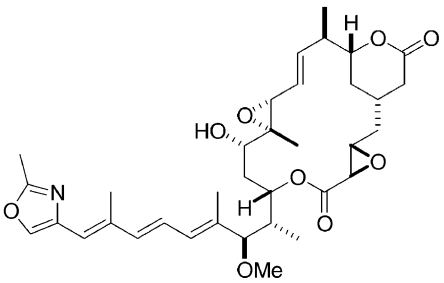
ELSEVIER

Tetrahedron

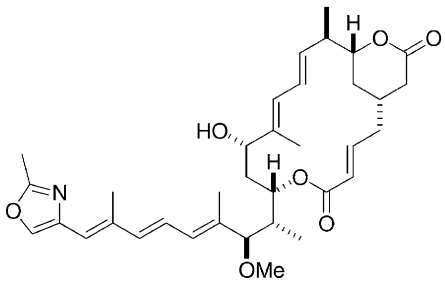
Tetrahedron Vol. 60, No. 27, 2004

Contents

REPORT

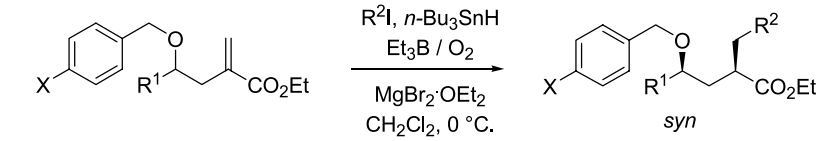


Rhizoxin

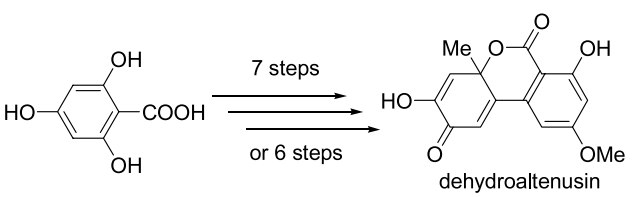


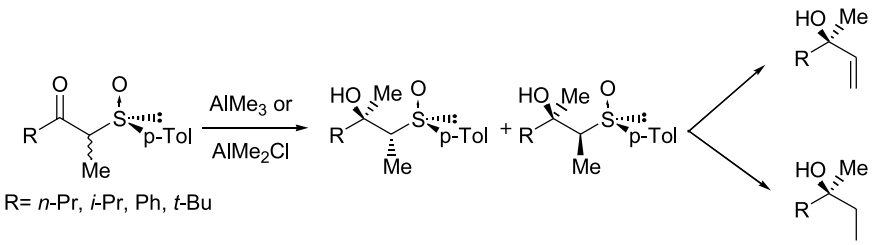
Rhizoxin D

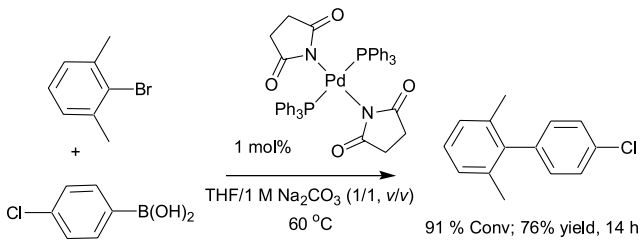
ARTICLES

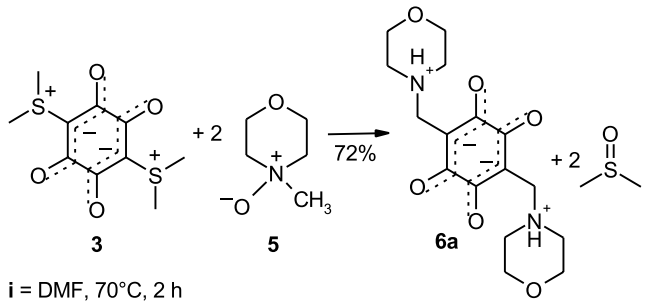


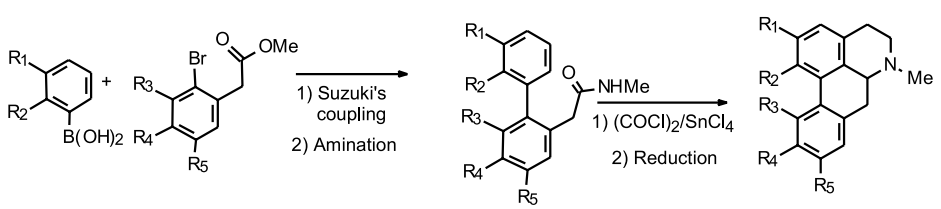
X = H, Me, OMe, *i*-Pr, F, CF_3, CN, NO_2
R^1 = Ph, *i*-Pr; R^2 = Me, Et, *i*-Pr, *t*-Bu

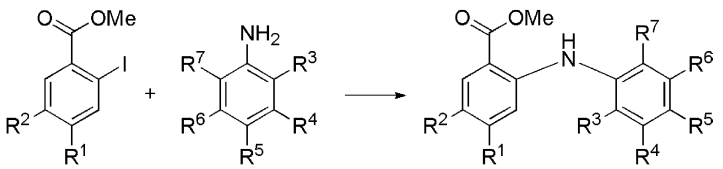


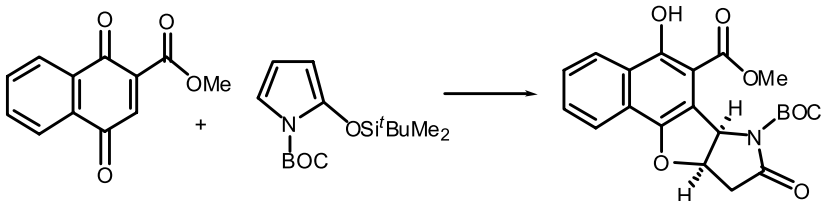


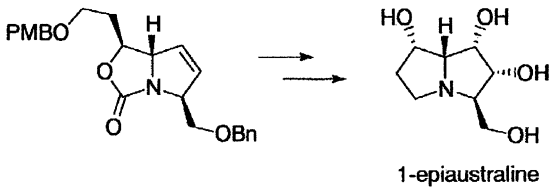


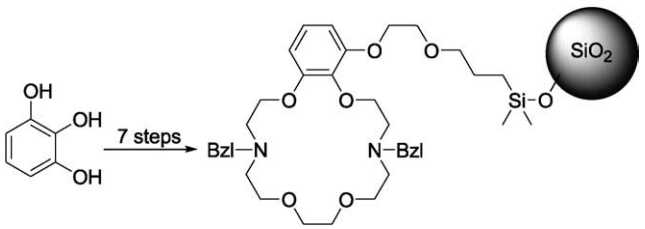


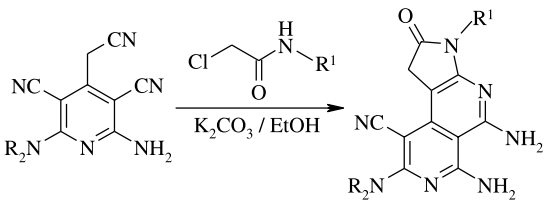




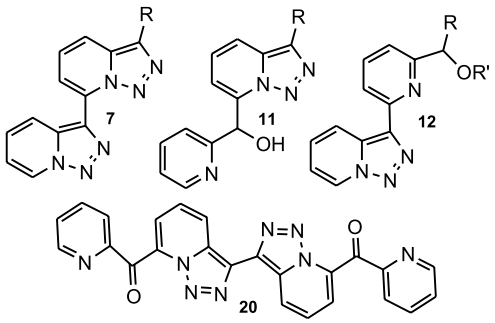


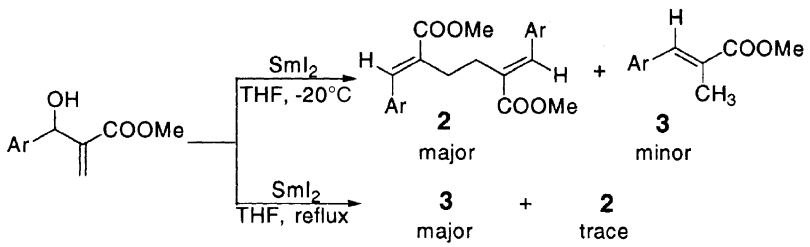


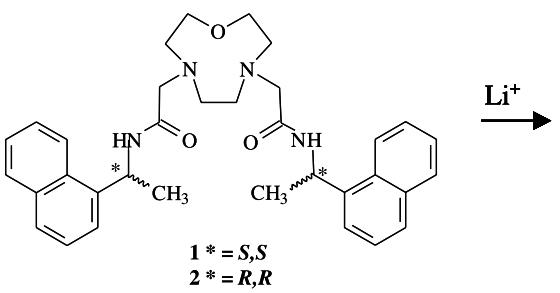


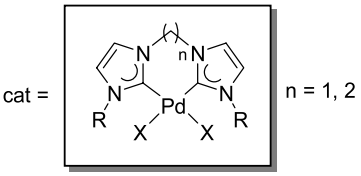


The synthesis of novel 7-{[1,2,3]triazolo[1,5-*a*]pyridin-3-yl}-[1,2,3]triazolo-[1,5-*a*]pyridines **7**, 2-pyridyl-[1,2,3]triazolo[1,5-*a*]pyrid-7-ylmethanols **11**, 3-(6-substituted-2-pyridyl)-[1,2,3]triazolo[1,5-*a*]pyridines **12**, and 7,7′-disubstituted-3,3′-bi[1,2,3]triazolo[1,5-*a*]pyridine **20**, interesting polynitrogenated ligands as potential helicating compounds or luminescent sensors, from [1,2,3]triazolo[1,5-*a*]pyridines is described.









Applications in Suzuki and Heck coupling reactions.

OTHER CONTENTS

*Corresponding author

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
Tetrahedron 60 (2004) 5653–5681

Tetrahedron report number 681

The chemistry and biology of rhizoxins, novel antitumor macrolides from *Rhizopus chinensis*

Jian Hong[a] and James D. White[b,*]

[a]*Eli Lilly Company, Indianapolis, IN 46285, USA*
[b]*Department of Chemistry, Oregon State University, Corvallis, OR 97331, USA*

Received 27 February 2004

Contents

1. Isolation and structure determination

Rhizoxin (**1** NSC-332598) and congeners such as **2**–**8** (Fig. 1) are a family of 16-membered macrolactones first isolated from the plant pathogenic fungus *Rhizopus chinensis* by Iwasaki and co-workers in 1984.[1] This fungus causes a disease known as rice seedling blight, for which the characteristic symptom is abnormal swelling of seedling roots believed to be due to inhibition of cell division. The relative and absolute configuration of rhizoxin and related compounds were determined by single crystal X-ray analysis and degradation studies.[2] The unprecedented structure of rhizoxin contains 11 stereogenic centers, two epoxides, a δ-lactone, a 16-membered macrocyclic lactone, and an oxazole-terminated side chain (Fig. 1). Didesepoxyrhizoxin (rhizoxin D, **3**), isolated from the same fungus, is the putative precursor of the bis-epoxide **1**. Studies detailing the biosynthesis of rhizoxin have been reported.[3]

* Corresponding author. Fax: +1-541-737-2660;
e-mail address: james.white@oregonstate.edu

2. Biological activity and mechanism of action

Biological studies have revealed that rhizoxin exhibits pronounced antimicrobial and antifungal activity as well as potent in vitro cytotoxicity and in vivo antitumor activity.[1c] In particular, rhizoxin has been found to be more potent and less toxic than vincristine.[4] The IC_{50} values for rhizoxin and vincristine in P388 leukemia cells are 0.91 and 2.10 nM, respectively. One striking feature of rhizoxin is that it has significant efficacy against vincristine- and adriamycin-resistant human lung tumor cells in vitro and in vivo, whereas other antimitotic agents such as maytansine have been found to be ineffective against these tumors. In vincristine-resistant tumor cells, the IC_{50} for rhizoxin is 3.84 nM.

In preclinical evaluation, moderate to good in vivo activity has been demonstrated by rhizoxin in studies with murine tumors such as B16 melanoma, M5076 sarcoma, L1210 and P388 leukemias and MH134 mouse hepatoma.[5] It is also active against several human tumor xenografts,

0040–4020/$ - see front matter
doi:10.1016/j.tet.2004.04.032

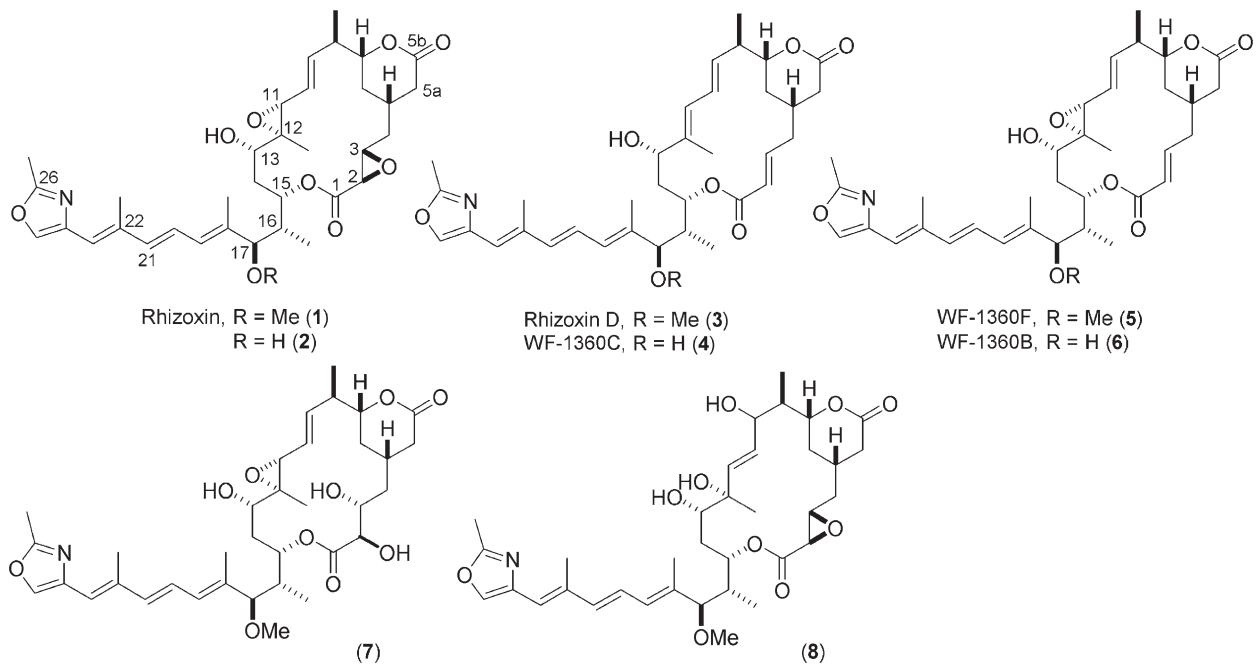


Figure 1. Antitumor macrolides from *Rhizopus chinensis*.

including LOX melanoma, MX-1 mammary carcinoma, A549 non-small-cell lung tumors, LXFS605 and LXFS650 small cell lung tumors.

Based on preclinical studies in the National Cancer Institute's disease-oriented screening program, rhizoxin has been selected for clinical evaluation by the NCI in the US, by the EORTC in Europe, and by Fujisawa in Japan. Phase I and phase II clinical trials have been completed with this agent for treatment of ovarian cancer, colorectal and renal cancer, breast cancer and melanoma, head and neck cancer, and non-small-cell lung cancer.[6,7]

The results from a phase I clinical study of rhizoxin in 19 patients with advanced solid malignancies have been reported.[8] The maximum tolerated dose (MTD) was determined to be 1.2 mg/m^2/72 h; the principal dose-limiting toxicities were severe neutropenia and mucositis. In a phase II clinical trial, rhizoxin was given to 31 patients who had not received previous chemotherapy.[7d] Almost half of the patients showed stabilization of their disease, and the median survival from the start of treatment was 6 months. Both stomatitis and neutropenia were the most commonly observed side effects.

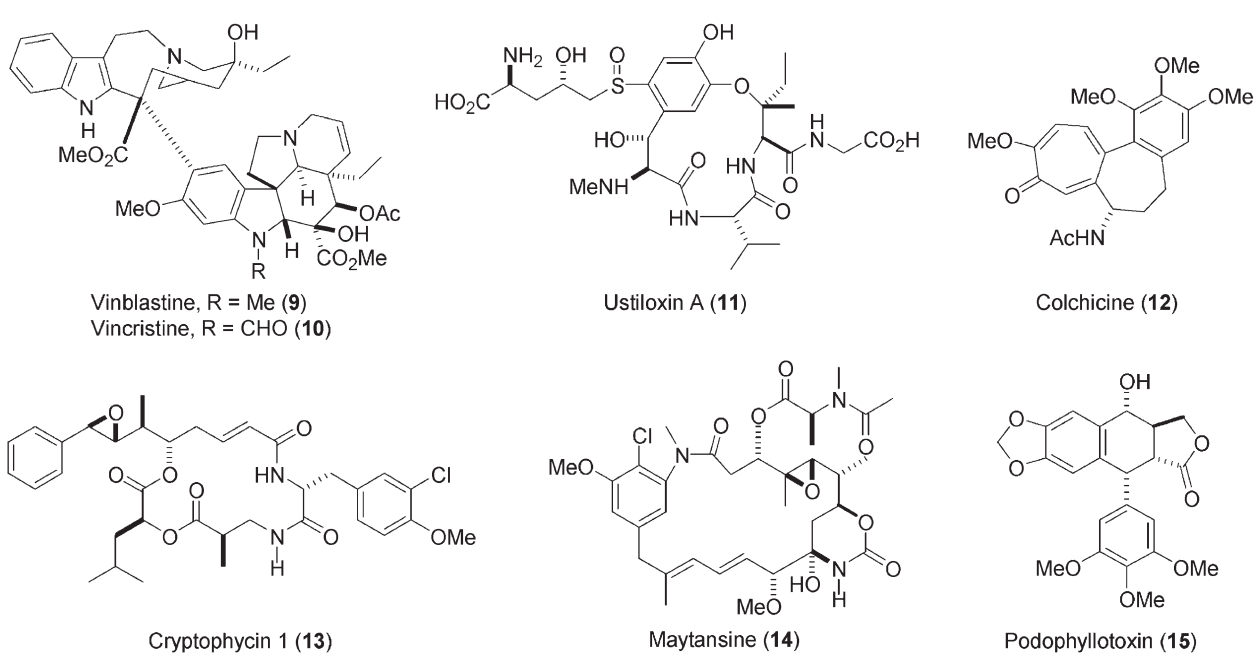


Figure 2. Selected tubulin polymerization inhibitors.

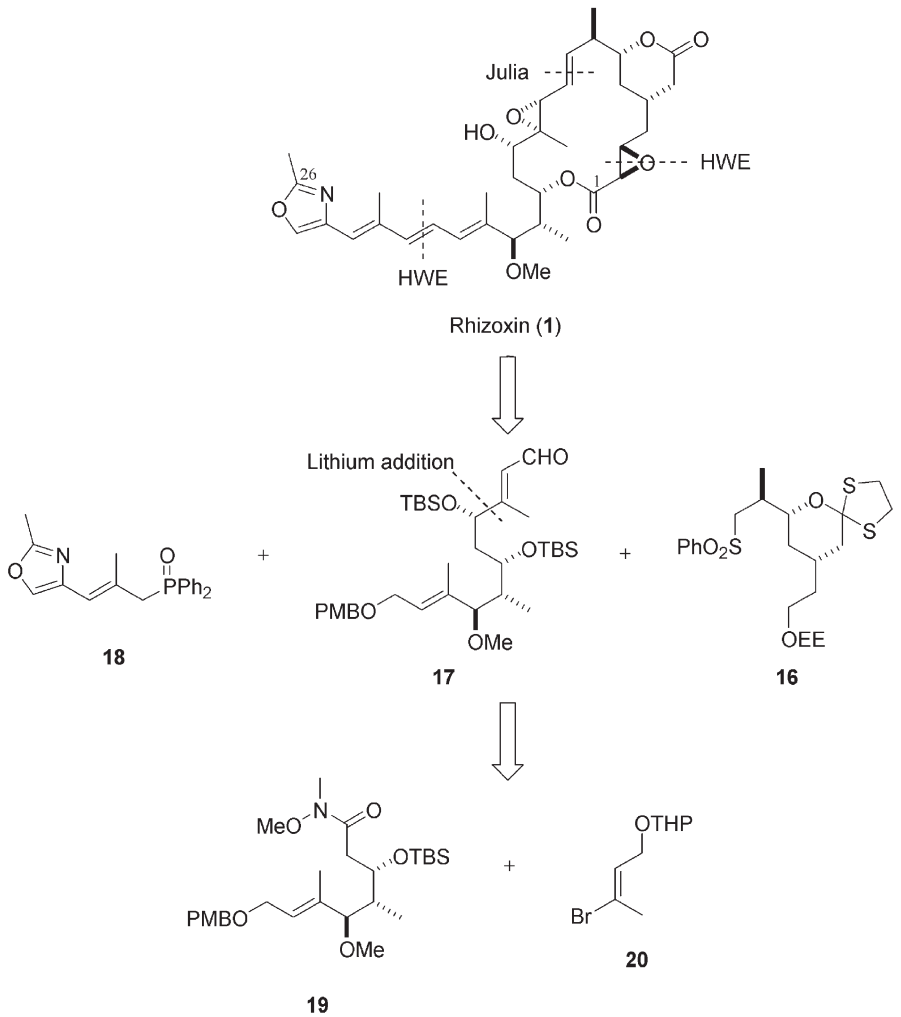
It is known that rhizoxin binds to β-tubulin at the vinca domain.[9] The mechanism of action is believed to involve its complexation with tubulin to prevent tubulin polymerization, leading to the inhibition of microtubule formation and thereby blocking cell mitosis.[10] Other well known tubulin polymerization inhibitors are shown in Figure 2.[11,12] They include vinblastine (**9**), vincristine (**10**), ustiloxin A (**11**), colchicine (**12**), cryptophycin 1 (**13**), maytansine (**14**), and podophyllotoxin (**15**).

Rhizoxin and maytansine share a related binding site on β-tubulin which is not identical to the receptor for other inhibitors such as colchicine, vinblastine, dolastatin and halichondrin.[13] Inspection of the structures of rhizoxin and maytansine reveals that their structures contain similarities (Fig. 2). For instance, both structures contain macrocycles, with the cyclic carbamate of maytansine structurally analogous to the δ-lactone of rhizoxin. These and other structural similarities suggest that rhizoxin and maytansine may complex with β-tubulin to inhibit microtubule formation by a similar mechanism. Maytansine, a member of the ansamacrolide family, has also been developed as a potential antitumor agent but has had disappointing results in clinical evaluation.

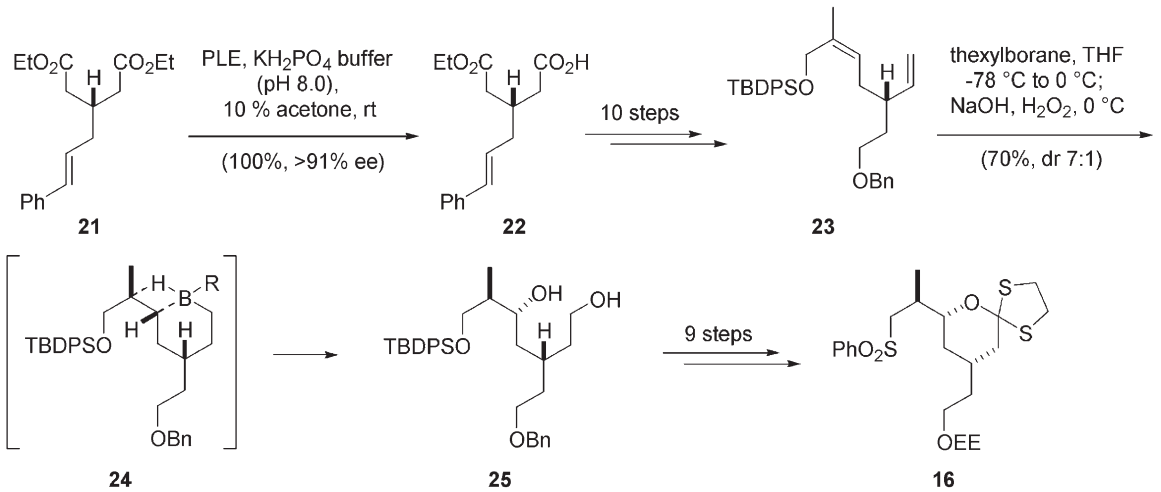
3. Structure-activity relationship and proposed binding model

Although the structure-activity relationship (SAR) of rhizoxin has not been studied in detail, several analogs have been evaluated for their effect on microtubule assembly.[14] The available SAR data is summarized as follows:

(1) The epoxides at C2–C3 and C11–C12 can be replaced by double bonds without loss of activity, but hydrolytic opening of these epoxides substantially reduces activity. No loss of activity was observed when the C17 methoxy substituent was replaced with a hydroxyl group.
(2) All changes made in the distal portion of the triene side chain beyond C21, had a relatively minor effect relative to that of rhizoxin itself. Although the C22–C26 portion of the rhizoxin side chain is not essential for activity, the C16 to C21 segment of the molecule is required for good antitumor activity. Insertion of a carbonyl oxygen or hydroxyl group at C21 led to complete loss of activity, whereas replacement of the vinyl carbon at C21 with a methylene group resulted in nearly full retention of activity.



Scheme 1. Ohno's strategy for the total synthesis of rhizoxin.



Scheme 2. Ohno's synthesis of the C3–C9 segment of rhizoxin.

(3) A free hydroxyl group at C13 is essential for activity. Significant loss of activity was observed when the C13 hydroxyl group was esterified.
(4) The carbonyl function at C5b is essential. Erasure of this carbonyl group caused complete loss of activity.

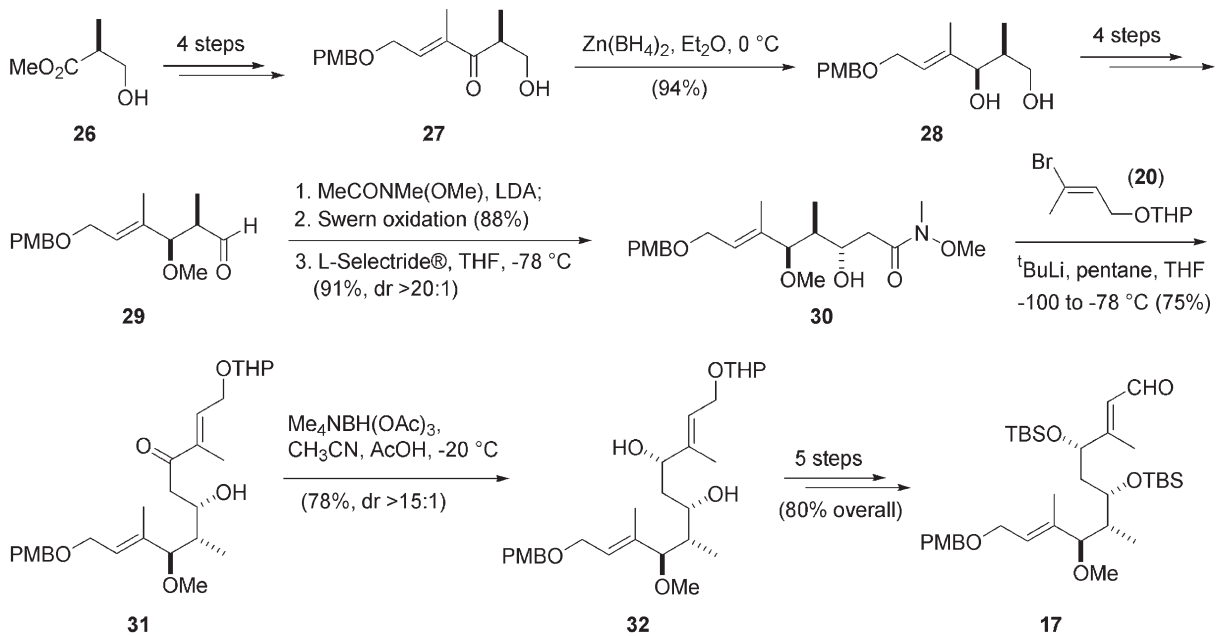
A schematic model for the interaction of rhizoxin with β-tubulin at the rhizoxin-maytansine binding site has been proposed by Iwasaki and co-workers.[14a] It was suggested that, upon binding to β-tubulin, the bicyclic portion of rhizoxin is incorporated into a hydrophobic pocket. The C13 hydroxyl group is thought to have a polar interaction with an amino acid residue in the tubulin molecule, and it has been reported that the C5b carbonyl group has an interaction with the Asn-100 residue.[15] The side chain is presumed to be outside the hydrophobic pocket of the tubulin structure.

Certain highly potent antimitotic drugs such as vinblastine and vincristine have serious side effects, especially on the neurological system. For this reason, it is highly desirable to develop new antitumor drugs that are more effective and less toxic than the standard treatments. Rhizoxin and its analogues constitute a new class of promising lead compounds for this purpose, and it is likely that they will serve in a complementary role to clinically effective agents for cancer chemotherapy in the near future. As a result of their unique structural complexity, their pronounced biological activity, and their potential as cancer chemotherapeutic agents, the rhizoxins have stimulated a great deal of research directed towards total synthesis of this class of antitumor agents. Successful efforts along these lines will be described in Section 4.

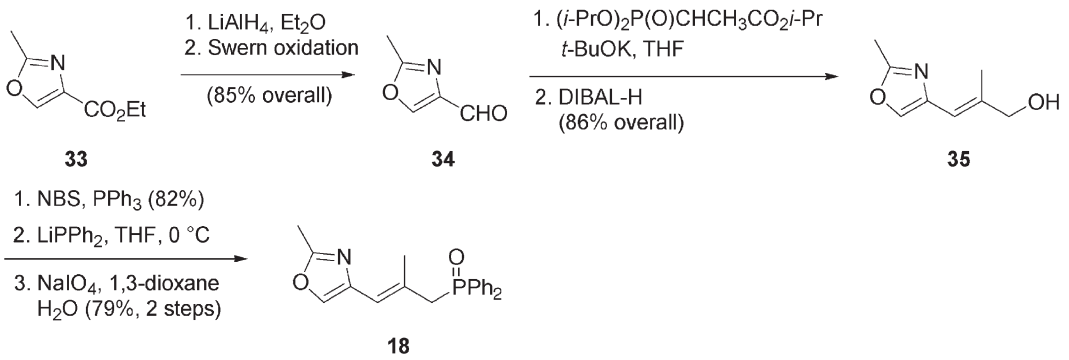
4. Total syntheses of rhizoxin and rhizoxin D

4.1. The Ohno synthesis of rhizoxin

In 1993, Ohno and co-workers reported the first and so far



Scheme 3. Ohno's synthesis of the C10–C20 segment of rhizoxin.



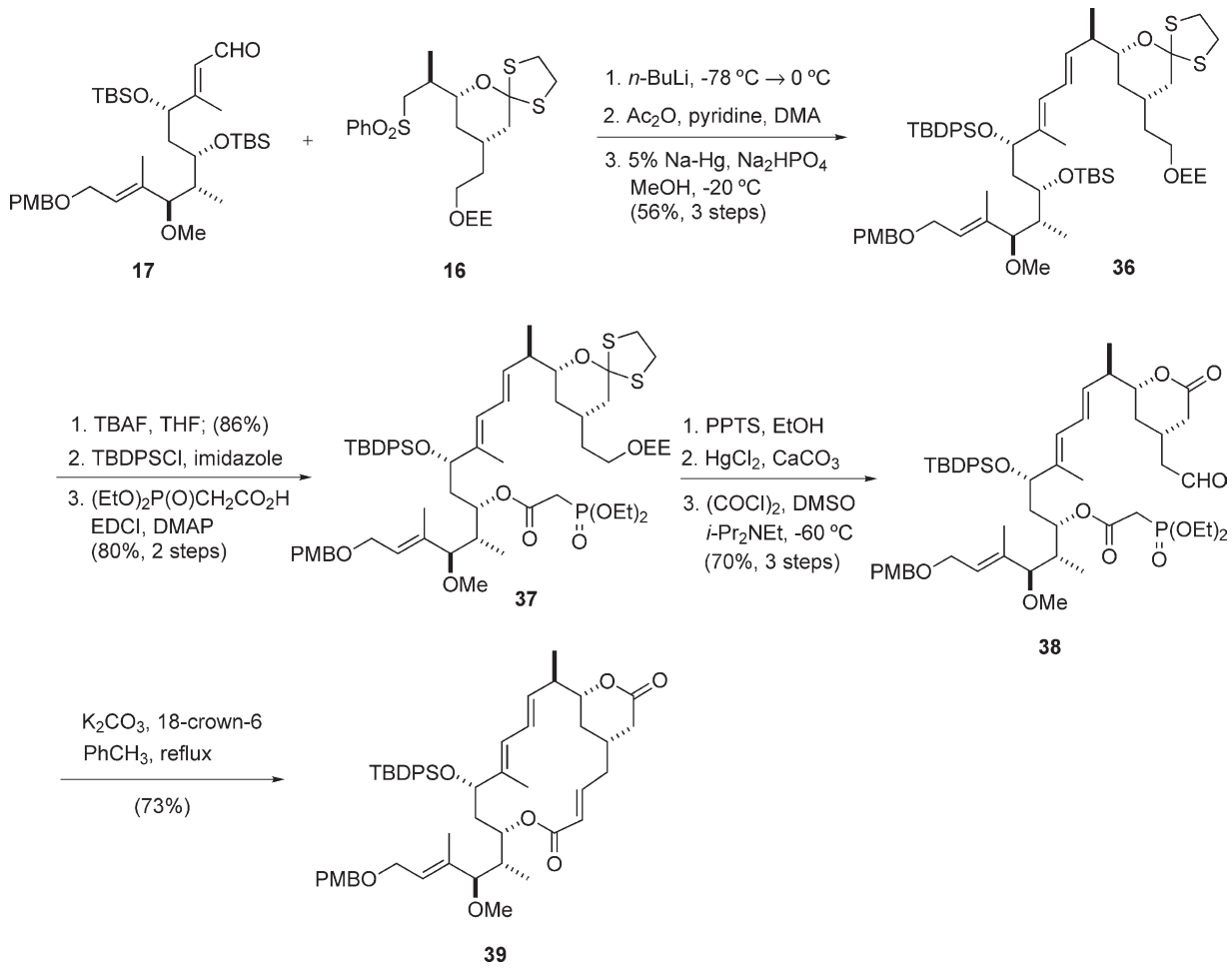
Scheme 4. Ohno's synthesis of the C21–C26 segment of rhizoxin.

only total synthesis of rhizoxin itself.[16] An analysis of their approach is shown in Scheme 1. Rhizoxin (**1**) was dissected into three subunits, **16**, **17**, and **18**, for which Horner-Emmons and Julia olefinations were planned as coupling strategies. The central subunit **17** was further disconnected into fragments **19** and **20**.

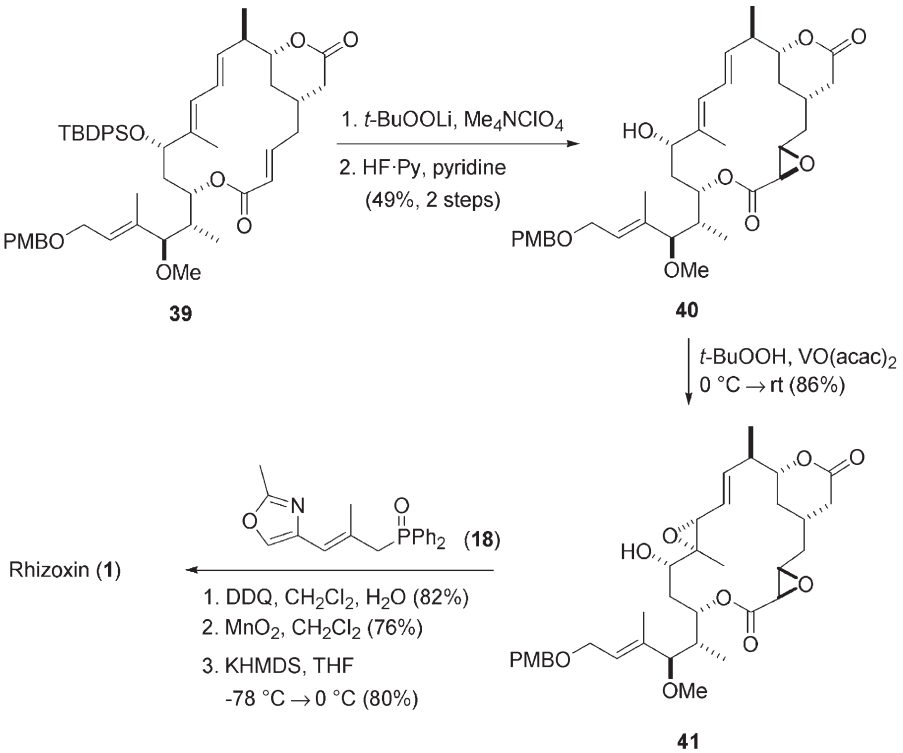
Ohno's synthesis of the C3–C9 segment **16** commenced from the carboxylic acid **22**, which was prepared by desymmetrization of the prochiral diester **21** using pig liver esterase.[17] The resolved carboxylic acid **22** was then advanced to diene **23** in 10 steps (Scheme 2).

Cyclic hydroboration of diene **23** afforded diol **25** with a diastereoselectivity of 7:1.[18] The bicyclic transition state **24** was proposed to explain the stereoselectivity. Diol **25** was then converted to a δ-lactone which was protected as the 1,3-dithiolane **16**, thus completing the synthesis of the C3–C9 subunit.

Ohno's synthesis of the C10–C20 segment **17** commenced with (*S*)-methyl-3-hydroxy-2-methylpropionate **26**, which was converted to (*E*)-α,β-unsaturated ketone **27** in four steps (Scheme 3). Selective reduction of **27** with zinc borohydride[19] yielded diol **28**, which was transformed to



Scheme 5. Ohno's assembly of the rhizoxin macrolactone.



Scheme 6. Completion of Ohno's synthesis of rhizoxin.

aldehyde **29** in a sequence of four steps which included methylation and Swern oxidation. An aldol reaction of **29** with the Weinreb amide of acetic acid afforded a 1:1 diastereomeric mixture of secondary alcohols, which was oxidized to the corresponding ketone. Subsequent reduction with L-Selectride furnished **30** stereoselectively (dr >20:1).[20] Treatment of Weinreb amide **30** with the lithio alkene derived from **20** afforded ketone **31**, which was reduced to alcohol **32** with tetramethylammonium acetoxyborohydride in a highly stereoselective manner (dr >15:1).[21] Hydroxyl group protection and a deprotection–oxidation sequence afforded the C10–C20 segment **17**.

The C21–C26 portion **18** of the rhizoxin side-chain was prepared as shown in Scheme 4. The known disubstituted oxazole **33** was converted to aldehyde **34** via a two-step reduction–oxidation sequence. This aldehyde was homologated and reduced to give allylic alcohol **35**, which was transformed into the corresponding bromide. Displacement with lithium diphenylphosphide and a subsequent oxidation afforded the phosphine oxide **18**.

The next stage of Ohno's rhizoxin synthesis was accomplished as indicated in Scheme 5. The C3–C9 and C10–C20 fragments **16** and **17** were first coupled via a Julia olefination to afford (*E*, *E*)-diene **36**.[22] Bis-desilylation of **36** and selective protection of the more reactive allylic hydroxyl group as its *tert*-butyldiphenylsilyl (TBDPS) ether were followed by esterification with diethylphosphonoacetic acid to give phosphonate **37**. Removal of the 1,3-dithiolane and the ethoxyethyl group of **37** yielded the corresponding primary alcohol, which was oxidized to aldehyde **38**. Macrolactonization of **38** was accomplished via an intramolecular Horner-Emmons olefination[23] and gave **39** in good yield.

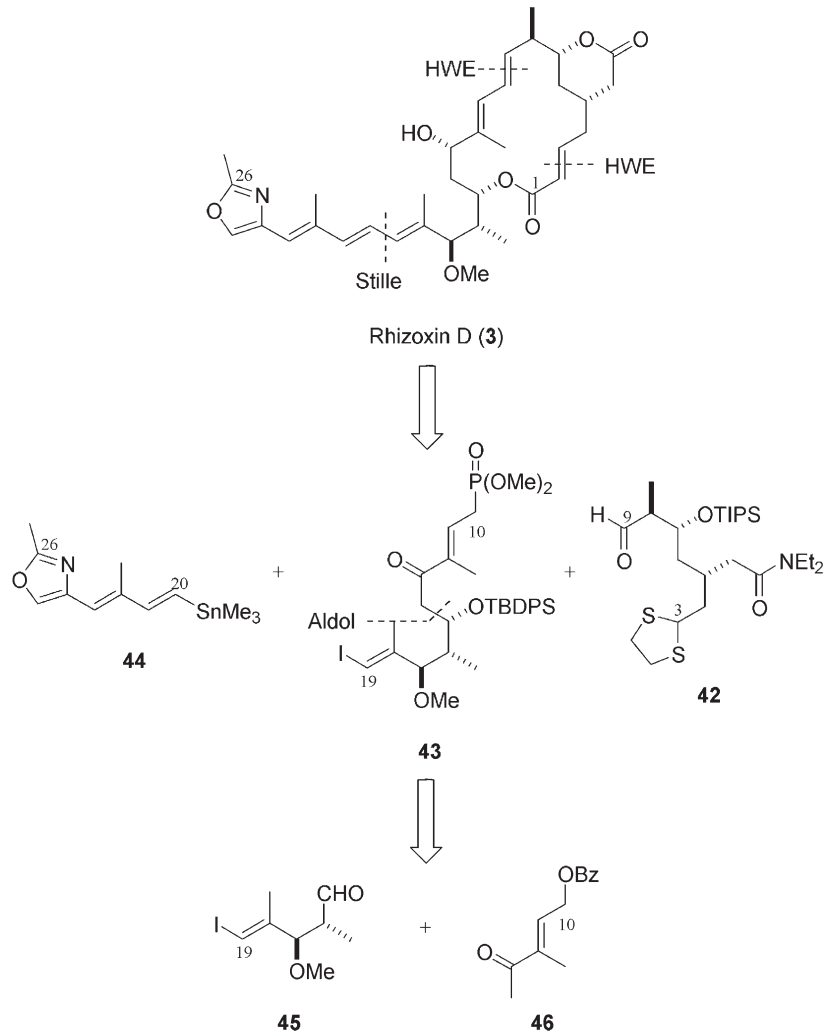
Functionalization of the macrolactone and completion of Ohno's rhizoxin synthesis is shown in Scheme 6. Nucleophilic epoxidation of the C2–C3 olefin with lithium *tert*-butylhydroperoxide in the presence of a quaternary ammonium salt was followed by desilylation at C13 to give the corresponding mono-epoxide. The C11–C12 epoxide was installed using a regio- and stereoselective hydroxyl-directed vanadium-catalyzed epoxidation to afford bis-epoxide **41**.[24] Removal of the *p*-methoxybenzyl group and oxidation of the resultant allylic alcohol gave an aldehyde, which was coupled with phosphine oxide **18** to yield rhizoxin.

4.2. Kende's synthesis of rhizoxin D

Kende and co-workers reported the first total synthesis of natural didesepoxyrhizoxin (rhizoxin D, **3**) using a triply convergent strategy.[25] As shown in Scheme 7, three subunits **42**, **43**, and **44** were planned for coupling protocols utilizing Horner-Emmons and Stille reactions. Further dissection of the central segment **43** led to fragments **45** and **46** as subgoals.

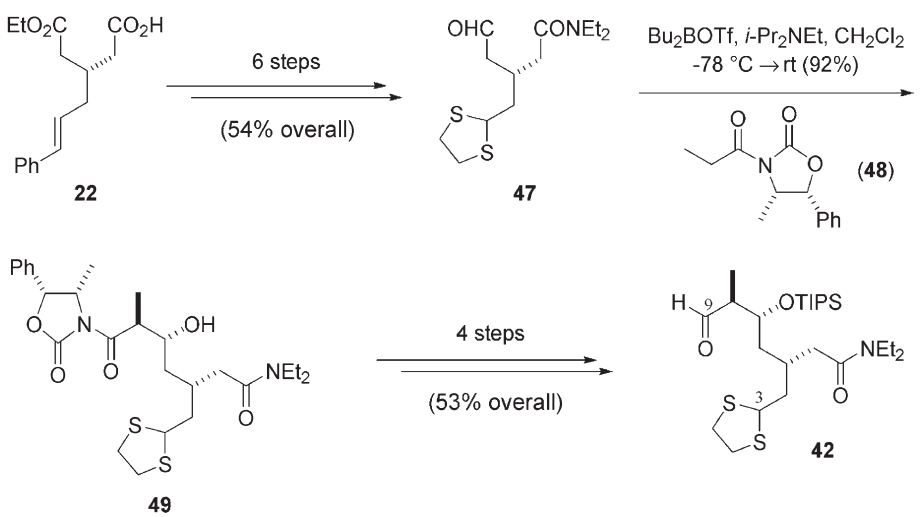
Synthesis of aldehyde **42** commenced with the same carboxylic acid **22** employed in Ohno's synthesis (Scheme 8). A six-step oxidation–reduction sequence produced aldehyde **47**, which underwent an Evans aldol reaction[26] with **48** to give alcohol **49** as a single diastereomer. The chiral auxiliary was removed by methanolysis, and the secondary alcohol was protected as a triisopropylsilyl (TIPS) ether. A subsequent two-step sequence led to the C3–C9 subunit **42**.

The C10–C19 segment **43** was prepared from the known ester **50** (Scheme 9). Methylation of **50** followed by

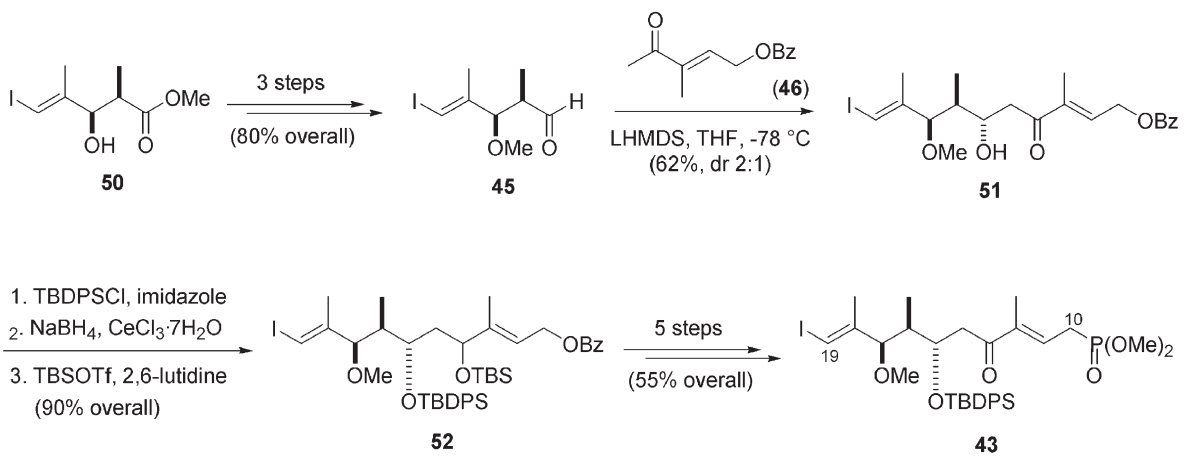


Scheme 7. Kende's strategy for the synthesis of rhizoxin D.

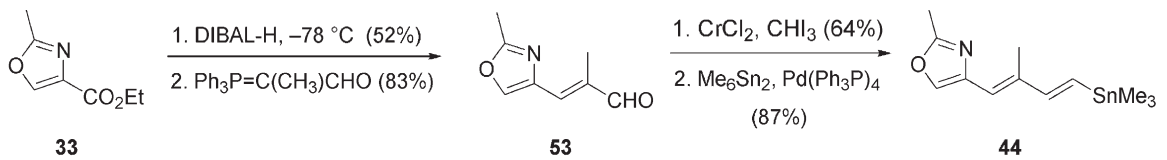
reduction and oxidation afforded aldehyde **45**, which was coupled with the lithium enolate of ketone **46** to give a 2:1 mixture of diastereomers favoring the anti-isomer **51**.[27] After purification by chromatography, this alcohol was protected as its *tert*-butyldiphenylsilyl ether. The resultant α,β-unsaturated enone was then reduced and protected to give *tert*-butyldimethylsilyl (TBS) ether **52**, which was converted to the phosphonate **43** in five steps.



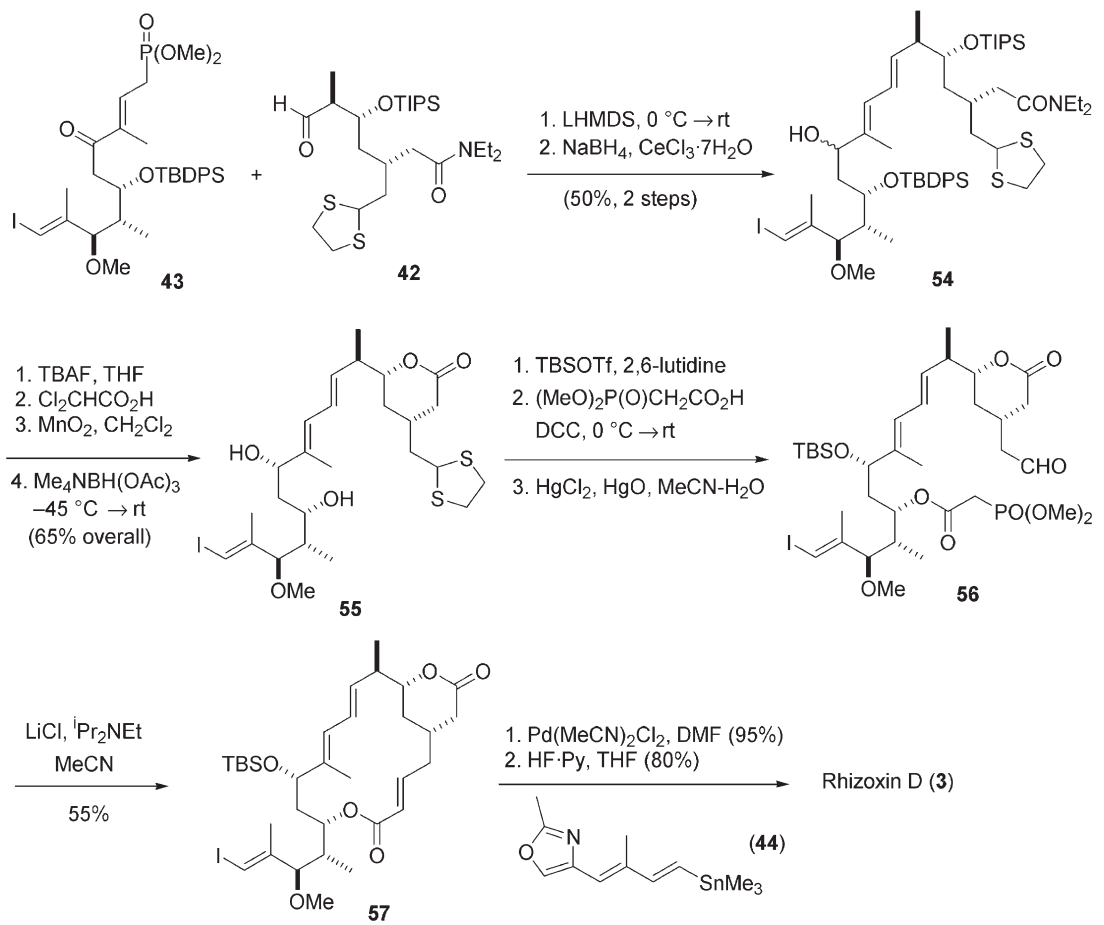
Scheme 8. Kende's synthesis of the C3–C9 segment of rhizoxin D.



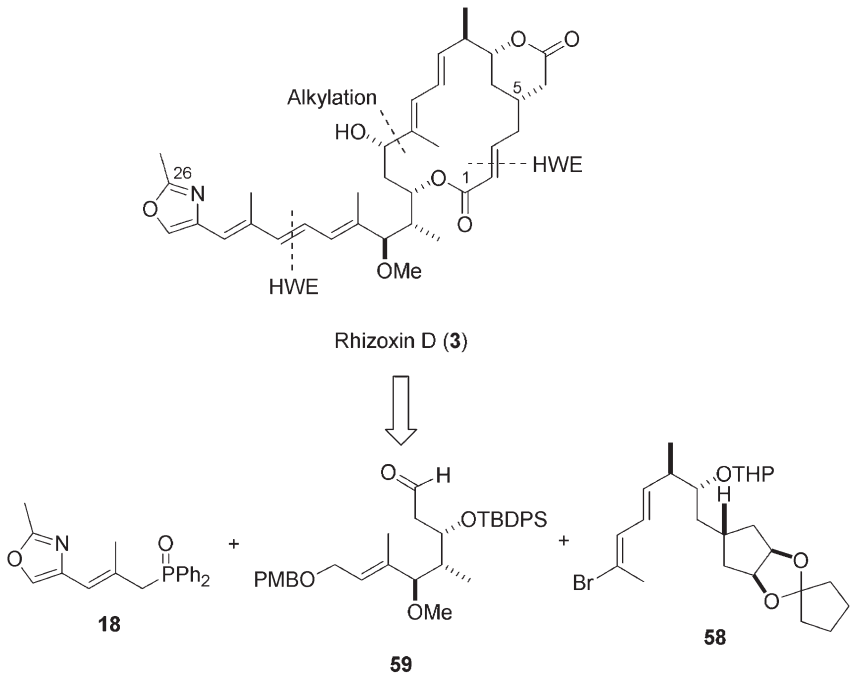
Scheme 9. Kende's synthesis of the C10–C19 segment of rhizoxin D.



Scheme 10. Kende's synthesis of the C20–C26 segment of rhizoxin D.



Scheme 11. Completion of Kende's synthesis of rhizoxin D.



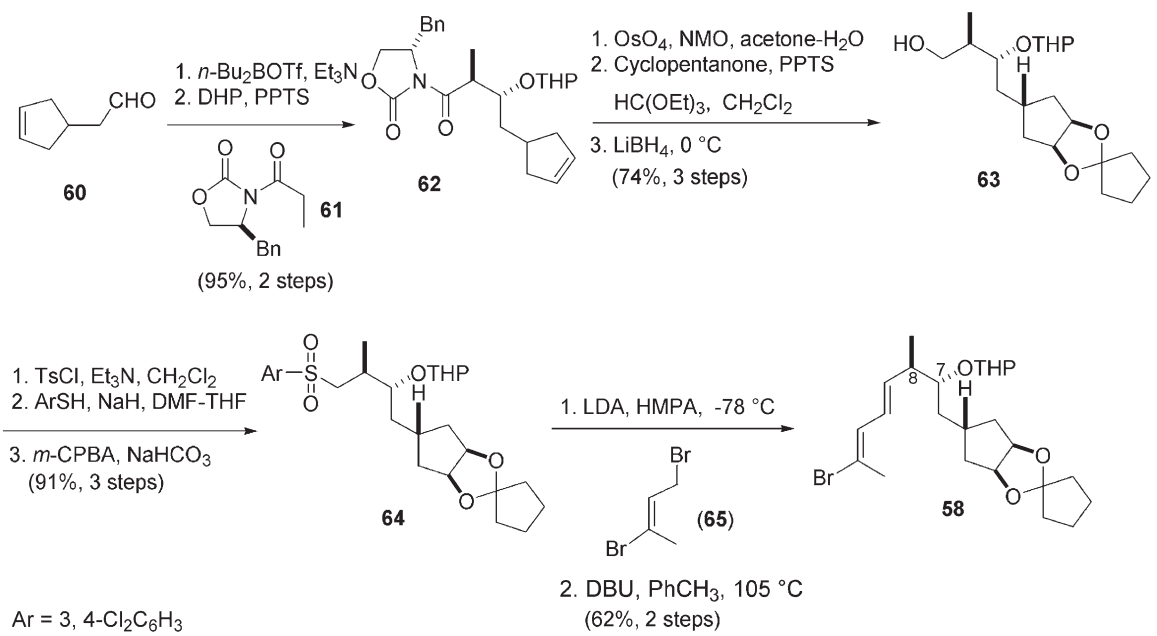
Scheme 12. Williams' strategy for the synthesis of rhizoxin D.

The C20–C26 segment **44** was prepared from the oxazolecarboxylic ester **33** in four steps, as shown in Scheme 10. Reduction of **33** and Wittig olefination gave enal **53**. A Takai reaction[28] of **53** afforded the corresponding *E*-vinyl iodide, which was transformed to vinylstannane **44**.

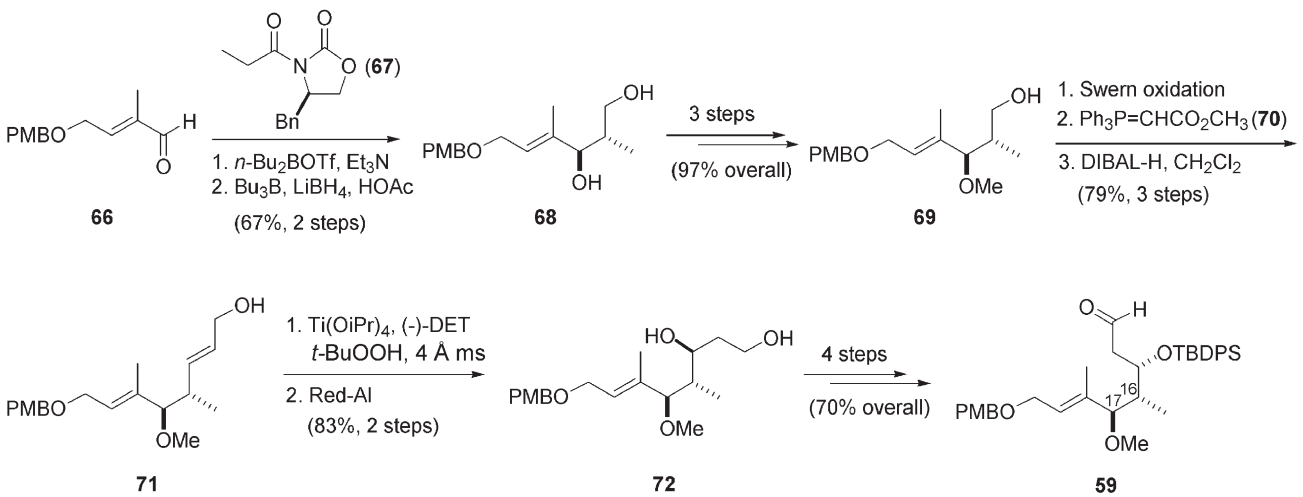
The endgame of Kende's synthesis of rhizoxin D is shown in Scheme 11. The crucial coupling of phosphonate **43** and aldehyde **42** proceeded smoothly to afford, after Luche reduction, diene **54** as a 1:1.5 mixture of epimeric alcohols. This mixture was converted to diol **55** in four steps. Selective silylation of the allylic alcohol, coupling with diethyl phosphonoacetic acid, and removal of the dithiane group gave aldehyde **56**. Subjection of **56** to intramolecular Horner-Emmons conditions[29] then furnished the macrolactone **57** in 55% yield. Final Stille coupling of **57** with **44** and removal of the *tert*-butyldimethylsilyl group completed the synthesis of didesepoxyrhizoxin (**3**).

4.3. Williams' synthesis of rhizoxin D

Williams' group at Indiana University reported a second total synthesis of rhizoxin D in 1997,[30] the retrosynthetic



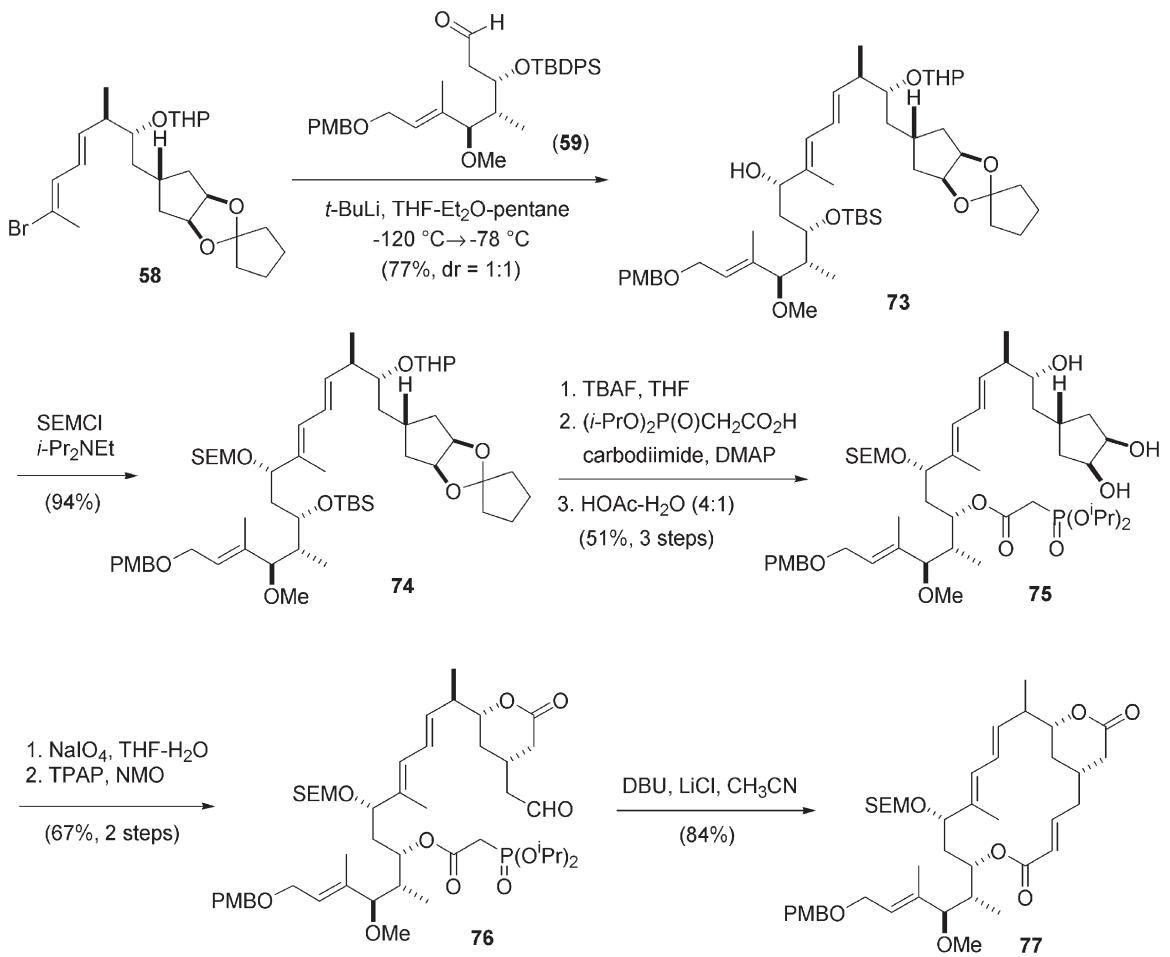
Scheme 13. Williams' synthesis of C3–C12 segment of rhizoxin D.



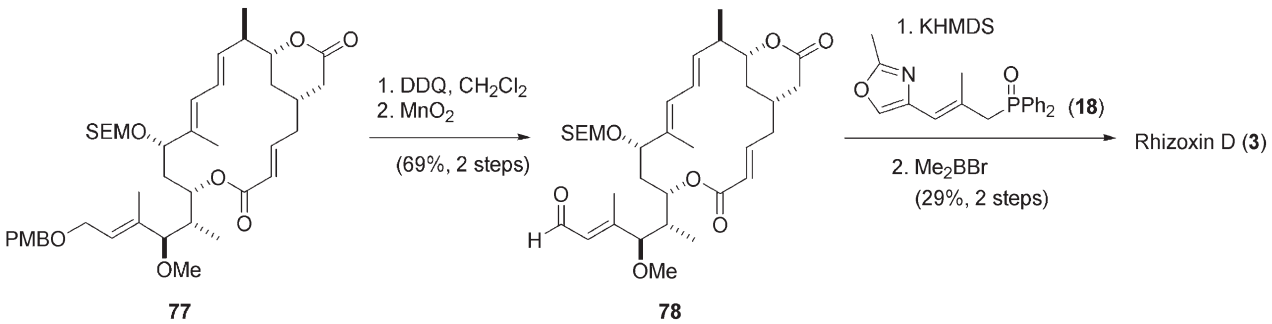
Scheme 14. Williams' synthesis of the C13–C20 segment of rhizoxin D.

analysis for which is shown in Scheme 12. In this approach, the target was subdivided into the three segments **18**, **58**, and **59**. As in Kende's synthesis, an intramolecular Horner-Wadsworth-Emmons process was used to close the macrolactone of rhizoxin D. A desymmetrization strategy was applied to a pseudosymmetric substrate, using the thermodynamic preference for a 1,3-diequatorial orientation of substituents on a six-membered ring to set the C5 stereocenter.

Williams' preparation of the C3–C12 fragment **58** began with the known 3-cyclopentenylacetaldehyde **60**, which underwent an Evans aldol reaction[26] with the *Z*-boron enolate of the (*S*)-oxazolidinone **61** to set the C7 and C8 stereogenic centers (Scheme 13). The resultant alcohol was protected as its tetrahydropyranyl (THP) ether, and subsequent dihydroxylation afforded a mixture of *cis* diols in a 7:1 ratio.[31] Ketalization of the diol and reductive removal of the chiral auxiliary gave alcohol **63**, which was



Scheme 15. Williams' assembly of the subunits of rhizoxin D.

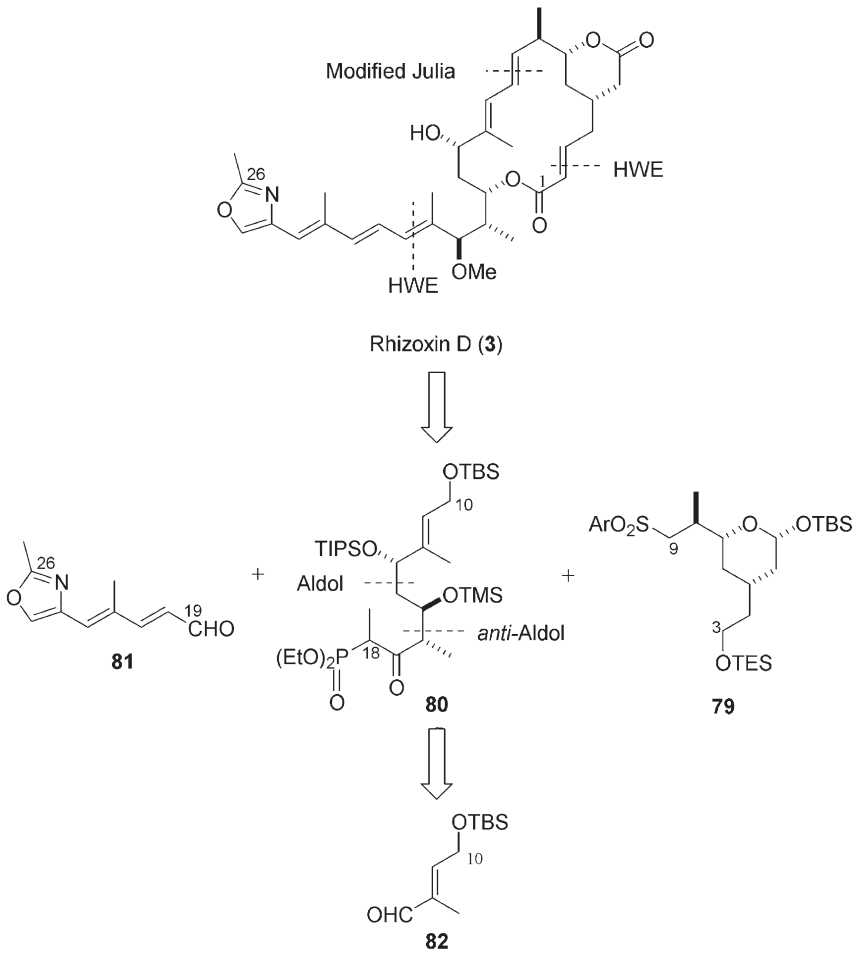


Scheme 16. Williams' completion of the synthesis of rhizoxin D.

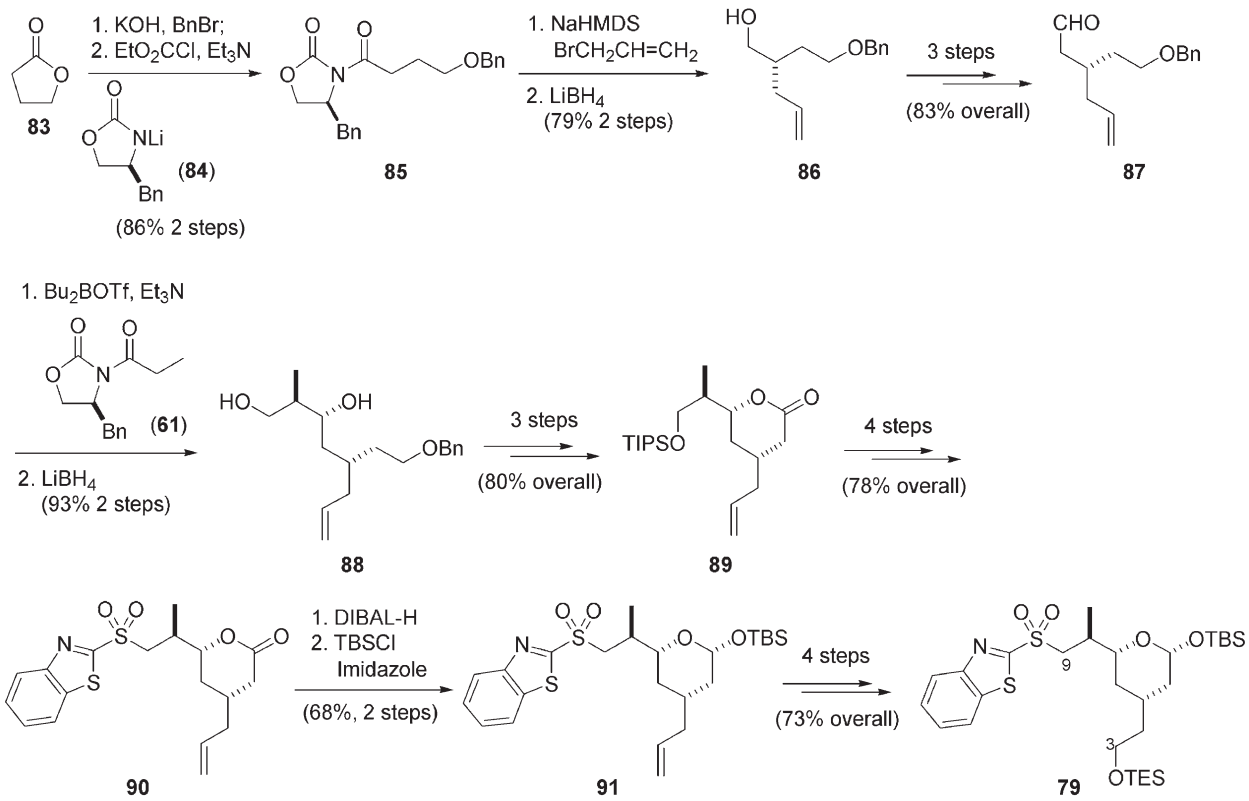
transformed to sulfone **64** in three steps. Alkylation of **64** with (*E*)-1,3-dibromo-2-butene followed by elimination of the allylic sulfone produced the *trans*-diene **58**.

Williams' synthesis of the C13–C20 fragment **59** commenced from aldehyde **66**. An Evans aldol reaction[26] of **66** with the *Z*-boron enolate derived from the (*R*)-oxazolidinone **67** set the C16 and C17 stereocenters, and the chiral auxiliary was reductively removed to give a diol which was transformed to alcohol **69** in three steps. Swern oxidation of **69**, Wittig chain extension, and reduction with diisobutylaluminum hydride afforded the *E*-allylic alcohol **71**. The C15 stereocenter was established by Sharpless asymmetric epoxidation[32] of **71**, and regioselective hydride opening of the resultant epoxy alcohol then gave diol **72**.[33] A subsequent four-step operation converted **72** to β-silyloxyaldehyde **59**, as shown in Scheme 14.

Coupling of the C3–C12 and C13–C20 segments was accomplished by addition of the lithiated derivative of **58** to **59**. This afforded a 1:1 diastereomeric mixture of C13 alcohols (Scheme 15), from which the desired (13*S*) alcohol **73** was separated and protected as its trimethylsilylethoxymethyl (SEM) ether **74**. Liberation of the C15 hydroxyl group with tetrabutylammonium fluoride, esterification with diisopropylphosphonoacetic acid, and concomitant hydrolysis of the tetrahydropyranyl ether and cyclopentylidene ketal produced triol **75**. Oxidative cleavage of the vicinal diol yielded two diastereomeric lactols which were oxidized by tetrapropylammonium perruthenate



Scheme 17. Leahy's strategy for the synthesis of rhizoxin D.



Scheme 18. Leahy's synthesis of the C3–C9 segment of rhizoxin D.

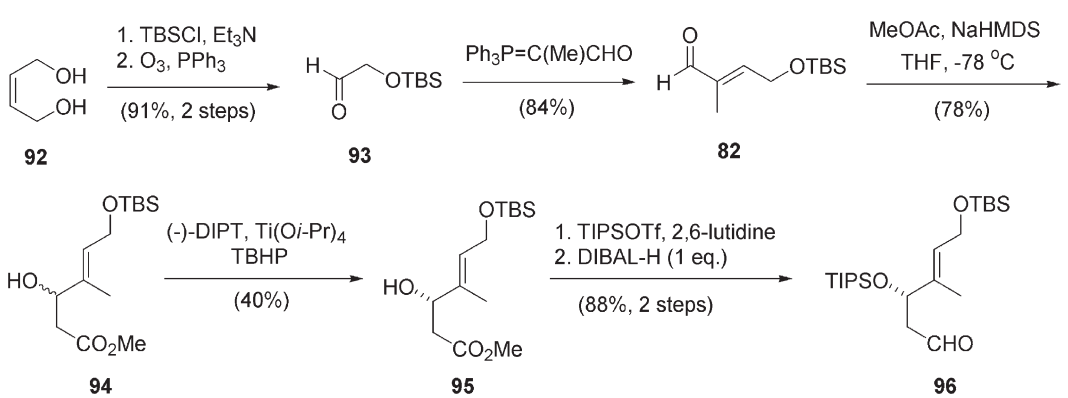
(TPAP)[34] to a single δ-lactone **76**. Macrocyclization of this substance was achieved by an intramolecular Horner-Wadsworth-Emmons reaction to give **77** in high yield.

Williams' synthesis of rhizoxin D was completed as shown in Scheme 16. Oxidative removal of the *p*-methoxybenzyl (PMB) group of **77** yielded the corresponding allylic alcohol, which was oxidized to aldehyde **78**. Horner-Wittig olefination of **78** with the phosphine oxide **18** and final cleavage of the SEM ether furnished rhizoxin D (**3**).

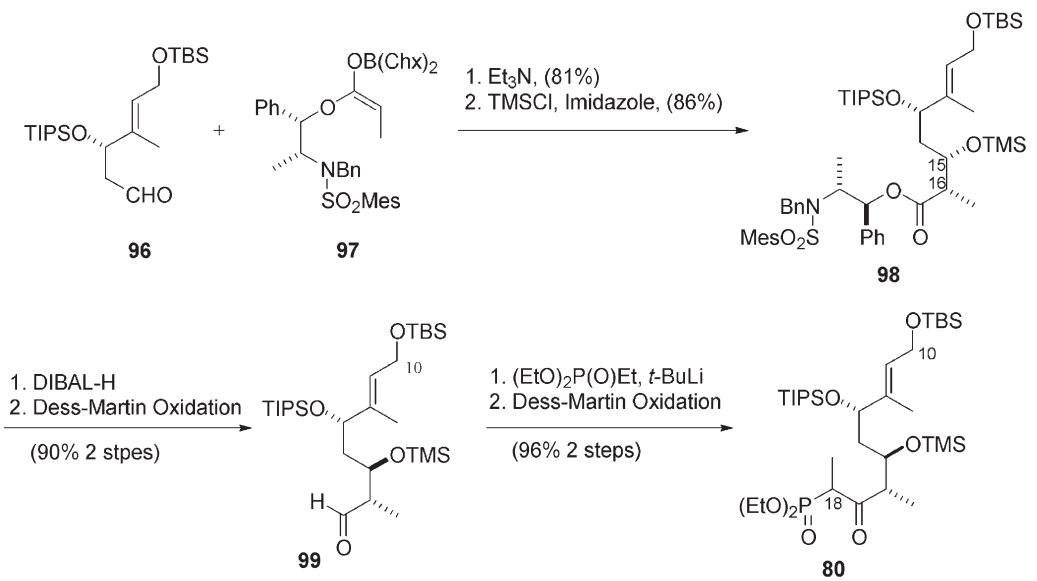
4.4. Leahy's synthesis of rhizoxin D

Leahy and co-workers reported their completed synthesis of rhizoxin D in 1999[35] after preliminary publications which described their preparation of C1–C9, C10–C18 and C19–C26 subunits **79**–**81**.[36] Leahy's strategy is outlined in Scheme 17 and is different from previous syntheses in that the oxazole side-chain was installed before construction of the macrolactone. In common with previous efforts, a modified Julia coupling and a Horner-Wadsworth-Emmons reaction were envisioned for connection of these fragments. Aldehyde **82** provided the template upon which the C10–C18 moiety **80** was built.

Leahy's synthesis of the C3–C9 subunit **79** began from γ-butyrolactone (**83**) (Scheme 18). After hydrolysis of **83** and protection of the resultant alcohol as its benzyl ether, the carboxylic acid was activated as a mixed anhydride and condensed with the lithiated oxazolidinone **84** to give the imide **85**. Alkylation of the *Z*-enolate of **85** with allyl bromide followed by reductive removal of the chiral auxiliary afforded alcohol **86** as a single diastereomer. A three-step sequence which included Dess-Martin oxidation



Scheme 19. Leahy's synthesis of the C10–CC15 segment of rhizoxin D.

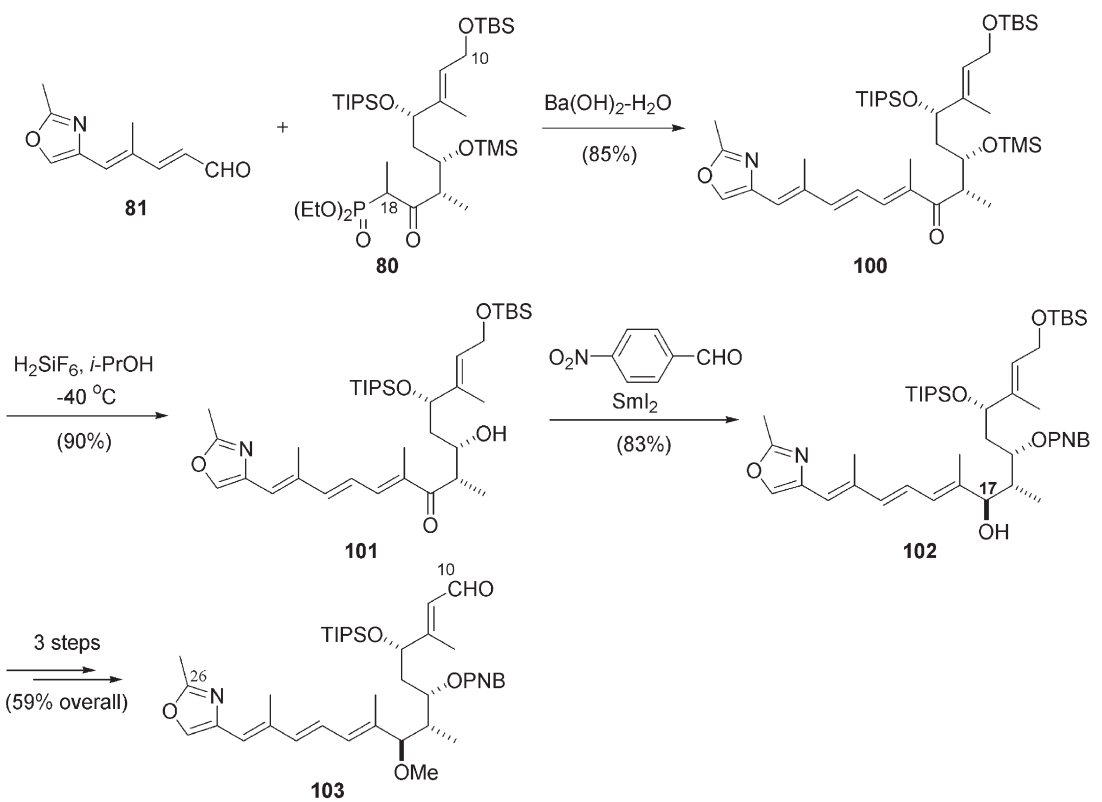


Scheme 20. Leahy's synthesis of the C10–C20 segment of rhizoxin D.

and a one-carbon homologation furnished aldehyde **87**. An Evans aldol condensation of this aldehyde with **61** followed by reductive cleavage of the chiral auxiliary produced diol **88** as a single diastereomer. The primary hydroxyl group of **88** was selectively silylated, and subsequent functional group manipulation led to δ-lactone **89**. The latter was converted to the sulfone **90** in four steps and 78% overall yield. The δ-lactone moiety of **90** was masked as an acetal and the vinyl terminus of **91** was converted to the corresponding triethysilyl ether **79**, representing the C3–C9 subunit of rhizoxin D.

The C10–C18 segment **80** was prepared by Leahy from diol **92** (Scheme 19). Bis-silylation and ozonolysis of **92** gave aldehyde **93**, which underwent Wittig olefination to afford enal **82** as a single stereoisomer. Treatment of aldehyde **82** with the sodium enolate of methyl acetate gave racemic alcohol **94**, which was kinetically resolved under Sharpless epoxidation conditions to afford (*S*)-alcohol **95** in 40% yield.[37] Silyl protection of this alcohol and reduction with diisobutylaluminum hydride led to aldehyde **96**.

Although Leahy explored numerous anti-aldol procedures



Scheme 21. Leahy's synthesis of the C10–C26 segment of rhizoxin D.

for installation of the C15 and C16 stereocenters, only the norephedrine-based methodology of Masamune[38] accomplished this with good diastereoselectivity. Thus, the reaction of aldehyde **96** with the boron enolate **97** gave aldol product **98** after silylation in 90% de (Scheme 20). A reduction–oxidation sequence then gave aldehyde **99**, and conversion of this material to the β-ketophosphonate **80** was achieved in two high yielding steps.

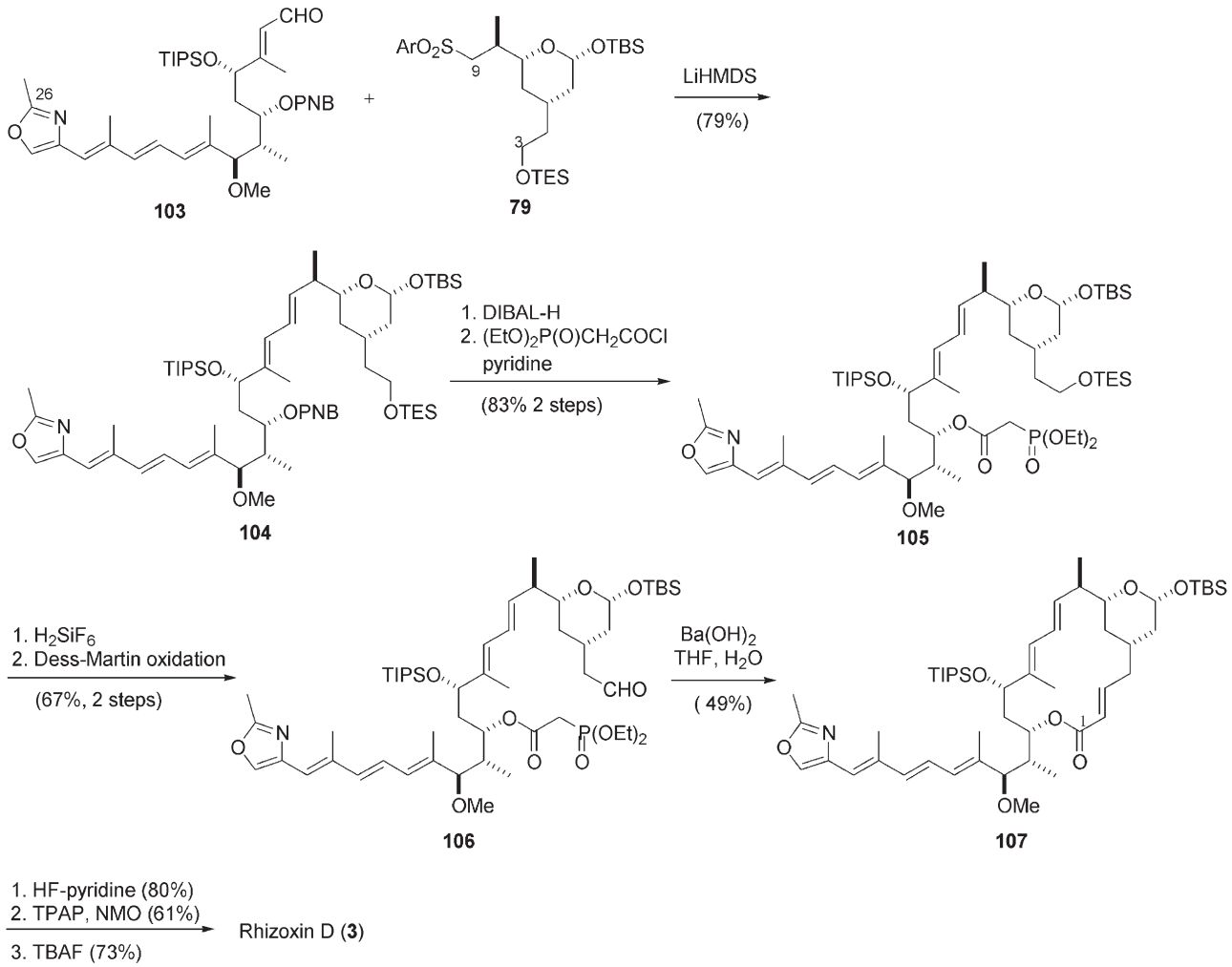
The β-ketophosphonate **80** was coupled to the oxazole aldehyde **81** using barium hydroxide[39] to give the desired triene **100** in high yield (Scheme 21). The potentially difficult selective removal of the trimethylsilyl protecting group was overcome by using fluorosilicic acid in isopropanol to afford β-hydroxy ketone **101**.[40] An Evans-Tishchenko reaction[41] with *p*-nitrobenzaldehyde was employed to install the C17 stereocenter of **102**, and this allylic alcohol was transformed to aldehyde **103** in three steps with 59% overall yield.

As shown in Scheme 22, the C3–C9 and C10–C26 subunits **79** and **103** were coupled smoothly to give the C3–C26 fragment **104** as a single isomer.[42] The *p*-nitrobenzoate at C15 was cleaved reductively, and the resultant alcohol was esterified with diethylphosphonoacetyl chloride to afford **105**. Fluorosilicic acid was used again to selectively cleave the triethylsilyl ether of **105**. The liberated alcohol was oxidized to aldehyde **106**, which closed to macrolide **107** in the presence of barium hydroxide. The final stages of Leahy's synthesis of rhizoxin D required only conversion of acetal **107** to a δ-lactone and deprotection of the triisopropyl ether.

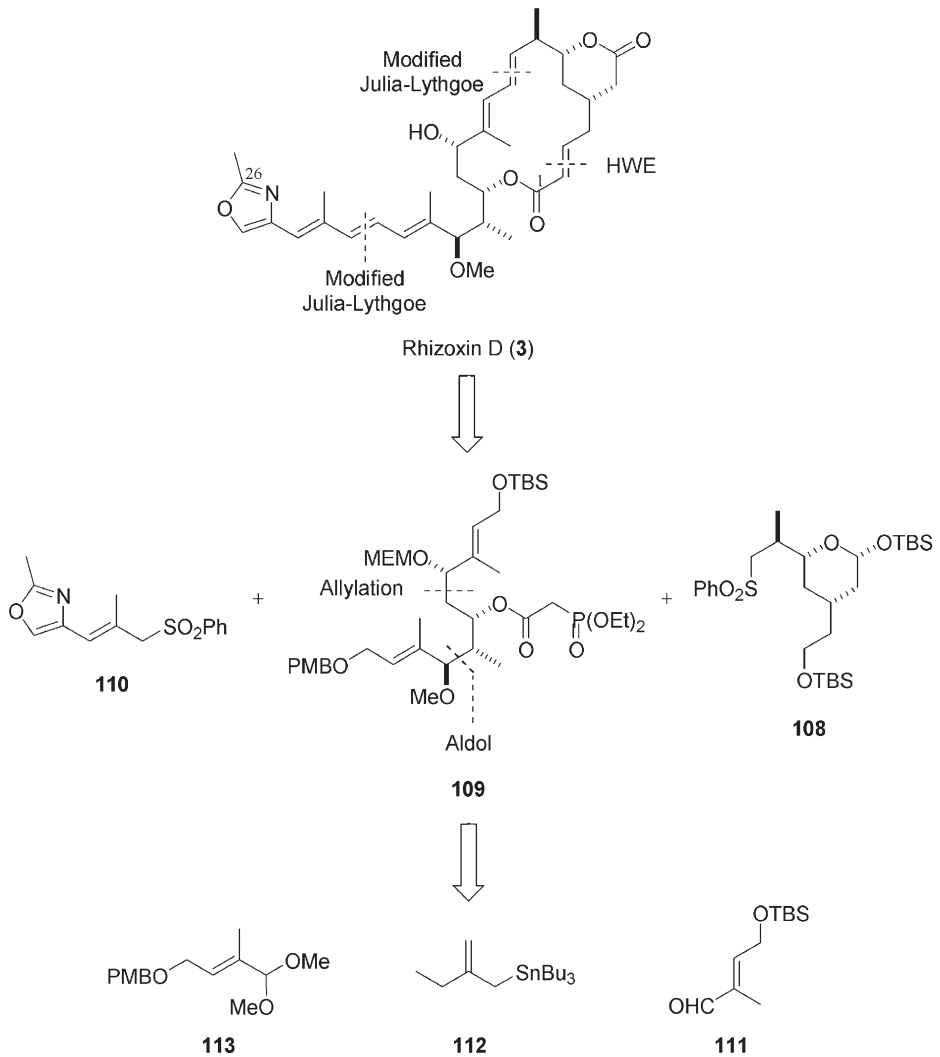
4.5. Keck's synthesis of rhizoxin D

Keck and co-workers reported a synthesis of rhizoxin D in 2001[43] employing the strategy summarized in Scheme 23.[44] The target was dissected into the three major segments, **108**, **109** and **110**, with assembly of these subunits envisioned by a modified Julia-Lythgoe protocol[45] and an intramolecular Horner-Wadsworth-Emmons reaction. The central fragment **109** was prepared from **111**, **112**, and **113** utilizing catalytic asymmetric allylation and aldol reactions as the key steps.

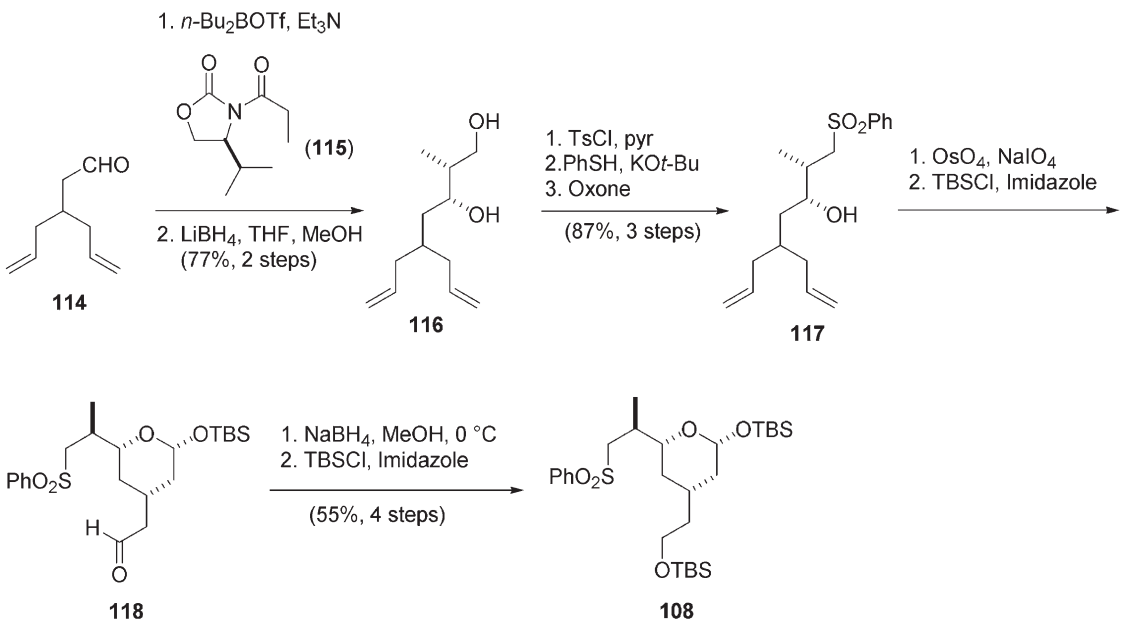
The C3–C9 segment **108** was synthesized by Keck using thermodynamic control to establish the correct stereochemistry at C5. As shown in Scheme 24, Keck's synthesis began with an Evans aldol reaction of (*S*)-oxazolidinone **115** with aldehyde **114**. Reductive removal of the chiral auxiliary gave the diol **116** as a single diastereomer, and selective tosylation of the primary alcohol followed by displacement with potassium phenylthiolate and oxidation



Scheme 22. Leahy's completion of the synthesis of rhizoxin D.



Scheme 23. Keck's strategy for the synthesis of rhizoxin D.



Scheme 24. Keck's synthesis of the C3–C9 segment of rhizoxin D.

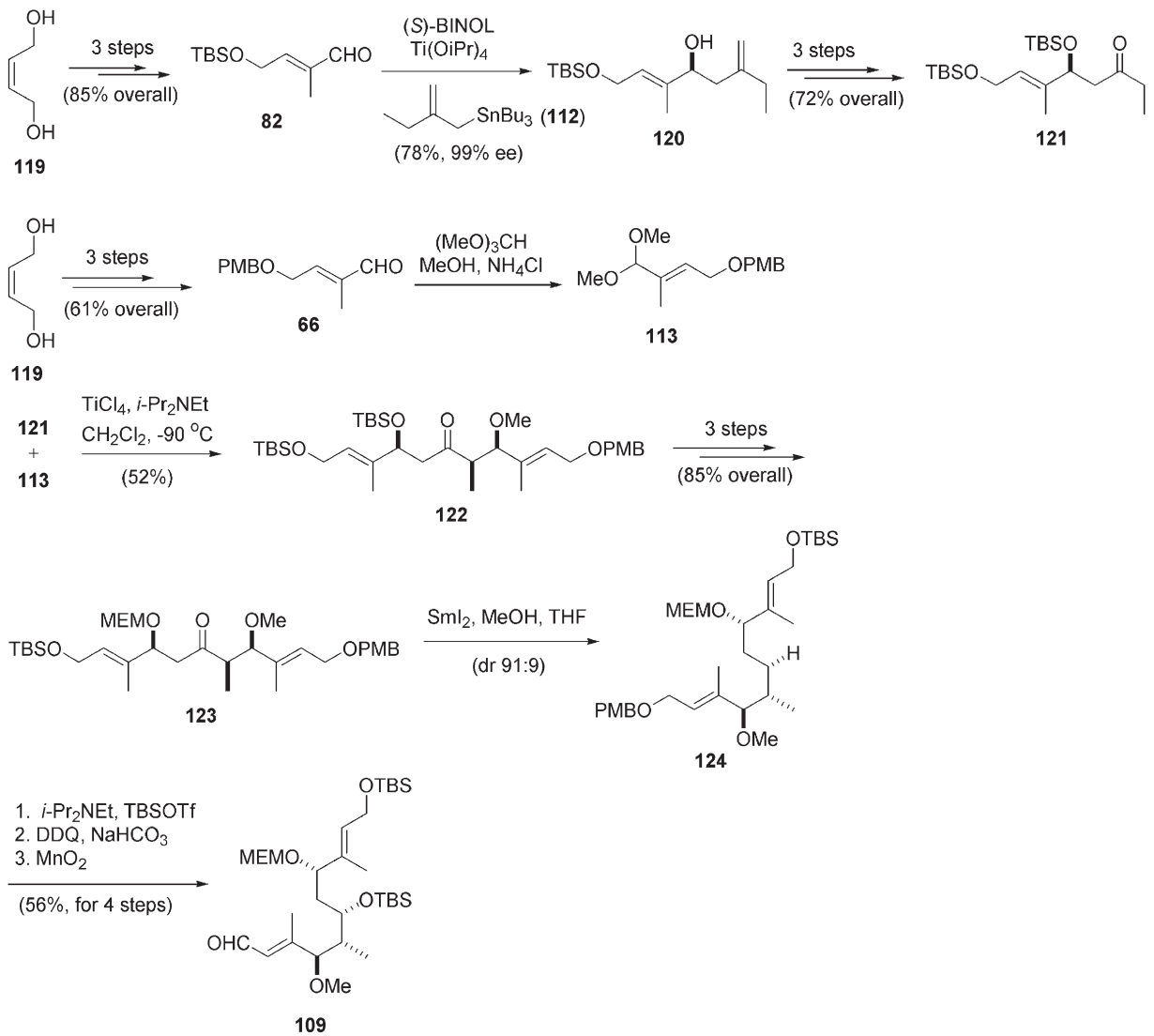
afforded sulfone **117**. Lemieux-Johnson cleavage of the pair of terminal vinyl groups produced an equilibrating mixture of lactols, which was silylated to yield a single silyl ether **118**. Subsequent reduction and silyl protection led to the C3–C9 subunit **108**.

Keck's approach to the C10–C20 portion **109** of rhizoxin D featured a more convergent strategy than that of previous routes. The synthesis of this moiety began with *cis*-2-butene-1,4-diol (**119**), as shown in Scheme 25. A three-step sequence involving bis-silyl protection, oxidative cleavage, and Wittig homologation afforded aldehyde **82**. An asymmetric allylation[46] of **82** with stannane **112** in the presence of a catalyst derived from (*S*)-BINOL and titanium tetraisopropoxide afforded the alcohol **120** in 78% yield and 99% ee. The alcohol was protected as a silyl ether, and the terminal alkene was cleaved oxidatively to furnish ethyl ketone **121**. The *E*-enal **66** was prepared in a similar fashion to **82** from **119** and was converted to the dimethyl acetal **113**. An aldol reaction of the titanium enolate of **121** with **113** under Evans' conditions[47] led to the adduct **122** as a single stereoisomer. The secondary silyl ether was exchanged for a methoxyethoxymethyl (MEM) ether, and upon treatment with samarium diiodide **123** gave an (*S*)-alcohol with good stereoselectivity (dr 91:9).[48] A three-step sequence which entailed silyl protection, removal of the *p*-methoxybenzyl ether and allylic oxidation afforded the C10–C20 subunit **109**.

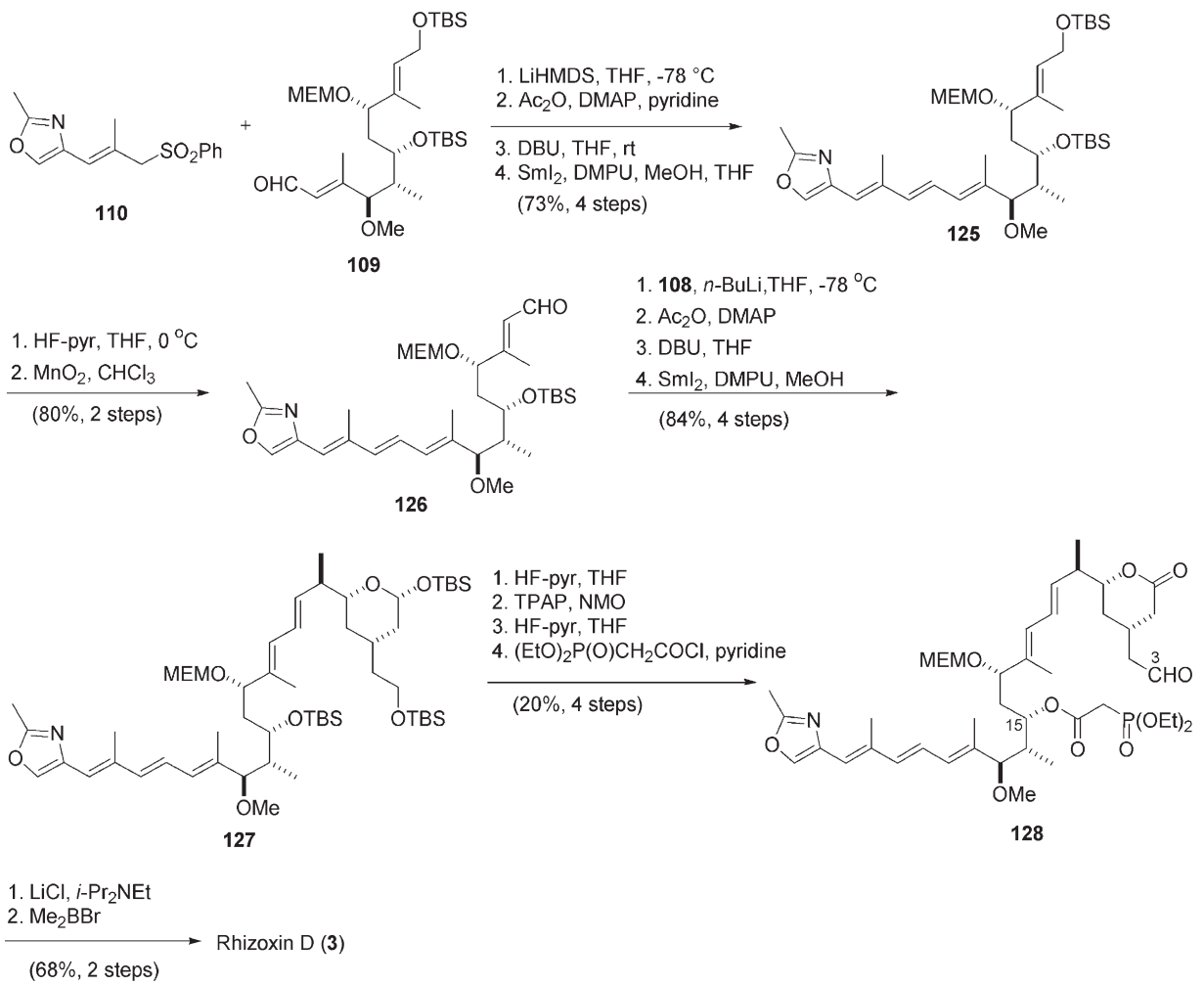
The fragment-assembly sequence in Keck's synthesis began with a modified Julia reaction to couple sulfone **110** and enal **109**, as shown in Scheme 26. This four-step sequence afforded *E*-triene **125** as a single isomer in 73% overall yield. Selective cleavage of the primary silyl ether was followed by allylic oxidation to give enal **126**. A second Julia reaction was employed to couple **126** with sulfone **108**, and the resultant triene **127** was obtained as a single all *E* isomer. A further four-step sequence led to **128** containing a C3 aldehyde and a phosphonylacetate at C15 for an intramolecular Horner-Emmons reaction. Final removal of the MEM group afforded rhizoxin D in 68% yield for the two steps from **128**.

4.6. Pattenden's synthesis of rhizoxin D

Pattenden reported an enantioselective synthesis of rhizoxin



Scheme 25. Keck's synthesis of the C10–C20 segment of rhizoxin D.



Scheme 26. Keck's completion of the synthesis of rhizoxin D.

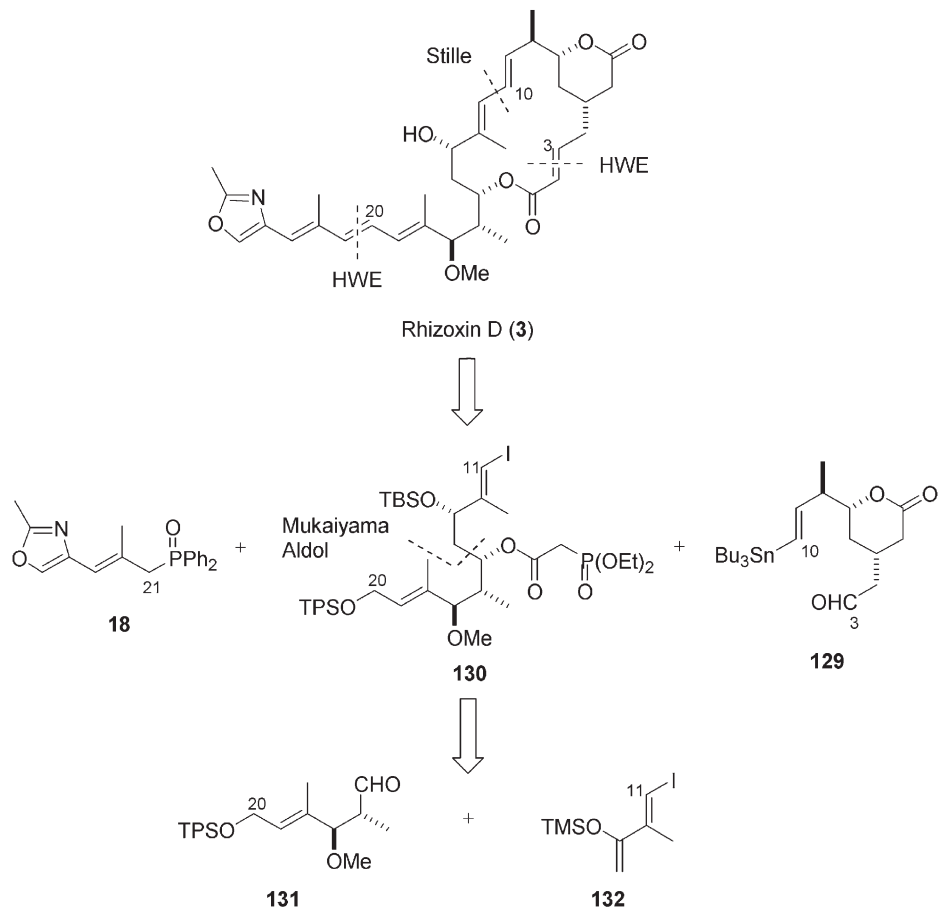
D[49] based on the strategy shown in Scheme 27. Three fragments, vinylstannane **129**, vinyl iodide **130** and phosphine oxide **18** were envisioned as the constituent substructures, and in contrast to previous routes an intramolecular Stille reaction was planned for formation of the 16-membered macrocyclic core. The oxazole containing side-chain was to be installed in a manner similar to other syntheses, using a Horner-Wittig olefination with phosphine oxide **18**. The central subunit **130** was further disconnected to aldehyde **131** and the silyl enol ether **132**. A Mukaiyama aldol reaction was programmed for coupling of these two fragments.

Pattenden's synthesis of the central subunit **130** is shown in Scheme 28. An aldol reaction between aldehyde **133** and the boron enolate of **67** afforded a secondary alcohol, which was methylated. Reductive cleavage of the chiral auxiliary yielded the primary alcohol **134**, which was converted to aldehyde **131** upon Dess-Martin oxidation. This aldehyde was coupled with the silyl enol ether **132** under chelation-controlled Mukaiyama aldol conditions to afford β-hydroxy ketone **135** with greater than 96% diastereoselectivity.[50] Subsequent reduction of this ketone with tetramethylammonium triacetoxyborohydride led to the 1,3-anti-diol **136** which was transformed into the vinyl iodide **130** in two steps.

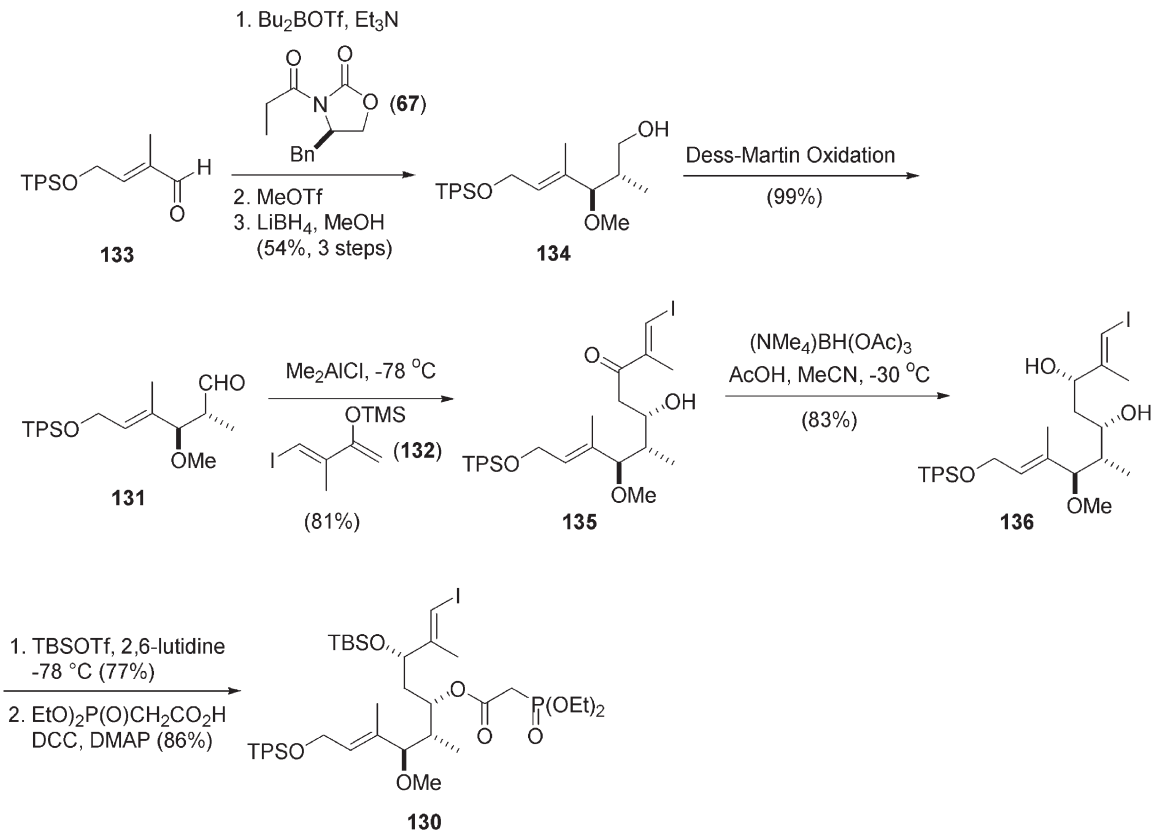
The synthesis of vinyl stannane **129** commenced from α,β-unsaturated ester **137**, as shown in Scheme 29. Reduction of the ester followed by vinyl ether formation afforded **138**, which underwent a smooth Claisen rearrangement to give the racemic aldehyde **139**. An aldol reaction of **139** with **48** afforded a 1:1 mixture of diastereomeric products **140** and **141**.

The desired diastereomer **140** was separated from the mixture by chromatography and the auxiliary was cleaved reductively (Scheme 30). The resulting primary alcohol was protected as its *p*-methoxybenzyl ether before hydroboration–oxidation of the terminal alkene was carried out. This sequence gave diol **142**, which afforded the δ-lactone **143** upon oxidation. A sequence of deprotection, oxidation, and one-carbon homologation led to the terminal alkyne **144**[51] which was transformed to (*E*)-vinylstannane **145**.[52] The latter was deprotected and oxidized to give aldehyde **129** as the C3–C10 subunit.

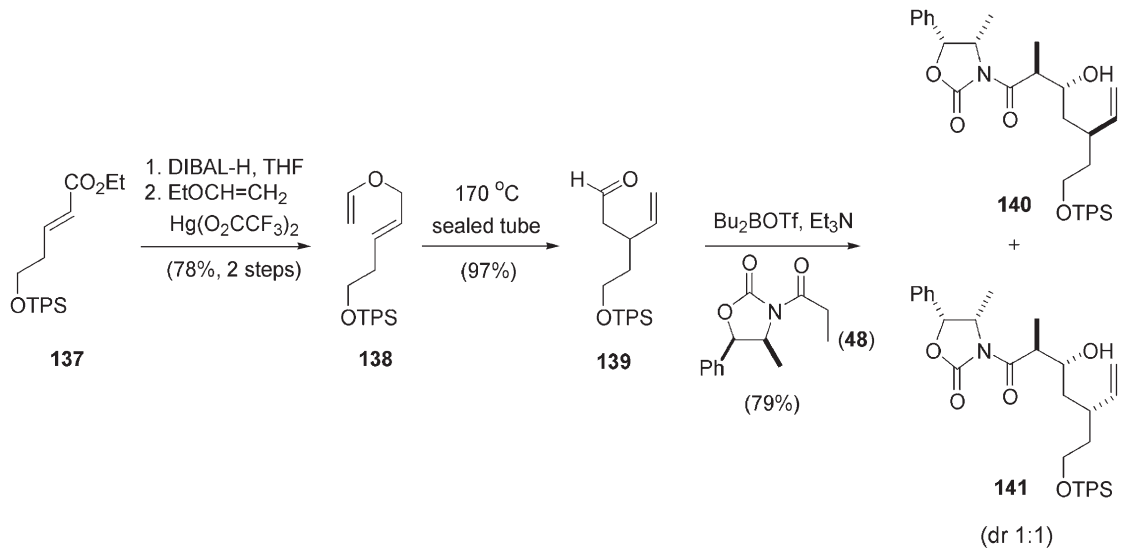
With the principal subunits in hand, aldehyde **129** and phosphonate **130** were coupled via a Horner-Wadsworth-Emmons reaction to give the (*E*)-alkene **146** (Scheme 31). An intramolecular Stille reaction was employed to form the 16-membered lactone **147**,[53] and selective removal of the triphenylsilyl (TPS) protecting group followed by allylic



Scheme 27. Pattenden's strategy for the synthesis of rhizoxin D.



Scheme 28. Pattenden's synthesis of the C11–C20 segment of rhizoxin D.



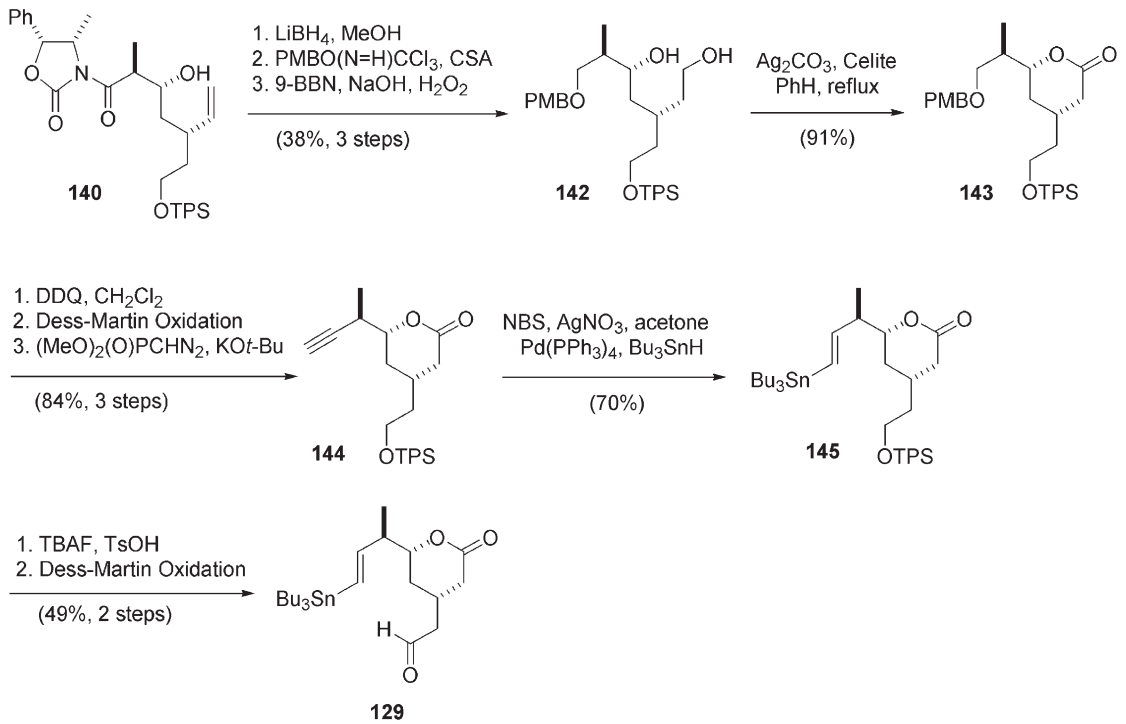
Scheme 29. Pattenden's synthesis of the C3–C9 segment of rhizoxin D.

oxidation then gave aldehyde **148**. This aldehyde was coupled with phosphine oxide **18** under Horner-Wittig olefination conditions to generate an all (*E*)-triene, and final cleavage of the silyl protecting group led to (+)-rhizoxin D (**3**).

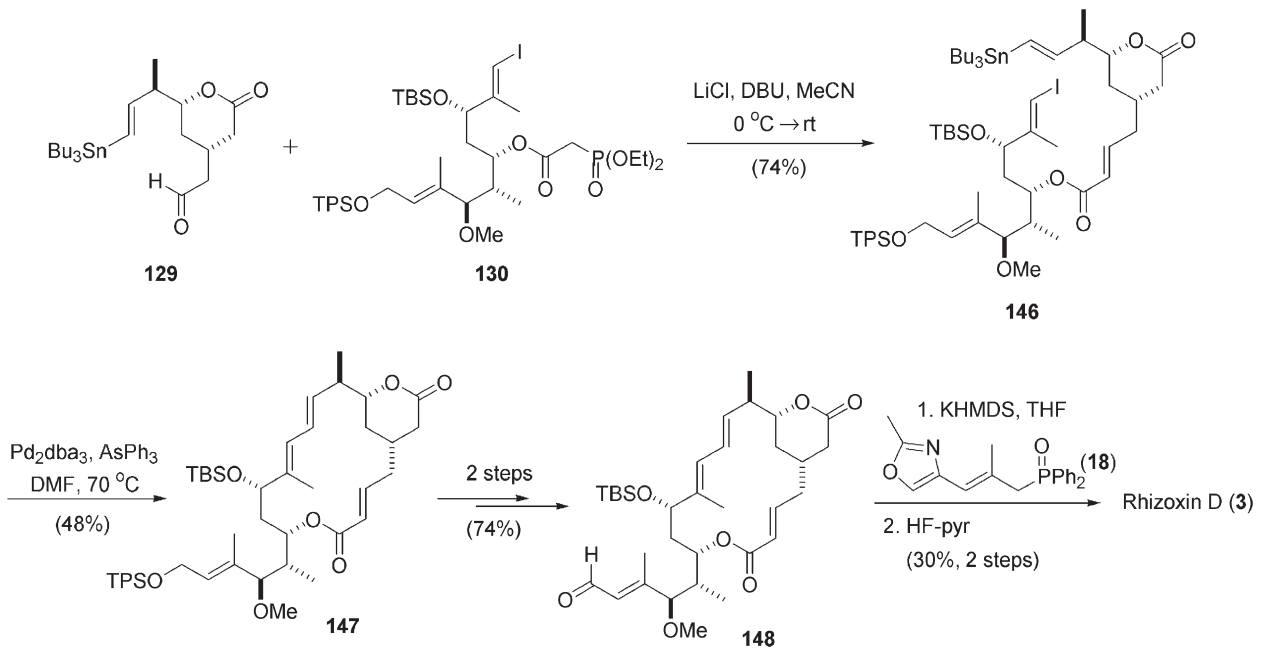
4.7. White's synthesis of rhizoxin D

White and co-workers reported a synthesis of rhizoxin D in 2002[54,55] in which a convergent strategy along lines shown in Scheme 32 was used. The three subunits **149**, **150** and **44** were assembled by means of an asymmetric aldol reaction, an intramolecular Horner-Wadsworth-Emmons macrocyclization, and a Stille coupling. Subunit **149** was foreseen from fragments **151** and **152** via a Wittig reaction, and acetal **151** was envisioned as the product of a novel radical cyclization.

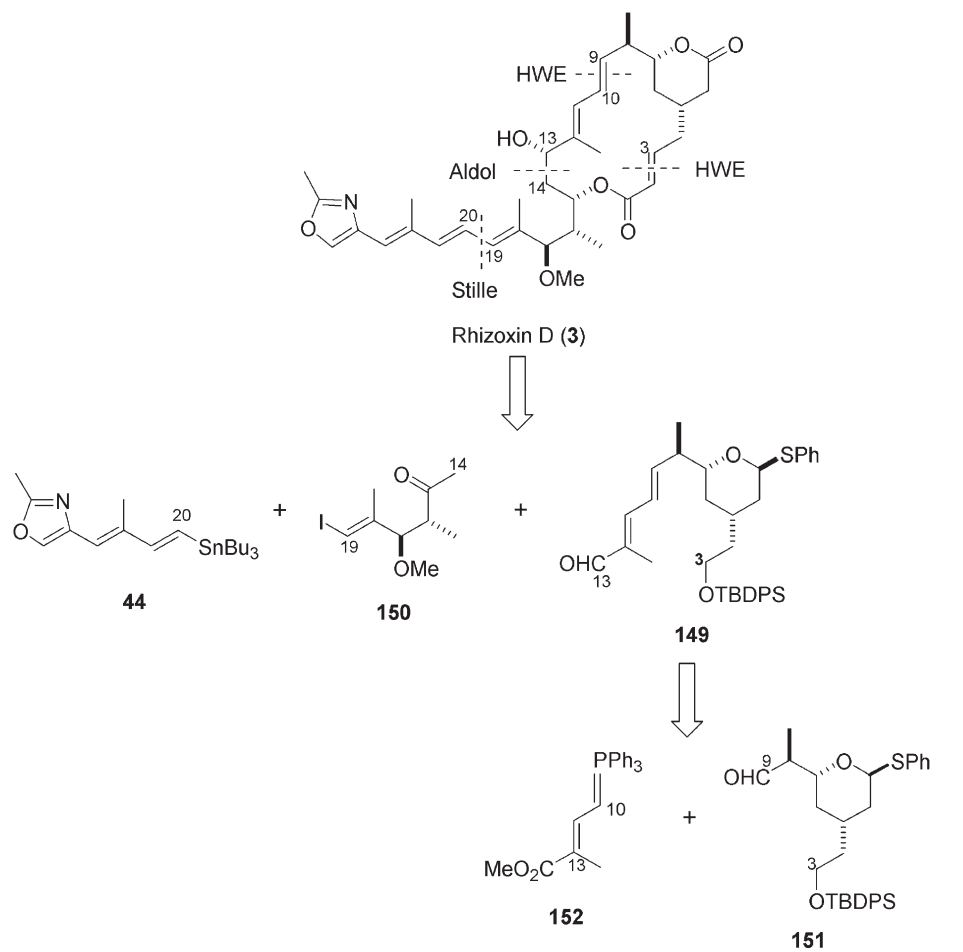
White's synthesis of the C3–C9 fragment **160** began with the known aldehyde **153** (Scheme 33). A chelation-controlled allylation[56] afforded anti-alcohol **154**, which was converted to ester **155** via a Mitsunobu reaction. After a three-step sequence involving a protecting group exchange and hydrolysis of the *p*-nitrobenzoate, alcohol **156** was obtained in 61% overall yield. Treatment of **156** with *N*-iodosuccinimide and ethyl vinyl ether furnished



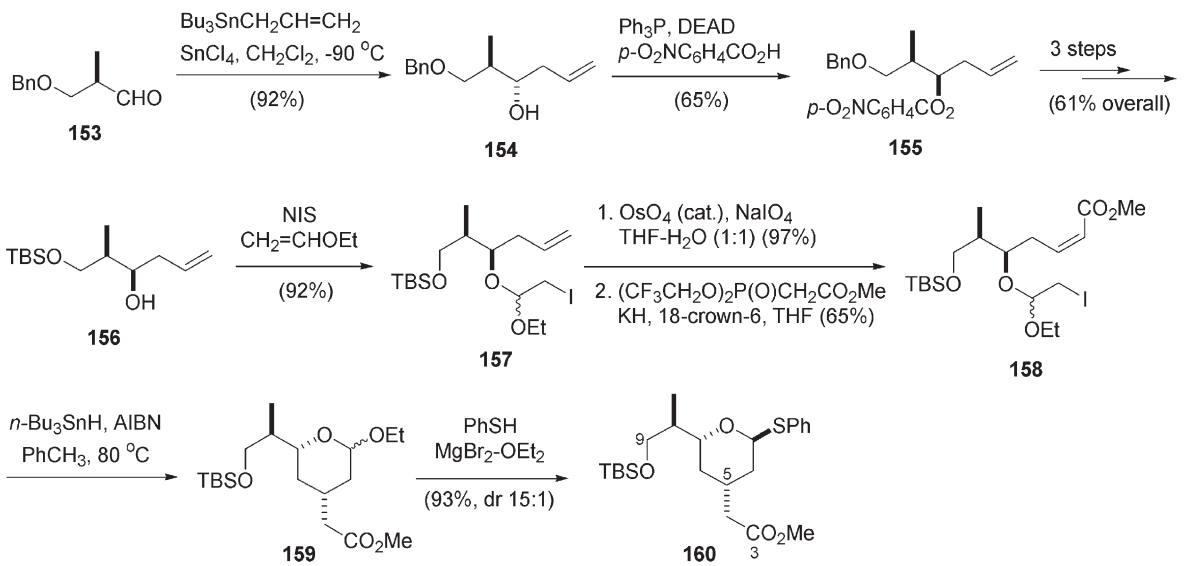
Scheme 30. Pattenden's synthesis of the C3–C10 segment of rhizoxin D.



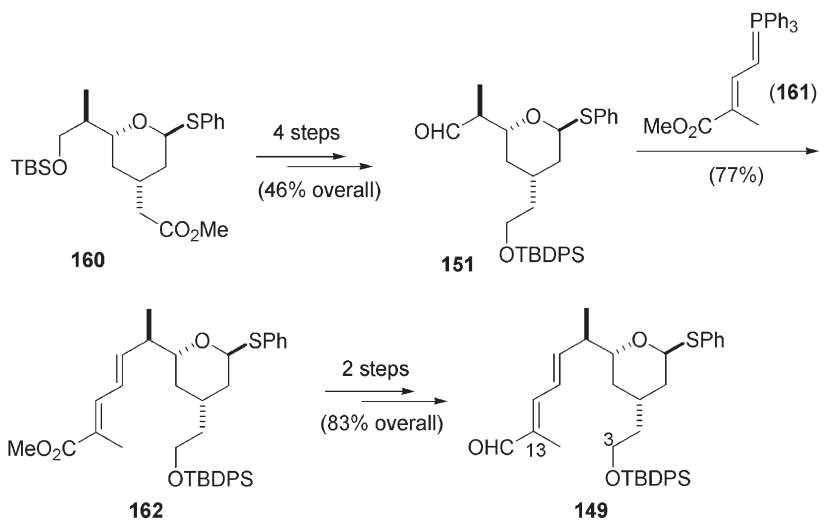
Scheme 31. Completion of Pattenden's synthesis of rhizoxin D.



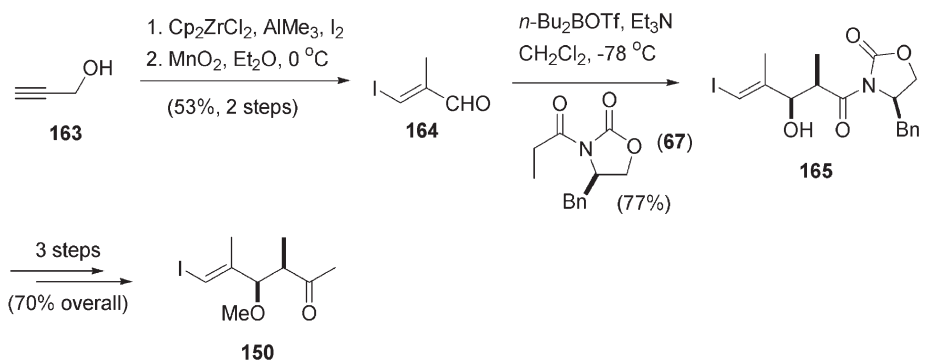
Scheme 32. White's strategy for the synthesis of rhizoxin D.



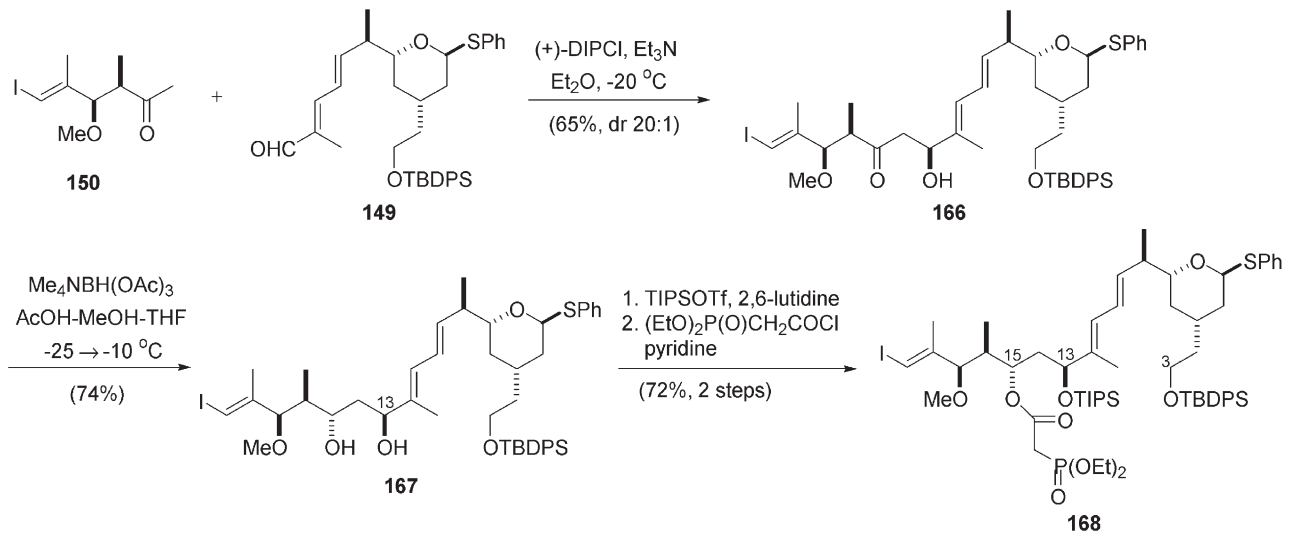
Scheme 33. White's synthesis of the C3–C9 segment of rhizoxin D.



Scheme 34. White's synthesis of the C3–C13 segment of rhizoxin D.



Scheme 35. White's synthesis of the C14–C19 segment of rhizoxin D.



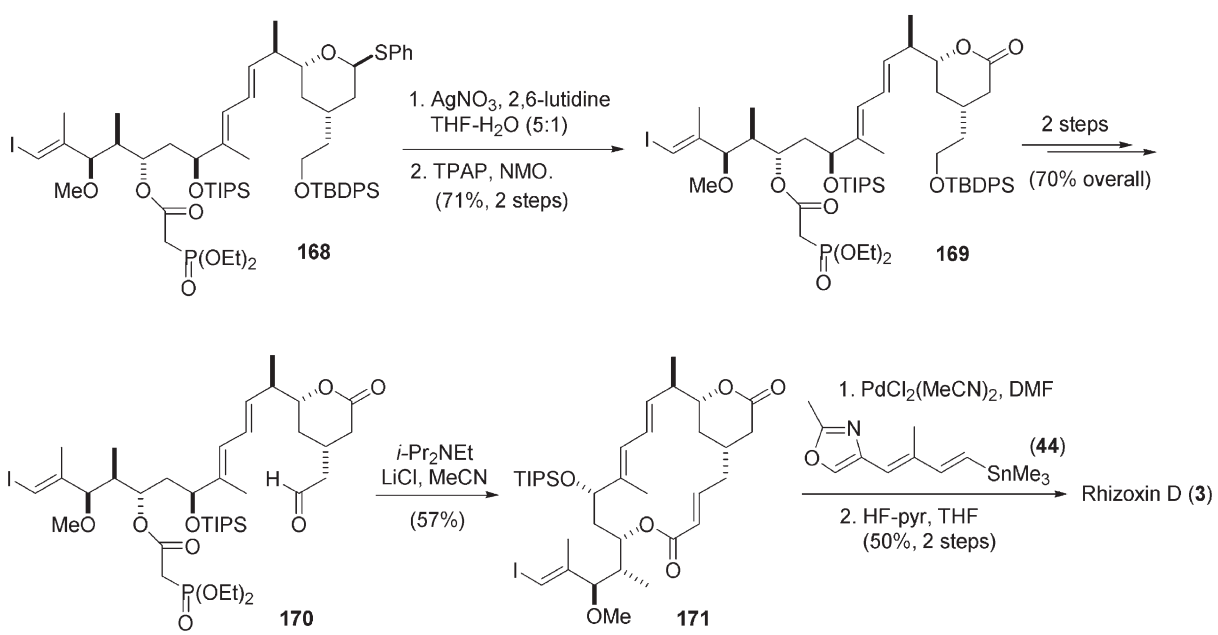
Scheme 36. White's coupling of the C3–C13 and the C14–C19 segments of rhizoxin D.

iodoacetal **157**,[57] which upon cleavage of the terminal vinyl group and coupling with the Gennari-Still phosphonate gave (*Z*)-α,β-unsaturated ester **158**.[58] Radical cyclization of **158** furnished **160** as a 15:1 mixture of C5 diastereomers after ketal exchange of **159** with thiophenol. Interestingly, radical cyclization of the (*E*)-α,β-unsaturated ester isomeric with **158** gave a much poorer stereoisomeric ratio with respect to the center at C5.

As shown in Scheme 34, the ester of **160** was reduced and the resulting primary alcohol was protected as a *tert*-butyldiphenylsilyl ether, after which the *tert*-butyldimethylsilyl group was removed and the primary alcohol oxidized to aldehyde **151**. A Wittig reaction of **151** with phosphorane **161** gave the (*E*,*E*)-diene **162**, which was transformed in straightforward fashion to the C3–C13 aldehyde **149**.

White's synthesis of the C14–C19 subunit **150** of rhizoxin D commenced from (*E*)-aldehyde **164** prepared by zirconation–methylation–iodination[59] of propargyl alcohol (**163**) followed by oxidation with manganese dioxide. An aldol reaction of **164** with the boron enolate of **67** furnished *syn* product **165**, which was converted to methyl ketone **150** in three steps (Scheme 35).

The pivotal aldol coupling of aldehyde **149** with the enolate of **150** was examined in detail for the purpose of optimizing the reaction conditions (Scheme 36). It was found that the (+)-diisopinyolcampheylboron (DIP) enolate of **150** and aldehyde **149** represented matched reactants and afforded the β-hydroxy ketone **166** in a 20:1 diastereomeric ratio.[60] Reduction of ketone **166** with tetramethylammonium acetoxyborohydride gave the 1,3-anti-diol **167**, and selective silyl protection of the C13 hydroxyl group followed by esterification of the C15 alcohol with diethylphosphonoacetyl chloride furnished **168**.



Scheme 37. White's completion of the synthesis of rhizoxin D.

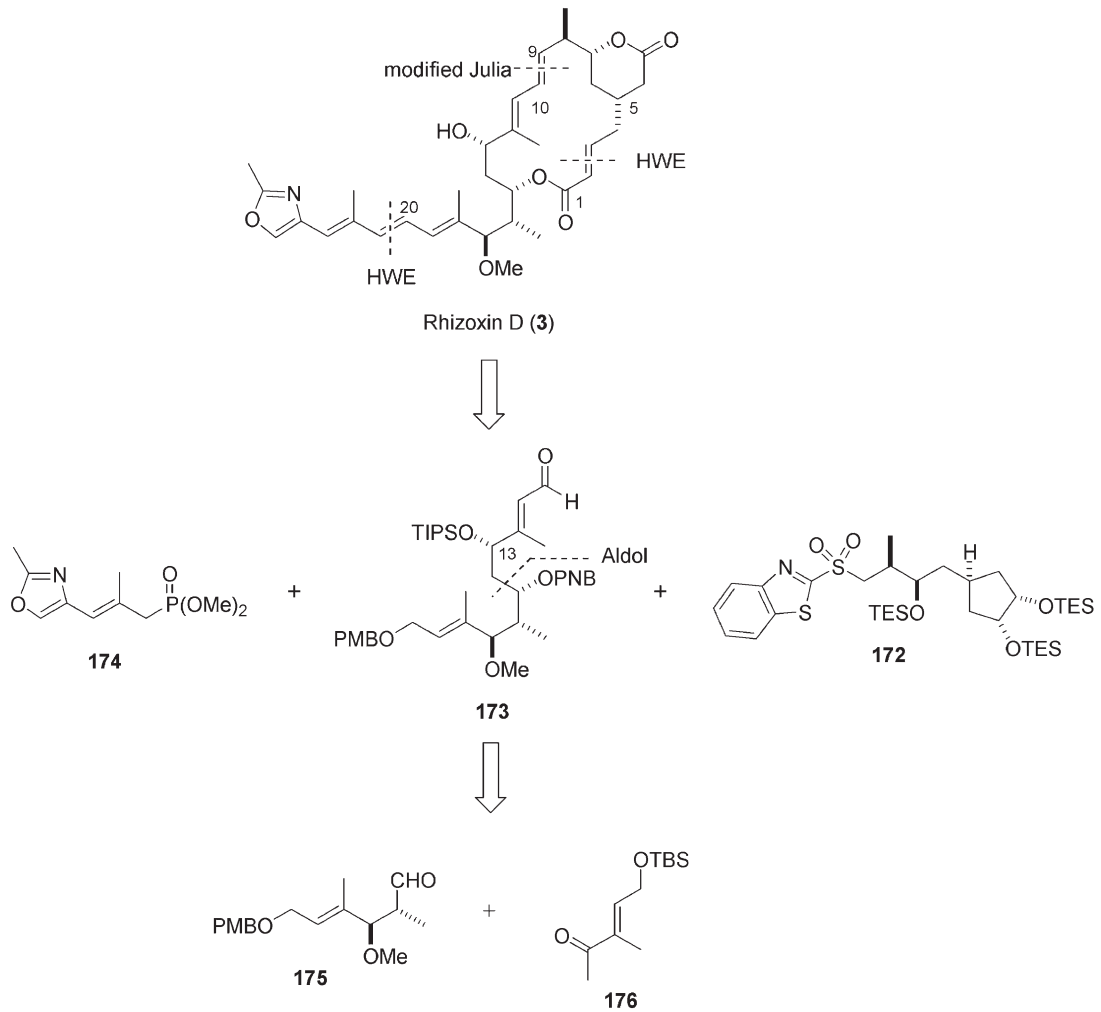
As shown in Scheme 37, thioacetal **168** was transformed to δ-lactone **169** by silver nitrate-catalyzed hydrolysis and oxidation of the intermediate hemiacetal with tetrapropylammonium perruthenate. Selective unmasking of the *tert*-butyldiphenylsilyl ether of **169** in the presence of the triisopropylsilyl ether at C13 was achieved with the mild fluoride source tris(dimethylamino)sulfur (trimethylsilyl)-difluoride (TASF). This furnished a primary alcohol which was oxidized to aldehyde **170**.[61] An intramolecular Horner-Wadsworth-Emmons reaction of **170** using Hunig's base and a large excess of lithium chloride in acetonitrile[29] produced α,β-unsaturated macrolactone **171**. Stille coupling[62] of **171** with stannane **44** and final desilylation afforded rhizoxin D.

4.8. Burke's synthesis of rhizoxin D

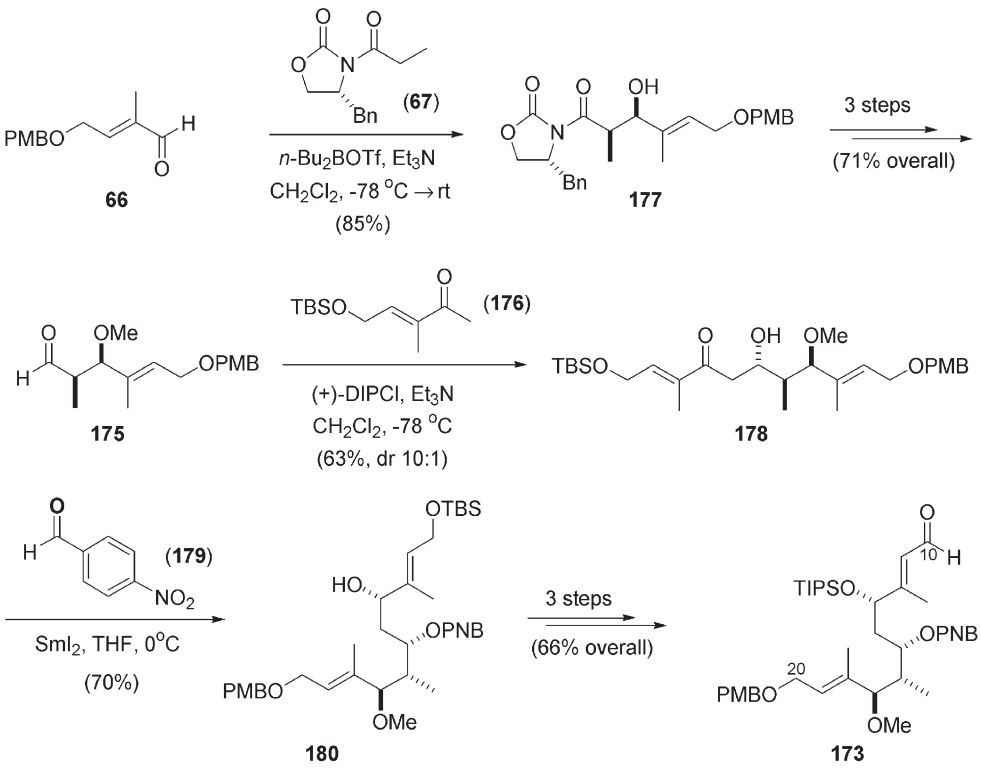
Burke's group has reported a stereoselective total synthesis of rhizoxin D employing the convergence of three segments, **172**, **173** and **174**, as shown in Scheme 38.[63,64] A modified Julia coupling and intra- and intermolecular Horner-Wadsworth-Emmons olefinations were used for construction of the macrolactone and the triene side-chain, respectively. The central subunit **173** was further dissected into aldehyde **175** and ketone **176**, and a (+)-DIPCl promoted asymmetric aldol reaction analogous to that employed in White's synthesis was planned for connection of these fragments. An Evans-Tischenko reduction of a β-hydroxy ketone established the C13 stereochemistry of **173**.

As shown in Scheme 39, Burke's synthesis of the central subunit **173** started from aldehyde **66**. An asymmetric aldol reaction of **66** with the boron enolate of **67** gave **177** with good diastereoselectivity, and this alcohol was converted to aldehyde **175** in three steps and 71% overall yield. The key aldol reaction of **175** with the enolate of methyl ketone **176**, prepared with (+)-chlorodiisopinocampheylborane, afforded a β-hydroxy ketone in 63% yield and a 10:1 diastereomeric ratio favoring the desired isomer **178**.[65] Evans-Tischenko reduction[41] of **178** in the presence of *p*-nitrobenzaldehyde **179** yielded alcohol **180** in which simultaneous formation of the C13 stereocenter and protection of the C15 hydroxyl group as its *p*-nitrobenzoate had occurred. A straightforward three-step sequence converted **180** into the C10–C20 aldehyde **173**.

Burke's synthesis of the C3–C9 subunit **172** is shown in Scheme 40. An aldol reaction of achiral aldehyde **114** with the boron enolate of **115** afforded an alcohol, which was protected as its silyl ether **181**. Ring-closing metathesis gave cyclopentene **183** in good yield,[66] and dihydroxylation of



Scheme 38. Burke's strategy for the total synthesis of rhizoxin D.

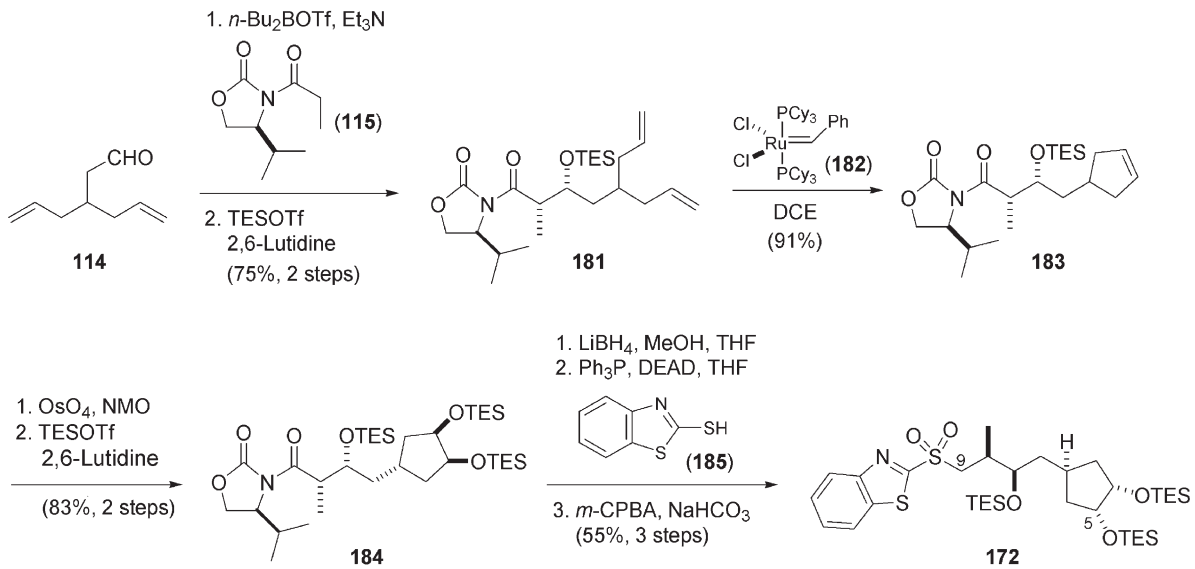


Scheme 39. Burke's synthesis of the C10–C20 segment of rhizoxin D.

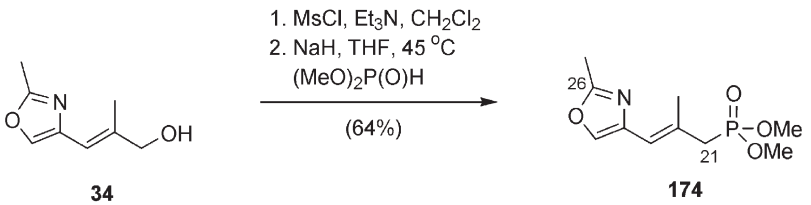
183 produced a *cis* diol, which was protected as the tris triethylsilyl ether **184**. The chiral auxiliary was reductively removed from **184** and the resulting alcohol was converted to sulfone **172** representing the C3–C9 subunit.

Synthesis of the phosphonate **174** corresponding to the C21–C26 subunit is shown in Scheme 41. The known alcohol **34** was mesylated to afford an allylic chloride, which was converted to phosphonate **174** in 64% overall yield.

The coupling of sulfone **172** with aldehyde **173** was performed in a one-pot, modified Julia reaction to give (*E*,*E*)-diene **186** as a single isomer (Scheme 42).[67] Reductive removal of the *p*-nitrobenzoate and esterification of the liberated alcohol with diethylphosphonoacetyl chloride afforded **187**, from which the three triethylsilyl groups were cleaved simultaneously to give a triol. Oxidative cleavage of the *cis* cyclopentan-1,2-diol moiety and oxidation gave aldehyde **188** in a reaction process reminiscent of the Williams[30] and Keck[44] routes to this segment. As in those syntheses, this tactic established the correct C5 configuration by taking advantage of the thermodynamic preference for a diequatorial arrangement



Scheme 40. Burke's synthesis of the C3–C9 subunit.



34 174

Scheme 41. Burke's synthesis of the C21–C26 phosphonate.

of the side-chains attached to the δ-lactone. Aldehyde **188** was subjected to an intramolecular Horner-Wadsworth-Emmons reaction to afford the macrolide **189**.

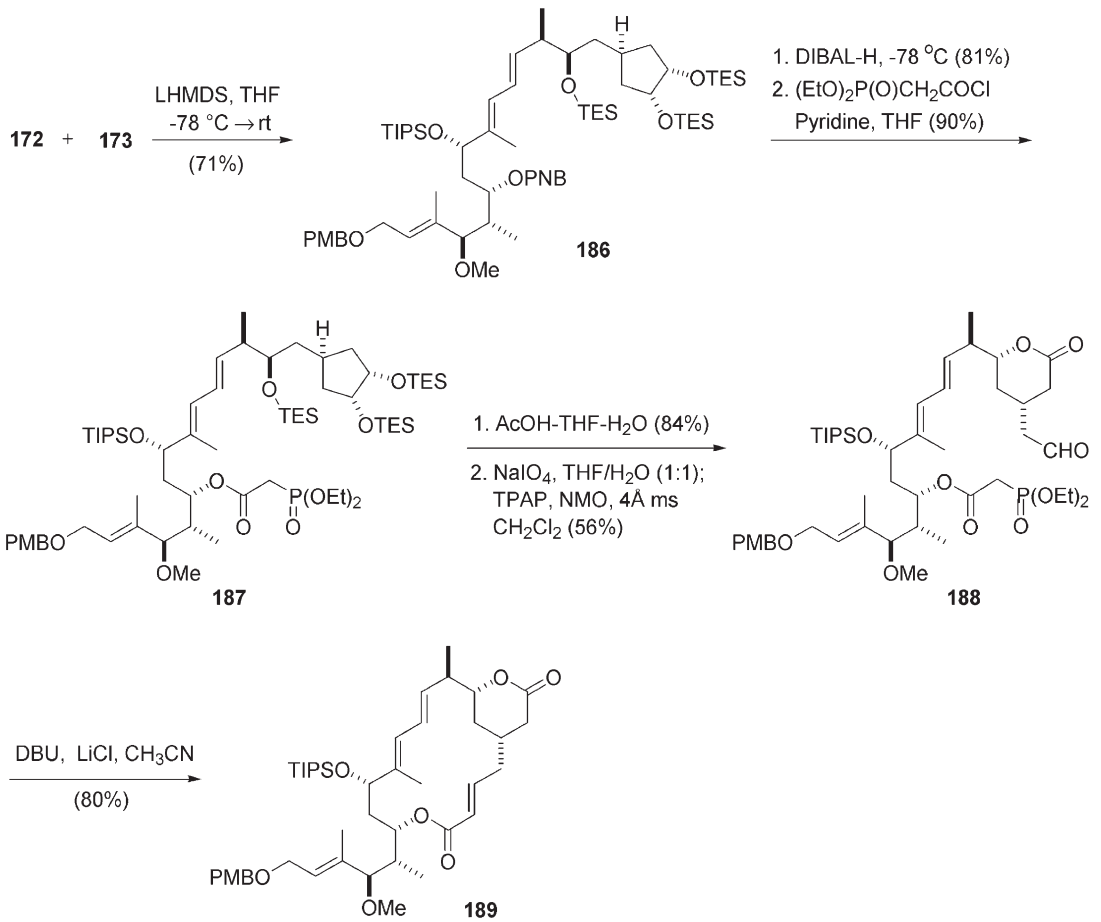
The final stages of Burke's synthesis entailed oxidative cleavage of the *p*-methoxybenzyl ether in **189** followed by allylic oxidation to give aldehyde **190**. A Horner-Emmons reaction of this aldehyde with phosphonate **174** afforded the all (*E*)-triene **191** as a single isomer.[68] Final deprotection of the silyl ether furnished rhizoxin D (Scheme 43).

4.9. Other synthetic studies on rhizoxins

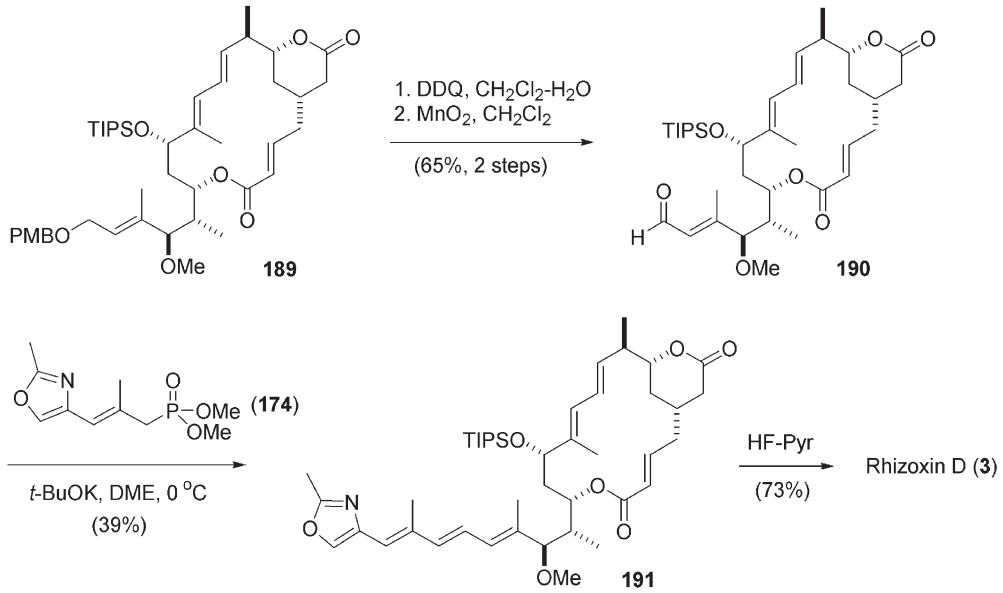
In addition to the completed syntheses of rhizoxin and rhizoxin D described above, several incomplete approaches have been published. Thus, Rama Rao and co-workers have reported their efforts toward a synthesis of rhizoxin[69] in which both the C1–C9 and the C12–C18 segments were constructed using stereoselective intramolecular radical cyclizations as the key steps. Also, Boger and co-workers have described their studies on the synthesis of the C13–C26 subunit of rhizoxin.[70]

5. Clinical prospects

Clinical development of rhizoxin for the treatment of cancer is proceeding at Fujisawa Pharmaceutical Company, and an acylated derivative of rhizoxin is also under investigation as a prodrug by Sankyo in Japan.[71] The prodrug, palmitoyl-rhizoxin (RS-1541), exhibits a much greater binding affinity to low-density lipoproteins (LDL) than rhizoxin. This allows palmitoylrhizoxin to use plasma protein as a carrier into tumor cells, which generally have higher LDL receptor activity. After being taken up by the tumor cell, the prodrug is converted to rhizoxin by lyosomal enzymes such as



Scheme 42. Burke's assembly of the fragments and macrocyclization.



Scheme 43. Burke's completion of the synthesis of rhizoxin D.

cholesterol esterase at the site where the drug can exert its cytotoxic activity. This strategy gives rhizoxin much greater selectivity towards tumor cells.

The isolation and structural elucidation of rhizoxin and its congeners 20 years ago spawned a vigorous effort by many research groups towards the synthesis of this family of natural products. As summarized in this review, several successful routes have been developed which are potentially useful for structure-activity studies of rhizoxins and ultimately for commercial development. Both synthetic organic chemistry and medicinal chemistry have been enriched by these efforts regardless of whether a new clinically useful drug for treatment of human cancers eventually emerges from this work.

References and notes

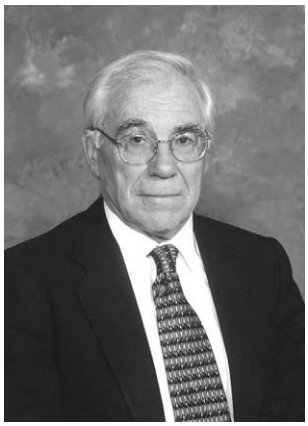
1. For isolation and structure elucidation of rhizoxin and its homologues, see: (a) Iwasaki, S.; Kobayashi, H.; Furukawa, J.; Namikoshi, M.; Okuda, S.; Sato, Z.; Matsuda, I.; Noda, T. *J. Antibiot.* **1984**, *37*, 354–362. (b) Iwasaki, S.; Namikoshi, M.; Kobayashi, H.; Furukawa, J.; Okuda, S. *Chem. Pharm. Bull.* **1986**, *34*, 1387–1390. (c) Kiyoto, S.; Kawai, Y.; Kawakita, T.; Kino, E.; Okuhara, M.; Uchida, I.; Tanaka, H.; Hashimoto, M.; Terano, H.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1986**, *39*, 762–772. (d) Takahashi, M.; Iwasaki, S.; Kobayashi, H.; Okuda, S.; Murai, T.; Sato, Y.; Haraguchi-Hiraoka, T.; Nagano, H. *J. Antibiot.* **1987**, *40*, 66–72.
2. Iwasaki, S.; Namikoshi, M.; Kobayashi, H.; Furukawa, J.; Kuda, S.; Itai, A.; Kasuya, A.; Iitaka, Y.; Sato, Z. *J. Antibiot.* **1986**, *39*, 424–429.
3. Kobayashi, H.; Iwasaki, S.; Yamada, E.; Okuda, S. *Chem. Commun.* **1986**, 1702–1703.
4. Tsuruo, T.; Oh-hara, T.; Iida, H.; Tsukagoshi, S.; Sato, Z.; Matsuda, I.; Iwasaki, S.; Okuda, S.; Shimizu, F.; Sasagawa, K.; Fukami, M.; Fukuda, K.; Arakawa, M. *Cancer Res.* **1986**, *46*, 381–385.
5. For preclinical studies of rhizoxin, see: Hendriks, H. R.; Plowman, J.; Berger, D. P.; Paull, K. D.; Fiebig, H. H.; Fodstad, O.; Dreef-van der Meulen, H. C.; Henrar, R. E. C.; Pinedo, H. M.; Schwartsmann, G. *Ann. Oncol.* **1992**, *3*, 755–763.
6. For phase I clinical trials of rhizoxin, see: (a) Graham, M. A.; Bissett, D.; Setanoians, A.; Hamilton, T.; Kerr, D. J.; Henrar, R.; Kaye, S. B. *J. Nat. Cancer Inst.* **1992**, *84*, 494–500. (b) Bissett, D.; Graham, M. A.; Setanoians, A.; Chadwick, G. A.; Wilson, P.; Koier, I.; Henrar, R.; Schwartsmann, G.; Cassidy, J.; Kaye, S. B.; Kerr, D. J. *Cancer Res.* **1992**, *52*, 2894–2898. (c) Beijnen, J. H.; Flora, K. P.; Halbert, G. W.; Henrar, R. E. C.; Slack, J. A. *Br. J. Cancer* **1995**, *72*, 210–218.
7. For phase II clinical trials of rhizoxin, see: (a) McLeod, H. L.; Murray, L. S.; Wanders, J.; Setanoians, A.; Graham, M. A.; Pavlidis, N.; Heinrich, B.; Huininl, W. W. T.; Wagener, D. J. T.; Aamdal, S.; Verweij, J. *Br. J. Cancer* **1996**, *74*, 1944–1948. (b) Hanauske, A. R.; Catimel, G.; Aamdal, S.; Huinink, W. T.; Paridaens, R.; Pavlidis, N.; Kaye, S. B.; Tevelde, A.; Wanders, J.; Verweij, J. *Br. J. Cancer* **1996**, *73*, 397–399. (c) Verweij, J.; Wanders, J.; Gil, J.; Schoffski, P.; Catimel, G.; Tevelde, A.; Demulder, P. H. M. *Br. J. Cancer* **1996**, *73*, 400–402. (d) Kaplan, S.; Hanauske, A. R.; Pavlidis, N.; Bruntsch, U.; Teveld, A.; Wanders, J.; Heinrich, B.; Verweij, J. *Br. J. Cancer* **1996**, *73*, 403–405. (e) Kerr, D. J.; Rustin, G. J.; Kaye, S. B.; Selby, P.; Bleehen, N. M.; Harper, P.; Brampton, M. H. *Br. J. Cancer* **1995**, *72*, 1267–1269.
8. Tolcher, A. W.; Aylesworth, C.; Rizzo, J.; Izbicka, E.; Campbell, E.; Kuhn, J.; Weiss, G.; Von Hoff, D. D.; Rowinsky, E. K. *Ann. Oncol.* **2000**, *11*, 333–338.
9. Hamel, E. *Pharmacol. Ther.* **1992**, *55*, 31–51.
10. For rhizoxin binding studies, see: (a) Tsuruo, T.; Oh-hara, T.; Iida, H.; Tsukagoshi, S.; Sato, Z.; Matsuda, I.; Iwasaki, S.; Okuda, S.; Shimizu, F.; Sasagawa, K.; Fukami, M.; Fukuda, K.; Arakawa, M. *Cancer Res.* **1986**, *46*, 381–385. (b) Takahashi, M.; Iwasaki, S.; Kobayashi, H.; Okuda, S.; Murai, T.; Sato, Y. *Biochim. Biophys. Acta* **1987**, *926*, 215–223. (c) Sullivan, A. S.; Prasad, V.; Roach, M. C.; Takahashi, M.; Iwasaki, S.; Luduena, R. F. *Cancer Res.* **1990**, *50*, 4277–4280.

11. Hamel, E. *Med. Res. Rev.* **1996**, *16*, 207–231.
12. Jordan, A.; Hadfield, J. A.; Lawrence, N. J.; McGown, A. T. *Med. Res. Rev.* **1998**, *18*, 259–296.
13. Gupta, S.; Bhattacharyya, B. *Mol. Cell. Biochem.* **2003**, *253*(1–2), 41–47.
14. (a) Iwasaki, S. *Med. Res. Rev.* **1993**, *13*, 183–198. (b) Hamel, E. *Pharmacol. Ther.* **1992**, *55*, 31–51. (c) Kato, Y.; Ogawa, Y.; Imada, T.; Iwasaki, S.; Shimazaki, N.; Kobayashi, T.; Komai, T. *J. Antibiot.* **1991**, *44*, 66–75.
15. (a) Li, Y.; Kobayashi, H.; Hashimoto, Y.; Iwasaki, S. *Biochem. Biophys. Res. Commun.* **1992**, *187*(2), 722–729. (b) Takahashi, M.; Matsumoto, S.; Iwasaki, S.; Yahara, I. *Mol. Gen. Genet.* **1990**, *222*(2–3), 169–175.
16. (a) Nakada, M.; Kobayashi, S.; Iwasaki, S.; Ohno, M. *Tetrahedron Lett.* **1993**, *34*, 1035–1038. (b) Nakada, M.; Kobayashi, S.; Shibasaki, M.; Iwasaki, S.; Ohno, M. *Tetrahedron Lett.* **1993**, *34*, 1039–1042. (c) Nakada, M. *J. Pharm. Soc. Jpn* **1997**, *117*, 486–508.
17. Nakada, M.; Kobayashi, S.; Ohno, M.; Iwasaki, S.; Okuda, S. *Tetrahedron Lett.* **1988**, *29*, 3951–3954.
18. Still, W. C.; Darst, K. P. *J. Am. Chem. Soc.* **1980**, *102*, 7385–7387.
19. Nakata, T.; Oishi, T. *Tetrahedron Lett.* **1980**, *21*, 1641–1644.
20. Midland, M. M.; Kwon, Y. C. *J. Am. Chem. Soc.* **1983**, *105*, 3725–3727.
21. Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560–3578.
22. Park, P. U.; Broka, C. A.; Johnson, B. F.; Kishi, Y. *J. Am. Chem. Soc.* **1987**, *109*, 6205–6207.
23. Stork, G.; Nakamura, E. *J. Org. Chem.* **1979**, *44*, 4010–4011.
24. Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136–6137.
25. Kende, A. S.; Blass, B. E.; Henry, J. R. *Tetrahedron Lett.* **1995**, *36*, 4741–4744.
26. (a) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129. (b) Gage, J. R.; Evans, D. A. *Org. Synth.* **1990**, *68*, 77–82.
27. Samokhvalov, G. I.; Vakulova, L. A.; Mairanovski, S. G.; Luk'yanova, L. V. *Zh. Obshch. Khim.* **1959**, *29*, 1936–1945.
28. Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408–7410.
29. Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfield, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183–2186.
30. (a) Williams, D. R.; Werner, K. M.; Feng, B. *Tetrahedron Lett.* **1997**, *38*, 6825–6828. (b) Williams, D. R.; Werner, K. M.; Feng, B. *211th ACS National Meeting*, New Orleans, March 24–28; 1996; Meeting Abstract ORGN 442.
31. McMurry, J. E.; Dushin, R. G. *J. Am. Chem. Soc.* **1990**, *112*, 6942–6949.
32. Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2024–2032, and references cited therein.
33. Fina, J. M.; Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 2719–2722.
34. Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639–666.
35. (a) Lafontaine, J. A.; Leahy, J. W. *Tetrahedron Lett.* **1995**, *36*, 6029–6032. (b) Provencal, D. P.; Gardelli, C.; Lafontaine, J. A.; Leahy, J. W. *Tetrahedron Lett.* **1995**, *36*, 6033–6036. (c) Lafontaine, J. A.; Provencal, D. P.; Leahy, J. W. *213th ACS National Meeting*, San Francisco, April 13–17; 1997; Meeting Abstract ORGN 625.
36. (a) Lafontaine, J. A.; Provencal, D. P.; Gardelli, C.; Leahy, J. W. *Tetrahedron Lett.* **1999**, *40*, 4145–4148. (b) Lafontaine, J. A.; Provencal, D. P.; Gardelli, C.; Leahy, J. W. *J. Org. Chem.* **2003**, *68*, 4215–4234.
37. Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780.
38. Abiko, A.; Liu, J.; Masamune, S. *J. Am. Chem. Soc.* **1997**, *119*, 2586–2587.
39. Paterson, I.; Yeung, K.; Smaill, J. B. *Synlett* **1993**, 774–776.
40. Pilcher, A. S.; DeShong, P. *J. Org. Chem.* **1993**, *58*, 5130–5134.
41. Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447–6449.
42. Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Tetrahedron Lett.* **1991**, *32*, 1175–1178.
43. Keck, G. E.; Wager, C. A.; Wager, T.; Savin, K. A.; Covel, J. A.; McLaws, M. D.; Krishnamurthy, D.; Cee, V. J. *Angew. Chem. Int. Ed.* **2001**, *40*, 231–234.
44. (a) Keck, G. E.; Park, M.; Krishnamurthy, D. *J. Org. Chem.* **1993**, *58*, 3787–3788. (b) Keck, G. E.; Savin, K. A.; Weglarz, M. A.; Cressman, E. N. K. *Tetrahedron Lett.* **1996**, *37*, 3291–3294. (c) Keck, G. E.; Krishnamurthy, D.; Savin, K. A.; Cee, V. J. *213th ACS National Meeting*, San Francisco, April 13–17, 1997; Meeting Abstract ORGN 559.
45. Keck, G. E.; Savin, K. A.; Weglarz, M. A. *J. Org. Chem.* **1995**, *60*, 3194–3204.
46. (a) Keck, G. E.; Tarbet, H. K.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467–8468. (b) Keck, G. E.; Krishnamurthy, D.; Grier, M. C. *J. Org. Chem.* **1993**, *58*, 6543–6544. (c) Keck, G. E.; Krishnamurthy, D. *Org. Synth.* **1998**, *75*, 12–18.
47. Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215–8216.
48. Keck, G. E.; Wager, C. A. *Org. Lett.* **2000**, *2*, 2307–2309.
49. Mitchell, I. S.; Pattenden, G.; Stonehouse, J. P. *Tetrahedron Lett.* **2002**, *43*, 493–497.
50. Evans, D. A.; Allison, B. D.; Yang, M. G. *Tetrahedron Lett.* **1999**, *40*, 4457–4460.
51. Seyforth, D.; Marmor, R. S.; Hilbert, P. *J. Org. Chem.* **1978**, *43*, 1011–1013.
52. (a) Boden, C. D. J.; Pattenden, G.; Ye, T. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2417–2419. (b) Zhang, H. X.; Guibe, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857–1867.
53. Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585–9595.
54. (a) Green, N. J.; White, J. D. *207th ACS National Meeting*, San Diego, March 13–17; 1994; Meeting Abstract ORGN 169. (b) Green, N. J.; Holoboski, M.; White, J. D. *213th ACS National Meeting*, San Francisco, April 13–17; 1997; Meeting Abstract ORGN 402. (c) White, J. D.; Nylund, C. S.; Green, N. J. *Tetrahedron Lett.* **1997**, *38*, 7329–7332. (d) White, J. D.; Holoboski, M. A.; Green, N. J. *Tetrahedron Lett.* **1997**, *38*, 7333–7336.
55. White, J. D.; Blakemore, P. R.; Green, N. J.; Hauser, E. B.; Holoboski, M. A.; Keown, K. E.; Nylund Kolz, C. S.; Phillips, B. W. *J. Org. Chem.* **2002**, *67*, 7750–7760.
56. Keck, G. E.; Park, M.; Krishnamurthy, D. *J. Org. Chem.* **1993**, *58*, 3787–3788.
57. Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1983**, *105*, 6765–6766.
58. Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405–4408.
59. Negishi, E.; Van Horn, D. E.; King, A. O.; Okukado, N. *Synthesis* **1979**, 501–502.
60. Paterson, I.; Goodman, J. M.; Lister, M. A.; Schumann, R. C.;

McClure, C. K.; Norcross, R. D. *Tetrahedron* **1990**, *46*, 4663–4684.
61. Scheidt, K. A.; Chen, H.; Follows, B. C.; Chemler, S. R.; Coffey, D. S.; Roush, W. R. *J. Org. Chem.* **1998**, *63*, 6436–6437.
62. Farina, V.; Krishnamurthy, V.; Scott, W. *J. Org. React.* **1997**, *50*, 1–652.
63. (a) Hong, J.; Burke, S. D. *213th ACS National Meeting*, San Francisco, April 13–17; 1997; Meeting Abstract ORGN 560. (b) Burke, S. D.; Hong, J.; Mongin, A. P. *Tetrahedron Lett.* **1998**, *39*, 2239–2242. (c) Burke, S. D.; Hong, J.; Lennox, J. R.; Mongin, A. P. *J. Org. Chem.* **1998**, *63*, 6952–6967.
64. (a) Jiang, Y.; Burke, S. D.; Hong, J. *38th National Organic Chemistry Symposium*, Bloomington, June 8–12; 2003; Meeting Abstract 95. (b) Burke, S. D.; Jiang, Y.; Hong, J. *Org. Lett.* **2004**, *6*, 1445–1448.
65. Paterson, I.; Goodman, J. M. *Tetrahedron Lett.* **1989**, *30*, 997–1000.
66. (a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **1995**, *34*, 2039–2041. (b) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100–110.
67. Bellingham, R.; Jarowiski, K.; Kocienski, P.; Martin, V. *Synthesis* **1996**, 285–296.
68. Roush, W. R.; Peseckis, S. M. *Tetrahedron Lett.* **1982**, *23*, 4879–4882.
69. (a) Rama Rao, A. V.; Bhanu, M. N.; Sharma, G. V. M. *Tetrahedron Lett.* **1993**, *34*, 707–710. (b) Rama Rao, A. V.; Sharma, G. V. M.; Bhanu, M. N. *Tetrahedron Lett.* **1992**, *33*, 3907–3910.
70. Boger, D. L.; Curran, T. T. *J. Org. Chem.* **1992**, *57*, 2235–2244.
71. (a) Kurihara, A.; Shibayama, Y.; Mizota, A.; Yasurno, A.; Ikeda, M.; Sasagawa, K.; Kobayashi, T.; Hisaoka, M. *Biol. Pharm. Bull.* **1996**, *19*, 252–258. (b) Kobayashi, T.; Sasagawa, K.; Shimizu, M.; Shimazaki, N.; Kamogari, M.; Kaneko, M.; Nishimura, T.; Tsuruo, T.; Tsukagoshi, S. *J. Cancer Res. Clin. Oncol.* **1990**, *116*(Suppl. 1), 445.

Biographical sketch

Jian Hong was born in Changchun, People's Republic of China. He received his BS degree in Chemistry from Peking University (1989), his MS degree from the University of Virginia (1992), and his PhD degree in Organic Chemistry at University of Wisconsin-Madison (1997) under the guidance of Prof. Steven D. Burke. After postdoctoral research with Prof. James D. White at Oregon State University (1997–1999), he joined Lilly Research Laboratories as a Senior Research Chemist. His research interests include asymmetric synthesis, natural products, and small molecule drug discovery.



James D. White was born in Bristol, England, and received his undergraduate education at Queens' College, Cambridge University (BA, 1959), after National Service in the Royal Air Force. He emigrated first to Canada, taking an MSc degree at the University of British Columbia under Prof. Raymond Bonnett (1961), and then to the United States where he received a PhD from MIT (1965) under Professor George Büchi. He began his independent academic as an Instructor at Harvard University, then moved to Oregon State University in 1971 where he is currently Emeritus Distinguished Professor. His research interests have centered around the development of new strategies for complex synthesis, with emphasis placed on the total synthesis of natural products of the terpenoid, alkaloid, and macrolide families. Of particular interest have been synthetic strategies which imitate biogenetic pathways, those which employ photochemistry in novel ways, and those which lead to complex target structures through the use of new design elements such as rearrangements, fragmentations, or ring constructions.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 5683–5693
Tetrahedron

Substituent effect on the diastereoselectivity in the chelation-controlled radical reactions of γ-(*p*-substituted-benzyloxy)-α-methylene esters with alkyl iodides

Tomoko Yajima, Kyoko Okada and Hajime Nagano*

Department of Chemistry, Faculty of Science, Ochanomizu University, Otsuka, Bunkyo-ku, Tokyo 112-8610, Japan

Received 23 April 2004; revised 12 May 2004; accepted 13 May 2004

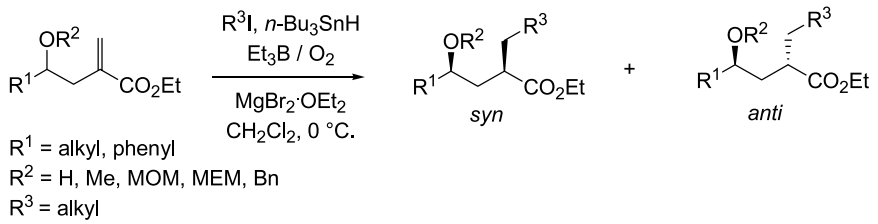
Abstract—A pronounced substituent effect on the diastereoselectivity in the chelation controlled radical reactions of ethyl γ-(*p*-substituted-benzyloxy)-α-methylenecarboxylates with alkyl iodides was observed. The *syn*-selectivity increased in the order of electron-donating ability NO_2<CN<CF_3<F<H<*i*-Pr, Me, OMe of the *p*-substituent, and the plot of the log(*syn*/*anti*) versus Hammett sigma constants gave a linear correlation. The complexation experiments of the substrates with Lewis acid using ^{1}H NMR spectroscopy and the competition experiments between *p*-isopropylbenzyloxy and *p*-trifluoromethylbenzyloxy esters showed that the electron-donating *p*-isopropyl group stabilized the seven-membered chelate ring to give high *syn*-selectivity.

1. Introduction

During the past decade the stereochemical control of acyclic radical reactions has received considerable attention and significant levels of diastereoselectivity in reactions involving stereogenic center adjacent to the radical center (1,2-asymmetric induction) have been achieved.[1] The use of mono- or bidentate Lewis acids expanded the scope of the stereoselective reactions.[2] However, to our knowledge, little is known about radical mediated 1,3-asymmetric induction.[3]

We have recently reported the chelation-controlled 1,3-asymmetric induction in the radical mediated additions to α-methylene-γ-oxycarboxylic acid esters (Scheme 1).[4] The radical reactions of γ-benzyloxy esters (R^2=Bn) with alkyl iodides performed in the presence of $MgBr_2{\cdot}OEt_2$ showed higher *syn*-selectivities compared to those of the corresponding γ-hydroxy, γ-methoxy, γ-methoxymethoxy and γ-methoxyethoxy esters (R^2=H, Me, MOM, MEM). Based on the conformational analysis of the radical intermediates obtained by combining CONFLEX and PM3 calculations,[5] we have revealed that the high *syn*-selectivity is referred to the H-atom transfer to the outside face of radical center in the sharply folded seven-membered chelate intermediates.[4c,d,6,7] In order to realize much higher diastereoselectivity in the radical reactions of γ-benzyloxy esters, we investigated the effect of *p*-substituent on the γ-benzyloxy group.

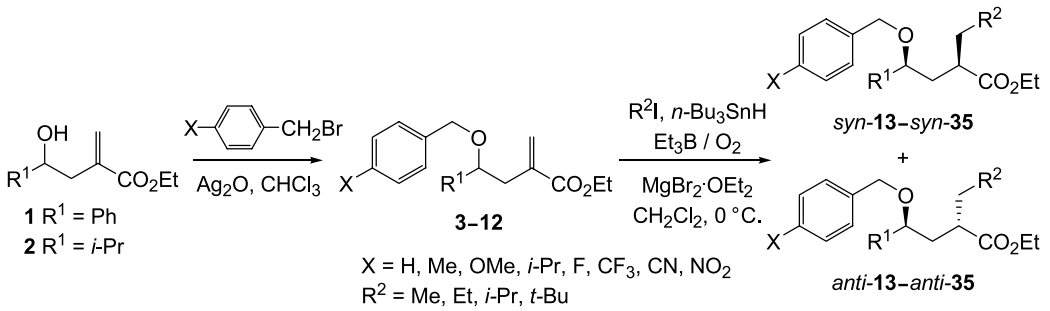
We report herein the substituent effect on the diastereoselectivity in the chelation controlled alkyl radical addition to γ-(*p*-substituted-benzyloxy)-α-methylenecarboxylic acid esters **3**–**12**. This work also includes experimental evidence for the origin of the substituent effect.



Scheme 1. Radical reactions of ethyl α-methylene-γ-oxycarboxylates with alkyl iodides.

Keywords: Radical reaction; 1,3-Asymmetric induction; Substituent effect; Seven-membered chelation.
* Corresponding author. Tel.: +81-3-5978-5348; fax: +81-3-5978-5715; e-mail address: nagano@cc.ocha.ac.jp

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.05.020



Scheme 2.

2. Results and discussion

The results of the radical reactions of γ-(*p*-substituted-benzyloxy)-α-methylene esters **3**–**12**, which were prepared by the benzylation of alcohols **1**[4a] and **2**[4b] with *p*-substituted benzyl bromides (Scheme 2), are shown in Table 1. All the reactions gave good yields except for the reaction of *p*-nitrobenzyloxy ester **3** (entry 1) and the diastereoselectivities were strongly affected by the benzyloxy substituents. In the reactions with isopropyl iodide, the *syn*-selectivity increased in the order of electron-donating ability NO_2<CN<CF_3<F<H<*i*-Pr, Me, OMe of the *p*-substituent (entries 1–8). The plot of the log(*syn*/*anti*) versus Hammett sigma constants[8,9] gave a linear correlation (r^2=0.94) with a negative slope ρ=−1.06 (Fig. 1). A similar tendency was observed in the reactions with ethyl iodide (entries 9–15) and the Hammett plot also showed a linear correlation (r^2=0.92, ρ=−1.00). Furthermore, in the reactions with methyl and *tert*-butyl radicals, the introduction of an electron-donating methyl group at the *p*-position enhanced *syn*-selectivities, however the increment of selectivity in the *tert*-butyl radical additions was smaller than those in the reaction with methyl, ethyl and isopropyl radicals (entries 16–19). The reactions of aliphatic substrate **12** with isopropyl and *tert*-butyl iodides showed that *p*-methyl substituent enhanced the *syn*-selectivities (entries 20–23). The lower *syn*-selectivity in the addition of methyl radical (entries 16 and 17) compared to the diastereoselectivities of the corresponding reactions with isopropyl and ethyl radicals (entries 5, 7, 12 and 14) has been explained by the conformational analysis of the seven-membered chelate intermediate, in which the ethoxy group of ester moiety with *E*-geometry shields the outside face of radical center.[4d,10] In the addition of *tert*-butyl radical (entries 18, 19, 22 and 23), however, the neopentyl group shields the outside face of radical center and consequently lowers the *syn*-selectivity.[4d,10]

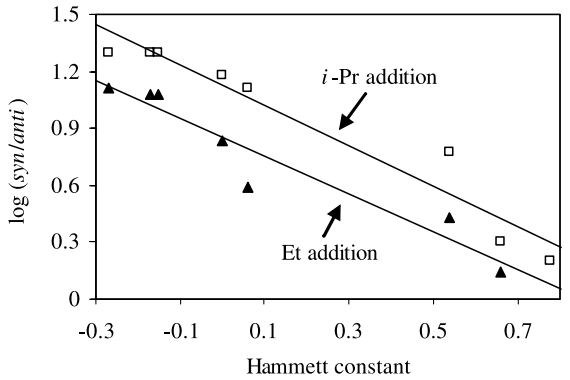


Figure 1. Plot of log(*syn*/*anti*) values versus Hammett sigma constants for the ethyl and isopropyl radical additions to **3**–**10**.

Table 1. Radical reactions of **3**–**12** with alkyl iodides R^2I in the presence of $MgBr_2{\cdot}OEt_2$[a]

Entry	Substrate	R^1	X	R^2	Product	Yield (%)	*syn*/*anti*[b]
1	**3**	Ph	NO_2	*i*-Pr	**13**	36	1.6:1
2	**4**	Ph	CN	*i*-Pr	**14**	84	2.0:1
3	**5**	Ph	CF_3	*i*-Pr	**15**	85	6.0:1
4	**6**	Ph	F	*i*-Pr	**16**	87	13:1
5[c]	**7**	Ph	H	*i*-Pr	**17**	86	15:1
6	**8**	Ph	*i*-Pr	*i*-Pr	**18**	94	>20:1
7	**9**	Ph	Me	*i*-Pr	**19**	86	>20:1
8	**10**	Ph	OMe	*i*-Pr	**20**	67	>20:1
9	**4**	Ph	CN	Et	**21**	63	1.4:1
10	**5**	Ph	CF_3	Et	**22**	97	2.7:1
11	**6**	Ph	F	Et	**23**	85	3.9:1
12	**7**	Ph	H	Et	**24**	82	6.8:1
13	**8**	Ph	*i*-Pr	Et	**25**	94	12:1
14	**9**	Ph	Me	Et	**26**	77	12:1
15	**10**	Ph	OMe	Et	**27**	63	13:1
16	**7**	Ph	H	Me	**28**	71	3.0:1
17	**9**	Ph	Me	Me	**29**	71	5.0:1
18	**7**	Ph	H	*t*-Bu	**30**	85	3.6:1
19	**9**	Ph	Me	*t*-Bu	**31**	77	4.0:1
20	**11**	*i*-Pr	H	*i*-Pr	**32**	75	11:1
21	**12**	*i*-Pr	Me	*i*-Pr	**33**	71	>20:1
22	**11**	*i*-Pr	H	*t*-Bu	**34**	67	3.7:1
23	**12**	*i*-Pr	Me	*t*-Bu	**35**	78	5.0:1

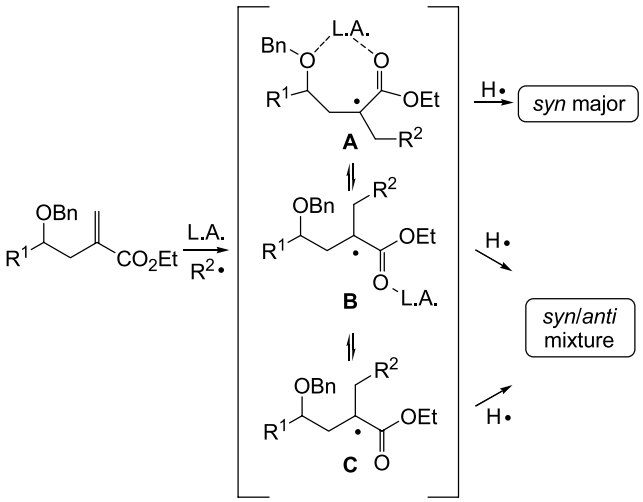
Reaction conditions: R^2I (3 equiv.), *n*-Bu_3SnH (2 equiv.), Et_3B (1 equiv.), $MgBr_2{\cdot}OEt_2$ (3 equiv.), CH_2Cl_2, 0 °C.

[a] For entries 5 and 18, see Ref. 4d; for entries 20 and 22, see Ref. 4e.

[b] The stereochemistries of the products **13**–**16**, **18**–**29** and **31** were determined by comparing their chemical shift values with those of **17** and **30**.[4d] The stereochemistries of the products **33** and **35** were determined by comparing their chemical shift values with those of **32** and **34**.[4e]

[c] Without Lewis acid, 35% yield and diastereomer ratio *syn*/*anti*=1:1.2. Use of $BF_3{\cdot}OEt_2$ (1 equiv.) instead of $MgBr_2{\cdot}OEt_2$ gave 82% yield and diastereomer ratio *syn*/*anti*=1.2:1.

The reactions would proceed through complexed radical intermediates **A** and **B** and non-complexed radical intermediate **C** being in equilibrium (Scheme 3). The seven-membered chelate intermediate **A** gives *syn*-product predominantly,[4d] while the intermediate **B** formed by monodentate coordination to the carbonyl oxygen atom and non-chelation intermediate **C** give *syn*/*anti* mixtures without stereoselectivity. The electron-donating substituents, *i*-Pr, Me and OMe, stabilize the seven-membered chelate ring and give a large population of chelate intermediate **A**. The *p*-substituents remote from the chelate ring would not affect the ring structure of intermediate **A**.



Scheme 3. Reaction pathways.

In order to gain insight into the chelate ring stability, we carried out complexation experiments of substrates **5**–**10** with $MgBr_2{\cdot}OEt_2$ using ^1H NMR spectroscopy.[11] The complexation of the substrate with 3 equiv. of $MgBr_2{\cdot}OEt_2$ in $CDCl_3$ was achieved by sonication at room temperature for 1 h.[4d] The $\Delta\delta$ values [δ_H(substrate+$MgBr_2{\cdot}OEt_2$)−δ_H(substrate)] of **5**–**10** are shown in Table 2. The chemical shift increments $\Delta\delta$ by adding the Lewis acid and in particular, the large difference of chemical shift increments between the diastereotopic β-methylene protons suggest the formation of bidentate complex. Figure 2 shows a plot of log(*syn*/*anti*) values in the ethyl and isopropyl radical additions to **5**–**10** versus $\Delta\delta$ values of one of the benzyl protons affording larger one. The increase of $\Delta\delta$ values with increasing the electron-donating ability CF_3<F<H<*i*-Pr, Me, OMe of the *p*-substituent suggests that the population of the chelate intermediates increases in the order.

Furthermore, we investigated the competition reactions of the substrates **5** and **8** bearing an electron-withdrawing trifluoromethyl group and an electron-donating isopropyl group, respectively (Scheme 4). The competition reactions

Table 2. ^1H NMR spectral data of **5**–**10** complexed with $MgBr_2{\cdot}OEt_2$

Entry	Substrate	Δδ values (ppm)			
	(X)	Bn	β-H	γ-H	Olefin
1	**5** (CF_3)	0.09 0.01	0.05 0.01	0.01	0.09 0.06
2	**6** (F)	0.20 0.01	0.15 0.02	0.01	0.18 0.15
3	**7** (H)	0.50 0.01	0.33 0.03	0.00	0.26 0.21
4	**8** (*i*-Pr)	0.56 0.02	0.34 0.05	0.22	0.22 0.19
5	**9** (Me)	0.62 0.02	0.38 0.09	0.25	0.25 0.21
6	**10** (OMe)	0.62 0.03	0.34 0.07	0.03	0.21 0.16

Δδ values: [δ_H(substrate+$MgBr_2{\cdot}OEt_2$)−δ_H(substrate)].

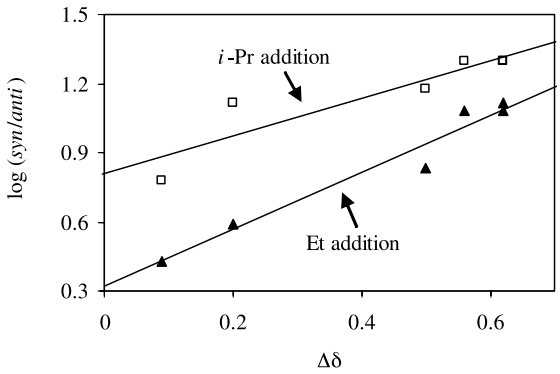


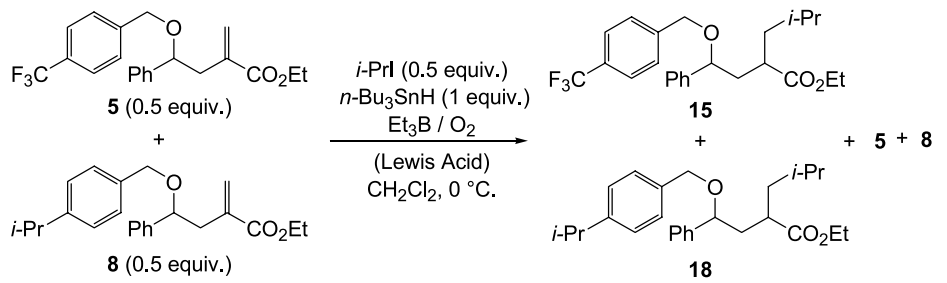
Figure 2. Plot of log(*syn*/*anti*) versus $\Delta\delta$ values [δ_H(substrate+$MgBr_2{\cdot}OEt_2$)−δ_H(substrate)] of benzyl proton for the ethyl and isopropyl radical additions to **5**–**10**.

of **5** (0.5 equiv.) and **8** (0.5 equiv.) with isopropyl iodide (0.5 equiv.), *n*-Bu_3SnH (1 equiv.) and Et_3B (1 equiv.) were carried out in the presence of Lewis acid, $MgBr_2{\cdot}OEt_2$ (3 equiv.) or $BF_3{\cdot}OEt_2$ (1 equiv.), and in the absence of Lewis acid. The unreacted substrates **5** and **8** were recovered and their ratios were obtained by integrating ^1H NMR signals. The substrates **5** and **8** showed equal reactivity in the absence of Lewis acid. The complexation with Lewis acids would lower the LUMO energy of the substrates and enhance the rate of the nucleophilic alkyl radical addition reactions.[12] Monodentate Lewis acid, $BF_3{\cdot}OEt_2$, coordinating to the carbonyl oxygen of the substrates **5** and **8**, enhanced the reactivity of both the substrates equally, but did not affect their diastereoselectivities (see, footnote c in Table 1). In the presence of $MgBr_2{\cdot}OEt_2$, however, substrate **8** reacted faster than **5**. The higher reactivity and higher *syn*-selectivity as well (Table 1, entries 3 and 6) of **8** represent the more efficient chelation of the *p*-isopropylbenzyloxy group with $MgBr_2{\cdot}OEt_2$ compared to *p*-trifluoromethylbenzyloxy group.

Finally, we compared the substituent effects with those of the chelation-controlled radical reactions of β-benzyloxy-α-methylene esters **36** and **37** derived from the corresponding Baylis–Hillman adducts (Scheme 5).[1,13] The isopropyl radical addition to β-benzyloxy-α-methylene ester **36** and *p*-methylbenzyloxy ester **37**[14] in the presence of $MgBr_2{\cdot}OEt_2$ performed at −78 °C gave **38** and **39** in good yields with *syn*-selectivities. Similarly to the reaction of **7** and **9** (Table 1, entries 5 and 7), the *syn*-selectivity of **37** was also higher than that of **36**. However, the reactions of **36** and **37** at 0 °C gave no substituent effect.

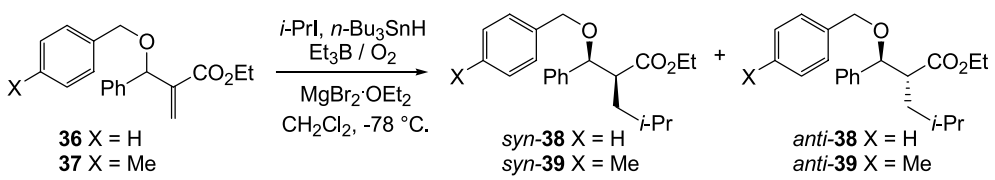
3. Conclusion

In summary, we have shown the substituent effect on chelation-controlled 1,3-asymmetric induction in the reactions of γ-(*p*-substituted-benzyloxy)-α-methylene esters with alkyl iodides. The *syn*-selectivity increased in the order of electron-donating ability NO_2<CN<CF_3<F<H<*i*-Pr, Me, OMe of the *p*-substituent, and the plot of log(*syn*/*anti*) versus Hammett sigma constants gave a linear correlation. The electron-donating substituents *i*-Pr, Me and OMe, stabilize the seven-membered chelate rings and yield *syn*-products predominantly.



	unreacted substrates 5 : 8
without Lewis Acid	1 : 1.1
with $BF_3{\cdot}OEt_2$	1.1 : 1
with $MgBr_2{\cdot}OEt_2$	1.7 : 1

Scheme 4. Competitive radical reactions of **5** and **8** with isopropyl iodide.



	yield (%)	*syn*	:	*anti*
X = H	88	4.6	:	1
X = Me	95	5.6	:	1

Scheme 5. Radical reactions of **36** and **37** with isopropyl iodide in the presence of $MgBr_2{\cdot}OEt_2$.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded on a JEOL GSX-270 (270 MHz) or GSX-400 (400 MHz) spectrometer with $CDCl_3$ as the solvent and tetramethylsilane as an internal standard. ^{13}C NMR spectra were recorded on the instruments operating at 67.9 or 100.5 MHz with $CDCl_3$ as the solvent and internal standard (δ 77.0). IR spectra were taken on a SHIMADZU FTIR-8700 spectrometer. Mass spectra (EI^+) were obtained on a JEOL JMS-700 mass spectrometer. Precoated Merck Kieselgel 60 F_{254} and Kanto silica gel 60 (spherical neutral) were used for thin layer chromatography and flash chromatography, respectively.

4.2. Preparation of the substrates 3–6, 8–10, 12, 36 and 37

Substrates **3**–**6** and **8**–**10** were prepared from **1** and *p*-nitrobenzyl bromide, *p*-cyanobenzyl bromide, *p*-trifluoromethylbenzyl bromide, *p*-fluorobenzyl bromide, *p*-isopropylbenzyl bromide, *p*-methylbenzyl bromide and *p*-methoxybenzyl bromide, respectively, following the procedures reported previously.[4c] Substrate **12** was prepared from **2** and *p*-methylbenzyl bromide following the procedures reported previously.[4d] Treatment of ethyl 2-(hydroxyphenylmethyl)propenoate with benzyl trichloroacetimidate and *p*-methylbenzyl trichloroacetimidate gave **36** and **37**, respectively.[14]

4.2.1. Ethyl 2-[2-(*p*-nitrobenzyloxy)-2-phenylethyl]propenoate 3. ^{1}H NMR (270 MHz) δ 8.16 (2H, d, J=8.9 Hz, *p*-$NO_2C_6H_2H_2$), 7.43 (2H, d, J=8.9 Hz, *p*-$NO_2C_6H_2H_2$), 7.32 (5H, m, Ph), 6.20 (1H, d, J=1.4 Hz, =C*H*H), 5.54 (1H, d, J=1.4 Hz, =CH*H*), 4.58 (1H, dd, J=8.1, 5.1 Hz, CH), 4.53 (1H, d, J=13.5 Hz, C*H*HPh), 4.37 (1H, d, J=13.5 Hz, CH*H*Ph), 4.16 (2H, q, J=7.0 Hz, $CO_2CH_2CH_3$), 2.87 (1H, ddd, J=14.0, 8.4, 1.1 Hz, CHC*H*H), 2.71 (1H, ddd, J=14.0, 5.4, 1.1 Hz, CHCH*H*), 1.28 (3H, t, J=7.0 Hz, $CO_2CH_2CH_3$); ^{13}C NMR (67.5 MHz) δ 166.8, 147.0, 146.1, 141.0, 136.8, 128.5, 127.9, 127.6, 127.5, 126.6, 123.4, 80.7, 69.3, 60.7, 41.2, 14.3; IR (neat) 2978, 2881, 2348, 1718, 1521, 1346, 1194, 1149, 1077, 855, 739, 702 cm^{-1}; MS *m*/*z* 310 (M^+−OEt, 1%), 242 (67), 173 (15), 167 (21), 136 (100), 129 (19), 105 (30), 91 (49); HRMS calcd for $C_{18}H_{16}NO_4$ [M^+−OEt] 310.1080, found 310.1101.

4.2.2. Ethyl 2-[2-(*p*-cyanobenzyloxy)-2-phenylethyl]propenoate 4. ^{1}H NMR (400 MHz) δ 7.60 (2H, d, J=8.1 Hz, *p*-$NCC_6H_2H_2$), 7.37 (2H, d, J=8.1 Hz, *p*-$NCC_6H_2H_2$), 7.30 (5H, m, Ph), 6.19 (1H, d, J=1.6 Hz, =C*H*H), 5.53 (1H, d, J=1.6 Hz, =CH*H*), 4.55 (1H, dd, J=8.4, 5.1 Hz, CH), 4.48 (1H, d, J=13.0 Hz, *p*-NCC_6H_4CHH), 4.32 (1H, d, J=13.0 Hz, *p*-NCC_6H_4CHH), 4.16 (2H, q, J=7.0 Hz, $CO_2CH_2CH_3$), 2.85 (1H, dd, J=14.0, 8.4 Hz, CHC*H*H), 2.69 (1H, dd, J=14.0, 5.1 Hz, CHCH*H*), 1.27 (3H, t, J=7.0 Hz, $CO_2CH_2CH_3$); ^{13}C NMR (100 MHz) δ 166.8, 144.0, 141.0, 133.3, 132.3, 131.9, 129.6, 128.4, 128.1, 127.5, 126.6, 111.0, 80.6, 69.5, 60.7, 41.1, 14.3; IR (neat) 2911, 2870, 2229, 1704, 1601, 1448, 1270, 1071, 1027, 950, 821, 703 cm^{-1}; MS *m*/*z* 290 (M^+−OEt, 4%), 223 (49), 219 (21), 173 (48), 129 (35), 116 (100), 105 (85), 91 (25); HRMS calcd for $C_{19}H_{16}NO_2$ [M^+−OEt] 290.1181, found 290.1176.

4.2.3. Ethyl 2-[2-(*p*-trifluoromethylbenzyloxy)-2-phenylethyl]propenoate 5. ^{1}H NMR (270 MHz) δ 7.55 (2H, d, J=8.1 Hz, p-$CF_3C_6H_2H_2$), 7.35 (2H, d, J=8.1 Hz, p-$CF_3C_6H_2H_2$), 7.33 (5H, m, Ph), 6.18 (1H, d, J=1.6 Hz, =C*H*H), 5.53 (1H, d, J=1.6 Hz, =CH*H*), 4.55 (1H, dd, J=8.0, 5.2 Hz, CH), 4.50 (1H, d, J=11.3 Hz, p-$CF_3C_6H_4$-C*H*H), 4.31 (1H, d, J=11.3 Hz, p-$CF_3C_6H_4CH$*H*), 4.14 (2H, q, J=7.0 Hz, $CO_2CH_2CH_3$), 2.83 (1H, dd, J=13.2, 8.0 Hz, CHC*H*H), 2.69 (1H, dd, J=13.2, 5.2 Hz, CHCH*H*), 1.25 (3H, t, J=7.0 Hz, $CO_2CH_2CH_3$); ^{13}C NMR (100 MHz) δ 166.9, 142.5, 141.3, 136.9, 129.5 (q, J_{C-F}=32 Hz), 128.4, 127.8, 127.5, 127.4, 126.6, 125.1 (q, J_{C-F}=3.6 Hz), 124.1 (q, J_{C-F}=270 Hz), 80.2, 69.6, 60.7, 41.2, 14.2; IR (neat) 2992, 2926, 1717, 1623, 1456, 1419, 1326, 1067, 1018, 823, 760, 702 cm^{-1}; MS m/z 219 ($M^+-CH_2C_6H_4CF_3$-p, 5%), 203 (7), 173 (13), 159 (10), 129 (13), 109 (25), 105 (29), 91 (19); HRMS calcd for $C_{13}H_{15}O_2$ [$M^+-CH_2C_6H_4CF_3$-p] 219.1021, found 219.0993.

4.2.4. Ethyl 2-[2-(*p*-fluorobenzyloxy)-2-phenylethyl]propenoate 6. ^{1}H NMR (400 MHz) δ 7.23–7.30 (9H, m, Ph, C_6H_4), 6.17 (1H, d, J=1.6 Hz, =C*H*H), 5.50 (1H, d, J=1.6 Hz, =CH*H*), 4.53 (1H, dd, J=8.0, 5.2 Hz, CH), 4.41 (1H, d, J=11.3 Hz, p-FC_6H_4C*H*H), 4.21 (1H, d, J=11.3 Hz, p-FC_6H_4CH*H*), 4.14 (2H, q, J=7.0 Hz, $CO_2CH_2CH_3$), 2.81 (1H, dd, J=14.0, 8.0 Hz, CHC*H*H), 2.66 (1H, dd, J=14.0, 5.2 Hz, CHCH*H*), 1.26 (3H, t, J=7.0 Hz, $CO_2CH_2CH_3$); ^{13}C NMR (100 MHz) δ 166.9, 162.1 (d, J_{C-F}=239 Hz), 141.5, 137.0, 134.1 (d, J_{C-F}=2.8 Hz), 129.2, 128.4, 127.7, 127.4, 126.7, 115.0 (d, J_{C-F}=21 Hz), 79.8, 69.8, 60.6, 41.2, 14.2; IR (neat) 2978, 1718, 1628, 1603, 1509, 1307, 1223, 1193, 1148, 1074, 948, 824, 759 cm^{-1}; MS m/z 219 ($M^+-CH_2C_6H_4F$-p, 12%), 215 (97), 173 (25), 129 (26), 110 (55), 109 (100), 105 (32), 91 (40); HRMS calcd for $C_{13}H_{15}O_3$ [$M^+-CH_2C_6H_4F$-p] 219.1021, found 219.0992.

4.2.5. Ethyl 2-[2-(*p*-isopropylbenzyloxy)-2-phenylethyl]propenoate 8. ^{1}H NMR (270 MHz) δ 7.18–7.35 (9H, m, Ph, C_6H_4), 6.18 (1H, d, J=1.6 Hz, =C*H*H), 5.51 (1H, d, J=1.6 Hz, =CH*H*), 4.55 (1H, dd, J=8.4, 5.4 Hz, C*H*Ph), 4.55 (1H, d, J=11.6 Hz, p-i-PrC_6H_4C*H*H), 4.22 (1H, d, J=11.6 Hz, p-i-PrC_6H_4CH*H*), 4.13 (2H, q, J=7.3 Hz, $CO_2CH_2CH_3$), 2.89 (1H, sep, J=7.0 Hz, C*H*$(CH_3)_2$), 2.81 (1H, dd, J=14.3, 8.4 Hz, CHC*H*H), 2.66 (1H, dd, J=14.3, 5.4 Hz, CHCH*H*), 1.24 (6H, d, J=7.0 Hz, CH$(CH_3)_2$), 1.24 (3H, t, J=7.3 Hz, $CO_2CH_2CH_3$); ^{13}C NMR (100 MHz) δ 166.9, 148.0, 144.0, 141.8, 137.0, 128.3, 127.7, 127.5, 127.4, 126.7, 126.2, 79.7, 70.4, 60.6, 41.2, 33.9, 24.1, 14.3; IR (neat) 2956, 2869, 1716, 1634, 1456, 1305, 1146, 1019, 817, 760, 701 cm^{-1}; MS m/z 219 ($M^+-CH_2C_6H_4i$-Pr-p, 8%), 204 (73), 173 (31), 158 (24), 149 (42), 134 (85), 133 (100), 129 (41), 118 (49), 105 (66), 91 (63); HRMS calcd for $C_{13}H_{15}O_3$ [$M^+-CH_2C_6H_4i$-Pr-p] 219.1021, found 219.0993.

4.2.6. Ethyl 2-[2-(*p*-methylbenzyloxy)-2-phenylethyl]propenoate 9. ^{1}H NMR (270 MHz) δ 7.09–7.35 (9H, m, Ph, C_6H_4), 6.17 (1H, d, J=1.4 Hz, =C*H*H), 5.51 (1H, d, J=1.4 Hz, =CH*H*), 4.54 (1H, dd, J=8.2, 5.1 Hz, CH), 4.42 (1H, d, J=11.6 Hz, p-MeC_6H_4C*H*H), 4.20 (1H, d, J=11.6 Hz, p-MeC_6H_4CH*H*), 4.13 (2H, q, J=7.3 Hz, $CO_2CH_2CH_3$), 2.80 (1H, dd, J=14.2, 8.2 Hz, CHC*H*H), 2.65 (1H, dd, J=14.2, 5.1 Hz, CHCH*H*), 2.33 (3H, s, p-Me), 1.23 (3H, t, J=7.3 Hz, $CO_2CH_2CH_3$); ^{13}C NMR (100 MHz) δ 166.9, 141.8, 137.0, 135.3, 128.8, 128.3, 127.7, 127.5, 127.4, 126.7, 126.2, 79.5, 70.3, 60.6, 41.1, 21.2, 14.2; IR (neat) 2986, 2926, 1718, 1634, 1456, 1307, 1191, 1148, 1074, 941, 803, 757, 702 cm^{-1}; MS m/z 219 ($M^+-CH_2C_6H_4$-Me-p, 5%), 209 (67), 149 (84), 129 (17), 117 (13), 105 (100), 91 (54); HRMS calcd for $C_{13}H_{15}O_2$ [$M^+-OCH_2C_6H_4$Me-p] 203.1072, found 203.1071.

4.2.7. Ethyl 2-[2-(*p*-methoxybenzyloxy)-2-phenylethyl]propenoate 10. ^{1}H NMR (270 MHz) δ 7.26–7.36 (5H, m, Ph), 7.18 (2H, d, J=12.8 Hz, p-$MeOC_6H_2H_2$), 6.84 (2H, d, J=12.8 Hz, p-$MeOC_6H_2H_2$), 6.15 (1H, d, J=1.6 Hz, =C*H*H), 5.49 (1H, d, J=1.6 Hz, =CH*H*), 4.53 (1H, dd, J=8.4, 4.9 Hz, CH), 4.39 (1H, d, J=11.6 Hz, p-$MeOC_6H_4$-C*H*H), 4.18 (1H, d, J=11.6 Hz, p-$MeOC_6H_4CH$*H*), 4.13 (2H, q, J=7.3 Hz, $CO_2CH_2CH_3$), 3.79 (3H, s, p-MeO), 2.80 (1H, dd, J=14.0, 8.4 Hz, CHC*H*H), 2.64 (1H, dd, J=14.0, 4.9 Hz, CHCH*H*), 1.25 (3H, t, J=7.3 Hz $CO_2CH_2CH_3$); ^{13}C NMR (100 MHz) δ 166.9, 159.0, 141.8, 137.0, 129.3, 129.2, 128.3, 127.5, 127.3, 126.7, 113.6, 79.4, 71.5, 60.6, 55.3, 41.1, 14.3; IR (neat) 2836, 1714, 1612, 1513, 1302, 1248, 1135, 820, 758, 702 cm^{-1}; MS m/z 340 (M^+, 2%), 258 (22), 219 (2), 203 (3), 137 (35), 121 (100); HRMS calcd for $C_{21}H_{24}O_4$ [M^+] 340.1674, found 340.1677.

4.2.8. Ethyl 2-[2-(*p*-methylbenzyloxy)-3-methylbutyl]propenoate 12. ^{1}H NMR (270 MHz) δ 7.10–7.24 (4H, m, C_6H_4), 6.19 (1H, d, J=1.6 Hz, =C*H*H), 5.63 (1H, d, J=1.6 Hz, =CH*H*), 4.43 (2H, s, p-$MeC_6H_4CH_2$), 4.18 (2H, q, J=7.0 Hz, $CO_2CH_2CH_3$), 3.38 (1H, dd, J=8.4, 4.1 Hz, i-PrC*H*), 2.56 (1H, dd, J=10.5, 4.1 Hz, CHC*H*H), 2.41 (1H, dd, J=13.4, 8.4 Hz, CHCH*H*), 2.32 (3H, s, p-Me), 1.89 (1H, m, C*H*$(CH_3)_2$), 1.29 (3H, t, J=7.0 Hz, $CO_2CH_2CH_3$), 0.95 (3H, d, J=6.8 Hz, CHCH_3), 0.94 (3H, d, J=6.8 Hz, CHCH_3); ^{13}C NMR (67.5 MHz) δ 167.2, 138.1, 136.8, 135.8, 128.8, 127.7, 126.9, 82.3, 72.0, 60.6, 34.0, 31.0, 21.2, 18.3, 17.9, 14.3; IR (neat) 2874, 1716, 1610, 1270, 1181, 1021, 808, 755 cm^{-1}; MS m/z 290 (M^+, 13%), 217 (15), 185 (3), 169 (3), 144 (18), 121 (18), 105 (100); HRMS calcd for $C_{18}H_{26}O_3$ [M^+] 290.1882, found 290.1843.

4.2.9. Ethyl 2-benzyloxyphenylmethyl propenoate 36. ^{1}H NMR (400 MHz) δ 7.21–7.40 (10H, m, 2×Ph), 6.35 (1H, s, CH), 6.01 (1H, s, =C*H*H), 5.34 (1H, s, =CH*H*), 4.48 (2H, s, CH_2Ph), 4.15 (2H, dq, J=7.3, 11.2 Hz, CO_2CH*H*CH_3), 4.12 (2H, dq, J=7.3, 11.2 Hz, CO_2CH*H*CH_3), 1.22 (3H, t, J=7.3 Hz, $CO_2CH_2CH_3$); ^{13}C NMR (100 MHz) δ 165.7, 141.4, 139.5, 138.1, 128.4, 128.2, 127.8, 127.7, 127.6, 127.5, 124.9, 78.6, 70.8, 60.7, 14.1; MS m/z 205 (M^+-Bn, 22%), 203 (7), 190 (41), 178 (16), 159 (17); HRMS calcd for $C_{12}H_{13}O_3$ [M^+-Bn] 205.0865, found 205.0873.

4.2.10. Ethyl 2-(*p*-methylbenzyloxy)phenylmethyl propenoate 37. ^{1}H NMR (400 MHz) δ 7.29–7.39 (5H, m, Ph), 7.21 (2H, d, J=7.3 Hz, $C_6H_2H_2$), 7.13 (2H, d, J=7.3 Hz, $C_6H_2H_2$), 6.35 (1H, s, CH), 6.00 (1H, s, =C*H*H), 5.33 (1H, s, =CH*H*), 4.44 (2H, s, CH_2Ph), 4.13 (2H, dq, J=7.3, 12.2 Hz, CO_2CH*H*CH_3), 4.10 (2H, dq, J=7.3, 12.2 Hz, CO_2CH*H*CH_3), 2.34, (3H, s, p-Me), 1.22 (3H, t, J=7.3 Hz, $CO_2CH_2CH_3$); ^{13}C NMR (100 MHz) δ 165.7, 141.4, 139.6, 137.1, 135.0, 128.9, 128.2, 127.7, 127.6, 127.5, 124.8, 78.4, 70.6, 60.7, 21.2, 14.1; MS m/z 205 $M^+-CH_2C_6H_4$Me-p,

5%), 190 (68), 144 (19), 121 (32), 116 (33); HRMS calcd for $C_{12}H_{13}O_3$ [$M^+-CH_2C_6H_4Me$-*p*] 205.0865, found 205.0873.

4.3. Radical reactions

General procedure of the radical reactions. To a solution of α-methylene ester (0.15 mmol) in dry CH_2Cl_2 (1.5 cm^3) was added $MgBr_2{\cdot}OEt_2$ (0.45 mmol, 3 equiv.), and the mixture was stirred at room temperature for 10 min. To the suspension cooled to 0 °C were added alkyl iodide (0.45 mmol, 3 equiv.), *n*-Bu_3SnH (0.30 mmol, 2 equiv.) and Et_3B (1.06 mol dm^{-3} in hexane; 0.15 mmol, 1 equiv.). The mixture was stirred at 0 °C for 3 h. KF and water were added and the reaction mixture was stirred at room temperature for 3 h. After filtration, the solvent was evaporated in vacuo. The residue was purified by flash chromatography on silica gel to give the product as an oily inseparable diastereomeric mixture.

4.3.1. Ethyl 4-methyl-2-[2-(*p*-nitrobenzyloxy)-2-phenylethyl]pentanoate 13 (*syn* and *anti*). IR (neat) 2870, 1726, 1606, 1522, 1453, 1364, 1097, 1015, 844, 739, 702 cm^{-1}; MS *m*/*z* 354 (M^+-OEt, 3%), 263 (16), 242 (83), 217 (71), 203 (17), 136 (100), 105 (40), 91(15); HRMS calcd for $C_{21}H_{24}NO_3$ [M^+-OEt] 354.1706, found 354.1720. *syn*: ^1H NMR (270 MHz) δ 8.16 (2H, d, *J*=8.9 Hz, *p*-$NO_2C_6H_2H_2$), 7.43 (2H, d, *J*=8.9 Hz, *p*-$NO_2C_6H_2H_2$), 7.32 (5H, m, Ph), 4.44 (1H, d, *J*=13.5 Hz, *p*-$NO_2C_6H_4CHH$), 4.34 (2H, m, PhC*H*, *p*-$NO_2C_6H_4CHH$), 4.03 (2H, m, $CO_2CH_2CH_3$), 2.83 (1H, m, $CHCO_2Et$), 1.96 (2H, m, $CHCH_2CH$), 1.58 (3H, m, $CH(CH_3)_2$, *i*-$PrCH_2$), 1.23 (3H, t, *J*=7.2 Hz, $CO_2CH_2CH_3$), 0.90 (3H, d, *J*=6.4 Hz, $CHCH_3$), 0.88 (3H, d, *J*=6.4 Hz, $CHCH_3$). *anti*: ^1H NMR (270 MHz) δ 8.16 (2H, d, *J*=8.9 Hz, *p*-$NO_2C_6H_2H_2$), 7.43 (2H, d, *J*=8.9 Hz, *p*-$NO_2C_6H_2H_2$), 7.32 (5H, m, Ph), 4.44 (1H, d, *J*=13.5 Hz, *p*-$NO_2C_6H_4CHH$), 4.34 (2H, m, *p*-$NO_2C_6H_4CHH$, PhC*H*), 4.03 (2H, m, $CO_2CH_2CH_3$), 2.47 (1H, m, $CHCO_2Et$), 2.32 (1H, m, $CHCHHCH$), 1.74 (1H, m, $CHCHHCH$), 1.58 (3H, m, $CH(CH_3)_2$, *i*-$PrCH_2$), 1.19 (3H, t, *J*=7.2 Hz, $CO_2CH_2CH_3$), 0.85 (3H, d, *J*=6.4 Hz, $CHCH_3$), 0.80 (3H, d, *J*=6.4 Hz, $CHCH_3$).

4.3.2. Ethyl 2-[2-(*p*-cyanobenzyloxy)-2-phenylethyl]-4-methylpentanoate 14 (*syn* and *anti*). IR (neat) 2966, 2870, 2228, 1729, 1456, 1269, 1176, 1021, 821, 703 cm^{-1}; MS *m*/*z* 334 (M^+-OEt, 3%), 263 (14), 247 (16), 222 (31), 217 (48), 116 (91), 105 (48), 91 (11); HRMS calcd for $C_{22}H_{24}NO_2$ [M^+-OEt] 334.1807, found 334.1768. *syn*: ^1H NMR (400 MHz) δ 7.28–7.69 (9H, m, Ph, C_6H_4), 4.44 (1H, d, *J*=12.8 Hz, *p*-NCC_6H_4CHH), 4.34 (1H, m, PhC*H*), 4.30 (1H, d, *J*=12.4 Hz, *p*-NCC_6H_4CHH), 4.07 (2H, m, $CO_2CH_2CH_3$), 2.82 (1H, m, $CHCO_2Et$), 1.95 (2H, m, $CHCH_2CH$), 1.55 (2H, m, *i*-$PrCH_2$), 1.26 (1H, m, $CH(CH_3)_2$), 1.23 (3H, t, *J*=7.2 Hz, $CO_2CH_2CH_3$), 0.90 (3H, d, *J*=6.4 Hz, $CHCH_3$), 0.87 (3H, d, *J*=6.4 Hz, $CHCH_3$); ^{13}C NMR (100 MHz) δ 176.1, 143.9, 141.5, 132.0, 128.5, 128.4, 128.2, 127.8, 126.6, 111.0, 80.4, 69.8, 60.1, 42.2, 41.7, 40.4, 20.1, 22.9, 22.3, 14.3. *anti*: ^1H NMR (400 MHz) δ 7.28–7.69 (9H, m, Ph, C_6H_4), 4.44 (1H, d, *J*=12.8 Hz, *p*-NCC_6H_4CHH), 4.34 (1H, m, PhC*H*), 4.30 (1H, d, *J*=12.4 Hz, *p*-NCC_6H_4CHH), 4.00 (2H, m, $CO_2CH_2CH_3$), 2.46 (1H, m, $CHCO_2Et$), 2.28 (1H, ddd, *J*=13.6, 8.4, 8.4 Hz, $CHCHHCH$), 1.73 (1H, ddd, *J*=14.0, 4.8, 4.8 Hz, $CHCHHCH$), 1.55 (2H, m, *i*-$PrCH_2$), 1.26 (1H, m, $CH(CH_3)_2$), 1.18 (3H, t, *J*=7.2 Hz, $CO_2CH_2CH_3$), 0.85 (3H, d, *J*=6.4 Hz, $CHCH_3$), 0.80 (3H, d, *J*=6.4 Hz, $CHCH_3$); ^{13}C NMR (100 MHz) δ 176.1, 143.9, 141.1, 132.0, 128.6, 128.4, 128.0, 127.7, 126.4, 111.0, 80.8, 69.4, 60.1, 42.5, 41.2, 41.1, 25.0, 22.9, 22.1, 14.4.

4.3.3. Ethyl 4-methyl-2-[2-phenylethyl-2-(*p*-trifluoromethylbenzyloxy)]pentanoate 15 (*syn* and *anti*). IR (neat) 2958, 2871, 2331, 1733, 1455, 1326, 1165, 1125, 1066, 1018, 823, 702 cm^{-1}; MS *m*/*z* 393 (M^+-Et, 17%), 377 (3), 265 (61), 247 (11), 217 (97), 159 (100), 109 (12), 105 (34); HRMS calcd for $C_{22}H_{24}O_3F_3$ [M^+-Et] 393.1678, found 393.1700. *syn*: ^1H NMR (400 MHz) δ 7.59 (2H, d, *J*=8.1 Hz, *p*-$CF_3C_6H_2H_2$), 7.43 (2H, d, *J*=8.1 Hz, *p*-$CF_3C_6H_2H_2$), 7.30 (5H, m, Ph), 4.46 (1H, d, *J*=11.3 Hz, *p*-$CF_3C_6H_4CHH$), 4.31 (1H, dd, *J*=9.6, 3.6 Hz, PhC*H*), 4.29 (1H, d, *J*=11.3 Hz, *p*-$CF_3C_6H_4CHH$), 4.07 (2H, m, $CO_2CH_2CH_3$), 2.84 (1H, m, $CHCO_2Et$), 1.97 (1H, ddd, *J*=14.0, 9.6, 4.0 Hz, $CHCHHCH$), 1.90 (1H, ddd, *J*=14.0, 9.2, 3.6 Hz, $CHCHHCH$), 1.55 (2H, m, *i*-$PrCH_2$), 1.25 (1H, m, $CH(CH_3)_2$), 1.22 (3H, t, *J*=7.0 Hz, $CO_2CH_2CH_3$), 0.90 (3H, d, *J*=6.4 Hz, $CHCH_3$), 0.87 (3H, d, *J*=6.4 Hz, $CHCH_3$); ^{13}C NMR (100 MHz) δ 176.1, 142.4, 141.7, 129.6 (q, J_{C-F}=32 Hz), 129.4, 128.5, 127.6, 126.4, 125.1 (q, J_{C-F}=3.6 Hz), 124.1 (q, J_{C-F}=270 Hz), 80.3, 70.0, 60.1, 42.2, 41.0, 40.4, 26.1, 22.9, 22.3, 14.4. *anti*: ^1H NMR (400 MHz) δ 7.59 (2H, d, *J*=8.1 Hz, *p*-$CF_3C_6H_2H_2$), 7.43 (2H, d, *J*=8.1 Hz, *p*-$CF_3C_6H_2H_2$), 7.30 (5H, m, Ph), 4.46 (1H, d, *J*=11.3 Hz, *p*-$CF_3C_6H_4CHH$), 4.33 (1H, dd, *J*=9.6, 3.6 Hz, PhC*H*), 4.29 (1H, d, *J*=11.3 Hz, *p*-$CF_3C_6H_4CHH$), 4.07 (2H, m, $CO_2CH_2CH_3$), 2.47 (1H, m, $CHCO_2Et$), 2.27 (1H, ddd, *J*=14.0, 9.6, 9.6 Hz, $CHCHHCH$), 1.72 (1H, ddd, *J*=14.0, 3.6, 3.6 Hz, $CHCHHCH$), 1.55 (2H, m, *i*-$PrCH_2$), 1.25 (1H, m, $CH(CH_3)_2$), 1.17 (3H, t, *J*=7.0 Hz, $CO_2CH_2CH_3$), 0.85 (3H, d, *J*=6.4 Hz, $CHCH_3$), 0.80 (3H, d, *J*=6.4 Hz, $CHCH_3$).

4.3.4. Ethyl 2-[2-(*p*-fluorobenzyloxy)-2-phenylethyl]-4-methylpentanoate 16 (*syn* and *anti*). IR (neat) 2870, 2359, 1734, 1509, 1224, 1016, 824, 702 cm^{-1}; MS *m*/*z* 327 (M^+-OEt, 3%), 263 (20), 247 (4), 219 (96), 144 (68), 125 (62), 109 (100), 101 (50); HRMS calcd for $C_{21}H_{24}O_2F$ [M^+-OEt] 327.1760, found 327.1754. *syn*: ^1H NMR (400 MHz) δ 7.26–7.38 (7H, m, Ph, *p*-$FC_6H_2H_2$), 6.99 (2H, m, *p*-$FC_6H_2H_2$), 4.37 (1H, d, *J*=11.2 Hz, *p*-FC_6H_4CHH), 4.28 (1H, dd, *J*=9.4, 4.0 Hz, PhC*H*), 4.19 (1H, d, *J*=11.2 Hz, *p*-FC_6H_4CHH), 4.06 (2H, m, $CO_2CH_2CH_3$), 2.83 (1H, m, $CHCO_2Et$), 1.91 (2H, m, $CHCH_2CH$), 1.54 (2H, m, *i*-$PrCH_2$), 1.24 (1H, m, $CH(CH_3)_2$), 1.23 (3H, t, *J*=7.2 Hz, $CO_2CH_2CH_3$), 0.89 (3H, d, *J*=6.4 Hz, $CHCH_3$), 0.86 (3H, d, *J*=6.4 Hz, $CHCH_3$); ^{13}C NMR (100 MHz) δ 176.2, 162.1 (d, J_{C-F}=243 Hz), 142.0, 134.0, 129.7 (d, J_{C-F}=8.2 Hz), 128.4, 127.8, 126.4, 115.0 (d, J_{C-F}=21 Hz), 79.6, 69.5, 59.7, 42.3, 41.6, 40.4, 26.0, 22.9, 22.2, 14.4. *anti*: ^1H NMR (400 MHz) δ 7.26–7.38 (7H, m, Ph, *p*-$FC_6H_2H_2$), 6.99 (2H, m, *p*-$FC_6H_2H_2$), 4.37 (1H, d, *J*=11.2 Hz, *p*-FC_6H_4CHH), 4.28 (1H, dd, *J*=9.4, 4.0 Hz, PhC*H*), 4.19 (1H, d, *J*=11.2 Hz, *p*-FC_6H_4CHH), 4.06 (2H, m, $CO_2CH_2CH_3$), 2.46 (1H, m, $CHCO_2Et$), 2.24 (1H, m, $CHCHHCH$), 1.70 (1H, m, $CHCHHCH$), 1.54 (2H, m, *i*-$PrCH_2$), 1.24 (1H, m, $CH(CH_3)_2$), 1.19 (3H, t, *J*=7.2 Hz, $CO_2CH_2CH_3$), 0.85 (3H, d, *J*=6.4 Hz, $CHCH_3$), 0.79 (3H, d, *J*=6.4 Hz, $CHCH_3$).

4.3.5. Ethyl 2-[2-(*p*-isopropylbenzyloxy)-2-phenylethyl]-4-methylpentanoate 18 (*syn* and *anti*). IR (neat) 2868, 2362, 1733, 1456, 1177, 1019, 818, 701 cm^{-1}; MS *m*/*z* 280 (M^+-CO_2Et-*i*-Pr, 4%), 247 (12), 217 (32), 149 (24), 133 (100), 101 (37); HRMS calcd for $C_{20}H_{24}O$ [M^+-CO_2Et-*i*-Pr] 280.1827, found 280.1828. *syn*: ^1H NMR (400 MHz) δ 7.17–7.36 (9H, m, Ph, C_6H_4), 4.37 (1H, d, J=11.2 Hz, *p*-*i*-PrC_6H_4CHH), 4.29 (1H, dd, J=9.2, 4.4 Hz, PhC*H*), 4.22 (1H, d, J=11.2 Hz, *p*-*i*-PrC_6H_4CHH), 4.07 (2H, m, $CO_2CH_2CH_3$), 2.90 (1H, sep, J=6.8 Hz, $CH(CH_3)_2$), 2.86 (1H, m, $CHCO_2Et$), 1.90 (2H, m, $CHCH_2CH$), 1.55 (3H, m, *i*-$PrCH_2$, $CH(CH_3)_2$), 1.24 (6H, d, J=6.8 Hz, $CH(CH_3)_2$), 1.23 (3H, t, J=7.6 Hz, $CO_2CH_2CH_3$), 0.89 (3H, d, J=6.4 Hz, $CHCH_3$), 0.86 (3H, d, J=6.4 Hz, $CHCH_3$); ^{13}C NMR (100 MHz) δ 176.3, 148.1, 142.3, 135.6, 128.4, 127.9, 127.5, 126.4, 126.3, 79.5, 70.7, 60.0, 42.3, 41.8, 40.4, 26.1, 24.1, 23.0, 22.2, 14.4, 14.1. *anti*: ^1H NMR (400 MHz) δ 7.17–7.36 (9H, m, Ph, C_6H_4), 4.37 (1H, d, J=11.2 Hz, *p*-*i*-PrC_6H_4CHH), 4.29 (1H, dd, J=9.2, 4.4 Hz, PhC*H*), 4.22 (1H, d, J=11.2 Hz, *p*-*i*-PrC_6H_4CHH), 4.07 (2H, m, $CO_2CH_2CH_3$), 2.90 (1H, sep, J=6.8 Hz, $CH(CH_3)_2$), 2.51 (1H, m, $CHCO_2Et$), 2.22 (1H, m, $CHCHHCH$), 1.55 (4H, m, *i*-$PrCH_2$, $CHCHHCH$, $CH(CH_3)_2$), 1.24 (6H, d, J=6.8 Hz, $CH(CH_3)_2$), 1.18 (3H, t, J=7.6 Hz, $CO_2CH_2CH_3$), 0.84 (3H, d, J=6.4 Hz, $CHCH_3$), 0.78 (3H, d, J=6.4 Hz, $CHCH_3$).

4.3.6. Ethyl 4-methyl-2-[2-(*p*-methylbenzyloxy)-2-phenylethyl]pentanoate 19 (*syn*). ^1H NMR (270 MHz) δ 7.13–7.37 (9H, m, Ph, C_6H_4), 4.37 (1H, d, J=11.3 Hz, *p*-MeC_6H_4CHH), 4.28 (1H, dd, J=9.3, 4.1 Hz, PhC*H*), 4.17 (1H, d, J=11.3 Hz, *p*-MeC_6H_4CHH), 4.06 (2H, m, $CO_2CH_2CH_3$), 2.84 (1H, m, $CHCO_2Et$), 2.34 (3H, s, *p*-Me), 1.86 (2H, m, $CHCH_2CH$), 1.58 (2H, m, *i*-$PrCH_2$), 1.37 (1H, m, $CH(CH_3)_2$), 1.23 (3H, t, J=7.3 Hz, $CO_2CH_2CH_3$), 0.89 (3H, d, J=6.8 Hz, $CHCH_3$), 0.86 (3H, d, J=6.8 Hz, $CHCH_3$); ^{13}C NMR (67.5 MHz) δ 176.4, 142.4, 137.3, 135.3, 128.9, 128.4, 128.0, 127.5, 126.5, 79.4, 70.6, 60.0, 42.3, 41.7, 40.3, 26.0, 22.9, 22.2, 21.2, 14.3; IR (neat) 2868, 1730, 1517, 1453, 1367, 1178, 1022, 801, 756, 702 cm^{-1}; MS *m*/*z* 368 (M^+, 2%), 247 (17), 225 (22), 217 (39), 209 (37), 144 (85), 133 (17), 121 (11), 105 (100); HRMS calcd for $C_{16}H_{23}O_2$ [$M^+-OCH_2C_6H_4Me$-*p*] 247.1699, found 247.1697.

4.3.7. Ethyl 2-[2-(*p*-methoxybenzyloxy)-2-phenylethyl]-4-methylpentanoate 20 (*syn* and *anti*). IR (neat) 2953, 2173, 1730, 1507, 1278, 1174, 1037 cm^{-1}; MS *m*/*z* 247 ($M^+-OCH_2C_6H_4OMe$-*p*, 7%), 222 (56), 217 (87), 144 (11), 116 (100), 105 (43), 101 (18); HRMS calcd for $C_{16}H_{23}O_2$ [$M^+-OCH_2C_6H_4OMe$-*p*] 247.1698, found 247.1718. *syn*: ^1H NMR (400 MHz) δ 7.33 (5H, m, Ph), 7.23 (2H, d, J=12.8 Hz, *p*-$MeOC_6H_2H_2$), 6.86 (2H, d, J=12.8 Hz, *p*-$MeOC_6H_2H_2$), 4.35 (1H, d, J=11.2 Hz, *p*-$MeOC_6H_4CHH$), 4.28 (1H, dd, J=9.2, 4.0 Hz, PhC*H*), 4.16 (1H, d, J=11.2 Hz, *p*-$MeOC_6H_4CHH$), 4.07 (2H, m, $CO_2CH_2CH_3$), 3.80 (3H, s, OMe), 2.84 (1H, m, $CHCO_2Et$), 1.89 (2H, m, $CHCH_2CH$), 1.54 (2H, m, *i*-$PrCH_2$), 1.28 (1H, m, $CH(CH_3)_2$), 1.24 (3H, t, J=7.2 Hz, $CO_2CH_2CH_3$), 0.89 (3H, d, J=6.4 Hz, $CHCH_3$), 0.86 (3H, d, J=6.4 Hz, $CHCH_3$); ^{13}C NMR (100 MHz) δ 176.2, 159.0, 142.3, 130.4, 129.4, 128.4, 127.5, 126.4, 113.0, 79.3, 70.5, 60.0, 55.3, 42.3, 41.8, 40.4, 26.1, 23.0, 22.2, 14.4. *anti*: ^1H NMR (400 MHz) δ 7.33 (5H, m, Ph), 7.23 (2H, d, J=12.8 Hz, *p*-$MeOC_6H_2H_2$), 6.86 (2H, d, J=12.8 Hz, *p*-$MeOC_6H_2H_2$), 4.35 (1H, d, J=11.2 Hz, *p*-$MeOC_6H_4CHH$), 4.28 (1H, dd, J=9.2, 4.0 Hz, PhC*H*), 4.16 (1H, d, J=11.2 Hz, *p*-$MeOC_6H_4CHH$), 4.07 (2H, m, $CO_2CH_2CH_3$), 3.77 (3H, s, OMe), 2.48 (1H, m, $CHCO_2Et$), 2.22 (1H, m, $CHCHHCH$), 1.65 (1H, m, $CHCHHCH$), 1.54 (2H, m, *i*-$PrCH_2$), 1.28 (1H, m, $CH(CH_3)_2$), 1.19 (3H, t, J=7.2 Hz, $CO_2CH_2CH_3$), 0.84 (3H, d, J=6.4 Hz, $CHCH_3$), 0.79 (3H, d, J=6.4 Hz, $CHCH_3$).

4.3.8. Ethyl 2-[2-(*p*-cyanobenzyloxy)-2-phenylethyl]-pentanoate 21 (*syn* and *anti*). IR (neat) 2931, 2873, 2228, 1729, 1454, 1269, 1176, 1070, 820, 702 cm^{-1}; MS *m*/*z* 320 (M^+-OEt, 4%), 249 (25), 233 (5), 222 (46), 203 (99), 116 (100); HRMS calcd for $C_{21}H_{22}NO_2$ [M^+-OEt] 320.1650, found 320.1602. *syn*: ^1H NMR (400 MHz) δ 7.30–7.64 (9H, m, Ph, C_6H_4), 4.44 (1H, d, J=12.4 Hz, *p*-NCC_6H_4CHH), 4.32 (1H, dd, J=9.6, 4.0 Hz, PhC*H*), 4.29 (1H, d, J=12.4 Hz, *p*-NCC_6H_4CHH), 4.08 (2H, m, $CO_2CH_2CH_3$), 2.76 (1H, m, $CHCO_2Et$), 2.01 (1H, ddd, J=14.0, 9.6, 3.2 Hz, $CHCHHCH$), 1.92 (1H, ddd, J=14.0, 9.6, 4.0 Hz, $CHCHHCH$), 1.60 (1H, m, $CHHEt$), 1.42 (1H, m, $CHHEt$), 1.32 (2H, m, $CH_2CH_2CH_3$), 1.23 (3H, t, J=7.2 Hz, $CO_2CH_2CH_3$), 0.89 (3H, t, J=7.2 Hz, $CH_2CH_2CH_3$); ^{13}C NMR (100 MHz) δ 175.8, 143.9, 141.5, 132.0, 128.5, 127.8, 127.7, 126.3, 118.8, 111.1, 80.3, 69.8, 60.1, 42.0, 41.1, 35.2, 20.5, 14.4, 14.0. *anti*: ^1H NMR (400 MHz) δ 7.30–7.64 (9H, m, Ph, C_6H_4), 4.41 (1H, d, J=12.8 Hz, *p*-NCC_6H_4CHH), 4.32 (1H, dd, J=8.8, 5.2 Hz, PhC*H*), 4.29 (1H, d, J=12.8 Hz, *p*-NCC_6H_4CHH), 4.07 (2H, m, $CO_2CH_2CH_3$), 2.38 (1H, m, $CHCO_2Et$), 2.32 (1H, ddd, J=13.6, 8.8, 8.8 Hz, $CHCHHCH$), 1.75 (1H, ddd, J=13.6, 5.2, 5.2 Hz, $CHCHHCH$), 1.54 (1H, m, $CHHEt$), 1.40 (1H, m, $CHHEt$), 1.27 (2H, m, $CH_2CH_2CH_3$), 1.19 (3H, t, J=7.2 Hz, $CO_2CH_2CH_3$), 0.85 (3H, t, J=7.2 Hz, $CH_2CH_2CH_3$); ^{13}C NMR (100 MHz) δ 175.9, 144.0, 141.3, 132.0, 128.6, 127.8, 127.7, 126.6, 118.8, 111.1, 80.8, 69.4, 60.1, 42.8, 40.7, 35.0, 20.4, 14.3, 14.0.

4.3.9. Ethyl 2-[2-(*p*-trifluoromethylbenzyloxy)-2-phenylethyl]pentanoate 22 (*syn* and *anti*). IR (neat) 2873, 1729, 1326, 1165, 1126, 1066, 1019, 823, 702 cm^{-1}; MS *m*/*z* 363 (M^+-OEt, 5%), 265 (40), 249 (30), 233 (22), 203 (88), 159 (100), 105 (38); HRMS calcd for $C_{21}H_{22}O_2F_3$ [M^+-OEt] 363.1572, found 363.1536. *syn*: ^1H NMR (400 MHz) δ 7.59 (2H, d, J=8.0 Hz, *p*-$CF_3C_6H_2H_2$), 7.43 (2H, d, J=8.0 Hz, *p*-$CF_3C_6H_2H_2$), 7.25–7.35 (5H, m, Ph), 4.45 (1H, d, J=12.0 Hz, *p*-$CF_3C_6H_4CHH$), 4.32 (1H, dd, J=9.6, 4.0 Hz, PhC*H*), 4.28 (1H, d, J=12.0 Hz, *p*-$CF_3C_6H_4CHH$), 4.07 (2H, m, $CO_2CH_2CH_3$), 2.77 (1H, m, $CHCO_2Et$), 2.00 (1H, ddd, J=14.0, 9.6, 4.0 Hz, $CHCHHCH$), 1.91 (1H, dd, J=14.0, 9.6, 4.0 Hz, $CHCHHCH$), 1.59 (1H, m, $CHHEt$), 1.43 (1H, m, $CHHEt$), 1.32 (2H, m, $CH_2CH_2CH_3$), 1.22 (3H, t, J=7.2 Hz, $CO_2CH_2CH_3$), 0.89 (3H, t, J=7.2 Hz, $CH_2CH_2CH_3$); ^{13}C NMR (100 MHz) δ 175.9, 142.4, 141.8, 129.6 (q, J_{C-F}=32 Hz), 128.5, 127.7, 127.5, 126.4, 125.1 (q, J_{C-F}=3.6 Hz), 124.1 (q, J_{C-F}=270 Hz), 80.0, 70.0, 60.1, 42.0, 41.2, 35.3, 20.5, 14.4, 14.0. *anti*: ^1H NMR (400 MHz) δ 7.59 (2H, d, J=8.0 Hz, *p*-$CF_3C_6H_2H_2$), 7.42 (2H, d, J=8.0 Hz, *p*-$CF_3C_6H_2H_2$), 7.25–7.35 (5H, m, Ph), 4.43 (1H, d, J=12.0 Hz, *p*-$CF_3C_6H_4CHH$), 4.32 (1H, dd, J=8.0, 4.8 Hz, PhC*H*), 4.28 (1H, d, J=12.0 Hz, *p*-$CF_3C_6H_4CHH$), 4.07 (2H, m, $CO_2CH_2CH_3$), 2.39 (1H, m, $CHCO_2Et$), 2.30 (1H, ddd, J=14.0, 8.0, 8.0 Hz, $CHCHHCH$), 1.74 (1H, ddd, J=14.0, 4.8, 4.8 Hz,

CHCH*H*CH), 1.59 (1H, m, C*H*HEt), 1.43 (1H, m, CH*H*Et), 1.32 (2H, m, $CH_2CH_2CH_3$), 1.18 (3H, t, J=7.2 Hz, $CO_2CH_2CH_3$), 0.84 (3H, t, J=7.2 Hz, $CH_2CH_2CH_3$); ^{13}C NMR (100 MHz) δ 175.9, 142.5, 141.4, 129.6 (q, J_{C-F}=32 Hz), 128.5, 127.7, 127.5, 126.7, 125.9 (q, J_{C-F}=3.6 Hz), 124.1 (q, J_{C-F}=270 Hz), 80.4, 69.5, 60.1, 42.8, 40.7, 34.9, 20.4, 14.3, 14.0.

4.3.10. Ethyl 2-[2-(*p*-fluorobenzyloxy)-2-phenylethyl]-pentanoate 23 (*syn* and *anti*). IR (neat) 2956, 2873, 1729, 1511, 1455, 1223, 1157, 824, 759, 702 cm^{-1}; MS *m*/*z* 249 ($M^+-CH_2C_6H_4F$-*p*, 15%), 233 (2), 203 (69), 130 (50), 109 (100), 105 (32); HRMS calcd for $C_{15}H_{21}O_3$ [$M^+-CH_2C_6H_4F$-*p*] 249.1490, found 249.1526. *syn*: ^{1}H NMR (400 MHz) δ 7.26–7.38 (7H, m, Ph, *p*-$FC_6H_2H_2$), 7.01 (2H, m, *p*-$FC_6H_2H_2$), 4.37 (1H, d, J=11.2 Hz, *p*-FC_6H_4-C*H*H), 4.29 (1H, dd, J=10.0, 3.6 Hz, PhC*H*), 4.18 (1H, d, J=11.2 Hz, *p*-FC_6H_4CHH), 4.08 (2H, m, $CO_2CH_2CH_3$), 2.75 (1H, m, C*H*CO_2Et), 1.92 (2H, m, CHCH_2CH), 1.58 (1H, m, C*H*HEt), 1.42 (1H, m, CH*H*Et), 1.30 (2H, m, $CH_2CH_2CH_3$), 1.24 (3H, t, J=7.2 Hz, $CO_2CH_2CH_3$), 0.88 (3H, t, J=7.2 Hz, $CH_2CH_2CH_3$); ^{13}C NMR (100 MHz) δ 175.9, 162.1 (d, J_{C-F}=243 Hz), 142.1, 134.0, 129.6 (d, J_{C-F}=7.3 Hz), 128.4, 127.6, 126.4, 115.0 (d, J_{C-F}=21 Hz), 79.6, 70.1, 60.1, 42.0, 41.2, 35.3, 20.5, 14.4, 14.1. *anti*: ^{1}H NMR (400 MHz) δ 7.26–7.38 (7H, m, Ph, *p*-$FC_6H_2H_2$), 7.01 (2H, m, *p*-$FC_6H_2H_2$), 4.35 (1H, d, J=11.2 Hz, *p*-FC_6H_4-C*H*H), 4.29 (1H, dd, J=10.0, 3.6 Hz, PhC*H*), 4.18 (1H, d, J=11.2 Hz, *p*-FC_6H_4CHH), 4.04 (2H, m, $CO_2CH_2CH_3$), 2.38 (1H, m, C*H*CO_2Et), 2.25 (1H, ddd, J=13.6, 8.8, 8.8 Hz, CHC*H*HCH), 1.71 (1H, ddd, J=14.0, 5.2, 5.2 Hz, CHCH*H*CH), 1.55 (1H, m, C*H*HEt), 1.37 (1H, m, CH*H*Et), 1.24 (2H, m, $CH_2CH_2CH_3$), 1.19 (3H, t, J=7.2 Hz, $CO_2CH_2CH_3$), 0.83 (3H, t, J=7.2 Hz, $CH_2CH_2CH_3$); ^{13}C NMR (100 MHz) δ 175.9, 162.1 (d, J_{C-F}=243 Hz), 141.6, 134.1, 129.4 (d, J_{C-F}=7.3 Hz), 128.4, 127.8, 126.7, 115.0 (d, J_{C-F}=21 Hz), 79.8, 69.6, 60.1, 42.7, 40.7, 34.7, 20.4, 14.3, 14.0.

4.3.11. Ethyl 2-(2-benzyloxy-2-phenylethyl)pentanoate 24 (*syn* and *anti*). IR (neat) 2928, 2871, 1722, 1494, 1454, 1229, 1150, 1078, 736, 700 cm^{-1}; MS *m*/*z* 249 (M^+-Bn, 7%), 233 (19), 203 (23), 200 (12), 197 (40), 181 (37), 176 (17), 129 (12), 117 (33), 105 (82), 91 (100); HRMS calcd for $C_{15}H_{21}O_3$ [M^+-Bn] 249.1490, found 249.1507. *syn*:^{1}H NMR (400 MHz) δ 7.18–7.35 (10H, m, 2×Ph), 4.42 (1H, d, J=11.0 Hz, C*H*HPh), 4.31 (1H, dd, J=9.6, 4.3 Hz, BnOC*H*), 4.22 (1H, d, J=11.0 Hz, CH*H*Ph), 4.07 (2H, m, $CO_2CH_2CH_3$), 2.79 (1H, m, C*H*CO_2Et), 1.94 (2H, m, CHCH_2CH), 1.40 (4H, m, CH_2Et, CH_2CH_3), 1.23 (3H, t, J=7.2 Hz, $CO_2CH_2CH_3$), 0.88 (3H, t, J=7.2 Hz, CH_2CH_3); ^{13}C NMR (100 MHz) δ 176.0, 142.2, 138.3, 128.4, 128.2, 127.8, 127.5, 127.4, 126.4, 79.6, 70.8, 60.0, 42.0, 41.3, 35.3, 20.5, 14.4, 14.1. *anti*: ^{1}H NMR (400 MHz) δ 7.18–7.35 (10H, m, 2×Ph), 4.42 (1H, d, J=11.0 Hz, C*H*HPh), 4.31 (1H, dd, J=9.6, 4.3 Hz, BnOC*H*), 4.20 (1H, d, J=11.0 Hz, CH*H*Ph), 4.07 (2H, m, $CO_2CH_2CH_3$), 2.41 (1H, m, C*H*CO_2Et), 2.27 (1H, m, CHC*H*HCH), 1.40 (5H, m, CH_2Et, CHCH*H*CH, CH_2CH_3), 1.19 (3H, t, J=7.2 Hz, $CO_2CH_2CH_3$), 0.83 (3H, t, J=7.2 Hz, CH_2CH_3).

4.3.12. Ethyl 2-[2-(*p*-isopropylbenzyloxy)-2-phenylethyl]pentanoate 25 (*syn* and *anti*). IR (neat) 2958, 2872, 2330, 1730, 1456, 1176, 1067, 818, 701 cm^{-1}; MS *m*/*z* 382 (M^+, 2%), 249 (9), 233 (50), 203 (41), 159 (21), 149 (28), 133 (100); HRMS calcd for $C_{25}H_{34}O_3$ [M^+] 382.2508, found 382.2517. *syn*: ^{1}H NMR (400 MHz) δ 7.17–7.35 (9H, m, Ph, C_6H_4), 4.37 (1H, d, J=11.2 Hz, *p*-*i*-PrC_6H_4C*H*H), 4.31 (1H, dd, J=10.4, 3.2 Hz, PhC*H*), 4.19 (1H, d, J=11.2 Hz, *p*-*i*-PrC_6H_4CHH), 4.08 (2H, m, $CO_2CH_2CH_3$), 2.90 (1H, sep, J=6.8 Hz, C*H*$(CH_3)_2$), 2.80 (1H, m, C*H*CO_2Et), 1.97 (1H, ddd, J=14.0, 10.4, 3.6 Hz, CHC*H*HCH), 1.88 (1H, ddd, J=14.0, 9.6, 3.2 Hz, CHCH*H*CH), 1.59 (1H, m, C*H*HEt), 1.43 (1H, m, CH*H*Et), 1.29 (2H, m, $CH_2CH_2CH_3$), 1.24 (6H, d, J=6.8 Hz, CH$(CH_3)_2$), 1.23 (3H, t, J=7.2 Hz, $CO_2CH_2CH_3$), 0.88 (3H, t, J=7.2 Hz, $CH_2CH_2CH_3$); ^{13}C NMR (100 MHz) δ 176.1, 142.4, 135.6, 128.4, 128.0, 127.9, 127.5, 126.4, 126.3, 79.5, 70.7, 60.0, 42.0, 41.4, 35.4, 33.9, 24.1, 20.5, 14.4, 14.1. *anti*: ^{1}H NMR (400 MHz) δ 7.17–7.35 (9H, m, Ph, C_6H_4), 4.37 (1H, d, J=11.2 Hz, *p*-*i*-PrC_6H_4C*H*H), 4.31 (1H, dd, J=10.0, 3.2 Hz, PhC*H*), 4.19 (1H, d, J=11.2 Hz, *p*-*i*-PrC_6H_4CHH), 4.08 (2H, m, $CO_2CH_2CH_3$), 2.90 (1H, sep, J=6.8 Hz, C*H*$(CH_3)_2$), 2.41 (1H, m, C*H*CO_2Et), 2.24 (1H, m, CHC*H*HCH), 1.70 (1H, m, CHCH*H*CH), 1.59 (1H, m, C*H*HEt), 1.43 (1H, m, CH*H*Et), 1.29 (2H, m, $CH_2CH_2CH_3$), 1.24 (6H, d, J=6.8 Hz, CH$(CH_3)_2$), 1.18 (3H, t, J=7.2 Hz, $CO_2CH_2CH_3$), 0.83 (3H, t, J=7.2 Hz, $CH_2CH_2CH_3$).

4.3.13. Ethyl 2-[2-(*p*-methylbenzyloxy)-2-phenylethyl]-pentanoate 26 (*syn* and *anti*). IR (neat) 2930, 2872, 1729, 1454, 1379, 1176, 1067, 1022, 758, 702 cm^{-1}; MS *m*/*z* 354 (M^+, 6%), 307 (12), 249 (5), 233 (23), 209 (87), 130 (61), 105 (93); HRMS calcd for $C_{23}H_{30}O_3$ [M^+] 354.2195, found 354.2181. *syn*: ^{1}H NMR (400 MHz) δ 7.12–7.35 (9H, m, Ph, C_6H_4), 4.37 (1H, d, J=11.2 Hz, *p*-MeC_6H_4C*H*H), 4.29 (1H, dd, J=9.6, 3.6 Hz, PhC*H*), 4.17 (1H, d, J=11.2 Hz, *p*-MeC_6H_4CHH), 4.07 (2H, m, $CO_2CH_2CH_3$), 2.78 (1H, m, C*H*CO_2Et), 2.34 (3H, s, *p*-Me), 1.97 (1H, ddd, J=13.6, 10.2, 3.6 Hz, CHC*H*HCH), 1.86 (1H, ddd, J=13.6, 9.6, 3.6 Hz, CHCH*H*CH), 1.57 (1H, m, C*H*HEt), 1.42 (1H, m, CH*H*Et), 1.28 (2H, m, $CH_2CH_2CH_3$), 1.23 (3H, t, J=7.2 Hz, $CO_2CH_2CH_3$), 0.87 (3H, t, J=7.2 Hz, $CH_2CH_2CH_3$); ^{13}C NMR (100 MHz) δ 176.0, 142.3, 137.0, 135.2, 128.8, 128.3, 127.9, 127.4, 126.4, 79.4, 70.6, 60.0, 42.0, 41.3, 35.3, 21.2, 20.4, 14.4, 14.0. *anti*: ^{1}H NMR (400 MHz) δ 7.12–7.35 (9H, m, Ph, C_6H_4), 4.47 (1H, dd, J=9.6, 3.6 Hz, PhC*H*), 4.37 (1H, d, J=11.2 Hz, *p*-MeC_6H_4C*H*H), 4.16 (1H, d, J=11.2 Hz, *p*-MeC_6H_4CHH), 4.07 (2H, m, $CO_2CH_2CH_3$), 2.43 (1H, m, C*H*CO_2Et), 2.31 (3H, s, *p*-Me), 2.22 (1H, m, CHC*H*HCH), 1.70 (1H, m, CHCH*H*CH), 1.57 (1H, m, C*H*HEt), 1.42 (1H, m, CH*H*Et), 1.28 (2H, m, $CH_2CH_2CH_3$), 1.19 (3H, t, J=7.2 Hz, $CO_2CH_2CH_3$), 0.83 (3H, t, J=7.2 Hz, $CH_2CH_2CH_3$); ^{13}C NMR (100 MHz) δ 176.0, 141.9, 136.9, 135.1, 128.8, 128.5, 127.8, 127.6, 126.8, 79.2, 70.1, 60.4, 42.5, 40.8, 34.5, 21.1, 20.4, 14.3, 14.0.

4.3.14. Ethyl 2-[2-(*p*-methoxybenzyloxy)-2-phenylethyl]-pentanoate 27 (*syn* and *anti*). IR (neat) 2933, 2782, 1729, 1612, 1514, 1455, 1302, 1279, 1174, 1035, 822, 758, 702 cm^{-1}; MS *m*/*z* 370 (M^+, 3%), 234 (5), 203 (12), 137 (45), 121 (100); HRMS calcd for $C_{23}H_{30}O_4$ [M^+] 370.2144, found 370.2133. *syn*: ^{1}H NMR (400 MHz) δ 7.20–7.34 (7H, m, Ph, *p*-MeOCH_2H_2), 6.86 (2H, m, *p*-MeOCH_2H_2), 4.35

(1H, d, J=11.2 Hz, p-MeOC$_6$H$_4$C*H*H), 4.29 (1H, dd, J=9.2, 3.2 Hz, PhC*H*), 4.15 (1H, d, J=11.2 Hz, p-MeOC$_6$H$_4$CH*H*), 4.07 (2H, m, CO$_2$C*H*$_2$CH$_3$), 3.81 (3H, s, OMe), 2.77 (1H, m, C*H*CO$_2$Et), 1.96 (1H, ddd, J=14.0, 9.2, 3.6 Hz, CHC*H*HCH), 1.85 (1H, ddd, J=14.0, 9.6, 3.2 Hz, CHCH*H*CH), 1.57 (1H, m, C*H*HEt), 1.42 (1H, m, CH*H*Et), 1.30 (2H, m, CH$_2$C*H*$_2$CH$_3$), 1.24 (3H, t, J=7.2 Hz, CO$_2$CH$_2$C*H*$_3$), 0.87 (3H, t, J=7.2 Hz, CH$_2$CH$_2$C*H*$_3$); ^{13}C NMR (67.5 MHz) δ 176.0, 142.4, 130.6, 130.4, 129.4, 128.4, 127.4, 126.4, 113.6, 79.3, 70.5, 60.0, 55.3, 42.1, 41.4, 35.4, 20.5, 14.4, 14.0. *anti*: ^{1}H NMR (400 MHz) δ 7.20–7.34 (7H, m, Ph, p-MeOC*H*$_2$H$_2$), 6.86 (2H, m, p-MeOCH$_2$*H*$_2$), 4.29 (1H, d, J=11.2 Hz, p-MeOC$_6$H$_4$-C*H*H), 4.22 (1H, dd, J=9.6, 3.6 Hz, PhC*H*), 4.13 (1H, d, J=11.2 Hz, p-MeOC$_6$H$_4$CH*H*), 4.07 (2H, m, CO$_2$C*H*$_2$CH$_3$), 3.80 (3H, s, OMe), 2.39 (1H, m, C*H*CO$_2$Et), 2.23 (1H, ddd, J=14.4, 9.6, 3.6 Hz, CHC*H*HCH), 1.69 (1H, ddd, J=13.6, 9.6, 3.6 Hz, CHCH*H*CH), 1.57 (2H, m, C*H*$_2$Et), 1.26 (2H, m, CH$_2$C*H*$_2$CH$_3$), 1.20 (3H, t, J=7.2 Hz, CO$_2$CH$_2$C*H*$_3$), 0.83 (3H, t, J=7.2 Hz, CH$_2$CH$_2$C*H*$_3$); ^{13}C NMR (67.5 MHz) δ 176.0, 141.9, 130.4, 129.3, 127.6, 127.6, 126.8, 126.4, 113.7, 79.1, 70.0, 60.0, 57.8, 42.6, 40.8, 34.6, 20.4, 14.3, 14.0.

4.3.15. Ethyl 4-benzyloxy-2-ethyl-4-phenylbutanoate 28 (*syn* and *anti*). IR (neat) 2955, 2873, 1729, 1455, 1177, 1028, 735, 700 cm^{-1}; MS m/z 281 (M$^+$−OEt, 1%), 270 (18), 220 (15), 197 (22), 181 (100), 179 (62), 165 (31), 130 (12), 116 (27), 105 (30), 91 (96); HRMS calcd for C$_{19}$H$_{21}$O$_2$ [M$^+$−OEt] 281.1542, found 281.1523. *syn*: ^{1}H NMR (400 MHz) δ 7.18–7.35 (10H, m, 2×Ph), 4.42 (1H, d, J=11.0 Hz, C*H*HPh), 4.32 (1H, dd, J=9.6, 3.5 Hz, PhC*H*), 4.22 (1H, d, J=11.0 Hz, CH*H*Ph), 4.07 (2H, m, CO$_2$C*H*$_2$-CH$_3$), 2.71 (1H, m, C*H*CO$_2$Et), 1.93 (2H, m, CHC*H*$_2$CH), 1.57 (2H, m, C*H*$_2$CH$_3$), 1.23 (3H, t, J=7.2 Hz, CO$_2$CH$_2$-C*H*$_3$), 0.89 (3H, t, J=7.2 Hz, CH$_2$C*H*$_3$); ^{13}C NMR (100 MHz) δ 175.8, 142.2, 138.3, 128.4, 128.2, 127.8, 127.5, 127.4, 126.4, 79.6, 70.8, 60.0, 43.6, 40.9, 26.3, 14.4, 11.6. *anti*: ^{1}H NMR (400 MHz) δ 7.18–7.35 (10H, m, 2×Ph), 4.42 (1H, d, J=11.0 Hz, C*H*HPh), 4.31 (1H, dd, J=9.6, 3.5 Hz, PhC*H*), 4.21 (1H, d, J=11.0 Hz, CH*H*Ph), 4.07 (2H, m, CO$_2$C*H*$_2$CH$_3$), 2.46 (1H, m, C*H*CO$_2$Et), 2.29 (1H, m, CHC*H*HCH), 1.57 (3H, m, CHCH*H*CH, C*H*$_2$CH$_3$), 1.19 (3H, t, J=7.2 Hz, CO$_2$CH$_2$C*H*$_3$), 0.84 (3H, t, J=7.2 Hz, CH$_2$C*H*$_3$); ^{13}C NMR (100 MHz) δ 176.0, 141.8, 139.3, 128.3, 128.1, 127.7, 127.5, 127.3, 126.8, 79.6, 70.3, 59.1, 43.7, 41.3, 25.5, 14.3, 11.5.

4.3.16. Ethyl 2-ethyl-4-(*p*-methylbenzyloxy)-4-phenylbutanoate 29 (*syn* and *anti*). IR (neat) 2874, 3356, 1728, 1683, 1455, 1179, 1093, 807, 757, 702 cm^{-1}; MS m/z 235 (M$^+$−CH$_2$C$_6$H$_4$Me-p, 4%), 219 (4), 189 (33), 130 (10), 121 (13), 116 (51), 105 (100), 91 (18); HRMS calcd for C$_{14}$H$_{19}$O$_3$ [M$^+$−CH$_2$C$_6$H$_4$Me-p] 235.1334, found 235.1286. *syn*: ^{1}H NMR (400 MHz) δ 7.12–7.38 (9H, m, Ph, C$_6$H$_4$), 4.38 (1H, d, J=11.2 Hz, p-MeC$_6$H$_4$C*H*H), 4.31 (1H, dd, J=9.6, 3.6 Hz, PhC*H*), 4.17 (1H, d, J=11.2 Hz, p-MeC$_6$H$_4$CH*H*), 4.08 (2H, m, CO$_2$C*H*$_2$CH$_3$), 2.71 (1H, m, C*H*CO$_2$Et), 2.33 (3H, s, p-Me), 1.97 (1H, ddd, J=13.6, 10.0, 3.6 Hz, CHC*H*HCH), 1.86 (1H, ddd, J=13.6, 9.6, 3.6 Hz, CHCH*H*CH), 1.58 (2H, m, CHC*H*$_2$CH$_3$), 1.24 (3H, t, J=7.2 Hz, CO$_2$CH$_2$C*H*$_3$), 0.88 (3H, t, J=7.2 Hz, CHCH$_2$-C*H*$_3$); ^{13}C NMR (100 MHz) δ 175.9, 142.3, 137.1, 135.2, 128.9, 128.4, 127.9, 127.5, 126.4, 79.4, 70.6, 60.0, 43.6, 41.3, 26.3, 21.2, 14.4, 11.6. *anti*: ^{1}H NMR (400 MHz) δ 7.12–7.38 (9H, m, Ph, C$_6$H$_4$), 4.47 (1H, dd, J=9.6, 3.6 Hz, PhC*H*), 4.38 (1H, d, J=11.2 Hz, p-MeC$_6$H$_4$C*H*H), 4.16 (1H, d, J=11.2 Hz, p-MeC$_6$H$_4$CH*H*), 4.08 (2H, m, CO$_2$C*H*$_2$-CH$_3$), 2.48 (1H, m, C*H*CO$_2$Et), 2.33 (3H, s, p-Me), 2.18 (1H, m, CHC*H*HCH), 1.71 (1H, m, CHCH*H*CH), 1.58 (2H, m, CHC*H*$_2$CH$_3$), 1.20 (3H, t, J=7.2 Hz, CO$_2$CH$_2$C*H*$_3$), 0.84 (3H, t, J=7.2 Hz, CHCH$_2$C*H*$_3$); ^{13}C NMR (100 MHz) δ 176.0, 142.3, 137.0, 134.4, 128.8, 128.5, 127.9, 127.8, 126.7, 79.3, 71.7, 61.7, 42.0, 41.3, 25.5, 20.4, 14.0, 11.5.

4.3.17. Ethyl 4,4-dimethyl-2-[2-(*p*-methylbenzyloxy)-2-phenylethyl]pentanoate 31 (*syn* and *anti*). IR (neat) 2954, 2867, 1733, 1317, 1454, 1366, 1154, 1064, 1028, 802, 756, 701 cm^{-1}; MS m/z 277 (M$^+$−CH$_2$C$_6$H$_4$Me-p, 3%), 262 (14), 261 (9), 231 (35), 209 (7), 158 (84), 121 (15), 117 (11), 105 (100), 101 (62), 91 (21); HRMS calcd for C$_{17}$H$_{25}$O$_3$ [M$^+$−CH$_2$C$_6$H$_4$Me-p] 277.1803, found 277.1788. *syn*: ^{1}H NMR (400 MHz) δ 7.10–7.37 (9H, m, Ph, C$_6$H$_4$), 4.35 (1H, d, J=11.0 Hz, p-MeC$_6$H$_4$C*H*H), 4.24 (1H, dd, J=9.6, 3.6 Hz, PhC*H*), 4.21 (1H, d, J=11.0 Hz, p-MeC$_6$H$_4$CH*H*), 4.07 (2H, m, CO$_2$C*H*$_2$CH$_3$), 2.85 (1H, m, C*H*CO$_2$Et), 2.34 (3H, s, p-Me), 1.91 (2H, m, CHC*H*$_2$CH), 1.76 (2H, dd, J=14.4, 9.2 Hz, t-BuC*H*$_2$), 1.24 (3H, t, J=7.2 Hz, CO$_2$CH$_2$C*H*$_3$), 0.87 (9H, s, t-Bu); ^{13}C NMR (100 MHz) δ 177.1, 142.2, 137.0, 135.3, 128.9, 128.4, 127.9, 127.5, 126.4, 79.6, 70.8, 60.1, 47.0, 44.2, 39.0, 31.0, 29.5, 21.2, 14.3. *anti*: ^{1}H NMR (400 MHz) δ 7.10–7.37 (9H, m, Ph, C$_6$H$_4$), 4.30 (1H, dd, J=9.6, 3.6 Hz, PhC*H*), 4.35 (1H, d, J=11.0 Hz, p-MeC$_6$H$_4$C*H*H), 4.19 (1H, d, J=11.0 Hz, p-MeC$_6$H$_4$CH*H*), 4.07 (2H, m, CO$_2$C*H*$_2$CH$_3$), 2.52 (1H, m, C*H*CO$_2$Et), 2.33 (3H, s, p-Me), 2.20 (1H, m, CHC*H*HCH), 1.71 (1H, m, CHCH*H*CH), 1.65 (2H, dd, J=14.4, 9.2 Hz, t-BuC*H*$_2$), 1.19 (3H, t, J=7.2 Hz, CO$_2$-CH$_2$C*H*$_3$), 0.82 (9H, s, t-Bu); ^{13}C NMR (100 MHz) δ 177.0, 141.9, 136.9, 135.2, 128.8, 128.6, 127.9, 127.6, 126.7, 79.2, 70.2, 60.1, 46.1, 43.4, 39.3, 30.9, 29.4, 20.5, 14.1.

4.3.18. Ethyl 2-isobutyl-5-methyl-4-(*p*-methylbenzyloxy)hexanoate 33 (*syn* and *anti*). IR (neat) 2871, 1731, 1471, 1174, 1088, 797 cm^{-1}; MS m/z 334 (M$^+$, 5%), 291 (10), 264 (94), 234 (33), 213 (24), 209 (28), 121 (7), 105 (100); HRMS calcd for C$_{21}$H$_{34}$O$_3$ [M$^+$] 334.2508, found 334.2528. *syn*: ^{1}H NMR (400 MHz) δ 7.26 (2H, d, J=7.8 Hz, p-MeC$_6$H$_4$C*H*$_2$H$_2$), 7.15 (2H, d, J=7.8 Hz, p-MeC$_6$H$_4$CH$_2$*H*$_2$), 4.49 (1H, d, J=10.4 Hz, p-MeC$_6$H$_4$-C*H*H), 4.40 (1H, d, J=10.4 Hz, p-MeC$_6$H$_4$CH*H*), 4.10 (2H, m, CO$_2$C*H*$_2$CH$_3$), 3.10 (1H, m, i-PrC*H*), 2.67 (1H, m, C*H*CO$_2$Et), 2.33 (3H, s, p-Me), 1.95 (1H, m, C*H*(CH$_3$)$_2$), 1.76 (1H, ddd, J=14.0, 11.2, 2.4 Hz, CHC*H*HCH), 1.54 (4H, m, CHCH*H*CH, C*H*(CH$_3$)$_2$, i-PrC*H*$_2$), 1.23 (3H, t, J=7.2 Hz, CO$_2$CH$_2$C*H*$_3$), 0.90 (12H, m, 2×CH(C*H*$_3$)$_2$); ^{13}C NMR (100 MHz) δ 176.7, 136.9, 135.8, 128.8, 127.8, 82.3, 72.1, 59.9, 42.8, 40.3, 33.9, 30.5, 26.2, 23.1, 21.9, 18.6, 17.2, 14.4. *anti*: ^{1}H NMR (400 MHz) δ 7.26 (2H, d, J=7.8 Hz, p-MeC$_6$H$_4$C*H*$_2$H$_2$), 7.15 (2H, d, J=7.8 Hz, p-MeC$_6$H$_4$CH$_2$*H*$_2$), 4.49 (1H, d, J=10.4 Hz, p-MeC$_6$H$_4$-C*H*H), 4.40 (1H, d, J=10.4 Hz, p-MeC$_6$H$_4$CH*H*), 4.10 (2H, m, CO$_2$C*H*$_2$CH$_3$), 3.20 (1H, m, i-PrC*H*), 2.54 (1H, m, C*H*CO$_2$Et), 2.33 (3H, s, p-Me), 1.95 (1H, m, C*H*(CH$_3$)$_2$), 1.76 (1H, ddd, J=14.0, 11.2, 2.4 Hz, CHC*H*HCH), 1.54 (4H, m, CHCH*H*CH, C*H*(CH$_3$)$_2$, i-PrC*H*$_2$), 1.23 (3H, t,

J=7.2 Hz, $CO_2CH_2CH_3$), 0.90 (12H, m, 2×CH(CH_3)$_2$); ^{13}C NMR (100 MHz) δ 175.3, 137.1, 135.2, 129.0, 127.7, 81.5, 71.7, 59.9, 42.7, 40.8, 33.4, 29.9, 26.2, 23.3, 21.9, 18.0, 16.7, 14.1.

4.3.19. Ethyl 5-methyl-4-(*p*-methylbenzyloxy)-2-(2,2-dimethypropyl)hexanoate 35 (*syn* and *anti*). IR (neat) 2871, 1731, 1470, 1173, 1078, 796 cm^{-1}; MS *m*/*z* 227 ($M^+-CH_2C_6H_4Me$-*p*, 8%), 203 (5), 158 (88), 121 (20), 105 (100), 101 (63); HRMS calcd for $C_{14}H_{27}O_2$ [$M^+-CH_2C_6H_4Me$-*p*] 277.2011 found 277.2052. *syn*: ^{1}H NMR (400 MHz) δ 7.27 (2H, d, J=8.3 Hz, *p*-MeOC$_6$H$_4$CH_2H$_2$), 7.14 (2H, d, J=8.3 Hz, *p*-MeOC$_6$H$_4$CH$_2H_2$), 4.48 (1H, d, J=10.4 Hz, *p*-MeC$_6$H$_4$C*H*H), 4.43 (1H, d, J=10.4 Hz, *p*-MeC$_6$H$_4$CH*H*), 4.09 (2H, m, $CO_2CH_2CH_3$), 3.07 (1H, m, *i*-PrC*H*), 2.74 (1H, m, C*H*CO$_2$Et), 2.34 (3H, s, *p*-Me), 1.95 (1H, m, C*H*(CH_3)$_2$), 1.78 (2H, m, CHCH_2CH), 1.50 (2H, m, *t*-BuCH_2), 1.24 (3H, t, J=7.2 Hz, $CO_2CH_2CH_3$), 0.88 (6H, d, J=6.8 Hz, CH(CH_3)$_2$), 0.87 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz) δ 177.5, 136.9, 135.9, 128.9, 127.9, 82.3, 72.1, 60.0, 47.5, 38.8, 36.4, 31.0, 29.5, 21.2, 18.6, 17.2, 14.3. *anti*: ^{1}H NMR (400 MHz) δ 7.27 (2H, d, J=8.3 Hz, *p*-MeOC$_6$H$_4$CH_2H$_2$), 7.23 (2H, d, J=8.3 Hz, *p*-MeOC$_6$H$_4$-CH$_2H_2$), 4.48 (1H, d, J=10.4 Hz, *p*-MeC$_6$H$_4$C*H*H), 4.43 (1H, d, J=10.4 Hz, *p*-MeC$_6$H$_4$CH*H*), 4.01 (2H, m, CO_2-CH_2CH$_3$), 3.18 (1H, m, *i*-PrC*H*), 2.52 (1H, m, C*H*CO$_2$Et), 2.35 (3H, s, *p*-Me), 1.95 (1H, m, C*H*(CH_3)$_2$), 1.78 (2H, m, CHCH_2CH), 1.50 (2H, m, *t*-BuCH_2), 1.20 (3H, t, J=7.2 Hz, $CO_2CH_2CH_3$), 0.88 (6H, d, J=6.8 Hz, CH(CH_3)$_2$), 0.83 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz) δ 177.5, 137.0, 135.2, 128.8, 127.8, 81.5, 71.0, 60.1, 46.3, 39.1, 35.3, 30.5, 29.5, 21.4, 18.0, 17.5, 14.1.

4.3.20. Ethyl 4-methyl-2-(benzyloxyphenylmethyl)-pentanoate 38 (*syn* and *anti*). To a solution of α-methylene ester **36** (0.15 mmol) in dry CH_2Cl_2 (1.5 cm^3) was added $MgBr_2$·OEt_2 (0.75 mmol, 5 equiv.), and the mixture was stirred at room temperature for 10 min. To the suspension cooled to −78 °C were added isopropyl iodide (0.45 mmol, 3 equiv.), *n*-Bu_3SnH (0.30 mmol, 2 equiv.) and Et_3B (1.06 mol dm^{-3} in hexane; 0.03 mmol, 0.2 equiv.). The mixture was stirred at −78 °C for 6 h. KF and water were added and the reaction mixture was stirred at room temperature for 3 h. After filtration, the solvent was evaporated in vacuo. The residue was purified by flash chromatography on silica gel to give the product as an oily inseparable diastereomeric mixture. The stereochemistry was determined by comparing their chemical shift values with those of methyl 2-methyl-3-benzyloxy-3-phenyl-propanoate.[12] MS *m*/*z* 249 (M^+-Bn, 5%), 234 (24), 197 (82), 178 (19), 160 (24), 105 (26); HRMS calcd for $C_{15}H_{21}O_3$ [M^+-Bn] 249.1491, found 249.1503. *syn*:^{1}H NMR (400 MHz) δ 7.18–7.40 (10H, m, 2×Ph), 4.44 (1H, d, J=10.4 Hz, PhC*H*H), 4.39 (1H, d, J=8.8 Hz, BnOC*H*), 4.23 (1H, d, J=10.4 Hz, PhCH*H*), 3.82 (2H, q, J=6.8 Hz, $CO_2CH_2CH_3$), 2.84 (1H, m, C*H*CO$_2$Et), 1.75 (2H, m, CHCH_2CH), 1,50 (1H, m, C*H*(CH_3)$_2$), 0.99 (3H, d, J=6.2 Hz, CHCH_3), 0.90 (3H, t, J=6.8 Hz, $CO_2CH_2CH_3$), 0.87 (3H, d, J=6.2 Hz, CHCH_3); ^{13}C NMR (100 MHz) δ 173.4, 139.6, 138.1, 128.2, 128.1, 127.9, 127.7, 127.6, 127.5, 82.5, 70.5, 59.9, 52.4, 38.4, 26.6, 23.7, 21.6, 13.9. *anti*: ^{1}H NMR (400 MHz) δ 7.18–7.40 (10H, m, 2×Ph), 4.42 (1H, d, J=9.0 Hz, BnOC*H*), 4.35 (1H, d, J=10.4 Hz, PhC*H*H), 4.19 (1H, d, J=10.4 Hz, PhCH*H*), 4.21 (2H, q, J=6.8 Hz, $CO_2CH_2CH_3$), 2.87 (1H, m, C*H*CO$_2$Et), 1.50 (2H, m, CHCH_2CH), 1,37 (1H, m, C*H*(CH_3)$_2$), 1.26 (3H, t, J=6.8 Hz, $CO_2CH_2CH_3$), 0.75 (3H, d, J=6.2 Hz, CHCH_3), 0.73 (3H, d, J=6.2 Hz, CHCH_3); ^{13}C NMR (100 MHz) δ 174.8, 139.2, 138.0, 128.4, 128.2, 128.0, 127.8, 127.6, 127.3, 83.6, 70.5, 60.4, 51.6, 38.0, 26.1, 23.6, 21.1, 14.4.

4.3.21. Ethyl 4-methyl-2-[(*p*-methylbenzyloxy)phenyl-methyl]pentanoate 39 (*syn* and *anti*). The radical reaction of **37** was carried out according to the procedure as described above. MS *m*/*z* 249 ($M^+-CH_2C_6H_4Me$-*p*, 2%), 234 (62), 190 (35), 178 (36), 160 (44), 121 (30); HRMS calcd for $C_{15}H_{21}O_3$ [$M^+-CH_2C_6H_4Me$-*p*] 249.1491, found 249.1503. *syn*:^{1}H NMR (400 MHz) δ 7.06–7.40 (9H, m, Ph, C_6H_4), 4.37 (1H, d, J=8.8 Hz, PhC*H*), 4.32 (1H, d, J=11.8 Hz, PhC*H*H), 4.14 (1H, d, J=11.8 Hz, PhCH*H*), 3.80 (2H, q, J=6.8 Hz, $CO_2CH_2CH_3$), 2.84 (1H, m, C*H*CO$_2$Et), 2.34 (3H, s, *p*-Me), 1.74 (2H, m, CHCH_2CH), 1,49 (1H, m, C*H*(CH_3)$_2$), 0.93 (3H, t, J=6.8 Hz, CO_2CH_2-CH_3), 0.75 (3H, d, J=6.8 Hz, CHCH_3), 0.73 (3H, d, J=6.2 Hz, CHCH_3); ^{13}C NMR (100 MHz) δ 174.8, 139.7, 137.1, 135.0, 128.9, 128.1, 127.8, 127.7, 127.5, 82.3, 70.3, 59.9, 52.4, 38.4, 26.6, 23.7, 21.6, 21.2, 13.9. *anti*:^{1}H NMR (400 MHz) δ 7.06–7.40 (9H, m, Ph, C_6H_4), 4.42 (1H, d, J=11.8 Hz, PhC*H*H), 4.39 (1H, d, J=8.8 Hz, PhC*H*), 4.19 (1H, d, J=11.8 Hz, PhCH*H*), 4.14 (2H, m, $CO_2CH_2CH_3$), 2.85 (1H, m, C*H*CO$_2$Et), 2.32 (3H, s, *p*-Me), 1.49 (2H, m, CHCH_2CH), 1,35 (1H, m, C*H*(CH_3)$_2$), 1.26 (3H, t, J=6.8 Hz, $CO_2CH_2CH_3$), 0.89 (3H, d, J=6.8 Hz, CHCH_3), 0.87 (3H, d, J=6.2 Hz, CHCH_3); ^{13}C NMR (100 MHz) δ 174.8, 139.6, 139.3, 135.0, 128.9, 128.1, 127.8, 127.7, 127.5, 83.3, 70.2, 60.3, 51.5, 38.0, 26.1, 23.6, 21.6, 21.2, 14.4.

References and notes

1. For reviews and books, see: (a) Smadja, W. *Synlett* **1994**, 1–26. (b) Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296–304. (c) RajanBabu, T. V. *Acc. Chem. Res.* **1991**, *24*, 139–145. (d) Renaud, P.; Sibi, M. P. *Radicals in Organic Synthesis*; VCH: Weinheim, 2001; Vols. 1–2. (e) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1996.
2. For reviews, see: (a) Sibi, M. P.; Porter, N. A. *Acc. Chem. Res.* **1999**, *32*, 163–171. (b) Renaud, P.; Gerster, M. *Angew. Chem. Int. Ed.* **1998**, *37*, 2562–2579. (c) Guindon, Y.; Guérin, B.; Rancourt, J.; Chabot, C.; Makintosh, N.; Ogilvie, W. W. *Pure. Appl. Chem.* **1996**, *68*, 89–96. For recent examples, see: (d) Iserloh, U.; Curran, D. P.; Kanemasa, S. *Tetrahedron: Asymmetry* **1999**, *10*, 2417–2428. (e) Watanabe, Y.; Mase, N.; Furue, R.; Toru, T. *Tetrahedron Lett.* **2001**, *42*, 2981–2984. (f) Halland, N.; Jørgensen, K. A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1290–1295.
3. For a review on 1,3-asymmetric induction, see: (a) Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191–1223. For radical mediated 1,3-asymmetric inductions via eight-membered chelate rings, see: (b) Hayen, A.; Koch, R.; Metzger, J. O. *J. Am. Chem. Soc.* **2000**, *122*, 12458–12468.
4. (a) Nagano, H.; Toi, S.; Yajima, T. *Synlett* **1999**, 53–54. (b) Nagano, H.; Hirasawa, T.; Yajima, T. *Synlett* **2000**,

1073–1075. (c) Nagano, H.; Matsuda, M.; Yajima, T. *J. Chem. Soc., Perkin Trans. 1* **2001**, 174–182. (d) Nagano, H.; Toi, S.; Hirasawa, T.; Matsuda, M.; Hirasawa, S.; Yajima, T. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2525–2538. (e) Nagano, H.; Ohkouchi, H.; Yajima, T. *Tetrahedron* **2003**, *59*, 3649–3663.

5. (a) Goto, H.; Osawa, E. *J. Am. Chem. Soc.* **1989**, *111*, 8950–8953. (b) Goto, H.; Osawa, E. *J. Chem. Soc., Perkin Trans. 2* **1993**, 187–198.
6. For the reaction via seven-membered chelation with Lewis acid, see:(a) Yang, M. G.; Modi, D. P.; Wexler, R. R.; Olson, R. E. *Tetrahedron Lett.* **2004**, *45*, 111–112. (b) Krafft, M. E.; Dasse, O. A.; Jarrett, S.; Fievre, A. *J. Org. Chem.* **1995**, *60*, 5093–5101. (c) Angert, H.; Kunz, T.; Reissig, H.-U. *Tetrahedron* **1992**, *48*, 5681–5690.
7. For the conformation of seven-membered cyclic radicals, see; (a) Sibi, M. P.; Asano, Y.; Sausker, J. B. *Angew. Chem. Int., Ed.* **2001**, *40*, 1293–1296. For examples of five and six-membered cyclic radicals, see: (b) Giese, B. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 969–980. (c) Damm, W.; Giese, B.; Hartung, J.; Hasskerl, T.; Houk, K. N.; Hüter, O.; Zipse, H. *J. Am. Chem. Soc.* **1992**, *114*, 4067–4079. (d) Cai, Y.; Roberts, B. P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 467–476.
8. Hammett, L. P. *J. Am. Chem. Soc.* **1937**, *59*, 96–99.
9. For the correlations of diastereoselectivities versus Hammett sigma constants, see: (a) Galardon, E.; Le Maux, P.; Simonneaux, G. *Tetrahedron* **2000**, *56*, 615–621. (b) Morgan, A. J.; Masse, C. E.; Panek, J. S. *Org. Lett.* **1999**, *1*, 1949–1952. (c) Gugelchuk, M. M.; Chan, P. C.-M.; Sprules, T. J. *J. Org. Chem.* **1994**, *59*, 7723–7731. (d) Chini, M.; Crotti, P.; Minutolo, F.; Dezi, E.; Lombardozzi, A.; Pizzabiocca, A.; Renzi, G. *Tetrahedron* **1993**, *49*, 5845–5858. (e) Kunieda, N.; Nokami, J.; Kinoshita, M. *Bull. Chem. Soc. Jpn* **1992**, *65*, 526–529. (f) Kunieda, N.; Nakanishi, T.; Kinoshita, M. *Bull. Chem. Soc. Jpn* **1989**, *62*, 2229–2234. (g) Chini, M.; Crotti, P.; Ferretti, M.; Macchia, F. *Tetrahedron* **1988**, *44*, 2001–2014.
10. The radical reaction of **7** with *i*-PrI using *n*-Bu_3SnD showed the D-atom abstraction of the radical α to the ester carbonyl group. An alternative reaction mechanism involving the intramolecular 1,5-hydrogen atom transfer from the benzylic position was thus excluded. For the 1,5-hydrogen transfer from benzylic position, see: (a) Kunishima, M.; Hioki, K.; Kono, K.; Kato, A.; Tani, S. *J. Org. Chem.* **1997**, *62*, 7542–7543. (b) Benati, L.; Capella, L.; Montevecchi, P. C.; Spagnolo, P. *J. Org. Chem.* **1994**, *59*, 2818–2823. (c) Rochigneux, I.; Fontanel, M.-L.; Malanda, J.-C.; Doutheau, A. *Tetrahedron Lett.* **1991**, *32*, 2017–2020.
11. NMR studies on complexation of β-benzyloxy aldehyde with $MgBr_2{\cdot}OEt_2$, see: (a) Keck, G. E.; Castellino, S. *J. Am. Chem. Soc.* **1986**, *108*, 3847–3849. (b) Keck, G. E.; Castellino, S.; Wiley, M. R. *J. Org. Chem.* **1986**, *51*, 5480–5482.
12. Brown, D. J. *J. Appl. Chem. (London)* **1952**, *2*, 202–203.
13. Guindon, Y.; Rancourt, J. *J. Org. Chem.* **1998**, *63*, 6554–6565.
14. (a) Aggarwal, V. K.; Mereu, A. *Chem. Commun.* **1999**, 2311–2312. (b) Wessel, H.-P.; Iversen, T.; Bundle, D. R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2247–2249.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 5695–5700
Tetrahedron

Total synthesis of dehydroaltenusin

Shinji Kamisuki,[a] Shunya Takahashi,[b,*] Yoshiyuki Mizushina,[c] Shinya Hanashima,[b] Kouji Kuramochi,[d] Susumu Kobayashi,[d] Kengo Sakaguchi,[a,d] Tadashi Nakata[b] and Fumio Sugawara[a,d]

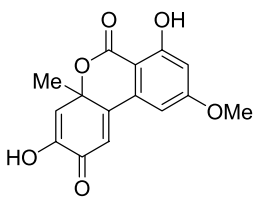
[a]*Department of Applied Biological Science, Tokyo University of Science, Noda, Chiba 278-8510, Japan*
[b]*RIKEN (The Institute of Physical and Chemical Research), Wako, Saitama 351-0198, Japan*
[c]*Department of Nutritional Science, Kobe-Gakuin University, Kobe, Hyogo 651-2180, Japan*
[d]*Genome and Drug Discovery Research Center, Tokyo University of Science, Noda, Chiba 278-8510, Japan*

Received 14 April 2004; revised 6 May 2004; accepted 10 May 2004

Abstract—The first total synthesis of dehydroaltenusin, a natural enzyme inhibitor, is described. The key step involves Suzuki-coupling reaction of an aryl triflate prepared from 2,4,6-trihydroxybenzoic acid with a catechol-derived boronic acid or boronic ester. The synthetic product was evaluated as a potent inhibitor against eukaryotic DNA polymerase α and other DNA polymerases.

1. Introduction

Eukaryotic multicellular organisms are known to contain at least 14 types of DNA polymerases.[1,2] DNA polymerase α is an essential enzyme for DNA replication and subsequently for cell division.[1] Aphidicolin, a well-known DNA polymerase α inhibitor, has been very useful for studying the DNA replication system,[3] however, there have been no previous reports of inhibitors capable of distinguishing among DNA polymerases α, δ and ϵ. Recently, we have isolated a powerful mammalian DNA polymerase α inhibitor (IC_{50}=0.68 μM) from *Acremonium* sp. 98H02B04-1 (2) and revealed it to be dehydroaltenusin (**1**),[4] which was discovered from mycelium extracts of *Alternaria tennuis* and *A. kikuchiana* by Rosett et al. in 1957[5] and then from a variety of fungi.[6,7] The structure was initially suggested to be a γ-lactone derivative of β-resorcylic acid monomethylether based on the chemical and spectroscopic data[6] and later revised to **1** possessing a δ-lactone ring by the X-ray crystallographic analyses (Fig. 1).[8] In 1995, **1** was also reported to inhibit the calmodulin-dependent activity of myosin light chain kinase (MLCK).[9]



dehydroaltenusin (**1**)

Figure 1.

Compound **1** inhibits only mammalian DNA polymerase α activity, but does not influence the activities of mammalian DNA polymerase δ and ϵ, nor DNA polymerase α from other vertebrates in vitro, and found to be more potent inhibitor of DNA polymerase α than aphidicolin.[4] We have also reported **1** suppressed the cell proliferation of the human gastric cell line NUGC-3 by inhibiting DNA polymerase α activity.[10] The specific inhibitors of mammalian DNA polymerase α are not only molecular tools and molecular probes to distinguish DNA polymerases and clarify their biological and in vivo functions, but should also be considered as a group of potentially useful cancer chemotherapy agents. However, its low producibility has prevented such utilization. Furthermore, no total synthesis of **1** has been reported so far. We report herein the first synthesis of racemic **1** and its inhibitory activity against a series of DNA polymerases.[11]

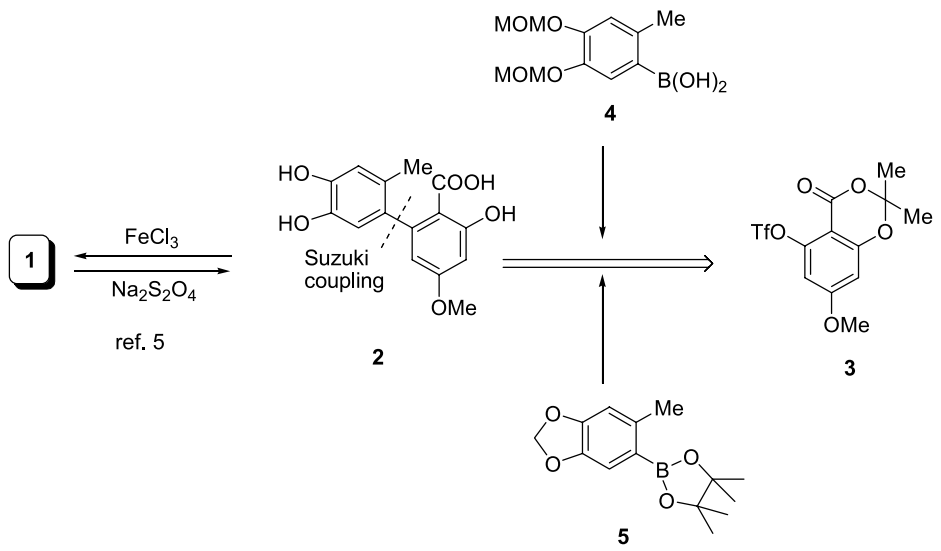
2. Results and discussion

2.1. Total synthesis of dehydroaltenusin

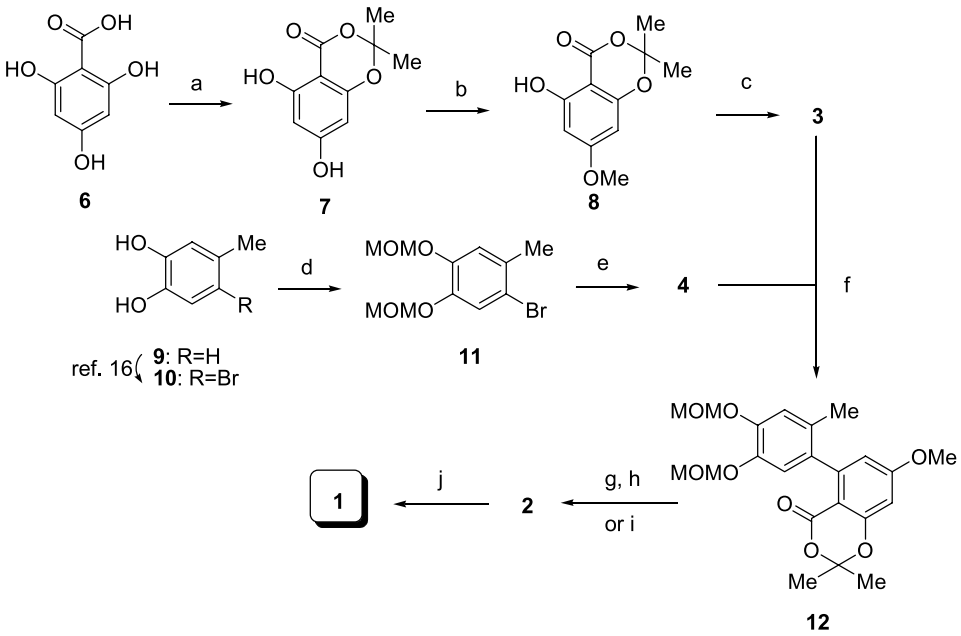
Rosett et al. has reported that $FeCl_3$-promoted oxidation of altenusin **2** afforded **1**.[5] Therefore, **2** was regarded as our

Keywords: Dehydroaltenusin; DNA polymerase α; Enzyme inhibitor.
* Corresponding author. Tel.: +81-48-462-1111-3627; fax: +81-48-462-4627; e-mail address: shunyat@riken.go.jp

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.05.017



Scheme 1. Retrosynthetic scheme of dehydroaltenusin (**1**).

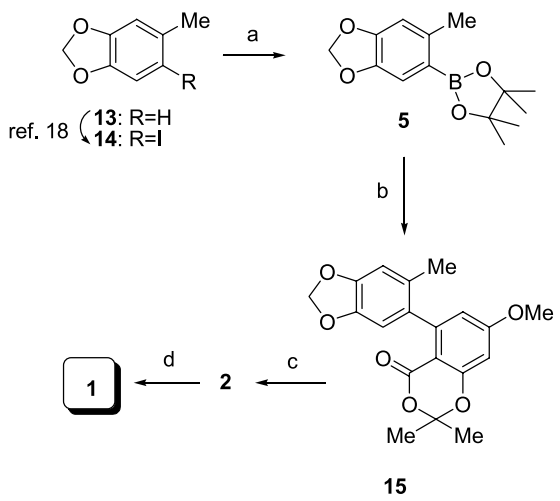


Scheme 2. Reagents and conditions: (a) acetone, $SOCl_2$, DMAP, DME, rt, 56%; (b) DIAD, Ph_3P, MeOH, THF, rt, 89%; (c) Tf_2O, pyridine, 0 °C, 94%; (d) MOMCl, NaH, DMF, 0 °C, 90%; (e) *n*-BuLi, THF, −78∼−40 °C, then $(i\text{-PrO})_3B$, Et_2O, −78 °C∼rt, 95%; (f) $(Ph_3P)_4Pd$, K_3PO_4, KBr, dioxane, 100 °C, 93%; (g) 2N KOH, EtOH, 60 °C; (h) 10% HCl–MeOH, CH_2Cl_2, rt, 64% (two steps); (i) BCl_3 (10 equiv.), CH_2Cl_2, 0 °C∼rt, 63%; (j) $FeCl_3$, aq. EtOH, rt, 82%.

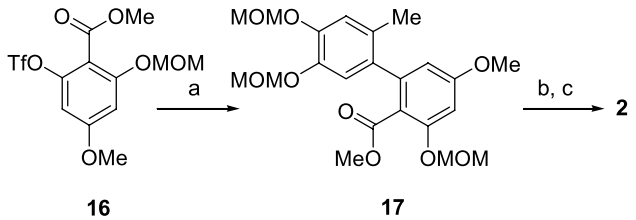
actual synthetic goal. Our synthetic efforts toward **2** involved Suzuki-coupling[12] reaction of an aryltriflate **3** with an aryl boronic acid **4** or boronic ester **5** as a key step (Scheme 1). Synthesis of the aryltriflate **3** started from commercially available 2,4,6-trihydroxybenzoic acid **6**. The benzoic acid **6** was reacted with thionyl chloride ($SOCl_2$) in the presence of *N*,*N*-dimethylaminopyridine (DMAP) in acetone[13] to give acetonide **7** in 56% yield, whereas in 43% yield by Danishefsky's method (trifluoroacetic acid–trifluoroacetic anhydride in acetone)[14] (Scheme 2). Danishefsky et al. has accomplished regioselective protection of 4-hydroxy group of **7** by the Mitsunobu conditions[15] with diisopropyl azodicarboxylate–triphenylphosphine in the presence of benzyl alcohol.[14] Regioselective methylation of **7** was performed according to this method, affording monomethyl ether **8** in 89% yield. Treatment of **8** with triflic anhydride-pyridine gave the corresponding triflate **3** in 94% yield. On the other hand, a 4-bromocatechol **10**[16] prepared from 4-methylcatechol (**9**) was subjected to methoxymethylation with sodium hydride (NaH) and methoxymethyl chloride (MOMCl), giving bis-MOM ether **11** in 90% yield. Halogen–lithium exchange of **11** with *n*-butyllithium in tetrahydrofuran (THF) at −78→−40 °C followed by trapping with triisopropyl borate (Et_2O, −78 °C→rt) afforded an aryl boronic acid **4** in 95% yield. This compound was, without purification, employed to the next coupling reaction, because of its instability. Introduction of a catechol moiety into **3** was best realized by using 1.5 mol equiv. of **4** in the presence of tetrakis(triphenylphosphine)palladium (0.05 mol equiv.), potassium

phosphate and potassium bromide in dioxane[17] at 100 °C to produce a coupled product **12** in 93% yield. Alkaline hydrolysis of **12** and subsequent acid treatment provided altenusin **2** in 64% yield. This compound was also obtained by the action of boron trichloride (BCl_3) in dichloromethane (CH_2Cl_2) from **12** in a single step (63%). Finally, $FeCl_3$-promoted oxidation[5] of **2** afforded dehydroaltenusin (**1**) in 82% yield.† The spectroscopic and physical properties of **1** were identical with those of natural **1** (vide infra).

Furthermore, we have also developed an alternative shorter route through boronic ester **5** (Scheme 3). 2-Iode-4,5-methylenedioxytoluene (**14**)[18] obtained from commercially available 3,4-methylenedioxytoluene (**13**) was treated with bis(pinacolato)diboron[19] in the presence of dichloro[1,1′-bis(diphenylphosphino)ferrocene]palladium {$PdCl_2$(dppf), 0.1 mol equiv.} and potassium acetate in *N*,*N*-dimethylformamide, giving boronic ester **5** in 81% yield. Triflate **3** was coupled with the boronic ester **5** (1.3 mol equiv.) using $PdCl_2$(dppf) (0.05 mol equiv.) and potassium carbonate (3.0 mol equiv.) in 1,2-dimethoxyethane (DME)[20] at 85 °C to provide **15** in 67% yield. Deprotection of **15** by BCl_3 yielded **2**, which was transformed into dehydroaltenusin (**1**).



Scheme 3. Reagents and conditions: (a) bis(pinacolato)diboron, $PdCl_2$-(dppf), KOAc, DMF, 80 °C, 81%; (b) **3**, $PdCl_2$(dppf), K_2CO_3, DME, 85 °C, 67%; (c) BCl_3, CH_2Cl_2, rt, 80%; (d) $FeCl_3$, aq. EtOH, rt, 82%.



Scheme 4. Reagents and conditions: (a) **4**, $(Ph_3P)_4Pd$, K_3PO_4, KBr, dioxane, 100 °C, 70%; (b) 2 N KOH, EtOH, 60 °C; (c) 10% HCl–MeOH, CH_2Cl_2, rt, 86% (two steps).

† Our initial approach to **1** was based on the coupling reaction of **4** and triflate **16** ((Scheme 4)). However, we did not adopt this route for large-scale synthesis of **1** because preparation of **16** from methyl 2,6-dihydroxy-4-methoxybenzoate[23] was found to be not practical.

2.2. Inhibition studies and discussion

DNA polymerase inhibition assay was performed as described previously.[21,22] Inhibitory activity of the synthetic compound **1** against the calf DNA polymerase α, rat DNA polymerase β, calf DNA polymerase δ and human DNA polymerase ϵ was examined and compared with that of natural **1**. As illustrated in Figure 2, the IC_{50} values of synthetic and natural **1** for DNA polymerase α were 0.8 and 0.7 μM, respectively, and both compounds had no inhibitory effect on DNA polymerase β, δ and ϵ. Therefore, the inhibitory activity of the two compounds was not distinguishable.

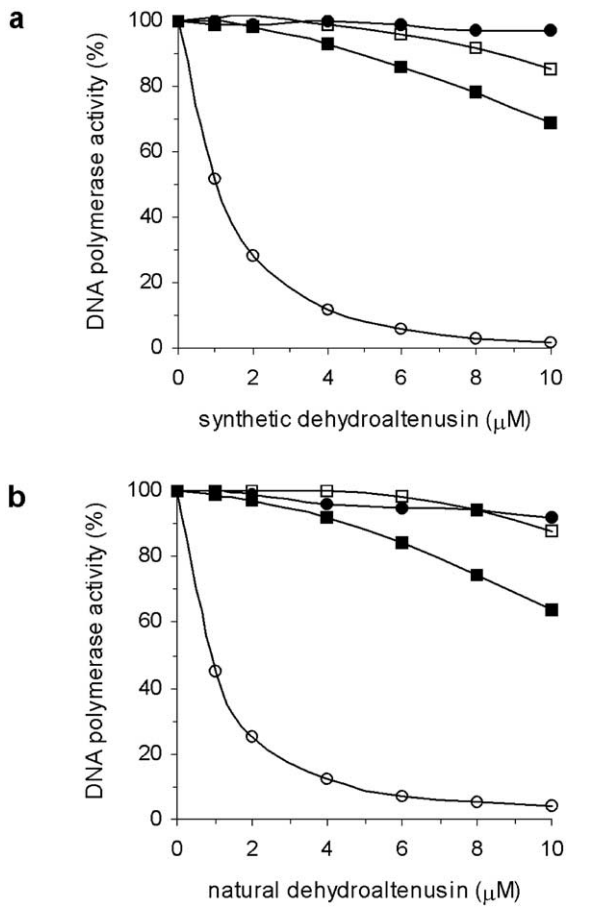


Figure 2. Dose–response curve of synthetic (a) and natural (b) dehydroaltenusin. Inhibition activity against eukaryotic DNA polymerase α, β, δ and ϵ are shown as open circle, closed circle, open square, and closed square symbols, respectively. DNA polymerase activity in the absence of compound was taken as 100%.

2.3. Conclusion

In summary, the first synthesis of dehydroaltenusin (**1**) has been accomplished in 7 steps with 23% yield or in 6 steps with 21% overall yield from a commercially available carboxylic acid **6**. These synthetic processes would be quite useful for preparation of large amounts of **1** suitable for in vitro and in vivo experiments on DNA polymerase α and future clinical usage.

3. Experimental

3.1. General procedures

^{1}H and ^{13}C NMR spectra were recorded at 400 MHz with Bruker DRX-400 spectrometer, using tetramethylsilan as the internal standard. IR spectra were recorded with a HORIBA FREEXACT-II FT-720 spectrophotometer. High-resolution mass spectra were obtained on Applied Biosystems QSTAR Mass Spectrometer using electron spray ionization (ESI) method. Column chromatography was performed on Kanto silica gel (spherical, neutral; 40–50 μm). Merck precoated silica gel 60 F_{254} 0.25 mm thickness, was used for analytical thin-layer chromatography. All reactions were performed under argon atmosphere. The solvent extracts were dried with sodium sulfate, and the solutions were evaporated under diminished pressure at 30–50 °C.

3.1.1. 5,7-Dihydroxy-2,2-dimethyl-4*H*-1,3-benzodioxin-4-one (7). To a solution of 2,4,6-trihydroxy-benzoic acid (**6**) (23.0 g, 135 mmol), *N*,*N*-dimethylaminopyridine (1.65 g, 13.4 mmol), and acetone (25.7 mL, 350 mmol) in 1,2-dimethoxyethane (100 mL) was added dropwise thionyl chloride (29 mL, 398 mmol) at 0 °C. The mixture was warmed slowly to rt and then stirred for 2 h. The mixture was poured into sat. $NaHCO_3$ solution, and extracted with EtOAc. The extracts were washed with water, dried, and concentrated. Chromatography on silica gel with hexane–EtOAc (13:7) as the eluent yielded **7** (16.0 g, 56%) as white solids: mp 200–201 °C (lit.[14] 203–204 °C); ^{1}H NMR (400 MHz, acetone-d_6): δ 1.72 (6H, s), 3.02 (1H, brs), 6.01 (1H, d, *J*=2.2 Hz), 6.08 (1H, d, *J*=2.2 Hz,), 10.46 (1H, s); ^{13}C NMR (100 MHz, acetone-d_6): δ 25.6, 93.0, 96.2, 98.0, 107.6, 158.1, 164.0, 165.8, 167.2; HRMS calcd for $C_{10}H_{10}O_5Na$ $[M+Na]^+$ 233.0420, found 233.0428.

3.1.2. 5-Hydroxy-7-methoxy-2,2-dimethyl-4*H*-1,3-benzodioxin-4-one (8). To a stirred solution of **7** (2.54 g, 12.1 mmol), methanol (0.53 mL, 13.0 mmol) and triphenylphosphine (3.40 g, 13.0 mmol) in tetrahydrofuran (40 mL) was added dropwise diisopropyl azodicarboxylate (2.6 mL, 13.0 mmol) at 0 °C, and then the mixture was stirred at 0 °C→rt for 4.5 h. The mixture was diluted with EtOAc, washed with water, brine, dried, and concentrated. Chromatography on silica gel with hexane→hexane–EtOAc (10:1) as the eluent yielded **8** (2.41 g, 89%) as white solids: mp 108–109 °C {hexane–EtOAc (20:1)}; IR (KBr) 3194, 2985, 2947, 2854, 1697, 1635, 1581, 1192, 1157 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.73 (6H, s), 3.82 (3H, s), 6.00 (1H, d, *J*=2.3 Hz), 6.15 (1H, d, *J*=2.3 Hz), 10.45 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.6, 55.7, 93.1, 94.6, 95.7, 106.9, 156.8, 163.1, 165.2, 167.7; HRMS calcd for $C_{11}H_{12}O_5Na$ $[M+Na]^+$ 247.0576, found 247.0587. Anal. Found: C, 58.91; H, 5.51. Calcd for $C_{11}H_{12}O_5$: C, 58.93; H, 5.39.

3.1.3. 7-Methoxy-2,2-dimethyl-5-[(trifluoromethyl)-sulfonyl]-4*H*-1,3-benzodioxin-4-one (3). To a stirred solution of **8** (1.0 g, 4.46 mmol) in pyridine (25 mL) was added dropwise triflic anhydride (0.83 mL, 4.91 mmol) at −10 °C, and then the mixture was stirred at 0 °C for 3.5 h. After addition of ice–water, the resulting mixture was vigorously stirred, and then extracted with ether. The extracts were washed with cold dilute HCl solution, water, sat. $NaHCO_3$ solution, water, brine, dried, and concentrated. Chromatography on silica gel with hexane→hexane–EtOAc (6:1) as the eluent yielded **3** (1.50 g, 94%) as white solids: mp 58–59 °C {hexane–EtOAc (50:1)}; IR (KBr) 2993, 2954, 2850, 1747, 1624, 1431, 1284, 1203, 1138, 1061 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.74 (6H, s), 3.89 (3H, s), 6.49 (1H, d, *J*=2.3 Hz), 6.53 (1H, d, *J*=2.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.5, 56.3, 100.9, 101.1, 105.3, 106.6, 118.7 (q, *J*=320 Hz), 149.9, 157.1, 158.8, 165.5; HRMS calcd for $C_{12}H_{11}F_3O_7SNa$ $[M+Na]^+$ 379.0069, found 379.0058. Anal. Found: C, 40.64; H, 2.93. Calcd for $C_{12}H_{11}F_3O_7S$: C, 40.45; H, 3.11.

3.1.4. 1-Bromo-4,5-bis(methoxymethoxy)-2-methylbenzene (11). To a stirred solution of **10** (5.83 g, 28.7 mmol) in *N*,*N*-dimethylformamide (95 mL) was added sodium hydride (60% in mineral oil, 2.87 g, 71.8 mmol) by portions at 0 °C, and then the mixture was stirred at 0 °C for 1 h. Chloro methylmethylether (5.45 mL, 71.8 mmol) was added dropwise at 0 °C, and then the mixture was stirred at 0 °C for 6 h. After addition of sat. NH_4Cl solution, the resulting mixture was extracted with ether. The extracts were washed with water, brine, dried, and concentrated. Chromatography on silica gel with hexane–EtOAc (30:1→20:1) as the eluent yielded **11** (7.54 g, 90%) as a colorless oil: IR (neat) 2957, 2933, 2829, 1500, 1255, 1151, 1080, 1003 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.31 (3H, s), 3.51 (6H, s), 5.17 (1H, d, *J*=6.7 Hz), 5.20 (1H, d, *J*=6.7 Hz), 7.03 (1H, brs), 7.32 (1H, brs); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.2, 56.0, 95.2, 95.4, 116.1, 118.5, 120.4, 131.3, 145.5, 146.1; HRMS calcd for $C_{11}H_{15}O_4{}^{79}Br$ ($C_{11}H_{15}O_4{}^{81}Br$) $[M+H]^+$ 290.0154 (292.0134), found 290.0156 (292.0129).

3.1.5. 5-[4,5-Bis(methoxymethoxy)-2-methylphenyl]-7-methoxy-2,2-dimethyl-4*H*-1,3-benzodioxin-4-one (12). To a stirred solution of **11** (2.32 g, 7.97 mmol) in tetrahydrofuran (21 mL) was added dropwise a 1.59 M solution of *n*-butyllithium (5.5 mL, 8.77 mmol) in hexane at −78 °C, and the mixture was stirred at −78→−40 °C for 1.4 h. Then a solution of triisopropyl borate (2.02 mL, 8.77 mmol) in ether (7 mL) was added dropwise at −78 °C, and the mixture was stirred at −78 °C→rt for 1 h and at rt for 3 h. After addition of 1 M HCl solution, the resulting mixture was stirred for 45 min, and then extracted with ether. The extracts were washed with water, brine, dried, and concentrated to give **4** (1.94 g, 95%), which was employed to the next without further purification. To a stirred mixture of the above boric acid **4** (1.12 g, 4.37 mmol), **3** (1.04 g, 2.91 mmol), potassium bromide (346 mg, 2.91 mmol) and potassium phosphate (928 mg, 4.37 mmol) in dioxane (12 mL) was added tetrakis(triphenylphosphine)palladium (169 mg, 0.15 mmol), and the mixture was stirred at 100 °C for 10.5 h, cooled, and then diluted with water. The resulting mixture was extracted with EtOAc. The extracts were washed with water, brine, dried, and concentrated. Chromatography on silica gel with hexane→hexane–EtOAc (4:1→2:1) as the eluent yielded **12** (1.14 g, 93%) as white solids: mp 146–147 °C {hexane–EtOAc (20:1)}; IR (KBr) 2989, 2958, 2908, 1732, 1612, 1577, 1281, 1254, 1149, 1057 cm^{-1}; ^{1}H NMR (400 MHz,

$CDCl_3$): δ 1.73 (6H, s), 2.04 (3H, s), 3.50 (3H, s), 3.55 (3H, s), 3.85 (3H, s), 5.16 (1H, d, J=6.6 Hz), 5.22 (1H, d, J=6.7 Hz), 5.23 (1H, d, J=6.6 Hz), 5.30 (1H, d, J=6.7 Hz), 6.44 (1H, d, J=2.7 Hz), 6.45 (1H, d, J=2.7 Hz), 6.91 (1H, s), 7.02 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.4, 25.3, 26.1, 55.7, 56.2, 56.2, 95.4, 95.9, 100.5, 105.0, 105.7, 113.2, 117.0, 117.6, 129.3, 134.1, 144.8, 146.5, 146.6, 158.5, 158.9, 164.6; HRMS calcd for $C_{22}H_{26}O_8Na$ $[M+Na]^+$ 441.1519, found 441.1518. Anal. Found: C, 63.02; H, 6.51. Calcd for $C_{22}H_{26}O_8$: C, 63.15; H, 6.26.

3.1.6. 4,4,5,5-Tetramethyl-2-(5-methyl-1,3-benzodioxol-6-yl)-1,3,2-dioxaborolane (5). To a stirred mixture of **14** (5.27 g, 20.1 mmol), bis(pinacolato)diboron (5.78 g, 22.8 mmol), and potassium acetate (5.99 g, 61.0 mmol) in *N*,*N*-dimethylformamide (150 mL) was added dichloro-[1,1′-bis(diphenylphosphino)ferrocene]palladium {$PdCl_2$-(dppf), 1.42 g, 1.94 mmol}. The mixture was stirred at 80 °C for 21 h, cooled and then diluted with EtOAc. The resulting mixture was filtered through a pad of celite, washed with brine, dried and concentrated. Chromatography on silica gel with hexane–EtOAc (9:1) as the eluent yielded **5** (4.29 g, 81%) as white solids: mp 64–65 °C; IR (KBr) 2974, 2931, 2885, 1612, 1423, 1369, 1311, 1296, 1146, 1111 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (12H, s), 2.47 (3H, s), 5.90 (2H, s), 6.65 (1H, s), 7.21 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.9, 24.8, 83.2, 100.6, 110.5, 114.7, 140.4, 144.9, 149.7; HRMS calcd for $C_{14}H_{19}BO_4Na$ $[M+Na]^+$ 285.1268, found 285.1271. Anal. Found: C, 64.19; H, 7.27. Calcd for $C_{14}H_{19}BO_4$: C, 64.15; H, 7.31.

3.1.7. 7-Methoxy-2,2-dimethyl-5-(5-methyl-1,3-benzodioxol-6-yl)-4*H*-1,3-benzodioxin-4-one (15). To a stirred mixture of **3** (2.33 g, 6.54 mmol), **5** (2.23 g, 8.51 mmol), potassium carbonate (2.71 g, 19.6 mmol) in 1,2-dimethoxyethane (10 mL) was added $PdCl_2$(dppf) (240 mg, 0.328 mmol), and the mixture was stirred at 85 °C for 10 h, cooled, diluted with EtOAc, and filtered through a pad of celite. The filtrate was washed successively with water and brine, dried and concentrated. Chromatography on silica gel with hexane–EtOAc (9:1→4:1→1:1) as the eluent yielded **15** (1.50 g, 67%) white solids: mp 170–171 °C {hexane–EtOAc (5:1)}; IR (KBr) 2997, 2943, 2904, 1732, 1608, 1577, 1485, 1281, 1203, 1030 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.73 (6H, s), 2.02 (3H, s), 3.85 (3H, s), 5.95 (1H, d, J=9.0 Hz), 5.96 (1H, d, J=9.0 Hz), 6.42 (1H, d, J=2.5 Hz), 6.45 (1H, d, J=2.5 Hz), 6.59 (1H, s), 6.70 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.6, 25.2, 26.0, 55.6, 100.5, 100.8, 105.0, 105.7, 108.5, 109.8, 113.1, 128.1, 132.9, 145.2, 146.8, 146.8, 158.5, 158.8, 164.6; HRMS calcd for $C_{19}H_{18}O_6Na$ $[M+Na]^+$ 365.0995, found 365.1001. Anal. Found: C, 66.54; H, 5.53. Calcd for $C_{19}H_{18}O_6$: C, 66.66; H, 5.30.

3.1.8. Altenusin (2) from 12. (i) A solution of **12** (367 mg, 0.88 mmol) in 2 M KOH–ethanol (1:1, 52 mL) was heated at 60 °C with stirring for 40 min, cooled and then diluted with water. The resulting mixture was washed with dichloromethane. The aqueous layer was acidified with cold HCl solution, and then extracted with EtOAc. The extracts were washed with brine, dried, and concentrated to give a syrup (238 mg), which was dissolved in dichloromethane–methanol (2:1, 9 mL). To this solution was added a 10% HCl solution in methanol (3 mL) and the mixture was stirred at rt for 12 h. After addition of $NaHCO_3$, the resulting mixture was filtered through a pad of celite, and concentrated. The residue was diluted with water, and acidified with cold HCl solution. The resulting mixture was extracted with EtOAc, washed with brine, dried and concentrated. The residue was treated with dichloromethane to give **2** (158 mg, 62% from **12**) as crystalline solids. The mother liquor was purified by preparative TLC {hexane–EtOAc–AcOH (25:25:1)} to give additional **2** (6 mg, 2%) as crystalline solids.

(ii) To a stirred solution of **12** (19.4 mg, 0.0464 mmol) in dichloromethane (1 mL) was added dropwise a 1.0 M solution of boron trichloride (BCl_3) in dichloromethane (0.46 mL) at 0 °C. The mixture was warmed slowly to rt and then stirred for 19.5 h. After addition of water, the resulting mixture was extracted with EtOAc. The extracts was washed with water, dried and concentrated. Chromatography on silica gel with chloroform–methanol–acetic acid (95:5:1→90:10:1) as the eluent yielded **2** (8.5 mg, 63%) as crystalline solids.

3.1.9. Altenusin (2) from 15. To a stirred solution of **15** (71.2 mg, 0.208 mmol) in dichloromethane (1 mL) was added dropwise a 1.0 M solution of BCl_3 in dichloromethane (1 mL) and then stirred for 19 h. Treatment as described above yielded **2** (48.1 mg, 80%): mp 192–194 °C (lit.[7] 194–196 °C); IR (KBr) 3309, 3012, 2974, 1651, 1612, 1577, 1520, 1254, 1207, 1157 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD): δ 1.90 (3H, s), 3.80 (3H, s), 6.16 (1H, d, J=2.6 Hz), 6.42 (1H, d, J=2.6 Hz), 6.48 (1H, s), 6.57 (1H, s); ^{13}C NMR (100 MHz, CD_3OD): δ 19.3, 55.9, 100.5, 107.0, 111.4, 116.6, 117.3, 127.3, 135.3, 143.2, 144.9, 148.0, 164.9, 165.8, 174.3; HRMS calcd for $C_{15}H_{14}O_6Na$ $[M+Na]^+$ 313.0682, found 313.0691.

3.1.10. Dehydroaltenusin (1). To a stirred solution of **2** (102 mg, 0.35 mmol) in ethanol–water (1:1, 2.2 mL) was added dropwise a 0.2 M solution of ferric chloride in water (ca. 4.0 mL) at rt. After 10 min, a yellow precipitate formed was filtered, washed with water, dried, and recrystallized from methanol–dichloromethane to **1** (62.1 mg, 61%) as yellow needles. The mother liquid collected was concentrated, subject to chromatography on silica gel {hexane–EtOAc (1:1)} and recrystallized from methanol–dichloromethane to additional **1** (20.6 mg, 21%) as yellow needles: mp 189–190 °C (lit.[5] 189–190 °C); IR (KBr) 3383, 3124, 2978, 1674, 1643, 1624, 1392, 1296, 1261, 1227, 1196, 1161, 1076 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.73 (3H, s), 3.91 (3H, s), 6.28 (1H, s), 6.41 (1H, s), 6.63 (1H, d, J=2.4 Hz), 6.69 (1H, s), 6.73 (1H, d, J=2.4 Hz), 11.29 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.6, 56.0, 79.1, 99.8, 103.6, 104.3, 116.1, 120.7, 134.9, 145.9., 152.9, 164.5, 166.2, 167.2, 180.6; HRMS calcd for $C_{15}H_{11}O_6$ $[M-H]^-$ 287.0561, found 287.0570.

Acknowledgements

This work was supported in part by Grant-in-Aid for JSPS Fellows from the Ministry of Education, Culture, Sports, Science and Technology of Japan, and the Chemical

Biology Project (RIKEN). We express our thanks to Ms E. Satake (Tokyo University of Science) for the elemental analyses.

References and notes

1. Kornberg, A.; Baker, T. A.; 2nd ed. *DNA replication*; Freeman: New York, 1992; Vol. 6. pp. 197–225.
2. Hubscher, U.; Maga, G.; Spadari, S. *Annu. Rev. Biochem.* **2002**, *71*, 133–163.
3. Ikegami, S.; Taguchi, T.; Ohashi, M. *Nature* **1978**, *275*, 458–460.
4. Mizushina, Y.; Kamisuki, S.; Mizuno, T.; Takemura, M.; Asahara, H.; Linn, S.; Yamaguchi, T.; Matsukage, A.; Hanaoka, F.; Yoshida, S.; Saneyoshi, M.; Sugawara, F.; Sakaguchi, K. *J. Biol. Chem.* **2000**, *275*, 33957–33961.
5. Rosett, T.; Sankhala, R. H.; Stickings, C. E.; Taylor, M. E. U.; Thomas, R. *Biochem. J.* **1957**, *67*, 390–400.
6. Coombe, R. G.; Jacobs, J. J.; Watson, T. R. *Aust. J. Chem.* **1970**, *23*, 2343–2351.
7. Ayer, W. A.; Racok, J. S. *Can. J. Chem.* **1990**, *68*, 2085–2094.
8. Rogers, D.; Williams, D. J.; Thomas, R. *J. Chem. Soc. Chem. Commun.* **1971**, 393.
9. Nakanishi, S.; Toki, S.; Saitoh, Y.; Tsukuda, E.; Kawahara, K.; Ando, K.; Matsuda, Y. *Biosci. Biotech. Biochem.* **1995**, *59*, 1333–1335.
10. Kamisuki, S.; Murakami, C.; Ohta, K.; Yoshida, H.; Sugawara, F.; Sakaguchi, K.; Mizushina, Y. *Biochem. Pharm.* **2002**, *63*, 421–427.
11. Takahashi, S.; Kamisuki, S.; Mizushina, Y.; Sakaguchi, K.; Sugawara, F.; Nakata, T. *Tetrahedron Lett.* **2003**, *44*, 1875–1877, Preliminary communication.
12. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483.
13. Hadfield, A.; Schweitzer, H.; Trova, M. P.; Green, K. *Synth. Commun.* **1994**, *24*, 1025–1028.
14. Dushin, R. G.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1992**, *114*, 655–659.
15. Mitsunobu, O. *Synthesis* **1981**, 1–28.
16. Mataka, S.; Eguchi, H.; Takahashi, K.; Hatta, T.; Tashiro, M. *Bull. Chem. Soc. Jpn* **1989**, *62*, 3127–3131.
17. Oh-e, T.; Miyaura, N.; Suzuki, A. *Synlett* **1990**, 221–222.
18. Kobayashi, S.; Kihara, M.; Hashimoto, T.; Shingu, T. *Chem. Pharm. Bull.* **1976**, *24*, 716–723.
19. Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508–7510.
20. Nicolaou, K. C.; Snyder, S. A.; Simonsen, K. B.; Koumbis, A. E. *Angew. Chem. Int. Ed.* **2000**, *39*, 3473–3478.
21. Mizushina, Y.; Tanaka, N.; Yagi, H.; Kurosawa, T.; Onoue, M.; Seto, H.; Horie, T.; Aoyagi, N.; Yamaoka, M.; Matsukage, A.; Yoshida, S.; Sakaguchi, K. *Biochim. Biophys. Acta* **1996**, *1308*, 256–262.
22. Mizushina, Y.; Yoshida, S.; Matsukage, A.; Sakaguchi, K. *Biochim. Biophys. Acta* **1997**, *1336*, 509–521.
23. Koreeda, M.; Dixon, L. A.; Hsi, J. D. *Synlett* **1993**, 555–556.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 5701–5710
Tetrahedron

Asymmetric synthesis of tertiary vinyl carbinols by highly stereoselective methylation of α-methyl-β-ketosulfoxides with aluminum reagents

José L. García Ruano,* M. Mercedes Rodríguez-Fernández and M. Carmen Maestro*

Departamento de Química Orgánica(C-I), Universidad Autónoma, Cantoblanco, 28049 Madrid, Spain

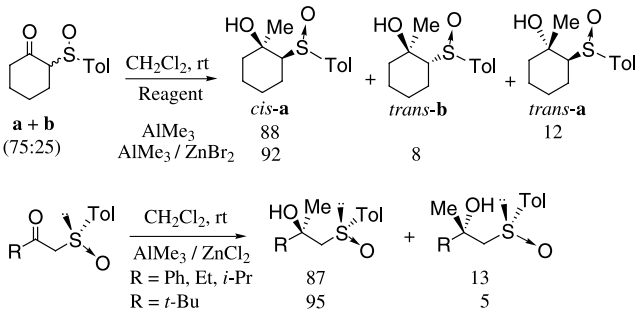
Received 2 March 2004; revised 7 May 2004; accepted 10 May 2004

Abstract—Methylation of chiral acyclic α-methyl-β-ketosulfoxides with Me_3Al and Me_2AlCl is reported. Induced configuration at hydroxylic carbon is mainly controlled by the configuration of the sulfinyl group, with de's higher than 90% in most of the cases regardless the configuration at C-α. The stereochemical pathway seems to be different with both reagents, thus affording a higher stereoselectivity with Me_2AlCl. Pyrolytic desulfinylation and hydrogenolysis of the C–S bond allowed the transformation of the resulting hydroxysulfoxides into interesting optically pure tertiary methyl carbinols.

1. Introduction

Aluminum reagents have been widely used in organic synthesis[1] mainly due to their Lewis acidic features, strongly dependent on the aluminum substituents. Their well-known reactivity as alkylating agents[2] has been used in asymmetric synthesis in the presence of chiral catalysis[3] or on substrates containing different chiral inductors.[4,5] In this context, the sulfinyl group has been used to control the stereoselectivity of the alkylations,[6,7] our group pioneering this field with the study of the reactions of Me_3Al with chiral cyclic[8] and α-unsubstituted acyclic[9] β-ketosulfoxides (Scheme 1). Although acyclic substrates afforded hydroxysulfoxides in good yields (90%) and high levels of asymmetric induction (de's >74%), their synthetic interest was limited because methyl carbinols (trialkylaluminum reagents different to Me_3Al were not efficient) resulting from the desulfinylation processes would not be chiral (Scheme 1).

In order to solve this problem in the case of acyclic compounds, it was necessary the use of α-substituted β-ketosulfoxides as the starting compounds. They would yield hydroxysulfoxides containing two chiral carbons which could be transformed into chiral tertiary carbinols by hydrogenolysis of the C–S bond or used to prepare other chiral compounds taking advantage of the reactivity of the sulfinyl group.



Scheme 1.

Herein we report the results obtained in the asymmetric methylation of acyclic α-methyl-β-ketosulfoxides with Me_3Al and Me_2AlCl, the rationalization of these results and some synthetic applicabilities of the resulting hydroxysulfoxides based on the reactivity of the sulfinyl group.

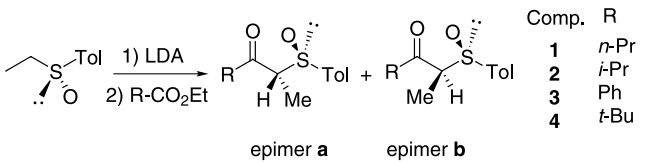
2. Results and discussion

The reactions of α-substituted β-ketosulfoxides with DIBAL[10] had shown to be highly stereoselective only when they were conducted in the presence of ZnX_2, presumably due to the formation of a chelated species activating the substrate. By contrast, a complete control of the stereoselectivity was observed in reactions of

Keywords: Stereoselective ketone methylation; Trimethylaluminum; Dimethylaluminum chloride; Chiral tertiary allylic alcohols; Hydroxysulfoxides.
* Corresponding authors. Fax: +34-914973966 (J.L.G.R.);
e-mail addresses: joseluis.garcia.ruano@uam.es; carmen.maestro@uam.es

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.05.016

β-ketosulfoxides with Et_2AlCN[11] regardless the presence of ZnX_2 as the catalyst. Regarding the methylation reactions of α-sulfinyl cycloalkanones with Me_3Al and Me_3Al/ZnX_2[8] (they are α-substituted β-ketosulfoxides) the stereoselectivity increased in the presence of ZnX_2, but the reactivity was scarcely modified. On the contrary, only these reactions of R-CO–CH_2–SOTol with $Me_3Al/ZnBr_2$ took place satisfactorily.[9] With these antecedents, we initiated the study of the methylation reactions with Me_3Al. We chose α-methyl β-ketosulfoxides **1**–**4** (Scheme 2), containing aryl and alkyl groups, as the substrates, in order to evaluate the influence of the nature and size of R on the stereoselectivity.



Scheme 2.

The synthesis of the starting sulfoxides **1**–**4** (R-CO–CHMe–SOTol) was accomplished following a previously described procedure by reaction of (*R*)-(+)-ethyl *p*-tolyl sulfoxide with the corresponding esters RCO_2Et in the presence of LDA[11b] (Scheme 2). These reactions yielded ~40:60 mixtures of the two possible epimers (**a** and **b**) at C-α. Only *t*-butyl derivatives **4a** and **4b** could be separated by flash chromatography and therefore isolated as pure diastereoisomers. Hence, mixtures of **a:b** epimers of compounds **1**–**3** were used as the starting materials in methylation reactions.

The reactions of compounds **1**–**4** with Me_3Al (4 equiv.) in CH_2Cl_2 under similar conditions (rt, 30 min) to those previously reported[8,9] afforded the results collected in Table 1. Starting from **1** and **3**, mixtures of the four possible stereoisomers of the corresponding adducts (**A** and **A′** derive from **a** epimers whereas **B** and **B′** derive from the **b** ones, see Scheme 3) were obtained. By contrast, the evolution of **2a** and **2b** was completely stereoselective and only two stereoisomers (**A** and **B**) were obtained from the starting mixture. Reactivity of the *t*-butyl derivatives was lower and **4b** needed 5 h (instead of 30 min required by **1**–**3**) at room temperature to evolve, with moderate yield, into **8B** in a completely stereoselective way. Compound **4a** was even less reactive and required 25 h to be transformed into a 70:30 mixture of diastereoisomers **8A** and **8A′**. A higher reactivity was also detected for **b** isomers of compounds **1** and **2**. The results obtained in the reactions of compounds **1** with Me_3Al/ZnX_2, as well as those conducted in toluene as the solvent, were much less satisfactory (low conversions and scarce stereoselectivity).

On the basis of the exceptionally high chelating power of Me_2AlCl with β-heterosubstituted carbonyl compounds,[12] that strongly increases their reactivity, we decided to evaluate the ability of this reagent as a methylating agent. It has been used as a catalyst to promote important reactions such as Diels–Alder cycloadditions,[12a,13] ene reactions,[14] conjugated additions,[5] additions to the carbonyl group,[12b,15] amide formation,[16] and formation of aluminium enolates,[17] but only in a few cases it simultaneously acted as a nucleophile on the activated substrate.[2a,c,18]

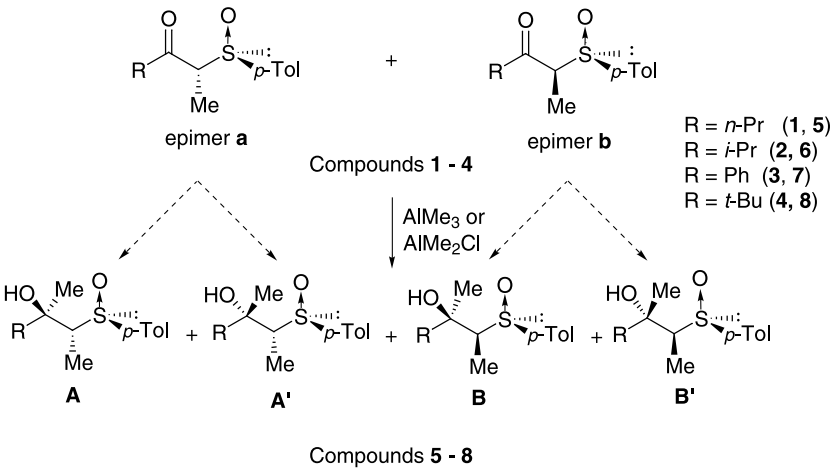
The reactions of ketosulfoxides **1**–**4** with $AlMe_2Cl$ were performed at room temperature in toluene or CH_2Cl_2 as the solvent. In Table 2 are indicated the diastereomeric ratios of the obtained carbinols **A**, **A′**, **B**, **B′** (Scheme 3), that were determined by HPLC from the reaction crudes obtained under different conditions. We first studied the behavior of the mixture **1a**+**1b** (R=*n*-Pr), that was used to evaluate the influence of different factors on the stereoselectivity and yield of the reactions. The order of the addition of the reagents (substrate must be added onto the $AlMe_2Cl$) was important to attain higher conversions (compare entries 4 and 5) and the number of equivalents of $AlMe_2Cl$ was also determinant. Reactions must be performed in the presence of a high excess of the reagent (3 or 4 equiv.), because with lower reagent proportion (2.2 equiv.) the reaction rate sharply decreased and a significant amount of starting ketosulfoxide was recovered (compare entries 8 and 9 with 6 and 7, respectively).

Concerning the stereoselectivity, the results show that the evolution of the epimer **1b** was highly stereoselective under all the studied conditions (de ~ 87–90%) whereas **1a** evolved with only moderated stereoselectivity (de ~ 30–50%). This situation was scarcely modified by any change in the solvent and the temperature. These factors have some influence on the reaction rate, which was slightly lower in CH_2Cl_2 than in toluene (compare entries 1 and 4 with 2 and 6, respectively) and decreased as the temperature became lower. Moreover the epimerization extent was much more significant in toluene and also when the temperature decreased (see Table 2). As the configuration at hydroxylated carbon is *R* for **A** and **B** and *S* for **A′** and **B′** (see Scheme 3), the best conditions from a stereoselective point of view are those optimized with 3 equiv. at 0 °C (at lower

Table 1. Methylation of compounds **1**–**4** with $AlMe_3$

Substrate (**a**:**b** ratio)	Reagent[a]	Product ratio **A**:**A′** : **B**:**B′**	Yield (%)	Recovered substrate % (**a**:**b**)
1 (39:61)	$AlMe_3$	13:10 : 67:10[b]	72	13 (44:56)
2 (36:64)	$AlMe_3$	29:0 : 71:0[c]	58	20 (81:19)
3 (44:56)	$AlMe_3$	33:10 : 38:19[c]	89	—
4a	$AlMe_3$[d]	70:30 : 0:0[c]	40	—
4b	$AlMe_3$[e]	0:0 : 100:0[c]	43	—

[a] Reactions conditions: rt, 30 min and 4 equiv. of Me_3Al in CH_2Cl_2.
[b] Determined by HPLC (column: Zorbax RX-C8; eluent: MeOH: CH_3CN:H_2O 37:13:50; 1.4 mL/min).
[c] Determined by ^1H NMR.
[d] Reaction time: 25 h.
[e] Reaction time: 5 h.



Scheme 3.

Table 2. Reaction of compounds **1**–**4** with Me_2AlCl

Entry	Substrate (**a:b** ratio)	*T* (equiv)	Products[a,b] **A**:**A′** : **B**:**B′**	Yield (%)	Recovered substrate % (**a**:**b**)
1	**1a**,**b** (39:61)	rt (4)[c]	25:13 : 57:5	76	
2	**1a**,**b** (38:62)	rt (4)	11:5 : 80:4	83	—
3	**1a**,**b** (38:62)	0 °C (4)	6:2 : 86:6	68	22(20:80)
4	**1a**,**b** (40:60)	rt (3)[c]	18:9 : 69:4	90	
5	**1a**,**b** (39:61)[d]	rt (3)	26:10 : 61:3	68	—
6	**1a**,**b** (38:62)	rt (3)	11:5 : 80:4	88	—
7	**1a**,**b** (38:62)	0 °C (3)	6:3 : 86:5	67	23(26:74)
8	**1a**,**b** (38:62)	rt (2.2)	10:4 : 82:4	60	28(34:66)
9	**1a**,**b** (38:62)	0 °C (2.2)	23:9 : 57:11[e]	48	46(52:48)
10	**2a**,**b** (36:64)	rt (3)	35:0 : 65:0	98	—
11	**3a**,**b** (44:56)	rt (3)	21 : 2 : 77:0	73	14(100:0)
12	**3a**,**b** (44:56)	rt (3)[f]	23:3 : 74:0	77[g]	—
13	**3a**,**b** (44:56)	0 °C (3)[h]	12:0 : 88:0	53	42(100:0)
14	**4a**	rt (3)[i]	—	—	100
15	**4b**	rt (3)	—	—	100

[a] Reaction conditions: 30 min in toluene.
[b] Diastereomeric ratio measured by HPLC (columm: Zorbax RX-C8; eluent: MeOH–CH_3CN–H_2O 37:13:50; 1.4 mL/min).
[c] Solvent: CH_2Cl_2.
[d] The reagent was added over the substrate.
[e] Reaction time: 43 h.
[f] Reaction time: 3 h.
[g] After separation of **7A′**.
[h] Reaction time: 10 h.
[i] Reaction time: 60 h.

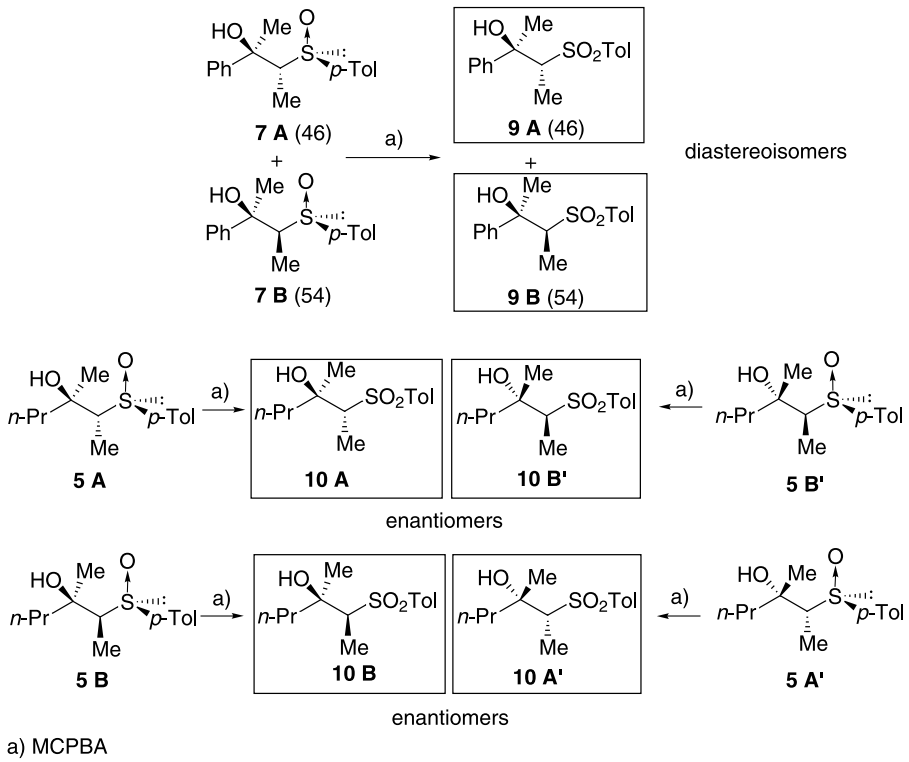
temperatures the reactions are quite slow) or room temperature in toluene (those of the entries 6 and 7), which yielded the higher **A**+**B**/**A′**+**B′** ratios.

Under these conditions the results obtained for compounds **2a**+**2b** and **3a**+**3b** were even better. In the first case, both epimers were quantitatively transformed into the alcohols after 30 min at room temperature with a complete control of the stereoselectivity (entry 10). Under the same conditions **3a**+**3b** gave a mixture of three alcohols (the evolution of **3b** was completely stereoselective) and a 14% of the epimer **a** was recovered, which indicates a slightly lower reactivity (entry 11). A complete conversion was observed after 3 h and a 77% of the mixture **7A**+**7B** could be isolated upon separation of **7A′** by chromatography (entry 12). Better stereoselectivity was obtained when the reaction was performed at 0 °C (entry 13), but the reaction is quite slow, and a 42% of the epimer **A** was recovered. By contrast, none of the *t*-butyl derivatives **4a** or **4b**, could be methylated under similar reaction conditions although the reaction times were increased (entries 14 and 15).

2.1. Configurational assignment

The assignment of the absolute configurations of the obtained α-methyl-β-hydroxysulfoxides was based on the following facts:

(a) The configuration (R_S $R_{C\text{-}\alpha}$) had been previously assigned to ketosulfoxides **a** and the (R_S $S_{C\text{-}\alpha}$) configuration to the epimers **b**.[11b] The complete stereoselectivity observed in reactions of **2a**, **2b**, and **3b** suggests that epimers **A** and **B** derive of the starting ketosulfoxides **a** and **b**, respectively. Therefore, **a** and **b** must exhibit the same configuration at sulfur and C-α than **A** and **B**, respectively.
(b) The oxidation of a 46:54 mixture of phenyl derivatives **7A** and **7B** afforded a mixture of diastereomeric



Scheme 4.

sulfones **9A** and **9B** (Scheme 4) in the same ratio than that of the starting sulfoxides. It indicates that these sulfones only differ in the configuration of one of their two chiral carbons. As a consequence, the configuration of the hydroxylated carbons must be identical for epimers **A** and epimers **B** (they exhibit different configuration at C-α).

(c) The hydroxylic proton of compound **6A** exhibits a long range coupling constant (^4J=1.6 Hz) with the methinic proton of the *i*-Pr group. As this is only possible for hydroxylic protons involved in intramolecular hydrogen bonding exhibiting a W coplanar arrangement with respect to the coupled protons,[19] the configuration of **6A** at the hydroxylic carbon must be *R* (Fig. 1).

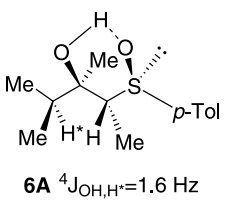


Figure 1. Stereochemistry of the presumably most stable conformation for compound **6A**.

According to these facts, we can assign the [R_S $R_{C\text{-}\alpha}$ R_{C-OH}] configuration to epimers **A** and the [R_S $S_{C\text{-}\alpha}$ R_{C-OH}] configuration to the epimers **B**. The X-ray diffraction analysis of **6A** (Fig. 2) and of a racemic sample of **7B**[20] support this assignment. The conformation exhibited by **6A** in solid state is identical to that shown in Figure 1, deduced from the NMR data.

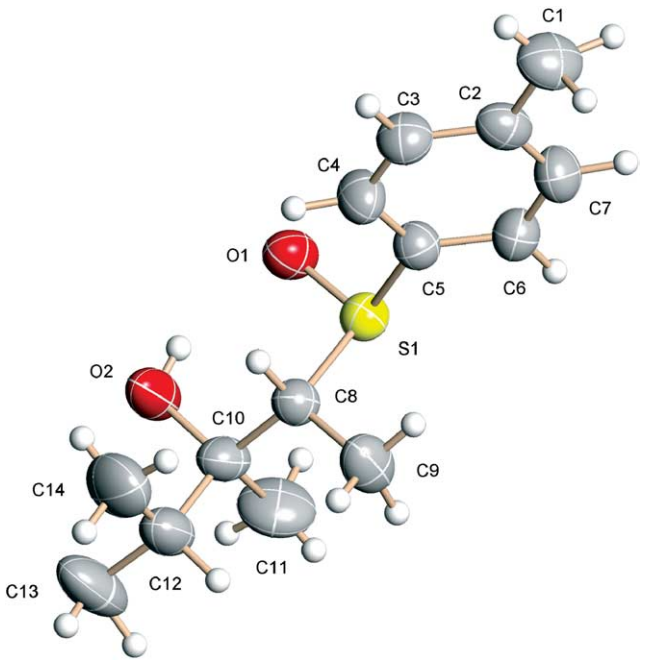


Figure 2. X-ray structure for compound **6A**.

The configuration of the **B′** isomers was unequivocally established in the case of hydroxysulfoxides **5A** and **5B′**. Once isolated from their mixtures, they were independently oxidized with MCPBA at room temperature, affording the corresponding hydroxysulfones **10A** and **10B′** (Scheme 4), which are enantiomers (they have identical spectroscopical properties). The same conclusions could be deduced for compounds **5A′** and **5B**. By assuming that the major compounds of the reaction mixtures, **5B** and **5A**, exhibit the

Table 3. Significant NMR parameters for configurational assignment of compounds **5**–**7**

Product	**5A**	**6A**	**7A**	**8A**	**5A′**	**7A′**	**8A′**	**5B**	**6B**	**7B**	**8B**	**5B′**
δ_{OH}[a]	5.53	5.41	6.11	5.42	5.23	6.50	5.21	2.69	3.16	3.96	—	2.68
$\delta_{\alpha\text{-Me}}$[a]	10.30	9.90	10.90	12.50	10.40	—	12.30	4.00	3.50	4.80	5.21	4.60

[a] Values of δ expressed in ppm.

same configuration than those obtained as sole products in reactions from **2a**+**2b** and **3a**+**3b**, we can assign the configurations [R_S $R_{C\text{-}\alpha}$ S_{C-OH}] and [R_S $S_{C\text{-}\alpha}$ S_{C-OH}] to the minor compounds **5A′** and **5B′**, respectively (and consequently to all **A′** and **B′** isomers).

In Table 3 are indicated the significant NMR parameters which are clearly different for epimers **A** (**A′**) and **B** (**B′**).

The δ values for the hydroxylic protons are clearly different [>5 ppm for isomers **A** (**A′**) but <4 ppm for the **B** (**B′**) ones]. That suggests that **A** epimers exhibit intramolecular hydrogen bonds[21] whereas this is not the case for the **B** epimers. On the other hand, the ^{13}C-δ value ca. 10 ppm observed for the *C*H$_3$–CH carbon in compounds **B** (**B′**) is quite different to the ca. 4 ppm observed for epimers **A** (**A′**). This strong difference, which is indicative of a substantial modification in the shielding patterns of both compounds, could also be a consequence of the formation of hydrogen bonds. In Figure 3 are indicated the presumably most stable conformations of the different isomers able to explain the observed differences in the NMR parameters. Epimers **B** and **B′** must be stabilized by the $n^2 \rightarrow d^0$ interaction between the lone electron pair at oxygen and the empty d orbital at sulfur, which has shown to be even more important than the hydrogen bond in many β-hydroxysulfoxides.[22] By contrast, **A** and **A′** isomers exhibit their predominant rotamers stabilized by intramolecular hydrogen bonding, because the conformation containing the $n^2 \rightarrow d^0$ interaction would be highly unstable due to the (Tol/Me) or (Tol/R) 1,3-parallel interaction. Taking into account the significant deshielding effect produced by the lone electron pair at sulfur on the carbon atoms adopting an antiperiplanar arrangement,[23] the ^{13}C-δ values shown in Table 3 are consistent with the stereochemistry of the conformations shown in Figure 3 for **A** and **B** epimers.

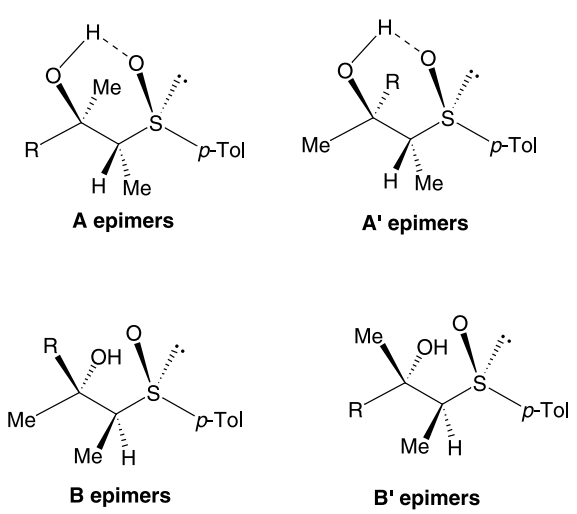


Figure 3. Favored conformations for the different isomers.

3. Mechanistic proposal

The main differences observed in the reactions with Me_3Al and Me_2AlCl are related to reactivity and stereoselectivity. The Me_3Al is able to react with *t*-butyl derivatives (**4b** required 5 h and **4a** more than 1 day), whereas Me_2AlCl did not react. The stereoselectivity was not identical but the epimer obtained as the major one with both reagents was the same (compare Tables 1 with 2).

According to the evolution proposed by Evans in reactions with Me_2AlCl,[12] our β-ketosulfoxides (epimers **a** and **b**) must be transformed into complexes $\mathbf{I_a}$ and $\mathbf{I_b}$ by chelation of the aluminum to both oxygen atoms of the substrate with elimination of the chloride anion, which is captured by a second Me_2AlCl molecule. A third molecule of the reagent must be therefore necessary to introduce the methyl group into the carbonyl moiety. It would explain that 3 equiv. of Me_2AlCl were required to achieve a high conversion (Fig. 4). On the basis of the higher stability of the half-chair structure of the chelate species and taking into account the tendency of the *p*-tolyl group (with higher size than the methyl one) to adopt the pseudoequatorial arrangement, we can propose $\mathbf{I_a}$ and $\mathbf{I_b}$ (Fig. 4) as the presumably most stable conformations resulting from the chelation of the epimers **a** and **b**. The approach of the reagent from the upper face (chair-like TS) would be favored with respect to the attack to the bottom face (twist-like TS) from a steric point of view. Moreover, the stabilizing interaction of the metal with the lone electron pair at sulfur makes even more favorable the approach to the upper face. According to this analysis, $k_1 > k_2$ and $k_3 > k_4$, this would explain why hydroxysulfoxides **A** and **B** were obtained as major isomers from epimers **a** and **b**, respectively. Additionally, $k_3 > k_1$ and $k_2 > k_4$, due to the steric hindrance of the methyl group at C-α in both epimers. It would explain the higher stereoselectivity observed in the evolution of the **b** epimers. Finally, the complete stereoselectivity observed in reaction from **2a** (R and R′=Me in $\mathbf{I_a}$) is not unexpected on the basis of the steric hindrance of the approach of the reagent to the bottom face exerted by R′ (see Fig. 4).

The stereochemical course of the reactions with Me_3Al must be similar. The factors controlling the preferences for the attack of the reagent to pentacoordinated aluminum species formed from Me_3Al[24] (Fig. 5) are the same indicated for the tetracoordinated species generated from Me_2AlCl (Fig. 4). The only difference is the presumable lower stability of the pentacoordinated species, which would explain the less stereoselective evolution observed in reactions with Me_3Al

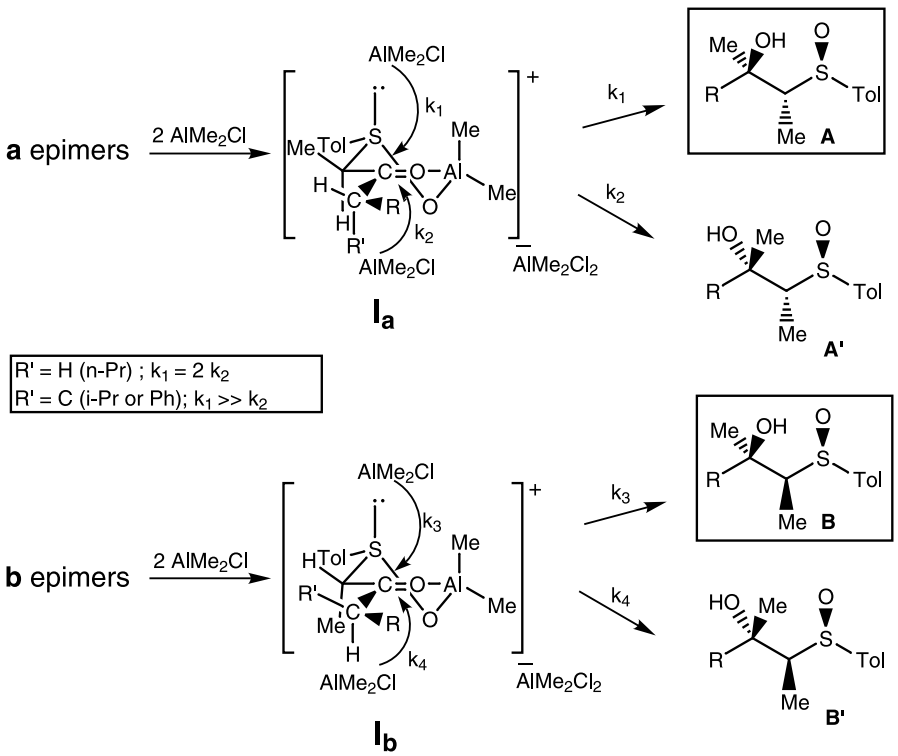


Figure 4. Stereochemical pathway of the reaction with Me_2AlCl.

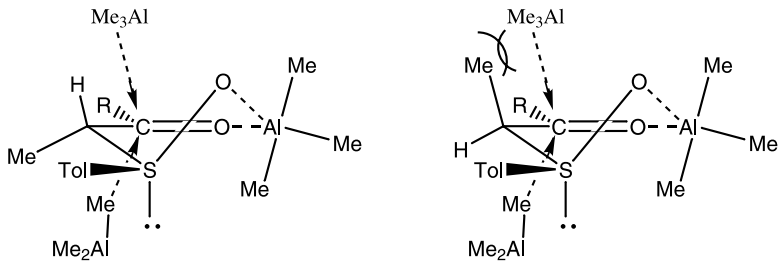
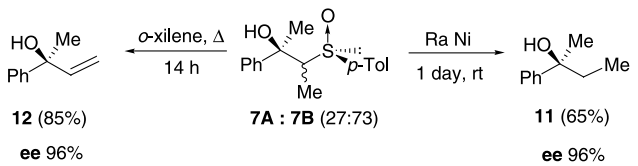


Figure 5. Stereochemical pathway of the reaction with Me_3Al.

(other nor chelated species could also evolve) as well as their higher reactivity.

4. Synthetic applications

The obtained hydroxysulfoxides can be used as starting molecules to prepare different enantiomerically pure compounds taking advantage of the reactivity of the sulfinyl group. As the configuration at the hydroxylated carbon is the same for epimers **A** and **B** (obtained as the major ones or even unique in these reactions), all the transformations involving the removal of the sulfur function can be performed by using a mixture of these epimers, with no previous separation. We have illustrated these possibilities with two of these reactions, hydrogenolysis of the C–S bond and pyrolytic desulfinylation, starting from the mixture **7A**+**7B** (Scheme 5). This mixture was obtained in 77% yield by chromatographic separation from the reaction mixture obtained from **3a**+**3b** (entry 12 of Table 2). Its



Scheme 5.

reaction with Raney Ni (Scheme 5) for 1 day at room temperature (shorter reaction times revealed the presence of the thioether derived from **7**) afforded compound **11** in 65% yield with high optical purity[25] (ee 96%). Otherwise, when the mixture **7A**+**7B** was heated with refluxing xylene in the presence of $NaHCO_3$, compound **12**[26] (ee 96% by chiral HPLC) was obtained in 85% yield (Scheme 5). These results illustrate the usefulness of our method for the preparation of enantiomerically pure tertiary vinyl carbinols,[27] which are not easily synthesized by other procedures.[26b,28]

5. Conclusion

The highly stereoselective methylation of acyclic α-methyl β-ketosulfoxides can be performed with Me_2AlCl. Resulting hydroxysulfoxides can be used in the synthesis of tertiary methyl vinyl and methyl ethyl carbinols in very high optical purities.

6. Experimental

6.1. General

Dry solvents and liquid reagents were distilled under argon just prior to use: THF and toluene were distilled from sodium and benzophenone ketyl; DIA was dried over sodium hydroxide and distilled over calcium hydride; CH_2Cl_2 was dried over P_2O_5 and stored over molecular sieves. All reaction vessels were flame-dried and flushed with argon. TLC was performed on silica gel F_{254} plates with silica gel G (Merck), spots being developed with phosphomolybdic acid in ethanol. Silica gel Merck 60 (230–400 mesh) was used for flash chromatography. Optical rotations were measured with a 241 Perkin–Elmer polarimeter at room temperature (20–23 °C) in the solvent and concentration indicated in each case (concentration in g/100 mL). Melting points were determined in a Gallenkamp MFB-595 apparatus in open capillary tubes and are uncorrected. ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75.5 MHz $CDCl_3$) spectra were performed with a Bruker AC-300 spectrometer. Chemical shifts are given in ppm (δ), relative to $SiMe_4$ as the internal reference; signal multiplicities are quoted as s, singlet; d, doublet; dd, double doublet; dq, double quartet; t, triplet; q, quartet; and m, multiplet. *J* Values are given in hertz. Mass spectra were recorded by the direct insertion technique by electronic impact (EI) at 70 eV or FAB using a VG AutoSpec spectrometer. Elemental analyses were obtained with a Perkin–Elmer 2400 CHNS/O series II. X-ray diffractions were collected with a Siemens P4RA difractometer. Starting ketosulfoxides **1**–**4** were synthesized and purified according to the previously described procedure.[11b] Dimethyl aluminum chloride (1.0 M solution in hexanes) and trimethylaluminum (1.0 M solution in heptane) was purchased from Aldrich. Yields and diastereisomeric ratios of alcohols were established by integration (^{1}H NMR) of well-separated signals of the diastereisomers in the crude reaction mixtures and/or by HPLC. Yields and diastereoisomeric ratios of hydroxysulfoxides **5**–**8** are listed in Tables 1 and 2.

6.2. General procedure for $AlMe_3$ addition. Method A

A solution of β-ketosulfoxide (0.283 mmol) in anhydrous toluene (1.3 mL) was dropwise added into a solution of trimethylaluminum (1.132 mmol) in anhydrous toluene (1.3 mL) under argon, and the mixture was stirred for 30 min at room temperature. Then the mixture was cooled to 0 °C and methanol (0.55 mL) was slowly added. When the mixture reached room temperature, it was treated with 9 mL of aqueous saturated solution of sodium potassium tartrate–ethyl acetate (1:1) and stirred for 30 min. The aqueous layer was extracted with ethyl acetate (3×6 mL) and the organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by chromatography (the eluent was indicated in each case).

6.3. General procedure for Me_2AlCl addition. Method B

A solution of β-ketosulfoxide (0.30 mmol) in anhydrous toluene (1.5 mL) was dropwise added into a solution of dimethyl aluminum chloride in anhydrous toluene (1.0 M, 0.90 mL, 0.90 mmol) under argon, and the mixture was stirred for 30 min at room temperature. Then the mixture was cooled to 0 °C and methanol (0.60 mL) was slowly added. When the mixture reached room temperature, it was treated with 10 mL of aqueous saturated solution of sodium potassium tartrate–ethyl acetate (1:1) and then stirred for 30 min. The aqueous layer was extracted with ethyl acetate (3×10 mL) and the organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica gel (the eluent was indicated in each case).

6.3.1. 3-Methyl-2-*p*-tolylsulfinylhexan-3-ol (5). The treatment of a 38:62 mixture of **1a**+**1b** following the method B afforded a diastereoisomeric mixture of hydroxysulfoxides **5A**, **5A′**, **5B**, and **5B′** as a colorless oil. The mixture was purified by chromatography (hexane–ethyl acetate 4:1) and yielded pure (**5A** and **5B**) and enriched (**5A′** and **5B′**) hydroxysulfoxides.

6.3.2. Compound [(2*R*,3*R*,(S)*R*)]5A. It was obtained as a colorless oil. Yield: 2%; $[\alpha]_D$=+181 (*c* 5.6, chloroform). ^{1}H NMR: δ 7.65 and 7.33 (AA′BB′ system, 4H, C_6H_4), 5.53 (bs, 1H, OH), 2.97 (q, 1H, *J*=7.3 Hz, CHS), 2.42 (s, 3H, CH_3Ar), 1.54 (s, 3H, CH_3COH), 1.53–1.19 (m, 4H, CH_2CH_2), 0.88 (t, 3H, *J*=7.1 Hz, CH_3CH_2), 0.83 (d, 3H, *J*=7.3 Hz, CH_3CH). ^{13}C NMR: δ 142.8, 139.4, 129.9, 126.1, 75.6, 66.5, 44.2, 23.2, 21.5, 15.6, 14.4, 10.3. MS: (*m*/*z*)(%): 254 (M+,<1), 239 (84), 221 (11), 149 (36), 140 (100), 139 (32), 115 (20), 92 (31), 91 (21), 83 (22), 71 (36), 57 (29), 55 (31). HRMS: calcd for $C_{14}H_{22}SO_2$ 254.1331; found 254.1340.

6.3.3. Compound [(2*R*,3*S*,(S)*R*)]5A′. It was characterized from a 55:45 mixture of **5A** and **5A′**. ^{1}H NMR: δ 7.65 and 7.33 (AA′BB′ system, 4H, C_6H_4), 5.23 (bs, 1H, OH), 2.97 (q, 1H, *J*=7.1 Hz, CHS), 2.42 (s, 3H, CH_3Ar), 2.02–1.70 (m, 4H, CH_2CH_2), 1.18 (s, 3H, CH_3COH), 1.00 (t, 3H, *J*=7.1 Hz, CH_3CH_2), 0.89 (d, 3H, *J*=7.1 Hz, CH_3CH). ^{13}C NMR: δ 142.8, 139.5, 129.9, 126.1, 76.1, 69.1, 38.7, 26.4, 23.2, 16.5, 14.6, 10.4.

6.3.4. Compound [(2*S*,3*R*,(S)*R*)]5B. It was obtained as a white solid (mp 156–159 °C). Yield: 32%. $[\alpha]_D$=+139 (*c* 2.4, chloroform). ^{1}H NMR: δ 7.40 and 7.32 (AA′BB′ system, 4H, C_6H_4), 2.69 (bs, 1H, OH), 2.51 (q, 1H, *J*=7.2 Hz, CHS), 2.42 (s, 3H, CH_3Ar), 1.77–1.65 (m, 2H, CH_2), 1.55 (s, 3H, CH_3COH), 1.52–1.25 (m, 2H, CH_2), 1.02 (d, 3H, *J*=7.2 Hz, CH_3CH), 0.97 (t, 3H, *J*=7.5 Hz, CH_3CH_2). ^{13}C NMR: δ 140.7, 139.0, 129.7, 124.0, 74.5, 67.7, 42.3, 25.9, 21.3, 16.8, 14.5, 4.0. IR (KBr): 3360, 1022. MS (FAB+): 255 (M+1)(100), 239 (77), 49 (56), 139 (62), 97 (82), 91 (22), 71 (36), 57 (47), 54 (54). HRMS (M+H): calcd for $C_{14}H_{22}SO_2$ 255.141; found 255.1426.

6.3.5. Compound [(2*S*,3*S*,(S)*R*)]5B′. It was characterized from a mixture of **5B** and **5B′**. ^{1}H NMR: δ 7.40 and 7.32 (AA′BB′ system, 4H, C_6H_4), 2.69 (bs, 1H, OH), 2.51 (q, 1H, J=7.2 Hz, CHS), 2.42 (s, 3H, CH_3Ar), 1.77–1.65 (m, 2H, CH_2), 1.55 (s, 3H, CH_3COH), 1.52–1.25 (m, 2H, CH_2), 1.02 (d, 3H, J=7.2 Hz, CH_3CH), 0.97 (t, 3H, J=7.5 Hz, CH_3CH$_2$). ^{13}C NMR: δ 140.6, 139.5, 129.9, 124.2, 74.6, 68.1, 43.8, 24.7, 23.7, 16.8, 14.5, 4.6.

6.3.6. 3,4-Dimethyl-2-*p*-tolylsulfinylpentan-3-ol (6). The treatment of a 36:64 mixture of **2a**+**2b** following the method B afforded a diastereoisomeric mixture of hydroxysulfoxides **6A** and **6B** as a colorless oil. The mixture was purified by chromatography (hexane–ethyl acetate 2:1) to yield pure hydroxysulfoxide **6A** and enriched **6B** hydroxysulfoxides.

6.3.7. Compound [(2*R*,3*R*,(S)*R*)]6A. It was obtained as a white solid (mp 77–79 °C). Yield: 35%; $[\alpha]_D$=+179.4 (*c* 9.1, chloroform). ^{1}H NMR: δ 7.68 and 7.35 (AA′BB′ system, 4H, C_6H_4), 5.41 (d, 1H, J=1.6 Hz, OH), 3.04 (q, 1H, J=7.2 Hz, CHS), 2.43 (s, 3H, CH_3Ar), 1.67 (m, 1H, CH(CH$_3$)$_2$), 1.54 (s, 3H, CH_3COH), 1.00 (d, 3H, J=6.9 Hz, CH_3CHCH$_3$), 0.89 (d, 3H, J=6.9 Hz, CH_3CHCH$_3$), 0.83 (d, 3H, J=7.2 Hz, CH_3CH). ^{13}C NMR: δ 142.8, 139.3, 129.9, 126.2, 76.7, 66.2, 35.5, 21.5, 21.4, 16.2, 16.1, 9.9. IR (KBr): 3335, 2993, 1083. MS: (*m*/*z*)(%): 254 (M^+,<1), 221 (15), 151 (20), 140 (100), 139 (49), 115 (22), 97 (13), 92 (49), 91 (29), 71 (57), 55 (31). Anal. calcd for $C_{14}H_{22}SO_2$: C, 66.34; H, 8.69; S, 12.51. Found: C, 66.10; H, 8.72; S, 12.61.

6.3.8. Compound [2*S*,3*R*,(S)*R*)]6B. It was characterized from a mixture of **6A** and **6B**. Yield: 65%. ^{1}H NMR: δ 7.39 and 7.29 (AA′BB′ system, 4H, C_6H_4), 3.16 (bs, 1H, OH), 2.58 (q, 1H, J=6.9 Hz, CHS), 2.39 (s, 3H, CH_3Ar), 2.03 (sep, 1H, J=6.9 Hz, CH(CH$_3$)$_2$), 1.52 (s, 3H, CH_3COH), 1.01 (d, 3H, J=6.9 Hz, CH_3CHCH$_3$), 0.99 (d, 3H, J=6.9 Hz, CH_3CHCH$_3$), 0.81 (d, 3H, J=6.9 Hz, CH_3CH). ^{13}C NMR: δ 140.8, 138.5, 129.8, 124.0, 76.5, 65.0, 34.8, 21.3, 20.8, 17.4, 16.3, 3.5. IR (KBr): 3480, 2950, 1500, 1380, 1010. MS (FAB): 255 (M+1, 100), 155 (13), 154 (38), 139 (55), 135 (50), 115 (21), 97 (71), 91 (31), 72 (91), 71 (49), 69 (33), 57 (36), 54 (49). HRMS (M+H): calcd for $C_{14}H_{22}SO_2$ 255.1419; found 255.1420.

6.3.9. 2-Phenyl-3-*p*-tolylsulfinylbutan-2-ol (7). The treatment of a 44:56 mixture of **3a**+**3b** following the method B afforded a diastereoisomeric mixture of hydroxysulfoxides **7A** and **7B** as a colorless oil. The mixture was purified by flash chromatography (hexane–ethyl acetate 3:1) yielding pure **7B** and enriched **7A**.

6.3.10. Compound [(2*R*,3*R*,(S)*R*)]7A. It was characterized from a 52:48 mixture of **7A** and **7B**. $[\alpha]_D$=+58 (*c* 1.8, chloroform). ^{1}H NMR: δ 7.64 and 7.16 (m, 9H, aromatic protons), 6.11 (bs, 1H, OH), 3.02 (q, 1H, J=7.1 Hz, CHS), 2.35 (s, 3H, CH_3Ar), 1.95 (s, 3H, CH_3COH), 0.55 (d, 3H, J=7.2 Hz, CH_3CH). ^{13}C NMR: δ 145.2, 141.0, 139.2, 129.9, 128.0, 127.4, 125.9, 124.6, 76.3, 68.6, 22.1, 21.4, 10.9. IR (KBr): 3480, 2950, 1500, 1380, 1010. MS: (*m*/*z*)(%): 151 (14), 148 (72), 140 (100), 139 (17), 105 (27), 92 (49), 91 (42), 79 (17), 77 (26), 71 (16).

6.3.11. Compound [(2*R*,3*S*,(S)*R*)]7B. It was obtained as a white solid (mp 101–103 °C). Yield: 31%; $[\alpha]_D$=+144 (*c* 6.8, chloroform). ^{1}H NMR: δ 7.47 and 7.22 (m, 9H, aromatic protons), 3.96 (bs, 1H, OH), 2.76 (q, 1H, J=6.9 Hz, CHS), 2.36 (s, 3H, CH_3Ar), 2.00 (s, 3H, CH_3COH), 0.74 (d, 3H, J=6.9 Hz, CH_3CH). ^{13}C NMR: δ 146.1, 141.1, 137.8, 129.8, 128.2, 126.9, 124.6, 124.1, 76.4, 66.7, 29.9, 21.3, 4.8. MS (*m*/*z*)(%): 151 (10), 148 (62), 140 (100), 139 (17), 105 (21), 92 (43), 91 (39), 79 (15), 77 (23), 71 (13). Anal. calcd for $C_{17}H_{20}SO_2$: C, 70.80; H, 6.99; S, 11.12. Found: C, 70.61; H, 6.79; S, 11.00.

6.3.12. 3,4,4-Trimethyl-2-*p*-tolylsulfinylpentan-3-ol (8). Starting from **4a**, method A afforded a diastereoisomeric mixture of hydroxysulfoxides **8A** and **8A′**. The mixture was purified by chromatography (hexane–ethyl acetate 2:1) to yield pure hydroxysulfoxides **8A** and **8A′** as a white solids. Starting from **4b**, hydroxysulfoxide **8B** was exclusively obtained. The product was purified by chromatography (hexane–ethyl acetate 2:1) to afford pure **8B** as a white solid.

6.3.13. Compound [(2*R*,3*R*,(S)*R*)]8A. It was obtained as a white solid (mp 88–91 °C). Yield: 27%; $[\alpha]_D$=+141.9 (*c* 1.69, chloroform). ^{1}H NMR: δ 7.68 and 7.38 (AA′BB′ system, 4H, C_6H_4), 5.42 (s 1H, OH), 3.21 (q, 1H, J=7.2 Hz, CHS), 2.43 (s, 3H, CH_3Ar), 1.46 (s, 3H, CH_3COH), 1.00 (s, 9H, (CH$_3$)$_3$C), 0.94 (d, 3H, J=7.2 Hz, CH_3CH). ^{13}C NMR: δ 142.6, 139.4, 129.9, 126.7, 78.9, 66.7, 39.9, 25.8, 21.5, 18.7, 12.5.

6.3.14. Compound [(2*R*,3*S*,(S)*R*)]8A′. It was obtained as a white solid (mp 88–91 °C). Yield: 13%; $[\alpha]_D$=+168.2 (*c* 0.65, chloroform). ^{1}H NMR: δ 7.67 and 7.34 (AA′BB′ system, 4H, C_6H_4), 5.21 (s 1H, OH), 3.12 (q, 1H, J=7.5 Hz, CHS), 2.43 (s, 3H, CH_3Ar), 1.33 (s, 3H, CH_3COH), 1.21 (s, 9H, (CH$_3$)$_3$C), 0.97 (d, 3H, J=7.5 Hz, CH_3CH). ^{13}C NMR: δ 142.6, 140.2, 129.9, 126.1, 80.9, 69.8, 40.1, 27.7, 26.2, 21.5, 12.3.

6.3.15. Compound [(2*S*,3*R*,(S)*R*)]8B. It was obtained as a white solid (mp 123–125 °C). Yield: 43%. $[\alpha]_D$=+124.5 (*c*0.6, chloroform). ^{1}H NMR: δ 7.44 and 7.31 (AA′BB′ system, 4H, C_6H_4), 2.88 (q, 1H, J=6.9 Hz, CHS), 2.42 (s, 3H, CH_3Ar), 1.57 (s, 3H, CH_3COH), 1.11 (d, 3H, J=6.9 Hz, CH_3CH), 1.13 (s, 9H, (CH$_3$)$_3$C). ^{13}C NMR: δ 140.6, 140.1, 129.7, 124.1, 76.6, 65.4, 39.4, 26.4, 21.7, 21.3, 5.21. Anal. calcd for $C_{15}H_{24}SO_2$: C, 67.12; H, 9.01; S, 11.95. Found: C, 66.95; H, 8.80; S, 11.81.

6.4. Sulfinyl group oxidation

A $CDCl_3$ solution of the corresponding hydroxysulfoxides was added to an NMR tube containing an excess of previously dried (anhydrous magnesium sulfate) MCPBA solution in the same solvent. The sulfone ratios and NMR signals were obtained from the crude mixtures.

6.4.1. 2-Phenyl-3-*p*-tolylsulfonylbutan-2-ol (9). Hydroxysulfone **9** was prepared as a 46:54 diastereoisomeric mixture of **9A** and **9B** by MCPBA oxidation of a 46:54 mixture of **7A** and **7B**, respectively.

6.4.2. Compound (2*R*,3*R*)9A. ^{1}H NMR: δ 8.10–7.31 (m, 9H, aromatic protons), 3.42 (q, 1H, J=7.1 Hz, CHS), 2.38 (s, 3H, CH_3Ar), 1.88 (s, 3H, CH_3COH), 0.88 (d, 3H, J=7.1 Hz, CH_3CH).

6.4.3. Compound (2*R*,3*S*)9B. ^{1}H NMR: δ 8.10–7.31 (m, 9H, aromatic protons), 3.38 (q, 1H, J=7.2 Hz, CHS), 2.37 (s, 3H, CH_3Ar), 1.82 (s, 3H, CH_3COH), 0.98 (d, 3H, J=7.2 Hz, CH_3CH).

6.4.4. (2*R*,3*R*) and (2*S*,3*S*)-3-Methyl-2-*p*-tolylsulfonyl-hexan-3-ol (10A) and (10B′). The MCPBA oxidation of hydroxysulfoxide **5A** yielded hydroxysulfone **10A**. **10B′** (enantiomer of **10A**) was obtained by oxidation of **5B′**. ^{1}H NMR: δ 8.10–7.31 (AA′BB′ system, 4H, C_6H_4), 3.20 (q, 1H, J=7.1 Hz, CHS), 2.48 (s, 3H, CH_3Ar), 1.55 (s, 3H, CH_3COH), 1.51–1.20 (m, 4H, CH_2CH_2), 1.21 (d, 3H, J=7.1 Hz, CH_3CH), 0.9 (t, 3H, J=7.0 Hz(CH_3CH_2).

6.4.5. (2*R*,3*S*) and (2*S*,3*R*)-3-Methyl-2-*p*-tolylsulfonyl-hexan-3-ol (10A′) and (10B). The MCPBA oxidation of hydroxysulfoxide **5A′** yielded hydroxysulfone **10A′**. **10B** (enantiomer of **10A′**) was obtained by oxidation of **5B**. ^{1}H NMR: δ 8.10–7.30 (AA′BB′ system, 4H, C_6H_4), 3.25 (q, 1H, J=7.2 Hz, CHS), 2.46 (s, 3H, CH_3Ar), 2.0–1.41 (m, 4H, CH_2CH_2), 1.30 (s, 3H, CH_3COH), 1.20 (d, 3H, J=7.2 Hz, CH_3CH), 0.95 (t, 3H, J=7.0 Hz(CH_3CH_2).

6.5. Sulfinyl group reductive elimination

6.5.1. (*S*)-2-Phenyl-2-butanol (11). To a solution of a 27:73 mixture of **7A** and **7B** (0.59 mmol) in EtOH was added a suspension of activated Raney nickel (1.726 g) in EtOH (4 mL). The reaction was stirred for 1 day at room temperature, filtered over Celite®, and the residue was purified by chromatography (hexane–ethyl acetate 99:1) to give a colorless oil. Yield: 65%. $[\alpha]_D$=−16.6 (*c* 3.5, acetone). [Lit. $[\alpha]_D$=−16.7 (*c* 1.50, acetone, 96% ee)].[25a] ^{1}H NMR: δ 7.26–7.19 (m, 5H, C_6H_5), 1.86 (q, 2H, J=7.5 Hz, CH_3CH_2), 1.79 (s, 1H, OH), 1.55 (s, 3H, CH_3COH), 0.80 (t, 3H, J=7.5 Hz, CH_3CH_2).

6.6. Sulfinyl group pyrolysis

6.6.1. (*S*)-2-Phenylbut-3-en-2-ol (12). A 25 mL two-necked round bottomed flask equipped with a stirrer and a reflux condenser and containing sodium bicarbonate (13.1 mmol), was flame-dried under Ar steam. A solution of a 27:73 of **7A** and **7B** (0.328 mmol) in *o*-xylene (6 mL) was added via cannula and was heated at 140 °C for 14 h. The reaction was filtered over Celite® and washed with dichlorometane. Dichlorometane was eliminated under reduced pressure without heating, in order to avoid evaporation of any reaction product. Flash chromatography using successively hexane (to remove the remaining *o*-xilene) and then hexane–ethyl acetate 9:1, yielded pure **12** (85%) as an oil $[\alpha]_D$=−28.3 (*c* 2.1, acetone, 96% ee).[26] The ee was determined by HPLC (Daicel CHIRALPAK AD, Hexane/ *i*-PrOH: 90/10, 0.8 mL/min). ^{1}H NMR: δ 7.51–7.24 (m, 5H, C_6H_5), 6.19 (dd, 1H, J=17.2, 10.8 Hz, $CH{=}CH_2$), 5.22 (dd, 2H, J=17.2, 1.1 Hz, $CH{=}CH_2$), 1.67 (s, 3H, CH_3COH).

Acknowledgements

We thank the CICYT (BQU2003-04012) for financial support.

References and notes

1. Negishi, E. *Organometallics in Organic Synthesis*; Wiley: New York, 1980.
2. (a) Ashby, E. C.; Noding, S. A. *J. Org. Chem.* **1979**, *44*, 4792. (b) Snider, B. B.; Rodini, D. J.; Karras, M.; Kirk, T. C.; Deutsch, E. A.; Cordova, R.; Price, R. T. *Tetrahedron* **1981**, *37*, 3927. (c) Rück, K.; Kunz, H. *Synthesis* **1993**, 1018. (d) Taniguchi, M.; Fujii, H.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1992**, *33*, 4353. (e) García Ruano, J. L.; Tito, A.; Culebras, R. *Tetrahedron* **1996**, *52*, 2177.
3. For addition of R_3Al to aldehydes see: (a) Pagenkopf, B. L.; Carreira, E. M. *Tetrahedron Lett.* **1998**, *39*, 9593. (b) Lu, J.-F.; You, J.-S.; Gau, H.-M. *Tetrahedron: Asymmetry* **2000**, *11*, 2531. (c) You, J.-S.; Hsieh, S.-H.; Gau, H.-M. *Chem. Commun.* **2001**, 1546.
4. Ley, S. V.; Cox, L. R.; Meek, G.; Metten, K.-H.; Piqué, C.; Worrall, J. M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3299.
5. (a) Castellino, S.; Dwight, W. J. *J. Am. Chem. Soc.* **1993**, *115*, 2986. (b) Amoroso, R.; Cardillo, G.; Sabatino, P.; Tomasini, C.; Trerè, A. *J. Org. Chem.* **1993**, *58*, 5615.
6. Fujisawa, T.; Fujimura, A.; Ukaji, Y. *Chem. Lett.* **1988**, 1541.
7. Recent references: (a) Carreño, M. C.; Pérez González, M.; Ribagorda, M.; Houk, K. N. *J. Org. Chem.* **1998**, *63*, 3687. (b) Almorín, A.; Carreño, M. C.; Somoza, A.; Urbano, A. *Tetrahedron Lett.* **2003**, *44*, 5597.
8. (a) Bueno, A. B.; Carreño, M. C.; Fischer, J.; García Ruano, J. L.; Peña, B.; Peñas, L.; Rubio, A. *Tetrahedron Lett.* **1991**, *32*, 3191. (b) Bueno, A. B.; Carreño, M. C.; García Ruano, J. L. *An. Quím.* **1994**, *90*, 442.
9. Carreño, M. C.; García Ruano, J. L.; Maestro, M. C.; Pérez González, M.; Bueno, A. B.; Fischer, J. *Tetrahedron* **1993**, *49*, 11009.
10. Barros, D.; Carreño, M. C.; García Ruano, J. L.; Maestro, M. C. *Tetrahedron Lett.* **1992**, *33*, 2733.
11. (a) García Ruano, J. L.; Martín Castro, A. M.; Rodriguez, J. H. *Recent Res. Devel. Org. Chem.* **2000**, *4*, 261. (b) García Ruano, J. L.; Martín Castro, A. M.; Rodriguez, J. H. *J. Org. Chem.* **1992**, *57*, 7235.
12. (a) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238. (b) Evans, D. A.; Allison, B. D.; Yang, M. G.; Masse, C. E. *J. Am. Chem. Soc.* **2001**, *123*, 10840. *N*-acyloxazolidinone-*n*Et_2AlCl complexes have been established by NMR. See Ref. 5(a).
13. Marshall, J. A.; Audia, J. E.; Grote, J.; Shearer, B. G. *Tetrahedron* **1986**, *42*, 2893.
14. (a) Snider, B. B.; Zhang, Q. *J. Org. Chem.* **1991**, *56*, 4908. (b) Houston, T. A.; Tanaka, Y.; Koreeda, M. *J. Org. Chem.* **1993**, *58*, 4287. (c) Masuya, K.; Tanino, K.; Kuwajima, I. *Tetrahedron Lett.* **1994**, *35*, 7965.
15. (a) Nakamura, S.; Yasuda, H.; Watanabe, Y.; Toru, T. *Org. Chem.* **2000**, *65*, 8640. (b) Ooi, T.; Morikawa, J.; Uraguchi, D.; Maruoka, K. *Tetrahedron Lett.* **1999**, *40*, 2993.
16. Shimizu, T.; Osako, K.; Nakata, T. *Tetrahedron Lett.* **1997**, *38*, 2685.
17. (a) Maruoka, K.; Hashimoto, S.; Kitagawa, Y.; Yamamoto, H.;

Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 7705. (b) Takahashi, A.; Shibasaki, M. *J. Org. Chem.* **1988**, *53*, 1227. (c) van der Steen, F. H.; van Mier, G. P. M.; Spek, A. L.; Kroon, J.; van Koten, G. *J. Am. Chem. Soc.* **1991**, *113*, 5742.
18. Rück, K.; Kunz, H. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 694.
19. Jochims, J.; Taigel, G.; Seeliger, A.; Lutz, P.; Driesen, H. E. *Tetrahedron Lett.* **1967**, *8*, 4363.
20. Crystallographic data for structures of **6A** and **7B** have been deposited with the Cambridge Crystallographic Data Center. Deposition No CCDC 230283 for **6A** and CCDC 230284 for **7B**. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: 144-(0)1223-336033; e-mail: deposit@ccdc.cam.ac.uk].
21. Brunet, E.; García Ruano, J. L.; Hoyos, M. A.; Rodriguez, J. H.; Alcudia, F. *J. Mol. Struct.* **1987**, *158*, 79.
22. (a) Brunet, E.; García Ruano, J. L.; Martínez, M. C.; Rodriguez, J. H.; Alcudia, F. *Tetrahedron* **1984**, *40*, 2023. (b) Carretero, J. C.; García Ruano, J. L.; Martínez, M. C.; Rodriguez, J. H.; Alcudia, F. *Tetrahedron* **1985**, *41*, 2419.
23. Carreño, M. C.; Carretero, J. C.; García Ruano, J. L.; Rodriguez, J. H. *Tetrahedron* **1990**, *46*, 5649.
24. Ooi, T.; Kagoshima, N.; Uraguchi, D.; Maruoka, K. *Tetrahedron Lett.* **1998**, *39*, 7105.
25. (a) García, C.; La Rochelle, L. K.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10970. (b) Archelas, A.; Furstoss, R. *J. Org. Chem.* **1999**, *64*, 6112. (c) Johnson, C.; Stark, C. J., Jr. *J. Org. Chem.* **1982**, *47*, 1193. (d) Weber, B.; Seebach, D. *Tetrahedron* **1994**, *50*, 6117.
26. (a) Tomooka, K.; Inoue, T.; Nakai, T. *Chem. Lett.* **2000**, 418. (b) Nelson, A.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2645.
27. For recent synthesis of natural products containing tertiary vinyl carbinol moieties see: (a) Díaz, S.; Cuesta, J.; González, A.; Bonjoch, J. *J. Org. Chem.* **2003**, *68*, 7400. (b) Marcos, I. S.; Laderas, M.; Díez, D.; Basabe, P.; Moro, R. F.; Garrido, N. M.; Urones, J. G. *Tetrahedron Lett.* **2003**, *44*, 5419.
28. (a) Buston, J. E. H.; Coldham, I.; Mulholland, K. R. *J. Chem. Soc., Perkin Trans. 1*, **1999**, 2327. (b) Rodriguez, C. M.; Martín, T.; Ramírez, M. A.; Martín, V. S. *J. Org. Chem.* **1994**, *59*, 4461. (c) Ohwa, M.; Kogure, T.; Eliel, E. L. *J. Org. Chem.* **1986**, *51*, 2599. (d) Dittmer, D. C.; Discordia, R. P.; Zhang, Y.; Murphy, C. K.; Kumar, A.; Pepito, A. S.; Wang, Y. *J. Org. Chem.* **1993**, *58*, 718. (e) Maurer, P. J.; Knudsen, C. G.; Palkowitz, A. D.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 325.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 5711–5718
Tetrahedron

Bis(triphenylphosphine)palladium(II)succinimide as a precatalyst for Suzuki cross-coupling—subtle effects exerted by the succinimide ligand

Ian J. S. Fairlamb,* Anant R. Kapdi, Jason M. Lynam, Richard J. K. Taylor and Adrian C. Whitwood

Department of Chemistry, University of York, Heslington, York YO10 5DD, UK

Received 1 March 2004; revised 7 May 2004; accepted 10 May 2004

Abstract—A new palladium(II) precatalyst for Suzuki cross-coupling of aryl halides and organoboronic acids has been identified, namely bis(triphenylphosphine)palladium(II)succinimide [$(Ph_3P)_2Pd(N\text{-}Succ)_2$] **2**. The precatalyst is easily prepared from palladium(0) precursors, such as $(Ph_3P)_4Pd$ or $Pd_2dba_3{\cdot}CHCl_3/Ph_3P$ and succinimide, is air, light and moisture stable, and may be employed with a variety of substrates to give the cross-coupled products, in good yields and in reasonable time, at relatively low catalyst loadings.

Palladium-catalysed reactions constitute some of the most important transformations available to the synthetic chemist.[1] Since the early 1970's, many different types of carbon–carbon and carbon-heteroatom forming bond technologies have been developed, such as the Hartwig–Buchwald,[2] Heck,[3] Negishi,[4] Sonogashira,[5] Stille[6] and Suzuki[7] cross-coupling processes. The latter reaction, where organohalides react with organoboronic acids in the presence of base and a Pd(0) catalyst, or a Pd(II) precatalyst, arguably represents one of the most applied reactions in academia and industry (Eq. 1). It is for this reason that Suzuki cross-coupling has become the benchmark by which new catalysts/precatalysts are most commonly evaluated. Highly active Pd-catalysts for this reaction have been recently developed by a number of research groups.[8] The differences between these catalysts most often arises through changes in the coordinating ligand, that is, use of electron rich alkyl phosphines, such as $(t\text{-Bu})_3P$ or biphenyl$(t\text{-Bu})_2P$, *N*-heterocyclic carbenes or phosphinites. The electronic and steric properties of these ligands are clearly important in tuning the catalytic properties of the palladium centre. Somewhat surprisingly the role of the halide ligand[9] in palladium(II) precatalysts has generally been ignored, and it has been questioned whether there is the possibility that alteration of this ligand might change the catalytic properties of the palladium centre. Studies by Amatore and Jutand have demonstrated that halide ligands from Pd(II) precatalysts are likely to play a role with the catalytic cycle—anionic Pd(0) species containing one halide ligand, of the type $[L_2Pd(0)X]^-$ (L=R_3P), are considered important.[10] This has led us to systematically investigate the importance of halides and pseudohalides in several Pd-catalysed cross-coupling reactions.

$$R\text{–}X + R'\text{–}B(OH)_2 \xrightarrow[\text{Base}]{[Pd]} R\text{–}R' \quad (1)$$

The incorporation of hemilabile imidate ligands, such as succinimide, maleimide and phthalimide with palladium would allow us to determine whether pseudohalides effect the palladium centre.[11] Imidate ligands have been described as pseudohalides, exerting unusual, but potentially exploitable effects for metal centres.[12] The hemilability of imidate ligands derives from their ability to act as either monodentate or bidentate ligands. Generally four coordination modes to transition metals are considered possible (**I**-**IV**, Fig. 1).

These interesting modes of coordination[13] might offer unique stabilizing properties for key catalytic intermediates. To this end, we have previously shown that the Stille cross-coupling reaction is promoted by succinimido based Pd(II)

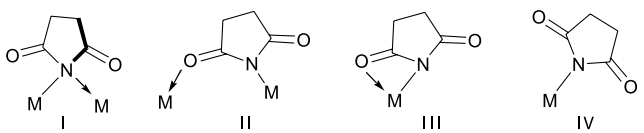
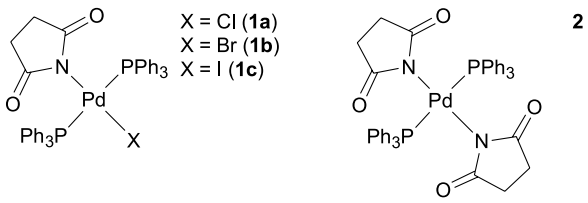


Figure 1. Possible coordination modes of succinimide ligands to metal centres.

Keywords: Suzuki cross-coupling; Biaryls; Palladium; Succinimide.
* Corresponding author. Tel.: +44-1904-434091; fax: +44-1904-432516; e-mail address: ijsf1@york.ac.uk

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.05.018

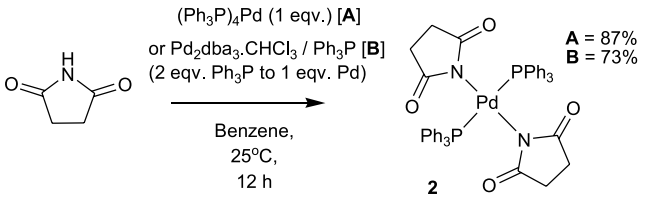
precatalysts (**1a-c**, Scheme 1), resulting in improved isolated yields of the products, as well as showing remarkable substrate selectivity.[14]



Scheme 1. General Suzuki cross-coupling reaction; known precatalysts **1a-c** and the novel precatalyst **2**.

In preliminary studies, we have further established that precatalyst **1b** is able to catalyze the Suzuki cross-coupling reaction of 4-nitro-bromobenzene and phenylboronic acid to give the cross-coupled product in good yield (74%), although 5 mol% of precatalyst is required. Lower catalyst loadings (0.5 mol%) gave incomplete conversion to products (~55%). In an effort to improve on these conversions and subsequent isolated yields, and to reduce the catalyst loading, we turned our attention to the related Pd(II)-complexes, containing two succinimide ligands.

The oxidative addition of succinimide to $(Ph_3P)_4Pt$ and $(Ph_3P)_4Pd$, to give $(Ph_3P)_2Pt(N\text{-Succ})H$ and $(Ph_3P)_2Pd(N\text{-Succ})_2$ **2**, respectively, has been described by Roundhill.[15] However, detailed structural information on **2** is very limited. Using a modified procedure (method A) to that reported, we found that $(Ph_3P)_4Pd$ reacted with 2 equiv. of succinimide in benzene at 25 °C after 12 h to give the *trans*-complex **2** in 87% yield. We were further able to access **2** starting from $Pd_2dba_3{\cdot}CHCl_3$ (dba=dibenzylidene acetone), by initial reaction with Ph_3P (Pd:Ph_3P, 1:2), generating a bis-ligated palladium(0) species '$(Ph_3P)_2Pd\text{-}\eta^2\text{-dba}$',[16] to give **2** in a slightly lower 73% yield (method B). The ^{31}P NMR spectrum of **2** in $CDCl_3$ exhibits one singlet at δ 20.42, however the geometry around the palladium centre cannot be confirmed by this, as the phosphorus signal for both the *cis* and *trans* isomers would be expected to appear as a singlet due to symmetry. The succinimide protons are shielded, appearing at δ 1.40 (^1H NMR). The shielding effects are presumably derived from π-stacking interactions between the carbonyl and phosphorus aromatic groups. Similar effects have been observed for other transition metal complexes containing succinimide ligands.[12] Single crystals of **2** suitable for X-ray analysis were grown from dichloromethane/diethyl ether (1:5, v/v, ~0.1 M solution) by slow vapour diffusion (Fig. 2 Scheme 2).[17]



Scheme 2. Synthesis of precatalyst **2**.

The X-ray crystallographic data confirms the *trans*-geometry around the Pd-centre. Interestingly, the carbonyl groups π-stack with alternatively positioned aromatic groups (Fig. 3) and the succinimide ligands deviate slightly from the plane, minimizing interactions with the nitrogen lone pair electrons (dihedral angle: C5–N2–N1–C1, θ=13°).

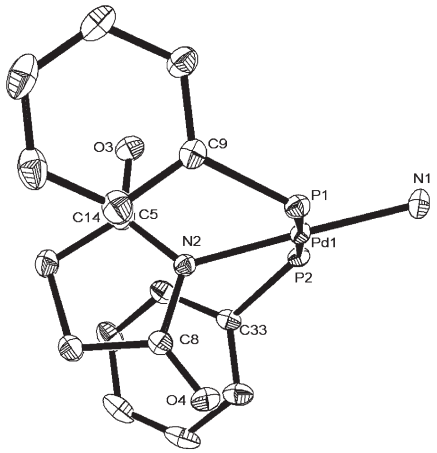


Figure 3. Selected atoms in complex **2** showing the key π-stacking interactions between the carbonyl groups and the overlapping phosphorus aromatic groups.

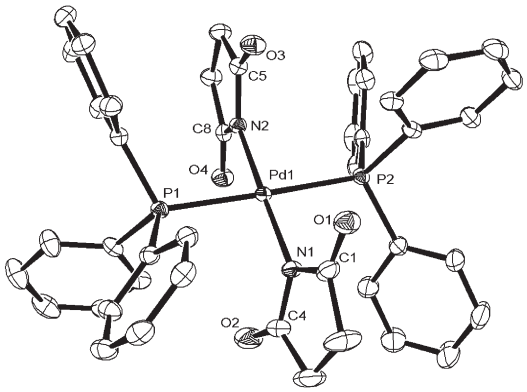
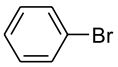
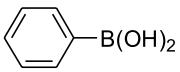
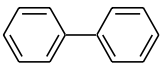
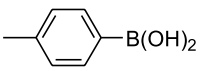
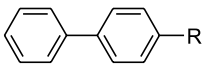
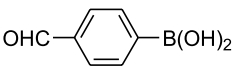
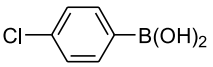
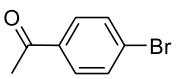
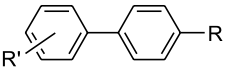
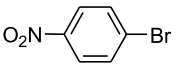
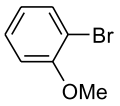
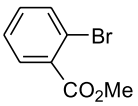
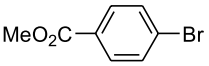
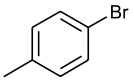
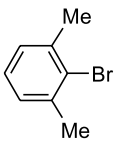
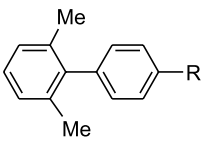


Figure 2. ORTEP representation of complex **2** with atomic labeling. Thermal ellipsoids are drawn at 50% probability. Selected bond lengths (Å): N(1)–Pd(1) 2.0364(15), N(2)–Pd(1) 2.0112(14), P(1)–Pd(1) 2.3476(5), P(2)–Pd(1) 2.3342(5); Selected bond angles: N(2)–Pd(1)–N(1) 178.34(6), N(2)–Pd(1)–P(2) 88.64(4), N(1)–Pd(1)–P(2) 90.28(5), N(2)–Pd(1)–P(1) 89.33(4), N(1)–Pd(1)–P(1) 91.75(5), P(2)–Pd(1)–P(1) 177.969(16).

The positioning of the substituents around the palladium centre is a consequence of intramolecular π-stacking interactions and not intermolecular interactions between molecules within the unit cell, which is negligible. The IR spectrum of a CH_2Cl_2 solution of **2** interestingly shows two absorptions at 1723 (w) and 1645 cm^{-1} (s). The lower ν(CO) frequency is attributable to the imidato-carbonyl, where Pd→σ-donation and π–π repulsions in the Pd–N bond promote delocalisation of the nitrogen lone pair on to the carbonyl group.[12] The higher stretching frequency mode at 1723 cm^{-1} is attributable to ν_{sym}(CO). This band has negligible intensity compared with the antisymmetric ν(CO) absorption. This data is consistent with previously reported Pd-complexes possessing succinimide ligands.[18]

Table 1. Suzuki cross-coupling of aryl halides and aryl boronic acids catalysed by $(Ph_3P)_2Pd(N\text{-Succ})_2$ **2**[a]

Entry	Aryl bromide	Aryl boronic acid	Product	Time/h	Yield/%[b]
1	 **3a**	 **4a**	 **5a**	8	94; **67**
2	**3a**	 **4b**	 R=Me, **5b**	8	87; **84**
3	**3a**	 **4c**	R=CHO, **5c**	8	93; **63**
4	**3a**	 **4d**	R=Cl, **5d**	8	83; **71**
5	 **3c**	**4a**	 R′=4-$COCH_3$, R=H, **5e**	3	85; **64**
6	**3c**	**4b**	R′=4-$COCH_3$, R=Me, **5f**	3	81; **71**
7	**3c**	**4c**	R′=4-$COCH_3$, R=CHO, **5g**	3	89; **74**
8	**3c**	**4d**	R′=4-$COCH_3$, R=Cl, **5h**	3	83; **73**
9	 **3d**	**4a**	R′=4-NO_2, R=H, **5i**	4	95; **74**
10	**3d**	**4b**	R′=4-NO_2, R=Me, **5j**	5	96; **69**
11	**3d**	**4c**	R′=4-NO_2, R=CHO, **5k**	5	96; **74**
12	**3d**	**4d**	R′=4-NO_2, R=Cl, **5l**	5	89; **71**
13	 **3e**	**4a**	R′=2-OMe, R=H, **5m**	10	86; **72**
14	 **3f**	**4a**	R′=2-CO_2Me, R=H, **5n**	10	94; **55**
15	**3f**	**4c**	R′=2-CO_2Me, R=CHO, **5o**	10	**66**
16	**3f**	**4d**	R′=2-CO_2Me, R=Cl, **5p**	14	**56**
17	**3f**	**4a**	R′=2-CO_2Me, R=Me, **5q**	10	**62**
18	 **3g**	**4a**	R′=4-CO_2Me, R=H, **5r**	8	**74**
19	**3g**	**4c**	R′=4-CO_2Me, R=CHO, **5s**	8	**58**
20	 **3h**	**4a**	R′=4-Me, R=H, **5b**	8	**70**
21	 **3i**	**4a**	 R=H, **5t**	14	79; **65**
22	**3i**	**4b**	R=Me, **5u**	14	84; **59**
23	**3i**	**4c**	R=CHO, **5v**	14	70; **52**
24	**3i**	**4d**	R=Cl, **5w**	14	91; **76**

[a] *Reaction conditions*: aryl bromide (1.05 equiv., 0.45 mmol), aryl boronic acid (1.0 equiv., 0.41 mmol), **2** (1 mol%), 1 M aq. Na_2CO_3 (1 mL), THF (1.5 mL), 60 °C.

[b] Conversion by ^1H NMR spectroscopy. Numbers in bold are isolated yields after chromatography.

1. Suzuki cross-coupling using $(Ph_3P)_2Pd(N\text{-Succ})_2$ (2)

The Suzuki cross-coupling of activated and deactivated aryl bromides (**3a**-**i**) with four aryl boronic acids (**4a**-**d**) were carried out in the presence of 1 mol% of precatalyst **2** to give the cross-coupled products (**5a**-**w**, Table 1). Bromobenzene **3a** reacted with phenylboronic acid **4a** in 8 h to give biphenyl **5a** in 67% isolated yield (94% conversion by ^{1}H NMR spectroscopy, entry 1). The more reactive 4-methylphenylboronic acid **4b** reacted with **3a** to give the cross-coupled product **5b** in 84% isolated yield (entry 2). Both 4-formylphenylboronic acid **4c** and 4-chlorophenylboronic acid **4d** reacted with **3a** to give **5c** and **5d**, respectively in good yields (entries 3 and 4). The activated 4-acetylbromobenzene **3c** reacted with **4a**-**d** in 3 h and gave good isolated yields (64–73%) of the corresponding cross-coupled products (**5e**-**h**, entries 5–8). Similarly, 4-nitrobromobenzene **3d** gave the cross-coupled products **5i**-**l** in good yield (entries 9–12). In all of these reactions percentage conversion to products was generally excellent (as adjudged by ^{1}H NMR spectra of the crude reaction mixtures). The deactivated substrate, 2-bromoanisole **3e** reacted with **4a** to give **5m** in 72% isolated yield (entry 13). The more activated, but more sterically congested ester substrate **3f**, reacted with **4a**, **4c**-**d** to give the cross-coupled products in generally good isolated yields (entries 14–16). The less sterically demanding ester substrate **3g** reacted similarly with **4a** and **4c** to give the cross-coupled products **5r** and **5s** in 74% and 58% yields, respectively (entries 18 and 19). The deactivated substrate, 4-bromotoluene **3h**, reacted with **4a** to give the cross-coupled product **5b** in 70% isolated yield in only 8 h (entry 20). The very sterically congested and deactivated substrate, 2,6-dimethylbromobenzene **3i** did react with **4a**-**d** to give the cross-coupled products **5t**-**w** in modest to good yields, but as might be expected, the reactions took substantially longer (entries 21–24). In these examples, the percentage conversion to products was generally good.

The kinetic profile for the reaction of 4-nitrobromobenzene **3d** with phenylboronic acid **4a** in the presence of 1 mol% of **2** to give **5i** was determined at 60 °C by GC analysis (Fig. 4).[19] This shows a slight induction period, which is expected for the generation of an active catalyst species.

On analysis of the reaction mixture after ca. 10 s, we see immediate loss of Ph_3P (1 equiv. with respect to **2**). At this point, the homo- or cross-coupled products were not detected. After 0.25 h, biphenyl, the homo-coupled product, was detected (0.01 equiv. overall). The reaction then enters into a linear regime, slowly decaying after 2.3 h (~83% conversion). The formation of biphenyl after 0.33 h indicates that phenylboronic acid **4a** is involved in conversion of the Pd(II) precatalyst **2** to a Pd(0) species. Exactly 2 equiv. of **4a** (0.02 equiv.) are required for this process. It should be noted that the total concentration of biphenyl does not increase throughout the course of the reaction. For comparison, the same reaction was run in the presence of $(Ph_3P)_2PdCl_2$ (1 mol%) under identical conditions (and concentration). The reaction was slightly slower and it failed to reach completion (~12% starting material was detected). The conversion of the Pd(II) precatalyst to a Pd(0) species can be quantified similarly

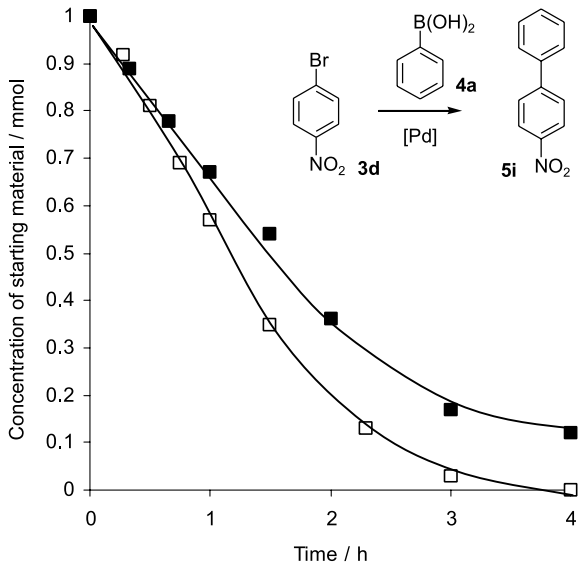


Figure 4. □ Reaction profile for the Suzuki cross-coupling reaction of 4-nitrobromobenzene **3d** (0.45 mmol) and phenylboronic acid **4a** (0.41 mmol) in THF/1 M aq. Na_2CO_3 (1.5 mL:1 mL) using precatalyst **2** (1 mol%) by GC analysis. ■ Identical reaction in the presence of $(Ph_3P)_2PdCl_2$ (1 mol%).

to precatalyst **2**. Unlike **2**, rapid loss of Ph_3P was not seen immediately. In terms of catalyst activity, **2** is similar to $(Ph_3P)_2PdCl_2$. The major advantage of **2**, for this substrate (**3d**) in particular, is that the reaction proceeded to completion under these conditions.

To assess whether **2** compares well against an alternative, but more deactivated substrate, a similar GC analysis of the reaction of 2-bromoanisole **3e** with phenylboronic acid **4a** to give **5m** under identical conditions was conducted (Fig. 5).

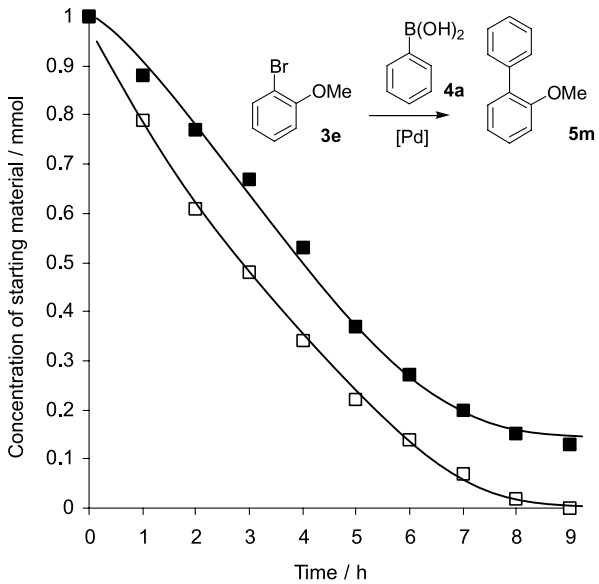


Figure 5. □ Reaction profile for the Suzuki cross-coupling reaction of 2-bromoanisole **3e** (0.45 mmol) and phenylboronic acid **4a** (0.41 mmol) in THF/1 M aq. Na_2CO_3 (1.5 mL:1 mL) using **2** (1 mol%) at 60 °C by GC analysis. ■ Identical reaction in the presence of $(Ph_3P)_2PdCl_2$ (1 mol%).

As with the reaction of **3d**, we see the rapid loss of Ph_3P (1 equiv. with respect to **2**). Biphenyl (0.01 equiv. overall)

was detected at 1 h, the concentration staying constant throughout remaining course of the reaction. An induction period for **2** was less obvious in this experiment. A small induction period is seen for the $(Ph_3P)_2PdCl_2$ precatalyst. The reaction follows a similar linear regime for $(Ph_3P)_2$-$PdCl_2$, however the reaction again fails to reach completion. Indeed, we have determined that it is necessary to use 2.5 mol% of $(Ph_3P)_2PdCl_2$ for complete consumption of starting material under the conditions used.

The effect of catalyst loading on the reaction of 4-nitrobromobenzene **3d** and phenylboronic acid **4a** was compared at 2.5, 1 and 0.25 mol% **2** (Fig. 6). The reaction is noticeably faster at 2.5 mol% **2**. However, the initial rapid consumption of **3d** (50%) is followed by noticeable deceleration during the latter stages (>2 h). After this time, at 1 mol% catalyst loading, a similar quantity of **3d** has been consumed (86% at 2.5 mol% and 87% at 1 mol%). The precipitation of palladium black at the higher catalyst loading could account for this. The initial loss of Ph_3P (detected) from precatalyst **2** suggests the initial formation of a mono-ligated phosphine T-shaped palladium(II) species **V** (Scheme 3). Based on the stabilizing properties of the succinimide (vide supra) this would be expected to be in equilibrium with a dimeric species **VI**. Conversion of either the monomeric or dimeric species with **4a** would then initially generate the homo-coupled product, biphenyl, and a mono-ligated phosphine species 'Ph_3P–Pd(0)', which presumably picks up the second free phosphine to generate a more reactive bis-ligated phosphine species '$(Ph_3P)_2Pd(0)$'.[20]

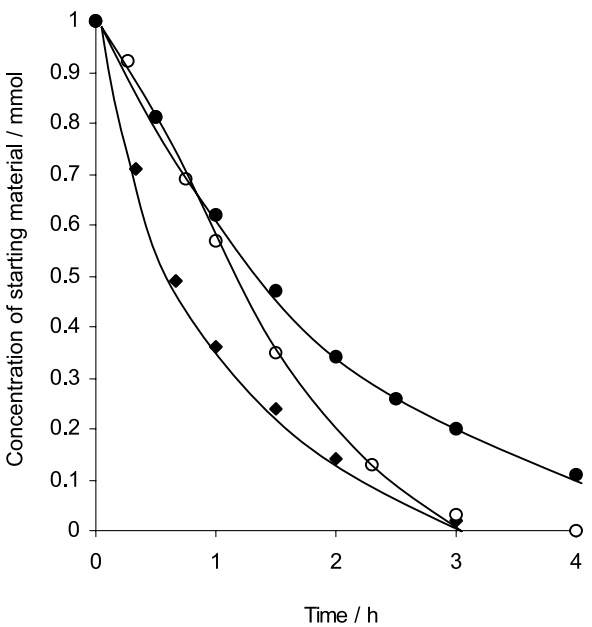
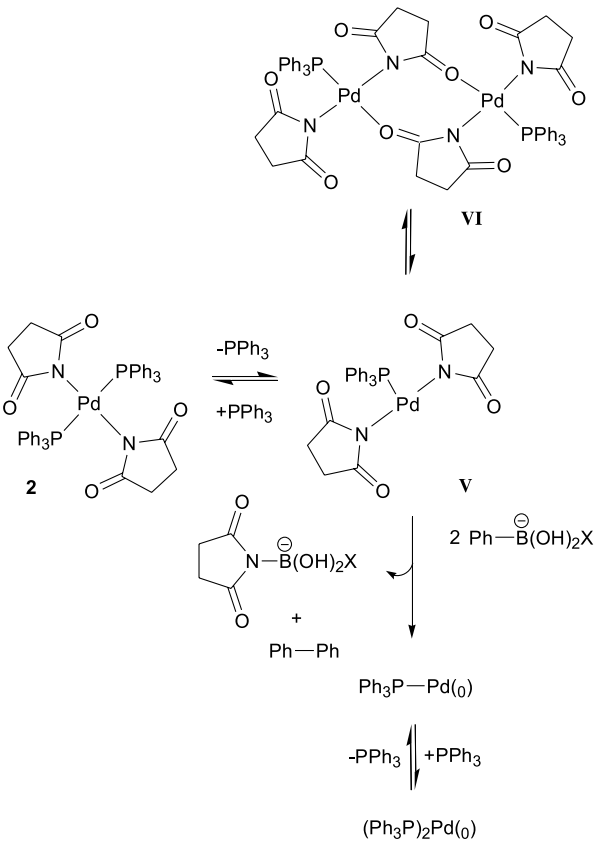


Figure 6. Reaction profile for the Suzuki cross-coupling reaction of 4-nitrobromobenzene **3d** (0.45 mmol) and phenylboronic acid **4a** (0.41 mmol) in THF/1 M aq. Na_2CO_3 (1.5 mL:1 mL) using **2** at different catalyst loadings by GC analysis: ◆ 2.5 mol% [Pd]; ○ 1.0 mol% [Pd] ● 0.25 mol% [Pd].

However, we are able to detect the presence of free phosphine throughout the course of the reaction (by GC). To gain further details of the reactive intermediates, which lead to the generation of the active catalytic palladium species, the reaction of **3d** and **4a** was followed by ^1H and ^{31}P NMR spectroscopy using 2.5 mol% **2** at 60 °C in d_8-THF/1 M Na_2CO_3 in D_2O (1.5/1, v/v) (Fig. 7).[21]



Scheme 3. Dissociation of Ph_3P and generation of the palladium(0) species.

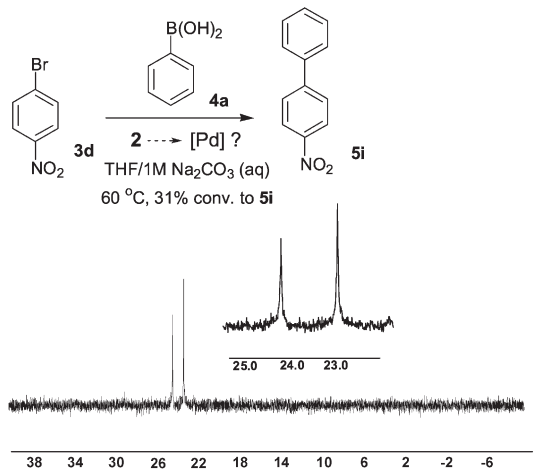
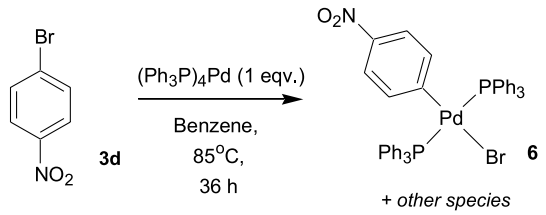


Figure 7. A snapshot of the reaction of **3d** with **4a** to give **5i** catalysed by precatalyst **2** (by ^{31}P NMR spectroscopy, 162 MHz).

The ^1H NMR spectrum (400 MHz) of the reaction mixture after ca. 1.5 h showed the presence of the cross-coupled product **5i** (31% conversion) based on consumption of **3d**. The ^{31}P NMR spectrum (162 MHz) exhibited two phosphorus signals (δ 23.09 and 24.19, integration ratio ~1.1:1) with no observable phosphorus spin–spin coupling. The signal at higher field appears to be attributable to precatalyst **2**, whereas the signal at lower field belongs to a new species. An obvious species that might be observed is the oxidative

addition intermediate of $(Ph_3P)_2Pd(0)$ and **3d**. We attempted to synthesise this complex independently from $(Ph_3P)_4Pd$ (1 equiv.) and **3d** (2 equiv.) in benzene at 85 °C for 36 h (Scheme 4). The solution goes from an orange to a yellow colour during the course of the reaction. On cooling to room temperature, a dark yellow solid precipitated out of solution, which was filtered and washed with ether (56% yield). The IR spectrum of this material in CH_2Cl_2 indicates the presence of a conjugated nitro group at 1520(s) and 1358(s) cm^{-1}, due to asymmetrical and symmetrical stretching of the NO bonds. However, the ^{31}P NMR spectrum run in d_8-THF shows four signals (δ 24.19, 23.88, 23.80 and 22.80, in a ratio of approximately 1:1:4:4). We would expect to observe $^2J_{PP}$ spin–spin coupling for the *cis*-form of **6** (the initial oxidative addition intermediate), however we do not.[22]



Scheme 4. Attempted synthesis of $(Ph_3P)_2Pd(Br)$-*p*-$C_6H_4NO_2$ **6**.

The ^{31}P NMR spectrum of the same material run using $CDCl_3$ as the solvent again showed the presence of four phosphorus signals (δ 24.21, 23.89, 23.68 and 22.63), but the ratio of these were approximately 1:3.2:8.5:4.9. This suggested to us that these species are in dynamic equilibrium. Presumably this explains why this complex has not been synthesised or characterised independently.[23] At the present time we cannot confirm whether the phosphorus containing species observed at δ 24.19 is **6** or a related Pd species. The fact that a signal attributable to the precatalyst **2** is seen at δ 23.09 is intriguing in itself, as the GC analysis of the same reaction (at 1 mol% catalyst loading) indicated that all the precatalyst had been converted from Pd(II) to Pd(0)—1 equiv. of homo-coupled product was observed in the initial stages of the reaction (vide supra).[24] This suggests that either succinimido or succinimide ligand could react to regenerate the Pd(II) bis(succinimide) complex **2**. Further studies with the ^{15}N labelled succinimide complex of **2** are being carried to study this in more detail.

In summary, we have identified **2** as an active palladium(II) precatalyst for the Suzuki cross-coupling reaction. These studies have shown that there is a subtle difference between the pseudohalide ligand—succinimide and the chloride ligand, and that although it is often assumed that Pd(II) precatalysts are converted into Pd(0) species, clearly the halide/pseudohalide has an effect on the 'real' catalytically active Pd intermediates. The true involvement of the succinimide ligand, whether as an anionic ligand or activator for the arylboronic acid, is part of ongoing mechanistic studies in our laboratories.

2. Experimental

2.1. General

THF was dried over sodium–benzophenone ketyl (distilled prior to use). All reactions were conducted under an inert atmosphere of Ar or N_2 on a Schlenk line. $Pd(PPh_3)_4$ was prepared by reduction of $(Ph_3P)_2PdCl_2$ with hydrazine.[25] $(PPh_3)_2PdCl_2$ was prepared from $PdCl_2$ in refluxing DMSO and PPh_3 (2 equiv.) using a known procedure.[26] Melting points were recorded on an electrothermal IA9000 Digital Melting Point Apparatus and are uncorrected. TLC analysis was performed on Merck 5554 aluminum backed silica gel plates and compounds visualized by ultraviolet light (254 nm), phosphomolybdic acid solution (5% in EtOH), or 1% ninhydrin in EtOH. ^1H NMR spectra were recorded at 270 MHz using a JEOL EX270 spectrometer or at 400 MHz using a JEOL ECX400 spectrometer; ^{13}C NMR spectra at 67.9 or 100.5 MHz. Chemical shifts are reported ins parts per million (δ) downfield from an internal tetramethylsilane reference. Coupling constants (J values) are reported in hertz (Hz), and spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), qn (quintet), sx (sextet), m (multiplet), br (broad).

GC conditions: Analysis was performed using a Varian CP-3800 GC equipped with a CP-8400 Autosampler. Separation was achieved using a DB-1 column (30 m×0.32 mm, 0.25 μm film thickness) with carrier gas flow rate of 3 ml min^{-1} and a temperature ramp from 50 to 250 °C at 20 °C min^{-1}. The injection volume was 1 μL with a split ratio of 50.

The following compounds were characterized by ^1H, ^{13}C NMR spectroscopy and mass spectrometry and compared to the known literature data: biphenyl **5a**,[27] 4-methylbiphenyl **5b**,[27] 4′-formylbiphenyl **5c**,[28] 4-chlorobiphenyl **5d**,[28] 4-acetylbiphenyl **5e**,[29] 4-acetyl-4′-methylbiphenyl **5f**,[30] 4-acetyl-4′-formylbiphenyl **5g**,[31] 4-acetyl-4′-chlorobiphenyl **5h**,[32] 4-nitrobiphenyl **5i**,[33] 4-nitro-4′-methylbiphenyl **5j**,[34] 4′-nitro-biphenyl-4-carbaldehyde **5k**,[35] 4-nitro-4′-chlorobiphenyl **5l**,[36] 2-methoxybiphenyl **5m**,[37] 2-methoxycarbonylbiphenyl **5n**,[38] 2-methoxycarbonyl-4′-formylbiphenyl **5o**,[39] 2-methoxycarbonyl-4′-chlorobiphenyl **5p**,[36] 2-methoxycarbonyl-4′-methylbiphenyl **5q**,[40] 4-methoxycarbonylbiphenyl **5r**,[38] 2-methoxycarbonyl-4′-formylbiphenyl **5s**,[39] 2,6-dimethylbiphenyl **5t**,[41] 2,6-dimethyl-4′-methylbiphenyl **5u**[29] and 2,6-dimethyl-4′-chlorobiphenyl **5w**.[42]

2.1.1. 2,6-Dimethyl-4′-formylbiphenyl (5v). ^1H NMR (400 MHz, $CDCl_3$) 9.99 (1H, s, CHO), 7.39 (2H, d, $^3J_{HH}$=6.7 Hz, 2×CH), 7.34 (1H, d, $^3J_{HH}$=6.7 Hz, CH), 7.31 (2H, m, 2×CH), 7.28 (2H, m, 2×CH), 2.37 (6H, s, 2×CH_3); ^{13}C NMR (400 MHz, $CDCl_3$) 192.10, 141.50, 138.34, 135.69, 134.28, 131.7, 129.95, 129.89, 126.55 and 23.84; MS (EI) *m*/*z* 210 (67, M+), 152 (54), 91 (85), 76 (26).

2.1.2. Synthesis of $(Ph_3P)_2Pd(N\text{-Succ})_2$ (2). Freshly prepared $(Ph_3P)_4Pd$ (170 mg, 0.147 mmol) was dissolved in dry benzene (10 cm^3) and succinimide (29.9 mg, 0.294 mmol) was added. The solution goes from an intense yellow colour to a pale yellow after only a few minutes, and a white crystalline salt begins to slowly appear. After ~12 h the solid was filtered (no special precautions), washed with benzene and dried in vacuo to give the complex as a white powder. A small quantity of the complex was crystallised from CH_2Cl_2/ether (1/5, v/v) to give colourless crystals. Yield: 100.3 mg, 82.6%. Mp=246–247 °C; MS (FAB)

(m/z): 827 [(M+1), 4%], 728 [(M−*N*-Succ), 32%], 629 [($(Ph_3P)_2$Pd-1), 17%]; IR (CH_2Cl_2, cm^{-1}) 1723 and 1645; ^1H NMR (400 MHz, $CDCl_3$) 7.79 (12H, m), 7.34 (18H, m), 1.40 (4H, s, 2×CH_2); ^{31}P NMR (162 MHz, $CDCl_3$) 20.42.

2.1.3. Typical Suzuki reaction. Phenylboronic acid (50 mg, 0.41 mmol), bromobenzene (70.7 mg, 0.45 mmol, 1.1 equiv.), Na_2CO_3 (1 M (aq.), 1 ml), THF (1.5 mL) and catalyst **1** (3.3 mg, 4.1 μmol, 1 mol%) were degassed via three 'freeze-pump-thaw' cycles. The resulting mixture was heated at 60 °C for the specified time. The reaction mixture was allowed to cool to room temperature and water (10 mL) added. The mixture was extracted with CH_2Cl_2 (3×10 mL) and the organic extracts dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by flash chromatography gave biphenyl as a white solid (42.3 mg, 67%).

Acknowledgements

The University of York is thanked for funding through an innovation and research priming fund grant (to I. J. S. F). Dr. Adam F. Lee (York) is thanked for providing analytical equipment and for use of his laboratory.

References and notes

1. (a) Heck, R. F. *Palladium Reagents in Organic Syntheses*; Academic: New York, 1985. (b) Tsuji, J. *Palladium Reagents and Catalysts*; Wiley: Chichester, 1995.
2. Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852, and references cited therein.
3. Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009.
4. Negishi, E.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979.
5. (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467. (b) Tykwinski, R. R. *Angew. Chem., Int. Ed.* **2003**, *42*, 1566. (c) Sonogashira, K. J. *Organomet. Chem.* **2002**, *653*, 46.
6. (a) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636. (b) Stille, J. K. *Angew. Chem. Int. Ed.* **1986**, *25*, 508. (c) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1.
7. (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Suzuki, A. J. *Organomet. Chem.* **1999**, *576*, 147. (c) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550. (d) Suzuki, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; VCH: Weinheim, 1998; p 49.
8. (a) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176. (b) Bedford, R. B. *Chem. Commun.* **2003**, 1787.
9. Fagnou, K.; Lautens, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 26, and references cited therein.
10. (a) Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314. (b) Amatore, C.; Jutand, A. J. *Organomet. Chem.* **1999**, *576*, 254, and references cited therein.
11. (a) Nestler, B.; Uhligh, E. Z. *Anorg. Allg. Chem.* **1985**, *530*, 196. (b) Serrano, J. L.; Zheng, Y.; Dilworth, J. R.; Sánchez, G. *Inorg. Chem. Commun.* **1999**, *2*, 407.
12. Adams, H.; Bailey, N. A.; Briggs, T. N.; McCleverty, J. A.; Colquhoun, H. M.; Williams, D. J. *J. Chem. Soc., Dalton Trans.* **1986**, 813.
13. Very recently we have been investigating the catalytic properties of bridged succinimide 'anionic' palladium(II) complexes, see: Serrano, J. L.; Fairlamb, I. J. S.; Sánchez, G.; García, L.; Pérez, J.; Vives, J.; López, G.; Crawforth, C. M.; Taylor, R. J. K. *Eur. J. Inorg. Chem.* **2004**. in press.
14. (a) Crawforth, C. M.; Burling, S.; Fairlamb, I. J. S.; Taylor, R. J. K.; Whitwood, A. C. *Chem. Commun.* **2003**, 2194. (b) Crawforth, C. M.; Fairlamb, I. J. S.; Taylor, R. J. K. *Tetrahedron Lett.* **2004**, *45*, 461.
15. Roundhill, D. M. *Inorg. Chem.* **1970**, *9*, 254.
16. Amatore, C.; Broeker, G.; Jutand, A.; Khalil, F. *J. Am. Chem. Soc.* **1997**, *119*, 5176.
17. The X-ray structure of **2** has been deposited to the Cambridge crystallographic database (UK): CCDC No. 228518.
18. Serrano, J. L.; Garcúá, L.; Pérez, J.; Pérez, E.; Vives, J.; Sánchez, G.; López, G.; Molins, E.; Orpen, A. G. *Polyhedron* **2002**, *21*, 1589.
19. Response factors for GC analysis: 4-nitrobromobenzene, 1.00; 4-nitrobiphenyl, 1.40; triphenylphosphine, 2.30: GC-MS analysis of selected quenched samples was performed to ascertain the identity of the components from the reaction mixture. Linear correlations were seen for three separate concentrations of each component. In the absence of the palladium precatalyst **2**, no reaction is observed under the conditions used.
20. It is not possible to rule out the formation of higher order polynuclear palladium species, whether they be palladium clusters or colloids, which could be responsible for the catalytic reaction. It should be noted that the formation of bis-ligated palladium(0) species is not a prerequsite for the Suzuki reaction—indeed mono-ligated palladium(0) is able to catalyse the Suzuki reaction more effectively (higher turnover frequencies) which is presumably associated with promoting the rate determining transmetallation step, see: Beeby, B.; Bettington, S.; Fairlamb, I. J. S.; Goeta, A. E.; Kapdi, A. R.; Niemelä, E. H.; Thompson, A. L. *New J. Chem.* **2004**, *28*, 600–605.
21. The higher catalyst loading was used to facilitate detection of the phosphorus containing species.
22. We have been unable to purify adduct **6** by regular silica-gel column chromatography from this mixture.
23. To the best of our knowledge this complex has not been synthesised independently. Given the fact that 4-nitro-phenyl bromide is often used as a benchmark substrate in Pd-catalysed cross-coupling reactions, this is surprising. All common databases, including the Cambridge Crystallographic Database, were searched for details of this complex.
24. We have not isolated any palladium complexes (in a zero or +two oxidation state) from silica-gel chromatography. No yellow bands, which could be indicative of a palladium(II) species, were also not seen.
25. (a) Coulson, D. R. *Inorg. Synth.* **1972**, *13*, 121. (b) King, R. B.; Kapoor, P. N. *Inorg. Chem.* **1972**, *11*, 1524.
26. Mann, F. G.; Purdie, D. *J. Chem. Soc.* **1935**, 1549.
27. Mathews, C. J.; Smith, P. J.; Welton, T. *Chem. Commun.* **2000**, 1249.
28. Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553.
29. Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550.
30. Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989.

31. Barrett, A. G. M.; Procopiou, P. A.; Voigtmann, U. *Org. Lett.* **2001**, *3*, 3165.
32. Idoux, J. P.; Kiefer, G. E.; Baker, G. R.; Puckett, W. E.; Spence, F. J. *J. Org. Chem.* **1980**, *45*, 441.
33. Leadbeater, N. E.; Marco, M. *Org. Lett.* **2002**, *4*, 2973.
34. Shudo, K.; Ohta, T.; Okamoto, T. *J. Am. Chem. Soc.* **1981**, *103*, 645.
35. Plas, P. A. J.; Mueller, F. *J. Heterocycl. Chem.* **1985**, *22*, 841.
36. Klement, I.; Rottlaender, M.; Tucker, C. E.; Majid, T. N.; Knochel, P. *Tetrahedron* **1996**, *52*, 7201.
37. Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513.
38. Kobayashi, Y.; William, A. D.; Mizojiri, R. *J. Organomet. Chem.* **2002**, *653*, 91.
39. Blettner, C. G.; König, W. A.; Stenzel, W.; Schotten, T. *Synlett* **1998**, 295.
40. Inada, K.; Miyaura, N. *Tetrahedron* **2000**, *56*, 8657.
41. Griffiths, C.; Leadbeater, N. E. *Tetrahedron Lett.* **2000**, *41*, 2487.
42. Bell, H. C.; Kalman, J. R.; Pinhey, J. T.; Sternhell, S. *Tetrahedron Lett.* **1974**, *15*, 857.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 5719–5723
Tetrahedron

Sulfonium ylides derived from 2-hydroxy-benzoquinones: crystal and molecular structure and their one-step conversion into Mannich bases by amine *N*-oxides

Thomas Rosenau,[a,*] Kurt Mereiter,[b] Christian Jäger,[c] Peter Schmid[a] and Paul Kosma[a]

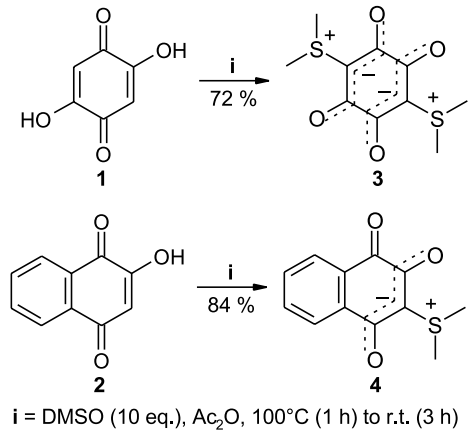
[a]*Department of Chemistry, University of Natural Resources and Applied Life Sciences Vienna, Muthgasse 18, A-1190 Vienna, Austria*
[b]*Department of Chemistry, Vienna University of Technology, Getreidemarkt 9, A-1060 Vienna, Austria*
[c]*Federal Institute of Materials Research and Testing, Project Group I.3903, Richard-Willstaetter-Str. 11, D-12489 Berlin, Germany*

Received 10 March 2004; accepted 7 May 2004

Abstract—Reaction of 2-hydroxy-*para*-benzoquinones with DMSO/Ac_2O produced dimethylsulfonium ylides, of which crystal structures as well as solid and liquid state NMR spectra were recorded. The ylides react with tertiary methylamine *N*-oxides in a one-pot, multi-step process to 3-methylamino-substituted benzoquinones. The mechanism starts with a deoxygenative deprotonation of the amine *N*-oxides, followed by a formal electrophilic displacement of DMSO by the resulting carbonium–iminium ion.

1. Introduction

In our studies on chromophore formation in the Lyocell process—a modern, environmentally benign technology for the production of cellulosic fibers without chemical cellulose derivatization—we treated a multi-component chromophore mixture with acetic anhydride for acetylation purposes. A small amount of a yellow precipitate resulted, the formation of which initially remained non-reproducible for the individual chromophore components, no matter which acetylation procedure was used. Only when we repeated the acetylation in the presence of small amounts of DMSO—following the idea that the original material might have contained residual DMSO-d_6 from NMR experiments—the precipitation reoccurred. By treatment with excess DMSO in acetic anhydride as the solvent yellow, high-melting precipitates were obtained from 2,5-dihydroxybenzoquinone (**1**) and 2-hydroxynaphthoquinone (**2**), which turned out to be the bis(dimethylsulfonium ylide) **3** and dimethylsulfonium ylide **4**, respectively (Scheme 1). A literature study quickly revealed that this reaction had already been reported,[1] albeit without comprehensive analytical characterization of the products and contradictory physical data. Treatment of **3** in glacial acetic acid had even be described to yield recrystallized **3**,[2] even though the product represents the bis(acetic acid) adduct. These inconsistencies prompted us to address the crystal and molecular structure of these ylides in more detail. Furthermore, studies of their behavior under Lyocell conditions, that is, in a melt of *N*-methylmorpholine-*N*-oxide monohydrate (NMMO) at temperatures of about 100 °C, lead to the finding of a hitherto unreported reaction, which we wish to communicate in this study in addition.



Scheme 1. Formation of sulfonium ylides by treatment of 2-hydroxy-benzoquinones with DMSO/acetic anhydride.

2. Results and discussion

Compound **3** is extremely insoluble in all non-polar and polar aprotic organic solvents tested. It even precipitates

Keywords: Sulfonium ylides; Amine *N*-oxides; Crystal structure; Benzoquinones.
* Corresponding author. Tel.: +43-1-36006-6071; fax: +43-1-36006-6059; e-mail address: thomas.rosenau@boku.ac.at

0040–4020/$ - see front matter © 2004 Published by Elsevier Ltd.
doi:10.1016/j.tet.2004.05.015

from hot DMSO if the formation reaction was carried out in this solvent. Being insoluble in organic amines and moderately soluble in hot acetic or formic acid, it has a very high solubility in water. Bisylide **3** can be recrystallized from concentrated aqueous solutions in large (side length up to 3 mm), yellow prisms, such as those used for obtaining the crystal structure in Figure 1. Crystallization from hot organic acids provides the bis(acid) adducts, such as the bis(acetic acid) adduct (**3** * 2HOAc) and the bis(formic acid) adduct (**3** * 2HCOOH). By analogy, treatment with HCl in organic media provides the microcrystalline bis(hydrochloride), treatment with nitric acid the bis(hydronitrate), while treatment with sulfuric acid failed to give the stoichiometric mono(sulfuric acid) adduct. The insolubility of **3** in organic media is evidently due to its high polarity: the molecule carries two positive and two negative charges located along a relatively small six-membered ring. However, it should be noted that despite the high charge concentration, the overall dipolar moment is zero. The high polarity of the molecule was also reflected in its high melting point, being above 300 °C. The acid adducts melt considerably lower at about 180 °C.

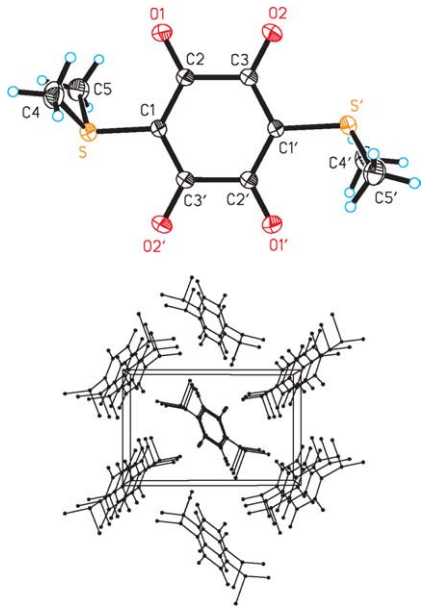


Figure 1. Crystal structure (40% thermal ellipsoid plot) of bis(dimethylsulfonium ylide) **3** and view of the crystal packing down the *a*-axis. The molecule is C_i-symmetric (close to C_{2h}); primed atoms are symmetry equivalents of unprimed ones.

The crystal structure of bisylide **3** is shown in Figure 1. Molecule **3** is highly symmetric. The C–O bond lengths are nearly identical, with 1.231 Å ranging between those of typical double and single bonds. The C1–C2 bond (1.421 Å) having partial double bond character is significantly shorter than the C2–C3 bond, which is a 'proper' single bond (1.549 Å). These values reflect the resonance stabilization of the molecule as shown in Scheme 1. The tight crystal packing with significant C–O dipole–dipole interactions and non-classical C–H···O/C–H···S hydrogen bonds for all methyl H atoms (C5···O=3.060–3.474 Å, C1···S=3.769 Å) agrees with the observed high melting point.

The solid state ^{13}C NMR spectrum of **3** shows two carbonyl resonances and two methyl resonances (Fig. 2). The signal splitting reflects the influence of packing effects in the crystal, which render C2/C3 as well as C4/C5 magnetically inequivalent in solid state. This inequivalence is lost in liquid state, and the solution state spectrum gives three resonances, with the four methyls and four carbonyl carbons, respectively, being magnetically equivalent.

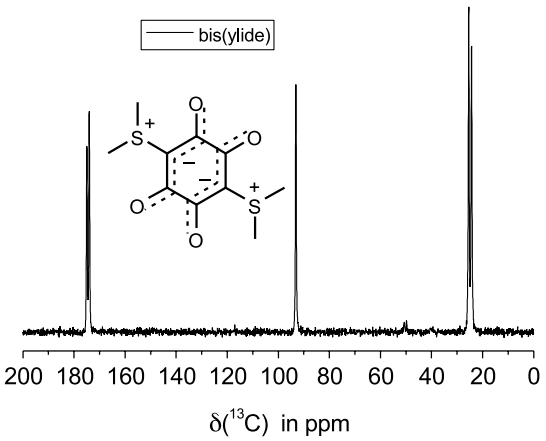


Figure 2. CPMAS ^{13}C NMR spectrum of bisylide **3**.

Similar structural features as described for the bisylide **3** were found for the monoylide **4**, its crystal structure being shown in Figure 3. Apart from the two methyl groups, the whole molecule lies within one plane. The bonds C1–O1 (1.244 Å) and C3–O2 (1.231) are longer than the C4–O3 double bond (1.213 Å). C1–C2 (1.427 Å) and C2–C3 (1.414 Å) are partial double bonds and thus shorter than the single bond C3–C4 (1.541 Å). This corresponds to the charge distribution which results from the participation of different resonance structures as shown in Scheme 1.

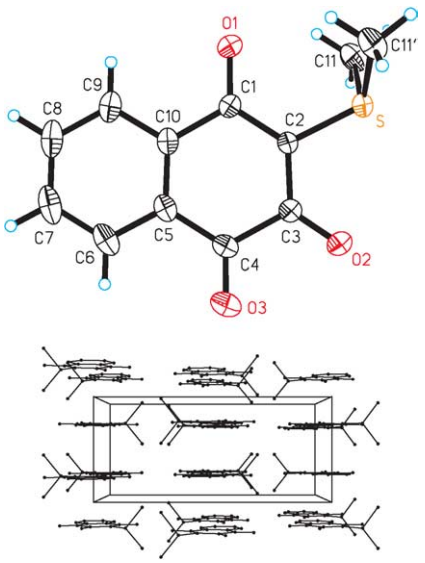
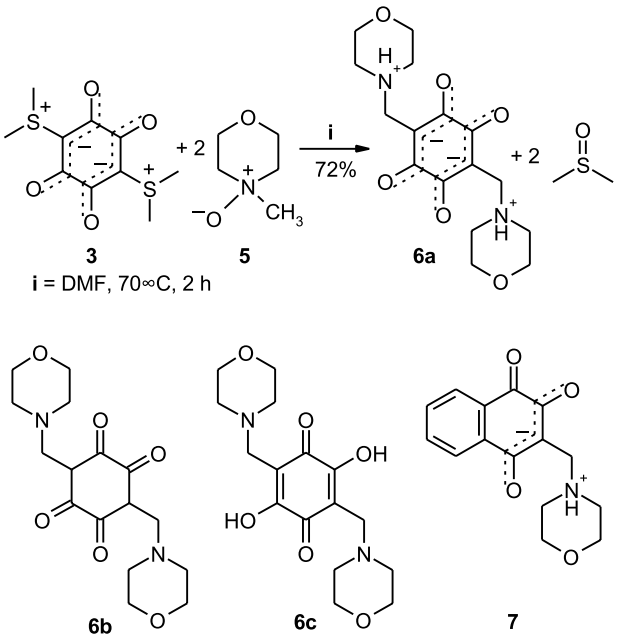


Figure 3. Crystal structure (40% thermal ellipsoid plot) of dimethylsulfonium ylide **4** and view of the crystal packing down the a-axis showing π-stacked layers of molecules. The molecule is C_s-symmetric; C11 and C11′ are symmetry equivalents.

Prompted by the ready formation of bis(hydrochlorides) and bis(carboxylic acid) adducts with **3**, we tried to obtain

crystal adducts with NMMO (**5**), which possesses a betaine structure, thus offering a separated positive and negative charge—similar to dissociated acids. Unfortunately co-crystallization did not succeed so far. Attempts to dissolve **3** in a melt of NMMO resulted in a spontaneous, uncontrollable reaction, the high exothermicity of which caused a complete charring of the mixture. While this reaction between the pure reactants at elevated temperatures was evidently useless for synthetic purposes, the reaction can be conducted safely in DMF at 50 °C. Reaction of equimolar amounts of **3** and NMMO under these conditions produced DMSO and bisbetaine **6a**, the intramolecular double salt of Mannich base **6b** or the corresponding benzoquinone **6c**, see Scheme 2.



Scheme 2. Reaction of dimethylsulfonium ylides with tertiary amine *N*-oxides.

Compound **6a** precipitated as red powder, moderately soluble in water and readily soluble in dilute mineral acids. It sublimated under decomposition at about 265 °C. These physical characteristics as well as the solution ^{13}C NMR data—four equivalent oxygen-bound carbonyls and down-field shifted *N*-methylene groups—favor the bisbetaine structure over the neutral Mannich base. This structure was also confirmed by X-ray analysis, which in addition showed **6a** to crystallize as tetrahydrate in large, orange prisms. Each hydrate water is donor of a regular and a bifurcated hydrogen bond (Fig. 4). In an analogous reaction, betain **7** was obtained from naphtho-ylide **4** in 87% yield. Preliminary experiments indicated that the reaction proceeded equally well with other tertiary amine *N*-oxides, such as *N*,*N*-dimethylbenzylamine *N*-oxide and *N*,*N*-dimethyl-dodecylamine *N*-oxide.[3] An authentic sample of **6a** was prepared by double morpholinomethylation of 2,5-dihydroxybenzoquinone.[4]

The reaction in Scheme 2 can be regarded as a superposition of substitution and redox reaction, it formally achieves

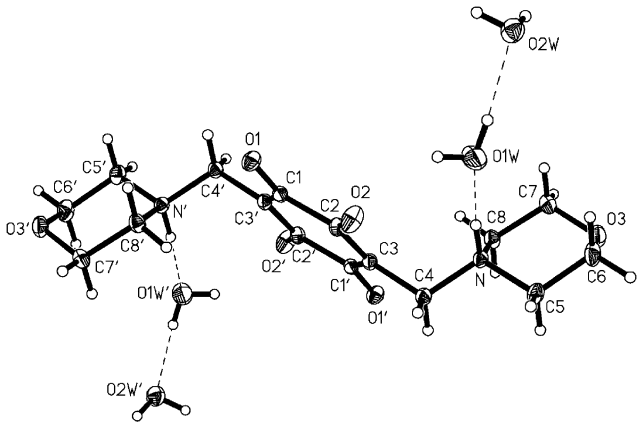
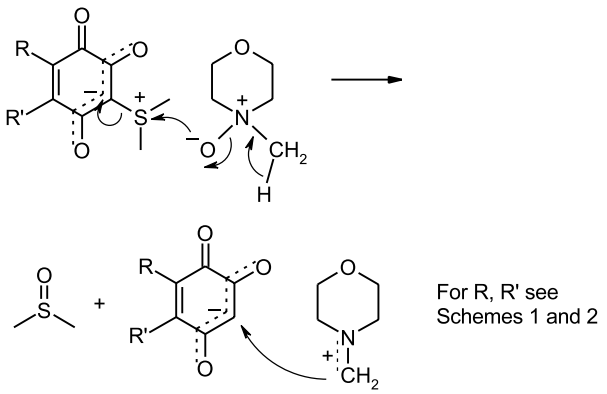


Figure 4. Crystal structure (20% thermal ellipsoid plot) of tetrahydrate of bisbetain **6a**.

displacement of a dimethylsulfonium group by a methylaminium group with concomitant oxygen transfer from the nitrogen in the amine *N*-oxide to the sulfur in the dimethylsulfonium group, which becomes the rather uncommon leaving group DMSO. The first step of the reaction mechanism is likely to be a nucleophilic attack of the negatively charged oxygen at the sulfur atom. Similar to degradation reactions in tertiary amine *N*-oxides starting with *O*-alkylation[5] or *O*-acylation[6], this process will induce a deoxygenation with simultaneous removal of a proton from the *N*-methyl group, giving a *N*-(methylene)morpholinium ion.[7] Neutral DMSO is released, and the resulting carbanion recombines with this carbonium–iminium ion (Scheme 3). If the reaction between sulfonium ylide and *N*-methylmorpholine *N*-oxide was carried out in the presence of *N*,*N*-dimethyl(methylene)ammonium iodide (Eschenmoser's salt), two products—either with dimethylammonium or morpholinium moiety—were found. The obvious competition between the two carbonium–iminium ions supports the above mechanistic proposal.



Scheme 3. Proposed mechanism of the reaction of dimethylsulfonium ylides with tertiary amine *N*-oxides.

3. Experimental

3.1. General

All chemicals were commercially available. Thin layer chromatography (TLC) was performed on silica gel 60

plates (5×10 cm, 0.25 mm) with fluorescence detection under UV light at 254 nm. Melting points, determined on a Kofler-type micro hot stage with a Reichert-Biovar microscope, are uncorrected.

X-ray data collection was performed with a Bruker AXS Smart APEX CCD diffractometer and graphite monochromatized Mo K_α radiation; corrections for absorption with the program SADABS, structure solution with direct methods, structure refinement on F^2 (Bruker AXS, 2001: programs SMART, version 5.626; SAINT, version 6.36A; SADABS version 2.05; XPREP, version 6.12; SHELXTL, version 6.10. Bruker AXS Inc., Madison, WI, USA).

CCDC-232906 and 232907 contain the supplementary crystallographic data for this paper. 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.

Crystal data for bis(sulfonium ylide) **3**. $C_{10}H_{12}O_4S_2$, M=260.32, monoclinic, space group $P2_1/c$, a=6.0629(4), b=7.7367(5), c=11.9325(7) Å, β=91.087(1)°, V=559.62(6) Å^3, Z=2, D_{calcd}=1.545 g/cm^3, T=300(2) K, μ=0.470 mm^{-1}, F(000)=272, yellow prism (0.70×0.35×0.35 mm), total/unique reflections 4181/1605, R_{int}=0.019. Final refinement: data/restraints/parameters 1605/0/78, GOF=1.08, R_1=0.027, wR_2=0.073 (all data).

Crystal data for sulfonium ylide **4**. $C_{12}H_{10}O_3S$, M=234.26, orthorhombic, space group $Pnma$, a=9.5360(12), b=9.5360(12), c=15.924(2) Å, V=1072.4(2) Å^3, Z=4, D_{calcd}=1. 451 g/cm^3, T=297(2) K, μ=0.289 mm^{-1}, F(000)=488, yellow prism (0.58×0.16×0.14 mm), total/unique reflections 7764/1611, R_{int}=0.025. Final refinement: data/restraints/parameters 1611/0/95, GOF=1.05, R_1=0.058, wR_2=0.143 (all data).

The solid state NMR measurements were recorded on a Bruker DMX Avance 400 spectrometer, using a double channel 4 mm CPMAS. The ^{13}C CPMAS spectra were acquired at a radio frequency of 100.62. MHz. The spinning frequency was 12500 Hz and was stabilized to ±2 Hz. 222 scans have been acquired using a repetition time of 6 s, a CP-time of 5 ms (50% ramp on proton channel) and TPPM decoupling[8] with a phase shift of 10° during the acquisition time.

Spectra in solution were recorded with a Bruker Avance DPX instrument operating at 300.13 MHz for ^{1}H and 75.47 MHz for ^{13}C using tetramethylsilane as internal standard. Homo- and heteronuclear 2D NMR spectroscopy was performed with Bruker standard software. Chemical shifts are given in ppm, coupling constants in Hz. ^{13}C peaks were assigned by means of APT, HMQC and HMBC spectra.

Bis(sulfonium ylide) **3**. 2,5-Dihydroxybenzoquinone (1.40 g, 10 mmol) was suspended in a mixture of acetic anhydride (20 mL) and DMSO (5 mL) and heated under stirring to 100 °C for 1 h. A yellow solid precipitated, which was collected by filtration after additional stirring for 3 h at rt. The solid was thoroughly washed with ethyl acetate and dried in vacuo to provide **3** (1.87 g, 72%), mp (H_2O) >300 °C. Crystals for X-ray diffraction were obtained by slow evaporation of a concentrated aqueous solution,. ^{1}H NMR (D_2O): δ 3.08 (s, 12H, Me). ^{13}C NMR (D_2O): δ 25.4 (Me), 94.4 (C–S), 177.0 (C–O). Anal. Calcd for $C_{10}H_{12}O_4S_2$ (260.33): C 46.14, H 4.65, S 24.63. Found: C 45.82, H 4.41. Recrystallization from glacial acetic acid provided the bis(acetic acid) adduct as yellow needles, mp 182–184 °C. ^{1}H NMR (D_2O): δ 2.22 (s, 6H, Me in Ac), 3.20 (s, 12H, Me). ^{13}C NMR (D_2O): δ 21.4 (Me in Ac), 25.8 (Me), 94.8 (C–S), 177.2 (C–O), 177.5 (C–O in Ac). Anal. Calcd for $C_{14}H_{20}O_8S_2$ (380.44): C 44.20, H 5.30, S 16.86. Found: C 44.08, H 5.40. Recrystallization from formic acid provided the bis(formic acid) adduct as yellow needles, mp 188–191 °C. ^{1}H NMR (D_2O): δ 3.22 (s, 12H, Me), 8.25 (s, 2H, HCO). ^{13}C NMR (D_2O): δ 25.6 (Me), 94.9 (C–S), 177.4 (C–O), 179.3 (HCO). Anal. Calcd for $C_{12}H_{16}O_8S_2$ (352.38): C 40.90, H 4.58, S 18.20. Found: C 41.19, H 4.82.

Sulfonium ylide **4**. Using 2-hydroxynaphthoquinone (**2**) (1.74 g, 10 mmol) instead of **1**, compound **4** was obtained according to the above procedure (1.97 g, 84%), mp 263–265 °C. Crystals for X-ray diffraction were obtained by slow cooling of a concentrated solution in water/methanol (v/v=2:1). ^{1}H NMR (DCOOD): δ 3.30 (s, 6H, Me), 7.82 (t, 1H, ^{Ar}H), 7.92 (t, 1H, ^{Ar}H), 8.11 (t, 2H, ^{Ar}H). ^{13}C NMR (DCOOD): δ 25.7 (Me), 98.5 (C–S), 127.5 (CH), 128.3 (CH), 131.3, 134.1, 134.3 (CH), 136.5 (CH), 172.2, 181.6, 182.4. Anal. Calcd for $C_{12}H_{10}O_3S$ (234.28): C 61.52, H 4.30, S 13.69. Found: C 61.09, H 4.20.

Mannich bisbetaine **6**. Bisylide **3** (0.52 g, 2 mmol) was suspended in DMF (50 mL) and heated to 70 °C. A solution of NMMO monohydrate (**5**, 0.57 g, 4.2 mmol) in DMF (10 mL) was added dropwise during 1 min. After complete addition, the red mixture became clear almost immediately, and a few minutes later a brick-red solid started to precipitate. The mixture was stirred for additional two hours and cooled to rt. The precipitate was isolated by filtration, washed thoroughly with ethyl acetate and dried in vacuo to give **6a** (0.49 g, 72%), mp 265 °C (decomp.). ^{1}H NMR (D_2O): δ 3.20 (t, 8H, N–CH_2–CH_2), 3.87 (m, 8H, O–CH_2), 3.95 (s, 4H, N–CH_2–C). ^{13}C NMR (D_2O): δ 51.8 (N–CH_2–CH_2), 52.2 (N–CH_2–C), 64.5 (O–CH_2), 103.6 (C), 180.1 (C–O). Anal. Calcd for the monohydrate $C_{16}H_{24}N_2O_7$ (356.38): C 53.93, H 6.79, N 7.86. Found: C 54.50, H 6.25, N 7.42.

Mannich betaine **7**. Employing naphtho-ylide **4** (0.47 g, 2 mmol) instead of **3**, compound **7** was obtained according to the above procedure in 87% yield, mp 192–196 °C. ^{1}H NMR (D_2O): δ 3.16 (t, 4H, N–CH_2–CH_2), 3.80 (t, 4H, O–CH_2), 3.92 (s, 2H, N–CH_2–C), 7.81 (t, 1H, ^{Ar}H), 7.90 (t, 1H, ^{Ar}H), 8.10 (t, 2H, ^{Ar}H). ^{13}C NMR (D_2O): δ 51.4 (N–CH_2–CH_2), 52.4 (N–CH_2–C), 64.3 (O–CH_2), 101.9, 127.0 (CH), 128.8 (CH), 131.1, 134.5 (CH), 134.6, 136.7 (CH), 177.8, 182.0, 183.1. Anal. Calcd for $C_{15}H_{15}NO_4$ (273.29): C 65.93, H 5.53, N 5.13. Found: C 66.08, H 5.71, N 4.97.

Acknowledgements

The authors would like to thank Dr. Andreas Hofinger, Department of Chemistry at the University of Natural Resources and Applied Life Sciences (BOKU), Vienna, for recording the solution NMR spectra.

References and notes

1. Moore, H. W.; Wikholm, R. J. *Tetrahedron Lett.* **1968**, *48*, 5049–5052. Wikholm, R. J.; Moore, H. W. *J. Am. Chem. Soc.* **1972**, *6152*, 6158.
2. Beaumont, P. C.; Edwards, R. L. *J. Chem. Soc. (C)* **1971**, 1000–1004.
3. Results and optimization towards a general synthetic procedure will be reported in due course.
4. Bheemasankara, C.; Venkateswarlu, V. *Tetrahedron* **1963**, *18*, 951.
5. *O*-alkylation can cause autocatalytic degradation of the amine *N*-oxide: Rosenau, T.; Potthast, A.; Kosma, P.; Chen, C. L.; Gratzl, J. S. *J. Org. Chem.* **1999**, *64*, 2166–2167.
6. Rosenau, T.; Potthast, A.; Kosma, P. *Tetrahedron* **2002**, *58*(49), 9808–9815.
7. For the chemistry of this carbonium–iminium ion see: Rosenau, T.; Potthast, A.; Kosma, P. *Tetrahedron* **2003**, *60*, 301–306.
8. Bennett, A. E.; Rienstra, C. M.; Auger, M.; Lakshmi, K. V.; Griffin, R. G. *J. Chem. Phys.* **1995**, *103*, 6951–6958.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 5725–5735
Tetrahedron

The palladium(0) Suzuki cross-coupling reaction as the key step in the synthesis of aporphinoids

R. Suau,[a,*] R. Rico,[a] F. Nájera,[a] F. J. Ortiz-López,[a] J. M. López-Romero,[a] M. Moreno-Mañas[b] and A. Roglans[b]

[a]*Dep. Química Orgánica, Facultad de Ciencias, Universidad de Málaga, 29071 Málaga, Spain*
[b]*Dep. Química, Universidad Autónoma de Barcelona, Cerdanyola, 08193 Barcelona, Spain*

Received 2 March 2004; revised 14 April 2004; accepted 7 May 2004

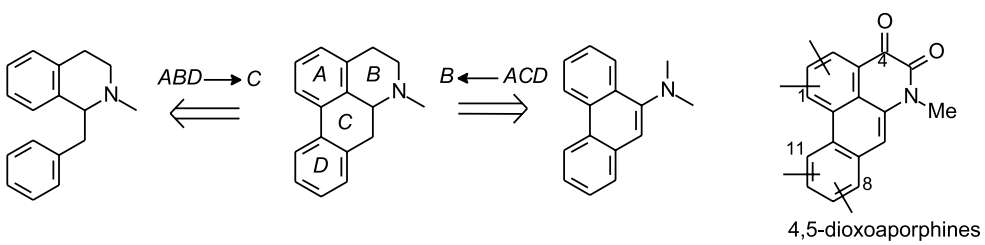
Abstract—We report a flexible approach to the total synthesis of 4,5-dioxoaporphines based on the palladium(0) catalyzed Suzuki cross-coupling of phenylboronic acids with sterically hindered 2-bromo phenyl acetates or bromo phenyl acetamides, followed by sequential bicyclization of biarylacetamides promoted by oxalyl chloride/Lewis acid. The reduction of 4,5-dioxoaporphines provides a chemoselective entry to aporphines, dehydroaporphines and 4-hydroxy-dehydroaporphines. A three-steps total synthesis for (±)-*O*,*O*′-dimethylapomorphine from readily accessible precursors is also reported.

1. Introduction

A number of approaches to the synthesis of 4*H*-dibenzo-[*de*,*g*]quinoline as the basic skeleton of the large group of aporphinoid alkaloids have been reported.[1] Most follow a biogenetic pathway the last step in which involves the cyclization of a suitably functionalized 1-benzylisoquinoline (*ABD*→*C* approach in Scheme 1). Methods used to obtain the aryl–aryl bond include the classical Pschorr reaction;[2] phenolic, monophenolic and non-phenolic oxidative coupling;[3] enamide photocyclization;[4] benzyne cyloaddition,[5] radical cyclization[6] and *ortho*-arylation.[7]

A non-biogenetic approach involving the construction of ring *B* at the final stage of the synthesis has been employed in the synthesis of aporphines and aporphine analogs[8] (particularly the highly oxidized aporphines, 4,5-dioxoaporphines,[9] which are believed to act as post-infectional phytoalexins in plants, and to exhibit significant cytotoxicity against various tumoral cell lines and DNA modifying bioactivity.[10]) This synthesis requires a suitably functionalized phenanthrene **I** as the key intermediate (*ACD*→*B* approach). These type of compounds (**I**) have been prepared following two different pathways; one starts from an accessible substrate with the preformed biaryl bond included in its structure (e.g., a functionalized fluorenone or dibenzopyrane[10a]) and the other from the radical cyclization of a functionalized stilbene prepared using the Horner protocol (Scheme 2).[10e]

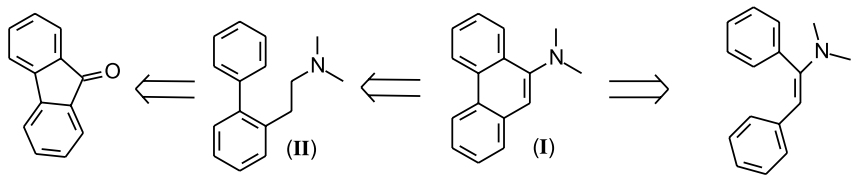
In the former case, oxidation of the fluorenone followed by homologation and Bischler–Napieralsky cyclization to the amino-phenanthrene **I** involved several steps (22% overall yield from 1-methoxyfluorenone). The latter approach



Scheme 1.

Keywords: Aporphinoids; Apomorphine; 4,5-Dioxoaporphine; 4-Hydroxy-dehydroaporphine; Aporphine; Palladium; Suzuki cross-coupling; Oxalyl chloride; Cascade cyclization; Reduction.
* Corresponding author. Tel.: +34-95213-1934; fax: +34-95213-2000; e-mail address: suau@uma.es

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.05.014



Scheme 2.

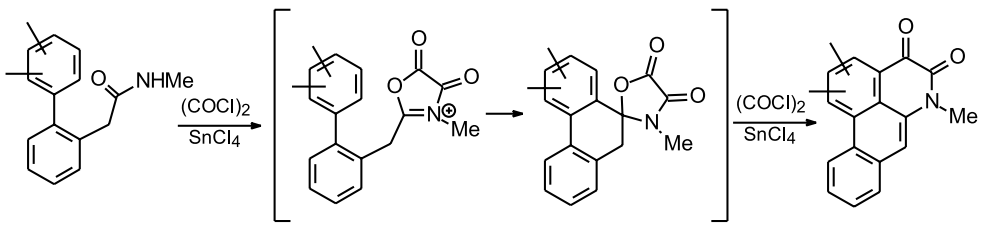
involves four steps, namely: formation of the phosphorylated benzamide, Horner reaction, radical cyclization and deprotection at nitrogen (48% average yield). In previous work we developed two different approaches to the formation of ring *B*; one involved photocyclization of α-chloroacetamides followed by oxidation or oxalyl chloride/Lewis acid reaction.[10a] Subsequently, we developed a much more direct approach based on the double cyclization of biphenyl acetamides promoted by oxalyl chloride/Lewis acid with sequential formation of rings *C* and *B* in a single step (Scheme 3).[11]

In this bicyclization, the oxalyl chloride activates the biphenylacetamide to give an electrophilic acyliminium ion which is the acylating agent that promotes the construction of ring *C*, gives the α-dicarbonyl system needed for the formation of ring *B*, and activates the Friedel–Crafts reaction in the final ring *B* closure.

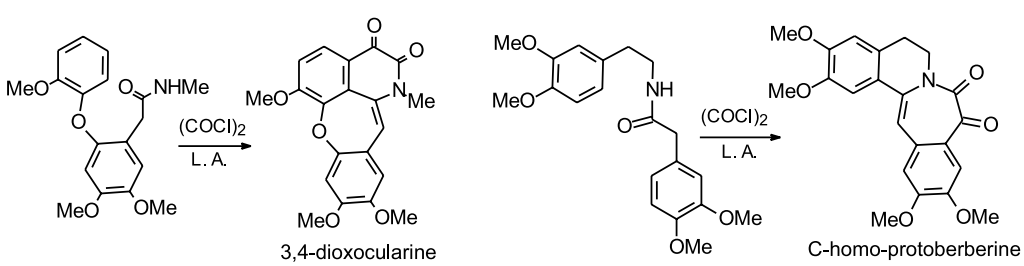
This double cyclization has also been successfully applied to the total synthesis of 3,4-dioxocularine alkaloids from aryloxy-phenylacetamides, and to the synthesis of C-homo-protoberberines that can be easily decarbonylated to the corresponding 8-oxo-berbines (Scheme 4).[12]

Although this double cyclization considerably shortens the synthesis of 4,5-dioxoaporphines, its use is limited by the availability of suitably substituted fluorenones or dibenzopyranes to match the oxygenated substitution pattern of naturally occurring 4,5-dioxoaporphines on the one hand, and by the long sequence required for homologation (reduction, halogenation, cyanation, hydrolysis and amidation) on the other. We thus focused on the synthesis of functionalized biphenyls as key intermediates (**II**, Scheme 2), using a more direct approach in order to circumvent the intermediate steps that decrease the overall yield and chose the Suzuki cross-coupling variant among the synthetic methods for biaryls.[13] This palladium-catalyzed cross-coupling of phenyl derivatives is a flexible, advantageous synthetic method for constructing C–C biaryl bonds under mild reaction conditions. It tolerates aqueous media; also, the inorganic products of the reaction can be easily eliminated, the boron compounds are stable, none of the products is toxic, and many of the aryl boronic acids are commercially available with an appropriate oxygenation aromatic pattern. However, the Suzuki biaryl cross-coupling reaction still requires some improvement, especially when sterically hindered substrates are involved. In addition, *ortho*-di and tri-substituted biaryls are also interesting because they are key structural elements of many pharmacologically active natural and synthetic products.[14]

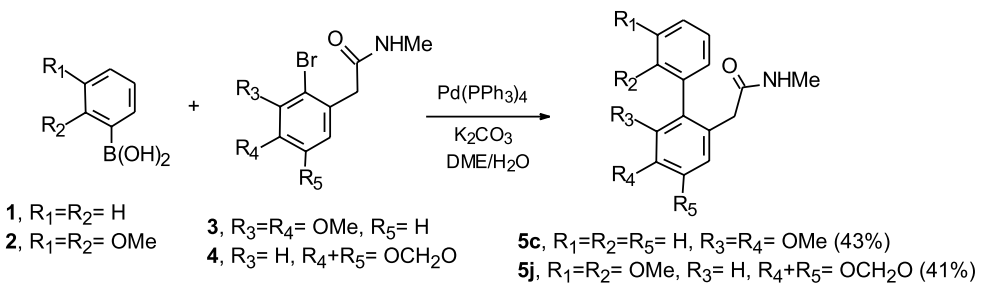
This paper reports our findings in using the Suzuki cross-coupling reaction for the synthesis of biaryl acetamides and esters, and its application to the synthesis of 4,5-dioxoaporphines, including the improvement in the cyclization of biarylacetamides promoted by oxalyl chloride/Lewis acid. This approach, which provides a convergent construction method for the aporphine skeleton in two steps, prompted us to explore the reduction of 4,5-dioxoaporphines to other aporphinoids. The results were applied to the total synthesis of (±)-*O*,*O*′-dimethylapomorphine in only three synthetic steps. The Suzuki coupling method and Meyers' protocol for the preparation of its key biphenylacetamide intermediate are compared.



Scheme 3.



Scheme 4.



Scheme 5.

2. Results and discussion

2.1. Suzuki cross-coupling

We first examined the coupling of arylboronic acid **1** or **2** with phenyl acetamides **3** and **4**, using the standard conditions for the Suzuki coupling, namely $Pd(PPh_3)_4$ as catalyst, K_2CO_3 as base and DME–H_2O as solvent. Under these conditions, total conversion was found by ^1H NMR of the reaction crude, and high yields of the cross-coupling compounds **5c** and **5j** (87 and 83%, respectively) were determined by GC–MS (Scheme 5). However, the presence of triphenylphosphine oxide, the R_f for which is very close to those of amides **5c**,**j**, hindered the purification of the amide derivatives by column chromatography, and resulted in significantly diminished yields for the isolated compounds (43% for **5c** and 41% for **5j**).

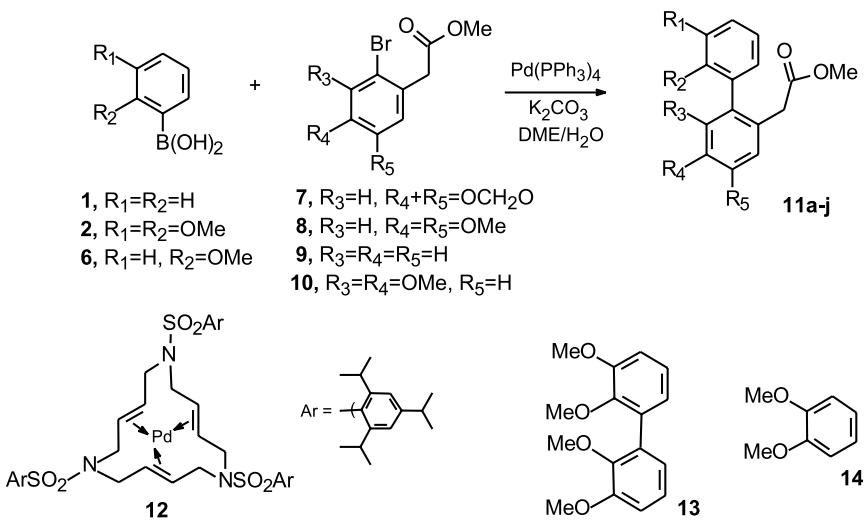
Table 1. Palladium catalyzed Suzuki cross-coupling of esters **7**–**10** with boronic acids **1**, **2** and **6** ($Pd(PPh_3)_4/K_2CO_3$/DME–H_2O)

Entry	R_1	R_2	R_3	R_4	R_5	Ester, **11**, yield, %[a]
1	H	OMe	H	H	H	**11a**, 64 (76)
2	OMe	OMe	H	H	H	**11b**, 56 (62)
3	H	H	OMe	OMe	H	**11c**, 83 (100)
4	H	OMe	OMe	OMe	H	**11d**, 58 (70)
5	OMe	OMe	OMe	OMe	H	**11e**, 31[b] (41)
6	H	OMe	H	OMe	OMe	**11f**, 67 (80)
7	OMe	OMe	H	OMe	OMe	**11g**, 45 (56)
8	H	H		OCH_2O		**11h**, 86 (100)
9	H	OMe	H	OCH_2O		**11i**, 76 (95)
10	OMe	OMe	H	OCH_2O		**11j**, 59 (69)

[a] (%) Yield by GC.
[b] 40% yield with DMF, K_3PO_4, and 10 mol% $Pd(PPh_3)_4$ as catalytic system.

Then, our attention was turned to the coupling of the ester derivatives instead of the amides in order to circumvent the purification difficulties. We first explored the coupling of 2-bromo-4,5-methylendioxy-phenylacetic methyl ester (**7**) with phenylboronic acid (**1**) (Table 1, entry 8). Under the above-described conditions, $Pd(PPh_3)_4/K_2CO_3$/DME–H_2O, refluxing compounds **1** and **7** for 18 h led to 100% conversion and, after purification, **11h** was obtained in a 86% yield. The coupling of boronic acids **1**, **2** and **6** with the bromide derivatives **7**–**10** under the same conditions afforded the biphenyl esters **11a**–**j** (Scheme 6, Table 1). Increasing the steric hindrance in the boronic acid (**6** and **2**) decreased the yield in the coupled products (entries 9 and 10, 76 and 59%, for **11i** and **11j**, respectively). The influence of the methoxy group *ortho* to the coupling position was also apparent in the reactions of bromide **10** with boronic acids **1**, **2** and **6** (entries 3–5).

The formation of the biaryl bond in highly sterically hindered biphenyls proved more difficult, as also observed in the preparation of the 1,2,1′,2′-tetramethoxylated biphenyl (**11e**), with three *ortho* substituents, and the yield dropping to 31% (Table 1, entry 5). It has been shown that improving the conditions for sterically hindered Suzuki coupling entails using of anhydrous conditions and phosphate. Using them in the coupling of **2** and **10** [DMF,



Scheme 6.

K_3PO_4, 10 mol% $Pd(PPh_3)_4$, 100 °C] raised the yield of **11e** to 40%.

Alternative catalysts and catalytic conditions were also tested. When the cross-coupling was conducted with the phosphine-free catalytic system $Pd_2(dba)_3$ in the presence of K_2CO_3, the coupling products **11h** and **11j** were obtained in lower yields (63 and 45%, respectively). The catalytic potential of the 15-membered macrocyclic triolefin palladium(0) complex (**12**), which can be recovered from reaction medium and reused with no loss of catalytic activity, was also examined.[15] The reaction of the bromide **7** with the phenylboronic acids **1** and **2**, revealed that catalyst **12** promotes the cross coupling, and biphenyls **11h** and **11j** were isolated, albeit with maximum yields around only 20%; as expected, the catalyst was quantitatively recovered in both cases after column chromatography on silica gel.

Differences in yield among biaryls exhibiting similar steric interactions can be ascribed to electronic effects.[16] Thus the decreased yield observed in the coupling of the *meta*-methoxy substituted boronic acid (**2**) (entries 2, 5, 7, 10, Table 1) can be ascribed to induction from this group of a lower electron density at position 1 of the boronic acid (**2**) compared to the unsubstituted acid (**6**), as suggested by electron density ab initio calculations (Fig. 1).[17] This effect on the yields is observed for the compound series. In fact, the dimerization product, 2,2′,3,3′-tetramethoxybiphenyl (**13**), and the deboronation product, veratrol (**14**), were always isolated from the reaction medium in the preparation of **11a**,**b**, **11d**,**e**, **11f**,**g** and **11i**,**j** (Scheme 6).

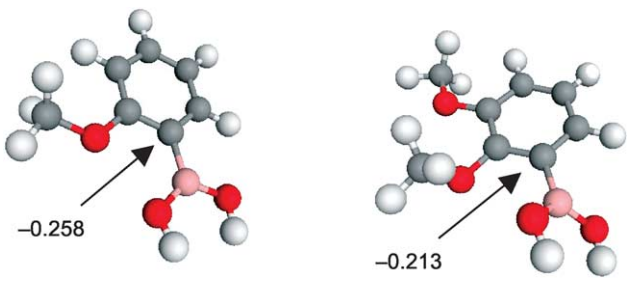


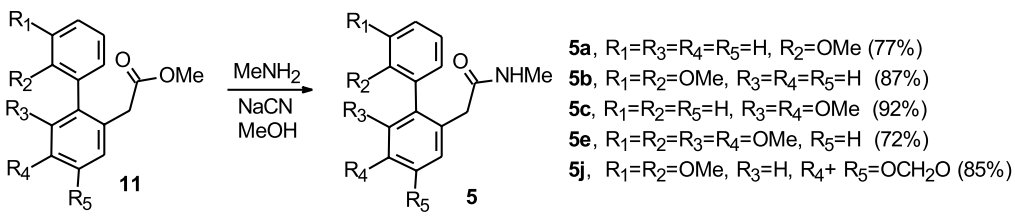
Figure 1. Electron density ab initio calculations for compounds **6** (left) and **2** (right).

Also, the presence of two methoxy groups in the molecule induces some deboronation due to an out-of-plane conformation of the boronic acid group in the more strained compound **2** which makes it more labile.

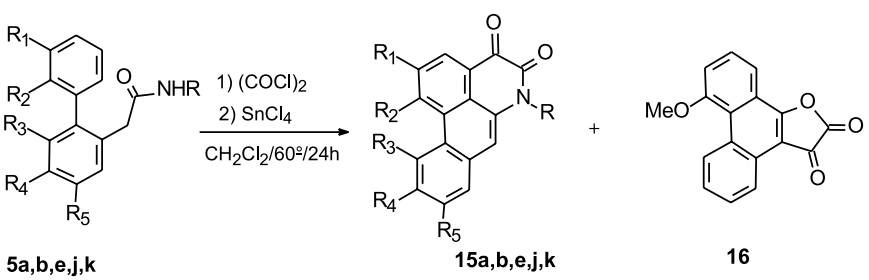
The biaryl esters **11a**–**c**, **11e** and **11j** were readily converted (yield 72–92%) to the biarylacetamides **5a**–**c**, **5e** and **5j** by aminolysis with 45% aqueous methylamine in the presence of sodium cyanide as catalyst (Scheme 7).[18]

2.2. Sequential bicyclization of biarylacetamides

The cyclization of amide **5a**, conducted under the previously described conditions[11] and using an excess of reagents [viz. 3 equiv. $(COCl)_2$ and 2.5 equiv. $SnCl_4$ in dichloromethane at 5 °C for 3 days] gave **15a** (80% yield) together with **16** (2%) and the uncyclized oxalylamidophenanthrene derivative (8%). We then standardized the reaction conditions with a larger excess of reagents (10 equiv. each), and heating at 60 °C, which shortened the reaction time (12–24 h) and raised the yield in **15a** (96%) (Scheme 8). Cepharadione-B (**15b**), which was previously obtained in 5% yield in a multistep sequence from 1-methoxyfluorenone, with formation of ring *B* by photocyclization of the corresponding phenanthryl-α-chloroacetamide, was now obtained in a 29% yield in three steps (52% biaryl coupling, 87% amidation and 65%

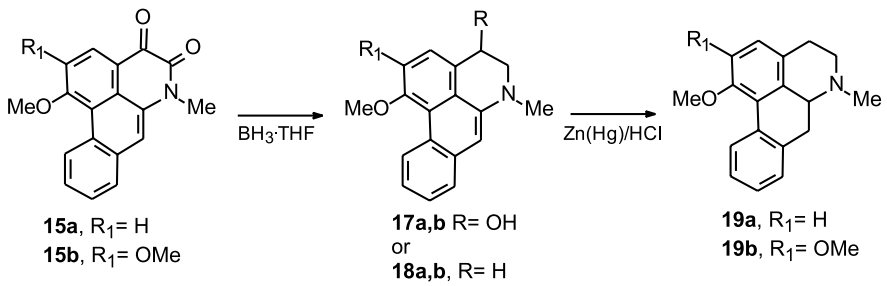


Scheme 7.



15a, **2-Demethoxy-cepharadione-B,** $R_1=R_3=R_4=R_5=H$, $R_2=OMe$, R=Me (96%)
15b, **Cepharadione B**, $R_3=R_4=R_5=H$, $R_1=R_2=OMe$, R=Me (65%)
15e, **4,5-Dioxodehydrocorydine**, $R_1=R_2=R_3=OMe$, $R_3=OH$, $R_5=H$, R=Me (73%)
15j, Corydione, $R_1=R_2=OMe$, $R_4+R_5=OCH_2O$, $R_3=H$, R=Me (39%)
15k, $R_1=R_3=R_4=R_5=H$, $R_2=OMe$, R=*p*-MeO-Ph (61%)

Scheme 8.



Scheme 9.

double cyclization). Cyclization of **5j** afforded the bioactive alkaloid corydione (**15j**) in a 20% overall yield from boronic acid **2**. The lower yield obtained in the cyclization of **5j** was probably due to the sensitivity of the methylenedioxo group to the reaction conditions.

Next, we attempted to expand the usefulness of this synthetic approach to the secondary amides, which could provide an entry to *N-nor*-dioxoaporphines and extend it to the synthesis of *nor*-aporphines. Direct access to these types of compounds following this synthetic pathway is limited because the reaction of oxalyl chloride with primary amides gives acyl isocyanates.[19] Protection of the nitrogen with a *p*-methoxy phenyl group, and cyclization of the secondary amide **5k**, afforded the *N-p*-methoxyphenyl substituted aporphinoid **15k** (together with the furandione **16**, Scheme 8). However, all attempts at N-deprotection using reagents such as CAN or silver nitrate, or anodic oxidation following described procedures were unsuccessful,[20] probably due to the low basicity of the nitrogen atom.

2.3. Reduction of 4,5-dioxoaporphines

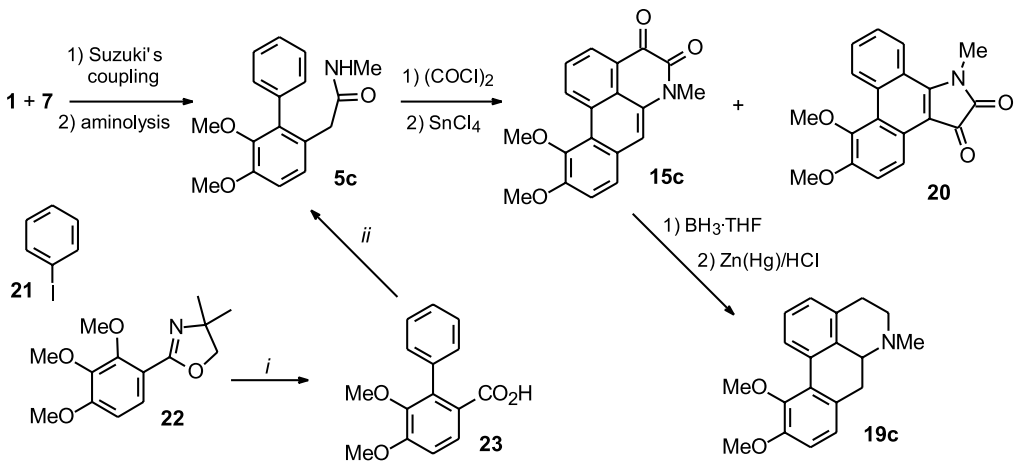
4,5-Dioxoaporphines **15a**,**b** were used as models to study the reduction to other aporphinoids (Scheme 9). Treatment with either LAH or $NaBH_4$ under variable conditions gave complex reaction mixtures. Treating **15a**,**b** with BH_3·THF at room temperature[21] provided in good yields the 4-hydroxy-dehydro aporphines **17a**,**b** (72 and 79%, respectively), which are in an oxidation state not found among naturally occurring aporphines. The same BH_3·THF procedure but heating at 60 °C instead led to the corresponding dehydroaporphines (**18a**,**b**). The completely reduced aporphine skeleton (**19a**,**b**) can be easily achieved by standard Clemmensen reduction of the 7–7a double bond (76% for **19a** and 83% for **19b**).

The attempted direct reduction of **15a** to the aporphine **19a** under Clemmensen conditions failed, probably because of the insolubility of these 4,5-dioxoaporphines under the reaction conditions used.

2.4. Synthesis of (±)-*O*,*O*′-dimethylapomorphine (19c)

Apomorphines are non-natural aporphines that result from the acid rearrangement of morphinanes. They have been widely investigated ever since the structural relationship between apomorphine and the neurotransmitter dopamine was realized.[22] Recently, it has been reported that apomorphines may play an important role in the prevention of Alzheimer's disease.[23]

Usually, apomorphine and its derivatives are obtained by semi-synthesis from morphine-related structures. Most of the reported total syntheses for apomorphine involve cathodic cyclization of 1-(*o*-iodobenzyl)isoquinolinum methiodide[24] followed by H_2/PtO_2 reduction, or start from a benzylisolquinoline diazonium salt prepared following a Bischler–Napieralski or Reissert procedure,[25] and having the *O*,*O*′-dimethyl derivative as intermediate.



Scheme 10.

Following the proposed approach, we accomplished the total synthesis of (±)-*O*,*O*′-dimethylapomorphine (**19c**). The process involved three steps, namely: coupling of the ester **7** with the boronic acid **1**, and aminolysis to the biphenylacetamide **5c** (76% total yield) and cyclization, promoted by oxalyl chloride and Lewis acid, to 4,5-dioxo-*O*,*O*′-dimethylapomorphine (**15c**), which was reduced with BH_3·THF and subjected to Clemmensen reaction with Zn(Hg)/HCl to afford (±)-**19c** in a 26% overall yield from the boronic acid **1** (Scheme 10). From the cyclization of **5c** the indanodione **20** was also isolated.[11b] Partial[26] or complete demethylation of methoxy groups in **19c** to obtain apomorphine can be readily accomplished by using various reported methods (e.g., refluxing with 57% HI in Ac_2O).

Meyers' coupling[27] is a widely used choice for biaryl coupling, so it was of interest to compare this methodology with the Suzuki coupling to prepare the biphenyl amide **5c** as the key intermediate in the synthesis of **19c**. The reaction of iodobenzene (**21**) with the oxazoline **22** gave the biphenylcarboxylic acid **23** in 61% yield; homologation of this acid led to the amide **5c** in a 55% overall yield from the oxazoline (Scheme 10). The Suzuki coupling approach therefore results in better yield (83 versus 61% in the biaryl bond formation) and is more expeditious as it avoids the need to homologate the side alkyl chain.

3. Conclusions

We prepared biphenyl acetamides and esters by palladium(0) catalyzed Suzuki cross-coupling of phenylboronic acids and phenyl bromides under very mild reaction conditions, all in moderate to good yields, even when the parent compounds were sterically hindered.

We developed a general approach to the total synthesis of aporphinoids in only three steps, namely: (i) Suzuki biaryl cross-coupling as the key step, (ii) sequential bicyclization promoted by oxalyl chloride/Lewis acid, and (iii) reduction of the α-dicarbonyl system. Compared to previously reported methods for the synthesis of aporphine alkaloids, the proposed method is expeditious, convergent on building the oxidized aporphinoids and divergent in its reduction, and cost-saving. Following this pathway, we successfully prepared *O*,*O*′-dimethylapomorphine in 29% yield from the commercial phenylboronic acid **1**.

4. Experimental

4.1. General procedures

Mps. were determined on a Gallenkamp instrument and are given uncorrected. UV spectra were recorded on a Hewlett–Packard 8452A spectrophotometer, and IR spectra on a Perkin–Elmer 883 spectrophotometer. Low resolution MS and GC/MS analyses were carried out on an HP 5988A mass spectrometer coupled to an HP 5980 gas chromatograph furnished with a fused silica capillary column (HP-1, 12 m×0.2 mm i.d., 0.33 mm film thickness). Helium, at a flow-rate of 1 mL min^{-1}, was used as the carrier gas. The column temperature was increased from 200 °C (hold 4 min) to 250 °C at 10 °C min^{-1} and then held at 250 °C for 15 min. High resolution mass spectra (EI and FAB) were recorded on a Kratos MS 50 spectrometer. NMR spectra were obtained on a Bruker WP-200 SY instrument, at 200 MHz for ^1H and 50.3 MHz for ^{13}C, or a Bruker ARX 400 model operating at 400 MHz for ^1H and 100 MHz for ^{13}C. ^1H Chemical shifts (δ_H) are given relative to residual $CHCl_3$ (δ_H 7.24 ppm) in deuteriochloroform, or to residual DMSO in DMSO-d_6. *J* values are in Hz. ^{13}C Chemical shifts (δ_C) are given relative to $CDCl_3$ (δ_C 77.0 ppm) in deuteriochloroform. TLC analyses were performed on silica gel 60 F 256 plates, and column chromatography (cc) on silica gel 60 (70–230 mesh).

Boronic acids **1** and **6** are commercially available and boronic acid **2** was prepared from 1,2-dimethoxy-benzene by treatment with *n*-BuLi, $B(OMe)_3$ followed by acid hydrolysis.[28] Compounds **7**, **8** and **9** were prepared from the corresponding phenylacetic acid, 3,4-dimethoxyphenylacetic acid and 3,4-methylendioxyphenylacetic acid, respectively, by bromination and esterification with $MeOH/H^+$.[29] 2-Bromo-3,4-dimethoxyphenyl acetic acid was prepared from vanillin, using the following synthetic sequence: (i) Br_2/AcOH, (ii) MeI/Na_2CO_3/DMF, (iii) $NaBH_4$/MeOH, (iv) $SOCl_2/CH_2Cl_2$, (v) NaCN/MeCN, (vi) KOH/EtOH–H_2O. From this acid, compounds **3** and **10** were prepared by amidation and esterification, respectively. Amide **4** was prepared from 3,4-methylendioxyphenylacetic acid by bromination and amidation.[30]

4.2. Suzuki cross-coupling reactions

4.2.1. Preparation of biaryl amides 5c and 5j. A mixture of $Pd(PPh_3)_4$ (0.17 mmol, 10 mol%) and bromide **3** or **4** (1.7 mmol) in DME (25 mL) was stirred for 15 min at 20 °C under argon. 2 M aqueous K_2CO_3 (5.9 mL, 11.8 mmol) was added to the mixture, followed by the corresponding boronic acid, **1** or **2** (3.5 mmol) in DME (8 mL). The mixture was refluxed for 18 h and then cooled at 20 °C. The reaction mixture was treated with water and ethyl ether. The organic extracts were washed with 1 M NaOH and water and dried over $MgSO_4$, the solvent being evaporated to dryness to give the biphenyls **5c** and **5j**, which were purified by column chromatography (silicagel, hexane–AcOEt).

(5,6-Dimethoxy)biphenyl-2′-yl N-methyl-acetamide (**5c**). 0.085 g (43%). White solid; mp 119–122 °C (AcOEt); ν (KBr) cm^{-1} 3273, 1644; λ_{max} ($CHCl_3$) nm (log ε) 284 (3.09), 244 (3.65); δ_H ($CDCl_3$) 7.4–7.3 (m, 3H, ArH), 7.2–7.1 (m, 2H, ArH), 7.05 (d, 1H, *J*=8.5 Hz, ArH), 6.91 (d, 1H, *J*=8.5 Hz, ArH), 5.1 (br s, 1H, NH), 3.89 (s, 3H, OCH_3), 3.50 (s, 3H, OCH_3), 3.26 (s, 2H, CH_2), 2.63 (d, 3H, *J*=4.8 Hz, $NHCH_3$); δ_C ($CDCl_3$) 171.7 (CO), 152.1 (C), 147.0 (C), 137.1 (C), 136.4 (C), 129.5 (2×CH), 128.2 (2×CH), 127.4 (CH), 126.3 (C), 125.9 (CH), 111.9 (CH), 60.6 (OCH_3), 55.8 (OCH_3), 40.8 (CH_2), 26.3 ($NHCH_3$); *m/z* (%) 285 (M^+, 97), 227 (76), 212 (100), 196 (57), 152 (53). Anal. calculated for $C_{17}H_{19}NO_3$: C 71.56, H 4.91, N 6.71%, found: C 71.74, H 4.72, N 6.85.

(2′,3′-Dimethoxy-4,5-methylendioxy)biphenyl-2′-yl N-methyl-acetamide (**5j**). 0.094 g (41%). White solid; mp 176–120 °C

(AcOEt); ν (KBr) cm^{-1} 3297, 1644; λ_{max} ($CHCl_3$) nm (log ε) 282 (3.25), 244 (3.88); δ_H ($CDCl_3$) 7.01 (t, 1H, J=8.0 Hz, ArH), 6.87 (dd, 1H, J=8.0, 1.5 Hz, ArH), 6.82 (s, 1H, ArH), 6.63 (m, 2H, ArH), 5.91 5.1 (br s, 1H, NH), 5.90 (d, 2H, J=2.2 Hz, OCH_2O), 3.83 (s, 3H, OCH_3), 3.55 (s, 3H, OCH_3), 3.39 (s, 2H, CH_2); 2.61 (d, 3H, J=4.7 Hz, $NHCH_3$); δ_C ($CDCl_3$) 171.9 (CO), 152.6 (C), 147.2 (C), 146.2 (C), 145.9 (C), 134.9 (C), 131.1 (C), 127.2 (C), 124.1 (CH), 122.8 (CH), 111.7 (CH), 109.9 (CH), 109.2 (CH), 101.0 (OCH_2O), 60.7 (OCH_3), 55.6 (OCH_3), 40.8 (CH_2), 26.2 ($NHCH_3$); *m/z* (%) 329 (M^+, 31), 272 (19), 240 (100). Anal. calculated for $C_{18}H_{19}NO_5$: C 65.63, H 5.82, N 4.25%, found: C 65.44, H 5.71, N 4.20.

4.2.2. Preparation of biaryl esters 11a–j. Suzuki coupling of bromo esters **7**–**10** with boronic acids **1**, **2** and **6** and work up were carried out as described above. Biaryl esters **11a**–**j** were purified by crystallization or column chromatography (silicagel, hexane–EtOAc) if necessary. An identical procedure was followed with $Pd(dba)_3$ as catalyst.

Reaction with catalyst **12**. A stirred mixture of bromide **7** (0.30 mmol), boronic acid **1** or **2** (0.32 mmol), K_2CO_3 (0.80 mmol), macrocyclic Pd(0) catalyst (**12**, 5 mol%) water (1 mL) and acetone (2 mL) was heated at 70 °C for 12 h. After cooling to room temperature, water and ether were added. The organic layer was separated, washed with water, dried over $MgSO_4$ and evaporated. Column chromatography of the residue on silica gel afforded the corresponding biphenyl esters **11h** and **11j**. Further elution (hexane–EtOAc, 10:5) provided quantitative recovery of the catalyst (**12**).

(2′-Methoxy)biphenyl-2-yl methyl acetate (**11a**). 0.28 g (64%). White solid; mp 39–42 °C (AcOEt); ν (KBr) cm^{-1} 1728 (ν_{CO}); λ_{max} ($CHCl_3$) nm (log ε) 280 (3.45), 250 (3.51); δ_H ($CDCl_3$) 7.39–7.30 (m, 4H, ArH), 7.23–7.19 (m, 1H, ArH), 7.15 (dd, 1H, J=7.6, 1.8 Hz, ArH), 7.01 (dt, 1H, J=7.6, 1.2 Hz, ArH), 6.94 (br d, 1H, J=7.6 Hz, ArH), 3.71 (s, 3H, OCH_3), 3.57 (s, 3H, OCH_3), 3.49 (s, 2H, CH_2); δ_C ($CDCl_3$) 172.2 (CO), 156.3 (C), 138.8 (C), 133.0 (C), 131.3 (CH), 130.4 (CH), 129.9 (CH), 129.6 (C), 129.0 (CH), 127.5 (CH), 127.0 (CH), 120.5 (CH), 110.5 (CH), 55.2 (OCH_3), 51.6 (OCH_3), 38.7 (CH_2); *m/z* (%) 256 (M^+, 83), 225 (35), 224 (97), 197 (37), 182 (57), 181 (76), 166 (32), 165 (100), 152 (53); HMRS FAB calculated for $C_{16}H_{17}O_3$ $[M+H]^+$ *m/z* 257.1178, found: 257.1170.

(2′,3′-Dimethoxy)biphenyl-2-yl methyl acetate (**11b**). 0.27 g (56%). Colorless syrup; ν (NaCl) cm^{-1} 1728 (ν_{CO}); λ_{max} ($CHCl_3$) nm (log ε) 280 (3.15), 244 (3.60); δ_H ($CDCl_3$) 7.5–7.2 (m, 4H, ArH), 7.09 (t, 1H, J=7.6 Hz, ArH), 6.94 (dd, 1H, J=7.6, 1.5 Hz, ArH), 6.72 (dd, 1H, J=7.6, 1.5 Hz, ArH), 3.88 (2×s, 2×3H, 2×OCH_3), 3.50 (s, 3H, OCH_3), 3.37 (s, 2H, CH_2); δ_C ($CDCl_3$) 174.9 (CO), 152.7 (C), 145.7 (C), 138.0 (C), 135.3 (C), 133.7 (C), 130.1 (C), 129.4 (CH), 128.1 (CH), 126.8 (CH), 124.4 (CH), 122.7 (CH), 111.9 (CH), 60.7 (OCH_3), 60.6 (OCH_3), 55.7 (OCH_3), 40.7 (CH_2); *m/z* (%): 286 (M^+, 100), 255 (20), 227 (66); HRMS FAB calculated for $C_{17}H_{19}O_4$ $[M+H]^+$ *m/z* 287.1283, found: 287.1289.

(5,6-Dimethoxy)biphenyl-2-yl methyl acetate (**11c**). 0.40 g (83%). Yellowish syrup; ν (KBr) cm^{-1} 1726 (ν_{CO}); λ_{max} ($CHCl_3$) nm (log ε) 282 (3.17), 246 (3.57); δ_H ($CDCl_3$) 7.40–7.31 (m, 3H, ArH), 7.25–7.17 (m, 2H, ArH), 7.03 (d, 1H, J=8.2 Hz, ArH), 6.90 (d, 1H, J=8.2 Hz, ArH), 3.87 (s, 3H, OCH_3), 3.55 (s, 3H, OCH_3), 3.51 (s, 3H, OCH_3), 3.35 (s, 2H, CH_2); δ_C ($CDCl_3$) 172.4 (CO), 151.9 (C), 146.7 (C), 137.1 (C), 136.5 (C), 129.6 (2×CH), 127.9 (2×CH), 127.1 (CH), 125.6 (C), 125.4 (CH), 111.5 (CH), 60.5 (OCH_3), 55.7 (OCH_3), 51.7 (OCH_3), 38.3 (CH_2); *m/z* (%): 286 (M^+, 100), 227 (61), 212 (80), 196 (45), 180 (22), 152 (29), 141 (18), 115 (25); HRMS FAB calculated for $C_{17}H_{19}O_4$ $[M+H]^+$ *m/z* 287.1283, found: 287.1292.

(2′,5,6-Trimethoxy)biphenyl-2-yl methyl acetate (**11d**). 0.31 g (58%). Yellowish syrup; ν (KBr) cm^{-1} 1724 (ν_{CO}); λ_{max} ($CHCl_3$) nm (log ε) 280 (3.66), 244 (3.65); δ_H ($CDCl_3$) 7.34 (ddd, 1H, J=7.9, 7.3, 1.8 Hz, ArH), 7.08 (dd, 1H, J=7.3, 1.8 Hz, ArH), 7.04 (d, 1H, J=8.2 Hz, ArH), 7.01–6.91 (m, 2H, ArH), 6.90 (d, 1H, J=8.2 Hz, ArH), 3.86 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 3.30 (s, 6H, 2×OCH_3), 3.30–3.29 (br s, 2H, CH_2); δ_C ($CDCl_3$) 172.3 (CO), 156.7 (C), 151.8 (C), 146.9 (C), 133.3 (C), 131.5 (CH), 129.0 (CH), 126.2 (C), 125.2 (CH), 125.1 (C), 120.3 (CH), 111.5 (CH), 110.5 (CH), 60.4 (OCH_3), 55.7 (OCH_3), 55.3 (OCH_3), 51.6 (OCH_3), 38.2 (CH_2); *m/z* (%) 316 (M^+, 100), 284 (26), 257 (31), 241 (28), 226 (77), 211 (29); HRMS FAB calculated for $C_{18}H_{21}O_5$ $[M+H]^+$ *m/z* 317.1389, found: 317.1379.

(2′,3′,5,6-Tetramethoxy)biphenyl-2-yl methyl acetate (**11e**). 0.18 g (31%). Colorless crystals; mp 63–66 °C; ν (KBr) cm^{-1} 1726 (ν_{CO}) 1726 (ν_{CO}); λ_{max} ($CHCl_3$) nm (log ε) 280 (3.50), 244 (3.63); δ_H ($CDCl_3$) 7.05 (dd, 1H, J=8.2, 7.6 Hz, ArH), 7.03 (d, 1H, J=8.2 Hz, ArH), 6.92 (dd, 1H, J=8.2, 1.8 Hz, ArH), 6.90 (d, 1H, J=8.2 Hz, ArH), 6.68 (dd, 1H, J=7.6, 1.8 Hz, ArH), 3.88 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.62 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 3.52 (s, 3H, OCH_3), 3.33–3.32 (sa, 2H, CH_2); δ_C ($CDCl_3$) 172.4 (CO), 152.7 (C), 151.7 (C), 146.7 (C), 146.6 (C), 133.2 (C), 130.7 (C), 126.2 (C), 125.1 (CH), 123.4 (CH), 123.2 (CH), 111.9 (CH), 111.6 (CH), 60.6 (OCH_3), 60.3 (OCH_3), 55.7 (2×OCH_3), 51.7 (OCH_3), 38.2 (CH_2); *m/z* (%) 346 (M^+, 41), 287 (11), 255 (100), 241 (22), 225 (18). Anal. calculated for $C_{19}H_{22}O_6$: C 65.88, H 6.40%, found: C 66.07, H 6.52.

From this reaction, the following compounds were also isolated: veratrol (**14**, 0.69 g) and 2,2′,3,3′-tetramethoxybiphenyl (**13**, 0.22 g), mp 96–99 °C (CH_2Cl_2).[31]

When the reaction was conducted as above, but using K_3PO_4 as base and anhydrous DMF as solvent, **11e** was isolated in a 40% yield.

(2′,4,5-Trimethoxy)biphenyl-2-yl methyl acetate (**11f**). 0.36 g (67%). Syrup that solidified on standing; mp 54–57 °C; ν (KBr) cm^{-1} 1726 (ν_{CO}); λ_{max} ($CHCl_3$) nm (log ε) 278 (3.70), 252 (3.71); δ_H ($CDCl_3$) 7.33 (ddd, 1H, J=8.2, 7.3, 1.8 Hz, ArH), 7.16 (dd, 1H, J=7.3, 1.8 Hz, ArH), 6.99 (dt, 1H, J=7.3, 1.8 Hz, ArH), 6.93 (br d, 1H, J=8.2 Hz, ArH), 6.87 (s, 1H, ArH), 6.72 (s, 1H, ArH), 3.90 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 3.40 (s, 2H, CH_2); δ_C ($CDCl_3$) 172.4 (CO), 156.4

(C), 148.0 (C), 147.6 (C), 131.5 (CH), 130.8 (C), 129.4 (C), 128.8 (CH), 124.9 (C), 120.4 (CH), 113.4 (CH), 112.8 (CH), 110.5 (CH), 55.8 (2×OCH_3), 55.2 (OCH_3), 51.6 (OCH_3), 38.2 (CH_2); *m/z* (%) 316 (M^+, 79), 257 (35), 226 (100), 211 (24), 181 (10); HRMS FAB calculated for $C_{18}H_{21}O_5$ $[M+H]^+$ *m/z* 317.1389, found: 317.1399.

(2′,3′,4,5-Tetramethoxy)biphenyl-2-yl methyl acetate (**11g**). 0.26 g (45%). Colorless crystals. Mp 63–65 °C; ν (KBr) cm^{-1} 1739 (ν_{CO}); λ_{max} ($CHCl_3$) nm (log ε) 282 (3.72), 248 (3.85); δ_H ($CDCl_3$) 7.05 (dd, 1H, *J*=8.2, 7.3 Hz, ArH), 6.89 (dd, 1H, *J*=8.2, 1.8 Hz, ArH), 6.84 (s, 1H, ArH), 6.76 (dd, 1H, *J*=7.3, 1.8 Hz, ArH), 6.75 (s,1H, ArH), 3.88 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.54 (s, 3H, OCH_3), 3.47–3.46 (br s, 2H, CH_2), 3.46 (s, 3H, OCH_3); δ_C ($CDCl_3$) 172.4 (CO), 152.7 (C), 148.1 (C), 147.4 (C), 146.5 (C), 134.8 (C), 130.5 (C), 124.7 (C), 123.6 (CH), 123.3 (CH), 113.3 (CH), 112.6 (CH), 111.5 (CH), 60.4 (OCH_3), 55.8 (OCH_3), 55.8 (2×OCH_3), 51.6 (OCH_3), 38.2 (CH_2); *m/z* (%) 346 (M^+, 100), 314 (25), 299 (25), 256 (75), 241 (32), 225 (20); HRMS FAB calculated for $C_{19}H_{23}O_6$ $[M+H]^+$ *m/z* 347.1495, found: 347.1498.

From this reaction, **13** (0.20 g) and **14** (0.10 g) were also isolated.

(4,5-Methylenedioxy)biphenyl-2-yl methyl acetate (**11h**). 0.39 g (86%). Yellowish syrup; ν (NaCl) cm^{-1} 1727; λ_{max} ($CHCl_3$) nm (log ε) 294 (3.91), 256 (3.89); δ_H ($CDCl_3$) 7.5–7.2 (m, 5H, ArH), 6.82 (s, 1H, ArH), 6.74 (s, 1H, ArH), 5.98 (s, 2H, OCH_2O), 3.63 (s, 3H, OCH_3), 3.49 (s, 2H, CH_2); δ_C ($CDCl_3$) 172.2 (CO), 146.8 (C), 146.4 (C), 140.7 (C), 135.8 (C), 129.1 (2×CH), 128.0 (2×CH), 126.8 (CH),124.7 (C), 109.9 (CH), 109.8 (CH), 101.0 (OCH_2O), 51.6 (OCH_3), 38.2 (CH_2); *m/z* (%) 270 (M^+, 61), 211 (22), 181 (100), 152 (29), 153 (28). Anal. calculated for $C_{16}H_{14}O_4$: C 71.09, H 5.22%, found: C 71.00, H 5.29.

(2′-Methoxy-4,5-methylenedioxy)biphenyl-2-yl methyl acetate (**11i**). 0.39 g (76%). White solid; mp 70–72 °C; ν (KBr) cm^{-1} 1736 (ν_{CO}); λ_{max} ($CHCl_3$) nm (log ε) 284 (3.79), 248 (3.68); δ_H ($CDCl_3$) 7.32 (ddd, 1H, *J*=8.2, 7.3, 1.8 Hz, ArH), 7.11 (dd, 1H, *J*=7.3, 1.8 Hz, ArH), 6.97 (dt, 1H, *J*=7.3, 1.1 Hz, ArH), 6.92 (br d, 1H, *J*=8.2 Hz, ArH), 6.84 (s, 1H, ArH), 6.68 (s, 1H, ArH), 5.96–5.95 (br d, 2H, OCH_2O), 3.71 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 3.36 (s, 2H, CH_2); δ_C ($CDCl_3$) 172.3 (CO), 156.5 (C), 147.0 (C), 146.5 (C), 132.0 (C), 131.5 (CH), 129.3 (C), 128.9 (CH), 126.2 (C), 120.5 (CH), 110.6 (CH), 110.5 (CH), 110.1 (CH), 101.1 (OCH_2O), 55.3 (OCH_3), 51.7 (OCH_3), 38.4 (CH_2); *m/z* (%) 300 (M^+, 51), 268 (25), 211 (100), 183 (23), 152 (20), 139 (27); HRMS FAB calculated for $C_{17}H_{17}O_5$ $[M+H]^+$ *m/z* 301.1076, found: 301.1063.

(2′,3′-Dimethoxy-4,5-methylenedioxy)biphenyl-2-yl methyl acetate (**11j**). 0.14 g (59%). White solid; mp 122–125 °C (AcOEt); ν (KBr) cm^{-1} 1730; λ_{max} ($CHCl_3$) nm (log ε) 288 (3.89), 252 (3.93); δ_H ($CDCl_3$) 7.07 (t, 1H, *J*=8.0 Hz, ArH), 6.91 (d, 1H, *J*=8.0 Hz, ArH), 6.84 (s, 1H, ArH), 6.74 (d, 1H, *J*=8.0 Hz, ArH), 6.73 (s, 1H, ArH), 5.99 (d, 2H, *J*=2.2 Hz, OCH_2O), 3.90 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 3.52 (s, 3H, OCH_3), 3.44 (s, 2H, CH_2); δ_C ($CDCl_3$) 172.3 (CO), 152.8 (C), 147.0 (C), 146.5 (C), 146.3 (C), 134.9 (C), 131.7 (C), 126.1 (C), 123.8 (CH), 123.4 (CH), 111.8 (CH), 110.2 (CH), 109.9 (CH), 101.1 (OCH_2O), 60.5 (OCH_3), 55.8 (OCH_3), 51.7 (OCH_3), 38.4 (CH_2); *m/z* (%) 330 (M^+, 50), 315 (70), 271 (18), 241 (100). Anal. calculated for $C_{18}H_{18}O_6$: C 65.43, H 5.50%, found: C 65.42, H 5.51.

4.3. Preparation of amides 5a–c, 5e and 5j

A solution of esters **11a–c**, **11e** and **11j** (1.2 mmol), sodium cyanide (5.8 mg, 0.12 mmol) and methylamine (5 mL, 58 mmol) in methanol (10 mL) held in a sealed round-bottom flask was stirred at 60 °C (bath temperature). After 2 h, the methanol was removed in vacuo, and the residue was dissolved in CH_2Cl_2. This solution was washed with water, dried and evaporated to dryness to obtain the corresponding amides (**5a–c**, **5e** and **5j**).

4.3.1. Compound 5a. 0.29 g (96%). White solid; mp 125–126 °C (Lit.[11] 125–126 °C). **5b**: 0.30 g (89%), white solid; mp 92–94 °C (Lit.[11] 93–96 °C). **5c**: 0.31 g (92%), white solid; mp 119–121 °C. **5e**: 0.34 g (82%), yellowish syrup.[11] **5j**: 0.33 g (85%), white solid; mp 176–180 °C.

4.3.2. Preparation of 5k. A mixture of ester **11a** (1.0 g, 3.9 mmol) and KOH (1.5 g, 26.3 mmol) in water (40 mL) was refluxed to complete dissolution of the ester (ca. 30 min). The reaction mixture was then cooled at room temperature and acidified with conc. HCl. The white solid was filtered off, dried and dissolved in benzene (60 mL). Over this solution cooled at 5 °C, pyridine (0.5 mL) and oxalyl chloride (6.11 mL, 70.2 mmol) were added, the latter dropwise. The mixture was stirred at 20 °C for 1 h. Benzene and excess reagent were removed in vacuo and the resulting acid chloride was dissolved in chloroform (3 mL). This solution was added to a cooled (0 °C) mixture of *p*-anisidine (3.1 mL, 35.1 mmol), TEA (1.3 mL) and chloroform (6 mL). The reaction mixture was stirred at 20 °C for 1/2 h and washed sequentially with 1 M NaOH, 1 M HCl and water. The organic solution was dried over anhydrous $MgSO_4$ and concentrated in vacuo to give the amide **5k** (1.04 g), in 85% yield, as a white solid; mp 124–126 °C (acetone); ν (KBr) cm^{-1} 3304, 2937, 1724, 1510; λ_{max} ($CHCl_3$) nm (log ε) 248 (3.84); δ_H ($CDCl_3$) 7.5–6.7 (m, 12H, ArH), 3.75 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3), 3.51 (s, 2H, CH_2); δ_C ($CDCl_3$) 169.1 (CO), 156.1 (2×C), 138.9 (C), 133.5 (C), 129.4 (C), 131.1 (CH), 130.9 (CH), 130.0 (CH), 129.2 (CH), 128.1 (CH), 127.4 (CH), 121.3 (2×CH), 120.9 (CH), 113.9 (2×CH), 111.0 (CH), 55.5 (OCH_3), 55.3 (CH_2), 42.3 (CH_2); *m/z* (%) 347 (M^+, 14), 165 (25), 181 (10), 182 (11), 123 (100). Anal. calculated for $C_{22}H_{21}NO_3$: C 76.05, H 6.10, N 4.03%, found: C 76.40, H 6.01, N 4.09.

4.3.3. Reaction of biarylacetamides 5a–c, 5e, 5j and 5k with $(COCl)_2/SnCl_4$. Over a N_2 degassed solution of the biphenyl acetamides (**5**, 4 mmol) in dichloromethane (8 mL) oxalyl chloride (0.83 mL, 10 mmol) was added. The flask was tightly sealed with a septum and heated at 60 °C, and stannyl chloride (1.2 mL, 10 mmol) was added. The reaction mixture was stirred at 60 °C (oil bath temperature) for 24 h, diluted with dichloromethane and supplied with 2 M HCl. The dichloromethane was separated and washed with water. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The reaction crude was

purified by preparative tlc (SiO_2, 20:0.4 CH_2Cl_2:CH_3OH) to obtain the aporphinoids **15a**–**c**, **15e**, **15j**,**k**.

2-Demethoxy-cepharadione-B (**15a**). 1.09 g (96%). Yellow-orange solid; mp 256–258 °C (EtOH) (Lit.[10a] 255–257 °C).

Cepharadione-B(**15b**). 0.84 g (65%). Orange solid; mp 266–270 °C (EtOH) (Lit.[32] 266–268 °C).

4,5-Dioxo-O,O′-dimethylapomorphine (**15c**). 0.55 g (43%). Red solid; mp 215–217 °C ($CHCl_3$/MeOH); ν (KBr) cm^{-1} 3480, 1652; λ_{max} (EtOH) nm (log ε): 460 (3.52), 374 (3.25), 318 (3.61), 250 sh (4.13), 240 (4.19), 204 (4.13); δ_H ($CDCl_3$) 10.09 (dd, 1H, *J*=8.5, 1.0 Hz, ArH), 8.62 (dd, 1H, *J*=8.5, 1.0 Hz, ArH), 7.88 (t, 1H, *J*=8.5 Hz, ArH), 7.67 (d, 1H, *J*=8.7 Hz, ArH), 7.52 (s, 1H, H-7), 7.39 (d, 1H, *J*=8.7 Hz, ArH), 4.05 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 3.84 (s, 3H, NCH_3); δ_C ($CDCl_3$) 176.7 (CO), 156.5 (CO), 152.2 (C), 146.9 (C), 136.0 (CH), 130.7 (C), 130.0 (C), 129.1 (CH), 128.0 (CH), 127.4 (C), 127.3 (C), 125.6 (CH), 123.4 (C), 121.7 (C), 115.1 (CH), 114.5 (CH), 59.8 (OCH_3), 55.5 (OCH_3), 30.5 (NCH_3); *m/z* (%) 321 (M^+, 100), 293 (12), 278 (34), 250 (32), 235 (38). Anal. calculated for $C_{19}H_{15}NO_4$: C 71.01, H 4.71, N 4.36%, found: C 71.05, H 4.80, N 4.39.

From the crude of this reaction, 1-methyl-6,7-dimethoxy-dibenzo[*e*,*g*]indano-4,5-dione (**20**) was also isolated: 64 mg (19%), red solid; mp 164–169 °C; ν (KBr) cm^{-1} 1698; λ_{max} ($CHCl_3$) nm (log ε): 414 (2.67), 346 sh (3.12), 304 (3.53), 258 (4.09); δ_H ($CDCl_3$) 9.79 (m, 1H, ArH), 8.66 (d, 1H, *J*=8.8 Hz, ArH), 8.49 (m, 1H, ArH), 7.82 (dt, 1H, *J*=8.6, 1.5 Hz, ArH), 7.64 (dt, 1H, *J*=8.6, 1.2 Hz, ArH), 7.37 (d, 1H, *J*=8.8 Hz, ArH), 4.03 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.79 (s, 3H, NCH_3); δ_C ($CDCl_3$) 182.0 (CO), 160.5 (CO), 154.5 (C), 151.3 (C), 147.0 (C), 136.3 (C), 131.6 (CH), 129.6 (CH), 127.1 (CH), 124.6 (CH), 122.2 (C), 121.8 (C), 121.6 (C), 120.2 (CH), 115.8 (CH), 60.0 (OCH_3), 56.5 (OCH_3), 31.7 (NCH_3); *m/z* (%) 321 (M^+, 100), 306 (7), 293 (7), 278 (28), 250 (25); HRMS calculated for $C_{19}H_{15}NO_4$ [M^+] *m/z* 321.1001, found: 321.1000.

4,5-Dioxodehydrocorydine (**15e**). 1.07 g (73%). Orange solid; mp 258–262 °C (EtOH) (Lit.[11] 258–262 °C).

Corydione (**15j**). 0.57 g (39%). Red solid; mp 267–272 °C (MeOH) (Lit.[33] 273–275 °C).

N-p-(Methoxyphenyl)-2-demethoxy-cepharadione-B (**15k**). 0.67 g (61%). Yellow solid; mp >300 °C ($CHCl_3$); ν (KBr) cm^{-1} 1650; δ_H (DMSO-d_6) 9.50 (br d, 1H, *J*=8.7 Hz, H-11), 8.64 (d, 1H, *J*=8.8 Hz, ArH), 7.78–7.74 (m, 2H, ArH), 7.70–7.57 (m, 2H, ArH), 7.40 (d, 2H, *J*=8.8 Hz, ArH), 7.20 (d, 2H, *J*=8.8 Hz, ArH), 6.94 (s, 1H, H-7), 4.32 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3); δ_C ($CDCl_3$+TFA) 176.0 (CO), 160.6 (C), 159.0 (CO), 134.1 (C), 131.7 (C), 131.5 (CH), 131.3 (CH), 130.4 (CH), 129.5 (CH), 129.3 (2×CH), 128.3 (CH), 128.0 (CH), 124.3 (C), 122.4 (C), 120.1 (C), 116.1 (2×CH), 115.0 (C), 114.8 (C), 114.7 (C), 112.1 (CH), 57.0 (OCH_3), 55.9 (OCH_3); *m/z* (%) 383 (M^+, 59), 355 (100), 340 (53). Anal. calculated for $C_{24}H_{17}NO_4$: C 75.17, H 4.47, N 3.66%, found: C 75.27, H 4.51, N 3.88.

From this reaction, 8-methoxy-phenanthro[9,10-*b*]furano-4,5-dione (**16**) was also isolated: 0.16 g (18%), red solid; mp 196–198 °C dec. (Lit.[11] 196–197 °C)..

4.4. Synthesis of 5c by Meyers' coupling

4.4.1. Preparation of 23. Iodobenzene **21** (3 g, 14.7 mmol) was added over a mixture of magnesium (0.39 g, 1.6 mmol) in dry THF (80 mL). After refluxing for 1 h, the reaction mixture was cooled. Then, a solution of the oxazoline **22**[27] (2.1 g, 7.9 mmol) in dry THF (60 mL) was added. After 30 min at 20 °C, the reaction mixture was refluxed for 5 h. The solvent was removed and the residue dissolved in CH_2Cl_2. The organic layer was washed with 1 M HCl, water, dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was treated with MeI (100 mL) at 20 °C for 12 h. The excess MeI was removed in vacuo and a 1:1 solution of methanol:20% aq. NaOH was added. The solution was refluxed for 12 h, the MeOH being removed in vacuo and the residue dissolved in 1 M NaOH. The aqueous layer was washed with TBME, acidified with concentrated HCl, diluted with water and filtered to obtain **23** as a white solid; overall yield: 1.3 g (61%); mp 190–195 °C (Et_2O); ν (KBr) cm^{-1} 3500–2300, 1685, 1673; λ_{max} ($CHCl_3$) nm (log ε): 286 sh (3.21), 252 (3.71); δ_H ($CDCl_3$+TFA) 7.94 (d, 1H, *J*=8.8 Hz, ArH), 7.4–7.3 (m, 3H, ArH), 7.25–7.15 (m, 2H, ArH), 7.01 (d, 1H, *J*=8.8 Hz, ArH), 3.97 (s, 3H, OCH_3), 3.53 (s, 3H, OCH_3); δ_C ($CDCl_3$+TFA) 172.9 (CO), 157.3 (C), 145.9 (C), 139.6 (C), 135.6 (C), 129.5 (CH), 128.8 (2×CH), 127.8 (2×CH), 127.6 (CH), 120.6 (C), 110.8 (CH), 61.0 (OCH_3), 56.0 (OCH_3); *m/z* (%) 258 (M^+, 100), 225 (36), 184 (29). Anal. calculated for $C_{45}H_{44}O_{13}$: C 68.17, H 5.59%, found: C 67.87, H 5.42.

4.4.2. Homologation reaction. A N_2 purged solution of **23** (1 g, 3.9 mmol) in dry THF (20 mL) was supplied with LAH (0.17 g, 4 mmol) in small portions over a period of 30 min. After stirring the reaction medium for 1 h at 20 °C, excess hydride was decomposed by addition of 1 M H_2SO_4 and the resulting suspension treated with more dilute acid and extracted with TBME. The extracts were carefully dried over $MgSO_4$ and the volume reduced to 15 mL. This ether solution was ice cooled and thionyl chloride (0.44 mL, 5.9 mmol) was added dropwise. The mixture was stirred at 20 °C for 30 min. TBME and excess thionyl chloride were removed in vacuo. The crude product was dissolved in acetonitrile (40 mL), NaCN (2 g, 40 mmol) being then added and the mixture refluxed for 48 h. After evaporation of the solvent, the residue was dissolved in H_2O, extracted with $CHCl_3$, dried over $MgSO_4$ and concentrated under reduced pressure to obtain a white solid.

To an ice cooled solution of this solid (0.9 g, 3.3 mmol) and pyridine (0.3 mL) in benzene (50 mL), oxalyl chloride (5.8 mL, 66 mmol) was added dropwise. The mixture was stirred at 20 °C for 30 min. Benzene and excess reagent were removed in vacuo and the resulting acid chloride was dissolved in acetone (3 mL). This solution was added to a cooled mixture of methylamine (40% in water, 2.6 mL, 33 mmol), TEA (1.2 mL) and water (2 mL). The reaction mixture was stirred at 20 °C for 1 h and washed sequentially with 1 M NaOH, 1 M HCl, and water. The organic solution

was dried over anhydrous $MgSO_4$ and concentrated in vacuo to obtain **5c**. Overall yield: 0.84 g (90%).

4.5. Reduction of 4,5-dioxoaporphines

4.5.1. Reduction with BH_3·THF. A mixture of the 4,5-dioxoaporphines **15a**,**b** (0.2 mmol) and BH_3·THF (3 mL) under an N_2 atmosphere at 0 °C was slowly warmed to 20 °C (3 h). The reaction mixture was concentrated to dryness and the residue dissolved in chloroform. The organic layer was washed with water, dried over $MgSO_4$ and concentrated in vacuo to obtain the 4-hydroxy-dehydroaporphines **17a**,**b**.

4-Hydroxy-2-demethoxy-dehydronuciferine (**17a**). 0.040 g (72%). Syrup; ν (KBr) cm^{-1} 3349; λ_{max} ($CHCl_3$) nm (log ε): 374 sh (3.17), 330 (3.67), 266 (4.09), 250 (4.16); δ_H ($CDCl_3$) 9.49 (br dd, 1H, *J*=8.3 Hz, H-11), 7.71 (dd, 1H, *J*=8.3, 1.3 Hz, H-8), 7.53, 7.16 (2×d, 2×1H, *J*=8.0 Hz, H-2, H-3), 7.5–7.3 (m, 2H, H-9, H-10), 6.86 (s, 1H, H-7), 4.95 (br t, 1H, H-4), 4.10 (s, 3H, OCH_3), 3.42 (dd, 1H, *J*=11.5, 3.5 Hz, H-5), 3.49 (dd, 1H, *J*=11.5, 2.7 Hz, H-5), 3.14 (s, 3H, NCH_3); δ_C ($CDCl_3$) 159.1 (C-1), 142.0 (C), 133.8 (C), 128.3 (CH), 127.8 (C), 126.6 (CH), 126.4 (CH), 126.1 (CH), 125.1 (C), 124.4 (C), 123.1 (CH), 121.4 (C), 108.7 (CH), 105.4 (CH), 68.0 (C-4), 57.5 (CH_2), 55.8 (OCH_3), 40.5 (NCH_3); *m*/*z* (%) 279 (M^+, 100), 264 (14), 246 (41). Anal. calculated for $C_{18}H_{17}NO_2{\cdot}1H_2O$: C 72.71, H 6.44, N 4.71%, found: C 72.81, H 6.47, N 4.80.

4-Hydroxy-dehydronuciferine (**17b**). 0.049 g (79%). Syrup; ν (KBr) cm^{-1} 3373; λ_{max} ($CHCl_3$) nm (log ε): 376 sh (2.85), 332 (3.50), 292 sh (3.44), 256 (4.01); δ_H ($CDCl_3$) 9.46 (br dd, 1H, *J*=8.0, 1.8 Hz, H-11), 7.67 (dd, 1H, *J*=8.0, 1.4 Hz, H-8), 7.47 (dt, 1H, *J*=8.0, 1.8 Hz, H-9), 7.36 (dt, 1H, *J*=8.4, 1.0 Hz, H-10), 7.32 (s, 1H, H-3), 6.67 (s, 1H, H-7), 4.92 (br t, 1H, H-4), 4.02 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.51 (dd, 1H, *J*=11.4, 2.6 Hz, H-5), 3.41 (dd, 1H, *J*=11.4, 3.8 Hz, H-5′), 3.11 (s, 3H, NCH_3); δ_C ($CDCl_3$) 151.5 (C-1), 147.2 (C-2), 142.0 (C), 134.4 (C), 130.4 (C), 127.7 (CH), 127.0 (CH), 126.6 (CH), 125.7 (C), 124.6 (C), 123.4 (CH), 118.1 (C), 111.6 (CH), 103.1 (CH), 68.3 (C-4), 59.7 (OCH_3), 57.6 (CH_2), 56.3 (OCH_3), 40.4 (NCH_3); *m*/*z* (%) 309 (M^+, 100); HRMS calculated for $C_{19}H_{19}NO_3$ [M^+] *m*/*z* 309.1365, found: 309.1364.

4.5.2. Reaction with BH_3·THF followed by Clemmensen reduction. A mixture of **15a**–**c** (0.2 mmol) and BH_3·THF (2 mL) under N_2 was refluxed for 5 h. The reaction mixture was concentrated in vacuo to obtain the corresponding dehydroaporphinoids **18** (^{1}H NMR), which, without further purification, were dissolved in conc. HCl (5 mL) and a mixture of Zn (dust, 1 g), $HgCl_2$ (0.06 g), conc. HCl (0.1 mL) and water (2 mL) was added. The reaction mixture was refluxed for 1 h, cooled and filtered, the filter being washed with 20% HCl. The filtrates were basified with 30% NaOH and extracted with chloroform. The organic extracts were washed with water, dried over $MgSO_4$ and concentrated to dryness to obtain the corresponding aporphinoids **19a**–**c**.

(±)-2-Demethoxy-nuciferine (**19a**). 0.040 g (76%). Syrup; ν (NaCl) cm^{-1} 1456, 1262, 1237, 1095, 1049, 799, 743; λ_{max} (EtOH) nm (log ε): 304 (3.47), 272 (3.75), 216 (4.11); δ_H ($CDCl_3$) 8.25 (m, 1H, H-11), 7.13–7.32 (m, 3H, ArH), 7.04 (d, 1H, *J*=8.4 Hz, ArH), 6.88 (d, 1H, *J*=8.4 Hz, ArH), 3.85 (s, 3H, OCH_3), 3.2–3.0 (m, 4H), 2.8–2.4 (m, 3H), 2.54 (s, 3H, NCH_3); δ_C ($CDCl_3$) 154.8 (C-1), 136.4 (C), 136.0 (C), 132.1 (C), 128.6 (CH), 128.4 (CH), 127.5 (CH), 126.7 (CH), 126.3 (CH), 125.3 (C), 121.8 (C), 110.7 (CH), 62.8 (C-6a), 55.6 (OCH_3), 53.2 (CH_2), 43.9 (NCH_3), 34.6, 28.4 (2×CH_2); *m*/*z* (%) 266 (M^+, 17), 265 (95), 264 (100), 222 (82); HRMS calculated for $C_{18}H_{19}NO$ [M^+] *m*/*z* 265.1466, found: 265.1461.

(±)-Nuciferine (**19b**). 0.037 g (83%). Yellowish syrup which crystallizes on standing; mp 133–136 °C (Lit.[4a] 134.5–135.5 °C).

(±)-O,O-Dimethylapomorphine (**19c**). 0.047 g (78%), yellowish syrup.[34]

Acknowledgements

Financial support from the Spanish Government (Project DGI BQU 2001/1890) is gratefully acknowledged. F. J. O. L. also wishes to acknowledge an award of a grant from this project.

References and notes

1. (a) Kametani, T. In *Aporphine Alkaloids. The Alkaloids*; Brossi, A., Ed.; Academic: New York, 1985; Vol. XXIV, pp 153–251, Chapter 4. (b) Shamma, M.; Moniot, J. L. *The Isoquinoline Alkaloids Research, 1972–1977*; Plenum: New York, 1978. (c) Shamma, M. The Isoquinoline Alkaloids. *Organic Chemistry*; Blomquist, A. T., Wasserman, H., Eds.; Academic: New York, 1972; Vol. 25. (d) Bentley, K. W. Aporphinoid Alkaloids. *The Isoquinoline Alkaloids*; Ravindranath, B., Ed.; Harwood Academic: Bangalore, 1998; Vol. 1, pp 131–181, part 8. (e) Bentley, K. W. *Nat. Prod. Rep.* **2003**, *20*, 342–365, and previous reviews on aporphinoids.
2. (a) Kametani, T.; Sugi, H.; Shibuya, S.; Fukumoto, K. *Chem. Pharm. Bull.* **1971**, *19*, 1513–1519. (b) Cava, M.; Lakshmikanthan, M. V. *J. Org. Chem.* **1970**, *35*, 1867–1869. (c) Suess, T.; Stermitz, F. R. *J. Nat. Prod.* **1981**, *44*, 688–692.
3. (a) Kametani, T.; Ihara, M.; Takemura, M.; Satoh, Y.; Terasawa, H.; Ohta, Y.; Fukumoto, K.; Takahashi, K. *J. Am. Chem. Soc.* **1977**, *99*, 3805–3808. (b) Kametani, T.; Ihara, M.; Takemura, M.; Satoh, Y.; Terasawa, H.; Ohta, Y.; Fukumoto, K.; Takahashi, K. *J. Am. Chem. Soc.* **1977**, *99*, 3805–3808. (c) Hoshino, O.; Umezawa, B. Lead tetraacetate oxidation in alkaloid synthesis. *The Alkaloids*; Brossi, A., Ed.; Academic: New York, 1989; Vol. 36, p 69, Chapter 2. (d) Hoshino, O.; Ogasawara, H.; Arasawa, M. *Heterocycles* **1993**, *35*, 1005–1014. (e) Hara, H.; Komoriya, S.; Mayashita, T.; Hoshino, O. *Tetrahedron: Asymmetry* **1995**, *6*, 1683–1692. (f) Landais, Y.; Rambault, D.; Robin, J.-P. *Tetrahedron Lett.* **1987**, *28*, 543–546. (g) Landais, Y.; Robin, J.-P. *Tetrahedron* **1992**, *48*, 7185–7196. (h) Planchenault, D.; Dhal, R.; Robin, J.-P. *Tetrahedron* **1993**, *49*, 5823–5830. (i) Czarnocki, Z.; MacLean, D. B.; Szarek, W. A. *Can. J. Chem.* **1987**, *65*,

2356–2361. (j) Gottlieb, L.; Meyers, A. I. *J. Org. Chem.* **1990**, *55*, 5659–5662.
4. (a) Cava, M. P.; Mitchell, M. J.; Havlizek, S. C.; Lindert, A.; Spangler, R. J. *J. Org. Chem.* **1970**, *35*, 175–179. (b) Lenz, G. R. *Synthesis* **1978**, 489–518. (c) Yang, N. C.; Lenz, G. R.; Shani, A. *Tetrahedron Lett.* **1966**, *7*, 2941–2946. (d) Lenz, G. R. *J. Org. Chem.* **1988**, *53*, 4447–4452. (e) Atanes, N.; Castedo, L.; Guitián, E.; Saá, J. M. *Heterocycles* **1987**, *26*, 1183–1184. (f) Cava, M. P.; Libsch, S. S. *J. Org. Chem.* **1974**, *39*, 577–578.
5. (a) Castedo, L.; Guitián, E.; Saá, J. M.; Suau, R. *Tetrahedron Lett.* **1982**, *23*, 457–458. (b) Saá, C.; Guitián, E.; Castedo, L.; Saá, J. M. *Tetrahedron Lett.* **1985**, *26*, 4559–4560. (c) Atanes, N.; Castedo, L.; Guitián, E.; Saá, C.; Saá, J. M.; Suau, R. *J. Org. Chem.* **1991**, *56*, 2984–2988. (d) Castedo, L.; Guitián, E.; Saá, C.; Suau, R.; Saá, J. M. *Tetrahedron Lett.* **1983**, *24*, 2107–2108. (e) Atanes, N.; Pérez, S.; Guitián, E.; Castedo, L.; Saá, J. M. *Tetrahedron* **1994**, *50*, 11257–11266. (f) Atanes, N.; Castedo, L.; Cobas, A.; Guitián, E.; Saá, C.; Saá, J. M. *Tetrahedron* **1989**, *45*, 7947–7956. (g) Gómez, B.; Martín, G.; Guitián, E.; Castedo, L.; Saá, J. M. *Tetrahedron* **1993**, *49*, 1251–1256.
6. (a) Estévez, J. C.; Villaverde, M. C.; Estévez, R. J.; Castedo, L. *Tetrahedron Lett.* **1991**, *32*, 529–530. (b) Estévez, J. C.; Villaverde, M. C.; Estévez, R. J.; Castedo, L. *Heterocycles* **1994**, *38*, 1–4. (c) Estévez, J. C.; Villaverde, M. C.; Estévez, R. J.; Castedo, L. *Tetrahedron* **1994**, *50*, 2107–2114. (d) Estévez, J. C.; Villaverde, M. C.; Estévez, R. J.; Castedo, L. *Tetrahedron* **1995**, *51*, 4075–4082. (e) Orito, K.; Uchiito, S.; Satoh, Y.; Tatsuzawa, T.; Harada, R.; Tokuda, M. *Org. Lett.* **2000**, *2*, 307–310.
7. (a) Fürstner, A.; Mamane, V. *Chem. Commun.* **2003**, 2112–2113. (b) Cuny, G. D. *Tetrahedron Lett.* **2003**, *44*, 8149–8152.
8. (a) Yasuda, M.; Hamasuna, S.; Yamano, K.; Kubo, J.-i.; Shima, K. *Heterocycles* **1992**, *34*, 965–977. (b) Lewis, F. D.; Reddy, G. D.; Cohen, B. E. *Tetrahedron Lett.* **1994**, *35*, 535–538. (c) Gerecke, M.; Brossi, A. *Helv. Chim. Acta* **1979**, *62*, 1549–1558. (d) Seijas, J. A.; de Lera, A. R.; Villaverde, M. C.; Castedo, L. *J. Chem. Soc. Chem. Commun.* **1985**, 839–840. (e) Seijas, J. A.; de Lera, A. R.; Villaverde, M. C.; Castedo, L. *Heterocycles* **1985**, *23*, 3079–3084. (f) Ramana, M. M. V.; Potnis, P. V. *Tetrahedron Lett.* **1996**, *37*, 1671–1672.
9. Guinaudeau, H.; Leboeuf, M.; Cave, A. *J. Nat. Prod.* **1994**, *57*, 1033–1135, and references therein.
10. (a) Suau, R.; López-Romero, J. M.; Rico, R.; Alonso, F. J.; Lobo, C. *Tetrahedron* **1996**, *52*, 11307–11320. (b) Wijeratne, E. M. K.; Gunatilaka, A. A. L.; Kingston, D. G. I.; Haltiwanger, R. C.; Eggleston, D. S. *Tetrahedron* **1995**, *51*, 7877–7882. (c) Stévigny, C.; Block, S.; de Pauw-Gillet, M. C.; de Hoffmann, E.; Llabrès, G.; Adjakidjé, V.; Quetin-Leclercq, J. *Planta Med.* **2002**, *68*, 1042–1044. (d) Jantan, I.; Abdul Rafi, I. A.; Jalil, J. *Planta Med.* **2001**, *67*, 466–467. (e) Hoarau, C.; Couture, A.; Deniau, E.; Grandclaudon, P. *Eur. J. Org. Chem.* **2001**, 2559–2567.
11. (a) Suau, R.; López-Romero, J. M.; Rico, R. *Tetrahedron Lett.* **1996**, *37*, 9357–9360. (b) Suau, R.; López-Romero, J. M.; Rico, R. *Tetrahedron* **1997**, *53*, 14397–14410.
12. (a) Suau, R.; Rico, R.; López-Romero, J. M.; Nájera, F.; Ruiz, A.; Ortiz, F. J. *Arkivoc* **2002**, *v*, 62–72. (b) Suau, R.; López-Romero, J. M.; Rico, R.; Ruiz, A. *Tetrahedron* **2000**, *56*, 993–998.
13. Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633–9695.
14. (a) Nicolau, K. C.; Boddy, C. N. C.; Bräse, S.; Winssinger, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2096–2152. (b) Shi, Q.; Chen, K.; Morris-Natschke, S. L.; Lee, K. H. *Curr. Pharm. Des.* **1998**, *4*, 219–248. (c) Gussio, R.; Zaharevitz, D. W.; McGrath, C. F.; Pattabiraman, N.; Kellogg, G.; Schultz, C.; Link, A.; Kunick, C.; Leost, M.; Meijer, L.; Sausville, E. A. *Anticancer. Drug Des.* **2000**, *15*, 53–66, and references therein. (d) Birkenhager, W. H.; de Leeuw, P. W. *J. Hypertens.* **1999**, *17*, 873–881.
15. (a) Cortés, J.; Moreno-Mañas, M.; Pleixats, R. *Eur. J. Org. Chem.* **2000**, 239–243. (b) Cerezo, S.; Cortés, J.; Galván, D.; Lago, E.; Marchi, C.; Molins, E.; Moreno-Mañas, M.; Pleixats, R.; Torrejón, J.; Vallribera, A. *Eur. J. Org. Chem.* **2001**, 329–337.
16. Moreno-Mañas, M.; Pérez, M.; Pleixats, R. *J. Org. Chem.* **1996**, *61*, 2346–2351.
17. The structures of the compounds studied were fully optimized using theoretical ab initio calculations involving the 6-31G* basis set.
18. Högberg, T.; Ström, P.; Ebner, M.; Rämsby, S. J. *J. Org. Chem.* **1987**, *52*, 2033–2036.
19. Speziale, A.; Smith, L. R. *J. Org. Chem.* **1962**, *27*, 3742–3742.
20. (a) N-Deprotection with CAN: Kronenthal, D. R.; Han, C. Y.; Taylor, M. K. *J. Org. Chem.* **1982**, *47*, 2765–2768. (b) With silver nitrate: Bhattarai, K.; Cainelli, G.; Panunzio, M. *Synlett* **1990**, 229–230. (c) Anodic oxidation: Corley, E. G.; Karady, S.; Abramson, N. L.; Ellison, D.; Weinstock, L. M. *Tetrahedron Lett.* **1988**, *29*, 1497–1500.
21. The BH_3·THF complex has been used for the reduction of isatin to indole, albeit in a moderate yield. Jiang, B.; Smallher, J. M.; Amaral-Ly, C.; Wuonola, M. A. *J. Org. Chem.* **1994**, *59*, 6823–6827.
22. Menon, M.; Clark, W. G.; Neumeyer, J. L. *Eur. J. Pharmacol.* **1978**, *52*, 1–9.
23. Lashuel, H.; Hartley, D. M.; Balakhaneh, D.; Aggarwal, A.; Teichberg, S.; Callaway, D. J. E. *J. Biol. Chem.* **2002**, *45*, 42881–42890.
24. Gottlieb, R.; Neumeyer, J. L. *J. Am. Chem. Soc.* **1976**, *98*, 7108–7109.
25. (a) Neumeyer, J. L.; Neustadt, B. R.; Weinhardt, K. K. *J. Pharm. Sci.* **1970**, *59*, 1850–1852. (b) Sugasawa, S.; Tachikawa, R. *Tetrahedron* **1958**, *4*, 205–212. (c) Neumeyer, J. L.; Neustadt, B. R.; Oh, K. H.; Weinhardt, K. K.; Boyce, C. B. *J. Med. Chem.* **1973**, *16*, 1223–1228.
26. Davis, P.; Abdel-Maksoud, H.; Trainor, T. M.; Vouros, P.; Neumeyer, J. L. *Biochem. Biophys. Res. Commun.* **1985**, *127*, 407–412.
27. Meyers, A.; Mihelich, E. D. *J. Am. Chem. Soc.* **1975**, *97*, 7383–7385.
28. Prévot-Halter, I.; Smith, T.; Weiss, J. *J. Org. Chem.* **1997**, *62*, 2186–2192.
29. Kulka, M.; Manske, R. *J. Am. Chem. Soc.* **1953**, *75*, 1322–1324.
30. Orito, K.; Miyazawa, M.; Kanbayashi, R.; Tokuda, M.; Suginome, H.; et al. *J. Org. Chem.* **1999**, *64*, 6583–6596.
31. Horner, L.; Weber, K. H. *Chem. Ber.* **1963**, *96*, 1568–1571.
32. Akasu, M.; Itokawa, H.; Fujita, M. *Tetrahedron Lett.* **1974**, *15*, 3609–3612.
33. Kiryakov, H.; Iskrenova, E. S. *Planta Med.* **1980**, *39*, 210–210.
34. Kim, C.; Kim, M. S.; Yoon, U. C. *Bull. Kor. Chem. Soc.* **1985**, *6*, 172–173.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron
Tetrahedron 60 (2004) 5737–5750

Convenient access to substituted acridines by a Buchwald–Hartwig amination

René Csuk,* Alexander Barthel and Christian Raschke

Institut für Organische Chemie, Martin-Luther-Universität Halle-Wittenberg, Kurt-Mothes-Str. 2, D-06120 Halle (Saale), Germany

Received 9 February 2004; revised 6 May 2004; accepted 7 May 2004

Abstract—A convenient, high yield procedure for the synthesis of anthranilic acids carrying a variety of different substituents as well as their straightforward transformation into the corresponding 9-chloroacridines could be established by using modified Buchwald–Hartwig amination conditions.

1. Introduction

Substituted acridines have been in use as antimalarials[1] for many years quite successfully and several of them[2–8] have exhibited excellent results in the chemotherapy of cancer. Quite recently, however, Prusiner et al. enlarged the scope of potential applications for these compounds dramatically due to their finding of quinacrine[9–12] (**1**) and related compounds[13] to show quite promising activity in vitro against prion based diseases. In addition, preliminary QSAR studies[14] attributed the observed activity both to the presence of an acridine ring and to the presence of a suitable spacer for the bisacridines **2**. Independent NMR binding studies[15] supported these conclusions by establishing a molecular interaction between the C-terminal helix of the prion protein and the quinacrine molecule. Up to now, however, no conclusive structure/activity relationships could be established due to the controversial interpretation of the biological data obtained in different biological screening systems[16–18] as well due to the lack of a sufficient large number of analogues synthesized and screened so far.

Acridines substituted at position C(9) are usually accessed from the corresponding 9-chloroacridines[19,20] the latter being prepared by the cyclization of suitably substituted *N*-phenylanthranilic acids. These compounds have been in the focus of synthetic interest in their own right due to the finding that flufenamic acid (**3**) has been used[21–24] quite successfully for the therapy of amyloidogenic diseases (Fig. 1).

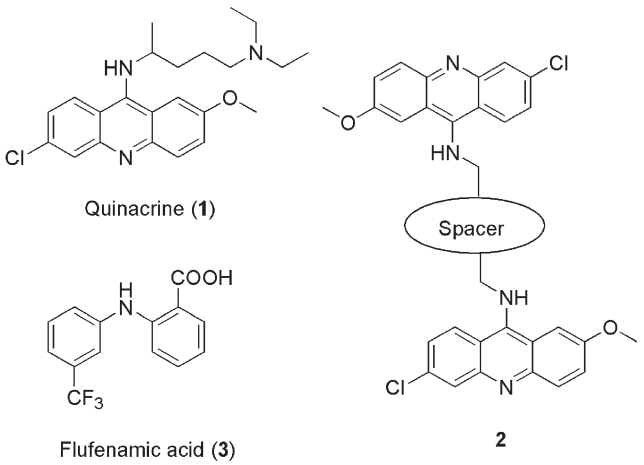


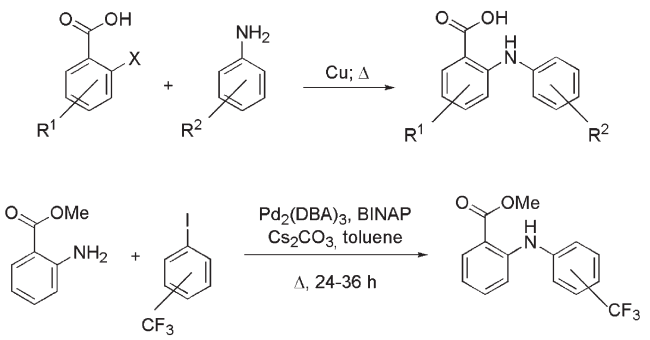
Figure 1. Structure of anti-Prion (**1**, **2**) or amyloidogenic (**3**) active compounds.

The majority of substituted *N*-phenylanthranilic acids have been synthesized using an Ullmann–Jourdan reaction[25–28] as the key step for establishing the C–N bond. These reactions despite the fact that several improvements[29–33] have been suggested over the years usually suffer from high reaction temperatures and from the need of using quite a large excess of copper or of copper salts. To obtain reasonably high yields electron withdrawing substituents are mandatory.[34] As an alternative the Pd(0) catalysed reaction of unsubstituted anthranilic acid with trifluoromethyl-iodobenzene has been suggested (Scheme 1).[21,35,36]

During our own investigations concerning the efficient synthesis of anti-prion active acridine derived compounds it became necessary to develop a reliable route providing these compounds in good yields even on a larger preparative

Keywords: Buchwald–Hartwig amination; Anthranilic acids; Acridines.
* Corresponding author. Tel.: +49-345-5525660; fax: +49-345-5527030; e-mail address: csuk@chemie.uni-halle.de

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.05.013

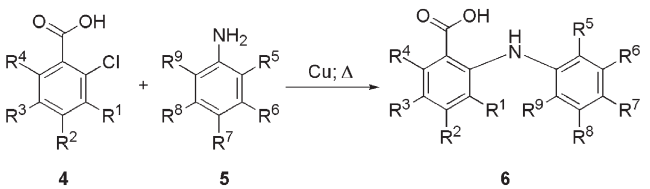


Scheme 1. Synthesis of *N*-phenyl-anthranilic acids.

scale. Thus, a more systematic investigation of the Ullmann–Jourdan reaction as well as of appropriate Pd(0)-mediated alternatives[21,35,36] was called for.

2. Results and discussion

In a first approach for the synthesis of substituted *N*-phenyl-anthranilic acids **6** we investigated their synthesis starting from substituted 2-chloro-benzoic acids **4** and aniline derivatives **5** in the presence of Cu or suitable Cu salts in more detail. Numerous variations concerning the choice of solvent (among these water,[37] ethanol, aqueous solution of sodium carbonate, DMF,[25] amyl alcohol as well as butane-2,3-diol), co-catalysts (Cu(I)[38] or Cu(II) salts, several diols, potassium iodide or pyridine[36]), the amount and particle size of the copper (or copper bronze) were performed in parallel



Scheme 2. Ullmann–Jourdan reactions.

synthesis technique. Finally the highest yields were obtained using copper–bronze (3%) in amyl alcohol as the solvent containing 15% of pyridine as a co-catalyst. Table 1 and Scheme 2 summarize our results for these Ullmann–Jourdan reactions under optimized conditions. Although the synthetic set-up is quite robust and the average yields for these couplings range between 40 and 60% this methodology is not optimal for scaling up and has to be optimized for each different substitution pattern.

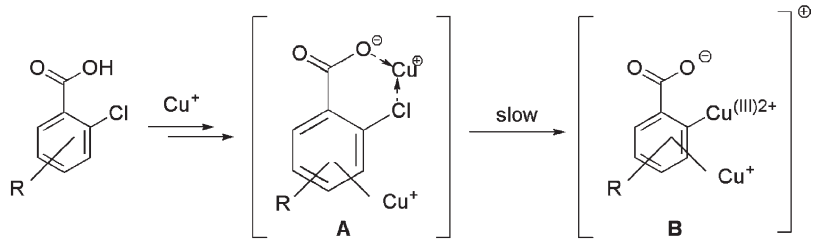
The problem usually arising with these reactions may be rationalized by the probable reaction mechanism[39] (cf. Scheme 3) for this reaction.

The initially formed copper complex **A** is believed to afford in a rate determinating step the reactive species **B**; addition of Cu(I) salts (as well as of Cu(II) salts that give upon symproportion with Cu(0) in situ formed Cu(I) species) have previously been used to enhance the speed of several coupling reactions, but in our own experiments the addition of a broad variety of different Cu(I) salts did not show any effect on the rate of the reactions at all. The formation of several by-products is encountered during these reactions; this finding is well explained by the high reactivity of intermediate **C** (Scheme 4) that upon reaction with a molecule of aniline following path I affords the desired anthranilic acid. Reaction of **C** with protic solvents that are used most often for these coupling reactions, yield either ethers (upon reaction with primary alcohols, path II) or salicylates[40] (with water as the solvent). In addition, a single-electron transfer affords (reaction path III) the radical species **D** whose reaction with **C** consequently yields biphenylic diacids or after protonation the corresponding benzoic acid, respectively.

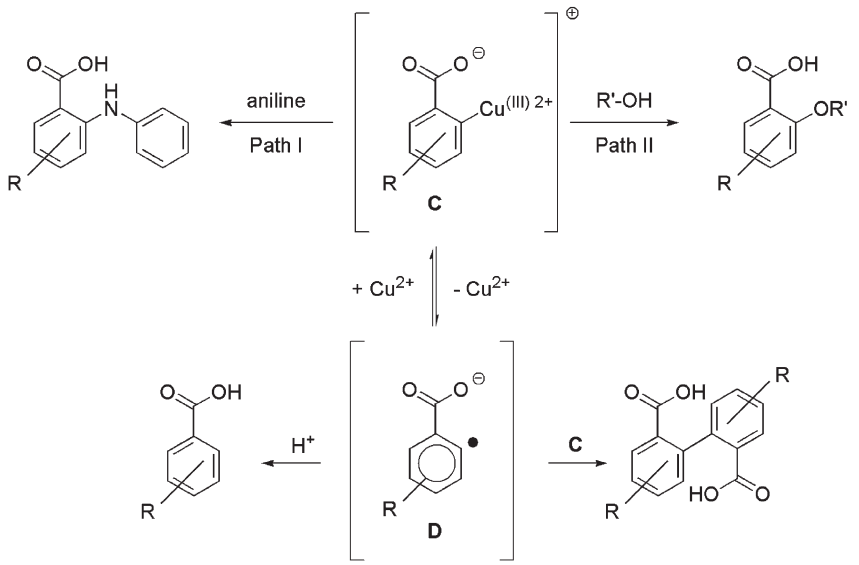
Due to these major drawbacks of the Ullmann–Jourdan reaction we focused our synthetic efforts on the investigation of Pd(0) catalysed reactions using the iodine-substituted benzoic acids as starting material. The latter have been accessed very easily by applying Sandmeyer

Table 1. Ullmann–Jourdan reactions (Scheme 2)

R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9	Product	Yield (%)
H	NO_2	H	H	H	H	OMe	H	H	**6a**	54
H	NO_2	H	H	H	H	H	H	OMe	**6b**	65
H	NO_2	H	H	H	H	OMe	H	OMe	**6c**	57
H	NO_2	H	H	H	OMe	H	H	OMe	**6d**	40
H	H	NO_2	H	H	H	H	H	OMe	**6e**	49
H	H	NO_2	H	H	H	H	OMe	H	**6f**	40
H	H	NO_2	H	H	H	OMe	H	OMe	**6g**	58
H	H	H	H	H	H	OMe	H	H	**6h**	52
H	Cl	H	H	H	H	OMe	H	H	**6i**	58



Scheme 3. Probable reaction mechanism for Ullmann–Jourdan reactions.



Scheme 4. Possible side reactions occurring during Ullmann–Jourdan reactions.

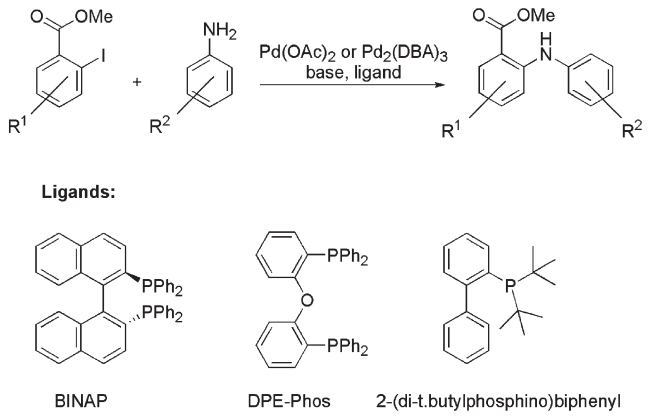


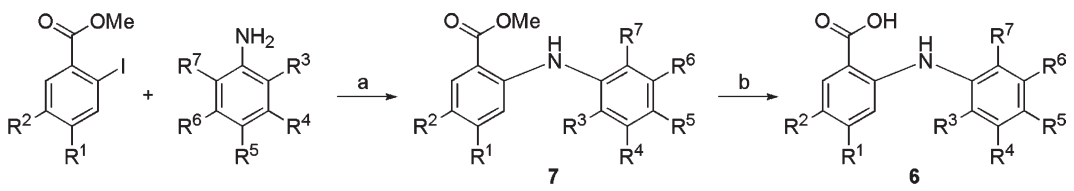
Figure 2. Pd(0) assisted synthesis of substituted *N*-phenyl-anthranilic acids.

reactions onto the corresponding 2-amino-benzoic acids[41] followed by esterification using the $SOCl_2$/methanol procedure.[42] Palladium-catalyzed coupling reactions are very important transformations both in academic and industrial laboratories. In order to establish optimised reaction conditions several model reactions were performed using potassium carbonate, potassium phosphate, cesium carbonate or potassium-*t*-butoxide as the base,[43] ±-BINAP, DPE-Phos[44] or 2-(di-*t*-butylphosphino)biphenyl as the phosphine ligand[45–48] and $Pd(OAc)_2$ as the source for the metal. From these preliminary screening experiments we deduced the reaction system DPE-Phos/$Pd(OAc)_2$/Cs_2CO_3 as best suited; these experiments also revealed that the premixing of $Pd(OAc)_2$ with the phosphine ligand and the aniline is a prerequisite for optimal reactions (Fig. 2).[49]

Table 2. Modified Buchwald–Hartwig aminations for the synthesis of substituted *N*-phenyl-anthranilic acids according to Scheme 5

R^1	R^2	R^3	R^4	R^5	R^6	R^7	Ester	Yield ester	Acid	Yield acid
H	H	H	H	OCF_3	H	H	**7j**	93	**6j**	95
H	H	H	Me	Me	H	NO_2	**7k**	89	**6k**	91
H	H	H	H	H	H	CO_2Me	**7l**	51	**6l**	80[a]
H	H	H	H	H	F	H	**7m**	94	**6m**	96
H	H	H	H	F	H	F	**7n**	98	**6n**	90
H	H	H	H	F	F	F	**7o**	94	**6o**	91
H	H	H	H	OMe	H	OMe	**7p**	97	**6p**	97
H	H	H	OMe	H	H	OMe	**7q**	73	**6q**	90
Cl	H	H	H	OCF_3	H	H	**7r**	90	**6r**	90
Cl	H	H	H	F	H	F	**7s**	86	**6s**	96
Cl	H	H	H	F	F	F	**7t**	54	**6t**	95
H	NO_2	H	H	OCF_3	H	H	**7u**	87	**6u**	95
H	NO_2	H	H	F	H	F	**7v**	85	**6v**	94
H	NO_2	H	H	F	F	F	**7w**	60	**6w**	93

[a] R^7=COOH.



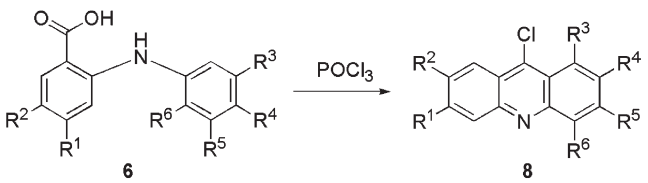
Scheme 5. Modified Buchwald–Hartwig aminations for the synthesis of substituted *N*-phenyl-anthranilic acids; (a) DPE-Phos, $Pd(OAc)_2$, Cs_2CO_3; (b) aqueous NaOH.

Following this procedure methyl anthranilates **7j–7w** were obtained in ca. 50–98% isolated yield (cf. Table 2 and Scheme 5).

Subsequent hydrolysis of these esters **7j–7w** resulted in the formation of the corresponding acids **6j–6w** that upon reaction with $POCl_3$ followed by work up under basic conditions furnished the corresponding 9-chloro-acridines **8** in good to excellent yields (cf. Table 3 and Scheme 6).

Table 3. Synthesis of the substituted 9-chloroacridines **8** according to Scheme 6

Starting material	R^1	R^2	R^3	R^4	R^5	R^6	Product	Yield (%)
6a	NO_2	H	H	OMe	H	H	**8a**	80
6b	H	NO_2	H	H	H	OMe	**8b**	75
6c	NO_2	H	H	OMe	H	OMe	**8c**	70
6f	NO_2	H	H	H	H	OMe	**8f**	79
6g	H	NO_2	H	OMe	H	OMe	**8g**	85
6h	H	H	H	OMe	H	H	**8h**	91
6i	Cl	H	H	OMe	H	H	**8i**	77
6j	H	H	H	OCF_3	H	H	**8j**	90
6m	H	H	H	H	F	H		
	H	H	F	H	H	H	**8m(2)**	37
	H	H	H	H	F	H	**8m(1)**	53
6n	H	H	H	F	H	F	**8n**	96
6o	H	H	H	F	F	F	**8o**	85
6p	H	H	H	OMe	H	OMe	**8p**	95
6q	H	H	OMe	H	H	OMe	**8q**	83
6r	Cl	H	H	OCF_3	H	H	**8r**	82
6s	Cl	H	H	F	H	F	**8s**	87
6t	Cl	H	H	F	F	F	**8t**	65
6u	H	NO_2	H	OCF_3	H	H	**8u**	84
6w	H	NO_2	H	F	F	F	**8w**	92



Scheme 6. Synthesis of the substituted 9-chloroacridines **8**.

In summary, a convenient, high yield procedure for the synthesis of anthranilic acids carrying a variety of different substituents as well as their straightforward transformation into the corresponding 9-chloroacridines could be established by using modified Buchwald–Hartwig amination conditions.

3. Experimental

3.1. General

Melting points are uncorrected (*Leica* hot stage microscope), optical rotations were obtained using a Perkin–Elmer 341 polarimeter (1 cm micro cell), NMR spectra were recorded using the Varian spectrometers Gemini 200, Gemini 2000 or Unity 500 (δ given in ppm, J in Hz, internal Me_4Si or internal CCl_3F), IR spectra (film or KBr pellet) on a Perkin–Elmer FT-IR spectrometer Spectrum 1000, MS spectra were taken on a Intectra GmbH AMD 402 (electron impact, 70 eV) or on a Finnigan MAT TSQ 7000 (electrospray, voltage 4.5 kV, sheath gas nitrogen) instrument; for elemental analysis a Foss-Heraeus Vario EL instrument was used; TLC was performed on silica gel (Merck 5554, detection by UV absorption or by treatment with a solution of 10% sulfuric acid, ammonium molybdate and cerium$^{(IV))}$ sulfate followed by gentle heating. The solvents were dried according to usual procedures.

3.2. General procedure for Ullmann–Jourdan reactions (GP1)

A mixture of the substituted chlorobenzoic acid (40.2 mmol) and the aniline derivative (79.6 mmol), potassium carbonate (6.9 g, 50.0 mmol) and Cu-powder (40 mesh, 0.24 g, 3 wt% with respect to the amount of benzoic acid used) was heated in amyl alcohol (40 ml) containing pyridine (1.21 g, 15 wt%) for 5 h under reflux. After cooling to room temperature, the solution was acidified with hydrochloric acid, the crude product was filtered off and recrystallized from ethanol to afford the product.

3.3. General procedure for Buchwald–Hartwig amination reactions (GP2)

Under argon a solution of $Pd(OAc)_2$ (40 mg, 2 mol%), DPEPhos (210 mg, 4 mol%) and the aniline derivative in dry toluene (15 ml) was stirred for 5 min. To this deep red solution the corresponding methyl 2-iodobenzoate (2.00 g, 7.60 mmol) and Cs_2CO_3 (3.48 g, 10.64 mmol) were added and stirring at 95 °C was continued until GC-MS and TLC showed the reaction to be completed (usually 2 days). The solid was filtered off and the filtrate concentrated in vacuo to afford a residue that was subjected to chromatography (silica gel, hexane/ethyl acetate 9:1→8:2) to afford the corresponding product.

3.4. General procedure for the saponification of the substituted methyl *N*-phenyl-anthranilates (GP3)

To a solution of the methyl anthranilate (2.0 g, 6.4 mmol) in acetone (100 ml) an aqueous solution of sodium hydroxide (5%, 20 ml) was added and the reaction mixture was stirred overnight at room temperature. After neutralization with diluted hydrochloric acid, the solvents were removed and the product was washed with water and dried to yield the corresponding acid.

3.5. General procedure for the synthesis of the substituted 9-chloroacridines (GP4)

The substituted *N*-phenyl-anthranilic acid (6.7 mmol) was dissolved in $POCl_3$ (15 ml) and heated under reflux for 6 h. After cooling to room temperature the reaction mixture was poured very carefully under vigorous stirring onto a mixture containing crushed ice (200 g), ammonia (100 ml) and chloroform (250 ml) keeping the pH during this operation always >8. The phases were separated and the aqueous phase was extracted with chloroform (2×100 ml), the organic phases were combined, dried ($CaCl_2$) and evaporated to yield the crude product that was pure enough for the further transformations. Analytically pure samples were obtained after flash-chromatography.

3.5.1. 2-(4-Methoxyanilino)-4-nitrobenzoic acid[50–52] (6a). Following GP1 from 2-chloro-4-nitrobenzoic acid (8.1 g, 40.2 mmol) and *p*-anisidine (9.8 g, 79.6 mmol) **6a** (6.2 g, 54%) was obtained as a red solid. Mp 241–245 °C (Lit.: 238–240 °C,[50] 235–237 °C,[51] 235–236 °C[52]). ^{1}H NMR (200 MHz, acetone-d_6): δ=3.78 (s, 3H, OCH_3), 6.96–7.07 (m, 2H, H_{arom}), 7.20–7.30 (m, 2H, H_{arom}), 7.42 (dd, 1H, J=8.3, 2.5 Hz, H_{arom}), 7.54 (d, 1H, J=2.5 Hz, H_{arom}), 8.08 (d, 1H, J=8.3 Hz, H_{arom}), 9.58 (s, 1H, NH). ^{13}C NMR (100 MHz, acetone-d_6): δ=55.2, 106.7, 109.6, 115.0, 115.9, 125.9, 131.5, 133.4, 149.3, 150.8, 156.9, 168.5. IR (KBr): ν=3357m, 2958m, 1678s, 1619w, 1584w, 1537s, 1516s, 1456w, 1426m, 1349s, 1251s, 1178w, 1144w, 1107w, 1070w cm^{-1}. UV–vis (methanol): λ_{max} (log ε)= 282 nm (4.27). MS (ESI, MeOH): m/z=287.3 (100%, $(M-H)^-$), 597.4 (20% $[(M-H)_2Na]^-$).

3.5.2. 2-(2-Methoxyanilino)-4-nitrobenzoic acid (6b). Compound **6b** (7.5 g, 65%) was obtained from 2-chloro-4-nitrobenzoic acid (8.1 g, 40.2 mmol) and *o*-anisidine (9.8 g, 79.6 mmol) following GP1. Mp 236–240 °C (Lit.: 187–189 °C[50]). ^{1}H NMR (400 MHz, acetone-d_6): δ=3.81 (s, 3H, OCH_3), 7.02 (ddd, 1H, J=7.9, 7.9, 1.7 Hz, H_{arom}), 7.13–7.22 (m, 2H, H_{arom}), 7.43 (dd, 1H, J=7.9, 1.7 Hz, H_{arom}), 7.47 (dd, 1H, J=8.7, 2.1 Hz, H_{arom}), 7.70 (d, 1H, J=2.1 Hz, H_{arom}), 8.09 (d, 1H, J=8.7 Hz, H_{arom}), 9.73 (s, 1H, NH). ^{13}C NMR (100 MHz, acetone-d_6): δ=55.6, 107.3, 110.3, 112.2, 120.7, 122.2, 125.3, 127.6, 133.3, 147.5, 150.6, 151.4, 151.8, 168.4. IR (KBr): ν=1691s, 1622m, 1597m, 1543s, 1494m, 1437s, 1426m, 1349s, 1263s, 1114m, 1029m, 1107w, 1070w cm^{-1}. UV–vis (methanol): λ_{max} (log ε)= 282 nm (3.90). MS (ESI, MeOH): m/z=287.2 (100%, $(M-H)^-$), 597.2 (20% $[(M-H)_2Na]^-$).

3.5.3. 2-(2,4-Dimethoxyanilino)-4-nitrobenzoic acid (6c). Compound **6c** (7.3 g, 57%) was obtained from 2-chloro-4-nitrobenzoic acid (9.8 g, 79.6 mmol) and 2,4-dimethoxyaniline (12.3 g, 80.3 mmol) following GP1. Mp 235–240 °C (Lit.: 259–260 °C[27]). ^{1}H NMR (400 MHz, DMSO-d_6): δ=3.76 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 6.60 (dd, 1H, J=8.7, 2.5 Hz, H_{arom}), 6.73 (d, 1H, J=2.5 Hz, H_{arom}), 7.27 (d, 1H, J=8.7 Hz, H_{arom}), 7.37–7.41 (m, 2H, H_{arom}), 8.06 (dd, 1H, J=6.6, 2.9 Hz, H_{arom}), 9.41 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ=55.4, 55.7, 99.7, 104.9, 106.8, 109.3, 115.8, 120.0, 125.9, 133.2, 149.3, 150.8, 154.1, 158.2, 168.5. IR (KBr): ν=1690s, 1624m, 1584m, 1542s, 1438m, 1350s, 1250s, 1211s, 1160m, 1129w, 1033w cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=286 nm (3.79). MS (ESI, MeOH): m/z=317.2 (100%, $(M-H)^-$), 657.5 (30% $[(M-H)_2Na]^-$).

3.5.4. 2-(2,5-Dimethoxyanilino)-4-nitrobenzoic acid (6d). Compound **6d** (5.1 g, 40%) was obtained from 2-chloro-4-nitrobenzoic acid (9.8 g, 79.6 mmol) and 2,5-dimethoxyaniline (12.3 g, 80.3 mmol) following GP1. Mp 206–209 °C (Lit.: 222–223 °C[53]). ^{1}H NMR (400 MHz, DMSO-d_6): δ=3.69 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 6.53 (dd, 1H, J=8.7, 2.9 Hz, H_{arom}), 6.92 (d, 1H, J=2.9 Hz, H_{arom}), 6.95 (d, 1H, J=8.7 Hz, H_{arom}), 7.37 (dd, 1H, J=8.3, 2.5 Hz, H_{arom}), 7.80 (d, 1H, J=2.5 Hz, H_{arom}), 8.02 (d, 1H, J= 8.3 Hz, H_{arom}), 11.95 (s, 1H, NH). ^{13}C NMR (100 MHz, acetone-d_6): δ=56.0, 56.9, 106.0, 106.9, 110.1, 110.9, 113.6, 123.8, 124.8, 131.9, 133.0, 145.8, 148.5, 154.0, 168.5. IR (KBr): ν=1628s, 1533s, 1431m, 1347m, 1218s, 1008m cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=292 nm (3.91). MS (ESI, MeOH): m/z=317.2 (100%, $(M-H)^-$), 657.5 (40% $[(M-H)_2Na]^-$).

3.5.5. 2-(2-Methoxyanilino)-5-nitrobenzoic acid (6e). Compound **6e** (5.9 g, 49%) was obtained from 2-chloro-5-nitrobenzoic acid (8.1 g, 40.2 mmol) and *o*-anisidine (9.8 g, 79.6 mmol) following GP1. Mp 218–224 °C (Lit.: 215 °C[54]). ^{1}H NMR (400 MHz, DMSO-d_6): δ=3.87 (s, 3H, OCH_3), 6.98–7.05 (m, 3H, H_{arom}), 7.28–7.32 (m, 1H, H_{arom}), 7.35 (dd, 1H, J=8.3, 1.7 Hz, H_{arom}), 8.14 (dd, 1H, J=9.5, 2.9 Hz, H_{arom}), 8.98 (d, 1H, J=2.5 Hz, H_{arom}), 9.88 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ=55.7, 110.8, 112.2, 113.3, 120.6, 124.0, 126.4, 126.7, 128.2, 129.0, 136.4, 152.0, 152.4, 168.5. IR (KBr): ν=3308w, 2937m, 1674s, 1602s, 1578s, 1537s, 1503s, 1466m, 1439m, 1333s, 1296s, 1262s, 1182m, 1152m, 1132m, 1118m, 1067w, 1050w, 1031m cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=233 nm (4.43). MS (ESI, MeOH): m/z=287.2 (100%, $(M-H)^-$), 597.3 (25% $[(M-H)_2Na]^-$).

3.5.6. 2-(3-Methoxyanilino)-5-nitrobenzoic acid (6f).[54,55] Compound **6f** (4.8 g, 40%) was obtained from 2-chloro-5-nitrobenzoic acid (8.1 g, 40.2 mmol) and *m*-anisidine (9.8 g, 79.6 mmol) following GP1. Mp 258–261 °C (Lit.: 253–254 °C[54]). ^{1}H NMR (400 MHz, DMSO-d_6): δ=3.77 (s, 3H, OCH_3), 6.84 (dd, 1H, J=7.5, 2.0 Hz, H_{arom}), 6.90–6.96 (m, 2H, H_{arom}), 7.18 (d, 1H, J=9.5 Hz, H_{arom}), 7.36 (t, 1H, J=8.3 Hz, H_{arom}), 8.18 (dd, 1H, J=9.5, 2.9 Hz, H_{arom}), 8.70 (d, 1H, J=2.9 Hz, H_{arom}), 10.31 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ=55.2, 109.4, 111.0, 111.5, 113.4, 115.8, 128.3, 129.2, 130.4, 136.5, 139.3, 152.1, 160.2, 168.4. IR (KBr): ν=3306w, 3087w, 1670s, 1601s, 1578s, 1530m, 1496s, 1466w, 1439m, 1423m, 1335s, 1268m, 1237s, 1200m, 1173m, 1160m, 1132m, 1043w cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=233 nm (3.27). MS (ESI, MeOH): m/z=287.2 (100%, $(M-H)^-$), 597.6 (20% $[(M-H)_2Na]^-$).

3.5.7. 2-(2,4-Dimethoxyanilino)-5-nitrobenzoic acid (6g). Compound **6g** (7.75 g, 58%) was obtained from 2-chloro-5-nitrobenzoic acid (8.1 g, 40.2 mmol) and 2,4-dimethoxyaniline (12.3 g, 80.3 mmol) following GP1. Mp 236–242 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ=3.77 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 6.59 (dd, 1H, J=8.3, 2.5 Hz, H_{arom}), 6.70–6.75 (m, 2H, H_{arom}), 7.26 (d, 1H, J=8.3 Hz, H_{arom}), 8.10 (dd, 1H, J=9.5, 2.9 Hz, H_{arom}), 8.67 (d, 1H, J=2.9 Hz, H_{arom}), 9.99 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ=55.4, 55.7, 100.2, 105.6, 110.6, 113.6, 119.6, 127.1, 128.8, 129.5, 136.3, 153.9, 154.8, 159.3, 169.0. IR (KBr): ν=3294w, 2938w, 2361m, 1689s, 1601s, 1582s, 1514s, 1438s, 1347s, 1307s, 1250s, 1209s, 1157m, 1131m, 1068w, 1030m cm^{-1}. UV–vis (methanol): λ_{max} (log ε)= 398 nm (3.74). MS (ESI, MeOH): m/z=317.3 (100%, $(M-H)^-$), 657.5 (20% $[(M-H)_2Na]^-$). HRMS for $C_{15}H_{14}N_2O_4$: calcd: 318.0852; found: 318.0852.

3.5.8. 2-(4-Methoxyanilino)benzoic acid (6h).[56–59] Compound **6h** (5.3 g, 52%) was obtained from 2-chlorobenzoic acid (6.3 g, 40.2 mmol) and *o*-anisidine (9.8 g, 79.6 mmol) following GP1. Mp 196–199 °C (Lit.: 187 °C;[56,57] 181–183 °C[58]). ^{1}H NMR (400 MHz, DMSO-d_6): δ=3.74 (s, 3H,

OCH_3), 6.67 (ddd, 1H, J=7.1, 7.1, 1.7 Hz, H_{arom}), 6.88–6.96 (m, 3H, H_{arom}), 7.13–7.18 (m, 2H, H_{arom}), 7.30 (ddd, 1H, J=7.1, 7.1, 1.7 Hz, H_{arom}), 7.84 (dd, 1H, J=8.3, 1.7 Hz, H_{arom}), 9.40 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ=55.5, 111.3, 112.9, 114.8, 116.3, 125.0, 131.7, 133.0, 134.1, 148.9, 156.1, 170.0. IR (KBr): ν=3327m, 2954m, 2836w, 2643w, 2569w, 1665s, 1597s, 1577s, 1513s, 1452s, 1442s, 1425m, 1330m, 1296w, 1270s, 1245s, 1172s, 1110w, 1086w, 1032m cm^{-1}. UV–vis (methanol): λ_{max} (log ε)= 225 nm (4.40). MS (ESI, MeOH): m/z=242.3 (100%, $(M-H)^-$), 507.4 (30% $[(M-H)_2Na]^-$).

3.5.9. 4-Chloro-2-(4-methoxyanilino)benzoic acid (6i). Compound **6i** (6.6 g, 58%) was obtained from 2,4-dichlorobenzoic acid (7.7 g, 40.1 mmol) and *p*-anisidine (9.8 g, 79.6 mmol) following GP1. Mp 206–208 °C (Lit.: 214–215 °C;[60,61] 213.5–214 °C;[62] 213–214 °C;[63] 202 °C;[64] 176–178 °C[65]). ^{1}H NMR (400 MHz, DMSO-d_6): 3.76 (s, 3H, OCH_3), 6.69 (dd, 1H, J=8.7, 2.1 Hz, H_{arom}), 6.75 (d, 1H, J=1.7 Hz, H_{arom}), 6.96–7.01 (m, 2H, H_{arom}), 7.17–7.22 (m, 2H, H_{arom}), 7.84 (d, 1H, J=8.3 Hz, H_{arom}), 9.49 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ=55.3, 110.0, 111.6, 114.9, 116.0, 125.9, 131.8, 133.5, 138.9, 150.0, 156.7, 169.2. IR (KBr): ν=3321m, 3008m, 2954m, 2833m, 1662s, 1596s, 1570s, 1515s, 1460s, 1426s, 1334w, 1250s, 1232s, 1178m, 1156m, 1102m, 1038w cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=233 nm (4.39). MS (ESI, MeOH): m/z=276.7 (100%, $(M-H)^-$).

3.5.10. 2-[4-(Trifluoromethoxy)anilino]benzoic acid (6j). Following GP3 from **7j** (2.0 g, 6.4 mmol) **6j** (1.8 g, 95%) was obtained as a solid. Mp 195–196 °C (Lit.: 175–176 °C[66]). ^{1}H NMR (500 MHz, DMSO-d_6): 6.75 (ddd, 1H, J=7.3, 0.9 Hz, H_{arom}), 7.23 (dd, 1H, J=8.0, 0.9 Hz, H_{arom}), 7.29–7.34 (m, 4H, H_{arom}), 7.40 (ddd, 1H, J=7.8, 6.9, 1.4 Hz, H_{arom}), 7.90 (dd, 1H, J=8.3, 1.8 Hz, H_{arom}), 9.63 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ=113.4, 114.1, 118.1, 120.1 (q, J=253.2 Hz), 122.0, 122.2, 131.8, 134.0, 140.0, 143.2, 146.2, 169.7. ^{19}F NMR (188 MHz, DMSO-d_6): δ=−57.9 (s, OCF_3). IR (KBr): ν=3338w, 3072w, 1660s, 1600s, 1580s, 1519s, 1450s, 1421m, 1330w, 1284s, 1253s, 1200s, 1164s, 1152s, 1108w, 1014w cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=234 nm (3.94). MS (ESI, MeOH): m/z=296.1 (100%, $(M-H)^-$), 615.2 (85% $[(M-H)_2Na]^-$). HRMS for $C_{14}H_{10}F_3NO_3$: calcd: 297.0613; found: 297.0614.

3.5.11. 2-(4,5-Dimethyl-2-nitroanilino)benzoic acid (6k). Compound **6k** (0.86 g, 91%) was obtained from **7k** (1.0 g, 3.3 mmol) following GP3. Mp 241–246 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ=2.23 (s, 6H, CH_3) 7.03 (ddd, 1H, J=6.9, 6.9, 1.4 Hz, H_{arom}), 7.42 (s, 1H, H_{arom}), 7.45–7.52 (m, 2H, H_{arom}), 7.91 (s, 1H, H_{arom}), 7.94 (dd, 1H, J= 7.8, 1.8 Hz, H_{arom}), 11.0 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ=18.4, 19.9, 117.7, 118.1, 119.8, 121.1, 125.8, 129.8, 131.7, 133.7, 135.2, 135.9, 142.6, 145.8, 168.7. IR (KBr): ν=2923m, 1689s, 1627m, 1583s, 1566s, 1505s, 1484s, 1453m, 1434m, 1405m, 1338s, 1291m, 1262s, 1247s, 1158w, 1085w, 1053w, 1020w cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=237 nm (4.17). MS (ESI, MeOH): m/z=285.6 (100%, $(M-H)^-$). HRMS for $C_{15}H_{14}N_2O_4$: calcd: 286.0954; found: 286.0954.

3.5.12. 2-(2-Carboxyanilino)benzoic acid (6l).[21,67–71] Compound **6l** (0.76 g, 80%) was obtained from **7l** (1.0 g, 3.5 mmol) following GP3. Mp 300–301 °C (Lit.: 314–316 °C;[67] 302–305 °C;[68] 295 °C[69,70]). ^{1}H NMR (400 MHz, DMSO-d_6): 6.94 (ddd, 2H, J=7.9, 6.2, 2.1 Hz, H_{arom}), 7.40–7.48 (m, 4H, H_{arom}), 7.89 (d, 2H, J=7.9 Hz, H_{arom}), 10.80 (s, 1H, NH) 13.00 (s, 2H, COOH). ^{13}C NMR (100 MHz, DMSO-d_6): δ=117.5, 117.6, 119.9, 131.7, 133.2, 143.5, 168.2. IR (KBr): ν=2970m, 2630m, 1668s, 1602m, 1581s, 1521s, 1449s, 1414m, 1325m, 1274s, 1250s, 1230s, 1166m, 1086w, 1044w cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=220 nm (4.49). MS (ESI, MeOH): m/z=256.3 (100%, $(M-H)^-$), 535.5 (302% $[(M-H)_2Na]^-$).

3.5.13. 2-(3-Fluoroanilino)benzoic acid (6m). Compound **6m** (1.4 g, 96%) was obtained from **7m** (1.5 g, 6.1 mmol) following GP3. Mp 190–192 °C (Lit.: 164 °C;[72] 162–164 °C[73]). ^{1}H NMR (400 MHz, DMSO-d_6): 6.57 (ddd, 1H, J=9.1, 9.1, 2.5 Hz, H_{arom}), 6.69 (ddd, 1H, J=7.5, 7.1, 1.3 Hz, H_{arom}), 6.84–6.88 (m, 2H, H_{arom}), 7.13–7.25 (m, 3H, H_{arom}), 7.90 (dd, 1H, J=7.9, 1.7 Hz, H_{arom}), 9.43 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ=104.0 (d, J=23.8 Hz), 106.5 (d, J=21.5 Hz), 114.0, 114.7, 118.3, 124.4, 130.4, 131.0 (d, J=10.0 Hz), 132.5, 144.2, 145.3 (d, J=10.0 Hz), 163.5 (d, J=240.9 Hz), 172.0. ^{19}F NMR (188 MHz, DMSO-d_6): δ=−112.9 (m, F). IR (KBr): ν=1606s, 1578s, 1544m, 1509s, 1448m, 1387m, 1284w, 1150s cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=231 nm (4.16). MS (ESI, MeOH): m/z=230.3 (100%, $(M-H)^-$), 483.5 (32% $[(M-H)_2Na]^-$).

3.5.14. 2-(2,4-Difluoroanilino)benzoic acid (6n). Compound **6n** (1.5 g, 90%) was obtained from **7n** (1.8 g, 6.8 mmol) following GP3. Mp 202–204 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 6.79 (ddd, 1H, J=7.9, 7.9, 0.8 Hz, H_{arom}), 6.84 (d, 1H, J=8.7 Hz, H_{arom}), 7.04–7.12 (m, 1H, H_{arom}), 7.30–7.40 (m, 2H, H_{arom}), 7.45–7.52 (m, 1H, H_{arom}), 7.89 (dd, 1H, J=7.9, 1.7 Hz, H_{arom}), 9.43 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ=104.9 (dd, J=24.9, 24.9 Hz), 111.8 (dd, J=21.2, 3.7 Hz), 112.5, 113.3, 117.7, 124.7 (dd, J=12.0, 2.8 Hz), 126.2 (dd, J=10.1, 2.8 Hz), 131.8, 134.5, 147.3, 155.8 (dd, J=246.7, 12.9 Hz), 158.6 (dd, J=243.5, 11.5 Hz), 170.1. ^{19}F NMR (188 MHz, DMSO-d_6): δ=−115.4 (dd, J=15.2, 6.1 Hz, F), −120.1 (dd, J=15.2, 9.1 Hz, F). IR (KBr): ν=1661s, 1600m, 1582s, 1519s, 1450m, 1430m, 1334w, 1264s, 1210w, 1166m, 1142m, 1095w, 1043w cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=234 nm (4.24). MS (ESI, MeOH): m/z=248.0 (100%, $(M-H)^-$). HRMS for $C_{14}H_9F_2NO_2$: calcd: 249.0601; found: 249.0600

3.5.15. 2-(2,3,4-Trifluoroanilino)benzoic acid (6o). Compound **6o** (1.6 g, 91%) was obtained from **7o** (1.8 g, 6.4 mmol) following GP3. Mp 210–215 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 6.83 (ddd, 1H, J=7.8, 7.8, 0.9 Hz, H_{arom}), 6.94 (d, 1H, J=8.3 Hz, H_{arom}), 7.24–7.34 (m, 2H, H_{arom}), 7.39 (ddd, 1H, J=7.3, 7.3, 1.8 Hz, H_{arom}), 7.97 (dd, 1H, J=8.3, 1.8 Hz, H_{arom}), 9.3 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ=112.2 (dd, J=17.5, 3.7 Hz), 113.1, 113.7, 118.3, 118.7 (d, J=6.5), 126.3 (dd, J=9.2, 2.8 Hz), 131.7, 134.3, 139.8 (ddd, J=248.6, 14.7, 14.7 Hz), 144.7 (ddd, J=247.6, 11.0, 3.7 Hz), 146.4, 147.6 (ddd,

J=243.9, 11.0, 2.8 Hz), 169.9. ^{19}F NMR (188 MHz, DMSO-d_6): δ=−141.3 (m, F), −144.9 (m, F), −160.1 (m, F). IR (KBr): ν=3308m, 3082m, 1674s, 1616m, 1590s, 1535s, 1513s, 1489m, 1454s, 1446s, 1413w, 1313w, 1265s, 1238w, 1224w, 1165w, 1086w, 1056m, 1042m cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=233 nm (4.37). MS (ESI, MeOH): m/z=266.3 (100%, (M−H)$^-$), 555.7 (50% [(M−H)$_2$Na]$^-$). HRMS for $C_{13}H_8F_3NO_2$: calcd: 267.0507; found: 267.0509.

3.5.16. 2-(2,4-Dimethoxyanilino)benzoic acid (6p). Compound **6p** (1.9 g, 97%) was obtained from **7p** (2.0 g, 7.0 mmol) following GP3. Mp 180 °C (Lit.: 158–162 °C[25]). ^{1}H NMR (400 MHz, DMSO-d_6): 3.76 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 6.53 (dd, 1H, J=8.7, 2.5 Hz, H_{arom}), 6.62–6.68 (m, 2H, H_{arom}), 6.80 (dd, 1H, J=8.3, 0.8 Hz, H_{arom}), 7.21 (d, 1H, J=8.3 Hz, H_{arom}), 7.28 (ddd, 1H, J=8.3, 7.1, 1.7 Hz, H_{arom}), 7.83 (dd, 1H, J=7.9, 1.7 Hz, H_{arom}), (s, 1H, NH), 12.8 (s, 1H, COOH). ^{13}C NMR (100 MHz, DMSO-d_6): δ=55.3, 55.6, 99.5, 104.4, 111.2, 112.5, 115.8, 121.5, 124.6, 131.4, 133.8, 148.6, 153.5, 156.9, 169.6. IR (KBr): ν=3333m, 2994s, 2968m, 2933m, 2641m, 1655s, 1611m, 1577s, 1518s, 1446s, 1421m, 1338w, 1314w, 1274s, 1256s, 1207s, 1155s, 1129s, 1039s cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=230 nm (4.66). MS (ESI, MeOH): m/z=272.4 (50%, (M−H)$^-$), 567.5 (100% [(M−H)$_2$Na]$^-$)

3.5.17. 2-(2,5-Dimethoxyanilino)benzoic acid (6q).[25,74,75] Compound **6q** (1.3 g, 90%) was obtained from **7q** (1.5 g, 5.2 mmol) following GP3. Mp 162–164 °C (Lit.: 167–168 °C;[74] 155–157 °C[25]). ^{1}H NMR (400 MHz, DMSO-d_6): 3.69 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 6.57 (dd, 1H, J=8.7, 2.9 Hz, H_{arom}), 6.78 (ddd, 1H, J=8.7, 6.6, 0.8 Hz, H_{arom}), 6.94 (d, 1H, J=2.9 Hz, H_{arom}), 6.97 (d, 1H, J=8.7 Hz, H_{arom}), 7.27 (d, 1H, J=8.3 Hz, H_{arom}), 7.40 (ddd, 1H, J=8.3, 7.1, 1.7 Hz, H_{arom}), 7.88 (dd, 1H, J=7.9, 1.7 Hz, H_{arom}), 9.60 (s, NH), 13.0 (s, COOH). ^{13}C NMR (100 MHz, DMSO-d_6): δ=55.3, 56.1, 106.0, 106.7, 112.5, 113.1, 113.9, 117.3, 130.2, 131.6, 133.9, 144.7, 145.9, 153.1, 169.3. IR (KBr): ν=2953m, 2826m, 2640w, 1674s, 1605s, 1578s, 1537s, 1496m, 1448m, 1428m, 1410w, 1321w, 1260s, 1216s, 1201m, 1170m, 1133m, 1060w, 1028m cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=236 nm (4.40). MS (ESI, MeOH): m/z=272.3 (55%, (M−H)$^-$), 567.6 (100% [(M−H)$_2$Na]$^-$).

3.5.18. 4-Chloro-2-[4-(trifluoromethoxy)anilino] benzoic acid (6r). Compound **6r** (1.7 g, 90%) was obtained from **7r** (2.0 g, 5.8 mmol) following GP3. Mp 180–185 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ=6.83 (dd, 1H, J=8.7, 2.1 Hz, H_{arom}), 7.09 (d, 1H, J=2.1 Hz, H_{arom}), 7.34–7.40 (m, 4H, H_{arom}), 7.89 (d, 1H, J=8.7 Hz, H_{arom}). ^{13}C NMR (100 MHz, DMSO-d_6): δ=111.7, 112.7, 117.6, 120.0 (q, J=255.5 Hz), 122.2, 123.4, 133.5, 138.7, 138.8, 143.9, 147.6, 168.8. ^{19}F NMR (188 MHz, DMSO-d_6): δ=−57.7 (s, OCF_3). IR (KBr): ν=1661s, 1599s, 1571s, 1513s, 1455m, 1428s, 1401m, 1333m, 1290s, 1255s, 1217s, 1150s, 1104s, 1015w cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=242 nm (3.99). MS (ESI, MeOH): m/z=330.7 (100%, (M−H)$^-$), 684.9 (70% [(M−H)$_2$Na]$^-$). Anal. calcd for $C_{14}H_9ClF_3NO_3$ (299.68): C, 50.70; H, 2.74; N, 4.22; found: C, 50.75; H, 2.88; N, 4.57.

3.5.19. 4-Chloro-2-(2,4-difluoroanilino)benzoic acid (6s). Compound **6s** (1.3 g, 95%) was obtained from **7s** (1.5 g, 5.0 mmol) following GP3. Mp 320 °C (decomp.). ^{1}H NMR (400 MHz, acetone-d_6): 6.54 (dd, 1H, J=8.3, 2.1 Hz, H_{arom}), 6.77 (t, 1H, J=1.7 Hz, H_{arom}), 6.95 (ddd, 1H, J=8.7, 2.9, 1.7 Hz, H_{arom}), 7.05 (ddd, 1H, J=9.1, 8.7, 2.9 Hz, H_{arom}), 7.37–7.45 (m, 1H, H_{arom}), 8.07 (d, 1H, J=8.3 Hz, H_{arom}), 11.42 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ=104.3 (t, J=25.0 Hz), 111.0, 111.3 (dd, J=21.5, 3.8 Hz), 116.1, 121.1, 123.2 (d, J=10.0 Hz), 126.1 (dd, J=13.0, 3.2 Hz), 133.3, 134.4, 146.7, 155.1 (dd, J=246.3, 12.3 Hz), 157.5 (dd, J=246.3, 12.3 Hz), 170.6. ^{19}F NMR (188 MHz, DMSO-d_6): δ=−118.1 (m, F), −121.4 (m, F). IR (KBr): ν=1610m, 1584s, 1426m, 1373m, 1298w, 1259m, 1192w, 1141w, 1094w cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=220 nm (4.14). MS (ESI, MeOH): m/z=282.6 (100%, (M−H)$^-$). HRMS for $C_{13}H_8ClF_2NO_2$: calcd: 283.0212; found: 283.0212.

3.5.20. 4-Chloro-2-(2,3,4-trifluoroanilino)benzoic acid (6t). Compound **6t** (0.92 g, 95%) was prepared from **7t** (1.0 g, 3.2 mmol) according to GP3 followed by column chromatography (silica gel, $CHCl_3$). Mp 280–287 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 6.64 (dd, 1H, J=8.3, 2.1 Hz, H_{arom}), 6.88 (d, 1H, J=0.9 Hz, H_{arom}), 7.14–7.24 (m, 2H, H_{arom}), 7.84 (d, 1H, J=8.0 Hz, H_{arom}). ^{13}C NMR (100 MHz, DMSO-d_6): δ=111.9, 112.1 (d, J=3.1 Hz), 115.5, 116.9 (m), 122.1 (m), 128.4, 133.6, 134.6, 139.9 (ddd, J=247.0, 16.1, 16.1 Hz), 143.7 (ddd, J=245.7, 7.8, 3.1 Hz), 145.0 (ddd, J=245.7, 9.3, 3.2 Hz), 146.4, 170.8. ^{19}F NMR (188 MHz, DMSO-d_6): δ=−144.2 (m, F), −147.4 (m, F), −160.6 (ddd, J=21.4, 21.4, 4.7 Hz, F). IR (KBr): ν=1607s, 1518s, 1485s, 1430m, 1371m, 1265m, 1168w, 1050s cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=237 nm (4.03). MS (ESI, MeOH): m/z=300.1 (100%, (M−H)$^-$), 623.1 (95% [(M−H)$_2$Na]$^-$). HRMS for $C_{13}H_7ClF_3NO_2$: calcd: 301.0117; found: 301.0119.

3.5.21. 5-Nitro-2-[4-(trifluoromethoxy)anilino] benzoic acid (6u). Compound **6u** (1.6 g, 95%) was prepared from **7u** (1.8 g, 5.1 mmol) following GP3. Mp 300 °C (decomp.). ^{1}H NMR (400 MHz, DMSO-d_6): 6.00 (d, 1H, J=9.9 Hz, H_{arom}), 6.77–6.82 (m, 2H, H_{arom}), 7.08–7.12 (m, 2H, H_{arom}), 7.37 (dd, 1H, J=9.5, 2.9 Hz, H_{arom}), 8.09 (d, 1H, J=2.9 Hz, H_{arom}). ^{13}C NMR (100 MHz, DMSO-d_6): δ=112.2, 120.3 (q, J=253.9 Hz), 121.6, 123.4, 125.7, 126.6, 128.3, 128.4, 141.7, 154.1, 159.5, 173.8. ^{19}F NMR (188 MHz, DMSO-d_6): δ=−57.7 (s, OCF_3). IR (KBr): ν=1630s, 1598s, 1531s, 1508s, 1482s, 1443s, 1385s, 1332s, 1296s, 1270s, 1204s, 1147s, 1133s, 1066m, 1015m cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=404 nm (3.97). MS (ESI, MeOH): m/z=341.3 (100%, (M−H)$^-$), 705.4 (40% [(M−H)$_2$Na]$^-$). HRMS for $C_{14}H_9F_3N_2O_4$: calcd: 342.0464; found: 342.0465.

3.5.22. 2-(2,4-Difluoroanilino)-5-nitro-benzoic acid (6v). Compound **6v** (1.4 g, 94%) was prepared from **7v** (1.5 g, 4.9 mmol) following GP3. Mp 300 °C (decomp.). ^{1}H NMR (400 MHz, acetone-d_6): δ=5.86 (dd, 1H, J=10.0, 2.1 Hz, H_{arom}), 6.80–6.93 (m, 2H, H_{arom}), 7.01 (ddd, 1H, J=9.1, 9.1, 2.1 Hz, H_{arom}), 7.39 (dd, 1H, J=10.0, 2.9 Hz, H_{arom}), 8.08 (d, 1H, J=2.9 Hz, H_{arom}). ^{13}C NMR (100 MHz, DMSO-d_6): δ=110.8 (dd, J=21.5, 3.0 Hz), 112.3, 124.8

(m), 125.5, 126.8, 128.1, 128.4, 138.7 (d, J=12.3 Hz), 154.1 (dd, J=241.7, 11.5 Hz), 155.8 (dd, J=237.9, 11.5 Hz), 160.5, 173.7. ^{19}F NMR (188 MHz, DMSO-d_6): δ=−122.3 (m, F) IR (KBr): ν=1638s, 1537s, 1451s, 1341s, 1289m, 1264m, 1194m, 1143m, 1096m, 1070m cm^{-1}. UV–vis (methanol): λ_{max} (log ε) 395 nm (3.82). MS (ESI, MeOH): m/z=293.3 (100%, $(M-H)^-$), 609.3 (30% $[(M-H)_2Na]^-$). HRMS for $C_{13}H_8F_2N_2O_4$: calcd: 294.0452; found: 294.0452.

3.5.23. 2-(2,3,4-Trifluoroanilino)-5-nitro-benzoic acid (6w). Compound **6w** (0.90 g, 93%) was prepared from **7w** (1.0 g, 3.1 mmol) following GP3. Mp 300 °C (decomp.). ^{1}H NMR (400 MHz, DMSO-d_6): 5.88 (dd, 1H, J=9.5, 2.1 Hz, H_{arom}), 6.63–6.71 (m, 1H, H_{arom}), 6.94–7.04 (m, 1H, H_{arom}), 7.41 (dd, 1H, J=9.5, 2.9 Hz, H_{arom}), 8.12 (d, 1H, J=2.9 Hz, H_{arom}). ^{13}C NMR (100 MHz, DMSO-d_6): 111.1 (dd, J=16.1, 3.1 Hz), 112.3, 118.3(m), 125.5, 127.4, 128.1, 128.2, 139.6 (ddd, J=245.2, 16.1, 16.1 Hz), 140.5 (m), 143.9 (dd, J=242.5, 5.8 Hz), 143.3 (dd, J=236.7, 11.1 Hz), 160.5, 173.6. ^{19}F NMR (188 MHz, DMSO-d_6): δ=−147.2 (dd, J=22.9, 9.2 Hz, F), −147.9 (m, F), −162.4 (ddd, J=22.9, 22.9, 9.2 Hz, F). IR (KBr): 1615s, 1456s, 1413m, 1381m, 1340s, 1294m, 1265m, 1150m, 1133w, 1071w, 1049m cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=389 nm (3.94). MS (ESI, MeOH): m/z=311.2 (100%, $(M-H)^-$). HRMS for $C_{13}H_7F_3N_2O_4$: calcd: 312.0358; found: 312.0359.

3.5.24. Methyl 2-[4-(trifluoromethoxy)anilino]benzoate (7j). Following GP2 from 4-trifluoromethoxyaniline (1.61 g, 9.12 mmol) and methyl 2-iodo-benzoate (2.00 g, 7.60 mmol) **7j** (2.2 g, 93%) was obtained as a red oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.89 (s, 3H, OCH_3), 6.75 (t, 1H, J=7.5 Hz, H_{arom}), 7.15–7.24 (m, 5H, H_{arom}), 7.32 (ddd, 1H, J=8.5, 7.1, 1.5 Hz, H_{arom}), 7.95 (dd, 1H, J=7.9, 1.7 Hz, H_{arom}), 9.45 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ=51.8, 112.3, 113.9, 117.6, 120.4 (q, J=256.2 Hz, OCF_3), 122.0, 123.1, 131.6, 134.0, 139.5, 144.6, 147.3, 168.7. ^{19}F NMR (188 MHz, $CDCl_3$): δ=−58.8 (s, OCF_3). IR (film): ν=3318m, 3037w, 2954m, 1690s, 1601s, 1584s, 1518s, 1456s, 1438s, 1406m, 1325s, 1254s, 1202s, 1163s, 1085s, 1048w, 1015w cm^{-1}. UV–vis (methanol): λ_{max} (log ε)= 237 nm (4.38). MS (ESI, MeOH+TFA): m/z=312.1 (100%, $(M+H)^+$). HRMS for $C_{15}H_{12}F_3NO_3$: calcd: 311.0777; found: 311.0770

3.5.25. Methyl 2-(4,5-dimethyl-2-nitroanilino)benzoate (7k). Compound **7k** (2.0 g, 89%) was obtained from methyl 2-iodobenzoate (2.0 g, 7.6 mmol) and 4,5-dimethyl-2-nitroaniline (1.5 g, 9.1 mmol) following GP2. Mp 150–152 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ=2.23 (s, 6H, CH_3), 3.94 (s, 3H, OCH_3), 6.98 (ddd, 1H, J=7.3, 7.8, 1.4 Hz, H_{arom}), 7.36 (s, 1H, H_{arom}), 7.41 (ddd, 1H, J=7.3, 8.3, 1.4 Hz, H_{arom}), 7.47 (dd, 1H, J=8.3, 1.4 Hz, H_{arom}), 7.92 (s, 1H, H_{arom}), 8.00 (dd, 1H, J=7.8, 1.4 Hz, H_{arom}), 11.0 (s, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ=18.8, 20.3, 52.2, 118.1, 118.6, 119.4, 121.1, 126.5, 129.3, 132.0, 133.3, 135.4, 136.8, 142.9, 145.2, 167.5. IR (KBr): ν=2922m, 1701s, 1628m, 1583s, 1566s, 1507s, 1457m, 1425m, 1336s, 1295m, 1273s, 1249s, 1180w, 1164w, 1080m cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=236 nm (4.34). MS (ESI, MeOH): m/z=301.1 (100%, $(M+)^+$). HRMS for $C_{16}H_{16}N_2O_4$: calcd: 300.1110; found: 300.1111.

3.5.26. Methyl 2-[2-(methoxycarbonyl)anilino]benzoate (7l). Compound **7l** (1.1 g, 51%) was obtained from methyl 2-iodobenzoate (2.0 g, 7.6 mmol) and methyl 2-amino-benzoate (1.4 g, 9.1 mmol) following GP2; the crude product was recrystallized from ethanol. Mp 90–95 °C (Lit.: 102–103 °C;[76] 96–98 °C[77]). ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.93 (s, 6H, OCH_3), 6.88 (t, 2H, J=7.5 Hz, H_{arom}), 7.35 (ddd, 2H, J=7.5, 7.5, 1.6 Hz, H_{arom}), 7.52 (d, 2H, J=8.3 Hz, H_{arom}), 7.97 (dd, 2H, J=7.9, 1.7 Hz, H_{arom}), 11.0 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ=52.1, 117.1, 117.6, 119.8, 131.7, 133.2, 144.1, 167.6. IR (KBr): ν=3030w, 2940w, 1698s, 1609m, 1582s, 1523s, 1449s, 1432m, 1320m, 1266s, 1221s, 1193m, 1161w, 1085s cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=237 nm (4.37). MS (ESI, MeOH): m/z=308.2 (100%, $(M+Na)^+$).

3.5.27. Methyl 2-(3-fluoroanilino)benzoate (7m). Compound **7m** (1.8 g, 94%) was obtained as an oil from methyl 2-iodobenzoate (2.0 g, 7.6 mmol) and *m*-fluoroaniline (1.0 g, 9.0 mmol) following GP2. ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.89 (s, 3H, OCH_3), 6.60–6.70 (m, 2H, H_{arom}), 6.96 (m, 2H, H_{arom}), 7.20–7.38 (m, 3H, H_{arom}), 7.96 (dd, 1H, J=7.5, 1.7 Hz, H_{arom}), 9.50 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ=51.9, 108.2 (d, J=24.2 Hz), 109.6 (d, J=24.2 Hz), 112.8, 114.5, 117.0, 117.9, 130.3 (d, J= 9.6 Hz), 131.6, 134.0, 142.6(d, J=10.0 Hz), 146.7, 163.4(d, J=244.7 Hz), 168.6. ^{19}F NMR (188 MHz, $CDCl_3$): δ= −112.5 (m, F). IR (film): ν=3318w, 2952w, 1690s, 1602s, 1580s, 1521s, 1492m, 1455s, 1437m, 1328m, 1263s, 1250s, 1231s, 1192m, 1164m, 1141m, 1085m, 1047w, 1002w cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=236 nm (4.36). MS (ESI, MeOH): m/z=246.3 (100%, $(M+H)^+$). HRMS for $C_{14}H_{12}FNO_2$: calcd: 245.0852; found: 245.0865.

3.5.28. Methyl 2-(2,4-difluoroanilino)benzoate (7n). Compound **7n** (2.0 g, 98%) was obtained from methyl 2-iodobenzoate (2.0 g, 7.6 mmol) and 2,4-difluoroaniline (1.2 g, 9.3 mmol) following GP2. Mp 62–63 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.90 (s, 3H, OCH_3), 6.74 (ddd, 1H, J=7.1, 1.2 Hz, H_{arom}), 6.82–6.94 (m, 3H, H_{arom}), 7.27–7.36 (m, 2H, H_{arom}), 7.95 (dd, 1H, J=8.3, 1.7 Hz, H_{arom}), 9.23 (s, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ=51.8, 104.8 (t, J=9.6 Hz), 111.2 (dd, J=22.1, 3.7 Hz), 112.1, 113.4, 117.5, 124.7 (dd, J=12.0, 3.7 Hz), 126.1 (dd, J=2.8, 9.2 Hz), 131.6, 134.2, 147.9, 156.5 (dd, J=246.7, 11.0 Hz), 159.3 (dd, J=250.4, 12.0 Hz), 168.9. ^{19}F NMR (188 MHz, $CDCl_3$): δ=−115.2 (m, F), −119.3 (m, F). IR (KBr): ν=3307w, 2953w, 1683s, 1587s, 1529s, 1458m, 1435m, 1332m, 1288m, 1254s, 1229s, 1190m, 1170m, 1148m, 1088s, 1054w cm^{-1}. UV–vis (methanol): λ_{max} (log ε)= 236 nm (4.17). MS (ESI, MeOH): m/z=264.1 (100%, $(M+H)^+$). HRMS for $C_{14}H_{11}F_2NO_2$: calcd: 263.0758; found: 263.0759

3.5.29. Methyl 2-(2,3,4-trifluoroanilino)benzoate (7o). Compound **7o** (1.9 g, 91%) was obtained from methyl 2-iodobenzoate (2.0 g, 7.6 mmol) and 2,3,4-trifluoroaniline (1.3 g, 9.1 mmol) according to GP2 followed by column chromatography (silica gel, $CHCl_3$). Mp 70–71 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 3.90 (s, 3H, OCH_3), 6.79 (ddd, 1H, J=7.9, 7.0, 1.2 Hz, H_{arom}), 6.91–6.95 (m, 2H, H_{arom}), 7.05–7.15 (m, 1H, H_{arom}), 7.32 (ddd, 1H, J=9.1, 7.1, 1.2 Hz, H_{arom}), 7.97 (dd, 1H, J=7.8, 1.2 Hz, H_{arom}), 9.3 (s,

1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ=52.0, 111.2 (dd, J=18.4, 4.6 Hz), 112.7, 113.7, 118.0, 118.1, 126.3 (dd, J=9.2, 3.1 Hz), 131.6, 134.1, 140.7 (ddd, J=250.9, 16.1, 16.1 Hz), 145.7 (ddd, J=247.1, 10.7, 2.3 Hz), 147.0, 147.4 (ddd, J=247.1, 10.7, 2.3 Hz), 145.7 (ddd, J=247.1, 10.7, 2.3 Hz), 168.6. ^{19}F NMR (188 MHz, $CDCl_3$): δ=−140.0 (m, F), −143.7 (d, J=20.1 Hz, F), −158.6 (ddd, J=23.1, 23.1, 8.4 Hz, F). IR (KBr): ν=3304m, 2997w, 2955m, 1682s, 1615s, 1589s, 1536s, 1514s, 1491s, 1455m, 1436s, 1330m, 1315m, 1293m, 1255s, 1221s, 1191m, 1168m, 1141m, 1090s, 1060m, 1042m cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=233 nm (4.47). MS (ESI, MeOH): m/z=282.0 (100%, $(M+H)^+$). HRMS for $C_{14}H_{10}F_3NO_2$: 281.0664; found: 281.0664.

3.5.30. Methyl 2-(2,4-dimethoxyanilino)benzoate (7p). Compound **7p** (2.1 g, 97%) was obtained from methyl 2-iodobenzoate (2.0 g, 7.6 mmol) and 2,4-dimethoxyaniline (1.4 g, 9.1 mmol) following GP2. ^{1}H NMR (500 MHz, $CDCl_3$): δ=3.80 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 6.46 (dd, 1H, J=8.5, 3.1 Hz, H_{arom}), 6.54 (d, 1H, J=3.1 Hz, H_{arom}), 6.64 (ddd, 1H, J=7.9, 6.7, 1.2 Hz, H_{arom}), 6.95 (d, 1H, J=8.5 Hz, H_{arom}), 7.21–7.26 (m, 2H, H_{arom}), 7.92 (dd, 1H, J=8.5, 1.2 Hz, H_{arom}), 9.13 (s, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ=51.6, 55.5, 55.7, 99.6, 103.9, 111.3, 113.4, 116.1, 122.7, 124.8, 131.5, 134.0, 149.1, 154.2, 157.4, 168.9. IR (kap.): ν=3333m, 3001w, 2950m, 2836w, 1686s, 1604s, 1578m, 1519s, 1454s, 1437s, 1415m, 1249s, 1209s, 1188m, 1159s, 1129m, 1084s, 1035m cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=233 nm (4.46). MS (ESI, MeOH): m/z=288.4 (100%, $(M+H)^+$). HRMS for $C_{16}H_{17}NO_4$: calcd: 287.1158; found: 287.1155.

3.5.31. Methyl 2-(2,5-dimethoxyanilino)benzoate (7q).[78] Compound **7q** (1.6 g, 73%) was obtained as an oil from methyl 2-iodobenzoate (2.0 g, 7.6 mmol) and 2,5-dimethoxyaniline (1.4 g, 9.1 mmol) following GP2. ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.75 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 6.51 (dd, 1H, J=9.1, 2.9 Hz, H_{arom}), 6.74 (ddd, 1H, J=7.1, 7.1, 1.3 Hz, H_{arom}), 6.83 (d, 1H, J=8.7 Hz, H_{arom}), 7.03 (d, 1H, J=2.9 Hz, H_{arom}), 7.32 (ddd, 1H, J=7.1, 6.6, 1.7 Hz, H_{arom}), 7.38 (dd, 1H, J=8.7, 1.3 Hz, H_{arom}), 7.95 (dd, 1H, J=7.9, 1.7 Hz, H_{arom}), 9.45 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ=51.8, 55.8, 56.5, 106.5, 106.7, 112.0, 113.2, 114.7, 117.4, 131.1, 131.5, 133.8, 145.5, 146.5, 153.6, 168.4. IR (film): ν=3328m, 3078w, 2999m, 2950m, 2834m, 1732m, 1690s, 1597s, 1579s, 1526s, 1455s, 1436s, 1314s, 1288s, 1260s, 1217s, 1200s, 1180s, 1164m, 1132s, 1085s, 1046s, 1026m cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=233 nm (4.50). MS (ESI, MeOH): m/z=288.1 (100%, $(M+H)^+$). HRMS for $C_{16}H_{17}NO_4$: calcd: 287.1158; found: 287.1159.

3.5.32. Methyl 4-chloro-2-[4-(trifluoromethoxy)anilino]-benzoate (7r). Compound **7r** (2.1 g, 90%) was obtained from methyl 4-chloro-2-iodobenzoate (2.0 g, 6.8 mmol) and 4-trifluoromethoxyaniline (1.5 g, 8.5 mmol) following GP2. Mp 104–105 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.89 (s, 3H, OCH_3), 6.70 (dd, 1H, J=8.3, 1.7 Hz, H_{arom}), 7.1 (d, 1H, J=2.1 Hz, H_{arom}), 7.16–7.24 (m, 4H, H_{arom}), 7.88 (d, 1H, J=8.3 Hz, H_{arom}), 9.53 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ=52.0, 110.4, 113.2, 117.8, 120.5 (q, J=256.6 Hz), 122.3, 124.1, 132.9, 138.6, 140.6, 145.5, 148.6, 168.2. ^{19}F NMR (188 MHz, $CDCl_3$): δ=−58.7 (s, OCF_3).IR (KBr): ν=3321m, 2957m, 1697s, 1599s, 1576s, 1516s, 1439m, 1425s, 1406m, 1321m, 1257s, 1226s, 1200s, 1153s, 1100s, 1080w, 1014w cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=243 nm (4.40). MS (ESI, MeOH): m/z=344.2 (100%, $(M-H)^-$). HRMS for $C_{15}H_{11}ClF_3NO_3$: calcd: 345.0380; found: 345.0381.

3.5.33. Methyl 4-chloro-2-(2,4-difluoroanilino)benzoate (7s). Compound **7s** (1.7 g, 86%) was obtained from methyl 4-chloro-2-iodobenzoate (2.0 g, 6.8 mmol) and 2,4-difluoroaniline (1.1 g, 8.5 mmol) following GP2. Mp 89–91 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.89 (s, 3H, OCH_3), 6.69 (dd, 1H, J=8.7, 2.1 Hz, H_{arom}), 6.78 (t, 1H, J=1.7 Hz, H_{arom}), 6.86–6.96 (m, 2H, H_{arom}), 7.28–7.34 (m, 1H, H_{arom}), 7.87 (d, 1H, J=8.7 Hz, H_{arom}), 9.30 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ=52.0, 105.0 (dd, J=23.8, 23.8 Hz), 110.3, 111.4 (dd, J=21.5, 3.8 Hz), 112.8, 117.6, 123.7 (dd, J=12.3, 3.1 Hz), 126.9 (dd, J=10.0, 2.3 Hz), 132.7, 140.6, 149.0, 156.9 (dd, J=247.1, 10.7 Hz), 159.9 (dd, J=250.1, 12.3 Hz), 168.1. ^{19}F NMR (188 MHz, $CDCl_3$): δ=−113.6 (m, F), −118.5 (m, F). IR (KBr): ν=3294w, 3070w, 2959w, 1693s, 1603m, 1579s, 1518s, 1435m, 1328m, 1287m, 1261s, 1245s, 1206m, 1186m, 1144m, 1101s, 1085m cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=242 nm (4.50). MS (ESI, MeOH): m/z=296.3 (100%, $(M-H)^-$). HRMS for $C_{14}H_{10}ClF_2NO_2$: calcd: 297.0368; found: 297.0366.

3.5.34. Methyl 4-chloro-2-(2,3,4-trifluoroanilino)benzoate (7t). Compound **7t** (1.2 g, 54%) was prepared from methyl 4-chloro-2-iodobenzoate (2.0 g, 6.8 mmol) and 2,3,4-trifluoroaniline (1.2 g, 8.1 mmol) following GP2. Mp 122–124 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 3.90 (s, 3H, OCH_3), 6.74 (dd, 1H, J=8.7, 2.1 Hz, H_{arom}), 6.83 (t, 1H, J=1.6 Hz, H_{arom}), 6.94–7.02 (m, 1H, H_{arom}), 7.04–7.12 (m, 1H, H_{arom}), 7.89 (d, 1H, J=8.7 Hz, H_{arom}), 9.39 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ=52.1, 110.7, 111.6 (dd, J=17.6, 3.8 Hz), 113.1, 118.2, 119.1 (dd, J=7.7, 3.8 Hz), 125.3 (dd, J=9.2, 3.1 Hz), 132.8, 140.6 (ddd, J=252.4, 14.6, 14.6 Hz), 140.6, 146.1 (ddd, J=249.4, 12.3, 3.8 Hz), 148.3 (ddd, J=247.8, 10.0, 2.3 Hz), 148.3, 168.1. ^{19}F NMR (188 MHz, $CDCl_3$): δ=−138.1 (m, F), −142.3 (m, F), −157.8 (ddd, J=23.1, 23.1, 8.4 Hz, F). IR (KBr): ν=3244m, 2969w, 1696s, 1617s, 1594s, 1534s, 1515s, 1491s, 1441m, 1419m, 1328m, 1293m, 1257s, 1217m, 1190w, 1168w, 1151w, 1105m, 1082w, 1049s cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=241 nm (4.42). MS (ESI, MeOH): m/z=300.3 (90%, $(M-H)^-$), 623.3 (100% $[(M-H)_2Na]^-$). HRMS for $C_{14}H_9ClF_3NO_2$: calcd: 315.0274; found: 315.0274.

3.5.35. Methyl 5-nitro-2-[4-(trifluoromethoxy)anilino]-benzoate (7u). Compound **7u** (2.0 g, 87%) was prepared from methyl 2-iodo-5-nitrobenzoate (2.0 g, 6.5 mmol) and 4-trifluoromethoxyaniline (1.4 g, 7.9 mmol) following GP2. Mp 49–52 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.96 (s, 3H, OCH_3), 7.03 (d, 1H, J=9.5 Hz, H_{arom}), 7.24–7.30 (m, 4H, H_{arom}), 8.13 (dd, 1H, J=9.5, 2.5 Hz, H_{arom}), 8.95 (d, 1H, J=2.5 Hz, H_{arom}), 10.13 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ=52.5, 110.5, 112.9, 120.4 (q, J=275.4 Hz), 122.4, 125.8, 128.8, 129.4, 137.0, 137.8, 146.8, 152.4, 167.6. ^{19}F NMR (188 MHz, $CDCl_3$): δ=−58.7 (s, OCF_3).

IR (KBr): ν=3254m, 2963m, 1702s, 1604s, 1586s, 1537m, 1509s, 1446m, 1348s, 1259s, 1209s, 1130s, 1109s, 1070m, 1014m cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=230 nm (4.33). MS (ESI, MeOH): *m*/*z*=355.4 (100%, (M−H)$^-$). HRMS for $C_{15}H_{11}F_3N_2O_4$: calcd: 356.0620; found: 356.0620.

3.5.36. Methyl 2-(2,4-difluoroanilino)-5-nitrobenzoate (7v). Compound **7v** (1.7 g, 85%) was prepared from methyl 2-iodo-5-nitrobenzoate (2.0 g, 6.5 mmol) and 2,4-difluoroaniline (1.0 g, 7.7 mmol) following GP2. Mp 178 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.96 (s, 3H, OCH_3), 6.74 (dd, 1H, *J*=9.1, 1.7 Hz, H_{arom}), 6.90–7.00 (m, 2H, H_{arom}), 7.29–7.35 (m, 1H, H_{arom}), 8.13 (dd, 1H, *J*=9.5, 3.0 Hz, H_{arom}), 8.90 (d, 1H, *J*=2.5 Hz, H_{arom}), 9.89 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ=52.5, 105.3 (dd, *J*=26.1, 26.8 Hz), 110.5, 111.9 (dd, *J*=22.3, 3.8 Hz), 112.9, 122.2 (dd, *J*=12.6, 4.2 Hz), 128.1 (dd, *J*=10.0, 2.3 Hz), 128.6, 129.3, 137.9, 152.7, 157.2 (dd, *J*=251.7, 12.3 Hz), 160.9 (dd, *J*=249.4, 11.5 Hz), 167.5. ^{19}F NMR (188 MHz, $CDCl_3$): δ=−111.0 (m, F), −116.7 (m, F). IR (KBr): ν=2926w, 1702s, 1612s, 1589s, 1542m, 1511s, 1439m, 1361m, 1331s, 1292m, 1266s, 1231m, 1198m, 1144m, 1095m, 1076m cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=230 nm (4.37). MS (ESI, MeOH): *m*/*z*=307.3 (100%, (M−H)$^-$). HRMS for $C_{14}H_{10}F_2N_2O_4$: calcd: 308.0609; found: 308.0610.

3.5.37. Methyl 2-(2,3,4-trifluoroanilino)5-nitro-benzoate (7w). Compound **7w** (1.3 g, 60%) was prepared from methyl 2-iodo-5-nitrobenzoate (2.0 g, 6.5 mmol) and 2,3,4-trifluoroaniline (1.1 g, 7.5 mmol) according to GP2 followed by column chromatography (silica gel, $CHCl_3$). Mp 216–217 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 3.98 (s, 3H, OCH_3), 6.80 (dd, 1H, *J*=9.1, 1.7 Hz, H_{arom}), 6.99–7.13 (m, 2H, H_{arom}), 8.15 (dd, 1H, *J*=9.1, 2.5 Hz, H_{arom}), 8.92 (d, 1H, *J*=2.5 Hz, H_{arom}), 9.96 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6, 50 °C): δ=52.5, 110.8, 112.4 (dd, *J*=17.5, 3.7 Hz), 114.0, 122.2 (d, *J*=8.3 Hz), 123.9 (dd, *J*=10.1, 3.7 Hz), 127.5, 129.2, 137.5, 139.7 (ddd, *J*=249.5, 16.5, 13.8 Hz), 146.0 (ddd, *J*=249.5, 9.2, 3.7 Hz), 148.5 (ddd, *J*=249.5, 10.1, 3.7 Hz), 151.6, 166.3. ^{19}F NMR (200 MHz, $CDCl_3$): δ=−136.2 (m, F), −141.3 (dd, *J*=18.4, 6.2 Hz, F), −158.1 (ddd, *J*=23.1, 23.1, 8.4 Hz, F). IR (KBr): ν=2925w, 1705m, 1616s, 1595s, 1545m, 1508s, 1486m, 1444m, 1332s, 1304m, 1272s, 1224m, 1138w, 1077w, 1049m cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=367 nm (4.38). MS (ESI, MeOH): *m*/*z*=325.4 (100%, (M−H)$^-$). HRMS for $C_{14}H_9F_3N_2O_4$: calcd: 326.0514; found: 326.0516.

3.5.38. 9-Chloro-2-methoxy-6-nitroacridine (8a). Compound **8a** (1.6 g, 80%) was prepared from **6a** (2.0 g, 6.9 mmol) following GP4. Mp 223–226 °C (Lit.: 229–230 °C;[79] 213–214 °C[80]). ^{1}H NMR (400 MHz, $CDCl_3$): 4.05 (s, 3H OCH_3), 7.48 (d, 1H, *J*=2.9 Hz, H_{arom}), 7.54 (dd, 1H, *J*=9.5, 2.9 Hz, H_{arom}), 8.12 (d, 1H, *J*=9.5 Hz, H_{arom}), 8.29 (dd, 1H, *J*=9.5, 2.5 Hz, H_{arom}), 8.47 (d, 1H, *J*=9.5 Hz, H_{arom}), 9.08 (d, 1H, *J*=2.5 Hz, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ=56.0, 99.7, 107.7, 119.8, 126.2, 126.3, 126.6, 126.8, 127.3, 132.0, 138.1, 145.1, 147.7, 159.7. IR (KBr): ν=1634m, 1613s, 1558m, 1538m, 1511m, 1477m, 1426m, 1404m, 1344s, 1271w, 1223s, 1076w, 1024w cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=272 nm (4.44). HRMS for $C_{14}H_9ClN_2O_3$: calcd: 288.0302, found: 288.0293.

3.5.39. 9-Chloro-5-methoxy-2-nitroacridine (8b). Compound **8b** (1.5 g, 75%) was prepared from **6b** (2.0 g, 6.9 mmol) following GP4. Mp 360 °C (Lit.: 265–267 °C[54]). ^{1}H NMR (400 MHz, $CDCl_3$): 4.17 (s, 3H OCH_3), 7.17 (d, 1H, *J*=8.3 Hz, H_{arom}), 7.63 (dd, 1H, *J*=9.1, 7.9 Hz, H_{arom}), 8.00 (dd, 1H, *J*=8.7, 1.2 Hz, H_{arom}), 8.47 (m, 2H, H_{arom}), 9.37 (d, 1H, *J*=1.2 Hz, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ=56.6, 108.8, 116.4, 122.3, 122.9, 122.9, 125.9, 128.5, 132.7, 144.0, 145.8, 148.2, 155.3, 158.4. IR (KBr): ν=1628m, 1609m, 1582m, 1542s, 1509m, 1468m, 1457m, 1401s, 1346s, 1337s, 1305w, 1278m, 1267m, 1219w, 1177w, 1135w, 1107m, 1069w cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=255 nm (3.76). MS (ESI, MeOH+TFA): *m*/*z*=289.2 (100%, (M+H)$^+$).

3.5.40. 9-Chloro-2,4-dimethoxy-6-nitroacridine (8c).[27,81] Compound **8c** (1.4 g, 70%) was prepared from **6c** (2.0 g, 6.3 mmol) following GP4. Mp 250–252 °C (Lit.: 225–227 °C[27]). ^{1}H NMR (400 MHz, $CDCl_3$): 4.03 (s, 3H OCH_3), 4.14 (s, 3H OCH_3), 6.80 (d, 1H, *J*=2.5 Hz, H_{arom}), 7.12 (d, 1H, *J*=2.5 Hz, H_{arom}), 8.32 (dd, 1H, *J*=9.5, 2.5 Hz, H_{arom}), 8.46 (d, 1H, *J*=9.5 Hz, H_{arom}), 9.27 (d, 1H, *J*=2.5 Hz, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ=56.0, 56.8, 92.4, 103.7, 120.2, 125.9, 127.0, 127.3, 127.6, 138.0, 141.7, 143.9, 147.8, 156.6, 160.4. IR (KBr): ν=2945w, 1631m, 1614m, 1570w, 1515s, 1421m, 1402m, 1346s, 1330s, 1244s, 1045w cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=273 nm (4.44). HRMS for $C_{15}H_{11}ClN_2O_3$: calcd: 318.0407, found: 318.0399.

3.5.41. 9-Chloro-5-methoxy-3-nitroacridine (8f). Compound **8f** (1.6 g, 79%) was prepared from **6f** (2.0 g, 6.9 mmol) following GP4. Mp 230–235 °C (Lit.: 204–205 °C[79]). ^{1}H NMR (400 MHz, $CDCl_3$): 4.18 (s, 3H OCH_3), 7.14 (d, 1H, *J*=7.1 Hz, H_{arom}), 7.65 (dd, 1H, *J*=8.7, 7.5 Hz, H_{arom}), 7.99 (dd, 1H, *J*=8.7, 0.8 Hz, H_{arom}), 8.32 (dd, 1H, *J*=9.5, 2.5 Hz, H_{arom}), 8.52 (d, 1H, *J*=9.5 Hz, H_{arom}), 9.31 (d, 1H, *J*=2.1 Hz, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ=56.6, 108.0, 116.3, 120.0, 126.3, 126.5, 126.6, 127.2, 129.2, 141.3, 143.6, 145.8, 148.4, 155.5. IR (KBr): ν=2924w, 1625w, 1566w, 1512s, 1455m, 1398s, 1347m, 1310m, 1270w, 1155w, 1069w cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=259 nm (4.49). HRMS for $C_{14}H_9ClN_2O_3$: calcd: 288.0302, found: 288.0303.

3.5.42. 9-Chloro-2,4-dimethoxy-7-nitroacridine (8g). Compound **8g** (1.7 g, 85%) was prepared from **6g** (2.0 g, 6.3 mmol) following GP4. Mp 258–261 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 4.04 (s, 3H OCH_3), 4.14 (s, 3H OCH_3), 6.85 (d, 1H, *J*=2.1 Hz, H_{arom}), 7.14 (d, 1H, *J*=2.5 Hz, H_{arom}), 8.40–8.46 (m, 2H, H_{arom}), 9.34 (dd, 1H, *J*=2.1, 0.8 Hz, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ=55.9, 56.7, 92.3, 104.5, 121.7, 123.4, 126.8, 132.6, 140.7, 141.9, 146.0, 146.6, 156.4, 159.7. IR (KBr): ν=1633s, 1560m, 1542s, 1509s, 1466s, 1420s, 1406s, 1343s, 1310m, 1246m, 1209s, 1169m, 1148m, 1115w, 1048m, 1012w cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=264 nm (4.28). MS (ESI, MeOH): *m*/*z*=319.2 (100%, (M+H)$^+$). HRMS for $C_{15}H_{11}ClN_2O_4$: calcd: 318.0407; found: 318.0435.

3.5.43. 9-Chloro-2-methoxyacridine (8h).[82–87] Compound **8h** (1.8 g, 91%) was prepared from **6h** (2.0 g, 8.2 mmol) following GP4. Mp 162–163 °C (Lit.: 154 °C;[82] 152 °C;[83] 153 °C;[84] 148–149 °C[85]). ^{1}H NMR (400 MHz, $CDCl_3$): 4.02 (s, 3H OCH_3), 7.47 (dd, 1H, J=9.5, 2.5 Hz, H_{arom}), 7.51 (d, 1H, J=2.5 Hz, H_{arom}), 7.61 (ddd, 1H, J=7.5, 6.6, 0.8 Hz, H_{arom}), 7.73 (ddd, 1H, J=7.9, 6.6, 1.2 Hz, H_{arom}), 8.09 (d, 1H, J=9.1 Hz, H_{arom}), 8.18 (dd, 1H, J=8.7, 0.8 Hz, H_{arom}), 8.37 (ddd, 1H, J=8.7, 1.2, 0.8 Hz, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ=55.7, 99.9, 102.2, 124.1, 124.5, 125.3, 125.9, 127.0, 129.3, 129.8, 131.5, 146.2, 147.3, 158.2. IR (KBr): ν=3012w, 2976w, 1636s, 1560m, 1552s, 1524w, 1479s, 1445m, 1426m, 1398m, 1350w, 1307w, 1280w, 1265s, 1223s, 1219w, 1203s, 1135w, 1182s, 1139m, 1116w, 1014m cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=271 nm (5.07). HRMS for $C_{14}H_{10}ClNO$: calcd: 243.0451, found: 243.0458.

3.5.44. 6,9-Dichloro-2-methoxyacridine (8i).[60,88–90] Compound **8i** (1.5 g, 77%) was prepared from **6i** (2.0 g, 7.2 mmol) following GP4. Mp 169–172 °C (Lit.: 164 °C;[88] 160–161 °C[60]). ^{1}H NMR (400 MHz, $CDCl_3$): 4.01 (s, 3H OCH_3), 7.44–7.49 (m, 2H, H_{arom}), 7.52 (dd, 1H, J=9.1, 2.1 Hz, H_{arom}), 8.05 (d, 1H, J=9.1 Hz, H_{arom}), 8.16 (d, 1H, J=2.1 Hz, H_{arom}), 8.28 (d, 1H, J=9.5 Hz, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ=56.3, 99.9, 122.8, 125.3, 125.6, 126.4, 128.2, 128.2, 131.5, 135.3, 138.3, 146.7, 147.1, 158.4. IR (KBr): ν=2925w, 1633s, 1554w, 1517w, 1476s, 1420s, 1262s, 1062w, 1027w cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=276 nm (4.07). HRMS for $C_{14}H_9Cl_2NO$: calcd: 277.0061, found: 277.0032. HRMS for $C_{14}H_9Cl_2NO$: calcd: 277.0061; found: 277.0032.

3.5.45. 9-Chloro-2-(trifluoromethoxy)acridine (8j). Following GP4 from **6j** (2.0 g, 6.7 mmol) **8j** (1.8 g, 90%) as a brown solid. Mp 250 °C (decomp.). ^{1}H NMR (400 MHz, $CDCl_3$): 7.63 (m, 2H, H_{arom}), 7.84 (ddd, 1H, J=6.6, 6.6, 1.3 Hz, H_{arom}), 8.20–8.28 (m, 3H, H_{arom}), 8.44 (dd, 1H, J=8.3, 0.9 Hz, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ=114.1, 120.5 (q, J=258.4 Hz), 124.1, 124.4, 124.5, 125.2, 127.7, 130.0, 130.9, 132.5, 140.9, 146.9, 147.2, 149.1. ^{19}F NMR (188 MHz, $CDCl_3$): δ=−58.3 (s, OCF_3). IR (KBr): ν=3041w, 2926w, 1636m, 1559m, 1522m, 1507m, 1476m, 1460m, 1439m, 1401m, 1267s, 1215s, 1170s, 1012w cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=269 nm (5.05). MS (ESI, MeOH): m/z=298.0 (100%, $(M+H)^+$).

3.5.46. 9-Chloro-3-fluoro-acridine (8m1) and 9-chloro-1-fluoro-acridine (8m2).[72,73,91] Following GP4 from **7m** (1.2 g, 5.2 mmol) **8m1** (0.64 g, 53%) and **8m2** (0.31 g, 26%) were obtained; the products were separated by chromatography (silica gel, $CHCl_3$).

Data for **8m1**: Mp 158–159 °C (Lit.: 151 °C;[72] 150–152 °C[73]). ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.16–7.30 (m, 1H, H_{arom}), 7.60–7.75 (m, 2H, H_{arom}), 7.82 (ddd, 1H, J=6.6, 6.6, 1.7 Hz, H_{arom}), 8.02 (d, 1H, J=8.3 Hz, H_{arom}), 8.18 (d, 1H, J=9.1 Hz, H_{arom}), 8.52 (d, 1H, J=9.1 Hz, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ=110.8 (d, J=23.1 Hz), 116.2 (d, J=8.8 Hz), 124.6, 125.1, 126.3 (d, J=5.6 Hz), 127.4, 129.2 (d, J=9.6 Hz), 129.6, 131.1, 138.5 (d, J=4.0 Hz), 148.9, 149.9, 157.4 (d, J=262.6 Hz). ^{19}F NMR (188 MHz, $CDCl_3$): δ=−111.1 (dd, J=12.2, 4.7 Hz, F). IR (KBr): ν=2923m, 1636s, 1553s, 1525m, 1466m, 1426s, 1393m, 1349m, 1316s, 1278m, 1256m, 1220m, 1140m, 1034m cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=272 nm (5.15). MS (ESI, MeOH+TFA): m/z=232.2 (100%, $(M+H)^+$).

Data for **8m2**: Mp 131–133 °C (Lit.: 130–131 °C[73]). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.45 (ddd, 1H, J=7.9, 7.9, 2.5 Hz, H_{arom}), 7.63 (ddd, 1H, J=6.6, 6.6, 1.2 Hz, H_{arom}), 7.79–7.85 (m, 2H, H_{arom}), 8.18 (d, 1H, J=8.7 Hz, H_{arom}), 8.40–8.48 (m, 2H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ=111.9 (d, J=20.0 Hz), 118.7 (d, J=27.1 Hz), 121.6, 123.7, 124.6, 126.7, 127.2 (d, J=10.4 Hz), 129.4, 131.0, 141.4, 149.4, 149.5, 163.5 (d, J=254.6 Hz). ^{19}F NMR (188 MHz, $CDCl_3$): δ=−107.5 (m, F). IR (KBr): ν=3060w, 2924w 1634m, 1616m, 1552m, 1522m, 1480m, 1458m, 1437m, 1400m, 1311w, 1278s, 1261m, 1178m, 1150m, 1136m, 1113w cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=262 nm (5.12). MS (ESI, MeOH+TFA): m/z=232.2 (100%, $(M+H)^+$).

3.5.47. 9-Chloro-2,4-difluoroacridine (8n). Compound **8n** (1.3 g, 96%) was prepared from **6n** (1.4 g, 5.6 mmol) following GP4. Mp 153–155 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 7.34 (ddd, 1H, J=10.0, 10.0, 2.9 Hz, H_{arom}), 7.68 (ddd, 1H, J=6.6, 6.6, 1.2 Hz, H_{arom}), 7.80–7.86 (m, 2H, H_{arom}), 8.30 (dd, 1H, J=8.7, 1.0 Hz, H_{arom}), 8.38 (d, 1H, J=8.7 Hz, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ=103.0 (dd, J=24.6, 5.5 Hz), 106.3 (dd, J=22.7, 22.3 Hz), 124.1, 125.0, 128.2, 130.4, 130.4, 130.8, 137.5 (d, J=13.0 Hz), 140.3 (dd, J=8.4, 5.4 Hz), 148.0, 158.4 (dd, J=262.8, 13.0 Hz), 159.0 (dd, J=151.0, 11.5 Hz). ^{19}F NMR (188 MHz, $CDCl_3$): δ=−107.8 (dd, J=15.3, 9.2 Hz, F), −117.7 (t, J=9.2 Hz, F). IR (KBr): ν=1646s, 1559m, 1526m, 1508m, 1473s, 1432s, 1402s, 1330s, 1277m, 1249m, 1207m, 1158m, 1129s, 1080w cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=269 nm (5.13). MS (ESI, MeOH): m/z=250.0 (100%, $(M+H)^+$). HRMS for $C_{13}H_6ClF_2N$: calcd: 249.0157; found: 249.0154.

3.5.48. 9-Chloro-2,3,4-trifluoroacridine (8o). Compound **8o** (1.2 g, 85%) was prepared from **6o** (1.4 g, 5.18 mmol) following GP4. Mp 327–333 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 7.70 (ddd, 1H, J=8.7, 6.6, 1.2 Hz, H_{arom}), 7.86 (ddd, 1H, J=8.7, 6.6, 1.2 Hz, H_{arom}), 7.96 (ddd, 1H, J=2.5, 7.9, 10.7 Hz, H_{arom}), 8.30 (dd, 1H, J=7.8, 1.1 Hz, H_{arom}), 8.38 (dd, 1H, J=7.8, 1.1 Hz, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ=104.0 (dd, J=20.3, 5.4 Hz), 120.2 (d, J=9.2 Hz), 124.2, 124.5, 128.1, 130.0, 131.3, 137.7 (d, J=10.4 Hz), 141.2 (ddd, J=259.7, 20.3, 19.5 Hz), 140.7, 145.0 (ddd, J=260.9, 10.4, 4.2 Hz), 148.6, 150.4 (dd, J=255.2, 15.0 Hz). ^{19}F NMR (188 MHz, $CDCl_3$): δ=−129.7 (m, F), −144.2 (dd, J=15.2, 6.2 Hz, F), −152.4 (m, F). IR (KBr): ν=3259m, 3179m, 3009m, 1660w, 1629s, 1599s, 1585s, 1542w, 1506s, 1474s, 1454s, 1399w, 1359w, 1321m, 1321m, 1294m, 1254w, 1199w, 1160w, 1131m, 1106m, 1047m cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=268 nm (4.72). MS (ESI, MeOH): m/z=268.2 (100%, $(M+H)^+$). HRMS for $C_{13}H_5ClF_3N$: calcd: 267.0063; found: 267.0090.

3.5.49. 9-Chloro-2,4-dimethoxyacridine (8p). Compound

8p (1.3 g, 95%) was prepared from **6p** (1.4 g, 5.1 mmol) following GP4. Mp 220–222 °C (Lit.: 170–172 °C[25]). ^{1}H NMR (400 MHz, $CDCl_3$): 4.00 (s, 3H OCH_3), 4.11 (s, 3H OCH_3), 6.74 (d, 1H, J=2.5 Hz, H_{arom}), 7.12 (d, 1H, J=2.5 Hz, H_{arom}), 7.61 (ddd, 1H, J=8.7, 6.6, 1.2 Hz, H_{arom}), 7.71 (ddd, 1H, J=9.1, 6.6, 1.7 Hz, H_{arom}), 8.30–8.36 (m, 2H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ=55.6, 56.5, 92.2, 102.4, 123.8, 124.9, 125.8, 127.3, 128.8, 130.5, 137.9, 139.7, 146.1, 156.2, 158.5. IR (KBr): ν=3136m, 1635s, 1564m, 1528s, 1468s, 1445s, 1419s, 1396s, 1327s, 1282w, 1245s, 1230m, 1201s, 1163s, 1152s, 1110m, 1043s, 1008m cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=284 nm (4.93). HRMS for $C_{15}H_{12}ClNO_2$: calcd: 273.0556, found: 273.0577.

3.5.50. 9-Chloro-1,4-dimethoxyacridine (8q).[25,92] Compound **8q** (1.2 g, 83%) was prepared from **6q** (1.4 g, 5.1 mmol) following GP4. Mp 152–154 °C (Lit.: 148–149 °C;[92] 107 °C[25]). ^{1}H NMR (400 MHz, $CDCl_3$): 3.08 (s, 3H OCH_3), 4.09 (s, 3H OCH_3), 6.80 (d, 1H, J=8.3 Hz, H_{arom}), 6.93 (d, 1H, J=8.3 Hz, H_{arom}), 7.62 (ddd, 1H, J=8.7, 6.6, 1.2 Hz, H_{arom}), 7.77 (ddd, 1H, J=8.7, 6.6, 1.2 Hz, H_{arom}), 8.32 (d, 1H, J=8.7 Hz, H_{arom}), 8.57 (d, 1H, J=8.7 Hz, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ=56.3, 56.6, 105.2, 106.1, 118.6, 124.8, 125.5, 127.1, 130.2, 130.3, 140.0, 142.9, 147.4, 149.4, 149.5. IR (KBr): ν=2934m, 2836m, 1625s, 1611m, 1534w, 1470s, 1409m, 1376m, 1329m, 1314s, 1266s, 1233m, 1169m, 1156w, 1116s, 1080m, 1043s cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=259 nm (4.60). HRMS for $C_{15}H_{12}ClNO_2$: calcd: 273.0556, found: 273.0562.

3.5.51. 6,9-Dichloro-2-(trifluoromethoxy)acridine (8r). Compound **8r** (1.2 g, 82%) was prepared from **6r** (1.5 g, 4.5 mmol) following GP4. Mp 250 °C (decomp.). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.87 (dd, 1H, J=9.5, 2.1 Hz, H_{arom}), 8.00 (dd, 1H, J=9.5, 2.1 Hz, H_{arom}), 8.36 (s, 1H, H_{arom}), 8.56 (d, 1H, J=9.5 Hz, H_{arom}), 9.13 (s, 1H, H_{arom}), 9.27 (d, 1H, J=9.5 Hz, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ=114.1, 118.9, 120.6, 121.5, 123.7 (q, J=234.5 Hz), 124.8, 126.6, 131.4, 131.7, 138.5, 140.2, 141.3, 145.0, 151.6. ^{19}F NMR (188 MHz, $CDCl_3$): δ=−58.5 (s, OCF_3). IR (KBr): ν=2925m, 1628m, 1489m, 1460m, 1421m, 1260s, 1212s, 1081m cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=273 nm (4.58). MS (ESI, MeOH+TFA): m/z=332.2 (100%, $(M+H)^+$). HRMS for $C_{14}H_6Cl_2F_3NO$: calcd: 330.9778; found: 330.9758.

3.5.52. 6,9-Dichloro-2,4-difluoroacridine (8s). Compound **8s** (0.87 g, 87%) was prepared from **6s** (1.0 g, 3.5 mmol) following GP4. Mp 171–175 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 7.39 (ddd, 1H, J=9.5, 8.3, 2.5 Hz, H_{arom}), 7.63 (dd, 1H, J=9.5, 2.1 Hz, H_{arom}), 7.83 (ddd, 1H, J=9.5, 2.5, 1.7 Hz, H_{arom}), 8.33 (d, 1H, J=9.1 Hz, H_{arom}), 8.40 (d, 1H, J=2.1 Hz, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ=103.4 (dd, J=24.5, 5.4 Hz), 107.3 (dd, J=31.5, 22.3 Hz), 123.4, 124.9 (dd, J=11.5, 2.5 Hz), 125.6, 128.2, 129.7, 137.5 (d, J=13 Hz), 137.7, 141.4, 147.3, 158.0 (dd, J=252.4, 10.7 Hz), 159.4 (dd, J=264.7, 13.4 Hz). ^{19}F NMR (188 MHz, $CDCl_3$): δ=−106.7 (dd, J=16.8, 9.2 Hz, F), −116.9 (t, J=9.2 Hz, F). IR (KBr): ν=1630s, 1591s, 1535m, 1485m, 1438m, 1284m, 1248m, 1130m, 1082m cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=274 nm (5.39). MS (ESI, MeOH+TFA): m/z=284.2 (100%, $(M+H)^+$). HRMS for $C_{13}H_5Cl_2F_2N$: calcd: 282.9767; found: 282.9757.

3.5.53. 6,9-Dichloro-2,3,4-trifluoroacridine (8t). Compound **8t** (0.51 g, 65%) was prepared from **6t** (0.8 g, 2.6 mmol) following GP4. Mp 173–176 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 7.61 (dd, 1H, J=9.5, 2.1, H_{arom}), 7.94 (ddd, 1H, J=10.7, 8.7, 2.5 Hz, H_{arom}), 8.28–8.34 (m, 2H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ=104.2 (dd, J=20.7, 5.4 Hz), 120.2 (d, J=9.2 Hz), 122.8, 125.6, 128.3, 129.4, 137.9, 138.1 (d, J=10.7 Hz), 141.0, 141.3 (ddd, J=260.9, 20.0, 13.8 Hz), 144.8 (ddd, J=261.6, 9.2, 4.6 Hz), 148.3, 150.6 (dd, J=257.8, 13.8 Hz). ^{19}F NMR (188 MHz, $CDCl_3$): δ=−128.9 (m, F), −143.8 (dd, J=15.3, 6.1 Hz, F), −151.4 (m, F). IR (KBr): ν=1658m, 1609m, 1573w, 1521s, 1496s, 1455s, 1444s, 1402s, 1336s, 1311m, 1288w, 1239w, 1216m, 1190m, 1147w, 1080m, 1064m, 1002s cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=272 nm (5.18). MS (ESI, MeOH): m/z=302.21 (100%, $(M+H)^+$). HRMS for $C_{13}H_4Cl_2F_3N$: calcd: 300.9672; found: 300.9698.

3.5.54. 9-Chloro-2-nitro-7-(trifluoromethoxy)acridine (8u). Compound **8u** (1.3 g, 84%) was prepared from **6u** (1.5 g, 4.4 mmol) following GP4. Mp 315 °C (decomp.). ^{1}H NMR (400 MHz, $CDCl_3$): 7.77 (dd, 1H, J=9.5, 2.5 Hz, H_{arom}), 8.30 (s, 1H, H_{arom}), 8.31 (d, 1H, J=9.5 Hz, H_{arom}), 8.35 (d, 1H, J=9.5 Hz, H_{arom}), 8.53 (dd, 1H, J=9.5, 2.5 Hz, H_{arom}), 9.40 (d, 1H, J=2.5 Hz, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ=113.8, 120.4 (q, J=259.0 Hz), 122.3, 122.9, 123.7, 124.8, 127.2, 132.3, 132.9, 144.1, 146.1, 148.1, 148.8, 149.5. ^{19}F NMR (188 MHz, $CDCl_3$): δ=−58.4 (s, OCF_3). IR (KBr): ν=3133m, 1636s, 1610s, 1579s, 1543m, 1517s, 1492s, 1404s, 1340s, 1266s, 1215s, 1150s, 1073m cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=255 nm (4.27). HRMS for $C_{14}H_6ClF_3N_2O_3$: calcd: 342.0019, found: 342.0007.

3.5.55. 9-Chloro-2,3,4-trifluoro-7-nitroacridine (8w). Compound **8w** (0.67 g, 84%) was prepared from **6w** (0.8 g, 2.6 mmol) following GP4. Mp 263–266 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 8.03 (ddd, 1H, J=10.4, 7.5, 2.1 Hz, H_{arom}), 8.45 (d, 1H, J=10.4 Hz, H_{arom}), 8.58 (dd, 1H, J=9.5, 2.5 Hz, H_{arom}), 9.39 (dd, 1H, J=2.5 Hz, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): 104.6 (dd, J=20.7, 5.4 Hz), 121.1 (d, J=9.2 Hz), 122.1, 123.2, 124.2, 132.4, 140.0 (dd, J=10.2, 3.2 Hz), 142.3 (ddd, J=263.2, 22.25, 13.5 Hz), 144.1, 145.2 (ddd, J=263.2, 10.0, 4.5 Hz), 146.3, 149.1, 151.3 (ddd, J=258.6, 14.2, 1.9 Hz). ^{19}F NMR (188 MHz, $CDCl_3$): δ=−126.3 (m, F), −142.6 (m, F), −148.3 (m, F). IR (KBr): ν=3166w, 1687m, 1625s, 1491s, 1408s, 1296s, 1140m, 1052m cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=259 nm (4.19). MS (ESI, MeOH+TFA): m/z=313.1 (100%, $(M+H)^+$). HRMS for $C_{13}H_4ClF_3N_2O_2$: calcd: 311.9913; found: 300.9917.

References and notes

1. Girault, S.; Grellier, P.; Berecibar, A.; Maes, L.; Mouray, E.; Lemière, P.; Debreu, M.; Davioud-Charvet, E.; Sergheraert, C. *J. Med. Chem.* **2000**, *43*, 2646–2654.

2. Demeunynck, M.; Charmantray, F.; Martelli, A. *Curr. Pharm. Des.* **2001**, *7*, 1703–1724.
3. Brana, M.; Cacho, M.; de Pascual-Teresa, B.; Ramos, A. *Curr. Pharm. Des.* **2001**, *7*, 1745–1780.
4. El-Subbagh, H.; Abadi, A. H.; Al-Khames, A. H. *Arch. Pharm. Pharm. Med. Chem.* **1997**, *330*, 277–284.
5. Cholody, W.; Horowska, B.; Paradziej-Lukowicz, J.; Martelli, S.; Konopa, J. *J. Med. Chem.* **1996**, *39*, 1028–1032.
6. Chen, T.; Fico, R.; Canellakis, E. S. *J. Med. Chem.* **1978**, *21*, 868–874.
7. Denny, W.; Atwell, G. J.; Baguley, B. C.; Wakelin, L. P. G. *J. Med. Chem.* **1985**, *28*, 1568–1574.
8. Rewcastle, G.; Atwell, G. J.; Chambers, D.; Baguley, B. C.; Denny, W. A. *J. Med. Chem.* **1986**, *29*, 472–477.
9. Aguzzi, A.; Heikenwalder, M. *Nature* **2003**, *423*, 127–129.
10. Korth, C.; May, B. C.; Cohen, F. E.; Prusiner, S. B. *Proc. Natl. Acad. Sci.* **2001**, *98*, 9836–9841.
11. Ryou, C.; Legname, G.; Peretz, D.; Craig, J. C.; Baldwin, M. A.; Prusiner, S. B. *Lab. Invest.* **2003**, *83*, 837–843.
12. Turnbull, S.; Tabner, B.; Brown, D. R.; Allsop, D. *Neuroreport* **2003**, *14*, 1743–1745.
13. Kocisko, D.; Baron, G. S.; Rubenstein, R.; Chen, J.; Kuizon, S.; Caughey, B. *J. Virol.* **2003**, *77*, 10288–10294.
14. May, B. C.; Fafarman, A. T.; Hong, S. B.; Rogers, M.; Deady, L. W.; Prusiner, S. B.; Cohen, F. E. *Proc. Natl. Acad. Sci.* **2003**, *100*, 3416–3421.
15. Vogtherr, M.; Grimme, S.; Elshorst, B.; Jacobs, D.; Fiebig, K.; Griesinger, C.; Zahn, R. *J. Med. Chem.* **2003**, *46*, 3563–3564.
16. Folette, P. *Science* **2003**, *299*, 191–192.
17. Barret, A.; Tagliavini, F.; Forloni, G.; Bate, C.; Salmona, M.; Colombo, L.; De Luigi, A.; Limido, L.; Suardi, S.; Rossi, G.; Auvré, F.; Adjou, K.; Salès, N.; Williams, A.; Lasmézas, C.; Deslys, J. P. *J. Virol.* **2003**, *77*, 8462–8469.
18. Scoazec, J.; Krolak-Salmon, E.; Casez, O.; Besson, G.; Thobois, S.; Kopp, N.; Perret-Liaudet, A.; Streichenberger, N. *Ann. Neurol.* **2003**, *53*, 546–547.
19. El-Subbagh, H.; Abadi, A. H.; Al-Khames, A. H. *Arch. Pharm. Pharm. Med. Chem.* **1997**, *330*, 277.
20. Mueller, D.; Hudson, R. A.; Lee, C. *J. Am. Chem. Soc.* **1981**, *103*, 1860–1862.
21. Oza, V.; Petrassi, H. M.; Purkey, H. E.; Kelly, J. W. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1–6.
22. Green, N.; Palaninathan, S. K.; Sacchettini, J. C.; Kelly, J. W. *J. Am. Chem. Soc.* **2003**, *125*, 13404–13414.
23. Oza, V.; Smith, C.; Raman, B.; Koepf, E. K.; Lashuel, H. A.; Petrassi, H. M.; Chiang, K. P.; Powers, E. T.; Sachettinni, J.; Kelly, J. W. *J. Med. Chem.* **2002**, *45*, 321–332.
24. Baures, P.; Oza, V. B.; Peterson, A.; Kelly, J. W. *Bioorg. Med. Chem.* **1999**, *7*, 1339–1347.
25. Monge, A.; Martínez-Crespo, F.; Santamaría, L.; Narro, S.; López de Ceráin, A. *J. Heterocyclic Chem.* **1994**, *31*, 1455–1460.
26. Reisch, J.; Probst, W. *Arch. Pharm.* **1987**, *320*, 1065–1072.
27. Ionescu, M.; Hopartean, I. *Stud. Univ. Babes-Bolyai Chem.* **1972**, *17*, 105–109.
28. SanFilippo, L. *J. Org. Prep. Proc. Int.* **1991**, *23*, 130–132.
29. Finet, J.; Fedorov, A.; Combes, S.; Boyer, G. *Curr. Org. Chem.* **2002**, *6*, 597–626.
30. Ma, D.; Cai, Q.; Zhang, H. *Org. Lett.* **2003**, *5*, 2453–2455.
31. Ma, D.; Xia, C. *Org. Lett.* **2001**, *3*, 2583–2586.
32. Wolter, M.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 3803–3805.
33. Kwong, F.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 581–584.
34. Gamage, S. A.; Spicer, J. A.; Rewcastle, G. W.; Milton, J.; Sohal, S.; Dangerfield, W.; Mistry, P.; Vicker, N.; Charlton, P. A.; Denny, W. A. *J. Med. Chem.* **2002**, *45*, 740–743.
35. Ali, M. A.; Buchwald, S. L. *J. Org. Chem.* **2001**, *66*, 2560–2565.
36. Pellón, R.; Mamposo, T.; Carrasco, R.; Rodés, L. *Synth. Commun.* **1996**, *26*, 3877–3883.
37. Pellón, R.; Carrasco, R.; Rodés, L. *Synth. Commun.* **1993**, *23*, 1447–1453.
38. Razavi, Z.; McCapra, F. *Luminescence* **2000**, *15*, 239–244.
39. Saphier, M.; Masarwa, A.; Cohen, H.; Meyerstein, D. *Eur. J. Inorg. Chem.* **2002**, *5*, 1226–1234.
40. Kondratov, S.; Litvak, V. V.; Shein, S. M. *J. Org. Chem. USSR (Engl. Transl.)* **1977**, *13*, 1112–1117.
41. Van Dort, M.; Robins, D. M.; Wayburn, B. *J. Med. Chem.* **2000**, *43*, 3344–3347.
42. Hosangadi, B.; Dave, R. H. *Tetrahedron Lett.* **1996**, *37*, 6375–6378.
43. Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144–1157.
44. Kranenburg, M.; van der Burgt, Y. E.; Kramer, P. C. J.; van Leeuwen, P. W. N. M.; Goubitz, K.; Fraanje, J. *Organometallics* **1995**, *14*, 3081–3089.
45. Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158–1174.
46. Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 3694–3703.
47. Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722–9723.
48. Zhang, X.; Harris, M. C.; Sadighi, J. P.; Buchwald, S. L. *Can. J. Chem.* **2001**, *79*, 1799–1805.
49. Ozawa, F.; Kubo, A.; Hayashi, T. *Chem. Lett.* **1992**, *11*, 2177–2180.
50. El-Subbagh, H. I.; Abadi, A. H.; Al-Khamees, A. H. *Arch. Pharm. Pharm. Med. Chem.* **1997**, *330*, 277–284.
51. Mueller, D. M.; Hudson, R. A.; Lee, C. *J. Am. Chem. Soc.* **1981**, *103*, 1860–1862.
52. Mietzsch, F.; Mauss, A. *Fortschr. Teerfarbenfabr. Verw. Industriezweige* **1932**, *19*, 1167.
53. Ionescu, M.; Hopartean, I. *Stud. Univ. Babes-Bolyai Chem.* **1970**, *15*, 77–80.
54. Kikhteva, V. I.; Dykhanov, N. N. *Metody Poluch Khim. Reakt. Prep.* **1964**, *10*, 78–80.
55. Reisch, J.; Probst, W. *Arch. Pharm.* **1987**, *320*, 1065–1072.
56. Krishnegowda, G.; Thimmaiah, P.; Hegde, R.; Dass, C.; Houghton, P. J.; Thimmaiah, K. N. *Biorg. Med. Chem.* **2002**, *10*, 2367–2380.
57. Lormier, A. T.; Boyer, G.; Faure, R.; Galy, J. P. *Heterocycles* **2002**, *57*, 449–463.
58. Chatterjee, A.; Raychaudhuri, R. J. *Org. Chem.* **1968**, *33*, 2546–2547.
59. Chen, M. H.; Beylin, V. G.; Iakovleva, E.; Kesten, S. J.; Magano, J.; Vrieze, D. *Synth. Commun.* **2002**, *32*, 411–418.
60. Mauss, A. *Fortschr. Teerfarbenfabr. Verw. Industriezweige* **1932**, *19*, 1176–1178.
61. Giral, F.; Calderon, L. *Ciencia (Mexico City)* **1945**, *6*, 369–370.
62. Ledochowski, Z.; Ledochowski, A.; Borowski, E.; Wysocka, B.; Kikmunter, A.; Morawski, B.; Gawle, K.; Wypych, H. *Rocz. Chem.* **1960**, *34*, 63–70.

63. Samarin, A. S.; Shchurova, I. G. *Izv. Vyssh. Uchebn. Zaved. Khim. Khim. Tekhnol.* **1971**, *14*, 256–257.
64. Legrand, L.; Lozag'h, N. *Bull. Soc. Chim. Fr.* **1967**, 2067–2074.
65. Hörlein, U. *Arch. Pharmaz.* **1971**, *304*, 80–99.
66. Endel'man, E. S.; Danilenko, V. S.; Trinus, F. P.; Yufa, P. A.; Fadeicheva, A. G.; Muravov, I. I.; Fialkov, Yu. A.; Yagupol'skii, L. M. *Pharm. Chem. J. (Engl. Transl.)* **1973**, *7*, 755–759.
67. Banerji, A.; Cass, J. C.; Katritzky, A. R. *J. Chem. Soc. Perkin Trans. 1* **1977**, *10*, 1162–1166.
68. Ege, G.; Beisiegel, E.; Arnold, P. *Chem. Ber.* **1972**, *105*, 2898–2912.
69. Hannig, E.; Brummer, R. *Pharmazie* **1971**, *26*, 135–137.
70. Ullmann, F. *Justus Liebigs Ann. Chem.* **1907**, *355*, 352–354.
71. Ramana, D. V.; Srinivas, R.; Mahalakshni, P. *Org. Mass Spectrom.* **1991**, *26*, 305–310.
72. Wilkinson, J. H.; Finar, I. L. *J. Chem. Soc.,* **1947**, 759–762.
73. Horowska, B.; Ledochowski, A. *Rocz. Chem.* **1971**, *45*, 1447–1455.
74. Horiguchi, Y.; Sakuma, S.; Suzuki, H.; Sano, T. *Heterocycles* **2000**, *53*, 1305–1316.
75. Alvares, M.; Feliu, L.; Ajana, W.; Joule, J. A.; Fernandes-Puentes, J. L. *Eur. J. Org. Chem.* **2000**, *5*, 849–856.
76. Hellwinkel, D.; Melan, M. *Chem. Ber.* **1971**, *104*, 1001–1016.
77. Kondratov, S. A.; Litvak, V. V.; Shein, S. M. *J. Org. Chem. USSR (Engl. Transl.)* **1977**, *13*, 1112–1117.
78. Hangar, W. G.; Howell, W. C.; Johnson, A. W. *J. Chem. Soc.* **1958**, 496–504.
79. Sukhomlinov, A. K.; Maksimets, V. P. *Khim. Geterotsikl. Soedin.* **1966**, *3*, 416–419.
80. Ledochowski, A.; Zielinski, J.; Glowacki, A.; Maruszewski, J.; Irzykowska, A.; Stepnowska, K. *Rocz. Chem.* **1976**, *50*, 341–345.
81. Mager, S.; Hopartean, I.; Binisor, D. *Monatsh. Chem.* **1978**, *109*, 1393–1401.
82. Drosdow, N. S.; Lesnowa, N. S. *Zhurn. Obsch. Khim.* **1935**, *5*, 690–700.
83. Lormier, A. T.; Boyer, G.; Faure, R.; Galy, J. P. *Heterocycles* **2002**, *57*, 449–464.
84. SanFilippo, L. *J. Org. Prep. Proc. Int.* **1991**, *23*, 130–132.
85. Goodall, R. R.; Kermack, W. O. *J. Chem. Soc.* **1936**, 1163–1166.
86. Mazagova, D.; Sabolova, D.; Kristian, P.; Imrich, J.; Antalik, M.; Podhradsky, D. *Collect. Czech. Chem. Commun.* **1994**, *59*, 203–212.
87. Gaidukevich, A. N.; Sidom, M. B.; Bezuglyi, V. D. *J. Anal. Chem. USSR (Engl. Transl.)* **1977**, *32*, 1435–1439.
88. Hall, D. M.; Turner, E. E. *J. Chem. Soc.,* **1945**, 694–699.
89. Kimura, M.; Okabayashi, I.; Kato, A. *Chem. Pharm. Bull.* **1989**, *37*, 697–701.
90. Robidoux, S.; Guo, Y.; Damha, M. J. *Tetrahedron Lett.* **1995**, *36*, 6651–6654.
91. Faure, R.; Galzy, J.; Barbe, J.; Boukir, A. L.; Vincent, E. *Bull. Soc. Chim. Belg.* **1991**, *100*, 639–646.
92. Horowska, B.; Ledochowski, A. *Rocz. Chem.* **1968**, *42*, 1351–1355.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 5751–5758
Tetrahedron

Synthesis of pyrrolo[3,2-*b*]benzofurans and pyrrolo[3,2-*b*]naphthofurans via addition of a silyloxypyrrole to activated quinones

Margaret A. Brimble,* Caryn Burgess, Rosliana Halim, Maria Petersson and Jayanta Ray

Department of Chemistry, University of Auckland, 23 Symonds St., Auckland 1000, New Zealand

Received 15 March 2004; revised 13 April 2004; accepted 6 May 2004

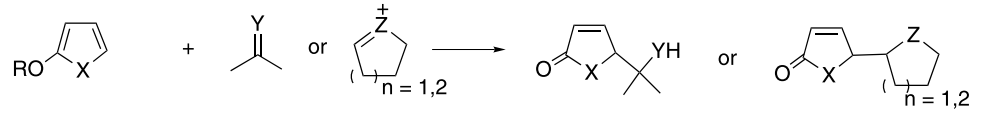
Abstract—The uncatalyzed reaction of *N*-(*tert*-butoxycarbonyl)-2-*tert*-butyldimethylsilyloxypyrrole **3** with 1,4-quinones bearing an electron withdrawing group at C-2 has been studied. Use of 1,4-quinones **4**, **5** bearing an ester group at C-2 provided an efficient synthesis of the respective pyrrolidinobenzofuran adduct **9** or pyrrolidinonaphthofuran adduct **10** whereas use of 1,4-quinones **6**, **7** and **8** bearing an acetyl group at C-2 afforded silyloxypyrroles **11**, **12** and **13** resulting from direct electrophilic substitution of the silyloxypyrrole by the electrophilic quinone. Addition of $Eu(fod)_3$ to the reaction of 2-acetyl-1,4-naphthoquinone **7** and 3-acetyl-5-methoxy-1,4-naphthoquinone **8** with *N*-(*tert*-butoxycarbonyl)-2-*tert*-butyldimethylsilyloxypyrrole **3** provided a method for obtaining the pyrrolidinonaphthofuran adducts **14** and **15** together with silyloxypyrroles **12** and **13**. Oxidative rearrangement of pyrrolidinonaphthofuran adduct **15** to pyrrolidino pyranonaphthoquinone **16** using ceric ammonium nitrate in acetonitrile provided a novel approach for the synthesis of an aza-analogue of the pyranonaphthoquinone antibiotic kalafungin.

1. Introduction

The silyl enolate d^4 synthons 2-trimethylsilyloxyfuran (TMSOF) **1**, 2-(*tert*-butyldimethylsilyloxy)thiophene (TBSOT) **2** and *N*-(*tert*-butoxycarbonyl)-2-*tert*-butyldimethylsilyloxypyrrole (TBSOP) **3** readily undergo vinylogous aldol-like reactions[1] with aldehydes, vinylogous imino–aldol reactions[2] (Mannich type addition) with imines and vinylogous addition to heteroatom-stablized carbenium ions (Scheme 1).[3] The resultant aldol-like products provide ready access to many bioactive molecules including the Annonaceous acetogenins,[4,5] carbasugars,[6] densely hydroxylated indolizidine alkaloids,[7] hydroxylated prolines,[8] aminosugars[9] and peptidyl *C*-glycosides.[10]

As an extension to this work we reported[11] the reaction of TMSOF **1** with 1,4-benzoquinones and 1,4-naphthoquinones bearing electron withdrawing substituents at C-2, proceeding via conjugate addition of TMSOF **1** to the 1,4-quinone before intramolecular cyclization to the corresponding furobenzofuran or furonaphthofuran. This atom efficient furofuran annulation formed our key step[12] in the synthesis of several pyranonaphthoquinone antibiotics[13] (e.g., kalafungin) by virtue of the fact that the furonaphthofuran adducts underwent facile oxidative cyclization to a pyranonaphthoquinone skeleton using ceric ammonium nitrate (CAN) (Scheme 2).

Prompted by the idea of preparing aza analogues of the pyranonaphthoquinone antibiotics via rearrangment of the analogous pyrrolidinofuran adducts we undertook a study of the addition of TBSOP **3** to several 1,4-quinones **4**-**8** bearing an electron withdrawing groups at C-2. Our preliminary communication[14] reported that the products obtained from

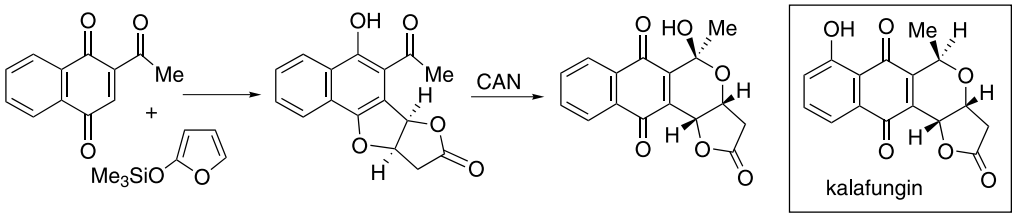


1: X = O; R = $SiMe_3$ Y = O, NH; Z = O, N
2: X = S; R= Si^tBuMe_2
3: X = $NCO_2{}^tBu$; R= Si^tBuMe_2

Scheme 1.

Keywords: Quinones; Pyrrole; Michael addition.
* Corresponding author. Tel.: +64-9-3737599; fax: +64-9-3737422; e-mail address: m.brimble@auckland.ac.nz

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.05.008



Scheme 2.

these reactions depended on the nature of the substituent at C-2 in the 1,4-quinone. Use of 2-acetyl-1,4-quinones afforded silyloxypyrrole adducts whereas 2-carbomethoxy-1,4-quinones afforded the desired pyrrolidinofuran adducts. We herein report the full details of this study together with a method for obtaining the pyrrolidinonaphthofuran adducts as well as the silyloxypyrrole intermediates in the addition of TBSOP **3** to 2-acetyl-1,4-naphthoquinones **7**,**8**. The pyrrolidinonaphthofuran products had hitherto eluded us. The preparation of pyrrolidinobenzofurans and pyrrolidinonaphthofurans is of interest due to their presence in BODIPY dyes[15] and the alkaloid phalarine.[16]

2. Results and discussion

Despite the fact that TBSOP **3** has been successfully used as a nucleophile in the addition to carbonyl and carbonyl-related compounds[1–3] its use as a nucleophile in Michael additions has been limited to using α-methylene lactones[17] as Michael acceptors. At the outset of this work a study of the addition of TBSOP **3** to quinones had not been reported however Garcia Ruano et al.[18] have since described the diastereoselective addition of TBSOP **3** to 2-(arylsulfinyl)-1,4-benzoquinones proceeding via the intermediacy of an α,β-unsaturated butyrolactam intermediate rather than a silyloxypyrrole intermediate. Earlier work by Eugster et al.[19] describes the addition of pyrroles to acetyl-1,4-quinones.

The synthesis of TBSOP **3** via silylation of 1,5-dihydropyrrol-2-one was carried out according to the previously reported procedure.[20] Quinones **4**,[21] **5**[22] and **6**[23] were prepared by mild oxidation of the corrresponding hydroquinones and quinones **7**[24] and **8**[25] were prepared by oxidation of 2-acetyl-1,4-dimethoxynaphthalene[26] and 3-acetyl-1,5-dimethoxy-4-naphthol,[25] respectively.

Uncatalyzed addition of TBSOP **3** (2.0 equiv.) to 2-methoxycarbonyl-1,4-benzoquinone **4** and 2-methoxycarbonyl-1,4-naphthoquinone **5** in acetonitrile at room temperature afforded pyrrolidinobenzofuran adduct **9** and pyrrolidinonaphthofuran adduct **10** in 36 and 54% isolated yield, respectively (Table 1). The adducts **9** and **10** decomposed substantially upon purification by flash chromatography and purification was also difficult due to the presence of significant quantities of *N*-Boc-pyrrol-2(5*H*)-one formed by thermal decomposition of TBSOP **3**. Adducts **9** and **10** were characterized by the magnitude of the bridgehead coupling constant $J_{3a,8b}$=5.1–5.4 Hz that clearly established the *cis*-fusion of the two five-membered rings.

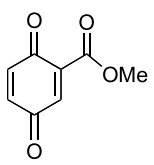
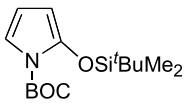
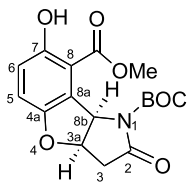
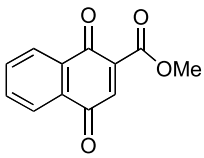
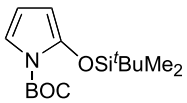
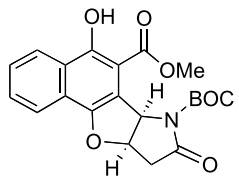
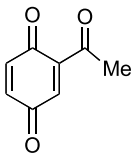
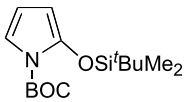
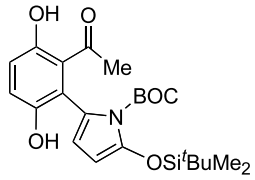
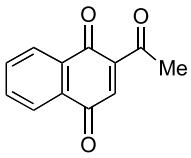
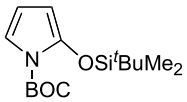
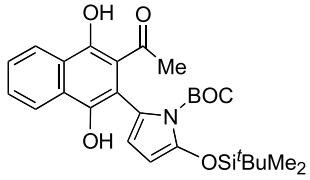
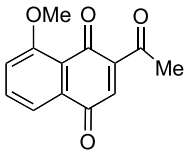
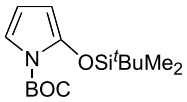
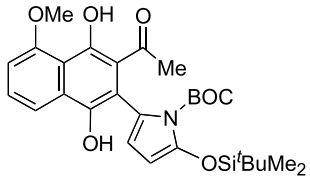
Analogous addition of TBSOP **3** to 2-acetyl-1,4-benzoquinone **6**, 2-acetyl-1,4-naphthoquinone **7** and 2-acetyl-8-methoxy-1,4-naphthoquinone **8** afforded hydroquinone-substituted silyloxypyrroles **11**, **12** and **13** in 56, 64 and 38% isolated yield, respectively. Thus, the use of the more electron deficient 2-acetyl substituted 1,4-quinones afforded products arising from direct electrophilic aromatic substitution of the pyrrole ring. Any evidence for formation of similar silyloxypyrroles in the ^{1}H NMR spectrum of the crude reaction mixtures obtained from addition of TBSOP **3** to the 2-methoxycarbonyl-substituted quinones **4** and **5** was not found.

The related study by Garcia Ruano et al.[18] on the addition of TBSOP **3** to 2-(arylsulfinyl)-1,4-benzoquinones reported the isolation of hydroquinone-substituted α,β-unsaturated butyrolactam intermediates rather than the hydroquinone-substituted silyloxypyrrole intermediates observed in the present work. These observations may be attributed to the reaction of 2-acetyl-1,4-quinones proceeding via a direct electrophilic substitution rather than a Michael addition pathway when using 2-(arylsulfinyl)-1,4-benzoquinones.

Despite the fact that subtle electronic differences in the nature of the quinone used afforded different products, it was hoped that silyloxypyrroles **12** and **13** could be converted to pyrrolidinonaphthofurans **14** and **15** which would then undergo oxidative rearrangement to a pyrrolidino pyranonaphthoquinone. In our earlier communication[14] we reported our inability to effect the smooth conversion of silyloxypyrroles **12** and **13** to the respective pyrrolidinonaphthofurans **14** and **15** using a variety of acidic, basic and fluoride-containing reagents. When the initial addition of TBSOP **3** to 2-acetyl-8-methoxy-1,4-naphthoquinone **8** was carried out in acetonitrile and pyridinium *p*-toluenesulfonate (PPTs) then added directly to the reaction mixture, pyrrolidinonaphthofuran **15** was afforded albeit in 13% yield. Garcio Ruano et al.[18] reported similar difficulties in inducing the cyclization of α,β-unsaturated butyrolactam intermediates to pyrrolidinobenzofurans using acidic conditions and they established that use of Eu(fod)$_3$ as a Lewis acid afforded the optimum yield of the pyrrolidinobenzofuran products rather than the butyrolactam intermediates.

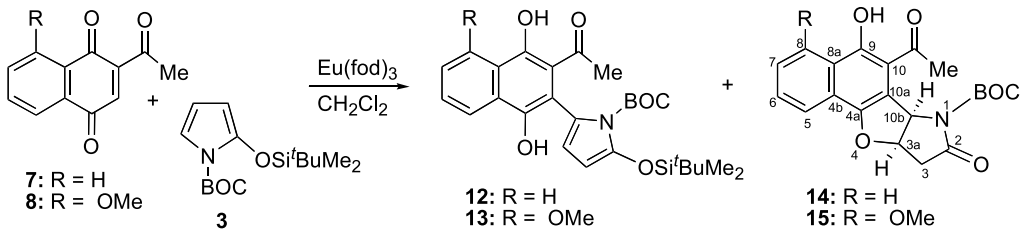
Prompted by the work of Garcia Ruano et al.[18] we subsequently investigated the use of Lewis acids to promote the addition of TBSOP **3** to 2-acetyl-1,4-naphthoquinone **7** hoping to access the pyrrolidinonaphthofuran **14** (Table 2). Use of $ZnBr_2$, $BF_3{\cdot}Et_2O$ and $SnCl_4$ met with little success and analogous to the work by Garcia Ruano et al.[18] the optimum results were obtained using Eu(fod)$_3$ as the Lewis acid.

Table 1. Uncatalyzed addition of *N*-(*tert*-butoxycarbonyl)-2-*tert*-butyldimethylsilyloxypyrole **3** to 2-substituted 1,4-benzoquinones and 1,4-naphthoquinones[a]

Quinone	Reagents	Product and yield %
 **4**		 **9** (36%)
 **5**		 **10** (54%)
 **6**		 **11** (56%)
 **7**		 **12** (64%)
 **8**		 **13** (38%)

[a] All reactions carried out using **3** (2.0 equiv.) in acetonitrile at room temperature for 16 h.

Table 2. $Eu(fod)_3$ catalyzed addition of *N*-(*tert*-butoxycarbonyl)-2-*tert*-butyldimethylsilyloxypyrole **3** to 2-acetyl-1,4-quinones



Quinone (1.0 equiv.)	equiv. of **3**	$Eu(fod)_3$ (equiv.)	Reaction temperature (time)[a]	Products (yield %)
7	2.0	2.0	−78 °C (30 min)	**14** (5%)
7	2.0	1.0	−78 °C (1 h) then rt (16 h)	**12** (46%) **14** (13%)
7	1.0	1.0	−78 °C (1 h) then rt (16 h)	**12** (43%) **14** (33%)
7	1.0	0.5	−78 °C (1 h) then rt (16 h)	**14** (3%)
8	1.0	1.0	−78 °C (1 h) then rt (16 h)	**13** (42%) **15** (38%)

[a] All reactions were carried out in dichloromethane.

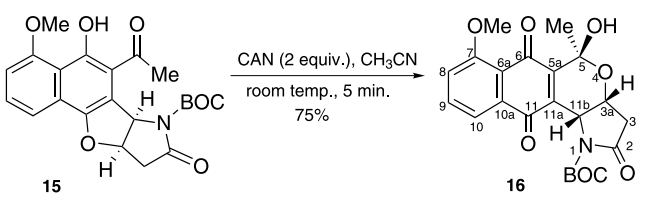
In the first attempt to carry out this reaction, TBSOP **3** (2.0 equiv.) was added to 2-acetyl-1,4-naphthoquinone **7** (1.0 equiv.) and Eu(fod)$_3$ (2 equiv.) in dichloromethane at −78 °C for 30 min. Disappointingly, this procedure afforded the desired adduct **14** in only 5% yield after purification by flash chromatography. In an attempt to improve the yield of the Lewis acid promoted reaction, the reaction was repeated several times varying the ratio of naphthoquinone: pyrrole: Eu(fod)$_3$ as well as extending the reaction time to 16 h.

The optimum conditions (entry 3, Table 2) involved the use of TBSOP **3** (1.0 equiv.), 2-acetyl-1,4-naphthoquinone **7** (1.0 equiv.) and Eu(fod)$_3$ (1.0 equiv.) in dichloromethane at −78 °C for 1 h followed by warming the reaction to room temperature for a further 16 h. This procedure afforded the desired adduct **14** in 33% yield together with silyloxypyrrole **12** in 43% yield. Use of 2.0 equiv. of TBSOP **3** (entry 2, Table 2) afforded less of the desired adduct (13%) and more of the silyloxypyrrole **12** (46%) whilst use of less Eu(fod)$_3$ (0.5 equiv.) (entry 4, Table 2) was ineffective. It was therefore concluded that the use of a stoichiometric quantity of the Lewis acid was necessary for optimum reaction.

Attempts to effect subsequent conversion of the silyloxypyrrole **12** isolated from this reaction to pyrrolidinonaphthofuran **14** using Eu(fod)$_3$ (2.0 equiv.) proceeded in only 5% yield. This result suggests that it is better to use Eu(fod)$_3$ as a Lewis acid in the initial addition of TBSOP **3** to 2-acetyl-1,4-naphthoquinone **7** to achieve optimum formation of pyrrolidinonaphthofuran **14**.

The spectroscopic data obtained for pyrrolidinonaphthofuran **14** supported the formation of the desired product. The high resolution mass spectrum exhibited a molecular ion at *m/z* 383.1371 (M^+) supporting the molecular formula $C_{21}H_{21}NO_6$. The ^{1}H NMR spectrum exhibited a characteristic singlet at δ_H 12.99 that was assigned to the newly introduced hydroxyl group. The characteristic downfield nature of this singlet was attributed to intramolecular hydrogen bonding to the acetyl group. Two single proton doublet of doublets at δ_H 3.02 and 3.13 were assigned to the two geminal H-3 protons consistent with the loss of aromaticity from the starting TBSOP **3**. Further distinctive resonances at δ_H 5.34 (triplet, $J_{3a,10b}$=5.1 Hz) and 5.84 (doublet, $J_{3a,10b}$=5.1 Hz) were assigned to the bridgehead protons H-3a and H-10b respectively. The magnitude of the bridgehead coupling constant, $J_{3a,10b}$=5.1 Hz, was consistent with *cis*-fusion of the two five membered rings.

In a similar fashion addition of TBSOP **3** (1.0 equiv.) to 2-acetyl-8-methoxy-1,4-naphthoquinone **8** (1.0 equiv.) in the presence of Eu(fod)$_3$ (1.0 equiv.) in dichloromethane at



Scheme 3.

−78 °C for 1 h afforded the pyrrolidinonaphthofuran **15** in 38% yield together with silyloxypyrrole **13** in 42% yield. It was then rewarding to find that pyrrolidinonaphthofuran **15** underwent smooth oxidative rearrangement to the desired pyrrolidino pyranonaphthoquinone **16** in good yield (Scheme 3) using ceric ammonium nitrate (CAN). The stereochemistry at the hydroxyl centre in **16** was assigned by analogy to that observed for similar rearrangements of furonaphthofurans to furonaphthopyrans.[12a] The successful formation of pyrrolidino pyranonaphthoquinone **16** provides a novel approch to the basic skeleton required for the synthesis of aza analogues of the pyranonaphthoquinone family of antibiotics such as kalafungin.

In summary a study of the addition of TBSOP **3** to several electron deficient quinones is reported. Uncatalyzed addition of TBSOP **3** to 1,4-quinones **4** and **5** bearing carbomethoxy substituents at C-2, affords pyrrolidinobenzofuran **9** or pyrrolidinonaphthofuran **10**, respectively. In the case of the 2-acetyl-1,4-quinones **6**, **7** and **8** the uncatalyzed reaction affords the silyloxypyrrole intermediates and the use of the Lewis acid Eu(fod)$_3$ is required to obtain significant amounts of the pyrrolidinonaphthofuran adducts. These pyrrolidinonaphthofuran adducts provide novel heterocyclic ring systems that can be further elaborated to provide aza analogues of natural products as demonstrated by the conversion of adduct **15** to an aza analogue **16** of the bioreductive alkylating agent kalafungin.

3. Experimental

3.1. General details

Melting points were determined using a Kofler hot stage apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer Spectrum One Fourier-transform infrared spectrophotometer as thin films or Nujol mulls between sodium chloride plates. Proton (^{1}H) nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 300 (300 MHz) or a Bruker DRX-400 (400 MHz) spectrometer at ambient temperature. Carbon (^{13}C) NMR spectra were recorded on a Bruker Avance 300 (75 MHz) or a Bruker DRX 400 (100 MHz) spectrometer at ambient temperature with complete proton decoupling. All spectra were recorded using $CDCl_3$ as the solvent with reference to residual $CHCl_3$ (^{1}H at 7.26 ppm and ^{13}C at 77.0 ppm). Low resolution mass spectra were recorded on a VG70-SE double focusing magnetic sector mass spectrometer operating with an ionisation potential of 70 eV. High resolution mass spectra were recorded at nominal resolution of 5000 or 10,000 as appropriate. Major fragments are given as percentages relative to the base peak and assigned where possible. Ionisation methods employed were either electron impact or chemical ionisation with ammonia or methane as reagent gas (CI). Fast atom bombardment (FAB) mass spectra were obtained using 3-nitrobenzyl alcohol as the matrix. Flash chromatography was performed using Merck Kieselgel 60 or Riedel-de-Haen Kieselgel S silica gel (both 230–400 mesh) with the indicated solvents. Compounds were visualized under ultraviolet light or by staining with iodine, alkaline permanganate or vanillin in methanolic sulfuric acid.

Acetonitrile was distilled from calcium hydride immediately before use.

3.1.1. *N*-(*tert*-Butoxycarbony)-2-*tert*-butyldimethylsilyl-oxypyrrole 3. To a solution of *tert*-butyl 2-oxo-1,5-dihydropyrrole-1-carboxylate and *tert*-butyl 2-oxo-1,3-dihydropyrrole-1-carboxylate[20] (2.87 g, 16.5 mmol) in anhydrous dichloromethane (12.0 mL) were added 2,6-lutidine (5.1 g, 47.2 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (4.64 g, 17.6 mmol) under nitrogen at room temperature. After the reaction mixture was stirred for 30 min, the solvent was removed under reduced pressure to afford a pale yellow oil. The oil was purified by flash chromatography using hexane–ethyl acetate (8:2) as eluent to afford the title compound **3** (3.45 g, 74%) as a yellow oil; δ_H (200 MHz, $CDCl_3$) 0.21 (6H, s, $SiMe_2$), 0.97 (9H, s, $SiMe_2^tBu$), 1.55 (9H, s, ^tBu), 5.21 (1H, dd, J=3.7, 2.0 Hz, H-3), 5.88 (1H, t, J=3.7 Hz, H-4), 6.67 (1H, dd, J=3.7, 2.0 Hz, H-5). The ^1H NMR data was in agreement with that reported in the literature.[27]

3.1.2. 2-Carbomethoxy-1,4-benzoquinone 4. A mixture of methyl 2,5-dihydroxybenzoate[28] (1.0 g, 6.0 mmol) and anhydrous sodium sulfate (1.5 g) in dry toluene (50.0 mL) was stirred with manganese dioxide (5.2 g, 60.0 mmol) for 2 h. The suspension was filtered through sodium sulfate and Celite and the filter cake was washed with toluene. The solvent was removed under reduced pressure to afford the title compound **4** (0.45 g, 46%) as an orange oil; δ_H (200 MHz, $CDCl_3$) 3.92 (3H, s, OMe), 6.83 (2H, d, J=1.2 Hz, H-5, H-6), 7.12 (1H, t, J=1.2 Hz, H-3). The NMR data was in agreement with the literature values.[21]

3.1.3. 2-Carbomethoxy-1,4-naphthoquinone 5. A mixture of methyl 1,4-dihydroxynaphthalene-2-carboxylate[22] (0.5 g, 2.29 mmol) and anhydrous sodium sulfate (2.0 g) in ethyl acetate (30 mL) was stirred with activated manganese dioxide (2.9 g, 34.4 mmol) at room temperature for 30 min. The suspension was filtered through Celite and the filter cake was washed with ethyl acetate. The solvent was removed under reduced pressure to afford the title compound **5** (0.25 g, 51%) as an orange solid. This material was satisfactory for use in the subsequent step without further purification; δ_H (200 MHz, $CDCl_3$) 3.81 (3H, s, OMe), 7.28 (1H, s, H-3), 7.82–8.16 (4H, m, H-5, H-6, H-7, H-8). The ^1H NMR data was in agreement with that reported in the literature.[22]

3.1.4. 2-Acetyl-1,4-benzoquinone 6. A mixture of 2,5-dihydroxyacetophenone (0.75 g, 4.9 mmol) and anhydrous sodium sulfate (1.25 g) in dry toluene (60.0 mL) was stirred with silver(I) oxide (5.6 g, 24.2 mmol) for 21 h. The suspension was filtered through sodium sulfate and Celite and the filter cake was washed with toluene. The solvent was removed under reduced pressure to afford orange crystals which were recrystallised from ether to afford the title compound **6** (0.51 g, 69%) as orange crystals, mp 63–65 °C (lit.[23] mp 64–65.5 °C); δ_H (200 MHz, $CDCl_3$) 2.57 (3H, s, Me), 6.83 (2H, apparent d, H-5, H-6), 7.01 (1H, t, J=1.8 Hz, H-3).

3.1.5. 2-Acetyl-1,4-naphthoquinone 7. 2-Acetyl-1,4-dimethoxynaphthalene[26] (40 mg, 0.17 mmol) and freshly prepared silver(II) oxide (340 mg, 2.78 mmol) were mixed in 1,4-dioxane (1.5 mL). To the mixture was added HNO_3 (0.46 mL, 6 mol L^{-1}) and the reaction stirred for 10 min. The reaction mixture was then quenched with H_2O (4 mL) and extracted with dichloromethane (4×8 mL). The organic layer was collected, washed with H_2O (20 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure to afford the title compound **7** (35 mg, 99%) as an orange solid, mp 81–83 °C (lit.[24] mp 80–84 °C).

3.1.6. 3-Acetyl-5-methoxy-1,4-naphthoquinone 8. A solution of ceric ammonium nitrate (470 mg, 0.86 mmol) in water (2.8 mL) was added dropwise to a solution of 3-acetyl-1,5-dimethoxy-4-naphthol[25] (85 mg, 0.34 mmol) in acetonitrile (7.2 mL). After stirring for 5 min, the mixture was diluted with dichloromethane (30 mL), washed with water (3×20 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure to give the title compound **8** (76.6 mg, 97%) as a yellow-orange solid, mp 102–104 °C (lit.[24] mp 101–105 °C).

3.1.7. *tert*-Butyl (3a*S,8b*S**)-8-methoxycarbonyl-7-hydroxy-2-oxo-2,3,3a,8b-tetrahydro-1*H*-[1]benzofuro[3,2-*b*]pyrrole-1-carboxylate 9.** To an ice-cooled solution of 2-methoxycarbonyl-1,4-benzoquinone 4 (200 mg, 1.2 mmol) dissolved in acetonitrile (8 mL) was added a solution of TBSOP 3 (700 mg, 2.36 mmol) in acetonitrile (12 mL) dropwise under nitrogen. After stirring for 2 h, the solution was warmed to room temperature then stirred for 18 h. The solvent was removed under reduced pressure to afford a brown residue that was purified by flash chromatography using hexane–ethyl acetate (gradient elution 9:1 to 4:6) as eluent to afford the title compound **9** (150 mg, 36%) as colourless crystals, mp 114–116 °C, (Found: M^+, 349.1159, $C_{17}H_{19}NO_7$ requires 349.1161); ν_{max} (film)/cm^{-1} 3295v (OH), 2984m, 1754m (C=O), 1728m (C=O), 1683m (C=O); δ_H (400 MHz, $CDCl_3$) 1.43 (9H, s, ^tBu), 2.94 (2H, apparent d, J=5.1 Hz, H-3), 3.95 (3H, s, OMe), 5.14 (1H, t, $J_{3a,8b}$=5.1 Hz, $J_{3a,3}$=5.1 Hz, H-3a), 5.81 (1H, d, $J_{3a,8b}$=5.1 Hz, H-8b), 6.93 (2H, apparent s, H-5, H-6), 9.65 (1H, s, OH); δ_C (100 MHz, $CDCl_3$) 27.8 (CH_3, C*Me*$_3$), 38.0 (CH_2, C-3), 52.1 (CH_3, OMe), 64.2 (CH, C-8b), 79.3 (CH, C-3a), 83.7 (C, *C*Me$_3$), 112.7 (C, C-8), 116.5 (CH, C-6), 119.9 (CH, C-5), 123.7 (C, C-8a), 150.2 (C, C-7), 154.0 (C, C-4a), 154.4 (C, NCO_2), 170.1 (C, C-2), 170.3 (C, CO_2Me); *m*/*z* 349 (M^+, 4%), 276 (M−O^{t}Bu, 3), 249 (70), 217 (100).

3.1.8. *tert*-Butyl (3a*S,10b*S**)-10-carbomethoxy-9-hydroxy-2-oxo-2,3,3a,10b-tetrahydro-1*H*-[1]naphthofuro[3,2-*b*]pyrrole-1-carboxylate 10.** To an ice-cooled solution of 2-carbomethoxy-1,4-naphthoquinone **5** (110 mg, 0.509 mmol) in acetonitrile (7 mL) was added a solution of TBSOP **3** (300 mg, 1.02 mmol) in acetonitrile (6 mL) dropwise under nitrogen. After stirring for 1 h, the solution was warmed to room temperature then stirred overnight. The solvent was removed under reduced pressure to afford a brown residue that was purified by flash chromatography using hexane–ethyl acetate (7:3) as eluent to afford the title compound **10** (110 mg, 54%) as a red solid, mp >300 °C decomp., (Found: M^+, 399.1316, $C_{21}H_{21}NO_7$ requires 399.1316); ν_{max} (film)/cm^{-1} 3053m (OH), 2986m, 1750m (C=O), 1729m (C=O), 1265s (C–O); δ_H (300 MHz,

$CDCl_3$) 1.41 (9H, s, ^{t}Bu), 3.04 (2H, apparent d, J=5.4 Hz, H-3), 3.99 (3H, s, OMe), 5.28 (1H, t, J=5.4 Hz, H-3a), 5.93 (1H, d, J=5.4 Hz, H-10b), 7.59 (2H, m, H-6 and H-7), 7.89 (1H, m, H-5), 8.59 (1H, m, H-8), 11.09 (1H, s, OH); δ_C (100 MHz, $CDCl_3$) 27.8 (CH_3, C*Me*$_3$), 38.1 (CH_2, C-3), 52.0 (CH_3, OMe), 65.7 (CH, C-10b), 79.4 (CH, C-3a), 83.5 (C, *C*Me$_3$), 105.1 (C, C-10), 114.5 (C, C-10a), 121.7 (CH, C-5), 123.5 (C, C-4b), 124.3 (C, C-8a), 126.2 (CH, C-7), 129.0 (CH, C-6), 150.2 (C, C-4a), 150.3 (C, NCO_2), 154.0 (C, C-9), 179.5 (C, C-2), 171.2 (C, CO_2Me); *m*/*z* 399 (M^+, 3%), 326 (M−O^{t}Bu, 1), 299 (62), 267 (100).

3.1.9. *tert*-Butyl 2-(2-acetyl-1,4-dihydroxy-3-phenyl)-5-(*tert*-butyldimethylsilyloxy)-1*H*-pyrrole-1-carboxylate 11. To an ice-cooled solution of 2-acetyl-1,4-benzoquinone **6** (200 mg, 1.33 mmol) dissolved in acetonitrile (6 mL) was added a solution of TBSOP **3** (790 mg, 2.66 mmol) in acetonitrile (14 mL) dropwise with stirring under nitrogen. After 20 h the solvent was removed under reduced pressure to afford a brown residue that was purified by flash chromatography using hexane–ethyl acetate as eluent (gradient elution 9:1 to 1:9) to afford the title compound **11** (334 mg, 56%) as yellow crystals, mp 94–97 °C, (Found: M^+, 447.2076, $C_{22}H_{33}NO_6Si$ requires 447.2077); ν_{max} (film)/cm^{-1} 3338v (OH), 2929m, 1763m (NC=O), 1621m (C=O), 1290m (Si–C); δ_H (400 MHz, $CDCl_3$) 0.25 (6H, s, Si*Me*$_2^t$Bu), 1.01 (9H, s, SiMe$_2^t$Bu), 1.20 (9H, s, ^{t}Bu), 2.03 (3H, s, COMe), 4.30 (1H, s, OH), 5.46 (1H, d, J=3.6 Hz, H-4), 6.00 (1H, d, J=3.6 Hz, H-3), 6.92 (1H, d, J=8.9 Hz, H-6′), 7.08 (1H, d, J=8.9 Hz, H-5′), 11.69 (1H, s, OH); δ_C (100 MHz, $CDCl_3$) −5.1 (CH_3, Si*Me*Me^{t}Bu), −4.9 (CH_3, SiMe*Me* ^{t}Bu), 18.1 (C, *C*Me$_3$), 25.5 (CH_3, SiMe$_2^t$Bu), 28.0 (CH_3, CO*Me*), 29.3 (CH_3, C*Me*$_3$), 92.6 (CH, C-4), 112.9 (CH, C-3), 116.8 (C, C-2), 119.0 (CH, C-6′), 120.4 (C, C-5), 121.1 (C, C-3′), 121.3 (C, C-2′), 122.7 (CH, C-5′), 145.7 (C, C-4′), 147.4 (C, C-1′), 155.5 (C, N*C*O$_2$), 205.9 (C, *C*OMe); *m*/*z* 447 (M^+, 11%), 391 (M−C_4H_8, 5), 347 (M−$C_4H_8CO_2$, 100), 316 (M−^{t}BuMe$_2$SiO, 20), 73 (O^{t}Bu, 90), 57 (C_4H_6, 62).

3.1.10. *tert*-Butyl 2-(3-acetyl-1,4-dihydroxy-2-naphthyl)-5-(*tert*-butyldimethylsilyloxy)-1*H*-pyrrole-1-carboxylate 12. To an ice-cooled solution of 2-acetyl-1,4-naphthoquinone **7** (16 mg, 0.08 mmol) in acetonitrile (1.5 mL) was added a solution of TBSOP **3** (47 mg, 0.16 mmol) in acetonitrile (1.5 mL) dropwise under nitrogen atmosphere. After 1 h, the mixture was warmed to room temperature and then left stirred overnight. The solvent was evaporated under reduced pressure to afford a brown residue that was purified by flash chromatography using hexane–ethyl acetate (95:5) as eluent to give the title compound **12** (25 mg, 64%) as a yellow oil, (Found: M^+, 497.2231, $C_{27}H_{35}NO_6Si$ requires 497.2234); ν_{max} (film)/cm^{-1} 3485v (OH), 2930m, 1754m (C=O), 1675m (C=O); δ_H (200 MHz, $CDCl_3$) 0.28 (6H, s, Si*Me*$_2^t$Bu), 1.02 (9H, s, SiMe$_2^t$Bu), 1.04 (9H, s, ^{t}Bu), 2.08 (3H, s, Me), 5.50 (1H, d, J=3.5 Hz, H-4), 6.14 (1H, d, J=3.5 Hz, H-3), 7.54–7.77 (2H, m, H-6′, H-7′), 8.18 (1H, d, J=8.0 Hz, H-5′), 8.48 (1H, d, J=7.7 Hz, H-8′); δ_C (50 MHz, $CDCl_3$) −4.9 (CH_3, $SiMe_2$), −4.8 (CH_3, SiMe2), 18.3 (C, Si*C*Me$_3$), 25.6 (CH3, SiC*Me*$_3$), 27.1 (CH_3, Me), 28.9 (CH_3, C*Me*$_3$), 84.0 (C, *C*Me$_3$), 92.6 (CH, C-4), 113.0 (CH, C-3), 114.5 (C, C-5), 117.0 (C, C-2), 119.4 (CH, C-8′), 122.6 (CH, C-5′), 124.5 (CH, C-6′), 126.9 (CH, C-7′), 127.8 (C, C-4a′), 143.3 (C, C-1′), 145.9 (C, C-4′), 157.4 (C, NCO), 205.4 (C, *C*OMe). Three quaternary carbons (C-2′, C-3′ and C-8a′) were not observed; *m*/*z* 497 (M^+, 12%), 366 (M−^{t}BuMe$_2$SiO, 33), 73 (O^{t}Bu, 100), 57 (C_4H_6, 46).

3.1.11. *tert*-Butyl 2-(3-acetyl-5-methoxy-1,4-dihydroxy-2-naphthyl)-5-(*tert*-butyldimethylsilyloxy)-1*H*-pyrrole-1-carboxylate 13. To an ice-cooled solution of 2-acetyl-8-methoxy-1,4-naphthoquinone **8** (30 mg, 0.156 mmol) in acetonitrile (2 mL) was added a solution of TBSOP **3** (78 mg, 0.313 mmol) in acetonitrile (1.5 mL) dropwise under nitrogen. After 1 h, the solution was warmed to room temperature then stirred overnight. The solvent was removed under reduced pressure to afford a brown residue which was purified by flash chromatography using hexane–ethyl acetate (4:1) as eluent to afford the title compound **13** (26 mg, 38%) as a yellow oil, (Found: M^+, 527.2334, $C_{28}H_{37}NO_7Si$ requires 527.2339); δ_H (300 MHz, $CDCl_3$) 0.27 (6H, d, J=1.6 Hz, *Me*$_2^t$BuSi), 1.01 (9H, s, Me$_2^t$BuSi), 1.10 (9H, s, ^{t}Bu), 2.22 (3H, s, COMe), 4.06 (3H, s, OMe), 5.41 (1H, d, J=3.5 Hz, H-4), 5.58 (1H, s, OH), 6.04 (1H, d, J=3.5 Hz, H-3), 6.91 (1H, d, J=8.0 Hz, H-6′), 7.45 (1H, t, J=8.0 Hz, H-7′), 7.82 (1H, d, J=8.0 Hz, H-8′), 11.32 (1H, s, OH); *m*/*z* 527 (M^+, 10%), 366 (M−^{t}BuMe$_2$SiO, 36), 73 (O^{t}Bu, 100), 57 (C_4H_6, 41).

3.1.12. *tert*-Butyl (3a*S,10b*S**)-10-acetyl-9-hydroxy-2-oxo-2,3,3a,10b-tetrahydro-1*H*-[1]naphthofuro[3,2-*b*]pyrrole-1-carboxylate 14.** To a solution of 2-acetyl-1,4-naphthoquinone **7** (30 mg, 0.15 mmol) in anhydrous dichloromethane (4 mL) was added Eu(fod)$_3$ (158 mg, 0.15 mmol) and the mixture was stirred under nitrogen at room temperature for 50 min. The mixture was then cooled to −78 °C and a solution of TBSOP **3** (43 mg, 0.15 mmol) in anhydrous dichloromethane (2 mL) was added dropwise. The mixture was then warmed to room temperature and stirred for 16 h. The reaction mixture was quenched with H_2O (5 mL) and extracted with dichloromethane (3×5 mL). The combined organic extracts were washed with H_2O (10 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure to give a red–brown oil that was purified by flash chromatography with hexane–ethyl acetate (9:1 then 8:2 then 1:1) as eluent to give the title compound **14** (19 mg, 33%) as a yellow oil, (Found: M^+, 383.1371, $C_{21}H_{21}NO_6$ requires 383.1369); ν_{max} (film)/cm^{-1} 3445br (OH), 1773m (C=O), 1714m (C=O); δ_H (300 MHz, $CDCl_3$) 1.38 (9H, s, ^{t}Bu), 2.83 (3H, s, CO*Me*), 3.02 (1H, dd, J=18.0, 5.1 Hz, H-3A), 3.13 (1H, d, J=18 Hz, H-3B), 5.34 (1H, t, J=5.1 Hz, H-3a), 5.84 (1H, d, J=5.1 Hz, H-10b), 7.57 (1H, ddd, J=7.5, 7.5, 1.5 Hz, H-7), 7.63 (1H, ddd, J=7.5, 7.5, 1.5 Hz, H-6), 7.89 (1H, ddd, J=7.5, 1.5, 0.6 Hz, H-5), 8.40 (1H, ddd, J=7.5, 1.5, 0.6 Hz, H-8), 12.99 (1H, s, OH); δ_C (75 MHz, $CDCl_3$) 27.7 (CH_3, C*Me*$_3$) 31.5 (CH_3, CO*Me*), 38.3 (CH_2, C-3), 66.2 (CH, C-10b), 78.3 (CH, C-3a), 83.0 (C, *C*Me$_3$), 84.0 (C, C-10), 113.2 (C, C-10a), 121.9 (CH, C-5), 123.9 (C, C-8a), 124.9 (CH, C-8), 127.0 (C, C-4b), 127.5 (CH, C-7), 129.6 (CH, C-6), 149.5 (C, C-4a), 150.6 (C, NCO_2), 155.1 (C, C-9), 169.1 (C, C-2), 204.1 (C, *C*OMe); *m*/*z* (EI) 383 (M^+, 3%), 310 (M−O^{t}Bu, 3), 283 (M−^{t}Bu–COMe, 66), 239 (M−CO_2^tBu–COMe, 70), 73 (O^{t}Bu, 100). Silyloxypyrrole **12** (32 mg, 43%) was also recovered from the reaction.

3.1.13. *tert*-Butyl (3a*S,10b*S**)-10-acetyl-9-hydroxy-8-methoxy-2-oxo-2,3,3a,10b-tetrahydro-1*H*-[1]naphtho-furo[3,2-*b*]pyrrole-1-carboxylate 15.** To a solution of 2-acetyl-8-methoxy-1,4-naphthoquinone **8** (36 mg, 0.16 mmol) in anhydrous dichloromethane (4 mL) was added $Eu(fod)_3$ (160 mg, 0.16 mmol) and the mixture was stirred under nitrogen at room temperature for 50 min. The mixture was then cooled to −78 °C and a solution of TBSOP **3** (46 mg, 0.16 mmol) in anhydrous dichloromethane (2 mL) was added dropwise. The mixture was then warmed to room temperature and stirred for 16 h. The reaction mixture was quenched with H_2O (5 mL) and extracted with dichloromethane (3×5 mL). The combined organic extracts were washed with H_2O (10 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure to give a red–brown oil that was purified by flash chromatography with hexane–ethyl acetate (9:1 then 8:2 then 1:1) as eluent to give the title compound **15** (24 mg, 38%) as a yellow oil, (Found: M^+, 413.1464, $C_{22}H_{23}NO_7$ requires 413.1475); ν_{max} (film)/cm^{-1} 3399b (OH), 1753m (C=O), 1638s (C=O), 1265s (C–O); δ_H (300 MHz, $CDCl_3$) 1.47 (9H, s, ^{t}Bu), 2.78 (3H, s, Me), 2.96–3.14 (2H, m, H-3), 4.09 (3H, s, OMe), 5.29 (1H, t, *J*=5.4 Hz, H-3a), 5.87 (1H, d, *J*=5.4 Hz, H-10b), 6.91 (1H, d, *J*=7.7 Hz, H-7), 7.43 (1H, t, *J*=7.7 Hz, H-6), 7.54 (1H, d, *J*=7.7 Hz, H-5), 9.73 (1H, s, OH); δ_C (75 MHz, $CDCl_3$) 29.0 (CH_3, C*Me*$_3$), 31.9 (CH_3, COMe), 38.3 (CH_2, C-3), 56.3 (CH_3, OMe), 63.5 (CH, C-10b), 79.4 (CH, C-3a), 83.5 (C, *C*Me_3), 106.5 (CH, C-7), 115.9 (CH, C-5), 115.9 (C, C-10a), 117.9 (C, C-8a), 121.1 (C, C-10), 123.5 (C, C-4b), 127.7 (CH, C-6), 148.3 (C, C-8), 150.3 (C, C-4a), 150.4 (C, NCO_2), 156.9 (C, C-8), 170.4 (C, C-2), 202.8 (C, COMe); *m*/*z* 413 (M^+, 4%), 340 (M−O^{t}Bu, 2), 73 (O^{t}Bu, 100). Silyloxypyrrole **12** (31 mg, 42%) was also recovered from the reaction.

3.1.14. *tert*-Butyl (3a*R,5*S**,11b*R**)-3,3a,5,11b-tetrahydro-5-hydroxy-7-methoxy-5-methyl-1*H*-[1]naphtho[2,3-*c*]pyran-2,6,11-trione-pyrrole-1-carboxylate 16.** To a solution of pyrrolidinonaphthofuran **15** (15 mg, 0.035 mmol) in acetonitrile (1.5 mL) was added dropwise a solution of ceric ammonium nitrate (39 mg, 0.07 mmol) in H_2O (1 mL) and the mixture stirred vigorously at 0 °C for 10 min. The reaction mixture was diluted with dichloromethane (5 mL) and H_2O (5 mL) and extracted with dichloromethane (3×5 mL). The combined organic extracts were washed with H_2O (5 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a yellow oil that was purified by flash chromatography using hexane–ethyl acetate (4:6) as eluent. Further purification by flash chromatography using hexane–ethyl acetate (8:2, then 7:3, then 1:1) afforded the title compound **16** (12 mg, 75%) as a yellow oil; (Found: MH^+, 430.1503, $C_{22}H_{24}NO_8$ requires 430.1502); ν_{max} (film)/cm^{-1} 3434br (OH), 1663m (C=O), 1262m (C–O); δ_H (400 MHz, $CDCl_3$) 1.39 (9H, s, ^{t}Bu), 1.73 (3H, s, Me), 2.67 (1H, d, *J*=17.2 Hz, H-3A), 2.81 (1H, dd, *J*=4.0, 17.2 Hz, H-3B), 4.03 (4H, s, OH and OMe), 4.52 (1H, dd, *J*=4.0, 2.4 Hz, H-3a), 5.06 (1H, d, *J*=2.4 Hz, H-11b), 7.32 (1H, dd, *J*=8.1, 1.5 Hz, H-8), 7.71–7.78 (2H, m, H-9, H-10); δ_C (100 MHz, $CDCl_3$) 27.9 (CH_3, C*Me*$_3$), 28.3 (CH_3, Me), 39.8 (CH_2, C-3), 50.0 (CH, C-11b), 56.5 (CH_3, OMe), 65.6 (CH, C-3a), 83.8 (C, CMe_3), 93.8 (C, C-5), 117.7 (CH, C-8), 119.5 (CH, C-10), 120.1 (C, *C*OCMe_3), 134.6 (C, C-10a), 135.6 (CH, C-9), 136.3 (C, C-11a), 143.8 (C, C-5a), 150.5 (C, C-6a), 159.6 (C, C-7), 171.5 (C, C-2), 183.5 (C, C-11), 184.5 (C, C-6); *m*/*z* (CI) 430 (MH^+, 1%), 154 (100), 136 (67).

Acknowledgements

Financial assistance from The University of Auckland Research Committee is gratefully acknowledged.

References and notes

1. For a recent review on the vinylogous aldol reaction see: Casiraghi, G.; Zanardi, F. *Chem. Rev.* **2000**, *100*, 1929.
2. For a recent review on the vinylogous Mannich reaction see: Bur, S. K.; Martin, S. F. *Tetrahedron* **2001**, *57*, 3221.
3. For reviews on the synthetic utility of these 2-silyloxy dienes see: (a) Rassu, G.; Zanardi, F.; Battistini, L.; Casiraghi, G. *Chem. Soc. Rev.* **2000**, *29*, 109. (b) Casiraghi, G.; Rassu, G. *Synthesis* **1995**, 607. (c) Casiraghi, G.; Rassu, G.; Zanardi, F.; Battistini, L. *Advances in Asymmetric Synthesis*; Hassner, A., Ed.; JAI: Stanford, 1998; Vol. 3, p 113.
4. Zanardi, F.; Battistini, L.; Rassu, G.; Auzzas, L.; Pinna, L.; Marzocchi, L.; Acquotti, D.; Casiraghi, G. *J. Org. Chem.* **2000**, *65*, 2048.
5. Pichon, M.; Jullian, J.-C.; Figadere, B.; Cave, A. *Tetrahedron Lett.* **1998**, *39*, 1755.
6. Rassu, G.; Auzzas, L.; Pinna, L.; Battistini, L.; Zanardi, F.; Marzocchi, L.; Acquottit, D.; Casiraghi, G. *J. Org. Chem.* **2000**, *65*, 6307.
7. Rassu, G.; Carta, P.; Pinna, L.; Battistini, L.; Zanardi, F.; Acquottit, D.; Casiraghi, G. *Eur. J. Org. Chem.* **1999**, 1395.
8. Zanardi, F.; Battistini, L.; Nespi, M.; Rassu, G.; Spanu, P.; Cornia, M.; Casiraghi, G. *Tetrahedron: Asymmetry* **1996**, *7*, 1167.
9. Spanu, P.; Rassu, G.; Ulgheri, F.; Zanardi, F.; Battistini, L.; Casiraghi, G. *Tetrahedron* **1996**, *52*, 4829.
10. Rassu, G.; Zanardi, F.; Batistini, L.; Casiraghi, G. *Tetrahedron: Asymmetry* **1995**, *6*, 371.
11. (a) Brimble, M. A.; Duncalf, L. J.; Reid, D. C. W. *Tetrahedron: Asymmetry* **1995**, *6*, 263. (b) Brimble, M. A.; Elliot, R. J. *Tetrahedron* **1997**, *53*, 7715. (c) Brimble, M. A.; McEwan, J. F.; Turner, P. *Tetrahedron: Asymmetry* **1998**, *9*, 1257.
12. (a) Brimble, M. A.; Stuart, S. J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 881. (b) Brimble, M. A. *Pure Appl. Chem.* **2000**, *72*, 1635.
13. For a review on the isolation and biological activity of pyranonaphthoquinone antibiotics see: Brimble, M. A.; Duncalf, L. J.; Nairn, M. R. *Nat. Prod. Rev.* **1999**, *16*, 267.
14. For a preliminary communication of this work see: Brimble, M. A.; Halim, R.; Petersson, M. *Tetrahedron Lett.* **2002**, *43*, 4777.
15. (a) Cheng, J.; Burhart, A.; Derecskei-Kovacs, A.; Burgess, K. *J. Org. Chem.* **2000**, *65*, 900. (b) Cheng, J.; Reibenspies, J.; Derecskei-Kovacs, A.; Burgess, K. J. *Chem. Commun.* **1999**, 2501.
16. Anderton, N.; Cockrum, P.; Peter, A.; Colegate, S. M.; Edgard, J. A.; Flower, K.; Gardner, D.; Willing, R. I. *Phytochemistry* **1999**, *51*, 153.

17. Marcos, I.; Redero, E.; Bermejo, F. *Tetrahedron Lett.* **2000**, *41*, 8451.
18. Aroyo, Y.; de Paz, M.; Rodriguez, J. F.; Sanz-Tejedor, M. A.; Garcia Ruano, J. L. *J. Org. Chem.* **2002**, *67*, 5638.
19. Kuser, P.; Frauenfelder, E.; Eugster, C. H. *Helv. Chim. Acta* **1971**, *54*, 969.
20. Casiraghi, G.; Rassu, G.; Spanu, P.; Pinna, L. *J. Org. Chem.* **1992**, *57*, 3760.
21. Schleusener, E.; Eugster, C. H. *Helv. Chim. Acta* **1972**, *55*, 986.
22. Brimble, M.; Spicer, J. A. *Aust. J. Chem.* **1991**, *44*, 197.
23. Kloetzel, M.; Dayton, R. P.; Abadir, B. Y. *J. Org. Chem.* **1955**, *20*, 38.
24. Read, G.; Ruiz, V. M. *J. Chem. Soc., Perkin Trans. 1* **1973**, 235.
25. Uno, H. *J. Org. Chem.* **1986**, *51*, 35.
26. Maruyama, M.; Kozuka, T. *Bull. Chem. Soc. Jpn* **1978**, *51*, 3586.
27. Rassu, G.; Zanardi, F.; Battistini, L.; Gaetani, E.; Casiraghi, G. *J. Med. Chem.* **1997**, *40*, 168.
28. Forest, J.; Petrow, V. *J. Chem. Soc.* **1950**, *3*, 2340.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 60 (2004) 5759–5767
Tetrahedron

Asymmetric synthesis of (+)-1-epiaustraline and attempted synthesis of australine

Minyan Tang and Stephen G. Pyne*

Department of Chemistry, University of Wollongong, Wollongong, Northfields Ave, New South Wales 2522, Australia

Received 7 March 2004; revised 14 April 2004; accepted 6 May 2004

Abstract—A diastereoselective synthesis of the pyrrolizidine alkaloid, (+)-1-epiaustraline has been achieved via a diastereoselective *syn*-dihydroxylation of a pyrrolo[1,2-*c*]oxazol-3-one precursor that was readily prepared by a RCM reaction. Attempts to extend this methodology to the synthesis of australine were not successful since the final pyrrolidine ring closure to produce the desired pyrrolizidine of the target molecule was not productive.

1. Introduction

Alexine (**1**) was the first alkaloid to be isolated with the 3-hydroxymethyl-2,3,5,6,7,7a-hexahydro-1*H*-pyrrolizine-1,2,7-triol structure in 1988.[1] In the same year its 7a-epimer, australine (**2**), was isolated from the seeds of *Castanospermum australe*.[2] Later reports described the isolation of other epimers of **2** from these seeds, including 1-epiaustraline **3**.[3,4] These alkaloids have been shown to have glycosidase inhibitory activities[2,3c,4] and other biological studies have revealed the potential of these and related polyhydroxylated pyrrolizidines as antiviral and anti-retroviral agents.[5] These interesting biological properties coupled with the polyfunctional and stereochemically rich nature of these compounds have attracted the attention of synthetic chemists resulting in the total synthesis of alexine,[6] and its epimers,[6,7] australine,[8] and its epimers,[7–11] and casuarine (Fig. 1).[12]

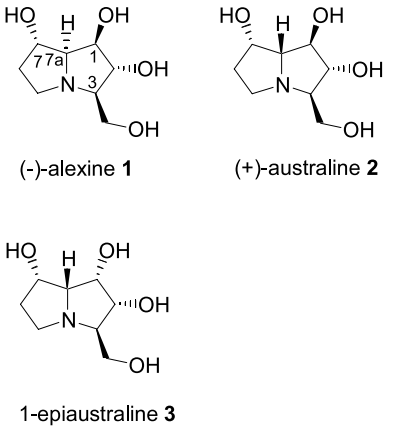


Figure 1. Structures of 3-hydroxymethyl pyrrolizidine.

In 2003 we reported a new and potentially general synthetic methodology for the synthesis of austaline and its epimers using aminolysis of a chiral vinyl epoxide and RCM as key reactions.[11] We demonstrated the viability of this synthestic methodology with the asymmetric synthesis of (−)-7-epiaustaline and (+)-1,7-diepiaustraline.[11] We report here, as an extension of this work, the synthesis of (+)-1-*epi*-australine and our attempts to prepare australine. These target molecules required that the starting vinyl epoxide **4** had the *cis*-[(3*R*, 4*S*)] stereochemistry rather than the *trans*-[(3*R*,4*R*)] stereochemistry used by us previously and it was of interest to examine the effect of this stereochemical difference on the diastereoselectivities of the reactions leading to our target molecules.

The starting vinyl epoxide (−)-(3*R*,4*S*)-**4** was prepared from the corresponding Sharpless epoxy alcohol (82% ee from ^{1}H NMR analysis of its Mosher ester, see experimental section) via Swern oxidation followed by a Wittig-olefination reaction.[11,13] A solution of the vinyl epoxide (−)-**4** and the (*S*)-allylamine **5**[14] (1.4 equiv., ca 99% ee) in acetonitrile was heated at 120 °C in a sealed tube using LiOTf (1.5 equiv.) as a catalyst for 3 days. This gave a mixture

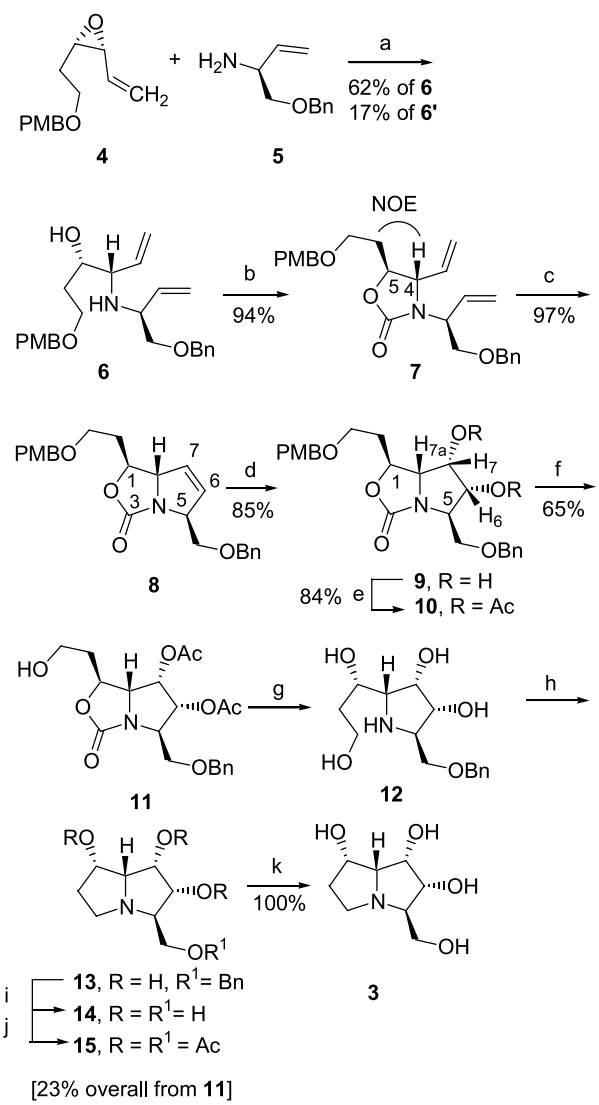
Keywords: Pyrrolizidine alkaloid; (+)-1-Epiaustraline; RCM.

Abbreviations: ArH, aromatic protons of PMB; Ar*H, aromatic protons of Bn or Ph; BzH, aromatic protons of Bz; $ArCH_2$, CH_2 of PMB; Ar*CH_2, CH_2 of Bn; ArC, quaternary aromatic carbons of PMB; Ar*C, quaternary aromatic carbons of Bn; ArCH, aromatic CH carbons of PMB; Ar*CH, aromatic CH carbons of Bn; BzCH, aromatic CH carbons of Bz.

* Corresponding author. Tel.: +612-4221-3511; fax: +612-4221-4287; e-mail address: spyne@uow.edu.au

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.05.010

of two diastereomeric products. Separation by PTLC gave the desired amino alcohol (+)-**6** in 62% yield and its diastereomer (structure not shown but referred to as compound **6′** in the experimental section) in 17% yield that arises from the reaction of *ent*-**4** with **5**. The amino-alcohol (+)-**6** was converted to the diastereomerically pure 2-oxazolidinone derivative (+)-**7** in 94% yield using triphosgene under basic conditions.[11,15] The minor diastereomeric amino-alcohol was converted to its corresponding 2-oxazolidinone derivative in 69% yield. In their ^{1}H NMR specta, $J_{4,5}$ for both 2-oxazolidinones was 7.5 Hz, while the NOESY spectra of these compounds showed strong cross peaks between H-4 and the *exo*-cyclic methylenes at C-5 (see Scheme 1 for details). This was consistent with both 2-oxazolidinones having the C-4, C-5 *trans*-stereochemistry which would arise from an S_N2 ring opening of **4** or *ent*-**4** with **5**.

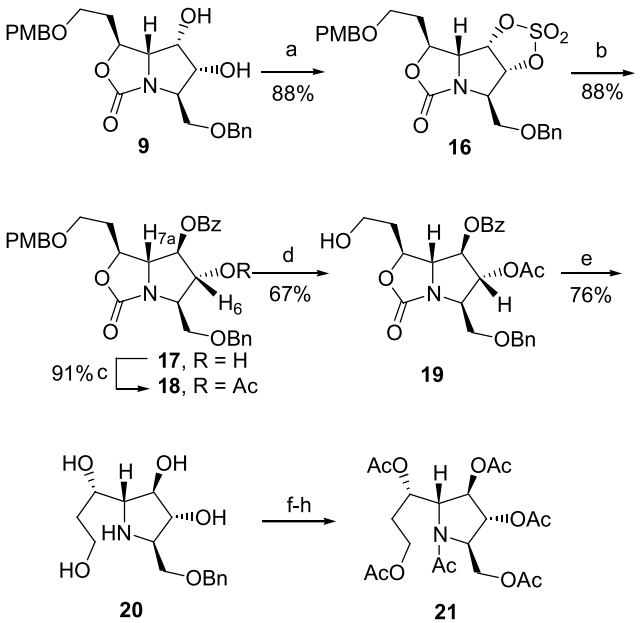


Scheme 1. Reagents and conditions: (a) LiOTf, CH_3CN, 120 °C, sealed tube, 72 h; (b) triphosgene, Et_3N, DCM, 0 °C, 2.5 h; (c) Grubbs' catalyst I, DCM, reflux, 3 days; (d) $K_2OsO_4{\cdot}2H_2O$, NMO, acetone, H_2O, RT, 21 h; (e) Ac_2O, pyridine, RT, 23 h; (f) DDQ, DCM, H_2O, RT, 5.5 h; (g) NaOH, EtOH, 70 °C, sealed tube, 37 h; (h) DIAD, PPh_3, pyridine, 0 °C, 4 h then RT 3 h; (i) $PdCl_2$, H_2, MeOH, RT, 1.5 h; (j) Ac_2O, pyridine, RT, 22 h; (k) Amberlyst A-26 (OH-form) resin, MeOH, RT, 2 h.

The RCM of **7** using standard conditions, 5–10 mol% of Grubbs I catalyst (benzylidenebis(tricyclohexylphosphine)ruthenium dichloride) in refluxing CH_2Cl_2 at high dilution (~4 mM) for 20 h, gave low conversion to the desired 2,5-dihydropyrrole (−)-**8**. However, by initiating the reaction using 22 mol% Grubbs I catalyst and then adding a further 9 mol% catalyst after 25 h, (−)-**8** could be isolated in 97% yield after a total of 42 h of heating at reflux.[16,17] Compound (−)-**8** was treated with 5 mol% $K_2OsO_4{\cdot}2H_2O$ and NMO (2.1 equiv.),[11,13] to effect *syn*-dihydroxylation (DH) of the double bond, giving diol (−)-**9** in good yield (85%). A small amount (<5%) of the C-6, C-7 di-epimeric diol was also formed but was readily separated by column chromatography. The stereochemistry of diol **9** was that expected from our previous studies with osmylation occurring from the concave face of the 2-oxazolidinone **8**.[11,17] This stereochemistry was evident from NOESY studies on its acetate **10** that showed significant cross peaks between H-6 and the *exo*-cyclic methylene at C-5 and between H-6 and H-7a. The absolute stereochemistry assigned to **9** was unequivocally confirmed by its conversion to (+)-1-epiaustraline (**3**).

Attempts to deprotect the primary PMB ether in **9** under oxidative conditions with DDQ[18] gave a poor yield of the desired primary alcohol due to the formation of several other products that could not be structurally identified. The diacetate derivative **10** however was smoothly converted to the primary alcohol **11** in 63% yield. Compound **11** was then converted to the pyrrolizidine-tetraacetate **15** in three synthetic steps. Base hydrolysis of **11** followed by ion-exchange chromatography gave **12** which was cyclized to the desired pyrrolizidine ring system under Mitsunobu conditions[12,19] in pyridine at 0 °C. The crude reaction mixture was then treated under hydrogenolysis conditions[12,13,20] and then peracetylation gave the pyrrolizidine-tetraacetate **15** in 23% over yield from **11**. Finally, methoxide catalysed removal of the acetates of **15** gave (+)-1-epiaustraline (**3**) in quantitative yield. This sample had identical spectral characteristics to those reported in the literature for (+)-**3**,[7c,10] and its specific rotation ($[\alpha]_D^{25}$=+14.3 (*c* 1.1, H_2O)) closely matched that previously reported (lit.[10a] ($[\alpha]_D^{25}$=+13.695 (*c* 1.72, H_2O)).

Scheme 2 outlines our attempted synthesis of australine (**2**). This synthesis required inversion of the stereochemistry at C-7 in the pyrrolo[1,2-*c*]oxazol-3-one **9**. Thus **9** was converted to its cyclic-sulfate **16** using thionyl chloride followed by oxidation of the resulting cyclic sulfite with catalytic ruthenium tetraoxide (88% yield for the two-step conversion).[11,21] Nucleophilic ring opening of the *S*,*S*-dioxo-dioxathiole ring of **16** with cesium benzoate,[11,21,22] followed by an acidic work up gave a 73:27 mixture of regioisomeric benzoates in 88% yield. The regioisomers were readily separated by column chromatography as their acetate derivatives. In this way the acetate **18** of the major regioisomer could be obtained in 66% yield while the acetate of the minor regioisomer was isolated in 25% yield. The structure of the major regioisomer **18** was established by NOESY experiments which showed significant cross peaks between H-6 the *exo*-cyclic methylene at C-5 and



Scheme 2. Reagents and conditions: (a) (i) $SOCl_2$, Et_3N, DCM, 0 °C, 30 min; (ii) $RuCl_3{\cdot}3H_2O$, $NaIO_4$, CCl_4:CH_3CN:H_2O=2:2:3, RT, 2 h; (b) (i) PhCOOH, Cs_2CO_3, DMF, 40 °C, 23 h; (ii) H_2SO_4 (conc.), THF, H_2O, RT, 18 h; (c) Ac_2O, pyridine, RT, 23 h; (d) DDQ, DCM, H_2O, RT, 2 h; (e) NaOH, EtOH, 70 °C, 19 h; (f) DIAD, PPh_3, THF, 0 °C, 3 h then RT, 3 h; (g) $PdCl_2$, H_2, MeOH, RT, 1 h; (h) Ac_2O, pyridine, RT, 15 h.

between H-6 and H-7a (see Scheme 2 for proton numbering). The modest regioselectivity found in the ring opening of **16** is in stark contrast to that of 1-*epi*-**16** which gave less than 5% of the other regioisomer resulting from attack of benzoate anion at C-6.[11] While, nucleophilic attack on **16** would be expected to occur preferentially at C-7, since backside attack at C-6 would be more sterically demanding due to the β-C-5 benzyloxymethyl substituent, the configuration at C-1 also clearly influences the regiochemistry of ring-opening. Thus the β-orientation of the C-1 substituent in **16** must be responsible for the reduced regioselectivity found in the ring opening of **16**. Oxidative removal of the primary PMB ether in **18** using DDQ gave the corresponding primary alcohol **19** in 67% yield. Base hydrolysis of the esters and the oxazolidinone ring of **19** gave the amino tetrol **20** in 76% yield. Attempted cyclization of **20** under Mitsunobu conditions proved problematic and hydrogenolysis of the crude reaction mixture and then peracetylation gave a mixture from which only the hexaacetate **21** could be isolated in low yield [12%, MS (ES+ve) *m/z* 460 ($M+H^+$, 27%)]. None of the desired peracetylated pyrrolizidine product could be detected. While we have always had poor yields for this type of cyclization reaction,[11,16] this is the first time it has not been successful.

In summary, we have developed diastereoselective synthesis of the pyrrolizidine alkaloid, (+)-1-*epi*-australine via a diastereoselective *syn*-dihydroxylation of a pyrrolo[1,2-*c*]oxazol-3-one precursor that was readily prepared by a RCM reaction. Attempts to extend this methodology to the synthesis of australine were not successful since the final pyrrolidine ring closure to produce the desired pyrrolizidine of the target molecule was not productive.

2. Experimental

2.1. General methods

All reactions were carried out under an atmosphere of nitrogen. All NMR spectra were obtained as a $CDCl_3$ solution at 300 MHz (^1H NMR) or 75 MHz (^{13}C NMR) unless otherwise stated and were referenced to the relevant solvent peak. ^{13}C NMR assignments were made from DEPT experiments. Silica gel chromatography was performed using Merck GF 254 flash silica gel packed by the slurry method. Small-scale separations (<2.0 g) were performed using either a 10 or 20 mm diameter column, and large-scale separations (>2.0 g) were performed using either a 30 or 50 mm diameter column, each with the stated solvent system. Specific rotations were measured using a 10 or a 50 mm cell, and the values quoted were an average of 5–10 measurements. They are reported by the following convention: optical rotation [10^{-1} deg cm^3 g^{-1}] (concentration, solvent). Acidic ion-exchange chromatography was performed using DOWEX 50WX8-50 acidic cation exchange resin, packed by the slurry method in 10 mm diameter column. In all cases the compounds were applied as their HCl salts dissolved in distilled water. The column was first eluted with water (100 mL) and then eluted with 14% ammonia solution (w/w). In all cases, HRMS (exact masses) were obtained on lieu of elemental analysis, and ^1H and ^{13}C NMR spectroscopy were used as criteria for purity.

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 1-(4′-methoxy)-benzyloxy-3-butyne (431 mg, 1.96 mmol) and quinoline (329 mg, 2.55 mmol) was added Pd/$CaCO_3$ (35.8 mg). The mixture was stirred at RT under a nitrogen atmosphere for 1.5 h. The mixture was then filtered through celite before the filtrate was washed with 1 M HCl (3×). The organic portion was dried with $MgSO_4$, filtered and evaporated to dryness in vacuo. Chromatography of the residue eluting with EtOAc/petrol (0–50%) gave the title compound (396 mg, 91%). ^1H NMR δ 7.22 (d, 2H, *J*=8.4 Hz, ArH), 6.85 (d, 2H, *J*=8.7 Hz, ArH), 5.73 (dt, 1H, *J*=10.8, 7.2 Hz, H-2), 5.53 (dt, 1H, *J*=10.8, 8.1 Hz, H-3), 4.41 (s, 2H, $ArCH_2$), 4.06 (d, 2H, *J*=6.9 Hz, H-1), 3.75 (s, 3H, OMe), 3.43 (t, 2H, *J*=6.0 Hz, H-5), 3.08 (bs, 1H, OH), 2.35 (td, 2H, *J*=7.2, 6.6 Hz, H-4); ^{13}C NMR δ 158.9 (ArC), 130.7 (CH-2), 129.7 (ArC), 129.1 (ArCH), 128.7 (CH-3), 113.5 (ArCH), 72.4 ($ArCH_2$), 68.6 (CH_2-5), 57.4 (CH_2-1), 54.9 (OMe), 27.7 (CH_2-4); MS (CI+ve) *m/z* 222 (M^+); HRMS (CI+ve) Calcd for $C_{13}H_{18}NO_3$ (M^+) 222.1256, found: 222.1253.

Step 2. (−)-5-(4-Methoxyphenyl)methoxy-2R,3S-epoxy-1-pentanol. To a mixture of titanium tetra-isopropoxide (1.6 mL, 5.35 mmol), 4 Å molecular sieves (1.93 g) in dry DCM (100 mL) were added D-(−)-diisopropyltartrate (1.4 mL, 6.42 mmol) and anhydrous *tert*-butyl hydroperoxide (5.3 mL, 26.2 mmol, 5.0 M) under N_2 at −40 °C. After 10 min, a solution of **1** (2.37 g, 10.7 mmol) in dry DCM (10 mL) was added. The resulting yellow mixture was stirred at −20 °C for 18 h. After this time, 10% aqueous tartaric acid (50 mL) was added dropwise and the mixture was allowed to warm to RT over 1 h until the solution was transparent. Then the organic layer was separated, washed

with brine and dried ($MgSO_4$). The solvent was evaporated in vacuo and the residue was chromatographed on silica gel. Elution with 30–100% EtOAc/petrol afforded the title compound (2.41 g, 95%) as a yellow oil. $[\alpha]_D^{24}=-10.5$ (*c*2.3, $CHCl_3$); ^{1}H NMR δ 7.25 (d, 2H, *J*=8.7 Hz, ArH), 6.89 (d, 2H, *J*=8.7 Hz, ArH), 4.47 (s, 2H, $ArCH_2$), 3.86 (ddd, 1H, *J*=12.0, 10.2, 5.1 Hz, H-1a), 3.80 (s, 3H, OMe), 3.68–3.54 (m, 2H, H-5), 3.46 (ddd, 1H, *J*=12.3, 8.7, 3.6 Hz, H-1b), 3.17 (dt, 1H, *J*=9.0, 4.5 Hz, H-2), 3.10 (dd, 1H, *J*=10.5, 3.3 Hz, OH), 3.02 (dt, 1H, *J*=9.6, 4.2 Hz, H-3), 2.09 (ddd, 1H, *J*=14.7, 3.9, 2.7 Hz, H-4a), 1.74 (dddd, 1H, *J*=14.4, 10.8, 9.3, 4.8 Hz, H-4b); ^{13}C NMR δ 159.4 (ArC), 129.6 (ArCH), 129.0 (ArC), 113.8 (ArCH), 73.1 ($ArCH_2$), 66.3 (CH_2-5), 59.8 (CH_2-1), 55.2 (CH-2), 55.1 (OMe), 54.8 (CH-3), 27.9 (CH_2-4); MS (CI+ve) *m/z* 238 (M^+); HRMS (CI+ve) Calcd for $C_{13}H_{18}NO_4$ (M^+) 238.1205, found: 238.1197.

Mosher ester analysis. (−)-5-(4-Methoxyphenyl)methoxy-2S,3S-epoxy-1-pentyl-(R)-α-methoxy-α(trifluoromethly)-phenyl acetate. 5-(4-Methoxy)benzyloxy-2*R*,3*S*-epoxy-1-pentanol (25 mg, 0.103 mmol) was dissolved in dry DCM (0.9 mL), then triethylamine (90 μL), 4-dimethylaminopyridine (13 mg, 0.108 mmol) and *R*-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (21 μL, 0.113 mmol) were added. The mixture was stirred at RT for 15 min. All the volatiles were removed in vacuo to give a dark semi-solid which was purified by column chromatography (15–30% EtOAc/petrol) to give a pale yellow oil (42 mg, 90, 82% ee). $[\alpha]_D^{24}=-31.0$ (*c* 2.1, $CHCl_3$); ^{1}H NMR (major diastereomer) δ 7.55–7.51 (m, 2H, Ar*H), 7.43–7.39 (m, 3H, Ar*H), 7.25 (d, 2H, *J*=8.4 Hz, ArH), 6.88 (d, 2H, *J*=8.7 Hz, ArH), 4.48 (dd, 1H, *J*=12.0, 3.9 Hz, H-1a), 4.44 (s, 2H, $ArCH_2$), 4.36 (dd, 1H, *J*=12.0, 7.2 Hz, H-1b), 3.79 (s, 3H, *Me*OAr), 3.60–3.56 (m, 2H, H-5), 3.57 (s, 3H, *Me*OC), 3.26–3.15 (m, 2H, H-2, H-3), 1.84 (apparent q, 2H, *J*=6.0 Hz, H-4); ^{1}H NMR (minor diastereomer, in part) δ 4.54 (dd, 1H, *J*=12.0, 3.9 Hz, H-1a), 4.31 (dd, 1H, *J*=12.3, 7.2 Hz, H-1b); ^{13}C NMR δ 166.4 (CO), 159.2 (ArC), 132.0 (Ar*C), 130.1 (ArC), 129.7 (Ar*CH), 129.2 (ArCH), 128.4 (Ar*CH), 127.2 (Ar*CH), 123.1 (q, $J_{C,F}$=287.1 Hz, CF_3), 113.7 (ArCH), 84.6 (q, $J_{C,F}$=27.6 Hz, *C*CF_3), 72.8 ($ArCH_2$), 66.5 (CH_2-5), 64.77 (CH_2-1), 55.5 (q, $J_{C,F}$=1.5 Hz, CO*Me*), 55.2 (*Me*OPh), 54.3 (CH-3), 53.0 (CH-2), 28.7 (CH_2-4); MS (CI+ve) *m/z* 453 ($M-1^+$); HRMS (CI+ve) Calcd for $C_{23}H_{25}O_6F_3$ (M^+) 454.1603, found: 454.1596.

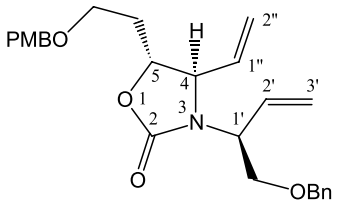
Steps 4 and 5. 5-(4-Methoxyphenyl)methoxy-2S,3S-epoxy-pentanal and (−)-6-(4-methoxyphenyl)methoxy-3R,4S-epoxy-1-hexene (**4**). To a stirred solution oxalyl chloride (0.5 mL, 5.72 mmol) in dry DCM (7 mL) was added slowly dimethyl sulfoxide (0.68 mL, 9.53 mmol) at −50 to −60 °C under N_2. The mixture was stirred for 5 min and 5-(4-methoxy)benzyloxy-2*R*,3*S*-epoxy-1-pentanol (907 mg, 3.81 mmol) in DCM (3 mL) was added within 5 min via cannula. Stirring was continued for an additional 40 min. Triethylamine (2.7 mL, 19.1 mmol) was then added and the mixture was stirred for 5 min and then allowed to warm to RT. After 20 min, the reaction was quenched by water (25 mL). The aqueous layer was re-extracted with additional DCM (3×). The combined organic portions were washed with saturated NaCl solution, HCl (1 M), water, aqueous Na_2CO_3 (sat.), water and dried ($MgSO_4$). The filtered solution was evaporated to give a yellow oil. The crude aldehyde product was used in the next step without further purification. A solution of potassium bis(trimethylsilyl)amide (22.1 mL, 11.1 mmol, 0.5 M in toluene) was cooled to −10 °C and transferred via cannula to a stirred suspension of methyltriphenylphosphonium bromide (4.09 g, 11.4 mmol) in dry THF (25 mL) at −10 °C under N_2. The bright yellow suspension was stirred at RT for 20 min, re-cooled to −10 °C and the above crude aldehyde in THF (8 mL) was added via cannula. TLC analysis (30% EtOAc/petrol) indicated complete disappearance of the crude 5-(4-methoxy)benzyloxy-2*S*,3*S*-epoxy-pentanal after 2.5 h. The reaction mixture was poured into brine and extracted with diethyl ether (3×). The combined organic extract was dried ($MgSO_4$). The solvent was evaporated under reduced pressure to give a semi-solid which was purified by column chromatography (10–35% EtOAc/petrol) to give the title compound **5** as a pale yellow oil (685 mg, 77% overall for 2 steps). $[\alpha]_D^{23}=-14.2$ (*c*2.1, $CHCl_3$); ^{1}H NMR δ 7.26 (dt, 2H, *J*=8.7, 2.7 Hz, ArH), 6.88 (dt, 2H, *J*=8.7, 3.0 Hz, ArH), 5.71 (ddd, 1H, *J*=17.4, 10.5, 6.9 Hz, H-2), 5.47 (ddd, 1H, *J*=17.4, 1.8, 0.6 Hz, H-1a), 5.35 (ddd, 1H, *J*=10.8, 1.8, 0.6 Hz, H-1b), 4.46 (s, 2H, $ArCH_2$), 3.80 (s, 3H, OMe), 3.60 (td, 2H, *J*=6.3, 0.9 Hz, H-6), 3.43 (dd, 1H, *J*=7.2, 4.5 Hz, H-3), 3.24 (ddd, 1H, *J*=6.9, 5.7, 4.5 Hz, H-4), 1.92–1.75 (m, 2H, H-5); ^{13}C NMR δ 159.1 (ArC), 132.3 (CH-2), 130.3 (ArC), 129.2 (ArCH), 120.5 (CH_2-1), 113.7 (ArCH), 72.7 ($ArCH_2$), 67.0 (CH_2-6), 56.9 (CH-3), 56.3 (CH-4), 55.2 (OMe), 28.4 (CH_2-5); MS (CI+ve) *m/z* 234 (M^+); HRMS (CI+ve) Calcd for $C_{14}H_{18}NO_3$ (M^+) 234.1256, found: 234.1254.

2.1.2. (+)-1-(4-Methoxyphenyl)methoxy-4*S*-[(1*S*-phenylmethoxymethyl)-2-propenyl]amino-5-hepten-3*S*-ol (6) and its diastereomer (−)-1-(4-methoxyphenyl)methoxy-4*R*-[(1*S*-phenylmethoxymethyl)-2-propenyl]amino-5-hepten-3*R*-ol (6′). To a mixture of **4** (860 mg, 3.68 mmol) and (2*S*)-1-(phenylmethoxymethyl)but-3-enyl amine **5** (761 mg, 4.30 mmol) in dry acetonitrile (2 mL), in a thick walled glass tube, was added lithium triflate (860 mg, 5.51 mmol). The vessel was flushed with nitrogen and sealed and then stirred and heated at 120 °C for 3 days. The mixture was then cooled to RT and all volatiles were removed in vacuo to give a dark sticky oil which was purified by column chromatography (0–10% methanol/DCM) and semi-preparative TLC (6% MeOH/DCM) to give compound **6** (943 mg, 62%) and the diastereomer **6′** (262 mg, 17%) as yellow oils. Spectral data for **6**: $[\alpha]_D^{24}=+3.4$ (*c*3.2, $CHCl_3$); ^{1}H NMR δ 7.38–7.28 (m, 5H, Ar*H), 7.25 (d, 2H, *J*=8.7 Hz, ArH), 6.86 (d, 2H, *J*=8.7 Hz, ArH), 5.56–5.42 (m, 2H, H-5, H-2′), 5.21 (dd, 1H, *J*=10.5, 2.1 Hz, x=CH_2(*Z*)), 5.19 (dd, 1H, *J*=17.4, 2.1 Hz,=CH_2(*E*)), 5.16 (dd, 1H, *J*=9.9, 2.1 Hz,=CH_2(*Z*)), 5.10 (dd, 1H, *J*=17.4, 1.8 Hz,=CH_2(*E*)), 4.53 (d, 1H, *J*=12.0 Hz, Ar*CH_aCH$_b$), 4.48 (d, 1H, *J*=12.0 Hz, Ar*CH$_a$CH_b), 4.44 (s, 2H, $ArCH_2$), 3.79 (s, 3H, OMe), 3.63 (dd, 2H, *J*=6.6, 6.0 Hz, H-1), 3.50–3.35 (m, 4H, H-3, H-1′, CH_2OBn), 2.88 (t, 1H, *J*=8.4 Hz, H-4), 1.86 (dddd, 1H, *J*=14.1, 7.2, 6.9, 2.7 Hz, H-2a), 1.62 (dddd, 1H, *J*=14.4, 9.3, 6.3, 6.0 Hz, H-2b); ^{13}C NMR δ 159.0 (ArC), 137.9 (Ar*C), 137.4, 136.8 (CH-5, CH-2′), 130.4 (ArC), 129.2 (ArCH), 128.3, 127.6,

127.5 (3×Ar*CH), 118.3, 118.3 (CH_2-6, CH_2-3′), 113.6 (ArCH), 73.2 (CH_2OBn), 72.8 (Ar*CH_2), 72.6 (ArCH_2), 70.7 (CH-3), 67.5 (CH_2-1), 63.5 (CH-4), 57.3 (CH-1′), 55.1 (OMe), 33.4 (CH_2-2); MS (CI+ve) *m/z* 412 ($M+1^+$, 100%); HRMS (CI+ve) Calcd for $C_{25}H_{34}NO_4$ (MH^+) 412.2488, found: 412.2505. Spectral data for **6′**: $[\alpha]_D^{25}=-5.6$ (*c*2.3, $CHCl_3$); ^{1}H NMR δ 7.34–7.27 (m, 5H, Ar*H), 7.24 (d, 2H, *J*=8.7 Hz, ArH), 6.86 (d, 2H, *J*=8.4 Hz, ArH), 5.80 (ddd, 1H, *J*=17.4, 10.2, 6.6 Hz, H-2′), 5.61 (ddd, 1H, *J*=17.1, 10.5, 8.1 Hz, H-5), 5.22–5.08 (m, 4H, H-6, H-3′), 4.52 (s, 2H, ArCH_2 or Ar*CH_2), 4.43 (s, 2H, ArCH_2 or Ar*CH_2), 3.79 (s, 3H, OMe), 3.67–3.60 (m, 2H,, H-1), 3.56–3.36 (m, 4H, H-2, H-1′, CH_2OBn), 2.99 (t, 1H, *J*=8.1 Hz, H-4), 1.86 (dtd, 1H, *J*=14.1, 6.3, 2.7 Hz, H-2a), 1.63 (ddt, 1H, *J*=14.1, 9.3, 6.3 Hz, H-2b); ^{13}C NMR δ 159.1 (ArC), 138.8 (CH-2′), 138.2 (Ar*C), 137.9 (CH-5), 130.3 (ArC), 129.2 (ArCH), 128.3, 127.6, 127.5 (3×Ar*CH), 117.8 (CH_2-6), 116.1 (CH_2-3′), 113.7 (ArCH), 73.1, 72.7 (Ar*CH_2 and ArCH_2), 72.9 (CH_2OBn), 71.6 (CH-3), 67.9 (CH_2-1), 65.0 (CH-4), 58.4 (CH-1′), 55.2 (OMe), 33.3 (CH_2-2); MS (CI+ve) *m/z* 412 ($M+1^+$, 100%); HRMS (CI+ve) Calcd for $C_{25}H_{34}NO_4$ (MH^+) 412.2488, found: 412.2474.

2.1.3. (+)-4*S*-Ethenyl-5*S*-[2-(4-methoxyphenyl)methoxy]-ethyl-3-(1*S*-phenylmethoxymethyl-2-propenyl)-1,3-oxazolidin-2-one (7). A solution of **6** (226 mg, 0.549 mmol) in dry DCM (15 mL) was cooled to 0 °C and triethylamine (311 mg, 0.43 mL, 3.075 mmol) was added. A solution of triphosgene (82 mg, 0.275 mmol) in dry DCM (1 mL) was cooled to 0 °C and was then added to the above amine solution at 0 °C. TLC analysis (34% EtOAc/petrol) indicated complete disappearance of the compound **6** after 2.5 h. The reaction was quenched with water (30 mL). The aqueous portion was extracted with DCM (4×). The combined organic portions were dried ($MgSO_4$) and filtered and the solvent was evaporated to give a yellow semi-solid. Chromatography of the residue eluting with (15–40%) EtOAc/petrol gave diastereomerically pure compound **7** (226 mg, 94%) as a pale yellow oil. $[\alpha]_D^{28}=+29.1$ (*c*3.6, $CHCl_3$); ^{1}H NMR (500 MHz) δ 7.35–7.26 (m, 5H, Ar*H), 7.22 (d, 2H, *J*=8.5 Hz, ArH), 6.86 (d, 2H, *J*=8.5 Hz, ArH), 5.81 (ddd, 1H, *J*=17.5, 10.5, 7.5 Hz, H-2′), 5.69 (ddd, 1H, *J*=17.0, 10.0, 9.0 Hz, H-1″), 5.22 (dt, 1H, *J*=17.5, 1.0 Hz, H-3′a (*E*)), 5.19 (dt, 1H, *J*=10.5, 1.0 Hz, H-2″a), 5.18 (dt, 1H, *J*=10.5, 1.0 Hz, H-3′b), 5.11 (dt, 1H, *J*=17.0, 1.0 Hz, H-2″b), 4.59 (d, 1H, *J*=12.0 Hz, Ar*CH_aCH_b), 4.44 (d, 1H, *J*=12.0 Hz, Ar*CH_aCH_b), 4.40 (d, 1H, *J*=11.0 Hz, ArCH_a-CH_b), 4.36 (d, 1H, *J*=11.5 Hz, ArCH_aCH_b), 4.36–4.32 (m, 1H, H-1′), 4.24 (td, 1H, *J*=7.5, 4.5 Hz, H-5), 3.90 (dd, 1H, *J*=9.0 7.5 Hz, H-4), 3.81 (dd, 1H, *J*=10.5, 9.5 Hz, CH_a-CH_bOBn), 3.77 (s, 3H, OMe), 3.61 (dd, 1H, *J*=10.0, 5.5 Hz, CH_aCH_bOBn), 3.57–3.54 (m, 2H, CH_2CH_2O), 1.95–1.84 (m, 2H, C$H_2$$CH_2$O); ^{13}C NMR δ 159.0 (ArC), 157.3 (CO), 137.6 (Ar*C), 135.9 (CH-2′), 133.3 (CH-1″), 123.0 (ArC), 129.2 (ArCH), 128.2, 127.8, 127.6 (3×Ar*CH), 120.3 (CH_2-2″), 118.4 (CH_2-3′), 113.6 (ArCH), 76.2 (CH-5), 72.7 (Ar*CH_2 and ArCH_2), 68.3 (CH_2OBn), 65.2 ($CH_2$$CH_2$O), 64.3 (CH-4), 56.0 (CH-1′), 55.1 (OMe), 33.4 ($CH_2$$CH_2$O); MS (CI+ve) *m/z* 438 ($M+1^+$); HRMS (CI+ve) Calcd for $C_{26}H_{32}NO_5$ (MH^+) 438.2280, found: 438.2262.

2.1.4. (+)-4*R*-Ethenyl-5*R*-[2-(4-methoxyphenyl)methoxy]-ethyl-3-(1*S*-phenylmethoxymethyl-2-propenyl)-1,3-oxazolidin-2-one (7′).



The same procedure described above for the preparation of **7** was used starting with **6′** (49 mg, 0.118 mmol) in dry DCM (5 mL), triethylamine (92 μL, 0.66 mmol) and triphosgene (18 mg, 0.059 mmol) in dry DCM (1 mL). Compound **7′** (36 mg, 69%) was obtained as a pale yellow oil. $[\alpha]_D^{27}=+12.7$ (*c*1.8, $CHCl_3$); ^{1}H NMR δ 7.36–7.29 (m, 5H, Ar*H), 7.23 (d, 2H, *J*=8.7 Hz, ArH), 6.87 (d, 2H, *J*=8.7 Hz, ArH), 5.95 (ddd, 1H, *J*=17.7, 9.9, 6.6 Hz, H-2′), 5.69 (ddd, 1H, *J*=17.4, 9.6, 8.7 Hz, H-1″), 5.29–5.20 (m, 4H, H-3′, H-2″), 4.54 (d, 1H, *J*=12.6 Hz, Ar*C$H_a$$CH_b$), 4.50 (d, 1H, *J*=12.3 Hz, Ar*CH_a-CH_b), 4.42 (d, 1H, *J*=11.4 Hz, ArC$H_a$$CH_b$), 4.37 (d, 1H, *J*=11.1 Hz, ArCH_aCH_b), 4.27 (ddd, 1H, *J*=7.8, 7.5, 4.8 Hz, H-5), 4.25–4.17 (m, 1H, H-1′), 3.98 (dd, 1H, *J*=8.7, 7.5 Hz, H-4), 3.91 (t, 1H, *J*=9.0 Hz, C$H_a$$CH_b$OBn), 3.80 (s, 3H, OMe), 3.59–3.53 (m, 3H, CH_aCH_bOBn, CH_2CH_2O), 1.98–1.81 (m, 2H, C$H_2$$CH_2$O); ^{13}C NMR (one Ar*CH could not be observed) δ 159.2 (ArC), 156.9 (CO), 137.9 (Ar*C), 135.7 (CH-1″), 132.6 (CH-2′), 130.1 (ArC), 129.3 (ArCH), 128.3, 127.6 (2×Ar*CH), 120.5 (CH_2-2″), 118.8 (CH_2-3′), 113.7 (ArCH), 76.5 (CH-5), 73.0 (Ar*CH_2), 72.8 (ArCH_2), 69.8 (CH_2OBn), 66.2 (CH-4), 65.3 ($CH_2$$CH_2$O), 56.1 (CH-1′), 55.2 (OMe), 33.8 ($CH_2$$CH_2$O); MS (CI+ve) *m/z* 438 ($M+1^+$); HRMS (EI+ve) Calcd for $C_{26}H_{31}NO_5$ (M^+) 437.2202, found: 437.2202.

2.1.5. (−)-(1*S*,5*S*,7a*S*)-1-[2-(4-Methoxyphenyl)methoxy]-ethyl-5-(phenylmethoxy)methyl-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-3-one (8). Grubbs' catalyst I (212 mg, 0.258 mmol) was added to a solution of **7** (520 mg, 1.19 mmol) in dry DCM (200 mL) under nitrogen. The mixture was heated at reflux under nitrogen for 25 h. TLC analysis (35% EtOAc/petrol) indicated incomplete conversion of compound **7**. Additional Grubbs' catalyst I (85.0 mg, 0.103 mmol) was added and the reaction was continued under the same conditions for another 17 h. The reaction mixture was cooled and then the solvent was removed in vacuo to give a brown oil which was purified by column chromatography (25–85% EtOAc/petrol) to give **8** (204 mg, 97%) as a light brown oil. $[\alpha]_D^{26}=-134.9$ (*c*2.1, $CHCl_3$); ^{1}H NMR (500 MHz) δ 7.34–7.26 (m, 5H, Ar*H), 7.23 (d, 2H, *J*=8.5 Hz, ArH), 6.87 (d, 2H, *J*=8.5 Hz, ArH), 5.96 (dt, 1H, *J*=5.5, 2.0 Hz, H-7), 5.87 (bd, 1H, *J*=6.0 Hz, H-6), 4.74–4.72 (m, 1H, H-5), 4.56 (d, 1H, *J*=12.0 Hz, Ar*C$H_a$$CH_b$), 4.53 (d, 1H, *J*=12.0 Hz, Ar*CH_aCH_b), 4.54–4.52 (m, 1H, H-1), 4.44 (d, 1H, *J*=11.5 Hz, ArC$H_a$$CH_b$), 4.44–4.43 (m, 1H, H-7a), 4.40 (d, 1H, *J*=11.5 Hz, ArCH_a-CH_b), 3.77 (s, 3H, OMe), 3.61 (apparent dd, 2H, *J*=7.0, 5.0 Hz, CH_2CH_2O), 3.53 (dd, 1H, *J*=10.0, 5.0 Hz, CH_a-CH_bOBn), 3.50 (dd, 1H, *J*=10.0, 5.5 Hz, CH_aCH_bOBn), 2.14–2.02 (m, 2H, C$H_2$$CH_2$O); ^{13}C NMR one ArC could not be observed δ 161.7 (CO), 158.8 (ArC), 137.5 (Ar*C), 131.4 (CH-7), 129.5 (CH-6), 128.9 (ArCH), 127.9, 127.2, 127.1 (3×Ar*CH), 113.3 (ArCH), 79.4 (CH-1), 72.8

(Ar^*CH_2), 72.5 ($ArCH_2$), 70.9 (CH_2OBn), 70.0 (CH-7a), 66.0 (CH-5), 65.2 (CH_2CH_2O), 54.8 (OMe), 35.1 (CH_2CH_2O); MS (CI+ve) *m/z* 410 ($M+1^+$); HRMS (CI+ve) Calcd for $C_{24}H_{28}NO_5$ (M^+) 410.1967, found: 410.1929.

2.1.6. (−)-(1*S*,5*S*,6*R*,7*S*,7a*S*)-1-[2-(4-Methoxyphenyl)-methoxy]ethyl-5-(phenylmethoxy)methyl-5,6,7,7a-tetrahydro-6,7-dihydroxy-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-3-one (9). To a solution of **8** (170 mg, 0.416 mmol) in acetone (3 mL) were added water (2 mL), 4-morpholine *N*-oxide (107 mg, 0.916 mmol) and potassium osmate dihydrate (15 mg, 0.042 mmol). The mixture was stirred at RT for 21 h. Then all volatiles were removed in vacuo. The residue was dissolved in toluene and evaporated to dryness in vacuo to give a dark, semi-solid which was chromatographed on silica gel (eluting with 0–7.5% methanol/DCM) to afford compound **9** as a brown oil (156 mg, 85%). $[\alpha]_D^{24}=-84.0$ (*c*1.3, $CHCl_3$); ^1H NMR (500 MHz) δ 7.26–7.17 (m, 5H, Ar^*H), 7.14 (d, 2H, *J*=8.0 Hz, ArH), 6.78 (d, 2H, *J*=9.0 Hz, ArH), 4.79 (ddd, 1H, *J*=7.5, 5.5, 2.5 Hz, H-1), 4.48 (d, 1H, *J*=12.0 Hz, $Ar^*CH_aCH_b$), 4.45 (d, 1H, *J*=12.0 Hz, $Ar^*CH_aCH_b$), 4.34 (d, 1H, *J*=11.5 Hz, $ArCH_aCH_b$), 4.30 (d, 1H, *J*=11.5 Hz, $ArCH_aCH_b$), 4.26 (dd, 1H, *J*=5.0, 4.0 Hz, H-6), 3.82 (bs, 1H, H-7), 3.70 (s, 3H, OMe), 3.64–3.62 (m, 2H, H-5, CH_aCH_bOBn), 3.57–3.54 (m, 2H, H-7a, CH_aCH_bOBn), 3.52–3.49 (m, 2H, CH_2CH_2O), 1.99–1.92 (m, 1H, $CH_aCH_bCH_2O$), 1.91–1.84 (m, 1H, $CH_aCH_bCH_2O$); ^{13}C NMR δ 161.8 (CO), 159.2 (ArC), 137.8 (Ar^*C), 129.9 (ArC), 129.4 (ArCH), 128.4, 127.8, 127.6 (3×Ar^*CH), 113.8 (ArCH), 76.9 (CH-6), 73.5 (Ar^*CH_2), 73.1 (CH-1), 73.0 ($ArCH_2$), 71.5 (CH-7), 70.2 (CH_2OBn), 66.6 (CH-7a), 65.7 (CH_2CH_2O), 62.0 (CH-5), 55.3 (OMe), 35.3 (CH_2CH_2O); MS (CI+ve) *m/z* 444 ($M+1^+$); HRMS (EI+ve) Calcd for $C_{24}H_{29}NO_7$ (M^+) 443.1944, found: 443.1943.

2.1.7. (−)-(1*S*,5*R*,6*R*,7*S*,7a*S*)-6,7-Diacetoxy-1-[2-(4-methoxyphenyl)methoxy]ethyl-5-(phenylmethoxy)-methyl-5,6,7,7a-tetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-3-one (10). Compound **9** (174 mg, 0.394 mmol) was dissolved in anhydrous pyridine (2.0 mL) and then Ac_2O (2.0 mL) was added. The mixture was stirred at RT for 23 h, then diluted with DCM (30 mL) and washed with saturated aqueous $NaHCO_3$ solution at 0 °C. The aqueous portion was extracted with DCM (4×). The combined organic portions were dried ($MgSO_4$), filtered and evaporated in vacuo to give an oil which was purified by column chromatography (30–50% EtOAc/petrol) to give product **10** as a pale yellow oil (174 mg, 84%). $[\alpha]_D^{26}=-13.9$ (*c*2.3, $CHCl_3$); ^1H NMR δ 7.33–7.27 (m, 5H, Ar^*H), 7.21 (d, 2H, *J*=8.7 Hz, ArH), 6.87 (d, 2H, *J*=8.4 Hz, ArH), 5.56 (dd, 1H, *J*=6.6, 3.6 Hz, H-6), 5.37 (t, 1H, *J*=3.6 Hz, H-7), 4.60 (ddd, 1H, *J*=7.5, 6.0, 3.9 Hz, H-1), 4.58 (d, 1H, *J*=11.7 Hz, $Ar^*CH_aCH_b$), 4.52 (d, 1H, *J*=12.0 Hz, $Ar^*CH_aCH_b$), 4.43 (d, 1H, *J*=11.4 Hz, $ArCH_aCH_b$), 4.38 (d, 1H, *J*=11.7 Hz, $ArCH_aCH_b$), 3.96–3.91 (m, 2H, H-5, H-7a), 3.79 (s, 3H, OMe), 3.70 (dd, 1H, *J*=10.2, 3.6 Hz, CH_aCH_bOBn), 3.63 (dd, 1H, *J*=10.2, 3.0 Hz, CH_aCH_bOBn), 3.56 (dd, 2H, *J*=6.6, 5.4 Hz, OCH_2CH_2), 2.15–1.94 (m, 2H, OCH_2CH_2), 2.10 (s, 3H, Ac), 1.99 (s, 3H, Ac); ^{13}C NMR δ 169.8 (CO, Ac), 169.6 (CO, Ac), 160.7 (CO-3), 159.2 (ArC), 137.6 (Ar^*C), 129.8 (ArC), 129.2 (ArCH), 128.3, 127.6, 127.4 (3×Ar^*CH), 113.7 (ArCH), 74.3 (CH-6), 73.3 (Ar^*CH_2), 72.9 (CH-1), 72.8 ($ArCH_2$), 72.1 (CH-7), 68.9 (CH_2OBn), 65.1 (OCH_2CH_2), 64.7 (CH-7a), 59.9 (CH-5), 55.1 (OMe), 35.0 (OCH_2CH_2), 20.5 (CH_3, Ac), 20.3 (CH_3, Ac); MS (CI+ve) *m/z* 528 ($M+1^+$); HRMS (CI+ve) Calcd for $C_{28}H_{34}NO_9$ (MH^+) 528.2234, found: 528.2257.

2.1.8. (−)-(1*S*,5*R*,6*R*,7*S*,7a*S*)-6,7-Diacetoxy-1-(2-hydroxy)ethyl-5-(phenylmethoxy) methyl-5,6,7,7a-tetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-3-one (11). To a solution of **10** (227 mg, 0.432 mmol) in dichloromethane (30 mL) and water (2.5 mL) was added 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) (137 mg, 0.604 mmol). After the mixture was stirred at RT for 2.5 h, TLC analysis (70% EtOAc/petrol) indicated the presence of compound **10**. Additional DDQ (59 mg, 0.259 mmol) was then added to the mixture. The reaction was continued for another 3 h. The mixture was diluted with water (25 mL) and extracted with DCM (4×). The combined organics were dried ($MgSO_4$) and filtered and the solvent was removed under reduced pressure to give a red, semi-solid that was purified by column chromatography (40–90% EtOAc/petrol) to give the product **11** as a pale yellow oil (114 mg, 65%). $[\alpha]_D^{25}=-4.6$ (*c*2.0, $CHCl_3$); ^1H NMR δ 7.36–7.24 (m, 5H, Ar^*H), 5.56 (dd, 1H, *J*=6.6, 3.6 Hz, H-6), 5.41 (t, 1H, *J*=3.6 Hz, H-7), 4.62 (ddd, 1H, *J*=7.8, 5.7, 3.6 Hz, H-1), 4.58 (d, 1H, *J*=12.0 Hz, $Ar^*CH_aCH_b$), 4.52 (d, 1H, *J*=12.3 Hz, $Ar^*CH_aCH_b$), 3.96–3.91 (m, 2H, H-7a, H-5), 3.78 (bt, 2H, *J*=5.7 Hz, CH_2CH_2OH), 3.71 (dd, 1H, *J*=10.2, 3.6 Hz, CH_aCH_bOBn), 3.62 (dd, 1H, *J*=10.2, 3.0 Hz, CH_aCH_bOBn), 2.22 (bs, 1H, OH), 2.13–1.85 (m, 2H, CH_2CH_2OH), 2.11 (s, 3H, Ac), 1.99 (s, 3H, Ac); ^{13}C NMR δ 170. 1, 169.8 (2×CO, Ac), 160.7 (CO-3), 137.6 (Ar^*C), 128.4, 127.7, 127.5 (3×Ar^*CH), 74.3 (CH-6), 73.4 (Ar^*CH_2), 73.0 (CH-1), 72.2 (CH-7), 68.9 (CH_2OBn), 64.9 (CH-7a), 59.9 (CH-5), 58.2 (CH_2CH_2OH), 37.3 (CH_2CH_2OH), 20.6, 20.4 (2×CH_3, Ac); MS (CI+ve) *m/z* 408 ($M+1^+$, 100%); HRMS (CI+ve) Calcd for $C_{20}H_{26}NO_8$ (MH^+) 408.1658, found: 408.1666.

2.1.9. Four step synthesis of (−)-(1*S*,2*R*,3*R*,7*S*,7a*R*)-1,2,7-triacetoxy-3-(acetoxymethyl)hexahydro-1*H*-pyrrolizine (15) from 13. *(+)-(2S,3R,4S,5R)-5-[(1S)-1,3-Dihydroxypropyl]-2-[(phenylmethoxy)methyl] pyrrolizine-3,4-diol* (**13**). To a solution of **12** (174 mg, 0.429 mmol) in ethanol (6 mL) was added sodium hydroxide (171 mg, 4.285 mmol). The reaction was heated at 70 °C in a sealed tube for 37 h. The volatiles were then removed in vacuo to give a yellow solid, and the residue was treated with 1 M hydrochloric acid (6 mL). The volatiles were removed in vacuo to give a yellow solid that was purified by acidic ion-exchange chromatography to give the desired compound **12** (ca 168 mg) as a yellow solid. This compound appeared pure by NMR analysis but from the mass recovery (>100%) this material was believed to contain salts. Spectral data for **12**: ^1H NMR (CD_3OD) δ 7.42–7.26 (m, 5H, Ar^*H), 4.66 (d, 1H, *J*=11.7 Hz, $Ar^*CH_aCH_b$), 4.60 (d, 1H, *J*=11.7 Hz, $Ar^*CH_aCH_b$), 4.24 (dd, 1H, *J*=8.7, 3.9 Hz, H-3), 4.22–4.16 (m, 2H, H-4, CHOH), 3.86 (dd, 1H, *J*=10.5, 3.3 Hz, CH_aCH_bOBn), 3.82–3.76 (m, 3H, CH_aCH_bOBn, CH_2CH_2OH), 3.69 (ddd, 1H, *J*=8.7, 6.0, 3.0 Hz, H-2), 3.53 (dd, 1H, *J*=9.0, 3.0 Hz, H-5), 1.92 (dtd, 1H, *J*=14.1, 7.2, 3.0 Hz, $CH_aCH_bCH_2OH$), 1.67 (ddt, 1H, *J*=14.4, 9.0, 5.7 Hz,

$CH_aCH_bCH_2OH$); ^{13}C NMR (CD_3OD) δ 138.9 (Ar*C), 129.4, 129.0, 128.9 (3×Ar*CH), 74.3 (Ar*CH_2), 73.5 (CH-3), 71.6 (CH-4), 67.9 (CH_2OBn), 67.6 (CH-5), 66.8 (CHOH), 61.7 (CH-2), 59.1 (CH_2CH_2OH), 37.5 (CH_2CH_2OH); MS (CI+ve) *m/z* 298 ($M+1^+$, 100%); HRMS (CI+ve) Calcd for $C_{15}H_{24}NO_5$ (MH^+) 298.1654, found: 298.1658.

2.1.10. (−)-(1*S*,2*R*,3*R*,7*S*,7a*R*)-1,2,7-Triacetoxy-3-(acetoxymethyl)hexahydro-1*H*-pyrrolizine (15). To a stirred mixture of **12** obtained above, triphenylphosphine (157 mg, 0.600 mmol) and anhydrous pyridine (5 mL) at 0 °C was added dropwise diisopropyl azodicarboxylate (0.12 mL, 0.60 mmol) under nitrogen. The mixture was stirred at 0 °C for 4 h and then warm up to RT for 3 h. The volatiles were removed in vacuo then 1 M hydrochloric acid (15 mL) and DCM (15 mL) were added. The aqueous layer was washed with DCM (15 mL) and then concentrated in vacuo to give a yellow solid, which was purified by acidic ion-exchange chromatography to give **13**. This material was dissolved in methanol (2 mL) and palladium chloride (21 mg, 0.118 mmol) was added. The mixture was stirred under one atmosphere of hydrogen (H_2 balloon) at RT for 1.5 h. The mixture was then filtered through a plug of cotton wool and the solvent was removed under reduced pressure to give **14** as a pale yellow oil. This oil was then dissolved in anhydrous pyridine (1 mL) and Ac_2O (1 mL) was added to the solution. The mixture was stirred at RT for 22 h, then diluted with DCM (20 mL) and washed with saturated $NaHCO_3$ solution at 0 °C. The aqueous portion was extracted with DCM (3×). The combined organic portions were dried ($MgSO_4$), filtered and evaporated in vacuo to give a solid which was purified by column chromatography (35–90% EtOAc/petrol) to give **15** as a pale yellow oil (21 mg, 23% overall for 4 steps). $[\alpha]_D^{26}=-19.0$ (*c*2.1, $CHCl_3$); ^1H NMR δ 5.44 (t, 1H, *J*=3.9 Hz, H-1), 5.31 (dd, 1H, *J*=15.3, 7.8 Hz, H-7), 5.10 (dd, 1H, *J*=9.3, 4.2 Hz, H-2), 4.20 (dd, 1H, *J*=11.4, 4.2 Hz, CH_aCH_bOAc), 4.04 (dd, 1H, *J*=11.4, 5.4 Hz, CH_aCH_bOAc), 3.87 (dd, 1H, *J*=7.5, 3.9 Hz, H-7a), 3.32 (ddd, 1H, *J*=9.6, 5.7, 4.2 Hz, H-3), 3.18 (dt, 1H, *J*=11.1, 7.8 Hz, H-5a), 2.95 (ddd, 1H, *J*=11.1, 7.2, 5.4 Hz, H-5b), 2.14–1.92 (m, 2H, H-6), 2.11 (s. 3H, Ac), 2.09 (s, 3H, Ac), 2.03 (s, 3H, Ac), 2.01 (s, 3H, Ac); ^{13}C NMR δ 170.8, 170.4, 169.6, 169.4 (4×CO), 74.4 (CH-7), 73.7 (CH-2), 71.7 (CH-1), 66.7 (CH-3), 65.0 (CH_2OAc), 64.7 (CH-7a), 52.3 (CH_2-5), 30.9 (CH_2-6), 21.0, 20.8, 20.7, 20.4 (4×CH_3, Ac); MS (CI+ve) *m/z* 358 ($M+1^+$, 100%); HRMS (CI+ve) Calcd for $C_{16}H_{24}NO_8$ (MH^+) 358.1502, found: 358.1485.

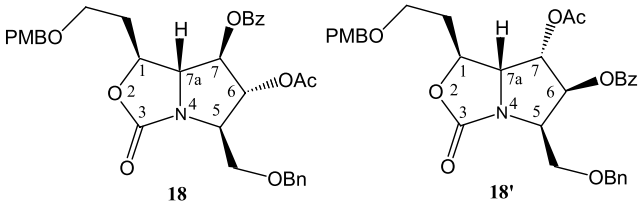
2.1.11. (+)-(1*S*,2*R*,3*R*,7*S*,7a*R*)-Hexahydro-3-hydroxymethyl-1*H*-pyrrolizine-1,2,7-triol, [(+)-1-epiaustraline] (1). To a solution of **15** (21 mg, 0.109 mmol) in methanol (2 mL) was added Amberlyst A-26 resin (50 mg). The reaction mixture was stirred for 2 h at RT. The TLC analysis indicated the complete conversion. The mixture was then filtered through a sintered glass frit and rinsed with methanol. The filtrate was concentrated to give the title compound (11 mg) as a colorless oil. $[\alpha]_D^{25}=+14.3$ (*c*1.1, H_2O) [lit.[10a] $[\alpha]_D^{25}=+13.695$ (*c*1.72, H_2O)]; The ^1H and ^{13}C NMR spectral data for this compound were essentially identical to that reported in the literature.[10] ^1H NMR (500 MHz, D_2O) δ 4.57 (dt, 1H, *J*=5.0, 4.5 Hz, H-7), 4.40 (t, 1H, *J*=5.0 Hz, H-1), 3.91 (dd, 1H, *J*=9.0, 4.5 Hz, H-2), 3.80 (dd, 1H, *J*=11.5, 4.0 Hz, CH_aCH_bOH), 3.63 (dd, 1H, *J*=11.5, 7.0 Hz, CH_aCH_bOH), 3.46 (t, 1H, *J*=5.0 Hz, H-7a), 3.17 (ddd, 1H, *J*=10.5, 7.0, 4.0 Hz, H-5a), 3.02 (ddd, 1H, *J*=9.0, 6.5, 4.0 Hz, H-3), 2.93 (ddd, 1H, *J*=10.5, 9.5, 6.5 Hz, H-5b), 2.04 (ddt, 1H, *J*=13.5, 6.5, 4.0 Hz, H-6a), 1.96 (dddd, 1H, *J*=13.5, 9.5, 7.0, 5.0 Hz, H-6b); ^{13}C NMR (D_2O) δ 75.2 (CH-2), 73.7 (CH-7), 72.7 (CH-1), 70.6 (CH-3), 66.6 (CH-7a), 63.6 (CH_2OH), 52.7 (CH_2-5), 35.9 (CH_2-6); MS (CI+ve) *m/z* 190 ($M+1^+$, 100%); HRMS (EI+ve) Calcd for $C_8H_{15}NO_4$ (M^+) 189.1001, found: 189.0995.

2.1.12. (−)-(3a*S*,3*bR*,4*S*,8*R*,8a*R*)-4-[2-(4-Methoxyphenyl)methoxy]ethyl-8-phenylmethoxylmethyltetrahydro-3a*H*-[1,3,2]dioxathiolo[4′,5′:3,4]pyrrolo[1,2-*c*][1,3]oxazol-6-one 2,2-dioxide (16). To a solution of **9** (190 mg, 0.430 mmol) in DCM (5 mL) was added Et_3N (0.14 mL, 0.988 mmol) followed by thionyl chloride (39.2 μL, 0.537 mmol) at 0 °C. The mixture was stirred for 30 min at 0 °C and water (15 mL) was added to the mixture. The aqueous layer was extracted with DCM (4×). The combined organic phases were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give a brown oil. The crude cyclic sulfite was used in the next step without further purification. The crude cyclic sulfite obtained above was dissolved in 7 mL of a solution of CCl_4: CH_3CN: H_2O (2: 2: 3, v/v/v) and $RuCl_3.3H_2O$ (6 mg, 0.024 mmol) was added followed by $NaIO_4$ (175 mg, 0.816 mmol). The mixture was stirred at RT for 2.5 h and then diluted with diethyl ether (20 mL) and water (20 ml). The organic layer was washed with saturated aqueous sodium bicarbonate solution followed by brine and then dried ($MgSO_4$). The solvent was evaporated and then purification of the residue by column chromatography (35–50% EtOAc/petrol) gave compound **16** (191 mg, 88%) as a pale yellow oil. $[\alpha]_D^{24}=-52.9$ (*c*2.0, $CHCl_3$); ^1H NMR δ 7.37–7.34 (m, 5H, Ar*H), 7.22–7.19 (m, 2H, Ar*H), 7.20 (d, 2H, *J*=8.7 Hz, ArH), 6.86 (d, 2H, *J*=8.7 Hz, ArH), 5.35 (dd, 1H, *J*=5.4, 0.9 Hz, H-8a), 5.04 (t, 1H, *J*=5.4 Hz, H-3a), 4.78 (td, 1H, *J*=6.6, 3.9 Hz, H-4), 4.49 (d, 1H, *J*=12.0 Hz, $ArCH_aCH_b$ or Ar*CH_aCH_b), 4.43–4.39 (m, 2H, $ArCH_aCH_b$ or Ar*CH_aCH_b and H-8), 4.39 (s, 2H, $ArCH_2$ or Ar*CH_2), 4.25 (dd, 1H, *J*=4.8, 3.9 Hz, H-3b), 3.78 (s, 3H, OMe), 3.73–3.57 (m, 4H, CH_2OBn and CH_2CH_2O), 2.14–2.07 (m, 2H, CH_2CH_2O); ^{13}C NMR δ 159.3 (ArC), 158. 7 (CO-6), 136.6 (Ar*C), 129.7 (ArC), 129.4, 128.7, 128.3, 127.7 (3×Ar*CH and 1×ArCH), 113.8 (ArCH), 87.6 (CH-8a), 84.4 (CH-3a), 73.8 ($ArCH_2$ or Ar*CH_2), 73.7 (CH-4), 73.1 (Ar*CH_2 or $ArCH_2$), 70.9 (CH_2OBn), 67.1 (CH-3b), 65.7 (CH_2CH_2O), 62.3 (CH-8), 55.2 (OMe), 34.9 (CH_2CH_2O); MS (CI+ve) *m/z* 506 ($M+1^+$); HRMS (EI+ve) Calcd for $C_{24}H_{27}NO_9S$ (M^+) 505.1407, found: 505.1426.

2.1.13. (−)-(1*S*,5*S*,6*R*,7*R*,7a*S*)-6-Hydroxyl-1-[2-(4-methoxyphenyl)methoxy]ethyl-7-phenylcarbonyloxy-5-phenylmethoxymethyltetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazol-3-one (17). To a solution of **16** (192 mg, 0.381 mmol) in DMF (8 mL) was added benzoic acid (79 mg, 0.65 mmol) followed by cesium carbonate (186 mg, 0.572 mmol). The mixture was stirred under nitrogen at 40 °C for 3 h. DMF was removed under reduced pressure and the residue was suspended in THF (8 mL). Water (20 drops) followed by concentrated sulfuric acid (4 drops) was added and the suspension became a clear solution. The

solution was stirred at RT for 9.5 h. The volatiles were removed in vacuo to give a semi-solid which was purified by column chromatography (20–60% EtOAc/petrol) to give **18** (184 mg, 88%) as a mixture (73:27) of regioisomers as a colourless oil. Spectral data for the major isomer: ^{1}H NMR δ 7.96 (d, 2H, J=7.8 Hz, BzH), 7.60 (td, 1H, J=7.5, 0.6 Hz, BzH), 7.43 (t, 2H, J=7.8 Hz, BzH), 7.32–7.26 (m, 5H, Ar*H), 7.18 (d, 2H, J=8.4 Hz, ArH), 6.81 (d, 2H, J=7.8 Hz, ArH), 5.01 (dd, 1H, J=6.3, 4.2 Hz, H-7), 4.97 (dt, 1H, J=7.2, 5.1 Hz, H-1), 4.61 (t, 1H, J=3.6 Hz, H-6), 4.58 (s, 2H, Ar*CH_2), 4.36 (s, 2H, ArCH_2), 4.10 (bdd, 1H, J=9.0, 5.1 Hz, H-5), 3.88 (dd, 1H, J=6.3, 5.1 Hz, H-7a), 3.76 (s, 3H, OMe), 3.75–3.58 (m, 4H, CH_2OBn, CH_2CH_2O), 2.11–2.00 (m, 2H, CH_2CH_2O); ^{13}C NMR δ 166.6 (CO, Bz), 160.6 (CO-3), 159.0 (ArC), 137.7 (Ar*C), 133.6 (CH, Bz), 123.0 (ArC), 129.7, 129.2, 128.5, 128.4, 127.7, 127.5 (1×ArCH, 3×Ar*CH and 2×BzCH), 128.7 (C, Bz), 113.7 (ArCH), 84.3 (CH-7), 79.0 (CH-6), 78.3 (CH-1), 73.3 (Ar*CH_2), 72.7 (ArCH_2), 69.6 (CH_2OBn), 67.7 (CH-7a), 65.4 (CH_2CH_2O), 64.4 (CH-5), 55.2 (OMe), 35.2 (CH_2CH_2O), 20.8 (CH_3, Ac); MS (ES+ve) m/z 548 (M+1$^+$, 25%), 570 (M+Na$^+$, 100%); HRMS (ES+ve) Calcd for $C_{31}H_{34}NO_8$ (MH$^+$) 548.2284, found: 548.2284.

2.1.14. (−)-(1*S*,5*R*,6*R*,7*R*,7a*S*)-6-Acetoxy-1-[2-(4-methoxyphenyl)methoxy]ethyl-7-phenylcarbonyloxy-5-phenylmethoxymethyltetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazol-3-one (18) and (1*S*,5*R*,6*S*,7*S*,7a*S*)-7-acetoxy-1-[2-(4-methoxyphenyl)methoxy]ethyl-6-phenylcarbonyloxy-5-phenylmethoxymethyltetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazol-3-one (18′).



The same procedure described above for the preparation of **10** was used starting with **17** (224 mg, 0.409 mmol), Ac_2O (2.0 mL) in anhydrous pyridine (2 mL). Compounds **18** (160 mg, 66%) and its regioisomer **18′** (61 mg, 25%) were obtained respectively, as pale yellow oils. Spectral data for **18**: $[\alpha]_D^{23}$=−30.1 (c1.1, $CHCl_3$); ^{1}H NMR δ 7.94 (dt, 2H, J=8.4, 1.2 Hz, BzH), 7.60 (tt, 1H, J=7.8, 1.2 Hz, BzH), 7.43 (t, 2H, J=8.1 Hz, BzH), 7.33–7.28 (m, 2H, Ar*H), 7.26–7.23 (m, 3H, Ar*H), 7.18 (d, 2H, J=9.0 Hz, ArH), 6.81 (d, 2H, J=9.0 Hz, ArH), 5.60 (t, 1H, J=3.6 Hz, H-6), 5.15 (dd, 1H, J=6.0, 3.3 Hz, H-7), 5.06 (ddd, 1H, J=7.8, 4.8, 3.9 Hz, H-1), 4.59 (s, 2H, Ar*CH_2), 4.36 (s, 2H, ArCH_2), 4.15 (dd, 1H, J=6.6, 3.9 Hz, H-5), 3.93 (dd, 1H, J=6.3, 4.2 Hz, H-7a), 3.86 (dd, 1H, J=9.6, 3.6 Hz, CH_aCH_bOBn), 3.78 (s, 3H, OMe), 3.72 (dd, 1H, J=9.6, 4.2 Hz, CH_aCH_bOBn), 3.64–3.57 (m, 2H, CH_2CH_2O), 2.19–1.98 (m, 2H, CH_2CH_2O), 2.09 (s, 3H, Ac); ^{13}C NMR δ 170.3 (CO, Ac), 166.0 (CO, Bz), 160.0 (CO-3), 159.1 (ArC), 137.7 (Ar*C), 133.6 (CH, Bz), 130.1 (ArC), 129.7, 129.2, 128.5, 128.4, 127.7, 127.3 (1×ArCH, 3×Ar*CH and 2×BzCH), 128.6 (C, Bz), 113.7 (ArCH), 82.7 (CH-7), 81.0 (CH-6), 78.3 (CH-1), 73.4 (Ar*CH_2), 72.7 (ArCH_2), 70.4 (CH_2OBn), 69.0 (CH-7a), 65.4 (CH_2CH_2O), 63.4 (CH-5), 55.2 (OMe), 35.3 (CH_2CH_2O), 20.8 (CH_3, Ac); MS (ES+ve) m/z 590 (M+1$^+$, 12%), 612 (M+Na$^+$, 100%); HRMS (ES+ve) Calcd for $C_{33}H_{36}NO_9$ (MH$^+$) 590.2390, found: 590.2379. HRMS (EI+ve) Calcd for $C_{33}H_{35}NO_9$ (M$^+$) 589.2312, found: 589.2300. Spectral data for **18′**: ^{1}H NMR (500 MHz) δ 7.91 (dd, 2H, J=8.0, 1.5 Hz, BzH), 7.60 (tt, 1H, J=7.5, 1.5 Hz, BzH), 7.43 (t, 2H, J=8.5 Hz, BzH), 7.20–7.13 (m, 7H, 2×ArH, 5×Ar*H), 6.76 (d, 2H, J=9.0 Hz, ArH), 5.74 (dd, 1H, J=6.0, 2.0 Hz, H-6), 5.26 (dd, 1H, J=4.0, 2.0 Hz, H-7), 4.53 (td, 1H, J=6.5, 4.0 Hz, H-1), 4.45–4.35 (m, 5H, ArCH_2, Ar*CH_2, H-5), 4.19 (t, 1H, J=4.0 Hz, H-7a), 3.71 (s, 3H, OMe), 3.80–3.57 (m, 4H, CH_2OBn, CH_2CH_2O), 2.11 (s, 3H, Ac), 2.17–2.04 (m, 2H, CH_2CH_2O); ^{13}C NMR (125 MHz) δ 169.6 (CO, Ac), 164.5 (CO, Bz), 160.9 (CO-3), 159.2 (ArC), 137.4 (Ar*C), 133.5 (CH, Bz), 131.5 (ArC), 129.7 (CH, Bz), 129.2, 128.5, 128.3, 127.6, 127.6 (1×ArCH, 3×Ar*CH, 1×BzCH), 129.0 (C, Bz), 113.7 (ArCH), 76.9 (CH-6), 75.8 (CH-7), 73.5, 73.0 (ArCH_2, Ar*CH_2), 73.5 (CH-1), 67.3 (CH_2OBn), 65.6 (CH_2CH_2O), 65.5 (CH-7a), 59.2 (CH-5), 55.1 (OMe), 35.2 (CH_2CH_2O), 20.7 (CH_3, Ac); MS (ES+ve) m/z 590 (M+1$^+$, 13%), 612 (M+Na$^+$, 100%); HRMS (ES+ve) Calcd for $C_{33}H_{36}NO_9$ (MH$^+$) 590.2390, found: 590.2374.

2.1.15. (−)-(1*S*,5*R*,6*R*,7*R*,7a*S*)-6-Acetoxy-1-(2-hydroxy)ethyl-7-phenylcarbonyloxy-5-(phenylmethoxy)-methyl-tetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazol-3-one (19).

The same procedure described above for the preparation of **11** was used starting with **18** (61 mg, 0.104 mmol) and DDQ (33 mg, 0.146 mmol) in a solution of DCM (10 mL) containing water (0.5 mL). After the mixture had stirred at RT for 3 h, TLC analysis (60% EtOAc/petrol) indicated the presence of compound **18**. Additional DDQ (14 mg, 0.062 mmol) was then added to the mixture. The reaction was continued for another 1 h. Compound **19** (33 mg, 67%) was obtained as a pale yellow oil. $[\alpha]_D^{24}$=−54.7 (c1.6, $CHCl_3$); ^{1}H NMR δ 7.96 (dt, 2H, J=8.4, 1.5 Hz, BzH), 7.62 (tt, 1H, J=7.5, 1.5 Hz, BzH), 7.45 (t, 2H, J=7.8 Hz, BzH), 7.33–7.29 (m, 2H, Ar*H), 7.27–7.21 (m, 3H, Ar*H), 5.63 (dd, 1H, J=3.0, 2.4 Hz, H-6), 5.15–5.09 (m, 2H, H-1, H-7), 4.61 (s, 2H, Ar*CH_2), 4.16 (td, 1H, J=3.9, 2.4 Hz, H-5), 3.90–3.85 (m, 2H, H-7a, CH_aCH_bOBn), 3.82–3.80 (m, 2H, CH_2CH_2OH), 3.74 (dd, 1H, J=9.6, 4.2 Hz, CH_aCH_bOBn), 2.16–1.95 (m, 2H, CH_2CH_2OH), 2.09 (s, 3H, Ac); ^{13}C NMR δ 170.3 (CO, Ac), 166.5 (CO, Bz), 159.8 (CO-3), 137.6 (Ar*C), 133.8, 129.8 (2×CH, Bz), 128.4 (C, Bz), 128.6, 128.4, 127.7, 127.3 (3×Ar*CH, 1×BzCH), 83.3 (CH-7), 81.1 (CH-6), 78.5 (CH-1), 73.4 (Ar*CH_2), 70.4 (CH_2OBn), 69.2 (CH-7a), 63.4 (CH-5), 58.5 (CH_2CH_2OH), 37.8 (CH_2CH_2OH), 20.8 (CH_3, Ac); MS (ES+ve) m/z 470 (M+1$^+$, 8%), 492 (M+Na$^+$, 100%); HRMS (ES+ve) Calcd for $C_{25}H_{28}NO_8$ (MH$^+$) 470.1815, found: 470.1797.

2.1.16. (+)-(2*S*,3*R*,4*R*,5*R*)-5-[(1*S*)-1,3-Dihydroxypropyl]-2-(phenylmethoxy)methyl pyrrolizine-3,4-diol (20).

The same procedure described above for the preparation of **12** was used starting with **19** (32 mg, 0.067 mmol) and sodium hydroxide (427 mg, 0.674 mmol) in a solution of ethanol (1 mL). Compound **20** (15 mg, 76%) was obtained as a pale yellow oil. $[\alpha]_D^{25}$=+21.4 (c1.5, MeOH); ^{1}H NMR (CD_3OD) δ 7.38–7.23 (m, 5H, Ar*H), 4.55 (s, 2H, Ar*CH_2), 3.84–3.69 (m, 5H, H-3, H-4, CHOH, CH_2CH_2OH), 3.64

(dd, 1H, J=9.6, 3.9 Hz, CH_aCH_bOBn), 3.51 (dd, 1H, J=9.6, 6.9 Hz, CH_aCH_bOBn), 3.10 (dt, 1H, J=6.9, 3.6 Hz, H-2), 2.80 (dd, 1H, J=6.9, 5.4 Hz, H-5), 1.78 (dtd, 1H, J=14.1, 6.9, 3.6 Hz, CH_aCH_bCH_2OH), 1.65 (ddt, 1H, J=14.7, 9.0, 5.7 Hz, CH_aCH_bCH_2OH); ^{13}C NMR (CD_3OD) δ 139.6 (Ar*C), 129.4, 128.9, 128.7 (3×Ar*CH), 80.1, 80.0 (CH-3, CH-4), 74.3 (Ar*CH_2), 72.5 (CH_2OBn), 69.7 (CHOH), 67.1 (CH-5), 62.3 (CH-2), 60.0 (CH_2CH_2OH), 38.0 (CH_2CH_2-OH); MS (ES+ve) m/z 298 ($M+1^+$, 100%); HRMS (ES+ve) Calcd for $C_{15}H_{24}NO_5$ (MH^+) 298.1654, found: 298.1654.

Acknowledgements

We thank the Australian Research Council and the University of Wollongong for supporting this research.

References and notes

1. Nash, R. J.; Fellows, L. E.; Dring, J. V.; Fleet, G. W. J.; Derome, A. E.; Hamor, T. A.; Scofield, A. M.; Watkin, D. J. *Tetrahedron Lett.* **1988**, *29*, 2487–2490.
2. Molyneux, R. J.; Benson, M.; Wong, R. Y.; Tropea, J. E.; Elbein, A. D. *J. Nat. Prod.* **1988**, *51*, 1198–1206.
3. (a) Nash, R. J.; Fellows, L. E.; Plant, A. C.; Fleet, G. W. J.; Derome, A. E.; Baird, P. D.; Hegarty, M. P.; Scofield, A. M. *Tetrahedron* **1988**, *44*, 5959–5964. (b) Harris, C. M.; Harris, T. M.; Molyneux, R. J.; Tropea, J. E.; Elbein, A. D. *Tetrahedron Lett.* **1989**, *30*, 5685–5688. (c) Nash, R. J.; Fellows, L. E.; Dring, J. V.; Fleet, G. W. J.; Girdhar, A.; Ramsden, N. G.; Peach, J. M.; Hegarty, M. P.; Scofield, A. M. *Phytochemistry* **1990**, *29*, 111–114.
4. Kato, A.; Kano, E.; Adachi, I.; Molyneux, R. J.; Watson, A. A.; Nash, R. J.; Fleet, G. W. J.; Wormald, M. R.; Kizu, H.; Ikeda, K.; Asano, N. *Tetrahedron: Asymmetry* **2003**, *14*, 325–331.
5. (a) Tropea, J. E.; Molyneux, R. J.; Kaushal, G. P.; Pan, Y. T.; Mitchell, M.; Elbein, A. D. *Biochemistry* **1989**, *28*, 2027–2034. (b) Fellows, L.; Nash, R. PCT Int. Appl. WO GB 89/7951; *Chem Abstr.* **1990**, *114*, 143777f. (c) Elbein, A. D.; Tropea, J. E.; Molyneux, R. J. US Patent Appl. 289 907; *Chem Abstr.* **1990**, *113*, P91444p.
6. (a) Fleet, G. W. J.; Haraldsson, M.; Nash, R. J.; Fellows, L. E. *Tetrahedron Lett.* **1988**, *29*, 5441–5444. (b) Yoda, H.; Katoh, H.; Takabe, K. *Tetrahedron Lett.* **2000**, *7661*, 7665.
7. (a) Romero, A.; Wong, C.-H. *J. Org. Chem.* **2000**, *65*, 8264–8268. (b) Pearson, W. H.; Hines, J. V. *J. Org. Chem.* **2000**, *65*, 5785–5793. (c) Ikota, N.; Nakagawa, H.; Ohno, S.; Noguchi, K.; Okuyama, K. *Tetrahedron* **1998**, *54*, 8985–8998. (d) Pearson, W. H.; Hines, J. V. *Tetrahedron Lett.* **1991**, *32*, 5513–5516.
8. (a) Denmark, S. E.; Martinborough, E. A. *J. Am. Chem. Soc.* **1999**, *121*, 3046–3056. (b) White, J. D.; Hrnciar, P.; Yokochi, A. F. T. *J. Am. Chem. Soc.* **1998**, *120*, 7359–7360. (c) White, J. D.; Hrnciar, P. *J. Org. Chem.* **2000**, *9129*, 9142.
9. (a) Denmark, S. E.; Herbert, B. *J. Am. Chem. Soc.* **1998**, *120*, 7357–7358. (b) Denmark, S. E.; Herbert, B. *J. Org. Chem.* **2000**, *2887*, 2896.
10. (a) Denmark, S. E.; Cottell, J. J. *J. Org. Chem.* **2001**, *66*, 4276–4284. (b) Ikota, N. *Tetrahedron Lett.* **1992**, *33*, 2553–2556. (c) Choi, S.; Bruce, I.; Fairbanks, A. J.; Fleet, G. W.; Jones, A. H.; Nash, R. J.; Fellows, L. E. *Tetrahedron Lett.* **1991**, *32*, 5517–5520.
11. Tang, M.; Pyne, S. G. *J. Org. Chem.* **2003**, *68*, 7818–7828.
12. (a) Denmark, S. E.; Hurd, A. R. *J. Org. Chem.* **2000**, *65*, 2875–2886. (b) Denmark, S. E.; Hurd, A. R. *Org. Lett.* **1999**, *1*, 1311–1314. (c) Bell, A. A.; Pickering, L.; Watson, A. A.; Nash, R. J.; Pan, Y. T.; Elbein, A. D.; Fleet, G. W. J. *Tetrahedron Lett.* **1997**, *38*, 5869–5872.
13. Lindsay, K. B.; Pyne, S. G. *J. Org. Chem.* **2002**, *67*, 7774–7780.
14. Trost, B. M.; Bunt, R. C.; Lemoine, R. C.; Calkins, T. L. *J. Am. Chem. Soc.* **2000**, *122*, 5968–5976.
15. Colson, P.-J.; Hegedus, L. S. *J. Org. Chem.* **1993**, *58*, 5918–5924.
16. Lindsay, K. B.; Tang, M.; Pyne, S. G. *Synlett* **2002**, 731–734.
17. Davis, A. S.; Gates, N. J.; Lindsay, K. B.; Tang, M.; Pyne, S. G. *Synlett* **2004**, 49–52.
18. Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 855–888.
19. (a) Bernotas, R. C.; Cube, R. V. *Tetrahedron Lett.* **1991**, *32*, 161–164. (b) Chen, Y.; Vogel, P. *J. Org. Chem.* **1994**, *2487*, 2496.
20. (a) Zhao, H.; Hans, S.; Chemg, X.; Mootoo, D. R. *J. Org. Chem.* **2001**, *66*, 1761–1767. (b) Zhou, W.-S.; Xie, W.-G.; Lu, Z.-H.; Pan, X.-F. *Tetrahedron Lett.* **1995**, *36*, 1291–1294.
21. Gao, Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 7538–7539.
22. For related reactions of six-membered rings see: (a) Trost, B. M.; Pulley, S. R. *J. Am. Chem. Soc.* **1995**, *127*, 10143–10144. (b) Pettit, G. R.; Melody, N.; Herald, D. L. *J. Org. Chem.* **2001**, *66*, 2583–2587.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron
Tetrahedron 60 (2004) 5769–5776

A new strategy for the synthesis of pendant benzodiazacoronands and their use as components of chromatographic stationary phases

Piotr Piątek,[a] Daniel T. Gryko,[b] Agnieszka Szumna[b] and Janusz Jurczak[a,b,*]

[a]*Department of Chemistry, Warsaw University, Pasteura 1, 00-273 Warsaw, Poland*
[b]*Department of Chemistry, Institute of Organic Chemistry of the Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland*

Received 3 March 2004; revised 13 April 2004; accepted 6 May 2004

Abstract—The synthesis of a novel class of functionalized benzophanes in which a (2′-hydroxy)ethoxy pendant arm is attached to the phenyl ring is reported. The reported approach, utilizes simple starting materials, and skillful organization of the synthetic steps allows for simultaneous transforms of the macrocyclic ring and the pendant arm. Binding studies of these systems with Pd^{2+} and Cd^{2+} cations is described. A chromatographic stationary phase containing the benzodiazacoronand moiety was also synthesized, and found to interact specifically with isomeric nitrobenzene derivatives.

1. Introduction

Pendant benzocoronands have received much attention due to their specific properties, diverse structures and wide applications. They can serve as intermediates in the construction of polymer-supported coronands,[1] sensors[2] and other interesting architectures.[3,4] In the field of liquid chromatography, functionalized benzocoronands have been used as components of the chromatographic stationary phases. These phases have been used to separate alkali and alkaline earth metal ions.[5] In contrast, azacoronands have rarely been applied in chromatography,[6] in spite of their interesting binding properties.[7]

The most common synthesis of pendant benzocoronands utilizes a two-step procedure, namely macrocyclization followed by functionalization of the benzene ring via an electrophilic aromatic substitution reaction. Because of the directional effect of the substituents, this strategy leads to coronands having a 4-substituted benzene ring.[8] Only a few examples of 3-substituted benzocoronands have been reported in the literature and their synthesis require special synthetic procedures.[9] Our general idea was to reverse the order of these steps, so as to obtain the appropriate benzene derivatives and use them in the macrocyclization reaction. Such a process would be the most efficient means of constructing this class of compounds since it allows parallel transformation of the original functional groups into suitable chemical handles. Most of the existing macrocyclization methods however are incompatible with our concept because highly reactive functional groups are present in both molecules. Thus, we have chosen the reaction of a α,ω-diamines with a esters of a α,ω-dicarboxylic acids leading to the macrocyclic diamides.[10–16]

Our interest in the development of the easily accessible stationary phases stems from our work in the field of enantioselective catalysis.[17] With the increasing occurrence of troublesome separations of enantiomers, new highly selective chiral columns are desirable. In this paper, we describe the synthesis and binding properties of a series of benzocoronands functionalized at the 3- as well as the 4-position of the benzene ring. A novel type of the crown-ether stationary phase was prepared and used as a new stationary phase in HPLC experiments. The selectivity of this stationary phase was evaluated by examining the separation of the positional isomers of chloronitrobenzene.

2. Results and discussion

We have proposed that tripodal esters could be used in a double-amidation reaction to afford appropriately substituted diazacoronands in just three steps starting from commercially available phenols. The crucial issue was whether such esters would react with diamines to give the respective diamides leaving one free ester group. Recently,

Keywords: Amides; Chromatography; Macrocyclization; Coronands.
* Corresponding author. Tel.: +4822-6323221; fax: +4822-6316681; e-mail address: jurczak@icho.edu.pl

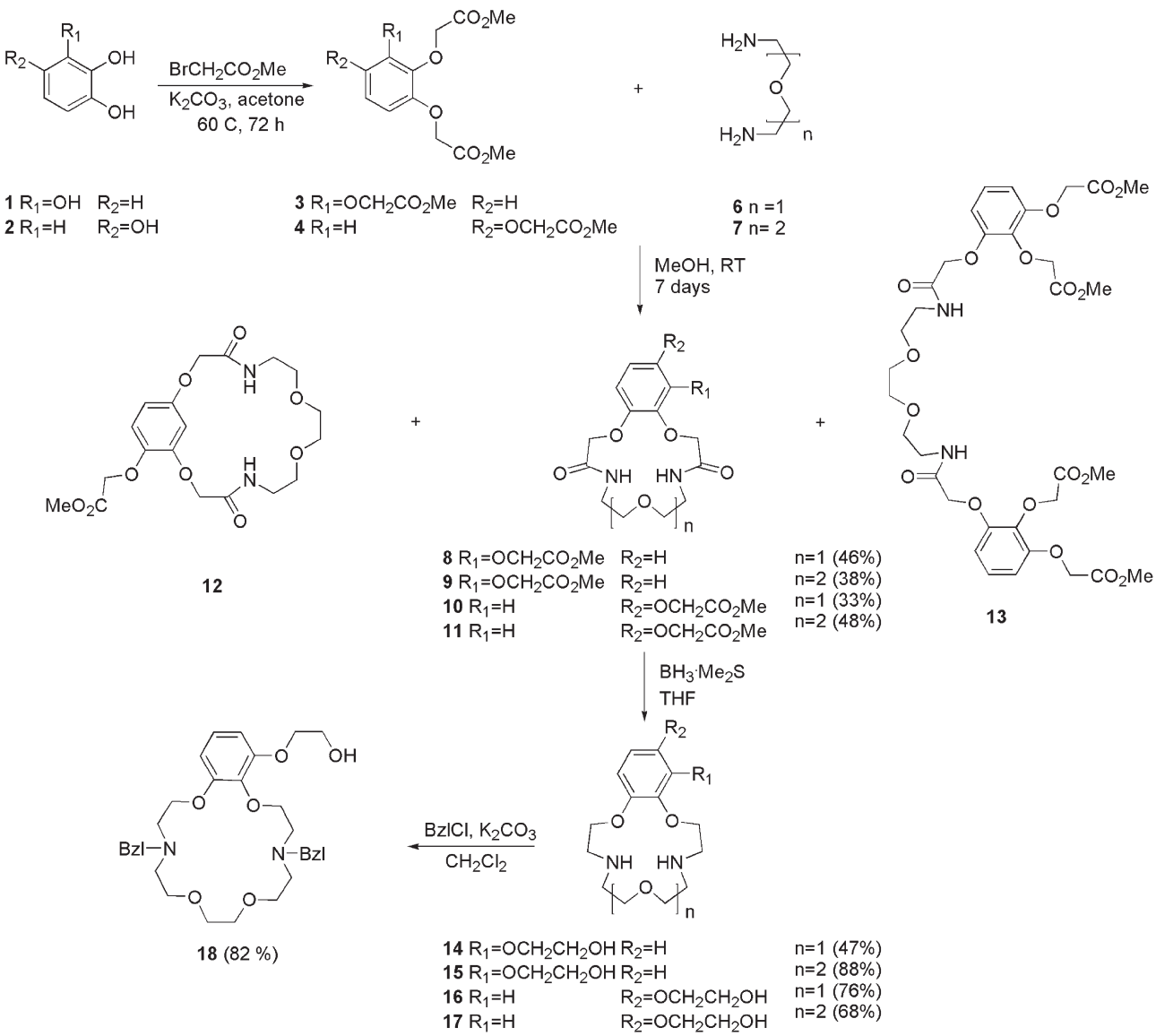
0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.05.012

we have shown that trimethyl pyridine-2,4,6-tricarboxylate reacts at only at 2- and 6-positions leaving a free ester group at 4-position.[16]

Thus, using well known conditions, pyrogallol **1** and 1,2,4-trihydroxybenzene **2** were elongated with methyl bromoacetate (Scheme 1). While ester **3** was obtained in almost quantitative yield (92%), the preparation of the ester **4** was much less efficient (42%). Therefore, we decided to also obtain *tert*-butyl ester **5**, hoping that this molecule would be also suitable for macrocyclization. The Williamson synthesis carried out in DMF gave ester **5** in 81% yield.

The trimethyl esters **2** and **4** reacted with stoichiometric amounts of α,ω-diamines **6** and **7** to afford functionalized macrocyclic diamides **8**-**11** in good yields (Scheme 1). The yields were approximately 30% lower than those of the non-armed analogs of esters **3** and **4** with the same diamines.[11] The presence of the side arm near the reaction centers, as in compound **3**, probably disturbs the closure of the macrocyclic ring and favors the formation of open-chain compounds. One such compound, **13**, was isolated and fully characterized. Interestingly, we proved previously that, for benzene derivatives, even a large group located *para* to the OCH_2CO_2Me arm did not influence the yield of macrocyclization.[11] Present results, (i.e., ester **4**) indicate that the additional arm diminishes yields of macrocyclic products. This is most likely because the additional arm reacts with diamines, giving rise to more non-macrocyclic products (similar to **13**) via intermediates which cannot cyclize. Decrease of the yield of formation of **9** could also be explained by the competitive 1,3-macrocyclization. Indeed, we isolated compound **12**, but only in 3% yield. Therefore, the competitive 1,3-macrocyclization reaction is not the main factor which decreases the yield of compounds **10** and **11**. It is known that *tert*-butyl esters are unreactive toward diamines but do react in the presence of DBU or analogous bases.[18,19] *tert*-Butyl ester **5** proved to be an exception and we failed to obtain any macrocyclic products from the reaction of **5** with **6** or **7** even in the presence of DBU.

We were able to obtain crystals suitable for X-ray analysis



Scheme 1.

for the macrocyclic diamide **9**. The 18-membered ring of diamide **9** is considerably distorted from the typical crown conformation (Fig. 1). For example, one of the amide groups is co-planar with the benzene ring and makes a short contact between amide hydrogen H19 and phenolic oxygen atom O22. Such a short 1,4 intramolecular contact is typical for the amide-ether based macrocycles.[11] Similarly, the other amide group makes a contact with the second phenolic oxygen atom (O7). However, the position of the amide group, as a whole, is quite different: the group is perpendicular to the benzene ring. This likely is due to the steric hindrance caused by the 'free' ester arm. Analysis of the non-bonding contacts implies that a co-planar positioning of this amide group would create unusually short contacts between the methylene group (C8) and the third phenolic oxygen (O23). Indeed, the unsubstituted 'arm-free' analogue of **9** exhibits crown-like conformation,[11] we conclude that the presence of an additional arm in the *ortho* position of the macrocyclic ring, albeit external, causes considerable changes in its conformation.

Reaction of diamides **8**-**11** with borane–methyl sulfide complex, followed by acid hydrolysis afforded diamines **14**-**17** respectively possessing side arms bearing hydroxyl groups. These compounds were isolated in yields between 47 and 88%. Compound **15** was chosen as substrate for the synthesis of stationary phase due to the two reasons: (1) pendant arm located at the position 3 can interact with macrocyclic ring and thereof play significantly bigger role in binding process than group located at the position 4; (2) availability of precursor (pyrogallol is drastically cheaper than 1,2,4-trihydroxybenzene). In order to introduce different functional groups into the macrocycle we converted diamine **15** into corresponding the N,N′-dibenzoyl derivative **18** (Scheme 1).

Before entering the next stage of our study, we decided to perform the preliminary binding studies of selected compounds with metal cations. Voltamperometric technique have allowed as to calculate the stability constants, and to determine the relative complexation dynamics. Our previous has shown that macrocyclic amides form strong complexes with Pd^{2+} and Cd^{2+} cations.[14,19] Therefore, we decided to test these cations as a probe of the binding abilities of macrocyclic diamide **9**, diamine **15**, bis(benzamide) **18** and benzo-1,10-diaza-18-crown-6. Diamine **15** displays the highest affinity for both Pd^{2+} and Cd^{2+} cations (Table 1). This binding is higher than that of benzo-1,10-diaza-18-crown-6 (log β 4.8 and 4.2, respectively) which indicates participation of the pendant hydroxy group in binding of cadmium(II). Although diamide **9** has the lowest affinity for Cd^{2+}, bis(benzamide) **18** having a hydroxyethylene arm forms complexes of moderate strength. Voltamperometric studies also reveal that the binding/release equilibrium is slow for both **9** and **12**. In contrast, the equilibrium of binding between ligand **18** and cadmium(II) is fast. Therefore, compound **18** appeared to be the most suitable candidate for use as chromatographic stationary

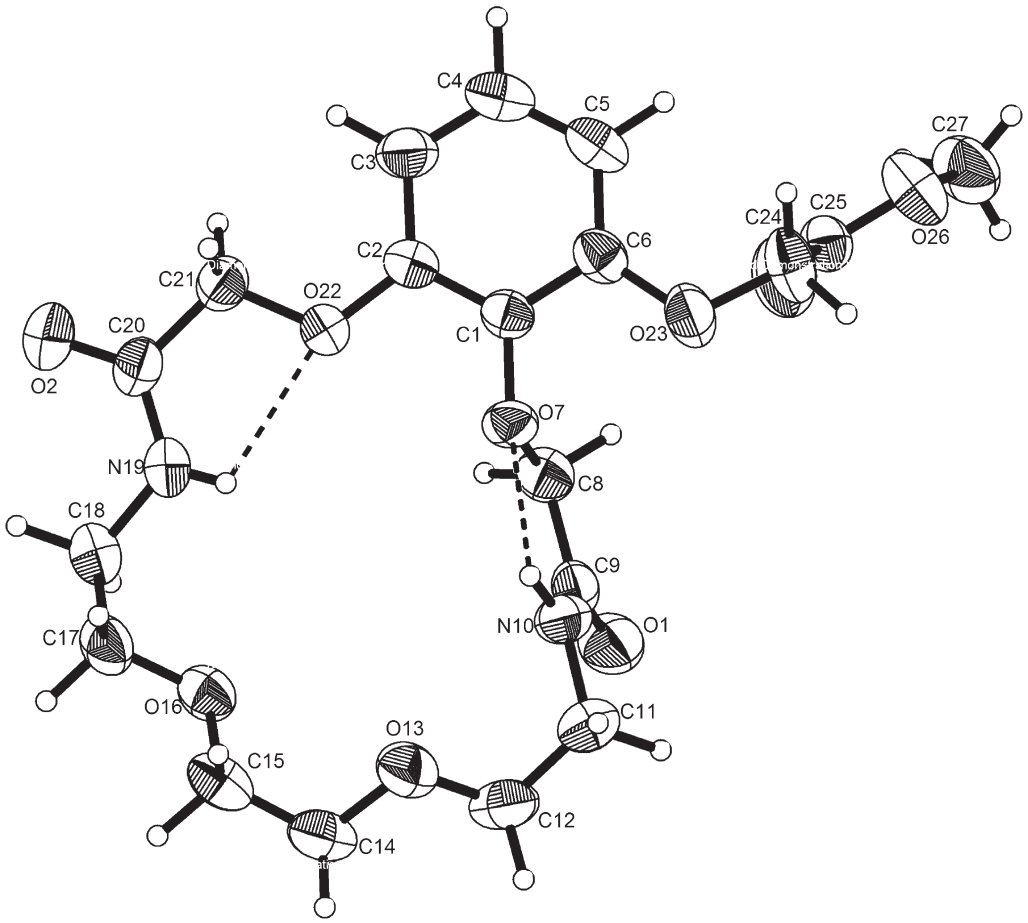


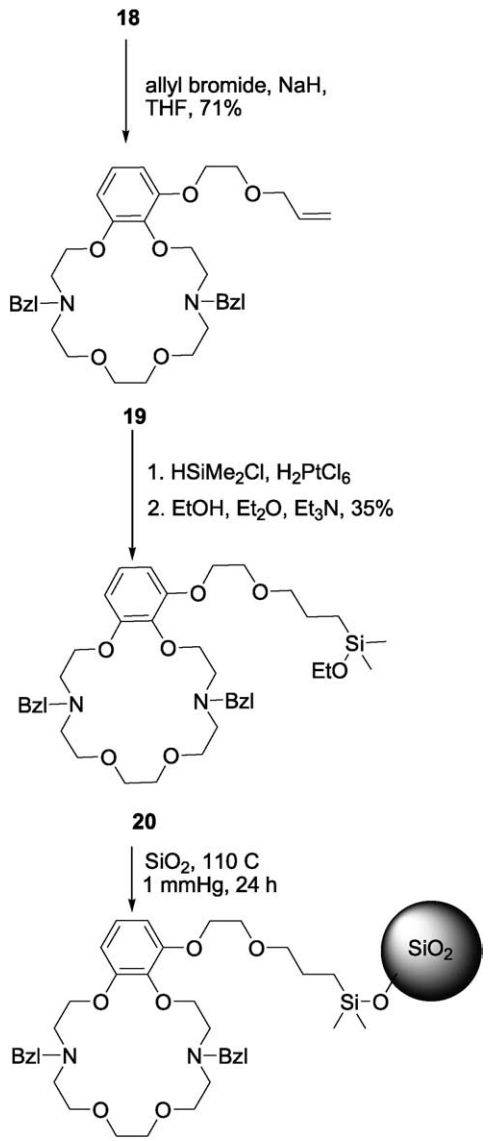
Figure 1. X-ray structure of bisamide **9**.

Table 1. Stability constants (log β) of complexes of Cd^{2+} and Pb^{2+} with benzo-1,10-diaza-18-crown-6 and compounds **9**, **15** and **18** in CH_3CN

	Benzo-1,10-diaza-18-crown-6	**9**	**15**	**18**
Cd^{2+}	4.2	2.5	4.8	3.5
Pb^{2+}	Not determined	4.3	4.8	Not determined

phase modifier. Furthermore, the terminal hydroxy group of **18** is perfectly suited for the Pirkle method for binding to silica gel.[20]

The synthesis of an attachable macrocycle starts from compound **18**. The terminal hydroxy group was alkylated by allyl bromide in the presence of sodium hydride. Hydrosilylation of **19** with chlorodimethylsilane followed by treatment with ethanol led to the benzodiazacoronand containing ethoxysilane, **20** (Scheme 2).[20] This ethoxy compound was heated with silica gel to form the benzodiazacoronand-modified chromatographic stationary phase **CSP-1**. Elemental analysis of the thoroughly dried bonded phase showed the loading to be approximately 0.14 mmol (based on carbon) of the macrocyclic selector per gram of the stationary phase **CSP-1**. This stationary phase was slurry-packed into a stainless-steel HPLC column and the residual silanol groups were endcapped with trimethylsilane groups to minimize nonspecific retention of analytes. To evaluate the nonspecific retention of the silica surface a reference column was packed with unmodified silica that was also endcapped.



Scheme 2.

The chromatographic performance of **CSP-1** was tested for its ability to separate isomers of nitrobenzene derivatives. In an initial chromatographic experiment, we attempted to separate the mixture of isomeric chloronitrobenzenes on the reference column. As shown in Figure 2, only *ortho*-chloronitrobenzene was resolved whereas the *para* and *meta* isomers remained unresolved. Next, chromatography was performed with the **CSP-1** column. The retention times of all three isomers of chloronitrobenzene increased (Fig. 3). Moreover, the *para* and *meta* isomers were separated with baseline resolution. These results clearly demonstrate that the benzodiazacoronand moiety interacts specifically with analytes. Currently, the nature of these interactions remains unknown. Similar results were obtained in comparative chromatographic experiments with nitrotoluene isomers (Fig. 4).

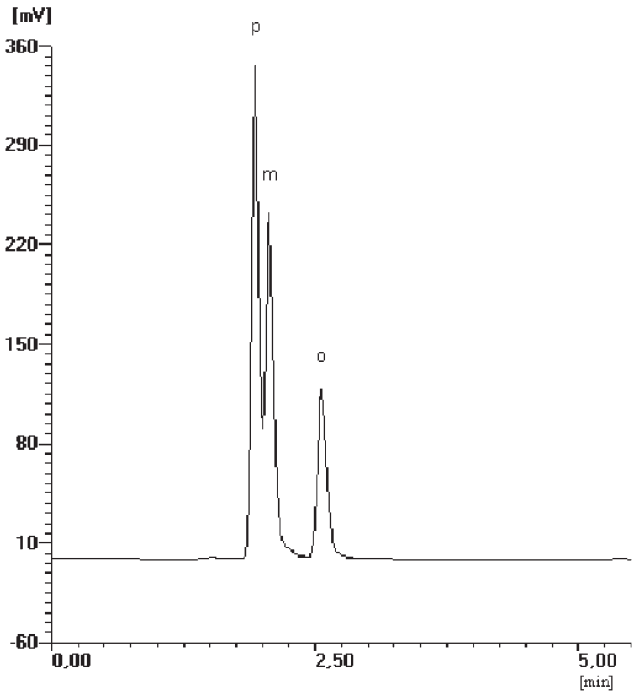


Figure 2.

In conclusion, we have established a convenient method for the synthesis of 3- as well as 4-pendant benzodiazacoronands. The dissymmetrization of simple substrates and parallel functional groups transformations make it possible to decrease the amount of steps necessary to synthesize these targets while maintaining their complex structure. The functionalized benzodiazacoronand was used to prepare the chromatographic stationary phase **CSP-1**. We have demonstrated that **CSP-1** selectively interacts with nitrobenzene derivatives. The data described herein is both

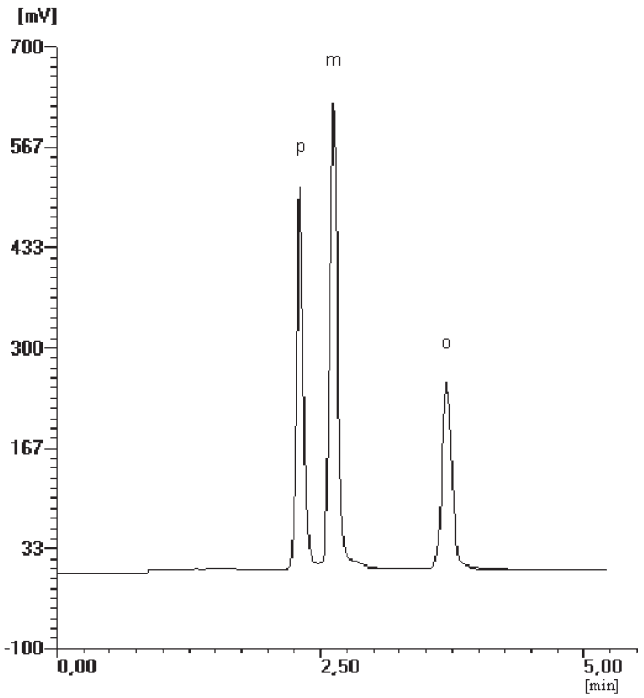


Figure 3.

synthetically valuable, and has implications for the design and development of chiral chromatographic stationary phases. Their synthesis and chromatographic behavior is currently being studied in our laboratory.

This work was supported by the State Committee for Scientific Research (Project 3T09A 12715). We wish to thank the Polish Science Foundation for additional financial support.

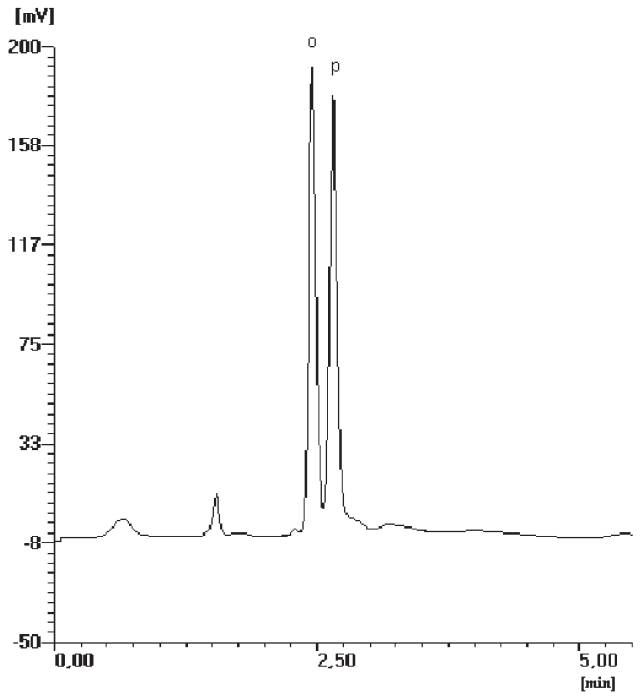


Figure 4.

3. Experimental

3.1. General methods

Melting points were measured with a Köfler type (Boetius) hot stage apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian Gemini (200 MHz) spectrometer in $CDCl_3$, or DMSO-d_6. ^{13}C NMR spectra were recorded on a Varian Gemini (50 MHz) spectrometer. All chemical shifts are quoted in parts per million relative to tetramethylsilane (δ 0.00 ppm) and coupling constants (J) are measured in Hertz. High-resolution mass spectrometry (HRMS) experiments were performed on an AMD-604 Intectra instrument using the electron impact (EI) or liquid secondary ion mass spectra (LSIMS) techniques. Column chromatography was performed on silica gel (Kieselgel-60, 200–400 mesh).

3.2. General procedures for the synthesis of trimethyl esters

To the solution of trihydroxybenzene (2.52 g, 20 mmol) in dry acetone, methyl bromoacetate (11.4 g, 75 mmol) and anhydrous K_2CO_3 (16.6 g, 120 mmol) were added. The mixture was stirred vigorously at 60 °C for 72 h. After cooling, the reaction mixture was filtered and the solvent was removed under reduced pressure to give a yellow-brown oil. This oil could be purified by vacuum distillation or crystallization from MeOH.

3.2.1. Triester 3. Colorless solid distilled at 170 °C (0.2 mm Hg) (92%); mp 68–69 °C; ^{1}H NMR ($CDCl_3$) δ 3.78 (s, 6H), 3.80 (s, 3H), 4.71 (s, 4H), 4.76 (s, 2H), 6.56 (d, J=8.0 Hz, 2H), 6.94 (dd, J_1=8.0 Hz, J_2=2.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 51.9, 52.1, 66.5, 69.6, 108.8, 123.9, 137.9, 151.5, 169.2, 169.7; HRMS m/z Calcd for $C_{15}H_{18}O_9$ $(M)^+$ 342.0958; found 342.0958. Anal. Calcd for $C_{15}H_{18}O_9$: C, 52.6%; H, 5.3%; found: C, 52.6%; H, 5.3%.

3.2.2. Triester 4. Colorless solid, crystallized from methanol (42%); mp 66–67 °C; ^{1}H NMR ($CDCl_3$) δ 3.79 (s, 3H), 3.80 (s, 3H), 3.81 (s, 3H), 4.56 (s, 2H), 4.67 (s, 2H), 4.70 (s, 2H), 6.45 (dd, J_1=8.8 Hz, J_2=2.9 Hz, 1H), 6.54 (d, J=2.9 Hz, 1H), 6.88 (d, J=8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 52.3, 52.4, 52.5, 66.0, 66.4, 67.8, 104.1, 106.4, 117.6, 143.0, 149.3, 153.8, 169.3, 169.5, 169.9; HRMS m/z Calcd for $C_{15}H_{18}O_9$ $(M)^+$ 342.0958; found 342.0942.

3.2.3. Triester 5. To the solution of 1,2,4-trihydroxybenzene (1.26 g, 10 mmol) in dry DMF, tert-butyl bromoacetate (7.8 g, 40 mmol) and anhydrous K_2CO_3 (6.2 g, 45 mmol) were added. The reaction mixture was vigorously stirred and refluxed for 1 h. After cooling, the reaction mixture was filtered and the solvent was evaporated under reduced pressure. The brown oil was chromatographed (silica, hexanes:EtOAc, 3/1) to afford pure **5** as a colorless oil. 81%; oil; ^{1}H NMR ($CDCl_3$) δ 1.47 (s, 9H), 1.48 (s, 18H), 4.43 (s, 2H), 4.54 (s, 2H), 4.56 (s, 2H), 6.38 (dd, J_1=9.2 Hz, J_2=3.0 Hz, 1H), 6.51 (d, J=2.9 Hz, 1H), 6.85 (d, J=8.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 28.0, 66.2, 66.6, 68.0, 81.8, 82.1, 82.2, 103.5, 105.9, 117.0, 142.8, 149.1, 152.5, 167.6, 167.9, 168.3; HRMS m/z Calcd for $C_{24}H_{36}O_9$ $(M)^+$ 468.2359; found 468.2344.

3.3. General procedures for the synthesis of macrocyclic lactams

An equimolar 0.1 M methanolic solution (5 mmol each) of the α,ω-diamine and the triester was left at ambient temperature for a period of 7 days. Then the solvent was evaporated and the residue was chromatographed on a silica gel column using 0.5–10% mixtures of methanol in chloroform.

3.3.1. Diamide 8. Colorless solid (46%); mp 254–255 °C; ^{1}H NMR ($CDCl_3$) δ 3.66–3.57 (m, 8H), 3.79 (s, 3H), 4.45 (s, 2H), 4.62 (s, 2H), 4.70 (s, 2H), 6.50–6.57 (m, 2H), 7.03 (t, J=8.4 Hz, 1H), 7.38 (br t, 2H); ^{13}C NMR ($CDCl_3$) δ 37.9, 38.2, 52.3, 65.5, 67.1, 68.4, 68.6, 71.6, 106.2, 106.8, 124.5, 135.6, 150.0, 151.6, 166.8, 168.6, 168.7; HRMS *m/z* Calcd for $C_{17}H_{22}N_2O_8$ $(M)^+$ 382.1376; found 382.1376. Anal. Calcd for $C_{17}H_{22}N_2O_8$: C, 53.4%; H, 5.8%; N, 7.3%; found: C, 53.0%; H, 5.8%.; N, 7.1%.

3.3.2. Diamide 9. Colorless solid (38%); mp 103–107 °C; ^{1}H NMR ($CDCl_3$) δ 3.56 (s, 4H), 3.62 (s, 8H); 3.79 (s, 3H), 4.57 (s, 2H), 4.59 (s, 2H), 4.70 (s, 2H), 6.50–6.63 (m, 2H), 7.02 (t, J=8.4 Hz, 1H), 7.15 (br s, 1H), 7.51 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 38.8, 38.9, 52.3, 65.5, 68.3, 69.1, 69.5, 70.0, 70.1, 71.8, 107.2, 107.3, 124.6, 136.4, 151.0, 151.4, 167.8, 168.6, 169.0; HRMS *m/z* Calcd for $C_{19}H_{26}N_2O_9$ $(M)^+$ 426.1638; found 426.1637. Anal. Calcd for $C_{19}H_{26}N_2O_9$: C, 53.5%; H, 6.1%; N, 6.6%; found: C, 53.5%; H, 6.3%.; N, 6.6%.

3.3.3. Diamide 10. Colorless solid (33%); mp 220–223 °C; ^{1}H NMR ($CDCl_3$) δ 3.62–3.71 (s, 8H), 3.81 (s, 3H); 4.43 (s, 2H), 4.44 (s, 2H), 4.61 (s, 2H), 6.41 (dd, J_1=8.4 Hz, J_2=2.8 Hz, 1H), 6.57 (t, J=2.8 Hz, 1H), 6.76 (d, J=8.8 Hz, 1H), 7.34 (br s, 2H); ^{13}C NMR ($CDCl_3$) δ 38.3, 52.3, 65.7, 66.8, 67.3, 68.9, 102.3, 104.9, 112.5, 141.2, 146.8, 152.9, 166.7, 167.2, 169.1; HRMS *m/z* Calcd for $C_{17}H_{22}N_2O_8$ $(M)^+$ 382.1376; found 382.1395.

3.3.4. Diamide 11. Colorless solid (49%); mp 187–189 °C; ^{1}H NMR ($CDCl_3$) δ 3.55–3.60 (m, 12H), 3.81 (s, 3H); 4.52 (s, 2H), 4.55 (s, 2H), 4.59 (s, 2H), 6.42 (dd, J_1=8.8 Hz, J_2=2.9 Hz, 1H), 6.60 (d, J=2.9 Hz, 1H), 6.79 (d, J=8.8 Hz, 1H), 7.11 (br s, 2H); ^{13}C NMR ($CDCl_3$) δ 38.7, 38.8, 52.4, 65.8, 67.7, 68.3, 69.7, 69.8, 70.2, 102.8, 105.7, 113.8, 141.8, 147.6, 153.2, 167.6, 168.1, 169.2; HRMS *m/z* Calcd for $C_{19}H_{26}N_2O_9$ $(M)^+$ 426.1638; found 426.1645. Anal. Calcd for $C_{19}H_{26}N_2O_9$: C, 53.5%; H, 6.1%; N, 6.6%; found: C, 53.3%; H, 6.2%.; N, 6.3%.

3.3.5. Diamide 12. Colorless solid (3%); mp 187–189 °C; ^{1}H NMR ($CDCl_3$) δ 3.41–3.60 (m, 12H), 3.79 (s, 3H); 4.47 (s, 2H), 4.65 (s, 2H), 4.67 (s, 2H), 6.37 (dd, J_1=8.8 Hz, J_2=2.8 Hz, 1H), 6.62 (d, J=2.8 Hz, 1H), 6.83 (d, J=8.8 Hz, 1H), 6.87 (br t, 1H), 6.92 (br t, 1H); ^{13}C NMR ($CDCl_3$) δ 38.5, 39.1, 52.2, 67.3, 67.6, 69.4, 69.5, 69.5, 69.7, 70.3, 70.9, 104.7, 104.8, 116.4, 142.9, 149.3, 153.0, 168.1, 168.7, 169.4; HRMS *m/z* Calcd for $C_{19}H_{26}N_2O_9$ $(M)^+$ 426.1638; found 426.1649.

3.3.6. Open-chain compound 13. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 3.53–3.63 (m, 12H), 3.78 (s, 12H); 4.51 (s, 2H), 4.63 (s, 2H), 4.69 (s, 2H), 4.77 (s, 2H), 6.49–6.60 (m, 4H), 6.91–7.02 (m, 1H), 7.14–7.24 (m, 1H), 7.84 (br s, 1H), 8.14 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 38.5, 38.6, 21.8, 52.0, 52.1, 65.5, 65.6, 68.4, 69.2, 69.6, 69.9, 72.8, 106.9, 107.4, 107.9, 123.8, 124.2, 125.1, 128. 0, 128.8, 137.4, 137.6, 150.7, 151.1, 168.2, 168.6, 168.8, 169.8, 170.3; HRMS *m/z* Calcd for $C_{34}H_{44}N_2O_{18}Na$ $(M+Na)^+$ 791.2487; found 791.2498.

3.4. General procedure for the reduction of macrocyclic lactams

Diamide (1 mmol) was dissolved in warm THF and 2 M solution of the borane–methyl sulfide complex in THF (9 mmol) was added. The reaction mixture was refluxed for 4 hours and cooled down. Evaporation of the solvent gave an oily residue that was dissolved in HCl (35%, 2 mL) and heated to 70 °C for 2 h. After cooling, the reaction mixture was made basic (pH was set at 13–14 using aqueous NaOH) and extracted into CH_2Cl_2. The combined extracts were dried (Na_2SO_4), filtered, concentrated and chromatographed (silica, $CHCl_3$/MeOH, 98:2, then 9:1 up to 1:1).

3.4.1. Diamine 14. 47%; oil; ^{1}H NMR ($CDCl_3$) δ 2.79–3.00 (m, 8H), 3.45 (br s, 3H), 3.61–3.69 (m, 4H), 3.86 (t, J=5.0 Hz, 2H), 4.15–4.02 (m, 6H), 6.50–6.55 (m, 2H), 6.91 (t, J=8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 46.3, 47.3, 48.9, 49.4, 60.6, 66.9, 67.8, 69.2, 70.8, 72.6, 105.6, 106.9, 123.6, 137.1, 152.3, 152.8.

3.4.2. Diamine 15. 88%; oil; ^{1}H NMR ($CDCl_3$) δ 2.79–2.95 (m, 8H), 3.53–3.65 (m, 8H), 3.87 (t, J=4.0 Hz, 2H), 4.03 (t, J=3.9 Hz, 2H), 4.09–4.17 (m, 4H), 6.59 (t, J=7.0 Hz, 2H), 6.94 (t, J=8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 47.8, 48.1, 48.4, 49.2, 60.3, 69.3, 69.5, 69.9, 70.1, 70.4, 70.8, 72.8, 107.1, 108.3, 123.5, 138.5, 152.5, 152.8; HRMS *m/z* Calcd for $C_{18}H_{31}N_2O_6$ $(M+H)^+$ 371.2182; found 371.2172.

3.4.3. Diamine 16. 76%; oil; ^{1}H NMR ($CDCl_3$) δ 2.75–2.93 (m, 8H), 3.53–3.60 (m, 4H), 3.76–3.79 (m, 2H), 3.89–4.03 (m, 6H), 6.40 (dd, J=8.8, 2.6 Hz, 1H), 6.61 (d, J=2.6 Hz, 1H), 6.81 (d, J=8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 61.9, 68.5, 69.3, 69.5, 69.9, 71.3, 103.1, 106.2, 115.1, 144.2, 150.7, 155.6; HRMS *m/z* Calcd for $C_{16}H_{25}N_2O_5$ $(M+H)^+$ 326.1841; found 326.1840.

3.4.4. Diamine 17. 68%; oil; ^{1}H NMR ($CDCl_3$) δ 2.80–2.85 (m, 4H), 3.02–3.29 (m, 4H), 3.59–3.64 (m, 8H), 3.81–3.85 (m, 2H), 3.96–4.10 (m, 6H), 6.30 (d, J=2.8 Hz, 1H), 6.45 (dd, J=8.8, 2.6 Hz, 1H), 6.86 (d, J=8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 61.9, 68.7, 69.2, 70.7, 71.3, 71.4, 72.1, 73.5, 102.9, 105.8, 114.3, 144.2, 150.6, 155.3; HRMS *m/z* Calcd for $C_{18}H_{30}N_2O_6$ $(M)^+$ 370.2103; found 370.2114.

3.4.5. Compound 18. To the solution of diazacoronand **15** (1.6 g, 4.4 mmol) in CH_2Cl_2 (25 mL) the solution of K_2CO_3 (12 g, 87 mmol) in H_2O was added. The reaction mixture was cooled to 10 °C, followed by addition of benzoyl chloride (4 mL, 34 mmol). The resulting mixture was stirred at RT for 30 min, then diluted with CH_2Cl_2 (80 mL) and the organic layer was washed with satd. $NaHCO_3$. After evaporation of the solvent under reduced pressure, the pale yellow oil was chromatographed (silica, $CHCl_3$, then $CHCl_3$/MeOH, 96:4), to give compound **18** as a colorless oil

(2.086 g) in 82% yield. ^{1}H NMR ($CDCl_3$) δ 3.51–3.65 (m, 8H), 3.71–3.82 (m, 6H), 3.95–4.13 (m, 6H), 4.21–4.34 (m, 4H), 6.50–6.63 (m, 2H), 6.93–6.97 (m, 1H), 7.37 (s, 10H); ^{13}C NMR ($CDCl_3$) δ 45.6, 46.3, 46.7, 49.5, 50.6, 60.8, 68.0, 69.1, 69.5, 69.7, 78.0, 105.4, 106.2, 123.7, 126.3, 128.2, 128.4, 129.3, 136.2, 152.5, 172.1, 172.5; HRMS *m/z* Calcd for $C_{32}H_{38}N_2O_8$ $(M)^+$ 578.2628; found 578.2618.

3.4.6. Compound 19. To a suspension of NaH (20 mg of 60% NaH in mineral oil, 0.6 mmol) in THF, a solution of compound **18** (290 mg, 0.5 mmol) was added dropwise. After 15 min of stirring at RT, freshly distilled allyl bromide (73 mg, 52 μL, 0.6 mmol) was added and the reaction mixture was refluxed for 6 h. After cooling, the excess of NaH was destroyed with small amount of water and all volatile components were evaporated under reduced pressure. Next, H_2O was added to the residue and it was extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and the solvent was removed. The residue was chromatographed (silica, acetone/hexanes, 1:1) to afford 219 mg of compound **19** (71%). ^{1}H NMR (DMSO-d_6) δ 3.41–3.74 (m, 8H), 3.91–4.14 (m, 16H), 4.99–5.21 (m, 2H), 5.70–5.88 (m, 1H), 6.53–6.61 (m, 2H), 6.79–6.92 (m, 1H), 7.23–7.34 (m, 10H); ^{13}C NMR (DMSO-d_6) δ 46.2, 49.2, 49.7, 50.0, 67.1, 67.9, 68.9, 69.6, 70.0, 78.0, 102.3, 105.5, 106.2, 115.1, 122.5, 125.3, 127.1, 127.3, 127.8, 128.0, 135.6, 151.3, 169.7, 169.9; HRMS *m/z* Calcd for $C_{35}H_{42}N_2O_8$ $(M)^+$ 618.2942; found 618.2934.

3.4.7. Compound 20. To a solution of **19** (0.946 g, 1.53 mmol) in dry CH_2Cl_2, dimethylchlorosilane (15 mL) was added followed by the solution of H_2PtCl_6 (10 mg) in dry isopropanol (100 μL). The reaction mixture was refluxed for 4 h. After cooling, the solvent and excess of Me_2SiHCl were removed under reduced pressure, and the residue was treated with absolute ethanol (10 mL), dry diethyl ether (10 mL) and triethylamine (10 mL). The suspension was stirred for 2 h at RT and the precipitate was removed by filtration. The supernatant was evaporated and the crude product was chromatographed (silica, $CHCl_3$, then $CHCl_3$/MeOH, 97:3) to yield 372 mg of **20** as a light yellow oil (35%). ^{1}H NMR ($CDCl_3$) δ 0.04 (t, J=5.4 Hz, 6H), 0.41–0.52 (m, 2H), 1.44–1.59 (m, 3H), 3.51–3.92 (m, 14H), 3.98–4.35 (m, 16H), 6.51–6.61 (m, 2H), 6.82–6.97 (m, 1H), 7.21–7.32 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 0.1, 13.9, 23.2, 46.1, 49.6, 49.9, 50.4, 60.6, 67.4, 68.8, 70.4, 73.9, 105.9, 106.9, 123.6, 126.2, 128.0, 128.2, 128.9, 129.1, 136.1, 152.4, 171.7, 171.9.

3.5. The chromatographic stationary phase CSP-1

The silica gel (2.5 g, Kromasil Si 60, 5 μm beads) was dried for 10 h at 110 °C and 1 mm Hg and then suspended in dry toluene (10 mL). A solution of compound **20** (350 mg, 0.48 mmol) in toluene (5 mL) was added to this suspension. Toluene was removed under reduced pressure and the dry residue was heated at 110 °C and 1 mm Hg for 24 h. Every 2 h, the modified silica gel was mixed ultrasonically for 5 min. After cooling, **CSP-1** was washed with CH_2Cl_2 (50 mL) and MeOH (50 mL). Evaporation of the solvents indicated that 100 mg of compound **20** remained unbound. The modified silica gel was then heated for 5 h at 110 °C at 1 mm Hg. Combustion analysis (C, 6.43%; H, 1.11%; N, 0.31%) indicated that the amount of the diazacoronand was 0.14 mmol per gram of the silica gel.

3.6. Preparation of the chromatographic column containing CSP-1

A stainless steel column (4.6 mm×10 cm) was filled with the suspension of **CSP-1** in MeOH under pressure of ca. 60 atm. Then column was washed with CH_2Cl_2 (20 mL) and solution of hexamethyldisilazane (5 mL) in CH_2Cl_2 (20 mL) maintaining the flow at 1.0 mL/min. The test column (containing unmodified silica) was prepared in an analogous manner.

3.7. The chromatographic experiments

The chromatographic experiments were undertaken using LaChrom L7100 pump (Merck) and UV 486 detector (Waters). The substances were detected by measuring the absorbance at 254 nm. Both columns were not thermostated and all experiments were done at RT. The mobile phase was 0.1% isopropanol in hexane; the flow was 1.0 mL/min. The sample volume was 2 μL.

3.8. The X-ray structure investigations

The crystal data for the structure were measured on MACH3 κ-diffractometer using Cu K_α radiation and ω–2θ scan mode. Structure were solved using direct methods (SHELXS program) and refined using SHELX97 program. The hydrogen atoms were treated in a mixed way. Those of N–H, were found from Fourier differential map. Crystal data for **9**: $C_{19}H_{26}N_2O_s$, M=426.42, orthorhombic, $Pca2_1$, a=9.694(1), b=12.9111(5), c=16.535(1) Å, V=2069.5(3) Å^3, Z=4, D_c=1.369 g/cm^3, μ=0.929 mm^{-1}, F_{000}=904, T=273(2) K, $2\theta_{max}$=66.38°, 1487 reflections collected, 1487 unique. Final GOF=1.028, $R1$=0.0400, $wR2$=0.1035, R indices based on 1487 unique reflections (refinement on F^2), 292 parameters, 1 restraint. Crystallographic data (excluding structure factors) have been deposited with Cambridge Crystallographic Data Centre as supplementary publication number CCDC 232678. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

3.9. The voltammetric studies

Voltammetric measurements were performed on a hanging-drop mercury electrode (SMDE1, Laboratorni Pristroje, Praha) using an Autolab electrochemical instrument (Eco Chemie, The Netherlands). The reference electrode was a Ag/AgCl electrode filled with 0.1 M solution of tetraethylammonium chloride in methanol connected to the cell with an electrolytic bridge containing 0.1 M solution of tetrabutylammonium perchlorate in acetonitrile. A piece of platinum foil served as a counter-electrode. In all experiments, 0.1 M solution of tetrabutylammonium perchlorate (Fluka, electrochem. grade) in acetonitrile (Fluka) was used as supporting electrolyte. All solutions were deoxygenated with argon before the measurement. The concentrations of cadmium and lead ions in the solution in the cell were typically at the level of 10^{-4} M, obtained by addition of

small volume of the concentrated stock solutions, $CdSO_4$ (BDH, England) and $Pb(ClO_4)_2$ (SERVA, Germany), respectively, directly to the cell. Concentrations of sodium and potassium ions were changed from approximately 10^{-4} to approximately 10^{-2} M by addition of concentrated $NaClO_4$ (Koch-Light, Great Britain) and KPF_6 (Fluka) solutions. For each metal cation, a series of measurements was made for various metal/ligand concentration ratios. For each metal/ligand ratio, the voltammograms were measured at scan rates of 0.05, 0.1, 0.2 and 0.4 V/s. Each voltammogram was measured twice and averaged. The conductometric measurements were carried out using CDM 210 conductometer (Radiometer, Denmark) equipped with a XE 110 probe, in a continuously stirred solution from which CO_2 was removed by bubbling with argon. All measurements were carried out at 20 ± 1 °C. The results obtained indirectly (Na^+, K^+) may be influenced by the variation in the ohmic drop in the solution which shifts the potential toward positive values and apparently increases β.

References and notes

1. Pugia, M. J.; Czech, A.; Czech, B. P.; Bartsch, R. A. *J. Org. Chem.* **1986**, *51*, 2945–2948.
2. (a) Micheloni, M.; Formica, M.; Fusi, V.; Romani, P.; Pontellini, R.; Dapporto, P.; Paoli, P.; Rossi, P.; Valtancoli, B. *Eur. J. Inorg. Chem.* **2000**, 51–57. (b) Gunnlaugsson, T.; Bichell, B.; Nolan, C. *Tetrahedron Lett.* **2002**, *43*, 4989–4992. (c) Miyaji, H.; Collinson, S. C.; Prokes, I.; Tucker, J. H. R. *Chem. Commun.* **2003**, 64–65. (d) Kryatova, O. P.; Kolchinski, A. G.; Rybak-Akimova, E. V. *Tetrahedron* **2003**, *59*, 231–239.
3. Shinkai, S.; Shigematsu, K.; Kusano, Y.; Manbe, O. *J. Chem. Soc., Perkin Trans. 1* **1981**, 3279–3283.
4. Percec, V.; Johansson, G.; Heck, J.; Ungar, G.; Batty, S. V. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1411–1419.
5. (a) Nakajiama, M.; Kimura, K.; Shono, T. *Anal. Chem.* **1983**, *55*, 463–467. (b) Iwachido, T.; Naito, H.; Samukawa, F.; Ishimaru, K.; Toei, K. *Bull. Chem. Soc. Jpn* **1986**, *59*, 1475–1480.
6. (a) Gasparrini, F.; Misiti, D.; Pierini, M.; Villani, C. *Org. Lett.* **2002**, *4*, 3993–3996. (b) Gong, Y.; Xiang, Y.; Yue, B.; Xue, G.; Bradshaw, J. S.; Lee, H. K.; Lee, M. L. *J. Chromatogr. A* **2003**, *1002*, 63–70. (c) Shi-Lu, D.; Yu-Qi, F.; Hui-Ning, D.; Yin-Han, G.; Yuan-Wei, Z. *J. Chromatogr. Sci.* **1999**, *37*, 137–144.
7. (a) Huszthy, P.; Oue, M.; Bradshaw, J. S.; Zhu, C. Y.; Wang, T.; Dalley, N. K.; Curtis, J. C.; Izatt, R. M. *J. Org. Chem.* **1992**, *57*, 5383–5394. (b) Gokel, G. W. *Chem. Commun.* **2003**, 2847–2852. (c) Formica, M.; Fusi, V.; Giorgi, L.; Guerri, A.; Sucarini, S.; Micheloni, M.; Paoli, P.; Pontellini, R.; Rossi, P.; Tarzia, G.; Zappia, G. *New J. Chem.* **2003**, *27*, 1575–1583. (d) Pearson, A. J.; Xiao, W. *J. Org. Chem.* **2003**, *68*, 5369–5376.
8. (a) Stott, P. E.; Bradshaw, J. S.; Parish, W. W.; Copper, J. W. *J. Org. Chem.* **1980**, *45*, 4716–4720. (b) Jeong, K.-S.; Pyun, S.-Y. *Tetrahedron Lett.* **1994**, *35*, 7041–7044. (c) Bereczki, R.; Agai, B.; Bitter, I. *J. Inclusion Phenom.* **2003**, *47*, 53–58. (d) Hayvali, Z.; Hayvali, M.; Kilic, Z.; Hoekelek, T.; Weber, E. *J. Inclusion Phenom.* **2003**, *45*, 285–294. (e) Gromov, S. P.; Dmitrieva, S. N.; Vedernikov, A. I.; Kuzmina, L. G.; Churakov, A. V.; Strelenko, Y. A.; Howard, J. A. K. *Eur. J. Org. Chem.* **2003**, 3189–3199.
9. (a) Czech, B. P.; Czech, A.; Bartsch, R. A. *J. Heterocycl. Chem.* **1985**, *22*, 1297–1300. (b) Dietl, F.; Gierer, G.; Merz, A. *Synthesis* **1985**, 626–631.
10. Jurczak, J.; Stankiewicz, T.; Sałański, P.; Kasprzyk, S.; Lipkowski, P. *Tetrahedron* **1993**, *49*, 1478.
11. Gryko, D. T.; Piątek, P.; Jurczak, J. *Tetrahedron* **1997**, *53*, 7957–7966.
12. Gryko, D. T.; Gryko, D.; Jurczak, J. *Synlett* **1999**, 1310–1312.
13. Solovev, V. P.; Strakhova, N. N.; Kazachenko, V. P.; Solotnov, A. F.; Baulin, V. E.; Raevsky, O. A.; Rudiger, V.; Eblinger, F.; Schneider, H. J. *Eur. J. Org. Chem.* **1998**, 1379.
14. Gryko, D. T.; Piątek, P.; Pęcak, A.; Pałys, M.; Jurczak, J. *Tetrahedron* **1998**, *54*, 7505.
15. Yuan, Q.; Fu, E.; Wu, X.; Fang, M.; Xue, P.; Wu, C.; Chen, J. *Tetrahedron Lett.* **2002**, *43*, 3935.
16. Gryko, D.; Gryko, D. T.; Sierzputowska-Gracz, H.; Piątek, P.; Jurczak, J. *Helv. Chim. Acta* **2004**, *87*, 156–166.
17. Kwiatkowski, P.; Wojaczyńska, E.; Jurczak, J. *Tetrahedron: Asymmetry* **2003**, *14*, 3643–3645.
18. Gryko, D. T.; Piątek, P.; Jurczak, J. *Synthesis* **1999**, 336–340.
19. Gryko, D. T.; Pęcak, A.; Kozmiński, W.; Piątek, P.; Jurczak, J. *Supramol. Chem.* **2000**, *12*, 229–235.
20. Pirkle, W. H.; Welch, C. J.; Lamm, B. *J. Org. Chem.* **1992**, *57*, 3854–3860.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron
Tetrahedron 60 (2004) 5777–5783

Synthesis of pyrrolo[2,3-*c*]2,7-naphthyridine derivatives by cascade heterocyclization reaction of 2-amino-4-cyanomethyl-6-dialkylamino-3,5-pyridinedicarbonitriles

Anton V. Tverdokhlebov,[a,*] Elizaveta V. Resnyanska,[a] Alexander V. Zavada,[b] Andrey A. Tolmachev,[c] Alexander N. Kostyuk[d] and Alexander N. Chernega[d]

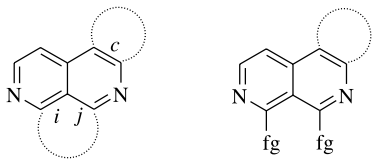
[a]*Enamine Ltd. Co., I. Kudri str. 31, apt. 17, 02042 Kiev, Ukraine*
[b]*Chernigov State University of Technology, Shevchenko str. 95, 14027 Chernigov, Ukraine*
[c]*Kiev National Taras Shevchenko University, Volodimirska str. 62, 01033 Kiev, Ukraine*
[d]*Institute of Organic Chemistry NAS, Murmanskaya str. 5, 02094 Kiev, Ukraine*

Received 15 February 2004; revised 13 April 2004; accepted 6 May 2004

Abstract—Alkylation of the title pyridinedicarbonitriles with *N*-substituted chloroacetamides was found to give 5,6-diamino-8-dialkylamino-2,3-dihydro-2-oxo-1*H*-pyrrolo[2,3-*c*]2,7-naphthyridine-9-carbonitriles. The structure of obtained compounds was unambiguously confirmed by X-ray crystallographic study. The heterocyclization reaction proceeded regioselectively involving 3-CN group of the starting pyridines without participation of 5-CN. The reasons of the selectivity were discussed. An interaction of prepared naphthyridine derivatives with acetic acid anhydride and cyclohexanone yielded 2-dialkylamino-6,8,9,10-tetrahydro-5-methyl-9-oxopyrimido[4,5,6-*ij*]-pyrrolo[2,3-*c*]2,7-naphthyridine-1-carbonitriles and 2-dialkylamino-4,5,6,8,9,10-hexahydro-9-oxospiro{pyrimido[4,5,6-*ij*]pyrrolo[2,3-*c*]-2,7-naphthyridine-5,1′-cyclohexane}-1-carbonitriles, respectively. All fused 2,7-naphthyridines obtained were derivatives of novel heterocyclic systems.

1. Introduction

2,7-Naphthyridine nucleus is known to be a part of a large number of alkaloids.[1–11] Thus, alangimaridine,[1] isoalamarine,[2] alamaridines,[3] nauclefine,[4,5] naulafine,[6] normalindine,[7] eudistones,[8] cystodytins,[9] kuanoniamines[10] and meridine[11] can be mentioned as examples of natural condensed 2,7-naphthyridines. Many of these alkaloids consist of 2,7-naphthyridine moiety fused at the sides *i*,*j* and *c*[8–11] (Fig. 1, structure **1**). Hence the [*c*]fused 2,7-naphthyridines bearing functional groups at appropriate positions



1 **2**

Figure 1. Dashed lines establish annulated rings. 'fg' is a functional group.

(Fig. 1, structure **2**) could be suitable precursors for natural compounds and their analogues. Therefore, the synthesis of the naphthyridines of type **2** is of interest.

While a considerable number of 2,7-naphthyridines of type **2** fused with six-membered rings has been described in the literature (for reviews see[12–16]), corresponding derivatives condensed with five-membered heterocycles have been less investigated.[17–28] Thus, pyrazolo-,[17,21] isoxazolo-,[21] cyclopenta-,[18] thieno-,[19,20,22–24,26–28] furo-,[22–24] and imidazo-[25] annulated 2,7-naphthyridines **2** were prepared. At the same time 2,7-naphthyridines fused at the side *c* with pyrrole nucleus are hitherto unknown. This prompted us to look for approaches to the pyrrolonaphthyridines of type **2**.

2. Results and discussion

Most of the above mentioned compounds **2** were obtained by the central pyridine ring formation starting from the suitable pyridine and five-membered cyclic precursors in one or several steps.[17–25] An alternative approach, including ring annulations to the readily available 2,7-naphthyridine, was applied for thieno derivatives only.[26,27] Over the last years so called cascade reactions have had an increasing

Keywords: Cascade reactions; Nitriles; Chloroacetamides; Pyrrolo[2,3-*c*]-2,7-naphthyridines; Spiro compounds.
* Corresponding author. Tel./fax: +380-44-558-6553;
e-mail address: atver@univ.kiev.ua

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.05.007

importance in heterocyclic chemistry,[29–32] since they allow creation of two or more rings at once at the expense of sequential chemical transformations induced one by another. It seems to be the most economical method for condensed heterocycles preparation. Thus, recently cascade process involving Smiles rearrangement and two sequential nucleophilic additions to nitrile has been used for thieno[2,3-*c*]2,7-naphthyridine synthesis.[28]

Previously we have shown utility of the readily available pyridines **4**–**6** for 2,7-naphthyridine derivative preparation by alkoxide induced 1,5-dinitrile cyclization reaction.[33] Continuing our researches in this field we assumed compounds **4**–**6** to be suitable starting materials for the target pyrrolonaphthyridines synthesis via cascade reaction with chloroacetamides. Thus, alkylation of the malonodinitrile, ethyl cyanoacetate and 2-benzothiazoleacetonitrile with *N*-substituted chloroacetamides was reported to yield aminopyrrolones **3**[34–40] (Fig. 2). Therefore, the similar alkylation of the pyridines **4**–**6** also containing a CH_2CN moiety should afford the intermediates **7** (Scheme 1) which should undergo further cyclization to give desired pyrrolonaphthyridines. However, there are two possibilities for ring closure in the intermediates **7** with participation of 3-CN or 5-CN leading to the isomers **8**–**10** or **11**, respectively. Of course, a mixture of products could also be formed. Nevertheless, reaction of the derivatives **4**–**6** with *N*-substituted chloroacetamides in ethanol in the presence of K_2CO_3 was found to result in the individual compounds isolated in 50–70% yields. Since the isomers **8**–**10** and **11** were difficult to distinguish using spectral data the structures **8**-**10** were assigned to the products on the basis of X-ray crystallographic study carried out for derivative **9b** (Fig. 3).

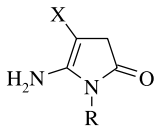


Figure 2. X=CN, CO_2Et, 2-benzothiazolyl.

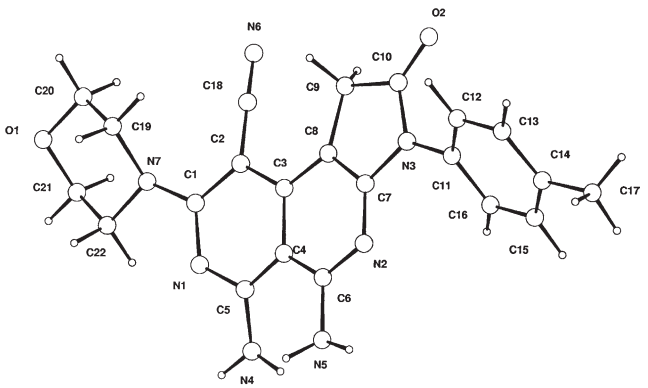
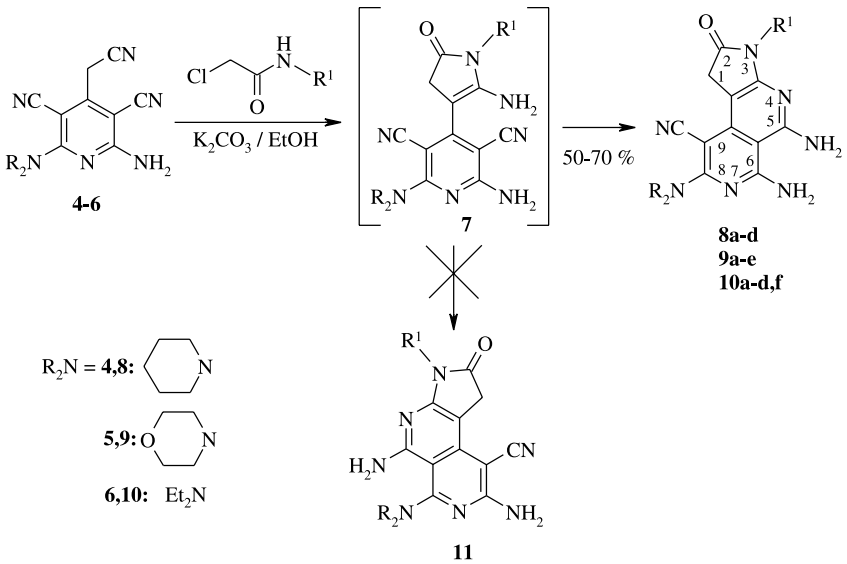


Figure 3. X-ray molecular structure of compound **9b** with the atom numbering used in the crystallographic analysis.

According to the crystal data† pyrrole and pyridine ring N2–C6–C4–C3–C8–C7 of compound **9b** are coplanar (with precision of 0.03 Å). Phenyl substituent is turned out from this plane at the angle 72°. The ring N1–C1–C2–C3–C4–C5 is slightly twisted. The atoms C1 and C5 are deviated from the other rings plane at −0.21 Å and +0.34 Å, respectively. Probably, this distortion is caused by interaction between amino groups, namely the formation of the intramolecular hydrogen bond N4–H···N5 with the length 3.01 Å and the angle N4–H–N5 150°. Of course, the



Scheme 1. R^1=**a**: 4-(*i*-Pr)C_6H_4, **b**: 4-$CH_3C_6H_4$, **c**: 3,4-$(MeO)_2C_6H_3$, **d**: 4-$MeOC_6H_4CH_2$, **e**: 3-ClC_6H_4, **f**: 4-ClC_6H_4.

† Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 230079. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax:+44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

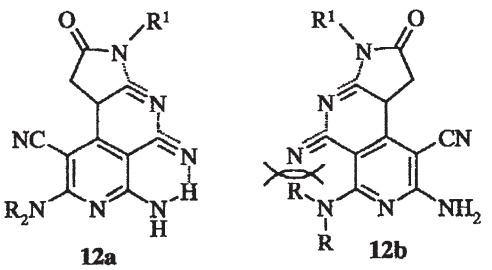


Figure 4.

distortions of the pyridine ring are small and the aromaticity of the naphthyridine moiety is not infringed.

It should be emphasized that there were no detectable amounts of the isomers **11** in the reaction mixtures. Hence the ring closure in the intermediates **7** proceeded regioselectively with participation of 3-CN. The selectivity was explained in the terms of transition state energy. Thus, nucleophilic additions to nitriles were assumed to occur synchronously or quickly one after another. Therefore, the transition states like **12** (Fig. 4) could be employed to describe the addition process. The transition state **12a** corresponding to the heterocyclization with 3-CN is additionally stabilized by intramolecular hydrogen bond. On the other hand the bulky dialkylamino group is not only unable to stabilize the alternative transition state **12b**, but seems to act destructively due to repulsion with neighbouring substituent. Consequently, the energy of the transition state **12a** is lower and the reaction proceeds through it resulting in pyrrolonaphthyridines **8**–**10**. It is noteworthy that predominant reactivity of 3-CN versus 5-CN in heterocyclization reactions of compounds **4**–**6** and related derivatives has been reported previously by us[33] and other researchers.[41]

The possibility of additional ring annulation to the compounds **8**–**10** using their amino groups was examined. Thus, treatment of the derivatives **8a**,**b**, **9e**, **10f** with excess of acetic acid anhydride or cyclohexanone yielded pyrimido[4,5,6-*ij*]pyrrolo[2,3-*c*]2,7-naphthyridines **13a**–**d** and spirocyclic compounds **14a**–**d**, respectively (Scheme 2). The structures of compounds **13** and **14** were confirmed by ^{1}H and ^{13}C NMR data. Furthermore the similar transformations are well known for 1,8-naphthalenediamine.[42–46] Apparently, fused naphthyridines **13** and **14** are the representatives of novel heterocyclic systems.

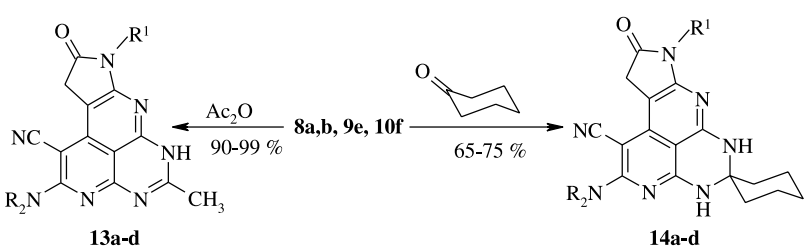
To summarize, the present investigation has resulted in a convenient method for the synthesis of pyrrolo[2,3-*c*]2,7-naphthyridines **8**–**10**, the derivatives of a hitherto unknown heterocyclic system. Furthermore, compounds **8**–**10** have been converted easily into more complex novel condensed and spirocyclic heterocycles **13**, **14**. It should be noted that the starting materials **4**–**6** were obtained by amination of 2-amino-6-chloro-4-cyanomethyl-3,5-pyridinedicarbonitrile (**15**) in quantitative yields.[33] The chloropyridine precursor **15** was in turn available from malonodinitrile and inorganic materials in two steps.[41] Hence derivatives **8**–**10** and **13**, **14** have been prepared from malonodinitrile in four and five steps, respectively. The other reagents used, such as amines, chloroacetamides, acetic anhydride and cyclohexanone, are also of general access. The simpler and cheaper sources for the preparation of complex heterocycles are difficult to be proposed. Of course, the corner-stone of the present synthetic pathway is the cascade heterocyclization reaction of the pyridines **4**–**6** occurred regioselectively with the 3-CN group. Moreover, potential of the pyridines **4**–**6** in heterocyclic synthesis is believed not to be limited to the present work and further research on their chemistry are in progress.

3. Experimental

The pyridines **4**–**6**[33] and chloroacetamides[47] were prepared as reported. Other reagents were commercially available. All melting points were determined in open capillary tubes in a Thiele apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Mercury 400 (400 MHz for ^{1}H and 100 MHz for ^{13}C) spectrometer in DMSO-d_6 solutions. Chemical shifts (δ) are given in ppm downfield from internal $SiMe_4$. *J* values are in Hz. The purity of all compounds prepared was checked by ^{1}H NMR.

3.1. Pyrrolo[2,3-*c*]2,7-naphthyridines 8–10. General procedure

Powdered K_2CO_3 (0.41 g, 3.0 mmol) and chloroacetamide (2.5 mmol) were added to a hot solution of the pyridines **4**–**6** (2.5 mmol) in absolute ethanol (10 ml) and the



13,14	a	b	c	d
R_2N	N	N	O N	Et_2N
R^1	4-(*i*-Pr)C_6H_4	4-$CH_3C_6H_4$	3-ClC_6H_4	4-ClC_6H_4

Scheme 2.

resulting mixture was refluxed for 30–40 min. After cooling the precipitated solid was filtered, thoroughly washed with water, dried and recrystallized from an appropriate solvent to give compounds **8–10**.

3.1.1. 5,6-Diamino-2,3-dihydro-2-oxo-8-(1-piperidinyl)-3-[4-(*i*-propyl)phenyl]-1*H*-pyrrolo[2,3-*c*]2,7-naphthyridine-9-carbonitrile (8a). Yield 64%. White needles. Mp 269 °C (from dioxane); ν_{max} (KBr tablets) 3460, 3330, 2955, 2880, 2200, 1735, 1620, 1590, 1550, 1460, 1345, 1300, 1215, 1160, 1130, 1040, 850, 815, 710 cm^{-1}. δ_H 7.34 (2H, d, J=6.8 Hz, H_{R1}), 7.28 (2H, d, J=6.8 Hz, H_{R1}), 7.18 (2H, s, NH_2), 6.55 (2H, s, NH_2) 3.86 (2H, s, 1-CH_2), 3.69 (4H, m, NCH_2), 2.94 (1H, m, *i*-Pr), 1.59 (6H, m, $CH_2CH_2CH_2$), 1.23 (6H, d, J=6.4 Hz, *i*-Pr). δ_C 178.2 (2-CO), 163.3 (9a-C), 156.4 (5-C), 156.1 (6-C), 151.7 (8-C), 142.3 (3a-C), 135.1 (1-C_{R1}), 130.9 (4-C_{R1}), 128.6 (3,5-C_{R1}), 127.0 (2,6-C_{R1}), 116.9 (CN), 97.9 (5a-C), 89.6 (9b-C), 70.8 (9-C), 52.2 (2,6-C_{NR2}), 36.4 (1-C), 34.5 (*i*-Pr), 25.2 (3,5-C_{NR2}), 22.0 (4-C_{NR2}), 18.9 (*i*-Pr). Found: 67.9% C, 6.0% H, 22.4% N; $C_{25}H_{27}N_7O$ requires 68.0% C, 6.2% H, 22.2% N.

3.1.2. 5,6-Diamino-2,3-dihydro-3-(4-methylphenyl)-2-oxo-8-(1-piperidinyl)-1*H*-pyrrolo[2,3-*c*]2,7-naphthyridine-9-carbonitrile (8b). Yield 69%. White powder. Mp 296 °C (from DMF); ν_{max} (KBr tablets) 3465, 3340, 2970, 2200, 1735, 1595, 1450, 1300, 880, 760, 705, 630 cm^{-1}. δ_H 7.27 (4H, m, H_{R1}), 7.12 (2H, s, NH_2), 6.48 (2H, s, NH_2), 3.86 (2H, s, 1-CH_2), 3.69 (4H, m, NCH_2), 2.36 (3H, s, CH_3), 1.61 (6H, m, $CH_2CH_2CH_2$). δ_C 176.8 (2-CO), 168.1 (9a-C), 160.6 (5-C), 159.7 (6-C), 152.9 (8-C), 138.2 (3a-C), 138.0 (4-C_{R1}), 135.5 (1-C_{R1}), 129.5 (3,5-C_{R1}), 126.5 (2,6-C_{R1}), 119.8 (CN), 99.3 (5a-C), 91.2 (9b-C), 68.8 (9-C), 57.1 (2,6-C_{NR2}), 35.7 (1-C), 27.2 (3,5-C_{NR2}), 20.1 (CH_3), 17.4 (4-C_{NR2}). Found: 67.0% C, 5.5% H, 23.9% N; $C_{23}H_{23}N_7O$ requires 66.8% C, 5.6% H, 23.7% N.

3.1.3. 5,6-Diamino-2,3-dihydro-3-(3,4-dimethoxyphenyl)-2-oxo-8-(1-piperidinyl)-1*H*-pyrrolo[2,3-*c*]2,7-naphthyridine-9-carbonitrile (8c). Yield 54%. Yellow prisms. Mp 172 °C (from EtOH); ν_{max} (KBr tablets) 3430, 3330, 2980, 2850, 2200, 1730, 1620, 1520, 1490, 1280, 1140, 1025, 820 cm^{-1}. δ_H 7.17 (2H, s, NH_2), 7.04 (1H, d, J=8.4 Hz, 5-H_{R1}), 6.98 (1H, d, J=2.0 Hz, 2-H_{R1}), 6.90 (1H, dd, J=8.4, 2.0 Hz, 6-H_{R1}), 6.55 (2H, s, NH_2), 3.85 (2H, s, 1-CH_2), 3.80 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.70 (4H, m, NCH_2), 1.61 (6H, m, $CH_2CH_2CH_2$). δ_C 179.2 (2-CO), 165.2 (9a-C), 159.9 (5-C), 154.6 (6-C), 152.3 (8-C), 150.2 (3-C_{R1}), 149.3 (4-C_{R1}), 142.7 (3a-C), 128.1 (1-C_{R1}), 122.4 (CN), 117.4 (2-C_{R1}), 116.2 (6-C_{R1}), 111.9 (5-C_{R1}), 97.7 (5a-C), 86.1 (9b-C), 69.5 (9-C), 56.4 (OCH_3), 55.2 (OCH_3), 52.1 (2,6-C_{NR2}), 40.8 (1-C), 23.4 (3,5-C_{NR2}), 22.6 (4-C_{NR2}). Found: 62.9% C, 5.4% H, 21.6% N; $C_{24}H_{25}N_7O_3$ requires 62.7% C, 5.5% H, 21.3% N.

3.1.4. 5,6-Diamino-2,3-dihydro-3-[(4-methoxyphenyl)-methyl]-2-oxo-8-(1-piperidinyl)-1*H*-pyrrolo[2,3-*c*]2,7-naphthyridine-9-carbonitrile (8d). Yield 56%. White powder. Mp 192 °C (from EtOH); ν_{max} (KBr tablets) 3450, 3375, 2960, 2880, 2205, 1710, 1615, 1585, 1460, 1370, 1335, 1305, 1260, 1190, 1040, 920, 870 cm^{-1}. δ_H 7.27 (2H, d, J=7.2 Hz, H_{R1}), 7.11 (2H, s, NH_2), 6.84 (2H, d, J=7.2 Hz, H_{R1}), 6.57 (2H, s, NH_2), 4.74 (2H, s, N3-CH_2), 3.73 (2H, s, 1-CH_2), 3.70 (3H, s, OCH_3), 3.67 (4H, m, NCH_2), 1.59 (6H, m, $CH_2CH_2CH_2$). δ_C 179.5 (2-CO), 167.8 (9a-C), 159.0 (6-C), 157.6 (4-C_{R1}), 155.0 (5-C), 153.3 (8-C), 139.5 (3a-C), 131.5 (1-C_{R1}), 127.1 (2,6-C_{R1}), 115.7 (3,5-C_{R1}), 115.5 (CN), 98.5 (5a-C), 91.8 (9b-C), 68.6 (9-C), 57.3 (2,6-C_{NR2}), 55.3 (OCH_3), 47.2 (NCH_2), 38.1 (1-C), 29.5 (3,5-C_{NR2}), 26.1 (4-C_{NR2}). Found: 65.1% C, 5.5% H, 22.0% N; $C_{24}H_{25}N_7O_2$ requires 65.0% C, 5.7% H, 22.1% N.

3.1.5. 5,6-Diamino-2,3-dihydro-8-(4-morpholinyl)-2-oxo-3-[4-(*i*-propyl)phenyl]-1*H*-pyrrolo[2,3-*c*]2,7-naphthyridine-9-carbonitrile (9a). Yield 62%. White powder. Mp 242 °C (from DMF); ν_{max} (KBr tablets) 3420, 3360, 2920, 2195, 1725, 1650, 1575, 1490, 1350, 1275, 1205, 1170, 1115, 1030, 805, 720 cm^{-1}. δ_H 7.35 (2H, d, J=8.0 Hz, H_{R1}), 7.29 (2H, d, J=8.0 Hz, H_{R1}), 7.24 (2H, s, NH_2), 6.57 (2H, s, NH_2), 3.86 (2H, s, 1-CH_2), 3.69 (8H, m, NR_2), 2.95 (1H, m, *i*-Pr), 1.24 (6H, d, J=8.0 Hz, *i*-Pr). δ_C 179.3 (2-CO), 160.0 (6-C), 159.2 (5-C), 158.4 (9a-C), 148.6 (8-C), 141.5 (3a-C), 136.2 (1-C_{R1}), 132.7 (4-C_{R1}), 127.7 (2,6-C_{R1}), 127.4 (3,5-C_{R1}), 115.6 (CN), 102.7 (5a-C), 96.2 (9b-C), 70.5 (9-C), 66.1 (OCH_2), 51.9 (NCH_2), 39.6 (1-C), 32.9 (*i*-Pr), 20.3 (*i*-Pr). Found: 64.9% C, 5.8% H, 22.1% N; $C_{24}H_{25}N_7O_2$ requires 65.0% C, 5.7% H, 22.1% N.

3.1.6. 5,6-Diamino-2,3-dihydro-3-(4-methylphenyl)-8-(4-morpholinyl)-2-oxo-1*H*-pyrrolo[2,3-*c*]2,7-naphthyridine-9-carbonitrile (9b). Yield 65%. Colorless prisms. Mp 286 °C (from DMF); ν_{max} (KBr tablets) 3395, 3345, 2980, 2220, 1745, 1560, 1465, 1305, 855, 775, 705, 670 cm^{-1}. δ_H 7.27 (4H, m, H_{R1}), 7.23 (2H, s, NH_2), 6.55 (2H, s, NH_2), 3.86 (2H, s, 1-CH_2), 3.68 (8H, m, NR_2), 2.36 (3H, s, CH_3). δ_C 179.7 (2-CO), 161.7 (5-C), 158.8 (9a-C), 158.1 (6-C), 146.9 (8-C), 140.6 (3a-C), 138.7 (1-C_{R1}), 137.9 (4-C_{R1}), 129.7 (3,5-C_{R1}), 129.3 (2,6-C_{R1}), 114.4 (CN), 104.1 (5a-C), 89.7 (9b-C), 69.7 (9-C), 67.9 (OCH_2), 53.6 (NCH_2), 35.5 (1-C), 20.5 (CH_3). Found 63.5% C, 5.2% H, 23.8% N; $C_{22}H_{21}N_7O_2$ requires 63.6% C, 5.1% H, 23.6% N.

3.1.7. 5,6-Diamino-2,3-dihydro-3-(3,4-dimethoxyphenyl)-8-(4-morpholinyl)-2-oxo-1*H*-pyrrolo[2,3-*c*]2,7-naphthyridine-9-carbonitrile (9c). Yield 57%. Light-brown powder. Mp 201 °C (from EtOH); ν_{max} (KBr tablets) 3415, 3345, 2935, 2220, 1740, 1600, 1550, 1450, 1270, 1130, 1035, 820 cm^{-1}. δ_H 7.23 (2H, s, NH_2), 7.04 (1H, d, J=8.1 Hz, 5-H_{R1}), 6.98 (1H, d, J=1.8 Hz, 2-H_{R1}), 6.90 (1H, dd, J=8.1, 1.8 Hz, 6-H_{R1}), 6.57 (2H, s, NH_2), 3.85 (2H, s, 1-CH_2), 3.80 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.69 (8H, m, NR_2). δ_C 178.8 (2-CO), 158.8 (5-C), 157.9 (6-C), 156.0 (9a-C), 152.2 (3-C_{R1}), 152.0 (4-C_{R1}), 150.2 (8-C), 143.9 (3a-C), 130.3 (1-C_{R1}), 118.6 (6-C_{R1}), 115.2 (CN), 109.5 (2-C_{R1}), 107.7 (5-C_{R1}), 98.6 (5a-C), 93.4 (9b-C), 68.5 (9-C), 63.5 (OCH_2), 56.0 (OCH_3), 55.9 (OCH_3), 50.7 (NCH_2), 41.4 (1-C). Found: 59.6% C, 4.9% H, 21.1% N; $C_{23}H_{23}N_7O_4$ requires 59.9% C, 5.0% H, 21.3% N.

3.1.8. 5,6-Diamino-2,3-dihydro-3-[(4-methoxyphenyl)-methyl]-8-(4-morpholinyl)-2-oxo-1*H*-pyrrolo[2,3-*c*]2,7-naphthyridine-9-carbonitrile (9d). Yield 51%. Colorless needles. Mp 217 °C (from dioxane); ν_{max} (KBr tablets) 3425, 3320, 2940, 2200, 1730, 1605, 1570, 1420, 1355, 1305, 1285, 1215, 1000, 940, 865 cm^{-1}. δ_H 7.31 (4H, m,

NH_2, H_{R1}), 6.88 (2H, d, J=8.0 Hz, H_{R1}), 6.71 (2H, s, NH_2), 4.77 (2H, s, N3–CH_2), 3.76 (2H, s, 1-CH_2), 3.73, (3H, s, OCH_3), 3.69 (8H, m, NR_2). δ_C 179.3 (2-CO), 168.2 (9a-C), 160.3 (5-C), 159.2 (4-C_{R1}), 156.6 (6-C), 146.5 (3a-C), 146.1 (8-C), 130.8 (2,6-C_{R1}), 129.3 (1-C_{R1}), 116.1 (CN), 115.8 (3,5-C_{R1}), 103.1 (5a-C), 92.4 (9b-C), 67.9 (9-C), 64.3 (OCH_2), 55.3 (OCH_3), 55.1 (NCH_2), 43.9 (N3–CH_2) 36.4 (1-C). Found: 62.2% C, 5.1% H, 21.9% N; $C_{23}H_{23}N_7O_3$ requires 62.0% C, 5.2% H, 22.0% N.

3.1.9. 3-(3-Chlorophenyl)-5,6-diamino-2,3-dihydro-8-(4-morpholinyl)-2-oxo-1*H*-pyrrolo[2,3-*c*]2,7-naphthyridine-9-carbonitrile (9e). Yield 70%. Light-gray powder. Mp >300 °C (from DMF); ν_{max} (KBr tablets) 3420, 3300, 2915, 2220, 1740, 1610, 1490, 1470, 1280, 1170, 1120, 1050, 940, 790 cm^{-1}. δ_H 7.48 (2H, m, 4,6-H_{R1}), 7.42 (1H, s, 2-H_{R1}), 7.38 (1H, t, J=6.6 Hz, 5-H_{R1}), 7.11 (2H, s, NH_2), 6.49 (2H, s, NH_2), 3.86 (2H, s, 1-CH_2), 3.71 (8H, m, NR_2). δ_C 181.1 (2-CO), 162.3 (6-C), 159.7 (5-C), 158.6 (9a-C), 149.4 (8-C), 147.1 (3a-C), 137.7 (1-C_{R1}), 135.5 (3-C_{R1}), 130.0 (4-C_{R1}), 128.9 (6-C_{R1}), 127.5 (5-C_{R1}), 123.4 (2-C_{R1}), 115.5 (CN), 104.7 (5a-C), 94.7 (9b-C), 66.3 (9-C), 65.4 (OCH_2), 53.4 (NCH_2), 37.5 (1-C). Found: 57.7% C, 4.2% H, 8.3% Cl, 22.6% N; $C_{21}H_{18}ClN_7O_2$ requires 57.9% C, 4.2% H, 8.1% Cl, 22.5% N.

3.1.10. 5,6-Diamino-8-diethylamino-2,3-dihydro-2-oxo-3-[4-(*i*-propyl)phenyl]-1*H*-pyrrolo[2,3-*c*]2,7-naphthyridine-9-carbonitrile (10a). Yield 63%. White needles. Mp 255 °C (from dioxane); ν_{max} (KBr tablets) 3410, 3345, 2980, 2210, 1730, 1670, 1435, 1300, 1275, 1205, 1195, 1100, 1060, 800, 725 cm^{-1}. δ_H 7.37 (2H, d, J=8.0 Hz, H_{R1}), 7.32 (2H, d, J=8.0 Hz, H_{R1}), 7.11 (2H, s, NH_2), 6.53 (2H, s, NH_2), 3.92 (2H, s, 1-CH_2), 3.66 (4H, q, J=6.4 Hz, NR_2), 2.97 (1H, m, *i*-Pr), 1.27 (12H, m, NR_2, *i*-Pr). δ_C 178.7 (2-CO), 159.9 (6-C), 158.3 (5-C), 157.5 (9a-C), 146.6 (8-C), 144.6 (3a-C), 134.8 (1-C_{R1}), 133.5 (4-C_{R1}), 130.7 (3,5-C_{R1}), 126.4 (2,6-C_{R1}), 117.1 (CN), 104.2 (5a-C), 91.5 (9b-C), 68.7 (9-C), 44.6 (C_{NR2}), 36.3 (1-C), 35.8 (*i*-Pr), 21.9 (*i*-Pr), 14.1 (C_{NR2}). Found: 67.0% C, 6.6% H, 22.9% N; $C_{24}H_{27}N_7O$ requires 67.1% C, 6.3% H, 22.8% N.

3.1.11. 5,6-Diamino-8-diethylamino-2,3-dihydro-3-(4-methylphenyl)-2-oxo-1*H*-pyrrolo[2,3-*c*]2,7-naphthyridine-9-carbonitrile (10b). Yield 66%. Colorless plates. Mp 225 °C (from DMF); ν_{max} (KBr tablets) 3440, 3330, 2950, 2210, 1735, 1610, 1445, 1340, 1215, 1125, 810, 735, 705, 600 cm^{-1}. δ_H 7.28 (2H, d, J=8.0 Hz, H_{R1}), 7.24 (2H, d, J=8.0 Hz, H_{R1}), 7.07 (2H, s, NH_2), 6.47 (2H, s, NH_2), 3.89 (2H, s, 1-CH_2), 3.63 (4H, q, J=6.4 Hz, NR_2), 2.35 (3H, s, CH_3), 1.20 (6H, t, J=6.4 Hz, NR_2). δ_C 179.6 (2-CO), 164.5 (9a-C), 158.9 (6-C), 158.3 (5-C), 156.0 (8-C), 139.9 (3a-C), 136.1 (4-C_{R1}), 133.5 (1-C_{R1}), 128.7 (3,5-C_{R1}), 126.4 (2,6-C_{R1}), 119.1 (CN), 96.7 (5a-C), 89.1 (9b-C), 69.8 (9-C), 47.3 (C_{NR2}), 37.9 (1-C), 17.5 (CH_3), 9.5 (C_{NR2}). Found: 65.7% C, 5.9% H, 24.2% N; $C_{22}H_{23}N_7O$ requires 65.8% C, 5.8% H, 24.4% N.

3.1.12. 5,6-Diamino-8-diethylamino-2,3-dihydro-3-(3,4-dimethoxyphenyl)-2-oxo-1*H*-pyrrolo[2,3-*c*]2,7-naphthyridine-9-carbonitrile (10c). Yield 58%. Yellow powder. Mp 132 °C (from EtOH); ν_{max} (KBr tablets) 3450, 3335, 2930, 2210, 1750, 1630, 1475, 1240, 1175, 1070, 850 cm^{-1}. δ_H 7.08 (2H, s, NH_2), 7.02 (1H, dd, J=8.4, 1.6 Hz, 6-H_{R1}), 6.97 (1H, d, J=1.6 Hz, 2-H_{R1}), 6.89 (2H, d, J=8.4 Hz, 5-H_{R1}), 6.50 (2H, s, NH_2), 3.90 (2H, s, 1-CH_2), 3.79 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.62 (4H, q, J=6.0 Hz, NR_2), 1.19 (6H, t, J=6.0 Hz, NR_2). δ_C 179.5 (2-CO), 161.6 (9a-C), 158.6 (5-C), 157.8 (6-C), 157.5 (8-C), 156.8 (3-C_{R1}), 148.9 (4-C_{R1}), 144.8 (3a-C), 127.8 (1-C_{R1}), 118.7 (CN), 118.2 (6-C_{R1}), 115.7 (5-C_{R1}), 111.7 (2-C_{R1}), 98.1 (5a-C), 92.2 (9b-C), 70.8 (9-C), 58.7 (OCH_3), 55.7 (OCH_3), 41.9 (C_{NR2}), 36.3 (1-C), 13.7 (C_{NR2}). Found: 62.0% C, 5.9% H, 22.0% N; $C_{23}H_{25}N_7O_3$ requires 61.7% C, 5.6% H, 21.9% N.

3.1.13. 5,6-Diamino-8-diethylamino-2,3-dihydro-3-[(4-methoxyphenyl)methyl]-2-oxo-1*H*-pyrrolo[2,3-*c*]2,7-naphthyridine-9-carbonitrile (10d). Yield 60%. White powder. Mp 193 °C (from EtOH); ν_{max} (KBr tablets) 3410, 3330, 2970, 2210, 1730, 1605, 1585, 1450, 1320, 1305, 1250, 1215, 1070, 945, 890 cm^{-1}. δ_H 7.28 (2H, d, J=7.6 Hz, H_{R1}), 7.05 (2H, s, NH_2), 6.84 (2H, d, J=7.6 Hz, H_{R1}), 6.58 (2H, s, NH_2), 4.73 (2H, s, N3–CH_2), 3.76 (2H, s, 1-CH_2), 3.70 (3H, s, OCH_3), 3.61 (4H, q, J=6.0 Hz, NR_2), 1.18 (6H, t, J=6.0 Hz, NR_2). δ_C 177.1 (2-CO), 159.5 (6-C), 158.7 (4-C_{R1}), 158.2 (8-C), 158.1 (5-C), 157.4 (9a-C), 146.5 (3a-C), 129.5 (2,6-C_{R1}), 127.4 (1-C_{R1}), 116.5 (CN), 115.2 (3,5-C_{R1}), 99.1 (5a-C), 87.6 (9b-C), 68.4 (9-C), 59.1 (OCH_3), 46.1 (C_{NR2}), 43.7 (NCH_2), 37.1 (1-C), 13.6 (C_{NR2}). Found: 63.9% C, 6.0% H, 23.0% N; $C_{23}H_{25}N_7O_2$ requires 64.0% C, 5.8% H, 22.7% N.

3.1.14. 3-(4-Chlorophenyl)-5,6-diamino-8-diethylamino-2,3-dihydro-2-oxo-1*H*-pyrrolo[2,3-*c*]2,7-naphthyridine-9-carbonitrile (10f). Yield 69%. Yellow needles. Mp 242 °C (from DMF); ν_{max} (KBr tablets) 3405, 3300, 2955, 2220, 1750, 1665, 1445, 1385, 1345, 1130, 1050, 840 cm^{-1}. δ_H 7.55 (2H, d, J=8.4 Hz, H_{R1}), 7.45 (2H, d, J=8.4 Hz, H_{R1}), 7.11 (2H, s, NH_2), 6.52 (2H, s, NH_2), 3.91 (2H, s, 1-CH_2), 3.64 (4H, q, J=7.2 Hz, NR_2), 1.20 (6H, t, J=7.2 Hz, NR_2). δ_C 177.2 (2-CO), 167.6 (9a-C), 158.5 (5-C), 155.4 (6-C), 154.6 (8-C), 144.4 (3a-C), 135.1 (1-C_{R1}), 133.9 (4-C_{R1}), 127.1 (2,6-C_{R1}), 124.9 (3,5-C_{R1}), 116.8 (CN), 98.5 (5a-C), 91.3 (9b-C), 68.5 (9-C), 46.5 (C_{NR2}), 36.2 (1-C), 9.9 (C_{NR2}). Found: 59.9% C, 4.5% H, 23.2% N, 8.6% Cl; $C_{21}H_{20}ClN_7O$ requires 59.8% C, 4.8% H, 23.2% N, 8.4% Cl.

3.2. Pyrimido[4,5,6-*ij*]pyrrolo[2,3-*c*]2,7-naphthyridines 13a–d. General procedure

A solution of pyrrolonaphthyridine **8a**,**b**, **9e**, **10f** (2 mmol) in acetic acid anhydride (5 ml) was refluxed for 30 min. After cooling the precipitate formed was filtered, washed with water and recrystallized from DMF to yield derivatives **13a–d**.

3.2.1. 5-Methyl-9-oxo-2-(1-piperidinyl)-8-[4-(*i*-propyl)-phenyl]-6,8,9,10-tetrahydropyrimido[4,5,6-*ij*]pyrrolo-[2,3-*c*]2,7-naphthyridine-1-carbonitrile (13a). Yield 95%. Pale-yellow powder. Mp >300 °C (from DMF); ν_{max} (KBr tablets) 2980, 2955, 2890, 2205, 1750, 1670, 1640, 1600, 1530, 1450, 1325, 1205, 1160, 1120, 1040, 920, 840, 685 cm^{-1}. δ_H 12.78 (1H, br s, NH), 7.37 (2H, d, J=8.0 Hz, H_{R1}), 7.33 (2H, d, J=8.0 Hz, H_{R1}), 3.85 (2H, s, 10-CH_2),

3.72 (4H, m, NCH_2), 2.97 (1H, m, *i*-Pr), 2.31 (3H, s, 5-CH_3), 1.62 (6H, m, $CH_2CH_2CH_2$), 1.25 (6H, d, J=6.8 Hz, *i*-Pr). δ_C 169.2 (9-CO), 151.8 (5-C), 150.3 (6a-C), 147.7 (3a-C), 146.3 (2-C), 145.4 (7a-C), 131.5 (4-C_{R1}), 130.8 (1-C_{R1}), 127.6 (3,5-C_{R1}), 122.1 (2,6-C_{R1}), 117.7 (10b-C), 107.1 (CN), 96.8 (10c-C), 89.2 (10a-C), 65.1 (1-C), 53.4 (2,6-C_{NR2}), 33.1 (*i*-Pr), 26.2 (3.5-C_{NR2}), 26.1 (10-C), 24.5 (4-C_{NR2}), 16.3 (5-CH_3), 15.8 (*i*-Pr). Found: 69.4% C, 5.7% H, 21.0% N; $C_{27}H_{27}N_7O$ requires 69.7% C, 5.9% H, 21.1% N.

3.2.2. 5-Methyl-8-(4-methylphenyl)-9-oxo-2-(1-piperidinyl)-6,8,9,10-tetrahydropyrimido[4,5,6-*ij*]pyrrolo-[2,3-*c*]2,7-naphthyridine-1-carbonitrile (13b). Yield 99%. Yellow plates. Mp >300 °C (from DMF); ν_{max} (KBr tablets) 3300, 2955, 2875, 2210, 1725, 1645, 1590, 1535, 1455, 1330, 1215, 1170, 825 cm^{-1}. δ_H 12.84 (1H, br s, NH), 7.30 (4H, m, H_{R1}), 3.85 (2H, s, 10-CH_2), 3.72 (4H, m, NCH_2), 2.37 (3H, s, CH_3), 2.31 (3H, s, CH_3), 1.62 (6H, m, $CH_2CH_2CH_2$). δ_C 170.9 (9-CO), 153.5 (5-C), 151.1 (2-C), 150.2 (6a-C), 144.7 (3a-C), 137.8 (7a-C), 135.1 (4-C_{R1}), 134.6 (1-C_{R1}), 125.1 (2,6-C_{R1}), 124.4 (3,5-C_{R1}), 120.4 (10b-C), 108.7 (CN), 100.9 (10c-C), 94.5 (10a-C), 62.3 (1-C), 47.2 (2,6-C_{NR2}), 26.5 (10-C), 23.4 (3.5-C_{NR2}), 17.7 (CH_3), 17.6 (4-C_{NR2}), 9.9 (5-CH_3). Found: 68.8% C, 5.5% H, 22.3% N; $C_{25}H_{23}N_7O$ requires 68.6% C, 5.3% H, 22.4% N.

3.2.3. 8-(3-Chlorophenyl)-5-methyl-2-(4-morpholinyl)-9-oxo-6,8,9,10-tetrahydropyrimido[4,5,6-*ij*]pyrrolo[2,3-*c*]-2,7-naphthyridine-1-carbonitrile (13c). Yield 91%. Pale-green powder. Mp >300 °C (from DMF); ν_{max} (KBr tablets) 2975, 2220, 1745, 1585, 1475, 1400, 1305, 1270, 1195, 1125, 1055, 970, 820 cm^{-1}. δ_H 12.96 (1H, br s, NH), 7.59 (1H, s, 2-H_{R1}), 7.54 (2H, m, 4,6-H_{R1}), 7.47 (1H, t, J=7.2 Hz, 5-H_{R1}), 3.83 (2H, s, 10-CH_2), 3.70 (4H, m, OCH_2), 3.67 (4H, m, NCH_2), 2.33 (3H, s, CH_3). δ_C 172.6 (9-CO), 151.1 (5-C), 149.9 (3a-C), 148.6 (6a-C), 147.8 (2-C), 139.9 (3-C_{R1}), 138.3 (7a-C), 133.2 (1-C_{R1}), 125.9 (4-C_{R1}), 125.8 (10b-C), 125.4 (5-C_{R1}), 125.3 (2-C_{R1}), 123.4 (6-C_{R1}), 108.8 (CN), 96.8 (10c-C), 87.6 (10a-C), 67.8 (OCH_2), 64.3 (1-C), 46.6 (NCH_2), 26.9 (10-C), 18.5 (5-CH_3). Found: 60.0 C, 4.1% H, 7.9% Cl, 21.2% N; $C_{23}H_{18}ClN_7O_2$ requires 60.1% C, 4.0% H, 7.7% Cl, 21.3% N.

3.2.4. 8-(4-Chlorophenyl)-2-diethylamino-5-methyl-9-oxo-6,8,9,10-tetrahydropyrimido[4,5,6-*ij*]pyrrolo[2,3-*c*]-2,7-naphthyridine-1-carbonitrile (13d). Yield 94%. Yellow prisms. Mp >300 °C (from DMF); ν_{max} (KBr tablets) 2955, 2210, 1750, 1650, 1445, 1365, 1330, 1160, 1105, 1030, 840 cm^{-1}. δ_H 12.83 (1H, br s, NH), 7.57 (2H, d, J=8.8 Hz, H_{R1}), 7.48 (2H, d, J=8.8 Hz, H_{R1}), 3.90 (2H, s, 10-CH_2), 3.67 (4H, q, J=7.2 Hz, NR_2), 2.31 (3H, s, CH_3); 1.23 (6H, t, J=7.2 Hz, NR_2). δ_C 168.7 (9-CO), 156.5 (5-C), 151.1 (2-C), 146.5 (6a-C), 145.4 (3a-C), 141.5 (7a-C), 132.7 (1-C_{R1}), 129.1 (4-C_{R1}), 121.6 (3,5-C_{R1}), 119.7 (2,6-C_{R1}), 119.4 (10b-C), 107.5 (CN), 95.0 (10c-C), 92.8 (10a-C), 61.0 (1-C), 37.6 (C_{NR2}), 25.2 (10-C), 10.8 (5-CH_3), 2.7 (C_{NR2}). Found: 62.1% C, 4.3% H, 7.8% Cl, 22.0% N; $C_{23}H_{20}ClN_7O$ requires 62.0% C, 4.5% H, 8.0% Cl, 22.0% N.

3.3. Spiro{pyrimido[4,5,6-*ij*]pyrrolo[2,3-*c*]2,7-naphthyridine-5,1′-cyclohexanes} 14a–d. General procedure

A solution of pyrrolonaphthyridine **8a**,**b**, **9e**, **10f** (2 mmol) in cyclohexanone (5 ml) was heated at 100 °C for 1 h. After cooling water (10 ml) was added resulting in a dark oil separation. The liquid was decanted; the oil was dissolved in ethanol and then precipitated again by water as pale crystals, which were filtered and recrystallized from an appropriate solvent to give compounds **14a–d**.

3.3.1. 4,5,6,8,9,10-Hexahydro-9-oxo-2-(1-piperidinyl)-8-[4-(*i*-propyl)phenyl]-sprio{pyrimido[4,5,6-*ij*]pyrrolo-[2,3-*c*]2,7-naphthyridine-5,1′-cyclohexane}-1-carbonitrile (14a). Yield 68%. White powder. Mp 278 °C (from dioxane); ν_{max} (KBr tablets) 3300, 2965, 2890, 2205, 1725, 1650, 1535, 1495, 1295, 1200, 1155, 1065, 875, 760 cm^{-1}. δ_H 8.06 (1H, s, NH), 7.77 (1H, s, NH), 7.34 (2H, d, J=8.0 Hz, H_{R1}), 7.27 (2H, d, J=8.0 Hz, H_{R1}), 3.81 (2H, s, 10-CH_2), 3.69 (4H, m, NCH_2), 2.94 (1H, m, *i*-Pr), 1.71 (4H, m, 2′,6′-CH_2), 1.60 (10H, m, NR_2, 3′,5′-CH_2), 1.30 (2H, m, 4′-CH_2), 1.22 (6H, d, J=6.8 Hz, *i*-Pr). δ_C 177.1 (9-CO), 160.6 (10b-C), 158.4 (3a-C), 156.6 (2-C), 156.4 (6a-C), 143.4 (7a-C), 136.7 (4-C_{R1}), 135.6 (1-C_{R1}), 127.6 (3,5-C_{R1}), 124.4 (2,6-C_{R1}), 117.6 (CN), 98.2 (10c-C), 88.3 (10a-C), 73.2 (5-C), 69.7 (1-C), 50.1 (2,6-C_{NR2}), 39.5 (2′,6′-C), 36.6 (10-C), 36.5 (*i*-Pr), 23.9 (4′-C), 23.6 (3,5-C_{NR2}), 20.5 (*i*-Pr), 19.9 (3′,5′-C), 19.7 (4-C_{NR2}). Found: 71.3% C, 6.9% H, 18.7% N; $C_{31}H_{35}N_7O$ requires 71.4% C, 6.8% H, 18.8% N.

3.3.2. 4,5,6,8,9,10-Hexahydro-8-(4-methylphenyl)-9-oxo-2-(1-piperidinyl)-sprio{pyrimido[4,5,6-*ij*]pyrrolo[2,3-*c*]-2,7-naphthyridine-5,1′-cyclohexane}-1-carbonitrile (14b). Yield 76%. Pale-pink powder. Mp >300 °C (from DMF–H_2O mixture); ν_{max} (KBr tablets) 3300, 2955, 2875, 2205, 1725, 1620, 1520, 1465, 1335, 1205, 1160, 1035, 810, 725 cm^{-1}. δ_H 8.06 (1H, s, NH), 7.77 (1H, s, NH), 7.28 (2H, d, J=8.8 Hz, H_{R1}), 7.22 (2H, d, J=8.8 Hz, H_{R1}), 3.80 (2H, s, 10-CH_2), 3.68 (4H, m, NCH_2), 2.35 (3H, s, CH_3), 1.70 (4H, m, 2′,6′-CH_2), 1.60 (10H, m, NR_2, 3′,5′-CH_2), 1.29 (2H, m, 4′-CH_2). δ_C 174.8 (9-CO), 164.2 (10b-C), 159.8 (2-C), 156.2 (6a-C), 155.6 (3a-C), 141.7 (7a-C), 137.7 (4-C_{R1}), 132.0 (1-C_{R1}), 129.9 (3,5-C_{R1}), 128.4 (2,6-C_{R1}), 121.2 (CN), 94.0 (10c-C), 90.7 (10a-C), 68.8 (5-C), 67.9 (1-C), 49.4 (2,6-C_{NR2}), 37.3 (2′,6′-C), 34.7 (10-C), 26.4 (3,5-C_{NR2}), 25.1 (4-C_{NR2}), 24.7 (4′-C), 21.3 (CH_3), 20.9 (3′,5′-C). Found: 70.7% C, 6.2% H, 19.9% N; $C_{29}H_{31}N_7O$ requires 70.6% C, 6.3% H, 19.9% N.

3.3.3. 8-(3-Chlorophenyl)-4,5,6,8,9,10-hexahydro-2-(4-morpholinyl)-9-oxosprio{pyrimido[4,5,6-*ij*]pyrrolo[2,3-*c*]-2,7-naphthyridine-5,1′-cyclohexane}-1-carbonitrile (14c). Yield 76%. White powder. Mp 288 °C (from DMF–H_2O mixture); ν_{max} (KBr tablets) 3420, 3335, 2975, 2885, 2210, 1750, 1625, 1495, 1450, 1335, 1285, 1190, 1120, 1045, 970, 800 cm^{-1}. δ_H 8.21 (1H, s, NH), 7.88 (1H, s, NH), 7.53 (2H, m, 2,5-H_{R1}), 7.46 (1H, d, J=7.2 Hz, 4-H_{R1}), 7.39 (1H, d, J=7.6 Hz, 6-H_{R1}), 3.82 (2H, s, 10-CH_2), 3.70 (8H, m, NR_2), 1.72 (4H, m, 2′,6′-CH_2), 1.58 (4H, m, 3′,5′-CH_2), 1.31 (2H, m, 4′-CH_2). δ_C 179.9 (9-CO), 160.6 (6a-C), 160.4 (10b-C), 156.6 (2-C), 153.5 (3a-C), 138.4 (7a-C), 137.7 (3-C_{R1}), 131.5 (1-C_{R1}), 126.3 (4-C_{R1}), 124.7 (5-C_{R1}), 123.6 (2-C_{R1}), 123.4 (6-C_{R1}), 118.8 (CN), 94.2 (10c-C), 92.2 (10a-C), 67.5 (1-C), 67.4 (5-C), 61.9 (OCH_2), 49.2 (NCH_2), 40.4 (2′,6′-C), 37.2 (10-C), 25.7 (3′,5′-C), 18.4 (4′-C). Found: 63.0% C, 5.0% H, 6.7% Cl, 18.9% N; $C_{27}H_{26}ClN_7O_2$ requires 62.9% C, 5.1% H, 6.9% Cl, 19.0% N.

3.3.4. 8-(4-Chlorophenyl)-2-diethylamino-4,5,6,8,9,10-hexahydro-9-oxosprio{pyrimido[4,5,6-*ij*]pyrrolo[2,3-*c*]-2,7-naphthyridine-5,1′-cyclohexane}-1-carbonitrile (14d). Yield 71%. White powder. Mp 164 °C (from DMF–EtOH mixture); ν_{max} (KBr tablets) 3340, 2955, 2210, 1745, 1625, 1515, 1445, 1335, 1105, 810, 715 cm^{-1}. δ_H 7.53 (1H, s, NH), 7.48 (3H, m, NH, H_{R1}), 7.42 (2H, d, J=8.4 Hz, H_{R1}), 3.86 (2H, s, 10-CH_2), 3.70 (4H, q, J=7.2 Hz, NR_2), 1.77 (4H, m, 2′,6′-CH_2), 1.62 (4H, m, 3′,5′-CH_2), 1.40 (2H, m, 4′-CH_2), 1.27 (6H, t, J=7.2 Hz, NR_2). δ_C 174.9 (9-CO), 165.2 (10b-C), 158.1 (3a-C), 155.6 (6a-C), 151.5 (2-C), 145.2 (7a-C), 137.5 (4-C_{R1}), 133.3 (1-C_{R1}), 126.7 (2,6-C_{R1}), 124.4 (3,5-C_{R1}), 116.8 (CN), 95.5 (10c-C), 87.4 (10a-C), 70.1 (5-C), 69.9 (1-C), 40.6 (C_{NR2}), 39.7 (2′,6′-C), 38.8 (10-C), 25.3 (4′-C), 21.1 (3′,5′-C), 10.5(C_{NR2}). Found: 64.8% C, 5.7% H, 7.2% Cl, 19.5% N; $C_{27}H_{28}ClN_7O$ requires 64.6% C, 5.6% H, 7.1% Cl, 19.5% N.

References and notes

1. Jahangir; Brook, M. A.; MacLean, D. B.; Holland, H. L. *Can. J. Chem.* **1987**, *65*, 2362–2368.
2. Chowdhury, U. S. *Tetrahedron* **1990**, *40*, 7893–7900.
3. Reinmann, E.; Renz, H. *Monatsh. Chem.* **1994**, *125*, 1397–1406.
4. Jahangir; Brook, M. A.; MacLean, D. B.; Holland, H. L. *Tetrahedron* **1987**, *43*, 5761–5768.
5. Vohra, R.; MacLean, D. B. *Heterocycles* **1994**, *39*, 445–448.
6. Repke, D. B.; Jahangir; Brook, M. A.; Clark, R. D.; Nelson, J. T. *Heterocycles* **1988**, *27*, 2289–2292.
7. Rey, A. W.; Szarek, W. A.; MacLean, D. B. *Heterocycles* **1991**, *32*, 1143–1151.
8. He, H. Y.; Faulkner, D. J. *J. Org. Chem.* **1991**, *56*, 5369–5371.
9. Ciufolini, M. A.; Bryne, N. E. *J. Am. Chem. Soc.* **1991**, *113*, 8016–8024.
10. Gunawardana, G. P.; Koehn, F. E.; Lee, A. Y.; Clardy, J.; He, H. Y.; Faulkner, D. J. *J. Org. Chem.* **1992**, *57*, 1523–1526.
11. McCarthy, P. J.; Pitts, T. P.; Gunawardana, G. P.; Kelly-Borges, M.; Pomponi, S. A. *J. Nat. Prod.* **1992**, *55*, 1664–1668.
12. Litvinov, V. P.; Roman, S. V.; Dyachenko, V. D. *Usp. Khim.* **2001**, *70*, 345–367, *Russ. Chem. Rev. (Engl. Transl.)* **2001**, *70*, 299–320.
13. Litvinov, V. P.; Roman, S. V.; Dyachenko, V. D. *Usp. Khim.* **2000**, *69*, 218–238, *Russ. Chem. Rev. (Engl. Transl.)* **2000**, *69*, 201–220.
14. Noravyan, A. S.; Paronikyan, E. G.; Vartanyan, S. A. *Khim.-farm. Zh.* **1985**, *7*, 790–800.
15. Van der Plas, H. C.; Wozniak, M.; van der Haak, H. J. W. *Adv. Heterocycl. Chem.* **1983**, *33*, 95–146.
16. Paudler, W. W.; Sheets, R. M. *Adv. Heterocycl. Chem.* **1983**, *33*, 147–184.
17. Winn, M. *J. Heterocycl. Chem.* **1975**, *12*, 523–524.
18. Wanner, M. J.; Koomen, G. J.; Pandit, U. K. *Tetrahedron* **1982**, *38*, 2741–2748.
19. Björk, P.; Hörnfeldt, A. B.; Gronowitz, S. *J. Heterocycl. Chem.* **1994**, *31*, 1161–1169.
20. Björk, P.; Aakermann, T.; Hörnfeldt, A. B.; Gronowitz, S. *J. Heterocycl. Chem.* **1995**, *32*, 751–754.
21. Winters, G.; Sala, A.; de Paoli, A.; Ferri, V. *Synthesis* **1984**, 1052–1054.
22. Goerlitzer, K.; Dobberkau, P. M. *Pharmazie* **1996**, *51*, 386–391.
23. Goerlitzer, K.; Dobberkau, P. M.; Jones, P. G. *Pharmazie* **1996**, *51*, 392–396.
24. Goerlitzer, K.; Dobberkau, P. M.; Ewert, H. J.; Heinrici, C.; Bartke, U. *Pharmazie* **1997**, *52*, 575–578.
25. Goerlitzer, K.; Klanck, S. *Pharmazie* **1999**, *54*, 814–819.
26. Artemov, V. A.; Shestopalov, A. M.; Litvinov, V. P. *Khim. Geterotsikl. Soedin.* **1996**, 512–515, *Chem. Heterocycl. Cmpd. (Engl. Transl.)* **1996**, *32*, 445–448.
27. Paronikyan, E. G.; Mirzoyan, G. V.; Noravyan, A. S.; Arzanunts, E. M.; Sukasyan, R. S.; Sarkisyan, I. S.; Nazaryan, I. M.; Dzhagatspanyan, I. A. *Khim.-farm. Zh.* **1997**, *31*(10), 34–36, *Pharm. Chem. J. (Engl. Transl.)* **1997**, *31*, 540–542.
28. Hirota, T.; Tomita, K.; Sasaki, K.; Okuda, K.; Yoshida, M.; Kashino, S. *Heterocycles* **2001**, *55*, 741–752.
29. Malacria, M. *Chem. Rev.* **1996**, *96*, 289–306.
30. Neuschultz, K.; Velker, J.; Neier, R. *Synthesis* **1998**, 227–255.
31. Rudler, H.; Audouin, M.; Chelain, E.; Denise, B.; Goumont, R.; Massoud, A.; Parlier, A.; Pacrean, A.; Rudler, M.; Yefsah, R.; Alvarez, C.; Delgado-Reyes, F. *Chem. Soc. Rev.* **1991**, *20*, 503–531.
32. Schobert, R. *Chem. Ber.* **1996**, *129*, 595–602.
33. Tverdokhlebov, A. V.; Resnyanska, E. V.; Tolmachev, A. A.; Zavada, A. V. *Monatsh. Chem.* **2003**, *134*, 1045–1052.
34. Schäfer, H.; Gewald, K. *Monatsh. Chem.* **1989**, *120*, 315–322.
35. Resnyanskaya, E. V.; Tverdokhlebov, A. V.; Volovenko, Yu. M.; Shishkin, O. V.; Zubatyuk, R. I. *Synthesis* **2002**, 2717–2724.
36. Berghot, M. A.; Hanna, M. A.; Girges, M. M. *Pharmazie* **1992**, *47*, 340–343.
37. Ghorab, M. M.; Abdel-Hamide, S. G.; El-Hakim, A. E. *Indian J. Heterocycl. Chem.* **1995**, *5*, 115–120.
38. Abdel-Hamide, S. G. *J. Indian Chem. Soc.* **1997**, *74*, 613–618.
39. Ghorab, M. M.; Nassar, O. M.; Heiba, H. I.; Amin, N. E. *Acta Pharm. (Zagreb)* **1988**, *48*, 101–110.
40. Abbady, M. A.; Abdel-Hafez, Sh. H. *Phosphorus, Sulfur Silicon Relat. Elem.* **2000**, *160*, 121–139.
41. Atkinson, J. D.; Johnson, M. C. *J. Chem. Soc. (C)* **1968**, 1252–1258.
42. Sachs, F. *Ber. Dtsch. Chem. Ges.* **1906**, *39*, 3006–3028.
43. Leonard, N. J.; Hyson, A. M. *J. Am. Chem. Soc.* **1949**, *71*, 1961–1964.
44. Wasulko, W.; Noble, A. C.; Popp, F. D. *J. Med. Chem.* **1966**, *9*, 599–601.
45. Zhitnikov, V. Ya.; Burmistrov, S. I. *Izv. Vyssh. Uchebn. Zaved. Khim. Khim. Tekhnol.* **1969**, *12*, 1069–1071, *Chem. Abstr.* **1970**, *72*, 31757.
46. Yavari, I.; Mostafavi, H.; Tahmassebi, D.; Hekmat-Shoar, R. *Monatsh. Chem.* **1997**, *128*, 675–679.
47. Balls, A. K.; Kohler, F. *Ber. Dtsch. Chem. Ges.* **1931**, *64*, 34.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 5785–5792
Tetrahedron

Triazolopyridines. Part 24: New polynitrogenated potential helicating ligands☆

Belén Abarca,* Rafael Ballesteros and Mimoun Chadlaoui

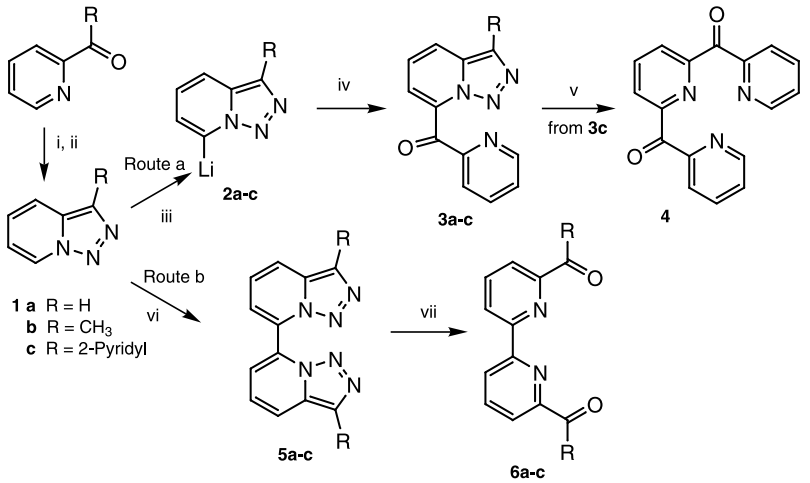
Departamento de Química Orgánica, Facultad de Farmacia, Universidad de Valencia, Avda. Vicente Andrés Estellés s/n, 46100 Burjassot (Valencia), Spain

Received 19 January 2004; revised 14 April 2004; accepted 3 May 2004

Abstract—The synthesis of novel 7-{[1,2,3]triazolo[1,5-*a*]pyridin-3-yl}-[1,2,3]triazolo[1,5-*a*]pyridines **7**, 2-pyridyl-[1,2,3]triazolo[1,5-*a*]-pyrid-7-ylmethanols **11**, 3-(6-substituted-2-pyridyl)-[1,2,3]triazolo[1,5-*a*]pyridines **12**, and 7,7′-disubstituted-3,3′-[1,2,3]triazolo[1,5-*a*]-pyridine **20**, interesting polynitrogenated ligands as potential helicating compounds or luminescent sensors, from [1,2,3]triazolo[1,5-*a*]-pyridines is described.

1. Introduction

The synthetic chemical mimicry of the double-helix structural motif is an interesting area of research with intense activity in recent years.[2] The formation of helicates, term introduced by Lehn and co-workers in 1987 for the description of a polymetallic helical double-stranded complex,[3] has become an important synthetic tool. Oligo-pyridines and related compounds are very useful helicating ligands.[2,4] We have recently discovered a facile route to new potential helicating ligands **3c**, **4**, **5a-c**, and **6a-c** from triazolopyridines **1a-c**,[5] (obtained by reaction of the corresponding acylpyridine with N_2H_4 and then oxidation with MnO_2), by regioselective lithiation at −40 °C, subsequent reaction with electrophiles and then triazolo ring opening with loss of dinitrogen,[6,7] (route a, Scheme 1) or by lithiation at −70 °C, giving 7,7′-bitriazolopyridines and then opening of the triazolo ring to produce 2,2′-bipyridines,[8] (route b, Scheme 1). Following this study we have designed new ligands **7**-**10**, which can be

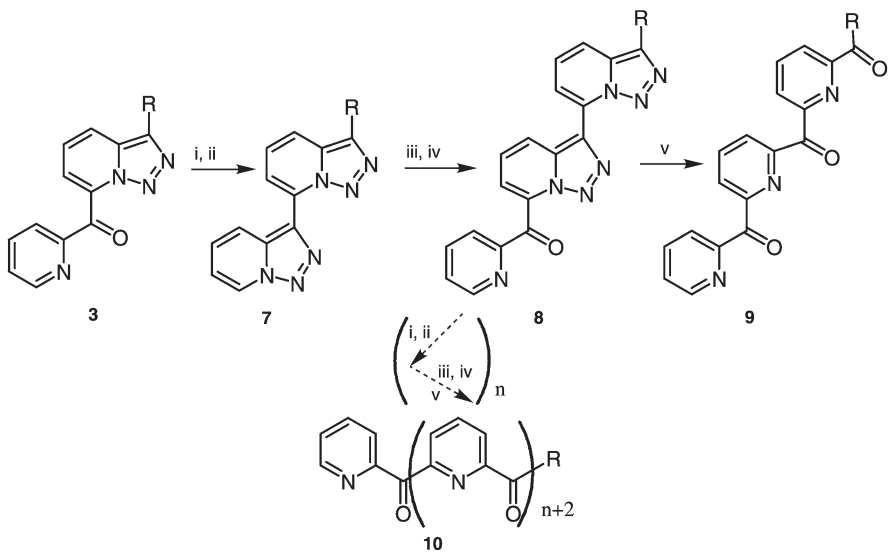


Scheme 1. (i) N_2H_4; (ii) MnO_2, CL_2CH_2; (iii) LDA, THF, −40 °C; (iv) 2-PyCHO/air; (v) SeO_2; (vi) LDA, THF, −70 °C; (vii) SeO_2.

☆ See Ref. 1.

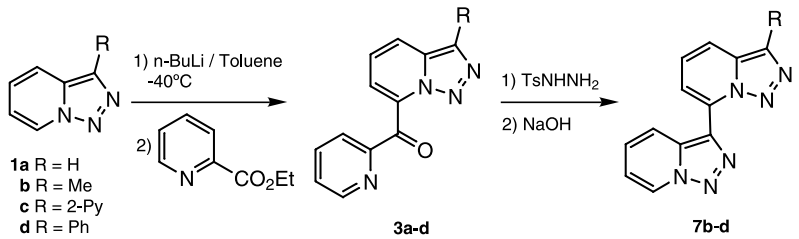
Keywords: Nitrogenated heterocycles; Helicating ligands; Lithiation; Luminescent sensors.
* Corresponding author. Tel. +34963544933; fax: +34963544939; e-mail address: belen.abarca@uv.es

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.05.002



Scheme 2. (i) N_2H_4; (ii) MnO_2,Cl_2CH_2; (iii) LDA, −40 °C; (iv) 2-Py-CHO/air; (v) SeO_2.

easily accessible from compounds **3** if the methodology summarised above in route a is applicable (see Scheme 2). The understanding that the availability of **3** is important to success, led us to attempt to improve the reported yield.[9] We wish to report here our new results in this project, that allow us to synthesize the novel polynitrogenated ligands **7b**,**d**, **7c′**, **11b**,**d**, **11c′**, **12**-**14**, **16**, **18**-**20**, liable to make helicates as versatile supramolecular complexes.[10] These compounds have other potential fields of applications based on its rich photophysical and photo-chemical properties,[11] or as luminescent molecular sensors.[12]



Scheme 3.

Table 1. ^{1}H NMR data for compounds **3a**-**d**

	H4	H5	H6	H7	H3′	H4′	H5′	H6′	Others
3a	7.84, dd, J_1=8.85 Hz, J_2=1.50 Hz	7.29, dd, J_1=8.85 Hz, J_2=6.78 Hz	7.37, dd, J_1=6.78 Hz, J_2=1.50 Hz	—	8.15, ddd, J_1=7.71 Hz, J_2=1.10 Hz, J_3=0.93 Hz	7.88, ddd, J_1=J_2=7.71 Hz, J_3=1.68 Hz	7.43, ddd, J_1=7.71 Hz, J_2=4.71 Hz, J_3=1.10 Hz	8.44, ddd, J_1=4.71 Hz, J_2=1.68 Hz, J_3=0.93 Hz	8.37, s, H3
3b	7.73, dd, J_1=8.85 Hz, J_2=1.50 Hz	7.23, dd, J_1=8.85 Hz, J_2=6.78 Hz	7.34, dd, J_1=6.78 Hz, J_2=1.50 Hz	—	8.15, ddd, J_1=7.71 Hz, J_2=1.10 Hz, J_3=0.93 Hz	7.88, ddd, J_1=J_2=7.71 Hz, J_3=1.68 Hz	7.43, ddd, J_1=7.71 Hz, J_2=4.71 Hz, J_3=1.10 Hz	8.45, ddd, J_1=4.71 Hz, J_2=1.68 Hz, J_3=0.93 Hz	2.57, s, CH_3
3c	8.01, ddd, J_1=9.0 Hz, J_2=1.1 Hz, J_3=0.9 Hz	7.10, ddd, J_1=6.0 Hz, J_2=9.0 Hz, J_3=0.9 Hz	6.95, ddd, J_1=6.9 Hz, J_2=6.0 Hz, J_3=1.1 Hz	8.65, ddd, J_1=6.9 Hz, J_2=J_3=0.9 Hz	8.01, ddd, J_1=7.5 Hz, J_2=1.3 Hz, J_3=0.9 Hz	7.85, ddd, J_1=7.3 Hz, J_2=7.5 Hz, J_3=1.6 Hz	7.47, ddd, J_1=7.3 Hz, J_2=4.8 Hz, J_3=1.3 Hz	8.73, ddd, J_1=4.8 Hz, J_2=1.6 Hz, J_3=0.9 Hz	8.40, dd, J_1=7.6 Hz, J_2=1.3 Hz, H3″, 7.92, dd, J_1=7.6 Hz, J_2=7.7 Hz, H4″, 7.98, dd, J_1=7.7 Hz, J_2=1.3 Hz, H5″
3d	7.90–7.87, m, 3H*	7.37–7.35, m, 3H* *	7.90–7.87, m, 3H*	—	8.17, ddd, J=7.92 Hz	7.90–7.87, m, 3H*	7.44–7.41, m, 3H* * *	8.46, d, J=4.71 Hz	8.11–8.08, m, 1H, (H_p), 7.44–7.41, m, 3H, ($2H_o$* * *), 7.37–7.35, m, 3H, ($2H_m$* *)

*, * *, * * * Assigned by COSY experiments.

2. Results and discussion

We had reported that reaction of triazolopyridine **1c** in THF solution at −40 °C with LDA gave the 7-lithio derivative **2c** which reacted with 2-pyridine carbaldehyde to form an unstable diarylmethyl alkoxide intermediate, which provides rapid access to ketone **3c** by spontaneous air oxidation in work-up, with 35% yield.[5] Since we had found later that lithiation reactions of triazolopyridines **1** give better results using toluene as solvent and *n*-BuLi as lithiating agent, we thought that under these conditions, and with 2-cyanopyridine as co-reagent, we would be able to improve the yield of **3c**. However the new reaction gave, as only characterised product, the compound **3c** in almost the same yield. This type of reaction was also performed with compounds **1a**,**b**. In the conditions above indicated, the 7-lithio derivatives **2a**,**b** were formed. Subsequent reactions with 2-cyanopyridine gave the corresponding 7-pyridylcarbonyl derivatives **3a**,**b** in low yields.[9] We have now improved the results using as co-reagent ethyl picolinate, and compounds **3a**-**d** are obtained in 78, 75, 90 and 78% yield, respectively (Scheme 3).

After a carefully study of the 300 MHz ^{1}H NMR data of these compounds, compiled in Table 1, we realized that the δ and J values for the compound obtained in the reaction from **1c** don't fit properly with the structure **3c** that we proposed.[5,9] If we look the δ and J values for protons in acylpyridine (H3′, H4′, H5′, H6′) and triazolopyridine (H4, H5, H6) part of the compounds **3a**,**b**,**d**, there are the expected similarity in all of them, nevertheless for the so-called **3c** there are protons corresponding to an acylpyridyl group, but there are interesting features in the rest of data. Signals at δ 8.65 (1H, ddd, J_1=6.9 Hz, J_2=J_3=0.9 Hz, H7), 6.95 (1H, ddd, J_1=6.9 Hz, J_2=6.0 Hz, J_3=1.1 Hz, H6), 7.10 (1H, ddd, J_1=9.0 Hz, J_2=6.0 Hz, J_3=0.9 Hz, H5), 8.01 (1H, ddd, J_1=9.0 Hz, J_2=0.9 Hz, J_3=1.1 Hz, H4) for a 3-substituted triazolopyridine and 8.40 (1H, dd, J_1=7.6 Hz, J_2=1.3 Hz, H3″), 7.92 (1H, dd, J_1=7.6 Hz, J_2=7.7 Hz, H4″), 7.98 (1H, dd, J_1=7.7 Hz, J_2=1.3 Hz, H5″) for a 2,6-disubstituted pyridine are more in agreement with structure **3c′**. To account for this structure we assume that, in solution, the first formed **3c** is in equilibrium with the diazo form **A**, this intermediate may undergo a new ring-chain isomerization,[13,14] giving **3c′** (Scheme 4). A X-ray study of this compound is in progress.

To obtain compounds **7** from **3** we tried the general procedure for the synthesis of triazolopyridines, reaction of an acylpyridine with $N_2H_4{\cdot}H_2O$, and without isolation of the corresponding hydrazone, oxidation with MnO_2.[15] When **3b** was the starting material compound **7b** (20%) was obtained together with a surprising alcohol **11b** (20%), and **3b** (25%) (Scheme 5). From **3c** the only identified compound was an alcohol, in the isomeric form **11c′**, and compound **3d** gave also an alcohol in the form **11d** (Fig. 1).

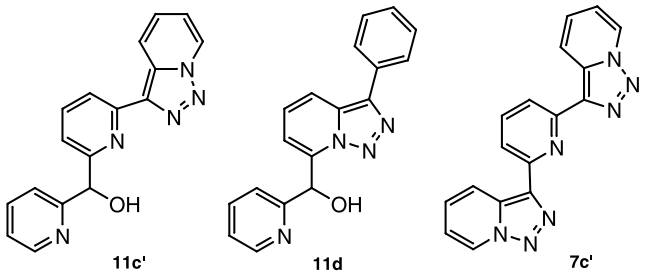
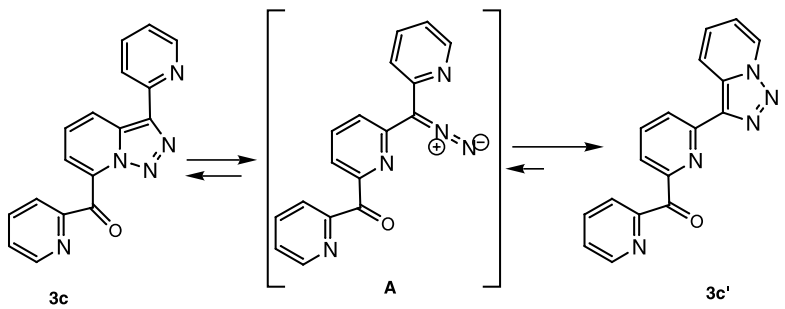
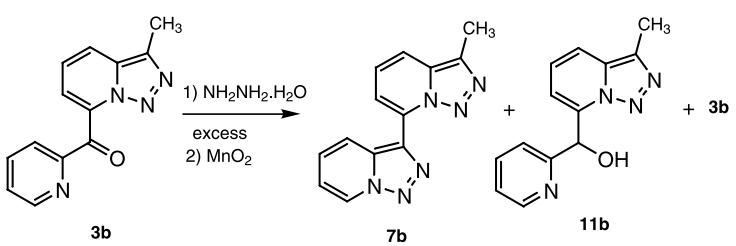


Figure 1.

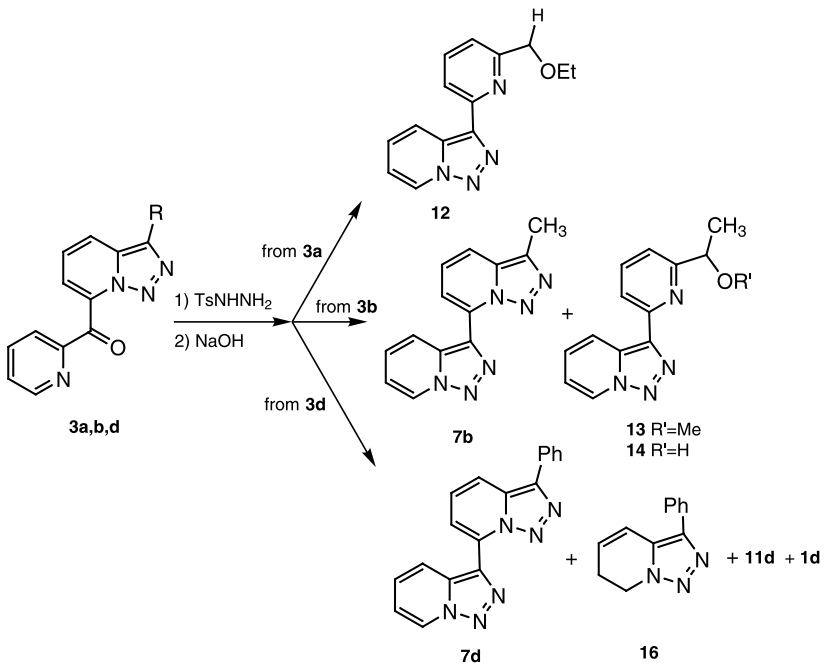
The formation of alcohols **11** is not easy to explain on treatment with an oxidizer. To check when they are formed we analysed the crude of the reaction with hydrazine, alcohols **11** are the only isolated compounds almost in quantitative yield. To account for its formation we believe that the hydrazones are formed and transformed to the diazo compounds by oxidation due to molecular oxygen,[16] that before to lie the equilibrium to triazolopyridines, loose nitrogen to form a carbene,[17] that is trapped by water to



Scheme 4.



Scheme 5.



Scheme 6.

form the alcohols.[18] We tried to avoid oxidation of the hydrazone to the diazo compound carrying out the reaction with **3b** under a nitrogen atmosphere but, a new reaction occurs giving two major products, triazolopyridine **1b** and an acylpyridine derivative.

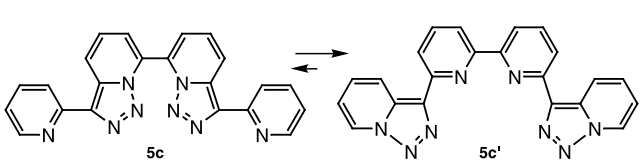
When $TsNHNH_2$ was used as co-reagent and the reaction work-up with aqueous sodium hydroxide,[19] compounds **7b**-**d** were finally synthesized in low or excellent yields, different secondary compounds were formed depending of the starting material. From **3a** in ethanol as solvent, an intractable mixture was formed from which could only be identified compound **12**. From **3b** in methanol as solvent, compounds **7b** (15%), **13** (15%), and **14** (15%) were isolated and identified (Scheme 6).

The formation of **12**, **13**, and **14** from the corresponding **7a**, or **7b** may be explained by the equilibrium between bitriazolopyrines **7a**,**b** and triazolopyridylpyridyl-diazoalkanes **15a**,**b** that could loose nitrogen to form a carbene trapped by solvents (ethanol, methanol, water) (Scheme 7).

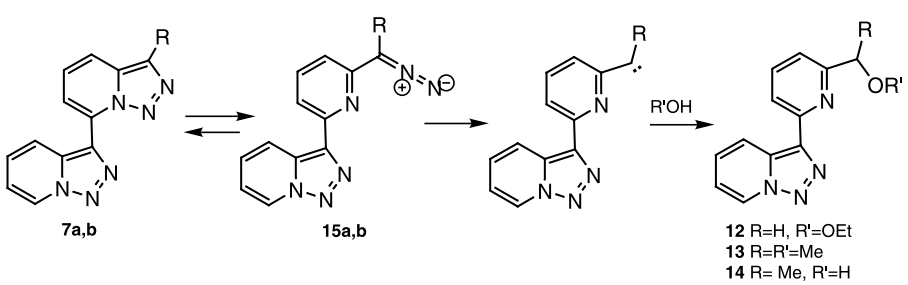
Best result was found with **3c**′, an unique product was formed in very good yield (96%). This compound shows a molecular ion of 313.1039 corresponding to a molecular formula of $C_{17}H_{11}N_7$. A carefully study of its ^1H and ^{13}C NMR data suggest a very symmetric structure with two 3-substituted triazolopyridines and a 2,6-disubstituted pyridine. We propose the structure **7c**′ for it (Fig. 1). That structure is resembling to terpyridines and the quelating properties could be similar.[4] Finally compound **3d** gave a mixture of **7d** (2%), **11d** (45%), **1d** (15%) and **16** (38%) (Scheme 6). Interesting the formation of **16**, we have verified that it is formed from **11d** in basic medium. A research is in progress to elucidate the mechanism and the scope of this transformation.

The structures proposed for **3c**′ and **7c**′ make us to turn to the structure of **5c**,[5] studying a more sensitive ^1H NMR spectrum we realised that the data fit better whit two 3-substituted triazolopyridines and one 6,6′-disubstituted-2,2′-bipyridine as in structure **5c**′ (Scheme 8).

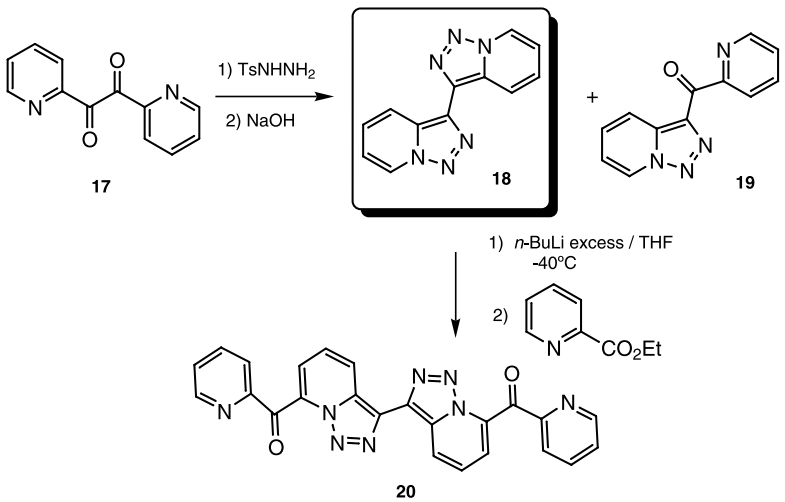
From 1,2-di(2-pyridyl)-1,2-ethanodione **17** by reaction



Scheme 8.



Scheme 7.



Scheme 9.

with $TsNHNH_2$ in basic medium we have synthesized 3,3′-bitriazolopyridine **18**. A secondary product was formed in this reaction that was identified as **19**. We have studied the behaviour of **18** with lithiating agents. Compound **18** is insoluble in toluene, we used THF as solvent and *n*-BuLi as co-reagent, after quenching with D_2O a 7,7′-dideuterio-3,3′-bitriazolopyridine was formed indicating the previous formation of a dilithium derivative. This intermediate is trapped by electrophiles. Reaction with two moles of ethyl picolinate gave **20** in 66% yield (Scheme 9). We have tried the lithiation of compound **7c′** in the same conditions, the 7,7′-dideuterio derivative have been identified after treatment of the dilithium derivative with D_2O, nevertheless reaction of dilithium compound with ethyl picolinate gave only polymeric compounds.

All new synthesized compounds have interesting ligand structures and should be able to form polynuclear complexes with different metal ions. We have studied the coordinating behaviour of **1b** with Cu(II),[20] and the spin crossover behaviour of some complex formed with **1c** and Fe(II).[21] We are at the present investigating the luminescence properties of **5c′** and **7c′** and their use as chemosensors.

3. Experimental

Melting points were determined on a Kofler heated stage and are uncorrected. NMR spectra were recorded on a Bruker AC 300 MHz in $CDCl_3$ as solvent. COSY experiments were done for all compounds. HRMS (EI) determinations were made using a VG Autospec Trio 1000 (Fisons). Infrared spectra were recorded in KBr discs on a Bio-Rad FTS-7. Ultraviolet spectra were recorded on a Shimazu UV-2101 instrument. All the lithiation reactions were done under inert atmosphere and dry solvents.[22]

[1,2,3]Triazolo[1,5-*a*]pyridine **1a**, 3-methyl-[1,2,3]triazolo[1,5-*a*]pyridine **1b**, 3-(2-pyridyl)-[1,2,3]triazolo[1,5-*a*]-pyridine **1c**, and 3-phenyl-[1,2,3]triazolo[1,5-*a*]pyridine **1d**. Prepared as described elsewhere.[13,19,23]

3.1. General procedure for lithiation of [1,2,3]triazolo-[1,5-*a*]pyridines 1a-d and reaction with ethyl picolinate

To a solution of the corresponding [1,2,3]triazolo[1,5-*a*]-pyridine **1** in anhydrous toluene at −40 °C, a solution of *n*-butyllithium in hexane (2.5 M) (20% excess) was added with stirring. A deep red colour developed. The mixture was kept at −40 °C (4 h). Treatment with a dry toluene solution (10 mL) of ethyl picolinate (20% excess) produced a colour change to yellow. The mixture was left at −40 °C (2 h) and allowed at room temperature overnight, then was treated with a saturated solution of ammonium chloride. The organic layer was separated and the aqueous layer extracted with dichloromethane. After dried over anhydrous Na_2SO_4 and evaporation of the organic solvents, a residue was obtained. Precipitation with ethyl acetate gave compounds **3a-d** as brown or yellow solids. In same cases the filtrate was evaporated to dryness and the residue purified by chromatotron with ethyl acetate/hexane as eluent, to obtain additional amount of compound **3**. The yield and conditions of purification are given for each compound.

3.1.1. 2-Pyridyl-[1,2,3]triazolo[1,5-*a*]pyrid-7-ylmethanone 3a. *Compound* **1a** (1 g, 8.4 mmol), toluene (40 mL), *n*-BuLi (4 mL), ethyl picolinate (1.5 mL), (78%). Purification by recrystallization from ethyl acetate. Mp 158–160 °C. Lit.[9] 158–160 °C.

3.1.2. 2-Pyridyl-3-methyl-[1,2,3]triazolo[1,5-*a*]pyrid-7-ylmethanone 3b. *Compound* **1b** (0.5 g, 3.75 mmol), toluene (20 mL), *n*-BuLi (1.9 mL), ethyl picolinate (0.7 mL), (75%). Purification by recrystallization from ethyl acetate. Mp 165–167 °C. Lit.[9] 165–167 °C.

3.1.3. 2-Pyridyl-6-[1,2,3]triazolo[1,5-*a*]pyrid-3-yl-2-pyridylmethanone 3c′. *Compound* **1c** (0.5 g, 2.5 mmol), toluene (20 mL), *n*-BuLi (1.6 mL), ethyl picolinate (0.4 mL), (90%). Purification by recrystallization from ethyl acetate/hexane give two crystalline phases. At 194–195 °C there is a phase transition forming needles that melt at 220–221 °C.[9] Lit.[5] 194–195 °C.

3.1.4. 2-Pyridyl-3-phenyl-[1,2,3]triazolo[1,5-*a*]pyrid-7-ylmethanone 3d. *Compound* **1d** (1 g, 5.13 mmol), toluene (40 mL), *n*-BuLi (4 mL), ethyl picolinate (1.5 mL), (78%). Purification by recrystallization from ethyl acetate/hexane. Mp 169–171 °C. HRMS found for M^+ 300.0993; $C_{18}H_{12}N_4O$ requires 300.1011. ν_{max} (KBr) (cm^{-1}) 1689 (CO), 1584, 1313, 1293, 1063, 758, 693. λ_{max} (nm) (log ε) (EtOH) 293.5 (4.04), 381.5 (3.58). ^{13}C NMR δ 188.40 (CO), 153.08 (C), 149.25 (CH), 138.09 (C), 137.36 (CH), 135.12 (C), 131.15 (C), 130.74 (C), 129.03 (2CH), 128.10 (CH), 127.72 (CH), 126.90 (2CH), 125.00 (CH), 123.75 (CH), 121.10 (CH), 118.15 (CH). MS *m*/*z* (%) 300 (6), 272 (100), 271 (59), 243 (41), 194 (25), 166 (41), 78 (49).

3.2. General procedure for reaction of 2-pyridyl-[1,2,3]triazolo[1,5-*a*]pyrid-7-yl methanones 3b-d with hydrazine hydrate

Procedure A. A solution of the corresponding 2-pyridyl-[1,2,3]triazolo[1,5-*a*]pyrid-7-ylmethanone in ethanol was added to an excess of hydrazine hydrate, and was heated under reflux. Then water (10 mL) was added and extracted with dichroromethane (3×10 mL). The organic layer was dried and evaporated, the residue was dissolved in chloroform (5 mL). Manganese oxide (50% excess) was added and the mixture heated to reflux, then was filtered and the solvent was evaporated. The residue was purified by chromatotron using hexane/ethyl acetate as eluent.

Procedure B. A solution of the corresponding 2-pyridyl-[1,2,3]triazolo[1,5-*a*]pyridin-7-ylmethanone in a organic solvent was added to an excess of hydrazine hydrate, and was heated under reflux. Then water (10 mL) was added and extracted with dichroromethane (3×10 mL). The organic layer was dried and evaporated. The residue was purified by chromatotron using hexane/ethyl acetate as eluent.

3.2.1. 3-Methyl-7-{[1,2,3]triazolo[1,5-*a*]pyrid-3-yl}-[1,2,3]triazolo[1,5-*a*]pyridine 7b. The title compound was obtained by procedure A from **3b** (100 mg, 0.42 mmol), refluxed 24 h and after addition of the oxidant an additional time (1 h 30 m) was refluxed, **7b** was the first eluted product (20%). Mp 218–220 °C (AcOEt). HRMS found M^+ 250.0971; $C_{13}H_{10}N_6$ requires 250.0966. ν_{max} (KBr) (cm^{-1}) 3110, 1643, 1627, 1536, 1407, 1218, 1162, 780, 740. λ_{max} (nm) (log ε) (Cl_2CH_2) 229 (4.08), 283 (4.08), 349.5 (3.96). ^1H NMR δ 8.74 (d, J=6.96 Hz, 1H, H7′), 8.41 (d, J=9.24 Hz, 1H, H4), 7.68 (dd, J_1=6.75 Hz, J_2=1.14 Hz, 1H, H6), 7.62 (dd, J_1=8.67 Hz, J_2=1.14 Hz, 1H, H4′), 7.31 (m, 2H, H5, H5′), 7.04 (ddd, J_1=6.96 Hz, J_2=6.78 Hz, J=1.14 Hz, 1H, H6′), 2.63 (s, 3H, CH_3). ^{13}C NMR δ 134.87 (C), 132.49 (C), 130.39 (C), 130.34 (C), 130.24 (C), 126.10 (CH), 125.35 (CH), 124.29 (CH), 122.49 (CH), 116.26 (CH), 115.92 (CH), 115.67 (CH), 10.51 (CH_3). MS *m*/*z* (%) 250 (29), 222 (12), 194 (33), 193 (100), 192 (31), 179 (16), 166 (12). Then starting material **3b** (25%) was eluted, further elution gave 2-pyridyl-3-methyl-[1,2,3]-triazolo-[1,5-*a*]pyrid-7-ylmethanol **11b** (20%). Mp 113–115 °C. Lit.[24] 113–115 °C (CH_2Cl_2/hexane).

3.2.2. 2-Pyridyl-3-methyl-[1,2,3]triazolo[1,5-*a*]pyrid-7-ylmethanol 11b. The title compound was obtained by procedure B from **3b** (10 mg, 0.042 mmol), solvent *n*-BuOH, refluxed 30 min, almost pure in quantitative yield.

3.2.3. 2-Pyridyl-6-{[1,2,3]triazolo[1,5-*a*]pyrid-3-yl}-2-pyridylmethanol 11c′. The title compound was obtained by procedure B from **3c′** (10 mg, 0.039 mmol), solvent *n*-BuOH, refluxed 30 m, almost pure in quantitative yield. Mp 124–126 °C (cyclohexane). HRMS found for M^+ 303.1122; $C_{17}H_{13}N_5O$ requires 303.1120. ν_{max} (KBr) (cm^{-1}) 3324, 3182, 1590, 1055, 745. λ_{max} (nm) (log ε) (EtOH) 207 (4.36), 268 (4.20), 326 (4.14). ^1H NMR δ 8.70 (d, J=6.99 Hz, 1H, H7), 8.53 (m, 2H, H4, H6″), 8.19 (dd, J_1=7.92 Hz, J_2=0.96 Hz, 1H, H5′), 7.73 (dd, J_1=7.92 Hz, J_2=7.71 Hz, 1H, H4′), 7.63 (ddd, J_1=7.71 Hz, J_2=7.92 Hz, J_3=1.5 Hz, 1H, H4″), 7.49 (d, J=7.92 Hz, 1H, H3″), 7.41 (d, J=7.71 Hz, 1H, H3′), 7.33 (ddd, J_1=6.78 Hz, J_2=9.06 Hz, J_3=0.96 Hz, 1H, H5), 7.19 (ddd, J_1=7.71 Hz, J_2=5.1 Hz, J_3=1.14 Hz, 1H, H5″), 7.00 (ddd, J_1=6.99 Hz, J_2=6.78 Hz, J_3=1.32 Hz, 1H, H6), 5.98 (s, 1H, *CH*–OH), 2.1 (brs, 1H, OH). ^{13}C NMR δ 160.72 (C), 151.19 (C), 147.91 (CH), 138.18 (CH), 137.99 (CH), 137.50 (C), 132.36 (C), 126.96 (CH), 125.78 (CH), 123.31 (CH), 123.32 (C), 122.11 (CH), 121.36 (CH), 119.93 (CH), 119.89 (CH), 116.25 (CH), 75.63 (CH–OH).

3.2.4. 2-Pyridyl-3-phenyl-[1,2,3]triazolo[1,5-*a*]pyrid-7-ylmethanol 11d. The title compound was obtained by procedure B from **3d** (50 mg, 0.19 mmol), solvent ethanol, refluxed 2 h, in 53% yield. Mp 157–158 °C (hexane). HRMS found for M^+ 302.1163; $C_{18}H_{14}N_4O$ requires 302.1167. ν_{max} (KBr) (cm^{-1}) 3201, 1591, 1549, 1477, 1451, 1263, 1223, 1182, 1080, 995, 790, 705. λ_{max} (nm) (log ε) (EtOH) 301.5 (4.01), 322 (3.93). ^1H NMR δ 8.46 (d, J=4.71 Hz, 1H, H6′), 7.81–7.88 (m, 4H, 2H*o*, H4, H3′), 7.58 (ddd, J_1=7.92 Hz, J_2=7.53 Hz, J_3=1.71 Hz, 1H, H4′), 7.38–7.44 (m, 2H, H*m*), 7.31 (ddd, J_1=7.32 Hz, J_2=J_3=1.32 Hz, 1H, H*p*), 7.24 (dd, J_1=J_2=8.85 Hz, 1H, H5), 7.15 (ddd, J_1=7.53 Hz, J_2=4.71 Hz, J_3=0.93 Hz, 1H, H5), 7.10 (d, J=6.78 Hz, 1H, H6), 6.68 (brs, 1H, CH), 5.75 (brs, 1H, OH). ^{13}C NMR δ 157.31 (C), 148.42 (CH), 140.15 (C), 138.12 (C), 137.18 (CH), 131.31 (C), 130.93 (C), 128.95 (2CH), 127.88 (CH), 126.63 (2CH), 126.10 (CH), 123.46 (CH), 122.16 (CH), 117.08 (CH), 112.84 (CH), 70.01 (CH). MS *m*/*z* (%) 302 (8), 274 (48), 257 (100), 168 (37), 78 (19).

3.3. General procedure for reaction of 2-pyridyl-[1,2,3]-triazolo[1,5-*a*]pyrid-7-yl methanones 3a-d with tosylhydrazine

A solution of the corresponding 2-pyridyl-[1,2,3]triazolo-[1,5-*a*]pyrid-7-ylmethanone in suitable alcohol was added to an equimolar solution of tosylhydrazine in ethanol, the mixture was boiled under reflux for 5 h, and then was treated with aqueous sodium hydroxide and refluxed for an additional time (1 h). The mixture was concentrated under reduced pressure to 10–15 mL and, in some cases, after cooling a precipitate was formed that was filtered and identified. The filtrate was extracted with an organic solvent (3×10 mL). The organic layer was dried (Na_2SO_4), evaporated, and the crude purified by chromatotron eluting with ethyl acetate/hexane. The yield and conditions of purification are given for each compound.

3.3.1. 3-[6-(1-Ethoxyethyl)-2-pyridyl]-[1,2,3]triazolo-[1,5-*a*]pyridine 12. *Compound* **3a** (0.1 g, 0.45 mmol), tosylhydrazine (0.11 g, 0.6 mmol), ethanol (50 mL), NaOH (3 mL, 2 N). No precipitate was formed, and the solution was extracted with dichloromethane. The only isolated compound as an oil was identified as 3-[6-(1-ethoxiethyl)-2-pyridyl]-[1,2,3]triazolo[1,5-*a*]pyridine **12** (26 mg, 23%). HRMS found for M^+ 254.1127; $C_{14}H_{14}N_4O$ requires 254.1167. ^{1}H NMR δ 8.67 (d, J=6.59 Hz, 1H, H7), 8.65 (d, J=8.29 Hz, 1H, H4), 8.16 (d, J_1=7.91 Hz, 1H, H5′), 7.73 (dd, J_1=7.91 Hz, J_2=7.70 Hz, 1H, 4H′), 7.32–7.27 (m, 2H, H5, H3′), 6.96 (ddd, J_1=6.97 Hz, J_2=6.59 Hz, J_3=1.32 Hz, 1H, H6), 4.65(s, 2H, CH2), 3.60 (c, J=6.97 Hz, 2H, CH2), 1.35 (t, J=6.97 Hz, 3H, CH_3). ^{13}C NMR δ 158.42 (C), 151.25 (C), 137.28 (CH), 136.57 (C), 132.00 (C), 126.23 (CH), 125.20 (CH), 120.53 (CH), 119.44 (CH), 118.92 (CH), 115.83 (CH), 73.82 (CH_2), 66.44 (CH_3), 15.32 (CH_3). MS *m/z* (%) 254 (22), 226 (39), 181 (100), 169 (16), 142 (10), 78 (11).

3.3.2. 3-Methyl-7-{[1,2,3]triazolo[1,5-*a*]pyrid-3-yl}-[1,2,3]triazolo[1,5-*a*]pyridine 7b. *Compound* **3b** (0.1 g, 0.44 mmol), tosylhydrazine (0.08 g, 0.42 mmol), methanol (10 mL), NaOH (7 mL, 2 N). The precipitate was 3-methyl-{7-[1,2,3]triazolo[1,5-*a*]pyridin-3-yl}-[1,2,3]triazolo[1,5-*a*]-pyridine **7b** almost pure (15 mg, 14%). The filtrate was extracting with ether (3×10 mL). The organic layer was dried (Na_2SO_4), evaporated, and the crude (66 mg) purified by chromatotron eluting with ethyl acetate/hexane. First was eluted 3-[6-(1-methoxyethyl)-2-pyridyl]-[1,2,3]triazolo[1,5-*a*]pyridine **13** (15 mg, 15%) as an oil. HRMS found for M^+ 254.1130; $C_{14}H_{14}N_4O$ requires 254.1167. ^{1}H NMR δ 8.68 (m, 2H, H4, H7), 8.17 (dd, J_1=7.92 Hz, J_2=0.96 Hz, 1H, H5′), 7.74 (dd, J_1=7.92 Hz, J_2=7.74 Hz, 1H, H4′), 7.30 (ddd, J_1=8.85 Hz, J_2=6.88 Hz, J_3=1.14 Hz, 1H, H5), 7.26 (dd, J_1=7.74 Hz, J_2=0.96 Hz, 1H, H3′), 6.97 (ddd, J_1=6.96 Hz, J_2=6.88 Hz, J_3=1.14 Hz, 1H, H6), 4.46 (c, J=6.57 Hz, 1H, CH), 3.31 (s, OCH_3) 2.50 (d, J=6.57 Hz, 3H, CH_3). ^{13}C NMR δ 162.44 (C), 151.28 (C), 137.40 (CH), 136.56 (C), 132.08 (C), 126.28 (CH), 125.20 (CH), 121.51 (CH), 118.94 (CH), 118.18 (CH), 115.83 (CH), 80.85 (CH), 56.96 (OCH_2), 22.18 (CH_3). MS *m/z* (%) 254 (24), 226 (50), 211 (45), 195 (100), 181 (37), 169 (14), 168 (37), 78 (19). The second fraction was an oil identified as 3-[6-(1-hydroxyethyl)-2-pyridyl]-[1,2,3]triazolo[1,5-*a*]pyridine **14** (16 mg, 15%). HRMS found M^+ 240.1022; $C_{13}H_{12}N_4O$ requires 240.1011. ^{1}H NMR δ 8.71 (d, J=7.17 Hz, 1H, H7), 8.52 (d, J=9.03 Hz, 1H, H4), 8.21 (d, J=7.74 Hz, 1H, H5′), 7.76 (dd, J_1=J_2=7.74 Hz, 1H, H4′), 7.34 (ddd, J_1=9.03 Hz, J_2=6.96 Hz, J_3=0.96 Hz, 1H, H5), 7.17 (d, J=7.74 Hz, 1H, H3′), 7.01 (ddd, J_1=6.96 Hz, J_2=7.17 Hz, J_3=1.14 Hz, 1H, H6), 4.94 (c, J=6.42 Hz, 1H, CH), 3.60 (brs, 1OH), 1.54 (d, J=6.42 Hz, 3H, CH_3). ^{13}C NMR δ 162.58 (C), 150.59 (C), 137.68 (CH), 137.07 (C), 131.87 (C), 126.66 (CH), 125.43 (CH), 120.74 (CH), 119.23 (CH), 118.17 (CH), 115.89 (CH), 69.22 (CH), 24.34 (CH_3). MS *m/z* (%) 240 (46), 212 (73), 197 (100), 169 (89), 78 (20).

3.3.3. 3-{6-([1,2,3]Triazolo[1,5-*a*]pyrid-3-yl)-2-pyridyl}-[1,2,3]triazolo[1,5-*a*]pyridine 7c′. *Compound* **3c′** (0.1 g, 0.33 mmol), ethanol (50 mL), tosylhydrazine (0.08 g, 0.42 mmol), ethanol (50 mL), NaOH (3 mL, 2 N). The precipitate was compound **7c′** almost pure (90 mg). The filtrate was extracting with dichloromethane (50 mL). The organic layer was dried (Na_2SO_4) and evaporated giving a crude, that was treated with ethanol (10 mL) and compound **7c′** was precipitated (10 mg) (total yield 96%). Mp 279–281 °C (EtOH/H_2O). HRMS found for M^+ 313.1039; $C_{17}H_{11}N_7$ requires 313.1075. ν_{max} (KBr) (cm^{-1}) 3087, 1631, 1595, 1570, 1529, 1448, 1402, 1162, 821, 740. λ_{max} (nm) (log ε) (EtOH) 294 (5.56), 336.5 (5.53). ^{1}H NMR δ 8.74 (ddd, J_1=6.99 Hz, J_2=J_3=0.93 Hz, 2H, H7, H7′), 8.54 (ddd, J_1=8.85 Hz, J_2=J_3=1.32 Hz, 2H, H4, H4′), 8.19 (d, J=7.71 Hz, 1H, H4″), 7.88 (t, J=7.71 Hz, 2H, H3″, H5″), 7.30 (ddd, J_1=8.85 Hz, J_2=6.78 Hz, J_3=0.93 Hz, 2H, H5, H5′), 7.01 (ddd, J_1=6.99 Hz, J_2=6.78 Hz, J_3=1.32 Hz, 2H, H6, H6′). ^{13}C NMR δ 151.39 (2C), 137.90 (2C), 137.58 (CH), 131.89 (2C), 126.34 (2CH), 125.59 (2CH), 120.49 (2CH), 119.62 (2CH), 115.77 (2CH). MS *m/z* (%), 313 (32), 285 (10), 257 (95), 256 (100), 229 (23), 179 (78), 78(13).

3.3.4. 3-Phenyl-7-{[1,2,3]triazolo[1,5-*a*]pyrid-3-yl}-[1,2,3]triazolo[1,5-*a*]pyridine 7d. *Compound* **3d** (0.2 g, 0.66 mmol), tosylhydrazine (0.36 g, 1.98 mmol), ethanol (110 mL), NaOH (6 mL, 2 N). A yellow solid was filtrated, identified as compound **7d** (4 mg, 2%) almost pure. Mp 218–220 °C (EtOH/H_2O). HRMS found for M^+ 312.1077; $C_{18}H_{12}N_6$ requires 312.1123. ^{1}H NMR δ 8.77 (ddd, J_1=6.96 Hz, J_2=1.14 Hz, J_3=0.93 Hz, 1H, H7′), 8.48 (ddd, J_1=9.21 Hz, J_2=1.14 Hz, J_3=0.93 Hz, 1H, H4′), 8.02 (dd, J_1=8.85 Hz, J_2=1.14 Hz, 1H, H4), 7.97–794 (m, 2H, H*o*), 7.78 (dd, J_1=6.96 Hz, J_2=1.14 Hz, 1H, H6), 7.54–7.41 (m, 3H, H5, 2H*m*), 7.39–7.33 (m, 2H, H5′, H*p*) 7.07 (ddd, J_1=6.96 Hz, J_2=6.78 Hz, J_3=1.14 Hz, 1H, H6′). MS *m/z*(%) 312 (8), 284 (9), 256 (58), 255 (100), 230 (8), 152 (5), 78 (6). First fraction eluted from chromatotron was 3-phenyl-[1,2,3]triazolo[1,5-*a*]pyridine **1d** (19 mg, 15%). The second fraction was a yellow solid identified as 3-phenyl-6,7-dihydro[1,2,3]triazolo[1,5-*a*]pyridine **16** (50 mg, 38%). Mp 100–102 °C (hexane). HRMS found for M^+ 197.0870; $C_{12}H_{11}N_3$ requires 197.0953. ^{1}H NMR δ 7.75 (dd, J_1=7.14 Hz, J_2=1.5 Hz, 2H, H*o*), 7.45 (dd, J_1=J_2=7.14 Hz, 2H, H*m*), 7.36 (dd, J_1=7.14 Hz, J_2=1.5 Hz, 1H, H*p*), 6.78 (ddd, J_1=9.99 Hz, J_2=J_3=1.89 Hz, 1H, H4), 6.19 (ddd, J_1=9.99 Hz, J_2=J_3=4.35 Hz, 1H, H5), 4.45 (t, J=7.74 Hz, 2H, H7, H7′), 2.67 (m, 2H, H6, H6′). ^{13}C NMR δ 142.06 (C), 131.23 (C), 128.85 (2CH), 127.97 (CH), 127.58 (CH), 126.93 (2CH), 126.17 (C), 116.25 (CH), 44.09 (CH_2), 23.92 (CH_2). MS *m/z* (%) 197 (58), 169 (100), 168 (93), 154 (50), 141 (46), 115 (36), 104 (20), 77 (12), 66 (44). The last fraction was 2-pyridy-3-phenyl-[1,2,3]triazolo-[1,5-*a*]pyridin-7-ylmethanol **11d** (89 mg, 45%).

3.3.5. 3,3′-Bi[1,2,3]triazolo[1,5-*a*]pyridine 18. A mixture of 1,2-di(2-pyridil)-1,2-ethanodione (1 g, 4.7 mmol) and tosylhydrazine (1.85 g, 9.9 mmol) in ethanol (50 mL) was boiled under reflux (8 h). After treating with aqueous sodium hydroxide (7 mL, 2 N) the reaction was refluxed for 2 h. Then the solvent was concentrated in vacuo to 10–15 mL and a precipitate was obtained. By filtration, compound **18** was separated (0.45 g) almost pure. Mp 262–264 °C (EtOH). Lit.[19] 254–255 °C (EtOH). No spectroscopical data is in the literature. HRMS found for M^+ 236.0806; $C_{12}H_8N_6$ requires 236.0810. ν_{max} (KBr) (cm^{-1}) 3113, 1630, 1530, 1504, 1152, 1015, 755. λ_{max} (nm) (log ε) (EtOH) 294.5 (5.36), 349.5 (5.29). ^{1}H NMR δ 8.71 (ddd,

J_1=6.99 Hz, J_2=J_3=0.96 Hz, 2H, H7, H7′), 8.62 (ddd, J_1=9.03 Hz, J_2=J_3=1.11 Hz, 2H, H4, H4′), 7.32 (ddd, J_1=9.03 Hz, J_2=6.99 Hz, J_3=0.96 Hz, 2H, H5, H5′), 7.01 (ddd, J_1=J_2=6.99 Hz, J_3=1.11 Hz, 2H, H6, H6′). ^{13}C NMR δ 134.22 (C3, C3′), 131.02 (C3a, C3a′), 125.65 (C7, C7′), 125.01 (C4, C4′), 120.50 (C5, C5′), 116.11 (C6, C6′). MS *m/z* (%) 236 (17), 180 (100). The filtrate was extracted with ether (3×25 mL). The organic layer was dried (Na_2SO_4), evaporated, and the crude purified by chromatotron, eluting with ethyl acetate hexane bitriazoplopyridine **18** was first eluted (0.08 g, total yield 48%), the second fraction was 2-pyridyl-[1,2,3]triazolo[1,5-*a*]pyridin-3-ylmethanone **19** (0.081 g, 8%). Mp 150–152 °C (MeOH/H_2O). Lit.[22] 151 °C (acetone). No spectroscopical data are in the literature. HRMS found for M^+ 224.0695; $C_{12}H_8N_4O$ requires 224.0698. ν_{max} (KBr) (cm^{-1}) 3077, 3030, 1655 (CO), 1626, 1514, 1418, 1229, 943, 770. λ_{max} (nm) (log ε) (EtOH) 327 (4.18). ^{1}H NMR δ 8.81 (m, 2H, H6′, H7), 8.48 (ddd, J_1=8.85 Hz, J_2=J_3=1.11 Hz, 1H, H4), 8.33 (ddd, J_1=7.71 Hz, J_2=J_3=0.93 Hz, 1H, H3′), 7.85 (ddd, J_1=J_2=7.71 Hz, J_3=1.68 Hz, 1H, H4′), 7.57 (ddd, J_1=8.85 Hz, J_2=6.78 Hz, J_3=0.93 Hz, 1H, H5), 7.44 (ddd, J_1=7.71 Hz, J_2=4.68 Hz, J_3=1.11 Hz, 1H, H5′), 7.15 (ddd, J_1=J_2=6.78 Hz, J_3=1.11 Hz, 1H, H6). ^{13}C NMR δ 185.40 (CO), 154.41 (C), 149.73 (CH), 136.77 (CH), 136.47 (C), 136.16 (C), 130.40 (CH), 126.36 (CH), 125.86 (CH), 125.42 (CH), 120.48 (CH), 117.04 (CH). MS *m/z* (%) 224 (10), 196 (9), 168 (100), 140 (12), 78 (12).

3.3.6. 7,7′-Di(2-pyridylcarbonyl)-3,3′-bi[1,2,3]triazolo[1,5-*a*]pyridine 20. To a solution of 3,3′-bi[1,2,3]triazolo[1,5-*a*]pyridine **18** (0.1 g, 0.42 mmol) in anhydrous THF (100 mL) at −40 °C, a solution of *n*-butyllithium in hexane (0.7 mL, 2.5 M, 4 equiv.) was added with stirring. A deep red colour developed. The mixture was kept at −40 °C (2 h). Further, a deep orange-yellow colour was developed and a new amount of *n*-BuLi (0.3 mL, 2 equiv.) was added. The mixture was kept at −40 °C (2 h). Then was treated with a dry THF solution (5 mL) of ethyl picolinate (0.2 g, 1.32 mmol, 3 equiv.). The mixture was left at −40 °C (2 h), and treated with a saturated solution of ammonium chloride. The organic layer was separated and the aqueous layer extracted with dichloromethane. After drying over anhydrous Na_2SO_4 and evaporation of the organic solvents, a residue was obtained (0.2 g). Precipitation with ethyl acetate gave the compound **20** as a yellow solid (0.1 g) almost pure. Mp 190–192 °C (AcOEt). HRMS found for M^+-2N_2 390.1137; $C_{24}H_{14}N_4O_2$ requires 390.1116. ν_{max} (KBr) (cm^{-1}) 3095, 3060, 2924, 2859, 1684 (CO), 1581, 1313, 1063, 743. λ_{max} (nm) (log ε) (EtOH) 291 (3.93), 402 (3.61). ^{1}H NMR δ 8.75 (dd, J_1=8.46 Hz, J_2=1.5 Hz, 1H, H4), 8.43 (ddd, J_1=4.71 Hz, J_2=1.68 Hz, J_3=0.75 Hz, 1H, H6′), 8.18 (d, J=7.71 Hz, 1H, H3′), 7.91 (ddd, J_1= J_2=7.71 Hz, J_3=1.68 Hz, 1H, H4′), 7.48–7.39 (m, 3H, H5′, H5, H6). ^{13}C NMR 186.46 (CO), 152.18 (C), 149.57 (CH), 138.11 (CH), 134.34 (C), 130.39 (C), 130.26 (C), 128.60 (CH), 126.91 (CH), 123.37(CH), 121.45 (CH), 118.71 (CH). MS *m/z* (%), 300 (6), 272 (100), 271 (59), 243 (41), 194 (25), 166 (41), 78 (49). The filtrate was evaporated and purified by chromatotron with ethyl acetate/hexane as eluent. An additional amount of compound **20** (0.017 g) was obtained (total yield 66%), ethyl picolinate (0.078 g, 38%) and starting material (0.005 g, 5%).

Acknowledgements

Our thanks are due to the Ministerio de Ciencia y Tecnología (Project ref. BQU2003-09215-C03-03) for its financial support, and to the SCSIE for the realization of the HRMS spectra.

References and notes

1. Last part in the series: Abarca, B.; Ballesteros, R.; Gay, B.; Domínguez, J. R. *Arkivoc* **2004**, *iv*, 42–47.
2. Amabilino, D. B.; Stodart, J. F. *Chem. Rev.* **1995**, *95*, 2725–2829.
3. Lehn, J. M.; Rigault, A.; Siegel, J.; Harrowfield, J.; Chevrier, B.; Moras, D. *Proc. Natl Acad. Sci. U.S.A.* **1987**, *84*, 2565.
4. Constable, E. C. *Tetrahedron* **1992**, *48*, 10013–10059.
5. Abarca, B.; Ballesteros, R.; Elmasnaouy, M. *Tetrahedron* **1998**, *54*, 15287–15292.
6. Jones, G.; Sliskovic, D. R. *J. Chem. Soc., Perkin Trans. 1* **1982**, 967–971.
7. Jones, G.; Mouat, D. J.; Tonkinson, D. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2719–2723.
8. Jones, G.; Pitman, M. A.; Lunt, E.; Lythgoe, D. J.; Abarca, B.; Ballesteros, R.; Elmasnaouy, M. *Tetrahedron* **1997**, *53*, 8257–8268.
9. Abarca, B.; Ballesteros, R.; Chadlaoui, M. *Arkivoc* **2002**, *x*, 52–60.
10. Piguet, C.; Bernardinelli, G.; Hopfgartner, G. *Chem. Rev.* **1997**, *97*, 2005–2062.
11. (a) Alpha, B.; Anklam, E.; Deschenaux, R.; Lehn, J.-M.; Pietraskiewicz, M. *Helv. Chim. Acta* **1988**, 1042–1052. (b) Williams, R. M.; De Cola, L.; Hartl, F.; Lagref, J. J.; Planeix, J. M.; De Cian, A.; Hosseine, M. W. *Coord. Chem. Rev.* **2002**, *230*, 253–261.
12. Rogers, C. W.; Wolf, M. O. *Coord. Chem. Rev.* **2002**, *233-234*, 341–350.
13. Boyer, J. H.; Borgers, R.; Wolford, L. T. *J. Am. Chem. Soc.* **1957**, *79*, 678–680.
14. Abarca, B.; Ballesteros, R.; Elmasnaouy, M. *Tetrahedron* **1999**, *55*, 12881–12884.
15. Eistert, B.; Endres, E. *Justus Liebigs Ann. Chem.* **1970**, *734*, 56–59.
16. Battaglia, L. P.; Carcelli, M.; Ferraro, F.; Mavilla, L.; Pellizzi, C.; Pellizzi, G. *J. Chem. Soc., Dalton Trans.* **1994**, 2651–2654.
17. Crow, W. D.; Wentrup, C. *Tetrahedron Lett.* **1968**, 6149.
18. Bethell, D.; Newell, R.; Stevens, G.; Whittaker, D. *J. Chem. Soc. (B)* **1969**, 749–754.
19. Boyer, J. H.; Goebel, N. *J. Org. Chem.* **1960**, *25*, 304–305.
20. Ballesteros, R.; Abarca, B.; Samadi, A.; Server-Carrión, J.; Escrivá, E. *Polyhedron* **1999**, *18*, 3129–3133.
21. Niel, V.; Gaspar, A. B.; Muñoz, M. C.; Abarca, B.; Ballesteros, R.; Real, J. A. *Inorg. Chem.* **2003**, *42*, 4782–4788.
22. Perrin, D. D.; Armarego, L. F. Purification of Laboratory Chemicals, 3rd ed., Pergamon Press.
23. Bower, J. D.; Ramage, G. R. *J. Chem. Soc.* **1957**, 4506–4510.
24. Abarca, B.; Ballesteros, R.; Elmasnaouy, M.; D'Ocón, P.; Ivorra, M. D.; Valiente, M. *Arkivoc* **2002**, *x*, 9–13.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron
Tetrahedron 60 (2004) 5793–5798

SmI_2-mediated elimination reaction of Baylis–Hillman adducts controlled by temperature: a facile synthesis of trisubstituted alkenes and 1,5-hexadiene derivatives with *E*-stereoselectivity

Jian Li,[a] Weixing Qian[a] and Yongmin Zhang[a,b,*]

[a]*Department of Chemistry, Zhejiang University (Campus Xixi), Hangzhou 310028, People's Republic of China*
[b]*State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, People's Republic of China*

Received 10 March 2004; revised 26 April 2004; accepted 30 April 2004

Abstract—Promoted by samarium diiodide, the Baylis–Hillman adducts undergo hydroxyl elimination to form trisubstituted alkenes with total (*E*)-stereoselectivity in good to excellent yields. The flexibility of this method also opens a new route to synthesize a class of 1,5-hexadiene derivatives by temperature tuning.

1. Introduction

As a class of important building block in natural products, the stereo-defined trisubstituted alkene moiety manifest their significance in the syntheses of terpenoids and insect pheromones.[1] Moreover, they are present in various biologically active molecules.[2,3] Consequently, a variety of methodologies for the syntheses of functionalized alkenes with stereo-defined trisubstituted double bonds have been well documented.[4]

The Baylis–Hillman reaction is one of the powerful carbon–carbon bond-forming method in organic synthesis.[5] The Baylis–Hillman reaction provides molecules possessing hydroxy, alkenyl, and electron-withdrawing groups in close proximity, which makes it valuable in a number of stereoselective processes.[6] Among these reactions, a few reagents such as $LiBEt_3H$ and $Pd(OAc)_2$ have been investigated towards the reduction of Baylis–Hillman adducts.[7] Though some reagents can provide good stereoselectivity, however, these reagents are generally expensive and not readily accessible. In addition, in most of the reactions Baylis–Hillman adducts must be acetylated before used as an additional step, which lower their attractiveness. Up to now, using Baylis–Hillman adducts directly in this reduction process only one report has been depicted with Low-Valent Titanium.[8] Nevertheless, the latter was also unsatisfactory in view of the low yields and the purity of products. Thus, to develop an alternative method for the reduction of Baylis–Hillman adducts with stereo-defined double bonds is still desirable.

As a powerful, versatile and ether-soluble one-electron transfer agent, SmI_2 has played an ever-increasing role in organic synthesis.[9] Among these methods, SmI_2 has proved to be a powerful tool to synthesize highly stereoselective alkenes and has been extensively developed.[10] Accordingly, we envision the possibility to synthesize stereo-defined alkenes from Baylis–Hillman adducts as direct elimination of hydroxy group promoted by SmI_2.[11] To the best of our knowledge, SmI_2-mediated reductive elimination process of Baylis–Hillman adducts has not been reported so far.

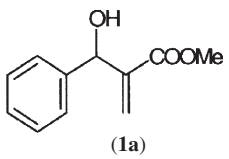
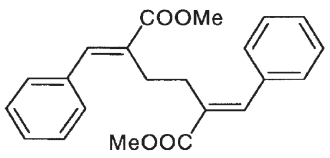
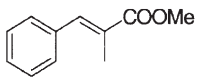
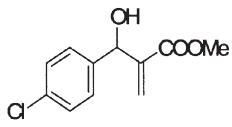
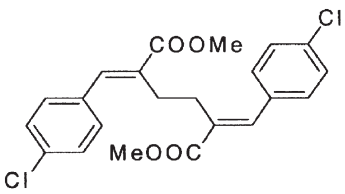
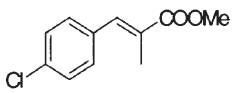
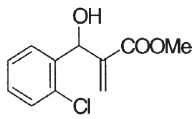
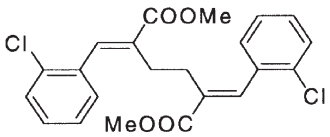
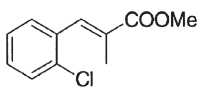
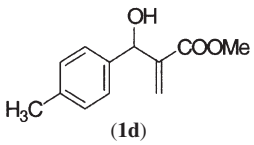
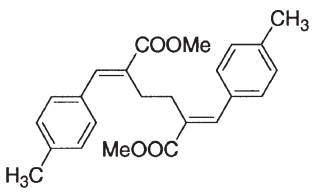
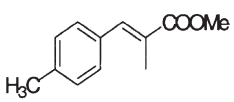
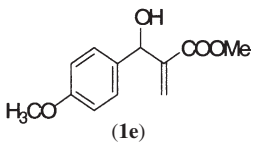
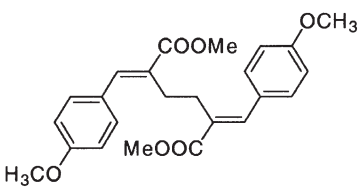
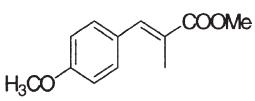
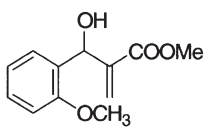
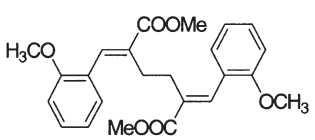
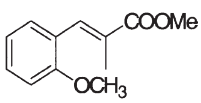
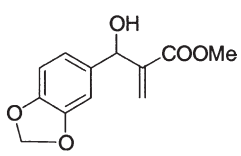
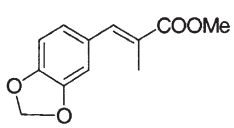
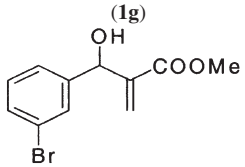
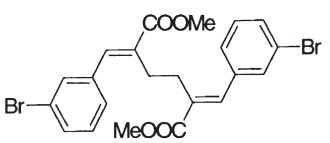
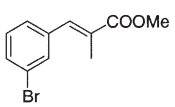
2. Results and discussion

Our first attempt was carried out by using Baylis–Hillman adducts **1d** as model substrate. When **1d** was treated with 2.2 equiv. SmI_2 in a solution of THF at room temperature, unprecedented result was observed (Table 1). Apart from the expected trisubstituted alkene **3d** with total stereoselectivity, to our surprise, we also obtained another white solid which was identified as substituted 1,5-hexadiene **2d** (Scheme 1). The *E*-configuration of **3d** was assigned on the basis of the chemical shift value of the olefinic proton in ^1H NMR spectra by comparison with reported ones.[8,12] The

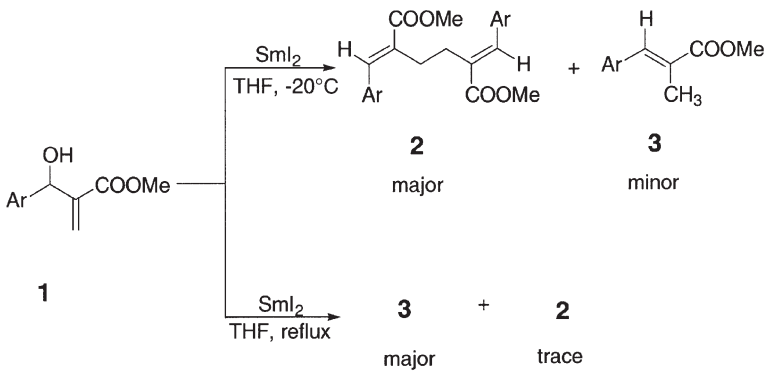
Keywords: Baylis–Hillman adducts; Reduction; Samarium diiodide; Elimination; Self-coupling; Trisubstituted alkene; 1,5-Hexadiene derivatives; (*E*)-stereoselectivity.
* Corresponding author; e-mail address: yminzhang@mail.hz.zj.cn

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.04.087

Table 1. SmI_2-mediated reductive elimination of Baylis–Hillman adducts[a]

Entry	Substrate **1**	Temp (°C)	Time (min)	Product **2** yield (%)[b]	Product **3** yield (%)[b]
1	 (**1a**)	−20	90		
				(**2a**) 82%	(**3a**) 17%
2		Reflux	5	(**2a**) 10%	(**3a**) 80%
3	 (**1b**)	−20	90		
				(**2b**) 92%	(**3b**) 7%
4		Reflux	5	(**2b**) 11%	(**3b**) 83%
5	 (**1c**)	−20	90		
				(**2c**) 50%	(**3c**) 43%
6		Reflux	8	—[c]	(**3c**) 92%
7	 (**1d**)	−20	90		
				(**2d**) 88%	(**3d**) 11%
8		25	20	(**2d**) 40%	(**3d**) 57%
9		Reflux	10	—[c]	(**3d**) 92%
10	 (**1e**)	−20	90		
				(**2e**) 90%	(**3e**) 8%
11		Reflux	10	—[c]	(**3e**) 94%
12	 (**1f**)	−20	90		
				(**2f**) 65%	(**3f**) 30%
13		Reflux	10	(**2f**) 50%	(**3f**) 47%
14	 (**1g**)	Reflux	5	—[c]	 (**3g**) 96%
15		−20	90		
				(**2h**) 40%	(**3h**) 50%
16	(**1h**)	Reflux	10	—[c]	(**3h**) 90%

[a] All reactions were carried out with 2.2 equiv. SmI_2 in a solution of THF.
[b] All new products were characterized by ^1H NMR, ^{13}C NMR, MS, IR and element analysis.
[c] In such case, product **2** was not isolated.



Scheme 1.

corresponding 1,5-diene **2d** was also obtained simultaneously with total *E*-stereoselectivity.[13]

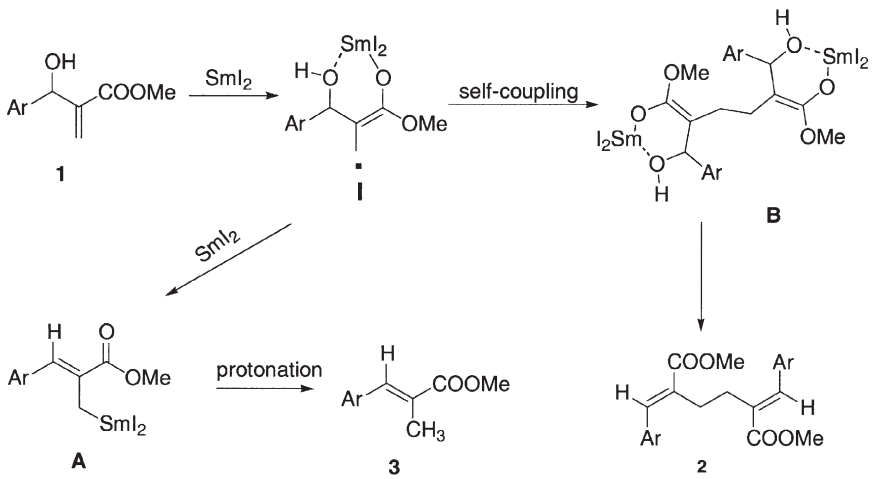
Accordingly, with a view to further investigate the reaction, the elimination processes with substrate **1d** were carried out under different temperatures and the representative results were listed in Table 1. When substrate **1d** was treated with a solution of SmI_2 at −20 °C, 1,5-diene **2d** was produced as major product in high yield (entry 7). Raising the reaction temperature resulted in the decreasing yield of **2d** and increasing yield of **3d**. Finally, when the reaction was conducted under reflux, product **3d** was afforded as the only product and no 1,5-diene **2d** was isolated (entry 9).

Encouraged by these experimental results, a variety of Baylis–Hillman adducts including electron-withdrawing and electron-donating substituents were tested in this reaction to establish the generality of the elimination reaction and the corresponding results were listed in Table 1.

In the cases of **3a**, **3b**, **3e** and **3f** comparison with the ^1H NMR values in the literature has also been carried out.[14] The following experimental features are particularly noteworthy: (1) The elimination provides a novel and efficient route to synthesize a new class of 1,5-hexadiene derivatives **2** which are difficult to synthesize by other methods. Generally speaking, 1,5-diene species are valuable synthetic intermediates and not readily available.[15] (2) In all cases, the desired trisubstituted alkenes **3** are obtained in good to excellent yield under reflux with total *E*-stereoselectivity. Nevertheless, in the case of **1f**, only 47% of **3f** is yielded even reaction proceeds under reflux (entry 13). This result is somewhat intriguing. (3) The present reaction is temperature controlled to a great extent, which is especially true when *para*-substituted substrates **1** are used. In a sense, lower temperature favors the generation of 1,5-dienes **2**, while higher temperature accelerates the conversion toward the trisubstituted alkenes **3**. By temperature changing we can obtain product **2** or **3** selectively. (4) When it comes to *ortho*- and *meta*- substituted substrates, the yields of 1,5-dienes **2** are relatively lower. We have also tried these substrates below −20 °C with prolonged reaction time, however, the yields of 1,5-dienes **2** are still unsatisfactory. This may be partly due to the steric hindrance during the radical coupling process.

The observed results and the *E*-stereochemistry in this reaction may be explained with a chelation-control model.[16] As shown in Scheme 2, chelation of the oxophilic Sm^{III} center with the oxygen atom of the hydroxyl group results in a six-membered ring intermediate **I**, which increases the capability of the hydroxyl group as a leaving group.

When this elimination reaction proceeded under higher temperature, the hydroxyl group was rapidly eliminated from intermediate **I** and then reacted with another mole of



Scheme 2.

SmI_2 to form **A**. Thus, protonation of **A** stereoselectively yielded product **3** with *E*-configuration. On the other hand, when this elimination reaction was conducted under lower temperature, the leaving of hydroxyl group from intermediate **I** became much slower. Under this condition, the chance of radical intermediate **I** for self-coupling was increasing. After elimination and protonation, the intermediate **B** gave product **2** with high *E*-stereoselectivity.

3. Conclusion

In conclusion, the SmI_2-mediated elimination reaction provides a unique and valuable route to synthesize a new class of 1,5-hexadiene derivatives **2** from easily accessible Baylis–Hillman adducts. Moreover, the methodology herein described also can serve as an efficient and alternative strategy to synthesize trisubstituted alkenes **3** in good to excellent yields. It is also worth mentioning that the reaction is highly *E*-stereoselective and temperature-dependent, which adds its attractiveness.

4. Experimental

4.1. General

Tetrahydrofuran was distilled from sodium-benzophenone immediately prior to use. All the reactions in this paper were performed under a nitrogen atmosphere. All ^{1}H NMR spectra were measured in $CDCl_3$ and recorded on Brucker AC-400 (400 MHz) spectrometer with TMS as the internal standard. ^{13}C NMR spectra were measured in $CDCl_3$ and recorded on Brucker AC-100 spectrometer with TMS as the internal standard. Chemical shifts (δ) are expressed in ppm and coupling constants *J* are given in Hz. IR spectra were taken as KBr discs or thin films with a Bruck vector 22 spectrometer. EIMS were measured with a HP5989B mass spectrometer. Melting points are uncorrected. Elemental analyses were performed on an EA-1110 instrument. Metallic samarium and all solvents were purchased from commercial sources and were used without further purification. The starting materials Baylis–Hillman adducts **1** were prepared according to the literature.[17]

4.2. General procedure for the preparation of 1,5-hexadiene (2a–2f, 2h)

A solution of Baylis–Hillman adduct (1 mmol) in dry THF (3 mL) was added to the solution of SmI_2 (2.2 mmol) in THF (20 mL) at −20 °C under a nitrogen atmosphere. After being stirred for about 90 min at −20 °C (Table 1), the deep blue color of the solution changed to yellow slowly. Then, the reaction mixture was quenched with 0.1 M hydrochloric acid (5 mL) and extracted with ether (3×20 mL). The organic phase was successively washed with brine (15 mL), water (20 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give the crude products, which were purified by preparative TLC using ethyl acetate and cyclohexane (1:7) as eluent.

4.2.1. 2,5-Dibenzylidene-hexanedioic acid dimethyl ester (2a). White solid, mp: 120–122 °C, ^{1}H NMR: δ 7.78 (2H, s), 7.51–7.33 (10H, m), 3.83 (6H, s), 2.86 (4H, s); ^{13}C NMR: δ 168.7, 140.3, 135.5, 132.0, 129.4, 128.5, 128.4, 52.0, 26.8; IR (KBr)/cm^{-1}: 1706, 1632, 1445; MS: *m*/*z* (%) 350 (M^+, 2.3), 175 (5.0), 115 (100); Anal. $C_{22}H_{22}O_4$. Calcd C, 75.41; H, 6.33. Found C, 75.23; H, 6.40%.

4.2.2. 2,5-Bis-(4-chloro-benzylidene)-hexanedioic acid dimethyl ester (2b). White solid, mp: 165–167 °C, ^{1}H NMR: δ 7.63 (2H, s), 7.41 (4H, d, *J*=8.0 Hz), 7.35 (4H, d, *J*=8.0 Hz), 3.78 (6H, s), 2.73 (4H, s); IR (KBr)/cm^{-1}: 1708, 1592, 1438; MS: *m*/*z* (%) 418 (M^+, 2.4), 209 (16), 149 (67), 115 (100); Anal. $C_{22}H_{20}Cl_2O_4$. Calcd C, 63.02; H, 4.81. Found C, 63.11; H, 4.72%.

4.2.3. 2,5-Bis-(2-chloro-benzylidene)-hexanedioic acid dimethyl ester (2c). White solid, mp: 143–144 °C, ^{1}H NMR: δ 7.72 (2H, s), 7.40–7.25 (8H, m), 3.67 (6H, s), 2.59 (4H, s); ^{13}C NMR: δ 167.9, 137.6, 134.2, 133.9, 133.7, 130.3, 129.5, 129.5, 126.6, 52.0, 26.9; IR (KBr)/cm^{-1}: 1702, 1588, 1435; MS: *m*/*z* (%) 418 (M^+, 1.7), 351 (59), 149 (63), 115 (100); Anal. $C_{22}H_{20}Cl_2O_4$. Calcd C, 63.02; H, 4.81. Found C, 62.91; H, 4.56%.

4.2.4. 2,5-Bis-(4-methyl-benzylidene)-hexanedioic acid dimethyl ester (2d). White solid, mp: 145–147 °C, ^{1}H NMR: δ 7.71 (2H, s), 7.41 (4H, d, *J*=8.0 Hz), 7.20 (4H, d, *J*=8.0 Hz), 3.81 (6H, s), 2.82 (4H, s), 2.38 (6H, s); ^{13}C NMR: δ 168.9, 140.3, 138.5, 132.6, 131.2, 129.6, 129.2, 51.9, 26.8, 21.3; IR (KBr)/cm^{-1}: 1703, 1608, 1435, 1066; MS: *m*/*z* (%) 378 (M^+, 2.3), 189 (20), 129 (100); Anal. $C_{24}H_{26}O_4$. Calcd C, 76.17; H, 6.92. Found C, 75.88; H, 7.00%.

4.2.5. 2,5-Bis-(4-methoxy-benzylidene)-hexanedioic acid dimethyl ester (2e). White solid, mp: 134–135 °C, ^{1}H NMR: δ 7.70 (2H, s), 7.53 (4H, d, *J*=8.0 Hz), 6.93 (4H, d, *J*=8.0 Hz), 3.85 (6H, s), 3.83 (6H, s), 2.84 (4H, s); ^{13}C NMR: δ 169.1, 159.9, 140.0, 131.5, 129.7, 127.9, 113.9, 55.3, 52.0, 26.8; IR (KBr)/cm^{-1}: 1700, 1602, 1510, 1439; MS: *m*/*z* (%) 410 (M^+, 2.1), 205 (69), 145 (100); Anal. $C_{24}H_{26}O_6$. Calcd C, 70.23; H, 6.38. Found C, 70.27; H, 6.15%.

4.2.6. 2,5-Bis-(2-methoxy-benzylidene)-hexanedioic acid dimethyl ester (2f). White solid, mp: 132–133 °C, ^{1}H NMR: δ 7.86 (2H, s), 7.42–7.31 (4H, m), 7.00–6.90 (4H, m), 3.85 (6H, s), 3.75 (6H, s), 2.73 (4H, s); ^{13}C NMR: δ 168.7, 157.5, 136.3, 132.1, 130.0, 129.9, 124.6, 120.3, 110.4, 55.5, 51.9, 27.2; IR (KBr)/cm^{-1}: 1712, 1626, 1598, 1461; MS: *m*/*z* (%) 410 (M^+, 2.5), 205 (17), 145 (100); Anal. $C_{24}H_{26}O_6$. Calcd C, 70.23; H, 6.38. Found C, 70.09; H, 6.61%.

4.2.7. 2,5-Bis-(3-bromo-benzylidene)-hexanedioic acid dimethyl ester (2h). White solid, mp: 163–165 °C, ^{1}H NMR: δ 7.61 (2H, s), 7.51–7.24 (8H, m), 3.76 (6H, s), 2.74 (4H, s); ^{13}C NMR: δ 168.2, 138.7, 137.5, 133.1, 132.0, 131.4, 130.0, 127.7, 122.5, 52.2, 26.5; IR (KBr)/cm^{-1}: 1707, 1560, 1432; MS: *m*/*z* (%) 506 (M^+, 1.2), 174 (56), 115 (100); Anal. $C_{22}H_{20}Br_2O_4$. Calcd C, 52.00; H, 3.97. Found C, 51.87; H, 4.00%.

4.3. General procedure for the preparation of trisubstituted alkenes (3a–3h)

A solution of Baylis–Hillman adduct (1 mmol) in dry THF (3 mL) was added to the solution of SmI_2 (2.2 mmol) in

THF (20 mL) at 65 °C under a nitrogen atmosphere. After being stirred for about 10 min at 65 °C (Table 1), the deep blue color of the solution changed to yellow rapidly. Then, the reaction mixture was quenched with 0.1 M hydrochloric acid (5 mL) and extracted with ether (3×20 mL). The organic phase was successively washed with brine (15 mL), water (20 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give the crude products, which were purified by preparative TLC using ethyl acetate and cyclohexane (1:7) as eluent.

4.3.1. 2-Methyl-3-phenyl-acrylic acid methyl ester (3a) (lit.[8]). Yellow oil, ^{1}H NMR: δ 7.77 (1H, s), 7.46–7.38 (5H, m), 3.89 (3H, s), 2.19 (3H, s); ^{13}C NMR: δ 169.2, 139.0, 135.9, 129.6, 128.4, 128.3, 128.3, 52.0, 14.0; IR (film)/cm^{-1}: 1709, 1606, 1512, 1435; MS: *m*/*z* (%) 176 (M^+, 48), 145 (31), 115 (100).

4.3.2. 3-(4-Chloro-phenyl)-2-methyl-acrylic acid methyl ester (3b) (lit.[8]). Yellow oil, ^{1}H NMR: δ 7.62 (1H, s), 7.36 (2H, d, *J*=8.0 Hz), 7.31 (2H, d, *J*=8.0 Hz), 3.82 (3H, s), 2.09 (3H, s); IR (film)/cm^{-1}: 1714, 1491, 1434; MS: *m*/*z* (%) 210 (M^+, 47), 150 (53), 115 (100).

4.3.3. 3-(2-Chloro-phenyl)-2-methyl-acrylic acid methyl ester (3c). Yellow oil, ^{1}H NMR: δ 7.78 (1H, s), 7.46–7.28 (4H, m), 3.86 (3H, s), 2.02 (3H, s); IR (film)/cm^{-1}: 1717, 1469, 1436; MS: *m*/*z* (%) 210 (M^+, 2.6), 175 (100), 115 (54); Anal. $C_{11}H_{11}ClO_2$. Calcd C, 62.72; H, 5.26. Found C, 62.85; H, 5.51%.

4.3.4. 2-Methyl-3-*p*-tolyl-acrylic acid methyl ester (3d). Yellow oil, ^{1}H NMR: δ 7.66 (1H, s), 7.30 (2H, d, *J*=8.0 Hz), 7.19 (2H, d, *J*=8.0 Hz), 3.80 (3H, s), 2.36 (3H, s), 2.11 (3H, s); IR (film)/cm^{-1}: 1711, 1632, 1435; MS: *m*/*z* (%) 190 (M^+, 100), 159 (48), 115 (57); Anal. $C_{12}H_{14}O_2$. Calcd C, 75.76; H, 7.42. Found C, 75.89; H, 7.31%.

4.3.5. 3-(4-Methoxy-phenyl)-2-methyl-acrylic acid methyl ester (3e) (lit.[8]). Yellow oil, ^{1}H NMR: δ 7.65 (1H, s), 7.38 (2H, d, *J*=8.0 Hz), 6.92 (2H, d, *J*=8.0 Hz), 3.82 (3H, s), 3.80 (3H, s), 2.14 (3H, s); ^{13}C NMR: δ 169.4, 159.7, 138.7, 131.5, 128.4, 126.0, 113.8, 55.3, 52.0, 14.1; IR (film)/cm^{-1}: 1709, 1606, 1512, 1435; MS: *m*/*z* (%) 206 (M^+, 100), 146 (89), 103 (57).

4.3.6. 3-(2-Methoxy-phenyl)-2-methyl-acrylic acid methyl ester (3f) (lit.[8]). Yellow oil, ^{1}H NMR: δ 7.84 (1H, s), 7.34–6.90 (4H, m), 3.86 (3H, s), 3.81 (3H, s), 2.06 (3H, s); IR (film)/cm^{-1}: 1711, 1598, 1436; MS: *m*/*z* (%) 206 (M^+, 53), 175 (100), 131 (92), 115 (23).

4.3.7. 3-Benzo[1,3]dioxol-5-yl-2-methyl-acrylic acid methyl ester (3g). White solid, mp: 75–76 °C, ^{1}H NMR: δ 7.59 (1H, s), 6.93–6.82 (3H, m), 5.99 (2H, s), 3.80 (3H, s), 2.11 (3H, s); ^{13}C NMR: δ 169.3, 147.7, 147.6, 138.7, 129.9, 126.6, 124.7, 109.6, 108.4, 101.3, 52.1, 14.2; IR (KBr)/cm^{-1}: 1691, 1600, 1501, 1449; MS: *m*/*z* (%) 220 (M^+, 99), 160 (100), 131 (40), 103 (30); Anal. $C_{12}H_{12}O_4$. Calcd C, 65.45; H, 5.49. Found C, 65.32; H, 5.70%.

4.3.8. 3-(3-Bromo-phenyl)-2-methyl-acrylic acid methyl ester (3h). Yellow oil, ^{1}H NMR: δ 7.60 (1H, s), 7.52–7.28 (4H, m), 3.82 (3H, s), 2.10 (3H, s); IR (film)/cm^{-1}: 1715, 1469, 1435; MS: *m*/*z* (%) 254 (M^+, 22), 196 (31), 115 (100); Anal. $C_{11}H_{11}BrO_2$. Calcd C, 51.79; H, 4.35. Found C, 52.01; H, 4.47%.

Acknowledgements

We are grateful to the National Natural Science Foundation of China (Project No. 20072033) and Specialized Research Fund for the Doctoral Program of Higher Education of China.

References and notes

1. (a) Marfat, A.; McGuirk, P. R.; Helquist, P. *J. Org. Chem.* **1979**, *44*, 3888–3901. (b) Anderson, R. J.; Coleman, J. E.; Piers, E.; Wallace, D. J. *Tetrahedron Lett.* **1997**, *38*, 317–320. (c) Tanaka, H.; Kuroda, A.; Marusawa, H.; Hatanaka, H.; Kino, T.; Goto, T.; Hashimoto, M. *J. Am. Chem. Soc.* **1987**, *109*, 5031–5033. (d) Ishibashi, Y.; Ohba, S.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1996**, *37*, 2997–3000.
2. Senokuchi, K.; Nakai, H.; Nakayama, Y.; Odagaki, Y.; Sakaki, K.; Kato, M.; Maruyama, T.; Miyazaki, T.; Ito, H.; Kamiyasu, K.; Kim, S.; Kawamura, M.; Hamanaka, N. *J. Med. Chem.* **1995**, *38*, 2521–2523.
3. Watanabe, T.; Hayashi, K.; Yoshimatsu, S.; Sakai, K.; Takeyama, S.; Takashima, K. *J. Med. Chem.* **1980**, *23*, 50–59.
4. (a) Denmark, S. E.; Amburgey, J. *J. Am. Chem. Soc.* **1993**, *115*, 10386–10387. (b) Kocienski, P.; Dixon, N. J.; Wadman, S. *Tetrahedron Lett.* **1988**, *29*, 2353–2356. (c) Myers, A. G.; Kukkola, P. J. *J. Am. Chem. Soc.* **1990**, *112*, 8208–8210. (d) Creton, I.; Marek, I.; Brasseur, D.; Jestin, J.-L.; Normant, J.-F. *Tetrahedron Lett.* **1994**, *35*, 6873–6876.
5. For reviews, see: (a) Ciganek, E. *Org. React.* **1997**, *51*, 201–350. (b) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001–8062. (c) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811–892.
6. For examples: (a) Kim, J. N.; Lee, H. J.; Lee, K. Y.; Gong, J. H. *Synlett* **2002**, 173–175. (b) Patra, A.; Roy, A. K.; Batra, S.; Bhaduri, A. P. *Synlett* **2003**, 1819–1822. (c) Kabalka, G. W.; Venkataiah, B.; Dong, G. *Org. Lett.* **2003**, *5*, 3803–3805. (d) Kabalka, G. W.; Venkataiah, B.; Dong, G. *Tetrahedron Lett.* **2003**, *44*, 4673–4675. (e) Chung, Y. M.; Gong, J. H.; Kim, T. H.; Kim, J. N. *Tetrahedron Lett.* **2001**, *42*, 9023–9026.
7. (a) Basavaiah, D.; Sarma, P. K. S. *J. Chem. Soc., Chem. Commun.* **1992**, 955–957. (b) Hoffmann, H. M. R.; Rabe, J. *J. Org. Chem.* **1985**, *50*, 3849–3859. (c) Pachamuthu, K.; Vankar, Y. D. *Tetrahedron Lett.* **1998**, *39*, 5439–5442. (d) Basavaiah, D.; Krishnamacharyulu, M.; Hyma, R. S.; Sarma, P. K. S.; Kumaragurubaran, N. *J. Org. Chem.* **1999**, *64*, 1197–1200.
8. Shadakshari, U.; Nayak, S. K. *Tetrahedron* **2001**, *57*, 4599–4602.
9. For reviews and representative examples, see: (a) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693–2698. (b) Krief, A.; Laval, A. M. *Chem. Rev.* **1999**, *99*, 745–777. (c) Molander, G. A. *Acc. Chem. Res.* **1998**, *31*, 603–609. (d) Molander, G. A.; Harris, C. R. *Tetrahedron* **1998**, *54*, 3321–3354. (e) Molander, G. A.; Harris, C. R.

Chem. Rev. **1996**, *96*, 307–338. (f) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29–68.

10. Selected references: (a) Concellón, J. M.; Bernad, P. J.; Pére-Andrés, J. A. *Angew. Chem., Int. Ed.* **1999**, *38*, 2384–2386. (b) Concellón, J. M.; Bernad, P. J.; Pére-Andrés, J. A.; Rodríguez-Solla, H. *Angew. Chem., Int. Ed.* **2000**, *39*, 2773–2775. (c) Concellón, J. M.; Bardales, E. *Org. Lett.* **2002**, *4*, 189–191. (d) Concellón, J. M.; Bernad, P. J.; Bardales, E. *Org. Lett.* **2001**, *3*, 937–939.
11. (a) Concellón, J. M.; Huerta, M. *Tetrahedron Lett.* **2003**, *44*, 1931–1934. (b) Li, J.; Xu, X. L.; Zhang, Y. M. *Tetrahedron Lett.* **2003**, *44*, 9349–9351.
12. According to literature, the chemical shift value of the olefinic proton in ^{1}H NMR appears obviously downfield to the aromatic ring proton, while the corresponding olefinic proton of Z-isomer often mixes with aromatic ring proton or appears upfield.[8] Furthermore, ^{1}H NMR and ^{13}C NMR spectral analyses indicate the absence of any (Z)-isomer.
13. The symmetrical structure of **2d** can be easily recognized from ^{1}H NMR and ^{13}C NMR. Furthurmore, the chemical shift value of olefinic proton in ^{1}H NMR and the allylic methylene carbon in ^{13}C NMR are quite in analog with **3d**. The *E*-stereochemistry of **2d** can be easily explained according to the following mechanism proposed (Scheme 2).
14. The chemical shift values in ^{1}H NMR spectra are in accordiance with reported ones.[8] The *E*-configuration of **3b** was also further assigned by a 2D NOESY experiment.
15. (a) Dumond, Y.; Negishi, E.-I. *J. Am. Chem. Soc.* **1999**, *121*, 11223–11224. (b) McMurry, J. E.; Silvsstri, M. *J. Org. Chem.* **1975**, *40*, 2687–2688.
16. Similar six-membered ring models have been proposed to explain the stereoselectivity in other reactions of SmI_2: (a) Concellón, J. M.; Bernad, P. J.; Pére-Andrés, J. A.; Rodríguez-Solla, H. *Angew. Chem., Int. Ed.* **2000**, *39*, 2773–2775. (b) Concellón, J. M.; Bernad, P. J.; Bardales, E. *Org. Lett.* **2001**, *3*, 937–939.
17. All Baylis–Hillman adducts are prepared from aromatic aldehydes and methyl acrylate according to literature: Hoffman, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed.* **1983**, *22*, 795–796.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 5799–5806
Tetrahedron

Fluorescent PET chemosensors for lithium

Thorfinnur Gunnlaugsson,* Bastien Bichell and Claire Nolan

Department of Chemistry, Trinity College Dublin, Dublin 2, Ireland

Received 16 January 2004; revised 5 April 2004; accepted 29 April 2004

Abstract—The synthesis of the chiral diaza-9-crown-3 derivatives **1** (*S*,*S*) and **2** (*R*,*R*) is described. These sensors were designed as luminescent chemosensors for lithium where the fluorescence emission from the naphthalene moieties was 'switched on' upon Li^+ recognition by the crown ether moiety in organic solvents, showing excellent selectivity over other group I and group II cations. Even though the recognition of Li^+ was not achieved in water (pH 7.4) or aqueous alcohol solution, the fluorescence (which was switched on at pH 7.4) was substantially modulated by spherical anions, where the fluorescence emission was quenched in the presence of Br^- and I^- but less by Cl^- and not by acetate. This indicates that the emission was quenched by heavy-atom affect. The recognition of Li^+ was also investigated by ^1H NMR in CD_3CN and by observing the changes in the circular dicromism spectra. For the former, the resonances for the crown ether moiety and α-methyl protons adjacent to the ring were sifted upfield and broadened, whereas for **1** the intensity of the CD signal for the π–π transition was substantially modulated upon Li^+ recognition.

1. Introduction

The design and synthesis of chemosensors for ions and neutral molecules has been an area of immeasurable study in recent years.[1] Chemical sensors have non-invasive and non-destructive properties, which has made them an important diagnostic tool in medicine and industry.[2] Many are based on the use of the 'fluorophore–spacer–receptor' model, where the fluorescence emission at the fluorophore site is modulated by ion or molecular recognition at the receptor site, which usually results in the suppression of photo-induced electron transfer (PET) quenching, operating between the two moieties.[3] Although PET sensors have been developed for a wide range of analytes such as neutral molecule, zwitterions, cations, Na^+, K^+, Ca^{2+}, Mg^{2+}, Cd^{2+} and Zn^{2+} anions such as acetates, halides, phosphates and biologically active bis-carboxylates and pyrophosphate,[5] then to the best of our knowledge, no Li^+ selective PET sensors have been reported in the literature prior to our investigation.[6,7] Li^+ is unusual as it is one of the smallest and lightest solid elements and has important clinical, pharmacological and biochemical properties.[8] Its beauty lies in its simplicity, activating brain cells to regulate abnormal mood cycles for the treatment of mentally ill patients, such as manic-depressives.[8,9] New uses of Li^+ include the treatment of skin diseases (such as dermatitis) and autoimmune and immunological diseases. It is usually administered orally as Li_2CO_3, at a total dose up to 30 mmol (approximately 2 g) per day for the treatment of mental illness. The therapeutic index for Li^+ is narrow and should lie between 0.4 and 0.8 mM in serum, 12 h after the dose has been administered. If the serum concentration is too high (around 1.5 mM), shaking, dizziness, drowsiness, vomiting and diarrhoea are experienced by the patient. These syndromes indicate serious toxicity effects and are usually seen 4 h after the drug has been administered. Long-term side effects include dermatological disorders, weight gain and some problems with kidney and thyroid functions.[8] In medicine, Li^+ determination in blood samples was traditionally carried out using atomic absorption spectroscopy and flame emission spectroscopy. The impracticalities of measuring serum samples on site using these methods led to the development of ion-selective electrodes, and ionophores which are more practical.[10–12] They work by measuring the activity in Li^+ solutions and are active within the clinical range (0.4–0.8 mM serum). This technique provides immediate feedback without long delays, high operation, instrumentation costs and bulkiness of instruments. Determination of Li^+ levels in serum must also be monitored in the presence of 140 mM sodium, 4.3 mM potassium and 1.26 mM calcium. Furthermore, Li^+ is important from a synthetic as well as an industrial point of view because of its use in batteries, but currently there is real momentum away from cadmium-based batteries towards the use of lithium in mobile phones. Lithium is thus also a potential environmental hazard in the future.

We have developed both fluorescent and lanthanide luminescent devices as luminescent switches,[13] sensors[14] and logic gate mimics.[15] We have focused our efforts particularly on the development of chemosensors for

Keywords: Fluorescent sensors; Chemosensors; Lithium; Photoinduced electron transfer; Supramolecular chemistry.
* Corresponding author. Tel.: +353-1-608-3459; fax: +353-1-671-2826; e-mail address: gunnlaut@tcd.ie

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.04.082

biologically relevant targets such as ions, small molecules and nucleic acids.[16] Here we describe our efforts towards developing novel PET sensors for Li^+.[6] We demonstrate that by using structurally simple motifs, whereby a small crown ether and two amide moieties are combined in a receptor, highly selective Li^+ chemosensing can be achieved in organic solvents such as CH_3CN. Although we were unable to achieve such sensing in an aqueous environment, this work achieved the objectives outlined, i.e. the selective sensing of Li^+ by employing PET chemosensing.

2. Results and discussion

2.1. Synthesis

The lithium-selective PET sensors **1** and **2** were designed using the PET principle by combining a small crown ether moiety with two naphthalene fluorophores, giving rise to a 'fluorophore–spacer–receptor–spacer–fluorophore'[3–7] model as developed by de Silva (Fig. 1). With the aim of maximizing the Li^+ selectivity over other competitive cations, the rather small diaza-9-crown-3 (1-oxo-4,7-diazacyclononane)[17] crown ether was chosen, which was functionalized with two amide pendent arms which could participate directly in the coordination of the ion. Such modifications have previously been demonstrated for competitive Li^+ recognition and transport across a liquid membrane.[18] We proposed that this design would ensure that Li^+ would not be complexed directly within the macrocycle cavity, but just below it, where Li^+ recognition would be assisted by the amide arms, i.e. by direct coordination to the oxygens of the carboxyamides. This would ensure enhanced Li^+ selectivity over Na^+. To achieve this additional chelating effect we selected the chiral amides **3** and **4**, synthesized from the chiral *S*- and *R*-1-(naphthyl)ethylamine, respectively.

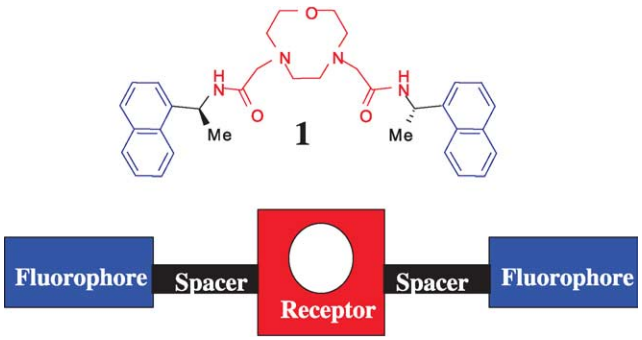


Figure 1. Diagram illustrating the 'fluorophore–spacer–receptor–spacer–fluorophore' model and the corresponding structure of **1**.

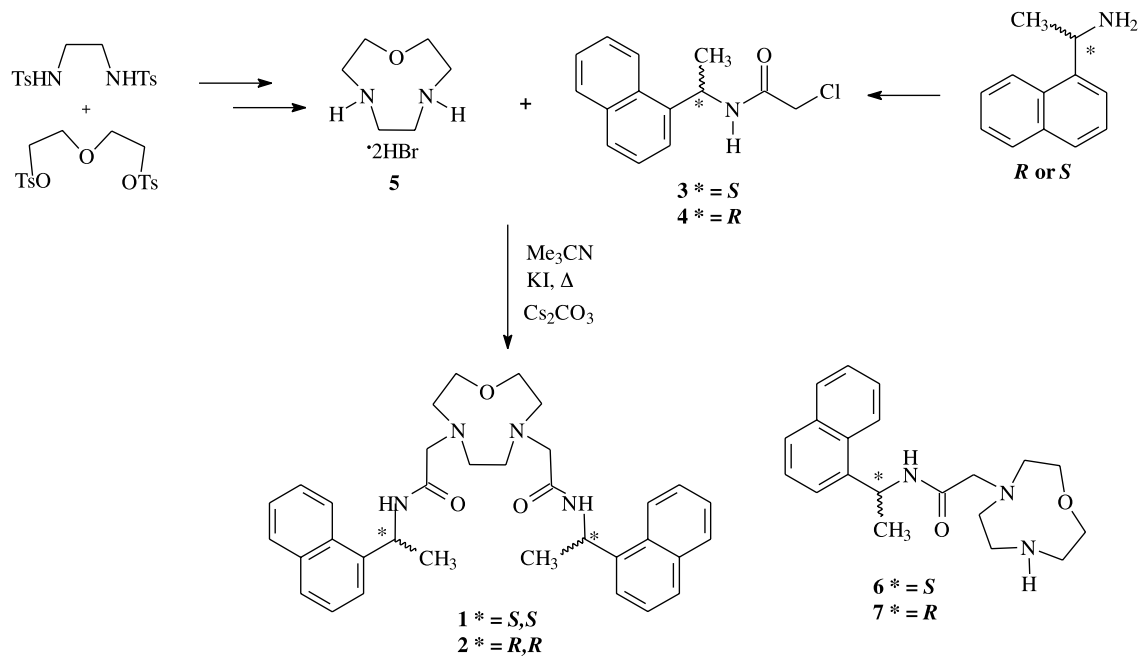
The synthesis of **1** and **2** is shown in Scheme 1.[†] The synthesis of both was achieved in two sequences. The first sequence was the synthesis of the diaza-9-crown-3-ether receptor **5**, which is a known compound, using conventional Williamson ether synthesis, from *N*,*N*-ditosyl diaminoethane and diethylene glycol ditosylate, which gave the *N*,*N*′-ditosyl-1,4-diaza-9-crown ether. This product was detosylated by refluxing in 48% HBr–AcOH solution for four days, yielding the HBr salts **5** in 87% yield. The α-chloroamide arms **3** and **4** were made in a single step by peptide coupling of chloroacetic acid with either *S*- or *R*-1-[1-naphtyl]ethylamine using EDCI and HOBt as reactants, giving approximately 87% yield for each. This compound and other related chiral derivatives have previously been reported by Parker et al. using a different synthesis.[19] The final step in the above synthesis involved the coupling of either **3** or **4** to the crown ether **5** in MeCN at 80 °C, giving **1** and **2**, initially in good yields of ca. 70% as a crude material, but in 33 and 30% yield respectively, after final workup. An increase in the reaction times did not improve the original yields nor prevent the one-armed systems **6** and **7** being formed in a small amount, ca. 10% (as crude material). No advantages were achieved by refluxing the reaction in DMF, in fact this resulted in lower yields of (~45%) with increased yield of the one-armed side product **6**. Both the *R*,*R*- and *S*,*S*- sensors had to be purified via alumina chromatography using DCM and 0⟶1% MeOH as an eluent. When flash silica chromatography was used the sensor became protonated. Consequently, it was necessary to treat the resulting fractions with 1 M NaOH to yield the free sensor. The final products were isolated as semi solids, and titurated from ether to give both products as powders. Both sensors were fully characterized by, ^1H and ^{13}C NMR, ES-MS, IR and CHN or accurate mass analysis using HRMS.

The ^1H NMR spectrum of either the *S*,*S*-isomer **1** or the *R*,*R*-isomer of **2** showed that the axial and equatorial positions of the aza-crown ring were not magnetically equivalent, with several multiplets occurring around 2.3 and 3.6 ppm. The diagnostic peak is a multiplet at 5.38 ppm representing the chiral CH group of the spacer. It was expected that this resonance would be a quartet, so its appearance as a multiplet suggests that the environments around this proton are non-equivalent. The electro-spray mass spectrum of **1** and **2** showed a single peak at 552.5 *m*/*z* for the molecular ion.

2.2. Ground and excited state evaluation of 1 and 2

The photophysical properties of **1** and **2** were evaluated in water, MeOH, in 50:50 MeOH/CH_3CN mixture and in CH_3CN solutions in the presence of several metal cations from groups IA and IIA. In water, using 160 mM NaCl to maintain constant ionic strength, the pK_a of both sensors was determined by observing the changes in the fluorescence emission spectrum at λ_F 337 nm, when excited at 280 nm. However, the changes in the absorption spectrum, which displayed typical naphthalene absorption bands with fine structure at 271, 281 and 293 nm, over the same pH range were only minor and not significant enough for accurate binding constant determination. This is due to the covalent spacers that separate the two naphthalene fluorophores from the crown ether receptor and thus minimize any π–n orbital interactions between the two moieties. In alkaline solution the fluorescence of the naphthalene unit of **1** was almost fully 'switched off', signifying the quenching

[†] In our earlier communication (Ref. 6), the naphthalene part of **1**, was shown to be connected through position two on the aromatic ring. However, the description of the synthesis in the text was correct. We apologize for this mistake.



Scheme 1. Synthesis of chemosensors **1** and **2** from the α-chloroamides **3**, **4** and the diaza-9-crown-3 (1-oxo-4,7-diazacyclononane) crown ether **5**. The mono products **6** and **7** were also observed in about 84–10% yields.

of the naphthalene excited state by efficient electron transfer from the amino moieties of the crown ether receptor to the naphthalene-excited state. This is typical PET quenching, as on protonation of the amino moiety, the oxidation potential of the receptor was increased, removing the thermodynamic pathway for the excited state quenching.[1,4] The corresponding changes in the fluorescence emission of **1** at 337 nm as a function of pH are shown in Figure 2. As the spacer between the amino moiety and the naphthalene moiety is made of four carbon bond lengths, which is significantly

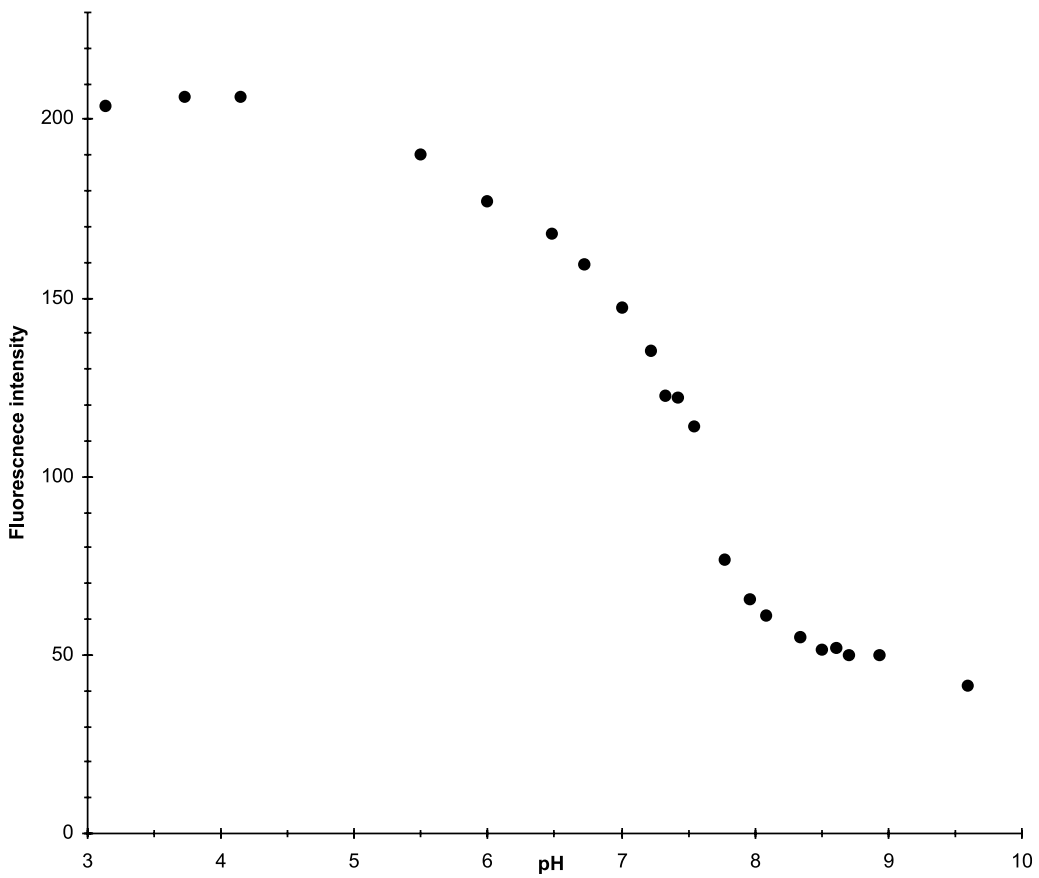


Figure 2. The changes in the fluorescence emission spectra of **1** at 337 nm upon pH titration in water. Excitation at 280 nm.

larger then the classical one or two carbon spacers usually used for PET sensors,[1,4] the efficiency of the quenching process is not ideal as the PET is distance dependent (function of $1/r^6$). Hence the emission is not fully switched off in alkaline solution. However, upon protonation of the amino receptor the emission was 'switched on' with a large order of magnitude enhancement in fluorescence, without any other substantial spectral shifts. This process was fully reversible, as upon addition of base to **1** in acidic solution, the emission was switched off. The changes in Figure 2 occur over ca. two pH units indicating that the protonation is due to 1:1 binding and a simple equilibrium.[4] We were unable to determine the second protonation of the amino crown ether, which suggests that it is either extremely low, due to repulsive effects by the first protonation, or that the small crown ether is operating like a pseudo proton sponge, where the proton is shared between the two amino moieties. It could also be the case that the second protonation simply does not affect the fluorescent properties of the molecule. We were however, unable to prove this explanation. From the above change, a pK_a of 7.2±0.1 was determined (Fig. 1). Similarly, upon carrying out a pH titration of **2**, the same pK_a value of 7.2 was determined. From these changes it is clear that pK_a's are too high for determination of Li^+ in water at pH 7.4, as the partial protonation of the amino crown ether would prevent the Li^+ sensing due to charge repulsion. This was indeed found to be the case as upon titration of **1** or **2** at this pH using LiCl, NaCl, KCl and $CaCl_2$ salts. The emission of these two sensors was not enhanced, which would have signified the suppression of the PET process. However, substantial quenching was observed. This indicated that the PET mechanism was not active, or at least not observed, due to other active quenching mechanisms. To investigate this further we carried out a series of titrations at pH 7.4 and 8.5, where the receptor would be expected to be in its 'not fully protonated' or 'free-form' respectively, using a range of lithium salts.

The changes in the fluorescence emission for LiBr, LiI and LiOAc are shown in Figure 3, for the changes in **1** at pH 7.4 (0.1 M buffer and 0.1 M ionic strength). No major changes were observed when LiOAc, NaOAc or KOAc were used. However, when using the above LiCl, LiBr or LiI solutions, substantial quenching was observed. As acetate did not give rise to any significant quenching, we propose that the quenching by Cl^-, Br^- and I^- was most likely due to a heavy-atom effect by these halide counter ion, since it was largely noticeable for spherical anions, in the concentration range of 04–2.5 mM. This is strengthened by the fact that other anions, such as perchlorate ClO_4- or sulfate, did not give rise to such quenching. To investigate this further we also carried out anion titrations using the α-chloronaphthalene ligand **4**. They strongly suggested that the anion was quenching fluorescence due to the heavy atom effect even in the absence of the crown ether, suggesting that the anion was not binding to the receptor. However, these changes were somewhat smaller than those seen for **1**, suggesting that some cooperative effect by the crown ether moiety. When the fluorescence emission was evaluated at pH 8.5, using the acetate salt of Li^+, Na^+ and K^+, no fluorescence enhancement were observed, signifying that the receptor was unable to extract the Li^+ from the highly solvated aqueous environment. Because of this, the Li^+ recognition was evaluated in less polar protic and aprotic solvents.

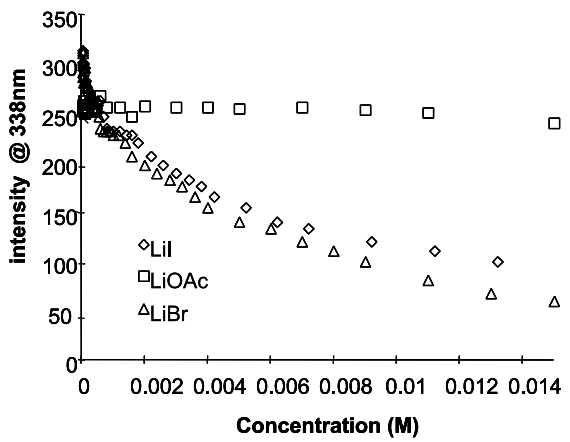


Figure 3. The changes in the fluorescence emission spectra of **1** at 338 nm in pH 7.4 titration in water.

The recognition of Li^+ using **1** was evaluated in MeOH, MeCN and in a mixture of both. In MeOH there were minor changes in fluorescence when titrated with Li^+ acetate. Again, no significant changes were seen in 50:50 MeCN/MeOH solution. However, in 80:20 MeCN/MeOH a slight increase in fluorescence was observed but this was insignificant, giving mere 0.8-fold enhancement in fluorescence. The above titrations were repeated in 100% MeCN using both lithium acetate and lithium perchlorate salts. Unlike previously observed, the fluorescent emission was greatly enhanced upon titration with Li^+, leading to a 9-fold increase in fluorescent intensity, as shown in Figure 4. The fluorescence quantum yield, Φ_F at high Li^+ concentration was measured to be 0.11, whereas in the absences of Li^+ it was 0.022. This is an order of magnitude fluorescent enhancement upon ion recognition, which is quite significant given the fact that the crown ether receptor (i.e. the electron donor) is separated form the naphthalene fluorophore by a four-carbon spacer. This would be expected to reduce the efficiency of the PET quenching, which is highly distance dependent, as previously discussed. Moreover, no significant spectral changes were observed in the fluorescence spectra when titrated with any other group I and II cations, as is evident from Figure 5, which shows the changes in the fluorescence emission of **1** at 337 nm as the function of the concentration of these ions. From Figures 4 and 5, it is clear that the fluorescence emission of **2** is highly dependent on the Li^+ concentration, which upon recognition by the receptor increases the oxidation potential of the receptor in a similar manner to that observed for the pH titration earlier. Furthermore, no other significant spectral changes were seen in the emission spectra (Fig. 4), e.g. no changes were seen in the λ_{max}, and no excimer emission was observed at longer wavelength. One can thus conclude that **1** is behaving like an ideal PET sensor.[1,4]

From the changes in the 337 nm wavelength we were able to determine the binding constant log β as 5.4 (±01) for **1** using the equation:

$$\log \beta = \log[(I_{max} - I)/(I - I_{min})] - \log[Li^+]$$

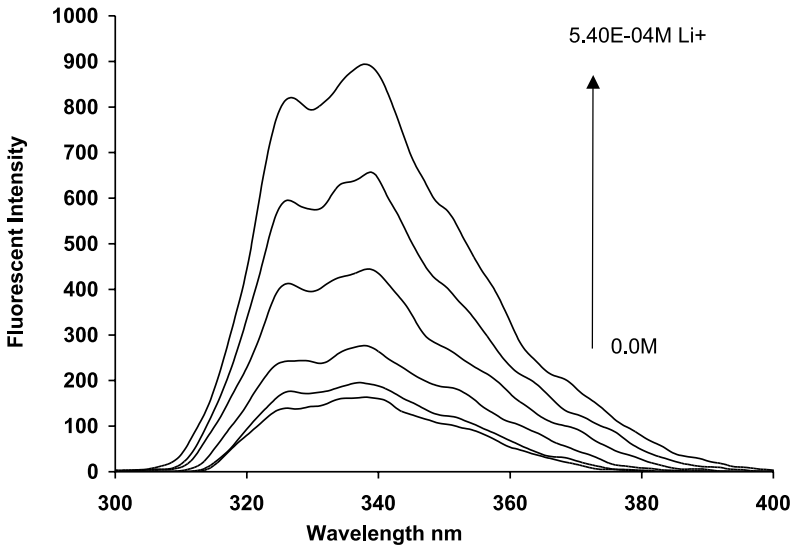


Figure 4. The changes in the fluorescence emission spectra of **1** upon titration with Li^+ in CH_3CN. Excitation at 280 nm.

where I is the fluorescent intensity at 337 nm, I_{max} is the maximum intensity observed at 337 nm and I_{min} is the minimum intensity observed at 337 nm. As can be seen from Figure 5, the selectivity of **1** towards Li^+ is very good, as only at very high concentration of other competitive group I and group II ions is the emission modulated. It is thus clear that **1** is highly selective and sensitive to Li^+ recognition in a non-aqueous environment. To the best of our knowledge, this is the first example of such a highly selective and sensitive PET sensor for Li^+. When these titrations were repeated for **2**, similar results were observed, as can be seen in Figure 6. Again, the fluorescence emission spectra were switched on, with no other major spectral changes. The quantum yield for the free sensor **2**, and with Li^+ was determined to be 0.11 and 0.22, respectively, mirroring that of **1** earlier. Furthermore, these changes occurred over two logarithmic units, indicating that the recognition was due to 1:1 binding and a simple equilibrium.

We also investigated the changes in the ^1H NMR of **1** upon titration with Li^+ in CD_3CN. We foresaw that the largest changes would be expected to occur for the resonances of the crown ether moiety and the α-position of the pendent arm. Indeed this was found to be the case, as upon titration of **1** with Li^+, the largest changes were encountered for the ring protons, causing minor upfield shift and broadening of these resonances. It was also noticeable that the aromatic resonances became broadened, which might suggest some minor interactions between the two naphthalene moieties upon Li^+ recognition or perhaps some contribution from cation−π type interactions.

To investigate the Li^+ recognition further we observed the changes in the circlar dicromism (CD) spectrum as a function of Li^+ concentration. Since the two pendent arms are chiral they could cause an enhancement in the CD spectra, where Li^+ recognition gives rise to significant changes in the CD intensity. We investigated these features

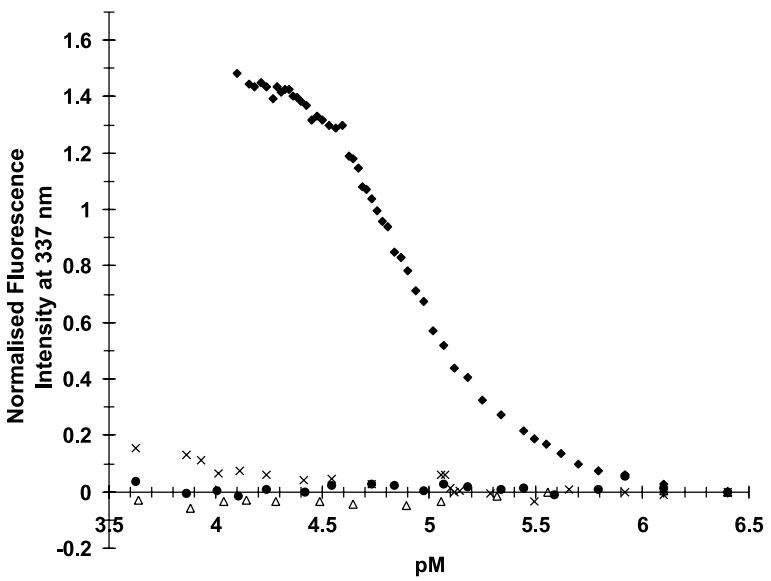


Figure 5. Titration profiles for **1** using perchlorate salts in CH_3CN. ◆=Li^+, ×=Ca^{2+}, ●=K^+, △=Na^+. Excitation at 280 nm.

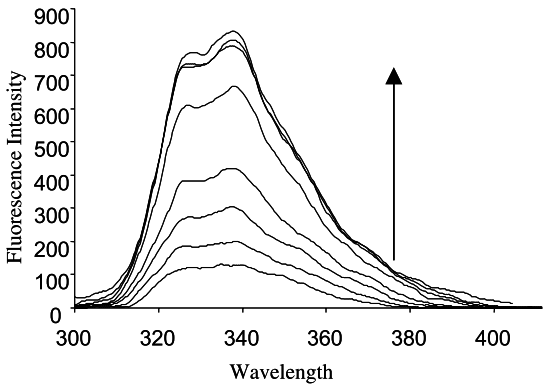


Figure 6. The changes in the fluorescence emission spectra of **2** (being switched on) upon titration with Li^+ in CH_3CN. Excitation at 280 nm.

for both **1** and **2**. The CD analysis of **1** and **2**, gave opposite spectra, where **1** had a negative absorption band and **2**, positive absorption for the $\pi \rightarrow \pi^*$ transition. The results for **1** are shown in Figure 7. Here it can be seen that **1** gave rise to three transitions in the CD spectra, centered at 230, 250 and 280 nm, respectively. Of these the 225 nm and the 280 nm transitions were substantially affected by the Li^+ recognition. Hence, the long 280 nm transition doubled in intensity and the short wavelength transition reduced in intensity by half. These changes were not investigated any further, but they do strongly suggest that upon Li^+ sensing, which is clearly observed by the fluorescence enhancements discussed above, conformational changes occur in **1**. Similar, but not identical changes were observed for **2**, where enhancements were seen in the 280 nm absorption band, indicating that the Li^+ complexation might be give rise to slightly different conformation within the molecule. Even though we are unable to support this further, then these results indicate that the amide functions are participating in the Li^+ coordination. We deduce this from the fact that the two chromophores in **1** are separated at a relatively long distance from the crown ether moiety to be actively affected if the ion was only coordinating to the nitrogens and the oxygens of the ring. Consequently, if the lithium ion was coordinating to the two oxygen of the carboxylic amides such a conformational effect would more likely to be observed strongly by the chromophores. However, we were unable to support this theory by X-crystallographic evidence, as various attempts to obtain crystals of **1** or **2** suitable for X-ray diffraction, or their corresponding Li^+ complexes failed.

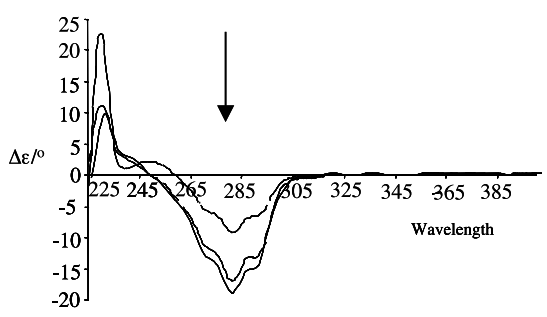


Figure 7. The changes in the CD spectrum of **1** upon titration with 0, 1 and 5 equiv. of Li^+ in CD_3CN.

3. Conclusion

In summary, we have synthesized two amide based crown ether ligands **1** and **2** for the detection of Li^+. Both were synthesized in two step synthesis form the corresponding *S* or *R* 1-(-1-naphtyl)ethylamine, and the 1,4-diaza-9-crown-3-ether that was made in short step synthesis. The ^1H NMR of the resulting sensors showed that the axial and the equatorial crown ether protons were magnetically inequivalent. The ability of these two sensors to detect Li^+ was investigated in various solutions. In water, the pK_a of 7.2 was determined for both from the changes in the fluorescence emission changes upon pH titration. Unfortunately, we were unable to show Li^+ detection in aqueous solution. However, in CH_3CN the fluorescence emissions were significantly modulated upon Li^+ recognition, where the emission was switched on with almost an order of magnitude enhancement in the fluorescence. In aqueous solutions, the emission was quenched, most likely due to vibrational heavy atom affect quenching by spherical anions such as Cl^-, Br^- and I^-. However, this quenching was only very minor using acetate or perchloride salts. The recognition was also evident from the ^1H NMR and the CD spectra which indicated that ion recognition was most likely involving the crown ether nitrogen and the oxygen moieties as well as the two oxygens of the carboxylic amides. We are currently initiating a research programme into the developments of PET sensors for Li^+ for use in aqueous solution.

4. Experimental

4.1. General

Starting materials were obtained from Sigma Aldrich, Strem Chemicals and Fluka. Solvents were used at GPR grade unless otherwise stated. Infrared spectra were recorded on a Mattson Genesis II FTIR spectrophotometer equipped with a Gateway 2000 4DX2-66 workstation. Oils were analyzed using NaCl plates, solid samples were dispersed in KBr and recorded as clear pressed discs. ^1H NMR spectra were recorded at 400 MHz using a Bruker Spectrospin DPX-400 instrument. Tetramethylsilane (TMS) was used as an internal reference standard, with chemical shifts expressed in parts per million (ppm or δ) downfield from the standard. ^{13}C NMR were recorded at 100 MHz using a Bruker Spectrospin DPX-400 instrument. Mass spectroscopy was carried out using HPLC grade solvents. Mass spectra were determined by detection using Electrospray on a Micromass LCT spectrometer, using a Shimadzu HPLC or Water's 9360 to pump solvent. The whole system was controlled by MassLynx 3.5 on a Compaq Deskpro workstation.

4.2. Modified peptide synthesis of 2-chloro-*N*-(2-naphthyl)ethylethanamide 3 and 4

1-(-1-Naphtyl)ethylamine (1 g, 0.63 mmol) and HOBt (0.8 g, 0.63 mmol), chloroacetic acid (0.6 g, 0.63 mmol) were stirred in DCM (25 mL) at −10 °C for 20 min under inert atmosphere. EDCl (1.2 g, 0.63 mmol) was then added and the reaction stirred overnight at room temperature under inert atmosphere. The solution was washed with 1 M

$NaHCO_3$ and brine. The organic layer was collected, dried over $MgSO_4$, filtered and evaporated to give a white solid.

4.2.1. 2-Chloro-*N*-[(*S*)-1-naphthyl]ethylethanamide 3. 0.58 g, 86.9% yield. Mp 140 °C; calcd for $C_{14}H_{14}NOCl$: C 67.88; H, 5.70; N, 5.65. Found C 67.63, H 5.77, N 5.86; ^1H NMR (400 MHz, CD_3CN): δ 8.16 (1H, d, Ar-H, J=8.5 Hz), 7.96 (1H, d, Ar-H, J=7.5 Hz), 7.87 (1H, d, Ar-H, J=7.5 Hz), 7.59 (1H, m, Ar-H), 7.25 (1H, sb, Ar-H,), 5.83 (1H, m, J=7.0 Hz), 4.04 (2H, s), 1.63 (3H, d, J=7.0 Hz); ^{13}C NMR (100 MHz, CD_3CN): 164.8, 138.8, 133.4, 130.2, 128.31, 127.3, 125.0, 125.3, 125.0, 122.6, 122.1, 42.2, 20.1; ES-MS: m/z 247.9 (M+); ν/cm^{-1} (KBr) 3295 (N–H), 1648 (C═O), 1541 (C═C), 780 (C–Cl).

4.2.2. 2-Chloro-*N*-[(*R*)-1-naphthyl]ethylethanamide 4. 0.60 g, 87.3% yield. Mp 140 °C; calcd for $C_{14}H_{14}NOCl$: C, 67.88;H, 5.70; N, 14.31. Found: C; 67.67;H, 5.81; N, 5.83; ^1H NMR (400 MHz, $CDCl_3$): δ 8.11 (1H, d, J=8.5 Hz), 7.92 (1H, d, J=8.6 Hz), 7.86 (1H, d, J=7.6 Hz), 7.56 (4H, m), 6.81 (1H, s, N–*H*), 4.15 (2H, q), 1.74 (3H, d, J=7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 164.4 ($_qC$), 137.0 ($_qC$), 133.5 ($_qC$), 130.5 ($_qC$), 128.5 (Ar-H), 128.2 (Ar-H), 126.2 (Ar-H), 125.5 (Ar-H), 124.8 (Ar-H), 122.6 (Ar-H), 122.1 (Ar-H), 44.8 (C H_2), 42.2 (C H_2), 20.4 (C H_3); ES-MS: m/z 247.9 (M^+); ν/cm^{-1} (KBr) 3290 (N–H), 1652 (C═O), 1540 (C═C), 782 (C–Cl).

4.3. General synthesis of the sensors 1 and 2

1,4-Diaza-9-crown-3-ether (1 equiv.), Cs_2CO_3 (6 equiv.) and KI (0.1 equiv.) were stirred in MeCN under inert atmosphere. The appropriate chromophore (2.1 equiv.) in MeCN was added via a pressure equalized dropping funnel. The mixture was left to reflux at 80 °C overnight under inert atmosphere. The reaction was filtered and the solvent evaporated. The yellow residue was dissolved in $CHCl_3$ and washed with 10% K_2CO_3 (3×20 mL). The organic layer was collected, dried over $MgSO_4$, filtered and evaporated to give a white solid. After purification by alumina chromatography with DCM: 0→5% MeOH, the product was washed and recrystallized from diethyl ether to yield a white solid.

4.3.1. Compound 1 (*S*,*S*). 0.22 g, 32.7% yield. Mp 107 °C; calcd for $C_{34}H_{40}N_4O_3$: C 73.88; H, 7.29; N, 10.14. Found C 73.39, H 7.14, N 9.66; ^1H NMR (400 MHz, CD_3CN): δ 8.12 (2H, d, Ar-H, J=8.5 Hz), 7.91 (2H, d, Ar-H, J=7.5 Hz), 7.81 (2H, d, Ar-H, J=8.0 Hz), 7.53 (8H, m, J=8.0 Hz), 5.80 (2H, m, J=7.0 Hz), 3.24 (4H, m), 3.05 (4H, s), 2.57 (8H, m), 1.68 (6H, d, J=7.0 Hz); ^{13}C NMR (100 MHz, CD_3CN): 139.2 133.4, 130.5, 128.2, 127.2, 125.8, 125.3, 124.9, 122.8, 122.2, 71.7, 60.2, 56.3, 55.1, 43.7, 19.8; ES-MS: m/z 553.5 (M^+), $\Delta\varepsilon/°$=+25 (at OD=0.1, 225 nm); λ_{max}/nm (CH_3CN) 260.8 (ε/dm^3 mol^{-1} cm^{-1} 10427) 281.6 (11801) 293.2 (6801.5); ν/cm^{-1} (KBr) 3287 (N–H); 2525, 2554 (ar C═H); 1650 (C═O amide); 1602, 1511 (ar C═C); 1450 (C–N amide); 1357 (C–N crown ether); 1126 (C–O–C crown ether).

4.3.2. Compound 2 (*R*,*R*). 0.18 g, 30.1% yield. Mp 107 °C. Accurate mass: calcd for $C_{34}H_{40}N_4O_3$: found $C_{34}H_{41}N_4O_3$; ^1H NMR (400 MHz, $CDCl_3$): δ 8.02 (2 ArH, d, J=8.4 Hz), 7.67 (5 ArH, dd, J=8.0 Hz), 7.53 (4H, d, Ar-H, J=8 Hz), 7.03 (2H, d, N–H), 5.59 (2H, d, C H(CH_3)NH), 3.22 (4H, m), 2.77 (4H, q), 2.40 (8H, m), 1.67 (6H, d, J=6.5 Hz, CH(CH_3)NH); ^{13}C NMR (100 MHz, CD_3CN): 169.8 (C═O), 137.7 (Ar-H), 133.4 (Ar-H), 130.9 (Ar-H), 128.3 (Ar-H), 128.0 (Ar-H), 126.1 (Ar-H), 125.5 (Ar-H), 124.7 (Ar-H), 123.1 (Ar-H), 122.3 (Ar-H), 71.6, 60.2, 56.0, 54.8, 43.5, 19.7 (CH(*C* H_3); ES-MS: m/z 552.9 (M^+); $\Delta\varepsilon/°$=−25 (at OD=0.1, 225 nm) λ_{max}/nm (CH_3CN) 260.7 (ε/dm^3 mol^{-1} cm^{-1} 10399) 281.6 (11750) 293.2 (6889.5); ν/cm^{-1} (KBr) 3272 (N–H); 2499, 2554 (ar C═H); 1656 (C═O amide); 1607, 1528 (ar C═C); 1468 (C–N amide); 1357 (C–N crown ether); 1132 (C–O–C crown ether).

Acknowledgements

We would like to thank Trinity College Dublin (Krieble Fund 2001-2002), and HEA (Higher Education Authority in Irealnd) under the PRTLI 98 (Molecular Cell Biology Programme) for financial support, Dr. John E. O'Brien for running NMR spectra, Dr. Hazel Moncrieff and Professor D. Clive Williams (Biochemistry TCD) for their valuable discussion.

References and notes

1. de Silva, A. P.; McCaughan, B.; McKinney, B. O. F.; Querol, M. *Dalton Trans.* **2003**, 1902. De Silva, A. P.; Fox, D. B.; Huxley, A. J. M.; Moody, T. S. *Coord. Chem. Rev.* **2000**, *205*, 41. Lavigne, J. J.; Anslyn, E. V. *Angew. Chem., Int. Ed.* **2001**, *40*, 3119. de Silva, A. P.; Fox, D. B.; Huxley, A. J. M.; Moody, T. S. *Coord. Chem. Rev.* **2000**, *205*, 41. Fabbrizzi, L.; Licchelli, M.; Rabaioli, G.; Taglietti, A. F. *Coord. Chem. Rev.* **2000**, *205*, 85. de Silva, A. P.; Fox, D. B.; Huxley, A. J. M.; McClenaghan, N. D.; Roiron, J. *Coord. Chem. Rev.* **1999**, *186*, 297.
2. *Chemical Sensors and Biosensors for Medical and Biological Applications*. Spichiger-Keller, U. S., Ed.; Wiley-VCH: Weinheim; Germany, 1998. *Chemosensors of Ion and Molecular Recognition*. Desvergne, J. P., Czarnik, A. W., Eds.; Kluwer Academic: Dordrecht, Netherland, 1997.
3. de Silva, A. P.; Gunaratne, H. Q. N.; Gunnlaugsson, T.; Huxley, A. J. M.; McCoy, C. P.; Rademacher, J. T.; Rice, T. E. *Chem. Rev.* **1997**, *97*, 1515. Czarnik, A. W. *Acc. Chem. Res.* **1994**, *27*, 302. *Fluorescent Chemosensors for Ion and Molecular Recognition*. Czarnik, A. W., Ed.; ACS Books: Washington, 1993.
4. Examples include: Gunnlaugsson, T.; Lee, C. T.; Parkesh, R. *Org. Lett.* **2003**, *5*, 4065. Gunnlaugsson, T.; Lee, C. T.; Parkesh, R. *Org. Biomol. Chem.* **2003**, *1*, 3265. He, H.; Mortellaro, M. A.; Leiner, M. J. P.; Fraatz, R. J.; Tusa, J. K. *J. Am. Chem. Soc.* **2003**, *125*, 1468. Tusa, J. K.; Leiner, M. J. P. *Ann. Biol. Clin-Paris* **2003**, *61*, 183. Gunnlaugsson, T.; Nieuwenhuyzen, M.; Richard, L.; Thoss, V. *J. Chem. Soc., Perkin Trans. 2* **2002**, 141. de Silva, A. P.; Gunaratne, H. Q. N.; Maguire, G. E. M. *J. Chem. Soc., Chem. Commun.* **1994**, 1213. Bissell, R. A.; de Silva, A. P.; Gunaratne, H. Q. N.; Lynch, P. L. M.; Maguire, G. E. M.; McCoy, C. P.; Sandanayake, K. R. A. S. *Top. Curr. Chem.* **1993**, *168*, 223. Huston, M. E.; Czarnik, A. W.; Engleman, C. *J. Am. Chem.*

Soc. **1990**, *112*, 7054. de Silva, A. P.; Sandanayake, K. R. A. S. *Angew. Chem., Int. Ed.* **1990**, *29*, 1173.
5. Gunnlaugsson, T.; Kruger, P. E.; Lee, T. C.; Parkesh, R.; Pfeffer, F. M.; Hussey, M. G. *Tetrhedron Lett.* **2003**, *44*, 6575. Gunnlaugsson, T.; Davis, A. P.; Glynn, M. *Org. Lett.* **2002**, *4*, 2449. Gunnlaugsson, T.; Davis, A. P.; Glynn, M. *Chem. Commun.* **2001**, 2556.
6. For a communicaton of this work see: Gunnlaugsson, T.; Bichell, B.; Nolan, C. *Tetrahedron Lett.* **2002**, *43*, 4989.
7. Examples of other types of fluorescent or optically based Li^+ sensors include: Obare, S. O.; Murphy, C. J. *New. J. Chem.* **2001**, *25*, 1600. Ajayaghosh, A.; Chenthamarkshan, C. R. *Tetrahedron Lett.* **1998**, *39*, 1795. Tsuchiya, S.; Ogawa, S. *Chem. Lett.* **1996**, 709. Bocheñska, M. *J. Incl. Phenom.* **1995**, *22*, 269. Blackburn, C.; LeCompte, M. B. K.; Langmuir, M. E. *Tetrahedron Lett.* **1994**, *35*, 1994. McCarrick, M.; Wu, B.; Harris, S. J.; Diamond, D.; Barrett, G.; McKervey, M. A. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1963. Hiratani, K.; Nomoto, M.; Sugihara, H.; Okada, T. *Analyst* **1992**, *117*, 1491. Sholl, A. F.; Sutherland, I. O. *J. Chem. Soc., Chem. Commun.* **1992**, 1716. Hiratani, K. *Analyst* **1988**, *113*, 1065. Nakashima, K.; Nagaoka, Y.; Nakatsuji, S.; Kaneda, T.; Tanigawa, I. *Bull. Chem. Soc. Jpn* **1987**, *60*, 3219.
8. Christian, G. D. *J. Pharm. Biomed. Anal.* **1996**, *14*, 899.
9. Birch, N. J. *Chem. Rev.* **1999**, *99*, 2659.
10. Lindoy, L. F. *The Chemistry of Macrocyclic Ligand Complexes*. Cambridge University Press: New York, 1989.
11. Hori, K.; Tsukbe, H. *J. Incl. Phenom. Mol. Recognit. Chem.* **1998**, *32*, 311. Kataky, R.; Nicholson, P. E.; Parker, D. *J. Chem. Soc., Perkin Trans. 2.* **1990**, 321. Kataky, R.; Nicholson, P. E.; Parker, D.; Covington, A. K. *Analyst* **1991**, *116*, 135–140. Kataky, R.; Nicholson, P. E.; Parker, D. *Tetrahedron Lett.* **1989**, *30*, 4559.
12. Kobiro, K. *Coord. Chem. Rev.* **1996**, *148*, 135.
13. Gunnlaugsson, T.; Harte, A. J.; Leonard, J. P.; Senechal, K. *J. Am. Chem. Soc.* **2003**, *125*, 12062. Gunnlaugsson, T.; Leonard, J. P. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1980. Gunnlaugsson, T.; Nieuwenhuyzen, M.; Richard, L.; Thoss, V. *J. Chem. Soc., Perkin Trans. 2* **2002**, 141. Gunnlaugsson, T.; Nieuwenhuyzen, M.; Richard, L.; Thoss, V. *Tetrahedron Lett.* **2001**, *42*, 4725.
14. Gunnlaugsson, T.; Leonard, J. P. *Chem. Commun.* **2003**, 2424. Gunnlaugsson, T.; Mac Dónaill, D. A.; Parker, D. *Chem. Commun.* **2000**, 93. Gunnlaugsson, T. *Tetrahedron Lett.* **2001**, *42*, 8901.
15. Gunnlaugsson, T.; Mac Dónaill, D. A.; Parker, D. *J. Am. Chem. Soc.* **2001**, *123*, 12866.
16. Gunnlaugsson, T.; Kelly, J. M.; Nieuwenhuyzen, M.; O'Brien, A. M. K. *Tetrahedron Lett.* **2003**, *44*, 8571. Gunnlaugsson, T.; Harte, A. J.; Leonard, J. P.; Nieuwenhuyzen, M. *Supramol. Chem.* **2003**, *15*, 505. Gunnlaugsson, T.; Harte, A. J.; Leonard, J. P.; Nieuwenhuyzen, M. *Chem. Commun.* **2002**, 2134.
17. Ewin, G.; Hill, J. *Chem. Res.* **1985**, 3501.
18. Dickens, R. S.; Howard, J. A. K.; Maupin, C. L.; Moloney, J. M.; Parker, D.; Peacock, R. D.; Riehl, J. P.; Siligardi, G. *New J. Chem.* **1998**, *22*, 891.
19. Bruce, J. I.; Dickins, R. S.; Govenlock, L. J.; Gunnlaugsson, T.; Lopinski, S.; Lowe, M. P.; Parker, D.; Peacock, R. D.; Perry, J. J. B.; Aime, S.; Botta, M. *J. Am. Chem. Soc.* **2000**, *122*, 9674.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 5807–5825
Tetrahedron

Palladium complexes with ethylene-bridged bis(*N*-heterocyclic carbene) for C–C coupling reactions

Hon Man Lee,* Chi Ying Lu, Chih Yuan Chen, Wen Ling Chen, Hung Ching Lin, Pei Ling Chiu and Pi Yun Cheng

Department of Chemistry, National Changhua University of Education, Changhua 50058, Taiwan, ROC

Received 23 December 2003; revised 12 April 2004; accepted 20 April 2004

Abstract—A series of new ethylene-bridged bis(imidazolium) halides with various *N*-substitutions were synthesized. Complexation of these imidazolium halides with $Pd(OAc)_2$ produced new Pd(II) ethylene-bridged bis(carbene) complexes. Crystallographic analyses of some of the new imidazolium salts and Pd(II) complexes were determined. Applications of these seven-member palladacycles in Suzuki and Heck coupling reactions produced comparable catalytic activities to those of six-member analogs.

1. Introduction

Recently, it has been shown that palladium complexes of *N*-heterocyclic carbene ligands offer distinctive advantages as possible alternatives for Pd/phosphine systems in the C–C coupling reactions.[1] Some highly active palladium systems with monodentate carbene ligands for the activation of aryl chlorides were developed.[2] Preparation of chelating ligands of *N*-heterocyclic carbene, which would provide extra air and moisture stability for the palladium centers, are receiving much attention.[3] For examples, some methylene-bridged bis(imidazolium) salts, in combination with $Pd(OAc)_2$, were equally efficient in Suzuki coupling with aryl chlorides as substrates.[4] Of all the reported *cis*-chelating bidentate ligands containing *N*-heterocyclic carbene, the palladium centers involved are exclusively of five- or six-member palladacycles.[3] To the best of our knowledge, there has been no report in employing seven-member palladacycles of bidentate carbene ligands in C–C coupling reactions. The reason is partly because the seven-member palladacycles were proven to be difficult to prepare.[3a,5] It has also been established that for monodentate or chelating ligands with *N*-heterocyclic carbene, bulky *N*-substitutions were essential for high catalytic activity in Suzuki–Miyaura coupling reactions.[6]

In view of the easy condensation of substituted benzyl chlorides with imidazoles, which provide availability of a large variety of *N*-substituted imidazoles, we report on the synthesis of a series of new methylene- and ethylene-bridged bis(imidazolium) salts and the successful preparations of their corresponding Pd(II) halide complexes. These Pd(II) complexes crystallized very readily in DMF/diethyl ether mixture and their molecular structures were determined by single-crystal X-ray crystallography. Crystallographic analyses on the ethylene-bridged bis(imidazolium) salts also reveal a possible conformation change stabilized by the presence of hydrogen bonding with an incorporated water molecule in the asymmetric unit. The activities of some of the palladium-catalyzed reactions, for example, co-polymerization of carbon monoxide and ethylene,[7] depend remarkably on the chelate size. As Pd(II) complexes of methylene-bridged bis(carbene) have already been demonstrated to be effective in C–C coupling reactions,[4a] we were interested to see if seven-member palladacycle can also mediate the catalytic reactions. Recently, research in functionalized *N*-heterocyclic carbene ligands is receiving much attention,[8] the study will contribute to the modular design strategies of employing seven-member palladacycle with *N*-heterocyclic carbene. Our results shows that the use of Pd(II) complexes with ethylene-bridged bis(carbene) in Suzuki and Heck coupling reactions produced comparable activities to the methylene-bridged analogs.

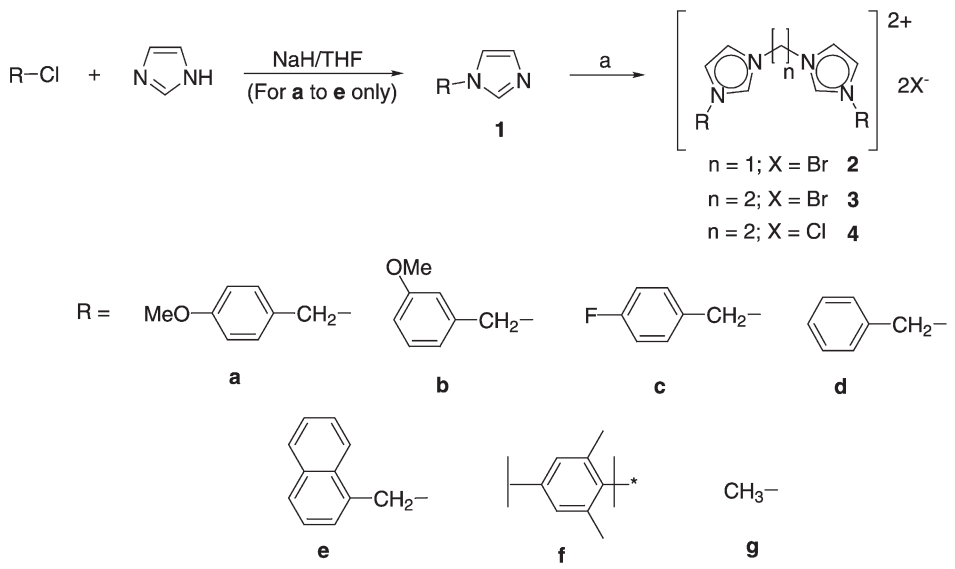
2. Results and discussion

2.1. Chelating bidentate ligand precursors

The ligand precursors of bis(carbene) employed are shown in Scheme 1. A series of substituted *N*-benzylimidazoles

Keywords: C–C Coupling reactions; Chelating *N*-heterocyclic carbenes; Palladium(II) complexes.
* Corresponding author. Tel.: +886-4-7232105x3523; fax: +886-4-7211190; e-mail address: leehm@cc.ncue.edu.tw

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.04.070



Conditions: (a) For **2a**-**2e**, neat dibromomethane, 70-80 °C, 1-2 d; for **3a**-**3g**, 1,2-dibromoethane/THF, 70-80 °C, 2-3 d; for **4a**-**4e**, 1,2-dichloroethane/THF, reflux, 2-3 d.

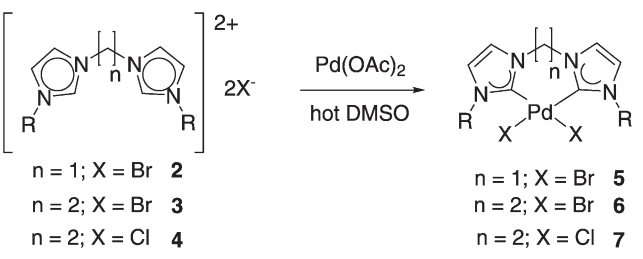
Scheme 1. Ligand precursors of bis(carbene).

1a–**1e** were firstly prepared by heating the corresponding substituted benzyl chloride and imidazole with 4 equiv. of NaH in THF overnight. Quantitative yields were achieved with our modified procedures and the products could be used for the next step without further purifications.[9] Previously, methylene-bridged bis(imidazolium) salts were obtained by reactions of 2 equiv. of *N*-substituted imidazole with an equivalent of CH_2Br_2 or CH_2I_2 in toluene or xylene.[10] The new methylene-bridged bis(imidazolium) bromides **2a**–**2e** were obtained with an alternative method of heating a solution of **1a**–**1e** in neat CH_2Br_2 at 70–80 °C for 1–2 d affording comparable yields. The bis(imidazolium) salts were slowly precipitated as white solids which were isolated in high purity after washing with THF. Interestingly, even though CH_2Br_2 was used in large excess, no mono-imidazolium salt was obtained. However, treatment of a solution of **1a**–**1g** in hot 1,2-dibromoethane did not result in the anticipated ethylene-bridged bis(imidazolium) bromides. Only mono-imidazolium bromides were obtained instead. Therefore, the ethylene-bridged bis(imidazolium) bromides **3a**–**3g** were synthesized by reacting 2 equiv. of **1a**–**1g** with an equivalent of 1,2-dibromoethane in refluxing THF. The ethylene-bridged bis(imidazolium) chlorides **4a**–**4g** were prepared similarly but with lower yields obtained.

2.2. Preparation and characterization of chelating bidentate palladium(II) complexes

Pd(II) complexes **5a**–**5e** were smoothly synthesized in high yields by following the reported protocol of treating the methylene-bridged bis(imidazolium) salt with $Pd(OAc)_2$ in hot DMSO (Scheme 2).[3b] Most remarkably, we applied the same methodology for the corresponding ethylene-bridged bis(imidazolium) halides and were able to obtain Pd(II) complexes **6** and **7**. It is likely that the successful application of the $Pd(OAc)_2$ protocol with bis(imidazolium) salts of ethylene spacer depends very much on the *N*-substitution as both previous attempts by Herrmann et al with *N*-^{t}Bu and our effort with *N*-Me substitutions were unsuccessful. Green et al. had already demonstrated that Ni(II) complexes with ethylene-bridged relative to methylene-bridged bis(carbene) ligands were sterically more congested.[11a] Consistently, the Pd(II) complex **5f** with bulky mesityl groups could be obtained from **2f**,[3b] but similar preparation from the ethylene-bridged analog **3f** was not successful. Only with bis(imidazolium) halides of *N*-benzyl or naphthylmethyl substitution, the corresponding Pd(II) complexes could be achieved with the $Pd(OAc)_2$ protocol. However, in general, lower yields compared with the methylene analogs were obtained. In fact, palladium black were observed during the course of reaction and filtration of the DMSO solution had to be done in the workup procedure. All the Pd(II) halide complexes obtained are stable in air and form crystals very readily (vide infra).

The ethylene-bridged bis(carbene) ligands were coordinated in chelating fashion around the palladium centers as evidenced by the fact that in the ^{1}H NMR spectrum of **6a**, for example, the resonance for the acidic protons of the organic ancillary at ca. δ 9.3 was no longer observed and the imidazole rings were symmetry-related. The ^{13}C signal for the carbene carbons was observed as a broad signal at ca. δ 157. In addition, the ethylene protons were split into two



Scheme 2. Synthesis of palladium complexes with chelating *N*-heterocyclic carbenes.

Table 1. Crystallographic data for **2a**, **4d**, and **4e**

	2a	**4d**	**4e**·H_2O
Empirical formula	$C_{23}H_{26}Br_2N_4O_2$	$C_{22}H_{24}Cl_2N_4$	$C_{30}H_{28}Cl_2N_4{\cdot}H_2O$
Formula weight	550.30	415.35	533.48
Color and Habit	Colorless needle	Colorless prism	Colorless parallelpipe
Crystal system	Monoclinic	Monoclinic	Triclinic
Space group	*C2/c*	$P2_1/c$	$P\bar{1}$
a (Å)	37.952(11)	5.941(3)	7.976(3)
b (Å)	5.2200(14)	12.728(6)	8.668(3)
c (Å)	12.383(3)	13.843(4)	19.359(7)
α (deg)	90	90	92.081(10)
β (deg)	99.929(5)	98.05(2)	90.37(2)
γ (deg)	90	90	99.961(19)
V (Å^3)	2416.4	1036.3(8)	1317.2(9)
T (K)	150(2)	150(2)	150(2)
Z	4	2	2
D_{calcd} (Mg/m^3)	1.513	1.331	1.345
μ (mm^{-1})	3.381	0.329	0.278
Range of transm. factor	1.00–0.68	0.81–0.80	0.96–0.81
No. of unique data	2397	2385	5800
No. of parameters refined	141	127	342
$R1[I>2\sigma I]$	0.0471	0.0284	0.0503
*wR*2 (all data)	0.1671	0.0782	0.1240
Residuals (eÅ^{-3})	0.429, −0.458	0.299, −0.211	0.364, −0.243

separate broad signals at δ 4.55 and 5.28, as a result of ligand coordination. The broadening of resonances could be attributed to the fluxionality of the seven-member palladacycle. Also, the benzylic protons were observed as two sets of AB doublets with geminal coupling of 14.6 Hz at δ 4.94 and 5.35, indicating hindered rotation of the *N*-substitutions around the C–N bonds. Similar phenomena were also observed for the *N*-substitutions in the methylene analogs **5a**–**5e**.

2.3. Molecular structures of ligand precursors 2a, 4d, and 4e

Crystals of **2a**, **4d**, and **4e** suitable for X-ray crystallographic analysis were obtained by slow diffusion of diethyl ether into a DMF solution of the corresponding salts. In all cases, colorless crystals were obtained after few days. The crystallographic data of **2a**, **4d**, and **4e** are listed in Table 1 and their molecular structures are shown in Figures 1–3 respectively. The ethylene-bridged imidazolium chloride **4d** crystallizes in the monoclinic space group $P2_1/c$ with one half of the cationic molecule and a chloride anion per asymmetric unit. The second half and the other chloride anion are generated by inversion through a center of symmetry. As a result, the two imidazole rings are parallel and in *anti* relationship to each other. Each of the chloride ions are situated on one side of the molecular cation. The separation between the two imidazole planes is 1.510 Å. The head to tail stacking of the π systems of phenyl rings is propagated by the screw axis forming infinite chains of molecular cation along *b*-axis (Fig. 4). The interplanar distance is 3.6316 Å. For the anion coordination environment of the compound, Figure 4 also clearly shows that in the crystal lattice the chloride anion interacts with the hydrogen atoms on the C(1) and C(4) (the carbenic hydrogen and the hydrogen of ethylene linkage), those on the C(2) and C(5) (the imidazole ring proton and the benzylic hydrogen) of a proximal molecule, and also the hydrogen atom on the C(4) of a third molecule, thus linking three molecular cations together. The contact distance of

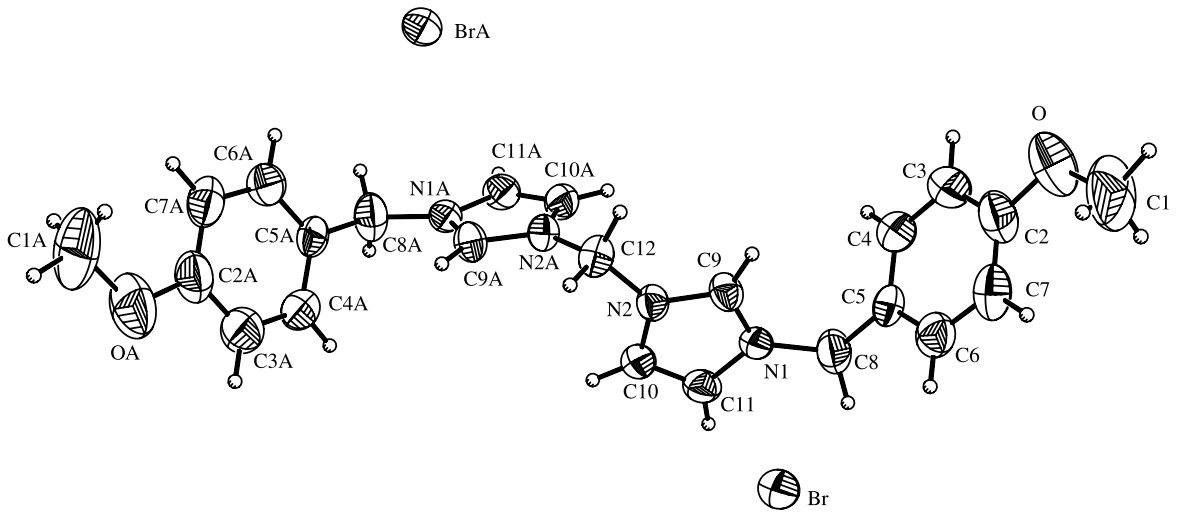


Figure 1. Molecular structure of **2a**.

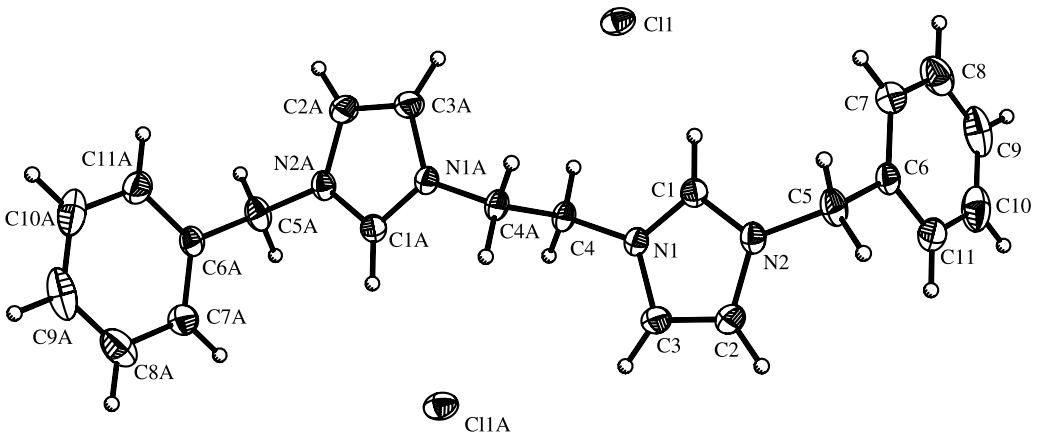


Figure 2. Molecular structure of **4d**.

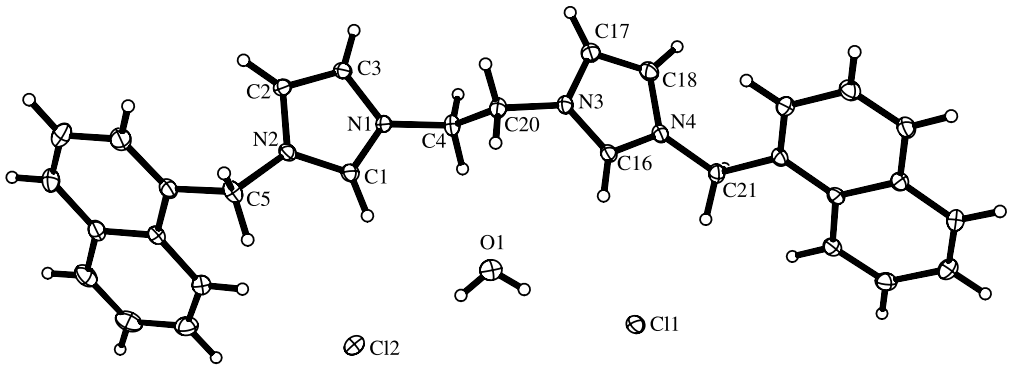


Figure 3. Molecular structure of **4e**·H_2O.

H···Cl of the hydrogen atoms on C(1) and C(4) are 2.627 and 2.636 Å, respectively. The distance with hydrogen atom on C(2) of the second molecule and C(4) of the third molecules are 2.644 and 2.764 Å, respectively. All these distances are within the van der Waals approach of H···Cl, i.e. <2.80–3.00 Å, and are therefore by definition hydrogen bonds (Table 2).[12]

The ethylene-bridged imidazolium chloride **4e** crystallizes in the triclinic space group $P\bar{1}$ with one ionic salt per

Table 2. Selected bond lengths (Å) and angles (°) for **2a**, **4d**, and **4e**

2a		**4d**		**4e**	
N(1)–C(9)	1.316(8)	N(1)–C(1)	1.3319(15)	N(1)–C(1)	1.334(3)
N(1)–C(11)	1.378(9)	N(1)–C(3)	1.3804(15)	N(1)–C(3)	1.378(3)
N(2)–C(9)	1.333(9)	N(1)–C(4)	1.4643(14)	N(1)–C(4)	1.464(3)
N(2)–C(10)	1.372(9)	N(2)–C(1)	1.3334(15)	N(2)–C(1)	1.327(3)
N(2)–C(12)	1.449(8)	N(2)–C(2)	1.3799(16)	N(2)–C(2)	1.380(3)
C(10)–C(11)	1.338(10)	C(2)–C(3)	1.3566(17)	N(3)–C(16)	1.327(3)
				N(3)–C(17)	1.385(3)
				N(3)–C(20)	1.467(3)
				N(4)–C(16)	1.328(3)
				N(4)–C(18)	1.380(3)
				C(2)–C(3)	1.351(3)
				C(17)–C(18)	1.345(3)
C(9)–N(1)–C(11)	109.4(7)	C(1)–N(1)–C(3)	109.31(10)	C(1)–N(1)–C(3)	108.74(18)
C(9)–N(2)–C(10)	108.2(6)	C(1)–N(2)–C(2)	109.04(10)	C(1)–N(2)–C(2)	109.06(18)
N(1)–C(9)–N(2)	108.2(7)	N(1)–C(1)–N(2)	107.98(10)	N(1)–C(1)–N(2)	108.24(19)
C(11)–C(10)–N(2)	107.9(2)	C(3)–C(2)–N(2)	107.03(10)	C(3)–C(2)–N(2)	106.8(2)
C(10)–C(11)–N(1)	106.3(7)	C(2)–C(3)–N(1)	106.64(10)	C(2)–C(3)–N(1)	107.13(19)
N(2A)–C(12)–N(2)	109.4(8)	N(1)–C(4)–C(4A)	109.12(11)	N(1)–C(4)–C(20)	110.03(18)
				C(16)–N(3)–C(17)	109.01(19)
				C(16)–N(4)–C(18)	108.28(19)
				N(3)–C(16)–N(4)	108.61(19)
				C(17)–C(18)–N(4)	107.8(2)
				C(18)–C(17)–N(3)	106.3(2)
				N(3)–C(20)–C(4)	108.76(18)

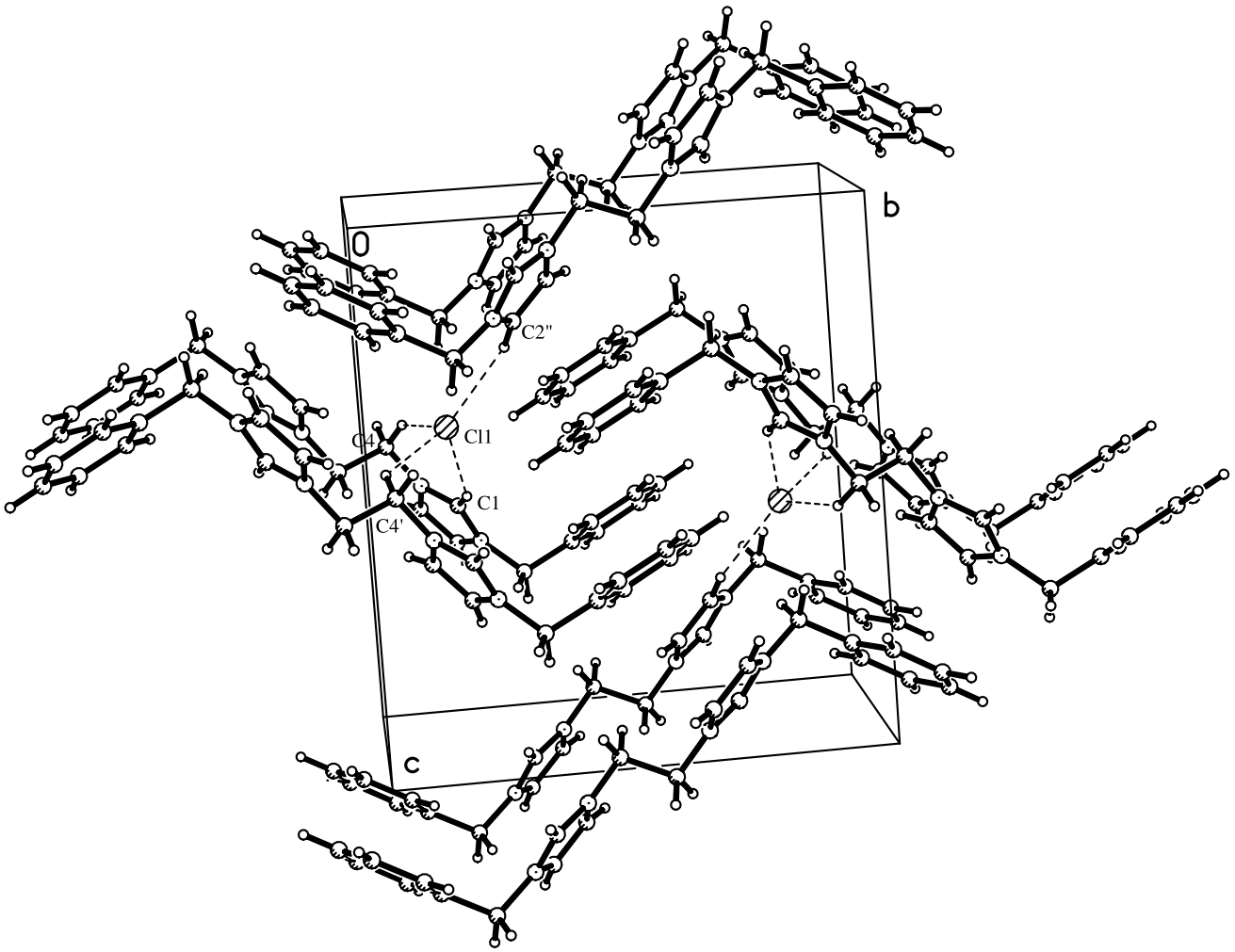


Figure 4. Packing diagram of **4d**. Dashed lines represent close contacts.

asymmetric unit. The striking differences between **4d** and **4e** are the *syn* relationship of the imidazole rings and the inclusion of a water molecule in the lattice. The water incorporated should come from the wet DMF solvent used. The separation between the two parallel imidazole planes (1.663 Å) is significantly bigger than that of **4d** (1.510 Å). The *syn* disposition may be attributed to the incorporated water molecule which forms extensive hydrogen contacts with the molecular cations and chloride anions. As shown in Figure 5, the two chloride ions form two hydrogen bonds with the hydrogen atoms on the water molecule (2.407 and 2.387 Å). The oxygen atom O(1) also interacts with the ethylene hydrogen atom on C(4) forming a H···O contact distance of 2.372 Å. The chloride ions Cl(2) make three hydrogen contacts with the carbenic hydrogen on C(1), the naphthyl ring proton on C(14), and the imidazole ring proton on C(2) of a proximal molecular cation. The contact distances are 2.606, 2.729, and 2.576 Å respectively. The other chloride ion Cl(1) make four contacts with the carbenic hydrogen on C(16) (2.755 Å), the methylene proton on C(21) (2.684 Å), and the imidazole ring protons on C(3) (2.798 Å) and C(17) (2.834 Å) of the neighboring molecular cation. The naphthyl rings are π-π stacked along the *a*-axis with interplanar distances of 3.479 Å.

The methylene-bridged bis(imidazolium) bromide **2a** crystallizes in the monoclinic space group *C2/c* with one half of the molecular cation and a bromide anion per asymmetric unit. The second half and the other bromide are generated by the symmetry operation of a C_2 rotational axis passing through C(12) along the *b*-axis. Unlike **4d** and **4e**, **2a** contains two methylene-linked imidazole rings which can not be parallel but making an angle of 78.6° to each other. Interestingly, because of the *p*-OMe group on the phenyl ring, the cationic molecules are connected by, instead of π−π stacking in **4d**, two intermolecular hydrogen bonds between O(1) and the hydrogen atom on C(1) of a proximal molecule, and the hydrogen atom on C(1) and O(1) of the proximal molecule, forming infinite chains along the *a*-axis (Fig. 6). Both of the two hydrogen bond distances are 2.689 Å. Similar to that in **4d**, a bromide anion also links up three cationic molecules through short hydrogen bonds. The H···Br contact distances with the hydrogen atoms upon the carbenic carbon C(9) and the methylene carbon of the parent molecule C(12) are 2.767 and 2.868 Å, respectively. The short contacts on a second cationic molecule are with the hydrogen atom upon C(10) of imidazole ring and C(4) of the phenyl ring, while that on a third molecule is with the hydrogen atom upon C(11) of imidazole ring. The contact distances are 2.773, 2.985, and 2.734 Å, respectively.

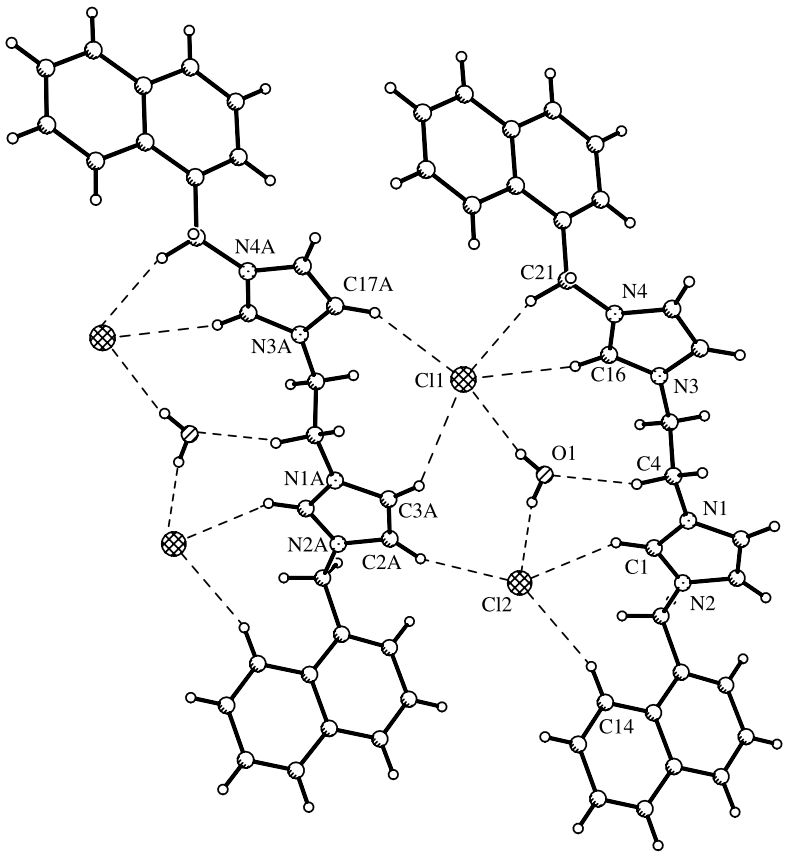


Figure 5. The hydrogen bonding interaction in **4e**. The hydrogen atoms of the water molecule were located in the difference map.

2.4. Molecular structures of palladium complexes of ethylene-bridged bis(carbene)

Single crystals of **6a**–**6e** can easily be grown from diffusion of diethyl ether into a DMF solution containing the palladium complexes. The molecular structures of **6a**–**6e** are shown in Figures 7–11. The crystallographic data are given in Table 3, and selected bond lengths and angles are listed in Tables 4–8. Each has fractional amounts of DMF incorporated as solvent of crystallization. For **6d**, there are two independent molecules in the asymmetric unit. In each of the structures, the palladium center adopts square planar coordination geometry. The sums of the angles at Pd(1) are 360.25° (**6a**), 359.83° (**6b**), 360.36° (**6c**), 360.54° (**6d**), and 360.04° (**6e**). Another common feature of the structures **6a**–**6e** is, rather unexpectedly, one of the benzyl/naphthylmethyl groups on the heterocyclic rings bends towards the palladium center. This is remarkably different from the

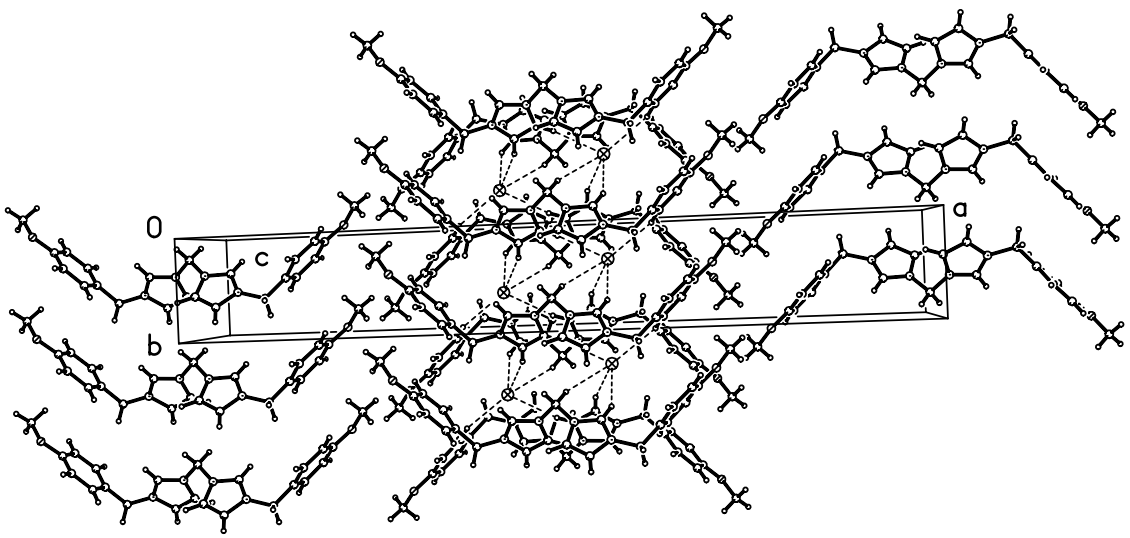


Figure 6. Packing diagram of **2a**. Dashed lines represent close contacts.

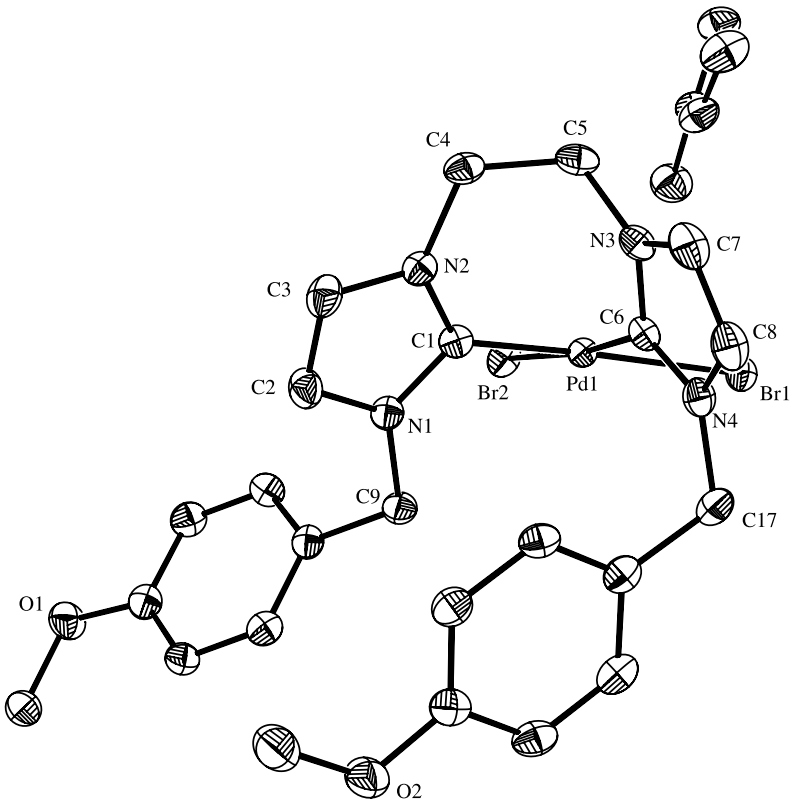


Figure 7. A drawing of the structure of **6a**·DMF. Hydrogen atoms are omitted for clarity.

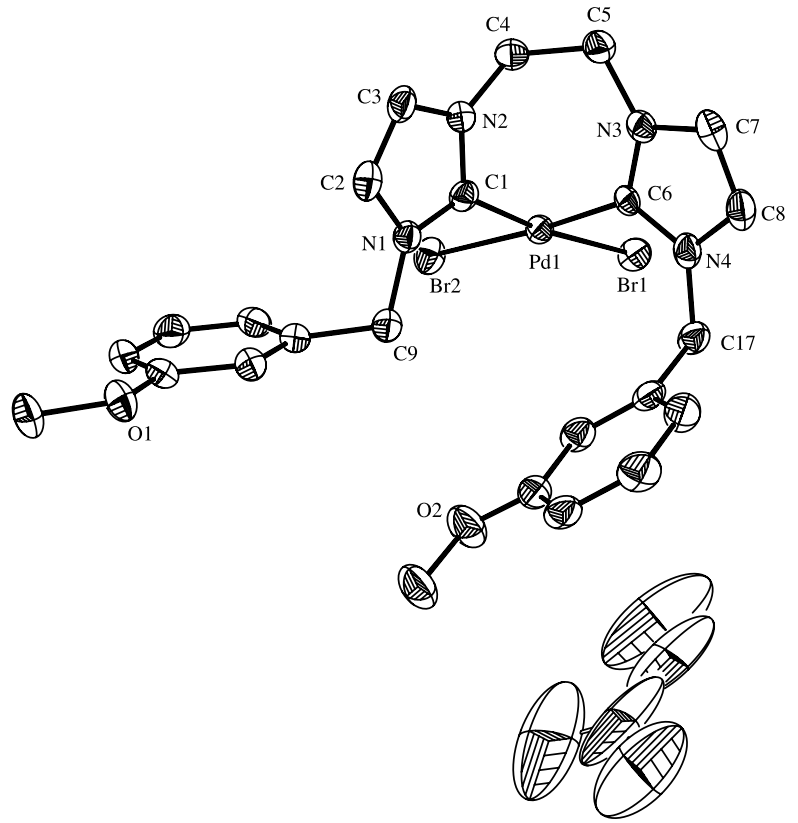


Figure 8. A drawing of the structure of **6b**·0.5DMF. Hydrogen atoms are omitted for clarity.

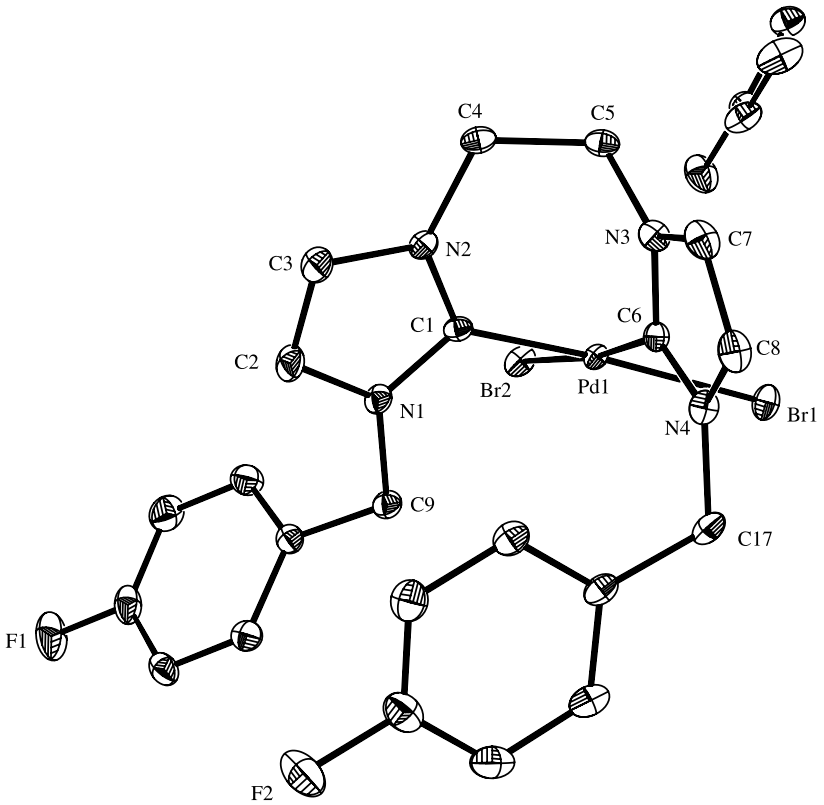


Figure 9. A drawing of the structure of **6c**·DMF. Hydrogen atoms are omitted for clarity.

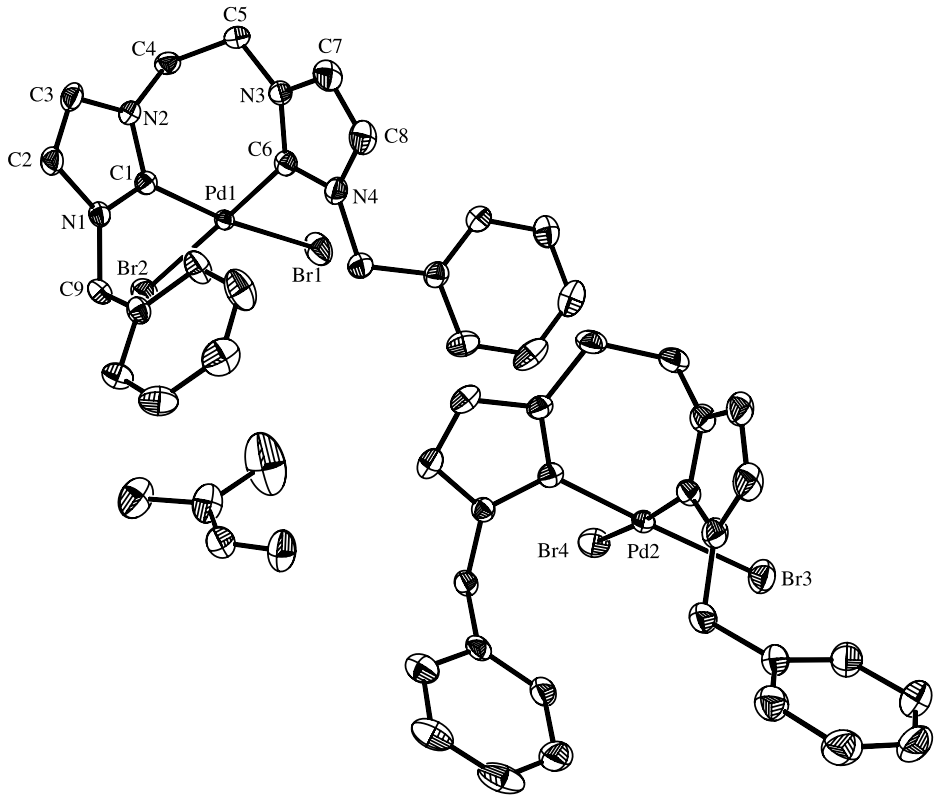


Figure 10. A drawing of the structure of **6d**·0.5DMF showing the two independent molecules and an incorporated DMF in the asymmetric unit. Hydrogen atoms are omitted for clarity.

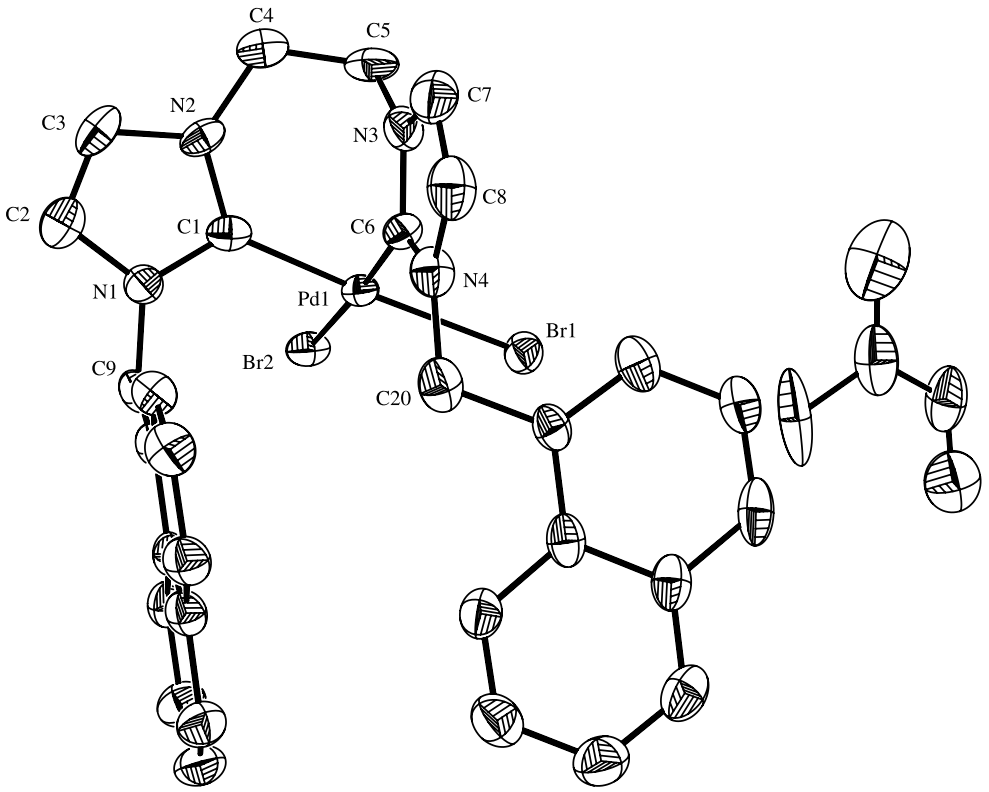


Figure 11. A drawing of the structure of **6e**·DMF. Hydrogen atoms are omitted for clarity.

solution structures by ^{1}H NMR which clearly shows the presence of mirror symmetry (vide supra). Previous to this paper, a similar palladium(II) methyl complex Pd(^{tbu}CC^{eth})Me$_2$ (^{tbu}CC^{eth}=1,2-ethylene-3,3′di-*tert*-butyl-diimidazol-2,2′-diylidene) (**8**),[13] nickel(II) complexes [Ni(^{tbu}CC^{eth})Cl(PMe$_3$)][BPh$_4$] (**9**)[11a] and Ni(^{tbu}CC^{eth})Me$_2$ (**10**)[11b] have been structurally characterized. Similar to these complexes, the seven-member palladacycles in **6a**–**6e**, also adopt boat-like conformations. However, the bite angles C(1)–Pd(1)–C(6) in **6a** (83.42°), **6b** (85.33°), **6c** (83.49°), **6d** (84.01°, 84.76° C(29)–Pd(2)–C(24)), and **6e** (84.56°) are significantly smaller than those in the three structures (88.1° in **8**; 88.38° in **9**; 88.93° in **10**), indicating the bigger steric bulkiness of the benzyl and naphthylmethyl groups. There is a wide distribution of the torsion angle of N(2)–C(4)–C(5)–N(3) in **6a** (50.81°), **6b** (44.20°), **6c** (48.85°), **6d** (42.25°, 54.30°), **6e** (50.66°) and the corresponding angles in **8** (50.76°), **9** (58.67°), and **10** (52.17°).

Table 3. Crystallographic data for **6a**–**6e**

	6a·DMF	**6b**·0.5DMF	**6c**·DMF	**6d**·0.5DMF	**6e**·DMF
Empirical formula	$C_{27}H_{33}Br_2N_5O_3Pd$	$C_{25.5}H_{29.5}Br_2N_{4.5}O_{2.5}Pd$	$C_{25}H_{27}Br_2F_2N_5OPd$	$C_{23.5}H_{25.5}Br_2N_{4.5}O_{0.5}Pd$	$C_{33}H_{33}Br_2N_5OPd$
Formula weight	741.80	705.26	717.74	1290.41	781.86
Color and Habit	Colorless prism	Colorless prism	Colorless prism	Colorless prism	Colorless parallelpipe
Crystal system	Triclinic	Monoclinic	Triclinic	Monoclinic	Monoclinic
Space group	$P\bar{1}$	$P2_1/n$	$P\bar{1}$	$P2_1/c$	$P2_1/c$
a (Å)	8.8637(6)	17.7146(18)	8.7820(19)	26.681(3)	10.4651(15)
b (Å)	8.8766(6)	8.3202(8)	8.792(2)	8.5241(7)	19.478(3)
c (Å)	18.7301(13)	19.639(2)	18.169(4)	20.0844(18)	15.232(2)
α (deg)	82.082(3)	90	83.475(11)	90	90
β (deg)	76.779(3)	109.703(6)	76.710(13)	99.247(7)	97.434(8)
γ (deg)	82.367(4)	90	83.582(11)	90	90
V (Å^3)	1413.07(17)	2725.0(5)	1351.1(5)	4846.4(7)	3078.8(8)
T (K)	150(2)	150(2)	150(2)	150(2)	150(2)
Z	2	4	2	8	4
D_{calcd} (Mg/m^3)	1.743	1.719	1.764	1.769	1.687
μ (mm^{-1})	3.522	3.646	3.686	4.086	3.234
Range of transm. factor	0.65–0.16	0.78–0.30	0.56–0.19	0.74–0.14	0.61–0.01
No. of unique data	6226	6110	5900	11007	7026
No. of parameters refined	343	328	325	568	379
$R1[I>2\sigma I]$	0.0221	0.0384	0.0338	0.0441	0.0480
$wR2$ (all data)	0.0550	0.1012	0.0952	0.1305	0.1235
Residuals (eÅ^{-3})	0.441, −0.326	1.363, −1.022	1.483, −1.420	1.647, −1.929	0.891, −0.761

Table 4. Selected bond lengths (Å) and angles (°) for **6a**

Pd(1)–C(6)	1.971(2)	Pd(1)–Br(1)	2.5041(3)
Pd(1)–C(1)	1.993(2)	Pd(1)–Br(2)	2.5055(3)
C(2)–C(3)	1.345(3)	C(7)–C(8)	1.344(3)
N(1)–C(1)	1.348(3)	N(2)–C(1)	1.360(3)
N(3)–C(6)	1.351(3)	N(4)–C(6)	1.344(3)
C(6)–Pd(1)–C(1)	83.42(8)	C(6)–Pd(1)–Br(1)	91.48(6)
C(1)–Pd(1)–Br(1)	173.94(6)	C(6)–Pd(1)–Br(2)	173.99(6)
C(1)–Pd(1)–Br(2)	93.09(6)	Br(1)–Pd(1)–Br(2)	92.260(10)
C(1)–N(1)–C(2)	110.65(18)	C(1)–N(1)–C(9)	124.96(18)
C(1)–N(2)–C(4)	129.74(18)	C(3)–N(2)–C(4)	120.14(18)
C(6)–N(3)–C(7)	110.53(19)	C(6)–N(3)–C(5)	121.49(18)
C(7)–N(3)–C(5)	127.76(19)	C(6)–N(4)–C(8)	110.34(19)
N(1)–C(1)–N(2)	105.28(18)	N(1)–C(1)–Pd(1)	123.80(15)
N(2)–C(1)–Pd(1)	130.64(16)	N(2)–C(4)–C(5)	115.25(18)
N(3)–C(5)–C(4)	112.20(17)	N(4)–C(6)–N(3)	105.56(18)
N(4)–C(6)–Pd(1)	132.75(16)	N(3)–C(6)–Pd(1)	121.66(15)

Table 5. Selected bond lengths (Å) and angles (°) for **6b**

Pd(1)–C(6)	1.990(4)	Pd(1)–Br(1)	2.5036(6)
Pd(1)–C(1)	1.966(4)	Pd(1)–Br(2)	2.4741(6)
C(2)–C(3)	1.340(7)	C(7)–C(8)	1.338(7)
N(1)–C(1)	1.360(5)	N(2)–C(1)	1.345(6)
N(3)–C(6)	1.361(6)	N(4)–C(6)	1.354(5)
C(6)–Pd(1)–C(1)	85.33(17)	C(6)–Pd(1)–Br(1)	91.55(11)
C(1)–Pd(1)–Br(1)	173.71(13)	C(6)–Pd(1)–Br(2)	174.37(12)
C(1)–Pd(1)–Br(2)	89.23(12)	Br(1)–Pd(1)–Br(2)	92.72(2)
C(1)–N(1)–C(2)	109.6(4)	C(1)–N(1)–C(9)	125.8(4)
C(1)–N(2)–C(4)	121.3(4)	C(3)–N(2)–C(4)	127.1(4)
C(6)–N(3)–C(7)	110.6(7)	C(6)–N(3)–C(5)	129.5(4)
C(7)–N(3)–C(5)	119.8(4)	C(6)–N(4)–C(8)	111.4(4)
N(1)–C(1)–N(2)	105.1(4)	N(1)–C(1)–Pd(1)	133.8(3)
N(2)–C(1)–Pd(1)	121.1(3)	N(2)–C(4)–C(5)	113.7(4)
N(3)–C(5)–C(4)	115.5(4)	N(4)–C(6)–N(3)	104.2(4)
N(4)–C(6)–Pd(1)	127.3(3)	N(3)–C(6)–Pd(1)	128.4(3)

Table 6. Selected bond lengths (Å) and angles (°) for **6c**

Pd(1)–C(6)	1.973(3)	Pd(1)–Br(1)	2.4844(6)
Pd(1)–C(1)	1.987(3)	Pd(1)–Br(2)	2.4960(6)
C(2)–C(3)	1.345(3)	C(7)–C(8)	1.340(5)
N(1)–C(1)	1.342(5)	N(2)–C(1)	1.364(4)
N(3)–C(6)	1.353(4)	N(4)–C(6)	1.337(4)
C(6)–Pd(1)–C(1)	83.49(12)	C(6)–Pd(1)–Br(1)	91.55(9)
C(1)–Pd(1)–Br(1)	173.40(9)	C(6)–Pd(1)–Br(2)	173.68(9)
C(1)–Pd(1)–Br(2)	92.85(9)	Br(1)–Pd(1)–Br(2)	92.47(2)
C(1)–N(1)–C(2)	111.1(3)	C(1)–N(1)–C(9)	124.0(3)
C(1)–N(2)–C(4)	129.5(3)	C(3)–N(2)–C(4)	120.4(3)
C(6)–N(3)–C(7)	110.1(3)	C(6)–N(3)–C(5)	121.8(3)
C(7)–N(3)–C(5)	127.9(3)	C(6)–N(4)–C(8)	110.5(3)
N(1)–C(1)–N(2)	105.1(3)	N(1)–C(1)–Pd(1)	123.8(2)
N(2)–C(1)–Pd(1)	130.6(2)	N(2)–C(4)–C(5)	114.8(3)
N(3)–C(5)–C(4)	112.1(3)	N(4)–C(6)–N(3)	105.8(3)
N(4)–C(6)–Pd(1)	132.9(2)	N(3)–C(6)–Pd(1)	121.3(2)

The wide range of torsion angles and the fact that **6d** crystallizes with two independent molecules of quite extreme torsion angles indicate that the seven-member metallocycle with the ethylene-bridged bis(carbene) ligands are quite flexible and can adopt multiple conformations. The conformational flexibility of the metallocycles were also shown by the two imidazole planes making an angle of 91.4° in **6a**, 85.2° in **6b**, 88.8° in **6c**, 86.4° (85.4° of second molecule) in **6d**, and 88.1° in **6e**, which are significantly bigger than those of 74.6° in **9** and 84.1° in **10** but smaller than that of 102.6° in **8**. The average Pd–C distance in **6a**–**6e** is 1.98 Å, which is shorter than that of 2.08 Å in **8**, reflecting the stronger donating property of the methyl ligand.

Table 7. Selected bond lengths (Å) and angles (°) for **6d**[a]

Pd(1)–C(6)	1.988(5)	Pd(1)–Br(1)	2.4580(6)
Pd(1)–C(1)	1.978(5)	Pd(1)–Br(2)	2.4622(6)
C(2)–C(3)	1.335(7)	C(7)–C(8)	1.333(8)
N(1)–C(1)	1.342(6)	N(2)–C(1)	1.341(6)
N(3)–C(6)	1.356(6)	N(4)–C(6)	1.357(6)
C(6)–Pd(1)–C(1)	84.01(18)	C(6)–Pd(1)–Br(1)	93.06(13)
C(1)–Pd(1)–Br(1)	172.96(13)	C(6)–Pd(1)–Br(2)	172.47(13)
C(1)–Pd(1)–Br(2)	90.59(13)	Br(1)–Pd(1)–Br(2)	92.88(2)
C(1)–N(1)–C(2)	109.3(4)	C(1)–N(1)–C(9)	125.3(4)
C(1)–N(2)–C(4)	122.5(4)	C(3)–N(2)–C(4)	126.9(4)
C(6)–N(3)–C(7)	110.1(4)	C(6)–N(3)–C(5)	129.3(4)
C(7)–N(3)–C(5)	120.6(4)	C(6)–N(4)–C(8)	110.7(4)
N(1)–C(1)–N(2)	106.3(4)	N(1)–C(1)–Pd(1)	132.4(3)
N(2)–C(1)–Pd(1)	121.2(3)	N(2)–C(4)–C(5)	112.1(4)
N(3)–C(5)–C(4)	115.0(4)	N(4)–C(6)–N(3)	104.9(4)
N(4)–C(6)–Pd(1)	124.6(3)	N(3)–C(6)–Pd(1)	129.3(4)

[a] Only one independent molecule of **6d** is listed.

Table 8. Selected bond lengths (Å) and angles (°) for **6e**

Pd(1)–C(6)	1.959(6)	Pd(1)–Br(1)	2.4742(7)
Pd(1)–C(1)	1.993(6)	Pd(1)–Br(2)	2.5058(8)
C(2)–C(3)	1.315(9)	C(7)–C(8)	1.344(10)
N(1)–C(1)	1.351(7)	N(2)–C(1)	1.353(7)
N(3)–C(6)	1.348(7)	N(4)–C(6)	1.342(7)
C(6)–Pd(1)–C(1)	84.6(2)	C(6)–Pd(1)–Br(1)	89.85(16)
C(1)–Pd(1)–Br(1)	174.40(16)	C(6)–Pd(1)–Br(2)	176.62(16)
C(1)–Pd(1)–Br(2)	92.18(3)	Br(1)–Pd(1)–Br(2)	92.18(3)
C(1)–N(1)–C(2)	111.6(5)	C(1)–N(1)–C(9)	124.5(5)
C(1)–N(2)–C(4)	130.1(5)	C(3)–N(2)–C(4)	120.4(5)
C(6)–N(3)–C(7)	110.5(5)	C(6)–N(3)–C(5)	121.2(5)
C(7)–N(3)–C(5)	128.1(5)	C(6)–N(4)–C(8)	109.1(5)
N(1)–C(1)–N(2)	104.5(5)	N(1)–C(1)–Pd(1)	125.8(4)
N(2)–C(1)–Pd(1)	129.6(4)	N(2)–C(4)–C(5)	115.8(5)
N(3)–C(5)–C(4)	113.1(5)	N(4)–C(6)–N(3)	106.5(5)
N(4)–C(6)–Pd(1)	132.7(4)	N(3)–C(6)–Pd(1)	120.7(4)

2.5. Molecular structures of palladium complexes of methylene-bridged bis(carbene)

Single crystals of **5b**–**5d** can be grown from diffusion of diethyl ether into a DMF solution containing the palladium complexes. The molecular structures of **5b**–**5d** are shown in Figures 12–14. The crystallographic data are given in Table 9, and selected bond lengths and angles are listed in Table 10. Similar Pd(II) halide complexes with methylene-bridged bis(carbene) ligand, (1,1′-dimethyl-3,3′methylenediimidazoline-2,2′-diylidene)palladium(II) diiodide (**11**),[4a] (1,1′-di-*tert*-butyl-3,3′methylenedi-imidazoline-2,2′-diylidene)palladium(II) diiodide (**12**)[3a] and (1,1′-bis(2-hydroxyethyl)-3,3′-methylenedi-imidazolin-2,2′-diylidene)palladium(II) diiodide (**13**)[14] are known in the literature. Even though **5b**, **5c** and **5d** were grown under identical conditions, **5b** crystallizes without any solvent of crystallization. **5c** incorporates one half of a DMF

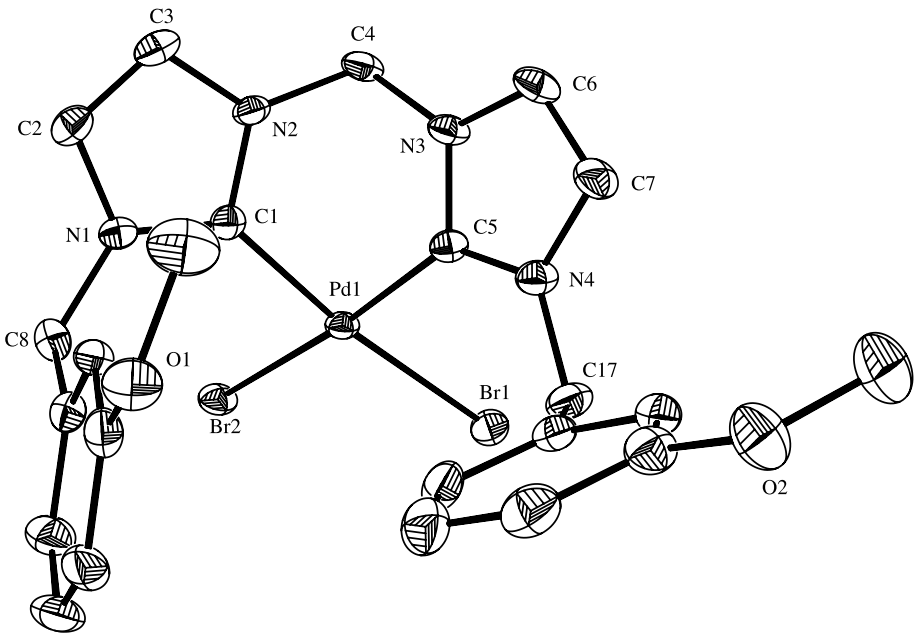


Figure 12. A drawing of the structure of **5b**. Hydrogen atoms are omitted for clarity.

molecule disordered at the center of inversion per asymmetric unit in the space group *C2/c*. **5d** crystallizes in the monoclinic space group of $P2_1/c$ with two complex molecules per asymmetric unit. One of the benzyl groups in the second molecule is disordered with the major orientation of 74% site occupancy. Although, the bite angles, internal angles at the methylene carbon in **5a**–**5d**, **12**, and **13** are quite similar, indicating the rigidity of the six-member palladacycles, the relative orientation of the imidazole rings can have certain degree of flexibility as shown by the distribution of inter-planar angles in **5a** (61.3°), **5c** (59.0°), **5d** (56.1°), **12** (70.9°), and **13** (63.6°).

2.6. Suzuki coupling

The catalytic applicability of Pd(II) complexes with ethylene-bridged bis(carbene) and its comparison with methylene-bridged analogs towards Suzuki coupling of aryl bromides and phenylboronic acid was investigated (Table 11). As shown in the table, both series are effective in the activation of aryl bromides. For electron-deficient substrate, the ethylene-bridged bis(carbene) complexes are even more efficient than the methylene-bridged analogs (compare entries 1–7 with entries 8–13). With bromoanisole and bromobenzene, the two series give similar results. It is noteworthy that the catalytic activities of both

Table 9. Crystallographic data for **5b**, **5c**, and **5d**

	5b	**5c**·0.5DMF	**5d**·DMF
Empirical formula	$C_{23}H_{24}Br_2N_4O_2Pd$	$C_{22.5}H_{21.5}Br_2F_2N_{4.5}O_{0.5}Pd$	$C_{24}H_{27}Br_2N_5OPd$
Formula weight	654.68	667.16	667.73
Color and habit	Colorless prism	Colorless prism	Colorless parallelpipe
Crystal system	Triclinic	Monoclinic	Monoclinic
Space group	$P\bar{1}$	*C2/c*	$P2_1/c$
a (Å)	8.032(4)	31.1566(6)	27.135(2)
b (Å)	9.673(5)	7.8468(14)	8.5617(5)
c (Å)	16.249(8)	22.966(5)	22.2462(15)
α (deg)	89.308(12)	90	90
β (deg)	76.010(10)	121.047(11)	101.300(6)
γ (deg)	77.729(17)	90	90
V (Å^3)	1036.3(8)	4810.2(16)	5068.2(6)
T (K)	150(2)	150(2)	150(2)
Z	2	8	8
D_{calcd} (Mg/m^3)	1.818	1.843	1.750
μ (mm^{-1})	4.144	4.131	3.912
Range of transm. factor	0.71–0.35	0.76–0.27	0.70–0.36
No. of unique data	5300	5473	11532
No. of parameters refined	289	317	596
$R1[I>2\sigma I]$	0.0376	0.0521	0.0439
*wR*2 (all data)	0.0924	0.1384	0.1163
Residuals (eÅ^{-3})	1.323, −1.052	1.416, −1.106	1.243, −0.635

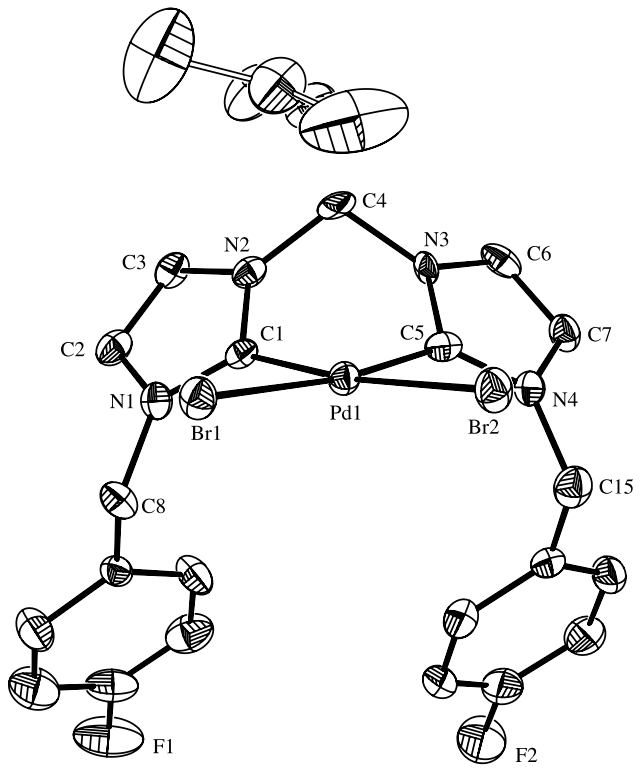


Figure 13. A drawing of the structure of **5c**·0.5DMF. Hydrogen atoms are omitted for clarity.

Table 10. Selected bond lengths (Å) and angles (°) for **5b**–**5d**[a]

	5b	**5c**	**5d**
Pd(1)–C(1)	1.975(4)	1.962(7)	1.962(7)
Pd(1)–C(5)	1.985(4)	1.986(7)	1.986(7)
Pd(1)–Br(1)	2.4767(10)	2.4830(9)	2.4888(9)
Pd(1)–Br(2)	2.4826(10)	2.4888(9)	2.4830(9)
N(1)–C(1)	1.336(6)	1.351(8)	1.351(8)
N(1)–C(2)	1.391(6)	1.400(8)	1.400(8)
N(2)–C(1)	1.357(6)	1.371(8)	1.371(8)
N(2)–C(3)	1.381(6)	1.380(8)	1.380(8)
N(2)–C(4)	1.455(6)	1.469(9)	1.469(9)
N(3)–C(5)	1.357(5)	1.363(8)	1.363(8)
N(3)–C(6)	1.369(5)	1.377(9)	1.377(9)
N(3)–C(4)	1.456(5)	1.464(8)	1.464(8)
N(4)–C(5)	1.330(5)	1.339(8)	1.339(8)
N(4)–C(7)	1.384(6)	1.399(8)	1.399(8)
C(2)–C(3)	1.332(7)	1.344(10)	1.344(10)
C(6)–C(7)	1.332(6)	1.335(10)	1.335(10)
C(1)–Pd(1)–C(5)	84.58(17)	84.2(3)	84.2(3)
C(1)–Pd(1)–Br(1)	173.13(13)	92.23(19)	92.23(19)
C(5)–Pd(1)–Br(1)	91.39(13)	172.87(19)	172.87(19)
C(1)–Pd(1)–Br(2)	92.77(12)	173.40(19)	173.40(19)
C(5)–Pd(1)–Br(2)	174.41(12)	92.4(2)	92.4(2)
Br(1)–Pd(1)–Br(2)	90.76(4)	90.55(3)	90.55(3)
C(1)–N(1)–C(2)	109.8(4)	110.9(6)	110.9(6)
C(1)–N(2)–C(3)	111.1(4)	111.2(6)	111.2(6)
C(1)–N(2)–C(4)	122.2(4)	121.4(5)	121.4(5)
C(3)–N(2)–C(4)	126.6(4)	127.2(5)	127.2(5)
C(5)–N(3)–C(6)	111.1(4)	110.5(6)	110.5(6)
C(5)–N(3)–C(4)	121.7(3)	122.3(5)	122.3(5)
C(5)–N(4)–C(7)	110.8(4)	109.8(6)	109.8(6)
C(6)–N(3)–C(4)	127.1(4)	127.2(5)	127.2(5)
N(1)–C(1)–N(2)	105.2(4)	104.2(5)	104.2(5)
N(1)–C(1)–Pd(1)	134.5(3)	134.4(5)	134.4(5)
N(2)–C(1)–Pd(1)	120.3(3)	121.4(5)	121.4(5)
C(3)–C(2)–N(1)	108.1(4)	106.7(6)	106.7(6)
C(2)–C(3)–N(2)	105.7(4)	106.9(6)	106.9(6)
N(2)–C(4)–N(3)	108.3(3)	107.9(5)	107.9(5)
N(4)–C(5)–N(3)	104.6(4)	105.5(6)	105.5(6)
N(4)–C(5)–Pd(1)	135.1(3)	134.0(5)	134.0(5)

[a] Only one independent molecule of **5d** is listed.

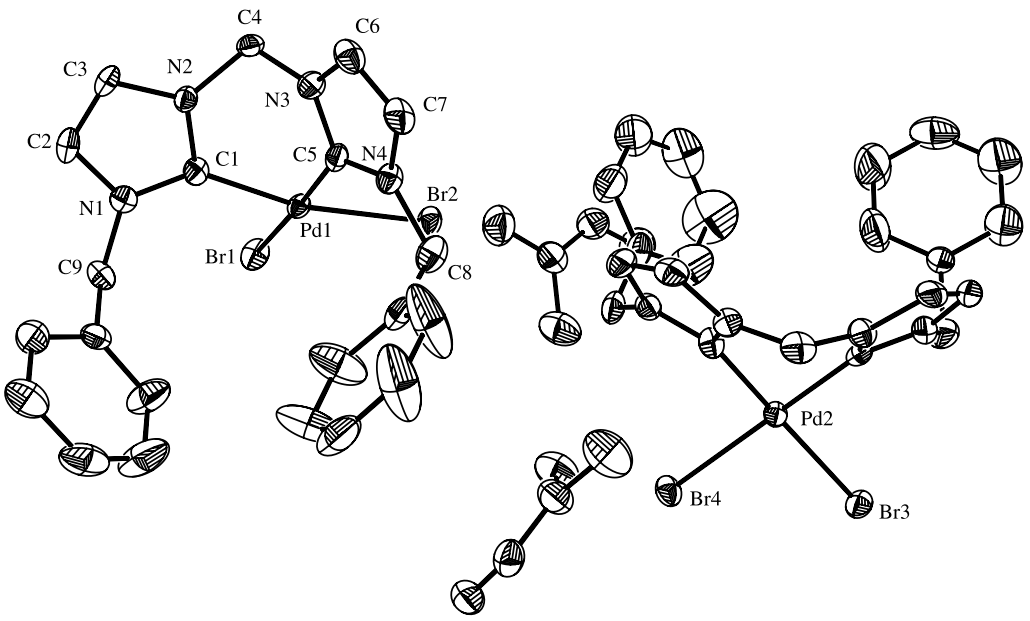
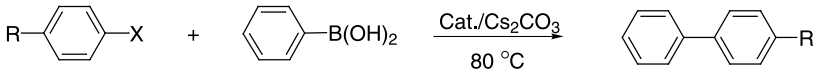


Figure 14. A drawing of the structure of **5d**·DMF showing the two independent molecules and incorporated DMF molecules in the asymmetric unit. Hydrogen atoms are omitted for clarity.

Table 11. Pd-catalyzed Suzuki coupling reaction between phenylboronic acid and aryl bromides[a]



Entry	Catalyst	X	R	Time (h)	Yield (%)	Entry	Catalyst	X	R	Time (h)	Yield (%)
1	**5a**	Br	$COCH_3$	1	74[b]	28	**3f**[c]	Br	H	1	91[d]
2	**5b**	Br	$COCH_3$	1	72[b]	29	**3g**[c]	Br	H	1	64[d]
3	**5c**	Br	$COCH_3$	1	69[b]	30	**5a**	Br	OMe	2	87[d]
4	**5d**	Br	$COCH_3$	1	79[b]	31	**5b**	Br	OMe	2	85[d]
5	**5e**	Br	$COCH_3$	1	90[b]	32	**5c**	Br	OMe	2	86[d]
6	**5f**	Br	$COCH_3$	1	98[b]	33	**5d**	Br	OMe	2	98[d]
7	**5g**	Br	$COCH_3$	1	62[b]	34	**5e**	Br	OMe	2	96[d]
8	**6a**	Br	$COCH_3$	1	100[b]	35	**5f**	Br	OMe	2	83[d]
9	**6b**	Br	$COCH_3$	1	100[b]	36	**5g**	Br	OMe	2	82[d]
10	**6c**	Br	$COCH_3$	1	100[b]	37	**6a**	Br	OMe	2	81[d]
11	**6d**	Br	$COCH_3$	1	100[b]	38	**6b**	Br	OMe	2	84[d]
12	**6e**	Br	$COCH_3$	0.5	95[b]	39	**6c**	Br	OMe	2	81[d]
13	**6e**	Br	$COCH_3$	1	100[b]	40	**6d**	Br	OMe	2	75[d]
14	**3f**[c]	Br	$COCH_3$	1	88[b]	41	**6e**	Br	OMe	2	86[d]
15	**3g**[c]	Br	$COCH_3$	1	64[b]	42	**3f**[c]	Br	OMe	2	89[d]
16	**5a**	Br	H	1	88[d]	43	**3g**[c]	Br	OMe	2	50[d]
17	**5b**	Br	H	1	97[d]						
18	**5c**	Br	H	1	95[d]						
19	**5d**	Br	H	1	79[d]						
20	**5e**	Br	H	1	90[d]						
21	**5f**	Br	H	1	88[d]						
22	**5g**	Br	H	1	84[d]						
23	**6a**	Br	H	1	78[d]						
24	**6b**	Br	H	1	78[d]						
25	**6c**	Br	H	1	97[d]						
26	**6d**	Br	H	1	84[d]						
27	**6e**	Br	H	1	89[d]						

[a] Reaction condition: 1 mmol of aryl bromide, 1.5 mmol of phenylboronic acid, 2.0 mmol of Cs_2CO_3, 0.5 mol % of Pd catalyst, 3 mL of 1,4-dioxane.
[b] Determined by ^1H NMR.
[c] In situ catalyst of imidazolium salt/$Pd(OAc)_2$.
[d] Isolated yield.

series are rather insensitive towards different substitutions on the benzyl and naphthylmethyl groups (for example, entries 1–5, 8–13 and 37–41, etc). Although previous investigator, had shown that steric bulkiness on bis(imidazolium) salts are essential for high catalytic activity,[6] our results show that methylene-bridged bis(carbene) ligands with *N*-methyl or mesityl substitutions, with the exception of 4-bromoacetophenone as substrate (entries 6–7), essentially gave similar activities (entries 21–22 and 35–36). Interestingly, even though, we were not able to prepare Pd(II) complexes with **3f**, in situ catalyst employing $Pd(OAc)_2$/**3f** gave comparable activities relative to other preformed complexes (entries 14, 28 and 42), suggesting a mono-carbene complex with a pendant imidazolium arm might be involved.[3a] The combination of $Pd(OAc)_2$/**3g** gave the lowest activities (entries 15, 29 and 43).

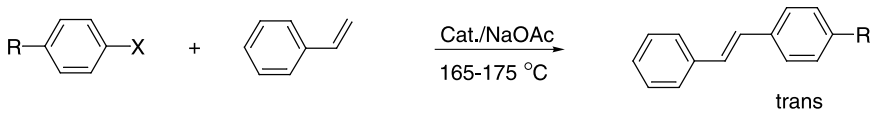
2.7. Heck coupling

The catalytic performance of the two series of Pd(II) complexes was also tested in the Heck coupling reaction of aryl bromides and styrene. As seen in Table 12, both complexes **5** and **6** are highly efficient. Entries 7, 14, 21, and 41 clearly shows that steric bulkiness on the nitrogen atoms are essential for high activities as the two bis(carbene) ligands with *N*-methyl groups gave the poorest results. Both complexes **5** and **6** were able to activate aryl chlorides but much longer reaction time and high catalysts loading were required (entries 42–45).

3. Conclusions

We have successfully prepared series of methylene and ethylene-bridged bis(imidazolium) halides employing substituted *N*-benzyl/naphthylmethyl imidazoles. The corresponding palladium(II) bis(*N*-heterocyclic carbene) complexes were also prepared by the $Pd(OAc)_2$ protocol. Crystallographic analysis of the palladium complexes with ethylene-bridged bis(carbene) shows that the seven-member palladacycles are conformationally more flexible compared with those of six-member analogs. The crystallographic determination on **4e** also reveals a possible conformational change induced by the presence of hydrogen bonding with the incorporated water molecule in the asymmetric unit. Even though Pd(II) bis(carbene) complexes are less reactive than those based on monodentate carbene ligands,[2] we demonstrated that the seven-member palladacycles are equally efficient with the six-member analogs in Suzuki and Heck coupling reactions. This finding indicates that the seven-member palladacycles can be a viable structural motif in the catalytic C–C coupling reactions and therefore opens up possibilities in the design of chelating ligands based on *N*-heterocyclic carbene.

Table 12. Pd-catalyzed Heck coupling reaction between styrene and aryl halides[a]



Entry	Catalyst	X	R	Time (h)	Yield (%)	Entry	Catalyst	X	R	Time (h)	Yield (%)
1	**5a**	Br	$COCH_3$	1	100[b]	28	**5a**	Br	OMe	4	89[b]
2	**5b**	Br	$COCH_3$	1	100[b]	29	**5b**	Br	OMe	4	87[b]
3	**5c**	Br	$COCH_3$	1	100[b]	30	**5c**	Br	OMe	4	86[b]
4	**5d**	Br	$COCH_3$	1	100[b]	31	**5d**	Br	OMe	4	91[b]
5	**5e**	Br	$COCH_3$	1	100[b]	32	**5e**	Br	OMe	4	92[b]
6	**5f**	Br	$COCH_3$	1	100[b]	33	**5f**	Br	OMe	4	86[b]
7	**5g**	Br	$COCH_3$	2	34[b]	34	**5g**	Br	OMe	4	43[b]
8	**6a**	Br	$COCH_3$	1	100[b]	35	**6a**	Br	OMe	4	88[b]
9	**6b**	Br	$COCH_3$	1	100[b]	36	**6b**	Br	OMe	2	62[b]
10	**6c**	Br	$COCH_3$	1	100[b]	37	**6c**	Br	OMe	2	79[b]
11	**6d**	Br	$COCH_3$	1	100[b]	38	**6d**	Br	OMe	4	90[b]
12	**6e**	Br	$COCH_3$	1	100[b]	39	**6e**	Br	OMe	4	90[b]
13	**3f**[c]	Br	$COCH_3$	1	100[b]	40	**3f**[c]	Br	OMe	4	57[b]
14	**3g**[c]	Br	$COCH_3$	1	59[b]	41	**3g**[c]	Br	OMe	4	9[b]
15	**5a**	Br	H	1	100[d]	42	**5e**[e]	Cl	Me	24	68[b]
16	**5b**	Br	H	1	100[d]	43	**6e**[e]	Cl	Me	24	72[b]
17	**5c**	Br	H	3	100[d]	44	**5e**[e]	Cl	$COCH_3$	24	81[b]
18	**5d**	Br	H	3	100[d]	45	**6e**[e]	Cl	$COCH_3$	24	96[b]
19	**5e**	Br	H	1	100[d]						
20	**5f**	Br	H	1	100[d]						
21	**5g**	Br	H	2	44[d]						
22	**6a**	Br	H	1	100[d]						
23	**6b**	Br	H	1	100[d]						
24	**6c**	Br	H	2	100[d]						
25	**6d**	Br	H	2	100[d]						
26	**6e**	Br	H	1	100[d]						
27	**3f**[c]	Br	H	1	100[d]						

[a] Reaction condition: 1 mmol of aryl halides, 1.4 mmol of styrene, 1.1 mmol of NaOAc, 0.5 mol% of Pd catalyst, 5 mL of DMA.
[b] Determined by ^1H NMR.
[c] In situ catalyst of imidazolium salt/$Pd(OAc)_2$.
[d] Isolated yield.
[e] 3 mol % of Pd catalyst.

4. Experimental

4.1. General procedure

All reactions were performed under a dry nitrogen atmosphere using standard Schlenk technique. Toluene and THF were dried by refluxing over sodium benzophenone ketyl. Dichloromethane and DMSO were dried by refluxing over calcium hydride. All solvents were distilled and stored in solvent reservoirs, which contained 4 Å molecular sieves, and purged with nitrogen. ^1H and $^{13}C\{^1H\}$ NMR spectra were recorded on a Bruker AMX-300 spectrometer. Chemical shifts for ^1H and ^{13}C spectra were recorded in ppm relative to residual proton of $CDCl_3$ (^1H: δ 7.24; ^{13}C: δ 77.0) and DMSO-d_6 (^1H: δ 2.50; ^{13}C: δ 39.5). Elemental analyses were performed on a Heraeus CHN-OS Rapid Elemental Analyzer at Instrument Center, National Chung Hsing University, Taiwan. 1-Benzyl-1*H*-imidazole,[15] 1-(4-fluorobenzyl)-1*H*-imidazole,[16] 1-(4-methoxybenzyl)-1*H*-imidazole,[15] and 1-(3-methoxybenzyl)-1*H*-imidazole[9] were previously reported and synthesized with an improved procedure with higher yields.

4.2. Preparation of crystals

Crystals suitable for X-ray diffraction were obtained by the following procedure. A sample of compound (ca. 5 mg) was dissolved in minimum amount of DMF (ca. 1 mL). The solution was filtered and placed in a 2 mL vial. The vial was then loosely capped and placed inside a 20 mL scintillation vial containing ca. 5 mL of diethyl ether. Crystals formed after the system stood undisturbed for 1–2 d.

4.3. X-ray data collection

The crystal was removed from the vial with a small amount of mother liquor and immediately coated with silicon grease on a weighting paper. A suitable crystal was mounted on a glass fiber with silicone grease and placed in the cold stream of a Bruker SMART CCD with graphite monochromated Mo K_α radiation (λ=0.71073 Å) at 150(2) K (**2a** was collected at 293(2) K). A full sphere of data was connected. No decay was observed in 50 duplicate frames at the end of the data collection.

4.4. Solution and structure refinements

Calculations for the structures were performed using SHELXS-97 and SHELXL-97. Tables of neutral atom scattering factors, f′ and f″, and absorption coefficient are from a standard source.[17] All atoms except hydrogen atoms were refined anisotropically. All hydrogen atoms were located in difference Fourier maps and included through the use of a riding model. Drawings of molecules were obtained

using SHELXP-97 with 50% probability displacement ellipsoids for the non-hydrogen atoms. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 227255-227265. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax:+44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.4.1. 1-(3-Methoxybenzyl)-1*H*-imidazole (1b). A mixture of imidazole (3.26 g, 0.048 mol), *p*-methoxylbenzyl chloride (5.0 mL, 0.048 mol), and NaH (4.61 g, 0.19 mol) was stirred in 30 mL of THF under reflux overnight. The solvent was removed completely under vacuum. Water (30 mL) and dichloromethane (30 mL) were added. The organic layer was thoroughly washed with water two more times and then separated. The solvent was removed completely under vacuum to give an orange liquid, which can be used without further purification. Yield: 5.1 g, 56%. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 4.88 (s, 2H, CH_2), 6.49 (s, 1H, 2-C*H*), 6.56 (d, $^3J_{HH}$=7.5 Hz, 1H, 4-C*H*), 6.67 (dd, $^3J_{HH}$=8.2 Hz, $^4J_{HH}$=2.3 Hz, 1H, 6-C*H*), 6.90 (s, 1H, imi-*H*), 6.72 (s, 1H, imi-*H*), 7.08 (t, $^3J_{HH}$=8.0 Hz, 1H, 5-C*H*), 7.35 (s, 1H, NC*H*N). ^{13}C{^{1}H} NMR (75.48 MHz, $CDCl_3$): δ 50.1 (Ar*C*H$_2$N), 54.8 (O*C*H$_3$), 112.7, 113.0, 119.1, 119.2, 129.2, 129.7, 137.1, 137.7, 159.7 (Ar-*C*, N*C*HN, imi-*C*).

4.4.2. 1-Naphthalen-1-ylmethyl-1*H*-imidazole (1e). The procedure follows that of **1b**. A brown viscous liquid was obtained. Yield: 99%. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 5.46 (s, 2H, CH_2), 6.89 (s, 1H, imi-*H*), 7.08 (s, 1H, imi-*H*), 7.13 (d, $^3J_{HH}$=7.1 Hz, 1H, Ar-*H*), 7.39–7.53 (m, 4H, NC*H*N, Ar-*H*), 7.82–7.88 (m, 3H, Ar-*H*). ^{13}C{^{1}H} NMR (75.48 MHz, $CDCl_3$): δ 48.1 (Ar*C*H$_2$N), 119.3 (imi-*C*), 122.2 (imi-*C*), 125.8, 126.0, 126.7, 128.6, 128.8, 128.9, 129.3, 130.5, 131.4, 133.5 (Ar-*C*), 137.3 (N*C*HN).

4.5. A typical procedure for the preparation of compound 2

A mixture of **1a** (0.50 g, 2.7 mmol) in neat dibromomethane (1.9 mL) was stirred at 70–80 °C overnight. The white solid formed was filtered, washed with THF and dried under vacuum.

4.5.1. 1,1′-Di(4-methoxybenzyl)-3,3′-methylenediimidazolium dibromide (2a). Yield: 32%. Anal. calcd for $C_{23}H_{26}Br_2N_4O_2$: C, 50.20; H, 4.76; N, 10.18. Found: C, 50.34; H, 4.95; N, 10.45. Mp 249 °C. ^{1}H NMR (300.13 MHz, DMSO-d_6): δ 3.77 (s, 6H, OCH_3), 5.41 (s, 4H, ArCH_2N), 6.65 (s, 2H, NCH_2N), 7.00 (d, $^3J_{HH}$=8.7 Hz, 4H, CH_{meta}), 7.44 (d, $^3J_{HH}$=8.7 Hz, 4H, CH_{ortho}), 7.88 (s, 2H, imi-*H*), 8.05 (s, 2H, imi-*H*), 9.56 (s, 2H, NC*H*N). ^{13}C{^{1}H} NMR (75.48 MHz, DMSO-d_6): δ 51.8 (Ar*C*H$_2$N), 55.2 (O*C*H$_3$), 58.2 (N*C*H$_2$N), 114.3 (*C*$_{meta}$), 122.4 (imi-*C*), 123.9 (imi-*C*), 125.8 (*C*$_{ipso}$), 130.4 (*C*$_{ortho}$), 137.3 (N*C*HN), 159.6 (*C*$_{para}$).

4.5.2. 1,1′-Di(3-methoxybenzyl)-3,3′-methylenediimidazolium dibromide (2b). Yield: 36%. Anal. calcd for $C_{23}H_{26}Br_2N_4O_2$: C, 50.20; H, 4.76; N, 10.18. Found: C, 50.03; H, 5.03; N, 9.98. Mp 238 °C. ^{1}H NMR (300.13 MHz, DMSO-d_6): δ 3.77 (s, 6H, OCH_3), 5.48 (s, 4H, ArCH_2N), 6.72 (s, 2H, NCH_2N), 6.98–7.05 (m, 4H, 4-, 6-CH), 7.10 (s, 2H, 2-CH), 7.36 (virtual t, $^3J_{HH}$=7.8 Hz, 2H, 5-C*H*), 7.94 (s, 2H, imi-*H*), 8.12 (s, 2H, imi-*H*), 9.70 (s, 2H, NC*H*N). ^{13}C{^{1}H} NMR (75.48 MHz, DMSO-d_6): δ 51.7 (Ar*C*H$_2$N), 54.8 (O*C*H$_3$), 57.8 (N*C*H$_2$N), 113.7, 114.0 (2-, 6-*C*), 120.2 (4-*C*), 122.0 (imi-*C*), 122.7 (imi-*C*), 129.7 (5-*C*), 135.0 (1-*C*), 137.2 (N*C*HN), 159.1 (3-*C*).

4.5.3. 1,1′-Di(4-fluorobenzyl)-3,3′-methylenediimidazolium dibromide (2c). Yield: 43%. Mp 281 °C (dec). ^{1}H NMR (300.13 MHz, DMSO-d_6): δ 5.52 (s, 4H, ArCH_2N), 6.72 (s, 2H, NCH_2N), 7.30 (virtual t, $^3J_{HF}$=$^3J_{HH}$=8.6 Hz, 4H, CH_{meta}), 7.58 (dd, $^3J_{HH}$=8.4 Hz, $^4J_{HF}$=5.4 Hz, CH_{ortho}), 7.92 (s, 2H, imi-*H*), 8.12 (s, 2H, imi-*H*), 9.68 (s, 2H, NC*H*N). ^{13}C{^{1}H} NMR (75.48 MHz, DMSO-d_6): δ 51.4 (s, Ar*C*H$_2$N), 58.2 (s, N*C*H$_2$N), 115.8 (d, $^2J_{CF}$= 21.7 Hz, *C*$_{meta}$), 122.5 (s, imi-*C*), 123.0 (s, imi-*C*), 130.3 (d, $^4J_{CF}$=2.9 Hz, *C*$_{ipso}$), 131.1 (d, $^3J_{CF}$=8.5 Hz, *C*$_{ortho}$), 137.6 (s, N*C*HN), 162.3 (d, $^1J_{CF}$=245.9 Hz, *C*F).

4.5.4. 1,1′-Dibenzyl-3,3′-methylenediimidazolium dibromide (2d). Yield: 81%. Anal. calcd for $C_{21}H_{22}Br_2N_4$: C, 51.45; H, 4.52; N, 11.43. Found: C, 51.25; H, 4.69; N, 11.25. Mp 278–280 °C. ^{1}H NMR (300.13 MHz, DMSO-d_6): δ 5.54 (s, 4H, PhCH_2N), 6.76 (s, 2H, NCH_2N), 7.43–7.48 (m, 10H, Ph-*H*), 7.94 (s, 2H, imi-*H*), 8.16 (s, 2H, imi-*H*), 9.76 (s, 2H, NC*H*N). ^{13}C{^{1}H} NMR (75.48 MHz, DMSO-d_6): δ 52.3 (Ph*C*H$_2$N), 58.3 (N*C*H$_2$N), 122.5 (imi-*C*), 123.2 (imi-*C*), 128.7 (*C*$_{meta}$), 128.9 (*C*$_{para}$), 129.0 (*C*$_{ortho}$), 134.2 (*C*$_{ipso}$), 137.7 (N*C*HN).

4.5.5. 1,1′-Di(1-naphthalenemethyl)-3,3′-methylenediimidazolium dibromide (2e). Yield: 54%. Anal. calcd for $C_{29}H_{26}Br_2N_4$: C, 59.00; H, 4.44; N, 9.49. Found: C, 58.85; H, 4.71; N, 9.73. Mp 271–274 °C. ^{1}H NMR (300.13 MHz, DMSO-d_6): δ 6.04 (s, 4H, ArCH_2N), 6.68 (s, 2H, NCH_2N), 6.60–7.66 (m, 8H, Ar-*H*), 7.96–8.18 (m, 10H, Ar-*H* and imi-*H*), 9.67 (s, 2H, NC*H*N). ^{13}C{^{1}H} NMR (75.48 MHz, DMSO-d_6): δ 50.3 (Ar*C*H$_2$N), 58.3 (N*C*H$_2$N), 122.4 (imi-*C*), 123.0 (imi-*C*), 123.5, 125.6, 126.5, 127.3, 128.2, 128.9, 129.4, 129.9, 130.5, 133.4 (Ar-*C*), 137.9 (N*C*HN).

4.6. A typical procedure for the preparation of compound 3

A mixture of **1a** (4.0 g, 21.3 mmol) and 1,2-dibromoethane (0.92 mL, 10.7 mmol) was stirred in THF (30 mL) at reflux for 2 d. The white solid formed was filtered, washed with THF and dried under vacuum.

4.6.1. 1,1′-Di(4-methoxybenzyl)-3,3′-ethylenediimidazolium dibromide (3a). Yield: 33%. Anal. calcd for $C_{24}H_{28}Br_2N_4O_2$: C, 51.08; H, 5.00; N, 9.93. Found: C, 51.02; H, 5.05; N, 9.84. Mp 241–242 °C. ^{1}H NMR (300.13 MHz, DMSO-d_6): δ 3.73 (s, 6H, OCH_3), 4.74 (s, 4H, NCH_2), 5.33 (s, 4H, ArCH_2), 6.94 (d, $^3J_{HH}$=8.4 Hz, 4H, CH_{meta}), 7.35 (d, 4H, $^3J_{HH}$=8.4 Hz, CH_{ortho}), 7.68 (s, 2H, imi-*H*), 7.75 (s, 2H, imi-*H*), 9.33 (s, 2H, NC*H*N). ^{13}C{^{1}H} NMR (75.48 MHz, DMSO-d_6): δ 48.5 (N*C*H$_2$), 51.9 (Ar*C*H$_2$N), 55.5 (O*C*H$_3$), 114.6 (*C*$_{meta}$), 122.8 (imi-*C*), 123.0 (imi-*C*), 126.4 (*C*$_{ipso}$), 130.4 (*C*$_{ortho}$), 136.6 (N*C*HN), 159.8 (*C*$_{para}$).

4.6.2. 1,1′-Di(3-methoxybenzyl)-3,3′-ethylenediimidazolium dibromide (3b). Yield: 51%. Anal. calcd for $C_{24}H_{28}Br_2N_4O_2$: C, 51.08; H, 5.00; N, 9.93. Found: C, 51.11; H, 5.10; N, 9.90. Mp 205–207 °C. ^{1}H NMR (300.13 MHz, DMSO-d_6): δ 3.77 (s, 6H, OCH_3), 4.81 (s, 4H, NCH_2), 5.43 (s, 4H, ArCH_2N), 6.96 (virtual t, $^3J_{HH}$=7.4 Hz, 4H, 4-, 6-C*H*), 7.08 (s, 2H, 2-C*H*), 7.33 (virtual t, $^3J_{HH}$=7.4 Hz, 2H, 5-C*H*), 7.80 (s, 2H, imi-*H*), 7.87 (s, 2H, imi-*H*), 9.48 (s, 2H, NC*H*N). ^{13}C{^{1}H} NMR (75.48 MHz, DMSO-d_6): δ 48.3 (N*C*H$_2$), 51.9 (Ar*C*H$_2$N), 55.3 (O*C*H$_3$), 114.3, 114.3 (2-, 6-*C*), 120.4 (4-*C*), 122.7 (2×imi-*C*), 130.1 (5-*C*), 135.9 (1-*C*), 136.7 (N*C*HN), 159.5 (3-*C*).

4.6.3. 1,1′-Di(4-fluorobenzyl)-3,3′-ethylenediimidazolium dibromide (3c). Yield: 49%. Mp 288–289 °C. ^{1}H NMR (300.13 MHz, DMSO-d_6): δ 4.78 (s, 4H, NCH_2), 5.47 (s, 4H, ArCH_2N), 7.26 (virtual t, $^3J_{HF}$=$^3J_{HH}$=8.3 Hz, 4H, CH_{meta}), 7.51 (virtual t, $^3J_{HH}$=$^4J_{HF}$=6.3 Hz, CH_{ortho}), 7.75 (s, 2H, imi-*H*), 7.85 (s, 2H, imi-*H*), 9.41 (s, 2H, NC*H*N). ^{13}C{^{1}H} NMR (75.48 MHz, DMSO-d_6): δ 48.4 (s, N*C*H$_2$), 51.2 (s, Ar*C*H$_2$N), 115.8 (d, $^2J_{CF}$=21.9 Hz, C_{meta}), 122.7 (s, imi-*C*), 122.9 (s, imi-*C*), 130.9 (d, $^3J_{CF}$=8.3 Hz, C_{ortho}), 136.7 (s, N*C*HN), 162.2 (d, $^1J_{CF}$=245.3 Hz, *C*F), C_{ipso} not observed.

4.6.4. 1,1′-Dibenzyl-3,3′-ethylenediimidazolium dibromide (3d). Yield: 52%. Anal. calcd for $C_{22}H_{24}Br_2N_4$: C, 52.40; H, 4.80; N, 11.11. Found: C, 52.36; H, 4.82; N, 11.20. Mp 259–264 °C. ^{1}H NMR (300.13 MHz, DMSO-d_6): δ 4.77 (s, 4H, NCH_2), 5.45 (s, 4H, PhCH_2N), 7.41 (s, 10H, Ph-*H*), 7.75 (s, 2H, imi-*H*), 7.84 (s, 2H, imi-*H*), 9.38 (s, 2H, NC*H*N). ^{13}C{^{1}H} NMR (75.48 MHz, DMSO-d_6): δ 48.4 (N*C*H$_2$), 52.0 (Ph*C*H$_2$N), 122.8 (2×imi-*C*), 128.3 (C_{meta}), 128.7 (C_{para}), 128.9 (C_{ortho}), 134.5 (C_{ipso}), 136.7 (N*C*HN).

4.6.5. 1,1′-Di(1-naphthalenemethyl)-3,3′-ethylenediimidazolium dibromide (3e). Yield: 35%. Anal. calcd for $C_{30}H_{28}Br_2N_4$: C, 59.62; H, 4.67; N, 9.27. Found: C, 59.58; H, 4.70; N, 9.31. Mp 242–244 °C. ^{1}H NMR (300.13 MHz, DMSO-d_6): δ 4.72 (s, 2H, NCH_2), 5.92 (s, 4H, ArCH_2N), 7.50–7.63 (m, 8H, Ar-*H*), 7.69 (s, 2H, imi-*H*), 7.78 (s, 2H, imi-*H*), 8.01–8.07 (m, 6H, Ar-*H*), 9.28 (s, 2H, NC*H*N). ^{13}C{^{1}H} NMR (75.48 MHz, DMSO-d_6): δ 48.5 (N*C*H$_2$), 50.1 (Ar*C*H$_2$N), 122.7 (imi-*C* or Ar-*C*), 122.91 (imi-*C* or Ar-*C*), 122.99 (imi-*C* or Ar-*C*), 125.63, 126.44, 127.25, 127.85, 128.9, 129.7, 130.4, 130.4, 133.4 (Ar-*C*), 136.9 (N*C*HN).

4.6.6. 1,1′-Di(mesityl)-3,3′-ethylenediimidazolium dibromide (3f). Yield: 45%. Anal. calcd for $C_{26}H_{32}Br_2N_4$: C, 55.73; H, 5.76; N, 10.00. Found: C, 55.69; H, 5.72; N, 10.01. Mp >320 °C. ^{1}H NMR (300.13 MHz, DMSO-d_6): δ 1.98 (s, 12H, *o*-CH_3), 2.33 (s, 6H, *p*-CH_3), 4.98 (s, 4H, CH_2), 7.14 (s, 4H, *m*-C*H*), 8.00 (s, 2H, imi-*H*), 8.06 (s, 2H, imi-*H*), 9.51 (s, 2H, NC*H*N). ^{13}C{^{1}H} NMR (75.48 MHz, DMSO-d_6): δ 17.0(*o*-*C*H$_3$), 20.6 (*o*-*C*H$_3$), 48.7 (*C*H$_2$), 123.3 (imi-*C*), 124.4 (imi-*C*), 129.3 (C_{ortho}), 130.9 (C_{para}), 134.1 (C_{meta}), 138.0 (N*C*HN), 140.5 (C_{ipso}).

4.6.7. 1,1′-Di(methyl)-3,3′-ethylenediimidazolium dibromide (3g). Yield: 79%. Anal. calcd for $C_{10}H_{16}Br_2N_4$: C, 34.12; H, 4.58; N, 15.91. Found: C, 34.23; H, 4.60; N, 15.89. Mp 230–234 °C. ^{1}H NMR (300.13 MHz, DMSO-d_6): δ 3.87 (s, 6H, CH_3), 4.78 (s, 4H, CH_2), 7.76 (s, 4H, imi-*H*), 9.28 (s, 2H, NC*H*N). ^{13}C{^{1}H} NMR (75.48 MHz, DMSO-d_6): δ 33.6 (*C*H$_3$), 48.2 (*C*H$_2$), 122.3 (imi-*C*), 123.7 (imi-*C*), 137.1 (N*C*HN).

4.7. A typical procedure for the preparation of compound 4

A mixture of **1a** (3.2 g, 16.9 mmol) and 1,2-dichloroethane (0.67 mL, 0.84 mmol) was stirred in THF (30 mL) at reflux for 2 d. The solvent was removed completely under vacuum. Dichloromethane was added to the residue to give a white solid, which was filtered and dried under vacuum.

4.7.1. 1,1′-Di(4-methoxybenzyl)-3,3′-ethylenediimidazolium dichloride (4a). Yield: 17%. Anal. calcd for $C_{24}H_{28}Cl_2N_4O_2$: C, 60.63; H, 5.94; N, 11.78. Found: C, 60.61; H, 5.89; N, 11.68. Mp 265–268 °C. ^{1}H NMR (300.13 MHz, DMSO-d_6): δ 3.75 (s, 3H, OCH_3), 4.77 (s, 4H, CH_2), 5.35 (s, 4H, CH_2), 6.96 (d, $^3J_{HH}$=8.6 Hz, 4H, CH_{meta}), 7.38 (d, $^3J_{HH}$=8.6 Hz, 4H, CH_{ortho}), 7.76 (s, 2H, imi-*H*), 7.79 (s, 2H, imi-*H*), 9.53 (s, 2H, NC*H*N).

4.7.2. 1,1′-Di(3-methoxybenzyl)-3,3′-ethylenediimidazolium dichloride (4b). Yield: 35%. Anal. calcd for $C_{24}H_{28}Cl_2N_4O_2$: C, 60.63; H, 5.94; N, 11.78. Found: C, 60.61; H, 5.90; N, 11.68. Mp 108–110 °C. ^{1}H NMR (300.13 MHz, DMSO-d_6): δ 3.77 (s, 6H, OCH_3), 4.80 (s, 4H, NCH_2), 5.40 (s, 4H, ArCH_2N), 6.95 (d, $^3J_{HH}$=7.7 Hz, 4H, 4-, 6-C*H*), 7.06 (s, 2H, 2-C*H*), 7.33 (t, $^3J_{HH}$=7.7 Hz, 2H, 5-C*H*), 7.80 (s, 2H, imi-*H*), 7.82 (s, 2H, imi-*H*), 9.59 (s, 2H, NC*H*N).

4.7.3. 1,1′-Di(4-fluorobenzyl)-3,3′-ethylenediimidazolium dichloride (4c). Yield: 8%. Mp 263–265 °C. ^{1}H NMR (300.13 MHz, DMSO-d_6): δ 4.79 (s, 4H, NCH_2), 5.45 (s, 4H, ArCH_2N), 7.25 (virtual t, $^3J_{HF}$=$^3J_{HH}$=8.9 Hz, 4H, CH_{meta}), 7.51 (virtual t, $^3J_{HH}$=$^4J_{HF}$=7.0 Hz, CH_{ortho}), 7.79 (s, 2H, imi-*H*), 7.83 (s, 2H, imi-*H*), 9.61 (s, 2H, NC*H*N).

4.7.4. 1,1′-Dibenzyl-3,3′-ethylenediimidazolium dichloride (4d). Yield: 34%. Anal. calcd for $C_{22}H_{24}Cl_2N_4$: C, 63.62; H, 5.82; N, 13.49. Found: C, 63.76; H, 6.03; N, 13.97. Mp 260 °C. ^{1}H NMR (300.13 MHz, DMSO-d_6): δ 4.82 (s, 4H, NCH_2), 5.46 (s, 4H, PhCH_2N), 7.41 (s, 10H, Ph-*H*), 7.84 (s, 4H, imi-*H*), 9.65 (s, 2H, NC*H*N). ^{13}C{^{1}H} NMR (75.48 MHz, DMSO-d_6): δ 48.3 (N*C*H$_2$), 52.0 (Ph*C*H$_2$N), 122.7 (imi-*C*), 122.9 (imi-*C*), 128.3 (C_{meta}), 128.7 (C_{para}), 128.9 (C_{ortho}), 134.6 (C_{ipso}), 137.0 (N*C*HN).

4.7.5. 1,1′-Di(1-naphthalenemethyl)-3,3′-ethylenediimidazolium dichloride (4e). Yield: 44%. Anal. calcd for $C_{30}H_{28}Cl_2N_4$: C, 69.90; H, 5.47; N, 10.87. Found: C, 69.65; H, 5.53; N, 10.61. Mp 248 °C (dec). ^{1}H NMR (300.13 MHz, DMSO-d_6): δ 4.72 (s, 2H, NCH_2), 5.91 (s, 4H, ArCH_2N), 7.48–7.62 (m, 8H, Ar-*H*), 7.70 (s, 2H, imi-*H*), 7.77 (s, 2H, imi-*H*), 8.01–8.07 (m, 6H, Ar-*H*), 9.37 (s, 2H, NC*H*N). ^{13}C{^{1}H} NMR (75.48 MHz, DMSO-d_6): δ 48.4 (N*C*H$_2$), 50.0 (Ar*C*H$_2$N), 122.7, 122.9, 123.0 (imi-*C*, Ar-*C*), 125.6, 126.4, 127.2, 127.7, 128.9, 129.7, 129.7, 130.3, 133.4 (Ar-*C*), 137.0 (N*C*HN).

4.8. A typical procedure for the preparation of compound 5

A mixture of **2a** (0.5 g, 0.88 mmol) and $Pd(OAc)_2$ (0.20 g, 0.88 mmol) in ca. 5 mL of DMSO was heated at 50 °C for 2 h and then slowly to 110 °C for 3 h. The solvent was then removed completely under vacuum. The residue was added with dichloromethane to produce a white solid, which was filtered and dried under vacuum.

4.8.1. {1,1′-Di(4-methoxybenzyl)-3,3′-methylenediimidazolin-2,2′diylidene}palladium(II) dibromide (5a). Yield: 82%. Anal. calcd for $C_{23}H_{24}Br_2N_4O_2Pd$: C, 42.20; H, 3.69; N, 8.56. Found: C, 42.16; H, 3.82; N, 8.54. Mp 272 °C (dec). ^{1}H NMR (300.13 MHz, DMSO-d_6): δ 3.78 (s, 6H, OCH_3), 5.26 (d, $^2J_{HH}$=14.1 Hz, 2H, ArCH_aH$_b$N), 5.90–5.94 (br m, 2H, ArCH$_a$$H_b$N), 6.30–6.32 (m, 2H, NC$H_2$N), 6.85 (d, $^3J_{HH}$=8.4 Hz, 4H, CH_{meta}), 7.22 (s, 2H, imi-*H*), 7.29 (d, $^3J_{HH}$=8.4 Hz, 4H, CH_{ortho}), 7.56 (s, 2H, imi-*H*). ^{13}C{^{1}H} NMR (75.48 MHz, DMSO-d_6): δ 52.9 (Ar*C*H$_2$N), 54.9 (O*C*H$_3$), 62.5 (N*C*H$_2$N), 113.9 (C_{meta}), 121.6 (imi-*C*), 121.9 (imi-*C*), 128.3 (C_{ipso}), 129.6 (C_{ortho}), 158.3, (br, N*C*N), 158.9 (C_{para}).

4.8.2. {1,1′-Di(3-methoxybenzyl)-3,3′-methylenediimidazolin-2,2′diylidene}palladium(II) dibromide (5b). Yield: 82%. Anal. calcd for $C_{23}H_{24}Br_2N_4O_2Pd$: C, 42.20; H, 3.69; N, 8.56. Found: C, 41.97; H, 3.67; N, 8.46. Mp 291 °C (dec). ^{1}H NMR (300.13 MHz, DMSO-d_6): δ 3.71 (s, 6H, OCH_3), 5.36 (d, $^2J_{HH}$=14.4 Hz, 2H, ArCH_aH$_b$N), 5.84–5.89 (br m, 2H, ArCH$_a$$H_b$N), 6.34–6.36 (m, 2H, NC$H_2$N), 6.79–6.88 (m, 4H, 4-, 6-C*H*), 7.01 (s, 2H, 2-C*H*), 7.19 (virtual t, $^3J_{HH}$=8.0 Hz, 2H, 5-C*H*), 7.24 (s, 2H, imi-*H*), 7.59 (s, 2H, imi-*H*). ^{13}C{^{1}H} NMR (75.48 MHz, DMSO-d_6): δ 52.8 (Ar*C*H$_2$N), 54.5 (O*C*H$_3$), 62.2 (N*C*H$_2$N), 112.7, 113.7 (2-, 6-*C*), 119.5 (4-*C*), 121.4 (imi-*C*), 121.5 (imi-*C*), 129.2 (5-*C*), 137.3 (1-*C*), 158.8 (3-*C*), the carbene carbon was not observed.

4.8.3. {1,1′-Di(4-fluorobenzyl)-3,3′-methylenediimidazolin-2,2′diylidene}palladium(II) dibromide (5c). Yield: 85%. Mp 293 °C (dec). ^{1}H NMR (300.13 MHz, DMSO-d_6): δ 5.39 (d, $^2J_{HH}$=14.4 Hz, 2H, PhCH_aH$_b$N), 5.83–5.97 (br m, 2H, PhCH$_a$$H_b$N), 6.33–6.35 (m, 2H, NC$H_2$N), 7.12 (virtual t, $^3J_{HF}$=$^3J_{HH}$=8.7 Hz, 4H, CH_{meta}), 7.27 (s, 2H, imi-*H*), 7.37–7.39 (br m, 4H, CH_{ortho}), 7.60 (s, 2H, imi-*H*). ^{13}C{^{1}H} NMR (75.48 MHz, DMSO-d_6): δ 52.9 (s, Ar*C*H$_2$N), 63.1 (s, N*C*H$_2$N), 115.9 (d, $^2J_{CF}$=21.1 Hz, C_{meta}), 122.3 (s, imi-*C*), 123.6 (s, imi-*C*), 130.6 (d, $^3J_{CF}$=8.3 Hz, C_{ortho}), 133.2 (C_{ipso}), 157.1 (br, N*C*N), 161.9 (d, $^1J_{CF}$=243.8 Hz, *C*F).

4.8.4. {1,1′-Dibenzyl-3,3′-methylenediimidazolin-2,2′diylidene}palladium(II) dibromide (5d). Yield: 99%. Anal. calcd for $C_{21}H_{20}Br_2N_4Pd$: C, 42.42; H, 3.39; N, 9.42. Found: C, 42.40; H, 3.32; N, 9.50. Mp 282–284 °C (dec). ^{1}H NMR (300.13 MHz, DMSO-d_6): δ 5.35 (d, $^2J_{HH}$=14.7 Hz, 2H, PhCH_aH$_b$N), 5.94–5.98 (br m, 2H, PhCH$_a$$H_b$N), 6.34–6.36 (m, 2H, NC$H_2$N), 7.25 (s, 2H, imi-*H*), 7.31 (s, 10H, Ph-*H*), 7.61 (s, 2H, imi-*H*). ^{13}C{^{1}H} NMR (75.48 MHz, DMSO-d_6): δ 53.5 (Ph*C*H$_2$N), 62.6 (N*C*H$_2$N), 121.9 (imi-*C*), 122.1 (imi-*C*), 128.0 (C_{meta}), 128.7 (C_{ortho}), 136.5 (C_{ipso}), the C_{para} and carbene carbons were not observed.

4.8.5. {1,1′-Di(1-naphthalenemethyl)-3,3′-methylenediimidazolin-2,2′diylidene}palladium(II) dibromide (5e). Yield: 50%. Anal. calcd for $C_{29}H_{24}Br_2N_4Pd$: C, 50.14; H, 3.48; N, 8.06. Found: C, 50.05; H, 3.42; N, 8.11. Mp 292 °C (dec). ^{1}H NMR (300.13 MHz, DMSO-d_6): δ 5.97 (d, $^2J_{HH}$=14.7 Hz, 2H, ArCH_aH$_b$N), 6.35 (br m, 2H, PhCH$_a$$H_b$N), 6.31–6.35 (m, 2H, NC$H_2$N), 6.39–643 (d, $^2J_{HH}$=6.9 Hz, 2H, Ar-*H*), 7.15–7.20 (m, 4H, Ar-*H*, imi-*H*), 7.36–7.61 (m, 8H, Ar-*H*, imi-*H*), 7.87–7.96 (m, 4H, Ar-*H*), 8.23 (d, $^2J_{HH}$=7.8 Hz, 2H, Ar-*H*). ^{13}C{^{1}H} NMR (75.48 MHz, DMSO-d_6): δ 52.0 (Ar*C*H$_2$), 63.2 (N*C*H$_2$N), 123.4, 123.6, 125.9, 126.5, 127.1, 129.0, 130.9, 132.3, 133.7 (imi-*C*, Ar-*C*), 159.9 (br, N*C*N).

4.9. A typical procedure for the preparation of compound 6

A mixture of **3a** (0.50 g, 0.89 mmol) and $Pd(OAc)_2$ (0.20 g, 0.89 mmol) in 5 mL of DMSO was heated at 50 °C for 2 h and then slowly to 110 °C for 3 h. The solution was then filtered through a small column of Celite and the solvent was removed completely under vacuum. The residue was added with dichloromethane to produce a white solid, which was filtered and dried under vacuum.

4.9.1. {1,1′-Di(4-methoxybenzyl)-3,3′-ethylenediimidazolin-2,2′diylidene}palladium(II) dibromide (6a). Yield: 30%. Anal. calcd for $C_{24}H_{26}Br_2N_4O_2Pd$: C, 43.11; H, 3.92; N, 8.38. Found: C, 43.09; H, 3.95; N, 8.31. Mp 295–296 °C (dec). ^{1}H NMR (300.13 MHz, DMSO-d_6): δ 3.72 (s, 6H, OCH_3), 4.53–4.55 (br m, 2H, NCH_aH$_b$), 4.94 (d, $^2J_{HH}$=14.6 Hz, 2H, ArCH_aH$_b$N), 5.28 (br m, 2H, NCH$_a$$H_b$), 5.20–5.35 (d, $^2J_{HH}$=14.6 Hz, 2H, ArCH$_a$$H_b$N), 6.89 (d, $^3J_{HH}$=8.4 Hz, 4H, *CH*$_{meta}$), 7.10 (s, 2H, imi-*H*), 7.16 (d, $^3J_{HH}$=8.4 Hz, 4H, CH_{ortho}), 7.40 (s, 2H, imi-*H*). ^{13}C{^{1}H} NMR (75.48 MHz, DMSO-d_6): δ 46.9 (N*C*H$_2$), 52.6 (Ar*C*H$_2$N), 55.1 (O*C*H$_3$), 114.0 (C_{meta}), 122.2 (imi-*C*), 123.0 (imi-*C*), 128.1 (C_{ipso}), 129.6 (C_{ortho}), 157.1, (br, N*C*N), 159.0 (C_{para}).

4.9.2. {1,1′-Di(3-methoxybenzyl)-3,3′-ethylenediimidazolin-2,2′diylidene}palladium(II) dibromide (6b). Yield: 38%. Anal. calcd for $C_{24}H_{26}Br_2N_4O_2Pd$: C, 43.11; H, 3.92; N, 8.38. Found: C, 43.09; H, 3.91; N, 8.27. Mp 247 °C (dec). ^{1}H NMR (300.13 MHz, DMSO-d_6): δ 3.71 (s, 6H, OCH_3), 4.56–4.59 (br m, 2H, NCH_aH$_b$), 4.96 (d, $^2J_{HH}$=14.7 Hz, 2H, ArCH_aH$_b$N), 5.25–5.35 (br m, 2H, NCH$_a$$H_b$), 5.40 (d, $^2J_{HH}$=14.7 Hz, 2H, ArCH$_a$$H_b$N), 6.74 (d, $^3J_{HH}$=7.2 Hz, 2H, 4-C*H*), 6.82 (s, 2H, 2-C*H*), 6.90 (d, $^3J_{HH}$=7.2 Hz, 2H, 6-C*H*), 7.15 (s, 2H, imi-*H*), 7.26 (virtual t, $^3J_{HH}$=7.8 Hz, 2H, 5-C*H*), 7.43 (s, 2H, imi-*H*). ^{13}C{^{1}H} NMR (75.48 MHz, DMSO-d_6): δ 46.9 (N*C*H$_2$), 52.9 (Ar*C*H$_2$N), 55.1 (O*C*H$_3$), 112.2, 113.9 (2-, 6-*C*), 120.1 (4-*C*), 122.4 (imi-*C*), 123.2 (imi-*C*), 129.8 (5-*C*), 137.7 (1-*C*), 159.4 (3-*C*), the carbene carbon was not observed.

4.9.3. {1,1′-Di(4-fluorobenzyl)-3,3′-ethylenediimidazolin-2,2′diylidene}palladium(II) dibromide (6c). Yield: 22%. Mp 268 °C (dec). ^{1}H NMR (300.13 MHz, DMSO-d_6): δ 4.55–4.58 (br m, 2H, NCH_aH$_b$), 5.10 (d, $^2J_{HH}$=14.7 Hz, 2H, ArCH_aH$_b$N), 5.27–5.29 (br m, 2H, NCH$_a$$H_b$), 5.41 (d, $^2J_{HH}$=14.7 Hz, 2H, ArCH$_a$$H_b$N), 7.15–7.18 (m, 4H, C$H_{meta}$), 7.21 (s, 2H, imi-*H*), 7.27–7.31 (m, 4H, CH_{ortho}),

7.43 (s, 2H, imi-*H*). $^{13}C\{^1H\}$ NMR (75.48 MHz, DMSO-d_6): δ 47.0 (s, N*C*H_2), 52.4 (s, Ar*C*H_2N), 115.5 (d, $^2J_{CF}$=21.1 Hz, C_{meta}), 122.4 (s, imi-*C*), 123.4 (s, imi-*C*), 130.3 (d, $^3J_{CF}$=7.5 Hz, C_{ortho}), 132.5 (C_{ipso}), 157.2 (br, N*C*N), 161.9 (d, $^1J_{CF}$=243.8 Hz, *C*F).

4.9.4. {1,1′-Dibenzyl-3,3′-ethylenediimidazolin-2,2′diylidene}palladium(II) dibromide (6d). Yield: 50%. Anal. calcd for $C_{22}H_{22}Br_2N_4Pd$: C, 43.41; H, 3.65; N, 9.20. Found: C, 43.47; H, 3.69; N, 9.20. Mp 260–262 °C (dec). ^1H NMR (300.13 MHz, DMSO-d_6): δ 4.57–4.59 (br m, 2H, NC$H_a$$H_b$), 4.93 (d, $^2J_{HH}$=14.6 Hz, 2H, ArC$H_a$$H_b$N), 5.24–5.32 (br m, 2H, NC$H_a$$H_b$), 5.43 (d, $^2J_{HH}$=14.6 Hz, 2H, ArC$H_a$$H_b$N), 7.13–7.44 (m, 14H, imi-*H*, Ph-*C*). $^{13}C\{^1H\}$ NMR (75.48 MHz, DMSO-d_6):δ 47.3 (N*C*H_2), 53.4 (Ar*C*H_2N), 122.8 (imi-*C*), 123.9 (imi-*C*), 128.4 (C_{meta}), 129.1 (C_{ortho}), 136.7 (C_{ipso}), the C_{para} and carbene carbons were not observed.

4.9.5. {1,1′-Di(1-naphthalenemethyl)-3,3′-ethylenediimidazolin-2,2′diylidene}palladium(II) dibromide (6e). Yield: 46%. Anal. calcd for $C_{30}H_{26}Br_2N_4Pd$: C, 50.84; H, 3.70; N, 7.90. Found: C, 50.86; H, 3.69; N, 7.88. Mp 282–284 °C (dec). ^1H NMR (300.13 MHz, DMSO-d_6): δ 4.65–4.67 (br m, 2H, NC$H_a$$H_b$), 5.30–5.38 (br m, 4H, ArC$H_a$$H_bN, NCH_a$$H_b$), 5.84 (d, $^2J_{HH}$=15.0 Hz, 2H, ArC$H_a$$H_b$N), 6.76 (d, $^2J_{HH}$=6.9 Hz, 2H, Ar-*H*), 7.04 (s, 2H, imi-*H*), 7.39–7.60 (m, 8H, Ar-*H*, imi-*H*), 7.85–8.01 (m, 6H, Ar-*H*). $^{13}C\{^1H\}$ NMR (75.48 MHz, DMSO-d_6): δ 47.0 (N*C*H_2), 51.2 (Ar*C*H_2N), 122.6 (imi-*C*), 123.1 (Ar-*C* and imi-*C*), 125.4, 125.6, 126.2, 126.7, 128.5, 128.6, 130.4, 131.7, 133.2 (Ar-*C*), 157.9 (br, N*C*N).

4.10. A typical procedure for the preparation of compound 7

A mixture of **4a** (0.42 g, 0.89 mmol) and $Pd(OAc)_2$ (0.20 g, 0.89 mmol) in 3 mL of DMSO was heated at 50 °C for 2 h and then slowly to 110 °C for 2 h. The solution was then filtered through a small column of Celite and the solvent was removed completely under vacuum. The residue was added with THF to produce a white solid, which was filtered and dried under vacuum.

4.10.1. {1,1′-Di(4-methoxybenzyl)-3,3′-ethylenediimidazolin-2,2′diylidene}palladium(II) dichloride (7a). Yield: 45%. Anal. calcd for $C_{24}H_{26}Cl_2N_4O_2Pd$: C, 49.72; H, 4.52; N, 9.66. Found: C, 49.88; H, 4.32; N, 9.77. Mp 242–246 °C (dec). ^1H NMR (300.13 MHz, DMSO-d_6): δ 3.63 (s, 6H, OCH_3), 4.37–4.39 (br m, 2H, NC$H_a$$H_b$), 4.93 (d, $^2J_{HH}$=14.7 Hz, 2H, ArC$H_a$$H_b$N), 5.09–5.15 (br m, 2H, NC$H_a$$H_b$), 5.20 (d, $^2J_{HH}$=14.7 Hz, 2H, ArC$H_a$$H_b$N), 6.74 (d, $^3J_{HH}$=8.4 Hz, 4H, CH_{meta}), 6.95 (s, 2H, imi-*H*), 7.06 (d, $^3J_{HH}$=8.4 Hz, 4H, CH_{ortho}), 7.22 (s, 2H, imi-*H*).

4.10.2. {1,1′-Di(3-methoxybenzyl)-3,3′-ethylenediimidazolin-2,2′diylidene}palladium(II) dichloride (7b). Yield: 23%. Anal. calcd for $C_{24}H_{26}Cl_2N_4O_2Pd$: C, 49.72; H, 4.52; N, 9.66. Found: C, 49.69; H, 4.50; N, 9.62. Mp 242–246 °C (dec). ^1H NMR (300.13 MHz, DMSO-d_6): δ 3.71 (s, 6H, OCH_3), 4.54–4.57 (br m, 2H, NC$H_a$$H_b$), 5.10 (d, $^2J_{HH}$=14.7 Hz, 2H, ArC$H_a$$H_b$N), 5.26–5.29 (br m, 2H, NC$H_a$$H_b$), 5.42 (d, $^2J_{HH}$=14.7 Hz, 2H, ArC$H_a$$H_b$N), 6.72–6.92 (m, 6H, 4-C*H*, 2-C*H*, 6-C*H*), 7.15 (s, 2H, imi-*H*), 7.26 (virtual t, $^3J_{HH}$=7.8 Hz, 2H, 5-C*H*), 7.40 (s, 2H, imi-*H*).

4.10.3. {1,1′-Di(4-fluorobenzyl)-3,3′-ethylenediimidazolin-2,2′diylidene}palladium(II) dichloride (7c). Yield: 37%. Mp 268 °C (dec). ^1H NMR (300.13 MHz, DMSO-d_6): δ 4.53–4.56 (br m, 2H, NC$H_a$$H_b$), 5.22 (d, $^2J_{HH}$=14.6 Hz, 2H, ArC$H_a$$H_b$N), 5.28 (br s, 2H, NC$H_a$$H_b$), 5.41 (d, $^2J_{HH}$=14.6 Hz, 2H, ArC$H_a$$H_b$N), 7.15–7.21 (m, 6H, C$H_{meta}$, imi-*H*), 7.31–7.36 (m, 4H, CH_{ortho}), 7.42 (s, 2H, imi-*H*). $^{13}C\{^1H\}$ NMR (75.48 MHz, DMSO-d_6): δ 47.0 (s, N*C*H_2), 52.0 (s, Ar*C*H_2N), 115.3 (d, $^2J_{CF}$=21.1 Hz, C_{meta}), 122.2 (s, imi-*C*), 123.1 (s, imi-*C*), 130.3 (d, $^3J_{CF}$=7.5 Hz, C_{ortho}), 132.6 (C_{ipso}), 155.6 (N*C*N), 161.7 (d, $^1J_{CF}$=243.8 Hz, *C*F).

4.10.4. {1,1′-Dibenzyl-3,3′-ethylenediimidazolin-2,2′diylidene}palladium(II) dichloride (7d). Yield: 15%. Anal. calcd for $C_{22}H_{22}Cl_2N_4Pd$: C, 50.84; H, 4.27; N, 10.78. Found: C, 50.85; H, 4.30; N, 10.72. Mp 304 °C (dec). ^1H NMR (300.13 MHz, DMSO-d_6): δ 4.54–4.57 (br m, 2H, NC$H_a$$H_b$), 5.07 (d, $^2J_{HH}$=15.0 Hz, 2H, ArC$H_a$$H_b$N), 5.24–5.30 (br m, 2H, NC$H_a$$H_b$), 5.43 (d, $^2J_{HH}$=15.0 Hz, 2H, ArC$H_a$$H_b$N), 7.13 (s, 2H, imi-*H*), 7.21–7.23 (m, 6H, Ph-*H*), 7.33–7.35 (m, 6H, Ph-*H*), 7.42 (s, 2H, imi-*H*).

4.10.5. {1,1′-Di(1-naphthalenemethyl)-3,3′-ethylenediimidazolin-2,2′diylidene}palladium(II) dichloride (7e). Yield: 52%. Anal. calcd for $C_{30}H_{26}Cl_2N_4Pd$: C, 58.13; H, 4.23; N, 9.04. Found: C, 58.32; H, 4.29; N, 8.82. Mp 282 °C (dec). ^1H NMR (300.13 MHz, DMSO-d_6): δ 4.62–4.65 (br m, 2H, NC$H_a$$H_b$), 5.34–5.38 (br m, 4H, ArC$H_a$$H_bN, NCH_a$$H_b$), 5.89 (d, $^2J_{HH}$=15.6 Hz, 2H, ArC$H_a$$H_b$N), 6.80 (d, $^2J_{HH}$=6.9 Hz, 2H, Ar-*H*), 7.01 (s, 2H, imi-*H*), 7.40–7.59 (m, 8H, Ar-*H*, imi-*H*), 7.94–8.01 (m, 6H, Ar-*H*). $^{13}C\{^1H\}$ NMR (75.48 MHz, DMSO-d_6): δ 46.6 (N*C*H_2), 50.3 (Ar*C*H_2N), 122.9, 122.4, 122.7 (imi-*C*, Ar-*C*), 124.9, 125.2, 125.7, 126.2, 128.1 (2×Ar-*C*), 130.0, 131.4, 132.7 (Ar-*C*), 156.1 (br, N*C*N).

4.11. General procedure for the Suzuki coupling reactions

In a typical run, a mixture of aryl bromides (1.0 mmol), phenylboronic acid (1.5 mmol), cesium carbonate (2.0 mmol) and 0.5 mol % of catalyst in 3 mL of 1,4-dioxane was stirred at 80 °C for 1–2 h under nitrogen. The solution was allowed to cool. A 1:1 mixture of diethyl ether/water (20 mL) was added. The organic layer was washed, separated, further washed with another 10 mL portion of diethyl ether, and dried with anhydrous $MgSO_4$. The solution was then filtered. The solvent and any volatiles were removed completely under high vacuum to give a crude product which either subject to column chromatography or analyzed by ^1H NMR.

4.12. General procedure for the Heck coupling reactions

In a typical run, a 50 mL two-neck flask equipped with a reflux condenser was charged with aryl halides (1.0 mmol), styrene (1.4 mmol), anhydrous sodium acetate (1.1 mmol) and 0.5 mol % of catalyst. The flask was thoroughly degassed, added with 5 mL of *N*,*N*-dimethylacetamide via

a syringe, and then placed in a preheated oil bath at 165–175 °C. In the cases of bromobenzene as substrate, after fixed time 10 mL of diethyl ether was added to the reaction mixture and the organic layer was washed with five times of water and dried with anhydrous $MgSO_4$. The solution was then filtered. The solvent and any volatiles were removed completely under high vacuum to give the isolated product. With all the other substrates, aliquots (0.2 mL) were removed from the reaction after fixed time and added to dichloromethane (10 mL). The organic portion was washed with five times of water and dried with anhydrous $MgSO_4$. The solution was filtered and the solvent was removed completely under vacuum. The residue was dissolved in $CDCl_3$ and analyzed by ^1H NMR.

Acknowledgements

We are grateful to the National Science Council of Taiwan for financial support of this work (Grant NSC 92-2113-M-018-005-).

References and notes

1. For recent reviews, see: (a) Hillier, A. C.; Grasa, G. A.; Viciu, M. S.; Lee, H. M.; Yang, C.; Nolan, S. P. *J. Organomet. Chem.* **2002**, *653*, 69–82. (b) Herrmann, W. A. *Angew. Chem. Int. Ed.* **2002**, *41*, 1290–1309.
2. (a) Zhang, C.; Huang, J.; Trudell, M. L.; Nolan, S. P. *J. Org. Chem.* **1999**, *64*, 3804–3805. (b) Böhm, V. P. W.; Gstöttmayr, C. W. K.; Weskamp, T.; Herrmann, W. A. *J. Organomet. Chem.* **2000**, *595*, 186–190. (c) Viciu, M. S.; Germaneau, R. F.; Navarro-Fernandez, O.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2002**, *21*, 5470–5472.
3. For examples, see: (a) Herrmann, W. A.; Schwarz, J.; Gardiner, M. G. *Organometallics* **1999**, *18*, 4082–4809. (b) Gardiner, M. G.; Herrmann, W. A.; Reisinger, C.-P.; Schwarz, J.; Spiegler, M. *J. Organomet. Chem.* **1999**, *572*, 239–247. (c) Clyne, D. S.; Jin, J.; Genest, E.; Callucci, J. C.; RajanBabu, T. V. *Org. Lett.* **2000**, *2*, 1125–1128. (d) César, V.; Bellemin-Laponnaz, B.; Gade, L. H. *Organometallics* **2002**, *21*, 5204–5208. (e) Albrecht, M.; Crabtree, R. H.; Mata, J.; Peris, E. *Chem. Commun.* **2002**, 32–33. (f) Albrecht, M.; Miecznikowski, J. R.; Samuel, A.; Faller, J. W.; Crabtree, R. H. *Organometallics* **2002**, *21*, 3596–3604.
4. (a) Hermann, W. A.; Reisinger, C.-P.; Spiegler, M. *J. Organomet. Chem.* **1998**, *557*, 93–96. (b) Zhang, C.; Trudell, M. L. *Tetrahedron Lett.* **2000**, *41*, 595–598.
5. Magill, A. M.; McGuinness, D. S.; Cavell, K. J.; Britovsek, G. J. P.; Gibson, V. C.; White, A. J. P.; Williams, D. J.; White, A. H.; Skelton, B. W. *J. Organomet. Chem.* **2001**, *617–618*, 546–560.
6. Grasa, G. A.; Viciu, M. S.; Huang, J.; Zhang, C.; Trudell, M. L.; Nolan, S. P. *Organometallics* **2002**, *21*, 2866–2873.
7. Drent, E.; Budzelaar, P. H. M. *J. Organomet. Chem.* **2000**, *593–594*, 211–225.
8. See for examples: (a) Bonnet, L. G.; Douthwaite, R. E. *Organometallics* **2003**, *22*, 4187–4189. (b) Simons, R. S.; Custer, P.; Tessier, C. A.; Youngs, W. J. *Organometallics* **2003**, *22*, 1979–1982. (c) Danopoulos, A. A.; Winston, S.; Gelbrich, T.; Hursthouse, M. B.; Tooze, R. P. *Chem. Commun.* **2002**, 482–483. (d) Tsoureas, N.; Danopoulos, A. A.; Tulloch, A. A. D.; Light, M. E. *Organometallics* **2003**, *22*, 4750–4758. (e) Yang, C.; Lee, H. M.; Nolan, S. P. *Org. Lett.* **2001**, *3*, 1511–1514.
9. Substituted *N*-benzylimidazoles were typically synthesized with inorganic bases such as K_2CO_3 in acetone or DMF. See: Baggaley, K. H.; Heald, M.; Hindley, R. M.; Morgan, B.; Tee, J. L.; Green, J. *J. Med. Chem.* **1975**, *18*, 833–836.
10. William, D. J.; Vanderveer, D.; Jones, R. L.; Menaldino, D. S. *Inorg. Chim. Acta.* **1989**, *165*, 173–178.
11. (a) Douthwaite, R. E.; Haüssinger, D.; Green, M. L. H.; Silcock, P. J.; Gomes, P. T.; Ana, M.; Martins, A. M.; Danopoulos, A. A. *Organometallics* **1999**, *18*, 4584–4590. (b) Douthwaite, R. E.; Green, M. L. H.; Silcock, P. J.; Gomes, P. T. *Organometallics* **2001**, *20*, 2611–2615.
12. Sutton, L. E. *Tables of Interatomic Distances and Configurations in Molecules and Ions*; Chemical Society Publications: UK, 1965.
13. Douthwaite, R. E.; Green, M. L. H.; Silcock, P. J.; Gomes, P. T. *J. Chem. Soc., Dalton Trans.* **2002**, 1386–1390.
14. Schwarz, J.; Bohm, V. P. W.; Gardiner, M. G.; Grosche, M.; Herrmann, W. A.; Hieringer, W.; Raudaschl-Sieber, G. *Chem. Eur. J.* **2000**, *6*, 1773–1780.
15. Milgrom, L. R.; Dempsey, P. J. F.; Yahioglu, G. *Tetrahedron* **1996**, *52*, 9877–9890.
16. Harper, J. L.; Smith, R. A. J.; Bedford, J. J.; Leader, J. P. *Tetrahedron* **1997**, *53*, 8211–8224.
17. Wilson, A. J. C. *International Tables for Crystallography*, Kluwer Academic: Dordrecht, 1992; Vol. C.