99, 130.13 (CH), 133.40 (CH), 138.54. IR: ν cm^{-1} 3592, 3054, 1493, 1265, 1134, 1072. HRMS: calcd for $C_{25}H_{46}O_5SSi_2$+Na, 537.2502, Found M+Na, 537.2508.

4.1.10. *p*-Tolyl 2,3,4-*O*-tris(acetyl)-6-*O*-(*tert*-butyldimethylsilyl)-1-thio-β-D-glucopyranoside (6b). To a round bottom flask equipped with a stirring bar under an atmosphere of nitrogen was added pyridine (13 ml), compound **18a** (2.17 g, 5.42 mmol), a solution of Ac_2O (2.21 g, 21.68 mmol) in 15 ml pyridine, and 5 mg of DMAP.[19] The flask was then heated to 60 °C for 4 h and diluted with 2 N HCl (60 ml), and 60 ml of a 50/50 Et_2O/hexanes solution. The resulting mixture was extracted three times with Et_2O and the combined ether extracts were washed three times with water, once with brine, and dried over Na_2SO_4. The solution was then filtered and the solvent removed under reduced pressure, and purified over silica gel column giving a white solid (mp 123–125 °C, 2.74 g, 96%).

$[\alpha]_D = -4.53$ (MeOH, $c=2.56$), ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.03 (3H, s), 0.05 (3H, s), 0.87 (9H, s), 1.93 (3H, s), 1.96 (3H, s), 2.03 (3H, s), 2.30 (3H, s), 3.50 (1H, ddd, $J=2.7$, 4.2, 9.7 Hz), 3.68 (2H, m), 4.64 (1H, d, $J=$ 9.9 Hz), 4.86 (1H, t, $J=9.7$ Hz), 4.97 (1H, t, $J=9.6$ Hz), 5.16 (1H, t, $J=9.2$ Hz), 7.05 (2H, d, $J=8.0$ Hz), 7.35 (2H, d, $J=8.1$ Hz), ^{13}C NMR (50 MHz, $CDCl_3$): δ −5.07 (CH_3), 18.70, 21.07 (CH_3), 21.21 (CH_3), 21.60 (CH_3), 26.24 (CH_3), 62.73 (CH_2), 68.85 (CH), 70.37 (CH), 74.89 (CH), 79.26 (CH), 86.04 (CH), 128.26, 130.83 (CH), 133.88 (CH), 138.83, 169.64, 169.66, 170.75. IR: ν cm^{-1} 2930, 2857, 1757, 1374, 837, 810, 779. HRMS: calcd for $C_{25}H_{38}O_8$-SSi+Na, 549.1954, Found M+Na: 549.1963.

4.1.11. *p*-Tolyl 2,4-*O*-bis(acetyl)-3,6-*O*-bis(*tert*-butyldimethylsilyl)-1-thio-β-D-glucopyranoside (6c). To a

round bottom flask was added 30 ml of pyridine, compound **18b** (6.2 g, 13.13 mmol), a solution of Ac_2O (5.36 g, 52.5 mmol) in 40 ml pyridine, and 5 mg of DMAP. The mixture was then heated to 60 °C for 4 h and diluted with 2 N HCl (60 ml), and 60 ml of a 50/50 Et_2O/hexanes solution. The resulting mixture was extracted three times with Et_2O and the combined ether extracts were washed three times with water, once with brine, and dried over Na_2SO_4. The solution was then filtered, concentrated, and purified over silica gel giving a white solid (mp 104–107 °C, 6.80 g, 87%).

$[\alpha]_D = -9.27$ ($CHCl_3$, $c=8.19$), ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.0–0.03 (12H, three singlet's), 0.79 (9H, s), 0.86 (9H, s), 2.04 (3H, s), 2.10 (3H, s), 2.29 (3H, s), 3.40 (1H, ddd, $J=9.4, 5.9, 3.2$ Hz), 3.61 (2H, m), 3.80 (1H, t, $J=8.9$ Hz), 4.53 (1H, d, $J=10.1$ Hz), 4.84 (1H, t, $J=10.0$ Hz), 4.88 (1H, t, $J=10.1$ Hz), 7.05 (2H, d, $J=8.0$ Hz), 7.36 (2H, d, $J=8.1$ Hz), ^{13}C NMR (50 MHz, $CDCl_3$): δ −5.03 (CH_3), −4.83 (CH_3), −4.06 (CH_3), −4.02 (CH_3), 18.19, 18.78, 21.57 (CH_3), 21.73 (CH_3), 21.90 (CH_3), 25.90 (CH_3), 26.32 (CH_3), 63.69 (CH_2), 72.08 (CH), 73.02 (CH), 74.97 (CH), 79.90 (CH), 87.43 (CH), 130.03 (CH), 130.45, 132.49 (CH), 138.07, 169.84. IR: ν cm^{-1} 2926, 1736, 1222, 1132, 1051. HRMS: calcd for $C_{29}H_{50}O_7SSi_2$+Na, 621.2714, Found M+Na, 621.2718.

4.1.12. Orthoester (19a). To a 10 ml round bottom flask was added 4 ml dry CH_2Cl_2, compound **6b** (103 mg, 0.20 mmol), compound (*R*)-**7** (42 mg, 0.30 mmol), and 0.4 g of molecular sieves. The mixture was stirred for 20 min at room temperature. While the mixture was stirring, dimethyldisulfide (55 mg, 0.59 mmol) and MeOTf (97 mg, 0.59 mmol) were allowed to mix in a separate vial to form a solid. After the mixture had fully crystallized, it was dissolved in 1.5 ml CH_2Cl_2. The mixture of **6b** and (*R*)-**7** was then cooled to 0 °C and the DMTST solution was slowly added. The mixture was stirred at 0 °C for 30 min, then 1 h at room temperature. Next, 0.6 ml of Et_3N was added to the mixture, which prompted a precipitate to form. The mixture was then filtered and diluted with CH_2Cl_2. The organic solution was washed with aq. $NaHCO_3$, brine, and dried over Na_2SO_4. Finally, the mixture was filtered, and the solvents removed under reduced pressure. The residue was purified over silica gel (15% EtOAc/hexanes) giving a yellow oil (79 mg, 74%).

$[\alpha]_D = +2.3$, (MeOH, $c=1.7$), ^{1}H NMR: (300 MHz, $CDCl_3$): δ 0.02 (3H, s), 0.03 (3H, s), 0.86 (9H, s), 1.68 (3H, s), 1.99 (2H, m), 2.04 (3H, s), 2.06 (3H, s), 2.07 (3H, s), 2.45 (1H, d, $J=2.2$ Hz), 3.59 (2H, m), 3.7 (3H, m), 4.28 (1H, ddd, $J=5.3, 3.1, 0.9$ Hz), 4.94 (1H, ddd, $J=9.0, 2.6, 0.9$ Hz), 5.15 (1H, t, $J=2.8$ Hz), 5.43 (1H, dt, $J=2.2, 6.9$ Hz), 5.67 (1H, d, $J=5.3$ Hz), ^{13}C NMR: (75 MHz, $CDCl_3$): δ −4.98 (CH_3), −4.94 (CH_3), 18.72, 20.96 (CH_3), 21.23 (CH_3), 21.31 (CH_3), 26.23 (CH_3), 34.87 (CH_2), 59.42 (CH_2), 61.38 (CH), 63.34 (CH_2), 68.49 (CH), 70.02 (CH), 70.36 (CH), 73.44 (CH), 80.95, 97.49 (CH), 121.55, 169.65, 170.00, 170.11. IR: ν cm^{-1} 2930, 2255, 1742, 1371, 1239, 911, 937, 779, 732. HRMS: calcd for $C_{25}H_{40}O_{11}Si$+Na, 567.2238, found M+Na=567.2245.

4.1.13. Orthoester (19b) and (3*S*)-3-acetoxy-4-pentynyl 2′,3′,4′-*O*-tri(acetyl)-6′-*O*-(*tert*-butyl dimethyl silyl)-β-D-gluco-pyranoside (20). To a 10 ml round bottom flask was added 4 ml of dry CH_2Cl_2, **6b** (103 mg, 0.20 mmol), (*S*)-**7** (42 mg, 0.30 mmol) and 0.4 g of molecular sieves. The mixture was stirred for 20 min at room temperature. While the mixture was stirring, dimethyldisulfide (55 mg, 0.59 mmol) and MeOTf (97 mg, 0.59 mmol) were allowed to mix in a separate vial. After a solid was formed, it was dissolved in 1.5 ml CH_2Cl_2. The mixture of **6b** and (−)-**7** was then cooled to 0 °C and the DMTST solution was slowly added. The mixture was stirred at 0 °C for 30 min, then 1 h at room temperature. Next, 0.6 ml Et_3N was added to the mixture, which prompted a precipitate to form. The mixture was then filtered and diluted with CH_2Cl_2. The organic solution was washed with $NaHCO_3$, brine, and dried over Na_2SO_4. Finally, the mixture was filtered, and the solvents removed under reduced pressure. The residue was purified over silica gel (15% EtOAc/hexanes) giving a yellow oil (12 mg, 11%, **19b**) and a clear oil (16 mg, 15%, **20**).

19b: $[\alpha]_D = +12.7$, (MeOH, $c=0.1$), ^{1}H NMR: (300 MHz, $CDCl_3$): δ 0.03 (3H, s), 0.03 (3H, s), 0.87 (9H, s), 1.68 (3H, s), 2.07 (2H, m), 2.08 (3H, s), 2.08 (3H, s), 2.07 (3H, s), 2.46 (1H, d, $J=2.2$ Hz), 3.60 (2H, m), 3.70 (1H, m), 3.72 (2H, m), 4.29 (1H, ddd, $J=5.2, 3.1, 0.9$ Hz), 4.95 (1H, ddd, $J=9.0, 2.5, 0.9$ Hz), 5.16 (1H, t, $J=2.8$ Hz), 5.44 (1H, dt, $J=2.1, 6.9$ Hz), 5.68 (1H, d, $J=5.2$ Hz), ^{13}C NMR: (75 MHz, $CDCl_3$): δ −4.96 (2 CH_3), 18.73, 20.98 (CH_3), 21.21 (CH_3), 21.29 (2 CH_3), 26.24 (CH_3), 34.90 (CH_2), 59.42 (CH_2), 63.37 (CH_2), 68.52 (CH), 70.06 (CH), 70.41 (CH), 73.49 (CH), 80.96, 97.50 (CH), 121.56, 169.66, 170.01, 170.13. IR: ν cm^{-1} 2930, 2255, 1742, 1371, 1239, 911, 937, 779, 732. HRMS: calcd for $C_{25}H_{40}O_{11}Si$+Na, 567.2238, found M+Na: 567.2241.

20: $[\alpha]_D = -13.5$, (MeOH, $c=0.15$), ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.02 (3H, s), 0.03 (3H, s), 0.86 (9H, s), 1.97 (3H, s), 1.99 (3H, s), 2.05 (3H, s), 2.06 (3H, s), 2.09 (2H, m), 2.44 (1H, d, $J=2.1$ Hz), 3.52 (1H, ddd, $J=9.9, 5.2, 2.7$ Hz), 3.63 (1H, m), 3.68 (2H, m), 3.99 (1H, dt, $J=10.0, 5.6$ Hz), 4.92 (1H, dd, $J=8.1, 9.7$ Hz), 4.98 (1H, t, $J=9.7$ Hz), 5.17 (1H, t, $J=9.5$ Hz), 5.35 (1H, dt, $J=2.1, 6.6$ Hz), ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.97 (CH_3), 18.70, 21.01 (CH_3), 21.04 (CH_3), 21.08 (CH_3), 21.24 (CH_3), 26.20 (CH_3), 34.76 (CH_2), 61.32 (CH), 62.84 (CH_2), 65.67 (CH_2), 69.38 (CH), 71.65 (CH), 73.53 (CH), 74.39, 75.18 (CH), 101.10 (CH), 169.78, 169.90, 170.82. IR: ν cm^{-1} 3019, 2121, 1756, 1371. HRMS: calcd for $C_{25}H_{40}O_{11}Si$+Na, 567.2238, Found M+Na: 567.2244.

4.1.14. (3*R*)-3-Acetoxy-4-pentynyl 2′,4′-*O*-bis(acetyl)-3′,6′-*O*-bis(*tert*-butyldimethylsilyl)-β-D-glucopyranoside (21). To a 25 ml round bottom flask was added 8 ml dry CH_2Cl_2, compound **6c** (289 mg, 0.48 mmol), compound (+)-**7** (103 mg, 0.72 mmol) and 0.8 g of molecular sieves. The mixture was stirred for 20 min at room temperature. While the mixture was stirring, dimethyldisulfide (136 mg, 1.44 mmol) and MeOTf (236 mg, 1.44 mmol) were allowed to mix in a separate vial to form a solid. After the mixture had fully crystallized, it was dissolved in 2.5 ml CH_2Cl_2. The mixture was then cooled to 0 °C and the DMTST solution was slowly added. The mixture was stirred at 0 °C

for 30 min, then allowed to warm to room temperature. TLC analysis indicated the disappearance of **6c**. Next, 0.6 ml Et_3N was added to the mixture, which led to a precipitate. The mixture was filtered and diluted with CH_2Cl_2. The organic solution was then washed with aq. $NaHCO_3$, brine and dried over Na_2SO_4. The mixture was filtered, and the solvents removed under reduced pressure. The residue was purified over silica gel (15% EtOAc/hexanes) giving a yellow oil (189 mg, 64%).

$[\alpha]_D=+19.4$ (MeOH, $c=2.3$), ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.00 (6H, s), 0.02 (6H, s), 0.78 (9H, s), 0.85 (9H, s), 1.99 (2H, m), 2.04 (3H), 2.07 (3H), 2.08 (3H), 2.42 (1H, d, $J=2.1$ Hz), 3.37 (1H, m), 3.46 (1H, m), 3.59 (2H, m), 3.80 (1H, t, $J=9.1$ Hz), 3.94 (1H, dt, $J=9.9$, 5.8 Hz), 4.28 (1H, d, $J=8.0$ Hz), 4.79 (1H, t, $J=9.2$ Hz), 4.84 (1H, t, $J=9.0$ Hz), 5.36 (1H, dt, $J=2.0$, 6.6 Hz), ^{13}C NMR (50 MHz, $CDCl_3$): δ −4.94 (CH_3), −4.83 (CH_3), −4.14 (CH_3), −4.03 (CH_3), 18.17, 18.75, 21.33 (CH_3), 21.61 (CH_3), 21.74 (CH_3), 25.88 (CH_3), 26.25 (CH_3), 35.17 (CH_2), 61.08 (CH), 63.65 (CH_2), 64.94 (CH_2), 72.45 (CH), 73.47 (CH), 74.05, 74.48 (CH), 75.66 (CH), 81.11 (CH), 101.10 (CH), 169.82, 169.90, 170.16. IR: ν cm^{-1} 3303, 2126, 1752. HRMS: calcd for $C_{29}H_{52}O_{10}Si_2+Na$, 639.2997, found M+Na, 639.2953.

4.1.15. 5-Bromo-2-penten-4-yn-1-ol (8). To a suspension of 2-penten-4-yn-1-ol (0.50 g, 6.09 mmol) and NBS (1.27 g, 7.13 mmol) in 50 ml acetone was added $AgNO_3$ (104 mg, 0.61 mmol). The mixture was stirred for 1 h at room temperature and then diluted with 50 ml of Et_2O, and 50 ml of water. The aqueous layer was extracted twice with Et_2O and then the combined organic extracts were dried over $MgSO_4$. The solvents were then removed under reduced pressure and the residue purified over silica gel (30% EtOAc/hexanes) giving a yellow oil (0.62 g, 63%).

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.16 (1H, s), 4.14 (2H, dd, $J=4.9$, 1.8 Hz), 5.68 (1H, dt, $J=15.9$, 1.8 Hz), 6.27 (1H, dt, 15.9, 4.9 Hz), ^{13}C NMR (50 MHz, $CDCl_3$): δ 50.47, 62.96 (CH_2), 78.45, 110.09 (CH), 143.93 (CH). IR: ν cm^{-1} 3429, 3034, 2166, 1636, 620.

4.1.16. 3′,6′-*O*-Bis(*tert*-butyldimethylsilyl)-2′,4′-*O*-bis-(acetyl) bidensyneoside C (22). To a 10 ml round bottom flask was added compound **21** (189 mg, 0.3 mmol), 1 ml of a 70% aq. $EtNH_2$ solution, 1 ml MeOH, and $NH_2OH\cdot HCl$ (1 mg, 0.015 mmol). Next, the mixture was cooled to 0 °C and CuCl (1.5 mg, 0.015 mmol) was added followed by slow addition of **8** (54 mg, 0.33 mmol) (keeping the bromoalkyne concentration low suppresses its homo-coupling). The mixture was allowed to stir until **21** had been consumed. Next, the mixture was quenched with a sat. KCN/NH_4Cl solution. The resulting mixture was extracted three times with Et_2O, and the combined extracts were washed with a solution of $NaHCO_3$, brine, and dried over $MgSO_4$. The solvents were removed under reduced pressure and the residue was purified over silica gel (50% EtOAc/hexanes) giving a yellow oil (110 mg, 56%).

$[\alpha]_D=-31.8$ (MeOH, $c=1.2$), ^{1}H NMR (200 MHz, $CDCl_3$): δ (0.01, (6H, two singlets), 0.03 (6H, s), 0.78 (9H, s), 0.85 (9H, s), 1.86 (2H, m), 2.02 (3H, s), 2.10 (3H, s), 3.38 (1H, m), 3.61 (2H, m), 3.80 (2H, m), 4.02 (1H, m), 4.22 (2H, d, $J=3.2$ Hz), 4.33 (1H, d, $J=8.1$ Hz), 4.59 (1H, m), 4.80 (1H, t, $J=9.1$ Hz), 4.84 (1H, dd, $J=9.0$, 8.2 Hz), 5.79 (1H, d, $J=15.9$ Hz), 6.39 (1H, dt, $J=15.9$, 4.7 Hz), ^{13}C NMR (50 MHz, $CDCl_3$): δ −4.94 (CH_3), −4.84 (CH_3), −4.11 (CH_3), −4.03 (CH_3), 18.19, 18.77, 21.73 (CH_3), 25.87 (CH3), 26.26 (CH_3), 36.76 (CH_2), 61.59 (CH), 63.02 (CH_2), 63.60 (CH_2), 66.72 (CH_2), 70.02, 72.38 (CH), 73.39 (CH), 74.25, 74.38 (CH), 75.67 (CH), 77.16, 82.74, 101.23 (CH), 108.93 (CH), 146.25 (CH), 169.95, 170.61. IR: ν cm^{-1} 3429, 2233, 1754, 1373, 1063, 837. HRMS: calcd for $C_{32}H_{54}O_{10}Si_2+Na$, 677.3153, found M+Na, 677.3196.

4.1.17. Bidensyneoside C (4). To a 100 ml round bottom flask was added compound **22** (270 mg, 0.41 mmol), HF·pyridine complex (5 ml), AcOH (4 ml) and THF (35 ml). The mixture was stirred overnight and was diluted with EtOAc and aq. $NaHCO_3$. The mixture was then saturated with NaCl and extracted 5 times with EtOAc. The solvents were removed under reduced pressure and the residue purified over silica gel (10% MeOH/$CHCl_3$) yielding a yellow/brown syrup (102 mg, 58%), which was used in the next step without further identification. To a solution of the syrup in 12 ml MeOH was added K_2CO_3 (1.6 mg). The mixture was stirred for 4 h. The reaction was monitored by TLC and the appearance of a single polar spot indicated the completion of the reaction. Then, about half of the solvent was removed under vacuum and the residue was purified over silica gel (35% MeOH/$CHCl_3$) giving a light brown oil (76 mg, 94%).

$[\alpha]_D=-50.84$ (MeOH, $c=0.83$), ^{1}H NMR (500 MHz, CD_3OD): δ 1.99 (2H, m), 3.19 (1H, t, $J=8.5$ Hz), 3.30 (2H, m), 3.37 (1H, m), 3.69 (1H, dd, $J=5.1$, 11.7 Hz), 3.76 (1H, dt, $J=10.0$, 6.5 Hz), 3.88 (2H, dd, $J=1.2$, 12.1 Hz), 4.02 (1H, dt, $J=10.1$, 5.7 Hz), 4.29 (1H, d, $J=4.8$ Hz), 4.68 (1H, t, $J=6.6$ Hz), 5.83 (1H, d, $J=15.9$ Hz), 6.42 (1H, dt, $J=15.9$, 4.5 Hz), ^{13}C NMR (125 MHz, Methanol-d_4): δ 38.88 (CH_2), 60.15 (CH), 62.60 (CH_2), 62.65 (CH_2), 66.76 (CH_2), 69.52, 71.51 (CH), 74.14, 75.03 (CH), 77.56, 77.84 (CH), 77.97 (CH), 84.31, 104.49 (CH), 108.54 (CH), 148.09 (CH). IR: ν cm^{-1} 3302, 2885, 2233, 1629, 1414, 1368, 1161, 1071, UV/Vis: $\lambda_{(max)}$nm: 283, 267, 253, 240. HRMS: Calculated for $C_{16}H_{22}O_8+Na$, 365.1212, found $C_{16}H_{22}O_8+Na$, 365.1219.

4.1.18. (3*R*)-3′-Acetoxy-5′-bromo-4′-pentynyl 2,4-*O*-bis(acetyl)-3,6-*O*-bis(*tert*-butyldimethylsilyl)-β-D-gluco-pyranoside (23). A 10 ml round bottom flask euipped with a stirring bar under an atmosphere of nitrogen was added 4 ml DMF, compound **21** (200 mg 0.32 mmol), and NBS (75 mg 0.42 mmol). The solution was then cooled to 0 °C and $AgNO_3$ (4.6 mg 0.032 mmol) was added. The mixture was allowed to warm to room temperature and after 1.5 h, 5 ml cold water was added to the mixture. The resulting solution was extracted with Et_2O (3×5 ml). The combined extracts were then washed with brine and dried over $MgSO_4$. After removal of solvent under reduced pressure, the crude mixture was purified over silica gel column (15% EtOAc/hexanes) giving a light yellow oil (140 mg, 63%).

$[\alpha]_D=+18$ ($CHCl_3$, $c=0.17$), ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.04 (3H, s), 0.05 (3H, s), 0.07 (3H, s), 0.08

(3H, s), 0.84 (9H, s), 0.94 (9H, s), 2.07 (2H, m), 2.09 (3H, s), 2.11 (3H, s), 2.13 (3H, s), 3.41(1H, ddd, $J=9.7$, 6.1, 3.6 Hz), 3.52 (1H, dt, $J=10.1$, 6.7 Hz), 3.64, (1H, dd, $J=11.6$, 3.4 Hz), 3.68 (1H, dd, $J=11.4$, 6.2 Hz), 3.83 (1H, t, $J=9.1$ Hz), 3.96 (1H, dt, $J=10.1$, 5.7 Hz), 4.32 (1H, d, $J=8.0$ Hz), 4.85 (1H, t. $J=9.1$ Hz), 4.88 (1H, t, $J=8.4$ Hz), 5.42 (1H, t, $J=6.6$ Hz), ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.97 (CH_3), −4.86 (CH_3), −4.16 (CH_3), −4.05 (CH_3), 18.17, 18.73, 21.27 (CH_3), 21.59 (CH_3), 21.73 (CH_3), 25.87 ($3\times CH_3$), 26.24 ($3\times CH_3$), 35.22 (CH_2), 46.67, 61.47 (CH), 63.66 (CH_2), 64.91 (CH_2), 72.46 (CH), 73.47 (CH), 74.05 (CH), 75.69 (CH), 77.55, 101.14 (CH), 169.74, 169.84, 170.05. IR: ν cm^{-1}, 2977, 2219, 1751, 1735, 1217, 1111. HRMS: calcd for $C_{29}H_{51}BrO_{10}Si_2+Na$, 717.2102, Found M+Na, 717.2089.

4.1.19. (8*Z*)-(3′*R*)-3′,Hydroxy-8′-decen-4′,6′-diynyl 3,6-*O*-bis(*tert*-butyldimethylsilyl)-2,4-*O*-bis(acetyl)-β-D-glucopyranoside (24). In the absence of light, a 5 ml round bottom flask equipped with a stir bar under an atmosphere of nitrogen was added MeOH (0.5 ml), $EtNH_2$ (0.5 ml), *Z*-3-pentene-1-yne (3 mg, 0.044 mmol) and NH_2OH–HCl (0.5 mg 0.007 mmol) at 0 °C in an ice bath. Next CuCl (0.2 mg, 2.2 μmol) was added followed by slow addition over 5 min of a solution of **23** (0.5 ml, 2.2 μmol). After 1 h at 25 °C, TLC analysis indicated the completion of the reaction. The mixture was then cooled to 0 °C and diluted with 2 ml EtOAc and 3 ml of a KCN/NH_4Cl solution. The aqueous layer was extracted with EtOAc (3×3 ml) and the combined extracts were washed with aq. $NaHCO_3$ and brine. The resulting solution was dried over $MgSO_4$ and purified over silica gel column (20% EtOAc/hexanes) giving a light yellow oil (12 mg, 86%).

$[\alpha]_D=-9.4$ (MeOH, $c=0.2$), ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.01 (3H, s), 0.02 (3H, s), 0.03 (6H, s), 0.79 (9H, s), 0.86 (9H, s), 1.89 (3H, dd, $J=6.9$, 1.7 Hz), 2.05 (3H, s), 2.10 (2H, m), 2.12 (3H, s), 3.39 (1H, ddd, $J=9.7$, 5.9, 3.5 Hz), 3.59 (1H, dd, $J=11.4$, 3.5 Hz), 3.64 (1H, dd, $J=11.4$, 6.0 Hz), 3.80 (1H, dt, $J=9.7$, 5.4 Hz), 3.81 (1H, t, $J=9.1$ Hz), 4.04 (1H, dt, $J=9.5$, 4.5 Hz), 4.34 (1H, d, $J=8.1$ Hz), 4.62 (1H, m), 4.80 (1H, dd, $J=9.9$, 9.1 Hz), 4.84 (1H, dd, $J=9.2$, 8.1 Hz), 5.49 (1H, dd, $J=10.8$, 1.6 Hz), 6.15 (1H, dq, $J=10.8$, 6.9 Hz), ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.97 (CH_3), −4.87 (CH_3), −4.15 (CH_3), −4.06 (CH_3), 16.87 (CH_3), 18.18, 18.74, 21.69 ($2\times CH_3$), 25.86 ($3\times CH_3$), 26.23 ($3\times CH_3$), 36.74 (CH_2), 61.72 (CH), 63.60 (CH_2), 66.77 (CH_2), 70.10, 72.37 (CH), 73.40 (CH), 74.33 (CH), 75.69 (CH), 76.00, 82.14, 83.23, 101.24 (CH), 109.25 (CH), 143.67 (CH), 169.82, 170.43. IR: ν cm^{-1}, 2930, 2250, 2219, 1751, 1735, 1220, 1063. HRMS: calcd for $C_{32}H_{54}O_9Si_2+Na$, 661.3204, Found M+Na, 661.3218.

4.1.20. Bidensyneoside A_2. In the absence of light, to a 5 ml round bottom flask equipped with a stirring bar under an atmosphere of nitrogen was added THF (1.3 ml) and **24** (9 mg, 0.014 mmol). The mixture was cooled to 0 °C with an ice bath and HF·pyridine complex (0.2 ml) was slowly added followed by acetic acid (0.13 ml). The mixture was allowed to warm to room temperature and stirring was continued for 18 h in the absence of light. After completion, the mixture was diluted with EtOAc (5 ml) and aq. $NaHCO_3$ (4 ml). The aqueous layer was saturated with NaCl and extracted with EtOAc (5×5 ml). The solvent was removed under reduced pressure. The residue was then dissolved in MeOH (1 ml) and transferred into a 5 ml round bottom flask in the absence of light. Next, K_2CO_3 (0.2 mg 1.4 μmol) was added and the solution was stirred at room temperature for 4 h until TLC analysis indicated a single spot. Next, approximately half of the MeOH was removed under reduced pressure and the resulting solution was purified over silica gel using mixed solvents (MeOH/H_2O/$CHCl_3$) giving a light brown residue (3.9 mg, 85%).

$[\alpha]_D=-152.5$ (MeOH, $c=0.012$), ^{1}H NMR (500 MHz, Methanol-d_4): δ 1.88 (3H, dd, $J=7.02$, 1.63 Hz), 1.97 (2H, m), 3.16 (1H, dd, $J=7.9$, 8.9 Hz), 3.26 (2H, m), 3.34 (1H, m), 3.67 (1H, dd, $J=11.7$, 5.0 Hz), 3.73 (1H, dt, $J=10.0$, 6.6 Hz), 3.85 (1H, dd, $J=11.7$, 1.9 Hz), 4.00 (1H, dt, $J=10.1$, 5.9 Hz), 7.26 (1H, d, $J=7.8$ Hz), 4.66 (1H, t, $J=6.6$ Hz), 5.53 (1H, dm $J=10.9$ Hz), 6.20 (1H, dq, $J=10.8$, 6.9 Hz), ^{13}C NMR (75 MHz, Methanol-d_4): δ 16.42 (CH_3), 38.97 (CH_2), 60.22 (CH), 62.73 (CH_2), 66.80 (CH_2), 69.45, 71.61 (CH), 75.11 (CH), 75.96, 77.96 (CH), 78.07 (CH), 78.46, 85.15, 104.59 (CH), 109.70 (CH), 144.00 (CH). IR: ν cm^{-1} 3330, 2918, 2231, 1611, 1162, 1071, UV/Vis: $\lambda_{(max)}$nm: 282, 266, 252, 240. HRMS: Calculated for $C_{16}H_{22}O_7+Na$ 349.1263, found 349.1267.

Acknowledgements

This research is supported in part by a grant from the National Institutes of Health (GM60263) and the Beckman Foundation. Acknowledgment is also made to the donors of the Petroleum Research Fund (PRF#36841-AC4) administered by the American Chemical Society. We thank Robert Falconer and Amanda Jones for preparing some of the starting materials.

References and notes

1. Wang, N. L.; Yao, X. S.; Ishii, R.; Kitanaka, S. *Chem. Pharm. Bull.* **2001**, *49*, 938–942.
2. Wang, N. L.; Yao, X. S.; Ishii, R.; Kitanaka, S. *Phytochemistry* **2003**, *62*, 741–746.
3. Garegg, P. J. Thioglycosides as glycosyl donors in oligosaccharide synthesis. In *Advances in Carbohydrate Chemistry and Biochemistry*, 1997; Vol. 52, pp 179–205.
4. Zhang, Z. Y.; Ollmann, I. R.; Ye, X. S.; Wischnat, R.; Baasov, T.; Wong, C. H. *J. Am. Chem. Soc.* **1999**, *121*, 734–753.
5. Burgess, K.; Jennings, L. D. *J. Am. Chem. Soc.* **1990**, *112*, 7434–7436.
6. Burgess, K.; Jennings, L. D. *J. Am. Chem. Soc.* **1991**, *113*, 6129–6139.
7. Schmidt, M.; Chatterjee, S. K.; Dobner, B.; Nuhn, P. *Chem. Phys. Lipids* **2002**, *114*, 139–147.
8. Fraserreid, B.; Udodong, U. E.; Wu, Z. F.; Ottosson, H.; Merritt, J. R.; Rao, C. S.; Roberts, C.; Madsen, R. *Synlett* **1992**, 927–942.
9. Marino, J. P.; McClure, M. S.; Holub, D. P.; Comasseto, J. V.; Tucci, F. C. *J. Am. Chem. Soc.* **2002**, *124*, 1664–1668.

10. Hofmeister, H.; Annen, K.; Laurent, H.; Wiechert, R. *Angew. Chem.* **1984**, *96*, 720–721.
11. Brandsma, L. *Preparative Acetylenic Chemistry*, 2nd ed.; 1988; Elsevier: New York, Vol. 34.
12. Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165–185.
13. Ireland, R. E.; Norbeck, D. W. *J. Org. Chem.* **1985**, *50*, 2198–2200.
14. Nomura, I.; Mukai, C. *Org. Lett.* **2002**, *4*, 4301–4304.
15. Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370–2374.
16. Fugedi, P.; Garegg, P. J. *Carbohydr. Res.* **1986**, *149*, C9–C12.
17. Fraser-Reid, B.; Madsen, R.; Campbell, A. S.; Roberts, C. S.; Merritt, J. R. Chemical synthesis of oligosaccharides. In *Bioorganic Chemistry: Carbohydrates*; Hecht, S. M., Ed.; Oxford University Press: New York, 1999; pp 89–133.
18. Ye, X. S.; Wong, C. H. *J. Org. Chem.* **2000**, *65*, 2410–2431.
19. Matsuoka, K.; Nishimura, S. I.; Lee, Y. C. *Bull. Chem. Soc. Jpn* **1995**, *68*, 1715–1720.
20. Wang, W.; Kong, F. *J. Org. Chem.* **1998**, *63*, 5744–5745.
21. Gung, B. W.; Kumi, G. *J. Org. Chem.* **2003**, *68*, 5956–5960.
22. One reviewer has given another reasonable explanation regarding the outcome of glycosylation versus orthoester formation: 'The C2-acetate stabilized oxycarbenium ion may be attacked by the incoming nucleophile at either the acetate carbonyl carbon, thus leading to the orthoester product, or at the anomeric carbon, leading to the desired glycosylation. The observed differences (between observed products with C3-OTBS versus C3-OAc protected donors) may simply reflect subtle differences in the kinetics of the attacks at these two centers: the more sterically congested OTBS protected substrate (which also yields a more stable oxycarbenium ion that 'demands less' in terms of stabilization by the C2-acetate relative to the C3-OAc protected donor) may not favor orthoester formation, as this would require developing unfavorable interactions (between the methyl group of the C2 acetate and the TBS group) in the transition state. Similar unfavorable interactions may deter the TBS-protected system from adopting a ring conformation that is favorable to orthoester formation.'

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 60 (2004) 9417–9424

Peptide dissociation in solution or bound to a polymer: comparative solvent effect

Luciana Malavolta and Clóvis R. Nakaie*

Department of Biophysics, Universidade Federal de São Paulo, Rua 3 de Maio 100, CEP 04044-020, São Paulo, SP, Brazil

Received 9 March 2004; revised 28 July 2004; accepted 5 August 2004

Abstract—Dissociation of peptide when in solution or attached to a polymer was investigated. Magnified solvation of peptide-resins occurred in solvent with similar polarity. Conversely the solubilization of peptides was not usually directly related to the medium polarity. The greater the difference between acidity and basicity of solvent and its potential to form van der Waals interaction, the stronger its solubilization strength. Solvents with similar electrophilicity and nucleophilicity usually did not solvate aggregated peptide-resins nor dissolve peptides. The peptide solubilization in water-containing mixed solvents depended on combination of acidity/basicity of both components. Some criteria for choosing suitable solvents for peptide-resin solvation or peptide solubilization could be advanced.
© 2004 Elsevier Ltd. All rights reserved.

1. Introduction

Complete understanding of the phenomenon of solute–solvent interaction has been eluding researchers for almost two centuries. Despite the exceptional relevance of this theme for all fields of science, this mystery has yet to be unravelled. The findings obtained to date only reinforce the difficulties in attaining a consensus about the rules that might govern this interaction. Amongst the innumerable factors that have been proposed over the years as controlling the solvent effect upon solute molecules, the relationship between the polarities of both components seems to be of utmost relevancy.[1] However, the so-called polarity parameter is not also easy to define or quantify and has been simply referred to as the overall solvation power of a solvent.[1,2]

In a conceptual departure from the great majority of approaches that have been applied to investigate this physico-chemical parameter, we have focused on interpreting the solute–solvent effect, deliberately using complex polymeric materials as examples of the solute component. Emphasis has been given to peptide resins and their interaction with a great number of solvents of varying polarities. This relationship has been assessed by measurement of peptide-resin solvation[3,4] or by determination of the dynamics of the interior of the solvated peptide–polymer network[5] using amino-acid type spin probes.[6] Starting from the knowledge that the presence of electrophilic and nucleophilic groups in a peptide bond (N–H and C=O moieties, respectively) might strongly affect the interaction of the solute with the solvent system, we have recently proposed the 1:1 sum of Gutman's[7] solvent electron acceptor number (AN) and solvent electron donor number (DN) as a novel, dimensionless and more accurate polarity scale.[3,4] Due to the presence of opposite concepts within the same parameter, the combined polarity term (AN+DN) was recently denoted amphoteric constant or scale.[8]

Hence, the present study aimed to pursue this approach of evaluating solvent effect upon peptide chains attached to a polymeric matrix. However, the solvent effect upon peptide chains that are free in homogeneous solution was also investigated. Needless to say, both approaches have enormous relevance. Improving the many solid-phase support processes has been crucial not only in the synthesis

Keywords: Peptide; Polymer; Solubility; Polarity; Solvent.

Abbreviations: Abbreviations for amino acids and nomenclature of peptide structure follow the recommendations of IUPAC-IUB (Commission on Biochemical Nomenclature (*J. Biol. Chem.* **1971**, *247* 997). Other abbreviations are as follows: AN, electron acceptor number; BHAR, benzhydrylamine resin; Boc, *tert*-butyloxycarbonyl; DCM, dichloromethane; DIC, diisopropylcarbodiimide; DIEA, diisopropylethylamine; DN, electron donor number; DMF, *N*,*N*′-dimethylformamide; DMSO, dimethylsulfoxide; HF, hydrogen fluoride; HOBt, 1-hydroxybenzotriazole; HFIP, hexafluoroisopropanol; HPLC, high-performance liquid chromatography; *i*PrOH, isopropanol; MBHAR, methylbenzhydrylamine resin; MeCN, acetonitrile; MeOH, methanol; NMP, *N*-methylpiperidine; PAM, 4-(oxymethyl)-phenylacetamidomethyl-resin; PEG, poly(ethylene glycol); PIP, piperidine; TBTU, 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate; TEA, triethylamine; TFA, trifluoroacetic acid; TFE, trifluoroethanol; THF, tetrahydrofuran.

* Corresponding author. Tel.: +55-11-5539-0809; fax: +55-11-5575-9617; e-mail: clovis.biof@epm.br

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.08.013

of peptides[9] and other macromolecules[10–11] but also for the unique solid-phase based combinatorial strategy that allowed the generation of peptide libraries[12] and development of new therapeutic drugs through solid-phase organic synthesis.[13] In respect to the attempt at investigating solubilization and aggregation phenomenon of peptide segments in solution, the physico-chemical findings could be further extended to any other homogeneous or heterogeneous types of macromolecule interactions. Special attention might be also given to well known degenerative disorders induced by pronounced peptide aggregation in physiological conditions such as those seen in Alzheimer's,[14–16] prion-related diseases[17] and type 2 diabetes mellitus.[18]

The main assumption addressed in this work is related to the application of electron acceptor and electron donor properties, either of the solvent or of the solute components. The strategy has its origins in the findings of previous studies,[3,4] in which mixed solvents composed of strong electrophilic solvents, such as trifluoroethanol (TFE), or strong nucleophilic solvents, such as dimethyl sulfoxide (DMSO) and dimethylformamide (DMF), were unable to dissociate aggregating peptide sequence attached to a polymeric backbone. As a consequence, swelling of beads was less than that predicted by its polarity value. In this sense, we rationalize that even single solvents, when characterized by rather small differences between AN and DN values, might also be poor solvating agents, not only in peptide-resin solvation but also in dissociation of peptide chains in solution. Typically, acetonitrile (MeCN), acetone and isopropanol (*i*PrOH) would be representative of this class of solvents, as their AN/DN values are 18.9/14.1; 12.5/17.0 and 33.5/36.0, respectively.[7] The maximum difference between both properties for the three solvents is therefore not higher than 4.8 (MeCN). In complement, these two distinct peptide chain dissociation processes (peptide-resin solvation and peptide solubilization in solution) are herein evaluated in solvent systems having as great a difference as possible between acidity and basicity. In addition, other factors such as the polarity of the media, potential of the solvent to induce van der Waals interactions, effect of water and urea in the medium, pH and the strength of peptide-chain aggregation are also considered.

2. Results and discussion

2.1. Peptide chain dissociation bound to a polymeric matrix

Table 1 depicts the AN, DN and (AN+DN) values for 31 single and mixed solvents, together with the swelling degrees of the following resins: (**1**) benzhydrylamine resin (BHAR), a copolymer of styrene and 1% divinylbenzene, containing a low 0.30 mmol/g of phenylmethylamine groups;[19] (**2**) PAC-PEG-PS, a 0.18 mmol/g substituted polyethylene glycol (PEG) grafted polystyrene-1% divinylbenzene copolymer, containing the proanthocyanidin (PAC) spacer[20] (Millipore, Bedford, CA, USA); (**3**) the peptide resin $(NANP)_3$-Nle, corresponding to the immunodominant epitope of the sporozoite of *Plasmodium falciparum* malaria parasite;[21] (**4**) the peptide resin [VHHQKLVFFAEDV-amide], the 12–24 fragment[22] of the Aβ amyloid peptide responsible for formation of amyloid fibril plaques in the nervous system, inducing the appearance of Alzheimer's disease.[23] Both peptide sequences were deliberately assembled in a very highly substituted (2.6 mmol/g) methylbenzhydrylamine resin (MBHAR).[24] These last two resins have peptide contents of 82 and 72%, respectively, which will magnify the effect of peptide chains on the overall resin solvation behavior. The solvation properties of polymers were estimated by measuring, under microscopy, the swelling of dry and swollen beads[25,26] in 31 single or mixed solvents that encompass almost the entirety of the polarity scale.

Following previously established rules for polymer solvation as a function of the solvent polarity,[3,4,8] the areas of maximum solvation for the lesser polar resins **1** and **2** in terms of solvent polarity values (AN+DN) are located at <20 and ± 25, respectively (Fig. 1(A) and (B)). The presence of a greater number of polar peptide bonds in the peptide resins **3** and **4** shifted their areas of maximum solvation for solvents having polarity values of about 40–50 (Fig. 1(C) and (D)). These results confirm that polymeric materials achieve maximum solvation in solvents with polarities similar to that of their backbone,[3,4,8,27] thus revealing a clear relationship between peptide-resin solvation and polarity of the medium.

As discussed above, the solvents 21 and 22 (open circles) are composed of a strong electron acceptor (TFE) and strong electron donors (DMF and DMSO, respectively), and these components tend to interact with each other rather than disrupt closely associated peptide chains throughout the resin network (Table 1). As a consequence, the swellings observed for these two mixed systems were less extensive than what had been expected based upon their polarity values (Fig. 1(C) and (D)). Accordingly, this effect was even less pronounced when the solutes under study were peptide-free polymers (Fig. 1(A) and (B)).

In agreement with our initial presupposition of a self-neutralizing effect occurring in some single solvents when their electrophilicity and nucleophilicity powers are comparable, a clear lack of swelling was observed for MeCN, acetone and *i*PrOH (open circles 29–31, respectively), mainly towards peptide resins **3** and **4**. Interestingly, even in the peptide-free polymers **1** and **2**, MeCN and acetone were unable to solvate the resin matrices completely. In conclusion, these single solvents seem to typify organic solvents with a very weak solute solvation capacity, which is induced by an internal self-neutralizing effect in terms of electron acceptor/electron donor capacities. These findings confirm that the use of the electrophilicity and nucleophilicity terms is advantageous in interpreting solvent effect upon polymer-type solutes. None of the solvation data found for mixed 21 and 22 or for single 29–31 solvents could be explained if, for instance, other classical one-component polarity scales, such as Hildebrand's δ parameter,[28] Dimroth–Reichardt's E_T30[29] or even the classical dielectric constant ε,[30] were used in this approach.

Of note is that the present results emphasize the low resin-swelling capacity of MeCN, acetone and *i*PrOH and point

Table 1. Solvent parameters and swelling degrees of resins

Entry	Solvent	AN[a]	DN[a]	(AN+DN)	Resin[b]			
					1	2	3	4
1	Toluene	3.3	0.1	3.4	87	64	26	40
2	DCM	20.4	1.0	21.4	84	79	46	52
3	Chloroform	23.1	4.0	27.1	83	83	53	64
4	NMP	13.3	27.3	40.6	67	75	70	64
5	DMF	16.0	26.6	42.6	70	70	75	57
6	DMSO	19.3	29.8	49.1	51	71	76	65
7	TFE	53.5	0.0	53.5	28	77	63	60
8	EtOH	37.1	32.0	69.1	19	53	38	40
9	MeOH	41.3	30.0	71.3	17	59	45	41
10	Formamide	39.8	24.0	63.8	23	61	61	46
11	50% TFE/Toluene	28.4	0.1	28.5	71	82	62	64
12	20% TFE/DCM	27.0	0.8	27.5	72	78	70	60
13	50% TFE/DCM	36.9	0.5	37.5	56	80	73	58
14	80% TFE/DCM	46.9	0.2	47.4	42	80	75	65
15	20% DMSO/NMP	14.5	27.8	42.3	73	71	65	61
16	50% DMSO/THF	13.7	24.9	38.6	65	68	62	55
17	65% NMP/THF	11.5	24.8	36.1	79	75	68	66
18	50% DCM/DMF	18.2	13.8	32.0	70	76	66	61
19	50% DCM/DMSO	19.9	15.4	35.3	68	69	68	65
20	50% MeOH/DMSO	30.3	29.9	60.2	25	66	72	56
21	50% TFE/DMF	34.8	13.3	48.1	27	69	29	47
22	50% TFE/DMSO	36.4	14.9	51.3	28	70	31	47
23	10% TEA/DCM	18.5	6.6	25.1	76	81	60	62
24	10% TEA/DMF	14.5	30.0	44.5	66	78	69	65
25	10% TEA/DMSO	17.5	32.9	50.4	47	72	71	64
26	20% PIP/DCM	16.3	8.8	25.1	78	76	55	nd
27	20% PIP/DMF	12.8	29.3	42.1	73	75	66	nd
28	20% PIP/DMSO	15.4	31.8	47.2	62	71	70	nd
29	Acetonitrile	18.9	14.1	33.0	32	65	24	36
30	Acetone	12.5	17.0	29.5	48	63	21	40
31	2-Propanol	33.5	36.0	69.5	14	46	10	37

nd = not determined.
[a] Reference.[4,7]
[b] [(Swollen volume–dry volume)/swollen volume]×100 using the following values for measured diameters of dry beads: resins: **1** = 50 μm; **2** = 114 μm; **3** = 87 μm; **4** = 94 μm.

out to the need for caution in the application of some types of column chromatography in which these solvents are routinely used as a mobile phase.

2.2. Peptide solubilization

Paralleling previous correlation studies comparing peptide-resin solvation and polarity of the medium, solubility of four model peptide sequences was determined in 18 single or mixed solvents (Table 2). Differing from the resin solvation approach, water (single or mixed) was deliberately involved, together with other solvent systems previously applied in the evaluation of insolubility problems related to peptides and other macromolecules. The peptides coded **A** and **B** are those attached to resins **3** ($[NANP]_3$-Nle) and **4** (VHHQKLVFFAEDV), respectively. They were cleaved from the resin, purified conventionally by HPLC until homogeneous. The vasoactive bradykinin (RPPGFSPFR, BK) and the hydrophobic VVLGAAIV-amide segment[31] corresponding to the 291–298 fragment of the murine H-2K protein[32] were also introduced in this investigation as peptides **C** and **D**, respectively. Experimentally, a 10 mg/mL solution of each peptide was centrifuged for 1 h at 14,000 rpm and the supernatant and the precipitate were lyophilized until a constant weight was attained. In addition to values of the percentages of solubilization of each peptide, Table 2 also displays the AN, DN, (AN+DN) and (AN−DN) parameters of most of the solvent systems used in this study.

Differing from what was observed with peptide resins, no clear correlation was observed between degree of solubilization and polarity of solvent represented by the (AN+DN) or by any other scales (Fig. 2). This lack of correlation was also observed when the hydrophobicity of each sequence (values of 8.2, 45.7, 27.8 and 37.5 for peptides **A**–**D**, respectively), calculated from their amino-acid composition as previously reported,[33] was plotted against the polarity of the solvents (figure not shown). These findings stress the difference, in terms of dependence upon the polarity of the medium, between peptide chains that are free in solution and those that are bound to a polystructural network. The fundamental aspect distinguishing these two situations is the fact that, when attached to a polymer backbone, the overall degree of freedom, as well as the intra- or interchain association propensity of peptide chains, is, perforce, affected by the nature and structure of the neighboring polymeric environment. Conversely, in the case of peptide chains free in solution, they are characterized by having a higher range of mobility and a complex set of structural characteristics that influence the type and intensity of their intra- or interchain associations.

Despite the lack of an acceptable relationship with the polarity of the medium, the solubilization factor of peptides

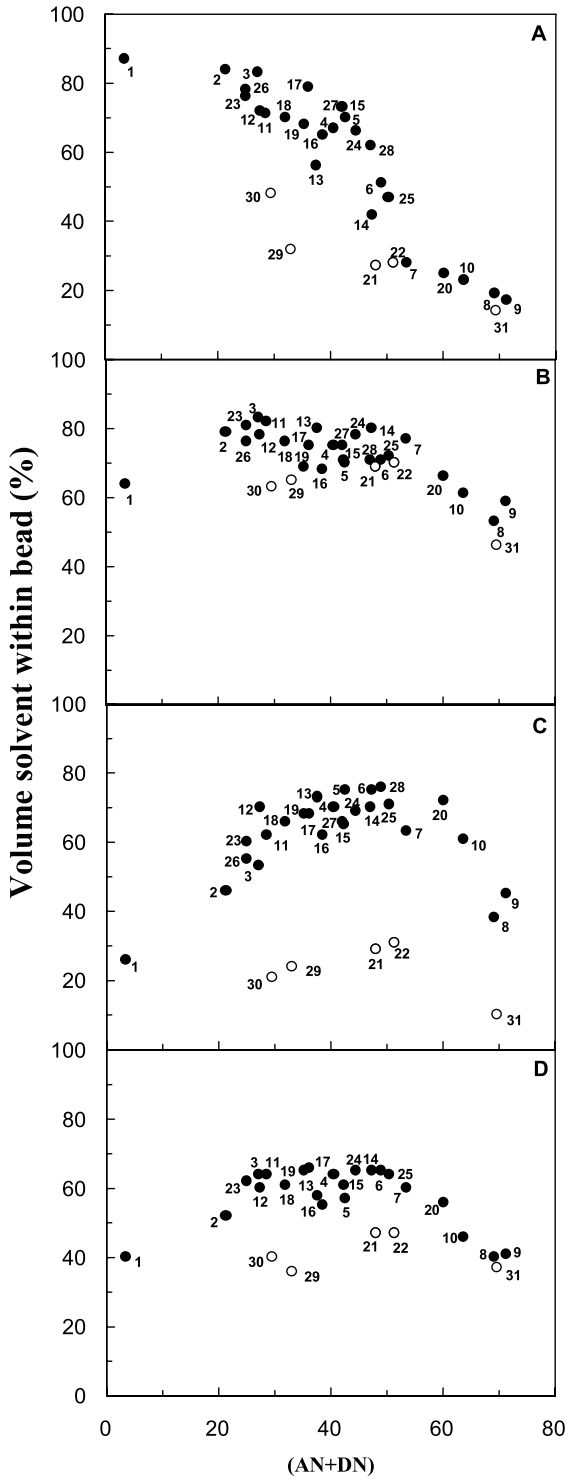


Figure 1. Swelling of resins (**1**), BHAR, 0.3 mmol/g [**A**], (**2**), PAC-PEG-PS, 0.18 mmol/g [**B**], (**3**), $(NANP)_3$-Nle-MBHAR, 2.6 mmol/g [**C**] and (**4**), VHHQKLVFFAEDV-MBHAR, 2.6 mmol/g [**D**] as a function of solvent polarity (AN+DN) values.

showed some correlation with the Lewis acid and Lewis basic properties of the medium, as represented by the AN and DN terms, respectively. In this context, the expected complementary participation of other factors, mainly the van der Waals forces, seems to be crucial for better evaluating the solubilization factor of each peptide sequence.

2.3. Effect of self-neutralizing (or heterogeneous) solvents

Initially, the results shown in Table 2 demonstrated that, in close agreement with their low capacity for disruption of peptide chains when bound to resins (low bead solvation), those single solvents denoted self-neutralizing, such as MeCN, acetone and *i*PrOH, also failed to dissolve peptides in solution, regardless of the sequence. However, their solubilization capacity changed profoundly when they were mixed with water, a strong electrophilic (or hydrogen bonding donor) solvent, characterized by an AN number of 54.8 (Table 2). Except for the strong aggregating peptide **D**, where the addition of water did not significantly increase their solubilization properties, the peptides were almost entirely dissolved in MeCN, acetone and *i*PrOH when cosolvated with 50% (v/v) water. These results may be attributable to the increased difference between AN and DN values (higher electrophilicity) in the mixed solvents resulting from the presence of water molecules (Table 2, AN−DN term). This may therefore favor the interaction of aqueous mixed solvents over that of single solvents, in which the difference in this physico-chemical parameter is quite low.

This unique effect of the water molecule is entirely governed by its overall hydrogen bonding property. However, due to its simple structure, it is, for instance, unable to promote the number of van der Waals (hydrophobic) interactions necessary for disruption of strongly aggregated chains, as can be seen for peptide **D** in water (Table 2). In this context, the further interpretation of solubilization data from more structured segments will be of great relevance in elucidating some rules that may control solubilization of peptides and macromolecules in general.

Many authors[34,35] have made mention of the tendency of these self-neutralizing solvents (mainly MeCN) to induce β-sheet strands rather than disordered or α-helix-type conformations in most peptide sequences, usually leading to aggregated states. However, none of these reports interpreted these findings in the light of the AN and DN concepts as detailed herein.

Relevant again for column chromatographic application, MeOH presented much higher peptide solubility power than did MeCN or *i*PrOH, both typifying organic solvents often applied in HPLC studies. Although this solubilization property increased proportionately with increased water in the mixture, it must be remembered that, as previously stated, these two weak solvating agents (MeCN and *i*PrOH) presented poor polymer solvation capability. This underscores the need for caution when these solvent systems are to be used in such experiments.

2.4. Effect of strong electrophilic or nucleophilic solvents

In general, only solvents comprising the strong electron donor DMSO (DN of 29.8) or the strong electron acceptor hexafluoroisopropanol (HFIP; AN of 88.0)[36] seemed able to completely dissolve aggregation sequences such as peptide **D**. In this case, solubilization percentages of 84 and 80%, respectively, were achieved. In contrast, the less

Table 2. Solvent parameters and solubility of individual peptides

Solvent	Parameter				Solubility of Peptide (%)			
	AN[a]	DN[a]	(AN+DN)	(AN-DN)	A	B	C	D
1. H_2O pH 3.0 and 9.0	54.8	18.0	72.8	36.8	100	100	100	0
2. MeCN	18.9	14.1	33.0	4.8	0	8	0	0
3. 50% MeCN/H_2O	36.9	16.1	53.0	20.8	100	76	100	0
4. Acetone	12.5	17.0	29.5	-4.5	0	0	0	0
5. 50% Acetone/H_2O	33.7	17.5	51.2	16.2	100	84	100	11
6. iPrOH	33.5	36.0	69.5	-2.5	0	0	0	10
7. 50% iPrOH/H_2O	44.2	27.0	71.2	17.2	100	100	88	25
8. MeOH	41.3	30.0	71.3	11.3	100	100	92	33
9. 50% MeOH/H_2O	48.1	24.0	72.1	24.1	100	100	88	26
10. TFE	53.5	0.0	53.5	53.5	100	100	92	20
11. 50% TFE/H_2O	54.2	9.0	63.2	45.2	100	100	100	60
12. HFIP	88.0	0.0	88.0	88.0	100	100	100	80
13. 50% HFIP/H_2O	71.4	9.0	80.4	62.4	100	100	100	70
14. DMSO	19.3	29.8	49.1	-10.5	100	100	100	84
15. 50% DMSO/H_2O	37.1	23.9	60.9	13.2	100	100	100	32
16. 3.0 M Urea	nd	nd	nd	nd	100	100	100	0
17. 6.0 M Urea	nd	nd	nd	nd	100	80	96	0

nd = not determined.
[a] Reference.[4,7]

electrophilic TFE (AN of 53.5) displayed much lower solubilization power in comparison with HFIP (20%). This significant difference in solubilization capacity between TFE and HFIP seems to be clearly due to the difference in their electrophilicity (AN increased from 53.5 to 88.0, respectively). However, to the strength of the van der Waals interaction induced by the presence of a second $-CF_3$ group in the HFIP structure is equally relevant. The appropriate combination of both effects (hydrogen bonding and hydrophobic or van der Waals forces) seems to play a crucial role in the significant increase in the disruption power of aggregated peptides, which is more pronounced when in HFIP.

The effect of the addition of water to single solvents is very complex but of great relevancy, as observed in the case of

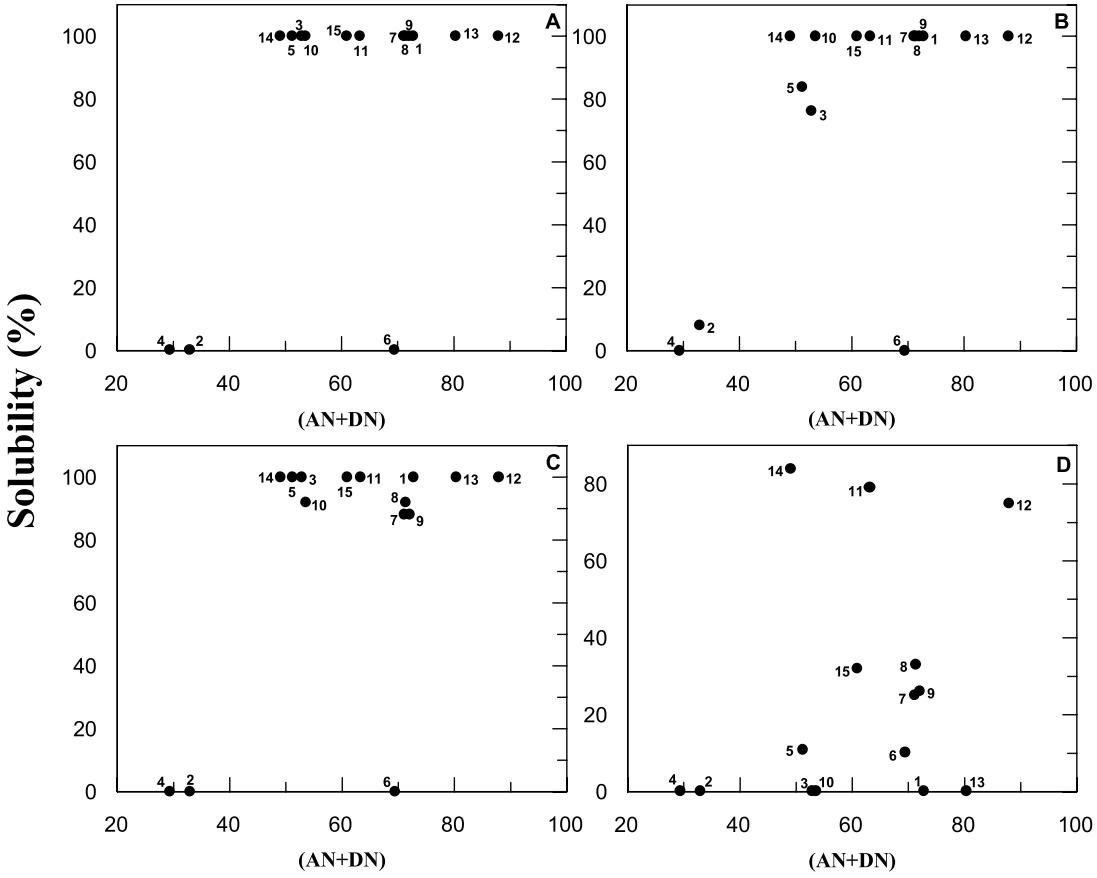


Figure 2. Solubility of peptides (**A**), $(NANP)_3$-Nle-amide, (**B**), VHHQKLVFFAEDV-amide, (**C**), RPPGFSPFR and (**D**), VVLGAAIV-amide as a function of solvent polarity (AN+DN) values.

the 'poor' solvents discussed in the previous section. When water was added to the strong polar organic solvents DMSO or HFIP, the solubilization yield decreased from 84 to 32% and from 80 to 70%, respectively (Table 2). These results indicate that the effect of the addition of water seems to be highly dependent upon the type of organic solvent to be mixed (electron acceptor or electron donor) and also on the particular characteristic of peptide sequence (degree of aggregation). When added to DMSO, the nucleophilicity of this polar aprotic solvent are partially neutralized by the strong electrophilicity of the water molecule, thus partially reducing the solubilization properties of the DMSO/water mixture. This effect is quite similar to the previously discussed solvation behavior of the heterogeneous mixed solvents 21 and 22, which are composed of strongly electrophilic and nucleophilic components (Table 1).

In contrast, when electrophilic water is added to other strong electrophilic solvents such as TFE or HFIP, a homogeneous solution is formed and the degree of alteration in their peptide chain dissolution potential seems very complex. For instance, in the case of HFIP, the addition of water slightly reduced the degree of peptide **D** solubilization (from 80 to 70%, respectively), whereas more significant variation (increases) in solubilization occurred in pure TFE or in TFE/water mixture (20 and 60%, respectively). Again, this result shows that the more pronounced effect seen when water was added to TFE than when it was added to HFIP could be credited to the much stronger electrophilicity of the latter fluorinated solvent, in combination with a higher potential to produce van der Waals interaction with aggregated peptide **D**.

In the literature, a great number of studies have examined peptide or other macromolecule solubility with the aim of finding rules that govern the effects of solvents with weak or strong dissociations.[18,34–38] In addition to these efforts, no clear explanation has been proffered for the apparently random way in solvents are currently chosen. For example, why would one consider opposite DMSO solvents to be more suitable than HFIP/TFE solvents? We have presented an alternative and, in some cases, consistent approach to address this extremely complex issue of solvent effects upon solute molecules. This approach relied mainly on the conjugated use of AN and DN terms (sum or difference), as well as on the potential for hydrophobic interaction, of all solvents involved in the interaction process, and on the specific characteristics of the peptide or peptide-resin solute components.

Due to the great complexity of the solute–solvent interaction, especially in cases involving peptide or peptide–polymer solutes, many further studies are warranted. In an attempt to depict this complexity, we have also included, in Table 2, dissolution data obtained when we used aqueous urea solutions, which are often proposed for use in the dissolution of proteins and peptides. A failure of such solutions to dissolve peptide **D** was observed, as well as, notably, an inverse relationship between solubility and urea concentration in peptide **B** dissolution. Otherwise, no correlation between solubility and media pH was observed, suggesting the absence of an ionization effect in some subgroups of the four peptides evaluated herein. Much larger numbers of solvent systems and solute models are currently under investigation in an attempt to further establish rules that might not only facilitate selection of the most suitable solvent for peptide dissolution or peptide-resin solvation but also be extended to many other solute–solvent interactions.

3. Conclusions

Despite the huge amount of data already existing in the literature, the solute–solvent interaction effect has eluded the scientific community for many decades. In a recent investigation, we combined the electron acceptor (AN) and electron donor (DN) parameters in order to build an alternative solvent polarity scale. As a continuation of this, we have, in the present study, evaluated these same physicochemical properties in order to interpret the complex dissociation process of peptide chains, comparing those free in solution with those coupled to polymers.

After investigating model peptides and peptide-resins solvated in a large number of solvent systems, we have reached several conclusions. First, in contrast to improved solvation of peptide-resins in solvents with similar polarities, the solubilization yield of a peptide in solution is not always directly related to the polarity of the medium. Second, optimal solubilization of peptides is strongly dependent upon the difference between AN and DN values of the solvent and of its ability to induce van der Waals attraction. In addition, mixed solvents with rather equivalent electrophilicity and nucleophilicity are not able to solvate aggregated peptide-resins or dissolve peptide sequences. This rule is also applicable to single solvents that present similar AN and DN values and induce a molecular self-neutralizing effect, thereby precluding dissociation of peptides in solution or solvation of peptide-resins. Furthermore, this self-neutralizing effect occurring in mixed or single solvents must be also considered for other biotechnological applications (such as in column chromatography) since it may affect solute solubilization and resin solvation simultaneously. Moreover, whether the addition of the strongly electrophilic water molecule to a mixture for peptide solubilization will be advantageous or not is clearly dependent on the relationship between acidity and basicity of both components. Finally, the peptide solubilization effect of urea in the solution is sequence dependent and, in some cases, involves an inverse correlation between solubility and urea concentration. Therefore, in light of the Lewis acidity and Lewis basicity properties of solvent systems, some relevant rules could be established for the complex processes of peptide dissolution and peptide-resin solvation.

4. Experimental

All amino-acid derivatives were purchased from Bachem (Torrance, CA, USA). Solvents and reagents were purchased from Fluka (Buchs, Switzerland), Aldrich-Sigma (Steinheim, Germany) and Advanced Chemtech (Louisville, KY, USA). The PAC-PEG-PS resin was acquired from Millipore (Bedford, CA, USA) and batches

of BHAR or MBHAR (0.3 and 2.6 mmol/g, respectively) were synthesized in our laboratory, following guidelines laid out in previous reports.[19,26]

4.1. Peptide synthesis

The peptides were synthesized manually according to the standard Boc[8] protocol. The following Boc amino-acid derivatives were used: Boc-Glu(OcHex), Boc-Asp(OcHex), Boc-Lys(2-Cl-Z), Boc-Ser(Bzl) and Boc-His(Tos). In the Boc chemistry, after coupling the C-terminal amino acid to the resin, the successive α-amino group deprotection and neutralization steps were performed in 30% TFA/DCM (30 min) and 10% DIEA/DCM (10 min). The amino acids were coupled using DIC/HOBt in DMF and, if necessary, TBTU in the presence of HOBt and DIEA using 20% DMSO/NMP as a solvent system. After a 2 h coupling period, the qualitative ninhydrin test was performed to estimate the completeness of the reaction. To check the purity of the synthesized peptide sequence attached to the resin, cleavage reactions with small aliquots of resin were carried out with the low-high HF procedure. Analytical HPLC, as well as LC/MS (electrospray) mass spectrometry (Micromass, Manchester, UK) and amino-acid analysis (Biochrom 20 Plus, Amersham Biosciences, Uppsala, Sweden), were used to check the homogeneity of each synthesized resin-bound peptide sequence.

4.2. Analytical HPLC

Analysis was performed in a system consisting of two model 510 HPLC pumps (Waters, Milford, MA, USA), an automated gradient controller, Rheodyne manual injector, 486 detector and 746 data module. Unless otherwise stated, peptides were analyzed on a 4.6×150 mm^2 column with a 300 Å pore size and a 5 μm particle size (C18; Vydac, Hesperia, CA, USA) using the solvent systems: A (H_2O containing 0.1% TFA) and B (60% MeCN in H_2O containing 0.1% TFA). A linear gradient of 10–90% B in 30 min was applied at a flow rate of 1.5 mL/min and detection at 220 nm.

4.3. Preparative HPLC

Purification of peptides was carried out using solvent A (H_2O containing 0.1% TFA) or solvent B (90% MeCN in H_2O containing 0.1% TFA). A linear gradient was applied which was dependent upon the retention time determined in the HPLC analysis of the peptide, using the same solvent systems. The flow rate was of 10 ml/min and the detection of peaks was carried out at 220 nm.

The following peptides deemed requisite for solubilization experiments were synthesized through Boc strategy:

(a) $(NANP)_3$-Nle-amide: this peptide was synthesized at 0.53 mmol scale starting from MBHAR resin (2.63 mmol/g). The crude peptide yielded 250 mg and, after HPLC purification, 165 mg of pure compound were obtained. ESI-MS, *m*/*z*: 1319 (theoretical), 1320 (obtained).

(b) VHHQKLVFFAEDV-amide: this peptide was synthesized in MBHAR (2.63 mmol/g) at 0.53 mmol scale. A total of 424 mg of crude peptide were obtained and, after HPLC purification, 104 mg of pure compound remained. ESI-MS, *m*/*z*: 1569 (theoretical); obtained (1569.2).

(c) VVLGAAIV-amide: this peptide was also synthesized in MBHAR (2.63 mmol/g) at 0.53 mmol scale After cleavage with HF procedure, 452 mg of crude peptide were obtained which yielded 126 mg after HPLC purification. ESI-MS, *m*/*z*: 740 (theoretical); 740.4 (obtained).

(d) RPPGFSPFR (BK): this peptide was synthesized in Boc-Arg(Tos)-PAM resin (0.6 mmol/g) at 0.5 mmol scale. After cleavage with HF procedure, 433 mg of crude peptide were obtained which yielded 273.4 mg after HPLC purification. ESI-MS, *m*/*z*: 1060 (theoretical); 1059 (obtained).

4.4. Measurements of bead swellings

Before use in peptide synthesis or microscopic measurement of bead sizes, most resin batches were sized by sifting through metal sieves to lower the standard deviation of resin diameters to about 4%. Swelling studies of these narrowly sized populations of beads have been previously conducted.[3] In short, 150–200 dry and swollen beads of each resin, allowed to solvate overnight, were spread over a microscope slide and measured directly with an Olympus model SZ11 microscope coupled with Image-Pro Plus version 3.0.01.00 software. Since the sizes in a sample of beads are log-normally rather than normally distributed, the more accurate geometric mean values and geometric standard deviations were used to estimate the central value and the distribution of the particle diameters. The resins were measured with their amino groups in the deprotonated form, obtained by 3×5 min washes in TEA/DCM/DMF (1:4.5:4.5, v/v/v), followed by 5×2 min washes in DCM/DMF (1:1, v/v) and 5×2 min DCM washings. Resins were dried in vacuum using an Abderhalden-type apparatus with MeOH reflux.

4.5. Solubility measurement of peptides

The solubility of each peptide was determined by dissolving 2.5 mg of pre-purified peptide in 0.25 mL (ca. 10 mM) of each of the solvents described in Table 2. The solution was centrifuged for 1 h at 14,000 rpm and the supernatant and the precipitate were lyophilized until constant weight was attained. Solubility data are expressed as percentages.

Acknowledgements

Grants from the Brazilian governmental agencies FAPESP and CNPq are gratefully acknowledged. L. M. is fellow of FAPESP and C. R. N. is a recipient of research fellowships from CNPq and FADA.

References and notes

1. (a) Katritzky, A. R.; Fara, D. C.; Hongfang, Y.; Tämm, K.

Chem. Rev. **2004**, *104*, 175–198. (b) Reichardt, C. *Chem. Rev.* **1994**, *94*, 2319–2358.
2. (a) Markus, Y. *Chem. Soc. Rev.* **1993**, *22*, 409–416. (b) Pytela, O. *Coll. Czech. Chem. Commun.* **1988**, *53*, 1333–1423.
3. Cilli, E. M.; Oliveira, E.; Marchetto, R.; Nakaie, C. R. *J. Org. Chem.* **1996**, *61*, 8992–9000.
4. Malavolta, L.; Oliveira, E.; Cilli, E. M.; Nakaie, C. R. *Tetrahedron* **2002**, *58*, 4383–4394.
5. (a) Cilli, E. M.; Marchetto, R.; Schreier, S.; Nakaie, C. R. *Tetrahedron Lett.* **1997**, *38*, 517–520. (b) Cilli, E. M.; Marchetto, R.; Schreier, S.; Nakaie, C. R. *J. Org. Chem.* **1999**, *64*, 9118–9123.
6. Marchetto, R.; Schreier, S.; Nakaie, C. R. *J. Am. Chem. Soc.* **1993**, *115*, 11042–11043.
7. (a) Gutmann, V. *The Donor–Acceptor Approach to Molecular Interactions*; Plenum: New York, 1978. (b) Gutmann, V. *Electrochim. Acta* **1976**, 21, 661–670.
8. Oliveira, E.; Cilli, E. M.; Miranda, A.; Jubilut, G. N.; Albericio, A.; Andreu, A.; Paiva, A. C. M.; Schreier, S.; Nakaie, C. R. *Eur. J. Org. Chem.* **2002**, *21*, 3686–3694.
9. (a) Barany, G.; Merrifield, R. B. *The Peptides*; Academic Press: New York, 1980, p 1. (b) Stewart, J. M.; Young, J. D.; *Solid Phase Peptide Synthesis*; Pierce Chemical Company: Rockford, 1984; Vol. III. (c) Fields, G. B.; Noble, R. L. *Int. J. Pept. Protein Res.* **1990**, 35, 161–214.
10. (a) Letsinger, R. L.; Finnan, J. L.; Heavner, G. A.; Lunsford, W. B. *J. Am. Chem. Soc.* **1975**, *85*, 3278–3279. (b) Amarnath, V. D.; Broom, A. *Chem. Rev.* **1977**, *77*, 183–217.
11. (a) Fréchet, J. M.; Schuerch, C. *J. Am. Chem. Soc.* **1971**, *93*, 492–498. (b) Zehavi, U.; Patchornik, A. *J. Am. Chem. Soc.* **1973**, *95*, 5673–5678.
12. (a) Jung, G.; BeckSickinger, A. G. *Angew. Chem. Int. Ed. Eng.* **1992**, *31*, 367–383. (b) Lam, K. S.; Lebl, M.; Krchanak, V. *Chem. Rev.* **1997**, *97*, 411–448. (c) Lam, K. S.; Salmon, S. E.; Hersh, E. M.; Hruby, V. J.; Kazmierski, W. M.; Knapp, R. J. *Nature* **1991**, *354*, 82–84.
13. (a) Fridkin, M.; Patchornik, A.; Kachalski, E. *J. Am. Chem. Soc.* **1966**, *88*, 3164–3166. (b) Frechet, J. M. J. *Tetrahedron* **1981**, *37*, 663–683. (c) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. *Tetrahedron* **1996**, *52*, 4527–4554. (d) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *95*, 555–600.
14. Gordon, D. J.; Meredith, S. C. *Biochemistry* **2003**, *42*, 475–485.
15. Srisailam, S.; Kumar, T. K. S.; Rajalingam, D.; Kathir, K. M.; Sheu, H. S.; Jan, F. J.; Chao, P. C.; Yu, C. *J. Biol. Chem.* **2003**, *278*, 17701–17709.
16. Banerjee, A.; Maji, S. K.; Drew, M. G. B.; Haldar, D.; Banerjee, A. *Tetrahedron Lett.* **2003**, *44*, 335–339.
17. Zahn, R.; Liu, A.; Lührs, T.; Riek, R.; von Schroetter, C.; Garcia, F. L.; Billeter, M.; Calzolai, L.; Wider, G.; Wüthrich, K. *Proc. Natl Acad. Sci.* **2000**, *97*, 145–150.
18. Nilsson, M. R.; Nguyen, L. L.; Raleigh, D. P. *Anal. Biochem.* **2001**, *288*, 76–82.
19. Pietta, P. G.; Cavallo, P. F.; Takahashi, K.; Marshall, G. R. *J. Org. Chem.* **1974**, *39*, 44–48.
20. Jensen, K. J.; Alsina, J.; Songster, M. F.; Vágner, J.; Albericio, F.; Barany, G. *J. Am. Chem. Soc.* **1998**, *120*, 5441–5452.
21. Dame, J. B.; Williams, J. L.; McCtchan, T. F.; Weber, J. L.; Wirtz, R. A.; Hockmeyer, W. T.; Maloy, W. L.; Haynes, J. D.; Schneider, I.; Roberts, D.; Sanders, G. S.; Reddy, E. P.; Diggs, C. L.; Miller, L. H. *Science* **1984**, *225*, 593–599.
22. Abe, H.; Kawasaki, K.; Nakanishi, H. *Jpn Biochem. Soc.* **2002**, *132*, 863–874.
23. (a) Balbach, J. J.; Tshii, Y.; Antzutkin, O. N.; Leapman, R. D.; Rizzo, N. W.; Dyda, F.; Reed, J.; Tyeko, R. *Biochemistry* **2000**, *39*, 13748–13759. (b) Rabanal, F.; Tusell, J. M.; Sastre, L.; Quintero, M. R.; Cruz, M.; Grillo, D.; Pons, M.; Alberício, F.; Serratosa, J.; Giralt, E. *J. Pept. Sci.* **2002**, *8*, 578–588.
24. Matsueda, G. R.; Stewart, J. M. *Peptides* **1981**, *2*, 45–50.
25. (a) Sarin, V. K.; Kent, S. B. H.; Merrifield, R. B. *J. Am. Chem. Soc.* **1980**, *102*, 5463–5470. (b) Tam, J. P.; Lu, Y. A. *J. Am. Chem. Soc.* **1995**, *117*, 12058–12063.
26. Marchetto, R.; Etchegaray, A.; Nakaie, C. R. *J. Braz. Chem. Soc.* **1992**, *3*, 30–37.
27. Burton, A. F. M. *Chem. Rev.* **1975**, *75*, 731–753.
28. Hildebrand, J. H. *Chem. Rev.* **1949**, *44*, 37–45.
29. Dimroth, K.; Reichardt, C.; Siepmann, T.; Bohlman, F. *Liebigs Ann. Chem.* **1963**, *661*, 1–37.
30. Parker, A. J. *Chem. Rev.* **1969**, *69*, 1–32.
31. Narita, M.; Chen, J. Y.; Sato, H.; Kim, Y. *Bull. Chem. Soc. Jpn* **1985**, *58*, 2494–2501.
32. Brown, J. L.; Kato, K.; Silver, J.; Nathenso, S. G. *Biochemistry* **1974**, *13*, 3174–3178.
33. Meek, J. L.; Rossetti, Z. L. *J. Chromatogr.* **1981**, *211*, 15–28.
34. Sen, S.; Dash, D.; Pasha, S.; Brahmachari, S. K. *Protein Sci.* **2003**, *12*, 953–962.
35. Vieira, E. P.; Hermel, H.; Möhwald, H. *Biochim. Biophys. Acta* **2003**, *1645*, 6–14.
36. Narita, M.; Honda, S.; Umeyama, H.; Obana, S. *Bull. Chem. Soc. Jpn* **1988**, *61*, 281–284.
37. (a) Hirota-Nakaoka, N.; Hasegawa, K.; Naiki, H.; Goto, Y. *J. Biochem.* **2003**, *134*, 159–164. (b) Cheong, W. J.; Keum, Y. I.; Ko, J. H. *Bull. Kr. Chem. Soc.* **2002**, *23*, 65–70. (c) Chen, S.; Wetzel, R. *Protein Sci.* **2001**, *10*, 887–891.
38. (a) Formaggio, F.; Bettio, A.; Moretto, V.; Crisma, M.; Toniolo, C.; Broxterman, Q. B. *J. Pept. Sci.* **2003**, *9*, 461–466. (b) Sirangelo, I.; Piaz, F. D.; Malmo, C.; Casillo, M.; Birolo, L.; Pucci, P.; Marino, G.; Irace, G. *Biochemistry* **2003**, *42*, 312–319.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 60 (2004) 9425–9431

Intramolecular 9-membered hydrogen bonding of 2-arylmethylphenols having carbonyl groups at 2′-position

Yasuharu Yoshimi,[a] Hajime Maeda,[b] Minoru Hatanaka[a] and Kazuhiko Mizuno[b,*]

[a]*Department of Applied Chemistry and Biotechnology, Faculty of Engineering, Fukui University, 3-9-1 Bunkyo, Fukui, Fukui 910-8507, Japan*
[b]*Department of Applied Chemistry, Graduate School of Engineering, Osaka Prefecture University, 1-1 Gakuen-cho, Sakai, Osaka 599-8531, Japan*

Received 26 May 2004; revised 3 August 2004; accepted 4 August 2004

Abstract—Thermodynamic parameters of nine-membered intramolecular hydrogen bonding between carbonyl groups and phenolic hydroxyl groups of 2-arylmethylphenols having methoxycarbonyl, dimethylcarbamoyl, and formyl groups were determined by variable temperature ^{1}H NMR studies and van't Hoff analysis. The enthalpy of the hydrogen bonding was related to the electron-withdrawing ability of the substituents on the phenol and the basicity of the carbonyl group. The entropy loss of the hydrogen bonding was dependent on the rotation freedom of the phenol group.
© 2004 Elsevier Ltd. All rights reserved.

1. Introduction

Intramolecular hydrogen bonding plays an important role in the conformation of biomolecules and biochemical reactions. Recently, much attention has been paid to the intramolecular hydrogen bonding of unnatural polymers such as β,γ,δ-peptides,[1] oligoanthranilamides,[2] and oligocarbohydrate amino acids.[3] Despite the fact that phenolic compounds are well known as antioxidants in the biological system and are used as additives in food, polymers, paints to prevent oxidation of these materials, the intramolecular hydrogen bonding of these compounds has been less discussed except the chemical behavior of salicylic ester and its related compounds which form the typical 6-membered hydrogen bonding.[4] The intramolecular hydrogen bonding of these phenolic compounds substantially changes their chemical and physical properties. In particular, the ability of an antioxidant in ubiquinol is dependent on the formation of intramolecular hydrogen bonding of the phenolic hydroxyl group.[5] Interestingly, the phenolic hydrogen atom which forms the intramolecular hydrogen bonding is more easily abstracted by the radical than the one which forms intermolecular hydrogen bonding.

We have recently reported a novel 9-membered intramolecular hydrogen bonding between ester carbonyl and phenolic hydroxyl groups both in the solid state and in $CDCl_3$ solution.[6] This is a rare example of medium-ring size hydrogen bonding[7] in phenolic compounds, and it was found that the variable temperature ^{1}H NMR chemical shifts of phenolic protons showed the equilibrium of the intramolecular hydrogen bonding. In this paper, we now report that 2-arylmethylphenols having ester, amide, and aldehyde at the 2′-position could form an intramolecular 9-membered hydrogen bonding between aromatic carbonyl and phenolic hydroxyl groups in $CDCl_3$ solution, and the substituent effects of these compounds indicated that the intramolecular hydrogen bonding depended on the acidity of the phenol and the basicity of the carbonyl group. The phenolic proton chemical shifts with variable temperature gave the thermodynamic parameters, which could reveal the details of the intramolecular 9-membered hydrogen bonding.

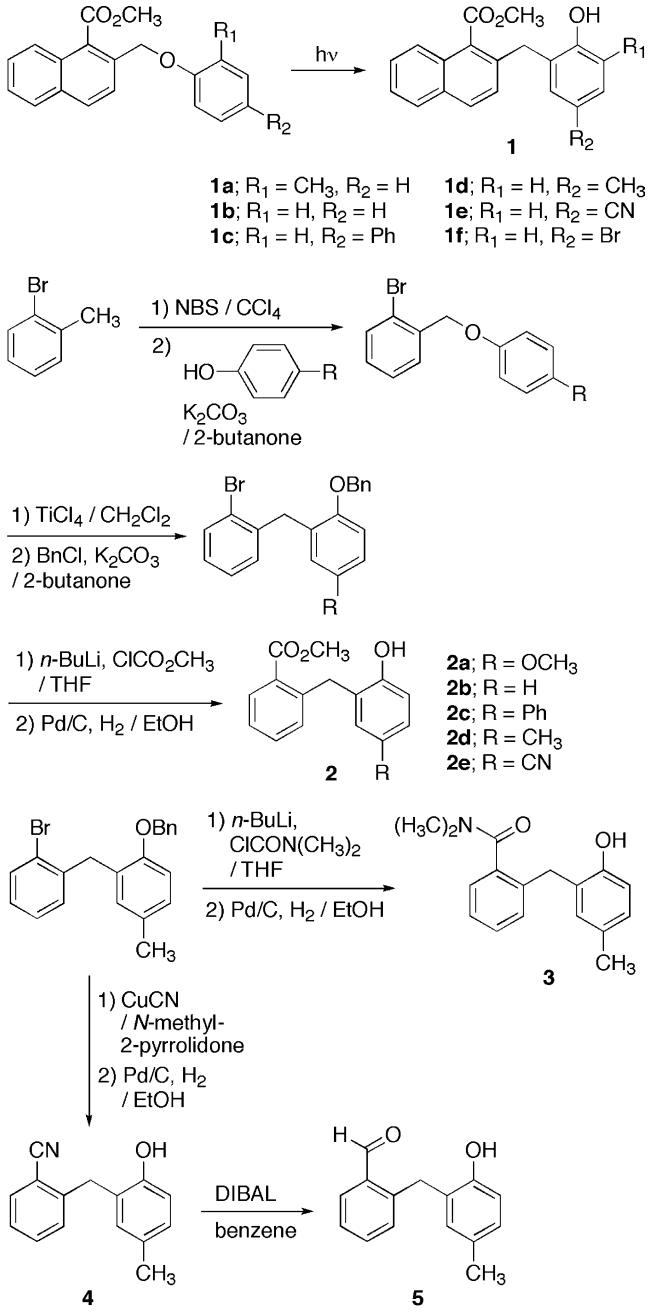
2. Results and discussion

2.1. Preparation of 2-arylmethylphenol derivatives

2-(1-Methoxycarbonyl-2-naphthyl)methylphenol and its derivatives **1a–f** have been prepared by photo-Claisen type rearrangement as reported before (Scheme 1).[8] The preparation of 2-(1-methoxycarbonyl-2-phenyl)methylphenol derivatives **2a–e** from 1-bromo-2-methylbenzene is

Keywords: Intramolecular hydrogen bonding; 2-Arylmethylphenol; Variable temperature ^{1}H NMR; van't Hoff analysis.
* Corresponding author. Tel.: +81722549289; fax: +81722549289; e-mail: mizuno@chem.osakafu-u.ac.jp

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.08.007

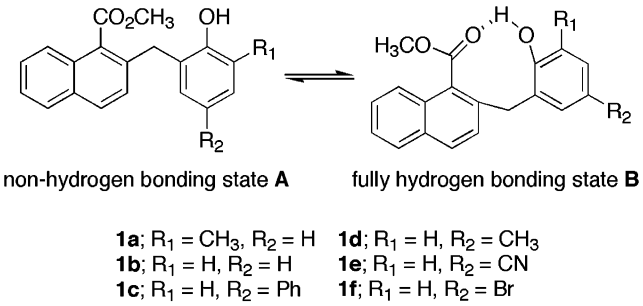


Scheme 1.

shown in Scheme 1. The 2-bromobenzyl phenyl ethers were synthesized by bromination and etherification of 1-bromo-2-methylbenzene. Then, the ethers were rearranged to the *ortho*-position by $TiCl_4$, and were protected by the benzyl group. **2a–e** were given by the esterification, followed by deprotection with Pd/C and H_2. The amide derivative **3** was obtained by a similar method. DIBAL reduction of **4**, which was prepared by cyanation and deprotection from the corresponding bromo derivative, gave the aldehyde **5**.

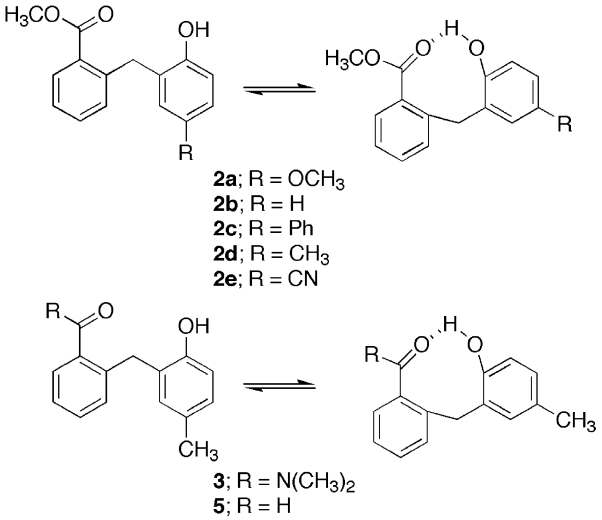
2.2. Intramolecular 9-membered hydrogen bonding between aromatic carbonyl and phenolic hydroxyl groups in $CDCl_3$ solution

The X-ray crystallographic analysis of **1a** showed the possibility of the intramolecular 9-membered hydrogen bonding in crystalline state.[5] The ^1H NMR studies of **1a–f** (5 mM) in $CDCl_3$ at 20 °C indicated a significant downfield shift of the phenolic hydrogen (7.36, 7.49, 7.25, 6.93, 7.65, 8.91 ppm) compared to those of the reference compounds, such as 2-methylphenol (5 mM, 4.63 ppm), phenol (5 mM, 4.70 ppm), 4-phenylphenol (5 mM, 4.78 ppm), 4-methylphenol (5 mM, 4.52 ppm), 4-bromophenol (5 mM, 4.80 ppm), and 4-cyanophenol (5 mM, 5.52 ppm), respectively. The ^1H NMR chemical shifts of **1a–f** at 20 °C were independent of those concentrations (1–50 mM). These results suggested that **1a–f** formed the intramolecular hydrogen bonding in $CDCl_3$ solution. In addition, the FT-IR spectrum of **1a** in $CHCl_3$ (5 mM) at room temperature showed two carbonyl absorptions at 1721 (weak) and 1702 (strong) cm^{-1}. The former absorption indicated the existence of a free ester carbonyl group, and the latter one was assigned to the hydrogen-bonded ester carbonyl group. These results suggest the existence of equilibrium between the non-hydrogen bonding state A and the fully hydrogen bonding state B (Scheme 2).



Scheme 2.

The ^1H NMR studies of the corresponding benzoyl derivatives **2a–e**, **3**, **5** also gave results similar to those of **1a–f**, which clearly indicated that they formed the intramolecular 9-membered hydrogen bonding in $CDCl_3$ (Scheme 3). On the other hand, the cyano derivative **4** having no carbonyl group did not form the intramolecular hydrogen bonding, since the phenolic proton chemical shifts



Scheme 3.

of **4** with variable temperature showed the same chemical shifts of 4-methylphenol.

2.3. Substituent effects of intramolecular hydrogen bonding

Figure 1 shows the temperature dependence of the phenolic proton chemical shifts of **1a–f** in $CDCl_3$, and its $\Delta\delta/\Delta T$ is shown in Table 1. The chemical shifts of phenolic protons of **1a–f** linearly moved to downfield with lowered temperature, and were shifted to upfield with elevated temperature. Proton exchange of the intramolecular hydrogen bonding was rapid in the NMR time scale, and the observed chemical shifts were averaged. The downfield chemical shift of the phenolic proton indicated that the proportion of the intramolecular hydrogen bonding state **B** is larger than that of the non-hydrogen bonding state **A**. The amount of the intramolecular hydrogen bonding state at the equilibrium was increased with the decrease of temperature. The intramolecular hydrogen bonding of **1e** having an electron-withdrawing group (cyano group) was much stronger than that of **1d** having an electron-donating group (methyl group), because the phenolic proton chemical shifts of **1e** were shifted to further downfield than that of **1d** compared to the reference phenols.

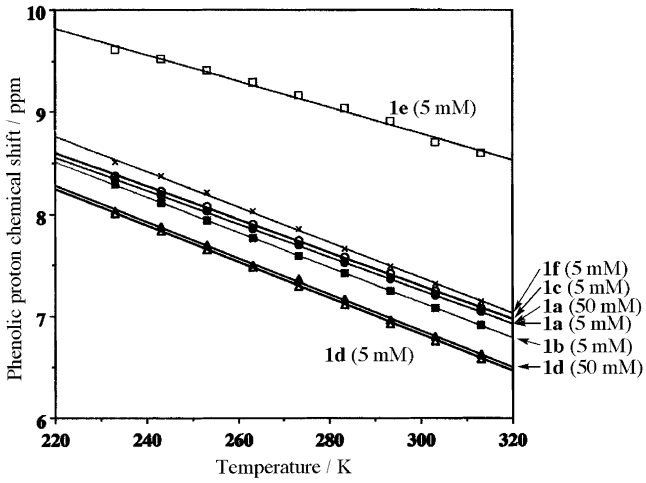


Figure 1. Temperature dependence of the phenolic proton chemical shifts of **1a–f** (5, 50 mM) in $CDCl_3$.

Table 1. $\Delta\delta/\Delta T$ of the intramolecular hydrogen bonding of **1a–f**

1[a]	R_1	R_2	$\Delta\delta/\Delta T$ ($\times 10^{-2}$)
1a	CH_3	H	−1.63
1a[b]	CH_3	H	−1.63
1b	H	H	−1.73
1c	H	Ph	−1.74
1d	H	CH_3	−1.78
1d[b]	H	CH_3	−1.78
1e	H	CN	−1.28
1f	H	Br	−1.60

[a] [**1**]=5 mM.
[b] [**1**]=50 mM.

The temperature dependence of the phenolic proton chemical shifts of **2a–e** in $CDCl_3$ and its $\Delta\delta/\Delta T$ are shown in Figure 2 and Table 2, respectively. Similarly, the substituent effect of **2a–e** revealed that the hydrogen

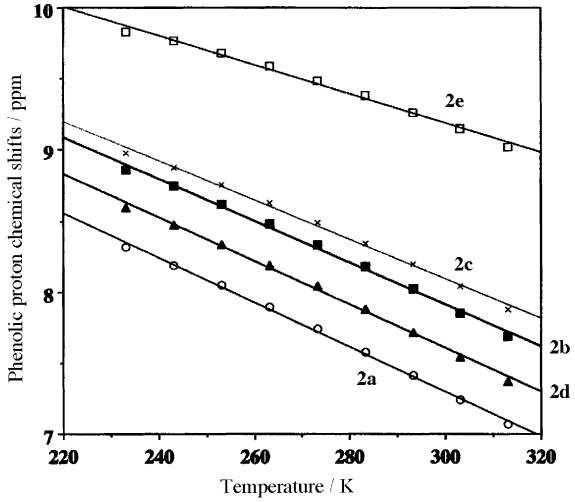


Figure 2. Temperature dependence of the phenolic proton chemical shifts of **2a–e** (5 mM) in $CDCl_3$.

Table 2. $\Delta\delta/\Delta T$ of the intramolecular hydrogen bonding of **2a–e**

2[a]	R	$\Delta\delta/\Delta T$ ($\times 10^{-2}$)
2a	OCH_3	−1.57
2b	H	−1.48
2c	Ph	−1.38
2d	CH_3	−1.53
2e	CN	−1.02

[a] [**2**]=5 mM.

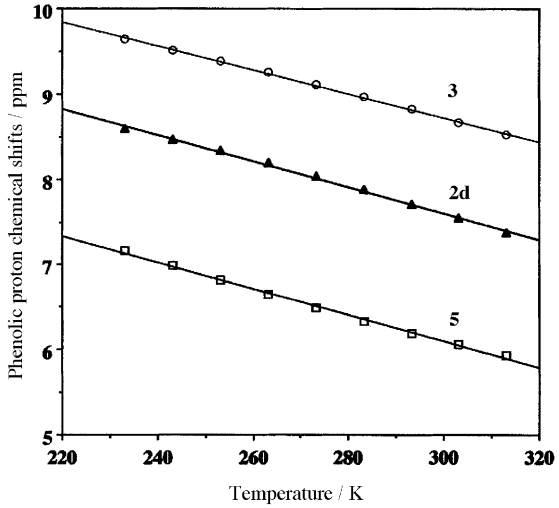


Figure 3. Temperature dependence of the phenolic proton chemical shifts of **2d**, **3**, **5** (5 mM) in $CDCl_3$.

Table 3. $\Delta\delta/\Delta T$ of the intramolecular hydrogen bonding of **2d**, **3**, **5**

Compound[a]	R	$\Delta\delta/\Delta T$ ($\times 10^{-2}$)
2d	OCH_3	−1.53
3	$N(CH_3)_2$	−1.41
5	H	−1.54

[a] [**2d**, **3**, **5**]=5 mM.

bonding of **2e** was much stronger than that of **2a**. These results indicated that the intramolecular hydrogen bonding depended on the acidity of the phenol.

Figure 3 shows the temperature dependence of the chemical shifts of phenolic protons of **2d**, **3**, and **5** in $CDCl_3$, and its $\Delta\delta/\Delta T$ is shown in Table 3. The substituent effect on the carbonyl group showed that the hydrogen bonding of **3**, having a more electron-donating group on the carbonyl group, was much stronger than that of **5**. This means that the intramolecular hydrogen bonding depends on the basicity of the carbonyl group.

2.4. Thermodynamic parameter of intramolecular hydrogen bonding

According to Eq. 1 (van't Hoff analysis), it is possible to determine the thermodynamic parameters (ΔH and ΔS) of a hydrogen bonding by ^{1}H NMR chemical shifts.[9]

$$\ln K = -\frac{\Delta H}{R}\frac{1}{T} + \frac{\Delta S}{R},\quad K = \frac{\delta_{obs} - \delta_n}{\delta_b - \delta_{obs}}$$

δ_{obs} : observed chemical shift

δ_n : chemical shift of non − hydrogen bond state

δ_b : chemical shift of full − hydrogen bond state

(1)

Although the value of δ_b was not directly obtained, the value of δ_n was given by the phenolic proton chemical shifts of the corresponding *para*-substituted phenols under the same conditions. Since **1d**,**e**,**f** had roughly the same-size substitution at the *para*-position, we estimated that the entropy loss (ΔS) of the intramolecular hydrogen bonding of **1d**,**e**,**f** was equal. Calculation of unknown constants ΔH and δ_b to let ΔS values of **1d**,**e**,**f** become a same value gave δ_b= 10.15 ppm. Figure 4 shows the van't Hoff plot of these compounds **1a**–**f** using δ_b=10.15 ppm.

The van't Hoff plot gave enthalpy and entropy values of the intramolecular 9-membered hydrogen bonding of **1a**–**f** as shown in Table 4. The thermodynamic parameters of

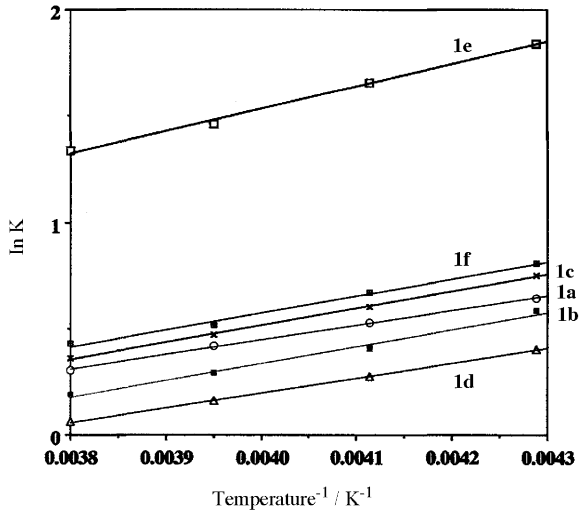


Figure 4. van't Hoff plot in ranging from 233 to 263 K.

Table 4. Thermodynamic parameters of the intramolecular hydrogen bonding of **1a**–**f** and **2a**–**e**

Compound	Hammett constant (σ^-)	ΔH (kcal mol^{-1})	ΔS (e.u.)
1a (*ortho*-CH_3)	—	−1.374	−4.61
1b (H)	0	−1.578	−5.64
1c (*para*-Ph)	0.20	−1.584	−5.31
1d (*para*-CH_3)	−0.17	−1.595	−5.17
1e (*para*-CN)	0.96	−2.079	−5.27
1f (*para*-Br)	0.23	−1.374	−5.24
2a (*para*-OCH_3)	−0.27	−1.117	−3.54
2b (H)	0	−1.363	−3.67
2c (*para*-Ph)	0.20	−1.372	−3.50
2d (*para*-CH_3)	−0.17	−1.226	−3.48
2e (*para*-CN)	0.96	−1.925	−3.52

compounds **2a**–**e** were also obtained by the same method using the value of δ_b=10.15 ppm. From these results, the enthalpy of the hydrogen bonding was related to electron-withdrawing ability of the substituents on the phenol. Since the acidity of the phenol group was dependent on the electron-withdrawing ability of the substituent, the gain of enthalpy of the intramolecular hydrogen bonding increased with increase of the electron-withdrawing ability of the substituent, in other words, with increase of the Hammett constant (σ^-).

Table 4 also shows that the entropy loss of the intramolecular hydrogen bonding of **1b** having a non-substituent on the phenol group was the largest value, and that of **1a** having a methyl group at the *ortho*-position was the smallest value, and those of other compounds **1c**–**f** having a substituent at the *para*-position were roughly the same value. These results suggested that the entropy loss of the hydrogen bonding was dependent on the rotation freedom of the phenol group. Since the *ortho*-methyl group of **1a** strongly prevented the rotation of the phenol group when it was the non-hydrogen bonding state **A**, the entropy loss caused by the hydrogen bonding was smaller. On the other hand, the rotation of **1b** was less prevented, and the entropy loss was larger. The intramolecular hydrogen bonding of 2-(1-methoxycarbonyl-2-phenyl)methylphenol derivatives **2a**–**e** showed similar results as shown in Table 4. The intramolecular hydrogen bonding of **1** was enthalpically favored relative to that of **2**, because the naphthyl group can act as a more electron-donating group to get more basicity of the carbonyl group. The hydrogen bonding of **1** was entropically disfavored relative to that of **2**, because the *peri*-hydrogen gave a more rigid intramolecular hydrogen bonding structure.

Figure 5 shows that the Hammett constant versus Gibbs free energy ΔG obtained by ΔH and ΔS at 253 K is a good linear relationship. The linear free energy relationship clarified that the assumption (δ_b=10.15 ppm) was correct.

3. Conclusion

It was found that the phenol derivatives **1**–**3**, **5** having two chromophores formed a novel intramolecular 9-membered hydrogen bonding between aromatic carbonyl and phenolic hydroxyl groups in $CDCl_3$ solution. The chemical shifts of the phenolic protons with variable temperature could give

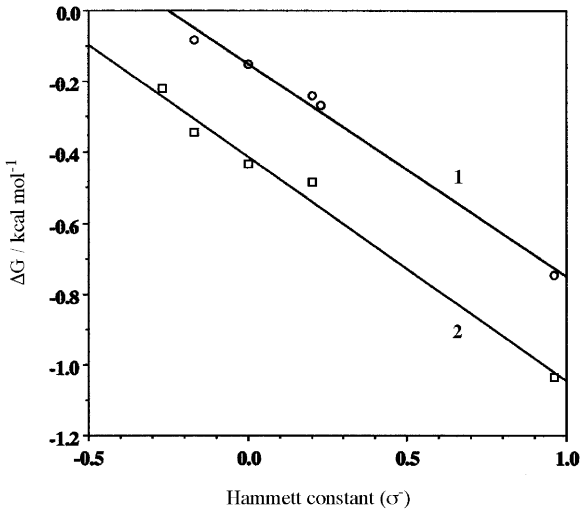


Figure 5. Hammett constant versus ΔG at 253 K.

the thermodynamic parameters of the intramolecular hydrogen bonding. These thermodynamic parameters revealed that the intramolecular hydrogen bonding depended on the acidity of the phenols and the basicity of the carbonyl groups. They also indicated that the intramolecular hydrogen bonding of **1** having a naphthalene ring was enthalpically favored, but entropically disfavored relative to that of **2**. In addition, the intramolecular hydrogen bonding was entropically dependent on the position of the substituent on the phenol group.

4. Experimental

4.1. General

Melting points were taken on a hot stage and were uncorrected. ^{1}H NMR and variable temperature ^{1}H NMR spectra were recorded on Varian Mercury (300 MHz) spectrometer and for solutions in $CDCl_3$ containing tetramethylsilane as an internal standard. ^{13}C NMR spectra were recorded on a Varian Mercury (75 MHz) spectrometer in $CDCl_3$ with chloroform (77.05 ppm) as an internal standard. IR spectra were obtained on JASCO FT/IR-230, mass spectra on a JMS-AX 500 mass spectrometer. Elemental analyses were carried out on a Yanaco MT-3 elemental analyzer. The light source was Eiko-sha PIH 300 W high-pressure mercury arc. High resolution mass spectra were obtained on a JEOL MStation (MS700).

4.2. Materials

$CDCl_3$ and $CHCl_3$ were freshly distilled before use from CaH_2 under N_2, and were stored in the presence of molecular sieves 4 Å. 1-Bromo-2-methylbenzene, NBS, $TiCl_4$, $ClCON(CH_3)_2$, CuCN, 10% Pd/C, and DIBAL were purchased.

4.3. General procedure for the photo-Claisen rearrangement

A solution of 2-(1-methoxycarbonylnaphthyl)methyl aryl ethers (10 mM) in benzene was purged with argon for 15 min and irradiation of the solution through Pyrex filter with a 300 W high-pressure mercury lamp (>280 nm) afforded *ortho*-rearranged products as main products accompanying 1-methoxycarbonyl-2-methylnaphthalene, 1,2-bis(1-methoxycarbonyl-2-naphthyl)ethane, and phenols.[8] The progress of the reaction was monitored by GLC (Silicone OV-17 5%), HPLC, and TLC. These products were isolated by column chromatography on silica gel using hexane and ethyl acetate as eluents.

4.3.1. 2-Methyl-6-[(1-methoxycarbonyl-2-naphthyl)-methyl]phenol (1a). Colorless crystals; mp 111 °C; ^{1}H NMR ($CDCl_3$): δ 7.87 (d, 1H, J=8.1 Hz), 7.81–7.75 (m, 2H), 7.56–7.45 (m, 2H), 7.36 (d, 1H, J=8.5 Hz), 7.30 (s, 1H), 7.16 (d, 1H, J=6.7 Hz), 7.05 (d, 1H, J=6.9 Hz), 6.82 (t, 1H), 4.14 (s, 3H), 4.08 (s, 2H), 2.17 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 171.8, 153.3, 136.2, 131.9, 130.8, 129.9, 129.8, 129.0, 128.2, 128.1, 127.2, 127.1, 126.0, 125.3, 124.8, 124.3, 119.4, 53.1, 35.3, 16.3; IR (KBr) 3353, 1698 cm^{-1}; Ms m/z 306 (M^+). Anal. Calcd for $C_{20}H_{18}O_3$: C 78.41, H 5.92, O 15.67. Found: C 78.51, H 5.92, O 15.39.

4.3.2. 2-(1-Methoxycarbonyl-2-naphthyl)methylphenol (1b). Colorless crystals; mp 91 °C; ^{1}H NMR ($CDCl_3$): δ 7.87 (d, 1H, J=8.2 Hz), 7.79 (d, 2H, J=8.4 Hz), 7.57–7.46 (m, 2H), 7.35 (d, 1H, J=8.8 Hz), 7.29 (s, 1H), 7.09–7.13 (m, 2H), 6.89 (t, 1H), 6.81 (d, 1H, J=8.2 Hz), 4.13 (s, 3H), 4.11 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 171.7, 155.0, 136.1, 132.0, 131.4, 130.8, 129.8, 128.6, 128.5, 128.2, 127.3, 127.2, 126.1, 125.0, 120.1, 116.6, 53.1, 35.1; IR (KBr) 3385, 1726 cm^{-1}; Ms m/z 292 (M^+). Anal. Calcd for $C_{18}H_{16}O_3$: C 78.07, H 5.52, O 16.41. Found: C 78.07, H 5.36, O 16.57.

4.3.3. 4-Phenyl-2-[(1-methoxycarbonyl-2-naphthyl)-methyl]phenol (1c). Colorless crystals; mp 146–147 °C; ^{1}H NMR ($CDCl_3$): δ 7.88 (d, 1H, J=8.4 Hz), 7.80 (d, 2H, J=8.4 Hz), 7.61–7.25 (m, 12H), 6.88 (d, 1H, J=8.2 Hz), 4.17 (s, 2H), 4.15 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 171.8, 154.8, 140.8, 136.0, 132.0, 130.9, 130.1, 129.9, 128.7, 128.4, 128.2, 127.3, 127.3, 127.2, 126.7, 126.5, 126.1, 125.2, 124.9, 117.1, 53.2, 35.5; IR (KBr) 3427, 1692 cm^{-1}; Ms m/z 368 (M^+). Anal. Calcd for $C_{25}H_{20}O_3$: C 81.50, H 5.47, O 13.03. Found: C 81.39, H 5.43, O 13.18.

4.3.4. 4-Methyl-2-[(1-methoxycarbonyl-2-naphthyl)-methyl]phenol (1d). Colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.86 (d, 1H, J=8.6 Hz), 7.79 (d, 2H, J=8.2 Hz), 7.57–7.45 (m, 2H), 7.36 (d, 1H, J=8.6 Hz), 7.01 (s, 1H), 6.95 (d, 1H, J=8.1 Hz), 6.91 (s, 1H), 6.72 (d, 1H, J=8.1 Hz), 4.12 (s, 3H), 4.08 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 171.5, 152.6, 136.2, 131.9, 131.8, 130.6, 129.8, 129.1, 128.9, 128.6, 128.1, 127.3, 127.2, 126.0, 124.9, 124.8, 116.3, 53.0, 35.0, 20.6; IR (neat) 3423, 1719 cm^{-1}; Ms m/z 306 (M^+). Anal. Calcd for $C_{20}H_{18}O_3$: C 78.41, H 5.92, O 15.67. Found: C 78.60, H 5.93, O 15.47.

4.3.5. 4-Cyano-2-[(1-methoxycarbonyl-2-naphthyl)-methyl]phenol (1e). Colorless crystals; mp 91 °C; ^{1}H NMR ($CDCl_3$): δ 8.81 (s, 1H), 7.92–7.81 (m, 3H), 7.65–7.44 (m, 4H), 7.29 (d, 1H, J=8.5 Hz), 6.85 (d, 1H, J=8.5 Hz), 4.18 (s, 3H), 4.10 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 163.1, 159.7, 141.5, 138.7, 135.6, 135.1, 132.4, 131.7,

128.5, 128.3, 127.9, 127.1, 126.7, 126.4, 125.2, 118.2, 105.8, 53.7, 35.3; IR (KBr) 3244, 2239, 1715 cm^{-1}; Ms *m/z* 317 (M^+). Anal. Calcd for $C_{20}H_{15}NO_3$: C 75.70, H 4.76, N 4.41, O 15.12. Found: C 75.68, H 4.93, N 4.40, O 14.99.

4.3.6. 4-Bromo-2-[(1-methoxycarbonyl-2-naphthyl)-methyl]phenol (1f). Colorless oil; ^1H NMR ($CDCl_3$): δ 7.89–7.79 (m, 3H), 7.58–7.41 (m, 3H), 7.41 (s, 1H), 7.43 (d, 1H, $J=8.6$ Hz), 7.24 (d, 1H, $J=8.4$ Hz), 6.68 (d, 1H, $J=8.4$ Hz), 4.14 (s, 3H), 4.05 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 171.9, 154.4, 135.4, 133.6, 132.1, 131.3, 131.1, 129.8, 128.4, 128.2, 127.4, 127.1, 126.3, 124.9, 118.5, 111.7, 53.2, 35.0; IR (neat) 3371, 1700 cm^{-1}; Ms *m/z* 372 (M^+). Anal. Calcd for $C_{19}H_{15}O_3Br$: C 66.88, H 4.43. Found: C 67.04, H 4.31.

4.4. General procedure for the preparation of 2

1-Bromo-2-methylbenzene was added to a solution of NBS in CCl_4 containing BPO, and the mixture was refluxed for 5 h. The mixture is filtrated, concentrated, and recrystallized to give 1-bromo-2-bromomethylbenzene (94%). 1-Bromo-2-bromomethylbenzene was etherified by the 4-substituted phenols with K_2CO_3. Then the ethers in CH_2Cl_2 were added by $TiCl_4$ under argon atmosphere. The mixture was stirred at room temperature, and quenched by water. The products were extracted, dried (Na_2SO_4), concentrated, and purified by column chromatography on silica gel (eluent: hexane and ethyl acetate) to give *ortho*-rearranged phenols. The amount of $TiCl_4$, reaction time, and product yields were dependent on the substituent at 4-position. In the case of **1e** having an electron-withdrawing group (cyano group), the CH_2Cl_2 solution (200 ml) containing 1-bromo-2-[(4-cyanophenoxy)methyl]benzene (4.5 g, 15.7 mmol) and 5 equiv of $TiCl_4$ (8.6 ml, 78.5 mmol) was stirred for 24 h at room temperature under argon atmosphere, quenched by water, and purified to give **1e** in very low yield (2%). On the other hand, the CH_2Cl_2 solution (50 ml) containing the other ethers (10 mmol) and 1 equiv of $TiCl_4$ (10 mmol) was stirred for 3 h at room temperature, quenched by water, and purified to give **1a–d** in moderate yields (ca. 20–40%).

These phenols (4 mmol) were protected by benzyl chloride (5 mmol) in the presence of K_2CO_3 (4 g) to give the ethers (>90%). *n*-BuLi (15 wt% in *n*-hexane solution, 14.6 ml, 22.8 mmol) was added drop-wise to the ethers (19 mmol) in THF (100 ml) at −60 °C. The mixture was stirred for 2 h at −60 °C under argon atmosphere, and $ClCO_2CH_3$ (1.8 ml, 23 mmol) in THF (15 ml) was added. Then the mixture was stirred for 1 h at room temperature, and 3 N HCl was added. The product was extracted with ether, washed with H_2O, dried (Na_2SO_4), and concentrated. Purification by column chromatography on silica gel (eluent: hexane and ethyl acetate) gave the corresponding ester derivatives in moderate yields (ca. 60%). Then, the esters (3.5 mmol) in ethanol (150 ml) were stirred for 8 h with 10% Pd/C (140 mg) under hydrogen atmosphere to afford **2a–e**, respectively (90%).

4.4.1. 4-Methoxy-2-[(1-methoxycarbonyl-2-phenyl)-methyl]phenol (2a). Colorless oil; ^1H NMR ($CDCl_3$): δ 7.85 (d, 1H, $J=7.9$ Hz), 7.46–7.36 (m, 3H), 7.28–7.23 (m, 1H), 6.80–6.77 (m, 2H), 6.71–6.67 (m, 1H), 4.22 (s, 2H), 3.95 (s, 3H), 3.76 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 170.1, 153.0, 148.7, 141.2, 132.5, 131.5, 130.4, 128.5, 127.0, 126.3, 117.0, 116.8, 112.8, 55.8, 52.9, 34.0; IR (neat) 3384, 1719 cm^{-1}; Ms *m/z* 272 (M^+); HRMS (EI) Calcd for $C_{16}H_{16}O_4$: 272.1049. Found: 272.1061.

4.4.2. 2-(1-Methoxycarbonyl-2-phenyl)methylphenol (2b). Colorless oil; ^1H NMR ($CDCl_3$): δ 7.93 (s, 1H), 7.83 (d, 1H, $J=7.4$ Hz), 7.45–7.36 (m, 2H), 7.28–7.22 (m, 2H), 7.17–7.11 (m, 1H), 6.89–6.83 (m, 2H), 4.24 (s, 2H), 3.98 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 170.5, 154.9, 141.3, 132.5, 131.5, 131.0, 128.4, 128.2, 126.3, 126.0, 119.9, 116.6, 53.0, 33.8; IR (neat) 3368, 1698 cm^{-1}; Ms *m/z* 242 (M^+). Anal. Calcd for $C_{15}H_{14}O_3$: C 74.36, H 5.83. Found: C 74.70, H 5.84.

4.4.3. 4-Phenyl-2-[(1-methoxycarbonyl-2-phenyl)-methyl]phenol (2c). Colorless crystals; mp 103 °C; ^1H NMR ($CDCl_3$): δ 8.14 (s, 1H), 7.85 (d, 1H, $J=7.7$ Hz), 7.61–7.24 (m, 10H), 6.94 (d, 1H, $J=8.2$ Hz), 4.32 (s, 2H), 4.00 (s, 3H), 2.29 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 170.1, 152.4, 141.1, 133.0, 132.6, 130.3, 129.8, 128.6, 128.4, 127.0, 126.7, 126.5, 126.4, 126.2, 117.0, 53.2, 34.1; IR (KBr) 3324, 1696 cm^{-1}; Ms *m/z* 318 (M^+). Anal. Calcd for $C_{21}H_{18}O_3$: C 79.22, H 5.70. Found: C 78.92, H 5.54.

4.4.4. 4-Methyl-2-[(1-methoxycarbonyl-2-phenyl)-methyl]phenol (2d). Colorless oil; ^1H NMR ($CDCl_3$): δ 7.83 (d, 1H, $J=7.7$ Hz), 7.71 (s, 1H), 7.46–7.27 (m, 2H), 7.28–7.22 (m, 1H), 7.06 (s, 1H), 6.94 (d, 1H, $J=8.2$ Hz), 6.74 (d, 1H, $J=8.2$ Hz), 4.21 (s, 2H), 3.97 (s, 3H), 2.29 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 170.3, 152.6, 141.4, 132.4, 131.5, 131.4, 130.2, 128.9, 128.7, 128.4, 126.2, 125.7, 116.4, 53.0, 33.8, 20.6; IR (neat) 3371, 1700 cm^{-1}; Ms *m/z* 256 (M^+); HRMS (EI) Calcd for $C_{16}H_{16}O_3$: 256.1099. Found: 256.1074.

4.4.5. 4-Cyano-2-[(1-methoxycarbonyl-2-phenyl)-methyl]phenol (2e). Colorless oil; ^1H NMR ($CDCl_3$): δ 9.20 (s, 1H), 7.85 (d, 1H, $J=7.5$ Hz), 7.60 (s, 1H), 7.51–7.42 (m, 2H), 7.36–7.26 (m, 2H), 6.88 (d, 1H, $J=8.4$ Hz), 4.21 (s, 2H), 4.01 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 171.0, 159.3, 140.0, 135.1, 133.6, 132.9, 132.7, 131.5, 130.4, 128.3, 127.2, 126.9, 119.5, 117.8, 53.4, 33.5; IR (neat) 3315, 2225, 1718 cm^{-1}; Ms *m/z* 267 (M^+); HRMS (EI) Calcd for $C_{16}H_{13}O_3N$: 267.0895. Found: 267.0858.

4.5. General procedure for the preparation of 3–5

The amide derivative **3** was synthesized by the amidation of the corresponding bromo derivative according to a similar method of esterification (by $ClCON(CH_3)_2$, 30% yield).

The cyano derivative **4** was also obtained by the cyanation according to the method described in the literature, followed by deprotection. A mixture of the bromo derivatives (1.1 mmol), CuCN (5.5 mmol), and *N*-methyl-2-pyrrolidone (10 ml) was heated at 180 °C for 20 min under argon. After cooling to room temperature, 10% aqueous ammonia solution (50 ml) and dichloromethane (50 ml) were added to the solution and filtered. The filtrate was combined with Et_2O, washed with H_2O, and dried (Na_2SO_4). After removal of *N*-methyl-2-pyrrolidone in vacuo, column chromatography on silica gel (eluent: hexane and ethyl acetate)

afforded the cyano derivative (95%), and then similarly deprotection by Pd/C and H_2 gave **4** (78%).

DIBAL solution (0.2 ml, 0.2 mmol) was added drop-wise to the benzene solution of cyano derivative **4** (40 mg, 0.18 mmol) under argon atmosphere at 0 °C. The mixture was stirred for 1 h at 0 °C, and quenched by 5% H_2SO_4. The product was extracted, washed with H_2O, dried (Na_2SO_4), and concentrated. Purification by column chromatography on silica gel (eluent: hexane and ethyl acetate) gave the aldehyde derivative **5** (95%).

4.5.1. 4-Methyl-2-[(2-*N*,*N*-dimethylcarbamoylphenyl)-methyl]phenol (3). Colorless crystals; mp 112 °C; ^{1}H NMR ($CDCl_3$) δ 10.18 (s, 1H), 7.80 (d, 1H, J=7.7 Hz), 7.57–7.52 (m, 1H), 7.44–7.29 (m, 2H), 6.93–6.91 (m, 2H), 6.73 (d, 1H, J=8.6 Hz), 6.20 (s, 1H), 4.33 (s, 2H), 2.23 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 194.7, 151.4, 142.2, 134.1, 133.5, 133.4, 131.6, 131.1, 129.7, 128.4, 126.8, 125.7, 116.0, 32.3, 20.6; IR (KBr) 3057, 1663 cm^{-1}; MS *m*/*z* 226 (M^+); HRMS (EI) Calcd for $C_{17}H_{19}O_2N$: 269.1416. Found: 269.1440.

4.5.2. 4-Methyl-2-[(2-cyanophenyl)methyl]phenol (4). Colorless crystals; mp 128–129 °C; ^{1}H NMR (300 MHz) δ 7.65–7.62 (m, 1H), 7.49–7.44 (m, 1H), 7.30–7.25 (m, 2H), 6.95–6.92 (m, 2H), 6.67 (d, 1H, J=7.7 Hz), 4.67 (s, 1H), 4.18 (s, 2H), 2.25 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 151.1, 144.6, 132.7, 132.6, 131.6, 130.3, 129.7, 128.5, 126.4, 125.0, 118.3, 115.4, 112.5, 34.4, 20.6; IR (KBr) 3398, 2228 cm^{-1}; MS *m*/*z* 223 (M^+); HRMS (EI) Calcd for $C_{15}H_{13}ON$: 223.0997. Found: 223.0925.

4.5.3. 4-Methyl-2-[(2-formylphenyl)methyl]phenol (5). Colorless crystals; mp 38 °C; ^{1}H NMR (300 MHz) δ 8.82 (s, 1H), 7.34–7.15 (m, 4H), 7.01 (s, 1H), 6.92 (d, 1H, J=8.1 Hz), 6.72 (d, 1H, J=8.1 Hz), 3.87 (s, 2H), 3.16 (s, 3H), 2.92 (s, 3H), 2.28 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 172.6, 153.3, 138.3, 133.8, 131.6, 130.7, 129.6, 128.6, 128.1, 126.2, 125.6, 125.7, 117.1, 39.5, 35.2, 34.5, 20.5; IR (KBr) 3316, 1622 cm^{-1}; MS *m*/*z* 269 (M^+); HRMS (EI) Calcd for $C_{15}H_{14}O_2$: 226.0994. Found: 226.0929.

Acknowledgements

This work was supported by a Grant-in-Aid for Young Scientists (B) (15750081 and 16750039) from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan.

Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2004.08.007

References and notes

1. β-Peptides; Appella, D. H.; Christianson, L. A.; Karle, I. L.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1996**, *118*, 13071. Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173. Appella, D. H.; Barchi, J. J.; Durell, S. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1999**, *121*, 2309. Abele, S.; Guichard, G.; Seebach, D. *Helv. Chim. Acta* **1998**, *81*, 2176. Motorina, I. A.; Huel, C.; Quiniou, E.; Mispelter, J.; Adjadj, E.; Grierson, D. S. *J. Am. Chem. Soc.* **2001**, *123*, 8. γ-Peptides; Hintermann, T.; Gademann, K.; Jaun, B.; Seebach, D. *Helv. Chim. Acta* **1998**, *81*, 983. Hanessian, S.; Lou, X.; Schaum, R.; Michnick, S. *J. Am. Chem. Soc.* **1998**, *120*, 8569. Hanessian, S.; Lou, X.; Schaum, R. *Tetrahedron Lett.* **1999**, *40*, 4925. δ-Peptides; Szabo, L.; Smith, B. L.; McReynolds, K. D.; Parrill, A. L.; Morris, E. R.; Gervay, J. *J. Org. Chem.* **1998**, *63*, 1074.
2. Hamuro, Y.; Geib, S. J.; Hamilton, A. D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 446. Hamuro, Y.; Geib, S. J.; Hamilton, A. D. *J. Am. Chem. Soc.* **1996**, *118*, 7529. Hamuro, Y.; Geib, S. J.; Hamilton, A. D. *J. Am. Chem. Soc.* **1997**, *119*, 10587.
3. Long, D. D.; Hungerford, N. L.; Smith, M. D.; Brittain, D. E. A.; Marquess, D. G.; Claridge, T. D. W.; Fleet, G. W. J. *Tetrahedron Lett.* **1999**, *40*, 2195. Smith, M. D.; Claridge, T. D. W.; Tranter, G. E.; Sansom, M. S. P.; Fleet, G. W. J. *Chem. Commum.* **1998**, 2041.
4. Porte, A. L.; Gutowsky, H. S.; Hunsberger, I. M. *J. Am. Chem. Soc.* **1960**, *82*, 5057. Reeves, L. W.; Allan, E. A.; Stromme, K. O. *Can. J. Chem.* **1960**, *38*, 1249. Allan, E. A.; Reeves, L. W. *J. Phys. Chem.* **1962**, 613. Hay, R. W.; Wikkiams, P. P. *J. Chem. Soc.* **1964**, 2270. Palmer, M. H.; Scollick, N. M. *J. Chem. Soc. (B)* **1968**, 1353. Yasunaga, T.; Tatsumoto, N.; Inoue, H.; Miura, M. *J. Phys. Chem.* **1969**, *3*, 477.
5. Heer, M. I.; Korth, H.; Mulder, P. *J. Org. Chem.* **1999**, *64*, 6969. Heer, M. I.; Mulder, P.; Korth, H.; Ingold, K. U.; Lusztyk, J. *J. Am. Chem. Soc.* **2000**, *122*, 2355.
6. Yoshimi, Y.; Sugimoto, A.; Maeda, H.; Mizuno, K. *Tetrahedron Lett.* **2001**, *42*, 2341.
7. Very few examples of 9-membered hydrogen bonding structures have been reported, but they did not discuss about the hydrogen bonding in detail: Abell, A. D.; Morris, K. D.; McKee, V. *Aust. J. Chem.* **1990**, *43*, 765. Anjaneyulu, A. S. R.; Venugopal, M. J. R. V.; Sarada, P.; Clardy, J.; Lobkovsky, E. *Tetrahedron Lett.* **1998**, *39*, 139.
8. Yoshimi, Y.; Sugimoto, A.; Maeda, H.; Mizuno, K. *Tetrahedron Lett.* **1998**, *39*, 4683. Yoshimi, Y.; Sugimoto, A.; Maeda, H.; Mizuno, K.; Ichinose, N.; Tanaka, T.; Kawanishi, S. *Chem. Lett.* **2001**, 252.
9. Similar analysis of the intramolecular hydrogen bonding has been performed by Gellman et al. Gellman, S. H.; Dado, G. P.; Liang, G.; Adam, B. R. *J. Am. Chem. Soc.* **1991**, *113*, 1164. Dado, G. P.; Gellman, S. H. *J. Am. Chem. Soc.* **1993**, *115*, 4228.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 60 (2004) 9433–9439
Tetrahedron

Synthesis of aryl phosphines via phosphination with triphenylphosphine by supported palladium catalysts

Yanchun Wang, Chi Wai Lai, Fuk Yee Kwong, Wen Jia and Kin Shing Chan*

Department of Chemistry, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong, China

Received 25 May 2004; revised 23 July 2004; accepted 4 August 2004

Abstract—The palladium catalyzed phosphination of functionalized aryl bromides, triflates, and chlorides with triphenylphosphine to yield aryldiphenylphosphines was catalyzed by thermally stable palladium catalysts supported on charcoal and aluminia. The addition of NaI promoted both the rates and yields in the phosphination with Pd/C.
© 2004 Elsevier Ltd. All rights reserved.

1. Introduction

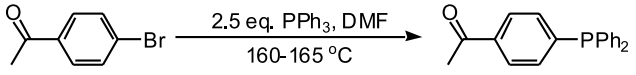
A synthesis of aryl phosphines by the phosphination of aryl bromides[1] and triflates[2] with triarylphosphines using 10 mol% of palladium catalysts such as $Pd(OAc)_2$ and $Pd(dba)_2$ has been previously reported by us. Extension of the method to the synthesis of aryl arsines is also successful.[3] Application in solvent-free conditions furnishes a green chemical synthesis.[4] The methods are direct and applicable to functionalized substrates using air-stable and economical starting materials.[5] However, the use of these homogeneous palladium catalysts suffers from frequent decomposition at elevated temperatures in the course of the reactions to form catalytically inactive palladium black precipitates. No further catalysis then proceeds. Application of more active and recyclable palladium catalysts in phosphination therefore would be most desirable.

Newly-developed palladium heterogeneous catalysts have been reported in the literature. Examples of non-phosphine ligated heterogeneous palladium catalysts, include the palladium nanoparticles,[6] Pd/nanofibers,[7] Pd/C,[8,9] Pd/alumina,[10] Pd/glass,[11] Pd/hydroxyapatite,[12] Pd/zeolites,[13,14] Pd supported on resins,[15] and Pd supported on polymers.[16] Pd/C and Pd/alumina are the most attractive since they are commercially available as well as thermally and air-stable. They have also been extensively utilized in various catalytic reactions such as hydrogenation,[7,16,17] dehydrogenation,[18] allylation,[6] homo-coupling,[19] Sonogashira,[14,20] Stille,[21] Suzuki,[22] and Negishi[23] cross couplings, Heck reactions,[24] carbonylation,[25] and carbon-hydrogenation activation.[26] We have previously employed Pd/C as a thermally stable catalyst for phosphination of aryl halides[27] and now disclose the full details of the applications of Pd/C and Pd/alumina catalysts in the phosphination of aryl halides including electron-deficient aryl chlorides.

2. Results and discussion

The effect of the catalyst loading was examined in phosphination. Table 1 shows the effect of Pd/C catalyst loading in phosphination using the prototypical substrate of 4-bromoacetophenone with 2.5 equiv of Ph_3P in DMF at 160 °C.[1,2] Amounts of Pd/C catalyst from 1 to 10 mol% had little difference on the rate and/or yield of the reaction while less than 1 mol% increased the reaction time significantly and lowered the yield slightly. The use of higher reaction temperature of 160 °C allowed a lower catalyst loading of just 1% making this process more attractive compared to the

Table 1. Effect of Pd/C catalyst loading in phosphination

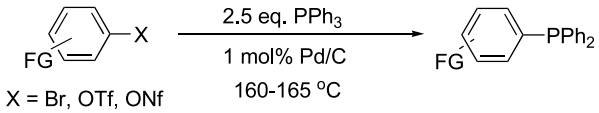


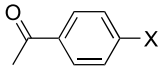
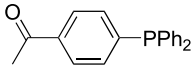
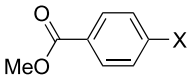
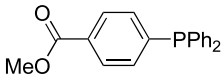
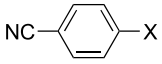
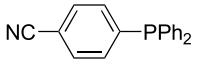
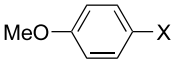
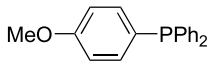
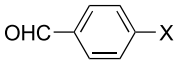
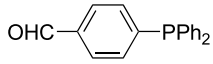
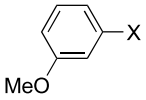
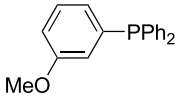
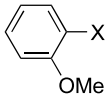
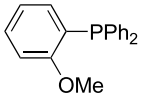
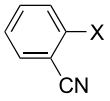
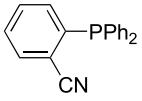
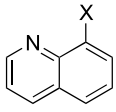
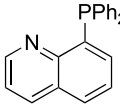
Entry	Pd/C mol%	Time/h	Yield %
1	10	30	45
2	5	32	44
3	1	32	46
4	0.5	96	39
5	0.2	168	37
6	0.1	288	28

Keywords: Palladium catalyst; Phosphination; Aryl halides.
* Corresponding author. Tel.: +852-2609-6376; fax: +852-2603-5057; e-mail: ksc@cuhk.edu.hk

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.08.020

Table 2. Pd/C catalyzed phosphination



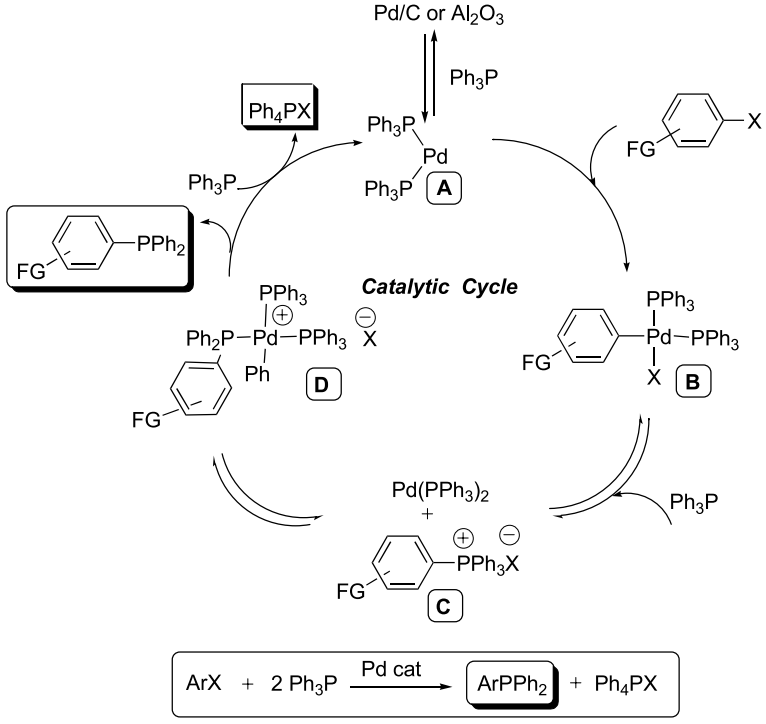
Entry	Substrate	X	Product	Time/h	Yield %
1		X=Br		32	46
2		X=OTf		20	39
3		X=Br		No reaction after 9 d	
4		X=OTf		42	20
5		X=ONf		12	35
6		X=Br		73	53
7		X=OTf		47	44
8		X=Br		37	33
9		X=OTf		15	29
10		X=Br		75	31
11		X=OTf		46	20
12		X=Br		52	35
13		X=OTf		20	30
14		X=Br		No reaction after 5 d	
15		X=OTf		26	24
16		X=Br		No reaction after 10 d	
17		X=OTf		168	16
18		X=OTf		33	29

reactions at 110 °C with the use of 10 mol% of $Pd(OAc)_2$ catalyst.[1,2]

Table 2 shows the successful phosphination of functionalized aryl bromides, triflates and nonaflate using the optimized conditions. In general, aryl triflates or nonaflate reacted faster than aryl bromides, in the order of leaving group ability.[1,2] In some cases (entries 14–17), only the aryl triflates reacted. A variety of functional groups such as ketone, aldehyde, ester, pyridine, and cyanide were compatible with the reaction without the need of a protective group. The reactions were conducted in neutral media which allowed broader functional group compatiablity.[1,2] Electron deficient substrates (entries 1, 2, 6, and 7) gave higher yields than electron rich substrates (entries 8 and 9). Likely, these electro-deficient substrates facilitate the catalysis in the oxidative addition either at the aryl-halogen or triflate bond of the starting materials or at the phosphonium salt of the intermediate (see mechanistic discussion below, Scheme 1). For those substrates that reacted, the starting materials were completely consumed. The low yields of products therefore may be due to unfavorable equilibrium position of the products in the reaction mixture and/or a less efficient catalyst in converting any phosphonium salt intermediates into the products (Scheme 1).[1,2] Sterically more hindered 2-substituted aryl triflates (entries 15 and 17) and the 8-quinolinyl triflate (entry 18) reacted smoothly while the corresponding bromides were not reactive at all.

The Pd/C catalyst could be used twice without diminishing its activity by loading the catalyst in a thimble. After reaction, the products were removed by washing with excess solvents. Then, a new run was started. During the third run, no catalysis occurred. Presumably, the palladium species which dissolved in the course of reaction did not re-deposit efficiently or completely on charcoal after the reaction,[24,28] that is, the leaching rate of the palladium was too fast to allow multiple re-use.

The proposed mechanism of the phosphination is shown in Scheme 1.[1,2] Palladium on charcoal dissolves into solution

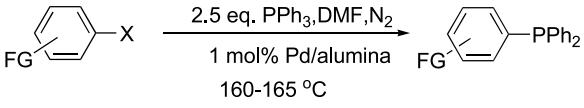


Scheme 1. A plausible mechanism for palladium-catalyzed phosphination.

to form $Pd(Ph_3P)_2$ **A** after ligand substitution with Ph_3P. Subsequent oxidative addition with an aryl halide yields complex **B**. Reductive elimination generates the aryltriphenyl phosphonium salt[29] and the catalyst **A** again. Re-oxidative addition of **A** into a phenyl–carbon bond in **C** produces **D**. The sequence from **B** to **D** constitutes the aryl-Pd/aryl-P exchange[30] through C–P activation.[31] Finally, ligand substitution of **D** and subsequent reductive elimination give the aryldiphenylphosphine product and tetraphenyl phosphonium salt. Therefore, 2 equiv of triphenylphosphine are required by the stoichiometry of the reaction.[1,2]

Another commercially available Pd catalyst, Pd on alumina, was also found to be an efficient catalyst used in 1 mol%

Table 3. Catalytic phosphination by Pd/Al_2O_3



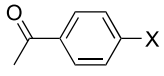
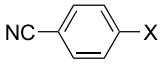
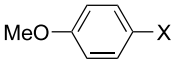
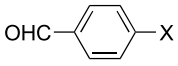
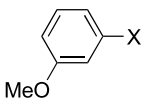
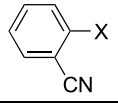
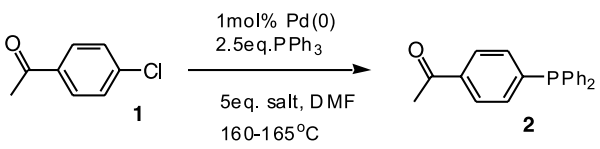
Entry	Substrate	X	Pd/Al_2O_3	
			Time/h	Yield %
1		X=Br	18	59
2		X=OTf	57	29
3		X=Br	62	62
4		X=OTf	72	14
5		X=Br	5.5	9
6		X=Br	64	44
7		X=Br	5.5	30
8		X=Br	14d	0
9		X=OTf	5d	12

Table 4. Salt effects in palladium-catalyzed phosphination of ArCl[a]



Entry	Salt	Time/h	Yield %
1	None	20	21
2	NaI	8	45
3	NaBr	62	26
4	NaCl	62	25
5	NaOAc	45	12
6	$NaBF_4$	10	43
7	$NaNO_3$	12	38
8	LiI	14.5	35
9	KI	14	37
10	NiI_2	12	36
11	Et_4NI	4 d	~0
12	NH_4PF_6	5 d	0

[a] 10 mol% of Pd/C was used.

loading with very similar activity (Table 3). For unhindered substrates (Table 3, entries 1–4), the bromides reacted faster and gave higher yields than the corresponding triflates. For hindered substrate, only the triflates reacted to give low yield of product (entries 8 and 9). The reason of the difference in reactivity in Pd/C or Pd/alumina is unclear. We speculate that the alumina support may act as a Lewis acid in interacting with the bromide to form a better leaving group in the oxidative addition of the C–Br bond.

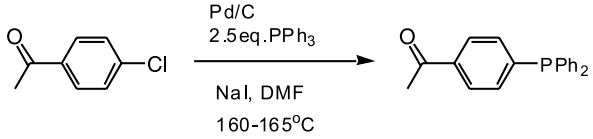
To further enhance the catalytic efficiency, halide additives were examined as they are known promoters in various catalytic processes[32] such as the Negishi cross coupling, Sonogoshira reaction, and etc.[33] presumably via the formation of more nucleophilic anionic palladium complex.[34] However, initial screenings showed little promoting effect in the phosphination of aryl bromides using either Pd/C or Pd/alumina with the addition of 5 equiv of NaI.

We then switched our attention to the phosphination of aryl chlorides. As aryl chlorides are readily available and inexpensive, conversion into the corresponding aryl phosphines would be highly desirable. Furthermore, the activation of stronger Ar–Cl bond is more challenging. (The bond dissociation energy of Ph–Cl and Ph–Br are respectively 96 and 81 kcal mol^{-1}).[35] 4-Chloroacetophenone was used as the prototypical substrate for the initial study of phosphination. $Pd(OAc)_2$ was not compatible since it decomposed and formed the catalytically inactive palladium black within 1 day when the reaction was heated at 160 °C. The thermally more robust palladium catalyst Pd/C (10 mol% of Pd(0) on charcoal) was then employed. Indeed, 4-(diphenylphosphino)acetophenone was obtained in 21% yield when the reaction was heated at 160 °C for 20 h in the presence of 10 mol% Pd/C (equivalent to 1 mol% Pd(0)) (Table 4, entry 1). When additives were added, the rates and yields of reaction changed dramatically (Table 4). Among the additives, sodium iodide was found to be the best promoter (Table 4, entry 2). Sodium bromide or sodium chloride gave similar yields of the product but lower rates of reaction (Table 4, entries 3 and 4). Other metal iodides did enhance the yield of the product though in a lesser extent (Table 4, entries 8–10). However, ammonium salts were found to be detrimental without any product formed (Table 4, entries 11 and 12).

The amount of sodium iodide loading in this reaction was also optimized (Table 5). The addition of 1–3 equiv (with respect to ArCl) of sodium iodide enhanced the yield of the product **2** (Table 5, entries 2 and 3). The optimal NaI loading was found to be 5 equiv (Table 5, entry 4). Higher loading of 10 equiv of NaI gave slightly lower yield of **2** (Table 5, entry 5). Presumably the presence of a large amount of NaI formed a saturation solution and even a suspension and the enhancement leveled off. A lower catalyst loading (1 mol% Pd(0)) also gave similar yield of the product, however, lower rate of reaction was observed (Table 5, entry 6). A comparable yield of **2** was also obtained when the reaction temperature was lowered to 125 or 140 °C though longer reaction time was required (Table 5, entries 7 and 8).

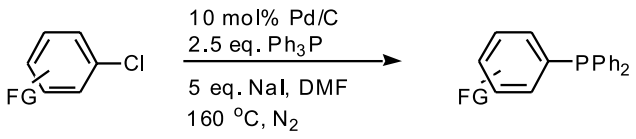
The optimized reaction conditions were found to require 10 mol% Pd/C, 2.5 equiv of PPh_3, and 5 equiv of NaI in DMF at 160 °C under a nitrogen atmosphere. The reaction conditions were applied to various functionalized aryl chlorides (Table 6). Both methyl and phenyl ketone

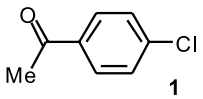
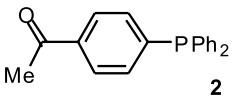
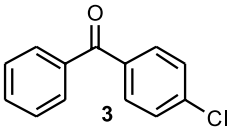
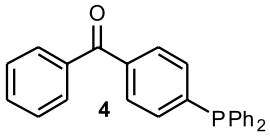
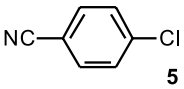
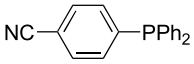
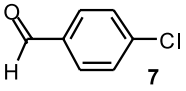
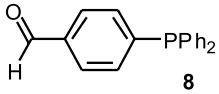
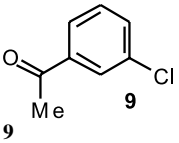
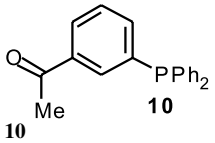
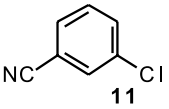
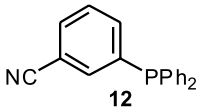
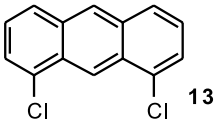
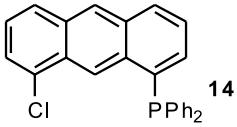
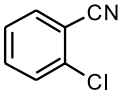
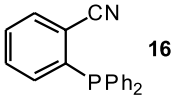
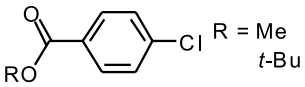
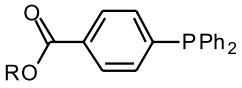
Table 5. Effect of NaI loading in Pd-catalyzed phosphination



Entry	Equiv of NaI	Pd/C (mol%)	Time/h	Yield %
1	None	10	20	21
2	1	10	10	31
3	3	10	10	38
4	5	10	8	45
5	10	10	10	40
6	5	1	6 d	45
7	5	10 (140 °C)	46	44
8	5	20 (125 °C)	110	43

Table 6. Palladium-catalyzed phosphination of ArCl



Entry	Substrate	Product	Time/h[a]	Yield %[a,b]
1	 **1**	 **2**	8 (22)	45 (50)
2	 **3**	 **4**	6 (37)	35 (42)
3	 **5**	 **6**	4.5 (8)	48 (61)
4	 **7**	 **8**	4 (8)	51 (63)
5	 **9**	 **10**	24 (49)	25 (46)
6	 **11**	 **12**	12 (22)	32 (55)
7[c]	 **13**	 **14**	60	33
8	 **15**	 **16**	99 (19)	17 (0)
9[d]	 R = Me, *t*-Bu		12 days	0
10[d]			131	0

[a] Data in bracket are reactions at 140 °C.
[b] Isolated yield.
[c] 5 equiv of PPh_3 were used.
[d] Aryl chlorides consumed completely.

substituted aryl chlorides gave satisfactory results (Table 6, entries 1 and 2). This method was tolerable with nitrile and aldehyde functional groups (Table 6, entries 3 and 4). However, the ester functional group (methyl or *tert*-butyl ester) was found to be incompatible (Table 6, entries 9 and 10). The electron rich 4-methoxylphenyl chloride did not react at all and could be reasoned to have a much slower rate of oxidative addition. The *meta*-substituted aryl chlorides gave slightly lower yield phosphine products **10** and **12** than the *para* aryl chlorides (Table 6, entries 5 and 6 vs. 1 and 4). 1,8-Dichloroanthracene (**13**) surprisingly gave the mono-phosphinated product **14** despite 5 equiv of triphenyl-phosphine were added (Table 6, entry 7). Apparently, excess phosphine did not form significant amounts of catalytically inactive, coordinatively saturated palladium complex at elevated temperature in which the rate of ligand dissociation is very rapid. Further diposphination did not occur presumably due to the steric hindrance of the 8-diphenylphosphino group in **14**. 2-Chlorobenzonitrile (**15**) was successfully phosphinated. Very slow rate of

reaction and low product yield were observed. Likely the *ortho*-cyano group slowed down the rate of oxidative addition of carbon–chloride bond either by steric hindrance or coordination to palladium (Table 6, entry 8). Heterocyclic substrates such as 2-chlorothiophene, 2- and 3-chloropyridines remained unsuccessful. Pd/Al_2O_3 was equally effective but $Pd(OH)_2$ was not effective at all.

The effect of temperature was also investigated. In most cases, longer reaction times and higher product yields were observed at a lower temperature of 140 °C (Table 6, entries 1–8, data in brackets). Higher yields could be rationalized due to slower phosphination of the product with any unreacted aryl chloride or phosphonium salt intermediate to undergo double phosphination.[3] However, the less reactive 2-chlorobenzonitrile gave no product at 140 °C. A higher temperature was necessary.

In conclusion, a variety of functionalized phosphines were prepared by the operationally simple phosphination of aryl bromides, triflates and chlorides using triphenylphosphine with Pd/C or Pd/alumina catalyst. Sodium iodide (5 equiv) was shown to enhance the yields of the phosphination of aryl chlorides.

3. Experimental

3.1. General considerations

Unless otherwise noted, all reagents were purchased from commercial suppliers and used without purification. Hexane for chromatography was distilled from anhydrous calcium chloride. *N*,*N*-Dimethylformamide was distilled from magnesium sulfate under reduced pressure. Thin layer chromatography was performed on Merck precoated silica gel 60 F_{254} plates. Silica gel (Merck, 70–230 and 230–400 mesh) was used for column chromatography. ^{1}H NMR spectra were recorded on a Brüker DPX 300 (300 MHz) spectrometer. Spectra were referenced internally to the residual proton resonance in $CDCl_3$ (δ 7.26 ppm), or with tetramethylsilane (TMS, δ 0.00 ppm) as the internal standard. Chemical shifts (δ) were reported as part per million (ppm) in δ scale downfield from TMS. ^{13}C NMR spectra were recorded on a Brüker DPX 300 (75 MHz) spectrometer and referenced to $CDCl_3$ (δ 77.00 ppm). Coupling constants (J) were reported in Hertz (Hz). High resolution mass spectra (HRMS) were obtained on a Finnigan Mat 95XL mass spectrometer (ESIMS). All the known products had been fully characterized.[2c]

3.2. General procedure

To a mixture of 4-chlorobenzonitrile (68 mg, 0.5 mmol), 10% (w/w) palladium on charcoal (53.2 mg, 0.05 mmol), triphenylphosphine (328 mg, 1.25 mmol) and NaI (375 mg, 2.5 mmol) was added anhydrous DMF (2 mL) in a Telfon screw-capped flask under nitrogen. The reaction mixture was heated to 160–165 °C for 4.5 h and the color of the solution remained black throughout the reaction. 4-(Diphenylphosphino)-benzonitrile was obtained (70 mg, 41%) as a white solid after purification by column chromatography on silica gel eluting using hexanes/CH_2Cl_2 (10/1).

3.2.1. (4-Diphenylphosphino)benzophenone (4). White solid; yield: 42%; mp 127–129 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.33–7.45 (m, 10H), 7.47–7.62 (m, 4H), 7.67–7.85 (m, 5H); HRMS Calcd for $C_{25}H_{19}PO$ (M^+) m/z 366.1174, found 366.1185.

3.2.2. (8-Chloroanthracen-1-yl)diphenylphosphine (14). Yellow solid; yield: 39%; mp 185–187 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.10 (t, 3H, J=2.1 Hz), 7.32 (m, 13H), 7.87 (d, 1H, J=8.4 Hz), 7.99 (d, 1H, J=8.4 Hz), 8.46 (s, 1H), 9.38 (d, 1H, J=4.2 Hz); HRMS Calcd for $C_{26}H_{18}PCl$ (M^+) m/z 396.0835, found 396.0855. Anal. Calcd for $C_{26}H_{18}PCl$: C, 78.69; H, 4.57. Found: C, 78.54; H, 4.72.

Acknowledgements

We thank the Direct Grant of the Chinese University of Hong Kong and an anonymous donor for financial support.

References and notes

1. Kwong, F. Y.; Chan, K. S. *Chem. Commun.* **2000**, 1069–1070. For correction, see Kwong, F. Y.; Chan, K. S. *Chem. Commun.* **2000**, 1447–1447.
2. (a) Kwong, F. Y.; Chan, K. S. *Organometallics* **2001**, *20*, 2570–2596. (b) Kwong, F. Y.; Lai, C. W.; Tian, Y.; Chan, K. S. *Tetrahedron Lett.* **2000**, *41*, 10285–10289. (c) Kwong, F. Y.; Lai, C. W.; Yu, M.; Tian, Y.; Chan, K. S. *Tetrahedron* **2003**, *59*, 10295–10305.
3. Kwong, F. Y.; Lai, C. W.; Chan, K. S. *J. Am. Chem. Soc.* **2001**, *123*, 8864–8865.
4. Kwong, F. Y.; Lai, C. W.; Chan, K. S. *Tetrahedron Lett.* **2002**, *43*, 3537–3539.
5. For the use of air-sensitive and expensive phosphinating reagent, see (a) Cai, D. W.; Payack, J. F.; Bender, D. R.; Hughes, D. L.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem.* **1994**, 59 1994, 7180–7181. (b) Cai, D. W.; Payack, J. F.; Bender, D. R.; Hughes, D. L.; Verhoeven, T. R.; Reider, P. J.; *Organic Synthesis*, Collect. Vol. 76 1999 pp 6–11. (c) Herd, O.; Hessler, A.; Hingst, M.; Machnitzki, P.; Tepper, M.; Stelzer, O. *Catal. Today* **1998**, 42 1998, 413–420. (d) Ager, D. J.; East, M. B.; Eisenstadt, A.; Laneman, S. A. *Chem. Commun.* 1997, 2359–2360.
6. For a leading reference: Jansat, S.; Go'mez, M.; Philippot, K.; Muller, G.; Guiu, E.; Claver, C.; Castillo, S.; Chaudret, B. *J. Am. Chem. Soc.* **2004**, *126*, 1592–1593.
7. Pham-Huu, C.; Keller, N.; Charbonniere, L. J.; Ziessel, R.; Ledoux, M. J. *Chem. Commun.* **2000**, 1871–8172.
8. For a recent reference of $Pd(OH)_2$: Mori, Y.; Seki, M. *J. Org. Chem.* **2003**, *68*, 1571–1574.
9. For a leading reference Pd/C: LeBlond, C. R.; Andrews, A. T.; Sun, Y.; Sowa, J. R. *Org. Lett.* **2001**, *10*, 1555–1557.
10. Bronstein, L. M.; Chernyshov, D. M.; Karlinsey, R.; Zwanziger, J. W.; Matveeva, V. G.; Sulman, E. M.; Demidenko, G. N.; Hentze, H.-P.; Antonietti, M. *Chem. Mater.* **2003**, *15*, 2623–2631.
11. Anson, M. S.; Lesse, M. P.; Tonks, L.; Williams, J. M. J. *J. Chem. Soc., Dalton Trans.* **1998**, 3529–3538.

12. Mori, K.; Yamaguchi, K.; Hara, T.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *J. Am. Chem. Soc.* **2002**, *124*, 11572–11573.
13. Mehnert, C. P.; Weaver, D. W.; Ying, J. Y. *J. Am. Chem. Soc.* **1998**, *120*, 12289–12296.
14. Djakovitch, L.; Rollet, P. *Tetrahedron Lett.* **2004**, *45*, 1367–1370.
15. Uozumi, Y.; Tanaka, H.; Shibatomi, K. *Org. Lett.* **2003**, *6*, 281–283.
16. (a) Buchmesier, M. *Chem. Rev.* **2000**, 1433–1604. (b) Fu, Y. S.; Yu, S. *Angew. Chem., Int. Ed.* **2001**, *40*, 437–440. (c) Akiyama, R.; Kobayashi, S. *J. Am. Chem. Soc.* **2003**, *125*, 3412–3413.
17. (a) Falorni, M.; Giacomelli, G.; Porcheddu, A.; Taddei, M. *J. Org. Chem.* **1999**, *64*, 8962–8964. (b) Sajikl, H.; Harrori, K.l.; Aoki, F.; Yasunaga, K.; Hirota, K. *Synlett* **2002**, *7*, 1149–1151.
18. (a) Fabian, R. H.; Klassen, D. M.; Sonntag, R. W. *Inorg. Chem.* **1980**, *19*, 1977–1982. (b) Li, Y.; Kawakami, Y. *Macromolecules* **1999**, *32*, 6871–6873.
19. (a) Venkatraman, S.; Li, C.-J. *Org. Lett.* **1999**, *1*, 1133–1136. (b) Bamfield, P.; Quan, P. M. *Synthesis* **1978**, 537.
20. Bleicher, L.; Cosford, N. D. P. *Synth. Lett.* **1995**, 1115–1116.
21. Roth, G. P.; Farina, V.; Liebeskind, L. S.; Peña-Cabrera, E. *Tetrahedron Lett.* **1995**, *36*, 2191–2194.
22. (a) Marck, G.; Villiger, A.; Bucherker, R. *Tetrahedron Lett.* **1994**, *35*, 3277–3280. (b) Ennis, D. S.; McManus, J.; Wood-Kaczmar, W.; Richarson, J.; Smith, G. E.; Carstairs, A. *Org. Process. Res. Dev.* **1999**, *3*, 248–252. (c) Gala, D.; Stamford, A.; Jenkins, J.; Kugelman, M. *Org. Process. Res. Dev.* **1997**, *1*, 163–164. (d) Dyer, U. C.; Shapland, P. D.; Tiffin, P. D. *Tetrahedron Lett.* **2001**, *42*, 1765–1767.
23. Rossi, R.; Bellina, F.; Carpita, A.; Gori, R. *Synth. Lett.* **1995**, 344–345.
24. (a) Hallberg, A.; Westfelt, L. *J. Chem. Soc., Perkin Trans. 1* **1984**, 933–935. (b) Zhao, F.; Bhanage, B. M.; Shirai, M.; Arai, M. *Chem. Eur. J.* **2000**, *6*, 843–848. (c) Kohler, K.; Heidenreich, R. G.; Krauter, J. G. E.; Pietsch, J. *Chem. Eur. J.* **2002**, *8*, 622–631.
25. (a) Jayasree, S.; Seayad, A.; Chaudhari, R. V. *Chem. Commun.* **1999**, 1067–1068. (b) Chaudhari, B. M.; Madhi, S.; Kantam, M. L.; Sreedhar, B.; Iwasawa, Y. *J. Am. Chem. Soc.* **2004**, *126*, 2292–2293.
26. Lin, Y.-S.; Alper, H. *Angew. Chem., Int. Ed.* **2001**, *40*, 779–781.
27. Ishiyama, T.; Ishida, K.; Takagi, J.; Miyaura, N. *Chem. Lett.* **2001**, 1082–1083.
28. Lai, C. W.; Kwong, F. Y.; Wang, Y.; Chan, K. S. *Tetrahedron Lett.* **2001**, *42*, 4883–4885.
29. Migita, T.; Nagai, T.; Kiuchi, K.; Kosugi, M. *Bull. Chem. Soc. Jpn* **1983**, *56*, 2869–2870.
30. For mechanistic studies of Pd-aryl/P-aryl exchange using stoichiometric amount of palladium complexes, see: (a) Kong, K. C.; Cheng, C. H. *J. Am. Chem. Soc.* **1991**, *113*, 6313–6315. (b) Goodson, F. E.; Wallow, T. I.; Novak, B. M. *J. Am. Chem. Soc.* **1997**, *119*, 12441–12453. (c) Grushin, V. V. *Organometallics* **2000**, *19*, 1888–1900.
31. Garrou, P. E. *Chem. Rev.* **1985**, *85*, 171–185.
32. Davies, I. W.; Matty, L.; Hughes, D. L.; Reider, P. J. *J. Am. Chem. Soc.* **2001**, *123*, 101392–110140.
33. (a) For examples: Piber, M.; Jensen, A. E.; Rottländer, M.; Knochel, P. *Org. Lett.* **1999**, *1*, 1323–1326. (b) Dai, W.-M.; Guo, D.-S.; Sun, L.-P. *Tetrahedron Lett.* **2001**, *42*, 5275–5278. (c) Herrmann, W. A.; Brossmer, C.; Reisinger, C.-P.; Riedermeier, T. H.; Öfele, K.; Beller, M. *Chem. Eur. J.* **1997**, *3*, 1357–1361. (d) Powell, N. A.; Rychnovsky, S. D. *Tetrahedron Lett.* **1996**, *37*, 7901–7904. (e) Nakamura, K.; Okubo, H.; Yamaguchi, M. *Synlett* **1999**, 549–552. (f) Albanese, D.; Landini, D.; Penso, M.; Petricci, S. *Synlett* **1999**, 199. (g) Nguefack, J.-F.; Bollit, V.; Sinou, D. *Tetrahedron Lett.* **1996**, *37*, 5527–5530. (h) Wright, S. W.; Hageman, D. L.; McClure, L. D. *J. Org. Chem.* **1994**, *59*, 6095–6099.
34. Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314–321.
35. Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176–4211.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 60 (2004) 9441–9446
Tetrahedron

Nuclear magnetic resonance spectroscopic study on ionic liquids of 1-alkyl-3-methylimidazolium salts

Shaw-Tao Lin,* Mei-Fang Ding, Cha-Wen Chang and Sue-Sing Lue

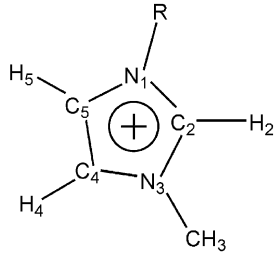
Department of Applied Chemistry, Providence University, Sha-Lu, Taichung Hsien, 433, Taiwan, ROC

Received 16 April 2004; revised 23 July 2004; accepted 4 August 2004

Abstract—Chemical shifts of ^{1}H and ^{13}C NMR of series of methylimidazolium salts (MIM^{+}, $X=Br^{-}$, BF_4^{-} and PF_6^{-}) function on the length of alkyl groups on the ring, type of solvents and the concentration. The bromides series demonstrate more chemical shift variation on H2 upon the change of solvents and concentration. Unexpected H–D exchange reactions were also observed in the $MIM^{+}Br^{-}$ by using CD_3OD and D_2O. The exchange rates strongly depend on the length of the alkyl group, which could cause more steric factor to reduce the interaction between deuterium atom from solvent and C2 of the ring.
© 2004 Elsevier Ltd. All rights reserved.

1. Introduction

Nuclear magnetic resonance (NMR) technique is known with higher sensitive in the electron density around the nucleus. The chemical shifts of proton (^{1}H) and carbon-13 (^{13}C) NMR are the most common and versatile analytic methods to reveal the environment on the nucleus. A nucleus with higher electron density will lead to a resonance appears at higher field.[1] Ionic liquids (ILs) are classified as the 'green solvents' because of no measurable vapor pressure, and recyclable.[2] Another important advantage by using ionic liquids as solvents for organic reactions is that organic products are easily and efficiently extracted from the reaction mixtures.[3] ILs are supported to be present as a cationic ion and anionic ion state at an ambient condition. The degree of dissociation of ion liquids will create different electron densities on the atoms, which would be the potential ionic state. Currently, the derivatives of $MIM^{+}X^{-}$ are the most common used ILs and their application as solvents for organic reactions is increasing tremendously.[4] The results indicate that these modifications result in ILs have remarkable effects on the outcome of different reactions.[5] This series of ionic liquids have been discovered since 1982,[6] some NMR studies have been reported, such as spin-echo study of spin diffusion,[7] study of spin diffusion in a H,H-NOESY,[8] and study of the evidence of hydrogen bonding of imidazolium ions.[9] Those studies related to the translational diffusion and the interaction between imidazolium ions with itself as well as with its counterions. However, as we know, only one study on the effect of the anion on the chemical shifts of the aromatic hydrogen atoms of 1-butyl-3-methylimidazolium ($BMIM^{+}$) salts was reported.[10] The authors concluded that owing to the intimate interaction of the ions of $BMIM^{+}BF_4^{-}$, its aromatic hydrogen atoms are less sensitive to solvation effects than the hydrogen atoms of $BMIM^{+}PF_6^{-}$. In continuation of our interest in the NMR spectroscopic study, we will investigate the chemical shifts of the imidazolium salts function on the anions, the lengths of alkyl groups, solvents as well as concentration. Figure 1 shows the structure of these salts being studied in this work. From the limited data currently available, it is clear that the cation, the substituents on the cation, and the anion can be chosen to enhance or suppress



R: C_2H_5 (**1**), C_3H_7 (**2**), C_4H_9 (**3**), C_5H_{11} (**4**), C_6H_{13} (**5**), C_7H_{15} (**6**), C_8H_{17}(**7**)

X^{-}: Br^{-} (**a**), BF_4^{-} (**b**), PF_6^{-} (**c**)

Figure 1. Structure of 1-alkyl-3-methylimidazolium salts.

Keywords: Nuclear magnetic resonance; Methylimidazolium salts; Chemical shifts.
* Corresponding author. Tel.: +886-4-2362-9901; fax: +886-4-2362-7554; e-mail: sdlin@pu.edu.tw

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.08.022

the solubility of ILs in other compounds and the solubility of other compounds in the ionic liquids. For instance, an increase in alkyl chain length decrease the mutual solubility with water, but some anions ($[BF_4]^-$, for example) can increase mutual solubility with water (compared to $[PF_6]^-$).[11] In this study, we limited the chain length ranging from ethyl to octyl group with the anions of Br^-, BF_4^- and PF_6^-. Due to the limitation of solubility of those ionic liquids, nonpolar solvents were excluded from this study.

2. Results and discussion

2.1. Alkyl group and anion effect

The longer length of alkyl group on the imidazolium ring is expected to increase the electron density of that ring. In general, the substituent on the N1 does not influence the chemical shifts on the hydrogens and carbon on the imidazolium ring obtained in CD_3OD as shown in Table 1. The chemical shift of H4 is very close to that of H5, but H2 exhibits a much down-field shift. The ^{13}C NMR data exhibits similar character as that observed in ^1H NMR analyses. The C2 (H2) is located between two electronegative nitrogen atoms, and hence C2 (H2) shall be less electron density and H2 shall be more acidic than H4 or H5. This suggests the positive charge is more likely to localize at N1–C2–N3. The slight different chemical shifts of C4(H4) and C5(H5) owing to the different substituents bonded to the nitrogen atoms. This fact is not consistent with the ab initio calculations on the partial charges of the hydrogen atoms of the imidazolium cation as shown in Figure 2.[11] While the calculated charge densities of H4 and H5 are lower than that of H2.

The nature of anion will lead to different degree of interaction with a cation on the ring. Among the used anions, bromide ion is less ionizable and tends to interact with the cation; on the other hand, BF_4^- and PF_6^- tend to be present as naked ion. Due to the different character of those anions, the proton and carbon chemical shifts of ion liquids will be varied upon the presence of type of anions. We observed the small down-field shift (9.0 ppm) for H2 in bromide series (**1a**–**7a**) in comparison with the others (**1b**, **3b**, **7b**, **1c**, **3c**, **7c**) at the range of 8.8–8.9 ppm (Table 1). However, even smaller downfield shifts appear in the carbon

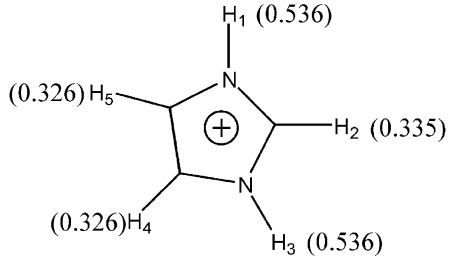


Figure 2. RHF/6-31+G* partial charges (shown in parentheses) for the hydrogen atoms of the imidazolium cation.[11]

shifts. This information indicates that there is an interaction between H2 and bromide ion which enlongs the distance of that C2–H2 bond. The interaction between H2 and chloride ions have been concluded by using IR and variable-temperature ^1H NMR analysis.[9b]

2.2. Solvent effect

The shielding ability, relative permittivity of solvents and the van der Waals interaction between analyte and solvent, plays an important role in the chemical shifts of analytes.[12] Due to the ionic nature of our analytes, the weaker van der Waals interaction can be ignored in this study. For the interaction field of a polar molecule in a medium of relative permittivity, ε_r, the ^{13}C screening constants in substituted methanes depend linearly on the function, $(\varepsilon_r-1)/(2+2n)$, where n is the refractive index of the solvent molecules.[12] The latter can be more important to polarized bond because that solvent with higher relative permittitivity should be able to stabilize the polarized bond better and result in redistribution of the electron density of that bond. The shielding ability is governed by the shape of molecule (dish-shape, rode shape) and the number of halogen in a molecule.[12] Due to the ionic character of MIM^+X^-, only higher polar solvents can be used for this study. The chemical shifts of 1-ethyl-3-methylimidazolium salts ($EMIM^+X^-$, 0.16 M) in various solvents are summarized in Tables 2 and 3.

Table 2 shows the diversified variation on the hydrogens of the ring and relatively consistence for the hydrogens of alkyl group. Among them the H2 on the ring of **1a** displays at downfield shift comparing that of **1b** and **1c**. The variation of the chemical shifts for H2 might indicate the interaction

Table 1. ^1H and ^{13}C chemical shift values of 1-alkyl-3-methylimidazolium salts in CD_3OD at 298 K. Solution concentrations are 0.16 M for the used compounds

	H2	H4	H5	C2	C4	C5
1a	9.04	7.71	7.63	137.91	125.54	123.62
2a	8.98	7.65	7.59			
3a	8.99	7.66	7.59	137.86	124.96	123.68
4a	8.99	7.66	7.59			
5a	8.99	7.67	7.60			
6a	9.00	7.66	7.59			
7a	9.00	7.66	7.54	137.84	124.95	123.66
1b	8.89	7.66	7.58	137.86	125.19	123.54
3b	8.87	7.62	7.55	137.83	124.92	123.61
7b	8.85	7.61	7.55	137.80	124.90	123.59
1c	8.79	7.59	7.52	137.497	124.87	123.41
3c	8.81	7.59	7.53	137.76	124.88	123.58
7c	8.81	7.59	7.53	137.57	124.86	123.55

Table 2. ^{1}H chemical shift values of 1-ethyl-3-methylimidazolium salts in different deuterated solvents at 298 K. Solution concentrations are 0.16 M for the used compounds

	H2	H4	H5	Others		
[$^{2}H_6$] Dimethylsulfoxide						
1a	9.21	7.81	7.72	4.19	3.84	1.59
1b	9.06	7.75	7.66	4.17	3.82	1.39
1c	8.71	7.48	7.41	4.08	3.74	1.35
[$^{2}H_5$] Pyridine						
1a	10.35	7.81	7.72	4.25	3.91	1.26
1b	9.18	7.61	7.55	4.07	3.77	1.23
1c	9.24	7.67	7.61	4.14	3.83	1.33
[$^{2}H_4$] Methanol						
1a	9.04	7.71	7.63	4.32	3.99	1.58
1b	8.89	7.66	7.58	4.29	3.96	1.57
1c	8.79	7.59	7.52	4.24	3.91	1.52
[$^{2}H_3$] Nitromethane						
1a	9.04	7.49	7.44	4.30	3.96	1.51
1b	8.52	7.45	7.40	4.26	3.92	1.50
1c	8.48	7.47	7.42	4.29	3.96	1.55
[$^{2}H_3$] Acetonitrile						
1a	9.02	7.52	7.46	4.27	3.92	1.52
1b	8.50	7.45	7.39	4.22	3.88	1.52
1c	8.46	7.44	7.38	4.22	3.88	1.51
[^{2}H] Chloroform						
1a	10.21	7.53	7.52	4.38	4.08	1.57
1b	8.59	7.40	7.27	4.30	4.01	1.58
1c	8.82	7.29	7.24	4.26	3.97	1.59
[$^{2}H_2$] Water						
1a	8.71	7.48	7.41	4.22	3.89	1.49
1b	8.68	7.47	7.41	4.22	3.88	1.49
1c	8.68	7.47	7.40	4.21	3.87	1.49

between H2 and the solvents. The chemical shifts of H2 of **1a** show the substantial downfield shift in C_5D_5N (10.35 ppm) and $CDCl_3$ (10.21 ppm), but those downfield shifts don't reflect in the chemical shifts of C2. If the electron delocalization occurred in the imidazolium ring in a specific solvent, the chemical shifts shall move in the same direction for ^{1}H and ^{13}C NMR spectrum. From the Tables 2 and 3, we can find that the downfield shifts for H2 are

Table 3. ^{13}C chemical shift values of 1-ethyl-3-methylimidazolium salts in different deuterated solvents at 298 K. Solution concentrations are 0.16 M for the used compounds

	C2	C4	C5	Others		
[$^{2}H_6$] Dimethylsulfoxide						
1a	136.46	123.77	122.20	44.32	35.94	15.38
1b	136.43	123.80	122.20	44.37	35.92	15.33
1c	136.74	124.63	123.02	45.62	36.83	16.03
[$^{2}H_5$] Pyridine						
1a	137.92	124.39	122.66	45.36	36.49	15.82
1b	137.09	124.40	122.80	45.48	36.31	15.40
1c	135.88	123.42	121.77	44.47	35.25	14.25
[$^{2}H_4$] Methanol						
1a	137.91	125.54	123.62	46.34	36.83	15.94
1b	137.86	125.19	123.54	46.27	36.66	15.81
1c	137.49	124.87	123.41	45.98	36.35	15.44
[$^{2}H_3$] Nitromethane						
1a	134.99	122.55	120.89	43.95	34.60	13.39
1b	134.48	122.69	120.99	44.05	34.58	13.26
1c	134.40	122.77	121.07	44.15	34.65	13.26
[$^{2}H_3$] Acetonitrile						
1a	136.58	124.63	122.96	45.83	36.78	15.48
1b	136.04	123.49	121.85	44.70	35.77	14.56
1c	135.70	123.58	121.92	44.76	35.72	14.46
[^{2}H] Chloroform						
1a	137.02	123.51	121.71	45.22	36.66	15.56
1b	135.68	123.59	122.01	44.85	35.82	14.92
1c	135.35	123.40	121.76	44.85	35.63	14.46
[$^{2}H_2$] Water						
1a	138.26	126.14	124.57	47.48	38.31	17.18
1b	138.26	126.15	124.56	47.47	38.26	17.15
1c	138.28	126.14	124.56	46.67	38.25	17.14

Table 4. ^{1}H chemical shifts change of 1-ethyl-3-methylimidazolium salts in various solvents at 298 K. Solution concentrations are varied from 0.01 to 1.28 M for the used compounds[a]

	H2	H4	H5	Others		
[$^{2}H_6$] Dimethylsulfoxide						
1a	−0.26	−0.1	−0.10	—	—	−0.10
1b	0.12	—	—	—	—	—
1c	—	—	—	—	—	—
[$^{2}H_5$] Pyridine						
1a	0.37	−0.33	−0.32	0.10	0.11	—
1b	0.34	0.14	0.14	—	—	—
1c	0.53	0.24	0.24	0.12	0.11	—
[$^{2}H_4$] Methanol						
1a	−0.18	−0.11	−0.12	−0.10	—	—
1b	0.14	—	—	—	—	—
1c	0.23	0.11	0.10	—	—	—
[$^{2}H_3$] Nitromethane						
1a	−0.75	−0.16	−0.16	—	—	—
1b	—	—	—	—	—	—
1c	—	—	—	—	—	—
[$^{2}H_3$] Acetonitrile						
1a	−0.77	−0.22	−0.20	—	—	—
1b	0.11	—	—	—	—	—
1c	—	—	—	—	—	—
[$^{2}H_2$] Water						
1a	—	—	—	—	—	—
1b	—	—	—	—	—	—
1c	—	—	—	—	—	—

[a] The difference in chemical shifts is defined as the shifts from the values obtained from 0.01 M to that from 1.28 M. The positive values represent the up-field shifts.

substantially larger than C2 in compound **1a**. Therefore, we can exclude the electron delocalization in the ring when C_5D_5N and $CDCl_3$ were used. Herein [$^{2}H_5$] pyridine and polyhalomethanes are known as the deshield solvents and able to deshieding the molecule of analyte.[13] The nature of ILs in the imidazolium ions creates an acidic hydrogen which might interacts with pyridine and chloroform to receive more deshielding effect.

2.3. Concentration effect

The concentration of solute shall influence the dissociation of solute. Low concentration will result in high degree of dissociation. The ionic liquids are presumed present in the ionic state, i.e. the compounds are completely dissociated into cation and anion. The nature of shielding by solvents also contributes to the shifts in the various concentrations. It will be interesting to study the concentration effect on the chemical shifts of $EMIM^{+}X^{-}$.

The chemical shifts function on the concentrations were conducted at 0.01, 0.04, 0.16, 0.64, and 1.28 M, respectively. Due to the limitation of solubility in this study, D_2O and $CDCl_3$ are excluded. The H2 of bromide (**1a**) demonstrates down-field shifts upon increasing the concentration except in C_5D_5N in which H4 and H5 show small up-field shifts. Higher concentration of analytes means every analyte experience less interaction with the solvent molecules. Under lower concentration, the analytes will tend to dissociate or change from the tie-ion paired to the solvent separated ion paired in this system. The used solvents are polar molecules except for pyridine. The pyridine is classified as a dish-like molecule and is able to deshield the analytes leading to the opposite shift for H2. The hydrogen-bonding between H2 and $CD_3S(O)CD_3$ and CD_3OD might also cause down-field shifts. On the other hand, the chemical shifts for protons on the ring of **1b** and **1c** are rather constant except for C_5D_5N and CD_3OD. Since compounds **1b** and **1c** are supposed to be presence as the separated ions regardless to the concentration; again, the hydrogen-bonding might play a role in this change (Tables 4 and 5).

The ^{13}C NMR spectroscopic study seems to be more sensitive on the variation of concentration and type of anions. Meanwhile, the $CD_3S(O)CD_3$, CD_3OD, and [$^{2}H_5$]-pyridine are able to form an interaction with either C2 or H2 leading to up-field shift in the lower concentration. Nitromethane-d_3 and CD_3CN might lead to the more charge localization resulting to diver shift for C2 vs. C4 and C5 upon the variation of concentration.

2.4. Exchange study

The H(2) is known as an acidic hydrogen. The pK_a of 1,3-diisopropyl-4,5-dimethyl-imidazolium in DMSO was estimated at 24.[14] It is also known that the different hydrogen atoms of 1-alkyl-3-methylimidazolium salts are capable of the formation of hydrogen bonding.[15] Recently, the hydrogen bonding between a hydrogen of imidazolium and either cyclopentadienyl or fluorenide (C–H$\cdots$C(π)) were verified from single crystal X-ray analysis.[16] During the H–D exchange studies, we assumed that the peak areas of H4 and H5 are steady throughout the experiment. Therefore, the rate of H–D exchange can be measured from the disappearance of H2 via the decreasing in the peak area ratios of H2 and H4. When the bromide ion as anion and CD_3OD and D_2O were used as a solvent, the chemical shifts of H2 slowly disappear depending on the size of alkyl groups. The H2 signal of dimethyl derivative **1a** completely

Table 5. ^{13}C chemical shifts change of 1-ethyl-3-methylimidazolium salts in various solvents at 298 K. Solution concentrations are varied from 0.01 to 1.28 M for the used compounds[a]

	C2	C4	C5	Others		
[$^2H_6$] Dimethylsulfoxide						
1a	—	0.14	—	—	—	−0.10
1b	—	−0.10	−0.10	−0.23	—	—
1c	−0.18	—	—	—	—	0.14
[$^2H_5$] Pyridine						
1a	0.64	0.12	−0.22	0.11	−0.39	−0.20
1b	0.25	0.58	0.34	0.33	0.30	−0.20
1c	0.31	—	—	−0.13	—	—
[$^2H_4$] Methanol						
1a	0.14	—	—	—	−0.38	−0.27
1b	0.36	0.25	0.19	0.17	0.10	0.13
1c	0.24	0.26	0.31	0.14	0.10	0.21
[$^2H_3$] Nitromethane						
1a	−0.54	0.91	0.49	0.88	0.44	—
1b	—	0.15	0.17	0.23	0.18	—
1c	−0.10	0.14	0.16	0.20	0.17	—
[$^2H_3$] Acetonitrile						
1a	−0.28	0.33	0.28	0.39	0.13 —	
1b	−0.24	—	—	—	—	—
1c	−0.10	0.14	0.16	0.20	0.17	—
[$^2H_2$] Water						
1a	0.15	0.12	0.17	—	—	—
1b	—	—	—	—	—	—
1c	—	—	—	—	—	—

[a] The difference in chemical shifts is defined as the shifts from the values obtained from 0.01 M to that from 1.28 M. The positive values represent the up-field shifts.

disappears within 6 h in both CD_3OD and D_2O. Longer alkyl group lead to slow exchange rate and no H–D exchange takes place for the heptyl derivative **7a** in both solvents for a week as shown in Table 6. The exchange rates are faster in D_2O than that in CD_3OD which is rationalized as a less steric factor and has stronger hydrogen bonding ability of water. As we know, this will be the first report on the H–D exchange reaction of imidazolium salts. This observation is presumed that the interaction of deuterium of CD_3OD and the C2 of imidazolium ring lead to the exchange reaction. After the exchange was complete, that the signal C2 became a triplet (J 33 Hz) with 0.26 ppm up-field shift indicated the presence of deuterium on that carbon. This nucleus in the heavier isotopomer is usually more shielded. It may be rationalized in terms of a shortening of the carbon–hydrogen bond for replacement of C–H by C–D.[17] This coupling constant is larger than that of CD_3 in CD_3OD (21 Hz), CD_3CN (21 Hz) and $CD_3S(O)CD_3$ (21 Hz), but comparable with the case of $CDCl_3$ (32 Hz) and $CD_3C(O)CD_3$ (31 Hz). The larger coupling constant also indicates the longer bond distance and weaker bonding of C2–H2 in MIM^+. The exchange reaction only occurs at the ILs, which contain bromide anion but not on BF_4^- or PF_6^- as a counter-ion. Therefore, we rationalized as that the bromide anion is able to interact with the H2 atom and to enhance the electron density of C2 to receive a hydrogen or deuterium from a protic solvent. This assumption has been discussed in the previous section. The hydrogen bonding is a different fashion from literatures. In the previous section, we have concluded that the size of alkyl group does not change much in the chemical shifts of the ring, and suggested that the electron density doesn't vary much upon the change of the alkyl group. Therefore, this rate function on the size of alkyl group must be mainly attributed to the steric factor.

3. Conclusion

The ILs of MIM^+X^- **1b** and **1c** are presented as ionic character, the chemical shifts of hydrogens and carbons of the MIM^+ ring don't receive much influence by the variation of the type of solvents, concentration of analytes or even the length of alkyl group at N3 position. The bromide ion is a less ionizable in compound **1a** and its analogous resulted in more variation on both ^1H and ^{13}C NMR chemical shifts upon the variation of solvents and the concentration. The variations of H2 in ^1H chemical shifts are significantly larger than that of C2 in ^{13}C NMR, which might indicate the interaction between H2 and solvents rather than the electron delocalization of MIM^+ ring due to the relative permeability of solvents. The H–D exchange

Table 6. The H–D exchange of various ionic liquids with bromide ion in CD_3OD (D_2O).[a] Solution concentrations are 0.16 M for the used compounds

	1a	**2a**	**3a**	**4a**	**5a**	**6a**	**7a**
2 h	0.40 (0.20)	0.62 (0.34)	0.78 (0.52)	0.86 (0.81)	0.92 (0.86)	0.96 (0.90)	1.00 (1.00)
4 h	0.14 (0.05)	0.41 (0.14)	0.64 (0.30)	0.70 (0.68)	0.84 (0.77)	0.93 (0.87)	1.00 (1.00)
6 h	0.00 (0.00)	0.30 (0.00)	0.55 (0.23)	0.65 (0.56)	0.79 (0.70)	0.90 (0.81)	1.00 (1.00)

[a] Ratios are defined as the $(\text{peak area})_{H2}/(\text{peak area})_{H4}$.

reaction between MIM^+Br^- and CD_3OD or D_2O suggests the hydrogen bonding between the deuterium atom of solvents and C2 and between H2 and the oxygen atom of solvents. The presence of a positive charge on N2 might be a driving force to the formation of this type of interaction.

4. Experimental

The syntheses of 1-alkyl-3-methylimidazolium salts were carried out as described in the literature.[18] The inorganic salts was removed by repeated extraction with water and the organic solvents was removed under vacuum with heating at 60 °C for 24 h. Both processes are to ensure the high purity of ionic liquids. Due to the hygroscopic character and possible decompose (in case of BF_4^- and PF_6^- ions), all of MIM^+X^- must be kept under nitrogen after purification.[4] All salts are free of contaminate from the ^1H NMR analysis and free of MIM from the colorimetric determination based on the lack of the formation of blue $[Cu(MIM)_4]^{2+}$.[19] For each salt in the NMR tube was evacuated (0.1 Torr) at 60 °C for 6 h to remove the water, which was absorbed during storage.[11] The solvent was added to that NMR tube via a syringe against the nitrogen stream. All of used solvents are preserved with molecular sieve to remove the possible moisture.

The used ionic liquids can be dissolved well in the wide range of concentrations in CD_3OD. The study on the effects on the chemical shifts by alkyl groups, anions, and concentration were carried in the solutions of CD_3OD. The NMR data were recorded on a Bruker AC-250 spectrometer at 250 and 62.9 MHz for ^1H and ^{13}C, respectively. All chemical shifts were measured relative to $SiMe_4$ and in proton noise decoupled spectra for ^{13}C NMR.

Acknowledgements

Financial support from the National Science Council of the ROC (NSC 93-2113-M-126-005) and technique information support by HSCC are gratefully acknowledged.

References and notes

1. Silverstein, R. M.; Webster, F. X. *Spectrometric Identification of Organic Compounds*. 6th ed.; Wiley: New York, NY, 1998. Chapter 4–7.
2. (a) Welton, T. *Chem. Rev.* **1999**, *99*, 2071–2084. (b) Wasserscheider, P.; Keim, W. *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 3772–3789.
3. Dyson, P. J.; Ellis, D. J.; Parker, D. G.; Welton, T. *J. Chem. Soc., Chem. Commun.* **1999**, 25–26.
4. Wasserscheider, P., Welton, T., Eds.; *Ionic Liquids in Synthesis*. Wiley-VCH: KgaA, German, 2003.
5. Chauvin, Y.; Mussmann, L.; Olivier, H. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2698–2700.
6. Wilkes, J. S.; Levisky, J. A.; Wilson, R. A.; Hussey, C. L. *Inorg. Chem.* **1982**, *21*, 1263–1264.
7. Palmer, G.; Richter, J.; Zeidler, M. D. *Z. Naturforsch.* **2004**, *59a*, 59–63.
8. Heimer, N. E.; Del Sesto, R. E.; Carper, W. R. *Magn. Reson. Chem.* **2004**, *42*, 71–75.
9. (a) Huang, J. F.; Chen, P. Y.; Sun, I. W.; Wang, S. P. *Inorg. Chim. Acta* **2001**, *320*, 7–11. (b) Campbell, J. L. E.; Johnson, K. E.; Torkelson, J. R. *Inorg. Chem.* **1994**, *33*, 3340–3345.
10. (a) Anthony, J. L.; Maginn, E. J.; Brennecke, J. F. *J. Phys. Chem. B* **2001**, *105*, 10942–10949. (b) Fadeev, A. G.; Meagher, M. M. *Chem. Commun.* **2001**, 295–296. (c) Seddon, K. R.; Stark, A.; Torres, M. J. *Pure Appl. Chem.* **2000**, *72*, 2275–2287.
11. Headley, A. D.; Jackson, N. M. *J. Phys. Org. Chem.* **2002**, *15*, 52–55.
12. Seidman, K.; Maciel, G. E. *J. Am. Chem. Soc.* **1977**, *99*, 659–671.
13. (a) Laszlo, P. *Prog. NMR Spectrosc.* **1967**, *3*, 231–402. (b) Ueji, S.; Kitadani, M.; Sugiura, M.; Takao, N.; Miyazawa, T. *J. Chem. Soc. Perkin Trans. 2* **1989**, 425–429.
14. Alder, R. W.; Allen, P. R.; Williams, S. J. *J. Chem. Soc., Chem. Commun.* **1995**, 1267–1268.
15. Filipponi, S.; Jones, J. N.; Johnson, J. A.; Cowley, A. H.; Grepioni, F.; Braga, D. *J. Chem. Soc., Chem. Commun.* **2003**, 2716–2717.
16. (a) Wilkes, J. S.; Zaworotko, M. J. *J. Chem. Soc., Chem. Commun.* **1992**, 965–967. (b) Tait, S.; Osteryoung, R. A. *Inorg. Chem.* **1984**, *23*, 4352–4360. (c) Abdul-Sada, A. K.; Greenway, A. M.; Hitchcock, P. B.; Mohammed, T. J.; Seddon, K. R.; Zora, J. A. *J. Chem. Soc., Chem. Commun.* **1986**, 1753–1754. (d) Dieter, K. M.; Dymek, C. J.; Heimer, N. E.; Rovvang, J. W.; Wikes, J. S.; Haworth, D. *J. Am. Chem. Soc.* **1988**, *110*, 2722–2726. (e) Fuller, J.; Carlin, R. T.; De Long, H. C.; Haworth, D. *J. Chem. Soc., Chem. Commun.* **1994**, 299–300. (f) Dymek, C. J.; Grossie, D. A.; Fratini, A. V.; Adams, W. W. *J. Mol. Struct.* **1989**, *213*, 25–34.
17. Jameson, C. J. *Bull. Magn. Res.* **1980**, *3*, 3–12.
18. (a) Dzyuba, S. V.; Bartsch, R. A. *Tetrahedron Lett.* **2002**, *43*, 4657–4659. (b) Huddleston, J. G.; Visser, A. E.; Reichert, W. M.; Willauer, H. D.; Broker, G. A.; Rogers, R. D. *Green Chem.* **2001**, *3*, 156–164. (c) Suarez, P. A. Z.; Dullius, J. F. L.; Einloft, J.; DeSouza, R. F.; Dupont, J. *Polyhedron* **1996**, *15*, 1217–1219.
19. Holbery, J. A.; Seddon, K. R.; Wareing, R. *Green Chem.* **2001**, *3*, 33–36.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 60 (2004) 9447–9451
Tetrahedron

Intramolecular-activation evidence for the unexpected Beckmann fragmentation of C(1)-substituted-7-bromonorbornane-2-ones

Antonio García Martínez,[a,*] Enrique Teso Vilar,[b] Amelia García Fraile,[b] Santiago de la Moya Cerero[a,*] and Beatriz Lora Maroto[b]

[a]*Departamento de Química Orgánica I, Facultad de Químicas, Universidad Complutense de Madrid, 28040 Madrid, Spain*
[b]*Departamento de Química Orgánica y Biología, Facultad de Ciencias, UNED, Senda del Rey 9, 28040 Madrid, Spain*

Received 28 May 2004; revised 22 July 2004; accepted 3 August 2004

In Memoriam to our friend Dr. del Amo Aguado, victim of the terrorist bombing in Madrid, March 11, 2004

Abstract—The competitive pathway timing for the previously described unexpected bromo-assisted Beckmann fragmentation of 7-*anti*-bromo-3,3-dimethyl-2-oxonorbornane-1-carboxamide has been investigated. It is concluded that this unusual process is activated by a synergic effect exerted by both the C(7)-*anti*-bromo and C(1)-aminocarbonyl groups. The effect consists in a specific intramolecular activation of the bromo-assistance by the bridgehead aminocarbonyl group.
© 2004 Elsevier Ltd. All rights reserved.

1. Introduction

In a previous publication, we described the unexpected in situ Beckmann fragmentation of enantiopure 7-*anti*-bromo-3,3-dimethyl-2-oxonorbornane-1-carboxamide **1** under simple hydroxylamine treatment (Scheme 1).

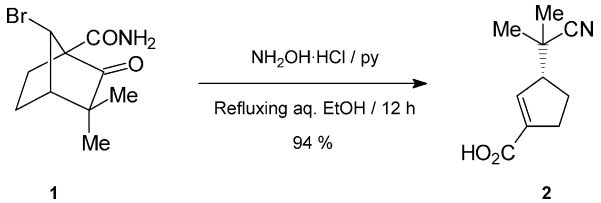
The process resulted to be highly interesting, since it constitutes the first example in which a C(1)-electronwithdrawing substituted 3,3-dimethylnorbornan-2-one experiments an in situ Beckmann fragmentation of the C(1)–C(2) norbornane bond (leading to the valuable enantiopure synthetic intermediate **2**),[1] instead of the expected oxime formation and subsequent C(2)–C(3) Beckmann fragmentation.[2] This unexpected fragmentation was initially attributed to a single effect exerted by the bromo substituent located at the C(7)-*anti*-norbornane position (bromo assistance).[2]

Going in this sense, we were interested in extending this synthetically valuable fragmentative process to other differently substituted 2-norbornanones. For this purpose, the establishment of the structural factors controlling the considered fragmentation was necessary, since other 2-bromonorbornanones (e.g., 7-*anti*-bromofenchone) do not experiment such fragmentation in the same reaction conditions in which **1** does (vide infra). For this purpose, we have revisited and investigated the fragmentation of **1** to **2** (Scheme 1).

2. Results and discussion

Since during the considered reaction (Scheme 1), not only Beckmann fragmentation takes place, but also hydrolysis of the aminocarbonyl group (note the presence of the carboxyl group in final product **2**, Scheme 1), we were interested in investigating the mechanism of such reaction in order to determine the timing of the individual processes (oxime formation, amide hydrolysis and Beckmann fragmentation). Thus, three possible reaction pathways (A, B and C) can be proposed on the base of three different timing possibilities. These reaction pathways are shown in Scheme 2.

Thus, the starting bromonorbornanone **1** can undergo two different individual processes: (1) oxime formation, giving

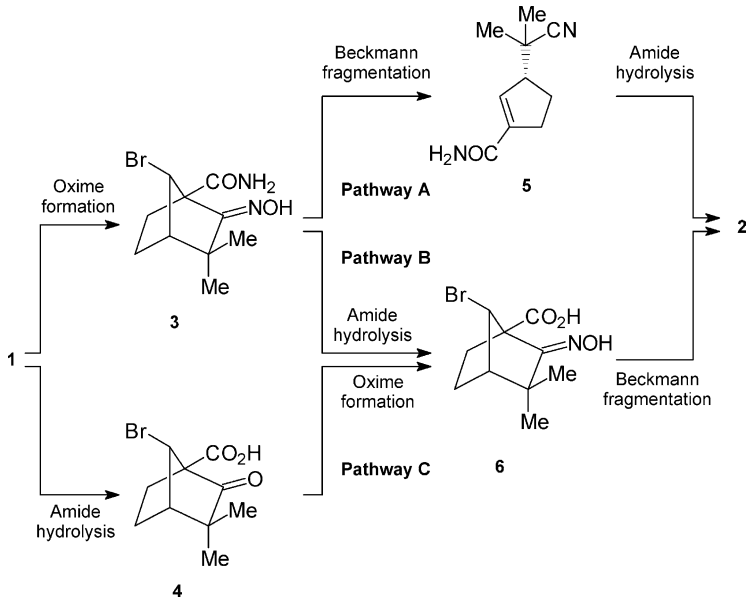


1 2

Scheme 1. Unexpected in situ Beckmann fragmentation of **1**.

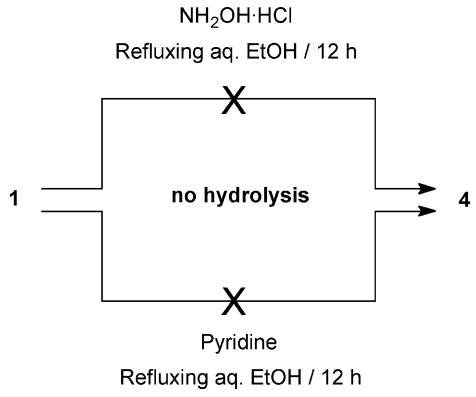
Keywords: Substituent effects; Cleavage reactions; Bicycles; Bridgehead compounds.
* Corresponding authors. Tel.: +91-394-4236; fax: +91-394-4103; e-mail: santmoya@quim.ucm.es

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.08.002



Scheme 2. Proposed reaction pathways.

place to norbornanone oxime **3** and, (2) amide hydrolysis, to generate bridgehead carboxylic acid **4**. Of course, both individual processes could also occur competitively. Nevertheless, we have discarded the amide-hydrolysis process by two simple experiments: (1) treatment of **1** with hydroxylamine chlorhydrate in absence of base (acid medium) and, (2) treatment of **1** with pyridine (basic medium). In both cases, the reaction was carried out in refluxing aqueous ethanol (Scheme 3).[2]

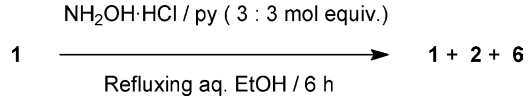


Scheme 3. Discarding hydrolysis as the first-occurring process.

Oxime formation is not observed in any of these experiments (free hydroxylamine is not present in the reaction media), but the existence of an acid, or basic, medium could promote the amide hydrolysis (acid or basic catalysis). However, as expected for a sterically hindered amide,[3] the hydrolysis of the bridgehead aminocarbonyl group of **1** does not occur in the mild (acid or basic) reaction conditions (Scheme 3). Therefore, reaction pathway C, consisting of a first amide hydrolysis, subsequent oxime formation and final Beckmann fragmentation (**1**→**4**→**6**→**2**, see Scheme 2) can be discarded.

Once established that the first-occurring process is the oximination of **1** to **3**, the formed oxime could undergo: (1) a Beckmann fragmentation to **5**, followed by amide hydrolysis to **2** (reaction pathway A) or; (2) an amide hydrolysis to **6** and subsequent Beckmann fragmentation to **2** (reaction pathway B). Of course, once again, both possibilities could also occur competitively.

Trying to detect some reaction intermediate (**3**, **5** or **6**), we quenched the reaction (**1**→**2**, Scheme 1) at a short time (Scheme 4). Thus, when **1** is treated with $NH_2OH·HCl$/pyridine (mol equiv: 3:3) in refluxing aqueous ethanol for only 6 h, a mixture of starting **1**, final **2** and oxime intermediate **6**[4] is obtained (**1**/**2**/**6**=4:64:32).[5]



Scheme 4. Detecting intermediates.

Detection of intermediate **6** indicates that pathway B (**1**→**3**→**6**→**2**) works. Nevertheless, it is not possible to discard the competition of reaction pathway A (**1**→**3**→**5**→**2**).

Moreover, detection of **6**, but not **5**, seems to show that amide-group hydrolysis of oxime **3** (**3**→**6** in Scheme 2) is more activated than the analogue amide hydrolysis of starting ketone **1** (**1**→**4** in Scheme 2). This activation could be probably due to an intramolecular effect exerted by the hydroxyl group of the oxime function (Fig. 1).[6]

In the case of a possible competition between pathways A and B, the last step in pathway A (**5**→**2**) must be faster than the last step in pathway B (**6**→**2**), since intermediate **6** is

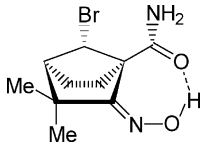
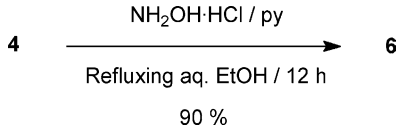


Figure 1. Proposed amide hydrolysis activation by the oxime function.

detected at short reaction times, whereas **5** is not (cf. Schemes 2 and 4). A way to test this possible competition is comparing the reactions of C(1)-aminocarbonyl-substituted bromonorbornan-2-one **1** and C(1)-carboxyl-substituted bromonorbornan-2-one **4**[3a] with hydroxylamine in the same reaction conditions (Scheme 5).



Scheme 5. Reaction of interemediate **4** with hidroxylamine.

Thus, after 12 h of reaction with $NH_2OH \cdot HCl$/pyridine (3:3) at refluxing aqueous ethanol, norbornanone **1** is totally reacted to final **2** (Scheme 1), whereas **4** gives place to the formation of the corresponding oxime **6** (Scheme 4).[4,5] Nevertheless, increasing the reaction time to 3 days allows to detect a minor product **2** together with major **6** (**6/2**= 91:9).[4,5]

Consequently, reaction pathway A has to be the main one, since transformation of **4** to **2** under hydroxylamine treatment (indefectible through intermediate **6**, see Scheme 2) is slower than transformation of **1** to **2** (either through detected intermediate **6** or through undetected intermediate **5**, cf. pathways B and A in Scheme 2).

On the other hand, since intermediate **5** is not detected, the slow steps (limiting steps) of the overall process **1** to **2** must be the Beckmann-fragmentation steps (**3**→**5** for pathway A, and **6**→**2** for pathway B). Additionally, since Beckmann fragmentation **3**→**5** takes place faster (easily) than the Beckmann fragmentation **6**→**2**, the differential C(1)-group (aminocarbonyl for **3** and carboxyl for **4**) has to play some important role in activating such fragmentation.

In order to explain these experimental facts, we have postulated a specific intramolecular activation of the bromo assistance for the fragmentation. This intramolecular activation would be exerted by the C(1)-group, due to its nucleophile (bromophile) character (Fig. 2). Thus, the activating effect should be stronger for the C(1)-aminocarbonyl group than for the C(1)-carboxyl one, which would explain the higher facility for Beckmann fragmentation exhibited by **3**, when compared with **6**.[7]

Additionally, the postulated intramolecular electronic activation of the bromo-assistance for the Beckmann fragmentation of **3** (see Fig. 2) would also explain the unexpected fast hydrolysis of the amide intermediate generated after the fragmentation[8] since such intermediate would not be the primary amide **5**, but the highly reactive (undetected) *N*-bromo-substituted amide **Br-5** (Scheme 6).

We have tested the existence of this possible synergic effect by submitting to hydroxylamine treatment an analogous 7-*anti*-bromonorbornan-2-one bearing a C(1)-group without the possibility of exerting such activating effect. The chosen norbornanone was 7-*anti*-bromo-1,3,3-trimethylnorbornan-2-one (7-*anti*-bromofenchone) **7**,[9] due to its synthetic availability (Fig. 2). As expected, when **7** was submitted to hydroxylamine treatment in the same reaction conditions in which **1** and **4** were reacted,[2] corresponding 2-norbornane oxime **8** was detected as the only reaction product (Scheme 7).[5,10] This fact also discards a controlling intermolecular bromophile-reaction activation.[7]

Finally, a referee has proposed a possible participation of free ammonia (coming from the activated amide hydrolysis of **3** to **6**, see Scheme 2 and Fig. 1) as the possible responsible of the bromo-activation instead of the bridge-head amide group. This intermolecular activation would be more effective than the analogue free-pyridine or free-hydroxylamine activation, due to the stronger base character of ammonia (cf. pK_a 9.2 for ammonium and pK_a 5.2 for hydroxylammonium or pyridinium). In order to test this possibility, we have try to activate the fragmentation of oxime **6**, treating such oxime with ethanolamine (pK_a 9.5 for ethanolamonium) in the standard reaction conditions. Nevertheless, such activation was not observed, being the oxime recovered unaltered.

3. Summary

The competitive reaction pathways for the unexpected in situ Beckmann fragmentation of 7-*anti*-bromo-3,3-dimethyl-2-oxonorbornane-1-carboxamide have been investigated. It is concluded that the main reaction pathway consists probably in a first oxime-formation process, subsequent Beckmann fragmentation and final amide hydrolysis. This pathway seems to be competitive with a secondary one, in which the amide hydrolysis of oxime intermediate **3** occurs before Beckmann fragmentation. Furthermore, the differential behavior exhibited by the norbornanones **1**, **4** and **7** in their reactions with hydroxylamine, has allowed to conclude that the Beckmann fragmentation process is probably promoted by a synergic

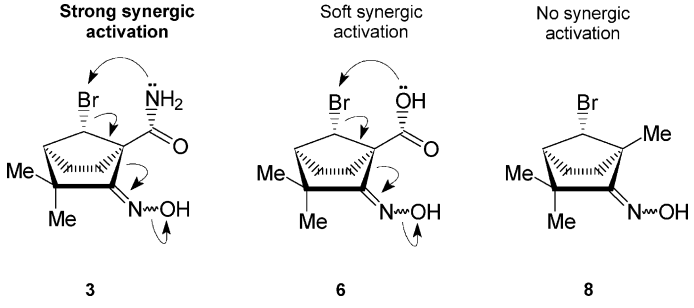
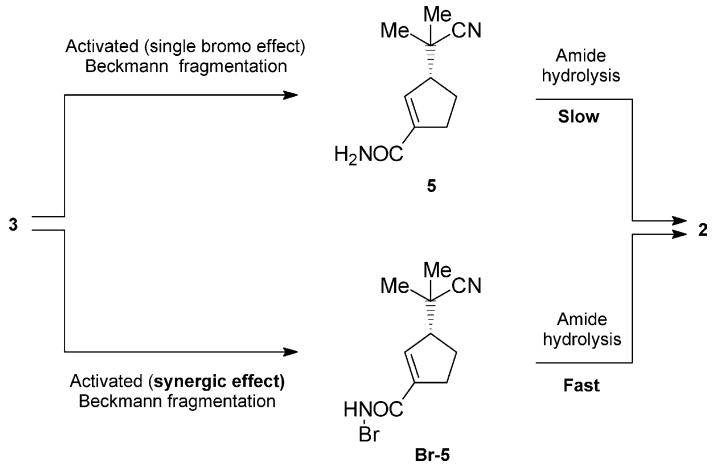
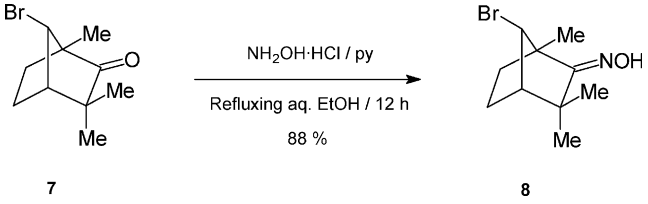


Figure 2. Intramolecular bromophile-reaction activation.



Scheme 6. Effect of the synergic activation on the amide-hydrolysis rate.



Scheme 7. Reaction of **7** with hydroxylamine.

effect, consisting in a specific intramolecular electronic activation of the bromo-assistance exerted by the amino-carbonyl group. When such electronic activation is inexistent (e.g., in 7-*anti*-bromonorbornan-2-one **7**), in situ Beckmann fragmentation does not take place after hydroxylamine treatment. Further investigation on the application of the postulated synergic effect, as synthetic tool promoting the Beckmann fragmentation of 7-halonorbornanones, is in progress.

4. Experimental

4.1. General

All starting materials and reagents were obtained from well-known commercial suppliers and were used without further purification. Anhydrous solvents were properly dried under standard conditions. Flash chromatography was performed over silica gel (150 mesh). ^{1}H and ^{13}C NMR were recorded on 200-MHz and 300-MHz spectrometers. Chemical shifts (δ) for ^{1}H and ^{13}C NMR were recorded in ppm downfield relative to the internal standard tetramethylsilane (TMS), and coupling constants (J) are in Hz. IR spectra were recorded on a FT spectrometer. Mass spectra were recorded on a 60 eV mass spectrometer. For gas–liquid chromatography (GLC), a chromatograph equipped with capillary silicon-gum column (TRB-1) was used. HRMS were recorded in a mass VG Autospec spectrometer, using the FAB technique.

4.1.1. Synthesis of 7-*anti*-bromo-3,3-dimethyl-2-oxonorbornane-1-carboxamide 1. Norbornane-1-carboxamide **1** was prepared from 3-*endo*-bromocamphor, as previously described by us.[2a] Pale yellow solid. Mp 156–158 °C. $[\alpha]_D^{20}=-68.1$ (1.04, $CHCl_3$). HRMS: 180.1031 (calculated for $C_{10}H_{14}NO_2$, 180.1025). ^{1}H NMR ($CDCl_3$, 200 MHz), δ: 6.75 (br s, 1H), 6.42 (br s, 1H), 4.72 (s, 1H), 2.45–2.26 (m, 3H), 2.01 (m, 1H), 1.69 (m, 1H), 1.19 (s, 3H), 1.18 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz), δ: 212.6 (CO), 169.6 ($CONH_2$), 68.6 (C), 55.0 (CH), 52.3 (CH), 49.8 (C), 25.9 (CH_2), 25.8 (Me), 22.6 (CH_2), 22.3 (Me) ppm. FTIR (CCl_4), ν: 3331, 1755, 1668 cm^{-1}. MS, *m/z*: 180 ($M^{+\cdot}-Br$, 3), 28 (100).

4.1.2. Synthesis of 7-*anti*-bromo-3,3-dimethyl-2-oxonorbornane-1-carboxylic acid 4. Norbornane-1-carboxylic acid **4** was prepared from 3-*endo*-bromocamphor, as previously described by us.[3a] White solid. Mp 145–146 °C (decomposes). $[\alpha]_D^{20}=-58.6$ (3.21, $CHCl_3$). HRMS: 181.0864 (calculated for $C_{10}H_{13}O_3$, 181.0865). ^{1}H NMR ($CDCl_3$, 200 MHz), δ: 10.62 (br s, 1H), 4.73 (s, 1H), 2.48–2.22 (m, 3H), 1.98–1.67 (m, 2H), 1.19 (s, 6H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz), δ: 210.2 (CO), 173.0 (CO_2H), 69.6 (C), 54.1 (CH), 52.6 (CH), 50.0 (C), 24.6 (CH_2), 23.3 (Me), 22.3 (Me), 22.2 (CH_2) ppm. FTIR (CCl_4), ν: 2986 (broad), 1749, 1701 cm^{-1}. MS, *m/z*: 181 ($M^{+\cdot}-Br$, 11), 41 (100).

4.1.3. Synthesis of 7-*anti*-bromo-1,3,3-trimethylnorbornan-2-one (7-*anti*-bromofenchone) 7. Norbornanone **7** was prepared from fenchone, as previously described by us.[9] White solid. Mp 45–46 °C. $[\alpha]_D^{20}=+163.1$ (2.23, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 4.27 (d, $J=1.1$ Hz, 1H), 2.34 (d, $J=3.8$ Hz, 1H), 2.22 (m, 1H), 1.90–1.75 (m, 2H), 1.37 (m, 1H), 1.15 (s, 3H), 1.13 (s, 3H), 1.10 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz), δ: 217.1 (CO), 61.3 (CH), 58.8 (C), 52.7 (CH), 49.1 (C), 29.4 (CH_2), 23.1 (Me), 22.9 (CH_2), 22.5 (Me), 12.7 (Me) ppm. FTIR (CCl_4), ν: 1747 cm^{-1}. MS, *m/z*: 151 ($M^{+\cdot}-Br$, 2), 81 (100).

4.2. Reaction of 7-*anti*-bromonorbornan-2-ones with hydroxylamine. General procedure

For comparison, 7-*anti*-bromonorbornan-2-ones **1**, **4** and **7** were reacted with hydroxylamine ($NH_2OH\cdot HCl$/pyridine) following the same standard conditions described previously for **1** (refluxing aqueous ethanol for 12 h).[2a]

4.2.1. Reaction of 4 with hydroxylamine: 7-*anti*-bromo-2-hydroxyimino-3,3-dimethylnorbornane-1-carboxylic

acid 6. Detected in the reaction-extract mixture as a couple of stereoisomers.[4,5] Yield 90%. An analytical sample of the enriched major isomer of oxime **6** was obtained after purification by elution chromatography (silica gel and CH_2Cl_2/ether 8:2). ^{1}H NMR ($CDCl_3$, 200 MHz), δ: 9.89 (br s, 1H), 4.39 (s, 1H), 2.40 (m, 1H), 2.28–2.10 (m, 2H), 1.88 (m, 1H), 1.70 (m, 1H), 1.28 (s, 3H), 1.24 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz), δ: 174.6 (CO_2H), 164.3 (CNOH), 61.5 (C), 57.7 (CH), 53.9 (CH), 43.8 (C), 26.6 (Me), 25.2 (CH_2), 25.0 (Me), 22.4 (CH_2) ppm. FTIR (CCl_4), ν: 3103 (broad), 1716 cm^{-1}.

4.2.2. Reaction of 7 with hydroxylamine: 7-*anti*-bromo-1,3,3-trimethylnorbornan-2-one oxime (7-*anti*-bromofenchone oxime) 8. Detected in the reaction-extract mixture as a single stereoisomer (probably the *anti* one), as it occurs in the oximination of other related 3,3-dimethylsubstituyted norbornan-2-ones.[11] Purification was realized by elution chromatography (silica gel and CH_2Cl_2). Yield: 88%. White solid. Mp 133–135 °C. $[\alpha]_D^{20} = -34.0$ (1.80, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 8.71 (s, 1H), 4.13 (s, 1H), 2.13–2.02 (m, 2H), 1.89–1.74 (m, 2H), 1.45 (m, 1H), 1.41 (s, 3H), 1.35 (s, 3H), 1.89 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz), δ: 168.9 (CNOH), 61.7 (CH), 54.9 (CH), 54.9 (C), 43.7 (C), 31.3 (CH_2), 23.0 (CH_2), 22.8 (Me), 22.7 (Me), 14.7 (Me) ppm.

Acknowledgements

We would like to thank the Ministerio de Educación, Ciencia y Tecnología of Spain (BQU2001-1347-C02-02) and UNED (research project 2001V/PROYT/18) for the financial support of this work. B. L. M. wishes to thank the Ministerio de Educación, Cultura y Deporte for a post-graduate grant.

References and notes

1. Enantiopure cyclopentene nitriles and cyclopentene carboxylic acids are important intermediates in the preparation of valuable natural products with biological activities. Some interesting example are: (a) Trost, B. M.; Chan, M. T. *J. Am. Chem. Soc.* **1983**, *105*, 2315 and references cited therein. (b) García Martínez, A.; Teso Vilar, E.; García Fraile, A.; de la Moya Cerero, S.; Maichle, L. R.; Subramanian, L. R. *Tetrahedron: Asymmetry* **1994**, *5*, 949. (c) García Martínez, A.; Teso Vilar, E.; García Fraile, A.; de la Moya Cerero, S.; Martínez Ruiz, P.; Subramanian, L. R. *Tetrahedron: Asymmetry* **1996**, *7*, 2177. (d) García Martínez, A.; Teso Vilar, A.; García Fraile, A.; de la Moya Cerero, S.; de Oro Osuna, S.; Lora Maroto, B. *Tetrahedron Lett.* **2001**, *42*, 7795 and references cited therein.
2. (a) García Martínez, A.; Teso Vilar, E.; García Fraile, A.; de la Moya Cerero, S.; Lora Maroto, B. *Eur. J. Org. Chem.* **2002**, 781 and supporting references therein. On the importance of the stero- and regiocontrol in the alkenyl-function formation at Bekmann fragmentations, see a related silicon-directed Beckmann fragmentation in (b) Nishiyama, H.; Sakuta, K.; Osaka, N.; Arai, H.; Matsumoto, M.; Itho, K. *Tetrahedron* **1988**, *44*, 2413 and references therein.
3. On the hydrolysis conditions of related bridgehead carboxylic-acid derivatives, see: (a) García Martínez, A.; Teso Vilar, E.; García Fraile, A.; de la Moya Cerero, S.; Lora Maroto, B. *Tetrahedron: Asymmetry* **2002**, *13*, 1837. (b) García Martínez, A.; Teso Vilar, E.; García Fraile, A.; de la Moya Cerero, S.; González-Fleitas de Diego, J. M.; Subramanian, L. R. *Tetrahedron: Asymmetry* **1994**, *5*, 1599. On the dependence of the rate of amide hydrolysis on the substitution near the amide group see: (c) Cason, J.; Gataldo, C.; Glusker, D.; Allinger, J.; Ash, L. B. *J. Org. Chem.* **1953**, *18*, 1129. (d) de Roo, M.; Bruylants, A. *Bull. Soc. Chim. Belg.* **1954**, *63*, 140.
4. Intermediate oxime **6** was detected by NMR of corresponding reaction extracts as a couple of stereoisomers (*E*/*Z*) in near 3:1 ratio.
5. Determined by ^{1}H NMR analysis of the reaction extract mixture.
6. On a related intramolecular amide-hydrolysis activation produced by the hydroxyl group of a carboxyl function see, for example: (a) Kirby, A. J.; Lancaster, P. W. *J. Chem. Soc., Perkin Trans. 2* **1972**, 1206. (b) Kluger, R.; Lam, C. H. *J. Am. Chem. Soc.* **1978**, *100*, 2191.
7. At this point, a controlling activation via an intermolecular 'X-philic' reaction Zefirov, N. S.; Makhon'kov, D. I. *Chem. Rev.* **1982**, *82*, 615, involving attack at bromo by pyridine or free hydroxylamine can be discarded, since such activation should play a similar role in both intermediated **6** and **3**.
8. It is well known the low reactivity of α,β-unsaturated amides towards hydrolysis for example see: Robinson, B. A.; Tester, J. W. *Int. J. Chem. Kinet.* **1990**, *22*, 431.
9. García Martínez, A.; Teso Vilar, E.; García Fraile, A.; de la Moya Cerero, S.; Lora Maroto, B. *Tetrahedron: Asymmetry* **2003**, *14*, 1607.
10. This experiment also demonstrates that the Beckmann fragmentation of the studied C(1)-substituted 7-*anti*-bromo-norbornan-2-one oximes probably takes place synchronously, since a stepped process (through an α-substituted cyclopentyl-carbocation intermediate) would be more favored for a methyl α-group (electron-donor group), than for an aminocarbonyl, or carboxyl, α-group (electron-acceptor group).
11. García Martínez, A.; Teso Vilar, E.; García Fraile, A.; de la Moya Cerero, S.; Díaz Oliva, C.; Subramanian, L. R.; Maichle, C. *Tetrahedron: Asymmetry* **1994**, *5*, 949 and references cited therein.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 60 (2004) 9453–9461

The effect of vicinyl olefinic halogens on cross-coupling reactions using Pd(0) catalysis

Michael G. Organ,* Haleh Ghasemi and Cory Valente

The Department of Chemistry, York University, 4700 Keele Street, Toronto, Ont., Canada M3J 1P3

Received 4 May 2004; revised 6 July 2004; accepted 3 August 2004

Available online 3 September 2004

Abstract—(*trans*) 1-Chloro-2-iodoethylene (**3**), (*trans*) 1-bromo-2-iodoethylene (**4**), (*trans*) 1,2-diiodoethylene (**5**) and (*cis* and *trans*) 1,2-dibromoethylene (**11**) were reacted under Suzuki, Sonogashira and Negishi cross-coupling conditions using Pd catalysis to obtain mono coupled products. Only olefin template **3** provided the desired coupling products reliably under all reaction conditions. Compound **5** did not provide cross coupled products under any of the reaction conditions used. The Negishi reaction was the only one that worked for templates **4** and **11**. Studies indicate that oxidative addition of the most reactive carbon–halogen bond to Pd(0) is followed by elimination of the second halide, when the second halide is a bromide or an iodide. This happens to a much lesser degree when the second halogen is a chloride.
© 2004 Elsevier Ltd. All rights reserved.

1. Introduction

We,[1] and others,[2] have been developing small, polyfunctional olefin building blocks (templates) for use in modular organic synthesis using transition metal catalysis. The premise here is to use the template as a linchpin to 'stitch' two or more pieces (that have been prepared separately) of the target molecule together, thus making the synthesis convergent and highly efficient. In many cases, the functional groups are the same, such as *cis* 1,2-dichloroethylene (**1a**)[2a,b] or *trans* 1,2-dichloroethylene (**1b**)[2c] and *trans* 1,2-di(trialkylstannyl)ethylenes (**2**).[2f,g] However, such building blocks frequently suffer from poor selectivity in oxidative addition to metals such as Pd with substrates like **1**[3] or metal–metal exchange with substrates resembling **2**,[2f] resulting in significant bis coupling. Only with sterically differentiated functional groups is there significant selectivity, such as is seen with geminal vinyl dibromides (e.g., **6**) in cross-coupling reactions.[4] It is for this reason that we have focused on the preparation of olefin templates that possess electronically differentiated oxidative addition or metal–metal exchange partners.

We have demonstrated previously the selectivity and synthetic usefulness of *trans* 1-chloro-2-iodoethylene (**3**) as an effective olefin template to prepare *trans* 1,2-disubstituted olefinic products.[1,5] Negishi and his co-workers have demonstrated also similar utility of *trans* 1-bromo-2-iodoethylene (**4**) employed in the coupling of organozinc reagents (i.e., the Negishi coupling).[6] His group has demonstrated remarkable selectivity with these couplings at the iodide site of **4**, after which they have then gone on to couple the bromide site with a different organozinc reagent to create unsymmetrical olefins. The benefit of using template **4** is that the bromide is quite reactive toward oxidative addition, once the iodide has reacted already. However, organozinc couplings are much more facile than other analogous transformations such as the Stille, Suzuki, or Sonogashira reactions.

Many Negishi couplings are performed at or below room temperature due to the relative ease of the Zn/Pd exchange. Unfortunately, as reactions are heated (as would be the case for the aforementioned transformations), the amount of unwanted bromide oxidative addition, i.e. over coupling, in the first step will necessarily increase due to simple reaction kinetics. We were attracted to using **3** because we believed that we could achieve absolute selectivity in oxidative addition to the iodide, regardless of the reaction conditions. Activation of the remaining chloride in the subsequent coupling will be more sluggish, which, of course, is the reason for the pronounced selectivity in the first oxidative addition. However, there are many new highly reactive catalysts available to alleviate this concern if necessary.[7]

We have illustrated the use of template **3** as a lynch pin in the synthesis of bupleurynol[5a] and (13*E*,15*E*,18*Z*,20*Z*)-1-hydroxypentacosa-13,15,18,20-tetraen-11-yn-4-one 1-acetate (**8**).[5b] During the synthesis of the later, we discovered that not only was **3** a selective and useful template, but in fact it

Keywords: Palladium; Catalysis; Cross coupling.
* Corresponding author. Tel.: +1-4167365313; fax: +1-4167365936; e-mail: organ@yorku.ca

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.08.006

was the only dihalo template that worked in the final coupling sequence outlined in Figure 1. For instance, *trans* 1,2-diiodoethylene (**5**) did not appear to react at all and the dimer of the boronic ester **9** was the only product isolated. Further, we found in a separate study that while both of the geminal dibromides on **6** could be reacted sequentially in Suzuki reactions, the vicinyl bromides on **7** appeared not to participate at all in these reactions. These results encouraged us to look more closely into the effect of vicinyl halides on oxidative addition and subsequent coupling with a variety of organometallic partners.

2. Results and discussion

An array of experiments using Pd catalysis with templates **3**, **4**, **5** and **11** (as a 50:50 mixture of *cis* and *trans* isomers) and boron-, zinc-, and copper-based organometallic coupling partners was conducted and the results are outlined in the following subsections.

2.1. Suzuki coupling reactions

Suzuki couplings were conducted between templates **3**, **4**, **5**, and **11** and a number of aryl- (**12a–c**) and alkenyl- (**12d** and **12e**) boronic acids under identical reaction conditions (Scheme 1, Table 1). When the couplings were performed with template **3** at rt, there was no discernable activity. However, when heated, all couplings proceeded until the template was consumed and the dominant products were the expected mono coupled compounds **13** (Table 1, entries 1, 5, 9, 13 and 16).

In some cases, there was over coupling that gave rise to **14** (Table 1, entries 1 and 9), but this was eliminated by simply halting the reactions sooner. That is, all reactions were run for the same time period with a slight excess of boronic acid but if couplings were monitored and halted when **3** was consumed, **13** was the sole product. The only other product was the boronic acid homo-coupled product **15** that was minimal in reactions involving **3** indicating that this process, presumably initiated by Pd(II), was slow relative to the anticipated coupling.

In stark contrast, Suzuki couplings involving templates **4**, **5** or **11** never provided the anticipated mono coupled products **13** (see Table 1). In every case, the dominant products were the homo-coupled products **15** demonstrating that coupling of the first halide on the templates appeared now to be a slow process and not competitive with the dimerization of boronic acids **12**. That said, the yields of the dimerization products were only about 10%. This may indicate that the catalyst is not long lived in solution or that it is not readily re-oxidized to Pd(II) to continue the boronic acid dimerization process. It was observed visually that reactions with **3** remained light in colour for some time while reactions with the other templates, especially **5** became almost black (although not 'blacked out') within minutes. One other interesting observation with these reactions is the presence of the di coupled adduct **14** in the product mixture in reactions not involving template **3**, despite there being none of compound **13** observed. This implies that while coupling of the first halide is slow with templates **4**, **5**, and **11**, coupling of the remaining halide once the first one is gone is not necessarily so.

2.2. Sonogashira coupling reactions

The same four templates were then subjected to coupling with the copper acetylide of hexyne (**16**), which is a simple and very suitable coupling partner for such reactions[1] (Scheme 2, Table 2). The results obtained from these Sonogashira reactions were similar to those seen in the Suzuki couplings. When compound **3** was used, the mono coupled enyne **17** was produced, albeit in moderate recovery (Table 2, entry 1), whereas it was not detected at all in the product mixtures from templates **4**, **5**, and **11** (Table 2, entries 2–4). The formation of dimer **19** certainly

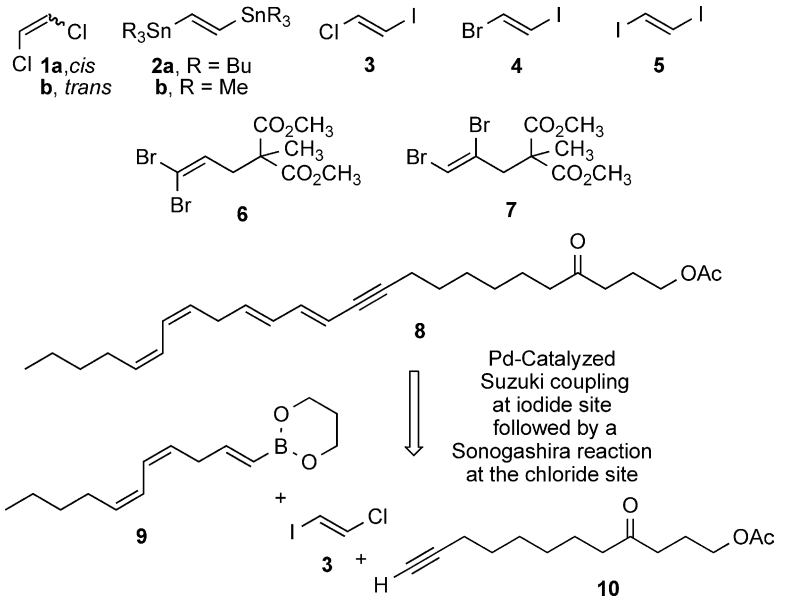
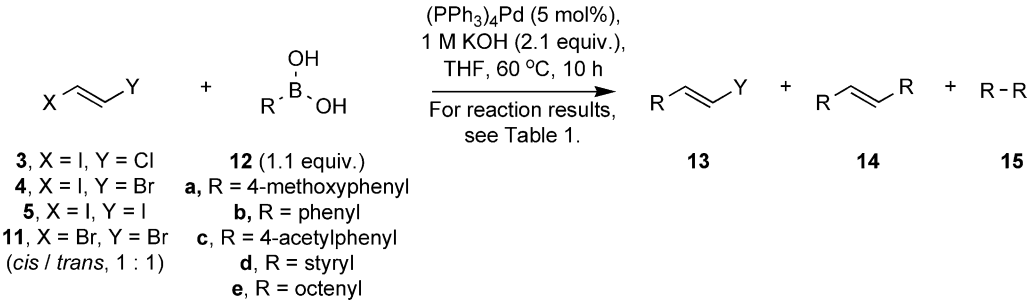
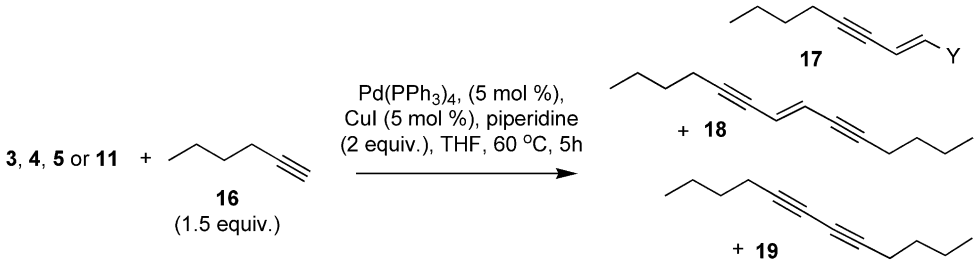


Figure 1. Structure of selected olefin templates and the use of template **3** in the synthesis of (13*E*,15*E*,18*Z*,20*Z*)-1-hydroxypentacosa-13,15,18,20-tetraen-11-yn-4-one 1-acetate (**8**).



Scheme 1.



Scheme 2.

is not a surprise as it is a common side product initiated by Cu in Sonogashira couplings.[3]

2.3. Negishi cross-coupling reaction

While template **4** failed to provide the simple mono coupled products under Sonogashira or Suzuki cross-coupling conditions, it could be reacted selectively using Negishi coupling conditions (Scheme 3, Table 2, entries 2 and 5). This is consistent with results communicated by Negishi.[6] As seen with Suzuki and Sonogashira results, template **3** also smoothly and selectively mono coupled. However, template **5** did not appear to react and the dimer products **19** and **23** were the sole products (Table 3, entries 3 and 6). It had been reported already that template **11** undergoes Negishi coupling with aryl zinc reagents so these experiments were not repeated here.[9] It is interesting to note that the authors report that only the *trans* 1,2-dibromoethylene isomer reacts in their coupling experiments and the *cis* is usually recovered intact.

Table 2. Sonogashira reaction between templates **3**, **4**, **5** and **11** with 1-hexyne

Entry	Template	Yield (%)[a]
1	**3**	42 (**17a**)
2	**4**	62 (**19**)
3	**5**	51 (**19**)
4	**11**	42 (**19**)

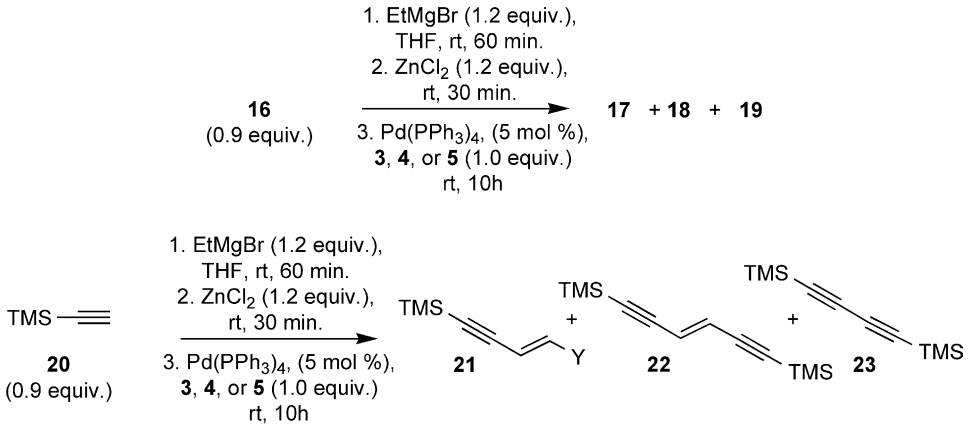
[a] Yields were determined following flash chromatography.

We are also doing work with trifunctionalized templates in an attempt to devise convergent and general approaches to

Table 1. Reaction conditions and results from Suzuki coupling with a variety of boronic acids and olefin templates **3**, **4**, **5** and **11**

Entry	Template	Boronic acid	Ratio of **13**, **14** and **15**[a]			Yield (%) of **13**+**14**+**15**
1	**3**	**12a**	86 (**13a**)	3 (**14a**)	11 (**15a**)	80
2	**4**	**12a**	0	11 (**14a**)	89(**15a**)	10
3	**5**	**12a**	0	10 (**14a**)	90 (**15a**)	10
4	**11**	**12a**	0	34 (**14a**)	66 (**15a**)	11
5	**3**	**12b**	83 (**13b**)	0 (**14b**)	17 (**15b**)	62
6	**4**	**12b**	0	3 (**14b**)	97 (**15b**)	10
7	**5**	**12b**	0	5 (**14b**)	95 (**15b**)	10
8	**11**	**12b**	0	36 (**14b**)	64 (**15b**)	20
9	**3**	**12c**[b]	78 (**13c**)	7 (**14c**)	15 (**15c**)	26
10	**4**	**12c**[b]	0	0 (**14c**)	100 (**15c**)	10
11	**5**	**12c**[b]	0	45 (**14c**)	55 (**15c**)	10
12	**11**	**12c**[b]	0	10 (**14c**)	90 (**15c**)	10
13	**3**	**12d**	91 (**13d**)	0 (**14d**)	9 (**15d**)	54
14	**4**	**12d**	0	0 (**14d**)	100 (**15d**)	10
15	**5**	**12d**	0	10 (**14d**)	90 (**15d**)	10
16	**3**	**12e**	95 (**13e**)	0 (**14e**)	5 (**15e**)	51
17	**4**	**12e**	0	45 (**14e**)	55 (**15e**)	10[8]
18	**5**	**12e**	0	5 (**14e**)	95 (**15e**)	10

[a] Compounds **13** were readily isolable from **14** and **15** by flash chromatography. However, the latter two compounds were inseparable and relative ratios were determined by ^{1}H NMR spectroscopy.
[b] 4-Acetyl phenol was a major byproduct formed in this reaction.



Scheme 3.

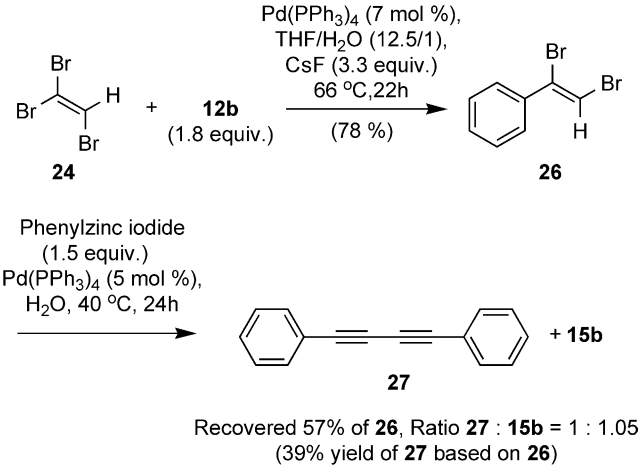
trisubstituted olefinic products. One result stood out, given the results described above. Treatment of tribromoethyelene (**24**) with Suzuki conditions smoothly led to the mono cross coupled product **26** in good recovery (Scheme 4). Yet, attempts to couple one of the remaining bromides, even under Negishi conditions, failed and the product of apparent elimination and homo coupling (**27**) prevailed along with the simple homo-coupled product of phenylzinc iodide (**15b**). Thus, geminal bromides appear to have an activating effect on each other that overrides the presence of a vicinyl bromide that appears to suppress the 'normal' catalytic cycle associated with cross-coupling from all of the previous results presented (vide supra).

It has been known for some time that all of the chlorides on polychloroethyelenes (i.e., vicinyl chorides, even tetrachloroethylene) can be cross-coupled successively with no apparent trouble.[12] However, the present results clearly show that when chloride is replaced by bromide, or iodide especially, that cross-coupling becomes significantly impaired. Of course, the fact that there are little, or none of the cross coupled products with templates **4**, **5**, or **11** (other than Negishi coupling) does not necessarily mean that oxidative insertion of the C–X bond does not occur. Rather, it could be that addition is taking place, but other events are now competitive with the metal–metal exchange that is required to give the reductive elimination product. The presence of **27** in the reaction of **26** suggests that one of two likely explanations could be operative in this case and therefore possibly applicable to the dihaloethylenes examples. First, the basic reaction conditions could induce elimination of the elements of HBr to yield 1-bromo-2-phenylacetylene that is dimerizing in the presence of Pd. In the case of substrates **4**, **5**, or **11**, such elimination products would be highly volatile, thus no coupling products would be observed or recovered. Conversely, oxidative addition of the most reactive halide bond on **4**, **5**, or **11** could be happening, but the superior leaving group ability of the remaining Br or I, relative to Cl, would lead to elimination of that halide producing acetylene, thus maintaining the oxidation state of Pd (i.e., $(PPh_3)_2PdXY$, where X and Y = Br or I).

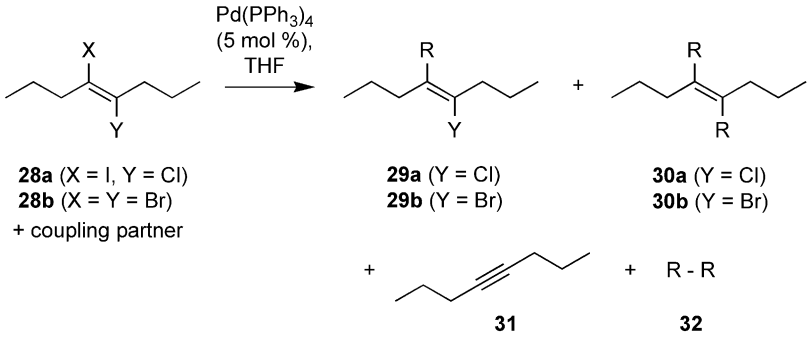
Table 3. Negishi cross-coupling reaction between templates **3**, **4**, and **5** and alkynes **16** or **20**

Entry	Template	Alkyne	Yield (%)
1	**3**	**16**	68 (**17a**)[10]
2	**4**	**16**	72 (**17b**)[12]
3	**5**	**16**	23 (**19**)
4	**3**	**20**	59 (**21a**)[10]
5	**4**	**20**	68 (**21b**)[11]
6	**5**	**20**	16 (**23**)

To address these questions, we performed the same series of coupling reactions, as discussed above, with *E*-4,5-dihalo-4-octenes **28a** and **28b**. Assuming that no significant steric or electronic perturbation would arise from the addition of the two propyl chains, we were hoping that these substrates would mimic **3** and **11**, the difference being that there was no possible HX elimination across the olefin. Thus, any alkyne formation would have to be taking place via initial oxidative addition of the C–X bond to Pd. Unfortunately however, as we see in Scheme 5, the alkyl groups did exert a significant effect. We did not observe much of the anticipated mono- or di cross coupled products under Suzuki, Sonogashira, or Negishi conditions with **28a**, given that **3** coupled very well under all of these conditions (vide supra). Of interest though, we observed production of 4-octyne (**31**) suggesting that, while there was no observed cross-coupling, there was oxidative addition taking place, most notably with **28b**. Although there are only the three representative reactions given, many more examples were conducted but the results were essentially identical.



Scheme 4.



template	coupling partner	conditions	product mixture ratios
28a	4-methoxyphenyl boronic acid (**12a**) 1.1 equiv.)	KOH (2.1 equiv.), 60 °C, 10 h	**28** : **29** : **30** : **31** : **32**
28a	phenyl zinc iodide (**33**) (1.1 equiv.)	rt, 3h	62 : 6 : 0 : 32 : 40
28a	TMS acetylene (**20**) (1.5 equiv.)	piperidine (2.0 equiv.), CuI (5%), 60 °C, 24 h	86 : 0 : 0 : 14 : 25
28b	4-methoxyphenyl boronic acid (**12a**) 1.1 equiv.)	KOH (2.1 equiv.), 60 °C, 10 h	75 : 0 : 0 : 25 : 16
28b	phenyl zinc iodide (**33**) (1.1 equiv.)	rt, 3h	62 : 6 : 0 : 31 : 24
28b	TMS acetylene (**20**) (1.5 equiv.)	piperidine (2.0 equiv.), CuI (5%), 60 °C, 24 h	65 : 0 : 0 : 35 : 27 75 : 0 : 0 : 25 : 6

Scheme 5.

For clarity, it should be noted that ratios were calculated in such a way that the first four product mixture components added up to 100%, being that they all are derived from either **28a** or **28b**. The simple dimer product **32** was listed as a molar ratio relative to the other products, although there was 1.1 equiv of it used in each experiment. Alkyne formation occurred to the greatest extent in the Suzuki reactions, which are arguably the harshest and most basic conditions (assuming that organozinc reagents are relatively non basic). The next issue to be addressed was the effect that the basic conditions might be having on this transformation. Hence, two additional sets of control experiments were carried out (Scheme 6).

Treatment of **28a** or **28b** with just base, i.e., without boronic acid or catalyst, did not lead to any significant conversion to **31**, which confirms that elimination is not a simple base-mediated process. When the reaction was run with just catalyst, i.e. without boronic acid or base, a small amount of conversion was observed with **28a**. In the presence of both base and catalyst, but no boronic acid, significant alkyne was formed in the case of **28a**, although this was not mirrored in the case of **28b**. However, when **28b** was reacted with a stoichiometric amount of Pd, a steady conversion to **31** was observed over 6 h. Although the control experiments with just base showed no direct involvement of hydroxide in the elimination, when it was present with stoichiometric Pd the rate of elimination significantly increased. It may be possible that the base plays a role in reducing the Pd(II) generated in the oxidative addition/elimination, or that it is activating the catalyst to oxidative addition, or perhaps both.

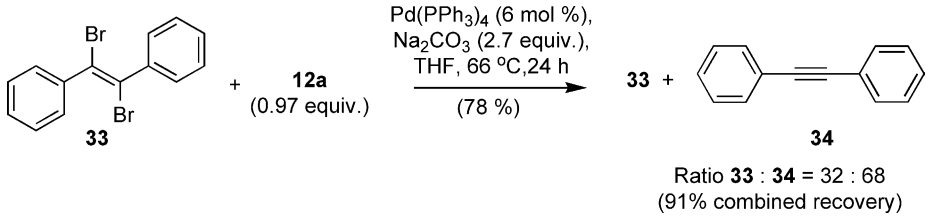
28 —THF, 60 °C, 18 h→ **28** + **31**

template	conditions	product mixture ratios **28b** : **31**
28a	KOH (2.1 equiv.)	99 : trace
28b	KOH (2.1 equiv.)	100 : 0
28a	$Pd(PPh_3)_4$ (5 mol %)	96 : 4
28b	$Pd(PPh_3)_4$ (5 mol %)	100 : 0
28a	$Pd(PPh_3)_4$ (5 mol %), KOH (2.1 equiv.)	72 : 28
28b	$Pd(PPh_3)_4$ (5 mol %), KOH (2.1 equiv.)	99 : trace
28b	$Pd(PPh_3)_4$ (1.05 equiv.)	
	15 min.	94 : 6
	75 min.	61 : 39
	135 min.	31 : 69
	185 min.	16 : 84
	360 min.	8 : 92
28b	$Pd(PPh_3)_4$ (1.05 equiv.), KOH (2.1 equiv.)	
	15 min.	85 : 15
	75 min.	28 : 72
	135 min.	7 : 93
	185 min.	0 : 100
	360 min.	--

Scheme 6.

It is feasible that the alkyne could be formed *via* an intermediate allenyl species formed by Pd activation of one of the allylic hydrogen atoms. To explore this possibility, *E*-dibromostilbene was reacted under Suzuki conditions. While no cross-coupling was observed, diphenyl acetylene (**34**) was obtained in good recovery demonstrating that it is not necessary to invoke allenyl intermediates to account for the X–Y eliminations observed in this report (Scheme 7).

Thus, it appears that the reactivity profile of 1,2-dihaloalkenes toward Pd-catalyzed cross-coupling reactions is quite variable and substrate specific. In general, when the alkene substrate has chloride on it as one of the halides, cross-coupling seems to proceed more smoothly and reliably. When dibromo alkenes are the substrates for cross-coupling, only Negishi coupling seems to work and then only the *trans* 1,2-dibromoethylene has been reported to couple.[9] Interesting though, a recent report by Rathmore and co-workers shows that *E* 4,5-dibromo-4-octene (compound **28b** used in this study which gave very little cross coupled product) gave nearly quantitative cross-coupling at both sites when reacted with pentamethylphenyl magnesium bromide![13] Three additional pieces of information can be gleaned from their study. Mono coupled product was never seen. Even with limiting Grignard reagent, only the di coupled product was isolated, which was also observed in the present study in the Suzuki reaction with templates **4**, **5**



Scheme 7.

and **11**. Second, the only aromatic Grignard reagent that led to coupled product had two *ortho* methyl groups flanking the metal center, which seems counterintuitive. For example, 4-methylphenyl magnesium bromide led primarily to the alkyne elimination product (**31**) and the homo-coupled Grignard reagent. Finally, only the *Z* olefin product was isolated (from the *E* dibromide) indicating that the mechanism leading to the formation of the final product is clearly far more involved than presently accepted cross-coupling mechanistic dogma can explain.

From evidence collected in the present report, it appears that Pd catalyzed reactions that lead to elimination of the dihalide are not base induced. Rather, oxidative addition appears to take place followed by subsequent elimination of good leaving groups, such as bromide or iodide. In the case of reactions catalytic in Pd, the elimination does not proceed too far which might be due to the lack of an efficient reduction pathway to regenerate Pd(0) following elimination. It could be interpreted that metal–metal exchange is now the rate-determining step in these transformations, which allows elimination to become a strongly competing process. Reactions involving **28a** (*E* 4-chloro-5-iodo-4-octene) clearly show a strong dependence on the substrate's structure, in addition to the structure of the metal coupling partner as shown by Rathmore. While **3** coupled very nicely in all of the reactions employed, **28a** did not which might imply that the increased steric hinderence of the propyl group has slowed metal–metal exchange enough to make chloride elimination now the kinetically favored event.

3. Experimental

3.1. General

All reactions were performed in a flame dried round bottom flask equipped with magnetic stir bar. Reactions were carried out under positive pressure of nitrogen gas that had been pre dried through a Drierite® column. Tetrahydrofuran was freshly distilled from sodium benzophenone ketyl. ^{1}H NMR and ^{13}C NMR spectra were recorded using a Bruker Avance 400 MHz NMR spectrometer (100 MHz for carbon). All ^{1}H NMR and ^{13}C NMR spectra were referenced to 7.26 and 77.23 ppm for chloroform solvent, respectively. For ^{13}C NMR APT spectra, positive peaks (indicated by +) represent quarternary carbons as well as carbon atoms attached to an even number of protons. Negative peaks (indicated by −) represent carbon atoms attached to an odd number of protons.

3.1.1. (*E*)-1-Bromo-2-iodoethene (4). Acetylene gas was bubbled continuously for 1 h through a solution of 6 g of IBr (29.01 mmol) in 40 mL of HBr (48%) at 0 °C, after which the temperature was then brought to rt and stirring continued for 5 h. The reaction mixture was extracted with pentane (2×) and the pooled organic layers washed successively with brine and aqueous $Na_2S_2O_3$. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo to obtain 3.8 g of **4** (56% yield) as a colorless liquid. ^{1}H NMR: δ 6.88 (d, J=13.6 Hz, 1H), 6.76 (d, J=13.6 Hz, 1H); ^{13}C NMR: δ 110.1 (−), 76.8 (−). NMR data were consistent with literature values.[14]

3.2. General procedure for Suzuki cross-coupling reactions

To a solution of boronic acid **12** (1.1 equiv) in THF was added a solution of 1 M KOH (2.1 equiv), $(PPh_3)_4Pd$ (0.05 equiv) and the olefin template (i.e., **3**, **4**, **5**, or **11**; 1.0 equiv). The reaction mixture was stirred at 60 °C for the designated time or it was halted when the reaction was judged complete by TLC analysis. Solid Na_2SO_3 was added to the reaction mixture and the suspension was stirred for 5 min. The solvent was removed in vacuo and the crude product was purified by column chromatography on silica gel.

3.2.1. 1-[(1*E*)-2-Chloroethenyl]-4-methoxy benzene (13a). The reaction mixture contained 100 mg of **12a** (1.1 equiv, 0.66 mmol), 2 mL of THF, 1.2 mL of KOH (2.1 equiv, 0.68 mmol), 37 mg of $(PPh_3)_4Pd$ (0.05 equiv, 0.032 mmol) and 113 mg of **3** (1.0 equiv, 0.60 mmol). The crude product was purified by column chromatography (R_f=0.9; 5% ether in pentane) to obtain 81 mg of **13a** (80% yield) along with a small amount of **14a** and **15a**. ^{1}H NMR: δ 7.23 (d, J=8.8 Hz, 2H), 6.86 (d, J=8.8 Hz, 2H), 6.78 (d, J=13.6 Hz, 1H), 6.50 (d, J=13.6 Hz, 1H), 3.82 (s, 3H); ^{13}C NMR: δ 159.6 (+), 134.9 (−), 127.7 (+), 127.6 (−), 117.5 (−), 112.9 (−), 57.7 (−). NMR data were consistent with literature values.[15]

3.2.2. [(1*E*)-2-Chloroethenyl] benzene (13b). The reaction mixture contained 100 mg of **12b** (1.1 equiv, 0.82 mmol), 2 mL THF, KOH (2.1 equiv, 1.55 mmol), 43 mg of $(PPh_3)_4Pd$ (0.05 equiv, 0.040 mmol) and 140 mg of **3** (1.0 equiv, 0.74 mmol). The crude product was purified by column chromatography (R_f=0.95; pentane) to obtain 63 mg of **13b** (62% yield) along with a small amount of **14b** and **15b**. ^{1}H NMR: δ 7.31 (m, 5H), 6.84 (d, J=13.6 Hz, 1H), 6.65 (d, J=13.6 Hz, 1H); ^{13}C NMR: δ 135.8 (−), 133.3 (−), 128.8 (−), 128.2 (−), 126.1 (−), 118.7 (−). NMR data were consistent with literature values.[16]

3.2.3. 1-[4-(*E*)(2-Chloroethenyl)phenyl] ethanone (13c). The reaction mixture contained 110 mg of **12c** (1.1 equiv,

0.67 mmol), 2 mL THF, KOH (2.1 equiv, 1.22 mmol), 35 mg of $(PPh_3)_4Pd$ (0.05 equiv, 0.030 mmol) and 115 mg of **3** (1.0 equiv, 0.61 mmol). The crude product was purified by column chromatography (R_f=0.9; 5% diethyl ether in pentane) to obtain 28 mg of **13c** (26% yield) along with a small amount of **14c** and **15c**. ^{1}H NMR: δ 7.92 (d, J=8.4 Hz, 2H), 7.38 (d, J=8.4 Hz, 2H), 6.88 (d, J=13.6 Hz, 1H), 6.79 (d, J=13.6 Hz, 1H), 2.60 (s, 3H); ^{13}C NMR: δ 202.2 (+), 139.3 (+), 136.6 (+), 132.9 (−), 128.2 (−), 126.2 (−), 122.0 (−), 25.1 (−); HRMS calcd for $C_{10}H_9OCl$ 180.0342, found 180.0316.

3.2.4. [(1*E*,3*E*)-4-Chloro-1,3-butadienyl] benzene (13d). The reaction mixture contained 100 mg of **12d** (1.1 equiv, 0.68 mmol), 2 mL THF, KOH solution (2.1 equiv, 1.29 mmol), 35 mg of $(PPh_3)_4Pd$ (0.05 equiv, 0.030 mmol) and 116 mg of **3** (1.0 equiv, 0.62 mmol). The crude product was purified by column chromatography (R_f=0.9; pentane) to obtain 54 mg of **13d** (54% yield) along with a small amount of **14d** and **15d**. ^{1}H NMR: δ 7.35 (m, 5H), 6.67 (m, 3H), 6.33 (d, J=12.8 Hz, 1H); ^{13}C NMR: δ 136.7 (+), 133.9 (−), 133.3 (−), 128.7 (−), 128.0 (−), 126.5 (−), 124.7 (−), 121.0 (−). NMR data were consistent with literature values.[17]

3.2.5. (1*E*,3*E*)-1-Chloro-1,3-decadiene (13e). The reaction mixture contained 50 mg of **12e** (1.1 equiv, 0.32 mmol), 1.2 mL THF, KOH solution (2.1 equiv, 0.61 mmol), 17 mg of $(PPh_3)_4Pd$ (0.05 equiv, 0.014 mmol) and 55 mg of **3** (1.0 equiv, 0.29 mmol). The crude product was purified by column chromatography (R_f=0.9; 2% diethyl ether in pentane) to obtain 26 mg of **13e** (51% yield) along with a small amount of **14e** and **15e**. ^{1}H NMR: δ 6.42 (dd, J=13.2, 10.8 Hz, 1H), 6.08 (d, J=13.2 Hz, 1H), 5.97 (m, 1H), 5.70 (m, 1H), 2.07 (m, 4H), 1.36 (m, 6H), 0.89 (t, J=6.8 Hz, 3H); ^{13}C NMR: δ 136.2 (−), 133.8 (−), 127.0 (−), 117.3 (−), 32.6 (+), 31.8 (+), 29.4 (+), 28.9 (+), 22.8 (+), 19.2 (−). NMR data were consistent with literature values.[18]

3.2.6. (1*E*)-1-Chloro-3-yn-1-octen (17a). To a solution of **3** (1.0 equiv, 0.53 mmol) in 2 mL THF was added 65 mg of **16** (1.5 equiv, 0.80 mmol), 0.1 mL piperidine (2.0 equiv, 1.1 mmol), 31 mg of $(PPh_3)_4Pd$ (0.05 equiv, 0.026 mmol), 5 mg of CuI (0.05 equiv, 0.03 mmol) and the reaction mixture was stirred at 60 °C for 5 h. When the reaction was judged complete, it was quenched with saturated ammonium chloride and the organic layer was separated. The aqueous layer was extracted with diethyl ether and the combined organic layers were dried over anhydrous $MgSO_4$. After filtering, the solvent was removed in vacuo and the crude product was purified by column chromatography (R_f=0.8; 5% ether in pentane) to provide 35 mg of **17a** (42% yield) along with a trace amount of **18**. ^{1}H NMR: δ 6.41 (d, J=13.6 Hz, 1H), 5.94 (d, J=13.6 Hz, 1H), 2.28 (t, J=6.2 Hz, 2H), 1.59 (m, 4H), 0.91 (t, J=6.4 Hz, 3H). NMR data were consistent with literature values.[19]

3.3. General procedure for Negishi cross-coupling reactions

To a suspension of Mg (1.4 equiv) in THF was added bromoethane (1.2 equiv) and this was stirred at rt for 2 h. The resultant Grignard was added to a second flask containing the alkyne (i.e., **16** or **20**; 0.9 equiv) and this was stirred at rt for 3 h. To this was added a solution of $ZnCl_2$ in THF (1.2 equiv) after which the mixture was stirred at rt for 30 min. At this time, the template (i.e., **3**, **4**, or **5**; 1.0 equiv) and $(PPh_3)_4Pd$ (0.02 equiv) were added and stirring continued for 10 h. The mixture was then passed through a short silica gel pad and the filtrate concentrated in vacuo. The crude product was purified by column chromatography.

3.3.1. (1*E*)-1-Chloro-3-yn-1-octen (17a). The reaction mixture contained 18 mg of Mg (1.4 equiv, 0.740 mmol), 1.6 mL of THF, 70 mg of bromoethane (1.2 equiv, 0.64 mmol), 40 mg of **16** (0.9 equiv, 0.48 mmol, 56 μL), 0.64 mL of $ZnCl_2$ (1.2 equiv, 0.64 mmol, 1 M solution in THF), 100 mg of **3** (1.0 equiv, 0.53 mmol) and 12 mg of $(PPh_3)_4Pd$ (0.02 equiv, 0.01 mmol). The crude product was purified by column chromatography (R_f=0.85; 2% ether in pentane) to provide 51 mg of **17a** (68% yield).[6]

3.3.2. (1*E*)-1-Bromo-3-yn-1-octen (17b). The reaction mixture contained 30 mg of Mg (1.4 equiv, 1.20 mmol), 2 mL of THF, 112 mg of bromoethane (1.2 equiv, 1.63 mmol), 64 mg of **16** (0.9 equiv, 0.772 mmol, 90 μL), 1.03 mL of $ZnCl_2$ (1.2 equiv, 1.03 mmol, 1 M solution in THF), 200 mg of **4** (1.0 equiv, 0.86 mmol) and 20 mg of $(PPh_3)_4Pd$ (0.02 equiv, 0.02 mmol). The crude product was purified by column chromatography (R_f=0.85; 2% ether in pentane) to provide 115 mg of **17b** (72% yield). ^{1}H NMR: δ 6.57 (d, J=14.4 Hz, 1H), 6.20 (d, J=14.4 Hz, 1H), 2.27 (t, J=7.6 Hz, 2H), 1.51 (m, 2H), 1.42 (m, 2H), 0.92 (t, J=7.6 Hz, 3H); ^{13}C NMR: δ 119.4 (−), 118.3 (−), 93.2 (+), 77.4 (+), 30.5 (+), 22.0 (+), 19.1 (+), 14.9 (−). NMR data were consistent with literature values.[20]

3.3.3. [(3*E*)-4-Chloro-3-buten-1-ynyl] trimethyl silane (21a). The reaction mixture contained 30 mg of Mg (1.4 equiv, 1.20 mmol), 2 mL of THF, 112 mg of bromoethane (1.2 equiv, 1.63 mmol), 75 mg of **20** (0.9 equiv, 0.77 mmol), 1.03 mL of $ZnCl_2$ (1.2 equiv, 1.03 mmol, 1 M solution in THF), 162 mg of **3** (1.0 equiv, 0.86 mmol) and 20 mg of $(PPh_3)_4Pd$ (0.02 equiv, 0.02 mmol). The crude product was purified by column chromatography (R_f=0.90; 2% ether in pentane) to provide 80 mg of **21a** (59% yield). ^{1}H NMR: δ 6.58 (d, J=13.6 Hz, 1H), 5.95 (d, J=13.6 Hz, 1H), 0.20 (s, 9H); ^{13}C NMR: δ 131.4 (−), 113.7 (−), 99.4 (+), 97.5 (+), −0.3 (−). NMR data were consistent with literature values.[21]

3.3.4. [(3*E*)-4-Bromo-3-buten-1-ynyl] trimethyl silane (21b). The reaction mixture contained 30 mg of Mg (1.4 equiv, 1.20 mmol), 2 mL of THF, 112 mg of bromoethane (1.2 equiv, 1.63 mmol), 75 mg of **20** (0.9 equiv, 0.77 mmol), 1.03 mL of $ZnCl_2$ (1.2 equiv, 1.03 mmol, 1 M solution in THF), 200 mg of **4** (1.0 equiv, 0.86 mmol) and 20 mg of $(PPh_3)_4Pd$ (0.02 equiv, 0.02 mmol). The crude product was purified by column chromatography (R_f=0.90; 2% ether in pentane) to provide 118 mg of **21b** (68% yield). ^{1}H NMR: δ 6.74 (d, J=14.0 Hz, 1H), 6.22 (d, J=14.0 Hz, 1H), 0.19 (s, 9H); ^{13}C NMR: δ 120.0 (−), 118.3 (−), 101.0 (+), 97.4 (+), 0.0 (−). NMR data were consistent with literature values.[22]

3.3.5. (*cis*)-α,β-Dibromostyrene (26). To a solution of **24** (1.0 equiv, 0.43 mmol, 113 mg) and $Pd(PPh_3)_4$ (0.07 equiv, 0.03 mmol, 35 mg) in 2.5 mL of THF was added **12b** (1.8 equiv, 0.75 mmol, 91 mg), CsF (3.3 equiv, 1.40 mmol, 213 mg) and 0.2 mL of water. After refluxing for 22 h, the mixture was cooled to rt and 5 mL of water was added. The layers were separated and the aqueous layer extracted with ether (3×). The combined organic extracts were dried with anhydrous $MgSO_4$ and the solvent removed in vacuo. The resulting crude product was purified by column chromatography (R_f=0.45; in pentane) providing 87 mg of **26** (78% yield) as a pale yellow oil. ^{1}H NMR: δ 7.52 (t, J=5.6 Hz, 2H), 7.37 (t, J=5.6 Hz, 3H), 7.07 (s, 1H). ^{13}C NMR: δ 138.5 (+), 131.1 (+), 129.4 (−), 128.6 (−), 127.8 (−), 108.9 (−). NMR data were consistent with literature values.[23]

3.3.6. 1,4-Diphenyl-1,3-butadiyne (27). Phenyl iodide (2.0 equiv, 0.46 mmol, 93.8 mg) was dissolved in 2.0 mL of THF and the mixture was cooled to −78 °C. *n*-BuLi (0.29 mL of 1.6 M solution in hexanes, 2.0 equiv, 0.46 mmol) was then added and the solution stirred for an additional 30 min. To this reaction was added 0.92 mL of 0.5 M anhydrous $ZnCl_2$ in THF (2.0 equiv, 0.46 mmol) after which the solution was stirred for 40 min at rt. To a separate flask was added **26** (1.0 equiv, 0.23 mmol, 60 mg), $Pd(PPh_3)_4$ (0.05 equiv, 0.01 mmol, 13 mg) and 0.5 mL THF, followed by the contents of the first flask. Reaction was stirred for 18 h at rt and then for 24 h at 40 °C. Water (5 mL) was added, the layers separated and the aqueous layer was extracted with ether (3×). The combined organic extracts were dried with anhydrous $MgSO_4$ and the solvent removed in vacuo. The crude product was purified by column chromatography (R_f=0.5; in pentane) providing 34 mg of **27** (57% recovery), 9.1 mg (0.090 mmol) of bis-coupled product **27** (39% yield) and 14.5 mg (0.094 mmol) of biphenyl (**15b**). ^{1}H NMR for **27**: δ 7.54 (d, J=2 Hz, 2H), 7.35 (d, J=2 Hz, 3H); ^{13}C NMR: δ 135.5 (−), 129.3 (−), 128.1 (−),121.9 (+), 81.7 (+), 73.9 (+). NMR data were consistent with literature values.[24]

3.3.7. (*E*)-4-Chloro-5-iodooct-4-ene (28a). To a solution of 1.0 g of 4-octyne (1.0 equiv, 9.1 mmol) in 30 mL of dichloromethane was added 3.3 g of iodomonochloride (2.2 equiv, 20.3 mmol) and the reaction mixture was stirred at rt for 5 h. When the reaction was judged complete by TLC analysis, it was concentrated in vacuo and the crude product was subjected to column chromatography on silica gel (R_f= 0.9; in pentane) to provide 2.1 g (85%) of product as a slightly pink liquid. ^{1}H NMR δ 2.67 m, 4H), 1.60 (m, 4H), 0.95 (m, 6H); ^{13}C NMR δ 131.6 (+), 99.3 (+), 44.8 (+), 43.7 (+), 21.8 (+), 20.5 (+), 14.2 (−), 14.1 (−).[25]

3.3.8. (*E*)-4,5-Dibromo-4-octene (28b). To a solution of 1.0 g of 4-octyne (1.0 equiv, 9.1 mmol) in 45 mL of dichloromethane was added 2.2 g of bromine (1.5 equiv, 13.6 mmol) and the reaction mixture was stirred at rt for 1 h. When the reaction was judged complete by TLC analysis, it was concentrated in vacuo and the crude product was subjected to column chromatography on silica gel (R_f=0.8; in pentane) to provide 2.2 g (90%) of product as a colorless liquid. ^{1}H NMR δ 2.67 (t, J=7.2 Hz, 4H), 1.49 (m, 4H), 0.97 (t, J=7.6 Hz, 6H); ^{13}C NMR δ 121.7 (+), 42.8 (+), 20.9 (+), 15.1 (−). Spectra were consistent with literature data.[26]

3.3.9. (*E*)-1,2-Dibromo-1,2-diphenylethene (33). To a solution of 0.3 g of diphenylacetylene (1.0 equiv, 1.7 mmol) in 8 mL of dichloromethane was added 0.3 g of bromine (1.1 equiv, 1.9 mmol) and the reaction mixture was stirred at rt for 1 h. When the reaction was judged complete by ^{1}H NMR analysis, it was filtered and the precipitate was washed with dichloromethane to provide 0.52 g (90%) of product as a white crystal. ^{1}H NMR δ 7.59 (m, 4H), 7.40 (m, 6H); mp 216–218 °C (lit. 215–216 °C).[27]

Acknowledgements

This work was supported by funding from NSERC Canada and the Ontario Research and Development and Challenge Fund.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2004.08.006

References and notes

1. Organ, M. G.; Cooper, J. T.; Rogers, L. R.; Soleymanzadeh, F.; Paul, T. *J. Org. Chem.* **2000**, *65*, 7959–7970.
2. (a) Ratovelomanana, V.; Guillerm, D.; Limstrumelle, G. *Tetrahedron Lett.* **1984**, *25*, 6001–6004. (b) Magnus, P.; Lewis, R. T.; Huffman, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 6921–6923. (c) Ratovelomanana, V.; Limstrumelle, G. *Tetrahedron Lett.* **1981**, *22*, 315–318. (d) Hyuga, S.; Chiba, Y.; Yamashina, N.; Hara, S.; Suzuki, A. *Chem. Lett.* **1987**, 1757–1760. (e) Hyuga, S.; Yamashina, N.; Hara, S.; Suzuki, A. *Chem. Lett.* **1988**, 809–812. (f) Shair, M. D.; Yoon, T.; Danishefsky, S. J. *J. Org. Chem.* **1994**, *59*, 3755–3756. (g) Nicolaou, K. C.; Chakraborty, T. K.; Piscopio, A. D.; Minowa, N.; Bertinato, P. *J. Am. Chem. Soc.* **1993**, *115*, 4419–4420.
3. Rossi, R.; Carpita, A.; Bellina, F. *Org. Prep. Proc. Int.* **1995**, 129–160.
4. (a) Roush, W. R.; Moriarty, K. J.; Brown, B. B. *Tetrahedron Lett.* **1990**, *31*, 6509–6512. (b) Baldwin, J. E.; Chesworth, R.; Paker, J. S.; Russel, A. T. *Tetrahedron Lett.* **1995**, *36*, 9551–9554. (c) Shen, W. *Synlett* **2000**, 737–739.
5. (a) Organ, M. G.; Antunes, L. M. *Tetrahedron Lett.* **2003**, *44*, 6805–6808. (b) Organ, M. G.; Ghasemi, H. *J. Org. Chem.* **2004**, *69*, 695–700.
6. Zeng, F.; Negishi, E.-i. *Org. Lett.* **2001**, *3*, 719–722.
7. Hundertmark, T.; Littke, A. F.; Buchwald, S. L.; Fu, G. C. *Org. Lett.* **2000**, *2*, 1729–1731.
8. Zhang, S.; Zhang, D.; Liebeskind, L. S. *J. Org. Chem.* **1997**, *62*, 2312–2313.
9. Carpita, A.; Rossi, R. *Tetrahedron Lett.* **1986**, *27*, 4351–4354.

10. Alami, M.; Gueugnot, S.; Domingues, E.; Linstrumelle, G. *Tetrahedron* **1995**, *51*, 1209–1220.
11. Zeng, F.; Negishi, E.i. *Org. Lett.* **2001**, *3*, 719–722.
12. Ratovelomanana, V.; Linstrumelle, G.; Normant, J.-F. *Tetrahedron Lett.* **1985**, *26*, 2575–2576.
13. Rathmore, R.; Deselnicu, M.; Burns, C. L. *J. Am. Chem. Soc.* **2002**, *124*, 14832–14833.
14. Negishi, E.-i.; Alimardanov, A.; Xu, C. *Org. Lett.* **2000**, *2*, 65–67.
15. Chowdhury, S.; Roy, S. *J. Org. Chem.* **1997**, *62*, 199–200.
16. Miller, B. R.; McGarvey, G. *J. Org. Chem.* **1978**, *43*, 4424–4431.
17. Nagashima, E.; Suzuki, K.; Ishikawa, M.; Sekiya, M. *Heterocycles* **1985**, *23*, 1873–1879.
18. Ratovelomanana, V.; Linstrumelle, G. *Tetrahedron Lett.* **1984**, *25*, 6001–6004.
19. Chemin, D.; Linstrumelle, G. *Tetrahedron* **1994**, *50*, 5335–5344.
20. Carpita, A.; Rossi, R. *Tetrahedron Lett.* **1986**, *27*, 4351–4354.
21. Alami, M.; Gueugnot, S.; Domingues, E.; Linstrumelle, G. *Tetrahedron* **1995**, *51*, 1209–1220.
22. Zeng, F.; Negishi, E.i. *Org. Lett.* **2001**, *3*, 719–722.
23. Barhate, N. B.; Gajare, A. S.; Wakharkar, R. D.; Bedekar, A. V. *Tetrahedron* **1999**, *55*, 11127–11142.
24. NMR data for compound **27** and **31** were compared to the spectra reported in the Aldrich NMR database
25. Uemura, S.; Okazaki, H.; Onoe, A.; Okano, M. *J. Chem. Soc., Perkin Trans 1* **1977**, *6*, 676–680.
26. Kabalka, G. W.; Yang, K. *Synth. Commun.* **1998**, *28*, 3807–3809.
27. Espenson, J. H.; Zhu, Z.; Zauche, T. H. *J. Org. Chem.* **1999**, *64*, 1191–1196.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 60 (2004) 9463–9469

One-pot syntheses of dihydro benzo[*b*][1,4]thiazepines and -diazepines via coupling–isomerization–cyclocondensation sequences

Roland U. Braun and Thomas J. J. Müller*

Organisch-Chemisches Institut der Ruprecht-Karls-Universität Heidelberg, Im Neuenheimer Feld 270, D-69120 Heidelberg, Germany

Received 1 July 2004; revised 29 July 2004; accepted 2 August 2004

Dedicated to Professor Dr. Klaus Theodor Wanner on the occasion of his 50th birthday

Abstract—2,4-Di(hetero)aryl substituted 2,3-dihydro benzo[*b*][1,4]heteroazepines **7** and **9** (hetero = S, NH) can be readily synthesized in a one-pot process initiated by a coupling–isomerization sequence of an electron poor (hetero)aryl halide **4** and a terminal propargyl alcohol **5** subsequently followed by a cyclocondensation with 2-mercapto or 2-amino anilines **6** or **8**, respectively. In addition, the structures were established unambiguously by an X-ray structure analysis of **9b**.
© 2004 Elsevier Ltd. All rights reserved.

1. Introduction

Sequential transformations and multicomponent reactions are steadily gaining a considerable academic, economic and ecological interest since they address very fundamental principles of synthetic efficiency and reaction design.[1] Mastering unusual combinations of elementary organic reactions under similar conditions is the major conceptual challenge in engineering novel types of sequences. Transition metal catalyzed reactions with exceptionally mild reaction conditions are of a paramount benefit if they can be directed in a domino fashion generating a suitable reactive functionality en route.[2] Additionally, the prospect of extending one-pot sequences into combinatorial and solid phase syntheses[1c,3] promises manifold opportunities for developing novel lead structures of pharmaceuticals, catalysts and even novel molecule based materials. As part of our program designed to develop new multicomponent methodologies initiated by transition metal catalyzed CC-bond formation, we have recently discovered and developed an new mode of alkyne activation by a detouring outcome of the Sonogashira coupling, that is, a coupling–isomerization reaction (CIR).[4] Conceptually, the cross-coupling reaction of an electron deficient halide with a terminal alkyne not only activates the newly formed internal triple bond towards Michael-type additions, but also stimulates the propargyl position, for example, towards an alkyne–allene isomerization (Scheme 1).

In particular, the Sonogashira coupling of electron poor halides with 1-(hetero)aryl propargyl alcohols furnishes chalcones in good to excellent yields. With this new enone synthesis in hand and based upon the inherent bifunctional electrophilicity of the in situ generated Michael acceptor as a pivotal point, we have disclosed novel three- and four-component syntheses of various heterocycles in the sense of sequential one-pot reactions (Scheme 2).[4–8h] Here, we report a facile one-pot synthesis of 2,4-di(hetero)aryl substituted 2,3-dihydro benzo[*b*][1,4]diazepines and thiazepines based upon a CIR sequence with a subsequent cyclocondensation with 2-amino or 2-mercapto anilines.

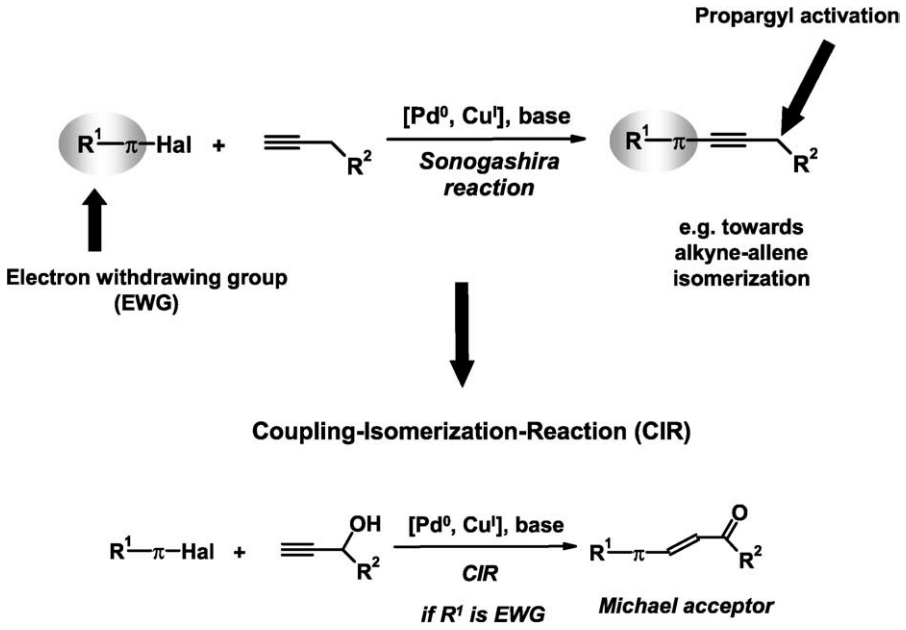
2. Results and discussion

Dihydro benzodiazepines **1** and **2** (Fig. 1) constitute an important class of psychopharmaca.[9] In particular, derivatives of dihydro benzo[*b*][1,4]diazepines **2** have aroused considerable interest as CNS active anticonvulsant drugs,[10] but also as in vitro non-nucleoside inhibitors of HIV-1 reverse transcriptase.[11]

Besides these compounds, also the dihydro 1,4-benzothiazepines **3** (Fig. 1) have become increasingly interesting since they show anti-fungal, anti-bacterial,[12] anti-feedant,[13]

Keywords: Catalysis; Cross-couplings; Cyclocondensations; Heterocycles; Multicomponent reactions.
* Corresponding author. Tel.: +49-6221-546207; fax: +49-6221-546579; e-mail: thomas_j.j.mueller@urz.uni-heidelberg.de

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.08.001



Scheme 1. The coupling–isomerization-reaction (CIR) as a new mode of alkyne activation by cross-coupling.

anti-inflammatory, analgesic,[14] and anti-convulsant[15] activity. Furthermore, they can be oxidized to 1,4-benzothiazepines under mild conditions.[16]

Our new CIR-chalcone synthesis (vide supra) opens a straightforward convergent and modular access to 2,3-dihydro benzo[*b*][1,4]heteroazepines in a one-pot fashion. Thus, upon reacting electron poor (hetero)aryl halides **4** and 1-phenyl propynol (**5a**) under the reaction conditions of the Sonogashira coupling in boiling mixture of triethylamine and THF and the subsequent addition of 2-amino thiophenols **6** as suitable 1,4-dinucleophilic component and acetic acid, the beige to yellow 2,3-dihydro benzo[*b*][1,4]thiaazepines **7** were isolated in 38–85% yield (Scheme 3).

Likewise, the addition of *ortho*-phenylene diamine (**8**) after the CIR of electron poor (hetero)aryl halides **4** and 1-aryl propynol **5** furnishes the beige to yellow 2,3-dihydro benzo[*b*][1,4]diazepines **9** in 39–79% yield (Scheme 4).

The structures of the benzothiazepines **7** and benzodiazepines **9** were unambiguously assigned by ^{1}H, ^{13}C, COSY, and NOESY NMR experiments. As a consequence of the Michael addition–cyclocondensation of the amino thiophenols and *o*-phenylene diamine to the transient enone functionality three distinct aliphatic proton resonances, a methine and two diastereotopic methylene protons, appear most characteristically in the ^{1}H spectra as splitting patterns (doublets of doublets) of ABM spin systems. Therefore, due to the characteristic geminal and vicinal coupling constants (^{2}J=12.3–13.9 Hz, ^{3}J=4.3–4.9 Hz, ^{3}J=6.8–9.6 Hz) the signals at δ 2.72–3.29 and δ

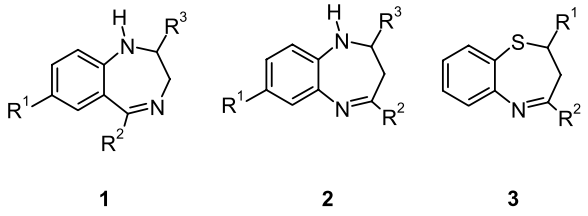
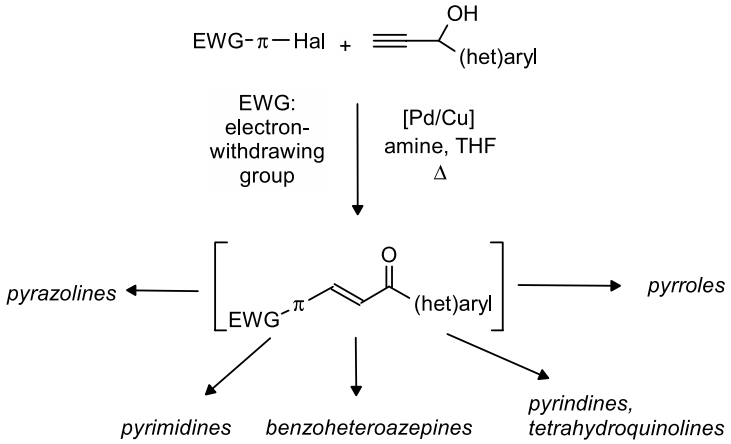
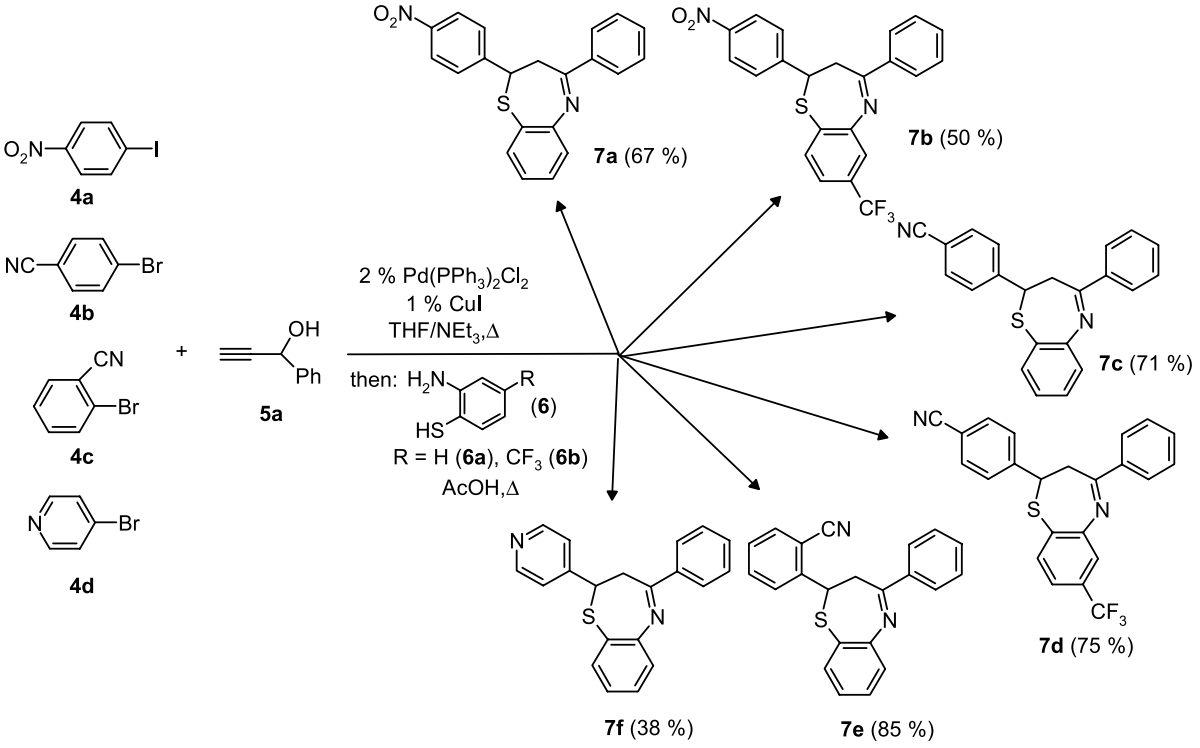


Figure 1.



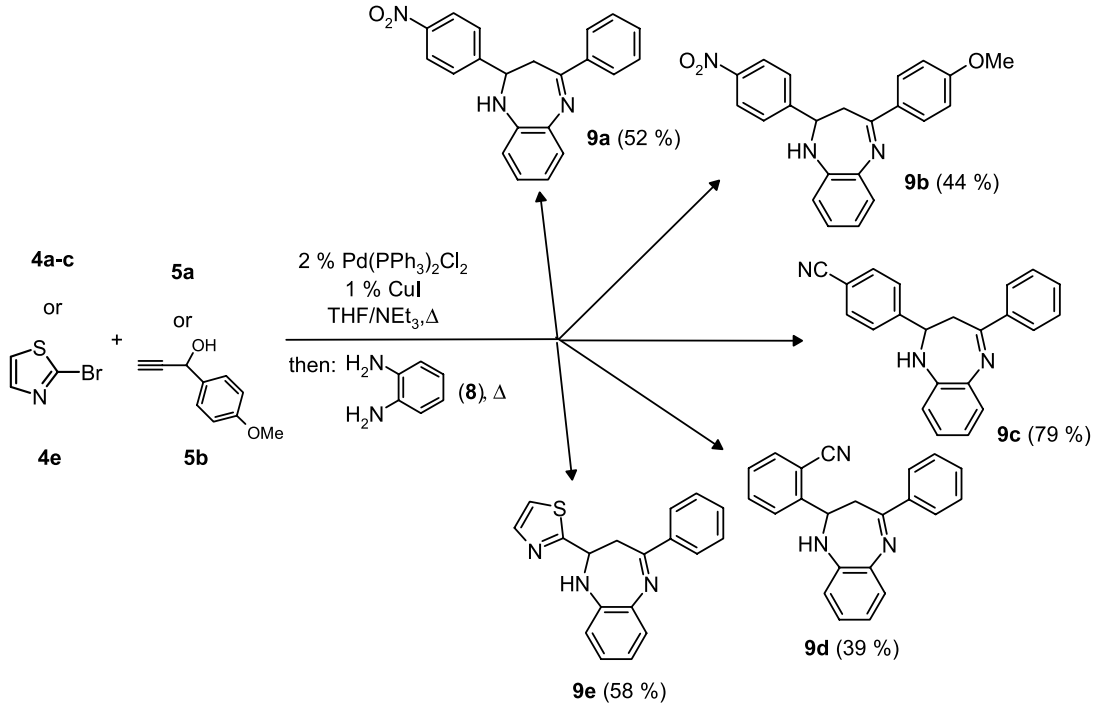
Scheme 2. One-pot syntheses of heterocycles based upon a CIR sequence.



Scheme 3. One-pot threecomponent synthesis of 2,3-dihydro benzo[*b*][1,4]thiazepines **7**.

2.90–3.50 can be assigned to the diastereotopic methylene protons. Conformation analyses applying the Karplus correlation of coupling constants and dihedral angles suggests that the thi- or diazepine core of the bicyclic molecules only displays low conformational flexibility. Furthermore, the appearance of vicinal coupling constants (^3J=4.3–4.9 Hz, ^3J=6.5–9.6 Hz) for the signals at δ 4.24–5.84 completes the assignment of the methine resonances. Furthermore, the signals of the (hetero)aromatic and aliphatic protons can be detected with expected chemical shifts.

Most indicatively, in the carbon NMR spectra the quaternary carbonyl resonances of the imine carbon nuclei are found between δ 158.1–170.3. The methine and methylene carbon nuclei resulting from the Michael



Scheme 4. One-pot threecomponent synthesis of 2,3-dihydro benzo[*b*][1,4]diazepines **9**.

addition appear at δ 57.4–73.3 and δ 35.1–37.4, respectively.

Another strong spectroscopic support of benzoheteroazepine formation can be derived from the mass spectra, revealing that a benzyl and an α-cleavage (with respect to the imine group) furnish the by far most dominant fragment ($[M\text{-Acc-}\pi\text{-CH}{=}CH_2]^+$). In the IR spectra typical CN-valence vibrations of imines are found between 1604 and 1635 cm^{-1}.

Furthermore, the structure of benzodiazepines **9** was unambiguously corroborated by an X-ray crystal structure analysis (Fig. 2) of compound **9b**.[17] The imine functionality is almost fully conjugated with the anisyl substitutent and the annealed benzo ring as clearly supported by dihedral angles of 14.0° (C21–C16–C8–N2) and 2.3° (N2–C7–C6–H6). Interestingly, the seven-membered ring adopts a chair/twist conformation as indicated by the angle (33.2°) between the plane formed by C1–C8–C9 and the annealed benzo ring.

Although, several attempts were tested to expand the scope of this facile coupling–condensation sequence to aliphatic heteroazepines no satisfying results were obtained. Conformationally flexible dinucleophiles like ethylene diamine or cysteine methylester give rise to a complex mixture of products, some of them are definitely aldol cleavage products as detected by mass spectrometry and proton NMR analysis. Structurally rigid aliphatic diamines such as (*R*,*R*)-1,2-diamino cyclohexane react in analogy to *ortho*-phenylene diamine according to NMR and mass spectrometry of the crude product furnishing a single diastereomer, however, upon purification (column chromatography or recrystallization from reasonably polar solvents) solvolysis lead to the isolation of the chalcone precursor. Hence, at this point the coupling–condensation sequence to heteroazepines is restricted to the formation of benzo derivatives.

In conclusion, we have disclosed a straightforward convergent and modular one-pot synthesis of 2,3-dihydro benzo[*b*][1,4]thiazepines **7** and 2,3-dihydro benzo[*b*][1,4]diazepines **9** based upon a CIR–cyclocondensation sequence of electron poor (hetero)aryl halides, 1-aryl propargyl alcohols, and 2-mercapto anilines or *ortho*-phenylene diamine, respectively. Further studies to enhance molecular diversity in pharmaceutically interesting targets and extension to a combinatorial approach to 2,3-dihydro benzo[*b*][1,4]heteroazepines are currently under investigation.

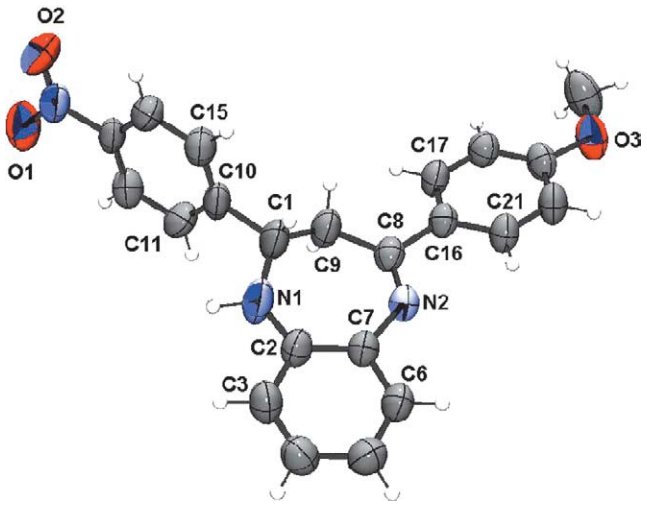


Figure 2. ORTEP-plot of benzodiazepine **9b**.

3. Experimental

All reactions involving water-sensitive compounds were carried out in oven-dried Schlenk glassware under a nitrogen atmosphere. The solvents were dried according to standard procedures[18] and were distilled prior to use. Column chromatography: silica gel 60 M (mesh 230–400) Macherey-Nagel or aluminium oxide 5016 A basic Fluka. Thin layer chromatography (TLC): silica gel layered aluminium foil (60 F_{254} Merck, Darmstadt) or aluminum oxide layered aluminium foil (60 F_{254} Merck, Darmstadt). Melting points (uncorrected): Büchi Melting Point B-540. The aryl propynols **5** were synthesized according to literature procedures.[19] Electron-poor (hetero)aryl halides **4**, 2-mercapto anilines **6** and *ortho*-phenylene diamine (**8**) were purchased from ACROS or Merck and used without further purification. ^1H and ^{13}C NMR spectra: Bruker ARX250, Bruker DRX 300, Bruker ARX 300, Varian VXR 400S, Bruker DRX500 or Bruker AC300 with $CDCl_3$ as a solvent. The assignments of quaternary C, CH, CH_2 and CH_3 was made on the basis of DEPT spectra. IR: Bruker Vector 22 FT-IR or Perkin Elmer Models Lambda 16. UV/VIS: Hewlett Packard HP8452 A. MS: Finnigan MAT 90, MAT 95 Q, Jeol JMS-700 and Finnigan TSQ 700. Elemental analyses were carried out in the microanalytical laboratories of Department Chemie der Universität München and the Organisch-Chemisches Institut der Universität Heidelberg.

3.1. General procedure for the one-pot synthesis of benzodiazepines and benzothiazepines

A magnetically stirred solution of 1.00 mmol of halogen compound **4**, 1.05 mmol of propargyl alcohol **5**, 14 mg (0.02 mmol) of $Pd(PPh_3)_2Cl_2$, and 2 mg (0.01 mmol) of CuI in 5 mL of degassed triethylamine under nitrogen was heated to reflux temperature for 16 h (for experimental details see Table 1). After cooling to room temperature a solution of 1.1 mmol of a 2-amino thiophenol **6** and 1.6 mL of acetic acid or 1.1 mmol of *o*-phenylene diamine (**8**) were added and the reaction mixture was heated to reflux temperature for the times indicated. After cooling 15 mL of diethylether was added and the mixture was filtered (for benzodiazepines **9**). Then, the solvents were removed from the filtrate in vacuo. For benzothiazepines **7** the reaction mixture was poured into a saturated aqueous solution of potassium carbonate. The aqueous phase was extracted with diethylether and the combined organic layers were dried with anhydrous sodium sulfate and filtered. The solvents were removed in vacuo. Crude **7** and **9** were chromatographed on silica gel and/or recrystallized to give the analytically pure benzothiazepines **7** or benzodiazepines **9**.

Table 1. Experimental details of the one-pot synthesis of 2,3-dihydro benzo[*b*][1,4]thiazepines **7** and 2,3-dihydro benzo[*b*][1,4]diazepines **9**

Aryl halide **4**	Propargyl alcohol **5**	Aniline **6/8**	THF (mL)	NEt_3 (mL)	Time (h)	Yield
249 mg (1.00 mmol) of **4a**	139 mg (1.05 mmol) of **5a**	137 mg (1.09 mmol) of **6a**	6.0	3.5	20	242 mg (67%) of **7a**
249 mg (1.00 mmol) of **4a**	139 mg (1.05 mmol) of **5a**	253 mg (1.10 mmol) of **6b**[a]	6.0	3.5	24	242 mg (50%) of **7b**
182 mg (1.00 mmol) of **4b**	139 mg (1.05 mmol) of **5a**	137 mg (1.09 mmol) of **6a**	6.0	3.5	14	241 mg (71%) of **7c**
182 mg (1.00 mmol) of **4b**	139 mg (1.05 mmol) of **5a**	253 mg (1.10 mmol) of **6b**[a]	6.0	3.5	24	307 mg (75%) of **7d**
182 mg (1.00 mmol) of **4c**	139 mg (1.05 mmol) of **5a**	137 mg (1.09 mmol) of **6a**	6.0	3.5	24	289 mg (85%) of **7e**
195 mg (1.00 mmol) of **4d**[b]	139 mg (1.05 mmol) of **5a**	137 mg (1.09 mmol) of **6a**	6.0	3.5	8.5	120 mg (38%) of **7f**
249 mg (1.00 mmol) of **4a**	139 mg (1.05 mmol) of **5a**	119 mg (1.10 mmol) of **8**	6.0	3.0	24	269 mg (52%) of **9a**
249 mg (1.00 mmol) of **4a**	162 mg (1.05 mmol) of **5b**	119 mg (1.10 mmol) of **8**	10	5.0	23	163 mg (44%) of **9b**
182 mg (1.00 mmol) of **4b**	139 mg (1.05 mmol) of **5a**	119 mg (1.10 mmol) of **8**	3.0	2.0	36	254 mg (79%) of **9c**
182 mg (1.00 mmol) of **4c**	139 mg (1.05 mmol) of **5a**	119 mg (1.10 mmol) of **8**	10	5.0	16	125 mg (39%) of **9d**
164 mg (1.00 mmol) of **4e**	139 mg (1.05 mmol) of **5a**	119 mg (1.10 mmol) of **8**	3.0	2.0	36	177 mg (58%) of **9e**

[a] As **3b** hydrochloride.
[b] As **1d** hydrochloride.

3.1.1. 2-(4-Nitro-phenyl)-4-phenyl-2,3-dihydro-benzo[*b*][1,4]thiazepine (7a). According to the standard procedure and after chromatography on silica gel (petrolether/ethyl acetate 4:1) and after recrystallization from ethanol **7a** was isolated as pale yellow needles, mp 185 °C (181 °C).[20] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.09 (m, 1H), 3.40 (dd, J=4.9, 12.8 Hz, 1H), 5.04 (dd, J=4.8, 12.5 Hz, 1H), 7.26–7.20 (m, 1H), 7.62–7.45 (m, 8H), 8.18 (d, J=8.7 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 37.3 (CH_2), 59.2 (CH), 122.3 ($C_{quat.}$), 124.2 (CH), 124.2 ($C_{quat.}$), 125.9 (CH), 126.4 (CH), 127.0 (CH), 127.9 (CH), 129.1 (CH), 130.6 (CH), 132.2 (CH), 135.1 (CH), 136.2 ($C_{quat.}$), 147.4 ($C_{quat.}$), 150.4 ($C_{quat.}$), 169.8 ($C_{quat.}$). EI MS (70 eV, *m/z* (%)): 360 (M^+, 7), 224 (14), 211 ($M^+ - O_2NC_6H_4CHCH_2$, 100). IR (KBr): $\tilde{\nu}$ 1608 cm^{-1}, 1596, 1574, 1517, 1452, 1348, 1320, 1245, 1214, 1110, 1024, 856, 827, 787, 748, 700, 689, 613, 484. UV/Vis ($CHCl_3$): λ_{max} (ε) 264 nm (25,800), 322 (8000). Anal. calcd for $C_{21}H_{16}N_2O_2S$ (360.5): C 69.77, H 4.48, N 7.77, S 8.90. Found: C 69.78, H 4.45, N 7.73, S 8.78.

3.1.2. 2-(4-Nitro-phenyl)-4-phenyl-7-trifluoromethyl-2,3-dihydro-benzo[*b*][1,4]thiazepine (7b). According to the standard procedure and after chromatography on silica gel (petrolether/ethyl acetate 1:1) and after recrystallization from ethanol **7a** was isolated as a colorless solid, mp 166–167 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.13 (m, 1H), 3.50 (dd, J=4.9, 13.1 Hz, 1H), 5.14 (dd, J=4.3, 12.3 Hz, 1H), 7.46 (d, J=9.1 Hz, 2H), 7.50–7.66 (m, 4H), 7.74–7.85 (m, 2H), 8.12–8.17 (m, 2H), 8.23 (d, J=9.1 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 36.8 (CH_2), 59.5 (CH), 121.9 (q, J_{CF}=3.5 Hz, CH), 122.7 (q, J_{CF}=3.8 Hz, CH), 124.3 (CH), 126.3 (q, J=271.1 Hz $C_{quat.}$), 127.0 (CH), 127.5 (CH), 128.1 ($C_{quat.}$), 128.5 ($C_{quat.}$), 128.6 ($C_{quat.}$), 128.9 ($C_{quat.}$), 129.0 (CH), 131.9 (CH), 135.7 (q, J=29.1 Hz $C_{quat.}$), 135.3 (CH), 147.5 ($C_{quat.}$), 169.5 ($C_{quat.}$). EI MS (70 eV, *m/z* (%)): 428 (M^+, 8), 292 (19), 279 ($M^+ - O_2NC_6H_4CHCH_2$, 100). IR (KBr): $\tilde{\nu}$ 1614 cm^{-1}, 1576, 1522, 1407, 1348, 1331, 1256, 1201, 1169, 1131, 1084, 901, 700. UV/Vis ($CHCl_3$): λ_{max} (ε) 268 (27,700) nm. Anal. calcd for $C_{22}H_{15}F_3N_2O_2S$ (428.5): C 61.68, H 3.53, N 6.54. Found: C 61.40, H 3.67, N 6.40.

3.1.3. 2-(4-Cyanophenyl)-4-phenyl-2,3-dihydro-benzo[*b*][1,4]thiazepine (7c). According to the standard procedure and after chromatography on silica gel (petrolether/ethyl acetate 4:1) and after recrystallization from ethanol **7c** was isolated as pale yellow needles, mp 192–193 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.03 (m, 1H), 3.30 (dd, J=4.9, 12.9 Hz, 1H), 4.97 (dd, J=7.7, 12.6 Hz, 1H), 7.16 (dt, J=1.4, 7.5 Hz, 1H), 7.32 (dd, J=1.9, 7.8 Hz, 1H), 7.41 (d, J=8.3 Hz, 2H), 7.61–7.46 (m, 7H), 8.04 (dd, J=1.4, 7.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 36.7 (CH_2), 59.4 (CH), 111.3 ($C_{quat.}$), 118.3 ($C_{quat.}$), 121.6 ($C_{quat.}$), 125.2 (CH), 125.3 (CH), 126.6 (CH), 127.1 (CH), 128.6 (CH), 130.0 (CH), 131.0 (CH), 132.4 (CH), 134.7 (CH), 137.1 ($C_{quat.}$), 148.6 ($C_{quat.}$), 152.2 ($C_{quat.}$), 168.1 ($C_{quat.}$). EI MS (70 eV, *m/z* (%)): 340 (M^+, 8), 211 ($M^+ - NCC_6H_4CHCH_2$, 100), 108 ($C_6H_4S^+$, 15). IR (KBr): $\tilde{\nu}$ 3054 cm^{-1}, 2229, 1609, 1574, 1500, 1452, 1434, 1414, 1324, 1246, 1214, 1182, 1110, 1064, 1020, 834, 792, 761, 694, 563, 484, 454. UV/Vis ($CHCl_3$): λ_{max} (ε) 244 nm (28,700). Anal. calcd for $C_{22}H_{16}N_2S$ (340.5): C 77.62, H 4.74, N 8.23, S 9.42. Found: C 77.48, H 4.76, N 8.26, S 9.52.

3.1.4. 2-(4-Cyanophenyl)-4-phenyl-7-trifluoromethyl-2,3-dihydro-benzo[*b*][1,4]thiazepine (7d). According to the standard procedure and after triturating with ethanol and after recrystallization from ethanol **7d** was isolated as a colorless solid, mp 178–179 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.08 (m, 1H), 3.45 (dd, J=4.7, 12.9 Hz, 1H), 5.05 (dd, J=4.6, 12.4 Hz, 1H), 7.39–7.48 (m, 3H), 7.55–7.65 (m, 5H), 7.72–7.78 (m, 2H), 8.12 (d, J=7.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 37.3 (CH_2), 59.6 (CH), 112.6 ($C_{quat.}$), 119.2 ($C_{quat.}$), 122.4 (q, J=3.7 Hz, CH), 123.0 (q, J=3.7 Hz, CH), 126.3 (q, J=271.1 Hz $C_{quat.}$), 127.7 (CH), 128.1 (CH), 129.0 (CH), 132.5 (CH), 133.4 ($C_{quat.}$), 133.5 (CH), 133.6 (q, J=29.1 Hz $C_{quat.}$), 136.2 (CH), 137.6 ($C_{quat.}$), 149.1 ($C_{quat.}$), 153.6 ($C_{quat.}$), 170.3 ($C_{quat.}$). EI MS (70 eV, *m/z* (%)): 408 (M^+, 5), 292 (16), 279 ($M^+ - NCC_6H_4CHCH_2$, 100), IR (KBr): $\tilde{\nu}$ 3062 cm^{-1}, 2230, 1611, 1576, 1502, 1452, 1407, 1331, 1304, 1256, 1202, 1169, 1125, 1082, 1021, 899, 830, 769, 755, 690, 563. UV/Vis ($CHCl_3$): λ_{max} (ε) 242 nm (25,200), 266 (21,200). Anal. calcd for $C_{23}H_{15}F_3N_2S$ (408.4): C 67.64, H 3.70, N 6.86. Found: C 67.62, H 3.42, N 6.84.

3.1.5. 2-(2-Cyanophenyl)-4-phenyl-2,3-dihydro-benzo[*b*][1,4]thiazepine (7e). According to the standard procedure and after triturating with ethanol and after recrystallization from ethanol **7e** was isolated as a beige solid, mp 183–184 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.95 (m, 1H), 3.44 (dd, J=4.9, 12.9 Hz, 1H), 5.49 (dd, J=4.9, 12.5 Hz, 1H), 7.17–7.23 (m, 1H), 7.34–7.41 (m, 2H), 7.48–7.58 (m, 5H), 7.62–7.70 (m, 2H), 7.77 (d, J=8.0 Hz, 1H),

8.19–8.22 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 37.4 (CH_2), 57.4 (CH), 109.9 ($C_{quat.}$), 117.4 ($C_{quat.}$), 122.4 ($C_{quat.}$), 125.8 (CH), 125.9 (CH), 127.4 (CH), 127.8 (CH), 128.2 (CH), 129.0 (CH), 130.3 (CH), 131.8 (CH), 132.7 (CH), 133.5 (CH), 135.0 (CH), 136.6 ($C_{quat.}$), 147.4 ($C_{quat.}$), 151.7 ($C_{quat.}$), 168.9 ($C_{quat.}$). EI MS (70 eV, *m/z* (%)) 340 (M^+, 17), 338 (M^+-H_2, 17), 236 (M^+-H_2–$NCC_6H_4^+$, 11), 224 (97), 211 ($M^+-NCC_6H_4CHCH_2$, 100), 108 ($C_6H_4S^+$, 10). IR (KBr): $\tilde{\nu}$ 3053 cm^{-1}, 2220, 1612, 1598, 1575, 1478, 1451, 1320, 1259, 1244, 1214, 1064, 1024, 834, 796, 760, 744, 688, 559, 475. UV/Vis ($CHCl_3$): λ_{max} (ε) 264 nm (18,200), 336 (4500). Anal. calcd for $C_{22}H_{16}N_2S$ (340.4): C 77.62, H 4.74, N 8.23, S 9.42. Found: C 77.45, H 4.81, N 8.17, S 9.49.

3.1.6. 4-Phenyl-2-(4-pyridyl)-2,3-dihydro-benzo[*b*][1,4]thiazepine (7f). According to the standard procedure and after chromatography on silica gel (petrolether/ethyl acetate 4:1) and after recrystallization from ethanol **7f** was isolated as brown resin. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.72 (dd, J=9.5, 13.7 Hz, 1H), 2.90 (dd, J=5.4, 13.8 Hz, 1H), 4.24 (dd, J=5.4, 9.6 Hz, 1H), 7.09–7.11 (m, 2H), 7.18–7.59 (m, 7H), 7.80–8.11 (m, 2H), 8.56 (br, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 36.3 (CH_2), 73.3 (CH), 119.8 ($C_{quat.}$), 127.3 (CH), 127.8 (CH), 128.3 (CH), 128.5 (CH), 129.1 (CH), 129.2 (CH), 129.7 (CH), 131.5 (CH), 137.3 ($C_{quat.}$), 143.0 ($C_{quat.}$), 147.6 ($C_{quat.}$), 149.0 (CH), 158.1 ($C_{quat.}$). EI MS (70 eV, *m/z* (%)) 316 (M^+, 2), 224 (100). EI HRMS (70eV, *m/z*) calcd for $C_{20}H_{16}N_2S$: 316.1034, found: 316.1047. IR (KBr): $\tilde{\nu}$ 2924 cm^{-1}, 1635, 1597, 1467, 1445, 1375, 1254, 1218, 1179, 1072, 992, 761, 690. UV/Vis ($CHCl_3$): λ_{max} (ε) 260 (15,800).

3.1.7. 2-(4-Nitrophenyl)-4-phenyl-2,3-dihydro-benzo[*b*][1,4]diazepine (9a). According to the standard procedure and after chromatography on silica gel (petrolether/ethyl acetate 5:1) and after recrystallization from ethanol **9a** was isolated as orange crystals, mp 189–190 °C (189–190 °C).[21] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.10 (dd, J=7.1, 13.5 Hz, 1H), 3.23 (dd, J=4.4, 13.5 Hz, 1H), 3.78 (br, 1H, NH), 5.41 (dd, J=4.4, 7.0 Hz, 1H), 6.84–6.87 (m, 1H), 7.07–7.11 (m, 2H), 7.29–7.38 (m, 4H), 7.61 (d, J=8.6 Hz, 2H), 7.70–7.73 (m, 2H), 8.14 (d, J=8.7 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 36.6 (CH_2), 70.5 (CH), 120.7 (CH), 122.2 (CH), 124.0 (CH), 126.7 (CH), 126.8 (CH), 127.1 (CH), 128.4 (CH), 128.7 (CH), 130.4 (CH), 137.7 ($C_{quat.}$), 138.7 ($C_{quat.}$), 139.8 ($C_{quat.}$), 147.5 ($C_{quat.}$), 151.5 ($C_{quat.}$), 166.8 ($C_{quat.}$).

3.1.8. 4-(4-Methoxyphenyl)-2-(4-nitrophenyl)-2,3-dihydro-benzo[*b*][1,4]diazepine (9b). According to the standard procedure and after chromatography on silica gel (petrolether/ethyl acetate 3:1) and after recrystallization from ethanol **9b** was isolated as a yellow solid, mp 186–187 °C (186–187 °C).[22] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.05 (dd, J=6.8, 13.5 Hz, 1H), 3.19 (dd, J=4.7, 13.5 Hz, 1H), 3.82 (s, 3H), 5.40 (dd, J=4.7, 6.5 Hz, 1H), 6.82 (d, J=8.9 Hz, 2H), 6.83–6.86 (m, 1H), 7.05–7.09 (m, 2H), 7.31–7.34 (m, 1H), 7.62 (d, J=8.7 Hz, 2H), 7.67 (d, J=8.9 Hz, 2H), 8.15 (d, J=8.7 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 36.2 (CH_2), 55.4 (CH_3), 70.7 (CH), 113.3 ($C_{quat.}$), 113.7 (CH), 120.8 (CH), 122.3 (CH), 124.0 (CH), 126.2 (CH), 127.1 (CH), 128.5 (CH), 128.6 (CH), 131.3 ($C_{quat.}$), 137.6 ($C_{quat.}$), 147.5 ($C_{quat.}$), 151.6 ($C_{quat.}$), 161.6 ($C_{quat.}$), 166.3 ($C_{quat.}$). EI MS (70 eV, *m/z* (%)): 373 (M^+, 85), 358 (M^+-CH_3, 45), 266 ($M^+-C_6H_4OMe$, 20), 224 ($M^+-O_2NC_6H_4CHCH_2$, 100), 209 ($C_6H_4N{=}CC_6H_4OMe^+$, 24), 181 (24), 133 ($MeOC_6H_4CCH_2^+$, 32), 119 ($MeOC_6H_4C^+$, 19), 77 (Ph^+, 13). IR (KBr): $\tilde{\nu}$ 3372 cm^{-1}, 3071, 2836, 1604, 1570, 1514, 1479, 1417, 1346, 1288, 1251, 1175, 1108, 1038, 855, 833, 756, 699, 628, 531. UV/Vis ($CHCl_3$): λ_{max} (ε) 275 nm (26,200), 351 (8800). Anal. calcd for $C_{22}H_{19}N_3O_3$ (373.4): C 70.76, H 5.13, N 11.25. Found: C 70.58, H 5.19, N 11.40.

3.1.9. 2-(4-Cyanophenyl)-4-phenyl-2,3-dihydro-benzo[*b*][1,4]diazepine (9c). According to the standard procedure and after chromatography on silica gel (petrolether/ethyl acetate 3:1) and after recrystallization from isopropanol **9c** was isolated as a beige solid, mp 183 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.06 (dd, J=7.2, 13.4 Hz, 1H), 3.20 (dd, J=4.4, 13.4 Hz, 1H), 3.74 (br, 1H), 5.34 (dd, J=4.4, 7.2 Hz, 1H), 6.82–6.85 (m, 1H), 7.03–7.11 (m, 2H), 7.29–7.41 (m, 4H), 7.52–7.59 (m, 4H), 7.68–7.71 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 36.7 (CH_2), 70.6 (CH), 111.7 ($C_{quat.}$), 118.6 ($C_{quat.}$), 120.6 (CH), 122.0 (CH), 126.6 (CH), 126.8 (CH), 126.9 (CH), 128.4 (CH), 128.9 (CH), 130.4 (CH), 132.6 (CH), 137.7 ($C_{quat.}$), 138.7 ($C_{quat.}$), 149.6 ($C_{quat.}$), 155.9 ($C_{quat.}$), 166.9 ($C_{quat.}$). EI MS (70 eV, *m/z* (%)): 323 (M^+, 62), 308 (M^+-NH, 23), 246 ($M^+-C_6H_5$, 29), 221 ($M^+-NCC_6H_4$, 28), 194 ($M^+-NCC_6H_4CHCH_2$, 100). IR (KBr): $\tilde{\nu}$ 3058 cm^{-1}, 2227, 1608, 1498, 1475, 1448, 1350, 1330, 1298, 1249, 1230, 1113, 1099, 833, 761, 693, 566. UV/Vis ($CHCl_3$): λ_{max} (ε) 242 nm (23,022), 260 (19,200), 362 (4800). Anal. calcd for $C_{22}H_{17}N_3$ (323.4): C 81.71, H 5.30, N 12.99. Found: C 81.42, H 5.24, N 12.83.

3.1.10. 2-(2-Cyanophenyl)-4-phenyl-2,3-dihydro-benzo[*b*][1,4]diazepine (9d). According to the standard procedure and after chromatography on silica gel (petrolether/ethyl acetate 4:1) and after recrystallization from ethanol **9d** was isolated as a yellow orange solid, mp 161–163 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.19 (dd, J=6.4, 13.5 Hz, 1H), 3.27 (dd, J=4.6, 13.5 Hz, 1H), 3.81 (br, 1H, NH), 5.84 (m, 1H), 6.89 (d, J=6.8 Hz, 1H), 7.04–7.12 (m, 2H), 7.26–7.36 (m, 5H), 7.42–7.47 (m, 1H), 7.63 (d, J=7.6 Hz, 1H), 7.72 (d, J=6.8 Hz, 2H), 7.87 (d, J=8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 35.7 (CH_2), 68.6 (CH), 109.7 ($C_{quat.}$), 117.3 ($C_{quat.}$), 120.7 (CH), 122.0 (CH), 126.6 (CH), 126.8 (CH), 127.4 (CH), 128.1 (CH), 128.3 (CH), 128.9 (CH), 130.2 (CH), 132.9 (CH), 133.2 (CH), 138.0 ($C_{quat.}$), 138.7 ($C_{quat.}$), 139.7 ($C_{quat.}$), 148.4 ($C_{quat.}$), 166.9 ($C_{quat.}$). EI MS (70 eV, *m/z* (%)): 323 (M^+, 25), 320 (M^+-H_2–H, 100), 308 (M^+-NH, 14), 246 (M^+-Ph, 22), 219 ($M^+-C_6H_4N_2$, 57), 194 ($M^+-NCC_6H_4CHCH_2$, 53). IR (KBr): $\tilde{\nu}$ 3064 cm^{-1}, 2222, 1612, 1573, 1478, 1448, 1335, 1264, 1108, 858, 764, 693, 528. UV/Vis ($CHCl_3$): λ_{max} (ε) 263 nm (20,300), 362 (27,900). Anal. calcd for $C_{22}H_{17}N_3$ (323.4): C 81.71, H 5.30, N 12.99. Found: C 81.71, H 5.31, N 12.88.

3.1.11. 4-Phenyl-2-(2-thiazolyl)-2,3-dihydro-benzo[*b*][1,4]diazepine (9e). According to the standard procedure and after chromatography on silica gel (petrolether/ethyl acetate 2:1) and after crystallization from isopropanol **9e** was isolated as yellow resin. ^{1}H NMR ($CDCl_3$,

300 MHz): δ 3.29 (dd, J=4.8, 13.9 Hz, 1H), 3.30 (dd, J=5.7, 13.4 Hz, 1H), 5.67–5.71 (m, 1H), 6.87–6.90 (m, 1H), 7.03–7.13 (m, 3H), 7.25–7.34 (m, 4H), 7.70–7.75 (m, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 35.1 (CH_2), 69.5 (CH), 119.1 (CH), 121.0 (CH), 122.5 (CH), 126.1 (CH), 126.6 (CH), 128.0 (CH), 128.1 (CH), 130.0 (CH), 136.7 ($C_{quat.}$), 138.4 ($C_{quat.}$), 140.6 ($C_{quat.}$), 142.6 (CH), 167.1 ($C_{quat.}$), 175.1 ($C_{quat.}$). EI MS (70 eV, *m/z* (%)): 305 (M^+, 96), 303 ($M^+ - H_2$, 30), 228 ($M^+ - C_6H_5$, 20), 221 (M^+ − thiazolyl, 35) 194 (M^+ − thiazolylCHCH$_2$, 100), 179 ($C_6H_5C{=}NC_6H_4^+$, 22), 84 (thiazolyl$^+$, 69), 77 ($C_6H_5^+$, 14). EI HRMS (70eV, *m/z*) calcd for $C_{18}H_{15}N_3S$: 305.0993, found: 305.0988. IR (KBr): $\tilde{\nu}$ 3057 cm^{-1}, 1609, 1569, 1496, 1473, 1445, 1345, 1314, 1293, 1256, 1226, 1180, 1139, 1111, 1054, 769, 753, 729, 691. UV/Vis ($CHCl_3$): λ_{max} (ε) 254 nm (18,500), 352 (5200). Anal. calcd for $C_{18}H_{15}N_3S$ (305.4): C 70.79, H 4.95, N 13.76, S 10.50. Found: C 70.47, H 5.21, N 12.97, S 10.19.

Acknowledgements

The financial support of the Deutsche Forschungsgemeinschaft (Graduiertenkolleg 850), Fonds der Chemischen Industrie and the Dr.-Otto-Röhm Gedächtnisstiftung is gratefully acknowledged. The authors wish to thank Dr. Kurt Polborn for the X-ray structure analysis of compound **9b**.

References and notes

1. (a) Ugi, I.; Dömling, A.; Werner, B. *J. Heterocycl. Chem.* **2000**, *37*, 647–658. (b) Posner, G. H. *Chem. Rev.* **1986**, *86*, 831–844. (c) Weber, L.; Illgen, K.; Almstetter, M. *Synlett* **1999**, 366–374.
2. For recent excellent reviews on transition metal assisted sequential transformations and domino processes, see e.g. (a) Balme, G.; Bossharth, E.; Monteiro, N. *Eur. J. Org. Chem.* **2003**, 4101–4111. (b) Battistuzzi, G.; Cacchi, S.; Fabrizi, G. *Eur. J. Org. Chem.* **2002**, 2671–2681. (c) Negishi, E.-I.; Copéret, C.; Ma, S.; Liou, S.-Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 365–393. (d) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136.
3. Kobayashi, S. *Chem. Soc. Rev.* **1999**, *28*, 1–15.
4. Müller, T. J. J.; Ansorge, M.; Aktah, D. *Angew. Chem., Int. Ed.* **2000**, *39*, 1253–1256.
5. Müller, T. J. J.; Braun, R.; Ansorge, M. *Org. Lett.* **2000**, *2*, 1967–1970.
6. Braun, R. U.; Zeitler, K.; Müller, T. J. J. *Org. Lett.* **2000**, *2*, 4181–4184.
7. Braun, R. U.; Zeitler, K.; Müller, T. J. J. *Org. Lett.* **2001**, *3*, 3297–3330.
8. Yehia, N. A. M.; Polborn, K.; Müller, T. J. J. *Tetrahedron Lett.* **2002**, *43*, 6907–6910.
9. For reviews, see e.g., (a) Archer, G. A.; Sternbach, L. H. *Chem. Rev.* **1968**, *68*, 747–784. (b) Popp, F. D.; Noble, A. C. *Adv. Heterocycl. Chem.* **1967**, *8*, 21–82. (c) Sternbach, L. H. *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 34–43. (d) Vanderheyden, J. L.; Vanderheyden, J. E. *J. Pharm. Belg.* **1981**, *36*, 354–364. (e) Jones, G. R.; Singer, P. P. *Adv. Anal. Toxicol.* **1989**, *2*, 1–69. (f) Bremner, J. B. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 9, pp 183–189.
10. For synthetic and pharmacological studies, see e.g., (a) Zellou, A.; Cherrah, Y.; Hassar, M.; Essassi, E.-M. *Ann. Pharm. Fr.* **1998**, *56*, 169–174. (b) Savelli, F.; Boido, A.; Mule, A.; Piu, L.; Alamanni, M. C.; Pirisino, G.; Satta, M.; Peana, A. *Farmaco* **1989**, *44*, 125–140. (c) Nawojski, A.; Nawrocka, W.; Liszkiewicz, H. *Pol. J. Pharmacol. Pharm.* **1985**, *37*, 69–72. (d) Wilimowski, M.; Orzechowsa-Juzwenko, K.; Barczynska, J.; Kedzierska-Gozdzik, L.; Witkowska, M.; Wojewodzki, W.; Dus, E.; Plawiak, T.; Gryska, J.; Maska, H. *Pol. J. Pharmacol. Pharm.* **1983**, *35*, 89–102. (e) Srivastava, V. K.; Satsangi, R. K.; Kishore, K. *Arzneim.-Forsch.* **1982**, *32*, 1512–1514.
11. For synthetic and pharmacological studies, see e.g., (a) Parker, K. A.; Dermatakis, A. *J. Org. Chem.* **1997**, *62*, 4164–4167. (b) Hargrave, K. D.; Schmidt, G.; Engel, W.; Austel, V. Patent Application: US 91-650141 19910204. Patent Priority: US 89-340937 19890420; US 89-372728 19890628; US 89-438922 19891117; US 90-600554 19901019.
12. (a) Mane, R. A.; Ingle, D. B. *Indian J. Chem., Sect. B* **1982**, *21B*, 973–974. (b) Jadhav, K. P.; Ingle, D. B. *Indian J. Chem., Sect. B* **1983**, *22B*, 180–182. (c) Attia, A.; Abdel-Salam, O. I.; Abo-Ghalia, M. H.; Amr, A. E. *Egypt. J. Chem.* **1995**, *38*, 543–554.
13. Reddy, R. J.; Ashok, D.; Sarma, P. N. *Indian J. Chem., Sect. B* **1993**, *32B*, 404–406.
14. Satyanarayana, K.; Rao, M. N. A. *Indian J. Pharm. Sci.* **1993**, *55*, 230–233.
15. De Sarro, G.; Chimirri, A.; De Sarro, A.; Gitto, R.; Grasso, S.; Zappala, M. *Eur. J. Med. Chem.* **1995**, *30*, 925–929.
16. (a) Swellem, R. H.; Allam, Y. A.; Nawwar, G. A. M. *Z. Naturforsch. B* **1999**, *54*, 1197–1201. (b) Dubey, P. K.; Naidu, A.; Kumar, C. R.; Reddy, P. V. V. P. *Indian J. Chem. Sect. B* **2003**, *42*, 1701–1705.
17. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-246148 (**9b**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223/336-033; e-mail: deposit@ccdc.cam.ac.uk).
18. *Organikum*, 20th ed.; Becker, H. G. O.; Berger, W.; Domschke, G.; Fanghänel, E.; Faust, J.; Fischer, M.; Gentz, F.; Gewald, K.; Gluch, R.; Mayer, R.; Müller, K.; Pavel, D.; Schmidt, H.; Schollberg, K.; Schwetlick, K.; Seiler, E.; Zeppenfeld, G.; Johann Ambrosius Barth Verlag: Heidelberg, Leipzig, 1996.
19. (a) Brandsma, L. *Preparative Acetylenic Chemistry*; Elsevier: Amsterdam, 1988. (b) Krause, N.; Seebach, D. *Chem. Ber.* **1987**, 120, 1845–1851.
20. Levai, A.; Bognar, R. *Acta Chim. Acad. Sci. Hung.* **1976**, *88*, 293–297.
21. Orlov, V. D.; Kolos, N. N.; Yaremenko, F. G.; Lavrushin, V. F. *Chem. Heterocycl. Compd. (Engl. Transl.)* **1980**, *16*, 547–550.
22. Orlov, V. D.; Kolos, N. N.; Abramov, A. F. *Chem. Heterocycl. Compd. (Engl. Transl.)* **1984**, *20*, 1370–1374.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 60 (2004) 9471–9478

Biphenyl macrolactams in anion complexation. Selective naked-eye fluoride recognition

Ana M. Costero,[a,*] M. José Bañuls,[a] M. José Aurell,[a] Michael D. Ward[b] and Stephen Argent[b]

[a]*Departamento de Química Orgánica, Universitat de València, Dr. Moliner 50, 46100 Bujassot, Valencia, Spain*
[b]*Department of Chemistry, University of Sheffield, UK*

Received 6 April 2004; revised 27 July 2004; accepted 29 July 2004

Abstract—Two colorimetric anion sensors **1** and **2** allow for the selective differentiation of fluoride in the presence of other anions. Two different types of species have been observed in the complexation process, one of them is a co-ordination complex and the other is a salt generated by ligand deprotonation. The deprotonation reaction induces a conformational change, giving rise to a symmetrical species. This species is responsible for colour development. Ligand **3** has a similar structure and does not give rise to any colour modification due to presence of the dimethylamino groups in the biphenyl moiety. The X-ray structure of ligand **2** is also reported and compared with that of ligand **1**, that had been previously described.
© 2004 Elsevier Ltd. All rights reserved.

The molecular recognition of anions with synthetic receptors is an expanding field of research. In view of the role played by anionic species in chemical as well as in biological processes, their binding by synthetic receptor molecules is of widespread interest.[1] An enormous number of receptors have been synthesised, some of them quite successfully, for the halide anions specifically, including a wide variety of conformation, binding sites, geometry and interactions types.[2] From among all the described receptors only a few of them are able to act as a colorimetric sensor for halide anions. The first colorimetric recognition of a fluoride anion was reported by Sessler et al. by using pyrrolic systems.[3,4] In addition, colorimetric fluoride sensing with a boron-containing π-electron system[5,6] and polythiophene derivatives have been described.[7] Finally, several colorimetric sensors have also been described for halide anions containing di- or polyamide groups,[8] urea or tiourea derivatives[9] or related functional groups. In each case, different explanations to the observed colour have been proposed. Thus, both Gale[10] and Kruger[11] affirm that the basic character of the F^- gives rise to deprotonation reactions in the ligands, where the new generated species are responsible for the observed colour. By contrast, Piatek[12] tentatively ascribed the observed changes to the charge transfer interactions between the amide bound anion and the electron-deficient 3,5-dinitrobenzene moiety present in the ligand. Finally, Sessler proposes a combination of electronic and conformational effects that modify the optical characteristics of the ligand.

We now report the use of two amide-based macrocyclic anion sensors **1** and **2** in complexation of anion species and the selective colorimetric sensing of fluoride (Chart 1). The described compounds include two aromatic systems: a 4,4′-dinitrobiphenyl moiety and a pyridine ring, and both aromatic systems are connected through chains containing two amide groups. In addition, **1** and **2** show a different cavity sizes in order to study the influence of this factor. Ligand **3** has also been used in complexation experiments to determine the influence of the nitro groups in the interaction with the studied anions.

1. Synthesis and structural studies

The synthesis of ligands **1** and **3** together with their cation complexation ability have been previously described.[13] Ligand **2** was prepared by a reaction of compound **4** with the dichloride of 4,4′-dinitro-2,2′-diphenic acid (Scheme 1). The open chain **4** was prepared with 2,6-pyridinediacyl chloride and 2-(2-aminoethoxy)ethanol in dry dichloromethane in the presence of anhydrous potassium carbonate.[14]

Ligand **2** has been studied by X-ray diffraction (Fig. 1). A monocrystal suitable for X-ray studies was obtained by recrystallization in acetonitrile. The carbonyl groups of the amide systems are slightly twisted with respect to the

Keywords: Sensor; Anion; Bipehnyl; Fluoride; Colorimetric.
* Corresponding author. Tel.: +34-963544410; fax: +34-963543152; e-mail: ana.costero@uv.es

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.07.088

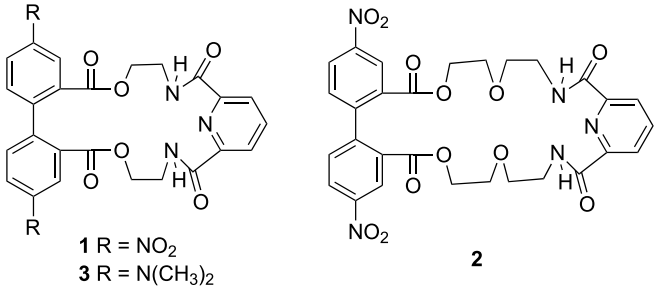
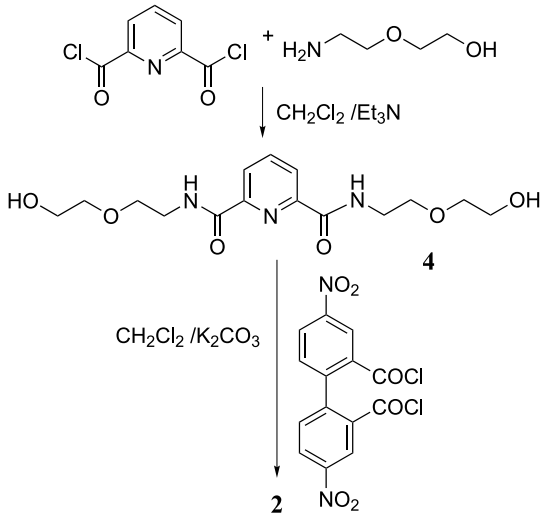


Chart 1.



Scheme 1.

pyridine ring lying on the opposite sides of the mean plane of the pyridine ring (C(33)–C(32)–C(49)–O(49) = −9.07° and C(35)–C(36)–C(59)–O(59) = 8.30°. By contrast, the carbonyl groups of the ester systems are largely twisted in relation to the corresponding biphenyl aromatic ring (C(26)–C(21)–C(51)–O(51) = 37.89° and C(16)–C(11)–C(41)–O(41) = 153.19°). The carbonyl oxygen of one ester points inward with regard to the cavity centre and the other points outward. The ligand crystallizes with one molecule of water binding by hydrogen bonds to both ether oxygen and both NH groups. Additionally, hydrogen bonds are also observed between N–H_{amide} and N of the pyridine ring (Table 1).

Table 1. Hydrogen bond geometry for $2 \cdot H_2O$

D	H–A	*D* (Å)
O(100)	H(48)N(48)	2.24
O(100)	H(58)N(58)	2.12
N(31)	H(48)N(48)	2.25
N(31)	H(58)N(58)	2.35
O(45)	H(101)O(100)	2.21
O(55)	H(102)O(100)	1.87

The biphenyl unit shows a dihedral angle between the aromatic rings 103.28°, similar to that observed in other related compounds,[15] but clearly higher than the value shown by ligand **1**.[13]

2. Complexation experiments

Anion complexation experiments were carried out, where a first step was conducted in acetonitrile by an addition of 10 equiv of the corresponding anion (F^-, Cl^-, Br^-, I^-, $H_2PO_4^-$ and HSO_4^- added as their tetrabutylammonium salts) to 1×10^{-2} M solutions of receptors **1** and **2**. The most remarkable effect was the selective colour change in the presence of fluoride, changing from colourless to orange due to the appearance of a broad new band centred at ca. 450 and 479 nm for **1** and **2**, respectively. Competitive assays

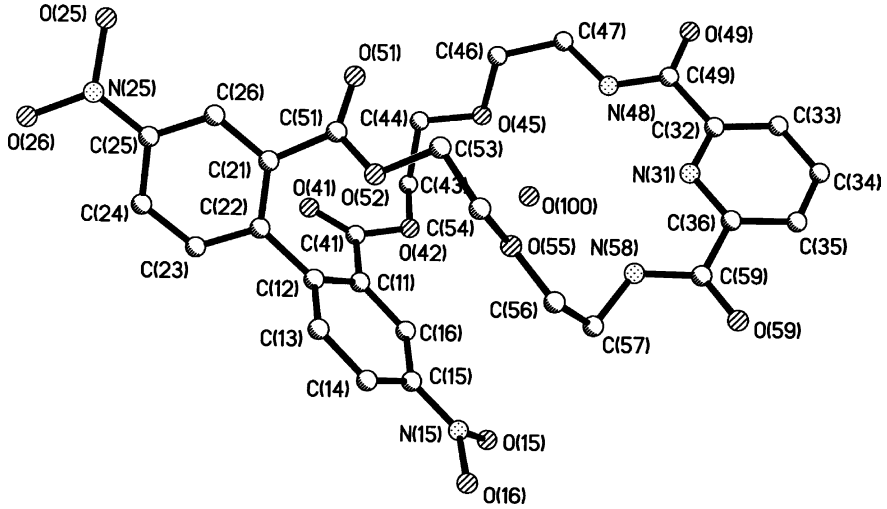


Figure 1. Molecular structure with crystallographic numbering scheme for $2 \cdot H_2O$.

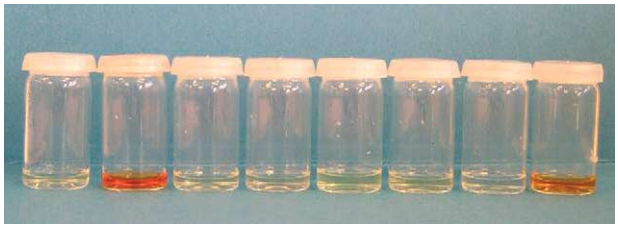


Figure 2. Colour changes observed in CH_3CN solutions (1×10^{-2} M). From left to right (a) free ligand **1**, (b) **1**+F^-, (c) **1**+Cl^-, (d) **1**+Br^-, (e) **1**+I^-, (f)**1**+HSO_4^-, (g) **1**+$H_2PO_4^-$, (h) **1**+F^-+Cl^-+Br^-+I^- (10 equiv of tetrabuthylammonium salts for each anion were used).

indicated that the systems were selective to fluoride in the presence of the other halides. Thus, an addition of a mixture of Cl^-, Br^-, I^-, and F^- to acetonitrile solutions of **1** and **2** resulted in a UV–vis spectra similar to those obtained for the F^- anion (Fig. 2).

Proton NMR studies were performed in order to assess the affinity of the receptors for anions. Results with ligand **1** demonstrated that among all the studied anions only fluoride gave rise to observable interactions and most interestingly, two different types of species were observed, depending on the experimental conditions. One of these complexes is a co-ordination complex that shows two different sets of signals for the hydrogen atoms of the biphenyl moiety. The other species is a 1:2 system; it is a symmetrical species and it is also responsible for the colour development. Additionally, this last complex is generated from the co-ordination complex, where the transformation is a function of time, temperature and anion concentration. In any case, the formation of both species at room temperature is a slow process, as can be concluded by observing the results presented in Figure 3.

The complexation process was studied by ^{1}H NMR and the stoichiometry of the complex was established by using the molar ratio method[16] under thermodynamic conditions. This stoichiometry was confirmed by the peak at 566 in the negative FAB MS spectrum. The obtained data suggest a constant value higher than 10^5 M^{-1}, calculated by using the Climp 2.0 program.[17] In addition, structural studies in solution were carried out using NMR. Thus, a different set of signals was observed for each aromatic ring, showing that some hydrogen atoms experiment a clear shielding effect due to the proximity of the fluoride (Table 2). The strong shielding observed in the H_b, hydrogen of one of the biphenyl rings seems to indicate some CH-anion interaction

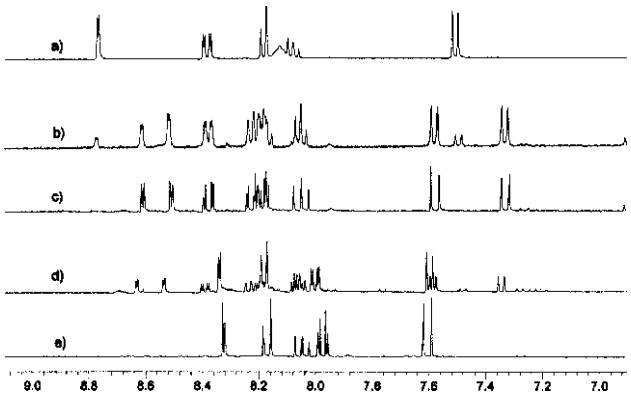


Figure 3. Aromatic zone of ^{1}H NMR spectrum of **1** in CD_3CN in the presence of TBAF (5 equiv) (a) free ligand 1, (b) fresh prepared, (c) after 36 h, (d) after 3 days, (e) after 7 days.

due to the strong electron withdrawing effect of the nitro group present in the biphenyl system.[18–20] In addition, a shift was observed in the two NH hydrogen atoms; one shifted from 8.2 to 10.20 ppm, while the other shifted from 8.2 to 10.65 ppm, due to the hydrogen bond interactions. Finally, NOESY experiments carried out with this complex showed a NOE between the H_a proton of the phenyl ring less affected by the anion, and the H_d of the pyridine moiety. For all these reasons it is possible to propose the geometry for this complex, which is shown in Figure 4.

When more than one TBAF equivalent was added, the amount of the co-ordination complex decreased and a deprotonation of the amide group was observed. This reaction is complete when two TBAF equivalents have been added, which might suggest the formation of the bifluoride (HF_2^-).[11] The participation of bifluoride in this reaction is in accordance with the ^{19}F NMR spectrum that shows a resonance a $\delta=146.93$ ppm.[21,22]

The obtained salt is responsible for the colour and it is a symmetrical species with both aromatic rings, equivalents from the NMR point of view. In addition, no signals corresponding to the amide hydrogen were observed. This fact can be related to the fast interchange produce by the hydrogen bound between both amidic nitrogens. Furthermore, H_a and H_b experiment a clear shielding effect (from 8.77 to 8.39 ppm, respectively, in the free ligand to 8.31 and 7.97 ppm, respectively, in the complex). Finally, clear NOE was observed between the –CH_2–N protons and H_a, that is in accordance with one structure, like that shown in Figure 5.

Table 2. Value of the chemical shifts for the biphenyl and NH hydrogen in the presence of different tetrabuthylammonium salts

	$\delta(H_a)$	$\Delta\delta$	$\delta(H_b)$	$\Delta\delta$	$\delta(H_c)$	$\Delta\delta$	δ(NH)	$\Delta\delta$
1	8.77		8.39		7.52		8.2	
1·TBAF	8.66	−0.11	8.35	−0.04	7.49	−0.03	10.20	2.00
	8.60	−0.17	8.09	−0.30	7.30	−0.22	10.65	2.45
1$^-$·TBA^+	8.31	−0.46	7.97	−0.42	7.60	0.08	—	—
1·TBAAcO	8.60	−0.17	8.35	−0.04	7.50	−0.02	10.20	2.00
	8.57	−0.20	8.10	−0.29	7.29	−0.23	10.64	2.45
1·TBAt-BuO	8.61	−0.16	8.35	−0.04	7.58	0.06	10.15	1.95
	8.52	−0.25	8.20	−0.19	7.35	−0.17	10.57	2.37
1·TBAOH	8.61	−0.16	8.29	−0.06	7.58	0.06	—	—
	8.53	−0.24	8.19	−0.16	7.34	−0.18	—	—
1$^-$·TBA^+	8.44	−0.33	8.01	−0.34	7.49	−0.03	—	—

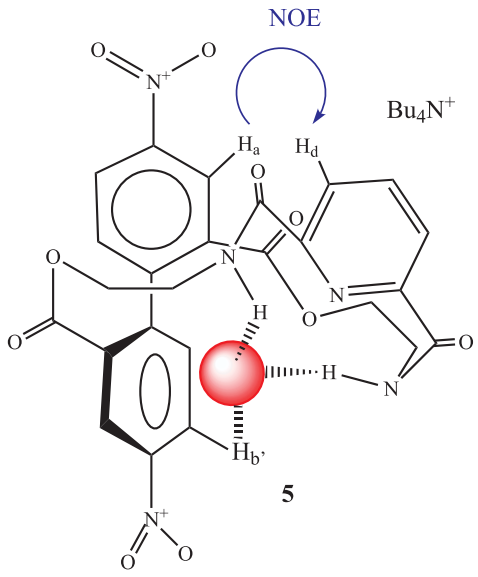


Figure 4. Structure of **1**·TBAF (**5**).

Colour development can be due to the formation of an internal charge transfer (ICT).[11] This proposal is reinforced by the behaviour of ligand **3** in which the presence of the dimethylamino groups, rather than the nitro groups, preclude the formation of this type of charge transfer process, and it is unable to develop colour after anion addition.

Kinetic studies of this process were carried out and the following kinetic equations could be established:

$$\mathbf{1} + \mathrm{TBAF} \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} [\mathbf{1}\cdot\mathrm{TBAF}] \xrightarrow{k_2} [\mathbf{1}^- \cdot \mathrm{TBA}^+] + \mathrm{TBAHF_2}$$

$$V_1 = k_1[\mathbf{1}][\mathrm{TBAF}];\ \ k_1 = 15.29\ \mathrm{M}^{-1}\ \mathrm{min}^{-1}$$

$$V_2 = k_2[\mathbf{1}\cdot\mathrm{TBAF}][\mathrm{TBAF}];\ \ k_2 = 6\times10^{-3}\ \mathrm{M}^{-1}\ \mathrm{min}^{-1}$$

Additional experiments were carried out using TBA (*t*-BuO), TBAAcO and TBAOH to determine the influence of the anion basicity on complexation. With the two first anions, no colour was developed and the proton NMR spectra showed the formation of the co-ordination complex with a similar geometry to that described in the fluoride complexation (Table 2). These complexes did not experiment any modification after a long time (they were studied after 24 h, a week and a month), even in the presence of large amounts of the anion. One explanation to this behaviour can be found in the steric hindrance that preclude these anions as being close enough to the NH groups, which gives rise to the deprotonation reaction. When TBAOH was used in the complexation process, an instantaneous colour was developed. ^{1}H NMR experiments showed that in addition to the co-ordination complex and the deprotonated species, a small amount of the partial hydrolysed compound was obtained.

Ligand **2** showed a similar behaviour to that described for ligand **1**. Thus, the co-ordination complexes were formed in the presence of F^- in CH_3CN (log K=1.5) in addition to the deprotonate species, and colour developed as a consequence of this later reaction. On the other hand, the co-ordination complex shows ^{1}H NMR data similar to those observed for ligand **1**, which allows for a similar geometry with the fluoride anion, close to that of the nitrobenzene ring, to be proposed. However, several differences were also observed: (a) the colour development was almost instantaneous, where the rate constants for this reaction were k_1= 115 $\mathrm{M}^{-1}\ \mathrm{min}^{-1}$ and $k_2 = 3.5\times10^{-3}\ \mathrm{M}^{-1}\ \mathrm{min}^{-1}$; (b) anions such as Cl^-, $H_2PO_4^-$ and AcO^- give rise to co-ordination complexes with a different geometry. With these anions, the most affected moiety was the pyridine ring, indicating that the anion remains at a distance from the biphenyl unit after the corresponding hydrogen bound was formed (Fig. 6).

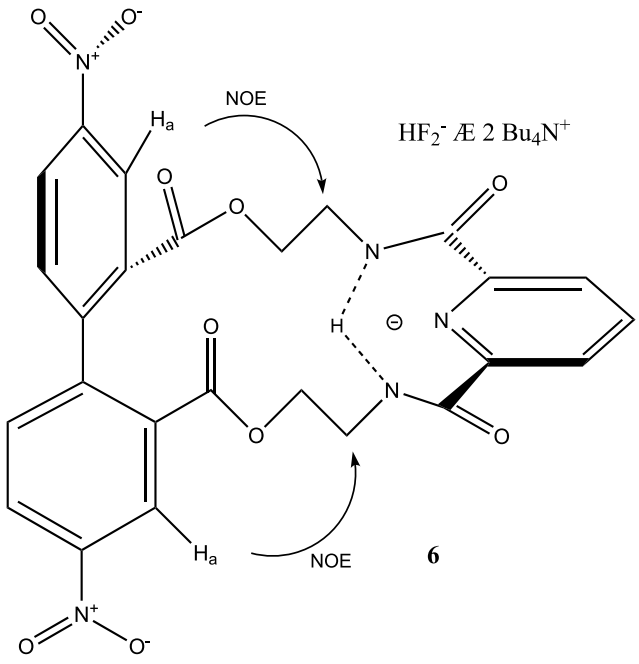


Figure 5. Structure of $\mathbf{1}^-\cdot\mathrm{TBA}^+$ (**6**).

The ability of ligand **2** to form complexes with these anions can be related to the cavity size which is larger here than in ligand **1**, and allowed the anion to be close enough to the amide group in order to form hydrogen bonds. In addition, ^{1}H NMR experiments showed that the anions in the co-ordination complexes are now closer to the pyridine than to the nitrobiphenyl moiety. This fact is reflected in the shift observed in the resonance values of the aromatic hydrogen (see Table 3).

The behaviour of ligands **1** and **2** in the presence of anions was studied in different solvents. Thus, in DMSO similar results were observed with both ligands: ligand **1** and **2** show an orange–violet colour in the presence of fluoride anion. As expected and due to the mechanism that is responsible for developing colour, the presence of appreciable quantities of water in the solution precludes the generation of colour due to the protonation of the ligand salt.

3. Conclusions

Two macrolactams derived from biphenyl have been

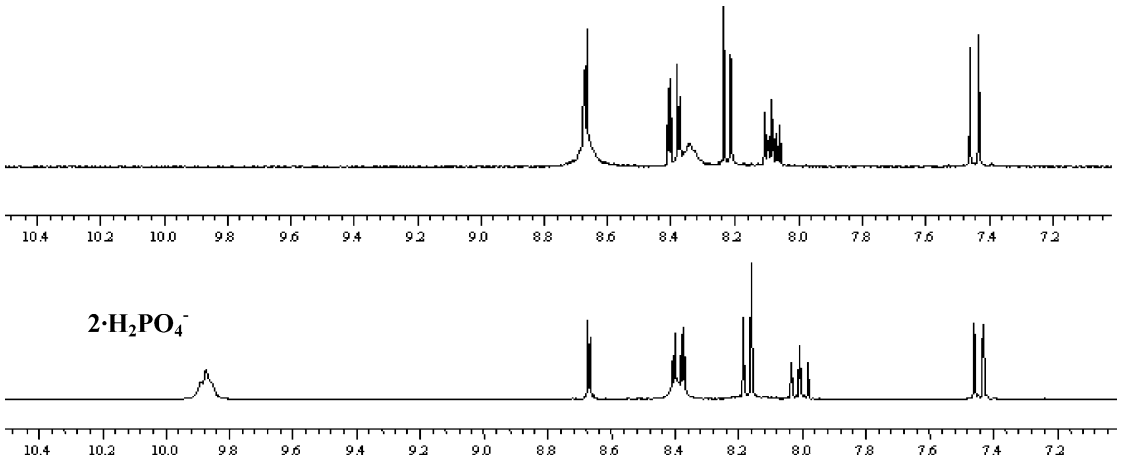


Figure 6. Aromatic zone of ^{1}H NMR spectrum of **2** in CD_3CN (a) free ligand (b) in the presence of $TBAH_2PO_4$ (5 equiv).

Table 3. Value of the chemical shifts for the biphenyl, pyridine and NH hydrogen in the presence of different tetrabuthylammonium salts

	$\delta(H_a)$	$\delta(H_b)$	$\delta(H_c)$	$\delta(H_d)$	$\delta(H_{d'})$	$\delta(H_e)$	δ(NH)
2	8.71	8.42	7.49	8.13	8.11	8.27	8.38
2·TBAF	8.84	8.29	7.44	8.16	8.16	8.16	10.65
	8.49	8.18	7.27	−7.99	−7.99	−7.99	10.25
$\mathbf{2}^-\cdot TBA^+$	8.31	7.98	7.60	8.11	8.11	8.0	—
2·TBACl	8.71	8.66	7.47	8.21	8.21	8.06	9.12
							10.00
2·TBA H_2PO_4	8.70	8.41	7.47	8.11	8.02	8.19	8.70
							10.62
2·TBA AcO	8.71	8.42	7.49	8.08	8.02	8.20	9.94
							10.43

studied in anion complexation. Ligands **1** and **2** develop colour in the presence of fluoride, probably due a charge-transfer complex. For this reason the colour disappears in the presence of appreciable quantities of water. The response is selective for this anion even in the presence of other anions with a similar basic character or other halides. Ligand **1** is able to form co-ordination complexes with F^-, AcO^-, *t*-BuO^- and OH^-, and all of them show a similar geometry. By contrast, ligand **2** gives rise to a different geometry with F^- than it does with Cl^-, $H_2PO_4^-$ and AcO^-. The different behaviour showed by ligands **1** and **2** in front of Cl^- and $H_2PO_4^-$ can not be related to the functional groups present in these ligands but others factors such as size of the cavity, flexibility of the systems or solvation effects that can be different for both ligands. Finally, ligand **3**, does not develop colour because the presence of the dimethylamino groups precludes the formation of the coloured complex. On the other hand, no complexation with the larger anions was observed due to the size of its cavity.

4. Experimental

4.1. General methods

All commercially available reagents were used without further purification. Water sensitive reactions were performed under argon. Column chromatography was carried out on SDS activated neutral aluminium oxide (0.05–0.2 mm; activity degree 1). IR spectra were recorded on a Perkin–Elmer 1750 FT-IR and a Bruker Equinox 55 FT-IR. NMR spectra were recorded with Bruker Avance 300/500 and Varian Unity-300/400 spectrometers. Chemical shifts are reported in parts per million downfield from TMS. Spectra were referenced to residual undeuterated solvent. High resolution mass spectra were taken with a Fisons VG-AUTOSPEC and those using the eletrospray ionizing technique were recorded on an HPLC-MS with ion trap Bruker 3000-Esquire Plus. UV spectra were run at 20 °C (thermostated) on a Shimadzu UV-2102 PC.

4.1.1. Synthesis of *N*,*N*′-bis(5-hydroxy-3-oxa-pentyl)-2,6-pyridinedicarboxamide (4). The reaction was carried out under dry conditions. Over a cold (0 °C) solution of 2(2-aminoethoxy)ethanol (2.103 g, 20 mmol) and triethylamine (4.2 ml, 30 mmol) in dry dichloromethane (30 ml), 2,6-pyridinediacyl chloride (2.035 g, 10 mmol) in dry dichloromethane (25 ml) was added dropwise. The mixture was stirred for 1 h at room temperature and then dichloromethane was evaporated. Column chromatography (neutral alumina, CH_2Cl_2/MeOH 98:2) gave **4** as a pale yellow oil (2.557 g, 75%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.99 (2H, bt, NH); 8.19 (2H, d, J=7.89 Hz, Py); 7.90 (1H, t, J=7.92 Hz, Pyr); 3.67 (4H, bt, J=3.96 Hz, CH_2OH); 3.60 (8H, m, CH_2O); 3.54 (4H, t, J=4.5 Hz, CH_2N). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.3; 149.1; 139.1; 125.1; 72.5; 70.2; 61.8; 39.8. HRMS (FAB) Calcd for $C_{15}H_{24}N_3O_6$ 342.166511. Found 342.168011.

4.1.2. Synthesis of ligand 2. The reaction was carried out under dry conditions. Two solutions were prepared. Solution A: 2,6-pyridinedicarboxamide **4** (0.545 g, 1.6 mmol) in dry dichloromethane (18 ml). Solution B: 4,4′-dinitro-2,2′-biphenyl dichloride (0.590 g, 1.6 mmol) in dry dichloromethane (18 ml). Both solutions were added dropwise, simultaneously at the same speed over a stirring, cold (0 °C) solution of anhydrous potassium carbonate (0.692 g, 5 mmol) and tetrabutylammonium iodide (4 mg) in dry dichloromethane (165 ml). The solution remained stirred during 5 days at room temperature. After that, the suspension was filtered off, washed with ethyl acetate and the solvent was evaporated under vacuum. Purification by column chromatography (neutral alumina CH_2Cl_2:AcOEt 50:50), to compound **2** as an orange oil (0.1972 g, 19%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.76 (2H, d, J=2.3 Hz, Ar); 8.42 (2H, dd, J_1=2.3 Hz, J=8.46 Hz, Ar); 8.31 (2H, d, J=7.7 Hz, Py); 8.04 (1H, t, J=7.7 Hz, Py); 7.90 (2H, bt, NH); 7.42 (2H, d, J=8.49 Hz, Ar); 4.63 (4H, m, $COOCH_2$); 4.31 (4H, m, CH_2NH); 3.92 (4H, m, CH_2O); 3.70 (4H, m, CH_2O). ^{13}C NMR (75 MHz, $CDCl_3$): 164.9; 164.0; 149.0; 148.1; 147.8; 139.3; 131.1; 130.9; 126.7; 125.8; 125.3; 70.5; 68.9; 64.7; 39.5. HRMS (FAB): Calcd for $C_{29}H_{27}N_5O_{12}$ 638.173447. Found 638.175458. Anal. Calcd for $C_{29}H_{27}N_5O_{12}\cdot H_2O$: C, 53.13%; H, 4.46%; N, 10.68%. Found: C, 52.72%; H, 4.42%; N, 10.63%.

4.2. Complexation experiment. General method

To the corresponding ligand (4×10^{-5} mol) dissolved in the minimum amount of acetonitrile (ca. 1.5 ml), the stated salt (4×10^{-5} mol) in the same solvent (ca. 1.5 ml) was added and the mixture stirred for 4 h at room temperature. Then, the solvent was removed in vacuum.

4.2.1. 1·TBAF (5). ^{1}H NMR (300 MHz, CD_3CN) δ: 8.68 (d, H_a, 1H, J=2.46 Hz), 8.615 (d, H_a', 1H, J=2.43 Hz), 8.34 (dd, H_b', 1H, J_1=8.49 Hz, J_2=2.46 Hz), 8.17 (d, H_d, 2H, J=5.46 Hz), 8.10 (dd, H_b, 1H, J_1=8.28 Hz, J_2=2.64 Hz), 8.02 (dd, H_e, 1H, J_1=8.31 Hz, J_2=6.99 Hz), 7.50 (d, H_c', 1H, J=8.49 Hz), 7.32 (d, H_c, 1H, J=8.28 Hz), 4.53–4.45 (m, CH_2OOC, 2H), 3.88–3.83 (m, CH_2OOC, 2H), 3.72–3.40 (bm, CH_2NHCO, 4H). ^{13}C NMR (75 MHz, CD_3CN) δ: 164.5, 163.2, 163.0, 162.5, 148.7, 146.3, 145.9, 144.2, 138.3, 137.5, 130.9, 130.3, 129.2, 128.6, 124.7, 124.3, 123.2, 123.0, 122.7, 121.6, 121.0, 63.2, 58.8, 41.7, 37.2. Anal. Calcd for $C_{41}H_{55}N_6O_{10}F\cdot1.5H_2O$: C, 59.20%; H, 6.97%; N, 9.38%, F, 2.12%. Found: C, 59.25%; H, 7.10%; N, 9.53; F, 2.10%.

4.2.2. $1^-\cdot TBA^+$ (6). ^{1}H NMR (300 MHz, CD_3CN) δ: 8.33 (d, H_a, 2H, J=2.46 Hz), 8.17 (d, H_d, 2H, J=7.17 Hz), 8.06 (dd, 1H, H_e, J_1=6.96 Hz, J_2=8.46 Hz) 7.97 (dd, H_b, 2H, J_1=2.64 Hz, J_2=8.67 Hz), 7.60 (d, H_c, 2H, J=8.64 Hz), 3.67–3.66 (m, CH_2OOC, 2H), 3.47–3.45 (m, CH_2OOC, 2H), 3.27–3.18 (bm, CH_2NHCO, 4H). ^{13}C NMR (75 MHz, CD_3CN) δ: 164.7, 164.1, 162.5, 150.4, 139.4, 132.6, 132.1, 130.7, 124.1, 123.8, 120.7, 61.3, 44.9. Anal. Calcd for $C_{41}H_{54}N_6O_{10}\cdot2H_2O$: C, 59.56%; H, 7.02%; N, 10.17%. Found: C, 58.02%; H, 7.13%; N, 9.98%.

4.2.3. 2·TBAF (7). ^{1}H NMR (300 MHz, CD_3CN) δ: 10.7 (1H, bs, NH), 8.84 (1H, d, J=2.64 Hz, Ar–H), 8.51 (1H, d, J=2.46 Hz, Ar–H), 8.31 (1H,dd, J_1=2.46 Hz, J_2=8.49 Hz, Ar–H), 8.19 (1H, dd, J_1=2.46 Hz, J_2=8.49 Hz, Ar–H), 8.16 (2H, d, J=8.1 Hz, Py–H), 8.04 (1H, t, J=8.1 Hz, Py–H), 7.46 (1H, d, J=8.49 Hz, Ar–H), 7.29 (1H, d, J=8.46 Hz, Ar–H), 3.77 (4H, t, J=4.71 Hz, CH_2–O), 3.58 (12H, m, CH_2–O, CH_2–N). ^{13}C NMR (75 MHz, CD_3CN) δ: 164.5; 164.1; 163.8; 151.2; 149.1; 147.2; 146.9; 146.8; 146.2; 141.2; 138.4; 131.0; 130.2; 124.7; 124.6; 124.5; 123.7; 123.3; 72.6; 72.1; 68.3; 60.9; 60.5; 39.2; 39.0; 38.9. Anal. Calcd for $C_{45}H_{63}N_6O_{12}F\cdot2H_2O$: C, 57.69%; H, 7.37%; N, 8.97%, F, 2.03%. Found: C, 57.72%; H, 7.23%; N, 8.80%; F, 1.99%.

4.2.4. $2^-\cdot TBA^+$ (8). ^{1}H NMR (300 MHz, CD_3CN) δ: 8.31 (2H, d, J=2.46 Hz, Ar–H), 8.11 (2H, d, J=8.28 Hz, Py–H), 8.00 (1H, t, J=8.28 Hz, Py–H), 7.98 (2H, dd, J_1=2.46 Hz, J_2=8.49 Hz, Ar–H), 7.60 (2H, d, J=8.49 Hz, Ar–H), 3.71 (4h, t, J=5.64 Hz, CH_2–O), 3.52 (12H, m, CH_2–N, CH_2–O). ^{13}C NMR (75 MHz, CD_3CN) δ: 164.9; 164.3; 149.3; 146.7; 144.9; 144.1; 142.9; 138.2; 123.8; 122.4; 119.); 73.7; 69.4; 60.6. Anal. Calcd for $C_{45}H_{62}N_6O_{12}\cdot H_2O$: C, 60.27%; H, 7.14%; N, 9.37%. Found: C, 59.92%; H, 7.25%; N, 9.70%.

4.3. Kinetic constant determination. 1st reaction (general procedure)

Three mixtures of the ligand and TBAF were prepared and their ^{1}H NMR spectra were registered after a short and known interval of time. Taking into account the Eq. 1

$$\mathbf{1} + \mathrm{TBAF} \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} [\mathbf{1}\cdot\mathrm{TBAF}] \quad (1)$$

Rate$=k_1[L]^m[TBAF]^n-k_{-1}[L\cdot TBAF]$ being the $k_{-1}\ll k_1$ due to the value of K, the equation can be transformed into:

$$\mathrm{Rate}\approx k_1[L]^m[TBAF]^n.$$

Making use of the ^{1}H NMR integrations, concentration of the free ligand and complex and rate for the reaction could be determined employing the following equations:

$$[L] = [L]0/(\mathbf{1} + I_{LTBAF}/I_L)$$

$$[LF] = I_{LTBAF}/I_L\cdot[L]$$

$$v = ([L] - [L]_0)/\Delta t$$

The ratio between the speeds afforded the order of TBAF for the first kinetic, and so the kinetic constant.

$$v = k[\bar{L}]^m[TBA\bar{F}]^n$$

$$v_1/v_2 = ([\bar{L}]_1/[\bar{L}]_2)^1\cdot([TBA\bar{F}]_1/[TBA\bar{F}]_2)^n$$

Being [L]=free ligand concentration; $[L]_0$=initial ligand concentration; I_{LTBAF}/I_L=integration relation in ^{1}H NMR spectra; [LTBAF]=free concentration of the complex; m=order of the reaction respect to the ligand; n=order of the reaction respect to the salt.

Each experiment was repeated three times and error higher than 2% were not observed in any case in the value of the constants.

Ligand **1**

[**1**]	[TBAF]	t (min)
9.1×10^{-3}	3.9×10^{-3}	11.85
9.1×10^{-3}	7.8×10^{-3}	6.4
7.8×10^{-3}	7.8×10^{-3}	5.33

$k_1=15.29\ M^{-1}\ min^{-1}$, $m=1$, $n=1$.

Ligand **2**

[**2**]	[TBAF]	t (min)
7.4×10^{-3}	11×10^{-2}	7.4
7.4×10^{-3}	6.7×10^{-2}	11.27
4.7×10^{-3}	6.7×10^{-2}	11.8

$k=115\ M^{-1}\ min^{-1}$, $m=1$, $n=1$.

4.4. Kinetic constant determination. 2nd reaction (general procedure)

To a solution of L (9.1×10^{-3} M), 100 equiv of TBAF were added, NMR ^{1}H was registered every 30 min for 6 h. The plot ln[L] versus t gave a straight line ($R=0.99$), so we concluded a 1st order kinetic for L (see Supplementary material).

In order to determine the order of TBAF two mixtures of the ligand and TBAF were prepared and their ^{1}H NMR spectra were registered after a short and known interval of time.

$$[L\cdot TBAF] + TBAF \xrightarrow{k_2} [L^-\cdot TBA^+] + TBAHF_2$$

Making use of the ^{1}H NMR integrations, concentration of the free ligand and complex and speed for the reaction could be determined employing the following equations:

$$[L] = [L]_0/(\mathbf{1} + I_{LF}/I_L)$$

$$[LF] = I_{LF}/I_L\cdot[L]$$

$$v = ([L]-[L]_0)/\Delta t$$

The ratio between the speeds afforded the order of TBAF for the second kinetic, and so the kinetic constant.

$$v = k[\bar{L}]^m[\bar{F}]^n$$

$$v_1/v_2 = ([\bar{L}]_1/[\bar{L}]_2)^1\cdot([\bar{F}]_1/[\bar{F}]_2)^n$$

Being [L]=free ligand concentration; $[L]_0$=initial ligand concentration; I_{LTBAF}/I_L=integration relation in ^{1}H NMR spectra; [LTBAF]=free concentration of the complex; m=order of the reaction respect to the ligand; n=order of the reaction respect to the salt.

Each experiment was repeated three times and error higher than 2% were not observed in any case in the value of the constants.

Ligand **1**

[**1**]	[TBAF]	t (min)
5.98×10^{-2}	0.17	17.7
9.1×10^{-2}	0.91	70

$K_2=6\times10^{-3}\ M^{-1}\ min^{-1}$, $m=1$, $n=1$.

Ligand **2**

[**2**]	[TBAF]	t (min)
5.4×10^{-3}	0.224	18.6
5.4×10^{-2}	0.37	14.7

$K_2=3.5\times10^{-3}\ M^{-1}\ min^{-1}$, $m=1$, $n=1$.

4.5. X-ray structure analysis

Information concerning crystallographic data collection and refinement for compound **2** are summarized in Table 4. Intensity measurements were made on a Bruker-AXS Smart diffractometer at 173 K using a single crystal of dimensions $0.4\times0.2\times0.1$ mm. Graphite-monochromated Mo K_α radation ($\lambda=0.71073$ Å) and ω-scan technique was used. Data collection was carried out at room temperature. Three reference reflections were measured every two hours as an intensity and orientaction check and no significant fluctuation was noticed. Lorentz-polaritation correction was made. The crystal structure was solved by directs methods using the SHELXS system[23] and refined by full-matrix least-squares techniques[24] on F^2. The non-hydrogen atoms were refined anisotropically and all the hydrogen atoms were found by Fourier synthesis. A list of anisotropic displacement parameters for non-hydrogen atoms, bond lengths and angles, hydrogen atoms coordinates have been deposited as Supplementary material at the Cambridge

Table 4. Crystal data and structure refinement for **2**

Empirical formula	C29 H29 N5 O13
Formula weight	655.57
Temperature	173(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	p-1
Unit cell dimensions	a=8.2192(11) Å, alpha=84.510(14)° b=14.0690(19) Å, beta=89.147(18)° c=14.852(2) Å, gamma=74.540(14)°
Volume	1647.6(4) Å^3
Z	2
Density (calculated)	1.321 mg/m^3
Absorption coefficient	0.106 mm^{-1}
F(000)	684
Crystal size	$0.4\times0.2\times0.1$ mm
Theta range for data collection	1.38–27.50°
Index ranges	$-10\le h\le10$, $-18\le k\le18$, $-19\le l\le19$
Reflections collected	17602
Independent reflections	7504 [R(int)=0.0249]
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	7504/0/430
Goodness-of-fit on F^2	1.042
Final R indices [$I>2\sigma(I)$]	$R1$=0.0814, $wR2$=0.2453
R indices (all data)	$R1$=0.1072, $wR2$=0.2730
Largest diff. peak and hole	0.695 and −0.679 e A^{-3}

Crystallographic Data Centre, CCDC, 12 Union Road, Cambridge CB2 1EZ, United Kingdom (CCDC 234814). The list of F_0/F_c structure data is available directly form the author until a year after the paper is published.

Acknowledgements

The present research has been financed by DGCYT (PPQ2002-00986). We acknowledge the Universitat de Valencia (S.C.I.E.) for most of the equipment employed. One of us (M.J.B.) acknowledges the Generallitat Valenciana for a PhD grant.

Supplementary data

Supplementary data associated with this article can be found at doi: 10.1016/j.tet.2004.07.088

References and notes

1. Beer, P. D.; Gale, P. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 486–516, and references therein.
2. Ilioudis, C. A.; Hancock, K. S. B.; Georganopoulou, D. G.; Steed, J. W. *New J. Chem.* **2000**, *24*, 787–798, and references therein.
3. Black, C. B.; Andrioletti, B.; Try, A. C.; Ruiperez, C.; Sessler, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 10438–10439.
4. Miyaji, H.; Sato, W.; Sessler, J. L. *Angew. Chem., Int. Ed.* **2000**, *39*, 1777–1780.
5. Yamaguchi, S.; Akiyam, S.; Tamao, K. *J. Am. Chem. Soc.* **2001**, *123*, 11372–11375.
6. Kubo, Y.; Yamamoto, M.; Ikeda, M.; Takeuchi, M.; Shinkai, S.; Yamaguchi, S.; Tamao, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 2036–2040.
7. Ho, H. A.; Leclerc, M. *J. Am. Chem. Soc.* **2003**, *125*, 4412–4413.
8. Bondy, C. R.; Loeb, S. J. *Coord. Chem. Rev.* **2003**, *240*, 77–99.
9. Jiménez, D.; Martínez-Máñez, R.; Sancenón, F.; Soto, J. *Tetrahedron Lett.* **2002**, *43*, 2823–2825.
10. Camiolo, S.; Gale, P. A.; Hursthouse, M. B.; Light, M. E. *Org. Biomol. Chem.* **2003**, 741–744.
11. Gunnlaugsson, T.; Kruger, P. E.; Jensen, P.; Pfeffer, F. M.; Hussey, G. M. *Tetrahedron Lett.* **2003**, *44*, 8909–8913.
12. Piatek, P.; Jurczak, J. *Chem. Commun.* **2002**, 2450–2451.
13. Costero, A. M.; Aurell, M. J.; Bañuls, M. J.; Ochando, L. E.; Tamarit, F. J.; Domenech, A. *J. Inclusion Phenom. Macrocycl. Chem.* **2003**, *45*, 241–249.
14. Kumar, S.; Hundal, M. S.; Kaur, N.; Singh, R.; Singh, H.; Hundal, G.; Ripoll, M. M.; Aparicio, J. S. *J. Org. Chem.* **1996**, *61*, 7819–7825.
15. Costero, A. M.; Andreu, C.; Martínez-Máñez, R.; Soto, J.; Ochando, L. E.; Amigó, J. M. *Tetrahedron* **1998**, *54*, 8159–8170.
16. Whitlock, B. J.; Whitlock, H. W. *J. Am. Chem. Soc.* **1990**, *112*, 3910–3915.
17. Available from Kholin Y. V.; Konyaev D. S.; Merny S. A. in http://www.bestnet.kharkov.ua/kholin/clinp.html.
18. Hyejae, I.; Sunggoo, Y.; Heon, G. K.; Jung, K. K.; Kwang, S. K. *Org. Lett.* **2002**, *4*, 2897–2900.
19. Wallace, K. J.; Belcher, W. J.; Turner, D. R.; Syed, K. F.; Steed, J. W. *J. Am. Chem. Soc.* **2003**, *125*, 9699–9715.
20. Gale, P. A.; Hursthouse, M. B.; Light, M. E.; Sessler, J. L.; Warriner, C. N.; Zimmerman, R. S. *Tetrahedron Lett.* **2001**, *42*, 6759–6762.[22]
21. Schah-Mohammedi, P.; Shenderovich, I. G.; Detering, C.; Limbach, H.-H.; Tolstoy, P. M.; Smirnov, S. N.; Denisov, G. S.; Golubev, N. S. *J. Am. Chem. Soc.* **2000**, *122*, 12878–12879.
22. Kornath, A.; Neumann, F. *Inorg. Chem.* **2003**, *42*, 2894–2901.
23. Sheldrick, G. M. *Shelxs86: Program for the crystal structure determination*, University of Cambridge: England.
24. Sheldrick, G. M. *Shelxs93: Program for the crystal structure refinement*, University of Gottingen: Germany.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 60 (2004) 9479–9484
Tetrahedron

Synthesis and applications of chiral bis-THF in asymmetric synthesis

Alexandre Alexakis,* Axel Tomassini and Stéphane Leconte

Department of Organic Chemistry, University of Geneva, 30 quai Ernest-Ansermet, 1211 Genève 4, Switzerland

Received 15 June 2004; revised 26 July 2004; accepted 29 July 2004

Abstract—The synthesis of enantiopure bis-THF is described, starting from D-mannitol. Bis-THF is used as chiral ligand for organolithium reagents in four different reactions. The enantioselectivity provided by this ligand is moderate, and the asymmetric induction is in line with the expected model.
© 2004 Elsevier Ltd. All rights reserved.

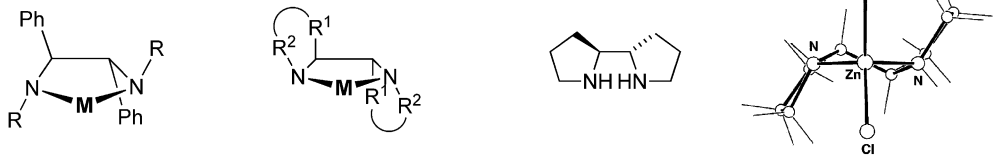
1. Introduction

Metal-mediated asymmetric synthesis is a prominent way to access to enantiopure compounds.[1] The required metal is commonly chelated by a *C*2 symmetrical chiral ligand which discriminates the space around the metal.[2] Among such ligands, particularly for main group metals, chiral diamines are have found widespread applications.[3] We have extensively used chiral diphenyl ethanediamine and its derivatives.[4] More recently described the synthesis of enantiopure bis-pyrrolidine, a ligand which discriminates the space in a different way.[5] In diphenyl ethanediamine, the substituents on the nitrogen atom are oriented *trans* to the substituent on the next carbon, whereas with bis-pyrrolidine they are oriented *cis*, due to the ring strain of the azadicyclooctane framework. This is clearly seen of the bis-pyrrolidine·$ZnCl_2$ complex (Scheme 1).[5]

With strong nucleophilic reagents, such as organolithiums, the nitrogen atom has to be fully substituted to avoid deprotonation of the secondary amine. This brings a tremendous changes in the Li–diamine complex. The space is no more discriminated, unless two of the substituents of the nitrogen are of different size (Scheme 2).[6] A solution to this problem was brought by Tomioka, by the use of diethers instead of diamines.[7] Although ethers binds less strongly than amines, Tomioka has shown impressive results with diphenyl dimethoxyethane **1**. By analogy to our bis-pyrrolidine·$ZnCl_2$ complex (Scheme 1), we expected that bis-THF **2** could also adopt the same stair-like conformation (Scheme 2). We describe herein an efficient synthesis of enantiopure bis-THF, and some applications in asymmetric transformations involving organolithium reagents.

2. Results

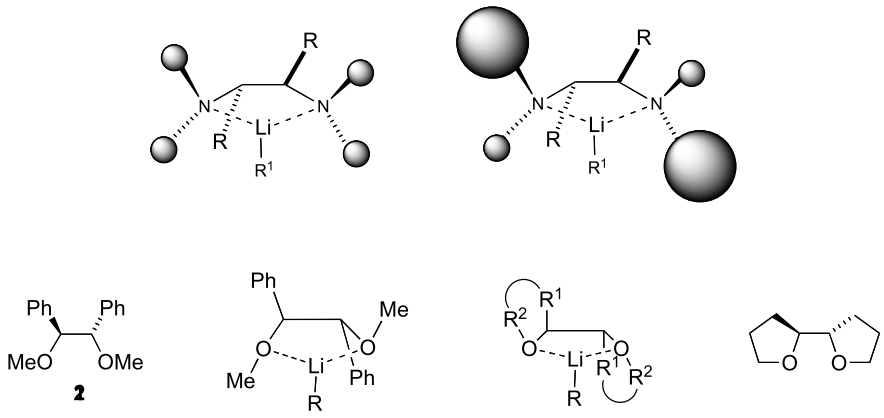
Many syntheses of bis-THF **2** have been described in the literature,[8] but none concerning the enantiopure compound.[9] Our synthetic approach was inspired by Kotsuki's synthesis of 2,2′-pyrrolidine.[10] It starts from the easily available monoacetonide of D-mannitol **3** (Scheme 3). After selective cleavage of the 1,2 diol moiety, the crude



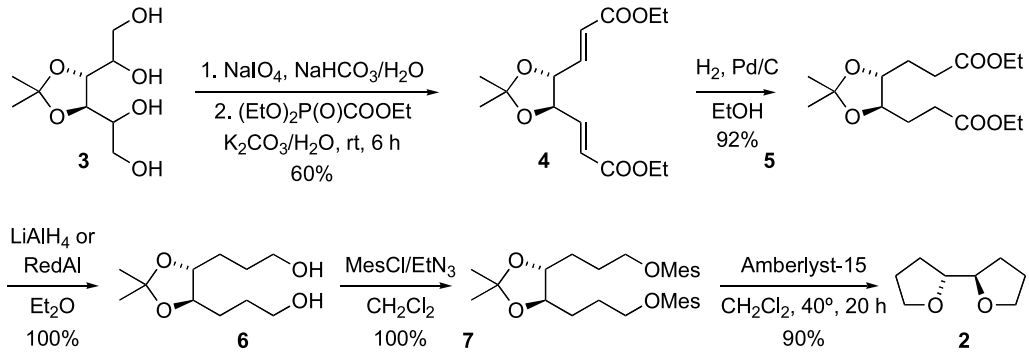
Scheme 1.

Keywords: Asymmetric synthesis; Chirality; Diether; Organolithium reagents; Coordination.
* Corresponding author. Tel.: +41-22-379-6522; fax: +41-22-379-3215; e-mail: alexandre.alexakis@chiorg.unige.ch

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.07.091



Scheme 2.

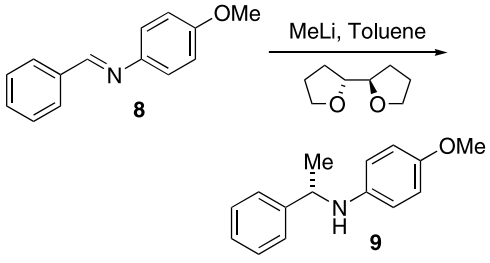


Scheme 3.

dialdehyde is submitted to a double Wittig–Horner olefination to afford the bis-α,β-ethylenic ester **4**, in 60% overall yield. Both double bonds could easily be hydrogenated with palladium over charcoal under hydrogen atmosphere. The saturated diester **5** was transformed, quantitatively, to diol **6** by reduction with LAH or RedAl. The formation of bismesylate **7** was carried out in dichloromethane with methanesulfonyl chloride and triethylamine. Octahydro-2,2′-bifuranyl (bis-THF) **2** was obtained by cleavage of the isopropylidene group in the presence of Amberlyst-15 at 40 °C, followed by direct in situ cyclisation.[11]

This sequence could be done on large scale (0.2 mol) without intermediate purifications, with only a final distillation. Octahydro-2,2′-bifurannyl (bis-THF) **2** was obtained as a colourless liquid (bp: 45 °C/15 mm Hg), easy to handle, and soluble in all solvents.[12] The next step was to evaluate the synthetic potential of bis-THF **2** in asymmetric synthesis. This was achieved with four different reactions for which comparative data were available.

The first test reaction was the addition of MeLi to an imine **8**. This is a well known reaction, already reported with diamine ligands (sparteine: 31% ee,[13] a cyclohexane diamine derivative: 67%,[6] a bis-aziridine: 67% ee[14]), with bis-oxazolines (89% ee[15]) and with Tomioka's diether **1** (46% ee).[16] With 2 equiv of bis-THF **2**, as ligand, in toluene at −78 °C, we obtained the amine **9** with 41% ee (Scheme 4). However, with substoichiometric amounts of ligand **2**, the ee fell to 20%. Interestingly, a higher temperature is beneficial to the enantioselectiviy (32% ee at −50 °C). This reaction was also carried out in THF and Et_2O to test the coordination power of bis-THF. Unfortunately no enantiomeric excess as obtained in THF, which proved that octhydro-2,2′-bisfuranyl **2** could not displace a polar solvent such as tetrahydrofuran. However, we obtained 37% enantiomeric excess in ether. So the coordination ability of this ligand **2** should be somewhere between ether and THF (Scheme 4).

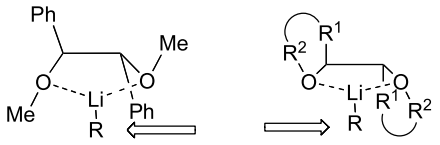


2 equiv.	temp. -78°	yield: 95%	ee: 41%
0.5 equiv.	-78°	97%	20%
0.5 equiv.	-50°	80%	32%

Scheme 4.

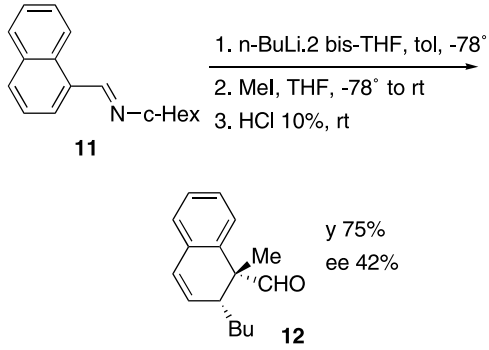
The ee value obtained with bis-THF **2** is rather similar to that of diether **1**, but clearly lower to that obtained with diamines or bisoxazolines. Interestingly, the absolute configuration of the product is the opposite to that reported by Tomioka with his diether **1**,[16] although they have the

same absolute configuration. This is in agreement with our conceptual hypothesis (Scheme 5), where it is the position of the substituents on oxygen that determines the space around the Li atom, and not the configuration of the backbone (Scheme 5).



Scheme 5.

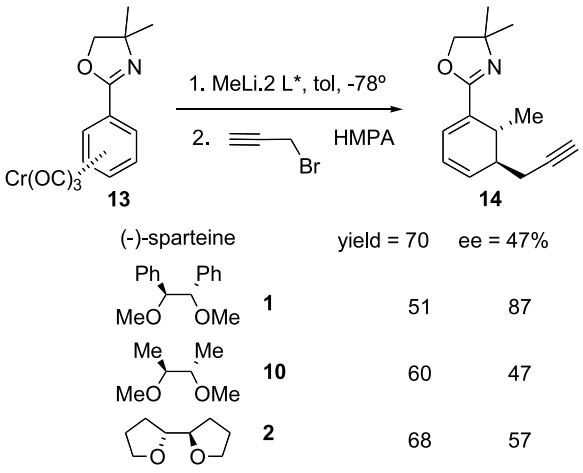
The next test reaction was the 1,4 addition of *n*-BuLi to 1-naphthyl imine **11** (Scheme 6). The addition was performed in toluene, at −78 °C, with 2 equiv of bis-THF **2**. To avoid rearomatization of the adduct, we employed Meyers' technique to quench the intermediate metallo-imine with MeI.[17] Tomioka reported a 91% ee on this addition with diether **1**, and 53% ee with 2,3-dimethoxy butane **10**.[18] The adduct **12** obtained with bis-THF **2** (42% ee) shows that it is comparable to 2,3-dimethoxy butane **10** but far away from diether **1**. Again, a reaction performed in THF gave only racemic product. As above, the absolute configuration of the adduct is opposite to that obtained with diether **1** (Scheme 6).



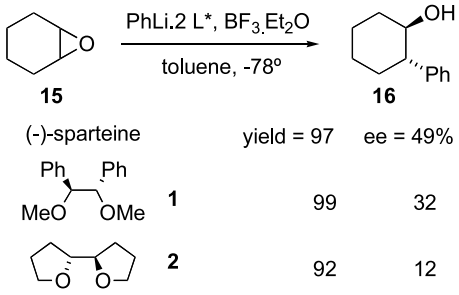
Scheme 6.

Another test reaction was a carbolithiation of an arene-chromium derivative **13** (Scheme 7), followed by trapping with propargyl bromide. Kundig reported excellent results, for product **14**, with Tomioka's diether **1**, whereas (−)-sparteine and 2,3-dimethoxybutane **10** gave only moderate enantioselectivities.[19] The reaction performed with bis-THF **2** gave 57% ee, somewhat better than (−)-sparteine or 2,3-dimethoxybutane **10**, but, still, much lower than Tomioka's diether **1**. As before, the absolute configuration of the adduct was opposite (Scheme 7).

A last test reaction was the BF_3 promoted ring opening of *meso* epoxides by organolithium reagents (Scheme 8).[20] Comparative data were known for diether **1**[21] and (−)-sparteine.[22] Thus, cyclohexene oxide **15** was treated, in toluene at −78 °C, with the precomplexed PhLi·2 ligands. Upon addition of $BF_3{\cdot}Et_2O$, the cleavage reaction is quantitative. *Trans* phenyl cyclohexanol **16** was obtained in excellent yield, but with only 12% ee. Thus, in this reaction, bis-THF **2** behaves very poorly (Scheme 8).



Scheme 7.



Scheme 8.

In summary, we have efficiently synthesized chiral bis-THF **2**[24] and we have evaluated it for some representative reaction. In general, bis-THF induces moderate enantioselectivities and is clearly inferior to Tomioka's diether **1** or to diamines or bisoxazolines. Although the discrimination of the space exerted by bis-THF corresponds to our starting hypothesis, the degree of this selectivity does not make it a valuable ligand for asymmetric synthesis. Modifications on the α,α' carbons may be needed to increase the steric effects and improve the steric bias.

3. Experimental

3.1. General

All reactions were carried out under an atmosphere of nitrogen or argon using flame-dried glassware. Solvents were distilled from CaH_2 (dichloromethane, triethylamine, toluene) or Na/Benzophenone (tetrahydrofuran, diethylether) prior to use. Commercially available solid products were generally used without purification, liquids were freshly distilled when it was necessary.

^1H and ^{13}C, NMR spectra were recorded on Varian XL-200 or Brucker-AMX400 in $CDCl_3$, or C_6D_6. Chemical shifts were given in ppm relative to TMS, coupling constants *J* are expressed in Hertz (multiplicity: s=singlet, d=doublet, dd=double doublet, t=triplet, dt=double triplet, q=quadruplet, m=multiplet, b=broad). IR spectra were recorded on Perkin–Elmer 1600 FT-IR using NaCl solution

cells. Optical rotations were measured in $CHCl_3$ (c=g/ml) on Perkin–Elmer 241 polarimeter using a quartz cell (l=10 cm), with a high-pressure sodium lamps (λ=589 cm).

Gas chromatography (GC) was performed on a Hewlett Packard 5890 instrument, GC–MS was performed on Hewlett Packard 6890 column OPTIMA delta-3 (30 m×0.25 mm) and mass selective detector Hewlett Packard 5973 with EI (70 eV) as source. Supercritical Fluid Chromatography (SFC) was performed on Berger Instruments Inc. with Hewlett Packard 1100 DAD detector. Mass spectra (MS) were obtained with Varian CH-4, or Finnigan 4023, relative intensities are given in parenthesis.

3.1.1. (4*R*,5*R*)-4,5-*O*-Isopropylidene-4,5-dihydroxy-2,6-octadiene-dioate 4. To a stirred solution of 3,4-*O*-isopropylidene-D-mannitol[23] **3** (37 mmol, 8.2 g) in 5% aqueous solution of sodium hydrogenocarbonate (75 ml), was added a solution of $NaIO_4$ (111 mmol, 23.7 g) in water (75 ml) at 0 °C. The resulting mixture was stirred for 1 h at room temperature. Then, ethyl diethoxyphosphinylacetate (148 mmol, 29.5 ml) was added, followed by a 10 N aqueous solution of potassium carbonate (145 ml) at 0 °C. Stirring was continued for 16 h at room temperature. The mixture was extracted with dichloromethane (4×150 ml^2), the combined organic layers were washed with a saturated solution of brine (150 ml), dried over potassium carbonate, filtered and concentrated to give crude oil **4**. The product could be purified by chromatography with silicagel using pentane(8/2)ethyl acetate as solvent to yield 6.6 g (60%) of pure product. ^{1}H NMR: (400 MHz, $CDCl_3$): δ (ppm) 1.30 (t, J=7.0 Hz, 6H), 1.48 (s, 6H), 4.23 (q, J=7.0 Hz, 4H), 4.23–4.25 (m, 2H), 6.15 (d, J=15.7 Hz, 2H), 6.88 (ddd, J=1.8, 3.8 and 15.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 14.2, 26.8, 60.7, 79.7, 110.8, 123.7, 141.88, 165.6. GC–MS (EI 70 eV) m/z (%): 283 (42) [M−15], 241 (22), 195 (38), 170 (15), 149 (8), 125 (23), 112 (98), 97 (43), 84 (100), 59 (11), 43 (24), 29 (14).

3.1.2. (4*R*,5*R*)-4,5-*O*-Isopropylidene-4,4-dihydroxy-dioate 5. To a stirred solution of (4*R*,5*R*)-4,5-*O*-isopropylidene-4,5-dihydroxy-2,6-octadiene-dioate **4** (1.5 g, 5.03 mmol) in ethanol (50 ml), was added Pd/C—10 wt% (53 mg, 0.05 mmol). The mixture was stirred under a hydrogen atmosphere overnight. The resulting mixture was filtered through celite and the residue was washed by ethanol, the solvent was removed to yield 1.5 g of (4*R*,5*R*)-4,5-*O*-isopropylidene-4,5-dihydroxy-dioate **5** (99%). ^{1}H NMR: (400 MHz, $CDCl_3$): δ (ppm) 1.6 (t, J=7.2 Hz, 6H), 1.6–2.0 (m, 2H), 1.36 (s, 6H), 1.7–1.85 (m, 2H), 1.9–2.05 (m, 2H), 2.4–2.6 (m, 4H), 3.60–3.66 (m, 2H), 4.14 (q, J=7.2 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 14.2, 27.2, 28.7, 30.6, 60.1, 60.4, 79.5, 108.4, 173.1. GC–MS (EI 70 eV) m/z (%): 287 (63) [M−15], 227 (4), 199 (100), 171 (19), 153 (51), 135 (29), 115 (42), 101 (8), 85 (25), 59 (7), 43 (20), 29 (10).

3.1.3. (4*R*,5*R*)-4,5-*O*-Isopropylidene-4,5-dihydroxy-diol 6 with $LiAlH_4$. To a stirred solution of $LiAlH_4$ (245 mg, 6.4 mmol) in ether (35 ml), was added (4*R*,5*R*)-4,5-*O*-isopropylidene-1,7-dihydroxy-dioate **5** (1.4 g, 4.62 mmol) in ether (14 ml) at 0 °C. The mixture was stirred overnight at room temperature. The mixture was quenched by a drop of water at 0 °C, the mixture was filtered through celite, and washed with ethyl acetate. The solvent was removed to yield pure product **6** 1.01 g (4.62 mmol, 100%). ^{1}H NMR: (400 MHz, $CDCl_3$): δ (ppm) 1.37 (s, 6H), 1.5–1.8 (m, 8H), 2.3 (s b, 2H), 3.5–3.8 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 27.7, 29.8, 29.8, 62.9, 80.3, 108.7. GC–MS (EI 70 eV) m/z (%): 203 (20) [M−15], 143 (100), 130 (26), 115 (10), 107 (15), 97 (39), 85 (30), 71 (48), 59 (73), 43 (56), 31 (24), 18 (10). $[\alpha]_D^{21}=-29.2$ (c=0.01, $CHCl_3$, Lit.[10] (*S*,*S*)=−29.8 (c=0.01, $CHCl_3$)).

3.1.4. (4*R*,5*R*)-4,5-*O*-Isopropylidene-4,5-dihydroxy-diol 6 with RedAl®. To a stirred solution of RedAl® (26 ml, 91.4 mmol) in ether (170 ml), was added (4*R*,5*R*)-4,5-*O*-isopropylidene-1,7-dihydroxy-dioate **5** (11 g, 36.9 mmol) in ether (114 ml) at 0 °C. The mixture was stirred overnight at room temperature. The mixture was quenched by a drop of water at 0 °C, the mixture was filtered through celite, and washed with ethyl acetate. The solvent was removed to yield pure product **6** whose spectroscopic data are identical to above. 8.04 g (36.9 mmol, 100%).

3.1.5. (4*R*,5*R*)-4,5-*O*-Isopropylidene-1,7-dihydroxy-methanesulfonate 7. To a stirred solution of (4*R*,5*R*)-4,5-*O*-isopropylidene-4,5-dihydroxy-diol **6** (5.6 g, 25.7 mmol) in anhydrous dichloromethane (150 ml), under nitrogen atmosphere, cooled to 0 °C, were added Et_3N (7.5 ml, 56.5 mmol) and methanesulfonyl chloride (4.2 ml, 56.5 mmol). The mixture was warmed to room temperature and stirred for 5 h. Ether was added to precipitate the triethylamine hydrochloride, the solution was filtered and the solvent was removed to afford 9.6 g of (4*R*,5*R*)-4,5-*O*-isopropylidene-1,7-dihydroxymethanesulfonate **7** (100%). ^{1}H NMR: (400 MHz, $CDCl_3$): δ (ppm) 1.37 (s, 6H), 1.49–1.65 (m, 2H), 1.65–2.05 (m, 6H), 3.02 (s, 6H), 3.11–3.21 (m, 1H), 3.56–3.65 (m, 1H), 4.18–4.37 (m, 4H), ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 26.0, 27.2, 28.4, 37.4, 69.7, 80.0, 108.5.

3.1.6. Octahydro-2,2′-bifuranyl 2 (bis-THF). To a stirred solution of (4*R*,5*R*)-4,5-*O*-isopropylidene-4,5-dihydroxy-dimesylate **7** (1.5 g, 4.12 mmol) in dichloromethane (80 ml) under a nitrogen atmosphere, 1.7 g of amberlyst-15 was added. The solution was warmed up to 40 °C overnight. After cooling to room temperature, the solution was filtered through celite, and the solution was stirred over potassium carbonate to remove excess methanesulfonic acid, then filtered, the solvent was removed to yield crude bis-THF **2**. The crude product was distilled (77–80 °C/13 mm Hg) to give pure bis-THF (530 mg, 90%). ^{1}H NMR: (400 MHz, $CDCl_3$): δ (ppm) 1.5–2.1 (m, 8H), 3.6–4.0 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 25.8, 28.1, 68.3, 81.4. GC–MS (EI 70 eV) m/z (%): 142 (2), 71 (100), 43 (30). $[\alpha]_D^{21}=-2$ (c=0.011, $CHCl_3$). Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found C, 67.42; H, 9.87.

3.1.7. *N*-Phenylmethylene-4-methoxybenzenamine 8.[16] A mixture of *p*-methoxyaniline (25 mmol, 3.07 g), and benzaldehyde (25 mmol, 2.54 ml), was stirred at 40 °C for 1 h and diluted with diethyl ether (50 ml). The solution was successively washed with 5% aqueous. AcOH, brine and dried over potassium carbonate. Concentration and

recrystallization from ethanol (10 ml) gave 4.4 g (83%) of *N*-phenylmethylene-4-methoxybenzenamine **8** as white solid. ^{1}H NMR: (400 MHz, $CDCl_3$): δ (ppm) 3.82 (s, 3H), 6.91 (d, J=9.0 Hz, 2H), 7.23 (d, J=9.0 Hz, 2H), 7.3–7.5 (m, 3H), 7.8–8.0 (m, 2H), 8.47 (s, 1H), GC–MS (EI 70 eV) *m/z* (%): 211 (81), 196 (100), 167 (21), 141 (6), 115 (6), 92 (5), 77 (7), 63 (6), 18 (18).

3.1.8. Addition of MeLi to *N*-phenylmethylene-4-methoxybenzenamine 8. To a cooled (−78 °C) stirred solution of *N*-phenylmethylene-4-methoxybenzenamine **8** (0.25 mmol, 52.5 mg) and bis-THF **2** (0.5 mmol, 71 mg) in dry toluene (5 ml) under an inert atmosphere, was added an ether solution of MeLi (low halide, 1.36 M in ether, 0.5 mmol, 367 µl) at −78 °C over a period of 5 min. The mixture was stirred at −78 °C for 20 min and quenched with water (5 ml). The organic layer was washed with brine and dried over K_2CO_3. Concentration followed by standard silicagel purification gave (*R*)-*N*-(4-methoxyphenyl)-α-methylbenzenemethanamine **9**[16] as a pale yellow oil. ^{1}H NMR: (400 MHz, $CDCl_3$): δ (ppm) 1.49 (d, J=6.8 Hz, 3H), 3.68 (s, 3H), 4.39 (q, J=6.8 Hz, 1H), 6.46 (d, J=9.0 Hz, 2H), 6.70 (d, J=9.0 Hz, 2H), 7.1–7.5 (m, 5H), GC–MS (EI 70 eV) *m/z* (%): 227 (77), 212 (91), 196 (4), 168 (6), 150 (6), 123 (46), 105 (75), 77 (22), 18 (100). The enantiomeric excess (41%) was measured by SFC, on Chiracel OD-H column, 200 bar, 2 ml/min, 2% MeOH in CO_2, 30 °C, *R* (major) t_1=8.34 min, *S* (minor) t_2=8.82 min.

3.1.9. 1-Naphthaldehyde cyclohexylimine 11.[16] To a stirred solution of 1-naphthaldehyde (4.68 g, 30 mmol) in dichloromethane (50 ml) with $MgSO_4$, cyclohexylamine (3.27 g, 33 mmol) was added. The solution was stirred overnight, then filtered through celite, the solvent was evaporated to yield quantitatively pure imine **11** with 5/95 of *cis*/*trans*. ^{1}H NMR: (200 MHz, $CDCl_3$): δ (ppm) 1.2–1.6 (m, 3H), 1.6–2.1 (m, 7H), 3.2–3.4 (m, 1H), 7.4–7.6 (m, 3H), 7.8–8.0 (m, 3H), 8.4 (s, 1H, *cis*), 8.9 (d, J=8.0 Hz, 1H), 9.0 (s, 1H, *trans*). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 25.3, 26.2, 35.1, 71.4, 112.8, 124.8, 125.8, 126.4, 127.4, 128.7, 129.1, 131.1, 131.8, 132.6, 134.3, 158.4. GC–MS (EI 70 eV) *m/z* (%): 237 (100), 222 (2), 208 (15), 194 (36), 180 (26), 167 (17), 154 (71), 141 (16), 127 (21), 18 (25).

3.1.10. Addition to imine 11 with bis-THF 2 as chiral ligand. To a stirred solution of imine **11** (24 mg, 0.1 mmol) in toluene (5 ml) was added bis-THF **2** (20 mg, 0.14 mmol). The solution was stirred at −80 °C, and *n*-BuLi (160 µl, 0.13 mmol of a 1.6 M solution in *n*-hexane) was added. The solution was stirred at −80 °C overnight. The 15 ml of cooled (−78 °C) dry tetrahydrofuran was added slowly via cannula followed by MeI (0.3 mmol, 19 µl). The mixture was stirred for 1 h at −78 °C then the temperature was raised up to room temperature and quenched by addition of a 10% aqueous HCl. The mixture was then stirred 24 h. The aqueous phase was extracted three times with ether, and the organic phase was washed with brine and dried over K_2CO_3. The solvent was removed in vacuo, and the crude product **12**[17] was purified by standard silicagel chromatography. The enantiomeric excess (42%) was measured by SFC: Chiracel OD-H, 200 bar, 2.0 ml/min, 2% MeOH in CO_2, 30 °C, 1*R*,2*R* (major) t_1=3.49 min, 1*S*,2*S* (minor) t_2=4.58 min. ^{1}H NMR: (400 MHz, $CDCl_3$): δ (ppm) 0.90 (t, J=7.1 Hz, 3H), 1.18–1.55 (m, 5H), 1.44 (s, 3H), 1.55–1.67 (m, 1H), 2.46–2.54 (m, 1H), 5.99 (dd, J=3.8, 9.9 Hz, 1H), 6.48 (dd, J=2.0, 9.9 Hz, 1H), 7.10–7.30 (m, 4H), 9.84 (s, 1H), ^{13}C NMR: (100 MHz, $CDCl_3$): δ (ppm) 13.9, 19.3, 22.6, 29.6, 29.7, 42.8, 52.4, 126.5, 126.8, 127.0, 128.1, 130.4, 133.5, 135.1, 203.7, GC–MS (EI 70 eV) *m/z* (%): 228 (4), 199 (34), 155 (4), 143 (100), 128 (27), 115 (4), 57 (8), 41 (5), 29 (5), 18 (16).

3.1.11. Carbometallation of arene chromium complex 13.[19] To a stirred solution of complex **13**[19] (311 mg, 1 mmol), and bis-THF (284 mg, 2 mmol), in dry toluene (10 ml), was added at −78 °C MeLi (68 µl, 1.1 mmol of an 1.4 M in *n*-hexane solution). The reaction was left 4 h at −78 °C, then propargyl bromide (380 ml, 5 mmol) and HMPA (1.75 ml, 10 mmol) were added. The temperature was warmed up to room temperature and the reaction was left overnight. The solvent was removed under vacuum and the crude product **14**[19] was purified by flash chromatography on silica gel. ^{1}H NMR: (400 MHz, $CDCl_3$): δ (ppm) 1.06 (d, J=7.0 Hz, 3H), 1.30 (s, 3H), 1.34 (s, 3H), 1.96 (t, J=2.5 Hz, 1H), 2.08–2.33 (m, 3H), 2.81 (q, J=7.1 Hz, 1H), 3.92 (d, J=8.1 Hz, 1H), 3.97 (d, J=8.1 Hz, 1H), 6.03–6.10 (m, 2H), 6.60–6.62 (m, 1H), ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 18.5, 22.4, 28.1, 28.3, 32.0, 39.6, 67.3, 69.1, 78.4, 82.5, 122.7, 126.2, 128.8, 132.4, 161.9, GC–MS (EI 70 eV) *m/z* (%): 229 (16), 190 (100), 189 (10), 174 (9), 168 (3), 160 (10), 158 (3), 145 (5), 136 (15), 128 (4), 119 (75), 104 (17), 91 (36), 77 (12) The enantiomeric excess (57%) was measured by SFC Chiracel OD-H, 200 bar, 2 ml/min, 10 °C, 1% MeOH in CO_2, 5*S*,6*R* (major) t_1=2.94 min, 5*R*,6*S* (minor) t_2=3.19 min.

3.1.12. Ring opening of cyclohexene oxide 15.[22] To a cooled (−78 °C) solution of bis-THF **2** (0.5 mmol, 71 mg) and PhI (0.5 mmol, 56 µl) in ether (4 ml), under an inert atmosphere, was added *n*-BuLi (0.5 mmol, 312 µl of 1.6 M solution in *n*-hexane). After 1 h, cyclohexene oxide **15** (0.25 mmol, 25 µl) was added, followed slowly by $BF_3{\cdot}Et_2O$ (0.37 mmol, 47 µl) in ether (1 ml) in order to maintain the temperature below −78 °C. After stirring for an additional 10 min, the reaction was quenched with MeOH (1 ml) and Et_3N (1.5 ml) and then the temperature was allowed to raise to room temperature. An 5% aqueous solution of H_2SO_4 (5 ml) was slowly added to the reaction mixture, the aqueous layer was extracted with Et_2O (3× 17 ml^2), the combined organic phases were washed with brine, dried over $MgSO_4$ and the solvent was removed under vacuum to yield the crude product. The product was purified by silicagel column chromatography to yield 92% of *trans*-phenyl cyclohexanol **16**. ^{1}H NMR: (400 MHz, $CDCl_3$): δ (ppm) 1.39 (m, 5H), 1.78 (m, 1H), 1.89 (m, 2H), 2.15 (m, 1H), 2.45 (ddd, J=3.5; 10; 12 Hz, 1H), 3.66 (dt, J=4.2; 10 Hz, 1H), 7.24 (m, 5H), ^{13}C NMR: (100 MHz, $CDCl_3$): δ (ppm) 25.0, 26.0, 33.3, 34.4, 53.2, 74.4, 126.8, 127.8, 128.7, 143.2, GC–MS (EI 70 eV) *m/z* (%): 176 (42), 158 (6), 143 (9), 130 (34), 117 (26), 104 (30), 91 (65), 18 (100) The enantiomeric excess (12%) was determined by SFC Chiracel OJ, 200 bar, 2.0 ml/min, 2% MeOH in CO_2, 30 °C, 1*S*,2*R* (major) t_1=6.75 min, 1*R*,2*S* (minor) t_2=7.33 min.

Acknowledgements

The authors thank Stephane Rosset for help, Professor E. P. Kündig for providing complex **13**, Professor G. Poli for informing us about his sulfur analog,[24] The Swiss National Research Foundation No. 20-068095.02 and COST action D24/0003/01 (OFES contract No. C02.0027) for financial support.

References and notes

1. (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994. (b) Ojima, I. *Catalytic Asymmetric Synthesis*; Wiley: Weinheim, 1993. (c) Morrison, J. D. *Asymmetric Synthesis*; Academic: New York, 1983.
2. (a) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis*; Springer: Berlin, 2000. (b) Tomioka, K. *Synthesis*, 541. (c) Whitesell, J. K. *Chem. Rev.* **1989**, 89, 1581–1590.
3. (a) Bennani, Y. L.; Hanessian, S. *Chem. Rev.* **1997**, *97*, 3161–3195. (b) Lucet, D.; Le Gall, T. *Angew. Chem. Int. Ed.* **1998**, *37*, 2580–2627.
4. (a) Alexakis, A.; Mangeney, P. *Advanced Asymmetric Synthesis*; Stephenson, G. R., Ed.; Chapman & Hall, London, 1996; Chapter 5, pp 93–110. (b) Alexakis, A.; Mangeney, P.; Lensen, N.; Tranchier, J.-P.; Gosmini, R.; Raussou, S. *Pure Appl. Chem.* **1996**, *68*, 531–534. (c) Alexakis, A.; Aujard, I.; Kanger, T.; Mangeney, P. *Org. Synth.* **1998**, *76*, 23–26.
5. Alexakis, A.; Tomassini, A.; Chouillet, C.; Roland, S.; Mangeney, P.; Bernarrddinelli, G. *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 4093–4095.
6. Kizirian, J.-C.; Caille, J.-C.; Alexakis, A. *Tetrahedron Lett.* **2003**, *44*, 8893–8895.
7. (a) Fujieda, H.; Kanai, M.; Kambara, T.; Iida, A.; Tomioka, K. J. *J. Am. Chem. Soc.* **1997**, *119*, 2060–2061. (b) Inoue, I.; Shindo, M.; Koga, K.; Kanai, M.; Tomioka, K. *Tetrahedron: Asymmetry* **1995**, *6*, 2527–2533. (c) Shindo, M.; Koga, K.; Tomioka, K. *J. Am. Chem. Soc.* **1992**, *114*, 8732–8733.
8. (a) Reichstein, T. A.; Grüssner, H.; Zschokke, H. *Helv. Chim. Acta* **1932**, *15*, 1066–1074. (b) Kondo, H.; Suzuki, H.; Takeda, K. *J. Pharm. Soc. Jpn* **1935**, *55*, 142–144. (c) Fieser, L. F.; Fry, E. M.; Jones, R. N. *J. Am. Chem. Soc.* **1939**, *61*, 1849–1853. (d) Shima, K.; Tsutsumi, S. *Bull. Chem. Soc. Jpn* **1963**, *36*, 121–123. (e) Micovic, V. M.; Stojcic, S.; Mladenovic, S.; Stefanovic, M. *Tetrahedron Lett.* **1965**, *21*, 1559–1563. (f) Van Tamelen, E. E.; Schwartz, J.; Brauman, J. I. *J. Am.Chem. Soc.* **1970**, *92*, 5798–5799. (g) Sakakibara, T.; Haraguchi, K. *Bull. Chem. Soc. Jpn* **1980**, *53*, 279–280. (h) Yanagida, S.; Azuma, T.; Kawakani, H.; Kizumoto, H.; Sakuraï, H. *J. Chem. Soc., Chem. Commun.* **1984**, *1*, 21–22. (i) Yanagida, S.; Azuma, T.; Midori, Y.; Pac, C. *J. Chem. Soc. Perkin Trans. 2* **1985**, 1487–1494. (j) Kharrat, A.; Gardat, C.; Maillard, B. *Can. J. Chem.* **1984**, *62*, 2385–2390. (k) Bourgeoit, M. J.; Maillard, B.; Montaudon, E. *Tetrahedron* **1986**, *42*, 5309–5320. (l) Zeug, N.; Büchelev, J.; Kisch, H. *J. Am. Chem. Soc.* **1985**, *107*, 1459–1465. (m) Shine, H. J.; Soroka, M. *Tetrahedron* **1986**, *42*, 6111–6121. (n) Shine, H. J.; Soroka, M. *Tetrahedron* **1986**, *42*, 6111–6121. (o) Crabtree, H.; Brown, S. H. *J. Am. Chem. Soc.* **1989**, *111*, 2946–2953. (p) Lukevics, E.; Gavars, M.; Liepins, E.; Priede, E.; Gerorgyan, V. *J. Organomet. Chem.* **1990**, *393*, 333–338. (q) Kim, Y. H.; Choi, H. C.; Jung, J. C. *Tetrahedron Lett.* **1993**, *34*, 3581–3584. (r) Murai, A.; Fujiward, K.; Nayashi, N. *Tetrahedron* **1997**, *53*, 12425–12468. (s) Severin, T.; Wieser, K.; Negele, S. *J. Org. Chem.* **1998**, *63*, 1138–1143. (t) Kelly, D. R.; Nally, J. *Tetrahedron Lett.* **1999**, *40*, 2209–2212.
9. A single report could be found in the PhD Thesis of Kensaku Nakayama, *Diss. Abstr. Int. B*, **1986**, *47*, 1562; *Chem. Abstr.*, **1986**, *106*, 67029s.
10. Kotsuki, H.; Kuzume, H.; Ghoda, T.; Fukuhara, M.; Ochi, M.; Oishi, T.; Hirama, M.; Shiro, M. *Tetrahedron: Asymmetry* **1995**, *9*, 2227–2236.
11. Trost, B. M.; Calkins, T. L.; Bochet, C. G. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2632–2635.
12. The exact optical purity could not be determined, as bis-THF could not be separated on any chiral GC column. However, the ee should be very high ($>95\%$) as a racemization implies the inversion of two stereogenic centers altogether. Moreover, the rotation value agrees with that reported.[9]
13. Arrasate, S.; Lete, E.; Sotomayor, N. *Tetrahedron: Asymmetry* **2001**, *12*, 2077–2082.
14. Andersson, P. G.; Johansson, F.; Tanner, D. *Tetrahedron* **1998**, *54*, 11549–11566.
15. (a) Denmark, S. E.; Nakajima, N.; Nicaise, O. *J. Am. Chem. Soc.* **1994**, *116*, 8797–8798. (b) Denmark, S. E.; Stiff, C. M. *J. Org. Chem.* **2000**, *65*, 5875–5878.
16. Inoue, I.; Shindo, M.; Koga, K.; Tomioka, K. *Tetrahedron* **1994**, *50*, 4429–4438.
17. (a) Barner, B. A.; Meyers, A. I. *J. Am. Chem. Soc.* **1984**, *106*, 1865–1866. (b) Meyers, A. I.; Brown, J. D.; Laucher, D. *Tetrahedron Lett.* **1987**, *28*, 5274–5282.
18. (a) Tomioka, K.; Shindo, M.; Koga, K. *J. Am. Chem. Soc.* **1989**, *111*, 8266–8268. (b) Mitsuru, S.; Koga, K.; Tomioka, K. *J. Org. Chem.* **1998**, *63*, 9351–9358.
19. Amurrio, D.; Khan, K.; Kundig, E. P. *J. Org. Chem.* **1996**, *61*, 2258–2259.
20. Eis, M. J.; Wrobel, J. E.; Ganem, B. *J. Am. Chem. Soc.* **1984**, *106*, 3693–3694.
21. (a) Mizuno, M.; Kanai, M.; Iida, A.; Tomioka, K. *Tetrahedron: Asymmetry* **1996**, *7*, 2483–2484. (b) Mizuno, M.; Kanai, M.; Iida, A.; Tomioka, K. *Tetrahedron* **1997**, *53*, 10699–10708.
22. Alexakis, A.; Vrancken, E.; Mangeney, P. *Synlett* **1998**, 1165–1167.
23. (a) Takano, S.; Kurotaki, A.; Ogasawara, K. *Synthesis* **1987**, 1075–1078. (b) Wiggins, L. F. *J. Chem. Soc.* **1946**, 13–16.
24. For a structurally related *S* analogue, derived from benzothiophene, see: Madec, D.; Mingoia, F.; Maitro, G.; Giambatista, G.; Poli, G. *Eur. J. Org. Chem.* Submitted for publication.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 60 (2004) 9485–9491

(2*S*,5*R*/2*R*,5*S*)-Aminoethylpipecolyl *aepip*-*aeg*PNA chimera: synthesis and duplex/triplex stability

Pravin S. Shirude, Vaijayanti A. Kumar* and Krishna N. Ganesh*

Division of Organic Chemistry (Synthesis), National Chemical Laboratory, Pune 411008, Maharashtra, India

Received 26 March 2004; revised 8 July 2004; accepted 28 July 2004

Abstract—This article reports the design and facile synthesis of novel chiral six-membered PNA analogues (2*S*,5*R*/2*R*,5*S*)-1-(*N*-Boc-aminoethyl)-5-(thymin-1-yl)pipecolic acid, *aepip*PNA **IV** that upon incorporation into standard *aeg*PNA sequences effected stabilization of complexes with complementary target DNA. Substitution of *aeg*PNA unit by the designed monomer at the C-terminus was more effective than substitution at N-terminus. The stabilizing behaviour improved with degree of substitution and was found to be dependent on their relative positions in the sequence. The six-membered piperidine ring in the design may freeze the rigid chair conformations and the relative stereochemistry of the substituents may in effect direct the complex formation with DNA/RNA by sequence-specific nucleobase recognition. In the present *aepip*PNA analogues, the L-*trans* stereochemical disposition of the substituents seems to lead to the favorable pre-organization of the PNA oligomers for complex formation with DNA. The results reported here further expand the repertoire of cyclic PNA analogues.
© 2004 Published by Elsevier Ltd.

1. Introduction

Peptide nucleic acids (*aeg*PNA), a new class of DNA (**I**) (Fig. 1) mimics invented a decade ago are gaining importance as novel potential antigene and antisense agents in the field of medicinal chemistry. In *aeg*PNA (**II**), the charged sugar-phosphate backbone of DNA is replaced by a neutral and achiral polyamide backbone consisting of *N*-(2-aminoethyl)glycyl units.[1] The nucleobases are attached to this backbone through a rigid tertiary acetamide linker group and PNA binding to the target DNA/RNA sequences occurs with high sequence specificity and affinity.[2] In spite of its resistance to cellular enzymes such as nucleases and proteases, the major limitations confounding its application are ambiguity in orientational selectivity of binding, poor solubility in aqueous media and inefficient cellular uptake.[3,4] The (2-aminoethyl)-glycyl fused segment constituting the *aeg*PNA backbone is highly flexible and slowly reorganizes to the energetically preferred conformation for complex formation with DNA/RNA. Preorganizing the *aeg*PNA backbone into hybridization competent conformations should have entropic advantages. Our efforts[5–7] and those of others[8] to improve the properties of *aeg*PNA by optimal tuning of the PNA backbone to bind the complementary nucleic acids through a pre-organization strategy has resulted in a number of five-membered pyrrolidinyl PNA analogues. The configuration of the pyrrolidine ring and the mode of attachment of the nucleobase to the ring were found to be primarily responsible for the observed effects on the binding efficiency of chimeric pyrrolidinyl-*aeg*PNAs.[5,8] The five-membered pyrrolidine ring in *aep*PNA **III** is probably conformationally quite flexible, and the selection between parallel/antiparallel modes of binding to complementary DNA, although better than *aeg*PNA, was not

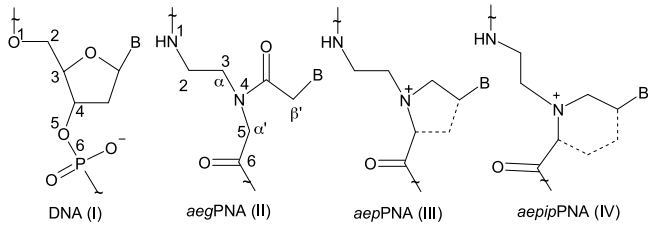


Figure 1. Structure of DNA, PNA, and modified PNAs.

Keywords: Peptide nucleic acids; Pipecolic acid PNA; *aepip*PNA.
* Corresponding authors. Tel./fax: +91-20-2589-3153; e-mail: kng@ems.ncl.res.in

0040–4020/$ - see front matter © 2004 Published by Elsevier Ltd.
doi:10.1016/j.tet.2004.07.080

comparable with DNA itself.[5] Also, the binding efficiency was found to be nucleobase-dependent.[6] The fairly rigid six-membered ring structures as in hexose[9] and hexitol[10] nucleic acids have shown excellent section of parallel/antiparallel modes of binding to DNA. This has triggered interest in six-membered PNA analogs,[11] although with some initial misgivings.[12]

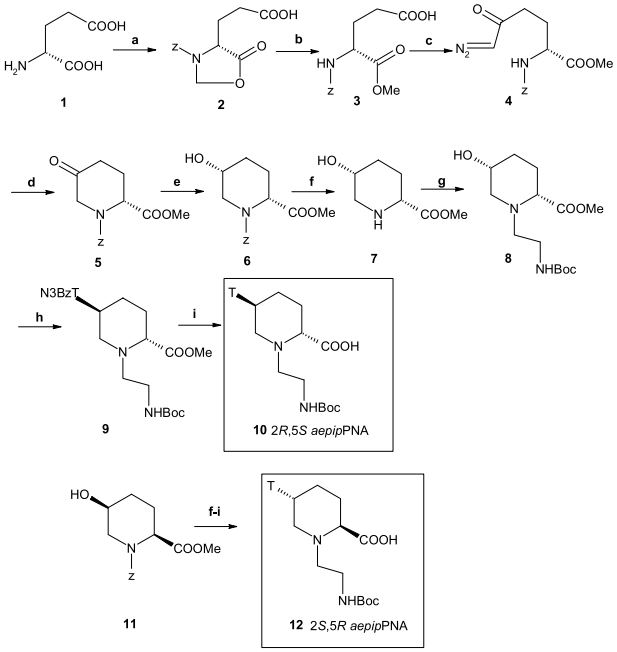
Recently, we reported the synthesis of chimeric PNAs, in which one of the isomers (2*S*,5*R*) of aminoethylpipecolyl PNA, *aepip*PNA **IV**,[13] was introduced at pre-determined sites of the oligomers. This six-membered homologue of *aep*PNA is derived by bridging the α′-C atom of the glycyl unit and the β′-C atom of linker to nucleobase in PNA with an ethylene bridge instead of a methylene bridge in **III**. The nucleobase in **IV** is directly attached to the piperidine ring at the C5 position, without altering the net number of backbone atoms connecting two successive nucleobases. In this article, we report the detailed synthesis and characterization of its enantiomer (2*R*,5*S*) from D-glutamic acid. The synthesis of chimeric, chiral (*aeg-aepip*PNA backbone) triplex forming (polypyrimidine) and duplex forming (mixed purine-pyrimidine) PNA sequences and their hybridization properties with the complementary DNA are presented.

1.1. Chemical syntheses of *aepip*PNA monomers

The syntheses of the (2*R*,5*S*) and (2*S*,5*R*) 1-(*N*-Boc-aminoethyl)-5-(*N*3-benzoylthymin-1-yl)pipecolic acid methyl ester was achieved in 10 steps starting from the D-glutamic acid **1** and the naturally occurring L-glutamic acid, respectively (Scheme 1). The selective protection of the α-amino group in D-glutamic acid **1** was achieved via formation of the oxazolidinone **2** followed by ring opening with sodium methoxide to yield the α-ester **3** in 82% yield. This, upon treatment with ethyl chloroformate, gave the corresponding mixed anhydride that on reaction with diazomethane generated the diazoketone **4** in 65% overall yield from **3**. The direct conversion of diazoketone **4** to the protected 5-oxopipecolic acid **5** was achieved by ring closure carbene insertion into the N–H bond using rhodium (II) acetate as catalyst. Finally, stereospecific reduction with sodium borohydride gave the *cis*-5-hydroxy-D-pipecolic acid ester **6**, which was *N*1-deprotected to give **7**. *N*1-Alkylation of the piperdine ring in the pipecolic acid methyl ester **7** with *N*-Boc-aminoethyl mesylate[6] afforded the (1-*N*-Boc-aminoethyl)pipecolic acid ester **8**. The replacement of the 5*R*-hydroxyl function in **8** with *N*3-benzoylthymine under Mitsunobu reaction conditions yielded the (2*R*,5*S*)-5-(*N*3-benzoylthymin-1-yl) pipecolate ester **9**, accompanied by inversion of stereochemistry at C5. The simultaneous hydrolysis of the methyl ester and removal of N3-benzoyl protecting group of thymine was achieved by treatment with 1 M sodium hydroxide in aqueous methanol to obtain (2*R*,5*S*)-1-(*N*-Boc-aminoethyl)-5-(thymin-1-yl)pipecolic acid **10** as the desired monomer. Synthesis of the enantiomeric (2*S*,5*R*) **12** was accomplished[13] starting from *cis*-5*S*-hydroxy-2*S*-*N*1-benzyloxycarbonyl pipecolate methyl ester **11** obtained from L-glutamic acid according to Bailey et al.[14,15] The structural integrity of the *aepip*PNA monomers **10** and **12** was confirmed by spectral analysis (^{1}H, ^{13}C NMR and mass spectrometry) and optical rotation with opposite signs as shown in Section 4.

1.2. Solid phase synthesis of *aeg-aepip*PNA oligomers

PNA oligomers containing the *aepip*PNA units were assembled by solid-phase peptide synthesis on Merrifield resin derivatized with *N*-Boc-β-alanine. The *aepip*PNA monomers **12** and **10** were suitably incorporated into the PNA octamer sequence H-T$_8$-NHCH$_2$CH$_2$COOH at



Scheme 1. Synthesis of *aepip*PNA monomers. a. (i) Benzyloxy carbonyl chloride, $NaHCO_3$ (94%) (ii) $(CH_2O)_n$, TsOH, benzene, reflux (82%); b. NaOMe, MeOH (93%); c. (i) EtOCOCl, Et_3N, THF (ii) CH_2N_2, Et_2O (65%); d. $[Rh(OAc)_2]_2$, benzene, reflux (52%); e. $NaBH_4$, MeOH (93%); f. H_2/Pd–C, 60 psi (92%); g. BOC-NH-$(CH_2)_2$OMs, DIPEA, ACN:DMF (37%); h. *N*3-BzT, DIAD, PPh_3, THF (32%); i. 1 M NaOH, MeOH/water (95%).

predefined positions to yield the modified *aeg*PNAs **13**–**14** and **18**–**21**, respectively. The modified monomer (2*S*,5*R*) **12** was also incorporated into a mixed base homopyrimidine sequence **15**. For control studies, the unmodified *aeg*PNA sequences H-T_8-$NHCH_2CH_2$-COOH **16** and H-TTCTCTTT-$NHCH_2CH_2$-COOH **17** were synthesized by similar procedures. The oligomers after solid phase assembly were cleaved from the support by treatment with TFA-TFMSA[16] to yield the corresponding PNAs carrying β-alanine at the carboxy terminus. PNAs (**13**–**26**) were purified by FPLC on a PepRPC column, and the purity of the oligomers was rechecked by HPLC on RPC-18 column and these were characterized by MALDI-TOF mass spectrometry.[17]

The modified *aeg*-*aepip*PNA oligomers **13**, **14**, **18**–**21** permit the study of the positional effects on PNA_2:DNA triplex stability, while the mixed base PNA sequences **25**–**26** allow explicit testing of the relative stereochemical effects of (2*S*,5*R*) and (2*R*,5*S*) *aepip*PNA units on duplex formation. The complementary DNA oligomer **22** having CG/GC lock at the end to prevent slippage, complementary DNA for mixed homopyrimidine sequence **23**, and a mismatched sequence **24** and DNA **27**–**28** for constituting the duplexes were synthesized on an automated DNA synthesiser using standard phosphoramidite chemistry,[18] followed by ammonia deprotection. These were purified by gel filtration and their purities checked by HPLC.

The pK_a of the piperidine ring nitrogen of the *aepip*PNA monomer was determined by acid–base titration and found to be 6.76, not very much different from 6.72 for the pyrrolidine nitrogen in *aep*PNA.[5] The constituted PNA oligomers are thus expected to be partially protonated under physiological conditions. No precipitation was observed in samples of *aepip*PNA even after prolonged storage, suggesting improved solubility of *aepip*PNA oligomers.

2. Results and discussion

2.1. UV-T_m studies on PNA_2–DNA triplexes

The polypyrimidine PNA oligomers (**13**–**21**, Tables 1 and 2) are homopyrimidine sequences that are well known to form DNA:PNA_2 triplexes.[19] The DNA:*aeg*-*aepip*PNA stoichiometry in these complexes was found to be 1:2 from mixing curves (Job's plot) generated from CD ellipticity data at 260 nm. Hence, all complementation studies were performed with 1:2 stoichiometries of DNA and *aeg*/*aepip*PNA (Fig. 2).

Table 2. UV-T_m (°C) of DNA:PNA_2 complexes[a]

Entry		PNA	T_m
1	**18**	H-T T T T **t** T T T-(β-Ala)-OH	44 (10.9)
2	**19**	H-T T T T T **t** T **t**-(β-Ala)-OH	52 (26.7)
3	**20**	H-T T T **t** T T T **t**-(β-Ala)-OH	51 (25.2)
4	**21**	H-T **t** T T T T T **t**-(β-Ala)-OH	49 (14.3)

[a] DNA: **22**, 5′-GCAAAAAAAACG-3′; **23**, 5′-AAAGAGAA-3′; **24**, 5′-GCAAAATAAACG-3′; T=*aeg*-PNA; **t**=*aepip*PNA; Buffer: 10 mM sodium phosphate, pH 7.30. T_m values are accurate to (±)0.5 °C. Experiments were repeated at least three times and the T_m values were obtained from the peaks in the first derivative plots. Values in parentheses represent % hyperchromicity.

The thermal stabilities of PNA_2:DNA complexes were studied by temperature dependent UV absorbance measurements. The temperature-percent hyperchromicity first derivative plots for DNA:PNA_2 triplexes indicated a single transition (Figs. 3 and 4B), characteristic of both PNA strands dissociating simultaneously from DNA in a single step. The T_m values (entries 1 and 2, Table 1) indicate that the *aepip*PNA oligomers **13** and **14** having single modification of either stereomer at N or C-terminus exhibited stabilization compared to the unmodified PNA T_8 homooligomer (**16**). While a (2*S*,5*R*) *aepip* unit at the N-terminus has better stability of its complex with the complementary DNA **22** compared to (2*R*,5*S*), the situation was reversed for corresponding modification at C-terminus; the (2*R*,5*S*) oligomer forming the much more stable hybrid compared to that of the (2*S*,5*R*) oligomers (entry 2). As the percent hyperchromicity of this particular transition was found to be very low, the complex formation was confirmed by a CD

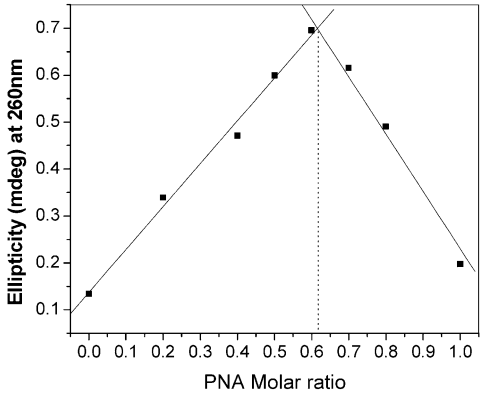


Figure 2. A CD mixing curve (Job's plot) of complex **14**:**22**(2*R*,5*S*).

Table 1. UV-T_m (°C) of DNA:PNA_2 complexes[a]

Entry		PNA	PNA_2:DNA	UV-T_m (°C)	
				2*S*,5*R*	2*R*,5*S*
1	**13**	H-**t** T T T T T T T-(β-Ala)-OH	**13**:**22**	43 (23.4)	36 (8.0)
2	**14**	H-T T T T T T T **t**-(β-Ala)-OH	**14**:**22**	48 (19.2)	76 (2.3)
			14:**24**	24 (3.7)	23 (3.3)
3	**15**	H-**t** T C T C T T T-(β-Ala)-OH	**15**:**23**	60 (26.7)	56 (26.6)
4	**16**	H-T T T T T T T T-(β-Ala)-OH	**16**:**22**	43 (18.3)	
5	**17**	H-T T C T C T T T-(β-Ala)-OH	**17**:**23**	51 (18.5)	

[a] DNA: **22**, 5′-GCAAAAAAAACG-3′; **23**, 5′-AAAGAGAA-3′; **24**, 5′-GCAAAATAAACG-3′; T=*aeg*-PNA; **t**=*aepip*PNA; Buffer: 10 mM sodium phosphate, pH 7.30. T_m values are accurate to (±)0.5 °C. Experiments were repeated at least three times and the T_m values were obtained from the peaks in the first derivative plots. Values in parentheses represent % hyperchromicity.

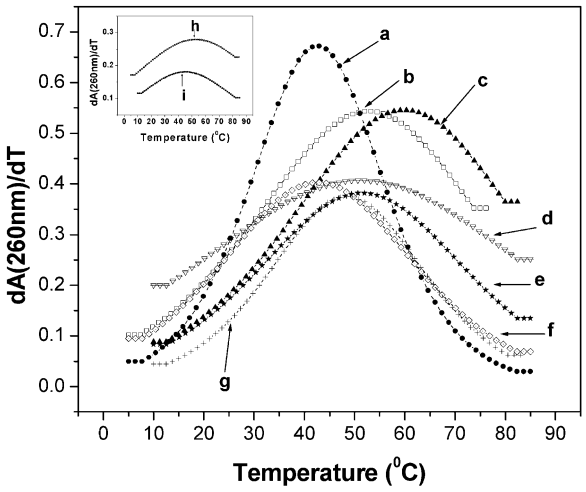


Figure 3. UV-melting first derivative curves of PNA_2:DNA (2*S*,5*R*) complexes. a. **13**:**22**; b. **19**:**22**; c. **15**:**23**; d. **20**:**22**; e. **17**:**23**; f. **16**:**22**; g. **21**:**22**. Inset: h. **14**:**22**, i. **18**:**22**.

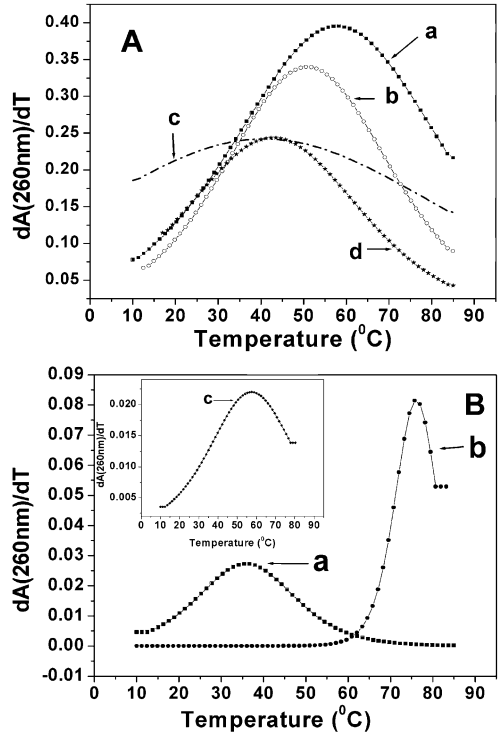


Figure 4. UV-melting first derivative curves. (A) (2*S*,5*R*) PNA:DNA duplexes. a. **25**:**27**; b. **26**:**27**; c. **25**:**28**; d. **26**:**28**. (B) (2*R*,5*S*) PNA_2:DNA triplexes. a. **13**:**22**; b. **14**:**22**; inset c. **15**:**22**.

mixing curve (Job's plot) and was found to be 2:1 PNA_2:DNA complex. The complex formation **14**:**22** was further confirmed by the introduction of single mismatched base in **14**:**24**. The mismatched complex **14**:**24** was destabilized by a larger extent (ΔT_m −53 °C) for (2*R*,5*S*) *aepip* stereochemistry and by $\Delta T_m \sim -24$ °C for (2*S*,5*R*) *aepip* stereochemistry. The control mismatch complex with unmodified PNA (**16**:**24**) showed a linear increase in absorbance without any sigmoidal transition.

The stability of the DNA complexes of *aeg-aepip*-PNA oligomers with mixed pyrimidine base sequence and N-terminus modifications (**15**:**23**) was higher by 5 °C for (2*R*,5*S*) and 9 °C for (2*S*,5*R*) as compared to that of the control complex **17**:**23** (entries 3 and 5 Table 1). The percent hyperchromicity was enhanced compared to the control complex in these transitions when chiral unit is at the N-terminus. Only in the case of the complex **14**:**22** (2*R*,5*S*) and **18**:**22** (2*S*,5*R*),(Table 2) where the *aepip* unit is in the center of the sequence, percent hyperchromicity accompanying the melting was found to be low.

A single (2*S*,5*R*) *aepip* modification in the middle of the sequence did not affect the stability of the DNA hybrid (Table 2, entry 1). Increasing the number of *aepip*PNA modifications further enhanced the T_m (Table 2, entry 2–4). PNA oligomers with one *aepip* modification at C-terminus and a second *aepip* unit at the third (**19**), fifth (**20**) or seventh (**21**) base positions, respectively, were used to study the relative positional effects of the modifications. A synergistic stabilizing effect was observed with a second modified *aepip* unit in all the cases (**19**:**22**, **20**:**22** and **21**:**22**). The maximum benefit per additional unit was observed (ΔT_m + 4 °C) when the second *aepip*PNA unit was separated by one base (**19**:**22**). (Table 2).

The mixed purine-pyrimidine *aeg-aepip*PNA (**25**) and *aeg*PNA (**26**) oligomers were synthesized to examine the orientational selectivity in binding to DNA. The UV-T_m profiles of complexes of PNAs **25** and **26** with DNA sequences **27** and **28** designed to bind in antiparallel and parallel orientations, respectively, is shown in Fig. 4 and values given in Table 3. In both PNAs, the antiparallel duplex was more stable than the parallel duplex. However, the modified *aeg-aepip*PNA **25** (2*S*,5*R*) stabilized the antiparallel duplex (DNA **27**) by 17 °C compared to the 8 °C by *aeg*PNA over the parallel duplex. The complex formation was confirmed by a CD mixing curve (Job's plot) and was found to be a 1:1 PNA:DNA complex (Supplementary material).

Table 3. UV-T_m (°C) of DNA:PNA (2*S*,5*R*) duplexes[a]

	PNA	PNA:DNA	UV-T_m (°C)
25	H- A T G **t** T C T C T T T-(β-Ala)-OH (*ap*)	**25**:**27**	57.8 (20.2)
	(*p*)	**25**:**28**	40.8 (15.0)
26	H- A T G T T C T C T T T-(β-Ala)-OH (*ap*)	**26**:**27**	51.2 (16.2)
	(*p*)	**26**:**28**	43.0 (11.3)

[a] T, C, A, G=*aeg*-PNA; **t**=*aepip*PNA; DNA: **27**, 5′-AAAGAGAACAT-3′; **28**, 3′-TACAAGAGAAA-5′; Buffer: 10 mM sodium phosphate, pH 7.30. T_m values are accurate to (±)0.5 °C. Experiments were repeated at least three times and the T_m values were obtained from the peaks in the first derivative plots. Values in parentheses represent % hyperchromicity.

The PNA_2:DNA triplexes and PNA:DNA duplexes are expected to differ in the base stacking patterns, and this should be reflected in their circular dichroism (CD) spectra. The CD profile for single stranded *aepip*PNA **13** (2*S*,5*R*) and (2*R*,5*S*) were observed as mirror images of each other (Supplementary data). Figure 5A shows the CD profiles of *aeg*PNA and selected *aeg-aepip*PNA (2*S*,5*R*) triplexes while Figure 5B shows the CD profiles of *aeg*PNA and *aeg-aepip*PNA (2*S*,5*R*) duplexes. The positive double hump profile seen in 250–265 nm region is characteristic of polyT.polyA.polyT triplexes. The duplexes show a different CD profile compared to triplexes and the overall CD patterns suggest that incorporation of chiral pipecolic units does not very much alter the base stacking.

Thus overall, the substitution of the six-membered *aepip*PNA monomer in both enantiomeric (2*S*,5*R*) and (2*R*,5*S*) forms into the *aeg*PNA backbone increased the T_m of the derived complexes with DNA. This is interesting since in an earlier study[12] it had been remarked that the six-membered piperidine rings are unlikely to stabilize the derived PNA structures for complex formation. In the present *aepip*PNA analogues the stereochemical dispositions of substituents seem to lead to a favorable pre-organization of PNA backbone for the formation of stable triplexes with DNA. In this context, work on *aepip*PNAs derived from other nucleobases and on the duplex and triplex stability is under progress.

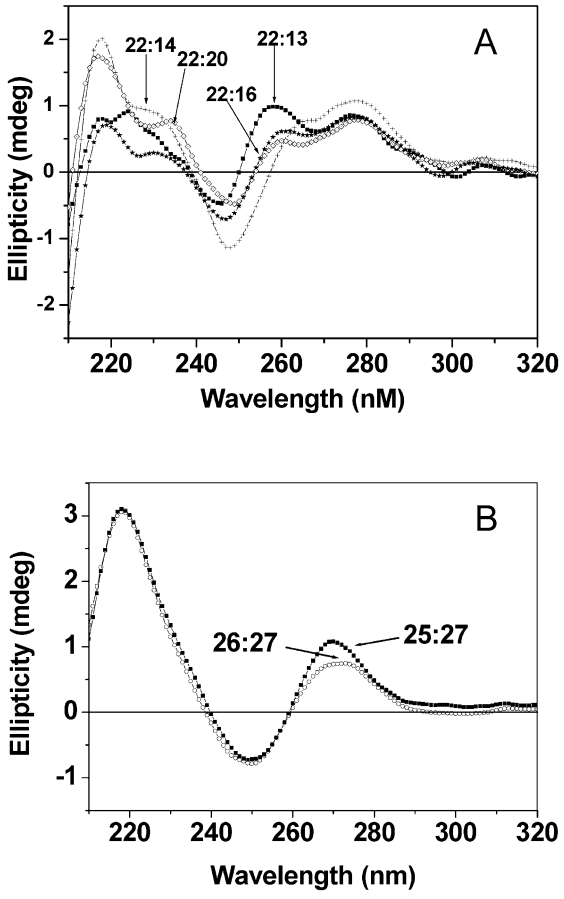


Figure 5. CD spectra of *aeg-aepip*PNA:DNA complexes. A. (2*S*,5*R*) triplexes. B. (2*S*,5*R*) duplexes.

3. Conclusion

In summary, this article reports the design and synthesis of novel six-membered pipecolic acid derived PNA analogues (2*S*,5*R* and 2*R*,5*S*)-1-(*N*-Boc-aminoethyl)-5-(thymin-1-yl)pipecolic acid. The homopyrimidine-*aeg*PNA backbone comprising these units effect stabilization of the resulting triplexes with complementary DNA strands depending upon stereochemistry and position of the modified unit. A single modified 2*S*,5*R* *aepip*PNA unit in the center of a mixed purine-pyrimidine duplex forming oligomer discriminates the parallel versus antiparallel DNA sequence much better than the unmodified *aeg*PNA. The results reported here further expand the repertoire of cyclic PNA analogues to six-membered series and future work is focused on studying the properties of other nucleobases.

4. Experimental

4.1. General

The chemicals used were of laboratory or analytical grade and the solvents used were purified according to the literature procedures.[20] The reactions were monitored by TLC and usual work-up implies sequential washing of the organic extract with water and brine followed by drying over anhydrous sodium sulfate and evaporation under vacuum. Column chromatography was performed for purification of compounds on silica gel (60–120 mesh). TLCs were carried out on pre-coated silica gel GF_{254} aluminium sheets. TLCs were performed using dichloromethane–methanol or petroleum ether–ethyl acetate solvent systems for most compounds. Free acids were chromatographed by TLC using a solvent system of methanol/acetic acid/water in the proportion 9:1:1. The compounds were visualized with UV light and/or by spraying with Ninhydrin reagent subsequent to Boc-deprotection (exposing to HCl vapors) and heating. The DNA oligomers were synthesized on CPG solid support by β-cyanoethyl phosphoramidite chemistry followed by ammonia treatment[21] and their purities checked by HPLC prior to use. *aeg*PNA monomers were synthesized according to literature procedures.[22]

4.1.1. 5-(*S*/*R*)-Hydroxy-*N*-benzyloxycarbonyl-2-(*S*/*R*)-pipecolic acid methyl ester (6). A cooled (0 °C) solution of 5-oxo-*N*-benzyloxycarbonyl-2-(*S*/*R*)-pipecolic acid methyl ester **5** (3.2 g, 10.8 mmol) in methanol (50 mL) was treated with sodium borohydride (0.62 g, 16.3 mmol). After stirring for 2 h, the reaction mixture was concentrated in vacuo and the residue was dissolved in ethyl acetate (100 mL). The organic solution was washed with 10% ammonium chloride solution, brine, dried over sodium sulfate and concentrated. The resulting residue was chromatographed to give colourless oil **6** (3.0 g, 93%).[10]

4.1.2. 5-(*S*)-Hydroxy-*N*-benzyloxycarbonyl-2-(*S*)-pipecolic acid methyl ester. ^{1}H NMR ($CDCl_3$) δ: 7.35 (s, 5H), 5.14 (s, 2H), 4.90 and 4.78 (br d, $J=4.4$ Hz, 1H), 4.30–4.10 (m, 1H), 3.73–3.55 (m, 4H), 2.89–2.72 (m, 1H), 2.35–2.28 (m, 1H) 2.00–1.66 (m, 3H), 1.35–1.15 (m, 1H): $[\alpha]_{589}^{25} = -17.8$ (*c* 0.9, CH_3OH) (lit.[14] not reported).

4.1.3. 5-(*R*)-Hydroxy-*N*-benzyloxycarbonyl-2-(*R*)-pipecolic acid methyl ester. ^{1}H NMR ($CDCl_3$) δ: 7.35 (s, 5H), 5.15 (s, 2H), 4.89–4.77 (m, 1H), 4.27–4.21 (m, 1H), 3.73–3.65 (m, 4H), 2.85–2.71 (m, 1H), 2.48–2.26 (m, 2H) 1.98–1.73 (m, 2H): $[\alpha]_{D\ 589}^{25} = +15.38$ (*c* 0.26, CH_3OH).

4.1.4. 5-(*S*)-Hydroxy-2-(*S*)-pipecolic acid methyl ester (7). The N-deprotection of methyl ester **6** (2.20 g, 7.8 mmol) was done under hydrogenation over Pd–C (10%) to obtain **7** (1.10 g, 92%). ^{1}H NMR ($CDCl_3$) δ: 3.83–3.81 (m, 1H), 3.74 (s, 3H), 3.40–3.33 (t, $J=6.6$ Hz, 1H), 3.08–3.00 (dd, $J=2.4$, 12 Hz, 1H) 2.88–2.80 (dd, $J=2$, 12.2 Hz, 1H), 1.90–1.83 (m, 3H), 1.74–1.61 (m, 1H).

4.1.5. 1-(*N*-Boc-aminoethyl)-5-(*S*/*R*)-hydroxy-2-(*S*/*R*)-pipecolic acid methyl ester (8). To a cooled solution of 5-(*S*/*R*)-hydroxy-2-(*S*/*R*)-pipecolic acid methyl ester **7** (1.0 g, 6.3 mmol), DIPEA (2.7 mL, 15.7 mmol), DMAP (0.15 g, 1.3 mmol) in dry DMF/acetonitrile (1:1) (10 mL) was added with stirring for 15 min. *N*-Boc aminoethyl mesylate (1.50 g, 6.3 mmol) in DMF (3 mL) was then added and the reaction mixture was heated to 50 °C for 20 h. Evaporation of the solvent followed by column chromatography gave thick brown oil of **8** (0.7 g, 37%).

4.1.6. 1-(*N*-Boc-aminoethyl)-5-(*S*)-hydroxy-2-(*S*)-pipecolic acid methyl ester. ^{1}H NMR ($CDCl_3$) δ: 5.18 (br s, 1H), 3.93–3.82 (m, 1H), 3.73 (s, 3H), 3.54–3.50 (m, 3H), 3.05–2.99 (m, 1H) 2.75–2.50 (m, 3H), 1.90–1.64 (m, 4H), 1.45 (s, 9H): ^{13}C NMR ($CDCl_3$) δ: 175.1, 161.2, 79.2, 64.9, 62.8, 55.3, 55.1, 51.8, 40.6, 37.2, 29.1, 28.3: $[\alpha]_{D\ 589}^{25} = -10.7$ (*c* 0.56, CH_3OH). MS: (ESI) M_{calc}: 302.37, M_{obs}: 302.

4.1.7. 1-(*N*-Boc-aminoethyl)-5-(*R*)-hydroxy-2-(*R*)-pipecolic acid methyl ester. ^{1}H NMR ($CDCl_3$) δ: 5.34 (br s, 1H), 3.96–3.93 (m, 1H), 3.75 (s, 3H), 3.41–3.25 (m, 3H), 3.16–3.13 (m, 1H) 2.69–2.63 (m, 3H), 1.96–1.66 (m, 4H), 1.45 (s, 9H): ^{13}C NMR ($CDCl_3$) δ: 173.47, 156.26, 79.13, 65.67, 64.90, 55.69, 54.98, 51.55, 40.60, 37.70, and 28.43: $[\alpha]_{D\ 589}^{25} = +11.9$ (*c* 0.42, CH_3OH). MS: (ESI) M_{calc}: 302.37, M_{obs}: 302.

4.1.8. 1-(*N*-Boc-aminoethyl)-5-(*R*/*S*)-(*N*3-benzoylthymin-1-yl)-2-(*S*/*R*)-pipecolic acid methyl ester (9). To a stirred solution of 1-(*N*-Boc-aminoethyl)-5-(*S*/*R*)-hydroxy-2-(*S*/*R*)-pipecolic acid methyl ester **8** (0.55 g, 1.8 mmol), *N*3-benzoylthymine (0.84 g, 3.6 mmol) and triphenyl phosphine (0.95 g, 3.6 mmol) in dry THF (10 mL) at 0 °C, was added dropwise diethylazodicarboxylate (DIAD, 0.47 mL, 3.6 mmol). After completion of the reaction as indicated by TLC (24 h), the solvent was removed in vacuo and residue purified by silica gel column chromatography to get the pure product **9** (0.3 g, 32% yield).

4.1.9. 1-(*N*-Boc-aminoethyl)-5-(*R*)-(*N*3-benzoylthymin-1-yl)-2-(*S*)-pipecolic acid methyl ester. ^{1}H NMR ($CDCl_3$) δ: 7.92 (s, 1H), 7.88 (s, 1H), 7.62–7.44 (m, 4H) 5.28 (br s, 1H), 3.74 (s, 1H), 3.72 (s, 3H), 3.48–3.22 (m, 3H), 2.94–2.69 (m, 3H) 2.14–2.00 (m, 1H), 2.00 (s, 3H), 2.00–1.63 (m, 4H), 1.42 (s, 9H): ^{13}C NMR ($CDCl_3$) δ: 175.3, 169.0, 163.2, 156.0, 150.3, 142.5, 138.8, 131.6, 130.3, 129.1, 109.5, 79.5, 66.6, 64.7, 56.0, 52.2, 51.2, 39.7, 29.4, 28.4, 27.7, 12.2: $[\alpha]_{D\ 589}^{25} = +10.0$ (*c* 0.5, CH_3OH). MS: (ESI) M_{calc}: 514.58, M_{obs}: 514.

4.1.10. 1-(*N*-Boc-aminoethyl)-5-(*S*)-(*N*3-benzoylthymin-1-yl)-2-(*R*)-pipecolic acid methyl ester. ^{1}H NMR ($CDCl_3$) δ: 7.90–7.89 (m, 2H), 7.68–7.45 (m, 4H) 5.24 (br s, 1*H*), 3.75 (s, 1H), 3.72 (s, 3H), 3.46–3.22 (m, 3H), 3.00–2.68 (m, 3H) 2.16–2.00 (m, 1H), 2.00 (s, 3H), 1.96–1.67 (m, 4H), 1.43 (s, 9H): ^{13}C NMR ($CDCl_3$) δ: 175.55, 169.36, 163.50, 156.27, 150.57, 142.84, 135.13, 131.91, 130.62, 129.39, 109.76, 79.82, 66.87, 64.97, 56.26, 52.50, 51.51, 39.99, 29.67, 28.66, 28.02, 12.53: $[\alpha]_{D\ 589}^{25} = -12.0$ (*c* 0.25, CH_3OH). MS: (ESI) M_{calc}: 514.58, M_{obs}: 515.

4.1.11. 1-(*N*-Boc-aminoethyl)-5-(*R*/*S*)-(thymin-1-yl)-2-(*S*/*R*)-pipecolic acid (10). To a solution of the methyl ester **9** (0.36 g, 0.7 mmol) in methanol (2 mL), was added aqueous 2 M NaOH (2 mL). The reaction mixture was further stirred overnight followed by neutralization with Dowex-50 H^+ resin, which was then filtered off. The filtrate was concentrated under vacuum and the residue was taken up in water. This was washed with ethyl acetate before concentrating it to dryness to obtain the product **10** (0.25 g, 95%) as white solid foam.

4.1.12. 1-(*N*-Boc-aminoethyl)-5-(*R*)-(thymin-1-yl)-2-(*S*)-pipecolic acid. ^{1}H NMR (D_2O) δ: 7.50 (s, 1H) 4.52–4.44 (m, 1H), 4.21–3.94 (m, 3H) 3.50–3.45 (m, 4H), 2.34–2.24 (m, 4H), 1.89 (s, 3H), 1.45 (s, 9H): $[\alpha]_{D\ 589}^{25} = +32.0$ (*c* 0.1, CH_3OH). MS: (ESI) M_{calc}: 396.45, M_{obs}: 396.

4.1.13. 1-(*N*-Boc-aminoethyl)-5-(*S*)-(thymin-1-yl)-2-(*R*)-pipecolic acid. ^{1}H NMR (D_2O) δ: 7.55 (1H) 4.55–4.48 (m, 1H), 4.26–3.94 (m, 3H) 3.54–3.42 (m, 4H), 2.50–2.32 (m, 3H), 1.81–1.72 (m, 1H), 1.96 (s, 3H), 1.51 (s, 9H): $[\alpha]_{D\ 589}^{25} = -34.0$ (*c* 0.1, CH_3OH). MS: (ESI) M_{calc}: 396.45, M_{obs}: 398.

4.2. Solid phase synthesis of the PNA oligomers on the solid support

The PNA oligomers were synthesized manually by solid phase peptide synthesis using the Boc-protection strategy and employing diisopropylcarbodiimide (DIPCDI) or *O*-(Benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′ tetramethyl-uronium hexafluorophosphate (HBTU) and 1-hydroxy-benzotriazole (HOBt) as the coupling agents. The solid support used was Merrifield resin derivatized with β-alanine (0.17 mequiv/g resin). The synthesis involved repetitive cycles, each comprising (i) deprotection of the N-protecting Boc-group using 50% trifluoroacetic acid (TFA) in CH_2Cl_2, (ii) neutralization of the TFA salt formed with DIPEA (5% solution in CH_2Cl_2, v/v) and (iii) coupling of the free amine with the free carboxylic acid group of the incoming monomer (4 equiv) in the presence of DIPCDI and HOBt, in DMF or NMP as the solvent. The deprotection of the *N*-Boc protecting group and the coupling reaction were monitored by Kaiser's test.[23] The coupling efficiencies were found to be >98%.

The PNA oligomers were cleaved from the solid support using TFA-TFMSA to yield oligomers with free carboxy terminus.[10] The resin-bound PNA oligomer (10 mg) was

stirred in an ice-bath with thioanisole (20 μL) and 1,2-ethanedithiol (8 μL) for 10 min. TFA (120 μL) was then added and the stirring was continued for another 10 min followed by TFMSA (16 μL) while cooling in an ice-bath and stirring for 2 h. The reaction mixture was filtered through a sintered funnel, the residue washed with TFA (3×2 mL) and the combined filtrate and washings were evaporated under vacuum. The residual pellet was re-dissolved in methanol (~0.1 mL) and re-precipitated by adding ether to obtain the crude PNA oligomer. This was desalted by gel filtration over Sephadex G25 and the purity of the PNA oligomer as checked by RP HPLC on a C18 column was found to be >90%.

4.3. UV-melting

The concentration of the PNA oligomers was calculated on the basis of the absorption at 260 nm, assuming the molar extinction coefficients of the nucleobases to be as in DNA, T, 8.8 cm^2/μmol; C, 7.3 cm^2/μmol; G, 11.7 cm^2/μmol and A, 15.4 cm^2/μmol. The PNA oligomers (**13–21**) and the appropriate complementary DNA oligonucleotide (**22/23/24**) were mixed together in a 2:1 molar ratio, while PNA oligomers (**25–26**) and the appropriate complementary DNA oligonucleotide (**27/28**) were mixed together in a 1:1 molar ratio in 0.01 M sodium phosphate buffer, pH 7.3 to get a final strand concentration of 1.5 and 2 μM, respectively The samples were annealed by heating at 85 °C for 1–2 min, followed by slow cooling to room temperature, kept at room temperature for ~30 min and then, refrigerated overnight. The samples were heated at a rate of 0.2 or 0.5 °C rise per minute and the absorbance at 260 nm was recorded at every minute. The percent hyperchromicity at 260 nm was plotted as a function of temperature and the melting temperature was deduced from the peak in the first derivative plots.

Acknowledgements

P. S. S thanks DST and CSIR, New Delhi for research scholarship and V. A. K. thanks the Department of Science and Technology, New Delhi.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2004.07.080

References and notes

1. (a) Nielsen, P. E. *Annu. Rev. Biophys. Biomol. Struct.* **1995**, *24*, 167–183. (b) Ganesh, K. N.; Nielsen, P. E. *Curr. Org. Chem.* **2000**, *4*, 931–943. (c) Hyrup, B.; Nielsen, P. E. *Bioorg. Med. Chem. Lett.* **1996**, *4*, 5–23. (d) Good, L.; Nielsen, P. E. *Antisense Nucleic Acids Drug Dev.* **1997**, *7*, 431–437.
2. Egholm, M.; Buchardt, O.; Christensen, L.; Behrens, C.; Freier, S. M.; Driver, D. A.; Berg, R. H.; Kim, S. K.; Norden, B.; Nielsen, P. E. *Nature* **1993**, *365*, 566–568.
3. Uhlmann, E.; Peyman, A.; Breipohl, G.; Will, D. W. *Angew. Chem., Int. Ed.* **1998**, *37*, 2796–2823.
4. Hanvey, J. C.; Peffer, N. J.; Bisi, J. E.; Thomson, S. A.; Cadilla, R.; Josey, J. A.; Ricca, D. J.; Hassman, F.; Bonham, M. A.; Au, K. G.; Carter, S. G.; Bruckenstein, D. A.; Boyd, A. L.; Noble, S. A.; Babiss, L. E. *Science* **1992**, *258*, 1481–1485.
5. D'Costa, M.; Kumar, V. A.; Ganesh, K. N. *Org. Lett.* **1999**, *1*, 1513–1516. D'Costa, M.; Kumar, V. A.; Ganesh, K. N. *Tetrahedron Lett.* **2002**, *43*, 883–887.
6. D'Costa, M.; Kumar, V. A.; Ganesh, K. N. *Org. Lett.* **2001**, *3*, 1281–1284.
7. Kumar, V. A. *Eur. J. Org. Chem.* **2002**, 2021–2032.
8. (a) Vilaivan, T.; Lowe, G. *J. Am. Chem. Soc.* **2002**, *124*, 9326–9327. (b) Hickman, D. T.; King, P. M.; Cooper, M. A.; Slater, J. M.; Mickelfield, J. *Chem. Commun.* **2000**, 2251–2252. (c) Puschl, A.; Boesen, T.; Zuccarello, G.; Dahl, O.; Pitsch, S.; Nielsen, P. E. *J. Org. Chem.* **2001**, *66*, 707–712.
9. Eschenmoser, A.; Dobler, M. *Helv. Chim. Acta* **1992**, *75*, 218–259.
10. Lescrinier, E.; Esnouf, R.; Schraml, J.; Busson, R.; Heus, H. A.; Hilbers, C. W.; Herdewijn, P. *Chem. Biol.* **2000**, *7*, 719–731.
11. Lonkar, P. S.; Kumar, V. A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2147–2149.
12. Püschl, A.; Boesen, T.; Tedeschi, T.; Dahl, O.; Nielsen, P. E. *J. Chem. Soc., Perkin Trans. 1* **2001**, *21*, 2757–2763.
13. Shirude, P. S.; Kumar, V. A.; Ganesh, K. N. *Tetrahedron Lett.* **2004**, *45*, 3085–3088.
14. Bailey, P. D.; Bryans, J. S. *Tetrahedron Lett.* **1988**, *29*, 2231–2234.
15. Adams, D. R.; Bailey, P. D.; Heffernan, J. H.; Stokes, S. *Chem. Commun.* **1996**, 349–350.
16. Fields, G. B.; Fields, C. G. *J. Am. Chem. Soc.* **1991**, *113*, 4202–4207.
17. PNA **13**: M_{obsd}=2232; M_{calcd}=2231.17, PNA **14**: M_{obsd}=2232; M_{calcd}=2231.17, PNA **18**: M_{obsd}=2232; M_{calcd}=2231.17, PNA **19**: M_{obsd}=2243; M_{calcd}=2244.23, PNA **20**: M_{obsd}=2243; M_{calcd}=2244.23; PNA **21**: M_{obsd}=2243; M_{calcd}=2244.23; PNA **15**: M_{obsd}=2233; M_{calcd}=2201.14, PNA **16**: M_{obsd}=2220; M_{calcd}=2219.11, PNA **17**: M_{obsd}=2189; M_{calcd}=2189.10)
18. Gait, M. J. *Oligonucleotide Synthesis, A Practical Approach*; IRL: Oxford, 1984.
19. Kim, S. H.; Nielsen, P. E.; Egholm, M.; Buchardt, O. *J. Am. Chem. Soc.* **1993**, *115*, 6477–6489.
20. Perrin, D.D.; Amarego, W. L. F. In *Purification of Laboratory Chemicals*. 3rd ed.; Pergamon: Oxford, 1989.
21. Barawkar, D. A.; Rajeev, K. G.; Kumar, V. A.; Ganesh, K. N. *Nucleic Acids Res.* **1996**, *24*, 1229–1237.
22. Meltzer, P. C.; Liang, A. Y.; Matsudaira, P. *J. Org. Chem.* **1995**, *60*, 4305–4308.
23. Kaiser, E.; Colescott, R. L.; Bossinger, C. D.; Cook, P. I. *Anal. Biochem.* **1970**, *34*, 595–598.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 60 (2004) 9493–9501
Tetrahedron

Face selectivity in the reactions of 2,4-disubstituted adamantanes and their modification by inclusion in β-cyclodextrin solutions

Jean-Ho Chu,[a] Wan-Sheung Li,[b] Ito Chao[b,*] and Wen-Sheng Chung[a,*]

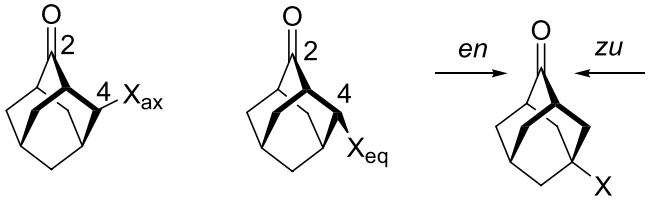
[a]*Department of Applied Chemistry, National Chiao Tung University, Hsinchu 30050, Taiwan, ROC*
[b]*Institute of Chemistry, Academia Sinica, Taipei 11529, Taiwan, ROC*

Received 27 April 2004; revised 9 July 2004; accepted 21 July 2004

Abstract—Sodium borohydride reduction reactions on 4-X-adamantan-2-ones (where X=ethyleneketal **11**, ethylenethioketal **12**, and methylene **15**) were studied, which gave *Z*-alcohols **16** and **17** (from *en*-face attack) as the predominant products for ketones **11** and **12**, but gave 1:1 mixture of *Z*- and *E*-**18** alcohols for ketone **15**. The *en*/*zu* face selectivity of **15** in sodium borohydride reduction was enhanced to 32/68 in β-CD solution. Both 1,3-dipolar addition and dichlorocarbene addition reactions on 4-ethyleneketal-2-methyleneadamantane **13** underwent again predominant *en*-face attack to give products in an *E*/*Z* ratio of >99:1 and 92:8, respectively. The exceptional high *zu*-face selectivity on the dichlorocarbene addition reaction of **15** may be explained by a temporal complexation between the carbene and the C_4-oxo group. In the epoxidation reaction of **13** and **15** the *zu*-face attack products were favored despite their steric congestions suggesting that hydrogen bonding interaction between the peroxide reagent and the C_4-oxo or 4-ethyleneketal is involved.
© 2004 Elsevier Ltd. All rights reserved.

1. Introduction

Many experimental probes have been devised to identify the various steric and electronic factors that influence π-facial selectivity in nucleophilic, electrophilic, and cycloaddition reactions, among them, sterically unbiased systems offer intrinsic advantage in isolating and evaluating electronic effects.[1–4] Relatively fewer studies have been reported on the reactions of 4-substituted adamantan-2-ones **1**- and **2**-**X** comparing to the very popular and more thoroughly studied 5-substituted adamantan-2-ones **3**-**X**. One barrier for using 4-substituted-adamantan-2-ones **1**- and **2**–**X** is the multi-step syntheses involved in the preparation of these probes. Furthermore, an axial (but not equatorial) 4-substituent is expected to have a strong steric influence on the chemical reactivity of a nearby trigonal center; rendered it difficult in studying pure electronic effects. Despite the difficulties involved, there are some scattered reports[5,6] on the face selectivity of 4-substituted adamantanes.



1-X **2-X** **3-X**

The steric effect of an axial substituent makes itself felt with even the smallest fluoro substituent: sodium borohydride attacks **1**-**F** exclusively at the *en* face to give the pure diaxial alcohol **4**-**F**. Similar data were found for the reduction of **1**-**Br**.[5,6] An equatorial fluoro substituent in **2**-**F**, however, give the diequatorial alcohol **5**-**F** and isomer **6**-**F** in a ratio of 67:33 which resembles the face selectivity in **3**-**F**.[1a] In the sodium borohydride reduction of **7**, adamantan-2-one with two equatorial β-bromosubstituents, a higher face selectivity was found (**8**:**9**=86:14) and the results were reconciled with Cieplak's model (see Chart 1).[1a,5]

Adamantane derivatives have received considerable attention because of their diverse biological activity;[7] especially when substituted with spiro-cyclopropane or spiro-pyrrolidine groups, they are known to have antiviral activity.[7c] We report here facile syntheses of some 2,4-disubstituted adamantanes **11**–**15** and face selectivity studies on these probes that yielded various spiro acetals, cyclopropanes, oxiranes, and isoxazolines. Despite the difficulties in

Keywords: Face selectivity; 2,4-Disubstituted adamantanes; β-Cyclodextrin; Inclusion complex; Neighboring group participation.
* Corresponding authors. E-mail: wschung@cc.nctu.edu.tw

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.07.075

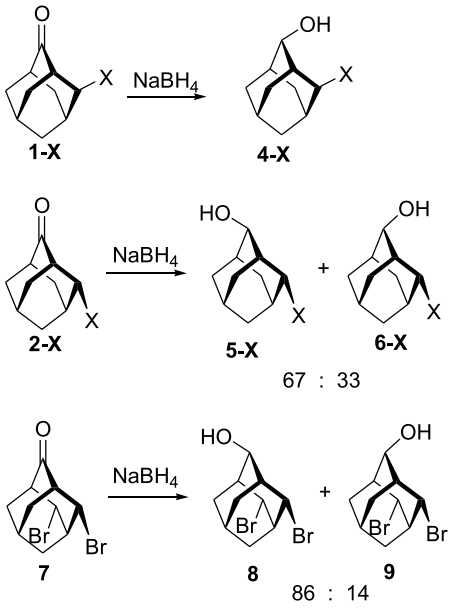
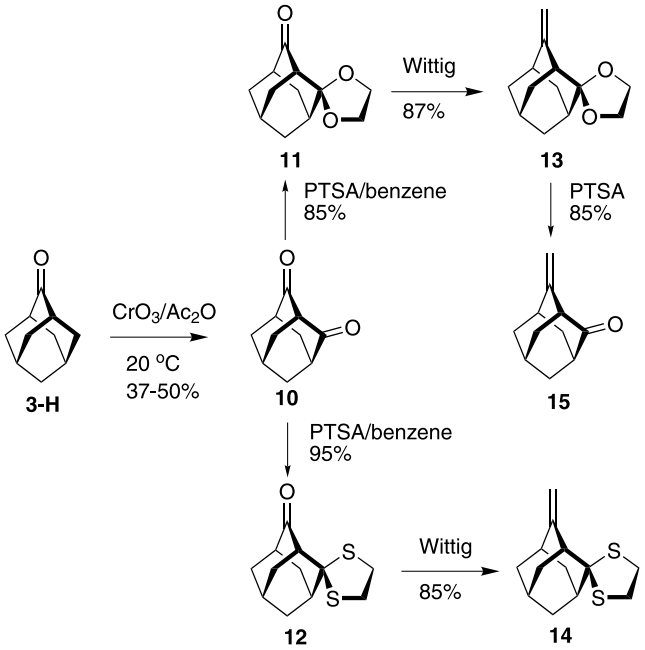


Chart 1.

dissecting electronic effects from these sterically biased probes, we found evidences to support 'neighboring group participation' in some of the reactions, furthermore, an unexpected *syn*-face enhancement in sodium borohydride reduction reactions of a **15**·β-CD complex is observed.

2. Results and discussion

Adamantane-2,4-dione **10** was first synthesized by Wynberg[8] in 1968 and latter by McKervey[9] and Duddeck[10] all through multiple-step syntheses. In 1985 Gilbert reported[11a] a direct oxidation of adamantan-2-one **3-H** by CrO_3 in acetic anhydride gave **10** in 20% yield. We followed the procedures by Gilbert and obtained a good yield (typical yields are in 37–50% range) of **10**.[11b] Compounds **11** and **12** were prepared through the protection of carbonyl group by ethylene glycol and 1,2-ethanedithiol, respectively. Compounds **13** and **14** were prepared in high yields by the Wittig reaction of **11** and **12**, respectively. The acid catalyzed deprotection of **13** gave **15** in 85% yield. The synthetic pathways are outlined in Scheme 1.



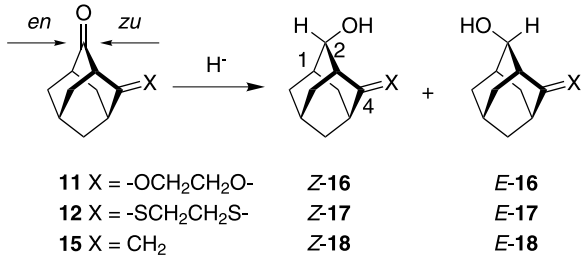
Scheme 1.

Sodium borohydride (or LAH) reduction of 4-ketaladamantan-2-one **11** or 4-thioketal-adamantan-2-one **12**, through *en*-face attack by hydride, gave *Z*-alcohols (*Z*-**16** or *Z*-**17**) as the only products. On the other hand, the reduction of 4-methyleneadamantan-2-one **15** gave *Z*- and *E*-**18** alcohols as a 1:1 mixture (Scheme 2 and Table 1). The reduction of **11** that led to *Z*-**16** as the only product has been reported in literature.[12a] Similarly, the major reduction product of thioketal-**12** is expected to be *Z*-**17** due to severe steric hindrance caused by the 4-thioketal group. The configuration of the reduction products *Z*- and *E*-**18** can be easily judged from their ^{1}H NMR spectra where the 4-methyleneprotons show two doublets (AB pattern) in *Z*-**18** but a singlet in *E*-**18** due to the magnetic anisotropy effect exerted by the 2-hydroxy group. Furthermore, the structure of *Z*-**18** can be independently synthesized from the acid-catalyzed deprotection of *Z*-**16** to *Z*-**19** followed by a Wittig reaction[12b] to give *Z*-**18** exclusively (see Scheme 3). Thus, 4-methylene group seems to play no effect on the reduction

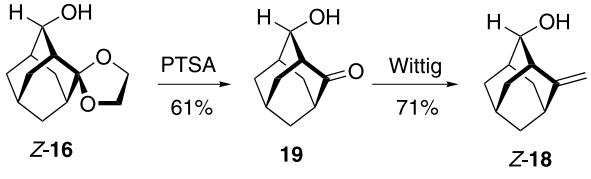
Table 1. Sodium borohydride and lithium aluminum hydride reduction reactions of 4-substituted-adamantan-2-ones **11**, **12**, and **15**

Compound	Reaction conditions[a]	*Z*/*E* ratios[b]	Isolated yield, %
11	$NaBH_4$/MeOH	**16** (>99:1) 98	98
11	$LiAlH_4$/THF	**16** (>99:1)	70[c]
12	$NaBH_4$/MeOH	**17** (>99:1)	98
12	$LiAlH_4$/THF	**17** (>99:1)	71
15	$NaBH_4$/MeOH	**18** (51:49)	98
15	$LiAlH_4$/THF	**18** (49:51)	73

[a] Reaction was carried out at 25 °C for 1 h.
[b] Note that *en* attack of hydride leads to *Z*-alcohol. Product ratios were analyzed by GC and the error bars were estimated to be ±2%.
[c] Data is consistent with that reported in Ref. 12a.



Scheme 2.



Scheme 3.

of 4-methylene-adamantan-2-one **15**. Similar results have been reported by Duddeck[10c] where *tert*-butyllithium addition of **15** gave a 1:1 mixture of *E*- and *Z*-alcohols. To our delight, the face selectivity on the reduction of **15** can be altered by inclusion of itself into β-CD cavity, but the results are opposite to our expectation based on previous model of **3-X** in β-CD[13a] (vide infra).

The 50/50 *en*/*zu* face selectivity of the sodium borohydride reduction of **15** in THF or methanol becomes 45/55 in water. The effect of β-CD complexation on the *en*/*zu* selectivity of **15** in sodium borohydride reduction is shown in Figure 1, which reaches a maximum value of 32/68 at 15 mM of β-CD. The yields of *Z*- and *E*-**18** alcohols from these reactions were in the range of 75–82% when β-CD was below 3 mM, but slightly decreased to 70–73% when β-CD concentration was above 6 mM. The product ratio varies with the concentration of β-CD in the way expected from the fact that saturation will be approached if the concentration of β-CD is made sufficiently high.[13,14] Based on the binding constants (260 M^{-1}) of **15** with β-CD (vide infra) and assuming a 1:1 complex, one can calculate the percentage of compound **15** bound by β-CD to be 75% if the starting concentration of **15** is 5 mM and β-CD is 15 mM. Accordingly, after correcting for the unbound **15** the theoretical value of *en*/*zu* face selectivity in the reduction of **15**·β-CD should be 22:78 instead of the observed 32:68. The enhanced *zu*-face attack in **15**·β-CD complex is surprising because one would have expected the opposite had its conformation been similar to that of the reported **3-X**·β-CD.[13a] In order to gain some insights on the structures of **15**·β-CD complexes, both ^{1}H NMR titration experiments and molecular dynamic calculations were carried out (see Supporting Information).

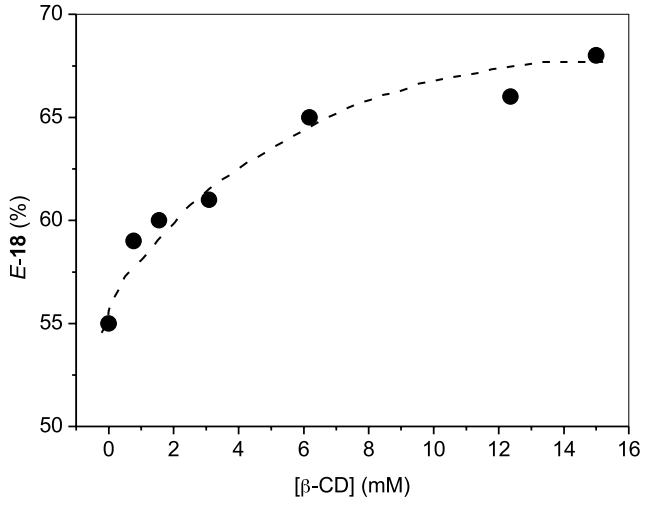


Figure 1. The percentage *E*-**18** product obtained in the sodium borohydride reduction reactions of **15** (5 mM) in aqueous solution as a function of added β-CD.

Evidences for complexation of **15** by β-CD were obtained from ^{1}H NMR spectra, which show that H_3 ($\Delta\delta = -0.055$ ppm) and H_5 ($\Delta\delta = -0.087$ ppm) of β-CD (which are oriented toward the interior of the CD cavity) are shifted upfield considerably in the presence of **15**. By contrast, H_1, H_2, and H_4, all located on the exterior wall of CD, either have small downfield shifts or are unaffected (Fig. 2).[15] On the other hand, the $H_{1'}$, $H_{3'}$, and $H_{5'}$ of 4-methyleneadamantan-2-one **15** are substantially downfield shifted in the presence of β-CD and their chemical shift difference $\Delta\delta$ is: +0.18, +0.11, and +0.13 ppm, respectively (Fig. 3).[15] These observations are consistent with the notion that a complex is formed between β-CD and **15** and they most likely have 1:1 stoichiometric ratio, similar to those of adamantane derivatives found in several X-ray crystallography data.[16] The binding constant for complexes of **15** with β-CD was determined to be $260 \pm 20\ M^{-1}$ by Benesi–Hilderbrand plot (Figs. S-1 and S-2),[14,17] where the reciprocal chemical shift differences of guest **15** are plotted with the reciprocal concentration of β-CD.

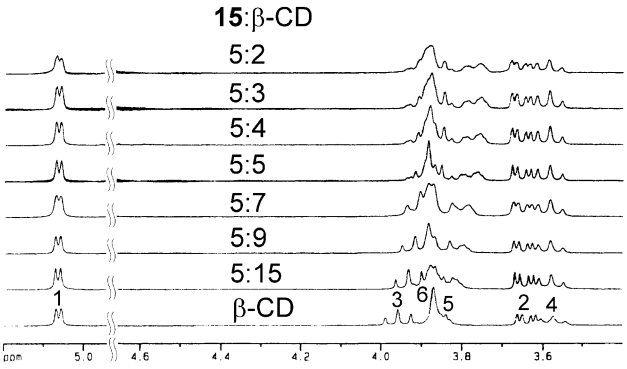


Figure 2. Effects of **15** on the ^{1}H NMR spectra of β-CD in D_2O; where the concentration of **15** was fixed at 5 mM but the concentration of β-CD decreased gradually from bottom (15 mM) to top (2 mM). Spectra were measured at 300 K.

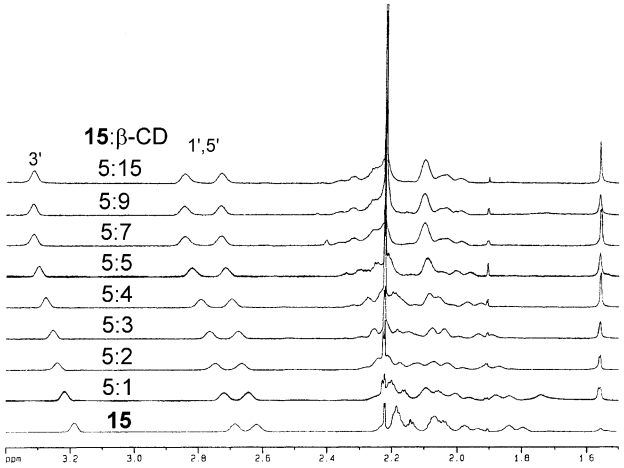


Figure 3. Effects of β-CD on the ^{1}H NMR spectra of **15** (5 mM) in D_2O solution; where the concentrations of β-CD increases gradually from bottom (0 mM) to top (15 mM). The signals of protons on the C_4-methylidene of **15** were buried in the huge water peak and were omitted. Spectra were measured at 300 K.

Four of the most likely conformations of **15** in β-CD are shown in Chart 2 and they are complexes **A**–**D**. The results of sodium borohydride reduction reactions on the complex of **15** in β-CD is out of our expectation, because if complexes **C** and **D** are the major conformations (similar to those reported for 5-substituted-adamantan-2-ones **3-X**·β-CD)[13a] one would expect that predominant *Z*-alcohol **18** be

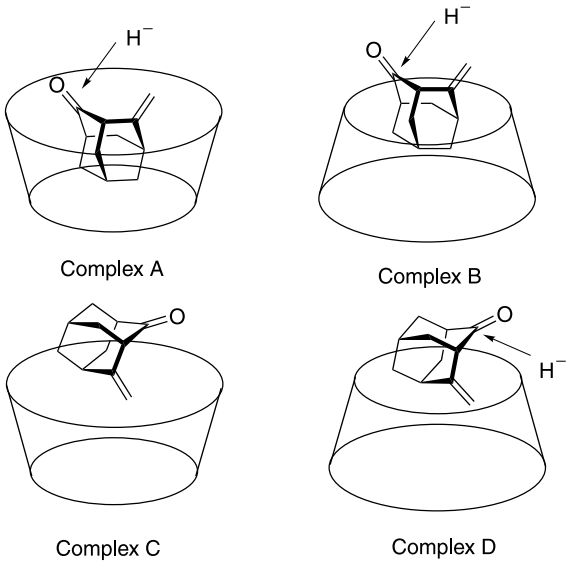
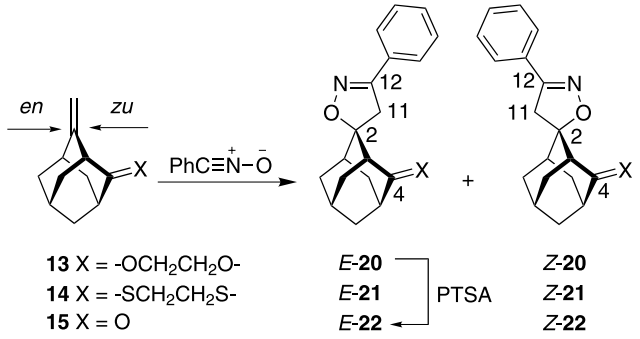


Chart 2.

formed. On the contrary, *E*-alcohol **18** became the major product when 3 equiv. of β-CD vs. **15** was used. Alternatively, if complexes **A** and **B** are the major conformations of the **15**·β-CD complexes, one may easily explain why more *E*-**18** was formed at high [β-CD] because the torus of β-CD protects the *en*-face of **15** from hydride attacks. Theoretical calculations were thus carried out to gain more insight about the conformations of **15**·β-CD complexes.

Snapshots from the MD simulations showed that preferred complexes are **C** and **D**, both with the hydrophobic methylidene groups pointing towards the CD cavity. The results are in accord with the previous proposed model **3-X**·β-CD, where a dramatic reversal in face selectivity was achieved by partial blockage of the π-face *zu* to the bulky 5-substituent of a **3-X**·β-CD complex by the CD host.[13a] Thus, the results from the simulations would predict the reduction reaction to yield the *Z*-**18** alcohol as the dominant product by partial blockage of the *zu*-face of **15** from hydride attack. Yet, the predominant formation of the *E*-**18** may indicate that β-CD has mediated the reaction through hydrogen bonding interaction of its hydroxyl groups with the metal hydride; it therefore favors a *zu*-face attack.[17b]

The 1,3-dipolar cycloaddition reactions of the 4-substituted-2-methyleneadamantane **13**–**15** with benzonitrile oxide



Scheme 4.

were studied next (Scheme 4).[18] Only *E*-isoxazolines **20** and **21** were formed in the reaction of **13** and **14**, whereas, a 1:1 mixture of *E*- and *Z*-isoxazolines **22** were obtained in the reaction of **15** (Table 2). The *E*-adducts **20** and **21** were obtained from the expected attack of benzonitrile oxide on the less-hindered side, namely, the *en*-face that is opposite to the 4-X substituents. The face selectivity in the 1,3-dipolar reactions of **13** and **14** is similar to that of reduction in **11** and **12**, but the reaction of **14** gave a very poor yield of product. Most of the starting material **14** could be recovered from the 1,3-dipolar reaction due to its poor reactivity.

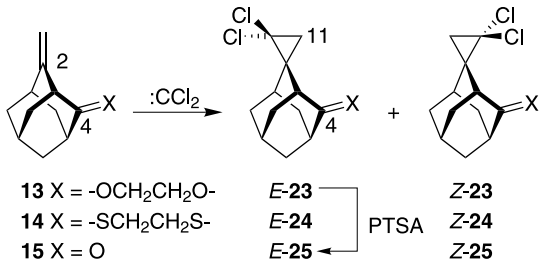
Table 2. Product ratios and yields in the 1,3-dipolar addition, carbene addition, and *m*CPBA epoxidation reactions of 4-substituted-2-methyleneadamantanes **13**–**15**

Substrate	*E*/*Z* product ratio[a] (yield, %)		
	1,3-Dipolar addition	Dichlorocarbene addition	*m*CPBA epoxidation
13	*E*-**20**:*Z*-**20** >99:1 (49%)	*E*-**23**:*Z*-**23** 92:8 (98%)	*E*-**26**:*Z*-**26** 49:51 (80%)
14	*E*-**21**:*Z*-**21** >99:1 (trace)	*E*-**24**:*Z*-**24** No reaction	*E*-**27**:*Z*-**27** Complex mixture
15	*E*-**22**:*Z*-**22** 49:51 (51%)	*E*-**25**:*Z*-**25** 1:>99[b] (48%)	*E*-**28**:*Z*-**28** 33:67[b] (71%)

[a] Product ratios determined by ^{1}H NMR spectroscopy with an estimated error of ±5% unless otherwise specified. Note that in the three types of reactions, *en* attack of reagents leads to *E*-products.
[b] Ratios determined by GC with an estimated error of ±2%.

The *E* and *Z* configuration of isoxazolines **20** and **21** are assigned by inspecting the splitting patterns of the methylene protons on C_{11}, in which a larger chemical shift difference $\Delta\nu_{AB}$ is expected for the *E*-isomer than for the *Z*-isomer due to their closer interaction with 4-ketal or 4-thioketal groups. For example, the $\Delta\nu_{AB}$ of the methylene protons on C_{11} of *E*-**21** was found to be 0.62 ppm but was 0.26 ppm for the *Z*-**21**. The assignments of *E*- and *Z*-**22** were further confirmed by an independent synthesis of *E*-**22** through PTSA catalyzed conversion of *E*-**20** to *E*-**22**. Lightner et al. reported[12a] that the magnetic anisotropy of the C_4-oxo group can deshield the C_{11} carbon in a very similar structure and our observations are consistent with their statements; for example, the chemical shift of C_{11} is 43.6 ppm as an axial substituent (*E*-**22**) but is 43.0 ppm as an equatorial one (*Z*-**22**). The 1:1 face selectivity of **15** by nitrile oxide is unexpected if one considers the C_4-oxo to be an electron-withdrawing group, where the Cieplak's model[19] would have predicted a favored *Z*-**22** product (from *zu*-face attack). On the other hand, an electrostatic repulsion between the nitrile oxide and the C_4-oxo group of **15** should disfavor a *zu*-face attack, thus counter-balanced the face preference by hyperconjugative effect. The photoreactions of **15** with acetone and benzophenone were reported by Mlinarić–Majerski[20a] to give *E*-oxetanes (from *en*-face attack) as the major product (in 70:30 ratios); where, both steric effect and the electronic effect of C_4-oxo group were used to rationalize the observed products.

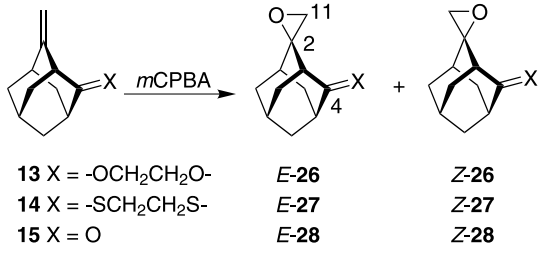
The electrophilic addition reactions of dichlorocarbene on 4-substituted-2-methylene-adamantanes **13**–**15** were carried out next (Scheme 5 and Table 2). The addition of



Scheme 5.

dichlorocarbene with **13** gave *E*- and *Z*-spirocyclopropanes **23** in 98% yield, in a ratio of 92:8 (determined by ^{1}H NMR analysis). However, no reaction was found when **14** replaced **13** in a similar reaction conditions for carbene additions. To our surprise, the addition of dichlorocarbene with 4-methylene-2-adamantanone **15** gave *Z*-spirocyclopropanes **25** as the predominant product (based on GC analysis, *E*/*Z*-**25**=1:>99) in 48% isolated yield. The configuration assignment of *E*- and *Z*-spirocyclopropanes **23**–**25** can again be judged from the splitting pattern of the methylene protons of C_{11} on the spirocyclopropanes, in which a larger chemical shift difference $\Delta\nu_{AB}$ is expected for the *E*-isomer than the *Z*-isomer due to their closer interaction with 4-ketal or 4-thioketal groups. Furthermore, the structure of *E*-**25** can be independently synthesized from the acid catalyzed deprotection of *E*-**23**. The exclusive formation of *Z*-**25** reminds us about the Simmons–Smith reaction of homoallylic 4-cyclohexenols[21] which gave specifically *syn* cyclopropane product. The results imply that the C_4-oxo group of **15** may have directed the dichlorocarbene to the *zu*-face; therefore, leads to high yield of *Z*-**25**.

In all reactions carried out on **13**, the *en*-face attack had almost always been the predominant one; we were therefore a bit surprised to find that the epoxidation of **13** by *m*CPBA gave *E*- and *Z*-oxiranes **26** as a 1:1 mixture (Scheme 6). Moreover, complex mixtures were obtained in the epoxidation of **14** presumably due to the attack of *m*CPBA on the sulfur atoms of sulfide, because the 2-methylene group was found to be intact by ^{1}H NMR analysis. For comparison, the epoxidation of **15** gave *E*- and *Z*-oxiranes **28** (33:67) in 71% yield (Table 2). The somewhat high *zu*-face reactivity on **13** and **15** despite their steric congestions, suggests that hydrogen-bonding interaction between the *m*CPBA and C_4-oxo or ketal groups is quite likely. Remember that the hydroxyl group of an allylic alcohol is well-known to direct *m*CPBA in a highly stereoselective *syn* epoxidation reaction,[22] here, the C_4-oxo seems to play a similar role. It is worth noting that the *zu*-face epoxidation is more favored



Scheme 6.

on **15** than on **13** and we believe that the results are consistent with the Cieplak's model.[19] In other words, since C_4-oxo is considered to be stronger electron-withdrawing than the ethylene ketal group, therefore, the reaction on C=C double bond of **15** (or **13**) is expected to occur preferentially from a direction anti to the more electron-rich C–C bonds.

The configuration of *E*- and *Z*-**26** was judged from the ^{1}H NMR spectrum of the ketal group, where the splitting pattern of *Z*-**26** is more complex than *E*-**26** due to its close interaction with oxirane. On the other hand, the configuration assignments of *E*- and *Z*-**28** can also be judged from the splitting pattern of the methylene protons (of C_{11}) of the oxirans, in which a larger chemical shift difference $\Delta\nu_{AB}$ is expected for the *E*-isomer (0.11 ppm) than for the *Z*-isomer (0.08 ppm) due to their closer interaction with C_4-oxo group. Furthermore, the protons on C_{11} are more downfield for the *E*-**28** than those for the *Z*-**28** due to their interactions with C_4-oxo. Independent syntheses of *E*- and *Z*-**28** from acid-catalyzed deprotection of **26** with PTSA were unsuccessful because the oxirane rings tend to be opened by the acid too.

3. Conclusion

The results studied here indicate that in the reduction and 1,3-dipolar addition reactions of 4-disubstituted-2-adamantylidene or adamantan-2-one **11**–**14** steric hindrance is the dominating factor in determining the face selectivity. Despite the difficulties in isolating electronic effects from these steric biased probes, we found valuable information about 'neighboring group participation' in the carbene addition and epoxidation reactions. Finally, an enhanced *zu*-face attack of hydride on **15** can be achieved by complexation with β-CD which is opposite to our expectation based on previously proposed model.[13a,17b] Molecular dynamic calculations as well as ^{1}H NMR titration experiments support the 1:1 inclusion complexes of **15** with β-CD.

4. Experimental

4.1. General

4.1.1. The preparation of adamantane-2,4-dione (10).[11a,b] To a chromium oxide solution (66.7 g, 0.67 mol) in acetic anhydride (300 mL) was added dropwise a solution of 2-admantanone (**3**-**H**) (16.7 g in 200 mL of acetic anhydride) through addition funnel under nitrogen. The solution was vigorously stirred and the temperature was controlled at 20 °C by a circulator. After ten days, the solution was neutralized with saturated sodium bicarbonate solution and extracted several times (100 mL×6) with methylene chloride. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated. The mixture was recrystallized in *n*-hexane/ethyl acetate (5/1) to give **10** (5.5 g, 33.5 mmol) and the residue from recrystallization was purified on a silica gel column by elution with *n*-hexane/ethyl acetate to give **10** (3.3 g, 20.1 mmol). The total amount of **10** is 8.8 g (an average of 37–50%).

Colorless solid; mp 279–281 °C (lit.[8] 280–282 °C, lit.[10a] 282–283 °C); δ_H 1.75–1.80 (m, 1H), 1.99–2.18 (m, 6H), 2.41 (bs, 2H), 2.77 (bs, 2H), 3.38 (bs, 1H); δ_C 27.0 (CH), 30.1 (CH_2), 38.3 (CH_2), 44.2 (CH_2), 45.2 (CH), 68.4 (CH), 208.6 (Cq); MS (EI, *m/z*) 164 (M^+, 28), 95 (40), 79 (100), 66 (50), 55 (59), 53 (39); HRMS *m/z* calcd for $C_{10}H_{12}O_2$ 164.0838, found 164.0830. The preparation of 4-ethyleneketaladamantan-2-one (**11**) followed a literature procedure.[5]

4.1.2. Synthesis of 4-ethylenethioketaladamantan-2-one (12).[20b] The procedure for the synthesis of **12** is similar to that of **11**, and the amount of reagents used is as follows: **10** (104 mg, 0.63 mmol), ethane-1,2-dithiol (64 mg, 0.68 mmol), PTSA·H_2O (30 mg, 0.16 mmol) and benzene (6 mL). The yield is 95%. Colorless liquid; (lit.[20b] mp 56–59 °C); δ_H 1.89–2.00 (m, 6H), 2.15–2.19 (m, 3H), 2.37–2.45 (m, 2H), 2.64 (bs, 1H), 3.18–3.24 (m, 4H); δ_C 25.7 (CH), 36.1 (CH_2), 36.6 (CH_2), 38.4 (CH_2), 38.7 (CH_2), 39.2 (CH_2), 39.4 (CH_2), 40.7 (CH), 45.0 (CH), 60.8 (CH), 76.3 (Cq), 213.9 (Cq); MS (EI, *m/z*) 240 (M^+, 100), 212 (78), 184 (34); HRMS *m/z* calcd for $C_{12}H_{16}OS_2$ 240.0644, found 240.0651.

4.1.3. Synthesis of 4-ethyleneketal-2-methyleneadamantane (13). To a solution of methyltriphenylphosphonium bromide (941 mg, 2.51 mmol) in dried tetrahydrofuran (10 mL) at 0 °C was slowly added *n*-butyllithium (2.5 M in *n*-hexane, 2.50 mmol) via syringe under nitrogen. After the solution was stirred for 1–2 h at room temperature, **11** (253 mg, 1.21 mmol) in dried tetrahydrofuran (10 mL) was added gradually and refluxed for 24 h. After cooling, the solution was washed with water and separated into organic and water layers. The water layer was extracted several times (30 mL×4) with methylene chloride. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The residue was purified on a silica gel column by elution with *n*-hexane/ethyl acetate to give **13** (217 mg, 87%). Colorless liquid; δ_H 1.72–2.18 (m, 10H), 2.41 (m, 2H), 3.94–3.98 (m, 4H), 4.61, 4.66 (AX, J= 1.8 Hz, 2H); δ_C 26.8 (CH), 34.3 (CH_2), 35.0 (CH_2), 36.0 (CH), 37.1 (CH_2), 37.6 (CH), 39.0 (CH_2), 47.5 (CH), 64.2 (2×CH_2), 103.7 (CH_2), 111.2 (Cq), 154.5 (Cq); MS (EI, *m/z*) 206 (M^+, 100), 91 (32), 73 (47), 57 (36); HRMS *m/z* calcd for $C_{13}H_{18}O_2$ 206.1307, found 206.1297.

4.1.4. Synthesis of 4-ethylenethioketal-2-methyleneadamantane (14). The procedure for the synthesis of **14** is similar to that of **13**. The amount of reagents used is as follows: **12** (900 mg, 3.75 mmol), methyltriphenylphosphonium bromide (2.19 g, 5.77 mmol), dried tetrahydrofuran (100 mL) and *n*-butyllithium (2.5 M in *n*-hexane, 5.63 mmol). The yield is 85%. Colorless solid; mp 51–52 °C; δ_H 1.69–1.84 (m, 6H), 2.01 (bs, 1H), 2.14–2.26 (m, 3H), 2.40 (bs, 1H), 2.58 (bs, 1H), 3.14–3.24 (m, 4H), 4.60, 4.62 (AB, J=2.2 Hz, 2H); δ_C 26.4 (CH), 35.9 (CH_2), 37.1 (CH), 38.2 (CH_2), 38.5 (CH_2), 39.1 (CH_2), 39.3 (CH_2), 39.4 (CH_2), 41.9 (CH), 52.6 (CH), 77.6 (Cq), 104.7 (CH_2), 154.3 (Cq); MS (EI, *m/z*) 238 (M^+, 27), 210 (32), 185 (49), 183 (100), 108 (59); HRMS *m/z* calcd for $C_{13}H_{18}S_2$ 238.0851, found 238.0854. Anal. calcd for $C_{13}H_{18}S_2$: C, 65.49; H, 7.61, found: C, 65.38; H, 7.66.

4.1.5. Synthesis of 4-methyleneadamantan-2-one (15). A well-stirred solution of **13** (755 mg, 3.70 mmol) in 70% acetone (aq) (20 mL) was added PTSA·H_2O (84.5 mg, 0.44 mmol) as a catalyst and maintained at 35 °C for 22 h. The solution was washed with water and separated into two layers. The water layer was extracted several times (5 mL× 4) with methylene chloride. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The residue was purified on a silica gel column by elution with *n*-hexane/ethyl acetate to give **15** (566 mg, 85%). Colorless solid; mp 280–281 °C (lit.[23] 135–138 °C; lit.[24] 280–282 °C); δ_H 1.88–2.12 (m, 9H), 2.59–2.62 (m, 2H), 3.14 (bs, 1H), 4.62, 4.66 (AB, J=15 Hz, 2H); δ_C 27.5 (CH), 37.6 (CH), 37.6 (CH_2), 37.9 (CH_2), 39.1 (CH_2), 42.2 (CH_2), 46.2 (CH), 58.4 (CH), 105.1 (CH_2), 152.7 (Cq), 214.4 (Cq); MS (EI, *m/z*) 162 (M^+, 69), 134 (31), 119 (29), 105 (32), 93 (79), 92 (100), 91 (80), 79 (43), 77 (39); HRMS *m/z* calcd for $C_{11}H_{14}O$ 162.1045, found 162.1048.

4.2. General procedure for the reduction of 4-substituted-admantan-2-ol (*Z*-16, *Z*-17 and *Z*-, *E*-18)

(a) Sodium borohydride reduction. The procedure for *Z*-**16** is given as an example. To a solution of **11** (25.8 mg, 0.01 mmol) in methanol (4 mL) was added sodium borohydride (6.7 mg, 0.02 mmol) in one portion at room temperature. After stirred for 1 h, the solution was washed with saturated ammonium chloride and extracted several times (3 mL×4) with methylene chloride. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated to give *Z*-**16** in 98% yield. For other reduction the yields are as follows: *Z*-**17**, 98%; *Z*- and *E*-**18** (1:1), 98%. (b) Lithium aluminum hydride reduction. The procedure for *Z*-**16** is given as an example. To a well-stirred solution of lithium aluminum hydride in dried tetrahydrofuran (THF) at 0 °C under nitrogen was added **11** (in THF) via syringe and stirred for 1 h. The solution was worked up with THF/water (1/1) and washed with water. The water layer was extracted several times (3 mL×4) with methylene chloride. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The residue was purified on a silica gel column by elution with *n*-hexane/ethyl acetate and the yields are as follows: *Z*-**16**, 70%; *Z*-**17**, 71%; *Z*- and *E*-**18** (1:1), 73%.

4.2.1. Data for 4-ethyleneketaladamantan-2$_a$-ol (*Z*-16).[24] Colorless liquid; δ_H 1.60–2.00 (m, 12H), 2.15–2.22 (m, 1H), 3.86 (bs, 1H), 3.93–4.01 (m, 4H); δ_C 25.5 (CH), 29.0 (CH_2), 34.0 (CH_2), 34.3 (CH), 34.6 (CH_2), 36.07 (CH), 36.09 (CH_2), 41.1 (CH), 63.7 (CH_2), 64.4 (CH_2), 76.2 (CH), 111.8 (Cq); MS (EI, *m/z*) 210 (M^+, 32), 208 (100), 192 (36), 182 (31), 148 (32), 137 (36), 112 (31), 99 (61), 79 (45), 55 (35); HRMS *m/z* calcd for $C_{12}H_{18}O_3$ 210.1256, found 210.1258.

4.2.2. Data for 4-ethylenethioketaladamantan-2$_a$-ol (*Z*-17). Colorless solid; mp 87–88 °C; δ_H 1.68–1.79 (m, 6H), 1.93 (bs, 1H), 2.08–2.18 (m, 2H), 2.22–2.32 (m, 3H), 3.18–3.31 (m, 4H), 3.85 (d, J=7.3 Hz, OH), 3.97 (m, 1H); δ_C 25.4 (CH), 31.4 (CH_2), 33.7 (CH), 36.6 (CH_2), 36.9 (CH_2), 37.3 (2×CH_2), 38.2 (CH_2), 41.3 (CH), 46.2 (CH), 75.1 (Cq), 77.1 (CH); MS (EI, *m/z*) 242 (M^+, 92), 214 (91), 196 (63), 182 (65), 180 (45), 154 (49), 149 (76), 131 (43), 121 (100), 112 (45), 91 (61), 79 (68), 69 (52), 55 (25); HRMS *m/z* calcd for $C_{12}H_{18}OS_2$ 242.0800, found 242.0796.

4.2.3. Data for 4-methyleneadamantan-2$_a$-ol (*Z*-18).[25] Colorless solid; mp 86–87 °C; δ_H 1.67–2.01 (m, 11H), 2.43–2.48 (m, 2H), 3.88 (bs, 1H), 4.67, 4.77 (AX, $J=2.1$ Hz, 2H); δ_C 26.8 (CH), 33.8 (CH_2), 34.5 (CH), 35.9 (CH_2), 37.9 (CH_2), 38.2 (CH), 38.7 (CH_2), 46.1 (CH), 75.2 (CH), 106.7 (CH_2), 153.4 (Cq); MS (EI, *m/z*) 164 (M^+, 100), 94 (31), 93 (33); HRMS *m/z* calcd for $C_{11}H_{16}O$ 164.1202, found 164.1197.

4.2.4. Data for 4-methyleneadamantan-2$_e$-ol (*E*-18).[25] Compound *E*-**18** was not separated from its geometric isomers but its spectrum can be differentiated from the 1:1 mixture, because *Z*-**18** was obtained through an independent synthesis from *Z*-**19**. Colorless solid; δ_H 1.51–1.96 (m, 11H), 2.12–2.25 (m, 2H), 3.84 (bs, 1H), 4.60 (s, 2H); δ_C 27.4 (CH), 30.6 (CH_2), 32.6 (CH_2), 34.3 (CH), 36.6 (CH_2), 37.6 (CH), 39.1 (CH_2), 45.5 (CH), 74.7 (CH), 103.3 (CH_2), 155.5 (Cq); GC-MS (EI, *m/z*) 164 (M^+, 100), 94 (61), 93 (68).

4.3. General procedures for ^{1}H NMR titration studies of 15 with β-CD

Solutions containing different proportions of guest-to-β-CD were prepared by stirring 5 mM of **15** with 0, 1, 2, 3, 4, 5, 7, 9, and 15 mM of β-CD solutions (15 mM stock solution in D_2O) in 1 mL D_2O for *ca*. 3 h before measurements. The NMR spectra of all the β-CD complexes, β-CD and **15** in D_2O and $CDCl_3$ with a coaxial external standard ($CDCl_3$) were recorded with a 300 MHz NMR and the results are shown in Figures 2 and 3.

4.3.1. Synthesis of 4$_a$-hydroxyadamantan-2-one (19). The procedure for the synthesis of **19**[25,26] is similar to that of **15**. And the amounts of reagents used are as follows: *Z*-**16** (250 mg, 1.20 mmol), PTSA·H_2O (50 mg, 0.26 mmol) and 70% acetone (aq) (17 mL). The yield for **19** is 61%. Colorless solid; mp not determined (lit.[9] mp 316–320 °C); δ_H 1.82–2.06 (m, 9H), 2.39–2.51 (m, 2H), 2.72 (bs, 1H), 2.73 (bs, 1H), 4.23 (bs, 1H); δ_C 26.2 (CH), 33.2 (CH_2), 33.5 (CH), 35.1 (CH_2), 37.6 (CH_2), 38.9 (CH_2), 46.5 (CH), 54.3 (CH), 78.1 (CH), 217.7 (Cq); MS (EI, *m/z*) 166 (M^+, 72), 148 (53), 138 (80), 96 (55), 79 (100), 78 (76); HRMS *m/z* calcd for $C_{10}H_{14}O_2$ 166.0994, found 166.0986.

4.4. General procedure for the 1,3-dipolar reaction of 13–15

To a well-stirred solution of **13** (38.6 mg, 0.19 mmol) and benzohydroximinoyl chloride (43.5 mg, 0.28 mmol) in dried tetrahydrofuran (5 mL) under nitrogen was added triethylamine (31.9 mg, 0.32 mmol) via syringe and refluxed for 24 h. After cooled down to room temperature, the solution was washed with water and the water layer was extracted several times (3 mL×4) with methylene chloride. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The residue was purified on a silica gel column by elution with *n*-hexane/ethyl acetate to give *E*-**20**. The yields are as follows: *E*-**20** (from **13**), 49%; *E*- and *Z*-**22** (1:1) (from **15**), 51%. Only recovered starting material **14** was obtained under this reaction condition.

4.4.1. Data for (*E*)-4-ethyleneketalspiro[adamantane-2,5′-3′-phenyl-Δ^2-isoxazoline] (*E*-20). Colorless liquid; δ_H 1.49–1.55 (m, 1H), 1.63–2.05 (m, 9H), 2.29–2.35 (m, 2H), 3.08, 3.56 (AX, $J=17.7$ Hz, 2H), 3.93–3.96 (m, 4H), 7.37–7.40 (m, 3H), 7.68–7.71 (m, 2H); δ_C 25.2 (CH), 30.8 (CH_2), 31.0 (CH_2), 32.7 (CH_2), 34.5 (CH_2), 35.7 (CH), 35.7 (CH), 44.0 (CH_2), 44.4 (CH), 63.8 (CH_2), 64.4 (CH_2), 90.8 (Cq), 111.5 (Cq), 126.4 (CH), 128.5 (CH), 129.7 (CH), 130.3 (Cq), 157.6 (Cq); MS (EI, *m/z*) 325 (M^+, 100), 179 (50), 99 (35), 91 (32), 77 (70), 55 (32); HRMS *m/z* calcd for $C_{20}H_{23}O_3N$ 325.1678, found 325.1680.

4.4.2. Data for (*E*)-spiro[adamantan-2-one-4:5′-3′-phenyl-Δ^2-isoxazoline] (*E*-22). Colorless solid; mp 131–132 °C; δ_H 1.82–1.92 (m, 3H), 2.03–2.12 (m, 5H), 2.41–2.45 (m, 1H), 2.60–2.68 (m, 3H), 2.97, 3.06 (AB, $J=16.7$ Hz, 2H), 7.36–7.40 (m, 3H), 7.60–7.63 (m, 2H); δ_C 25.8 (CH), 32.3 (CH_2), 33.4 (CH_2), 35.1 (CH_2), 36.6 (CH), 38.7 (CH_2), 43.6 (CH_2), 45.6 (CH), 56.2 (CH), 90.4 (Cq), 126.4 (CH), 128.6 (CH), 129.4 (Cq), 130.1 (CH), 156.6 (Cq), 214.2 (Cq); MS (EI, *m/z*) 281 (M^+, 100), 144 (31), 117 (47), 77 (36); HRMS *m/z* calcd for $C_{18}H_{19}O_2N$ 281.1416, found 281.1414. Anal. calcd for $C_{18}H_{19}O_2N$: C, 76.84; H, 6.81; N, 4.98, found: C, 76.64; H, 6.83; N, 5.01.

4.4.3. Data for (*Z*)-spiro[adamantan-2-one-4:5′-3′-phenyl-Δ^2-isoxazoline] (*Z*-22). Colorless solid; mp 118–119 °C; δ_H 1.92–2.13 (m, 9H), 2.52–2.67 (m, 3H), 3.24, 3.34 (AB, $J=16.8$ Hz, 2H), 7.41 (m, 3H), 7.66 (m, 2H); δ_C 26.3 (CH), 33.2 (CH_2), 34.6 (CH_2), 36.4 (CH), 37.7 (CH_2), 39.1 (CH_2), 43.0 (CH_2), 45.3 (CH), 55.4 (CH), 93.7 (Cq), 126.5 (CH), 128.7 (CH), 129.7 (Cq), 130.1 (CH), 155.7 (Cq), 213.6 (Cq); MS (EI, *m/z*) 281 (M^+, 100), 146 (30), 144 (45), 117 (65), 91 (39), 77 (51); HRMS *m/z* calcd for $C_{18}H_{19}O_2N$ 281.1416, found 281.1422. Anal. calcd for $C_{18}H_{19}O_2N$: C, 76.84; H, 6.81; N, 4.98, found: C, 76.55; H, 6.87; N, 5.07.

4.5. General procedure for the synthesis of 4-substituted-11-dichlorocyclopropylspiro-adamantane (*E*-23 and *E*-, *Z*-25)

The procedure for *E*-**23** is given as an example. To a well-stirred solution of **13** (69.5 mg, 0.34 mmol) and triethylbenzylammonium chloride (10 mg, 0.04 mmol) in chloroform (1 mL) was added 50% NaOH (aq) (1 mL) at room temperature and stirred overnight. The solution was washed with water and extracted several times (5 mL×4) with methylene chloride. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The residue was purified on a silica gel column by elution with *n*-hexane/ethyl acetate to give *E*-**23**. The yields are as follows: *E*-**23**, 98%; *E*- and *Z*-**25** (1:>99), 48%.

4.5.1. Data for (*E*)-4-ethylketal-11-dichlorocyclopropylspiroadamantane (*E*-23). Colorless liquid; δ_H 1.21, 1.41 (AX, $J=7.4$ Hz, 2H), 1.58–2.01 (m, 12H), 3.84–3.94 (m, 4H); δ_C 25.7 (CH), 32.4 (CH_2), 32.9 (CH_2), 33.2 (CH_2), 33.8 (CH_2), 34.2 (CH), 35.2 (CH_2), 35.5 (CH), 37.9 (Cq), 41.9 (CH), 64.1 (CH_2), 64.3 (CH_2), 66.0 (Cq), 111.3 (Cq); MS (EI, *m/z*) 292 (M^++4, 2), 290 (M^++2, 10), 288 (M^+, 13), 253 (100), 99 (45); HRMS *m/z* calcd for $C_{14}H_{18}O_2^{35}Cl_2$ 288.0685, found 288.0682. Anal. calcd for $C_{14}H_{18}O_2Cl_2$: C, 58.14; H, 6.27, found: C, 57.99; H, 6.36. For characteristic ^{1}H NMR peaks of *Z*-**23** see Fig. S-35.

4.5.2. Data for (*Z*)-11-dichlorocyclopropylspiroadamantan-2-one (*Z*-25). Colorless solid; mp 53–54 °C; δ_H 1.27, 1.37 (AB, $J=7.2$ Hz, 2H), 1.80–2.08 (m, 9H), 2.09–2.13 (m, 1H), 2.43 (bs, 1H), 2.64 (bs, 1H); δ_C 26.5 (CH), 30.7 (CH_2), 33.8 (CH), 34.7 (CH_2), 35.7 (CH_2), 38.3 (CH_2), 38.8 (CH_2), 41.2 (Cq), 45.6 (CH), 51.5 (CH), 65.9 (Cq), 214.4 (Cq); MS (EI, *m/z*) 248 ($M^+ +4$, 7), 246 ($M^+ +2$, 39), 244 (M^+, 61), 209 (38), 181 (87), 178 (86), 152 (33), 145 (75), 139 (56), 138 (49), 105 (39), 91 (65), 79 (100); HRMS *m/z* calcd for $C_{12}H_{14}O^{35}Cl_2$ 244.0423, found 244.0415. Anal. calcd for $C_{12}H_{14}OCl_2$: C, 58.79; H, 5.76, found: C, 58.65; H, 5.82.

4.5.3. Data for (*E*)-11-dichlorocyclopropylspiroadamantan-2-one (*E*-25). Which was obtained from the acid catalyzed hydrolysis of *E*-**22**, a colorless liquid; δ_H 1.15, 1.31 (AB, $J=7.3$ Hz, 2H), 1.85 (bs, 1H), 1.95–2.15 (m, 8H), 2.29–2.35 (m, 2H), 2.56 (bs, 1H); δ_C 26.3 (CH), 31.2 (CH_2), 34.0 (CH), 34.4 (CH_2), 35.5 (CH_2), 37.6 (CH_2), 38.2 (CH_2), 40.5 (Cq), 45.3 (CH), 52.4 (CH), 64.4 (Cq), 214.6 (Cq); MS (EI, *m/z*) 248 ($M^+ +4$, 9), 246 ($M^+ +2$, 51), 244 (M^+, 76), 209 (34), 181 (100), 145 (69), 91 (91), 79 (94); HRMS *m/z* calcd for $C_{12}H_{14}O^{35}Cl_2$ 244.0423, found 244.0418.

4.6. General procedure for the synthesis of 4-substituted-2-oxacyclopropyladamantane (*Z*-, *E*-26 and *Z*-, *E*-28)

The procedure for *Z*-, *E*-**26** is given as an example. To a well-stirred solution of **13** (40.5 mg, 0.20 mmol) in methylene chloride (2 mL) was added 70–75% *m*CPBA (48.2 mg, 0.28 mmol) at room temperature and kept stirred for 1.5 h. The solution was washed with water and the water layer was extracted several times (3 mL×4) with methylene chloride. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated to give *Z*-, *E*-**26**. The yields are as follows: *Z*- and *E*-**26** (1:1), 80%; *Z*- and *E*-**28** (67:33), 71%.

4.6.1. Data for (*Z*)-4-ethyleneketal-2-oxacyclopropyladamantane (*Z*-26). Colorless liquid; δ_H 1.33 (bs, 1H), 1.41 (bs, 1H), 1.65–1.84 (m, 7H), 1.95–2.00 (m, 1H), 2.12–2.28 (m, 2H), 2.52, 2.57 (AB, $J=4.8$ Hz, 2H), 3.88–4.02 (m, 4H); δ_C 25.9 (CH), 31.6 (CH_2), 34.1 (CH_2), 34.6 (CH_2), 35.0 (CH), 35.4 (CH), 36.6 (CH_2), 43.9 (CH), 51.5 (CH_2), 64.0 (CH_2+Cq), 64.6 (CH_2), 110.9 (Cq); MS (EI, *m/z*) 222 (M^+, 62), 221 ($M^+ -1$, 87), 192 (53), 179 (36), 151 (39), 149 (62), 99 (100), 91 (74), 79 (66), 55 (62); HRMS *m/z* calcd for $C_{13}H_{18}O_3$ 222.1256, found 222.1266.

4.6.2. Data for (*E*)-4-ethyleneketal-2-oxacyclopropyladamantane (*E*-26). Colorless liquid; δ_H 1.36 (bs, 2H), 1.62–1.84 (m, 5H), 1.96–2.02 (m, 5H), 2.66, 2.71 (AB, $J=4.7$ Hz, 2H), 3.86–3.94 (m 4H); δ_C 25.6 (CH), 31.9 (CH_2), 32.4 (CH_2), 34.1 (CH_2), 34.4 (CH_2), 34.6 (CH), 35.7 (CH), 44.1 (CH), 55.7 (CH_2), 63.2 (Cq), 64.2 (2×CH_2), 111.5 (Cq); MS (EI, *m/z*) 222 (M^+, 100), 221 (67), 193 (46), 192 (43), 149 (35), 99 (71), 91 (32); HRMS *m/z* calcd for $C_{13}H_{18}O_3$ 222.1256, found 222.1261.

4.6.3. Data for (*Z*)-4-oxacyclopropyladamantan-2-one (*Z*-28). Colorless solid; mp 96–98 °C; δ_H 1.86–1.91 (m, 2H), 2.01–2.11 (m, 7H), 2.18–2.21 (m, 1H), 2.37–2.41 (m, 1H), 2.60 (bs, 1H), 2.64, 2.72 (AB, $J=4.5$ Hz, 2H); δ_C 26.3 (CH), 33.0 (CH_2), 33.8 (CH_2), 34.6 (CH), 37.4 (CH_2), 38.7 (CH_2), 45.3 (CH), 54.4 (CH_2), 54.9 (CH), 63.9 (Cq), 214.0 (Cq); MS (EI, *m/z*) 178 (M^+, 60), 150 (100), 105 (31), 92 (60), 91 (34); HRMS *m/z* calcd for $C_{11}H_{14}O_2$ 178.0994, found 178.0988.

4.6.4. Data for (*E*)-4-oxacyclopropyladamantan-2-one (*E*-28). Colorless solid; mp 99–100 °C; δ_H 1.56 (bs, 1H), 2.00–2.19 (m, 10H), 2.59 (bs, 1H), 2.63, 2.74 (AB, $J=4.5$ Hz, 2H); δ_C 26.4 (CH), 34.3 (CH_2), 34.9 (CH), 35.7 (CH_2), 38.7 (CH_2), 39.0 (CH_2), 45.6 (CH), 52.8 (CH_2), 54.6 (CH), 66.4 (Cq), 214.2 (Cq); MS (EI, *m/z*) 178 (M^+, 68), 150 (100), 93 (32), 92 (65), 91 (30); HRMS *m/z* calcd for $C_{11}H_{14}O_2$ 178.0994, found 178.0991. Anal. calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92, found: C, 73.79; H, 8.00.

Acknowledgements

We thank the National Science Council of Republic of China for financial support. We also thank National Chiao Tung University for a financial support to the Center for Interdisciplinary Molecular Science.

Supplementary Data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2004.07.075

References and notes

1. (a) Kaselj, M.; Chung, W.-S.; le Noble, W. J. *Chem. Rev.* **1999**, *99*, 1387 and references cited therein. (b) Adcock, W.; Trout, N. A. *Chem. Rev.* **1999**, *99*, 1415. (c) Ohwada, T. *Chem. Rev.* **1999**, *99*, 1337.
2. (a) Tomoda, S.; Kaneno, D. *Org. Lett.* **2003**, *5*, 2947. (b) Knoll, W.; Bobek, M. M.; Malchhauser, H.; Rosenberg, M. G.; Brinker, U. H. *Org. Lett.* **2003**, *5*, 2943. (c) Tomoda, S.; Senju, T.; Kawamura, M.; Ikeda, T. *J. Org. Chem.* **1999**, *64*, 5396. (d) Knoll, W.; Bobek, M. M.; Giester, G.; Brinker, U. H. *Tetrahedron Lett.* **2001**, *42*, 9161.
3. Lange, H.; Gleiter, R.; Fritzsche, G. *J. Am. Chem. Soc.* **1998**, *120*, 6563.
4. (a) Mehta, F.; Uma, R. *J. Org. Chem.* **2000**, *65*, 1685. (b) Mehta, G.; Khan, F. A.; Gadre, S. R.; Shirsat, R. N.; Ganguly, B.; Chandrasekhar, J. *Angew. Chem. Int. Ed.* **1994**, *33*, 1390. (c) Mehta, G.; Gunasekaran, G.; Gadre, S. R.; Shirsat, R. N.; Ganguly, B.; Chandrasekhar, J. *J. Org. Chem.* **1994**, *59*, 1953. (d) Mehta, G.; Praveen, M. *Tetrahedron Lett.* **1992**, *33*, 1759.
5. Kaselj, M.; le Noble, W. J. *J. Org. Chem.* **1996**, *61*, 4157.
6. Cuddy, B. D.; Grant, D.; McKervey, M. A. *J. Chem. Soc. (C)* **1971**, 3173.
7. (a) Maurin, J. K.; Lasek, W.; Gorska, A.; Switzj, T.; Wamil, M.; Mlynarczuk, I.; Kazimierczuk, Z. *Anti-Cancer Drug. Design.* **2001**, *16*, 73. (b) Chen, C. S. H.; Shen, D.-M.;

Wentzek, S. E. PCT Int. Appl. WO 94 28.885, 1994; *Chem. Abstr.* **1995**, *122*, 239227. (c) Kolocouris, N.; Foscolos, G. B.; Kolocouris, A.; Marakos, P.; Pouli, N.; Fytas, G.; Ikeda, S.; De Clercq, E. *J. Med. Chem.* **1994**, *37*, 2896.
8. Udding, A. C.; Strating, J.; Wynberg, H. *Tetrahedron Lett.* **1968**, 1345.
9. McKervey, M. A.; Faulkun, D.; Hamill, H. *Tetrahedron Lett.* **1970**, 1971.
10. (a) Duddeck, H.; Wiskamp, V.; Rosenbaum, D. *J. Org. Chem.* **1981**, *46*, 5332. (b) Duddeck, H.; Feuerhelm, H.-T.; Snatzke, G. *Tetrahedron Lett.* **1979**, 829. (c) Duddeck, H.; Rosenbaum, D. *J. Org. Chem.* **1991**, *56*, 1700.
11. (a) Gilbert, E. E. *Synth. Commun.* **1985**, *15*, 53. (b) Chu, J.-H. Master Thesis, National Chiao Tung University, Hsinchu, Taiwan, 1999. Surprisingly, we later found that similar synthesis of **10** by exactly the same method was reported contemporarily, see: Bobek, M. M.; Brinker, U. H. *Synth. Commun.* **1999**, *29*, 3221.
12. (a) Lightner, D. A.; Bouman, T. D.; Wijekoon, W. M. D.; Hansen, A. E. *J. Am. Chem. Soc.* **1986**, *108*, 4484. (b) Olah, G. A.; Krishnamurthy, V. V. *J. Am. Chem. Soc.* **1982**, *104*, 3987.
13. (a) Chung, W.-S.; Wang, N.-J.; Liu, Y.-D.; Leu, Y.-J.; Chiang, M. Y. *J. Chem. Soc., Perkin Trans. 2* **1995**, 307 and earlier references cited therein. (b) Li, W.-S.; Chung, W.-S.; Chao, I. *Chem. Eur. J.* **2003**, *9*, 951.
14. For reviews of the determination of host–guest complexation: (a) Diederich, F. *Angew. Chem., Int. Ed.* **1988**, 27, 362 and references cited therein. (b) Connors, K. A. *Binding Constants, the Measurement of Molecular Complex Stability*; Wiley: New York, 1987.
15. Similar results in ^{1}H NMR spectroscopy in the studies of β-CD complexes were observed. For example: (a) Greatbanks, D.; Pickford, R. *Magn. Reson. Chem.* **1987**, *25*, 208. (b) Reddy, G. D.; Usha, G.; Ramanathan, K. V.; Ramamurthy, V. *J. Org. Chem.* **1986**, *51*, 3085. (c) Eaton, D. F. *Tetrahedron* **1987**, *43*, 1551.
16. (a) Hamilton, J. A.; Steinrauf, L. K.; vanEtten, R. L. *Acta Crystallogr.* **1968**, *B24*, 1560. (b) Crugler, M.; Eckle, E.; Stezowski, J. *J. Chem. Soc., Chem. Commun.* **1981**, 1291.
17. (a) Benesi, H. A.; Hilderbrand *J. Am. Chem. Soc.* **1949**, *71*, 2703. (b) Similar results have been observed in Indium mediated allylation of **3**-**X** in β-CD: Jan, M. -D. MS Thesis, National Chiao Tung University, 1999 and Proceeding of the 11th IUPAC Symposium on OMCOS, p. 319, July 22-26, Taipei, 2001.
18. For 1,3-dipolar addition reaction on **3**-**X** see (a) Chung, W.-S.; Tsai, T.-L.; Ho, C.-C.; Chiang, M. Y. N.; le Noble, W. J. *J. Org. Chem.* **1997**, *62*, 4672. (b) Tsai, T.-L.; Chen, W.-C.; Yu, C.-H.; le Noble, W. J.; Chung, W.-S. *J. Org. Chem.* **1999**, *64*, 1099.
19. (a) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4550. (b) Cieplak, A. S.; Tait, B. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 8447. (c) Johnson, C. R.; Tait, B. D.; Cieplak, A. S. *J. Am. Chem. Soc.* **1987**, *109*, 5875. (d) Cieplak, A. S. *Chem. Rev.* **1999**, *99*, 1265.
20. (a) Mlinarić-Majerski, K.; Pavlović, D.; Veljković, J.; Šindler-Kulyk, M. *Croat. Chem. Acta* **1993**, *66*, 385. (b) Mlinarić-Majerski, K.; Vinković, M.; Škare, D.; Marchand, A. P. *Arkivoc* **2002**, 30 part IV.
21. Chan, J. H.; Rickborn, B. *J. Am. Chem. Soc.* **1968**, *90*, 6406.
22. Adam, W.; Wirth, T. *Acc. Chem. Res.* **1999**, *32*, 703.
23. (a) Mlinarić-Majerski, K.; Majerski, Z. *J. Am. Chem. Soc.* **1980**, *102*, 1418. (b) Mlinarić-Majerski, K.; Majerski, Z. *J. Am. Chem. Soc.* **1983**, *105*, 7389.
24. Henkel, J. G.; Spector, J. H. *J. Org. Chem.* **1983**, *48*, 3657.
25. Grob, C. A.; Wittwer, G.; Rao, K. R. *Helv. Chim. Acta* **1985**, *68*, 760.
26. Faulkner, D.; McKervey, M. A. *J. Chem. Soc. (C)* **1971**, 3906.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 60 (2004) 9503–9515
Tetrahedron

Concise, asymmetric total synthesis of spirotryprostatin A

Tomoyuki Onishi, Paul R. Sebahar and Robert M. Williams*

Department of Chemistry, Colorado State University, 1301 Center Avenue, Fort Collins, CO 80523, USA

Received 13 February 2004; revised 19 July 2004; accepted 20 July 2004

Abstract—The structurally intriguing cell-cycle inhibitor spirotryprostatin A has been synthesized utilizing an azomethine ylide dipolar cycloaddition reaction as the key step. This pentacyclic alkaloid contains a prenylated tryptophan-derived oxindole moiety that has been created in a regiocontrolled and stereocontrolled manner in a single step.
© 2004 Elsevier Ltd. All rights reserved.

1. Introduction

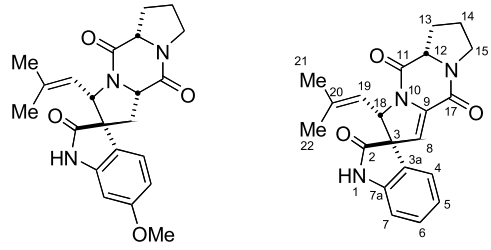
The spirotryprostatins,[1] tryprostatins[2] and cyclotryprostatins[3] represent a promising class of antimitotic arrest agents. Isolated from *Aspergillus fumigatus*, spirotryprostatin A (**1**, Fig. 1) and spirotryprostatin B (**2**) were shown to completely inhibit the progression of cells at concentrations greater than 253 and 34.4 μM, respectively.[1] The spirotryprostatins are characterized by a unique *spiro*-oxindole substituted *cis*-prolyl-prolyl-diketopiperazine that is prenylated at C-18. The detailed mechanism of action by which these substances inhibit microtubule assembly is presently not known and studies to discover the target of these natural products have been hampered by the small quantities of these substances that can be conveniently isolated from the producing organism. Despite their relatively modest biological activity relative to other members of this family, the spirotryprostatins have nonetheless garnered the most attention due to their intriguing molecular structures.

Since the isolation of the natural products in 1996, numerous groups have embarked on research programs directed towards the total synthesis of spirotryprostatins A and B. Various research groups have focused their efforts on the development of synthetic methodology of just the *spiro*-oxindole pyrrolidine portion of the natural products. Recent approaches include [5+2]-cycloaddition of enantiomerically pure η^3-pyridinyl molybdenum complexes,[4] directed radical cyclizations,[5] ring expansion of cyclopropanes by aldimines[6] and iodide ion-induced rearrangement of [(*N*-aziridinomethylthio)methylene]-oxindoles.[7] In addition to the generation of the *spiro*-oxindole quaternary carbon, a total synthesis endeavor must contend with the prenyl side-chain, three or four stereogenic centers which pose formidable synthetic challenges, and the enamide moiety in the case of spirotryprostatin B. These issues have been addressed by various strategies and have culminated in the total synthesis of spirotryprostatin B (**2**) by the groups of Williams,[8] Danishefsky,[9] Ganesan,[10] Overman,[11] Fuji[12] and Carreira.[13,14] On the other hand, only one total synthesis of spirotryprostatin A using the classical halohydrin to oxindole *spiro*-ring-forming contraction sequence has been reported thus far by Danishefsky.[15] We previously described the total synthesis of spirotryprostatin B (**2**) using a stereochemically distinct three-component asymmetric azomethine ylide [1,3]-dipolar cycloaddition reaction.[8] Herein, we report a concise asymmetric total synthesis of spirotryprostatin A (**1**).[16]

2. Results and discussion

2.1. Initial synthetic route to spirotryprostatin A

In contemplating the synthesis of spirotryprostatin A (**1**), it was envisioned that the core pyrrolidine ring could be formed through an asymmetric [1,3]-dipolar cycloaddition



1, spirotryprostatin A **2**, spirotryprostatin B

Figure 1. Structures of spirotryprostatins A and B.

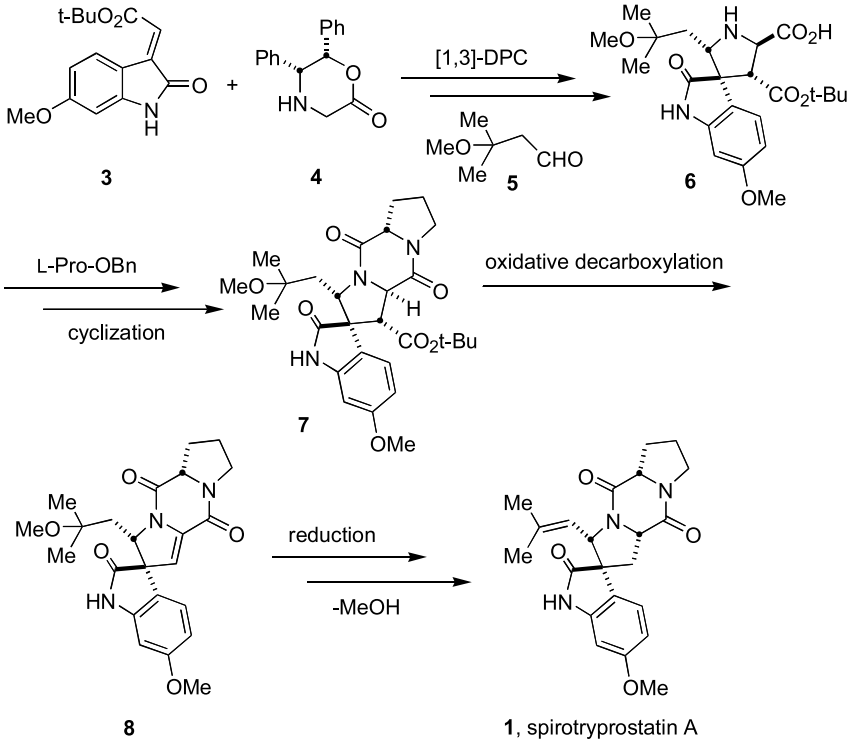
Keywords: Spirotryprostatin A; Dipolar cycloaddition; Azomethine ylide.
* Corresponding author. Tel.: +1-970-491-6747; fax: +1-970-491-5610; e-mail: rmw@chem.colostate.edu

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.07.047

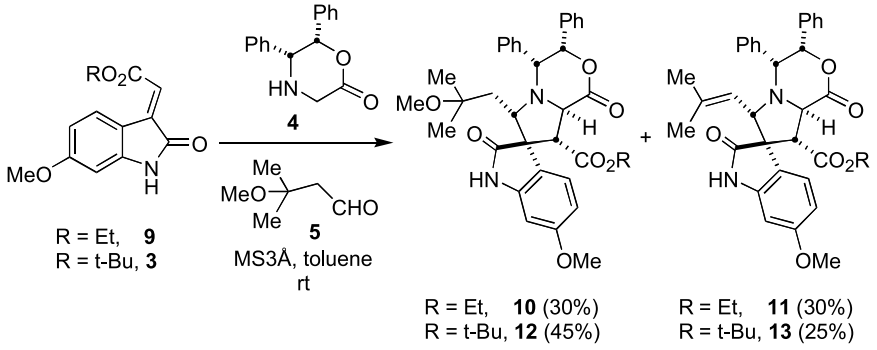
similar to that employed in our spirotryprostatin B synthesis.[8] Spirotryprostatin A (**1**) differs from spirotryprostatin B (**2**) in that it is saturated at C-8 and C-9 and is substituted at C-6 by a methoxy group whereas spirotryprostatin B (**2**) is absent of functionality in the aromatic ring and contains the characteristic C-8, C-9-enamide moiety. The enamide of spirotryprostatin B was installed via a Barton-modified Hunsdiecker reaction through an oxidative decarboxylation of a carboethoxy group that was introduced at C-8 in the initial dipolar cycloaddition reaction. First, we attempted to apply the same strategy, which was developed for spirotryprostatin B, to the total synthesis of spirotryprostatin A (Scheme 1). This approach would have to account for the substitution of the aromatic ring and the formation of the fourth stereogenic center. Thus, [1,3]-dipolar cycloaddition with methoxy-substituted oxindolylidene acetate **3** would yield *spiro*-oxindole pyrrolidine amino acid **6** upon reductive cleavage of the chiral auxiliary. Coupling of **6** to L-proline benzyl ester and concomitant cyclization would afford diketopiperazine **7**. Deprotection of the carboxyl group followed by a Barton-modified Hunsdiecker reaction as deployed previously, would result in the formation of enamide **8**. Palladium-catalyzed reduction of the olefin was reasonably expected to occur from the least hindered face opposite the isopropylidene group and the aromatic ring to *cis*-diketopiperazine. Final acid-catalyzed elimination of methanol would then afford spirotryprostatin A (**1**).

In the synthesis of spirotryprostatin B, ethyl oxindolylidene acetate was synthesized via Wittig reaction of commercially available 1H-indole-2,3-dione (isatin) and the requisite stabilized ylide. For spirotryprostatin A, 6-methoxy-isatin[17] was not commercially available and necessitated preparation from *m*-anisidine by a Sandmeyer reaction.[18] Wittig reaction with (carbethoxymethylene)triphenyl phosphorane then afforded 6-methoxy-ethyl oxindolylidene acetate **9**. Crystallization of the product mixture afforded only the desired *E*-isomer. Addition of dipolarophile **9** to the azomethine ylide derived from morpholinone **4** and aldehyde **5** yielded cycloadducts **10** and **11** (Scheme 2). The reaction proceeded in only modest yields (60%) and afforded the two products as a ~1:1 mixture. It was suspected that the yield and selectivity were a result of the poor solubility of ethyl oxindolylidene acetate (**9**) in toluene at room temperature. It was reasoned that this slowed the cycloaddition down relative to the analogous system used quite successfully in our spirotryprostatin B synthesis, allowing for a competing pathway via formation and cycloaddition of an incipient unsaturated azomethine ylide that results in the formation of the unsaturated cycloadduct (**11**) to prevail.[8] It was speculated that an increase in the lipophilicity of the dipolarophile might aid in the solubility of this species and suppress formation of the unsaturated azomethine ylide. Therefore, the *tert*-butyl ester **3** was synthesized which proved to be readily soluble in toluene at room temperature. Subjecting **3** to the standard reaction conditions for the [1,3]-dipolar cycloaddition resulted in an improved yield (70%) and an increase in the ratio (ca. 2:1) of the desired cycloadduct **12** over the unsaturated cycloadduct **13**.

Construction of the diketopiperazine began with palladium-catalyzed hydrogenolysis of cycloadduct **12** (Scheme 3). The resulting amino acid **6**[19] was coupled without purification to L-proline benzyl ester with BOP as the activating agent. Reduction of the resulting dipeptide-benzyl ester, followed by intramolecular cyclization afforded diketopiperazine **7** in 39% yield over three steps. This is in contrast to the 69% yield observed for the

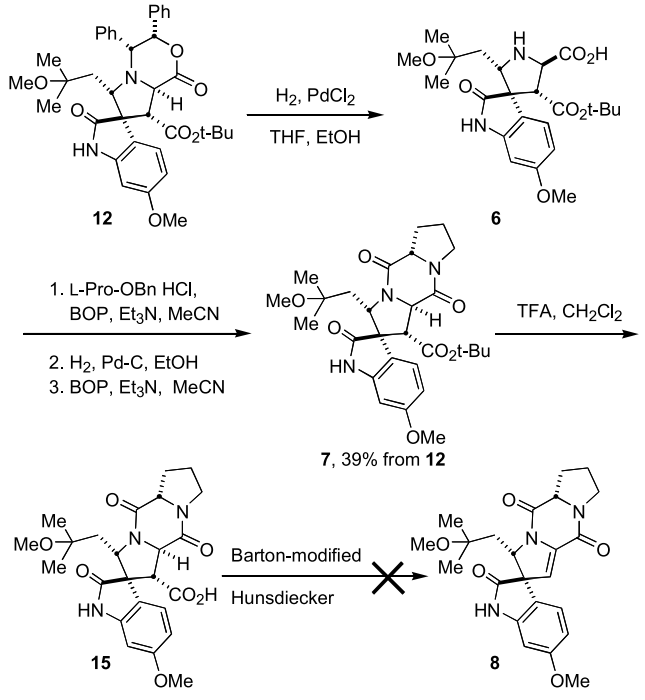


Scheme 1. Initial strategy to spirotryprostatin A (**1**).



Scheme 2. [1,3]-Dipolar cycloaddition with 6-methoxy-alkyl oxindolylidene acetate **9** and **3**.

analogous sequence employed in the spirotryprostatin B synthesis.[8] It is not currently understood why substitution of the aromatic ring or exchange of the ethyl ester for a *tert*-butyl ester caused such a decrease in the overall yield. Completion of the synthesis of spirotryprostatin A required hydrolysis of the ester functionality and the Barton-modified Hunsdiecker reaction to afford enamide **8**. The *tert*-butyl ester **7** was hydrolyzed using trifluoroacetic acid in yields ranging from 42–58%. However, subjecting the resulting carboxylic acid **15** to the same oxidative decarboxylation conditions employed successfully in the spirootryprostatin B synthesis failed to provide enamide **8**. Kochi-type conditions ($Pb(OAc)_4$; and thermal or photolytic cleavage of a benzophenone oxime ester) were also unsuccessful. Attempted reductive decarboxylation conditions resulted in decomposition of the starting material. Attempts to affect either the oxidative or the reductive decarboxylation at an earlier stage in the synthesis were similarly unsuccessful. The complications in the elimination of the carboxyl group and the relatively lower yields observed for the previous steps warranted exploration of a new strategy.



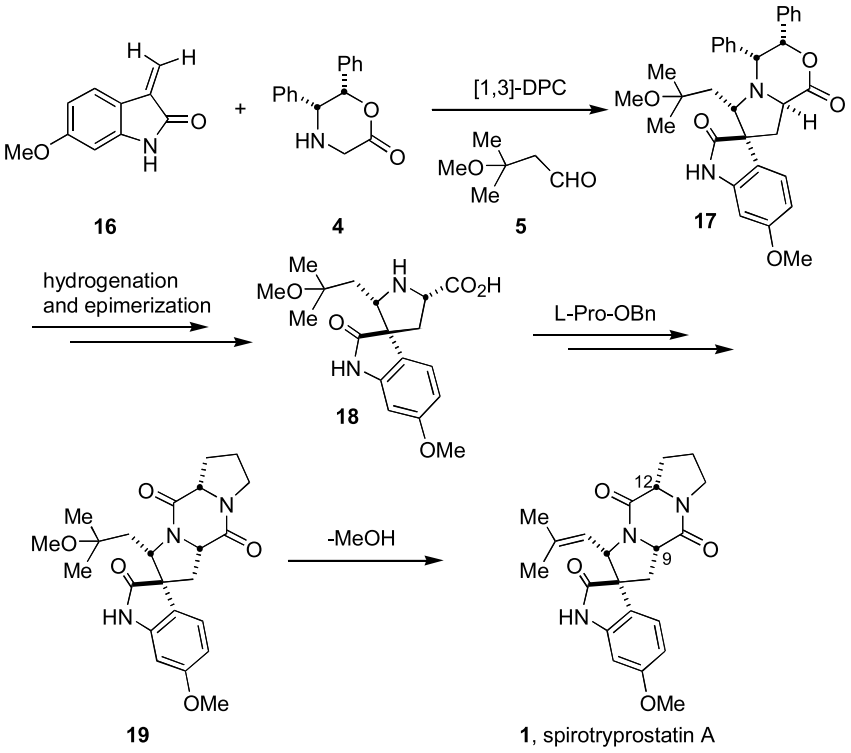
Scheme 3. Elaboration to diketopiperazine **7** and attempted decarboxylation of **15**.

2.2. Revised synthetic route to spirotryprostatin A

A new approach, one that avoided the problematic oxidative decarboxylation step, was eventually devised as outlined in Scheme 4. Since it is not necessary to install a carboxyl group as a precursor for the saturated pyrrolidine moiety, the strategy revolved around formation of 6-methoxy-3-methylene-1,3-dihydro-indol-2-one (**16**). Elimination of the carboalkoxy group from the dipolarophile at the outset would alleviate the problems associated with its ultimate removal. If the synthesis of this dipolarophile could be accomplished, [1,3]-dipolar cycloaddition with **4** and **5** would generate a cycloadduct **17** that would have the correct configuration at the adjacent C-3 quaternary and C-18 stereogenic centers. However, based on the established facial selectivity of azomethine ylide reactions derived from **4**, the α-proton (C-9) would need to be epimerized before elaboration to the diketopiperazine **19**. This was anticipated to be a non-trivial operation since, as our spirotryprostatin B synthesis had shown, the thermodynamic instability of the *trans*-diketopiperazines in this structural family resulted in the facile epimerization of the prolyl-stereogenic center.[8] Finally, elimination of the tertiary methyl ether of **19** would afford the natural product (**1**).

Recently, Horvath and co-workers reported that azomethine ylides generated from silylaminonitriles and 3-methyleneindolin-2-one react to give the corresponding cycloadduct in 70% yield.[20] However, the dipolarophile was generated by flash vacuum pyrolysis and did not seem compatible with the synthesis of the methoxy-substitued derivative we required. After extensive exploration, we found that the Peterson olefination,[21] which has proven to be an efficient method for the generation of terminal olefins, afforded a suitable method for the formation of **16**. As shown in Scheme 5, addition of trimethylsilylmethyllithium to 6-methoxy-isatin[17] (**20**) afforded tertiary alcohol **21** in 85% yield. The *exo*-methylene species **16** could be prepared in situ by the treatment of **21** with trifluoroacetic acid at 0 °C.

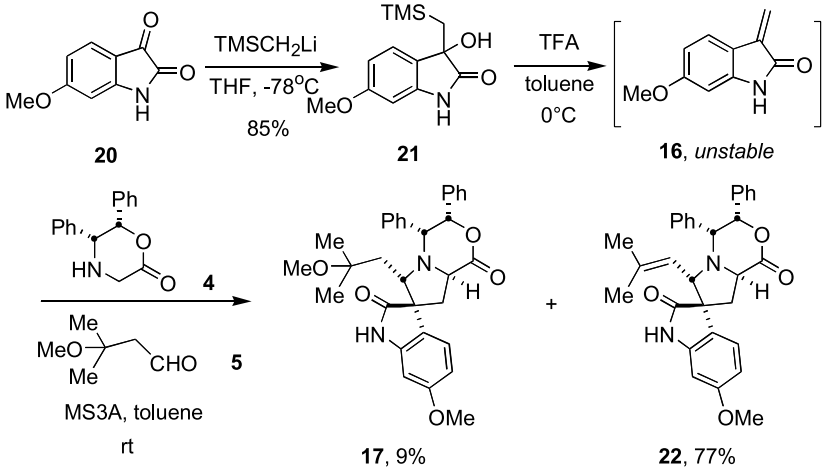
Compound **16** proved to be an unstable species that was not isolable due to polymer formation upon concentration. Thus, after neutralization with triethylamine, the reaction mixture containing crude **16** was directly and rapidly used for the cycloaddition. By the addition of **4** and **5** to the



Scheme 4. Revised strategy to spirotryprostatin A.

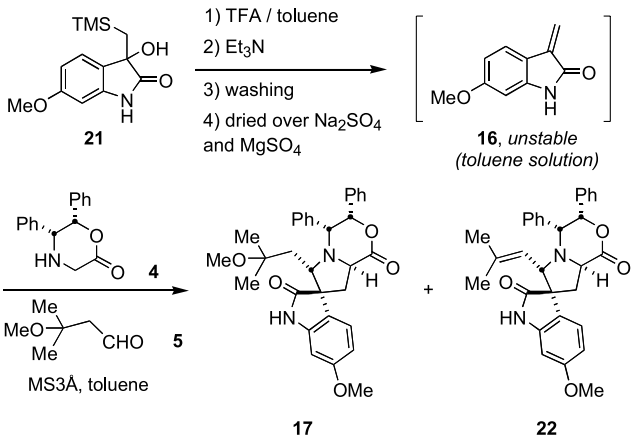
resultant crude mixture of **16** thus prepared, the [1,3]-dipolar cycloaddition proceeded rapidly to give a mixture of cycloadducts (**17** and **22**). We were unable to detect the generation of alternate regio- or diastereoisomers as products in the crude reaction mixture. In initial attempts performed at room temperature, the ratio of products unfortunately heavily favored the methanol elimination product **22**. Although a strategy utilizing **22** as a potential intermediate was explored, the olefin and oxindole functionalities proved incompatible with the conditions required to remove the chiral auxiliary.

This initially discouraging result prompted us to carefully explore the cycloaddition to elucidate crucial factors to control the reaction and suppress formation of **22**. First, the amount of the oxindole **21** was increased from 1.5 to 2 equiv since the yield would be influenced by amount of the unstable intermediate **16**; however, the yield for the desired product **17** was not improved. Next, we evaluated the effect of washing the reaction mixture after neutralization with triethylamine. First, the cycloaddition was performed without washing to give the methanol elimination product **22** exclusively (Table 1). When the reaction mixture was washed with saturated aqueous sodium bicarbonate solution or saturated aqueous citric acid solution, these attempts also afforded **22** exclusively. However, when just water was, the cycloaddition gave the desired compound **17** in 24% yield along with 42% of **22**. ^{1}H NMR studies were then conducted to decipher at what stage during the reaction methanol was being eliminated. After mixing aldehyde **5** and 0.83 equiv of **4** for 5 min in C_6D_6 at room temperature, we observed the generation of a significant amount (>50%) of 3-methyl-2-



Scheme 5. [1,3]-Dipolar cycloaddition with methylene indolinone **16**: an initial attempt.

Table 1. Optimization studies for the azomethine ylide dipolar cycloaddition



Entry	Washing	Temperature (°C)	Yield	
			17	**22**
1	No washing	rt	ND	61
2	H_2O and sat. $NaHCO_3$	rt	ND	40
3	H_2O and sat. citric acid	rt	ND	46
4	H_2O	rt	24	42
5	H_2O	−15–0 °C	44	20

N.D.: not detected (i.e. <trace).

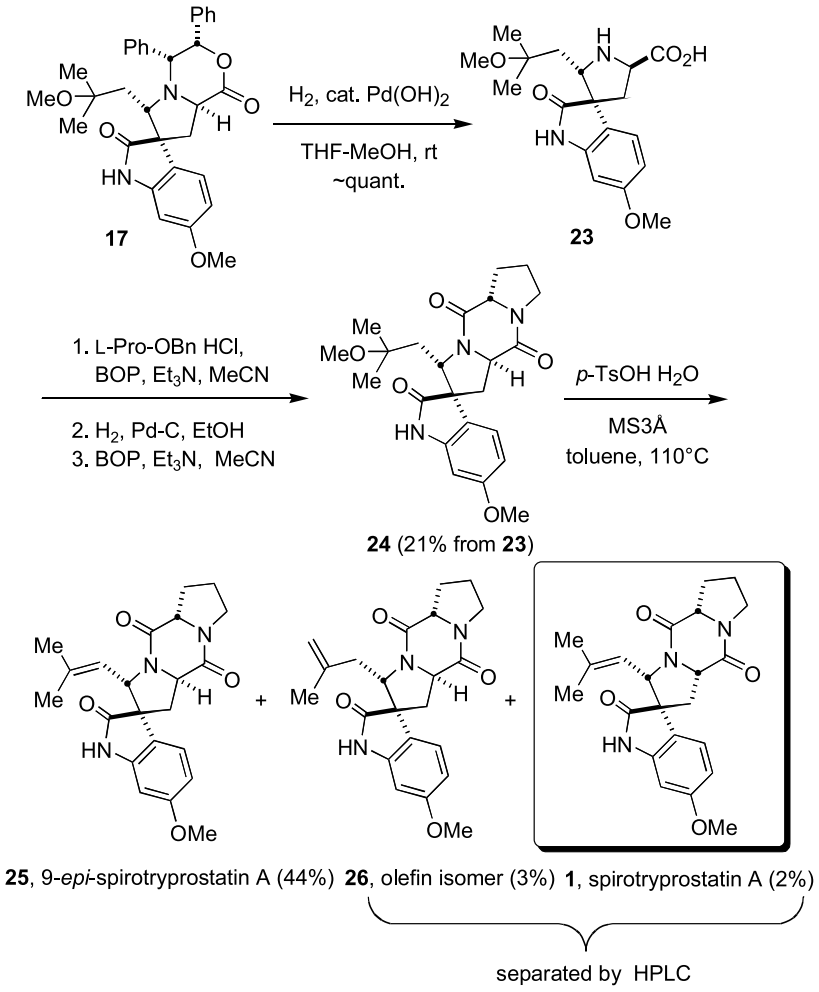
butenal whereas **4** remained intact. This indicated that elimination of methanol from **5** proceeds rapidly at room temperature. In an attempt to obviate the elimination before the dipolar cycloaddition reaction, the cycloaddition was then performed at 0 °C. Under these conditions, the desired cycloadduct **17** was isolated in 44% yield as a major product along with 20% of **22**.

The regiochemistry of **17** was ascertained by the doublet of doublets observed in the ^{1}H NMR spectrum for the α proton (to become C-9) and the relative configuration was confirmed by NOESY. As anticipated, these data indicated that the cycloadduct possesses the incorrect relative stereochemistry at C-9 (spirotryprostatin numbering). However, a strategy utilizing **17** as an intermediate would potentially be warranted for further investigation since catalytic hydrogenation can be used for removal of the chiral auxiliary. Actually, amino acid **23** was cleanly produced from catalytic hydrogenation of **17** using $Pd(OH)_2$ as a catalyst in quantitative yield (Scheme 6). First, we attempted epimerization of the α-proton (C-9) after conversion to the *trans*-diketopiperazine **24** since, during the last methanol elimination step, we anticipated that the prolyl-stereogenic centers (C-9 or C-12) could be epimerized to give a mixture of *cis*-diketopiperazines (i.e. spirotryprostatin A (**1**) and its *bis*-epimer at C-9 and C-12), which are thermodynamically more stable than the corresponding *trans*-diketopiperazines for cyclic anhydrides of proline.[8,22] To obtain diketopiperazine **24**, compound **23** was directly coupled with L-proline benzyl ester and BOP as the activating agent to give the corresponding dipeptide. Reduction of the benzyl ester followed by BOP-mediated cyclization afforded diketopiperazine **24**, a useful precursor of 9-*epi*-spirotryprostatin A, in 21% yield from **23**. The modest yield seemed to be associated with the difficulty of the isolation procedure to remove HMPA (a by-product from BOP-mediated coupling) from the product since diketopiperazine **24** proved to be quite hydrophilic. Additionally, it was observed that some of the product (less than 18%) were partitioned into the aqueous layer in the presence of HMPA.

Next, diketopiperazine **24** was subjected to treatment with *p*-TsOH-H_2O in refluxing toluene to give 9-*epi*-spirotryprostatin A (**25**) in 44% yield along with the olefin isomer of 9-*epi*-spirotryprostatin A (**26**, 3%). The relative configuration of **25** was confirmed by NOESY to be a *trans*-fused diketopiperazine. Unexpectedly, only a trace amount (2%) of the *cis*-fused substance (spirotryprostatin A, **1**), which could be isolated from **26** by HPLC, was generated. We were unable to detect the generation of 9,12-*bis*-*epi*-spirotryprostatin A. This result is in stark contrast to that observed for our spirotryprostatin B synthesis, in which epimerization readily occurred at the prolyl-stereogenic center (C-12) to give the thermodynamically more stable *cis*-fused diketopiperazine.[8]

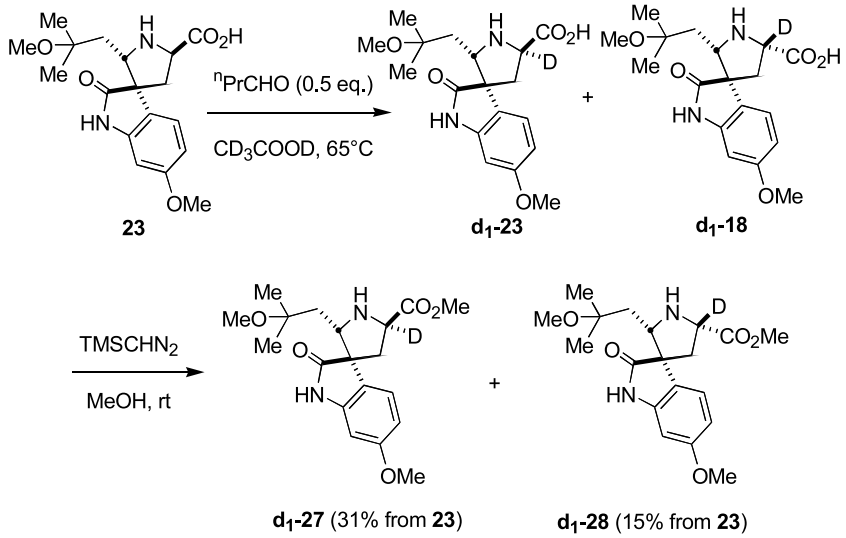
We next turned to examining the epimerization of the α-proton of **23** in the presence of an aldehyde and acid.[23] Butyraldehyde (0.5 equiv) and **23** were dissolved in CD_3COOD and the mixture was heated to 65 °C (Scheme 7). It was observed by ^{1}H NMR that the α-proton of the amino acid was gradually exchanged for deuterium and that thermodynamic epimerization had occurred. After conversion into the corresponding methyl ester by the treatment with $TMSCHN_2$, these diastereomers could be isolated by PTLC.

By substituting acetic acid for CD_3COOD, **23** was epimerized to give an inseparable diastereomeric mixture of amino acids (**29**, Scheme 8). Separation by PTLC was possible only after conversion to the pentacyclic substances **24** and **19** by the following three-step sequence.[8] Coupling

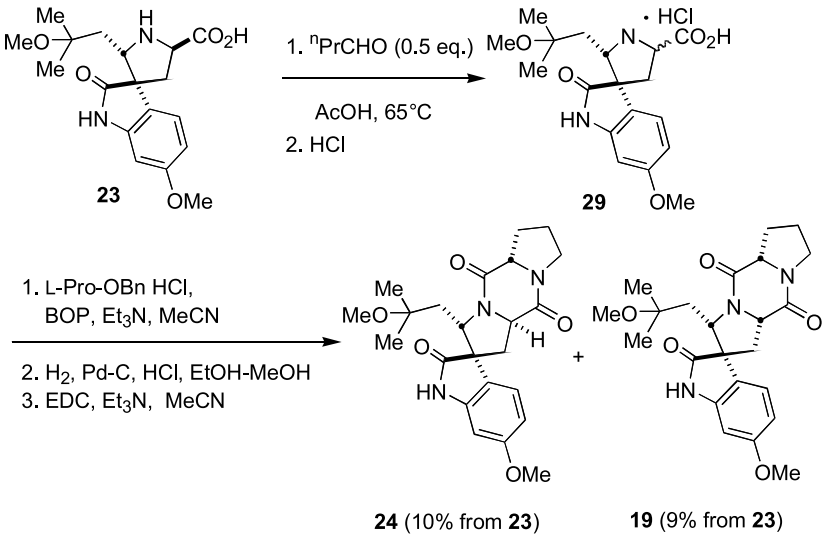


Scheme 6. Synthesis of 9-*epi*-spirotryprostatin A (**25**).

of **29** with L-proline benzyl ester in the presence of BOP afforded a diastereomeric mixture of dipeptides that was used without purification for the next reaction. Reduction of the benzyl ester followed by WSC-mediated cyclization afforded the *cis*-fused product **19** (9% from **23**), which has the correct relative and absolute configuration for the synthesis of spirotryprostatin A, plus the *trans*-fused substance (**24**, 10% from **23**), which was converted into 9-*epi*-spirotryprostatin A as shown in Scheme 6. The highly hydrophilic character of compounds **19** and **24** have resulted in lower yields due to loss of material in the aqueous work-up procedure.



Scheme 7. Epimerization of the α-proton of **23** in the presence of butyraldehyde and acetic acid.



Scheme 8. Elaboration to *cis*-fused diketopiperazine **19**.

Finally, **19** was subjected to treatment with *p*-TsOH-H_2O in refluxing toluene to give spirotryprostatin A (**1**) in 43% yield along with tertiary alcohol **30** (31%) (Scheme 9). Aiming to improve the yield, anhydrous camphorsulfonic acid, was used instead as a protic acid; however, elimination of methanol was not observed under these conditions.

3. Conclusion

In summary, a concise asymmetric total synthesis of spirotryprostatin A utilizing the asymmetric azomethine ylide [1,3]-dipolar cycloaddition reaction of methylene indolinone **16** has been achieved. The synthesis recorded herein requires only twelve steps (seven steps in the longest linear sequence) from commercially available reagents. The effects of compound **25**, 9-*epi*-spirotryprostatin A, on the cell cycle and microtubule assembly will be reported separately.

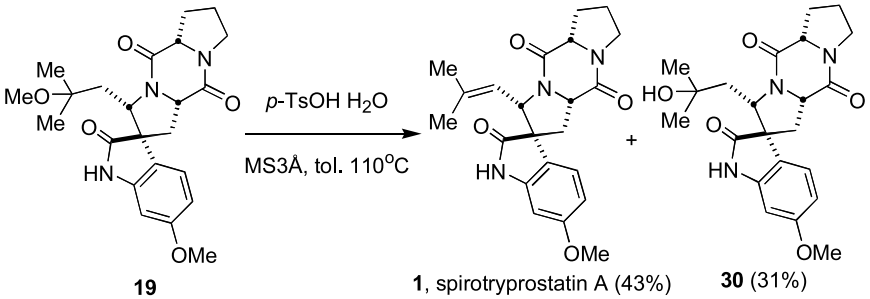
4. Experimental

4.1. General

Unless otherwise noted, materials were obtained from commercially available sources and used without purification. Toluene was freshly distilled from calcium hydride. Diethyl ether and tetrahydrofuran were freshly distilled from sodium benzophenone ketyl. 3 Å Molecular sieves were activated by heating for three minutes at the highest setting in a microwave followed by cooling under argon. All reactions requiring anhydrous conditions were performed under a positive pressure of argon using oven-dried glassware (120 °C) that was cooled in a dessicator, unless stated otherwise. Column chromatography was performed on Merck silica gel Kiesel 60 (230–400 mesh).

Mass spectra were obtained on Fisons VG Autospec. ^{1}H NMR, ^{13}C NMR, HSQC and NOE experiments were recorded on a Varian 300 or 400 MHz spectrometer. Spectra were recorded in $CDCl_3$ and chemical shifts (δ) were given in ppm and were relative to $CHCl_3$. Proton ^{1}H NMR were tabulated in the following order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet), coupling constant in hertz, and number of protons. When appropriate, the multiplicity of a signal is denoted as 'br' to indicate the signal was broad. IR spectra were recorded on a Perkin–Elmer 1600 series FT-IR spectrometer. Optical rotations were determined with a Rudolph Research Autopol III automatic polarimeter referenced to the D-line of sodium.

4.1.1. *tert*-Butyl (6-methoxy-2-oxo-1,2-dihydroindol-3-ylidene)acetate (3). To an oven-dried 25 mL round bottom flask with stir bar was added 6-methoxy isatin (0.50 g, 2.8 mmol) and carbo-*tert*-butoxy triphenylphosphylidene (1.15 g, 3.1 mmol). An oven-dried condensor was attached and the system flushed with argon. Dimethoxyethane (30 mL) was added via syringe and the system heated to



Scheme 9. The final stage: elimination of methanol to give spirotryprostatin A (**1**).

reflux with stirring. Heating continued for 14 h followed by filtering through a pad of celite. The solution was then evaporated to dryness and recrystallized from methanol to yield **3** (0.42 g, 54%) as an orange solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ $CHCl_3$: 1.56 (s, 9H), 3.84 (s, 3H), 4.30 (q, J=7.5 Hz, 2H), 6.43 (d, J=2.1 Hz, 1H), 6.53 (dd, J=2.1, 8.7 Hz, 1H), 6.65 (s, 1H), 8.50 (d, J=8.7 Hz, 1H), 9.25 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ $CHCl_3$: 28.5, 55.9, 81.7, 97.1, 108.0, 113.7, 121.6, 130.9, 137.3, 145.5, 163.4, 165.5, 171.0; IR (NaCl/neat) 3219, 1726, 1700; HRMS (FAB+) calcd for $C_{15}H_{17}O_4N$ (*m*/*z*) 275.1157, found (*m*/*z*) 275.1156.

4.1.2. Spiro[3H-indole-3,7′(6′H)-[1H]pyrrolo[2,1-*c*][1,4]oxazine]-8′-carboxylic acid, 1,2,3′,4′,8′,8′a-hexahydro-6-methoxy-6′-(2-methoxy-2-methylpropyl)-1′,2-dioxo-3′-4′-diphenyl-, *tert*-butyl ester, (3*S*,3′*S*,4′*R*,6′*S*,8′*R*,8′a*R*) (12) and Spiro[3H-indole-3,7′(6′H)-[1H]pyrrolo[2,1-*c*][1,4]oxazine]-8′-carboxylic acid, 1,2,3′,4′,8′,8′a-hexahydro-6-methoxy-6′-(2-methyl-1-propenyl)-1′,2-dioxo-3′-4′-diphenyl-, *tert*-butyl ester, (3*S*,3′*S*,4′*R*,6′*S*,8′*R*,8′a*R*) (13). To a flame-dried 100 mL round bottom flask with stir bar was added **3** (0.60 g, 2.2 mmol), (5*R*,6*S*)-2,3,5,6-tetrahydro-5,6-diphenyl-1,4-oxazin-2-one (0.40 g, 1.5 mmol) and 3 Å molecular sieves (2.5 g). An oven-dried condensor was attached and the system flushed with argon. Distilled toluene (25 mL) was added via syringe followed by the addition of 3-methoxy-3-methyl butanal (0.22 g, 1.8 mmol) via syringe. The reaction mixture was kept at room temperature for 14 h while stirring. The reaction was then filtered through a pad of celite with toluene as the eluent and the resulting solution was evaporated under reduced pressure. Column chromatography with 3:1 hexane/AcOEt furnished cycloadduct **12** (0.44 g, 45%) and cycloadduct **13** (0.25 g, 25%).

Compound **12**. A white solid: $[\alpha]_D^{25}$=86.3 ($CHCl_3$, c=0.63); ^{1}H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$: 0.97 (s, 9H), 1.03 (s, 3H), 1.05 (s, 3H), 1.14 (dd, J=1.6, 16.4 Hz, 1H), 1.63 (dd, J=1.6, 16.4 Hz, 1H), 3.03 (s, 3H), 3.76 (s, 3H), 3.80 (d, J=7.2 Hz, 1H), 3.92 (d, J=1.6 Hz, 1H), 4.50 (d, J=7.2 Hz, 1H), 4.99 (d, J=3.2 Hz, 1H), 6.34 (d, J=3.2 Hz, 1H), 6.45–6.49 (m, 2H), 7.00 (d, J=8.8 Hz, 1H), 7.12–7.38 (m, 8H), 7.39 (d, J=8.8 Hz, 1H), 8.10 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ $CHCl_3$: 22.6, 26.0, 27.5, 44.3, 49.7, 55.2, 55.7, 56.0, 56.2, 60.0, 64.8, 73.5, 75.9, 82.0, 97.1, 107.2, 119.9, 125.1, 127.3, 127.4, 128.4, 128.5, 129.5, 136.7, 137.5, 142.6, 160.8, 167.7, 172.1, 178.2; IR (NaCl/neat) 1733, 1628; HRMS (FAB+) calcd for $C_{37}H_{43}O_7N_2$ (*m*/*z*) 627.3070, found (*m*/*z*) 627.3074; NOE data: irradiation of H_7 enhanced H_5 (1.12%) and H_9 (2.21%).

Compound **13**. White amorphous solid: $[\alpha]_D^{25}$=−12.7 ($CHCl_3$, c=0.29); ^{1}H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$: 0.99 (s, 9H), 1.44 (s, 3H), 1.67 (s, 3H), 3.76 (s, 3H), 3.93 (d, J=7.2 Hz, 1H), 4.33 (d, J=3.2 Hz, 1H), 4.41 (d, J=9.2 Hz, 1H), 4.48 (d, J=9.2 Hz, 1H), 4.76 (d, J=7.2 Hz, 1H), 6.03 (d, J=3.2 Hz, 1H), 6.42 (d, J=2.0 Hz, 1H), 6.49 (dd, J=2.0, 8.2 Hz, 1H), 7.08 (d, J=7.2 Hz, 1H), 7.15–7.24 (m, 10H), 7.52 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ $CHCl_3$: 18.9, 26.3, 27.5, 54.7, 55.7, 57.0, 59.3, 60.2, 68.8, 77.9, 82.1, 97.1, 106.8, 119.3, 119.9, 126.1, 126.9, 127.7, 128.0, 128.3, 128.6, 129.3, 136.2, 136.6, 140.8, 142.4, 160.6, 167.7, 171.9, 177.6; IR (NaCl/neat) 1730, 1632 cm^{-1}; HRMS (FAB+) calcd for $C_{36}H_{39}O_6N_2$ (*m*/*z*) 595.2808, found (*m*/*z*) 595.2804; NOE data: irradiation of H_9 enhanced H_7 (2.02%) and H_6 (1.31%).

4.1.3. Spiro[3H-indole-3,3′-pyrrolidine]-4′,5′-dicarboxylic acid, 1,2-dihydro-6-methoxy-2′-(2-methoxy-2-methylpropyl)-2-oxo, 4′-*tert*-butyl ester, 5′-metyl ester, (2′*S*,3*S*,4′*R*,5′*R*) (14). Cycloadduct **12** was added to a sealable pressure tube and dissolved in 1:1 THF/EtOH. The solvent was purged with argon for 5 min and palladium dichloride (1.0 equiv) was added. The tube was sealed and flushed with H_2 before finally pressurizing to 70 PSI. The reaction was stirred for 36 h and then filtered through celite to remove the palladium catalyst. Concentration afforded a viscous oil which was triturated with freshly distilled diethyl ether to afford the crude amino acid **6** as a white solid. For characterization purposes, a small amount of **6** was converted to the methyl ester. The carboxylic acid **6** was dissolved in 1:1 CH_2Cl_2/MeOH. To the solution was added 2 M (trimethylsilyl)diazomethane in hexane until a yellow color persisted. The reaction was stirred 5 min and then concentrated under reduced pressure. The residue was purified by preparative thin layer chromatography (silica gel, 1:1 hexane/AcOEt) to give **14** as a white amorphous solid.

$[\alpha]_D^{25}$=−17.2 ($CHCl_3$, c=0.64); ^{1}H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$: 0.89 (d, J=13.6 Hz, 1H), 0.98 (s, 9H), 1.00 (s, 3H), 1.10 (s, 3H), 1.17–1.21 (m, 1H), 3.09 (s, 4H), 3.64 (d, J=6.4 Hz, 2H), 3.76 (s, 6H), 4.49 (brs, 1H), 6.43 (d, J=2.0 Hz, 1H), 6.48 (d, J=8.4 Hz, 1H), 7.25 (s, 1H), 7.78 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ $CHCl_3$: 21.8, 24.0, 24.9, 28.0, 30.1, 39.8, 44.8, 48.9, 55.7, 57.0, 60.4, 60.5, 61.6, 74.5, 82.6, 97.4, 106.9, 116.6, 129.2, 143.1, 160.9, 162.9, 166.2, 168.7, 181.1; IR (NaCl/neat) 1724, 1662 cm^{-1}; HRMS (FAB+) calcd for $C_{24}H_{35}O_7N_2$ (*m*/*z*) 463.2444, found (*m*/*z*) 463.2444.

4.1.4. Spiro[1H,5H-dipyrrolo[1,2-a:1′,2′-*d*]pyrazine-2(3H),3′-[3H]indole]-1-carboxylic acid, 1′,2′,5a,6,7,8,10,10a-octahydro-6′-methoxy-3-(2-methoxy-2-methylpropyl)-2′,5,10-trioxo-, *tert*-butyl ester, (1*R*,2*S*,3*S*,5a*S*,10a*R*) (7). Cycloadduct **12** (389 mg, 0.62 mmol) was added to a sealable pressure tube and dissolved in 1:1 THF/EtOH (7.8 mL). The solvent was purged with argon for 5 min and palladium dichloride (109 mg, 0.62 mmol) was added. The tube was sealed and flushed with H_2 before finally pressurizing to 70 PSI. The reaction was stirred for 36 h and then filtered through celite to remove the palladium catalyst. Concentration afforded a viscous oil which was triturated with freshly distilled diethyl ether to afford the crude amino acid **6** as a white amorphous solid. To a 50 mL round-bottom flask that contained the crude amino acid **6** was added BOP reagent (0.30 g, 0.68 mmol) and L-proline benzyl ester hydrochloride (0.16 g, 0.68 mmol). The flask was flushed with argon, 15 mL of acetonitrile was added and the reaction mixture cooled to 0 °C. With stirring, triethylamine (0.19 mL, 1.3 mmol) was added dropwise and the solution allowed to warm to room temperature and stir for 8 h. The solvent was then evaporated, replaced with

10 mL of ethyl acetate, washed with 1 M HCl (2×2.5 mL), H_2O (1×2.5 mL), 5% $NaHCO_3$ (2×2.5 mL), sat. brine sol. (1×1 mL), dried over Na_2SO_4, filtered and evaporated to yield the crude dipeptide as a brown foam which was taken on crude. To the foam was added a stir bar and ethanol (10 mL). Argon was bubbled through for 5 min and 10% Pd/C (0.04 g) was added. The system was flushed with H_2 and a balloon of H_2 was attached. The solution was stirred vigorously for 1.5 h and then filtered through celite, evaporated and placed on high vacuum overnight. To the crude mixture was added a stir bar, BOP reagent (0.27 g, 0.62 mmol) and acetonitrile (5 mL). Triethylamine (0.086 mL, 0.62 mmol) was added dropwise and the reaction was allowed to stir for 8 h at which time the solvent was evaporated. Purification via column chromatography with 75:20:5 CH_2Cl_2/AcOEt/^{i}PrOH afforded **7** (127 mg, 39%) as a white amorphous solid.

$[\alpha]_D^{25}=-57.3$ (CH_2Cl_2, $c=1.1$); ^{1}H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$: 1.05 (s, 3H), 1.15 (s, 3H), 1.21 (s, 9H), 1.70 (dd, $J=4.0$, 18.4 Hz, 2H), 1.78 (quint, $J=8.4$ Hz, 1H), 1.85–1.96 (m, 1H), 1.96–2.08 (m, 1H), 2.15 (dd, $J=9.6$, 14.0 Hz, 1H), 2.49 (quint, $J=6.0$ Hz, 1H), 2.95 (s, 3H), 3.43 (d, $J=9.6$ Hz, 1H), 3.39 (ddd, $J=3.6$, 10.0, 13.6 Hz, 1H), 3.76 (s, 3H), 3.89 (dt, $J=8.0$, 12.4 Hz, 1H), 4.24 (dd, $J=6.0$, 11.6 Hz, 1H), 4.80 (dd, $J=4.4$, 9.6 Hz, 1H), 4.96 (d, $J=10.0$ Hz, 1H), 6.45 (d, $J=2.0$ Hz, 1H), 6.47 (dd, $J=2.0$, 8.4 Hz, 1H), 7.13 (d, $J=8.4$ Hz, 1H), 8.01 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ $CHCl_3$: 12.9, 20.7, 23.1, 23.7, 29.1, 38.4, 43.8, 47.9, 53.3, 56.1, 59.3, 59.6, 60.1, 60.6, 73.5, 109.6, 121.1, 123.6, 126.3, 128.5, 141.0, 161.8, 165.2, 168.8, 179.5; IR (NaCl/neat) 3244, 1763, 1667, 1665 cm^{-1}; HRMS (FAB+) calcd for $C_{28}H_{38}O_7N_3$ (*m/z*) 528.2710, found (*m/z*) 528.2714.

4.1.5. 3-Hydroxy-6-methoxy-3-trimethylsilyl-1,3-dihydroindole-2-one (21). To a suspension of 6-methoxy-1H-indole-2,3-dione (3.22 g, 20 mmol) in tetrahydrofuran (200 mL) was gradually added a 1.0 M solution of (trimethylsilyl)methyllithium in pentane (50 mL, 50 mmol) at −78 °C. After stirring for 3 h at −78 °C, saturated aqueous ammonium chloride solution was added. The product was extracted with ethyl acetate and dichloromethane. The combined organic layer was dried over anhydrous sulfate and concentrated to give **21** (4.49 g, 85%) as a white solid. The compound **21** was used for the next reaction without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$: −0.22 (s, 9H), 1.49 (d, $J=10.2$ Hz, 1H), 1.53 (d, $J=10.2$ Hz, 1H), 2.65 (s, 1H), 3.79 (s, 3H), 6.45 (d, $J=1.8$ Hz, 1H), 6.56 (dd, $J=1.8$, 6.3 Hz, 1H), 7.23 (d, $J=6.3$ Hz, 1H), 7.88 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ $CHCl_3$: −1.1, 28.3, 55.5, 75.5, 97.5, 107.5, 123.4, 125.4, 141.1, 161.2, 180.6; IR (NaCl/neat) 3388, 1714, 1634, 1507, 1351, 1251, 1151, 1125, 840 cm^{-1}; HRMS (FAB+) calcd for $C_{13}H_{19}O_3NSi$ (*m/z*) 265.1134, found (*m/z*) 265.1132.

4.1.6. Spiro[3H-indole-3,7′(6′H)-[1H]pyrrolo[2,1-*c*][1,4]oxazine], 1,2,3′,4′,8′,8′a-hexahydro-6-methoxy-6′-(2-methoxy-2-methylpropyl)-1′,2-dioxo-3′-4′-diphenyl-, (3*S*,3′*S*,4′*R*,6′*S*,8′a*R*) (17) and Spiro[3H-indole-3,7′(6′H)-[1H]pyrrolo[2,1-*c*][1,4]oxazine], 1,2,3′,4′,8′,8′a-hexahydro-6-methoxy-6′-(2-methyl-1-propenyl)-1′,2-dioxo-3′-4′-diphenyl-, (3*S*,3′*S*,4′*R*,6′*S*,8′a*R*) (22). To a suspension of oxyindole **21** (199 mg, 0.750 mmol) in toluene (10 mL) was added trifluoroacetic acid (97 μl, 1.25 mmol) at once at 0 °C. After stirring for 15 min at 0 °C, triethylamine (174 μl, 1.25 mmol) was added at once. After stirring for additional 5 min at 0 °C, water (6.1 mL) and toluene (10 mL) were added and the mixture was filtrated through celite. The residue was washed by toluene (2.5 mL). The organic layer was separated by phase separation and was dried over anhydrous sodium sulfate (2.5 g) and anhydrous magnesium sulfate (2.5 g) for 20 min. The drying reagents were removed by filtration and the residue was washed with toluene (1 mL). To the combined toluene solution were added 0.5 g of activated 3 Å molecular sieves, (5*R*,6*S*)-2,3,5,6-tetrahydro-5,6-diphenyl-1,4-oxazin-2-one (127 mg, 0.5 mmol), 3-methyl-3-methoxybutanal (70 mg, 0.6 mmol) and toluene (4 mL) at −15 °C. After stirring for 25 h at 0 °C, the mixture was filtrated through celite to remove the sieves and concentrated in vacuo. The product was purified by thin layer chromatography (eluted with 1:2 hexane/AcOEt) to give **17** (115 mg, 44%) and **22** (51 mg, 20%).

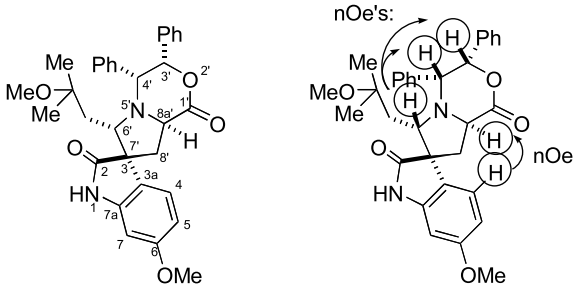
Compound **17**. A pale yellow amorphous solid: $[\alpha]_D^{24}=-46.0$ ($CHCl_3$, $c=1$); ^{1}H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$: 1.02 (s, 3H), 1.09 (s, 3H), 1.36 (dd, $J=5.6$, 15.6 Hz, 1H), 1.61 (dd, $J=2.1$, 15.6 Hz, 1H), 2.44 (dd, $J=8.0$, 12.6 Hz, 1H), 2.69 (dd, $J=10.4$, 12.6 Hz, 1H), 3.04 (s, 3H), 3.81 (s, 3H), 4.01 (dd, $J=2.1$, 5.6 Hz, 1H), 4.46 (dd, $J=8.0$, 10.4 Hz, 1H), 4.85 (d, $J=2.6$ Hz, 1H), 6.29 (d, $J=2.6$ Hz, 1H), 6.55 (d, $J=2.1$ Hz, 1H), 6.57 (dd, $J=2.1$, 8.4 Hz, 1H), 6.99–7.05 (m, 2H), 7.13–7.33 (m, 9H), 8.35 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ $CHCl_3$: 23.5, 25.0, 41.4, 44.5, 49.1, 55.5, 56.5, 56.7, 59.2, 64.6, 73.3, 76.4, 97.3, 107.4, 122.6, 125.5, 125.7, 127.2, 127.6, 128.0, 128.3, 128.8, 136.8, 136.8, 141.6, 160.2, 172.2, 179.2; IR (NaCl/neat) 1726, 1631, 1505, 1271, 1238, 1193, 1148, 755, 698 cm^{-1}; HRMS (FAB+) calcd for $C_{32}H_{35}O_5N_2$ (*m/z*) 527.2546, found (*m/z*) 527.2540.

Compound **22**. A pale yellow amorphous solid: $[\alpha]_D^{24}=-36.4$ ($CHCl_3$, $c=0.55$); ^{1}H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$: 1.54 (s, 3H), 1.74 (s, 3H), 2.48 (dd, $J=8.4$, 13.0 Hz, 1H), 2.75 (dd, $J=9.6$, 13.0 Hz, 1H), 3.80 (s, 3H), 4.27 (d, $J=3.0$ Hz, 1H), 4.52 (d, $J=9.4$ Hz, 1H), 4.54 (dd, $J=8.4$, 9.6 Hz, 1H), 4.70 (d, $J=9.4$ Hz, 1H), 6.18 (d, $J=3.0$ Hz, 1H), 6.48 (d, $J=2.3$ Hz, 1H), 6.56 (dd, $J=2.3$, 8.4 Hz, 1H), 7.02–7.07 (m, 2H), 7.15–7.33 (m, 9H), 7.75 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ $CHCl_3$: 18.6, 26.2, 40.0, 55.5, 56.3, 56.6, 60.2, 67.5, 97.2, 107.2, 120.8, 122.1, 125.6, 125.7, 127.4, 127.9, 128.0, 128.4, 128.9, 136.2, 136.4, 139.9, 141.2, 160.1, 168.5, 171.9, 178.3; IR (NaCl/neat) 3261, 1723, 1631, 1504, 1453, 1193, 1153, 755, 698 cm^{-1}; HRMS (FAB+) calcd for $C_{31}H_{31}O_4N_2$ (*m/z*) 495.2284, found (*m/z*) 495.2267.

4.2. Confirmation of the relative configuration of 17 by NOESY

NOE's were obrserved between the proton at position 4 of the oxyindole and the proton at 8′a, between the proton at 6′

and the proton at 3′, and between the proton at 6′ and the proton at 4′.



4.2.1. Spiro[3H-indole-3,3′-pyrrolidine]-5′-carboxylic acid, 1,2-dihydro-6-methoxy-2′-(2-methoxy-2-methylpropyl)-2-oxo, (2′*S*,3*S*,5′*R*) (23). To a solution of compound **17** (640 mg, 1.22 mmol) in dry tetrahydrofuran (6.2 mL) and methanol (6.2 mL) was added 20 wt% palladium hydroxide on carbon (215 mg). After stirring for 77 h at room temperature under H_2 atmosphere, the reaction mixture was filtrated through celite and concentrated in vacuo. The residue was washed by ethyl acetate (6 mL, 3 times) to give **23** (424 mg, 100%) as an off-white solid.

$[\alpha]_D^{23} = -18.4$ (MeOH, $c=1$); ^{1}H NMR (400 MHz, CD_3OD) δ MeOH: 1.17 (s, 3H), 1.20 (s, 3H), 1.29 (dd, $J=2.0$, 14.8 Hz, 1H), 1.72 (dd, $J=9.9$, 14.8 Hz, 1H), 2.49 (dd, $J=9.0$, 13.1 Hz, 1H), 2.57 (dd, $J=9.0$, 13.1 Hz, 1H), 3.24 (s, 3H), 3.85 (s, 3H), 4.19 (dd, $J=2.0$, 9.9 Hz, 1H), 4.51 (t, $J=9.0$ Hz, 1H), 6.62 (d, $J=2.0$ Hz, 1H), 6.70 (dd, $J=2.0$, 8.4 Hz, 1H), 7.32 (d, $J=8.4$ Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ MeOH: 22.2, 25.0, 40.8, 42.6, 49.6, 56.0, 59.1, 61.3, 63.7, 75.1, 98.9, 108.4, 121.3, 125.8, 144.2, 162.5, 172.3, 178.6; IR (NaCl/neat) 2968, 1716, 1633, 1600, 1507, 1456, 1346, 1193, 1156 cm^{-1}; HRMS (FAB+) calcd for $C_{18}H_{25}O_5N_2$ (*m*/*z*) 349.1764, found (*m*/*z*) 349.1778.

4.2.2. Spiro[1H,5H-dipyrrolo[1,2-a:1′,2′-*d*]pyrazine-2(3H),3′-[3H]indole], 1′,2′,5a,6,7,8,10,10a-octahydro-6′-methoxy-3-(2-methoxy-2-methylpropyl)-2′,5,10-trioxo-, (2*S*,3*S*,5a*S*,10a*R*) (24). To a solution of **23** (143 mg, 0.291 mmol), L-proline benzyl ester hydrochloride (84.5 mg, 0.349 mmol) and triethylamine (97.3 μl, 0.698 mmol) in acetonitrile (2.9 mL) was added BOP (153 mg, 0.349 mmol) at 0 °C. After stirring for 11 h at room temperature, the mixture was concentrated in vacuo. After the addition of 1 M hydrochloric acid, the product was extracted with ethyl acetate. The organic layer was washed by sat. $NaHCO_3$ aq. and brine, and was dried over anhydrous sodium sulfate. The solvent was removed in vacuo and the residue was dissolved in ethanol (7.4 mL) and methanol (3.7 mL). To a solution was added 10 wt% palladium on carbon (20 mg). After stirring for 5 h at room temperature under H_2 atmosphere, the reaction mixture was filtrated through celite and concentrated in vacuo. To the residue were added triethylamine (31.8 μl, 0.228 mmol) and acetonitrile (3.4 mL). To the mixture was added BOP (90.7 mg, 0.207 mmol). After stirring for 10 h at room temperature, the mixture was concentrated in vacuo. After the addition of 1 M hydrochloric acid, the product was extracted with ethyl acetate and was purified by preparative thin layer chromatography (silica gel, 10:1 CH_2Cl_2/MeOH) to give **24** (25.6 mg, 21%) as a colorless amorphous solid.

$[\alpha]_D^{25} = -77.0$ ($CHCl_3$, $c=0.2$); ^{1}H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$: 1.02 (s, 3H), 1.19 (s, 3H), 1.76–1.86 (m, 2H), 1.87–2.08 (m, 3H), 2.41–2.53 (m, 3H), 2.93 (s, 3H), 3.40 (ddd, $J=3.6$, 9.4, 12.4 Hz, 1H), 3.80 (s, 3H), 3.94 (dt, $J=12.4$, 8.3 Hz, 1H), 4.22 (dd, $J=5.4$, 11.4 Hz, 1H), 4.61 (t, $J=8.8$ Hz, 1H), 4.81 (t, $J=6.8$ Hz, 1H), 6.47 (s, 1H), 6.54 (d, $J=8.2$ Hz, 1H), 7.09 (d, $J=8.2$ Hz, 1H), 7.58 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ $CHCl_3$: 21.7, 23.2, 24.7, 30.0, 40.6, 40.7, 44.7, 48.5, 54.8, 55.5, 58.8, 60.7, 61.0, 74.4, 97.5, 106.7, 121.3, 125.9, 142.0, 160.3, 163.6, 165.8, 181.0; IR (NaCl/neat) 2927, 1718, 1653, 1506, 1456, 1343, 1303, 1194, 1157 cm^{-1}; HRMS (FAB+) calcd for $C_{23}H_{30}O_5N_3$ (*m*/*z*) 428.2185, found (*m*/*z*) 428.2193.

4.2.3. Spiro[1H,5H-dipyrrolo[1,2-a:1′,2′-*d*]pyrazine-2(3H),3′-[3H]indole], 1′,2′,5a,6,7,8,10,10a-octahydro-6′-methoxy-3-(2-methyl-1-propenyl)-2′,5,10-trioxo-, (2*S*,3*S*,5a*S*,10a*R*) (25; 9-*epi*-spirotryprostatin A), Spiro[1H,5H-dipyrrolo[1,2-a:1′,2′-*d*]pyrazine-2(3H),3′-[3H]indole], 1′,2′,5a,6,7,8,10,10a-octahydro-6′-methoxy-3-(2-methyl-2-propenyl)-2′,5,10-trioxo-, (2*S*,3*S*,5a*S*,10a*R*) (26) and Spiro[1H,5H-dipyrrolo[1,2-a:1′,2′-*d*]pyrazine-2(3H),3′-[3H]indole], 1′,2′,5a,6,7,8,10,10a-octahydro-6′-methoxy-3-(2-methyl-1-propenyl)-2′,5,10-trioxo-, (2*S*,3*S*,5a*S*,10a*S*) (1; spirotryprostatin A). To a solution of compound **24** (33.9 mg, 0.0793 mmol) in toluene (2.4 mL) were added *p*-toluenesulfonic acid (15.1 mg, 0.0793 mmol) and 144 mg of activated 3 Å molecular sieves. After stirring for 5 h at 110 °C, the mixture was allowed to cool to room temperature. After the addition of sodium bicarbonate, the product was extracted with ethyl acetate and was purified by preparative thin layer chromatography (silica gel, 18:5:2 CH_2Cl_2/AcOEt/^{i}PrOH) to give **25** (13.8 mg, 44%) and a mixture of **26** and **1**. Both compounds could be isolated by reversed-phase high performance liquid chromatography eluting with a gradient of 25% MeCN in H_2O to give **26** (0.9 mg, 3%) and **1** (0.6 mg, 2%).

Compound **25**. A colorless amorphous solid: $[\alpha]_D^{25} = +30.0$ ($CHCl_3$, $c=0.4$); ^{1}H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$: 1.42 (s, 3H), 1.67 (s, 3H), 1.85–2.10 (m, 2H), 2.30 (dt, $J=5.5$, 8.2 Hz, 2H), 2.51 (dd, $J=9.0$, 13.4 Hz, 1H), 2.94 (dd, 5.2, 13.4 Hz, 1H), 3.57 (ddd, $J=3.5$, 8.2, 11.6 Hz, 1H), 3.68 (dt, $J=11.6$, 8.2 Hz, 1H), 3.79 (s, 3H), 4.24 (t, $J=8.2$ Hz, 1H), 4.62 (dd, $J=5.2$, 9.0 Hz, 1H), 5.11 (s, 2H), 6.46 (d, $J=2.3$ Hz, 1H), 6.51 (dd, $J=2.3$, 8.3 Hz, 1H), 7.01 (d, $J=8.3$ Hz, 1H), 7.88 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ $CHCl_3$: 18.1, 23.3, 25.7, 27.8, 35.9, 45.7, 54.2, 55.5, 58.9, 60.0, 61.6, 97.0, 106.9, 119.1, 119.6, 125.7, 138.4, 142.1, 160.3, 165.6, 166.1, 179.7; IR (NaCl/neat) 1720, 1662, 1598, 1506, 1426, 1342, 1310, 1278, 1193, 1156 cm^{-1}; HRMS (FAB+) calcd for $C_{22}H_{26}O_4N_3$ (*m*/*z*) 396.1923, found (*m*/*z*) 396.1915.

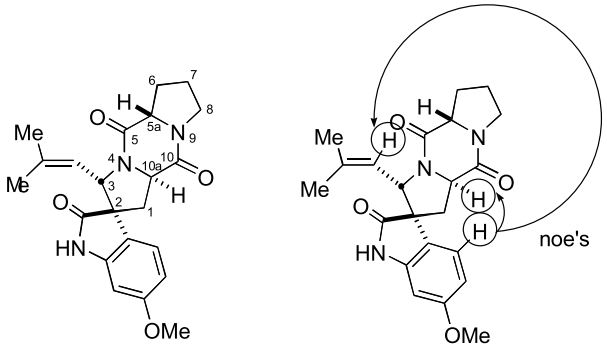
Compound **26**. A colorless amorphous solid: $[\alpha]_D^{25} = +38.8$ ($CHCl_3$, $c=0.08$); ^{1}H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$: 1.65 (s, 3H), 1.85–2.09 (m, 2H), 2.13 (dd, $J=7.7$, 13.1 Hz, 1H), 2.19–2.35 (m, 2H), 2.43 (dd, $J=7.8$, 13.2 Hz, 1H),

2.79 (dd, J=7.8, 13.2 Hz, 1H), 2.85 (dd, J=7.7, 13.1 Hz, 1H), 3.51–3.69 (m, 2H), 3.80 (s, 3H), 4.18 (s, 1H), 4.25 (t, J=8.0 Hz, 1H), 4.55 (s, 1H), 4.60 (t, J=7.8 Hz, 1H), 4.65 (t, J=7.7 Hz, 1H), 6.46 (d, J=2.4 Hz, 1H), 6.56 (dd, J=2.4, 8.4 Hz, 1H), 7.09 (d, J=8.4 Hz, 1H), 7.40 (brs, 1H); IR (NaCl/neat) 2924, 1718, 1662, 1507, 1457, 1429, 1341, 1310, 1157 cm^{-1}; HRMS (FAB+) calcd for $C_{22}H_{26}O_4N_3$ (m/z) 396.1923, found (m/z) 396.1919.

Compound **1**. A colorless amorphous solid: see below.

4.3. Confirmation of the relative configuration of 25 by NOESY

A NOE was obrserved between the proton at position 4 of the oxyindole and the olefinic proton of the 2-methyl-1-propenyl group. A NOE was also obrserved between the proton at position 9 of the oxyindole and the proton at position 9.



4.3.1. Spiro[3H-indole-3,3′-pyrrolidine]-5′-carboxylic acid, 1,2-dihydro-6-methoxy-2′-(2-methoxy-2-methylpropyl)-2-oxo, methyl ester, (2′*S*,3*S*,5′*R*) (27).

To a solution of compound **17** (101 mg, 0.193 mmol) in dry tetrahydrofuran (1 mL) and methanol (1 mL) was added palladium dichloride (34.2 mg, 0.193 mmol). After stirring for 54 h at room temperature under H_2 atmosphere, the reaction mixture was filtrated and concentrated in vacuo. The residue was dissolved in methanol (1.9 mL) and to the solution was added 2 M (trimethylsilyl)diazomethane in hexane (483 μl, 0.965 mmol). After stirring for 2 h at room temperature, a few drops of acetic acid were added and the reaction mixture was concentrated in vacuo. After the addition of aqueous sodium bicarbonate solution, the product was extracted with ethyl acetate and was purified by preparative thin layer chromatography (silica gel, 1:2 hexane/AcOEt) to give **27** (26.2 mg, 37% (2 steps)) as a pale yellow solid.

$[\alpha]_D^{25}=-32.0$ ($CHCl_3$, c=1); ^{1}H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$: 0.96 (dd, J=2.0, 14.3 Hz, 1H), 1.05 (s, 3H), 1.13 (s, 3H), 1.28 (dd, J=9.7, 14.3 Hz, 1H), 2.30 (dd, J=9.0, 13.1 Hz, 1H), 2.50 (dd, J=6.8, 13.1 Hz, 1H), 3.11 (s, 3H), 3.72 (dd, J=2.0, 9.7 Hz, 1H), 3.77 (s, 3H), 3.80 (s, 3H), 4.12 (dd, J=6.8, 9.0 Hz, 1H), 6.46 (d, J=2.1 Hz, 1H), 6.54 (dd, J=2.1, 8.1 Hz, 1H), 7.32 (d, J=8.1 Hz, 1H), 7.80 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ $CHCl_3$: 24.3, 25.6, 39.8, 41.2, 49.2, 52.3, 55.5, 57.4, 57.7, 62.4, 74.3, 96.9, 107.0, 124.0, 125.7, 141.0, 159.8, 175.8, 179.7; IR (NaCl/neat) 2972, 2359, 1711, 1633, 1558, 1506, 1457, 1341, 1194, 1153, 1020, 771 cm^{-1}; HRMS (FAB+) calcd for $C_{19}H_{27}O_5N_2$ (m/z) 363.1920, found (m/z) 363.1923.

4.3.2. 5′-d$_1$-Spiro[3H-indole-3,3′-pyrrolidine]-5′-carboxylic acid, 1,2-dihydro-6-methoxy-2′-(2-methoxy-2-methylpropyl)-2-oxo, methyl ester, (2′*S*,3*S*,5′*R*), (d$_1$-27) and 5′-d$_1$-Spiro[3H-indole-3,3′-pyrrolidine]-5′-carboxylic acid, 1,2-dihydro-6-methoxy-2′-(2-methoxy-2-methylpropyl)-2-oxo, methyl ester, (2′*S*,3*S*,5′*S*), (d$_1$-28).

Amino acid **23** (20.3 mg, 0.0583 mmol) and butyraldehyde (2.60 μl, 0.0292 mmol) were dissolved in d_4-acetic acid (0.7 mL). After stirring for several hours at 65 °C, it was obrserved by NMR that α-proton of the amino acid was converted to deuterium and that epimerization of the wrong chiral center proceeded. After stirring for 31 h at 65 °C, the mixture was concentrated in vacuo. The residue was dissolved in methanol (0.7 mL) and 2 M (trimethylsilyl)-diazomethane in hexane (146 μl, 0.292 mmol) was added. After stirring for 5 h at room temperature, the mixture was concentrated in vacuo. After the addition of aqueous sodium bicarbonate solution, the product was extracted with ethyl acetate and was purified by preparative thin layer chromatography (silica gel, 1:3 hexane/AcOEt) to give d$_1$-**27** (6.6 mg, 31% (2 steps)) and d$_1$-**28** (3.2 mg, 15% (2 steps)).

Compound d$_1$-**27**. A pale yellow amorphous solid: $[\alpha]_D^{25}=-17.6$ ($CHCl_3$, c=0.25); ^{1}H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$: 0.96 (d, J=14.0 Hz, 1H), 1.05 (s, 3H), 1.13 (s, 3H), 1.28 (dd, J=8.8, 14.0 Hz, 1H), 2.31 (d, J=12.6 Hz, 1H), 2.50 (d, J=12.6 Hz, 1H), 3.12 (s, 3H), 3.73 (d, J=8.8 Hz, 1H), 3.78 (s, 3H), 3.80 (s, 3H), 6.45 (d, J=2.3 Hz, 1H), 6.55 (dd, J=2.3, 8.2 Hz, 1H), 7.35 (d, J=8.2 Hz, 1H), 7.54 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ $CHCl_3$: 24.2, 25.6, 39.7, 41.2, 49.3, 52.4, 55.5, 57.3, 57.7, 62.4, 74.3, 97.0, 107.0, 123.9, 125.8, 140.9, 159.9, 175.7, 179.5; IR (NaCl/neat) 1710, 1630, 1505, 1461, 1270, 1244, 1193, 1153, 1122 cm^{-1}; HRMS (FAB+) calcd for $C_{19}H_{25}DO_5N_2$ (m/z) 363.1904, found (m/z) 363.1906.

Compound d$_1$-**28**. A pale yellow amorphous solid: $[\alpha]_D^{25}=-18.6$ ($CHCl_3$, c=0.167); ^{1}H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$: 1.02 (d, J=14.4 Hz, 1H), 1.08 (s, 3H), 1.10 (s, 3H), 1.31 (dd, J=9.2, 14.4 Hz, 1H), 2.13 (d, J=13.8 Hz, 1H), 2.76 (d, J=13.8 Hz, 1H), 3.09 (s, 3H), 3.54 (d, J=9.2 Hz, 1H), 3.77 (s, 3H), 3.79 (s, 3H), 6.44 (d, J=2.4 Hz, 1H), 6.54 (dd, J=2.4, 8.0 Hz, 1H), 7.24 (brs, 1H), 7.41 (d, J=8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ $CHCl_3$: 24.3, 25.4, 38.0, 40.6, 41.2, 49.2, 52.3, 55.5, 57.4, 65.0, 74.1, 97.0, 107.1, 123.4, 125.7, 140.9, 159.8, 175.7, 180.1; IR (NaCl/neat) 1722, 1630, 1506, 1463, 1275, 1194, 1155, 1123, 1077 cm^{-1}; HRMS (FAB+) calcd for $C_{19}H_{25}DO_5N_2$ (m/z) 363.1904, found (m/z) 363.1910.

4.3.3. Spiro[1H,5H-dipyrrolo[1,2-a:1′,2′-*d*]pyrazine-2(3H),3′-[3H]indole], 1′,2′,5a,6,7,8,10,10a-octahydro-6′-methoxy-3-(2-methoxy-2-methylpropyl)-2′,5,10-trioxo-, (2*S*,3*S*,5a*S*,10a*R*) (24) and Spiro[1H,5H-dipyrrolo[1,2-a:1′,2′-*d*]pyrazine-2(3H),3′-[3H]indole], 1′,2′,5a,6,7,8,10,10a-octahydro-6′-methoxy-3-(2-methoxy-2-methylpropyl)-2′,5,10-trioxo-, (2*S*,3*S*,5a*S*,10a*S*) (19).

To a solution of compound **23** (58.2 mg, 0.167 mmol) in acetic acid (1.7 mL) was added n-butyraldehyde (7.4 μL, 0.083 mmol).

After stirring for 6 h at 60 °C, the reaction mixture was concentrated in vacuo. The residue was dissolved in methanol (1.7 mL) and 37% hydrochloric acid (17 μl, 0.20 mmol) was added. The mixture was concentrated to give a pale yellow solid. To the solid were added L-proline benzyl ester hydrochloride (61 mg, 0.251 mmol), triethylamine (88.5 μl, 0.635 mmol) and acetonitrile (1.7 mL). To the mixture was added BOP (95 mg, 0.216 mmol) at 0 °C. After stirring for 55 h at room temperature, the mixture was concentrated in vacuo. After the addition of 1 M hydrochloric acid (7.5 mL), the product was extracted with ethyl acetate (15 mL, 3 times). The organic layer was washed by sat. $NaHCO_3$ aq. (15 mL) and brine (15 mL), and was dried over anhydrous sodium sulfate. The solvent was removed in vacuo and the residue was dissolved in ethanol (3 mL), methanol (1.5 mL) and 37% hydrochloric acid (15 μl, 0.18 mmol). To a solution was added 10 wt% palladium on carbon (33 mg). After stirring for 34 h at room temperature under H_2 atmosphere, the reaction mixture was filtrated through celite and concentrated in vacuo. To the residue were added triethylamine (51.2 μl, 0.368 mmol) and acetonitrile (3.4 mL). To the mixture was added 1-(3-dimethylpropyl)-3-ethylcarbodiimide hydrochloride (38.4 mg, 0.200 mmol). After stirring for 123 h at room temperature, the mixture was concentrated in vacuo. After the addition of 1 M hydrochloric acid (10 mL), the product was extracted with ethyl acetate (20 mL, 3 times) and was purified by preparative thin layer chromatography (silica gel, 100:7.5 CH_2Cl_2/MeOH) to give **24** (7.2 mg, 10%) and **19** (6.3 mg, 9%).

Compound **24**. A colorless amorphous solid: see above.

Compound **19**. A colorless amorphous solid: $[\alpha]_D^{25} = -60.0$ ($CHCl_3$, $c=0.33$); ^{1}H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$: 0.93 (s, 6H), 1.86–2.24 (m, 5H), 2.30–2.66 (m, 3H), 2.83 (s, 3H), 3.57 (dd, $J=5.4$, 8.2 Hz, 2H), 3.79 (s, 3H), 4.20–4.27 (m, 2H), 4.77 (t, $J=8.8$ Hz, 1H), 6.43 (s, 1H), 6.54 (d, $J=8.4$ Hz, 1H), 7.04 (d, $J=8.4$ Hz, 1H), 7.64 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ $CHCl_3$: 23.3, 23.6, 24.9, 27.9, 30.0, 34.9, 40.8, 45.0, 48.7, 55.5, 58.4, 59.8, 61.4, 74.0, 97.1, 106.5, 121.4, 126.3, 142.0, 160.2, 166.7, 168.1, 181.4; IR (NaCl/neat) 1716, 1665, 1633, 1506, 1461, 1343, 1193, 1157, 732 cm^{-1}; HRMS (FAB+) calcd for $C_{23}H_{30}O_5N_3$ (*m*/*z*) 428.2185, found (*m*/*z*) 428.2193.

4.3.4. Spiro[1H,5H-dipyrrolo[1,2-a:1′,2′-*d*]pyrazine-2(3H),3′-[3H]indole], 1′,2′,5a,6,7,8,10,10a-octahydro-6′-methoxy-3-(2-methyl-1-propenyl)-2′,5,10-trioxo-, (2*S*, 3*S*,5a*S*,10a*S*) (1; spirotryprostatin A) and Spiro [1H,5H-dipyrrolo[1,2-a:1′,2′-*d*]pyrazine-2(3H),3′-[3H]indole], 1′,2′,5a,6,7,8,10,10a-octahydro-6′-methoxy-3-(2-hydroxy-2-methylpropyl)-2′,5,10-trioxo-, (2*S*,3*S*,5a*S*,10a*S*) (30). To a solution of compound **19** (6.3 mg, 0.0147 mmol) in toluene (0.5 mL) were added *p*-toluenesulfonic acid (2.8 mg, 0.0147 mmol) and 75 mg of activated 3 Å molecular sieves. After stirring for 5 h at 110 °C, the mixture was allowed to cool to room temperature. After the addition of sodium bicarbonate, the product was extracted with ethyl acetate and was purified by preparative thin layer chromatography (silica gel, 73:20:7 CH_2Cl_2/AcOEt/^{i}PrOH) to give **1** (2.5 mg, 43%) and **30** (1.9 mg, 31%).

Compound **1**. A colorless amorphous solid: $[\alpha]_D^{25} = -30.5$ ($CHCl_3$, $c=0.2$); ^{1}H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$: 1.17 (s, 3H), 1.64 (s, 3H), 1.86–2.08 (m, 2H), 2.20–2.39 (m, 2H), 2.38 (dd, $J=7.2$, 13.5 Hz, 1H), 2.60 (dd, $J=10.7$, 13.5 Hz, 1H), 3.50–3.68 (m, 2H), 3.79 (s, 3H), 4.27 (t, 8.4 Hz, 1H), 4.77 (d, $J=9.0$ Hz, 1H), 4.99 (dd, $J=7.2$, 10.7 Hz, 1H), 5.02 (d, $J=9.0$ Hz, 1H), 6.41 (d, $J=2.4$ Hz, 1H), 6.49 (dd, $J=2.4$, 8.5 Hz, 1H), 6.92 (d, $J=8.5$ Hz, 1H), 7.48 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ $CHCl_3$: 18.0, 23.7, 25.5, 27.4, 34.4, 45.2, 55.5, 58.5, 60.2, 60.2, 61.0, 96.6, 106.7, 118.7, 121.4, 127.3, 138.4, 141.6, 160.4, 167.1, 168.2, 180.5; IR (NaCl/neat) 2924, 1716, 1669, 1653, 1635, 1507, 1457, 1419, 1340, 1157 cm^{-1}; HRMS (FAB+) calcd for $C_{22}H_{26}O_4N_3$ (*m*/*z*) 396.1923, found (*m*/*z*) 396.1909.

Compound **30**. A colorless amorphous solid: $[\alpha]_D^{25} = -25.0$ ($CHCl_3$, $c=0.1$); ^{1}H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$: 0.62 (s, 3H), 1.11 (s, 3H), 1.79 (dd, $J=4.3$, 15.4 Hz, 1H), 1.92 (dd, $J=4.3$, 15.4 Hz, 1H), 1.89–2.10 (m, 2H), 2.16–2.40 (m, 2H), 2.46 (dd, $J=8.7$, 13.6 Hz, 1H), 2.65 (dd, $J=8.7$, 13.6 Hz, 1H), 3.60 (dd, $J=5.4$, 8.2 Hz, 2H), 3.79 (s, 3H), 4.29 (t, $J=8.2$ Hz, 1H), 4.36 (t, $J=4.3$ Hz, 1H), 4.45 (brs, 1H), 4.87 (t, $J=8.7$ Hz, 1H), 6.46 (d, $J=2.4$ Hz, 1H), 6.56 (dd, $J=2.4$, 8.4 Hz, 1H), 6.97 (d, $J=8.4$ Hz, 1H), 7.40 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ $CHCl_3$: 23.6, 27.0, 27.7, 31.5, 33.9, 43.3, 45.2, 55.5, 59.0, 59.4, 61.0, 68.7, 77.2, 97.5, 107.1, 120.4, 126.3, 142.0, 160.7, 168.1, 168.3, 181.4; IR (NaCl/neat) 2923, 2850, 1717, 1683, 1652, 1636, 1507, 1456, 1433, 1158 cm^{-1}; HRMS (FAB+) calcd for $C_{22}H_{28}O_5N_3$ (*m*/*z*) 414.2029, found (*m*/*z*) 414.2020.

Acknowledgements

This work was supported by the National Science Foundation (Grant CHE 0202827). We are grateful to Ajinomoto Co. Inc., for financial support (to T.O.). Mass spectra were obtained on instruments supported by the National Institutes of Health Shared Instrumentation Grant GM49631. We are grateful to Dr. Hiroyuki Osada of the RIKEN institute, Japan, for providing spectra of natural spirotryprostatin A. We thank Dr. Kunisuke Izawa of Ajinomoto Co. Inc. for helpful discussions.

References and notes

1. (a) Cui, C. B.; Kakeya, H.; Osada, H. *J. Antibiot.* **1996**, *49*, 832. (b) Cui, C. B.; Kakeya, H.; Osada, H. *Tetrahedron* **1996**, *51*, 12651.
2. Cui, C. B.; Kakeya, H.; Osada, H. *Tetrahedron* **1997**, *53*, 59.
3. (a) Cui, C. B.; Kakeya, H.; Okada, G.; Ubukata, M.; Takahashi, I.; Isono, K.; Osada, H. *J. Antibiot.* **1995**, *48*, 1382. (b) Cui, C. B.; Kakeya, H.; Okada, G.; Onose, R.; Osada, H. *J. Antibiot.* **1996**, *49*, 527. (c) Cui, C. B.; Kakeya, H.; Osada, H. *J. Antibiot.* **1996**, *49*, 534.
4. Malinakova, H. C.; Liebeskind, L. S. *Org. Lett.* **2000**, *2*, 4083.
5. (a) Cossy, J.; Cases, M.; Pardo, D. M. *Tetrahedron Lett.* **1998**, *39*, 2331. (b) Hilton, S. T.; Ho, T. C.; Pljevaljcic, G.; Jones, K. *Org. Lett.* **2000**, *2*, 2639.

6. Alper, P. B.; Meyers, C.; Lerchner, A.; Siegel, D. R.; Carreria, E. M. *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 3186.
7. Kumar, U. K. S.; Ila, H.; Junjappa, H. *Org. Lett.* **2002**, *4*, 2639.
8. (a) Sebahar, P. R.; Williams, R. M. *J. Am. Chem. Soc.* **2000**, *122*, 5666. (b) Sebahar, P. R.; Osada, H.; Usui, T.; Williams, R. M. *Tetrahedron* **2002**, *58*, 6311.
9. von Nussbaum, F.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2000**, *39*, 2175.
10. Wang, H.; Ganesan, H. *J. Org. Chem.* **2000**, *65*, 4685.
11. Overman, L. E.; Rosen, M. D. *Angew. Chem. Int. Ed.* **2000**, *39*, 4596.
12. Bagul, T. D.; Lakshmaiah, G.; Kawabata, T.; Fuji, K. *Org. Lett.* **2002**, *4*, 249.
13. Meyers, C.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2003**, *42*, 694.
14. For a review, see: (a) Lindel, T. *Nachrichten aus der Chemie* **2000**, *48*, 1498. (b) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209. (c) Lindel, T. *Org. Synth. Highlights V* **2003**, 360.
15. (a) Edmonson, S. D.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 1138. (b) Edmonson, S.; Danishefsky, S. J.; Sepp-Lorenzino, L.; Rosen, N. *J. Am. Chem. Soc.* **1999**, *121*, 2147.
16. Onishi, T.; Sebahar, P. R.; Williams, R. M. *Org. Lett.* **2003**, *5*, 3135.
17. Giovannini, E.; Portmann, P. *Helv. Chim. Acta* **1948**, *31*, 1381.
18. Booker-Milburn, K. I.; Dunkin, I. R.; Kelly, F. C.; Khalaf, A. I.; Learmonth, D. A.; Proctor, G. R.; Scopes, D. I. C. *J. Chem. Soc., Perkin Trans. 1* **1997**, *21*, 3261.
19. Amino acid **6** was converted to methyl ester **14** by the treatment with $TMSCHN_2$ to ascertain the structure.
20. Bell, S. E. V.; Brown, R. F. C.; Eastwood, F. W.; Horvath, J. M. *Aust. J. Chem.* **2000**, *53*, 183.
21. (a) Chan, T.-H.; Chang, E.; Vinokur, E. *Tetrahedron Lett.* **1970**, 1137. (b) Hudrlik, P. F.; Peterson, D. *Tetrahedron Lett.* **1972**, 1785. After our own discovery of the utility of the Peterson olefination in the generation of 3-methylene oxindole, another group recently reported similar findings see Rossiter, S. *Tetrahedron Lett.* **2002**, *43*, 4671.
22. Eguchi, C.; Kakuta, A. *J. Am. Chem. Soc.* **1974**, *96*, 3985.
23. Yamada, S.; Hongo, C.; Chibata, I. *Agric. Biol. Chem.* **1977**, *41*, 2413.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 60 (2004) 9517–9524

A novel route to 2-imidazolin-5-one derivatives via oxidative cyclization of aryl-substituted (*Z*)-*N*-acetyl-α-dehydroalanines having a dialkylamino group

Atsushi Kawasaki,[a] Kei Maekawa,[a] Kanji Kubo,[b] Tetsutaro Igarashi[a] and Tadamitsu Sakurai[a,*]

[a]*Department of Applied Chemistry, Faculty of Engineering, Kanagawa University, Kanagawa-ku, Yokohama 221-8686, Japan*
[b]*Institute for Materials Chemistry and Engineering, Kyushu University, Kasugakoen, Kasuga 816-8580, Japan*

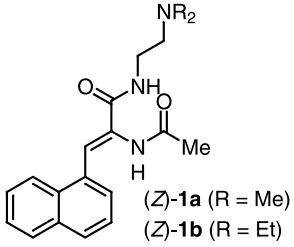
Received 9 June 2004; accepted 14 July 2004

Abstract—It was found that the reaction of the title compounds [(*Z*)-**1**] with oxygen in methanol proceeds according to the first-order kinetics to give (*Z*)-2-imidazolin-5-one derivatives and hydrogen peroxide in quantitative yields. Analysis of substituent and solvent effects on the rate constant for this oxidative cyclization led us to propose that electron transfer from the dialkylamino nitrogen in (*Z*)-**1** to oxygen, amide-proton abstraction by superoxide and the subsequent intramolecular electron transfer are all rate-determining steps. The synthetic utility of the novel cyclization reaction of aryl-substituted (*Z*)-*N*-acetyl-α-dehydroalanine derivatives was discussed.
© 2004 Elsevier Ltd. All rights reserved.

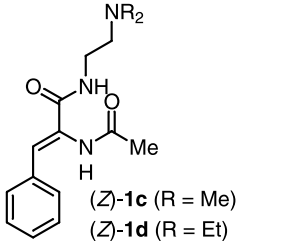
1. Introduction

In recent years much attention is being devoted to the synthetic application of photoinduced electron transfer reactions, owing to the fact that many of these reactions enable the construction of various heterocyclic rings.[1,2] In the course of our systematic study toward the characterization of the excited-state reactivities of substituted α-dehydroamino acids, we discovered an interesting photocyclization of *N*-acyl-α-dehydrophenylalanine derivatives,[3] as well as photoinduced reductive cyclization of substituted *N*-acyl-α-dehydro(1-naphthyl)alanines.[4] The former photocyclization afforded isoquinoline, 1-azetine and/or quinolinone derivatives in relatively good yields, depending on the steric bulkiness and electronic properties of the substituents introduced into the phenylalanines. The highly efficient and selective formation of dihydrobenzoquinolinone derivatives was observed through the latter electron transfer-initiated cyclization, demonstrating that *N*-acyl-α-dehydroamino acids containing a dialkylamino group or in the presence of a tertiary amine readily undergo one electron reduction to afford a radical ion pair intermediate.

Since tertiary amines are able to form charge-transfer complexes with oxygen in nonpolar solvents,[5] it is possible that the presence of oxygen in polar solvents thermally activates the tertiary amino nitrogen introduced into aryl-substituted α-dehydroalanine derivatives, thus allowing us to expect that the oxidatively activated amino nitrogen may induce a novel cyclization reaction. In a previous communication,[6] we found that the reaction of some aryl-substituted (*Z*)-*N*-acetyl-α-dehydroalanines having a dialkylamino group with oxygen in methanol gives the corresponding (*Z*)-2-imidazolin-5-one derivatives in quantitative yields. In order to expand the study of this fascinating oxidative cyclization reaction, we designed and synthesized aryl-substituted (*Z*)-*N*-acyl-α-dehydroalanines [(*Z*)-**1a**–**k**] having a 2-(dialkylamino)ethyl or a 3-(dimethylamino)propyl group attached to the carboxamide nitrogen, and investigated the substituent and solvent effects on the reactivity of (*Z*)-**1** in the presence of oxygen, hoping to shed much light on the mechanism of the novel oxidative cyclization reaction found by us.



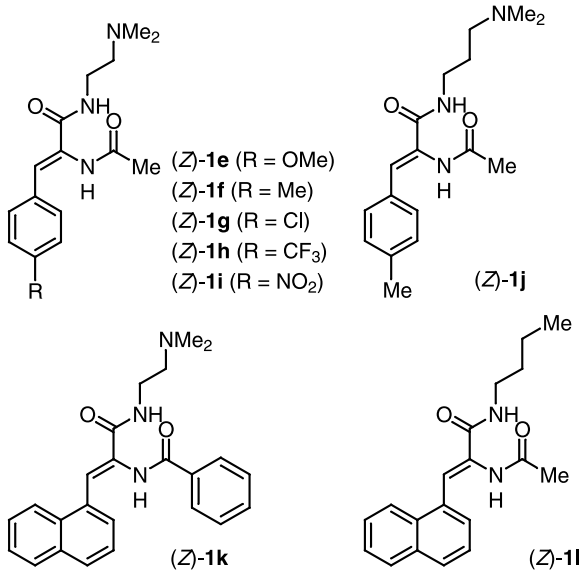
(*Z*)-**1a** (R = Me)
(*Z*)-**1b** (R = Et)



(*Z*)-**1c** (R = Me)
(*Z*)-**1d** (R = Et)

Keywords: α-Dehydroamino acid derivatives; Oxidative cyclization; 2-Imidazolin-5-ones; Kinetics.
* Corresponding author. Fax: +81-45-491-7915;
e-mail: sakurt01@kanagawa-u.ac.jp

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.07.068



2. Results and discussion

2.1. Product analysis

The starting (*Z*)-isomers were prepared in good yields by the ring-opening reactions of aryl-substituted oxazolones with 2-(dimethylamino)ethylamine (**1a**, **1c**, **1e–i** and **1k**), 2-(diethylamino)ethylamine (**1b** and **1d**), or 3-(dimethylamino)propylamine (**1j**).[7] Each methanol solution of (*Z*)-**1** (10 mL, 1.0×10^{-4} mol dm^{-3}) was purged with air for 10 min and then heated at 80 °C in a sealed tube for a given period of time. As typically shown in Figure 1, on heating the solution in an atmosphere of air, the UV absorption of the starting **1a** at 312 nm decreased gradually with appearance of the 378 nm absorption, while there were three isosbestic points at 252, 276 and 334 nm during the reaction. Similar UV spectral changes were observed for the other derivatives, except for **1k** which exhibited a negligible change in its UV absorption under the same reaction conditions. In order to isolate the product and determine its structure, an oxygen-saturated methanol solution of (*Z*)-**1a** (100 mL, 5.0×10^{-3} mol dm^{-3}; $[O_2]=1.02\times10^{-2}$ mol dm^{-3})[8] was heated at 80 °C for 48 h in a sealed tube. The reaction mixture obtained was subjected to short column chromatography over silica gel, which allowed us to isolate 1-[2-(dimethylamino)ethyl]-2-methyl-4-(1-naphthylmethylene)-2-imidazolin-5-one (**2a**) in 95% yield. The reactions of **1b–j** with oxygen under the same conditions gave the corresponding 2-imidazolin-5-one derivatives (**2b–j**) in greater than 80% isolated yields. As shown in Figure 2, a ^{1}H NMR spectral analysis of the mixture derived from the reaction of **1c** (2.0×10^{-3} mol dm^{-3}) with oxygen in methanol confirmed that the cyclization reaction proceeds cleanly to give only **2c**. The structure of **2a–j** was determined based on their spectroscopic and physical properties including ^{1}H–^{1}H COSY, ^{13}C–^{1}H COSY and HMBC spectra. In addition, the crystal structure of **2c** provided conclusive evidence for the imidazolinone ring as well as for the (*Z*)-configuration of **2** (Fig. 3),[9] indicating no occurrence of geometrical isomerization during the cyclization process of the starting (*Z*)-isomer. On the other

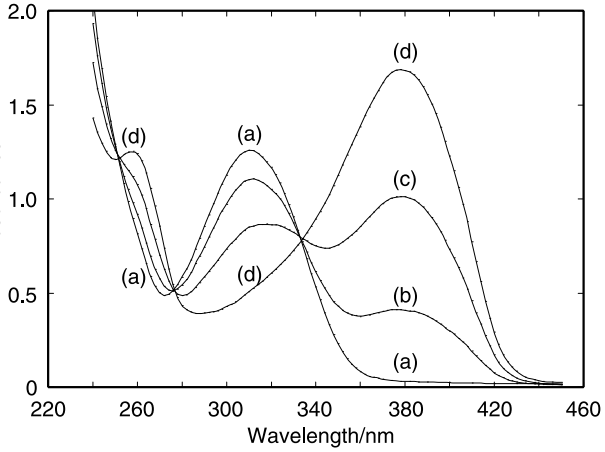


Figure 1. UV absorption spectra of air-saturated methanol solutions of (*Z*)-**1a** (1.0×10^{-4} mol dm^{-3}) heated for 0 h (curve a), 0.6 h (curve b), 1.8 h (curve c) and 24 h (curve d) at 80 °C.

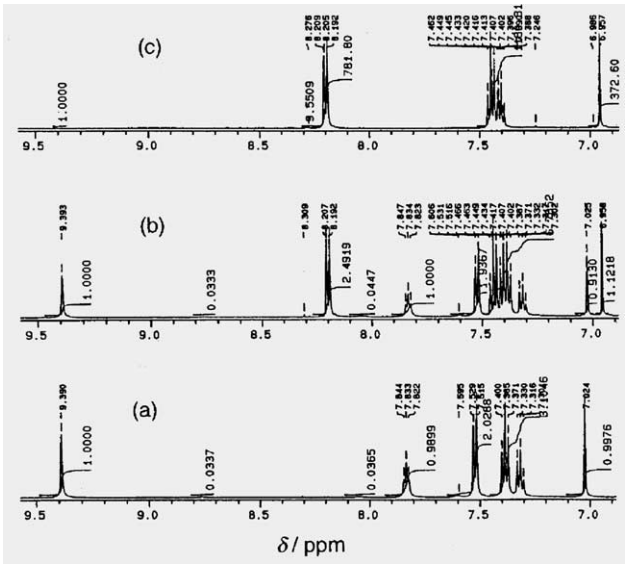


Figure 2. ^{1}H NMR spectra of dimethyl sulfoxide-d_6 solutions of the reaction mixtures obtained by heating an oxygen-saturated methanol solution of (*Z*)-**1c** (2.0×10^{-3} mol dm^{-3}) for 0 h (a), 5 h (b) and 32 h (c) at 80 °C, followed by evaporating the methanol solution to dryness.

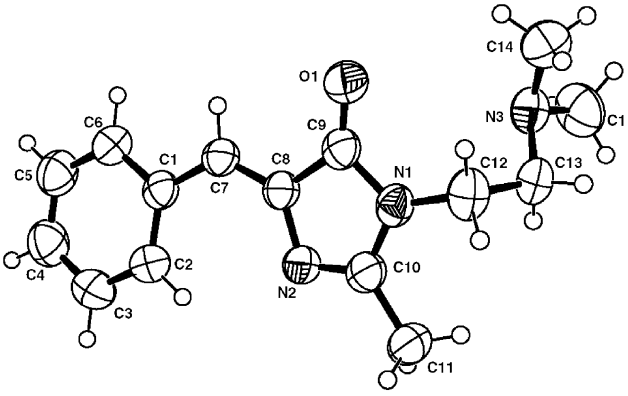
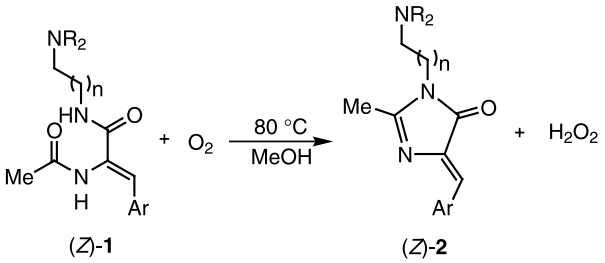


Figure 3. ORTEP drawing of (*Z*)-**2c**.



Ar = aryl; R = alkyl; n = 1,2

Scheme 1.

hand, the finding that two amide hydrogens in **1** disappear on generating **2** in the presence of oxygen strongly suggests the appearance of hydrogen peroxide as an oxygen-derived product (Scheme 1). After an oxygen-saturated methanol solution of (*Z*)-**1a** (100 mL, 5.0×10^{-3} mol dm^{-3}) was heated at 80 °C for 48 h in a sealed tube, 10 mL aliquot of the reaction mixture was diluted with an aqueous solution of KCl (10 mL, 0.20 mol dm^{-3}) and subjected to voltammetric analysis. The formation of **2a** and hydrogen peroxide in comparable yields to each other was confirmed by a comparison of oxidation currents of this sample solution (2.4 μA) and the reference solution (3.2 μA) containing **2a** and hydrogen peroxide (2.5×10^{-3} mol dm^{-3}) at 0.70 V.

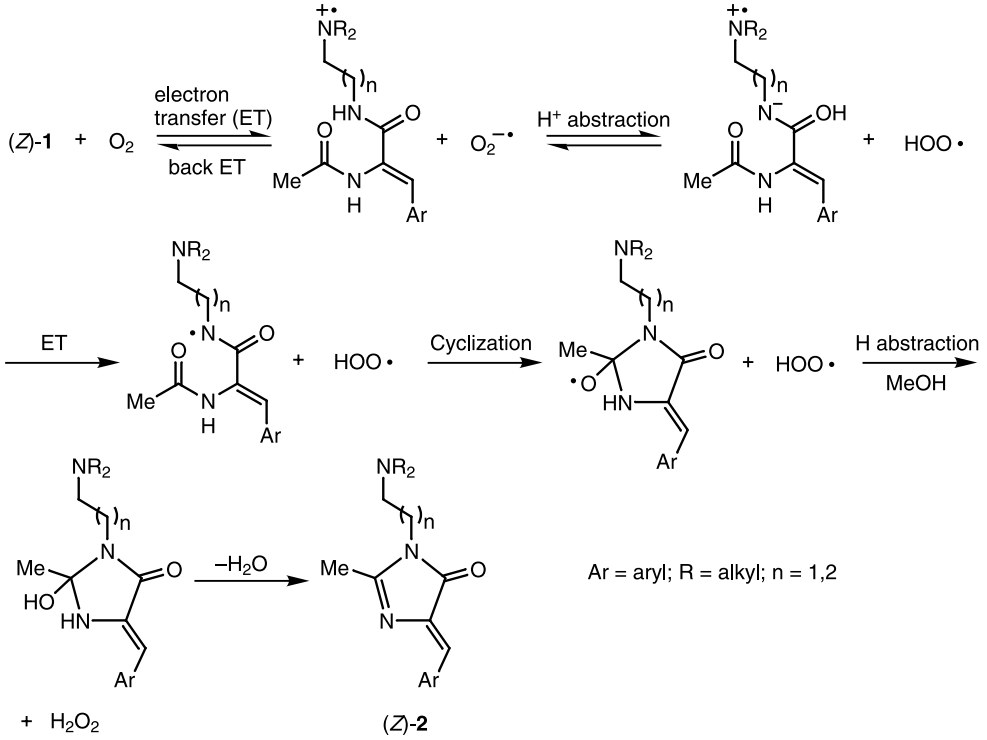
2.2. Substituent and solvent effects on the rate constant for the reaction

The findings that no reaction occurs in an atmosphere of argon and also without the dialkylamino group, like **1l**, even in oxygen-saturated methanol suggest the participation of electron transfer from the tertiary amino nitrogen to oxygen in the reaction, as already suggested. Based on the simplified Weller equation (Eq. 1),[10] where E_{ox} and E_{red} are the oxidation potential of triethylamine (0.76 V versus SCE in MeCN)[11] and the reduction potential of oxygen (−0.94 V versus SCE in MeCN),[12] respectively, free energy change in this electron transfer (ΔG_{et}) was estimated

$$\Delta G_{et}/\text{kJ mol}^{-1} = 96.5\,(E_{ox} - E_{red}) \quad (1)$$

to be 164 kJ mol^{-1}. Thus, the thermally-activated electron transfer is thermodynamically unfavorable process, allowing us to propose Scheme 2 in which reverse electron transfer affording the starting dehydroamino acids and oxygen should proceed preferentially, namely, the electron transfer equilibrium should lie greatly to the left. It is likely that the presence of the oxidized dialkylamino ($-N^{+}\cdot R_2$) and amide carbonyl groups having strong electron-withdrawing abilities in the **1**-derived cation radical enables basic superoxide to abstract the amide proton affording the amido anion and the hydroperoxyl radical.[13] Intramolecular electron transfer in the former intermediate should give the amidyl radical. The final product (*Z*)-**2** may be obtained by dehydration of the amino alcohol formed via the cyclization of this amidyl radical and the subsequent hydrogen abstraction from methanol.

Fortunately, the reaction of (*Z*)-**1** (1.0×10^{-4} mol dm^{-3}) in air-saturated methanol ($[O_2]=2.1\times10^{-3}$ mol dm^{-3})[8] at 80 °C proceeded according to the first-order kinetics in **1**, as typically shown in Figure 4. In addition, the reaction in any air-saturated solvents examined was first order in **1** (Fig. 5), so that we are able to scrutinize the substituent and solvent effects on the rate for the reaction. In Table 1 are



Scheme 2.

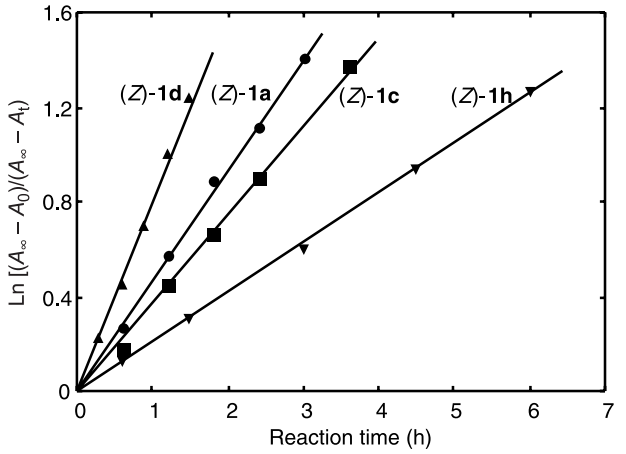


Figure 4. First-order plots for the reactions of (*Z*)-**1a** (●), (*Z*)-**1c** (■), (*Z*)-**1d** (▲) and (*Z*)-**1h** (▼, 1.0×10^{-4} mol dm^{-3}) with oxygen in air-saturated methanol at 80 °C. A_∞, A_0 and A_t refer to as the final absorbance, the initial absorbance and the absorbance after time, *t*, of the corresponding reaction mixture at a given wavelength, respectively.

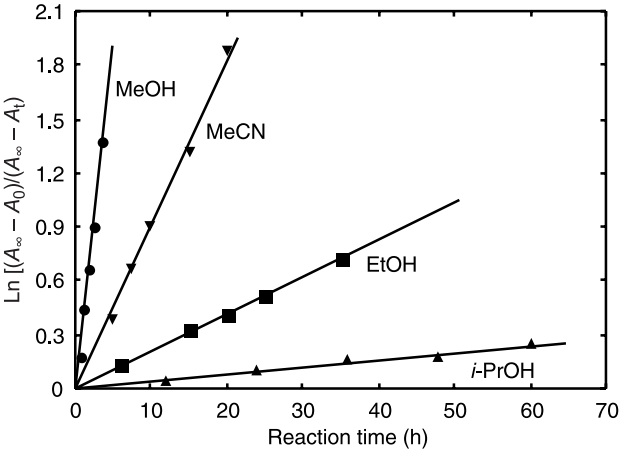


Figure 5. First-order plots for the reactions of (*Z*)-**1c** (1.0×10^{-4} mol dm^{-3}) with oxygen in air-saturated methanol(●), ethanol (■), 2-propanol (▲) and acetonitrile (▼) at 80 °C. A_∞, A_0 and A_t refer to as the final absorbance, the initial absorbance and the absorbance after time, *t*, of the reaction mixture at 348 nm, respectively.

summarized the rate constants estimated from the slopes of linear first-order plots. An inspection of the *N*-alkyl and aryl substituent effects on the reaction rate confirms that the rate constant is not much different between **1a** and **1b** and also between **1c** and **1d**. An increase in the steric bulkiness of *N*-alkyl substituent is considered to suppress attack of oxygen at the amino nitrogen and, in contrast, to enhance the stability of a cation radical intermediate ($-N^{+\cdot}R_2$). Because the former effect lowers the reaction rate which is increased by the latter effect, the result of *N*-alkyl substituent effect makes it highly probable that these two effects are compensated each other. On the other hand, the replacement of 1-naphthyl group (**1a**,**b**) by phenyl group (**1c**,**d**) exerts only a small effect on the rate constant for the reaction. Interestingly, the change in the polarity of protic solvents affects the reaction rates for both **1a** and **1c** to a much greater extent, as compared to that in the substituent R: the rate constants decrease markedly with decreasing polarity of the solvents. Furthermore, the use of acetonitrile (having almost the same polarity as methanol) as a solvent decreased the reaction rate by a factor of about 3–4.[14] The former observation is consistent with the fact that an increase in solvent polarity accelerates electron transfer reaction, and the latter observation reveals that the solvation of $-N^{+\cdot}R_2$ by the hydroxy oxygen of methanol plays a critical role in determining the reaction rate. The considerations described above, therefore, allow us to propose that electron transfer from the dialkylamino nitrogen to oxygen is a rate-determining step in the reaction sequence.

As already proposed, the combined action of the electron-withdrawing amide carbonyl and oxidized dialkylamino groups may enable basic superoxide to abstract the amide proton affording an amido anion intermediate (Scheme 2). It is, thus, predicted that addition of one more methylene spacer chain to **1f** slows down the reaction rate, owing to the increased interatomic distance between the amide and dimethylamino nitrogens. A comparison of the rate constants for **1f** and **1j** reveals that the oxidative cyclization rate of the latter is less than that of the former by a factor of 12 (Table 1). This finding is consistent with our prediction and, hence, amide-proton abstraction by superoxide, proceeding reversibly, is also a rate-determining step, as shown in Scheme 2. Interestingly, a comparison of the rate constants for **1c** and **1e–i** confirms that an increase in the electron-withdrawing ability of the substituent R has a clear tendency to decrease the reaction rate. This increase in electron-withdrawing ability is considered to accelerate amide-proton abstraction by superoxide and, in contrast, to slow down intramolecular electron transfer in an amido anion intermediate. Thus the finding that the replacement of methoxy group by electron-withdrawing trifluoromethyl or nitro group reduces the rate constant by only half strongly suggests that the effects of the substituent R on the proton abstraction and the subsequent electron transfer are compensated each other and both of these two processes are rate-determining steps. On the other hand, we previously showed that as compared to *N*-acetyl group, *N*-benzoyl group exerts a much greater steric effect on the cyclization process of substituted (*Z*)-*N*-acyl-α-dehydrophenylalanines

Table 1. Rate constants (*k*) for the reactions of (*Z*)-**1** (1.0×10^{-4} mol dm^{-3}) with oxygen at 80 °C

Compound	Solvent (ε)[a]	$[O_2]^b/10^{-3}$ mol dm^{-3}	$k/10^{-4}$ s^{-1}
1a	MeOH (32.66)	2.1	1.3
1b	MeOH		1.5
1c	MeOH		1.1
1d	MeOH		2.3
1a	EtOH (24.55)	2.1	0.12
1a	*i*-PrOH (19.92)	2.1	0.026
1a	MeCN (35.94)	1.9	0.52
1c	EtOH (24.55)		0.059
1c	*i*-PrOH (19.92)		0.012
1c	MeCN (35.94)		0.26
1e	MeOH		1.3
1f	MeOH		1.2
1g	MeOH		0.74
1h	MeOH		0.59
1i	MeOH		0.71
1j	MeOH		0.10

[a] Relative permittivity at 25 °C. See Ref. 13.
[b] See Ref. 7.

to completely inhibit the formation of isoquinoline derivatives.[3] This result allows us to speculate that the negligible formation of 2-imidazolin-5-one derivative in the reaction between **1k** and oxygen is due to a large steric hindrance of the *N*-benzoyl phenyl group to the intramolecular attack of amidyl radical on the benzoyl carbonyl moiety.

2.3. Synthetic utility of the reaction

Although many synthetic routes to 2-imidazolin-5-one derivatives are known,[15] there is no synthetic method (of these derivatives) which employs the cyclization of aryl-substituted *N*-acetyl-α-dehydroalanines activated by electron transfer to oxygen. The procedure for preparing the starting (*Z*)-α-dehydroamino acids [(*Z*)-**1**] is simple and easily applicable to its related compounds, as demonstrated in the preceding sections. In addition, the cyclodehydration reaction of (*Z*)-**1** proceeds without any dehydrating agent to quantitatively afford the corresponding (*Z*)-2-imidazolin-5-one derivatives [(*Z*)-**2**] and, hence, provides a novel and clean route to (*Z*)-**2**. Pretreatment of the concentrated reaction mixtures with a short column of silica gel is effective for obtaining (*Z*)-**2a–j** in high purities as well as in high isolated yields.

3. Experimental

3.1. General

^{1}H and ^{13}C NMR and IR spectra were taken with a JEOL JNM-A500 spectrometer and a Hitachi 270–30 infrared spectrometer, respectively. Chemical shifts were determined using tetramethylsilane as an internal standard. UV absorption spectra were recorded on a Hitachi UV-3300 spectrophotometer. A cell with a 10-mm pathlength was used. Elemental analyses were performed on a Perkin–Elmer PE2400 series II CHNS/O analyzer. X-ray crystal data collection was performed with Mo K_α radiation (λ= 0.71069 Å) on a Rigaku RAXIS-RAPID equipped with an imaging plate. Oxidation current-potential curves were measured with a Yanaco P-1100 polarographic analyzer. Mass spectra were recorded on a JEOL 01SG-2 spectrometer. MeOH, EtOH, *i*-PrOH and MeCN were purified according to the standard procedures.[14] All other reagents used were obtained from commercial sources and of the highest grade available.

3.2. General procedure for the synthesis of (*Z*)-2-methyl-4-(4-substituted benzylidene)-5(4*H*)-oxazolones, (*Z*)-2-methyl-4-(1-naphthylmethylene)-5(4*H*)-oxazolone and (*Z*)-2-phenyl-4-(1-naphthylmethylene)-5(4*H*)-oxazolone

N-Acylglycine (0.13 mol), 1-arylaldehyde (0.15 mol) and sodium acetate (0.10 mol) were added to acetic anhydride (100 mL) and the resulting mixture was heated at 75–85 °C for 2–7 h with stirring. The mixture was cooled with ice and the solid separated out was collected by filtration with suction and washed with water, small amounts of cold EtOH and then with dry hexane. After the crude product had been air-dried at room temperature, it was recrystallized from hexane–$CHCl_3$ to give yellow crystals (30–60%). Physical and spectroscopic properties of (*Z*)-2-methyl-4-(4-methoxybenzylidene)-5(4*H*)-oxazolone, (*Z*)-2-methyl-4-(4-methybenzylidene)-5(4*H*)-oxazolone, (*Z*)-2-methyl-4-benzylidene-5(4*H*)-oxazolone, (*Z*)-2-methyl-4-(4-chlorobenzylidene)-5(4*H*)-oxazolone, (*Z*)-2-methyl-4-[4-(trifluoromethyl) benzylidene]-5(4*H*)-oxazolone, (*Z*)-2-methyl-4-(1-naphthylmethylene)-5(4*H*)-oxazolone and (*Z*)-2-phenyl-4-(1-naphthylmethylene)-5(4*H*)-oxazolone were consistent with those of the previously prepared samples.[3c,4d]

3.2.1. (*Z*)-2-Methyl-4-(4-nitrobenzylidene)-5(4*H*)-oxazolone. Mp 182.0–183.0 °C. IR (KBr): 1822, 1794, 1664, 1520, 1344, 1270 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.46 (3H, s), 7.14 (1H, s), 8.25 (2H, d, J=9.2 Hz), 8.28 (2H, d, J=9.2 Hz).

3.3. General procedure for the synthesis of (*Z*)-2-acetylamino-*N*-dialkylaminoalkyl-3-aryl-2-propenamides [(*Z*)-1a–j], (*Z*)-2-benzoylamino-*N*-dimethylaminoethyl-3-(1-naphthyl)-2-propenamide [(*Z*)-1k] and (*Z*)-2-acetylamino-*N*-butyl-3-(1-naphthyl)-2-propenamide [(*Z*)-1l]

(*Z*)-2-Methyl-4-(4-substituted benzylidene)-5(4*H*)-oxazolone (for **1c–j**), (*Z*)-2-methyl-4-(1-naphthylmethylene)-5(4*H*)-oxazolone (for **1a**, **1b** and **1l**), or (*Z*)-2-phenyl-4-(1-naphthylmethylene)-5(4*H*)-oxazolone (for **1k**, 0.020 mol) was added to dry chloroform (200 mL) containing *N*,*N*-dialkylaminoalkylamine (for **1a–k**) or butylamine (for **1l**, 0.021 mol) and the resulting solution was allowed to stand for 1.0 h with stirring in an ice bath. The reaction mixture was concentrated to dryness and the resulting residue was dissolved in ethanol (50 mL) and then treated with activated charcoal powder. After removal of the solvent under reduced pressure, the crystalline solid obtained was recrystallized twice from ethanol–hexane affording colorless crystals (40–70%). Physical and spectroscopic properties of (*Z*)-**1l** were consistent with those of the previously prepared sample.[4c]

3.3.1. (*Z*)-2-Acetylamino-*N*-dimethylaminoethyl-3-(1-naphthyl)-2-propenamide [(*Z*)-1a]. Mp 157.5–158.5 °C. IR (KBr): 3298, 3196, 2938, 1620 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.84 (3H, s,), 2.19 (6H, s), 2.37 (2H, t, J=7.0 Hz), 3.28 (2H, dt, J=6.1, 6.7 Hz), 7.51–7.58 (5H, m), 7.90–7.96 (4H, m), 9.25 (1H, s). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 22.6, 37.3, 45.2 (2C), 58.0, 124.1, 124.2, 125.5, 126.0, 126.2,126.3, 128.35, 128.42, 131.0, 131.3, 132.5, 133.2, 164.6, 169.4. Anal. Calcd (Found) for $C_{19}H_{23}N_3O_2$: C, 70.13 (70.35); H, 7.12 (7.06); N, 12.91% (12.85%).

3.3.2. (*Z*)-2-Acetylamino-*N*-diethylaminoethyl-3-(1-naphthyl)-2-propenamide [(*Z*)-1b]. Mp 155.0–156.0 °C. IR (KBr): 3298, 3118, 2968, 1623 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.99 (6H, t, J=7.0 Hz), 1.84 (3H, s,), 2.49–2.53 (6H, m), 3.24 (2H, dt, J=6.4, 7.0 Hz), 7.51–7.58 (5H, m), 7.90–7.95 (4H, m), 9.27 (1H, s). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 12.0 (2C), 22.6, 37.4, 46.7 (2C), 51.3, 124.1, 124.3, 125.5, 126.0, 126.2, 126.3, 128.35, 128.44, 131.0, 131.3, 132.5, 133.2, 164.5, 169.4. Anal. Calcd (Found) for $C_{21}H_{27}N_3O_2$: C, 71.36 (71.13); H, 7.70 (7.73); N, 11.89% (11.58%).

3.3.3. (*Z*)-2-Acetylamino-*N*-dimethylaminoethyl-3-phenyl-2-propenamide [(*Z*)-1c]. Mp 129.0–130.0 °C. IR (KBr): 3220, 2980, 1611 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 1.98 (3H, s,), 2.14 (6H, s), 2.31 (2H, t, J=6.7 Hz), 3.20 (2H, dt, J=6.1, 6.7 Hz), 7.02 (1H, s), 7.30 (1H, dd, J=7.3, 7.3 Hz), 7.37 (2H, dd, J=7.3, 7.3 Hz), 7.51 (2H, d, J=7.3 Hz), 7.83 (1H, t, J=6.1 Hz), 9.38 (1H, s). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 22.9, 37.4, 45.2 (2C), 58.0, 127.7, 128.6 (3C), 129.3 (2C), 130.2, 134.2, 164.9, 169.5. Anal. Calcd (Found) for $C_{15}H_{21}N_3O_2$: C, 65.43 (65.50); H, 7.69 (7.42); N, 15.26% (15.47%).

3.3.4. (*Z*)-2-Acetylamino-*N*-diethylaminoethyl-3-phenyl-2-propenamide [(*Z*)-1d]. Mp 122.0–123.5 °C. IR (KBr): 3208, 2968, 1620 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 0.97 (6H, t, J=7.3 Hz), 1.99 (3H, s,), 2.47 (2H, t, J=7.6 Hz), 2.49 (4H, q, J=7.3 Hz), 3.19 (2H, dt, J=6.1, 7.6 Hz), 7.05 (1H, s), 7.32 (1H, dd, J=7.3, 7.3 Hz), 7.39 (2H, dd, J=7.3, 7.3 Hz), 7.52 (2H, d, J=7.3 Hz), 7.78 (1H, t, J=6.1 Hz), 9.40 (1H, s). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 11.9 (2C), 22.8, 37.3, 46.7 (2C), 51.3, 127.7, 128.5 (3C), 129.3 (2C), 130.1, 134.2, 164.6, 169.3. Anal. Calcd (Found) for $C_{17}H_{25}N_3O_2$: C, 67.30 (67.04); H, 8.30 (7.96); N, 13.85% (14.02%).

3.3.5. (*Z*)-2-Acetylamino-*N*-dimethylaminoethyl-3-(4-methoxyphenyl)-2-propenamide [(*Z*)-1e]. Mp 133.5–134.5 °C. IR (KBr): 3328, 2944, 1653 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 2.00 (3H, s,), 2.15 (6H, s), 2.31 (2H, t, J=6.7 Hz), 3.21 (2H, dt, J=6.1, 6.7 Hz), 3.77 (3H, s), 6.95 (2H, d, J=8.6 Hz), 7.04 (1H, s), 7.50 (2H, d, J=8.6 Hz), 7.77 (1H, t, J=6.1 Hz), 9.32 (1H, s). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 22.9, 37.3, 45.2 (2C), 55.2, 58.1, 114.0 (2C), 126.6, 127.9, 128.0, 131.0 (2C), 159.5, 165.0, 169.4. Anal. Calcd (Found) for $C_{16}H_{23}N_3O_3$: C, 62.93 (63.20); H, 7.59 (7.45); N, 13.76% (13.64%).

3.3.6. (*Z*)-2-Acetylamino-*N*-dimethylaminoethyl-3-(4-methylphenyl)-2-propenamide [(*Z*)-1f]. Mp 130.5–131.5 °C. IR (KBr): 3214, 2986, 1671 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 1.99 (3H, s,), 2.16 (6H, s), 2.31 (3H, s), 2.32 (2H, t, J=6.7 Hz), 3.22 (2H, dt, J=6.1, 6.7 Hz), 7.01 (1H, s), 7.20 (2H, d, J=7.9 Hz), 7.42 (2H, d, J=7.9 Hz), 7.82 (1H, t, J=6.1 Hz), 9.35 (1H, s). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 20.9, 22.9, 37.3, 45.2 (2C), 58.0, 127.8, 129.1 (2C), 129.30 (2C), 129.34, 131.4, 138.1, 164.9, 169.3. Anal. Calcd (Found) for $C_{16}H_{23}N_3O_2$: C, 66.41 (66.08); H, 8.01 (7.98); N, 14.52% (14.64%).

3.3.7. (*Z*)-2-Acetylamino-*N*-dimethylaminoethyl-3-(4-chlorophenyl)-2-propenamide [(*Z*)-1g]. Mp 132.0–133.0 °C. IR (KBr): 3214, 2980, 1656 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 1.98 (3H, s,), 2.15 (6H, s), 2.31 (2H, t, J=6.7 Hz), 3.22 (2H, dt, J=5.5, 6.7 Hz), 6.99 (1H, s), 7.49 (2H, d, J=8.5 Hz), 7.53 (2H, d, J=8.5 Hz), 7.91 (1H, t, J=5.5 Hz), 9.43 (1H, s). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 22.9, 37.4, 45.2 (2C), 58.0, 125.9, 128.5 (2C), 130.8, 130.9 (2C), 132.8, 133.2, 164.6, 169.3. Anal. Calcd (Found) for $C_{15}H_{20}ClN_3O_2$: C, 58.16 (58.27); H, 6.51 (6.76); N, 13.56% (13.71%).

3.3.8. (*Z*)-2-Acetylamino-*N*-dimethylaminoethyl-3-[4-(trifluoromethyl)phenyl]-2-propenamide [(*Z*)-1h]. Mp 131.0–132.0 °C. IR (KBr): 3400, 2980, 1659 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 1.99 (3H, s,), 2.16 (6H, s), 2.33 (2H, t, J=6.7 Hz), 3.23 (2H, dt, J=6.1, 6.7 Hz), 7.01 (1H, s), 7.70 (2H, d, J=7.9 Hz), 7.74 (2H, d, J=7.9 Hz), 7.99 (1H, t, J=6.1 Hz), 9.51 (1H, s). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 22.8, 37.2, 45.2 (2C), 57.9, 124.1 (1C, q, J=272 Hz), 124.9, 125.2 (2C, q, J=4 Hz), 128.0 (1C, q, J=31 Hz), 129.6 (2C), 132.3, 138.5, 164.5, 169.2. Anal. Calcd (Found) for $C_{16}H_{20}F_3N_3O_2$: C, 55.97 (55.79); H, 5.87 (6.10); N, 12.24% (12.61%).

3.3.9. (*Z*)-2-Acetylamino-*N*-dimethylaminoethyl-3-(4-nitrophenyl)-2-propenamide [(*Z*)-1i]. Mp 147.5–148.0 °C. IR (KBr): 3228, 2952, 1658, 1512, 1342 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 2.00 (3H, s,), 2.16 (6H, s), 2.33 (2H, t, J=6.7 Hz), 3.24 (2H, dt, J=6.4, 6.7 Hz), 7.00 (1H, s), 7.74 (2H, d, J=8.9 Hz), 8.05 (1H, t, J=6.4 Hz), 8.22 (2H, d, J=8.9 Hz), 9.60 (1H, s). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 22.9, 37.4, 45.2 (2C), 57.9, 123.5 (2C), 128.7, 130.1 (2C), 133.4, 141.5, 145.4, 164.5, 169.2. Anal. Calcd (Found) for $C_{15}H_{20}N_4O_4$: C, 56.24 (56.02); H, 6.29 (6.34); N, 17.49% (17.50%).

3.3.10. (*Z*)-2-Acetylamino-*N*-dimethylaminopropyl-3-(4-methylphenyl)-2-propenamide [(*Z*)-1j]. Mp 125.0–126.0 °C. IR (KBr): 3220, 2944, 1650 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 1.57 (2H, tt, J=6.7, 7.3 Hz), ?.98 (3H, s,), 2.12 (6H, s), 2.22 (2H, t, J=7.3 Hz), 2.31 (3H, s), 3.15 (2H, dt, J=6.1, 6.7 Hz), 7.01 (1H, s), 7.19 (2H, d, J=7.9 Hz), 7.42 (2H, d, J=7.9 Hz), 8.00 (1H, t, J=6.1 Hz), 9.29 (1H, s). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 20.8, 22.8, 26.7, 37.9, 45.1 (2C), 57.1, 127.6, 129.0 (2C), 129.2 (2C), 129.4, 131.3, 138.0, 164.7, 169.1. Anal. Calcd (Found) for $C_{17}H_{25}N_3O_2$: C, 67.30 (67.42); H, 8.30 (8.27); N, 13.85% (13.92%).

3.3.11. (*Z*)-2-Benzoylamino-*N*-dimethylaminoethyl-3-(1-naphthyl)-2-propenamide [(*Z*)-1k]. Mp 176.0–177.0 °C. IR (KBr): 3244, 3064, 2938, 1620 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 2.16 (6H, s), 2.38 (2H, t, J=6.7 Hz), 3.29 (2H, dt, J=5.5, 6.7 Hz), 7.42 (2H, dd, J=7.3, 7.9 Hz), 7.42 (1H, dd, J=7.3, 7.9 Hz), 7.51 (1H, dd, J=7.9, 7.9 Hz), 7.55 (1H, dd, J=7.3, 7.9 Hz), 7.56 (1H, dd, J=7.3, 7.9 Hz), 7.61 (1H, d, J=7.3 Hz), 7.75 (1H, s), 7.81 (2H, d, J=7.3 Hz), 7.85 (1H, d, J=7.9 Hz), 7.92 (1H, d, J=7.3 Hz), 8.02 (1H, d, J=7.9 Hz), 8.09 (1H, t, J=5.5 Hz), 9.75 (1H, s). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 37.4, 45.2 (2C), 58.0, 124.2, 125.3, 125.98, 126.03, 126.1, 126.4, 127.7 (2C), 128.1 (2C), 128.40, 128.43, 131.1, 131.4, 131.5, 132.3, 133.1, 133.8, 164.6, 166.2. Anal. Calcd (Found) for $C_{24}H_{25}N_3O_2$: C, 74.39 (74.28); H, 6.50 (6.44); N, 10.84% (10.86%).

3.4. General procedure for the reactions of (*Z*)-1 and oxygen

In order to determine the rate constant for the pseudo-first order reaction of (*Z*)-**1** with oxygen in a given solvent, each solution of (*Z*)-**1** (10 mL, 1.0×10^{-4} mol dm^{-3}) was purged with air for 10 min and sealed into a Pyrex vessel, which was immersed in an oil bath thermostated at 80 °C. At appropriate time intervals, the vessels were taken out one by one and cooled in an ice-water bath in order to stop the reaction. By following a gradual increase in the first UV absorption band of (*Z*)-**2** which appeared in the

wavelength region of 350–380 nm, the rate constant for the reaction was estimated. The UV absorption spectrum of a given solution (measured after the reaction was completed) was in nearly agreement with that of the corresponding solution of (*Z*)-**2** (1.0×10^{-4} mol dm^{-3}) isolated. Similarly, an oxygen-saturated MeOH solution of (*Z*)-**1** (10 mL, 2.0×10^{-3} mol dm^{-3}) was heated at 80 °C in a sealed tube for a given period of time and then concentrated to dryness *in vacuo*. The residue obtained was dissolved in DMSO-d_6 and subjected to the ^{1}H NMR spectral analysis.

For isolating and identifying products, a MeOH solution of (*Z*)-**1** (100 mL, 5.0×10^{-3} mol dm^{-3}) was saturated with oxygen and sealed into a Pyrex vessel, which was immersed in an oil bath thermostated at 80 °C. After completion of the reaction was confirmed by measuring the UV absorption spectrum of the mixture, 10 mL aliquot of this mixture was diluted in a volumetric flask to 20 mL with water containing 0.2 mol dm^{-3} KCl. The resulting solution was subjected to the voltammetric analysis using a glassy carbon electrode. Oxidation potentials were determined with reference to the Ag/AgCl electrode. The remaining reaction mixture was concentrated to dryness under reduced pressure and the resulting crystalline solid was subjected to short column chromatography over silica gel (230 mesh, Merck) eluting with EtOAc–MeOH (9:1 v/v) in order to obtain analytical-grade (*Z*)-**2**, which was, if necessary, recrystallized from EtOAc–hexane. Physical and spectroscopic properties of (*Z*)-2-imidazolin-5-one derivatives (**2a–j**) thus obtained are as follows.

3.4.1. (*Z*)-1-[2-(Dimethylamino)ethyl]-2-methyl-4-(1-naphthylmethylene)-2-imidazolin-5-one [(*Z*)-2a]. Mp 88.0–89.0 °C. IR (KBr): 2956, 1719, 1644 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.20 (6H, s,), 2.43 (3H, s), 2.44 (2H, t, J=6.4 Hz), 3.70 (2H, t, J=6.4 Hz), 7.60 (1H, dd, J=7.3, 7.9 Hz), 7.63 (1H, dd, J=7.9, 7.9 Hz), 7.66 (1H, dd, J=7.0, 7.3 Hz), 7.72 (1H, s), 8.00 (1H, d, J=7.3 Hz), 8.02 (1H, d, J=7.3 Hz), 8.31 (1H, d, J=7.9 Hz), 8.88 (1H, d, J=7.0 Hz). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 15.5, 38.1, 45.3 (2C), 57.5, 119.5, 122.8, 125.6, 126.1, 127.3, 128.9, 129.5, 130.4, 130.9, 131.7, 133.3, 139.6, 165.2, 169.8. Anal. Calcd (Found) for $C_{19}H_{21}N_3O$: C, 74.24 (74.05); H, 6.89 (6.91); N, 13.67% (13.68%). HR EI-MS *m*/*z* calcd for $C_{19}H_{21}N_3O$: 307.1685. Found: 307.1685.

3.4.2. (*Z*)-1-[2-(Diethylamino)ethyl]-2-methyl-4-(1-naphthylmethylene)-2-imidazolin-5-one [(*Z*)-2b]. Mp 88.0–88.5 °C. IR (KBr): 2962, 1701, 1632 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.92 (6H, t, J=7.3 Hz), 2.44 (3H, s,), 2.50 (4H, q, J=7.3 Hz), 2.56 (2H, t, J=6.1 Hz), 3.65 (2H, t, J=6.1 Hz), 7.60 (1H, dd, J=6.7, 7.9 Hz), 7.64 (1H, dd, J=7.3, 7.3 Hz), 7.66 (1H, dd, J=7.9, 8.5 Hz), 7.72 (1H, s), 8.00 (1H, d, J=6.7 Hz), 8.01 (1H, d, J=7.3 Hz), 8.30 (1H, d, J=8.5 Hz), 8.89 (1H, d, J=7.3 Hz). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 11.9 (2C), 15.6, 39.1, 46.8 (2C), 50.9, 119.3, 122.8, 125.6, 126.2, 127.3, 128.9, 129.5, 130.4, 130.9, 131.7, 133.3, 139.7, 165.5, 169.9. Anal. Calcd (Found) for $C_{21}H_{25}N_3O$: C, 75.19 (75.24); H, 7.51 (7.45); N, 12.53% (12.60%).

3.4.3. (*Z*)-1-[2-(Dimethylamino)ethyl]-2-methyl-4-benzylidene-2-imidazolin-5-one [(*Z*)-2c]. Mp 89.5–90.0 °C. IR (KBr): 2980, 1719, 1644 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.18 (6H, s), 2.40 (3H, s), 2.41 (2H, t, J=6.4 Hz), 3.65 (2H, t, J=6.4 Hz), 6.96 (1H, s), 7.40 (1H, dd, J=7.0, 7.0 Hz), 7.45 (2H, dd, J=7.0, 7.3 Hz), 8.20 (2H, d, J=7.3 Hz). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 15.5, 38.1, 45.3 (2C), 57.4, 124.7, 128.6 (2C), 129.9, 131.8 (2C), 134.1, 138.7, 164.3, 169.8. Anal. Calcd (Found) for $C_{15}H_{19}N_3O$: C, 70.01 (69.94); H, 7.44 (7.35); N, 16.33% (16.19%). HR FAB-MS *m*/*z* calcd for $C_{15}H_{20}N_3O$: 258.1606. Found: 258.1609.

3.4.4. (*Z*)-1-[2-(Diethylamino)ethyl]-2-methyl-4-benzylidene-2-imidazolin-5-one [(*Z*)-2d]. Mp 39.5–40.5 °C. IR (KBr): 2968, 1710, 1644 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.90 (6H, t, J=7.3 Hz), 2.41 (3H, s,), 2.47 (4H, q, J=7.3 Hz), 2.52 (2H, t, J=6.1 Hz), 3.60 (2H, t, J=6.1 Hz), 6.95 (1H, s), 7.40 (1H, dd, J=6.7, 6.7 Hz), 7.45 (2H, dd, J=6.7, 7.3 Hz), 8.20 (2H, d, J=7.3 Hz). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 11.9 (2C), 15.5, 39.0, 46.7 (2C), 50.8, 124.5, 128.6 (3C), 129.8, 131.8, 134.1, 138.8, 164.5, 169.9. Anal. Calcd (Found) for $C_{17}H_{23}N_3O$: C, 71.55 (71.23); H, 8.12 (7.98); N, 14.72% (14.58%).

3.4.5. (*Z*)-1-[2-(Dimethylamino)ethyl]-2-methyl-4-(4-methoxybenzylidene)-2-imidazolin-5-one [(*Z*)-2e]. Mp 74.0–74.5 °C. IR (KBr): 2938, 1707, 1644 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.18 (6H, s), 2.38 (3H, s), 2.40 (2H, t, J=6.7 Hz), 3.64 (2H, t, J=6.7 Hz), 3.82 (3H, s), 6.93 (1H, s), 7.02 (2H, d, J=8.6 Hz), 8.18 (2H, d, J=8.6 Hz). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 15.4, 38.0, 45.3 (2C), 55.3, 57.5, 114.3 (2C), 124.9, 126.8, 133.8 (2C), 136.8, 160.7, 162.7, 169.8. Anal. Calcd (Found) for $C_{16}H_{21}N_3O_2$: C, 66.88 (67.11); H, 7.37 (7.35); N, 14.62% (14.73%).

3.4.6. (*Z*)-1-[2-(Dimethylamino)ethyl]-2-methyl-4-(4-methylbenzylidene)-2-imidazolin-5-one [(*Z*)-2f]. Mp 78.5–79.0 °C. IR (KBr): 2944, 1712, 1646 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.18 (6H, s), 2.34 (3H, s), 2.39 (3H, s), 2.40 (2H, t, J=6.4 Hz), 3.65 (2H, t, J=6.4 Hz), 6.93 (1H, s), 7.26 (2H, d, J=7.9 Hz), 8.10 (2H, d, J=7.9 Hz). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 15.4, 21.1, 38.1, 45.3 (2C), 57.5, 124.9, 129.3 (2C), 131.4, 131.9 (2C), 138.0, 140.0, 163.6, 169.8. Anal. Calcd (Found) for $C_{16}H_{21}N_3O$: C, 70.82 (70.74); H, 7.80 (7.88); N, 15.49% (15.49%).

3.4.7. (*Z*)-1-[2-(Dimethylamino)ethyl]-2-methyl-4-(4-chlorobenzylidene)-2-imidazolin-5-one [(*Z*)-2g]. Mp 115.5–116.5 °C. IR (KBr): 2980, 1713, 1644 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.18 (6H, s), 2.40 (3H, s), 2.40 (2H, t, J=6.1 Hz), 3.65 (2H, t, J=6.1 Hz), 6.97 (1H, s), 7.52 (2H, d, J=8.5 Hz), 8.23 (2H, d, J=8.5 Hz). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 15.4, 38.1, 45.2 (2C), 57.4, 123.1, 128.7 (2C), 132.9, 133.3 (2C), 134.4, 139.1, 164.8, 169.6. Anal. Calcd (Found) for $C_{15}H_{18}ClN_3O$: C, 61.75 (62.01); H, 6.22 (6.35); N, 14.40% (14.70%).

3.4.8. (*Z*)-1-[2-(Dimethylamino)ethyl]-2-methyl-4-[4-(trifluoromethyl)benzylidene]-2-imidazolin-5-one [(*Z*)-2h]. Mp 117.5–118.0 °C. IR (KBr): 2948, 1716, 1650 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.17 (6H, s), 2.40 (2H, t, J=6.1 Hz), 2.41 (3H, s), 3.65 (2H, t, J=

6.1 Hz), 7.02 (1H, s), 7.79 (2H, d, $J=8.5$ Hz), 8.38 (2H, d, $J=8.5$ Hz). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 15.6, 38.2, 45.3 (2C), 57.4, 122.4, 124.1 (1C, q, $J=273$ Hz), 125.4 (2C, q, $J=4$ Hz), 129.1 (1C, q, $J=31$ Hz), 132.1 (2C), 138.0, 140.5, 166.2, 169.7. Anal. Calcd (Found) for $C_{16}H_{18}F_3N_3O$: C, 59.07 (58.94); H, 5.58 (5.77); N, 12.92% (12.87%).

3.4.9. (*Z*)-1-[2-(Dimethylamino)ethyl]-2-methyl-4-(4-nitrobenzylidene)-2-imidazolin-5-one [(*Z*)-2i]. Mp 137.0–138.0 °C. IR (KBr): 2980, 1716, 1641, 1508, 1340 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.18 (6H, s), 2.42 (2H, t, $J=6.1$ Hz), 2.45 (3H, s), 3.68 (2H, t, $J=6.1$ Hz), 7.08 (1H, s), 8.29 (2H, d, $J=8.5$ Hz), 8.45 (2H, d, $J=8.5$ Hz). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 15.7, 38.2, 45.3 (2C), 57.3, 121.4, 123.6 (2C), 132.5 (2C), 140.6 141.3, 147.2, 167.2, 169.7. Anal. Calcd (Found) for $C_{15}H_{18}N_4O_3$: C, 59.59 (59.46); H, 6.00 (5.76); N, 18.53% (18.41%).

3.4.10. (*Z*)-1-[2-(Dimethylamino)propyl]-2-methyl-4-(4-methylbenzylidene)-2-imidazolin-5-one [(*Z*)-2j]. Oily liquid. IR (neat): 2943, 1709, 1643 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.69 (2H, tt, $J=6.9$, 7.6 Hz), 2.12 (6H, s,), 2.20 (2H, t, $J=6.9$ Hz), 2.34 (3H, s), 2.38 (3H, s), 3.58 (2H, t, $J=7.6$ Hz), 6.91 (1H, s), 7.26 (2H, d, $J=8.2$ Hz), 8.10 (2H, d, $J=8.2$ Hz). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 15.3, 21.1, 26.3, 38.2, 45.0 (2C), 56.0, 124.8, 129.3 (2C), 131.4, 131.9 (2C), 138.0, 140.0, 163.5, 169.9. Anal. Calcd (Found) for $C_{17}H_{23}N_3O$: C, 71.55 (71.38); H, 8.12 (7.87); N, 14.72% (14.54%).

Acknowledgements

This research was partially supported by a 'High-Tech Research Project' from the Ministry of Education, Sports, Culture, Science and Technology, Japan.

References and notes

1. Mariano, P. S.; Stavinoha, J. L. *Synthetic Organic Photochemistry*; Horspool, W. H., Ed.; Plenum: New York, 1984; p 145–257.
2. (a) Lewis, F. D. *Acc. Chem. Res.* **1979**, *12*, 152–158. (b) Lewis, F. D.; Reddy, G. D. *J. Am. Chem. Soc.* **1989**, *111*, 6465–6466. (c) Lewis, F. D.; Reddy, G. D.; Bassani, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 6468–6469. (d) Lewis, F. D.; Bassani, D. M.; Reddy, G. D. *J. Org. Chem.* **1993**, *58*, 6390–6393. (e) Lewis, F. D.; Reddy, G. D.; Bassani, D. M.; Schneider, S.; Gahr, M. *J. Am. Chem. Soc.* **1994**, *116*, 597–605. (f) Lewis, F. D.; Bassani, D. M.; Burch, E. L.; Cohen, B. E.; Engleman, J. A.; Reddy, G. D.; Schneider, S.; Jaeger, W.; Gedeck, P.; Gahr, M. *J. Am. Chem. Soc.* **1995**, *117*, 660–669.
3. (a) Kubo, K.; Yaegashi, S.; Sasaki, K.; Sakurai, T.; Inoue, H. *Tetrahedron Lett.* **1996**, *37*, 5917–5920. (b) Kubo, K.; Koshiba, M.; Hoshina, H.; Sakurai, T. *Heterocycles* **1998**, *48*, 25–29. (c) Hoshina, H.; Kubo, K.; Morita, A.; Sakurai, T. *Tetrahedron* **2000**, *56*, 2941–2951. (d) Hoshina, H.; Tsuru, H.; Kubo, K.; Igarashi, T.; Sakurai, T. *Heterocycles* **2000**, *53*, 2261–2274. (e) Maekawa, K.; Kajiwara, H.; Iseya, Y.; Igarashi, T.; Sakurai, T. *Heterocycles* **2003**, *60*, 637–654. (f) Hoshina, H.; Maekawa, K.; Taie, K.; Igarashi, T.; Sakurai, T. *Heterocycles* **2003**, *60*, 1779–1786.
4. (a) Kubo, K.; Ishii, Y.; Sakurai, T.; Makino, M. *Tetrahedron Lett.* **1998**, *39*, 4083–4086. (b) Sakurai, T.; Morioka, Y.; Maekawa, K.; Kubo, K. *Heterocycles* **2000**, *53*, 271–276. (c) Maekawa, K.; Igarashi, T.; Kubo, K.; Sakurai, T. *Tetrahedron* **2001**, *57*, 5515–5526. (d) Motohashi, T.; Maekawa, K.; Kubo, K.; Igarashi, T.; Sakurai, T. *Heterocycles* **2002**, *57*, 269–292. (e) Maekawa, K.; Kubo, K.; Igarashi, T.; Sakurai, T. *Hterocycles* **2002**, *57*, 1591–1597.
5. (a) Tsubomura, H.; Yagishita, T.; Toi, H. *Bull. Chem. Soc. Jpn* **1973**, *46*, 3051–3055. (b) Maeda, K.; Nakane, A.; Tsubomura, H. *Bull. Chem. Soc. Jpn* **1975**, *48*, 2448–2450.
6. Oshimi, K.; Kubo, K.; Kawasaki, A.; Maekawa, K.; Igarashi, T.; Sakurai, T. *Tetrahedron Lett.* **2002**, *43*, 3291–3294.
7. (a) Rao, Y. S.; Filler, R. *Synthesis* **1975**, 749–764. (b) Rzeszotarska, B.; Karolak-Wojciechowska, J.; Broda, M. A.; Galdecki, Z.; Trzezwinska, B.; Koziol, A. E. *Int. J. Pept. Protein Res.* **1994**, *44*, 313–319.
8. Murov, S. L.; Carmichael, I.; Hug, G. L. *Handbook of Photochemistry*. 2nd ed.; Marcel Dekker: New York, 1993 pp 289–293.
9. Crystallographic data of (*Z*)-**2c** have been deposited at the CCDC 183850, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk) and copies can be obtained on request, free of charge, by quoting our publication.
10. (a) Rehm, D.; Weller, A. *Isr. J. Chem.* **1970**, *8*, 259–271. (b) Rehm, D.; Weller, A. *Z. Phys. Chem.* **1970**, *69*, 183–200.
11. Kavarnos, G. J.; Turro, N. J. *Chem. Rev.* **1986**, *86*, 401–449.
12. Eriksen, J.; Foote, C. S. *J. Am. Chem. Soc.* **1980**, *102*, 6083–6088.
13. Sawyer, D. T.; Valentine, J. S. *Acc. Chem. Res.* **1981**, *14*, 393–400.
14. Riddick, J. A.; Bunger, W. B.; Sakano, T. K. *Organic Solvents*. 4th ed.; Wiley: Chichester, 1986.
15. (a) Awad, W. I.; Allah, A. E. A. G. *J. Org. Chem.* **1960**, *25*, 1242–1243. (b) Lempert, K.; Nyitrai, J.; Sohar, P.; Zauer, K. *Tetrahedron Lett.* **1964**, 2679–2684. (c) Mustafa, A.; Asker, W.; Harhash, A. H.; Abdin, T. M. S.; Zayed, E. M. *Liebigs Ann. Chem.* **1968**, *714*, 146–154. (d) Bird, C. W.; Twibell, J. D. *J. Chem. Soc., (C)* **1971**, 3155–3158. (e) Simig, G.; Lempert, K.; Tamas, J. *Tetrahedron* **1973**, *29*, 3571–3578. (f) Schoellkopf, U.; Hausberg, H.-H.; Segal, M.; Reiter, U.; Hoppe, I.; Saenger, W.; Lindner, K. *Liebigs Ann. Chem.* **1981**, 439–458. (g) Rasmussen, J. K.; Heilmann, S. M.; Krepski, L. R.; Smith, H. K.; Katritzky, A. R.; Sakizadeh, K. *J. Polym. Sci., Polym. Chem. Ed.* **1986**, *24*, 2739–2747. (h) Jain, A.; Mukerjee, A. K. *J. Indian Chem. Soc.* **1990**, *67*, 973–975. (i) Homami, S.-S.; Mukerjee, A. K. *Indian J. Chem. Sect. B* **1991**, *30*, 288–289. (j) Hassan, H. M.; Habib, O. M. O.; Darwish, Y. M. *Rev. Roum. Chim.* **1992**, *37*, 1029–1033. (k) Mazik, M.; Boese, R.; Sustmann, R. *Liebigs Ann.* **1996**, 1665–1671. (l) Grivas, S.; Schuisky, P. *Heterocycles* **1998**, *48*, 1575–1580. (m) Nalepa, K.; Zednikova, G.; Marek, J.; Travnicek, Z. *Monatsh. Chem.* **1999**, *130*, 471–479. (n) Shafi, P. M.; Sobha, T. D. *Indian J. Chem. Sect. B* **1999**, *38*, 378–379.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 60 (2004) 9525

Corrigendum

Corrigendum to "A straightforward anionic coupling for the synthesis of *ortho*-bromobiaryls" [Tetrahedron 60 (2004) 6853]

Jean-Michel Becht, Silvère Ngouela, Alain Wagner* and Charles Mioskowski*

Laboratoire de Synthèse Bioorganique, UMR 7514 associée au CNRS, Faculté de Pharmacie, Université Louis Pasteur de Strasbourg, 74 Route du Rhin, 67400 Illkirch, France

Available online 27 August 2004

On page 6854, lines 33–37, the sentence should have read 'As shown in Table 1, the reactivity of the 1-bromo-2-halobenzenes is increased with the decrease of the alpha-acidifying (F > Cl > Br) and the increase of the leaving group ability of the halogen (F < Cl < Br)'.

doi of original article 10.1016/j.tet.2004.06.010
* Corresponding authors. Tel.: +33-3-90-24-42-95; fax: +33-3-90-24-43-06; e-mail: alwag@aspirine.u-strasbg.fr

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.07.037

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 60 (2004) 9527

Erratum

Erratum to "Asymmetric synthesis of (+)-1-epiaustraline and attempted synthesis of australine" [Tetrahedron 60 (2004) 5759]

Minyan Tang and Stephen G. Pyne*

Department of Chemistry, University of Wollongong, Northfields Ave, New South Wales 2522, Australia

Available online 27 August 2004

Page 5761 of the above article should read:

2.1.1. Synthesis of (−)-6-(4-methoxyphenyl)methoxy-3*R*,4*S*-epoxy-1-hexene (4). *Step 1. 5-(4-Methoxyphenyl)methoxy-2Z-penten-1-ol*. To the solution of 5-(4′-methoxy)benzyloxy-2-pentyn-1-ol (431 mg, 1.96 mmol) and quinoline (329 mg, 2.547 mmol) in EA (20 mL) was added $Pd/CaCO_3$ (36 mg). The mixture was stirred at RT under a hydrogen atmosphere for 1.5 h.

doi of original article 10.1016/j.tet.2004.05.010
* Corresponding author. Tel.: +612-4221-3511; fax: +612-4221-4287; e-mail: spyne@uow.edu.au

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.07.065