ELSEVIER

Tetrahedron

Tetrahedron Vol. 60, No. 43, 2004

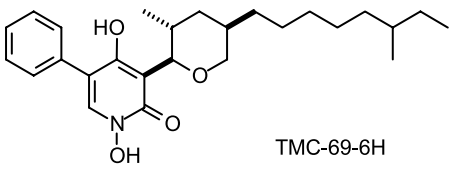
Tetrahedron Symposium-in-Print Number 108

Catalytic tools enabling total synthesis

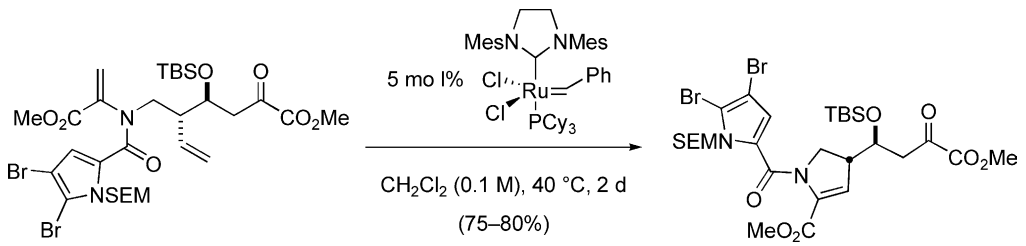
Guest editor: Alois Fürstner (Tetrahedron Chair 2004)

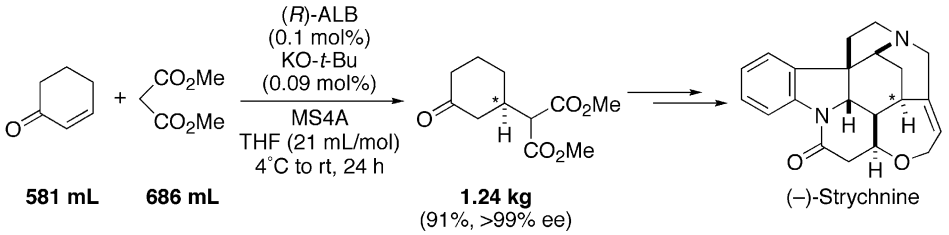
Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1, D-45470 Mülheim/Ruhr, Germany

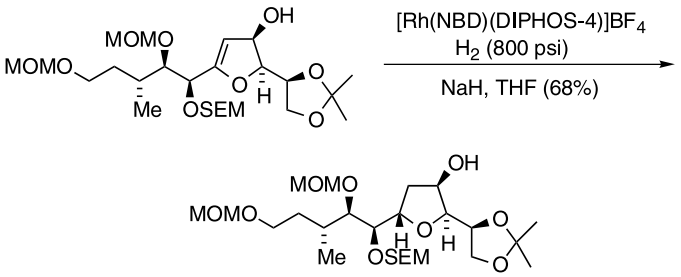
Contents

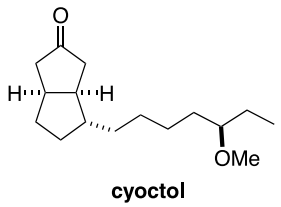


TMC-69-6H

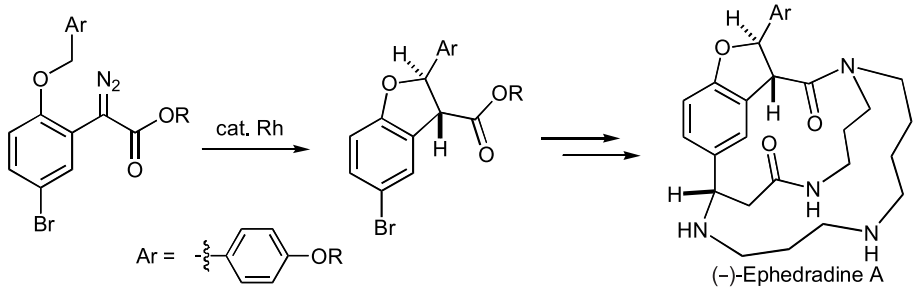


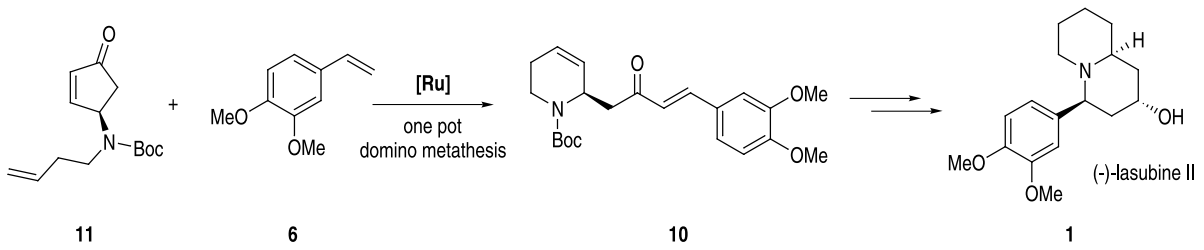


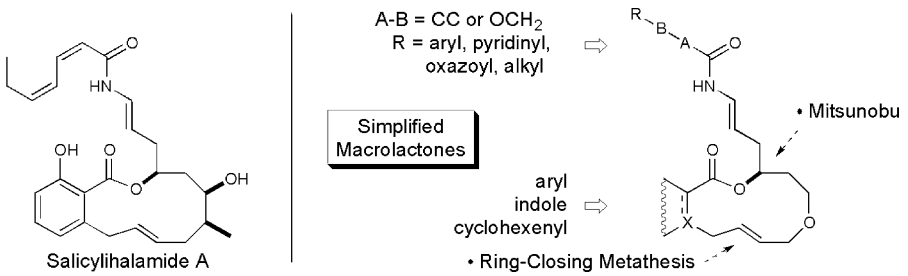


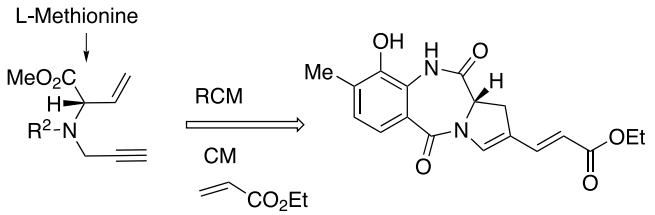


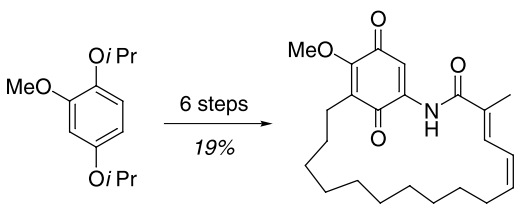
All eight stereoisomers of the putative anti-androgen cyoctol have been prepared and tested biologically.

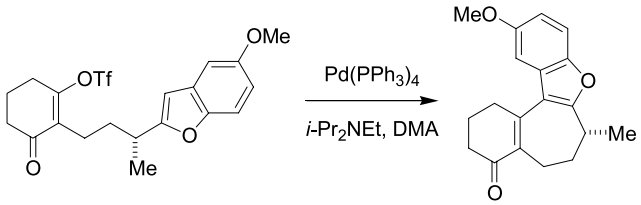


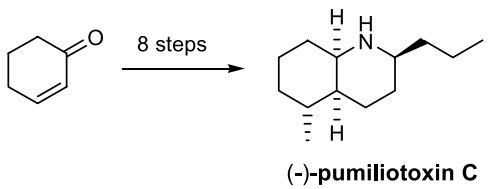


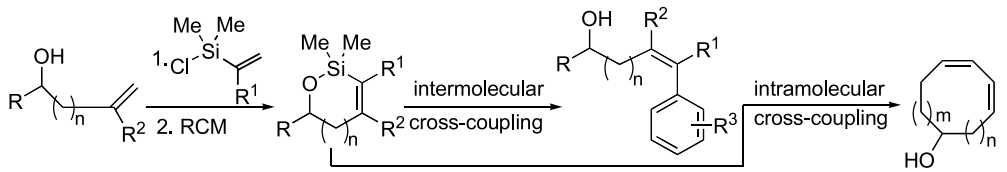


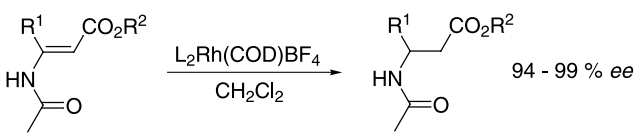


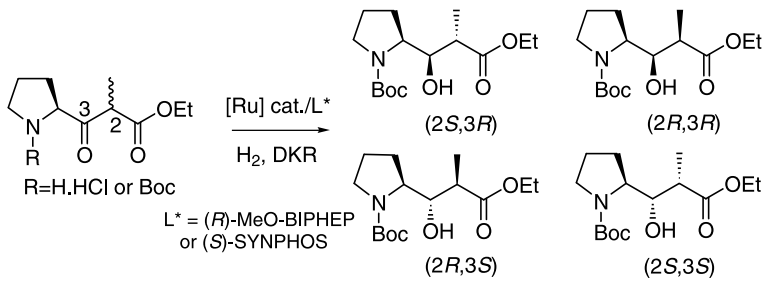


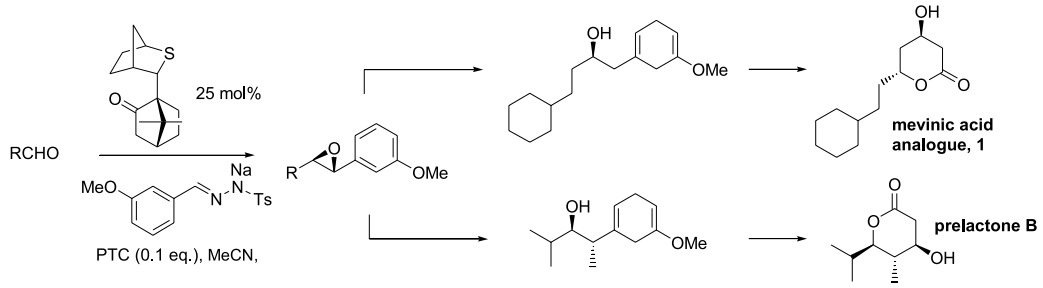


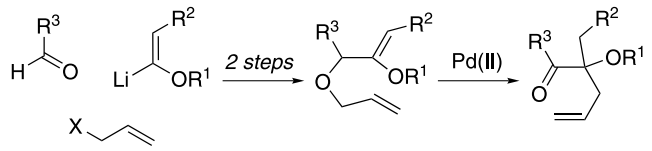


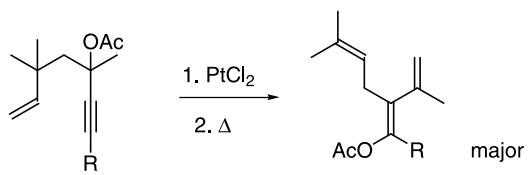


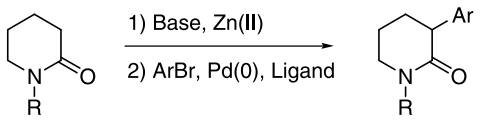


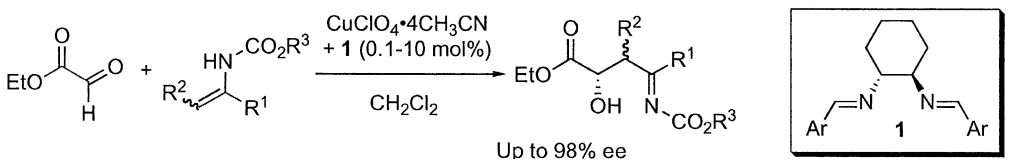












Enecarbamates reacted with ethyl glyoxylate smoothly in the presence of a complex derived from copper(I)-diimine **1** to afford the corresponding adducts in high yields with high enantioselectivities. Concerted aza-ene type mechanism has been proposed, and the proton on the nitrogen of the enecarbamate has been found to be important.

OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

The front cover shows a selection of natural products made by catalysis based synthesis routes as described in this issue. The broad range of biological activities elicited by these compounds are symbolized by the stained cell line shown in the background. *Tetrahedron*, **2004**, *60*, 9529–9784.

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

ELSEVIER

ISSN 0040-4020

Tetrahedron Symposia-in-Print

Series Editor
Professor H. H. Wasserman, Department of Chemistry, Yale University, P.O. Box 208107, New Haven, CT 06520-8107, U.S.A.

Tetrahedron Symposia-in-Print comprise collections of original research papers covering timely areas of organic chemistry.

Each symposium is organized by a Symposium Editor who will invite authors, active in the selected field, to submit original articles covering current research, complete with experimental sections. These papers will be rapidly reviewed and processed for publication by the Symposium Editor under the usual refereeing system.

Authors who have not already been invited, and who may have obtained recent significant results in the area of the announced symposium, may also submit contributions for Editorial consideration and possible inclusion. Before submitting such papers authors should send an abstract to the Symposium Editor for preliminary evaluation. Firm deadlines for receipt of papers will allow sufficient time for completion and presentation of ongoing work without loss of the freshness and timeliness of the research results.

Symposia-in-Print—already published

1. Recent trends in organic photochemistry, Albert Padwa, Ed. *Tetrahedron* **1981**, *37*, 3227–3420.
2. New general synthetic methods, E. J. Corey, Ed. *Tetrahedron* **1981**, *37*, 3871–4119.
3. Recent developments in polycyclopentanoid chemistry, Leo A. Paquette, Ed. *Tetrahedron* **1981**, *37*, 4357–4559.
4. Biradicals, Josef Michl, Ed. *Tetrahedron* **1982**, *38*, 733–867.
5. Electron-transfer initiated reactions, Gary B. Schuster, Ed. *Tetrahedron* **1982**, *38*, 1025–1122.
6. The organic chemistry of animal defense mechanisms, Jerrold Meinwald, Ed. *Tetrahedron* **1982**, *38*, 1853–1970.
7. Recent developments in the use of silicon in organic synthesis, Hans Reich, Ed. *Tetrahedron* **1983**, *39*, 839–1009.
8. Linear tetrapyrroles, Ray Bonnett, Ed. *Tetrahedron* **1983**, *39*, 1837–1954.
9. Heteroatom-directed metallations in heterocyclic synthesis, George R. Newkome, Ed. *Tetrahedron* **1983**, *39*, 1955–2091.
10. Recent aspects of the chemistry of β-lactams, J. E. Baldwin, Ed. *Tetrahedron* **1983**, *39*, 2445–2608.
11. New spectroscopic techniques for studying metabolic processes, A. I. Scott, Ed. *Tetrahedron* **1983**, *39*, 3441–3626.
12. New developments in indole alkaloids, Martin E. Kuehne, Ed. *Tetrahedron* **1983**, *39*, 3627–3780.
13. Recent aspects of the chemistry of nucleosides, nucleotides and nucleic acids, Colin B. Reese, Ed. *Tetrahedron* **1984**, *40*, 1–164.
14. Bioorganic studies on receptor sites, Koji Nakanishi, Ed. *Tetrahedron* **1984**, *40*, 455–592.
15. Synthesis of chiral non-racemic compounds, A. I. Meyers, Ed. *Tetrahedron* **1984**, *40*, 1213–1418.
16. Control of acyclic stereochemistry, Teruaki Mukaiyama, Ed. *Tetrahedron* **1984**, *40*, 2197–2344.
17. Recent aspects of anthracyclinone chemistry, T. Ross Kelly, Ed. *Tetrahedron* **1984**, *40*, 4537–4794.
18. The organic chemistry of marine products, Paul J. Scheuer, Ed. *Tetrahedron* **1985**, *41*, 979–1108.
19. Recent aspects of carbene chemistry, Matthew Platz, Ed. *Tetrahedron* **1985**, *41*, 1423–1612.
20. Recent aspects of singlet oxygen chemistry of photooxidation, Isao Saito and Teruo Matsuura, Eds. *Tetrahedron* **1985**, *41*, 2037–2236.
21. Synthetic applications of dipolar cycloaddition reactions. Wolfgang Oppolzer, Ed. *Tetrahedron* **1985**, *41*, 3447–3568.
22. Selectivity and synthetic applications of radical reactions, Bernd Giese, Ed. *Tetrahedron* **1985**, *41*, 3887–4302.
23. Recent aspects of organoselenium chemistry, Dennis Liotta, Ed. *Tetrahedron* **1985**, *41*, 4727–4890.
24. Application of newer organometallic reagents to the total synthesis of natural products, Martin Semmelhack, Ed. *Tetrahedron* **1985**, *41*, 5741–5900.
25. Formal transfers of hydride from carbon–hydrogen bonds, James D. Wuest, Ed. *Tetrahedron* **1986**, *42*, 941–1208.
26. Synthesis of non-natural products: challenge and reward, Philip E. Eaton, Ed. *Tetrahedron* **1986**, *42*, 1549–1916.
27. New synthetic methods—II, F. E. Ziegler, Ed. *Tetrahedron* **1986**, *42*, 2777–3028.
28. Structure and reactivity of organic radical ions, Heinz D. Roth, Ed. *Tetrahedron* **1986**, *42*, 6097–6350.
29. Organic chemistry in anisotropic media, V. Ramamurthy, J. R. Scheffer and N. J. Turro, Eds. *Tetrahedron* **1987**, *43*, 1197–1746.
30. Current topics in sesquiterpene synthesis, John W. Huffman, Ed. *Tetrahedron* **1987**, *43*, 5467–5722.
31. Peptide chemistry: design and synthesis of peptides, conformational analysis and biological functions, Victor J. Hruby and Robert Schwyzer, Eds. *Tetrahedron* **1988**, *44*, 661–1006.
32. Organosilicon chemistry in organic synthesis, Ian Fleming, Ed. *Tetrahedron* **1988**, *44*, 3761–4292.
33. α-Amino acid synthesis, Martin J. O'Donnell, Ed. *Tetrahedron* **1988**, *44*, 5253–5614.
34. Physical-organic/theoretical chemistry: the Dewar interface, Nathan L. Bauld, Ed. *Tetrahedron* **1988**, *44*, 7335–7626.
35. Recent developments in organocopper chemistry, Bruce H. Lipshutz, Ed. *Tetrahedron* **1989**, *45*, 349–578.
36. Organotin compounds in organic synthesis, Yoshinori Yamamoto, Ed. *Tetrahedron* **1989**, *45*, 909–1230.

37. Mycotoxins, Pieter S. Steyn, Ed. *Tetrahedron* **1989**, *45*, 2237–2464.
38. Strain-assisted syntheses, Léon Ghosez, Ed. *Tetrahedron* **1989**, *45*, 2875–3232.
39. Covalently linked donor–acceptor species for mimicry of photosynthetic electron and energy transfer, Devens Gust and Thomas A. Moore, Eds. *Tetrahedron* **1989**, *45*, 4669–4912.
40. Aspects of modern carbohydrate chemistry, S. Hanessian, Ed. *Tetrahedron* **1990**, *46*, 1–290.
41. Nitroalkanes and nitroalkenes in synthesis, Anthony G. M. Barrett, Ed. *Tetrahedron* **1990**, *46*, 7313–7598.
42. Synthetic applications of anodic oxidations, John S. Swenton and Gary W. Morrow, Eds. *Tetrahedron* **1991**, *47*, 531–906.
43. Recent advances in bioorganic chemistry, Dale L. Boger, Ed. *Tetrahedron* **1991**, *47*, 2351–2682.
44. Natural product structure determination, R. B. Bates, Ed. *Tetrahedron* **1991**, *47*, 3511–3664.
45. Frontiers in natural products biosynthesis. Enzymological and molecular genetic advances, D. E. Cane, Ed. *Tetrahedron* **1991**, *47*, 5919–6078.
46. New synthetic methods—III, S. E. Denmark, Ed. *Tetrahedron* **1992**, *48*, 1959–2222.
47. Organotitanium reagents in organic chemistry, M. T. Reetz, Ed. *Tetrahedron* **1992**, *48*, 5557–5754.
48. Total and semi-synthetic approaches to taxol, J. D. Winkler, Ed. *Tetrahedron* **1992**, *48*, 6953–7056.
49. Synthesis of optically active compounds—prospects for the 21st century, Kenji Koga and Takayuki Shioiri, Eds. *Tetrahedron* **1993**, *49*, 1711–1924.
50. Peptide secondary structure mimetics, Michael Kahn, Ed. *Tetrahedron* **1993**, *49*, 3433–3689.
51. Transition metal organometallics in organic synthesis, Anthony J. Pearson, Ed. *Tetrahedron* **1993**, *49*, 5415–5682.
52. Palladium in organic synthesis, Jan-E. Bäckvall, Ed. *Tetrahedron* **1994**, *50*, 285–572.
53. Recent progress in the chemistry of enediyne antibiotics, Terrence W. Doyle and John F. Kadow, Eds. *Tetrahedron* **1994**, *50*, 1311–1538.
54. Catalytic asymmetric addition reactions, Stephen F. Martin, Ed. *Tetrahedron* **1994**, *50*, 4235–4574.
55. Mechanistic aspects of polar organometallic chemistry, Manfred Schlosser, Ed. *Tetrahedron* **1994**, *50*, 5845–6128.
56. Molecular recognition, Andrew D. Hamilton, Ed. *Tetrahedron* **1995**, *51*, 343–648.
57. Recent advances in the chemistry of zirconocene and related compounds, Ei-ichi Negishi, Ed. *Tetrahedron* **1995**, *51*, 4255–4570.
58. Fluoroorganic chemistry: synthetic challenges and biomedicinal rewards, Giuseppe Resnati and Vadim A. Soloshonok, Eds. *Tetrahedron* **1996**, *52*, 1–330.
59. Novel applications of heterocycles in synthesis, A. R. Katritzky, Ed. *Tetrahedron* **1996**, *52*, 3057–3374.
60. Fullerene chemistry, Amos B. Smith III, Ed. *Tetrahedron* **1996**, *52*, 4925–5262.
61. New synthetic methods—IV. Organometallics in organic chemistry, István E. Markó, Ed. *Tetrahedron* **1996**, *52*, 7201–7598.
62. Cascade reactions, Ron Grigg, Ed. *Tetrahedron* **1996**, *52*, 11385–11664.
63. Applications of solid-supported organic synthesis in combinatorial chemistry, James A. Bristol, Ed. *Tetrahedron* **1997**, *53*, 6573–6706.
64. Recent applications of synthetic organic chemistry, Stephen F. Martin, Ed. *Tetrahedron* **1997**, *53*, 8689–9006.
65. Chemical biology, Gregory L. Verdine and Julian Simon, Eds. *Tetrahedron* **1997**, *53*, 11937–12066.
66. Recent aspects of S, Se, and Te chemistry, Richard S. Glass and Renji Okazaki, Eds. *Tetrahedron* **1997**, *53*, 12067–12318.
67. Modern organic chemistry of polymerization, H. K. Hall Jr., Ed. *Tetrahedron* **1997**, *53*, 15157–15616.
68. New synthetic methods—V, John L. Wood, Ed. *Tetrahedron* **1997**, *53*, 16213–16606.
69. New developments in organonickel chemistry, Bruce H. Lipshutz and Tien-Yau Luh, Eds. *Tetrahedron* **1998**, *54*, 1021–1316.
70. Solution phase combinatorial chemistry, David L. Coffen, Ed. *Tetrahedron* **1998**, *54*, 3955–4150.
71. Heterocycles in asymmetric synthesis, Alexandre Alexakis, Ed. *Tetrahedron* **1998**, *54*, 10239–10554.
72. Recent advances of phase-transfer catalysis, Takayuki Shioiri, Ed. *Tetrahedron* **1999**, *55*, 6261–6402.
73. Olefin metathesis in organic synthesis, Marc L. Snapper and Amir H. Hoveyda, Eds. *Tetrahedron* **1999**, *55*, 8141–8262.
74. Stereoselective carbon–carbon bond forming reactions, Harry H. Wasserman, Stephen F. Martin and Yoshinori Yamamoto, Eds. *Tetrahedron* **1999**, *55*, 8589–9006.
75. Applications of combinatorial chemistry, Miles G. Siegel and Stephen W. Kaldor, Eds. *Tetrahedron* **1999**, *55*, 11609–11710.
76. Advances in carbon–phosphorus heterocyclic chemistry, François Mathey, Ed. *Tetrahedron* **2000**, *56*, 1–164.
77. Transition metal organometallics in organic synthesis, Kenneth M. Nicholas, Ed. *Tetrahedron* **2000**, *56*, 2103–2338.
78. Organocopper chemistry II, Norbert Krause, Ed. *Tetrahedron* **2000**, *56*, 2727–2904.
79. Carbene complexes in organic chemistry, James W. Herndon, Ed. *Tetrahedron* **2000**, *56*, 4847–5044.
80. Recent aspects of the chemistry of β-lactams—II, Marvin J. Miller, Ed. *Tetrahedron* **2000**, *56*, 5553–5742.
81. Molecular assembly and reactivity of organic crystals and related structures, Miguel A. Garcia-Garibay, Vaidhyanathan Ramamurthy and John R. Scheffer, Eds. *Tetrahedron* **2000**, *56*, 6595–7050.
82. Protein engineering, Richard Chamberlin, Ed. *Tetrahedron* **2000**, *56*, 9401–9526.
83. Recent advances in peptidomimetics, Jeffrey Aubé, Ed. *Tetrahedron* **2000**, *56*, 9725–9842.
84. New synthetic methods—VI, George A. Kraus, Ed. *Tetrahedron* **2000**, *56*, 10101–10282.
85. Oxidative activation of aromatic rings: an efficient strategy for arene functionalization, Stéphane Quideau and Ken S. Feldman, Eds. *Tetrahedron* **2001**, *57*, 265–424.
86. Lewis acid control of asymmetric synthesis, Keiji Maruoka, Ed. *Tetrahedron* **2001**, *57*, 805–914.
87. Novel aromatic compounds, Lawrence T. Scott and Jay S. Siegel, Eds. *Tetrahedron* **2001**, *57*, 3507–3808.
88. Asymmetric synthesis of novel sterically constrained amino acids, Victor J. Hruby and Vadim A. Soloshonok, Eds. *Tetrahedron* **2001**, *57*, 6329–6650.
89. Recognition-mediated self-assembly of organic systems, Vincent M. Rotello, Ed. *Tetrahedron* **2002**, *58*, 621–844.
90. Synthesis of marine natural products containing polycyclic ethers, Masahiro Hirama and Jon D. Rainier, Eds. *Tetrahedron* **2002**, *58*, 1779–2040.

91. Fluorous chemistry, John A. Gladysz and Dennis P. Curran, Eds. *Tetrahedron* **2002**, *58*, 3823–4132.
92. Recent developments in chiral lithium amide base chemistry, Peter O'Brien, Ed. *Tetrahedron* **2002**, *58*, 4567–4734.
93. Beyond natural product synthesis (Tetrahedron Prize for Creativity in Organic Chemistry 2001 - Yoshito Kishi), Harry H. Wasserman and Stephen F. Martin, Eds. *Tetrahedron* **2002**, *58*, 6223–6602.
94. Strained heterocycles as intermediates in organic synthesis, Amy R. Howell, Ed. *Tetrahedron* **2002**, *58*, 6979–7194.
95. Molecular design of Lewis and Brønsted acid catalysts—the key to environmentally benign reagents (Tetrahedron Chair 2002), Hisashi Yamamoto, Ed. *Tetrahedron* **2002**, *58*, 8153–8364.
96. Recent developments in dendrimer chemistry, David K. Smith, Ed. *Tetrahedron* **2003**, *59*, 3787–4024.
97. Art, science and technology in total synthesis (Tetrahedron Prize for Creativity in Organic Chemistry 2002 - K. C. Nicolaou), Stephen F. Martin and Harry H. Wasserman, Eds. *Tetrahedron* **2003**, *59*, 6667–7070.
98. New synthetic methods—VII, Brian M. Stoltz, Ed. *Tetrahedron* **2003**, *59*, 8843–9030.
99. Oxiranyl and aziridinyl anions as reactive intermediates in synthetic organic chemistry, S. Florio, Ed. *Tetrahedron* **2003**, *59*, 9683–9864.
100. Recent advances in rare earth chemistry, Shū Kobayashi, Ed. *Tetrahedron* **2003**, *59*, 10339–10598.
101. Biocatalysts in synthetic organic chemistry, S. M. Roberts, Ed. *Tetrahedron* **2004**, *60*, 483–806.
102. Recent advances in the chemistry of zirconocenes, Keisuke Suzuki and Peter Wipf, Eds. *Tetrahedron* **2004**, *60*, 1257–1424.
103. Atropisomerism, Jonathan Clayden, Ed. *Tetrahedron* **2004**, *60*, 4325–4558.
104. Chemistry of biologically and physiologically intriguing phenomena, Daisuke Uemura, Ed. *Tetrahedron* **2004**, *60*, 6959–7098.
105. Olefin metathesis: a powerful and versatile instrument for organic synthesis (Tetrahedron prize for creativity in organic chemistry 2003 – R. H. Grubbs), Stephen F. Martin and Harry H. Wasserman, Eds. *Tetrahedron* **2004**, *60*, 7099–7438.
106. From synthetic methodology to biomimetic target assembly (Tetrahedron prize for creativity in organic chemistry 2003 – D. Seebach), Léon A. Ghosez, Ed. *Tetrahedron* **2004**, *60*, 7439–7794.
107. Solid and solution phase combinatorial chemistry, Rolf Breinbauer and Herbert Waldmann, Eds. *Tetrahedron* **2004**, *60*, 8579–8738.
108. Catalytic tools enabling total synthesis (Tetrahedron Chair 2004), Alois Fürstner, Ed. *Tetrahedron* **2004**, *60*, 9529–9784.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron
ELSEVIER
Tetrahedron 60 (2004) 9539

Foreword

The Tetrahedron Chair in Organic Synthesis 2004

The Tetrahedron Chair in Organic Synthesis 2004 was awarded to Professor Alois Fürstner of the Max-Planck-Institut für Kohlenforschung, Mülheim/Ruhr, Germany, at the Tenth Belgian Organic Synthesis Symposium (BOSS-X) in Louvain-la-Neuve, Belgium, on Monday 12th July 2004.

As is the tradition of the Tetrahedron Chair, the recipient presents a full-day lecture course on a specific topic in organic synthesis, during which both their own research, and the results of other scientists, are reviewed. Professor Fürstner enthralled the audience throughout four 1-hour lectures over the course of the day, with a fascinating series of lectures entitled 'Metathesis and Beyond', with coverage of Alkene and Alkyne Metathesis, plus the final lecture of the day – Beyond Metathesis.

As Tetrahedron Chair, Professor Fürstner was awarded €7,000 and a certificate from the Organic Chemistry Group at Elsevier, the publishers of the Tetrahedron publications and the sponsors of the Tetrahedron Chair.

0040–4020/$ - see front matter
doi:10.1016/j.tet.2004.09.038

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron
Tetrahedron 60 (2004) 9541

Preface

Catalytic tools enabling total synthesis

Catalysis is an enabling science. Therefore, it may not come as a surprise that catalysis in general and homogeneous catalysis in particular are rapidly gaining importance in the context of target oriented synthesis, both in an academic as well as in the industrial context. The synthesis of complex natural products of biological significance arguably constitutes the ultimate test for the scope and efficiency of a given transformation. The fact that the scientific community is increasingly prepared to subject even highly elaborate and most valuable material to catalytic processes reflects a considerable degree of confidence in the maturity of this technology. At the same time, natural product synthesis provides a formidable stimulus for the development of novel methods and constitutes a remarkably effective matrix for discovery in the realm of catalysis research.

The contributions to this *Symposium-in-Print* manifest the notion that catalysis and natural product synthesis are cross-fertilizing disciplines. The chemistry described therein is representative for the wide range of activities in both areas, illustrating impressive methodological advances on one hand and a host of advanced applications on the other. I am deeply indebted to all colleagues who kindly agreed to share their insight and expertise with us by disseminating some of their latest exciting results via this *Symposium-in-Print*.

Alois Fürstner
Max-Planck-Institut für Kohlenforschung,
Kaiser-Wilhelm-Platz 1,
D-45470 Mülheim/Ruhr, Germany
E-mail address: fuerstner@mpi-muelheim.mpg.de

Available online 24 August 2004

doi:10.1016/j.tet.2004.07.046

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 60 (2004) 9543–9558

Synthesis and evaluation of the antitumor agent TMC-69-6H and a focused library of analogs

Alois Fürstner,[a,*] Fabian Feyen,[a] Heino Prinz[b] and Herbert Waldmann[b]

[a]*Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1, D-45470 Mülheim/Ruhr, Germany*
[b]*Max-Planck-Institut für Molekulare Physiologie, D-44227 Dortmund, Germany*

Received 26 April 2004; revised 1 June 2004; accepted 3 June 2004

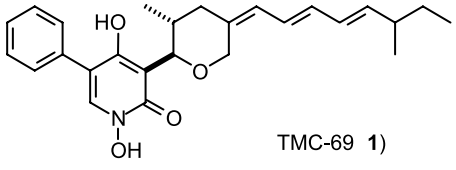
Available online 21 August 2004

Abstract—A concise, efficient and flexible total synthesis of the potent antitumor agent TMC-69-6H (**2**) is described. Key steps involve the palladium catalyzed regioselective addition of 4-hydroxy-2-pyridone **5** to pyranyl acetate **6** which is accompanied by a spontaneous 1,4-addition of the phenolic –OH group to the emerging enone to give the tricyclic product **7** in excellent yield. When this reaction is carried out with optically enriched (*S*)-**6** (conveniently prepared by a lipase catalyzed kinetic dynamic resolution) in the presence of the chiral ligand (*S*,*S*)-**12** and allylpalladium chloride dimer, the ensuing matched situation delivers the key building block (−)-**7** in 96% ee. Its further elaboration into **2** involves a Julia–Kocienski olefination with tetrazolylsulfone **19** and a final *N*-oxidation effected by the peroxomolybdenum complex [(pyridine)MoO_5(HMPA)] to form the hydroxamic acid motif. The flexibility inherent to this route allows for the preparation of a focused library of analogues for biochemical evaluation. The results obtained show that *N*-hydroxy-2-pyridone derivatives constitute a promising new class of selective phosphatase inhibitors. In contrast to previous reports in the literature, however, TMC-69-6H and congeners are found to exhibit pronounced activities against the tyrosine protein phosphatase PTB1B, the dual specific phosphatase VHR, and the serine/threonine phosphatase PP1, while being only weak inhibitors for the dual specific phosphatases Cdc25 A and B. Two key intermediates of the synthesis route have been characterized by X-ray crystallography.

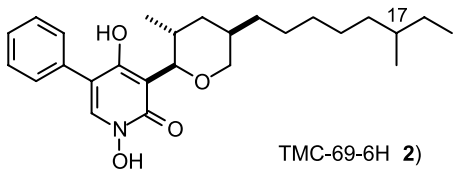
1. Introduction

Reversible phosphorylations of proteins mediate innumerable biological processes, and aberrant phosphorylation can cause the development of human diseases such as cancer and diabetes.[1] As a consequence, all enzymes involved in the regulation of protein phosphorylation sates represent potential targets for current medicinal chemistry and chemical biology research. While the phosphorylating protein kinases have already been intensively studied,[2] it was only recently that their natural antagonists, the protein phosphatases (PPs) responsible for the catalyzed hydrolysis of phosphate esters on tyrosine, serine and threonine, received similar attention.[3–7]

Among them, the dual specific protein phosphatases (PP's) of the Cdc25 family are particularly attractive for their eminent role in cell cycle control.[8] Their physiological substrates are cyclin-dependent kinases which, in turn, trigger key transitions in the process of eukaryotic cellular division. Hence, the homologous Cdc25 enzymes exert crucial regulatory functions at the crossroads between cellular proliferation, cell cycle arrest, and apoptosis. Their oncogenic properties together with the fact that Cdc25A and B are overexpressed in many human tumors render these isoenzymes molecular targets of utmost interest in the quest for anticancer drugs.[7–9]



TMC-69 **1**)



TMC-69-6H **2**)

The number of small molecules that qualify as lead structures in the search for selective inhibitors of Cdc25 phosphatases, however, is rather limited. A particularly promising candidate is the *N*-hydroxy-2-pyridone derivative TMC-69 (**1**) isolated from the culture broth of the fungus

Keywords: Heterocycles; Julia–Kocienski olefination; *N*-oxidation; Palladium; Phosphate inhibitors.
* Corresponding author. Tel.: +49-208-306-2342; fax: +49-208-306-2994; e-mail: fuerstner@mpi-muelheim.mpg.de

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.06.139

Chrysosporium sp. TC 1068.[10] According to the literature, this compound is distinguished by IC_{50} values in the low micromolar range as well as by a surprising selectivity for Cdc25 A and B over other phosphatases. While **1** itself is inherently labile and degrades within 2 weeks even at 0 °C, hydrogenation of its triene moiety results in a significantly improved stability and was reported to enhance the inhibitory activity as well as the cytotoxicity even further. Importantly, TMC-69-6H (**2**) thus formed has also proven effective in vivo for the treatment of P388 murine leukemia and B16 melanoma in nude mice, leading to an increase on life span of up to 105.9% at a dose of 1.25 mg/kg i.p.[10]

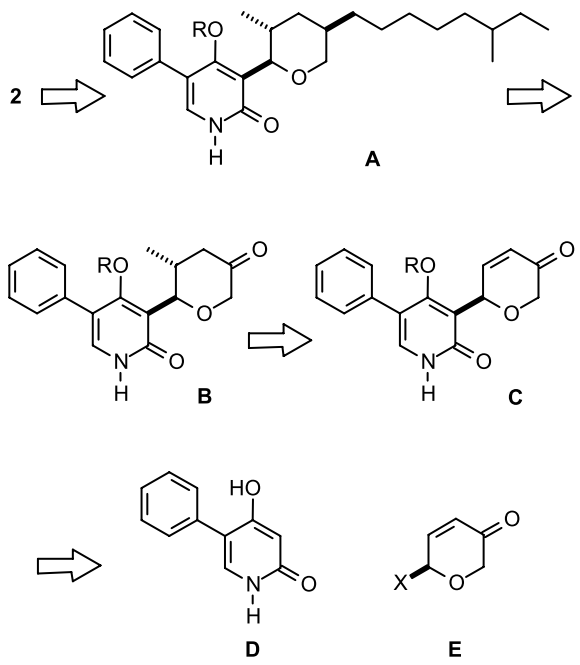
Due to this favorable profile, TMC-69-6H was selected for further study in our program directed at the identification and development of novel classes of phosphatase inhibitors.[11–13] Outlined below is the first total synthesis of both the (17*R*)- and the (17*S*)-configured isomers of **2**, since the absolute stereochemistry at this remote chiral center in the natural product **1** and its derivative **2** has not yet been established.[14] The chosen route is based on a novel palladium catalyzed fragment coupling process for the assembly of the core structure. Moreover, its inherent flexibility allowed for the synthesis of a focused library of analogues which enabled first insights into structure/activity relationships (SAR). Surprisingly though, the consistent set of biochemical data obtained with these samples is not in accord with the claims previously made in the literature.[10] Rather than being potent inhibitors of Cdc25A and B, we find pyridone derivatives of this series to inhibit the tyrosine protein phosphatase PTB1B, the dual specific phosphatase VHR, and the serine/threonine phosphatase PP1 much more effectively. The relevance of this finding, which results in the re-definition of the activity profile of TMC-69-6H, is outlined below.

2. Results and discussion

2.1. Retrosynthetic analysis

Since the hydroxamic acid function likely contributes to the lability of **2**, it was decided to install this group at a late stage of the synthesis by *N*-oxidation of the pyridone precursor **A** (Scheme 1). The alkyl side chain of the latter can be attached to the heterocyclic core by an olefination/hydrogenation sequence which provides opportunities for structural variations of this part of the molecule at a later stage. The required precursor **B** featuring two *trans*-disposed substituents might be secured by a 1,4-addition of a suitable methyl donor to the corresponding enone **C** which should derive from pyridone **D** and the pyranone **E**.

Although one might envisage to join these building blocks by established oxo-carbenium cation chemistry,[15] recourse to palladium catalyzed C–C-bond formations should allow to control the absolute stereochemistry at the ring junction and therefore provide a more attractive solution.[16] To this end, however, the metal template has to force the ambident pyridone **D** to act exclusively as a *C*- (rather than *O*- or *N*-) nucleophile and its equally ambident reaction partner **E** to behave solely as an allylcation equivalent rather than as a Michael acceptor. Such a reactivity pattern cannot be taken

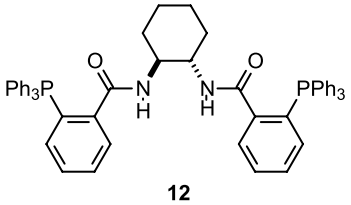


Scheme 1. Retrosynthetic analysis of TMC-69-6H (**2**).

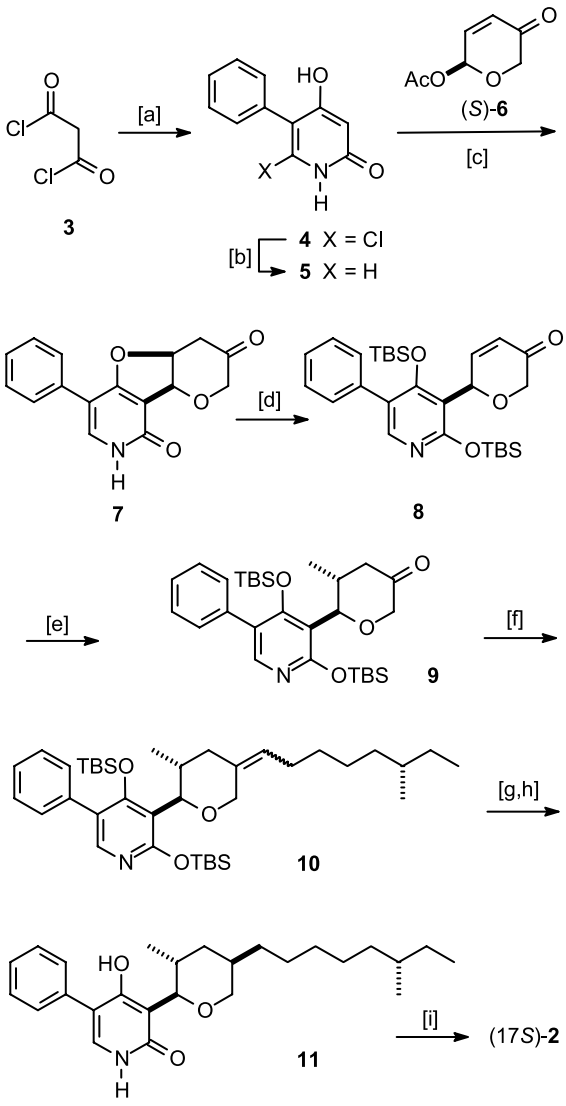
as granted because 2-pyridones tend to react with allylic substrates at their *N*-atom in the presence of palladium catalysts,[17] and palladium catalyzed transformations of 6-hydroxy-6*H*-pyran-3-one **E** (X=OR) derivatives are rather scarce and seem to be restricted to reactions with *O*-nucleophiles.[18] To the best of our knowledge, no Pd-catalyzed *C*-arylation of such a compound with a phenol derivative has previously been described. If successful, however, the envisaged fragment coupling process would greatly contribute to the overall flexibility of the synthesis route and add a new facet to organopalladium chemistry in general.[19,20]

2.2. Total synthesis

The required 4-hydroxypyridone **5** was prepared on a large scale by condensation of malonic acid dichloride **3** with 2-phenylacetonitrile followed by hydrogenolytic removal of the residual chloride in **4** (Scheme 2).[21] We were pleased to see that compound **5** reacted smoothly and regioselectively at its 'enolic' site with *rac*-**6**[22] in the presence of $Pd(PPh_3)_4$ cat. and Et_3N in DMF to give the tricyclic product (±)-**7** in 89% yield. The palladium-catalyzed C–C-bond formation is accompanied by a spontaneous 1,4-addition of the 4-OH group to the enone entity of the emerging product; we are unaware of any precedence for this transformation. Attempts to perform this reaction enantioselectively using *rac*-**6** as the substrate and the chiral diphosphine **12**[23] as ligand to Pd were unrewarding (ee ~30%).



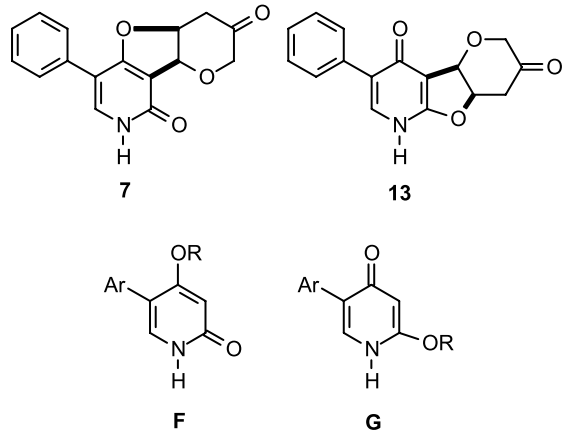
12



Scheme 2. Synthesis of (17*S*)-**2**: [a] phenylacetonitrile, 4d, 50%; [b] H_2 (1 atm), Pd/C, EtOH, 60 °C, 97%; [c] $[(allyl)PdCl]_2$ (0.5%), ligand **12** (1.5%), DMF, 65% (ee=96%); [d] TBSCl, Et_3N, 18 h, 78%; [e] Me_2CuLi, THF, −70 °C; [f] LiHMDS, (*S*)-**19**, THF, −78 °C, 69% (over both steps); [g] H_2, Pd/C, EtOH; [h] TBAF, THF, 69% (over both steps); [i] (i) $HN(SiMe_3)_2$, TMSCl cat., reflux; (ii) (pyridine)MoO_5(HMPA), CH_2Cl_2; (iii) sat. aq. EDTA-Na, EtOAc, 71%.

Gratifyingly though, the use of **12** in combination with enantiomerically enriched (*S*)-**6** (ee=81%), which is easily prepared on a multigram scale by a lipase catalyzed dynamic resolution,[24] served our purpose very well, delivering the tricyclic ketone (−)-**7** in good yield (65%) and excellent optical purity (ee=96%) (Scheme 2). Thereby it is essential to keep the catalyst loading low to avoid partial racemization of the intermediates via ligand transfer processes.

It is worth mentioning that an unambiguous structure assignment of this tricyclic product is not trivial. Specifically, one has to consider that the 2-hydroxy-4-pyridone tautomer of **5** might come into play and lead to the formation of compound **13**, which is difficult to distinguish from **7** by NMR and IR. Recent studies, however, revealed that such tautomeric ethers show distinctly different UV spectra.[21,25] While chromophors of the general type **F** have an absorption maximum in the range of λ_{max}=245–247 nm, their constitutional isomers **G** absorb at λ_{max}=233–235 nm. Since the tricyclic product formed in the palladium-catalyzed fragment coupling process shows a λ_{max} at 245 nm, we ascribe the 2(1*H*)-pyridinone structure **7** to this key building block.



The cyclic ether moiety in **7** acts as a temporary protecting group for the enone, which can be released by a retro-Michael reaction on treatment with oxophilic reagents in the presence of a base.[26] Optimal results were obtained with TBSCl in combination with Et_3N. The bis-TBS-ether **8**, though labile, can be isolated in pure form, whereas its TMS-counterpart is too unstable to be of practical use. The structure of this compound in the solid state is shown in Figure 1. As can be seen, one π-face of the enone (C7A–C8A) is strongly shielded by the bulky silyl group attached to O4A. Although it has not been investigated if this product adopts a similar conformation in solution, this particular steric arrangement augured for a good selectivity in the subsequent 1,4-addition reaction.

In fact, exposure of compound **8** to Me_2CuLi afforded the somewhat sensitive *trans*-disubstituted ketone **9** in good yield and excellent diastereoselectivity (de >90%). Crystals suitable for X-ray analysis could be obtained from the closely related compound **25** carrying a chloride substituent on the pyridone ring (see below). Its structure in the solid state is shown in Figure 2.

Although ketone **9** can be isolated in pure form, it turned out to be rather unstable. Therefore the crude product was immediately subjected to a Julia–Kocienski olefination reaction for the introduction of the aliphatic side chain.[27,28] The required sulfones were prepared from citronellene **14** as shown in Scheme 3 for (*R*)-**19**. Selective ozonolysis of the more highly substituted double bond[29,30] followed by routine elaboration of the resulting aldehyde **15** gave alcohol **17**, which condensed with commercial 1-phenyl-1*H*-tetrazol-5-thiol under Mitsunobu conditions[31] to give sulfide **18**. Oxidation with aqueous H_2O_2 in the presence of catalytic amounts of ammonium molybdate furnished sulfone (*R*)-**19** in good overall yield. Since both isomers of citronellene are commercially available, the antipodal sulfone (*S*)-**19** is equally accessible by this route.

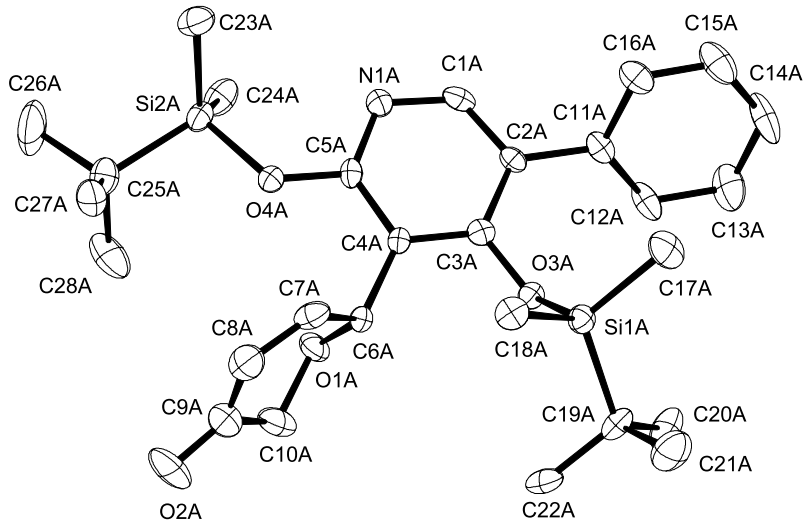
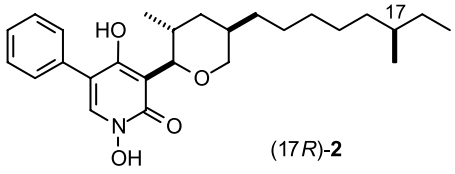


Figure 1. Molecular structure of compound **8** in the solid state. Anisotropic displacement parameters are shown at the 50% probability level, hydrogen atoms are omitted for clarity. Only one of the two independent molecules in the unit cell is depicted. Selected bond length (Å) and angles (°): C(1A)–N(1A) 1.341(6), C(1A)–C(2A) 1.371(7), C(2A)–C(3A) 1.409(7), C(3A)–C(4A) 1.383(6), C(4A)–C(5A) 1.401(6), C(5A)–N(1A) 1.330(6), C(6A)–C(7A) 1.488(7), C(7A)–C(8A) 1.352(7), C(8A)–C(9A) 1.439(8), C(9A)–O(2A) 1.229(7), C(9A)–C(10A) 1.488(9), C(10A)–O(1A) 1.427(6), C(6A)–O(1A) 1.435(5), C(3A)–O(3A) 1.375(6), C(5A)–O(4A) 1.350(5), C(8A)–C(7A)–C(6A) 120.9(5), C(7A)–C(8A)–C(9A) 120.3(6), O(2A)–C(9A)–C(8A) 122.8(7), O(1A)–C(6A)–C(7A) 111.5(4), O(1A)–C(10A)–C(9A) 113.5(5).

Reaction of the lithiated sulfone (*S*)-**19** with the crude ketone **9** provided alkene **10** as a 1:1 mixture of isomers. HPLC analyses on chiral columns and comparison with the racemic series confirmed that no racemization had occurred during this or any of the preceding steps (ee = 97%). Subsequent hydrogenation of the (*E*,*Z*)-mixture of **10** over Pd/C followed by cleavage of the –OTBS groups furnished a separable 5:1 mixture of the desired product **11** and its C-10 diastereomer in 69% yield over both steps. The axial orientation of the alkyl chain on the tetrahydropyran ring in **11** was evident from an analysis of the pertinent coupling constants and NOESY data (Scheme 4).

For the final *N*-oxidation to the desired hydroxamic acid derivative,[33] compound **11** was refluxed with hexamethyldisilazane (HMDS) and the resulting bis-silylether was treated with the peroxomolybdenum complex [(pyridine)MoO_5(HMPA)].[34] An aqueous work-up of the reaction mixture with EDTA to sequester all metal cations completed the first total synthesis of (17*S*)-TMC-69-6H (17*S*-**2**).



(17*R*)-**2**

As mentioned earlier, no secured information concerning the absolute stereochemistry of the remote chiral center on the lateral chain of compound **2** derived from natural sources is presently available.[10] Therefore the same

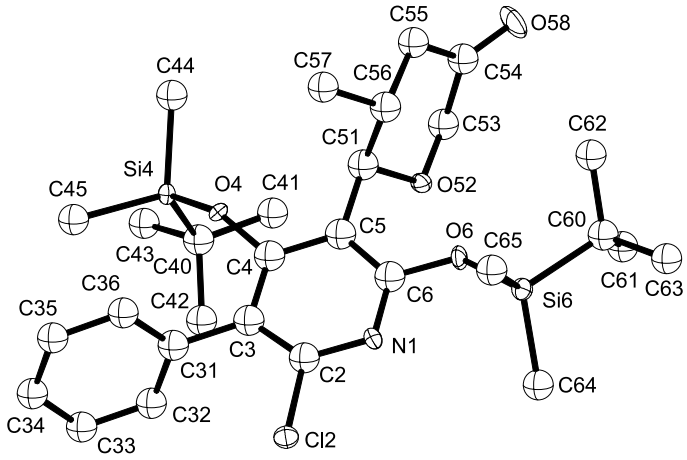
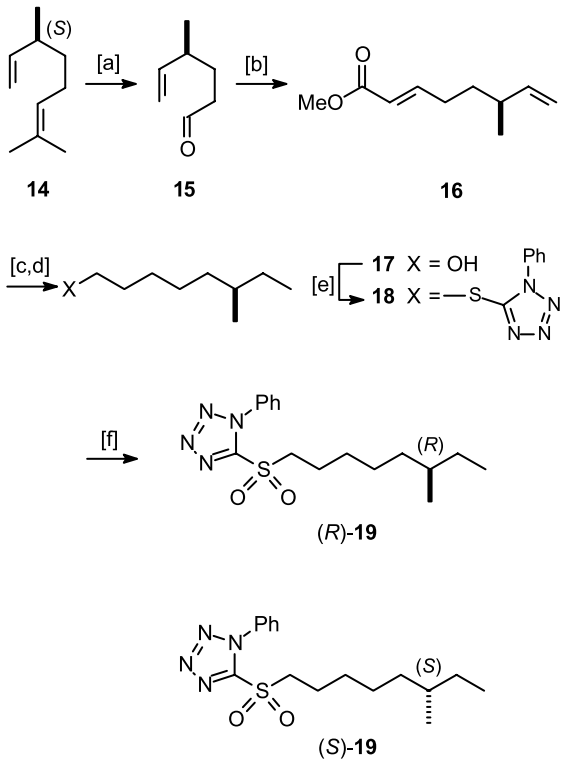


Figure 2. Molecular structure of compound **25** in the solid state. Anisotropic displacement parameters are shown at the 50% probability level, hydrogen atoms are omitted for clarity. Selected bond length (Å) and angles (°): N(1)–C(2) 1.335(6), N(1)–C(6) 1.342(6), C(2)–C(3) 1.385(7), C(3)–C(4) 1.408(7), C(4)–C(5) 1.395(7), C(5)–C(6) 1.398(7), O(4)–C(4) 1.361(6), O(6)–C(6) 1.342(6), C(51)–C(56) 1.527(7), C(55)–C(56) 1.533(7), C(54)–C(55) 1.496(8), C(54)–O(58) 1.201(6), C(53)–C(54) 1.504(8), O(52)–C(53) 1.420(6), C(51)–O(52) 1.445(6), C(57)–C(56)–C(51) 110.6(4), C(51)–C(56)–C(55) 108.9(4), C(5)–C(51)–C(56) 113.8(4), O(52)–C(51)–C(5) 106.3(4).

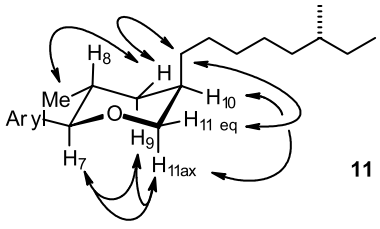


Scheme 3. [a] O_3, CH_2Cl_2, −78 °C, then Me_2S, 98%; [b] $(EtO)_2P(O)CH_2$-COOMe, NaH, THF, −78 °C, 87%; [c] Dibal-H, Et_2O, 91%; [d] H_2, Pd/C, 88%; [e] 1-phenyl-1*H*-tetrazole-5-thiol, DEAD, PPh_3, THF, 68%; [f] $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (0.1 equiv.), H_2O_2 (10 equiv.), EtOH, 93%.

sequence of reactions was repeated using ketone (−)-**9** and the antipodal sulfone (*R*)-**19** to give (17*R*)-**2** in similar overall yield. The diastereomeric compounds (17*R*)-**2** and (17*S*)-**2** thus obtained, however, are virtually indistinguishable by NMR and match the literature data reported for TMC-69-6H very well. Even a direct comparison of their spectra recorded at 600 MHz with those of an authentic sample does not allow us to rigorously assign the absolute stereochemistry of TMC-69-6H at that distal site (Tables 1 and 2).[35]

2.3. Analogues

In view of the promising biochemical and biological properties of TMC-69 and TMC-69-6H described in the literature,[10] the preparation of analogues was called for. Taking advantage of the flexibility inherent to the synthesis route described above we prepared a small collection of analogues for biological evaluation in order to gain first insights into structure/activity relationships.



Scheme 4. Schematic representation of compound **11** with characteristic NOESY data. The following coupling constants indicate a chair conformation of the tetrahydropyran ring: $^3J_{H7,H8}=10.4$ Hz, $^3J_{H10,H11ax}=2.5$ Hz, $^3J_{H10,H11eq}\leq 1$ Hz (TMC-69-6H numbering).[32]

The ketone group in **9** provides an opportunity for late stage divergent modification that might allow to probe the importance of the aliphatic tail for binding to the protein. To this end, compound **9** was subjected to Julia–Kocienski olefination reactions with the two unbranched alkyl sulfones **20a**,**b**.[27,36] The olefins **21a**,**b** thus formed were hydrogenated over Pd/C and the major stereoisomers of the resulting products (d.r.=5:1) were separated and *N*-oxidized with [(pyridine)MoO_5(HMPA)] as outlined above to give products **23a**,**b**, respectively, differing from the lead compound **2** only in their lipophilicity (Scheme 5).

Next, the synthesis was repeated with the 6-chloropyridone derivative **4**[21] which was formed as the primary product in the condensation reaction shown in Scheme 2. Gratifyingly, the aryl halide did neither interfere in the palladium-catalyzed fragment coupling step to give optically active tricyclic ketone **24** (ee=95%) nor in the cuprate addition reaction introducing the methyl branch. However, dehalogenation competes with the hydrogenation of the double bond in product **26**; therefore careful monitoring of the reaction was necessary to obtain product **27** in 44% yield, which was oxidized according to the established protocol to give the desired analogue **28** for biological evaluation (Scheme 6).

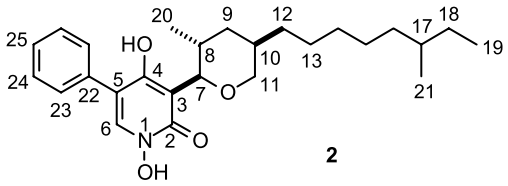
Finally, more substantial structural modifications were made by substituting the entire lipophilic segment of the natural product by bare alkyl chains attached to C-3 of the pyridone (Scheme 7). For this purpose, we investigated if simple allylic esters undergo similar palladium catalyzed cross coupling reactions with pyridone **5** as does the more activated substrate **6** used in the total synthesis of **2**. In fact, acetates **29a**,**b** afforded the desired C-allylated products **30a**,**b**, although more forcing conditions were required and the yields were lower than those obtained with **6**. Subsequent hydrogenation followed by *N*-oxidation proceeded uneventfully and afforded product **32** as a simplified analogue of TMC-69-6H.

2.4. Biochemical investigations: Re-assessment of the phosphatase inhibitory activity of TMC-69-6H and analogues

The excellent match between the analytical and spectroscopic data of (17*R*)-**2** and (17*S*)-**2** prepared by total synthesis with those reported in the literature leaves no doubt about the structural integrity of these compounds. Therefore we were surprised to find that their phosphatase inhibitory activity significantly deviates from the reported profile both in terms of potency and selectivity. In contrast to what has been claimed,[10] the compounds prepared by total synthesis as well as the authentic sample of **2** all turned out to be only rather weak inhibitors for Cdc25A ($IC_{50}>30$ μM) in our assay. Instead, they exhibit promising activities against the tyrosine protein phosphatase PTB1B, the dual specific phosphatase VHR, and the serine/threonine phosphatase PP1 (Table 3).

PTP1B is a key negative regulator of insulin-receptor

Table 1. Comparison of the ^{13}C NMR data of (17*R*)-**2** and (17*S*)-**2** in $CDCl_3$ with those of the authentic material published in the literature;[10] the accuracy of the recorded data is ± 0.1 ppm. Arbitrary numbering scheme as shown in the insert



2

Position	(17*S*)-**2**	(17*R*)-**2**	Authentic sample	Literature[10]
2	157.2	157.2	157.4	157.0
3	109.3	109.5	109.3	109.3
4	160.9	161.0	161.0	160.9
5	113.5	113.7	113.7	113.5
6	131.1	130.5	130.8	129.9
7	81.6	81.6	81.6	81.7
8	31.0	31.0	31.0	31.0
9	36.1	36.1	36.1	36.1
10	33.0	34.0	34.0	34.0
11	72.4	72.4	72.4	72.5
12	30.8	30.8	30.8	30.9
13	30.0	29.9	29.9	30.0
14	27.1	27.0	27.0	27.1
15	27.8	27.8	27.8	27.8
16	36.5	36.5	36.5	36.9
17	34.4	34.4	34.4	34.4
18	29.5	29.5	29.5	29.5
19	11.4	11.4	11.4	11.4
20	17.8	17.8	17.8	17.9
21	19.2	19.2	19.2	19.2
22	133.2	133.1	133.2	133.2
23	129.2	129.2	129.2	129.2
24	128.4	128.4	128.4	128.4
25	127.7	127.7	127.7	127.7

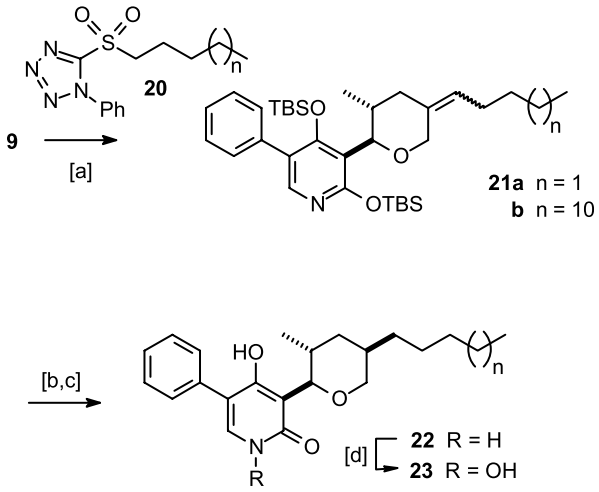
activity, and PTP1B-inhibitors are expected to enhance insulin sensitivity and act as effective therapeutics for the treatment of Type II diabetes, insulin resistance and obesity.[6] The vaccinia VH1-related phosphatase VHR is a physiological regulator of various members of the MAP kinase family and therefore influences signaling cascades via the MAP kinase pathway.[37] PP1 is a major enkaryotic phosphatase that regulates diverse cellular processes such as signal transduction, cell cycle progression, protein synthesis, muscle contraction, carbohydrate metabolism and transcription. All of these phosphatases have been subject to intense research activities aimed at the development of inhibitors for biological studies and drug development.[1–7,38]

The evaluation of TMC-69-6H, its analogues and isomers described above allows us to draw further conclusions. First, the comparison of the IC_{50} values for, e.g. (17*S*)-**2** with those of the precursor amide (17*S*)-**11** indicate that the presence of the *N*-OH group in the heterocycle, though not strictly required for phosphatase inhibition, enhances the potency of such compounds. Secondly, (17*S*)-**2** and (17*R*)-**2** are equally effective inhibitors within the error margins, thus showing that the configuration at the lateral methyl branch is hardly relevant. In line with this notion, analogues **23a**,**b** bearing straight-chain alkyl residues were both active, with the more lipophilic compound **23b** being significantly more potent. Furthermore, alkene groups embedded in the alkyl side chain are tolerated and their configuration is of minor importance since both isomers of **10** and **30b** led to respectable phosphatase inhibition. The chloride substituent on the pyridone ring in **28** is well accommodated, indicating that further variations in the aromatic part of **2** might be worthwhile. Equally promising is the fact that even more severe structural changes as those found in compounds **30**–**32** do not annihilate the inhibitory capacity for relevant phosphatases at all.

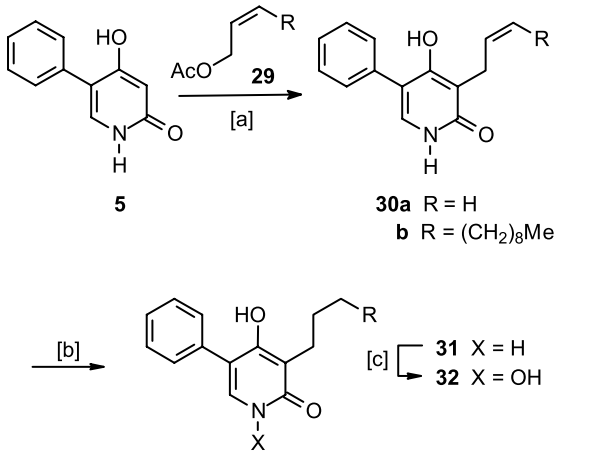
Although we are unable to reconcile our findings concerning

Table 2. Comparison of pertinent ^1H NMR data of (17*R*)-**2** and (17*S*)-**2** in $CDCl_3$ with those of the authentic material published in the literature;[10] the full set of data is compiled in the Section 3; arbitrary numbering scheme as shown in the insert to Table 1

Position	(17*S*)-**2**	(17*R*)-**2**	Literature[10]
–OH	9.52	9.52	9.51
6	7.67	7.67	7.67
7	4.68 (d, $J=10.5$ Hz)	4.68 (d, $J=10.5$ Hz)	4.68 (d, $J=10.5$ Hz)
8	2.06 (m)	2.07 (m)	2.08 (m)
9a	1.76 (d, $J=12.2$ Hz)	1.76 (d, $J=11.0$ Hz)	1.77 (d, $J=12.0$ Hz)
10	1.62 (m)	1.61 (m)	1.63 (m)
11a	3.96 (d, $J=11.5$ Hz)	3.96 (d, $J=11.8$ Hz)	3.96 (d, $J=11.6$ Hz)
11b	3.72 (dd, $J=11.5$, 2.3 Hz)	3.72 (dd, $J=11.6$, 2.5 Hz)	3.72 (dd, $J=11.6$, 2.5 Hz)

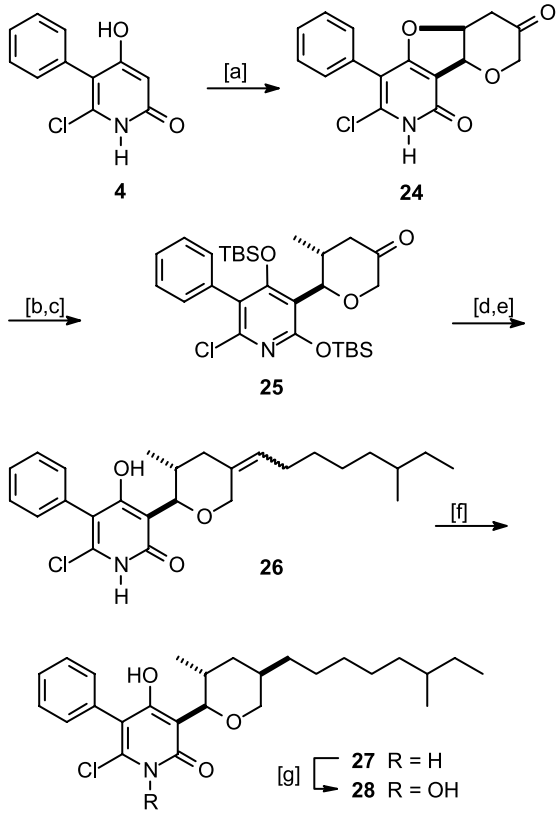


Scheme 5. [a] LiHMDS, **20a**,**b**, THF, −78 °C; [b] H_2, Pd/C, EtOH; [c] TBAF, THF, 32% (**21a** over three steps), 17% (**21b**, over three steps); [d] (i) $HN(SiMe_3)_2$, TMSCl cat., reflux; (ii) (pyridine)MoO_5(HMPA), CH_2Cl_2; (iii) sat. aq. EDTA-Na, EtOAc, 80% (**23a**), 85% (**23b**).



Scheme 7. [a] $Pd(PPh_3)_4$ (5 mol%), Et_3N, DMF, 110 °C, 59% (**30a**, R=H); or: $Pd(PPh_3)_4$ (7.5 mol%), NaH, DMF, 125 °C, 49% (**30b**, R=$(CH_2)_8$Me); [b] H_2 (1 atm), Pd/C, EtOH, quant. 60% (R=$(CH_2)_8$Me); [c] (i) HMDS, TMSCl cat., reflux; (ii) (pyridine)MoO_5(HMPA), CH_2Cl_2; (iii) sat. aq. EDTA-Na, EtOAc.

the physiological activity profile of TMC-69-6H with the literature reports,[10] the excellent reproducibility of our results, the internal control against authentic **2**, the consistency within the individual series, and the established validity of our Cdc25-assay[11–13] leave no room for interpretation. More importantly, these data make clear that *N*-hydroxy-2-pyridone derivatives constitute a promising new class of selective phosphatase inhibitors which allow for substantial structural variations and therefore constitute relevant lead compounds for further optimization.[39] Notably, TMC-69-6H incorporates a structural framework not present in any of the PTP1B- and PP1 inhibitors developed so far. Its proven activity in cellular assays as well as in vivo[10] renders further research activities in this field promising. In particular it seems lucrative to investigate the inhibitory profile of other natural products containing an *N*-hydroxy-2-pyridone motif similar to the one found in TMC-69.[40]



Scheme 6. [a] Compound (*S*)-**6**, [(allyl)PdCl]$_2$ (0.5%), ligand **12** (1.5%), DMF, 71% (ee=95%); [b] TBSCl, Et_3N, 1 h, 39%; [c] Me_2CuLi, THF, −70 °C; [d] LiHMDS, **19**, THF, −78 °C; [e] TBAF, THF, *E*/*Z*=1:1, 82% (over three steps); [f] H_2, Pd/C, EtOH, 44%, d.r.=3:1; [g] (i) $HN(SiMe_3)_2$, TMSCl cat., reflux; (ii) (pyridine)MoO_5(HMPA), CH_2Cl_2; (iii) sat. aq. EDTA-Na, EtOAc, 77%.

3. Experimental

3.1. General

All reactions were carried out under Argon in flame-dried glassware using Schlenk techniques. The solvents were dried by distillation over the indicated drying agents and were stored and transferred under Argon: CH_2Cl_2, Et_3N, DMF (CaH_2), toluene, THF, DME (Na), MeOH, EtOH (Mg), Et_2O (Mg-anthracene). Flash chromatography: Merck silica gel (230–400 mesh) using either hexanes/ethyl acetate or pentanes/diethyl ether in various proportions as the eluents. NMR: Spectra were recorded on a Bruker DPX 300, AMX 400, DMX 600 spectrometer in $CDCl_3$ or CD_2Cl_2 as indicated. Chemical shifts (δ) are given in ppm relative to the residual peak of $CHCl_3$ or $CHDCl_2$; coupling constant (J) in Hz. IR: Nicolet FT-7199, wavenumbers in cm^{-1}. MS: Varian CH-5 (70 eV), HRMS: Finnigan MAT SSQ 7000 (70 eV). Elemental analyses: H. Kolbe, Mülheim. Commercialy available reagents (Aldrich, Fluka, Strem, Lancaster) were used as received.

3.1.1. 1-Phenyl-3,4b(*S*),8,8a(*R*)-tetrahydro-5,9-dioxa-3-aza-flouren-4,7-dione (7). A solution of pyridone **5** (1.00 g, 5.34 mmol)[21] in DMF (25 mL) and Et_3N (0.5 mL) was stirred for 10 min before [(allyl)PdCl]$_2$ (9.8 mg, 0.03 mmol) and (−)-1,2-bis-N-[2′-(diphenylphosphino)-

Table 3. IC_{50} values [μM] of authentic and synthetic TMC-69-6H, its immediate precursors and analogues against different phosphatases[a]

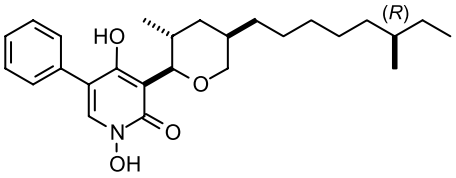
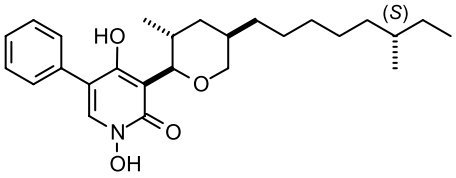
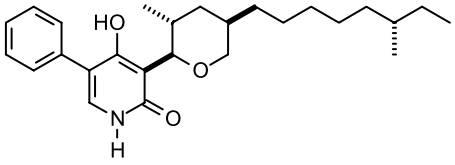
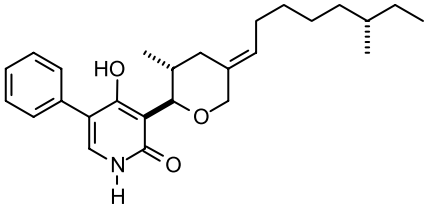
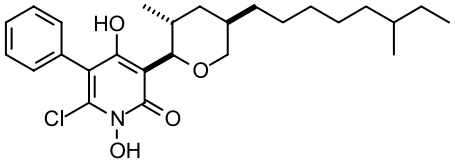
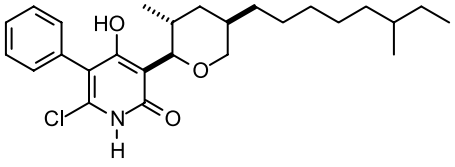
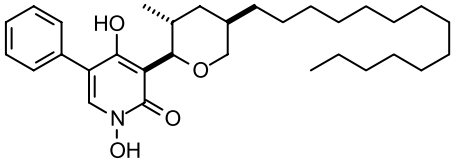
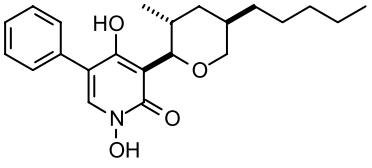
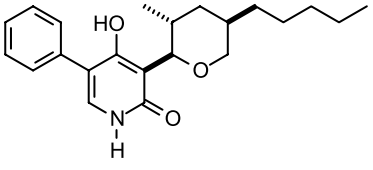
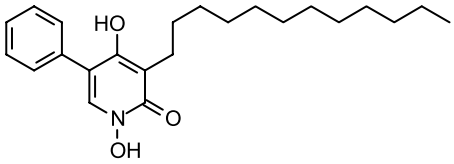
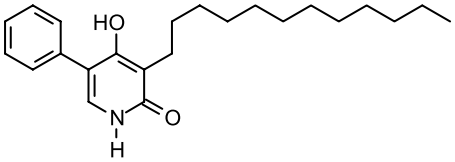
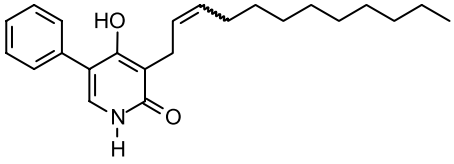
Compound		Cdc25A	PTP1B	VHR	PP1
Authentic **2**		≥50	3.2±1.6	7.0±3.5	6±3
	(17*R*)-**2**	45±23	4±2.0	6±3	8.5±4.5
	(17*S*)-**2**	32±16	3.5±1.7	5.5±3	8±4
	(17*S*)-**11**	≥50	11±5.5	9±5	30±5
	(17*S*)-**10a**	≥50	23±11	11±5.5	32±16
	**28**	>50	5.9±4.2	26±16.5	38.5±13
	**27**	>50	11.3±5.6	18.9±14	47±6
	**23b**	>50	2.8±1.5	26±13	
	**23a**	>50	12±6	19±8	
	**22a**	>50	14.1±8.3	3.1±1.4	>50

Table 3 (*continued*)

Compound		Cdc25A	PTP1B	VHR	PP1
	**32**	>50	4.7±1.2	3.1±1.6	47
	**31b**	>50	6.1±3.3	9.5±8.6	33±15
	**30b**[b]	>50	9.2±4.6	26±13	>50

[a] The enzymatic activity was determined by hydrolysis of *para*-nitrophenyl phosphate in standard buffers for PTP1B, VHR and PP1.
[b] 1:1 Mixture of isomers.

benzoyl]-1(*S*),2(*S*)-diaminocyclohexane (*S*,*S*)-**12** (55.5 mg, 0.08 mmol) were introduced. The resulting mixture was added dropwise to a solution of acetate (*S*)-**6** (1.12 g, 7.20 mmol, ee=81%)[24] in DMF (15 mL) and stirring was continued for 25 min before the reaction was quenched with aq. sat. NH_4Cl. A standard extractive work up followed by flash chromatography of the crude product (EtOAc/EtOH, 20:1+Et_3N (0.1%, v/v)) afforded compound **7** as a pale yellow solid (834 mg, 65%). The enantiomeric excess (ee=96%) was determined by HPLC on a chiral column (Chiralcel OJ-R, ∅ 4.6×150 mm; MeCN/water 20:80, 0.5 mL min^{-1}; 308 K; 3.6 MPa; retention times: (−)-**7**: 9.435 min, (+)-**7**: 10.237 min). $[\alpha]_D^{20}=-185°$ ($c=1.0$, $CHCl_3$/MeOH=9:1). ^1H NMR (400 MHz, DMSO-d_6) δ 11.66 (s, 1H), 7.64 (s, 1H), 7.50–7.30 (m, 5H), 5.47 (d, J=7.3 Hz, 1H), 5.37 (dt, J=7.0, 4.0 Hz, 1H), 4.01 (d, J=18.1 Hz, 1H), 3.64 (d, J=18.1 Hz, 1H), 3.19 (dd, J=16.2, 4.0 Hz, 1H), 2.88 (dd, J=16.2, 4.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 208.5, 167.9, 160.3, 137.8, 132.9, 128.7, 127.5, 127.2, 107.7, 105.5, 82.0, 73.8, 68.5, 39.6; IR (KBr) 3144, 3055, 2973, 2875, 1739, 1662, 1438, 1199, 1086, 775, 698; UV [ε_{max} (λ)]: 14200 (245 nm), 11600 (210 nm); MS (EI) *m*/*z* (rel. intensity) 283 ([M^+], 72), 224 (41), 212 (55), 211 (100), 196 (12), 144 (5), 102 (7), 77 (5); HR-MS (ESI-pos) ($C_{16}H_{13}NO_4$) calcd 283.084270, found 283.084457.

3.1.2. 2-Chloro-1-phenyl,3,4b(*S*),8,8a(*R*)-tetrahydro-5,9-dioxa-3-aza-flouren-4,7-dione (24). Prepared as described above from pyridone **4** (200 mg, 0.90 mmol) and acetate (*S*)-**6** (210 mg, 1.34 mmol). Pale yellow powder (205 mg, 71%). ee=95.3% (Chiralcel OD-R, ∅ 4.6×250 mm; MeCN/water 35:65, 0.5 mL/min; 298 K; 3.3 MPa; retention times: (+)-(**24**): 14.465 min, (−)-(**24**): 16.119 min). $[\alpha]_D^{20}=-222°$ ($c=0.52$, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 8.75 (s, 1H), 7.46–7.25 (m, 5H), 5.69 (d, J=7.3 Hz, 1H), 5.28 (m, 1H), 4.11 (d, J=18.1 Hz, 1H), 3.86 (d, J=18.3 Hz, 1H), 3.06 (dd, J=16.3, 3.9 Hz, 1H), 2.99 (dd, J=15.3, 3.9 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 206.5, 170.2, 161.6, 139.8, 130.2, 129.9, 128.6, 128.4, 109.9, 104.5, 83.0, 73.8, 69.1, 39.3; IR (film) 2869, 1737, 1650, 1613, 1544, 1432, 1211, 1094, 1074, 1025, 957, 900, 772, 702; UV [ε_{max} (λ)]: 12300 (240 nm), 11600 (219 nm); MS (EI) *m*/*z* (rel. intensity) 317 ([M^+], 88), 258 (35), 245 (100), 222 (22), 209 (45), 167 (7), 153 (12), 115 (13), 89 (19), 43 (27); HR-MS (ESI-pos) ($C_{16}H_{12}NO_4Cl$) calcd 317.0455, found 317.0450.

3.1.3. (*R*)-6-[2,4-Bis-(*tert*-butyl-dimethyl-silanyloxy)-5-phenyl-pyridin-3-yl]-6*H*-pyran-3-one (8). A solution of compound **7** (50 mg, 0.18 mmol), TBSCl (140 mg, 0.93 mmol) and Et_3N (0.5 mL) was stirred for 18 h at ambient temperature. The mixture was adsorbed on silica and the product was purified by flash chromatography (hexanes/Et_2O, 10:1+Et_3N (0.5%, v/v)) to give compound **8** as a colorless, moisture-sensitive solid (70 mg, 78%). $[\alpha]_D^{20}=-8.35°$ ($c=3.5$, THF). ^1H NMR (400 MHz, CD_2Cl_2) δ 7.97 (s, 1H), 7.45–7.34 (m, 5H), 7.17 (dd, J=10.4, 1.7 Hz, 1H), 6.20 (dd, J=10.5, 2.7 Hz, 1H), 5.76 (dd, J=4.4, 2.2 Hz, 1H), 4.31 (d, J=16.4 Hz, 1H), 4.20 (dd, J=16.2, 2.1 Hz, 1H), 0.95 (s, 9H), 0.93 (s, 9H), 0.34 (s, 3H), 0.30 (s, 3H), −0.26 (s, 3H), −0.37 (s, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 194.2, 162.4, 160.0, 153.4, 149.0, 136.6, 130.0, 129.5, 128.4, 126.7, 124.9, 113.1, 72.8, 68.2, 25.8, 25.6, 18.4, 18.2, −4.0, −4.3, −4.5, −4.9; IR (film) 3063, 2955, 2929, 2885, 2858, 1702, 1582, 1461, 1255, 1066, 976, 843, 787, 701; MS (EI) *m*/*z* (rel. intensity) 511 ([M^+], <1) 496 (3), 456 (13), 454 (100), 424 (12), 396 (4), 368 (3), 338 (7), 294 (2), 199 (1), 156 (5), 129 (3), 73 (19); HR-MS (ESIpos) ($C_{28}H_{42}NO_4Si_2$) calcd 512.265241, found 512.265080 (M+H).

3.1.4. (*R*)-6-[2,4-Bis-(*tert*-butyl-dimethyl-silanyloxy)-5-phenyl-pyridin-3-yl]-(*R*)-5-methyl-tetrahydro-pyran-3-one (9). A cooled solution (−78 °C) of enone **8** (140 mg, 0.27 mmol) in THF (4 mL) was slowly added to a solution

of Me_2CuLi [freshly prepared from $CuBr \cdot Me_2S$ (259 mg, 1.26 mmol) and MeLi (1.6 M in Et_2O, 1.57 mL) in THF (8 mL) at 0 °C] and the resulting mixture was stirred for 2 h at −70 °C. Addition of aq. NH_4OH/NH_4Cl (pH 8–9) followed by a standard extractive work up provided crude **9** (205 mg, dr >9:1) which is moisture sensitive and therefore used without further purification in the next step. Characteristic data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.42–7.30 (m, 5H), 4.79 (d, J=10.0 Hz, 1H), 4.22 (dd, J=15.9, 1.7 Hz, 1H), 3.97 (d, J=15.9 Hz, 1H), 3.07 (m, 1H), 2.78 (ddd, J=16.0, 5.3, 1.5 Hz, 1H), 2.20 (dd, J=16.0, 11.2 Hz, 1H), 0.98 (s, 9H), 0.94 (s, 9H), 0.86 (m, 3H), 0.36 (s, 3H) 0.35 (s, 3H), −0.01 (s, 3H), −0.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.9, 161.8, 159.7, 148.0, 136.7, 129.9, 128.3, 127.1, 124.5, 113.6, 76.5, 74.3, 46.5, 33.1, 26.0, 26.0, 18.4, 18.2, 18.2, −3.9, −3.9, −4.4, −4.9; IR (film) 3061, 2956, 2930, 2895, 2858, 1733, 1582, 1456, 1445, 1256, 1056, 976, 840, 784, 700; MS (EI) *m/z* (rel. intensity) 527 ([M^+], <1), 512 (4), 470 (100), 442 (5), 412 (22), 340 (13), 314 (21), 258 (5), 207 (2), 157 (2), 73 (21); HR-MS (ESI-pos) ($C_{29}H_{46}NO_4Si_2$) calcd 528.296541, found 528.296878 (M+H).

3.1.5. (*R*)-6-[2,4-Bis-(*tert*-butyl-dimethyl-silanyloxy)-5-phenyl-6-chloro-pyridin-3-yl]-(*R*)-5-methyl-tetrahydro-pyran-3-one (25). Prepared analogously. Characteristic data: $[\alpha]_D^{20}=-28°$ (c=0.14, $CHCl_3$). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.47–7.25 (m, 5H), 4.70 (d, J=10.0 Hz, 1H), 4.15 (dd, J=15.7, 1.7 Hz, 1H), 3.98 (d, J=15.7 Hz, 1H), 3.02 (m, 1H), 2.74 (ddd, J=15.9, 5.1, 1.5 Hz, 1H), 2.20 (dd, J=15.9, 11.6 Hz, 1H), 1.01 (s, 9H), 0.89 (s, 9H), 0.83 (m, 3H), 0.38 (s, 3H), 0.38 (s, 3H), 0.02 (s, 3H), −0.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.0, 162.0, 160.2, 147.2, 134.8, 132.4, 128.0, 127.9, 122.8, 113.2, 76.3, 74.3, 46.4, 33.2, 25.9, 25.9, 18.5, 18.1, 17.9, −4.0, −4.1, −4.3, −5.0; IR (film) 2956, 2931, 2897, 2859, 1733, 1571, 1541, 1428, 1251, 1158, 1140, 1105, 1077, 951, 841, 824, 812, 785, 701; MS (EI) *m/z* (rel. intensity) 561 ([M^+], <1), 548 (2), 507 (15), 506 (46), 504 (100), 448 (12), 446 (26), 374 (13), 350, (9), 348 (23), 292 (3), 224 (2), 174 (3), 129 (3), 73 (35); HR-MS (ESI-pos) ($C_{29}H_{45}NO_4Si_2Cl$) calcd 562.257569, found 562.257635 (M+H).

3.1.6. 2,4-Bis-(*tert*-butyl-dimethyl-silanyloxy)-3-[(*R*)-3-methyl-5-((*S*)-6-methyl-octyliden)-tetrahydro-pyran-2-(*R*)-yl]-5-phenyl-pyridine (10). A solution of LiHMDS (100 mg, 0.60 mmol) in DME (2 mL) was added to a solution of sulfone (*S*)-**19** (160 mg, 0.48 mmol) in DME (4 mL) at −78 °C. The resulting, bright yellow mixture was stirred for 15 min before a solution of ketone **9** (200 mg, 0.38 mmol) in DME (4 mL) was introduced and stirring was continued at that temperature for 30 min. The reaction was quenched with aq. NH_4Cl/NH_4OH (pH=8, 10 mL), the aqueous layer was repeatedly extracted with EtOAc, the combined organic layers were dried and evaporated, and the crude product was purified by flash chromatography (Et_2O/Et_3N/pentane, 1:1:100) to give product **10** as a colorless syrup which is moisture sensitive and immediately used in the next step (120 mg, 69% over two steps, *E*/*Z*=1:1). Characteristic data: ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.89 (s, 2H), 7.45–7.30 (m, 12H), 5.30–5.25 (m, 2H), 4.63 (d, J=12.4 Hz, 1H), 4.54 (m, 2H), 4.05 (d, J=12.0 Hz, 1H), 4.00 (d, J=11.9 Hz, 1H), 3.76 (d, J=12.5 Hz, 1H), 2.80 (dd, J=13.5, 2.7 Hz, 1H), 2.58 (m, 2H), 2.40, (d, J=13.5, 2.6 Hz, 1H), 2.15–0.80 (m, 30H), 1.00 (s, 18H) 0.96 (s, 18H), 0.74, (d, J=6.7 Hz, 6H), 0.70 (d, J=6.7 Hz, 6H), 0.37 (s, 6H), 0.32 (s, 6H), 0.06 (s, 6H), −0.65 (s, 6H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 162.1, 159.6, 147.2, 137.2, 134.3, 134.0, 130.0, 128.3, 128.1, 127.0, 124.6, 124.2, 115.2, 115.1, 78.0, 74.1, 66.5, 42.7, 36.6, 35.0, 34.5, 34.5, 34.2, 33.4, 30.6, 30.3, 29.8, 29.7, 29.6, 27.3, 27.1, 27.0, 27.0, 26.1, 26.0, 25.9, 25.8, 19.1, 18.4, 18.2, 17.8, 17.5, 11.3, 11.3, −4.1, −4.2, −4.2, −4.3, −4.6, −5.3; IR (film) 2956, 2928, 2857, 1582, 1455, 1444, 1254, 1136, 1058, 1004, 842, 784, 699; MS (EI) *m/z* (rel. intensity) 637 ([M^+], <1), 622 (2), 582 (18), 580 (100), 562 (8), 550 (14), 448 (5), 398 (12), 332 (3), 284 (4), 256 (2), 95 (2), 73 (17), 57 (2), 43 (2); HR-MS (ESI-pos) ($C_{38}H_{65}NO_3Si_2$) calcd 638.442476, found 638.442434 (M+H).

3.1.7. 2,4-Bis-(*tert*-butyl-dimethyl-silanyloxy)-3-[(*R*)-3-methyl-5-(pentyliden)-tetrahydro-pyran-2-(*R*)-yl]-5-phenyl-pyridine (21a). Prepared analogously using sulfone **20a**. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.88 (s, 2H), 7.46–7.27 (m, 10H), 5.30–5.25 (m, 2H), 4.63 (d, J=12.4 Hz, 1H), 4.53 (dd, J=9.8, 9.7 Hz, 1H), 4.06 (d, J=12.0 Hz, 1H), 3.99 (d, J=11.9 Hz, 1H), 3.74 (d, J=12.4 Hz, 1H), 2.78 (dd, J=13.5, 2.7 Hz, 1H), 2.58 (m, 2H), 2.40 (d, J=13.5, 2.6 Hz, 1H), 2.08 (m, 4H), 1.70 (m, 1H), 1.42–1.26 (m, 10H), 1.10–0.80 (m, 42H), 0.74 (d, J=6.7 Hz, 3H), 0.70 (d, J=6.7 Hz, 3H), 0.37 (s, 6H), 0.32 (s, 6H), 0.06 (s, 6H), −0.65 (s, 6H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 162.0, 159.6, 147.2, 137.1, 134.3, 134.0, 130.0, 128.2, 126.9, 124.5, 124.1, 115.1, 78.0, 74.0, 66.4, 65.7, 42.6, 35.0, 34.2, 34.0, 33.4, 32.3, 32.1, 29.8, 29.7, 26.9, 26.6, 25.9, 25.8, 25.8, 22.5, 22.5, 18.4, 18.1, 17.7, 17.5, 15.2, 13.9, −4.2, −4.3, −4.3, −4.7, −5.3; IR (film) 2956, 2929, 2858, 1582, 1455, 1443, 1254, 1136, 1057, 1004, 839, 783, 699; MS (EI) *m/z* (rel. intensity) 581 ([M^+], <1), 566 (2), 526 (16), 525 (43), 524 (100), 506 (9), 494 (13), 398 (10), 386 (5), 342 (3), 332 (3), 284 (4), 256 (2), 75 (2), 73 (19), 67 (2); HR-MS (ESI-pos) ($C_{34}H_{56}NO_3Si_2$) calcd 582.37988, found 582.37987 (M+H).

3.1.8. 2,4-Bis-(*tert*-butyl-dimethyl-silanyloxy)-3-[(*R*)-3-methyl-5-(tetradecyliden)-tetrahydro-pyran-2-(*R*)-yl]-5-phenyl-pyridine (21b). Prepared analogously using sulfone **20b**. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.88 (s, 2H), 7.45–7.26 (m, 10H), 5.30–5.25 (m, 2H), 4.62 (d, J=12.4 Hz, 1H), 4.53 (dd, J=9.8, 9.7 Hz, 1H), 4.06 (d, J=12.0 Hz, 1H), 3.98 (d, J=11.9 Hz, 1H), 3.75 (d, J=12.5 Hz, 1H), 2.78 (dd, J=13.5, 2.7 Hz, 1H), 2.57 (m, 2H), 2.38, (d, J=13.5, 2.6 Hz, 1H), 2.02 (m, 5H), 1.68 (m, 1H), 1.43–1.21 (m, 45H), 0.98 (s, 18H), 0.96 (s, 18H), 0.88 (t, J=6.5 Hz, 6H), 0.72 (d, J=6.7 Hz, 3H), 0.69 (d, J=6.7 Hz, 3H), 0.37 (s, 6H), 0.32 (s, 6H), 0.06 (s, 6H), −0.67 (s, 6H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 162.0, 159.6, 147.2, 137.1, 133.9, 130.0, 128.2, 126.9, 124.5, 124.2, 115.1, 78.0, 74.0, 66.4, 65.7, 42.6, 35.0, 34.2, 34.0, 33.4, 32.3, 32.0, 30.2, 29.9, 29.8, 29.8, 29.7, 29.7, 29.5, 29.5, 29.5, 27.2, 27.0, 25.9, 25.8, 25.8, 22.8, 18.4, 18.1, 17.7, 17.5, 14.0, −4.2, −4.3, −4.3, −4.7, −5.3; IR (film) 2956, 2926, 2855, 1582, 1455, 1444, 1406, 1254, 1136, 1057, 1004, 840, 810, 784, 699; MS (EI) *m/z* (rel. intensity) 707 ([M^+], <1), 652 (21), 651 (53), 650 (100), 632 (6), 620 (11), 536 (2), 518 (4), 398 (11), 386 (6), 332 (2), 314 (2), 284 (3), 256 (2), 73 (14), 57 (2); HR-MS

(ESIpos) ($C_{43}H_{74}NO_3Si_2$) calcd 708.72053, found 708.71976 (M+H).

3.1.9. 2,4-Bis-(*tert*-butyl-dimethyl-silanyloxy)-3-[(*R*)-3-methyl-5-((*S*)-6-methyl-octyliden)-tetrahydro-pyran-2-(*R*)-yl]-5-phenyl-6-chloro-pyridine. Prepared analogously as a *E*/*Z*=1:1 mixture of isomers. Characteristic data: ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.50–7.28 (m, 10H), 7.25 (s, br, 2H), 5.30–5.25 (m, 2H), 4.62 (d, J=12.5 Hz, 1H), 4.53 (t, J=9.7 Hz, 1H), 4.07 (d, J=12.0 Hz, 1H), 3.98 (d, J=11.9 Hz, 1H), 3.76 (d, J=12.5 Hz, 1H), 2.78 (d, J=13.5 Hz, 1H), 2.60 (m, 2H), 2.39 (d, J=13.5 Hz, 1H), 2.08 (m, 3H), 1.78 (m, 1H), 1.45–1.22 (m, 9H), 1.20–0.79 (m, 58H), 0.74 (d, J=6.7 Hz, 3H), 0.70 (d, J=6.7 Hz, 3H), 0.38 (s, 6H), 0.34 (s, 6H), 0.06 (s, 6H), −0.61 (s, 6H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 161.8, 160.4, 146.4, 135.1, 134.0, 133.7, 132.4, 131.8, 127.9, 127.7, 124.4, 122.5, 114.5, 77.8, 74.0, 66.4, 42.5, 36.6, 34.9, 34.5, 34.5, 34.2, 33.4, 30.6, 30.3, 29.6, 27.3, 27.1, 27.0, 27.0, 26.1, 25.9, 25.8, 25.8, 22.5, 19.1, 18.5, 18.1, 17.7, 17.5, 11.3, −4.3, −4.4, −4.45, −4.5, −5.0; IR (film) 2957, 2928, 2857, 1572, 1541, 1427, 1399, 1255, 1158, 1140, 1070, 1004, 953, 841, 825, 812, 784, 700; MS (EI) *m*/*z* (rel. intensity) 671 ([M$^+$], <1), 616 (47), 614 (100), 586 (9), 584 (18), 482 (5), 434 (8), 432 (14), 270 (6), 73 (23); HR-MS (ESI-pos) ($C_{38}H_{63}NO_3Si_2Cl$) calcd 672.40350, found 672.40365 (M+H).

3.1.10. 3-((2*R*,3*R*)-Tetrahydro-3-methyl-5-(6-methyl-octyliden)-2*H*-pyran-2-yl)-4-hydroxy-5-phenyl-6-chloro-pyridin-2(1*H*)-one (26). TBAF (1 M in THF, 0.36 ml, 0.36 mmol) was added to a solution of the pyridone described above (115 mg, 0.171 mmol) in THF (5 mL) and the resulting mixture was stirred for 30 min. The solution was adsorbed on Celite and the product was purified by flash chromatography (hexanes/EtOAc, 5:1) to afford product **26** as a colorless solid (74 mg, 99%, *E*/*Z*=1:1). Characteristic data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.5 (br, 2H), 7.50–7.27 (m, 10H), 5.28 (m, 2H), 4.85 (m, 2H), 4.71 (d, J=12.5 Hz, 1H), 4.12 (m, 2H), 3.91 (d, J=12.7 Hz, 1H), 3.00 (m, 1H), 2.72 (d, J=11.5 Hz, 1H), 2.35 (dd, J=13.0, 2.1 Hz, 2H), 2.20–1.75 (m, 10H), 1.40–0.70 (m, 34H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8, 162.8, 138.3, 132.6, 132.3, 132.1, 130.7, 128.1, 127.9, 126.0, 116.0, 107.0, 80.2, 67.1, 41.6, 38.3, 37.6, 36.4, 34.3, 34.3, 34.2, 30.2, 29.8, 29.5, 29.4, 27.1, 26.8, 26.6, 19.1, 18.0, 17.8, 11.4, 11.3; IR (film) 3200, 2959, 2926, 2854, 1635, 1614, 1449, 1359, 1236, 1050, 954, 838, 762, 697; MS (EI) *m*/*z* (rel. intensity) 443 ([M$^+$], 57), 427 (9), 425 (23), 408 (5), 387 (17), 358 (9), 330 (12), 326 (16), 261 (51), 250 (100), 237 (12), 234 (43), 221 (22), 144 (8), 82 (14), 55 (21); HR-MS (ESI-pos) ($C_{26}H_{34}NO_3ClNa$) calcd 466.21249, found 466.21292 (M+Na).

3.1.11. 3-((2*R*,3*R*,5*R*)-Tetrahydro-3-methyl-5-((*S*)-6-methyloctyl)-2*H*-pyran-2-yl)-4-hydroxy-5-phenylpyridin-2(1*H*)-one (11). A suspension of compound **10** (*E*/*Z* mixture, 120 mg, 0.19 mmol) and Pd/C (10% *w*/*w*, 30 mg) in EtOH (6 mL) was stirred under an atmosphere of H_2 (1 atm) for 24 h. The catalyst was filtered off and was carefully washed with hot EtOH (containing 1% Et_3N) and EtOAc (containing 1% Et_3N), the combined filtrates were evaporated and the crude product was directly subjected to the subsequent desilylation reaction. Characteristic data: ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.86 (s, 1H), 7.43–7.28 (m, 5H), 4.34 (d, J=10.2 Hz, 1H), 3.81 (d, J=11.3 Hz, 1H), 3.58 (dd, J=11.3, 2.6 Hz, 1H), 2.60 (m, 1H), 1.80 (d, J=10.4 Hz, 1H), 1.63–1.46 (m, 4H), 1.40–1.20 (m, 9H), 1.15–1.05 (m, 2H), 1.02 (s, 9H), 0.96 (s, 9H), 0.94–0.76 (m, 6H), 0.61 (d, J=6.7 Hz, 3H), 0.38 (s, 3H), 0.35 (s, 3H), 0.08 (s, 3H), 0.08 (s, 3H); IR (film) 3058, 2955, 2926, 2856, 1646, 1582, 1454, 1444, 1256, 1060, 839, 785, 700; MS (EI) *m*/*z* (rel. Intensität) 639 ([M$^+$], <1), 624 (3), 584 (19), 583 (48), 582 (100), 468 (20), 398 (3), 314 (1), 272 (2), 73 (30), 55 (7); HR-MS (ESI-pos) ($C_{38}H_{66}NO_3Si_2$) calcd 640.458126, found 640.457570 (M+H). For this purpose, TBAF (1 M in THF, 0.40 mL, 0.38 mmol) was added to a solution of the crude product in THF (5 mL) and the resulting mixture was stirred for 5 min. The reaction mixture was adsorbed on Celite and the product was purified by flash chromatography (EtOAc/hexanes, 2:1) to give product **11** as a mixture of diastereomers (52 mg, 69% over two steps, d.r.=5:1). The major isomer was separated by preparative HPLC (Nucleosil-5-120-C18/A, ∅ 4.5×125 mm; MeOH/water 80:20, 0.8 mL min^{-1}; 308 K; 8.6 MPa; retention time: 51.64 min). $[\alpha]_D^{20}=+94.5°$ (c=1.0, MeOH). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 12.77 (s, br, 1H), 9.65 (s, br, 1H), 7.44–7.30 (m, 5H), 7.26 (s, 1H), 4.67 (d, J=10.5 Hz, 1H), 3.99 (d, J=11.5 Hz, 1H), 3.74 (dd, J=11.6, 2.5 Hz, 1H), 2.10 (m, 1H), 1.80 (d, J=13.1 Hz, 1H), 1.68–1.47 (m, 4H), 1.40–1.20 (m, 9H), 1.15–1.05 (m, 2H), 0.89–0.80 (m, 9H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 164.4, 164.1, 134.2, 133.5, 129.2, 128.2, 127.3, 115.5, 110.1, 81.4, 72.5, 36.6, 36.2, 34.5, 34.2, 31.2, 30.9, 30.1, 29.5, 27.8, 27.1, 19.0, 17.9, 11.2; MS (EI) *m*/*z* (rel. intensity) 411 ([M$^+$], 61), 393 (33), 368 (18), 366 (23), 284 (34), 266 (15), 226 (31), 216 (30), 201 (100), 187 (40), 146 (6), 118 (11), 91 (4), 57 (18), 55 (16), 43 (20), 41 (18); HR-MS (EI) ($C_{26}H_{37}NO_3$) calcd 411.277343, found 411.277067.

3.1.12. 3-((2*R*,3*R*,5*R*)-Tetrahydro-3-methyl-5-pentyl-2*H*-pyran-2-yl)-4-hydroxy-5-phenyl-pyridin-2(1*H*)-one (22a, *n*=1). Prepared analogously. The major isomer was purified by preparative HPLC (Nucleosil-100-5-C18/A, ∅ 4.5×125 mm; MeOH/water 75:25; 0.8 mL min^{-1}; 308 K; 12.1 MPa). $[\alpha]_D^{20}=98.5°$ (c=0.51, $CHCl_3$). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 12.65 (s, br, 1H), 9.70 (s, br, 1H), 7.48–7.26 (m, 5H), 7.25 (s, 1H), 4.66 (d, J=10.5 Hz, 1H), 3.99 (d, J=11.5 Hz, 1H), 3.74 (dd, J=11.6, 2.4 Hz, 1H), 2.10 (m, 1H), 1.78 (d, J=11.7 Hz, 1H), 1.68–1.40 (m, 3H), 1.40–1.20 (m, 7H), 0.95–0.80 (m, 6H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 164.3, 164.1, 134.2, 133.5, 129.2, 128.2, 127.3, 115.5, 110.1, 81.4, 72.5, 36.2, 34.2, 32.0, 31.2, 30.8, 27.5, 22.7, 17.9, 14.0; IR (film) 3131, 2956, 2926, 2855, 1646, 1600, 1457, 1233, 1053, 698; MS (EI) *m*/*z* (rel. intensity) 355 ([M$^+$], 43), 337 (24), 325 (7), 312 (18), 310 (17), 284 (24), 266 (17), 242 (22), 229 (12), 226 (32), 216 (29), 201 (100), 200 (76), 187 (44), 155 (10), 146 (6), 144 (5), 130 (6), 118 (10), 91 (7), 55 (14), 41 (13); HR-MS (EI) ($C_{22}H_{29}NO_3$) calcd 355.214744, found 355.214445.

3.1.13. 3-((2*R*,3*R*,5*R*)-Tetrahydro-3-methyl-5-tetradecyl-2*H*-pyran-2-yl)-4-hydroxy-5-phenylpyridin-2(1*H*)-one (22b, *n*=10). Prepared analogously. The major isomer was purified by preparative HPLC (Nucleosil-100-5-C18/A ∅ 4.5×125 mm; MeOH/water 95:5; 0.8 mL min^{-1}; 308 K; 6.1 MPa; retention time 14.271 min). $[\alpha]_D^{20}=68.6°$ (c=0.55, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) 9.82 (s, br, 1H),

7.48–7.26 (m, 6H), 4.68 (d, J=10.5 Hz, 1H), 3.99 (d, J=11.5 Hz, 1H), 3.74 (dd, J=11.6, 2.3 Hz, 1H), 2.10 (m, 1H), 1.79 (d, J=12.3 Hz, 1H), 1.68–1.44 (m, 4H), 1.40–1.18 (m, 24H), 0.95–0.80 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 163.2, 133.6, 133.4, 129.1, 128.4, 127.7, 116.9, 109.6, 81.2, 72.5, 36.1, 34.0, 31.9, 31.0, 30.9, 29.7 (m), 29.6, 29.6, 29.3, 27.8, 22.7, 18.0, 14.1; IR (film) 3143, 2958, 2922, 2852, 1645, 1601, 1457, 1435, 1380, 1230, 1051, 801, 759, 697; MS (EI) m/z (rel. intensity) 481 ([M^+], 21), 463 (23), 451 (6), 438 (13), 436 (14), 382 (2), 298 (9), 284 (20), 266 (11), 242 (23), 229 (10), 228 (17), 227 (9), 226 (22), 216 (21), 201 (100), 200 (64), 187 (20), 146 (3), 118 (4), 97 (3), 95 (2), 91 (3), 67 (2), 43 (14); HR-MS (ESI-pos) ($C_{31}H_{48}NO_3$) calcd 482.363419, found 482.36352 (M+H).

3.1.14. 3-((2*R*,3*R*,5*R*)-Tetrahydro-3-methyl-5-(6-methyloctyl)-2H-pyran-2-yl)-4-hydroxy-5-phenyl-6-chloropyridin-2(1*H*)-one (27). Prepared analogously. The major isomer was purified by preparative HPLC (Asahipak, ∅ 4.5×250 mm; MeCN/TEAA buffer (pH 6.96)=70:30; 0.8 mL min^{-1}; 308 K; 6.5 MPa). $[\alpha]_D^{20}=-83.0°$ (c=0.7, $CHCl_3$). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.50–7.29 (m, 5H), 4.64 (d, J=10.5 Hz, 1H), 3.94 (d, J=11.8 Hz, 1H), 3.72 (dd, J=11.8, 2.6 Hz, 1H), 2.04 (m, 1H), 1.77 (d, J=12.7 Hz, 1H), 1.70–1.38 (m, 4H), 1.35–1.17 (m, 10H), 1.19–1.00 (m, 2H), 0.93–0.78 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 162.7, 139.2, 132.9, 130.8, 128.2, 128.1, 128.0, 116.4, 107.5, 81.0, 72.4, 36.6, 36.2, 34.4, 34.0, 31.1, 30.8, 29.4, 27.8, 27.0, 19.2, 18.0, 11.4; IR (film) 3189, 2959, 2926, 2855, 1634, 1614, 1590, 1460, 1380, 1263, 1235, 1076, 1056, 982, 762, 698; MS (EI) m/z (rel. intensity) 445 ([M^+], 100), 427 (17), 402 (14), 400 (14), 318 (16), 276 (19), 275 (10), 274 (11), 223 (17), 221 (42), 211 (19), 144 (11), 129 (5), 116 (6), 115 (6), 82 (7), 57 (19), 43 (28), 41 (29); HR-MS (ESI-pos) ($C_{26}H_{37}NO_3Cl$) calcd 446.24619, found 446.24617.

3.1.15. 3-((2*R*,3*R*,5*R*)-Tetrahydro-3-methyl-5-((*S*)-6-methyloctyl)-2*H*-pyran-2-yl)-1,4-dihydroxy-5-phenylpyridin-2(1*H*)-one, (17*S*)-TMC-69-6H, ((17*S*)-2). A mixture of pyridone **11** (25 mg, 0.06 mmol), HMDS (0.50 mL) and freshly distilled TMSCl (9 μL) was refluxed for 6 h before all volatile components were removed in vacuo. The remaining yellow syrup was dissolved in CH_2Cl_2 (1 mL) and treated with (pyridine)MoO_5(HMPA) (52.5 mg, 0.12 mmol).[34] After the mixture had been stirred for 16 h, the mixture was diluted with EtOAc (2.5 mL) and sat. aq. EDTA-Na_4 (2.5 mL), causing a color change from dark red to pale yellow. The pH of the solution was adjusted to 7–7.5 upon addition of aq. HCl (0.1 M) before the aqueous phase was separated and repeatedly extracted with EtOAc. The combined organic layers were evaporated and the residue was dried in vacuo (10^{-4} Torr) to provide compound (17*S*)-**2** as a colorless powder (18.9 mg, 71%). $[\alpha]_D^{20}=88.6°$ (c=0.95, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.52 (s, br, 1H), 7.67 (s, 1H), 7.47–7.29 (m, 5H), 4.68 (d, J=10.5 Hz, 1H), 3.96 (d, J=11.5 Hz, 1H), 3.72 (dd, J=11.5, 2.3 Hz, 1H), 2.06 (m, br, 1H), 1.76 (d, J=12.2 Hz, 1H), 1.62 (m, br, 1H), 1.58–1.40 (m, 3H), 1.35–1.19 (m, 9H), 1.13–1.00 (m, 2H), 0.89–0.81 (m, 6H), 0.79 (d, J=6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 157.2, 133.2, 131.1, 129.2, 128.4, 127.7, 113.5, 109.3, 81.6, 72.4, 36.5, 36.1, 34.4, 33.9, 31.0, 30.8, 30.0, 29.5, 27.8, 27.1, 19.2, 17.8, 11.4; IR (film) 3180, 2958, 2925, 2854, 1640, 1580, 1556, 1455, 1381, 1220, 1054, 775, 698, 658; MS (EI) m/z (rel. intensity) 427 ([M^+], 32), 410 (72), 392 (60), 382 (14), 380 (11), 368 (10), 314 (5), 284 (12), 282 (4), 266 (11), 258 (10), 244 (11), 242 (16), 240 (15), 238 (11), 232 (11), 226 (27), 216 (59), 214 (34), 211 (13), 200 (100), 187 (19), 144 (4), 97 (5), 67 (4), 55 (15), 43 (14), 41 (13); HR-MS (EI) ($C_{26}H_{37}NO_4$) calcd 427.272259, found 427.272083.

3.1.16. 3-((2*R*,3*R*,5*R*)-Tetrahydro-3-methyl-5-((*R*)-6-methyloctyl)-2*H*-pyran-2-yl)-1,4-dihydroxy-5-phenylpyridin-2(1*H*)-one, (17*R*)-TMC-69-6H, ((17*R*)-2). Prepared analogously. $[\alpha]_D^{20}=102.3°$ (c=0.6, MeOH). ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.52 (s, br, 1H), 7.67 (s, 1H), 7.47–7.31 (m, 5H), 4.68 (d, J=10.5 Hz, 1H), 3.96 (d, J=11.8 Hz, 1H), 3.72 (dd, J=11.6, 2.5 Hz, 1H), 2.07 (m, br, 1H), 1.76 (d, J=11.0 Hz, 1H), 1.63 (m, br, 1H), 1.58–1.44 (m, 3H), 1.35–1.18 (m, 9H), 1.13–1.02 (m, 2H), 0.87–0.81 (m, 6H), 0.79 (d, J=6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.0, 157.2, 133.1, 130.5, 129.2, 128.4, 127.7, 113.7, 109.5, 81.6, 72.4, 36.5, 36.1, 34.4, 34.0, 31.0, 30.8, 29.9, 29.5, 27.8, 27.0, 19.2, 17.8, 11.4; IR (film) 3187, 2958, 2924, 2854, 1643, 1580, 1557, 1456, 1381, 1220, 1054, 984, 775, 699; MS (EI) m/z (rel. intensity) 427 ([M^+], 45), 410 (100), 392 (74), 382 (15), 380 (12), 367 (9), 314 (6), 284 (5), 282 (5), 266 (7), 258 (13), 244 (13), 242 (10), 240 (17), 238 (11), 232 (16), 226 (18), 216 (66), 214 (37), 211 (14), 200 (87), 187 (12), 144 (5), 97 (6), 57 (15), 55 (22), 43 (22), 41 (21); HR-MS (EI) ($C_{26}H_{37}NO_4$) calcd 427.272259, found 427.271906.

3.1.17. 3-((2*R*,3*R*,5*R*)-Tetrahydro-3-methyl-5-(pentyl)-2*H*-pyran-2-yl)-1,4-dihydroxy-5-phenyl-pyridin-2(1*H*)-one (23a, *n*=1). Prepared analogously. $[\alpha]_D^{20}=88.8°$ (c=0.8, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.52 (s, br, 1H), 7.67 (s, 1H), 7.50–7.30 (m, 5H), 4.68 (d, J=10.5 Hz, 1H), 3.96 (d, J=11.5 Hz, 1H), 3.73 (dd, J=11.6, 2.5 Hz, 1H), 2.08 (br, m, 1H), 1.76 (d, J=11.0 Hz, 1H), 1.68–1.42 (m, 4H), 1.38–1.19 (m, 6H), 0.92–0.86 (t, J=7.0 Hz, 3H), 0.82 (d, J=6.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.9, 157.1, 133.1, 130.3, 129.2, 128.4, 127.7, 113.7, 109.5, 81.6, 72.4, 36.1, 34.0, 31.0, 30.8, 29.7, 27.6, 22.4, 17.9, 14.0; IR (film) 3181, 2957, 2922, 2852, 1736, 1639, 1579, 1556, 1455, 1381, 1260, 1218, 1048, 801, 775, 697; MS (EI) m/z (rel. intensity) 371 ([M^+], 24), 354 (39), 336 (29), 312 (13), 284 (17), 266 (15), 242 (17), 216 (43), 200 (100), 187 (30), 155 (13), 118 (9), 97 (10), 69 (12), 55 (22); HR-MS (EI) ($C_{22}H_{29}NO_4$) calcd 371.209659, found 371.209745.

3.1.18. 3-((2*R*,3*R*,5*R*)-Tetrahydro-3-methyl-5-(tetradecyl)-2*H*-pyran-2-yl)-1,4-dihydroxy-5-phenylpyridin-2(1*H*)-one (23b, *n*=10). Prepared analogously. $[\alpha]_D^{20}=66.0°$ (c=1.9, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.63 (s, br, 1H), 7.67 (s, 1H), 7.48–7.27 (m, 5H), 4.69 (d, J=10.5 Hz, 1H), 3.98 (d, J=11.4 Hz, 1H), 3.73 (d, J=11.7, 1H), 2.10 (m, 1H), 1.78 (d, J=12.5 Hz, 1H), 1.69–1.42 (m, 4H), 1.37–1.18 (m, 24H), 0.92–0.80 (m, 6H); IR (film) 3136, 2923, 2853, 1644, 1601, 1581, 1555, 1456, 1381, 1221, 1053, 801, 698; MS (ESI) m/z (rel. intensity) 497 ([M^+], <1), 482 (100), 433 (6), 390 (4), 180 (13); HR-MS

(ESI-pos) ($C_{31}H_{48}NO_4$) calcd 498.35833, found 498.35885 (M+H).

3.1.19. 3-((2*R*,3*R*,5*R*)-Tetrahydro-3-methyl-5-(6-methyloctyl)-2*H*-pyran-2-yl)-1,4-dihydroxy-5-phenyl-6-chloropyridin-2(1*H*)-one (28). Prepared analogously. $[\alpha]_D^{20}=+24.0°$ ($c=0.5$, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.96 (s, br, 1H), 9.38 (s, br, 1H), 7.50–7.25 (m, 5H), 4.62 (d, $J=10.2$ Hz, 1H), 3.91 (d, $J=11.0$ Hz, 1H), 3.67 (d, $J=11.0$ Hz, 1H), 2.02 (m, br, 1H), 1.73 (d, $J=12.1$ Hz, 1H), 1.62–1.37 (m, 4H), 1.36–1.00 (m, 11H), 0.86–0.70 (m, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.7, 156.8, 130.8, 128.4, 128.3, 128.2, 113.0, 107.0, 81.5, 72.4, 36.5, 36.1, 34.4, 33.9, 31.1, 30.8, 30.2, 29.9, 29.5, 27.8, 27.0, 19.2, 17.8, 11.4; IR (film) 3168, 2959, 2924, 2854, 1625, 1532, 1453, 1379, 1260, 1215, 1090, 1054, 912, 802, 698; MS (EI) *m/z* (rel. intensity) 461 ([M$^+$], 16), 446 (35), 445 (48), 444 (73), 428 (12), 427 (13), 426 (26), 416 (11), 400 (6), 398 (5), 320 (2), 318 (6), 302 (4), 300 (8), 276 (13), 274 (11), 260 (12), 252 (12), 250 (44), 234 (100), 221 (20), 211 (13), 180 (4), 144 (7), 55 (14), 43 (12), 41 (11); HR-MS (ESI-pos) ($C_{26}H_{37}NO_4Cl$) calcd 462.24111, found 462.24080 (M+H).

3.1.20. 3-Dodecyl-1,4-dihydroxy-5-phenyl-1*H*-pyridin-2-one (32). Prepared analogously from pyridone **31**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60–7.29 (m, 6H), 2.68 (m, 2H), 2.10–1.50 (m, 2H), 1.40–1.15 (m, 18H) 0.88 (t, $J=6.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (signals for C-2 and C-4 were not detected), 132.3, 129.8, 128.7, 128.2, 127.8, 118.0, 113.9, 42.0, 31.9, 29.7, 29.6, 29.6, 29.4, 29.3, 29.3, 22.7, 22.7, 14.1; IR (film) 3252, 2921, 2852, 1716, 1622, 1543, 1497, 1463, 1344, 1262, 1198, 1088, 771, 697; MS (EI) *m/z* (rel. intensity) 371 ([M$^+$], 33), 354 (3), 272 (2), 216 (7), 200 (6), 176 (12), 175 (100), 146 (20), 118 (10), 91 (5), 55 (6), 43 (9); HR-MS (ESI-pos) ($C_{23}H_{33}NO_3Na$) calcd 394.23581, found 394.23593 (M+Na).

3.1.21. (*S*)-4-Methylhex-5-enal (15).[29] Ozone was bubbled through a solution of (+)-(*S*)-citronellene **14** (8.2 g, 59 mmol, 91% ee) in CH_2Cl_2 (120 mL) at −78 °C until TLC showed complete consumption of the starting material. At this point, Me_2S (7.0 mL, 148 mmol) was added and the resulting mixture was stirred for 1 h at −30 °C. Excess Me_2S was pumped off in vacuo at that temperature before all volatile components were evaporated at ambient temperature and the crude product was purified by distillation (bp 52–55 °C, 50 mbar) to give aldehyde **15** as a colorless liquid (6.45 g, 98%). $[\alpha]_D^{20}=+3.5°$ ($c=1.0$, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (s, 1H), 5.70–5.58 (m, 1H), 5.02–4.94 (m, 2H), 2.46–2.40 (m, 2H), 2.20–2.10 (m, 1H), 1.72–1.53 (m, 2H), 1.02 (d, $J=6.7$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.6, 143.3, 113.8, 41.8, 37.4, 28.5, 20.2.

3.1.22. (*S*,*E*)-Methyl 6-methylocta-2,7-dienoat (16). Methyl diethylphosphonoacetate (1.41 g, 6.69 mmol) was added dropwise to a suspension of NaH (160 mg, 6.69 mmol) in THF (15 mL) at 0 °C and the resulting mixture was stirred for 30 min at ambient temperature. The solution was cooled to −78 °C before aldehyde **15** (500 mg, 4.46 mmol) was introduced via syringe and the resulting mixture was allowed to reach ambient temperature. A standard extractive work up followed by flash chromatography (hexanes/Et_2O, 10:1) afforded product **16** as a colorless liquid (650 mg, 87%). $[\alpha]_D^{20}=+16.2°$ ($c=1.0$, $CHCl_3$/MeOH=9:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (dt, $J=15.6$, 7.0 Hz, 1H), 5.81 (m, 1H), 5.70–5.60 (m, 1H), 5.01–4.90 (m, 2H), 3.72 (s, 3H), 2.18–2.05 (m, 3H), 1.47–1.40 (m, 2H), 1.01 (d, $J=6.7$ Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 166.8, 149.2, 143.4, 120.6, 113.0, 51.0, 37.0, 34.4, 29.6, 19.8; IR (film) 3077, 2954, 2928, 1728, 1658, 1436, 1273, 994, 913; MS (EI) *m/z* (rel. intensity) 168 ([M$^+$], <1), 153 (17), 139 (16), 126 (8), 113 (53), 111 (23), 109 (35), 100 (84), 94 (50), 87 (19), 81 (43), 79 (27), 71 (13), 69 (65), 59 (21), 55 (78), 41 (100), 29 (23); HR-MS (ESI-pos) ($C_{10}H_{16}O_2$) calcd 169.122855, found 169.122843 (M+H).

3.1.23. (*R*)-6-Methyloctan-1-ol (17). Dibal-H (1.0 M in hexane, 25.6 mL, 25.6 mmol) was added dropwise to a solution of ester **16** (1.50 g, 8.92 mmol) in Et_2O (20 mL) at 0 °C. After stirring for 2 h, the reaction was carefully quenched with MeOH at −78° C. A standard extractive work up followed by flash chromatography (Et_2O/hexanes, 1:2) afforded (*S*,*E*)-6-methylocta-2,7-dien-1-ol as a colorless liquid (1.13 g, 91%) which showed the following analytical and spectroscopic properties: $[\alpha]_D^{20}=+14.0°$ ($c=1.0$, $CHCl_3$/MeOH=9:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.72–5.58 (m, 3H), 5.01–4.90 (m, 2H), 4.10–4.05 (m, 2H), 2.18–1.97 (m, 3H), 1.43–1.33 (m, 2H), 0.99 (d, $J=6.7$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4, 133.3, 129.0, 112.8, 63.8, 37.2, 35.9, 29.8, 20.1; IR (film) 3329, 3077, 2961, 2925, 1640, 1454, 1373, 971; MS (EI) *m/z* (rel. intensity) 140 ([M$^+$], <1), 122 (3), 109 (17), 107 (22), 93 (37), 83 (28), 79 (25), 70 (22), 68 (64), 67 (70), 57 (30), 55 (97), 51 (5), 41 (100), 31 (11), 29 (41); HR-MS (CI) ($C_9H_{16}O$) calcd 141.127940, found 141.127788 (M+H). A suspension of this alcohol (100 mg, 0.70 mmol) and Pd/C (10% w/w, 20 mg) in MeOH (5 mL) was stirred for 6 h under an atmosphere of H_2 (1 atm). The catalyst was filtered off and was carefully rinsed with CH_2Cl_2, the combined filtrates were evaporated and the crude product was purified by flash chromatography (Et_2O/hexanes, 2:1) to give product **17** as a colorless liquid (90 mg, 88%). ^{1}H NMR (400 MHz) ($CDCl_3$) δ 3.59 (m, 2H), 1.56–1.51 (m, 3H), 1.37–1.25 (m, 4H), 1.20–1.07 (m, 4H), 0.92–0.86 (m, 6H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 63.0, 36.7, 34.5, 33.1, 29.6, 27.0, 26.2, 19.1, 11.3.

3.1.24. 5-((*R*)-6-Methyloctylthio)-1-phenyl-1*H*-tetrazol ((*R*)-18).[41] DEAD (202 mg, 1.00 mmol) was added to a solution of alcohol **17** (80 mg, 0.55 mmol), 1-phenyl-1*H*-tetrazole-5-thiol (**45**) (198 mg, 1.10 mmol) and PPh_3 (218 mg, 0.83 mmol) in THF (5 mL) and the resulting mixture was stirred for 10 min. A standard extractive work up followed by flash chromatography (hexanes/EtOAc=30:1) afforded sulfide **18** as a colorless syrup (114 mg, 68%) which was immediately subjected to the subsequent oxidation. Characteristic data: $[\alpha]_D^{20}=-2.5°$ ($c=1.0$, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57–7.53 (m, 5H), 3.38 (m, 2H), 1.83–1.78 (m, 2H), 1.44–1.06 (m, 9H), 0.86–0.82 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 133.8, 130.0, 129.7, 123.8, 36.3, 34.2, 33.4, 29.4, 29.1, 28.9, 26.5, 19.1, 11.3; IR (film) 2958, 2927, 2856, 1597, 1500, 1462, 1386, 1243, 761, 694, 552.

3.1.25. 5-((*R*)-6-Methyloctylsulfonyl)-1-phenyl-1*H*-tetrazol ((*R*)-19). A solution of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (550 mg, 0.45 mmol) in aq. H_2O_2 (30%, 5.84 g, 51.50 mmol) was added to a solution of sulfide (*R*)-**18** (1.60 g, 5.26 mmol) in EtOH (25 mL) and the resulting mixture was stirred for 18 h at ambient temperature. For work up, the mixture was diluted with water and EtOAc, the organic phase was washed with aqueous sodium thiosulfate (5%, w/w) before it was dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography (EtOAc/hexanes, 1:8) to give sulfone (*R*)-**19** as a colorless syrup (1.64 g, 93%). $[\alpha]_D^{20}=-2.7°$ ($c=3.0$, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72–7.55 (m, 5H), 3.73 (m, 2H), 1.96 (m, 2H), 1.56–1.42 (m, 2H), 1.41–1.23 (m, 5H), 1.20–1.06 (m, 2H), 0.90–0.83 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 133.0, 131.4, 129.7, 125.1, 56.1, 36.1, 34.3, 29.4, 28.5, 26.4, 22.0, 19.1, 11.3; IR (film) 2958, 2928, 2872, 2859, 1498, 1463, 1341, 1152, 763, 688, 629; MS (EI) *m/z* (rel. intensity) 336 ([M^+], <1), 243 (2), 173 (9), 160 (3), 147 (12), 145 (10), 119 (17), 118 (100), 117 (28), 97 (6), 91 (7), 77 (9), 70 (6), 65 (11), 57 (25), 55 (23), 43 (33), 41 (23), 29 (11); HR-MS (CI) ($C_{16}H_{24}N_4SO_2$) calcd 337.169409, found 337.169423 (M+H); Anal. calcd for $C_{16}H_{23}N_4SO_2$: C 57.12, H 7.19, N 16.65, found: C 57.19, H 7.11, N 16.73.

3.1.26. 3-Allyl-4-hydroxy-5-phenylpyridin-2(1*H*)-one (30a). A solution of allyl acetate **29a** (59 mg, 0.59 mmol) in DMF (2 mL) was slowly added to a solution of pyridone **5** (100 mg, 0.53 mmol) and $Pd(PPh_3)_4$ (31 mg, 0.03 mmol) in DMF (3 mL) and Et_3N (0.91 ml, 0.57 mmol), and the resulting mixture was stirred at 110 °C for 2 h. A standard extractive work up followed by flash chromatography of the crude product (EtOAc→EtOAc/MeOH, 20:1) provided product **30a** as a colorless solid (71 mg, 59%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.28 (s, br, 1H), 9.45 (s, br, 1H), 7.68–7.24 (m, 6H), 5.82 (m, 1H), 5.01 (dd, $J=2.1$, 17.2 Hz, 1H), 4.92 (dd, $J=2.1$, 10.1 Hz, 1H), 3.30 (d, $J=6.0$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.1, 160.4, 136.1, 135.3, 132.0, 129.2, 128.3, 126.8, 114.4, 113.9, 109.4, 27.1; IR (film) 3051, 1643, 1479, 1433, 1270, 1095, 756, 728, 694; MS (EI) *m/z* (rel. intensity) 227 ([M^+], 61), 212 (100), 200 (5), 144 (3), 128 (4), 118 (14), 106 (2), 63 (4), 51 (4); HR-MS (EI) ($C_{14}H_{13}NO_2$) calcd 227.094629, found 227.094368.

3.1.27. 3-(Dodec-2-enyl)-4-hydroxy-5-phenylpyridin-2(1*H*)-one (30b). Prepared analogously as a mixture of isomers (*E*/*Z*=1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80–7.20 (m, 12H), 5.62 (m, 4H), 3.43 (d, $J=6.1$, 4H), 2.00 (m, 4H), 1.47–1.13 (m, 24H), 0.87 (t, $J=7.0$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 162.0, 132.1, 132.0, 129.1, 128.9, 128.8, 128.5, 128.4, 127.8, 126.3, 115.7, 110.2, 31.4, 31.8, 29.5, 29.4, 29.3, 29.2 (m), 27.3, 26.4, 22.6, 14.0; MS (EI) *m/z* (rel. intensity) 353 ([M^+], 35), 336 (4), 324 (3), 282 (4), 241 (11), 240 (35), 226 (25), 224 (5), 212 (29), 200 (100), 187 (7), 146 (4), 118 (6), 91 (7), 77 (3), 55 (6), 43 (10); HR-MS (EI) ($C_{23}H_{31}NO_2$): calcd 353.235479, found 353.235538.

3.1.28. 3-Dodecyl-4-hydroxy-5-phenyl-1*H*-pyridin-2-one (31). A suspension of olefin **30b** (83 mg, 0.23 mmol) and Pd/C (20 mg, 10%, w/w) in MeOH (2.5 mL) was stirred under an atmosphere of H_2 (1 atm) for 72 h. The catalyst was filtered off through a short pad of Celite and was successively washed with hot MeOH and hot EtOAc, the combined filtrates were evaporated and the crude product was purified by HPLC (Nucleosil-100-5-C18/A, ∅ 4.5× 125 mm; MeOH/water 90:10; 0.8 mL min^{-1}; 308 K; 12.5 MPa; retention time: 4.88 min) to give compound **31** as a colorless solid (60%). ^{1}H NMR (400 MHz, CD_2Cl_2+CD_3OD) δ 7.45–7.32 (m, 6H), 2.55 (m, 2H), 1.51–1.40 (m, 2H), 1.42–1.17 (m, 18H), 0.83 (t, $J=6.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CD_2Cl_2+CD_3OD$) δ 166.1, 162.8, 135.5, 132.1, 130.5, 129.8, 128.9, 117.3, 114.6, 33.1, 31.0, 30.9, 30.8, 30.6, 29.6 (m), 24.5, 23.9, 14.9; IR (film) 2923, 2852, 1640, 1620, 1600, 1455, 1434, 1208, 1132, 1082, 881, 760, 699; MS (EI) *m/z* (rel. intensity) 355 ([M^+], 17), 338 (10), 214 (13), 201 (100), 200 (46), 188 (1), 173 (1), 146 (2), 130 (3), 118 (2), 91 (3), 55 (3), 43 (3), 41 (2); HR-MS ($C_{23}H_{33}NO_2$+Na) calcd 378.24054, found 378.24059 (M+Na).

3.2. Enzymatic assays

PTP1B-inhibition. PTP1B was purchased from Calbiochem (human recombinant). The enzyme (0.001 U) was pre-incubated with the inhibitors in a buffer (pH 7.2)[42] containing HEPES (25 mM), EDTA (2.5 mM), NaCl (50 mM), DTT (2 mM) and BSA (0.1%) for 15 min at room temperature. Then p-NPP was added (end concentration 50 μM) and the read-out (405 nm) was recorded on a microplate-reader at 37 °C continuously for 80 min. The reaction rate was determined from the absorption difference between 30 and 60 min reaction time.

Cdc25A-inhibition. The clone pET9d/His-Cdc25A was expressed in the *E. coli* strain BL21-DE3 and purified in the presence of 8M urea. 30 μg of the purified enzyme was pre-incubated with the inhibitors in a buffer pH 8.0 containing 50 mM Tris, 50 mM NaCl and 2 mM DTE for 15 min at room temperature.[43,44]

3.3. X-ray crystallographic study

Suitable crystals were obtained by recrystallization from *n*-hexane (**8**) and *n*-heptane (**25**). Data were recorded using an Enraf-Nonius KappaCCD diffractometer with graphite-monochromated Mo K_α-radiation ($\lambda=0.71073$ Å). The crystal was mounted in a stream of cold nitrogen gas. The structures were solved by direct methods (SHELXS-97)[45] and refined by full-matrix least-squares techniques against F^2 (SHELXL-97).[46] Hydrogen atoms were inserted from geometry consideration using the HFIX option of the program. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 236780 (**8**) and 236781 (**25**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1 EZ, UK (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

Selected X-ray crystallographic data for compound **8**. $C_{28}H_{41}NO_4Si_2$, $M_r=511.80$ g mol^{-1}, colorless, crystal size $0.44\times0.08\times0.06$ mm, orthorhombic, $P2_12_12$ [No. 18], $a=18.2689(2)$, $b=26.2118(3)$, $c=12.40800(10)$ Å,

$V=5941.70(11)$ Å^3, $Z=8$, $D_{calc}=1.144$ Mg m^{-3}, $\mu=0.150$ mm^{-1}, $T=100$ K, 74260 reflections collected, 13582 independent reflections, 8780 reflections with $I>2\sigma(I)$, $\theta_{max}=27.45°$, 651 refined parameters, $R=0.0686$, $R_w=0.1666$, $S=1.492$, largest diff. peak and hole $=0.547/-0.503$ e Å^{-3}.

Selected X-ray crystallographic data for compound **25**. $C_{29}H_{44}ClNO_4Si_2$, $M_r=562.28$ g mol^{-1}, colorless, crystal size $0.34\times0.04\times0.03$ mm^3, monoclinic, $P2_1$ [No. 4], $a=7.8949(3)$, $b=15.8034(6)$, $c=12.3838(5)$ Å, $\beta=92.396(2)°$, $V=1543.73(10)$ Å^3, $Z=2$, $D_{calc}=1.210$ Mg m^{-3}, $\mu=0.234$ mm^{-1}, $T=100$ K, 18212 reflections collected, 4405 independent reflections, 3171 reflections with $I>2\sigma(I)$, $\theta_{max}=23.25°$, 189 refined parameters, $R=0.0598$, $R_w=0.1175$, $S=1.032$, largest diff. peak and hole $=0.479/-0.431$ e Å^{-3}.

Acknowledgements

We thank Dr. J. Kohno, Tanabe Seiyaku Co. Ltd, Japan, for providing an authentic sample of TMC-69-6H for comparison and Dr. C. W. Lehmann for solving the X-ray structures. Financial support by the DFG (Leibniz award to A. F.), the Fonds der Chemischen Industrie and the Merck Research Council is acknowledged with gratitude.

References and notes

1. Hunter, T. *Cell* **2000**, *100*, 113–127.
2. For a recent success story see: Capdeville, R.; Buchdunger, E.; Zimmermann, J.; Matter, A. *Nat. Rev. Drug Discov.* **2002**, *1*, 493–502, and literature cited therein.
3. Zolnierowicz, S.; Bollen, M. *EMBO J.* **2000**, *19*, 483–488.
4. (a) Hinterding, K.; Alonzo-Díaz, D.; Waldmann, H. *Angew. Chem.* **1998**, *110*, 716–780. Hinterding, K.; Alonzo-Díaz, D.; Waldmann, H. *Angew. Chem. Int. Ed.* **1998**, *37*, 688–749. (c) Sheppeck, J. E.; Gauss, C.-M.; Chamberlin, A. R. *Bioorg. Med. Chem.* **1997**, *5*, 1739–1750.
5. McCluskey, A.; Sim, A. T. R.; Sakoff, J. A. *J. Med. Chem.* **2002**, *45*, 1151–1175.
6. (a) van Huijsduijnen, R. H.; Bombrun, A.; Swinnen, D. *Drug Discov. Today* **2002**, *7*, 1013–1019. (b) Zhang, Z.-Y. *Curr. Opin. Chem. Biol.* **2001**, *5*, 416–423. (c) Johnson, T. O.; Ermolieff, J.; Jirousek, M. R. *Nat. Rev. Drug Discov.* **2002**, *1*, 696–709.
7. (a) Lyon, M. A.; Ducruet, A. P.; Wipf, P.; Lazo, J. S. *Nat. Rev. Drug Discov.* **2002**, *1*, 961–976. (b) Vogt, A.; Cooley, K. A.; Brisson, M.; Tarpley, M. G.; Wipf, P.; Lazo, J. S. *Chem. Biol.* **2003**, *10*, 733–742.
8. (a) Galaktionov, K.; Lee, A. K.; Eckstein, J.; Draetta, G.; Meckler, J.; Loda, M.; Beach, D. *Science* **1995**, *269*, 1575–1577. (b) Draetta, G.; Eckstein, J. *Biochim. Biophys. Acta* **1997**, *1332*, M53–M63. (c) Nilsson, I.; Hoffmann, I. *Prog. Cell Cycle Res.* **2000**, *4*, 107–114.
9. For representative studies see: (a) Cangi, M. G.; Cukor, B.; Soung, P.; Signoretti, S.; Moreira, G.; Ranashinge, M.; Cady, B.; Pagano, M.; Loda, M. *J. Clin. Invest.* **2000**, *106*, 753–761. (b) Dixon, D.; Moyana, T.; King, M. *J. Exp. Cell Res.* **1998**, *240*, 236–243. (c) Gasparotto, D.; Maestro, R.; Piccinin, S.; Vukosavljevic, T.; Barzan, L.; Sulfaro, S.; Boiocchi, M. *Cancer Res.* **1997**, *57*, 2366–2368. (d) Wu, W.; Fan, Y. H.; Kemp, B. L.; Walsh, G.; Mao, L. *Cancer Res.* **1998**, *58*, 4082–4085.
10. (a) Hirano, N.; Kohno, J.; Tsunoda, S.; Nishio, M.; Kishi, N.; Okuda, T.; Kawano, K.; Komatsubara, S.; Nakanishi, N. *J. Antibiot.* **2001**, *54*, 421–427. (b) Kohno, J.; Hirano, N.; Sugawara, K.; Nishio, M.; Hashiyama, T.; Nakanishi, N.; Komatsubara, S. *Tetrahedron* **2001**, *57*, 1731–1735. (c) Sugawara, K.; Kohno, J.; Nakanishi, N.; Hashiyama, T. *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu* **2000**, *42*, 661–666. *Chem. Abstr.* **2001**, *134*, 340370.
11. (a) Fürstner, A.; Ruiz-Caro, J.; Prinz, H.; Waldmann, H. *J. Org. Chem.* **2004**, *69*, 459–467. (b) Fürstner, A. *Eur. J. Org. Chem.* **2004**, 943–958.
12. Brohm, D.; Philippe, N.; Metzger, S.; Bhargava, A.; Müller, O.; Lieb, F.; Waldmann, H. *J. Am. Chem. Soc.* **2002**, *124*, 13171–13178.
13. (a) Bialy, L.; Waldmann, H. *Angew. Chem.* **2002**, *114*, 1819–1822. (b) Bialy, L.; Waldmann, H. *Angew. Chem. Int. Ed.* **2002**, *41*, 1748–1751. (c) Bialy, L.; Waldmann, H. *Chem. Commun.* **2003**, 1872–1873.
14. Preliminary communication: Fürstner, A.; Feyen, F.; Prinz, H.; Waldmann, H. *Angew. Chem.* **2003**, *115*, 5519–5522. Fürstner, A.; Feyen, F.; Prinz, H.; Waldmann, H. *Angew. Chem. Int. Ed.* **2003**, *42*, 5361–5364.
15. (a) Grynkiewicz, G.; Zamojski, A. *Z. Naturforsch. B: Anorg. Chem. Org. Chem.* **1980**, *35*, 1024–1027. (b) Reetz, M. T.; Müller-Starke, H. *Liebigs Ann. Chem.* **1983**, 1726–1738.
16. Pertinent reviews: (a) Trost, B. M.; van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395–422. (b) Helmchen, G. *J. Organomet. Chem.* **1999**, *576*, 203–214. (c) Pfaltz, A.; Lautens, M. In *Comprehensive Asymmetric Catalysis*, Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H.; Eds.; Springer: Berlin; Vol. 2, 1999, pp 833–884.
17. Moreno-Manas, M.; Pleixats, R.; Villarroya, M. *Tetrahedron* **1993**, *49*, 1457–1464.
18. (a) van der Deen, H.; van Oeveren, A.; Kellogg, R. M.; Feringa, B. L. *Tetrahedron Lett.* **1999**, *40*, 1755–1758. (b) Comely, A. C.; Eelkema, R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2003**, *125*, 8714–8715. (c) Babu, R. S.; O' Doherty, G. A. *J. Am. Chem. Soc.* **2003**, *125*, 12406–12407.
19. (a) Negishi, E., Ed.; *Handbook of Organopalladium Chemistry for Organic Synthesis*. Wiley: New York, 2002. (b) Tsuji, J. Palladium Reagents and Catalysts: Innovations in Organic Synthesis, Wiley: New York, 1996.
20. For previous applications of allylpalladium chemistry to the synthesis of bioactive targets from this laboratory see: (a) Fürstner, A.; Weintritt, H. *J. Am. Chem. Soc.* **1997**, *119*, 2944–2945. (b) Fürstner, A.; Weintritt, H. *J. Am. Chem. Soc.* **1998**, *120*, 2817–2825. (c) Fürstner, A.; Gastner, T.; Rust, J. *Synlett* **1999**, 29–32. (d) Fürstner, A.; Gastner, T. *Org. Lett.* **2000**, *2*, 2467–2470. (e) Fürstner, A. *Angew. Chem. Int. Ed.* **2003**, *42*, 3582–3603. (f) Fürstner, A.; Krause, H. *J. Org. Chem.* **1999**, *64*, 8281–8286.
21. (a) Snider, B. B.; Lu, Q. *J. Org. Chem.* **1996**, *61*, 2839–2844. (b) Buck, J.; Madeley, J. P.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1992**, 67–77. (c) Hung, N. C.; Bisagni, E. *Synthesis* **1984**, 765–766. (d) Davis, S. J.; Elvidge, J. A.; Foster, A. B. *J. Chem. Soc. C* **1962**, 3638–3644.
22. (a) Achmatowicz, O.; Bukowski, P.; Szechner, B.;

Zwierzchowska, Z.; Zamoijski, A. *Tetrahedron* **1971**, *27*, 1973–1996. (b) Hoffmann, H. M. R.; Krumwiede, D.; Mucha, B.; Oehlerking, H. H.; Prahst, G. W. *Tetrahedron* **1993**, *49*, 8999–9018.

23. (a) Trost, B. M.; Van Vranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327–9343. (b) Trost, B. M.; Lee, C. B. *J. Am. Chem. Soc.* **2001**, *123*, 3671–3686.
24. van den Heuvel, M.; Cuiper, A. D.; van der Deen, H.; Kellogg, R. M.; Feringa, B. L. *Tetrahedron Lett.* **1997**, *38*, 1655–1658.
25. Sakemi, S.; Bordner, J.; DeCosta, D. L.; Dekker, K. A.; Hirai, H.; Inagaki, T.; Kim, Y.-J.; Kojima, N.; Sims, J. C.; Sugie, Y.; Sugiura, A.; Sutcliffe, J. A.; Tachikawa, K.; Truesdell, S. J.; Wong, J. W.; Yoshikawa, N.; Kojima, Y. *J. Antibiot.* **2002**, *55*, 6–18.
26. (a) Robins, M. J.; Kaneko, C.; Kaneko, M. *Can. J. Chem.* **1981**, *59*, 3356–3359. (b) Snider, B. B.; Lu, Q. *Tetrahedron Lett.* **1994**, *35*, 531–534.
27. (a) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26–28. (b) For a recent review see Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563–2585.
28. For a recent application of a Julia–Kocienski olefination in natural product synthesis from this laboratory see: (a) Fürstner, A.; Albert, M.; Mlynarski, J.; Matheu, M.; DeClercq, E. *J. Am. Chem. Soc.* **2003**, *125*, 13132–13142. (b) Fürstner, A.; Mlynarski, J.; Albert, M. *J. Am. Chem. Soc.* **2002**, *124*, 10274–10275.
29. (a) Barrett, A. M. G.; Carr, R. A. E.; Attwood, S. V.; Richardson, G.; Walshe, N. D. A. *J. Org. Chem.* **1986**, *51*, 4840–4856. (b) Banwell, M. G.; Bui, C. T.; Simpson, G. W. *J. Chem. Soc. Perkin Trans. 1* **1998**, 791–800.
30. Fürstner, A.; De Souza, D.; Parra-Rapado, L.; Jensen, J. T. *Angew. Chem.* **2003**, *115*, 5516–5518. Fürstner, A.; DeSouza, D.; Parra-Rapado, L.; Jensen, J. T. *Angew., Chem. Int. Ed.* **2003**, *42*, 5358–5360.
31. Mitsunobu, O. *Synthesis* **1981**, 1–28.
32. The corresponding coupling constants of the minor product formed in the hydrogenation step are in full accord with an equatorial orientation of its alkyl side chain, cf. $^{3}J_{H7,H8}=$ 10.0 Hz, $^{3}J_{H10,H11ax}=11.3$ Hz, $^{3}J_{H10,H11eq}=2.6$ Hz
33. (a) Matlin, S. A.; Sammes, P. G.; Upton, R. M. *J. Chem. Soc. Perkin Trans. 1* **1979**, 2481–2487. (b) Rigby, J. H.; Qabar, M. *J. Org. Chem.* **1989**, *54*, 5852–5853.
34. (a) Vedejs, E.; Larsen, S. *Org. Synth.* **1986**, *64*, 127–137. (b) Mimoun, H.; de Roch, I. S.; Sajus, L. *Bull. Soc. Chim. Fr.* **1969**, 1481–1492.
35. Likewise, the optical rotations and the CD spectra do not allow an unambiguous decision. While the CD spectra of (17*R*)- and (17*S*)-**2** are indistinguishable, the optical rotation reported for TMC-69-6H is $[\alpha]^{25}=+143.4$ ($c=0.48$, MeOH);[10] the optical rotation of the authentic sample of **2** made available to us, however, was lower than this reported value. When corrected for the residual water in the sample, we record an $[\alpha]^{20}\approx+99$ ($c=0.18$, MeOH). The data of our analytically pure synthetic compounds are as follows: (17*R*)-**2**. $[\alpha]^{20}=+102.3$ ($c=0.6$, MeOH); (17*S*)-**2**. $[\alpha]^{20}=+88.6$ ($c=0.95$, MeOH), cf. Section 3
36. Crich, D.; Dudkin, V. *J. Am. Chem. Soc.* **2002**, *124*, 2263–2266.
37. (a) Todd, J. L.; Tanner, K. G.; Denu, J. M. *J. Biol. Chem.* **1999**, *274*, 13271–13280. (b) Usui, T.; Kojima, S.; Kidokoro, S.; Ueda, K.; Osada, U.; Sodeoka, M. *Chem. Biol.* **2001**, *8*, 1209–1220. (c) Ishibashi, T.; Bottaro, D. P.; Chan, A.; Miki, T.; Aaronson, S. *Proc. Natl. Acad. Sci. USA* **1992**, *89*, 12170–12174.
38. (a) Zhang, Z.-Y. *Curr. Opin. Chem. Biol.* **2001**, *5*, 416–423. (b) Johnson, T. O.; Ermolieff, J.; Jirousek, M. R. *Nat. Rev. Drug Discov.* **2002**, *1*, 696–709. (c) Aggen, J. B.; Nairn, A. C.; Chamberlin, R. *Chem. Biol.* **2000**, *7*, R13–R23. (d) McCluskey, A.; Sakoff, J. A. *Mini-Rev. Med. Chem.* **2001**, *1*, 43–55.
39. For a structurally different 2-pyridone derivative bearing a *N*-methylphosphonate moiety which exhibits phosphatase inhibiting properties see: Fu, J.-M.; Castelhano, A. L. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2813–2816.
40. While several other bioactive natural products containing an *N*-hydroxy-2-pyridone motif are known in the literature, it appears that none of them has been tested for phosphatase inhibition. The same pertains to structurally related 2-pyridone alkaloids that are not oxidized on nitrogen. For characteristic members of these series see: (a) Militarinone A: Schmidt, K.; Günther, W.; Stoyanova, S.; Schubert, B.; Li, Z.; Hamburger, M. *Org. Lett.* **2002**, *4*, 197–199. (b) Militarinone D: Schmidt, K.; Riese, U.; Li, Z.; Hamburger, M. *J. Nat. Prod.* **2003**, *66*, 378–383. (c) Tenellin: El Basyousni, S. H.; Brewer, D.; Vining, L. C. *Can. J. Bot.* **1968**, *46*, 441–448. (d) Bassianin: Wat, C.-K.; McInnes, A. G.; Smith, D. G.; Wright, J. L. C.; Vining, L. C. *Can. J. Chem.* **1977**, *55*, 4090–4098. (e) Fischerin: Fujimoto, H.; Ikeda, M.; Yamamoto, K.; Yamazaki, M. *J. Nat. Prod.* **1993**, *56*, 1268–1275. (f) Pyridomacrolidin: Takahashi, S.; Kakinuma, N.; Uchida, K.; Hashimoto, R.; Yanagisawa, T.; Nakagawa, A. *J. Antibiot.* **1998**, *51*, 596–598. (g) Leporin A: TePaske, M. R.; Gloer, J. B.; Wicklow, D. T.; Dowd, P. F. *Tetrahedron Lett.* **1991**, *32*, 5687–5690. (h) Fusaricide: McBrien, K. D.; Gao, Q.; Huang, S.; Klohr, S. E.; Wang, R. R.; Pirnik, D. M.; Neddermann, K. M.; Bursuker, I.; Kadow, K. F.; Leet, J. E. *J. Nat. Prod.* **1996**, *59*, 1151–1153. (i) Pyridoxatin: Teshima, Y.; Shin-ya, K.; Shimazu, A.; Furihata, K.; Chul, H. S.; Furihata, K.; Hayakawa, Y.; Nagai, K.; Seto, H. *J. Antibiot.* **1991**, *44*, 685–687. (j) BN-227: Itoh, J.; Amano, S.; Ogawa, Y.; Kodama, Y.; Ezaki, N.; Yamada, Y. *J. Antibiot.* **1980**, *33*, 377–382. (k) Funiculosin: Ando, K.; Matsuura, I.; Nawata, Y.; Endo, H.; Sasaki, H.; Okytomi, T.; Saehi, T.; Tamura, G. *J. Antibiot.* **1978**, *31*, 533–538. (l) Sambutoxin: Kim, J.-C.; Lee, Y.-W.; Tamura, H.; Yoshizawa, T. *Tetrahedron Lett.* **1995**, *36*, 1047–1050. (m) Oxysporidinone: Breinholt, J.; Ludvigsen, S.; Rassing, B. R.; Rosendahl, C. N.; Nielsen, S. E.; Olsen, C. E. *J. Nat. Prod.* **1997**, *60*, 33–35. (n) Harzianopyridone: Dickinson, J. M.; Hanson, J. R.; Hitchcock, P. B.; Claydon, N. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1885–1887.
41. Compostella, F.; Franchini, L.; Panza, L.; Prosperi, D.; Ronchetti, F. *Tetrahedron* **2002**, *58*, 4425–4428.
42. Hamaguchi, T.; Masuda, A.; Morino, T.; Osada, H. *Chem. Biol.* **1997**, *4*, 279.
43. Blomberg, I.; Hoffmann, I. *Mol. Cell. Biol.* **1999**, *19*, 6183.
44. Baratte, B.; Meijer, L.; Galaktionov, K.; Beach, D. *Anticancer Res.* **1992**, *12*, 873.
45. Sheldrick, G. M. *SHELXS-97: Program for the determination of crystal structures*; University of Göttingen: Germany, 1997.
46. Sheldrick, G. M. *SHELXL-97: Program for least-squares refinement of crystal structures*; University of Göttingen: Germany, 1997.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 60 (2004) 9559–9568

Studies towards the total synthesis of palau'amine. Formation of 4,5-dihydropyrrole-2-carboxylate intermediates by alkene–enamide ring-closing metathesis

Jason D. Katz[†] and Larry E. Overman*

Department of Chemistry, 516 Rowland Hall, University of California at Irvine, Irvine, CA 92697-2025, USA

Received 9 April 2004; revised 7 June 2004; accepted 9 June 2004

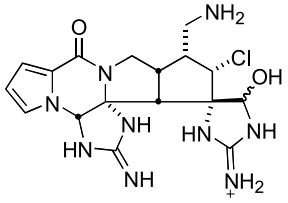
Available online 27 August 2004

Dedicated to Professor Alois Fürstner on receipt of the 2004 Tetrahedron Chair in Organic Synthesis

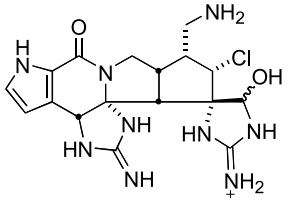
Abstract—A highly functionalized 4,5-dihydropyrrole-2-carboxylate is assembled by alkene–enamide ring-closing metathesis. Subsequent intramolecular azomethine imine dipolar cycloaddition provides a triazacyclopenta[*cd*]pentalene intermediate of potential use in a total synthesis of palau'amine.

1. Introduction

A diverse array of secondary metabolites displaying a broad range of biological activities have been isolated from sponges.[1] A number of these metabolites contain one or more guanidine functional groups embedded in novel polycyclic ring systems.[2] The palau'amines, styloguanidines and konbu'acidin, exemplified by palau'amine (**1**) and styloguanidine (**2**), are some of the most structurally intricate members of this group of marine guanidine alkaloids.[3–5]



palau'amine (**1**)



styloguanidine (**2**)

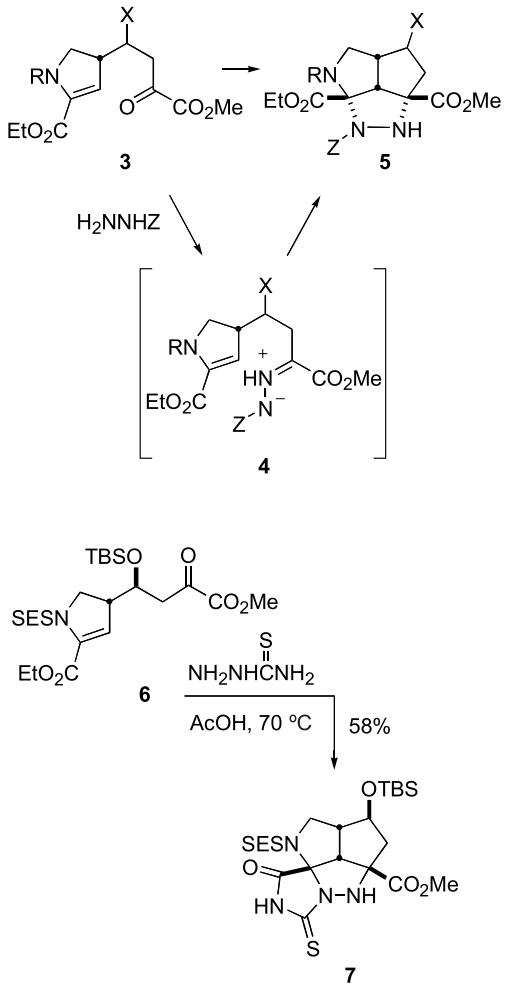
The diverse biological activities of palau'amine, in particular its substantial immunosupressive activity and apparent low toxicity, make this alkaloid an important target for total synthesis.[3] Much of the structural complexity of palau'amine resides in its 3-azabicyclo[3.3.0]octane ring system, a central fragment that contains six contiguous stereocenters. Five of these stereogenic carbons comprise the cyclopentane ring, which is substituted on the concave α face at every carbon. This density of functionality, combined with the two proximal spiroguanidine fragments, make palau'amine an unusually challenging synthetic target.[6] Published reports from other groups have focused largely on installing the functionality of the cyclopentane ring.[7–10] In contrast, previous work from our laboratories has addressed the issue of relating the configuration of the two spiroguanidine units to that of the central 3-azabicyclo-[3.3.0]octane unit.[11,12] Our approach to this objective has been to employ an intramolecular azomethine imine 1,3-dipolar cycloaddition to construct triazacyclopenta-[*cd*]pentalenes that encode these structural features of palau'amine: **3**→**4**→**5** (Scheme 1).

We recently described the preparation of cycloaddition precursor **6** having a siloxy substituent on the side chain and demonstrated that it, and its siloxy epimer, successfully condensed with thiosemicarbazide to form the desired triazacyclopenta[*cd*]pentalene (azatriquinane) products.[12] However, the Dieckmann cyclization strategy we employed to assemble the 4,5-dihydropyrrole-2-carboxylate moiety of **6** was inefficient, and would not be useful in a total synthesis endeavor directed at palau'amine.

Only a few methods have been described for the synthesis of 4,5-dihydropyrrole-2-carboxylates. Most involve functionalization of proline analogs by either elimination of a heteroatom from the α-[13,14] or β-position[12,15] of a prolinate, or by rearrangement of the double bond of a pyrroline

Keywords: Palau'amine; Enamide; Ring-closing metathesis; 4,5-Dihydropyrrole-2-carboxylate; Azomethine imine cycloaddition.
* Corresponding author. Tel.: +1-949-824-7156; fax: +1-949-824-3866; e-mail: leoverma@uci.edu
[†] Current address: Department of Medicinal Chemistry, Merck & Co., Inc.; P.O. Box 2000; Rahway, NJ 07065, USA.

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.06.140



Scheme 1.

precursor.[16,17] Other constructions that have been used to access these heterocycles employ as key steps: oxidative decarboxylations;[18] metalation of enamides;[19] carbonylation of lactam-derived enol triflates[20] or enol phosphates;[21] or intramolecular Mitsunobu alkylations.[22] In this paper, we report the development of a convergent strategy to prepare potential palau'amine precursors that utilizes an alkene–enamide ring-closing metathesis (RCM) to construct the 4,5-dihydropyrrole-2-carboxylate ring system of the cycloaddition substrates.

1.1. Synthesis plan

The retrosynthetic analysis that led to the convergent synthesis sequence described herein is outlined in Scheme 2. We saw the 4,5-dihydropyrrole-2-carboxylate **8** arising by RCM of densely-functionalized diene **9**.[23] The dehydroalanine functionality of diene **9** would be formed from an appropriate amino acid analog, whereas the α-keto ester functionality would be installed by elaboration of an aldehyde precursor. Thus, diene amino ester **9** simplifies to pyrrole acid **10** and unsaturated α-aminoester **11**. Further retrosynthetic simplification of aminoester **11** leads to the simple α-amino ester and homoallylic alcohol precursors **12** and **13**, respectively.

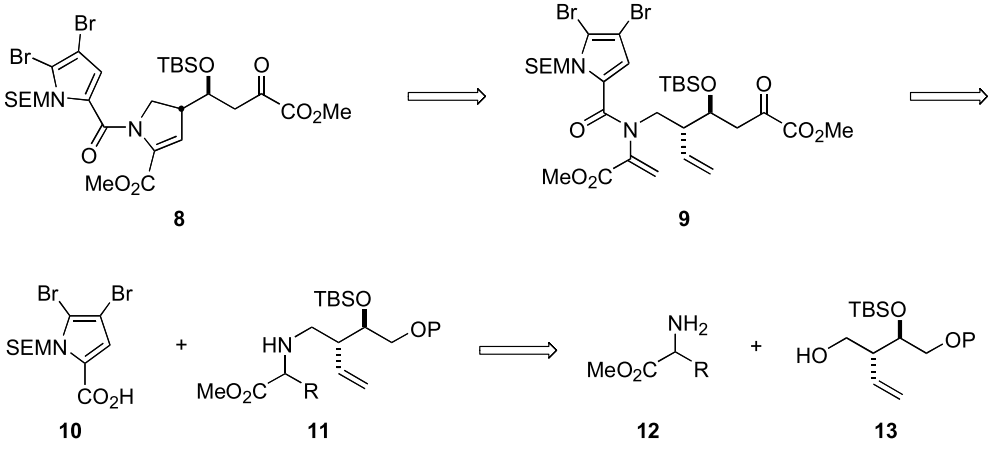
2. Results and discussion

2.1. Model system for the ring-closing metathesis

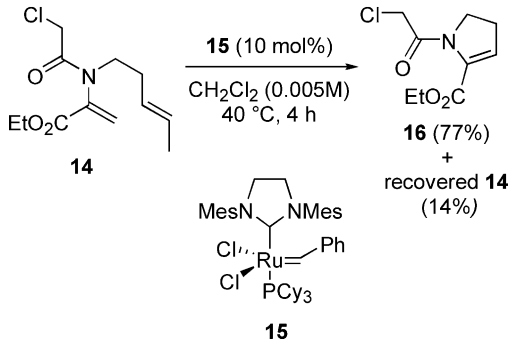
As there were no previous examples of forming 4,5-dihydropyrrole-2-carboxylates by RCM of dehydroalanine precursors,[23–27] we decided to pursue this transformation initially with a simple model substrate. The known diene **14**[28] was chosen for these studies (Scheme 3). We were pleased to observe that addition of 10 mol% of the Grubbs *N*-heterocyclic carbene catalyst **15**[23] to diene **14** at 40 °C led to the formation of the desired 4,5-dihydropyrrole-2-carboxylate **16** in 77% yield after only 4 h. We turned to prepare more elaborate dehydroalanine precursors.

2.2. Synthesis of homoallylic amines 22

The synthesis of the RCM precursors was designed so that enantioenriched intermediates could be prepared from a readily available enantioenriched epoxy alcohol precursor.[29] However, for convenience, our initial survey of this chemistry was carried out in a racemic series. Thus, preparation of homoallylic alcohol **19** began with *m*-CPBA epoxidation[30] of allylic alcohol **17**,[31] followed by copper catalyzed regioselective opening of the epoxy alcohol product with vinylmagnesium bromide to produce 1,3-diol



Scheme 2.



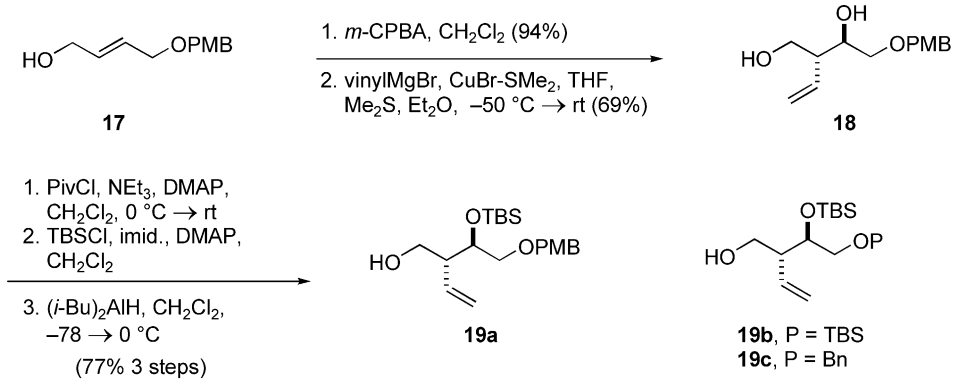
Scheme 3.

18 in 65% overall yield (Scheme 4).[32] Employing CuI or CuI–PBu_3 in the epoxide opening step was less effective because significant quantities of a product resulting from halide opening of the epoxide were produced; the use of CuBr–SMe_2 minimized formation of this halide by-product. The secondary alcohol of diol **18** could be selectively protected to provide homoallylic alcohol **19a** in good yield by a three step sequence that involved sequential masking of the primary alcohol as a pivalate ester, protection of the secondary alcohol, and reductive cleavage of the pivalate.[32c] A similar sequence was employed to prepare congeners **19b**,**c**.

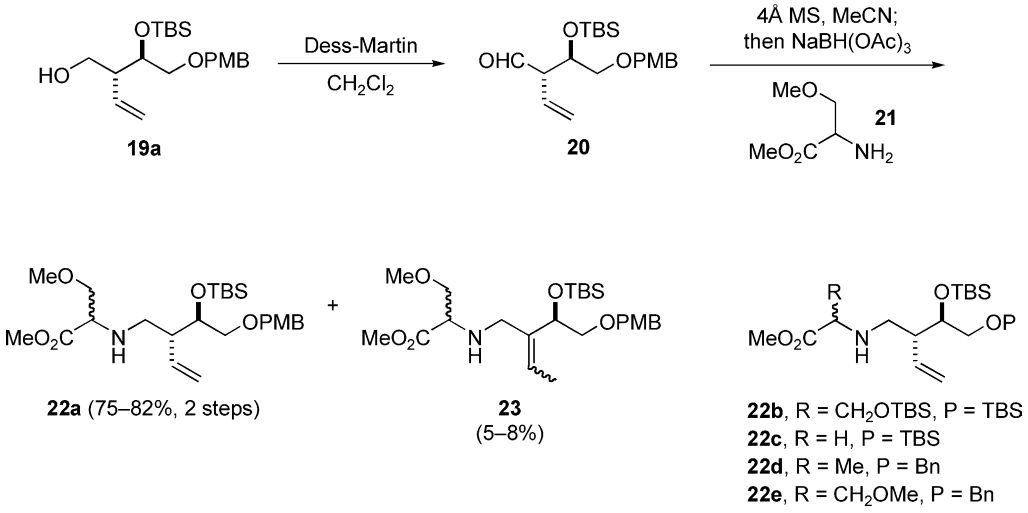
With the homoallylic alcohols in hand, it was necessary to elaborate these intermediates to α-aminoesters. Initial attempts at alkylating serine methyl ester with a triflate derivative of **19b** were unsuccessful, so a reductive amination sequence was developed (Scheme 5). Alcohol **19a** could be oxidized cleanly to the β,γ-unsaturated aldehyde **20** with negligible double bond migration by reaction with the Dess–Martin periodinane.[33] Subsequent reductive amination of this intermediate with serine-derived amino ester **21**[34] and sodium triacetoxyborohydride provided secondary amine **22a** in 70% yield from the alcohol. A small amount of allylic amine **23**, resulting from isomerization of the double bond during the reductive amination step, was also produced. The analogous homoallylic secondary amines **22b–e** were prepared by a similar series of transformations.

2.3. Coupling of the homoallyl amines 22 with pyrrole carboxylic acid 10

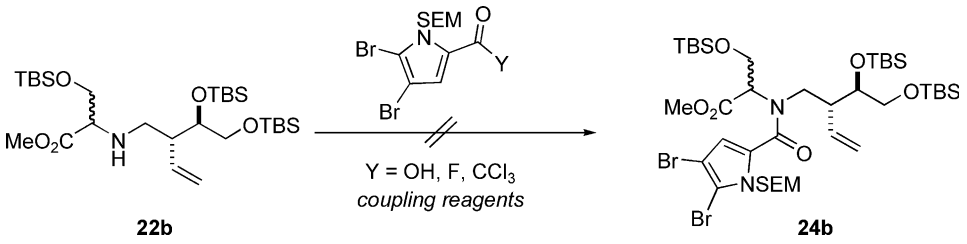
Coupling of the homoallylic amine to the acylpyrrole fragment proved to be quite demanding. Initial attempts to couple the TBS-protected serine analog **22b** with pyrrole acid **10**, mediated by standard coupling reagents (PyBrOP, HATU, or DCC), were unsuccessful (Scheme 6). Related condensations of **22b** with the corresponding pyrrole



Scheme 4.

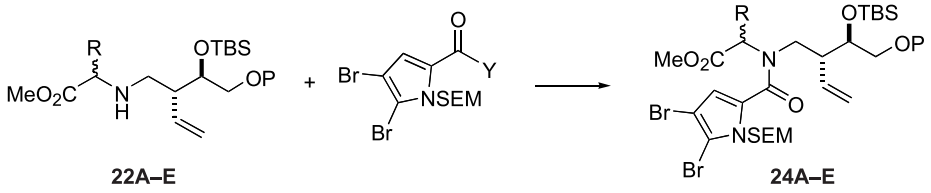


Scheme 5.



Scheme 6.

Table 1.



Amine	R	P	Y	Coupling agent	Amide	Yield (%)
22b	CH_2OTBS	TBS	OH	PyBrOP[a]	**24b**	0
22c	H	TBS	OH	PyBrOP[a]	**24c**	95
22d	Me	Bn	OH	PyBrOP[a]	**24d**	78
22e	CH_2OMe	Bn	OH	PyBrOP[a,b]	**24e**	0
22e	CH_2OMe	Bn	OH	HATU[c]	**24e**	0
22e	CH_2OMe	Bn	OC_6F_5	N/A[d]	**24e**	0
22e	CH_2OMe	Bn	OH	BOPCl[e]	**24e**	87
22a	CH_2OMe	PMB	OH	BOPCl[e]	**24a**	>95

[a] PyBrOP, *i*-Pr_2NEt, DMAP, CH_2Cl_2, rt.
[b] PyBrOP, *i*-Pr_2NEt, DMAP, DMF, rt.
[c] HATU, HOAt, *i*-Pr_2NEt, DMF, rt.
[d] *i*-Pr_2NEt, DMAP, CH_2Cl_2 or NaH, THF, rt.
[e] BOPCl, *i*-Pr_2NEt, MeCN, 0 °C to rt.

carboxylic acid fluoride or trichloromethyl ketone failed also.

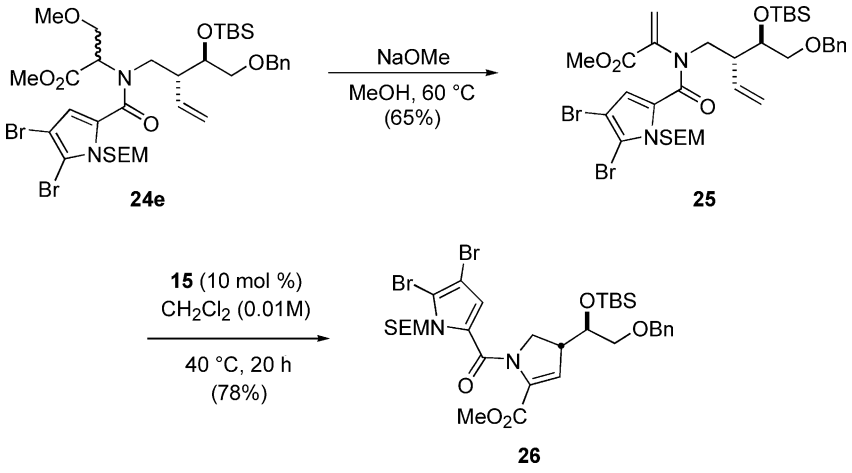
To examine the role of the steric environment around the amino acid substituent in the amide formation, we investigated the coupling of simpler amino acid analogs with the pyrrole acid. As can be seen in Table 1, PyBrOP-mediated coupling of pyrrole acid **10** with glycine derivative **22c** proceeded in high yield.[35] Under the same reaction conditions, alanine derivative **22d** was converted to the amide **24d** in 78% yield. Taken together with the failure of the TBS-protected serine derivative **22b** to couple with pyrrole acid **10**, these experiments indicated that the size of the amino acid side chain had a large effect on the efficiency of the amide coupling. Fortunately, we discovered that the *O*-methyl serine analog **22e** could be coupled to pyrrole acid **10** if BOPCl, rather than PyBrOP, was used as the coupling agent. Using BOPCl, secondary amines **22a** and **22e** were converted to amides **24a** and **24e** in >95 and 87% yields, respectively.‡

‡ After these results were obtained, BOPCl-mediated coupling of the TBS derivative **22b** with acid **10** was attempted; however this reaction proceeded to only 10–15% conversion.

2.4. Ring-closing metathesis and assembly of the potential palau'amine precursor 31

With the acylpyrrole installed, we turned to investigate formation of the dehydroalanine functionality (Scheme 7). Treatment of the methyl ether derivative **24e** with sodium methoxide in methanol resulted in elimination of methanol to give the dehydroamino ester **25** in an unoptimized 65% yield, 89% based on consumed starting material.[36] Exposure of this diene to metathesis catalyst **15** delivered dihydropyrrole **26** in 78% yield, demonstrating that alkene–enamide RCM would be a viable strategy for forming highly functionalized 4,5-dihydropyrrole-2-carboxylates.

In our earlier preparations of substrates for intramolecular azomethine imine cycloadditions, a Horner–Emmons reaction was employed to install the α-ketoester functionality.[12] We hypothesized that the basic conditions employed to generate the dehydroalanine might also facilitate the Horner–Emmons reaction.[37] To pursue this possibility, *p*-methoxybenzyl ether **24a** was cleaved selectively with DDQ to give primary alcohol **27** in high yield (Scheme 8). This intermediate was then oxidized with the Dess–Martin reagent and the aldehyde product was immediately condensed at room temperature with phosphonate **28**[38] in the presence of sodium *tert*-butoxide in a *tert*-butanol-THF solvent mixture. As hoped, these conditions promoted both

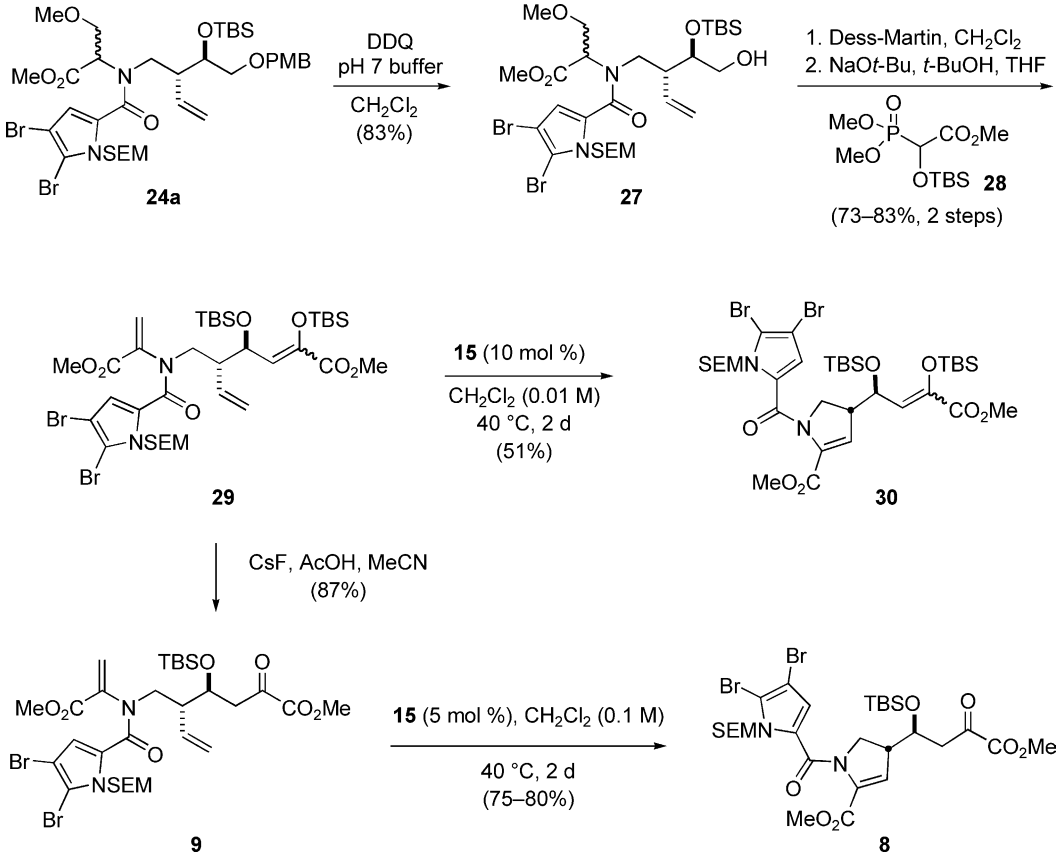


Scheme 7.

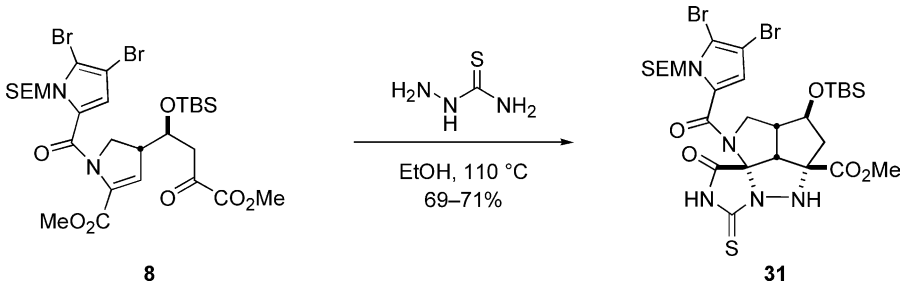
the Horner–Emmons condensation and the β-elimination of methanol to deliver dehydroalanine derivative **29** in 73–83% yield as an inconsequential 2:1 mixture of enoxysilane stereoisomers.

We turned to examine RCM for generating a fully constituted cycloaddition substrate. Cyclization of **29** using the RCM conditions optimized earlier with less intricate substrates provided dihydropyrrole **30** in 51% yield, together with 28% of recovered starting material (Scheme 8). It was significant that the dihydropyrrole product was highly enriched in one enoxysilane stereoisomer, whereas recovered diene **29** was enriched in the other geometric isomer. Obviously, ring formation was occurring more rapidly with one of the two side chain stereoisomers. To avoid this complication, we decided to examine the pivotal RCM step after discharge of the siloxy group. Therefore, siloxy diene **29** was allowed to react with buffered CsF to generate α-keto ester **9**. Cyclization of this intermediate with RCM catalyst **15** at 40 °C for 2 days at substrate concentrations as high as 0.1 M now delivered the desired dihydropyrrole **8** in excellent yield (75–80%).

Although the main focus of this study was to develop a practical route to fully functionalized cycloaddition substrates such as **8**, we briefly examined the condensation of **8**



Scheme 8.



Scheme 9.

with thiosemicarbazide to form triazatriquinane **31**. Using conditions we had employed earlier with less elaborate substrates (AcOH, 70 °C),[12] this conversion was extremely slow, requiring >7 days to go to completion. After a brief survey of reaction conditions, we found that heating an ethanolic solution of dihydropyrrole **8** and thiosemicarbazide in a sealed tube at 110 °C provided triazacyclopenta[*cd*]pentalene **31** in 69–71% yield after only two days (Scheme 9).

3. Conclusion

A RCM is the central step in the practical synthesis of 4,5-dihydropyrrole-2-carboxylate **8**. As this product contains a wealth of diverse functionality—acylpyrrole, bromide, α,β-unsaturated ester, α-keto ester and silyl ether—this RCM reaction superbly highlights the remarkable functional group tolerance of the Grubbs ruthenium metathesis catalysts.[23] Efforts to further elaborate triazacyclopenta-[*cd*]pentalene-containing cycloadducts such as **31** to palau'amine and congeners are underway.

4. Experimental

4.1. General methods

The procedure we employ to purify THF, CH_2Cl_2, Et_2O, DME, and toluene has been described: Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J.; *Organometallics* **1996**, *15*, 1518–1520. Triethylamine, *i*-Pr_2NEt, DMF, and MeCN were purified in a similar manner using modified alumina columns provided by GlassContour. All reactions were conducted using flame-dried glassware under a nitrogen atmosphere unless stated otherwise. Commercial reagents were used as received unless otherwise indicated.

Analytical thin layer chromatography was carried out using 0.25 mm silica plates from Merck. Eluted plates were visualized first with UV light and then by staining with ceric sulphate/molybic acid or basic potassium permanganate. Flash chromatography was performed using 230–400 mesh (particle size 0.04–0.063 mm) silica gel purchased from Merck. ^1H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were obtained on Bruker 500 FT NMR instruments. NMR spectra were typically recorded in $CDCl_3$ as solvent and were reported as δ values in ppm relative to chloroform. Infrared (IR) spectra were obtained were obtained using a ASI React IR module.

Although certain compounds were isolated as inseparable mixtures of diastereomers, the various resonances are distinct in the ^1H NMR spectra. In these instances, the signal has been reported in the following format: [3.30 (s), 3.25 (s), 3H]. This particular example would represent a methyl ether present in the diastereomeric mixture. In one diastereomer, the methyl group appears as a singlet at δ 3.30, whereas in the other diastereomer it appears at δ 3.25 as a singlet.

4.1.1. 4-(4-Methoxybenzyloxy)-2-vinylbutane-1,3-diol (18). A 3 L three-neck reaction flask equipped with a low temperature thermometer and an addition funnel was charged with freshly prepared CuBr–SMe_2 (7.65 g, 37.2 mmol), 1.7 L of Et_2O, and 335 mL of SMe_2 at room temperature. This clear, colorless solution was cooled to −50 °C, during which time a small amount of a fine white precipitate formed. A solution of freshly prepared vinylmagnesium bromide (370 mL of a 1 M solution in THF, 370 mmol) was added via cannula such that the internal temperature remained below −50 °C, then the slurry was maintained at −50 °C for an additional 1 h. The slurry initially turned a deep brown color upon addition of the Grignard reagent and over the course of the addition changed to a greenish-yellow and then a reddish-brown color. A solution of the (*E*)-2,3-epoxy-4-(4-methoxybenzyloxy)butanol (21.0 g, 93.0 mmol) in 170 mL of Et_2O was added dropwise via an addition funnel such that the internal temperature remained below −50 °C, then the slurry was maintained at −50 °C for an additional 1 h. The slurry was allowed to warm to −30 °C over 2 h then maintained at −30 °C for an additional 2 h. The reaction mixture was cooled to −45 °C and then allowed to warm to 10 °C over an 11 h period to give a purplish solution. Excess Grignard reagent was quenched by the addition of 100 mL of a 2:1 solution of saturated aqueous NH_4Cl-concentrated NH_4OH, then the mixture was poured into an additional 1.5 L of this buffer and was stirred vigorously until all of the solids had dissolved and the aqueous layer was a deep blue. The layers were separated and the organic layer was washed with this ammonia buffer solution (200 mL) and brine (200 mL). This solution was dried (Na_2SO_4) and concentrated to give a yellow oil containing crude **18** and the regioisomeric 1,2-diol.

This yellow oil was diluted with 230 mL of MeOH, 50 mL of THF, and 230 mL of H_2O, and then $NaIO_4$ (19.8 g, 93.0 mmol) was added in one portion. The $NaIO_4$ initially starts to dissolve, but a heavier white precipitate quickly forms. After the suspension was rapidly stirred for 1 h, it was poured into 1 L of EtOAc and washed with saturated

aqueous $NaHCO_3$ (3×100 mL) and brine (100 mL). The combined aqueous layers were back-extracted with EtOAc (3×50 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated. Purification of the residue on silica gel (gradient elution, 30% EtOAc–hexanes to 45% EtOAc–hexanes) gave 15.8 g of **18** as a pale yellow oil that was contaminated with approximately 340 mg of the starting epoxide and 460 mg of material from bromide opening of the epoxide. Another 2.11 g of material was isolated that contained an additional 2.1 mmol of diol **18** along with 5.1 mmol of bromide. Total yield of diol **18** was 69%: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24–7.28 (m, 2H), 6.88–6.92 (m, 2H), 5.62 (ddd, J=17.3, 10.3, 9.0 Hz, 1H), 5.13–5.19 (m, 2H), 4.48 (AB_q, J_{AB}=11.5 Hz, $\Delta\nu_{AB}$=14.9 Hz, 2H), 3.80–3.90 (m, 2H), 3.82 (s, 3H), 3.66–3.71 (m, 1H), 3.56 (dd, J=9.8, 3.3 Hz, 1H), 3.39 (dd, J=9.8, 7.3 Hz, 1H), 2.80 (br s, 1H), 2.73 (br s, 1H), 2.38–2.45 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.6, 135.6, 130.0, 129.6, 118.6, 114.1, 73.3, 73.1, 72.8, 65.4, 55.5, 49.1; IR (film) 3391, 3082, 2904, 1614, 1514, 1305, 1244, 1174, 1081 cm^{-1}; HRMS (CI) calcd for $C_{14}H_{20}O_4$ (M): 252.1362, found: 252.1362.

4.1.2. 2,2-Dimethylpropionic acid 2-[1-hydroxy-2-(4-methoxybenzyloxy)-ethyl]but-3-enyl ester. The mixture of diol **18** (15.8 g, 62.7 mmol) contaminated with bromide (460 mg, 1.5 mmol) and epoxide (340 mg, 1.5 mmol) impurities was diluted with 1.3 L of CH_2Cl_2 and NEt_3 (22.6 mL, 161 mmol) and cooled to 0 °C. Pivaloyl chloride (8.34 mL, 67.4 mmol) and DMAP (393 mg, 3.21 mmol) were added and the solution was allowed to warm to room temperature overnight. The yellow solution was poured into saturated aqueous $NaHCO_3$ (400 mL) and the organic layer was washed with $NaHCO_3$ (200 mL) and brine (200 mL), then dried (Na_2SO_4) and concentrated. Purification of the residue on silica gel (gradient elution, 8% EtOAc–hexanes to 15% EtOAc–hexanes to 25% EtOAc–hexanes) gave 19.9 g (92%) of a pale yellow oil that consisted of a 9.9:1 mixture of the primary and secondary pivalate esters: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24–7.28 (m, 2H), 6.87–6.91 (m, 2H), 5.62–5.71 (m, 1H), 5.11–5.16 (m, 2H), 4.48 (AB_q, J_{AB}=11.3 Hz, $\Delta\nu_{AB}$=11.7 Hz, 2H), 4.31 (dd, J=11.0, 6.5 Hz, 1H), 4.21 (dd, J=11.0, 4.5 Hz, 1H), 3.82 (s, 3H), 3.74–3.80 (m, 1H), 3.56 (dd, J=9.5, 3.0 Hz, 1H), 3.40 (dd, J=9.5, 7.0 Hz, 1H), 2.57 (d, J=4.5 Hz, 1H), 2.50–2.57 (m, 1H), 1.19 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.7, 159.5, 135.6, 130.1, 129.6, 118.5, 114.1, 73.3, 72.4, 70.2, 64.5, 55.5, 47.1, 39.0, 27.4; IR (film) 3494, 3078, 2975, 2906, 2871, 1725, 1613, 1515, 1285, 1248, 1165 cm^{-1}; HRMS (CI) calcd for $C_{19}H_{28}O_5$ (M): 336.1937, found: 336.1937.

4.1.3. 2,2-Dimethylpropionic acid 2-[1-(*tert*-butyldimethylsiloxy)-2-(4-methoxybenzyloxy)ethyl]but-3-enyl ester. The 9.9:1 mixture of pivalate esters (23.2 g, 69.2 mmol combined) was diluted in 350 mL of CH_2Cl_2. Imidazole (20.7 g, 304 mmol) was added and the mixture was allowed to stir until all of the imidazole had dissolved. Then TBSCl (20.9 g, 138 mmol) was added (a colorless precipitate immediately formed), followed by the addition of DMAP (422 mg, 3.46 mmol). The slurry was allowed to stir overnight, then poured into saturated aqueous $NaHCO_3$ (100 mL) and the organic layer was washed with $NaHCO_3$ (100 mL) and brine (100 mL) then dried (Na_2SO_4) and concentrated. Purification of the residue on silica gel (gradient elution, hexanes to 5% EtOAc–hexanes) gave 30.5 g (98%) of a pale yellow oil that consisted of a 9.9:1 mixture of regioisomers: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23–7.28 (m, 2H), 6.86–6.90 (m, 2H), 5.69–5.77 (m, 1H), 5.08–5.13 (m, 2H), 4.40–4.46 (m, 2H), 4.22 (dd, J=11.0, 5.0 Hz, 1H), 4.16 (dd, J=11.0, 7.3 Hz, 1H), 3.89 (ddd, J=5.8, 5.8, 4.3 Hz, 1H), 3.82 (s, 3H), 3.49 (dd, J=10.0, 4.5 Hz, 1H), 3.38 (dd, J=10.0, 5.8 Hz, 1H), 2.59–2.67 (m, 1H), 1.19 (s, 9H), 0.88 (s, 9H), 0.053 (s, 3H), 0.050 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.6, 159.3, 136.7, 130.5, 129.5, 117.6, 113.9, 73.2, 72.5, 64.1, 55.4, 47.2, 39.0, 27.4, 26.1, 18.4, −4.0, −4.8; IR (film) 2958, 2931, 2858, 1729, 1613, 1515, 1465, 1362, 1248, 1036 cm^{-1}; HRMS (CI) calcd for $C_{25}H_{43}O_5Si$ $(M+H)^+$: 451.2880, found: 451.2879.

4.1.4. 2-[1-(*tert*-Butyldimethylsiloxy)-2-(4-methoxybenzyloxy)ethyl]but-3-en-1-ol (19a). A three-neck reaction flask equipped with a mechanical stirrer, a low temperature thermometer, and an addition funnel was charged with the 9.9:1 mixture of TBS ethers (30.5 g, 67.6 mmol combined) and 750 mL of CH_2Cl_2. The solution was cooled to −78 °C and a solution of DIBAL-H (99.0 mL of a 1.5 M solution in toluene, 149 mmol) was added dropwise via addition funnel over 90 min. After the addition was complete, the solution was maintained at −78 °C for 40 min, then allowed to warm to 0 °C. Excess DIBAL-H was quenched by the careful addition of 500 mL of a half-saturated potassium–sodium tartrate solution to give a gelatinous mixture. Then 100 mL of THF were added and the mixture was stirred rapidly for 2 h at room temperature, during which time it gradually turned from a gel to a heterogeneous mixture. The layers were separated and the organic layer was washed with H_2O (2×100 mL) and brine (100 mL). The combined aqueous layers were back extracted with EtOAc (100 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated. Purification of the residue on silica gel (gradient elution, 5% EtOAc–hexanes to 20% EtOAc–hexanes) gave 21.1 g of isomerically pure **19a** (94% based on the amount of primary pivalate ester in the starting mixture) as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23–7.27 (m, 2H), 6.86–6.90 (m, 2H), 5.84 (ddd, J=17.0, 10.5, 8.5 Hz, 1H), 5.15–5.20 (m, 2H), 4.44 (AB_q, J_{AB}=11.5 Hz, $\Delta\nu_{AB}$=6.1 Hz, 2H), 3.94 (app q, J=5.5 Hz, 1H), 3.82 (s, 3H), 3.74–3.80 (m, 1H), 3.67–3.73 (m, 1H), 3.52 (dd, J=10.0, 5.5 Hz, 1H), 3.43 (dd, J=10.0, 5.5 Hz, 1H), 2.52–2.57 (m, 1H), 2.44–2.51 (m, 1H), 0.89 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5, 137.3, 130.2, 129.6, 117.8, 114.0, 74.4, 73.3, 73.0, 63.3, 55.5, 49.1, 26.1, 18.3, −4.1, −4.7; IR (film) 3445, 3074, 2935, 2858, 1614, 1514, 1468, 1251 cm^{-1}; HRMS (CI) calcd for $C_{16}H_{25}O_4Si$ $(M-t\text{Bu})^+$: 309.1522, found: 309.1521.

4.1.5. 2-{2-[1-(*tert*-Butyldimethylsiloxy)-2-(4-methoxybenzyloxy)ethyl]but-3-enylamino}-3-methoxypropionic acid methyl ester (22a). To a solution of alcohol **19a** (10.3 g, 28.1 mmol) in 400 mL of wet CH_2Cl_2 was added Dess–Martin periodinane (17.9 g, 42.1 mmol). A fine white precipitate quickly formed to give a milky suspension. After 30 min, the mixture was diluted with 400 mL of Et_2O and

then 200 mL of a 1:1 solution of saturated aqueous $NaHCO_3$ −10% (w/w) aqueous $Na_2S_2O_3$ was added, and the mixture was allowed to stir until all of the solids had dissolved. The layers were separated and the organic layer was washed with the 1:1 solution (2×100 mL) and brine (100 mL), then dried (Na_2SO_4) and concentrated. The crude aldehyde was passed through a short plug of silica gel (10% EtOAc–hexanes) then concentrated to give a pale yellow oil, which was immediately used in the following reaction.

The crude aldehyde **20** was dissolved in 280 mL of MeCN, then 4 Å molecular sieves (23 g) were added and the mixture was allowed to stir for 5 min. A solution of serine methyl ester **21**[34] (7.48 g, 56.1 mmol) in 10 mL of MeCN was added via syringe. The mixture was allowed to stir for 10 min, then $NaBH(OAc)_3$ (23.8 g, 112.0 mmol) was added in one portion. After stirring for 1 h, 300 mL of a half-saturated potassium–sodium tartrate solution was added, and the mixture was stirred vigorously for an additional 1 h. The mixture was diluted with EtOAc (600 mL), washed with $NaHCO_3$ (2×75 mL) and brine (75 mL), then dried (Na_2SO_4) and concentrated. Purification of the residue on silica gel (gradient elution, 10% EtOAc–hexanes to 15% EtOAc–hexanes to 35% EtOAc–hexanes) gave 11.1 g (82%) of **22a** as a pale yellow oil that was contaminated with small quantities of the isomeric internal olefins **23**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22–7.27 (m, 2H), 6.85–6.90 (m, 2H), 5.67–5.76 (m, 1H), 5.11–5.19 (m, 2H), 4.38–4.44 (m, 2H), 3.74–3.84 (m, 1H), 3.81 (s, 3H), [3.731 (s), 3.728 (s), 3H], 3.51–3.62 (m, 2H), 3.40–3.49 (m, 2H), 3.31–3.38 (m, 1H), [3.334 (s), 3.331 (s), 3H], [2.88 (dd, J=11.0, 4.0 Hz), 2.72 (dd, J=11.0, 4.0 Hz), 1H], [2.59 (dd, J=9.5, 9.5 Hz), 2.52 (dd, J=11.0, 9.0 Hz), 1H], 2.41–2.50 (m, 1H), 1.79 (br s, 1H), [0.88 (s), 0.87 (s), 9H], [0.041 (s), 0.037 (s), 0.03 (s), 6H]; ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 173.6, 159.3, 138.4, 130.7, 129.44, 129.43, 129.2, 117.9, 117.7, 113.9, 74.0, 73.9, 73.6, 73.4, 73.3, 73.2, 73.12, 73.11, 62.0, 61.8, 59.4, 59.3, 55.5, 52.1, 52.0, 48.6, 48.4, 47.9, 47.8, 34.5, 26.13, 26.11, 18.4, −3.9, −4.67, −4.69; IR (film) 3346, 2929, 2856, 1740, 1613, 1515, 1472, 1246, 1036 cm^{-1}; HRMS (EI) calcd for $C_{25}H_{44}NO_6Si$ $(M+H)^+$: 482.2938, found: 482.2947.

4.1.6. 2-{{2-[1-(*tert*-Butyldimethylsiloxy)-2-(4-methoxybenzyloxy)ethyl]but-3-enyl}-[4,5-dibromo-1-(2-trimethylsilylethoxymethyl)-1H-pyrrole-2-carbonyl]-amino}-3-methoxypropionic acid methyl ester (24a). To a suspension of pyrrole acid **10** (31.1 g, 79.9 mmol) in 500 mL of MeCN at 0 °C was added BOPCl (23.4 g, 91.8 mmol) and the mixture was stirred at 0 °C for 90 min. Then a solution of amine **22a** (13.4 g, 27.8 mmol) in 50 mL of MeCN was added via syringe (30 mL plus 2×10 mL rinses), followed by the addition of *i*-Pr_2NEt (20.8 mL, 120.0 mmol). The mixture was allowed to warm to room temperature and the solids slowly dissolved. The reaction mixture was stirred overnight, during which time a white precipitate formed. This slurry was diluted with EtOAc (500 mL), washed with saturated aqueous $NaHCO_3$ (2× 200 mL) and brine (200 mL), then dried (Na_2SO_4) and concentrated. Purification of the residue on silica gel (gradient elution, 5% EtOAc–hexanes to 10% EtOAc–hexanes) gave 17.4 g (93% recovered) of the acid anhydride together with 23.3 g (99%) of amide **24a** as a pale yellow oil. NMR spectra are complex due to slow rotation on the NMR timescale so only distinct resonances are noted: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22–7.28 (m, 2H), 6.85–6.90 (m, 2H), 6.57 (br s, 1H), 4.38–4.44 (m, 2H), 3.81 (s, 3H), [3.72 (s), 3.71 (s), 3H], 3.51 (app t, J=3.0 Hz, 2H), 3.34 (s, 3H), [2.69–2.77 (m), 2.58–2.66 (m), 1H], [0.87 (s), 0.86 (s), 9H]; ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 169.5, 159.4, 138.1, 137.8, 129.55, 129.52, 128.1, 128.0, 113.91, 113.89, 99.5, 75.5, 73.6, 73.19, 73.16, 66.6, 66.32, 66.29, 59.1, 59.0, 55.5, 52.5, 47.1, 44.1, 41.6, 26.0, 18.3, 18.1, 18.0, −1.18, −1.22, −3.90, −3.94, −4.8; IR (film) 2954, 2896, 1744, 1636, 1515, 1248, 1094 cm^{-1}; HRMS (EI) calcd for $C_{36}H_{58}Br_2N_2O_8Si_2Na$ $(M+Na)^+$: 885.1980, found: 885.1970.

4.1.7. 2-{{2-[1-(*tert*-Butyldimethylsiloxy)-2-hydroxyethyl]but-3-enyl}-[4,5-dibromo-1-(2-trimethylsilylethoxymethyl)-1H-pyrrole-2-carbonyl]amino}-3-methoxypropionic acid methyl ester (27). To a solution of PMB ether **24a** (10.27 g, 11.90 mmol) in 115 mL of CH_2Cl_2 and 6.8 mL of pH 7 phosphate buffer was added DDQ (3.92 g, 17.3 mmol) in one portion. The mixture turned an initial bright green color then slowly faded to a brownish-green color. After 2 h, the mixture was quenched with aqueous $NaHCO_3$ (100 mL) and diluted with EtOAc (300 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ until the washes were no longer colored yellow (4× 100 mL) and then washed with brine (100 mL). The combined aqueous layers were extracted with EtOAc (100 mL) and then the combined organic layers were dried (Na_2SO_4) and concentrated. Purification of the residue on silica gel (gradient elution, 10% EtOAc–hexanes to 30% EtOAc–hexanes) gave 7.37 g (83%) of the alcohol **27** as a pale yellow oil: NMR spectra are complex due to slow rotation on the NMR timescale so only distinct resonances are noted; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.50–6.70 (m, 1H), [3.74 (s), 3.72 (s), 3H], 3.52 (app t, J=8.0 Hz, 2H), [3.38 (s), 3.36 (s), 3H], 2.63–2.78 (m, 1H), [0.90 (s), 0.89 (s), 9H], 0.04–0.10 (m, 6H), [−0.01 (s), −0.02 (s), 9H]; ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.6, 169.4, 137.7, 127.9, 127.7, 99.60, 99.57, 75.6, 75.5, 74.5, 66.4, 64.5, 64.3, 59.2, 59.1, 52.6, 34.5, 26.0, 18.2, 18.1, −1.2, −4.05, −4.10, −4.57, −4.58; IR (film) 3464, 3120, 3078, 2954, 1744, 1629, 1530, 1250, 1094 cm^{-1}; HRMS (EI) calcd for $C_{28}H_{50}Br_2N_2O_7Si_2Na$ $(M+Na)^+$: 765.1404, found: 765.1402.

4.1.8. 2,4-Bis-(*tert*-butyldimethylsiloxy)-5-{[[4,5-dibromo-1-(2-trimethylsilylethoxymethyl)-1H-pyrrole-2-carbonyl]-(1-methoxycarbonylvinyl)amino]methyl}-hepta-2,6-dienoic acid methyl ester (29). To a solution of alcohol **27** (2.62 g, 3.53 mmol) in 50 mL of wet CH_2Cl_2 was added Dess–Martin periodinane (2.24 g, 5.29 mmol). A fine white precipitate quickly formed to give a milky suspension. After 30 min, the mixture was diluted with 150 mL of Et_2O and then 75 mL of a 1:1 solution of saturated aqueous $NaHCO_3$—10% (w/w) aqueous $Na_2S_2O_3$, and the mixture was allowed to stir until all of the solids had dissolved. The layers were separated and the organic layer was washed with the 1:1 solution (3×50 mL) and brine (50 mL), then dried (Na_2SO_4) and concentrated. The crude aldehyde was diluted in 15 mL of CH_2Cl_2 then dried (Na_2SO_4) and

concentrated to give a pale yellow oil which was immediately used in the following reaction.

This crude aldehyde and phosphonate **28** (1.65 g, 5.29 mmol) were dissolved in 70 mL of THF. Then NaO*t*-Bu (14.1 mL of a 0.5 M solution in *t*-BuOH, 7.06 mmol) was added dropwise via syringe to give a bright yellow solution. The resulting solution was poured into saturated aqueous $NaHCO_3$ (100 mL) and then diluted with Et_2O (150 mL). The layers were separated and the organic layer was washed with saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL), then dried (Na_2SO_4) and concentrated. Purification of the residue on silica gel (5% EtOAc–hexanes) gave 2.30 g (73% from **27**) of the enol ether **29** as a pale yellow oil (on smaller scales the yield approached 83%): ^{1}H NMR (500 MHz, $CDCl_3$) δ [6.34 (s), 6.33 (s), 1H], [6.10 (s), 6.08 (s), 1H], [5.89 (d, J=9.0 Hz), 5.34 (d, J=9.0 Hz), 1H], 5.69–5.84 (m, 1H), 5.56–5.67 (m, 2H), [5.48 (d, J=10.5 Hz), 5.47 (d, J=10.5 Hz), 1H], [5.11 (dd, J=9.0, 6.5 Hz), 4.69 (dd, J=8.5, 5.0 Hz), 1H], 4.99–5.08 (m, 2H), 4.01–4.12 (m, 1H), [3.77 (s), 3.76 (s), 3H], [3.69 (s), 3.67 (s), 3H], 3.64–3.71 (m, 1H), 3.55–3.62 (m, 2H), 2.55–2.69 (m, 1H), [0.96 (s), 0.94 (s), 9H], [0.878 (s), 0.881 (s), 9H], 0.85–0.97 (m, 2H), −0.02−0.21 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.1, 164.9, 164.49, 164.47, 162.0, 141.2, 140.9, 140.2, 139.7, 137.6, 137.4, 128.80, 128.76, 126.4, 122.8, 122.4, 121.7, 118.2, 118.0, 116.6, 116.4, 110.0, 109.9, 99.3, 75.6, 70.1, 69.5, 66.5, 66.4, 52.80, 52.78, 52.3, 51.9, 51.3, 49.9, 49.2, 49.1, 26.2, 26.0, 25.8, 18.9, 18.4, 18.3, 18.23, 18.17, −1.2, −3.7, −3.8, −4.09, −4.14, −4.5, −4.6, −4.8, −4.9; IR (film) 3078, 2954, 2860, 1731, 1648, 1524, 1437, 1324, 1250, 1198 cm^{-1}; HRMS (EI) calcd for $C_{36}H_{62}Br_2N_2O_8Si_3Na$ $(M+Na)^+$: 915.2078, found: 915.2073.

4.1.9. 4-(*tert*-Butyldimethylsiloxy)-5-{[[4,5-dibromo-1-(2-trimethylsilyl ethoxymethyl)-1H-pyrrole-2-carbonyl]-(1-methoxycarbonylvinyl)-amino]methyl}-2-oxo-hept-6-enoic acid methyl ester (9). To a solution of enol ether **29** (2.30 g, 2.57 mmol) and AcOH (0.72 mL, 12.9 mmol) in 51 mL of MeCN at 0 °C was added CsF (977 mg, 6.43 mmol) in one portion. The mixture was allowed to warm to room temperature and then stirred for an additional 75 min. The reaction mixture then was diluted with 200 mL of EtOAc and 50 mL of saturated aqueous $NaHCO_3$. The layers were separated and the organic layer was washed with saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL), then dried (Na_2SO_4) and concentrated. Purification of the residue on silica gel (gradient elution, 10% EtOAc–hexanes to 15% EtOAc–hexanes) gave 1.74 g (87%) of the α-keto ester **9** as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.34 (s, 1H), 6.12 (s, 1H), 5.76 (ddd, J=17.0, 10.0, 9.0 Hz, 1H), 5.62 (s, 1H), 5.52 (AB_q, J_{AB}=10.5 Hz, $\Delta\nu_{AB}$=23.8 Hz, 2H), 5.05–5.15 (m, 2H), 4.32 (dt, J=6.5, 5.5 Hz, 1H), 3.86 (s, 3H), 3.72–3.86 (m, 2H), 3.69 (s, 3H), 3.56–3.61 (m, 2H), 3.21 (dd, J=17.5, 5.0 Hz, 1H), 3.02 (dd, J=17.5, 6.5 Hz, 1H), 2.60–2.67 (m, 1H), 0.87–0.95 (m, 2H), 0.84 (s, 9H), 0.07 (s, 3H), 0.01 (s, 3H), 0.00 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.2, 164.3, 162.0, 161.4, 140.9, 137.0, 128.5, 122.2, 118.8, 116.6, 110.3, 99.3, 75.6, 69.7, 66.5, 53.2, 52.9, 49.3, 49.2, 44.5, 25.9, 18.2, 18.1, −1.2, −4.4, −4.5; IR (film) 2954, 2858, 1731, 1654, 1621, 1524, 1248, 1092, 1081 cm^{-1}; HRMS (EI) calcd for $C_{30}H_{48}Br_2N_2O_8Si_2Na$ $(M+Na)^+$: 801.1213, found: 801.1237.

4.1.10. 4-[1-(*tert*-Butyldimethylsiloxy)-3-methoxycarbonyl-3-oxo-propyl]-1-[4,5-dibromo-1-(2-trimethylsilyl-ethoxymethyl)-1H-pyrrole-2-carbonyl]-4,5-dihydro-1H-pyrrole-2-carboxylic acid methyl ester (8). A flame dried 25 mL two-neck reaction flask was equipped with a reflux condenser topped with a three-way gas flow adapter and a teflon stopcock (all ground glass connections were greased). Diene **9** (414 mg, 0.530 mmol) was transferred to the reaction apparatus in 4.3 mL of CH_2Cl_2 (degassed by sparging with Ar for 2 h) via syringe. A solution of the metathesis catalyst **15** (1.0 mL of a 0.027 M solution in CH_2Cl_2, 0.027 mmol) was added via syringe and the solution was brought to reflux. After 23 h, ^{1}H NMR analysis of an aliquot indicated the reaction had gone to about 90% completion. After 41 h, the brown solution was concentrated and purified on silica gel (gradient elution, hexanes to 5% EtOAc–hexanes to 7.5% EtOAc–hexanes to 15% EtOAc–hexanes) to give 414 mg (80%) of dihydropyrrole **8** as an oil, along with 25 mg of recovered diene **9**; keto ester **8** is a 8:1 mixture of keto and enol tautomers in $CDCl_3$. Only the keto peaks are reported in the ^{1}H NMR, but all the peaks are reported in the ^{13}C NMR; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.63 (s, 1H), 5.99 (d, J=2.5 Hz, 1H), 5.73 (d, J=10.5 Hz, 1H), 5.61 (d, J=10.5 Hz, 1H), 4.34 (dt, J=7.0, 5.0 Hz, 1H), 4.13 (dd, J=11.0, 10.0 Hz, 1H), 4.01 (dd, J=7.0, 6.5 Hz, 1H), 3.88 (s, 3H), 3.71 (s, 3H), 3.59 (app dd, J=8.5, 7.5 Hz, 2H), 3.22–3.28 (m, 1H), 3.09 (dd, J=17.0, 7.0 Hz, 1H), 2.87 (dd, J=17.0, 5.0 Hz, 1H), 0.86–0.92 (m, 2H), 0.84 (s, 9H), 0.07 (s, 3H), 0.02 (s, 3H), −0.02 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.0, 161.5, 161.1, 160.0, 140.3, 138.7, 138.3, 127.5, 124.0, 123.3, 117.5, 117.1, 113.0, 112.0, 99.8, 75.3, 68.9, 68.6, 66.52, 66.48, 53.7, 53.45, 53.40, 52.9, 52.5, 52.4, 49.3, 48.5, 44.3, 25.9, 18.2, 18.14, 18.10, −1.0, −1.2, −1.4, −4.3, −4.4, −4.5, −4.9; IR (film) 3450, 3124, 2954, 2858, 1733, 1632, 1524, 1426, 1391, 1250, 1082 cm^{-1}; HRMS (EI) calcd for $C_{28}H_{44}Br_2N_2O_8Si_2Na$ $(M+Na)^+$: 773.0901, found: 773.0904.

4.1.11. Azomethine imine cyclization product 31. A sealable tube was charged with α-keto ester **8** (433 mg, 0.575 mmol), thiosemicarbazide (315 mg, 3.45 mmol) and 12 mL of EtOH. The mixture was sparged with argon for 20 minutes, then the vessel was sealed and heated to 110 °C. After 2 d, the bright yellow solution was cooled to below 78 °C, the tube was opened, and the mixture was adsorbed onto silica gel with 10% CH_3OH/CH_2Cl_2 and purified on silica gel (gradient elution, 7.5% EtOAc–hexanes to 15% EtOAc–hexanes) to give 82 mg (71%) of cycloadduct **31** as a colorless solid:[§] ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.65 (s, 1H), 5.65 (d, J=11.0 Hz, 1H), 5.50 (d, J=10.5 Hz, 1H), 5.35 (s, 1H), 4.41–4.47 (m, 1H), 4.08 (d, J=10.0 Hz, 1H), 4.01 (app d, J=5.0 Hz, 2H), 3.71 (s, 3H), 3.48–3.56 (m, 2H), 2.79 (ddt, J=10.5, 10.5, 5.8 Hz, 1H), 2.36 (dd, J=14.5, 5.5 Hz, 1H), 2.26 (dd, J=14.5, 7.3 Hz, 1H), 0.86–0.93

[§] Under these conditions, an unidentified by-product is isolated in approximately 5–8% yield. This product appears when the reaction is carried out at temperatures greater than 70 °C. Attempts to conduct the condensation with thiosemicarbazide at temperatures greater than 110 °C resulted in larger amounts of this byproduct.

(m, 2H), 0.89 (s, 9H), 0.11 (s, 3H), 0.01 (s, 3H), 0.00 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.4, 171.6, 168.6, 161.7, 126.5, 117.3, 112.2, 100.0, 91.2, 78.5, 78.0, 75.8, 66.7, 58.6, 54.8, 53.5, 49.8, 42.6, 25.8, 18.14, 18.07, −1.2, −4.3, −4.5; IR (film) 3272, 2954, 2858, 1773, 1750, 1640, 1426, 1252, 1200, 1094 cm^{-1}; HRMS (EI) calcd for $C_{28}H_{44}Br_2N_5O_6SSi_2Na$ $(M+H)^+$: 792.0917, found: 792.0941.

Acknowledgements

This research was funded by the National Heart, Lung, and Blood Institute (HL-25854). J. D. K. was supported by an NIH NRSA postdoctoral fellowship (5 F32 GM064946). NMR and mass spectra were determined at UC Irvine using instruments acquired with the assistance of NSF and NIH shared instrumentation grants.

References and notes

1. Faulkner, D. J. *Nat. Prod. Rep.* **2002**, *19*, 1–48, and earlier reviews in this series.
2. Berlinck, R. G. S. *Nat. Prod. Rep.* **2002**, *19*, 617–649, and earlier reviews in this series.
3. (a) Kinnel, R. B.; Gehrken, H.-P.; Scheuer, P. J. *J. Am. Chem. Soc.* **1993**, *115*, 3376–3377. (b) Kinnel, R. B.; Gehrken, H.-P.; Swali, R.; Skoropowski, G.; Scheuer, P. J. *J. Org. Chem.* **1998**, *63*, 3281–3286.
4. Kato, T.; Shizuri, Y.; Izumida, H.; Yokoyama, A.; Endo, M. *Tetrahedron Lett.* **1995**, *36*, 2133–2136.
5. Kobayashi, J.; Sukuzi, M.; Tsuda, M. *Tetrahedron* **1997**, *53*, 15681–15684.
6. For a recent review of synthetic efforts, see: Hoffmann, H.; Lindel, T. *Synthesis* **2003**, 1753–1783.
7. Starr, J. T.; Koch, G.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 8793–8794.
8. (a) Lovely, C. J.; Du, H.; Dias, H. V. R. *Org. Lett.* **2001**, *3*, 1319–1322. (b) Lovely, C. J.; Du, H.; He, Y.; Dias, H. V. R. *Org. Lett.* **2004**, *6*, 735–738.
9. Dilley, A. S.; Romo, D. *Org. Lett.* **2001**, *3*, 1535–1538.
10. Koenig, S. G.; Miller, S. M.; Leonard, K. A.; Löwe, R. S.; Chen, B. C.; Austin, D. J. *Org. Lett.* **2003**, *5*, 2203–2206.
11. Overman, L. E.; Rogers, B. N.; Tellew, J. E.; Trenkle, W. C. *J. Am. Chem. Soc.* **1997**, *119*, 7159–7160.
12. Bélanger, G.; Hong, F.-T.; Overman, L. E.; Rogers, B. N.; Tellew, J. E.; Trenkle, W. C. *J. Org. Chem.* **2002**, *67*, 7880–7883.
13. Shono, T.; Matsumura, Y.; Inoue, K. *J. Chem. Soc., Chem. Commun.* **1983**, 1169–1171.
14. Klein, C.; Schulz, G.; Steglich, W. *Liebigs Ann. Chem.* **1983**, *9*, 1623–1637.
15. Pauly, R.; Sasaki, N. A.; Potier, P. *Tetrahedron Lett.* **1994**, *35*, 237–240.
16. Häusler, J. *Liebigs Ann. Chem.* **1981**, *6*, 1073–1088.
17. Ezquerra, J.; Escribano, A.; Rubio, A.; Remuiñán, M. J.; Vaquero, J. J. *Tetrahedron Lett.* **1995**, *36*, 6149–6152.
18. Osada, S.; Fumoto, T.; Kodama, H.; Kondo, M. *Chem. Lett.* **1998**, 675–676.
19. Meyers, A. I.; Edwards, P. D.; Bailey, T. R.; Jagdmann, G. E. *J. Org. Chem.* **1985**, *50*, 1019–1026.
20. Luker, T.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, *62*, 8131–8140.
21. Nicolaou, K. C.; Shi, G.-Q.; Namoto, K.; Bernal, F. *Chem. Commun.* **1998**, 1757–1758.
22. Kimura, R.; Nagano, T.; Kinoshita, H. *Bull. Chem. Soc. Jpn* **2002**, *75*, 2517–2525.
23. For recent reviews, see: (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29. (b) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012–3043. (c) Fürstner, A. *Adv. Synth. Catal.* **2002**, *6/7*, 567–793.
24. For the synthesis of other 2-substituted-4,5-dihydropyrroles by ring-closing metathesis, see: Kinderman, S. S.; van Maarseveen, J. H.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *Org. Lett.* **2001**, *3*, 2045–2048.
25. For the synthesis of indoles by ring-closing metathesis: Arisawa, M.; Terada, Y.; Nakagawa, M.; Nishida, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4732–4734.
26. For the synthesis a cyclic dienamide by ring-closing metathesis of an ynamide: Saito, N.; Sato, Y.; Mori, M. *Org. Lett.* **2002**, *4*, 803–805.
27. For the ring-closing metathesis of α-alkoxy acrylates: Hekking, K. F. W.; van Delft, F. L.; Rutjes, F. P. J. T. *Tetrahedron* **2003**, *59*, 6751–6758.
28. Baker, S. R.; Burton, K. I.; Parsons, A. F.; Pons, J.-F.; Wilson, M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 427–436.
29. Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780.
30. Thurner, A.; Faigl, F.; Töke, L.; Mordini, A.; Valacchi, M.; Reginato, G.; Czira, G. *Tetrahedron* **2001**, *57*, 8173–8180.
31. Synthesized in 2 steps from but-2-yn-1,4-diol in 62% yield, see: Hatakeyama, S.; Yoshida, M.; Esumi, T.; Iwabuchi, Y.; Irie, H.; Kawamoto, T.; Yamada, H.; Nishizawa, M. *Tetrahedron Lett.* **1997**, *38*, 7887–7890.
32. (a) Tius, M. A.; Fauq, A. H. *J. Org. Chem.* **1983**, *48*, 4131–4132. (b) Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 6339–6348. (c) Richardson, T. I.; Rychnovsky, S. D. *Tetrahedron* **1999**, *55*, 8977–8996. (d) Izzo, I.; Scioscia, M.; Del Gaudio, P.; De Riccardis, F. *Tetrahedron Lett.* **2001**, *42*, 5421–5424.
33. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156.
34. Andurkar, S. V.; Stables, J. P.; Kohn, H. *Tetrahedron: Asymmetry* **1998**, *9*, 3841–3854.
35. For a review of hindered amide couplings and some leading references see: Humphrey, J. M.; Chamberlin, A. R. *Chem. Rev.* **1997**, *97*, 2243–2266.
36. (a) Kochetkov, K. A.; Babievskii, K. K.; Tarbalinskaya, N. S.; Belikov, F. M. *Bull. Acad. Sci. USSR Div. Chem. Sci. (Engl. Transl.)* **1982**, *31*, 2217–2222. (b) Kochetkov, K. A.; Babievskii, K. K.; Tarbalinskaya, N. S.; Belikov, F. M. *Izv. Akad. Nauk. SSSR Ser. Khim.* **1982**, *11*, 2515–2520.
37. Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* **1984**, 53–60.
38. (a) Nakamura, E. *Tetrahedron Lett.* **1981**, *22*, 663–666. (b) Horne, D.; Gaudino, J.; Thompson, W. J. *Tetrahedron Lett.* **1984**, *25*, 3529–3532. (c) Itoh, H.; Kaneko, T.; Tanami, K.; Yoda, K. *Bull. Chem. Soc. Jpn* **1988**, *61*, 3356–3358.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 60 (2004) 9569–9588
Tetrahedron

Enantioselective total synthesis of (−)-strychnine: development of a highly practical catalytic asymmetric carbon–carbon bond formation and domino cyclization

Takashi Ohshima, Youjun Xu, Ryo Takita and Masakatsu Shibasaki*

Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

Received 15 May 2004; revised 4 June 2004; accepted 7 June 2004

Available online 24 August 2004

Dedicated to Professor Alois Fürstner in recognition of his receipt of the Tetrahedron Chair in Organic Synthesis 2004

Abstract—An enantioselective total synthesis of (−)-strychnine was accomplished through the use of the highly practical catalytic asymmetric Michael reaction (0.1 mol% of (*R*)-ALB, greater than kilogram scale, without chromatography, 91% yield and >99% ee), and a domino cyclization that simultaneously constructed the B- and D- rings of strychnine (>77% yield). Newly-developed reaction conditions for thionium ion cyclization, $NaBH_3CN$ reduction of the imine moiety in the presence of a Lewis acid to prevent the ring-opening reaction, and chemoselective reduction of the thioether (desulfurization) in the presence of exocyclic olefin were pivotal to complete the synthesis. The described chemistry paves the way for the synthesis of more advanced *Strychnos* alkaloids.

1. Introduction

The use of catalytic asymmetric reactions for the synthesis of highly enantiomerically enriched chiral compounds is of growing importance in organic chemistry and in industrial production in terms of atom economy.[1] A number of highly efficient asymmetric catalyses, such as Rh(I)-catalyzed hydrogenation of olefins,[2] Ru(II)-catalyzed hydrogenation of ketones,[3] Ti(IV)-catalyzed epoxidation of allylic alcohols,[4] Cu-catalyzed cyclopropanation of olefins,[5] and Rh(I)-catalyzed isomerization of allylic amines,[6] etc. have been successfully utilized for the syntheses of various complex natural products and industrial applications. Most catalytic asymmetric carbon–carbon bond formations, however, are difficult to produce on a large scale in terms of catalyst efficiency, enantioselectivity, or chemical yield, resulting in only a few synthetic applications. To address this issue, intensive efforts have been focused on developing a practical asymmetric carbon–carbon bond formation[1,7] and only a few manufacturing scale syntheses have been achieved.[5] Herein, we present the development of a highly practical catalytic asymmetric Michael reaction[8] and a full account of its synthetic application to the enantioselective total synthesis of (−)-strychnine (Fig. 1),[9,10] demonstrating the high potency of the catalytic asymmetric carbon–carbon bond formation. Other key reactions to realize enantioselective synthesis of strychnine were a novel domino cyclization promoted by Zn for simultaneous construction of the B- and D-rings of strychnine, a modified intramolecular alkylation by dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF) (C-ring formation), a selective imine reduction by $NaBH_3CN$ with a Lewis acid, and a chemoselective reduction of thioether in the presence of *exo*-olefin.

2. Results and discussion

2.1. Retrosynthetic analysis of (−)-strychnine

(−)-Strychnine (**1**) is the flagship compound of the family of *Strychnos* alkaloids and, considering its molecular

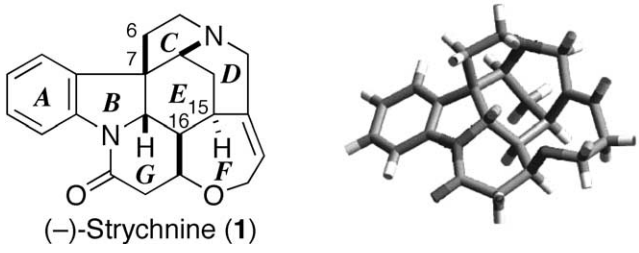


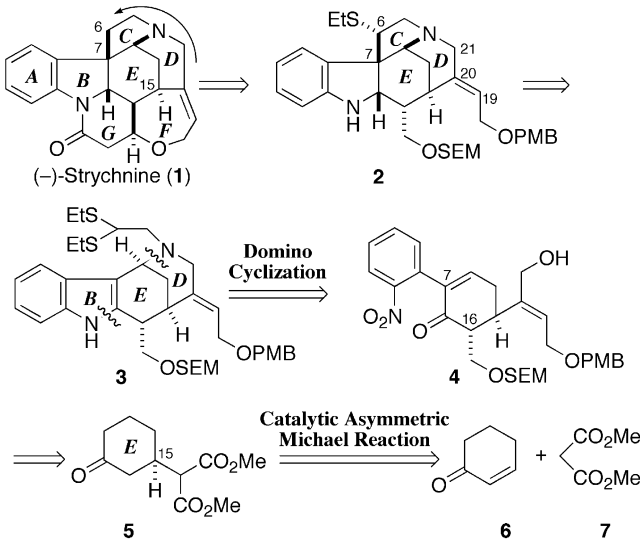
Figure 1. 2D (left) and 3D (right) structure of (−)-strychnine (**1**).

Keywords: Enantioselective total synthesis; (−)-Strychnine; Catalytic asymmetric Michael reaction; Domino cyclization.
* Corresponding author. Tel.: +81-3-5684-0651; fax: +81-3-5684-5206; e-mail: mshibasa@mol.f.u-tokyo.ac.jp

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.06.141

weight, is one of the most complex natural products.[11] Only 24 skeletal atoms are assembled in 7 rings and its structure contains 6 contiguous asymmetric carbon atoms, 5 of which are included within 1 saturated 6-membered ring (E-ring). Strychnine was first isolated in 1818 from the Southeast Asian *Strychnos nux-vomica* and *Strychnos ignatti*.[12] Extensive degradative and structural studies culminated in the elucidation of strychnine's structure in 1946.[13] The relative[14a–d] and absolute[14e,f] configurations were later confirmed by X-ray crystal analyses. Strychnine toxicity results from a block of postsynaptic inhibition in the spinal cord and lower brain stem, where it acts as a competitive ligand at the neuronal glycine receptor.[15] This property has made strychnine very useful as a tool in experimental pharmacology.

The structural complexity of strychnine coupled with its biological activity has served as the impetus for numerous synthetic investigations. The first total synthesis, one of the most significant achievements in the history of organic synthesis, was reported by Woodward in 1954.[16a] Nearly 40 years after Woodward's pioneering work, a number of groups reported the total synthesis,[16] and four of which culminated in an enantioselective synthesis of the natural enantiomer.[16c,e,g,j] As summarized in Bonjoch's excellent review,[11a] the major stumbling blocks in the synthesis are the generation of the spirocenter at C7 and the assembly of the bridged framework (CDE core ring). In previous strategies, the C6–C7 bond was generated in the early stage of synthesis, probably due to difficulties generating the C7 quaternary center; thus, in many cases, the CDE ring system was assembled in the direction of the C-ring to D-ring. Although an intramolecular alkylation strategy was applied for the construction of the C-ring in the synthesis of structurally simpler indole alkaloids,[17,18] this strategy has not been utilized for the synthesis of strychnine. The reason for this might be that intramolecular alkylation of dithioacetal is the only method that affords a cyclic product, thus desulfurization in the presence of exocyclic olefin is inevitable. We previously developed a catalytic asymmetric Michael reaction of malonates to cyclic enones.[19] To effectively utilize the Michael product **5** in our synthesis, we planned to assemble the CDE ring system from the D-ring to the C-ring and constructed the C7 spirocenter in the last stage by intramolecular alkylation. Our final retrosynthetic analysis after several unsatisfactory attempts (vide infra) is shown in Scheme 1.



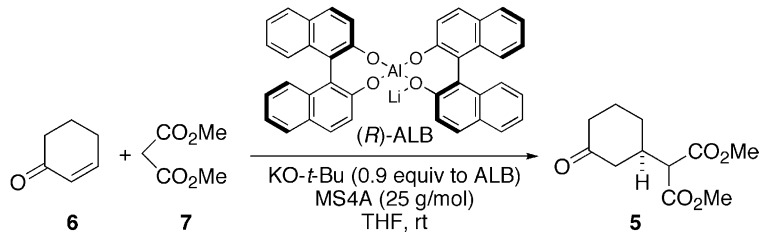
Scheme 1. Retrosynthetic analysis of (−)-strychnine (**1**).

2.2. Catalytic asymmetric Michael reaction

The catalytic asymmetric Michael reaction is an efficient method for enantioselective carbon–carbon bond formations because of the usefulness of the corresponding enantiomerically-enriched Michael adducts as an attractive chiral source.[18–21] Therefore, the development of a highly practical method to synthesize Michael adducts is very desirable. In 1996, we reported that the multifunctional asymmetric catalyst, AlLibis(binaphthoxide) complex (ALB), which was prepared from $LiAlH_4$ and BINOL in a ratio of 1:2, was highly effective for the catalytic asymmetric Michael reaction of cyclic enones with malonates (Table 1, entry 1).[19c] Later, this catalyst system was improved by using additional base (KO-*t*-Bu) and MS4A, accelerating the reaction with a slight improvement in both chemical yield and enantioselectivity (entry 2).[18a] Although there are several efficient asymmetric catalysts for the asymmetric Michael reaction,[19–21] including the $LaNa_3$-tris(binaphthoxide) complex,[19b] GaNabis(binaphthoxide) complex,[19d] and La–O-linked-BINOL complex,[19e–g] ALB is the most effective catalyst for the present Michael reaction in terms of catalyst efficiency.[22] In addition, all materials in the reaction, including each enantiomer of BINOL, are inexpensive and commercially available. Even using the improved procedure, however, 1 mol% of the catalyst was required to obtain the product in excellent yield and high enantiomeric excess (entry 2), and 0.3 mol% of the catalyst required 120 h at room temperature to complete the reaction (entry 3).[18a] To apply this chemistry to a complex natural product synthesis as well as a manufacturing scale synthesis, we attempted to further improve not only catalyst efficiency, such as reducing catalyst loading and reaction time, but also the work-up procedure, such as eliminating the need for chromatographic separation. We first focused on acceleration of the reaction at ambient temperature. We examined the additive effects, solvent effects, and ligand tuning, and eventually discovered that under highly concentrated conditions even 0.25 mol% of the catalyst induced the reaction to proceed very quickly (15 h) without lowering the chemical yield (95% combined yield for two successive recrystallizations, vide infra) or high enantiomeric excess (>99% ee) (entry 4). The catalyst loading was further reduced. The use of only 0.05 mol% of the catalyst forced the reaction to completion with a similar chemical yield (94%) and enantioselectivity (98% ee), although it required 48 h to complete (entry 8). In addition, a relatively large-scale reaction (0.5 mol scale) proceeded smoothly without any difficulty (entry 9).[8]

We also examined the work-up procedure of the reaction. In our previous procedure, chromatographic separation was necessary to obtain a high yield (total 96% yield) after two successive crystallizations from toluene/hexane (82% combined yield).[18a] Moreover, recovery of BINOL from the crude mixture using chromatographic separation is not very easy on a large-scale because of the small difference in

Table 1. Catalytic asymmetric Michael reaction promoted by ALB



Entry	Scale (mol)	ALB (mol%)	Total amount of THF (mL/mol)	Time (h)	ee (%)[a]	Yield (%)[b]	ee (%)[c]
1[d]	0.001	10.0	1690	72	93	90	—
2	0.5	1.0	895	72	99	96	—
3	0.002	0.3	752	120	99	94	—
4	0.005	0.25	51	15	>99	95[e]	>99
5	0.005	0.20	41	24	>99	95[e]	>99
6	0.005	0.10	21	10	98	74[e]	>99
7	0.005	0.10	21	24	98	92[e]	>99
8	0.005	0.05	10	48	98	94[e]	>99
9	0.5	0.10	21	24	98	92[e]	>99

[a] Enantiomeric excess of the crude product determined by HPLC analysis.
[b] Isolated yield.
[c] Enantiomeric excess of the crystal determined by HPLC analysis.
[d] Reaction was performed without the addition of KO-*t*-Bu or MS4A.
[e] Combined yield of **5** after two successive crystallizations.

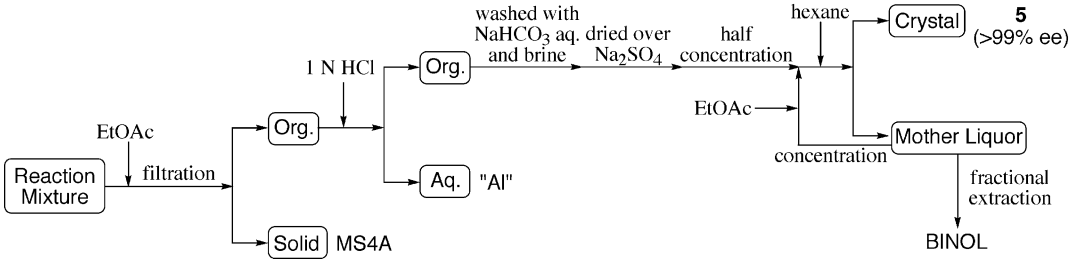
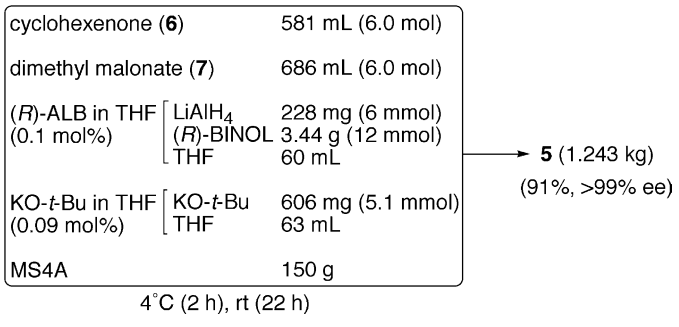


Figure 2. The improved work-up procedure of the catalytic asymmetric Michael reaction promoted by ALB.

polarity between BINOL and the product **5**. The new improved procedure (Fig. 2) was streamlined by eliminating the need for chromatographic separation to obtain the product **5** in reasonable yield (>90%) in an optically and chemically pure manner. After an ordinary quenching procedure, the organic layer was half concentrated and treated with hexane with maintenance of the solvent ratio (EtOAc–hexane, 1:4) to afford a pure Michael adduct **5** as a white crystal in more than 90% yield. After concentration of the mother liquor followed by one successive recrystallization from EtOAc–hexane (1:4), the combined yield was up to 95% (Table 1, entries 4 and 5, 1st: 93%, 2nd: 2%). In addition, BINOL was recovered from the mother liquor in approximately 80% yield by subsequent fractional extraction (See Section 4).

Having achieved a highly practical catalytic asymmetric synthesis of the Michael adduct **5**, we next performed pre-manufacturing scale (greater than kilogram scale) synthesis (Scheme 2). From an industrial point of view, we used



Scheme 2. Catalytic asymmetric Michael reaction promoted by ALB on a greater than kilogram scale.

0.1 mol% of the catalyst to complete the reaction in 24 h at ambient temperature. 2-Cyclohexen-1-one (**6**) (581 mL, 6.0 mol) was added to a suspension of dried MS4A (150 g), dimethyl malonate (**7**) (686 mL, 6.0 mol), 0.1 mol% of (*R*)-ALB in THF (containing only 3.4 g of BINOL), and 0.09 mol% of KO-*t*-Bu in THF at 4 °C (ice-water bath). Because there was a significant increase in the reaction temperature (>30 °C) without cooling, the reaction temperature was maintained at ca. 4 °C using an ice-water bath for 2 h. After additional stirring at ambient temperature (20–25 °C) for 22 h, 1.24 kg of the desired product **5** was obtained as a white crystal in 91% combined yield following three successive crystallizations (1st: 76%, 2nd, 11%, 3rd: 4%). HPLC analysis revealed that the enantiomeric excess of the crude product and the crystal was 98% and greater than 99%, respectively. The purity of the crystal was estimated to be greater than 99% on the basis of elemental analysis and ^{1}H and ^{13}C NMR spectra. To the best of our knowledge, the described method is one of the most practical and efficient catalytic asymmetric carbon–carbon bond forming reactions with great enantioselectivity.[23] This greater than kilogram scale reaction can be performed with a conventional 2 L flask because of the very high concentration of the reaction.[8]

2.3. Stereoselective elaboration of the hydroxyethylidene substituent

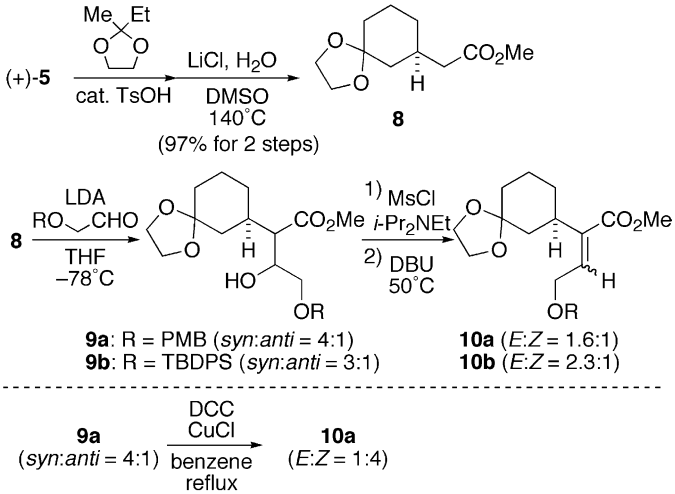
With large quantities of pure (+)-**5** in hand, we focused on the transformation of **5** to the key intermediate **4** for the synthesis of strychnine (Scheme 1). Our first step was the introduction of the hydroxyethylidene substituent in an *E*-selective manner. We initially investigated the synthesis of **10** through a *syn*-selective aldol reaction and subsequent *anti*-elimination of the corresponding mesylate under basic conditions as in our previous synthesis of (−)-tubifolidine and (−)-19,20-dihydroakuammicine (Scheme 3).[18,24] *Syn*-selectivity of the aldol reaction, however, was moderate (up to 4:1), and there was a decrease in stereoselectivity due to the rapid epimerization at the α-position of the ester during the elimination under basic conditions. Epimerization did not proceed during *syn*-elimination under neutral conditions (DCC, CuCl), although the major product was the undesired *Z*-product. These findings suggested the possibility of selective synthesis of the *anti*-aldol product and subsequent *syn*-elimination to obtain the *E*-product.

Because of the difficult selective preparation of the *anti*-aldol product **9** by an aldol reaction of **8**, we synthesized the *anti*-aldol product using *anti*-selective reduction of the β-keto ester **12**, which was prepared by alkylation of **8** using a Weinreb amide **11** in 72% yield (conversion 82%) (Table 2). Examination of several reduction conditions indicated that *anti*-selective reduction of β-keto ester **12** by $NaBH_3CN$ with $TiCl_4$ at −78 °C and subsequent *syn*-elimination by DCC-CuCl under neutral conditions, as reported by Overman,[16c] gave the best result (61% for 2 steps, *E*/*Z*=5.7:1). In this case, yield and selectivity of the reduction were highly dependent on the reaction temperature. An internal temperature of −55 °C was best in terms of both yield and selectivity, which reached 72% (conversion 79%) and 15.7:1, respectively (entry 4). The *anti*-selective reduction should proceed through an unusual 7-membered chelate conformation, proposed by Overman.[16c]

2.4. Transformation to the key intermediate for construction of the BCDE-ring system of strychnine

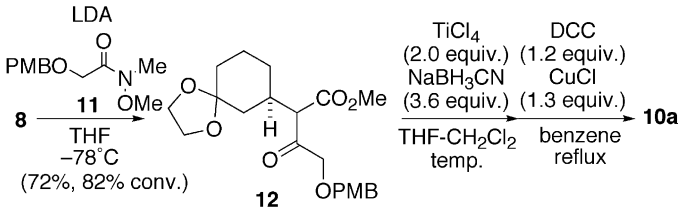
DIBAL reduction of **10a** (inseparable mixture of *E*- and *Z*-isomers, *E*/*Z*=15.7:1) followed by silylation of the primary alcohol with TIPSOTf and conversion of the acetal to ketone afforded, after silica gel chromatography, pure (*E*)-**14** (Scheme 4). Regioselective enol silyl ether formation was facilitated by the action of a sterically bulky base: lithium 2,2,6,6-tetramethylpiperidide to form the corresponding enol silyl ether regioselectively (**15**:**16**=>6:1). A subsequent Saegusa–Ito reaction[25] under conventional stoichiometric conditions (1.2 equiv of $Pd(OAc)_2$) provided the enone in 79% yield as an inseparable mixture of regioisomers (**17**:**18**=>6:1).

Large-scale synthesis, however, required a catalytic process for this reaction.[26] Tsuji et al. established a catalytic Saegusa–Ito reaction using allyl carbonate as an oxidant, in which a catalytic amount of $Pd(OAc)_2$, with or without a



Scheme 3. Initial attempts to elaborate the hydroxyethylidene substituent in an *E*-selective manner.

Table 2. Temperature effects on *anti*-selective reduction of **12**



Entry	Temperature (°C)[a]	Yield (%)[b]	Yield (%)[c]	*E*/*Z*[d]
1	−78	61	91	5.7:1
2	−65	73	79	9.1:1
3	−60	71	81	11.5:1
4	−55	72	79	15.7:1
5	−50	58	62	11.3:1
6	−45	67	—	10.2:1

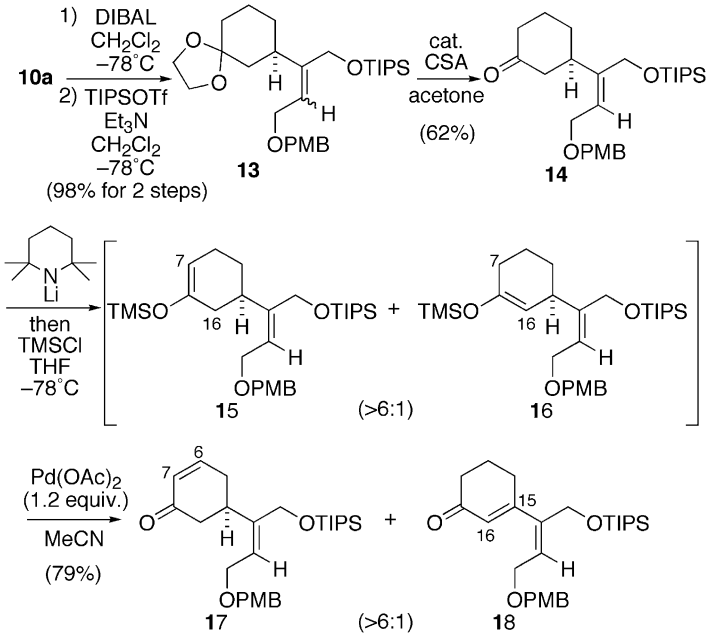
[a] Internal temperature of the reaction.
[b] Isolated yield of **10a** a mixture of *E* and *Z*-isomers.
[c] Conversion yield of **10a** based on the recovery of **12**.
[d] *E*/*Z* ratio of **10a** determined by ^{1}H NMR analysis.

phosphine ligand, usually gave successful results.[27] Unfortunately, in our system, both conditions gave unsatisfactory results (Table 3, entry 1 and 3). Finally, this stoichiometric process evolved into a catalytic process by using $Pd_2(dba)_3 \cdot CHCl_3$ instead of Pd(II) in the absence of a phosphine ligand in superb yield (90% for 2 steps, conversion 99%) without any loss of selectivity. Under these conditions, DBA might act as a weak ligand to prevent decomposition of the Pd(0) species.

Using an inseparable mixture of **17** and **18**, α-iodination of enone **17** was successfully promoted by DMAP (89%) instead of commonly used pyridine (half conversion), and undesired isomer **18** remained unchanged, making it possible to easily separate the regioisomers because of the large difference in polarity between **19** and **18** (Scheme 5).[28,29] To introduce the A-ring moiety, we selected a Stille coupling reaction based on its mild reaction conditions as compared with other Pd-catalyzed coupling reactions.[30] Although extremely poor results (<5%) were obtained using several combinations of Pd sources and ligands, a catalytic amount of CuI dramatically accelerated the reaction to afford **21** in quantitative yield. Finally, removal of the TIPS group using a very mild desilylation reagent, $3HF \cdot Et_3N$,[31] provided **22** in excellent yield (quant).[32]

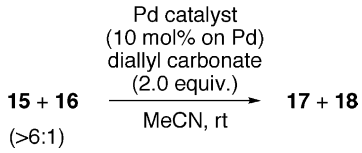
2.5. Examination of D-ring formation (1): simple 1,4-addition of amine to enone

We then focused on construction of the BCDE-ring system. Initially, we examined a 1,4-addition of the secondary amine to the enone after introduction of the amine moiety at



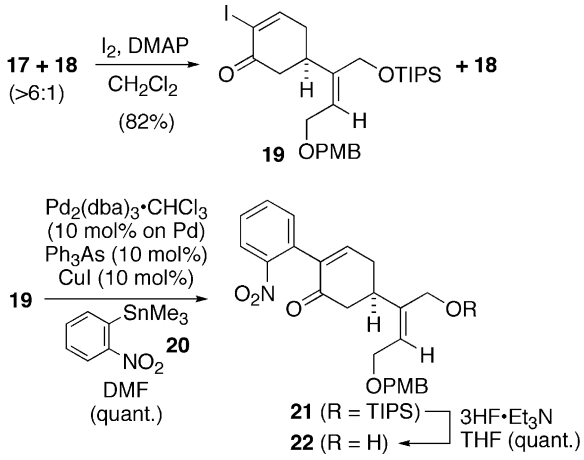
Scheme 4. Regioselective enone formation using a stoichiometric amount of Pd.

Table 3. Regioselective enone formation using a catalytic amount of Pd with diallyl carbonate



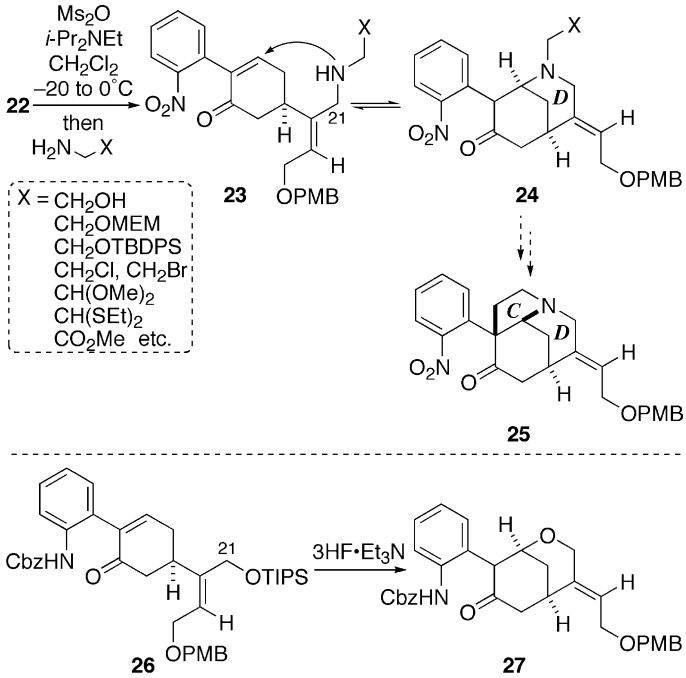
Entry	Pd catalyst	Ligand[a]	Yield (%)[b]	**17**:**18**[c]
1	$Pd(OAc)_2$	DPPE	Trace	—
2[d]	$Pd(OAc)_2$	DPPE	46	2.9:1
3	$Pd(OAc)_2$	—	19	>6:1
4	$Pd_2(dba)_3 \cdot CHCl_3$	—	90	>6:1

[a] 10 mol% of ligand was used.
[b] Isolated yield as an inseparable mixture of **17** and **18**.
[c] Ratio of **17** and **18** determined by ^1H NMR analysis.
[d] Reaction was performed under reflux conditions.

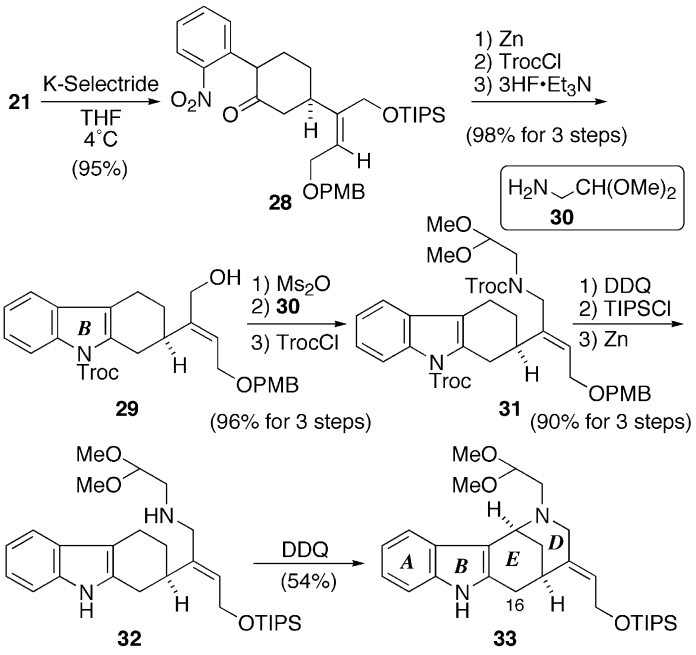


Scheme 5. α-Iodination and Stille coupling reaction.

C21 of **22** for D-ring formation (Scheme 6). This approach, however, was very difficult to utilize for the present synthesis. Amination via an allylic mesylate intermediate[33] provided an equilibrium mixture of the open form **23** and the cyclic form **24**, which was too unstable to isolate and be used for the next C-ring formation (**24**→**25**) because of the rapid retro reaction (**24**→**23**). To prevent the retro reaction, we examined a domino cyclization[34] (D- and C-ring formation) by introducing the leaving group on the amine side-chain (e.g. X=CH_2Br or CO_2Me) and another sequential cyclization (e.g. X=$CH(OMe)_2$ or $CH(SEt)_2$), however, all attempts were unsatisfactory (very low yield and low reproducibility). In contrast, in the case of an aniline analogue **26**, which was prepared from **19** using [2-(benzyloxycarbonylamino)phenyl]trimethylstannane for the Stille coupling reaction instead of **20**, even the hydroxyl group cyclized easily to afford stable cyclic ether **27**.[35] Although the reason for the dramatic difference in stability



Scheme 6. Examination of D-ring formation by 1,4-addition of amine to enone.



Scheme 7. Examination of D-ring formation by oxidative cyclization after indole formation.

between **24** and **27** is not clear, the instability of **27** is probably caused by the nitro group on the A-ring.[36]

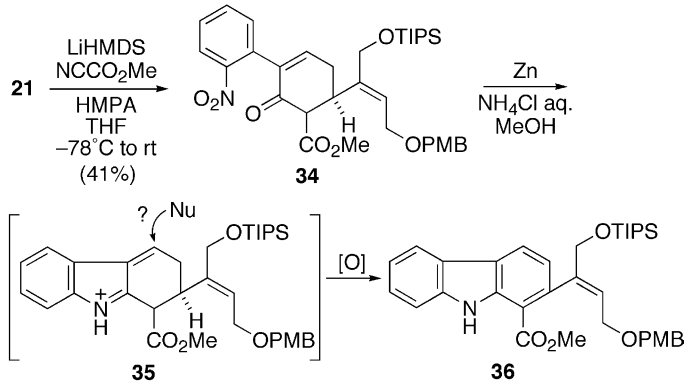
2.6. Examination of D-ring formation (2): oxidative cyclization after indole formation

We assembled the ABDE-ring system using a conventional stepwise process, including a one-pot oxidative cyclization (**32**→**33**) that we previously developed (Scheme 7).[18] This process required 11 steps, however, even using a model compound, which did not have one carbon unit at C16. In addition, we were unable to synthesize a dithioacetal derivative instead of dimethoxyacetal using this strategy (vide infra).

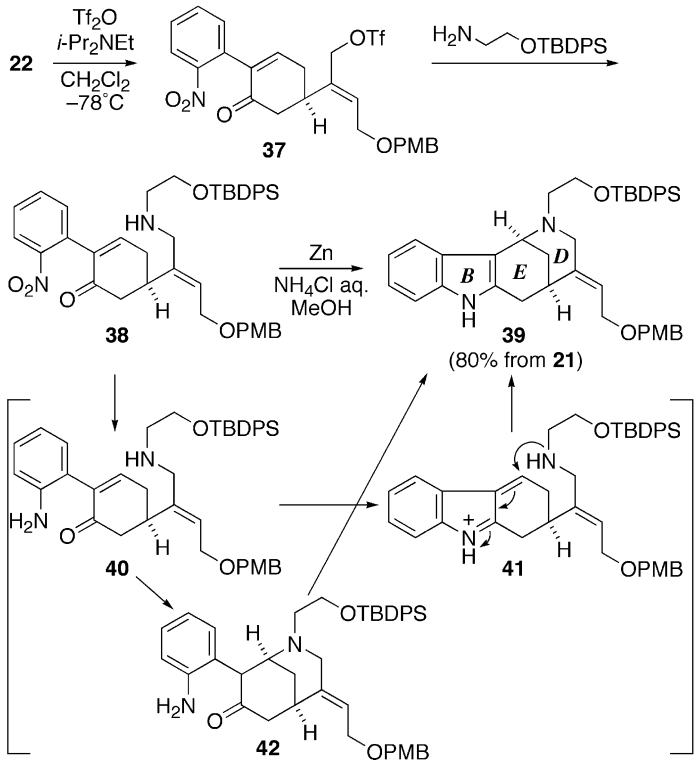
When enone **34** was used for the indole formation instead of ketone **28**, cyclized product **35** easily underwent aromatization to afford **36** (Scheme 8). This result suggested that if an appropriate nucleophile existed in the reaction, it might proceed to a 1,4-addition to the unstable, very reactive iminium cation intermediate **35**.

2.7. Examination of D-ring formation (3): domino cyclization constructing B- and D-rings

The above-mentioned unsuccessful trials prompted us to consider the feasibility of domino cyclization using **38** (Scheme 9).[37] After introduction of the amine moiety via allylic triflate **37**, the crude **38**, which existed as an equilibrium mixture of the open and cyclic forms as shown in Scheme 6, was simply treated with Zn in MeOH and aq NH_4Cl to provide the desired tetracyclic compound **39** in 80% yield. This domino cyclization might proceed by the following sequence: (1) reduction of the nitro group to amine by Zn (**38**→**40**), (2) indole formation (**40**→**41**), and (3) 1,4-addition of the secondary amine (**41**→**39**) (see Scheme 8) or (1) reduction of the nitro group to amine by Zn (**38**→**40**), (2) 1,4-addition of the secondary amine (**40**→**42**), and (3) irreversible indole formation of the aniline moiety with the resulting ketone (**42**→**39**) (see Scheme 6). Remarkably, the present process made it possible to skip more than 8 steps in the synthesis as compared with the step-wise route shown in Scheme 7.



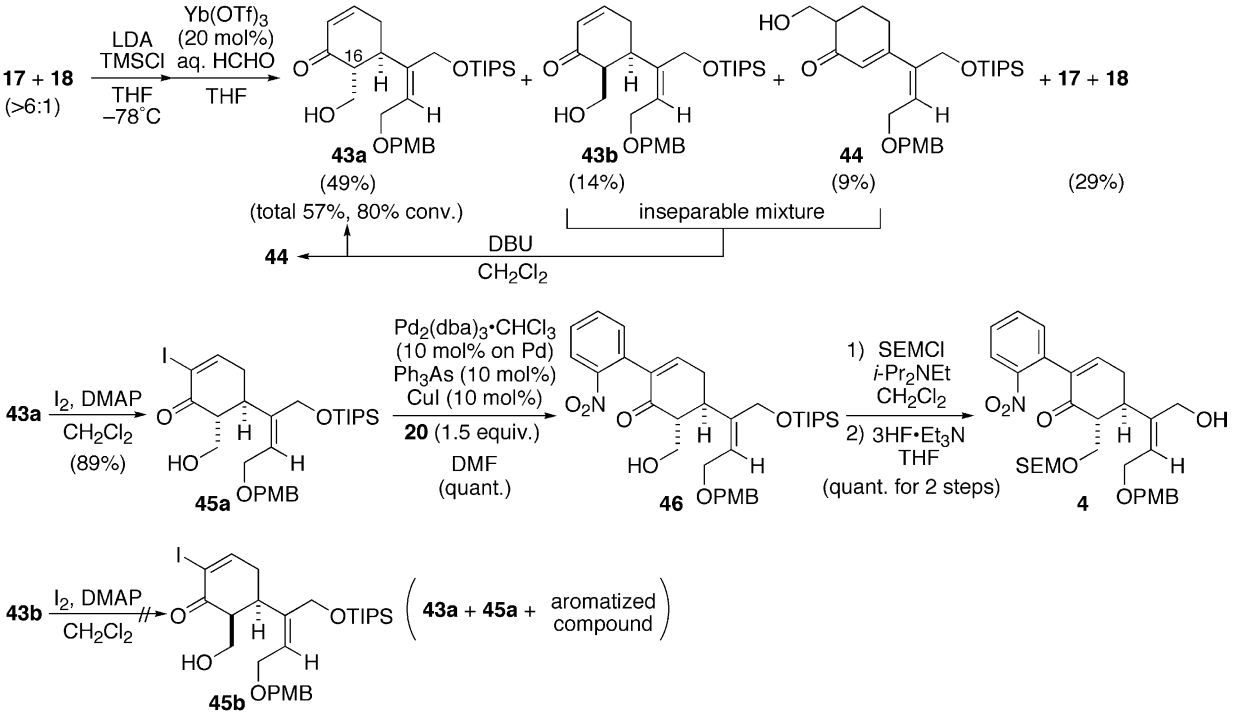
Scheme 8. Indole formation using enone **34**.



Scheme 9. Construction of B- and D-rings by domino cyclization promoted by Zn.

2.8. Introduction of the C1 unit at the C16 position and further transformation

Because of difficulty introducing one carbon unit at C16 after the indole formation, we next attempted methoxycarbonylation and hydroxymethylation prior to the above-mentioned domino cyclization. In most cases, however, aromatization of the corresponding cyclic β-keto ester and elimination of the corresponding β-hydroxyketone to the enone occurred. Instead, the mild aldol reaction of enol silyl ether in aqueous formaldehyde developed by Kobayashi et al.[38] was effective for the formation of **43** (C16α/C16β= 3.5:1) (Scheme 10).[39] Both diastereomers were expected to be applicable to the synthesis because the C16 stereocenter



Scheme 10. Hydroxymethylation at C16 and transformation to the key intermediate **4**.

can be epimerized in the last stage,[16] whereas using **43b** desired product **45b** was not obtained and unexpected aromatization proceeded in the next iodination step with C16 epimers **43a** and **45a**. Thus, **43b** was converted to the thermodynamically more stable **43a** by treatment with DBU prior to the iodination (57% from the mixture of regioisomers **17** and **18**, conversion 80%). Subsequent α-iodination of **43a** with DMAP (89%) and the Stille coupling reaction in the presence of CuI (quant.) effectively produced **46**. Finally, protection of the primary alcohol with SEMCl and removal of the TIPS group provided the key intermediate **4** in excellent yield (quant. for 2 steps).

2.9. C-ring formation

Domino cyclization using **4** after introduction of the amine moiety via allylic triflate also proceeded very efficiently to afford tetracyclic indole compound **3** in 77% yield (Scheme 11). Our next goal was to construct the C-ring by connecting the C6–C7 bond. We initially attempted to employ C-ring formation using β-haloamine, β-sulfonyloxyamine, β,β-dialkoxyamine, α-aminoaldehyde, and α-aminoester derivatives instead of β,β-bis(ethylthio)amine to avoid problematic desulfurization in the later stage. All trials failed (very low yield), however, probably due to the difficulty of selective activation of an electrophile in the presence of an indole moiety.[40] We then examined the intramolecular electrophilic attack of a thionium ion to generate a C7 spirocenter. C-ring formation using a variety of silver salts,[17c] hypervalent iodine, and DMTSF,[17a,b,18,41] however, provided unsatisfactory results: no reaction, decomposition, low yield (<20%), respectively. With DMTSF, aldehyde was generated, an unknown dimmer was formed, and over reaction of the desired product **47** occured. To prevent such side reactions and optimize this reaction, we examined the additive, reaction temperature, concentration, etc., and succeeded in improving the yield (up to 86%) under the following conditions: DMTSF (5 equiv), activated MS4A, CH_2Cl_2 (0.005 M), room temperature, and direct purification by silica gel chromatography without an aqueous work-up and concentration before purification.[42]

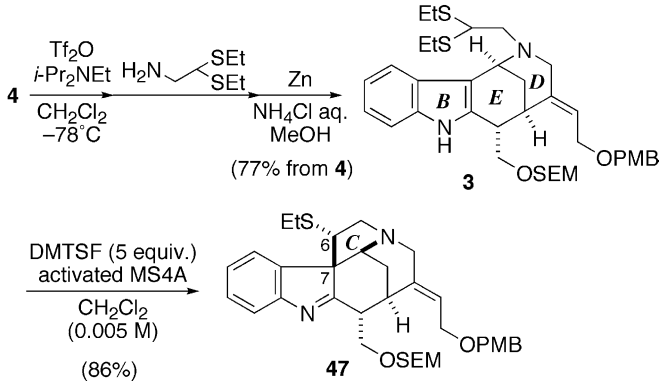
2.10. Reduction of imine to amine

Reduction of the imine **47** to amine **2**, in turn, was more problematic than we expected based on previous successful results.[16–18] Reductions of imine in similar indole alkaloids under neutral conditions, or in the presence of weak acids, often result in the cleavage of the C3–C7 bond. For example, under neutral conditions ($NaBH_4$ in MeOH) the ring-opening reaction proceeded through **48**, and was superior to the imine reduction, resulting in **49** (60%) without formation of **2** (Scheme 12). Other neutral reduction conditions, such as $LiAlH_4$, DIBAL, and H_2/cat. $[Rh(nbd)(dppe)]^+BF_4^-$, were also unsuccessful. Acidic conditions, such as $NaBH_3CN$ in AcOH[16e] and Zn in 10% H_2SO_4 in MeOH reflux,[16b,c] consistently solved this problem to give the desired related indole product. The reported conditions improved selectivity to afford the desired indole **2**. Under acidic conditions, however, significant decomposition of **47** proceeded through elimination of the 'SEMO' moiety (**47**→**51**). For example, treatment of **47** with AcOH at 4 °C for 30 min without reductant provided **51** in ca. 80% yield. Yield and/or reproducibility were not acceptable even after optimization, probably due to the instability of **47** against Brønsted acid.

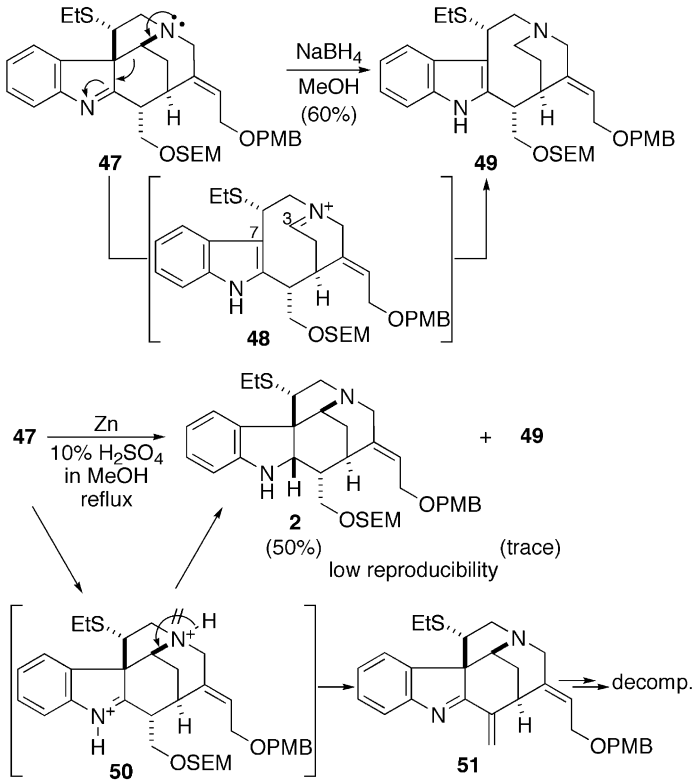
After testing numerous neutral or acidic conditions, we discovered a workable new method. To prevent an undesired ring-opening reaction (**47**→**49**) and elimination (**47**→**51**), we examined the addition of a Lewis acid to the reaction at low temperature. At this point, we expected that the Lewis acid would coordinate to not only the imine but also to the tertiary amine more strongly; thus, the former coordination would accelerate imine reduction (even under very low temperature) and the latter coordination would effectively prevent ring-opening reaction. Indeed, treatment with 5 equiv of $TiCl_4$ at −78 °C before the addition of $NaCH_3CN$ effectively prevented the ring-opening reaction and, as a result, **2** was obtained in 68% yield with ca. 6% of **49** with high reproducibility (Scheme 13).[43]

2.11. Chemoselective reduction of thioether (desulfurization) in the presence of *exo*-olefin

The stage was now set for the completion of the synthesis. The last major hurdle involved chemoselective reduction of thioether (desulfurization)[44] in the presence of *exo*-olefin. A Raney Ni (W-2) reduction was the first choice for this purpose. Even deactivated Raney Ni in acetone, however, promoted considerable migration of *exo*-olefin to *endo*-olefin to afford **54** (Scheme 14).[45,46] To prevent undesired olefin migration, new deactivation methods were further



Scheme 11. Domino cyclization of **4** and C-ring formation using DMTSF under optimized conditions (construction of BCDE-ring system).



Scheme 12. Reduction of imine moiety on **47** under neutral and acidic conditions.

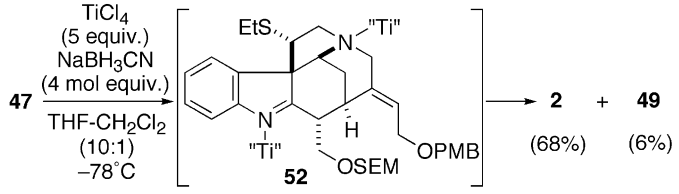
examined. The addition of a newly designed allyl amine mimic, *N*-allylpiperidine (**57**), effectively improved the selectivity. For example, a relatively reactive C–S bond (allylic thio ether) in **49** was efficiently cleaved in 82% yield with high selectivity (>20:1), while, without the additive, the migration was the major process. This additive also slightly improved the desulfurization of **2** and **58** (<1:10 to 1:5). Fortunately, the selectivity was further improved to ca. 1:1 by changing the protecting group of the allylic alcohol from PMB to TIPS, which can shield the *exo*-olefin moiety. Raney Ni, however, has several drawbacks, such as its pyrophoric nature, loss of activity on storage, and difficulty in determining the amount of Ni used. In light of the low selectivity and low reproducibility, we examined alternative desulfurization methods. Toward this end, Bu_3SnH-AIBN, lithium naphthalide, NiCRA, and a combination of a transition metal with aluminum hydride or borohydride species were tested.[44] Ni Boride[47] emerged as a promising candidate. The conventional protocol caused another side reaction: over reduction instead of migration.[48] By changing the solvent (EtOH–MeOH=4:1) and addition order (simultaneous addition of EtOH and MeOH to a mixture of $NaBH_4$ and $NiCl_2$), however, the desired product **62** was obtained in 91% yield based on consumed starting material with high selectivity (>10:1). A pre-mixed 4:1 mixture of EtOH and MeOH caused more over-reduction (**62**:**64**=3.6:1). After repeating this process twice (total three times), the isolated yield reached 61% as an inseparable mixture of **62** and its 19,20-dihydro derivative **64** (>10:1).

2.12. Completion of the total synthesis of (−)-strychnine

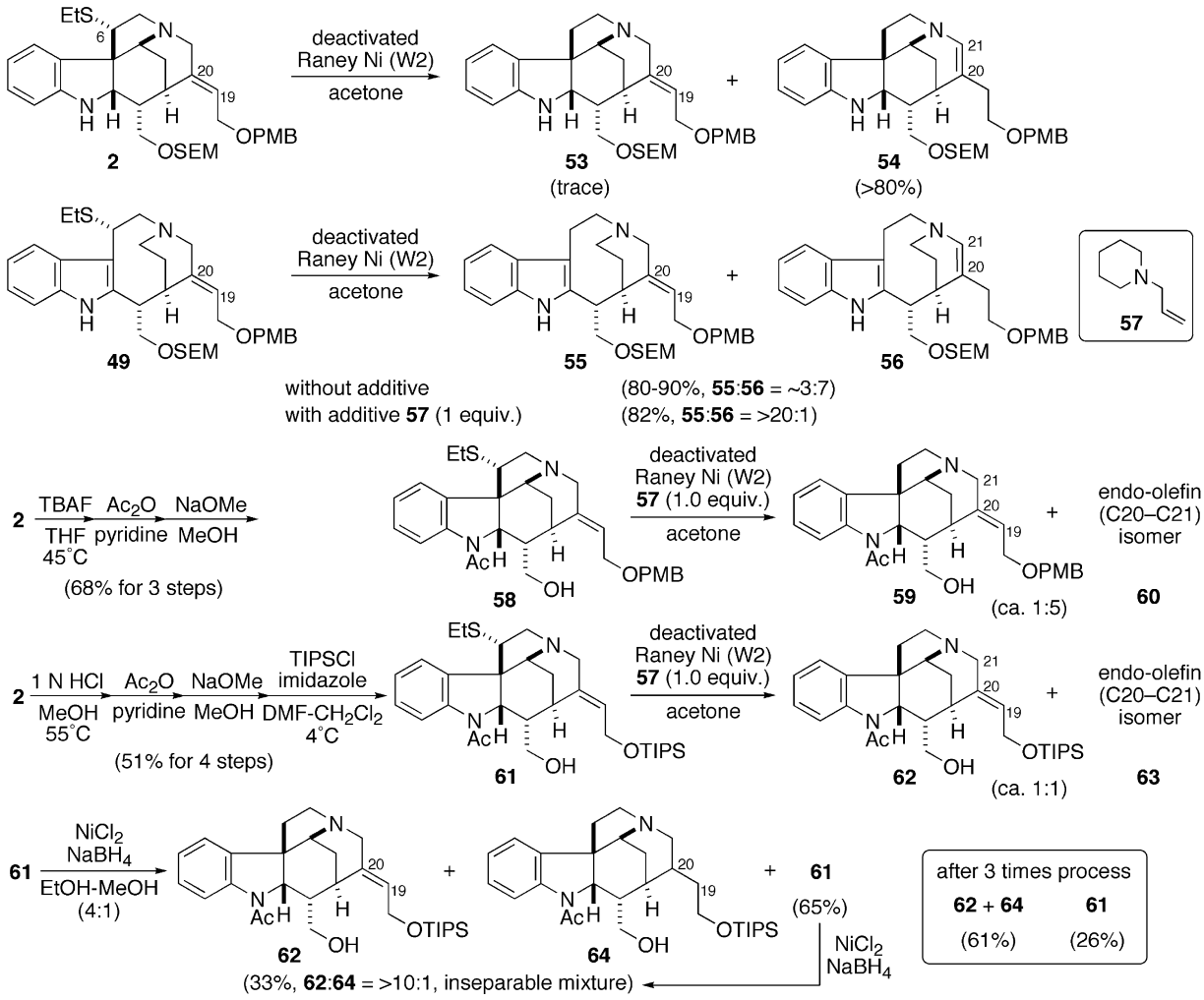
Consecutive SO_3·Py oxidation of the primary alcohol and removal of the TIPS group afforded (+)-diaboline (**65**)[49,50] ($[\alpha]_D$+39.5, lit. $[\alpha]_D$+27.8) through epimerization of the C16 stereocenter (Scheme 15). Finally, removal of the acetyl group provided the crude Wieland–Gumlich aldehyde (**66**), which was converted to (−)-strychnine (**1**)[16,50] ($[\alpha]_D$ −136, lit. $[\alpha]_D$ −139) by the established method.[16]

3. Conclusion

An enantioselective total synthesis of (−)-strychnine was achieved through the use of the highly practical catalytic asymmetric Michael reaction as well as a domino

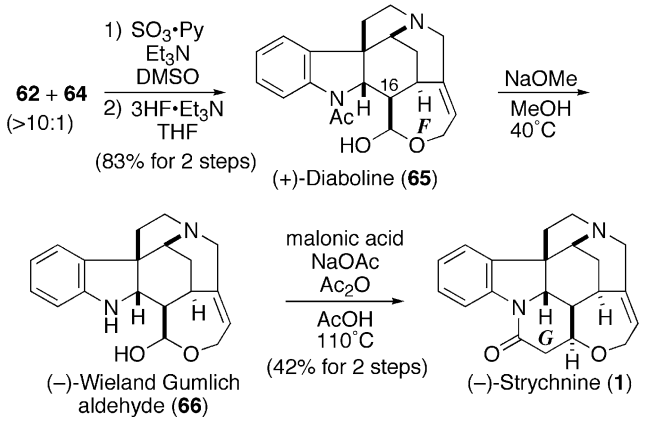


Scheme 13. Reduction of the imine moiety on **47** in the presence of Lewis acid.



Scheme 14. Chemoselective reduction of thioether (desulfurization) in the presence of *exo*-olefin.

cyclization that simultaneously construct the B- and D-rings. Moreover, newly-developed reaction conditions for the thionium ion cyclization, reduction of the imine moiety, and desulfurization were pivotal to complete the synthesis. The described chemistry paves the way for the synthesis of more advanced *Strychnos* alkaloids, especially those with further functionalities on the A- and C-rings, for chemical biology studies.



Scheme 15. Completion of the total synthesis of (−)-strychnine (**1**) via (+)-diaboline (**65**) and (−)-Wieland–Gumlich aldehyde (**66**).

4. Experimental

4.1. General

All reactions were carried out under an argon atmosphere with dry solvents, unless otherwise stated. Reagents were purified by the usual methods. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm Merck silica gel plates (60F-254). Column chromatography was performed with silica gel Merck 60 (230–400 mesh ASTM) or activated alumina (Wako, 300 mesh). Infrared (IR) spectra were recorded on a JASCO FT/IR 410 Fourier transform infrared spectrophotometer. NMR spectra were recorded on a JEOL JNM-LA500 spectrometer, operating at 500 MHz for ^{1}H NMR and 125.65 MHz for ^{13}C NMR and calibrated using residual undeuterated solvent as an internal reference. Optical rotations were measured on a JASCO P-1010 polarimeter. ESI mass spectra were measured on a Finnigan LCQ ion trap mass spectrometer (Finnigan MAT, San Jose, CA, USA) coupled with an electrospray ionization source (for MS-MS) or a Waters micromass ZQ with Waters 2695 Separation Module (for LC-MS). Experiments were performed in positive ion mode. HR-MS spectra were measured on a quadruple time-of-flight (Q-TOF) mass spectrometer (ABI, USA) equipped with a TurboIonSpray interface operated in positive ion mode. Calibration

calculations were automatically performed by the instrumental software (Bruker Xacq). All ^{1}H and ^{13}C NMR data for the new compounds were assigned by DEPT, COSY and HMQC experiments. ^{1}H, ^{13}C and DEPT NMR spectra were attached to the Supporting Information of Ref. 9. The numbering system based on the biogenetic interrelationship of indole alkaloids is used for assignment of ^{1}H and ^{13}C NMR.[10]

4.1.1. Catalytic asymmetric Michael reaction on a greater than kilogram scale: synthesis of (*R*)-3-[bis(methoxycarbonyl)methyl]cyclohexanone (5). A dried 2 L round-bottomed flask containing dried powdered MS4A (150 g) was purged with argon and cooled to 4 °C in an ice-water bath. Dimethyl malonate (**7**) (686 mL, 6.0 mol), 0.1 M THF solution of (*R*)-ALB[8,18,19c] (60 mL, 0.1 mol%), and 0.086 M THF solution of KO-*t*-Bu (63 mL, 0.09 mol%) were successively added to the flask. Finally, 2-cyclohexenone (**6**) (581 mL, 6.0 mol) was slowly added to the mixture within 30 min. After stirring for 90 min, the ice-water bath was removed and the reaction mixture was allowed to warm to room temperature and stirred for 22 h. At this point, the desired Michael adduct **5** precipitated out as a white solid. The precipitate was dissolved with EtOAc (1 L) and the resulting suspension was filtered through a Celite pad eluting with EtOAc (3×200 mL) to remove MS4A. The combined organic layers were washed with 1 N HCl (2×200 mL), saturated aqueous $NaHCO_3$ solution (200 mL), and brine (2×200 mL). The organic extract was dried over Na_2SO_4 and concentrated to ca. 2 L, containing ca. 700 mL of EtOAc, under reduced pressure. The enantiomeric excess of the crude product was determined to be 98% ee after purification of an analytical amount (ca. 20 mg) of the crude product by silica gel column chromatography (acetone–hexane, 1:9). Hexane (3 L) was added to the residue with vigorous stirring to afford **5** (1st: 1036 g) as a white crystal. The mother liquor was concentrated and crystallized from EtOAc–hexane (1:4) to afford **5** (2nd: 154 g). After one additional crystallization (3rd: 53 g), the combined yield reached 91%. The enantiomeric excess of each crystal was determined to be greater than 99% ee [DAICEL CHIRALPAK AS, hexane/2-propanol (87.5:12.5, v/v), flow rate: 0.5 mL/min, retention time: 47 min (*R*)-isomer and 67 min (*S*)-isomer, detected at 210 nm]. In addition, (*R*)-BINOL was recovered from the mother liquor as follows. After separation of the product **5** by three successive crystallizations, the mother liquor was concentrated under reduced pressure, and the residue was dissolved with toluene (200 mL) and extracted with 1 N NaOH (2×150 mL). The combined aqueous layers were acidified to pH 3 with 1 N HCl and extracted with EtOAc (2×200 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated under reduced pressure to afford BINOL (2.73 g, ca.79%) as a pale yellow solid. The enantiomeric excess of the recovered BINOL was determined to be greater than 99% ee [DAICEL CHIRALPAK AD, hexane/2-propanol (90:10, v/v), flow rate: 0.75 mL/min, retention time: 24 min (*R*)-isomer and 28 min (*S*)-isomer, detected at 254 nm]. The spectral data and analytical data of **5** were in agreement with those previously reported.[19c] Anal. calcd for $C_{11}H_{16}O_5$: C, 57.88; H, 7.07; found: C, 57.90; H, 7.12; $[\alpha]_D^{28}+3.75$ (*c* 2.28, $CHCl_3$) (>99% ee); mp 54.5–55.5 °C.

4.1.2. Synthesis of methyl (*R*)-1,4-dioxaspiro[4.5]decane-7-acetate (8). $TsOH\cdot H_2O$ (5.70 g, 30 mmol, 30 mol%) was added to a solution of **5** (228 g, 1.00 mol) in 2,2-ethylenedioxybutane (267 g, 2.3 mol, 2.3 equiv) at rt. After stirring for 16 h at the same temperature, the reaction mixture was quenched by the addition of saturated $NaHCO_3$ aqueous solution and extracted with CH_2Cl_2 (three times). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to afford crude acetal, which was used for the next step without further purification. The residue was dissolved in DMSO (500 mL, 2.0 M) and water (19.8 mL, 1.10 mol, 1.1 equiv.), and then LiCl (89 g, 2.1 mol, 2.1 equiv) was added. The reaction mixture was stirred for 17 h at 140 °C, cooled to rt, quenched by the addition of water, and extracted with EtOAc (twice). The combined organic layers were washed with 1 N HCl aqueous solution, saturated $NaHCO_3$ aqueous solution and brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography (silica gel, 10% EtOAc in hexane) to afford **8** (208 g, two steps 97%) as a colorless oil: $R_f=0.54$ (silica gel, EtOAc–hexane, 1:1); $[\alpha]_D^{24}+3.34$ (*c* 1.1, $CHCl_3$); FT-IR (neat) ν_{max} 2939, 1738, 1436, 1355, 1286, 1172, 1095 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.94 (s, 4H; OCH_2CH_2O), 3.66 (s, 3H; CO_2CH_3), 2.23 (d, $J=7.5$ Hz, 2H; H-20), 2.14–2.05 (m, 1H; H-15), 1.78 (br-d, $J=12.5$ Hz, 1H; H-16α), 1.75–1.68 (m, 3H; H-3β, H-7α, H-14α), 1.59–1.50 (m, 1H; H-3α), 1.42 (td, $J=13.5$, 3.5 Hz, 1H; H-7β), 1.23 (t, $J=12.5$ Hz, 1H; H-16β) 0.98–0.90 (m, 1H; H-14β); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9 (C-21), 108.8 (C-2), 64.2 (OCH_2CH_2O), 64.1 (OCH_2CH_2O), 51.4 (CO_2CH_3), 41.13 (C-20), 41.06 (C-16), 34.6 (C-7), 32.6 (C-15), 31.4 (C-14), 22.8 (C-3); MS (ESI (+)) *m/z* 215 ($M+H^+$). Anal. calcd for $C_{11}H_{18}O_4$: C 61.66, H 8.47; found C 64.41, H 8.40.

4.1.3. Synthesis of methyl (7*R*)-α-[[(4-methoxyphenyl)-methoxy]acetyl]-1,4-dioxaspiro[4.5]decane-7-acetate (12). A 1.57 N hexane solution of BuLi (64.8 mL, 102 mmol, 1.2 equiv) was added to a solution of diisopropylamine (14.4 mL, 110 mmol, 1.3 equiv) in THF (112 mL) at −78 °C. After stirring for 1 h at the same temperature, a solution of **8** (18.16 g, 84.8 mmol), which was azeotroped with toluene prior to being used, in THF (50 mL) was added dropwise to the mixture via cannula. After stirring for 1 h at the same temperature, a solution of *N*-methoxy-2-(4-methoxybenzyloxy)-*N*-methylacetamide (**11**)[51] (24.3 g, 102 mmol, 1.2 equiv), which was azeotroped with toluene prior to being used, in THF (50 mL) was added dropwise to the mixture via cannula. After stirring for additional 18 h at the same temperature, the reaction mixture was quenched by the addition of saturated NH_4Cl aqueous solution and extracted with EtOAc (twice). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography (silica gel, 10 to 50% EtOAc in hexane) to afford ca. 1:1 diastereomixture of β-keto esters **12** (18.4 g, 72%, conv. 82%) as a colorless oil with recovery of **8** (1.65 g, 12%) and **11** (5.76 g): $R_f=0.46$ (silica gel, EtOAc–hexane, 1:1); $[\alpha]_D^{24}$ −9.6 (*c* 1.5, $CHCl_3$); FT-IR (neat) ν_{max} 2947, 2880, 1723, 1612, 1514, 1435, 1249, 1172,

1092, 1032 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, $J=8.5$ Hz, 2H; Ar), 6.88 (d, $J=8.5$ Hz, 2H; Ar), 4.50 (s, 2H; ArCH_2O), 4.10 and 4.09 (s, 2H; H-18), 4.00–3.85 (m, 4H; OCH_2CH_2O), 3.81 (s, 3H; ArOCH_3), 3.66 (s, 3H; CO_2CH_3), 3.54 and 3.53 (d, $J=8.5$, 8.0 Hz, respectively, 1H; H-20), 2.50–2.43 (m, 1H; H-15), 1.77–1.53 (m, 5H; H-3α, H-3β, H-7α, H-14α, H-16α), 1.47–1.40 (m, 1H; H-7β), 1.32–1.23 (m, 1H; H-16β), 1.05–0.93 (m, 1H; H-14β); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.7 and 202.5 (C-19), 168.7 and 168.6 (C-21), 159.4 (Ar), 129.5 (Ar, 2 C), 128.9 (Ar), 113.8 (Ar, 2 C), 108.5 and 108.4 (C-2), 74.41 and 74.39 (C-18), 72.91 and 72.89 (ArCH_2O), 64.16 (OCH_2CH_2O), 64.14 (OCH_2CH_2O), 60.6 and 59.9 (C-20), 55.2 (ArOCH_3), 52.09 and 52.08 (CO_2CH_3), 38.8 and 38.4 (C-16), 34.8 and 34.6 (C-15), 34.60 and 34.57 (C-7), 29.4 and 28.8 (C-14), 22.7 and 22.4 (C-3); MS (ESI (+)) *m/z* 807 ($2M+Na^+$), 415 ($M+Na^+$), 410 ($M+NH_4^+$). Anal. calcd for $C_{21}H_{28}O_7$: C 64.27, H 7.19; found C 63.98, H 7.39.

4.1.4. Synthesis of methyl (α*E*,7*R*)-α-[2-[(4-methoxyphenyl)-methoxy]ethylidene]-1,4-dioxaspiro[4.5]decane-7-acetate (10a) by *anti*-selective reduction and following *syn*-elimination. A 2.5 M CH_2Cl_2 solution of $TiCl_4$ (35.6 mL, 89.0 mmol, 2.0 equiv) was added to a white suspension of $NaBH_3CN$ (10.2 g, 162 mmol, 3.64 mol equiv) in THF (200 mL) at −78 °C. A solution of **12** (17.45 g, 44.5 mmol) in THF (76 mL) was added dropwise over 30 min to the resulting yellow suspension via cannula, then the reaction mixture was maintained at −55 °C (internal temperature) for 10 h, quenched by the addition of saturated NH_4Cl aqueous solution, diluted with EtOAc, washed with 1 N HCl aqueous solution. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography (silica gel, 40 to 60% EtOAc in hexane) to afford diastereomixture of the corresponding β-hydroxy esters (ca. 16.77 g, ca. 96%) as a colorless oil. A solution of the residue in benzene (20 mL) was added to a white suspension of CuCl (5.47 g, 55.3 mmol, 1.3 equiv) and DCC (10.5 g, 51.0 mmol, 1.2 equiv) in benzene (85 mL) via cannula, then the reaction mixture was refluxed for 5 h, filtered through Celite pad eluting with toluene, washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography (silica gel, 20 to 60% EtOAc in hexane) to afford inseparable *E*/*Z* mixture (>15:1) of α,β-unsaturated esters **10a** (11.73 g, two steps 70%) as a colorless oil: $R_f=0.35$ (silica gel, EtOAc–hexane, 1:3); $[\alpha]_D^{23}+21.8$ (*c* 0.8, $CHCl_3$); FT-IR (neat) ν_{max} 2934, 2871, 1714, 1613, 1514, 1435, 1247, 1091 cm^{-1}; For (*E*)-isomer: ^1H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, $J=8.5$ Hz, 2H; Ar), 6.88 (d, $J=8.5$ Hz, 2H; Ar), 6.71 (t, $J=5.5$ Hz, 1H; H-19), 4.47 (s, 2H; ArCH_2O), 4.24 (dd, $J=14.0$, 5.5 Hz, 1H; H-18), 4.21 (dd, $J=14.0$, 5.5 Hz, 1H; H-18), 3.95–3.87 (m, 4H, OCH_2CH_2O), 3.80 (s, 3H; ArOCH_3), 3.70 (s, 3H; CO_2CH_3), 2.69 (tt, $J=12.5$, 3.5 Hz, 1H; H-15), 2.05 (t, $J=12.5$ Hz, 1H; H-16β), 1.78–1.70 (m, 3H; H-3β, H-7α, H-14α), 1.56 (br-d, $J=12.5$ Hz, 1H; H-16α), 1.57–1.46 (m, 3H; H-3α, H-7β, H-14β), For (*Z*)-isomer: δ 6.00 (td, $J=5.5$, 1.5 Hz, 1H; H-19); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4 (C-21), 159.3 (Ar), 138.5 (C-19), 136.6 (C-20), 129.8 (Ar), 129.4 (Ar, 2 C), 113.8 (Ar, 2 C), 108.9 (C-2), 72.4 (ArCH_2O), 66.0 (C-18), 64.2 (OCH_2CH_2O), 64.1 (OCH_2CH_2O), 55.3 (ArOCH_3), 51.5 (CO_2CH_3), 38.6 (C-16), 36.1 (C-15), 34.4 (C-7), 29.0 (C-14), 23.4 (C-3); MS (ESI (+)) *m/z* 394 ($M+NH_4^+$), 377 ($M+H^+$). Anal. calcd for $C_{21}H_{28}O_6$: C 67.00, H 7.50; found C 66.73, H 7.37.

4.1.5. Synthesis of [[(2*E*)-2-(7*R*)-1,4-dioxaspiro[4.5]dec-7-yl-4-[(4-methoxyphenyl)methoxy]-2-butenyl]oxy]tris-(1-methylethyl)silane (13). A 1.0 M hexane solution of DIBAL (24.0 mL, 24 mmol, 3.0 equiv) was added to a solution of **10a** (3.01 g, 7.98 mmol, *E*/*Z* mixture >15:1) in CH_2Cl_2 (56 mL, 0.14 M) at −78 °C. After stirring for 1 h at the same temperature, the reaction mixture was quenched by the addition of saturated NH_4Cl aqueous solution, followed by 1 N HCl aqueous solution, extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated to afford allyl alcohol, which was used for the next step without further purification. The residue was dissolved with CH_2Cl_2 (27 mL, 0.3 M), and then triethylamine (2.08 mL, 12.0 mmol, 1.5 equiv) and TIPSOTf (2.36 mL, 8.78 mmol, 1.1 equiv) were added at −78 °C. After stirring for 10 min at the same temperature, the reaction mixture was quenched by the addition of saturated NH_4Cl aqueous solution, extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography (silica gel, 10% EtOAc in hexane) to afford TIPS ether **13** (3.93 g, two steps 98%, *E*/*Z* mixture >15:1) as a colorless oil: $R_f=0.54$ (silica gel, EtOAc–hexane, 1:3); $[\alpha]_D^{22}+14.3$ (*c* 0.8, $CHCl_3$); FT-IR (neat) ν_{max} 2942, 2865, 1613, 1513, 1463, 1245, 1085 cm^{-1}; For (*E*)-isomer: ^1H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, $J=8.5$ Hz, 2H; Ar), 6.87 (d, $J=8.5$ Hz, 2H; Ar), 5.74–5.67 (m, 1H; H-19), 4.44 (s, 2H; ArCH_2O), 4.22–4.11 (m, 4H; H-18; H-21), 3.93–3.87 (m, 4H, OCH_2-CH_2O), 3.80 (s, 3H; ArOCH_3), 2.76–2.68 (m, 1H; H-15), 1.77–1.70 (m, 2H; H-3β, H-7α), 1.65–1.60 (m, 2H; H-16), 1.58–1.32 (m, 4H; H-3α, H-7β, H-14α, H-14β), 1.20–1.02 (m, 21H; TIPS); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1 (Ar), 144.5 (C-20), 130.7 (Ar), 129.3 (Ar, 2 C), 120.9 (C-19), 113.7 (Ar, 2 C), 109.0 (C-2), 71.6 (ArCH_2O), 65.6 (C-18), 64.3 (OCH_2CH_2O), 64.1 (OCH_2CH_2O), 64.0 (C-21), 55.3 (ArOCH_3), 39.4 (C-16), 36.2 (C-15), 34.7 (C-7), 30.0 (C-14), 23.5 (C-3), 18.1 (SiCH(CH_3)$_2$, 6 C), 12.0 (SiCH(CH_3)$_2$, 3 C); MS (ESI (+)) *m/z* 522 ($M+NH_4^+$). Anal. calcd for $C_{29}H_{48}O_5Si$: C 69.00, H 9.58; found C 68.86, H 9.56.

4.1.6. Synthesis of (3*R*)-3-[(1*E*)-3-[(4-methoxyphenyl)-methoxy]-1-[[[tris(1-methylethyl)silyl]oxy]methyl]-1-propenyl]cyclohexanone (14). The TIPS ether **13** (7.23 g, 14.3 mmol, *E*/*Z* mixture >15:1) was treated with 0.01 M acetone solution of *dl*-CSA (71 mL, 0.71 mmol, 5 mol%) at rt. After stirring for 2 d at the same temperature, the reaction mixture was quenched by the addition of saturated $NaHCO_3$ aqueous solution, and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography (silica gel, 5 to 10% EtOAc in hexane) to afford pure (*E*)-**14** (4.08 g, 62%, conv. 90%) as a colorless oil with (*Z*)-**14** (ca. 260 mg, 4%) and the recovery of **13** (2.27 g, 31%): $R_f=0.49$ (silica gel, EtOAc–hexane, 1:3); $[\alpha]_D^{22}+15.4$ (*c* 1.6, $CHCl_3$); FT-IR (neat) ν_{max} 2948, 2865, 1715, 1613, 1514, 1464, 1249, 1056 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, $J=8.5$ Hz, 2H; Ar), 6.87 (d, $J=8.5$ Hz, 2H; Ar), 5.70 (t, $J=6.5$ Hz, 1H; H-19), 4.43 (s, 2H; ArCH_2O), 4.27 (d, $J=12.5$ Hz, 1H; H-21), 4.22 (d, $J=12.5$ Hz, 1H; H-21), 4.06 (dd, $J=12.0$, 6.5 Hz, 1H; H-18),

4.01 (dd, J=12.0, 6.5 Hz, 1H; H-18), 3.80 (s, 3H; ArOCH_3), 2.77 (tt, J=12.5, 3.5 Hz, 1H; H-15), 2.60 (t, J=12.5 Hz, 1H; H-16β), 2.37 (br-d, J=14.5 Hz, 1H; H-7α), 2.33 (br-d, J=12.5 Hz, 1H; H-16α), 2.30–2.21 (m, 1H; H-7β), 2.10–2.06 (m, 1H; H-3β), 1.85 (qd, J=12.5, 3.5 Hz, 1H; H-14β), 1.75 (br-d, J=12.5 Hz, 1H; H-14α), 1.63–1.56 (m, 1H; H-3α), 1.27–0.96 (m, 21H; TIPS); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.0 (C-2), 159.2 (Ar), 143.0 (C-20), 130.2 (Ar), 129.4 (Ar, 2 C), 123.1 (C-19), 113.8 (Ar, 2 C), 71.9 (ArCH_2O), 65.08 (C-18), 65.05 (C-21), 55.3 (ArOCH_3), 46.5 (C-16), 41.2 (C-7), 39.5 (C-15), 29.7 (C-14), 25.8 (C-3), 18.1 (SiCH(CH_3)$_2$, 6 C), 11.9 (SiCH(CH$_3$)$_2$, 3 C); MS (ESI (+)) m/z 478 ($M+NH_4^+$). Anal. calcd for $C_{27}H_{44}O_4Si$: C 70.39, H 9.63; found C 70.14, H 9.50.

4.1.7. Synthesis of (5*R*)-5-[(1*E*)-3-[(4-methoxyphenyl)-methoxy]-1-[[[tris(1-methylethyl)silyl]oxy]methyl]-1-propenyl]-2-cyclohexen-1-one (17) by catalytic Saegusa–Ito reaction. A 1.48 N hexane solution of BuLi (0.79 mL, 1.22 mmol, 1.4 equiv) was added to a solution of 2,2,6,6-tetramethylpiperidine (0.22 mL, 1.31 mmol, 1.5 equiv) in THF (6.0 mL) at 4 °C (ice-water bath). After stirring for 1 h at the same temperature, the reaction mixture was cooled to −78 °C. TMSCl (0.17 mL, 1.22 mmol, 1.4 equiv) was then added, followed by addition of a solution of **14** (402 mg, 0.873 mmol) in THF (6.0 mL) via cannula. After stirring for 2 h at the same temperature, the reaction mixture was quenched by the addition of saturated $NaHCO_3$ aqueous solution, extracted with Et_2O, dried over Na_2SO_4, and concentrated to afford crude enol silyl ether, which was used for the next step without further purification. The residue was dissolved with CH_3CN (4.7 mL, 0.125 M), then diallyl carbonate (0.17 mL, 1.2 mmol, 1.4 equiv) and $Pd_2(dba)_3\cdot CHCl_3$ (61 mg, 59 μmol, 7 mol%) were added at rt. After stirring for 12 h at the same temperature, the reaction mixture was quenched by the addition of saturated $NaHCO_3$ aqueous solution, extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography (silica gel, 15 to 20% EtOAc in hexane) to afford an inseparable mixture of regioisomers (>6:1) **17** and **18** (361.3 mg, two steps 90%) as a colorless oil with the recovery of **14** (35 mg, 9%): R_f=0.43 (silica gel, EtOAc–hexane, 1:3); $[\alpha]_D^{24}$+37.6 (c 2.8, $CHCl_3$); FT-IR (neat) ν_{max} 2946, 2865, 1682, 1613, 1513, 1464, 1386, 1248, 1106 cm^{-1}; For the major regioisomer **17**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, J=9.0 Hz, 2H; Ar), 7.00–6.96 (m, 1H; H-3), 6.87 (d, J=9.0 Hz, 2H; Ar), 6.03 (dd, J=10.0, 3.6 Hz, 1H; H-7), 5.76 (t, J=6.5 Hz, 1H; H-19), 4.44 (d, J=11.5 Hz, 1H; ArCHHO), 4.42 (d, J=11.5 Hz, 1H; ArCHHO), 4.28 (d, J=13.5 Hz, 1H; H-21), 4.24 (d, J=13.5 Hz, 1H; H-21), 4.06 (dd, J=15.0, 6.5 Hz, 1H; H-18), 4.02 (dd, J=15.0, 6.5 Hz, 1H; H-18), 3.80 (s, 3H; ArOCH_3), 3.19–3.12 (m, 1H; H-15), 2.68 (dd, J=15.5, 14.5 Hz, 1H; H-16β), 2.68–2.61 (m, 1H; H-14β), 2.40 (dd, J=15.5, 3.5 Hz, 1H; H-16α), 2.27 (dt, J=14.0, 5.5 Hz, 1H; H-14α), 1.15–1.03 (m, 21H; TIPS); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.5 (C-2), 159.2 (Ar), 150.2 (C-3), 142.3 (C-20), 130.1 (Ar), 129.4 (C-7 and Ar, 3 C), 124.2 (C-19), 113.8 (Ar, 2 C), 72.0 (ArCH_2O), 65.3 (C-21), 65.0 (C-18), 55.3 (ArOCH_3), 42.5 (C-16), 35.7 (C-15), 31.0 (C-14), 18.0 (SiCH(CH_3)$_2$, 6 C), 11.9 (SiCH(CH$_3$)$_2$, 3 C); MS (ESI (+)) m/z 476 ($M+NH_4^+$), 459 ($M+H^+$). Anal. calcd for $C_{27}H_{42}O_4Si$: C 70.70, H 9.23; found C 70.57, H 9.25.

4.1.8. Synthesis of (5*R*,6*R*)-6-(hydroxymethyl)-5-[(1*E*)-3-[(4-methoxyphenyl)methoxy]-1-[[[tris(1-methylethyl)-silyl]oxy]methyl]-1-propenyl]-2-cyclohexen-1-one (43a). A 1.51 N hexane solution of BuLi (2.76 mL, 4.16 mmol, 1.2 equiv) was added to a solution of diisopropylamine (0.73 mL, 5.21 mmol, 1.5 equiv) in THF (50 mL) at −78 °C. After stirring for 1 h at the same temperature, TMSCl (0.53 mL, 4.16 mmol, 1.2 equiv) was added to the reaction mixture, followed by the addition of a solution of **17** and **18** (1.59 g, 3.47 mmol, mixture of regioisomers >6:1) in THF (20 mL) via cannula. After stirring for 2 h at the same temperature, the reaction mixture was quenched by the addition of saturated $NaHCO_3$ aqueous solution, extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated to afford crude enol silyl ether, which was used for the next step without further purification. The residue was dissolved with THF (28.0 mL, 0.125 M), then 37% aqueous solution of formaldehyde (7.0 mL, 0.50 M) and $Yb(OTf)_3$ (430 mg, 0.69 mmol, 20 mol%) were added at rt. After stirring for 3 d at the same temperature, the reaction mixture was quenched by the addition of saturated $NaHCO_3$ aqueous solution, extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated. The residue was roughly purified by flash column chromatography (silica gel, 20 to 50% EtOAc in hexane) to afford regio- and diastereomixture of aldol products (**43a**, **43b**, and **44**) (ca 1.3 g) as a colorless oil with the recovery of starting material (**17**:**18**=>6:1) (0.47 g, 29%). A mixture of the aldol products was dissolved with CH_2Cl_2 (10 mL) and treated with DBU at rt. After stirring for 1 h at the same temperature, the reaction mixture was quenched by the addition of saturated NH_4Cl aqueous solution, extracted with Et_2O, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography (silica gel, 30 to 50% EtOAc in hexane) to afford (6*R*)-aldol product **43a** (0.963 g, 57%, conv. 80%) as a colorless oil, which became a white solid after storage in refrigerator: R_f=0.20 (silica gel, EtOAc–hexane, 1:3); mp 35–36 °C; $[\alpha]_D^{24}$+19.0 (c 1.0, $CHCl_3$); FT-IR (neat) ν_{max} 3459, 2941, 2865, 1672, 1613, 1514, 1464, 1389, 1249, 1106 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, J=8.5 Hz, 2H; Ar), 6.98 (ddd, J=10.1, 5.0, 2.0 Hz, 1H; H-3), 6.85 (d, J=8.5 Hz, 2H; Ar), 6.05 (dd, J=10.0, 2.0 Hz, 1H; H-7), 5.92 (t, J=7.0 Hz, 1H; H-19), 4.44 (d, J=11.5 Hz, 1H; ArCHHO), 4.42 (d, J=11.5 Hz, 1H; ArCHHO), 4.29 (s, 2H; H-21), 4.08 (dd, J=12.0, 7.0 Hz, 1H; H-18), 4.01 (dd, J=12.0, 7.0 Hz, 1H; H-18), 3.95 (br-d, J=11.5 Hz, 1H, H-17), 3.80 (s, 3H; ArOCH_3), 3.19–3.12 (m, 1H; H-15), 2.68 (dd, J=15.5, 14.5 Hz, 1H; H-16β), 2.68–2.61 (m, 1H; H-14β), 2.40 (dd, J=15.5, 3.5 Hz, 1H; H-16α), 2.27 (dt, J=14.0, 5.5 Hz, 1H; H-14α), 1.15–1.03 (m, 21H; TIPS); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.4 (C-2), 159.3 (Ar), 150.0 (C-3), 141.3 (C-20), 129.8 (Ar), 129.5 (C-7 and Ar, 3 C), 125.7 (C-19), 113.8 (Ar, 2 C), 72.2 (ArCH_2O), 64.9 (C-18), 64.7 (C-21), 59.8 (C-17), 55.2 (ArOCH_3), 50.9 (C-16), 36.7 (C-15), 30.7 (C-14), 18.0 (SiCH(CH_3)$_2$, 6 C), 11.9 (SiCH(CH$_3$)$_2$, 3 C); MS (ESI (+)) m/z 999 ($2M+Na^+$), 489 ($M+H^+$). Anal. calcd for $C_{28}H_{44}O_5Si$: C 68.81, H 9.07; found C 68.55, H 9.07.

4.1.9. Synthesis of (5*R*,6*R*)-6-(hydroxymethyl)-2-iodo-5-[(1*E*)-3-[(4-methoxyphenyl)methoxy]-1-[[[tris(1-methyl-ethyl)silyl]oxy]methyl]-1-propenyl]-2-cyclohexen-1-one (45a). A 0.05 M CH_2Cl_2 solution of I_2 (214 mL, 10.7 mmol,

1.2 equiv) was added dropwise over 20 min to a solution of **43a** (4.35 g, 8.90 mmol) and DMAP (2.17 g, 17.8 mmol, 2.0 equiv) in CH_2Cl_2 (50 mL) at rt. After stirring for 5 h at the same temperature, the reaction mixture was quenched by the addition of water and extracted with CH_2Cl_2. The organic layer was washed with 1 N HCl aqueous solution, water, 10% $Na_2S_2O_3$ aqueous solution, water and brine, extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography (silica gel, 10 to 20% EtOAc in hexane) to afford iodide **45a** (4.86 g, 89%) as a pale yellow oil: R_f=0.37 (silica gel, EtOAc–hexane, 1:3); $[\alpha]_D^{23}$+4.53 (*c* 1.1, $CHCl_3$); FT-IR (neat) ν_{max} 3434, 2942, 2867, 1682, 1612, 1514, 1463, 1248, 1173, 1080 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.73 (dd, *J*=6.5, 2.0 Hz, 1H; H-3), 7.22 (d, *J*=8.5 Hz, 2H; Ar), 6.86 (d, *J*=8.5 Hz, 2H; Ar), 5.92 (t, *J*=7.0 Hz, 1H; H-19), 4.43 (d, *J*=11.5 Hz, 1H; ArC*H*HO), 4.41 (d, *J*=11.5 Hz, 1H; ArC*H*HO), 4.27 (s, 2H; H-21), 4.06 (dd, *J*=12.0, 7.0 Hz, 1H; H-18), 4.04–4.00 (m, 1H; H-17), 3.98 (dd, *J*=12.0, 7.0 Hz, 1H; H-18), 3.80 (s, 3H; ArOCH_3), 3.60 (ddd, *J*=11.5, 5.5, 4.5 Hz, 1H, H-17), 3.33 (ddd, *J*=13.5, 11.5, 4.5 Hz, 1H; H-15), 2.99 (dd, *J*=8.0, 5.5 Hz, 1H; O*H*), 2.89 (ddd, *J*=18.5, 11.5, 2.0 Hz, 1H; H-14β), 2.81 (ddd, *J*=13.5, 4.5, 2.5 Hz, 1H; H-16), 2.32 (ddd, *J*=18.5, 6.5, 4.5 Hz, 1H; H-14α), 1.14–1.00 (m, 21H; TIPS); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.1 (C-2), 159.3 (Ar), 158.6 (C-3), 140.6 (C-20), 129.6 (Ar), 129.5 (Ar, 2 C), 126.5 (C-19), 113.8 (Ar, 2 C), 103.1 (C-7), 72.3 (Ar*C*H_2O), 65.0 (C-21), 64.7 (C-18), 60.0 (C-17), 55.2 (ArO*C*H_3), 51.3 (C-16), 36.7 (C-15), 34.6 (C-14), 18.0 (SiCH(*C*H_3)$_2$, 6 C), 11.8 (Si*C*H(CH_3)$_2$, 3 C); MS (ESI (+)) *m*/*z* 1251 (2M+Na^+), 632 (M+NH_4^+), 615 (M+H^+). Anal. calcd for $C_{28}H_{43}IO_5Si$: C 54.72, H 7.05; found C 54.61, H 6.92.

4.1.10. Synthesis of (5*R*,6*R*)-6-(hydroxymethyl)-5-[(1*E*)-3-[(4-methoxyphenyl)methoxy]-1-[[[tris(1-methylethyl)silyl]oxy]methyl]-1-propenyl]-2-(2-nitrophenyl)-2-cyclohexen-1-one (46) by Stille coupling reaction. $Pd_2(dba)_3\cdot CHCl_3$ (13 mg, 12.2 μmol, 5.0 mol%, 10 mol% on Pd), Ph_3As (15 mg, 48.8 μmol, 20 mol%), and CuI (4.6 mg, 24.4 μmol, 10 mol%) were added to a solution of **45a** (150 mg, 0.244 mmol) and trimethyl(2-nitrophenyl)-stannane[52] (105 mg, 0.366 mmol, 1.5 equiv) in DMF (4.9 mL, 0.05 M) at rt. After being degassed by a freeze-pump-thaw cycle, the reaction mixture was stirred for 48 h at rt, quenched by the addition of saturated NH_4Cl aqueous solution, extracted with Et_2O (three times). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (silica gel, 5 to 30% EtOAc in hexane) to afford **46** (151 mg, quant) as a pale yellow oil: R_f=0.19 (silica gel, EtOAc–hexane, 1:3); $[\alpha]_D^{22}$+86.8 (*c* 1.5, $CHCl_3$); FT-IR (neat) ν_{max} 3445, 2940, 2862, 1681, 1612, 1530, 1463, 1354, 1247, 1101 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.03 (dd, *J*=8.0, 1.0 Hz, 1H; H-12), 7.60 (td, *J*=8.0, 1.0 Hz, 1H; H-10), 7.48 (td, *J*=8.0, 1.0 Hz, 1H; H-11), 7.26–7.24 (m, 3H; H-9, Ar (2H)), 6.99 (dd, *J*=6.5, 2.0 Hz, 1H; H-3), 6.85 (d, *J*=9.0 Hz, 2H; Ar), 5.95 (t, *J*=7.0 Hz, 1H; H-19), 4.46 (d, *J*=11.5 Hz, 1H; ArC*H*HO), 4.43 (d, *J*=11.5 Hz, 1H; ArC*H*HO), 4.34 (s, 2H; H-21), 4.14–4.07 (m, 2H; H-18), 4.00–3.96 (m, 1H; H-17), 3.96 (s, 3H; ArOCH_3), 3.70–3.60 (m, 1H; H-17), 3.40 (ddd, *J*=13.5, 11.5, 4.5 Hz, 1H; H-15), 2.97 (ddd, *J*=18.5, 11.5, 2.0 Hz, 1H; H-14β), 2.87–2.82 (m, 2H; H-16, O*H*), 2.50 (ddd, *J*=18.5, 6.5, 4.5 Hz, 1H; H-14α), 1.19–1.03 (m, 21H; TIPS); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.6 (C-2), 159.2 (Ar), 148.4 (C-13), 146.1 (C-3), 140.8 (C-20), 139.0 (C-7), 133.4 (C-10), 131.8 (C-9), 131.7 (C-8), 130.0 (Ar), 129.5 (Ar, 2 C), 128.9 (C-11), 126.0 (C-19), 124.3 (C-12), 113.8 (Ar, 2 C), 72.2 (Ar*C*H_2O), 65.1 (C-21), 64.8 (C-18), 59.8 (C-17), 55.2 (ArO*C*H_3), 51.2 (C-16), 36.5 (C-15), 30.9 (C-14), 18.0 (SiCH(*C*H_3)$_2$, 6 C), 11.9 (Si*C*H(CH_3)$_2$, 3 C); MS (ESI (+)) *m*/*z* 1241 (2M+Na^+), 627 (M+NH_4^+), 610 (M+H^+). Anal. calcd for $C_{34}H_{47}NO_7Si$: C 66.96, H 7.77, N 2.30; found C 66.73, H 7.97, N 2.07.

4.1.11. Synthesis of (5*R*,6*R*)-5-[(1*E*)-3-[(4-methoxyphenyl)methoxy]-1-[[[tris(1-methylethyl)silyl]oxy]methyl]-1-propenyl]-2-(2-nitrophenyl)-6-[[[2-(trimethylsilyl)-ethoxy]methoxy]methyl]-2-cyclohexen-1-one. SEMCl (0.054 mL, 0.308 mmol, 1.5 equiv) was added to a solution of **46** (125 mg, 0.205 mmol) and *N*,*N*-diisopropylethylamine (0.11 mL, 0.615 mmol, 3.0 equiv) in CH_2Cl_2 (2.0 mL, 0.1 M) at 4 °C (ice-water bath). After stirring for 24 h at rt, the reaction mixture was quenched by the addition of saturated NH_4Cl aqueous solution, extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography (silica gel, 20% EtOAc in hexane) to afford SEM ether (152 mg, quant) as a pale yellow oil: R_f=0.58 (silica gel, EtOAc–hexane, 1:3); $[\alpha]_D^{24}$+119.6 (*c* 0.9, $CHCl_3$); FT-IR (neat) ν_{max} 2944, 2857, 1681, 1612, 1529, 1356, 1248, 1105 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, *J*=8.0 Hz, 1H; H-12), 7.59 (td, *J*=8.0, 1.5 Hz, 1H; H-10), 7.48 (td, *J*=8.0, 1.5 Hz, 1H; H-11), 7.28–7.25 (m, 3H; H-9, Ar (2H)), 6.98 (dd, *J*=6.0, 2.0 Hz, 1H; H-3), 6.87 (d, *J*=8.5 Hz, 2H; Ar), 5.92 (t, *J*=7.0 Hz, 1H; H-19), 4.57 (d, *J*=6.5 Hz, 1H; OC*H*HO), 4.51 (d, *J*=6.5 Hz, 1H; OC*H*HO), 4.48 (s, 2H; ArCH_2O), 4.35 (s, 2H; H-21), 4.24 (dd, *J*=11.5, 7.0 Hz, 1H; H-18), 4.14–4.07 (m, 2H; H-17, H-18), 3.79 (s, 3H; ArOCH_3), 3.56–3.44 (m, 4H; H-15, H-17, OCH_2CH_2Si (2H)), 2.95 (dd, *J*=18.5, 11.5 Hz, 1H; H-14β), 2.85 (br-d, *J*=8.0 Hz, 1H; H-16), 2.51 (dt, *J*=18.5, 5.5 Hz, 1H; H-14α), 1.17–1.03 (m, 21H; TIPS), 0.88 (t, *J*=8.5 Hz, 2H; OCH$_2$CH_2Si), −0.04 (s, 9H; Si(CH_3)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.1 (C-2), 159.1 (Ar), 148.6 (C-13), 145.4 (C-3), 140.2 (C-20), 139.1 (C-7), 133.1 (C-10), 132.1 (C-8), 131.8 (C-9), 130.3 (Ar), 129.3 (Ar, 2 C), 128.7 (C-11), 126.0 (C-19), 124.2 (C-12), 113.7 (Ar, 2 C), 95.3 (O*C*H_2O), 72.0 (Ar*C*H_2O), 65.7 (C-18), 64.9 (O*C*H_2CH$_2$Si), 64.8 (C-21), 63.6 (C-17), 55.2 (ArO*C*H_3), 49.8 (C-16), 36.5 (C-15), 30.9 (C-14), 18.1 (SiCH(*C*H_3)$_2$, 6 C), 18.0 (OCH$_2$*C*H$_2$Si), 11.9 (Si*C*H(CH_3)$_2$, 3 C), −1.5 (Si(CH_3)$_3$, 3 C); MS (ESI (+)) *m*/*z* 757 (M+NH_4^+). Anal. calcd for $C_{40}H_{61}NO_8Si_2$: C 64.92, H 8.31, N 1.89; found C 64.70, H 8.24, N 1.78.

4.1.12. Synthesis of (5*R*,6*R*)-5-[(1*E*)-1-(hydroxymethyl)-3-[(4-methoxyphenyl)methoxy]-1-propenyl]-2-(2-nitrophenyl)-6-[[[2-(trimethylsilyl)ethoxy]methoxy]methyl]-2-cyclohexen-1-one (4). $3HF\cdot Et_3N$ (0.56 mL, 3.46 mmol, 10 equiv) was added to a solution of the SEM ether (256 mg, 0.346 mmol) in THF (3.5 mL, 0.1 M) at rt. After stirring for 50 h at rt (more than 25 °C), the reaction mixture was cooled with ice-water bath, quenched carefully by the addition of saturated $NaHCO_3$ aqueous solution, extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated. The

residue was purified by flash column chromatography (silica gel, 50 to 60% EtOAc in hexane) to afford **4** (202 mg, quant.) as a colorless oil, which became a white solid after storage in refrigerator: R_f=0.33 (silica gel, EtOAc–hexane, 1:1); mp 64–65 °C; $[\alpha]_D^{24}$+126.1 (*c* 1.5, $CHCl_3$); FT-IR (neat) ν_{max} 3439, 2951, 2876, 1678, 1527, 1355, 1249, 1065 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, *J*=8.0 Hz, 1H; H-12), 7.61 (dd, *J*=8.0, 1.5 Hz, 1H; H-10), 7.49 (dd, *J*=8.0, 1.5 Hz, 1H; H-11), 7.27–7.25 (m, 3H; H-9, Ar (2H)), 6.99 (dd, *J*=6.5, 2.0 Hz, 1H; H-3), 6.87 (d, *J*=8.5 Hz, 2H; Ar), 5.87 (dd, *J*=6.5, 6.0 Hz, 1H; H-19), 4.58 (d, *J*=7.0 Hz, 1H; OC*H*HO), 4.55 (d, *J*=7.0 Hz, 1H; OC*H*HO), 4.46 (s, 2H; ArCH_2O), 4.30 (dd, *J*=13.5, 6.5 Hz, 1H; H-21), 4.20 (dd, *J*=13.5, 4.5 Hz, 1H; H-21), 4.18 (dd, *J*=12.5, 6.5 Hz, 1H; H-18), 4.08 (dd, *J*=12.5, 6.0 Hz, 1H; H-18), 3.86 (dd, *J*=10.0, 4.5 Hz, 1H; H-17), 3.78 (s, 3H; ArOCH_3), 3.78 (dd, *J*=10.0, 2.5 Hz, 1H; H-17), 3.58–3.47 (m, 2H; OCH_2CH_2Si), 3.40 (td, *J*=11.5, 4.5 Hz, 1H; H-15), 2.99–2.92 (m, 2H; H-14β, H-16), 2.52 (ddd, *J*=19.0, 6.5, 4.5 Hz, 1H; H-14α), 2.37 (dd, *J*=6.5, 4.5 Hz, 1H; O*H*), 0.89 (t, *J*=8.5 Hz, 2H; OCH$_2$CH_2Si), −0.01 (s, 9H; Si(CH_3)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.0 (C-2), 159.2 (Ar), 148.5 (C-13), 145.3 (C-3), 141.2 (C-20), 138.9 (C-7), 133.3 (C-10), 131.9 (C-8), 131.8 (C-9), 130.0 (Ar), 129.4 (Ar, 2 C), 128.8 (C-11), 127.3 (C-19), 124.2 (C-12), 113.8 (Ar, 2 C), 95.2 (O*C*H$_2$O), 72.3 (Ar*C*H$_2$O), 65.5 (C-18), 65.2 (O*C*H$_2$CH$_2$Si), 65.0 (C-21), 64.3 (C-17), 55.2 (ArO*C*H$_3$), 50.4 (C-16), 37.9 (C-15), 30.9 (C-14), 17.9 (OCH$_2$*C*H$_2$Si), −1.5 (Si(CH_3)$_3$, 3 C); MS (ESI (+)) *m/z* 1189 (2M+Na^+), 601 (M+NH_4^+). Anal. calcd for $C_{31}H_{41}NO_8Si$: C 63.78, H 7.08, N 2.40; found C 63.58, H 7.30, N 2.38.

4.1.13. Synthesis of (1*S*,4*E*,5*R*,6*S*)-2-[2,2-bis(ethylthio)-ethyl]-2,3,4,5,6,7-hexahydro-4-[2-[(4-methoxyphenyl)-methoxy]ethylidene]-6-[[[2-(trimethylsilyl)ethoxy]-methoxy]methyl]-1,5-methano-1*H*-azocino[4,3-b]indole (3) by domino cyclization. A 0.2 M CH_2Cl_2 solution of Tf_2O (0.80 mL, 0.16 mmol, 1.2 equiv) was added dropwise to a solution of **4** (77.9 mg, 0.133 mmol) and *N*,*N*-diisopropylethylamine (69 μL, 0.40 mmol, 3.0 equiv) in CH_2Cl_2 (0.67 mL, 0.2 M) at −78 °C. After stirring for 30 min at the same temperature, a 0.2 M CH_2Cl_2 solution of 2,2-bis(ethylthio)ethylamine[53] (1.0 mL, 0.20 mmol, 1.5 equiv) was added to the reaction mixture. After stirring for additional 60 min at the same temperature, the reaction was quenched by the addition of saturated $NaHCO_3$ aqueous solution, warmed to rt, extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated to afford crude allyl amine, which was used for the next step without further purification. The residue was dissolved with MeOH (13 mL, 0.01 M) and saturated NH_4Cl aqueous solution (1.3 mL, 1.0 M), and then Zn dust (Aldrich, 869 mg, 13.3 mmol, 100 equiv) was added at rt. After vigorous stirring for 2 h at the same temperature, the reaction mixture was quenched by the addition of saturated $NaHCO_3$ aqueous solution, filtered through Celite pad eluting with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography (alumina, 20% EtOAc in hexane) to afford **3** (70.0 mg, 2 steps 77%) as a colorless oil: R_f=0.57 (silica gel, EtOAc–hexane, 1:1); $[\alpha]_D^{24}$+94.5 (*c* 0.9, $CHCl_3$); FT-IR (neat) ν_{max} 3397, 2925, 1612, 1513, 1458, 1248, 1036, 835 cm^{-1}; ^1H NMR (500 MHz, CD_2Cl_2) δ 8.55 (br-s, 1H, N*H*), 7.57 (d, *J*=8.0 Hz, 1H; H-12), 7.33 (d, *J*=8.0 Hz, 1H; H-9), 7.29 (d, *J*=8.5 Hz, 2H; Ar), 7.11 (t, *J*=8.0 Hz, 1H; H-10), 7.06 (t, *J*=8.0 Hz, 1H; H-11), 6.89 (d, *J*=8.5 Hz, 2H; Ar), 5.45 (t, *J*=7.0 Hz, 1H; H-19), 4.68 (s, 2H; OCH_2O), 4.46 (s, 2H; ArCH_2O), 4.21 (br-s, 1H; H-3), 4.10 (d, *J*=7.0 Hz, 2H; H-18), 4.04 (dd, *J*=7.5, 6.5 Hz, 1H; H-6), 3.80 (s, 3H; ArOCH_3), 3.68–3.53 (m, 4H; H-17, OCH_2CH$_2$Si), 3.10 (dd, *J*=13.5, 7.5 Hz, 1H; H-5), 3.03–2.94 (m, 3H; H-15, H-16, H-21), 2.84 (d, *J*=12.5 Hz, 1H; H-21), 2.79–2.59 (m, 4H; SCH_2CH$_3$), 2.51 (dd, *J*=13.5, 6.5 Hz, 1H; H-5), 2.04 (br-d, *J*=12.5 Hz, 1H; H-14), 1.92 (br-d, *J*=12.5 Hz, 1H; H-14), 1.29 (t, *J*=7.0 Hz, 3H; SCH$_2$CH_3), 1.24 (t, *J*=7.0 Hz, 3H; SCH$_2$CH_3), 0.89 (t, *J*=8.0 Hz, 2H; OCH$_2$CH_2Si), −0.04 (s, 9H; Si(CH_3)$_3$); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 159.6 (Ar), 143.4 (C-20), 137.9 (C-2), 136.2 (C-13), 131.0 (Ar), 129.6 (Ar, 2 C), 127.8 (C-8), 121.5 (C-10), 120.2 (C-19), 119.7 (C-11), 118.9 (C-12), 113.9 (Ar, 2 C), 111.0 (C-9), 107.8 (C-7), 95.4 (O*C*H$_2$O), 72.2 (Ar*C*H$_2$O), 71.0 (C-17), 65.8 (C-18), 65.5 (O*C*H$_2$CH$_2$Si), 62.4 (C-5), 55.5 (ArO*C*H$_3$), 53.9 (C-21), 51.5 (C-3), 50.1 (C-6), 40.0 (C-16), 32.2 (C-15), 30.7 (C-14), 24.7 (S*C*H$_2$CH$_3$), 24.6 (S*C*H$_2$CH$_3$), 18.3 (OCH$_2$*C*H$_2$Si), 14.8 (SCH$_2$*C*H$_3$, 2 C), −1.5 (Si(CH_3)$_3$, 3 C); MS (ESI (+)) *m/z* 683 (M+H^+); HRMS (TOF (+)) calcd for $C_{37}H_{55}N_2O_4S_2Si$ (M+H^+): 683.3367; found 683.3362.

4.1.14. Synthesis of (6*R*,16α,19*E*)-1,2,19,20-tetradehydro-6-(ethylthio)-18-[(4-methoxyphenyl)methoxy]-17-[[2-(trimethylsilyl)ethoxy]methoxy]curan (47) by intramolecular alkylation of dithioacetal. A suspension of DMTSF (158 mg, 0.81 mmol, 5.0 equiv) and MS4A (1.61 g), which was dried by heat-gun prior to being used, in CH_2Cl_2 (16 mL) was stirred for 1 h at rt. A solution of **3** (110 mg, 0.161 mmol), which was azeotroped with toluene prior to being used, in CH_2Cl_2 (16 mL) was added dropwise to the mixture via cannula. After stirring for 2 h at the same temperature, the reaction mixture was directly purified by flash column chromatography (silica gel deactivated with Et_3N, 60 to 100% EtOAc in hexane) to afford **47** (86.6 mg, 86%) as a colorless oil: R_f=0.17 (silica gel, EtOAc–hexane, 1:1); $[\alpha]_D^{26}$ −29.3 (*c* 0.9, $CHCl_3$); FT-IR (neat) ν_{max} 2923, 1612, 1566, 1513, 1455, 1248, 1059, 836 cm^{-1}; ^1H NMR (500 MHz, CD_2Cl_2) δ 7.48 (d, *J*=7.5 Hz, 1H; H-9), 7.37 (d, *J*=7.5 Hz, 1H; H-12), 7.31 (t, *J*=7.5 Hz, 1H; H-10), 7.24 (d, *J*=8.5 Hz, 2H; Ar), 7.15 (t, *J*=7.5 Hz, 1H; H-11), 6.86 (d, *J*=8.5 Hz, 2H; Ar), 5.61 (t, *J*=7.5 Hz, 1H; H-19), 4.74 (d, *J*=6.5 Hz, 1H; OC*H*HO), 4.70 (d, *J*=6.5 Hz, 1H; OC*H*HO), 4.45 (d, *J*=11.5 Hz, 1H; ArC*H*HO), 4.44 (d, *J*=11.5 Hz, 1H; ArC*H*HO), 4.33 (dd, *J*=11.5, 7.5 Hz, 1H; H-18), 4.32 (dd, *J*=9.5, 4.5 Hz, 1H; H-17), 4.16 (dd, *J*=11.5, 7.5 Hz, 1H; H-18), 4.05 (br-s, 1H; H-3), 3.94 (d, *J*=15.5 Hz, 1H; H-21), 3.88 (dd, *J*=12.0, 6.0 Hz, 1H; H-6), 3.78 (s, 3H; ArOCH_3), 3.74 (t, *J*=9.5 Hz, 1H; H-17), 3.65 (dd, *J*=9.0, 7.5 Hz, 2H; OCH_2CH$_2$Si), 3.48 (dd, *J*=12.5, 6.0 Hz, 1H; H-5α), 3.39 (dd, *J*=6.5, 4.5 Hz, 1H; H-16), 3.38 (t, *J*=12.5 Hz, 1H; H-5β), 3.25 (br-s, 1H; H-15), 3.19 (d, *J*=15.5 Hz, 1H; H-21), 2.25–2.17 (m, 2H; SCH_2CH$_3$), 1.97 (br-d, *J*=15.0 Hz, 1H; H-14), 1.20 (br-d, *J*=15.0 Hz, 1H; H-14), 1.00–0.94 (m, 5H; SCH$_2$CH_3, OCH$_2$CH_2Si), 0.02 (s, 9H; Si(CH_3)$_3$); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 188.0 (C-2), 159.6 (Ar), 155.7 (C-13), 145.6 (C-8), 142.0 (C-20), 131.1 (Ar), 129.6 (Ar, 2 C), 128.5 (C-10), 124.9 (C-11), 123.9 (C-12), 122.8 (C-19), 120.4 (C-9), 114.0 (Ar,

2 C), 95.5 (O*C*H_2O), 72.5 (Ar*C*H_2O), 68.6 (C-7), 68.5 (C-3), 68.4 (C-17), 66.6 (C-5), 65.61 (C-18), 65.57 (O*C*H_2CH_2Si), 57.0 (C-21), 55.6 (ArO*C*H_3), 49.9 (C-6), 46.6 (C-16), 34.5 (C-15), 26.7 (S*C*H_2CH_3), 25.6 (C-14), 18.4 (OCH_2*C*H_2Si), 15.3 (SCH_2*C*H_3), −1.4 (Si(C*H*$_3$)$_3$, 3 C); MS (ESI (+)) *m/z* 621 (M+H$^+$); HRMS (TOF (+)) calcd for $C_{35}H_{49}N_2O_4SSi$ (M+H$^+$): 621.3177; found 621.3172.

4.1.15. Synthesis of (6*R*,16α,19*E*)-19,20-didehydro-6-(ethylthio)-18-[(4-methoxyphenyl)methoxy]-17-[[2-(trimethylsilyl)ethoxy]methoxy]curan (2) by $NaBH_3CN$ reduction in the presence of $TiCl_4$. A 1.0 M CH_2Cl_2 solution of $TiCl_4$ (0.19 mL, 0.19 mmol, 5.0 equiv) was added to a solution of **47** (23.3 mg, 37.5 μmol) in THF (1.9 mL, 0.02 M) at −78 °C. After stirring for 5 min at the same temperature, $NaBH_3CN$ (9.4 mg, 0.15 mmol, 4.0 mol equiv) was added to the reaction mixture. After stirring for additional 60 min at the same temperature, the reaction was quenched by the addition of saturated $NaHCO_3$ aqueous solution, warmed to rt, followed by 25% ammonia aqueous solution, and extracted with CH_2Cl_2 (three times). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (silica gel deactivated with Et_3N, 50 to 70% EtOAc in hexane) to afford **2** (16.0 mg, 68%) as a colorless oil: R_f=0.12 (silica gel, EtOAc–hexane, 1:1); $[\alpha]_D^{25}$ −30.6 (*c* 0.5, $CHCl_3$); FT-IR (neat) ν_{max} 3372, 2925, 1608, 1514, 1465, 1248, 1102, 1059 cm^{-1}; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.25 (d, *J*=8.5 Hz, 2H; Ar), 7.19 (d, *J*=7.5 Hz, 1H; H-9), 7.04 (t, *J*=7.5 Hz, 1H; H-11), 6.87 (d, *J*=8.5 Hz, 2H; Ar), 6.70 (t, *J*=7.5 Hz, 1H; H-10), 6.58 (d, *J*=7.5 Hz, 1H; H-12), 5.48 (t, *J*=6.0 Hz, 1H; H-19), 4.60 (d, *J*=7.0 Hz, 1H; OC*H*HO), 4.55 (d, *J*=7.0 Hz, 1H; OC*H*HO), 4.42 (d, *J*=11.5 Hz, 1H; ArC*H*HO), 4.39 (d, *J*=11.5 Hz, 1H; ArC*H*HO), 4.07–4.00 (m, 2H; H-18), 3.86 (d, *J*=6.0 Hz, 1H; H-3), 3.79 (s, 3H; ArOC*H*$_3$), 3.62 (d, *J*=14.5 Hz, 1H; H-21), 3.67–3.57 (m, 2H; OCH_2CH$_2$Si), 3.53 (t, *J*=9.5 Hz, 1H; H-17), 3.46–3.42 (m, 2H; H-2, H-17), 3.38–3.30 (m, 2H; H-6, H-5β), 3.28 (d, *J*=14.5 Hz, 1H; H-21), 3.12 (dd, *J*=11.5, 7.5 Hz, 1H; H-5α), 2.56 (br-s, 1H; H-15), 2.34–2.26 (m, 1H; SC*H*HCH$_3$), 2.21–2.15 (m, 2H; H-16, SC*H*HCH$_3$), 1.88 (br-d, *J*=14.0 Hz, 1H; H-14), 1.72 (br-d, *J*=14.0 Hz, 1H; H-14), 1.09 (t, *J*=7.5 Hz, 3H; SCH$_2$C*H*$_3$), 0.93 (t, *J*=8.0 Hz, 2H; OCH$_2$C*H*$_2$Si), 0.02 (s, 9H; Si(C*H*$_3$)$_3$); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 159.7 (Ar), 151.3 (C-13), 142.6 (C-20), 131.1 (Ar), 129.9 (C-8), 129.7 (Ar, 2 C), 128.6 (C-11), 125.8 (C-9), 121.5 (C-19), 118.4 (C-10), 114.1 (Ar, 2 C), 109.5 (C-12), 95.5 (O*C*H_2O), 72.3 (Ar*C*H_2O), 69.9 (C-17), 65.9 (O*C*H_2CH$_2$Si), 65.7 (C-18), 63.7 (C-3), 63.2 (C-2), 62.2 (C-5), 58.5 (C-7), 55.6 (ArO*C*H_3), 54.1 (C-21), 52.4 (C-6), 40.3 (C-16), 30.4 (C-15), 27.0 (S*C*H_2CH$_3$), 23.4 (C-14), 18.5 (OCH$_2$*C*H_2Si), 14.9 (SCH$_2$*C*H_3), −1.3 (Si(C*H*$_3$)$_3$, 3 C); MS (ESI (+)) *m/z* 623 (M+H$^+$); HRMS (TOF (+)) calcd for $C_{35}H_{51}N_2O_4SSi$ (M+H$^+$): 623.3333; found 623.3308.

4.1.16. Synthesis of (6*R*,16α,19*E*)-1-acetyl-19,20-didehydro-6-(ethylthio)-18-[[tris(1-methylethyl)silyl]oxy]-curan-17-ol (61). The indoline **2** (27.0 mg, 43.3 μmol) was treated with 1.0 N HCl in MeOH (0.87 mL, 0.87 mmol, 20 equiv) for 3 h at 55 °C. After cooling to rt, the reaction was concentrated under reduced pressure to give crude diol, which was used for the next step without further purification. The residue was dissolved with pyridine (0.35 mL, 4.33 mmol, 100 equiv), and then Ac_2O (0.20 mL, 2.17 mmol, 50 equiv) was added at rt. After stirring for 36 h at the same temperature, the reaction mixture was quenched by the addition of saturated $NaHCO_3$ aqueous solution, and extracted with CH_2Cl_2 (three times). The combined organic layers were dried over Na_2SO_4 and concentrated to give crude triacetate, which was used for the next step without further purification. The residue was dissolved with MeOH (0.86 mL, 0.05 M), and then 1.0 M NaOMe in MeOH (0.35 mL, 0.346 mmol, 8 equiv) was added at rt. After stirring for 30 min at the same temperature, the reaction mixture was quenched by the addition of saturated $NaHCO_3$ aqueous solution, saturated with NaCl, and extracted with CH_2Cl_2 (three times). The combined organic layers were dried over Na_2SO_4, concentrated, and filtrated through short pad alumina column (10% MeOH in EtOAc) to remove water and less polar side products, such as *p*-methoxybenzyl methyl ether. After concentration, the residue was pumped-up for several hours to remove residual MeOH to afford *N*-acetyl diol as a white solid, which was dissolved with DMF (0.86 mL, 0.05 M), then imidazole (58.8 mg, 0.864 mmol, 20 equiv) and 1.0 M CH_2Cl_2 solution of TIPSCl (0.108 mL, 0.108 mmol, 2.5 equiv) was added at 4 °C (ice-water bath). After stirring for 1 h at the same temperature, additional 1.0 M CH_2Cl_2 solution of TIPSCl (0.108 mL, 0.108 mmol, 2.5 equiv) was added dropwise at the same temperature. After stirring for additional 1 h at the same temperature, the reaction was quenched by the addition of saturated $NaHCO_3$ aqueous solution, extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography (alumina, 5 to 20% EtOAc in hexane) to afford **61** (12.6 mg, 4 steps 51%) as a white solid with diTIPS compound (4.8 mg, 4 steps 20%) as a colorless oil. This by-product was converted to the *N*-acetyl diol in ca. 80% yield by treatment of 3HF·Et_3N in THF: R_f=0.49 (silica gel, EtOAc); mp 90–94 °C; $[\alpha]_D^{25}$+13.5 (*c* 0.6, $CHCl_3$); FT-IR (KBr) ν_{max} 3398, 2925, 2865, 1655, 1459, 1399, 1052 cm^{-1}; For the major isomer of rotamers: ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.01 (d, *J*=8.0 Hz, 1H; H-12), 7.32 (d, *J*=8.0 Hz, 1H; H-9), 7.26 (d, *J*=8.0 Hz, 1H; H-11), 7.08 (d, *J*=8.0 Hz, 1H; H-10), 5.54 (t, *J*=6.0 Hz, 1H; H-19), 4.39–4.33 (m, 2H; H-18), 4.13 (d, *J*=7.5 Hz, 2H; H-17), 4.03 (br-s, 1H; H-3), 3.79 (d, *J*=16.0 Hz, 1H; H-21), 3.36 (dd, *J*=11.5, 6.5 Hz, 1H; H-5), 3.31 (dd, *J*=11.0, 5.0 Hz, 1H; H-17), 3.23 (d, *J*=11.5 Hz, 1H; H-5), 3.17–3.12 (m, 2H; H-6, O*H*), 3.07–3.04 (m, 1H; H-15), 3.01 (d, *J*=11.0 Hz, 1H; H-17), 2.89 (d, *J*=16.0 Hz, 1H; H-21), 2.51 (br-s, 1H, H-16), 2.26 (s, 3H; C(O)C*H*$_3$), 1.94 (br-d, *J*=14.0 Hz, 1H; H-14), 1.86–1.81 (m, 1H; SC*H*HCH$_3$), 1.64–1.58 (m, 1H; SC*H*HCH$_3$), 1.57 (br-d, *J*=14.0 Hz, 1H; H-14), 1.15–0.96 (m, 21H; TIPS), 0.88 (t, *J*=7.5 Hz, 3H; SCH$_2$C*H*$_3$); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 168.7 (*C*(O)CH$_3$), 143.9 (C-20), 138.2 (C-13), 132.1 (C-8), 129.0 (C-11), 127.8 (C-19), 124.9 (C-9), 123.9 (C-10), 116.8 (C-12), 66.8 (C-2), 61.1 (C-17), 60.8 (C-18), 59.6 (C-5), 56.8 (C-7), 54.9 (C-21), 53.7 (C-6), 45.8 (C-16), 30.0 (C-15), 26.9 (S*C*H$_2$CH$_3$), 23.6 (C(O)*C*H$_3$), 18.9 (C-14), 18.2 (SiCH(*C*H$_3$)$_2$, 6 C), 14.3 (SCH$_2$*C*H$_3$), 12.4 (Si*C*H(CH$_3$)$_2$, 3 C); MS (ESI (+)) *m/z* 571 (M+H$^+$); HRMS (TOF (+)) calcd for $C_{32}H_{51}N_2O_3SSi$ (M+H$^+$): 571.3390; found 571.3390.

4.1.17. Synthesis of (−)-diabolene (65) through desulfurization. EtOH (2.88 mL) and MeOH (0.72 mL) were simultaneously added to a mixture of $NaBH_4$ (136 mg, 3.60 mmol, 200 equiv) and $NiCl_2$ (233 mg, 1.80 mmol, 100 equiv) at rt with vigorous generation of H_2. After stirring for 10 min, a solution of **61** (10.3 mg, 18.0 μmol) in EtOH (0.2 mL) was added. After stirring additional 30 min, the reaction mixture was filtered through short pad alumina column eluting with 20% MeOH in EtOAc and concentrated. The selectivity of this reaction was 32:65:2:<1 for **62**:**61**:**64**:**63**, which was estimated based on the results of LC-MS (ESI) analysis of the crude mixture. The residue was purified by flash column chromatography (alumina, 20 to 100% EtOAc in hexane followed by 10% MeOH in EtOAc) to afford inseparable mixture of **62** and its 19,20-dihydro derivative **64** (3.2 mg, 33%, >10:1 selectivity) with the recovery of **61** (6.7 mg, 65%). Both over reduction and migration of **61** were not observed. After repeating this process twice (total three times), yield of **62** was reached to 61% (5.6 mg, >10:1 selectivity) with **61** (2.7 mg, 26%). The mixture of **62** (5.6 mg, 11.0 μmol) was dissolved in DMSO (0.11 mL, 0.1 M), and then triethylamine (45 μL, 0.33 mmol, 30 equiv) and $SO_3\cdot Py$ (18 mg, 0.11 mm***pl, 10 equiv) were added at rt. After stirring for 1 h, the reaction mixture was quenched by the addition of saturated $NaHCO_3$ aqueous solution and extracted with Et_2O (three times). The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated to give crude aldehyde, which was used for the next step without further purification. $3HF\cdot Et_3N$ (36 μL, 0.22 mmol, 20 equiv) was added to a solution of the crude aldehyde in THF (0.22 mL, 0.05 M) at rt. After stirring for 12 h at the same temperature (more than 25 °C), the reaction mixture was cooled with ice-water bath, quenched carefully by the addition of saturated $NaHCO_3$ aqueous solution, extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography (alumina, 10% MeOH in EtOAc) to afford diabolene (**65**) (3.2 mg, 2 steps 83%) as a white solid: $R_f=0.09$ (silica gel, 2% Et_3N and 30% MeOH in EtOAc); mp 182–185 °C: lit. 185–187 °C (crystals from EtOAc); $[\alpha]_D^{25}+74$ (*c* 1.3, MeOH); $[\alpha]_D^{25}+39$ (*c* 0.5, $CHCl_3$): lit. $[\alpha]_D^{20}+36$ (*c* 0.8, $CHCl_3$); FT-IR (KBr) ν_{max} 3375, 2925, 1655, 1479, 1395, 1125, 1075 cm^{-1}; For major isomer: ^1H NMR (500 MHz, CD_2Cl_2) δ 7.87 (d, $J=8.0$ Hz, 1H; H-12), 7.25–7.20 (m, 1H; H-11), 7.16–7.08 (m, 2H; H-9, H-10), 5.84 (br-s, 1H; H-19), 5.32–5.23 (m, 1H; H-17), 4.83 (dd, $J=13.5$, 4.0 Hz, 1H; H-18), 4.20 (d, $J=11.5$ Hz, 1H; H-2), 3.93–3.85 (m, 1H; H-3), 3.71–3.64 (m, 2H; H-18, H-21), 3.39 (br-s, 1H; H-15), 3.29–3.25 (m, 1H; H-5), 2.88–2.83 (m, 1H; H-5), 2.68 (d, $J=15.5$ Hz, 1H; H-21), 2.00 (s, 3H; C(O)CH_3), 2.22 (br-d, $J=14.0$ Hz, 1H; H-14), 1.92 (dd, $J=12.5$, 6.0 Hz, 1H; H-6), 1.67–1.61 (m, 1H; H-6), 1.51 (d, $J=11.5$ Hz, 1H; H-16), 1.38 (br-d, $J=14.0$ Hz, 1H; H-14); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 170.2 (*C*(O)CH_3), 143.9 (C-13), 142.8 (C-20), 135.4 (C-8), 127.9 (C-11), 126.2 (C-19), 125.0 (C-10), 122.1 (C-9), 119.9 (C-12), 94.1 (C-17), 65.3 (C-2), 59.3 (C-3), 55.7 (C-18), 53.7 (C-21), 52.9 (C-7), 51.9 (C-5), 47.5 (C-16), 39.1 (C-6), 29.1 (C-15), 25.9 (C-14), 23.4 (C(O)*C*H_3); MS (ESI (+)) *m/z* 353 ($M+H^+$); HRMS (TOF (+)) calcd for $C_{21}H_{25}N_2O_3$ ($M+H^+$): 353.1860; found 353.1855.

4.1.18. Completion of total synthesis of (−)-strychnine (1). Diaboline (**65**) (13.0 mg, 36.9 μmol) was treated with 1.0 M MeOH solution of NaOMe (0.5 mL, 14 equiv) at 40 °C for 2 d. The reaction was quenched by the addition of saturated NH_4Cl aqueous solution followed by saturated $NaHCO_3$ aqueous solution, and extracted with CH_2Cl_2 (three times). The combined organic layers were dried over Na_2SO_4 and concentrated to give crude Wieland–Gumlich aldehyde (**66**). The crude Wieland–Gumlich aldehyde was converted to (−)-strychnine (**1**) (5.2 mg, 2 steps 42%) by treatment of HOAc (0.5 mL), NaOAc (67 mg, 0.80 mmol, 22 equiv), malonic acid (67 mg, 0.63 mmol, 17 equiv), and Ac_2O (13 μL, 0.13 mmol, 3.5 equiv) under reflux condition.[16c]: $R_f=0.17$ (silica gel, 2% Et_3N and 50% MeOH in EtOAc); $[\alpha]_D^{25}$ −136 (*c* 0.26, $CHCl_3$): lit. $[\alpha]_D^{25}$ −139 (*c* 2.0 $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) were indistinguishable from those of natural strychnine.

Acknowledgements

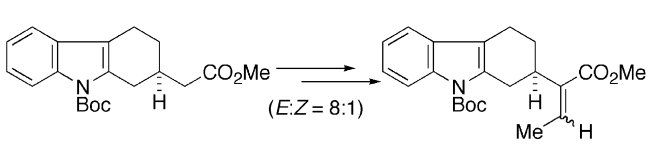
This work was supported by the RFTF and Encouragement of Young Scientists (A) of Japan Society for the Promotion of Science, a Grant-in-Aid for Scientific Research on Priority Areas (A) 'Exploitation of Multi-Element Cyclic Molecules' from the Ministry of Education, Culture, Sports, Science, and Technology, Japan, Grant-in-Aid from the Tokyo Biochemical Research Foundation, and fellowship from Heiwa Nakajima Foundation (to Y.X.). We thank Dr. S. Shimizu for his contribution in our initial investigation and Dr. D. Zhong (Syehyang Pharmaceutical University) for help with structural determination using ESI (MS–MS) and TOF mass analyses.

References and notes

1. For general reviews, see: (a) Ojima, I. *Catalytic Asymmetric Synthesis*, 2nd ed.; Wiley: New York, 2000. (b) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999. (c) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994.
2. (a) Knowles, W. S.; Sabacky, M. J.; Vineyard, B. D.; Weinkauff, D. J. *J. Am. Chem. Soc.* **1975**, *97*, 2567. (b) Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J.; Bachman, G. L.; Weinkauff, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 5946 and references cited therein.
3. (a) Noyori, R.; Ikeda, T.; Ohkuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T.; Taketomi, T.; Kumobayashi, H. *J. Am. Chem. Soc.* **1989**, *111*, 9134. (b) Noyori, R. *Chem. Soc. Rev.* **1989**, *18*, 187. (c) Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345. (d) Noyori, R. *CHEMTECH* **1992**, *22*, 360 and references cited therein.
4. (a) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765. (b) Klunder, J. M.; Onami, T.; Sharpless, K. B. *J. Org. Chem.* **1989**, *54*, 1295 and references cited therein.
5. (a) Aratani, T.; Yoneyoshi, Y.; Nagase, T. *Tetrahedron Lett.*

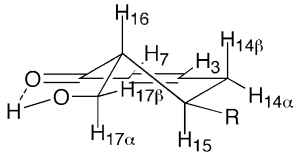
1977, 2599. (b) Aratani, T.; Yoneyoshi, Y.; Nagase, T. *Tetrahedron Lett.* **1982**, *23*, 685. (c) Aratani, T. *Pure Appl. Chem.* **1985**, *57*, 1839 and references cited therein.

6. Tani, K.; Yamagata, T.; Akutagawa, S.; Kumobayashi, H.; Taketomi, T.; Takaya, H.; Miyashita, A.; Noyori, R.; Otsuka, S. *J. Am. Chem. Soc.* **1984**, *106*, 5208. See also Ref. 3b–d.
7. For recent reviews, see: (a) Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1236. (b) Shibasaki, M. *CHEMTRACTS-ORGANIC CHEMISTRY* **1999**, *12*, 978. (c) Shibasaki, M. *Enantiomer* **1999**, *4*, 513. (d) Shibasaki, M.; Kanai, M. *Chem. Pharm. Bull.* **2001**, *49*, 551. (e) Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187.
8. Xu, Y.; Ohori, K.; Ohshima, T.; Shibasaki, M. *Tetrahedron* **2002**, *58*, 2585.
9. Ohshima, T.; Xu, Y.; Takita, R.; Shimizu, S.; Zhong, D.; Shibasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 14546. Additions and Corrections **2003**, *125*, 2014.
10. The numbering system and ring labeling based on the biogenetic interrelationship of indole alkaloids is used throughout this paper: Le Men, J.; Taylor, W. I. *Experientia* **1965**, *21*, 508.
11. For representative reviews, see: (a) Bonjoch, J.; Solé, D. **2000**, *100*, 3455. (b) Nicolaou, K. C.; Sorensen, E. J. Strychnine.; VCH: New York, 1996; p 21.
12. (a) Pelletier, P. J.; Caventou, J. B. *Ann. Chim. Phys.* **1818**, *8*, 323. (b) Pelletier, P. J.; Caventou, J. B. *Ann. Chim. Phys.* **1819**, *10*, 142.
13. (a) Briggs, L. H.; Openshaw, H. T.; Robinson, R. *J. Chem. Soc.* **1946**, 903. (b) Holmes, H. L.; Openshaw, H. T.; Robinson, R. *J. Chem. Soc.* **1946**, 910.
14. (a) Robertson, J. H.; Beevers, C. A. *Nature* **1950**, *165*, 690. (b) Robertson, J. H.; Beevers, C. A. *Acta Crystallogr.* **1951**, *4*, 270. (c) Bokhoven, C.; Schoone, J. C.; Bijvoet, J. M. *Acta Crystallogr.* **1951**, *4*, 275. (d) Mostad, A. *Acta Chem. Scand.* **1985**, *39B*, 705. (e) Peerdeman, A. F. *Acta Crystallogr.* **1956**, *9*, 824. (f) Nagarajan, K.; Weissmann, Ch.; Schmid, H.; Karrer, P. *Helv. Chim. Acta* **1963**, *46*, 1212.
15. Aprison, M. H. In *Glycine Neurotransmision*; Otterson, O. P., Storm-Mathisen, J., Eds.; Wiley: New York, 1990; pp 1–23.
16. (a) Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. *J. Am. Chem. Soc.* **1954**, *76*, 4749. Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. *Tetrahedron* **1963**, *19*, 247. (b) Magnus, P.; Giles, M.; Bonnert, R.; Kim, C. S.; McQuire, L.; Merritt, A.; Vicker, N. *J. Am. Chem. Soc.* **1992**, *114*, 4403. Magnus, P.; Giles, M.; Bonnert, R.; Johnson, G.; McQuire, L.; Deluca, M.; Merritt, A.; Kim, C. S.; Vicker, N. *J. Am. Chem. Soc.* **1993**, *115*, 8116. (c) Knight, S. D.; Overman, L. E.; Pairaudeau, G. *J. Am. Chem. Soc.* **1993**, *115*, 9293. Knight, S. D.; Overman, L. E.; Pairaudeau, G. *J. Am. Chem. Soc.* **1995**, *117*, 5776. (d) Stork, G. Disclosed at the Ischia Advanced School of Organic Chemistry, Ischia Porto, Italy, Sep 21; 1992. (e) Kuehne, M. E.; Xu, F. *J. Org. Chem.* **1993**, *58*, 7490. Kuehne, M. E.; Xu, F. *J. Org. Chem.* **1998**, *63*, 9427. (f) Rawal, V. H.; Iwasa, S. *J. Org. Chem.* **1994**, *59*, 2685. (g) Solé, D.; Bonjoch, J.; García-Rubio, S.; Peidró, E.; Bosch, J. *Angew. Chem., Int. Ed.* **1999**, *38*, 395. Solé, D.; Bonjoch, J.; García-Rubio, S.; Peidró, E.; Bosch, J. *Chem. Eur. J.* **2000**, *6*, 655. (h) Eichberg, M. J.; Dorta, R. L.; Lamottke, K.; Vollhardt, K. P. C. *Org. Lett.* **2000**, *2*, 2479. Eichberg, M. J.; Dorta, R. L.; Grotjahn, D. B.; Lamottke, K.; Schmidt, M.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **2001**, *123*, 9324. (i) Ito, M.; Clark, C. W.; Mortimore, M.; Goh, J. B.; Martin, S. F. *J. Am. Chem. Soc.* **2001**, *123*, 8003. (j) Nakanishi, M.; Mori, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 1934. (k) Bodwell, G. J.; Li, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 3261.
17. (a) Amat, M.; Alvarez, M.; Bonjoch, J.; Casamitjana, N.; Gràcia, J.; Lavilla, R.; Garcías, X.; Bosch, J. *Tetrahedron Lett.* **1990**, *31*, 3453. (b) Amat, M.; Linares, A.; Bosch, J. *J. Org. Chem.* **1990**, *55*, 6299. (c) Shin, K.; Moriya, M.; Ogasawara, K. *Tetrahedron Lett.* **1998**, *39*, 3765 and references therein.
18. (a) Shimizu, S.; Ohori, K.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1998**, *63*, 7547. (b) Ohori, K.; Shimizu, S.; Ohshima, T.; Shibasaki, M. *Chirality* **2000**, *12*, 400.
19. For catalytic asymmetric Michael reactions of malonates reported by our group, see: (a) Sasai, H.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1994**, *116*, 1571. (b) Sasai, H.; Arai, T.; Satow, Y.; Houk, K. N.; Shibasaki, M. *J. Am. Chem. Soc.* **1995**, *117*, 6194. (c) Arai, T.; Sasai, H.; Aoe, K.; Okamura, K.; Date, T.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 104. (d) Arai, T.; Yamada, Y. M. A.; Yamamoto, N.; Sasai, H.; Shibasaki, M. *Chem. Eur. J.* **1996**, *2*, 1368. (e) Kim, Y. S.; Matsunaga, S.; Das, J.; Sekine, A.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 6506. (f) Matsunaga, S.; Ohshima, T.; Shibasaki, M. *Tetrahedron Lett.* **2000**, *41*, 8473. (g) Takita, R.; Ohshima, T.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 4661. For a recent example using β-keto esters instead of malonates, see: (h) Majima, K.; Takita, R.; Okada, A.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 15837.
20. For recent reviews of catalytic asymmetric Michael reactions, see: (a) Kanai, M.; Shibasaki, M. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley: New York, 2000; p 569. (b) Tomioka, K.; Nagaooka, Y. In *Comprehensive Asymmetric Catalysis*; Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 3, Chapter 31.1. (c) Sibi, M.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033. (d) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171. (e) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221. (f) Christoffers, J.; Baro, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1688.
21. For other examples of catalytic asymmetric Michael reactions of malonates, see: (a) Yamaguchi, M.; Shiraishi, T.; Hirama, M. *J. Org. Chem.* **1996**, *61*, 3520. (b) Perrard, T.; Plaquevent, J.-C.; Desmurs, J.-R.; Hebrault, D. *Org. Lett.* **2000**, *2*, 2959. (c) Halland, N.; Aburel, P. S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 661. (d) Annamalai, V.; DiMauro, E. F.; Carroll, P. J.; Kozlowski, M. C. *J. Org. Chem.* **2003**, *68*, 1973. See also Ref. 20b.
22. In terms of substrate generality, the La–O-linked-BINOL complex is the most effective catalyst for the present Michael reaction of malonate, see Ref. 19e,g.
23. A industrial-scale reaction (>50 kg) is now under investigation.
24. *Syn*-selective aldol reaction of indole compound and following *anti*-elimination gave moderate selectivity (*E*/*Z*=8:1)



25. Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.
26. Enone formation through phenylselenenylation or allyl carbonate formation resulted in very low yield (<20%).
27. General catalytic Saegusa–Ito reaction was established by Tsuji, see: Minami, I.; Takahashi, K.; Shimizu, I.; Kimura, T.; Tsuji, J. *Tetrahedron* **1986**, *42*, 2971 and references therein.

28. Djuardi, E.; Bovonsombat, P.; McNelis, E. *Synth. Commun.* **1997**, *27*, 2497.
29. α-Iodination using iodine and $PhI(OCOCF_3)_2$ gave worse results (<30%). See: Benhida, R.; Blanchard, P.; Fourrey, J.-L. *Tetrahedron Lett.* **1998**, *39*, 6849.
30. (a) Labadie, J. W.; Teuting, D.; Stille, J. K. *J. Org. Chem.* **1983**, *48*, 4634. (b) Labadie, J. W.; Stille, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 669. (c) Labadie, J. W.; Stille, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 6126. For representative reviews, see: (d) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (e) Farina, V.; Krishnamurphy, V.; Scott, W. J. *Organic Reactions*; Wiley: New York, 1997; Vol. 50.
31. (a) Franz, R. *J. Fluorine Chem.* **1980**, *15*, 423. (b) Gatner, K. *Pol. J. Chem.* **1993**, *67*, 1155. For a review, see: (c) McClinton, M. A. *Aldrichim. Acta* **1995**, *28*, 31.
32. Other desilylation reagents such as TBAF and HF·Py gave unsatisfactory results (decomposition and deprotection of PMB group, respectively).
33. The corresponding allylic chloride and bromide showed very low reactivity as compared with mesylate. Thus, allylic alcohol **22** was first converted to the mesylate using methanesulfonic anhydride, not methanesulfonic chloride, which gave a mixture of allylic mesylate and chloride even at low temperature. The corresponding tosylate, which was prepared using *p*-toluenesulfonic anhydride, gave lower yield
34. For a general review of domino reaction, see: Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115.
35. Aniline derivative **25** did not introduce an amine side-chain due to rapid cyclization of the hydroxyl group after removal of the TIPS group.
36. In contrast, Bonjoch et al. reported that 8-aryl-2-azabicyclo-[3.3.1]nonane-7-ones easily underwent a retro-1,4-addition, even using an aniline-type analogue. See: Bonjoch, J.; Quirante, J.; Solé, D.; Castells, J.; Galceran, M.; Bosch, J. *Tetrahedron* **1991**, *47*, 4417.
37. Although we initially used the term 'tandem cyclization' for the reaction shown in Scheme 9 (Ref. 9), we use herein 'domino cyclization' based on Prof. Tietze's suggestion. See Ref. 34.
38. (a) Kobayashi, S. *Chem. Lett.* **1991**, 2087. (b) Kobayashi, S.; Hachiya, I. *J. Org. Chem.* **1994**, *59*, 3590.
39. The stereochemistry at C16 was determined by ^{1}H NMR coupling constant analysis of **43a**, **45a**, **46** and **4**. For example, **44a**: $H_{14\alpha}$–H_{15}: 11.5 Hz, $H_{14\beta}$–H_{15}: 5.0 Hz, H_{15}–H_{16}: 13.5 Hz, H_{16}–$H_{17\alpha}$: 5.0 Hz, H_{16}–$H_{17\beta}$: 3.0 Hz)



40. Bosch et al. (Ref. 17b) and Magnus et al. also investigated other types of cyclization, see: Magnus, P.; Sear, N. L.; Kim, C. S.; Vicker, N. *J. Org. Chem.* **1992**, *57*, 70.
41. Trost, B. M.; Murayama, E. *J. Am. Chem. Soc.* **1981**, *103*, 6529.
42. The stereochemistry at C6 was inferred from the upfield shift of the EtS group compared with dithioacetal **3** (SCH_2CH_3: from 2.79–2.59 to 2.21, SCH_2CH_3: from 1.29 and 1.24 to 0.97). See Ref. 17b.
43. Other Lewis acids such as $BF_3\cdot Et_2O$ and $AlCl_3$ gave a lower yield and selectivity than $TiCl_4$.
44. For a general review of reduction of C–S bond, see: Caubère, P.; Coutrot, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Freming, I., Eds.; Pergamon: Oxford, 1991; Vol. 8, p 835. Chapter 4.3 and references therein.
45. The transformation of strychnine (*exo*-olefin) to neostrychnine (*endo*-olefin) using normal Raney Ni in EtOH was reported, see: Beddoes, R. L.; Gorman, A. A.; Prescott, A. L. *Acta Crystallogr.* **1994**, *C50*, 447 and references therein.
46. Isomerization of *endo*-olefin to *exo*-olefin did not proceed at all under various conditions. Preliminary molecular orbital calculations (AM1) suggested that the *endo*-olefin product was thermodynamically more stable than the *exo*-olefin product, probably due to an n–π^* interaction.
47. Boar, R. B.; Hawikns, D. W.; McGhie, J. M. *J. Chem. Soc., Perkin Trans. 1* **1973**, 654.
48. When EtOH was used as a solvent, the reaction proceeded very fast with low selectivity (**62**:**64** = ~1:1). On the other hand, MeOH had low reactivity (half conversion even with large reagent excess) and high selectivity (**62**:**64** = >50:1).
49. (a) Nicoletti, M.; Goulart, M. O. F.; De Lima, R.; Goulart, A. E.; Delle Monache, F.; Marini, B. G. B. *J. Nat. Prod.* **1984**, *47*, 953. (b) Wenkert, E.; Cheung, H. T. A.; Gottlieb, H. E. *J. Org. Chem.* **1978**, *43*, 1099 and references therein. (c) Transformation of diaboline (**65**) to Wieland–Gumlich aldehyde (**66**) was reported although details were not described, see: Grossert, J. S.; Hugo, J. M.; Klemperer, M. E. V.; Warren, F. L. *J. Chem. Soc., Abstracts* **1965**, 2812.
50. The spectroscopic data for synthetic **65** and **1** matched those reported previously, see Section 4.
51. Stockley, M.; Clegg, W.; Fontana, G.; Golding, B. T.; Martin, N.; Rigoreau, L. J. M.; Smith, G. C. M.; Griffin, R. J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2837.
52. The tin reagent **20** was prepared from 1-iodo-2-nitrobenzene under the following conditions: $Me_3SnSnMe_3$ (1.2 equiv), $PdCl_2(PPh_3)_2$ (2 mol%), *i*-Pr_2NEt (2.0 equiv), toluene (0.2 M), 80 °C for 2 h, 92% yield. For the data, see: Li, D.; Zhao, B.; LaVoie, E. J. *J. Org. Chem.* **2000**, *65*, 2802.
53. Thioacetal was prepared from 2,2-dimethoxyethylamine under the following conditions: $BF_3(Et_2O$ (10 equiv) ethanethiol (6 equiv), CH_2Cl_2, 0 °C to rt for 12 h. The obtained product was purified by distillation (76–78 °C/4 mm Hg). The two-step yield of amination and domino cyclization was highly dependent on the purity of the thioacetal.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 60 (2004) 9589–9598

Alkoxide precoordination to rhodium enables stereodirected catalytic hydrogenation of a dihydrofuranol precursor of the C29-40 F/G sector of pectenotoxin-2

Xiaowen Peng, Dmitriy Bondar and Leo A. Paquette*

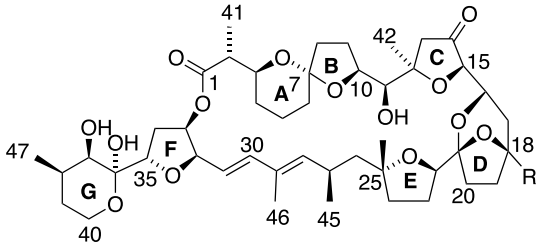
Evans Chemical Laboratories, The Ohio State University, Columbus, OH 43210 USA

Received 28 April 2004; revised 16 June 2004; accepted 18 June 2004

Available online 25 August 2004

Abstract—An enantioselective synthesis of the stereochemically fully endowed C(29-40) fragment of pectenotoxin-2 is detailed. The highlight of the synthesis is an alkoxide-directed hydrogenation in which ionic complexation of the deprotonated substrate to [Rh(NBD)(DIPHOS-4)]BF_4, accomplished by the co-addition of an equivalent of sodium hydride in THF, completely deters a kinetic tendency for dehydration and properly sets the critical stereochemistry at C-35. The dual objectives made possible by this catalytic technology are expected to have far-ranging applications.

Diarrhetic shellfish poisoning (DSP), first formally recognized in northeastern Japan about 30 years ago,[1] is now known to occur worldwide.[2] DSP is caused by eating scallops, mussels, or clams that have ingested toxigenic dinoflagellates and accumulated the toxins in this manner. The major symptoms of DSP are gastrointestinal disorders such as diarrhea, nausea, vomiting and abdominal pain.[3] Several dinoflagellate members of the genus *Dinophysis* have been identified as the organisms responsible for transmittal of the toxins to shellfish.[1] In 1985, Yasumoto et al. isolated these substances from the digestive gland of *Patinopecten yessoensis*, identified them to constitute a family of polyether macrolides, and assigned to them the name pectenotoxins (PTX's).[4] The structures of six of the 10 known PTX's are illustrated.



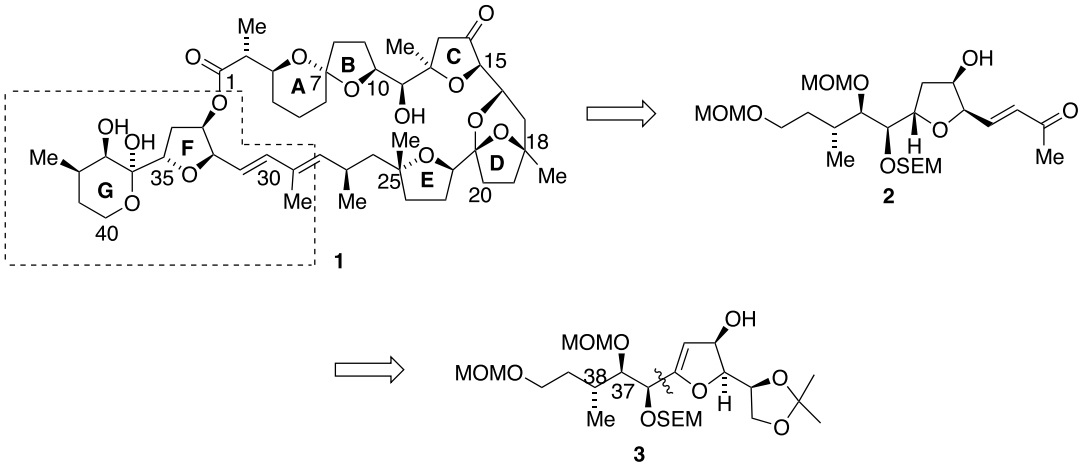
The structural variations arise from differences in the oxidation level of the R group attached to C-18 and the specific stereochemistry at C-7. The absolute configurations follow from a combination of X-ray crystallographic and comparative ^{1}H NMR analyses.[4] The hepatotoxic properties of PTX-1 and PTX-2 have been detailed.[5] Beyond this, PTX-2 exhibits selective nanomolar cytotoxicity against several human cancer cell lines[6] and an impressive capacity for site-specific interaction with the actin cytoskeleton.[7] In combination with these interesting biological properties are the exquisitely complex structural features consisting of 19 stereocenters (six are quaternary), a pair of spiroacetals, and several additional oxygenated rings housed in a 33-carbon macrolide ring. Not unexpectedly, this formidable synthetic challenge has attracted the attention of several research

R	C-7
PTX-1: CH_2OH	R
PTX-2: CH_3	**R**
PTX-3: CHO	R
PTX-4: CH_2OH	S
PTX-6: COOH	R
PTX-7: COOH	S

groups. Stereocontrolled routes to the C8–C18,[8] C11–C26,[9] C31–C40,[10] and C29–C40 fragments[11] of PTX-2 have been reported. Particularly noteworthy are the total asymmetric syntheses of PTX-4 and PTX-8 recently completed by the Evans group.[12]

Keywords: Stereodirected hydrogenation; Ionic complexation; Rhodium catalysis; *anti*-Aldol; 2-Lithio-4,5-dihydrofuran.
* Corresponding author. Tel.: +1-614-292-2520; fax: +1-614-292-1685; e-mail: paquette.1@osu.edu

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.06.142



Scheme 1.

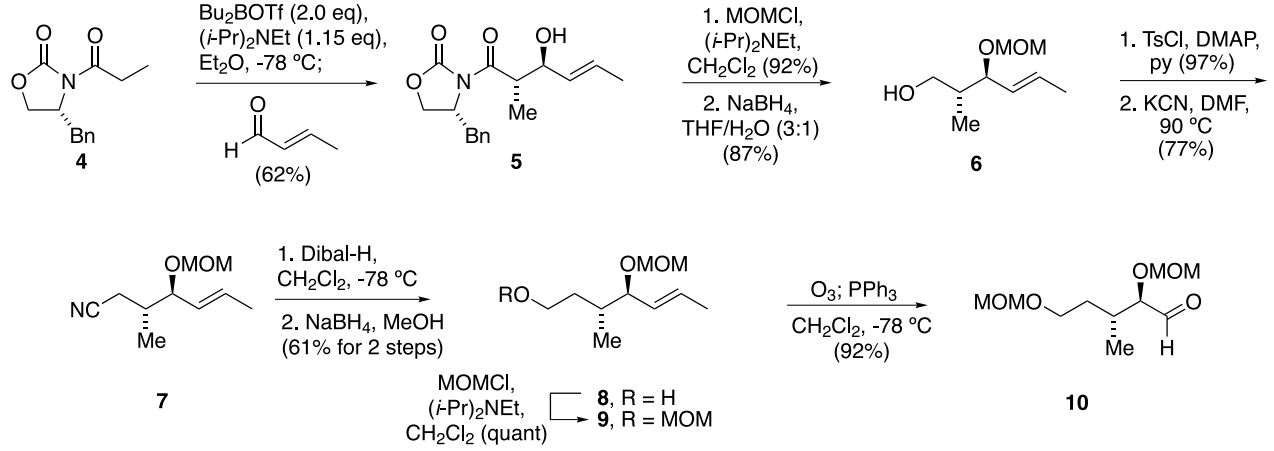
1. Results and discussion

From the outset, we envisioned an approach to the F/G sector of **1** that was to be based on the generation of **2** via stereocontrolled reduction of the double bond resident in **3**.[11] This advanced intermediate would in turn be assembled by the coupling of two simpler fragments as indicated in Scheme 1. As matters turned out, **3** exhibits a flagrant tendency to undergo dehydration when subjected to a variety of hydrogenation conditions. In the final analysis, a new, ultramild, catalytic protocol capable of circumventing this problem had to be developed. In the spirit of the present symposium-in-print, the merits of ionic complexation involving alkali metal alkoxides and a cationic rhodium catalyst are established. These conditions were also met with enhanced π-facial selectivity, thus boosting its overall value to targeted organic synthesis.

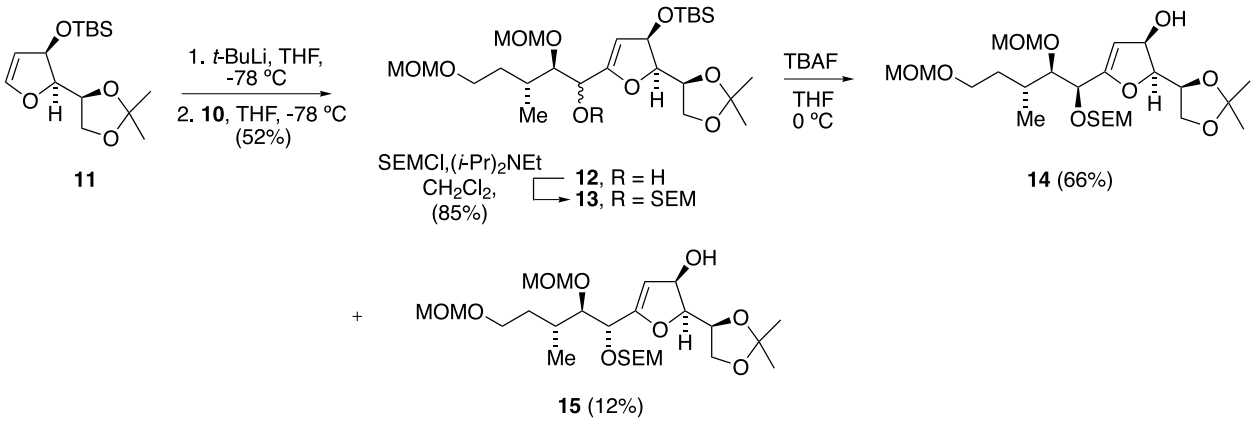
The configurational relationship of the methyl group and MOM ether at C-37 and C-38 in **3** suggested the application of an anti-aldol reaction[13] involving the *Z*-enolate of chiral oxazolidinone **4**[14] in the presence of 2 equiv. of the Lewis acid dibutylboron triflate.[15] With crotonaldehyde as the reaction partner, the desired product **5** was obtained as a single diastereomer when the condensation was performed on small (~200 mg) scale (Scheme 2). As the quantities were increased, selectivity decreased. The second diastereomer could be separated by careful column chromatography. The stereochemical assignment to **5** was consistent with the observed ^1H–^1H coupling constant ($J_{H\alpha,H\beta}=7.2$ Hz). Typical values are $J=3.2$–6.4 Hz for *syn* aldols and 7.2–9.6 Hz for their *anti* counterparts.[13b]

Following conversion to the MOM-protected derivative, the chiral auxiliary was cleaved with sodium borohydride in aqueous tetrahydrofuran[16] to afford alcohol **6**. One-carbon homologation was brought about by S_N2 displacement of the subsequently introduced tosylate group by cyanide ion. Dibal-H reduction of nitrile **7** made available the aldehyde, which was treated with sodium borohydride to gain access to alcohol **8**. Protection of the OH group as a MOM ether was followed by ozonolytic cleavage of the double bond to deliver the target aldehyde **10**.

At this point, attention was directed to the elaboration of dihydrofuran **14** (Scheme 3). The ready availability of enantiomerically pure **11** from D-mannose[17] prompted consideration of its deployment as starting material. In line with precedent, **11** proved suited to lithiation with *tert*-butyllithium at −78 °C.[18] The vinyl anion so formed reacted rapidly (<5 min) with **10** at this temperature to furnish **12**, which was immediately protected[19] as its SEM ether **13**. ^{13}C NMR analysis of this intermediate clearly revealed the presence of two diastereomers which could not



Scheme 2.



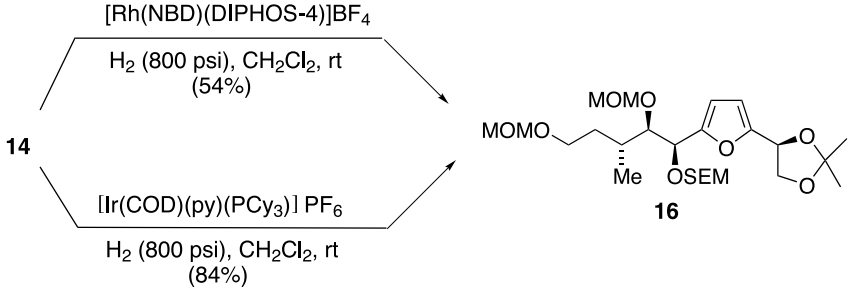
Scheme 3.

be separated by flash column chromatography. Fortunately, the diastereomers **14** and **15**, obtained in a ratio of 5:1 following selective desilylation with tetrabutylammonium fluoride at 0 °C, were amenable to purification in this manner. Although the absolute configuration of C-36 in both **14** and **15** could not be unequivocally ascertained, this issue was of little consequence since this center has to be oxidized to the ketone level at one of the final steps of the synthesis. Consequently, both intermediates are serviceable. For convenience, only the pure diastereomer **14**, arbitrarily assigned the β configuration, was utilized almost exclusively in the sequel. This configuration is consonant with predominant adherence to the Cram chelate transition state during 1,2-addition to aldehyde **10**.

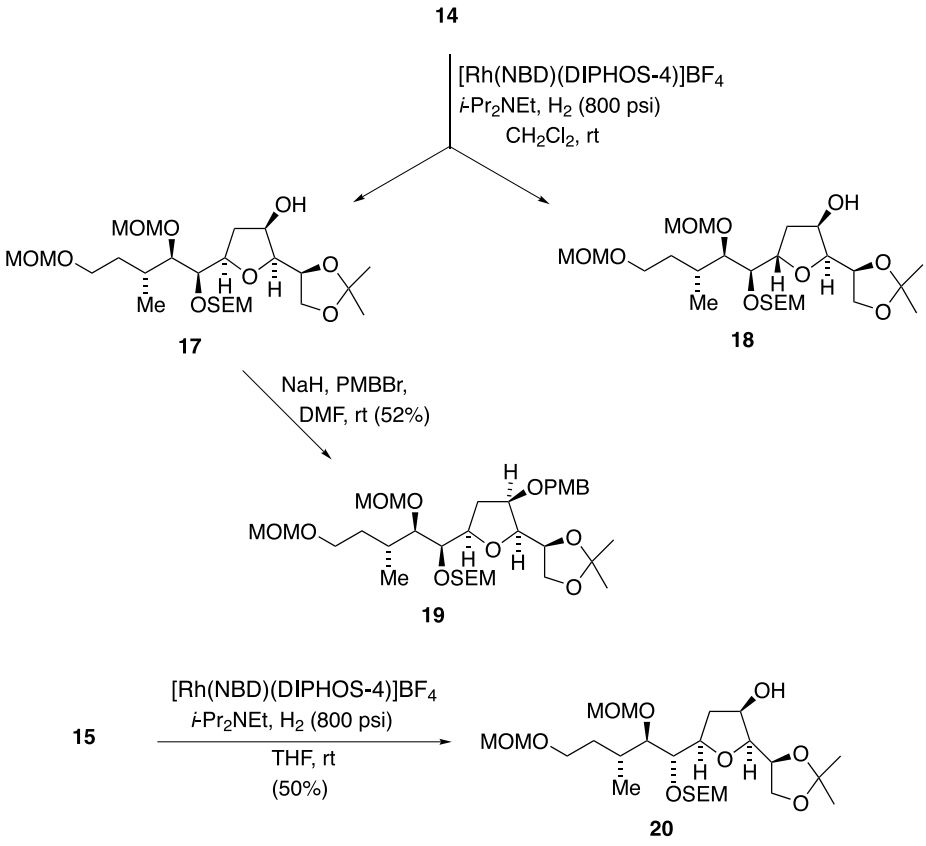
The feasibility of this route to **14** set the stage for a hydroxyl-directed hydrogenation[20] to serve as the means for establishing the third stereogenic center in tetrahydrofuran ring F. However, the pronounced tendency of **14** to undergo the elimination of water during attempted saturation had to be dealt with properly. For example, stirring a 0.07 M CH_2Cl_2 solution of the dihydrofuranol with 20 mol% [Rh(NBD)(DIPHOS-4)]BF_4[21] under 800 psi of hydrogen for 17 h furnished **16** as the major product (Scheme 4). The entirely comparable response accorded to experiments involving [Ir(COD)(py)(PCy_3)]PF_6[22] (84% of **16**) led us to consider the Lewis-acidic nature of these catalysts as a potential source of the difficulty. Since the rhodium-based reagent is known to be stable to triethylamine, recourse was made to the inclusion of 2–3 equiv. of Hünig's base in the reaction medium. This tactic did serve successfully to deter the production of **16**. However, the reputed hydroxyl-directing capability of this rhodium catalyst did not surface. In the case of **14**, **17** and **18** were formed (46% and 3%) and an appreciable amount (46%) of unreacted starting material was recovered (Scheme 5). A similar reaction performed on **15** but with a solvent change to tetrahydrofuran revealed no advantageous medium effect. Other than return of 20% of the reactant, there was produced 50% of **20**.

The structural assignment to **17** was facilitated by its conversion to the *p*-methoxybenzyl ether **19**. NOESY analysis of this derivative performed in $CDCl_3$ solvent allowed for clean differentiation of H-34α and H-34β and the establishment of their spatial relationship to H-33 and H-35. There was no question that the undesired configuration had been set at C-35. Direct spectral comparison of the ^{1}H NMR spectral features of **17** and **20** confirmed that neither of the two well-known hydroxyl-directing hydrogenation catalysts was suited to the task in the present context. Rather, our results suggest that Hünig's base found it possible to coordinate to rhodium with activation of the catalyst. Subsequent mechanistic events conspired to cause approach from the less hindered face of the double bond to be kinetically favored.

The complication prompted a more in-depth investigation into the phenomenon. In particular, we were attracted to a 1974 report by Thompson and McPherson that described a significant enhancement in π-facial discrimination with Wilkinson's catalyst upon covalent bonding of an alkoxide to the rhodium center.[23] Disappointingly, the subjection of **14** to these conditions resulted in the absence of any detectable reaction. This observation led to alternative examination of the merits of ionic complexation between the alkali metal salts of **14** and **15** and the cationic catalyst [Rh(NBD)(DIPHOS-4)]BF_4. Hydrogenation of the potassium salt of **15** in THF gave rise to a product mixture



Scheme 4.

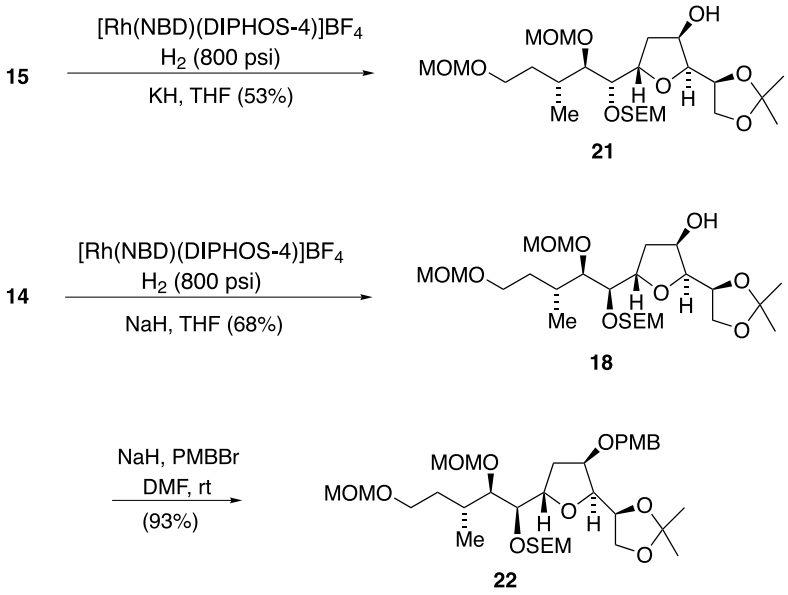


Scheme 5.

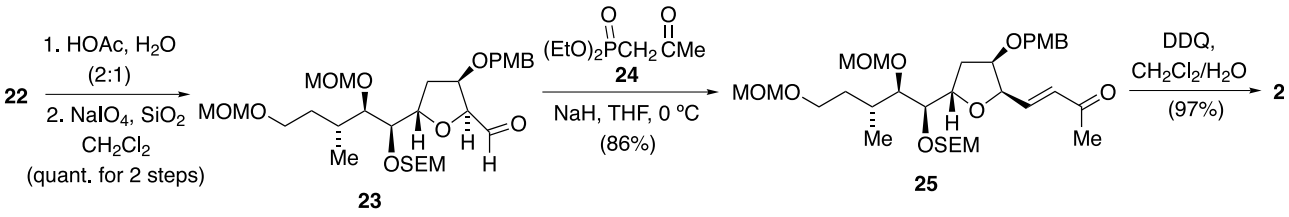
consisting predominantly of **21** (Scheme 6). Comparable processing of **14** in THF solution containing sodium hydride gave only **18** (68% at 80% conversion). The optimization studies that followed demonstrated that excellent reproducibility and efficiency were attainable with 1.05 equiv. of NaH in THF when the reaction time was extended to three days. The adoption of these mild basic reaction conditions is enthusiastically endorsed in difficult cases such as those faced here.

To complete our passage to **2**, intermediate **22** was hydrolyzed in aqueous acetic acid to unmask the 1,2-diol, the subsequent cleavage of which was effected with sodium periodate on silica gel[24] (Scheme 7). The homologation of aldehyde **23** with phosphonate ester **24**[25] and subsequent exposure to DDQ[26] gave rise efficiently to **2**.

In summary, a means for the concise assembly of the C29–C40 subunit of pectenotoxin-2 has been defined. The key



Scheme 6.



Scheme 7.

step of the undertaking is an alkoxide-directed hydrogenation. The optimized conditions effectively skirt as well the tendency of **14** to experience dehydration with formation of furan **16**. The feasibility of this scenario was the centerpiece of a stereocontrolled 18-step route that provided **2** in 3.2% overall yield.

2. Experimental.[27]

2.1. Data for compounds

2.1.1. Aldol product 5. To a solution of **4** (182 mg, 0.78 mmol) in 3 mL of dry ether cooled to 0 °C was added dibutylboron triflate (0.39 mL, 1.56 mmol) dropwise followed by diisopropylethylamine (0.16 mL, 0.90 mmol). The mixture was stirred at 0 °C for 40 min before being cooled to −78 °C. A solution of crotonaldehyde (0.081 mL, 0.97 mmol) in 1 mL of ether was introduced dropwise at −78 °C. The reaction mixture was stirred for 30 min, diluted with 2 mL of ether, quenched with 1.5 mL of 1 M tartaric acid solution at −78 °C, and stirred at rt for an additional 2 h. The separated aqueous phase was extracted with ether. The combined organic phases were washed with saturated $NaHCO_3$ solution and cooled to 0 °C prior to the addition of a solution containing 3:1 MeOH/30% H_2O_2 (2 mL). The mixture was stirred at rt for 30 min, diluted with ether, and washed with saturated $NaHCO_3$ solution and brine prior to drying. The solvent was removed under vacuum and the residue was purified by flash column chromatography (silica gel, hexane–EtOAc/7:1) to give **5** (0.146 g, 62%) as a white solid, mp 110.0–111.0 °C; IR (CH_2Cl_2, cm^{-1}) 3486, 1776, 1696; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36–7.23 (m, 5H), 5.86–5.72 (m, 1H), 5.58–5.50 (m, 1H), 4.73–4.66 (m, 1H), 4.24–4.14 (m, 3H), 3.94 (dd, J=7.2, 7.2 Hz, 3H), 3.29 (dd, J=3.2, 13.4 Hz, 1H), 2.78 (dd, J=9.4, 13.4 Hz, 1H), 1.73 (dt, J=6.5, 0.7 Hz, 1H), 1.17 (d, J=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6, 153.6, 135.3, 131.6, 129.6 (2C), 129.2, 129.1 (2C), 127.4, 75.9, 66.1, 55.6, 43.4, 37.9, 17.9, 14.6; ES HRMS m/z $(M+Na)^+$ calcd 326.1368, obsd 326.1363; $[\alpha]_D^{22}=-39.6$ (c 0.54, $CHCl_3$).

Anal. Calcd for $C_{17}H_{21}O_4N$: C, 67.31, H, 6.98. Found: C, 67.18, H, 7.04.

2.1.2. MOM protection of 5. MOMCl (0.889 mL, 11.7 mmol) was added dropwise to a solution of **5** (1.42 g, 4.68 mmol) and diisopropylethylamine (2.45 mL, 14.0 mmol) at −78 °C. The reaction mixture was stirred at rt overnight, saturated $NaHCO_3$ solution (30 mL) was added to quench the reaction, and the separated aqueous phase was extracted with CH_2Cl_2 (35 mL×2). The combined organic phases were dried and evaporated to leave a residue, purification of which by flash chromatography (silica gel, hexane–EtOAc 9:1) afforded the MOM ether (1.51 g, 92%) as a white solid, mp 70.5–71.0 °C; IR (CH_2Cl_2, cm^{-1}) 1780, 1699; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36–7.24 (m, 5H), 5.85–5.74 (m, 1H), 5.34–5.25 (m, 1H), 4.77–4.69 (m, 2H), 4.46 (d, J=6.7 Hz, 1H), 4.32 (dd, J=7.2, 7.2 Hz, 1H), 4.21–4.04 (m, 3H), 3.33 (s, 3H), 3.25 (dd, J=3.3, 13.4 Hz, 1H), 2.79 (dd, J=9.1, 13.5 Hz, 1H), 1.76 (dd, J=1.6, 6.5 Hz, 3H) 1.09 (d, J=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8, 153.3, 135.39, 133.0, 129.6, 129.5, 129.0, 128.6, 128.2, 127.4, 93.1, 78.9, 65.7, 55.8, 55.1, 42.0, 37.9, 17.9, 14.2; ES HRMS m/z $(M+Na)^+$ calcd 370.1630, obsd 370.1642; $[\alpha]_D^{22}=+1.4$ (c 0.20, $CHCl_3$).

Anal. Calcd for $C_{19}H_{25}O_5N$: C, 65.69, H, 7.25. Found: C, 65.75, H, 7.17.

2.1.3. MOM ether 6. Sodium borohydride (0.307 g, 8.12 mmol) was added in one portion to a solution of protected **5** (1.41 g, 4.06 mmol) in 40 mL of THF/H_2O (3:1) at 0 °C. The reaction mixture was stirred overnight. More $NaBH_4$ was added to allow completion of the reaction. HCl (1 M) was introduced carefully and the product was extracted into ether. The combined organic phases were washed with brine, dried, and freed of solvent. The residue was purified by flash chromatography (silica gel, hexane–EtOAc 5:1) to give **6** (0.617 g, 87%) as a colorless oil; IR (neat, cm^{-1}) 3444, 1670, 1453; ^1H NMR (300 MHz, $CDCl_3$) δ 5.71–5.60 (m, 1H), 5.31–5.22 (m, 1H), 4.60 (AB quartet, J=6.7 Hz, 2H), 3.86 (dd, J=8.4, 8.4 Hz, 1H), 3.70–3.57 (m, 2H), 3.38 (s, 3H), 2.88 (br s, 1H), 1.86–1.75 (m, 1H), 1.72 (dd, J=6.5, 1.7 Hz, 3H), 0.85 (d, J=7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.3, 129.4, 93.1, 82.1, 66.9, 55.8, 39.9, 17.8, 13.9; ES HRMS m/z $(M+Na)^+$ calcd 197.1148, obsd 197.1148; $[\alpha]_D{}^{22}=+170$ (c 0.82, $CHCl_3$).

2.1.4. Nitrile 7. To a solution of **6** in pyridine (5 mL) was added *p*-toluenesulfonyl chloride (0.624 g, 3.27 mmol) in one portion followed by a catalytic amount of DMAP. The reaction mixture was stirred overnight. Saturated $NaHCO_3$ solution (6 mL) was added and stirring was continued for 45 min. The solution was extracted with EtOAc. The combined organic phases were washed with 1 M HCl until TLC indicated that no pyridine remained. The organic phase was washed with saturated $NaHCO_3$ solution and brine, dried and freed of solvent under vacuum to provide the tosylate (0.693 g, 97%) as a pale yellow oil.

The tosylate was dissolved in 5 mL of DMF. KCN (0.429 g, 6.33 mmol) was introduced. After being stirred at 90 °C overnight, the reaction mixture was diluted with ether/petroleum ether (1/1) (100 mL) and washed with saturated

$NaHCO_3$ solution, water, and brine prior to being freed of solvent under vacuum. The residue was purified by flash chromatography (silica gel, hexane–EtOAc 20:1) to furnish **7** (0.297 g, 77%) as a colorless oil; IR (neat, cm^{-1}) 2246, 1460, 1384; ^1H NMR (300 MHz, $CDCl_3$) δ 5.72–5.60 (m, 1H), 5.19–5.10 (m, 1H), 4.65 (d, $J=6.8$ Hz, 1H), 4.40 (d, $J=6.8$ Hz, 1H), 3.71 (dd, $J=8.2$, 8.2 Hz, 1H), 3.31 (s, 3H), 2.52–2.34 (m, 2H), 1.94–1.82 (m, 1H), 1.68 (dd, $J=1.5$, 6.5 Hz, 3H), 1.00 (d, $J=6.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.1, 128.1, 118.9, 93.0, 79.0, 55.6, 35.0, 20.7, 17.7, 15.9; ES HRMS m/z $(M+Na)^+$ calcd 206.1157, obsd 206.1151; $[\alpha]_D^{22}=+165.5$ (c 0.87, $CHCl_3$).

2.1.5. Alcohol 8. To a solution of **7** (0.350 g, 1.91 mmol) in 5 mL of CH_2Cl_2 was added DIBAL-H (1 M in hexane, 2.86 mL, 2.86 mmol) dropwise at −78 °C. The reaction mixture was stirred at this temperature for 2 h before being transferred via cannula into saturated Rochelle salt (potassium sodium tartrate tetrahydrate) solution (5 mL). The aqueous phase was extracted with CH_2Cl_2 (10 mL×2). The combined organic phases were dried and freed of solvent under vacuum to furnish the aldehyde.

The unpurified aldehyde was dissolved in 10 mL of MeOH. Sodium borohydride (0.088 g, 2.29 mmol) was added in one portion at 0 °C. The reaction mixture was stirred in the cold for 30 min. The solvent was removed and the residue was dissolved in CH_2Cl_2. The combined organic phases were washed with 1 M HCl solution, saturated $NaHCO_3$ solution, and brine, then dried and freed of solvent. The residue was purified by flash chromatography (silica gel, hexane–EtOAc/2:1) to give **8** (0.180 g, 61%) as a colorless oil; IR (neat, cm^{-1}) 3418, 1669, 1453; ^1H NMR (300 MHz, $CDCl_3$) δ 5.86–5.55 (m, 1H), 5.30–5.20 (m, 1H), 4.69 (d, $J=6.7$ Hz, 1H), 4.46 (d, $J=6.7$ Hz, 1H), 3.75–3.56 (m, 3H), 3.34 (s, 3H), 2.36 (br s, 1H), 1.82–1.67 (m, 5H), 1.46–1.34 (m, 1H), 0.88 (d, $J=6.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.7, 129.0, 93.2, 81.1, 60.9, 55.6, 35.9, 34.8, 17.8, 16.1; ES HRMS m/z $(M+Na)^+$ calcd 211.1305, obsd 211.1319; $[\alpha]_D^{22}=+145$ (c 0.50, $CHCl_3$).

2.1.6. MOM protection of 8. To a solution of **8** (0.060 g, 0.319 mmol) and diisopropylethylamine (0.139 mL, 0.797 mmol) in 2 mL of CH_2Cl_2 was added MOMCl (0.048 mL, 0.637 mmol) dropwise at −78 °C. The reaction mixture was stirred at rt overnight. Saturated $NaHCO_3$ solution (30 mL) was added and the separated aqueous phase was extracted with ether. The combined organic phases were dried and freed of solvent. The residue was purified by flash chromatography (silica gel, hexane–EtOAc 4.5:1) to afford **9** (0.074 g, quant.) as a pale yellow oil; IR (CH_2Cl_2, cm^{-1}) 1450, 1380; ^1H NMR (300 MHz, $CDCl_3$) δ 5.67–5.55 (m, 1H), 5.30–5.20 (m, 1H), 4.69 (d, $J=6.8$ Hz, 1H), 4.59 (d, $J=0.9$ Hz, 1H), 4.46 (d, $J=6.7$ Hz, 1H), 3.76–3.72 (m, 1H), 3.62–3.52 (m 2H), 3.33 (s, 3H), 1.92–1.72 (m, 2H), 1.69 (dd, $J=6.4$, 1.6 Hz, 3H), 1.39–1.23 (m, 1H), 0.88 (d, $J=6.8$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.6, 128.9, 96.4, 93.2, 80.7, 66.0, 55.5, 55.2, 34.6, 32.7, 17.9, 15.4; ES HRMS m/z $(M+Na)^+$ calcd 255.1572, obsd 255.1574; $[\alpha]_D^{22}=+112$ (c 0.68, $CHCl_3$).

2.1.7. Aldehyde 10. Ozone was purged through a solution of **9** (0.063 g, 0.27 mmol) in 2 mL of CH_2Cl_2 at −78 °C until a pale blue color persisted. After an excess amount of triphenylphosphine was added, the mixture was allowed to return to rt and stirred for 1 h. The solvent was removed and the residue was purified by flash chromatography (silica gel, hexane–EtOAc 6:1) to give **10** (0.055 g, 92%) as a colorless oil; IR (neat, cm^{-1}) 1732, 1461; ^1H NMR (300 MHz, $CDCl_3$) δ 9.62 (d, $J=2.2$ Hz, 1H), 4.71 (d, $J=6.8$ Hz, 1H), 4.66 (d, $J=6.8$ Hz, 1H), 4.57 (s, 2H), 3.74 (dd, $J=5.2$, 2.2 Hz, 1H), 3.58–3.50 (m, 2H), 3.39 (s, 3H), 3.32 (s, 3H), 2.22–2.13 (m, 1H), 1.87–1.76 (m, 1H), 1.55–1.38 (m, 1H), 1.01 (d, $J=6.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.4, 97.04, 96.4, 86.2, 65.3, 56.1, 55.3, 32.0, 31.5, 15.8; ES HRMS m/z $(M+O+Na)^+$ calcd 259.1158, obsd 259.1172; $[\alpha]_D^{22}=+43.7$ (c 0.75, $CHCl_3$).

2.1.8. Coupling of 10 to 11. To a solution of **11** (4.33 g, 14.4 mmol) in 10 mL of THF was added t-BuLi (1.42 M in pentane, 10.15 mL, 14.4 mmol) dropwise at −78 °C. The mixture was stirred at −78 °C for 1 h and transferred via cannula into a solution of **10** (1.38 g, 6.27 mmol) in 15 mL of THF at −78 °C. After being stirred for 30 min in the cold, the reaction mixture was quenched with water and extracted with EtOAc. The combined organic phases were washed with saturated $NaHCO_3$ solution and brine, dried, and freed of solvent under vacuum. The residue was purified by flash chromatography (silica gel, hexane–EtOAc/5:1) to furnish **12** (1.69 g, 52%) as a colorless oil, which was immediately subjected to protection; IR (CH_2Cl_2, cm^{-1}) 3443, 1650, 1472; ^1H NMR (300 MHz, C_6D_6) δ 5.24–5.22 (m, 1H), 4.74–4.69 (m, 1H), 4.61 (dd, $J=6.2$, 5.9 Hz, 1H), 4.56–4.49 (m, 3H), 4.48–4.35 (m, 2H), 4.23–4.15 (m, 2H), 3.65–3.51 (m, 2H), 3.22 and 3.21 (s, 3H), 3.17 and 3.08 (s, 3H), 2.33–2.31 (m, 1H), 2.14–1.96 (m, 2H), 1.55–1.28 (m, 2H), 1.50 and 1.47 (s, 3H), 1.34 and 1.33 (s, 3H), 0.98 (d, $J=6.9$ Hz, 3H), 0.95 and 0.90 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 163.4, 163.3, 109.4, 109.2, 102.4, 102.1, 100.6, 100.5, 100.4, 99.2, 98.7, 97.0, 89.7, 86.7, 86.6, 86.5, 74.4, 74.3, 74.1, 73.5, 69.0, 67.2, 66.8, 66.7, 66.4, 56.4, 56.1, 55.3, 33.3, 33.0, 32.8, 32.1, 27.3, 26.4, 26.3, 25.9, 25.6, 18.8, 18.7, 17.2, 16.9, −4.0, −4.1, −4.5, −4.7; ES HRMS m/z $(M+Na)^+$ calcd 543.2965, obsd 543.2957.

2.1.9. Dihydrofuran 13. To a solution of **12** (1.475 g, 2.83 mmol) and diisopropylethylamine (1.97 mL, 11.3 mmol) in 12 mL of CH_2Cl_2 was added SEMCl (1.50 mL, 8.50 mmol) dropwise at 0 °C. The reaction mixture was stirred at rt overnight, saturated $NaHCO_3$ solution (30 mL) was added, and the separated aqueous phase was extracted with EtOAc. The combined organic layers were washed with saturated $NaHCO_3$ solution and brine, dried, and freed of solvent. The residue was purified by flash chromatography (silica gel, hexane–EtOAc 15:1) to afford **13** (1.565 g, 85%) as a pale yellow oil; IR (CH_2Cl_2, cm^{-1}) 1658, 1472; ^1H NMR (300 MHz, $CDCl_3$) δ 5.10 (d, $J=2.5$ Hz, 1H), 4.86–4.82 (m, 1H), 4.73–4.50 (m, 6H), 4.43–4.38 (m, 1H), 4.34–4.23 (m, 2H), 4.10–4.04 (m, 1H), 3.92 (dd, $J=6.4$, 8.5 Hz, 1H), 3.73–3.67 (m, 1H), 3.61–3.45 (m, 4H), 3.35 (d, $J=5.7$ Hz, 3H), 3.32 (d, $J=1.4$ Hz, 3H), 2.00–1.81 (m, 2H), 1.39 (s, 3H), 1.33 (s, 3H), 1.00 (dd, $J=2.7$, 6.7 Hz, 3H), 0.93–0.81 (m, 3H), 0.84 (s, 9H), 0.03 (s, 3H), 0.02 (d, $J=1.6$ Hz, 3H), −0.01 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 159.1, 108.7, 108.6, 104.1, 103.8, 98.4, 97.4, 96.4, 92.9, 92.8, 85.7, 85.3, 83.1, 82.5,

73.6, 73.5, 73.3, 73.1, 72.9, 72.5, 66.41, 66.36, 66.3, 66.2, 65.7, 65.6, 56.2, 56.1, 55.1, 31.8, 31.6, 31.3, 31.2, 26.64, 26.56, 25.8, 25.5, 25.4, 18.1, 18.03, 17.98, 16.9, 16.7, −1.3, −1.4, −4.5, −4.5, −5.0; ES HRMS *m/z* $(M+Na)^+$ calcd 673.3779, obsd 673.3770.

2.1.10. Dihydrofuranyl alcohols 14 and 15. To a solution of **13** (0.100 g, 0.15 mmol) in 3 mL of THF was added TBAF (1.0 M in THF, 0.23 mL, 0.23 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h before being diluted with 30 mL of ether. The organic phase was washed with saturated $NaHCO_3$ solution and brine, dried, and freed of solvent. The residue was purified by flash chromatography (silica gel, 1% Et_3N, hexane–EtOAc 1:1) to furnish the major isomer (assumed to be **14**, 0.054 g, 66%) and minor isomer (assumed to be **15**, 0.010 g, 12%) both as colorless oils.

For **14**. IR (neat, cm^{-1}) 3472, 1651, 1455; ^1H NMR (500 MHz, C_6D_6) δ 5.18 (d, $J=2.7$ Hz, 1H), 5.11 (d, $J=6.4$ Hz, 1H), 4.79 (d, $J=6.6$ Hz, 2H), 4.62–4.58 (m, 4H), 4.44 (s, 2H), 4.25 (t, $J=6.2$ Hz, 1H), 4.16–4.09 (m, 2H), 4.20 (dd, $J=2.2$, 8.0 Hz, 1H), 3.82–3.77 (m, 1H), 3.58–3.47 (m, 3H), 3.29 (s, 3H), 3.19 (s, 3H), 2.13–2.09 (m, 1H), 1.98–1.94 (m, 1H), 1.52–1.46 (m, 1H), 1.43 (s, 3H), 1.30 (s, 3H), 1.14 (d, $J=6.8$ Hz, 3H), 1.00–0.95 (m, 2H), 0.53 (br s, 1H), 0.02 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 159.4, 109.1, 105.6, 99.1, 96.4, 92.9, 86.9, 83.5, 75.6, 73.5, 73.1, 66.8, 65.5, 65.4, 56.0, 31.4, 30.4, 27.0, 25.6, 18.3, 17.0, −1.2 (3C); ES HRMS *m/z* $(M+Na)^+$ calcd 559.2909, obsd 559.2876; $[\alpha]_D^{22}=-48.9$ (*c* 0.35, $CHCl_3$).

For **15**. IR (neat, cm^{-1}) 3457, 1659, 1456; ^1H NMR (500 MHz, C_6D_6) δ 5.25 (d, $J=2.6$ Hz, 1H), 4.78 (d, $J=6.8$ Hz, 1H), 4.75 (d, $J=6.5$ Hz, 2H), 4.69–4.66 (m, 2H), 4.56–4.52 (m, 4H), 4.24 (t, $J=6.6$ Hz, 1H), 4.12–4.09 (m, 2H), 3.91–3.88 (m, 1H), 3.80–3.74 (m, 3H), 3.21 (s, 3H), 3.20 (s, 3H), 2.39–2.29 (m, 1H), 2.28–2.23 (m, 1H), 1.65–1.59 (m, 1H), 1.43 (s, 3H), 1.30 (s, 3H), 1.11 (d, $J=6.9$ Hz, 3H), 1.00–0.92 (m, 3H), 0.01 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 161.0, 109.2, 103.9, 97.8, 96.6, 93.7, 86.2, 82.9, 73.6, 73.5, 73.2, 67.0, 66.4, 66.0, 56.0, 55.0, 31.9, 31.6, 27.0, 25.6, 18.3, 17.1, −1.3 (3C); ES HRMS *m/z* $(M+Na)^+$ calcd 559.2909, obsd 559.2930; $[\alpha]_D^{22}=+42.3$ (*c* 0.31, $CHCl_3$).

2.1.11. Formation of furan 16. *(A) Rhodium catalysis*. [Rh(NBD)(DIPHOS-4)]BF_4 (14 mg, 20 mol%) was added to a solution of **14** (0.054 g, 0.101 mmol) in 1.5 mL of CH_2Cl_2. The reaction mixture was placed in a stainless steel reactor, purged three times with H_2, and stirred at 800 psi and rt for 17 h. The spent catalysis was filtered and washed with EtOAc. The solvent was removed under vacuum. The residue was purified by flash column chromatography (silica gel, 1% Et_3N, hexane–EtOAc 5:1) to afford **16** (29 mg, 54%) as a colorless oil; IR (CH_2Cl_2, cm^{-1}) 1557, 1462; ^1H NMR (300 MHz, $CDCl_3$) δ 6.31–6.27 (m, 2H), 5.05 (dd, $J=6.8$, 6.8 Hz, 1H), 4.77–4.70 (m, 2H), 4.66–4.53 (m, 5H), 4.21 (dd, $J=6.4$, 8.2 Hz, 1H), 4.01 (dd, $J=7.3$, 8.3 Hz, 1H), 3.75–3.66 (m, 2H), 3.57–3.38 (m, 2H), 3.37 (s, 3H), 3.31 (s, 3H), 1.79–1.59 (m, 2H), 1.46 (s, 3H), 1.42 (s, 3H), 1.44–1.29 (m, 1H), 1.00 (d, $J=6.9$ Hz, 3H), 0.93–0.83 (m, 2H), −0.01 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.5, 152.3, 110.1, 109.9, 108.5, 98.3, 96.3, 92.7, 83.8, 73.0, 71.4, 68.3, 66.1, 65.4, 56.2, 55.2, 31.9, 31.0, 26.5, 26.0, 18.0, 16.8, 0.0 (3C); ES HRMS *m/z* $(M+Na)^+$ calcd 541.2803, obsd 541.2795; $[\alpha]_D^{22}=-33$ (*c* 0.36, $CHCl_3$).

(B) Iridium catalysis. [Ir(COD)(py)(PCy_3)]PF_6 (3.6 mg, 20 mol%) was added to a solution of **14** (0.012 g, 0.022 mmol) in 1.0 mL of CH_2Cl_2. The reaction mixture was placed in a stainless steel reactor, purged three times with H_2 and stirred at 800 psi and rt for 17 h. The solvent was removed under vacuum. The residue was purified by flash chromatography (silica gel, 1% Et_3N, hexane–EtOAc 5:1) to afford **16** (9.6 mg, 84%) as a colorless oil; IR (CH_2Cl_2, cm^{-1}) 1557, 1462; ^1H NMR (300 MHz, $CDCl_3$) δ 6.31–6.27 (m, 2H), 5.05 (dd, $J=6.8$, 6.8 Hz, 1H), 4.77–4.70 (m, 2H), 4.66–4.53 (m, 5H), 4.21 (dd, $J=6.4$, 8.2 Hz, 1H), 4.01 (dd, $J=7.3$, 8.3 Hz, 1H), 3.75–3.66 (m, 2H), 3.57–3.38 (m, 2H), 3.37 (s, 3H), 3.31 (s, 3H), 1.79–1.59 (m, 2H), 1.46 (s, 3H), 1.42 (s, 3H), 1.44–1.29 (m, 1H), 1.00 (d, $J=6.9$ Hz, 3H), 0.93–0.83 (m, 2H), −0.01 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.5, 152.3, 110.1, 109.9, 108.5, 98.3, 96.3, 92.7, 83.8, 73.0, 71.4, 68.3, 66.1, 65.4, 56.2, 55.2, 31.9, 31.0, 26.5, 26.0, 18.0, 16.8, 0.0 (3C); ES MS HR *m/z* $(M+Na)^+$ calcd 541.2803, obsd 541.2795; $[\alpha]_D^{22}=-33$ (*c* 0.36, $CHCl_3$).

2.1.12. Hydrogenation of 14 in the presence of Hünig's base. [Rh(NBD)(DIPHOS-4)]BF_4 (3.0 mg, 20 mol%) was added to a solution of **14** (12 mg, 0.022 mmol) and *i*-Pr_2NEt (15 μL, 0.068 mmol) in 1.0 mL of CH_2Cl_2. The reaction mixture was placed in a stainless steel reactor, purged three times with H_2, and stirred at 800 psi and rt for 17 h. The solvent was removed under vacuum. The residue was purified by flash chromatography (silica gel, 1% Et_3N, hexane–EtOAc 3:1) to afford **17** (5.5 mg, 25%) as a colorless oil, **14** (5.4 mg, 46%) and **18** (0.4 mg, 3%).

For **17**. ^1H NMR (300 MHz, C_6D_6) δ 4.87 (d, $J=6.0$ Hz, 1H), 4.78 (d, $J=6.9$ Hz, 2H), 4.60 (q, $J=6.1$ Hz, 1H), 4.56 (d, $J=6.5$ Hz, 1H), 4.49 (d, $J=1.5$ Hz, 2H), 4.24–4.18 (m, 2H), 4.14–4.10 (m, 1H), 4.05–4.00 (m, 2H), 3.75 (dd, $J=16.8$ Hz, $J=8.2$ Hz, 1H), 3.64 (dd, $J=17.5$ Hz, $J=8.7$ Hz, 1H), 3.54–3.24 (m, 5H), 3.22 (s, 3H), 3.19 (s, 3H), 2.00–1.77 (m, 5H), 1.46 (s, 3H), 1.36 (s, 3H), 1.04 (d, $J=6.8$ Hz, 3H), 0.95–0.87 (m, 2H), 0.01 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6) δ 109.4, 97.3, 97.1, 85.2, 83.8, 79.8, 78.9, 74.3, 71.8, 68.4, 67.1, 66.3, 56.3, 55.3, 45.7, 35.9, 32.4, 31.8, 27.5, 26.1, 18.6, 17.7, −0.9 (3C).

2.1.13. Formation of PMB ether 19. A suspension of **17** (16 mg, 0.030 mmol) and NaH (60% in mineral oil, 36 mg, 0.15 mmol) in 1 mL of DMF was stirred at rt for 1 h before *p*-methoxybenzyl bromide (0.018 g, 0.089 mmol) was added. The reaction mixture was stirred at rt for 4 h and quenched with saturated $NaHCO_3$ solution (3 mL). The solution was extracted with ether/pet ether (1/1, 50 mL), washed with brine, dried, and freed of solvent. The residue was purified by flash chromatography (silica gel, hexane–EtOAc 4:1) to furnish **19** (16 mg, 82%) as a pale yellowish oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26–7.23 (m, 2H), 6.87–6.84 (m, 2H), 4.83 (d, $J=6.9$ Hz, 1H), 4.76 (d, $J=6.6$ Hz, 1H), 4.71 (d, $J=6.9$ Hz, 1H), 4.66 (d, $J=6.6$ Hz, 1H), 4.61–4.50 (m, 3H), 4.40–4.31 (m, 2H), 4.13–4.09 (m, 1H), 4.06–

3.90 (m, 3H), 3.86–3.83 (m, 1H), 3.80 (s, 3H), 3.78–3.76 (m, 1H), 3.66–3.41 (m, 5H), 3.40 (s, 3H), 3.39 (s, 3H), 2.34–2.26 (m, 1H), 2.17–2.06 (m, 1H), 1.98–1.85 (m, 2H), 1.30 (s, 3H), 1.37 (s, 3H), 0.97 (d, $J=6.8$ Hz, 3H), 0.92–0.89 (m, 2H), 0.01 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 130.6, 129.1 (2C), 113.8 (2C), 108.6, 98.5, 96.5, 96.4, 83.2, 83.0, 79.9, 78.6, 78.5, 73.9, 70.8, 67.0, 66.3, 65.8, 56.4, 55.4, 55.2, 33.6, 32.0, 31.9, 26.8, 25.8, 18.2, 16.7, −1.3 (3C).

2.1.14. Hydrogenation of 15 in the presence of Hünig's base. [Rh(NBD)(DIPHOS-4)]BF_4 (4 mg, 20 mol%) was added to a solution of **14** (15 mg, 0.028 mmol) and *i*-Pr_2NEt (12 μL, 0.084 mmol) in 1.5 mL of THF. The reaction mixture was placed in a stainless steel reactor, purged three times with H_2 and stirred at 800 psi and rt for 18 h. The solvent was removed under vacuum. The residue was purified by flash chromatography (silica gel, 1% Et_3N, hexane–EtOAc 3:1) to afford **20** (7.5 mg, 50%) as a colorless oil and **15** (3 mg, 20%).

For **20**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.83 (d, $J=6.5$ Hz, 1H), 4.81 (d, $J=6.5$ Hz, 1H), 4.78 (d, $J=6.5$ Hz, 1H), 4.62–4.58 (m, 3H), 4.37–4.34 (m, 1H), 4.33–4.25 (m, 2H), 4.11–4.08 (m, 1H), 3.98–3.95 (m, 1H), 3.81–3.75 (m, 1H), 3.65–3.52 (m, 6H), 3.40 (s, 3H), 3.35 (s, 3H), 2.37–2.31 (m, 1H), 2.04–1.92 (m, 3H), 1.47–1.39 (m, 1H), 1.41 (s, 3H), 1.36 (s, 3H), 1.05 (d, $J=6.8$ Hz, 3H), 0.95–0.87 (m, 2H), 0.02 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 109.4, 98.3, 96.6, 96.4, 83.9, 83.7, 80.1, 78.8, 74.2, 72.9, 68.1, 66.2, 66.0, 56.3, 55.3, 37.4, 31.8, 31.6, 27.0, 25.4, 18.3, 16.9, −1.3 (3C).

2.1.15. Hydrogenation of 15 in the presence of potassium hydride. To a slurry of potassium hydride (3.9 mg of 30% in oil, 0.029 mmol) in deoxygenated THF (0.50 mL) was added a solution of **15** (15 mg, 0.028 mmol) in the same solvent (0.50 mL). The contents of the vial were stirred for 10 min before a solution of [Rh(NBD)(DIPHOS-4)]BF_4 (4 mg, 20 mol%) in deoxygenated THF (0.5 mL) was quickly introduced. The vial was placed in a stainless steel reactor, flushed with argon, and pressurized to 800–900 psi of hydrogen. After overnight stirring (17 h), the pressure was released and the reaction mixture was subjected directly to chromatography on silica gel (elution with 2:1 hexanes–ethyl acetate) to afford **21** (8 mg, 53%), starting material **15** (1.5 mg, 10%) and small amount of **20**.

For **21**. ^{1}H NMR (300 MHz, C_6D_6) δ 4.81 (d, $J=3.1$ Hz, 1H), 4.80 (d, $J=6.6$ Hz, 1H), 4.80–4.68 (m, 2H), 4.54 (d, $J=6.6$ Hz, 1H), 4.54–4.52 (m, 1H), 4.52 (d, $J=2.0$ Hz, 1H), 4.40–4.31 (m, 2H), 4.20–4.15 (m, 1H), 4.08–4.02 (m, 2H), 3.85 (dd, $J=3.3$, 8.2 Hz, 1H), 3.78–3.66 (m, 2H), 3.65–3.50 (m, 4H), 3.26 (s, 3H), 3.20 (s, 3H), 2.33–1.87 (m, 3H), 1.83 (br s, 1H), 1.54–1.31 (m, 1H), 1.38 (s, 3H), 1.24 (s, 3H), 1.03–0.93 (m, 5H), 0.01 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6) δ 109.3, 97.3, 97.2, 85.2, 83.8, 79.5, 78.9, 74.2, 71.8, 68.4, 67.1, 66.0, 56.3, 55.5, 45.7, 35.5, 32.2, 32.0, 27.5, 26.1, 18.4, 17.7, −0.9 (3C).

2.1.16. Hydrogenation of 14 in the presence of sodium hydride. To a slurry of sodium hydride (3.9 mg of 60% in oil, 0.098 mmol, 1.05 equiv.) in deoxygenated THF (0.50 mL) was added a solution of **14** (50 mg, 0.093 mmol) in the same solvent (0.50 mL). The contents of the vial were stirred for 10 min before a solution of [Rh(NBD)(DIPHOS-4)]BF_4 (13.5 mg, 20 mol%) in deoxygenated THF (1.5 mL) was quickly introduced. The vial was placed in a stainless steel reactor, flushed with argon, and pressurized to 800–900 psi of hydrogen. After 3 days of stirring, the pressure was released and the reaction mixture was subjected directly to chromatography on silica gel (elution with 2:1 hexane/ethyl acetate) to afford **18** as a colorless oil (34 mg, 68%) and recovered **14** (10 mg, 20%).

For **18**. IR (CH_2Cl_2, cm^{-1}) 3450, 1370, 1249; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.87 (d, $J=7.0$ Hz, 1H), 4.78 (d, $J=7.0$ Hz, 1H), 4.74 (d, $J=6.7$ Hz, 1H), 4.64 (d, $J=6.7$ Hz, 1H), 4.62–4.58 (m, 2H), 4.50 (m, 1H), 4.45–4.41 (m, 1H), 4.26–4.22 (m, 1H), 4.14–4.11 (m, 1H), 3.93 (dd, $J=5.0$, 8.5 Hz, 1H), 3.84 (dd, $J=3.5$, 8.5 Hz, 1H), 3.67–3.46 (m, 6H), 3.40 (s, 3H), 3.35 (s, 3H), 2.22 (br s, 1H), 2.09–2.04 (m, 2H), 1.97–1.94 (m, 1H), 1.87–1.83 (m, 1H), 1.45–1.35 (m, 1H), 1.41 (s, 3H), 1.35 (s, 3H), 1.02 (d, $J=6.8$ Hz, 3H), 0.95–0.87 (m, 2H), 0.01 (s, 9H); ^{13}C NMR (12 MHz, $CDCl_3$) δ 109.4, 98.3, 96.6, 96.4, 83.9, 83.7, 80.1, 78.8, 74.2, 72.9, 68.1, 66.2, 66.0, 56.3, 55.3, 37.4, 31.8, 31.6, 27.0, 25.4, 18.3, 16.9, −1.3 (3C); ES MS HR *m/z* $(M+Na)^+$ calcd 561.3071, obsd 561.3080; $[\alpha]_D^{22}=+14.5$ (*c* 0.20, $CHCl_3$).

2.1.17. Formation of PMB ether 22. A suspension of **21** (0.007 g, 0.013 mmol) and NaH (60% in mineral oil, 0.010 g, 0.26 mmol) in 1 mL of DMF was stirred at rt for 1 h before *p*-methoxybenzyl bromide (0.013 g, 0.065 mmol) was added. The reaction mixture was stirred at rt for 4 h and quenched with saturated $NaHCO_3$ solution (3 mL). The solution was extracted with ether/petroleum ether (1/1, 50 mL), washed with brine, dried and freed of solvent. The residue was purified by flash chromatography (silica gel, hexane–EtOAc 4:1) to furnish **22** (0.008 g, 93%) as a yellowish oil; IR (neat, cm^{-1}) 1613, 1514, 1458; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28–7.26 (m, 2H), 6.88–6.85 (m, 2H), 4.91 (d, $J=7.0$ Hz, 1H), 4.76 (d, $J=7.0$ Hz, 1H), 4.73 (d, $J=6.8$ Hz, 1H), 4.64 (d, $J=6.8$ Hz, 1H), 4.60–4.55 (m, 3H), 4.48 (d, $J=11.5$ Hz, 1H), 4.37–4.31 (m, 2H), 4.13 (t, $J=5.4$ Hz, 1H), 4.06 (dd, $J=6.3$, 8.4 Hz, 1H), 3.96–3.91 (m, 2H), 3.80 (s, 3H), 3.67–3.50 (m, 5H), 3.43 (t, $J=5.4$ Hz, 1H), 3.38 (s, 3H), 3.33 (s, 3H), 2.22 (dd, $J=5.9$, 13.1 Hz, 1H), 2.99–1.94 (m, 1H), 1.89–1.82 (m, 2H), 1.44–1.35 (m, 1H), 1.39 (s, 3H), 1.37 (s, 3H), 1.00 (d, $J=6.8$ Hz, 3H), 0.91 (dd, $J=7.6$, 9.5 Hz, 2H), 0.01 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 130.6, 129.0 (2C), 113.7 (2C), 108.6, 98.3, 96.4, 96.2, 84.1, 83.2, 80.0, 78.9, 78.8, 73.9, 71.1, 67.2, 66.1, 65.9, 56.2, 55.3, 55.1, 34.5, 31.7, 31.5, 26.7, 25.7, 18.2, 16.7, −1.4 (3C); ES HRMS *m/z* $(M+Na)^+$ calcd 681.3641, obsd 681.3662; $[\alpha]_D^{22}=-11.6$ (*c* 0.26, $CHCl_3$).

2.1.18. Selective deprotection of 22. A solution of **22** (0.008 g, 0.012 mmol) in 2 mL of AcOH–H_2O (2:1) was stirred at rt for 4.5 h. Saturated $NaHCO_3$ solution (10 mL) was carefully introduced, the solution was extracted with ether (50 mL), and the combined organic phases were washed with saturated $NaHCO_3$ solution and brine, dried, and freed of solvent. The residue was purified by flash chromatography (silica gel, hexane–EtOAc 1:2) to afford the diol (0.008 g, quant. yield) as a colorless oil; IR (neat,

cm^{-1}) 3321, 1516, 1249; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26–7.24 (m, 2H), 6.90–6.87 (m, 2H), 4.90 (d, $J=6.9$ Hz, 1H), 4.77 (d, $J=6.9$ Hz, 1H), 4.74 (d, $J=6.7$ Hz, 1H), 4.63 (dd, $J=6.6$, 17.8 Hz, 1H), 4.59 (d, $J=6.5$ Hz, 1H), 4.41–4.36 (m, 2H), 4.30 (t, $J=3.9$ Hz, 1H), 3.95–3.90 (m, 2H), 3.81 (s, 3H), 3.79–3.77 (m, 1H), 3.69–3.59 (m, 5H), 3.56–3.51 (m, 1H), 3.46 (t, $J=5.3$ Hz, 1H), 3.39 (s, 3H), 3.35 (s, 3H), 2.30–2.26 (m, 1H), 1.99–1.89 (m, 2H), 1.88–1.83 (m, 1H), 1.45–1.39 (m, 1H), 1.01 (d, $J=6.8$ Hz, 3H), 0.94–0.91 (m, 2H), 0.02 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.9, 130.0, 129.7 (2C), 114.5 (2C), 98.7, 96.9, 96.6, 84.3, 81.9, 80.0, 79.7, 79.1, 71.4, 70.6, 66.5, 66.4, 65.3, 56.7, 55.7, 55.6, 34.2, 32.1, 31.9, 18.6, 17.1, −1.0 (3C); ES HRMS *m/z* $(M+Na)^+$ calcd 641.3328, obsd 641.3356; $[\alpha]_D^{22}=-27.5$ (*c* 0.12, $CHCl_3$).

2.1.19. Aldehyde 23. An excess amount (ca. 20 mg) of silica gel-supported $NaIO_4$ was added to a solution of the above diol (0.008 g, 0.013 mmol) in 1 mL of CH_2Cl_2. The suspension was stirred at rt for 1 h. The solid was removed by filtration and the solvent was removed under vacuum to furnish **23** (0.008 g, quant.) as a yellowish oil; IR (neat, cm^{-1}): 1732, 1613, 1586; ^1H NMR (300 MHz, C_6D_6), δ 9.80 (d, $J=1.9$ Hz, 1H), 7.14–7.09 (m, 2H), 6.79–6.74 (m, 2H), 4.88 (s, 2H), 4.83–4.77 (m, 2H), 4.59 (d, $J=6.5$ Hz, 1H), 4.51 (dd, $J=6.4$, 9.0 Hz, 2H), 4.29–4.22 (m, 3H), 4.15 (d, $J=11.2$ Hz, 1H), 3.79–3.67 (m, 2H), 3.64–3.50 (m, 3H), 3.29 (s, 3H), 3.23 (s, 3H), 3.20 (s, 3H), 2.24–2.19 (m, 1H), 2.13–1.99 (m, 2H), 1.90–1.82 (m, 1H), 1.56–1.48 (m, 1H), 1.15 (d, $J=6.8$ Hz, 3H), 1.00–0.89 (m, 3H), 0.01 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6), δ 201.3, 160.2, 130.3, 129.6 (2C), 114.5 (2C), 98.7, 97.0, 96.9, 86.8, 84.6, 82.1, 81.0, 80.7, 71.7, 66.4, 66.2, 56.2, 55.2, 55.0, 35.0, 32.3, 32.2, 18.6, 17.8, −1.0 (3C); ESHR MS *m/z* $(M+Na)^+$ calcd 609.3065, obsd 609.3022; $[\alpha]_D^{22}=-21.6$ (*c* 0.19, $CHCl_3$).

2.1.20. Chain extension of 23. Diethyl(2-oxopropyl)phosphonate (**24**, 0.095 mL, 0.543 mmol) was added dropwise to a suspension of NaH (60% in mineral oil, 0.0217 g, 0.543 mmol) in 5 mL of THF. The mixture was stirred at rt for 15 min before being cooled to 0 °C. A solution of **23** (0.063 g, 0.109 mmol) in 2.5 mL of THF was added. The reaction was complete in 15 min at 0 °C. Saturated NH_4Cl solution was added, the solution was extracted with ether, and the combined organic phases were washed with brine, dried, and evaporated. The residue was purified by flash chromatography (silica gel, hexane–EtOAc 2:1) to afford **25** (0.058 g, 86%) as a colorless oil; IR (neat, cm^{-1}) 1698, 1633, 1614; ^1H NMR (300 MHz, $CDCl_3$) δ 7.21–7.17 (m, 2H), 6.88–6.78 (m, 3H), 6.25 (dd, $J=1.4$, 16.1 Hz, 1H), 4.89 (d, $J=6.9$ Hz, 1H), 4.79 (d, $J=6.9$ Hz, 1H), 4.75 (d, $J=6.6$ Hz, 1H), 4.65 (d, $J=6.6$ Hz, 1H), 4.62–4.57 (m, 3H), 4.54 (d, $J=11.7$ Hz, 1H), 4.50–4.43 (m, 1H), 4.36 (d, $J=11.7$ Hz, 1H), 4.21–4.17 (m, 1H), 3.80 (s, 3H), 3.69–3.49 (m, 6H), 3.39 (s, 3H), 3.34 (s, 3H), 2.27 (s, 3H), 2.24–2.19 (m, 1H), 2.09–1.97 (m, 2H), 1.87–1.81 (m, 1H), 1.44–1.42 (m, 1H), 1.04 (d, $J=6.8$ Hz, 3H), 0.95–0.89 (m, 2H), 0.01 (s, 9H); ^{13}C NMR (75M Hz, $CDCl_3$) δ 198.5, 143.9, 131.1, 130.0, 129.2 (2C), 114.0 (2C), 96.6, 96.5, 84.2, 81.6, 80.7, 80.4, 78.5, 71.4, 66.2, 66.1, 56.4, 55.4, 55.3, 34.6, 31.7, 31.5, 29.8, 27.2, 18.3, 17.1, −1.3 (3C); ES HRMS *m/z* $(M+Na)^+$ calcd 649.3378, obsd 649.3368; $[\alpha]_D^{22}=+3.6$ (*c* 0.11, $CHCl_3$).

2.1.21. Hydroxy ketone 2. To a solution of **25** (0.058 g, 0.092 mmol) in 5.7 mL of CH_2Cl_2/H_2O (18:1) was added DDQ (0.031 g, 0.139 mmol). The reaction mixture was stirred at rt for 1.5 h, quenched with saturated $NaHCO_3$ solution, and extracted with EtOAc. The combined organic phases were washed with brine, dried, and freed of solvent. The residue was purified by flash chromatography (silica gel, hexane–EtOAc 1.5:1) to furnish **2** (0.046 g, 97%) as a colorless oil; IR (CH_2Cl_2, cm^{-1}) 3438, 1677, 1250; ^1H NMR (300 MHz, $CDCl_3$) δ 6.78 (dd, $J=4.8$, 16.0 Hz, 1H), 6.47 (dd, $J=1.6$, 16.0 Hz, 1H), 4.87 (d, $J=6.9$ Hz, 1H), 4.79 (d, $J=6.9$ Hz, 1H), 4.75 (d, $J=6.6$ Hz, 1H), 4.64 (d, $J=6.6$ Hz, 1H), 4.62–4.57 (m, 3H), 4.55–4.48 (m, 1H), 4.45–4.43 (m, 1H), 3.69–3.49 (m, 6H), 3.40 (s, 3H), 3.35 (s, 3H), 2.28 (s, 3H), 2.27–2.11 (m, 2H), 2.02–1.97 (m, 1H), 1.87–1.75 (m, 2H), 1.47–1.25 (m, 1H), 1.04 (d, $J=6.8$ Hz, 3H), 0.95–0.89 (m, 2H), 0.01 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.3, 142.5, 131.9, 98.4, 96.6, 96.5, 84.1, 82.4, 80.4, 78.2, 74.2, 66.2, 66.1, 56.3, 55.3, 37.9, 31.7, 31.4, 27.6, 18.3, 17.0, −1.3 (3C); ES HRMS *m/z* $(M+Na)^+$ calcd 529.2803, obsd 529.2791; $[\alpha]_D^{22}=-2.4$ (*c* 0.17, $CHCl_3$).

Acknowledgements

This research was financed in part by unrestricted grants from the Eli Lilly Company and Aventis Pharmaceuticals, Inc.

References and notes

1. Yasumoto, T.; Oshima, Y.; Yamaguchi, M. *Bull. Jpn. Soc. Sci. Fish.* **1978**, *44*, 1249.
2. (a) Yasumoto, T.; Oshima, Y.; Sugawara, W.; Fukuyo, Y.; Oguri, H.; Igarashi, T.; Fujita, N. *Bull. Jpn. Soc. Sci. Fish.* **1980**, *46*, 1405. (b) Kat, M. Anderson, D. M., White, A. W., Baden, D. G., Eds.; *Toxic Dinoflagellate Blooms*. Elsevier: Amsterdam; 1985. p. 215. (c) Kumagai, M.; Yanagi, T.; Murata, M.; Yasumoto, T.; Kat, M.; Lassus, P.; Rodriguez- Vazquez, J. A. *Agric. Biol. Chem.* **1986**, *50*, 2853. (d) Hu, T.; Doyle, J.; Jackson, D.; Marr, J.; Nixon, E.; Pleasance, S.; Quilliam, M. A.; Walter, J. A.; Wright, J. L. C. *J. Chem. Soc., Chem. Commun.*; 1992, 39. (e) Boni, L.; Poletti, A.; Popei, M. Smayda, T. J., Shimizu, Y., Eds.; *Toxic Phytoplankton Blooms in the Sea*. Elsevier: Amsterdam; 1993. p. 475. (f) Quilliam, M. A.; Gilgan, M. W.; Pleasance, S.; Defreitas, A. S. W.; Douglas, D.; Fritz, L.; Hu, T.; Marr, J. C.; Smyth, C.; Wright, J. L. C. Smayda, T. J., Shimizu, Y., Eds.; *Toxic Phytoplankton Blooms in the Sea*. Elsevier: Amsterdam; 1993. p. 547. (g) Draisci, R.; Lucentini, L.; Giannetti, L.; Boria, P.; Poletti, R. *Toxicon* **1996**, *34*, 923.
3. Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897.
4. (a) Yasumoto, T.; Murata, M.; Oshima, Y.; Sano, M.; Matsumoto, G. K.; Clardy, J. *Tetrahedron* **1985**, *41*, 1019. (b) Murata, M.; Sano, M.; Iwashita, T.; Naoki, H.; Yasumoto, T. *Agric. Biol. Chem.* **1986**, *50*, 2693. (c) Yasumoto, T.; Murata, M.; Lee, J.-S.; Torigoe, K.; Natori, S., Hashimoto, K., Ueno, Y., Eds.; *Bioactive Molecules: Mycotoxins and*

Phycotoxins; Vol. 88. Elsevier: Amsterdam; 1989. p. 375. (d) Sasaki, K.; Wright, J. L. C.; Yasumoto, T. *J. Org. Chem.* **1998**, *63*, 2475. (e) Daiguji, M.; Satake, M.; James, K. J.; Bishop, A.; Mackenzie, L.; Naoki, H.; Yasumoto, T. *Chem. Lett.*; 1998, 653.

5. (a) Ishige, M.; Satoh, N.; Yasumoto, T. *Reps. Hokkaido Inst. Health* **1988**, *38*, 15. (b) Zhou, Z.-H.; Komiyama, M. K.; Terao, K.; Shimada, Y. *Natural Toxins* **1994**, *2*, 132.
6. Jung, J. H.; Sim, C. J.; Lee, C.-O. *J. Nat. Prod.* **1995**, *58*, 1722.
7. Spector, I.; Braet, F.; Shochet, N. R.; Bubb, M. R. *Microscop. Res. Tech.* **1999**, *47*, 18.
8. Awakura, D.; Fujiwara, K.; Murai, A. *Synlett* **2000**, 1733.
9. Micalizio, G. C.; Roush, W. R. *Org. Lett.* **2001**, *3*, 1949.
10. Amano, S.; Fujiwara, K.; Murai, A. *Synlett* **1997**, 1300.
11. Paquette, L. A.; Peng, X.; Bondar, D. *Org. Lett.* **2002**, *4*, 937.
12. (a) Evans, D. A.; Rajapakse, H. A.; Stenkamp, D. *Angew. Chem. Int. Ed.* **2002**, *41*, 4569. (b) Evans, D. A.; Rajapakse, H. A.; Chin, A.; Stenkamp, D. *Angew. Chem. Int. Ed.* **2002**, *41*, 4573.
13. (a) Raimundo, B. C.; Heathcock, C. H. *Synlett* **1995**, 1213. (b) Yang, J.; Cohn, S. T.; Romo, D. *Org. Lett.* **2000**, *2*, 763. (c) Walker, M. A.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 5747. (d) Danda, H.; Hansen, M. M.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 173.
14. (a) Gage, J. R.; Evans, D. A. *Org. Synth.* **1990**, *68*, 77. (b) Gage, J. R.; Evans, D. A. *Org. Synth.* **1990**, *68*, 83.
15. (a) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099. (b) Inoue, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn* **1980**, *53*, 174.
16. Prashad, M.; Har, D.; Kim, H.-Y.; Repic, O. *Tetrahedron Lett.* **1998**, *39*, 7067.
17. (a) Ghosh, A. K.; McKee, S. P.; Thompson, W. J. *J. Org. Chem.* **1991**, *56*, 6500. (b) Freudenberg, K.; Wolf, A. *Chem. Ber.* **1927**, *60*, 232. (c) Ireland, R. E.; Thaisrivongs, S.; Vanier, N.; Wilcox, C. S. *J. Org. Chem.* **1980**, *45*, 48. (d) Ireland, R. E.; Norbeck, D. W.; Mandel, G. S.; Mandel, N. S. *J. Am. Chem. Soc.* **1985**, *107*, 3285.
18. Parker, K. A.; Su, D.-S. *J. Org. Chem.* **1996**, *61*, 2191.
19. Lipshutz, B. H.; Pegram, J. J. *Tetrahedron Lett.* **1980**, *21*, 3343.
20. (a) For a review, see Brown, J. M. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 190. (b) Smith, M. E. B.; Derrien, N.; Lloyd, M. C.; Taylor, S. J. C.; Chaplin, D. A.; McCague, R. *Tetrahedron Lett.* **2001**, *42*, 1347.
21. (a) Evans, D. A.; Morrissey, M. M. *J. Am. Chem. Soc.* **1984**, *106*, 3866. DIPHOS-4 is 1,4-bis(diphenylphosphino)butane. (b) Brown, J. M.; Naik, R. G. *J. Chem. Soc., Chem. Commun.* **1982**, 348.
22. (a) Crabtree, R. H.; Davis, M. W. *J. Org. Chem.* **1986**, *51*, 2655. (b) Stork, G.; Kahne, D. E. *J. Am.Chem. Soc.* **1983**, *105*, 1072.
23. Thompson, H. W.; McPherson, E. *J. Am. Chem. Soc.* **1974**, *96*, 6232.
24. Zhong, Y.-L.; Shing, T. K. M. *J. Org. Chem.* **1997**, *62*, 2622.
25. Wadsworth, W. S. *Org. React.* **1977**, *25*, 73.
26. Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885.
27. For a prior listing of general experimental conditions, consult Paquette, L. A.; Arbit, R. M.; Funel, J.-A.; Bolshakov, S. *Synthesis* **2002**, 2105.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 60 (2004) 9599–9614

Stereocontrolled synthesis of all eight stereoisomers of the putative anti-androgen cyoctol

Johann Mulzer,* Ulrich Kaselow, Klaus-Dieter Graske, Holger Kühne, Andreas Sieg and Harry J. Martin

Institut für Organische Chemie der Universität Wien, Währinger Strasse 38, A-1090 Wien, Austria

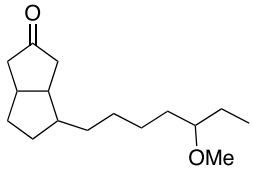
Received 28 April 2004; revised 7 June 2004; accepted 9 June 2004

Available online 21 August 2004

Abstract—All eight stereoisomers (**1**-**4** and enantiomers) of the putative anti-androgen cyoctol have been synthesized along stereochemically unambiguous routes. The biological tests of all isomers indicated that cyoctol is not an anti-androgen, contrary to the patent literature.

1. Introduction and biological background

The carbacyclin derivative cyoctol has been described as an androgen receptor blocker which induces a wide variety of interesting biological effects.



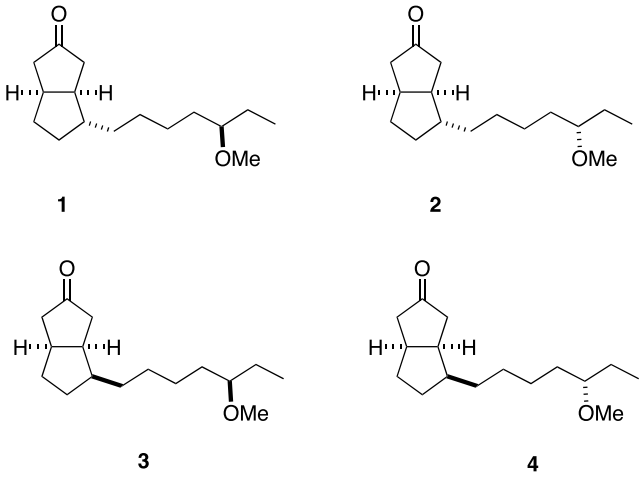
cyoctol

For instance, various forms of alopecia or male pattern baldness are treated by concomitant administration of potassium channel openers and cyoctol.[1] Another interesting phenomenon was that cyoctol was completely metabolized when passing through the skin as no unchanged cyoctol could be detected in ipsilateral plasma samples. This may eliminate the occurrence of adverse systemic effects after dermal application.[2] The effects of cyoctol or 13-*cis*-retinoic acid on binding of ^{3}H-labeled dihydrotestosterone (DHT) by human facial skin fibroblasts in culture were studied at final ratios of either cyoctol or 13-*cis*-retinoic acid to DHT between 0:1 and 104:1. 13-*cis*-Retinoic acid did not inhibit DHT binding even at ratios at 104:1. By contrast, cyoctol inhibited 78–93% of the DHT binding. Apparently, 13-*cis*-retinoic acid does not function as an anti-androgen, whereas cyoctol does.[3] Because cyoctol has in vitro efficacy and very low toxicity in experimental animals, investigations as to its clinical use as a topical anti-androgen for the treatment of acne and other diseases of localized androgen excess are indicated.[4] Fibroblast cultures were established from both frontal and occipital skin from patients with clinical diagnosis of androgenic alopecia undergoing hair transplantation. The DHT receptor activity from fibroblasts from the frontal region was 19.9 compared to 4.5 fmol per mg tissue protein in the occipital region. Cyoctol blocked a mean of 80% of the DHT binding in the fibroblasts derived from the frontal region and only 22% of that from the occipital region.[5] Anti-androgens, like cyoctol, may help in prevention and treatment of keloid and abnormal scar formation.[6] Cyoctol may have a role in anti-fungal therapy.[7] Intra-abdominal adhesions are the most common post-infective and postoperative complications. Cyoctol may be clinically useful in this problem.[8] Skin preparations for aging prevention contain cyoctol and at least one blood-circulation promoter selected from the group comprising γ-aminobutyric acid, vitamin E orotate, diisopropylamine dichloroacetate, hyaluronic acid, elastin, water-soluble collagen, Swertia japonica extract, and ginseng extract. The preparations stimulate skin functions, prevent dryness, and show anti-wrinkling effects in a short period of time.[9] A hair tonic was formulated containing Swertia extract 10.0, cyoctol 0.01, EtOH 60.0, polyoxyethylene hydrogenated castor oil 0.5 glycerin 5.0, perfume 0.1, and water to 100% by weight. The preparation significantly promoted the hair growth in mice and humans.[10] Cyoctol was effective in vitro as an anti-androgen without effect on either the estrogen or the progesterone receptors in carcinomas of the breast,

Keywords: Putative anti-androgen cyoctol; 13-*cis*-Retinoic; Cyoctol.
* Corresponding author. Tel.: +431427752190; fax: +431427752189; e-mail: johann.mulzer@univie.ac.at

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.06.143

ovary, and prostate as well as in malignant melanomas. In a clonogenic assay, cyoctol was more effective against carcinomas of the breast, the kidney, the ovary, and the prostate than conventional anti-neoplastic agents in the majority of tumors tested.[11]



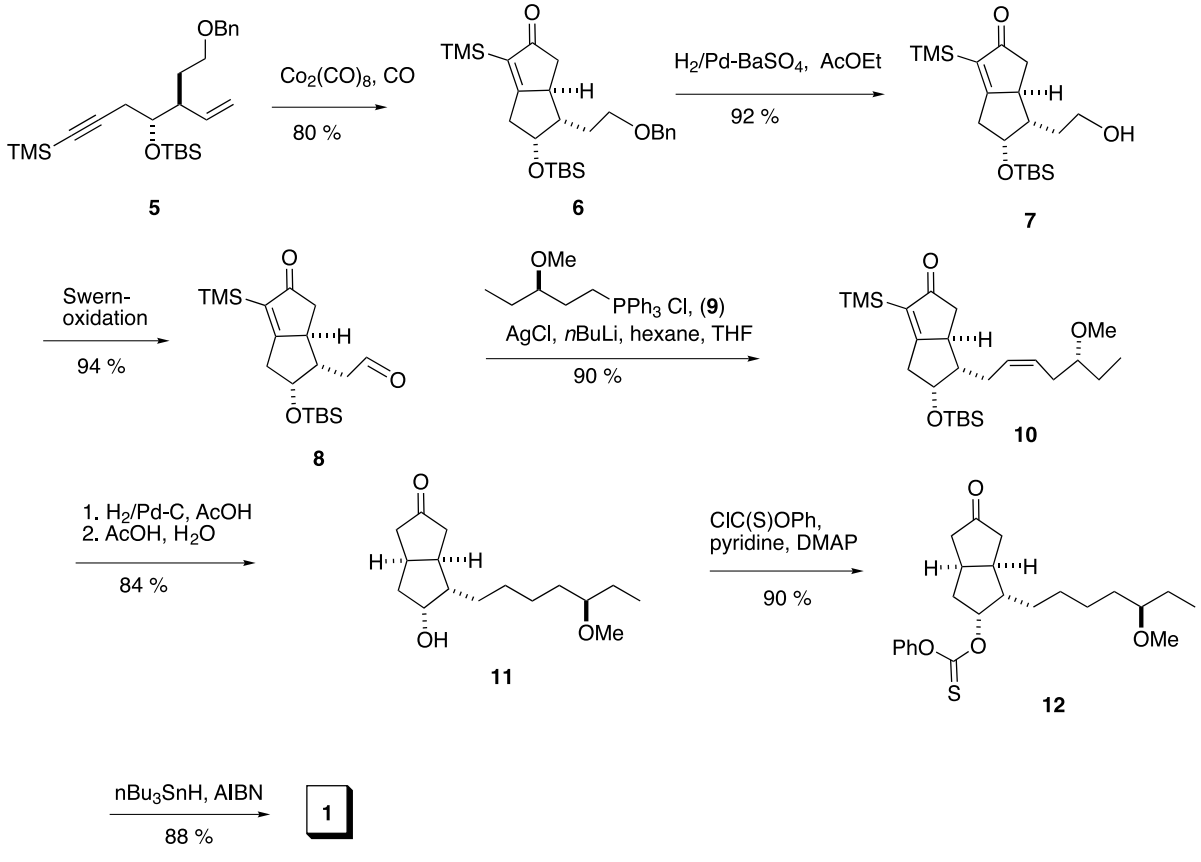
Intrigued by the manifold applicability of cyoctol we were puzzled by the fact that all biological data had been gained from a racemic mixture of diastereomers.[12] So it was unclear whether all stereoisomers or only a limited number thereof was responsible for the biological profile. Thus we decided to develop stereocontrolled approaches to all possible eight stereoisomers (**1**-**4** and enantiomers) of cyoctol and to subject these to conclusive biological testing in order to discriminate the influence of chirality on the biological activity.

1.1. Total synthesis

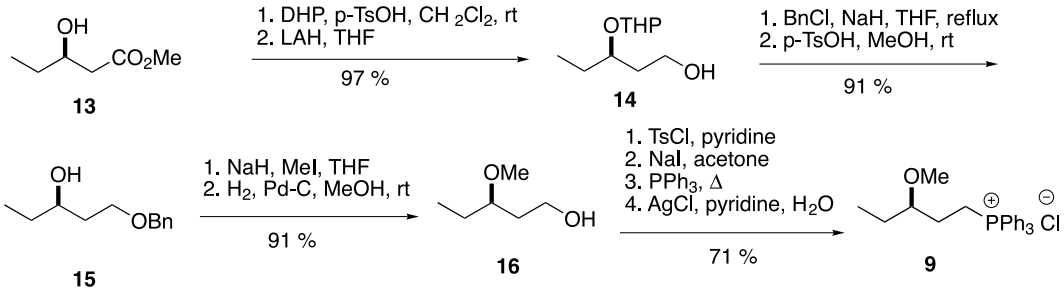
All our approaches are convergent. The carbacyclin core and an appropriately functionalized sidechain were prepared separately with defined stereochemistry and then united by efficient CC-connecting reactions.

In the first synthesis we made use of an intramolecular Pauson–Khand cyclization[13a] to prepare the carbacyclin core to which the sidechain was attached via a Wittig olefination. Specifically (Scheme 1) known enyne **5**[13b] was converted with $Co_2(CO)_8$ into the bicyclic enone **6** under forced Pauson Khand conditions (*n*-octane, 30 bar CO, 105 °C, 5d).[13b] Catalytic hydrogenation under controlled conditions removed the OBn protecting group without touching the endocyclic double bond to deliver alcohol **7** which was oxidized under Swern conditions to aldehyde **8**.

Wittig reaction with phosphonium chloride **9** (prepared along the straightforward route shown in Scheme 2) gave low yields, until silver(I)chloride was added in substoichiometric amounts. With this additive the yield rose to 90% obviously due to a catalytic effect of the silver salt which may act as a mild Lewis acid and facilitate the formation of the oxaphosphetane intermediate. Olefin **10** was formed *Z*-selectively and was converted into hydroxy cyoctol **11** in two steps. Reductive removal of the hydroxyl function via



Scheme 1.



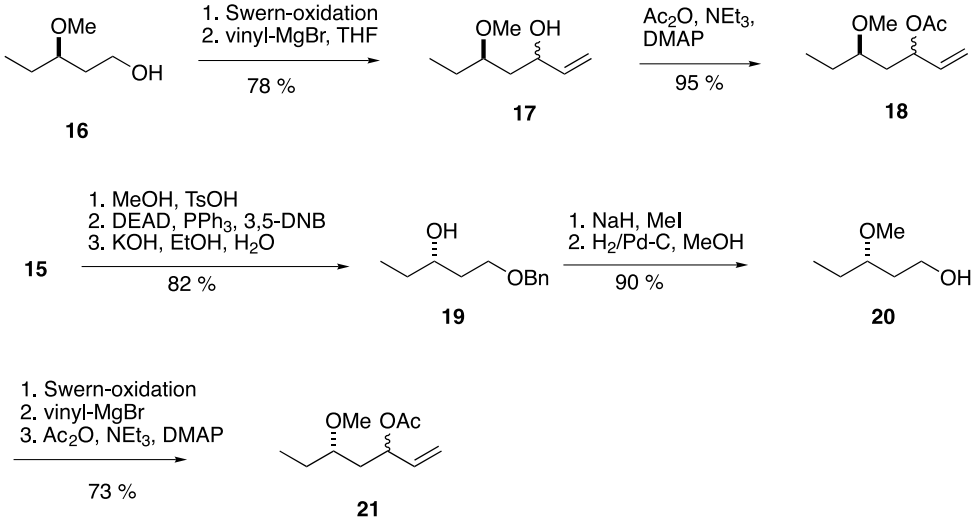
Scheme 2.

the Barton–McCombie protocol[14] furnished cyoctol **1** in stereochemically pure form (HPLC, ^{1}H and ^{13}C NMR) (Scheme 3).

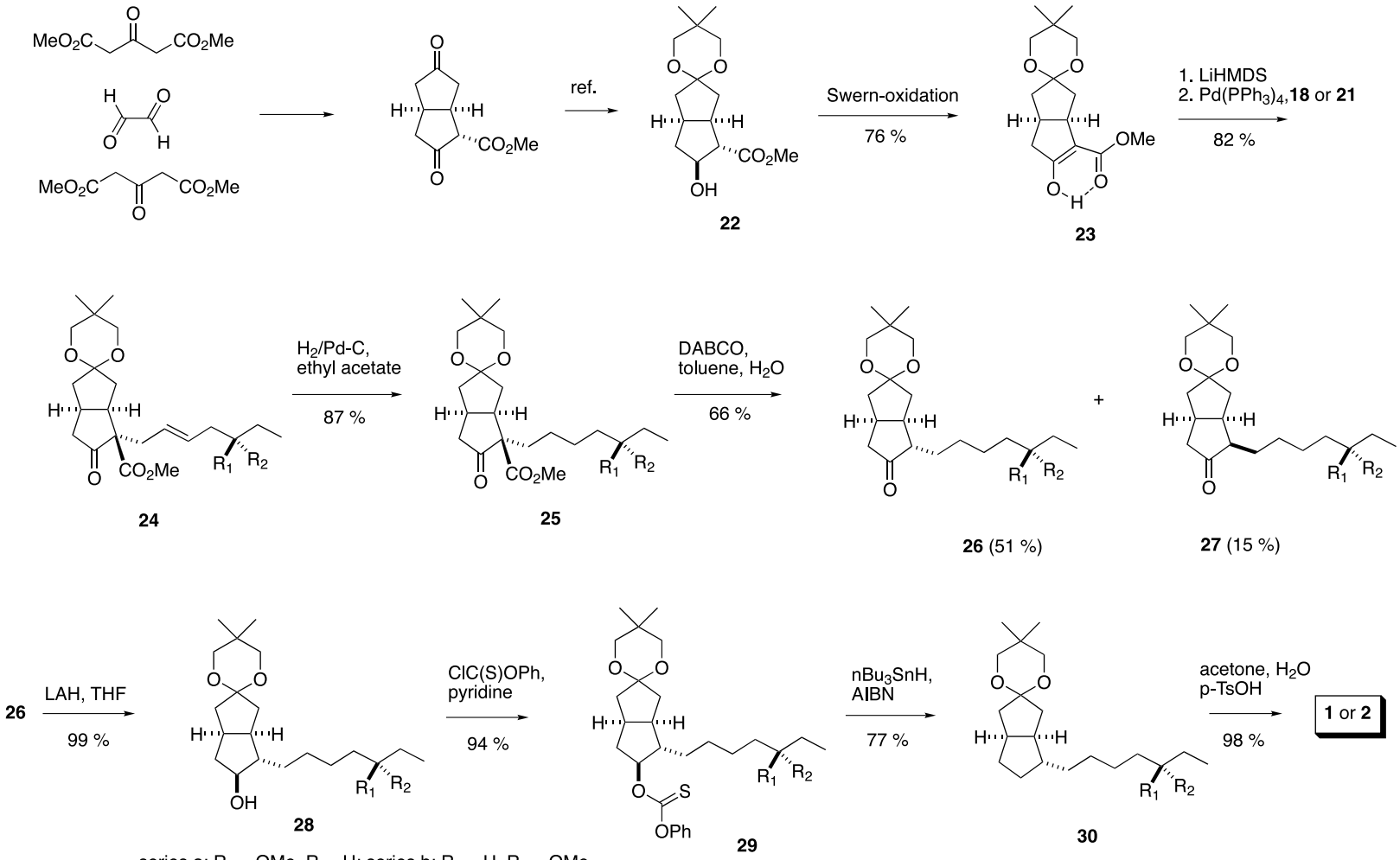
An alternative access to the bicyclic carbacyclin core (Scheme 4) was efficiently provided by the Weiss-reaction of dimethyl acetone dicarboxylate and glyoxal which, after enzymatic kinetic resolution and further transformation led to hydroxyester **22** in diastereo- and enantiopure form. Both enantiomers of **22** were thus available in multigram quantities.[15] Swern oxidation of **22** led to the keto-enol ester **23** which was subjected to a Trost–Tsuji allylation[16] with acetates **18** and **21**, respectively. Acetate **18** was prepared from alcohol **16** as shown in Scheme 3; Mitsunobu inversion[17] of alcohol **15** gave **19** which was transformed into allyl acetate **21** as shown. The allylation exclusively occurred from the less hindered *exo* face to furnish keto-ester **24** in diastereomerically pure form. Catalytic hydrogenation followed by Taber's decarbomethoxylation[18] generated ketones **26** and **27** in a 3:1—ratio, which means that the kinetic protonation of the corresponding enolate is not selective. After longer treatment with base, however, the ratio was shifted to 16:1 most likely due to thermodynamic control. After chromatographic separation diastereomer **26** was converted into cyoctol **1** via Barton–McCombie dehydroxylation and ketal hydrolysis.

To gain access to the *endo*-cyoctol series (Scheme 5) keto ester **24** was reduced with sodium borohydride to give hydroxyester **31** stereoselectively. Again the reagent attack occurred exclusively from the *exo*-face. Saponification of the ester led to hydroxy acid **32** which was treated with DEAD and triphenylphosphine to form olefin **33** via a dehydrative decarboxylation[19] Catalytic hydrogenation generated the *endo*-cyoctol derivative **34** stereoselectively, again via an *exo*-attack of the reagent. After ketal hydrolysis cyoctol **3** and **4** were obtained in stereochemically pure form (Scheme 6).

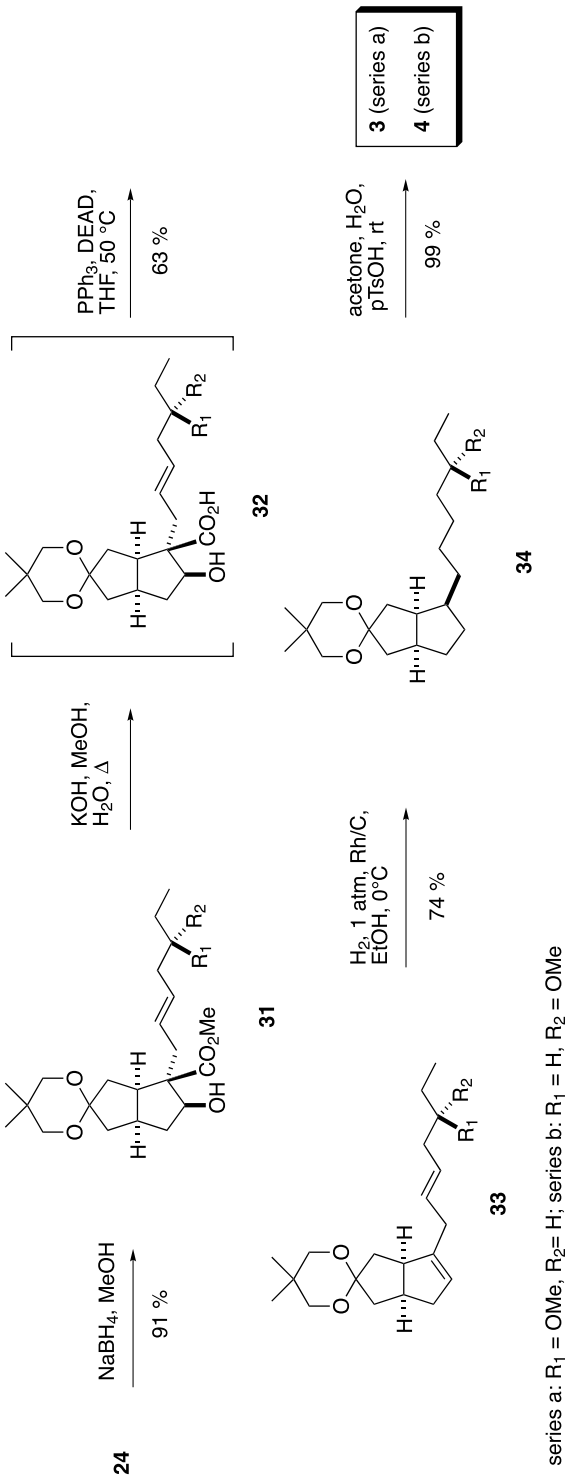
Instead of using the Trost–Tsuji reaction for attaching the cyoctol sidechain a stereocontrolled alternative route was developed (Scheme 7). Hydroxy ester **22** was reduced to the mono alcohol **40** via the mesylate. Alcohol **40** was then converted into the sulfone **41** which was deprotonated and alkylated with bromides (*R*)- or (*S*)-**39** to furnish **42**. Desulfonation with sodium amalgam led to a mixture of **43** and minor amounts of olefin **44**, which were transformed into cyoctols **1** and **2**. Alternatively (Scheme 8) **22** was dehydrated to the enoate **46**. This transformation involves a *syn* elimination of water which was not possible via the mesylate or tosylate. Instead, a Mitsunobu reaction was used to create bromide **45** under inversion of configuration,[20] which immediately underwent an *anti*-1,2-elimination of hydrogen bromide to form **46**. DIBALH-reduction generated the allylic alcohol **47** which was hydrogenated from the *exo* face to form the *endo* diastereomer **48**. Further



Scheme 3.


MeO2C
CO2Me
ref.
Swern-oxidation
76 %
1. LiHMDS
2. Pd(PPh3)4, 18 or 21
82 %
22
23
H2/Pd-C,
ethyl acetate
87 %
DABCO,
toluene, H2O
66 %
24
25
26 (51 %)
27 (15 %)
26
LAH, THF
99 %
ClC(S)OPh,
pyridine
94 %
nBu3SnH,
AIBN
77 %
acetone, H2O
p-TsOH
98 %
1 or 2
28
29
30
series a: R1 = OMe, R2= H; series b: R1 = H, R2 = OMe

Scheme 4.



Scheme 5.

manipulation as in the *exo* series led to cyoctol **4** in stereochemically pure form. The requisite bromide **39** were prepared via an enantioselective catalytic addition of diethyl zinc to aldehyde **36** (Scheme 6). According to a known protocol[21] diamine triflate (*R*,*R*)-**37** was treated with $Ti(OiPr)_4$ to form a titanium complex which was used for activating the diethylzinc. Alcohol **38** was formed with high yield and ee and was then transformed into the bromide (*R*)-**38** by routine operations. Analogously, (*S*)-**39** was prepared using (*S*,*S*)-**37** as the source of chirality.

In conclusion by combining the enantiomers of the *exo*- and *endo*-carbacyclin core with both enantiomers of the side-chain all eight stereoisomers of cyoctol have been prepared via totally stereocontrolled routes in quantities of ca. 1 g per stereoisomer. Catalysis has played a central role in all syntheses. The absolute and relative configurations of the products unambiguously follow from the individual synthetic routes. It can be seen that the ^1H NMR spectra of the *exo* (**1**)- and the *endo* (**3**)-cyoctols are significantly different (Figs. 1 and 2); however, the configuration of the sidechain is not reflected in the spectra. For further support, the crystal structure of sulfone **50** was elucidated via a single crystal diffraction.[22] (Fig. 3).

1.2. Biological tests

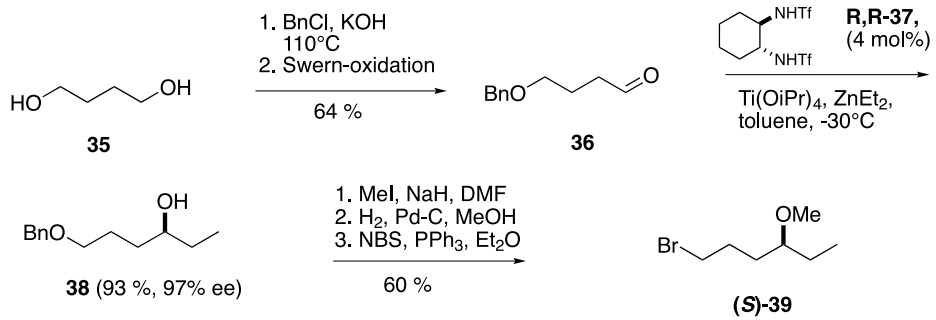
All eight stereoisomers of cyoctol were subjected individually to two different biological tests:

1. a receptor binding test should provide information about the affinity of the compounds to the binding site of the cytosolic androgen receptor of rat prostate
2. the effect of cyoctol as a topical anti-androgen was tested with the aid of the lipogenesis at the gold hamster ear

Ad 1. Androgen receptors was procured from rat prostate cytosol. 3H-Methyltrienolone was used as a reference for the binding affinity in presence of the test compound and the release of radioactivity would indicate a competitive binding of the cyoctol to the receptor. None of the eight stereoisomers showed any significant effect.

Ad 2. A 1% acetone solution of the test compound was applied to one ear of a castrated male Syrian gold hamster and as a reference, acetone was applied to the second ear. After 21 days the animals were killed and from each ear a segment of 8 mm diameter was removed and incubated with ^{14}C labelled acetate for 4 h. Then the tissue was digested proteolytically and the solutions were tested for their radioactivity. The higher the radioactivity the more lipids have been produced, and, hence, the higher the anti-androgenic effect of the substance. Again, none of the cyoctol stereoisomers had any significant effect on the lipogenesis.

These results were very confusing in the light of the patent literatur cited in the introduction. A possible explanation may be seen in the different sources of the androgen receptors applied, so that cyoctol may have a selectivity for certain kinds of receptors. Regarding the lipogenesis test the failure may be due to this particular kind of a biological test



Scheme 6.

and human skin cells may be different. All in all a discrepancy exists between our results and the patent literature, and it appears that additional biological tests will be needed to clarify the situation.

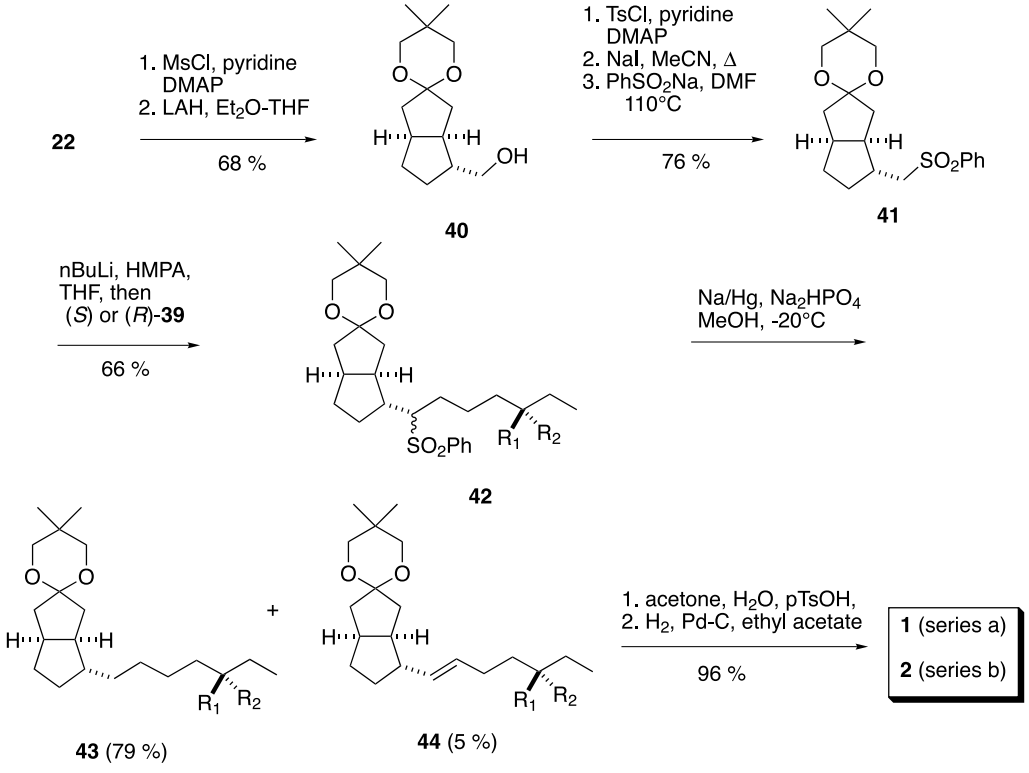
2. Experimental

2.1. General

Fourier transform infrared spectra were calibrated on an internal standard and are reported in wavenumbers (cm^{-1}). ^{1}H and ^{13}C NMR spectra were taken on 250, 400 and 600 MHz NMR machines. Proton chemical shifts are reported in δ, using the residual $CHCl_3$ as internal reference (7.26 ppm). Carbon chemical shifts are reported in δ, using $CDCl_3$ as an internal standard (77.0 ppm). Mass spectra were obtained under electron impact (EI).

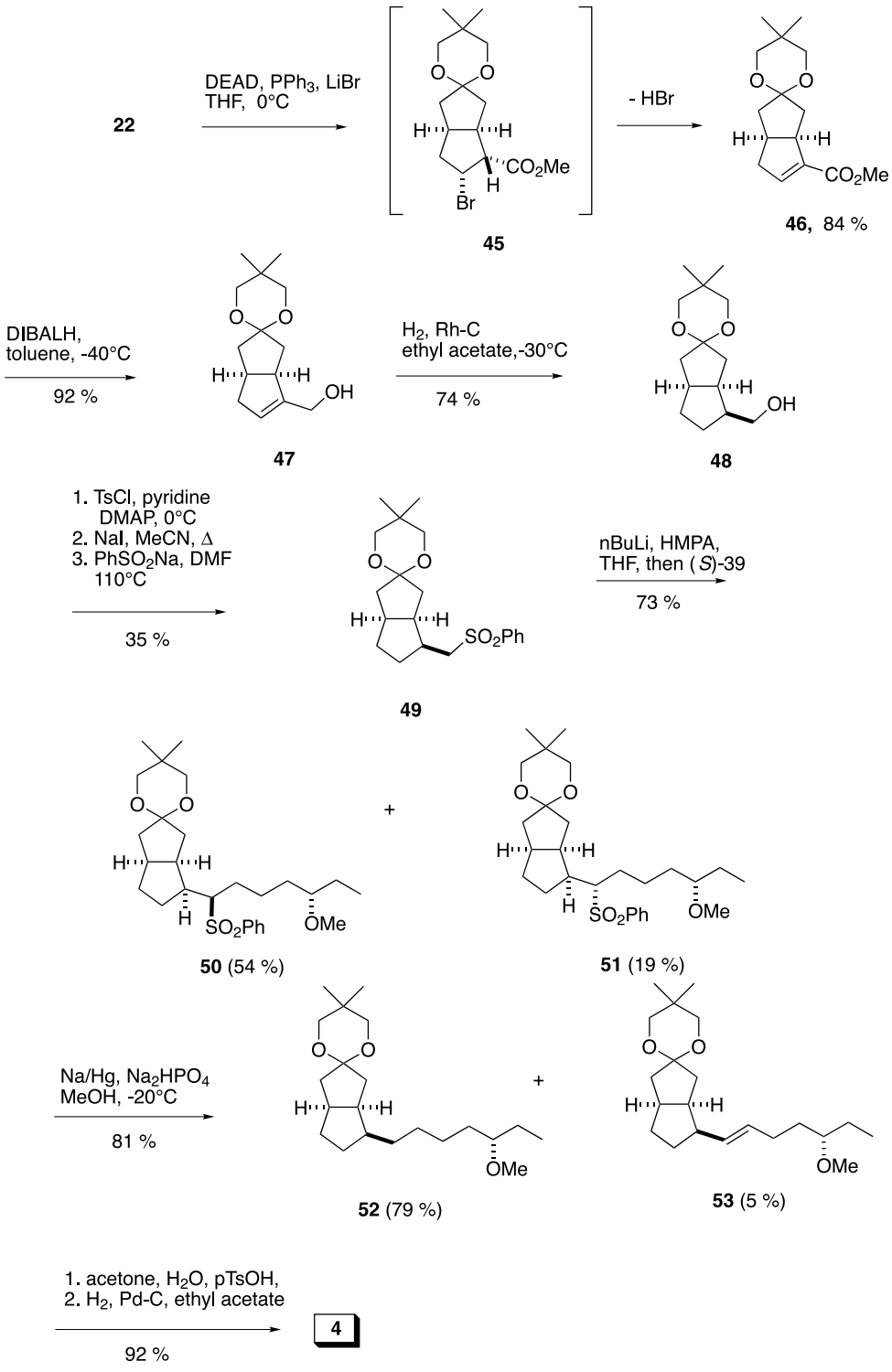
Commercially available chemicals were used without further purification. Where appropriate, reactions were performed in flame-dried glassware under an argon atmosphere.

Ether (Et_2O), tetrahydrofuran (THF) and toluene were freshly distilled from sodium benzophenone ketyl under an argon atmosphere. Dichloromethane (DCM), diisopropylamine (iPr_2NH), triethylamine (Et_3N), and dimethyl sulfoxide (DMSO) were distilled from calcium hydride. Hexanes and ethyl acetate (EtOAc) were distilled to remove higher boiling fractions.



series a: R_1 = OMe, R_2= H; series b: R_1 = H, R_2 = OMe

Scheme 7.



Scheme 8.

Silica gel 60 (230–400 mesh) was used for column chromatography. Precoated aluminium sheets 60 were used for analytical thin layer chromatography (TLC). Compounds were visualised with UV light, *p*-anisaldehyde stain, or phosphomolybdic acid in EtOH.

2.2. Typical procedures (TPs)

TP 1. Swern oxidation. Oxalyl chloride (1 mL, 11 mmol) in dichloromethane (25 mL) was treated with DMSO (1.7 mL, 25 mmol) at −78 °C. The mixture was stirred for 15 min at −78 °C, then the alcohol (10 mmol) in dichlorometane (10 mL) was added and the mixture was stirred at −78 °C for 1 h. NEt_3 (5.5 mL, 40 mmol) was added and the cooling was removed. The completeness of the reaction was checked via TLC. Water (25 mL) was added, the organic layer was separated, washed with brine, dried over magnesium sulfate and concentrated

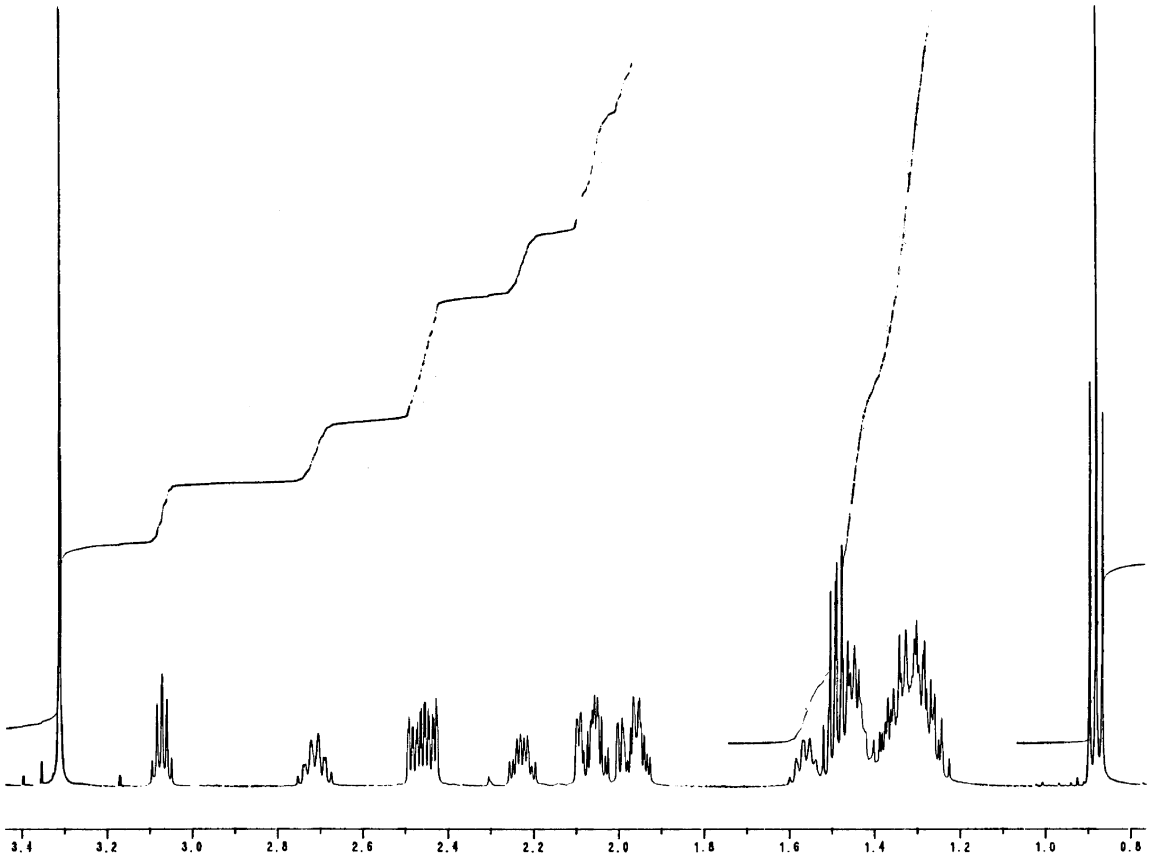


Figure 1. [1]H NMR spectrum of **1** (500 MHz).

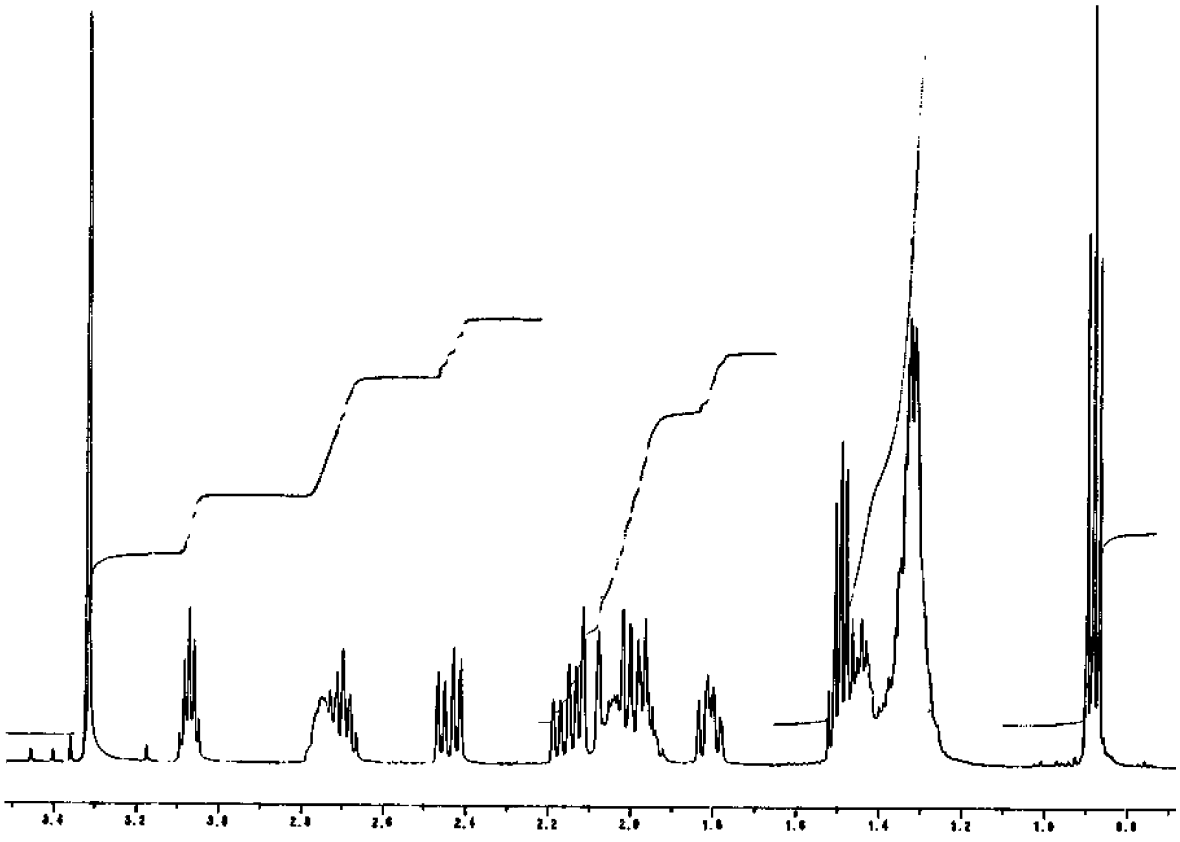


Figure 2. [1]H NMR Spectrum of **3** (500 MHz).

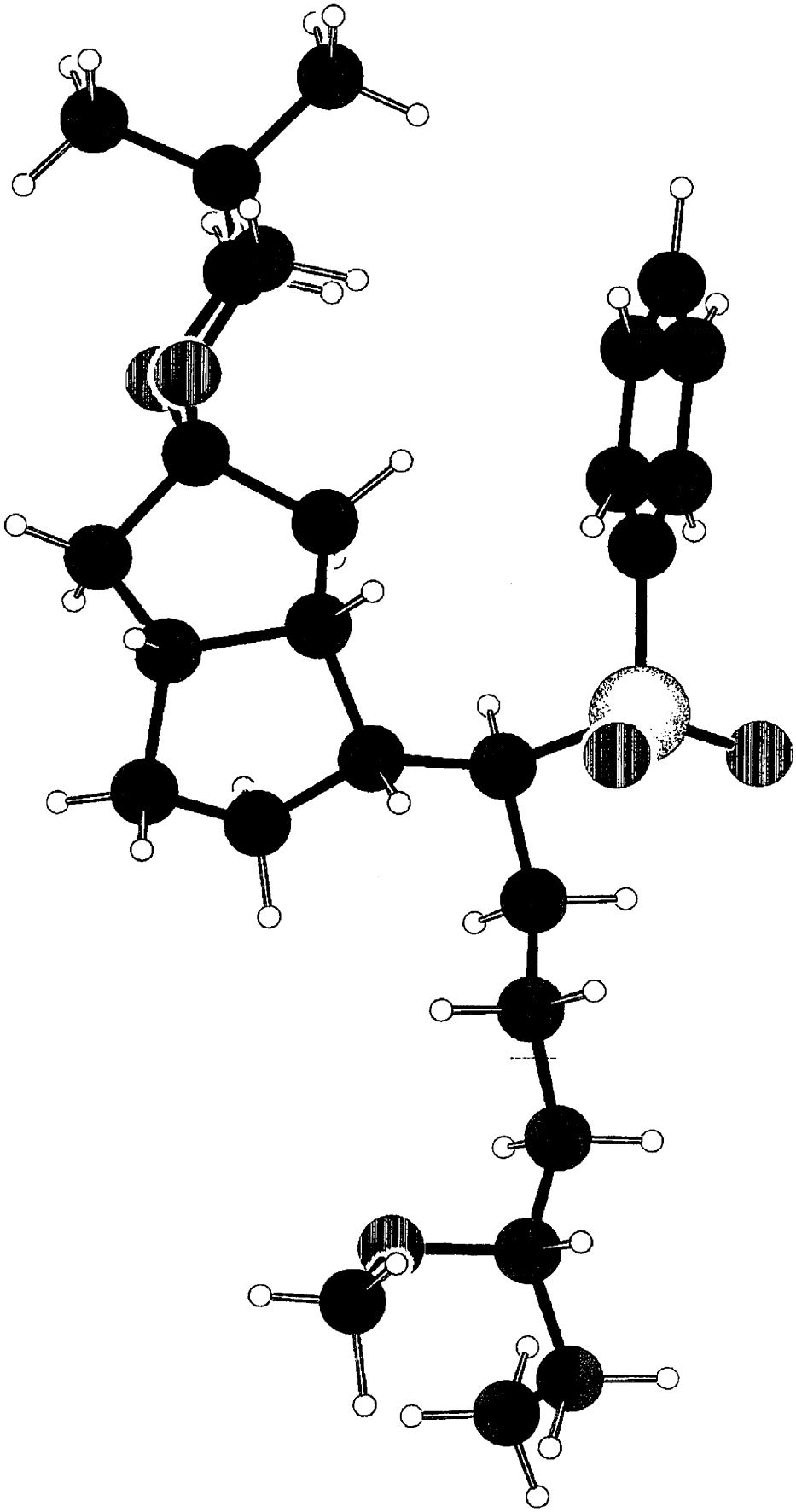


Figure 3. Crystal structure of sulfone **50**.

under reduced pressure. The residue was purified by chromatography.

TP 2. DIBALH reduction of esters. The ester (10 mmol) in diethylether (25 mL) was cooled to −90 °C and treated dropwise with a 1.2 M solution (10 mL, 12 mmol) DIBAL-H in toluene at a temperature of below −85 °C. The mixture was stirred for 2 h at −90 °C. A satd. aqueous solution of tartaric acid (10 mL) was added, the organic layer was separated, washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by chromatography.

2.2.1. Synthesis of 1 by Pauson–Khand-cyclization. Compound **6** (22.94 g, 50.0 mmol) in ethyl acetate (150 mL) was added dropwise to a suuspension of Pd/$BaSO_4$ (10%, 1.50 g) in ethyl acetate (60 mL) and stirred under a hydrogen atmosphere (1 bar) at 0 °C until no more hydrogen was absorbed. The mixture was filtered over silica gel, concentrated under reduced pressure and chromatographed (ethyl acetate/hexanes 1:2) to furnish **7** (16.98 g, 92%) as a colorless oil which crystallized in long needles of mp 77 °C. ^{1}H NMR ($CDCl_3$): δ [ppm]=0.08, 0.09 (two s, 6H), 0.17 (s, 9H), 0.90 (s, 9H), 1.48–1.61 (m, 1H), 1.67 (br. 1H), 1.79 (dq, J=14, 7 Hz, 1H), 1.92 (dq, J=14, 7 Hz, 1H), 2.06 (dd, J=18, 4.5 Hz, 1H), 2.54–2.63 (m, 2H), 2.91 (dd, J=19, 4.5 Hz, 1H), 2.96–3.07 (m, 1H), 3.72 (mc, 2H), 4.42 (t, J=4.5 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ [ppm]=−5.04, −4.47, −1.29, 17.92, 25.74, 31.63, 40.01, 42.58, 47.05, 49.97, 60.77, 75.02, 135.69, 196.23, 214.14 ppm. IR (KBr): ν=2955, 2928, 1691, 1608, 840, 777 cm^{-1}. $[\alpha]_D$=65.6 (c=1.4, $CHCl_3$). Anal. Calcd for $C_{19}H_{36}O_3Si_2$: C, 61.90; H 9.84. Found: C, 62.06, H, 9.86.

2.2.2. Swern-oxidation. Swern-oxidation of **7** (8.40 g, 22.8 mmol) was performed according to TP1. Aldehyde **8** (8.02 g, 96%) was obtained as colorless needles of mp 67 °C. ^{1}H NMR ($CDCl_3$): δ [ppm]=0.03, 0.07 (two s, 6H), 0.18 (s, 9H), 0.89 (s, 9H), 1.83–1.95 (m, 1H), 2.01 (dd, J=17, 4.5 Hz, 1H), 2.52 (dd, J=17, 7 Hz, 1H), 2.57 (d, J=19.5 Hz, 1H), 2.62 (dd, J=18, 5 Hz, 1H), 2.85–3.05 (m, 3H), 4.55 (t, J=5 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ [ppm]=−5.09, −4.54, −1.30, 17.86, 25.72, 39.75, 41.79, 43.04, 44.49, 49.48, 74.26, 136.40, 193.95, 201.02, 212.88. IR (KBr): ν=2935, 1716, 1685, 1602, 840 cm^{-1}. $[\alpha]_D$=53.8 (c=1.4, $CHCl_3$). Anal. Calcd for $C_{19}H_{34}O_3Si_2$: C, 62.24; H 9.35. Found: C, 61.91, H, 9.44.

2.2.3. Wittig reaction of 8 with 9 to form 10. Phosphonium salt **9** (8.0 g, 18.5 mmol) and AgCl (0.85 g, 5.9 mmol) in THF (80 mL) was treated dropwise with *n*-butyllithium (1.6 M in hexane, 14.4 mL) at 26 °C. The mixture was cooled to −78 °C and **8** (2.70 g, 7.36 mmol) in THF (15 mL) was added dropwise and the mixture was stirred for 15 more min. Workup with water and hexanes furnished after chromatography (ethyl acetate/hexanes 1:10) olefin **10** (2.99 g, 90%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ [ppm]=0.08 (s, 6H), 0.17 (s, 9H), 0.89 (t, J=7.5 Hz, 1H), 0.90 (s, 9H), 1.36–1.56 (m, 1H), 2.02 (dd, J=17.5, 4.5 Hz, 1H), 2.17–2.44 (m, 1H), 2.55 (dd, J=17.5, 6.5 Hz, 1H), 2.58 (d, J=19.5 Hz, 1H), 2.91 (dd, J=19.5, 4.5 Hz, 1H), 2.96–3.04 (m, 1H), 3.13 (quint, J=6 Hz, 1H), 3.35 (s, 3H), 4.41 (t, J=4.5 Hz, 1H), 5.40–5.56 (m, 2H). ^{13}C NMR ($CDCl_3$): δ [ppm]=−4.98, −4.44, −1.23, 9.43, 17.99, 25.79, 25.96, 26.85, 30.76, 40.06, 42.98, 50.23, 51.10, 56.56, 75.04, 81.95, 126.67, 129.36, 135.84, 195.66, 213.83. IR (KBr): ν=2926, 1690, 1606, 835, 774 cm^{-1}. $[\alpha]_D$=34.1 (c=1.1, $CHCl_3$). Anal. Calcd for $C_{25}H_{46}O_3Si_2$: C, 66.61; H 10.29. Found: C, 66.50, H, 10.21.

2.2.4. Catalytic hydrogenation of 10. To **10** (2.34 g, 5.19 mmol) in acetic acid (50 mL) was added Pd/C (10%, 120 mg) and the mixture was hydrogenated at 3 bar for 6 h. The mixture was filtered, 5 mL of water was added and the solution was heated to 50 °C for 15 h, concentrated under reduced pressure, diluted with ether, dried (MgSO4) and chromatographed (ethyl acetetae/hexanes 1:10) to give **11** (1.17 g, 84%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ [ppm]=0.89 (t, J=7.5 Hz, 1H), 1.26–1.65 (m, 13H), 1.97 (ddd, J=19.5, 6.5, 1.5 Hz, 1H), 2.02–2.24 (m, 2H), 2.48–2.65 (m, 3H), 2.97 (m, 1H), 3.10 (quint, J=5.5 Hz, 1H), 3.33 (s, 3H), 4.30 (br, 1H). ^{13}C NMR ($CDCl_3$): δ [ppm]=9.26, 25.50, 25.63, 28.28, 28.49, 32.74, 36.33, 42.87, 43.21, 43.35, 44.98, 52.65, 56.23, 74.74, 81.93, 220.60. IR (KBr): ν=2930, 1735, 1090. cm^{-1}. $[\alpha]_D$=−27.5 (c=1.1, $CHCl_3$). Anal. Calcd for $C_{16}H_{28}O_3$: C, 71.60; H 10.52. Found: C, 71.25, H, 10.52.

2.2.5. Barton–McCombie-dehydroxylation of 11 to give 1. *Compound* **11** (700 mg, 2.61 mmol), pyridine (619 mg, 7.83 mmol), and phenoxy-chlorothioformate (585 mg, 3.89 mmol) in methylene chloride (5 mL) were stirred at rt for 16 h. Workup with water and ether furnished after chromatography (ethyl acetate/hexanes 1:10) **12** (953 mg, 90%) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ [ppm]=0.89 (t, J=7.5 Hz, 1H), 1.26–1.56 (m, 10H), 1.69–1.86 (m, 2H), 2.00 (ddd, J=19, 7, 1.5 Hz, 1H), 2.09–2.22 (m, 1H), 2.47–2.68 (m, 4H), 2.96 (mc, 1H), 3.09 (quint, J=5.5 Hz, 1H), 3.33 (s, 3H), 5.75 (t, J=4 Hz, 1H), 7.12, 7.31, 7.44 (three mc, 3H). ^{13}C NMR ($CDCl_3$): δ [ppm]=9.21, 25.36, 25.64, 28.05, 28.38, 32.73, 36.24, 40.03, 43.13, 43.90, 44.72, 51.13, 56.27, 74.74, 81.70, 88.82, 121.72, 126.37, 129.34, 153.10, 194.09, 219.15. IR (KBr): ν=2936, 1737, 1276, 692 cm^{-1}. $[\alpha]_D$=−29.8 (c=1.6, $CHCl_3$). Anal. Calcd for $C_{23}H_{32}O_4S$: C, 68.28; H 7.97. Found: C, 68.27, H, 7.93.

Compound **12** (750 mg, 1.85 mmol) and tributyltin hydride (646 mg, 2.22 mmol) and AIBN (5 mg) in toluene (10 mL) were heated to 90 °C for 2 h. Additional tributyl tinhydride (110 mg, 0.38 mmol) was added and the heating was continued for another 30 min. The mixture was concentrated under reduced pressure and chromatographed (ethyl acetate/hexanes 1:10). The eluate was treated with NaOH (7% in water, 10 mL), washed with water, dried ($MgSO_4$) and chromatographed (ethyl acetate/hexanes 1:10) to give **1** (416 mg, 89%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ [ppm]=0.89 (t, J=7.5 Hz, 1H), 1.18–1.61 (m, 13H), 1.69–1.86 (m, 2H), 1.89–2.13 (m, 4H), 2.16–2.28 (m, 1H), 2.40–2.53 (m, 2H), 2.72 (mc, 1H), 3.08 (quint, J=5.5 Hz, 1H), 3.33 (s, 3H. ^{13}C NMR ($CDCl_3$): δ [ppm]=9.19, 25.43, 25.67, 28.61, 32.87, 35.4, 39.19, 43.85, 44.72, 46.16, 47.19, 56.21, 81.83, 220.64. IR (KBr): ν=2858, 1736, 1093 cm^{-1}. $[\alpha]_D$=−14.8 (c=1.6, $CHCl_3$). MS (80 eV, 40 °C): m/z=252, 223, 73. Anal. Calcd for $C_{16}H_{28}O_2$: C, 76.14; H 11.18. Found: C, 76.06, H, 11.15.

2.3. Trost–Tsuji-reaction for attaching the sidechain. Synthesis of 1, 2, 3, and 4

2.3.1. Synthesis of 23. Enantiomerically (>99% ee) pure carbacyclin **22** (40.45 g, 142 mmol) was oxidized under Swern oxidation (TP) to give, after chromatography (ethyl acetate/hexanes 1:3) ester **23** (60:40 keto-enol mixture) (32.21 g, 87%) as a yellowish oil which solidified to give waxy crystals of mp 60–63 °C. ^{1}H NMR ($CDCl_3$): δ [ppm]=0.94, 0.99 and 0.96, 0.97 (all s, 6H), 1.59–3.0 (m, 8H), 3.28 (m, 0.6H), 3.45, 3.49, 3.51 (all s, 4H), 3.76, 3.80 (all s, 3H), 10.26 (0.4H). ^{13}C NMR ($CDCl_3$): δ [ppm]= 22.34, 22.39, 22.50, 30.04, 33.53, 35.01, 37.68, 38.72, 38.89, 40.59, 41.00, 42.11, 44.63, 50.92, 52.38, 60.62, 71.63, 71.80, 72.29, 72.52, 101.07, 108.69, 109.15, 170.18. IR (KBr): ν=2960, 1665, 1615, 1440, 1325, 1275, 1250, 1110 cm^{-1}. Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H 7.85. Found: C, 62.98, H, 7.62.

2.3.2. Synthesis of 24b. Ester **23** (8.00 g, 28.1 mmol) in THF (50 mL) was added dropwise to a suspension of NaH (60% in mineral oil) (1.24 g, 31 mmol) in THF (50 mL) at room temperature. The mixture was refluxed for 5 min and then added to a mixture of $Pd(PPh_3)_4$ (3.28 g, 2.80 mmol), triphenylphophine (15.2 g, 56.2 mmol) and allylacetate **21** (5.50 g, 29.5 mmol) which had previously been stirred at room temperature for 1 h. The new mixture was stirred at 70 °C for 4 h, concentrated under reduced pressure, diluted with DCM, chromatographed (ethyl acetate/hexanes 1:4) and purified by HPLC (*i*-PrOH/*n*-hexane 2:98) to obtain **24b** (6.90 g, 60%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ [ppm]=0.87 (t, J=7.5 Hz, 1H), 0.95, 0.97 (two s, 6H), 1.36–1.56 (m, 2H), 1.66–1.72 (m, 1H), 1.78 (dd, J=13.8, 4.5 Hz, 1H), 2.18 (t, J=7.5 Hz, 2H), 2.30 (t, J=7.5 Hz, 1H), 2.28–2.34 (m, 2H), 2.50–2.74 (m, 2H), 2.55 (t, 2H), 2.57–2.90 (m, 1H), 3.09 (m, 1H), 3.44, 3.48 (two s, 4H), 3.71 (s, 3H), 5.27–5.42 (m, 1H), 5.43–5.80 (m, 1H). ^{13}C NMR ($CDCl_3$): δ [ppm]=9.28, 22.21, 22.29, 25.73, 29.95, 33.51, 35.95, 36.65, 38.38, 40.80, 44.79, 46.82, 56,.41, 63.41, 71.28, 72.68, 81.62, 108.79, 125.87, 131.65, 171.30, 214.26. IR (film): ν=2960, 1765, 1735, 1330, 1240, 1210, 1120, 1100, 1010 cm^{-1}. $[\alpha]_D$=−33.4 (c=1.4, $CHCl_3$). MS(EI, 80 eV, 40 °C): m/z=408, 393, 377, 349, 335, 128, 73, 41. HRMS Calcd for $C_{23}H_{36}O_6$: m/z=408.2512. Found: 408.2532.

2.3.3. Hydrogenation to 25b. Pd/C (10%, 258 mg) in ethyl acetate (30 mL) was treated with **24b** (2.58 g, 6.32 mmol) and then hydrogenated under normal pressure for 15 h. After filtration over celite the mixture was chromatographed (ethyl acetate/hexanes 1:3) to give **25b** (2.25 g, 87%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ [ppm]=0.86 (t, J= 7.5 Hz, 1H), 0.95, 0.97 (two s, 6H), 1.08–1.56 (m, 8H), 1.54–1.96 (m, 4H), 2.24–2.48,2.58–2.82 (2m, 6H), 2.96–3.10 (m, 1H), 3.30 (m, 3H), 3.44, 3.48 (two s, 4H), 3.72 (s, 3H). ^{13}C NMR ($CDCl_3$): δ [ppm]=9.15, 22.13, 22.19, 24.43, 25.41, 25.60, 29.87, 32.48, 33.56, 36.69, 40.78, 44.51, 48.22, 51.71, 52.20, 63.29, 71.25, 72.53, 81.62, 108.69, 171.32, 213.97. IR (film): ν=2960, 1745, 1730, 1330, 1240, 1205, 1120, 1095, 1010 cm^{-1}. $[\alpha]_D$=−36.1 (c=1.0, $CHCl_3$). Anal. Calcd for $C_{23}H_{38}O_6$: C, 67.29; H 9.33. Found: C, 67.09, H, 9.36.

2.3.4. Decarboxymethylation of 25b to 26b. *Compound* **25b** (2.18 g, 5.30 mmol) in *o*-xylene (10 mL) and water (0.9 mL) was treated with DABCO (6.00 g, 53 mmol) and refluxed for 16 h. The mixture solidified on cooling and was dissolved in toluene and chromatographed to give a 3:1 mixture of **26b** and **27b** (1.27 g, 67%) which was treated with NaOMe (0.077 mmol) in MeOH/THF (1:1, 4 mL) for 17 h at room temperature. The mixture was concentrated under reduced pressure, diluted with ether, extracted with satd. aq. ammonium chloride (10 mL), dried ($MgSO_4$) and purified by HPLC (hexane/*i*-PrOH 99:1) to give **26b** (1.16 g, 62%) and **27b** (70 mg, 4%) as colorless oils.

Compound **26b**. ^{1}H NMR ($CDCl_3$): δ [ppm]=0.88 (t, J= 7.5 Hz, 1H), 0.92, 0.98 (two s, 6H), 1.18–1.58 (m, 9H), 1.60–1.80 (m, 2H), 1.90 (dd, J=13.5, 4.0 Hz, 1H), 2.02–2.15 (m, 1H), 2.16–2.54 (m, 5H), 2.66–2.84 (m 1H), 3.00–3.14 (m, 1H), 3.32 (s, 3H), 3.44, 3.48 (two s, 4H.). ^{13}C NMR ($CDCl_3$): δ [ppm]=9.30, 22.39, 25.37, 25.80, 27.41, 30.01, 30.77, 32.80, 34.78, 41.11, 41.20, 43.64, 43.82, 54.34, 56.31, 71.93, 72.25, 81.94, 109.67, 221.13. IR (film): ν= 2940, 2860, 1730,1150, 1095 cm^{-1}. $[\alpha]_D$=27.4 (c=0.9, $CHCl_3$). Anal. Calcd for $C_{21}H_{36}O_4$: C, 71.55; H 10.29. Found: C, 71.40, H, 10.34.

Compound **b** ^{1}H NMR ($CDCl_3$): δ [ppm]=0.88 (t, J= 7.5 Hz, 1H), 0.96, 0.98 (two s, 6H), 1.10–1.58 (m, 10H), 1.72–1.96 (m, 2H),2.04 (dd, J=18, 7 Hz, 1H); 2.24–2.41 (m, 2H), 2.50–2.77 (m, 2H), 2.80–2.96 (m, 1H), 3.07 (quint., 1H), 3.32 (s, 3H), 3.43 and 3.50 (two s, 4H): 2.24–2.48, 2.58–2.82 (2m, 6H), 2.96–3.10 (m, 1H), 3.30 (m, 3H), 3.44, 3.48 (two s, 4H), 3.72 (s, 3H).

2.3.5. Synthesis of 28b. $LiAlH_4$ (63 mg, 1.7 mmol) in THF (5 mL) at 0 °C was treated dropwise with **26b** (580 mg, 1.65 mmol) in THF (5 mL) for 15 min. The mixture was warmed to room temperature and stirred for additional 2 h. Workup with water and NaOH delivered after chromatography (ethyl acetate/hexanes 1:1) **28b** (581 mg, 99%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ [ppm]=0.88 (t, J= 7.5 Hz, 1H), 0.95, 0.98 (two s, 6H), 1.10–1.88 (m, 15H), 1.96–2.28 (m, 4H), 2.30–2.50 (m, 1H), 3.08 (quint, 1H)), 3.32 (s, 3H), 3.46, 3.47 (two s, 4H.). ^{13}C NMR ($CDCl_3$): δ [ppm]=9.32, 22.47, 22.50, 25.75, 28.14, 30.04, 32.86, 33.61, 36.12, 40.17, 40.75, 41.77, 44.38, 54.38, 56.28, 71.28, 72.25, 79.73, 82.01, 110.40. IR (film): ν=3430, 29940, 1460, 1325, 1110, 1040, 1015 cm^{-1}. Anal. Calcd for $C_{21}H_{38}O_4$: C, 71.15; H 10.80. Found: C, 71.30, H, 10.95.

2.3.6. Synthesis of 29b. *Compound* **28b** (579 mg, 1.6 mmol) in DCM (5 mL) were treated at 0 °C with pyridine (0.4 g, 7.49 mmol) and *O*-phenylchlorothioformate (0.42 g, 2.42 mmol) in DCM (2 mL) at 0 °C. The mixture was stirred at room temp. for 3 h and then subjected to aqueous workup to give, after chromatography (ethyl acetate/hexanes 1:6) **29b** (748 mg, 94%) of a slightly yellow oil.

^{1}H NMR ($CDCl_3$): δ [ppm]=0.91 (t, J=7.5 Hz, 1H), 0.98, 1.00 (two s, 6H), 1.20–1.90 (m, 13H), 1.98–2.36 (m, 4H), 2.40–2.62 (m, 2H), 3.08 (quint, 1H)), 3.32 (s, 3H), 3.48 (s, 4H.), 5.10–5.28 (m, 1H), 7.00–7.16, 7.22–7.32, 7.34–7.48 (m, 5H). ^{13}C NMR ($CDCl_3$): δ [ppm]=9.33, 22.48, 22.50,

25.62, 25.80, 27.90, 30.08, 32.92, 33.28, 36.54, 36.70, 39.93, 40.40, 43.76, 50.55, 56.37, 71.78, 72.40, 81.99, 91.16, 109.94, 121.97, 126.38, 129.42, 153.37, 194.73.

IR (film): ν=2940, 1490, 1470, 1460, 1300, 1100, 1015 cm^{-1}. HRMS Calcd for $C_{21}H_{37}O_3$ ($M-C_7H_5O_2S$): m/z=337.27427. Found: 337.274160.

2.3.7. Synthesis of 2. *Compound* **28b** (1.29 g, 2.63 mmol) was reduced with tributyltin hydide as described for **12** to give **30b** (685 mg, 77%) as a colorless oil. ^1H NMR ($CDCl_3$): δ [ppm]=0.88 (t, J=7.5 Hz, 1H), 0.95, 0.96 (two s, 6H), 1.06–1.68 (m, 15H), 1.76–1.94 (m, 2H), 1.95–2.09 (m, 1H), 2.22 (dd, J=13.5, 8.8 Hz, 2H), 2.36–2.58 (m, 1H), 3.08 (quint, 1H)), 3.32 (s, 3H), 3.44, 3.48 (two s, 4H.). ^{13}C NMR ($CDCl_3$): δ [ppm]=9.32, 22.51, 25.83, 28.77, 30.05, 33.00, 33.84, 35.37, 40.08, 40.27, 47.47, 56.29, 71.63, 72.40, 82.07, 110.56. IR (film): ν=2940, 1460, 1115, 1040, 1015 cm^{-1}. $[\alpha]_D$=−18.9 (c=1.3, $CHCl_3$). Anal. Calcd for $C_{21}H_{38}O_3$: C, 74.51; H 11.31. Found: C, 74.69, H, 11.25. **30b** (650 mg, 1.92 mmol) in water/acetone (v/v 5:95, 130 mL) was stirred with *p*-TsOH (183 mg) at room temperature for 16 h and then neutralized with solid $NaHCO_3$, concentrated under reduced pressure, diluted with water, and extracted with ether. The ether phase was washed with water, dried ($MgSO_4$) and chromatographed (hexanes/ethyl acetate 1:10) to furnish **2** (484 mg, 99%) as a colorless oil. $[\alpha]_D$=−14.4 (c=1.1, $CHCl_3$). The spectral data are within the limits of detection identical with those of **1**.

2.3.8. Synthesis of 31a. Keto ester **24a** (4.90 g, 12.00 mmol) in methanol (80 mL) was treated in portions at −40 °C with solid sodium borohydride (240 mg, 6.2 mmol) and stirred for 2 h. after additional 1 h at room temperature the mixture was concentrated under reduced pressure and diluted with ether (200 mL), washed with water, dried ($MgSO_4$) and chromatographed (hexanes/ethyl acetate 1:1 to give **31a** (4.48 g, 91%) as a colorless oil. ^1H NMR ($CDCl_3$): δ [ppm]=0.87 (t, J=7.5 Hz, 1H), 0.91, 1.00 (two s, 6H), 1.08–1.95 (m, 14H), 2.04–2.18 (m, 1H), 2.23–2.33 (m, 1H), 2.44–2.65(m, 3H), 2.99–3.08 (m, 1H)), 3.30 (s, 3H), 3.44, 3.45, 3.48, 3.50 (4s, 4H.). ^{13}C NMR ($CDCl_3$): δ [ppm]=9.24, 22.35,22.49, 25.37, 25.67, 25.71, 30.60, 32.73, 37.59, 37.93, 38.15, 38.83, 40.04, 48.85, 51.38, 56.34, 61.45, 71.15, 72.89, 79.32, 81.82, 109.06, 176.35. IR (film): ν=2940, 1710, 1115, 1095, 1015 cm^{-1}. MS (EI, 80 eV, 80 °C): m/z=412, 397, 351, 335, 295, 284, 265, 181, 168, 128, 95, 69, 41. $[\alpha]_D$=7.7 (c=1.3, $CHCl_3$). Anal. Calcd for $C_{23}H_{40}O_6$: C, 66.96; H 9.77. Found: C, 66.67, H, 7.75.

2.3.9. Synthesis of 33a. *Compound* **31a** (4.80 g, 11.63 mmol) in methanol/water (v/v 2:1, 75 mL)) was treated with KOH (4.0 g, 7.13 mmol) in water (10 mL) and the mixture was stirred at 100 °C for 20 h, concentrated under reduced pressure and extracted with ether. The aqueous phase was acidified with 2 N HCl to pH 3 and extracted with ether. The ether phase was washed with water, dried ($MgSO_4$) and evaporated to dryness to give **32a** (4.30 g, 95%) as a colorless foam, which was dissolved in THF (250 mL) and treated with triphenylphosphane (2.83 g, 10.8 mmol). Diethyl azodicarboxylate (DEAD, 1.88 g, 10.8 mmol) was added dropwise at 50 °C, until no more carbon dioxide was evolved. The solvent was removed under reduced pressure and the residue was dissolved in ether (170 mL) and pentane (30 mL). The crystalline residue of hydrazo ester and phophine oxide was removed by filtration and the filtrate was chromatographed (hexanes/ethyl acetate) to give olefin **33a** (2.37 g, 61%) as a colorless oil. ^1H NMR ($CDCl_3$): δ [ppm]=0.88 (t, J=7.5 Hz, 1H), 0.96 (s, 6H), 1.28–1.62 (m, 10H), 1.84–2.18 (m, 3H), 2.25–2.42 (m, 2H), 2.48–2.58 (m, 1H), 2.66–2.80 (m, 1H)), 2.92–3.16 (m, 2H), 3.32 (s, 3H), 3.46, 3.51 (2s, 4H., 5.16 (s, 1H). ^{13}C NMR ($CDCl_3$): δ [ppm]=9.27, 22.45, 25.24, 25.80, 27.78, 29.38, 30.03, 32.86, 37.66, 38.04, 38.26, 41.04, 48.97, 56.27, 71.42, 72.49, 81.93, 109.49, 121.16, 146.60. IR (film): ν=3940, 3860, 1115, 1095 cm^{-1}. MS (EI, 80 eV, 40 °C): m/z=336, 218, 189, 176, 160, 147, 128, 105, 91, 79, 69, 55, 41. $[\alpha]_D$=−8.24 (c=1.5, $CHCl_3$). Anal. Calcd for $C_{21}H_{36}O_3$: C, 74.96; H 10.78. Found: C, 74.75, H, 10.87.

2.3.10. Synthesis of 34a. Olefin **33a** (2.25 g, 6.69 mmol) in ethanol (100 mL) was hydrogenated with Rh/C (5%) (113 mg) at 0 °C under normal pressure for 8 h. The mixture was filtered over celite and evaporated under reduced pressure and chromatographed (hexanes/ethyl acetate 10:1) to furnish **34a** (1.69 g, 75%) as a colorless oil. ^1H NMR ($CDCl_3$): δ [ppm]=0.89 (t, J=7.5 Hz, 1H), 0.94 and 0.98 (two s, 6H), 1.12–1.66 (m, 16H), 1.67–1.84 (m, 1H), 2.04 (m, 1H), 2.36–2.60 (m, 3H), 3.07 (m, 1H), 3.32 (s, 3H), 3.46, 3.49 (2s, 4H. ^{13}C NMR ($CDCl_3$): δ [ppm]=9.30, 22.48, 25.70, 25.84, 29.14, 29.54, 30.09, 30.83, 32.26, 33.04, 34.13, 39.05, 40.88, 42.59, 43.37, 56.33, 71.26, 73.06, 82.08, 109.15. IR (film): ν=2940, 1435, 1110, 1095 cm^{-1}. MS (EI, 80 eV, 40 °C): m/z=338, 323, 309, 265, 241, 223, 209, 181, 167, 141, 128, 95, 81, 73, 55, 41. $[\alpha]_D$=−35.2 (c=1.5, $CHCl_3$). Anal. Calcd for $C_{21}H_{38}O_3$: C, 74.51; H 11.31. Found: C, 74.19, H, 11.36.

2.3.11. Synthesis of 3. *Compound* **34a** (1.55 g, 4.58 mmol) in acetone/water (20:1, 250 mL) was treated with *p*-TsOH (220 mg, 1.15 mmol) for 20 h at room temperature. The mixture was neutralized with NaHCO3, concentated under reduced pressure and extracted with ether. The ether phase was washed with brine, dried ($MgSO_4$) and chromatographed (hexanes/ethyl acetate (5:1) to give **3** (1.12 g, 97%) as a slightly yellow oil. ^1H NMR ($CDCl_3$): δ [ppm]=0.89 (t, J=7.5 Hz, 1H), 1.12–1.66 (m, 16H), 1.24–1.55 (m, 12H), 1.78–1.87 (m, 1H), 1.91–2.23 (m, 5H), 2.44 (ddd, J=19, 8, 2 Hz, 1H), 2.6–2.84 (m, 2H), 3.07 (m, 1H),3.32 (s, 3H). ^{13}C NMR ($CDCl_3$): δ [ppm]=9.19, 25.46, 25.72, 28.97, 30.07, 31.60, 31.48, 32.92, 37.68, 39.40, 43.48, 43.58, 45.46, 56.24, 81.90, 220.38. IR (film): ν=2930, 2850, 1740, 1465, 1400, 1200, 1155, 1090 cm^{-1}. MS (EI, 80 eV, 40 °C): m/z=252, 223, 191, 173, 133, 95, 81, 73, 67, 55, 41. $[\alpha]_D$=−113.4 (c=1.0, $CHCl_3$). Anal. Calcd for $C_{16}H_{28}O_2$: C, 76.14; H 11.18. Found: C, 76.13, H, 11.24.

2.3.12. Synthesis of 4. The title compound was performed analogously from **24b**. The spectra were indistinguishable from those of **3**. $[\alpha]_D$=−105.4 (c=1.0, $CHCl_3$). Anal. Calcd for $C_{16}H_{28}O_2$: C, 76.14; H 11.18. Found: C, 75.92, H, 10.99.

2.4. Synthesis of 1, 2 and 4 via sulfone-alkylation

2.4.1. Synthesis of 39. Butane-1,4-diol (443 mL, 5.00 mol) was treated with KOH (132.0 g, 2.00 mol). Water was removed under reduced pressure at 110 °C. Benzyl chloride (230 mL, 2.0 mol) was added dropwise, so that the temperature was above 90 °C. The mixture was stirred at 130 °C for 2 h, cooled to room temperature and diluted with water (1 L), extracted with ether. The ether phase was dried ($MgSO_4$), the solvent was removed under reduced pressure and the residue was distilled at 0.5 mbar to give the monobenzyl ether (238 g, 66%) as a colorless oil, of which 18.00 g (99.9 mmol) were oxidized under Swern conditions (TP) to give aldehyde **36** (17.18 g, 97%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ [ppm]=0.92 (t, J=7.8 Hz, 1H), 1.36–1.52 (m, 3H), 1.53–1.81(m, 3H), 2.63 (s, 1H), 3.49 (t, J=6 Hz, 2H), 3.49 (m, 1H), 4.50 (s, 2H), 7.30 (m, 5H). ^{13}C NMR ($CDCl_3$): δ [ppm]=9.89, 26.02, 30.04, 33.89, 70.42, 72.69, 72.82, 127.45, 128.24, 138.12.

2.4.2. Synthesis of (*S*)-38. Ditriflate (*R*,*R*-**37**) (927 mg, 2.45 mmol) in toluene (30 mL) was treated with Ti(O*i*Pr)$_4$ (21.9 mL, 73.6 mmol) and the mixture was stirred at 40 °C for 1 h. The mixture was cooled to −78 °C and diethylzinc (1 M in hexane, 135 mL) was added dropwise. A dark red solution was obtained which was treated dropwise with aldehyde **36** (10.93 g, 61.3 mmol) in toluene (10 mL) and the mixture was stirred at −30 °C for 5 h. The reaction was quenched with 2 N HCl (120 mL) and the ether phase was washed with brine, dried ($MgSO_4$) and chromatographed (hexanes/ethyl acetate 5:1) to furnish (*S*)-**38** (11.87 g, 93%) as a yellowish oil. ^{1}H NMR ($CDCl_3$): δ [ppm]=0.92(t, J=7.8 Hz, 1H), 1.36–1.52 (m, 3H), 1.53–1.81 (m, 3H), 2.63 (s, 1H), 3.49 (t, J=6 Hz, 2H), 3.49 (m, 1H), 4.50 (s, 2H), 7.30 (m, 5H). ^{13}C NMR ($CDCl_3$): δ [ppm]=9.89, 26.02, 30.04, 3.89, 70.42, 72.69, 72.82, 127.45, 128.24, 138.12. IR (film): ν=3415, 2934, 2858, 1495, 1453, 1362, 1099, 994, 962 cm^{-1}. MS (EI, 80 eV, 40 °C): m/z=208, 190, 179, 161, 147, 117, 107, 91, 71, 41. $[\alpha]_D$=7.1 (c=1.92, $CHCl_3$). Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H 9.68. Found: C, 74.22, H, 9.48.

2.4.3. Synthesis of (*S*)-39. *Compound* (*S*)-**38** (17.85 g, 85.7 mmol) in DMF (400 mL) was deprotonated with NaH (80%, 6.0 g, 214 mmol) at 0 °C.The mixture was stirred at room temperature for 1 h, cooled to 0 °C and treated dropwise with methyl iodide (21.3 mL, 343 mmol) in DMF (50 mL). The mixture was stirred overnight, quenched with water. The product was extracted with ether and the ether phase was dried ($MgSO_4$) and chromatographed (hexanes/ethyl acetate 5:1) to give the methyl ether (18.72 g, 98%) as a colorless oil. For debenzylation the methyl ether (18.72 g, 84 mmol) in MeOH (300 mL) was hydrogenated over Pd/C (5%, 400 mg) at normal pressure. After filtration the solvent was removed under reduced pressure and the residue was chromatographed (hexanes/ethyl acetate 1:1) to give the mono alcohol (11.13 g, 100%) as a colorless oil. To prepare the bromide (*S*)-**39**, the alcohol (500 mg, 3.78 mmol) in DCM (8 mL) was added dropwise to mixture of triphenyl phosphine (2.78 mg, 10.58 mmol) and NBS (2.02 g, 11.34 mmol) in DCM (24 mL) and stirred overnight. The mixture was diluted with aqueous $NaHCO_3$ and extracted with ether. The ethereal extract was washed with brine, dried ($MgSO_4$) and evaporated to dryness. The residue was diluted with pentane, filtered and distilled (85–90 °C, 12 mbar) to give (*S*)-**39** (520 mg, 71%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ [ppm]=0.90(t, J=7.6 Hz, 1H), 1.40–1.72 (m, 4H), 1.79–2.07 (m, 2H), 3.13 (quint, J=6 Hz, 1H), 3.32 (s, 3H), 3.44 (t, J=7 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ [ppm]=9.30, 25.73, 28.62, 31.49, 34.20, 56.38, 81.14. IR (film): ν=2984, 2934, 2877, 1092 cm^{-1}. MS (EI, 80 eV, 40 °C): m/z=195, 193, 167, 165, 109, 107, 85, 73, 55, 45. $[\alpha]_D$=4.7 (c=3.03, $CHCl_3$). HRMS Calcd for $C_7H_{15}OBr$: 193.02281. Found: C, 193.02278.

2.5. Synthesis of 1 and 2

2.5.1. Synthesis of 40. Ester **22** (15.20 g, 53.4 mmol) in pyridine (60 mL) was treated with DMAP (100 mg) and then MsCl (8.3 mL, 107 mmol) was added dropwise. The mixture was stirred overnight at room temperature, water (50 mL) and ether (50 mL) were added. The phases were separated and the ethereal phase was washed with brine, dried ($MgSO_4$) and evaporated to give the mesylate as a colorless solid (18.09 g, 49.9 mmol) of mp 84–85 °C.

The mesylate (9.00 g, 24.8 mmol) in ether (150 mL) and treated dropwise at −20 °C with $LiALH_4$ (1.6 M in THF, 31.3 mL) for 15 min. The mixture was warmed to room temperature and stirred for another 90 min and quenched with *i*PrOH and then water. $MgSO_4$ and silicagel were added and the mixture was stirred overnight, filtered and chromatographed to furnish alcohol **40** (4.33 g, 73%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ [ppm]=0.94 (s, 3H), 1.36 (m, 2H), 1.63 (m, 3H), 1.87 (m, 3H), 2.21 (m, 3H), 2.51 (m, 1H), 3.46 (s, 2H), 3.50 (m, 1H). ^{13}C NMR ($CDCl_3$): δ [ppm]=22.46, 29.97, 30.04, 32.29, 39.60, 40.20, 40.28, 49.72, 66.31, 71.69, 72.34, 110.23. IR (film): ν=3428, 2949, 2866, 1109 cm^{-1}. MS (EI, 80 eV, 40 °C): m/z=240, 225, 209, 197, 181, 167, 155, 141, 128, 95, 81,69, 55. $[\alpha]_D$=22.6 (c=1.0, $CHCl_3$). Anal. Calcd for $C_{14}H_{24}O_2$: C, 69.96; H 10.07. Found: C, 70.22, H, 9.88. For the preparation of the tosylate, alcohol **40** (9.13 g, 38.0 mmol) in pyridine (45 mL) was treated with DMAP (300 mg) and tosyl chloride (10.9 g, 57 mmol) was added in portions at 0 °C and the mixture was stirred for 16 h at room temperature. The reaction was quenched with water and the mixture was extracted with ether. The organic phase was washed with 2 N HCl, water, $NaHCO_3$ and brine, dried ($MgSO_4$) and chromatographed (hexanes/ethyl acetate 2:1) to give the tosylate (14.66 g, 98%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ [ppm]=0.94 (s, 3H), 1.16–1.43 (m, 2H), 1.60 (m, 2H), 1.80 (m, 2H), 1.95–2.18 (m, 4H), 2.45 (s, 3H), 2.47 (m, 1H), 3.43 (s, 2H), 3.44 (s, 2H), 3.90 (d, J=7 Hz, 2H), 7.34 (d, J=9 Hz, 2H), 7.78 (d, J=9 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ [ppm]=21.62, 22.46, 30.08, 32.19, 38.97, 40.12, 40.25, 43.56, 46.06, 71.83, 72.20, 73.38, 109.96, 127.84, 129.78, 144.60. IR (film): ν=2952, 2867, 1362, 1109 cm^{-1}. MS (EI, 80 eV, 40 °C): m/z=394, 239, 223, 209, 167, 137, 91, 69, 41. $[\alpha]_D$=28.7 (c=1.4, $CHCl_3$). Anal. Calcd for $C_{21}H_{30}O_5S$: C, 63.93; H 7.66. Found: C, 63.76, H, 7.45. To prepare the iodide, the tosylate (13.05 g, 33.1 mmol) in acetonitrile (130 mL) was treated with sodium iodide (10.91 g, 72.8 mmol) and the mixture was refluxed for 3 h. After cooling to room temperature water and ether were added and the ether phase was washed with

water, sodium thiosulfate and brine, dried ($MgSO_4$), and evaporated to give the iodide (11.58 g, 100%) as a slightly yellow oil ($[\alpha]_D=-20.1$ ($c=1.21$, $CHCl_3$)) which was used for the next step without purification. Sodium phenylsulfinate (8.15 g, 49.7 mmol) in DMF (200 mL) was added and the mixture was stirred at 110 °C overnight, cooled to room temperature, quenched with $NaHCO_3$ and extracted with ether. The ether phase was washed with brine, dried ($MgSO_4$) and chromatographed (hexanes/ethyl acetate 2:1) to give sulfone **41** (9.49 g, 79%) along with the sulfinate (1.99 g, 17%).

Compound **41**. Solid with mp 60–61 °C: ^{1}H NMR ($CDCl_3$): δ [ppm]=0.89 (s, 3H), 1.20–1.44 (m, 2H), 1.55–1.74 (m, 2H), 1.88 (m, 1H), 2.02 (m, 1H), 2.07–2.25 (m, 4H), 2.49 (m, 1H), AB-part of an ABX system: δ_A 3.05, δ_B 3.17, (J= 14, 7, 5.8 Hz, 2H), 3.41 (d, J=11 Hz, 1H), 3.46 (d, J= 11 Hz, 1H), 7.60 (m, 3H), 7.92 (m, 2H). ^{13}C NMR ($CDCl_3$): δ [ppm]=22.40, 22.58, 30.00, 32.58, 33.91, 39.55, 40.99, 47.29, 61.26, 71.86, 72.06, 109.84, 127.86, 129.22, 133.49, 140.06. IR (film): ν=2952, 2868, 1462, 1109, 1086 cm^{-1}. MS (EI, 80 eV, 40 °C): m/z=364, 279, 223, 209, 167, 137, 109, 95, 69, 55, 41. $[\alpha]_D=-30.2$ ($c=2.28$, $CHCl_3$). Anal. Calcd for $C_{20}H_{28}O_4S$: C, 65.90; H 7.74. Found: C, 65.62, H, 7.51.

Sulfinate. ^{1}H NMR ($CDCl_3$): δ [ppm]=0.95 (s, 3H), 0.96 (s, 3H), 1.13–1.43 (m, 2H), 1.60 (m, 2H), 1.81 (m, 2H), 1.92–2.21 (m, 4H), 2.46 (m, 1H), 3.42 (s, 2H), 3.44 (s, 2H), 3.45 (m, 1H), 3.92 (m, 1H), 7.54 (m, 3H), 7.70 (m, 2H). ^{13}C NMR ($CDCl_3$): δ [ppm]=22.50, 30.04, 30.33, 32.33, 39.24, 40.15, 43.79, 46.77, 46.85, 67.31, 71.79, 72.25, 110.06, 125.24, 128.98, 131.99. IR (film): ν=2867, 1444, 1132, 1108, 944 cm^{-1}. MS (EI, 80 eV, 40 °C): m/z=364, 279, 239, 223, 209, 208, 167, 137, 125, 95, 81, 69, 55.

2.5.2. Alkylation of sulfone 41. Preparation of 42a. Sulfone **41** (2.00 g, 5.49 mmol) in THF (8 mL) was treated dropwise with *n*BuLi (1.6 M in hexane, 3.95 mL, 6.31 mmol) at −20 °C. The mixture was slowly warmed to room temperature, then cooled to −20 °C and HMPA (3.82 mL) was added dropwise and the mixture was stirred at room temperature for 30 min. Then the mixture was cooled to −30 °C and treated dropwise with bromide (*S*)-**39** (1.29 g, 6.59 mmol) in THF (1 mL). Workup with water and ether furnished after HPLC (hexane/*i*PrOH 99.2:1) **42a** (1.58 g, 60%) as a diastereomeric mixture. First diastereomer: ^{1}H NMR ($CDCl_3$): δ [ppm]=0.80 (t, J=7.6 Hz, 3H), 0.90 (s, 3H), 1.01 (s, 3H),1.19–1.69 (m, 10H), 1.70–1.99 (m, 4H), 2.39 (m, 1H), 2.43 (m, 4H), 2.96 (m, 2H), 3.22 (s, 3H), AB-system: δ_A 3.42, δ_B 3.53, (J=11.6 Hz, 2H), 7.60 (m, 3H), 7.90 (m, 2H). ^{13}C NMR ($CDCl_3$): δ [ppm]=9.25, 22.36, 22.63, 24.37, 25.54, 26.54, 30.04, 32.61, 33.06, 34.18, 39.19, 40.89, 41.24, 42.60, 45.31, 56.29, 67.47, 71.70, 72.31, 81.20, 110.33, 128.45, 129.08, 133.33, 139.42. Second diastereomer: ^{1}H NMR ($CDCl_3$): δ [ppm]=0.84 (t, J=7.6 Hz, 3H), 0.86 (s, 3H), 0.96 (s, 3H),1.21–1.50 (m, 8H), 1.53–1.74(m, 3H), 1.83–2.27 (m, 7H), 2.42 (m, 1H), 3.00 (m, 2H), AB-system: δ_A 3.20, δ_B 3.27, (J=11.4 Hz, 2H), 3.27 (s, 3H), 3.40 (s, 2H), 7.60 (m, 3H), 7.90 (m, 2H). ^{13}C NMR ($CDCl_3$): δ [ppm]=9.18, 22.42, 22.55, 24.97, 25.16, 25.72, 29.35, 29.93, 32.92, 33.23, 37.40, 39.40, 40.63, 44.93, 45.40, 56.48, 66.63, 71.66, 72.05, 81.56, 110.07, 128.55, 129.08, 133.36, 139.03. IR (film): ν=2952, 2869, 1462, 1109, 1086 cm^{-1}. MS (EI, 80 eV, 40 °C): m/z=364, 279, 223, 209, 167, 137, 109, 95, 69, 55, 41. Anal. Calcd for $C_{27}H_{42}O_5S$: C, 67.75; H 8.84. Found: C, 67.51, H, 7.83.

2.5.3. Synthesis of 43a. The diastereomeric mixture of sulfones **42a** (1.54 g, 3.22 mmol) in methanol (35 mL) was treated at −20 °C with di-sodiumhydrogenphosphate (1.83 g, 12.88 mmol) and sodium amalgam (10 g, 6%) and stirred for 3 h. Water was added and the mixture was stirred for 30 min. The mercury was removed by decantation and the aqueous phase was extracted with ether. The ethereal phase was washed with brine, dried ($MgSO_4$), and chromatographed (hexanes/ethyl acetate 10:1) to give **43a** (910 mg, 84%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ [ppm]=0.89 (t, J=7.6 Hz, 3H), 0.95 (s, 3H), 0.97 (s, 3H),1.09–1.63 (m, 15H), 1.84 (m, 2H), 2.01 (m, 1H), 2.23 (dd, J=9.0, 13.0 Hz, 2H) 2.47 (m, 1H), 3.07 (quint, J= 5.6 Hz, 1H), 3.32 (s, 3H), 3.46 (s, 2H), 3.49 (s, 2H). ^{13}C NMR ($CDCl_3$): δ [ppm]=9.34, 22.53, 25.64, 25.80, 30.08, 32.67, 32.98, 33.82, 35.38, 40.05, 40.25, 40.30, 47.07, 47.49, 56.35, 71.64, 72.42, 82.04, 110.55. IR (film): ν= 2934, 2854, 1462, 1111 cm^{-1}. MS (EI, 80 eV, 40 °C): m/z=338, 323, 309, 265, 241, 223, 209, 181, 167, 141, 128, 73, 69, 55. $[\alpha]_D=-19.3$ ($c=2.01$, $CHCl_3$). Anal. Calcd for $C_{21}H_{38}O_3$: C, 74.51; H 11.31. Found: C, 74.33, H, 10.75.

2.5.4. Synthesis of 1. *Compound* **43a** (2.66 g, 7.86 mmol) in acetone (450 mL) and water (22 mL) was treated with *p*-TsOH (373 mg, 1.96 mmol) and stirred at room temperature for 20 h. The mixture was neutralized with $NaHCO_3$ and concentrated under reduced pressure. The residue was extracted with ether, and the ether phase was washed with brine, dried ($MgSO_4$), and chromatographed (hexanes/ethyl acetate 10:1) to give **1** (1.90 g, 96%) as a colorless oil. All analytical data were fully in agreement with those reported above.

2.5.5. Synthesis of alcohol 48. Hydroxy ester **22** (5.00 g, 17.59 mmol) in THF was treated with triphenyl phosphane (4.73 g, 18.0 mmol), DEAD (3.13 g, 18.0 mmol) and lithium bromide (3.34 g, 18.0 mmol) at 0 °C for 5 h. The solvent was removed under reduced pressure and the residue was treated with ether to crystallize the hydrazo ester and the phosphine oxide. The mixture was filtered and the filtrate was chromatographed (hexanes/ethyl acetate 3:1) to give ester **46** (4.07 g, 85%) as a colorless oil, which was reduced with DIBALH (1.6 M in toluene, 12 mL) at −30 °C for 1 h (TP 2) to give, after aqueous workup allylic alcohol **47** (3.86 g, 92%), which was hydrogenated in ethyl acetate (700 mL) over Rh/C (5%, 1 g) at −30 °C for 6 h under normal pressure. The mixture was filtered and evaporated to dryness. The residue was chromatographed (hexanes/ethyl acetate 2:1) to give **48** (2.84 g, 74%) as a colorless solid of mp 58–59 °C. ^{1}H NMR ($CDCl_3$): δ [ppm]=0.95 (s, 3H), 0.97 (s, 3H),1.22–1.49 (m, 4H), 1.56 (s, 1H), 1.60–1.77 (m, 2H), 1.98–2.23 (m, 2H), 2.41 (m, 1H), 2.58 (m, 2H), 3.47 (s, 2H), 3.49 (s, 2H), AB-part of an ABX system: δ_A 3.60, δ_B 3.65, (J=10, 8, 7.6 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ [ppm]= 22.41, 22.49, 26.63, 30.11, 32.14, 33.37, 39.18, 41.14, 41.22, 45.87, 64.04, 71.28, 73.06, 109.20. IR (film): ν= 3459, 2936, 2862, 1110, 1033, 999, 977 cm^{-1}. MS (EI,

80 eV, 40 °C): *m/z*=240, 225, 209, 197, 181, 167, 155, 141, 128, 95, 81, 69, 55. $[\alpha]_D=-28.6$ (*c*=1.05, $CHCl_3$). Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H 10.06. Found: C, 69.79, H, 9.88.

2.5.6. Synthesis of sulfone 49. Alcohol **48** (4.82 g, 20.0 mmol) in pyridine (25 mL) was treated with DMAP (300 mg) and tosyl chloride (5.72 g, 30.0 mmol). The mixture was stirred at room temperature overnight and then quenched with water. The mixture was extracted with DCM and the DCM phase was washed with brine, dried ($MgSO_4$) and the tosylate was crystallized by addition of hexane. 7.23 g (92%) was obtained as colorless crystals of mp 131–132 °C. ^{1}H NMR ($CDCl_3$): δ [ppm]=0.92 (s, 3H), 0.96 (s, 3H),1.08–1.30 (m, 3H), 1.38 (m, 1H), 1.62 (m, 2H), 1.97 (m, 1H), 2.17 (m, 1H), 2.35 (m, 1H), 2.45 (s, 3H), 2.53 (m, 2H), AB-system $\delta_A=3.37$, $\delta_B=3.42$ (*J*=11 Hz, 2H), 3.44 (s, 2H), ABX-system: $\delta_A=3.94$, $\delta_B=4.02$ (*J*=9.0, 9.0, 7.0 Hz, 2H), 7.34 (d, *J*=9.7 Hz, 2H), 7.82 (d, *J*=9.7 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ [ppm]=21.67, 22.52, 26.56, 30.15, 31.99, 33.12, 39.16, 41.27, 41.41, 42.17, 71.35, 71.68, 72.06, 108.93, 127.95, 129.86. IR (film): ν=2966, 2868, 1175, 1110, 951, 811 cm^{-1}. MS (EI, 80 eV, 40 °C): *m/z*=394, 309, 239, 223, 209, 167, 137, 91, 69. $[\alpha]_D=-13.4$ (*c*=1.04, $CHCl_3$). Anal. Calcd for $C_{21}H_{30}O_5S$: C, 63.93; H 7.66. Found: C, 63.77, H, 7.43.

For the synthesis of the iodide, the tosylate (7.18 g, 18.2 mmol) and sodium iodide (6.00 g, 40 mmol) in acetonitrile (70 mL) was refluxed for 20 h. After cooling to room temperature water was added and the product was extracted with ether. The organic phase was washed with brine ($MgSO_4$) and chromatographed (hexanes/ethyl acetate 7:1) to give the iodide (5.62 g, 88%) as a slightly brown oil. ^{1}H NMR ($CDCl_3$): δ [ppm]=0.97 (s, 6H), 1.18–1.54 (m, 4H), 1.64–1.83 (m, 2H), 2.26 (m, 2H), 2.43 (m, 1H), 2.59 (m, 2H), ABX-system: $\delta_A=3.07$, $\delta_B=3.24$ (*J*=9.8, 9.8, 7.0 Hz, 2H), 3.47 (s, 2H), 3.50 (s, 2H). ^{13}C NMR ($CDCl_3$): δ [ppm]=7.29, 22.42, 30.08, 30.16, 32.47, 32.88, 39.12, 41.37, 43.35, 46.93, 71.28, 73.05, 108.65. MS (EI, 80 eV, 40 °C): *m/z*=350, 265, 223, 167, 137, 109, 95, 69, 55. $[\alpha]_D=-72.7$ (*c*=1.81, $CHCl_3$). HRMS *m/z* Calcd for $C_{14}H_{23}O_2$: 350.07416. Found 350.07414.

The iodide (5.60 g, 16.0 mmol) was converted into sulfone **49** (2.49 g, 43%) as described for **41**. Colorless solid of mp 144 °C. ^{1}H NMR ($CDCl_3$): δ [ppm]=0.91 (s, 3H), 0.98 (s, 3H), 1.12–1.47 (m, 4H), 1.62 (m, 1H), 1.75 (m, 1H), 2.20–2.42 (m, 2H), 2.56 (m, 2H), AB-part of an ABX-system: $\delta_A=3.12$, $\delta_B=3.19$ (*J*=14.0, 6.6, 7.0 Hz, 2H), 3.43 (s, 4H), 7.64 (m, 3H), 7.95 (m, 2H). ^{13}C NMR ($CDCl_3$): δ [ppm]= 22.33, 22.48, 29.41, 30.06, 31.80, 33.78, 37.04, 38.52, 41.86, 42.82, 57.98, 71.23, 73.05, 108.42, 127.90, 129.25, 133.58, 139.88. IR (film): ν=2953, 2865, 1444, 1290, 1148, 1109, 1012, 997 cm^{-1}. MS (EI, 80 eV, 40 °C): *m/z*=364, 279, 223, 167, 137, 109, 95, 69, 55. $[\alpha]_D=-37.1$ (*c*=2.45, $CHCl_3$). Anal. Calcd for $C_{20}H_{28}O_4S$: C, 65.90; H 7.74. Found: C, 65.52, H, 7.59.

The sulfone **49** (2.33 g, 6.39 mmol) in THF (8 mL) was alkylated with bromide *S*-**39** as described for **42a** to give after HPLC (hexane/*i*PrOH 98:2) diastereomers **50** (crystals of mp 88 °C, 1.76 g, 58%) and **51** (colorless oil, 0.47 g, 15%).

Compound **50**. ^{1}H NMR ($CDCl_3$): δ [ppm]=0.84 (t, *J*= 7.6 Hz, 3H), 0.89 (s, 3H), 1.02 (s, 3H), 1.10–1.83 (m, 14H), 2.31 (m, 3H), 2.55 (m, 1H), 2.79 (m, 1H), 2.98 (m, 2H), 3.27 (s, 3H), 3.44 (m, 4H), 7.60 (m, 3H), 7.92 (m, 2H). ^{13}C NMR ($CDCl_3$): δ [ppm]=9.18, 22.28, 22.60, 22.92, 25.62, 27.57, 29.43, 30.08, 31.25, 33.04, 33.72, 38.46, 42.30, 42.99, 56.35, 65.83, 71.20, 73.11, 81.37, 108.30, 128.69, 129.06, 133.45, 138.96. IR (KBr): ν=2963, 2924, 2862, 1445, 1297, 1145 1114, 1087 cm^{-1}. MS (EI, 80 eV, 40 °C): *m/z*=478, 463, 449, 393, 377, 361, 337, 219, 128, 95, 69. Anal. Calcd for $C_{27}H_{42}O_5S$: C, 67.75; H 8.84. Found: C, 67.38, H, 8.52.

Compound **51**. ^{1}H NMR ($CDCl_3$): δ [ppm]=0.82 (t, *J*= 7.6 Hz, 3H), 0.88 (s, 3H), 1.02 (s, 3H), 1.10–1.81 (m, 13H), 1.94–2.14 (m, 2H), 2.25 (m, 1H), 2.50 (m, 2H), 2.63 (m, 1H), 2.96 (m, 2H), 3.26(s, 3H), 3.42 (d, *J*=11.0 Hz, 1H), 3.47 (d, *J*=11.0 Hz, 1H), 3.42 (d, *J*=11.0 Hz, 1H), 3.53 (d, *J*=11.0 Hz, 1H), 7.60 (m, 3H), 7.88 (m, 2H). ^{13}C NMR ($CDCl_3$): δ [ppm]=9.27, 22.10, 22.26, 22.50, 25.67, 27.85, 29.25, 30.07, 32.51, 33.20, 36.21, 37.78, 39.52, 42.08, 42.76, 56.37, 66.87, 71.31, 73.04, 81.51, 108.55, 128.29, 129.03, 133.27, 139.96.

2.5.7. Synthesis of 52. The mixture of **50/51** (2.23 g, 4.66 mmol) in methanol (50 mL) was desulfonated as described for **43a** to furnish **52** (1.27 g, 81%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ [ppm]=0.89 (t, *J*=7.6 Hz, 3H), 0.95 (s, 3H), 0.99 (s, 3H), 1.17–1.66 (m, 16H), 1.74 (m, 1H), 2.04 (m, 1H), 2.47 (m, 3H), 3.07 (quint, *J*=5.8 Hz, 1H), 3.32 (s, 3H), 3.47 (s, 2H), 3.50 (s, 2H). ^{13}C NMR ($CDCl_3$): δ [ppm]=9.30, 22.46, 25.64, 25.78, 29.14, 29.49, 30.10, 30.79, 32.25, 33.00, 34.07, 38.95, 40.82, 42.29, 43.34, 56.35, 71.24, 73.06, 82.03, 109.10. IR (KBr): ν=2935, 2856, 1463, 1329, 1114, cm^{-1}. MS (EI, 80 eV, 40 °C): *m/z*=338, 323, 309, 295, 265, 241, 223, 209, 181, 167, 141, 128, 95, 81, 73, 69, 55. $[\alpha]_D=-26.7$ (*c*=2.35, $CHCl_3$). HRMS: *m/z* Calcd for $C_{16}H_{28}O_2$: 252.20893. Found 252.20889.

2.5.8. Synthesis of 4. *Compound* **52** (1.20 g, 3.55 mmol) in acetone (190 mL) and water (9 mL) was treated with *p*-TsOH (170 mg) at room temperature overnight. Workup was performed as described for the synthesis of **1** and the crude product was hydrogenated in ethyl acetate with Pd/C at room temperature and normal pressure. Chromatography (hexane/ethyl acetate 10:1) furnished **4** (820 mg, 92%) as a colorless oil. $[\alpha]_D=-112.6$ (*c*=1.33, $CHCl_3$). The analytical data were identical with those described above.

Acknowledgements

We thank Professor Töpert from the Schering AG, Berlin for performing the biological tests, Dr. J. Buschmann and Professor Dr. P. Luger, Institut für Kristallographie und Mineralogie der Freien Universität Berlin, for determining the crystal structure of **50**.

References and notes

1. Schostarez, H. J.; Diani, A. R. PCT Int. Appl., CODEN: PIXXD2 WO 9209259 A1 19920611, Upjohn Co.: USA, 1992.
2. Wiechers, J. W.; Herder, R. E.; Drenth, B. F. H.; De Zeeuw, R. A. *Int. J. Pharm.* **1990**, *65*(1–2), 77–84.
3. King, D.; Newcomer, V.; Burnison, C.; Reisner, R.; Mickus, K.; Suzuki-Chavez, F.; Ford, L. C. *Recent Advances in Chemotherapy*, Proceedings of the 14th International Congress Chemotherapy, Antimicrobial Sect. 1; Ishigami, J., Ed.; University of Tokyo Press, Tokyo: Japan, 1985; pp 269–270.
4. King, D.; Newcomer, V.; Reisner, R.; Ford, L. C. *Recent Advances in Chemotherapy*, Proceedings of the 14th International Congress Chemotherapy, Antimicrobial Sect. 1; Ishigami, J., Ed.; University of Tokyo Press, Tokyo: Japan, 1985; pp 267–268.
5. Ford, L. C.; King, D.; Goldman, P.; Reisner, R.; Newcomer, V. *Recent Advances in Chemotherapy*, Proceedings of the 14th International Congress Chemotherapy, Antimicrobial Sect. 1; Ishigami, J., Ed.; University of Tokyo Press, Tokyo: Japan, 1985; pp 261–262.
6. King, D. F.; Burnison, C.; Newcomer, V.; Mickus, K.; Suzuki-Chavez, F.; Ford, L. C. *Recent Advances in Chemotherapy*, Proceedings of the 14th International Congress Chemotherapy, Antimicrobial Sect. 1; Ishigami, J., Ed.; University of Tokyo Press: Tokyo, Japan, 1985; pp 259–260
7. Hammill, H. A.; Mickus, K.; Suzuki-Chavez, F.; Andeshak, J.; Andres, D.; Ford, L. C.; Burnison, C. *Recent Advances in Chemotherapy*, Proceedings of the 14th International Congress Chemotherapy, Antimicrobial Sect. 1; Ishigami, J., Ed.; University of Tokyo Press: Tokyo, Japan, 1985; pp 263–264.
8. Ford, L. C.; Hammill, H. A.; Mickus, K.; Suzuki-Chavez, F.; Lebherz, T. B.; Burnison, C. S. *Recent Advances in Chemotherapy*, Proceedings of the 14th International Congress Chemotherapy, Antimicrobial Sect. 1; Ishigami, J., Ed.; University of Tokyo Press: Tokyo, Japan, 1985; pp 265–266.
9. Ogawa, Tadatake; Miyamoto, Tatsu; Sada, Masahiro; Abe, Takashi; Nishijima, Yasushi. (Kanebo, Ltd., Japan), Jpn. Kokai Tokkyo Koho, 1986, 7.
10. Miyamoto, T.; Abe, T.; Nishijima, Y. *Japan Kokai Tokkyo Koho*, CODEN: JKXXAF JP 61056118 A2 19860320 Showa, Kanebo, Ltd.: Japan, 1986, p 8.
11. Ford, L. C.; Kasha, W.; Chang, C.; DeLange, R. J. *Chemotherapy, (Basel)* **1985**, *31*(5), 362–365.
12. Kasha, US Patent 4689, 345, 4689, 349, 1987
13. (a) Pauson, P. L. *Tetrahedron* **1985**, *41*, 5855. Magnus, P.; Principe, L. M.; Slater, J. *J. Org. Chem.* **1987**, *52*, 1483. Magnus, P.; Becker, D. P. *J. Am. Chem. Soc.* **1987**, *109*, 7495. (b) Mulzer, J.; Graske, K.-D.; Kirste, B. *Liebigs Ann. Chem.* **1988**, 891.
14. Barton, D. H.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.
15. Petzoldt, K.; Dahl, H.; Skuballa, W.; Gottwald, M. *Liebigs Ann. Chem.* **1990**, 1087.
16. Trost, B. M. *Acc. Chem. Res.* **1980**, *11*, 385.
17. Mitsunobu, O. *Synthesis* **1980**, 1.
18. Taber, D. F.; Anedio, J. C.; Gulino, F. *J. Org. Chem.* **1989**, *54*, 3474.
19. Mulzer, J.; Lammer, O. *Angew. Chem.* **1983**, *95*, 629.
20. Loibner, H.; Zbiral, E. *Helv. Chim. Acta* **1976**, *59*, 2100. Manna, S.; Flack, J. R. *Synth. Commun.* **1985**, *15*, 663.
21. Knochel, P.; Rozema, M. J.; Sidduri, A. *J. Org. Chem.* **1992**, *57*, 1956.
22. Formula $C_{27}H_{42}O_5S$, molecular weight 478.70 g/mol, crystal system monoclinic space group $P2_1$, lattice constants: $a=$ 11.056(1) Å $b=5.941(1)$ Å $c=20.677(4)$ Å; $\alpha=98.71(1)^\circ$, cell volume 1342.5(7) $Å^3$, $Z=2$, density (Calcd) 1.184 g/cm^3, crystal size $0.03\times0.08\times1.2$ mm, radiation Cu K_α, linear absorption coefficient 13.0 cm^{-1}, number of reflexes 4770, number of independent reflexes 2817, Reflexes with $I>0$ 2803, *R*-value 0.042, *wR* 0.051, *S*-value 2.35. Crystallographic data (excluding structure factors) for the structure have been deposited with the Cambridge Crystallographic Centre as supplementary publication number CCDC 237229. 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).

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 60 (2004) 9615–9628

Total synthesis of (−)-ephedradine A: an efficient construction of optically active dihydrobenzofuran-ring via C–H insertion reaction

Wataru Kurosawa, Hideki Kobayashi, Toshiyuki Kan and Tohru Fukuyama*

Graduate School of Pharmaceutical Sciences, University of Tokyo, Japan Science and Technology Corporation, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

Received 7 May 2004; revised 4 June 2004; accepted 5 June 2004

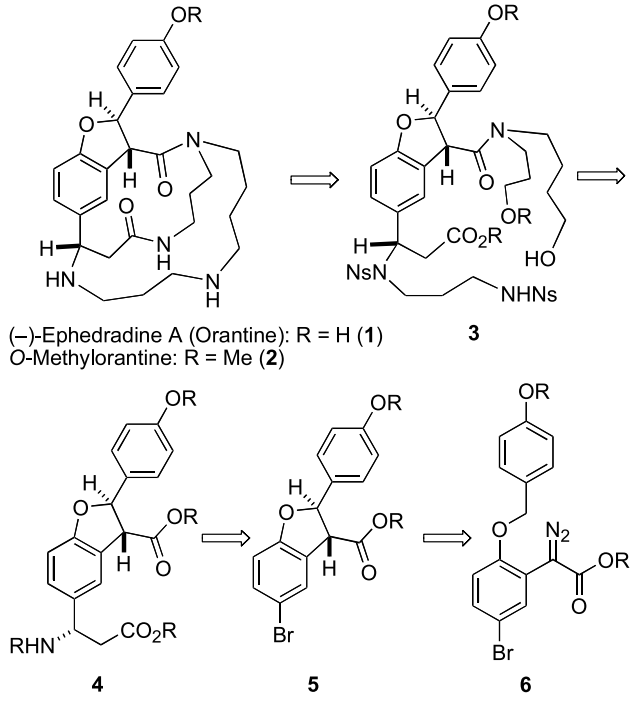
Available online 24 August 2004

Abstract—The stereocontrolled total synthesis of (−)-ephedradine A (**1**) has been accomplished. Construction of optically active dihydrobenzofuran-ring was performed by a novel asymmetric C–H insertion reaction. After an intramolecular ester–amide exchange reaction and a Sharpless asymmetric aminohydroxylation reaction, construction of the complex macrocyclic ring was performed by Ns-strategy and an intramolecular aza-Wittig reaction.

1. Introduction

(−)-Ephedradine A (orantine, **1**) is a complex macrocyclic spermine alkaloid isolated by Hikino and co-workers in 1979 as one of the hypotensive components of the Chinese traditional drug 'mao-kon'.[1,2] While synthesis of racemic *O*-methylated orantine (**2**) was achieved by Wasserman and co-workers in 1985,[3] total synthesis of **1** has not been reported to date. Clearly, construction of the two macrocyclic rings in the presence of a labile dihydrobenzofuran moiety constitutes the major challenge in the total synthesis of **1**. Recently we have developed a highly efficient methodology for the construction of medium- and large-sized cyclic amines via 2-nitrobenzenesulfonamides (Ns-strategy).[4,5] We envisioned this strategy being applied to the construction of the macrocyclic ring of **1**. Herein we report an efficient total synthesis of (−)-ephedradine A (**1**) by the stereocontrolled synthesis of optically active intermediate **4** and the subsequent construction of the macrocyclic polyamine ring by the Ns-strategy.[6]

The heart of our synthetic plan is illustrated in Scheme 1. Construction of the macrocyclic lactam and the secondary amine of **1** would be performed in the precursor **3**. Since **3** would be derived from **4** by stepwise incorporation of the polyamine chains, the dihydrobenzofuran containing the β-amino ester moiety **4** was envisaged as an appropriate platform for the preparation of **1**. Introduction of β-amino ester moiety of **4** would be achieved by Heck reaction and Sharpless aminohydroxylation reaction of **5**, therefore, the construction of optically active dihydrobenzofuran **5** would be important task for the total synthesis. Since the



Scheme 1. Retrosynthetic analysis of ephedradine A (**1**).

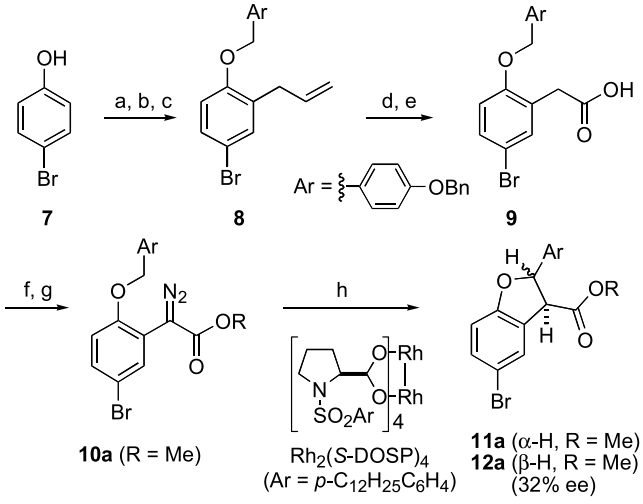
Keywords: Dihydrobenzofuran-ring; Asymmetric C–H insertion reaction; Ns-strategy; Macrocyclization; Aza-Wittig reaction.
* Corresponding author. Tel.: +81-3-5802-4777; fax: +81-3-5802-8694; e-mail: fukuyama@mol.f.u-tokyo.ac.jp

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.06.144

dihydrobenzofuran derivatives are often found in bioactive compounds and pharmaceuticals, an efficient synthesis has attracted much interest. Although many synthetic efforts have been reported to date, including a biomimetic oxidative dimerization of cinnamic acid derivatives,[7] there are still only a few examples of enantioselective synthesis.[8] Recently, asymmetric C–H insertion reactions of metal-carbenoids have been the subject of intensive investigation.[9] Furthermore, Davies has recently reported that a chiral rhodium-carbenoid, derived from an aryl diazoester, underwent inter- or intramolecular asymmetric C–H insertion reaction.[10,11] We envisioned that intramolecular C–H insertion of the carbenoid generated from **6** would provide the optically active **5**.[12]

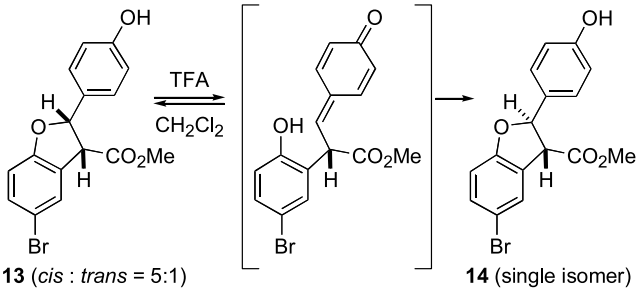
2. Results and discussion

As shown in Scheme 2, the C–H insertion precursor **10a** was



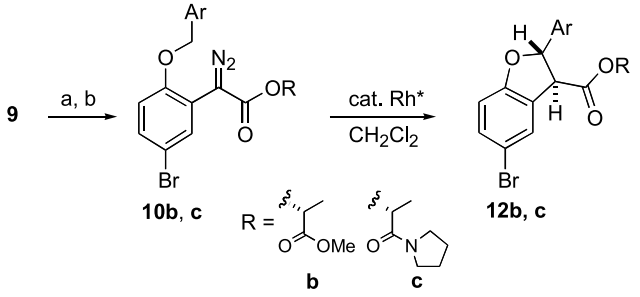
Scheme 2. Preparation of diazoester **10a** and the C–H insertion reaction. Reagents and conditions: (a) allyl bromide, K_2CO_3, DMF, 60 °C (99%); (b) diethylaniline, 210 °C (88%); (c) K_2CO_3, 4-(benzyloxy)benzyl chloride,[13] DMF, 60 °C (95%); (d) O_3, CH_2Cl_2/MeOH, −78 °C; Me_2S, −78 °C to rt; (e) $NaClO_2$, 2-methyl-2-butene, $NaH_2PO_4 \cdot 2H_2O$, *t*-BuOH/H_2O (77% in 2 steps); (f) CH_2N_2, Et_2O (81%); (g) *p*-$AcNHC_6H_4SO_2N_3$, DBU, CH_3CN (71%); (h) Rh_2(*S*-DOSP)$_4$ (5 mol%), CH_2Cl_2 (72%, **11a**:**12a**=5:1).

readily prepared in a seven-step sequence from 4-bromophenol (**7**). Thus, allylation of phenol **7**, Claisen rearrangement, and subsequent introduction of a 4-(benzyloxy)benzyl group[13] to the resultant phenol provided **8**. Ozonolysis of the double bond in **8** followed by treatment with $NaClO_2$ furnished the carboxylic acid **9**. After esterification of **9**, diazotransfer reaction was carried out by treatment with *p*-acetamidobenzenesulfonyl azide and DBU. With the requisite diazoester **10a** in hand, the C–H insertion reaction by chiral rhodium catalyst was next investigated. Upon treatment of **10a** with 5 mol% of Davies' catalyst, Rh_2(*S*-DOSP)$_4$, the reaction proceeded smoothly to afford the dihydrobenzofuran in 72% yield as a 5:1 mixture of **11a** and **12a**. Fortunately, the undesired 2,3-*cis*-benzofuran was readily converted to the thermodynamically more stable *trans*-isomer as shown in Scheme 3. After the removal of the benzyl group, the treatment of **13** with TFA resulted in



Scheme 3. Transformation of *cis*-dihydrobenzofuran **13** to *trans*-isomer **14**.

the predominant formation of the *trans*-isomer **14**. During the transformation, the α-position of the ester **14** was unaffected based on the fact that no deuterium incorporation was observed in **14** when **13** was treated with CF_3CO_2D in CD_2Cl_2. However, the enantiomeric excess of the *trans*-isomer was 32%. In order to improve the enantioselectivity, the incorporation of the chiral auxiliary to the ester moiety of **10a** was investigated (Scheme 4).



Scheme 4. Incorporation of chiral auxiliary **15b** and **c** into the carboxylic acid **9**. Reagents and conditions: (a) ROH (**15b**, **c**), WSCD·HCl, DMAP, CH_2Cl_2; (b) *p*-$AcNHC_6H_4SO_2N_3$, DBU, CH_3CN (75% for **10b** and 73% for **10c** in 2 steps).

Davies reported earlier that high diastereoselectivity of intermolecular Rh-carbenoid-mediated cyclopropanation was achieved by using α-hydroxy ester derivatives as the chiral auxiliaries.[14] Similarly, we have observed high diastereoselectivity in the C–H insertion reaction when **10b** and **10c** were employed. Thus, carboxylic acid **9** was coupled with methyl (*S*)-lactate (**15b**) and pyrrolidinyl (*S*)-lactamide[15] (**15c**) followed by the diazo transfer reaction to give the cyclization precursors **10b** and **10c**, respectively (Scheme 3).

Upon treatment with rhodium catalyst (5 mol%), the C–H insertion reactions of **10b** and **10c** proceeded smoothly to afford exclusively the *trans*-dihydrobenzofurans **12b** and **12c** (Table 1). Presumably, the increased bulk of the ester moiety is responsible for the high *trans*-selectivity.

Table 1. Diastereoselectivity of the Rh-carbenoid-mediated intramolecular C–H insertion reaction of **10b** and **10c**

Run	Cat. Rh[a]	**12b**[b]	**12c**[b]
1	$Rh_2(Oac)_4$	7:2	3:1
2	Rh_2(*S*-DOSP)$_4$	5:2	8:1
3	Rh_2(*R*-DOSP)$_4$	7:1	13:1

[a] All reactions were carried out in CH_2Cl_2 using 5 mol% of Rh catalyst.
[b] Diastereoselectivity was determined by ^1H NMR.

Furthermore, it is interesting to note that the C–H insertion products **12b** and **c** possessed the same configuration (2*S*,3*S*) regardless of the chirality of the catalyst (run 2 and 3). Thus, the asymmetric induction was strongly dependent on the chiral auxiliaries and not on the catalyst.[16] The high diastereoselectivities of **12b** and **c** indicate that the carbenoid intermediate might have strong interaction with the carbonyl group of the chiral auxiliary as illustrated in Figure 1. The highest diastereoselectivity was attained by combination of the diazoester **10c** and Rh_2(*R*-DOSP)$_4$ to afford **12c** in 84% yield and 86% de. However, the treatment of the diazoester **10c** containing the pyrrolidinyl (*S*)-lactamide chiral auxiliary with Rh_2(*R*-DOSP)$_4$ gave the (2*S*,3*S*)-dihydrobenzofuran **12c**, the stereochemistry of which was opposite to (−)-ephedradine A. In order to obtain the (2*R*,3*R*)-dihydrobenzofuran **12c**, the combination of the inversion of the chiral auxiliary and the use of Rh_2(*S*-DOSP)$_4$ were necessary.

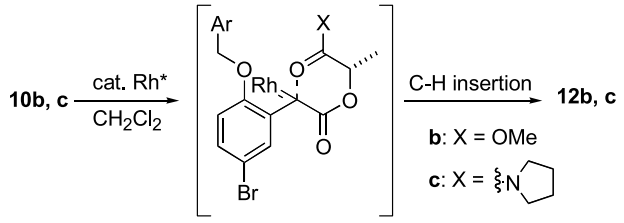
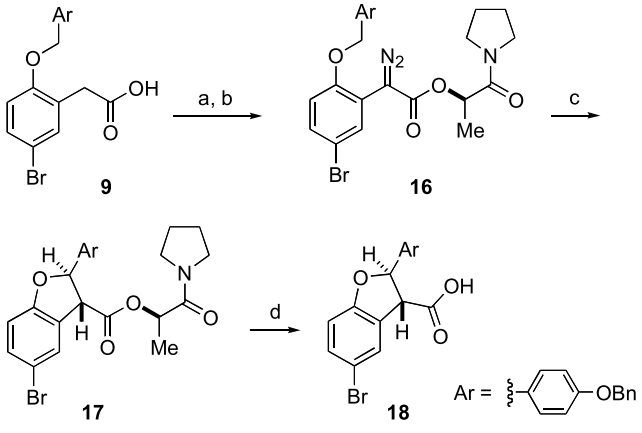


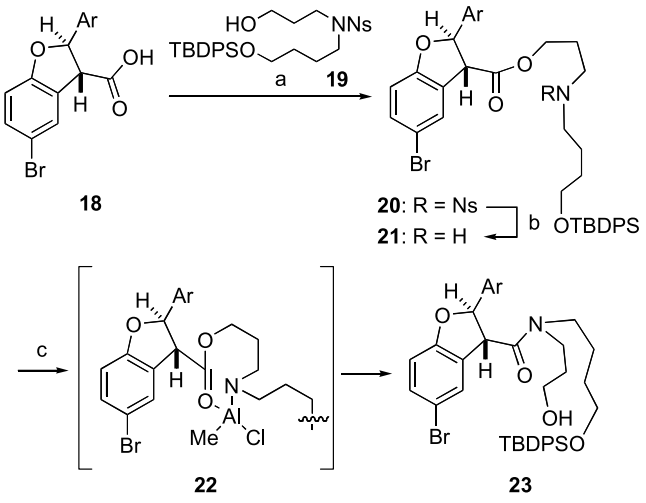
Figure 1.

As shown in Scheme 5, the cyclization precursor **16** was prepared by condensation of carboxylic acid **9** with the lactamide-type chiral auxiliary **15c** under Mitsunobu conditions[17] and subsequent diazo transfer reaction. Upon treatment of **16** with 0.3 mol% of the Davies catalyst,[10] the C–H insertion reaction proceeded smoothly to afford exclusively the *trans*-dihydrobenzofuran **17** in 63% yield (2 steps) and high diastereoselective manner (13:1). Removal of the chiral auxiliary by hydrolysis and subsequent recrystallization gave the optically pure carboxylic acid **18**.

Direct condensation of **18** with secondary amine derivatives of **19** was unsuccessful due to the decomposition of the dihydrobenzofuran ring brought about by activation of the carboxylic acid **18**. After numerous efforts to construct the amide bond, an intramolecular ester–amide exchange reaction of **21** was found to be suitable for the synthesis of **23**. Upon treatment of **18** and the alcohol **19**[5] with DEAD and PPh_3, the condensation reaction proceeded smoothly to give **20** (Scheme 6). Removal of the Ns group of **20** and subsequent treatment of the secondary amine **21** with dimethylaluminum chloride[18,19] in refluxing CH_2Cl_2 gave the amide **23** in 67% yield. The amide formation would be promoted by the dual activation of the aluminum which coordinate both of the ester-group and the secondary amine in **22**.



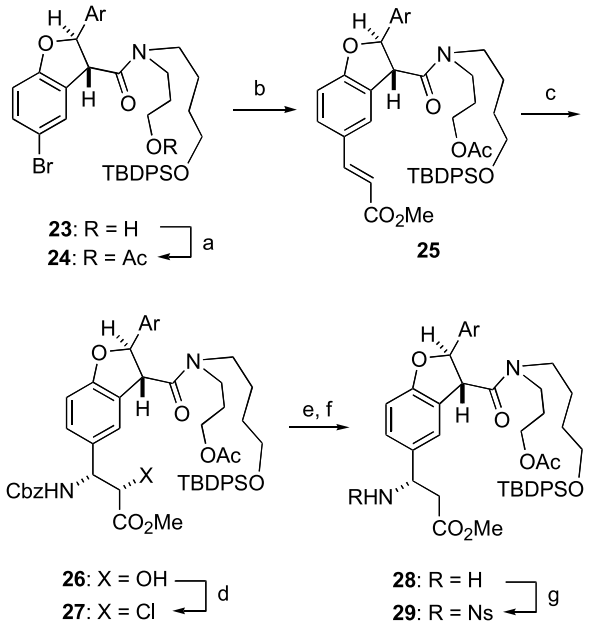
Scheme 5. Construction of dihydrobenzofuran ring **18**. Reagents and conditions: (a) **15c**, PPh_3, DEAD, toluene (80%); (b) $AcNHC_6H_4SO_2N_3$, DBU, CH_3CN; (c) Rh_2(*S*-DOSP)$_4$ (0.3 mol%), CH_2Cl_2 (63% in 2 steps); (d) $Ba(OH)_2 \cdot 8H_2O$, THF/MeOH/H_2O (90%).



Scheme 6. Synthesis of key intermediate **23**. Reagents and conditions: (a) **19**, PPh_3, DEAD, toluene (96%); (b) PhSH, K_2CO_3, DMF/CH_3CN, 50 °C (88%); (c) Me_2AlCl, CH_2Cl_2, reflux, (67%).

Next we turned our attention to the construction of the β-amino ester moiety. Acetylation of the alcohol **23** followed by a conventional Heck reaction[20] of **24** with methyl acrylate furnished the cinnamate derivative **25**. Facile and diastereoselective incorporation of the nitrogen atom in **25** was achieved by the Sharpless asymmetric aminohydroxylation reaction[21] to afford **26** as the predominant product (12:1). After conversion of the hydroxyl group of **26** to the corresponding chloride by treatment with PPh_3 and CCl_4, removal of the chlorine of **27** under transfer hydrogenation conditions provided the β-amino ester with concomitant cleavage of the Cbz group and benzyl ether. Selective protection of the resultant phenol with the benzyl group under Mitsunobu conditions and subsequent introduction of the Ns group on the primary amine **28** furnished the sulfonamide **29** Scheme 7.

The next challenge in the synthesis was the crucial construction of the 16-membered polyamine ring (Scheme 8). Coupling between the sulfonamide **29** and the alcohol **30**[22] under Mitsunobu conditions to afforded **31**. Since the undesired β-elimination of the alkylsulfonamide **31** occurred readily, the protecting group was switched from the Ns to the corresponding *N*-Cbz derivative yielded **32**. Acid-catalyzed selective deprotection of the TBS group of **32**, coupling with $NsNH_2$ under Mitsunobu conditions and subsequent cleavage of the TBDPS ether furnished the



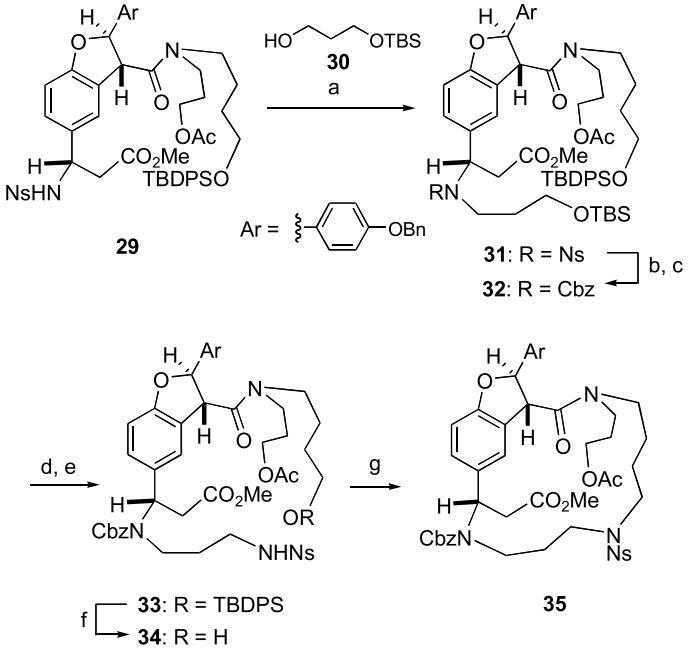
Scheme 7. Synthesis of β-amino ester **29**. Reagents and conditions: (a) Ac_2O, pyr (88%); (b) methyl acrylate, $Pd(OAc)_2$ (6 mol%), P(*o*-tol)$_3$ (18 mol%), Et_3N, DMF, 100 °C (84%); (c) CbzNClNa, $K_2OsO_2(OH)_4$ (6 mol%), $(DHQD)_2PHAL$ (8 mol%), *n*-PrOH/H_2O (66%); (d) PPh_3, CCl_4, toluene, 100 °C (87%); (e) Pd/C (20 mol%), HCO_2NH_4, MeOH, 60 °C; (f) BnOH, PPh_3, DEAD, toluene, 60 °C (61% in 2 steps); (g) NsCl, Na_2CO_3, CH_2Cl_2/H_2O (72%).

cyclization precursor **34**. Upon treatment of **34** with DEAD and PPh_3 in 0.05 M solution of toluene at room temperature, the desired cyclization reaction proceeded smoothly to afford **35** in 77% yield.

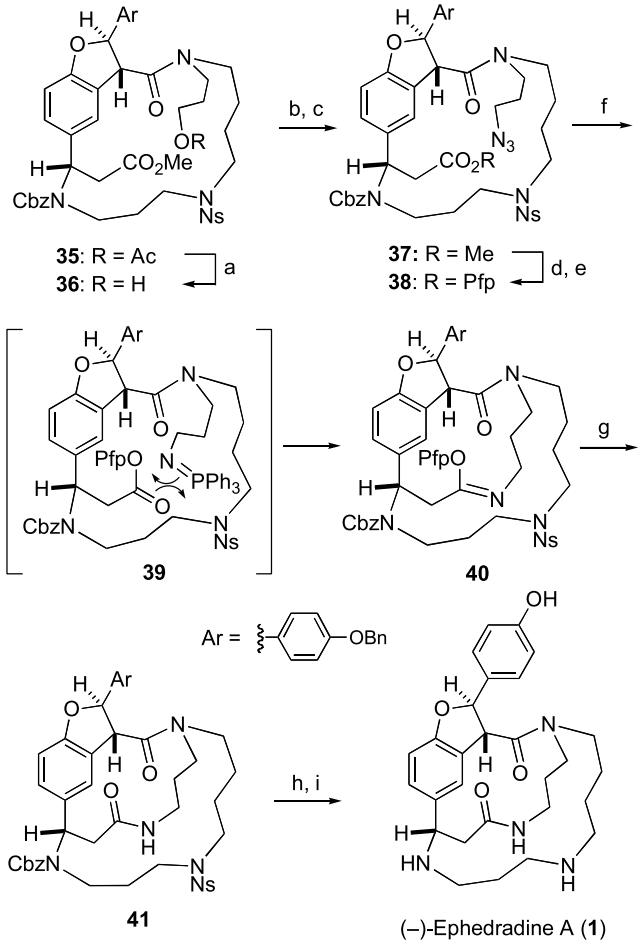
With the desired macrocyclic polyamine in hand, we next focused on the construction of the 13-membered macrolactam ring. The cyclization precursor **38** bearing an activated ester was prepared from **35** in a five-step sequence involving deprotection of the acetyl group, mesylation of the alcohol, displacement of the mesylate with NaN_3, basic hydrolysis of the methyl ester and condensation of the resultant carboxylic acid with pentafluorophenol. While generation of the amine moiety from the azide **38** under hydrogenation conditions resulted in exclusive dimerization, treatment with PPh_3 in refluxing toluene under high-dilution conditions (7.0 mM) successfully afforded the 13-membered iminoether **40** via the Staudinger[23] and the intramolecular aza-Wittig reactions.[24,25] Subsequent hydrolysis of **40** by refluxing in CH_3CN–H_2O afforded the desired 13-membered macrolactam **41** in 73% yield (2 steps).[26] Removal of the Ns group and simultaneous cleavage of the Cbz group and benzyl ether with BCl_3 yielded (−)-ephedradine A (**1**), the spectral data of which (^1H NMR, ^{13}C NMR, IR, and HRMS) were in full agreement with those of the natural product Scheme 9.[1]

3. Conclusion

In conclusion, we have developed an efficient synthetic method for the optically active *trans*−2,3-dihydrobenzofuran derivatives by combination of Davies' Rh catalyst and pyrrolidinyl lactamide chiral auxiliary. This protocol would be amenable to large-scale preparations of the dihydrobenzofuran derivative. Additionally, Sharpless' asymmetric aminohydroxylation reaction was suitable for the preparation of the desired β-amino ester **29**. Furthermore, our synthesis features the construction of all the secondary amines using Ns-strategy including macrocyclization and formation of the two amide bonds by the intramolecular ester–amide exchange reaction and the aza-Wittig reaction.



Scheme 8. Construction of 16-membered polyamine ring. Reagents and conditions: (a) **30**, PPh_3, DEAD, toluene, 60 °C (95%); (b) PhSH, KOH, CH_3CN, 60 °C (93%); (c) CbzCl, $NaHCO_3$, CH_2Cl_2/H_2O (91%); (d) CSA, MeOH (94%); (e) $NsNH_2$, DEAD, PPh_3, toluene/THF (quant.); (f) aq. HF, CH_3CN (84%); (g) PPh_3, DEAD, toluene (77%).



Scheme 9. Total synthesis of (−)-ephedradine A (**1**). Reagents and conditions: (a) K_2CO_3, MeOH/THF (96%); (b) MsCl, Et_3N, CH_2Cl_2, 0 °C; (c) NaN_3, DMF, 60 °C (82% in 2 steps); (d) LiOH, MeOH/THF/H_2O (97%); (e) pentafluorophenol, WSCD·HCl, CH_2Cl_2 (93%); (f) PPh_3, toluene, reflux; (g) CH_3CN/H_2O, reflux (73% in 2 steps); (h) PhSH, KOH, CH_3CN, 50 °C (75%); (i) BCl_3, CH_2Cl_2, −78 to 0 °C (73%).

4. Experimental

4.1. General methods

Unless otherwise noted, solvents and reagents were reagent grade and used without purification. Dichloromethane (CH_2Cl_2) and toluene were distilled from calcium hydride. IR spectra were recorded on a JASCO FT/IR-410 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were obtained as solutions in $CDCl_3$ unless otherwise indicated, and chemical shifts are reported in parts per million (ppm, δ) downfield from internal standard tetramethylsilane (TMS), which were taken on a JEOL JNM-LA400. Coupling constants are reported in hertz (Hz). Spectra splitting patterns are designated as s, singlet; br, broad; d, doublet; t, triplet; m; multiplet. Mass spectra (MS) and high-resolution mass spectra (HRMS) were measured with a JEOL JMS-GCmate instrument.

4.1.1. 1-Allyloxy-4-bromo-benzene. To a mixture of 4-bromophenol (**7**) (200 g, 1.16 mol) and K_2CO_3 (207 g, 1.50 mol, 1.3 equiv.) in DMF (600 ml) was added allyl bromide (110 ml, 1.27 mol, 1.1 equiv.), and the mixture was heated at 60 °C for 50 min. After cooling, the reaction mixture was poured into water, and extracted with Et_2O. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (10% AcOEt in *n*-hexane) to afford the above allyl ether (244 g, 1.15 mol, 99%). IR (film, cm^{-1}) 3083, 2910, 2868, 1648, 1590, 1578, 1489, 1285, 1242, 1072, 821. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37 (d, J=9.1 Hz, 2H), 6.80 (d, J=9.1 Hz, 2H), 5.98–6.08 (m, 1H), 5.40 (dq, J=17.2, 1.6 Hz, 1H), 5.29 (dq, J=10.6, 1.4 Hz, 1H), 4.51 (dt, J=5.1, 1.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.5, 132.7, 132.0, 117.6, 116.3, 112.7, 68.7; HRMS (FAB) Calcd for C_9H_9BrO (M^+) 211.9837, found 211.9830.

4.1.2. 2-Allyl-4-bromo-phenol. The allyl ether (244 g, 1.15 mol) was dissolved in 600 ml of *N*,*N*-diethylaniline, and the mixture was heated at 210 °C for 9 h. After cooling, the reaction mixture was poured into 3 N aqueous HCl, and extracted with AcOEt. The extracts were washed with water, followed by saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (20% AcOEt in *n*-hexane) to afford **25** (216 g, 1.01 mol, 88%). as an oil. IR (film, cm^{-1}) 3465, 3079, 2978, 2911, 1637, 1584, 1492, 1413, 1319, 1264, 809; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.20–7.27 (m, 2H), 6.70 (d, J=6.8 Hz, 1H), 5.92–6.03 (m, 1H), 5.14–5.21 (m, 2H), 5.00 (s, 1H), 3.37 (d, J=6.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.1, 135.4, 132.9, 130.5, 127.7, 117.5, 117.1, 112.8, 34.7; HRMS (FAB) Calcd for C_9H_9BrO (M^+) 211.9837, found 211.9837.

4.1.3. 1-(4-Benzyloxy-benzyloxy)-2-allyl-4-bromo-benzene (8). To a mixture of the above phenol (216 g, 1.01 mol) and K_2CO_3 (206 g, 1.49 mol, 1.5 equiv.) in DMF (600 ml) was added 4-benzyloxy-benzyl chloride (252 g, 1.08 mol, 1.1 equiv.), and the mixture was heated at 60 °C. After 3 h, 4-benzyloxy-benzyl chloride (11.7 g, 0.0504 mol, 0.050 equiv.) and K_2CO_3 (14.0 g, 0.101 mol, 0.10 equiv.) were added, and the mixture was stirred at 60 °C for 2hr. After cooling, the reaction mixture was poured into water, and extracted with Et_2O. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (10% AcOEt in *n*-hexane) to afford **8** (394 g, 0.966 mol, 95%) as an oil. IR (film, cm^{-1}): 3343, 2933, 2859, 1543, 1413, 1364, 1339, 1165, 1126, 1059, 853, 783, 741. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.30 (4H, m), 1.50 (2H, m), 1.53 (4H, m), 3.09 (2H), 3.63 (2H), 5.25 (1H, m), 7.75 (2H, m), 7.87 (1H, m), 8.14 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.5, 26.4, 28.8, 29.5, 32.5, 43.8, 62.9, 125.4, 131.1, 132.8, 133.5, 133.8, 149.8. FAB-MS: 317 (MH^+); HRMS (FAB): 317.1180 ($C_{13}H_{21}O_2N_5S$, MH^+). Exact mass 317.1177 (MH^+).

4.1.4. [2-(4-Benzyloxy-benzyloxy)-5-bromo-phenyl]-acetic acid (9). To a solution of **8** (170 g, 0.416 mol) in CH_2Cl_2 (1500 ml) and MeOH (500 ml) was bubbled ozone at −78 °C for 7.5 h. To the mixture was bubbled Ar gas, then added dimethyl sulfide (190 ml, 2.59 mol, 6.2 equiv.) at the same temperature. The mixture was allowed to reach ambient temperature, and stirred for 1 h. The reaction

mixture was concentrated under reduced pressure to give the crude aldehyde, which was used in the next reaction without further purification. To a mixture of the crude aldehyde, 2-methyl-2-butene (200 ml, 1.89 mol, 4.5 equiv.) and $NaH_2PO_4 \cdot 2H_2O$ (64.8 g, 0.415 mol, 1.0 equiv.) in *t*-butanol (1000 ml) and water (200 ml) was slowly added sodium chlorite (79%, 166 g, 1.45 mol, 3.5 equiv.) at 0 °C. The mixture was allowed to room temperature, and stirred for 72 h. To the mixture were added $NaH_2PO_4 \cdot 2H_2O$ (64.8 g, 0.415 mol, 1.0 equiv.) and sodium chlorite (79%, 47.4 g, 0.414 mol, 1.0 equiv.), then the mixture was stirred for further 12 h. The reaction mixture was quenched with $NaHSO_3$ (303 g, 7.0 equiv.) at 0 °C, poured into 10% citric acid, and extracted with AcOEt. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (40% AcOEt in *n*-hexane), then crystallized with AcOEt/*n*-hexane to afford **9** (137 g, 0.321 mol, 77% in 2 steps) as a white powder; IR (film, cm^{-1}) 3033, 2924, 2869, 1710, 1612, 1585, 1512, 1489, 1382, 1241, 1128, 808, 738; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.50–8.09 (br, 1H), 7.19–7.44 (m, 9H), 6.91 (d, $J=8.3$ Hz, 2H), 6.74 (d, $J=8.5$ Hz, 1H), 4.99 (s, 2H), 4.91 (s, 2H), 3.59 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.1, 158.6, 155.7, 136.9, 133.7, 131.3, 128.8, 128.7, 128.6, 128.0, 127.5, 125.2, 114.9, 113.6, 112.8, 70.1, 70.0, 35.8; HRMS (FAB) Calcd for $C_{22}H_{20}BrO_4$ $(M+H)^+$ 427.0544, found 427.0531.

4.1.5. [2-(4-Benzyloxy-benzyloxy)-5-bromo-phenyl]-acetic acid methyl ester. To a stirred solution of the carboxylic acid **9** (250 mg, 0.60 mmol) in Et_2O added diazomethane which was generated from *N*-methyl-*N*-nitrosourea in KOH/Et_2O dropwise at 0 °C. The reaction mixture was allowed to room temperature, and stirred for 2 h. When the reaction was completed, AcOH was added into the mixture. Then the mixture was evaporated with toluene as a white solid (214 mg, 0.486 mmol, 81%). IR (film, cm^{-1}) 3059, 2949, 1739, 1612, 1587, 1514, 1490, 1437, 1242, 1174, 1119, 1011, 808, 745, 721, 696. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.67–7.65 (3H, m), 7.57–7.28 (6H, m), 7.00 (2H, $J=8.4$ Hz), 6.79 (1H, $J=8.4$ Hz), 5.07 (2H, s), 4.97 (2H, s), 3.63 (3H, s), 3.58 (2H, s) ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.8, 156.0, 137.0, 133.8, 132.3, 132.2, 132.1, 129.0, 128.8, 128.6, 128.2, 127.6, 125.8, 115.1, 113.7, 70.3, 70.2, 52.1, 35.9; HRMS (FAB) Calcd for $C_{23}H_{22}BrO_4$ (MH^+) 441.0701, found 441.0693.

4.1.6. [2-(4-Benzyloxy-benzyloxy)-5-bromo-phenyl]-diazo-acetic acid methyl ester (10a). To a stirred solution of the above methyl ester (151 mg, 0.343 mol), and *p*-acetoamidobenzenesulfonylazide (111 mg, 0.463 mol, 1.35 equiv.) in MeCN (3.4 ml) were added DBU (0.15 ml, 1.01 mmol, 2.94 equiv.). The mixture was stirred for 4 h. Then the mixture was quenched with NH_4Cl aq, partitioned between Et_2O and NH_4Cl aq. Organic layers were washed with brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography as a yellow solid (114 mg, 0.243 mmol, 71%). IR (film, cm^{-1}): 2104, 1741, 1703, 1612, 1514, 1487, 1381, 1244, 1174, 1018, 812, 742, 696. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.73 (s, 1H), 7.25–7.44 (m, 8H), 6.83 (d, $J=9.2$ Hz, 1H), 5.07 (s, 2H), 4.99 (s, 2H), 3.82 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.1, 159.1, 153.4, 138.7, 132.2, 130.8, 130.3, 129.3, 129.0, 128.6, 128.1, 128.0, 127.5, 115.1, 115.0, 114.2, 70.4, 70.0, 52.1; HRMS (FAB): 439.0547 ($C_{23}H_{20}O_4Br$, $MH^+ - N_2$). Exact mass 439.0544 ($MH^+ - N_2$).

4.1.7. 2-(4-Benzyloxy-phenyl)-5-bromo-2,3-dihydro-benzofuran-3-carboxylic acid methyl ester (11a, 12a). To a stirred solution of **10a** (42 mg, 0.090 mmol) in CH_2Cl_2 (0.90 ml) was added Rh_2(*S*-DOSP)$_4$ (10 mg, 0.0053 mmol, 0.058 equiv.). The mixture was stirred for 10 min, and the residue was evaporated under reduced pressure. The ratio of cis:trans was determined by ^1H NMR.

4.1.8. 2-{[2-(4-Benzyloxy-benzyloxy)-5-bromo-phenyl]-acetoxy}-propionic acid methyl ester. To a stirred solution of **9** (260 mg, 0.63 mmol) in CH_2Cl_2 (2.5 ml) was added WSCD·HCl (250 mg, 1.30 mmol, 2.07 equiv.) and (*S*)-methyl lactate (0.085 ml, 0.90 mmol, 1.43 equiv.) and DMAP (5 mg, 0.041 mmol, 0.07 equiv.) at 0 °C. The mixture was allowed to room temperature, and stirred for 1.5 h. The reaction mixture was partitioned between CH_2Cl_2 and H_2O, washed with brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography as a yellow oil (290 mg, 0.565 mmol, 90%). IR (film, cm^{-1}) 2951, 1745, 1612, 1514, 1491, 1242, 1174, 1012, 810, 742. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.24–7.44 (m, 9H), 6.97 (d, $J=8.0$ Hz, 2H), 6.78 (d, $J=8.4$ Hz, 1H), 5.08 (s, 2H), 4.97 (s, 2H), 4.29 (q, $J=7.2$ Hz, 1H), 3.78 (s, 3H), 3.70 (s, 2H), 1.42 (d, $J=7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.0, 171.1, 158.5, 155.7, 136.8, 133.5, 131.1, 128.7, 128.5, 127.9, 127.3, 125.1, 114.8, 113.4, 112.6, 70.0, 68.8, 66.6, 52.2, 35.2, 16.7; HRMS (FAB) Calcd for $C_{26}H_{26}BrO_6$ $(M+H^+)$ 513.0912, found 513.0929.

4.1.9. 2-{[2-(4-Benzyloxy-benzyloxy)-5-bromo-phenyl]-diazo-acetoxy}-propionic acid methyl ester (10b). To a stirred solution of the above ester (280 mg, 0.545 mmol), and *p*-acetoamidobenzenesulfonylazide (170 mg, 0.708 mmol, 1.30 equiv.) in MeCN (5.0 ml) were added DBU (0.20 ml, 1.34 mmol, 2.45 equiv.). The mixture was stirred for 1 h. Then the mixture was quenched with NH_4Cl aq, partitioned between Et_2O and NH_4Cl aq. Organic layers were washed with brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography as a yellow solid (235 mg, 0.436 mmol, 80%). IR (film, cm^{-1}): 2955, 2106, 1755, 1703, 1612, 1514, 1491, 1246, 1155, 1097, 1007, 823, 741, 696. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.51 (3H, d, $J=7.6$ Hz), 3.76 (3H, s), 4.99 (2H, s), 5.07 (2H, s), 5.22 (1H, q, $J=7.2$ Hz), 6.82 (1H, d, $J=8.4$ Hz), 6.98 (2H, d, $J=8.4$ Hz), 7.27–7.44 (8H, m), 7.77 (1H, d, $J=2.8$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.2, 158.9, 153.3, 136.8, 132.0, 129.4, 129.3, 128.6, 128.0, 127.9, 127.4, 115.8, 114.9, 113.7, 70.8, 70.0, 69.0, 52.4; HRMS (FAB) Calcd for $C_{26}H_{24}BrO_6N_2$ $(M+H)^+$ 539.0817, found 539.0840.

4.1.10. 2-(4-Benzyloxy-phenyl)-5-bromo-2,3-dihydro-benzofuran-3-carboxylic acid 1-methoxycarbonyl-ethyl ester (12b). To a stirred solution of **10b** (11.5 mg, 0.021 mmol) in CH_2Cl_2 (0.40 ml) was added Rh_2(*S*-DOSP)$_4$ (1.9 mg, 0.001 mmol, 0.048 equiv.). The mixture

was stirred for 10 min, and the residue was evaporated under reduced pressure. The ratio of cis:trans was determined by ^{1}H NMR.

4.1.11. (1′*R*)-[2-(4-Benzyloxy-benzyloxy)-5-bromo-phenyl]-acetic acid 1′-methyl-2′-oxo-2′-pyrrolidin-1′-yl-ethyl ester. To a mixture of **9** (180 g, 0.422 mol), **15c** (72.3 g, 0.506 mol, 1.2 equiv.) and triphenylphosphine (132 g, 0.504 mol, 1.2 equiv.) in toluene (500 ml) was added DEAD (40% in toluene, 210 ml, 0.463 mol, 1.1 equiv.) for 2 h at 0 °C. The mixture was allowed to room temperature, and stirred for further 2 h. The reaction mixture was filtered through a pad of Celite, and concentrated under reduced pressure. The residue was purified by flash chromatography (60% AcOEt in *n*-hexane) to afford the above ester (186 g, 0.337 mol, 80%) as a colorless oil; $[\alpha]_D^{27}+19°$ ($c=0.75$, $CHCl_3$); IR (film, cm^{-1}) 3064, 3033, 2976, 2875, 1739, 1654, 1513, 1490, 1457, 1434, 1242, 1174, 1033, 810, 742; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.24–7.45 (m, 9H), 6.97 (d, $J=8.6$ Hz, 2H), 6.76 (d, $J=8.8$ Hz, 1H), 5.14 (q, $J=6.7$ Hz, 1H), 5.05 (s, 2H), 4.96 (s, 2H), 3.74 (d, $J=16.5$ Hz, 1H), 3.63 (d, $J=16.5$ Hz, 1H), 3.54 (dt, $J=9.8$, 6.7 Hz, 1H), 3.48 (dt, $J=12.2$, 6.8 Hz, 1H), 3.39 (dt, $J=12.2$, 6.8 Hz, 1H), 3.27 (dt, $J=9.8$, 6.7 Hz, 1H), 1.89 (ddt, $J=6.7$, 6.7, 6.6 Hz, 2H), 1.78 (ddt, $J=6.8$, 6.8, 6.6 Hz, 2H), 1.35 (d, $J=6.7$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.8, 168.5, 158.4, 155.6, 136.7, 133.6, 131.1, 128.8, 128.6, 128.5, 127.9, 127.3, 125.2, 114.7, 113.4, 112.7, 69.9, 69.9, 68.7, 45.9, 45.9, 35.2, 26.0, 23.8, 16.3; HRMS (FAB) Calcd for $C_{29}H_{30}BrNO_5$ (M^+) 551.1307, found 551.1326.

4.1.12. (1′*R*,2*R*,3*R*)-2-(4-Benzyloxy-phenyl)-5-bromo-2,3-dihydro-benzofuran-3-carboxylic acid 1′-methyl-2′-oxo-2′-pyrrolidin-1′-yl-ethyl ester (17). To a mixture of the above ester (8.12 g, 14.7 mmol) and *p*-acetamidobenzenesulfonyl azide (4.24 g, 17.7 mmol, 1.2 equiv.) in CH_3CN (70 ml) was slowly added DBU (2.90 ml, 19.4 mmol, 1.3 equiv.) at 0 °C. The mixture was allowed to room temperature, and stirred for 10 h. The reaction mixture was poured into 10% citric acid, and extracted with AcOEt. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (50% AcOEt in *n*-hexane) to afford desired diazoester and inseparable co-products. To the mixture in CH_2Cl_2 (50 ml) was added Rh_2(*S*-DOSP)$_4$ (83.7 mg, 0.0440 mmol, 0.0030 equiv.) at 0 °C. After stirring for 30 min at the same temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (50% AcOEt in *n*-hexane) to afford **17** (5.10 g, 9.27 mmol, 63% in 2 steps) as a colorless powder; $[\alpha]_D^{26}-53°$ ($c=0.18$, $CHCl_3$); IR (film, cm^{-1}) 3066, 3033, 2977, 2952, 2876, 1740, 1656, 1514, 1472, 1433, 1236, 1175, 1025, 829, 737; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37 (s, 1H), 7.11–7.29 (m, 8H), 6.80 (d, $J=8.8$ Hz, 2H), 6.60 (d, $J=8.8$ Hz, 1H), 5.95 (d, $J=7.3$ Hz, 1H), 5.08 (q, $J=6.7$ Hz, 1H), 4.88 (s, 2H), 4.24 (d, $J=7.3$ Hz, 1H), 1.61–1.83 (m, 4H), 1.36 (d, $J=6.7$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.1, 168.2, 159.0, 158.6, 136.8, 136.8, 132.5, 132.4, 128.6, 128.5, 128.0, 127.4, 127.3, 126.0, 115.1, 112.5, 111.4, 86.0, 70.0, 69.6, 54.9, 46.1, 46.1, 26.2, 23.9, 16.5; HRMS (FAB) Calcd for $C_{29}H_{28}BrNO_5$ (M^+) 549.1151, found 549.1140.

4.1.13. (2*R*,3*R*)-2-(4-Benzyloxy-phenyl)-5-bromo-2,3-dihydro-benzofuran-3-carboxylic acid (18). To a solution of **17** (5.10 g, 9.27 mmol) in THF (40 ml) and MeOH (40 ml) was added $Ba(OH)_2\cdot 8H_2O$ (3.21 g, 10.2 mmol, 1.1 equiv.) at 0 °C. The mixture was allowed to room temperature, and stirred for 3 h. The reaction mixture was poured into 10% citric acid, and extracted with AcOEt. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (4% MeOH in CH_2Cl_2) to afford **18** (3.55 g, 8.35 mmol, 90%). $[\alpha]_D^{26}-75°$ ($c=1.1$, $CHCl_3$); IR (film, cm^{-1}) 2910, 1715, 1613, 1587, 1514, 1472, 1417, 1381, 1237, 1175, 827, 737; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.46–10.67 (br, 1H), 7.51 (s, 1H), 7.26–7.42 (m, 8H), 6.95 (d, $J=8.8$ Hz, 2H), 6.75 (d, $J=8.8$ Hz, 2H), 6.01 (d, $J=7.6$ Hz, 1H), 5.04 (s, 2H), 4.28 (d, $J=7.6$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.2, 159.0, 158.3, 136.6, 132.7, 131.9, 128.6, 128.3, 128.0, 127.4, 127.2, 125.4, 115.2, 112.7, 111.5, 85.7, 70.0, 55.1; HRMS (FAB) Calcd for $C_{22}H_{17}BrO_4$ (M^+) 424.0310, found 424.0324.

4.1.14. (2*R*,3*R*)-2-(4′-Benzyloxy-phenyl)-5-bromo-2,3-dihydro-benzofuran-3-carboxylic acid 3-[[4′-(*tert*-butyl-diphenyl-silanyloxy)-butyl]-(2′-nitro-benzenesulfonyl)-amino]-propyl ester (20). To a mixture of **18** (35.0 g, 82.4 mmol), **19** (55.8 g, 97.9 mmol, 1.2 equiv.) and triphenylphosphine (23.7 g, 90.5 mmol, 1.1 equiv.) in toluene (200 ml) and THF (10 ml) was added DEAD (40% in toluene, 41.0 ml, 90.5 mmol, 1.1 equiv.) at 0 °C. The mixture was allowed to room temperature, and stirred for 30 min. The reaction mixture was filtered through a pad of Cellite, and concentrated under reduced pressure. The residue was purified by flash chromatography (50% AcOEt in *n*-hexane) to afford the above ester **20** (77.4 g, 79.1 mmol, 96%). $[\alpha]_D^{27}-37°$ ($c=0.72$, $CHCl_3$); IR (film, cm^{-1}) 3070, 2931, 2859, 1732, 1613, 1588, 1540, 1513, 1471, 1373, 1236, 1162, 1111, 824, 736; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.90–7.93 (m, 1H), 7.51–7.68 (m, 7H), 7.23–7.45 (m, 15H), 6.95 (d, $J=8.8$ Hz, 2H), 6.74 (d, $J=8.5$ Hz, 1H), 6.03 (d, $J=7.6$ Hz, 1H), 5.04 (s, 2H), 4.23 (d, $J=8.5$ Hz, 1H), 4.20 (t, $J=6.3$ Hz, 2H), 3.61 (t, $J=6.0$ Hz, 2H), 3.39 (dt, $J=7.1$, 7.6 Hz, 2H), 3.30 (t, $J=7.6$ Hz, 2H), 1.90–1.99 (m, 2H), 1.44–1.65 (m, 4H), 1.01 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.0, 159.0, 158.4, 148.0, 136.7, 135.5, 133.7, 133.4, 133.3, 132.4, 132.3, 131.5, 130.6, 129.6, 128.5, 128.1, 127.9, 127.6, 127.4, 127.2, 126.1, 124.1, 115.1, 112.5, 111.4, 86.0, 70.0, 63.1, 62.9, 55.2, 47.5, 44.2, 29.4, 27.6, 26.8, 24.6, 19.1; HRMS (FAB) Calcd for $C_{51}H_{53}BrN_2NaO_9SSi$ $(M+Na)^+$ 999.2322, found 999.2294.

4.1.15. (2*R*,3*R*)-2-(4-Benzyloxy-phenyl)-5-bromo-2,3-dihydro-benzofuran-3-carboxylic acid 3-[4-(*tert*-butyl-diphenyl-silanyloxy)-butylamino]-propyl ester (21). To a mixture of the above ester **20** (56.9 g, 58.2 mmol) and K_2CO_3 (16.2 g, 117 mmol, 2.0 equiv.) in DMF (80 ml) and CH_3CN (100 ml) was added thiophenol (7.80 ml, 76.4 mmol, 1.3 equiv.), and the mixture was heated at 50 °C for 40 min. After cooling, the reaction mixture was

poured into 5% NaCl in water, and extracted with AcOEt. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography (100% AcOEt) to afford **21** (40.7 g, 51.4 mmol, 88%). $[\alpha]_D^{27}-45°$ ($c=0.53$, $CHCl_3$); IR (film, cm^{-1}) 3392, 3069, 2931, 2858, 1739, 1613, 1587, 1513, 1471, 1428, 1372, 1237, 1112, 824, 737; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.64–7.68 (m, 4H), 7.24–7.47 (m, 15H), 6.95 (d, $J=8.6$ Hz, 2H), 6.78 (d, $J=3.9$ Hz, 1H), 6.05 (d, $J=7.4$ Hz, 1H), 5.05 (s, 2H), 4.20 (d, $J=7.4$ Hz, 1H), 4.15–4.33 (m, 2H), 3.66 (t, $J=5.9$ Hz, 2H), 2.67 (t, $J=7.2$ Hz, 2H), 2.59 (t, $J=6.8$ Hz, 2H), 1.86 (tt, $J=6.8$, 6.8 Hz, 2H), 1.51–1.62 (br, 4H), 1.04 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.2, 159.0, 158.4, 136.7, 135.6, 135.5, 134.0, 132.5, 132.3, 129.5, 128.6, 128.6, 128.2, 128.0, 127.6, 127.4, 127.3, 126.3, 115.2, 112.6, 111.5, 86.0, 70.0, 64.1, 63.8, 55.4, 49.7, 46.2, 30.3, 29.0, 26.9, 26.2, 19.2; HRMS (FAB) Calcd for $C_{45}H_{51}BrNO_5Si$ $(M+H)^+$ 792.2720, found 792.2770.

4.1.16. (2*R*,3*R*)-2-(4-Benzyloxy-phenyl)-5-bromo-2,3-dihydro-benzofuran-3-carboxylic acid [4′-(*tert*-butyl-diphenyl-silanyloxy)-butyl]-(3′-hydroxy-propyl)-amide (23). To a solution of **21** (21.0 g, 26.5 mmol) in CH_2Cl_2 (200 ml) was added dimethylaluminium chloride (0.98 M in CH_2Cl_2, 35.1 ml, 34.4 mmol, 1.3 equiv.) at 0 °C, and the mixture was allowed to room temperature. After 1 h, the mixture was heated at reflux for 3 h. After cooling, the reaction mixture was carefully poured into cold saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography (40% AcOEt in *n*-hexane) to afford **23** (14.1 g, 17.8 mmol, 67%). $[\alpha]_D^{26}-50°$ ($c=0.90$, $CHCl_3$); IR (film, cm^{-1}) 3435, 3069, 2932, 2858, 1960, 1888, 1629, 1587, 1513, 1381, 1240, 1174, 1111, 824, 738; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.57–7.67 (m, 4H), 7.23–7.42 (m, 14H), 7.09 (s, 1H), 6.95 (d, $J=8.6$ Hz, 2H×1/4), 6.89 (d, $J=8.8$ Hz, 2H×3/4), 6.77 (d, $J=8.6$ Hz, 1H×3/4), 6.74 (d, $J=8.5$ Hz, 1H×1/4), 6.09 (d, $J=9.3$ Hz, 1H×1/4), 6.00 (d, $J=9.0$ Hz, 1H×3/4), 5.04 (s, 2H×1/4), 4.96 (s, 2H×3/4), 4.69 (d, $J=9.3$ Hz, 1H×1/4), 4.49 (d, $J=9.0$ Hz, 1H×3/4), 3.05–3.71 (m, 8H), 1.53–1.85 (m, 4H), 1.21–1.45 (m, 2H), 1.05 (s, 9H×1/4), 1.00 (s, 9H×3/4); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.4, 170.0, 159.0, 136.6, 135.4, 133.8, 133.5, 132.2, 131.8, 131.5, 129.6, 128.9, 128.5, 127.9, 127.6, 127.3, 126.4, 115.1, 112.6, 111.6, 88.9, 88.7, 69.9, 63.4, 62.9, 58.2, 53.7, 52.9, 47.9, 46.0, 44.1, 42.5, 31.2, 30.5, 29.9, 29.2, 26.8, 26.0, 24.2, 19.0; HRMS (FAB) Calcd for $C_{45}H_{51}BrNO_5Si$ $(M+H)^+$ 792.2720, found 792.2744.

4.1.17. (2′*R*,3′*R*)-Acetic acid 3-{[2′-(4″-benzyloxy-phenyl)-5′-bromo-2′,3′-dihydro-benzofuran-3′-carbonyl]-[4′-(*tert*-butyl-diphenyl-silanyloxy)-butyl]-amino}-propyl ester (24). To a solution of **23** (27.1 g, 34.2 mmol) in pyridine (80 ml) was added acetic anhydride (4.20 ml, 44.6 mmol, 1.3 equiv.) at 0 °C. The mixture was allowed to room temperature, and stirred for 8 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by flash chromatography (30% AcOEt in *n*-hexane) to afford the above acetate **24** (25.1 g, 30.1 mmol, 88%). $[\alpha]_D^{26}-51°$ ($c=1.1$, $CHCl_3$); IR (film, cm^{-1}) 3069, 2931, 2858, 1739, 1651, 1613, 1587, 1514, 1471, 1385, 1243, 1174, 1111, 824, 738; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.66 (d, $J=7.8$ Hz, 4H×1/3), 7.60 (d, $J=6.8$ Hz, 4H×2/3), 7.23–7.41 (m, 14H), 7.10 (s, 1H), 6.95 (d, $J=8.6$ Hz, 2H×1/3), 6.89 (d, $J=8.8$ Hz, 2H×2/3), 6.76 (d, $J=8.5$ Hz, 1H), 6.02 (d, $J=9.3$ Hz, 1H×2/3), 6.04 (d, $J=9.3$ Hz, 1H×1/3), 5.04 (s, 2H×1/3), 4.95 (s, 2H×2/3), 4.49 (d, $J=9.3$ Hz, 1H×1/3), 4.45 (d, $J=9.3$ Hz, 1H×2/3), 3.69–4.10 (m, 8H), 2.03 (s, 3H×2/3), 1.87 (s, 3H×1/3), 1.89–1.95 (br, 2H), 1.52–1.80 (br, 2H), 1.22–1.44 (br, 2H), 1.06 (s, 9H×1/3), 1.00 (s, 9H×2/3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.8, 170.4, 169.9, 169.8, 158.9, 136.6, 135.4, 133.8, 133.5, 132.0, 131.9, 131.8, 129.7, 129.5, 129.0, 128.5, 127.9, 127.6, 127.3, 127.1, 126.5, 115.1, 112.6, 111.5, 88.7, 69.9, 63.4, 62.9, 62.0, 60.8, 53.5, 48.1, 46.3, 44.7, 43.8, 29.8, 29.2, 28.6, 27.1, 26.7, 26.0, 24.3, 20.8, 20.6, 19.2, 19.0; HRMS (FAB) Calcd for $C_{47}H_{53}BrNO_6Si$ $(M+H)^+$ 834.2826, found 834.2847.

4.1.18. (2′*R*,3′*R*)-3-[3′-{(3″-Acetoxy-propyl)-[4″-(*tert*-butyl-diphenyl-silanyloxy)-butyl]-carbamoyl}-2′-(4″-benzyloxy-phenyl)-2′,3′-dihydro-benzofuran-5′-yl]-acrylic acid methyl ester (25). To a mixture of the above acetate (12.7 g, 15.2 mmol), tris(*o*-tolyl)phosphine (833 mg, 2.74 mmol, 0.18 equiv.) and methyl acrylate (8.20 ml, 91.1 mmol, 6.0 equiv.) in DMF (50 ml) was added palladium acetate (205 mg, 0.915 mmol, 0.060 equiv.), and the mixture was heated at 100 °C for 24 h. After cooling, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (40% AcOEt in *n*-hexane) to afford **25** (10.7 g, 12.7 mmol, 84%). $[\alpha]_D^{24}-80°$ ($c=0.96$, $CHCl_3$); IR (film, cm^{-1}) 3069, 2950, 2858, 1715, 1650, 1606, 1514, 1488, 1385, 1239, 1111, 823, 738; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.59–7.68 (m, 5H), 7.24–7.44 (m, 14H), 7.20 (s, 1H), 6.96 (d, $J=8.5$ Hz, 1H), 6.89 (d, $J=8.6$ Hz, 2H), 6.28 (d, $J=15.8$ Hz, 1H×2/3), 6.26 (d, $J=15.9$ Hz, 1H×1/3), 6.08 (d, $J=8.8$ Hz, 1H×1/2), 6.08 (d, $J=9.0$ Hz, 1H×1/2), 5.05 (s, 2H×1/3), 4.96 (s, 2H×2/3), 4.50 (d, $J=9.0$ Hz, 1H×1/3), 4.49 (d, $J=8.8$ Hz, 1H×2/3), 4.03–4.21 (m, 1H), 3.80–3.99 (m, 1H), 3.78 (s, 3H×2/3), 3.75 (s, 3H×1/3), 3.60–3.73 (m, 2H), 3.12–3.57 (m, 4H), 2.04 (s, 3H×6/11), 2.03 (s, 3H×2/11), 1.87 (s, 3H×3/11), 1.90–1.97 (br, 2H), 1.53–1.84 (br, 2H), 1.28–1.45 (br, 2H), 1.06 (s, 9H×1/3), 1.00 (s, 9H×2/3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.0, 170.5, 170.2, 170.1, 167.7, 167.6, 161.8, 161.7, 159.1, 159.0, 144.6, 144.6, 136.7, 135.5, 135.4, 133.8, 133.5, 133.5, 132.0, 131.8, 130.5, 129.7, 129.6, 128.6, 128.5, 128.0, 128.0, 127.9, 127.9, 127.8, 127.7, 127.6, 127.4, 127.4, 127.3, 127.2, 123.3, 115.2, 115.1, 115.1, 110.5, 110.4, 89.0, 70.0, 69.9, 63.4, 63.0, 62.0, 60.9, 53.3, 53.3, 51.6, 48.2, 46.4, 44.9, 43.7, 29.9, 29.3, 28.7, 27.2, 26.9, 26.8, 26.1, 24.3, 20.9, 20.7, 19.2, 19.1; HRMS (FAB) Calcd for $C_{51}H_{57}NO_8Si$ (M^+) 839.3853, found 839.3887.

4.1.19. (2*S*,3*R*,2′*R*,3′*R*)-3-[3′-{(3″-Acetoxy-propyl)-[4″-(*tert*-butyl-diphenyl-silanyloxy)-butyl]-carbamoyl}-2′-(4-benzyloxy-phenyl)-2′,3′-dihydro-benzofuran-5′-yl]-3-benzyloxycarbonylamino-2-hydroxy-propionic acid methyl ester (26). To a solution of benzyl carbamate (7.42 g, 49.1 mmol, 3.2 equiv.) in *n*-propyl alcohol (40 ml) at room temperature was added 1.6 M NaOH (29.7 ml,

47.5 mmol, 3.1 equiv.), followed by a freshly prepared solution of *t*-butyl hypochrorite (5.35 ml, 47.6 mmol, 3.1 equiv.). After 15 min, a solution of the ligand $(DHQD)_2$-PHAL (95%, 1.00 g, 1.22 mmol, 0.080 equiv.) in *n*-propyl alcohol (1 ml) was added. To the mixture was added **25** (12.9 g, 15.4 mmol), followed by a solution of $K_2OsO_2(OH)_4$ (339 mg, 0.920 mmol, 0.060 equiv.) in H_2O (1.0 ml), and the mixture was stirred for 4 h. The reaction mixture was quenched with $NaHSO_3$ (16.0 g, 10 equiv.), poured into 10% citric acid, then extracted with AcOEt. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (60% AcOEt in *n*-hexane) to afford **26** (10.2 g, 10.1 mmol, 66%). $[\alpha]_D^{26}-46°$ ($c=1.0$, $CHCl_3$); IR (film) 3363, 3068, 2952, 2858, 1731, 1644, 1587, 1514, 1384, 1239, 1111, 824, 739 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.66 (d, $J=6.8$ Hz, 4H×3/10), 7.60 (dd, $J=6.6$, 1.0 Hz, 4H×7/10), 7.16–7.43 (m, 20H), 6.92–7.14 (m, 1H), 6.79–6.90 (m, 2H), 5.94–6.13 (m, 1H), 5.67–5.90 (br, 1H), 5.04 (s, 2H×1/3), 4.97–5.25 (br, 3H), 4.93 (s, 2H×2/3), 4.34–4.66 (br, 2H), 3.04–4.19 (br, 11H), 1.82–2.08 (br, 5H), 1.50–1.75 (br, 2H), 1.18–1.40 (br, 2H), 1.05 (s, 9H×1/3), 1.01 (s, 9H×2/3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.0, 171.4, 170.5, 159.4, 158.9, 156.4, 155.7, 136.7, 136.3, 135.4, 133.6, 132.1, 129.6, 128.4, 127.9, 127.6, 127.3, 122.6, 115.1, 109.8, 88.5, 88.2, 73.5, 69.9, 66.8, 63.4, 62.9, 62.0, 60.9, 60.1, 59.7, 56.4, 53.7, 52.8, 52.5, 47.9, 46.3, 44.7, 42.9, 42.3, 29.8, 29.3, 28.6, 26.8, 25.8, 24.2, 20.8, 20.6, 19.1; HRMS (FAB) Calcd for $C_{59}H_{66}N_2NaO_{11}Si$ $(M+Na)^+$ 1029.4334, found 1029.4352.

4.1.20. (2*R*,3*R*,2′*R*,3′*R*)-3-[3′-{(3″-Acetoxy-propyl)-[4″-(*tert*-butyl-diphenyl-silanyloxy)-butyl]-carbamoyl}-2′-(4″-benzyloxy-phenyl)-2′,3′-dihydro-benzofuran-5′-yl]-3-benzyloxycarbonylamino-2-chloro-propionic acid methyl ester (27). To a mixture of **26** (3.01 g, 2.99 mmol) and triphenylphosphine (1.56 g, 5.95 mmol, 2.0 equiv.) in toluene (10 ml) was added carbon tetrachloride (4.31 ml, 44.9 mmol, 15 equiv.), and the mixture was heated at 100 °C for 2 h. After cooling, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (40% AcOEt in *n*-hexane) to afford the above chloride **27** (2.68 g, 2.61 mmol, 87%). $[\alpha]_D^{26}-55°$ ($c=1.2$, $CHCl_3$); IR (film, cm^{-1}) 3419, 3321, 3068, 2952, 2858, 1732, 1650, 1587, 1456, 1242, 1111, 824, 737; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.66 (d, $J=6.8$ Hz, 4H×1/3), 7.60 (d, $J=6.6$ Hz, 4H×2/3), 7.21–7.45 (m, 19H), 7.08–7.18 (m, 1H), 6.95 (d, $J=8.3$ Hz, 1H), 6.87 (d, $J=8.3$ Hz, 2H×2/3), 6.82 (d, $J=8.0$ Hz, 2H×1/3), 6.51 (brd, $J=8.6$ Hz, 1H), 6.07 (d, $J=9.0$ Hz, 1H×3/4), 6.01 (d, $J=8.6$ Hz, 1H×1/4), 5.22–5.37 (br, 1H), 5.05 (s, 2H×1/3), 5.01–5.15 (br, 2H), 4.92 (s, 2H×2/3), 4.71 (brd, $J=5.1$ Hz, 1H×1/2), 4.55–4.66 (br, 1H×1/2), 4.47 (d, $J=8.6$ Hz, 1H×1/4), 4.45 (d, $J=9.0$ Hz, 1H×3/4), 3.67 (s, 3H×2/3), 3.63 (s, 3H×1/9), 3.61 (s, 3H×2/9), 3.56–4.20 (br, 3H), 3.35–3.55 (br, 3H), 3.01–3.25 (m, 2H), 1.82–2.06 (m, 3H), 1.51–2.06 (br, 4H), 1.21–1.39 (br, 2H), 1.05 (s, 9H×2/7), 1.00 (s, 9H×5/7); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.6, 170.4, 168.4, 159.9, 159.0, 155.7, 136.7, 136.3, 135.5, 133.9, 133.6, 132.0, 129.7, 129.1, 128.5, 128.1, 127.7, 127.4, 122.3, 115.2, 110.0, 88.7, 70.0, 67.1, 63.5, 63.0, 62.0, 61.0, 58.8, 57.3, 53.7, 53.1, 47.9, 46.4, 44.9, 42.7, 29.8, 29.4, 28.7, 27.2, 26.9, 25.9, 24.3, 20.9, 19.2; HRMS (FAB) Calcd for $C_{59}H_{65}ClN_2O_{10}Si$ (M^+) 1024.4097, found 1024.4128

4.1.21. (3*R*,2′*R*,3′*R*)-3-[3′-{(3″-Acetoxy-propyl)-[4″-(*tert*-butyl-diphenyl-silanyloxy)-butyl]-carbamoyl}-2′-(4″-benzyloxy-phenyl)-2′,3′-dihydro-benzofuran-5′-yl]-3-amino-propionic acid methyl ester (28). A mixture of cholide **27** (230 mg, 0.225 mmol), ammonium formate (141 mg, 2.24 mmol, 10 equiv.) and 10% palladium on carbon (47.5 mg, 0.0446 mmol, 0.20 equiv.) in MeOH (3.0 ml) was heated at 60 °C for 75 min. After cooling, the reaction mixture was filtered through a pad of Celite, and concentrated under reduced pressure. The residue was poured into saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was used in the next reaction without further purification. To a mixture of the crude product, benzyl alcohol (30.0 μl, 0.290 mmol, 1.3 equiv.) and triphenylphosphine (71.0 mg, 0.271 mmol, 1.2 equiv.) in toluene (2.0 ml) was added DEAD (40% in toluene, 0.120 ml, 0.264 mmol, 1.2 equiv.) at 0 °C. The mixture was allowed to room temperature, then heated at 60 °C for 2 h. The reaction mixture was filtered through a pad of Celite, and concentrated under reduced pressure. The residue was purified by flash chromatography (5% MeOH in AcOEt) to afford the above amine **28** (118 mg, 0.138 mmol, 61% in 2 steps). $[\alpha]_D^{27}-53°$ ($c=1.1$, $CHCl_3$); IR (film, cm^{-1}) 3380, 3305, 3068, 2931, 2858, 1732, 1651, 1514, 1487, 1384, 1243, 1111, 824, 740, 703; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.64–7.66 (m, 2H), 7.59–7.61 (m, 2H), 7.24–7.45 (m, 13H), 7.15–7.21 (m, 1H), 7.05 (s, 1H), 6.95 (d, $J=4.3$ Hz, 1H), 6.87 (d, $J=13.7$ Hz, 2H×1/2), 6.85 (d, $J=13.4$ Hz, 2H×1/2), 6.03 (d, $J=9.0$ Hz, 1H×2/3), 6.02 (d, $J=8.9$ Hz, 1H×1/3), 5.05 (s, 2H×1/3), 4.95 (s, 2H×2/3), 4.48 (d, $J=8.9$ Hz, 1H×1/3), 4.46 (d, $J=9.0$ Hz, 1H×2/3), 4.36 (dd, $J=13.3$, 6.7 Hz, 1H), 3.80–4.13 (m, 2H), 3.68 (s, 3H×2/3), 3.66 (s, 3H×1/3), 3.40–3.56 (m, 2H), 3.10–3.37 (m, 2H), 2.60–2.63 (m, 2H), 2.02 (s, 3H×2/3), 1.88 (s, 3H×1/3), 1.75–1.97 (m, 4H), 1.52–1.72 (m, 2H), 1.22–1.44 (m, 2H), 1.04 (s, 9H×1/3), 1.00 (s, 9H×2/3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.6, 171.0, 170.6, 159.1, 137.6, 136.8, 135.5, 133.7, 132.5, 129.8, 128.6, 128.0, 127.7, 127.4, 121.4, 115.1, 110.0, 88.4, 70.1, 63.5, 63.1, 62.1, 61.0, 53.8, 52.4, 51.7, 48.2, 46.4, 44.9, 44.2, 43.6, 29.9, 29.5, 28.8, 27.2, 26.9, 26.1, 24.3, 20.9, 19.2; HRMS (FAB) Calcd for $C_{51}H_{60}N_2NaO_8Si$ $(M+Na)^+$ 879.4017, found 879.3998.

4.1.22. (3*R*,2′*R*,3′*R*)-3-[3′-{(3″-Acetoxy-propyl)-[4″-(*tert*-butyl-diphenyl-silanyloxy)-butyl]-carbamoyl}-2′-(4″-benzyloxy-phenyl)-2′,3′-dihydro-benzofuran-5-yl]-3-(2-nitro-benzenesulfonylamino)-propionic acid methyl ester (29). To a mixture of the amine **28** (3.78 g, 4.41 mmol) and Na_2CO_3 (935 mg, 8.82 mmol, 2.0 equiv.) in CH_2Cl_2 (20 ml) and water (15 ml) was added 2-nitro-benzensulfonyl chloride (1.26 g, 5.70 mmol, 1.3 equiv.), and the mixture was stirred for 4 h. The reaction mixture was poured into water, and extracted with CH_2Cl_2. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash

chromatography (40% AcOEt in *n*-hexane) to afford **29** (3.33 g, 3.20 mmol, 72%). $[\alpha]_D^{26}-113°$ ($c=0.26$, $CHCl_3$); IR (film, cm^{-1}) 3314, 3069, 2932, 2858, 1737, 1646, 1612, 1541, 1513, 1490, 1362, 1241, 1171, 1112, 1046, 854, 824, 740; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.51–7.80 (m, 8H), 7.19–7.47 (m, 14H), 6.37–7.05 (m, 5H), 5.86 (d, $J=9.6$ Hz, 1H×2/3), 5.84 (d, $J=10.0$ Hz, 1H×1/3), 5.04 (s, 2H), 4.88–4.98 (m, 1H), 4.30 (d, $J=10.0$ Hz, 1H×1/3), 4.29 (d, $J=9.6$ Hz, 1H×2/3), 4.13 (t, $J=6.8$ Hz, 2H), 3.61 (s, 3H), 3.09–4.03 (m, 6H), 2.79–2.99 (m, 2H), 2.09 (s, 3H×2/3), 1.90 (s, 3H×1/3), 1.75–2.07 (m, 2H), 1.52–1.68 (br, 2H), 1.22–1.37 (br, 2H), 1.06 (s, 9H×1/3), 1.01 (s, 9H×2/15), 0.99 (s, 9H×8/15); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.7, 170.7, 170.6, 169.7, 169.6, 159.3, 159.3, 158.9, 147.2, 136.7, 135.5, 135.5, 134.1, 133.9, 133.9, 133.6, 133.6, 133.1, 133.0, 132.6, 132.2, 132.2, 132.0, 131.7, 131.6, 131.5, 130.6, 130.5, 129.8, 129.6, 129.0, 128.6, 128.5, 128.1, 128.0, 127.7, 127.7, 127.5, 127.4, 127.4, 127.2, 127.2, 127.0, 125.9, 125.6, 121.5, 121.1, 115.2, 115.0, 109.3, 109.2, 88.6, 88.5, 70.0, 69.9, 63.4, 63.0, 62.2, 61.2, 55.2, 53.4, 53.3, 51.9, 48.3, 46.6, 45.0, 43.5, 41.6, 41.5, 30.0, 29.4, 28.9, 27.3, 26.9, 26.8, 26.0, 24.4, 21.0, 20.7, 19.3, 19.1; HRMS(FAB) Calcd for $C_{57}H_{63}N_3NaO_{12}SSi$ $(M+Na)^+$ 1064.3799, found 1064.3848.

4.1.23. (3*R*,2′*R*,3′*R*)-3-[3′-{(3″-Acetoxy-propyl)-[4″-(*tert*-butyl-diphenyl-silanyloxy)-butyl]-carbamoyl}-2′-(4″-benzyloxy-phenyl)-2′,3′-dihydro-benzofuran-5′-yl]-3-{(2″-nitro-benzenesulfonyl-[3′-(*tert*-butyl-dimethyl-silanyloxy)-propyl]-amino)-propionic acid methyl ester (31). To a mixture of **29** (3.31 g, 3.18 mmol), **30** (905 mg, 4.76 mmol, 1.5 equiv.) and triphenylphosphine (1.08 g, 4.12 mmol, 1.3 equiv.) in toluene (20 ml) was added DEAD (40% in toluene, 1.87 ml, 4.12 mmol, 1.3 equiv.) at 0 °C. The mixture was allowed to room temperature, and heated at 60 °C for 1 h. After cooling, the reaction mixture was filtered through a pad of Celite, and concentrated under reduced pressure. The residue was purified by flash chromatography (30% AcOEt in *n*-hexane) to afford **31** (3.66 g, 3.01 mmol, 95%). $[\alpha]_D^{27}-65°$ ($c=1.8$, $CHCl_3$); IR (film, cm^{-1}) 3073, 2953, 2930, 2894, 2857, 1739, 1648, 1613, 1588, 1544, 1513, 1490, 1429, 1372, 1241, 1172, 1111, 835, 742; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.86–7.93 (m, 1H), 7.54–7.70 (m, 7H), 7.25–7.44 (m, 14H), 7.07–7.23 (m, 1H), 6.96 (d, $J=8.6$ Hz, 2H×1/3), 6.89 (d, $J=8.8$ Hz, 2H×2/3), 6.75 (d, $J=8.3$ Hz, 1H×2/3), 6.73 (d, $J=8.6$ Hz, 1H×1/3), 6.12 (d, $J=9.0$ Hz, 1H×2/3), 6.08 (d, $J=9.0$ Hz, 1H×1/3), 5.42–5.50 (m, 1H), 5.06 (s, 2H×1/3), 4.95 (s, 2H×2/3), 4.43 (d, $J=9.0$ Hz, 1H×1/3), 4.40 (d, $J=9.0$ Hz, 1H×2/3), 4.11 (t, $J=6.3$ Hz, 2H×1/2), 4.11 (t, $J=6.3$ Hz, 2H×1/2), 3.54 (s, 3H×5/8), 3.53 (s, 3H×3/8), 3.41–4.00 (m, 6H), 3.10–3.40 (m, 5H), 2.81–2.96 (m, 1H), 2.04 (s, 3H×2/3), 1.88 (s, 3H×1/3), 1.25–1.71 (br, 8H), 1.05 (s, 9H×1/3), 1.01 (s, 9H×2/3), 0.91 (s, 9H×1/8), 0.88 (s, 9H×7/8), 0.02 (s, 6H×2/3), 0.01 (s, 6H×1/3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.1, 170.6, 170.4, 170.3, 170.0, 159.8, 159.7, 158.9, 158.9, 147.9, 136.7, 135.5, 135.5, 133.9, 133.9, 133.9, 133.8, 133.7, 133.3, 132.3, 132.2, 131.7, 131.4, 131.4, 129.8, 129.7, 129.6, 128.6, 128.5, 128.3, 128.2, 128.0, 128.0, 127.7, 127.7, 127.5, 127.4, 127.2, 127.1, 124.3, 124.1, 123.9, 115.2, 115.0, 109.6, 88.5, 88.3, 70.0, 69.9, 63.5, 63.0, 62.2, 61.1, 60.5, 57.3, 57.3, 53.4, 53.3, 52.0, 48.1, 46.5, 44.9, 43.6, 43.6, 37.6, 33.5, 30.0, 29.4, 28.7, 27.1, 26.9, 26.8, 25.9, 25.8, 24.3, 21.0, 20.7, 19.2, 19.2, 18.2, −5.4; HRMS (FAB) Calcd for $C_{66}H_{83}N_3NaO_{13}SSi_2$ $(M+Na)^+$ 1236.5083, found 1236.5085

4.1.24. (3*R*,2′*R*,3′*R*)-3-[3′-{(3″-Acetoxy-propyl)-[4″-(*tert*-butyl-diphenyl-silanyloxy)-butyl]-carbamoyl}-2′-(4″-benzyloxy-phenyl)-2′,3′-dihydro-benzofuran-5′-yl]-3-[3′-(*tert*-butyl-dimethyl-silanyloxy)-propylamino]-propionic acid methyl ester. To a mixture of **31** (3.66 g, 3.01 mmol) and thiophenol (1.62 ml, 15.9 mmol, 5.3 equiv.) in CH_3CN (20 ml) was added 5.0 M aqueous KOH (1.58 ml, 7.90 mmol, 2.6 equiv.), and the mixture was heated at 60 °C for 2 h. After cooling, the reaction mixture was filtered through a pad of Celite, and concentrated under reduced pressure. The residue was purified by flash chromatography (5% MeOH in AcOEt) to afford the amine (2.88 g, 2.80 mmol, 93%). $[\alpha]_D^{26}-43°$ ($c=0.31$, $CHCl_3$); IR (film, cm^{-1}) 3336, 3070, 3034, 2930, 2857, 1739, 1651, 1612, 1513, 1485, 1362, 1245, 1173, 1111, 835, 740; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.66 (d, $J=6.4$ Hz, 4H×1/3), 7.60 (dd, $J=6.4$, 1.5 Hz, 4H×2/3), 7.26–7.45 (m, 14H), 7.19 (br, 1H×1/2), 7.17 (br, 1H×1/2), 6.95 (d, $J=8.6$ Hz, 2H×1/2), 6.88 (d, $J=8.6$ Hz, 2H×1/2), 6.84 (d, $J=8.3$ Hz, 1H), 6.06 (d, $J=9.0$ Hz, 1H×2/3), 6.03 (d, $J=9.0$ Hz, 1H×1/3), 5.05 (s, 2H×1/3), 4.94 (s, 2H×2/3), 4.46 (d, $J=9.0$ Hz, 1H×1/3), 4.44 (d, $J=9.0$ Hz, 1H×2/3), 3.62 (s, 3H×2/3), 3.59 (s, 3H×1/3), 3.57–4.15 (br, 7H), 3.50 (brt, $J=5.9$ Hz, 2H), 3.11–3.38 (m, 2H), 2.46–2.70 (m, 4H), 2.03 (s, 3H×2/3), 1.88 (s, 3H×1/3), 1.79–2.00 (br, 2H), 1.53–1.69 (br, 4H), 1.24–1.43 (br, 2H), 1.05 (s, 9H×2/5), 1.00 (s, 9H×3/5), 0.87 (s, 9H), 0.023 (s, 6H×3/5), 0.019 (s, 6H×2/5); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.3, 172.3, 171.0, 170.5, 170.4, 159.1, 159.1, 158.9, 158.8, 136.8, 135.6, 135.5, 135.5, 133.9, 133.9, 133.6, 132.6, 132.5, 129.7, 129.6, 128.6, 128.5, 128.0, 128.0, 127.7, 127.7, 127.4, 127.4, 127.3, 127.2, 126.8, 122.2, 122.0, 115.1, 115.0, 109.9, 88.3, 88.2, 70.0, 69.9, 63.5, 63.1, 62.1, 61.6, 61.0, 59.2, 53.8, 53.7, 51.6, 48.2, 46.4, 44.9, 44.5, 43.7, 43.1, 43.1, 33.0, 32.9, 29.9, 29.4, 28.7, 27.2, 26.9, 26.8, 26.0, 25.9, 24.3, 20.9, 20.7, 19.2, 19.1, 18.3, 14.4, −5.3; HRMS (FAB) Calcd for $C_{60}H_{81}N_2O_9Si_2$ $(M+H)^+$ 1029.5481, found 1029.5527.

4.1.25. (3*R*,2′*R*,3′*R*)-3-[3′-{(3″-Acetoxy-propyl)-[4″-(*tert*-butyl-diphenyl-silanyloxy)-butyl]-carbamoyl}-2′-(4″-benzyloxy-phenyl)-2′,3′-dihydro-benzofuran-5′-yl]-3-{benzyloxycarbonyl-[3′-(*tert*-butyl-dimethyl-silanyloxy)-propyl]-amino}-propionic acid methyl ester (32). To a mixture of the amine (2.88 g, 2.80 mmol) and $NaHCO_3$ (800 mg, 9.52 mmol, 3.4 equiv.) in CH_2Cl_2 (20 ml) and water (15 ml) was added benzyl chloroformate (0.680 ml, 4.78 mmol, 1.7 equiv.), and the mixture was stirred for 1 h at room temperature. The reaction mixture was poured into saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (30% AcOEt in *n*-hexane) to afford the above silyl ether (2.95 g, 2.54 mmol, 91%). $[\alpha]_D^{27}-50°$ ($c=1.8$, $CHCl_3$); IR (film, cm^{-1}) 3069, 3033, 2952, 2857, 1736, 1698, 1648, 1612, 1586, 1513, 1362, 1246, 1174, 1110, 834, 776, 739; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.63–7.68 (m, 2H),

7.58–7.62 (m, 2H), 7.25–7.44 (m, 19H), 7.01–7.20 (br, 1H), 6.94 (d, J=8.6 Hz, 2H×1/3), 6.87 (d, J=8.8 Hz, 2H×2/3), 6.82 (d, J=8.3 Hz, 1H), 6.01–6.08 (br, 1H), 5.47–5.65 (br, 1H), 5.14 (s, 2H), 5.05 (s, 2H×1/3), 4.93 (s, 2H×2/3), 4.35–4.49 (br, 1H), 4.00–4.14 (m, 2H), 3.60 (s, 3H×2/3), 3.57 (s, 3H×1/3), 3.29–3.96 (m, 8H), 2.89–3.27 (m, 6H), 2.02 (s, 3H×1/2), 1.85 (s, 3H×1/2), 1.49–1.75 (br, 4H), 1.19–1.43 (br, 2H), 1.05 (s, 9H×1/3), 1.00 (s, 9H×2/3), 0.86 (s, 9H), −0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.2, 171.1, 171.0, 170.5, 170.2, 159.4, 159.4, 158.9, 158.9, 136.8, 136.7, 135.5, 135.5, 133.9, 133.9, 133.6, 132.4, 132.3, 132.2, 129.7, 129.6, 128.6, 128.5, 128.4, 128.0, 128.0, 127.9, 127.7, 127.7, 127.4, 127.4, 127.3, 127.2, 115.1, 115.0, 109.7, 88.5, 88.3, 70.0, 69.9, 67.0, 63.4, 63.0, 62.1, 60.9, 53.6, 53.5, 51.8, 48.0, 46.4, 44.8, 43.7, 42.7, 37.5, 32.7, 29.9, 29.4, 28.6, 27.1, 26.9, 26.8, 25.9, 24.2, 20.9, 20.7, 19.2, 19.1, 18.2, −5.4; HRMS (FAB) Calcd for $C_{68}H_{86}N_2NaO_{11}Si_2$ $(M+Na)^+$ 1185.5668, found 1185.5679.

4.1.26. (3*R*,2′*R*,3′*R*)-3-[3′-{(3″-Acetoxy-propyl)-[4″-(*tert*-butyl-diphenyl-silanyloxy)-butyl]-carbamoyl}-2′-(4″-benzyloxy-phenyl)-2′,3′-dihydro-benzofuran-5′-yl]-3-[benzyloxycarbonyl-(3′-hydroxy-propyl)-amino]-propionic acid methyl ester. To a solution of silyl ether **32** (344 mg, 0.296 mmol) in MeOH (2.0 ml) was added CSA (6.00 mg, 0.0283 mmol, 0.10 equiv.), and the mixture was stirred for 20 min at room temperature. The reaction mixture was quenched with triethylamine (13.0 μml, 0.0930 mmol, 0.30 equiv.), and concentrated under reduced pressure. The residue was purified by flash chromatography (5% MeOH in CH_2Cl_2) to afford the alcohol (293 mg, 0.279 mmol, 94%). $[\alpha]_D^{26}$ −74° (c=0.39, $CHCl_3$); IR (film, cm^{-1}) 3463, 2952, 2859, 1739, 1694, 1644, 1587, 1513, 1366, 1243, 1174, 1112, 824, 769, 738.^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.57–7.69 (m, 4H), 7.25–7.46 (m, 19H), 6.77–7.22 (br, 4H), 5.63–6.03 (br, 2H), 5.19 (brs, 2H), 5.05 (s, 2H×2/5), 4.96 (s, 2H×3/5), 4.42–4.58 (br, 1H), 4.01–4.13 (br, 2H), 3.56 (s, 3H), 2.91–3.95 (br, 14H), 2.03 (s, 3H×1/2), 1.88 (s, 3H×1/4), 1.70 (s, 3H×1/4), 1.21–1.69 (br, 6H), 1.05 (s, 9H×2/5), 1.00 (s, 9H×3/5); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.1, 170.5, 159.7, 159.7, 159.2, 159.1, 136.6, 136.6, 135.5, 135.5, 133.8, 133.8, 133.6, 133.6, 131.9, 131.8, 129.8, 129.6, 128.6, 128.6, 128.5, 128.1, 128.0, 127.7, 127.7, 127.5, 127.4, 127.4, 127.3, 122.1, 122.0, 115.3, 115.2, 110.3, 89.0, 88.9, 70.0, 69.9, 63.4, 63.0, 62.9, 62.0, 61.9, 61.0, 55.6, 55.5, 53.9, 51.8, 48.1, 46.5, 44.8, 43.7, 41.0, 29.8, 29.4, 28.5, 27.1, 26.9, 26.8, 25.9, 24.2, 20.9, 20.7, 19.2, 19.1; HRMS (FAB) Calcd for $C_{62}H_{72}N_2NaO_{11}Si$ $(M+Na)^+$ 1071.4803, found 1071.4781.

4.1.27. (3*R*,2′*R*,3′*R*)-3-[3′-{(3″-Acetoxy-propyl)-[4″-(*tert*-butyl-diphenyl-silanyloxy)-butyl]-carbamoyl}-2′-(4″-benzyloxy-phenyl)-2′,3′-dihydro-benzofuran-5-yl]-3-{benzyloxycarbonyl-[3′-(2″-nitro-benzenesulfonyl-amino)-propyl]-amino}-propionic acid methyl ester (33). To a mixture of the above alcohol (2.17 g, 1.97 mmol), 2-nitrobenzenesulfonamide (996 mg, 4.93 mmol, 2.5 equiv.) and triphenylphosphine (672 mg, 2.56 mmol, 1.3 equiv.) in toluene (15 ml) and THF (7.5 ml) was added DEAD (40% in toluene, 1.16 ml, 2.56 mmol, 1.3 equiv.) at 0 °C. The mixture was allowed to room temperature, and stirred for 40 min. The reaction mixture was filtered through a pad of Celite, and concentrated under reduced pressure. The residue was purified by flash chromatography (50% AcOEt in n-hexane) to afford the sulfonamide (2.43 g, 1.97 mmol, quant.). $[\alpha]_D^{26}$ −53° (c=1.3, $CHCl_3$); IR (film, cm^{-1}) 3258, 3068, 3030, 2952, 2932, 2897, 2856, 1739, 1696, 1643, 1542, 1514, 1491, 1428, 1365, 1243, 1171, 1113, 825, 741; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.98–8.10 (br, 1H), 7.55–7.79 (br, 7H), 7.19–7.46 (br, 19H), 6.29–7.10 (br, 4H), 5.59–5.86 (br, 2H), 5.15 (brs, 2H), 5.05 (s, 2H×3/7), 4.98 (s, 2H×4/7), 4.60 (brd, J=8.5 Hz, 1H×1/3), 4.55 (brd, J=8.5 Hz, 1H×2/3), 4.17–4.25 (br, 1H), 4.01–4.12 (br, 1H), 3.84–4.00 (br, 1H), 3.63–3.78 (br, 1H), 3.43–3.62 (br, 4H), 3.24–3.39 (br, 1H), 2.68–3.21 (br, 8H), 2.03 (s, 3H×1/2), 1.87 (s, 3H×1/2), 1.21–1.76 (br, 8H), 1.05 (s, 9H×1/3), 0.99 (s, 9H×2/3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.1, 170.6, 159.8, 159.7, 159.2, 159.1, 147.9, 136.6, 136.6, 135.5, 135.4, 133.9, 133.6, 133.1, 132.3, 131.7, 130.7, 129.7, 129.6, 128.6, 128.5, 128.5, 128.0, 127.7, 127.6, 127.6, 127.4, 127.4, 124.7, 124.6, 122.3, 122.1, 115.3, 115.2, 110.2, 89.3, 89.1, 70.0, 69.9, 63.5, 62.9, 62.2, 62.0, 61.0, 54.1, 51.8, 48.0, 43.5, 41.3, 29.8, 29.4, 28.2, 27.0, 26.9, 26.8, 25.7, 24.0, 20.9, 20.7, 19.2, 19.1, 14.4; HRMS (FAB) Calcd for $C_{68}H_{77}N_4O_{14}SSi$ $(M+H)^+$ 1233.4926, found 1233.4966.

4.1.28. (3*R*,2′*R*,3′*R*)-3-[3′-[(3″-Acetoxy-propyl)-(4″-hydroxy-butyl)-carbamoyl]-2′-(4″-benzyloxy-phenyl)-2′,3′-dihydro-benzofuran-5-yl]-3-{benzyloxycarbonyl-[3′-(2″-nitro-benzenesulfonylamino)-propyl]-amino}-propionic acid methyl ester (34). To a solution of above sulfonamide (2.43 g, 1.97 mmol) in CH_3CN (20 ml) was added HF (48 wt% solution in H_2O, 1.20 ml, 28.8 mmol, 15 equiv.), and the mixture was stirred for 90 min. The reaction mixture was carefully poured into cold saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (5% MeOH in AcOEt) to afford **34** (1.65 g, 1.66 mmol, 84%). $[\alpha]_D^{24}$ −68° (c=0.69, $CHCl_3$); IR (film, cm^{-1}) 3464, 3092, 3065, 3033, 2948, 1738, 1694, 1634, 1542, 1492, 1366, 1341, 1243, 1171, 1125, 830, 739 ; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.05 (brs, 1H), 7.74–7.81 (m, 1H), 7.64–7.73 (m, 2H), 7.28–7.46 (m, 14H), 7.00 (d, J=8.6 Hz, 2H×1/2), 6.99 (d, J=8.8 Hz, 2H×1/2), 6.80 (brd, J=7.3 Hz, 1H), 5.84 (d, J=9.0 Hz, 1H×2/3), 5.83 (d, J=8.8 Hz, 1H×1/3), 5.63–5.73 (br, 1H), 5.11–5.20 (br, 2H), 5.09 (s, 2H×1/2), 5.08 (s, 2H×1/2), 4.54–4.64 (br, 1H), 2.77–4.14 (br, 17H), 2.05 (s, 3H), 1.30–1.83 (br, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.2, 170.6, 159.8, 159.2, 155.9, 147.9, 136.7, 136.6, 133.3, 132.4, 131.9, 130.8, 128.6, 128.5, 128.1, 127.6, 127.5, 124.8, 122.4, 115.3, 115.3, 110.3, 89.2, 89.0, 70.1, 62.3, 62.0, 61.0, 54.0, 53.9, 51.9, 51.9, 48.1, 45.8, 44.6, 43.7, 41.5, 41.5, 29.7, 29.5, 28.3, 27.0, 26.1, 24.1, 21.0, 20.7; HRMS (FAB) Calcd for $C_{52}H_{59}N_4O_{14}S$ $(M+H)^+$ 995.3749, found 995.3709.

4.1.29. (13*R*,19*R*,20*R*)-3-(3′-Acetoxy-propyl)-19-(4′-benzyloxy-phenyl)-13-methoxycarbonylmethyl-8-(2′-nitro-benzenesulfonyl)-2-oxo-18-oxa-3,8,12-triaza-tricyclo[12.5.2.0^{0,0}]heneicosa-14(21),15,17(20)-triene-12-carboxylic acid benzyl ester (35). To a mixture of **34** (1.65 g, 1.66 mmol) and triphenylphosphine (564 mg, 2.15 mmol,

1.3 equiv.) in toluene (33 ml) was added DEAD (40% in toluene, 0.970 ml, 2.14 mmol, 1.3 equiv.) at 0 °C. The mixture was allowed to room temperature, and stirred for 40 min. The reaction mixture was filtered through a pad of Celite, and concentrated under reduced pressure. The residue was purified by flash chromatography (70% AcOEt in *n*-hexane) to afford **35** (1.24 g, 1.27 mmol, 77%) as a yellow oil. $[\alpha]_D^{27}-86°$ ($c=0.57$, $CHCl_3$); IR (film, cm^{-1}) 3091, 3066, 3032, 2951, 2870, 1739, 1695, 1644, 1612, 1546, 1513, 1492, 1455, 1372, 1241, 1173, 986, 851, 830, 750; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.53–7.90 (m, 4H), 7.25–7.50 (m, 13H), 6.95 (d, $J=8.8$ Hz, 2H), 6.85–7.24 (m, 2H), 6.13 (d, $J=8.3$ Hz, 1H), 5.48–5.65 (br, 1H), 5.16 (s, 2H), 5.04–5.11 (br, 2H), 4.43–4.56 (br, 1H), 3.63–4.35 (br, 4H), 3.61 (s, 3H), 2.66–3.49 (br, 10H), 1.88 (s, 3H), 1.39–2.00 (br, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.4, 171.0, 170.8, 170.6, 159.6, 159.0, 155.5, 148.3, 136.7, 136.5, 133.5, 132.4, 132.3, 131.6, 130.4, 128.6, 128.5, 128.0, 128.0, 127.8, 127.5, 127.4, 127.1, 126.9, 126.8, 124.1, 120.3, 115.3, 115.2, 110.8, 88.2, 70.0, 67.3, 62.0, 60.8, 56.3, 53.5, 51.9, 49.2, 47.4, 44.2, 37.6, 30.8, 29.4, 28.4, 26.9, 26.7, 26.4, 25.3, 25.0, 21.0, 20.7; HRMS (FAB) Calcd for C52H56N4O13S (M+) 976.3565, found 976.3542.

4.1.30. 19-(4-Benzyloxy-phenyl)-3-(3-hydroxy-propyl)-13-methoxycarbonylmethyl-8-(2-nitro-benzenesulfonyl)-2-oxo-18-oxa-3,8,12-triaza-tricyclo[12.5.2.0^{0,0}]-heneicosa-14(21),15,17(20)-triene-12-carboxylic acid benzyl ester (36). To a solution of **35** (1.24 g, 1.27 mmol) in MeOH (12 ml) and THF (3.0 ml) was added K_2CO_3 (228 mg, 1.65 mmol, 1.3 equiv.), and the mixture was stirred at room temperature for 1 h. The reaction mixture was poured into 10% citric acid, and extracted with CH_2Cl_2. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (5% MeOH in AcOEt) to afford the above alchohol (1.14 g, 1.22 mmol, 96%).as a colorless oil; $[\alpha]_D^{26}-64°$ ($c=0.40$, $CHCl_3$); IR (film, cm^{-1}) 3382, 3060, 2949, 1739, 1694, 1643, 1588, 1546, 1514, 1494, 1436, 1372, 1241, 1173, 1120, 1059, 986, 851, 830, 772, 735; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.51–7.94 (m, 4H), 7.26–7.50 (m, 13H), 6.96 (d, $J=8.8$ Hz, 2H), 6.82–7.21 (m, 2H), 6.23 (d, $J=6.8$ Hz, 1H×1/7), 6.18 (d, $J=8.6$ Hz, 1H×5/7), 5.87 (d, $J=10.3$ Hz, 1H×1/7), 5.50–5.70 (br, 1H), 5.29 (s, 2H×2/5), 5.17 (s, 2H×3/5), 5.05–5.09 (m, 2H), 4.58–4.78 (br, 1H), 4.19–4.34 (m, 2H), 3.68–3.88 (m, 2H), 3.62 (s, 3H×1/6), 3.61 (s, 3H×1/6), 3.60 (s, 3H×2/3), 2.61–3.50 (m, 12H), 1.41–2.00 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.3, 171.5, 171.1, 159.6, 159.2, 158.8, 158.8, 155.6, 148.3, 136.7, 136.5, 133.7, 133.5, 133.3, 132.9, 132.6, 132.4, 132.1, 132.0, 132.0, 132.0, 131.9, 131.6, 131.6, 131.0, 130.7, 130.4, 130.2, 128.6, 128.6, 128.5, 128.5, 128.2, 128.0, 128.0, 127.8, 127.5, 127.4, 127.4, 127.1, 127.0, 124.1, 124.1, 120.4, 115.3, 115.1, 110.8, 109.6, 89.5, 88.2, 70.1, 70.0, 67.3, 58.3, 58.1, 56.2, 54.7, 53.5, 53.0, 52.8, 52.0, 52.0, 49.1, 47.0, 43.6, 42.1, 37.7, 31.0, 29.9, 29.3, 26.5, 25.4, 25.0; HRMS (FAB) Calcd for $C_{50}H_{55}N_4O_{12}S$ $(M+H)^+$ 935.3537, found 935.3573.

4.1.31. 3-(3-Azido-propyl)-19-(4-benzyloxy-phenyl)-13-methoxycarbonylmethyl-8-(2-nitro-benzenesulfonyl)-2-oxo-18-oxa-3,8,12-triaza-tricyclo[12.5.2.0^{0,0}]heneicosa-14(21),15,17(20)-triene-12-carboxylic acid benzyl ester (37). To a mixture of the above alcohol **36** (93.0 mg, 0.0995 mmol) and triethylamine (20.0 μl, 0.144 mmol, 1.5 equiv.) in CH_2Cl_2 (0.80 ml) at 0 °C was added methanesulfonyl chloride (9.0 μl, 0.117 mmol, 1.2 equiv.), and the mixture was stirred at the same temperature for 20 min. The reaction mixture was poured into saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. To a solution of crude product in DMF (0.80 ml) was added sodium azide (20.0 mg, 0.308 mmol, 3.1 equiv.), and the mixture was heated at 60 °C for 30 min. After cooling, the reaction mixture was poured into 5% NaCl in water, and extracted with AcOEt. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (70% AcOEt in *n*-hexane) to afford the above mesylate (77.9 mg, 0.0811 mmol, 82% in 2 steps). as a yellow oil. $[\alpha]_D^{26}-83°$ ($c=0.34$, $CHCl_3$); IR (film, cm^{-1}) 3089, 3062, 3033, 2948, 2873, 2100, 1739, 1693, 1643, 1612, 1548, 1513, 1493, 1454, 1242, 1173, 985, 851, 830, 772, 735; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.73–7.91 (br, 1H), 7.53–7.70 (m, 3H), 7.24–7.48 (m, 13H), 6.98 (d, $J=8.8$ Hz, 2H), 6.93–7.24 (br, 1H+1H×1/2), 6.86 (d, $J=8.3$ Hz, 1H×1/2), 6.19 (d, $J=7.4$ Hz, 1H×1/10), 6.13 (d, $J=8.6$ Hz, 1H×4/5), 5.87 (d, $J=10.0$ Hz, 1H×1/10), 5.43–5.66 (br, 1H), 5.17 (s, 2H), 5.05–5.10 (br, 2H), 4.48–4.58 (br, 1H), 4.23–4.33 (br, 1H), 3.62 (s, 3H), 2.63–3.83 (br, 13H), 1.33–1.90 (br, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.0, 159.6, 159.0, 155.5, 148.3, 136.8, 136.5, 133.6, 133.5, 133.4, 132.4, 132.2, 131.6, 131.6, 130.7, 130.4, 130.3, 128.6, 128.5, 128.2, 128.1, 128.0, 128.0, 127.8, 127.5, 127.5, 127.4, 127.2, 127.2, 126.8, 124.1, 120.3, 115.3, 115.2, 110.9, 88.4, 70.0, 67.3, 56.3, 53.5, 52.0, 49.1, 48.0, 47.2, 44.1, 28.3, 25.0; HRMS (FAB) Calcd for $C_{50}H_{54}N_7O_{11}S$ $(M+H)^+$ 960.3602, found 960.3563.

4.1.32. 3-(3-Azido-propyl)-19-(4-benzyloxy-phenyl)-13-carboxymethyl-8-(2-nitro-benzenesulfonyl)-2-oxo-18-oxa-3,8,12-triaza-tricyclo[12.5.2.0^{0,0}]heneicosa-14(21),15,17(20)-triene-12-carboxylic acid benzyl ester. To a solution of the above methyl ester (77.9 mg, 0.0811 mmol) in MeOH (1.0 ml) and THF (0.10 ml) was added 2.0 M lithium hydroxide (0.240 ml, 0.480 mmol, 6.0 equiv.), and the mixture was stirred for 5 h. The reaction mixture was poured into 10% citric acid, and extracted with AcOEt. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (5% MeOH in CH_2Cl_2) to afford the above carboxylic acid (74.3 mg, 0.0785 mmol, 97%). $[\alpha]_D^{24}-80°$ ($c=0.28$, $CHCl_3$); IR (film, cm^{-1}) 3091, 3063, 3033, 2941, 2871, 2100, 1696, 1645, 1612, 1543, 1514, 1492, 1455, 1373, 1242, 1173, 984, 830, 737; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.71–7.97 (br, 1H), 7.50–7.69 (br, 3H), 7.00–7.50 (m, 14H), 6.97 (d, $J=8.5$ Hz, 2H), 6.83 (d, $J=7.8$ Hz, 1H), 6.12 (d, $J=8.6$ Hz, 1H), 5.29–5.70 (br, 1H), 5.13 (brs, 2H), 5.05 (brs, 2H), 4.47–4.61 (br, 1H), 4.20–4.33 (br, 1H), 2.60–3.86 (br, 13H), 1.21–1.90 (br, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.8, 171.5, 159.6, 159.0, 155.7, 148.3, 136.8, 136.4, 133.5, 132.3, 132.2, 132.1, 131.6,

131.2, 130.6, 130.3, 130.2, 128.6, 128.5, 128.0, 128.0, 127.8, 127.5, 127.5, 127.5, 127.2, 126.9, 124.1, 120.4, 115.3, 115.2, 110.8, 88.5, 70.0, 67.4, 60.4, 56.1, 53.4, 49.1, 48.0, 47.1, 44.1, 43.6, 37.7, 29.3, 28.3, 26.5, 25.0, 21.1; HRMS (FAB) Calcd for $C_{49}H_{52}N_7O_{11}S$ $(M+H)^+$ 946.3446, found 946.3463.

4.1.33. 3-(3-Azido-propyl)-19-(4-benzyloxy-phenyl)-13-pentfluororphenoxycarbonylmethyl-8-(2-nitro-benzene-sulfonyl)-2-oxo-18-oxa-3,8,12-triaza-tricyclo[12.5.2.0^{0,0}]-heneicosa-14(21),15,17(20)-triene-12-carboxylic acid benzyl ester (38). To a mixture of the above acid (83.0 mg, 0.0877 mmol) and pentafluorophenol (24.2 mg, 0.132 mmol, 1.5 equiv.) in CH_2Cl_2 (2.0 ml) was added WSCD·HCl (41.9 mg, 0.219 mmol, 2.5 equiv.) at 0 °C. The mixture was allowed to room temperature, and stirred for 30 min. The reaction mixture was poured into 10% citric acid, and extracted with AcOEt. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (50% AcOEt in *n*-hexane) to afford **38** (90.9 mg, 0.082 mmol, 93%) as a colorless oil; $[\alpha]_D^{26}-61°$ ($c=0.28$, $CHCl_3$); IR (film, cm^{-1}) 3064, 3034, 2936, 2101, 1787, 1697, 1645, 1612, 1586, 1546, 1520, 1456, 1373, 1244, 1173, 1101, 996, 830, 773, 738; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.75–7.90 (br, 1H), 7.54–7.70 (m, 3H), 7.14–7.45 (m, 13H), 7.07 (s, 1H), 6.98 (d, $J=8.8$ Hz, 2H), 6.90 (d, $J=8.3$ Hz, 1H), 6.20 (d, $J=7.1$ Hz, 1H×1/7), 6.14 (d, $J=8.3$ Hz, 1H×6/7), 5.61–5.73 (br, 1H), 5.19 (s, 2H), 5.05–5.10 (br, 2H), 4.57 (d, $J=8.3$ Hz, 1H×6/7), 4.53 (d, $J=7.1$ Hz, 1H×1/7), 4.21–4.33 (br, 1H), 2.96–3.84 (br, 11H), 2.61–2.90 (br, 2H), 1.32–1.90 (br, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.4, 166.5, 160.0, 159.1, 155.5, 148.3, 142.2, 140.8, 139.8, 139.1, 138.4, 136.8, 136.6, 136.3, 133.5, 133.4, 132.3, 132.2, 131.6, 130.4, 129.7, 128.6, 128.1, 128.0, 127.9, 127.5, 127.4, 127.1, 124.1, 120.2, 115.3, 115.2, 115.2, 111.1, 88.5, 70.0, 67.5, 53.4, 49.3, 47.9, 44.1, 30.7, 29.7, 28.4, 27.1, 26.4, 25.0; HRMS (FAB) Calcd for $C_{55}H_{51}F_5N_7O_{11}S$ $(M+H)^+$ 1112.3287, found 1112.3262

4.1.34. *O*-Benzyloxy-*N*1-benzyloxycarbonyl-*N*2-nitro-benzensulfonyl-ephedradine-A (41). To a solution of triphenylphosphine (69.0 mg, 0.263 mmol, 2.5 equiv.) in toluene (10 ml) at reflux was added a solution of **38** (117 mg, 0.105 mmol) in toluene (5.0 ml) *via* syringe pump for 4 h. After the addition, the mixture was heated at the same temperature for 4 h. After cooling, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in CH_3CN (5.0 ml) and water (1.0 ml), and heated at reflux for 60 h. The reaction mixture was poured into water, and extracted with CH_2Cl_2. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (5% MeOH in AcOEt) to afford **41** (69.3 mg, 0.0768 mmol, 73%) as a colorless as a colorless oil; $[\alpha]_D^{23}-60°$ ($c=0.21$, $CHCl_3$); IR (film, cm^{-1}) 3413, 3353, 3089, 3065, 3033, 2932, 2873, 1691, 1649, 1544, 1513, 1454, 1372, 1173, 1125, 828, 736; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.76–7.93 (m, 1H), 7.28–7.72 (m, 16H), 7.09 (brd, $J=8.2$ Hz, 1H), 6.98 (d, $J=8.8$ Hz, 2H), 6.85 (d, $J=8.2$ Hz, 1H), 6.36 (d, $J=10.8$ Hz, 1H), 5.86 (dd, $J=5.6$, 5.4 Hz, 1H), 5.16–5.30 (m, 2H), 5.07 (s, 2H), 4.45 (d, $J=10.8$ Hz, 1H), 1.40–4.38 (m, 22H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.5, 169.2, 159.6, 159.0, 156.6, 156.0, 148.2, 136.8, 133.0, 132.6, 131.9, 131.8, 131.4, 130.7, 130.6, 130.1, 128.6, 128.6, 128.1, 128.0, 127.8, 127.7, 127.5, 125.9, 123.9, 123.5, 115.0, 110.4, 87.9, 70.0, 67.3, 60.1, 53.9, 48.5, 46.7, 45.4, 45.1, 42.9, 37.8, 29.7, 28.3, 26.8, 24.8; HRMS (FAB) Calcd for $C_{49}H_{52}N_5O_{10}S$ $(M+H)^+$ 902.3435, found 902.3466.

4.1.35. *O*-Benzyloxy-*N*1-benzyloxycarbonyl-ephedradine-A. To a mixture of **41** (75.9 mg, 0.0841 mmol) and thiophenol (34.0 μl, 0.333 mmol, 4.0 equiv.) in CH_3CN (4.0 ml) was added 5.0 M aqueous KOH (42.0 μl, 0.210 mmol, 2.5 equiv.), and the reaction mixture was heated at 50 °C for 70 min. After cooling, the reaction mixture was filtered through a pad of Celite, and concentrated under reduced pressure. The residue was purified by flash chromatography (*i*-$PrNH_2$/MeOH/AcOEt=1/1/8) to afford the above amine (45.3 mg, 0.0632 mmol, 75%) as a colorless as a colorless oil; $[\alpha]_D^{22}-94°$ ($c=0.43$, $CHCl_3$); IR (film, cm^{-1}) 3309, 3062, 3034, 2954, 2932, 2871, 1690, 1645, 1513, 1496, 1454, 1414, 1241, 1130, 1114, 828, 736; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.27–7.53 (m, 13H), 7.15 (d, $J=8.2$ Hz, 1H), 6.97 (d, $J=8.8$ Hz, 2H), 6.83 (d, $J=8.2$ Hz, 1H), 6.43 (d, $J=10.2$ Hz, 1H×2/3), 6.33 (d, $J=10.7$ Hz, 1H×1/3), 5.54 (brs, 1H), 5.21 (s, 2H×1/2), 5.20 (s, 2H×1/2), 5.07 (s, 2H), 4.44 (d, $J=10.0$ Hz, 1H), 1.36–4.23 (m, 22H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.0, 171.4, 169.4, 169.1, 159.3, 159.0, 158.9, 136.9, 136.8, 132.7, 132.5, 132.0, 130.7, 128.6, 128.5, 128.0, 128.0, 127.9, 127.8, 127.7, 127.7, 127.5, 127.4, 124.9, 124.3, 115.0, 111.1, 110.3, 87.4, 70.0, 67.1, 57.6, 56.0, 54.1, 49.1, 49.0, 47.6, 47.1, 47.0, 41.4, 41.0, 37.4, 30.2, 29.7, 28.5, 28.0, 27.4, 23.6, 22.8, 22.2; HRMS (FAB) Calcd for $C_{43}H_{48}N_4O_6$ $(M+H)^+$ 717.3653, found 717.3649.

4.1.36. Ephedradine-A (1). To a solution of the above amine (16.2 mg, 0.0226 mmol) in CH_2Cl_2 (0.60 ml) was added BCl_3 (1.0 M in CH_2Cl_2, 0.090 ml, 0.090 mmol, 4.0 equiv.) at −78 °C, and the mixture was stirred for 30 min at the same temperature. The mixture was allowed to 0 °C, and stirred for 90 min. The reaction mixture was poured into saturated aqueous $NaHCO_3$, and extracted with 10% MeOH in CH_2Cl_2. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by PTLC (*i*-$PrNH_2$/MeOH/CH_2Cl_2 =5/5/90) to afford Ephedradine A (**1**) (8.17 mg, 0.0166 mmol, 73%) as a colorless oil; $[\alpha]_D^{25}-72°$ ($c=0.25$, $CHCl_3$/MeOH=9/1); IR (film, cm^{-1}) 3287 (br), 2929, 1641, 1519, 1488; ^1H NMR (CD_3OD, 400 MHz) δ 7.29 (d, $J=8.7$ Hz, 2H), 7.21 (brs, 1H), 7.13 (dd, $J=8.0$, 1.0 Hz, 1H), 6.78 (d, $J=8.7$ Hz, 2H), 6.77 (d, $J=8.0$ Hz, 1H), 6.01 (d, $J=11.3$ Hz, 1H), 4.59 (d, $J=11.3$ Hz, 1H), 4.13 (dd, $J=13.9$, 8.5 Hz, 1H), 3.62–3.98 (m), 2.52–3.00 (m), 2.04–2.45 (m), 1.43–1.92 (m); ^{13}C NMR (CD_3OD, 100 MHz) δ 173.6, 171.7, 160.2, 159.4, 136.8, 131.1, 130.7, 129.1, 129.1, 127.3, 123.7, 116.5, 116.5, 110.0, 89.5, 61.6, 54.7, 49.7, 48.5, 47.8, 47.1, 44.9, 43.1, 38.4, 29.5, 27.7, 27.6, 25.8; HRMS (FAB) Calcd for $C_{28}H_{36}N_4O_4$ $(M+H)^+$ 493.2816, found 493.2824.

Acknowledgements

We thank Professor Yoshiteru Oshima (Tohoku University) for providing spectral data of the natural product. The authors also thank Dr. H. Naoki (Suntory Institute for Bioorganic Research) for kindly measuring the HRMS. This work was financially supported by CREST, JST, and a Grant-in-Aid from the Ministry of Education, Science, Sports, Culture and Technology, Japan.

References and notes

1. (a) Tamada, M.; Endo, K.; Hikino, H.; Kabuto, C. *Tetrahedron Lett.* **1979**, 873–876. (b) Dätwyler, P.; Bosshardt, H.; Johne, S.; Hesse, M. *Helv. Chim. Acta* **1979**, *62*, 2712–2723.
2. Ahmad, V. U.; Sultana, V. *J. Nat. Prod.* **1990**, *53*, 1162–1167.
3. Wasserman, H. H.; Brunner, R. K.; Buynak, J. D.; Carter, C. G.; Oku, T.; Robinson, R. P. *J. Am. Chem. Soc.* **1985**, *107*, 519–521.
4. For a review on Ns chemistry, see: (a) Kan, T.; Fukuyama, T. *J. Synth. Org. Chem. Jpn* **2001**, *59*, 779–789. (b) Kurosawa, W.; Kan, T.; Fukuyama, T. *Org. Synth.* **2002**, *79*, 186–195. (c) Kan, T.; Fukuyama, T. *Chem. Commun.* **2004**, 353–359.
5. (a) Fujiwara, A.; Kan, T.; Fukuyama, T. *Synlett* **2000**, 1667–1669. (b) Kan, T.; Kobayashi, H.; Fukuyama, T. *Synlett* **2002**, 697–699. (c) Kan, T.; Fujiwara, A.; Kobayashi, H.; Fukuyama, T. *Tetrahedron* **2002**, *58*, 6267–6276.
6. Kurosawa, W.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2003**, *125*, 8112–8113.
7. For construction of dihydrobenzofuran rings by oxidative dimerization, see: (a) Rummakko, P.; Brunow, G.; Orlandi, M.; Rindone, B. *Synlett* **1999**, 333–335. (b) Bolzacchini, E.; Brunow, G.; Meinardi, S.; Orlandi, M.; Rindone, B.; Rummakko, P.; Setala, H. *Tetrahedron Lett.* **1998**, *39*, 3291–3294. (c) Maeda, S.; Masuda, H.; Tokoroyama, T. *Chem. Pharm. Bull.* **1994**, *42*, 2536–2545. (d) Maeda, S.; Masuda, H.; Tokoroyama, T. *Chem. Pharm. Bull.* **1994**, *42*, 2500–2505. (e) Antus, S.; Gottsegen, Á.; Kolonits, P.; Wagner, H. *Liebigs Ann. Chem.* **1989**, 593–594. (f) Antus, S.; Bauer, R.; Gottsegen, A.; Seligmann, O.; Wagner, H. *Liebigs Ann. Chem.* **1987**, 357–360.
8. For other methods for constructing dihydrobenzofuran rings, see: (a) Russell, M. G. N.; Baker, R.; Ball, R. G.; Thomas, S. R.; Tsou, N. N.; Castro, J. L. *J. Chem. Soc., Perkin Trans. 1* **2000**, 893–899. (b) Russell, M. G. N.; Baker, R.; Castro, J. L. *Tetrahedron Lett.* **1999**, *40*, 8667–8690. (c) Prakash, O.; Tanwar, M. P. *Bull. Chem. Soc. Jpn* **1995**, *68*, 1168–1171. (d) Baker, R.; Cooke, N. G.; Humphrey, G. R.; Wright, S. H. B.; Hirshfield, J. *J. Chem. Soc., Chem. Commun.* **1987**, 1102–1104.
9. For a review on asymmetric intermolecular C–H activation, see: Davies, H. M. L.; Antoulinakis, E. G. *J. Organomet. Chem.* **2001**, *617*, 47–55.
10. Davies, H. M. L.; Grazini, M. V. A.; Aouad, E. *Org. Lett.* **2001**, *3*, 1475–1477.
11. Davies, H. M. L.; Hansen, T.; Churchill, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 3063–3070.
12. Kurosawa, W.; Kan, T.; Fukuyama, T. *Synlett* **2003**, 1028–1030.
13. Since the 4-(benzyloxy)benzyl chloride was not commercially available, it was prepared from 4-(hydroxy)benzaldehyde in the following three-step sequence: (a) K_2CO_3, BnBr, DMF, 60 °C, quant; (b) $NaBH_4$, THF/H_2O, 99%; (c) $SOCl_2$, CH_2Cl_2, 98%.
14. Davies, H. M. L.; Huby, N. J. S.; Cantrell, J.r.; W, R.; Olive, J. L. *J. Am. Chem. Soc.* **1993**, *115*, 9468–9479.
15. High diastereoinduction with pyrrolidinyl (*S*)-lactamide as a chiral auxiliary has been reported by Tschaen in the S_N2 reaction of α-haloester derivatives: Devine, P. N.; Dolling, U.-H.; Heid, R. M. Jr.; Tschaen, D. M. *Tetrahedron Lett.* **1996**, *37*, 2683–2686.
16. For double asymmetric induction in intramolecular C–H insertion reactions, see: Hashimoto, S.; Watanabe, N.; Kawano, K.; Ikegami, S. *Synth. Commun.* **1994**, *24*, 3277–3287.
17. (a) Mitsunobu, O. *Synthesis* **1981**, 1–28. (b) Hughes, D. L. *Org. React.* **1992**, *42*, 335–656.
18. Lipton, M. F.; Basha, A.; Weinreb, S. M. *Org. Synth.* **1979**, *59*, 49–52.
19. Shimizu, T.; Osako, K.; Nakata, T. *Tetrahedron Lett.* **1997**, *38*, 2685–2688.
20. Heck, R. F. *Org. React.* **1982**, *27*, 345–390.
21. Li, G.; Angert, H. H.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **1996**, *35*, 2813–2817.
22. McDougal, P. G.; Rico, J. G.; Oh, Y. I.; Condon, B. C. *J. Org. Chem.* **1986**, *51*, 3388–3390.
23. Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635–646.
24. Gololobov, Y. G.; Kasukhin, L. F. *Tetrahedron* **1992**, *48*, 1353–1406.
25. Bosch, I.; Romea, P.; Urpi, F.; Vilarrasa, J. *Tetrahedron Lett.* **1993**, *34*, 4671–4674.
26. Recently we found that the Staudinger and the aza-Wittig protocol was also effective for the construction of medium-sized lactams, see: Fuwa, H.; Okamura, Y.; Morohashi, Y.; Tomita, T.; Iwatsubo, T.; Kan, T.; Fukuyama, T.; Natsugari, H. *Tetrahedron Lett.* **2004**, *45*, 2323–2326.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 60 (2004) 9629–9634
Tetrahedron

Concise enantioselective synthesis of (−)-lasubine II

Mirko Zaja and Siegfried Blechert*

Institu fur Organische Chemie, Technische Universität Berlin, Strasse des 17. Juni 135, Sekr.TC 2, D-10623 Berlin, Germany

Received 4 May 2004; revised 8 June 2004; accepted 10 June 2004

Available online 25 August 2004

Abstract—An enantioselective synthesis of the quinolizidine alkaloid (−)-lasubine II **1** is reported. Two different pathways to the key intermediate **2** are described. The first case involving a sequence of ring rearrangement metathesis (RRM), simple functional group interconversion operations, followed by a stereoselective cross metathesis (CM) and in the second case a domino ring opening-/ring closing-/cross metathesis step is involved. In both cases, following the metathesis reactions, exclusively the *E*-isomer was obtained. The final cyclisation towards the quinolizidine skeleton is achieved by an intramolecular Michael reaction. This concept represents the first example of a highly stereoselective RRM-CM combination in the synthesis of a natural product.

1. Introduction

Several biologically important and structurally interesting quinolizidine alkaloids possessing both *cis* and *trans* junctures have been isolated from plants of the *Lythraceae* family. Two of these alkaloids, **1** and its 3,4-dimethoxy-cinnamate ester (+)-subcosine II bearing a *trans* C-4, C-10 hydrogen relationship, were isolated in 1978 by Fuji et al. from the leaves of *Lagerstroemia subcostata* Koehne (Fig. 1).[1] Whereas numerous syntheses of **1** in racemic form have been described, only a few asymmetric syntheses have been reported since the first enantioselective synthesis in 1998 by Remuson et al.[2]

Olefin metathesis has become a useful method for the preparation of chiral heterocyclic ring systems in natural product synthesis.[3] Besides the most widely used ring-closing metathesis (RCM) combinations of RCM and ring-opening metathesis (ROM), such as the RRM, are also suitable for natural product synthesis, thereby a chiral carbocycle is transformed into a heterocyclic product, without loss of stereochemical information.[4] The first generation Grubbs catalyst [Ru-**1**][5] was found to efficiently catalyse these transformations (Fig. 2). In addition to these well established reactions CM is gaining importance as a powerful tool for the formation of carbon–carbon bonds.[6] The problem of arised *E*/*Z* selectivities can be evaded by CM reactions between terminal alkyl-substituted and electron-deficient olefins. Ruthenium complexes bearing N-heterocyclic carbene ligands such as the second generation Grubbs catalyst [Ru-**2**][7] and its phosphine-free variant [Ru-**3**],[8] have proved to be efficient catalysts to afford CM products in good to excellent yields and high *E*/*Z* selectivities.

A ruthenium-catalysed ring rearrangement metathesis and a stereoselective cross metathesis were planned as key steps of the synthesis for the key intermediate **2** (Scheme 1). The quinolizidine skeleton could be built upon N-deprotection and intramolecular Michael addition. The alkaloid would be available after stereoselective reduction of the ketone and hydrogenation of the endocyclic double bond. The enone **2** could be derived from piperidine derivative **3** after deprotection of the alcohol, oxidation to the corresponding α,β-unsaturated ketone and stereoselective CM with 1,2-dimethoxy-4-vinylbenzene **6**. From our previous studies, it was foreseen that **3** could be obtained after RRM of **4**. The RRM precursor **4** is readily available by asymmetric palladium-catalysed allylic amination of monoacetate **7**.

2. Results and discussion

2.1. Synthesis of the key intermediate 10

Initial studies towards the key intermediate **10** considered the monoacetate **7** as starting material (Scheme 2), which could be prepared easily on a multi gram scale in high enantiomeric purity (>99% ee) by enzymatic hydrolysis of the racemic *meso* diacetate.[9] The cyclopentene derivative **8a** was obtained by η^3-allyl-Pd(0) substitution with but-3-enylamine[10] in the presence of catalytic amounts of $Pd(PPh_3)_4$, followed by the protection of the nitrogen with

Keywords: Ring rearrangement metathesis; Cross metathesis; Ruthenium; Alkaloids.
* Corresponding author. Tel.: +49-30-314-222-55; fax: +49-30-314-23619; e-mail: blechert@chem.tu-berlin.de

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.06.145

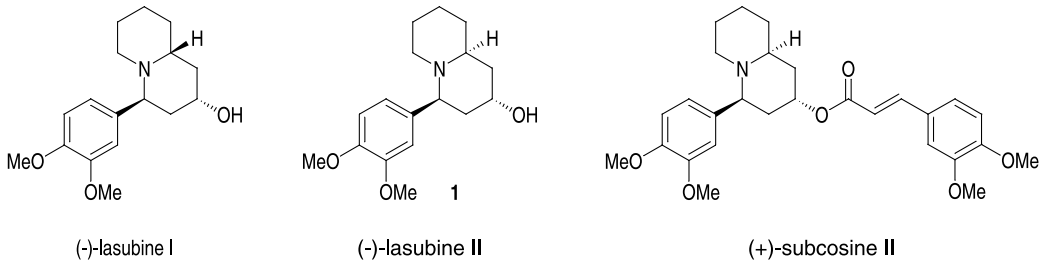


Figure 1. *Lythraceae* alkaloids.

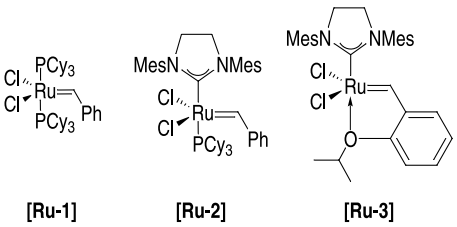
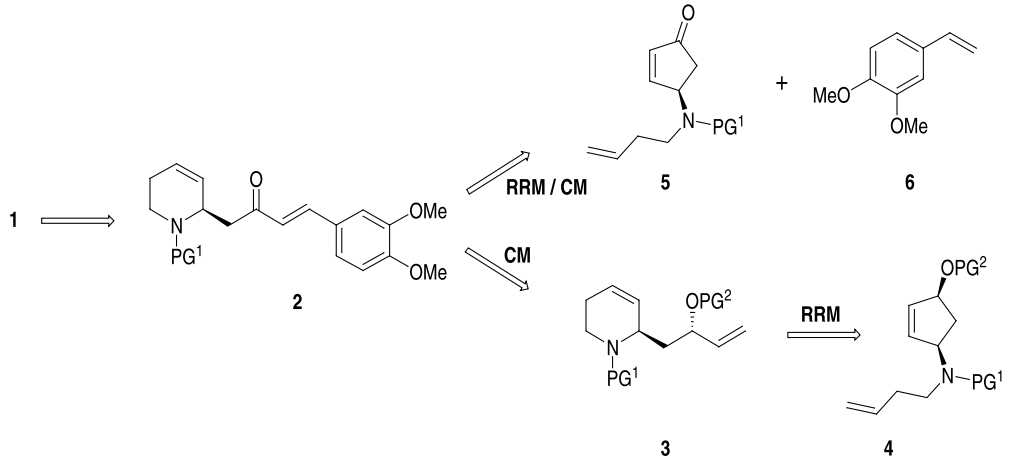


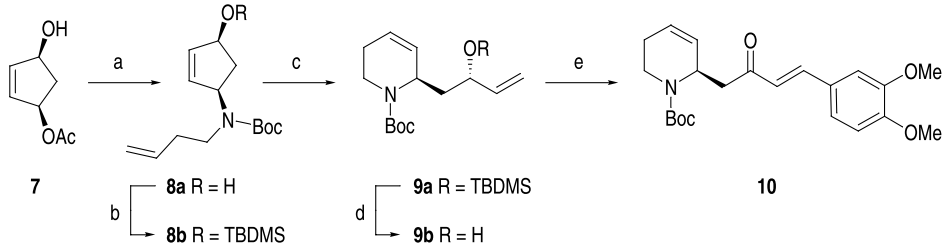
Figure 2. Ruthenium based olefin metathesis catalysts.

$(Boc)_2O$ in 65% yield (2 steps).[11] Protection of the alcohol with TBDMSCl gave the metathesis precursor **8b**. In the following RRM **8b** was converted to the piperidine derivative **9a** in 98% yield, utilising 2 mol% of [Ru-**1**] in DCM at room temperature after 57 h. For the introduction of the aryl unit a separate stereoselective CM step with **6** was envisaged. [Ru-**3**] is known to be a versatile catalyst for CM with high *E*-selectivities involving acceptor substituted alkenes, and styrenes are known to give also CM products with high *E*-selectivities.[12] To obtain an acceptor substituted olefin for the following CM step the TBDMS-group was removed with TBAF in THF to give the alcohol **9b** in 96% yield. After oxidation with Dess–Martin periodinane and filtration over silica gel the corresponding α,β-unsaturated ketone could be coupled, without any further purification, with **6**,[13] utilising 5 mol% of [Ru-**3**] in boiling DCM, to give exclusively the *E*-isomer of the key intermediate **10** after 6 h in gratifying 85% yield (2 steps).

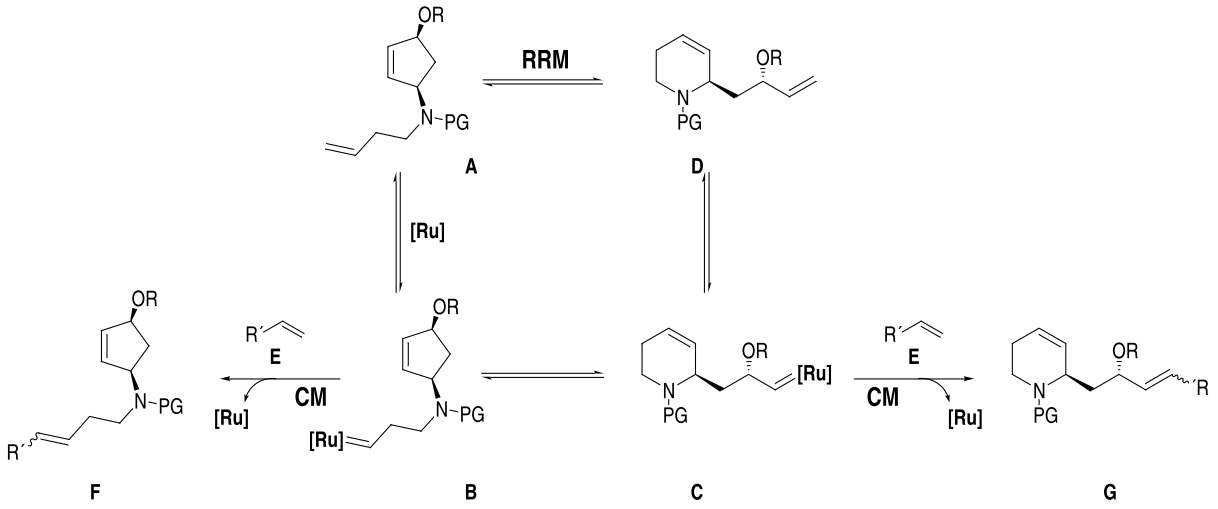
The question arose if it was possible to reduce the number of synthetic operations by combining the previously separate RRM and CM steps into one domino metathesis step. Scheme 3 shows the assumed mechanism of the ruthenium catalysed ring rearrangement of **A**, via **B** and **C**, to give the RRM product **D**. Initially the catalyst reacts with the most accessible terminal double bond of the cyclopentene derivative **A** to form the ruthenium carbene complex **B**. If the intramolecular formation of a metallacyclobutane with



Scheme 1. Retrosynthetic approach to **1**.



Scheme 2. Synthesis of **10** via sequential RRM and CM. Reagents and conditions: (a) (i) but-3-enylamine, NEt_3, THF, rt, 1 h, (ii) 5 mol% $Pd(PPh_3)_4$, 40 °C, 15 h, (iii) Boc_2O, NEt_3, MeOH, 70 °C, 4 h (65%); (b) TBDMSCl, imidazole, DMF, rt, 48 h (99%); (c) 2 mol% [Ru-**1**], DCM, reflux, 57 h (98%); (d) (i) TBAF, THF, rt, 1 h (96%); (e) (i) DMP, DCM, rt, 30 min, (ii) **6**, 5 mol% [Ru-**3**], DCM, reflux, 6 h (85%).



Scheme 3. Proposed mechanism for RRM-CM.

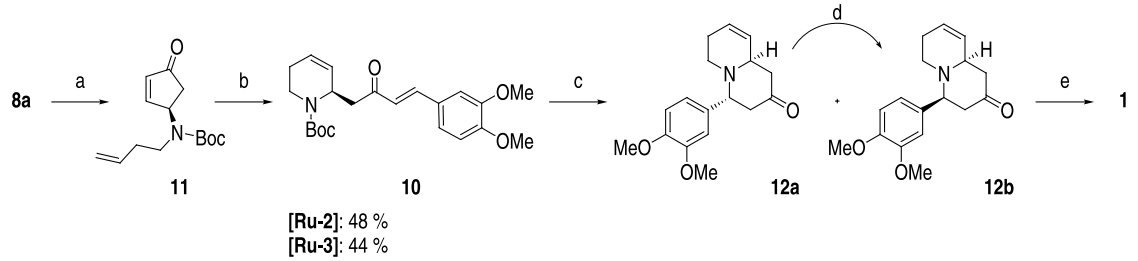
the endocyclic double bond in **B**, followed by [2+2]-cycloreversion is fast, the ruthenium carbene complex **C** should be obtained. The catalytic cycle is closed by the reaction of **C** with a molecule ethylene leading to **D** and reformation of the propagating ruthenium species.

If a CM partner **E** is added, we suppose that after the RCM/ROM sequence **C** could react with **E** to give the desired RRM/CM product **G**. Our earlier attempts to use cyclopentene derivatives like **A** as starting materials and [Ru-**1**] for this type domino metathesis have shown that after the RRM the final CM step occurs yielding only small amounts of **G**.[3d] These investigations have shown that introduction of a bulky group R, for example a TBDMS group, has a favourable effect on the equilibrium of the ring rearrangement but it was supposed that the steric effects account for the failing final CM step. The use of Schrock's highly reactive molybdenum complex [$PhMe_2CCH{=}Mo{=}N(2,6\text{-}(iPr_2C_6H_3)(OCMe(CF_3)_2)_2]$[14] resulted mainly in the CM product **F**.

Our synthesis began by investigating the one pot domino metathesis of the cyclopentenone derivative **11**, which can be obtained in 98% yield after oxidation of **8a** with MnO_2 in acetone, with **6** as CM partner. The absence of the bulky TBDMS-group could prevent the RRM step, however it should allow the final CM step to proceed. The acceptor substituted endocyclic double bond in **11** should lead solely to the *E*-configurated CM product (Scheme 4). Utilisation of 1.0 equiv cyclopentenone **11** and a excess of 3.0 equiv **6** in boiling DCM and 5 mol% of [Ru-**1**], yielded none of the desired product after 12 h. The reaction resulted only in traces of CM of the terminal double bond of **11** with **6**. However under the same reaction conditions and utilisation of 5 mol% [Ru-**2**] or [Ru-**3**] product **10** was obtained in a gratifying yield of 48% respectively 44%. In both cases the main byproduct being the CM of the terminal double bond of **11** with **6**.

2.2. Synthesis of (−)-lasubine II from key intermediate 10

Following the deprotection of the carbamate **10** in DCM with TFA at room temperature the quinolizidone derivative was obtained as a 3:2 mixture of diastereomers **12a** and **12b** by treatment with DBU at room temperature, through an intramolecular Michael reaction.[15] Treatment of **12a** with 2 N NaOH in methanol afforded the thermodynamically more stable **12b** in 98% yield, presumably through a retro Michael fragmentation–recyclisation step.[16] Unfortunately the direct reduction of **12b** with $NaBH_4$ in MeOH gave the undesired *S*-configurated quinolizin-2-ol in 99% yield, also the reduction of **12b** with L-selectride in THF at −78 °C resulted in a unsatisfactory 1:1 mixture of the two diastereomeric quinolizin-2-ols in 82% yield. For this reason the double bond was removed by hydrogenation in the presence of catalytic amounts of Pd/C in ethyl acetate to obtain the quinolizidin-2-one. Final stereoselective reduction[2e] with L-selectride in THF at −78 °C provided (−)-lasubine II in 74% yield in excellent agreement with



Scheme 4. Synthesis of **1** via one pot domino metathesis. Reagents and conditions: (a) (i) MnO_2, acetone, rt, 15 h (98%); (b) **6**, 5 mol% [Ru], DCM, reflux, 12 h; (c) (i) TFA, DCM, 0 °C, 1h, (ii) DBU, DCM, rt, 24 h (77%, **12a/12b** 3:2); (d) NaOH, MeOH, rt, 48 h (98%); (e) (i) H_2, Pd/C, ethyl acetate, 12 h, (ii) L-selectride, THF, −78 °C (74%).

previously reported values ($[\alpha]_D^{20}=-48$ (*c* 0.79, MeOH); lit.[1] $[\alpha]_D^{20}=-34.7$ (*c* 0.32, MeOH); lit.[2a] $[\alpha]_D^{20}=-41$ (*c* 3.7, MeOH); lit.[2b] $[\alpha]_D^{20}=-50$ (*c* 0.37, MeOH); lit.[2c] $[\alpha]_D^{20}=-47.5$ (*c* 3.7, MeOH); lit.[2d] $[\alpha]_D^{20}=-46.0$ (*c* 2.1, MeOH); lit.[2e] $[\alpha]_D^{20}=-53$ (*c* 0.13, MeOH).

3. Conclusion

In summary, we have demonstrated that a sequence of RRM and stereoselective CM can be combined to a one pot domino metathesis step and applied this concept successfully in the concise enantioselective synthesis of the quinolizidine alkaloid (−)-lasubine II. The variability of the side chain length of the cyclopentenone derivative and the possible free choice of CM partner makes this strategy a powerful method for synthesis of quionolizidine, indolizidine and pyrrolizidine alkaloids. Further investigations and syntheses based on this concept are currently under study in our laboratories and the results will be reported in due course.

4. Experimental

4.1. General

Each reaction with air- and moisture-sensitive components was carried out under a nitrogen atmosphere unless otherwise indicated. Tetrahydrofuran was distilled from sodium/benzophenone, and dichloromethane was distilled from calcium hydride. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) were recorded on Bruker DRX 500 in the solvent and at temperatures indicated. NMR chemical shifts are expressed in ppm upfield, relative to the internal solvent peak. Mass spectra were recorded using a Finnegan MAT 95 SQ at an ionizing potential of 70 eV. IR spectra were recorded on a Nicolet FT-750 spectrometer by attenuated total reflectance (ATR). Optical rotations were determined on a Perkin–Elmer polarimeter 341 as solutions in a 10 cm unit cell at 589 nm. Microanalysis were determined on a Elementar Varion EI. Flash chromatography was carried out using standard commercially available silica gel. Those chemicals which were purchased were used without further purification.

4.1.1. But-3-enyl-((1*R*,4*S*)-4-hydroxy-cyclopent-2-enyl)-carbamic acid *tert*-butylester (8a). To a mixture of **7**[9] (2.63 g, 18.50 mmol) and but-3-enylamine[10] (3.29 g, 46.25 mmol) in THF (70 mL) was added triethylamine (7.7 mL) and the solution was stirred for 1 h at room temperature. Then $Pd(PPh_3)_4$ (1.07 g, 0.93 mmol) was added in ten portions over 60 min, and the mixture was stirred for 15 h at 40 °C. The solution was concentrated in vacuo and the residue was taken up in methanol (40 mL), triethylamine (2.54 mL, 18.3 mmol) and Boc_2O (4.04 g, 18.5 mmol) were added and the mixture stirred at 70 °C for 4 h. The solution was concentrated in vacuo. Purification of the residue by flash chromatography (hexane/MTBE 1:1) afforded **8a** as a colourless oil (3.05 g, 65%). ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C): δ 5.90 (d, $J=5.1$ Hz, 1H), 5.77 (m, 1H), 5.71 (d, $J=5.1$ Hz, 1H), 5.04 (d, $J=17.2$ Hz, 1H), 4.99 (d, $J=10.3$ Hz, 1H), 4.85 (bs, 1H), 4.56 (bs, 1H), 4.46 (m, 1H), 3.13 (m, 2H), 2.53 (m, 1H), 2.27 (m, 2H), 1.46–1.36 (bs, 10H). ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 154.1 (C_q), 136.5 (CH), 135.3 (CH), 131.6 (CH), 115.0 (CH_2), 78.1 (C_q), 72.6 (CH), 59.2 (CH), 41.7 (CH_2), 38.7 (CH_2), 33.4 (CH_2), 27.6 ($3\times CH_3$). IR ν 3421, 2976, 2933, 1691, 1669, 1410, 1366, 1169, 1145 cm^{-1}. MS *m*/*z* (%) 253 (1), 212 (10), 112 (78), 94 (90), 83 (33), 57 (100); HR-MS Calcd for $C_{14}H_{23}NO_3$ [M^+] 253.1678, found 253.1676. $[\alpha]_D^{20}=+89$ (*c* 0.77, $CHCl_3$). Anal. Calcd for $C_{14}H_{23}NO_3$: C, 66.37; H, 9.15; N, 5.53. Found: C, 66.24; H, 8.84; N, 5.56.

4.1.2. But-3-enyl-[(1*R*,4*S*)4-(*tert*-butyl-dimethyl-silanyloxy)-cyclopent-2-enyl]-carbamic acid *tert*-butylester (8b). The mixture of alcohol **8a** (1.51 g, 5.96 mmol), TBDMSCl (898 mg, 5.96 mmol) and imidazole (609 mg, 8.94 mmol) in DMF (7 mL) was stirred for 48 h at room temperature, after this time TBDMSCl (45 mg, 0.30 mmol) was added and the solution was stirred for a further 2 h. DCM (50 mL) was added and the solution was washed with saturated NH_4Cl solution (30 mL), the organic layers were dried over $MgSO_4$, and concentated in vacuo. The residue was purified by flash chromatography (hexane/MTBE 5:1), affording **8b** (2.19 g, 99%) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$, 50 °C): δ 5.86 (d, $J=5.2$ Hz, 1H), 5.80–5.69 (m, 2H), 5.08 (bs, 1H), 5.03 (d, $J=17.3$ Hz, 1H), 4.98 (d, $J=10.2$ Hz, 1H), 4.69 (bs, 1H), 3.14 (m, 2H), 2.61 (dt, $J=14.5$, 7.8 Hz, 1H), 2.33 (m, 1H), 2.24 (m, 1H), 1.48 (bs, 10H), 0.91 (s, 9H), 0.09 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$, 50 °C) δ 155.6 (C_q), 136.7 (CH), 135.9 (CH), 133.2 (CH), 115.9 (CH_2), 79.5 (CH), 75.3 (CH), 59.6 (C_q), 42.4 (CH_2), 39.8 (CH_2), 34.9 (CH_2), 28.6 ($3\times CH_3$), 25.9 ($3\times CH_3$), 18.13 (C_q), −4.66 ($2\times CH_3$). IR ν 3077, 2956, 2930, 2857, 1693, 1408, 1366, 1253, 1170, 1145, 1085, 903, 836, 775 cm^{-1}. MS *m*/*z* (%) 367 (3), 326 (13), 254 (68), 226 (80), 172 (22), 94 (100), 75 (38), 73 (35), 57 (96); HR-MS Calcd for $C_{20}H_{37}NO_3Si$ [M^+] 367.2543, found 367.2550. $[\alpha]_D^{20}=+12$ (*c* 0.92, $CHCl_3$). Anal. Calcd for $C_{20}H_{37}NO_3Si$: C, 65.35; H, 10.15; N, 3.81. Found: C, 65.36; H, 10.17; N, 3.71.

4.1.3. (*R*)-6-[(*S*)-2-(*tert*-Butyl-dimethyl-silanyloxy)-but-3-enyl]-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butylester (9a). Compound **8b** (6.44 g, 17.52 mmol) was dissolved in DCM (360 mL), and ethylene gas (50 mL) was bubbled slowly through the solution. [Ru-**1**] (288 mg, 0.35 mmol) was added, and the mixture was stirred for 57 h at room temperature under N_2 atmosphere. The solvent was removed in vacuo, and the residue was chromatographed on silica gel (hexane/MTBE 5:1) to give **9a** (6.31 g, 98%) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$, 50 °C): δ 5.93 (ddd, $J=17.1$, 10.4, 5.8 Hz, 1H), 5.76 (m, 1H), 5.72 (m, 1H), 5.23 (d, $J=17.1$ Hz, 1H), 5.06 (d, $J=10.4$ Hz, 1H), 4.48 (bs, 1H), 4.23 (dt, $J=6.1$, 6.1 Hz, 1H), 4.10 (bs, 1H), 2.85 (t, *J* 10.7 Hz, 1H), 2.20 (bs, 1H), 1.90 (dt, $J=17.3$, 4.1 Hz, 1H), 1.83 (dt, $J=13.4$, 6.8 Hz, 1H), 1.65 (dt, $J=13.4$, 6.8 Hz, 1H), 1.46 (s, 9H), 0.90 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, 50 °C) δ 154.6 (C_q), 141.2 (CH), 129.0 (CH), 125.0 (CH), 114.0 (CH_2), 79.4 (C_q), 71.3 (CH), 49.1 (CH), 42.8 (CH_2), 36.7 (CH_2), 28.6 ($3\times CH_3$), 25.9 ($3\times CH_3$), 25.1 (CH_2), 18.22 (C_q), −4.3 (CH_3), −4.9 (CH_3). IR ν 2957, 2929, 2857, 1695, 1417, 1364, 1251, 1173, 1106, 836, 775 cm^{-1}. MS

m/z (%) 367 (2), 254 (100), 126 (52), 82 (28), 57 (28); HR-MS Calcd for $C_{20}H_{37}NO_3Si$ [M^+] 367.2543, found 367.2551. $[\alpha]_D^{20}=-144$ (*c* 0.67, $CHCl_3$). Anal. Calcd for $C_{20}H_{37}NO_3Si$: C, 65.35; H, 10.15; N, 3.81. Found: C, 65.38; H, 9.68; N, 3.66.

4.1.4. (*R*)-6-((*S*)-2-Hydroxy-but-3-enyl)-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butylester (9b). To a solution of **9a** (2.00 g, 5.44 mmol) in THF (80 mL) was added 1.0 M solution of TBAF in THF (6.0 mL, 5.98 mmol). The mixture was stirred for 1 h at room temperature, concentrated in vacuo and the resulting yellow oil was chromatographed on silica gel (hexane/MTBE 5:1) to achieve **9b** (1.32 g, 96%) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$, 50 °C): δ 5.88 (ddd, $J=17.2$, 10.4, 5.1 Hz, 1H), 5.78 (m, 1H), 5.67 (m, 1H), 5.23 (d, $J=$ 17.2 Hz, 1H), 5.03 (d, $J=10.4$ Hz, 1H), 4.53 (bs, 1H), 4.25 (bs, 1H), 4.00 (bs, 1H), 2.85 (dt, $J=13.1$, 3.1 Hz, 1H), 2.18 (t, $J=10.9$ Hz, 1H), 1.90 (dt, $J=17.2$, 3.1 Hz, 1H), 1.76 (t, $J=6.3$ Hz, 2H), 1.44 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$, 50 °C) δ 155.0 (C_q), 141.1 (CH), 129.0 (CH), 125.2 (CH), 113.6 (CH_2), 79.9 (C_q), 70.4 (CH), 49.5 (CH), 41.0 (CH_2), 37.1 (CH_2), 28.5 ($3\times CH_3$), 24.9 (CH_2). IR ν 3429, 2977, 2931, 2919, 1692, 1670, 1420, 1365, 1251, 1171, 1110, 1056 cm^{-1}. MS *m/z* (%) 253 (1), 182 (16), 126 (100), 82 (49), 57 (47); HR-MS Calcd for $C_{14}H_{23}NO_3$ [M^+] 253.1678, found 253.1689. $[\alpha]_D^{20}=-202$ (*c* 0.58, $CHCl_3$). Anal. Calcd for $C_{14}H_{23}NO_3$: C, 66.37; H, 9.15; N, 5.53. Found: C, 66.12; H, 9.22; N, 5.10.

4.1.5. (*R*)-6-[(*E*)-4-(3,4-Dimethoxy-phenyl)-2-oxo-but-3-enyl]-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butylester (10). (a) From alcohol **9b**. Alcohol **9b** (1.27 g, 5.01 mmol) was dissolved in DCM (30 mL) and Dess–Martin periodinane (2.34 g, 5.51 mmol) was added. After stirring at room temperature for 30 min, the suspension was filtered over a short pad of silica, 70 mL DCM and **6** (1.65 g, 10.03 mmol) were added to the solution. The mixture was heated to reflux under a N_2 atmosphere and [Ru-**3**] (126 mg, 4 mol%) was added, and stirring was continued for 14 h. The solution was concentrated in vacuo, and the residue was purified by flash chromatography (hexane/MTBE 3:1→1:1) to afford **10** (1.65 g, 85%) as a light yellow oil.

(b) From cyclopentenone **11**. Compound **11** (1.16 g, 4.62 mmol) and **6** (2.27 g, 13.85 mmol) were refluxed in DCM (90 mL) under a N_2 atmosphere. [Ru-**2**] (196 mg, 5 mol%) was added and the solution was stirred for further 12 h. The solution was concentrated in vacuo, and the residue was purified by flash chromatography (hexane/MTBE 3:1→1:1) to give **10** (859 mg, 48%) as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, 50 °C): δ 7.53 (d, $J=16.1$ Hz, 1H), 7.13 (dd, $J=8.3$, 1.6 Hz, 1H), 7.08 (s, 1H), 6.88 (d, $J=8.3$ Hz, 1H), 6.64 (d, $J=16.1$ Hz, 1H), 5.85 (m, 1H), 5.75 (m, 1H), 4.88 (bs, 1H), 4.15 (bs, 1H), 3.91 (s, 6H), 2.93 (m, 2H), 2.85 (dd, $J=14.3$, 8.4 Hz, 1H), 2.23 (m, 1H), 1.98 (dt, $J=17.3$, 3.8 Hz, 1H), 1.47 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$, 50 °C) δ 197.4 (C_q), 154.2 (C_q), 151.6 (C_q), 149.5 (C_q), 142.9 (CH), 127.9 (CH), 127.6 (C_q), 125.6 (CH), 124.6 (CH), 122.9 (CH), 111.5 (CH), 110.5 (CH), 79.7 (C_q), 55.9 ($2\times CH_3$), 49.4 (CH), 45.0 (CH_2), 36.9 (CH_2), 28.3 ($3\times CH_3$), 24.9 (CH_2). IR ν 2972, 2932, 1688, 1595, 1512, 1418, 1264, 1162, 1140, 1107, 1023 cm^{-1}. MS *m/z* (%) 387 (13), 331 (25), 286 (24), 191 (100), 126 (58), 95 (21), 82 (46), 57 (61); HR-MS Calcd for $C_{22}H_{29}NO_5$ [M^+] 387.2046, found 387.2030. $[\alpha]_D^{20}=-129$ (*c* 0.61, $CHCl_3$). Anal. Calcd for $C_{22}H_{29}NO_5$: C, 68.20; H, 7.54; N, 3.62. Found: C, 68.38; H, 7.63; N, 3.52.

4.1.6. But-3-enyl((*R*)-4-oxo-cyclopent-2-enyl)-carbamic acid *tert*-butylester (11). To a solution of alcohol **8a** (1.30 g, 5.13 mmol) in acetone (70 mL) was added MnO_2 (17.85 g, 205 mmol), and the mixture was stirred for 15 h at room temperature. Then the mixture was filtered through a small pad of silica. The filtrate was concentrated in vacuo, and the residue was purified by flash chromatography (hexane/MTBE 4:1) to give **11** (1.26 g, 98%) as a light yellow oil. ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C): δ 7.60 (dd, $J=5.7$, 2.3 Hz, 1H), 6.19 (dd, $J=5.7$, 2.3 Hz, 1H), 5.78 (m, 1H), 5.07 (d, $J=17.2$ Hz, 1H), 5.03 (d, $J=10.3$ Hz, 1H), 4.93 (bs, 1H), 3.24 (dt, $J=14.2$, 6.9 Hz, 1H), 3.16 (dt, $J=14.2$, 6.9 Hz, 1H), 2.64 (dd, $J=18.2$, 6.7 Hz, 1H), 2.31–2.22 (m, 3H), 1.42 (s, 9H). ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 204.9 (C_q), 162.6 (CH), 153.7 (C_q), 135.0 (CH), 133.4 (CH), 115.5 (CH_2), 78.9 (C_q), 56.8 (CH), 44.9 (CH_2), 39.4 (CH_2), 32.9 (CH_2), 27.4 ($3\times CH_3$). IR ν 3077, 2976, 2932, 1719, 1691, 1459, 1401, 1366, 1173, 1157 cm^{-1}. MS *m/z* (%) 251 (2), 210 (8), 195 (14), 154 (13), 110 (94), 81 (38), 57 (100), 53 (17); HR-MS Calcd for $C_{14}H_{21}NO_3$ [M^+] 251.1521, found 251.1519. $[\alpha]_D^{20}=+101$ (*c* 1.19, $CHCl_3$). Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 66.63; H, 8.30; N, 5.36.

4.2. 4-(3,4-Dimethoxy-phenyl)-1,3,4,6,7,10-hexahydro-quinolizin-2-ones (12a, 12b)

To a solution of **10** (322 mg, 0.83 mmol) in DCM (2.5 mL) was added TFA (3.3 mL) at 0 °C. After 1 h at 0 °C the mixture was concentrated in vacuo and the residue was taken up in DCM (3 mL), DBU (0.21 mL, 1.40 mmol) was then added, and the reaction mixture stirred for 24 h at room temperature. The solvent was removed in vacuo and the residue was chromatographed on silica gel (hexane/MTBE 1:1) to give a mixture of **12a** (107 mg, 45%) and **12b** (76 mg, 32%) as yellow oils.

4.2.1. (4*R*,10*R*)-4-(3,4-Dimethoxy-phenyl)-1,3,4,6,7,10-hexahydroquinolizin-2-one (12a). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 6.80 (d, $J=8.3$ Hz, 1H), 6.75 (s, 1H), 6.73 (d, $J=8.3$ Hz, 1H), 5.77 (m, 1H), 5.43 (d, $J=9.5$ Hz, 1H), 4.28 (dd, $J=6.1$, 4.4 Hz, 1H), 3.86 (s, 6H), 3.54 (bs, 1H), 2.97 (m, 1H), 2.88 (dd, $J=14.7$, 6.1 Hz, 1H), 2.72 (d, $J=14.7$ Hz, 1H), 2.53 (m, 2H), 2.39 (dd, $J=14.5$, 10.5 Hz, 1H), 2.33 (m, 1H), 2.03 (d, $J=16.6$ Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C) δ 209.6 (C_q), 148.6 (C_q), 148.4 (C_q), 131.4 (C_q), 128.5 (CH), 125.5 (CH), 120.6 (CH), 111.5 (CH), 110.6 (CH), 63.3 (CH), 55.9 (CH_3), 55.8 (CH_3), 52.2 (CH), 47.2 (CH_2), 46.5 (CH_2), 46.3 (CH_2), 25.0 (CH_2). IR ν 2930, 2907, 2833, 1710, 1515, 1257, 1145, 1025 cm^{-1}. MS *m/z* (%) 287 (34), 206 (16), 191 (16), 175 (18), 164 (100), 149 (20), 108 (22), 95 (40), 82 (52), 77 (24); HR-MS Calcd for $C_{17}H_{21}NO_3$ [M^+] 287.1521, found 287.1527. $[\alpha]_D^{20}=+25$ (*c* 1.19, $CHCl_3$). Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.88. Found: C, 71.49; H, 7.43; N, 4.75.

4.2.2. (4*S*,10*R*)-4-(3,4-Dimethoxy-phenyl)-1,3,4,6,7,10-hexahydroquinolizin-2-one (12b). To a solution of **12a** (94 mg, 0.33 mmol) in MeOH (0.6 mL) was added 2 N NaOH (0.6 mL), and the mixture was stirred for 48 h at room temperature. MTBE (40 mL) was added and the solution was washed with water (15 mL), the organic layers were dried over $MgSO_4$, and concentated in vacuo. The residue was purified by flash chromatography (hexane/MTBE 1:1), affording **12b** (92 mg, 98%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 6.93 (d, J=1.4 Hz, 1H), 6.84 (m, 2H), 5.83 (m, 1H), 5.44 (d, J=9.8 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.38 (dd, J=11.6, 3.4 Hz, 1H), 3.09 (d, J=12.7 Hz, 1H), 2.83 (dd, J=11.3, 5.6 Hz, 1H), 2.69 (dd, J=14.3, 11.6 Hz, 1H), 2.51 (m, 2H), 2.40 (dt, J=11.6, 2.5 Hz, 1H), 2.26 (m, 1H), 2.01 (dt, J=11.3, 3.7 Hz, 1H), 1.94 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C) δ 207.4 (C_q), 149.5 (C_q), 148.5 (C_q), 134.6 (C_q), 128.7 (CH), 126.4 (CH), 119.7 (CH), 111.1 (CH), 109.5 (CH), 68.4 (CH), 60.5 (CH), 56.0 (CH_3), 55.9 (CH_3), 50.9 (CH_2), 47.5 (CH_2), 47.4 (CH_2), 26.5 (CH_2). IR ν 2957, 2929, 2833, 1720, 1515, 1258, 1236, 1135, 1027 cm^{-1}. MS *m/z* (%) 287 (20), 206 (24), 191 (25), 164 (100), 91 (56), 82 (42); HR-MS Calcd for $C_{17}H_{21}NO_3$ [M^+] 287.1521, found 287.1527. $[\alpha]_D^{20}=-69$ (*c* 0.71, $CHCl_3$). Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.88. Found: C, 71.20; H, 7.48; N, 4.62.

4.2.3. (2*R*,4*S*,10*R*)-4-(3,4-Dimethoxy-phenyl)-octahydro-quinolizin-2-ol ((−)-lasubine II (1)). A solution of **12b** (62 mg, 0.21 mmol) in absolute ethyl acetate (2 mL) containing palladium on charcoal (10%) was hydrogenated at room temperature for 12 h. The catalyst was removed by filtration over Celite and the solution concentrated in vacuo to give a yellow oil. This was dissolved in 2 mL THF and a 1.0 M solution of L-selectride in THF (0.26 mL, 0.26 mmol) was added dropwise at −78 °C. After 12 h at −78 °C the mixture was stirred for 3 h at room temperature. Then 1.0 M KOH solution (1 mL) was added and the mixture was stirred for 1 h. The mixture was extracted with MTBE (2×15 mL) and the combined organic extracts were concentrated in vacuo. The oily residue was taken up in MeOH (1 mL) and stirred for 14 h at room temperature, the resulting solution was poured onto 5% aqueous $NaHCO_3$ (5 mL), and the organic solvent was removed under reduced pressure. The aqueous phase was extracted with MTBE (2×25 mL) and the combined organic extracts were dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography (DCM/MeOH 30:1) afforded **1** (46 mg, 74%) as white crystals. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 6.96–6.75 (m, 3H), 4.14 (bs, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.31 (dd, J=11.8, 2.8 Hz, 1H), 2.69 (d, J=11.3 Hz, 1H), 2.39 (m, 1H), 1.92–1.23 (m, 12H). ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C) δ 149.0 (C_q), 147.8 (C_q), 137.2 (C_q), 119.7 (CH), 110.9 (CH), 110.5 (CH), 65.1 (CH), 63.4 (CH), 56.4 (CH), 56.0 (CH_3), 55.9 (CH_3), 53.2 (CH_2), 42.8 (CH_2), 40.4 (CH_2), 33.7 (CH_2), 26.2 (CH_2), 24.9 (CH_2). IR ν 3406, 2931, 2835, 1516, 1507, 1261, 1230, 1134, 1029 cm^{-1}. MS *m/z* (%) 291 (100), 246 (20), 191 (20), 164 (70), 154 (70), 126 (20), 110 (23), 84 (22); HR-MS Calcd for $C_{17}H_{25}NO_3$ [M^+] 291.1834, found 291.1833. $[\alpha]_D^{20}=-48$ (*c* 0.79, MeOH).

Acknowledgements

We would like to thank the Fonds der Chemischen Industrie for financial support.

References and notes

1. Fuji, K.; Yamada, T.; Fujita, E.; Murata, H. *Chem. Pharm. Bull.* **1978**, *26*, 2515–2521.
2. (a) Chalard, P.; Remuson, R.; Gelas-Mialhe, Y.; Gramain, J.-C. *Tetrahedron: Asymmetry* **1998**, *9*, 4361–4368. (b) Ukaji, Y.; Ima, M.; Yamada, T.; Inomata, K. *Heterocycles* **2000**, *52*, 563–566. (c) Davis, F. A.; Chao, B. *Org. Lett.* **2000**, *2*, 2623–2625. (d) Ma, D.; Zhu, W. *Org. Lett.* **2001**, *3*, 3927–3929. (e) Back, T. G.; Hamilton, M. D. *Org. Lett.* **2002**, *4*, 1779–1781.
3. For recent reviews, see: (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29. (b) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012–3043. (c) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450. (d) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 317–388. (e) Fürstner, A. *Top. Organomet. Chem.* **1998**, *1*, 37–72. (f) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036–2056.
4. (a) Buschmann, N.; Rückert, A.; Blechert, S. *J. Org. Chem.* **2002**, *67*, 4325–4329. (b) Stragies, R.; Blechert, S. *J. Am. Chem. Soc.* **2000**, *122*, 9584–9591. (c) Weatherhead, G. S.; Ford, J. G.; Alexanian, E. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 1828–1829. (d) Voigtmann, U.; Blechert, S. *Org. Lett.* **2000**, *2*, 3971–3974. (e) Stragies, R.; Blechert, S. *Tetrahedron* **1999**, *55*, 8179–8188.
5. Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039–2041.
6. (a) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900–1923. (b) Randl, S.; Blechert, S. *J. Org. Chem.* **2003**, *68*, 8879–8882. (c) Randl, S.; Blechert, S. *Tetrahedron Lett.* **2004**, *45*, 1167–1169.
7. Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956.
8. (a) Gessler, S.; Randl, S.; Blechert, S. *Tetrahedron Lett.* **2000**, *41*, 9973–9976. (b) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179.
9. (a) Liu, W.; Ghosh, A. K. *J. Org. Chem.* **1997**, *62*, 7908–7909. (b) Johnson, C. R.; Bis, S. J. *Tetrahedron Lett.* **1992**, *48*, 7287–7290.
10. Yoon, N. M.; Brown, H. C. *J. Am. Chem. Soc.* **1968**, *90*, 2927–2938.
11. Schaudt, M.; Blechert, S. *J. Org. Chem.* **2003**, *68*, 2913–2920.
12. Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.
13. LeBigot, Y.; Delmas, M.; Gaset, A. *Synth. Commun.* **1982**, *12*, 107–112.
14. Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875.
15. (a) Pilli, R. A.; Dias, L. C.; Maldaner, A. O. *J. Org. Chem.* **1995**, *60*, 717–722. (b) Pilli, R. A.; Dias, L. C.; Maldaner, A. O. *Tetrahedron Lett.* **1993**, *34*, 2729–2732.
16. Quick, J.; Meltz, C. *J. Org. Chem.* **1979**, *44*, 573–578.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 60 (2004) 9635–9647

Ring-closing metathesis: a powerful tool for the synthesis of simplified salicylihalamide-based V-ATPase inhibitors

Sylvain Lebreton,[a] Xiao-Song Xie,[b] Deborah Ferguson[c] and Jef K. De Brabander[a,*]

[a]*Department of Biochemistry, University of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Blvd., Dallas, TX 75390-9038, USA*
[b]*Eugene McDermott Center for Human Growth and Development, University of Texas Southwestern Medical Center at Dallas, Dallas, TX 75390, USA*
[c]*Reata Discovery, Inc., Richardson, TX 75081, USA*

Received 4 May 2004; revised 7 June 2004; accepted 9 June 2004

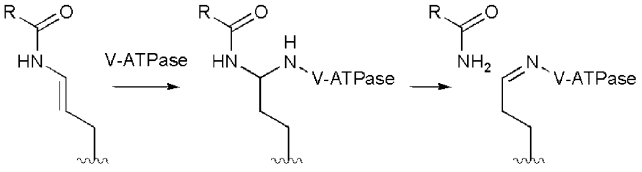
Available online 21 August 2004

Abstract—Based on our synthetic strategy developed for the total synthesis of the macrocyclic salicylate natural product salicylihalamide, we describe herein the synthesis of a series of simplified salicylihalamide-based analogs. Alterations in the aromatic fragment, the macrolactone scaffold and side-chain were evaluated for in vitro inhibition of V-ATPase activity and human tumor cell growth.

1. Introduction

The past seven years has witnessed the disclosure of a variety of marine and terrestrial metabolites grouped into a common structural family by virtue of a signature *N*-acyl-enamine appended macrocyclic salicylate–salicylihalamide A (**1**) the first to be isolated (Fig. 1).[1–5] These compounds have been attributed growth-inhibitory activities against cultured human tumor cells and oncogene-transformed cell-lines through mechanisms distinct from standard clinical antitumor agents.[1–3,5] Boyd and co-workers subsequently found that the NCI 60 cell-line profiles of salicylihalamides, lobatamides, oximidines and apicularens gave consistently high correlations with the historical database profiles of bafilomycin and concanamycin, prototypical vacuolar (H^+)-ATPase (V-ATPase) inhibitors.[6] Biochemical studies have confirmed the ability of these compounds to inhibit mammalian V-ATPase activity, but unlike any previously known inhibitor of this enzyme, not those of yeast or other fungi.[6] V-ATPases are potential therapeutic targets for the development of pharmacological agents to treat a variety of diseases, notably osteoporosis and cancer.[7,8] Despite substantial efforts, the lack of tissue specificity, structural complexity and chemical stability associated with previous inhibitors has hampered progress towards the development of clinically useful compounds.[8]

The prospect to target specific subsets of V-ATPases with compounds potentially resulting from a chemical program around these structurally novel macrocyclic salicylates has prompted intense research activities by us, as well as others.[9,10] Based on a synthetic blueprint that resulted in the total synthesis of salicylihalamide by our group, we have prepared and evaluated numerous side-chain modified derivatives for structure-function studies.[11] Biochemical studies have further revealed that salicylihalamides bind to the *trans*-membranous proton-translocating domain (Vo) of the V-ATPase through a mechanism distinct from bafilomycin.[12] They are conditionally irreversible inhibitors, and experimental information gathered with carefully crafted side-chain modifications has led us to suggest a covalent binding mechanism initiated by enamine protonation and capture of a transient *N*-acyl iminium by an active site lysine residue, followed by a fragmentation to a covalent protein/small molecule imine complex with loss of the side chain (Eq. (1)).[12]



(1)

Total synthesis has been crucial to advance our knowledge of salicylihalamide's molecular pharmacology and define the structure-function boundaries related to the side chain.[13] The aspiration to advance a synthetic salicylihalamide-like

Keywords: Olefin-metathesis; Macrocyclic; Natural product; Vacuolar ATPase; Cancer.
* Corresponding author. Tel.: +1-214-648-7808; fax: +1-214-648-0320; e-mail: jdebra@biochem.swmed.edu

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.06.146

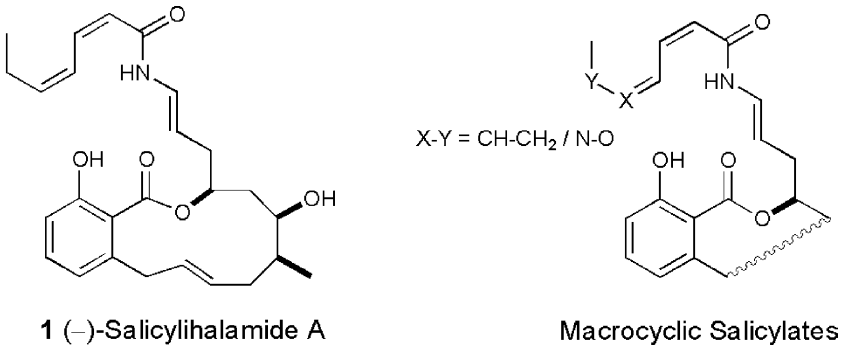


Figure 1.

small molecule through preclinical development prompted us to investigate simplified macrolactone scaffolds that could be prepared by shorter, scalable routes. Initial results related to this goal are detailed in this manuscript.

2. Results and discussion

Our scaffold selection and synthetic approach are depicted in Figure 2. Smith and co-workers have shown that deletion of the C_{12}-Me and C_{13}-OH substituents had no dramatic impact on activity at the cell-based level.[14] A direct consequence of our RCM approach, the endocyclic double bond was perceived as a beneficial conformation-restricting unit. Incorporation of the cyclic ether derives from synthetic considerations. Influenced by our earlier work,[11] a convergent combination of an allyl-substituted (hetero)cyclic carboxylic acid (**B**) and an allylated 1,3,5-pentanetriol derivative (**C**) via Mitsunobu esterification / RCM and final installation of the side chain was projected to efficiently generate the desired targets (**A**).

As shown in Scheme 1, we selected a series of readily accessible aryl, indole, cyclohexenyl and proline derived carboxylic acid building blocks **B** (**1**–**5**)[15] for incorporation into the macrocyclic scaffolds. The acyclic fragment **7** was prepared in three steps from aldehyde **6**,[11] an intermediate for the synthesis of salicylihalamide A, via reduction, allylation and silyl deprotection. Treatment of alcohol **7** with the respective carboxylic acids **1**–**5** under Mitsunobu reaction conditions cleanly afforded the bis-olefins **8a**,**c**–**f** in 76–99% yields.[16] The phenol in salicylate ester **8a** was protected as the acetate **8b** prior to the subsequent ring-closing olefin metathesis.

Ring-closing olefin metathesis with ruthenium carbene complexes was shown to be a powerful method to form the macrocyclic skeleton of the salicylihalamides.[9,17] In line with a highly significant study from the Grubbs lab,[18] which provided the inspiration for our RCM studies, we had observed that first generation pre-catalyst **i** induces kinetic selectivity whereas the H_2IMes-containing pre-catalyst **ii** affords thermodynamic selectivity. Not expected however, was the highly selective formation of the *E*-isomer under kinetic conditions (9–10:1, *E*/*Z*) contrasting the rather non-selective thermodynamic ratio (2:1) obtained with the second generation catalyst.[11b] In addition, Fürstner and co-workers reported a dramatic influence of the phenolic protecting group on *E*/*Z* ratios in their synthetic work on salicylihalamides.[19] In light of these results, we explored the

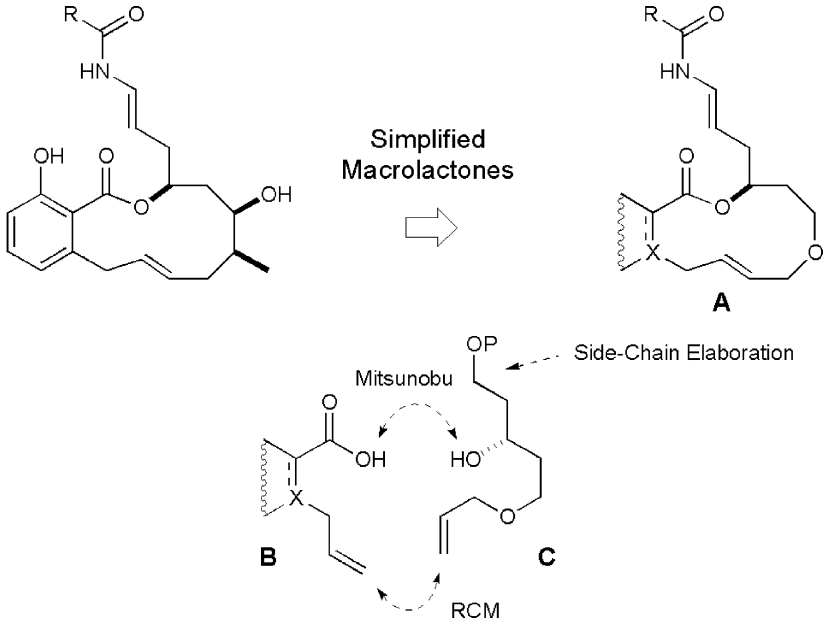
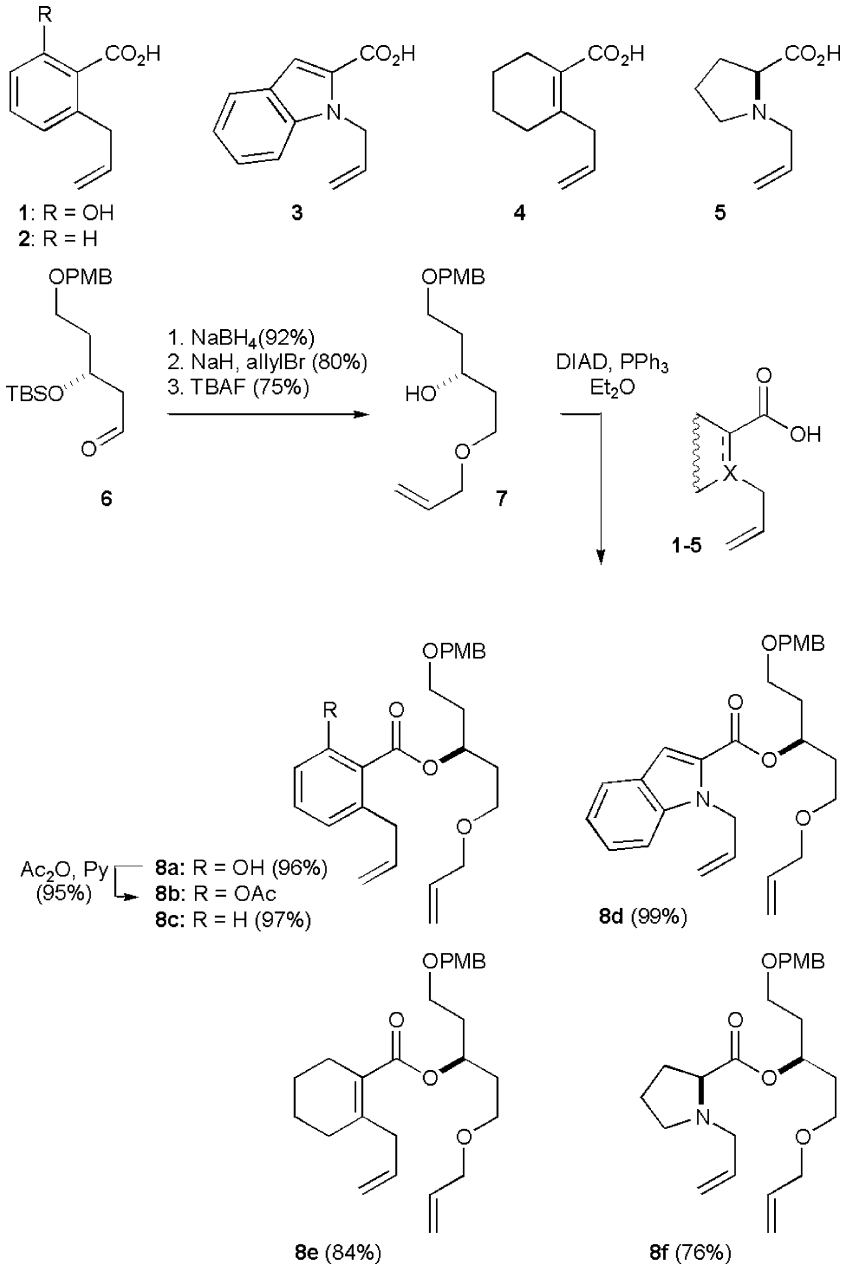
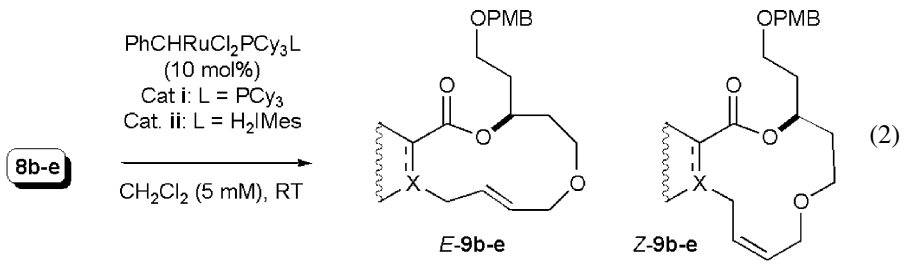


Figure 2.



Scheme 1.

RCM reactions of substrates **8b–f** with both first and second generation catalysts to empirically identify the most *E*-selective conditions.[20]



(2)

Our results are presented in Eq. (2) and Table 1. In contrast to salicylihalamide, salicylic macrocycle **9b** was obtained as an almost equimolar mixture of *E*/*Z*-isomers under kinetic RCM conditions, despite displaying the same ring-size, olefin position, and aromatic fragment as the salicylihalamide macrocycle. Similar results were obtained for the non-substituted benzoate counterpart **9c**. In both of these cases, a thermodynamic cyclization with second generation catalyst **ii** was now significantly favoring formation of the *E*-isomer. Re-exposure of isomerically pure *E*-**9c** and *Z*-**9c** to the reaction conditions confirmed that thermodynamic

Table 1. Ring-closing olefin metathesis studies

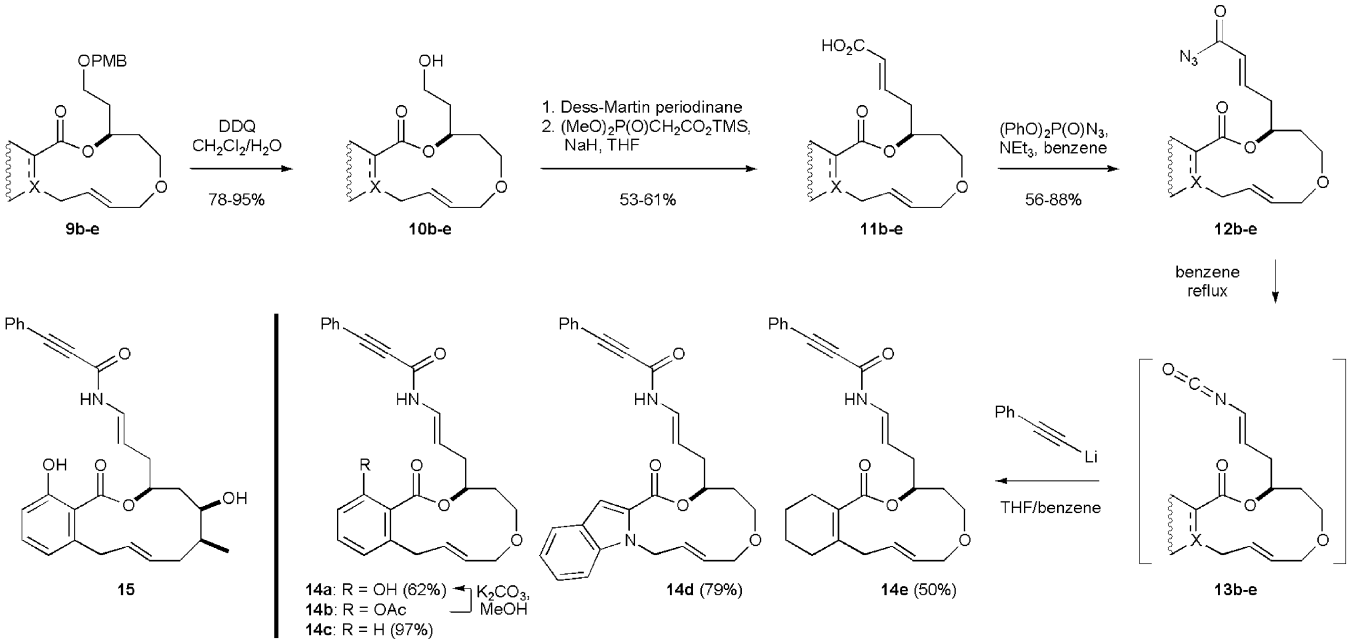
Substrate	*t* (h)	Product	*E*/*Z* ratio[a] (% conversion)[a]	
			Catalyst **i**	Catalyst **ii**
8b	1.3	**9b**	42:48 (80)	95:5 (95)
8b	6.3	**9b**	54:46 (92)[b]	98:2 (100)[b]
8c	1.3	**9c**	52:48 (>80)	82:18 (>90)
8c	6.3	**9c**	54:46 (100)[b]	84:16 (100)[b]
8d	6.3	**9d**	45:55 (80)[c]	32:68 (80)[c]
8e	4	**9e**	29:71 (70)	49:51 (90)[d]
8f	4	—[e]	—	—
E-**9c**	5	**9c**	98:2 (−)	89:11 (−)
Z-**9c**	5	**9c**	11:89 (−)	82:18 (−)

[a] Determined by ^{1}H NMR analysis of crude product mixtures.
[b] Isolated yields between 90–99%.
[c] Some decomposition occurred; 34–41% isolated yield.
[d] 75% Isolated yield.
[e] No reaction; higher temperatures or the addition of $BF_3 \cdot OEt_2$ or $Ti(O^iPr)_4$ led to decomposition of the starting material.

equilibrium was reached with catalyst **ii**, but not with catalyst **i**. Interestingly, cyclohexenyl- and indolyl-tethered substrates **8d** and **8e** respectively, behaved quite differently and no *E*-selective conditions could be identified—*Z*-selectivity predominated with catalyst **ii** for indolyl substrate **8d** and with catalyst **i** for the cyclohexenyl substrate **8e**. Also, reaction with the indolyl substrate **8d** gave low yields of product **9d**, the remainder accounted for as starting material and decomposition products. These results are fascinating because all these products (**9b–e**) have an identical macrocycle fused with the smaller ring through sp^2-hybridized atoms. Evidently, subtle effects influenced by the nature of the fused ring are at play here. The proline-derived bis-olefin **8f** was not a viable substrate for RCM under all conditions explored.

With four macrocyclic lactones **9b–e** at hand, we were set to complete the synthesis by appending an *N*-acyl enamide side chain following our sequence described previously (Scheme 2).[11] Thus, oxidative deprotection of the primary *p*-methoxybenzyl ether provided four primary alcohols **10b–e** in 78–95% yield. Dess–Martin periodinane oxidation delivered the corresponding aldehydes,[21] which were subsequently homologated via HWE-reaction with trimethylsilyl dimethylphosphonoactetate. Aqueous work-up provided the α,β-unsaturated acids **11b–e** with high *E*-selectivity in 53–61% yield for the two steps. These materials were converted to acylazides **12b–e**, precursors for the corresponding isocyanates **13b–e**. For the first series of analogs, we opted for the addition of lithium phenylacetylide. The corresponding analog **15** with salicylihalamide's macrolactone was found to be equipotent to salicylihalamide (**1**) but prepared in higher yields and more resistant to decomposition.[11] In the event, addition of in situ prepared isocyanate **13b–e** (benzene, reflux) to a cold (−78 °C) solution of freshly deprotonated phenylacetylene (BuLi, THF) resulted in a clean conversion to compounds **14b–e** (50–97% yields). A portion of acetate **14b** was stirred in a basic methanol solution (K_2CO_3) to liberate the free phenol **14a**.

Comparing the biological activity of this series of compounds with the corresponding analog **15** would (1) indicate if the endocyclic allyl ether presents a viable alternative to the more complex macrocyclic backbone of salicylihalamide, and (2) provide the first SAR-data related to the nature of the fused ring (aryl, indole, cyclohexenyl). As shown in Table 2, direct comparison of analogs **14a** and **15** indicates that this simplified allyl ether scaffold (**14a**) retains the ability to potently inhibit proton-pumping of purified V-ATPase (~4.5-fold less than **15**). Larger differences (~10-fold) are observed in the growth inhibition assay with two selected lung tumor cell lines, perhaps related to altered drug transport and availability characteristics. Compared to phenol **14a**, the similar cytotoxicity, but not in vitro potency of the corresponding acetate **14b**, is likely a manifestation of esterase-mediated release of phenol **14a** in the cell-based assay. Any other permutation



Scheme 2.

Table 2. Biological properties of selected compounds

Compound	V-ATPase inhibition (H^+-pumping) IC_{50} (nM)[a]	Cell growth inhibition[b]	
		A549 IC_{50} (μM)	NCI-H460 IC_{50} (μM)
15	1.0	0.086	0.018
14a	4.5	1.03	0.20
14b	125	1.38	0.31
14c	No inhibition[c]	—[d]	—[d]
14d	>1000[e]	—[d]	—[d]
14e	No inhibition[c]	—[d]	—[d]
16[f]	16	3.05	1.03
17	2300	1.50	1.23
18	1000	0.88	0.55
19	30	4.62	1.62
20	4	—[d]	—[d]
21	1900	>10[g]	>10[g]

[a] Assay performed as in Ref. 12.
[b] See Section 3 for details.
[c] Up to 1 μM.
[d] Not measured.
[e] 10% Inhibition at 1 μM.
[f] Racemic mixture.
[g] 20–29% Inhibition at 10 μM.

of the aromatic phenol (i.e. compounds **14c–e**) virtually abrogated in vitro V-ATPase inhibition, manifesting the importance for a fused *ortho*-hydroxy benzoate (i.e. salicylate) scaffold.

Having identified a promising, highly simplified salicylate scaffold, we next prepared and evaluated a variety of side-chain modifications in this series. To this end, we added isocyanate **13b** (from **12b**) to a 2-fluorophenyl-, 2-pyridinyl-, or 2-oxazoyl-substituted acetylide followed by acetate hydrolysis (K_2CO_3, MeOH) to deliver the corresponding analogs **16–18** (Scheme 3). Benzyl-, pentyl-, and 2-oxazoylmethyl carbamates **19–21** are obtained directly from heating acylazide **12b** in the presence of the corresponding alcohols and acetate hydrolysis as before.

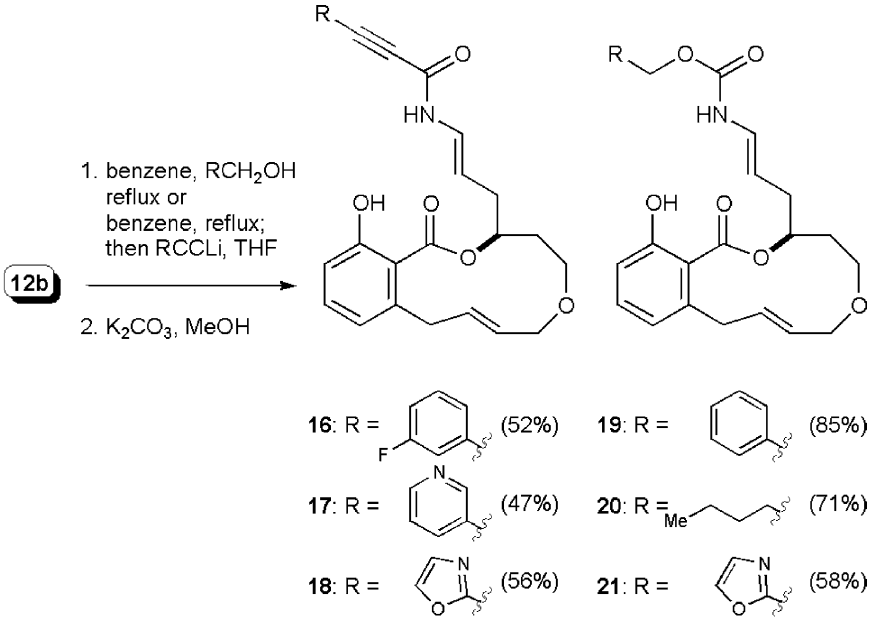
While compounds **16**, **19** and **20** still inhibit V-ATPase activity (4–30 nM) in line with our previous observations within the salicylihalamide series,[11,12] heteroaromatic substituents (**17**, **18**, **21**) are deleterious. The more surprising result however, is that this 'heteroatom effect' does not translate to the cytotoxicity assay. Pyridinyl and oxazoyl substituted derivatives **17** and **18** are still able to inhibit cell growth at similar concentrations to compound **14a**. These observations might indicate that **17** and **18** induce cytotoxicity through a different mechanism, or that they target a different V-ATPase isoform than the one used in this study.[22]

In conclusion, we have identified a series of simplified analogs (**14a**,**b**, **16**, **19**, **20**) of the macrocyclic salicylate natural product salicylihalamide A that retain the ability to potently inhibit the V-ATPase. These and other derivatives were conveniently prepared via a convergent assembly of a series of allyl-substituted carboxylic acids **1–4** and the allyl ether derivative **7** via Mitsunobu esterification and ring-closing olefin metathesis. We also uncovered subtle effects on *E*/*Z*-stereochemistry during RCM related to the nature of the small ring fused to the macrocycle. Finally, structure-function studies indicate that the salicylate moiety is indispensable for activity and that heteroaryl terminating side-chains behave differently than other inhibitors in the salicylate family. Continuing efforts to study this intriguing family of compounds are ongoing.

3. Experimental

3.1. General procedures

Commercially available materials were used without further purification. All solvents used were of HPLC- or ACS-grade. Solvents used for moisture sensitive operations were distilled from drying agents under a nitrogen atmosphere: Et_2O and THF from sodium benzophenone ketyl; benzene



Scheme 3.

from sodium; CH_2Cl_2 and NEt_3 from CaH_2. All moisture sensitive reactions were carried out under a nitrogen atmosphere with magnetic stirring. Flash chromatography (FC) was performed using E Merck silicagel 60 (240–400 mesh). Thin Layer chromatography was performed using precoated plates purchased from E. Merck (silicagel 60 PF254, 0.25 mm) that were visualized using a $KMnO_4$ or Ce(IV) stain.

Nuclear magnetic resonance (NMR) spectra were recorded on either a Varian Inova-400 or Mercury-300 spectrometer at operating frequencies of 400/300 MHz (^{1}H NMR) or 100/75 MHz (^{13}C NMR). Chemical shifts (δ) are given in ppm relative to residual solvent and coupling constants (J) in Hz. Multiplicity is tabulated as s for singlet, d for doublet, t for triplet, q for quadruplet, and m for multiplet, whereby the prefix app is applied in cases where the true multiplicity is unresolved, and br when the signal in question is broadened. High-resolution mass spectra (HRMS) were recorded at the NIH regional mass spectrometry facility at the University of Washington, St. Louis, MO. Optical rotations were measured at 23 °C on a Perkin–Elmer 241 MC polarimeter.

3.1.1. 3-(*tert*-Butyl-dimethyl-silanyloxy)-5-(4-methoxy-benzyloxy)-pentan-1-ol. To a solution of aldehyde **6** (8.95 g, 25.38 mmol) in absolute ethanol (300 mL) at 0 °C was added sodium borohydride (2.40 g, 63.45 mmol) portionwise. After stirring at rt for 45 min, the reaction mixture was cooled down to 0 °C and quenched with water (300 mL) and acetic acid to pH ~ 5. Following removal of EtOH in vacuo, the mixture was extracted with EtOAc (2×300 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by FC (20% EtOAc in hexanes) to give 8.3 g (92%) of the desired alcohol as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (2H, d, J=8.8 Hz), 6.87 (2H, d, J=8.8 Hz), 4.44 (1H, d, J=11.2 Hz), 4.39 (1H, d, J=11.2 Hz), 4.09 (1H, quent, J=5.2 Hz), 3.82–3.77 (1H, m), 3.80 (3H, s), 3.73–3.67 (1H, m), 3.49 (2H, app.t, J=6.4 Hz), 2.43 (1H, t, J=5.0 Hz), 1.89–1.76 (3H, m), 1.65 (1H, dddd, J=16.0, 6.0, 6.0, 3.6 Hz), 0.89 (9H, s), 0.08 (6H, d, J=8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 130.6, 129.5, 114.0, 72.9, 69.2, 66.7, 60.2, 55.5, 38.5, 36.9, 26.0, 18.1, −4.4; MS (ES) m/z 377.25 $[M+Na]^+$; calcd for $C_{19}H_{34}O_4SiNa$: 377.21.

3.1.2. [1-(2-Allyloxy-ethyl)-3-(4-methoxy-benzyloxy)-propoxy]-tert-butyl-dimethyl-silane. To a suspension of sodium hydride (902 mg, 22.56 mmol, prewashed with benzene) in THF (30 mL) was added 3-(tert-Butyl-dimethyl-silanyloxy)-5-(4-methoxy-benzyloxy)-pentan-1-ol (2 g, 5.64 mmol). After stirring at rt for 45 min, a solution of allylbromide (1.95 mL, 22.56 mmol) in THF (5 mL) was added dropwise and the reaction was stirred for another 20 h. The mixture was quenched with water (5 mL) and brine (150 mL) was added. The separated aqueous phase was extracted with EtOAc (2×150 mL). The combined organic layers were washed with brine (2×150 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by FC (5% EtOAc in hexanes) to give 1.73 g (78%) of the desired product as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (2H, d, J=8.8 Hz), 6.87 (2H, d, J=8.8 Hz), 5.90 (1H, dddd, J=17.2, 10.8, 5.2, 5.2 Hz), 5.26 (1H, dd, J=17.2, 1.6 Hz), 5.16 (1H, dd, J=10.4, 1.6 Hz), 4.42 (1H, d, J=11.2 Hz), 4.39 (1H, d, J=11.2 Hz), 3.98 (1H, app.t, J=6.0 Hz), 3.93 (2H, d, J=6.0 Hz), 3.80 (3H, s), 3.51 (2H, t, J=6.8 Hz), 3.48 (2H, t, J=6.8 Hz), 1.82–1.68 (4H, m), 0.87 (9H, s), 0.04 (6H, d, J=2.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 135.2, 130.9, 129.5, 116.9, 113.9, 72.8, 72.0, 67.1, 66.9, 59.8, 55.5, 37.6, 37.5, 26.1, 18.3, −4.4; MS (ES) m/z 417.20 $[M+Na]^+$; calcd for $C_{22}H_{38}O_4SiNa$: 417.24.

3.1.3. 1-Allyloxy-5-(4-methoxy-benzyloxy)-pentan-3-ol 7. To a solution of [1-(2-Allyloxy-ethyl)-3-(4-methoxy-benzyloxy)-propoxy]-tert-butyl-dimethyl-silane (1.65 g, 4.18 mmol) in THF (30 mL) at 0 °C was added TBAF (1.0 M in THF, 12.54 mL, 12.54 mmol). The reaction was stirred at rt for 5 h and water (200 mL) was added. The mixture was extracted with CH_2Cl_2 (3×150 mL). The combined organic phases were washed with brine (300 mL) and dried over $MgSO_4$. After concentration in vacuo, the residue was purified by FC (20% EtOAc in hexanes) to give 866 mg (74%) of **7** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (2H, d, J=8.8 Hz), 6.86 (2H, d, J=8.8 Hz), 5.88 (1H, dddd, J=16.8, 10.4, 5.2, 5.2 Hz), 5.26 (1H, dd, J=17.6, 1.6 Hz), 5.17 (1H, dd, J=10.0, 1.6 Hz), 4.44 (2H, s), 3.97 (2H, dt, J=5.6, 1.2 Hz), 3.97–3.93 (1H, m), 3.78 (3H, s), 3.68–3.55 (4H, m), 3.38 (1H, br.s), 1.78–1.71 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 134.7, 130.3, 129.4, 117.0, 113.9, 76.8, 72.1, 69.4, 68.4, 68.3, 55.3, 36.9; MS (ES) m/z 303.10 $[M+Na]^+$; calcd for $C_{16}H_{24}O_4Na$: 303.15.

3.1.4. Mitsunobu coupling. To a solution of acid **1**–**5** (1.5 equiv), alcohol **7** (1.0 equiv), and PPh_3 (1.6 equiv) in Et_2O (0.1 M with respect to the alcohol) at 0 °C was added diisopropylazodicarboxylate (1.6 equiv). The reaction was stirred at rt until all alcohol reacted (2–12 h). The reaction mixture was filtrated off and washed with Et_2O. The filtrate was washed with water. The aqueous phase was extracted twice with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was then purified by FC (EtOAc in hexanes) to give the corresponding ester **8a**–**f**.

3.1.4.1. 2-Allyl-6-hydroxy-benzoic acid 1-(2-allyloxy-ethyl)-3-(4-methoxy-benzyloxy)-propyl ester 8a. In the case of compound **8a**, a 1:6 adduct:product resulted from esterification of the phenolic group, which was hydrolyzed in MeOH in the presence of K_2CO_3 (1 equiv) over 1 h. After adding water, an extraction was performed with EtOAc. The combined extracts were dried, concentrated in vacuo, and purified by FC (20% EtOAc in hexanes) to give 1.26 g (96% yield) of product **8a** as pale yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.1 (1H, s), 7.31 (1H, t, J=8.0 Hz), 7.20 (2H, d, J=8.8 Hz), 6.87 (1H, d, J=8.8 Hz), 6.82 (2H, d, J=8.8 Hz), 6.72 (1H, d, J=7.2 Hz), 5.96 (1H, dddd, J=16.4, 10.4, 6.4, 6.4 Hz), 5.85 (1H, dddd, J=16.0, 10.4, 5.6, 5.6 Hz), 5.59–5.53 (1H, m), 5.22 (1H, dd, J=16.8, 1.2 Hz), 5.13 (1H, dd, J=10.4, 1.2 Hz), 5.00 (1H, dd, J=10.0, 1.2 Hz), 4.90 (1H, dd, J=16.8, 1.6 Hz), 4.42 (1H, d, J=11.6 Hz), 4.38 (1H, d, J=11.6 Hz), 3.92 (2H, d, J=5.6 Hz), 3.77 (3H, s), 3.64 (2H, br.d, J=6.0 Hz), 3.55–3.47 (4H, m), 2.05–1.97 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 162.5, 159.4, 142.7, 138.0, 134.8, 134.2, 130.3, 129.6, 122.6, 117.3, 116.4, 115.6, 113.9, 113.0, 73.0, 72.2, 72.0,

66.7, 66.4, 55.4, 40.1, 34.7; MS (ES) *m/z* 463.20 $[M+Na]^+$; calcd for $C_{26}H_{32}O_6Na$: 463.21.

3.1.4.2. 2-Allyl-benzoic acid 1-(2-allyloxy-ethyl)-3-(4-methoxy-benzyloxy)-propyl ester 8c. Reaction mixture purified by FC (10% EtOAc in hexanes) to give 295 mg (97% yield) of product **8c**. $[\alpha]_D=-9.9$ ($c=1.60$, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (1H, d, $J=7.6$ Hz), 7.43 (1H, t, $J=7.6$ Hz), 7.28–7.22 (4H, m), 6.83 (2H, d, $J=8.4$ Hz), 6.00 (1H, dddd, $J=16.4$, 10.0, 6.4, 6.4 Hz), 5.87 (1H, dddd, $J=16.8$, 10.0, 5.6, 5.6 Hz), 5.42–5.36 (1H, m), 5.23 (1H, dd, $J=17.2$, 1.6 Hz), 5.13 (1H, dd, $J=10.4$, 1.6 Hz), 5.02 (1H, dd, $J=10.0$, 1.6 Hz), 4.99 (1H, dd, $J=17.2$, 1.6 Hz), 4.41 (2H, s), 3.93 (2H, br.d, $J=5.6$ Hz), 3.77 (3H, s), 3.74 (2H, d, $J=6.4$ Hz), 3.56–3.49 (4H, m), 2.04–1.97 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 159.3, 141.6, 137.7, 135.0, 132.0, 131.1, 130.6, 130.3, 129.5, 126.3, 117.1, 115.8, 113.9, 72.9, 72.1, 70.4, 66.9, 66.6, 55.4, 38.4, 34.9; MS (ES) *m/z* 447.20 $[M+Na]^+$; calcd for $C_{26}H_{32}O_5Na$: 447.22.

3.1.4.3. 1-Allyl-1*H*-indole-2-carboxylic acid 1-(2-allyloxy-ethyl)-3-(4-methoxy-benzyloxy)-propyl ester 8d. Reaction mixture purified by FC (10% EtOAc in hexanes) to give 755 mg (100% yield) of product **8d** as pale yellowish oil. $[\alpha]_D=-11.2$ ($c=1.18$, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (1H, d, $J=8.0$ Hz), 7.37–7.31 (2H, m), 7.28 (1H, s), 7.20 (2H, d, $J=8.8$ Hz), 7.15 (1H, ddd, $J=8.0$, 6.4, 1.6 Hz), 6.78 (2H, d, $J=8.4$ Hz), 5.99 (1H, dddd, $J=16.8$, 10.0, 4.8, 4.8 Hz), 5.86 (1H, dddd, $J=17.2$, 10.8, 5.6, 5.6 Hz), 5.44–5.37 (1H, m), 5.22 (1H, dd, $J=17.2$, 3.2 Hz), 5.21–5.20 (2H, m), 5.12 (1H, dd, $J=10.4$, 2.8 Hz), 5.08 (1H, dd, $J=10.8$, 2.4 Hz), 4.89 (1H, dd, $J=17.2$, 3.26 Hz), 4.39 (2H, s), 3.93 (2H, ddd, $J=5.6$, 1.2, 1.2 Hz), 3.71 (3H, s), 3.57–3.50 (4H, m), 2.05–1.98 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.6, 159.3, 139.4, 135.0, 134.2, 130.5, 129.5, 127.7, 126.2, 125.2, 122.8, 120.9, 117.1, 116.1, 113.9, 110.8, 110.7, 73.0, 72.2, 70.0, 66.8, 66.6, 55.4, 47.0, 35.0, 21.8; MS (ES) *m/z* 486.15 $[M+Na]^+$; calcd for $C_{28}H_{33}NO_5Na$: 486.23.

3.1.4.4. 2-Allyl-cyclohex-1-enecarboxylic acid 1-(2-allyloxy-ethyl)-3-(4-methoxy-benzyloxy)-propyl ester 8e. Reaction mixture purified by FC (5% EtOAc in hexanes) to give 272 mg (84% yield) of product **8e**. ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (2H, d, $J=8.4$ Hz), 6.86 (2H, d, $J=8.4$ Hz), 5.88 (1H, dddd, $J=17.2$, 10.8, 5.6, 5.6 Hz), 5.80 (1H, dddd, $J=16.8$, 10.0, 6.8, 6.8 Hz), 5.25 (1H, dd, $J=17.2$, 1.6 Hz), 5.22–5.17 (1H, m), 5.15 (1H, dd, $J=10.4$, 1.6 Hz), 5.02 (1H, dd, $J=17.2$, 1.6 Hz), 4.99 (1H, dd, $J=10.4$, 1.6 Hz), 4.4 (2H, s), 3.93 (2H, dt, $J=5.6$, 1.6 Hz), 3.80 (3H, s), 3.50–3.43 (4H, m), 3.08 (2H, br.d, $J=6.4$ Hz), 2.25–2.19 (2H, m), 2.13–2.08 (2H, m), 1.91 (4H, app.quent., $J=6.4$ Hz), 1.60–1.56 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 159.3, 146.1, 142.8, 136.3, 135.1, 130.7, 129.5, 125.8, 117.1, 115.9, 114.0, 72.9, 72.1, 69.3, 67.0, 66.6, 55.5, 39.9, 34.9, 30.9, 26.8, 22.5; MS (ES) *m/z* 451.20 $[M+Na]^+$; calcd for $C_{26}H_{36}O_5Na$: 451.25.

3.1.4.5. 1-Allyl-pyrrolidine-2-carboxylic acid 1-(2-allyloxy-ethyl)-3-(4-methoxy-benzyloxy)-propyl ester 8f. Reaction mixture purified by FC (30% EtOAc in hexanes) to give 305 mg (72% yield) of product **8f**. $[\alpha]_D=-36.3$ ($c=1.23$, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (2H, d, $J=8.8$ Hz), 6.86 (2H, d, $J=8.8$ Hz), 5.96–5.83 (2H, m), 5.24 (1H, dd, $J=17.2$, 1.6 Hz), 5.20–5.15 (1H, m), 5.16 (1H, dd, $J=17.6$, 1.2 Hz), 5.15 (1H, dd, $J=10.4$, 1.2 Hz), 5.07 (1H, dd, $J=10.4$, 1.2 Hz), 4.42 (1H, d, $J=11.6$ Hz), 4.39 (1H, d, $J=11.6$ Hz), 3.92 (2H, dt, $J=5.6$, 1.6 Hz), 3.80 (3H, s), 3.51–3.39 (4H, m), 3.32 (1H, ddt, $J=13.2$, 6.4, 1.2 Hz), 3.16–3.10 (2H, m), 3.07 (1H, app.ddt, $J=13.2$, 7.2, 1.2 Hz), 2.37 (1H, app.q, $J=8.0$ Hz), 2.13–2.06 (1H, m), 1.93–1.76 (7H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 159.4, 135.7, 135.0, 130.6, 129.5, 117.5, 117.2, 113.9, 72.9, 72.1, 69.8, 66.7, 66.5, 65.4, 57.7, 55.4, 53.5, 34.8, 29.7, 23.2, 22.1; MS (ES) *m/z* 418.25 $[M+H]^+$; calcd for $C_{24}H_{36}NO_5$: 418.26.

3.1.5. 2-Acetoxy-6-allyl-benzoic acid 1-(2-allyloxy-ethyl)-3-(4-methoxy-benzyloxy)-propyl ester 8b. To a solution of phenol **8a** (1.23 g, 2.79 mmol) equiv) in CH_2Cl_2 (20 mL) at 0 °C was added pyridine (243 mg, 3.07 mmol), acetic anhydride (314 mg, 3.07 mmol) and a catalytic amount of DMAP. After stirring at rt for 3 h the reaction mixture was concentrated in vacuo, and purified by FC (10% EtOAc in hexanes) to give 1.28 g (95% yield) of the product **8b** as a colorless oil. $[\alpha]_D=-7.5$ ($c=0.15$, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (1H, t, $J=8.0$ Hz), 7.25 (2H, d, $J=8.4$ Hz), 7.12 (1H, d, $J=7.6$ Hz), 7.01 (1H, d, $J=7.6$ Hz), 6.86 (2H, d, $J=8.4$ Hz), 5.97–5.84 (2H, m), 5.37 (1H, app.quint, $J=6.0$ Hz), 5.26 (1H, dd, $J=16.8$, 1.2 Hz), 5.16 (1H, dd, $J=10.4$, 1.2 Hz), 5.07 (1H, dd, $J=10.0$, 1.2 Hz), 5.04 (1H, dd, $J=17.2$, 1.2 Hz), 4.45 (1H, d, $J=11.6$ Hz), 4.41 (1H, d, $J=11.6$ Hz), 3.95 (2H, d, $J=5.6$ Hz), 3.80 (3H, s), 3.58–3.49 (4H, m), 3.44 (2H, d, $J=6.4$ Hz), 2.24 (3H, s), 2.04–1.95 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 166.2, 159.4, 148.2, 139.6, 136.4, 134.9, 130.7, 130.5, 129.5, 127.5, 127.0, 121.1, 117.1, 117.0, 114.0, 72.9, 72.1, 71.5, 66.6, 66.5, 55.5, 37.7, 34.6, 34.5, 21.1; MS (ES) *m/z* 505.25 $[M+Na]^+$; calcd for $C_{28}H_{34}O_7Na$: 505.22.

3.1.6. Ring closure metathesis. A solution of bis-olefin **8b–e** in degassed CH_2Cl_2 (0.07 M) and a solution of Grubbs catalyst (10 mol%) in degassed CH_2Cl_2 (0.01 M) were added dropwise simultaneously to a flask containing degassed CH_2Cl_2 (0.07 M with respect to bis-olefin). The reaction was stirred at rt until no further evolution (as monitored by TLC) was observed (4–6 h). The solvent was removed in vacuo and the residue was purified by FC to give the corresponding lactone **9b–e**.

3.1.6.1. Acetic acid 7-[2-(4-methoxy-benzyloxy)-ethyl]-5-oxo-8,9,11,14-tetrahydro-5H,7H-6,10-dioxa-benzocyclododecen-4-yl ester *E*-9b. Reaction mixture purified by FC (10% EtOAc in hexanes) to give 93 mg (94% yield, catalyst **ii**) of product *E*-**9b** as a colorless oil. $[\alpha]_D=-34.0$ ($c=1.29$, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (1H, t, $J=8.0$ Hz), 7.26 (2H, d, $J=8.4$ Hz), 7.11 (1H, d, $J=7.2$ Hz), 7.03 (1H, d, $J=8.4$ Hz), 6.88 (2H, d, $J=8.4$ Hz), 5.62 (1H, dddd, $J=14.8$, 10.0, 4.0, 1.6 Hz), 5.49 (1H, ddd, $J=14.8$, 10.8, 3.2 Hz), 5.22 (1H, dddd, $J=12.8$, 6.4, 6.4, 2.0 Hz), 4.48 (1H, d, $J=11.6$ Hz), 4.43 (1H, d, $J=11.6$ Hz), 4.13 (1H, br.dd, $J=11.6$, 3.2 Hz), 3.90 (1H, dd, $J=14.0$, 11.2 Hz), 3.80 (3H, s), 3.61–3.58 (2H, m), 3.46 (1H, ddd, $J=10.4$, 3.6, 2.4 Hz), 3.37 (1H, dd,

J=12.0, 10.4 Hz), 3.28 (1H, ddd, J=12.0, 10.8, 1.2 Hz), 3.20 (1H, dddd, J=14.0, 3.6, 1.6, 1.6 Hz), 2.21 (3H, s), 2.08–2.00 (1H, m), 1.94–1.83 (2H, m), 1.54 (1H, dddd, J=14.4, 12.4, 2.0, 2.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 166.6, 159.4, 148.2, 139.6, 133.1, 130.6, 130.5, 129.7, 129.6, 127.9, 127.7, 121.6, 114.0, 73.0, 70.6, 69.8, 67.0, 61.9, 55.4, 37.7, 36.2, 35.1, 21.0; MS (ES) m/z 477.15 $[M+Na]^+$; calcd for $C_{26}H_{30}O_7Na$: 477.19.

3.1.6.2. 7-[2-(4-Methoxy-benzyloxy)-ethyl]-8,9,11,14-tetra-hydro-7*H*-6,10-dioxa-benzocyclododecen-5-one *E*-9c. Reaction mixture purified by FC (10% EtOAc in hexanes) to give 237 mg of product *E*-**9c** (94% yield, catalyst **ii**) as a colorless oil. $[\alpha]_D=-72.8$ (c=1.66, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (1H, app.t, J=8.0 Hz), 7.29 (1H, d, J=7.6 Hz), 7.26 (2H, d, J=8.4 Hz), 7.21 (1H, d, J=8.8 Hz), 7.20 (1H, app.t, J=8.0 Hz), 6.85 (2H, d, J=8.8 Hz), 5.63 (1H, dddd, J=14.8, 10.4, 4.4, 1.6 Hz), 5.44 (1H, ddd, J=14.8, 10.8, 3.6 Hz), 5.35 (1H, dddd, J=11.6, 4.8, 4.8, 2.0 Hz), 4.45 (1H, d, J=11.6 Hz), 4.41 (1H, d, J=11.6 Hz), 4.13 (1H, dd, J=12.0, 4.4 Hz), 4.02 (1H, dd, J=14.0, 11.2 Hz), 3.79 (3H, s), 3.60 (2H, app.t, J=6.8 Hz), 3.45 (1H, dt, J=12.8, 2.8 Hz), 3.36 (1H, dd, J=12.0, 10.4 Hz), 3.28 (1H, ddd, J=12.0, 10.4, 1.6 Hz), 3.15 (1H, br.d, J=14.0 Hz), 2.05–1.95 (2H, m), 1.87 (1H, dddd, J=14.8, 12.0, 3.6, 2.4 Hz), 1.63 (1H, dddd, J=14.4, 12.4, 2.0, 2.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 159.3, 138.3, 134.6, 133.3, 130.6, 130.4, 129.8, 129.6, 127.8, 126.6, 113.9, 73.0, 70.7, 69.4, 67.0, 62.1, 55.4, 37.7, 35.6, 35.1; MS (ES) m/z 419.15 $[M+Na]^+$; calcd for $C_{24}H_{28}O_5Na$: 419.18.

3.1.6.3. 7-[2-(4-Methoxy-benzyloxy)-ethyl]-8,9,11,14-tetra-hydro-7*H*-6,10-dioxa-benzocyclododecen-5-one *Z*-9c. $[\alpha]_D=-73.2$ (c=1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (1H, d, J=7.6 Hz), 7.35 (1H, t, J=7.6 Hz), 7.29 (1H, d, J=7.6 Hz), 7.25 (2H, d, J=8.4 Hz), 7.12 (1H, t, J=7.6 Hz), 6.82 (2H, d, J=8.4 Hz), 5.78 (1H, dt, J=10.8, 6.0 Hz), 5.64–5.58 (1H, m), 5.51 (1H, dddd, J=12.8, 9.2, 4.0, 1.6 Hz), 4.52 (1H, dd, J=12.0, 12.0 Hz), 4.48 (1H, d, J=11.6 Hz), 4.42 (1H, d, J=11.6 Hz), 4.03 (1H, t, J=9.2 Hz), 3.77 (1H, app.t, J=10.8 Hz), 3.72 (3H, s), 3.64–3.55 (4H, m), 3.20 (1H, dd, J=12.8, 6.0 Hz), 2.04–1.88 (3H, m), 1.76 (1H, dddd, J=15.6, 4.4, 2.0, 2.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 159.3, 140.3, 137.5, 132.3, 131.1, 130.8, 130.4, 129.9, 129.6, 125.8, 124.1, 114.0, 73.0, 71.8, 69.2, 66.0, 65.1, 55.4, 35.7, 35.5, 30.6; MS (ES) m/z 419.15 $[M+Na]^+$; calcd for $C_{24}H_{28}O_5Na$: 419.18.

3.1.6.4. 12-[2-(4-Methoxy-benzyloxy)-ethyl]-5,8,11,12-tetrahydro-10*H*-9,13-dioxa-4b-aza-cyclododeca[a]-inden-14-one *E*-9d. Reaction mixture purified by FC (20% EtOAc in hexanes) to give 86 mg of product *E*-**9d** (18% yield *E*-isomer, catalyst **i**; 41% combined yield $E+Z$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (1H, d, J=8.0 Hz), 7.42 (1H, d, J=8.4 Hz), 7.33 (1H, app.t, J=8.0 Hz), 7.27 (2H, d, J=8.8 Hz), 7.15 (1H, t, J=8.0 Hz), 6.91 (1H, s), 6.85 (2H, d, J=8.8 Hz), 5.80 (1H, ddd, J=15.2, 10.0, 4.4 Hz), 5.49–5.43 (1H, m), 5.38 (1H, ddd, J=14.8, 10.0, 3.6 Hz), 5.02 (1H, dd, J=14.4, 10.0 Hz), 4.88 (1H, br.d, J=14.4 Hz), 4.47 (1H, d, J=11.6 Hz), 4.43 (1H, d, J=11.6 Hz), 4.10 (1H, dd, J=12.0, 4.8 Hz), 3.78 (3H, s), 3.60 (2H, ddd, J=6.4, 2.0, 2.0 Hz), 3.45 (1H, ddd, J=10.0, 3.6, 3.6 Hz), 3.39 (1H, dd, J=12.4, 10.4 Hz), 3.27 (1H, ddd, J=11.6, 9.6, 2.0 Hz), 2.03–1.89 (3H, m), 1.69 (1H, dddd, J=14.4, 12.0, 2.4, 2.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0, 159.3, 138.4, 132.8, 131.4, 130.6, 130.2, 129.6, 126.9, 124.3, 122.5, 120.8, 114.0, 110.0, 107.3, 73.1, 70.0, 66.8, 62.6, 55.4, 46.1, 35.6, 35.4; MS (ES) m/z 458.15 $[M+Na]^+$; calcd for $C_{26}H_{29}NO_5Na$: 458.19.

3.1.6.5. 7-[2-(4-Methoxy-benzyloxy)-ethyl]-1,2,3,4,8,9,11,14-octahydro-7*H*-6,10-dioxa-benzocyclododecen-5-one *E*-9e. Reaction mixture purified by FC (15% EtOAc in hexanes) to give 172 mg of non-separable *E*- and *Z*-isomers (75% combined yield, catalyst **ii**) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (2H, d, J=8.0 Hz), 6.86 (2H, d, J=8.0 Hz), 5.48–5.34 (2H, m), 5.15 (1H, dddd, J=11.6, 6.0, 6.0, 2.0 Hz), 4.43 (1H, d, J=11.6 Hz), 4.38 (1H, d, J=11.6 Hz), 4.09 (1H, br.dd, J=11.2, 3.2 Hz), 3.80 (3H, s), 3.50–3.35 (6H, m), 2.27 (2H, br.d, 14.0), 2.15 (2H, br.s), 2.0–1.92 (1H, m), 1.87 (2H, app.dt, J=6.8, 6.4 Hz), 1.82 (1H, dddd, J=16.4, 14.8, 3.6, 2.4 Hz), 1.66–1.61 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 159.3, 138.8, 132.4, 130.5, 129.6, 128.5, 114.0, 73.0, 70.6, 69.3, 66.8, 61.9, 55.4, 36.9, 35.6, 35.1, 32.4, 27.0, 22.7, 21.8; MS (ES) m/z 423.15 $[M+Na]^+$; calcd for $C_{24}H_{32}O_5Na$: 423.21.

3.1.7. PMB deprotection. To a solution of the lactone **9b–e** (1 equiv) in CH_2Cl_2 (0.05 M with respect to the lactone) and water (1.0 M with respect to the lactone) was added DDQ (1.2 equiv). After stirring for 2–3 h, the slurry was poured into sat. aq. $NaHCO_3$ and water and extracted with EtOAc (4×). The combined organic layers were dried, concentrated in vacuo, and purified by FC.

3.1.7.1. Acetic acid 7-(2-hydroxy-ethyl)-5-oxo-8,9,11,14-tetrahydro-5H,7H-6,10-dioxa-benzocyclododecen-4-yl ester 10b. Reaction mixture purified by FC (60% EtOAc in hexanes) to give 760 mg (95% yield) of product **10b**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (1H, t, J=8.0 Hz), 7.14 (1H, d, J=7.6 Hz), 7.05 (1H, d, J=7.6 Hz), 5.63 (1H, dddd, J=14.8, 10.4, 4.0, 1.6 Hz), 5.51 (1H, ddd, J=14.8, 11.2, 3.6 Hz), 5.33 (1H, dddd, J=10.8, 8.4, 2.4, 2.4 Hz), 4.15 (1H, br.d, J=12.4 Hz), 3.92 (1H, dd, J=13.6, 10.8 Hz), 3.77–3.73 (2H, m), 3.48 (1H, dt, J=10.0, 2.8 Hz), 3.38 (1H, dd, J=12.0, 10.0 Hz), 3.28 (1H, ddd, J=12.0, 10.4, 1.6 Hz), 3.22 (1H, ddt, J=14.0, 3.2, 1.6 Hz), 2.94 (1H, dd, J=7.6, 6.0 Hz), 2.22 (3H, s), 1.99–1.91 (1H, m), 1.82 (1H, dddd, J=16.4, 12.8, 3.6, 2 Hz), 1.69 (1H, ddt, J=13.6, 10.0, 3.2 Hz), 1.62–1.56 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 168.4, 148.3, 139.8, 133.3, 130.9, 129.7, 128.0, 127.2, 121.7, 70.5, 69.3, 61.8, 58.3, 39.0, 37.6, 35.6, 21.0; MS (ES) m/z 357.10 (100%) [$(M+Na)^+$; calcd for $C_{18}H_{22}O_6Na$: 357.13].

3.1.7.2. 7-(2-Hydroxy-ethyl)-8,9,11,14-tetrahydro-7*H*-6,10-dioxa-benzocyclododecen-5-one 10c. Reaction mixture purified by FC (50% EtOAc in hexanes) to give 155 mg (94% yield) of product **10c**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (1H, app.t, J=7.6 Hz), 7.37 (1H, d, J=7.6 Hz), 7.27 (1H, app.t, J=7.6 Hz), 7.25 (1H, d, J=7.6 Hz), 5.63 (1H, dddd, J=15.2, 10.4, 4.4, 1.6 Hz), 5.46 (1H, ddd, J=14.8, 11.2, 3.2 Hz), 5.42–5.35 (1H, m), 4.15 (1H, br.dd, J=10.8,

4.0 Hz), 4.02 (1H, dd, J=13.6, 10.8 Hz), 3.76–3.64 (2H, m), 3.48 (1H, dt, J=10.0, 2.8 Hz), 3.37 (1H, dd, J=12.0, 10.4 Hz), 3.29 (1H, ddd, J=12.0, 10.4, 1.6 Hz), 3.15 (1H, br.d, J=13.6 Hz), 3.07 (1H, br. s), 1.99–1.80 (2H, m), 1.78 (1H, dddd, J=13.6, 10.0, 3.6, 3.6 Hz), 1.65 (1H, dddd, J=14.4, 12.4, 2.0, 2.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 138.3, 134.0, 133.5, 130.8, 130.5, 129.6, 127.7, 126.6, 70.6, 68.7, 62.0, 58.5, 38.4, 37.5, 35.5; MS (ES) m/z 299.00 $[M+Na]^+$; calcd for $C_{16}H_{20}O_4Na$: 299.13.

3.1.7.3. 12-(2-Hydroxy-ethyl)-5,8,11,12-tetrahydro-10*H*-9,13-dioxa-4b-aza-cyclododeca[a]inden-14-one 10d. Reaction mixture purified by FC (40% EtOAc in hexanes) to give 36 mg (94% yield) of product **10d**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (1H, d, J=8.0 Hz), 7.42 (1H, d, J=8.4 Hz), 7.33 (1H, ddd, J=8.0, 7.2, 1.2 Hz), 7.16 (1H, dd, J=7.2, 7.2 Hz), 6.99 (1H, s), 5.80 (1H, ddd, J=15.2, 10.0, 4.4 Hz), 5.47 (1H, dddd, J=11.2, 11.2, 2.4, 2.4 Hz), 5.38 (1H, ddd, J=14.0, 10.0, 3.2 Hz), 5.00 (1H, dd, J=14.4, 10.0 Hz), 4.87 (1H, br d, J=14.4 Hz), 4.14 (1H, dd, J=11.6, 4.0 Hz), 3.76–3.70 (2H, m), 3.47 (1H, dt, J=10.0, 3.2 Hz), 3.36 (1H, dd, J=12.4, 10.4 Hz), 3.25 (1H, ddd, J=12.0, 10.0, 1.6 Hz), 2.79 (1H, br.s), 1.99–1.83 (2H, m), 1.81 (1H, dddd, J=14.4, 10.8, 3.6 Hz), 1.71 (1H, dddd, J=14.0, 11.6, 2.0, 2.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 138.5, 132.7, 131.1, 130.4, 126.9, 124.6, 122.5, 121.0, 110.0, 107.6, 70.0, 69.7, 62.6, 58.6, 46.1, 38.1, 35.6; MS (ES) m/z 338.10 $[M+Na]^+$; calcd for $C_{18}H_{21}NO_4Na$: 338.14.

3.1.7.4. 7-(2-Hydroxy-ethyl)-1,2,3,4,8,9,11,14-octahydro-7*H*-6,10-dioxa-benzocyclododecen-5-one 10e. Reaction mixture purified by FC (30% EtOAc in hexanes) to give 42 mg (35% yield, 78% combined yield E+Z) of the *E*-isomer **10e**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.48–5.36 (2H, m), 5.25–5.18 (1H, m), 4.10 (1H, br.d, J=11.6 Hz), 3.64–3.61 (1H, m), 3.52–3.43 (3H, m), 3.39–3.32 (2H, m), 3.10 (1H, br. s), 2.36 (1H, br.d, J=17.6 Hz), 2.68 (1H, br.d, J=14.0 Hz), 2.17 (2H, m), 2.06 (1H, br.d, J=16.8 Hz), 1.84 (1H, dddd, J=17.2, 10.4, 5.6, 2.8 Hz), 1.79 (1H, dddd, J=16.0, 12.0, 3.2, 2.0 Hz), 1.69–1.56 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 139.7, 132.6, 129.4, 128.4, 70.6, 67.3, 61.8, 58.3, 38.4, 36.7, 35.6, 32.4, 26.8, 22.6, 21.8; MS (ES) m/z 303.05 $[M+Na]^+$; calcd for $C_{16}H_{24}O_4Na$: 303.16.

3.1.8. Oxidation and HWE olefination. To a solution of alcohol **10b–e** in CH_2Cl_2 (0.04 M) was added Dess Martin periodinane (3 equiv). The reaction was stirred at rt for 3–4 h, after which time the solvent was removed in vacuo and the residue was quickly passed through a short column of silica (50% EtOAc in hexanes) to give the aldehyde. To a suspension of NaH (60% in mineral oil, prewashed with benzene, 4.5 equiv with respect to alcohol) in THF (0.3 M) was added dimethyl(trimethylsiloxy-carbonylmethyl)-phosphonate (5.0 equiv) at 0 °C. After stirring for 30 min at the same temperature, the solution was added to a solution of the above prepared aldehyde (pre-washed with benzene) in THF (0.1 M with respect to aldehyde) and stirring was continued for 1 h after which time more phosphonate solution (same amounts) was added. The mixture was stirred at 0 °C for 30 min before being quenched with acetic acid. Water was added, and the solution was extracted with EtOAc (3×). The combined organic layers were dried over $MgSO_4$, concentrated in vacuo and purified by FC.

3.1.8.1. 4-(4-Acetoxy-5-oxo-8,9,11,14-tetrahydro-5H,7H-6,10-dioxa-benzocyclododecen-7-yl)-but-2-enoic acid 11b. Reaction mixture purified by FC (50% EtOAc in hexanes with 1% AcOH) to give 111 mg of product **11b** (61% yield for 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (1H, t, J=7.6 Hz), 7.16–7.09 (2H, m), 7.06 (1H, d, J=8.4 Hz), 5.96 (1H, d, J=15.6 Hz), 5.63 (1H, dddd, J=15.2, 10.4, 4.0, 1.6 Hz), 5.52 (1H, ddd, J=14.8, 10.8, 3.2 Hz), 5.24 (1H, dddd, J=11.6, 6.4, 4.8, 1.6 Hz), 4.16 (1H, br.dd, J=12.4, 3.6 Hz), 3.87 (1H, dd, J=13.6, 10.8 Hz), 3.53 (1H, ddd, J=10.0, 3.6, 2.4 Hz), 3.40 (1H, dd, J=12.4, 10.4 Hz), 3.29 (1H, ddd, J=12.0, 10.8, 1.2 Hz), 3.22 (1H, dddd, J=14.0, 3.2, 1.6, 1.6 Hz), 2.75–2.59 (2H, m), 2.27 (3H, s), 1.80 (1H, dddd, J=16.4, 12.8, 3.6, 1.6 Hz), 1.54 (1H, dddd, J=14.4, 12.8, 1.6, 1.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.6, 168.9, 166.6, 148.1, 146.1, 139.3, 133.6, 130.7, 130.4, 129.2, 128.7, 127.9, 127.5, 121.6, 70.7, 70.0, 61.9, 37.7, 34.1, 21.1; MS (ES) m/z 397.10 $[M+Na]^+$; calcd for $C_{20}H_{22}O_7Na$: 397.13.

3.1.8.2. 4-(5-Oxo-8,9,11,14-tetrahydro-5H,7H-6,10-dioxa-benzocyclododecen-7-yl)-but-2-enoic acid 11c. Reaction mixture purified by FC (40% EtOAc in hexanes with 1% AcOH) to give 100 mg (57% yield for 2 steps) of the product **11c**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.2 (1H, br.s), 7.37–7.22 (4H, m), 7.13 (1H, dt, J=15.6, 7.2 Hz), 5.96 (1H, d, J=15.6 Hz), 5.62 (1H, dddd, J=15.3, 10.5, 4.5, 1.8 Hz), 5.46 (1H, ddd, J=14.4, 10.8, 2.7 Hz), 5.37 (1H, dddd, J=11.7, 5.7, 5.7, 3.2 Hz), 4.17 (1H, br.dd, J=12.3, 4.2 Hz), 4.00 (1H, dd, J=13.8, 10.8 Hz), 3.52 (1H, dt, J=10.2, 2.4 Hz), 3.38 (1H, dd, J=12.3, 10.2 Hz), 3.29 (1H, ddd, J=12.3, 10.2, 2.1 Hz), 3.15 (1H, dddd, J=13.8, 3.3, 1.5, 1.5 Hz), 2.75–2.55 (2H, m), 1.85 (1H, dddd, J=15.9, 12.0, 3.3, 3.3 Hz), 1.63 (1H, dddd, J=14.4, 12.3, 2.1, 2.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.7, 171.4, 146.4, 138.1, 134.2, 133.7, 130.7, 130.5, 129.4, 127.5, 126.7, 123.9, 70.7, 70.0, 62.0, 38.0, 37.5, 34.3; MS (ES) m/z 339.00 $[M+Na]^+$; calcd for $C_{18}H_{20}O_5Na$: 339.12.

3.1.8.3. 4-(14-Oxo-5,8,11,12-tetrahydro-10H,14H-9,13-dioxa-4b-aza-cyclododeca[a]inden-12-yl)-but-2-enoic acid 11d. Reaction mixture purified by FC (50% EtOAc in hexanes with 1% AcOH) to give 21.4 mg of product **11d** (53% yield for 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.15 (1H, br s), 7.65 (1H, d, J=8.0 Hz), 7.42 (1H, d, J=8.4 Hz), 7.33 (1H, t, J=6.8 Hz), 7.16 (1H, t, J=7.2 Hz), 7.11 (1H, dt, J=15.2, 8.0 Hz), 6.9 (1H, s), 5.98 (1H, d, J=15.2 Hz), 5.79 (1H, ddd, J=14.8, 10.4, 4.0 Hz), 5.47 (1H, dddd, J=11.6, 6.0, 6.0, 2.0 Hz), 5.38 (1H, ddd, J=14.0, 10.0, 3.6 Hz), 5.00 (1H, dd, J=14.4, 10.0 Hz), 4.87 (1H, br.d, J=15.2 Hz), 4.12 (1H, dd, J=12.8, 6.0 Hz), 3.48 (1H, dt, J=10.0, 3.2 Hz), 3.38 (1H, dd, J=12.0, 10.0 Hz), 3.25 (1H, ddd, J=12.0, 10.0, 2.0 Hz), 2.70–2.61 (2H, m), 1.89 (1H, dddd, J=14.8, 12.0, 3.2, 3.2 Hz), 1.68 (1H, dddd, J=14.4, 12.0, 2.4, 2.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8, 146.3, 138.4, 132.7, 131.0, 130.4, 126.9, 124.5, 122.6, 120.9, 110.0, 107.5, 70.1, 69.8, 62.5, 46.1, 38.0, 34.7; MS (ES) m/z 378.05 $[M+Na]^+$; calcd for $C_{20}H_{21}NO_5Na$: 378.13.

3.1.8.4. 4-(5-Oxo-1,3,4,5,8,9,11,14-octahydro-2H,7H-6,10-dioxa-benzocyclododecen-7-yl)-but-2-enoic acid 11e. Reaction mixture purified by FC (30% EtOAc in hexanes with 1% AcOH) to give 25.5 mg of product **11e** (56% yield for 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (1H, dt, J=15.6, 8.0 Hz), 5.84 (1H, d, J=15.6 Hz), 5.45–5.34 (2H, m), 5.19 (1H, dddd, J=11.6, 5.6, 5.6, 2.0 Hz), 4.10 (1H, br.d, J=11.2 Hz), 3.53 (1H, dt, J=10.0, 2.8 Hz), 3.44–3.32 (3H, m), 2.63–2.55 (1H, m), 2.45 (1H, dddd, J=14.4, 8.0, 7.2, 0.8 Hz), 2.33–2.25 (2H, m), 2.18–2.02 (3H, m), 1.78 (1H, dddd, J=16.4, 12.4, 3.6, 2.4 Hz), 1.68–1.56 (5H, m);); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 170.3, 146.8, 138.9, 132.7, 129.8, 128.3, 123.6, 70.8, 67.8, 61.9, 37.9, 36.9, 34.4, 32.4, 26.5, 22.7, 21.8; MS (ES) m/z 343.05 $[M+Na]^+$; calcd for $C_{18}H_{24}O_5Na$: 343.15.

3.1.9. Acyl azide formation. To a stirred solution of the acid **11b–e** and diphenylphosphorylazide (4 equiv) in benzene (0.03 M) was added triethylamine (4.7 equiv). The reaction mixture was stirred at rt for 2 h and concentrated in vacuo prior to purification by FC.

3.1.9.1. Acetic acid 7-(3-azidocarbonyl-allyl)-5-oxo-8,9,11,14-tetrahydro-5H,7H-6,10-dioxa-benzocyclododecen-4-yl ester 12b. Reaction mixture purified by FC (10% EtOAc in hexanes) to give 82 mg (77% yield) of product **12b** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (1H, t, J=8.0 Hz), 7.12 (1H, d, J=7.2 Hz), 7.10 (1H, dt, J=15.6, 7.6 Hz), 7.06 (1H, d, J=8.4 Hz), 5.94 (1H, d, J=15.6 Hz), 5.62 (1H, dddd, J=14.8, 10.4, 4.4, 1.6 Hz), 5.51 (1H, ddd, J=14.8, 10.8, 3.6 Hz), 5.23 (1H, dddd, J=11.6, 6.4, 4.8, 1.6 Hz), 4.13 (1H, br.dd, J=12.0, 4.4 Hz), 3.87 (1H, dd, J=13.6, 10.4 Hz), 3.51 (1H, ddd, J=10.4, 3.2, 2.8 Hz), 3.39 (1H, dd, J=12.4, 10.4 Hz), 3.27 (1H, ddd, J=12.4, 10.8, 1.6 Hz), 3.21 (1H, dddd, J=14.0, 3.2, 1.6, 1.6 Hz), 2.71–2.55 (2H, m), 2.26 (3H, s), 1.78 (1H, dddd, J=16.4, 12.0, 3.6, 1.6 Hz), 1.53 (1H, dddd, J=14.4, 12.4, 2.0, 2.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 168.8, 166.7, 148.1, 146.1, 139.4, 133.5, 130.7, 129.4, 127.9, 125.7, 122.9, 121.6, 70.7, 69.9, 61.8, 37.7, 34.4, 21.2; MS (ES) m/z 356.20 $[M-H]^-$; calcd for $C_{18}H_{18}N_3O_5$: 356.13.

3.1.9.2. 4-(5-Oxo-8,9,11,14-tetrahydro-5H,7H-6,10-dioxa-benzocyclododecen-7-yl)-but-2-enoyl azide 12c. Reaction mixture purified by FC (10% EtOAc in hexanes) to give 61 mg (56% yield) of product **12c**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (1H, app.dt, J=7.6, 1.2 Hz), 7.33 (1H, d, J=7.6 Hz), 7.27 (1H, app.t, J=7.6 Hz), 7.23 (1H, d, J=7.6 Hz), 7.10 (1H, dt, J=15.2, 8.0 Hz), 5.95 (1H, d, J=15.2 Hz), 5.61 (1H, dddd, J=15.2, 10.4, 4.4, 1.6 Hz), 5.46 (1H, ddd, J=14.4, 10.8, 3.2 Hz), 5.37 (1H, dddd, J=12.0, 6.4, 6.4, 2.4 Hz), 4.14 (1H, dd, J=12.0, 4.4 Hz), 4.00 (1H, dd, J=14.0, 10.8 Hz), 3.49 (1H, dt, J=10.0, 2.8 Hz), 3.37 (1H, dd, J=12.4, 10.4 Hz), 3.27 (1H, ddd, J=12.0, 10.0, 1.6 Hz), 3.15 (1H, dddd, J=14.0, 3.2, 1.6, 1.6 Hz), 2.72–2.55 (2H, m), 1.82 (1H, dddd, J=16.4, 12.0, 3.6, 2.4 Hz), 1.61 (1H, dddd, J=13.6, 12.0, 2.0, 2.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 169.0, 146.6, 138.2, 134.2, 133.6, 130.7, 130.6, 129.5, 127.4, 126.7, 125.6, 70.7, 68.9, 61.9, 38.3, 37.6, 34.6; MS (ES) m/z 368.10 $[M-N_2+MeOH+Na]^+$; calcd for $C_{19}H_{23}NO_5Na$: 368.15.

3.1.9.3. 4-(14-Oxo-5,8,11,12-tetrahydro-10H,14H-9,13-dioxa-4b-aza-cyclododeca[a]inden-12-yl)-but-2-enoyl azide 12d. Reaction mixture purified by FC (10% EtOAc in hexanes) to give 20 mg (88% yield) of product **12d**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (1H, d, J=8.0 Hz), 7.42 (1H, d, J=8.4 Hz), 7.34 (1H, ddd, J=8.0, 7.2, 0.8 Hz), 7.16 (1H, t, J=7.6 Hz), 7.10 (1H, dt, J=15.2, 7.6 Hz), 6.96 (1H, s), 5.97 (1H, d, J=15.2 Hz), 5.79 (1H, ddd, J=15.2, 10.4, 4.8 Hz), 5.47 (1H, dddd, J=11.6, 6.8, 6.8, 2.4 Hz), 5.38 (1H, ddd, J=14.4, 10.0, 3.6 Hz), 5.00 (1H, dd, J=14.4, 10.0 Hz), 4.87 (1H, br.d, J=14.0 Hz), 4.12 (1H, dd, J=10.8, 3.6 Hz), 3.47 (1H, dt, J=10.0, 3.2 Hz), 3.37 (1H, dd, J=12.4, 10.4 Hz), 3.24 (1H, ddd, J=11.6, 10.0, 1.6 Hz), 2.68–2.61 (2H, m), 1.88 (1H, dddd, J=14.4, 11.6, 3.2, 3.2 Hz), 1.67 (1H, dddd, J=14.4, 12.4, 2.0, 2.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8, 146.3, 138.5, 132.7, 131.0, 130.3, 126.8, 125.8, 124.5, 122.6, 120.9, 110.0, 107.5, 70.1, 69.7, 62.4, 46.1, 38.2, 34.9; MS (ES) m/z 407.05 $[M-N_2+MeOH+Na]^+$; calcd for $C_{21}H_{24}N_2ONa$: 407.16.

3.1.9.4. 4-(5-Oxo-1,3,4,5,8,9,11,14-octahydro-2H,7H-6,10-dioxa-benzocyclododecen-7-yl)-but-2-enoyl azide 12e. Reaction mixture purified by FC (10% EtOAc in hexanes) to give 17 mg (67% yield) of product **12e**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (1H, dt, J=15.2, 7.6 Hz), 5.84 (1H, d, J=15.2 Hz), 5.45–5.36 (2H, m), 5.19 (1H, dddd, J=11.6, 5.6, 5.6, 2.0 Hz), 4.10 (1H, br.d, J=11.2 Hz), 3.52 (1H, dt, J=9.6, 2.4 Hz), 3.44–3.31 (3H, m), 2.57 (1H, app.dt, J=14.0, 6.8 Hz), 2.43 (1H, app.dt, J=14.0, 7.6 Hz), 2.36–2.25 (2H, m), 2.16–1.99 (3H, m), 1.76 (1H, dddd, J=16.8, 12.4, 3.6, 2.4 Hz), 1.68–1.53 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 170.3, 147.0, 139.1, 132.6, 129.7, 128.3, 125.4, 70.8, 67.7, 61.8, 38.3, 36.9, 34.6, 32.4, 26.5, 22.7, 21.8; MS (ES) m/z 372.10 $[M-N_2+MeOH+Na]^+$; calcd for $C_{19}H_{27}NO_5Na$: 372.18.

3.1.10. Curtius rearrangement and alkyne addition. A stirred solution of the acylazide **12b–e** in benzene (0.02 M) was heated at 80 °C for 5 h, after which the solvent was steamed off with nitrogen and the residue dried under vacuum for 10 min. To a solution of the alkyne (2.0 equiv) in THF (0.1 M) at −78 °C was added *n*-BuLi (2.5 M in hexanes, 1.7 equiv) or the alkyne was added to a freshly prepared solution of LDA in THF (0.1 M). The stirring was continued for 30 min, after which time a solution of the isocyanate mixture in THF was added. The reaction mixture was stirred at −78 °C for 30 min, and then quenched with saturated NH_4Cl and water. The mixture was extracted with Et_2O (3×). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. If no acetate group was present, the residue was purified by FC. When an acetate group was present, the residue was dissolved in MeOH and K_2CO_3 (1 equiv) was added. The mixture was stirred at rt for 1 h, after which time water was added and the mixture was extracted with Et_2O (3×). The combined organic layers were dried, concentrated in vacuo, and purified by FC.

3.1.10.1. 3-Phenyl-propynoic acid [3-(4-hydroxy-5-oxo-8,9,11,14-tetrahydro-5H,7H-6,10-dioxa-benzocyclododecen-7-yl)-propenyl]-amide 14a. *n*-BuLi was used. Reaction mixture purified by FC (40% EtOAc in hexanes) to give 23.6 mg (62% yield) of product **14a**. $[\alpha]_D$=−19.3

($c=1.52$, CH_2Cl_2). ^1H NMR (400 MHz, CD_3OD) δ 7.59 (2H, d, $J=7.2$ Hz), 7.48 (1H, t, $J=7.6$ Hz), 7.41 (2H, d, $J=8.0$ Hz), 7.15 (1H, t, $J=8.0$ Hz), 6.84 (1H, d, $J=14.4$ Hz), 6.77 (1H, d, $J=8.4$ Hz), 6.72 (1H, d, $J=7.6$ Hz), 5.56–5.53 (2H, m), 5.49 (1H, dt, $J=14.4$, 8.0 Hz), 5.11–5.05 (1H, m), 4.10 (1H, d, $J=10.8$ Hz), 3.71 (1H, dd, $J=13.2$, 10.0 Hz), 3.54 (1H, br d, $J=10.0$ Hz), 3.44 (1H, dd, $J=12.4$, 10.0 Hz), 3.38 (1H, d, $J=10.8$ Hz), 3.15 (1H, d, $J=13.2$ Hz), 2.49 (2H, dd, $J=6.4$, 6.4 Hz, m), 1.80 (1H, dd, $J=14.8$, 11.6 Hz), 1.60 (1H, dd, $J=14.4$, 12.4 Hz); ^{13}C NMR (75 MHz, CD_3OD_3) δ 170.5, 156.4, 152.4, 139.6, 135.3, 133.7, 131.7, 130.0, 129.9, 125.9, 123.9, 122.2, 121.5, 115.6, 111.7, 87.3, 83.7, 71.8, 71.6, 63.4, 38.7, 36.2, 34.7; MS (ES) m/z 454.20 $[M+Na]^+$; calcd for $C_{26}H_{25}NO_5Na$: 454.16.

3.1.10.2. 3-Phenyl-propynoic acid [3-(5-oxo-8,9,11,14-tetrahydro-5H,7H-6,10-dioxa-benzocyclododecen-7-yl)-propenyl]-amide 14c. *n*-BuLi was used. Reaction mixture purified by FC (40% EtOAc in hexanes) to give 9.3 mg (97% yield) of product **14c**. $[\alpha]_D=-66.8$ ($c=0.63$, CH_2Cl_2). ^1H NMR (400 MHz, CD_3OD) δ 7.58 (2H, d, $J=8.0$ Hz), 7.47 (1H, d, $J=7.2$ Hz), 7.43–7.37 (4H, m), 7.31–7.27 (2H, m), 6.89 (1H, d, $J=14.4$ Hz), 5.56 (1H, dddd, $J=15.2$, 10.4, 4.4, 1.6 Hz), 5.49 (1H, ddd, $J=14.4$, 10.0, 3.2 Hz), 5.45 (1H, dt, $J=15.2$, 8.4 Hz), 5.20 (1H, ddd, $J=11.6$, 6.0, 6.0, 2.0 Hz), 4.09 (1H, br.dd, $J=12.0$, 3.2 Hz), 3.92 (1H, dd, $J=14.0$, 10.8 Hz), 3.49 (1H, dt, $J=10.0$, 2.4 Hz), 3.40 (1H, dd, $J=12.0$, 9.6 Hz), 3.33–3.28 (1H, m), 3.19 (1H, br.d, $J=13.6$ Hz), 2.53–2.38 (2H, m), 1.84 (1H, dddd, $J=16.0$, 12.4, 3.6, 2.4 Hz), 1.60 (1H, dddd, $J=14.4$, 12.4, 2.0, 2.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 152.5, 139.2, 135.8, 134.9, 133.7, 131.7, 131.6, 130.6, 130.0, 128.6, 127.8, 125.9, 122.5, 11.5, 87.4, 83.6, 71.5, 71.3, 63.3, 38.4, 36.9, 35.2; MS (ES) m/z 438.15 $[M+Na]^+$; calcd for $C_{26}H_{25}NO_4Na$: 438.17.

3.1.10.3. 3-Phenyl-propynoic acid [3-(14-oxo-5,8,11,12-tetrahydro-10H,14H-9,13-dioxa-4b-aza-cyclododeca[a]inden-12-yl)-propenyl]-amide 14d. *n*-BuLi was used. Reaction mixture purified by FC (30% EtOAc in hexanes) to give 12 mg (79% yield) of product **14d**. $[\alpha]_D=-167.6$ ($c=0.50$, CH_2Cl_2). ^1H NMR (400 MHz, CD_3OD) δ 7.62 (1H, d, $J=8.0$ Hz), 7.57 (2H, d, $J=8.0$ Hz), 7.52 (1H, d, $J=8.4$ Hz), 7.45 (1H, d, $J=7.2$ Hz), 7.40 (2H, d, $J=8.0$ Hz), 7.30 (1H, dd, $J=7.2$, 7.2 Hz), 7.11 (1H, t, $J=7.6$ Hz), 6.95 (1H, s), 6.89 (1H, d, $J=14.4$ Hz), 5.72 (1H, ddd, $J=14.8$, 10.0, 4.8 Hz), 5.46 (1H, ddd, $J=14.4$, 6.8, 6.8 Hz), 5.42–5.28 (2H, m), 5.01 (1H, br.d, $J=10.4$ Hz), 4.92 (1H, br.d, $J=14.8$ Hz), 4.11–4.04 (1H, m), 3.46 (1H, br.d, $J=9.2$ Hz), 3.42 (1H, dd, $J=12.0$, 10.0 Hz), 3.31–3.26 (1H, m), 2.49–2.42 (2H, m), 1.90 (1H, dddd, $J=14.4$, 11.6, 3.2, 3.2 Hz), 1.65 (1H, dddd, $J=14.4$, 12.0, 2.4, 2.4 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 173.1, 165.4, 152.5, 139.9, 133.7, 133.6, 132.6, 131.8, 130.1, 130.0, 128.2, 126.0, 125.4, 123.3, 121.8, 121.5, 111.4, 111.1, 108.0, 87.4, 83.7, 72.3, 70.8, 63.8, 47.0, 36.8, 35.5; MS (ES) m/z 477.20 $[M+Na]^+$; calcd for $C_{28}H_{26}N_2O_4Na$: 477.18.

3.1.10.4. 3-Phenyl-propynoic acid [3-(5-oxo-1,3,4,5,8,9,11,14-octahydro-2H,7H-6,10-dioxa-benzocyclododecen-7-yl)-propenyl]-amide 14e. *n*-BuLi was used. Reaction mixture purified by FC (30% EtOAc in hexanes) to give 10 mg (50% yield) of product **14e**. $[\alpha]_D=-65.1$ ($c=0.48$, CH_2Cl_2). ^1H NMR (400 MHz, CD_3OD) δ 7.59 (2H, d, $J=8.4$ Hz), 7.49 (1H, app.t, $J=7.6$ Hz), 7.43 (2H, d, $J=7.6$ Hz), 6.76 (1H, d, $J=14.4$ Hz), 5.46 (1H, ddd, $J=14.8$, 10.8, 3.6 Hz), 5.39–5.33 (1H, m), 5.35 (1H, dt, $J=14.4$, 7.2 Hz), 5.03 (1H, dddd, $J=11.6$, 6.0, 6.0, 2.0 Hz), 4.05 (1H, br.dd, $J=12.0$, 3.6 Hz), 3.51 (1H, app.dt, $J=10.0$, 2.8 Hz), 3.40 (1H, dd, $J=12.0$, 10.0 Hz), 3.36–3.30 (2H, m), 2.40–2.16 (6H, m), 2.07–2.00 (1H, m), 1.78 (1H, dddd, $J=17.2$, 12.8, 4.0, 2.4 Hz), 1.68–1.60 (4H, m), 1.55 (1H, dddd, $J=14.4$, 12.4, 2.0, 2.0 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 170.6, 151.1, 138.6, 132.5, 132.4, 130.4, 129.9, 128.7, 128.0, 124.4, 120.1, 110.2, 86.0, 82.3, 70.2, 69.0, 61.8, 36.4, 35.4, 33.8, 31.9, 26.4, 22.5, 21.6; MS (ES) m/z 442.10 $[M+Na]^+$; calcd for $C_{26}H_{29}NO_4Na$: 442.20.

3.1.10.5. 3-(3-Fluoro-phenyl)-propynoic acid [3-(4-hydroxy-5-oxo-8,9,11,14-tetrahydro-5H,7H-6,10-dioxa-benzocyclododecen-7-yl)-propenyl]-amide 16. *n*-BuLi was used. Reaction mixture purified by FC (40% EtOAc in hexanes) to give 9.2 mg (52% yield) of product **16**. ^1H NMR (400 MHz, CD_3OD) δ 7.47–7.40 (2H, m), 7.34 (1H, ddd, $J=9.2$, 2.8, 1.6 Hz), 7.25 (1H, dddd, $J=10.8$, 8.8, 2.8, 1.6 Hz), 7.15 (1H, t, $J=7.6$ Hz), 6.83 (1H, d, $J=14.4$ Hz), 6.75 (1H, d, $J=8.4$ Hz), 6.73 (1H, d, $J=7.2$ Hz), 5.57–5.53 (2H, m), 5.50 (1H, dt, $J=14.4$, 8.0 Hz), 5.08 (1H, dddd, $J=11.6$, 5.6, 5.6, 2.4 Hz), 4.10 (1H, d, $J=12.0$ Hz), 3.71 (1H, dd, $J=13.6$, 10.0 Hz), 3.54 (1H, ddd, $J=10.4$, 3.6, 2.4 Hz), 3.44 (1H, dd, $J=12.4$, 10.0 Hz), 3.37 (1H, ddd, $J=12.0$, 10.4, 1.6 Hz), 3.15 (1H, br.d, $J=13.6$ Hz), 2.49 (2H, ddd, $J=7.2$, 6.0, 1.2 Hz), 1.80 (1H, dddd, $J=16.4$, 12.8, 4.0, 2.4 Hz), 1.60 (1H, dddd, $J=14.4$, 12.0, 1.6, 1.6 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 170.5, 165.6, 162.3, 156.5, 152.0, 139.6, 135.3, 132.1, 132.0, 131.7, 129.9, 125.8, 123.9, 122.1, 120.3, 120.0, 119.1, 118.8, 115.6, 112.0, 85.5, 84.3, 71.8, 71.6, 63.4, 38.7, 36.2, 34.8; MS (ES) m/z 472.25 $[M+Na]^+$; calcd for $C_{26}H_{24}FNO_5Na$: 472.15.

3.1.10.6. 3-Pyridin-3-yl-propynoic acid [3-(4-hydroxy-5-oxo-8,9,11,14-tetrahydro-5H,7H-6,10-dioxa-benzocyclododecen-7-yl)-propenyl]-amide 17. LDA was used. Reaction mixture purified by PTLC (neat EtOAc) to give 1.8 mg (47% yield) of product **17**. $[\alpha]_D=-8.22$ ($c=0.18$, CH_2Cl_2). ^1H NMR (400 MHz, CD_3OD) δ 8.75 (1H, d, $J=2.0$ Hz), 8.63 (1H, dd, $J=4.8$, 1.6 Hz), 8.04 (1H, ddd, $J=8.0$, 1.6, 1.6 Hz), 7.51 (1H, dd, $J=7.6$, 4.8 Hz), 7.16 (1H, t, $J=7.6$ Hz), 6.85 (1H, d, $J=14.4$ Hz), 6.76 (1H, d, $J=8.4$ Hz), 6.73 (1H, d, $J=7.6$ Hz), 5.58–5.49 (3H, m), 5.12–5.06 (1H, m), 4.11 (1H, d, $J=10.0$ Hz), 3.73 (1H, dd, $J=13.2$, 10.0 Hz), 3.56 (1H, br d, $J=10.0$ Hz), 3.45 (1H, dd, $J=12.4$, 10.0 Hz), 3.39 (1H, d, $J=10.4$ Hz), 3.16 (1H, br d, $J=13.2$ Hz), 2.51 (2H, dd, $J=6.4$, 6.4 Hz), 1.81 (1H, dd, $J=14.8$, 12.4 Hz), 1.62 (1H, dd, $J=14.8$, 12.0 Hz); MS (ES) m/z 455.10 $[M+Na]^+$; calcd for $C_{25}H_{24}N_2ONa$: 455.16.

3.1.10.7. 3-Oxazol-2-yl-propynoic acid [3-(4-hydroxy-5-oxo-8,9,11,14-tetrahydro-5H,7H-6,10-dioxa-benzocyclododecen-7-yl)-propenyl]-amide 18. LDA was used. Reaction mixture purified by FC (50% EtOAc in hexanes) to give 4.3 mg (56% yield) of product **18**.

$[\alpha]_D = -13.2$ ($c=0.25$, CH_2Cl_2). ^1H NMR (400 MHz, CD_3OD) δ 8.08 (1H, d, $J=0.8$ Hz), 7.37 (1H, d, $J=0.8$ Hz), 7.15 (1H, t, $J=8.0$ Hz), 6.83 (1H, d, $J=14.4$ Hz), 6.77 (1H, d, $J=8.4$ Hz), 6.73 (1H, d, $J=7.6$ Hz), 5.59–5.51 (3H, m), 5.09 (1H, dddd, $J=11.2$, 6.8, 4.8, 2.0 Hz), 4.10 (1H, br.d, $J=12.0$ Hz), 3.71 (1H, dd, $J=13.6$, 10.0 Hz), 3.55 (1H, br.d, $J=9.2$ Hz), 3.45 (1H, dd, $J=12.0$, 10.0 Hz), 3.38 (1H, d, $J=10.8$ Hz), 3.16 (1H, br.d, $J=13.6$ Hz), 2.53–2.48 (2H, m), 1.80 (1H, dddd, $J=16.8$, 12.4, 4.0, 2.4 Hz), 1.61 (1H, dd, $J=14.4$, 12.4 Hz); ^{13}C NMR (75 MHz, CD_3OD_3) δ 170.5, 156.5, 150.1, 143.8, 139.6, 135.3, 131.7, 130.1, 129.9, 125.5, 123.9, 122.1, 115.6, 113.0, 84.8, 71.7, 71.6, 63.4, 38.7, 36.2, 34.7; MS (ES) *m/z* 445.10 $[M+Na]^+$; calcd for $C_{23}H_{22}N_2O_6Na$: 445.14.

3.1.11. Curtius rearrangement and alcohol addition. To a stirred solution of acylazide **12b** in benzene (0.02 M) was added the alcohol (20 equiv). The reaction mixture was heated at 80 °C for 5 h, after which the solvent was steamed off with nitrogen. The residue was dissolved in MeOH and K_2CO_3 (1 equiv) was added. The mixture was stirred at rt for 1 h, after which time water was added and the mixture was extracted with Et_2O (3×). The combined organic layers were dried over $MgSO_4$, concentrated in vacuo, and purified by FC.

3.1.11.1. [3-(4-Hydroxy-5-oxo-8,9,11,14-tetrahydro-5H,7H-6,10-dioxa-benzocyclododecen-7-yl)-propenyl]-carbamic acid benzyl ester 19. Reaction mixture purified by FC (30% EtOAc in hexanes) to give 6.5 mg (85% yield) of product **19**. $[\alpha]_D = -6.8$ ($c=0.34$, CH_2Cl_2). ^1H NMR (400 MHz, CD_3OD) δ 7.37–7.30 (5H, m), 7.15 (1H, t, $J=8.0$ Hz), 6.74 (1H, d, $J=8.8$ Hz), 6.72 (1H, d, $J=8.0$ Hz), 6.52 (1H, d, $J=14.4$ Hz), 5.56–5.53 (2H, m), 5.17 (1H, dt, $J=14.0$, 8.0 Hz), 5.12 (2H, s), 5.05–4.99 (1H, m), 4.08 (1H, d, $J=10.8$ Hz), 3.70 (1H, dd, $J=13.6$, 10 Hz), 3.53 (1H, br d, $J=10$ Hz), 3.43 (1H, dd, $J=11.6$, 10 Hz), 3.36 (1H, br.t, $J=10.8$ Hz), 3.15 (1H, d, $J=13.2$ Hz), 2.45–2.39 (2H, m), 1.79 (1H, dd, $J=14.4$, 12.4 Hz), 1.57 (1H, dd, $J=13.6$, 13.2 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 170.6, 156.5, 139.6, 135.3, 131.7, 129.8, 129.7, 129.3, 129.1, 127.9, 124.0, 122.1, 115.6, 106.8, 101.8, 72.2, 71.6, 67.8, 63.5, 38.7, 36.0, 34.5; MS (ES) *m/z* 460.10 $[M+Na]^+$; calcd for $C_{25}H_{27}NO_6Na$: 460.17.

3.1.11.2. [3-(4-Hydroxy-5-oxo-8,9,11,14-tetrahydro-5H,7H-6,10-dioxa-benzocyclododecen-7-yl)-propenyl]-carbamic acid pentyl ester 20. $[\alpha]_D = -58.9$ ($c=2.21$, CH_2Cl_2); Reaction mixture purified by FC (20% EtOAc in hexanes) to give 7 mg (71% yield) of product **20**. ^1H NMR (400 MHz, CD_3OD) δ 7.16 (1H, t, $J=8.0$ Hz), 6.76 (1H, d, $J=8.0$ Hz), 6.74 (1H, d, $J=8.0$ Hz), 6.51 (1H, d, $J=14.4$ Hz), 5.57–5.54 (2H, m), 5.15 (1H, dt, $J=14.8$, 8.0 Hz), 5.03 (1H, dddd, $J=12.0$, 6.8, 4.4, 2.4 Hz), 4.12–4.06 (3H, m), 3.71 (1H, dd, $J=14.0$, 10.4 Hz), 3.55 (1H, ddd, $J=10.4$, 3.6, 2.4 Hz), 3.44 (1H, dd, $J=12.4$, 10.4 Hz), 3.37 (1H, ddd, $J=12.4$, 10.4, 2.0 Hz), 3.16 (1H, d, $J=13.6$ Hz), 2.46–2.38 (2H, m), 1.81 (1H, dddd, $J=16.8$, 12.4, 3.6, 2.4 Hz), 1.67–1.62 (2H, m), 1.58 (1H, ddt, $J=14.4$, 12.0, 2.4 Hz), 1.39–1.37 (4H, m), 0.94 (3H, t, $J=7.2$ Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 170.5, 156.4, 139.6, 135.3, 131.7, 129.9, 128.0, 124.0, 122.1, 115.5, 106.4, 72.2, 71.6, 66.4, 63.5, 38.7, 36.1, 34.5, 30.0, 29.3, 23.6, 14.5; MS (ES) *m/z* 440.20 $[M+Na]^+$; calcd for $C_{23}H_{31}NO_6Na$: 440.20; 481.30 $[M+CH_3CN+Na]^+$; calcd for $C_{25}H_{34}N_2O_6Na$: 481.23.

3.1.11.3. [3-(4-Hydroxy-5-oxo-8,9,11,14-tetrahydro-5H,7H-6,10-dioxa-benzocyclododecen-7-yl)-propenyl]-carbamic acid oxazol-2-ylmethyl ester 21. Reaction mixture purified by FC (50% EtOAc in hexanes) to give 6.2 mg (58% yield) of product **21**. $[\alpha]_D = -11.0$ ($c=0.26$, CH_2Cl_2). ^1H NMR (400 MHz, CD_3OD) δ 7.94 (1H, s), 7.19 (1H, s), 7.15 (1H, t, $J=8.0$ Hz), 6.75 (1H, d, $J=8.0$ Hz), 6.72 (1H, d, $J=8.0$ Hz), 6.52 (1H, d, $J=14.4$ Hz), 5.56–5.54 (2H, m), 5.21 (1H, dt, $J=13.6$, 8.0 Hz), 5.20 (2H, s), 5.07–5.00 (1H, m), 4.10 (1H, br.d, $J=10.8$ Hz), 3.70 (1H, dd, $J=13.6$, 10.4 Hz), 3.54 (1H, ddd, $J=9.6$, 32, 2.4 Hz), 3.43 (1H, dd, $J=12.4$, 10.4 Hz), 3.36 (1H, ddd, $J=12.0$, 104, 1.6 Hz), 3.15 (1H, d, $J=13.6$ Hz), 2.44 (2H, app.t, $J=6.4$ Hz), 1.78 (1H, br.dd, $J=14.8$, 11.6 Hz), 1.59 (1H, br.dd, $J=14.4$, 12.4 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 170.5, 161.6, 156.4, 141.8, 139.6, 135.3, 131.7, 129.8, 128.2, 127.7, 124.0, 122.1, 115.5, 107.5, 72.1, 71.6, 63.4, 59.2, 38.7, 36.0, 34.5; MS (ES) *m/z* 451.10 $[M+Na]^+$; calcd for $C_{22}H_{24}N_2O_7Na$: 451.15.

3.2. Cytotoxicity assay

Human non-small cell lung tumor cells (A549 and NCI-H460) were plated in 96 well plates on Day 0. Cells were treated with serial dilutions of analogue between 0.1 nM and 10 μM (ranges were adjusted for the activity of each analogue) on Day 1. Control cells were treated with vehicle (DMSO) alone. The surviving fraction of cells in the presence of drug was calculated using the sulforhodamine B assay as previously described (Skehan, P. et al. New colorimetric cytotoxicity assay for anticancer-drug screening. *J. Natl. Cancer Inst.* **1990**, *82*, 1107–1112; Papazisis, K. T.; Geromichalos, G. D.; Dimitriadis, K. A.; Kortsaris, A. H. Optimization of the sulforhodamine B colorimetric assay. *J. Immunol. Methods* **1997**, *208*, 151–158). Briefly, the cells were fixed on Day 5 (96 h post-treatment) with 50% w/v trichloroacetic acid, dried overnight, and stained with 0.4% sulforhodamine B in 1% acetic acid. Fractional survival was determined by dividing the average absorbance (A_{492}) value of test wells by control wells. Each condition was replicated in 6 wells. The fractional survival values were plotted against the log[analog concentration] to determine the IC_{50} value for each analog and cell line.

Acknowledgements

Financial support provided by the Robert A. Welch Foundation and the National Institutes of Health through grants CA 90349 and CA 95471 (J.K. De Brabander) and DK 33627 (X.-S. Xie) is gratefully acknowledged. J.K. De Brabander is a fellow of the Alfred P. Sloan Foundation.

References and notes

1. Salicylihalamide: (a) Erickson, K. L.; Beutler, J. A.; Cardellina, J. H.; Boyd, M. R. *J. Org. Chem.* **1997**, *62*, 8188–8192. (b) For a structural revision, see: Wu, Y.; Esser, L.; De Brabander, J. K. *Angew. Chem. Int. Ed.* **2000**, *39*, 4308–4310. and Erickson, K. L.; Beutler, J. A.; Cardellina, J. H.; Boyd, M. R. *J. Org. Chem.* **2001**, *66*, 1532.
2. Lobatamides: (a) McKee, T. C.; Galinis, D. L.; Pannell, L. K.; Cardellina, J. H.; Laakso, J.; Ireland, C. M.; Murray, L.; Capon, R. J.; Boyd, M. R. *J. Org. Chem.* **1998**, *63*, 7805–7810. (b) Lobatamide A is identical to the structure of YM-75518, see: Suzumura, K.-I.; Takahashi, I.; Matsumoto, H.; Nagai, K.; Setiawan, B.; Rantiatmodjo, R. M.; Suzuki, K.-I.; Nagano, N. *Tetrahedron Lett.* **1997**, *38*, 7573–7576.
3. Apicularens: Jansen, R.; Kunze, B.; Reichenbach, H.; Höfle, G. *Eur. J. Org. Chem.* **2000**, 913–919.
4. CJ-12,950 and CJ-13,357: Dekker, K. A.; Aiello, R. J.; Hirai, H.; Inagaki, T.; Sakakibara, T.; Suzuki, Y.; Thompson, J. F.; Yamauchi, Y.; Kojima, N. *J. Antibiot.* **1998**, *51*, 14–20.
5. Oximidines: (a) Kim, J. W.; Shin-ya, K.; Furihata, K.; Hayakawa, Y.; Seto, H. *J. Org. Chem.* **1999**, *64*, 153–155. (b) Hayakawa, Y.; Tomikawa, T.; Shin-ya, K.; Arao, N.; Nagai, K.; Suzuki, K.-I. *J. Antibiot.* **2003**, *56*, 899–904. (c) Hayakawa, Y.; Tomikawa, T.; Shin-ya, K.; Arao, N.; Nagai, K.; Suzuki, K.-I.; Furihata, K. *J. Antibiot.* **2003**, *56*, 905–908.
6. Boyd, M. R.; Farina, C.; Belfiore, P.; Gagliardi, S.; Kim, J.-W.; Hayakawa, Y.; Beutler, J. A.; McKee, T. C.; Bowman, B. J.; Bowman, E. J. *J. Pharmacol. Exp. Ther.* **2001**, *297*, 114–120.
7. For an extensive review, see: Forgac, M. *Adv. Mol. Cell Biol.* **1998**, 403–453.
8. For a therapeutic focus, see: Farina, C.; Gagliardi, S. *Drug Discov. Today* **1999**, *4*, 163–172.
9. For literature prior to 2003, see the following extensive reviews; (a) Beutler, J. A.; McKee, T. C. *Curr. Med. Chem.* **2002**, *9*, 1241–1253. (b) Yet, L. *Chem. Rev.* **2003**, *103*, 4283–4306.
10. For more recent literature, see: (a) Nicolaou, K. C.; Kim, D. W.; Baati, R.; O'Brate, A.; Giannakakou, P. *Chem. Eur. J.* **2003**, *9*, 6177–6191. (b) Yadav, J. S.; Srihari, P. *Tetrahedron: Asymmetry* **2004**, *15*, 81–89. (c) Yang, K.; Blackman, B.; Diederich, W.; Flaherty, P. T.; Mossman, C. J.; Roy, S.; Ahn, Y. M.; Georg, G. I. *J. Org. Chem.* **2003**, *68*, 10030–10039. (d) Yang, K.; Haack, T.; Blackman, B.; Diederich, W. E.; Roy, S.; Pusuluri, S.; Georg, G. I. *Org. Lett.* **2003**, *5*, 4007–4009. (e) Herb, C.; Maier, M. E. *J. Org. Chem.* **2003**, *68*, 8129–8135. (f) Hilli, F.; White, J. M.; Rizzacasa, M. A. *Org. Lett.* **2004**, *6*, 1289–1292. (g) Su, Q.; Panek, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 2425–2430. (h) Graetz, B. R.; Rychnovsky, S. D. *Org. Lett.* **2003**, *5*, 3357–3360. (i) Haack, T.; Kurtkaya, S.; Snyder, J. P.; Georg, G. I. *Org. Lett.* **2003**, *5*, 5019–5022. (j) Harvey, J. E.; Raw, S. A.; Taylor, R. J. K. *Tetrahedron Lett.* **2003**, *44*, 7209–7212.
11. (a) Wu, Y.; Seguil, O. R.; De Brabander, J. K. *Org. Lett.* **2000**, *2*, 4241–4244. (b) Wu, Y.; Liao, X.; Wang, R.; Xie, X.-S.; De Brabander, J. K. *J. Am. Chem. Soc.* **2002**, *124*, 3245–3253.
12. Xie, X.-S.; Padron, D.; Liao, X.; Wang, J.; Roth, M. G.; De Brabander, J. K. *J. Biol. Chem.* **2004**, *279*, 19755–19763.
13. For analog synthesis related to other members of the family, see Refs. 9b and 10a
14. Smith, A. B.; Zheng, J. *Tetrahedron* **2002**, *58*, 6455–6471.
15. (a) Compound **1**: Fürstner, A.; Dierkes, T.; Thiel, O. R.; Blanda, G. *Chem. Eur. J.* **2001**, *7*, 5286–5298. (b) Compound **2**: see Ref. 10c. (c) Compound **3**: Perez-Serrano, L.; Casarrubios, L.; Dominguez, G.; Gonzalez-Perez, P.; Perez-Castells, J. *Synthesis* **2002**, 1810–1812. (d) Compound **4** Houpis, I. N. *Tetrahedron Lett.* **1991**, *32*, 6675–6678. (e) Compound **5**: Tsukamoto, H.; Suzuki, T.; Kondo, Y. *Synlett* **2003**, 1105–1108.
16. Mitsunobu, O. *Synthesis* **1981**, 1–28.
17. For a comprehensive overview of applications of RCM in organic synthesis, see: Handbook of Metathesis; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, 2003; Vol. 2.
18. Lee, W. C.; Grubbs, R. H. *Org. Lett.* **2000**, *2*, 2145–2147 correction: *Org. Lett.* **2000**, *2*, 2559.
19. See Ref. 15a and Fürstner, A.; Thiel, O. R.; Blanda, G. *Org. Lett.* **2000**, *2*, 3731–3734.
20. For an excellent illustration of kinetic versus thermodynamic control in RCM reactions to form 10-membered lactones en route to herbarumin and pinolidoxin natural products, see: Fürstner, A.; Radkowski, K.; Wirtz, C.; Goddard, R.; Lehmann, C. W.; Mynott, R. *J. Am. Chem. Soc.* **2002**, *124*, 7061–7069.
21. Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.
22. For the role of plasmalemmal V-ATPase isoforms in cancer biology, see the following review: Sennoune, S. R.; Luo, D.; Martinez-Zaguilan, R. *Cell Biochem. Biophys.* **2004**, *40*, 185–206.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 60 (2004) 9649–9657
Tetrahedron

Synthetic study of (+)-anthramycin using ring-closing enyne metathesis and cross-metathesis

Tsuyoshi Kitamura, Yoshihiro Sato and Miwako Mori*

Graduate School of Pharmaceutical Sciences, Hokkaido University, Sapporo 060-0812, Japan

Received 18 June 2004; revised 5 July 2004; accepted 7 July 2004

Available online 28 August 2004

Abstract—Synthesis of (+)-anthramycin was examined. A pyrrolobenzodiazepine skeleton could be synthesized by reductive cyclization of pyrrolidine derivative, which was obtained by enyne metathesis. The conjugated enamide ester part of (+)-anthramycin derivative was constructed by cross-metathesis.

1. Introduction

(+)-Anthramycin, which has an antitumor activity, was isolated by Leimgruber[1a,b] in 1965, and the total synthesis of anthramycin was achieved by the same group[1c] and later by Stille.[1d] The remarkable structural feature of this skeleton is that it possesses a pyrrolobenzodiazepine skeleton and a dienamide group conjugated with nitrogen in a pyrrolidine ring. Since we have been interested in the structure of the dienamide group conjugated with nitrogen in a pyrrolidine ring, the total synthesis of (+)-anthramycin was planned because this structure would be constructed by ring-closing enyne metathesis[2,3] (RCM) and cross-metathesis[4] (CM) followed by isomerization of the resulting double bond (Fig. 1).

Our retrosynthetic analysis is shown in Scheme 1. The conjugated amide part of (+)-anthramycin should be formed by cross-metathesis with an alkene part of the diene moiety in pyrrolobenzodiazepine derivative **1** followed by olefin isomerization. A pyrrolobenzodiazepine skeleton of **1** should be constructed by reductive cyclization of a nitro group and an ester group of pyrrolidine derivative **2**, which should be obtained by enyne metathesis[5] of **3**. The starting enyne **3** would be obtained from L-methionine.

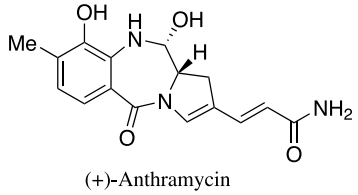
2. Construction of a pyrrolobenzodiazepine skeleton

Esterification of L-methionine followed by alkylation[6] with propargyl bromide and then protection of the secondary amine with the carbobenzyloxy group gave **4**. Conversion of sulfide **4** into sulfoxide **5** by treatment with $NaIO_4$ smoothly proceeded, and β-hydrogen elimination of the sulfoxymethyl group of **5** gave the desired enyne **3a** (Scheme 2).

To construct the pyrrolidine ring, enyne metathesis was carried out. When a CH_2Cl_2 solution of enyne **3a** and 5 mol% of first-generation of ruthenium carbene complex **6a** was stirred at room temperature under ethylene gas[5d] for 24 h, the desired pyrrolidine derivative **7** was obtained in 76% yield (Scheme 3).

Deprotection of the benzyloxy group of **7** with TMSCl in the presence of NaI[7] followed by condensation of *o*-nitrobenzoyl chloride **8a** gave **2a** in 76% yield. Construction of a pyrrolobenzodiazepine skeleton was carried out by treatment of **2a** with zinc-acetic acid[8] in CH_2Cl_2 and treatment of the resultant crude product with dil. HCl in THF to give **1a** in 86% yield via aniline derivative **9a**. Thus, a novel procedure for synthesis of a pyrrolobenzodiazepine skeleton could be developed (Scheme 4).

Subsequently, elongation of the carbon one-unit to the alkene part in **1a** was examined by cross-metathesis. When a CH_2Cl_2 solution of **1a**, (*Z*)-1,4-diacetoxy-but-2-ene **10** (10 equiv) and 15 mol% of second-generation ruthenium

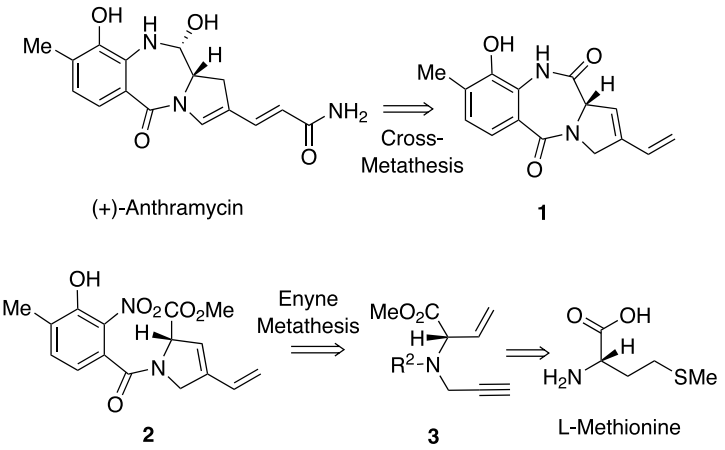


(+)-Anthramycin

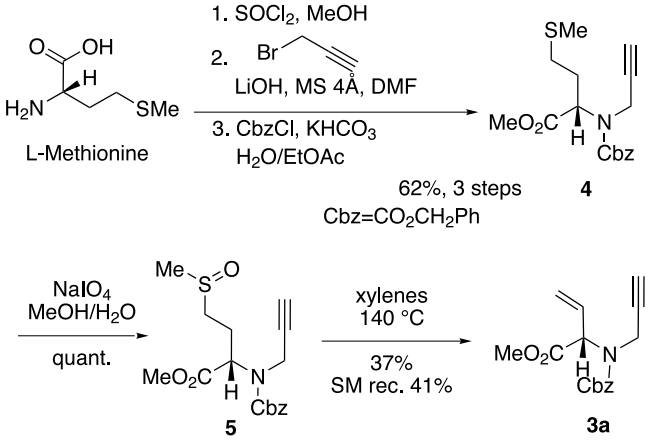
Figure 1.

Keywords: (+)-Anthramycin; Pyrrolobenzodiazepine skeleton; Deprotection.
* Corresponding author. Tel./fax: +81-11-706-4982;
e-mail: mori@pharm.hokudai.ac.jp

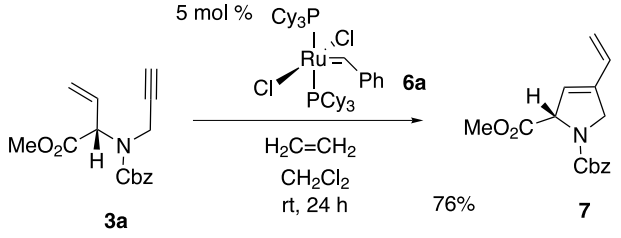
0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.07.040



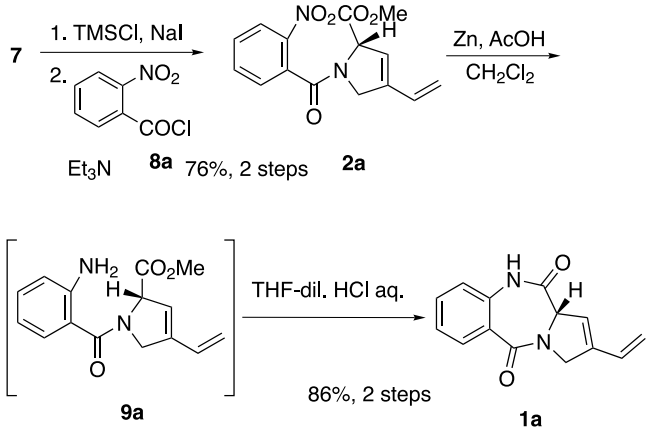
Scheme 1. Retrosynthetic analysis of anthramycin.



Scheme 2. Synthesis of substrates.



Scheme 3. Synthesis of a pyrrolidine derivative using enyne metathesis.



Scheme 4. Synthesis of a benzodiazepine derivative.

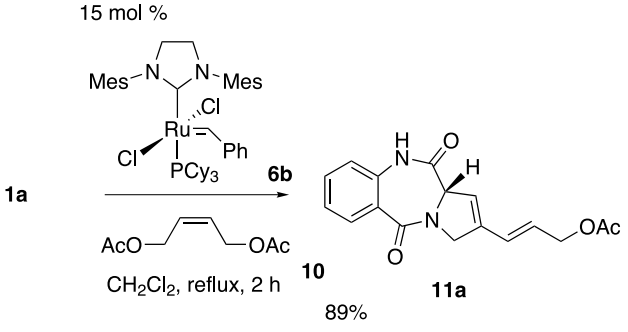
carbene complex **6b** was refluxed for 2 h, the desired cross-metathesis product **11a** was obtained in 89% yield (Scheme 5).

Thus, the carbon framework of anthramycin was constructed using RCM and CM as key steps.

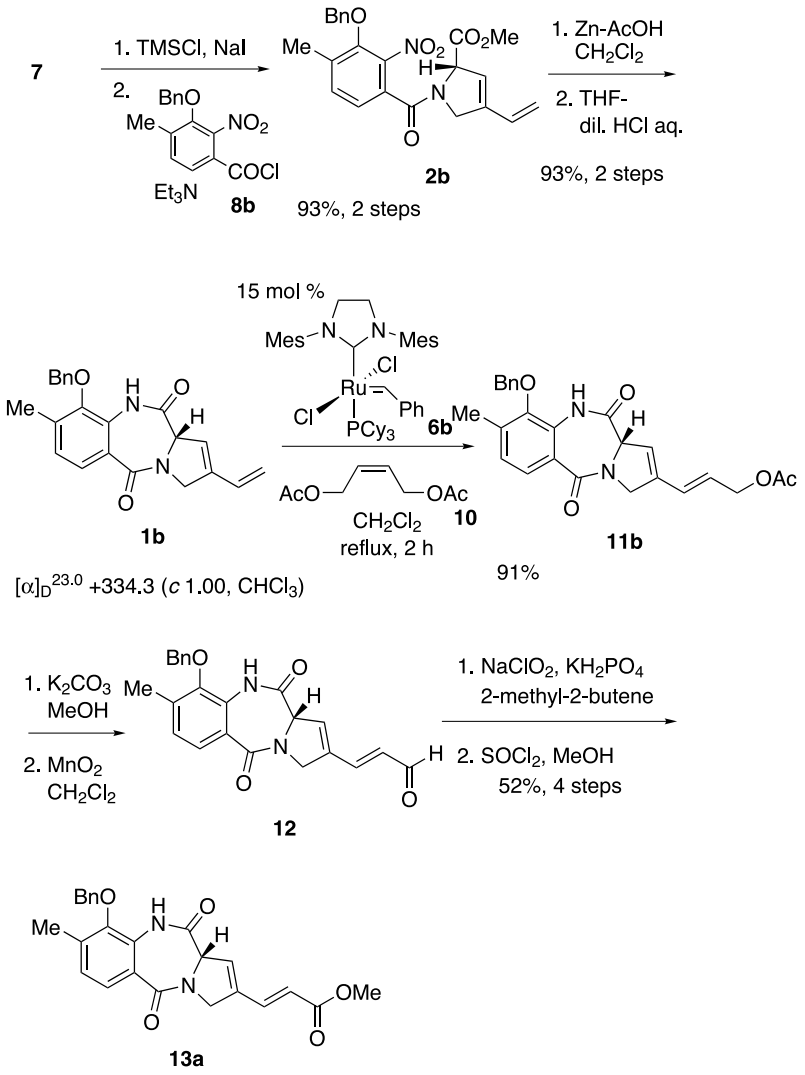
3. Synthetic study of anthramycin

Since a pyrrolobenzodiazepine skeleton was constructed from L-methionine, the total synthesis of anthramycin was examined. Deprotection of the benzyloxy group of **7** followed by condensation with 2-nitro-3-benzyloxy-4-methyl-benzoyl chloride **8b** afforded compound **2b**, which was treated in a similar manner to give **1b** in high yield. The $[\alpha]_D$ value +334.3 of this compound indicated that an optically active benzodiazepine derivative was produced in these processes. Cross metathesis of **1b** with **10** using **6b** smoothly proceeded to give **11b** in 91% yield. Then the ally alcohol part was converted into an ester group. Deprotection of the acetoxy group followed by treatment with MnO_2 gave aldehyde **12**, which was converted into ester **13a** in the usual manner (Scheme 6).

Further study of cross-metathesis was carried out to shorten the steps. When a CH_2Cl_2 solution of **1b**, 10 mol% of **6b** and methyl acrylate (10 equiv) was refluxed for 24 h, the desired compound **13a** was obtained in 41% yield. Furthermore, compound **1b** was treated with **6c** developed by Blechert[9] at room temperature to give **13a** in 63% yield (Scheme 7).

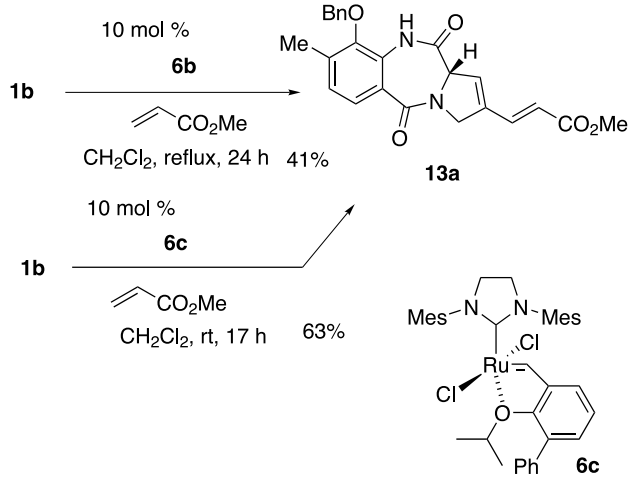


Scheme 5. Cross-metathesis.



Scheme 6. Synthesis of an anthramycine derivative.

Isomerization of the double bond in a pyrrolidine ring was carried out. When a toluene solution of **13a** was refluxed in the presence of a catalytic amount of $RuHCl(CO)(PPh_3)_3$ for 8 h, further isomerized pyrrole derivative **14** was obtained in 66% yield. On the other hand, when an EtOH solution of **13a** and $RhCl_3 \cdot 3H_2O$[10] was heated at 110 °C in a sealed tube, the desired isomerization product **15a** was obtained along with the corresponding ethyl ester **15b**. Thus, **13b** was prepared from **1b** and ethyl acrylate using **6c** and was treated with $RhCl_3 \cdot 3H_2O$ in EtOH at 110 °C to give **15b** in 50% yield (Scheme 8).

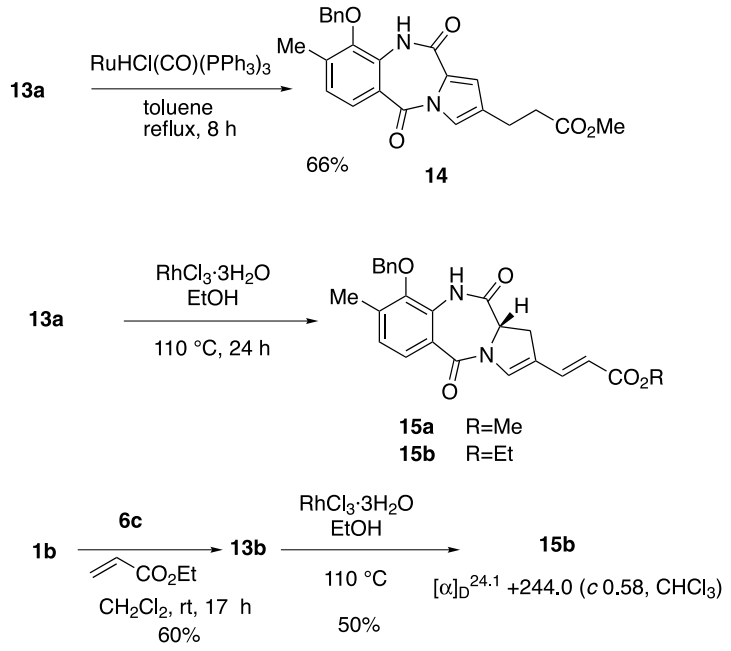


Scheme 7. Cross-metathesis.

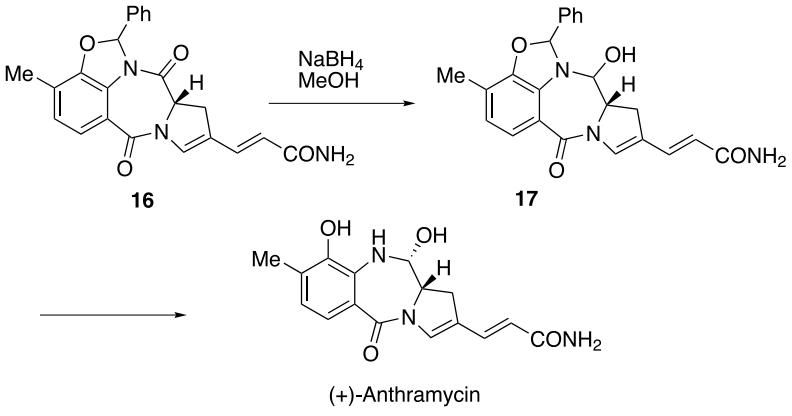
Stille has succeeded in the total synthesis of (+)-anthramycin.[2] In his total synthesis, the aminal part of **17** was constructed by treatment of **16** with $NaBH_4$ and deprotection of **17** gave (+)-anthramycin (Scheme 9).

Thus, debenzylation of **15b** was carried out by treatment with CF_3CO_2H and $BF_3 \cdot Et_2O$ followed by protection of the phenol and the amide nitrogen as a benzylidene acetal to give **19**, which was treated with $NaBH_4$ to give aminal **20** (Scheme 10).

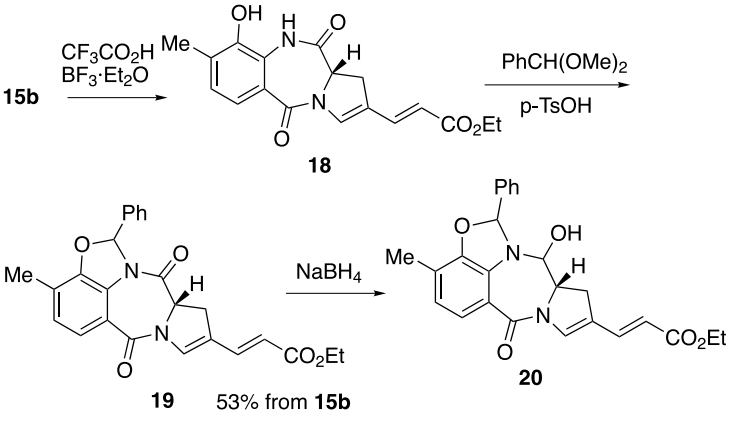
Thus, we succeeded in the synthesis of an anthramycin derivative **20** having the desired functional groups from commercially available L-methionine using ring-closing enyne metathesis and cross-metathesis as the key steps. Coversion of the ester group into an amide group for the total synthesis of (+)-anthramycin is further investigated.



Scheme 8. Isomerization of the double bond.



Scheme 9. Stille's synthesis of anthramycin.



Scheme 10. Conversion of **15b** into aminal **20**.

4. Experimental

4.1. General

All manipulations were carried out under an atmosphere of argon unless otherwise mentioned. Ethylene gas was purified by passage through the aqueous CuCl solution (2 g of CuCl in 180 mL of saturated NH_4Cl aqueous) and concentrated H_2SO_4 and then KOH tubes. Ruthenium complexes **6a** and **6b** were purchased from Strem Chemicals. Ruthenium complex **6c** was prepared according to the literature procedure.[9] All other solvents and reagents were purified when necessary using standard procedure.

4.1.1. (*S*)-4-Methylsulfanyl-2-prop-2-ynylamino-butyric acid methyl ester (A). To a solution of activated MS 4 Å (13 g) in DMF (50 mL) was added $LiOH \cdot H_2O$ (2.26 g, 53.8 mmol), and the suspension was stirred at 0 °C for 20 min. To this mixture was added L-methionine methyl ester hydrochloride (5 g, 25 mmol), and the suspension was stirred at 0 °C for 45 min. To this mixture was added propargyl bromide (2.3 mL, 25 mmol), and the mixture was stirred at room temperature for 28 h. After the solution was filtered through celite, the filtrate was washed with brine, dried over Na_2SO_4. The solvent was removed and the residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate 9:1) to yield title compound **A** (3.1 g, 62%) as a colorless oil. IR (neat) ν 3287, 2950, 2917, 2840, 1732, 1435, 1204, 1168, 1129 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.85–2.03 (m, 2H), 2.10 (s, 3H), 2.23 (dd, J=2.4, 2.4 Hz, 1H), 2.36 (br, 1H), 2.60 (m, 2H), 3.42 (dd, J=2.4, 17.2 Hz, 1H), 3.48 (dd, J=2.4, 17.2 Hz, 1H), 3.59 (dd, J=7.6, 5.6 Hz, 1H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.3 (CH_3), 30.2 (CH_2), 32.4 (CH_2), 36.8 (CH_2), 51.8 (CH_3), 58.7 (CH), 71.6 (CH), 81.1 (C), 174.6 (C); LRMS *m/z* 201 (M^+), 186, 162, 154, 142, 127, 114, 94; HRMS Calcd for $C_9H_{15}NO_2S$ (M^+) 201.0823, found 201.0803. Anal. Calcd for $C_9H_{15}NO_2S$: C, 53.70; H, 7.51; N, 6.96. Found: C, 53.72; H, 7.47; N, 6.99. $[\alpha]_D^{23.9} = -14.2$ (*c* 1.00, $CHCl_3$).

4.1.2. (*S*)-2-(Benzyloxycarbonyl-prop-2-ynyl-amino)-4-methylsulfanyl-butyric acid methyl ester (4). To a solution of **A** (2.86 g, 14.2 mmol) and $KHCO_3$ (7.1 g, 71 mmol) in EtOAc/H_2O (1/1, 140 mL) was added CbzCl (3.0 mL, 21 mmol), and the solution was stirred at 0 °C for 14 h. The organic layer was washed with 10% HCl aq., brine, and dried over Na_2SO_4. After the solvent was removed, the residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate 4:1) to yield **4** (4.76 g, quant.) as colorless oil. IR (neat) ν 3285, 2952, 2917, 2120, 1740, 1704, 1455, 1410, 1318, 1257, 1119 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ two rotamers 2.06 (s, 1.5H), 2.11 (s, 1.5H), 2.17–2.34 (m, 2H), 2.26 (br, 1H), 2.55–2.71 (m, 2H), 3.60 (s, 1.5H), 3.72 (s, 1.5H), 4.00–4.25 (m, 2H), 4.65 (m, 0.5H), 4.82 (m, 0.5H), 5.11–5.24 (m, 2H), 7.30–7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ two rotamers 15.3 (CH_3), 28.9 (CH_2), 29.2 (CH_2), 30.8 (CH_2), 35.5 (CH_2), 36.5 (CH_2), 52.2 (CH_3), 52.3 (CH_3), 57.9 (CH), 58.2 (CH), 67.7 (CH_2), 67.8 (CH_2), 72.0 (CH), 72.3 (CH), 79.1 (C), 79.4 (C), 127.5 (CH), 127.9 (CH), 128.0 (CH), 128.1 (CH), 128.3 (CH), 135.8 (C), 136.0 (C), 155.4 (C), 155.5 (C), 171.2 (C), 171.3 (C); LRMS *m/z* 335 (M^+), 304, 276, 261, 244, 200, 170, 91; HRMS Calcd for $C_{17}H_{21}NO_4S$ (M^+) 335.1191, found 335.1185. Anal. Calcd for $C_{17}H_{21}NO_4S$: C, 60.87; H, 6.31; N, 4.18. Found: C, 60.79; H, 6.39; N, 4.23. $[\alpha]_D^{23.4} = -50.9$ (*c* 1.00, $CHCl_3$).

4.1.3. (*S*)-2-(Benzyloxycarbonyl-prop-2-ynyl-amino)-4-methanesulfinyl-butyric acid methyl ester (5). To a solution of **4** (4.38 g, 13.0 mmol) in MeOH/H_2O (1/1, 64 mL) was added $NaIO_4$ (2.9 mL, 13.6 mmol) slowly, and the solution was stirred at 0 °C for 4 h. After the solution was filtered through celite, the filtrate was washed with brine, dried over $MgSO_4$. The solvent was removed and the residue was purified by flash column chromatography on silica gel (MeOH/ethyl acetate 1:10) to yield **5** (4.56 g, quant.) as colorless oil. IR (neat) ν 3282, 2953, 1740, 1700, 1456, 1413, 1257, 1048 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ two diastereomers (ratio 3:2) 2.29 (t, J=2.4 Hz, 1H), 2.37 (br, 1H), 2.47–2.61 (m, 4H), 2.76–2.83 (m, 2H), 3.60 (s, 1.2H), 3.73 (s, 1.8H), 4.06–4.25 (m, 2H), 4.53 (m, 0.4H), 4.74 (m, 0.6H), 5.09–5.20 (m, 2H), 7.34–7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ two diastereomers 22.2 (CH_2), 22.6 (CH_2), 22.9 (CH_2), 23.6 (CH_2), 35.4 (CH_2), 35.6 (CH_2), 36.4 (CH_2), 36.7 (CH_2), 38.1 (CH_3), 38.6 (CH_3), 50.3 (CH_2), 50.5 (CH_2), 50.9 (CH_2), 52.3 (CH_3), 58.1 (CH), 58.4 (CH), 67.7 (CH_2), 72.5 (CH), 72.8 (CH), 78.8 (C), 79.0 (C), 127.4 (CH), 127.8 (CH), 128.1 (CH), 128.2 (CH), 128.2 (CH), 135.4 (C), 135.6 (C), 155.4 (C), 155.3 (C), 170.1 (C); LRMS *m/z* 351 (M^+), 320, 288, 261, 228, 152, 91; HRMS Calcd for $C_{17}H_{21}NO_5S$ (M^+) 351.1140, found 351.1128. Anal. Calcd for $C_{17}H_{21}NO_5S$: C, 58.10; H, 6.02; N, 3.99. Found: C, 57.88; H, 6.03; N, 4.06.

4.1.4. (*S*)-2-(Benzyloxycarbonyl-prop-2-ynyl-amino)-but-3-enoic acid methyl ester (3a). A solution of **5** (13 g) in xylene (50 mL) was refluxed at 140 °C for 60 h. To this solution was added ethyl acetate and the solution was washed with 3% H_2O_2 aq., brine, and dried over Na_2SO_4. After the solvent was removed, the residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate 9:1) to yield **3a** (3.1 g, 37%) as colorless oil, and **5** (5 g, 41%) was recovered. IR (neat) ν 3288, 2953, 2122, 1746, 1710, 1560, 1449, 1409, 1255 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ two rotamers 2.24 (br, 1H), 3.60 (br, 2H), 3.75 (br, 3H), 4.20 (br, 1H), 5.20 (br, 2H), 5.38 (m, 2H), 6.14 (ddd, J=6.2, 10.3, 17.0 Hz, 1H), 7.34–7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) two rotamers δ 35.3 (CH_2), 36.3 (CH_2), 52.2 (CH_3), 61.2 (CH), 67.7 (CH_2), 71.7 (CH), 72.2 (CH), 79.0 (C), 79.5, (C), 119.6 (CH_2), 120.0 (CH_2), 127.5 (CH), 127.9 (CH×2), 128.2 (CH×2), 130.5 (CH), 130.8 (CH), 135.7 (C), 135.9 (C), 154.8 (C), 155.2 (C), 170.1 (C); LRMS *m/z* 287 (M^+), 272, 255, 228, 196, 184, 152, 91; HRMS Calcd for $C_{14}H_{14}NO_2$ ($M^+ - CO_2Me$) 228.1024, found 228.1034. Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88. Found: C, 66.81; H, 6.08; N, 4.90. $[\alpha]_D^{24.8} = -13.6$ (*c* 0.25, $CHCl_3$).

4.1.5. (*S*)-4-Vinyl-2,5-dihydro-pyrrole-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (7). To a solution of **3a** (1.1 g, 3.8 μmol) in CH_2Cl_2 (77 mL, 0.05 M) was added **6a** (158 mg, 191 μmol, 5 mol%), and the solution was stirred under an atmosphere of ethylene for 24 h. To this solution was added an excess of ethyl vinyl ether. After the solvent was removed, the residue was purified by flash

column chromatography on silica gel (hexane/ethyl acetate 4:1) to yield **7** (840 mg, 76%) as a colorless crystal. Mp 58–60 °C; IR (film) ν 3065, 2952, 2868, 1754, 1713, 1645, 1596, 1416, 1355, 1205, 1117 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ two rotamers 3.59 (s, 1.5H), 3.75 (s, 1.5H), 4.34–4.45 (m, 2H), 5.06–5.29 (m, 5H), 5.64 (s, 0.5H), 5.69 (s, 0.5H), 6.42 (dd, J=17.6, 10.8 Hz, 0.5H), 6.43 (dd, J=17.6, 11.2 Hz, 0.5H), 7.29–7.41 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ two rotamers 52.1 (CH_2), 52.3 (CH_3), 52.4 (CH_3), 52.6 (CH_2), 66.5 (CH), 66.8 (CH), 67.1 (CH_2), 67.2 (CH_2), 117.9 (CH_2), 118.3 (CH_2), 121.6 (CH), 121.8 (CH), 127.7 (CH), 127.8 (CH), 127.9 (CH), 128.0 (CH), 128.3 (CH), 128.4 (CH), 129.5 (CH), 129.6 (CH), 136.3 (C), 136.3 (C), 140.5 (C), 140.6 (C), 153.7 (C), 154.2 (C), 170.0 (C), 170.3 (C); LRMS m/z 287 (M^+), 256, 243, 228, 196, 184, 152, 91; HRMS Calcd for $C_{16}H_{17}NO_4$ (M^+) 287.1158, found 287.1144. Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88. Found: C, 66.83; H, 5.95; N, 4.89. $[\alpha]_D^{20.8}=-241.1$ (c 1.00, $CHCl_3$).

4.1.6. (*S*)-1-(2-Nitro-benzoyl)-4-vinyl-2,5-dihydro-1*H*-pyrrole-2-carboxylic acid methyl ester (2a). To a solution of **7** (92 mg, 0.32 μmol) in CH_3CN (3 mL) was added NaI (330 mg, 2.2 mmol) and TMSCl (0.26 mL, 2 mmol) at 0 °C and the solution was stirred at room temperature for 10 h. To this solution was added MeOH (1 mL) at 0 °C. After the solvent was removed, the residue was dissolved in CH_2Cl_2 (1 mL). To this solution was added Et_3N (1 mL) and *o*-nitrobenzoyl chloride (107 mg, 0.6 mmol) in CH_2Cl_2 (4 mL) at 0 °C. The whole solution was stirred at 0 °C for 8 h. To this solution were added MeOH and saturated $Na_2S_2O_3$ aq., and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography on silica gel (hexane/ether 2:1) to yield **2a** (73.5 mg, 76%, 2 steps) as pale yellow oil. IR (neat) ν 1742, 1659, 1595, 1531, 1485, 1424, 1348, 1265, 1207, 1004 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (two rotamers, major/minor 3/1) major rotamer 3.81 (s, 3H), 4.09 (d, J=16.0 Hz, 1H), 4.23–4.27 (m, 1H), 4.93 (d, J=17.6 Hz, 1H), 5.18 (d, J=10.8 Hz, 1H), 5.49 (br, 1H), 5.81 (br, 1H), 6.41 (dd, J=17.6, 10.8 Hz, 1H), 7.56–7.71 (m, 2H), 7.77 (m, 1H), 8.22 (d, J=8.0 Hz, 1H), minor rotamer 3.54 (s, 3H), 4.53–4.58 (m, 1H), 4.79 (m, 1H), 4.86 (d, J=15.2 Hz, 1H), 5.31 (d, J=17.6 Hz, 1H), 5.35 (d, J=10.8 Hz, 1H), 5.61 (br, 1H), 6.47 (dd, J=17.6, 10.8 Hz, 1H), 7.45 (d, J=7.6 Hz, 1H), 7.56–7.71 (m, 2H), 8.19 (d, J=8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ major rotamer 52.7 (CH_3), 53.6 (CH_2), 66.1 (CH), 118.0 (CH_2), 121.9 (CH), 124.6 (CH), 128.4 (CH), 129.4 (CH), 130.2 (CH), 132.5 (C), 134.6 (CH), 139.7 (C), 144.8 (C), 165.9 (C), 169.4 (C), minor rotamer 52.5 (CH_3), 53.6 (CH_2), 67.7 (CH), 119.1 (CH_2), 120.8 (CH), 124.7 (CH), 129.1 (CH), 129.3 (CH), 130.3 (CH), 131.8 (C), 134.1 (CH), 140.4 (C), 144.7 (C), 166.4 (C), 169.7 (C); LRMS m/z 303 ($M^+ + 1$), 270, 243, 150, 93; HRMS Calcd for $C_{13}H_{11}N_2O_3$ ($M^+ - CO_2Me$) 243.0769, found 243.0765. $[\alpha]_D^{21.2}=-200.6$ (c 0.59, $CHCl_3$).

4.1.7. (*S*)-2-Vinyl-3,11a-dihydro-10*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepine-5,11-dione (1a). To a solution of **2a** (46 mg, 0.15 μmol) and Zn dust (400 mg) in CH_2Cl_2 (2 mL) was slowly added AcOH (0.1 mL) at 0 °C. The solution was stirred at room temperature for 30 min and then the solution was filtered through celite. The filtrate was washed with saturated $NaHCO_3$ aq., brine, and dried over Na_2SO_4. After the solvent was removed, the crude aniline **9a** was dissolved in THF (5 mL) and 0.2% HCl aq. (5 mL). The whole solution was stirred at room temperature for 12 h. The aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate 1:1) to yield **1a** (31 mg, 86%, 2 steps) as a colorless crystal. Mp 210 °C (dec.); IR (nujol) ν 3223, 2855, 1693, 1655, 1614, 1484, 1457, 1376, 1252, 1215 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.52 (dd, J=2.4, 15.2 Hz, 1H), 4.72 (d, J=15.2 Hz, 1H), 4.94 (br, 1H), 5.29 (d, J=17.6 Hz, 1H), 5.35 (d, J=10.8 Hz, 1H), 5.93 (br, 1H), 6.59 (dd, J=17.6, 10.8 Hz, 1H), 6.98 (d, J=8.4 Hz, 1H), 7.31 (dd, J=8.4, 8.0 Hz, 1H), 7.51 (ddd, J=1.6, 8.0, 8.0 Hz, 1H), 7.77 (br, 1H), 8.05 (dd, J=8.0, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.0 (CH_2), 63.9 (CH), 118.5 (CH_2), 120.8 (CH), 121.1 (CH), 125.2 (CH), 126.1 (C), 129.7 (CH), 131.3 (CH), 132.6 (CH), 135.0 (C), 139.8 (C), 164.9 (C), 171.0 (C); LRMS m/z 240 (M^+), 211, 120; HRMS Calcd for $C_{14}H_{12}N_2O_2$ (M^+) 240,0899, found 240,0894. $[\alpha]_D^{23.9}=+499.1$ (c 1.00, $CHCl_3$).

4.1.8. (11a*S*, *E*)-Acetic acid 3-(5,11-dioxo-5,10,11,11a-tetrahydro-3*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepin-2-yl)-allyl ester (11a). To a solution of **1a** (4.3 mg, 18 μmol) and **10** (29 μL, 0.18 mmol) in CH_2Cl_2 (0.5 mL) was added **6b** (2.4 mg, 3 μmol, 15 mol%), and the solution was degassed through freeze–pump–thaw cycle. The whole solution was refluxed 50 °C for 2 h. After the solvent was removed, the residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate 3:1–1:1) to yield **11a** (5 mg, 89%) as a colorless crystal. Mp 185 °C (dec.); IR (film) ν 3240, 1745, 1688, 1640, 1264, 734, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.10 (s, 3H), 4.49 (dd, J=3.2, 16.0 Hz, 1H), 4.68 (d, J=6.0 Hz, 2H), 4.72 (m, 1H), 4.94 (br, 1H), 5.80 (dt, J=15.6, 6.0 Hz, 1H), 5.97 (br, 1H), 6.52 (d, J=15.6 Hz, 1H), 7.04 (d, J=8.0 Hz, 1H), 7.51 (ddd, J=1.6, 8.0, 8.0 Hz, 1H), 8.04 (dd, J=1.6, 8.0 Hz, 1H), 8.47 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9 (CH_3), 53.1 (CH_2), 63.9 (CH_2), 64.1 (CH), 121.1 (CH), 121.6 (CH), 125.3 (CH), 125.9 (C), 126.1 (CH), 127.9 (CH), 131.3 (CH), 132.7 (CH), 135.0 (C), 138.5 (C), 164.8 (C), 170.5 (C), 170.8 (C); LRMS m/z 312 (M^+), 281, 252, 224, 191, 133, 120; HRMS Calcd for $C_{17}H_{16}N_2O_4$ (M^+) 312.1110, found 312.1106. $[\alpha]_D^{20.7}=+402.0$ (c 0.93, $CHCl_3$).

4.1.9. (2*S*)-1-(3-Benzyloxy-4-methyl-2-nitro-benzoyl)-4-vinyl-2,5-dihydro-1*H*-pyrrole-2-carboxylic acid methyl ester (2b). To a solution of **7** (70 mg, 0.24 μmol) in CH_3CN (2 mL) was added NaI (298 mg, 2 mmol) and TMSCl (0.26 mL, 2 mmol) at 0 °C and the solution was stirred at room temperature for 5 h. To this solution was added MeOH (1 mL) at 0 °C. After the solvent was removed, the residue was dissolved in CH_2Cl_2 (1 mL). To this solution was added Et_3N (1 mL) and *o*-nitrobenzoyl chloride **8b** (83 mg, 0.29 mmol) in CH_2Cl_2 (4 mL) at 0 °C. The whole solution was stirred at 0 °C for 12 h. To this solution was added MeOH (1 mL) and saturated $Na_2S_2O_3$ aq., and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated.

The residue was purified by column chromatography on silica gel (hexane/ether 1:1) to yield **2b** (93 mg, 93%) as pale yellow oil. IR (neat) ν 1748, 1658, 1641, 1563, 1538, 1493, 1429, 1364, 1265, 1209, 1181, 1056, 1030, 1002 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (two rotamers, major/minor 3/1) major rotamer 2.42 (s, 3H), 3.78 (s, 3H), 4.27 (d, J= 13.6 Hz, 1H), 4.39–4.44 (m, 1H), 4.99 (d, J=10.4 Hz, 1H), 5.02 (d, J=17.6 Hz, 1H), 5.12 (d, J=10.4 Hz, 1H), 5.23 (d, J=10.8 Hz, 1H), 5.42 (br, 1H), 5.79 (s, 1H), 6.43 (dd, J= 17.6, 10.8 Hz, 1H), 7.24 (d, J=8.0 Hz, 1H), 7.34–7.45 (m, 6H), minor rotamer δ 2.37 (s, 3H), 3.64 (s, 3H), 4.46–4.51 (m, 1H), 4.74 (d, J=15.6 Hz, 1H), 4.94–5.11 (blind, 3H), 5.28 (d, J=17.6 Hz, 1H), 5.34 (d, J=10.8 Hz, 1H), 5.66 (s, 1H), 6.56 (blind, 1H), 7.06 (d, J=8.0 Hz, 1H), 7.34–7.45 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) major rotamer δ 16.4 (CH_3), 52.5 (CH_3), 53.9 (CH_2), 66.1 (CH), 76.5 (CH_2), 117.9 (CH_2), 121.6 (CH), 121.7 (CH), 122.2 (CH), 128.1 (CH×2), 128.4 (CH×2), 129.3 (CH), 129.5 (C), 133.9 (CH), 135.6 (C), 135.9 (C), 139.7 (C), 143.1 (C), 149.2 (C), 164.8 (C), 169.1 (C), minor rotamer δ 16.4 (CH_3), 52.3 (CH_2), 52.5 (CH_3), 67.9 (CH), 76.5 (CH_2), 118.9 (CH_2), 121.0 (CH), 121.0 (CH), 122.4 (CH), 128.2 (CH×2), 128.4 (CH×2), 129.1 (C), 129.2 (CH), 133.7 (CH), 135.5 (C), 135.9 (C), 140.2 (C), 142.8 (C), 149.1 (C), 165.2 (C), 169.8 (C); LRMS m/z 422 (M^+), 363, 270, 91; HRMS Calcd for $C_{23}H_{22}N_2O_6$ (M^+) 422.1477, found 422.1489. $[\alpha]_D^{22.1}=-230.4$ (c 0.90, $CHCl_3$).

4.1.10. (11a*S*)-9-Benzyloxy-8-methyl-2-vinyl-3,11a-dihydro-10*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepine-5,11-dione (1b). To a solution of **2b** (570 mg, 1.35 μmol) and Zn dust (6.0 g) in CH_2Cl_2 (15 mL) was slowly added AcOH (1.2 mL) at 5 °C and the solution was stirred at room temperature for 20 min and was filtered through celite. The filtrate was washed with brine, and dried over Na_2SO_4. After the solvent was removed, the crude aniline was dissolved in THF (10 mL) and 0.2% HCl aq. (30 mL). The whole solution was stirred at room temperature for 24 h. The aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate 2:1) to yield **1b** (451 mg, 93%, 2 steps) as a colorless crystal. IR (nujol) ν 2924, 2854, 1703, 1654, 1622, 1606, 1566, 1497, 1461, 1428, 1376, 1262, 1211, 1070 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.43 (s, 3H), 4.43 (dd, J=4.0, 16.0 Hz, 1H), 4.50 (br, 1H), 4.65 (d, J=16.0 Hz, 1H), 4.88 (d, J=10.8 Hz, 1H), 4.96 (d, J=10.8 Hz, 1H), 5.24 (d, J=17.6 Hz, 1H), 5.31 (d, J= 10.8 Hz, 1H), 5.81 (s, 1H), 6.55 (dd, J=17.6, 10.8 Hz, 1H), 7.12 (d, J=8.0 Hz, 1H), 7.31–7.37 (m, 5H), 7.70 (d, J= 8.0 Hz, 1H), 7.83 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.6 (CH_3), 52.8 (CH_2), 63.6 (CH), 75.2 (CH_2), 118.2 (CH_2), 120.7 (CH), 124.7 (C), 126.2 (CH), 127.2 (CH), 128.5 (CH), 128.6 (CH), 128.9 (C), 129.6 (C), 129.7 (CH), 135.3 (C), 135.4 (C), 139.6 (C), 145.6 (C), 164.4 (C), 169.7 (C); LRMS m/z 360 (M^+), 269, 241, 91; HRMS Calcd for $C_{22}H_{20}N_2O_3$ (M^+) 360.1474, found 360.1472. Anal. Calcd for $C_{22}H_{20}N_2O_3$: C, 73.32; H, 5.59; N, 7.77. Found: C, 73.19; H, 5.69; N, 7.86. $[\alpha]_D^{23.0}=+334.3$ (c 1.00, $CHCl_3$).

4.1.11. (11a*S*,*E*)-Acetic acid 3-(9-benzyloxy-8-methyl-5,11-dioxo-5,10,11,11a-tetrahydro-3*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepin-2-yl)-allyl ester (11b). To a solution of **1b** (115 mg, 0.32 μmol) and **10** (0.5 μL, 0.3 mmol) in CH_2Cl_2 (6.4 mL) was added **6b** (13.5 mg, 16 μmol, 5 mol%), and the solution was degassed through freeze–pump–thaw cycle. The whole solution was refluxed for 12 h. After the solvent was removed, the residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate 3:1–1:1) to yield **11b** (126 mg, 91%) as a colorless crystal. Mp 138–140 °C; IR ($CHCl_3$) ν 3242, 1737, 1692, 1637, 1568, 1500, 1462, 1425, 1361, 1229, 1074 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.10 (s, 3H), 2.43 (s, 3H), 4.41 (dd, J=3.2, 15.6 Hz, 1H), 4.51 (br, 1H), 4.63 (d, J= 15.6 Hz, 1H), 4.66 (d, J=5.6 Hz, 2H), 4.88 (d, J=11.2 Hz, 1H), 4.96 (d, J=11.2 Hz, 1H), 5.77 (dt, J=16.0, 5.6 Hz, 1H), 5.85 (s, 1H), 6.49 (d, J=16.0 Hz, 1H), 7.12 (d, J= 8.0 Hz, 1H), 7.31–7.37 (m, 5H), 7.70 (d, J=8.0 Hz, 1H), 7.81 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.7 (CH_3), 20.9 (CH_3), 53.0 (CH_2), 63.6 (CH), 64.0 (CH_2) 75.3 (CH_2), 121.6 (CH), 124.3 (C), 126.1 (CH), 126.3 (CH), 127.3 (CH), 127.8 (CH), 128.7 (CH×2), 128.7 (CH), 128.9 (CH×2), 129.6 (C), 135.3 (C), 138.3 (C), 145.6 (C), 164.4 (C), 169.5 (C) 170.4 (C); LRMS m/z 432 (M^+), 372, 341, 281, 91; HRMS Calcd for $C_{25}H_{24}N_2O_5$ (M^+) 432.1685, found 432.1675. $[\alpha]_D^{19.8}=+331.7$ (c 1.00, $CHCl_3$).

4.1.12. (11a*S*)-3-(9-Benzyloxy-8-methyl-5,11-dioxo-5,10,11,11a-tetrahydro-3*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepin-2-yl)-acrylic acid methyl ester (13a). A solution of **11b** (22 mg, 51 μmol) in MeOH (2 mL) was added K_2CO_3 (12 mg, 87 μmol) at 0 °C and the solution was stirred at 0 °C for 9 h. To this solution was added saturated NH_4Cl aq. and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated to yield crude alcohol (21 mg) as a colorless crystal. To the solution of crude alcohol (21 mg) in CH_2Cl_2 (2 mL) was added MnO_2 (70 mg) and the whole suspension was stirred at room temperature for 3 days. The solution was filtered through celite and the filtrate was concentrated to give crude aldehyde **12** (20.5 mg), which was dissolved in *t*-BuOH/H_2O (1 mL, 3.5/1). To this solution was added KH_2CO_3 (73 mg, 0.5 mmol), 2-methyl-2-butene (0.2 mL, 2 mmol), and $NaClO_2$ (23 mg, 0.25 mmol) and the solution was stirred at room temperature for 3 h. To this solution was added saturated $Na_2S_2O_3$ aq. and the aqueous layer was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated to yield carboxylic acid (25 mg) as a colorless solid. A solution of crude carboxylic acid (25 mg) in MeOH (2 mL) was added $SOCl_2$ (10 drops) at 0 °C and the solution was stirred at room temperature for 18 h. After the solvent was removed, the residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate 1:1) to yield **13a** (11 mg, 52%, 4 steps) as a colorless crystal. Mp 189–191 °C; IR (nujol) ν 3215, 3065, 2854, 1722, 1699, 1645, 1623, 1565, 1499, 1462, 1376, 1315, 1261, 1225, 1174, 1072, 1001 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.45 (s, 3H), 3.79 (s, 3H), 4.45 (dd, J=3.6, 16.0 Hz, 1H), 4.55 (m, 1H), 4.66 (d, J=16.0 Hz, 1H), 4.69 (d, J=11.2 Hz, 1H), 4.98 (d, J=11.2 Hz, 1H), 5.89 (d, J=15.6 Hz, 1H), 6.21 (br, 1H), 7.14 (d, J=8.0 Hz, 1H), 7.31–7.38 (m, 5H), 7.47 (d, J=15.6 Hz, 1H), 7.70 (d, J=8.0 Hz, 1H), 7.76 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.7 (CH_3), 51.9 (CH_3), 52.7 (CH_2), 63.9 (CH), 75.4 (CH_2) 121.9 (CH), 124.1 (C), 126.4 (CH), 127.5 (CH), 128.6 (CH), 128.7 (CH×2),

128.8 (CH), 129.0 (CH×2), 129.6 (C), 135.3 (C), 135.7 (C), 136.2 (CH), 137.6 (C), 145.7 (C), 164.5 (C), 166.5 (C) 169.1 (C); LRMS *m/z* 418 (M^+), 327, 91; HRMS Calcd for $C_{24}H_{22}N_2O_5$ (M^+) 418.1528, found 418.1529. $[\alpha]_D^{20.5} = +313.4$ (*c* 1.00, $CHCl_3$).

4.1.13. (11a*S*)-3-(9-Benzyloxy-8-methyl-5,11-dioxo-5,10,11,11a-tetrahydro-3*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepin-2-yl)-acrylic acid methyl ester (13a). To a solution of **1b** (19 mg, 50 μmol) and methyl acrylate (0.05 μL, 0.5 mmol) in degassed CH_2Cl_2 (1 mL) was added **6c** (5.0 mg, 7 μmol, 13 mol%), and the solution refluxed for 17 h. After the solvent was removed, the residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate 2:1–1:1) to yield **13a** (13.8 mg, 63%) as a colorless crystal.

4.1.14. (11a*S*)-3-(9-Benzyloxy-8-methyl-5,11-dioxo-5,10,11,11a-tetrahydro-3*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepin-2-yl)-acrylic acid ethyl ester (13b). To a solution of **1b** (105 mg, 0.29 μmol) and ethyl acrylate (0.3 μL, 2.9 mmol) in degassed CH_2Cl_2 (2.8 mL) was added a solution of **6c** (21 mg, 30 μmol, 10 mol%) in degassed CH_2Cl_2 (3 mL), and the solution was stirred at room temperature for 17 h. After the solvent was removed, the residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate 1:1) to yield **13b** (75.3 mg, 60%) as an amorphous solid. IR ($CHCl_3$) *ν* 1702, 1630, 1570, 1500, 1463, 1423, 1370, 1313, 1230, 1210, 1207, 1183, 1073 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) *δ* 1.32 (t, *J*=7.1 Hz, 3H), 2.44 (s, 3H), 4.24 (q, *J*=7.3 Hz, 2H), 4.44 (dd, *J*=3.6, 15.7 Hz, 1H), 4.56 (m, 1H), 4.66 (d, *J*=15.7 Hz, 1 H), 4.89 (d, *J*=11.2 Hz, 1H), 4.97 (d, *J*=11.2 Hz, 1H), 5.89 (d, *J*=16.0 Hz, 1H), 6.20 (s, 1H), 7.13 (d, *J*=8.2 Hz, 1H), 7.31–7.33 (m, 2H), 7.36–7.38 (m, 3H), 7.45 (d, *J*=16.0 Hz, 1H), 7.70 (d, *J*=8.2 Hz, 1H), 7.78 (br, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 14.1 (CH_3), 16.6 (CH_3), 52.7 (CH_2), 60.7 (CH_2), 63.8 (CH), 75.4 (CH_2) 122.4 (CH), 124.2 (C), 126.4 (CH), 127.5 (CH), 128.5 (CH), 128.7 (CH×2), 128.8 (CH), 129.0 (CH×2), 129.7 (C), 135.4 (CH), 135.7 (C), 135.9 (CH), 137.7 (C), 145.8 (C), 164.5 (C), 166.1 (C) 169.2 (C); LRMS *m/z* 432 (M^+), 360, 341, 269, 91; HRMS Calcd for $C_{25}H_{24}N_2O_5$ (M^+) 432.1685, found 432.1683. $[\alpha]_D^{23.5} = +312.1$ (*c* 1.00, $CHCl_3$).

4.1.15. 3-(9-Benzyloxy-8-methyl-5,11-dioxo-10,11-dihydro-5*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepin-2-yl)-propionic acid methyl ester (14). To a solution of **13a** (3 mg, 18 μmol) in toluene (1 mL) was added $RuHCl(CO)(PPh_3)_3$ (1 mg), and the solution was stirred at 120 °C for 8 h. After the solvent was removed, the residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate 1:1) to yield **14** (2 mg, 66%) as a colorless crystal. ^1H NMR (270 MHz, $CDCl_3$) *δ* 2.40 (s, 3H), 2.65 (t, *J*=7.6 Hz, 2H), 2.89 (t, *J*=7.6 Hz, 2H), 3.70 (s, 3H), 4.91 (s, 2H), 7.08 (d, *J*=8.6 Hz, 1H), 7.40–7.50 (m, 6H), 7.92 (m, 1H), 8.16 (d, *J*=8.6 Hz, 1H), 8.75 (brs, 1H); LRMS *m/z* 418 (M^+), 387, 344, 327, 299, 243, 176, 148, 120.

4.1.16. (11a*S*,*E*)-3-(9-Benzyloxy-8-methyl-5,11-dioxo-5,10,11,11a-tetrahydro-1*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepin-2-yl)-acrylic acid ethyl ester (15b). A solution of **13b** (4.3 mg, 18 μmol), $RhCl_3 \cdot 3H_2O$ (2.4 mg, 3 μmol, 15 mol%) and degassed EtOH (0.5 mL) was added in a sealed tube and was stirred at 110 °C for 24 h. After the solvent was removed, the residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate 3:1–1:1) to yield **15b** (5 mg, 50%) as a colorless crystal. IR (film) *ν* 3247, 2980, 2931, 1698, 1621, 1569, 1499 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) *δ* 1.31 (t, *J*=7.3 Hz, 3H), 2.46 (s, 3H), 2.85 (dd, *J*=11.7, 16.1 Hz, 1H), 3.65 (dd, *J*=3.3, 16.1 Hz, 1H), 4.14 (dd, *J*=3.3, 11.7 Hz, 1H), 4.23 (q, *J*=7.3 Hz, 2H), 4.88 (d, *J*=11.3 Hz, 1H), 4.98 (d, *J*=11.3 Hz, 1H), 5.81 (d, *J*=15.6 Hz, 1H), 7.15 (d, *J*=8.1 Hz, 1H), 7.27 (s, 1H), 7.28–7.31 (m, 2H), 7.36–7.37 (m, 3H), 7.47 (d, *J*=15.6 Hz, 1H), 7.68 (d, *J*=8.1 Hz, 1H), 7.74 (br, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 14.3 (CH_3), 16.7 (CH_3), 29.2 (CH_2), 56.7 (CH), 60.4 (CH_2), 75.5 (CH_2) 118.7 (CH), 122.9 (C), 123.9 (C), 126.8 (CH), 127.8 (CH), 128.8 (CH×2), 128.9 (CH), 129.2 (CH×2), 129.6 (C), 132.0 (CH), 135.3 (C), 136.5 (C), 137.1 (CH), 146.0 (C), 162.1 (C), 166.8 (C) 167.5 (C); LRMS *m/z* 432 (M^+), 387, 341, 295, 176, 120, 91; HRMS Calcd for $C_{25}H_{24}N_2O_5$ (M^+) 432.1685, found 432.1689. $[\alpha]_D^{24.1} = +244.0$ (*c* 0.58, $CHCl_3$).

4.1.17. (11a*S*)-3-(9-Hydroxy-8-methyl-5,11-dioxo-5,10,11,11a-tetrahydro-1*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepin-2-yl)-acrylic acid ethyl ester (18). A mixture of crude **15b** (17 mg), TFA (1 mL), and $BF_3 \cdot Et_2O$ (0.05 mL) was stirred at room temperature for 10 min. To this solution were added MeOH and H_2O, and the aqueous layer was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated to yield crude **18** (17 mg) as a colorless crystal. ^1H NMR (400 MHz, $CDCl_3$) *δ* 1.32 (t, *J*=6.8 Hz, 3H), 2.36 (s, 3H), 2.97 (dd, *J*=11.2, 15.6 Hz, 1H), 3.76 (dd, *J*=15.6, 3.6 Hz, 1H), 4.23 (q, *J*=6.8 Hz, 2H), 4.63 (dd, *J*=11.2, 3.6 Hz, 1H), 5.83 (d, *J*=16.0 Hz, 1H), 7.07 (d, *J*=8.4 Hz, 1H), 7.34 (s, 1H), 7.37 (br, 1H), 7.50 (d, *J*=16.0 Hz, 1H), 7.51 (d, *J*=8.4 Hz, 1H), 8.36 (br s, 1H); LRMS *m/z* 342 (M^+), 313, 297, 268, 176, 149, 120, 92.

4.1.18. Benzylidene acetal (19). A mixture of crude **18** (17 mg), benzaldehyde dimethylacetal (0.5 mL), and *p*-TsOH (1.7 mg) was warmed to 100 °C for 40 h. To this solution was added brine and EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate 2:1) to yield **19** (9 mg, 53%) as a colorless crystal. IR ($CHCl_3$) *ν* 1698, 1650, 1593, 1499, 1457, 1398, 1259, 1223, 1177, 1143 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 1.32 (t, *J*=6.8 Hz, 3H), 2.40 (s, 3H), 2.91 (dd, *J*=11.2, 15.2 Hz, 1H), 3.76 (dd, *J*=15.2, 4.0 Hz, 1H), 4.23 (q, *J*=6.8 Hz, 2H), 4.41 (dd, *J*=11.2, 4.0 Hz, 1H), 5.84 (d, *J*=16.0 Hz, 1H), 7.16 (d, *J*=8.0 Hz, 1H), 7.34–7.56 (m, 8H), 7.72 (d, *J*=8.0 Hz, 1H); LRMS *m/z* 430 (M^+), 401, 385, 373, 356, 266, 236, 209, 121, 91; HRMS Calcd for $C_{25}H_{22}N_2O_5$ (M^+) 430.1528, found 430.1543.

4.1.19. Aminal (20). To a solution of **19** (2 mg) in MeOH (1 mL) was added $NaBH_4$ (4.4 mg) at 0 °C and the solution was stirred at 0 °C for 4 h. To this solution was added H_2O, and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate 1:1) to

yield **20** (1.7 mg, 84%) as a colorless crystal. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30 (t, J=7.1 Hz, 3H), 2.08 (d, J=8.4 Hz, 1H), 2.19 (s, 3H), 2.92 (dd, J=15.6, 4.9 Hz, 1H), 3.13 (dd, J=11.4, 3.7 Hz, 1H), 4.22 (q, J=7.1 Hz, 2H), 4.29 (dd, J=11.2, 4.8 Hz, 1H), 4.84 (d, J=8.6 Hz, 1H), 5.63 (d, J=15.6 Hz, 1H), 6.55 (s, 1H), 6.66 (d, J=8.5 Hz, 1H), 7.35 (d, J=8.5 Hz, 1H), 7.43–7.53 (m, 7H); LRMS *m/z* 432 (M^+), 414, 385, 356, 266, 238, 209; HRMS Calcd for $C_{25}H_{24}N_2O_5$ (M^+) 432.1685, found 432.1680.

References and notes

1. Isolation and characterization: (a) Leimgruber, W.; Stefanovic, V.; Schenker, F.; Karr, A.; Berger, J. *J. Am. Chem. Soc.* **1965**, *87*, 5791. (b) Leimgruber, W.; Batcho, A. D.; Schenker, F. *J. Am. Chem. Soc.* **1965**, *87*, 5793. Total syntheses: (c) Leimgruber, W.; Batcho, A. D.; Czajkowski, R. C. *J. Am. Chem. Soc.* **1968**, *90*, 5641. (d) Pena, M. R.; Stille, J. K. *J. Am. Chem. Soc.* **1989**, *111*, 5417.
2. (a) Grubbs, R. H. *Handbook of Metathesis*; Wiley-VCH: New York, 2003. (b) Fürstner, A. *Topics in Organometallic Chemistry*; Springer: Berlin Heidelberg, 1998; Vol. 1.
3. Recent reviews for olefin metathesis: (a) Grubbs, R. H.; Miller, S. J. *Acc. Chem. Res.* **1995**, *28*, 446. (b) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed.* **1997**, *36*, 2036. (c) Schmalz, H.-G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1833. (d) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (e) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371. (f) Phillips, A. J.; Abell, A. D. *Aldrichim. Acta* **1999**, *32*, 75. (g) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3013. (h) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. (i) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592. (j) Connnon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900. Review for enyne metathesis: (k) Mori, M. *Top. Organomet. Chem.* **1998**, *1*, 133. (l) Poulsen, C. S.; Madsen, R. *Synthesis* **2003**, 1.
4. Review for cross-metathesis: (a) Connnon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900. For examples: (b) Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 3171. (c) Choi, T.-L.; Lee, C. W.; Chatterjee, A. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 10417. (d) Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 3171, and references cited therein.
5. For reports from our laboratory: (a) Kinoshita, A.; Mori, M. *Synlett* **1994**, 1020. (b) Kinoshita, A.; Mori, M. *J. Org. Chem.* **1996**, *61*, 8356. (c) Kinoshita, A.; Mori, M. *Heterocycles* **1997**, *46*, 287. (d) Mori, M.; Sakakibara, N.; Kinoshita, A. *J. Org. Chem.* **1998**, *63*, 6082. (e) Kinoshita, A.; Sakakibara, N.; Mori, M. *J. Am. Chem. Soc.* **1997**, *119*, 12388. (f) Kinoshita, A.; Sakakibara, N.; Mori, M. *Tetrahedron* **1999**, *55*, 8155. (g) Mori, M.; Kitamura, T.; Sakakibara, N.; Sato, Y. *Org. Lett.* **2000**, *2*, 543. (h) Mori, M.; Kitamura, T.; Sato, Y. *Synthesis* **2001**, 654. (i) Kitamura, T.; Mori, M. *Org. Lett.* **2001**, *3*, 1161. (j) Mori, M.; Kuzuba, Y.; Kitamura, T.; Sato, Y. *Org. Lett.* **2002**, *4*, 3855. (k) Kitamura, T.; Sato, Y.; Mori, M. *Chem. Commun.* **2001**, 1258. (l) Kitamura, T.; Sato, Y.; Mori, M. *Adv. Synth. Catal.* **2002**, *344*, 678. (m) Mori, M.; Tonogaki, K.; Nishiguchi, N. *J. Org. Chem.* **2002**, *67*, 224. (n) Saito, N.; Sato, Y.; Mori, M. *Org. Lett.* **2002**, *4*, 803. (o) Tonogaki, K.; Mori, M. *Tetrahedron Lett.* **2002**, *43*, 2235.
6. Cho, J. H.; Kim, B. M. *Tetrahedron Lett.* **2002**, *43*, 1273.
7. Olah, G. A.; Narang, S. C.; Gupta, B. G. B.; Malhotra, R. *J. Org. Chem.* **1979**, *44*, 1247.
8. Fay, W. N.; Lin, H.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 9812.
9. (a) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168. (b) Gessler, S.; Randl, S.; Blechert, S. *Tetrahedron Lett.* **2000**, *41*, 9973. (c) Wakamatsu, H.; Blechert, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 2403.
10. Grieco, P. A.; Nishizawa, M.; Marinovic, N.; Ehmann, W. *J. Am. Chem. Soc.* **1976**, *98*, 7102.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 60 (2004) 9659–9673

Synthesis of a *para*-quinone macrolactam related to geldanamycin by ring closing metathesis

Aude Lemarchand and Thorsten Bach*

Lehrstuhl für Organische Chemie I, Department of Chemistry, Technische Universität München, Lichtenbergstr. 4, 85747 Garching, Germany

Received 26 April 2004; revised 16 June 2004; accepted 18 June 2004

Available online 24 August 2004

Abstract—Model studies conducted with the α,β,γ,δ-unsaturated 3-alkenyl-2,4,5-trimethoxyanilides **11** revealed that a ring closing metathesis (RCM) of these compounds is possible if the ansa chain contains more than 14 atoms. The (*Z*)-configurated products **12c**–**e** were obtained in good yields (77–87%) and with perfect simple diastereoselectivity. Since the oxidation of the 2,4,5-trimethoxyanilides led predominantly to undesired *ortho*-quinones such as **15** or to *para*-azaquinones such as **16** the macrocyclic 2,5-di-*iso*-propoxy-4-methoxyanilide **22** was prepared. The *iso*-propyl protecting groups could be selectively cleaved and the intermediate *para*-hydroquinone oxidized on air to the desired *para*-quinone **2** (86% yield). The compound shows some key features (macrolactam ring with the same ring size, α,β,γ,δ-unsaturated anilide, *para*-quinone) of geldanamycin.

1. Introduction

Geldanamycin (**1**)[1] is an antitumor agent with a medium 50% growth inhibition (GI_{50}) of 180 nM against 60 tumor cell lines tested by the national cancer institute (NCI). The GI_{50} against the most sensitive cell lines was found to be as low as 13 nM.[2] Its antitumor activity is attributed to a binding to the heat shock protein 90 (Hsp 90)[3,4] although other modes of action have been discussed.[5] Structures of Hsp 90–geldanamycin complexes have been elucidated and the most important binding motifs have been identified.[6] Geldanamycin binds to the N-terminal ATP/ADP-binding domain of Hsp 90 and inhibits the ATPase activity which is essential for the function of the enzyme. Based on its molecular structure, geldanamycin can be classified as an ansamycin.[7] It differs from other ansamycins (e.g., herbimycin A) by the additional methoxy substituent at the quinone ring (C-17) and by the substitution in the ansa chain. Early synthetic efforts by Schill et al.[8] established the possibility to construct the macrocycle by C–C bond (C-15/C-16) formation at a suitable arene and subsequent macrolactamization. After the discovery of its antitumor activity geldanamycin was the target of many modification studies from which more active bioavailable compounds derived.[9] The first total synthesis of geldanamycin was recently accomplished by Andrus and co-workers.[10]

We envisioned an access to the geldanamycin macrocycle by ring closing metathesis (RCM)[11] between carbon atoms C-4 and C-5. Preliminary studies revealed that this strategy is feasible.[12] A first target, which contains the same *para*-quinone chromophore, the (*E*,*Z*)-α,β,γ,δ-unsaturated anilide, and an ansa chain identical in chain length to geldanamycin, is compound **2** the synthesis of which was undertaken (Fig. 1).

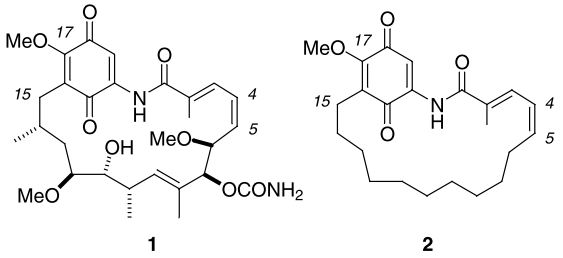
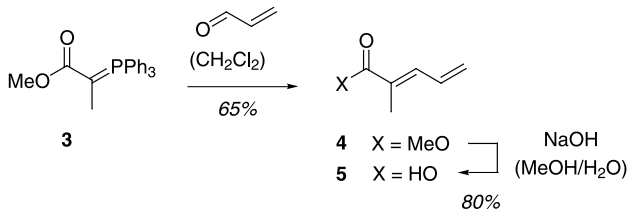


Figure 1. Geldanamycin (**1**) and the *para*-quinone macrolactam **2**.

In this account, we provide full details on the synthesis of appropriate precursors which allowed us to study the RCM for the preparation of macrocycles with different ring sizes. We discuss the oxidation of the initially studied 2,4,5-trimethoxyanilides and report on the structure elucidation of the oxidation products. The mechanism of the oxidation is briefly discussed. Finally, the synthesis of compound **2** is described starting from 1,4-di-*iso*-propoxy-2-methoxybenzene.

Keywords: Ring closing metathesis; Ansa chain; Geldanamycin.
* Corresponding author. Tel.: +49-89-28913330; fax: +49-89-28913315; e-mail: thorsten.bach@ch.tum.de

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.06.147



Scheme 1. Preparation of 2-methyl-2,4-pentadienoic acid (**5**).

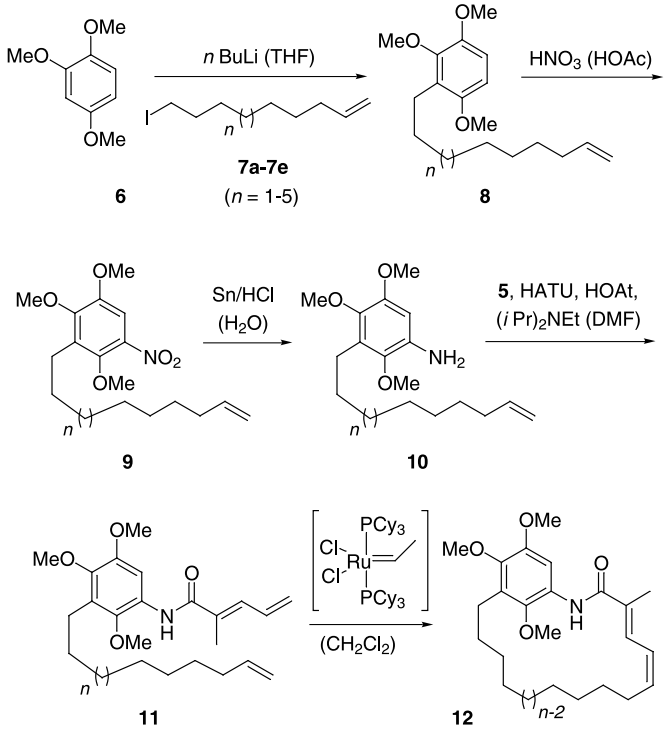
2. Ring closing metathesis

Studies on the RCM commenced with attempts to synthesize suitable 3-ω-alkenyl-2,4,5-trimethoxyanilides of 2-methyl-2,4-pentadienoic acid (**5**). The acid itself was prepared (Scheme 1)[13] from Wittig reagent **3** and acrolein via its methyl ester which was subsequently saponified to the free acid.

The lithiation of 1,2,4-trimethoxybenzene (**6**) with *n*-butyl lithium (1.1 equiv) was optimized by quenching the lithiated intermediate with iodine and by subsequent GLC analysis. The reaction proceeded slowly at −78 °C and at 0 °C in THF as the solvent (<50% conversion after 1 h). At ambient temperature the conversion was rapid and lithiation was complete after less than an hour. Prolonged stirring at room temperature led to decomposition.

Based on the preliminary experiments the lithiation of **6** was conducted by adding *n*-butyl lithium to the arene and keeping the reaction mixture for 45 min at room temperature. After cooling to 0 °C, the corresponding alkyl halide was added. Although Schill et al. had used bromoalkanes in their alkylation experiments[8] we found the iodides superior allowing a smoother and cleaner conversion than the corresponding bromides and—more importantly—avoiding the use of an excess of the halide. The ω-alkenyliodides **7** employed as electrophiles in the alkylation step are literature known and were prepared according to reported procedures.[14–18] The alkylation reaction proceeded nicely and yielded the ω-alkenylarenes **8** (Scheme 2). Regioselective nitration using nitric acid in acetic acid[8] as the solvent furnished the nitro compounds **9** in very good yields. The reduction to the anilines **10** was accomplished by treatment of the nitroarenes with tin in aqueous hydrochloric acid at 60 °C (Table 1).[19]

The acylation of anilines **10** was initially projected with the chloride of acid **5** or via a mixed anhydride. Despite several attempts with $SOCl_2$ or $(COCl)_2$ as reagents, the chloride could not be obtained from **5**. Contrary to that, sorboyl chloride,[20] for example, was readily accessible from sorboic acid using common conditions ($SOCl_2$ in refluxing benzene). The acylation of aniline **10c** with sorboyl chloride was facile but it was not further optimized (56% yield). Upon attempted activation of acid **5** with pivaloyl chloride and subsequent reaction with aniline **10c** the sole product obtained was the corresponding *N*-pivaloyl aniline (63% yield). Experiments to use an in situ activation with common peptide coupling reagents commenced with dicyclohexyl carbodiimide (DCC). Minor product formation (27% yield) was observed when aniline **10c** was treated with DCC and 1-hydroxybenzotriazole (HOBt) in CH_2Cl_2 at ambient temperature for three days. An improvement in yield and in the rate of conversion was achieved upon addition of bases and upon changing the solvent to DMF. The best result was recorded with di-*iso*-propylethylamine (Hünig base) in DMF (36% yield). Further improvements were due to a modification of the additive. Both 1-hydroxy-7-azabenzotriazole (HOAt) and 3-hydroxy-4-oxo-3,4-dihydro-1,2,3-benzotriazole (HOOBt)



Scheme 2. Preparation of the RCM precursors **11** and RCM to products **12** (for yields and further comments see Table 1).

Table 1. Yields of isolated products for the five individual steps in the conversion of arene **6** to the RCM products **12** (cf. Scheme 2)

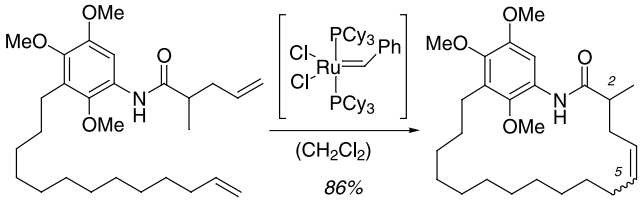
n	Iodide	**8** (%)	**9** (%)	**10** (%)	**11** (%)	**12** (%)
1	**7a**	59	73	82	72	—[a]
2	**7b**	76	95	77	58	—[b]
3	**7c**	76	98	84	66	66[c]
4	**7d**	73	95	79	68	77
5	**7e**	73	94	83	63	87

[a] Only starting material (50%) and dimer/oligomer (25%) were isolated.
[b] Only starting material (84%) and dimer/oligomer (10%) were isolated.
[c] Starting material (14%) was isolated. The yield based on recovered starting material is 77%.

gave better yields than HOBt under otherwise identical conditions (up to 56% yield). Still, the reaction was unsatisfactory being not fully reproducible and sluggish at times. A significant breakthrough was achieved by substituting the activation reagent DCC. *O*-(7-Azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU) in the presence of HOAt[21] turned out to be the reagent combination of choice which guaranteed significantly better conversions in a generally applicable reaction. The anilides **11** were so obtained in 58–72% yield.

Details of the RCM have been discussed already in our preliminary paper.[12] Key issues are a low concentration of the substrate (0.5 mM) in CH_2Cl_2 as the solvent, the use of conventional Grubbs I catalyst (10 mol%) with an ethylidene or benzylidene ligand at the ruthenium center, and the alkenyl chain length as the determining factor for the success of the RCM. Indeed, ring sizes of 18–20 (compounds **12c**–**e**) were readily accessible whereas the formation of the 16- or 17-membered ansa compounds **12a** and **12b** could not be achieved. Apparently, the nonenyl and docenyl group do under the given restriction by the α,β,γ,δ-unsaturated anilide not reach the terminal double bond of the diene and an ansa chain with less than 15 atoms does not form. The double bonds which are in the course of the metathesis reaction established between carbon atom C-4 and C-5 of the products **12c**–**e** are uniformly configurated. The coupling constant between the protons H-4 and H-5 in all compounds **12c**–**e** is around $J \cong 10$ Hz. Strong NOE contacts were observed for these protons in compound **12e** supporting the assignment of the double bond configuration as (*Z*). Further ^{1}H NMR NOESY data which are in line with a C-4/C-5 (*Z*)-configuration were obtained from oxidation products of compounds **12c** and **12e** (vide infra).

If the conformational restriction exerted by the C-2/C-3 double bond in the 3-alkenyl-2,4,5-trimethoxyanilide is removed the RCM is not stereoselective any more. When the anilide **13** of 2-methyl-2-pentenoic acid was employed as a substrate the 20-membered ansa compound **14** was obtained as a mixture of (*E*)- and (*Z*)-isomers (Scheme 3). Since the isomers were not separable, configurations could not be assigned to the individual isomers.



13 **14** (d.r. = 66/34)

Scheme 3. RCM of ω-alkenylanilide **13** to a mixture of diastereomeric lactams **14**.

3. Oxidation reactions

Although there is literature precedence for the oxidation of 1,2,4-trimethoxybenzenes to 2-methoxy-*para*-benzoquinones,[19,22] ansa compounds related to **12c**–**e** had earlier been shown to give the 4-methoxy-*ortho*-benzoquinones upon oxidation with concentrated nitric acid in acetic acid solution.[8] This result was corroborated in recent studies by Andrus et al.[10,23] Upon oxidation of an immediate geldanamycin precursor with 70% nitric acid they obtained in 55% yield a 10:1 mixture of the undesired *ortho*- and the desired *para*-geldanamycin. Oxidation with other reagents (Ag_2O or MnO_2 impregnated with nitric acid) led to the formation of a *para*-azaquinone. Subsequent model studies showed that conformationally unrestricted 3-alkyl-2,4,5-trimethoxyanilides yielded predominantly *ortho*-quinones upon oxidation.[23]

Our oxidation experiments were conducted with ceric ammonium nitrate (CAN) and pyridine-2,6-dicarboxylic acid *N*-oxide[24] in acetonitrile/water at 0 °C. They confirmed that an oxidation of either precursor **12c**–**e** to a *para*-quinone was not possible. The reactions with substrates **12c** and **12e** led to well defined oxidation products in moderate yields. Compound **12c** gave *ortho*-quinone **15** (30% yield) and compound **12e** furnished *para*-azaquinone **16** (64% yield). ^{1}H NMR NOESY studies (Fig. 2) revealed that the 18-membered ansa compound **15** is perfectly planar in the region C-16 (arene) to C-6 while the 20-membered ring is somewhat twisted. This fact is indicated by weak NOE contacts between H-3 and H-4 as well as between H-19 and

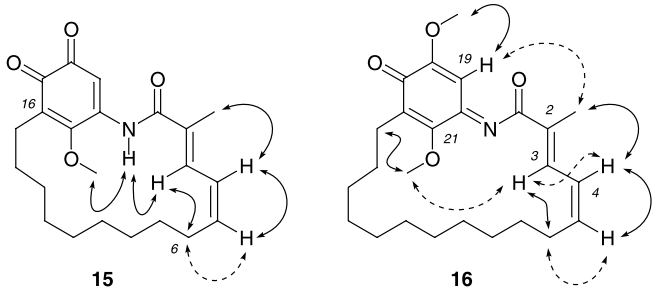


Figure 2. Significant NOE contacts (- - - weak, — strong) recorded in the oxidation products **15** and **16** obtained from anilides **12c** and **12e** by CAN oxidation.

the methyl group at C-2. If the precursor **12e** exhibits a similar conformation the NH proton may be removed by a base in an intermediate radical cation (or cation) which in turn is formed by single electron oxidation. In our opinion, the removal of the NH proton, which competes with the hydroxy-de-methoxylation[24a,25] at carbon atoms C-18 or C-17, governs the chemoselectivity of the oxidation process. In the twisted compound **12e** the deprotonation is facile and accounts for the formation of the azaquinone, in the flat compound **12c** and in other acyclic systems the hydroxy-de-methoxylation is faster and leads to the *ortho*-quinone. The hydroxy-de-methoxylation at the less accessible carbon atom C-21 is slow possibly due to steric reasons.

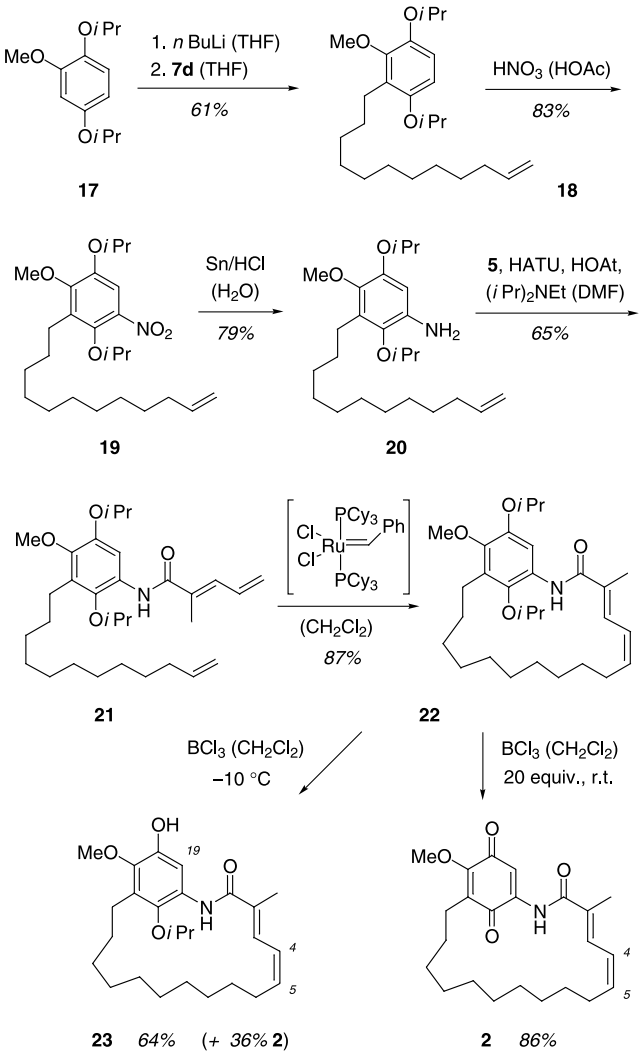
Selective demethylation reactions by strong nucleophiles (LiI) or Lewis acids (BBr_3) were attempted with model compounds but led only to degradation. BCl_3 facilitated a demethylation but the yields and the regioselectivity were not satisfactory. Consequently, we looked for alternative protection strategies for the 1,4-hydroquinone. A minimal change in reactivity and a maximum coincidence with the previous results was expected upon replacing the methyl protecting groups by other alkyl groups. The *iso*-propyl group was considered to be a reasonable choice and work along these line continued.

4. Synthesis of *para*-quinone 2

Model studies proved that 3-alkyl-2,5-di-*iso*-propoxy-4-methoxyanilides are readily deprotected with BCl_3 at -10 °C in CH_2Cl_2 and yield upon work-up without addition of an oxidizing agent the corresponding *para*-quinones.

Based on these results the readily available 1,4-di-*iso*-propoxy-2-methoxybenzene (**17**)[26] was lithiated in 3-position with *n*-butyl lithium and subsequently alkylated with iodide **7d** (Scheme 4). A side product was found (4% yield) which arose from deprotonation at the 6-position. All further reactions starting from arene **18** were conducted in analogy to our previous work. Selective nitration led to nitroarene **19** which was reduced to aniline **20**. After amide bond formation the anilide underwent the RCM smoothly and gave the desired lactam **22** in excellent yield. The deprotection occurred less readily than in the test system. At -10 °C there was a monodeprotection to phenol **23**. After addition of an excess of BCl_3 and by warming to room temperature the deprotection could be driven to completion and the desired compound **2** was isolated as the sole reaction product. The total yield in which *para*-quinone **2** was obtained from arene **17** was 19%.

Both products **23** and **2** were intensively studied by ^1H NMR NOESY experiments. The phenol OH proton in compound **23** showed a strong NOE to H-19 which proves the regioselectivity of the deprotection. The (*Z*)-configuration of the double bond formed in the RCM step was in both products unequivocally proven by the relatively small coupling constants and by strong NOE contacts between H-4 and H-5. The other NOEs in the area C-1 to C-6 were similar to the signals recorded for compound **15** supporting a s-*trans* amide bond (C-1/NH).



Scheme 4. Synthesis of the phenol **23** and the *para*-quinone **2** from 1,4-di-*iso*-propoxy-2-methoxybenzene (**17**).

In conclusion, the study has shown that the construction of *para*-quinones related to geldanamycin is feasible based on a RCM strategy. The *iso*-propyl group was used as a protecting group for the latent *para*-quinone moiety in the corresponding hydroquinone di-*iso*-propyl ether. The amide bond formation between the aniline nitrogen atom and carbon atom C-1 of 2-methyl-2,4-pentadienoic acid was achieved by use of the reagent combination HATU/HOAt. The synthesis of compound **2** was achieved in an overall yield of 19% starting from 1,4-di-*iso*-propoxy-2-methoxybenzene (**17**). There are of course many further challenges ahead if this strategy is to be applied to a successful synthesis to geldanamycin. The selective introduction of the nitro group into a more highly functionalized precursor, the generation of the appropriate stereogenic centers and the protection of the hydroxy groups as well as the carbamate formation before or after *para*-quinone deprotection are among the most important aspects to be addressed. Work along these lines is currently pursued in our laboratory.

5. Experimental

5.1. General

All reactions involving water-sensitive chemicals were carried out in flame-dried glassware with magnetic stirring under Ar. Tetrahydrofuran and diethyl ether were distilled from sodium immediately prior to use. *N*,*N*-Di-*iso*-propylethylamine (DIPEA) and dichloromethane were distilled from calcium hydride. All other chemicals were either commercially available or prepared according to the cited references. TLC: Merck glass sheets (0.25 mm silica gel 60, F_{254}), eluent given in brackets. Detection by UV or coloration with cerium ammonium molybdate (CAM). Optical rotation: Perkin–Elmer 241 MC. NMR: Bruker AC-250, AV-360, AV-500. ^1H and ^{13}C NMR spectra were recorded at ambient temperature. Chemical shifts are reported relative to tetramethylsilane as internal standard. Apparent multiplets which occur as a result of the accidental equality of coupling constants of magnetically non-equivalent protons are marked as virtual (v.). The multiplicities of the ^{13}C NMR signals were determined by DEPT experiments. IR: Perkin–Elmer 1600 FT-IR. MS: Finnigan MAT 8200 (EI). Elemental Analysis: Elementar Vario EL. Flash chromatography was performed on silica gel 60 (Merck, 230–400 mesh) (ca. 50 g for 1 g of material to be separated) with the indicated eluent. Common solvents for chromatography [pentane (P), ethyl acetate (EA), dichloromethane (DCM)] were distilled prior to use.

Procedure A. Alkylation of 1,2,4-trimethoxybenzene. To a solution of 1,2,4-trimethoxybenzene in THF (1 mL/mmol), *n*-butyl lithium (2.5 M in hexane, 1.1 equiv) was slowly added at rt. After 10 min, a white precipitate appeared indicating the formation of the lithiated compound. The mixture was allowed to stir for 30 to 45 min at room temperature and was subsequently cooled to 0 °C. The iodide (1.05–1.1 equiv) was added at this temperature. The mixture was stirred for 14 h at rt. Then, diethyl ether (3 mL/mmol) and water (3 mL/mmol) were added. The aqueous layer was extracted twice with diethyl ether (2×5 mL/mmol). The combined organic layers were washed once with brine (5 mL/mmol), dried (Na_2SO_4) and concentrated under reduced pressure. The product was purified by flash chromatography (P/EA).

Procedure B. General procedure for the nitration of arenas. To a solution of the arene in acetic acid (2.8 mL/mmol), concentrated nitric acid (70% w/w, 0.58 mL/mmol) in acetic acid (1.8 mL/mmol) was slowly added at room temperature. After 5 min the solution takes an orange color, which turns after a few minutes into a yellow color. The mixture was stirred for 60 min at rt. Water (5 mL/mmol) and diethyl ether (5 mL/mmol) were added. $NaHCO_3$ was carefully added and the solution was stirred for 30 min. The layers were separated and the aqueous layer was extracted three times with diethyl ether (3×5 mL/mmol). The combined organic layers were washed once with a saturated solution of $NaHCO_3$ in water (5 mL/mmol), brine (5 mL/mmol), dried (Na_2SO_4) and concentrated under reduced pressure. The product was purified by flash chromatography (P/EA).

Procedure C. General procedure for the reduction of nitroarenes. To the nitroarene and tin powder (8 equiv) under argon atmosphere, concentrated hydrochloric acid (8 equiv, 2.8 mL/mmol) was added. The mixture was heated for 2 h at 60 °C and cooled to 0 °C. The reaction was then quenched by addition of aqueous NaOH (10% w/w). The pH was adjusted to 10. The aqueous layer was extracted three times with DCM (3×5–10 mL/mmol). The combined organic layers were washed once with brine (5–10 mL/mmol), dried (Na_2SO_4) and concentrated in vacuum. The product was purified by flash chromatography (P/EA).

Procedure D. General procedure for the peptide bond formation with HATU/HOAt. To 2-methyl-2,4-pentadienoic acid dissolved in DMF (1.8 mL/mmol) and cooled to 0 °C, DIPEA (2.5 equiv) was added slowly. After being stirred 30 min at this temperature, HOAt (1.0 equiv) dissolved in DMF (0.6 mL/mmol) was added. The mixture was stirred for 30 min at 0 °C and HATU (1.0 equiv) dissolved in DMF (0.6 mL/mmol) was added. After being stirred for 15 min at 0 °C and 15 min at rt, the corresponding aniline (1.0 equiv) dissolved in DMF (3.0 mL/mmol) was added. The mixture was stirred for 48 h at rt. DCM (50 mL/mmol) and water (50 mL/mmol) were added. The aqueous layer was extracted twice with DCM (2×50 mL/mmol). The combined organic layers were washed with a saturated aqueous $NaHCO_3$ solution (5 mL/mmol), brine (5 mL/mmol), dried (Na_2SO_4) and concentrated in vacuo. The product was purified by flash chromatography (P/EA).

Procedure E. General procedure for the macrocyclization. To refluxing CH_2Cl_2 (1.9 L/mmol), a solution of catalyst (0.10 equiv) in CH_2Cl_2 (20 mL/mmol) was added under argon atmosphere. After 5 min a solution of the anilide in CH_2Cl_2 (80.0 mL/mmol) was added. The solution was refluxed until the reaction was complete (TLC). The solvent was removed in vacuo and the product was purified by flash chromatography (P/EA).

Procedure F. Oxidation with CAN. To a solution of the anilide and pyridine-2,6-dicarboxylic acid *N*-oxide (2.5 equiv) in acetonitrile (5.0 mL/mmol) and water (1.5 mL/mmol) cooled to 0 °C, a solution of CAN (2.5 equiv) in acetonitrile (2.5 mL/mmol) and water (2.5 mL/mmol) was slowly added. The resulting solution was stirred at 0 °C until no more starting material remained according to TLC. The mixture was dissolved in water (45 mL/mmol) and extracted three times with DCM (3×75 mL/mmol). The combined organic layers were washed with brine (5 mL/mmol), dried (Na_2SO_4) and concentrated.

Procedure G. Alkylation of 1,4-di-iso-propoxy-2-methoxybenzene. To a solution of 1,4-di-*iso*-propoxy-2-methoxybenzene in THF (1 mL/mmol), *n*-butyl lithium (2.5 M in hexane, 1.1 equiv) was slowly added at rt. The mixture was stirred 30 to 45 min at rt, and was cooled to 0 °C. The iodide (1.05 equiv) was added at this temperature. The mixture was stirred for 14 h at rt. Then, diethyl ether (5 mL/mmol) and water (5 mL/mmol) were added. The aqueous layer was extracted twice with diethyl ether (2×4 mL/mmol). The combined organic layers were washed once with brine (5 mL/mmol), dried (Na_2SO_4) and concentrated under

reduced pressure. The product was purified by chromatography (P/EA).

5.1.1. 1,2,4-Trimethoxy-3-non-8-enylbenzene (8a). Procedure A was performed with 9-iodonon-1-ene (**7a**)[14] (3.32 g, 13.2 mmol) and 1,2,4-trimethoxybenzene (2.02 g, 12.2 mmol). After flash chromatography (P/EA 90/10), the product was obtained (2.09 g, 7.16 mmol, 59%) as a colorless oil. TLC: R_f=0.77 (P/EA 90/10) [CAM, UV]; IR (film): $\tilde{\nu}$ (cm^{-1})=3075 (w, =CH_2), 2927 (v. s, CH_2), 2854 (s, CH_2), 1639 (m, C=C), 1593 (m, C_{ar}=C_{ar}), 1487 (m, CH_2), 1255 (s, COC), 1224 (m), 1162 (s, COC), 1092 (s, COC), 1024 (m); 909 (m, RCH=CH_2), 789 (w, CH), 718 (w, CH_{ar}); ^{1}H NMR (360 MHz, $CDCl_3$): δ (ppm)=6.68 (d, ^3J=8.9 Hz, 1H, C_{ar}H), 6.53 (d, ^3J=8.9 Hz, 1H, C_{ar}H), 5.79 (ddt, ^3J=17.1 Hz, ^3J=10.2 Hz, ^3J=6.7 Hz, 1H, CH_2=C*H*R), 5.00–4.97 (m, 1H, H_{trans}CH=CHR), 4.94–4.91 (m, 1H, H_{cis}CH=CHR), 3.82 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 2.63 (v. t, $^3J\cong$7.7 Hz, 2H, CH_2Ar), 2.08 (v. q, $^3J\cong$6.6 Hz, 2H, CH_2=CHCH_2), 1.53–1.34 (m, 10H, CH_2); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ (ppm)=152.34 (C_{ar}OMe), 148.05 (C_{ar}OMe), 147.14 (C_{ar}OMe), 139.18 (HR*C*=CH_2), 126.07 ($C_{ar}CH_2$), 114.2 (HRC=*C*H_2), 109.6 (C_{ar}H), 105.3 (C_{ar}H), 60.7 (OCH_3), 56.1 (OCH_3), 55.8 (OCH_3), 33.8 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 29.3 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 23.9 (CH_2); MS (EI, 70 eV), *m*/*z* (%): 292 (100) [M^+], 277 (5), 181 (46), 166 (30), 151 (8), 123 (6), 91 (8), 41 (5). Anal. $C_{18}H_{28}O_3$ (292.4): calcd C, 73.93; H, 9.65; found C, 73.95; H: 9.76.

5.1.2. 2-Dec-9-enyl-1,3,4-trimethoxybenzene (8b). Procedure A was performed with 10-iododec-1-ene (**7b**)[15] (2.70 g, 10.2 mmol) and 1,2,4-trimethoxybenzene (1.56 g, 9.30 mmol). After flash chromatography (P/EA 90/10), the product was obtained (2.15 g, 7.03 mmol, 76%) as a colorless oil. TLC: R_f=0.65 (P/EA 9/1) [CAM, UV]; IR (film): $\tilde{\nu}$ (cm^{-1})=3075 (w, =CH_2), 2927 (v. s, CH_2), 2854 (s, CH_2), 1639 (m, C=C), 1593 (m, C_{ar}=C_{ar}), 1487 (m, CH_2), 1255 (s, COC), 1224 (m), 1162 (s, COC), 1092 (s, COC), 1024 (m); 909 (m, RCH=CH_2), 789 (w, CH), 718 (w, CH_{ar}); ^{1}H NMR (360 MHz, $CDCl_3$): δ (ppm)=6.70 (d, ^3J=8.9 Hz, 1H, C_{ar}H), 6.54 (d, ^3J=8.9 Hz, 1H, C_{ar}H), 5.82 (ddt, ^3J=17.1 Hz, ^3J=10.2 Hz, ^3J=6.7 Hz, 1H, CH_2=C*H*R), 5.00–4.95 (m, 1H, H_{trans}CH=CHR), 4.94–4.91 (m, 1H, H_{cis}CH=CHR), 3.83 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 2.64 (v. t, $^3J\cong$7.7 Hz, 2H, CH_2Ar), 2.04 (v. q, $^3J\cong$6.8 Hz, 2H, CH_2=CHCH_2), 1.53–1.31 (m, 12H, CH_2); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ (ppm)=152.5 (C_{ar}OMe), 148.2 (C_{ar}OMe), 147.3 (C_{ar}OMe), 139.4 (HR*C*=CH_2), 126.4 ($C_{ar}CH_2$), 114.4 (HRC=*C*H_2), 109.7 (C_{ar}H), 105.5 (C_{ar}H), 60.9 (OCH_3), 56.3 (OCH_3), 56.0 (OCH_3), 33.9 (CH_2), 30.1 (CH_2), 30.0 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 24.1 (CH_2); MS (EI, 70 eV), *m*/*z* (%): 306 (100) [M^+], 181 (41), 166 (41), 151 (5); HRMS: *m*/*z* calcd for $C_{19}H_{30}O_3$: 306.2195; found 306.2191.

5.1.3. 1,2,4-Trimethoxy-3-undec-10-enylbenzene (8c). Procedure A was performed with 11-iodoundec-1-ene (**7c**)[16] (1.80 g, 6.42 mmol) and 1,2,4-trimethoxybenzene (1.01 g, 6.00 mmol). After flash chromatography (P/EA 95/05), the product was obtained (1.46 g, 4.56 mmol, 76%) as a colorless oil. TLC: R_f=0.46 (P/EA 95/05) [CAM, UV]; IR (film): $\tilde{\nu}$ (cm^{-1})=3075 (w, =CH_2), 2927 (v. s, CH_2), 2854 (s, CH_2), 1639 (m, C=C), 1593 (m, C_{ar}=C_{ar}), 1487 (m, CH_2), 1255 (s, COC), 1224 (m), 1162 (s, COC), 1092 (s, COC), 1024 (m); 909 (m, RCH=CH_2), 789 (w, CH), 718 (w, CH_{ar}); ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm)=6.68 (d, ^3J=8.9 Hz, 1H, C_{ar}H), 6.53 (d, ^3J=8.9 Hz, 1H, C_{ar}H), 5.78 (ddt, ^3J=17.1 Hz, ^3J=10.2 Hz, ^3J=6.7 Hz, 1H, CH_2=C*H*R), 4.99–4.94 (m, 1H, H_{trans}CH=CHR), 4.93–4.90 (m, 1H, H_{cis}CH=CHR), 3.81 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 2.61 (v. t, $^3J\cong$7.6 Hz, 2H, CH_2Ar), 2.04 (v. q, $^3J\cong$6.7 Hz, 2H, CH_2=CHCH_2), 1.51–1.27 (m, 14H, CH_2); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ (ppm)=152.5 (C_{ar}OMe), 148.2 (C_{ar}OMe), 147.3 (C_{ar}OMe), 139.4 (HR*C*=CH_2), 126.4 ($C_{ar}CH_2$), 114.4 (HRC=*C*H_2), 109.7 (C_{ar}H), 105.5 (C_{ar}H), 60.9 (OCH_3), 56.3 (OCH_3), 56.0 (OCH_3), 33.9 (CH_2), 30.1 (CH_2), 30.0 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 24.1 (CH_2); MS (EI, 70 eV), *m*/*z* (%): 320 (100) [M^+], 181 (31), 166 (33). Anal. $C_{20}H_{32}O_3$ (320.5): calcd C, 74.96; H, 10.06; found C, 75.03; H: 10.15.

5.1.4. 2-Dodec-11-enyl-1,3,4-trimethoxybenzene (8d). Procedure A was performed with 12-iodododec-1-ene (**7d**)[17] (956 mg, 3.26 mmol) and 1,2,4-trimethoxybenzene (538 mg, 3.20 mmol). After flash chromatography (P/EA 97/03), the product was obtained (778 mg, 2.33 mmol, 73%) as a colorless oil. TLC: R_f=0.81 (P/EA 9/1) [CAM, UV]; IR (film): $\tilde{\nu}$ (cm^{-1})=3075 (w, =CH_2), 2927 (v. s, CH_2), 2854 (s, CH_2), 1639 (m, C=C), 1593 (m, C_{ar}=C_{ar}), 1487 (m, CH_2), 1255 (s, COC), 1224 (m), 1162 (s, COC), 1092 (s, COC), 1024 (m); 909 (m, RCH=CH_2), 789 (w, CH), 718 (w, CH_{ar}); ^{1}H NMR (360 MHz, $CDCl_3$): δ (ppm)=6.69 (d, ^3J=8.8 Hz, 1H, C_{ar}H), 6.54 (d, ^3J=8.8 Hz, 1H, C_{ar}H), 5.81 (ddt, ^3J=17.1 Hz, ^3J=10.2 Hz, ^3J=6.7 Hz, 1H, CH_2=C*H*R), 5.02–4.97 (m, 1H, H_{trans}CH=CHR), 4.95–4.92 (m, 1H, H_{cis}CH=CHR), 3.83 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 2.65 (v. t, $^3J\cong$7.7 Hz, 2H, CH_2Ar), 2.05 (v. q, $^3J\cong$7.0 Hz, 2H, CH_2=CHCH_2), 1.56–1.30 (m, 16H, CH_2); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ (ppm)=152.5 (C_{ar}OMe), 148.2 (C_{ar}OMe), 147.3 (C_{ar}OMe), 139.4 (HR*C*=CH_2), 126.3 ($C_{ar}CH_2$), 114.2 (HRC=*C*H_2), 109.7 (C_{ar}H), 105.4 (C_{ar}H), 60.8 (OCH_3), 56.3 (OCH_3), 55.9 (OCH_3), 33.9 (CH_2), 30.1 (CH_2), 30.0 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 24.1 (CH_2); MS (EI, 70 eV), *m*/*z* (%): 334 (100) [M^+], 181 (59), 166 (47), 151 (8), 121(6), 91 (10), 55 (5). Anal. $C_{21}H_{34}O_3$ (334.5): calcd C, 75.41; H, 10.25; found C, 75.63; H: 10.34.

5.1.5. 1,2,4-Trimethoxy-3-tridec-12-enylbenzene (8e). Procedure A was performed with 13-iodotridec-1-ene (**7e**)[18] (765 mg, 2.48 mmol) and 1,2,4-trimethoxybenzene (378 mg, 2.25 mmol). After flash chromatography (P → P/EA 95/05), the product was obtained (570 mg, 1.64 mmol, 73%) as a colorless oil. TLC: R_f=0.40 (P/EA 95/05) [CAM, UV]; IR (film): $\tilde{\nu}$ (cm^{-1})=3075 (w, =CH_2), 2927 (v. s, CH_2), 2854 (s, CH_2), 1639 (m, C=C), 1593 (m, C_{ar}=C_{ar}), 1487 (m, CH_2), 1255 (s, COC), 1224 (m), 1162 (s, COC), 1092 (s, COC), 1024 (m); 909 (m, RCH=CH_2), 789 (w, CH), 718 (w, CH_{ar}); ^{1}H NMR (360 MHz, $CDCl_3$): δ (ppm)=6.67 (d, ^3J=8.8 Hz, 1H, C_{ar}H), 6.52 (d, ^3J=8.8 Hz, 1H, C_{ar}H), 5.80 (ddt, ^3J=17.1 Hz, ^3J=10.2 Hz, ^3J=6.7 Hz, 1H, CH_2=C*H*R), 4.98–4.93 (m, 1H,

H_{trans}CH=CHR), 4.92–4.89 (m, 1H, H_{cis}CH=CHR), 3.81 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 2.62 (v. t, $^3J\cong7.7$ Hz, 2H, CH_2Ar), 2.04 (v. q, $^3J\cong7.0$ Hz, 2H, CH_2=CHCH_2), 1.56–1.23 (m, 18H, CH_2); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ (ppm)=152.5 (C_{ar}OMe), 148.2 (C_{ar}OMe), 147.3 (C_{ar}OMe), 139.4 (HR*C*=CH_2), 126.3 ($C_{ar}CH_2$), 114.2 (HRC=*C*H_2), 109.7 (C_{ar}H), 105.4 (C_{ar}H), 60.8 (OCH_3), 56.3 (OCH_3), 55.9 (OCH_3), 33.9 (CH_2), 30.1 (CH_2), 30.1 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 24.1 (CH_2); MS (EI, 70 eV), *m*/*z* (%): 348 (100) [M^+], 181 (32), 166 (25), 121 (3). Anal. $C_{22}H_{36}O_3$ (348.5): calcd C, 75.82; H, 10.41; found C, 75.80; H: 10.30.

5.1.6. 1,2,4-Trimethoxy-5-nitro-3-non-8-enylbenzene (9a). Procedure B was performed with 1,2,4-trimethoxy-3-non-8-enylbenzene (**8a**) (1.97 g, 6.73 mmol). After flash chromatography (P/EA 90/10), the product was obtained (1.66 g, 4.93 mmol, 73%) as a yellow oil. TLC: R_f=0.69 (P/EA90/10) [CAM, UV]; IR (film): $\tilde{\nu}$ (cm^{-1})=2919 (v. s, CH_2), 2854 (s, CH_2), 1640 (m, C=C), 1573 (m, C=C), 1523 (s, NO_2), 1480 (s, C=C_{ar}), 1424 (m, CH_2), 1343 (m, CNO_2), 1246 (m, COC), 1108 (m), 1053 (m), 1004 (w, RCH=CH_2), 964 (m), 909 (w, RCH=CH_2), 847 (w, CH_{ar}), 770 (w, CH_{ar}); ^{1}H NMR (360 MHz, $CDCl_3$): δ (ppm)=7.32 (s, 1H, C_{ar}H), 5.76 (ddt, ^3J=17.1 Hz, ^3J=10.2 Hz, ^3J=6.7 Hz, 1H, CH_2=C*H*R), 4.98–4.93 (m, 1H, H_{trans}-CH=CHR), 4.91–4.88 (m, 1H, H_{cis}CH=CHR), 3.89 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 2.62 (v. t, $^3J\cong7.8$ Hz, 2H, CH_2C_{ar}), (v. q, $^3J\cong6.7$ Hz, 2H, CH_2=CHCH_2), 1.28–1.52 (m, 10H, CH_2); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ (ppm)=152.4 (C_{ar}OCH$_3$), 148.5 (C_{ar}OCH$_3$), 147.4 (C_{ar}OCH$_3$), 139.1 (HR*C*=CH_2), 138.0 (C_{ar}), 132.8 (C_{ar}), 114.1 (HRC=*C*H_2), 106.6 (C_{ar}H), 62.6 (OCH_3), 60.9 (OCH_3), 56.1 (OCH_3), 33.7 (CH_2), 30.1 (CH_2), 29.8 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 24.7 (CH_2); MS (EI, 70 eV), *m*/*z* (%): 337 (100) [M^+], 320 (15), 226 (25), 211 (15), 196 (10), 181 (10), 166 (26), 151 (10), 137 (7), 55 (7). Anal. $C_{18}H_{27}NO_5$ (337.4): calcd C, 64.07; H, 8.07; found C, 64.03; H: 7.99.

5.1.7. 3-Dec-9-enyl-1,2,4-trimethoxy-5-nitrobenzene (9b). Procedure B was performed with 2-dec-9-enyl-1,3,4-trimethoxybenzene (**8b**) (2.07 g, 6.76 mmol). After flash chromatography (P/EA 95/5), the product was obtained (2.28 g, 6.49 mmol, 95%) as a yellow oil. TLC: R_f=0.45 (P/EA 90/10) [CAM, UV]; IR (film): $\tilde{\nu}$ (cm^{-1})=2919 (v. s, CH_2), 2854 (s, CH_2), 1640 (m, C=C), 1573 (m, C=C), 1523 (s, NO_2), 1480 (s, C=C_{ar}), 1424 (m, CH_2), 1343 (m, CNO_2), 1246 (m, COC), 1108 (m), 1053 (m), 1004 (w, RCH=CH_2), 964 (m), 909 (w, RCH=CH_2), 847 (w, CH_{ar}), 770 (w, CH_{ar}); ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm)=7.34 (s, 1H, C_{ar}H), 5.78 (ddt, ^3J=17.1 Hz, ^3J=10.2 Hz, ^3J=6.7 Hz, 1H, CH_2=C*H*R), 4.98–4.93 (m, 1H, H_{trans}-CH=CHR), 4.92–4.89 (m, 1H, H_{cis}CH=CHR), 3.90 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 2.64 (v. t, $^3J\cong7.8$ Hz, 2H, CH_2C_{ar}), (v. q, $^3J\cong6.7$ Hz, 2H, CH_2=CHCH_2), 1.28–1.52 (m, 12H, CH_2); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ (ppm)=152.4 (C_{ar}OCH$_3$), 148.5 (C_{ar}OCH$_3$), 147.3 (C_{ar}OCH$_3$), 139.1 (HR*C*=CH_2), 138.5 (C_{ar}), 132.8 (C_{ar}), 114.0 (HRC=*C*H_2), 106.6 (C_{ar}H), 62.6 (OCH_3), 60.9 (OCH_3), 56.1 (OCH_3), 33.7 (CH_2), 30.2 (CH_2), 29.8 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 24.7 (CH_2); MS (EI, 70 eV), *m*/*z* (%): 351 (100) [M^+], 334 (15), 226 (25), 211 (15), 196 (10), 181 (15), 166 (28), 151 (10), 137 (7), 55 (7); HRMS: *m*/*z* calcd for $C_{19}H_{29}NO_5$: 351.2046; found 351.2045.

5.1.8. 1,2,4-Trimethoxy-5-nitro-3-undec-10-enylbenzene (9c). Procedure B was performed with 1, 2, 4-trimethoxy-3-undec-10-enylbenzene (**8c**) (1.38 g, 4.31 mmol). The amount of reagents and solvents was adjusted accordingly. After flash chromatography (P/EA 90/10), the product was obtained (1.54 g, 4.22 mmol, 98%) as a yellow oil. TLC: R_f=0.42 (P/EA90/10) [CAM, UV]; IR (film): $\tilde{\nu}$ (cm^{-1})=2919 (v. s, CH_2), 2854 (s, CH_2), 1640 (m, C=C), 1573 (m, C=C), 1523 (s, NO_2), 1480 (s, C_{ar}=C_{ar}), 1424 (m, CH_2), 1343 (m, CNO_2), 1246 (m, COC), 1108 (m), 1053 (m), 1004 (w, RCH=CH_2), 964 (m), 909 (w, RCH=CH_2), 847 (w, CH_{ar}), 770 (w, CH_{ar}); ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm)=7.35 (s, 1H, C_{ar}H), 5.78 (ddt, ^3J=17.1 Hz, ^3J=10.2 Hz, ^3J=6.7 Hz, 1H, CH_2=C*H*R), 4.98–4.93 (m, 1H, H_{trans}CH=CHR), 4.92–4.89 (m, 1H, H_{cis}CH=CHR), 3.91 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 2.65 (v. t, ^3J=7.8 Hz, 2H, CH_2C_{ar}), 2.04 (v. q, $^3J\cong6.7$ Hz, 2H, CH_2=CHCH_2), 1.50 (m, 2H, CH_2), 1.35–1.23 (m, 12H, CH_2); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ (ppm)=152.4 (C_{ar}OCH$_3$), 148.5 (C_{ar}OCH$_3$), 147.3 (C_{ar}OCH$_3$), 139.1 (HR*C*=CH_2), 138.5 (C_{ar}), 132.8 (C_{ar}), 114.0 (HRC=*C*H_2), 106.6 (C_{ar}H), 62.6 (OCH_3), 60.9 (OCH_3), 56.1 (OCH_3), 33.7 (CH_2), 30.2 (CH_2), 29.8 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 24.7 (CH_2); MS (EI, 70 eV), *m*/*z* (%): 365 (100) [M^+], 348 (20), 226 (36), 211 (17), 196 (18), 181 (24), 166 (28), 151 (10), 137 (10), 107 (9), 97 (8), 91 (8), 55 (20), 41 (15); HRMS: *m*/*z* calcd for $C_{20}H_{31}NO_5$: 365.2202; found 365.2202.

5.1.9. 3-Dodec-11-enyl-1,2,4-trimethoxy-5-nitrobenzene (9d). Procedure B was performed with 2-dodec-11-enyl-1,3,4-trimethoxybenzene (**8d**) (415 mg, 1.24 mmol). After flash chromatography (P/EA 90/10), the product was obtained (448 mg, 1.18 mmol, 95%) as a yellow oil. TLC: R_f=0.60 (P/EA90/10) [CAM, UV]; IR (film): $\tilde{\nu}$ (cm^{-1})=2919 (v. s, CH_2), 2854 (s, CH_2), 1640 (m, C=C), 1573 (m, C=C), 1523 (s, NO_2), 1480 (s, C_{ar}=C_{ar}), 1424 (m, CH_2), 1343 (m, CNO_2), 1246 (m, COC), 1108 (m), 1053 (m), 1004 (w, RCH=CH_2), 964 (m), 909 (w, RCH=CH_2), 847 (w, CH_{ar}), 770 (w, CH_{ar}); ^{1}H NMR (360 MHz, $CDCl_3$): δ (ppm)=7.32 (s, 1H, C_{ar}H), 5.76 (ddt, ^3J=17.1 Hz, ^3J=10.2 Hz, ^3J=6.7 Hz, 1H, CH_2=C*H*R), 4.98–4.93 (m, 1H, H_{trans}CH=CHR), 4.91–4.88 (m, 1H, H_{cis}CH=CHR), 3.88 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 2.62 (v. t, $^3J\cong7.8$ Hz, 2H, CH_2C_{ar}), 2.00 (v. q, $^3J\cong6.7$ Hz, 2H, CH_2=CHCH_2), 1.50 (m, 2H, CH_2), 1.35–1.23 (m, 14H, CH_2); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ (ppm)=152.4 (C_{ar}OCH$_3$), 148.5 (C_{ar}OCH$_3$), 147.3 (C_{ar}OCH$_3$), 139.1 (HR*C*=CH_2), 138.5 (C_{ar}), 132.8 (C_{ar}), 114.0 (HRC=*C*H_2), 106.6 (C_{ar}H), 62.6 (OCH_3), 60.9 (OCH_3), 56.1 (OCH_3), 33.7 (CH_2), 30.2 (CH_2), 29.8 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 24.7 (CH_2); MS (EI, 70 eV), *m*/*z* (%): 379 (100) [M^+], 362 (20), 334 (15), 320 (15), 306 (8), 290 (8), 226 (23), 211 (10), 196 (10), 181 (16), 166 (14), 151 (11), 137 (9), 121 (5), 107 (8), 97 (8), 91 (8), 83 (5), 55 (14), 41 (14). Anal. $C_{21}H_{33}NO_5$ (379.5): calcd C, 66.68; H, 8.86; found C, 66.46; H: 8.76.

5.1.10. 1,2,4-Trimethoxy-5-nitro-3-tridec-12-enylbenzene (9e). Procedure B was performed with 1,2,4-trimethoxy-3-tridec-12-enylbenzene (**8e**) (458 mg, 1.31 mmol). After flash chromatography (P/EA 90/10), the product was obtained (484 mg, 1.23 mmol, 94%) as a yellow oil. TLC: R_f=0.67 (P/EA 90/10) [CAM, UV]; IR (film): $\tilde{\nu}$ (cm^{-1})=2919 (v. s, CH_2), 2854 (s, CH_2), 1640 (m, C=C), 1573 (m, C=C), 1523 (s, NO_2), 1480 (s, C_{ar}=C_{ar}), 1424 (m, CH_2), 1343 (m, CN), 1246 (m, COC), 1108 (m), 1053 (m), 1004 (w, RCH=CH_2), 964 (m), 909 (w, RCH=CH_2), 847 (w, CH_{ar}), 770 (w, CH_{ar}); ^{1}H NMR (360 MHz, $CDCl_3$): δ (ppm)=7.32 (s, 1H, $C_{ar}H$), 5.79 (ddt, ^3J=17.1 Hz, ^3J=10.2 Hz, ^3J=6.7 Hz, 1H, CH_2=C*H*R), 4.98–4.93 (m, 1H, H_{trans}CH=CHR), 4.92–4.89 (m, 1H, H_{cis}CH=CHR), 3.89 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 2.62 (v. t, $^3J\cong$7.8 Hz, 2H, CH_2C_{ar}), 2.00 (v. q, $^3J\cong$6.7 Hz, 2H, CH_2=CHCH_2), 1.50 (m, 2H, CH_2), 1.35–1.23 (m, 16H, CH_2); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ (ppm)=152.4 ($C_{ar}OCH_3$), 148.5 ($C_{ar}OCH_3$), 147.5 ($C_{ar}OCH_3$), 139.2 (HR*C*=CH_2), 138.5 (C_{ar}), 132.9 (C_{ar}), 114.0 (HRC=*C*H_2), 106.7 ($C_{ar}H$), 62.7 (OCH_3), 61.0 (OCH_3), 56.2 (OCH_3), 33.8 (CH_2), 30.2 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 24.7 (CH_2); MS (EI, 70 eV), *m/z* (%): 393 (100) [M^+], 376 (20), 359 (15), 348 (8), 226 (21), 196 (10), 181 (14), 166 (8), 151 (8), 123 (6), 95 (5), 69 (5), 55 (14), 41 (8). Anal. $C_{22}H_{35}NO_5$ (393.5): calcd C, 67.15; H, 9.05; found C, 67.58; H: 8.96.

5.1.11. 2,4,5-Trimethoxy-3-non-8-enylphenylamine (10a). Procedure C was performed using the nitro arene **9a** (215 mg, 0.64 mmol). After flash chromatography (P/EA 90/10), the product was obtained (162 mg, 0.52 mmol, 82%) as a colorless oil. TLC: R_f=0.16 (P/EA 90/10) [CAM, UV]; IR (film): $\tilde{\nu}$ (cm^{-1})=3430 (w, NH_2), 3358 (m, NH_2), 3095 (w, =CH_2), 2926 (v. s, CH_2), 2854 (s, CH_2), 1614 (m, N–H), 1490 (m, CH_2), 1363 (s, COC), 1224 (s), 1120 (m, COC), 1058 (m), 1011 (m, RCH=CH_2), 909 (w, RCH=CH_2), 821 (w, CH); ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm)=6.18 (s, 1H, $C_{ar}H$), 5.76 (ddt, ^3J=17.1 Hz, ^3J=10.2 Hz, ^3J=6.7 Hz, 1H, CH_2=C*H*R), 4.98–4.93 (m, 1H, H_{trans}CH=CHR), 4.92–4.89 (m, 1H, H_{cis}CH=CHR), 3.74 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 3.50 (br. s, 2H, NH_2), 2.53 (v. t, $^3J\cong$7.9 Hz, 2H, CH_2C_{ar}), 2.00 (v. q, $^3J\cong$6.9 Hz, 2H, CH_2=CHCH_2), 1.52 (m, 2H, CH_2), 1.33–1.25 (m, 8H, CH_2); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ (ppm)=149.5 ($C_{ar}OCH_3$), 139.5 (HR*C*=CH_2), 139.1 ($C_{ar}OCH_3$), 138.9 ($C_{ar}OCH_3$), 135.6 (C_{ar}), 130.3 (C_{ar}), 114.0 (HRC=*C*H_2), 98.5 ($C_{ar}H$), 60.8 (OCH_3), 59.9 (OCH_3), 55.7 (OCH_3), 33.7 (CH_2), 30.6 (CH_2), 29.9 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 24.7 (CH_2); MS (EI, 70 eV), *m/z* (%): 307 (100) [M^+], 292 (87), 208 (5), 192 (8), 182 (17), 167 (25), 152 (10), 138 (17), 122 (10), 55 (7). Anal. $C_{18}H_{29}NO_3$ (307.4): calcd C, 70.32; H, 9.51; found C, 69.99; H: 9.46.

5.1.12. 2,4,5-Trimethoxy-3-dec-9-enylphenylamine (10b). Procedure C was performed using the nitro arene **9b** (1.99 g, 5.67 mmol). After flash chromatography (P/EA 75/25), the product was obtained (1.40 g, 4.37 mmol, 77%) as a light brown oil. TLC: R_f=0.47 (P/EA 75/25) [CAM, UV]; IR (film): $\tilde{\nu}$ (cm^{-1})=3430 (w, NH_2), 3358 (m, NH_2), 3095 (w, =CH_2), 2926 (v. s, CH_2), 2854 (s, CH_2), 1614 (m, N–H), 1490 (m, CH_2), 1363 (s, COC), 1224 (s), 1120 (m, COC), 1058 (m), 1011 (m, RCH=CH_2), 909 (w, RCH=CH_2), 821 (w, CH); ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm)=6.21 (s, 1H, $C_{ar}H$), 5.80 (ddt, ^3J=17.1 Hz, ^3J=10.2 Hz, ^3J=6.7 Hz, 1H, CH_2=C*H*R), 4.97–4.92 (m, 1H, H_{trans}CH=CHR), 4.91–4.88 (m, 1H, H_{cis}CH=CHR), 3.77 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.63 (br. s, 2H, NH_2), 2.58 (v. t, $^3J\cong$7.9 Hz, 2H, CH_2C_{ar}), 2.02 (v. q, $^3J\cong$6.9 Hz, 2H, CH_2=CHCH_2), 1.52 (m, 2H, CH_2), 1.33–1.25 (m, 10H, CH_2); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ (ppm)=150.0 ($C_{ar}OCH_3$), 139.9 ($C_{ar}OCH_3$), 138.6 ($C_{ar}OCH_3$), 139.3 (HR*C*=CH_2), 136.0 (C_{ar}), 130.8 (C_{ar}), 114.4 (HRC=*C*H_2), 98.8 ($C_{ar}H$), 61.3 (OCH_3), 60.4 (OCH_3), 56.2 (OCH_3), 34.2 (CH_2), 31.2 (CH_2), 30.4 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 25.1 (CH_2); MS (EI, 70 eV), *m/z* (%): 321 (100) [M^+], 306 (90), 192 (5), 182 (28), 167 (18), 152 (12), 138 (12), 122 (9). Anal. $C_{19}H_{31}NO_3$ (321.4): calcd C, 70.99; H, 9.72; found C, 71.00; H: 9.70.

5.1.13. 2,4,5-Trimethoxy-3-undec-10-enylphenylamine (10c). Procedure C was performed using the nitro arene **9c** (2.30 g, 6.30 mmol). The amount of reagents and solvents was adjusted accordingly. After flash chromatography (P/EA 90/10), the product was obtained (1.77 g, 5.29 mmol, 84%) as a light brown oil. TLC: R_f=0.16 (P/EA 90/10) [CAM, UV]; IR (film): $\tilde{\nu}$ (cm^{-1})=3430 (w, NH_2), 3358 (m, NH_2), 3095 (w, =CH_2), 2926 (v. s, CH_2), 2854 (s, CH_2), 1614 (m, N–H), 1490 (m, CH_2), 1363 (s, COC), 1224 (s), 1120 (m, COC), 1058 (m), 1011 (m, RCH=CH_2), 909 (w, RCH=CH_2), 821 (w, CH); ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm)=6.19 (s, 1H, $C_{ar}H$), 5.75 (ddt, ^3J=17.1 Hz, ^3J=10.2 Hz, ^3J=6.7 Hz, 1H, CH_2=C*H*R), 4.97–4.92 (m, 1H, H_{trans}CH=CHR), 4.91–4.88 (m, 1H, H_{cis}CH=CHR), 3.75 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 3.49 (br. s, 2H, NH_2), 2.56–2.54 (m, 2H, CH_2C_{ar}), 2.00 (v. q, $^3J\cong$6.9 Hz, 2H, CH_2=CHCH_2), 1.53–1.51 (m, 2H, CH_2), 1.35–1.26 (m, 12H, CH_2); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ (ppm)=150.0 ($C_{ar}OCH_3$), 139.9 ($C_{ar}CH_3$), 139.6 (HR*C*=CH_2), 139.3 ($C_{ar}OCH_3$), 136.0 (C_{ar}), 130.8 (C_{ar}), 114.6 (HRC=*C*H_2), 98.8 ($C_{ar}H$), 61.3 (OCH_3), 60.4 (OCH_3), 56.2 (OCH_3), 34.2 (CH_2), 31.2 (CH_2), 30.5 (CH_2), 29.9 (2CH_2), 29.8 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 25.1 (CH_2); MS (EI, 70 eV), *m/z* (%): 335 (100) [M^+], 306 (78), 182 (18), 167 (20), 152 (10), 138 (10), 122 (9). Anal. $C_{20}H_{33}NO_3$ (335.5): calcd C, 71.60; H, 9.91; found C, 71.53; H: 9.86.

5.1.14. 2,4,5-Trimethoxy-3-dodec-11-enylphenylamine (10d). Procedure C was performed using the nitro arene **9d** (448 mg, 1.18 mmol). After flash chromatography (P/EA 90/10), the product was obtained (326 mg, 0.93 mmol, 79%) as a transparent oil. TLC: R_f=0.15 (P/EA 90/10) [CAM, UV]; IR (film): $\tilde{\nu}$ (cm^{-1})=3450 (w, NH_2), 3358 (m, NH_2), 3095 (w, =CH_2), 2926 (v. s, CH_2), 2854 (S, CH_2), 1614 (m, NH), 1490 (m, CH_2), 1363 (S, COC), 1224 (S), 1120 (m, COC), 1058 (m), 1011 (m, RCH=CH_2), 909 (w, RCH=CH_2), 821 (w, CH); ^{1}H NMR (360 MHz, $CDCl_3$): δ (ppm)=6.19 (s, 1H, $C_{ar}H$), 5.79 (ddt, ^3J=17.1 Hz, ^3J=10.2 Hz, ^3J=6.7 Hz, 1H, CH_2=C*H*R), 4.99–4.94 (m, 1H, H_{trans}CH=CHR), 4.92–4.89 (m, 1H, H_{cis}CH=CHR), 3.75 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 3.60 (br. s, 2H, NH_2), 2.58–2.56 (m, 2H, CH_2C_{ar}), 2.00 (v. q,

$^3J \cong 6.9$ Hz, 2H, CH_2=CHCH_2), 1.53–1.51 (m, 2H, CH_2), 1.35–1.25 (m, 14H, CH_2); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ (ppm) = 149.6 ($C_{ar}OCH_3$), 139.6 ($C_{ar}OCH_3$), 139.2 (HR*C*=CH_2), 139.0 ($C_{ar}OCH_3$), 135.6 (C_{ar}), 130.4 (C_{ar}), 114.0 (HRC=*C*H_2), 98.5 (C_{ar}H), 60.9 (OCH_3), 59.7 (OCH_3), 55.8 (OCH_3), 33.7 (CH_2), 30.7 (CH_2), 30.0 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (2 CH_2), 29.1 (CH_2), 28.9 (CH_2), 25.1 (CH_2); MS (EI, 70 eV), *m/z* (%): 349 (100) [M^+], 334 (66), 182 (18), 167 (12), 152 (6), 138 (6), 122 (6). Anal. $C_{21}H_{35}NO_3$ (349.5): calcd C, 72.17; H, 10.09; found C, 72.28; H: 10.06.

5.1.15. 2,4,5-Trimethoxy-3-tridec-12-enylphenylamine (10e). Procedure C was performed using the nitro arene **9e** (210 mg, 0.53 mmol). After flash chromatography (P/EA 80/20), the product was obtained (159 mg, 0.44 mmol, 83%) as a transparent oil. TLC: R_f = 0.21 (P/EA 80/20) [CAM, UV]; IR (film): $\tilde{\nu}$ (cm^{-1}) = 3450 (w, NH), 3358 (m, NH), 3095 (w, =CH_2), 2926 (v. s, CH_2), 2854 (s, CH_2), 1614 (m, N–H), 1490 (m, CH_2), 1363 (s, COC), 1224 (s), 1120 (m, COC), 1058 (m), 1011 (m, RCH=CH_2), 909 (w, RCH=CH_2), 821 (w, CH); ^{1}H NMR (360 MHz, $CDCl_3$): δ (ppm) = 6.19 (s, 1H, C_{ar}H), 5.79 (ddt, ^3J = 17.1 Hz, ^3J = 10.2 Hz, ^3J = 6.7 Hz, 1H, CH_2=C*H*R), 4.99–4.94 (m, 1H, H_{trans}CH=CHR), 4.93–4.90 (m, 1H, H_{cis}CH=CHR), 3.73 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 3.64 (s, 3H, OCH_3), 3.60 (br. s, 2H, NH_2), 2.57–2.55 (m, 2H, CH_2C_{ar}), 2.00 (v. q, $^3J \cong 6.9$ Hz, 2H, CH_2=CHCH_2), 1.53–1.51 (m, 2H, CH_2), 1.35–1.26 (m, 16H, CH_2); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ (ppm) = 149.6 ($C_{ar}OCH_3$), 139.7 ($C_{ar}OCH_3$), 139.2 (HR*C*=CH_2), 139.0 ($C_{ar}OCH_3$), 135.6 (C_{ar}), 130.5 (C_{ar}), 114.0 (HRC=*C*H_2), 98.5 (C_{ar}H), 60.9 (OCH_3), 60.0 (OCH_3), 55.8 (OCH_3), 33.8 (CH_2), 30.7 (CH_2), 30.1 (CH_2), 29.7 (CH_2), 29.6 (2 CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 24.8 (CH_2); MS (EI, 70 eV), *m/z* (%): 363 (100) [M^+], 348 (54), 182 (18), 167 (12), 152 (8), 138 (8), 122 (8), 55 (6), 41 (6) [$C_3H_4^+$]. Anal. $C_{22}H_{37}NO_3$ (363.5): calcd C, 72.69; H, 10.26; found C, 72.57; H: 10.28.

5.1.16. 2-Methylpenta-2,4-dienoic acid (2,4,5-trimethoxy-3-non-8-enylphenyl)-amide (11a). Procedure D was performed with the aniline **10a** (50 mg, 163 μmol). After flash chromatography (P/EA 80/20), the product was obtained (47 mg, 117 μmol, 72%) as a light yellow oil. TLC: R_f = 0.32 (P/EA 90/10) [CAM, UV]; IR (film): $\tilde{\nu}$ (cm^{-1}) = 3436 (m, NH), 2926 (v. s, CH_2), 2854 (s, CH_2), 1673 (s, C=O), 1600 (m, C=C), 1514 (s), 1455 (s), 1410 (s), 1221 (s, CN), 1171 (m), 1104 (s), 1058 (s), 1007 (s, RCH=CH_2), 909 (m, RCH=CH_2), 851 (m, CH); ^{1}H NMR (360 MHz, $CDCl_3$): δ (ppm) = 8.07 (s, 1H, NH), 8.00 (s, 1H, C_{ar}H), 7.01 [d, ^3J = 10.2 Hz, 1H, CH_2=CH–C*H*=C(CO)], 6.68 (ddd, ^3J = 16.7 Hz, ^3J = 10.2 Hz, ^3J = 10.0 Hz, 1H, CH_2=C*H*–CH=C), 5.80 (ddt, ^3J = 17.1 Hz, ^3J = 10.2 Hz, ^3J = 6.7 Hz, 1H, CH_2=C*H*R), 5.56 (d, ^3J = 16.7 Hz, 1H, H_{trans}CH=CH–CH=C), 5.45 (d, ^3J = 10.2 Hz, 1H, H_{cis}-CH=CH–CH=C), 4.99–4.93 (m, 1H, H_{trans}CH=CHR), 4.91–4.88 (m, 1H, H_{cis}CH=CHR), 3.86 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 2.62 (v. t, $^3J \cong 6.4$ Hz, 2H, CH_2C_{ar}), 2.09 (d, ^4J = 0.9 Hz, 3H, =CCH_3), 2.03 (v. q, $^3J \cong 7.0$ Hz, 2H, CH_2=CHCH_2), 1.57–1.31 (m, 10H, CH_2); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ (ppm) = 166.6 (C=O), 149.2 ($C_{ar}OCH_3$), 143.5 ($C_{ar}OCH_3$), 141.0 ($C_{ar}OCH_3$), 139.2 (HR*C*=CH_2), 134.5 (C_{olef}H), 131.9 (C_{olef}H), 131.3 (C_{ar}), 129.5 (C_{ar}), 127.4 (=*C*CH_3), 123.5 (=CH–HC=*C*H_2), 114.1 (HRC=*C*H_2), 102.8 (C_{ar}H), 61.4 (OCH_3), 60.8 (OCH_3), 55.9 (OCH_3), 33.8 (CH_2), 30.5 (CH_2), 29.9 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 24.7 (CH_2), 13.0 (CH_3); MS (EI, 70 eV), *m/z* (%): 401 (100) [M^+], 386 (8), 370 (10), 153 (7), 95 (66), 67 (20); HRMS: *m/z* calcd for $C_{24}H_{35}NO_4$: 401.2566; found 401.2566.

5.1.17. 2-Methylpenta-2,4-dienoic acid (3-dec-9-enyl-2,4,5-trimethoxyphenyl)-amide (11b). Procedure D was performed with the aniline **10b** (122 mg, 380 μmol). After flash chromatography (P/EA 95/05), the product was obtained (92 mg, 221 μmol, 58%) as a light brown oil. TLC: R_f = 0.32 (P/EA 90/10) [CAM, UV]; IR (film): $\tilde{\nu}$ (cm^{-1}) = 3436 (m, NH), 2926 (v. s, CH_2), 2854 (s, CH_2), 1673 (s, C=O), 1600 (m, C=C), 1514 (s), 1455 (s), 1410 (s), 1221 (s, CN), 1171 (m), 1104 (s), 1058 (s), 1007 (s, RCH=CH_2), 909 (m, RCH=CH_2), 851 (m, CH); ^{1}H NMR (360 MHz, $CDCl_3$): δ (ppm) = 8.07 (s, 1H, NH), 8.00 (s, 1H, C_{ar}H), 7.01 [d, ^3J = 11.1 Hz, 1H, CH_2=CH–C*H*=C(CO)], 6.68 (ddd, ^3J = 16.8 Hz, ^3J = 11.1 Hz, ^3J = 10.1 Hz, 1H, CH_2=C*H*–CH=C), 5.80 (ddt, ^3J = 17.1 Hz, ^3J = 10.2 Hz, ^3J = 6.7 Hz, 1H, CH_2=C*H*R), 5.56 (d, ^3J = 16.8 Hz, 1H, H_{trans}CH=CH–CH=C), 5.45 (d, ^3J = 10.2 Hz, 1H, H_{cis}-CH=CH–CH=C), 4.98 (m, 1H, H_{trans}CH=CHR), 4.90 (m, 1H, H_{cis}CH=CHR), 3.86 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 2.62 (t, ^3J = 6.4 Hz, 2H, CH_2C_{ar}), 2.09 (br. s, 3H, =CCH_3), 2.03 (v. q, $^3J \cong 7.0$ Hz, 2H, CH_2=CHCH_2), 1.58–1.53 (m, 2H, CH_2), 1.37–1.30 (m, 10H, CH_2); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ (ppm) = 166.6 (C=O), 149.2 ($C_{ar}OCH_3$), 143.5 ($C_{ar}OCH_3$), 141.0 ($C_{ar}OCH_3$), 139.2 (HR*C*=CH_2), 134.5 (C_{olef}H), 131.9 (C_{olef}H), 131.3 (C_{ar}), 129.5 (C_{ar}), 127.3 (=*C*CH_3), 123.5 (=CH–HC=*C*H_2), 114.1 (HRC=*C*H_2), 102.7 (C_{ar}H), 61.4 (OCH_3), 60.8 (OCH_3), 55.9 (OCH_3), 33.8 (CH_2), 30.5 (CH_2), 30.0 (CH_2), 29.4 (2 CH_2), 29.1 (CH_2), 28.9 (CH_2), 24.7 (CH_2), 13.0 (CH_3); MS (EI, 70 eV), *m/z* (%): 415 (100) [M^+], 384 (10), 332 (5), 166 (6), 95 (57), 67 (17). Anal. $C_{25}H_{37}NO_4$ (415.6): calcd C, 72.26; H, 8.97; found C, 72.15; H: 8.85.

5.1.18. 2-Methylpenta-2,4-dienoic acid (2,4,5-trimethoxy-3-undec-10-enylphenyl)-amide (11c). Procedure D was performed with the aniline **10c** (200 mg, 597 μmol). After flash chromatography (P/EA 90/10), the product was obtained (169 mg, 393 μmol, 66%) as a light brown oil. TLC: R_f = 0.33 (P/EA 90/10) [CAM, UV]; IR (film): $\tilde{\nu}$ (cm^{-1}) = 3436 (m, NH), 2926 (v. s, CH_2), 2854 (s, CH_2), 1673 (s, C=O), 1600 (m, C=C), 1514 (s), 1455 (s), 1410 (s), 1221 (s, CN), 1171 (m), 1104 (s), 1058 (s), 1007 (s, RCH=CH_2), 909 (m, RCH=CH_2), 851 (m, CH); ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 8.08 (s, 1H, NH), 7.99 (s, 1H, C_{ar}H), 7.02 [d, ^3J = 11.1 Hz, 1H, CH_2=CH–C*H*=C(CO)], 6.67 (ddd, ^3J = 16.8 Hz, ^3J = 11.1 Hz, ^3J = 10.1 Hz, 1H, CH_2=C*H*–CH=C), 5.80 (ddt, ^3J = 17.1 Hz, ^3J = 10.2 Hz, ^3J = 6.7 Hz, 1H, CH_2=C*H*R), 5.55 (d, ^3J = 16.8 Hz, 1H, H_{trans}CH=CH–CH=C), 5.46 (d, ^3J = 10.2 Hz, 1H, H_{cis}-CH=CH–CH=C), 4.97 (m, 1H, H_{trans}CH=CHR), 4.91 (m, 1H, H_{cis}CH=CHR), 3.86 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 2.61 (t, ^3J = 6.4 Hz, 2H, CH_2C_{ar}), 2.09 (br. s, 3H, =CCH_3), 2.02 (v. q, $^3J \cong 7.0$ Hz, 2H, CH_2=CHCH_2), 1.60–1.54 (m, 2H, CH_2), 1.35–1.27 (m,

12H, CH_2); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ (ppm)=166.9 (C=O), 149.6 ($C_{ar}OCH_3$), 143.9 ($C_{ar}OCH_3$), 141.4 ($C_{ar}OCH_3$), 139.6 (HR*C*=CH_2), 135.0 ($C_{olef}H$), 132.3 ($C_{olef}H$), 131.7 (C_{ar}), 130.0 (C_{ar}), 127.7 (=*C*CH_3), 124.0 (=CH–HC=*C*H_2), 114.4 (HRC=*C*H_2), 103.1 ($C_{ar}H$), 61.8 (OCH_3), 61.3 (OCH_3), 56.2 (OCH_3), 34.2 (CH_2), 31.0 (CH_2), 30.4 (CH_2), 29.9 (2 CH_2), 29.8 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 25.1 (CH_2), 13.4 (CH_3); MS (EI, 70 eV), *m*/*z* (%): 429 (95) [M^+], 414 (15), 398 (10), 346 (9), 320 (9), 167 (6), 95 (100), 67 (26), 41 (6). Anal. $C_{26}H_{39}NO_4$ (429.6): calcd C, 72.69; H, 9.15; found C, 72.59; H: 9.01.

5.1.19. 2-Methylpenta-2,4-dienoic acid (2,4,5-trimethoxy-3-dodec-11-enylphenyl)-amide (11d). Procedure D was performed with the aniline **10d** (191 mg, 547 μmol). The amount of reagents and solvents was adjusted accordingly. After flash chromatography (P/EA 90/10), the product was obtained (165 mg, 372 μmol, 68%) as a light brown oil. TLC: R_f=0.38 (P/EA 90/10) [CAM, UV]; IR (film): $\tilde{\nu}$ (cm^{-1})=3436 (m, NH), 2926 (v. s, CH_2), 2854 (s, CH_2), 1673 (s, C=O), 1600 (m, C=C), 1514 (s), 1455 (s), 1410 (s), 1221 (s, CN), 1171 (m), 1104 (s), 1058 (s), 1007 (s, RCH=CH_2), 909 (m, RCH=CH_2), 851 (m, CH); ^1H NMR (360 MHz, $CDCl_3$): δ (ppm)=8.03 (s, 1H, NH), 7.96 (s, 1H, $C_{ar}H$), 6.97 [d, ^3J=11.1 Hz, 1H, CH_2=CH–C*H*=C(CO)], 6.66 (ddd, ^3J=16.8 Hz, ^3J=11.1 Hz, ^3J=10.1 Hz, 1H, CH_2=C*H*–CH=C), 5.78 (ddt, ^3J=17.1 Hz, ^3J=10.2 Hz, ^3J=6.7 Hz, 1H, CH_2=C*H*R), 5.55 (d, ^3J=16.8 Hz, 1H, H_{trans}CH=CH–CH=C), 5.46 (d, ^3J=10.2 Hz, 1H, H_{cis}-CH=CH–CH=C), 4.97–4.91 (m, 1H, H_{trans}CH=CHR), 4.89–4.86 (m, 1H, H_{cis}CH=CHR), 3.82 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 2.58 (v. t, $^3J\cong$6.4 Hz, 2H, CH_2C_{ar}), 2.06 (br. s, 3H, =CCH_3), 2.02 (v. q, $^3J\cong$7.0 Hz, 2H, CH_2=CHCH_2), 1.53 (m, 2H, CH_2), 1.35–1.27 (m, 14H, CH_2); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ (ppm)=166.4 (C=O), 149.2 ($C_{ar}OCH_3$), 143.5 ($C_{ar}OCH_3$), 141.0 ($C_{ar}OCH_3$), 139.1 (HR*C*=CH_2), 134.4 ($C_{olef}H$), 131.9 ($C_{olef}H$), 131.3 (C_{ar}), 129.4 (C_{ar}), 127.3 (=*C*CH_3), 123.4 (=CH–HC=*C*H_2), 114.0 (HRC=*C*H_2), 102.7 ($C_{ar}H$), 61.3 (OCH_3), 60.7 (OCH_3), 55.8 (OCH_3), 33.7 (CH_2), 30.4 (CH_2), 29.9 (CH_2), 29.5 (CH_2), 29.4 (2 CH_2), 29.3 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 24.7 (CH_2), 12.9 (CH_3); MS (EI, 70 eV), *m*/*z* (%): 443 (100) [M^+], 428 (10), 95 (80), 67 (12), 40 (6). Anal. $C_{27}H_{41}NO_4$ (443.6): calcd C, 73.10; H, 9.32; found C, 73.05; H: 9.41.

5.1.20. 2-Methylpenta-2,4-dienoic acid (2,4,5-trimethoxy-3-tridec-12-enylphenyl)-amide (11e). Procedure D was performed with the aniline **10e** (131 mg, 361 μmol). After flash chromatography (P/EA 90/10), the product was obtained (105 mg, 229 μmol, 63%) as a light brown oil. TLC: R_f=0.33 (P/EA 90/10) [CAM, UV]; IR (film): $\tilde{\nu}$ (cm^{-1})=3436 (m, NH), 2926 (v. s, CH_2), 2854 (s, CH_2), 1673 (s, C=O), 1600 (m, C=C), 1514 (s), 1455 (s), 1410 (s), 1221 (s, C–N), 1171 (m), 1104 (s), 1058 (s), 1007 (s, RCH=CH_2), 909 (m, RCH=CH_2), 851 (m, CH); ^1H NMR (360 MHz, $CDCl_3$): δ (ppm)=8.05 (s, 1H, NH), 7.98 (s, 1H, $C_{ar}H$), 6.98 [d, ^3J=11.1 Hz, 1H, CH_2=CH–C*H*=C(CO)], 6.67 (ddd, ^3J=16.8 Hz, ^3J=11.1 Hz, ^3J=10.1 Hz, 1H, CH_2=C*H*–CH=C), 5.80 (ddt, ^3J=17.1 Hz, ^3J=10.2 Hz, ^3J=6.7 Hz, 1H, CH_2=C*H*R), 5.55 (d, ^3J=16.8 Hz, 1H, H_{trans}CH=CH–CH=C), 5.46 (d, ^3J=10.2 Hz, 1H, H_{cis}-CH=CH–CH=C), 4.99–4.93 (m, 1H, H_{trans}CH=CHR), 4.92–4.88 (m, 1H, H_{cis}CH=CHR), 3.84 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 2.61 (t, ^3J=6.4 Hz, 2H, CH_2C_{ar}), 2.08 (d, ^4J=1.1 Hz, 3H, =CCH_3), 2.02 (v. q, $^3J\cong$7.0 Hz, 2H, CH_2=CHCH_2), 1.56–1.49 (m, 2H, CH_2), 1.35–1.27 (m, 16H, CH_2); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ (ppm)=166.6 (C=O), 149.3 ($C_{ar}OCH_3$), 143.6 ($C_{ar}OCH_3$), 141.1 ($C_{ar}OCH_3$), 139.2 (HR*C*=CH_2), 134.5 ($C_{olef}H$), 132.0 ($C_{olef}H$), 131.4 (C_{ar}), 129.6 (C_{ar}), 127.4 (=*C*CH_3), 123.5 (=CH–HC=*C*H_2), 114.0 (HRC=*C*H_2), 102.8 ($C_{ar}H$), 61.4 (OCH_3), 60.9 (OCH_3), 55.9 (OCH_3), 33.8 (CH_2), 30.6 (CH_2), 30.0 (CH_2), 29.7 (CH_2), 29.6 (2 CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 24.8 (CH_2), 13.0 (CH_3); MS (EI, 70 eV), *m*/*z* (%): 457 (100) [M^+], 442 (10), 426 (8), 374 (5), 167 (6), 149 (8), 95 (74), 67 (12), 57 (6), 40 (6). Anal. $C_{28}H_{43}NO_4$ (457.6): calcd C, 73.48; H, 9.47; found C, 73.53; H: 9.30.

5.1.21. (4*E*,6*Z*)-18,19,21-Trimethoxy-4-methyl-2-azabicyclo[15.3.1]henicosa-1(21),4,6,17,19-pentaen-3-one (12c). Procedure E was performed with the anilide **11c** (50 mg, 116 μmol) and Grubbs catalyst (9.5 mg, 11.5 μmol, 10 mol%) in DCM (230 mL). After flash chromatography (P/EA 90/10), the product was obtained (31 mg, 77 μmol, 66%) as a white solid. Starting material was isolated (7 mg, 16 μmol, 14%). TLC: R_f=0.32 (P/EA 90/10) [CAM, UV]; ^1H NMR (360 MHz, $CDCl_3$): δ (ppm)=8.35 (s br, 1H, NH), 8.01 (s, 1H, $C_{ar}H$), 7.01 [d, ^3J=11.3 Hz, 1H, CH=CH–C*H*=C(CO)], 6.28 [v. t, $^3J\cong$10.9 Hz, 1H, CH=C*H*–CH=C(CO)], 5.97 [v. q, $^3J\cong$9.1 Hz, 1H, C*H*=CH–CH=C(CO)], 3.85 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 2.61 (br, 1H, CH_2), 2.09 (br, 1H, CH_2), 2.02 (br. s, 3H, =CCH_3), 1.58–1.10 (m, 16H, CH_2); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ (ppm)=168.6 (C=O), 149.5 ($C_{ar}OCH_3$), 142.8 ($C_{ar}OCH_3$), 141.2 ($C_{ar}OCH_3$), 138.5 ($C_{olef}H$), 133.2 (C_{ar}), 128.8 (C_{ar}), 127.9 (=*C*CH_3), 127.4 ($C_{olef}H$), 123.7 ($C_{olef}H$), 100.7 ($C_{ar}H$), 61.3 (OCH_3), 61.0 (OCH_3), 55.9 (OCH_3), 30.1 (CH_2), 30.0 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 28.7 (CH_2), 28.0 (CH_2), 27.4 (CH_2), 25.9 (CH_2), 22.1 (CH_2), 12.4 (CH_3); MS (EI, 70 eV), *m*/*z* (%): 401 (100) [M^+], 386 (22), 370 (50), 206 (6), 182 (7), 167 (8), 152 (7). Anal. $C_{24}H_{35}NO_4$ (401.5): calcd C, 71.79; H, 8.79; found C, 71.77; H: 8.66.

5.1.22. (4*E*,6*Z*)-19,20,22-Trimethoxy-4-methyl-2-azabicyclo[16.3.1]docosa-1(22),4,6,18,20-pentaen-3-one (12d). Procedure E was performed with the anilide **11d** (50 mg, 112 μmol) and Grubbs catalyst (9.0 mg, 11.2 μmol, 10 mol%) in DCM (220 mL). After flash chromatography (P/EA 90/10), the product was obtained (35 mg, 86 μmol, 77%) as a transparent to light green transparent oil. TLC: R_f=0.29 (P/EA/DCM 50/10/50) [CAM, UV]; IR (film): $\tilde{\nu}$ (cm^{-1})=3428 (br, NH), 2974 (s, CH_3), 2926 (v. s, CH_2), 2854 (v. s, CH_2), 1667 (s, C=O), 1592 (m, C=C), 1504 (s, NH), 1434 (s, C=C), 1229 (m), 1105 (s, C–O–C), 1027 (m), 954 (w), 909 (w), 852 (w), 734 (w); ^1H NMR (360 MHz, $CDCl_3$): δ (ppm)=8.23 (br. s, 1H, NH), 7.95 (s, 1H, $C_{ar}H$), 6.99 [d, ^3J=11.3 Hz, 1H, CH=CH–C*H*=C(CO)], 6.32 [v. t, $^3J\cong$10.9 Hz, 1H, CH=C*H*–CH=C(CO)], 5.96 [v. q, $^3J\cong$9.1 Hz, 1H, C*H*=CH–CH=C(CO)], 3.87 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3), 2.70 (t, ^3J=6.5 Hz, 2H, CH_2), 2.21 (v. q, $^3J\cong$8.0 Hz, 2H, CH_2), 2.04 (d, ^4J=0.7 Hz, 3H, =CCH_3), 1.68–1.65 (m, 2H, CH_2), 1.47–1.10 (m, 14H, CH_2); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ

(ppm) = 168.4 (C=O), 149.4 ($C_{ar}OCH_3$), 143.3 ($C_{ar}OCH_3$), 141.2 ($C_{ar}OCH_3$), 137.9 ($C_{olef}H$), 133.5 (C_{ar}), 128.8 (C_{ar}), 127.6 (=CCH_3), 126.7 ($C_{olef}H$), 124.1 ($C_{olef}H$), 101.4 ($C_{ar}H$), 61.3 (OCH_3), 60.9 (OCH_3), 55.9 (OCH_3), 29.7 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 28.8 (CH_2), 28.6 (CH_2), 28.5 (CH_2), 28.1 (CH_2), 27.4 (CH_2), 27.2 (CH_2), 22.1 (CH_2), 12.6 (CH_3); MS (EI, 70 eV), *m/z* (%): 415 (100) [M^+], 400 (22), 384 (23), 182 (6), 167 (8), 152 (6). Anal. $C_{25}H_{37}NO_4$ (415.6): calcd C, 72.26; H, 8.97; found C, 72.42; H: 9.11.

5.1.23. (4*E*,6*Z*)-20,21,23-Trimethoxy-4-methyl-2-aza-bicyclo[17.3.1]tricosa-1(23),4,6,19,21-pentaen-3-one (12e). Procedure E was performed with the anilide **11e** (50 mg, 109 μmol) and first generation of Grubbs catalyst (8.3 mg, 11.0 μmol, 10 mol%) in DCM (200 mL). After flash chromatography (P/EA 90/10), the product was obtained (41 mg, 96 μmol, 87%) as a white solid. TLC: R_f = 0.57 (P/EA/DCM 50/10/50) [CAM, UV]; ^{1}H NMR (360 MHz, $CDCl_3$): δ (ppm) = 8.29 (s br, 1H, NH), 7.99 (s, 1H, $C_{ar}H$), 7.03 [d, ^3J = 11.1 Hz, 1H, CH=CH–C*H*=C(CO)], 6.33 [v. t, $^3J \cong$ 11.0 Hz, 1H, CH=C*H*–CH=C(CO)], 5.90 [v. q, $^3J \cong$ 9.0 Hz, 1H, C*H*=CH–CH=C(CO)], 3.87 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 2.65 (t, ^3J = 7.1 Hz, 2H, CH_2), 2.27 (v. q, $^3J \cong$ 7.1 Hz, 2H, CH_2), 2.04 (s, 3H, =CCH_3), 1.61–1.57 (m, 2H, CH_2), 1.47–1.27 (m, 16H, CH_2); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ (ppm) = 167.5 (C=O), 149.4 ($C_{ar}OCH_3$), 143.0 ($C_{ar}OCH_3$), 141.1 ($C_{ar}OCH_3$), 138.4 ($C_{olef}H$), 133.0 (C_{ar}), 129.4 (C_{ar}), 127.7 (=CCH_3), 126.2 ($C_{olef}H$), 123.7 ($C_{olef}H$), 101.6 ($C_{ar}H$), 61.1 (OCH_3), 61.0 (OCH_3), 55.9 (OCH_3), 29.6 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 28.5 (CH_2), 28.0 (CH_2), 27.9 (CH_2), 27.7 (CH_2), 27.7 (CH_2), 27.2 (CH_2), 22.7 (CH_2), 12.6 (CH_3); MS (EI, 70 eV), *m/z* (%): 429 (100) [M^+], 414 (21), 398 (22), 386 (8), 365 (7), 335 (7), 322 (7), 292 (14), 280 (10), 249 (8), 236 (5), 206 (6), 182 (8), 167 (8), 152 (7), 95 (6), 40 (7). Anal. $C_{26}H_{39}NO_4$ (429.6): calcd C, 72.69; H, 9.15; found C, 72.79; H: 8.98.

5.1.24. 2-Methylpent-2-enoic acid (2,4,5-trimethoxy-3-tridec-12-enylphenyl)-amide (13). To 2-methylpent-2-enoic acid (30 mg, 263 μmol) dissolved in THF (0.3 mL), HOBt (42 mg, 322 μmol) and DCC (66 mg, 322 μmol) were added. The mixture was placed under argon atmosphere and stirred for 5 min at rt. Aniline **10e** (30 mg, 83 μmol) dissolved in THF (0.2 mL) was added. The mixture was stirred for 48 h at rt. Diethyl ether (5 mL) and water (5 mL) were added. The aqueous layer was extracted twice with diethyl ether (2×5 mL). The combined organic layers were washed with saturated $NaHCO_3$ (10 mL), brine (10 mL), dried (Na_2SO_4) and concentrated in vacuo. After flash chromatography (P/EA 90/10), the product was obtained (26 mg, 57 μmol, 69%) as a transparent oil. TLC: R_f = 0.39 (P/EA 90/10) [CAM, UV]; ^{1}H NMR (360 MHz, $CDCl_3$): δ (ppm) = 7.92 (s, 1H, $C_{ar}H$), 7.68 (s, 1H, NH), 5.82 (m, 2H, CH_2=C*H*), 5.13 (d, ^3J = 17.2 Hz, 1H, H_{trans}CH=CH), 5.06 (d, ^3J = 10.2 Hz, 1H, H_{cis}CH=CH), 4.98 (br. d, ^3J = 17.2 Hz, 1H, H_{trans}CH=CH), 4.91 (br. d, ^3J = 10.2 Hz, 1H, H_{cis}CH=CH_2), 3.84 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 2.61 (v. t, $^3J \cong$ 6.4 Hz, 2H, C*H*$_2C_{ar}$), 2.52–2.47 (m, 2H, CH_2=CHC*H*$_2$), 2.28–2.22 [m, 1H, CH_2C*H*(CO)CH_3], 2.02 (v. q, $^3J \cong$ 7.0 Hz, 2H, CH_2=CHC*H*$_2$), 1.56–1.50 (m, 2H, CH_2), 1.36–1.26 (m, 19H, CH_3, CH_2); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ (ppm) = 174.0 (C=O), 149.3 ($C_{ar}O$), 143.5 ($C_{ar}O$), 140.1 ($C_{ar}O$), 139.4 (H*C*=CH_2), 135.6 (CH_2H*C*=CH_2), 129.5 (C_{ar}), 127.3 (C_{ar}), 117.4 (HRC=*C*H$_2$), 114.2 (HC=*C*H$_2$), 102.9 ($C_{ar}H$), 61.5 (OCH_3), 61.0 (OCH_3), 56.0 (OCH_3), 42.7 [C*H*(CO)CH_3], 38.5 [C*H*$_2$CH(CO)CH_3], 33.9 (CH_2), 30.7 (CH_2), 30.1 (CH_2), 29.8 (CH_2), 29.7 (2 CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 24.9 (CH_2), 17.6 (CH_3); MS (ESI), *m/z* (%): 460.9 (100) [M+H^+].

5.1.25. 20,21,23-Trimethoxy-4-methyl-2-aza-bicyclo-[17.3.1]tricosa-1(23),6,19,21-tetraen-3-one (14). Procedure E was performed with anilide **13** (26 mg, 57 μmol) and Grubbs catalyst (4.7 mg, 5.7 μmol, 10 mol%) in DCM (113 mL). After flash chromatography (P/EA 90/10), the product was obtained (21 mg, 49 μmol, 86%) as a white solid. The d.r. of the product was 66:34. It was not possible to determine which isomer was the major product. TLC: R_f = 0.62 (P/EA/DCM 50/10/50) [CAM, UV]; ^{1}H NMR (360 MHz, $CDCl_3$): δ (ppm) = 7.96 (br. s, 0.33H, NH-minor), 7.93 (br. s, 0.66H, NH-major), 7.72 (s, 0.33H, C_{ar}H-minor), 7.66 (s, 0.66H, $C_{ar}H$), 5.50 (m, 2H, CH=CH), 3.85 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.63 (s, 3H, OCH_3), 2.65–1.97 (m, 6H, CH_2), 1.63–1.58 (m, 2H, CH_2), 1.30–1.27 (m, 20H, CH_2); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ (ppm) = 174.2 (C=O, major), 174.1 (C=O, minor), 149.3 (C_{ar}-OCH_3, major), 149.3 ($C_{ar}OCH_3$, minor). 143.6 ($C_{ar}OCH_3$), 141.3 ($C_{ar}OCH_3$), 134.2 ($C_{olef}H$, major), 133.3 ($C_{olef}H$, minor). 129.3 (C_{ar}), 129.4 (C_{ar}), 127.3 (=CCH_3), 126.7 ($C_{olef}H$, major), 126.0 ($C_{olef}H$, minor), 102.9 ($C_{ar}H$, major), 102.5 ($C_{ar}H$, minor), 61.2 (OCH_3 minor), 61.1 (OCH_3, major), 61.0 (OCH_3 minor), 61.0 (OCH_3, major), 56.0 (OCH_3), 43.7 (CH_2), 43.3 (CH_2), 37.8 (CH_2), 32.5 (CH_2), 32.2 (CH_2, major), 29.5 (CH_2), 28.9 (CH_2), 28.7 CH_2), 28.6 CH_2), 28.6 (CH_2), 28.5 (CH_2), 28.3 (CH_2), 28.1 (CH_2), 27.8 (CH_2), 27.2 (CH_2), 27.2 (CH_2), 24.2 (CH_2), 23.6 (CH_2), 22.7 (CH_2), 18.1 (CH_3, major), 17.1 (CH_3, minor); MS (EI, 70 eV), *m/z* (%): 431 (100) [M^+], 416 (21), 400 (5), 208 (5), 182 (8), 167 (10), 149 (10), 71 (6), 57 (12), 41 (7); HRMS: *m/z* calcd for $C_{26}H_{41}NO_4$: 431.3036; found 431.3033.

5.1.26. (4*E*,6*Z*)-21-Methoxy-4-methyl-2-aza-bicyclo-[15.3.1]henicosa-1(21),4,6,17,18(21)-tetraen-3,18,19-trione (15). General procedure F was performed with compound **12c** (28 mg, 69 μmol). The product was purified by flash chromatography (P/EA 75/25). The *ortho*-quinone (8.0 mg, 21 μmol, 30%) was isolated as a red film. TLC: R_f = 0.22 (P/EA 75/25) [CAM, UV]. ^{1}H NMR (360 MHz, $CDCl_3$): δ (ppm) = 8.57 (s br, 1H, NH), 7.31 (s, 1H, $C_{quin}H$), 7.05 [d, ^3J = 11.1 Hz, 1H, CH=CH–C*H*=C(CO)], 6.33 [v. t, $^3J \cong$ 10.9 Hz, 1H, CH=C*H*–CH=C(CO)], 6.12 [v. q, $^3J \cong$ 9.1 Hz, 1H, C*H*=CH–CH=C(CO)], 3.94 (s, 3H, OCH_3), 2.66 (br, 1H, CH_2), 2.29 (br, 2H, CH_2), 2.19 (s, 3H, =CCH_3), 1.58–1.24 (m, 16H, CH_2); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ (ppm) = 180.3 (C_{quin}=O), 179.4 (C_{quin}=O), 168.2 (C=O), 159.3 (C-20), 144.1 (C_{quin}), 140.9 (C-5), 131.9 (C-2), 129.5 (C_{quin}), 129.2 (C-3), 123.3 (C-4), 107.1 (C-18), 62.6 (OCH_3), 29.6 (CH_2), 29.6 (CH_2), 29.3 (CH_2), 28.6 (CH_2), 28.0 (CH_2), 27.7 (CH_2), 27.4 (CH_2), 26.0 (CH_2), 21.8 (CH_2), 12.3 (CH_3); MS (EI, 70 eV), *m/z* (%): 371 (100) [M^+], 354 (22), 340 (10), 328 (12), 274 (6), 244 (6), 178 (5), 152 (24), 138 (14), 110 (44), 95 (30), 79

(32), 67 (40), 55 (22), 41 (36); HRMS: *m/z* calcd for $C_{22}H_{29}NO_4$: 371.2097; found 371.2086.

5.1.27. (*4E,6Z*)-21,23-Dimethoxy-4-methyl-2-aza-bicyclo[17.3.1]tricosa-1,4,6,19(23),21-pentaen-3,20-dione (16). General procedure F was performed with compound **12e** (38 mg, 89 μmol). The amount of reagents and solvents was adjusted accordingly. The mixture was stirred at −10 °C during 40 min. After the work-up, the product was purified by flash chromatography (P/EA 90/10). The aza-quinone (24 mg, 57 μmol, 64%) was isolated as a yellow film. TLC: R_f=0.67 (P/EA 50/50) [CAM, UV]; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm)=7.28 (d, ^3J=11.1 Hz, 1H, CH=CH–C*H*=C(CO)], 6.36 [v. t, $^3J\cong$10.9 Hz, 1H, CH=C*H*–CH=C(CO)], 5.92 [v. q, $^3J\cong$9.1 Hz, 1H, C*H*=CH–CH=C(CO)], 5.80 (s, 1H, $C_{quin}H$), 4.01 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 2.55 (v. t, $^3J\cong$7.0 Hz, 1H, $C_{quin}CH_2$), 2.20 (v. q, $^3J\cong$7.9 Hz, 2H, CH_2), 2.04 (s, 3H, =CCH_3), 1.52–1.24 (m, 20H, CH_2); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ (ppm)=182.3 (C_{quin}=O), 182.3 (C_{quin}=N), 158.7 (C=O), 159.3 (C-20), 155.7 (C_{quin}), 153.8 (C_{quin}), 141.9 (C-5), 136.0 (C-3), 132.5 (C-2), 131.0 (C_{quin}), 123.9 (C-4), 107.1 ($C_{quin}H$), 62.6 (C-22-O*C*H_3), 56.1 (C-19-O*C*H_3) 28.8 (CH_2), 28.5 (CH_2), 28.3 (CH_2), 28.0 (CH_2), 28.0 (CH_2), 27.9 (CH_2), 27.6 (CH_2), 27.6 (CH_2), 27.0 (CH_2), 26.9 (CH_2), 23.0 (CH_2), 11.6 (CH_3); MS (EI, 70 eV), *m/z* (%): 413 (100) [M^+], 398 (22), 382 (24), 354 (14), 318 (5), 274 (10), 242 (11), 229 (10), 180 (20), 164 (14), 136 (10), 110 (14), 95 (25), 79 (42), 67 (40), 55 (36), 41 (50); HRMS: *m/z* calcd for $C_{25}H_{35}NO_4$: 413.2566; found 413.2582.

5.1.28. 1,4-Di-*iso*-propoxy-2-methoxy-3-dodec-11-enyl-benzene (18). Procedure G was performed with 12-iodododec-1-ene (**7d**) (633 mg, 2.15 mmol) and 1,4-di-*iso*-propoxy-2-methoxy-benzene (**17**)[26] (3.06 g, 3.06 mmol). After flash chromatography (P/EA 99/01), the product was isolated (517 mg, 1.32 mmol, 61%) as a light yellow oil. A by product 2,5-di-*iso*-propoxy-1-methoxy-3-dodec-11-enyl benzene was also isolated (33mg, 0.08 mmol, 4%) as a colorless oil. TLC: R_f=0.51 (P/EA 95/5) [CAM, UV]; IR (film): $\tilde{\nu}$ (cm^{-1})=3075 (w, =CH_2), 2929 (v. s, CH_2), 2856 (s, CH_2), 1640 (m, C=C), 1587 (w, C_{ar}=C_{ar}), 1478 (s, CO), 1251 (s, COC), 1118 (s, COC), 983 (m, RCH=CH_2), 909 (m, RCH=CH_2), 787 (m), 775 (w, CH); ^{1}H NMR (360 MHz, $CDCl_3$): δ (ppm)=6.68 (d, ^3J=8.9 Hz, 1H, $C_{ar}H$), 6.51 (d, ^3J=8.9 Hz, 1H, $C_{ar}H$), 5.82 (ddt, ^3J=17.1 Hz, ^3J=10.2 Hz, ^3J=6.2 Hz, 1H, CH_2=C*H*R), 5.03–4.98 (m, 1H, H_{trans}CH=CHR), 4.96–4.93 (m, 1H, H_{cis}-CH=CHR), 4.43 [sept., ^3J=6.2 Hz, 2H, OC*H*$(CH_3)_2$], 3.84 (s, 3H, OCH_3), 2.61 (t, ^3J=7.7 Hz, 2H, CH_2Ar), 2.04 (v. q, $^3J\cong$7.0 Hz, 2H, CH_2=CHCH_2), 1.55–1.49 (m, 2H, CH_2), 1.33–1.29 [m, 26H, CH_2, OCH(CH_3)$_2$]; ^{13}C NMR (90.6 MHz, $CDCl_3$): δ (ppm)=151.0 (C_{ar}O*i*Pr), 150.0 (C_{ar}O*i*Pr), 144.8 (C_{ar}OMe), 139.4 (HR*C*=CH_2), 127.5 ($C_{ar}CH_2$), 114.7 ($C_{ar}H$), 114.2 (HRC=*C*H_2), 108.4 ($C_{ar}H$), 71.9 [O*C*H$(CH_3)_2$], 70.5 [O*C*H$(CH_3)_2$], 60.7 (OCH_3), 34.0 (CH_2), 30.1 (CH_2), 30.1 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 24.3 (CH_2), 22.5 [CH(*C*H_3)$_2$], 22.4 [CH(*C*H_3)$_2$]; MS (EI, 70 eV), *m/z* (%): 390 (70) [M^+], 348 (22), 306 (100), 195 (6), 153 (47), 141 (6), 125 (14), 107 (10), 75 (6), 55 (10), 43 (13). Anal. $C_{25}H_{42}O_3$ (390.6): calcd C, 76.87; H, 10.74; found C, 76.86; H: 10.79.

5.1.29. 1,4-Di-*iso*-propoxy-3-dodec-11-enyl-2-methoxy-5-nitrobenzene (19). Procedure B was performed with 1,4-di-*iso*-propoxy-2-methoxy-3-dodec-11-enylbenzene (**18**) (507 mg, 1.30 mmol). After flash chromatography (P/EA 98/02), the product was obtained (472 mg, 1.08 mmol, 83%) as a yellow oil. TLC: R_f=0.43 (P/EA 95/05) [CAM, UV]; IR (film): $\tilde{\nu}$ (cm^{-1})=3075 (w, =CH), 2977 (s, CH_3), 2926 (v. s, CH_2), 2853 (s, CH_2), 1640 (m, C=C), 1570 (m, C_{ar}=C_{ar}), 1522 (s, NO_2), 1471 (s, C_{ar}=C_{ar}), 1383 (m, CH_3), 1371 (m, CH_3), 1345 (s, CN), 1241 (s, COC), 1122 (s, COC), 974 (w, RCH=CH_2), 910 (m, RCH=CH_2), 787 (w, CH); ^{1}H NMR (360 MHz, $CDCl_3$): δ (ppm)=7.28 (s, 1H, $C_{ar}H$), 5.81 (ddt, ^3J=17.0 Hz, ^3J=10.1 Hz, ^3J=6.8 Hz, 1H, CH_2=C*H*R), 5.01–4.97 (m, 1H, H_{trans}CH=CHR), 4.94–4.91 (m, 1H, H_{cis}-CH=CHR), 4.52 [sept., ^3J=6.1 Hz, 1H, OC*H*$(CH_3)_2$], 4.11 [sept., ^3J=6.1 Hz, 1H, OC*H*$(CH_3)_2$], 3.91 (s, 3H, OCH_3), 2.63 (t, ^3J=7.9 Hz, 2H, CH_2Ar), 2.04 (v. q, $^3J\cong$7.0 Hz, 2H, CH_2=CHCH_2), 1.55–1.49 (m, 2H, CH_2), 1.38–1.26 [m, 26H, CH_2, OCH(CH_3)$_2$]; ^{13}C NMR (90.6 MHz, $CDCl_3$): δ (ppm)=153.4 (C_{ar}O*i*Pr), 146.2 (C_{ar}O*i*Pr), 144.6 (C_{ar}OMe), 139.5 (C_{ar}), 139.4 (HR*C*=CH_2), 133.7 (C_{ar}), 114.2 (HRC=*C*H_2), 109.4 ($C_{ar}H$), 78.1 [O*C*H$(CH_3)_2$], 71.8 [O*C*H$(CH_3)_2$], 61.0 (OCH_3), 34.0 (CH_2), 30.2 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 25.5 (CH_2), 22.4 [CH(*C*H_3)$_2$], 22.1 [CH(*C*H_3)$_2$]; MS (EI, 70 eV), *m/z* (%): 435 (22) [M^+], 393 (100), 351 (8), 334 (26), 316 (56), 284 (20), 256 (5), 198 (24), 180 (22), 168 (30), 153 (18), 139 (9), 123 (12), 95 (12), 69 (18), 55 (32), 43 (60). Anal. $C_{25}H_{41}NO_5$ (435.6): calcd C, 68.93; H, 9.49; found C, 69.05; H: 9.55.

5.1.30. 1,4-Di-*iso*-propoxy-3-dodec-11-enyl-2-methoxy-phenyl amine (20). Procedure C was performed with 1,4-di-*iso*-propoxy-3-dodec-11-enyl-2-methoxy-5-nitrobenzene (**19**) (200 mg, 460 μmol). After flash chromatography (P/EA 90/10), the product was obtained (147 mg, 363 μmol, 79%) as a yellow oil. TLC: R_f=0.17 (P/EA 90/10) [CAM, UV]; IR (film): $\tilde{\nu}$ (cm^{-1})=3450 (w, NH_2), 3360 (w, NH_2), 3075 (w, =CH), 2973 (S, CH_3), 2925 (v. s, CH_2), 2853 (s, CH_2), 1640 (s, C=C), 1613 (s, N–H), 1483 (s, C_{ar}=C_{ar}), 1381 (m, CH_3), 1371 (m, CH_3), 1222 (s, COC), 1110 (s, COC), 1025 (s), 949 (w, RCH=CH_2), 910 (m, RCH=CH_2), 816 (w, CH); ^{1}H NMR (360 MHz, $CDCl_3$): δ (ppm)=6.19 (s, 1H, $C_{ar}H$), 5.80 (ddt, ^3J=17.0 Hz, ^3J=10.2 Hz, ^3J=6.6 Hz, 1H, CH_2=C*H*R), 5.01–4.96 (m, 1H, H_{trans}CH=CHR), 4.94–4.91 (m, 1H, H_{cis}CH=CHR), 4.39 [sept., ^3J=6.1 Hz, 1H, OC*H*$(CH_3)_2$], 4.16 [sept., ^3J=6.1 Hz, 1H, OC*H*$(CH_3)_2$], 3.75 (s, 3H, OCH_3), 3.38 (br. s, 2H, NH_2), 2.56 (t, ^3J=8.0 Hz, 2H, CH_2Ar), 2.04 (v. q, $^3J\cong$7.0 Hz, 2H, CH_2=CHCH_2), 1.55–1.49 (m, 2H, CH_2), 1.36–1.28 [m, 26H, CH_2, OCH(CH_3)$_2$]; ^{13}C NMR (90.6 MHz, $CDCl_3$): δ (ppm)=147.3 (C_{ar}O*i*Pr), 141.4 (C_{ar}O*i*Pr), 139.3 (HR*C*=CH_2), 137.3 (C_{ar}), 136.3 (C_{ar}), 131.2 (C_{ar}), 114.2 (HRC=*C*H_2), 102.2 ($C_{ar}H$), 75.0 [O*C*H$(CH_3)_2$], 71.1 [O*C*H$(CH_3)_2$], 60.8 (OCH_3), 33.9 (CH_2), 30.3 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 25.7 (CH_2), 22.9 [CH(*C*H_3)$_2$], 22.4 [CH(*C*H_3)$_2$]; MS (EI, 70 eV), *m/z* (%): 405 (60) [M^+], 362 (30), 320 (100), 288 (8), 178 (6), 167 (10), 152 (20), 138 (10), 123 (8), 55 (6), 43 (10). Anal. $C_{25}H_{43}NO_3$ (405.6): calcd C, 74.03; H, 10.73; found C, 73.99; H: 10.69.

5.1.31. 2-Methyl-penta-2,4-dienoic acid (1,4-di-*iso*-propoxy-3-dodec-11-enyl-2-methoxyphenyl)-amide (21). Procedure D was performed with the aniline **20** (116 mg, 286 μmol). After flash chromatography (P/EA 95/05), the product was obtained (93 mg, 186 μmol, 65%) as a light yellow oil. TLC: R_f=0.38 (P/EA 90/10) [CAM, UV]; IR (film): $\tilde{\nu}$ (cm^{-1})=3432 (m, NH), 2974 (s, CH_2), 2926 (v. s, CH_2), 2853 (s, CH_2), 1673 (s, C=O), 1600 (m, C=C), 1514 (s), 1468 (m), 1434 (m), 1420 (s), 1381 (m, CH_3), 1371 (m, CH_3), 1222 (s, C–N), 1110 (s, COC), 1031 (w), 1007 (s, RCH=CH_2), 914 (m, RCH=CH_2); ^{1}H NMR (360 MHz, $CDCl_3$): δ (ppm)=8.14 (s, 1H, NH), 8.01 (s, 1H, C_{ar}H), 7.03 [d, ^3J=10.2 Hz, 1H, CH_2=CH–C*H*=C(CO)], 6.66 (ddd, ^3J=16.9 Hz, ^3J=10.6 Hz, ^3J=10.2 Hz, 1H, CH_2=C*H*–CH=C), 5.80 (ddt, ^3J=17.2 Hz, ^3J=10.2 Hz, ^3J=6.8 Hz, 1H, CH_2=C*H*R), 5.54 (d, ^3J=16.9 Hz, 1H, H_{trans}-CH=CH–CH=C), 5.43 (d, ^3J=10.2 Hz, 1H, H_{cis}-CH=CH–CH=C), 5.01–4.95 (m, 1H, H_{trans}CH=CHR), 4.93–4.90 (m, 1H, H_{cis}CH=CHR), 4.57 [sept., ^3J=6.1 Hz, 1H, OC*H*(CH_3)$_2$], 4.13 [sept., ^3J=6.1 Hz, 1H, OC*H*(CH_3)$_2$], 3.81 (s, 3H, OCH_3), 2.58 (t, ^3J=7.9 Hz, 2H, CH_2Ar), 2.09 (d, ^4J=0.9 Hz, 3H, =CC*H*$_3$), 2.03 (v. q, $^3J\cong$7.0 Hz, 2H, CH_2=CHC*H*$_2$), 1.55–1.50 (m, 2H, CH_2), 1.33–1.29 [m, 26H, CH_2, OCH(C*H*$_3$)$_2$]; ^{13}C NMR (90.6 MHz, $CDCl_3$): δ (ppm)=166.3 (C=O), 147.0 (C_{ar}-O*i*Pr), 144.8 (C_{ar}OCH$_3$), 139.3 (HR*C*=CH_2), 138.6 (C_{ar}-O*i*Pr), 134.6 (C_{olef}H), 132.2 (C_{olef}H), 131.5 (=*C*CH$_3$), 130.1 ($C_{ar}CH_2$), 128.3 (C_{ar}NH), 123.4 (=CH–HC=*C*H$_2$), 114.2 (HRC=*C*H$_2$), 105.3 (C_{ar}H), 76.7 [O*C*H(CH_3)$_2$], 70.9 [O*C*H(CH_3)$_2$], 60.8 (OCH_3), 33.9 (CH_2), 30.3 (CH_2), 30.2 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 29.0 (CH_2), 25.6 (CH_2), 22.8 [CH(*C*H$_3$)$_2$], 22.4 [CH(*C*H$_3$)$_2$], 13.2 (CH_3); MS (EI, 70 eV), *m*/*z* (%): 499 (40) [M^+], 456 (16), 414 (20), 362 (5), 320 (14), 95 (100), 67 (23), 41 (6). Anal. $C_{31}H_{49}NO_4$ (499.7): calcd C, 74.51; H, 9.87; found C, 74.60; H: 9.88.

5.1.32. (4*E*,6*Z*)-20,22-Di-*iso*-propoxy-19-methoxy-4-methyl-2-aza-bicyclo[16.3.1]docosa-1(22),4,6,18,20-pentaen-3-one (22). Procedure E was performed with the anilide **21** (50 mg, 100 μmol) and Grubbs catalyst (8.2 mg, 10.1 μmol, 10 mol%) in DCM (200 mL). After flash chromatography (P/EA 90/10), the product was obtained (41 mg, 87 μmol, 87%) as a light green transparent oil. TLC: R_f=0.85 (P/EA/DCM 50/10/50) [CAM, UV]; IR (film): $\tilde{\nu}$ (cm^{-1})=3428 (br, NH), 2974 (s, $\tilde{\nu}$ CH_3), 2926 (v. s, CH_2), 2854 (v. s, CH_2), 1667 (s, C=O), 1592 (m, C=C), 1504 (s, NH), 1434 (s, C=C), 1382 [s, $(CH_3)_2$CH], 1332 [m, $(CH_3)_2$CH], 1229 (m), 1105 (s, C–O–C), 1027 (m), 954 (w), 909 (w), 852 (w), 734 (w); ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm)=8.24 (br. s, 1H, NH), 7.93 (s, 1H, C_{ar}H), 6.98 [d, ^3J=11.3 Hz, 1H, CH=CH–C*H*=C(CO)], 6.31 [v. t, $^3J\cong$10.9 Hz, 1H, CH=C*H*–CH=C(CO)], 5.94 [v. q, $^3J\cong$9.0 Hz, 1H, C*H*=CH–CH=C(CO)], 4.58 [sept., ^3J=6.1 Hz, 1H, OC*H*(CH_3)$_2$], 4.01 [sept., ^3J=6.1 Hz, 1H, OC*H*(CH_3)$_2$], 3.81 (s, 3H, OCH_3), 2.74–2.70 (m, 2H, CH_2), 2.04 (br, 3H, =CC*H*$_3$), 1.70–0.85 [m, 30H, CH_2, CH(C*H*$_3$)$_2$]; ^{13}C NMR (90.6 MHz, $CDCl_3$): δ (ppm)=168.1 (C=O), 147.2 (C_{ar}O), 144.6 (C_{ar}O), 139.0 (C_{ar}O), 137.9 (C_{olef}H), 133.9 (C_{ar}), 129.3 (C_{ar}), 128.4 (=*C*CH$_3$), 126.7 (C_{olef}H), 124.3 (C_{olef}H), 104.0 (C_{ar}H), 76.9 [O*C*H(CH_3)$_2$], 71.0 [O*C*H(CH_3)$_2$], 60.8 (OCH_3), 30.1 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 28.9 (CH_2), 28.7 (CH_2), 28.6 (CH_2), 28.0 (CH_2), 27.7 (CH_2), 27.4 (CH_2), 23.3 (CH_2), 22.9 [CH(*C*H$_3$)$_2$], 22.5 [CH(*C*H$_3$)$_2$], 22.4 [CH(*C*H$_3$)$_2$], 22.4 [CH(*C*H$_3$)$_2$], 12.8 (CH_3); MS (EI, 70 eV), *m*/*z* (%): 471 (72) [M^+], 428 (38), 386 (100), 358 (21), 152 (12), 150 (11), 123 (9), 95 (18), 67 (11), 55 (6), 41 (6); HRMS: *m*/*z* calcd for $C_{29}H_{45}NO_4$: 471.3349; found 471.3357.

5.1.33. (4*E*,6*Z*)-20-Hydroxy-22-*iso*-propoxy-19-methoxy-4-methyl-2-aza-bicyclo[16.3.1]docosa-1(21),4,6,18(22),19-pentaen-3-one (23). To a solution of the macrocyclic compound **22** (24.0 mg, 51.0 μmol) in DCM (4.0 mL) cooled to −10 °C under argon atmosphere, BCl_3 (1.0 mL, 1.0 mmol, 1.0 M in hexane) was slowly added. The resulting solution was stirred at −10 °C for 40 min. No more starting material remained according to TLC (P/EA 75/25). The mixture was then quenched by the careful addition of 3.0 mL of NaOH (4.0 M in water). Separation of the organic layer was followed by further extraction of the aqueous layer with DCM (2×5 mL). The combined organic layers were washed, dried over Na_2SO_4 and concentrated. After flash chromatography (P/EA 80/20), the *para*-quinone was obtained (7.0 mg, 18.2 μmol, 36%) as a yellow oil. The mono-deprotected (14.0 mg, 32.6 μmol, 64%) compound was isolated as a white solid. TLC: R_f=0.29 (P/EA 75/25) [CAM, UV]; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm)=8.29 (br. s, 1H, NH), 8.03 (s, 1H, CarH), 7.18 (s, 1H, OH), 6.97 [d, $^3J\cong$11.3 Hz, 1H, CH=CH–C*H*=C(CO)], 6.31 [v. t, $^3J\cong$10.9 Hz, 1H, CH=C*H*–CH=C(CO)], 5.95 [v. q, $^3J\cong$9.1 Hz, 1H, C*H*=CH–CH=C(CO)], 4.00 [sept., ^3J=6.1 Hz, 1H, OC*H*(CH_3)$_2$], 3.83 (s, 3H, OCH_3), 2.76–2.70 (m, 2H, CH_2), 2.37–2.35 (m, 1H, CH_2), 2.06–2.05 (m, 3H, =CCH_3), 1.70–0.85 [m, 23H, CH_2, CH(C*H*$_3$)$_2$]; ^{13}C NMR (90.6 MHz, $CDCl_3$): δ (ppm)=168.8 (C=O), 146.2 (C_{ar}OH), 142.2 (C_{ar}OCH$_3$), 138.7 (C_{ar}O*i*Pr), 138.1 (C_{olef}H), 133.7 (C_{ar}), 128.7 (C_{ar}), 127.1 (C_{olef}H), 124.2 (C_{olef}H), 104.8 (C_{ar}H), 77.1 [O*C*H(CH_3)$_2$], 60.9 (OCH_3), 30.0 (CH_2), 29.6 (CH_2), 28.9 (CH_2), 28.6 (CH_2), 28.4 (CH_2), 28.0 (CH_2), 27.7 (CH_2), 27.3 (CH_2), 23.4 (CH_2), 22.8 [CH(*C*H$_3$)$_2$], 22.3 [CH(*C*H$_3$)$_2$], 12.9 (CH_3).

5.1.34. 19-Methoxy-4-methyl-2-aza-bicyclo[16.3.1]dodocosa-1(21),4,6,18-tetraene-3,20,22-trione (2). To a solution of the macrocyclic compound **22** (45.0 mg, 106 μmol) in DCM (10.4 mL) cooled to −10 °C under argon atmosphere, BCl_3 (1.0 mL, 1.0 mmol, 1.0 M in hexane, 10 equiv) was slowly added. The resulting solution was stirred at −10 °C for 2 h. Some mono deprotected material remained according to TLC (P/EA 75/25). BCl_3 (1.0 mL, 1.0 mmol, 1.0 M in hexane, 10 equiv) was slowly added. The mixture was then allowed to warm up to rt and stirred for 4 h. After a TLC control showing the completion of the reaction, the mixture was quenched by the careful addition of 5.0 mL of NaOH (4.0 M in water). Separation of the organic layer was followed by further extraction of the aqueous layer with DCM (2×10 mL). The combined organic layers were washed, dried over Na_2SO_4 and concentrated. After flash chromatography (P/EA 75/25), the *para*-quinone was obtained (31.0 mg, 90.9 μmol, 86%) as a yellow orange microcrystalline solid. TLC: R_f=0.84 (P/EA 75/25) [CAM, UV]; IR: $\tilde{\nu}$ (cm^{-1})=3557 (br, NH), 2917 (s, CH_2), 2847 (v. s, CH_2), 1695 (s, C=O), 1649 (s, C=O), 1607 (s, C=O), 1497 (s, NH), 1361 (s), 1320 (s), 1247 (m), 1194 (s, COC), 1042 (m), 962 (w), 864 (m), 798

(w), 737 (w), 691 (m); ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 8.86 (s, 1H, NH), 7.25 (s, 1H, C_{quin}H), 7.07 [d, ^3J = 11.3 Hz, 1H, CH=CH–C*H*=C(CO)], 6.30 [v. t, $^3J \cong 11.0$ Hz, 1H, CH=C*H*–CH=C(CO)], 6.04 [v. q, $^3J \cong 9.1$ Hz, 1H, C*H*=CH–CH=C(CO)], 4.12 (s, 3H, OCH_3), 2.52 (t, $^3J = 6.7$ Hz 2H, $C_{quin}CH_2$), 2.24 (v. q, $^3J \cong 8.0$ Hz 2H, =CHCH_2), 1.98–1.96 (m, 3H, =CCH_3), 1.55–1.23 (m, 30H, CH_2); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ (ppm) = 184.5 (C_{quin}=O), 183.8 (C_{quin}=O), 168.8 (C=O), 156.9 (C_{quin}OMe), 140.2 (CH_2CH=CH), 138.1 (C_{quin}NH), 132.0 [CH=*C*(CO)], 129.2 *C*H=C(CO)], 128.6 (C_{quin}-CH_2), 123.8 (CH_2CH=*C*H), 111.3 (C_{quin}H), 61.7 (OCH_3), 29.6 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 28.8 (CH_2), 28.6 (CH_2), 28.2 (CH_2), 27.9 (CH_2), 27.2 (CH_2), 27.2 (CH_2), 20.8 (CH_2), 12.5 (CH_3); MS (EI, 70 eV), *m*/*z* (%): 385 (100) [M^+], 368 (38), 342 (10), 314 (5), 300 (3), 274 (8), 272 (7), 244 (5), 152 (20), 121 (14), 110 (31), 95 (30), 67 (32), 55 (30), 41 (30). Anal. $C_{23}H_{31}NO_4$ (385.5): calcd C, 71.66; H, 8.11; found C, 71.78; H: 8.10.

Acknowledgements

Support of our research by the Deutsche Forschungsgemeinschaft (DFG) and by the Fonds der Chemischen Industrie is gratefully acknowledged. A.L. thanks the Deutsche Akademische Austauschdienst for a graduate fellowship. We thank Dr. Volker P. Böhm (BASF AG) for a generous donation of metathesis catalysts.

References and notes

1. (a) De Boer, C.; Meulman, P. A.; Wnuk, R. J.; Peterson, D. H. *J. Antibiot.* **1970**, *23*, 442–447. (b) Sasaki, K.; Rinehart, K. J.; Slomp, G.; Grostic, M. F.; Olson, E. C. *J. Am. Chem. Soc.* **1970**, *92*, 7591–7593.
2. Supko, J. G.; Hickman, R. L.; Grever, M. R.; Malspeis, L. *Cancer Chemother. Pharmacol.* **1995**, *36*, 305–315.
3. Reviews: (a) Buchner, J.; Walter, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 1098–1113. (b) Buchner, J.; Richter, K. *J. Cell. Phys.* **2001**, *188*, 281–290. (c) Buchner, J. *Trends Biochem. Sci.* **1999**, *24*, 136–141.
4. Whitesell, L.; Mimnaugh, E. G.; De Costa, B.; Myers, C. E.; Neckers, L. M. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 8324–8328.
5. (a) Dolinski, K. J.; Cardenas, M. E.; Heitman, J. *Mol. Cell Biol.* **1998**, *18*, 7344–7352. (b) Webb, C. P.; Hose, C. D.; Koochekpour, S.; Jeffers, M.; Oskarsson, M.; Sausville, E.; Monks, A.; Vande Wourde, G. F. *Cancer Res.* **2000**, *60*, 342–349.
6. (a) Stebbins, C. E.; Russo, A. A.; Schneider, C.; Rosen, N.; Hartl, F. U.; Pavletich, N. P. *Cell* **1997**, *89*, 239–250. (b) Roe, S. M.; Prodromou, C.; O'Brien, R.; Ladbury, J. E.; Piper, P. W.; Pearl, L. H. *J. Med. Chem.* **1999**, *42*, 260–266.
7. Review: Funayama, S.; Cordell, G. A. *Stud. Nat. Prod. Chem.* **2000**, *23*, 51–106.
8. Schill, G.; Merkel, C.; Zürcher, C. *Liebigs Ann. Chem.* **1977**, 288–296.
9. (a) Schnur, R. C.; Corman, M. L.; Gallaschun, R. J.; Cooper, B. A.; Dee, M. F.; Doty, J. L.; Muzzi, M. L.; DiOrio, C. I.; Barbacci, E. G.; Miller, P. E.; Morin, M. J.; Foster, B. A.; Pollack, V. A.; Savage, D. M.; Sloan, D. E.; Pustilnik, L. R.; Moyer, J. D.; Moyer, M. P. *J. Med. Chem.* **1995**, *38*, 3806–3812. (b) Schnur, R. C.; Corman, M. L.; Gallaschun, R. J.; Cooper, B. A.; Dee, M. F.; Doty, J. L.; Muzzi, M. L.; DiOrio, C. I.; Barbacci, E. G.; Miller, P. E.; Pollack, V. A.; Savage, D. M.; Sloan, D. E.; Pustilnik, L. R.; Moyer, J. D.; Moyer, M. P. *J. Med. Chem.* **1995**, *38*, 3813–3820. (c) Kuduk, S. D.; Zheng, F. F.; Sepp-Lorenzino, L.; Ouerfelli, Q.; Rosen, N.; Danishefsky, S. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1233–1238. (d) Kuduk, S. D.; Harris, C. R.; Zheng, F. F.; Sepp-Lorenzino, L.; Ouerfelli, Q.; Rosen, N.; Danishefsky, S. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1025–1028. (e) Kasuya, Y.; Lu, Z.-R.; Kopeckova, P.; Kopeček, J. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1303–1306. (f) Kasuya, Y.; Lu, Z.-R.; Kopeckova, P.; Kopeček, J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2089–2091. (g) Hargreaves, R.; Davis, C. L.; Whitesell, L.; Skibo, E. B. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3075–3078.
10. (a) Andrus, M. B.; Meredith, E. L.; Simmons, B. L.; Soma Sekhar, B. B. V.; Hicken, E. J. *Org. Lett.* **2002**, *4*, 3549–3552. (b) Andrus, M. B.; Meredith, E. L.; Hicken, E. J.; Simmons, B. L.; Glancey, R. R.; Ma, W. *J. Org. Chem.* **2003**, *68*, 8162–8169.
11. Recent reviews: (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29. (b) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012–3043. (c) Maier, M. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073–2077. (d) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450. (e) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed.* **1997**, *36*, 2036–2056.
12. Bach, T.; Lemarchand, A. *Synlett* **2002**, 1302–1304.
13. (a) House, H. O.; Rasmusson, G. R. *J. Org. Chem.* **1961**, *26*, 4278–4281. (b) Piers, E.; Jung, G. L.; Ruediger, E. H. *Can. J. Chem.* **1987**, *65*, 670–682. (c) Elemes, Y.; Foote, C. S. *J. Am. Chem. Soc.* **1992**, *114*, 6044–6050. (d) Jefford, C. W.; Wang, Y.; Houk, K. N. *J. Org. Chem.* **1991**, *56*, 856–858.
14. (a) Takahashi, S.; Kusumi, T.; Sato, Y.; Inouye, Y.; Kakisawa, H. *Bull. Chem. Soc. Jpn* **1981**, *54*, 1777–1780. (b) Stefani, H. A.; Costa, I. M.; Zeni, G. *Tetrahedron Lett.* **1999**, *40*, 9215–9218.
15. Paquette, L. A.; Fabris, F.; Tae, J.; Gallucci, J. C.; Hofferberth, J. E. *J. Am. Chem. Soc.* **2000**, *122*, 3391–3398.
16. Garelli, N.; Vierling, P. *J. Org. Chem.* **1992**, *57*, 3046–3051.
17. (a) Nokami, J.; Ohtsuki, H.; Sakamoto, Y.; Mitsuoka, M.; Kunieda, N. *Chem. Lett.* **1992**, 1647–1650. (b) Dhillon, R. S.; Nayar, K.; Singh, J. *Tetrahedron Lett.* **1992**, *33*, 6015–6016.
18. (a) Chuit, P.; Boelsing, F.; Hausser, J.; Malet, G. *Helv. Chim. Acta* **1927**, *10*, 113–121. (b) Dabideen, D.; Blumenstein, M.; Mootoo, D. R. *Tetrahedron* **2000**, *56*, 9203–9211. (c) Mori, K.; Nishio, H. *Liebigs Ann. Chem.* **1991**, 253–257.
19. (a) Kitahara, Y.; Nagaoka, Y.; Matsumura, T.; Kubo, A. *Heterocycles* **1994**, *38*, 659–678. (b) Kitahara, Y.; Nakahara, S.; Shimizu, M.; Yonezawa, T.; Kubo, A. *Heterocycles* **1993**, *36*, 1909–1924.
20. Lee, V. J.; Branfman, A. R.; Herrin, T. R.; Rinehart, K. L. *J. Am. Chem. Soc.* **1978**, *100*, 4225–4236.
21. (a) Carpino, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 4397–4398. (b) Carpino, L. A.; El-Fayam, A. *J. Org. Chem.* **1994**, *59*, 695–698.
22. (a) Cameron, D. W.; Feutrill, G. I.; Patti, A. F.; Perlmutter, P.; Sefton, M. A. *Aust. J. Chem.* **1982**, *35*, 1501–1508. (b) Witiak, D. T.; Loper, J. T.; Ananthan, S.; Almerico, A. M.; Verhoef,

V. L.; Fillpi, J. A. *J. Med. Chem.* **1989**, *32*, 1636–1642. (c) Kozuka, T. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2415–2423. (d) Cheng, A. C.; Castagnoli, N. *J. Med. Chem.* **1984**, *27*, 513–518. (e) Michael, J. P.; Cirillo, P. F.; Denner, L.; Hosken, G. D.; Howard, A. S.; Tinkler, O. S. *Tetrahedron* **1990**, *46*, 7923–7932. (f) Luly, J. R.; Rapoport, H. *J. Org. Chem.* **1981**, *46*, 2745–2752. (g) Carreño, M. C.; Garcia Ruano, J. L.; Toledo, M. A.; Urbano, A. *Tetrahedron: Asymmetry* **1997**, *8*, 913–922.

23. Andrus, M. B.; Hicken, E. J.; Meredith, E. L.; Simmons, B. L.; Cannon, J. F. *Org. Lett.* **2003**, *5*, 3859–3862.
24. (a) Jacob, P.; Callery, P. S.; Shulgin, A. T.; Castagnoli, N. *J. Org. Chem.* **1976**, *41*, 3627–3629. (b) Syper, L.; Kloc, K.; Mlochowski, J.; Szulc, Z. *Synthesis* **1979**, 521–523. (c) Fanchiang, Y.-T.; Thomas, J. C.; Heh, J. C. K.; Gould, E. S. *Inorg. Chem.* **1977**, *16*, 1942–1945.
25. Snyder, C. D.; Rapoport, H. *J. Am. Chem. Soc.* **1972**, *94*, 227–231.
26. (a) Sala, T.; Sargent, M. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2593–2598. (b) Iinuma, M.; Iwashima, K.; Matsuura, S. *Chem. Pharm. Bull.* **1984**, *32*, 4935–4941.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 60 (2004) 9675–9686

Palladium-catalyzed couplings to nucleophilic heteroarenes: the total synthesis of (−)-frondosin B

Chambers C. Hughes and Dirk Trauner*

Department of Chemistry, Center for New Directions in Organic Synthesis, University of California, 419 Latimer Hall, Berkeley, CA 94720, USA

Received 23 June 2004; revised 1 July 2004; accepted 2 July 2004

Available online 27 August 2004

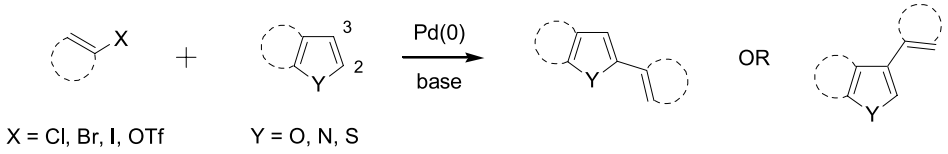
Abstract—The total synthesis of (−)-frondosin B, the enantiomer of naturally-occuring (+)-frondosin B, is described, wherein a palladium-catalyzed cyclization is used to establish the tetracyclic ring system of the natural product.

1. Introduction

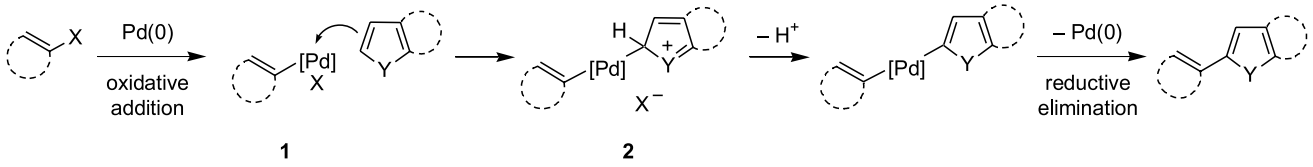
The direct, palladium-catalyzed coupling of nucleophilic heteroarenes to halides (or triflates) is an emerging synthetic tool in heterocyclic chemistry (Scheme 1). Furans, pyrroles, indoles, and thiophenes—among others—have been shown to participate in the reaction, which, at least formally, represents a 'heteroaryl Heck reaction'.[1] Uniquely, this method of carbon–carbon bond formation does not require prior functionalization of the heterocycle via halogenation or metallation. In combination with the mildness and functional group tolerance of palladium-catalyzed cross couplings, this reaction offers significant advantages in the synthesis of complex heteroarenes, for instance, certain natural products and pharmaceuticals.

Several mechanisms have been proposed for the reaction, including those that involve migratory insertion onto the heteroarene or oxidative addition of Pd(II) into one of the heteroarene C–H bonds. Miura and co-workers first suggested a mechanism wherein the organopalladium(II) species **1**, formed from initial oxidative addition of Pd(0), is nucleophilically attacked at the Pd(II) center by the electron-rich heteroarene (Scheme 2).[2a] Loss of a proton from the resulting cationic intermediate **2**, followed by reductive elimination of Pd(0), then affords the coupled product. Further discussion of this mechanism has been provided by Sharp[2b] and Gevorgyan.[2c]

The literature is replete with examples of Heck couplings to C2 of the heteroarenes.[3] Some selected examples are shown



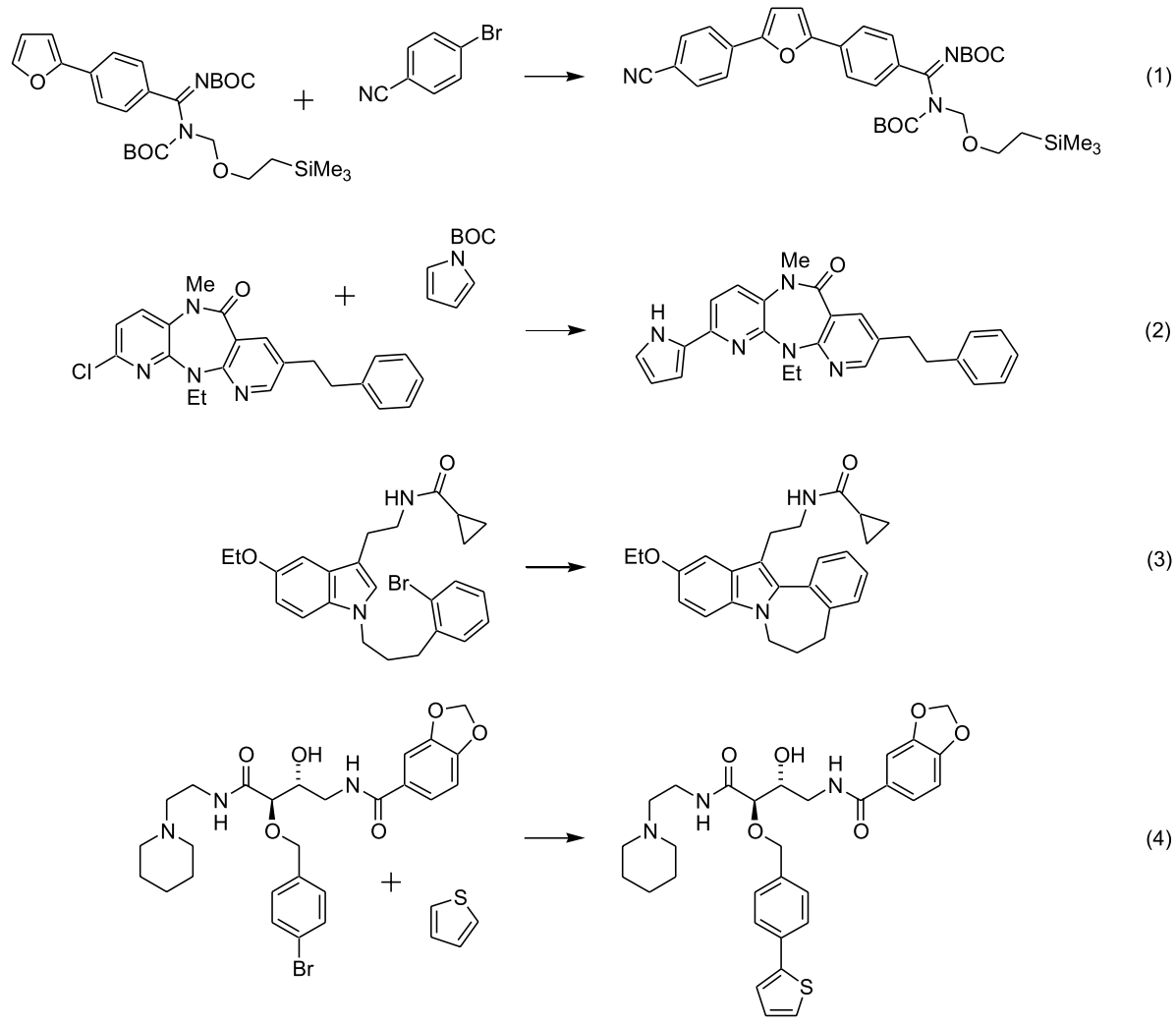
Scheme 1.



Scheme 2. Miura's mechanism.

Keywords: Frondosin; Heck reaction; Palladium catalysis; Total synthesis.
* Corresponding author. Tel.: +1-510-643-5507; fax: +1-510-643-9480; e-mail: trauner@cchem.berkeley.edu

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.07.041



Scheme 3. Palladium-catalyzed coupling to C2. Reagents and conditions: $Pd(PPh_3)_4$, KOAc, 120–160 °C.

in Scheme 3 (Eqs. 1–4).[3a–d] Notably, only *aryl* halides and triflates are known to couple to C2.

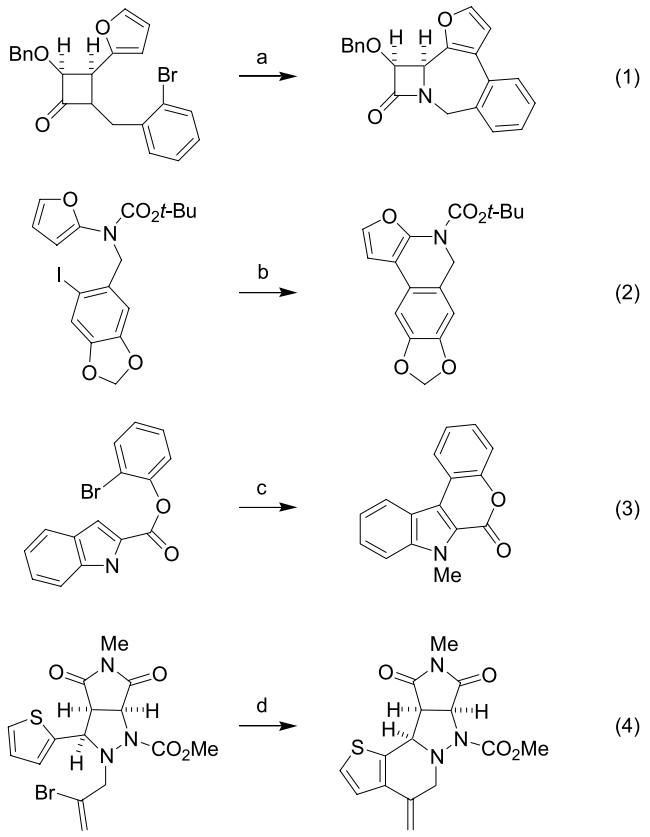
Relatively few examples exist showing coupling to C3.[4] Nevertheless, furan, pyrrole, indole, and thiophene have all been demonstrated to couple at C3, and some notable examples are depicted below (Scheme 4, Eqs. 1–4).[4a–d] As a whole, efficient Heck coupling to C3 of these heteroarenes requires elevated temperatures and is realized only in an intramolecular sense. That selective C3-arylation/vinylation is accomplished, in most cases, only when C2 is either already substituted or geometrically unaccessible lends credence to the electrophilic palladation mechanism discussed above, as C2 of these heteroarenes is usually more nucleophilic than C3.

Our own interest in this chemistry emerged during efforts toward the total synthesis of a marine natural product frondosin B (Fig. 1, **4**). In 2002, we described an enantioselective total synthesis of this norsesquiterpenoid in a short communication.[5] We now report the full details of our synthesis and give an account of its evolution.

Frondosin B is one of a family of marine terpenoids isolated from the Micronesian sponge *Dysidea frondosa*.[6] These compounds, especially frondosin A (**3**), have been found to be inhibitors of interleukin-8 (IL-8) in the low micromolar range. IL-8 receptor antagonists interfere with the inflammatory cascade and could potentially be used to prevent autoimmune disorders. Equally important, members of the frondosin family have been shown to exhibit HIV-inhibitory properties.[7]

Frondosin B (**4**) has attracted much attention from the synthetic community. The first asymmetric total synthesis by the Danishefsky group confirmed the structure and led to the assignment of an absolute configuration.[8b] Our communication describing the synthesis of (−)-frondosin B soon followed,[5] and Flynn and co-workers have recently disclosed an expedient, three-component racemic synthesis.[9]

Our original plan foresaw the implementation of the Arcadi–Cacchi reaction to form the key C10–C11 bond (Scheme 5).[10] According to this proposal, oxidative addition of Pd(0) to phenol **8** produces species **9**, in which the palladium is coordinated to the internal alkyne. This coordination event promotes the nucleophilic attack of the electron-deficient alkynyl ligand by the neighboring phenoxide. Subsequent reductive elimination furnishes tetracycle **10**.



Scheme 4. Palladium-catalyzed coupling to C3. Reagents and conditions: (a) $Pd(OAc)_2$, PPh_3, Tl_2CO_3, 110 °C; (b) $Pd(OAc)_2$, KOAc, *t*-$BuNH_3Cl$, 100 °C; (c) $Pd(PPh_3)_4$, Et_3N, 100 °C; (d) $Pd(OAc)_2$, PPh_3, TlOAc, MeCN, 80 °C.

2. Model studies

In order to gain rapid insight into the feasibility of the key cyclization, the synthesis of achiral phenol **11** was initially undertaken, in the hope that its reactivity would model that of its chiral analogue (**8**) (Scheme 6). In this case, commercially available 4-pentyn-1-ol (**12**) would be coupled to 4-methoxyphenol (**13**) via Sonogashira coupling and to cyclohexa-1,3-dione (**14**) via nucleophilic displacement of a leaving group on the alkyne.

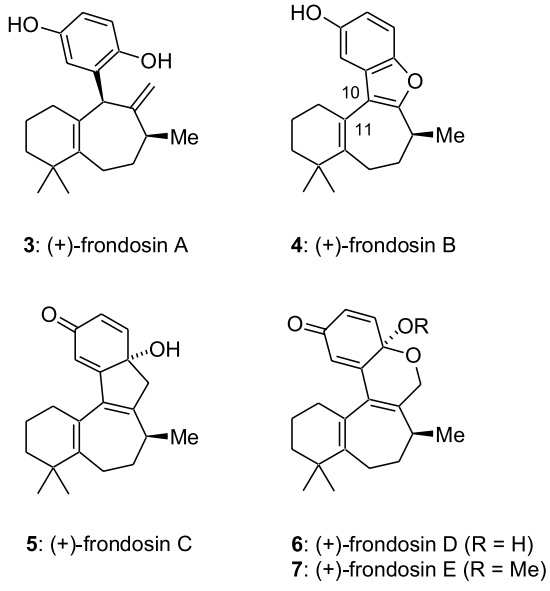


Figure 1. The frondosins. The absolute stereochemistry of frondosin A and C-E (**3**, **5**–**7**) is based on that determined for B (**4**) and has not been independently established.

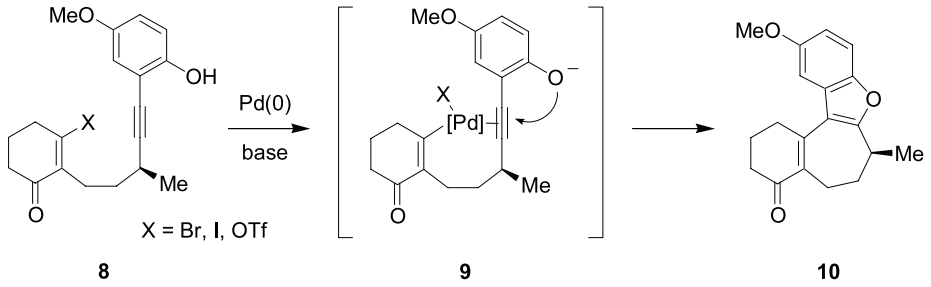
The synthesis of **11** required careful choice of protecting groups. Though it had been previously demonstrated that the phenol functionality in frondosin B could be efficiently protected as a methyl ether throughout its synthesis,[8] the choice of protecting group for the free phenol in **11**, which is to be revealed directly before the key step, needed to be thoroughly considered. The tetrahydropyanyl (THP) protecting group was initially chosen for this purpose, as the strong tendency of this group to direct *ortho*-lithiation would also facilitate the synthesis. The selective hydrolysis of similar ether protecting groups in the presence of a vinyl triflate had been previously reported.[11]

Treatment of 4-methoxyphenol (**13**) with dihydropyran (DHP) and TFA was followed by regioselective lithiation at the *ortho* position and iodination to afford **15** (Scheme 7). Sonogashira coupling gave **16a** in good yield.[12] The alcohol was converted to the iodide and subsequently reacted with dimethoxylithiocyclohexadiene using the Piers protocol to afford a mixture of adduct **17a** and the adduct resulting from hydrolysis of *one* enol ether.[13] Selective hydrolysis of the enol ethers to procure compound **18a**, however, could not be achieved. Various conditions resulted in the formation of a complex mixture of deprotected phenols.

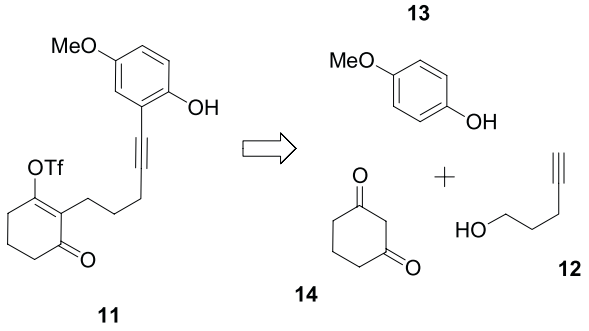
Believing a methoxymethyl (MOM) protecting group would exhibit greater stability than the THP protecting group,[14] the former was used in a second attempt to synthesize the model cyclization precursor. 4-Methoxyphenol was protected as the MOM ether, and the resulting intermediate was then lithiated and iodinated as before. Interestingly, however, the MOM ether was not able to effect selective *ortho*-lithiation, and a 1:1 mixture of regioisomeric products was formed. Since the selectivity of this reaction remained low, another method for making the *ortho* halide needed to be devised.

To this end, 4-methoxyphenol was treated with tetrabutylammonium tribromide ($TBABr_3$) to yield the brominated phenol in good yield (see Scheme 7). After protection of the phenol, bromide **19** was subjected to the same conditions as those described for the THP-protected iodide **15**, that is, Sonogashira coupling followed by nucleophilic displacement of the iodide with dimethoxylithiocyclohexadiene. Again, however, the protecting group was not stable to the conditions required to hydrolyze the enol ethers, and the crude product was composed of a mixture of deprotected phenol, from which none of **18b** could be isolated.

Realizing that an acid-labile protecting group would not survive the conditions required to hydrolyze the enol ethers, we were compelled to consider an alternative. Accordingly, alcohol **16b** was deprotected directly after Sonogashira coupling to produce phenol **20**, which was then reprotected as allyl ether **21** (Scheme 8). The dimethoxycyclohexadienyl moiety was introduced as before. **22** was successfully hydrolyzed to the protected diketone, and since the material



Scheme 5. The proposed key cyclization.



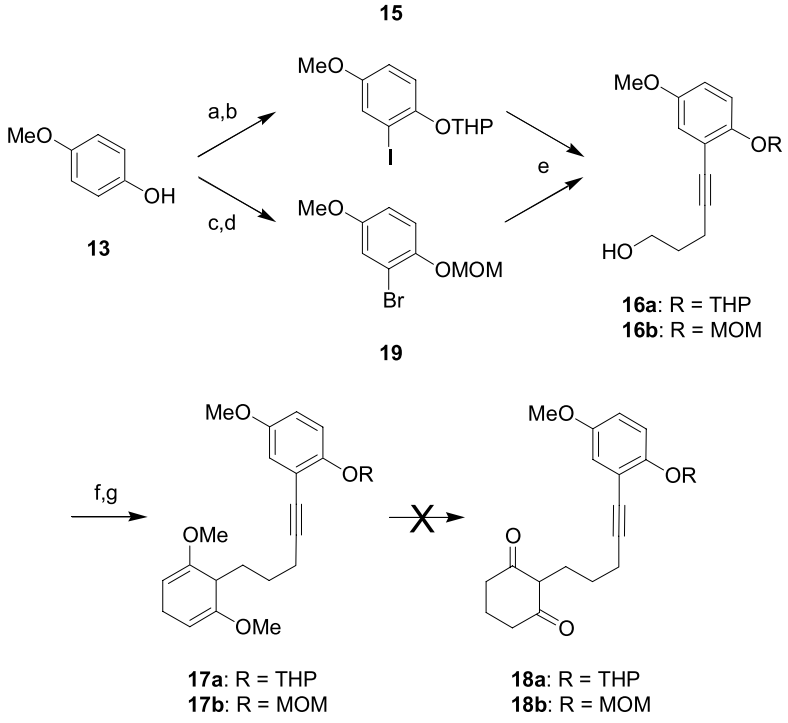
Scheme 6. Retrosynthetic analysis of the model cyclization precursor **11**.

readily decomposed on standing, it was immediately treated with sodium bis(trimethylsilyl)amide (NaHMDS) and *N*-phenyltrifluoromethanesulfonimide ($PhNTf_2$) to afford triflate **23**. Deprotection of the phenol using tetrakis(triphenylphosphine)palladium(0) [$Pd(PPh_3)_4$] and tributyltin hydride (Bu_3SnH) gave the model cyclization precursor **11**.

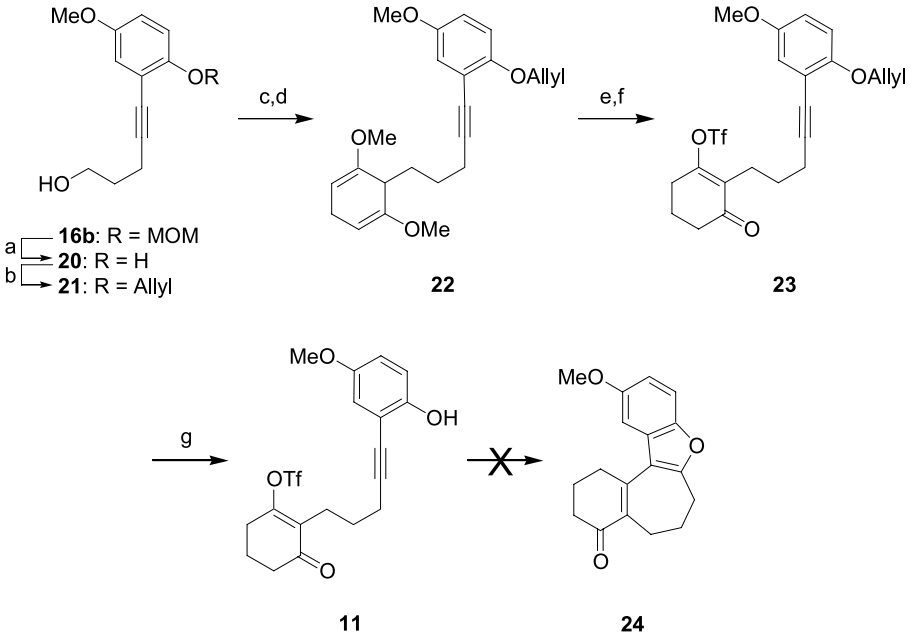
Despite efforts to convert **11** into **24** with a range of palladium reagents, however, we were unable to effect the desired cyclization. Instead, extensive decomposition of the starting material took place.

Contemplating the mechanism of the Arcadi–Cacchi reaction we wondered whether base-catalyzed benzofuran formation might actually precede formation of an organopalladium(II) species. In this case, benzofuran **25** would be a distinct intermediate along the reaction pathway (Scheme 9). The missing C–C bond would be formed from this intermediate through a Heck-type process.

Luckily, benzofuran **25** was already in our hands at this time. Formed serendipitously from **23** when the crude deallylation reaction mixture was left standing at room temperature, **25** was subjected to a catalytic amount of palladium(II) acetate [$Pd(OAc)_2$]. Much to our delight, the desired cyclization occurred. Thus, we found that efficient, palladium-catalyzed bond formation could indeed be



Scheme 7. Reagents and conditions: (a) DHP, TFA, 0 °C to rt, 32%; (b) *n*-BuLi, THF, −78 °C to rt, then I_2, −30 °C, 70%; (c) $TBABr_3$, MeOH, CH_2Cl_2, rt, 81%; (d) NaH, DMF, 0 °C, then MOMCl, 98%; (e) 4-pentyn-1-ol, $Pd(PPh_3)_2Cl_2$, CuI, *n*-$BuNH_2$, reflux, **16a**: 75%, **16b**: 67%; (f) MsCl, Et_3N, THF, 0 °C; NaI, Me_2CO, reflux, from **16a**: 66%, from **16b**: 94%; (e) 1,5-dimethoxylithiocyclohexa-1,4-diene, HMPA, THF, −78 °C, **17a**: 37% (mono-enol ether: 8%), **17b**: 53% (mono-enol ether: 13%).



Scheme 8. Reagents and conditions: (a) HCl, H_2O, MeOH, rt, 65%; (b) allyl bromide, K_2CO_3, DMF, rt, 82%; (c) MsCl, Et_3N, THF, 0 °C; NaI, Me_2CO, reflux, 97%; (d) 1,5-dimethoxylithiocyclohexa-1,4-diene, HMPA, THF, −78 °C, 57% (mono-enol ether: 13%); (e) HCl, Me_2CO, 0 °C; (f) NaHMDS, THF, 0 °C, then $PhNTf_2$, 62% (two steps); (g) $Pd(PPh_3)_4$, *p*-nitrophenol, Bu_3SnH, CH_2Cl_2, rt, 58%.

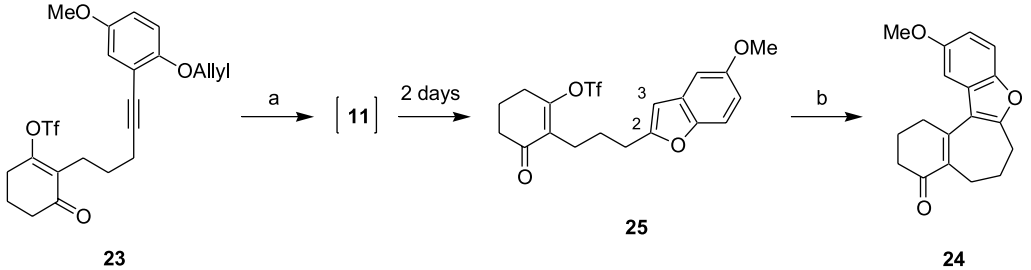
achieved provided the benzofuran moiety was already in place. This reaction, representing the first known Heck-type cyclization onto C3 of a benzofuran, closed the central seven-membered ring of **24** and assembled the tetracyclic ring system found in frondosin B.

3. The natural product

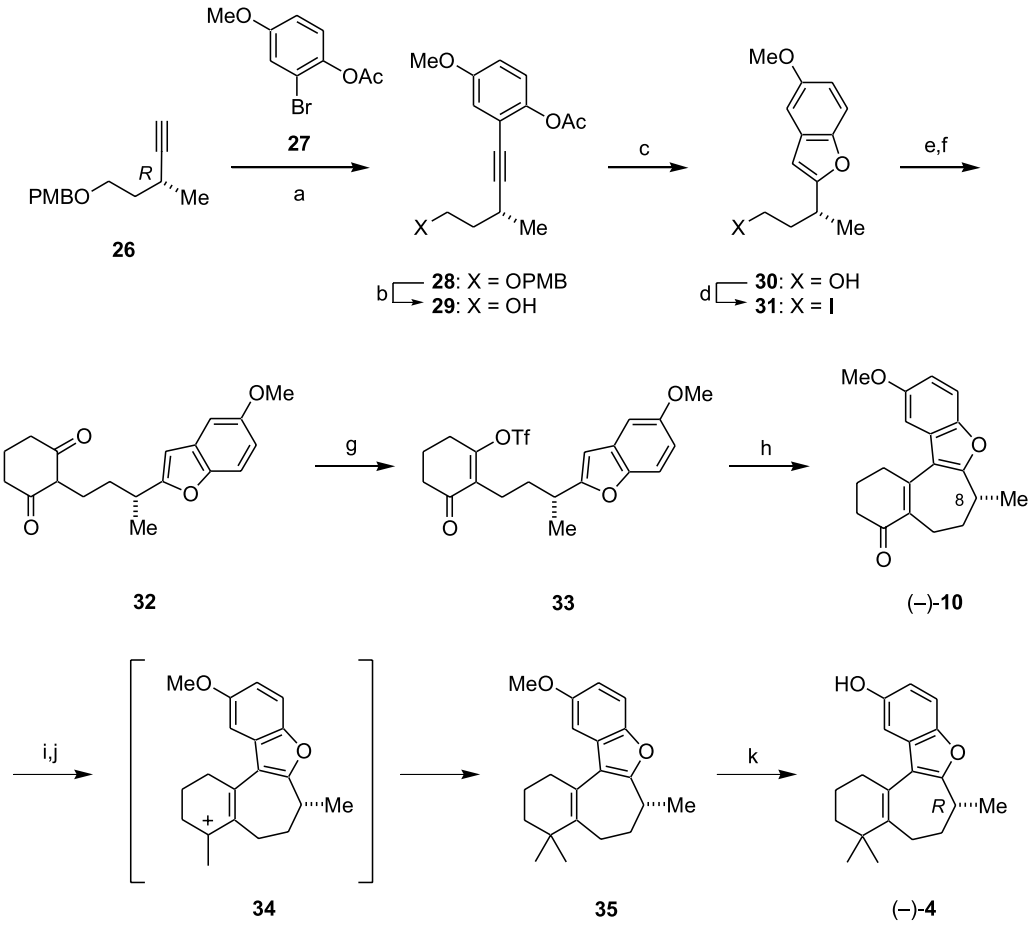
Encouraged by the success of the model studies, we began work toward the asymmetric total synthesis of (+)-frondosin B, starting with the known *R*-configured alkyne **26** (obtained in 91% ee by means of a Sharpless epoxidation) and the known aryl bromide **27**. (Scheme 10).[15,16] An acetate ester, **27** is well-suited for Sonogashira coupling relative to **15** and **19** since oxidative addition of Pd(0) should be enhanced by the electron-withdrawing nature of this substituent. Indeed, coupling of these two components was achieved in high yield, provided alkyne **26** was added slowly to the reaction mixture with a syringe pump. Following acidic deprotection to yield primary alcohol **29**,[17] treatment with K_2CO_3 in methanol effected saponification of the phenolic acetate and concomitant cyclization to afford benzofuran **30** directly.[18] Alkylation of dimethoxylithiocyclohexadiene with iodide **31** followed by hydrolysis afforded cyclohexa-1,3-dione **32**. As before, the diketone decomposed on standing and was therefore immediately converted into enol triflate **33**, setting the stage for the key cyclization.

Treatment of **33** with a catalytic amount of $Pd(PPh_3)_4$ and Hünig's base in dimethyl acetamide (DMA) at 90 °C resulted in the formation of the strategic C10–C11 bond. Importantly, no detectable racemization of the C8 stereocenter occurred under these conditions.[19] The conversion of the carbonyl group into a *gem*-dimethyl moiety was achieved by using a protocol developed by Reetz et al.[20] Reaction of ketone **10** with MeMgBr gave the corresponding crude, highly acid-sensitive tertiary alcohol, which was subsequently subjected to the action of Me_2TiCl_2 (formed in situ from Me_2Zn and $TiCl_4$). Upon addition of the reagent, an intense dark violet color was observed, which presumably originates from the stabilized carbocation **34** formed as an intermediate. Overall, this procedure afforded *O*-methyl frondosin B (**35**) in good yield without contamination by double bond isomers. Finally, *O*-demethylation following a previously reported procedure gave frondosin B (**4**) in high optical purity.[8]

To our surprise, however, the optical rotation of the



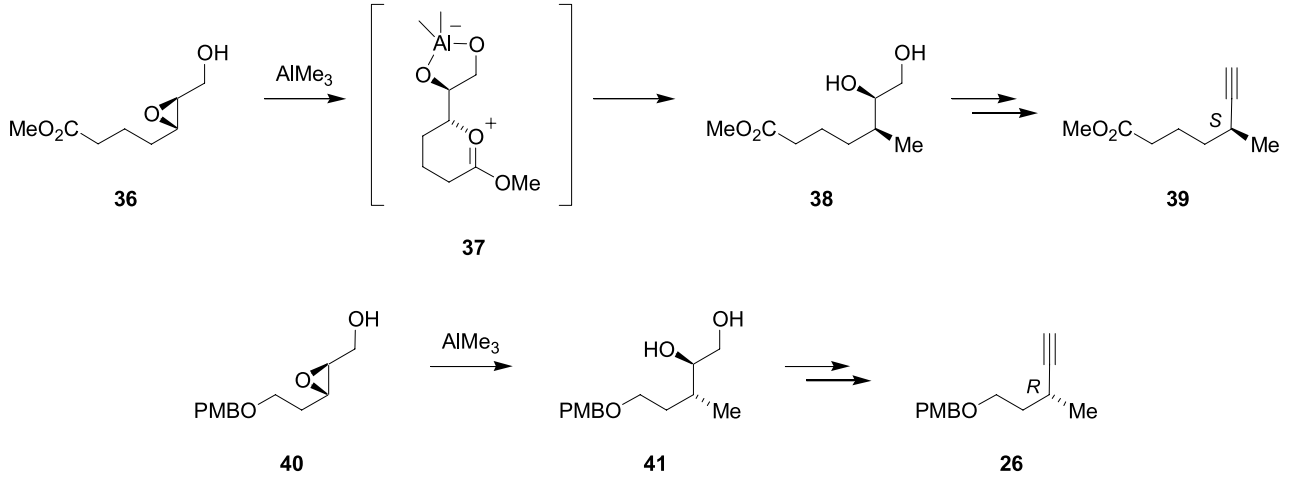
Scheme 9. Reagents and conditions: (a) $Pd(PPh_3)_4$, *p*-nitrophenol, Bu_3SnH, CH_2Cl_2, rt, 28%; (b) $Pd(OAc)_2$, PPh_3, Et_3N, MeCN, reflux, 54%.



Scheme 10. The total synthesis of (−)-frondosin B. Reagents and conditions: (a) $Pd(PPh_3)_4$, CuI, Et_3N, MeCN, reflux, 94%; (b) TFA, CH_2Cl_2, rt, 83%; (c) K_2CO_3, MeOH, reflux, 92%; (d) MsCl, Et_3N, THF, 0 °C; NaI, Me_2CO, reflux, 93%; (e) 1,5-dimethoxylithiocyclohexa-1,4-diene, HMPA, THF, −78 °C to rt, 67% (mono-enol ether: 17%); (f) ion-exchange resin, Me_2CO, H_2O, reflux; (g) NaHMDS, THF, Et_2O, 0 °C, then $PhNTf_2$, 75% (2 steps); (h) $Pd(PPh_3)_4$, *i*-Pr_2NEt, DMA, 90 °C, 70%; (i) MeMgBr, THF, −78 °C to rt; (j) Me_2Zn, $TiCl_4$, CH_2Cl_2, −78 °C to rt, 82% (2 steps); (k) NaSEt, DMF, reflux, 90%.

R-configured material thus obtained was opposite to that of the natural product ($[\alpha]_D = -16.8$ compared to $[\alpha]_D = +18.6$). Though the natural product had been assigned the *R* configuration in the synthesis by Danishefsky et al., according to our work, (+)-frondosin B is *S*-configured. To reconcile this discrepancy, we put forward the notion that Danishefsky's material underwent an unnoticed inversion of configuration at an early stage of the synthesis (Scheme 11).

The most likely candidate for such a switch is the nucleophilic opening of an epoxy alcohol **36** with trimethylaluminum ($AlMe_3$), which probably proceeded with unwanted retention of configuration through



Scheme 11. Double inversion of a stereocenter.

participation of the ester carbonyl group to produce **38** (via transition state **37**).[21] This diol was elaborated to *S*-configured alkyne **39** and ultimately to the *S*-configured natural product. Presumably, this double inversion of configuration did not occur when, in our case, epoxy alcohol **40** was likewise treated with $AlMe_3$ to give **41**. Here, the resulting diol was elaborated to *R*-configured alkyne **26**, as expected.

4. Conclusion

We have achieved a facile, asymmetric total synthesis of (−)-frondosin B [(−)-**4**] from simple starting materials (22% overall yield from the known alkyne **26**) by means of a novel, intramolecular Heck reaction onto a benzofuran. The previously proposed absolute configuration of the natural product was reassigned through our synthesis. The key coupling reaction, which can effect substitution at C3 (and C2) of a variety of aromatic heterocycles, might be successfully employed in other total syntheses as well. In fact, studies toward the total synthesis of rhazinilam, an axially chiral phenylpyrrole isolated from *Rhazya stricta*,[22] using a similar methodology are currently underway in our laboratories and will be reported in due course.

5. Experimental

5.1. General

Tetrahydrofuran (THF) was distilled from Na/benzoquinone, triethylamine (Et_3N) and Hünig's base (*i*-Pr_2NEt) were distilled from CaH_2, and dichloromethane (CH_2Cl_2) and ether (Et_2O) were dried by passing through a column of activated alumina prior to use. Hexamethylphosphoramide (HMPA) was distilled from CaH_2 and stored in a Schlenk tube over 4 Å molecular sieves. 2-(2-Iodo-4-methoxy-phenoxy)-tetrahydro-pyran (**15**) and 2-bromo-4-methoxy-phenol (**42**) were synthesized according to literature methods.[23,24] Acetic acid 2-bromo-4-methoxy-phenyl ester (**27**) was made by treating a solution of **42** in pyridine with acetic anhydride. 1,5-Dimethoxy-cyclohexa-1,4-diene was prepared via Birch reduction of 1,5-dimethoxybenzene.[13] $Pd(PPh_3)_4$ was triturated repeatedly with DMSO, rinsed with MeOH, and dried under vacuum. *n*-Butyllithium (*n*-BuLi) and *t*-butyllithium (*t*-BuLi) were titrated periodically with diphenylacetic acid. All other starting materials and solvents are commercially available and were used without further purification. Chromatography was carried out with ICN SiliTech 32-63 D 60 Å silica gel. Reactions and chromatography fractions were analyzed with Merck silica gel 60 F_{254} plates. Extracts were dried over $MgSO_4$, and solvents were removed with a rotary evaporator at aspirator pressure. Melting points were determined with an electrothermal apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ (7.27 ppm) on a Bruker AM 400 MHz spectrometer.

5.2. Compounds

5.2.1. 5-[5-Methoxy-2-(tetrahydro-pyran-2-yloxy)-phenyl]-pent-4-yn-1-ol (16a). To a solution of **15** (1.70 g, 5.09 mmol) in *n*-$BuNH_2$ (10.2 mL) was added 4-pentyn-1-ol (0.52 mL, 5.6 mmol), CuI (97 mg, 0.51 mmol), and $Pd(PPh_3)_2Cl_2$ (179 mg, 0.255 mmol). The solution, initially green, was heated at reflux for 2 h, cooled, diluted with water (100 mL), and extracted with ether (3×50 mL). The combined organic extracts were washed once with brine (20 mL), dried, filtered, and concentrated. The product was purified by column chromatography (50% EtOAc in hexanes) to afford 1.11 g (75%) of **16a** as a yellowish-brown oil: IR (film): 3422 (br), 2944 cm^{-1}; ^1H NMR: δ 7.02 (d, J=9.2 Hz, 1H), 6.89 (d, J=3.2 Hz, 1H), 6.77 (dd, J=9.2, 3.2 Hz, 1H), 5.37 (t, J=3.2 Hz, 1H), 4.00 (m, 1H), 3.87–3.78 (m, 2H), 3.75 (s, 3H), 3.62–3.55 (m, 1H), 2.58 (t, J=6.8 Hz, 2H), 2.11–1.79 (m, 6H), 1.75–1.55 (m, 3H); ^{13}C NMR: δ 154.1, 151.7, 117.8, 117.4, 115.2, 115.0, 97.7, 93.2, 77.4, 61.9, 61.7, 55.6, 31.3, 30.2, 25.2, 18.6, 16.2; HRMS (EI+): *m/z* (M+) calcd for $C_{17}H_{22}O_4$, 290.1518; found 290.1515.

5.2.2. 2-[2-(5-Iodo-pent-1-ynyl)-4-methoxy-phenyoxy]-tetrahydro-pyran (43a). To a solution of **16a** (1.01 g, 3.48 mmol) in THF (12 mL) at 0 °C was added Et_3N (0.53 mL, 3.8 mmol) followed by MsCl (0.29 mL, 3.5 mmol). After 1 h at 0 °C, the solution was filtered through Celite with ether washings and then concentrated. The mesylated alcohol was dissolved in dry acetone (17 mL), and NaI (2.09 g, 13.9 mmol) was added. The solution was heated at reflux for 2 h, cooled, and filtered through Celite with acetone washings. The product was purified by column chromatography (10% EtOAc in hexanes) to yield 919 mg (66%) of **43a** as a pale yellow oil: IR (film): 2942 cm^{-1}; ^1H NMR: δ 7.00 (d, J=9.2 Hz, 1H), 6.87 (d, J=3.2 Hz, 1H), 6.75 (dd, J=9.2, 3.2 Hz, 1H), 5.35 (t, J=3.2 Hz, 1H), 3.93 (m, 1H), 3.70 (s, 3H), 3.60–3.51 (m, 1H), 3.36 (t, J=6.8 Hz, 2H), 2.56 (t, J=6.4 Hz, 2H), 2.11–1.95 (m, 3H), 1.95–1.77 (m, 2H), 1.73–1.52 (m, 3H); ^{13}C NMR: δ 154.0, 151.7, 117.6, 117.4, 115.0, 97.4, 91.5, 78.0, 61.7, 55.5, 32.2, 30.4, 25.3, 20.6, 18.7, 5.6, 5.5; HRMS (EI+): *m/z* (M+) calcd for $C_{17}H_{21}IO_3$, 400.0535; found 400.0538.

5.2.3. 2-{2-[5-(2,6-Dimethoxy-cyclohexa-2,5-dienyl)-pent-1-ynyl]-4-methoxy-phenoxy}-tetrahydro-pyran (17a) and 3-methoxy-2-{5-[5-methoxy-2-(tetrahydro-pyran-2-yloxy)-phenyl]-pent-4-ynyl}-cyclohex-3-enone (44a). To a solution of *t*-BuLi in pentane (1.5 mL, 1.5 M, 2.3 mmol) at −78 °C was added THF (11.5 mL). A solution of 1,5-dimethoxy-cyclohexa-1,4-diene (311 mg, 2.22 mmol) in THF (2.2 mL) was added dropwise via syringe. After 1 h at −78 °C, HMPA (0.45 mL, 2.7 mmol) was added, followed 15 min later by a solution of **43a** (810 mg, 2.02 mmol) in THF (2.2 mL). After an additional 15 min, the solution was allowed to warm to rt for 1.5 h, then poured into brine (100 mL) and extracted with ether (3×40 mL). The combined organic extracts were washed once with brine (20 mL), dried, filtered, and concentrated. The product was purified by column chromatography (10% EtOAc to 60% EtOAc in hexanes) to give 309 mg (37%) of **17a** and 65 mg (8%) of **44a**, both as colorless oils: **17a**: IR (film): 2942, 1692, 1661 cm^{-1}; ^1H NMR: δ 7.00 (d, J=9.2 Hz, 1H), 6.89 (d, J=3.2 Hz, 1H), 6.76 (dd, J=9.2, 3.2 Hz, 1H), 5.39 (t, J=3.2 Hz, 1H), 4.71 (t, J=3.6 Hz, 2H), 4.07–3.98 (m, 1H), 3.74 (s, 3H), 3.61–3.48 (m, 7H),

2.96 (m, 1H), 2.83–2.76 (m, 2H), 2.39 (t, J=7.2 Hz, 2H), 2.15–1.78 (m, 5H), 1.76–1.42 (m, 5H); ^{13}C NMR: δ 154.2, 151.6, 118.4, 117.4, 116.0, 114.6, 97.7, 94.5, 91.5, 76.4, 61.6, 55.5, 542, 40.5, 30.2, 29.2, 25.3, 24.4, 24.1, 19.8, 18.5; HRMS (EI+): m/z (M+) calcd for $C_{25}H_{32}O_5$, 412.2250; found 412.2245. **44a**: IR (film): 2942, 1649, 1602 cm^{-1}; ^{1}H NMR: δ 6.98 (d, J=9.2 Hz, 1H), 6.86 (d, J=3.2 Hz, 1H), 6.74 (dd, J=9.2, 3.2 Hz, 1H), 5.37–5.32 (m, 1H), 5.30 (s, 1H), 4.01–3.92 (m, 1H), 3.71 (s, 3H), 3.65 (s, 3H), 3.59–3.50 (m, 1H), 2.52–2.21 (m, 5H), 2.12–1.50 (m, 12H); ^{13}C NMR: δ 199.2, 180.9, 154.1, 151.5, 118.0, 118.0, 117.5, 115.4, 114.8, 101.8, 97.5, 97.5, 93.3, 77.2, 61.7, 61.7, 55.5, 55.5, 37.8, 30.3, 30.2, 25.9, 25.2, 18.5; HRMS (EI+) m/z (M+) calcd for $C_{24}H_{30}O_5$, 398.2093; found 398.2088.

5.2.4. 2-Bromo-4-methoxy-1-methoxymethyl-benzene (19). To a solution of **42** (11.7 g, 57.8 mmol) in DMF (200 mL) at 0 °C was added NaH (2.54 g, 60% dispersion in oil, 63.5 mmol) over 5 min. After 10 min at 0 °C, the solution was allowed to warm to rt over 30 min. The mixture was cooled again to 0 °C, and MOMCl (4.40 mL, 57.9 mmol) was slowly added via syringe. The solution, after being stirred at rt for 2 h, was diluted with water (1 L) and extracted with ether (4×200 mL). The combined organic extracts were washed with 1 M NaOH (2× 100 mL) and brine (100 mL), then dried, filtered, and concentrated to afford 14.0 g (98%) of **19** as a colorless oil, which was taken on into the next step without further purification: IR (film): 2957, 2905 cm^{-1}; ^{1}H NMR: δ 7.12–7.04 (m, 2H), 6.81–6.75 (m, 1H), 5.15 (s, 2H), 3.74 (s, 3H), 3.52 (s, 3H); ^{13}C NMR: δ 155.0, 147.8, 118.4, 117.8, 113.8, 113.5, 96.0, 56.2, 55.7; HRMS (EI+): m/z (M+) calcd for $C_9H_{11}BrO_3$, 245.9892; found 245.9891.

5.2.5. 5-(5-Methoxy-2-methoxymethoxy-phenyl)-pent-4-yn-1-ol (16b). The procedure followed was the same as described above for **16a**. The product was purified by column chromatography (50% EtOAc in hexanes) to afford 1.90 g (67%) of **16b** as a yellowish-brown oil: IR (film): 3427 (br), 2949 cm^{-1}; ^{1}H NMR: δ 6.99 (d, J=9.2 Hz, 1H), 6.88 (d, J=3.2 Hz, 1H), 6.76 (dd, J=9.2, 3.2 Hz, 1H), 5.14 (s, 2H), 3.80 (t, J=5.6 Hz, 2H), 3.72 (s, 3H), 3.49 (s, 3H), 2.60–2.46 (m, 3H), 1.89–1.79 (m, 2H); ^{13}C NMR: δ 154.2, 151.8, 117.6, 117.2, 115.1, 114.9, 95.7, 93.6, 77.2, 61.7, 56.1, 55.5, 31.2, 16.4; HRMS (EI+): m/z (M+) calcd for $C_{14}H_{18}O_4$, 250.1205; found 250.1203.

5.2.6. 2-(5-Iodo-pent-1-ynyl)-4-methoxy-1-methoxymethoxy-benzene (43b). The procedure followed was the same as described above for **43a**. The product was purified by column chromatography (10% EtOAc in hexanes) to furnish 2.76 g (94%) of **43b** as a pale yellow oil: IR (film): 2952, 2903 cm^{-1}; ^{1}H NMR: δ 6.99 (d, J=9.2 Hz, 1H), 6.89 (d, J=3.2 Hz, 1H), 6.77 (dd, J=9.2, 3.2 Hz, 1H), 5.15 (s, 2H), 3.72 (s, 3H), 3.50 (s, 3H), 3.38 (t, J=6.8 Hz, 2H), 2.58 (t, J=6.8 Hz, 2H), 2.11–2.01 (m, 2H); ^{13}C NMR: δ 154.2, 151.9, 117.7, 117.3, 115.0, 95.8, 91.8, 77.9, 56.1, 55.6, 32.1, 20.6, 5.5, 5.4; HRMS (EI+): m/z (M+) calcd for $C_{14}H_{17}IO_3$, 360.0222; found 360.0215.

5.2.7. 2-[5-(2,6-Dimethoxy-cyclohexa-2,5-dienyl)-pent-1-ynyl]-4-methoxy-1-methoxymethoxy-benzene (17b) and 3-methoxy-2-[5-(5-methoxy-2-methoxymethoxy-phenyl)-pent-4-ynyl]-cyclohex-3-enone (44b). The procedure followed was the same as described above for **17a/44a**. The product was purified by column chromatography (15% EtOAc to 60% EtOAc in hexanes) to give 1.06 g (53%) of **17b** and 257 mg (13%) of **44b**, both as colorless oils: **17b**: IR (film): 2948, 2903, 2827, 1691 cm^{-1}; ^{1}H NMR: δ 6.96 (d, J=9.2 Hz, 1H), 6.89 (d, J=3.2 Hz, 1H), 6.72 (dd, J=9.2, 3.2 Hz, 1H), 5.12 (s, 2H), 4.67 (t, J=3.2 Hz, 2H), 3.69 (s, 3H), 3.50 (s, 6H), 3.48 (s, 3H), 2.94 (m, 1H), 2.81–2.72 (m, 2H), 2.37 (t, J=7.2 Hz, 2H), 1.90–1.79 (m, 2H), 1.54–1.41 (m, 2H); ^{13}C NMR: δ 154.4, 154.2, 151.7, 117.9, 117.8, 115.9, 114.5, 96.0, 94.6, 91.5, 76.5, 55.9, 55.3, 54.0, 40.5, 29.1, 24.4, 24.0, 19.7; HRMS (EI+): m/z (M+) calcd for $C_{22}H_{28}O_5$, 372.1937; found 372.1946. **44b**: IR (film): 2941, 1649, 1602 cm^{-1}; ^{1}H NMR: δ 6.94 (d, J=9.2 Hz, 1H), 6.83 (d, J=3.2 Hz, 1H), 6.70 (dd, J=9.2, 3.2 Hz, 1H), 5.26 (s, 1H), 5.07 (s, 2H), 3.67 (s, 3H), 3.61 (s, 3H), 3.43 (s, 3H), 2.49–2.32 (m, 4H), 2.27–2.17 (m, 1H), 2.08–1.94 (m, 1H), 191–1.73 (m, 2H), 1.73–1.50 (m, 3H); ^{13}C NMR: δ 199.1, 180.9, 154.2, 151.7, 117.8, 117.6, 115.3, 114.7, 101.7, 95.9, 93.5, 77.1, 56.0, 55.5, 55.5, 37.8, 33.9, 30.2, 26.4, 25.8, 19.6; HRMS (EI+): m/z (M+) calcd for $C_{21}H_{26}O_5$, 358.1780; found 358.1783.

5.2.8. 2-(5-Hydroxy-pent-1-ynyl)-4-methoxy-phenol (20). To a solution of **16b** (2.34 g, 9.34 mmol) in MeOH (46 mL) was added conc. HCl (1.8 mL) dropwise. After 4 h the reaction mixture was diluted with water (200 mL) and extracted with ether (3×100 mL). The combined organic extracts were washed once with brine (50 mL), dried, filtered, and concentrated. The product was purified by column chromatography (50% EtOAc in hexanes) and recrystallized from ether to yield 1.26 g (65%) of **20** as a white solid: mp 80–82 °C; IR (KBr): 3423, 3079 (br), 2954 cm^{-1}; ^{1}H NMR: δ 6.83–6.72 (m, 3H), 3.83 (t, J=5.6 Hz, 2H), 3.72 (s, 3H), 2.94 (br s, 1H), 2.57 (t, J=6.8 Hz, 2H), 1.90–1.79 (m, 2H), phenolic –OH group exchanged; ^{13}C NMR: δ 152.7, 151.3, 116.3, 115.5, 115.4, 110.2, 96.2, 75.8, 61.8, 55.7, 30.9, 16.5; HRMS (EI+): m/z (M+) calcd for $C_{12}H_{14}O_3$, 206.0943; found 206.0940.

5.2.9. 5-(2-Allyloxy-5-methoxy-phenyl)-pent-4-yn-1-ol (21). To a solution of **20** (1.19 g, 5.77 mmol) in DMF (30 mL) was added K_2CO_3 (2.39 g, 17.3 mmol) followed by allyl bromide (0.65 mL, 7.5 mmol). The mixture was diluted 12 h later with water (200 mL) and extracted with CH_2Cl_2 (3×50 mL). The combined organic extracts were dried, filtered, and concentrated. The product was purified by column chromatography (50% EtOAc in hexanes) to afford 1.16 g (82%) of **21** as a colorless oil: IR (film): 3374 (br), 2948 cm^{-1}; ^{1}H NMR: δ 6.91–6.86 (m, 1H), 6.78–6.70 (m, 2H), 6.04 (m, 1H), 5.40 (m, 1H), 5.25 (m, 1H), 4.52 (m, 2H), 3.80 (t, J=6.0 Hz, 2H), 3.72 (s, 3H), 2.55 (t, J=6.8 Hz, 2H), 2.52 (br s, 1H), 1.84 (m, 2H); ^{13}C NMR: δ 153.3, 153.3, 133.4, 117.8, 117.2, 114.7, 114.2, 114.2, 93.7, 76.7, 70.2, 61.7, 55.6, 31.2, 16.4; HRMS (EI+): m/z (M+) calcd for $C_{15}H_{18}O_3$, 246.1256; found 246.1251.

5.2.10. 1-Allyloxy-2-(5-iodo-pent-1-ynyl)-4-methoxy-benzene (45). The procedure followed was the same as described above for **43a**. The product was purified by column chromatography (10% EtOAc in hexanes) to furnish 1.57 g (97%) of **45** as a pale yellow oil: IR (film):

2936 cm^{-1}; ^1H NMR: δ 6.93–6.89 (m, 1H), 6.80–6.73 (m, 2H), 6.06 (m, 1H), 5.44 (m, 1H), 5.28 (m, 1H), 4.52 (m, 2H), 3.74 (s, 3H), 3.40 (t, $J=6.8$ Hz, 2H), 2.60 (t, $J=6.8$ Hz, 2H), 2.09 (m, 2H); ^{13}C NMR: δ 153.5, 153.3, 133.4, 117.9, 117.3, 114.8, 114.62, 114.1, 92.0, 77.9, 70.2, 55.6, 32.2, 20.7, 5.6; HRMS (EI+): *m/z* (M+) calcd for $C_{15}H_{17}IO_2$, 356.0273; found 356.0277.

5.2.11. 1-Allyloxy-2-[5-(2,6-dimethoxy-cyclohexa-2,5-dienyl)-pent-1-ynyl]-4-methoxy-benzene (22) and 2-[5-(2-allyloxy-5-methoxy-phenyl)-pent-4-ynyl]-3-methoxy-cyclohex-3-enone (46). The procedure followed was the same as described above for **17a/44a**. The product was purified by column chromatography (10% EtOAc to 60% EtOAc in hexanes) to give 2.05 g (57%) of **22** and 458 mg (13%) of **46**, both as colorless oils: **22**: IR (film): 2937, 2832, 1692, 1661 cm^{-1}; ^1H NMR: δ 6.93 (d, $J=2.8$ Hz, 1H), 6.81–6.71 (m, 2H), 6.07 (m, 1H), 5.44 (m, 1H), 5.26 (m, 1H), 4.72 (t, $J=3.2$ Hz, 2H), 4.55 (m, 2H), 3.75 (s, 3H), 3.55 (s, 6H), 3.01–2.93 (m, 1H), 2.85–2.78 (m, 2H), 2.41 (t, $J=7.2$ Hz, 2H), 1.90–1.80 (m, 2H), 1.57–1.45 (m, 2H); ^{13}C NMR: δ 154.2, 153.5, 153.3, 133.6, 118.1, 117.0, 114.9, 114.7, 144.4, 95.0, 91.5, 76.3, 70.5, 55.6, 54.2, 40.5, 29.2, 24.4, 24.1, 19.9; HRMS (EI+): *m/z* (M+) calcd for $C_{23}H_{28}O_4$, 368.1988; found 368.1983. **46**: IR (film): 2940, 2865, 1650, 1602 cm^{-1}; ^1H NMR: δ 6.90 (d, $J=2.4$ Hz, 1H), 6.80–6.72 (m, 2H), 6.03 (m, 1H), 5.42 (m, 1H), 5.32 (s, 1H), 5.24 (m, 1H), 4.53 (m, 2H), 3.74 (s, 3H), 3.67 (s, 3H), 2.56–2.39 (m, 4H), 2.34–2.23 (m, 1H), 2.13–2.01 (m, 1H), 1.96–1.80 (m, 2H), 1.80–1.60 (m, 3H); ^{13}C NMR: δ 199.3, 181.0, 153.4, 153.3, 133.5, 118.1, 117.0, 114.6, 114.4, 114.3, 101.8, 93.7, 77.1, 70.2, 55.6, 55.6, 37.9, 34.0, 30.3, 26.5, 25.9, 19.7; HRMS (EI+): *m/z* (M+) calcd for $C_{22}H_{26}O_4$, 354.1831; found 354.1828.

5.2.12. Trifluoro-methanesulfonic acid 2-[5-(2-allyloxy-5-methoxy-phenyl)-pent-4-ynyl]-3-oxo-cyclohex-1-enyl ester (23). To a solution of **22** (3.47 g, 9.42 mmol) and **46** (0.730 g, 2.06 mmol) in acetone (120 mL) at 0 °C was added 1 M HCl (5.7 mL, 5.7 mmol). After 3.5 h the solution was neutralized to pH 7 with a saturated $NaHCO_3$ solution and diluted with water (200 mL). The mixture was extracted with CH_2Cl_2 (3×50 mL), and the combined organic extracts were then dried, filtered, and concentrated in an ice bath. The crude diketone was immediately dissolved in THF (115 mL) and cooled to 0 °C. A solution of NaHMDS in THF (13.7 mL, 1.0 M, 13.7 mmol) was added dropwise via syringe, followed 30 min later by a solution of $PhNTf_2$ (4.89 g, 13.7 mmol) in THF (12 mL). After 2 h at 0 °C, the solution was diluted with brine (100 mL) and extracted with ether (3×100 mL). The combined organic extracts were washed once with brine (50 mL), dried, filtered, and concentrated. The product was purified by column chromatography (20% EtOAc in hexanes) to yield 3.32 g (62% over two steps) of **23** as a pale yellow oil: IR (film): 2940, 1690 cm^{-1}; ^1H NMR: δ 6.94 (d, $J=2.4$ Hz, 1H), 6.81–6.73 (m, 2H), 6.06 (m, 1H), 5.42 (m, 1H), 5.25 (m, 1H), 4.55 (m, 2H), 3.75 (s, 3H), 2.76 (t, $J=6.4$ Hz, 2H), 2.58–2.41 (m, 6H), 2.06 (m, 2H), 1.74 (m, 2H); ^{13}C NMR: δ 197.1, 162.1, 153.4, 153.4, 133.5, 131.4, 118.1 (q, $J=320$ Hz), 117.9, 117.0, 114.9, 114.6, 114.50, 93.4, 77.2, 70.4, 55.6, 36.7, 28.6, 27.2, 23.2, 20.5, 19.7; HRMS (FAB+): *m/z* (M+) calcd for $C_{22}H_{23}F_3O_6S$ 472.1167; found 472.1170.

5.2.13. Trifluoro-methanesulfonic acid 2-[5-(2-hydroxy-5-methoxy-phenyl)-pent-4-ynyl]-3-oxo-cyclohex-1-enyl ester (11). To a solution of $Pd(PPh_3)_4$ (59 mg, 0.051 mmol) in CH_2Cl_2 (8 mL) was added a solution of **23** (240 mg, 0.508 mmol) in CH_2Cl_2 (2 mL). *p*-Nitrophenol (707 mg, 5.08 mmol) was added, followed by Bu_3SnH (0.47 mL, 1.8 mmol) dropwise via syringe. After 30 min the solution was diluted with water (50 mL) and extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were washed once with brine (20 mL), dried, filtered, and concentrated. The product was purified by preparative HPLC (20% EtOAc in hexanes) to furnish 127 mg (58%) of **11** as a pale yellow oil: IR (film): 3500 (br), 2942, 1687 cm^{-1}; ^1H NMR: δ 6.92–6.73 (m, 3H), 6.03 (br s, 1H), 3.74 (s, 3H), 2.76 (t, $J=6.0$ Hz, 2H), 2.61–2.43 (m, 6H), 2.08 (m, 2H), 1.73 (m, 2H); ^{13}C NMR: δ 197.6, 162.5, 152.7, 151.1, 131.2, 118.1 (q, $J=320$ Hz), 116.5, 115.4, 115.4, 110.0, 96.0, 75.7, 55.6, 36.6, 28.5, 26.9, 22.7, 20.4, 19.4; HRMS (FAB+): *m/z* (M+) calcd for $C_{19}H_{19}F_3O_6S$ 432.0854; found 432.0858.

5.2.14. Trifluoro-methanesulfonic acid 2-[3-(5-methoxy-benzofuran-2-yl)-propyl]-3-oxo-cyclohex-1-enyl ester (25). To a solution of $Pd(PPh_3)_4$ (470 mg, 0.406 mmol) in CH_2Cl_2 (70 mL) was added a solution of **23** (1.92 g, 4.06 mmol) in CH_2Cl_2 (10 mL). *p*-Nitrophenol (2.82 g, 20.3 mmol) was added, followed by Bu_3SnH (3.70 mL, 13.8 mmol) dropwise via syringe. After 6 h the solution was diluted with brine (100 mL) and extracted with CH_2Cl_2 (4× 50 mL). The combined organic extracts were dried, filtered, and concentrated. The crude product was left standing at rt for ~2 d and was then diluted with CH_2Cl_2 (300 mL). The solution was washed successively with 1 M NaOH (3× 100 mL), water (100 mL), brine (50 mL), dried, filtered, and concentrated. The product was purified by column chromatography (20% EtOAc in hexanes), then by preparative HPLC (15% EtOAc in hexanes) to give 448 mg (28%) of **25** as a pale yellow oil: IR (film): 2940, 1687 cm^{-1}; ^1H NMR: δ 7.28 (d, $J=9.2$ Hz, 1H), 6.95 (d, $J=2.4$ Hz, 1H), 6.80 (dd, $J=9.2$, 2.4 Hz, 1H), 6.36 (s, 1H), 3.83 (s, 3H), 2.77 (t, $J=7.2$ Hz, 2H), 2.71 (t, $J=6.4$ Hz, 2H), 2.50–2.40 (m, 4H), 2.00 (m, 2H), 1.86 (m, 2H); ^{13}C NMR: δ 197.2, 162.1, 159.3, 155.6, 149.5, 131.3, 129.4, 118.3 (q, $J=320$ Hz), 111.4, 110.9, 103.0, 102.3, 55.8, 36.6, 28.5, 28.3, 25.9, 23.3, 20.4; HRMS (EI+): *m/z* (M+) calcd for $C_{19}H_{19}F_3O_6S$ 432.0854; found 432.0857.

5.2.15. 11-Methoxy-1,2,3,5,6,7-hexahydro-8-oxa-dibenzo[*a,h*]azulen-4-one (24). To a solution of **25** (448 mg, 1.04 mmol) in MeCN (26 mL) was added $Pd(OAc)_2$ (37 mg, 0.16 mmol), PPh_3 (55 mg, 0.21 mmol), and Et_3N (0.29 mL, 2.1 mmol). The reaction mixture was heated at reflux for 14 h, cooled, diluted with water (100 mL), and extracted with CH_2Cl_2 (3×50 mL). The combined organic extracts were washed once with brine (50 mL), dried, filtered, and concentrated. The product was purified by preparative HPLC (15% EtOAc in hexanes) to afford 160 mg (54%) of **24** as a white solid: mp 133–135 °C; IR (KBr) 2940, 1645 cm^{-1}; ^1H NMR: δ 7.30 (d, $J=9.2$ Hz, 1H), 7.13 (d, $J=2.4$ Hz, 1H), 6.85 (dd, $J=9.2$, 2.4 Hz, 1H), 3.84 (s, 3H), 3.05 (t, $J=7.2$ Hz, 2H), 2.99 (t, $J=6.0$ Hz, 2H), 2.60 (m, 2H), 2.53 (t, $J=6.4$ Hz, 2H), 2.10 (m, 2H), 1.94 (m, 2H); ^{13}C NMR: δ 197.5, 161.1, 155.8, 149.2, 148.8, 136.4, 128.2, 116.5, 111.4, 111.2, 105.5, 56.0, 37.6, 30.5,

29.5, 25.6, 23.4, 22.7; HRMS (EI+): *m/z* (M+) calcd for $C_{18}H_{18}O_3$ 282.1256; found 282.1252.

5.2.16. Acetic acid 4-methoxy-2-[(*R*)-5-(4-methoxy-benzyloxy)-3-methyl-pent-1-ynyl]-phenyl ester (28). A solution of **27** (4.40 g, 18.0 mmol) in Et_3N (15 mL) and MeCN (15 mL) was purged for 15 min with a gentle stream of argon. $Pd(PPh_3)_4$ (518 mg, 0.448 mmol) and CuI (171 mg, 0.898 mmol) were then added. The mixture was heated at reflux, and a solution of **26** (1.96 g, 8.98 mmol) in MeCN (5 mL), previously purged with argon as well, was added via syringe pump over 6 h. The solution was heated at reflux for an additional 16 h, cooled, poured into a saturated $NaHCO_3$ solution (200 mL), and extracted with ether (3× 100 mL). The combined organic extracts were washed once with brine (50 mL), dried, filtered, and concentrated. The product was purified by column chromatography (20% EtOAc in hexanes) to furnish 3.24 g (94%) of **28** as a pale yellow oil: $[\alpha]_D=-70.0$ ($c=1.00$, $CHCl_3$); IR (film): 2935, 2861, 1765, 1612 cm^{-1}; ^1H NMR: δ 7.31–7.26 (m, 2H), 6.99–6.81 (m, 5H), 4.48 (s, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 3.69–3.60 (m, 2H), 2.95–2.84 (m, 1H), 2.92 (s, 3H), 1.89–1.71 (m, 2H), 1.27 (d, $J=6.8$ Hz, 3H); ^{13}C NMR: δ 169.4, 159.4, 157.2, 145.4, 130.8, 129.4, 122.9, 118.6, 117.5, 115.1, 114.0, 99.2, 76.1, 72.9, 68.0, 55.8, 55.4, 37.1, 23.8, 21.3, 21.0; HRMS (FAB+): *m/z* (M+) calcd for $C_{23}H_{26}O_5$ 382.1780; found 382.1786.

5.2.17. Acetic acid 2-((*R*)-5-hydroxy-3-methyl-pent-1-ynyl)-4-methoxy-phenyl ester (29). To a solution of **28** (1.04 g, 2.72 mmol) in CH_2Cl_2 (25 mL) was added TFA (2.7 mL) dropwise via syringe. After 10 min the mixture was poured into a saturated $NaHCO_3$ solution (200 mL) and extracted with ether (3×100 mL). The combined organic extracts were washed once with brine (50 mL), dried, filtered, and concentrated. The product was purified by column chromatography (50% EtOAc in hexanes) to furnish 591 mg (83%) of **29** as a pale yellow oil: $[\alpha]_D=-37.1$ ($c=1.00$, $CHCl_3$); IR (film): 3449 (br), 2935, 1765 cm^{-1}; ^1H NMR: δ 6.98–6.91 (m, 2H), 6.86–6.80 (m, 1H), 3.89–3.79 (m, 2H), 3.78 (s, 3H), 2.86 (m, 1H), 2.31 (s, 3H), 1.91–1.65 (m, 3H), 1.29 (d, $J=6.8$ Hz, 3H); ^{13}C NMR: δ 169.5, 157.2, 145.4, 123.0, 118.4, 117.4, 115.3, 98.9, 76.5, 61.1, 55.8, 39.6, 23.7, 21.3, 21.0; HRMS (EI+): *m/z* (M+) calcd for $C_{15}H_{18}O_4$ 262.1205; found 262.1205.

5.2.18. (*R*)-3-(5-Methoxy-benzofuran-2-yl)-butan-1-ol (30). To a solution of **29** (580 mg, 2.21 mmol) in MeOH (22 mL) was added K_2CO_3 (733 mg, 5.30 mmol), and the mixture was heated at reflux for 5 h. The solution was cooled, poured into a saturated NH_4Cl solution (200 mL), and extracted with CH_2Cl_2 (3×100 mL). The combined organic extracts were dried, filtered, and concentrated. The product was purified by column chromatography (40% EtOAc in hexanes) to yield 450 mg (92%) of **30** as a colorless oil: $[\alpha]_D=-33.0$ ($c=1.00$, $CHCl_3$); IR (film): 3349 (br), 2936, 1615, 1602 cm^{-1}; ^1H NMR: δ 7.31 (d, $J=9.2$ Hz, 1H), 6.98 (d, $J=2.4$ Hz, 1H), 6.83 (dd, $J=9.2$, 2.4 Hz, 1H), 6.35 (s, 1H), 3.84 (s, 3H), 3.69 (m, 2H), 3.14 (m, 1H), 2.08–1.98 (m, 1H), 1.92–1.81 (m, 1H), 1.62 (br s, 1H), 1.37 (d, $J=7.2$ Hz, 3H); ^{13}C NMR: δ 164.1, 156.0, 149.7, 129.5, 111.8, 111.4, 103.5, 101.4, 60.9, 56.1, 38.5, 30.5, 19.3; HRMS (EI+): *m/z* (M+) calcd for $C_{13}H_{16}O_3$ 220.1099; found 220.1099.

5.2.19. 2-((*R*)-3-Iodo-1-methyl-propyl)-5-methoxy-benzofuran (31). The procedure followed was the same as described above for **43a**. The product was purified by column chromatography (5% EtOAc in hexanes) to yield 1.18 g (93%) of **31** as a light brown oil: $[\alpha]_D=-86.8$ ($c=1.00$, $CHCl_3$); IR (film): 2966, 2933, 1616, 1602 cm^{-1}; ^1H NMR: δ 7.32 (d, $J=8.8$ Hz, 1H), 6.99 (d, $J=2.4$ Hz, 1H), 6.85 (dd, $J=8.8$, 2.4 Hz, 1H), 6.40 (s, 1H), 3.85 (s, 3H), 3.28–3.19 (m, 1H), 3.17–3.06 (m, 2H), 2.36–2.23 (m, 1H), 2.17–2.05 (m, 1H), 1.37 (d, $J=7.2$ Hz, 3H); ^{13}C NMR: δ 162.4, 156.0, 149.8, 129.3, 112.0, 111.4, 103.5, 102.2, 56.2, 39.2, 34.8, 18.7, 4.3; HRMS (EI+): *m/z* (M+) calcd for $C_{13}H_{15}IO_2$ 330.0117; found 330.0116.

5.2.20. 2-[(*R*)-3-(2,6-Dimethoxy-cyclohexa-2,5-dienyl)-1-methyl-propyl]-5-methoxy-benzofuran (47) and 3-methoxy-2-[(*R*)-3-(5-methoxy-benzofuran-2-yl)-butyl]-cyclohex-3-enone (48). The procedure followed was the same as described above for **17a/44a**. The product was purified by column chromatography (8% EtOAc to 60% EtOAc in hexanes) to furnish 743 mg (67%) of **47** and 182 mg (17%) of **48**, both as colorless oils: **47**: $[\alpha]_D=+17.6$ ($c=1.00$, $CHCl_3$); IR (film): 2935, 2830, 1692 cm^{-1}; ^1H NMR: δ 7.30 (d, $J=8.8$ Hz, 1H), 6.97 (d, $J=2.4$ Hz, 1H), 6.81 (dd, $J=8.8$, 2.4 Hz, 1H), 6.28 (m, 1H), 4.74 (t, $J=3.6$ Hz, 2H), 3.84 (s, 3H), 3.54 (s, 3H), 3.52 (s, 3H), 3.00–2.71 (m, 4H), 1.85–1.69 (m, 2H), 1.69–1.56 (m, 1H), 1.49–1.37 (m, 1H), 1.29 (d, $J=6.8$ Hz, 3H); HRMS (FAB+): *m/z* (M+) calcd for $C_{21}H_{26}O_4$ 342.1831; found 342.1825. **48**: $[\alpha]_D=-34.6$ ($c=1.00$, $CHCl_3$); IR (film): 2939, 1737, 1659, 1602 cm^{-1}; ^1H NMR: δ 7.30 (d, $J=8.8$ Hz, 1H), 6.98 (d, $J=2.4$ Hz, 1H), 6.82 (dd, $J=8.8$, 2.4 Hz, 1H), 6.33 (s, 1H), 5.31 (t, $J=3.6$ Hz, 1H), 3.84 (s, 3H), 3.66 (s, 3H), 3.00–2.85 (m, 1H), 2.49–2.33 (m, 2H), 2.33–2.21 (m, 1H), 2.11–2.00 (m, 1H), 1.94–1.45 (m, 5H), 1.34 (d, $J=6.8$ Hz, 3H); HRMS (FAB+): *m/z* (MH+) calcd for $C_{20}H_{25}O_4$ 329.1753; found 329.1749.

5.2.21. Trifluoro-methanesulfonic acid 2-[(*R*)-3-(5-methoxy-benzofuran-2-yl)-butyl]-3-oxo-cyclohex-1-enyl ester (33). To a solution of **47** (743 mg, 2.17 mmol) and **48** (182 mg, 0.55 mmol) in acetone (46 mL) and water (9 mL) was added a strongly acidic cation exchange resin (400 mg, Bio-Rad® AG MP-50, 100-200 mesh), and the mixture was heated at reflux for 18 h. Additional resin (800 mg) was added in increments, and after continued refluxing for 24 h, the solution was filtered through Celite, diluted with brine (50 mL), and extracted with ether (5×100 mL). The combined organic extracts were dried, filtered, and concentrated to about 20 mL: HRMS (EI+): *m/z* (M+) calcd for $C_{19}C_{22}O_4$ 314.1518; found 314.1517. The solution was passed through a plug of silica, concentrated again to about 20 mL, and then diluted with THF (27 mL). A solution of NaHMDS in THF (3.5 mL, 1.0 M, 3.5 mmol) was added via syringe. After 30 min, a solution of $PhNTf_2$ (1.07 g, 3.00 mmol) in THF (6.0 mL) was added dropwise via cannula. After 2 h, the solution was diluted with water (100 mL) and extracted with ether (3×100 mL). The combined organic extracts were washed once with brine (50 mL), dried, filtered, and concentrated. The product was purified by column chromatography (15% EtOAc in

hexanes) to afford 892 mg (74%) of **33** as a colorless oil: $[\alpha]_D = -8.4$ ($c = 1.00$, $CHCl_3$); IR (film): 2967, 2938, 1690 cm^{-1}; ^1H NMR: δ 7.30 (d, $J = 8.8$ Hz, 1H), 6.97 (d, $J = 2.4$ Hz, 1H), 6.81 (dd, $J = 8.8$, 2.4 Hz, 1H), 6.38 (s, 1H), 3.84 (s, 3H), 2.95 (m, 1H), 2.66 (m, 2H), 2.45–2.37 (m, 4H), 2.00–1.83 (m, 3H), 1.76–1.65 (m, 1H), 1.35 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR: δ 197.5, 163.9, 162.2, 156.0, 149.8, 131.8, 129.6, 118.5 (q, $J = 320$ Hz), 111.8, 111.4, 103.4, 101.5, 56.2, 37.0, 34.1, 33.5, 28.8, 21.9, 20.6, 19.2; HRMS (FAB+): m/z (M+) calcd for $C_{20}H_{21}F_3O_6S$ 446.1011; found 446.1005.

5.2.22. (*R*)-11-Methoxy-7-methyl-1,2,3,5,6,7-hexahydro-8-oxa-dibenzo[*a*,*h*]azulen-4-one [(−)-10]. To a degassed solution of *i*-Pr_2NEt (0.78 mL, 4.5 mmol) in DMA (110 mL) was added $Pd(PPh_3)_4$ (65 mg, 0.056 mmol), and the mixture was heated to 90 °C. A solution of **33** (500 mg, 1.12 mmol) in DMA (5 mL), previously degassed as well, was then added via syringe pump over 3 h. The mixture was stirred at 90 °C for an additional 36 h, cooled, diluted with a saturated $NaHCO_3$ solution (500 mL) and water (200 mL), and extracted with ether (4×200 mL). The combined organic extracts were washed with water (2×100 mL), brine (50 mL), dried, filtered, and concentrated. The product was purified by column chromatography (15% EtOAc in hexanes) to give 234 mg (70%) of (−)-**10** as a colorless oil: $[\alpha]_D = -36.1$ ($c = 1.00$, $CHCl_3$); IR (film): 2934, 1656 cm^{-1}; ^1H NMR: δ 7.34 (d, $J = 8.8$ Hz, 1H), 7.17 (d, $J = 2.4$ Hz, 1H), 6.88 (dd, $J = 8.8$, 2.4 Hz, 1H), 3.86 (s, 3H), 3.29 (m, 1H), 3.10–2.93 (m, 2H), 2.86–2.76 (m, 1H), 2.63–2.46 (m, 2H), 2.41–2.31 (m, 1H), 2.20–2.03 (m, 3H), 1.56 (m, 1H), 1.39 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR: δ 197.6, 164.5, 156.0, 149.3, 149.1, 137.2, 128.3, 115.8, 111.7, 111.5, 105.9, 56.3, 37.9, 36.1, 35.1, 30.9, 23.7, 21.4, 20.6; HRMS (EI+): m/z(M+) calcd for $C_{19}H_{20}O_3$ 296.1412; found 296.1414. The enantiomeric excess was determined by HPLC [Chiralpak AD™ column, 2% *i*-PrOH in hexanes at 1.0 mL/min; t_R (major enantiomer) = 25.8 min, t_R (minor enantiomer) = 33.8 min] to be 91%.

5.2.23. (*R*)-11-Methoxy-4,4,7-trimethyl-2,3,4,5,6,7-hexahydro-1*H*−8-oxa-dibenzo[*a*,*h*]azulene (35). To a solution of (−)-**10** (274 mg, 0.925 mmol) in THF (9.3 mL) at −78 °C was added a solution of MeMgBr in ether (1.2 mL, 3.0 M, 3.6 mmol) dropwise via syringe. After 20 min at −78 °C, the solution was allowed to warm to rt for 1 h. The mixture was cooled to 0 °C, and the reaction was quenched with MeOH. The solution was diluted with water (200 mL) and brine (100 mL) and extracted with ether (3×100 mL). The combined organic extracts were washed once with brine (50 mL), dried, filtered, and concentrated. To a solution of $TiCl_4$ in CH_2Cl_2 (0.93 mL, 1.0 M, 0.93 mmol) at 0 °C was added a solution of $ZnMe_2$ in toluene (0.93 mL, 2.0 M, 1.8 mmol) dropwise via syringe. After 10 min a solution of the crude alcohol in CH_2Cl_2 (9.3 mL) was added dropwise via cannula, and after 10 min the solution was allowed to warm to rt. 2 h later the mixture was cooled to 0 °C, and the reaction was again quenched with MeOH. The mixture was diluted with water (200 mL) and brine (100 mL) and extracted with ether (3×100 mL). The product was purified by column chromatography (3% EtOAc in hexanes) to yield 236 mg (82%) of **35** as a pale yellow oil: $[\alpha]_D = -36.1$ ($c = 1.00$, $CHCl_3$); IR, NMR, and HRMS are consistent with the literature.[8]

5.2.24. (*R*)-Frondosin B [(−)-4]. (−)-**4** was prepared from **35** according to the literature:[8] $[\alpha]_D = -16.8$ ($c = 1.00$, $CHCl_3$).

References and notes

1. (a) Malleron, J.-L.; Fiaud, J.-C.; Legros, J.-Y. *Handbook of Palladium-Catalyzed Organic Reactions*; Academic: San Diego, 1997. (b) Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry*; Pergamon: Amsterdam, 2000.
2. (a) Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467. (b) Glover, B.; Harvey, K. A.; Liu, B.; Sharp, M. J.; Tymoschenko, M. F. *Org. Lett.* **2003**, *5*, 301. (c) Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. *Org. Lett.* **2004**, *6*, 1159.
3. (a) Anbazhagan, M.; Saulter, J. Y.; Hall, J. E.; Boykin, D. W. *Heterocycles* **2003**, *60*, 1133. (b) Klunder, J. M.; Hoermann, M.; Cywin, C. L.; David, E.; Brickwood, J. R.; Schwartz, R.; Barringer, K. J.; Pauletti, D.; Shih, C.-K.; Erickson, D. A.; Sorge, C. L.; Joseph, D. P.; Hattox, S. E.; Adams, J.; Grob, P. M. *J. Med. Chem.* **1998**, *41*, 2960. (c) Ruediger, F.; Garratt, P. J.; Jones, R.; Teh, M.-T.; Tsotinis, A.; Panoussopoulou, M.; Calogeropoulou, T.; Teh, M.-Y.; Sugden, D. *J. Med. Chem.* **2000**, *43*, 1050. (d) Dahlgren, A.; Kvarnstroem, I.; Vrang, L.; Hamelink, E.; Hallberg, A.; Rosenquist, A.; Samuelsson, B. *Bioorg. Med. Chem.* **2003**, *11*, 827. See also: (e) Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2003**, *125*, 5274.
4. (a) Burwood, M.; Davies, B.; Diaz, I.; Grigg, R.; Molina, P.; Sridharan, V.; Hughes, M. *Tetrahedron Lett.* **1995**, *36*, 9053. (b) Padwa, A.; Brodney, M. A.; Lynch, S. M. *J. Org. Chem.* **2001**, *66*, 1716. (c) Malapel-Andrieu, B.; Mérour, J.-Y. *Tetrahedron* **1998**, *54*, 11079. (d) Fishwick, C. W. G.; Grigg, R.; Sridharan, V.; Virica, J. *Tetrahedron* **2003**, *59*, 4451. See also: (e) Kozikowski, A. P.; Ma, D. *Tetrahedron Lett.* **1991**, *32*, 3317. (f) Smet, M.; Van Dijk, J.; Dehaen, W. *Syn lett* **1999**, *4*, 495. (g) Okazawa, T.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2002**, *124*, 5286. (h) Matsuda, Y.; Kohra, S.; Katou, K.; Uemura, T.; Yamashita, K. *Heterocycles* **2003**, *60*, 405.
5. Hughes, C. C.; Trauner, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 1569. *Erratum: Angew. Chem., Int. Ed.* **2002**, *41*, 2227.
6. Patil, A. D.; Freyer, A. J.; Killmer, L.; Offen, P.; Carte, B.; Jurewicz, A. J.; Johnson, R. K. *Tetrahedron* **1997**, *53*, 5047.
7. Hallock, Y. F.; Cardellina, J. H.; Boyd, M. R. *Nat. Prod. Lett.* **1998**, *11*, 153.
8. (a) Inoue, M.; Frontier, A. J.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 761. (b) Inoue, M.; Carson, M. W.; Frontier, A. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 1878.
9. Kerr, D. J.; Willis, A. C.; Flynn, B. L. *Org. Lett.* **2004**, *6*, 457.
10. Arcadi, A.; Cacchi, S.; Del Rosario, M.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, *61*, 9280.
11. (a) Sarandeses, L. A.; Mascarenas, J. L.; Castedo, L.; Mourino, A. *Tetrahedron Lett.* **1992**, *33*, 5445. (b) Tius, M. A.; Kannangara, G. S. K.; Kerr, M. A.; Grace, K. J. S. *Tetrahedron* **1993**, *49*, 3291.
12. Campbell, I. B. *Organocopper Reagents: A Practical Approach*; Taylor, R. J. K., Ed.; Oxford: Oxford, 1994.
13. (a) Piers, E.; Grierson, J. R. *J. Org. Chem.* **1977**, *42*, 3755.

(b) Laschat, S.; Narjes, F.; Overman, L. E. *Tetrahedron* **1994**, *50*, 347.
14. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; Wiley: New York, 1999.
15. Oka, T.; Murai, A. *Tetrahedron* **1998**, *54*, 1.
16. Johnston, K. M.; Jacobsen, R. E.; Williams, G. H. *J. Chem. Soc.* **1969**, 1424.
17. Yan, L.; Kahne, D. *Synlett* **1995**, 523.
18. Bates, R. W.; Gabel, C. J.; Ji, J.; Rama-Devi, T. *Tetrahedron* **1995**, *51*, 8199.
19. At elevated temperatures (110 °C), partial racemization was observed.
20. Reetz, M. T.; Westermann, J.; Steinbach, R. *J. Chem. Soc., Chem. Commun.* **1981**, 237.
21. Suzuki, T.; Saimoto, H.; Tomioka, H.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1982**, *23*, 3597.
22. (a) Banerji, A.; Majumder, P. L.; Chatterjee, A. *Phytochemistry* **1970**, *9*, 1491. (b) Abraham, D. J.; Rosenstein, R. D. *Tetrahedron Lett.* **1972**, *13*, 909.
23. Höger, S. *Liebigs Ann.* **1997**, 273.
24. Curran, D. P.; Xu, J. *J. Am. Chem. Soc.* **1996**, *118*, 3142.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 60 (2004) 9687–9693
Tetrahedron

The asymmetric synthesis of (−)-pumiliotoxin C using tandem catalysis

Ewold W. Dijk, Lavinia Panella, Pedro Pinho, Robert Naasz, Auke Meetsma, Adriaan J. Minnaard* and Ben L. Feringa*

Department of Organic and Molecular Inorganic Chemistry, Stratingh Institute, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands

Received 28 April 2004; revised 8 June 2004; accepted 12 June 2004

Available online 21 August 2004

Abstract—The potent neurotoxin (−)-pumiliotoxin C has been prepared in 8 steps starting from 2-cyclohexenone. Key steps are a tandem asymmetric conjugate addition–allylic substitution reaction and a tandem Heck-allylic substitution reaction.

1. Introduction

Among the alkaloids isolated from *Dendrobates* spp. (poison dart frogs), pumiliotoxin C (**1**), first isolated from *Dendrobates pumilio*, is one of the most prominent members.[1] Pumiliotoxin C is a potent neurotoxin that acts as a noncompetitive blocker for acetylcholine receptor-channels and therefore has attracted considerable attention from a pharmaceutical standpoint.[2] Because of its structure, a *cis*-fused perhydroquinoline skeleton featuring four stereogenic centers, an impressive effort has been devoted to the synthesis of **1**.[3] A number of total syntheses has been reported either of the racemate,[4] the natural enantiomer,[5] or its antipode.[6] The strategies applied for the synthesis of (−)-**1** until now relied on starting materials from the chiral pool, the use of chiral auxiliaries, for example, in the concise synthesis by Comins and coworkers,[7] or the application of a (enzymatic) kinetic resolution. No catalytic asymmetric synthesis of pumiliotoxin C is known (Fig. 1).

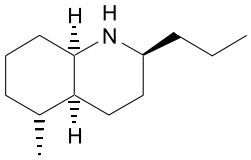
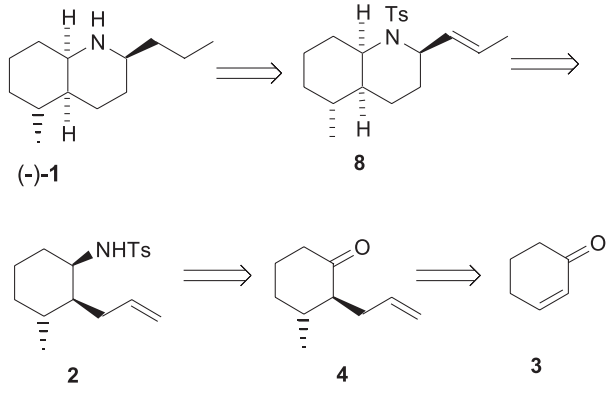


Figure 1. (−)-Pumiliotoxin (**1**).

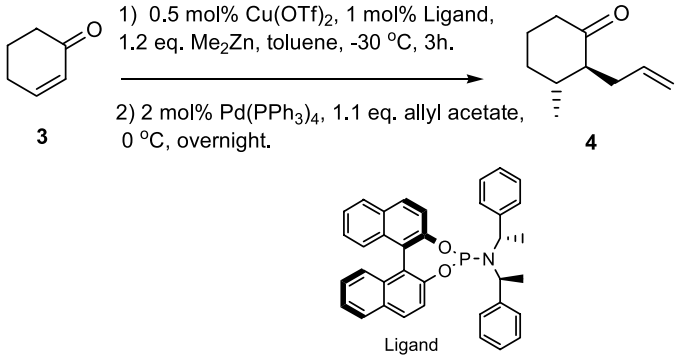
Tandem[8] or domino[9] catalytic reactions comprise a rapidly growing field in organic synthesis. Especially the use of reactive intermediates, formed in the first step, for a subsequent reaction in a multistep conversion allows the preparation of complicated structures in a limited number of steps. The catalytic asymmetric synthesis of (−)-pumiliotoxin C (**1**) presented here is based on two tandem catalytic reactions elaborated upon in our laboratory. In the retrosynthetic scheme (Scheme 1), it is shown that the nitrogen containing six-membered ring in **1** can be constructed by a tandem Heck-allylic substitution reaction starting from **2**. Reduction of the double bond and detosylation leads directly to **1**. In turn, **2** can be prepared starting from 2-cyclohexenone **3** by a tandem asymmetric conjugate addition–allylic substitution reaction, followed by conversion of the carbonyl group into the required *N*-tosylamine.



Scheme 1. Retrosynthesis of **1**.

Keywords: Alkaloids; Heck-allylic substitution; Pumiliotoxin C.
* Corresponding authors. Tel.: +31-50-3634258; fax: +31-503634296; e-mail addresses: minnaard@chem.rug.nl; feringa@chem.rug.nl

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.06.148



Scheme 2. Tandem asymmetric conjugate addition–allylic substitution reaction.

2. Results and discussion

The synthesis started with the copper-phosphoramidite catalyzed addition of dimethylzinc to 2-cyclohexenone (**3**, Scheme 2).[10] Using the depicted phosphoramidite ligand, this reaction proceeds with an excellent enantioselectivity of 96%. The resulting zinc enolate reacted with catalytic $Pd(PPh_3)_4$ and allyl acetate to give **4**.[11] This reaction was carried out on 5 g scale using 0.5 mol% of copper catalyst and 2 mol% of palladium catalyst and afforded **4** in 84% yield as a mixture of *trans*/*cis* isomers (ratio 8:1).

In order to convert ketone **4** into its corresponding amine **7** with the correct stereochemistry, several methods were applied. Whereas reduction of the corresponding oxime with $LiAlH_4$ led predominantly to the undesired isomer, reductive amination using Leuckart's method[12] was accompanied by the formation of side products. It was therefore decided to reduce **4** to alcohol **5** and use this in a subsequent Mitsunobu amination reaction (Scheme 3).

Reduction of **4** with $LiAlH_4$ at low temperature afforded **5** in virtually quantitative yield as a 2:1 mixture of diastereomers together with the residual diastereomer at C2. After purification by flash chromatography, **5** was isolated in 46% yield and 90% diastereomeric purity.

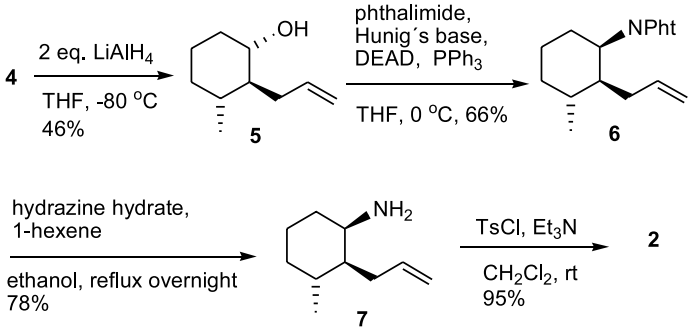
Alcohol **5** was subjected to Mitsunobu-type reactions.[13] As an *N*-tosyl functionality was required, initially both *N*-tosyl formamide[14] and *N*-tosyl *t*-butoxycarbamate[15] were explored as nucleophiles. After reaction, mild cleavage of the formyl or BOC group, respectively, would afford the corresponding tosyl amide. With cyclohexanol as a model substrate and using standard Mitsunobu conditions (DEAD, Ph_3P and Hünig's base) the reaction with *N*-tosyl *t*-butoxycarbamate was successful, whereas *N*-tosyl formamide showed no reaction. Using **5** as the substrate, however, only a very slow reaction was observed and therefore these nucleophiles were abandoned.

Contrary, using phthalimide as the nucleophile, **6** was obtained in a reasonable yield (66%) and after hydrazinolysis and subsequent reaction of the amine **7** with tosyl chloride, **2** was obtained as a crystalline compound. In order to ascertain the correct 1,2-*cis*-2,3-*trans* stereochemistry of **2**, crystals were grown from heptane and an X-ray structure was obtained.[16] As can be seen in Figure 2, **2** possesses the desired relative and absolute stereochemistry. In addition, the crystallization increased the ee of **2** to >99.5% according to chiral HPLC analysis.

With **2** in hand, the tandem Heck-allylic substitution reaction was studied using 1-bromopropene as the alkenyl halide.[17,18] This palladium-catalyzed reaction was performed using the conditions initially developed by Larock and coworkers using tri-*o*-tolylphosphine as the ligand (Scheme 4).

In this mechanistically quite complicated reaction, the alkylpalladium species resulting from the Heck reaction rearranges to the corresponding allylic palladium intermediate by a β-hydride elimination–readdition mechanism (Fig. 3).[19]

Intramolecular attack of the deprotonated *N*-tosylamide affords the six-membered ring, thereby liberating the palladium catalyst. At the outset of the synthesis it was not clear which stereochemistry would result from this



Scheme 3.

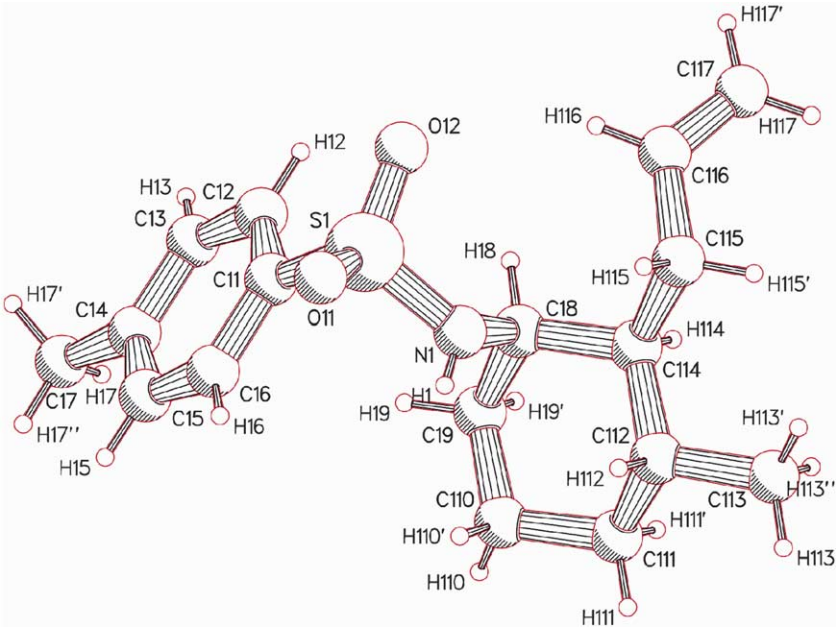
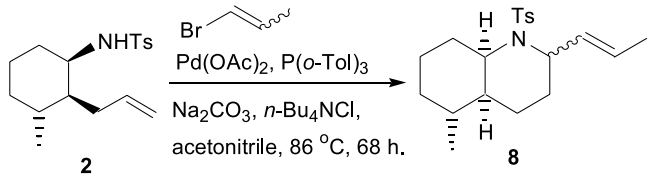


Figure 2. Ortep plot of the structure of **2**.



Scheme 4.

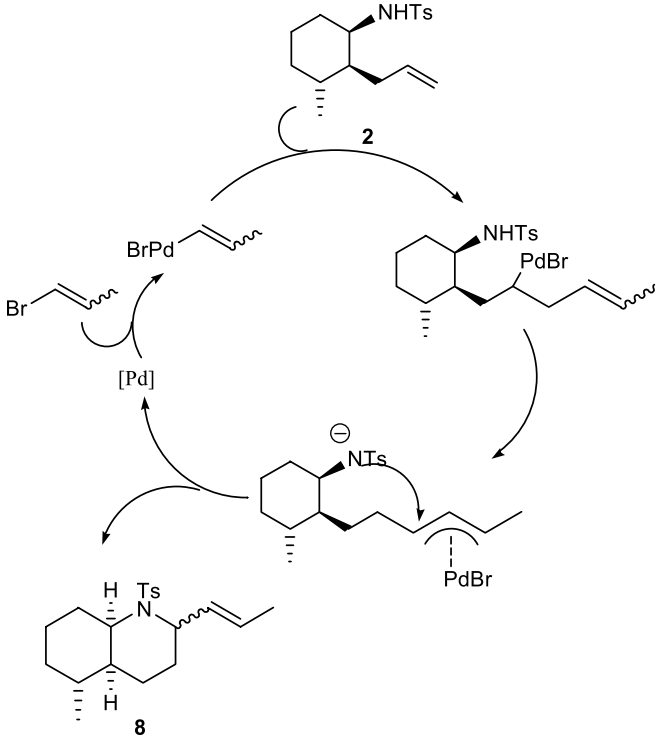
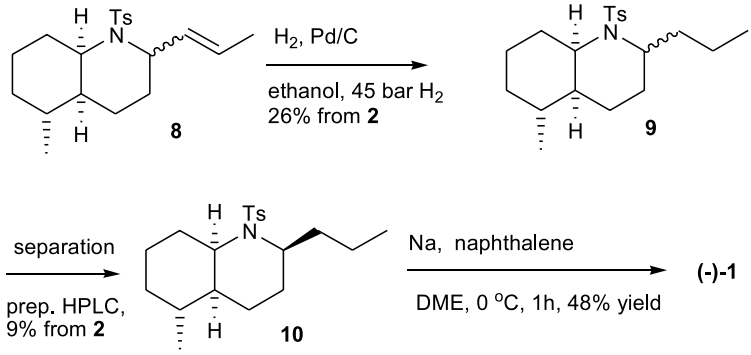


Figure 3. The Heck-allylic substitution reaction (ligands are omitted for clarity).



Scheme 5.

reaction and molecular models did not give a conclusive answer.

Inspection of the crude product mixture by GC-MS revealed that several stereoisomers of **8** had been formed in the reaction. As *cis*,*trans* isomers of the olefin moiety could not be excluded, it was decided to take the crude product through the next step without purification. Hydrogenation of the double bond with H_2 and Pd/C afforded a mixture that consisted mainly of two stereoisomers of **9**, according to GC-MS, and a number of side products that could not be identified (Scheme 5). One of the two stereoisomers of **9** could be purified by flash chromatography. After removal of the tosyl group by treatment with Na/naphthalene this isomer could tentatively be identified as 2-*epi*-pumiliotoxin according to GC-MS.[20]

As the other isomer of **9** could not be obtained pure by flash chromatography, preparative HPLC was applied. This afforded a pure isomer of **9** which, after removal of the tosyl group and purification by acid/base extraction, afforded (−)-**1** in 48% yield. All spectral data are in accordance with those reported in the literature.[21]

To conclude; a short, catalytic asymmetric synthesis of (−)-pumiliotoxin C has been developed that is based on two tandem catalytic reactions. Starting with an asymmetric conjugate addition–allylic substitution reaction, two stereocenters are created in high yield with excellent enantioselectivity and high diastereoselectivity. After functional group modification, a tandem Heck-allylic substitution reaction creates the perhydroquinoline skeleton, albeit in moderate yield, with both the natural and unnatural configuration at the C2 stereocenter. Two additional steps complete the synthesis of (−)-pumiliotoxin C.

3. Experimental

3.1. General

General experimental information: Unless noted otherwise, all materials were obtained from commercial suppliers and used without further purification. THF was dried and distilled from sodium/benzophenone, CH_3CN and DME were dried and distilled from CaH_2 and ether was dried and distilled from P_2O_5. The *n*-Bu_4NCl was crystallized by addition of dry ether to a saturated solution in reagent grade acetone and upon removal of the solvents dried at 70 °C under vacuum for 32 h. The needed volume of dry CH_3CN to afford a 1 M solution was then added and the reagent kept and used as such. Dry Na_2CO_3 was purchased from commercial suppliers and stored in a Schlenk flask after further drying under vacuum at 120 °C for 24 h. Flash chromatography was performed on silica gel Merck Type 9385 230–400 mesh. All NMR spectra were recorded on a Varian XL 300 MHz in $CDCl_3$ solutions using the residual solvent peak as internal reference. Mass spectra and HRMS data were obtained using an AEI MS-902. Melting points were determined on a Mettler FP1.

3.1.1. (2*S*, 3*R*)-2-Allyl-3-methylcyclohexanone (4). $Cu(OTf)_2$ (94 mg, 0.26 mmol, 0.5 mol%) and (*R*,*S*,*S*)-phosphoramidite ligand[10a] (280 mg, 0.52 mmol, 1.0 mol%) were dissolved in dry toluene in a flame-dried Schlenk tube under an atmosphere of nitrogen. After stirring for 1 h at room temperature, the solution was cooled to −30 °C and freshly distilled 2-cyclohexenone (5.03 mL, 52 mmol) was added. After stirring for an additional 10 min at the same temperature, Me_2Zn (31.2 mL of a 2 M solution in toluene, 62.4 mmol, 1.2 equiv) was added dropwise to the solution which turned bright yellow. After stirring for an additional 3 h at −30 °C, $Pd(PPh_3)_4$ (1.20 g, 1.04 mmol, 2.0 mol%) and allyl acetate (6.17 mL, 57.2 mmol, 1.14 equiv) were added. The resulting mixture was warmed to 0 °C and stirred overnight at this temperature. GC analysis of a reaction mixture aliquot on a DB-1 column showed complete conversion to the product with a *trans*/*cis* ratio of 8.5:1 (*trans*: T_r=12.28 min, *cis*: T_r=13.40 min). The reaction mixture was quenched by pouring it into 200 mL of 2 M aqueous HCl. The layers were separated, the aqueous layer was extracted with diethyl ether (4×100 mL), the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residual zinc and palladium salts were removed by flash chromatography of the resulting yellow oil over a small column of silica, eluted with toluene. Crude yield: 7.51 g (49.3 mmol, 95%) of a yellowish oil, which was used without further purification. ^1H NMR of a sample purified by flash chromatography (SiO_2, hexanes:diethyl ether 3:1): δ_H 0.81 (3H, d, J=6.9 Hz, of minor diastereomer), 1.05 (3H, d, J=6.2 Hz), 1.43–1.59 (1H, m), 1.64–2.11 (6H, m), 2.21–2.40 (5H, m), 4.95–5.05 (2H, m), 5.74–5.85 (1H, m); δ_C 20.2 (q), 25.4 (t), 30.8 (t), 33.4 (t), 37.8 (d), 41.5 (t), 56.7 (d), 115.8 (t), 136.5 (d), 212.1 (s); *m*/*z* (EI) 152 (M^+, 23), 137 (100), 97 (54). An ee of 96.2% was determined by chiral GC

on a Chiraldex G-TA column, 30 m×0.25 mm, He-flow: 1.0 mL/min, 100 °C, 15 min, 10 °C/min, 150 °C, 30 min; T_r=13.14 min (major enantiomer), T_r=14.96 min (minor enantiomer), T_r=15.54 min (both enantiomers of the minor diastereomer).

3.1.2. (1*S*,2*S*,3*R*)-2-Allyl-3-methylcyclohexanol (5). To a stirred suspension of $LiAlH_4$ (3.74 g, 98.6 mmol) in 100 mL of THF at −80 °C in flame-dried glassware under a nitrogen atmosphere, was added in a dropwise fashion 7.5 g (49.3 mmol) crude **4** as a solution in 20 mL of THF. The reaction mixture was stirred at this temperature until the reaction was completed as indicated by TLC (approx. 3 h). The reaction was quenched by adding 2 mL of water, 1 mL of 15% aqueous NaOH after 15 min and 1 mL of water after an additional 30 min. This procedure avoids problems with aluminum salts. The resulting slurry was then divided between water and diethyl ether and the aqueous layer was extracted with diethyl ether (3×100 mL). After drying the combined organic layers over $MgSO_4$, the solvent was removed under reduced pressure yielding 7.26 g (47.1 mmol, 99%) of the crude product. The diastereomeric mixture was separated by flash chromatography (SiO_2, heptanes:diethyl ether 2:1) yielding **5** as a colorless oil which solidified upon standing at 5 °C. 3.5 g (22.6 mmol) of crystalline **5** was obtained, melting at ambient temperature. ^{1}H NMR showed 90% diastereomeric purity. ^{1}H NMR: δ_H 0.86–1.09 (3H, m), 0.96 (3H, d, J=5.3 Hz), 1.22–1.30 (4H, m), 1.58–1.79 (4H, m), 1.94–1.96 (1H, m), 2.22–2.30 (1H, m), 2.51–2.58 (1H, m), 3.38–3.44 (1H, m), 4.94–5.15 (2H, m), 5.82–5.97 (1H, m); δ_C 19.7 (q), 23.9 (t), 32.3 (t), 33.7 (d), 35.1 (t), 35.7 (t), 50.9 (d), 72.4 (d), 116.3 (t), 136.3 (d); *m/z* (CI) 172 $(M+NH_4)^+$. $[\alpha]_D=-8°$ (c=1.01, $CHCl_3$).

3.1.3. 2-[(1*R*,2*S*,3*R*)-2-Allyl-3-methylcyclohexyl]-1*H*-isoindole-1,3(2*H*)-dione (6). To a solution of **5** (3.13 g, 20.3 mmol), triphenylphosphine (10.64 g, 40.58 mmol, 2 equiv), phthalimide (5.97 g, 40.58 mmol, 2 equiv) and distilled di-*i*-propylethylamine (7.1 mL, 40.58 mmol, 2 equiv) in 200 mL of THF in a flame-dried Schlenk tube under a nitrogen atmosphere was added dropwise via syringe diethyl azodicarboxylate (6.4 mL, 40.58 mmol, 2 equiv) over 15 min, allowing the reaction temperature to rise to 30 °C. After 3.5 h of stirring, no starting material remained as indicated by TLC. After evaporation of the solvent, 14.4 g of a viscous bright orange oil was obtained. After adding 100 mL of heptane, a yellow semi-solid, consisting of diethyl 1,2-hydrazinedicarboxylate and triphenylphosphine oxide, remained. After filtration and evaporating the mixture, 3.2 g of a yellow oil was obtained. Further extraction of the residue with heptane yielsded an additional 0.6 g of crude product. Purification by flash chromatography (SiO_2, heptanes:diethyl ether 5:1) yielded 3.79 g (13.38 mmol, 66%) of **6** as a colorless oil. δ_H 0.81–0.89 (2H, m), 1.16 (3H, d, J=7.0 Hz), 1.21–1.28 (2H, m), 1.57–1.81 (5H, m), 2.07–2.18 (2H m), 2.30–2.41 (1H, m), 2.60–2.72 (1H, m), 4.53–4.59 (1H, m), 4.58–4.96 (2H, m), 5.53–5.67 (1H, m), 7.67–7.72 (2H, m), 7.77–7.83 (2H, m); δ_C 19.2 (q), 21.0 (t), 25.6 (t), 26.5 (t), 30.3 (d), 34.7 (t), 44.2 (d), 50.9 (d), 115.6 (t), 122.8 (d), 131.8 (s), 133.6 (d), 137.5 (d), 169.2 (s); *m/z* (EI) 283 (M^+, 42), 186 (25), 136 ({M−phthaloyl-H}$^+$,100), 95 (44). HRMS 283.1565, $C_{18}H_{21}NO_2$ requires 283.1572.

3.1.4. (1*R*,2*S*,3*R*)-2-Allyl-3-methylcyclohexylamine (7). To a solution of **6** (2.94 g, 10.38 mmol) and 1-hexene (6.5 mL, 51.5 mmol, 5 equiv) in 55 mL of ethanol in a 3-necked roundbottom flask under a nitrogen atmosphere, hydrazine hydrate (2.5 mL, 48.4 mmol, 4.7 equiv) was added. This mixture was heated at reflux overnight. After cooling, the solvent was removed under reduced pressure, and the remaining oil was taken up in 50 mL of ethyl acetate and extracted with 50 mL of 0.1 M aqueous NaOH. The aqueous layer was extracted with ethyl acetate (3×50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and evaporated. 1.24 g (8.12 mmol, 78%) of **7** was obtained which was used without further purification. δ_H 0.80–1.02 (1H, m), 0.88 (3H, d, J=6.4 Hz), 1.12–1.23 (1H, m), 1.48–1.53 (6H, m), 1.58–1.63 (2H, br d, J=12.8 Hz), 1.87–1.98 (1H, m), 2.29–2.33 (1H, m), 3.05 (1H, m), 4.96–5.08 (2H, m), 5.72–5.82 (1H, m); δ_C 19.9 (t), 20.1 (q), 30.3 (d), 33.9 (t), 34.1 (t), 34.8 (t), 47.1 (d), 47.4 (d), 115.3 (t), 138.0 (d); *m/z* (CI) 154 $(M+H)^+$.

3.1.5. *N*-[(1*R*,2*S*,3*R*)-2-Allyl-3-methylcyclohexyl]-4-toluenesulfonamide (2). To a solution of **7** (682 mg, 4.45 mmol) in 15 mL of dichloromethane was added *p*-toluenesulfonyl chloride (933 mg, 4.94 mmol, 1.1 equiv) and triethylamine (1.34 mL, 9.6 mmol, 2.2 equiv). The mixture was stirred for 60 h under a nitrogen atmosphere. After removal of the solvent, the residue was dissolved in diethyl ether (50 mL), and sequentially washed with 2 M aqueous HCl (2×50 mL), aqueous saturated sodium bicarbonate (2×50 mL) and brine (50 mL). After drying over $MgSO_4$, filtration and evaporation, an oil (1.39 g, 4.52 mmol) was isolated. Crystallisation from heptane afforded **2** (900 mg 2.93 mmol, 66%) as colorless crystals; mp 92–94 °C. A second crop of 395 mg (29%, 1.28 mmol) proved to be equally pure. δ_H 0.89 (3H, d, J=6.0 Hz), 0.95–1.01 (1H, m), 1.13–1.64 (8H, m), 1.91–2.01 (1H, m), 2.11–2.19 (1H, m), 2.43 (3H, s), 3.56–3.58 (1H, m), 4.79–4.82 (1H, m), 4.86–4.92 (2H, m), 5.56–5.71 (1H, m), 7.29 (2H, d, J=8.0 Hz), 7.78 (2H, d, J=7.3 Hz). δ_C 19.9 (t), 20.1 (q), 21.5 (q), 30.6 (t), 31.3 (d), 33.0 (t), 33.6 (t), 47.2 (d), 51.5 (d), 116.1 (t), 127.0 (d), 129.6 (d), 137.0 (d), 138.5 (s), 143.1 (s); *m/z* (EI) 307 (M^+,18), 155 (Ts^+, 44), 152 ({M−Ts}$^+$,100), 91 (tropylium$^+$, 57). HRMS 307.1599, $C_{17}H_{25}NO_2S$ requires 307.1606. Anal. Found: C, 66.26; H, 8.22; N, 4.56; S, 10.11. $C_{17}H_{25}NO_2S$ requires C, 66.41; H, 8.20; N, 4.56; S, 10.41. $[\alpha]_D=-36.8°$ (c=1.01, $CHCl_3$). An ee of 99.5% was determined by chiral HPLC on a Chiralpak AS column, 250×4.6 mm, eluted with *n*-heptane: *i*-propanol 95:5, flow: 1 mL/min, at 40 °C.

Selected X-ray data of **2**.[16] $C_{17}H_{25}NO_2S$, M_r=307.45, monoclinic, $P2_1$, a=11.3300(5), b=10.9724(5), c=13.7035(7) Å, β=98.732(1)°, V=1683.84(14) Å^3, Z=4, D_x=1.213 g cm^{-3}, $F(000)$=664, μ=1.96 cm^{-1}, λ(Mo K$_\alpha$)=0.71073 Å, T=100(1) K, 16062 reflections measured, $GooF$=1.029, $wR(F^2)$=0.1700 for 8539 unique reflections and 392 parameters, 23 restraints and $R(F)$=0.0629 for 8285 reflections obeying $Fo\geq 4.0\sigma(Fo)$ criterion

of observability. The asymmetric unit consists of two molecules of the title compound.

3.1.6. (2*S*,4a*S*,5*R*,8a*R*)-5-Methyl-1-(4-toluenesulfonyl)-2-*n*-propyl decahydro-quinoline (10). A flame-dried reseal-able tube with a teflon cap was loaded with dry Na_2CO_3 (268 mg, 2.53 mmol, 3 equiv) and suspended in 1.41 mL of dry, distilled CH_3CN under a nitrogen atmosphere. To the stirring mixture was then sequentially added tri-*o*-tolylphos-phine (154 mg, 0.51 mmol, 0.6 equiv), palladium acetate (5.08 mL of a 0.05 M stock solution in CH_3CN, 0.25 mmol, 0.3 equiv), tetra-*n*-butylammonium chloride (1.69 mL of a 1 M solution in CH_3CN, 1.69 mmol, 2 equiv), **2** (260 mg, 0.85 mmol), and 1-bromo-1-propene (0.29 mL, 3.39 mmol, 4 equiv, mixture of *cis* and *trans*). The amount of solvent was adapted so as to afford a 0.1 M solution of **2**. The mixture was then frozen at −40 °C, sealed under vacuum and slowly heated to 86 °C. After stirring at this temperature for 68 h, the mixture was flashed over a plug of silica with pentanes:ethyl acetate 1:1 and concentrated to afford 384 mg of a yellow oil. GC-MS analysis showed a 1:1 mixture of diastereomers with the correct mass ($m/z=347$) together with some unidentified side products. The product mixture was hydrogenated without further purification: 500 mg of the mixture was dissolved in 10 mL of ethanol, placed in an autoclave and 50 mg of 10% Pd/C was added. The mixture was stirred overnight at room temperature under 45 bar of hydrogen pressure. After filtration over a plug of silica with ethanol 132 mg (0.38 mmol, 26%) of a mixture of two epimers (**9**) with an m/z of 349 (GC-MS) was obtained together with a number of side products that could not be identified. Purification by flash chromatography (SiO_2, hexanes:diethyl ether 10:1) afforded a pure compound that after removal of the tosyl group by Na/naphthalene (vide infra) gave 2-*epi*-pumiliotoxin C (*epi*-**1**).[20]

Separation of the remaining mixture by preparative HPLC yielded 26 mg (0.075 mmol) of **10** as a colorless solid. δ_H 0.93 (3H, d, $J=4.0$ Hz), 0.95 (3H, t, $J=4.0$ Hz), 1.07–1.83 (16H, m), 2.42 (3H, s), 3.95–4.04 (2H, m), 7.27 (2H, d, $J=8.1$ Hz), 7.71 (2H, d, $J=8.1$ Hz). δ_C 14.0 (q), 18.4 (q), 18.9 (q), 20.5 (t), 20.6 (t), 20.9 (t), 21.4 (d), 26.3 (t), 28.2 (t), 29.9 (t), 34.4 (d), 38.3 (t), 51.7 (d), 52.5 (d), 126.6 (d), 129.4 (d), 139.2 (s), 142.4 (s): m/z (EI) 349 (M^+, 1.1), 306 ({M−*n*-Pr}$^+$, 100), 155 (Ts^+, 6), 135 (20), 91 (tropylium$^+$, 12). HRMS 349.2087. $C_{20}H_{31}NO_2S$ requires 349.2075.

3.1.7. (2*S*,4a*S*,5*R*,8a*R*)-5-Methyl-2-*n*-propyl decahydro-quinoline, (−)-pumiliotoxin C (1). Naphthalene (47.7 mg, 0.37 mmol, 5 equiv) was dissolved in 2 mL of dry and degassed DME under an argon atmosphere. To this solution was added metallic sodium (approx. 9 mg, 0.39 mmol, 5.2 equiv) in small slices and the mixture was sonicated until a deep-green solution of sodium naphthalenide had formed (5 min). The solution was then stirred for an additional 2 h at room temperature under argon, cooled to 0 °C and 26 mg of **10** (0.075 mmol) was added as a solution in 1 mL of dry DME. The mixture was stirred for 60 min at 0 °C and then quenched by adding 1 mL of saturated aqueous NH_4Cl. Subsequently, 5 mL of 2 M aqueous HCl was added and the aqueous layer was washed with heptane (3×5 mL). The aqueous layer was brought to pH 14 by addition of 10% aqueous NaOH followed by extraction with dichloromethane (4×5 mL). After drying over $MgSO_4$ and evaporation of the solvent, 7 mg (0.036 mmol, 48%) of pure (−)-pumiliotoxin C (**1**) was obtained. All spectroscopic data were in accordance with the literature. Comparison of the mass spectrum with the NIST Mass Spectral Library (1995) showed 94% correspondence.

^{1}H NMR: δ 0.85 (d, $J=6.3$ Hz, 3H), 0.91 (t, $J=6.5$ Hz, 3H), 1.08–1.18 (m, 2H), 1.26–1.49 (m, 8H), 1.52–1.69 (m, 5H), 1.81–1.98 (m, 2H), 2.53–2.56 (m, 1H), 2.85–2.86 (m, 1H). ^{13}C NMR: δ 57.74 (d), 55.98 (d), 42.56 (d), 39.68 (t), 35.91 (t), 33.37 (t), 27.37 (d), 27.32 (t), 27.04 (t), 21.25 (t), 19.91 (q), 19.15 (t), 14.31 (q). The free amine was converted into its hydrochloride by bubbling HCl gas through a solution in *i*-propanol, giving a temperature rise to about 50 °C. After cooling in ice and no further observation of heat develop-ment, the solvent was removed under reduced pressure giving 5 mg of a yellowish solid. Crystallisation from *i*-propanol gave a tiny amount of small colorless needles, mp 190–191 °C (dec., lit.[5j] 220–225 °C).

Acknowledgements

T. Tiemersma is gratefully acknowledged for the assistance with HPLC separations.

References and notes

1. (a) Daly, J. W.; Tokuyama, T.; Habermehl, G.; Karle, I. L.; Witkop, B. *Lieb. Ann. Chem.* **1969**, *729*, 198. For an overview of the natural occurence of pumiliotoxin C and analogues, see (b) Spande, T. F.; Jain, P.; Garraffo, H. M.; Pannell, L. K.; Yeh, H. J. C.; Daly, J. W.; Fukumoto, S.; Imamura, K.; Tokuyama, T.; Torres, J. A.; Snelling, R. R.; Jones, T. H. *J. Nat. Prod.* **1999**, *62*, 5. (c) Michael, J. P. *Nat. Prod. Rep.* **1998**, *15*, 595.
2. (a) Daly, J. W.; Nishizawa, Y.; Padgett, W. L.; Tokuyama, T.; McCloskey, P. J.; Waykole, L.; Schulz, A. G.; Aronstam, R. S. *Neurochem. Res.* **1991**, *16*, 1207. (b) Schulz, A. G.; Wang, A. H.; Alva, C.; Sebastian, A.; Glick, S. D.; Deecher, D. C.; Bidlack, J. M. *J. Med. Chem.* **1996**, *39*, 1956.
3. For a review of the literature until 1976 see: Inubushi, Y.; Ibuka, T. *Heterocycles* **1977**, *8*, 633.
4. (a) Akashi, M.; Sato, Y.; Mori, M. *J. Org. Chem.* **2001**, *66*, 7873. (b) Padwa, A.; Heidelbaugh, T. M.; Kuethe, J. T. *J. Org. Chem.* **2000**, *65*, 2368. (c) Shieh, Y.; Yeh, M. P.; Rao, U. N. *J. Chin. Chem. Soc.* **2000**, *47*, 283. (d) Back, T. G.; Nakajima, K. *Tetrahedron Lett.* **1997**, *38*, 989. (e) Kuethe, J. T.; Padwa, A. *Tetrahedron Lett.* **1997**, *38*, 1505. (f) Mehta, G.; Praveen, M. *J. Org. Chem.* **1995**, *60*, 279. (g) Meyers, A. I.; Milot, G. *J. Am. Chem. Soc.* **1993**, *115*, 6652. (h) Paulvannan, K.; Stille, J. R. *Tetrahedron Lett.* **1993**, *34*, 6673. (i) Polniaszek, R. P.; Dillard, L. D. *J. Org. Chem.* **1992**, *57*, 4103. (j) Brandi, A.; Cordero, F. M.; Goti, A.; Guarna, A. *Tetrahedron Lett.* **1992**, *33*, 6697. (k) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1991**, *32*, 5697. (l) LeBel, N. A.; Balasubramanian, N. *J. Am. Chem. Soc.* **1989**, *111*, 3363. (m) Abe, K.; Tsugoshi, T.; Nakamura, N. *Bull. Chem. Soc. Jpn* **1984**, *57*, 3351. (n) Hattori, K.; Matsumura, Y.; Miyazaki, T.; Maruoka, K.; Yamamoto, H. *J. Am. Chem.*

Soc. **1981**, *103*, 7368. (o) Overman, L. E.; Jessup, P. J. *J. Am. Chem. Soc.* **1978**, *100*, 5179. (p) Ibuka, T.; Mori, Y.; Inubushi, Y. *Chem. Pharm. Bull.* **1978**, *26*, 2442. (q) Oppolzer, W.; Fehr, C.; Warneke, J. *Helv. Chim. Acta* **1977**, *60*, 48. (r) Habermehl, G.; Andres, H.; Miyahara, K.; Witkop, B.; Daly, J. W. *Lieb. Ann. Chem.* **1976**, 1577. (s) Ibuka, T.; Mori, Y.; Inubushi, Y. *Tetrahedron Lett.* **1976**, *17*, 3169. (t) Oppolzer, W.; Fröstl, W.; Weber, H. P. *Helv. Chim. Acta* **1975**, *58*, 593. (u) Habermehl, G.; Andres, H.; Witkop, B. *Naturwissenschaften* **1975**, *62*, 345. (v) Ibuka, T.; Masaki, N.; Saji, I.; Tanaka, K.; Inubushi, Y. *Chem. Pharm. Bull.* **1975**, *23*, 2779. (w) Ibuka, T.; Inubushi, Y.; Saji, I.; Tanaka, K.; Masaki, N. *Tetrahedron Lett.* **1975**, *16*, 323.

5. (a) Oppolzer, W.; Flaskamp, E.; Bieber, L. W. *Helv. Chim. Acta* **2001**, *84*, 141–145. (b) Back, T. G.; Nakajima, K. *J. Org. Chem.* **1998**, *63*, 6566. (c) Riechers, T.; Krebs, H. C.; Wartchow, R.; Habermehl, G. *Eur. J. Org. Chem.* **1998**, 2641. (d) Naruse, M.; Aoyagi, S.; Kibayashi, C. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1113. (e) Davies, S. G.; Bhalay, G. *Tetrahedron: Asymmetry* **1996**, *7*, 1595. (f) Naruse, M.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **1994**, *35*, 9213. (g) Comins, D. L.; Dehghani, A. *J. Chem. Soc., Chem. Commun.* **1993**, 1838. (h) Murahashi, S.; Sasao, S.; Saito, E.; Naota, T. *Tetrahedron* **1993**, *49*, 8805. (i) Murahashi, S.; Sasao, S.; Saito, E.; Naota, T. *J. Org. Chem.* **1992**, *57*, 2521. (j) Bonin, M.; Royer, J.; Grierson, D. S.; Husson, H.-P. *Tetrahedron Lett.* **1986**, *27*, 1569. (k) Maruoka, K.; Miyazaki, T.; Ando, M.; Matsumura, Y.; Sakane, S.; Hattori, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1983**, *105*, 2831. (l) Oppolzer, W.; Flaskamp, E. *Helv. Chim. Acta* **1977**, *60*, 204.
6. (a) Toyota, M.; Asoh, T.; Fukumoto, K. *Heterocycles* **1997**, *45*, 147. (b) Toyota, M.; Asoh, T.; Matsumura, M.; Fukumoto, K. *J. Org. Chem.* **1996**, *61*, 8687. (c) Toyota, M.; Asoh, T.; Fukumoto, K. *Tetrahedron Lett.* **1996**, *37*, 4401. (d) Schultz, A. G.; McCloskey, P. J.; Court, J. J. *J. Am. Chem. Soc.* **1987**, *109*, 6493. (e) Masamune, S.; Reed, L. A.; Davis, J. T.; Choy, W. *J. Org. Chem.* **1983**, *48*, 4441.
7. Comins, D. L.; Dehghani, A. *J. Chem. Soc., Chem. Commun.* **1993**, 1838.
8. Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; VCH: Weinheim, 1996.
9. Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115.
10. (a) Feringa, B. L.; Pineschi, M.; Arnold, L. A.; Imbos, R.; De Vries, A. H. M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2621. (b) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346.
11. Naasz, R.; Arnold, L. A.; Minnaard, A. J.; Feringa, B. L. *Chem. Commun.* **2001**, 735.
12. Moore, M. L. *Org. React.* **1949**, *5*, 301.
13. Hughes, D. L. *Org. React.* **1992**, *42*, 335.
14. Prepared from formic acid and tosyl isocyanide, see Feldman, K. S.; Bruendl, M. M.; Schildknegt, K.; Bohnstedt, A. C. *J. Org. Chem.* **1996**, *61*, 5440.
15. Henry, J. R.; Marcin, L. R.; McIntosh, M. C.; Scola, P. M.; Harris, G. D.; Weinreb, S. B. *Tetrahedron Lett.* **1989**, *30*, 5709.
16. Data have been deposited at the CCDC Nr. 234521.
17. (a) Larock, R. C.; Tu, C. *Tetrahedron* **1995**, *51*, 6635, and references cited therein. (b) Larock, R. C.; Yang, Y.; Weinreb, S. M.; Herr, R. J. *J. Org. Chem.* **1994**, *59*, 4172.
18. Pinho, P.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2003**, *5*, 259.
19. (a) Patel, B. A.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 3898. (b) Heck, R. F. *Org. React.* **1982**, *27*, 345.
20. Ref. 4d. The compound showed 45–90% correspondence with the mass spectrum of pumiliotoxin C from the NIST Mass Spectral Library (1995). See also Ref. 1b
21. Akashi, M.; Sato, Y.; Mori, M. *J. Org. Chem.* **2001**, *66*, 7873.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 60 (2004) 9695–9708

Sequential ring-closing metathesis/Pd-catalyzed, Si-assisted cross-coupling reactions: general synthesis of highly substituted unsaturated alcohols and medium-sized rings containing a 1,3-*cis–cis* diene unit

Scott E. Denmark* and Shyh-Ming Yang

Department of Chemistry, Roger Adams Laboratory, University of Illinois, 600 South Mathews Avenue, Urbana, IL 61801, USA

Received 30 April 2004; revised 8 June 2004; accepted 12 June 2004

Available online 11 September 2004

Abstract—A sequential ring-closing metathesis/silicon-assisted cross-coupling protocol has been developed. Alkenyldimethylsilyl ethers of allylic, homoallylic and bis(homoallylic) alcohols undergo facile ring closure with Schrock's catalyst to afford 5-, 6-, and 7-membered cycloalkenylsiloxanes, respectively, in some cases with substituents on both alkenyl carbons. These siloxanes are highly effective coupling partners that afford styrenes and dienes (with various aryl and alkenyl halides) in high yield and specificity as well as good functional group compatibility. The siloxanes bearing a *Z*-iodoalkenyl tether undergo an intramolecular coupling process in the presence of $[allylPdCl]_2$ which constitutes a powerful method for the construction of medium-sized rings with an internal 1,3-*cis–cis* diene unit. The formation of 9-, 10-, 11-, and 12-membered carbocyclic dienes is achieved in good yield. Extension to the synthesis of 9-membered ring unsaturated ethers has also been accomplished. Noteworthy features of this process include: (1) highly stereospecific intramolecular coupling, (2) flexible positioning of the revealed hydroxy group, and (3) potential extension to other medium-sized carbocycles and heterocycles.

1. Introduction

The formation of carbon–carbon bonds by transition metal-catalyzed cross-coupling reactions, has evolved into a general and powerful synthetic method over the past three decades.[1] Among the most notable and commonly employed procedures are the Suzuki coupling of organoboranes, the Stille coupling of organostannanes, and the Negishi coupling of organozinc compounds. In recent years, the cross-coupling reactions of organosilicon compounds have been extensively developed and emerged as an extremely viable alternative in view of the high chemical stability, low toxicity, and ease of handling of the precursors.[2,3] A series of reports from these laboratories[4] has demonstrated the ability of organosilicon components (including silacyclobutanes,[4a–d] silanols,[4e,j] silyl hydrides,[4f] cyclic silyl ethers,[4g,k,m,n] and even oligosiloxanes[4h]) to serve as donors in Pd-catalyzed cross-coupling reactions. The practical advantages of this process include: (1) the ease of introduction of the silicon containing moiety, (2) the mildness of reaction conditions, (3) the stereospecificity with respect to both of the addends, and (4) the broad functional group compatibility.

In response to the growing interest in the palladium-catalyzed cross-coupling reactions, a number of methods are now available to introduce silicon-based functionality into molecules.[5] The ability to introduce the silicon donor in a regio- and stereocontrolled fashion is a prerequisite for stereocontrolled construction of alkenes. This feature of the method has been demonstrated in the intramolecular hydrosilylation/cross-coupling[4g] and intramolecular silylformylation/cross-coupling reactions[4m] to efficiently and stereoselectively prepare homoallylic alcohols. In those studies, a temporary silicon tether was employed to set the geometry of an exo alkylidenylsiloxane by hydrosilylation or silylformylation. A recent report by Trost and Ball also describes an intramolecular endo-dig hydrosilylation catalyzed by a cationic ruthenium complex to afford a cycloalkenylsiloxane which contains a geometrically defined alkene in the ring.[6] We envisioned an alternative construction of the cycloalkenylsiloxane that would employ ring-closing metathesis (RCM) of a vinylsilyl ether of an unsaturated alcohol to create the cycloalkenylsiloxane in regio- and stereo-defined form. This cyclic silane could then participate as a coupling partner in Pd-catalyzed cross-coupling reactions.

Keywords: Palladium; Cross-coupling; Organosilicon; RCM; Medium-sized ring.

* Corresponding author. Tel.: +1-217-333-0066; fax: +1-217-333-3984; e-mail: denmark@scs.uiuc.edu

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.06.149

Ring-closing metathesis of 1,ω-dienes, catalyzed by Mo or Ru complexes, has revolutionized the way in which carbocycles and heterocycles are constructed.[7] There are now several reports of RCM of silicon tethered allylic ethers that employ Grubbs ruthenium alkylidene complexes **1** as the catalyst (Fig. 1).[8] Synthesis of structurally defined and functionalized conjugated dienes via silicon-tethered enyne metathesis with complexes **1** or **2** was also disclosed recently.[9] Moreover, asymmetric RCM of an allylsilyl ether has attracted attention in recent years by the use of a chiral Mo-based complex as the catalyst.[10] Certain vinylsilanes are particularly competent substrates for metathesis reactions. For example, trialkoxyvinylsianes undergo cross metathesis reactions with alkenes upon treatment with catalyst **2**.[11] In addition, a 2-trialkoxysilyl-substituted 1,7-octadiene undergoes ring closure easily to afford the corresponding 1-trialkoxysilylcycloalkene using complex **2**.[5g] However, RCM of sterically more demanding vinylsilyl ethers of unsaturated alcohols requires the sterically less sensitive molybdenum carbene complex **3**, developed by Schrock.[12]

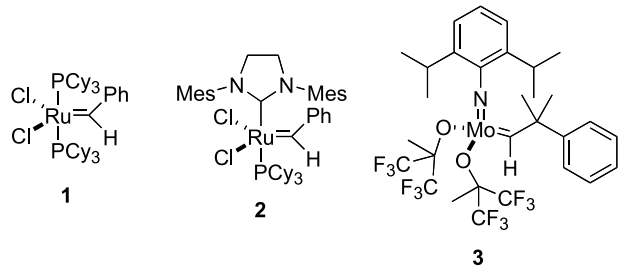
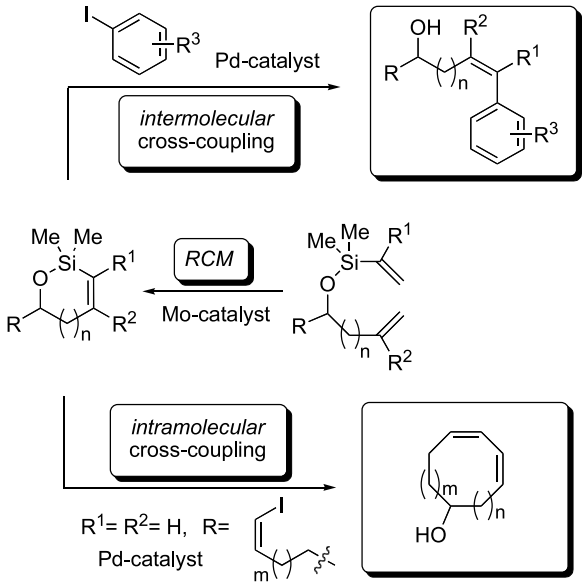


Figure 1. Representative catalysts for RCM.

The main goal of the program described herein was the development of a sequential RCM/Pd-catalyzed, Si-assisted cross-coupling reaction. The precursor cycloalkenylsiloxanes should be easily available by RCM of the vinylsilyl ether of unsaturated alcohols using Mo-complex as catalyst. These cyclosiloxanes would, in turn, be subjected to intermolecular cross-coupling reaction leading to stereocontrolled preparation of highly substituted alkenyl alcohols (Scheme 1). If the siloxane product of RCM contains a suitably disposed electrophile, then the ensuing intramolecular cross-coupling would afford medium-sized rings with an internal, 1,3-*cis*–*cis* diene unit. The synthesis of medium-sized rings,[13] particularly with a conjugated diene unit is well known to be challenging because of unfavorable entropic and enthalpic factors.[14] Indeed palladium-catalyzed intramolecular cross-coupling, especially the Stille coupling of organostannanes, has been widely employed for construction of macrocycles containing an internal diene unit.[15] However, the formation of medium-sized rings with an internal 1,3-diene unit by intramolecular Stille coupling strategies are scarce.[15b] Although significant progress had been recorded in the intermolecular process, the intramolecular cross-coupling reactions of organosilanes have yet to be investigated. We report in full the successful realization of this approach for the stereocontrolled construction of highly substituted unsaturated alcohols as well as 9- to 12-membered carbocycles.[16,17] An extension to the synthesis of medium-sized ring ethers are described as well.

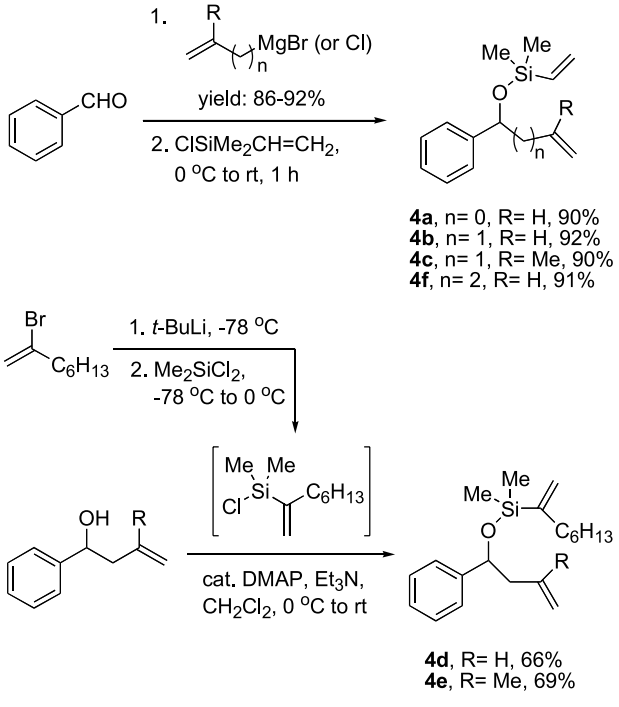


Scheme 1. Sequential RCM/Pd-catalyzed, Si-assisted cross-coupling reactions.

2. Results

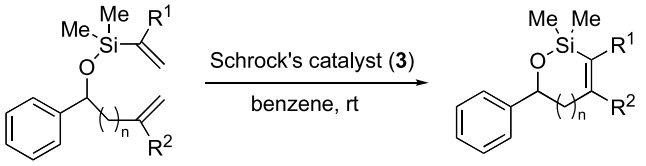
2.1. Sequential RCM/Pd-catalyzed, Si-assisted intermolecular cross-coupling reactions

2.1.1. RCM of olefinic vinylsilyl ethers 4. To test the feasibility of the overall transformation and to further explore the influence of tether length (i.e., ring size) and substituents on the RCM/cross-coupling process, vinylsilyl



Scheme 2. Synthesis of olefinic alkenylsilyl ethers **4**.

Table 1. Molybdenum-catalyzed ring-closing metathesis of **4**[a]



4 **5**

Entry	Substrate, *n*	R^1	R^2	Catalyst, mol%	Time, h	Product	Yield,[b] %
1	**4a**, 0	H	H	7.0	3	**5a**	89
2	**4b**, 1	H	H	5.0	1	**5b**	95
3	**4c**, 1	H	Me	8.0	15	**5c**	91
4	**4d**, 1	C_6H_{13}	H	7.0	12	**5d**	90
5	**4e**, 1	C_6H_{13}	Me	—	—	—	—
6[c]	**4f**, 2	H	H	7.0	12	**5e**	81

[a] Reactions were performed in 0.1 M concentration.
[b] Yields of analytically pure materials.
[c] 91% conversion was observed by ^{1}H NMR analysis.

ethers **4** were prepared (Scheme 2). Vinylsilyl ethers **4a–c** and **4f** could be readily obtained in good yield (90–92%) by the addition of organomagensium bromides (or chlorides) to benzaldehyde followed by silylation of the resulting alcohols with commercially available chlorodimethylvinylsilane. Further, treatment of 1-phenyl-3-buten-1-ol and 1-phenyl-3-methyl-3-buten-1-ol with (1-hexylvinyl)dimethylchlorosilane (generated in situ from 2-bromo-1-octene) gave the corresponding alkenylsilyl ethers **4d–e** in 66–69% yield.

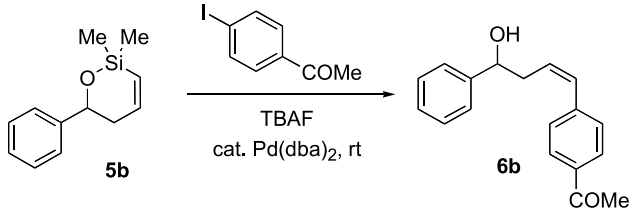
Initial studies on the RCM reaction of **4b** using the Grubbs alkylidene complex **1** failed; none of the desired product, **5b**, was observed by ^{1}H NMR analysis. All variations in conditions, including change of solvent (CH_2Cl_2 or benzene) and/or temperature (rt, 45 or 80 °C) were unsuccessful. Even the more reactive 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene-substituted ruthenium complex **2** ('second generation' Grubbs catalyst) failed to promote the RCM reaction.[18] Gratifyingly, substrate **4b** did undergo the RCM process by the use of the molybdenum complex **3** as the catalyst.[19] After careful optimization, a near quantitative yield of **5b** was obtained with 5 mol% of **3** in benzene (0.1 M) at ambient temperature (Table 1, entry 2).

The allylic ether **4a** (a five-membered ring precursor) suffered RCM under the standard conditions (5 mol% of Mo complex **3** in benzene, 1 h); however, only 75% conversion could be obtained after 1 h. This problem was solved by increasing the catalyst loading; using 7 mol% of catalyst **3**, the complete consumption of **4a** was achieved within 3 h to afford the product **5a** in 89% yield (Table 1, entry 1). However, for the preparation of a seven-membered siloxane **5e**, the reaction only went to 91% completion, giving an 81% yield under these conditions (entry 6). With a monosubstituted alkene or vinylsilane (entries 3 and 4), the RCM process proceeded slowly compared to **4b** albeit ultimately to completion to afford **5c–d** in 91 and 90%, respectively. Unfortunately, substitution on both the alkene and vinylsilane (entry 5) did not lead to a successful closure (even under harsher conditions) presumably due to the significant increase in steric crowding.

2.1.2. Pd-catalyzed intermolecular cross-coupling reactions. Optimization of the Pd(0)-catalyzed coupling of siloxane **5b** with 4-iodoacetophenone employed the conditions developed in these laboratories for alkenylsilanols[4e] (Table 2). Thus, siloxane **5b** was dissolved with a 1.0 M solution of tetrabutylammonium fluoride (TBAF·$3H_2O$) in THF at room temperature, followed by the sequential addition of 4-iodoacetophenone and 5 mol% of $Pd(dba)_2$. The reaction proceeded cleanly to completion in only 10 min (Table 2, entry 1). Decreasing the loading of $Pd(dba)_2$ (3 mol%) only marginally affected the rate of the coupling process (entry 2). However, with a lower catalyst loading (1.0 mol%, entry 3) or less TBAF (1.0 equiv., entry 4), the reaction did not go to completion and a significant amount of 4-iodoacetophenone (5 and 19%, respectively) was recovered.

With suitable conditions for both reactions in hand, we turned our attention to expanding the scope of this process with various aryl iodides. Both the nature and position of substituents on the aromatic ring were studied under the

Table 2. Optimization of the cross-coupling reaction of **5b** with 4-iodoacetophenone[a]

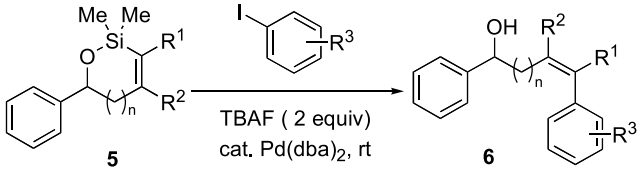


5b **6b**

Entry	$Pd(dba)_2$, mol%	TBAF, equiv.	Time, min	Yield,[b] %
1	5.0	2.0	10	89
2	3.0	2.0	30	86
3	1.0	2.0	180	80[c]
4	5.0	1.0	180	65[d]

[a] All reactions employed 1.1 equiv. of **5b** and 1.0 equiv. of 4-iodoacetophenone at room temperature.
[b] Yield of isolated **6b**.
[c] 5% of 4-iodoacetophenone was recovered.
[d] 19% of 4-iodoacetophenone was recovered.

Table 3. Palladium-catalyzed cross-coupling of **5** with aryl iodides[a]



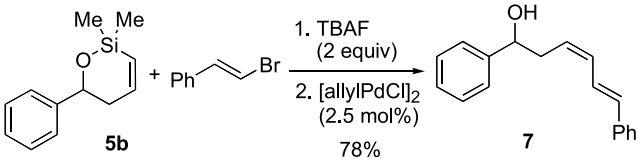
5 **6**

Entry	Substrate, *n*	R^1	R^2	R^3	$Pd(dba)_2$, mol%	Time, min	Product	Yield,[b] %
1	**5a**, 0	H	H	4-CO_2Et	3.0	30	**6a**	85
2	**5b**, 1	H	H	4-COMe	5.0	10	**6b**	90[c]
3	**5b**, 1	H	H	4-OMe	3.0	30	**6c**	92
4	**5b**, 1	H	H	3-CO_2Et	3.0	30	**6d**	93
5	**5b**, 1	H	H	2-Me	3.0	30	**6e**	89
6	**5b**, 1	H	H	2-NO_2	3.0	90	**6f**	86
7	**5b**, 1	H	H	2-CH_2OH	5.0	180	**6g**	90
8	**5b**, 1	H	H	2-CO_2Me	5.0	360	**6h**	84
9	**5c**, 1	H	Me	2-Me	3.0	45	**6i**	83
10[d]	**5d**, 1	C_6H_{13}	H	3-CO_2Et	10.0	24 h	**6j**	81
11	**5e**, 2	H	H	4-OMe	3.0	30	**6k**	85[c]

[a] All reactions employed: **5** (1.1 equiv.), TBAF (2.0 equiv.), aryl iodide (1.0 equiv.) and $Pd(dba)_2$ (3.0 mol%) at room temperature unless otherwise specified.
[b] Yields of analytically pure materials.
[c] Yield of chromatographically homogeneous material.
[d] $Pd(dba)_2$ (2.5 mol%/3 h) and (0.25 mmol/3 h) were added portionwise.

optimized conditions: 3.0–5.0 mol% of $Pd(dba)_2$ as the catalyst and 2.0 equiv. of TBAF as the activator at ambient temperature. The results with all aryl iodides examined are complied in Table 3. The coupling of 5-membered siloxane **5a** with ethyl 4-iodobenzoate using a 3.0 mol% catalyst loading, was complete in 30 min to afford **6a** in 85% yield with excellent stereospecificity (Table 3, entry 1). The coupling products showed slight decomposition upon distillation. However, they could be secured in analytically pure form after silica gel chromatography. Although the stereospecificity could not be determined by GC, no other isomer was see by ^{1}H NMR analysis. The 11.6 Hz vicinal coupling constant between the olefinic protons indicated that the *Z*-olefin geometry was maintained. The reaction of the 6-membered siloxane **5b** with 4-iodoacetophenone gave, as expected, **6b** in 90% yield in 10 min with a 5.0 mol% catalyst loading (entry 2). Electrophiles bearing an electron-donation group (entry 3) or an electron-withdrawing group (entry 4), both gave the desired products **6c** and **6d** in 92 and 93% yield, respectively. Sterically hindered substrates, such as in 2-iodotoluene (entry 5) or 2-nitroiodobenzene (entry 6), also gave the expected products **6e** and **6f** in excellent yield (89 and 86%, respectively). The reaction of 2-iodobenzyl alcohol (entry 7) and methyl 2-iodobenzoate (entry 8) proceeded more slowly than the previously mentioned electrophiles to afford **6g** (90%) and **6h** (84%). Even using a 5.0 mol% catalyst loading, reactions of these substrates still required 3–6 h to reach completion. The effect of substitution on the α- and β-positions of the alkenylsilyl group, such as in siloxanes **5c** and **5d**, was also examined with various aryl iodides. Cross-coupling of **5c** with 2-iodotoluene proceeded to completion in 45 min to afford **6i** in 83% yield (entry 9). The α-substituted alkenylsilane **5d** did undergo the coupling process with ethyl 3-iodobenzoate (entry 10), however, at a significantly reduced reaction rate compared to the related silanes. Moreover, the reaction mixture contained a substantial amount of self-coupling of ethyl 3-iodobenzoate. The use of additives[4c] ($AsPh_3$ or *t*-Bu_3P) and/or slightly elevated temperatures (35–45 °C) did not improve the results. Fortunately, the addition of the iodide in portions satisfactorily suppressed the formation of the self-coupling product.[4g] Moreover, increasing the loading and portionwise addition of the Pd(0) complex also provided complete conversion and kept the palladium from precipitating in this slow reaction. By using a 10 mol% catalyst loading, the coupling product **6j** can be obtained in 81% yield after 24 h. Finally, the reaction of 7-membered siloxane **5e** with 4-iodoanisole proceeded similarly to give **6k** in 85% yield (entry 11).

The cross-coupling of **5b** was also successful with (*E*)-2-bromostyrene (Scheme 3). The reaction rate and yield were slightly lower than those obtained with aryl iodides. After 5 h, **7** could be isolated in 78% yield with 2.5 mol% of $[allylPdCl]_2$ as the catalyst.

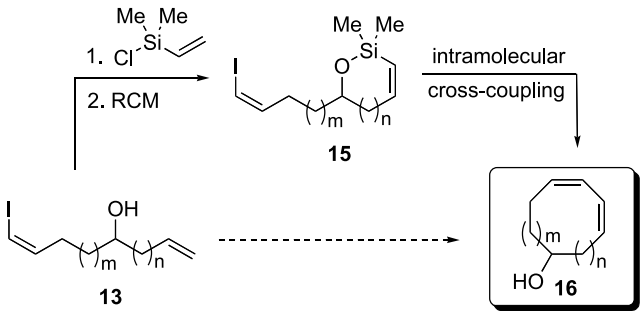


5b **7**

Scheme 3. Cross-coupling of **5b** with (*E*)-2-bromostyrene.

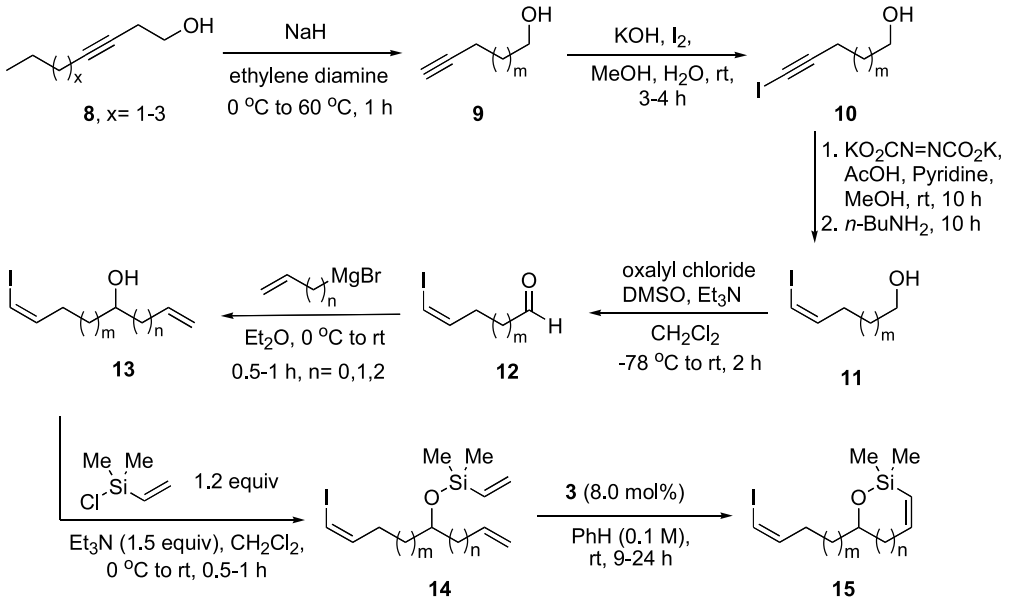
2.2. Sequential RCM/Pd-catalyzed, Si-assisted intramolecular cross-coupling reactions

With the sequential RCM/Pd-catalyzed, silicon-assisted intermolecular cross-coupling reaction successfully demonstrated, we turned our attention toward investigation of the intramolecular coupling process. The strategy, outlined in Scheme 4, involves the generation of cyclic silyl ethers **15**



Scheme 4. Strategy for intramolecular silicon-assisted cross-coupling.

isomerization of internal alkynyl alcohols **8** ($x=1$–3) with sodium 2-aminoethylamide generated in situ from sodium hydride and ethylenediamine.[20] Iodination of **9** with iodine in aqueous KOH gave the iodoalkynyl alcohols **10** in excellent yield (90–95%). Next, *cis*-reduction of **10** with diimide, (generated in situ from potassium azodicarboxylate), afforded the corresponding iodoalkenyl alcohols **11** in moderate yield (56–64%). A small amount of the over-reduction product could be easily removed by treatment of crude material with *n*-$BuNH_2$. Oxidation by the method of Swern was chosen to convert the primary alcohol to the aldehyde in 82–88% yield. The addition of various Grignard reagents to the aldehydes afforded the desired iododienyl



Scheme 5. Synthesis of **15**, precursors for intramolecular cross-coupling.

by Mo-catalyzed RCM and their subsequent participation as nucleophilic partners in Pd-catalyzed intramolecular cross-coupling with an alkenyl iodide appended at a remote position. In these siloxanes, variables, *m* and *n* combine to determine the size of the ring and the location of the hydroxyl group relative to the diene unit.

2.2.1. Synthesis of siloxanes 15. To test the feasibility and generality of the overall transformation, substrates **15** were prepared from terminal alkynyl alcohols **9** as depicted in Scheme 5. The results of the overall transformation are compiled in Tables 4 and 5. Alkynyl alcohols **9a–b** are commercially available materials and substrates **9c–e** were readily available in 82–84% yield by base-promoted alcohols **13** in 85–93% yield. Finally, silylation of **13** with commercially available chlorodimethylvinylsilane gave the targeted vinylsilyl ethers **14** in 86–95% yield. From earlier studies, we already knew that RCM of vinylsilyl ethers required the use of Schrock's molybdenum complex **3**. Gratifyingly, substrates **14** also underwent the RCM process smoothly with **3** without competitive reaction of the vinyl iodide unit. Unfortunately, substrate **14g** (for a five-membered ring precursor) did not lead to a successful closure in the RCM process. Even using 12 mol% of catalyst **3**, only a 21% conversion of **15g** was observed after 60 h at ambient temperature according to ^{1}H NMR analysis. Under slightly harsher conditions (45 °C), no improvement in

Table 4. Preparation of **9**, **10**, **11**, and **12**

m	**9** (yield, %)[a]	**10** (yield, %)[a]	**11** (yield, %)[a]	**12** (yield, %)[a]
1	**9a** (–)	**10a** (91)	**11a** (56)	**12a** (85)
2	**9b** (–)	**10b** (94)	**11b** (61)	**12b** (85)
3	**9c** (83)	**10c** (94)	**11c** (60)	**12c** (86)[b]
4	**9d** (84)	**10d** (95)	**11d** (64)[b]	**12d** (82)[b]
5	**9e** (82)	**10e** (90)	**11e** (61)[b]	**12e** (88)[b]

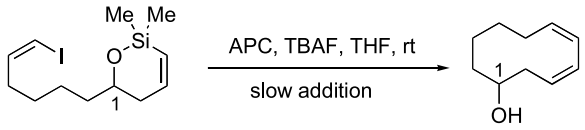
[a] Yields of chromatographically homogeneous material.
[b] Yields of analytically pure material.

Table 5. Preparation of alcohols **13**, silyl ethers **14**, and siloxanes **15**

m, *n*	Alcohol **13** (yield, %)[a]	Silyl ether **14** (yield, %)[a]	Siloxane **15** (yield, %)[a]
1, 1	**13a** (93)	**14a** (86)	**15a** (83)
2, 1	**13b** (91)	**14b** (95)	**15b** (81)
3, 1	**13c** (88)	**14c** (94)	**15c** (82)
4, 1	**13d** (92)	**14d** (93)	**15d** (81)
5, 1	**13e** (91)	**14e** (93)	**15e** (83)
2, 2	**13f** (91)	**14f** (95)	**15f** (80)
4, 0	**13g** (85)	**14g** (87)	**15g** (–)

[a] Yields of analytically pure materials.

Table 6. Optimization of the intramolecular cross-coupling reaction of **15c**[a]



15c **16c**

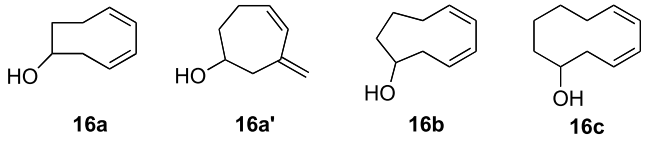
Entry	**15c** (M, in THF)	APC, mol%	TBAF, equiv.	Time, h	**16c** (%)[b]
1[c]	—	3.0	2.0	30	<10
2[d]	0.5	3.0	2.0	20	14
3	0.1	3.0	10.0	32	45
4	0.1	3.0	20.0	34	32
5	0.05	3.0	10.0	50	46
6	0.1	5.0	10.0	40	62
7	0.1	5.0	5.0	40	44
8	0.1	7.5	10.0	40	74
9	0.1	10.0	10.0	40	75
10[d]	0.1	7.5	10.0	43	75

[a] All reactions were performed on a 0.1 mmol scale by slow addition a solution of **15c** to a mixture of APC and TBAF solution unless otherwise specified.
[b] The percentage of product was determined by ^{1}H NMR analysis comparing the integrated area of the diene to the total integrated area of H(C1).
[c] The reaction was run in THF (0.01 M, dilute condition).
[d] 0.5 mmol scale.

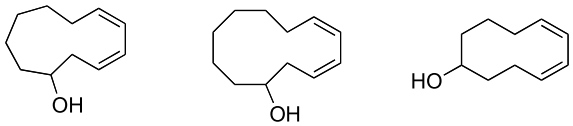
conversion was observed. Not surprisingly, the yields of these reactions are not influenced by chain length.

2.2.2. Optimization of intramolecular cross-coupling reaction. Optimization of the Pd-catalyzed, intramolecular cross-coupling reaction of **15c** (to form a 10-membered ring) employed allylpalladium chloride dimer (APC) as the catalyst and a 1.0 M solution of tetrabutylammonium fluoride (TBAF) in THF as the activator. We chose this substrate because in cycloalkenes, the maximum strain is found in the 10-membered ring.[14] The results from studies of the catalyst loading and the amount of activator are collected in Table 6. Typical conditions, which would favor intra- vs intermolecular coupling (high dilution, entry 1, or slow addition of substrate, entry 2) did not promote this intramolecular process well. Under these conditions, unreacted vinylsilanes and oligomers were observed by ^{1}H NMR analysis. Therefore, to maintain efficient fluoride activation, promote transmetalation and maintain a low concentration of **15c** (to prevent oligomerization), the amount of TBAF solution was increased. To our delight, the percentage of the desired product, **16c**, increased dramatically to 45% (entry 3). Neither increasing the amount of TBAF solution nor adding more dilute solutions of **15c** had a beneficial effect (entries 4–5). However, we found that the catalyst loading did have a significant effect on the success of this intramolecular process (entries 3, 6, 8, and 10). A great improvement in the production of **16c** to

Table 7. Pd-catalyzed intramolecular cross-coupling reactions of **15**[a]



16a **16a'** **16b** **16c**



16d **16e** **16f**

Entry	Substrate **15**	APC, mol%	Time, h	Product **16**, yield/%[b]
1	**15a**	7.5	60	**16a**+**16a′** (60%,1:1)[c,d]
2	**15b**	7.5	45	**16b** (70%)
3	**15c**	7.5	45	**16c** (63%)
4	**15d**	10.0	75	**16d** (55%)
5	**15e**	10.0	75	**16e** (72%)
6	**15f**	10.0	60	**16f** (71%)

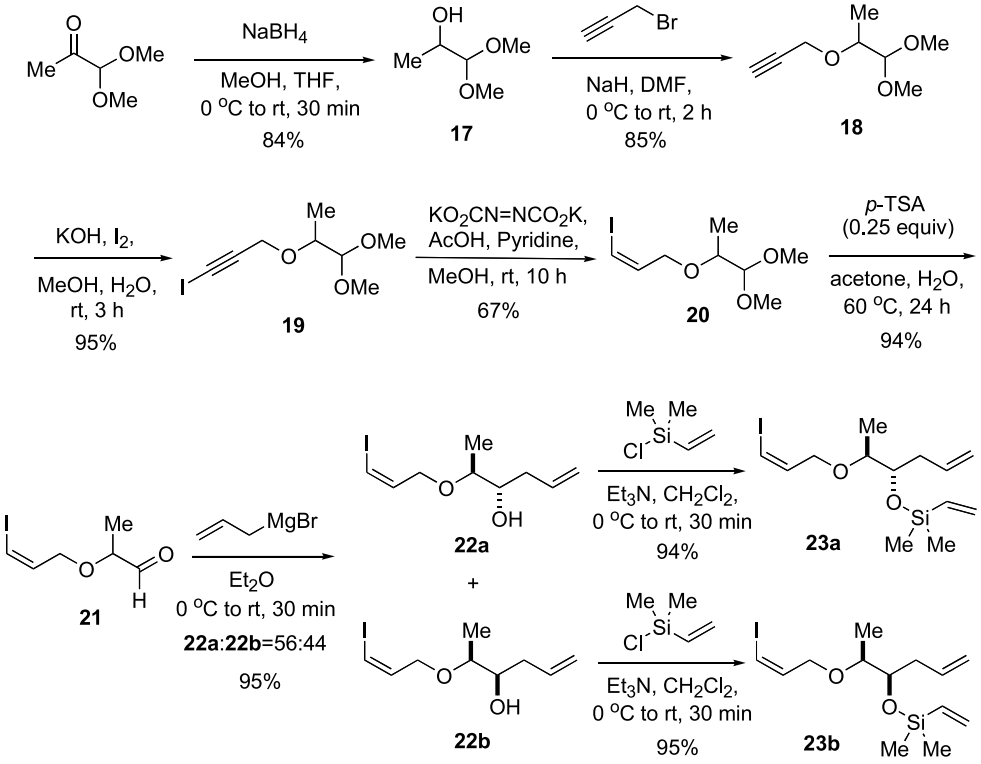
[a] All reactions were performed on a 1.0 mmol scale (0.1 M in THF), with TBAF (10.0 equiv.), and slow addition condition at room temperature.
[b] Yield of analytically pure materials.
[c] Yield of chromatographically homogeneous material.
[d] The ratio was determined by ^{1}H NMR analysis.

62% was obtained by using 5.0 mol% of APC (entry 6). Decreasing the amount of TBAF solution, decreased the percentage of **16c** to 44% (entry 7). Finally, by employing 7.5 mol% of APC, the percentage of **16c** in the coupling products jumped to 75% (entries 8 and 10). No further improvement was observed using even with 10 mol% of APC (entry 9).

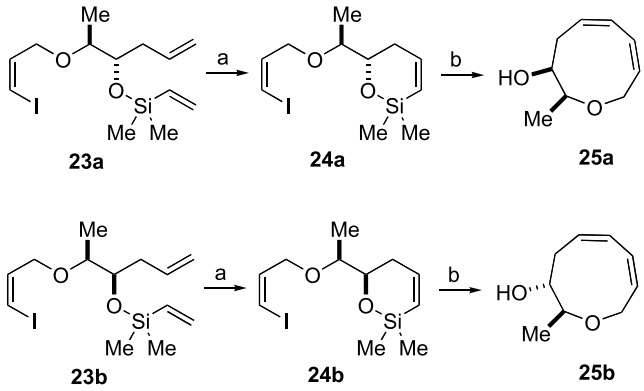
2.2.3. Scope and limitations of Si-assisted intramolecular cross-coupling reactions. The scope of this silicon-assisted, intramolecular cross-coupling process with regard to ring size was examined under the following conditions: 7.5–10.0 mol% of APC and 10.0 equiv. of TBAF solution at room temperature. The results with all substrates examined are compiled in Table 7. Under the optimal conditions, the 9-membered carbocycle **16b** containing a 1,3-*cis*–*cis* diene unit was obtained in 70% yield from siloxane **15b** after 45 h addition time (entry 2). Moreover, intramolecular coupling of **15c** gave the corresponding 10-membered cyclic product **16c** in 63% yield (entry 3). In the coupling of **15d**, the amount of **16d** observed was only 42% by ^{1}H NMR analysis under these conditions. Increasing the catalyst loading to 10 mol%, increased the yield of **16d** to 59% after a 42 h addition. Finally, by using 10 mol% of APC and increasing the addition time to 75 h, we were able to produce **16d** in 55% yield (67% by ^{1}H NMR). Similarly, only 49% of **16e** and 55% of **16f** were observed by ^{1}H NMR analysis under the standard conditions. By employing similar conditions used for **15d**, the desired coupling products **16e** and **16f** were obtained in 72 and 71% yield, respectively (entries 5–6). Unfortunately, substrate **15a** afforded a mixture of desired product **16a** and cine rearrangement product **16a′** in 60% yield in a 1:1 ratio, presumably due to the more difficult construction of a cyclooctadiene.

2.2.4. Formation of medium-sized ring ethers. To demonstrate the versatility and effectiveness of this process, we next investigated extension to medium-sized heterocycles. Medium ring ethers have attracted a great deal of attention as synthesis targets in view of their occurrence in several classes of marine natural product structures.[21] Thus, the diastereomeric silyl ethers **23a–b** were selected to test this application by generation of the corresponding 9-membered oxacyclic dienes[22] (Scheme 6). The preparation of **23a–b** began with the reduction of pyruvic aldehyde dimethoxy acetal with $NaBH_4$ in MeOH/THF to afford hydroxyl acetal **17** in 84% yield. Alkylation of the sodium alkoxide of **17** (from sodium hydride in DMF) with propargyl bromide afforded **18** in 85% yield. Conversion of **18** to **20** was achieved by iodination followed by a *cis*-reduction of iodoalkyne **19** to iodoalkene **20** employing the condition established above. Hydrolysis of dimethoxy acetal was effected by treatment of **20** with *p*-toluenesulfonic acid in an acetone/H_2O mixture to give aldehyde **21** in 94% yield. Treatment of aldehyde **21** with allylmagnesium bromide for 0.5 h afforded hydroxyl dienyliodide **22a–b** in 95% yield as a 56:44 mixture of diastereomers, which were easily separated by silica gel chromatography. Finally, silylation of the alcohols with chlorodimethylvinylsilane in CH_2Cl_2 for 30 min furnished **23a–b** in 94 and 95% yield, respectively.

With these materials in hand, the ring closing metathesis of **23a** was carried out using 10 mol% of the Mo complex **3** to afford the target siloxane **24a** in 81% yield. Similarly, RCM of **23b** proceeded smoothly to afford cyclic silyl ethers **24b** in 80% yield under the same conditions (Scheme 7). Gratifyingly, exposure of the siloxanes to the optimal conditions established above promoted the intramolecular



Scheme 6. Synthesis of **23a–b**.



Scheme 7. Formation of medium-sized ring ethers **25**. Reagents and conditions: (a) **3** (10.0 mol%), benzene (0.1 M), rt, 36 h, **24a** (81%); **24b** (80%). (b) APC (7.5 mol%), TBAF (10.0 equiv.), rt, 45 h, **25a** (72%); **25b** (77%).

cross-coupling effectively. Both diastereomers reacted with equal facility to afford the oxonane dienes **25a** and **25b**, in 72 and 77% yield, respectively with no difference in rate or efficiency.

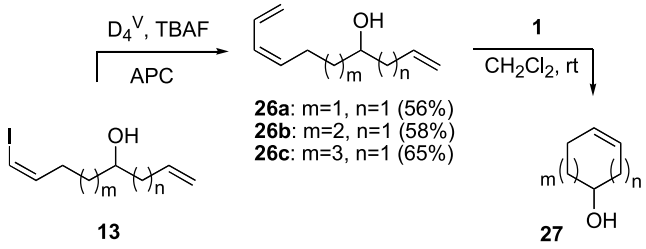
3. Discussion

3.1. Ring-closing metathesis of olefinic alkenylsilyl ethers

The RCM of alkenylsilyl ethers **4** proceeded smoothly as expected from the literature reports.[12] The more reactive Mo complex **3** is the catalyst of choice for all of the variants examined as the Ru-based complexes were ineffective. The formation of 5- or 7-membered siloxanes **5a** and **5e** (Table 1, entries 1 and 6) as well as substitution on the double bond (Table 1, entries 3–4) were associated with lower RCM reaction rates. This behavior was particularly apparent in the case of **4e**; all attempts to effect ring closure led to failure presumably due to the significant steric hindrance at both ends of the alkene. Interestingly, in the cases of **14a–f**, the RCM proceeded smoothly in the presence of an alkenyl iodide function. In fact, alkylidene **1** has been shown to react with acetylenic halides through halide exchange. Moreover, some dienes or dienynes containing a vinyl halide (Br or I) also failed to cyclize using either **1** or Mo-complex **3**.[12e,23] It has been hypothesized that formation of more stable and unreactive Fischer-type carbene complexes from vinyl bromides or vinyl ethers and Ru-alkylidene complexes might prevent the initiation step at the terminal alkene.[11c,23b,24] Although the reason for the failure of RCM with vinyl bromide containing dienes using catalyst **3** has not been determined, the successful ring closure of **14** indicated that the initiation step at the terminal alkene did occur, and that subsequent combination with the alkenylsilyl species proceeded without interference of the iodoalkenyl group. RCM of **14g** (a five-membered siloxane precursor) was not successful; only 21% conversion was observed. This was surprising in light of the successful RCM of **4a** to oxasilacyclopentene **5a** (Table 1). Perhaps, the smaller substituent at the allylic position of the oxasilacyclopentene ring permits the strained RCM product to compete with the starting material in this reversible process. Thus, **5a** with a sterically more demanding phenyl group deters RCM of the product.

3.2. Ring-closing metathesis of trienes

In formulating the intramolecular cross-coupling reaction, it was not lost upon us that the iodo alcohols **13** could also be converted to cycloalkadienes **16** by an inverted sequence of cross-coupling (vinylation) followed by RCM of the triene. Indeed, RCM of trienes have been reported recently for construction of macrolides containing a 1,3-diene system. Moreover, the more sterically sensitive Ru-complex **1** has been shown to react preferentially with the terminal double bond of a diene preferably to afford macrocycles with a internal diene unit.[25] To the best of our knowledge, formation of medium-sized ring with a diene unit by RCM is still rare.[26] Thus, to determine whether the intramolecular cross-coupling was of any tactical advantage, we undertook the preparation of the requisite trienes **26** and assayed their potential for RCM to dienes (Scheme 8). Vinylation of **13** was readily accomplished by our recently described method using 1,3,5,7-tetramethyl-1,3,5,7-tetravinylcyclotetrasiloxane (D_4^V) to afford the desired trienes **26a–c** in 56–65% yield.[4h] Initial studies on the RCM of trienes, **26a**, using Grubbs alkylidene complex **1** (5.0 mol%) produced only the six-membered ring compound **27a** in greater than 95% conversion in 6 h at room temperature. However, only 22% of the seven-membered ring product **27b** was obtained along with 58% of **26b** recovered under the same conditions. Furthermore, none of closure products of **27c** were observed under these conditions and complex mixtures were obtained in refluxing CH_2Cl_2. Clearly, closure on the internal double bond of the diene to afford smaller rings predominated.[27,28] We thus demonstrated the utility and further substantiated the advantages of the intramolecular cross-coupling method.



Scheme 8. RCM of trienes **26**.

3.3. Si-assisted cross-coupling reactions

The intermolecular cross-coupling of cycloalkenylsiloxanes **5** with various aryl iodides proceeded rapidly and efficiently. For all aryl iodides examined, the reaction conditions were mild and gave uniformly high yields. Noteworthy features of this process include: (1) electron-withdrawing or donating groups exhibit similar reactivity (Table 3, entries 2–4), (2) the steric effect of ortho substituents is minimal (Table 3, entry 5) except in the cases where possible coordination of the palladium may slow the reductive elimination step (Table 3, entries 6–8), (3) the reaction tolerates diverse functional groups such as

ester, ether, nitro and even a free hydroxyl group, and (4) the reactions of all iodides were stereospecific. The influence of the siloxane ring size as well as the substitution on the double bond in coupling reactions was systematically investigated. The results in Table 3 reveal that: (1) different cyclic alkenyl silanes exhibit similar reactivity in the coupling reaction (Table 3, entries 1, 3 and 11) and (2) substitution on the β-*trans*-position of the silyl group did not affect the reactivity significantly (Table 3, entry 9).

A comparison between these results and those described previously reveals that mono-substitution of alkenyl silanes (silacyclobutanes[4a–d] and silanols[4e]) in either the α- or the β-position does not affect the rate of the cross-coupling process significantly. The disubstituted alkenylsilanes including cyclic siloxanes[4g] and silyl hydrides[4f] are also very reactive in the coupling process except in the case of substitution on both of α- and β-*cis*-positions, as in **5d**. The steric influence may slow the coupling reaction and allow a competitive homocoupling of the aryl iodides to intervene.

In the cases of intramolecular cross-coupling, the results, compiled in Table 7, reveal good generality for the construction of 9-, 10-, 11-, and 12-membered cycloalkadienes, (Table 7, entries 2–6). With the exception of **15a**, all of the substrates examined gave the corresponding medium-sized rings bearing the 1,3-*cis*–*cis* diene unit stereospecifically in respectable yield from highly flexible starting materials without significant conformational constraints.[29] Notably, modulation of the location of the hydroxy group was successfully achieved by adjustment of chain length and ring size of the silyl ether (cf. Table 7, entries 3 and 6). An extension of the intramolecular coupling process for construction medium-sized ether rings, such as **25a** and **25b**, was examined under the standard reaction conditions. Interestingly, both diastereomers reacted similarly without significant difference in reaction rate and yield. This observation bodes well for the application of the process in the synthesis of complex, medium-ring ether natural products.[30]

4. Conclusion

The sequential RCM/cross-coupling reactions of olefinic alkenylsilyl ethers has been demonstrated. The cycloalkenylsiloxanes serve as competent donors in rapid and high-yielding cross-coupling reactions with various aryl and alkenyl halides. The intermolecular cross-coupling reactions proceeded with high stereospecificity and good functional group compatibility. In addition, the influences of siloxane ring size and olefin substitution are similar to those observed in the acyclic coupling processes. The Pd-catalyzed, silicon-assisted intramolecular cross-coupling reaction provides an effective and potentially powerful method for construction of medium-sized rings with an internal 1,3-*cis*–*cis* diene unit. Noteworthy features of this intramolecular process include: (1) a highly stereospecific intramolecular coupling process, (2) the flexible positioning of hydroxy group, and (3) the potential extension to other medium-sized carbocycles and heterocycles.

5. Experimental

5.1. General

All reactions were performed in oven-dried (140 °C) or flame-dried glassware under an inert atmosphere of dry Ar or N_2. The following reaction solvents were distilled from the indicated drying agents: diethyl ether (Na, benzophenone), THF (Na, benzophenone), CH_2Cl_2 (P_2O_5), benzene (Na), toluene (Na), methanol ($Mg(OMe)_2$), triethylamine (CaH_2). *n*-Butyllithium solutions were titrated following the method of Gilman.[31] Brine refers to a saturated aqueous solution of NaCl. Grignard solutions were titrated using 2,2′ -phenanthroline as an indicator. Kugelrohr distillations were performed on a Büchi GKR-50 Kugelrohr; boiling points (bp) corresponding to uncorrected air-bath temperatures (ABT). All reaction temperatures correspond to internal temperatures measured by Teflon-coated thermocouples unless otherwise noted.

^{1}H NMR spectra and ^{13}C NMR spectra were recorded on a Varian Unity 400 (400 MHz, ^{1}H; 100 MHz, ^{13}C), Unity 500 (500 MHz, ^{1}H; 126 MHz, ^{13}C). Spectra are referenced to residual chloroform (δ 7.26 ppm, ^{1}H; δ 77.0 ppm, ^{13}C) and residual acetone (δ 2.04 ppm, ^{1}H; δ 29.8 ppm, ^{13}C). Chemical shifts are reported in ppm (δ); multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Coupling constants, *J*, are reported in Hertz. Mass spectroscopy was performed by the University of Illinois Mass Spectrometer Center. Electron impact (EI) spectra were performed on a Finnigan-MAT CH-5 spectrometer. Data are reported in the form of *m*/*z* (intensity relative to base peak = 100). Infrared spectra (IR) were recorded on a Mattson Galaxy 5020 spectrophotometer. Peaks are reported in cm^{-1} with indicated relative intensities: s (strong, 67–100%); m (medium, 34–66%); w (weak, 0–33%). Elemental analyses were performed by the University of Illinois Microanalytical Service Laboratory.

Analytical thin-layer chromatography was performed on Merck silica or aluminum oxide, basic gel plates with QF-254 indicator. Visualization was accomplished with UV light and/or Iodide. Diethyl ether was of reagent grade and used as received; other solvents for chromatography and filtration were technical grade and distilled from the indicated drying agents: hexane and pentane ($CaCl_2$); CH_2Cl_2 ($CaCl_2$); ethyl acetate (K_2CO_3). Column chromatography was performed using EM Science 230–400-mesh silica gel or Aldrich 150-mesh aluminum oxide, activated, basic, Brockmann I.

Analytical capillary gas chromatography (GC) was performed using the following gas chromatography fitted with a flame ionization detector (H_2 carrier gas, 1 mL/min): Hewlett Packard 5890 Series II. The following column was used: HP-5 50-m cross-linked 5%-Phenyl methyl silicone gum phase or Ultra-2 50-m cross-linked 5%-Phenyl methyl silicone gum phase. The detector temperature was 300 °C. Retention times (t_R) and integrated ratios were obtained from Hewlett Packard 3393A integrators.

All commercial reagents were purified by distillation or

recrystallization prior to use. A 1.0 M solution of tetrabutylammonium fluoride in THF was prepared from solid tetrabutylammonium fluoride trihydrate ($TBAF\cdot 3H_2O$, Fluka) and distilled THF in a volumetric flask and was stored in a Schlenk bottle. Palladium bis(dibenzylideneacetone) ($Pd(dba)_2$) was purchased from Jansen and used without purification. π-Allylpalladium chloride dimer $[allylPdCl]_2$ (APC) was purchased from ACROS and was recrystallized from benzene prior to use.

5.2. Representative experiments

5.2.1. General procedure I: silylation with chlorodimethylvinylsilane. To a solution of the requisite unsaturated alcohol in CH_2Cl_2 was added Et_3N (1.5 equiv.) and dimethylvinylchlorosilane (1.2 equiv.) sequentially under N_2 atmosphere at 0 °C. The white suspension was allowed to warm to room temperature and was stirred for 0.5–1.0 h. The mixture was poured into ice water and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, then were dried (Na_2SO_4), and filtered. After removal of solvent, the residue was purified by silica gel chromatography followed by Kugelrohr distillation to afford the corresponding silyl ether.

5.2.1.1. Preparation of dimethyl[(1-phenyl-3-butenyl)oxy]vinylsilane (4b). Following General procedure I, a solution of 1-phenyl-3-buten-1-ol (3.19 g, 21.5 mmol) in CH_2Cl_2 (30 mL), chlorodimethylvinylsilane (3.86 mL, 28.0 mmol, 1.2 equiv.), and Et_3N (4.48 mL, 32.3 mmol, 1.5 equiv.) were combined. After being stirred at room temperature for 2 h, the mixture was then poured to ice water (30 mL) and the aqueous layer was extracted with CH_2Cl_2 (2×30 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed by rotary evaporation. The residue was distilled under reduced pressure to afford 4.59 g (92%) of **4b** as a colorless liquid. Bp 74–75 °C (0.1 mm Hg); R_f 0.13 (silica gel, hexane, PMA); IR (neat) ν 2960 (s), 1641 (m), 1407 (m), 1253 (s), 1087 (s), 1068 (s), 1009 (s), 916 (s), 836 (s), 785 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.26 (m, 5H), 6.11 (dd, J=19.8, 14.9 Hz, 1H), 6.00 (dd, J=14.9, 4.4 Hz, 1H), 5.80–5.78 (m, 1H), 5.77 (dd, J=20.0, 4.4 Hz, 1H), 5.11–5.05 (m, 2H), 4.74 (dd, J=7.6, 5.5 Hz, 1H), 2.59–2.43 (m, 2H), 0.18 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 144.6, 137.7, 135.1, 133.0, 128.0 (2 C), 127.0, 126.0 (2 C), 116.9, 75.0, 45.0, −1.5, −1.7; MS (CI, 130 eV) 233 (4, $M^+ + 1$), 217 (34), 205 (35), 191 (100), 155 (23), 131 (37), 85 (19). Anal. Calcd for $C_{14}H_{20}OSi$: C: 72.36; H: 8.67. Found: C: 72.22; H: 8.56.

5.2.1.2. Preparation of dimethyl{[(*Z*)-9-iodo-1,8-nonadienyl]-4-oxy}vinylsilane (14b). Following General procedure I, a solution of **13b** (3.99 g, 15 mmol) in CH_2Cl_2 (25 mL), chlorodimethylvinylslane (2.49 mL, 18.0 mmol, 1.2 equiv.), and Et_3N (3.13 mL, 22.5 mmol, 1.5 equiv.) were combined. After being stirred at room temperature for 1 h, the mixture was poured into ice water (50 mL) and the aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were washed with brine (50 mL), then were dried (Na_2SO_4), and filtered. After removal of solvent, the residue was purified by chromatography (silica gel, hexane/EtOAc, 49/1) followed by Kugelrohr distillation to afford 5.0 g (95%) of **14b** as a colorless liquid. Bp 120–125 °C (0.05 mm Hg, ABT); R_f 0.39 (silica gel, hexane/EtOAc, 49/1, PMA); IR (neat) ν 3073 (m), 2942 (s), 2861 (m), 1641 (m), 1407 (m), 1276 (m), 1251 (s), 1089 (s), 914 (s), 835 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.20–6.12 (m, 3H), 6.00 (dd, J=15.0, 4.0 Hz, 1H), 5.83–5.76 (m, 1H), 5.77 (dd, J=20.5, 4.0 Hz, 1H), 5.06–5.03 (m, 2H), 3.71 (quint, J=6.0 Hz, 1H), 2.21 (dd, J=7.5, 6.0 Hz, 2H), 2.13 (q, J=7.0 Hz, 2H), 1.57–1.39 (m, 4H), 0.19 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.2, 138.1, 135.1, 133.0, 117.0, 82.5, 72.1, 42.1, 36.1, 34.6, 23.9, −1.37, −1.39; MS (EI, 70 eV) 349 (1, $M^+ - 1$), 335 (10), 323 (8), 309 (73), 207 (13), 180 (8), 155 (14), 121 (15), 97 (38), 85 (100). Anal. Calcd for $C_{13}H_{23}IOSi$: C, 44.57; H, 6.62; I, 36.23. Found: C, 44.66; H, 6.56; I, 35.92.

5.2.1.3. Preparation of dimethyl{(2*S,3*S**)-{2-{[(*Z*)-3-iodo-2-propenyl]oxy}-5-hexenyl}-3-oxy}vinylsilane (23a).** Following General procedure I, a solution of **22a** (4.23 g, 15 mmol) in CH_2Cl_2 (15 mL), chlorodimethylvinylslane (2.48 mL, 18.0 mmol, 1.2 equiv.), and Et_3N (3.13 mL, 22.5 mmol, 1.5 equiv.) were combined. After being stirred at room temperature for 30 min, the mixture was poured into ice water (30 mL) and the aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were washed with brine (50 mL), then were dried (Na_2SO_4), and filtered. After removal of solvent, the residue was purified by chromatography (silica gel, hexane/EtOAc, 100/0 to 19/1) followed by Kugelrohr distillation to afford 5.16 g (94%) of **23a** as a colorless liquid. Bp 145–150 °C (0.3 mm Hg, ABT); R_f 0.16 (silica gel, hexane/EtOAc, 49/1, PMA); IR (neat) ν 3075 (m), 2971 (s), 2900 (m), 1691 (m), 1639 (m), 1616 (m), 1407 (m), 1276 (s), 1253 (s), 1093 (s), 1006 (s), 956 (m), 914 (s), 836 (s) cm^{-1}; ^1H NMR: (500 MHz, $CDCl_3$) δ 6.43 (dt, J=7.5, 5.5 Hz, 1H), 6.33 (dt, J=7.5, 1.5 Hz, 1H), 6.15 (dd, J=20.5, 15.0 Hz, 1H), 5.99 (dd, J=15.0, 4.0 Hz, 1H), 5.80 (ddt, J=17.5, 10.5, 7.5 Hz, 1H), 5.76 (dd, J=20.5, 4.0 Hz, 1H), 5.09–5.02 (m, 2H), 4.14 (ddd, J=13.5, 5.0, 1.5 Hz, 1H), 4.05 (ddd, J=13.5, 5.5, 1.5 Hz, 1H), 3.65 (dt, J=8.0, 4.5 Hz, 1H), 3.38 (qd, J=6.5, 4.5 Hz, 1H), 2.32 (dddt, J=14.0, 7.0, 6.0, 1.5 Hz, 1H), 2.15 (dtt, J=14.0, 7.5, 1.5 Hz, 1H), 1.12 (d, J=6.5 Hz, 3H), 0.19 (s, 6H); ^{13}C NMR: (126 MHz, $CDCl_3$) δ 139.0, 138.1, 135.5, 132.9, 116.9, 82.2, 77.5, 74.9, 72.0, 37.1, 15.0, −1.32, −1.33; MS (EI, 70 eV) 366 (0.3, M^+), 351 (0.5), 325 (4), 241 (7), 211 (12), 167 (78), 155 (100), 131 (35), 85 (74); GC: t_R **23a**, 9.57 min (HP-5, 200 °C, 15 psi). Anal. Calcd for $C_{13}H_{23}O_2ISi$: C, 42.63; H, 6.33; I, 34.64. Found: C, 42.79; H, 6.43; I, 34.81.

5.2.2. General procedure II: molybdenum-catalyzed ring-closing metathesis of 4, 14, or 23. In a flame-dried, 25-mL flask was placed freshly distilled benzene which was then moved into a dry box. Schrock's catalyst (0.05–0.1 equiv.) and compound **4**, **14**, or **23** (1.0 equiv.) were added sequentially to the flask. The yellow-brown solution was stirred at room temperature in the dry box and the reaction was monitored by ^1H NMR analysis. When the reaction was complete, the solvent was removed by rotary evaporation to give a brown residue, which was filtered through a short column of silica gel and was further eluted with hexane/EtOAc, 49/1. The filtrate was concentrated in

vacuo followed by Kugelrohr distillation to afford the product **5**, **15**, or **24**.

5.2.2.1. Preparation of 2,2-Dimethyl-6-phenyl-1-oxa-2-silacyclohex-3-ene (5b). Following General procedure II, benzene (10 mL), Schrock's catalyst (38 mg, 0.05 mmol, 0.05 equiv.), and **4b** (232 mg, 1.0 mmol) were combined and the mixture was stirred at room temperature for 1 h in the dry box. After removal of the solvent by rotary evaporation, the residue was filtered through a short column of silica gel which was eluted with 100 mL of hexane/EtOAc, 49/1. The filtrate was concentrated followed by Kugelrohr distillation to afford 193 mg (95%) of **5b** as a colorless liquid. Bp 95–100 °C (0.4 mm Hg ABT); R_f 0.15 (silica gel, hexane/EtOAc, 49/1, PMA); IR (neat) ν 1587 (s), 1521 (s), 1064 (s), 957 (s), 837 (s), 789 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (dd, $J=8.8$, 1.6 Hz, 2H), 7.37 (td, $J=8.8$, 1.6 Hz, 2H), 7.28 (tt, $J=8.8$, 1.6 Hz, 1H), 6.86 (ddd, $J=14.0$, 6.0, 2.4 Hz, 1H), 5.88 (ddd, $J=14.0$, 2.8, 0.8 Hz, 1H), 5.01 (dd, $J=10.0$, 3.6 Hz, 1H), 2.43–2.38 (m, 2H), 0.3 (s, 3H), 0.28 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 147.0, 144.4, 128.3 (2 C), 127.4, 127.2, 125.6 (2 C), 73.3, 39.0, −0.2, −0.6; MS (EI, 70 eV) 204 (37, M^+), 189 (7), 130 (100), 98 (35), 83 (22). Anal. Calcd for $C_{12}H_{16}OSi$: C, 70.53; H, 7.89. Found: C, 70.34; H, 7.96.

5.2.2.2. Preparation of 2,2-dimethyl-6-[(*Z*)-5-iodo-4-pentenyl]-1-oxa-2-silacyclohex-3-ene (15b). Following General procedure II, benzene (10 mL), **14b** (350 mg, 1.0 mmol), and Schrock's catalyst (61.2 mg, 0.08 mmol, 0.08 equiv.) were combined and the mixture was stirred at room temperature for 24 h in the dry box. After removal of solvent by rotary evaporation, the residue was purified by chromatography (silica gel, hexane/CH_2Cl_2, 19/1 to 4/1) followed by Kugelrohr distillation to afford 261 mg (81%) of **15b** as a colorless liquid. Bp 85–90 °C (0.02 mm Hg, ABT); R_f 0.30 (silica gel, hexane/EtOAc, 49/1, PMA); IR (neat) ν 2985 (m), 2926 (s), 1608 (m), 1587 (m), 1352 (m), 1275 (m), 1249 (s), 1163 (m), 1087 (m), 953 (s), 901 (m), 842 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.75 (ddd, $J=$ 14.5, 4.5, 3.5 Hz, 1H), 6.19–6.15 (m, 2H), 5.73 (dt, $J=14.5$, 1.5 Hz, 1H), 3.93–3.88 (m, 1H), 2.20–2.09 (m, 4H), 1.65–1.45 (m, 4H), 0.178 (s, 3H), 0.176 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.1, 141.3, 127.1, 82.4, 71.0, 37.1, 36.4, 34.5, 23.9, −0.4, −0.6; MS (EI, 70 eV) 322 (12, M^+), 307 (5), 195 (60), 180 (18), 153 (35), 127 (93), 98 (100), 75 (90). Anal. Calcd for $C_{11}H_{19}IOSi$: C, 41.00; H, 5.94; I, 39.38. Found: C, 41.03; H, 5.97; I, 38.97.

5.2.2.3. Preparation of ($6S^*$)-2,2-dimethyl-6-{($1S^*$)-1-{[(*Z*)-3-iodo-2-propenyl]oxy}ethyl}-1-oxa-2-silacyclohex-3-ene (24a). Following General procedure II, benzene (10 mL), **23a** (366 mg, 1.0 mmol), and Schrock's catalyst (61.2 mg, 0.08 mmol, 0.08 equiv.) were combined and the mixture was stirred at room temperature for 24 h in the dry box. Additional Schrock's catalyst (15.3 mg, 0.02 mmol, 0.02 equiv.) was added and then was stirred for 12 h. After removal of solvent by rotary evaporation, the residue was purified by chromatography (silica gel, hexane/Et_2O, 49/1 to 97/3) followed by Kugelrohr distillation to afford 273 mg (81%) of **24a** as a colorless liquid. Bp 125–130 °C (0.2 mm Hg, ABT); R_f 0.17 (silica gel, hexane/EtOAc, 97/3, PMA); IR (neat) ν 3070 (m), 2985 (s), 2896 (m), 1608 (m), 1587 (s), 1382 (m), 1276 (s), 1249 (s), 1157 (m), 1101 (s), 1062 (s), 952 (s), 902 (s), 842 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.79 (ddd, $J=14.0$, 6.0, 2.0 Hz, 1H), 6.44 (dt, $J=7.5$, 5.5 Hz, 1H), 6.34 (dt, $J=7.5$, 1.5 Hz, 1H), 5.73 (ddd, $J=14.0$, 3.0, 1.0 Hz, 1H), 4.19 (ddd, $J=13.5$, 5.5, 1.5 Hz, 1H), 4.13 (ddd, $J=13.5$, 6.0, 1.5 Hz, 1H), 3.94 (ddd, $J=11.0$, 4.5, 2.5 Hz, 1H), 3.49 (qd, $J=6.5$, 4.5 Hz, 1H), 2.29 (dddd, $J=17.5$, 11.0, 3.0, 2.5 Hz, 1H), 2.07 (dddd, $J=17.5$, 6.0, 2.5, 1.0 Hz, 1H), 1.17 (d, $J=6.5$ Hz, 3H), 0.19 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.2, 139.0, 127.0, 82.4, 77.9, 73.4, 72.1, 31.0, 15.0, −0.4, −0.6; MS (EI, 70 eV) 338 (0.2, M^+), 323 (1), 211 (2), 167 (22), 155 (14), 138 (9), 127 (100), 111 (13), 75 (15). Anal. Calcd for $C_{11}H_{19}O_2ISi$: C, 39.06; H, 5.66; I, 37.52. Found: C, 39.06; H, 5.66; I, 37.47.

5.2.3. General procedure III: palladium-catalyzed intermolecular cross-coupling of 5 with aryl or alkenyl halides. Substrate **5** (1.1 equiv.) was dissolved in a solution of TBAF (1.0 M in THF, 2.0 equiv.) under an Ar atmosphere at ambient temperature. After 2 min, aryl or alkenyl halide (1.0 equiv.) and the palladium catalyst (0.03–0.1 equiv.) were then added sequentially. The reaction was monitored by TLC analysis. When the halide was consumed, 2 mL of EtOAc/hexane, 7/3 were added. The mixture was filtered through a short column of silica gel, which was then eluted with EtOAc/hexane, 7/3 (150–200 mL). The filtrate was concentrated by rotary evaporation to give a crude product which was purified by silica gel chromatography.

5.2.3.1. Coupling reaction of 5b with ethyl 3-iodobenzoate. Preparation of ethyl 3-[(*Z*)-4-hydroxy-4-phenyl-1-butenyl]benzoate (6d). Following General procedure III, **5b** (225 mg, 1.1 mmol, 1.1 equiv.), a solution of TBAF in THF (1.0 M, 2.0 mL, 2.0 mmol, 2.0 equiv.), ethyl 3-iodobenzoate (276 mg, 1.0 mmol) and $Pd(dba)_2$ (17.2 mg, 0.03 mmol, 0.03 equiv.) were combined. The mixture was stirred at room temperature for 30 min and then 2 mL of EtOAc/hexane, 7/3 were added. The mixture was filtered through a short column of silica gel which was eluted with 150 mL of EtOAc/hexane, 7/3. The filtrate was concentrated to give a crude product which was purified by chromatography (silica gel, hexane/EtOAc, 9/1 to 4/1) to afford 276 mg (93%) of **6d** as a pale yellow (non-distillable) oil. R_f 0.34 (silica gel, hexane/EtOAc, 3/1, PMA); IR (neat) ν 3465 (s), 1718 (s), 1602 (m), 1280 (s), 1188 (s), 1106 (s), 759 (s), 701 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.90 (dd, $J=7.6$, 1.2 Hz, 1H), 7.43 (d, $J=7.6$ Hz, 1H), 7.39–7.26 (m, 6H), 6.58 (d, $J=11.6$ Hz, 1H), 5.80 (dt, $J=$ 11.6, 7.2 Hz, 1H), 4.82 (dd, $J=7.6$, 5.6 Hz, 1H), 4.37 (q, $J=7.2$ Hz, 2H), 2.83 (dtd, $J=15.2$, 7.6, 1.6 Hz, 1H), 2.76–2.69 (m, 1H), 2.26 (br s, 1H, HO), 1.39 (t, $J=7.2$ Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 166.6, 143.8, 137.3, 132.9, 130.6, 130.3, 129.8, 129.0, 128.4 (2 C), 128.2, 127.8, 127.6, 125.8 (2 C), 74.0, 61.0, 38.0, 14.3; MS (EI, 70 eV) 296 (0.2, M^+), 278 (2), 251 (5), 205 (3), 191 (100), 117 (54), 107 (39). Anal. Calcd for $C_{19}H_{20}O_3$: C: 76.99; H: 6.81. Found: C: 76.85; H: 6.75.

5.2.4. General procedure IV: Pd-catalyzed intramolecular cross-coupling of 15 or 24. Catalyst $[allylPdCl]_2$ (0.075–0.10 equiv.) was dissolved in a solution of TBAF in

THF (1.0 M, 10.0 equiv.) under an N_2 atmosphere at ambient temperature. To the mixture was added slowly a solution of **15** or **24** in THF (0.1 M) by syringe pump. After complete addition of **15** or **24**, the deep brown solution was stirred for additional 2 h. The solvent was removed by rotary evaporation and 5 mL of EtOAc/hexane, 7/3, were then added. The mixture was filtered through a short column of silica gel, which was then eluted with EtOAc/hexane, 7/3 (300–400 mL). The eluate was concentrated by rotary evaporation to give a crude product, which was purified by silica gel chromatography followed by Kugelrohr distillation to afford **16** or **25**.

5.2.4.1. Preparation of (3*Z*,5*Z*)-cyclononadienol (16b). Following General procedure IV, $[allylPdCl]_2$ (27.5 mg, 0.075 mmol, 0.075 equiv.) and a solution of TBAF in THF (1.0 M, 10.0 mL, 10.0 mmol, 10.0 equiv.) were combined. The solution of **15b** in THF (0.1 M, 322 mg, 1.0 mmol) was added slowly by syringe pump for 43 h. The solvent was removed by rotary evaporation and 5 mL of EtOAc/hexane, 7/3, were then added. The mixture was filtered through a short column of silica gel, which was then eluted with EtOAc/hexane, 7/3 (350 mL). The eluate was concentrated by rotary evaporation to give a crude product, which was purified by chromatography (silica gel, hexane/EtOAc, 9/1 to 4/1) followed by Kugelrohr distillation to afford 97 mg (70%) of **16b** as a colorless oil. Bp 75–80 °C (0.2 mm Hg, ABT); R_f 0.17 (silica gel, hexane/EtOAc, 4/1, PMA); IR (neat) ν 3350 (s), 3002 (s), 2929 (s), 2858 (s), 1637 (m), 1454 (s), 1356 (m), 1258 (m), 1064 (s), 996 (s), 903 (m), 803 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.96 (ddd, J= 11.0, 2.0, 1.0 Hz, 1H), 5.81 (d, J=11.0 Hz, 1H), 5.76–5.66 (m), 3.90 (quint, J=5.5 Hz, 1H), 2.39 (t, J=7.3 Hz, 2H), 2.15–2.00 (m, 2H), 1.84–1.78 (m, 2H), 1.60–1.52 (m, 2H), 1.40–1.33 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 133.1, 129.9, 128.5, 127.3, 71.2, 38.3, 36.2, 30.9, 19.7; MS (EI, 70 eV) 138 (12, M^+), 120 (5), 109 (27), 94 (47), 79(100), 67 (42). Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.16; H, 10.29.

5.2.4.2. Preparation of (8*S,9*S**)-8-hydroxy-9-methyl-1-oxa-3*Z*,5*Z*-cyclononadiene (25a).** Following General procedure IV, $[allylPdCl]_2$ (27.5 mg, 0.075 mmol, 0.075 equiv.) and a solution of TBAF in THF (1.0 M, 10.0 mL, 10.0 mmol, 10.0 equiv.) were combined. The solution of **24a** in THF (0.1 M, 338 mg, 1.0 mmol) was added slowly by syringe pump for 43 h. The solvent was removed by rotary evaporation and 5 mL of EtOAc/hexane, 7/3, were then added. The mixture was filtered through a short column of silica gel, which was then eluted with EtOAc/hexane, 7/3 (300 mL). The eluate was concentrated by rotary evaporation to give a crude product, which was purified by chromatography (silica gel, hexane/EtOAc, 19/1 to 17/3) followed by Kugelrohr distillation to afford 111 mg (72%) of **25a** as a colorless oil. Bp 80–85 °C (0.3 mm Hg, ABT); R_f 0.08 (silica gel, hexane/EtOAc, 4/1, PMA); IR (neat) ν 3407 (s), 3002 (s), 2969 (s), 2919 (s), 1625 (m), 1448 (m), 1415 (m), 1274 (m), 1245 (m), 1143 (s), 1124 (s), 1081 (s), 1052 (s), 1016 (s), 989 (s), 863 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.07 (ddq, J=11.5, 3.0, 1.5 Hz, 1H), 6.00 (dd, J=11.0, 1.0 Hz, 1H), 5.84 (dddd, J=11.5, 7.5, 6.5, 1,0 Hz, 1H), 5.68 (tdd, J=11.0, 5.5, 1.0 Hz, 1H), 4.35 (dd, J=12.5, 6.5 Hz, 1H), 3.74 (qd, J=6.5, 1.5 Hz, 1H), 3.65 (dd, J=12.5, 7.5 Hz, 1H), 3.55 (td, J=9.5, 4.5 Hz, 1H), 2.63 (dt, J=12.5, 11.0 Hz, 1H), 2.28 (dddt, J= 12.5, 5.5, 4.5, 1.5 Hz, 1H), 1.79 (br s, 1H, HO), 1.22 (d, J= 6.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 132.5, 129.61, 129.55, 129.45, 81.6, 73.5, 70.3, 35.7, 17.9; MS (EI, 70 eV) 154 (3, M^+), 139 (34), 128 (32), 115 (53), 92 (17), 77 (100), 64 (28). Anal. Calcd for $C_9H_{14}O_2$: C, 70.08; H, 9.16. Found: C, 69.98; H, 9.31.

Acknowledgements

We are grateful for the National Institutes of Health for generous financial support (R01 GM63167-01A1).

Supplementary data

Complete experimental details for all preparative procedures along with full characterization of all starting materials and products (94 pages) are provided.

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2004.06.149

References and notes

1. (a) Diederich, F., Stang, P. J., Eds.; *Metal-Catalyzed Cross-Coupling Reactions*. Wiley-VCH: Weinheim, 1998. (b) Tsuji, J. Palladium Reagents and Catalysts, Innovations in Organic Syntheses.. Wiley: Chichester, UK, 1995. (c) Heck, R. F. Palladium Reagents in Organic Synthesis. Academic: New York, 1985.
2. For a recent review, see: (a) Denmark, S. E.; Sweis, R. F. *Acc. Chem. Res.* **2002**, *35*, 835. (b) Denmark, S. E.; Sweis, R. F. *Chem. Pharm. Bull.* **2002**, *50*, 1531. (c) Denmark, S. E.; Ober, M. H. *Aldrichim. Acta* **2003**, *36*, 75. (d) Hiyama, T. Diederich, F., Stang, P. J., Eds.; *Metal-Catalyzed Cross-Coupling Reactions*. Wiley-VCH: Weinheim, 1998. Chapter 10. (e) Hiyama, T.; Hatanaka, Y. *Pure Appl. Chem.* **1994**, *66*, 1471. (f) Hatanaka, Y.; Hiyama, T. *Synlett* **1991**, 845.
3. For recent examples of silicon-based cross-coupling, see: (a) Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 918. (b) Tamao, K.; Kobayashi, K.; Ito, Y. *Tetrahedron Lett.* **1989**, *30*, 6051. (c) Suginome, M.; Kinugasa, H.; Ito, Y. *Tetrahedron Lett.* **1994**, *35*, 8635. (d) Mowery, M. E.; DeShong, P. *J. Org. Chem.* **1999**, *64*, 1684. (e) Mowery, M. E.; DeShong, P. *J. Org. Chem.* **1999**, *64*, 3266. (f) Lam, P. Y. S.; Deudon, S.; Averill, K. M.; Li, R.; He, M.; DeShong, P.; Lark, C. G. *J. Am. Chem. Soc.* **2000**, *122*, 7600. (g) Hirabayashi, K.; Kawashima, J.; Nishihara, Y.; Mori, A.; Hayama, T. *Org. Lett.* **1999**, *1*, 299. (h) Hirabayashi, K.; Kondo, T.; Toriyama, F.; Nishihara, Y.; Mori, A. *Bull. Chem. Soc. Jpn* **2000**, *73*, 749. (i) Lee, H. M.; Nolan, S. P. *Org. Lett.* **2000**, *2*, 2053. (j) Shibata, K.; Miyazawa, K.; Goto, Y. *Chem. Commun.* **1997**, 1309.

(k) Lee, J.-Y.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 5616.

4. (a) Denmark, S. E.; Choi, J. Y. *J. Am. Chem. Soc.* **1999**, *121*, 5821. (b) Denmark, S. E.; Wehrli, D.; Choi, J. Y. *Org. Lett.* **2000**, *2*, 2491. (c) Denmark, S. E.; Wang, Z. *Synthesis* **2000**, 999. (d) Denmark, S. E.; Wu, Z. *Org. Lett.* **1999**, *1*, 1495. (e) Denmark, S. E.; Wehrli, D. *Org. Lett.* **2000**, *2*, 565. (f) Denmark, S. E.; Neuville, L. *Org. Lett.* **2000**, *2*, 3221. (g) Denmark, S. E.; Pan, W. *Org. Lett.* **2001**, *3*, 61. (h) Denmark, S. E.; Wang, Z. *J. Organomet. Chem.* **2001**, *624*, 372. (i) Denmark, S. E.; Wang, Z. *Org. Lett.* **2001**, *3*, 1073. (j) Denmark, S. E.; Sweis, R. F. *J. Am. Chem. Soc.* **2001**, *123*, 6439. (k) Denmark, S. E.; Pan, W. *J. Organomet. Chem.* **2002**, *653*, 98. (l) Denmark, S. E.; Sweis, R. F. *Org. Lett.* **2002**, *4*, 3771. (m) Denmark, S. E.; Kobayashi, T. *J. Org. Chem.* **2003**, *68*, 5153. (n) Denmark, S. E.; Pan, W. *Org. Lett.* **2003**, *5*, 1119. For mechanistic studies, see: (o) Denmark, S. E.; Sweis, R. F. *J. Am. Chem. Soc.* **2004**, *125*, 4876. (p) Denmark, S. E.; Sweis, R. F.; Wehrli, D. *J. Am. Chem. Soc.* **2004**, *126*, 4865.
5. (a) Hirabayashi, K.; Ando, J.-i.; Kawashima, J.; Nishihara, Y.; Mori, A.; Hiyama, T. *Bull. Chem. Soc. Jpn* **2000**, *73*, 1409. (b) Mori, A.; Takahisa, E.; Kajiro, H.; Hirabayashi, K.; Nishihara, Y.; Hiyama, T. *Chem. Lett.* **1998**, 443. (c) Murata, M.; Ishikura, M.; Nagata, M.; Watanabe, S.; Masuda, Y. *Org. Lett.* **2002**, *4*, 1843. (d) Manoso, A. S.; DeShong, P. *J. Org. Chem.* **2001**, *66*, 7449. (e) Denmark, S. E.; Kallemeyn, J. M. *Org. Lett.* **2003**, *5*, 3483. (f) Trost, B. M.; Machacek, M. R.; Ball, Z. T. *Org. Lett.* **2003**, *5*, 1895. (g) Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2001**, *123*, 12726. (h) Ishiyama, T.; Sato, K.; Nishio, Y.; Miyaura, N. *Angew. Chem. Int. Ed.* **2003**, *42*, 5346.
6. Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2003**, *125*, 30.
7. For recent reviews, see: (a) Fürstner, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 3012. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (c) Schuster, M.; Blechert, S. *Angew. Chem. Int. Ed.* **1997**, *36*, 2036. (d) Fürstner, A., Ed.; *Alkene Metathesis in Organic Synthesis*. Springer: Berlin, 1998. (e) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. (f) Flepin, F.-X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693. (g) Prunet, J. *Angew. Chem. Int. Ed.* **2003**, *42*, 2826. (h) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127. (i) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371. (j) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446.
8. For some examples on silicon-tether RCM, see: (a) Taylor, R. E.; Engelhardt, F. C.; Yuan, H. *Org. Lett.* **1999**, *1*, 1257. (b) Taylor, R. E.; Schmitt, M. J.; Yuan, H. *Org. Lett.* **2000**, *2*, 601. (c) Taylor, R. E.; Engelhardt, F. C.; Schmitt, M. J.; Yuan, H. *J. Am. Chem. Soc.* **2001**, *123*, 2964. (d) Meyer, C.; Cossy, J. *Tetrahedron Lett.* **1997**, *38*, 7861. (e) Cassidy, J. H.; Marsden, S. P.; Stemp, G. *Synlett* **1997**, 1411. (f) Using $[RuCl_2(=C=C=CPh_2)(PCy_3)_2]$ or $[RuCl_4(=C=C=CPh_2)(PCy_3)(\eta^6\text{-}MeC_6H_4\text{-}4^iPr)]$ as the catalyst, see: Fürstner, A.; Hill, A. F.; Liebl, M.; Wilton-Ely, J. D. E. T. *Chem. Commun.* **1999**, 601. For a review, see: (g) Marciniec, B.; Pietraszuk, C. *Curr. Org. Chem.* **2003**, *7*, 691.
9. Yao, Q. *Org. Lett.* **2001**, *3*, 2069.
10. (a) Zhu, S. S.; Cefalo, D. R.; La, D. S.; Jamieson, J. Y.; Davis, W. M.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1999**, *121*, 8251. (b) Aeilts, S. L.; Cefalo, D. R.; Bonitatebus, P. J.; Houser, J. H.; Hoveyda, A. H.; Schrock, R. R. *Angew. Chem. Int. Ed.* **2001**, *40*, 1452. (c) Weatherhead, G. S.; Houser, J. H.; Ford, J. G.; Jamieson, J. Y.; Schrock, R. R.; Hoveyda, A. H. *Tetrahedron Lett.* **2000**, *41*, 9553. (d) Kiely, A. F.; Jernelius, J. A.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 2868. For a review, see: (e) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2003**, *42*, 4592.
11. (a) Pitetraszuk, C.; Marciniec, B.; Fischer, H. *Organometallics* **2000**, *19*, 913. (b) Pitetraszuk, C.; Fischer, H.; Kujawa, M.; Marciniec, B. *Tetrahedron Lett.* **2001**, *42*, 1175. (c) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783.
12. (a) Chang, S.; Grubbs, R. H. *Tetrahedron Lett.* **1997**, *38*, 4757. (b) Ahmed, M.; Barrett, A. G. M.; Beall, J. C.; Braddock, D. C.; Flack, K.; Gibson, V. C.; Procopiou, P. A.; Salter, M. M. *Tetrahedron* **1999**, *55*, 3219. (c) Barrett, A. G. M.; Beall, J. C.; Braddock, D. C.; Flack, K.; Gibson, V. C.; Salter, M. M. *J. Org. Chem.* **2000**, *65*, 6508. For a asymmetric study, see: (d) Kröll, R. M.; Schuler, N.; Lubbad, S.; Buchmeiser, M. R. *Chem. Commun.* **2003**, 2742. (e) The ruthenium carbene complex **1** is more sensitive to the substitution pattern of alkenes than molybdenum catalyst **3**, see: Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62*, 7310.
13. (a) Yet, L. *Chem. Rev.* **2000**, *100*, 2963. (b) Rousseau, G. *Tetrahedron* **1995**, *51*, 2777. (c) Roxburgh, C. J. *Tetrahedron* **1993**, *49*, 10749. (d) Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757. (e) Mehta, G.; Singh, V. *Chem. Rev.* **1999**, *99*, 881. (f) Evans, P. A.; Holmes, A. B. *Tetrahedron* **1991**, *47*, 9131. (g) Hoberg, J. O. *Tetrahedron* **1998**, *54*, 12631.
14. (a) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95. (b) Liebman, J. F.; Greenberg, A. *Chem. Rev.* **1976**, *76*, 311.
15. (a) Duncton, M. A. J.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1235. For the construction of a 10-membered ring diene with one exo double bond, see: (b) Hodgson, D. H.; Foley, A. M.; Boulton, L. T.; Lovell, P. J.; Maw, G. N. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2911.
16. Portions of this work have been communicated previously: (a) Denmark, S. E.; Yang, S.-M. *Org. Lett.* **2001**, *3*, 1749. (b) Denmark, S. E.; Yang, S.-M. *J. Am. Chem. Soc.* **2002**, *124*, 2102.
17. Some specific examples on medium-sized ring formation with diene unit, see: (a) Ma, S.; Negishi, E. *J. Am. Chem. Soc.* **1995**, *117*, 6345. (b) Nemoto, H.; Yoshida, M.; Fukumoto, K. *J. Org. Chem.* **1997**, *62*, 6450. (c) Piers, E.; Romero, M. A. *J. Am. Chem. Soc.* **1996**, *118*, 1215. (d) Huffman, M. A.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 4895.
18. Recently, the 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene-substituted ruthenium complex exhibited high reactivity in RCM, especially for di-, tri- or tetra-substituted cyclic alkenes, see: Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.
19. The molybdenum complex **3** is commercially available (Strem) and can be prepared according to a reported procedure with consistent purity and reactivity, see: (a) Fox, H. H.; Yap, K. B.; Robbins, J.; Cai, S.; Schrock, R. R. *Inorg. Chem.* **1992**, *31*, 2287. (b) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875. (c) Oskam, J. H.; Fox, H. H.; Yap, K. B.; McConville, D. H.; O'Dell, R.; Lichtenstein, B. J.; Schrock, R. R. *J. Organomet. Chem.* **1993**, *459*, 185. (d) Fox, H. H.; Lee, J.-K.; Park, L. Y.; Schrock, R. R. *Organometallics* **1993**, *12*, 759.
20. (a) Brown, C. A.; Yamashita, A. *J. Am. Chem. Soc.* **1975**, *97*, 891. (b) Macaulay, S. R. *J. Org. Chem.* **1990**, *46*, 6319.

21. (a) Erickson, K. L.; Scheuer, P. J., Ed.; *Marine Natural Products*; Vol. 5. Academic: New York; 1983. p. 131–257. (b) Faulkner, D. J. *Nat. Prod. Rep.* **2001**, *18*, 1–49.
22. Isobe et al. have reported the construction of medium ring ethers (7–10 rings) with an internal 1,3-diene unit through cyclization of an acetylene cobalt complex followed by reductive decomplexation. (a) Yenjai, C.; Isobe, M. *Tetrahedron* **1998**, *54*, 2509. (b) Hosokawa, S.; Isobe, M. *Tetrahedron Lett.* **1998**, *39*, 2609. (c) Kira, K.; Isobe, M. *Tetrahedron Lett.* **2000**, *41*, 5951.
23. Alkylidene **1** has been shown to react with acetylenic halides through halide exchange. Vinyl halide containing dienes were also failed to cyclize using either **1** or Mo-complex **3**, (a) Kim, S.-H.; Zuercher, W. J.; Bowden, N. B.; Grubbs, R. H. *J. Org. Chem.* **1996**, *61*, 1073. (b) A successful RCM of vinyl chloride was disclosed recently, see: Chao, W.; Weinreb, S. M. *Org. Lett.* **2003**, *5*, 2505.
24. Giessert, A. J.; Snyder, L.; Markham, J.; Diver, S. T. *Org. Lett.* **2003**, *5*, 1793.
25. (a) Wagner, J.; Cabrejas, L. M. M.; Grossmith, C. E.; Papagerogiou, C.; Senia, F.; Wagner, D.; France, J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 9255. (b) Dvorak, C. A.; Schmitz, W. D.; Poon, D. J.; Pryde, D. C.; Lawson, J. P.; Amos, R. A.; Meyers, A. I. *Angew. Chem. Int. Ed.* **2000**, *39*, 1664.
26. For an example of formation of a marocyclic triene by RCM of a tetraene see: (a) Wang, X.; Porco, J. A. *J. Am. Chem. Soc.* **2003**, *125*, 6040. (b) Evano, G.; Schaus, J. V.; Panek, J. S. *Org. Lett.* **2004**, *6*, 525.
27. Basu, K.; Cabral, J. A.; Paquette, L. A. *Tetrahedron Lett.* **2002**, *43*, 5453.
28. (a) Conformational constraints have a dramatic effect on the success of ring closure. For a recent review on synthesis of medium rings using RCM strategies, see: Maier, M. E. *Angew. Chem. Int. Ed.* **2000**, *39*, 2073. (b) The first 10-membered carbocycle prepared by RCM has been reported recently, see: Nevalainen, M.; Koskinen, A. M. P. *Angew. Chem. Int. Ed.* **2001**, *40*, 4060. An attempt to promote closure of simple acyclic dienes to 8-membered carbocycles with Ru-complex **1** met with failure, see Ref. 12e.
29. It has been proposed that the palladium catalyst could act as a template to coordinate both ends of the molecule through oxidative addition followed by coordination of the organostannane in intramolecular Stille couplings. Stille, J. K.; Tanaka, M. *J. Am. Chem. Soc.* **1987**, *109*, 3785.
30. For an application on the total synthesis of (+)-brasilenyne, see: Denmark, S. E.; Yang, S.-M. *J. Am. Chem. Soc.* **2002**, *124*, 15196.
31. Gilman, H.; Cartledge, F. K.; Sin, S.-Y. *J. Organomet. Chem.* **1963**, *1*, 8.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 60 (2004) 9709–9714

Combinatorial approach to the asymmetric hydrogenation of β-acylamino acrylates: use of mixtures of chiral monodentate P-ligands

Manfred T. Reetz* and Xiaoguang Li

Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1, 45470 Mülheim/Ruhr, Germany

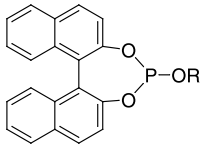
Received 22 June 2004; revised 2 July 2004; accepted 5 July 2004

Available online 25 August 2004

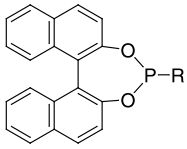
Abstract—The previously proposed concept of using mixtures of two different chiral monodentate P-ligands has been extended to the asymmetric Rh-catalyzed hydrogenation of β-acylamino acrylates with formation of chiral β-amino acid derivatives. Mixtures of BINOL-derived phosphites and phosphonites are particularly effective (*ee*=94–99% for five different substrates).

1. Introduction

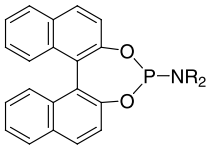
One of the remaining challenges in asymmetric olefin-hydrogenation concerns the need to develop readily accessible and cheap ligands which are easily modified so as to satisfy the requirements for high enantioselectivity in any given (industrial) case. The independent discovery in 2000 by three groups concerning the use of BINOL-derived phosphites **1**,[1] phosphonites **2**[2,3] and phosphoramidites **3**[4] as ligands in Rh-catalyzed olefin-hydrogenation constitutes an important step forward because: (1) BINOL is currently one of the cheapest chiral auxiliaries available;[5] and (2) the ligands **1**–**3** are modular, which means that a wide variety of derivatives are readily accessible, often leading to *ee*-values of >95% in olefin-hydrogenation.



1a R = CH_3
b R = Ph
c R = cC_6H_{11}
d R = $CH(CH_3)_2$
e R = CH_2Ph
f R = $CH_2C(CH_3)_3$
g R = $CH(C_2H_5)_2$

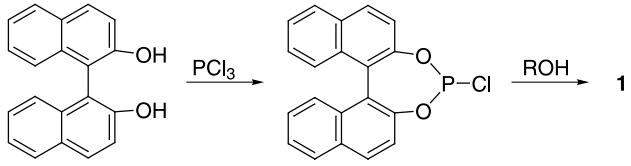


2a R = CH_3
b R = Ph
c R = cC_6H_{11}
d R = $C(CH_3)_3$
e R = $CH(CH_3)_2$



3

For example, phosphites **1** are best prepared in two simple steps starting from (*R*)- or (*S*)-BINOL (**4**). The second step involves an alcohol ROH, thousands of which are available in achiral (or chiral) form.[1,6] We have prepared more than 60 different phosphites **1**, which means that we can test this library for any given substrate. Other groups have extended the list of monodentate P-ligands of the type **1** and demonstrated their use in asymmetric olefin-hydrogenation.[7]



4 (*R*) or (*S*) **5**

The discovery that monodentate P-ligands of the type **1**–**3** are excellent ligands in Rh-catalyzed olefin-hydrogenation came as a surprise, because it was a previously accepted dogma that chelating bidentate ligands are required for high enantioselectivity. Although the precise source of enantioselectivity in hydrogenations using monodentate ligands has not yet been fully illuminated, our preliminary mechanistic studies point to the presence of two monodentate P-ligands in the transition state of the reaction.

These developments inspired us to propose in 2002 yet another practical tool in combinatorial asymmetric transition metal catalyzed reactions, namely the use of mixtures of two different monodentate ligands L^a and L^b leading to three different catalysts, namely two

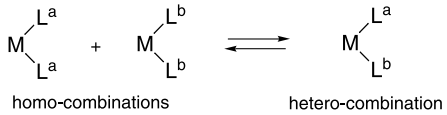
Keywords: Phosphonite; Phosphite; β-Acylamino acrylate.
* Corresponding author. Tel.: +49-208-306-2000; fax: +49-208-306-2985; e-mail: reetz@mpi-muelheim.mpg.de

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.07.042

Table 1. Rh-catalyzed hydrogenation of olefin **6a** (conditions: CH_2Cl_2; 60 bar H_2; r.t., 20 h; Rh: **6a** = 1:50; L^a:L^b = 1:1; Rh:total ligands = 1:2). Use of (*R*)-BINOL results in (*S*)-**7a**

Entry	Ligand	Conversion (%)	*ee* (%)
	Homo-combinations		
1	**1a / 1a**	95	75.0
2	**1b / 1b**	48	81.8
3	**1c / 1c**	95	98.2
4	**1d / 1d**	100	96.6
5	**1e / 1e**	100	82.6
6	**1f / 1f**	100	97.4
7	**1g / 1g**	100	94.6
8	**2a / 2a**	100	95.4
9	**2b / 2b**	75	77.0
10	**2c / 2c**	25	65.8
11	**2d / 2d**	83	44.6
12	**2e / 2e**	100	95.8
	Hetero-combinations		
Phosphite / Phosphonite			
13	**1a / 2a**	100	95.2
14	**1a / 2b**	84	91.4
15	**1a / 2c**	70	92.4
16	**1a / 2d**	100	98.8
17	**1a / 2e**	100	96.6
18	**1b / 2a**	86	91.5
19	**1b / 2b**	58	78.6
20	**1b / 2c**	62	86.8
21	**1b / 2d**	98	96.2
22	**1b / 2e**	94	90.0
23	**1c / 2a**	100	96.8
24	**1c / 2b**	not studied	
25	**1c / 2c**	74	94.0
26	**1c / 2d**	100	98.8
27	**1c / 2e**	68	94.8
28	**1d / 2a**	100	96.8
29	**1d / 2b**	96	95.4
30	**1d / 2c**	71	91.8
31	**1d / 2d**	100	97.0
32	**1d / 2e**	100	97.6
33	**1e /2a**	100	95.4
34	**1e / 2b**	96	94.2
35	**1e / 2c**	66	93.2
36	**1e / 2d**	100	97.6
37	**1e / 2e**	98	95.0
38	**1f / 2a**	100	96.6
39	**1f /2b**	98	94.2
40	**1f / 2c**	100	98.0
41	**1f / 2d**	98	94.2
42	**1f / 2e**	95	97.4
43	**1g / 2a**	100	96.0
44	**1g /2b**	100	96.4
45	**1g / 2c**	69	91.6
46	**1g / 2d**	100	98.6
47	**1g / 2e**	86	96.4
Two phosphites			
48	**1a / 1b**	80	75.4
49	**1a / 1c**	93	95.8
50	**1a / 1d**	100	92.1
51	**1a / 1e**	100	79.2
52	**1a / 1f**	94	90.4
53	**1a / 1g**	98	85.6
54	**1b / 1c**	not studied	
55	**1b / 1d**	91	90.8
56	**1b / 1e**	76	86.2
57	**1b / 1f**	92	91.4
58	**1b / 1g**	not studied	
59	**1c / 1d**	100	98.4
60	**1c / 1e**	not studied	
61	**1c / 1f**	100	95.4
62	**1c / 1g**	not studied	
63	**1d / 1e**	100	94.4
64	**1d / 1f**	99	94.8
65	**1d / 1g**	not studied	
66	**1e / 1f**	100	92.4
67	**1e / 1g**	not studied	
68	**1f / 1g**	not studied	
Two phosphonites			
69	**2a / 2b**	100	95.0
70	**2a / 2c**	80	93.2
71	**2a / 2d**	98	93.0
72	**2a / 2e**	100	95.0
73	**2b / 2c**	42	79.8
74	**2b / 2d**	90	84.0
75	**2b / 2e**	100	94.6
76	**2c / 2d**	12	41.8
77	**2c / 2e**	59	92.6
78	**2d / 2e**	81	90.6

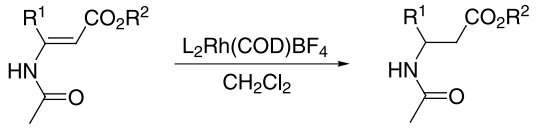
homo-combinations and one hetero-combination.[8] Since ligand exchange in solution is rapid, it is not possible to obtain the hetero-combination in pure form. This means that a given catalyst system will in fact contain three different catalysts. The relative amounts depend upon the nature of the ligands and the metal as well as the relative amounts of ligands L^a and L^b used.



If the hetero-combination is more reactive and more enantioselective than either of the homo-combinations,

then the *ee*-value will be higher than in separate experiments involving pure L^a or L^b. Since it is currently difficult to predict when these requirements are met (different substrates may behave differently), an empirical approach is necessary.[8] Once a library of monodentate P-ligands has been prepared and put on the shelf, the combinatorial approach allows immediate access to a wide range of new catalysts simply by the process of mixing. Indeed, pronounced enhancements in enantioselectivity were observed for such substrates as itaconic acid diester,[8] *N*-acyl acrylamides[8] and *N*-acyl enamides.[9] Recently Feringa has applied the concept to mixtures of phosphoramidites **3**.[10]

In the present paper, we extend the method to the hydrogenation of β-acylamino acrylates **6** with formation of β-amino acid derivatives **7**. The asymmetric hydrogenation leading to this important class of compounds is known to be a relatively slow process.[11,12] Here we show that certain phosphites **1** as homo-combinations but particularly mixtures of phosphites **1** and phosphonites **2** constitute one of the cheapest and most efficient catalyst systems in the production of **7**. Moreover, the data provides valuable information for future theoretical studies of these unusual effects.



6a $R^1 = CH_3$; $R^2 = CH_3$
b $R^1 = CH_3$; $R^2 = C_2H_5$
c $R^1 = C_2H_5$; $R^2 = CH_3$
d $R^1 = n\text{-}C_3H_7$; $R^2 = C_2H_5$
e $R^1 = C_6H_5$; $R^2 = C_2H_5$

7

In exploratory experiments we used **6a** as the model substrate and restricted the size of the libraries of phosphites **1** and phosphonites **2** to seven and five derivatives, respectively. Although not all permutations were considered, many hits were identified, i.e. ligand mixtures which result in higher *ee*-values than either of the respective homo-combinations themselves. Table 1 summarizes the results of this relatively short search encompassing 70 experiments (including the traditional homo-combinations for comparison).

Several homo-combinations give rise to acceptable enantioselectivity, the cyclohexyl-phosphite **1c/1c** (entry 3) being the best one (98.2% *ee*). Upon evaluating the hetero-combinations, the color code in Table 1 is useful in obtaining a quick overview. The red entries represent hits with the most pronounced positive effects relative to the performance of the respective homo-combinations. The green ones also show *ee*-enhancement but these are only moderate, while the black entries denote a decrease in enantioselectivity upon mixing ligands, relative to the *ee*-value of the respective best homo-combination (in addition to the homo-combinations themselves). Table 1 shows that hits occur most often when mixtures of phosphites **1** and phosphonites **2** are used. It can be seen that the strongest effects involve either the methyl- or benzyl-phosphite (**1a** or **1e**) in combination with a bulky phosphonite, as in entries 14, 15, 16, 34, 35 and 36. For example, the combination of the methyl-phosphite **1a** and the *t*-butyl-phosphonite **2d** (entry 16) results in an *ee*-value of 98.8%, in contrast to the corresponding homo-combinations which lead to *ee*-values of only 75.0% (entry 1) and 44.6% (entry 11), respectively. This particular hetero-combination (**1a/2d**) also constitutes the best catalyst system in the whole table. From a theoretical point of view, this is an intriguing observation, because it must be remembered that the system contains the two homo-combinations as well which catalyze the reaction with much lower enantioselectivity.

There seems to be a trend in that the combination of a 'small' ligand with a bulky partner results in positive effects. However, Table 1 also reveals several exceptions, so that this trend cannot be construed as a rule. For example, the combination of the methyl- and *t*-butyl-phosphonite (**2a/2d**) actually results in a slight decrease in enantioselectivity [93% *ee* (entry 71) versus 95.4% *ee* (entry 8) and 44.6% *ee* (entry 11)] for the two respective homo-combinations. Our previous conclusion regarding small/large ligand combinations was in fact based on results obtained from these two phosphonites.[8] Thus, the best way to proceed when studying new types of substrates is the empirical combinatorial approach. Nevertheless, upon screening other β-acylamino acrylates **6**, we were guided by the results in Table 1 and reduced the number of experiments drastically.

First, it was of interest to study the possible effect of varying the ester function in substrate **6**, specifically in going from the previous methyl ester **6a** to the ethyl analog **6b**. Two previous ligand hits were tested, namely **1a/2d** and **1e/2d**. In the case of **1a/2d**, the corresponding homo-combinations afford *ee*-values of 80.4% and 25.4%, respectively, while the hetero-combination results in 99.4% *ee* (100% conversion) under the standard conditions as defined in Table 1. The **1e/2d** hetero-combination leads to 99.2% *ee* (100% conversion), in contrast to the relevant homo-combinations (88.8% *ee* and 25.4% *ee*, respectively). Thus, the ethyl ester **6b** provides better results than the methyl analog **6a**.

The hydrogenation of two other alkyl-substituted β-acylamino acrylates **6c** and **6d** was then studied in an analogous way, although the search in ligand space was restricted to just a few hetero-combinations. The most striking trend as shown in Tables 2 and 3 is the finding that as before the hetero-combination **1a/2d** consistently represents the best mixed ligand system.

Finally, the hydrogenation of the phenyl-substituted β-acylamino acrylate **6e**, which is a notoriously 'difficult' substrate, was studied somewhat more extensively. Table 4 shows that it is again the hetero-combination **1a/2d** which leads to the best results, namely a respectable 94.2% *ee* which is considerably higher than the two respective homo-combinations **1a/1a** (82.8% *ee*) and **2d/2d** (31.2% *ee*). The best homo-combination in this case is the neopentyl phosphite **1f/1f**, which leads to an enantioselectivity of only 88.2% *ee*.

In conclusion, we have extended the concept of using

Table 2. Rh-catalyzed hydrogenation of olefin **6c** (conditions: as in Table 1). Use of (*R*)-BINOL results in (*S*)-**7c**

Entry	Ligand	Conversion (%)	*ee* (%)
	Homo-combinations		
1	**1a / 1a**	100	84.8
2	**1c / 1c**	100	98.2
3	**1e / 1e**	100	94.4
4	**1f / 1f**	100	97.8
5	**1g / 1g**	98	98.0
6	**2a / 2a**	97	92.2
7	**2c / 2c**	22	76.2
8	**2d / 2d**	49	33.6
	Hetero-combinations		
Phosphite / Phosphonite			
9	**1a / 2a**	97	90.2
10	**1a / 2c**	100	94.5
11	**1a / 2d**	100	98.8
12	**1c / 2a**	98	95.4
13	**1c / 2d**	98	95.4
14	**1e / 2a**	100	97.4
15	**1e / 2c**	86	95.4
16	**1e / 2d**	100	97.8
17	**1f / 2a**	100	97.6
18	**1f / 2c**	89	94.2
19	**1f / 2d**	100	98.8
20	**1g / 2a**	99	95.0
21	**1g / 2d**	100	98.0
Two phosphites			
22	**1e / 1f**	100	98.3
Two phosphonites			
23	**2a / 2d**	97	92.2
24	**2c / 2d**	100	51.0

Table 3. Rh-catalyzed hydrogenation of olefin **6d** (conditions: as in Table 1). Use of (*R*)-BINOL results in (*S*)-**7d**

Entry	Ligand	Conversion (%)	*ee* (%)
	Homo-combinations		
1	**1a / 1a**	100	85.0
2	**1c / 1c**	100	97.0
3	**1e / 1e**	97	90.6
4	**1f / 1f**	100	98.0
5	**1g / 1g**	100	97.2
6	**2a / 2b**	76	92.4
7	**2c / 2c**	8.8	51.0
8	**2d / 2d**	98	30.8
	Hetero-combinations		
Phosphite / Phosphonite			
9	**1a / 2a**	96	92.4
10	**1a / 2c**	68	92.4
11	**1a / 2d**	100	98.1
12	**1c / 2a**	98	96.2
13	**1c / 2d**	99	97.4
14	**1e / 2a**	82	91.8
15	**1e / 2c**	64	94.4
16	**1e / 2d**	100	97.9
17	**1f / 2c**	65	92.2
18	**1g / 2a**	100	96.0
19	**1g / 2d**	100	98.2
Two phosphites			
20	**1c / 1e**	100	97.1
21	**1e / 1f**	100	95.0
Two phosphonites			
22	**2c / 2d**	14	36.6

mixtures of chiral monodentate P-ligands in asymmetric transition metal-catalyzed reactions to include the hydrogenation of a particularly challenging class of olefins (β-acylamino acrylates). Several bidentate ligand systems also give rise to high enantioselectivities,[11] although their syntheses require a number of steps. In contrast, ligands **1**–**3** entail only two synthetic steps in which cheap components are easily assembled in a modular way. Recently, a BINOL-derived monophosphite **1**, in which the alcohol component is a mannitol derivative, was shown to be an excellent ligand in the asymmetric hydrogenation of β-acylamino acrylates **6** (and other olefins).[12] Of course, this ligand system is more complex and requires a higher degree of synthetic effort. The menthol-derivative of phosphite **1** has also been used in the hydrogenation of compounds **6** (up to 94% *ee*).[13] Certain phosphoramidites **3** are likewise well suited.[14]

We are currently carrying out mechanistic studies directed towards defining the source of enhanced rate and enantioselectivity in hydrogenations based on the use of hetero-combinations of monodentate P-ligands. On the synthetic side, the power of our combinatorial approach arises from the ready access to catalyst diversity without the need to synthesize new ligands. It remains to be seen whether such reaction types as asymmetric and regioselective hydroformylation can also be optimized by using mixtures of chiral monodentate P-ligands.

2. Experimental

2.1. General remarks

The preparation of all monodentate ligands **1**–**2** has been described previously.[1–3,6] The *E*-configurated substrates **6** were prepared by a known procedure.[11]

2.2. Standard procedure for hydrogenation

Eight dry 6-mL glass vials were placed in an autoclave, vacuum was applied and the vials were purged with argon three times. Then under an atmosphere of argon the vials were charged with a mixture of a 4.0 mM solution of the first ligand (0.5 mL) and a 4.0 mM solution of the second ligand (0.5 mL) in dry dichloromethane. The solution is treated with a 4.0 mM solution of $[Rh(cod)_2]BF_4$ (0.5 mL) in dichloromethane and stirred for 5 min at room temperature. Then a 0.10 M solution of substrate **6** in dichloromethane (1 mL) was added. After purging with H_2 three times, the autoclave was pressurized with H_2 to 60 bar and

Table 4. Rh-catalyzed hydrogenation of olefin **6e** (conditions: as in Table 1). Use of (*R*)-BINOL results in (*R*)-**7e**

Entry	Ligand	Conversion (%)	*ee* (%)
	Homo-combinations		
1	**1a / 1a**	87	82.8
2	**1c / 1c**	86	84.2
3	**1d / 1d**	87	87.4
4	**1e / 1e**	100	85.8
5	**1f / 1f**	94	88.2
6	**1g / 1g**	92	87.0
7	**2a / 2a**	100	71.0
8	**2b / 2b**	43	54.6
9	**2c / 2c**	28	21.8
10	**2d / 2d**	47	31.2
11	**2e / 2e**	90	76.2
Phosphite / Phosphonite			
12	**1a / 2a**	90	81.0
13	**1a / 2b**	72	78.2
14	**1a / 2c**	84	80.8
15	**1a / 2d**	95	94.2
16	**1a / 2e**	89	83.6
17	**1c / 2a**	89	79.4
18	**1c / 2b**	81	83.8
19	**1c / 2c**	77	61.0
20	**1c / 2d**	76	87.4
21	**1d / 2a**	97	82.8
22	**1d / 2b**	78	82.6
23	**1d / 2d**	86	92.0
24	**1d / 2e**	91	86.0
25	**1f / 2a**	97	83.8
26	**1f / 2b**	83	84.2
27	**1f / 2c**	81	82.2
28	**1f / 2d**	94	92.6
29	**1f / 2e**	93	85.2
30	**1f / 2a**	97	84.8
31	**1f / 2c**	90	83.2
32	**1f / 2d**	85	83.6
33	**1g / 2a**	92	81.4
34	**1g / 2b**	86	85.2
35	**1g / 2c**	88	71.0
36	**1f / 2d**	89	91.2
37	**1g / 2e**	95	86.6
Two phosphites			
38	**1a / 1c**	84	83.4
39	**1a / 1d**	89	85.6
40	**1a / 1e**	85	82.7
41	**1a / 1f**	83	85.2
42	**1c / 1e**	100	86.4
43	**1d / 1e**	95	84.8
44	**1e / 1f**	81	83.0
Two phosphonites			
45	**2a / 2c**	99	76.0
46	**2a / 2d**	89	78.0
47	**2c / 2d**	32	13.4

the reactions were magnetically stirred at room temperature for 20 h. Following dilution, conversion was determined by NMR spectroscopy. To determine the *ee* values, about 1.5 mL of the reaction solution can be passed through a small amount of silica gel prior to the GC analysis using chiral stationary phases. The absolute configuration was determined by comparison with known compounds described in the literature.[11]

Acknowledgements

We thank the Fonds der Chemischen Industrie for supporting this work.

References and notes

1. Reetz, M. T.; Mehler, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 3889–3890. (b) Reetz, M. T.; Mehler, G.; Meiswinkel, A. Patent application, WO 01/94278 A1, 2001. (c) Reetz, M. T.; Goossen, L. J.; Meiswinkel, A.; Paetzold, J.; Feldthusen, J. *J. Org. Lett.* **2003**, *5*, 3099–3101.
2. Reetz, M. T.; Sell, T. *Tetrahedron Lett.* **2000**, *41*, 6333–6336.
3. Claver, C.; Fernandez, E.; Gillon, A.; Heslop, K.; Hyett, D. J.; Martorell, A.; Orpen, A. G.; Pringle, P. G. *Chem. Commun. (Cambridge, UK)* **2000**, 961–962.
4. (a) van den Berg, M.; Minnaard, A. J.; Schudde, E. P.; van Esch, J.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *J. Am. Chem. Soc.* **2000**, *122*, 11539–11540. (b) Minnaard, A. J.; van den Berg, M.; Schudde, E. P.; van Esch, J.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *Chim. Oggi* **2001**, *19*, 12–13. (c) van den Berg, M.; Minnaard, A. J.; Haak, R. M.; Leeman, M.; Schudde, E. P.; Meetsma, A.; Feringa, B. L.; de Vries, A. H. M.; Maljaars, C. E. P.; Willans, C. E.; Hyett, D.; Boogers, J. A. F.; Henderickx, H. J. W.; de Vries, J. G. *Adv. Synth. Catal.* **2003**, *345*, 308–323. (d) Jia, X.; Guo, R.; Li, X.; Yao, X.; Chan, A. S. C. *Tetrahedron Lett.* **2002**, *43*, 5541–5544. (e) Fu, Y.; Xie, J.-H.; Hu, A.-G.; Zhou, H.; Wang, L.-X.; Zhou, Q.-L. *Chem. Commun. (Cambridge, UK)* **2002**, 480–481. (f) Hu, A.-G.; Fu, Y.; Xie, J.-H.; Zhou, H.; Wang, L.-X.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2002**, *41*, 2348–2350. (g) Doherty, S.; Robins, E. G.; Pál, I.; Newman, C. R.; Hardacre, C.; Rooney, D.; Mooney, D. A. *Tetrahedron: Asymmetry* **2003**, *14*, 1517–1527. (h) Bayer, A.; Murszat, P.; Thewalt, U.; Rieger, B. *Eur. J. Inorg. Chem.* **2003**, 2614–2624.
5. (*R*)- and (*S*)-BINOL cost about $400/kg for bulk quantities at: (a) Reuter Chemische Apparatebau KG, Freiburg, Germany; (b) Other commercial sources of BINOL are also available.
6. The synthesis of BINOL-derived monophosphites is well known: (a) Ovchinnikov, V. V.; Cherkasova, O. A.; Verizhnikov, L. V. *Zh. Obshch. Khim.* **1982**, *52*, 707–708. (b) Bartik, T.; Gerdes, I.; Heimbach, P.; Schulte, H.-G. *J. Organomet. Chem.* **1989**, *367*, 359–370. (c) Heimbach, P.; Bartik, T.; Drescher, U.; Gerdes, I.; Knott, W.; Rienäcker, R.; Schulte, H.-G.; Tani, K. *Kontakte (Darmstadt)* **1988**, *3*, 19–31. (d) Fuji, K.; Kinoshita, N.; Tanaka, K.; Kawabata, T. *Chem. Commun. (Cambridge, UK)* **1999**, 2289–2290. (e) Komarov, I. V.; Börner, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 1197–1200.

(f) Adams, D. J.; Chen, W.; Hope, E. G.; Lange, S.; Stuart, A. M.; West, A.; Xiao, J. *Green Chem.* **2003**, *5*, 118–122. (g) Gergely, I.; Hegedüs, C.; Gulyás, H.; Szöllösy, Á.; Monsees, A.; Riermeier, T.; Bakos, J. *Tetrahedron: Asymmetry* **2003**, *14*, 1087–1090. (h) Nakano, D.; Yamaguchi, M. *Tetrahedron Lett.* **2003**, *44*, 4969–4971.

7. (a) Hannen, P.; Militzer, H.-C.; Vogl, E. M.; Rampf, F. A. *Chem. Commun. (Cambridge, UK)* **2003**, 2210–2211. (b) Hua, Z.; Vassar, V. C.; Ojima, I. *Org. Lett.* **2003**, *5*, 3831–3834. (c) Chen, W.; Xiao, J. *Tetrahedron Lett.* **2001**, *42*, 2897–2899.
8. (a) Reetz, M. T.; Sell, T.; Meiswinkel, A.; Mehler, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 790–793. (b) Reetz, M. T. *Chim. Oggi* **2003**, *21*(10/11), 5–8. (c) Reetz, M. T.; Meiswinkel, A.; Sell, T.; Mehler, G. Patent application, DE-A 10247633.0, 2002.
9. Reetz, M. T.; Mehler, G.; Meiswinkel, A. *Tetrahedron: Asymmetry* **2004**, *15*, 2165–2167.
10. (a) Peña, D.; Minnaard, A. J.; Boogers, J. A. F.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *Org. Biomol. Chem.* **2003**, *1*, 1087–1089. (b) Duursma, A.; Hoen, R.; Schuppan, J.; Hulst, R.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2003**, *5*, 3111–3113.
11. (a) Tang, W.; Wu, S.; Zhang, X. *J. Am. Chem. Soc.* **2003**, *125*, 9570–9571. (b) Tang, W.; Wang, W.; Chi, Y.; Zhang, X. *Angew. Chem., Int. Ed.* **2003**, *42*, 3509–3511. (c) Wu, J.; Chen, X.; Guo, R.; Yeung, C.-H.; Chan, A. S. C. *J. Org. Chem.* **2003**, *68*, 2490–2493. (d) Holz, J.; Monsees, A.; Jiao, H.; You, J.; Komarov, I. V.; Fischer, C.; Drauz, K.; Börner, A. *J. Org. Chem.* **2003**, *68*, 1701–1707. (e) You, J.; Drexler, H.-J.; Zhang, S.; Fischer, C.; Heller, D. *Angew. Chem., Int. Ed.* **2003**, *42*, 913–916. (f) Tang, W.; Zhang, X. *Org. Lett.* **2002**, *4*, 4159–4161. (g) Zhou, Y.-G.; Tang, W.; Wang, W.-B.; Li, W.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 4952–4953. (h) Yasutake, M.; Gridnev, I. D.; Higashi, N.; Imamoto, T. *Org. Lett.* **2001**, *3*, 1701–1704. (i) Zhu, G.; Chen, Z.; Zhang, X. *J. Org. Chem.* **1999**, *64*, 6907–6910.
12. Huang, H.; Zheng, Z.; Luo, H.; Bai, C.; Hu, X.; Chen, H. *J. Org. Chem.* **2004**, *69*, 2355–2361.
13. Jerphagnon, T.; Renaud, J.-L.; Demonchaux, P.; Ferreira, A.; Bruneau, C. *Adv. Synth. Catal.* **2004**, *346*, 33–36.
14. Peña, D.; Minnaard, A. J.; de Vries, J. G.; Feringa, B. L. *J. Am. Chem. Soc.* **2002**, *124*, 14552–14553.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 60 (2004) 9715–9723

Synthesis of both *syn* and *anti* diastereoisomers of Boc-dolaproine from (*S*)-proline through DKR using ruthenium-catalyzed hydrogenation: a dramatic role of *N*-protecting groups

Céline Mordant, Sébastien Reymond, Virginie Ratovelomanana-Vidal* and Jean-Pierre Genêt*

Laboratoire de Synthèse Sélective Organique et Produits Naturels, E.N.S.C.P., UMR 7573, 11 rue P. et M. Curie, F-75231 Paris Cedex 05, France

Received 18 June 2004; revised 2 July 2004; accepted 6 July 2004

Available online 11 September 2004

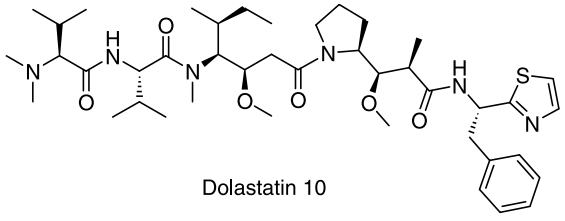
Abstract—The natural (2*R*,3*R*)-Boc-dolaproine and its unnatural (2*S*,3*S*) diastereoisomer were synthesized involving as key transformation the Ru(II)-promoted hydrogenation of the β-keto-α-methyl ester derived from (*S*)-*N*-Boc-proline. Interestingly, the asymmetric hydrogenation of this β-keto ester *N*-protected as an amine hydrochloride salt, provided the corresponding *anti* (2*S*,3*R*)- and (2*R*,3*S*)-β-hydroxy-α-methyl esters with significant level of selectivities through dynamic kinetic resolution.

1. Introduction

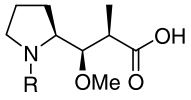
Naturally occurring (2*R*,3*R*)-dolaproine **1a** (Dap) is a key unit of dolastatin 10 originally isolated in 1987 from the Indian Ocean sea hare *Dolabella auricularia*. Dolastatin 10[1] is a potent inhibitor of microtubule assembly which displayed remarkable antineoplastic activity and is actually in phase II human cancer clinical trials (Fig. 1).[2,3]

Several groups have turned their attention towards the synthesis of dolaproine, which is the most complex unit of this marine natural product. The pioneering work of Pettit et al. was based on an aldol reaction of *N*-Boc-L-prolinal with the magnesium enolate of a chiral propionate leading to all four diastereoisomers in moderate yields and selectivities.[4,5] Subsequent efforts were focused on devising stereoselective and practical syntheses of dolaproine and its diastereoisomers. Shioiri et al. reported an efficient synthetic route to the synthesis of dolaproine[6–9] using Evans aldol methodology and condensation of *N*-Boc-L-prolinal with a chiral oxazolidinone in the presence of dibutylboron triflate, providing the desired *syn* compound with a complete diastereoselection.[10] Other syntheses of dolaproine involved aldol condensation with an achiral *Z*-boron enolate of thiophenyl propionate[11] or *Z*-crotylboronate[12] with moderate yields, while the use of benzyl propionate furnished a *syn*/*anti* mixture.[13] A convenient cobalt-mediated Reformatsky synthesis of Dap was also described by Pettit et al.[14] Another strategy was recently developed based on a Baylis–Hillman reaction between *N*-Boc-L-prolinal and methylacrylate which provided 91% of a diastereoisomeric mixture of *syn*/*anti* esters (83/17) after diastereoselective hydrogenation of the Baylis–Hillman adduct.[15]

Following our ongoing research devoted to the synthesis of natural products and industrially relevant molecules[16–19] using Ru-catalyzed hydrogenation reactions through dynamic kinetic resolution (DKR),[20–22] we have previously described a multigram-scale preparation of *anti* Boc-(2*S*,3*R*)-*iso*-dolaproine[23] with an excellent level of diastereoselectivity (d.e. 85%). This synthesis involving as key step the hydrogenation of the β-keto-α-methyl ester derived from the hydrochloride salt of (*S*)-proline turned out to be the first



Dolastatin 10

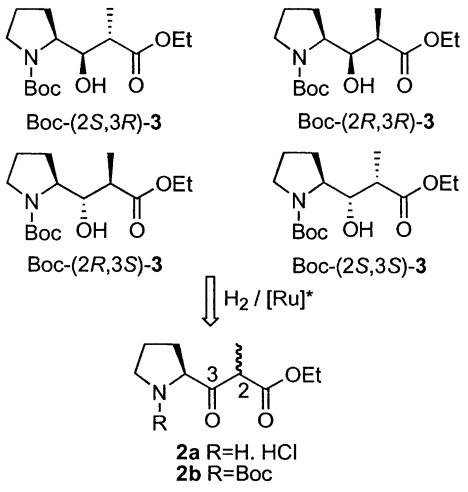


1a R = H, **dolaproine (Dap)**
1b R = Boc

Figure 1.

Keywords: Dolaproine; DKR; Asymmetric hydrogenation; Ruthenium.
* Corresponding authors. Tel.: +33-0144276743; fax: +33-0144071062; e-mail: genet@ext.jussieu.fr

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.07.043



Scheme 1.

example of an efficient DKR of a β-keto ester α-substituted by an alkyl group, bearing at the γ-position a stereogenic center. We have also recently disclosed a general method for the stereoselective synthesis, from the same common intermediate, of *syn* and *anti* α-amino-β-hydroxy esters,[24,25] precursors of medically important compounds. Whereas the hydrogenation of α-amido-β-keto esters led to the *syn* adducts, DKR of these β-keto esters α-substituted by a $NH_2 \cdot HCl$ group provided the corresponding *anti* β-hydroxy esters with excellent selectivities.

In connection with our efforts to synthesize dolastatin 10 and its analogs required for biological trials, an attractive solution would be to develop a practical stereoselective route to all diastereoisomers of dolaproine from the same β-keto-α-methyl ester intermediate derived from (*S*)-proline. We thus anticipated that the nature of the *N*-protecting group of the (*S*)-proline fragment might influence the stereochemical outcome of the hydrogenation reaction.

In this paper, a simple and direct preparation of the naturally occurring Boc-(2*R*,3*R*)-dolaproine **1b** and its related diastereoisomers Boc-(2*S*,3*S*)-*iso*-dolaproine and Boc-(2*R*,3*S*)-*iso*-dolaproine is reported.

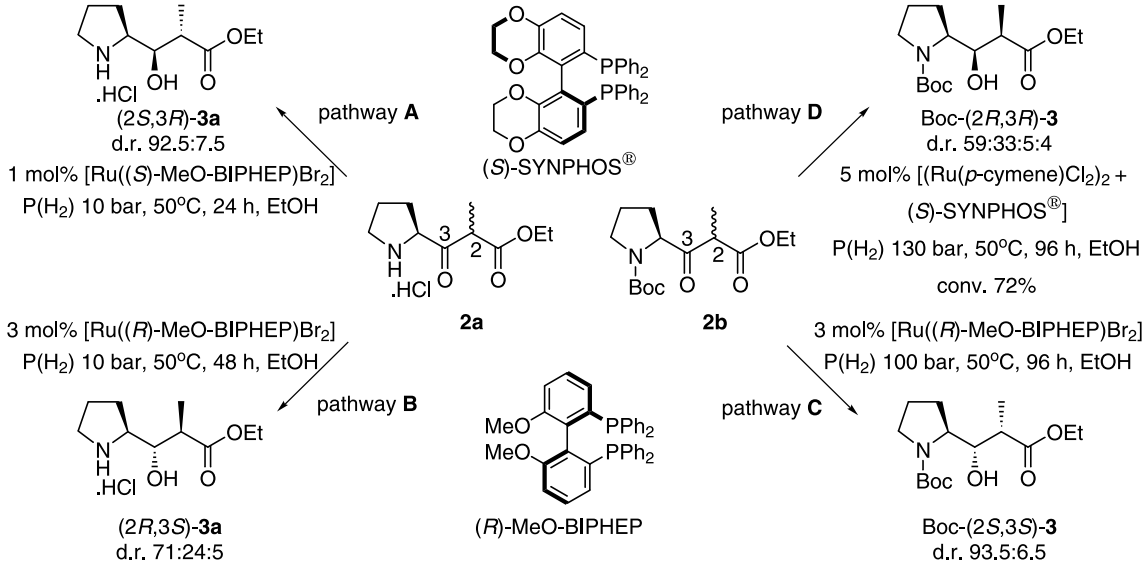
2. Results and discussion

The retrosynthetic approach for the required diastereoisomers of Boc-dolaproine **1b** was designed as follows (Scheme 1). Target compound **1b** would be obtained from the *N*-protected β-hydroxy esters **3**. The β-hydroxy-α-methyl esters **3** would be synthesized from the corresponding *N*-protected β-keto-α-methyl esters **2a** or **2b** by catalytic asymmetric hydrogenation.

The hydrogenation substrates **2a** and **2b** were easily prepared from the readily available (*S*)-*N*-Boc-proline.[23] The key hydrogenation was performed with the β-keto ester **2a** derived from the hydrochloride salt of (*S*)-proline (pathway **B**, Scheme 2). On the basis of our previous work (pathway **A**, Scheme 2),[23] we expected to obtain an *anti* diastereoselectivity.

The β-keto-α-methyl ester **2a** was hydrogenated under 10 bar at 50 °C for 48 h in ethanol with the in situ generated [Ru((*R*)-MeO-BIPHEP)Br_2] catalyst according to our convenient procedure.[26] Unlike the results described for the synthesis of Boc-(2*S*,3*R*)-*iso*-dolaproine involving the ligand of (*S*)-configuration,[23] we were surprised to find that the hydrogenation reaction with (*R*)-MeO-BIPHEP as ruthenium ligand proceeded rather slowly; 3 mol% of catalyst were required to ensure complete conversion. A moderate selectivity in favor of the *anti* β-hydroxy-α-methyl ester hydrochloride salt (2*R*,3*S*)-**3a** was observed. This lower diastereoselectivity could be the result of the following mismatched pair: chirality of the proline moiety and configuration of the ligand, as previously described in the literature.[27,28]

Spectroscopy analysis (^{1}H NMR in D_2O) of the crude hydrogenated product showed that the desired diastereoisomer (2*R*,3*S*)-**3a** was obtained in mixture with two other

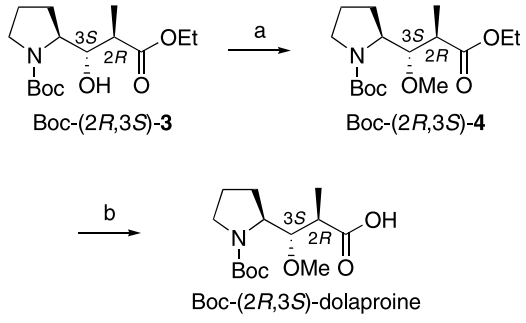


Scheme 2.

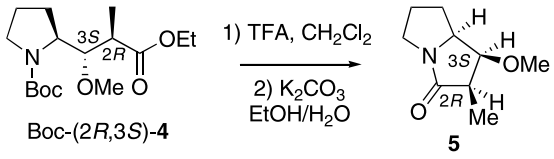
diastereoisomers, (2*S*,3*S*)-**3a** and (2*S*,3*R*)-**3a**, in a 71:24:5 diastereoisomeric ratio. This mixture was enriched up to 85:15 [(2*R*,3*S*)-**3a**:(2*S*,3*S*)-**3a**] by recrystallization in ethyl acetate.

Treatment of this mixture with Boc_2O in the presence of triethylamine afforded the corresponding *N*-protected compounds Boc-(2*R*,3*S*)-**3** and Boc-(2*S*,3*S*)-**3** which could not be separated by chromatography on silica gel. However the resulting 83:17 mixture was engaged in the *O*-methylation reaction with Me_3OBF_4 and proton sponge.[5] At this stage, optically pure *anti* Boc-(2*R*,3*S*)-**4** was isolated in 51% yield after flash chromatography (Scheme 3).

In order to confirm the stereochemistry of the diastereoisomer **3** obtained, Boc-(2*R*,3*S*)-**4** was treated with TFA and



Scheme 3. (a) Me_3OBF_4, proton sponge, CH_2Cl_2, 48 h, 51% yield. (b) NaOH, EtOH/H_2O, overnight.



Scheme 4.

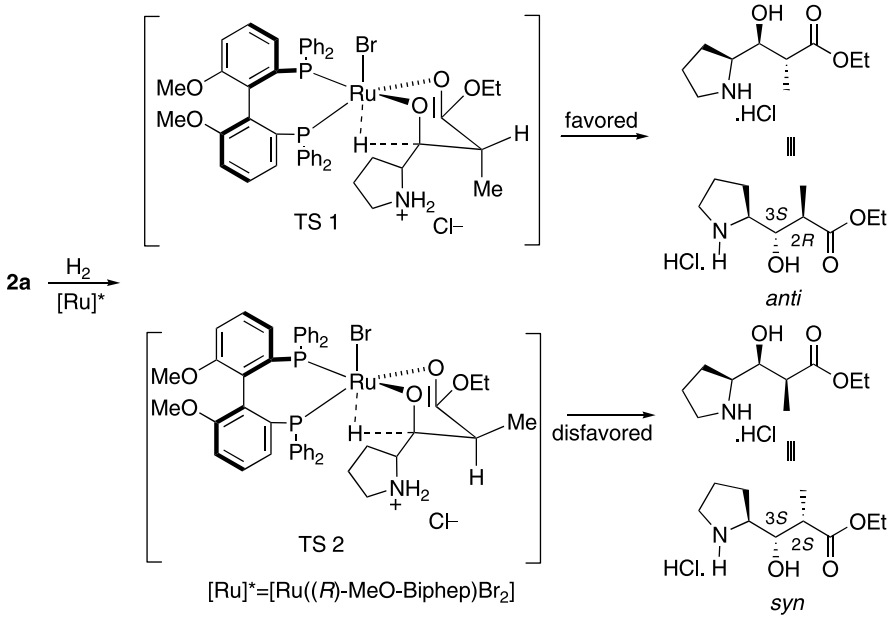
cyclized into the bicyclic lactam **5** by using potassium carbonate in a ethanol/water mixture (Scheme 4). The stereochemistry (2*R*,3*S*) of **3** was then assigned by NMR on the basis of NOE and COSY experiments.

The synthesis of *anti* Boc-(2*R*,3*S*)-*iso*-dolaproine was achieved by saponification of the ethyl ester function with sodium hydroxide (Scheme 3). Unfortunately, this reaction provided a mixture of the desired Boc-(2*R*,3*S*)-*iso*-dap and its isomerized diastereoisomer Boc-(2*S*,3*S*)-*iso*-dap.[29]

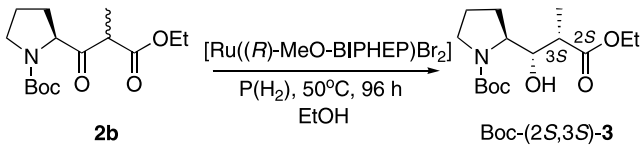
Although the origin of the *anti* diastereoselectivity is not clear at present, a chelated model could be speculated in which the substrate is coordinated to the metal by both its carbonyl oxygen functions (Scheme 5). Obviously, the chirality of (*R*)-MeO-BIPHEP as ruthenium ligand controls efficiently the stereofacial discrimination at the carbonyl function since the (3*S*) configuration is predominantly obtained, in agreement with the general sense of asymmetric hydrogenation.[30,31] Chair-like transition state TS1, where the methyl group adopts a pseudo-equatorial position is more favored than transition state TS2 exhibiting an axial methyl group. This could explain the predominant formation of the *anti* product.

Thus, we have demonstrated that the asymmetric Ru(II)-promoted hydrogenation reaction of the β-keto-α-methyl ester **2a** derived from the hydrochloride salt of (*S*)-proline provided the *anti* products (2*R*,3*S*)-**3** and (2*S*,3*R*)-**3**[23] as major diastereoisomers with moderate to good diastereoselectivities (41 and 85% d.e., respectively). The stereogenic center at the γ-position of the substrate seems to influence deeply the stereochemical outcome of the DKR.

According to our previous results obtained for the general synthesis of *syn* and *anti* α-amino-β-hydroxy esters,[24,25] we postulated that by simply changing the protecting group of the amine function of the proline moiety, the stereochemical course of the DKR of β-keto-α-methyl ester **2b** protected as



Scheme 5.



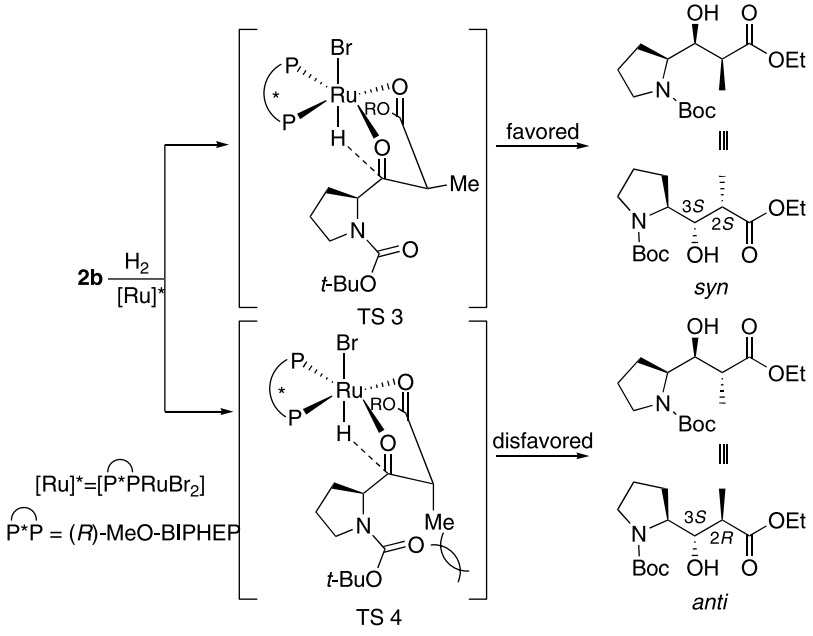
Scheme 6.

its *N*-Boc derivative would be in favor of the *syn* product as required for the dolaproine unit. In this context, we decided to examine the hydrogenation reaction of **2b** protected with a *tert*-butyloxycarbonyl group. Thus, we turned our attention to the synthesis of Boc-(2*R*,3*R*)-dolaproine **1b** (Dap) and its related diastereoisomer Boc-(2*S*,3*S*)-dolaproine.

The hydrogenation reaction of the β-keto ester derivative **2b** was first carried out in the presence of 1 mol% [Ru((*R*)-MeO-BIPHEP)Br_2] (Scheme 5, Table 1) at 50 °C under 95 bar of hydrogen pressure for 96 h. We were pleased to notice a remarkable reversal of the diastereoselectivity (entry 1). The *syn* (2*S*,3*S*) diastereoisomer was produced with high d.e. (entry 1, 83% d.e. on the crude product) but with a moderate conversion (66%). Thus we tried to optimize this reaction (Table 1). A complete conversion was ensured by increasing hydrogen pressure to 130 bar and the substrate/catalyst ratio to 5 and 3 mol% but unfortunately, lower chiral inductions were observed (entries 2 and 3, 72 and 77% d.e. on the crude product). Finally, the reaction was performed under 100 bar of hydrogen pressure at 50 °C with 3 mol%, affording the corresponding crude product Boc-(2*S*,3*S*)-**3** with an excellent control of the *syn* diastereoselectivity (entry 4, 87% d.e) (pathway **C**, Scheme 2). After chromatography on silica gel, Boc-(2*S*,3*S*)-**3** was isolated in 88% yield and 96% d.e. (Scheme 6).

The reversal of diastereoselectivity observed in the hydrogenation of the *N*-Boc protected proline derivative **2b** could be justified with the transition states proposed below (Scheme 7). As expected, the chirality of (*R*)-MeO-BIPHEP as ruthenium ligand controls the (3*S*) configuration of the product,[29,30] which was predominantly produced. Chair-like transition state TS3 having the methyl group and the bulky *N*-Boc-proline moiety in an 1,2 axial–equatorial relationship is rather favored compared to transition state TS4 where the methyl group adopts a pseudo-equatorial position. Even if at this stage we have no clear evidence, these suggested transition states TS3 and TS4 could explain the predominant formation of the *syn* Boc-(2*S*,3*S*)-**3**.

Considering the excellent asymmetric induction observed in the presence of [Ru((*R*)-MeO-BIPHEP)Br_2)], we focused our attention on the synthesis of the naturally occurring dolaproine (2*R*,3*R*)-Dap-**1b** which should be obtained by catalytic hydrogenation of **2b** with the opposite configuration of the ruthenium ligand ([Ru((*S*)-MeO-BIPHEP)Br_2)]). The hydrogenation reaction was conducted under 130 bar of hydrogen pressure at 50 °C for 96 h in ethanol with 5 mol% of catalyst. The reaction was not



Scheme 7.

Table 1. Asymmetric hydrogenation of compound **2b** using [Ru((*R*)-MeO-BIPHEP)Br_2]

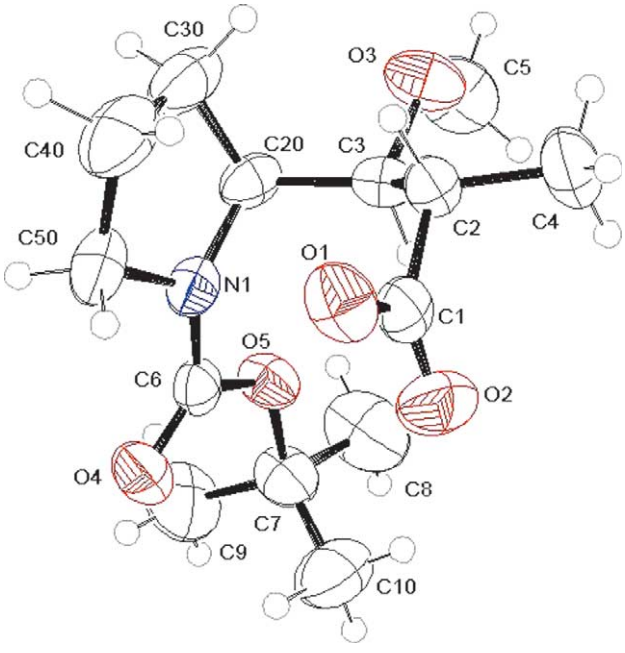
Entry	[Ru] (mol%)	P(H_2) (bar)	Conv. (%)	d.e. (2*S*,3*S*) (%)[a]
1	1	95	66	83
2	5	130	100	72
3	3	130	100	77
4	3	100	100	87

[a] d.e. determined on the crude product by ^{1}H NMR (300 MHz).

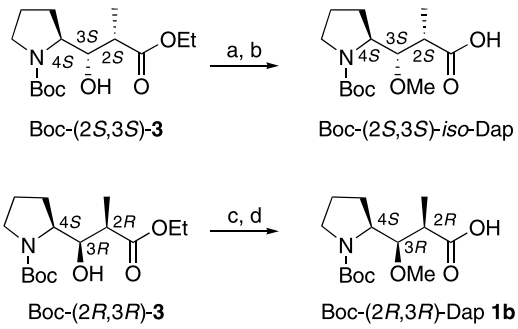
complete and the desired *syn* product Boc-(2*R*,3*R*)-**3** was obtained in mixture with the starting material **2b** (30–40%) and with the three other diastereoisomers. After flash chromatography, Boc-(2*R*,3*R*)-**3** was isolated in mixture with *anti* Boc-(2*S*,3*R*)-**3**. The conversion could be improved (up to 72%) and the proportion of the minor diastereoisomers *syn* Boc-(2*S*,3*S*)-**3** and *anti* Boc-(2*R*,3*S*)-**3** decreased (until 8%) by using the in situ generated catalyst simply prepared by mixing $[Ru(p\text{-cymene})Cl_2]_2$ and (*S*)-SYNPHOS® ligand recently developed in our group (pathway **D**, Scheme 2).[32] However *syn* Boc-(2*R*,3*R*)-**3** and *anti* Boc-(2*S*,3*R*)-**3** could not be separated and after chromatography on silica gel, a 2:1 d.r. was obtained in a 55% yield. The (3*R*) configuration is predominantly obtained suggesting that the ligand of (*S*) configuration controls quite well the enantiofacial discrimination; but in this case, the DKR is less efficient. Once again, the influence of the asymmetric center at the γ-position of the substrate is important for the control of selectivity.

Afterwards, the β-hydroxy esters Boc-(2*S*,3*S*)-**3** and Boc-(2*R*,3*R*)-**3** were subjected to the next synthetic steps: *O*-methylation and saponification (Scheme 9). The synthesis of *N*-Boc-*iso*-Dap (2*S*,3*S*)-**1** was achieved by *O*-methylation[5] followed by saponification of **6** to yield *N*-Boc-(2*S*,3*S*)-*iso*-Dap whose stereochemistry was unambiguously confirmed by X-ray analysis (Scheme 8).

After treatment of Boc-(2*R*,3*R*)-**3** with LHMDS in HMPA and MeOTf, the methoxy derivative Boc-(2*R*,3*R*) which led to the naturally occurring Boc-(2*R*,3*R*)-dolaproine **1b**, was isolated optically pure in a 45% yield after chromatography on silica gel, without any trace of *anti* (2*R*,3*S*) compound.[11]



Scheme 8. ORTEP drawing of Boc-(2*S*,3*S*)-*iso*-Dap (ellipsoïds, probability 50%)—selected bond distances (Å): C1–C2 = 1.518(5); C2–C4 = 1.538(6); C2–C3 = 1.529(5); C3–O3 = 1.427(4); O3–C5 = 1.378(5); C3–C20 = 1.542(5). Selected angles (°): C6–N1–C20 = 124.6(3); C6–N1–C50 = 119.4(3); C50–N1–C20 = 113.8(3); C5–O3–C3 = 115.6(3). Selected dihedral angles (calculated) (°): C30–C20–C3–O3 = −64.7; O3–C3–C2–C4 = −51.5. Nitrogen hybridization: (N1) (°) = 357.8.



Scheme 9. (a) Me_3OBF_4, proton sponge, CH_2Cl_2, rt, 24 h, 68% yield. (b) NaOH, EtOH/H_2O, 30 °C, 24 h, 73% yield. (c) (1) LHMDS, HMPA, THF, −78 °C, 25 min; (2) MeOTf, −20 °C, 15 min; 45% yield. (d) LiOH, EtOH/H_2O, overnight, 59% yield.

The absolute configuration of the *N*-Boc-Dap (2*R*,3*R*)-**1b** has been found to be identical to the previously synthesized compounds. All spectrometric data were in agreement with those reported in the literature (Scheme 9).[5]

3. Conclusions

In conclusion, we have succeeded in the synthesis of naturally occurring Boc-dolaproine **1b** and both (2*S*,3*S*)- and (2*R*,3*S*)-*iso*-dolaproine derivatives by developing a catalytic approach based on the ruthenium-promoted hydrogenation reaction via DKR as key transformation. The protecting group of the proline moiety turned out to play a crucial role in the stereochemical outcome of the asymmetric hydrogenation. The synthesis of dolastatin 10 and analogues is currently underway in our group and will be reported in due course.

4. Experimental

4.1. General methods

Dichloromethane was distilled from calcium hydride and tetrahydrofuran and diethyl ether from sodium-benzophenone. Acetone for the catalyst preparation was distilled over potassium carbonate. Other solvents were used without any purification. Triethylamine was distilled from potassium hydroxide. All air and/or water sensitive reactions were carried out under an argon atmosphere unless otherwise noted. ^1H NMR spectra were recorded on an Avance 300 at 300 MHz or an Avance 400 at 400 MHz; ^{13}C NMR spectra were recorded on an Avance 300 at 75 MHz or an Avance 400 at 100 MHz. Chemical shifts (δ) are reported in ppm downfield relative to internal Me_4Si. Coupling constants (*J*) are reported in Hz and refer to apparent peak multiplicities (recorded as s, singlet; d, doublet; t, triplet; q, quadruplet; qu, quintet; o, octet; m, multiplet; and br, broad). Mass spectra were determined on a Nermag R10-10C instrument. Ionization was obtained by chemical ionization with ammonia (DCI/NH_3) or by electrospray (on a API 3000 PE Sciex instrument). Optical rotations were measured on a Perkin–Elmer 241 polarimeter at 589 nm (sodium lamp). GC analyses of compounds **3** were

performed on a Agilent 6850 series equipped with a HP01 column capillary column (30 m, ∅ 0.25 μm): 70–210 °C, 5 °C/min, flow: 4 mL/min (He).

4.2. Typical procedure for hydrogenation

(*S*)- or (*R*)-MeO-BIPHEP (0.011 mmol, 1.1 equiv, 6.4 mg) and (cod)Ru(2-methylallyl)$_2$ (0.01 mmol, 1 equiv, 3.2 mg) were placed in a 15 mL flask and 1 mL of anhydrous acetone previously degassed was added. A methanolic solution of HBr (0.022 mmol, 2.2 equiv, 141 μL of a 0.156 N solution prepared by added 48% aqueous HBr in degassed methanol) was added to the resulting suspension and the reaction mixture was stirred at room temperature for 30 min. The solvent was thoroughly evaporated under vacuum. The orange solid residue was used directly as catalyst (1 mol%) for the hydrogenation reaction. A solution (previously degassed) of the β-keto ester (1 mmol) in ethanol (1 mL) was added via canula to the catalyst and the reaction vessel was placed then in a 500 mL stainless steel autoclave, under argon. The autoclave was pressurized to the suitable pressure of hydrogen, heated at 50 °C and the reaction was allowed to proceed until completion. The crude reaction mixture was evaporated.

4.2.1. Ethyl (2*R*,3*S*,4*S*)-3-(2′-pyrrolidinyl)-3-hydroxy-2-methyl-propanoate hydrochloride (2*R*,3*S*)-3a. The title compound was obtained from ethyl (4*S*)-3-(2′-pyrrolidinyl)-3-oxo-2-methyl-propanoate hydrochloride[23] (2 mmol, 472 mg) according to the general procedure with the catalyst [Ru((*R*)-MeO-BIPHEP)Br$_2$] (0.06 mmol, 3 mol%) under 10 bar of hydrogen for 48 h. ^{1}H NMR analysis of the crude product (brown oil) showed a complete conversion and a 71:24:5 mixture of (2*R*,3*S*), (2*S*,3*S*) and (2*S*,3*R*) diastereoisomers (d.e. (2*R*,3*S*) 42%). After recrystallization in ethyl acetate, this mixture was enriched up to a 85:15 mixture of (2*R*,3*S*):(2*S*,3*S*) diastereoisomers. ^{1}H NMR (D_2O, 300 MHz, 24 °C): δ (major diastereoisomer) 4.10 (q, *J*=7.1 Hz, 2H), 3.80 (dd, *J*=5.3, 7.1 Hz, 1H), 3.72 (dq, *J*=7.3, 9.5 Hz, 1H), 3.24 (app t, 2H, *J*=7.3 Hz), 2.69 (dq, 1H, *J*=5.3, 7.1 Hz), 2.11–2.20 (m, 1H), 1.88–2.08 (m, 2H), 1.63–1.77 (m, 1H), 1.18 (t, *J*=7.1 Hz, 3H), 1.13 (d, *J*=7.1 Hz, 3H); δ (minor diastereoisomer) identical except 4.05 (m, 1H), 3.55 (app q, *J*=7.7 Hz, IH), 1.07 (d, *J*=7.1 Hz, 3H); ^{13}C NMR (D_2O, 75 MHz, 24 °C): δ (major diastereoisomer) 175.7, 72.3, 62.5, 62.0, 45.4, 43.3, 26.9, 23.4, 13.3, 13.1; δ (minor diastereoisomer) 176.3, 71.2, 62.9, 62.2, 45.2, 42.8, 26.8, 23.4, 13.3, 9.3; MS (DCI, NH_3): *m*/*z* 202 (100%, $[M+H]^+$).

4.2.2. Ethyl (2*R*,3*S*,4*S*)-3-(*N*-*tert*-butoxycarbonyl-2′-pyrrolidinyl)-3-hydroxy-2-methyl-propanoate Boc-(2*R*,3*S*)-3. Tri-ethylamine (1.2 mmol, 1.2 equiv, 0.17 mL) and di-*tert*-butyl dicarbonate (1.05 mmol, 1.05 equiv, 229 mg) were added to a stirred solution of ethyl (2*R*,3*S*,4*S*)-3-(2′-pyrrolidinyl)-3-hydroxy-2-methyl- propanoate hydrochloride (1 mmol, 238 mg) in ethanol (2 mL). After being stirred overnight at room temperature, the mixture was concentrated under reduced pressure. Tetrahydrofuran (10 mL) was added to the residue and the mixture was stirred for 15 min. The resulting precipitate was removed by filtration on a celite pad and washed with tetrahydrofuran. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography using cyclohexane–ethyl acetate (9:1) as eluent to give the *N*-Boc β-hydroxy ester (295 mg, 98% yield) as a pale yellow oil in a 83:17 mixture of (2*R*,3*S*):(2*S*,3*S*) diastereoisomers confirmed by GC analysis (t_R (2*R*,3*S*) 22.0, t_R (2*S*,3*S*) 22.7). ^{1}H NMR ($CDCl_3$, 300 MHz, 24 °C): δ 4.16 (q, *J*=7.1 Hz, 2H), 4.08 (app dt, *J*=3.6, 7.9 Hz, 1H), 3.56 (dd, *J*=3.8, 7.9 Hz, 1H), 3.50 (m, 1H), 3.30 (m, 1H), 2.65 (dq, *J*=3.8, 7.1 Hz, 1H), 1.60–2.05 (m, 4H), 1.46 (s, 9H), 1.28 (d, *J*=7.1 Hz, 3H), 1.26 (t, *J*=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, 24 °C): δ broad peaks (conformers) 174.2, 155, 80.3, 68.2, 60.4, 59.8, 47.2, 43.2, 28.4, 24.0, 23.5, 14.2; MS (DCI, NH_3): *m*/*z* 302 (100%, $[M+H]^+$), 263 (6%, $[M-C_4H_8+NH_4]^+$), 246 (25%, $[M-C_4H_8+H]^+$); $[\alpha]_D^{21}=-67.8$ (*c*=1.01, $CHCl_3$).

4.2.3. Ethyl (2*S*,3*S*,4*S*)-3-(*N*-*tert*-butoxycarbonyl-2′-pyrrolidinyl)-3-hydroxy-2-methyl-propanoate Boc-(2*S*,3*S*)-3. Obtained from ethyl (4*S*)-3-(*N*-*tert*-butoxycarbonyl-2′-pyrrolidinyl)-3-oxo-2-methyl-propanoate[23] (2 mmol, 598 mg) according to the general procedure with the catalyst [Ru((*R*)-MeO-BIPHEP)Br$_2$] (0.03 mmol, 3 mol) under 100 bar of hydrogen for 96 h. ^{1}H NMR analysis of the crude product showed a complete conversion and a diastereoisomeric excess of 87%. Purification by silica gel column chromatography using cyclohexane–ethyl acetate (9:1) led to the β-hydroxy ester (435 mg, 88% yield) as a slightly yellow oil. ^{1}H NMR analysis showed a 98:2 mixture of (2*S*,3*S*):(2*R*,3*S*) diastereoisomers confirmed by GC analysis (t_R (2*S*,3*S*) 22.7, t_R (2*R*,3*S*) 22.0). ^{1}H ^{1}H NMR ($CDCl_3$, 300 MHz, 24 °C): δ 5.05 (br s, 1H, O*H*), 4.16 (dq, *J*=2.4, 7.2 Hz, 2H), 3.95 (m, 2H), 3.50 (m, 1H), 3.30 (ddd, *J*=5.5, 6.9, 10.9 Hz, 1H), 2.31 (dq, *J*=1.8, 6.9 Hz, 1H), 1.62–1.95 (m, 4H), 1.46 (s, 9H), 1.26 (t, *J*=7.2 Hz, 3H), 1.20 (d, *J*=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, 24 °C): δ 174.4, 158.0, 80.8, 76.1, 60.6, 60.4, 47.1, 42.9, 28.4, 28.4, 24.1, 14.2, 8.9; MS (DCI, NH_3): *m*/*z* 302 (100%, $[M+H]^+$), 263 (7%, $[M-C_4H_8+NH_4]^+$), 246 (48%, $[M-C_4H_8+H]^+$); $[\alpha]_D^{21}=-76.2$ (*c*=0.97, $CHCl_3$).

4.2.4. Ethyl (2*R*,3*R*,4*S*)-3-(*N*-*tert*-butoxycarbonyl-2′-pyrrolidinyl)-3-hydroxy-2-methyl-propanoate Boc-(2*R*,3*R*)-3. A solution of ethyl (4*S*)-3-(*N*-*tert*-butoxycarbonyl-2′-pyrrolidinyl)-3-oxo-2-methyl-propanoate[23] (3 mmol, 897 mg) in absolute ethanol (6 mL) was degassed by three vacuum-argon cycles at room temperature and added via canula to the mixture (5 mol%) [Ru(*p*-cymene)Cl$_2$]$_2$ (0.075 mmol, 46 mg)+(*S*)-SYNPHOS® (0.165 mmol, 105 mg). The Schlenk vessel was then placed under argon in a 250 mL stainless steel autoclave. The argon atmosphere was replaced with hydrogen by three cycles of pressurizing and the pressure adjusted to 130 bar. The autoclave was heated at 50 °C and stirring was maintained for 96 h. After cooling, the reaction mixture was concentrated under reduced pressure to afford the crude β-hydroxy ester as a brown oil. ^{1}H NMR analysis showed a 72% conversion. The crude product was purified by silica gel column chromatography using cyclohexane–ethyl acetate (9:1) as eluent to give the β-hydroxy ester (500 mg, 55% yield) as a slightly yellow oil. GC analysis showed a 2:1 mixture of (2*R*,3*R*):(2*S*,3*R*) diastereoisomers (t_R (2*R*,3*R*) 21.8, t_R (2*S*,3*R*) 21.9). ^{1}H NMR ($CDCl_3$, 300 MHz, 24 °C): δ 5.01 (br s, 1H, O*H*), 4.14 (q, *J*=7.1 Hz, 2H), 3.99 (app t, *J*=4.9 Hz, 1H), 3.95

(m, 1H), 3.50 (m, 1H), 3.25 (m, 1H), 2.54 (m, 1H), 1.71–1.97 (m, 4H), 1.46 (s, 9H), 1.25(m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz, 24 °C): δ broad peaks (conformers) 175.6, 155 (br), 79.9 (br), 73.8 (br), 60.5, 59.4, 47.3, 42.1, 28.5, 25.2, 24.3, 14.6, 14.1; MS (DCI, NH_3): *m/z* 302 (100%, $[M+H]^+$), 263 (4%, $[M-C_4H_8+NH_4]^+$), 246 (13%, $[M-C_4H_8+H]^+$); $[\alpha]_D^{21}=-47.7$ ($c=1.0$, $CHCl_3$).

4.2.5. Ethyl (2*R*,3*S*,4*S*)-3-(*N*-*tert*-butoxycarbonyl-2′-pyrrolidinyl)-3-methoxy-2-methyl-propanoate (2*R*,3*S*)-4. To a solution of ethyl (2*R*,3*S*,4*S*)-3-(*N*-*tert*-butoxycarbonyl-2′-pyrrolidinyl)-3-hydroxy-2-methyl-propanoate Boc-(2*R*,3*S*)-**3** (0.5 mmol, 150 mg) in dichloromethane (3 mL) was added 1,8-bis(dimethyl-amino)-naphtalene "proton sponge" (1 mmol, 2 equiv, 214 mg) followed by trimethyloxonium tetrafluoroborate (1.1 mmol, 2.2 equiv, 163 mg). The mixture was then stirred at room temperature for 24 h before a further addition of proton sponge (0.5 mmol, 1 equiv, 107 mg) and trimethyloxonium tetrafluoroborate (0.55 mmol, 1.1 equiv, 81 mg). The stirring was maintained for an additional 22 h before being filtered on a celite pad. The filtrate was washed successively with saturated aqueous citric acid and water, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using petroleum ether–ethyl acetate (9:1) as eluent to give the *N*-Boc β-methoxy ester (80 mg, 51% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz, 24 °C): δ 4.05–4.20 (m, 3H), 3.67 (m, 1H), 3.25–3.50 (m, 2H), 3.45 (s, 3H), 2.64 (dq, $J=2.6$, 7.0 Hz, 1H), 1.75–2.02 (m, 4H), 1.47 (m, 9H), 1.26 (t, $J=7.1$ Hz, 3H), 1.13 (br d, $J=7.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, 24 °C): δ broad peaks (conformers) 175.1, 154.5 (br), 84.0 (br), 79.2 (br), 60.2, 59.0 (br), 57.1, 47.5 (br), 42.8, 28.5, 29.6, 27.2, 14.6, 14.2; MS (DCI, NH_3): *m/z* 333 (3%, $[M+NH_4]^+$), 316 (100%, $[M+H]^+$), 277 (7%, $[M-C_4H_8+NH_4]^+$), 260 (21%, $[M-C_4H_8+H]^+$); $[\alpha]_D^{21}=-51.2$ ($c=0.16$, $CHCl_3$).

4.2.6. Ethyl (2*S*,3*S*,4*S*)-3-(*N*-*tert*-butoxycarbonyl-2′-pyrrolidinyl)-3-methoxy-2-methyl-propanoate (2*S*,3*S*)-4. To a solution of ethyl (2*S*,3*S*,4*S*)-3-(*N*-*tert*-butoxycarbonyl-2′-pyrrolidinyl)-3-hydroxy-2-methyl-propanoate Boc-(2*S*,3*S*)-**3** (1.20 mmol, 360 mg) in dichloromethane (5 mL) was added 1,8-bis(dimethyl-amino)-naphtalene 'proton sponge' (2.40 mmol, 2.0 equiv, 515 mg) followed by trimethyloxonium tetrafluoroborate (2.64 mmol, 2.2 equiv, 391 mg). The mixture was then stirred at room temperature for 24 h and then filtered over a celite pad and washed with dichloromethane. The filtrate was washed successively with saturated aqueous citric acid and water, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using cyclohexane–ethyl acetate (9:1) as eluent to give the *N*-Boc β-methoxy ester (257 mg, 68% yield) as a slightly yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz, 24 °C): δ 4.00–4.20 (m, 3H), 3.72–3.88 (m, 1H), 3.35–3.50 (m, 4H), 3.20 (m, 1H), 2.48 (m, 1H), 1.58–1.95 (m, 4H), 1.47 (m, 9H), 1.25 (t, $J=7.1$ Hz, 3H), 1.13 (d, $J=6.9$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, 24 °C): δ 174.8, 154.1 (br), 82.1, 79.4, 60.4, 59.6, 58.0, 47.3 (br), 41.0, 28.4, 26.9 (br), 23.9, 14.2, 13.9; MS (DCI, NH_3): *m/z* 316 (100%, $[M+H]^+$), 277 (2%, $[M-C_4H_8+NH_4]^+$); 260 (21%, $[M-C_4H_8+H]^+$); $[\alpha]_D^{21}=-64.0$ ($c=0.25$, $CHCl_3$).

4.2.7. Ethyl (2*R*,3*R*,4*S*)-3-(*N*-*tert*-butoxycarbonyl-2′-pyrrolidinyl)-3-methoxy-2-methyl-propanoate (2*R*,3*R*)-4. A solution of ethyl (2*R*,3*R*,4*S*)-3-(*N*-*tert*-butoxycarbonyl-2′-pyrrolidinyl)-3-hydroxy-2-methyl-propanoate Boc-(2*R*,3*R*)-**3** (2 mmol, 602 mg) in tetrahydrofuran (6 mL) was added to a solution of LHMDS (1 M in THF, 2.8 mmol, 1.4 equiv, 2.8 mL) in HMPA (3.2 mmol, 1.6 equiv, 557 μL) and tetrahydrofuran (3.2 mL) at −78 °C. The stirring was maintained for 25 min at −78 °C before the addition at −20 °C of MeOTf (6.0 mmol, 3.0 equiv, 679 μL). The mixture was stirred at −20 °C for an additional 15 min. The reaction was then quenched with saturated aqueous ammonium chloride. After extraction with ethyl acetate, the organic layer was washed with saturated aqueous sodium chloride, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using petroleum ether–ethyl acetate (9:1) as eluent to give the *N*-Boc β-methoxy ester (282 mg, 45% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz, 24 °C): δ 4.14 (br q, 2H, $J=7.1$ Hz), 3.70–3.95 (m, 2H), 3.53 (m, 1H), 3.41 (s, 3H), 3.22 (m, 1H), 2.47 (m, 1H), 1.80–2.05 (m, 3H), 1.65–1.77 (m, 1H), 1.49 (m, 9H), 1.25 (t, $J=7.1$ Hz, 3H), 1.23 (d, $J=7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, 24 °C): δ 174.6, 154.4 (br), 83.4, 79.6 (br), 61.0 (br), 60.4, 59.6 (br), 46.6 (br), 43.1, 28.5, 26.2 (br), 24.0 (br), 14.2, 13.6; MS (DCI, NH_3): *m/z* 333 (7%, $[M+NH_4]^+$), 316 (100%, $[M+H]^+$), 277 (7%, $[M-C_4H_8+NH_4]^+$), 260 (34%, $[M-C_4H_8+H]^+$); $[\alpha]_D^{21}=-50.8$ ($c=1.2$, $CHCl_3$).

4.2.8. (2*R*,3*S*,4*S*)-hexahydro-3-methoxy-2-methyl-1-pyrrolizinone 5. To an ice-cooled solution of ethyl (2*R*,3*S*,4*S*)-3-(*N*-*tert*-butoxycarbonyl-2′-pyrrolidinyl)-3-methoxy-2-methyl-propanoate (0.16 mmol, 50 mg) in dichloromethane (3 mL) was added trifluoroacetic acid (500 μL). After 15 min at 0 °C, the mixture was stirred 1 h at room temperature. The solvent was thoroughly evaporated under vacuum. 3 mL of a mixture ethanol–water (1:2) was added to the residue and the resulting solution was cooled to 0 °C. Potassium carbonate (0.48 mmol, 3 equiv, 66 mg) was added portionwise and after 15 min at 0 °C, the stirring was maintained for 4 h at room temperature. The reaction mixture was then diluted and extracted with dichloromethane (3×25 mL) after the addition of saturated aqueous sodium chloride (10 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure to give the bicyclic lactam as a slightly yellow oil which crystallized upon standing. ^{1}H NMR ($CDCl_3$, 400 MHz, 24 °C): δ 3.86 (m, 1H), 3.75 (app t, $J=4.4$ Hz, 1H), 3.45 (m, 1H), 3.35 (s, 3H), 3.03 (m, 1H) 2.82 (m, 1H), 1.95–2.08 (m, 2H), 1.74–1.85 (m, 2H), 1.14 (d, $J=7.3$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, 24 °C): δ 175.0, 81.2, 64.3, 59.7, 46.1, 41.2, 26.8, 23.7, 8.6.

4.2.9. (2*R*,3*S*,4*S*)-3-(*N*-*tert*-butoxycarbonyl-2′-pyrrolidinyl)-3-methoxy-2-methylpropanoic acid Boc-(2*R*,3*S*)-*iso*-dolaproine. To an ice-cooled solution of ethyl (2*R*,3*S*,4*S*)-3-(*N*-*tert*-butoxycarbonyl-2′-pyrrolidinyl)-3-methoxy-2-methyl-propanoate (0.6 mmol, 190 mg) in ethanol (5 mL) was added 1 N aqueous sodium hydroxide (1.80 mmol, 3 equiv, 1.8 mL). The mixture was stirred at 0 °C for 30 min then room temperature for 21 h. After further addition of 1 N aqueous sodium hydroxide

(2.43 mmol, 3 equiv, 2.43 mL), the mixture was stirred overnight at 30 °C. The resulting solution was acidified to pH 4 by adding 1 N aqueous hydrochloric acid and then extracted with a mixture ethyl acetate–toluene (1:1) (3× 30 mL). The organic extracts were washed with 1 M aqueous potassium hydrogen sulfate (20 mL) and saturated aqueous sodium chloride (30 mL), dried over sodium sulfate and concentrated under reduced pressure to give the crude product as a mixture of the desired (2*R*,3*S*)-Boc-*iso*-dolaproine and the isomerized stereoisomer (2*S*,3*S*)-Boc-*iso*-dolaproine. ^{1}H NMR ($CDCl_3$, 300 MHz, 24 °C): δ 4.11 (m, 1H), 3.50–3.72 (m, 1H), 3.47 (s, 3H), 3.30 (m, 1H), 2.68 (m, 1H), 1.80–1.97 (m, 2H), 1.60–1.72 (m, 2H), 1.47 (s, 9H), 1.24 (d, J=6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, 24 °C): δ 178.3, 155.0 (br), 83.8, 79.3 (br), 60.0, 57.4, 47.0 (br), 42.0, 28.4, 27.1 (br), 23.5 (br), 15.4; MS (DCI, NH_3): *m/z* 288 (100%, $[M+H]^+$), 249 (11%, $[M-C_4H_8+NH_4]^+$), 232 (32%, $[M-C_4H_8+H]^+$); HRMS (DCI^+): *m/z* calcd for $C_{14}H_{26}O_5N$: 288.1811, found: 288.1809; $[\alpha]_D^{24}=-37.0$ (c=0.6, $CHCl_3$).

4.2.10. (2*S*,3*S*,4*S*)-3-(*N*-*tert*-butoxycarbonyl-2′-pyrrolidinyl)-3-methoxy-2-methylpropanoic acid Boc-(2*S*,3*S*)-*iso*-dolaproine. To an ice-cooled solution of ethyl (2*S*,3*S*,4*S*)-3-(*N*-*tert*-butoxycarbonyl-2′-pyrrolidinyl)-3-methoxy-2-methyl-propanoate (0.81 mmol, 257 mg) in ethanol (5 mL) was added 1 N aqueous sodium hydroxyde (2.43 mmol, 3 equiv, 2.43 mL). The mixture was stirred at 0 °C for 30 min then heated at 30 °C overnight. After further addition of 1 N aqueous sodium hydroxide (2.43 mmol, 3 equiv, 2.43 mL), the mixture was stirred at 30 °C for an additional 6 h. The resulting solution was acidified to pH 4 by adding 1 N aqueous hydrochloric acid and then extracted with a mixture ethyl acetate–toluene (1:1) (3×30 mL). The organic extracts were washed with 1 M aqueous potassium hydrogen sulfate (20 mL) and saturated aqueous sodium chloride (30 mL), dried over sodium sulfate and concentrated under reduced pressure to give the crude product. The residue was purified by silica gel column chromatography using cyclohexane–ethyl acetate (7:3) as eluent to give the desired Boc-*iso*-dolaproine as an amorphous white powder (170 mg, 73% yield). ^{1}H NMR ($CDCl_3$, 400 MHz, 54 °C): δ 4.11 (m, 1H), 3.62 (m, 1H), 3.47 (s, 3H), 3.44–3.51 (m, 1H), 3.06 (m, 1H), 2.65 (m, 1H), 1.89–1.96 (m, 2H), 1.76–1.88 (m, 2H), 1.47 (s, 9H), 1.26 (d, J=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, 24 °C): δ 175.9, 157.2 (br), 86.5, 81.0, 61.8, 58.8 (br), 48.3 (br), 44.2, 28.3, 26.9, 23.8, 13.9; MS (DCI, NH_3): *m/z* 288 (100%, $[M+H]^+$), 249 (10%, $[M-C_4H_8+NH_4]^+$), 232 (16%, $[M-C_4H_8+H]^+$); calcd for $C_{14}H_{25}NO_5$: C 58.52, H 8.77, N 4.87; found C 58.85, H 8.77, N 4.71; $[\alpha]_D^{24}=-57.0$ (c=0.75, $CHCl_3$).

4.2.11. (2*R*,3*R*,4*S*)-3-(*N*-*tert*-butoxycarbonyl-2′-pyrrolidinyl)-3-methoxy-2-methylpropanoic acid Boc-(2*R*,3*R*)-dolaproine 1b. To an ice-cooled solution of ethyl (2*R*,3*R*,4*S*)-3-(*N*-*tert*-butoxycarbonyl-2′-pyrrolidinyl)-3-methoxy-2-methyl-propanoate (0.78 mmol, 247 mg) in a mixture of ethanol (5 mL) and water (1 mL) was added lithium hydroxide monohydrate (2.35 mmol, 3 equiv, 99 mg). The mixture was then stirred overnight at room temperature. After evaporation of the solvent, the residue was diluted with dichloromethane and washed with water. The aqueous layer was acidified to pH 4 by adding 1 N aqueous hydrochloric acid and then extracted with ethyl acetate followed by dichloromethane. The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure to give the desired product as a colorless viscous oil (132 mg, 59% yield). ^{1}H NMR ($CDCl_3$, 400 MHz, 24 °C): δ 4.11 (m, 1H), 3.62 (m, 1H, 3.47 (s, 3H), 3.44–3.51 (m, 1H), 3.06 (m, 1H), 2.65 (m, 1H), 1.89–1.96 (m, 2H), 1.76–1.88 (m, 2H), 1.47 (s, 9H), 1.26 (d, J=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, 24 °C): δ 179.8 (br), 154.3 (br), 83.0, 79.9, 61.2, 59.4, 46.6, 42.8, 28.5, 26.1, 24.0, 13.5; MS (DCI, NH_3): *m/z* 305 (4%, $[M+NH_4]^+$), 288 (100%, $[M+H]^+$), 249 (14%, $[M-C_4H_8+NH_4]^+$), 232 (30%, $[M-C_4H_8+H]^+$); HRMS (DCI^+): *m/z* calcd for $C_{14}H_{26}O_5N$: 288.1811, found: 288.1804; $[\alpha]_D^{24}=-60.0$ (c=1.03, MeOH).

Acknowledgements

We thank Dr. R. Schmid and Dr. M. Scalone (Hoffmann-La Roche) for samples of (*R*)- and (*S*)-MeO-BIPHEP=(*S*)-(−)-6,6′-dimethoxy-2,2′-bis(diphenylphosphino)-1,1′-biphenyl. A fellowship from C.N.R.S./D.G.A. (C. Mordant) is gratefully acknowledged. Dr. S. Reymond is grateful to C.N.R.S. for a post-doctoral fellowship.

References and notes

1. Pettit, G. R.; Kamano, Y.; Herald, C. L.; Tuinman, A. A.; Boettner, F. E.; Kizu, H.; Schmidt, J. M.; Baczynskyj, L.; Tomer, K. B.; Bontems, R. J. *J. Am. Chem. Soc.* **1987**, *109*, 6883–6885.
2. Madden, T.; Tran, H. T.; Beck, D.; Huie, R.; Newman, R. A.; Pusztai, L.; Wright, J. J.; Abbruzzese, J. L. *Clin. Cancer Res.* **2000**, *6*, 1293–1301.
3. Hoffman, M. A.; Blessing, J. A.; Lentz, S. S. *Gynec. Oncol.* **2003**, *89*, 95–98.
4. Pettit, G. R.; Singh, S. B.; Hogan, F.; Lloyd-Williams, P.; Herald, D. L.; Burkett, D. D.; Clewlow, P. J. *J. Am. Chem. Soc.* **1989**, *111*, 5463–5465.
5. Pettit, G. R.; Singh, S. B.; Herald, D. L.; Lloyd-Williams, P.; Kantoci, D.; Burkett, D. D.; Barkoczy, J.; Hogan, F.; Wardlaw, T. R. *J. Org. Chem.* **1994**, *59*, 6287–6295.
6. Hamada, Y.; Hayashi, K.; Shioiri, T. *Tetrahedron Lett.* **1991**, *32*, 931–934.
7. Hayashi, K.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1991**, *32*, 7287–7290.
8. Shioiri, T.; Hayashi, K.; Hamada, Y. *Tetrahedron* **1993**, *49*, 1913–1924.
9. Recent review: Shioiri, T.; Hamada, Y. *Synlett* **2001**, 184–201.
10. Pettit, G. R.; Burkett, D. D.; Barkoczy, J.; Breneman, G. L.; Pettit, W. E. *Synthesis* **1996**, 719–725.
11. Tomioka, K.; Kanai, M.; Koga, K. *Tetrahedron Lett.* **1991**, *32*, 2395–2398.
12. Roux, F.; Maugras, I.; Poncet, J.; Niel, G.; Jouin, P. *Tetrahedron* **1994**, *50*, 5345–5360.
13. Miyazaki, K.; Kobayashi, M.; Natsume, T.; Gondo, M.; Mikami, T.; Sakakibara, K.; Tsukagoshi, S. *Chem. Pharm. Bull.* **1985**, *43*, 1706–1718.

14. Pettit, G. R.; Grealish, M. P. *J. Org. Chem.* **2001**, *66*, 8640–8642.
15. Amleida, W. P.; Coelho, F. *Tetrahedron Lett.* **2003**, *44*, 937–940.
16. Girard, A.; Greck, C.; Ferroud, D.; Genet, J. P. *Tetrahedron Lett.* **1996**, *37*, 7967–7970.
17. Coulon, E.; Caño de Andrade, C.; Ratovelomanana-Vidal, V.; Genet, J. P. *Tetrahedron Lett.* **1998**, *39*, 6467–6470.
18. Phansavath, P.; Duprat de Paule, S.; Ratovelomanana-Vidal, V.; Genet, J. P. *Eur. J. Org. Chem.* **2000**, 3903–3907.
19. Mordant, C.; Caño de Andrade, C.; Touati, R.; Ratovelomanana-Vidal, V.; Ben Hassine, B.; Genet, J. P. *Synthesis* **2003**, 2405–2409.
20. Noyori, R.; Ikeda, T.; Ohkuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T.; Taketomi, T.; Kumobayashi, H. *J. Am. Chem. Soc.* **1989**, *111*, 9134–9135.
21. Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn* **1995**, *68*, 36–56.
22. Ratovelomanana-Vidal, V.; Genet, J. P. *Can. J. Chem.* **2000**, *78*, 846–851.
23. Lavergne, D.; Mordant, C.; Ratovelomanana-Vidal, V.; Genet, J. P. *Org. Lett.* **2001**, *3*, 1909–1912.
24. Mordant, C.; Dünkelmann, P.; Ratovelomanana-Vidal, V.; Genet, J. P. *Chem. Commun.* **2004**, 1296–1297.
25. Mordant, C.; Dünkelmann, P.; Ratovelomanana-Vidal, V.; Genet, J. P. *Eur. J. Org. Chem.* **2004**, 3017–3026.
26. Genet, J. P.; Pinel, C.; Ratovelomanana-Vidal, V.; Mallart, S.; Pfister, X.; Caño de Andrade, C.; Laffitte, J. A. *Tetrahedron: Asymmetry* **1994**, *5*, 675–690.
27. Ohtake, N.; Jona, H.; Okada, S.; Okamoto, O.; Imai, Y.; Ushijima, R.; Nakagawa, S. *Tetrahedron: Asymmetry* **1997**, *8*, 2939–2947.
28. Guerreiro, P.; Ratovelomanana-Vidal, V.; Genet, J. P. *Chirality* **2000**, *12*, 408–410.
29. Such epimerization has already been observed during the saponification of a thioester analog, see Ref. 11.
30. Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994; pp 1–93.
31. Genet, J. P. *Acc. Chem. Res.* **2003**, *36*, 908–918.
32. Duprat de Paule, S.; Jeulin, S.; Ratovelomanana-Vidal, V.; Genet, J. P.; Champion, N.; Dellis, P. *Eur. J. Org. Chem.* **2003**, 1931–1941, and references cited herein.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 60 (2004) 9725–9733

Application of sulfur ylide mediated epoxidations in the asymmetric synthesis of β-hydroxy-δ-lactones. Synthesis of a mevinic acid analogue and (+)-prelactone B

Varinder K. Aggarwal,[a,*] Imhyuck Bae[a,b] and Hee-Yoon Lee[b,*]

[a]*School of Chemistry, Cantock's Close, University of Bristol, Bristol BS8 1TS, UK*
[b]*Center for Molecular Design and Synthesis (CMDS), Department of Chemistry and School of Molecular Science (BK21), Korea Advanced Institute of Science and Technology (KAIST), Daejeon 305-701, South Korea*

Received 21 June 2004; revised 4 July 2004; accepted 6 July 2004

Available online 21 August 2004

Abstract—Catalytic and stoichiometric asymmetric sulfur ylide reactions were employed to prepare alkyl–aryl epoxide intermediates in a convergent manner. These epoxides were utilized in efficient syntheses of the mevinic acid analogue **1** and prelactone B.

1. Introduction

The asymmetric synthesis of epoxides from carbonyl compounds using sulfur ylide intermediates has emerged as a powerful method for not only creating C–C bonds with control of asymmetry but also for generating functionality suitable for further manipulation.[1] We have reported an efficient catalytic asymmetric process for the conversion of aldehydes into epoxides[2] and a complementary stoichiometric process for a range of problematic substrates, which had either given low yields or low selectivities in our catalytic process.[3] The broad substrate scope of the combined catalytic and stoichiometric processes now allows the sulfur ylide disconnection to be applied with confidence in total synthesis. The practicality of these methods have been demonstrated in the concise synthesis of CDP 840.[3] Most studies of asymmetric epoxidation of carbonyl compounds to date have focused on methodology development[4] rather than their use, but the power of new methodology is best illustrated with applications in synthesis. In this paper, we describe the application of catalytic and stoichiometric asymmetric sulfur ylide mediated epoxidation methodology in the synthesis of the β-hydroxy-δ-lactones which are present in a large number of biologically important molecules (Fig. 1).[5]

2. Results and discussion

Our general retrosynthetic analysis of β-hydroxy-δ-lactones **A1/A2** is shown in Scheme 1. The target lactone **A1/A2** could be generated from the corresponding hydroxy keto-ester via diastereoselective reduction. The hydroxy keto ester **B** could be obtained by sequential Birch reduction and ozonolysis of epoxide **D**,[6] which itself could potentially be obtained through our asymmetric sulfur ylide mediated epoxidation reaction employing sulfide **S**.[2] In this paper we report two successful syntheses of β-hydroxy-δ-lactones using this synthetic strategy.

We chose as our first target the β-hydroxy-δ-lactone **1**.[7] This lactone is a simplified structural analogue of the naturally occurring potent HMG-CoA reductase inhibitors, compactin and mevinolin.[8] Since their discovery, many synthetic approaches to these compounds as well as analogues have appeared[9] and it has been shown from SAR studies that the lactone moiety of the mevinic acids is essential for the biological activity.[10]

To synthesize lactone **1** we required epoxide **2**. In order to prepare epoxide **2**, we decided to employ the stoichiometric sulfur ylide reaction since we were aware that α-unsubstituted aldehydes gave epoxides with low diastereoselectivity (e.g. valeraldehyde, 3:1 *trans*/*cis*)[2] under catalytic conditions. Thus, sulfide **S** was converted into the required sulfonium salt and treated with 3-cyclohexane propanal (prepared from commercially available 3-cyclohexyl propanol) in the presence of the EtP_2[11,3] base. This furnished the desired epoxide **2** with almost perfect

Keywords: Sulfur ylide; Epoxides; Mevinic acid.
* Corresponding authors. Tel.: +44-117-9546315; fax: +44-117-9298611 (V.K.A.); e-mail: v.aggarwal@bristol.ac.uk

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.07.044

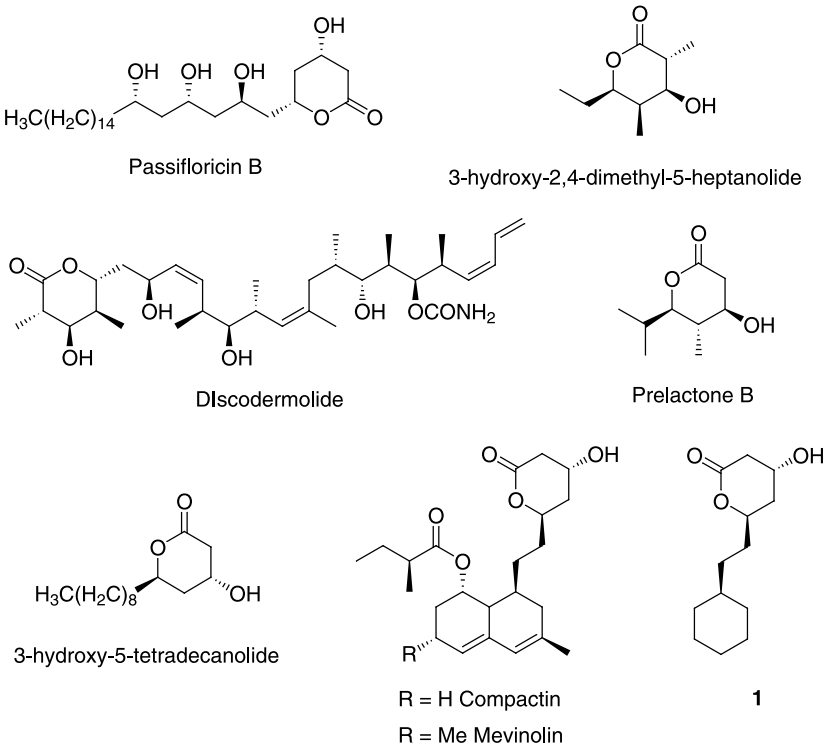
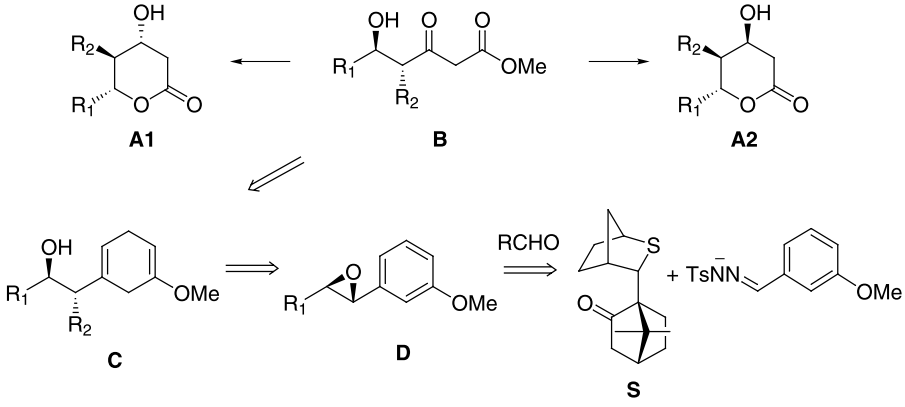


Figure 1. β-Hydroxy-δ-lactone structures in biologically important molecules.

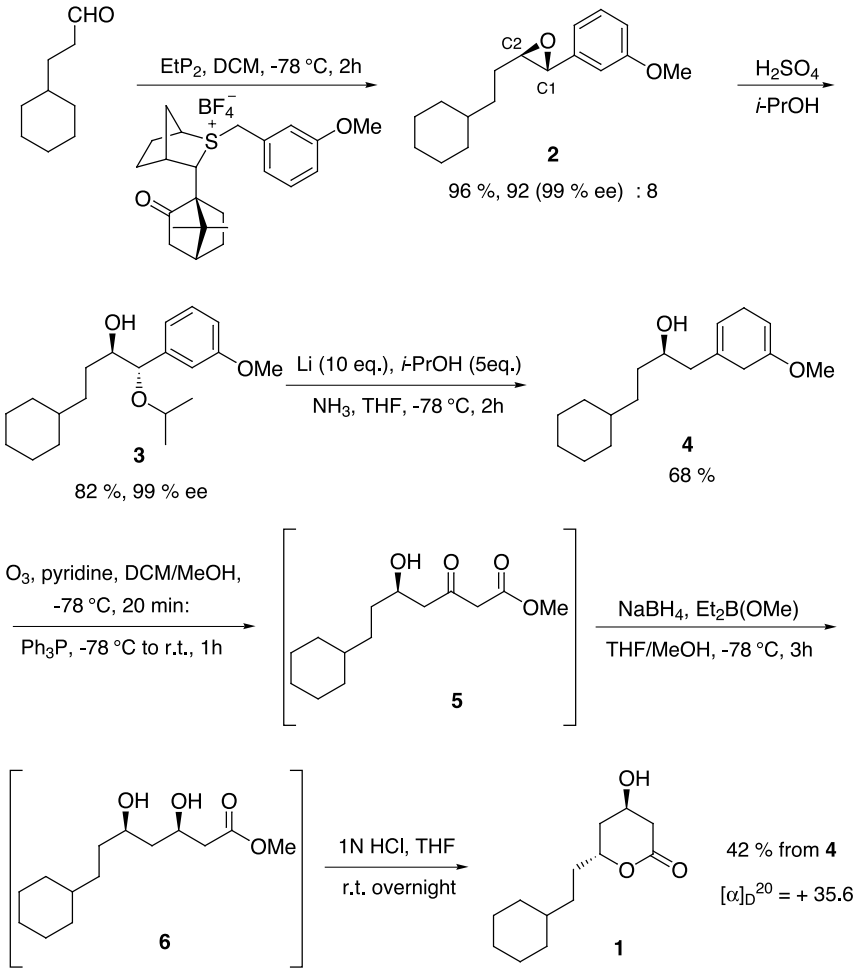


Scheme 1. Retrosynthetic analysis of β-hydroxy-δ-lactones **A1/A2**.

enantioselectivity (99% for *trans*) and good diastereoselectivity (92:8) in 96% yield (Scheme 2). Chiral sulfide **S** was recovered in 83% yield.

Separation of the *cis* and *trans* epoxides was required since they possess opposite stereochemistry at C2 and if they were both carried through would erode the enantioselectivity of the final product. However, all attempts to separate the two epoxides were unsuccessful. We therefore decided to open the epoxide with a suitable nucleophile to generate a separable diastereomeric mixture. Among a variety of possible nucleophiles, we considered alkoxides because such functionality could be easily removed during Birch reduction. Both methanol and *i*-PrOH were investigated and the isopropyl ether **3** gave a readily separable diastereomeric mixture. Thus, opening of epoxides with *i*-PrOH in the presence of catalytic concd H_2SO_4 gave two separable ethers from which the desired *anti* product **3** was isolated in 82% yield. Since the diastereomeric ratio of epoxide isomers correlated well with the ratio of ethers formed, it is believed that epoxide opening occurred with clean inversion.

Next, Birch reduction was carried out under standard conditions.[12] After a solution of alcohol **3** in NH_3 with 10 equiv of Li metal and 5 equiv of *i*-PrOH was refluxed for 2 h, diene **4** was generated in 68% yield. Ozonolysis of diene **4** afforded hydroxy keto ester **5** in moderate yield. However, the resulting keto ester **5** readily lactonized during purification on silica gel and decomposed in basic media. To avoid these problems, the crude material was quickly filtered through a silica gel pad, and used directly in the next step. *syn* Selective reduction of hydroxy keto ester **5** using $NaBH_4$ in the presence of $Et_2B(OMe)$ gave **6** with almost



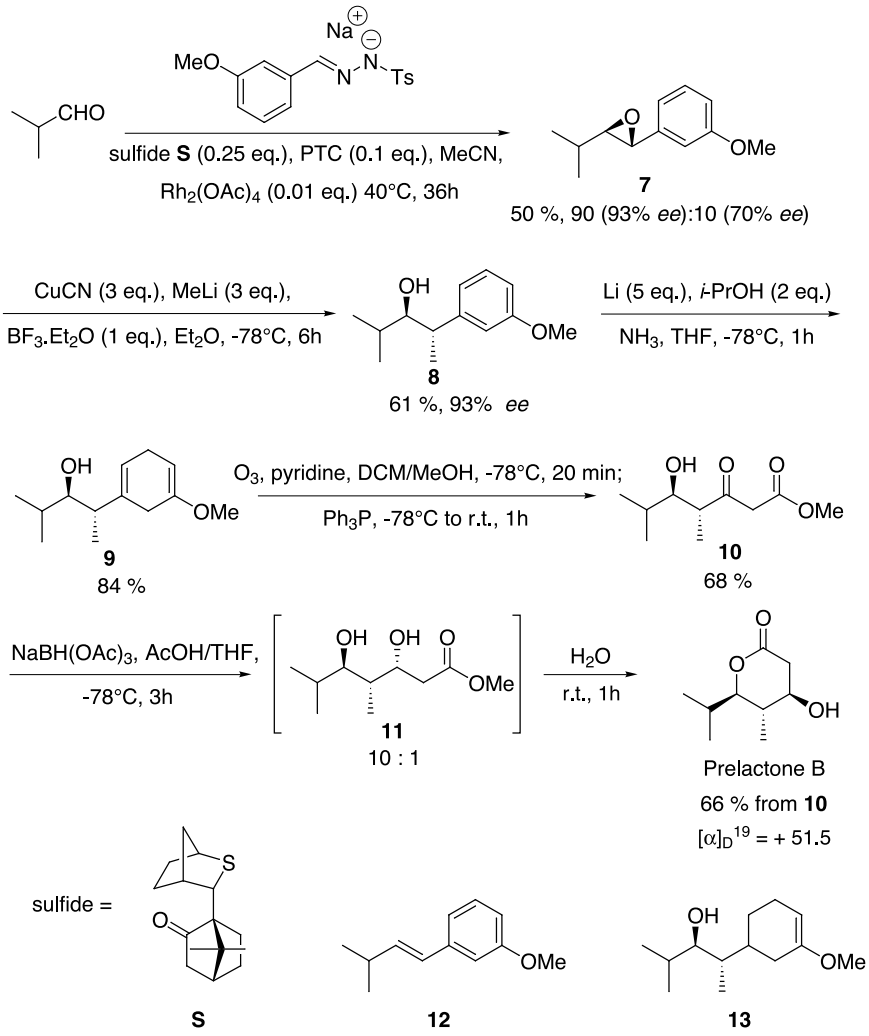
Scheme 2. Total synthesis of a mevinic acid analogue.

perfect diastereoselectivity (>98:2).[13] The *syn*-3,5-dihydroxy ester **6** slowly lactonized during purification on silica gel. We therefore treated the crude material with a few drops of 1 N HCl and this furnished the desired lactone **1** (42% over 3 steps). This material was identical to that reported in the literature (mp 70–72 °C, $[\alpha]_D^{20}=+35.6$ ($c=1.0$ in $CHCl_3$) [lit.[7a]: mp 69–70 °C, $[\alpha]_D^{20}=+34.1$ ($c=0.85$ in $CHCl_3$)]).

In the above synthesis, only one of the two stereogenic centers created in the epoxide was used, as the other was destroyed. We were keen to exemplify our methodology where both stereogenic centers were utilized and therefore turned our attention to the synthesis of the β-hydroxy-δ-lactone, (+)-prelactone B. This functionalized chiral δ-lactone was first isolated from bafilomycin-producing *Streptomyces griseus* by Zeeck and Bindseil in 1993, and it represents an early metabolite in the biosynthesis of polyketide antibiotics.[14]

Since the aryl epoxide required **7** bears branching at the α-position, we expected that our catalytic process would furnish the epoxide with good levels of diastereoselectivity. We therefore began our synthesis by treating isobutyraldehyde under our standard catalytic epoxidation conditions employing 25 mol% of the chiral sulfide **S**.[2] This furnished the desired epoxide in 50% yield as a 9:1 mixture of *trans* and *cis* isomers. The enantiomeric excesses for the two isomers were 93 and 70%, respectively.

Ring-opening reactions of the epoxide **7** with a variety of organometallic reagents was not straightforward. Neither MeLi nor Grignard reagents furnished the desired product even with $BF_3\cdot Et_2O$. Cuprates and Grignard reagents (MeMgBr or MeMgCl) with catalytic amount of various Cu salts under several different conditions were also examined[15] and despite partial success, yields were capricious and a significant amount of alkene **12** and unreacted starting epoxide were always observed. In addition, rearrangement of the epoxide to the corresponding ketone was occasionally observed. Trimethylaluminum was also tried[16] but in this case, the product was the undesired *syn* isomer regardless of the reaction conditions. Successful ring opening was finally achieved when the cuprate was employed in the presence of a Lewis acid.[17] Most importantly, careful control of the temperature and stoichiometry of the cuprate were critical to obtain reliable and reproducible results: 3 equiv of MeLi was slowly added to a suspension of 3 equiv of CuCN in Et_2O at 0 °C. After 30 min at 0 °C, the mixture was cooled to −78 °C and a solution of epoxide was slowly added to the cuprate followed by addition of $BF_3\cdot OEt_2$. Under the optimized conditions, the ring-opening reaction of the mixture of chiral epoxides proceeded smoothly to give alcohol **8** in



Scheme 3. Total synthesis of (+) prelactone B.

61% yield with 93% ee. The *trans* epoxide was converted into the *anti* alcohol **8** while the *cis* epoxide was largely untouched (Scheme 3).

Under identical Birch reduction conditions as used previously, the desired diene **9** was obtained in only 46% yield with 42% of over-reduced side-product **13**. It was believed that the presence of the free alcohol in close proximity to the double bond resulted in further reduction of the diene to the cylcohexene **13**.[18] We attempted to suppress unwanted over-reduction by protecting the free alcohol but this resulted in considerably slower and lower yielding reactions. Best results were obtained when the reaction was carried out with 5 equiv of Li and 2 equiv *i*-PrOH. Under these conditions, the desired diene **9** was obtained in 84% yield with negligible amounts of the over-reduced side product **13**.

After ozonolysis, the hydroxy keto ester **10** was then reduced to dihydroxy ester **11**. Of the several reducing agents tested, sodium triacetoxyborohydride[19] was found to be optimum giving good yields and selectivities (10:1). As the resulting dihydroxy ester **11** was unstable on silica gel, this compound was directly treated with acid. Interestingly, when the reduction reaction was quenched with water and left to stir for an additional 1 h at room temperature, the *anti*-dihydroxy ester **11** was converted into (+)-prelactone B while the minor *syn* dihydroxy ester remained in solution. Using a few drops of aqueous 1 N HCl resulted in complete conversion of the 10:1 mixture of diols into the same mixture of lactones. The synthetic sample of (+)-prelactone B (93% ee) was spectroscopically identical to that reported in the literature (mp 96–98 °C, $[\alpha]_D^{19} = +51.5$ ($c = 1.0$ in CH_3OH) [lit.[14b]: mp 97–98 °C, $[\alpha]_D^{19} = +62.1$ ($c = 1.72$ in CH_3OH)]). The lower alpha D observed probably reflects the enantioselectivity obtained in the epoxidation step (93% ee).

3. Conclusions

In conclusion, we have successfully synthesized naturally occurring and biologically important β-hydroxy-δ-lactones from enantiomerically enriched epoxides. These syntheses demonstrate the utility of enantioselective sulfur ylide mediated reactions in the convergent preparation of epoxides and their subsequent diverse applications in organic synthesis.

4. Experimental

4.1. General methods

All oxygen or moisture sensitive reactions were carried out in oven-dried glassware under the positive pressure of argon. Sensitive liquids and solutions were transferred by syringe or cannula and introduced through rubber septa through which a high flow of nitrogen was maintained. Concentration of solution was accomplished by using a Buchi rotary evaporator with a water aspirator. This was generally followed by removal of residual solvents on a vacuum line held at 0.1–1 Torr. Unless otherwise stated, all commercial reagents and solvents were used without additional purification. Chromatography grade hexane and ethyl acetate were technical grade and distilled before use. Et_2O and THF were distilled from sodium benzophenone ketyl under nitrogen. Triethylamine was distilled from sodium. Dichloromethane was distilled from P_2O_5. Analytical thin layer chromatography (TLC) was performed on Merck precoated silica gel 60 F_{254} plates. Visualization on TLC was achieved by use of UV light (254 nm), treatment with acidic anisaldehyde, potassium permanganate, 5% phosphomolybdic acid in ethanol, or ceric ammonium molybdate stain followed by heating. Flash column chromatography was undertaken on silica gel (Merck Kieselgel 60 F_{254} 400–630 mesh). Proton nuclear magnetic resonance spectroscopy (^{1}H NMR) was recorded on Bruker FT AM 400 (400 MHz). Chemical shifts were quoted in parts per million (ppm) referenced to the appropriate solvent peak or 0 ppm for TMSCl. The following abbreviations were used to describe peak patterns when appropriate: br=broad, s=singlet, d=doublet, t=triplet, q=quadruplet, m=multiplet. Coupling constant, J was reported in Hertz unit (Hz). Carbon 13 nuclear magnetic resonance spectroscopy (^{13}C NMR) was recorded on Brucker FT AM 400 (100 MHz) and was fully decoupled by broad band decoupling. Chemical shifts were reported in ppm referenced to the center line of a triplet at 77.0 ppm of chloroform-*d*. Infrared (IR) spectra were recorded neat in 0.5 mm path length sodium chloride cells on Bruker EQUINOX 55. Frequencies are given in reciprocal centimeters (cm^{-1}) and only selected absorbances are reported. Optical rotations were measured on an Autopol III of Rudolph instrument or a Perkin–Elmer 241 polarimeter at598 nm (Na D-line) with a path length of 1 dm. Concentrations (c) are quoted in g/100 mL. Low resolution mass spectra (m/z) were recorded on a VG Platform or VG Prospec with only (M+) and major peaks being reported with intensities being quoted as percentages of the base peak. High resolution mass spectra were recorded on a VG Prospec by using direct insertion probe (DIP) and EI or FAB method. High performance liquid chromatography (HPLC) data were obtained by using Agillent with chiralcel OD, OD-H, OJ or chiralpak AS-H column.

4.1.1. 3-Cyclohexylpropanal.[20] Neat DMSO (1.0 mL, 14 mmol) was added dropwise to a stirred solution of oxalyl chloride (440 μL, 5.0 mmol) in dichloromethane (20 mL) at −78 °C under argon atmosphere. After 15 min 3-cyclopropanol (610 μL, 4.0 mmol) was slowly added while the temperature was maintained at −78 °C. The solution was stirred for 1 h, during which the solution became cloudy. Triethylamine (5.0 mL) was added to the solution and the solution was warmed to room temperature slowly. Water (20 mL) was added and the layers were separated. The aqueous layer was extracted with dichloromethane (3×20 mL). The crude mixture was purified by flash chromatography (EtOAc/hexane=1/10). Colorless oil (500 mg, 89%); R_f=0.50 (EtOAc/hexane=1/10); ^{1}H NMR (300 MHz, $CDCl_3$) 0.80–0.92 (2H, m, CH_2), 1.04–1.26 (4H, m, CH_2×2), 1.49 (2H, q, J=7.5 Hz, CH_2CH), 1.57–1.71 (5H, m, CH_2×2+CH), 2.40 (2H, dt, J=2.0, 7.5 Hz, CH_2CHO), 9.73 (1H, t, J=2.0 Hz, CHO); ^{13}C NMR (75 MHz, $CDCl_3$) 26.2, 26.4, 29.3, 33.0, 37.2, 41.5, 203.1.

4.1.2. 2-(3-Methoxybenzyl)-3-[(1*R*)-7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl]-(3*S*)-2-thionia-bicyclo [2.2.1]-heptane tetrafluoroborate. To a rapidly stirred solution of chiral sulfide **S** (500 mg, 2.0 mmol) and 3-methoxybenzyl bromide (420 μL, 3.0 mmol) in dichloromethane (2 mL) was added silver tetrafluoroborate (778 mg, 4.0 mmol) in the dark under an argon atmosphere at room temperature. The reaction stirred for 48 h and 10 mL of CH_2Cl_2 was added. Silver bromide precipitate was filtered and the filtrate was concentrated in vacuo. The residual brown oil was purified by flash chromatography (0–5% MeOH/CH_2Cl_2) to give an off white foam. This was recrystallized from CH_2Cl_2 and Et_2O to give a white precipitate. (572 mg, 77%); R_f= 0.36 (MeOH/CH_2Cl_2=1/10); ν_{max}/cm^{-1} (neat) 2957, 1739, 1587, 1492, 1456, 1267, 1055; mp 168−169 °C; $[\alpha]_D^{19}$= −40.0 (c=1.0 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) 1.08 (3H, s, CH_3), 1.18 (3H, s, CH_3), 1.29 (2H, d, J=8.6 Hz, CH_2), 1.60 (2H, m, CH_2), 1.87–2.22 (7H, m, 2×CH_2+ CHHCO+SCHCHH), 2.54 (1H, ddd, J=2.6, 5.2, 18.8 Hz, CHHCO), 2.85 (1H, d, J=12.9 Hz, SCHCHH), 3.20 (1H, br s, SCHCH), 3.80 (3H, s, OCH_3), 4.11 (1H, d, J=5.0 Hz, SCHCH$_2$), 4.39 (1H, d, J=13.5 Hz, SCHHAr), 4.42 (1H, d, J=2.7 Hz, SCHCH), 4.62 (1H, d, J=13.5 Hz, SCHHAr), 6.88 (1H, dd, J=2.6, 8.6 Hz, ArH), 6.97 (1H, br s, ArH), 6.99 (1H, d, J=2.0 Hz, ArH), 7.26 (1H, t, J=8.2 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) 19.2, 21.9, 24.4, 26.7, 26.8, 33.3, 41.1, 43.5, 44.1, 45.1, 47.8, 49.9, 55.6, 57.6, 60.1, 68.9, 115.2, 116.2, 122.3, 129.8, 130.7, 160.5, 215.7; m/z (FAB) 371 ($M^+-BF_4^-$, 100%), 217 (30), 121 (43), 55 (33); (Found: $M^+-BF_4^-$ 371.2044 $C_{23}H_{31}SO_2$ requires m/z 371.2045).

4.1.3. 2-(2-Cyclohexylethyl)-3-(3-methoxyphenyl)oxirane (2). To a stirred solution of 2-(3-methoxybenzyl)-3-[(1*R*)-7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl]-(3*S*)-2-thioniabicyclo-[2.2.1]-heptane tetrafluoroborate (465 mg, 1.0 mmol) in dichloromethane (5.0 mL) was added *N*,*N*,*N*′,*N*′,-tetramethyl-*N*″-[tris(dimethylamino)phos-phoralidene]phosphoric triamide ethylimine (415 μL, 1.25 mmol) at −78 °C under argon. After 30 min, 3-cyclohexylpropanal (175 mg, 1.25 mmol) was added to the solution. After 2 h stirring, the mixture was warmed up to room temperature and then saturated NaCl solution (10 mL) was added. The organic layer was separated and the aqueous layer extracted with EtOAc (3×10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude mixture was purified by flash chromatography (EtOAc/hexane=1/50) to give a mixture of *trans*/*cis*=92:8 epoxides (249 mg, 96%) and chiral sulfide (259 mg, 83%); R_f=0.30 (EtOAc/hexane=

1/20); ν_{max}/cm^{-1} (neat) 2923, 1604, 1493, 1455, 1260, 1154, 1047, 891, 782; ^1H NMR (400 MHz, $CDCl_3$) 0.66–0.80 (*cis*, 2H, m, CH_2), 0.84–0.94 (*trans*, 2H, m, CH_2), 1.04–1.30 (4H, m, $CH_2\times2$), 1.30–1.44 (2H, m, CH_2), 1.62–1.74 (7H, m, $CH_2\times3+CH$), 2.89 (*trans*, 1H, dt, $J=2.2$, 5.7 Hz, C*H*(O)CHAr), 3.15 (*cis*, 1H, dt, $J=4.3$, 5.7 Hz, C*H*(O)CHAr), 3.57 (*trans*, 1H, d, $J=2.2$ Hz, CH(O)C*H*Ar), 3.78 (*trans*, 3H, s, OCH_3), 3.79 (*cis*, 3H, s, OCH_3), 4.03 (*cis*, 1H, d, $J=4.3$ Hz, CH(O)C*H*Ar), 6.77 (1H, m, Ar*H*), 6.81 (1H, ddd, $J=1.0$, 2.4, 8.0 Hz, Ar*H*), 6.85 (1H, m, Ar*H*), 7.23 (1H, t, $J=7.8$ Hz, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) *trans* isomer: 26.3 (2), 26.6, 29.6, 33.1, 33.3, 33.4, 37.3, 55.2, 58.6, 63.4, 110.4, 113.7, 118.0, 129.4, 139.7, 159.8 *cis* isomer: 24.0, 26.1, 26.2, 26.5, 33.0, 33.5, 33.7, 57.5, 59.0, 111.7, 113.2, 118.8, 129.0, 137.4, 159.3; *m/z* (EI) 260 (M^+, 70%), 177 (10), 163 (44), 149 (72), 136 (81), 121 (100), 109 (70), 95 (53), 91 (58), 81 (62), 67 (60), 55 (65); (Found M^+ 260.1786 $C_{17}H_{24}O_2$ requires *m/z* 260.1776); Chiracel OD-H, hexane/*i*-PrOH (99.5/0.5), 1.0 mL/min, 10 °C, major 9.9 min (2*R*,3*R*), minor 10.6 min (2*S*,3*S*) for *trans* isomer and major 9.2 min (2*R*,3*S*), minor 7.0 min (2*S*,3*R*) for *cis* isomer.

4.1.4. (1*S*,2*R*)-4-Cyclohexyl-1-isopropoxy-1-(3-methoxyphenyl)butan-2-ol (3). A solution of 2-(2-cyclohexylethyl)-3-(3-methoxyphenyl)oxirane (260 mg, 1.0 mmol) in *i*-PrOH (10 mL) was treated with catalytic amount of conc. H_2SO_4 at 0 °C. After 30 min, *i*-PrOH was removed under reduced pressure in the presence of $NaHCO_3$. The residue was dissolved with ether, and then after filtration of the mixture, the filtrate was concentrated in vacuo. The crude mixture was purified by flash chromatography (EtOAc/hexane=1/10) to give a colorless oil (262 mg, 82%); $R_f=0.22$ (EtOAc/hexane=1/10); ν_{max}/cm^{-1} (neat) 3568, 2923, 1488, 1453, 1263, 1050; $[\alpha]_D^{20}=+57.4$ ($c=1.0$ in CH_3OH); ^1H NMR (400 MHz, $CDCl_3$) 0.82 (2H, m, CH_2), 1.05–1.50 (8H, m, $CH_2\times4$), 1.09 (3H, d, $J=6.1$ Hz, $CH(CH_3)_2$), 1.13 (3H, d, $J=6.1$ Hz, $CH(CH_3)_2$), 1.55–1.70 (5H, m, $CH_2\times3+CH$), 1.79 (1H, br s, O*H*), 3.51 (1H, septet, $J=6.1$ Hz, $CH(CH_3)_2$), 3.62 (1H, m, C*H*OH), 3.78 (3H, s, OCH_3), 4.27 (1H, d, $J=5.3$ Hz, C*H*O(*i*-Pr)), 6.81 (1H, m, Ar*H*), 6.89 (1H, m, Ar*H*), 7.24 (1H, t, $J=8.1$ Hz, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) 21.2, 23.4, 26.4 (2), 26.9, 29.4, 33.2, 33.5 (2), 37.8, 55.2, 69.5, 75.1, 82.0, 113.0, 113.1, 120.1, 129.2, 141.4, 159.6; *m/z* (FAB) 343 (M^++Na, 98), 261 (100), 180 (47), 137 (65), 121 (58), 109 (28), 55 (16); (Found M^++Na 343.2251 $C_{20}H_{32}O_3Na$ requires *m/z* 343.2249); Chiracel OD-H, hexane/*i*-PrOH (98/2), 0.5 mL/min, 20 °C, major 12.8 min (1*S*,2*R*), minor 11.7 min (1*R*,2*S*).

4.1.5. (2*R*)-4-Cyclohexyl-1-(5-methoxycyclohexa-1,4-dienyl)-butan-2-ol (4). Well-dried NH_3 over Na was transferred to a two-neck flask containing Li (69 mg, 10.0 mmol). A solution of (1*S*,2*R*)-4-cyclohexyl-1-isopropoxy-1-(3-methoxyphenyl)butan-2-ol (385 mg, 1.2 mmol) in THF (1 mL) was added to the blue NH_3 solution via cannula followed by addition of *i*-PrOH (500 μL, 6.0 mmol). The mixture was refluxed for 2 h and cooled to −78 °C, and then treated sequentially with 2 mL of benzene and 850 mg of ammonium acetate. NH_3 was allowed to evaporate and the residue was partitioned between brine (10 mL) and ethyl acetate (10 mL). The mixture was extracted with ethyl acetate (3×10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude mixture was purified by flash chromatography (EtOAC/hexane=1/20) to give a colorless oil (214 mg, 67%); $R_f=0.18$ (EtOAc/hexane=1/10); ν_{max}/cm^{-1} (neat) 3418, 2994, 1696, 1665, 1449, 1390, 1221, 1136; ^1H NMR (400 MHz, C_6D_6) 0.80–0.95 (2H, m, CH_2), 1.05–1.45 (9H, m, $CH_2\times4+OH$), 1.60–1.75 (5H, m, $CH_2\times2+CH$), 1.99 (2H, d, $J=6.3$ Hz, $CHOHCH_2CH=C$), 2.70–2.90 (4H, m, $=CCH_2C=\times2$), 3.28 (3H, s, OCH_3), 3.51 (1H, m, C*H*OH), 4.44 (1H, br s, $CH=COCH_3$), 5.43 (1H, br s, $CH=C(CH_2)_2$); ^{13}C NMR (100 MHz, C_6D_6) 26.7, 26.8, 27.1, 27.2, 32.3, 33.6, 33.7, 33.8, 35.0, 38.1, 45.9, 53.6, 69.1, 90.2, 121.9, 132.1, 153.4; *m/z* (EI) 264 (M^+, 20%), 135 (31), 122 (100), 109 (37), 91 (14), 55 (17); (Found M^+ 264.2090 $C_{17}H_{28}O_2$ requires *m/z* 264.2089).

4.1.6. 6-(2-Cyclohexylethyl)-4-hydroxy-tetrahydropyran-2-one (1).[7a] Round-bottomed flask equipped with $CaCl_2$ drying tube was filled with a solution of (2*R*)-4-cyclohexyl-1-(5-methoxycyclohexa-1,4-dienyl)-butan-2-ol (110 mg, 0.42 mmol) and pyridine (100 μL) in 10 mL of dichloromethane and 2 mL of methanol at −78 °C. O_3 was bubbled until saturated, at which point blue color was persisted. The solution was degassed with O_2 until blue color disappeared. Triphenylphosphine (110 mg, 0.42 mmol) was added and stirring continued for 1 h at room temperature. NaCl solution was added and two layers were separated. The aqueous layer extracted with dichloromethane (3×10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated to give the desired product as a colorless oil, which was used in next step without further purification; $R_f=0.35$ (EtOAc/hexane=1/2); ν_{max}/cm^{-1} (neat) 3421, 2923, 2851, 1747, 1715, 1651, 1448, 1324; ^1H NMR (400 MHz, $CDCl_3$) 0.82–0.95 (2H, m, CH_2), 1.00–1.50 (10H, m, $CH_2\times5$), 1.55–1.78 (5H, m, $CH_2\times2+CH$), 2.61 (1H, dd, $J=8.8$, 17.4 Hz, $CHOHCH_2CO$), 2.70 (1H, dd, $J=3.1$, 17.4 Hz, $CHOHCH_2CO$), 3.46 (2H, s, $COCH_2CO_2CH_3$), 3.71 (3H, s, OCH_3), 4.00 (1H, m, C*H*OH); ^{13}C NMR (100 MHz, C_6D_6) 26.3 (2), 26.6, 33.0, 33.2, 33.3, 33.8, 37.5, 49.6 (2), 52.4, 67.8, 167.3, 203.6; *m/z* (FAB) 257 (M^++H, 100), 239 (49), 189 (35), 137 (60), 117 (44), 81 (43), 55 (40); (Found M^++H 257.1750 $C_{14}H_{25}O_4$ requires *m/z* 257.1753).

To a cooled (−78 °C) solution of resulting (5*R*)-7-cyclohexyl-5-hydroxy-3-oxo-heptanoic acid methyl ester in 5 mL of THF and 1 mL of methanol was added a solution of diethylmethoxyborane (1.0 M in THF, 420 μL). The reaction mixture stirred at −78 °C for 15 min and then sodium borohydride (77 mg, 2.0 mmol) was added in a portion. The mixture stirred for 2 h and quenched by adding 1 mL of 1 N HCl. Stirring continued 1 h and $NaHCO_3$ solution was added to neutralize the mixture. The aqueous layer extracted with ethyl acetate (3×5 mL). The combined organic layer were dried ($MgSO_4$), filtered and concentrated. Flash chromatography with EtOAc/hexane=1/2 gave the desired product as a white solid (40 mg, 42%); $R_f=0.15$ (EtOAc/hexane=1/2); mp 70–72 °C [lit.: 69–70 °C][7a]; $[\alpha]_D^{20}=+35.6$ ($c=1.0$ in $CHCl_3$) [lit.: $[\alpha]_D^{20}=+34.1$ ($c=0.85$ in $CHCl_3$)][7a]; ^1H NMR (300 MHz, $CDCl_3$) 0.75–0.95 (2H, m, CH_2), 1.05–1.95 (16H, m, $CH_2\times7+CH+OH$), 2.60 (1H, ddd, $J=1.5$, 3.8, 22.6 Hz, CH_2CO_2), 2.65

(1H, dd, $J=5.0$, 22.6 Hz, CH_2CO$_2$), 4.36 (1H, m, C*H*OH), 4.63 (1H, m, C*H*OCO).

4.1.7. *m*-Methoxybenzaldehyde tosylhydrazone. To a rapidly stirred suspension of *p*-toluenesulfonyl hydrazide (5.7 g, 30.0 mmol) in methanol (20 mL) was added *m*-anisaldehyde (3.75 mL, 30 mmol) dropwise. A mildly exothermic reaction ensued and the hydrazide dissolved. Within 5–10 min *m*-methoxybenzaldehyde tosylhydrazone began to precipitate. After approximately 30 min the mixture was cooled to 0 °C and the product removed by filtration, washed with a small quantity of ice-cold methanol. Recrystallization from methanol gave a white solid (8.25 g, 90%); ν_{max}/cm^{-1} (neat) 3463, 3158, 1597, 1327, 1270, 1171, 1064, 899, 665; mp 106–107 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 2.37 (3H, s, CH_3), 3.78 (3H, s, OCH_3), 6.88 (1H, dd, $J=2.5$, 8.2 Hz, Ar*H*), 7.08 (1H, d, $J=7.6$ Hz, Ar*H*), 7.12 (1H, s, Ar*H*), 7.22 (1H, t, $J=8.0$ Hz, Ar*H*), 7.28 (2H, d, $J=8.2$ Hz, Ar*H*), 7.73 (1H, s, C*H*=N), 7.86 (2H, d, $J=8.2$ Hz, Ar*H*), 8.32 (1H, br s, N*H*); ^{13}C NMR (100 MHz $CDCl_3$) 21.6, 55.3, 111.5, 116.7, 120.5, 127.9, 129.6, 129.7, 134.5, 135.2, 144.3, 147.7, 159.7; *m*/*z* (EI) 304 (M^+, 20%), 156 (18), 148 (100), 139 (13), 134 (46), 120 (97), 105 (15), 91 (81), 77 (31), 65 (28), 51 (22); (Found M^+ 304.0886 $C_{15}H_{16}N_2O_3S$ requires *m*/*z* 304.0882).

4.1.8. *m*-Methoxybenzaldehyde tosylhydrazone sodium salt. A 1.0 M sodium methoxide solution was prepared by adding sodium (635 mg, 27.5 mmol) to anhydrous methanol (27.5 mL) with external cooling. Once all of the metal had dissolved, *m*-methoxybenzaldehyde tosylhydrazone (8.25 g, 27 mmol) was added and the mixture stirred until the solid had dissolved. After stirring for a further 15 min, methanol was removed under reduced pressure at room temperature to yield hydrazone salt in quantitative yield. Solid hydrazone salt was then ground using a pestle and mortar to give a free flowing powder; ν_{max}/cm^{-1} (neat) 3459, 2959, 1600, 1237, 1129, 1084, 1031, 910; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) 2.27 (3H, s, CH3), 3.71 (3H, s, OCH3), 6.65 (1H, dd, $J=2.3$, 8.1 Hz, Ar*H*), 6.92 (2H, m, Ar*H*), 7.12 (1H, t, $J=7.2$ Hz, Ar*H*), 7.15 (2H, d, $J=8.2$ Hz, Ar*H*), 7.54 (1H, s, C*H*=N), 7.58 (2H, d, $J=8.2$ Hz Ar*H*); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) 20.8, 54.8, 109.5, 111.6, 117.6, 126.5, 128.1, 129.1, 136.2, 138.4, 139.9, 143.9, 159.2; *m*/*z* (FAB) 327 ($M^+ +1$, 21%), 201 (100), 176 (17); (Found: $[M+H]^+$ 327.0781 $C_{15}H_{16}O_3N_2SNa$ requires *m*/*z* 327.0779).

4.1.9. 2-Isopropyl-3-(3-methoxyphenyl)oxirane (7). A round bottomed flask was fitted with chiral sulfide (125 mg, 0.5 mmol), rhodium(II) acetate dimer (9 mg, 0.02 mmol), benzyl triethylammonium chloride (46 mg, 0.2 mmol), isobutyraldehyde (180 μL, 2.0 mmol) in anhydrous acetonitrile (6.0 mL) under nitrogen atmosphere. *m*-Methoxybenzaldehyde tosylhydrazone sodium salt (667 mg, 2.0 mmol) was added and the reaction mixture was stirred vigorously at room temperature for 10 min, then at 40 °C. Same amount of *m*-methoxybenzaldehyde tosylhydrazone sodium salt was added again after 12 and 24 h. After an additional 12 h stirring, the reaction was quenched by the addition of water (15 mL). The aqueous layer was washed with ethyl acetate (3×10 mL) and the combined organic phases dried over $MgSO_4$, filtered and concentrated in vacuo. The crude mixture was purified on silica gel (Et_2O/hexane=1/20) to give a desired product with some unknown impurities. Further purification was carried out by Kugelrohr distillation (6 Torr, 140 °C) to afford a pure mixture of *trans*/*cis*=90:10 (190 mg, 50%) as a colorless oil; $R_f=0.30$ (Et_2O/hexane=1/10); ν_{max}/cm^{-1} (neat) 2963, 1604, 1464, 1260, 1046; ^{1}H NMR (400 MHz, $CDCl_3$) 0.70 (*cis*, 3H, d, $J=6.7$ Hz, CH_3), 1.01 (*trans*, 3H, d, $J=6.8$ Hz, CH_3), 1.08 (*trans*+*cis*, 3H, d, $J=6.8$ Hz, CH_3), 1.24 (*cis*, 1H, m, CH(CH_3)$_2$), 1.66 (*trans*, 1H, octet, $J=6.8$ Hz, CH(CH_3)$_2$), 2.72 (*trans*, 1H, dd, $J=2.1$, 6.8 Hz, CO*H*CH), 3.63 (*trans*, 1H, d, $J=2.1$ Hz, ArCO*H*), 2.83 (*cis*, 1H, dd, $J=4.4$, 9.2 Hz, CO*H*CH), 3.78 (*trans*, 3H, s, OCH_3), 3.79 (*cis*, 3H, s, OCH_3), 4.06 (*cis*, 1H, d, $J=4.4$ Hz, ArCO*H*), 6.76–6.92 (3H, m, Ar*H*), 7.23 (1H, t, $J=7.9$ Hz, Ar*H*); ^{13}C NMR (100 MHz $CDCl_3$) *trans* isomer: 18.4, 19.0, 30.9, 55.2, 57.5, 68.3, 110.4, 113.7, 117.9, 129.4, 139.7, 159.8; *cis* isomer: 17.9, 19.9, 25.9, 55.2, 57.7, 65.1, 111.7, 112.9, 118.7, 129.0, 137.5, 159.3; *m*/*z* (EI); 192 (M^+, 79%), 176 (13), 161 (25), 149 (95), 136 (100), 121 (40), 109 (19), 91 (45), 77 (28), 71 (12), 55 (12); (Found M^+ 192.1152 $C_{12}H_{16}O_2$ requires *m*/*z* 192.1150); Chiracel OJ-H, hexane/*i*-PrOH (99.5/0.5), 1.0 mL/min, 10 °C, major 12.0 min (2*R*,3*R*), minor 13.1 min (2*S*,3*S*) for *trans* isomer and major 7.4 min (2*R*,3*S*), minor 8.1 min (2*S*,3*R*) for *cis* isomer.

4.1.10. (2*S*,3*R*)-2-(3-Methoxyphenyl)-4-methyl-pentan-3-ol (8). To a stirred suspension of CuCN (464 mg, 5.2 mmol) in Et_2O (20 mL) was quickly added MeLi (1.6 M in Et_2O, 3.25 mL) at 0 °C. After 20 min the mixture was cooled to −78 °C. A solution of 2-isopropyl-3-(3-methoxyphenyl)oxirane (322 mg, 1.73 mmol) in Et_2O (5 mL) was added followed by $BF_3\cdot Et_2O$ (220 μL, 1.73 mmol). Temperature was raised to room temperature after 6 h and 50 mL of NH_3Cl/NH_4OH solution (4/1) was added. The aqueous layer was washed with ethyl acetate (3×50 mL) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude material was purified by flash chromatography (EtOAc/hexane=1/20) to furnish a pale yellow oil (232 mg, 64%); $R_f=0.25$ (EtOAc/hexane=1/10); ν_{max}/cm^{-1} (neat) 3476, 2962, 1602, 1487, 1262; $[\alpha]_D^{17}=-19.1$ ($c=1.0$ in CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$) 0.92 (3H, d, $J=6.8$ Hz, (CH_3)$_2$CH), 1.01 (3H, d, $J=6.8$ Hz, (CH_3)$_2$CH), 1.20 (1H, br s, O*H*), 1.22 (3H, d, $J=7.0$ Hz, CH_3CHAr), 1.79 (1H, d-septet, $J=4.2$, 6.8 Hz, CH(CH_3)$_2$), 2.80 (1H, quintet, $J=7.2$ Hz, CH$_3$C*H*Ar), 3.41 (1H, dd, $J=4.2$, 7.6 Hz, COHC*H*), 3.79 (3H, s, OCH_3), 6.80 (3H, m, Ar*H*), 7.22 (1H, t, $J=7.7$ Hz, Ar*H*); ^{13}C NMR (100 MHz $CDCl_3$) 15.2, 18.5, 20.4, 29.9, 43.5, 55.1, 80.3, 111.7, 114.0, 120.5, 129.5, 145.8, 159.7; *m*/*z* (EI) 208 (M^+, 22%), 165 (12), 136 (100), 121 (63), 104 (14), 91 (11), 77 (8), 55 (9); (Found M^+ 208.1464. $C_{13}H_{20}O_2$ requires *m*/*z* 208.1463); Chiracel OD-H, hexane/*i*-PrOH (95/5), 0.5 mL/min, 20 °C, major 14.8 min (2*S*,3*R*), minor 13.0 min (2*R*,3*S*).

4.1.11. (2*S*,3*R*)-2-(5-Methoxycyclohexa-1,4-dienyl)-4-methylpentan-3-ol (9). Well-dried NH_3 over Na was transferred to a two-neck flask containing Li (53 mg, 7.5 mmol). A solution of (2*S*,3*R*)-2-(3-methoxyphenyl)-4-methyl-pentan-3-ol (314 mg, 1.5 mmol) in THF (2 mL) was

added to the blue NH_3 solution *via* cannula followed by the addition of *i*-PrOH (250 μL, 3.0 mmol). The mixture was refluxed for 2 h and cooled to −78 °C, and then treated sequentially with 2 mL of benzene and 850 mg of ammonium acetate. NH_3 was allowed to evaporate and the residue was partitioned between brine (20 mL) and ethyl acetate (20 mL). The mixture was extracted with ethyl acetate (3×20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude mixture was purified by flash chromatography (EtOAC/hexane=1/20) to give a colorless oil (265 mg, 84%); R_f=0.30 (EtOAc/hexane=1/10); ν_{max}/cm^{-1} (neat) 3553, 2962, 1695, 1389, 1221, 1156; $[\alpha]_D^{16}$=+14.7 (c=1.0 in PhH); ^{1}H NMR (400 MHz, C_6D_6) 0.79 (3H, d, J=7.1 Hz, CH_3CH), 0.88 (3H, d, J=6.8 Hz, (CH_3)$_2$CH), 1.04 (3H, d, J=6.8 Hz, (CH_3)$_2$CH), 1.39 (1H, br s, OH), 1.61 (1H, d-septet, J=3.2, 6.8 Hz, CH(CH$_3$)$_2$), 2.17 (1H, dq, J=7.1, 8.8 Hz, CH$_3$CH), 2.69 (2H, m, CH_2), 2.79 (2H, m, CH_2), 3.13 (1H, dd, J=3.2, 8.8 Hz, CHOH), 3.27 (3H, s, OCH_3), 4.41 (1H, br s, CH$_2$CH=C), 5.40 (1H, br s, CH$_2$CH=COCH$_3$); ^{13}C NMR (100 MHz C_6D_6) 14.6, 15.5, 20.9, 27.0, 28.8, 29.6, 45.1, 53.6, 76.3, 90.1, 121.6, 136.9, 153.6; *m/z* (EI) 210 (M^+, 21%), 149 (43), 138 (100), 121 (47), 109 (82), 105 (19), 91 (30), 77 (12), 55 (9); (Found M^+ 210.1619. $C_{13}H_{22}O_2$ requires *m/z* 210.1620).

4.1.12. (4*S*,5*R*)-5-Hydroxy-4,6-dimethyl-3-oxo-heptanoic acid methyl ester (10). A two-neck flask equipped with $CaCl_2$ drying tube was filled with a solution of (2*S*,3*R*)-2-(5-methoxycyclohexa-1,4-dienyl)-4-methylpentan-3-ol (210 mg, 1.0 mmol) and pyridine (100 μL) in 10 mL of CH_2Cl_2 and 2 mL of methanol at −78 °C. O_3 was bubbled until saturated, at which point blue color persisted, and then the solution was degassed with O_2 until blue color disappeared. Triphenyl phosphine (785 mg, 3.0 mmol) was added and stirring continued for 1 h at room temperature. After solvent was removed under reduced pressure, flash chromatography (25% EtOAc in hexane) gave the desire product as a pale yellow oil (135 mg, 67%); R_f=0.36 (EtOAc/hexane=1/2); ν_{max}/cm^{-1} (neat) 3525, 2964, 1747, 1713, 1457, 1317, 1159, 996; $[\alpha]_D^{17}$=−16.6 (c=1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 0.84 (keto 3H, d, J=6.8 Hz, (CH_3)$_2$CH), 0.88 (enol 3H, d, J=6.7 Hz, (CH_3)$_2$CH), 0.91 (enol, 3H, d, J=6.7 Hz, (CH_3)$_2$CH), 0.92 (keto, 3H, d, J=6.8 Hz, (CH_3)$_2$CH), 1.06 (keto, 3H, d, J=7.1 Hz, CHCH_3), 1.14 (enol, 3H, d, J=7.1 Hz, CHCH_3), 1.68 (enol, 1H, m, CH(CH$_3$)$_2$), 1.74 (keto, 1H, d-septet, J=2.8, 6.8 Hz, CH(CH$_3$)$_2$), 1.90 (enol, 1H, br s, OH), 2.00 (enol, 1H, br s, OH), 2.31 (keto, 1H, d, J=5.9 Hz, OH), 2.37 (enol, 1H, quintet, J=7.0 Hz, CHCH$_3$), 2.81 (keto, 1H, quintet, J=7.4 Hz, CHCH$_3$), 3.32 (enol, 1H, m, CHOH), 3.45 (keto, 1H, m, CHOH), 3.55 (keto, 2H, d, J=3.4 Hz, COCH_2), 3.68 (enol, 3H, s, OCH_3), 3.69 (keto, 3H, s, OCH_3), 5.03 (enol, 1H, s, COH=CH); ^{13}C NMR (100 MHz $CDCl_3$) keto: 13.5, 15.0, 19.8, 29.9, 49.1, 49.3, 52.2, 78.1, 167.7, 207.8 enol: 15.5, 16.2, 19.9, 30.8, 42.8, 51.2, 78.3, 89.9, 173.0, 180.3.

4.1.13. Prelactone B ((3*R*,4*S*,5*R*)-3-hydroxy-4,6-dimethylheptanoic acid-δ-lactone).[14b] Acetic acid (1.0 mL) was added to a suspension of NaBH(OAc)$_3$ (410 mg, 1.9 mmol) in THF (3 mL) at −78 °C under argon. After 10 min, a solution of (4*S*,5*R*)-5-hydroxy-4,6-dimethyl-3-oxo-heptanoic acid methyl ester (130 mg, 0.64 mmol) in THF (2 mL) was added. Reaction continued for 3 h, and then temperature was raised to room temperature. The reaction was quenched by adding water (5 mL) and two-phase mixture was stirred for an additional hour. After being neutralized by 20% NaOH solution, the aqueous layer extracted with ethyl acetate (3×10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. Flash chromatography (EtOAc/hexane=1/1) gave Prelactone B as a white solid (73 mg, 66%); R_f=0.26 (EtOAc/hexane=1/1); mp 96–98 °C [lit.: 97–98 °C][14b]; $[\alpha]_D^{19}$=+51.5 (c=1.0 in CH_3OH)[lit.: $[\alpha]_D^{19}$=+62.1 (c=1.72 in CH_3OH)][14b]; ^{1}H NMR (400 MHz, $CDCl_3$) 0.90 (3H, d, CH_3CH, J=6.9 Hz), 1.04 (3H, d, J=6.7 Hz, (CH_3)$_2$CH), 1.04 (3H, d, J=6.7 Hz, (CH_3)$_2$CH), 1.73 (1H, d-septet, J=2.2, 6.9 Hz, CHCH$_3$), 1.97 (1H, m, CH(CH$_3$)$_2$), 2.02 (1H, br s., OH), 2.46 (1H, dd, J=8.1, 17.3 Hz, CHHCO), 2.90 (1H, dd, J=5.9, 17.3 Hz, CHHCO), 3.74 (2H, m, CHOH+OCHCH); ^{13}C NMR (100 MHz $CDCl_3$) 13.6, 14.0, 20.0, 28.9, 38.9, 39.0, 69.8, 86.2, 170.9.

References and notes

1. Aggarwal, V. K.; Winn, C. L. *Acc. Chem. Res.* **2004**. ASAP.
2. (a) Aggarwal, V. K.; Alonso, E.; Bae, I.; Hynd, G.; Lydon, K. M.; Palmer, M. J.; Patel, M.; Porcelloni, M.; Richardson, J.; Stenson, R. A.; Studley, J. R.; Vasse, J.-L.; Winn, C. L. *J. Am. Chem. Soc.* **2003**, *125*, 10926. (b) Aggarwal, V. K.; Alonso, E.; Hynd, G.; Lydon, K. M.; Palmer, M. J.; Porcelloni, M.; Studley, J. R. *Angew. Chem., Int. Ed.* **2001**, *40*, 1430.
3. Aggarwal, V. K.; Bae, I.; Lee, H.-Y.; Richardson, J.; Williams, D. T. *Angew. Chem., Int. Ed.* **2003**, *42*, 3274.
4. (a) Furukawa, N.; Sugihara, Y.; Fujihara, H. *J. Org. Chem.* **1989**, *54*, 4222. (b) Breau, L.; Durst, T. *Tetrahedron: Asymmetry* **1991**, *2*, 367. (c) Solladié-Cavallo, A.; Diep-Vohuule, A.; Sunjic, V.; Vinkovic, V. *Tetrahedron: Asymmetry* **1996**, *7*, 1783. (d) Li, A.-H.; Dai, L.-X.; Hou, X.-L.; Huang, Y.-Z.; Li, F.-W. *J. Org. Chem.* **1996**, *61*, 489. (e) Julienne, K.; Metzner, P.; Henyron, V. *J. Chem. Soc., Perkin Trans. 1* **1999**, 731. In addition to our own previous example of applications of sulfur ylides in synthesis (Ref. 3), see also Solladié-Cavallo, A.; Diep-Vohuule, A. *J. Org. Chem.* **1995**, *60*, 3494.
5. (a) Echeverri, F.; Arango, V.; Quiñones, W.; Torres, F.; Escobar, G.; Rosero, Y.; Archbold, R. *Phytochemistry* **2001**, *56*, 881. (b) Donadio, S.; Staver, M. J.; McAlpine, J. B.; Swanson, S. J.; Katz, L. *Gene* **1992**, *115*, 97. (c) Gunasekera, S. P. *J. Org. Chem.* **1990**, *55*, 4912. (d) Yada, H. *Nat. Prod. Lett.* **1993**, *2*, 221.
6. Evans, D. A.; Gauchet-Prunet, J. A.; Carreira, E. M.; Charette, A. B. *J. Org. Chem.* **1991**, *56*, 741.
7. (a) Bonini, C.; Pucci, P.; Viggiani, L. *J. Org. Chem.* **1991**, *56*, 4050. (b) Johnson, W. S.; Kelson, A. B.; Elliott, J. D. *Tetrahedron Lett.* **1988**, *29*, 3757.
8. (a) Endo, A.; Kuroda, M.; Tsujita, Y. *J. Antibiot.* **1976**, *29*, 1346. (b) Endo, A.; Kuroda, M.; Tsujita, Y.; Tanzawa, K. *Eur. J. Biochem.* **1977**, *77*, 31.
9. Some examples of total synthesis, see: (a) Clive, D. L. J.; Murthy, K. S. K.; Wee, A. G. H.; Prasad, J. S.; da Silva, G. V. J.; Majewski, M.; Anderson, P. C.; Evans, C. F.; Haugen,

R. D.; Heerze, L. D.; Barrie, J. R. *J. Am. Chem. Soc.* **1990**, *112*, 3018. (b) Hagiwara, H.; Nakano, T.; Kon-no, M.; Uda, H. *J. Chem. Soc., Perkin Trans. 1* **1995**, 777. For a review, see Rosen, T.; Heathcock, C. H. *Tetrahedron* **1986**, *42*, 4909. Selected recent examples of analogues, see: (c) Ghosh, A. K.; Lei, H. *J. Org. Chem.* **2000**, *65*, 4779. (d) Bouzbouz, S.; Cossy, J. *Tetrahedron Lett.* **2000**, *41*, 3363. (e) Reddy, P. P.; Yen, K.-F.; Uang, B.-J. *J. Org. Chem.* **2002**, *67*, 1034. (f) Solladié, G.; Bauder, C.; Rossi, L. *J. Org. Chem.* **1995**, *60*, 7774.

10. Stokker, G. E.; Hoffman, W. F.; Alberts, A. W.; Gragoe, E. J.; Deana, A. A.; Gilfilan, J. L.; Huff, J. W.; Novello, F. C.; Prugh, J. D.; Smith, R. L.; Willard, A. K. *J. Med. Chem.* **1985**, *28*, 347.
11. EtP_2=*N*,*N*,*N*′,*N*′-tetramethyl-*N*″-[tris(dimethylamino)-phosphoranylidene]phosphoric triamide ethylimine (a) Solladié-Cavallo, A.; Diep-Vohuule, A.; Isarno, T. *Angew. Chem., Int. Ed.* **1998**, *37*, 1689. (b) Solladié-Cavallo, A.; Roje, M.; Isarno, T.; Sunjic, V.; Vinkovic, V. *Eur. J. Org. Chem.* **2000**, 1077. (c) Fei, X. S.; Verkade, J. G. *Heteroatom Chem.* **1999**, *10*, 538.
12. Rabideau, P. W.; Marcinow, Z. *Org. React.* **1992**, *42*, 1 and references therein.
13. Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repič, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155.
14. (a) Bindseil, K. U.; Zeeck, A. *Helv. Chim. Acta* **1993**, *76*, 150. (b) Hanefeld, U.; Hooper, A. M.; Staunton, J. *Synthesis* **1999**, 401. (c) Chakraborty, T. K.; Tapadar, S. *Tetrahedron Lett.* **2003**, *44*, 2541. (d) Pihko, P. M.; Erkkilä, A. *Tetrahedron Lett.* **2003**, *44*, 7607. (e) Csákÿ, A. G.; Mba, M.; Plumet, J. *Synlett* **2003**, 2092. (f) Fournier, L.; Gaudel-Siri, A.; Kocieński, P. J.; Pons, J.-M. *Synlett* **2003**, 107. (g) Enders, D.; Haas, M. *Synlett* **2003**, 2182. (h) Dias, L. C.; Steil, L. J.; Vasconcelos, V. A. *Tetrahedron: Asymmetry.* **2004**, *15*, 147.
15. (a) Klunder, J. M.; Posner, G. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford; 1991; Vol. 3, pp 223–226 and references therein. (b) Richard, J. K.; Casy, G. In *Organocopper Reagents*, Taylor, R. J. K., Ed.; Oxford University Press: Oxford, 1994; Chapter 2 and references therein.
16. Carde, L.; Davies, D. H.; Roberts, S. M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2455.
17. Schwink, L.; Knochel, P. *Chem. Eur. J.* **1998**, *4*, 950.
18. Cotsaris, E.; Paddon-Row, M. N. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1487.
19. Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.
20. Stratakis, M.; Nencka, R.; Rabalakos, C.; Adam, W.; Krebs, O. *J. Org. Chem.* **2002**, *67*, 8758.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 60 (2004) 9735–9744
Tetrahedron

Palladium(II)-catalyzed isomerization-Claisen rearrangement of 2-alkoxy diallyl ethers

Cristina Nevado and Antonio M. Echavarren*

Institute of Chemical Research of Catalonia (ICIQ), E-43007 Tarragona and Departamento de Química Orgánica, Universidad Autónoma de Madrid, Cantoblanco, E-28049 Madrid, Spain

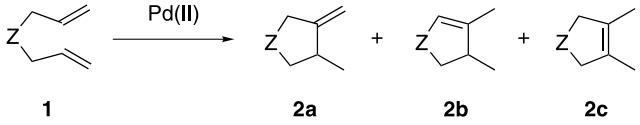
Received 30 April 2004; revised 8 June 2004; accepted 12 June 2004

Available online 27 August 2004

Abstract—Diallyl ethers bearing an enol ether react in the presence of $PdCl_2$ as catalyst to give α-allyl α-alkoxy ketones by selective isomerization via formal 1,2-H migration at the more substituted allyl group, followed by Claisen rearrangement. This rearrangement is also promoted by $AuCl_3$ and $IrCl_3$, although the yields are lower with these catalysts.

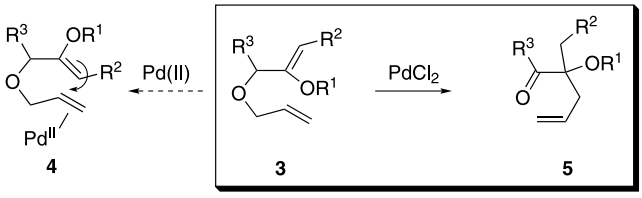
1. Introduction

Cyclization of 1,6-dienes **1** proceeds readily in the presence Pd(II) complexes[1–5] to give cyclopentane derivatives **2a**, along with products of double bond migration **2b–c** (Scheme 1). In particular, cationic allyl palladium complexes have been shown to be effective catalysts for these cyclizations.[2,4a,b,5b,c] Complexes of Rh(I),[1,6] Ru(II)[7] and other transition metals[5c] also catalyze the cycloisomerization of dienes.



Scheme 1.

As part of a broader study on the cyclization of 1,6-enynes catalyzed by electrophilic transition-metal halides or complexes,[8,9] we had examined the cyclization of enynes bearing enol ethers by using Pd(II) or Au(III) as catalysts.[10] This type of enynes undergo methoxycyclization in methanol as solvent to form carbo- and heterocycles with an acetal functional group.[10] We decided to assay substrates of type **3** in which an electron-rich enol ether could react as a nucleophile in an intramolecular reaction with a (η^2-alkene)palladium complex **4** to form 6-membered rings (Scheme 2). However, we have observed that $PdCl_2$ catalyzes the selective isomerization-Claisen rearrangement



Scheme 2.

of substrates of type **3** to give γ,δ-unsaturated ketones **5**. To a more limited extend, Au(III) and Ir(III) also catalyze this rearrangement.

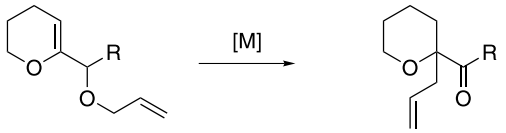
2. Results and discussion

We first examined the reaction of **6** and **7**, readily available by addition of 2-tetrahydropyranyl-lithium to benzaldehyde or 2-naphtaldehyde followed by alkylation of the secondary alcohol with allyl bromide and NaH in DMF. Reaction of **6** with $[Pd(MeCN)_2Cl_2]$ in toluene at 110 °C affords α-allyl ketone **8** in moderate yield (Table 1, entry 1). The reaction does not proceed satisfactorily with this catalyst in other solvents such as THF, CH_2Cl_2, or 1,2-dichloroethane. Decomposition was observed in the presence of a cationic complex formed in situ from $Pd(MeCN)_2Cl_2$ and $AgBF_4$ (Table 1, entry 2), while no reaction takes place with Pd(II) complexes bearing PPh_3 or $AsPh_3$ as ligands (Table 1, entries 3–5). Similarly, a Pd(0) catalyst is ineffective (Table 1, entry 6). The best results are obtained by simply using $PdCl_2$ in refluxing toluene (Table 1, entries 7 and 8). Lower conversions were realized in polar chlorinated solvents (Table 1, entries 9 and 10). The reaction also proceeds with $AuCl_3$ (Table 1, entry 11) and $IrCl_3$ (Table 1,

Keywords: Claisen rearrangement; Palladium; Isomerization; Enol ethers.
* Corresponding author. Tel.: +3491-977920218; fax: +3491-977920225; e-mail: aechavarren@iciq.es

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.06.150

Table 1. Isomerization-Claisen rearrangement of substrates **6–7**



6 R = Ph
7 R = 2-Napth

8 R = Ph
9 R = 2-Napth

Entry	Substrate	Catalyst (mol%)	Reaction conditions	Product (yield)
1	**6**	$[Pd(MeCN)_2Cl_2]$ (10)	Toluene, 110 °C, 17 h	**8** (50%)
2	**6**	$[Pd(MeCN)_2Cl_2]$ (10)+$AgBF_4$ (10)	Toluene, 110 °C, 17 h	—[a]
3	**6**	$[Pd(PPh_3)_2Cl_2]$ (10)	Toluene, 110 °C, 17 h	n.r.[b]
4	**6**	$[Pd(PPh_3)_2Cl_2]$ (10)+$AgBF_4$ (10)	Toluene, 110 °C, 17 h	—[a]
5	**6**	$[Pd(AsPh_3)_2Cl_2]$ (10)	Toluene, 110 °C, 17 h	n.r.[b]
6	**6**	$[Pd_2(dba)_3 \cdot dba]$ (10)	Toluene, 110 °C, 17 h	n.r.[b]
7	**6**	$PdCl_2$ (10)	Toluene, 110 °C, 17 h	**8** (84%)
8	**7**	$PdCl_2$ (10)	Toluene, 110 °C, 12 h	**9** (93%)
9	**6**	$PdCl_2$ (10)	CH_2Cl_2, 40 °C, 17 h	**8** (10%)
10	**6**	$PdCl_2$ (10)	1,2-Dichloroethane 83 °C, 17 h	**8** (10%)
11	**6**	$AuCl_3$ (5)	Toluene, 80 °C, 4 h	**8** (57%)
12	**6**	$AuCl_3$ (5)	CH_3NO_2, 80 °C, 14 h	—[a]
13	**7**	$IrCl_3$ (10)	Toluene, 110 °C, 12 h	**9** (70%)
14	**6**	$PtCl_2$ (5)	Toluene, 110 °C, 17 h	n.r.[b]
15	**6**	$FeCl_3$ (5)	Toluene, 0 °C, 1 h	—[a]
16	**6**	$RhCl_3$ (5)	Toluene, 80 °C, 20 h	n.r.[b]
17	**6**	$[Rh(PPh_3)_3Cl]$ (5)	Toluene, 80 °C, 20 h	n.r.[b]
18	**6**	$[Rh(OAc)_2]_2$ (5)	Toluene, 80 °C, 20 h	n.r.[b]
19	**6**	$[Rh(COD)_2$-μ-$Cl_2]$ (5)	Toluene, 80 °C, 20 h	n.r.[b]

[a] Decomposition of **6** was observed.
[b] Starting material was recovered.

entry 13), although the yields were lower and the reactions were not as clean as those catalyzed by $PdCl_2$. On the other hand, $PtCl_2$ or $FeCl_3$ gave no positive results (Table 1, entries 14 and 15). $RhCl_3$ and other rhodium complexes also failed to promote the rearrangement of **6** (Table 1, entries 16–19).

Acyclic derivatives **10** and **12** undergo rearrangement to give ketones **11** and **13**, respectively (Table 2, entries 1 and 2). Similarly, 2,3-dihydrofuranyl derivative **14** provides **15** in good yield (Table 2, entry 3). However, under identical conditions, substrate **16** gives a 1:1 mixture of **17a** and **17b** (Table 2, entry 4). The formation of **17b** by double-bond migration of **17a** is somewhat puzzling, since no alkene isomerizations were detected in similar compounds **8**, **9**, **11**, or **13** under these reaction conditions.

Substrates **18** and **20** (4:1 *E*/*Z* mixture) rearrange with moderate to good stereoselectivities to give **19** and **21**, respectively (Table 2, entries 5 and 6). Importantly, the reactions proceed with clean allylic inversion. Similarly, prenyl derivative **22** suffers allylic inversion to give exclusively **23**, albeit in modest yield (Table 2, entry 7). A substrate with an alkyl substituent α to the allylic oxygen failed to react under the standard conditions (Table 2, entry 8).

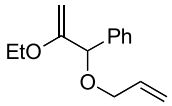
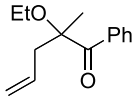
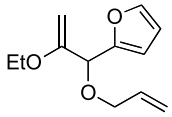
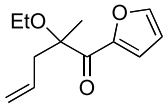
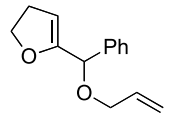
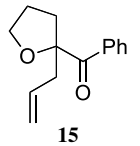
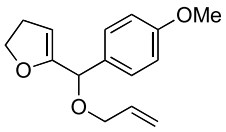
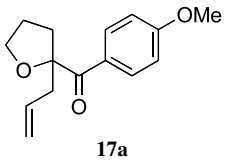
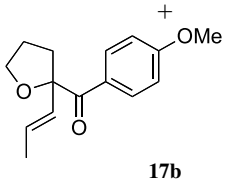
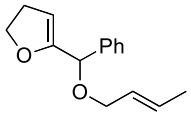
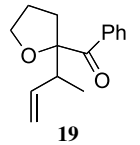
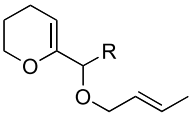
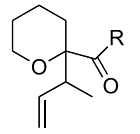
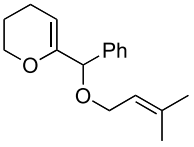
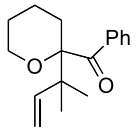
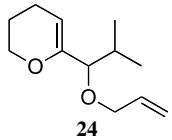
These results are consistent with the mechanism shown in Scheme 3. Accordingly, Pd(II) is probably involved in the selective, formal 1,2-H migration of **3** to give vinyl allyl ether intermediate **25**, which subsequently undergoes a Claisen rearrangement.[11] Although we cannot exclude a thermal [3,3] sigmatropic process for this second step, the known rate-acceleration of this reaction in the presence of Pd(II)[12,13] strongly suggest that $PdCl_2$ catalyzes this Claisen rearrangement.

Enyne **26**, in which a 2-butynyl group has replaced the allyl substituent, reacts with $AuCl_3$ in toluene to give a mixture of allene **27** and tricycle **28**[14] (Scheme 4). In this case, no reaction was observed with $PdCl_2$. Allene **27** results from a 1,2-H migration similar to that shown in Scheme 3 to form enol ether **29**, followed by a Claisen rearrangement.

A more functionalized substrate was prepared from TIPS-protected D-glucal (**30**)[15,16] (Scheme 5). Reaction of **30** with the 6 equiv. of *t*-Buli gives the 2-lithiated species,[15,16] which reacted with benzaldehyde to give **31** in 29% yield, along with recovered **30**. Under these conditions, **31** was isolated as a 6.5:1 mixture of epimers at the new stereocenter.[17] Allylation of the secondary alcohol of **31** furnished **32** (87%), whose reaction with $PdCl_2$ under the standard conditions was somewhat sluggish, although finally proceeded with a higher amount of catalyst to provide **33** in 78% yield as a 5.4:1 mixture of C-1 epimers. The configuration of the major epimer **33** was assigned on the basis of a NOESY experiment. In this case, in addition to the expected rearrangement, elimination of the C-4 silyloxy substituent has taken place.

The elimination of the substituent at C-4 indicates that, instead of a formal 1,2-H migration, the reaction is initiated

Table 2. Palladium-catalyzed isomerization-Claisen rearrangement of substrates **6–7**[a]

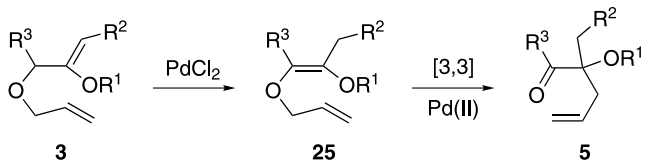
Entry	Substrate	Product	Isomeric ratio	Yield (%)
1	 **10**	 **11**	—	76
2	 **12**	 **13**	—	80
3	 **14**	 **15**	—	88
4	 **16**	 **17a** +  **17b**	1:1	70
5	 **18** (4:1 *E*/*Z*)	 **19**	2.5:1	88
6	 **20** R=2-Napth(4:1 *E*/*Z*)	 **21** R=2-Napth	6:1	80
7[b]	 **22**	 **23**	—	46
8	 **24**	n.r.[c]	—	—

[a] Reactions carried out with $PdCl_2$ (10 mol%) in toluene at 110 °C for 12 h.
[b] 20 mol% $PdCl_2$.
[c] Starting material was recovered.

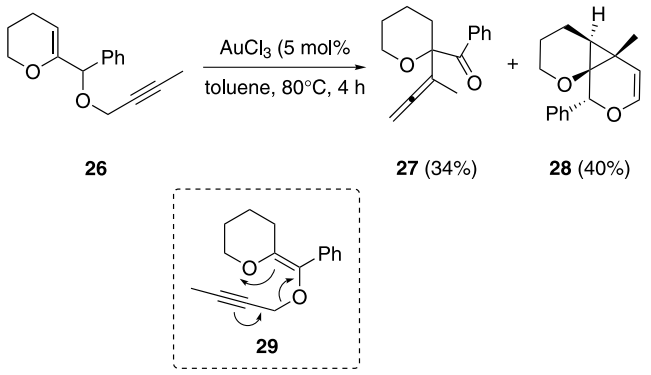
by formation of a (η^3-allyl)palladium complex **34** (Scheme 6), followed by a regioselective proton elimination[18] to give diene **35** (or its *Z* diastereomer),[19] which subsequently undergoes Claisen rearrangement.

3. Conclusion

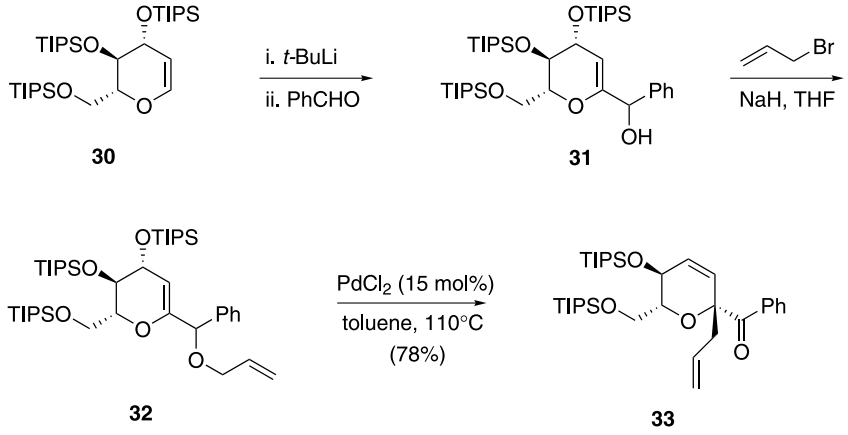
Diallyl ethers bearing an enol ether **3** undergo selective isomerization by formal 1,2-H migration at the more



Scheme 3.



Scheme 4.



Scheme 5.

substituted allyl in the presence of Pd(II), followed by Claisen rearrangement to give α-allyl α-alkoxy ketones **5**. This rearrangement is also promoted by $AuCl_3$ and $IrCl_3$, although the yields are lower with these catalysts. This reaction is regiocomplementary to that recently described by Nelson et al. using cationic Ir(I) complexes, which proceeds by initial formal 1,2-H migration at the least substituted allyl (Scheme 7).[20,21]

This palladium-catalyzed transformation allows for the synthesis of functionalized ketones **5** via intermediates **3**, which are easily assembled by the addition of the α-lithium derivatives of enol ethers to aldehydes, followed by allylation of the resulting secondary alcohols (Scheme 8).

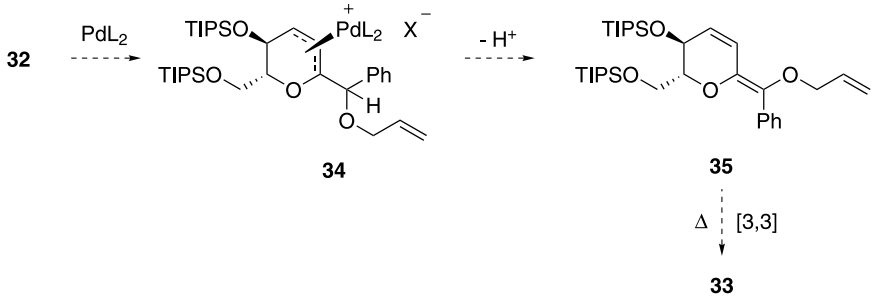
4. Experimental

4.1. General

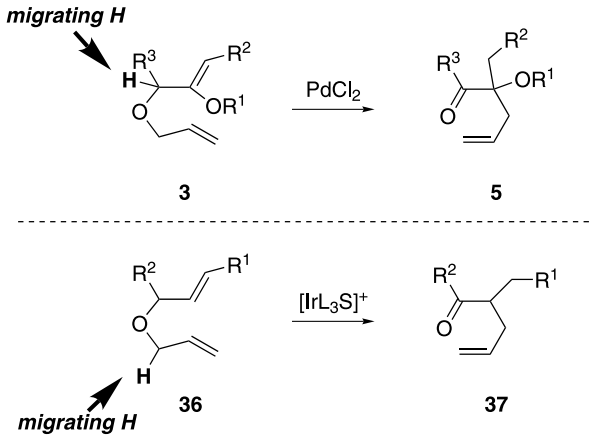
All reactions were carried out under Ar in dry freshly distilled solvents under anhydrous conditions. THF was dried by using 4 Å molecular sieves. Toluene and DMF were distilled from sodium/benzophenone and CaH_2 respectively and were kept with 4 Å. Aldehydes were distilled from $NaHCO_3$ under Ar or reduced pressure depending on the boiling points.

Thin layer chromatography was carried out using TLC-aluminium sheets with 0.2 mm of silica gel (Merk GF_{234}). Chromatography purifications were carried out using flash grade silica gel (SDS Chromatogel 60 ACC, 40–60 μm) with distilled solvents.

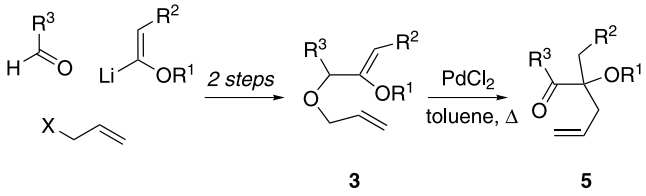
NMR spectra were recorded at 23 °C on a Bruker AC-300 and Bruker AMX-500 apparatus. Mass spectra (FAB, EI) were recorded on a HP1100MSD spectrometer. Elemental



Scheme 6.



Scheme 7.



Scheme 8.

analyses were performed on a LECO CHNS 932 microanalyzer. Melting points were determined using a Gallenkamp melting point apparatus.

4.2. General procedure for the preparation of benzylic alcohols

A solution containing 1.2 equiv. of the corresponding enol ether in dried THF (volume of THF necessary to make the concentration of enol ether 2 M) was cooled at −78 °C and 1 equiv. of *t*-BuLi was added dropwise. The mixture was warmed up to −5 °C and then stirred at that temperature for 5 h. The solution was then cooled at −78 °C and 1 equiv. of the aldehyde was slowly added. The mixture was warmed up to room temperature overnight and then quenched with 4 mL of a saturated NH_4Cl solution. The mixture was extracted with 3×20 mL of Et_2O and the combined organic layers were dried over $MgSO_4$. Solvent was removed under reduced pressure and the residue was purified by silica gel chromatography (15:1 hexane/EtOAc mixture containing 5% Et_3N was used as eluent). Reactions were carried out in a 30–50 mmol scale.

4.2.1. (5,6-Dihydro-4*H*-pyran-2-yl)(phenyl)methanol.[22] Yield: 66%. Yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.75–1.83 (m, 2H), 2.01–2.07 (m, 2H), 2.58 (d, J=5.3 Hz, 1H), 3.97–4.00 (m, 2H), 4.77 (t, J=3.6 Hz, 1H), 5.02 (d, J=4.8 Hz, 1H), 7.24–7.44 (m, 5H). ^{13}C NMR ($CDCl_3$, J=75 MHz) δ 20.64, 22.94, 67.17, 75.12, 98.79, 127.22, 128.25, 128.86, 141.94, 154.99.

4.2.2. (5,6-Dihydro-4*H*-pyran-2-yl)(naphthalen-2-yl)methanol. Yield: 75%. Pale yellow solid; mp 61–63 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.82–1.90 (m, 2H), 2.10–2.14 (m, 2H), 2.75 (bs, 1H), 4.06 (t, J=8.9 Hz, 2H), 4.88 (t, J=3.6 Hz, 1H), 5.26 (s, 1H), 7.55–7.49 (m, 2H), 7.59 (dd, J=8.5, 1.6 Hz, 1H), 7.86–7.91 (m, 3H), 7.95 (d, J=0.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz, DEPT) δ 20.66 (CH_2), 22.98 (CH_2), 67.24 (CH_2), 75.27 (CH), 99.00 (CH), 125.44 (CH), 125.99 (CH), 126.47 (CH), 126.64 (CH), 128.31 (CH), 128.51 (CH), 128.79 (CH), 133.69 (C), 133.92 (C), 139.44 (C), 155.08 (C). EI-HRMS Calcd for $C_{16}H_{16}O_2$: 240.1150. Found: 240.1147.

4.2.3. 2-Ethoxy-1-phenylprop-2-en-1-ol. Yield: 27%. Pale yellow solid; mp 48–50 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.32 (t, J=7.3 Hz, 3H), 2.58 (d, J=5.3 Hz, 1H), 3.82 (q, J=7.3 Hz, 2H), 4.13 (d, J=2.4 Hz, 1H), 4.23 (d, J=2.4 Hz, 1H), 5.16 (d, J=5.3 Hz, 1H), 7.50–7.31 (m, 5H). ^{13}C NMR ($CDCl_3$, J=75 MHz) δ 14.92, 63.89, 75.52, 83.32, 127.20, 128.33, 128.86, 142.67, 163.31. EI-HRMS Calcd for $C_{11}H_{13}O_2$ (M^+-1): 177.0920. Found: 177.0921.

4.2.4. 2-Ethoxy-1-(furan-2-yl)prop-2-en-1-ol. Yield: 53%. Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.33 (t, J=7.1 Hz, 3H), 2.83 (d, J=6.1 Hz, 1H), 3.85 (q, J=7.1 Hz, 2H), 4.15 (d, J=2.6 Hz, 1H), 4.29 (d, J=2.6 Hz, 1H), 5.15 (d, J=6.1 Hz, 1H), 6.33 (dt, J=3.2, 0.8 Hz, 1H), 6.36 (dd, J=3.2, 1.8 Hz, 1H), 7.40 (dd, J=1.8, 0.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, J=75 MHz, DEPT) δ 14.89 (CH_3), 64.02 (CH_2), 69.64 (CH), 83.55 (CH_2), 107.72 (CH), 110.90 (CH), 142.78 (CH), 154.94 (C), 161.12 (C). Anal. Calcd for $C_9H_{12}O_2$: C, 64.27; H, 7.19. Found: C, 64.06; H, 7.19.

4.2.5. (4,5-Dihydrofuran-2-yl)(phenyl)methanol. Yield: 60%. Yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.65 (d, J=4.4 Hz, 1H), 2.64 (tdd, J=9.3, 2.3, 1.6 Hz, 2H), 4.37 (t, J=9.3 Hz, 2H), 4.78 (td, J=2.4, 0.8 Hz, 1H), 5.25 (brs, 1H), 7.38–7.27 (m, 3H), 7.43 (dd, J=7.9, 1.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, J=75 MHz) δ 29.78, 70.22, 70.53, 96.89, 126.56, 127.93, 128.26, 140.56, 158.88. Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. EI-HRMS Calcd for $C_{11}H_{12}O_2$: 176.0837. Found: 176.0833.

4.2.6. (4,5-Dihydrofuran-2-yl)(4-methoxyphenyl)methanol. Yield: 83%. Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.68 (tdd, J=9.3, 2.8, 1.6 Hz, 2H), 3.84 (s, 3H), 4.44 (t, J=9.3 Hz, 2H), 4.83 (td, J=2.8, 1.2 Hz, 1H), 5.25 (brs, 1H), 6.93 (d, J=8.9 Hz, 2H), 7.39 (d, J=8.9 Hz, 2H) (OH signal was not observed). ^{13}C NMR ($CDCl_3$, J=75 MHz, DEPT) δ 31.23 (CH_3), 56.69 (CH_3), 70.61 (CH), 71.28 (CH_2), 98.11 (CH), 115.18 (CH), 129.34 (CH), 134.25 (C), 160.55 (C), 160.80 (C). EI-HRMS Calcd for $C_{12}H_{14}O_3$: 206.0943. Found: 206.0945. Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.58; H, 6.77.

4.2.7. (2*S*,3*R*,4*S*)-3,4-Dihydro-2-(triisopropylsilyloxymethyl)-2*H*-pyran-3,4-bistriisopropilsilyloxy-6-phenylmethanol (31). Yield: 29%, 6.5:1 mixture of epimers at the carbinol center. Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.06–1.09 (m, 63H), 2.57 (d, J=4.4 Hz, 1H), 3.83 (dd, J=11.3, 4.0 Hz, 1H), 4.01–4.08 (m, 3H), 4.31–4.36 (m, 1H), 4.89–4.91 (m, 1H), 5.15 (d, J=4.0 Hz, 1H), 7.30–7.38 (m, 3H), 7.47 (dd, J=8.1, 2.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, J=75 MHz, DEPT) δ 12.62 (CH), 12.95 (CH), 13.07 (CH), 18.69 (CH_3), 18.73 (CH_3), 18.77 (CH_3), 62.33 (CH_2), 66.60 (CH), 70.62 (CH), 74.56 (CH), 81.94 (CH), 97.80 (CH), 127.84 (CH), 128.38 (CH), 128.74 (CH), 141.25 (C), 153.87

(C). MALDI-HRMS (dithranol-NaI matrix) Calcd for $C_{40}H_{76}O_3NaSi_3$: 743.4898. Found: 743.4903.

4.3. General procedure for the alkylation of benzylic alcohols.

A solution containing 1.2 equiv. of NaH (60% in mineral oil) in dried DMF (volume of DMF necessary to make the concentration of NaH 1.0 M) was cooled at 0 °C. A 1 equiv. solution of the corresponding benzylic alcohol in DMF (volume of DMF necessary to make the concentration of the alcohol 1.0 M) was added dropwise. The mixture was warmed up to room temperature and stirred for 20 min and 1 equiv. of the alkylating agent was added. The reaction was stirred at room temperature for 4 h and then quenched with a water-ice mixture and diluted with Et_2O. The organic layer is washed several times with water and then dried over $MgSO_4$. Solvent was removed under reduced pressure and the residue was purified by silica gel chromatography (100:1 hexane/EtOAc containing 5% Et_3N was used as eluent). All reactions were carried out in a 5–15 mmol scale.

4.3.1. 6-[(Allyloxy)(phenyl)methyl]-3,4-dihydro-2*H*-pyran (6). Yield: 88%. Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.76–1.82 (m, 2H), 2.02–2.08 (m, 2H), 3.90–4.09 (m, 4H), 4.66 (s, 1H), 4.86 (t, J=3.6 Hz, 1H), 5.17 (dc, J=10.5, 1.2 Hz, 1H), 5.27 (dc, J=17.4, 2.0 Hz, 1H), 5.94 (ddt, J=17.4, 10.5, 5.7 Hz, 1H), 7.23–7.42 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.61, 140.50, 135.48, 128.73, 128.7, 127.75, 117.66, 99.70, 81.68, 70.33, 67.04, 22.98, 22.78. EI-HMRS Calcd for $C_{15}H_{18}O_2$: 230.1307. Found: 230.1300. Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.03, H, 8.14.

4.3.2. 6-[(Allyloxy)(naphthalen-2-yl]methyl)-3,4-dihydro-2*H*-pyran (7). Yield: 74%). Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.86 (q, J=6.0 Hz, 2H), 2.14 (td, J=6.0, 3.8 Hz, 2H), 4.01–4.12 (m, 2H), 4.14–4.23 (m, 2H), 4.93 (s, 1H), 5.02 (t, J=3.4 Hz, 1H), 5.28 (dq, J=10.1, 1.4 Hz, 1H), 5.39 (dq, J=17.0, 1.6 Hz, 1H), 6.00–6.14 (m, 1H), 7.49–7.56 (m, 2H), 7.63 (ddd, J=8.5, 1.6, 1.2 Hz, 1H), 7.88–7.93 (m, 3H), 7.96 (bs, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz, DEPT) δ 20.82 (CH_3), 23.00 (CH_3), 67.09 (CH_2), 70.40 (CH_2), 81.85 (CH), 99.79 (CH), 117.76 (CH_2), 125.84 (CH), 126.40 (CH), 126.55 (CH), 126.73 (CH), 128.30 (CH), 128.45 (CH), 128.77 (CH), 133.77 (C), 133.91 (C), 135.50 (CH), 138.04 (C), 153.70 (C). EI-HMRS Calcd for $C_{19}H_{20}O_2$: 280.1463. Found: 280.1469.

4.3.3. 1-[1-(Allyloxy)-2-ethoxyallyl]benzene (10). Yield: 73%. Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.29 (t, J=6.9 Hz, 3H), 3.78 (tdd, J=9.7, 7.0, 2.4 Hz, 2H), 4.10 (cdt, J=12.9, 5.7, 1.6 Hz, 2H), 4.14 (d, J=2.0 Hz, 1H), 4.38 (d, J=2.0 Hz, 1H), 4.79 (s, 1H), 5.25 (dc, J=10.5, 1.2 Hz, 1H), 5.36 (dc, J=17.4, 1.6 Hz, 1H), 6.01 (ddt, J=17.4, 10.5, 5.7 Hz, 1H), 7.50–7.29 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz, DEPT) δ 14.92 (CH_3), 63.72 (CH_2), 70.47 (CH_2), 81.93 (CH), 83.33 (CH_2), 117.64 (CH_2), 127.78 (CH), 128.26 (CH), 128.73 (CH), 135.42 (CH), 140.75 (C), 162.17 (C). EI-HMRS Calcd for $C_{14}H_{18}O_2$: 218.1307. Found: 218.1303.

4.3.4. 2-[1-(Allyloxy)-2-ethoxyallyl]furan (12). Yield: 62%. Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.33 (t, J=7.1 Hz, 3H), 3.89–3.80 (m, 2H), 4.17–4.04 (m, 2H), 4.21 (d, J=2.2 Hz, 1H), 4.43 (d, J=2.2 Hz, 1H), 4.85 (s, 1H), 5.24 (dc, J=11.3, 1.7 Hz, 1H), 5.35 (dc, J=17.4, 1.7 Hz, 1H), 5.98 (ddt, J=17.4, 11.3, 5.7 Hz, 1H), 6.36–6.40 (m, 2H), 7.42 (dd, J=1.6, 1.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz, DEPT) δ 14.91 (CH_3), 63.85 (CH_2), 70.55 (CH_2), 75.49 (CH), 84.11 (CH_2), 108.87 (CH), 110.77 (CH), 118.01 (CH_2), 135.07 (CH), 142.90 (CH), 153.56 (C), 159.83 (C). EI-HMRS Calcd for $C_{12}H_{16}O_3$: 208.1099. Found: 208.1094.

4.3.5. 5-[(Allyloxy)(phenyl)methyl]-2,3-dihydrofuran (14). Yield: 81%. Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.62 (dddd, J=9.3, 9.3, 2.6, 1.4 Hz, 2H), 4.01 (ddd, J=5.7, 1.6, 1.2 Hz, 2H), 4.36 (td, J=9.3, 2.8 Hz, 2H), 4.82 (td, J=2.4, 0.8 Hz, 1H), 4.92 (bs, 1H), 5.18 (dq, J=10.1, 1.2 Hz, 1H), 5.27 (dq, J=17.0, 1.6 Hz, 1H), 5.93 (ddt, J=17.0, 10.1, 5.7 Hz, 1H), 7.43–7.25 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 30.39 (CH_2), 70.52 (CH_2), 71.19 (CH_2), 77.13 (CH), 98.74 (CH), 118.04 (CH_2), 127.94 (CH), 128.64 (CH), 128.95 (CH), 135.17 (CH), 139.63 (C), 158.20 (C). EI-HMRS Calcd for $C_{14}H_{16}O_2$: 216.1150. Found: 216.1143.

4.3.6. 5-[(Allyloxy)(4-methoxyphenyl)methyl]-2,3-dihydrofuran (16). Yield: 83%. Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.63–2.70 (m, 2H), 3.85 (s, 3H), 4.03 (d, J=5.7 Hz, 2H), 4.41 (td, J=3.6, 9.7 Hz, 2H), 4.87 (td, J=2.4, 0.8 Hz, 1H), 4.91 (d, J=0.8 Hz, 1H), 5.22 (dq, J=10.1, 1.6 Hz, 1H), 5.31 (dq, J=7.0, 1.6 Hz, 1H), 5.97 (ddt, J=10.1, 7.0, 5.7 Hz, 1H), 6.93 (dd, J=8.5, 2.0 Hz, 2H), 7.38 (dd, J=8.5, 2.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz, DEPT) δ 30.37 (CH_2), 55.89 (CH_3), 70.33 (CH_2), 71.17 (CH_2), 76.80 (CH), 98.33 (CH), 114.34 (CH), 117.88 (CH_2), 129.23 (CH), 131.77 (C), 135.28 (CH), 158.49 (C), 160.02 (C). EI-HMRS Calcd for $C_{15}H_{18}O_3$: 246.1256. Found: 246.1255.

4.3.7. 5-[(But-2-enyloxy)(phenyl)methyl]-2,3-dihydrofuran (18). Yield: 38%. Colorless oil. 4:1 *E*/*Z*. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.62 (dt, J=5.1, 0.8 Hz, 3H, *Z* isomer), 1.75 (dc, J=4.7, 1.1 Hz, 3H, *E* isomer), 2.62–2.70 (m, 2H, *E* and *Z* isomers), 3.97–4.14 (m, 2H, *E* and *Z* isomers), 4.34–4.48 (m, 2H, *E* and *Z* isomers), 4.85 (td, J=2.6, 1.0 Hz, 1H, *E* and *Z* isomers), 4.96 (d, J=1 Hz, 1H, *E* and *Z* isomers), 5.60–5.74 (m, 2H, *E* and *Z* isomers), 7.30–7.48 (m, 5H, *E* and *Z* isomers). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (only signals for the major *E* isomer) 13.85, 18.44, 30.38, 64.86, 70.24, 71.13, 76.91, 77.09, 98.59, 98.69, 127.40, 127.97, 128.03, 128.54, 128.57, 128.82, 128.89, 130.48, 139.81, 158.39. EI-HMRS Calcd for $C_{15}H_{17}O_2$ (M^+-1): 229.1229. Found: 229.1223. Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.25, H, 7.83.

4.3.8. 6-[(But-2-enyloxy)(naphthalen-2-yl)methyl]-3,4-dihydro-2*H*-pyran (20). Yield: 69%. Yellow oil. 4:1 *E*/*Z*. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.63 (dt, J=5.1, 0.9 Hz, 3H, *Z* isomer), 1.74 (dq, J=3.8, 0.9 Hz, 3H, *E* isomer), 1.81 (m, 2H, *E* and *Z* isomers), 2.09 (m, 2H, *E* and *Z* isomers), 4.19–3.93 (m, 4H, *E* and *Z* isomers), 4.87 (s, 1H, *E* and *Z* isomers), 4.95 (t, J=3.6 Hz, 1H, *E* and *Z* isomers), 5.80–5.63 (m, 2H, *E* and *Z* isomers), 7.59–7.44 (m, 2H, *E* and *Z* isomers), 7.57 (dd, J=8.7, 1.8 Hz, 1H, *E* and *Z* isomers),

7.91–7.82 (m, 4H, *E* and *Z* isomers). ^{13}C NMR ($CDCl_3$, 75 MHz, DEPT) δ (only signals for the major *E* isomer) 13.99 (CH_3, *Z* isomer), 18.57 (CH_3, *E* isomer), 20.85 (CH_2), 23.03 (CH_2), 64.82 (CH_2, *Z* isomer), 67.13 (CH_2, *E* isomer) 70.17 (CH_2, *E* isomer), 81.62 (CH, *E* isomer), 81.79 (CH, *Z* isomer), 99.82 (CH, *E* isomer), 99.95 (CH, *Z* isomer), 125.92 (CH), 126.38 (CH), 126.54 (CH), 126.76 (CH), 127.72 (CH), 128.28 (CH), 128.31 (CH), 128.45 (CH), 128.64 (CH, *Z* isomer), 128.77 (CH, *E* isomer), 130.29 (CH, *Z* isomer), 133.75 (C, *E* isomer), 133.91 (C, *E* isomer), 138.15 (C, *E* isomer), 153.80 (C, *E* isomer). EI-HMRS Calcd for $C_{20}H_{22}O_2$: 294.1620. Found: 294.1621.

4.3.9. 6-[(3-Methylbut-2-enyloxy)(phenyl)methyl]-3,4-dihydro-2*H*-pyran (22). Yield: 59%. Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.65 (d, J=1.2 Hz, 3H), 1.79 (d, J=1.2 Hz, 3H), 1.82–1.88 (m, 2H), 2.13–2.08 (m, 2H), 3.96–4.12 (m, 4H), 4.70 (s, 1H), 4.90 (t, J=3.6 Hz, 1H), 5.45 (tq, J=16.9, 1.2 Hz, 1H), 7.28–7.40 (m, 3H), 7.45–7.48 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz, DEPT) δ 18.72 (CH_3), 20.77 (CH_2), 22.99 (CH_2), 26.46 (CH_3), 65.96 (CH_2), 67.02 (CH_2), 81.56 (CH), 99.58 (CH), 121.97 (CH), 127.82 (CH), 128.07 (CH), 128.69 (CH), 137.40 (C), 140.77 (C), 153.83 (C). EI-HMRS Calcd for $C_{17}H_{21}O_2$ (M^+-1): 257.1540. Found: 257.1538.

4.3.10. 2-[1-(Allyloxy)-2-methylpropyl]-tetrahydro-2*H*-pyran (24). Yield: 72%. Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.82 (d, J=6.5 Hz, 3H), 0.95 (d, J=6.5 Hz, 3H), 1.74–2.06 (m, 5H), 3.08 (d, J=8.1 Hz, 1H), 3.79 (dddd, J=14.9, 6.5, 1.6, 1.2 Hz, 1H), 3.90–4.10 (m, 3H), 4.65 (t, J=4.0 Hz, 1H), 5.11 (m, 1H), 5.23 (ddd, J=17.4, 3.7, 1.6 Hz, 1H), 5.88 (dddd, J=17.4, 10.5, 6.5, 5.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz, DEPT) δ 19.83 (CH_3), 19.88 (CH_3), 20.80 (CH_2), 23.20 (CH_2), 31.06 (CH), 66.70 (CH_2), 70.08 (CH_2), 86.59 (CH), 100.45 (CH), 117.04 (CH_2); 136.05 (CH), 152.13 (C). EI-HMRS Calcd for $C_{12}H_{20}O_2$: 196.1463. Found: 196.1455.

4.3.11. 6-[(But-2-ynyloxy)(phenyl)methyl]-3,4-dihydro-2*H*-pyran (26). Yield: 63%. White vitreous solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.75–1.79 (m, 2H), 1.84 (t, J=2.4 Hz, 3H), 2.04–2.09 (m, 2H), 3.91–4.03 (m, 2H), 4.10 (dc, J=15.4, 2.4 Hz, 1H), 4.17 (dc, J=15.4, 2.4 Hz, 1H), 4.89 (s, 1H), 4.91 (t, J=3.8 Hz, 1H), 7.24–7.36 (m, 3H), 7.40–7.44 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.78, 140.42, 128.73, 128.56, 128.12, 113.59, 74.07, 69.99, 64.87, 25.63, 22.95, 21.95, 16.15, 13.05. EI-HMRS Calcd for $C_{16}H_{18}O_2$: 242.1301. Found: 242.1296.

4.3.12. (2*S*,3*R*,4*S*)-6-[(Allyloxy)(phenyl)methyl]-3,4-bis-(triisopropylsilyloxy)-3,4-dihydro-2-(triisopropylsilyl-oxymethyl)-2*H*-pyran (32). Yield: 87%. Colorless oil. This product was purified by flash chromatography with hexane containing 5% Et_3N. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.98–1.08 (m, 63H), 3.86 (d, J=6.1 Hz, 2H), 3.70–4.27 (m, 5H), 4.72 (s, 1H), 5.15–5.20 (m, 2H), 5.30 (ddt, J=17.4, 3.4, 1.7 Hz, 1H), 5.95 (dddd, J=17.4, 10.5, 5.9, 5.1 Hz, 1H), 7.21–7.29 (m, 3H), 7.43 (dd, J=7.7, 1.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz, DEPT) δ 12.63 (CH), 13.02 (2×CH), 18.68 (CH_3), 18.79 (CH_3), 18.85 (CH_3), 62.71 (CH_2), 66.65 (CH), 70.53 (CH), 70.58 (CH_2), 81.24 (CH), 81.80 (CH), 97.86 (CH), 117.34 (CH_2), 127.64 (CH), 128.14 (CH), 128.59 (CH), 135.48 (CH), 140.39 (C), 152.27 (C). MALDI-HRMS (dithranol-NaI matrix) Calcd for $C_{43}H_{80}O_5NaSi_3$: 783.5211. Found: 783.5209.

4.4. General procedure for the isomerization-Claisen rearrangement

A mixture of the di-allylic ether (1 equiv.) and $PdCl_2$ (0.1 equiv.) was dissolved in dried toluene (volume of toluene necessary to make the concentration of the substrate 0.05 M). The solution was refluxed for 14 h and then filtered through a short path of Celite. The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography (100:1 hexane/EtOAc containing 5% Et_3N as eluent) to yield the corresponding ketones. Reactions were carried out in a 0.3–0.8 mmol scale.

4.4.1. (2-Allyltetrahydro-2*H*-pyran-2-yl)(phenyl)methanone (8). Yield: 84%. Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.38–1.63 (m, 4H), 1.68–1.74 (m, 1H), 2.35–2.44 (m, 1H), 2.56–2.70 (m, 2H), 3.29–3.38 (m, 1H), 3.78–3.85 (m, 1H), 4.98 (ddd, J=17.2, 2.0, 1.4 Hz, 1H), 5.05 (ddt, J=10.1, 2.0, 1.0 Hz, 1H), 5.71 (ddt, J=17.2, 10.1, 7.4 Hz, 1H), 7.42 (m, 2H), 7.54 (tt, J=7.3, 1.6 Hz, 1H), 8.30 (dt, J=7.3, 1.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz, DEPT) δ 20.26 (CH_2), 25.85 (CH_2), 32.07 (CH_2), 45.37 (CH_2), 66.37 (CH_2), 86.22 (C), 119.33 (CH_2), 128.93 (CH), 130.38 (CH), 132.57 (CH), 133.42 (CH), 136.34 (C), 203.97 (C). FAB-HRMS Calcd for $C_{15}H_{19}O_2$ (M^++1): 231.1385. Found: 231.1378.

4.4.2. (2-Allyltetrahydro-2*H*-pyran-2-yl)(naphthalen-2-yl)methanone (9). Yield: 93%. Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.46–1.81 (m, 5H), 2.49–2.55 (m, 1H), 2.74–2.78 (m, 2H), 3.43 (td, J=11.7, 2.4 Hz, 1H), 3.90 (dq, J=11.7, 2.0 Hz, 1H), 5.01 (c, J=1.6 Hz, 1H), 5.06–5.13 (m, 1H), 5.80 (ddt, J=17.4, 10.1, 7.3 Hz, 1H), 7.55–7.66 (m, 2H), 7.91 (dd, J=8.5, 2.0 Hz, 2H), 8.03 (d, J=8.9 Hz, 1H), 8.31 (dd, J=8.9, 1.6 Hz, 1H), 9.06 (d, J=1.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.89, 25.89, 32.18, 45.71, 66.49, 86.46, 119.37, 126.21, 127.07, 128.24, 128.53, 129.03, 130.64, 132.13, 132.59, 133.24, 133.54, 136.05, 203.73. EI-HRMS Calcd for $C_{19}H_{20}O_2$: 280.1463. Found: 280.1468. Anal. Calcd for $C_{19}H_{20}O_2$: C, 81.40; H, 7.19. Found: C, 81.21; H, 7.34.

4.4.3. 2-Ethoxy-2-methyl-1-phenylpent-4-en-1-one (11). Yield: 76%. Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.11 (t, J=6.9 Hz, 3H), 2.47 (s, 3H), 2.60 (dd, J=14.2, 6.9 Hz, 1H), 2.75 (dd, J=14.2, 6.9 Hz, 1H), 3.32–3.42 (m, 2H), 5.02 (dd, J=3.2, 1.2 Hz, 1H), 5.07–5.12 (m, 1H), 5.69–5.83 (m, 1H), 7.43 (m, 2H), 7.54 (tt, J=7.3, 1.2 Hz, 1H), 8.30 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz, DEPT) δ 16.06, 22.67, 42.61, 60.71, 85.39, 119.28, 128.87, 130.74, 133.30, 133.44, 135.81, 204.11. EI-HRMS Calcd for $C_{14}H_{19}O_2$ (M^++1): 219.1385. Found: 219.1394. Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.31; H, 8.24.

4.4.4. 2-Ethoxy-1-(furan-2-yl)-2-methylpent-4-en-1-one (13). Yield: 80%. Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.20 (t, J=6.9 Hz, 3H), 1.47 (s, 3H), 2.58 (dddd, J=14.4, 6.7, 1.4, 1.2 Hz, 1H), 2.72 (dddd, J=14.4,

6.7, 1.4, 1.2 Hz, 1H), 3.47 (dc, J=8.7, 6.9 Hz, 1H), 3.38 (dc, J=8.7, 6.9 Hz, 1H), 5.06–5.15 (m, 2H), 5.77 (dddd, J=17.0, 10.5, 7.9, 6.9 Hz, 1H), 6.57 (dd, J=3.6, 1.6 Hz, 1H), 7.64 (dd, J=3.6, 0.8 Hz, 1H), 7.66 (dd, J=1.6, 0.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, J=75 MHz) δ 16.09, 21.97, 42.65, 60.49, 84.21, 112.45, 119.27, 121.07, 133.07, 147.24, 150.94, 192.92. Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.44. Found: C, 69.05; H, 7.64.

4.4.5. (2-Allyltetrahydrofuran-2-yl)(phenyl)methanone (15). Yield: 88%. Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.81–2.01 (m, 3H), 2.56–2.69 (m, 2H), 2.80 (dddd, J=13.8, 6.6, 1.6, 0.8 Hz, 1H), 3.77–3.85 (m, 1H), 3.99–4.06 (m, 1H), 5.04–5.10 (m, 1H, overlapped), 5.12 (ddt, J=7.7, 2.0, 0.8 Hz, 1H), 5.80 (dddd, J=17.0, 10.1, 7.7, 6.6 Hz, 1H), 7.46 (m, 2H), 7.56 (tt, J=7.3, 1.2 Hz, 1H), 8.19 (dd, J=8.1, 1.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz, DEPT) δ 26.02 (CH_2), 34.44 (CH_2), 43.95 (CH_2), 69.58 (CH_2), 92.62 (C), 119.36 (CH_2), 128.73 (CH), 130.68 (CH), 133.11 (CH), 133.22 (CH), 136.34 (C), 204.11 (C). EI-HRMS Calcd for $C_{14}H_{17}O_2$ (M^++1): 217.1229. Found: 217.1238. Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 78.16; H, 7.42.

4.4.6. (2-Allyltetrahydrofuran-2-yl)(4-methoxyphenyl)-methanone (17a) and [tetrahydro-2-[(*E*)-prop-1-enyl]-furan-2-yl](4-methoxyphenyl)methanone (17b). Yield: 70%. Colorless oil. The regioisomers are obtained as a 1:1 inseparable mixture. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.71 (dd, J=3.2, 1.6 Hz, 3H), 1.77–1.99 (m, 6H), 2.59–2.75 (m, 4H), 3.77–3.87 (m, 2H), 3.88 (s, 3H), 3.89 (s, 3H), 3.97–4.07 (m, 2H), 5.02–5.04 (m, 1H), 5.07–5.11 (m, 1H), 5.72–5.87 (m, 3H), 6.91 (dd, J=8.9, 2.0 Hz, 2H), 6.94 (dd, J=8.9, 2.0 Hz, 2H), 8.19 (dd, J=8.9, 2.0 Hz, 2H), 8.26 (dd, J=8.9, 2.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz, DEPT) δ 18.52 (CH_3), 25.55 (CH_2), 25.92 (CH_2), 34.32 (CH_2), 36.06 (CH_2), 44.13 (CH_2), 55.99 (2×CH_3), 69.35 (CH_2), 69.44 (CH_2), 92.51 (C), 92.73 (C), 113.75 (CH), 113.90 (CH), 119.13 (CH), 126.86 (CH), 128.57 (C), 129.00 (C), 133.27 (CH), 133.37 (CH), 133.52 (CH), 133.63 (CH), 163.67 (2× C), 199.90 (C), 202.16 (C). EI-HRMS Calcd for $C_{15}H_{18}O_3$: 246.1256. Found: 246.1252. Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.58; H, 7.51.

4.4.7. [2-(But-3-en-2-yl)-tetrahydrofuran-2-yl](phenyl)-methanone (19). Yield: 88%. Colorless oil. 2.5:1 mixture of diastereomers. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.91 (d, J=6.9 Hz, 3H, minor isomer), 1.10 (d, J=6.9 Hz, 3H, major isomer), 1.59–1.87 (m, 2H major isomer, 3H minor isomer), 1.99 (ddd, J=12.7, 8.1, 8.1 Hz, 1H, major isomer), 2.43 (ddd, J=12.7, 8.1, 5.7 Hz, 1H, major isomer), 2.60–2.51 (m, 1H, minor isomer), 2.86–2.99 (m, 1H, both isomers), 3.69–3.79 (m, 2H, major isomer), 3.88–3.91 (m, 2H, minor isomer), 4.93–5.13 (m, 2H, both isomers), 5.67 (ddd, J=17.2, 10.3, 8.7 Hz, 1H, major isomer), 6.02 (ddd, J=18.4, 10.7, 6.9 Hz, 1H, minor isomer), 7.38–7.44 (m, 3H, major isomer), 7.8–7.54 (m, 3H, minor isomer), 8.18 (d, J=7.1, 1.6 Hz, 2H, major isomer), 8.20 (dt, J=7.1, 1.6 Hz, 2H, minor isomer). ^{13}C NMR ($CDCl_3$, 75 MHz, DEPT) δ 14.86 (CH_3, minor isomer), 15.82 (CH_3, major isomer), 26.28 (CH_2, major and minor isomer), 30.56 (CH_2, minor isomer), 32.40 (CH_2, major isomer), 44.07 (CH, minor isomer), 45.84 (CH, major isomer), 69.88 (CH_2, minor isomer), 69.91 (CH_2, major isomer), 95.13 (C, major isomer), 95.48 (C, minor isomer), 116.48 (CH_2, minor isomer), 116.87 (CH_2, major isomer), 128.69 (CH, both isomers), 130.65 (CH, major isomer), 130.87 (CH, minor isomer), 132.90 (CH, major isomer), 132.99 (CH, minor isomer), 136.58 (C, minor isomer), 137.07 (C, major isomer), 139.20 (CH, minor isomer), 139.56 (CH, major isomer), 203.75 (C, minor isomer), 205.06 (C, major isomer). EI-HRMS Calcd for $C_{15}H_{19}O_2$ (M^++1): 231.1385. Found: 231.1386. Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.23; H, 7.79.

4.4.8. [2-(But-3-en-2-yl)-tetrahydro-2*H*-pyran-2-yl](naphthalen-2-yl)methanone (21). Yield: 80%. Colorless oil. 6:1 mixture of diastereomers. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.91 (d, J=7.1 Hz, 3H, minor isomer), 1.27 (d, J=6.9 Hz, 3H, major isomer), 1.45–1.81 (m, 5H, both isomers), 2.37–2.52 (m, 1H, major isomer), 2.40–2.48 (m, 1H, minor isomer), 2.92–3.07 (m, 1H, both isomers), 3.39–3.49 (m, 1H, both isomers), 3.91–4.00 (m, 1H, both isomers), 4.79 (ddd, J=17.2, 1.8, 1.2 Hz, 1H, major isomer), 4.96 (ddd, J=10.3, 1.8, 0.8 Hz, 1H, major isomer), 5.16 (ddd, J=17.2, 1.8, 1.6 Hz, 1H, minor isomer), 5.23 (ddd, J=10.5, 1.6, 1.4 Hz, 1H, minor isomer), 5.67 (ddd, J=17.2, 10.3, 8.5 Hz, 1H, major isomer), 6.26 (ddd, J=17.2, 10.5, 6.3 Hz, 1H, minor isomer), 7.40–7.54 (m, 4H, minor isomer), 7.55–7.67 (m, 4H, major isomer), 7.91 (d, J=8.7 Hz, 1H, major isomer), 8.03 (d, J=8.9 Hz, 1H, minor isomer), 8.32 (dd, J=8.9, 1.8 Hz, 1H, major isomer), 8.38 (dd, J=8.7, 1.8 Hz, 1H, minor isomer), 9.06 (d, J=1.8 Hz, 1H, major isomer), 9.13 (d, J=1.8 Hz, 1H, minor isomer). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.07 (minor isomer), 15.03 (major isomer), 20.74 (major isomer), 24.33 (minor isomer), 25.40 (minor isomer), 26.05 (major isomer), 26.84 (minor isomer), 27.13 (major isomer), 45.09 (minor isomer), 46.89 (major isomer), 65.52 (minor isomer), 66.74 (major isomer), 88.84 (minor isomer), 88.92 (major isomer), 116.67 (major isomer), 116.05 (minor isomer), 126.44 (minor isomer), 126.48 (major isomer), 126.99 (major isomer), 127.06 (minor isomer), 128.09 (minor isomer), 128.21 (major isomer), 128.46 (major isomer), 128.54 (minor isomer), 128.95 (major isomer), 129.04 (minor isomer), 130.66 (both isomers), 132.21 (major isomer), 132.26 (minor isomer), 133.27 (major isomer), 133.65 (minor isomer), 134.17 (major isomer), 135.97 (major isomer), 136.03 (minor isomer), 138.93 (major isomer), 139.46 (minor, isomer), 203.65 (minor isomer), 203.79 (major isomer) (one ^{13}C signal of the minor diastereomer is missing due to overlapping). FAB-HMRS Calcd for $C_{20}H_{21}O_2$ (M^+−1): 293.1542. Found: 293.1554.

4.4.9. [Tetrahydro-2-(2-methylbut-3-en-2-yl)-2*H*-pyran-2-yl](phenyl)methanone (23). Yield: 46%. Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88–0.23 (m, 1H), 1.08 (s, 3H), 1.10 (s, 3H), 1.16–1.50 (m, 3H), 1.60–1.75 (m, 1H), 2.40–2.47 (m, 1H), 3.35 (td, J=12.1, 2.7 Hz, 1H), 3.78–3.84 (m, 1H), 4.92–4.99 (m, 2H), 6.12 (dd, J=17.4, 11.3 Hz, 1H), 7.40 (m, 2H), 7.50 (tt, J=7.3, 1.4 Hz, 1H), 8.28 (dd, J=8.1, 1.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, J=75 MHz) δ 21.51 (2×C), 23.10, 24.72, 25.78, 30.06, 66.68, 91.46, 112.70, 128.69, 131.18, 132.96, 145.76, 198.18 (one

^{13}C signal is missed due to overlapping). FAB-HRMS Calcd for $C_{17}H_{21}O_2$ (M^+-1): 257.1542. Found: 257.1549.

4.4.10. [2-(Buta-2,3-dien-2-yl)-tetrahydro-2*H*-pyran-2-yl](phenyl)methanone (27). Yield: 34%. Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.52–1.69 (m, 4H), 1.74 (t, J= 3.1 Hz, 3H), 1.78–1.83 (m, 1H), 2.31–2.40 (m, 1H), 3.46–3.53 (m, 1H), 3.79–3.83 (m, 1H), 4.84 (m, 2H), 7.44 (dd, J=8.7, 8.5 Hz, 2H), 7.55 (t, J=8.5 Hz, 1H), 8.22 (d, J= 8.7 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz, DEPT) δ 14.30 (CH_3), 20.27 (CH_2), 25.09 (CH_2), 31.13 (CH_2), 64.98 (CH_2), 77.28 (CH_2), 84.97 (C), 101.04 (C), 128.01 (CH), 129.87 (CH), 132.51 (CH), 133.67 (C), 200.77 (C), 206.60 (C). EI-HRMS Calcd for $C_{16}H_{18}O_2$: 242.1307. Found: 242.1287.

4.4.11. Tricycle 28. Yield: 40%. White solid: mp 58–59 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.41 (m, 2H), 7.39–7.28 (m, 3H), 6.14 (d, J=5.7 Hz, 1H), 5.13 (d, J=5.7 Hz, 1H), 4.56 (s, 1H), 3.31 (ddd, J=10.9, 4.4, 2.4 Hz, 1H), 2.27 (ddd, J=12.4, 10.9, 2.4 Hz, 1H), 1.82–1.74 (m, 2H), 1.45–1.26 (m, 2H), 1.19 (s, 3H), 1.18–1.10 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 140.41 (C), 140.40 (CH), 128.73 (CH), 128.56 (CH), 128.12 (CH), 113.59 (CH), 74.07 (CH), 69.99 (C), 64.87 (CH_2), 25.63 (CH), 22.95 (CH_2), 21.95 (C), 16.14 (CH_2), 13.05 (CH_3). Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.06; H, 7.36.

4.4.12. [(2*R*,5*S*,6*R*)-2-Allyl-5,6-dihydro-5-triisopropylsilyloxy-6-(triisopropylsilylxoymethyl)-2*H*-pyran-2-yl](phenyl)methanone (33). Yield: 78%. Pale yellow oil. This product was purified by flash chromatography with hexane containing 5% Et_3N as eluent. Mixture of epimers at C-2: 5.4:1. Only major isomer is described. Configuration of the new quaternary center was stablished by NOESY experiments. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.03–1.15 (m, 42H), 2.78 (ddt, J=14.4, 6.7, 1.4 Hz, 1H), 2.95 (ddt, J= 14.4, 7.9, 1.2 Hz, 1H), 3.78–3.90 (m, 2H), 4.04 (dd, J=9.7, 1.8 Hz, 1H), 4.39 (dt, J=7.7, 1.8 Hz, 1H), 5.04–5.13 (m, 2H), 5.81–6.05 (m, 3H), 7.35–7.57 (m, 3H), 8.12 (dd, J= 8.5, 1.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, J=75 MHz) δ 12.51, 13.37, 18.56, 18.78, 41.29, 64.13, 64.55, 76.71, 86.14, 118.90, 128.31, 128.61, 130.84, 131.12, 131.21, 132.74, 133.52, 201.79. MALDI-HRMS (dithranol-NaI matrix) Calcd for $C_{34}H_{58}O_4NaSi_2$: 609.3771. Found: 609.3766.

Acknowledgements

The present work was supported by the MCyT (Project PB97-0002-C2), the ICIQ Foundation, and the CAM (predoctoral fellowship to C. N.) We also thank Johnson Matthey PLC for a generous loan of transition metal salts.

References and notes

1. (a) Grigg, R.; Mitchell, T. R. B.; Ramasubbu, A. *J. Chem. Soc., Chem. Commun.* **1979**, 669–670. (b) Grigg, R.; Malone, J. F.; Mitchell, T. R. B.; Ramasubbu, A.; Scott, R. M. *J. Chem Soc., Perkin Trans. 1* **1984**, 1745–1754.
2. Radetich, B.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1998**, *120*, 8007–8008.
3. (a) Heumann, A.; Moukhliss, M. *Synlett* **1998**, 1211–1212. (b) Heumann, A.; Moukhliss, M. *Synlett* **1999**, 268.
4. (a) Widenhoefer, R. A.; Perch, N. S. *Org. Lett.* **1999**, *1*, 1103–1105. (b) Kisanga, P.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2000**, *122*, 10017–10126. (c) Kisanga, P.; Goj, L. A.; Widenhoefer, R. A. *J. Org. Chem.* **2001**, *66*, 635–637. (d) Goj, L. A.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2001**, *123*, 11133–11147. (e) Widenhoefer, R. A. *Acc. Chem. Res.* **2002**, *35*, 905–913.
5. (a) Bray, K. L.; Fairlamb, I. J. S.; Lloyd-Jones, G. C. *Chem. Commun.* **2001**, 187–188. (b) Bray, K. L.; Charmant, J. P. H.; Fairlamb, I. J. S.; Lloyd-Jones, G. C. *Chem. Eur. J.* **2001**, *7*, 4205–4215. (c) Lloyd-Jones, G. C. *Org. Biomol. Chem.* **2003**, *1*, 215–236.
6. Bright, A.; Malone, J. F.; Nicholson, J. K.; Powel, J.; Shaw, B. L. *J. Chem. Soc., Chem. Commun.* **1971**, 712–713.
7. (a) Yamamoto, Y.; Ohkoshi, N.; Kameda, M.; Itoh, K. *J. Org. Chem.* **1999**, *64*, 2178–2179. (b) Yamamoto, Y.; Nakagai, Y.; Ohkoshi, N.; Itoh, K. *J. Am. Chem. Soc.* **2001**, *123*, 6372–6380.
8. (a) Fernández-Rivas, C.; Méndez, M.; Echavarren, A. M. *J. Am. Chem. Soc.* **2000**, *122*, 1221–1222. (b) Méndez, M.; Muñoz, M. P.; Echavarren, A. M. *J. Am. Chem. Soc.* **2000**, *122*, 11549–11550. (c) Méndez, M.; Muñoz, M. P.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2001**, *123*, 10511–10520. (d) Fernández-Rivas, C.; Méndez, M.; Nieto-Oberhuber, C.; Echavarren, A. M. *J. Org. Chem.* **2002**, *67*, 5197–5201. (e) Nevado, C.; Charruault, L.; Michelet, V.; Nieto-Oberhuber, C.; Muñoz, M. P.; Méndez, M.; Rager, M.-N.; Genêt, J. P.; Echavarren, A. M. *Eur. J. Org. Chem.* **2003**, 706–713. (f) Nieto-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2402–2406.
9. Nevado, C.; Echavarren, A. M. *Chem. Soc. Rev.* **2004**, *33*, in press.
10. Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Chem. Eur. J.* **2003**, *9*, 2627–2635.
11. Recent review: Martín Castro, A. M. *Chem. Rev.* **2004**, *104*, 2939–3002.
12. (a) van der Baan, J. L.; Bickelhaupt, F. *Tetrahedron Lett.* **1986**, *27*, 6267–6270. (b) Mikami, K.; Takahashi, K.; Nakai, T. *Tetrahedron Lett.* **1987**, *28*, 5879–5882. (c) Sugiura, M.; Yanagisawa, M.; Nakai, T. *Synlett* **1995**, 447–448. (d) Sugiura, M.; Nakai, T. *Chem. Lett.* **1995**, 697–698.
13. (a) Overman, L. E. *Angew. Chem., Int. Ed.* **1984**, *23*, 579–586. (b) Lutz, R. P. *Chem. Rev.* **1984**, *84*, 206–247.
14. (a) Tricycle **28** is the product of an intramolecular cyclopropanation catalyzed by Au(III). Nevado, C.; Ferrer, C.; Echavasren, A. M. *Org. Lett.* **2004**, *6*, 010486573. (b) Related structures have been published in Pt(II)-catalyzed transformations. See: Fürstner, A.; Stelzer, F.; Szillat, H. *J. Am. Chem. Soc.* **2001**, *123*, 11863–11869.
15. (a) Friesen, R. W.; Loo, R. W.; Sturino, C. F. *Can. J. Chem.* **1994**, *72*, 1262–1272. (b) Friesen, R. W.; Loo, R. W. *J. Organomet. Chem.* **1991**, *56*, 4821–4823. (c) Friesen, R. W.; Sturino, C. F.; Daljeet, A. K.; Kolaczewska, A. *J. Org. Chem.* **1991**, *56*, 1944–1947. (d) Friesen, R. W.; Daljeet, A. K. *Tetrahedron Lett.* **1990**, *31*, 6133–6136. (e) Lellouche, J.-P.; Koeller, S. *J. Org. Chem.* **2001**, *66*, 693–696.
16. (a) Jakel, C.; Dotz, K. H. *J. Organomet. Chem.* **2001**, *624*,

172–185. (b) Dotz, K. H.; Otto, F.; Nieger, M. *J. Organomet. Chem.* **2001**, *621*, 77–88.

17. The stereoselectivity in the formation of alcohols like **31** from α-lithiated silyl protected glucal has not been studied in detail. (a) Reaction of α-lithiated TBS-protected glucal with acetaldehyde gives a 1:1 mixture of epimers: Paquette, L. A.; Oplinger, J. A. *Tetrahedron* **1989**, *45*, 107–124. (b) The stereoselectivity in the formation of similar alcohols from benzyl-protected glucal is low: Lesimple, P.; Beau, J. M.; Jaurand, G.; Sinay, P. *Tetrahedron Lett.* **1986**, *27*, 6201–6204. For the reactions of the 2-lithium derivative of **30** with a xylofuranose aldehyde, see: (c) Bearder, J. R.; Dewis, M. L.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1995**, 227–233. (d) Bearder, J. R.; Dewis, M. L.; Whiting, D. A. *Synlett* **1993**, 805–806.
18. (a) Andersson, P. G.; Schab, S. *Organometallics* **1995**, *14*, 1–2. (b) Takacs, J. M.; Lawson, E. C.; Clement, F. *J. Am. Chem. Soc.* **1997**, *119*, 5956–5957.
19. Silylation of a 2-formyl derivative of 4-deoxyglucal under kinetic conditions with TBSOTf and Et_3N proceeded with 3:1 *E*:*Z* stereoselectivity: Alvarez, E.; Díaz, M. T.; Pérez, R.; Ravelo, J. L.; Regueiro, A.; Vera, J. A.; Zurita, D.; Martín, J. D. *J. Org. Chem.* **1994**, *59*, 2848–2876.
20. Nelson, S. G.; Bungard, C. J.; Wang, K. *J. Am. Chem. Soc.* **2003**, *125*, 13000–13001.
21. For related isomerization-Claisen rearrangement: (a) Reuter, J. M.; Salomon, R. G. *J. Org. Chem.* **1977**, *42*, 3360–3364. (b) Ammar, H. B.; Le Nôtre, J.; Salem, M.; Kaddachi, M. T.; Dixneuf, P. H. *J. Organomet. Chem.* **2002**, *662*, 63–69.
22. Lebouc, A.; Delaunay, J.; Riobe, O. *Synthesis* **1979**, 610–613.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 60 (2004) 9745–9755
Tetrahedron

Tandem $PtCl_2$ catalyzed–thermal [3,3] rearrangements of enyne acetates

Kevin Cariou, Emily Mainetti, Louis Fensterbank* and Max Malacria*

Université Pierre et Marie Curie, Laboratoire de Chimie Organique, UMR CNRS 7611, Tour 44-54, case 229, 4, place Jussieu, 75252 Paris cedex 05, France

Received 26 May 2004; revised 15 June 2004; accepted 17 June 2004

Available online 24 August 2004

Abstract—1,6 Enyne systems flanked with an acetate group at the propargyl position undergo tandem $PtCl_2$-catalyzed–thermal [3,3] rearrangements leading to trienes. The scope of the transformation has been delineated by varying the nature of the alkynyl substituent R. For R=alkyl or phenyl, a direct 1,3-migration of the acetate group is proposed leading to an allenyl ester intermediate that undergoes a subsequent [3,3] rearrangement.

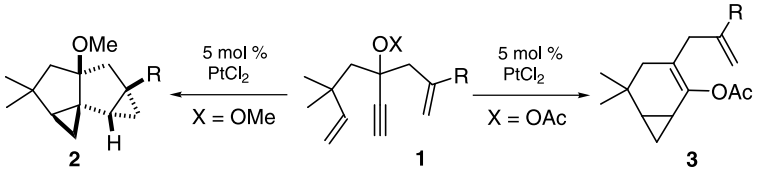
1. Introduction

The $PtCl_2$-catalyzed cycloisomerization of enyne systems is a recent addition to the palette of possible synthetic tools for the construction of cyclic derivatives.[1] The first report by Murai and Chatani established that this catalyst was ideal for promoting the formal metathesis of various enyne systems.[2] Applications of this process to the total synthesis of natural products,[3] as well as exploration of new partners[4] and mechanism rationalizations[5] have then followed rapidly. Most articles also show that the reactivity of this catalyst with enynes has largely extended beyond the simple metathesis process. Cyclopropanated hetero- and carbocycles resulting from carbenoid intermediates have been generated for instance.[5a,b] We have recently evidenced an interesting alteration of the reactivity of dienyne systems of type **1** by varying the nature of the protecting group of a hydroxy function at the propargylic position (Scheme 1).[6] Thus with a methoxy group, a domino process leads to diquinane **2** resulting from the formal transformation of the alkyne partner into a bis-carbene entity. However, with an acetate group, a 1,2-transposition step followed by an intramolecular cyclopropanation via a platinum carbene complex gives the bicyclic [4.1.0] derivative **3**. This reactivity could be extended to the preparation of cyclooctyl compounds.

The **1** to **3** transformation has incited further curiosity from us. First disclosed by Rautenstrauch on other ynol systems and catalyzed by $PdCl_2(MeCN)_2$ and in a minor extent by $PtCl_2(MeCN)_2$,[7] this reactivity has remained dormant for almost two decades until we initiated its renaissance,[6] soon accompanied by Uemura for the intermolecular version.[8] Several parameters have now been examined. Among all of them, we have notably concentrated on the substitution of the alkyne partner and, herein, we disclose the elements of reactivity of enynes of type **4**, which could by analogy with our previous findings give birth to bicyclic derivatives (Scheme 2).

2. Results and discussions

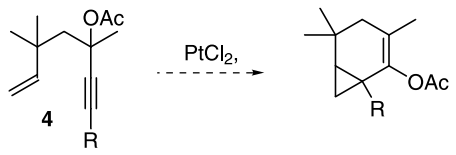
The general route to precursors is described on Scheme 3.



Scheme 1.

Keywords: Enyne; Cycloisomerization; Flash chromatography.
* Corresponding authors. Tel.: +33-1-44-27-35-85; fax: +33-1-44-27-73-60; e-mail addresses: fensterb@ccr.jussieu.fr; malacria@ccr.jussieu.fr

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.06.151



Scheme 2.

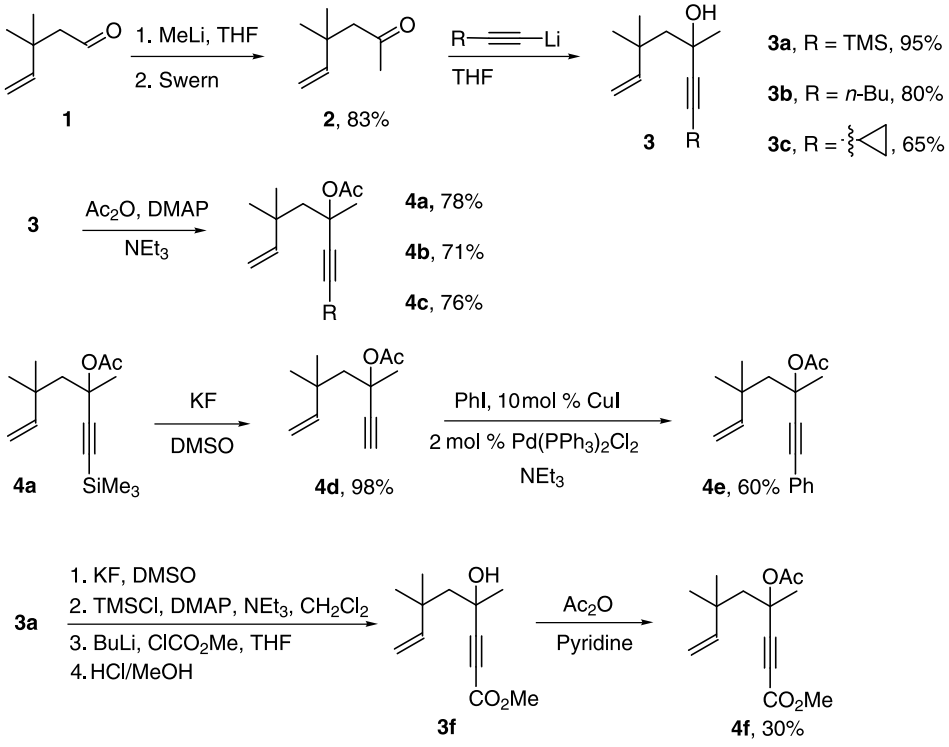
Known aldehyde **1**[9] was alkylated by methyllithium, and then oxidized to key building block, ketone **2**.[10]

Alkylation of this ketone by a series of lithium acetylides provided satisfactory yields of the corresponding alcohols **3a–c**, which were then acetylated to furnish **4a–c**. In the case of the cyclopropyl precursor, the lithium acetylide was generated from the cyclopropyldibromoolefin.[11] Phenyl substituted precursor **4e** was obtained through Sonagashira coupling, and precursor **4f** after methoxycarboxylation of a temporary *O*-silylated enynol substrate (Scheme 3).

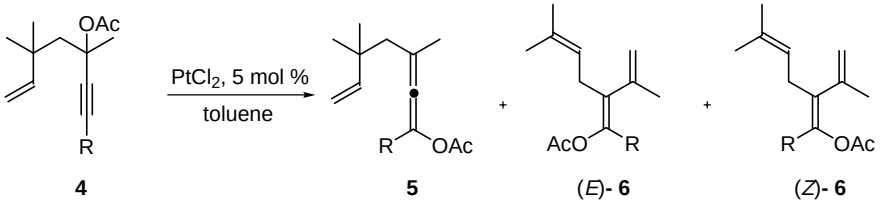
These precursors were then exposed to a catalytic amount of $PtCl_2$ (5 mol%) in toluene (0.025 M) under argon atmosphere at various temperatures (rt, 40 and 80 °C). Results of these reactions are given in Scheme 4. Thus, hexynyl substrate **4b** at 40 °C did not give any bicyclic adduct originating from the acetate 1,2-migration and carbene trapping. Instead, it underwent a smooth transformation in good yield to allenyl ester **5b** (entry 1), which results from a formal 1,3-migration of the acetate group and also corresponds to a [3,3] rearrangement of the propargyl acetate system. Interestingly, when this reaction was run at 80 °C, no allene **5b** was observed. A 9:1 mixture of two polyunsaturated, presumably isomeric products was isolated and careful spectroscopic analysis suggested trienic structures of type **6**. NOE analysis led to a *Z* relative configuration for the minor isomer of **6b** (Scheme 5).

Cyclopropyl precursor **4c** followed the same reactivity pattern: at 40 °C, no bicyclic adduct but allenyl ester **5c** (entry 3), and at 80 °C trienic adducts **6** in the same type of ratio and stereoselectivity (see also Scheme 5).

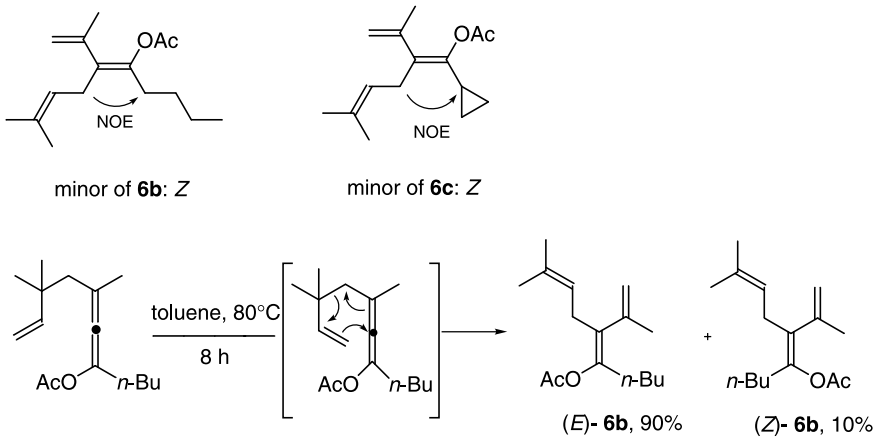
At that stage, it was interesting to have a better insight in the reactivity of these systems. Are allenes **5** intermediates between precursors **4** and trienes **6**? Then, would the transformation of **5** into **6** be platinum-catalyzed? We answered these questions by heating allenylester **5b** in toluene at 80 °C for a few hours, in the absence of $PtCl_2$. Very clean and complete conversion of **5b** to trienes **6b** was observed, suggesting that trienes **6** would originate from a



Scheme 3.



Scheme 4.



Scheme 5.

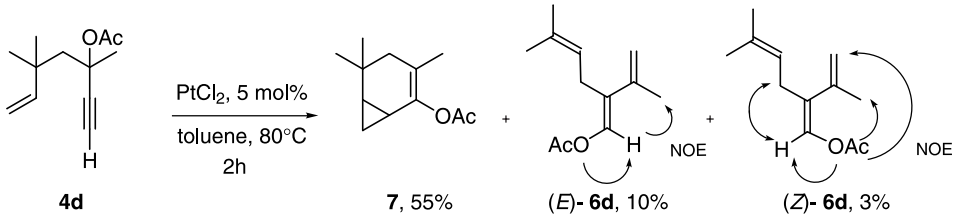
non metal catalyzed [3,3] (Cope type) rearrangement which involves an allene component[12] (Scheme 5).

Phenyl-substituted substrate **4d** proved more reactive since at rt a quasi equimolar mixture of allenyl ester **5d** and trienes **6d** was produced (Scheme 4, entry 5). Gentle heating to 40 °C is sufficient in that case (entry 6) to ensure complete formation of the trienes **6d**.[13] In sharp contrast, TMS precursor **4a** furnished very little amount of triene product **6a** among a complex mixture after 3 days in refluxing toluene.[14]

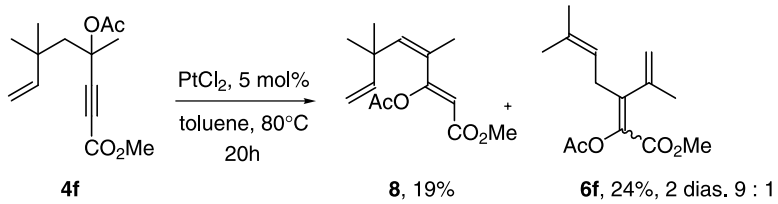
It was interesting to complete our study by examining the behavior of **4d** and **4f**. In the case of **4d** (Scheme 6), no reaction occurred at 40 °C after 4 h. However, at 80 °C, full consumption of the starting material was observed. As anticipated from our previous findings,[6] bicyclic adduct **7** was isolated in 55% yield, accompanied also by 13% of an inseparable mixture of triene derivatives **6d**, whose relative stereochemistries were attributed by NOE.

Reactivity of **4f** proved to be relatively sluggish. After prolonged reaction time (20 h) at 80 °C, starting material was consumed and an inseperable mixture of 3 products was isolated after chromatography in moderate overall yield (Scheme 7). Corresponding trienic derivatives **6f** were present in a 9:1 ratio with no determination of the relative stereochemistries. The second component of this mixture would correspond to another trienic derivative (**8**), whose structure is proposed after careful spectroscopic analysis and relative stereochemistry consistent with the following mechanism proposal (see below, Scheme 8).

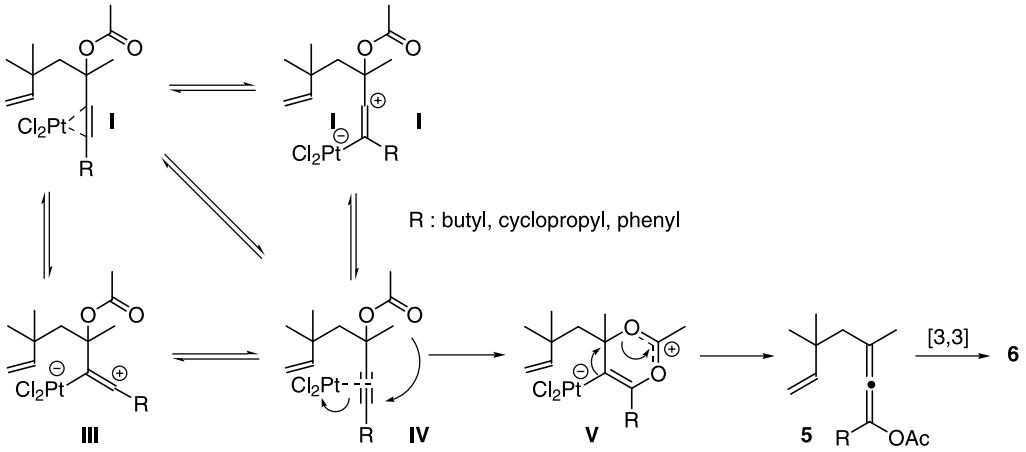
How to rationalize this new reactivity of the propargylic system and some of its divergent aspects? Clearly, substitution at the triple bond brings major alteration in the platinum-catalyzed step of the sequence, since no bicyclic adduct is formed. Allenyl esters are to a large extent the exclusively generated intermediates, which are formed in good yields and react further in a [3,3] rearrangement. π-Complexation of the alkyne moiety as in **I** can give birth to two σ-complexes **II** and **III**, whose potential intervention and relative contribution would be controlled by the nature of the R group. Thus, the presence of a R group that can stabilize a positively charged center will favor a species like **III** and this would take place through increasing donation from R=butyl, then cyclopropyl to phenyl.[15] Then, from **III**, anchimeric assistance from the best nucleophile, that is, the acetate group, would trigger the 1,3-migration of this group giving birth to the formal [3,3] product **5**.



Scheme 6.



Scheme 7.



Scheme 8.

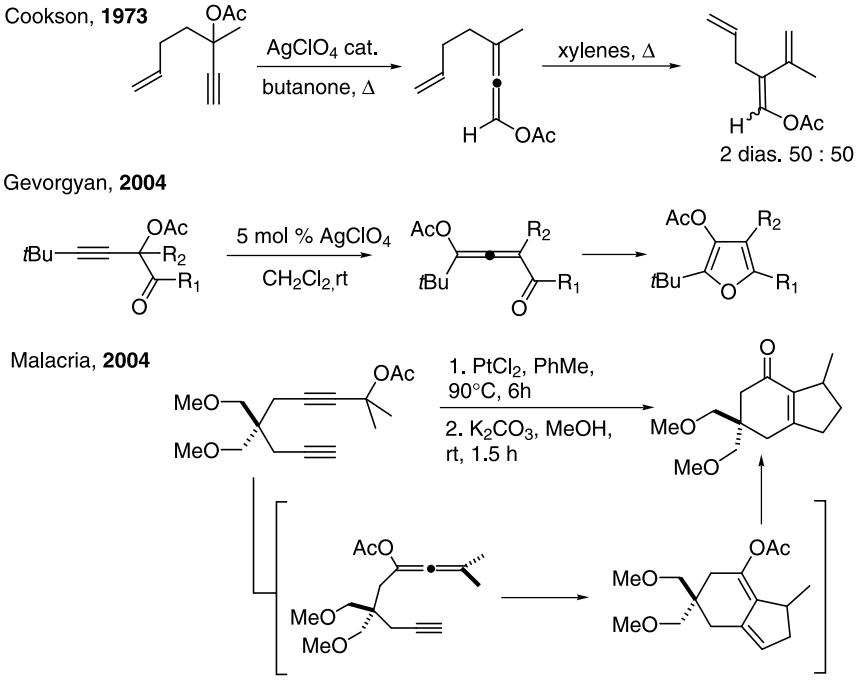
Interestingly, the observed order of reactivity correlates well with the R group stabilization ability.

Metal catalyzed [3,3] transposition of propargyl acetates have already been described with Ag(I)[16] and further exploited for an additional step. Thus, starting from a demethylated analog of **4d** and upon catalysis with $AgClO_4$, Cookson[17] observed a clean conversion to the corresponding allenyl ester intermediate, which was then further heated in boiling xylene to undergo an additional [3,3] rearrangement (Scheme 9).

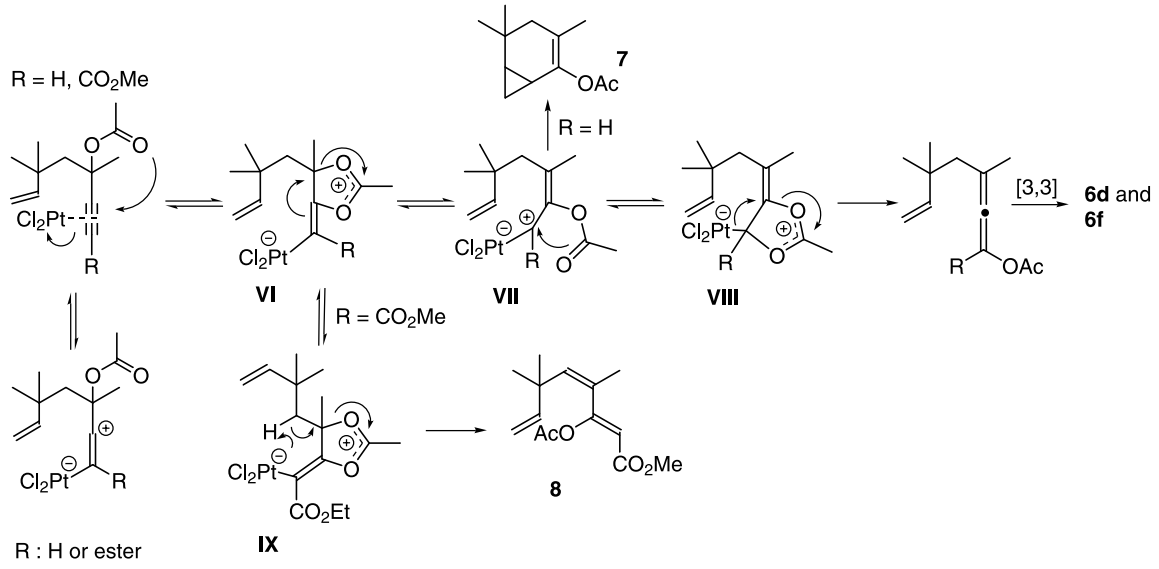
Very recently, Gevorgyan[18] has also used $AgClO_4$ for catalyzing a [3,3] rearrangement–1,2-migration–cycloisomerization cascade. We have also designed[4a] a $PtCl_2$-catalyzed [3,3] rearrangement–cycloisomerization tandem from a diyne acetate (Scheme 9). Thus, the formation of allenylesters from propargyl acetates has some precedent and can precede further interesting reactivity. In our case, the subsequent [3,3] rearrangement gives birth to a variety of trienes with a high diastereoselectivity that is not yet rationalized.

In the case of precursors **4d**, complex **III** (Scheme 8) is not stabilized and for **4f**, it is even destabilized. Presumably, 1,2-migration of the acetate takes place via **VI** (Scheme 10). A common path would consist of a second 1,2-migration of the acetate group (via **VII**) to give the allenyl ester. Then several paths are open. For R=H, cyclopropanation from carbenoid **VII** is the major pathway and provides **7** and for $R=CO_2Me$, platinum assisted elimination as in **IX** would yield to **8**.

Finally, this reactivity is not restricted to tertiary substrates. Secondary substrate **9** bearing an activating phenyl group on the triple bond could undergo the two consecutive [3,3]



Scheme 9.



Scheme 10.

transpositions to provide satisfactory yields of the trienic substrates **10** (Scheme 11), whose relative stereochemistries were also deduced from NOE analysis.

In conclusion, we have shown that enynes bearing an acetate group at the propargylic position and substitution on the triple bond can give birth to versatile transformations such as two consecutive [3,3] rearrangements, the first one being catalyzed by $PtCl_2$. The resulting trienes are formed stereoselectively. The scope of the transformation has been delineated by varying the nature of the alkynyl substituent R. For R=alkyl or phenyl, a direct 1,3-migration of the acetate group is proposed leading to an allenyl ester intermediate. Further applications of this valuable set of synthetic processes are underway, notably for the efficient preparation of relevant polyunsaturated building blocks.

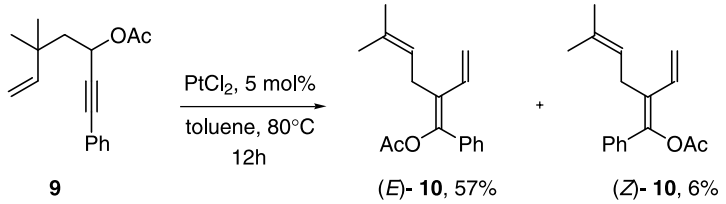
3. Experimental

3.1. General remarks

Reactions were carried out under an anhydrous atmosphere of Ar. Glassware was flame-dried under an argon gas flow prior to use. Anhydrous THF and Et_2O were obtained by distillation over sodium/benzophenone under nitrogen and used freshly distilled. Et_3N was dried then distilled from KOH; toluene and CH_2Cl_2 from CaH_2. *n*-Butyllithium was purchased as 2.5 M solutions in hexanes and titrated before use. Other reagents were commercially available and used without further purification unless otherwise indicated. NMR spectra (^1H, ^{13}C, DEPT, COSY ^1H–^1H and ^1H–^{13}C, NOE) were recorded on a 200 MHz ARX 200 or a 400 MHz AVANCE 400 Bruker spectrometers. ^1H NMR spectra are referenced at 7.26 ppm for $CDCl_3$ and 7.16 ppm for C_6D_6. ^{13}C NMR spectra are referenced at 77.23 ppm for $CDCl_3$ and 128.62 ppm for C_6D_6. Chemical shifts are given in ppm. IR spectra were recorded with a Tensor 27 (ATR diamond) Bruker spectrometer. IR is reported as characteristic bands (cm^{-1}) in their maximal intensity.

3.1.1. Synthesis of 2. Synthesis of 4,4-dimethyl-hex-5-en-2-ol: at −78 °C, MeLi (1.6 M in Et_2O, 18.4 mmol, 1.5 equiv) is added to a solution of aldehyde **1**[9] (1.4 g, 12.5 mmol, 1 equiv) in dry THF (15 mL). The mixture is allowed to heat up to rt, and then quenched with saturated NH_4Cl solution and extracted with diethylether. The combined organic layers are washed with brine, dried over $MgSO_4$ and evaporated to give the crude oil, which is engaged in the next step without further purification.

Synthesis of 4,4-dimethyl-hex-5-en-2-one **2**[10]: a 100 mL round bottom flask containing a solution of $(COCl)_2$ (1.4 mL, 16 mmol, 1.3 equiv) in CH_2Cl_2 (18 mL) is cooled at −78 °C, under an argon atmosphere. A solution of DMSO (2.2 mL, 31 mmol, 2.5 equiv) in CH_2Cl_2 (18 mL), is transferred, and after 5 min a solution of the crude alcohol (1.5 g, 12.5 mmol, 1 equiv) in CH_2Cl_2 (16 mL) is cannulated. After 15 min, Et_3N (9.6 mL, 69 mmol, 5.5 equiv) is added and after 15 min the mixture is allowed to warm up to rt. The mixture is quenched with saturated NH_4Cl solution and extracted with diethylether. The combined organic layers are washed with brine, dried over $MgSO_4$ and



Scheme 11.

evaporated to give crude **2**. The purification is done by simple filtration over silica gel and celite to give 1.3 g (10.4 mmol) of pure **2** (yield: 83% over 2 steps).

^{1}H NMR (400 MHz, $CDCl_3$): 5.91 (dd, $J=17.7$, 10.3 Hz, 1H, =CH), 4.95 (m, 2H, $=CH_2$), 2.43 (s, 2H, CH_2), 2.10 (s, 3H, CH_3), 1.11 (s, 6H, 2 CH_3).

3.1.2. 3,5,5-Trimethyl-1-trimethylsilanyl-hept-6-en-1-yn-3-ol 3a. A 50 mL round bottom flask, containing 20 mL of dry THF, is cooled at −78 °C, under an argon atmosphere. First TMSA (1.7 mL, 12 mmol, 1.5 equiv) and then *n*-BuLi (2.3 M in hexanes, 4.1 mL, 9.5 mmol, 1.2 equiv), are added. After 40 min the ketone **2** (1.0 g, 8 mmol, 1 equiv), diluted in 20 mL of dry THF, is transferred. The mixture is kept 30 min at −78 °C and then is allowed to heat up to rt. The mixture is quenched with saturated NH_4Cl solution and extracted with diethylether. The combined organic layers are washed with brine, dried over $MgSO_4$ and evaporated to give 1.75 g (8 mmol) of crude **3a** (yield: 98%), that was engaged in the next step without further purification.

IR (neat): 3550, 3080, 2960, 2930, 2170, 1640 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): 6.08 (dd, $J=17.5$, 10.7 Hz, 1H, =CH), 5.08 (dd, $J=17.5$, 1.3 Hz, 1H, =CH*H trans*), 5.02 (dd, $J=10.7$, 1.3 Hz, 1H, =C*H*H *cis*), 1.79 (s, 2H, CH_2), 1.44 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 0.15 (s, 9H, $Si(CH_3)_3$).

^{13}C NMR (100 MHz, $CDCl_3$): 149.1 (=CH), 111.8 ($=CH_2$), 110.7 (C), 88.6 (C), 67.9 (C), 54.8 (C), 37.3 (C), 32.9 (CH_3), 30.6 (CH_3), 26.6 (CH_3), 0.0 ($Si(CH_3)_3$).

3.1.3. 3,3,5-Trimethyl-undec-1-en-6-yn-5-ol 3b. A 50 mL flask, containing 6 mL of dry THF, is cooled at −78 °C, under an argon atmosphere. First hex-1-yne (550 μL, 4.8 mmol, 1.5 equiv) and then *n*-BuLi (2.3 M in hexanes, 1.7 mL, 3.9 mmol, 1.2 equiv), are added. After 40 min the ketone **2** (400 mg, 3.2 mmol, 1 equiv), diluted in 4 mL of dry THF, is transferred. The mixture is kept 30 min at −78 °C and then is allowed to heat up to rt. The mixture is quenched with saturated NH_4Cl solution and extracted with diethylether. The combined organic layers are washed with brine, dried over $MgSO_4$ and evaporated to give crude **3b**, that was engaged in the next step without further purification.

IR (neat): 3500, 3080, 2960, 2870, 2240, 1640 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): 6.06 (dd, $J=17.5$, 10.7 Hz, 1H, =CH), 5.03 (dd, $J=17.5$, 1.0 Hz, 1H, =CH*H trans*), 4.98 (dd, $J=10.7$, 1.3 Hz, 1H, =C*H*H *cis*), 2.14 (t, $J=6.9$ Hz, 2H, CH_2), 1.78 (d, $J=14.4$ Hz, 1H, CH_2), 1.75 (d, $J=14.4$ Hz, 1H, CH_2), 1.41 (s, 3H, CH_3), 1.52–1.28 (m, 4H, CH_2, CH_2), 1.25 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 0.88 (t, $J=7.2$ Hz, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): 149.1 (=CH), 111.1 ($=CH_2$), 84.8, 84.5 (2C), 67.5 (C), 54.8 (C), 37.0 (C), 33.1 (CH_3), 30.6 (CH_2), 30.1 (CH_3), 26.6 (CH_3), 22.0 (CH_2), 18.4 (C), 13.6 (CH_3).

3.1.4. Acetic acid 1-cyclopropylethynyl-1,3,3-trimethyl-pent-4-enyl ester 3c. Synthesis of (2,2-dibromovinyl)-cyclopropane: to a solution of CBr_4 (6.64 g, 20 mmol, 1.4 equiv) in CH_2Cl_2 (15 mL), a solution of PPh_3 (10.48 g, 40 mmol, 2.8 equiv) in CH_2Cl_2 (15 mL) is added at 0 °C. After 30 min of stirring a solution of cyclopropylcarboxaldehyde (1 g, 14.3 mmol, 1 equiv) in CH_2Cl_2 (15 mL) is added. The mixture is allowed to heat up to rt, after 1 h the reaction is complete. The mixture is poured in 300 mL of pentane, filtered over celite and concentrated. The residue is diluted in 200 mL of pentane, filtered over celite and concentrated to give the crude dibromoalkene, which is engaged in the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): 5.77 (d, $J=9.3$ Hz, 1H, =CH), 1.55–1.70 (m, 1H, CH), 0.85 (m, 2H, CH_2), 0.53 (m, 2H, CH_2). Identical to those of the literature.[11a]

3.1.5. 1-Cyclopropyl-3,5,5-trimethyl-hept-6-en-1-yn-3-ol 3c. To a solution of crude dibromoalkene (1.81 g, 8 mmol, 1.25 equiv) in dry THF (10 mL) 6.8 mL of *n*-Buli (2.3 M in hexanes, 15.7 mmol, 2.4 equiv) are added at −78 °C. After 30 min, a solution of ketone **2** (815 mg, 6.5 mmol, 1 equiv) in dry THF (10 mL) is added. The mixture is then allowed to heat up to rt. After 45 min the reaction is complete. The mixture is quenched with saturated NH_4Cl solution and extracted with diethylether. The combined organic layers are washed with brine, dried over $MgSO_4$ and evaporated to give crude oil, that is purified by flash chromatography on silica gel (petroleum ether/Et_2O, 95:5) to give 850 mg (1.8 mmol, 73%) of **3c**.

^{1}H NMR (400 MHz, $CDCl_3$): 6.09 (dd, $J=17.6$, 10.7 Hz, 1H, =CH), 5.07 (dd, $J=17.5$, 1.3 Hz, 1H, =CH*H trans*), 5.03 (dd, $J=10.7$, 1.3 Hz, 1H, =C*H*H *cis*), 1.81 (d, $J=14.4$ Hz, 1H, CH_2), 1.76 (d, $J=14.4$ Hz, 1H, CH_2), 1.43 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 1.25 (m, 1H, CH), 1.10 (s, 3H, CH_3), 0.75 (m, 2H, CH_2), 0.67 (m, 2H, CH_2).

3.1.6. Acetic acid 1-(2,2-dimethyl-but-3-enyl)-1-methyl-hept-2-ynyl ester 4a. To a solution of crude **3a** (255 mg, 1.14 mmol, 1 equiv) in NEt_3 (3 mL), DMAP (28 mg, 0.23 mmol, 0.2 equiv) and Ac_2O (650 μL, 4.6 mmol, 4 equiv) are added and the mixture is stirred at rt overnight. The mixture is quenched with saturated NH_4Cl solution and extracted with diethylether. The combined organic layers are washed with brine, dried over $MgSO_4$ and evaporated to give the crude oil, which is purified by flash chromatography on silica gel (pentane/Et_2O, 95:5) to give 235 mg (0.89 mmol, 78%) of pure **4a**.

IR (neat): 3080, 2960, 2170, 1750, 840 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): 5.95 (dd, $J=17.4$, 10.8 Hz, 1H, =CH), 4.89 (dd, $J=17.4$, 1.3 Hz, 1H, =CH*H trans*), 4.83 (dd, $J=10.8$, 1.3 Hz, 1H, =C*H*H *cis*), 2.13 (d, $J=14.6$ Hz, 1H, CH_2), 1.95 (s, 3H, $COCH_3$), 1.88 (d, $J=14.6$ Hz, 1H, CH_2), 1.67 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 1.13 (s, 3H, CH_3), 0.13 (s, 9H, $Si(CH_3)_3$).

^{13}C NMR (100 MHz, $CDCl_3$): 169.0 (C=O), 148.8 (=CH), 109.5 ($=CH_2$), 106.3 (C), 90.3 (C), 75.2 (C), 51.8 (C), 36.8

(C), 28.9 (CH_3), 28.5 (CH_3), 27.9 (CH_3), 22.2 (CH_2), −0.3 ($Si(CH_3)_3$).

3.1.7. Acetic acid 1-(2,2-dimethyl-but-3-enyl)-1-methyl-hept-2-ynyl ester 4b. Compound **3b** (132 mg, 0.63 mmol, 1 equiv) is acylated using the same procedure as for alcohol **3a**, with 25 mg (0.2 mmol, 0.3 equiv) of DMAP, 250 μL of Ac_2O (2.6 mmol, 4.2 equiv) in 3 mL of NEt_3. After purification by flash chromatography on silica gel (pentane/Et_2O, 95:5), 112 mg (0.45 mmol, 71%) of pure **4b** were isolated.

IR (neat): 3080, 2960, 2930, 2250, 1740, 1640 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): 5.95 (dd, $J=17.6$, 10.7 Hz, 1H, =CH), 4.88 (dd, $J=17.6$, 1.2 Hz, 1H, =CH*H trans*), 4.83 (dd, $J=10.7$, 1.2 Hz, 1H, =C*H*H *cis*), 2.16 (t, $J=7.1$ Hz, 2H, CH_2), 2.08 (d, $J=14.5$ Hz, 1H, CH_2), 1.94 (s, 3H, $COCH_3$), 1.86 (d, $J=14.5$ Hz, 1H, CH_2), 1.64 (s, 3H, CH_3), 1.53–1.30 (m, 4H, $2CH_2$), 1.12 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 0.87 (t, $J=7.2$ Hz, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): 169.3 (C=O), 149.0 (=CH), 109.2 (=CH_2), 86.6 (C), 81.2 (C), 75.5 (C), 52.3 (C), 36.8 (C), 30.4 (CH_2), 29.4 (CH_3), 28.4 (CH_3), 28.0 (CH_3), 22.0 (CH_2), 18.5 (C), 13.6 (CH_3).

Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.26; H, 10.93.

3.1.8. Acetic acid 1-cyclopropylethynyl-1,3,3-trimethyl-pent-4-enyl ester 4c. Compound **3c** (350 mg, 1.8 mmol, 1 equiv) is acylated using the same procedure as for alcohol **3a**, with 67 mg (0.55 mmol, 0.3 equiv) of DMAP, 0.5 mL of Ac_2O (5.25 mmol, 3 equiv) in 3 mL of NEt_3. After purification by flash chromatography on silica gel (pentane/Et_2O, 95:5), 321 mg (1.37 mmol, 76%) of pure **4c** were isolated.

IR (neat): 3290, 2970, 2880, 2120, 1750, 1650 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): 5.98 (dd, $J=17.4$, 10.6 Hz, 1H, =CH), 4.90 (dd, $J=17.4$, 1.3 Hz, 1H, =CH*H trans*), 4.85 (dd, $J=10.6$, 1.3 Hz, 1H, =C*H*H *cis*), 2.08 (d, $J=14.7$ Hz, 1H, CH_2), 1.96 (s, 3H, $COCH_3$), 1.84 (d, $J=14.4$ Hz, 1H, CH_2), 1.63 (s, 3H, CH_3), 1.24 (m, 1H, CH), 1.12 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 0.73 (m, 2H, CH_2), 0.67 (m, 2H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): 169.5 (C=O), 149.1 (=CH), 109.5 (=CH_2), 89.5 (C), 76.5 (C), 75.6 (C), 52.5 (C), 37.0 (C), 29.3 (CH_3), 28.5 (CH_3), 28.3 (CH_3), 22.8 (CH_3), 8.3 ($2CH_2$), 0.0 (CH).

Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.70; H, 9.63.

3.1.9. Acetic acid 1-ethynyl-1,3,3-trimethyl-pent-4-enyl ester 4d. Compound **4a** (280 mg, 1.05 mmol, 1 equiv) is diluted with 8 mL of DMSO. KF (100 mg, 1.7 mmol, 1.6 equiv) and a few drops of water are added. After 45 min the mixture is quenched with saturated NH_4Cl solution and extracted with diethylether. The combined organic layers are washed with brine, dried over $MgSO_4$ and evaporated to give 200 mg of **4d** (2.6 mmol, 98%), with no need of further purification.

IR (neat): 3290, 2970, 2880, 2140, 1750, 1650 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): 5.95 (dd, $J=17.5$, 10.7 Hz, 1H, =CH), 4.93 (dd, $J=17.5$, 1.3 Hz, 1H, =CH*H trans*), 4.88 (dd, $J=10.7$, 1.3 Hz, 1H, =C*H*H *cis*), 2.58 (s, 1H, CH), 2.11 (d, $J=14.7$ Hz, 1H, CH_2), 1.99 (s, 3H, $COCH_3$), 1.95 (d, $J=14.7$ Hz, 1H, CH_2), 1.70 (s, 3H, CH_3), 1.16 (s, 3H, CH_3), 1.14 (s, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): 169 (C=O), 149.1 (=CH), 110.1 (=CH_2), 85.2 (C), 74.9 (C), 74.7 (C), 52.3 (C), 37.3 (C), 29.1 ($2CH_3$), 28.2 (CH_3), 22.6 (CH_3).

3.1.10. Acetic acid 1,3,3-trimethyl-1-phenylethynyl-pent-4-enyl ester 4e. Compound **4d** (200 mg, 1.05 mmol, 1 equiv) is introduced under an argon atmosphere with PhI (120 μL, 1.08 mmol, 1.02 equiv). Dry NEt_3 (4 mL) is added and the solution is degassed with argon during 15 min. CuI (20 mg, 0.105 mmol, 0.1 equiv) and $PdPPh_3Cl_2$ (15 mg, 0.02 mmol, 0.02 equiv) are added, the mixture is heated at 70 °C. After 1 h the reaction is complete. The mixture is quenched with saturated NH_4Cl solution and extracted with diethylether. The combined organic layers are washed with brine, dried over $MgSO_4$ and evaporated to give the crude, which is purified by flash chromatography on silica gel (pentane/Et_2O, 95:5) to give 154 mg (0.57 mmol, 60%) of pure **4e**.

IR (neat): 3080, 2960, 2870, 2240, 1745, 1640 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): 7.42 (m, 2H, H_{Ar}), 7.28 (m, 3H, H_{Ar}), 6.02 (dd, $J=17.5$, 10.7 Hz, 1H, =CH), 4.96 (dd, $J=17.5$, 1.1 Hz, 1H, =CH*H trans*), 4.91 (dd, $J=10.7$, 1.1 Hz, 1H, =C*H*H *cis*), 2.23 (d, $J=14.7$ Hz, 1H, CH_2), 2.01 (s, 3H, $COCH_3$), 2.00 (d, $J=14.7$ Hz, 1H, CH_2), 1.79 (s, 3H, CH_3), 1.21 (s, 3H, CH_3), 1.20 (s, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): 169.3 (C=O), 148.9 (=CH), 131.6 (2 CH, Ar), 128.3 (CH, Ar), 128.0 (2 CH, Ar), 109.6 (=CH_2), 90.3 (C), 85.6 (C), 75.3 (C), 52.3 (C), 36.9 (C), 29.0 (CH_3), 28.4 (CH_3), 28.2 (CH_3), 22.3 (CH_3).

Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.46; H, 8.46.

3.1.11. 4-Acetoxy-4,6,6-trimethyl-oct-7-en-2-ynoic acid methyl ester 4f. Synthesis of 3,5,5-trimethyl-hept-6-en-1-yn-3-ol: crude alcohol **3a** (3.2 g, 14.3 mmol, 1 equiv) is diluted with 45 mL of DMSO. KF (1.34 g, 23 mmol, 1.6 equiv) and a few drops of water are added. After 45 min the reaction is complete. The mixture is quenched with saturated NH_4Cl solution and extracted with diethylether. The combined organic layers are washed with brine, dried over $MgSO_4$ and evaporated to give the crude, which is engaged in the next step without further purification.

^1H NMR (400 MHz, $CDCl_3$): 6.08 (dd, $J=17.5$, 10.7 Hz, 1H, =CH), 5.10 (dd, $J=17.5$, 1.3 Hz, 1H, =CH*H trans*), 5.02 (dd, $J=10.7$, 1.3 Hz, 1H, =C*H*H *cis*), 2.47 (s, 1H,

CH), 1.81 (s, 2H, CH_2), 1.48 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.09 (s, 3H, CH_3).

Synthesis of (1-ethynyl-1,3,3-trimethyl-pent-4-enyloxy)-trimethyl-silane: to a solution of the resulting alcohol (1.6 g, 10.5 mmol, 1 equiv) in CH_2Cl_2 (50 mL), 8.6 mL of NEt_3 (62 mmol, 6 equiv) and 380 mg of DMAP (3.1 mmol, 0.3 equiv) are added. The solution is cooled at 0 °C and the TMSCl (4 mL, 31.5 mmol, 3 equiv) is slowly added. The mixture is allowed to heat up to rt, the reaction is complete. The mixture is quenched with saturated NH_4Cl solution and extracted with diethylether. The combined organic layers are washed with brine, dried on $MgSO_4$ and evaporated to give crude silylether, which is engaged in the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): 6.02 (dd, $J=17.4$, 10.6 Hz, 1H, =CH), 4.90 (dd, $J=17.4$, 1.2 Hz, 1H, =CH*H trans*), 4.84 (dd, $J=10.6$, 1.2 Hz, 1H, =C*H*H *cis*), 2.45 (s, 1H, CH), 1.80 (d, $J=14.7$ Hz, 1H, CH_2), 1.76 (d, $J=14.5$ Hz, 1H, CH_2), 1.48 (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 1.13 (s, 3H, CH_3), 0.02 (s, 9H, $Si(CH_3)_3$).

4,6,6-Trimethyl-4-trimethylsilanyloxy-oct-7-en-2-ynoic acid methyl ester: to a solution of the crude resulting silylether (2.3 g, 10.5 mmol, 1 equiv) in dry THF (50 mL) 5 mL of a 2.3 M solution of *n*-BuLi (11.3 mmol, 1.1 equiv) is added at −78 °C. The $ClCO_2Me$ (2.4 mL, 31 mmol, 3 equiv) is added and the mixture is allowed to heat up to rt, the reaction is complete The mixture is quenched with saturated NH_4Cl solution and extracted with diethylether. The combined organic layers are washed with brine, dried over $MgSO_4$ and evaporated to give the crude methyl ethynate, which is engaged in the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): 6.00 (dd, $J=17.4$, 10.6 Hz, 1H, =CH), 4.92 (dd, $J=17.4$, 1.4 Hz, 1H, =CH*H trans*), 4.84 (dd, $J=10.6$, 1.4 Hz, 1H, =C*H*H *cis*), 3.77 (s, 3H, OCH_3), 1.80 (d, $J=14.7$ Hz, 1H, CH_2), 1.75 (d, $J=14.7$ Hz, 1H, CH_2), 1.50 (s, 3H, CH_3), 1.13 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 0.02 (s, 9H, $Si(CH_3)_3$).

Synthesis of 4-hydroxy-4,6,6-trimethyl-oct-7-en-2-ynoic acid methyl ester **3f**: a solution of crude silylated alcohol (3 g, 10.5 mmol), in methanol (50 mL), is cooled down to 0 °C. Then a few drops of concentrated HCl are added, the reaction is immediately complete. The mixture is quenched with saturated $NaHCO_3$ solution and extracted with diethylether. The combined organic layers are washed with brine, dried over $MgSO_4$ and evaporated to give crude **3f**, which is engaged in the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): 6.07 (dd, $J=17.7$, 10.6 Hz, 1H, =CH), 5.13 (d, $J=17.7$ Hz, 1H, =CH*H trans*), 5.07 (d, $J=10.6$ Hz, 1H, =C*H*H *cis*), 3.77 (s, 3H, OCH_3), 1.86 (s, 2H, CH_2), 1.50 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.09 (s, 3H, CH_3).

Synthesis of 4-acetoxy-4,6,6-trimethyl-oct-7-en-2-ynoic acid methyl ester **4f**: compound **3f** (2.2 g, 10.5 mmol, 1 equiv) is acylated using the same procedure as for alcohol **3d**, with 29 mL of Ac_2O (305 mmol, 30 equiv) in 45 mL of pyridine. After purification by flash chromatography on silica gel (PE/Et_2O 9:1) 800 mg (3.1 mmol, 30%, 5 steps) of pure **3f** were isolated.

IR (neat): 3080, 2960, 2870, 2240, 1750, 1715 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): 5.91 (dd, $J=17.4$, 10.6 Hz, 1H, =CH), 4.95 (dd, $J=17.4$, 1.4 Hz, 1H, =CH*H trans*), 4.89 (dd, $J=10.6$, 1.4 Hz, 1H, =C*H*H *cis*), 3.76 (s, 3H, OCH_3), 2.12 (d, $J=14.7$ Hz, 1H, CH_2), 2.01 (s, 3H, $COCH_3$), 1.97 (d, $J=14.7$ Hz, 1H, CH_2), 1.72 (s, 3H, CH_3), 1.13 (s, 3H, CH_3), 1.15 (s, 6H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): 169 (C=O), 149.1 (=CH), 110.1 (=CH_2), 85.2 (C), 74.9 (C), 74.7 (C), 52.3 (C), 37.3 (C), 29.1 ($2CH_3$), 28.2 (CH_3), 22.6 (CH_3).

3.2. Products from the $PtCl_2$-catalyzed reactions. General procedure for reactions involving $PtCl_2$

Reactions are carried out in anhydrous toluene. The enyne is introduced under an argon atmosphere. The solvent is then added and the solution ($c=0.025$ M) is submitted to argon bubbling during 15 min. The catalyst is then added, still under an argon atmosphere. The reaction requires stirring and heating. The reaction is monitored by TLC. When the reaction is complete, the solvent is evaporated and the crude is analyzed by ^{1}H NMR analysis before purification.

3.2.1. Acetic acid 1-trimethylsilyl-2-isopropenyl-5-methyl-hexa-1,4-dienyl esters *E*-6a. General procedure is applied to **4a** (146 mg, 0.55 mmol, 1 equiv), with 8.5 mg of $PtCl_2$ (0.032 mmol, 0.05 equiv), in 20 mL of toluene. The mixture is heated at reflux for 3d. After purification by flash chromatography on silica gel (pentane/CH_2Cl_2, 8:2), 11 mg (8%) of **6a** are isolated.

IR (neat): 3085, 2960, 2860, 1740, 840 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): 4.96 (th, $J=7.0$, 1.4 Hz, 1H, =CH), 4.92 (m, 1H, =CH_2), 4.89 (m, 1H, =CH_2), 2.80 (d, $J=7.0$ Hz, 2H, CH_2), 2.12 (s, 3H, $COCH_3$), 1.81 (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 0.12 (s, 9H, $Si(CH_3)_3$).

^{13}C NMR (100 MHz, $CDCl_3$): 169.9 (C=O), 148.6 (C), 147.0 (C), 142.8 (C), 132.2 (C), 120.7 (=CH), 116.6 (=CH_2), 27.9 (CH_2), 25.6 (CH_3), 21.8 (CH_3), 20.7 (CH_3), 17.7 (CH_3), 0.0 ($Si(CH_3)_3$).

3.2.2. Acetic acid 1-butyl-3,5,5-trimethyl-hepta-1,2,6-trienyl ester 5b. General procedure is applied to **4b** (95 mg, 0.38 mmol, 1 equiv), with 5 mg of $PtCl_2$ (0.02 mmol, 0.05 equiv), in 18 mL of toluene. The mixture is heated at 40 °C during 2 h. After purification by simple filtration over silica gel 70 mg (0.28 mmol, 74%) of **5b** are isolated.

IR (neat): 3080, 2960, 2860, 1980, 1735, 1640 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): 5.87 (dd, $J=17.4$, 10.6 Hz, 1H, =CH), 4.94 (dd, $J=17.4$, 1.3 Hz, 1H, =CH*H trans*),

4.92 (dd, $J=10.6$, 1.3 Hz, 1H, =C*H*H *cis*), 2.20 (m, 2H, CH_2), 2.12 (s, 3H, $COCH_3$), 2.09 (s, 2H, CH_2), 1.81 (s, 3H, CH_3), 1.32–1.48 (m, 4H, CH_2), 1.06 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 0.92 (t, $J=7.2$ Hz, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): 194.0 (C), 169.3 (C=O), 148.6 (=CH), 121.9 (C), 110.7 (=CH), 109.5 (C), 48.5 (CH_2), 37.0 (C), 31.9 (CH_2), 28.9 (CH_2), 27.4 (CH_3), 27.2 (CH_3), 22.9 (CH_3), 21.5 (CH_3, 22.5 (CH_2), 14.3 (CH_3).

Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.57; H, 10.61.

3.2.3. Acetic acid 1-butyl-2-isopropenyl-5-methyl-hexa-1,4-dienyl esters *E*-6b and *Z*-6b. General procedure is applied to **4b** (185 mg, 0.74 mmol, 1 equiv), with 10 mg of $PtCl_2$ (0.036 mmol, 0.05 equiv), in 30 mL of toluene. The mixture is heated at 80 °C during 15 h. After purification by flash chromatography on silica gel (pentane/Et_2O, 98:2), 110 mg (60%) of a mixture containing: *E*-**6b**/*Z*-**6b**, 9/1, are isolated.

IR (neat): 3080, 2960, 2860, 1750, 1640, 1610 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): 5.01 (th, $J=7.1$, 1.5 Hz, 1H, =CH), 4.97 (m, 1H, =CH_2, *E*-**6b**), 4.95 (m, 1H, =CH_2, *Z*-**6b**), 4.77 (m, 1H, =CH_2, *E*-**6b**), 4.68 (m, 1H, =CH_2, *Z*-**6b**), 2.78 (d, $J=7.1$ Hz, 2H, CH_2, *Z*-**6b**), 2.70 (d, $J=7.1$ Hz, 2H, CH_2, *E*-**6b**), 2.3 (t, $J=7.5$ Hz, 2H, CH_2), 2.14 (s, 3H, $COCH_3$, *E*-**6b**), 2.03 (s, 3H, $COCH_3$, *Z*-**6b**) 1.79 (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 1.24–1.40 (m, 4H, CH_2), 0.87 (t, $J=7.2$ Hz, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): 169.1 (C=O), 144.1 (C), 142.9 (C), 132.0 (C), 129.8 (C), 121.4 (=CH), 114.7 (=CH_2), 30.3 (CH_2), 29.7 (CH_2), 28.0 (CH_2), 25.7 (CH_3), 22.6 (CH_3), 22.4 (CH_2), 20.9 (CH_3), 17.7 (CH_3), 13.9 (CH_3).

3.2.4. Acetic acid 1-cyclopropyl-3,5,5-trimethyl-hepta-1,2,6-trienyl ester 5c. General procedure is applied to **4c** (147 mg, 0.63 mmol, 1 equiv), with 8.5 mg of $PtCl_2$ (0.03 mmol, 0.05 equiv), in 25 mL of toluene. The mixture is heated at 40 °C during 1 h. After purification by simple filtration over silica gel 110 mg (0.47 mmol, 75%) of **5c** are isolated.

IR (neat): 3080, 2960, 2870, 1940, 1750, 1640 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): 5.85 (dd, $J=17.5$, 10.7 Hz, 1H, =CH), 4.93 (dd, $J=17.5$, 1.5 Hz, 1H, =CH*H trans*), 4.90 (dd, $J=10.7$, 1.5 Hz, 1H, =C*H*H *cis*), 2.12 (s, 3H, $COCH_3$), 2.07 (s, 2H, CH_2), 1.78 (s, 3H, CH_3), 1.45 (m, 1H, CH), 1.05 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 0.70 (m, 2H, CH_2), 0.50 (m, 2H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): 193.2 (C), 168.9 (C=O), 148.1 (=CH), 123.4 (C), 110.5 (=CH_2), 110.0 (C), 48.0 (CH_2), 37.0 (C), 27.1 (CH_3), 26.8 (CH_3), 22.6 (CH_3), 21.1 (CH_3), 12.0 (CH), 6.0 (CH_2), 5.5 (CH_2).

3.2.5. Acetic acid 1-cyclopropyl-2-isopropenyl-5-methyl-hexa-1,4-dienyl esters *E*-6c and *Z*-6c. General procedure is applied to **4c** (93 mg, 0.4 mmol, 1 equiv), with 5.3 mg of $PtCl_2$ (0.02 mmol, 0.05 equiv), in 15 mL of toluene. The mixture is heated at 80 °C during 3 h. After purification by flash chromatography on silica gel (pentane/CH_2Cl_2, 8:2), 71 mg (76%) of a mixture containing: *E*-**6c**/*Z*-**6c**, 9/1, are isolated.

IR (neat): 3080, 2960, 2860, 1750, 1640, 1610 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): 5.09 (s, 1H, =CH_2), 5.00 (t, $J=7.1$ Hz, 1H, =CH), 4.91 (s, 1H, =CH_2), 3.00 (d, $J=6.6$ Hz, 2H, CH_2, *Z*-**6c**), 2.67 (d, $J=6.8$ Hz, 2H, CH_2, *E*-**6c**), 2.09 (s, 3H, $COCH_3$, *E*-**6c**), 2.00 (s, 3H, $COCH_3$, *Z*-**6c**), 1.84 (s, 3H, CH_3), 1.67 (s, 3H, CH_3, *Z*-**6c**), 1.65 (s, 3H, CH_3, *E*-**6c**), 1.62 (s, 3H, CH_3, *Z*-**6c**), 1.56 (s, 3H, CH_3, *E*-**6c**), 0.75 (m, 1H, CH_2), 0.57 (m, 2H, CH_2), 0.47 (m, 2H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): 171.5 (C=O), 169.8 (C, *Z*-**6c**), 169.4 (C, *E*-**6c**), 143.3 (C), 132.6 (C), 130.1 (C), 121.9 (=CH, *Z*-**6c**), 121.6 (=CH, *E*-**6c**), 115.9 (=CH_2, *E*-**6c**), 114.1 (=CH_2, *Z*-**6c**), 29.1 (CH_2), 26.0 (CH_3), 22.8 (CH_3), 20.8 (CH_3), 18.1 (CH_3), 12.2 (CH), 5.5 ($2CH_2$).

Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 77.22; H, 9.85.

3.2.6. Acetic acid 3,5,5-trimethyl-bicyclo[4.1.0]hept-2-en-2-yl ester 7 and acetic acid 2-isopropenyl-5-methyl-hexa-1,4-dienyl esters *E*-6d and *Z*-6d. General procedure is applied to **4d** (154 mg, 0.78 mmol, 1 equiv), with 10.5 mg of $PtCl_2$ (0.04 mmol, 0.05 equiv), in 30 mL of toluene. The mixture is heated at 80 °C during 2 h. After purification by flash chromatography on silica gel (pentane/Et_2O, 95:5), 85 mg (55%) of **7** and 20 mg (13%) of a mixture containing: *E*-**6d**/*Z*-**6d**, 75/25, are isolated.

3.2.7. Acetic acid 3,5,5-trimethyl-bicyclo[4.1.0]hept-2-en-2-yl ester 7. IR (neat): 3075, 2950, 2870, 1750, 1450, 1610 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): 2.22 (s, 3H, $COCH_3$), 1.82 (d, $J=16.5$ Hz, 1H, CH_2), 1.57 (dd, $J=16.5$, 2.0 Hz, 1H, CH_2), 1.50 (s, 3H, CH_3), 1.19–1.12 (m, 2H, CH_2), 1.12 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 0.85–0.64 (m, 2H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): 169.3 (C=O), 142.3 (C), 112.9 (C), 40.5 (CH_2), 29.5 (CH_3), 28.6 (CH_3), 28.0 (C), 26.4 (CH_3), 20.8 (CH_3), 16.5 (CH), 13.4 (CH), 9.7 (CH_2).

3.2.8. Acetic acid 2-isopropenyl-5-methyl-hexa-1,4-dienyl esters *E*-6d and *Z*-6d. IR (neat): 3080, 2960, 2860, 1750, 1640, 1610 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): 7.41 (s, 1H, =CH, *E*-**6d**), 6.96 (s, 1H, =CH, *Z*-**6d**), 5.09 (m, 1H, CH, *Z*-**6d**), 5.07 (s, 1H, =CH_2), 5.05 (m, 1H, =CH, *E*-**6d**), 4.98 (s, 1H, =CH_2), 3.08 (d, $J=6.8$ Hz, 2H, CH_2, *E*-**6d**), 2.82 (d, $J=6.8$ Hz, 2H, CH_2, *Z*-**6d**), 2.20 (s, 3H, $COCH_3$, *E*-**6d**), 2.14 (s, 3H, $COCH_3$, *Z*-**6d**), 1.97 (s, 3H, CH_3, *Z*-**6d**), 1.92 (s, 3H, CH_3, *E*-**6d**), 1.74 (s, 3H, CH_3, *E*-**6d**), 1.72 (s, 3H, CH_3, *Z*-**6d**), 1.70 (s, 3H, CH_3, *E*-**6d**), 1.64 (s, 3H, CH_3, *Z*-**6d**).

^{13}C NMR (100 MHz, $CDCl_3$): 167.9 (C=O), 139.8 (C), 133.0 (=CH), 126.0 (C), 122.3 (=CH), 115.1 (C), 113.5

(CH_2), 25.7 (CH_3), 24.9 (CH_2), 20.9 (CH_3), 20.6 (CH_3), 17.8 (CH_3).

3.2.9. Acetic acid 3,5,5-trimethyl-1-phenyl-hepta-1,2,6-trienyl ester 5e and acetic acid 2-isopropenyl-5-methyl-1-phenyl-hexa-1,4-dienyl ester *E*-6e and *Z*-6e. General procedure is applied to **4e** (50 mg, 0.18 mmol, 1 equiv), with 2.5 mg of $PtCl_2$ (0.009 mmol, 0.05 equiv), in 8 mL of toluene. The mixture is stirred at rt during 60 h. After purification by flash chromatography on silica gel (pentane/Et_2O, 99:1), 35 mg (70%) of a mixture containing: **5e**/*E*-**6e**/*Z*-**6e**, 55/41/4, are isolated.

3.2.10. Acetic acid 3,5,5-trimethyl-1-phenyl-hepta-1,2,6-trienyl ester 5e. IR (neat): 3090, 3060, 2970, 2860, 1950, 1750, 1640, 1610 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): 7.41 (m, 2H, H_{Ar}), 7.25 (m, 3H, H_{Ar}), 5.86 (dd, $J=17.4$, 10.6 Hz, 1H, =CH), 4.94 (dd, $J=17.4$, 1.5 Hz, 1H, =CH*H trans*), 4.89 (dd, $J=10.6$, 1.5 Hz, 1H, =C*H*H *cis*), 2.27 (s, 3H, $COCH_3$), 2.23 (s, 2H, CH_2), 1.94 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.07 (s, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): 195.3 (C), 168.8 (C=O), 147.9 (=CH), 132.2 (C), 128.3 ($2CH_{Ar}$), 127.8 ($2CH_{Ar}$), 124.5 (CH_{Ar}), 120.7 (C), 112.6 (C), 110.7 (CH_2), 48.0 (CH_2), 27.1 (CH_3), 26.9 (CH_3), 22.1 (CH_3), 21.0 (CH_3).

3.2.11. Acetic acid 2-isopropenyl-5-methyl-1-phenyl-hexa-1,4-dienyl ester *E*-6e and *Z*-6e. ^1H NMR (400 MHz, $CDCl_3$): 7.41 (m, 2H, H_{Ar}), 7.25 (m, 3H, H_{Ar}), 5.10 (m, 1H, =CH), 4.90 (m, 1H, $=CH_2$), 4.79 (m, 1H, $=CH_2$), 2.93 (d, $J=7.0$ Hz, 2H, CH_2, *E*-**6e**), 2.90 (d, $J=7.0$ Hz, 2H, CH_2, *Z*-**6e**), 2.16 (s, 3H, $COCH_3$, *E*-**6e**), 2.08 (s, 3H, $COCH_3$, *Z*-**6e**), 1.74 (s, 3H, CH_3), 1.71 (s, 3H, CH_3), 1.66 (s, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): 169.1 (C=O), 142.6 (C), 141.8 (C), 136.3 (C), 132.6 (C), 132.1 (C), 128.3 ($2CH_{Ar}$), 127.8 ($3CH_{Ar}$), 120.7 (=CH), 116.8 ($=CH_2$), 30.1 (CH_2), 25.7 (CH_3), 22.6 (CH_3), 20.9 (CH_3), 17.8 (CH_3).

3.2.12. 3-Acetoxy-4,6,6-trimethyl-octa-2,4,7-trienoic acid methyl ester 8 and 2-acetoxy-3-isopropenyl-6-methyl-hepta-2,5-dienoic acid methyl esters *E*-6f and *Z*-6f. General procedure is applied to **4f** (260 mg, 1.1 mmol, 1 equiv), with 14.5 mg of $PtCl_2$ (0.054 mmol, 0.05 equiv), in 40 mL of toluene. The mixture is heated at 80 °C during 20 h. After purification by flash chromatography on silica gel (pentane/Et_2O, 95:5), 115 mg (43%) a mixture containing: **8**/**6f**, 45/55, are isolated.

As we could not determine which isomer of **6f** was present in the mixture, we do not specify whether it is the *E* or the *Z* isomer.

Attribution between **8** and major dias. of **6f** was based on a H–C correlation NMR experiment.

^1H NMR (400 MHz, $CDCl_3$): 6.12 (s, 1H, =CH, **8**), 5.91 (dd, $J=17.4$, 10.6 Hz, 1H, =CH, **8**), 5.79 (s, 1H, =CH, **8**), 5.05 (dd, $J=17.4$, 1.4 Hz, 1H, =CH*H trans*, **8**), 5.00 (dd, $J=10.6$, 1.4 Hz, 1H, =C*H*H *cis*, **8**), 4.98 (s, 1H, $=CH_2$, **6f**), 4.92 (m, 1H, =CH, **6f**), 4.70 (s, 1H, $=CH_2$, **6f**), 3.71 (s, 3H, OCH_3, **6f**), 3.69 (s, 3H, OCH_3, **8**), 2.91 (d, $J=7.2$ Hz, 2H, CH_2, **6f**), 2.34 (s, 3H, $COCH_3$, **8**), 2.23 (s, 3H, $COCH_3$, **6f**), 1.94 (s, 3H, CH_3), 1.85 (s, 3H, CH_3), 1.70 (s, 3H, CH_3, **6f**), 1.64 (s, 3H, CH_3, **6f**), 1.22 (s, 6H, CH_3, **8**).

^{13}C NMR (50 MHz, $CDCl_3$): 169.6 (C=O), 168.6 (C=O), 165.5 (C=O), 160.5 (C=O), 146.3 (=CH, **8**), 144.7 (C), 143.4 (=CH, **8**), 143.0 (=CH), 134.5 (C), 130.3 (C), 128.9 (C), 128.7 (C), 129.3 (C), 119.2 (=CH, **6f**), 113.7 ($=CH_2$, **8**), 111.6 ($=CH_2$, **6f**), 104.6 (=CH, **8**), 52.2 (OCH_3), 51.7 (OCH_3), 39.0 (^3C, **8**), 30.9 (CH_2, **6f**), 29.2 (2 CH_3, **8**), 26.1 (CH_3, **6f**), 22.5 (CH_3), 21.3 (CH_3), 20.8 (CH_3), 15.7 (CH_3), 14.2 (CH_3).

3.2.13. Acetic acid 2-isopropenyl-1-phenyl-hexa-1,4-dienyl ester *E*-10 and *Z*-10. General procedure is applied to **9** (270 mg, 1.05 mmol, 1 equiv), with 14 mg of $PtCl_2$ (0.052 mmol, 0.05 equiv), in 40 mL of toluene. The mixture is heated at 80 °C during 15 h. After purification by flash chromatography on silica gel (pentane/CH_2Cl_2, 8:2), 170 mg (63%) of a mixture containing: *E*-**10**/*Z*-**10**, 9/1, were isolated.

IR (neat): 3090, 3020, 2970, 2860, 1760, 1640 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): 7.28–7.41 (m, 5H, H_{Ar}), 6.48 (dd, $J=17.4$, 11.1 Hz, 1H, =CH), 5.32 (dd, $J=17.4$, 1.0 Hz, 1H, =CH*H*, *trans*), 5.10 (dd, $J=11.1$, 1.0 Hz, 1H, =C*H*H, *cis*), 5.09 (m, 1H, =CH), 3.04 (d, $J=6.6$ Hz, 2H, CH_2, *E*-**10**), 2.99 (d, $J=6.6$ Hz, 2H, CH_2, *Z*-**10**), 2.16 (s, 3H, $COCH_3$, *E*-**10**), 2.08 (s, 3H, $COCH_3$, *Z*-**10**), 1.73 (s, 3H, CH_3), 1.71 (s, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): 169.8 (C=O), 146.4 (C), 135.2 (C), 133.6 (=CH), 131.8 (C), 129.5 ($2CH_{Ar}$), 128.5 (CH_{Ar}), 128.1 ($2CH_{Ar}$), 127.5 (C), 122.0 (=CH), 115.5 ($=CH_2$), 25.7 (CH_2), 25.7 (CH_3), 20.9 (CH_3), 17.9 (CH_3).

Acknowledgements

E.M. thanks the Ministère de la Recherche for an AMX grant. M.M. is member of Institut Universitaire de France, and we thank IUF for generous support of this research.

References and notes

1. For reviews, see: (a) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813. (b) Méndez, M.; Mamane, V.; Fürstner, A. *Chemtracts-Org. Chem.* **2003**, *16*, 397. (c) Lloyd-Jones, G. C. *Org. Biomol. Chem.* **2003**, *1*, 215.
2. Chatani, N.; Furukawa, N.; Sakurai, H.; Murai, S. *Organometallics* **1996**, *15*, 901.
3. (a) Trost, B. M.; Doherty, G. A. *J. Am. Chem. Soc.* **2000**, *122*, 3801. (b) Fürstner, A.; Szillat, H.; Gabor, B.; Mynott, R. *J. Am. Chem. Soc.* **1998**, *120*, 8305.
4. (a) Allenynes: Cadran, N.; Cariou, K.; Hervé, G.; Aubert, C.; Fensterbank, L.; Malacria, M.; Marco-Contelles, J. *J. Am.*

Chem. Soc. **2004**, *126*, 3408. (b) Ene-tosylynamides: Marion, F.; Coulomb, J.; Courillon, C.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2004**, *6*, 1509.

5. (a) Méndez, M.; Muñoz, M. P.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2001**, *123*, 10511. (b) Fürstner, A.; Stelzer, F.; Szillat, H. *J. Am. Chem. Soc.* **2001**, *123*, 11863. (c) Martín-Matute, B.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2003**, *125*, 5757. (d) Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Chem. Eur. J.* **2003**, *9*, 2627.
6. Mainetti, E.; Mouriès, V.; Fensterbank, L.; Malacria, M.; Marco-Contelles, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2132.
7. Rautenstrauch, V. *J. Org. Chem.* **1984**, *49*, 950.
8. Miki, K.; Ohe, K.; Uemura, S. *J. Org. Chem.* **2003**, *68*, 8505.
9. Ang, K. H.; Bräse, S.; Steinig, A. G.; Meuer, F. E.; Llebaria, A.; Voigt, K.; de Meijere, A. *Tetrahedron* **1996**, *52*, 11503–11528.
10. For another synthesis of ketone **2**, see: House, H. O.; Chu, C.-Y.; Phillips, W. V.; Sayer, T. S. B.; Yau, C.-C. *J. Org. Chem.* **1977**, *42*, 1709.
11. (a) Gajewski, J. J.; Olson, L. P.; Willcott, M. R. *J. Am. Chem. Soc*. **1996**, *118*, 299–306. (b) See also: Mainetti, E.; Fensterbank, L.; Malacria, M. *Synlett* **2002**, 923–926.
12. (a) Doutheau, A.; Balme, G.; Malacria, M.; Gore, J. *Tetrahedron* **1980**, *36*, 1953–1960 and references therein. (b) See also: Banert, K.; Fendel, W.; Schlott, J. *Angew. Chem., Int. Ed.* **1998**, *37*, 3289–3292.
13. Relative stereochemistry of trienes **6d** was deduced by analogy with the previous cases.
14. It is relatively a general trend that TMS-substituted alkynes react sluggishly in the $PtCl_2$-catalyzed process.
15. This is consistent with calculations by Echavarren on the polarization by $PtCl_2$ of the bonded alkyne, cf. Ref. 5d.
16. (a) Saucy, G.; Marbet, R.; Lindlar, H.; Isler, O. *Helv. Chim. Acta* **1959**, *XLII*, 1945–1955. (b) Schlossarczyk, H.; Sieber, W.; Hesse, M.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta* **1973**, *56*, 875. (c) Oelberg, D. G.; Schiavelli, M. D. *J. Org. Chem.* **1977**, *42*, 1804. See also: (d) Cookson, R. C.; Cramp, M. C.; Parsons, P. *J. Chem. Commun.* **1980**, 197.
17. Bowden, B.; Cookson, R. C.; Davis, H. A. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2634.
18. Sromek, A. W.; Kel'in, A. V.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2004**, *43*, 2280.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 60 (2004) 9757–9767
Tetrahedron

Palladium-catalyzed α-arylation of *N*-protected 2-piperidinones

Arnault de Filippis, Domingo Gomez Pardo and Janine Cossy*

Laboratoire de Chimie Organique associé au CNRS, ESPCI, 10 rue Vauquelin, 75231 Paris Cedex 05, France

Received 20 April 2004; revised 17 June 2004; accepted 21 June 2004

Available online 24 August 2004

Abstract—A very simple method for obtaining α-arylated *N*-protected 2-piperidinones in high yield is described. The use of $ZnCl_2$ and $Pd(dba)_2$ and the nature of the base are the key factors.

1. Introduction

The addition of nucleophiles to aryl halides can occur by three pathways: addition–elimination (via a Meisenheimer complex), elimination–addition (benzyne), or electron transfer (radical, anion-radical). The first of these routes requires electron-withdrawing groups on the aromatic substrate so that the intermediate is adequately stabilized, but this process is severely limited. The benzyne pathway requires a strong base for proton removal and is not always selective because of the high reactivity of the dihydrobenzene. The electron-transfer approach seems to be limited to highly stabilized nucleophiles or systems where large excess of nucleophiles can be tolerated.[1]

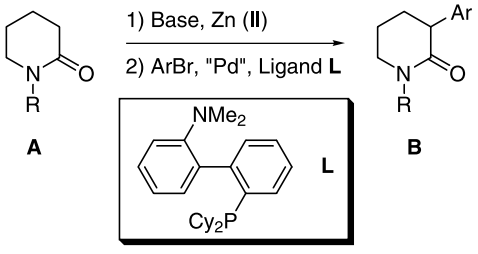
In 1997, palladium-catalyzed coupling reactions of aryl halides or pseudohalides with enolates has been developed.[2] Intermolecular coupling reactions of ketone[3] and ester[4] enolates with aryl halides, catalyzed with palladium, have been reported. Arylation of amides are less common.[5] To our knowledge, only one example of palladium-catalyzed intermolecular coupling of aryl halides with a five-membered ring lactam, the *N*-methyl-2-pyrrolidinone, has been reported.[5a] We would like to report here that α-arylation of *N*-substituted 2-piperidinones can be achieved with aryl bromides by using a palladium catalyst in the presence of the bulky electron-rich ligand, 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)-biphenyl **L** (Scheme 1).[6]

2. Results

2.1. $Pd(OAc)_2$-Catalyzed arylation conditions

Due to the greater acidity of the C3-proton in **B** than in **A**, we assumed that the abstraction of the C3-proton in the 3-aryl-2-piperidinones of type **B** by the enolate of the piperidinones of type **A** is possible (Scheme 1) (cf. vide infra). Therefore, 2 equiv. of the enolate of type **A** were prepared and treated with 1 equiv. of aryl bromide.

The initial attempt of α-arylation of 2-piperidinones was achieved on *N*-tosyl-2-piperidinone **1** by using the $Pd(OAc)_2$-catalyzed cross-coupling conditions employed in the arylation of esters (Buchwald's conditions).[4a] When *N*-tosyl-2-piperidinone **1** (2.3 equiv.) was treated under Buchwald's conditions [LiHMDS (2.5 equiv.), $Pd(OAc)_2$ (3.0 mol%), *o*-biphenylphosphine **L** (6.3 mol%), toluene, rt or 80 °C] with bromobenzene (1.0 equiv.), no arylation occurred (Table 1, entries 1 and 2). In order to increase the reactivity of the enolate, the zinc enolate of **1** was prepared by addition of $ZnCl_2$ on the lithium enolate.[7,8] As the zinc salt was not soluble in toluene, the solvent was replaced by THF. After treatment of *N*-tosyl-2-piperidinone **1** (2.2 equiv.) with LiHMDS (2.0 equiv.) and $ZnCl_2$ (2.2 equiv.) in THF at −20 °C, the resulting solution was added to a combination of $Pd(OAc)_2$ (5.0 mol%), ligand **L**

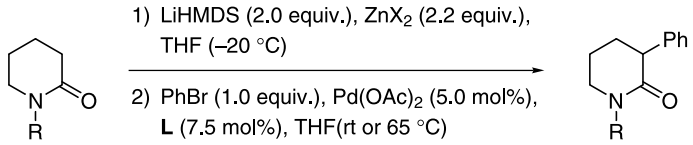


Scheme 1. α-Arylation of *N*-protected-2-piperidinones.

Keywords: Arylations; Lactams; Palladium; Zinc; Coupling.
* Corresponding author. Tel.: +33-1-40-79-44-29; fax: +33-1-40-79-46-60; e-mail: janine.cossy@espci.fr

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.06.152

Table 1. $Pd(OAc)_2$-catalyzed arylation of *N*-protected-2-piperidinones **1** and **3** with bromobenzene



1 (R = Ts)
3 (R = Bn)

2 (R = Ts)
4 (R = Bn)

Entry	Starting material	ZnX_2	*T* (°C)	Product	Yield %[a]
1[b]	**1**	—	rt	**2**	0
2[b]	**1**	—	80	**2**	Traces[c]
3	**1**	$ZnCl_2$	rt	**2**	48
4	**1**	$ZnBr_2$	rt	**2**	0
5[d]	**1**	$ZnCl_2$	rt	**2**	48
6	**3**	$ZnCl_2$	rt	**4**	22
7	**3**	$ZnCl_2$	65	**4**	85

[a] Calculated from bromobenzene.
[b] Buchwald's conditions: **1** (2.3 equiv.), PhBr (1.0 equiv.), LiHMDS (2.5 equiv.), $Pd(OAc)_2$ (3.0 mol%), **L** (6.3 mol%), one-pot in toluene.
[c] GC–MS.
[d] With $Pd(OAc)_2$ (10 mol%) and ligand **L** (15 mol%).

(7.5 mol%) and bromobenzene (1.0 equiv.). The *N*-tosyl-3-phenyl-2-piperidinone **2** was obtained after 8 h in 48% yield (calculated from bromobenzene) and the unreacted piperidinone **1** was recovered (Table 1, entry 3). It is worth noting that the use of $ZnBr_2$ did not lead to **2** (Table 1, entry 4). Furthermore, it has been noticed that the yield in **2** was not increased when 10 mol% of $Pd(OAc)_2$ and 15 mol% of ligand **L** were used to achieve the arylation of **1** (Table 1, entry 5). When the $Pd(OAc)_2$-catalyzed arylation conditions were applied to *N*-benzyl-2-piperidinone **3** (2.2 equiv.) and bromobenzene (1.0 equiv.) in THF at rt, *N*-benzyl-3-phenyl-2-piperidinone **4** was obtained in low yield (22%) (Table 1, entry 6). When the reaction was performed at 65 °C for 8 h, the yield was increased to 85% (Table 1, entry 7) and, as previously observed, the unreacted piperidinone **3** was recovered.

2.2. $Pd(dba)_2$-Catalyzed arylation conditions

In order to increase the yield in **4**, different palladium catalysts were tested.[9] Among them, $Pd(dba)_2$ appeared to be the best one as the treatment of the zinc enolate of **3** (2.0 equiv.) with bromobenzene (1.0 equiv.) in the presence of $Pd(dba)_2$ (5.0 mol%) and ligand **L** (7.5 mol%) in THF at 65 °C led to **4** in 98% yield (Table 2, entry 1). We have to point out that $Pd(dba)_2$-catalyzed arylation of the lithium enolate of **3** with bromobenzene occurred but the yield in **4** is lower (52%) than with the corresponding zinc enolate (Table 2, entry 2). Furthermore, the choice of the zinc salt to prepare the enolate is also important, as the yield in **4** is better with $ZnCl_2$ than with $ZnBr_2$ (98% versus 37%) (Table 2, entry 3).

2.3. Application to other aryl bromides

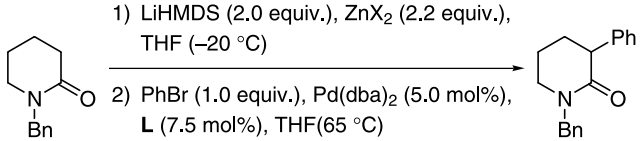
Due to these results, $Pd(dba)_2$ was used to achieve the arylation of *N*-benzyl-2-piperidinone **3** with different substituted aryl bromides. As previously, the zinc enolate was prepared by treatment of **3** (2.2 equiv.) with LiHMDS (2.0 equiv.) followed by the addition of $ZnCl_2$ (2.2 equiv.) at −20 °C and the resulting solution was added to a solution of $Pd(dba)_2$ (5.0 mol%), ligand **L** (7.5 mol%) and aryl bromide (1.0 equiv.) in THF. After heating at 65 °C for 8 h, the arylated products were isolated. The results are reported in Table 3. Whatever the substituent on the aryl bromide, with electron-rich (Table 3, entries 1, 2, 3, 6, 7 and 8) or electron-withdrawing properties (Table 3, entries 9, 10, 11, and 12), the arylated products were obtained in good yields, except for the most hindered aryl bromide, 2,6-dimethyl bromobenzene, for which the coupled product was not detected (Table 3, entry 4).

The best yield of the arylated product was obtained with an electron-rich aryl bromide, 2,4-dimethoxy-bromobenzene, as **12** was isolated with 84% yield (Table 3, entry 8). The reaction occurred also with bromonaphtalene in good yield (57%) as shown in entry 5. It is worth noting that for piperidinones, contrary to ketones and esters, the diarylation of enolates during the palladium-catalyzed coupling was not observed.

2.4. Application to other piperidinones

The arylation of *N*-substituted-2-piperidinones with electron withdrawing groups such as *N*-tosyl-2-piperidinone **1**

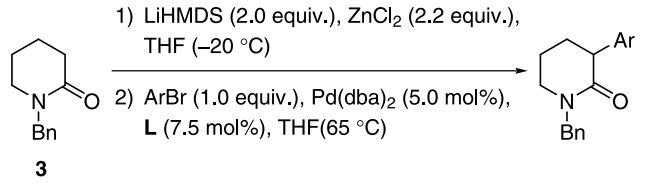
Table 2. $Pd(dba)_2$-catalyzed arylation of *N*-benzyl-2-piperidinone **3** with bromobenzene



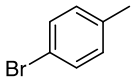
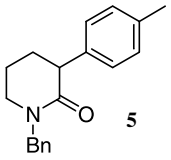
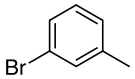
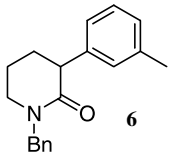
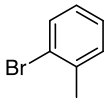
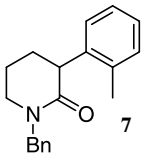
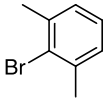
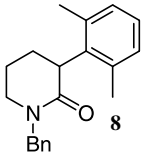
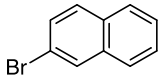
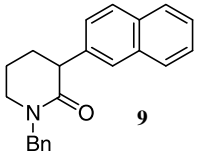
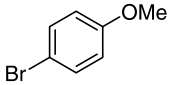
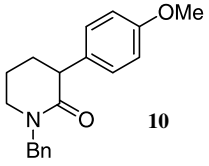
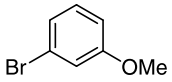
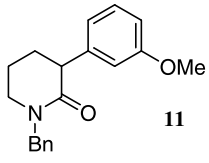
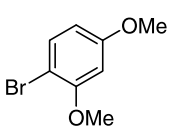
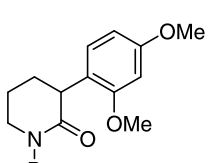
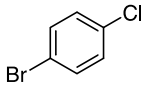
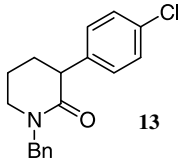
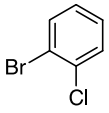
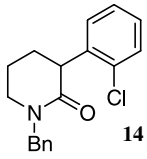
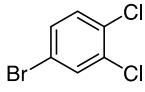
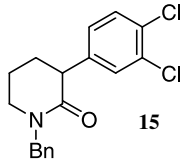
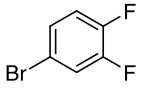
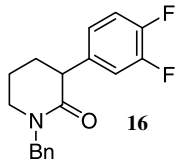
3 **4**

Entry	ZnX_2	Yield %
1	$ZnCl_2$	98
2	—	52
3	$ZnBr_2$	37

Table 3. α-Arylation of *N*-benzyl-2-piperidinone **3** with different aryl-bromides



3

Entry	ArBr	Product	Yield %
1		 **5**	52
2		 **6**	58
3		 **7**	46
4		 **8**	0
5		 **9**	57
6		 **10**	77
7		 **11**	50
8		 **12**	84
9		 **13**	70
10		 **14**	77
11		 **15**	50
12		 **16**	54

and *N*-benzoyl-2-piperidinone **20** has been also studied with different aryl bromides in the presence of $Pd(dba)_2$.

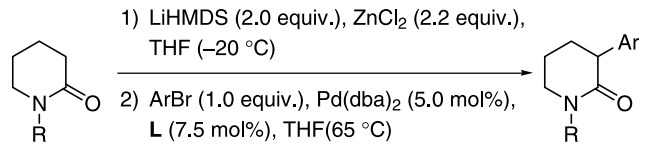
The results are summarized in Table 4. When the zinc enolate of piperidinones **1** or **20** were arylated with bromobenzene, the corresponding arylated products **2** (92% yield) or **21** (80% yield) were obtained in good yields (Table 4, entries 1 and 5). Whatever the substituents on the aryl bromide either electron-rich or electron-withdrawing substituents, the arylated products were isolated in good yield (from 50% to 80%) except for the more sterically hindered aryl bromide, *o*-bromotoluene, for which the arylated piperidinones **17** and **22** were obtained in modest yield (Table 4, entries 2 and 6).

3. Discussion

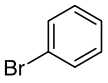
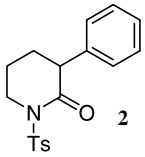
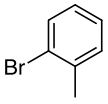
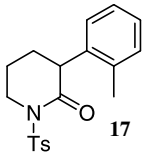
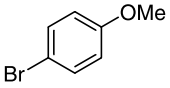
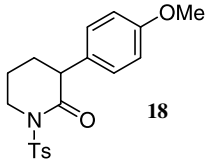
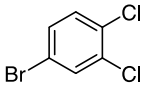
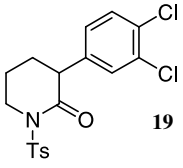
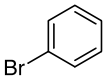
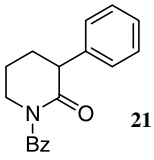
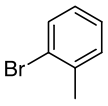
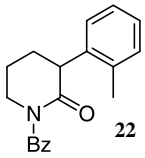
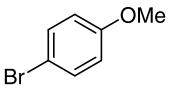
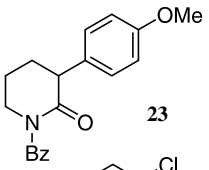
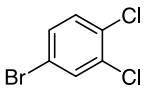
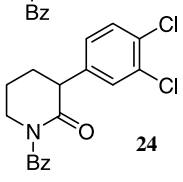
3.1. Mechanism

The α-arylation of *N*-protected piperidinones of type **A** can be explained according to a mechanism similar to the one previously proposed for the α-arylation of ketones except that the lithium enolate of type **B** is replaced by the zinc enolate of type **C** (Scheme 2). Oxidative addition of $Pd(0)L_n$ to the aryl bromide provides the Pd(II) organometallic intermediate **D**. Ligand substitution of the bromide by the zinc enolate leads to the Pd(II) organometallics **E** and/or **F**. Then, reductive elimination from these intermediate **E** and **F** gives the α-arylpiperidinone **G** and regeneration of the $Pd(0)L_n$ catalyst. As α,β-unsaturated 2-piperidinones were not observed, no β-hydride elimination pathway takes place.

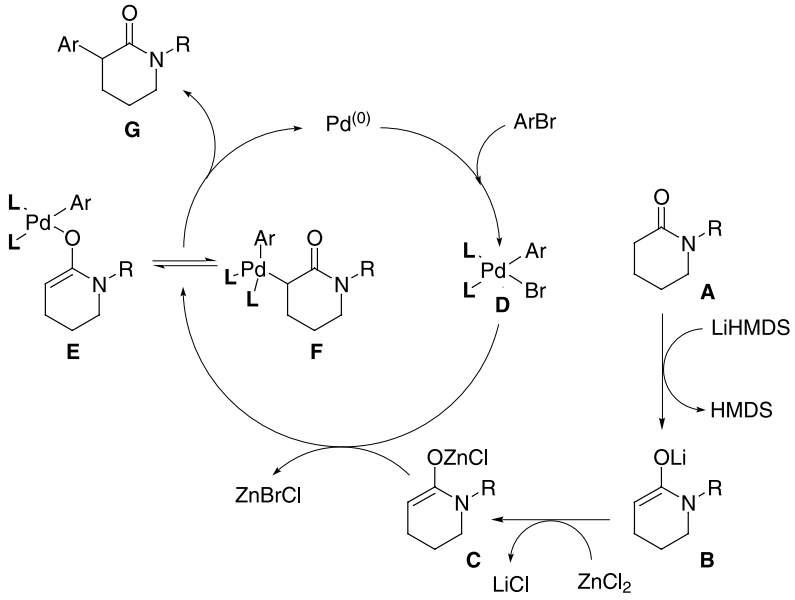
Table 4. α-Arylation of 2-piperidinones **1** and **20** with aryl-bromides



1 (R = Ts)
20 (R = Bz)

Entry	SM[a]	ArBr	Product	Yield %
1	**1**		 **2**	92
2	**1**		 **17**	41
3	**1**		 **18**	60
4	**1**		 **19**	80
5	**20**		 **21**	80
6	**20**		 **22**	37
7	**20**		 **23**	50
8	**20**		 **24**	60

[a] SM, starting material.



Scheme 2. Proposed mechanism.

This observation is in favor to the ability of the ligand **L** to render the palladium complexes L_4-coordinate.

3.2. Adjustment of the arylation of piperidinone 3

In order to increase the yield in α-arylated piperidinones, different factors have been studied in the arylation of *N*-benzyl-2-piperidinone **3** with *p*-bromotoluene and *m*-bromoanisole to get, respectively, piperidinones **5** and **11**. As we were aware that the enolate of **3** can abstract the C3-proton of *N*-benzyl-3-phenyl-2-piperidinone **4**, 2 equiv. of the zinc enolate of piperidinone **3** were used.

3.2.1. pK_a of the base. The palladium-catalyzed coupling of piperidinone enolates involves multiple equilibria. The ratio of the two enolates generated from the starting product and the arylated product is different at different stages of the reaction and can be different when bases having conjugated

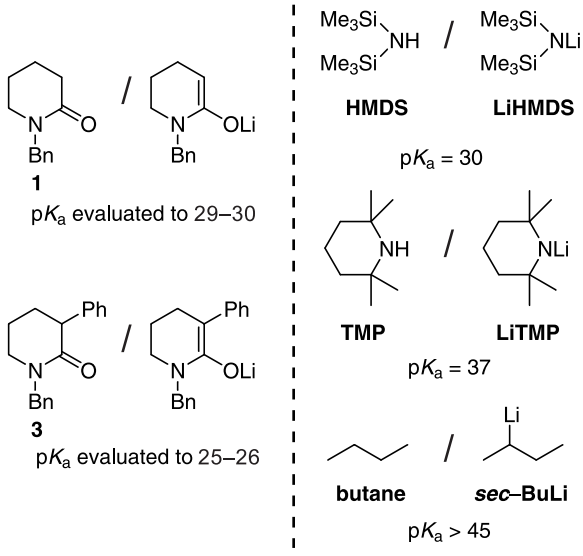


Figure 1. pK_a values in DMSO.

acids with different pK_a values are used. The pK_a data that are relevant to the equilibria of enolates in the coupling process are available in DMSO.[10] As the value of the same substrate in THF and DMSO are often within 2–3 pK_a units of each other, with the value in THF generally the lower of the two, the reasoning will be achieved with the pK_a values in DMSO. The pK_a of *N*-benzyl-3-phenyl-2-piperidinone **4** can be evaluated to 25–26 in DMSO and in consequence the pK_a value of the *N*-benzyl-2-piperidinone **3** should be around 29–30. The pK_a of hexamethyldisilazane in DMSO is 30 (Fig. 1).

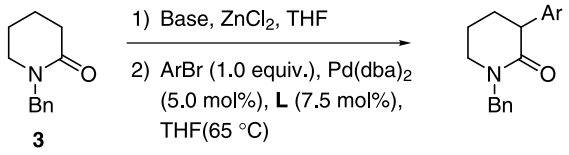
By using LiHMDS, a ratio of (1:1) of piperidinone **3** and enolate **3′** is present before the arylation and can be a limiting factor for obtaining the arylated piperidinones in good yield (Table 5, entries 1 and 6).

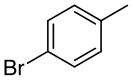
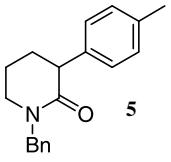
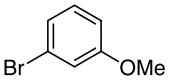
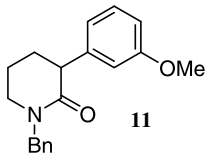
In order to transform **3** entirely to its corresponding enolate **3′**, piperidinone **3** was treated with a stronger base, LiTMP (pK_a=37 in DMSO). These new conditions increase the yield in the α-arylated products **5** and **11**, respectively to 92 and 79% (Table 5, entries 2 and 7) and the non-reacted starting material was recovered.

3.2.2. Chelation of zinc species by the amine. By forming zinc enolates, aggregates such as dimers of type **H** are probably present in the reaction media (Scheme 3). When secondary amines such as HMDS or TMP are present, the dimer **H** is probably chelated by the amine to form **I**. Moreover, in the case of HMDS, a considerable amount of the zinc enolate **H** can be protonated to form **3** (through proton transfer of the amine to the α-carbon atom of the enolate, complex **I**) and a new complex **J**.[11] The reactivity of **I** and **J** in the coupling reaction could be lower than the reactivity of the starting complex **H**.

To get rid of the complexation of the zinc enolate of **3** by amines (HMDS or TMP), the zinc enolate was generated by using *sec*-BuLi (pK_a>45). By using this base, the α-arylated products **5** and **11** were obtained in

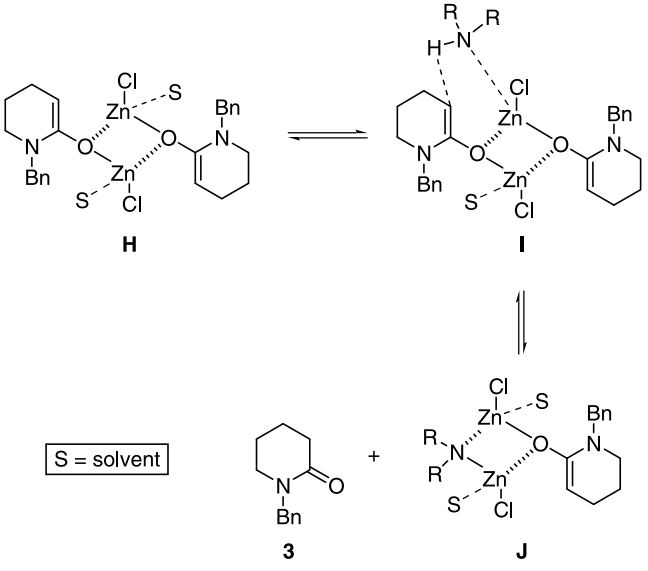
Table 5. α-Arylation of *N*-benzyl-2-piperidinone **3** with *p*-bromotoluene and *m*-bromoanisole



Entry	Piperidinone **3**	ArBr	Base	$ZnCl_2$	Product	Yield %
1	2.2 equiv.		LiHMDS (2.0 equiv.)	2.2 equiv.	 **5**	52
2	2.2 equiv.		LiTMP (2.0 equiv.)	2.2 equiv.		92
3	2.2 equiv.		*sec*-BuLi (2.0 equiv.)	2.2 equiv.		98
4	2.2 equiv.		*sec*-BuLi (2.0 equiv.)	—		47
5	1.3 equiv.		*sec*-BuLi (1.2 equiv.)	1.3 equiv.		44
6	2.2 equiv.		LiHMDS (2.0 equiv.)	2.2 equiv.	 **11**	50
7	2.2 equiv.		LiTMP (2.0 equiv.)	2.2 equiv.		79
8	2.2 equiv.		*sec*-BuLi (2.0 equiv.)	2.2 equiv.		95
9	2.2 equiv.		*sec*-BuLi (2.0 equiv.)	—		48
10	1.3 equiv.		*Sec*-BuLi (1.2 equiv.)	1.3 equiv.		45

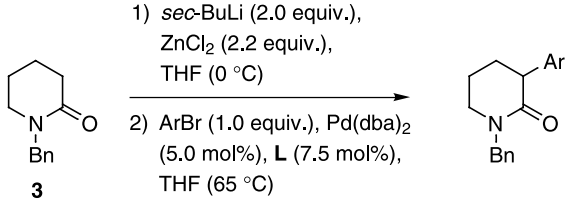
very good yield, 98 and 95%, respectively (Table 5, entries 3 and 8). These results mean that the absence of amines is beneficial to the formation of the α-arylated product, which is consistent with the chelation of the zinc species by amines. We have to point out that the zinc enolate is crucial as the lithium enolate, prepared with *sec*-BuLi, affords the arylated products **5** and **11** in lower yields (Table 5, entries 4 and 9).

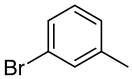
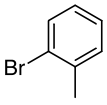
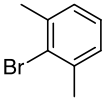
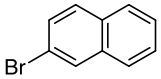
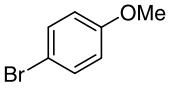
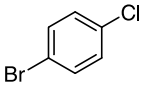
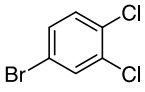
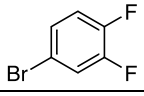
3.2.3. Proton exchange. When 1 equiv. of zinc enolate of **3** was prepared with *sec*-BuLi and treated with 1 equiv. of *p*-bromotoluene or *m*-bromoanisole, the arylated products were obtained in modest yields, 44% and 45%, respectively (Table 5, entries 5 and 10) and the non-reacted starting material was recovered. This last observation demonstrated that the abstraction of the C3-proton of the arylated piperidinone by the zinc enolate of **3** is faster than the palladium coupling process.[4c]



Scheme 3. Possible forms of the zinc enolate of **3**.

Table 6. α-Arylation of **3** with *sec*-BuLi and $ZnCl_2$



Entry	ArBr	Product	Yield %
1		**6**	97
2		**7**	83
3		**8**	0
4		**9**	81
5		**10**	99
6		**13**	84
7		**15**	70
8		**16**	82

The best experimental conditions found for obtaining **5** or **11** from **3** were the generation of the zinc enolate by using *sec*-BuLi and $ZnCl_2$. These conditions were utilized to arylate *N*-benzyl-2-piperidinone **3** with different aryl bromides. Whatever the aryl bromides employed, except the 2,6-dimethyl bromobenzene for which no trace of the coupling product was detected, the palladium-catalyzed coupling products were isolated in excellent yields (from 70 to 99%).[12] The results are reported in Table 6.

We have shown that the zinc enolate of *N*-substituted 2-piperidinones can be arylated by using $Pd(dba)_2$ catalyst in the presence of an electron rich *o*-biphenylphosphine ligand. The best yields in the *N*-benzyl-3-aryl-2-piperidinones were obtained when *sec*-BuLi and $ZnCl_2$ were used to generate the zinc enolate of the starting piperidinone **3**. We have also shown that the proton transfer between the enolate of the piperidinone **3** and the arylated product is faster than the palladium-catalyzed coupling process.

4. Experimental

4.1. General

Benzyl bromide, *p*-toluenesulfonyl chloride, *n*-butyllithium (2.5 M in hexanes), *s*-butyllithium (1.3 M in cyclohexane), δ-valerolactame, lithium bis(trimethylsilyl)amide (1.0 M in THF), palladium dibenzylidene acetone, aryl halides (Aldrich) and ligand **L**, 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)-biphenyl (Strem, weighed under argon), were used without further purification. Zinc chloride was flame-dried, cooled at rt under argon atmosphere and sonicated in THF. THF was distilled over Na/benzophenone.

Reactions were performed in oven-dried round flasks with magnetic stirring, under an argon atmosphere. Flash chromatography was carried out on Kieselgel 60 (230–400 mesh, Merck).

^1H and ^{13}C NMR spectra were respectively recorded on a Bruker AC 300 at 300 and 75 MHz. Spectra were recorder in $CDCl_3$ as solvent, and chemical shifts (δ) were expressed in ppm relative to residual $CHCl_3$ at $\delta=7.27$ for ^1H and to $CDCl_3$ at $\delta=77.1$ for ^{13}C. ^1H NMR *J* values are given in Hz. Mass spectra were obtained by GC/MS with electron impact (EI) ionization by using a 5971 Hewlett Packard instrument at 70 eV: only selected ions are reported. IR spectra were recorded as neat films (NaCl cell) and KBr pellets for solids on a Perkin–Elmer 298. HRMS were performed at the Laboratoire de Spectrochimie de l'Ecole Normale Supérieure in Paris. Elemental analysis were performed by the Centre Régional de Microanalyses (Université Pierre et Marie Curie, Paris VI).

4.1.1. *N*-Tosyl-2-piperidinone (1).[13] To a stirred solution of *n*-BuLi (15.8 mL, 1.13 equiv.) in THF (60 mL) at −78 °C was added a solution of δ-valerolactame (3.5 g, 1.0 equiv.) in THF (40 mL) via cannula. After 20 min at −78 °C, a solution of *p*-toluenesulfonyl chloride (6.7 g, 1.0 equiv.) in THF (40 mL) was added and the solution was slowly warmed to rt and stirred overnight. The reaction was then quenched with aqueous NH_4Cl and extracted with Et_2O. The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting white solid was purified by recrystallization from toluene to give 7.1 g (80%) of **1**. Mp: 148 °C. IR (KBr): 2955, 1683, 1594, 1438, 1350, 1261, 1172, 972, 827 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.89 (d, $J=8.5$ Hz, 2H), 7.30 (d, $J=8.5$ Hz, 2H), 3.90 (m, 2H), 2.41 (s, 3H), 2.40 (m, 2H), 1.93–1.85 (2H), 1.81–1.72 (2H). ^{13}C NMR ($CDCl_3$) δ: 170.5 (s), 145.0 (s), 136.4 (s), 129.6 (d), 129.0 (d), 47.2 (t), 34.4 (t), 23.6 (t), 21.9 (q), 20.7 (t). EI MS *m*/*z* (relative intensity) 189 (68), 160 (14), 155 (11), 146 (13), 133 (100), 120 (45), 108 (22), 98 (1), 91 (82), 82 (11), 77 (4), 65 (29), 55 (13), 51 (3).

4.1.2. *N*-Benzyl-2-piperidinone (3).[14] To a stirred solution of *n*-BuLi (18.4 mL, 1.13 equiv.) in THF (130 mL) at −78 °C was added a solution of δ-valerolactame (4.1 g, 1.0 equiv.) in THF (40 mL) via cannula. After 20 min at −78 °C, benzyl bromide (7.1 g, 1.0 equiv.) was added and the solution was slowly warmed to rt and stirred overnight. The reaction was then quenched with aqueous NH_4Cl and extracted with Et_2O. The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting oil was purified by distillation under reduced pressure (110 °C at 4.0×10^{-2} mbar) to give 7.7 g (97%) of **3**. IR (neat): 2939, 1635, 1490, 1448, 1352, 1261, 1177 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.26–7.12 (5H), 4.50 (s, 2H), 3.09 (m, 2H), 2.36 (m, 2H), 1.72–1.61 (4H). ^{13}C NMR ($CDCl_3$) δ: 169.7 (s), 137.3 (s), 128.5 (d), 128.0 (d), 127.2 (d), 50.0 (t), 47.2 (t), 32.4 (t), 23.1 (t), 21.3 (t). EI MS *m*/*z* (relative intensity) 189 ($M^{+\cdot}$, 100), 160 (10), 146 (3), 132 (8), 118 (3), 112 (2), 106 (22), 98 (31), 91 (62), 85 (16), 77 (5), 70 (2), 65 (11), 55 (8), 51 (3).

4.1.3. *N*-Benzoyl-2-piperidinone (20).[15] To a stirred solution of *n*-BuLi (18.2 mL, 1.13 equiv.) in THF (100 mL) at −78 °C was added a solution of δ-valerolactame (4.0 g, 1.0 equiv.) in THF (40 mL) via cannula. After 20 min at −78 °C, benzoyl chloride (5.7 g, 1.0 equiv.) was added and the solution was slowly warmed to rt and stirred overnight. The reaction was then quenched with aqueous NH_4Cl and extracted with Et_2O. The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting white solid was purified by recristallization from toluene to give 5.7 g (70%) of **20**. Mp: 110 °C. IR (KBr): 2955, 1694, 1672, 1466, 1444, 1388, 1288, 1244, 1144, 1100, 983, 938, 822 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.56–7.52 (2H), 7.47 (m, 1H), 7.40–7.35 (2H), 3.79 (m, 2H), 2.55 (m, 2H), 2.00–1.88 (4H). ^{13}C NMR ($CDCl_3$) δ: 174.9 (s), 173.7 (s), 136.4 (s), 131.7 (d), 128.4 (d), 128.1 (d), 46.4 (t), 34.9 (d), 23.1 (t), 21.7 (t). EI MS *m*/*z* (relative intensity) 203 ($M^{+\cdot}$, 20), 175 (20), 146 (5), 119 (10), 105 (100), 98 (5), 77 (40), 70 (2), 55 (2), 51 (8).

4.2. Reaction procedure for α-arylation of *N*-protected-2-piperidinones with LiHMDS

To a stirred solution (or suspension) of a *N*-protected 2-piperidinone (1.1 mmol, 2.2 equiv.) in THF (2 mL) at −20 °C was added a solution of LiHMDS (1.0 mL, 2.0 equiv.). After 20 min at −20 °C, a solution of $ZnCl_2$ (0.150 g, 1.1 mmol, 2.2 equiv.) in THF (1 mL) was added. After another 20 min at −20 °C, the solution of zinc enolate

was cannulated into a solution of 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl **L** (0.015 g, 37.5 μmol, 7.5 mol%), $Pd(dba)_2$ (0.014 g, 25.0 μmol, 5.0 mol%) and aryl bromide (0.5 mmol, 1.0 equiv.) in THF (1 mL). The solution was then heated in an oil bath at 65 °C for 8 h, cooled to rt, quenched with aqueous NH_4Cl and extracted with Et_2O. The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was then purified by chromatography on silica gel using 80:20 cyclohexane/ethyl acetate, unless otherwise stated.

4.2.1. *N*-Tosyl-3-phenyl-2-piperidinone (2).[6] Following the procedure outlined above, bromobenzene (78.5 mg, 0.5 mmol) and *N*-tosyl-2-piperidinone **1** (280 mg, 1.1 mmol) gave **2** (152 mg, 92%) after chromatography. IR (neat): 2950, 1690, 1595, 1452, 1353, 1282, 1169, 1088, 1008 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.93 (d, $J=8.5$ Hz, 2H), 7.30 (d, $J=8.5$ Hz, 2H), 7.26–7.20 (3H), 7.07–7.02 (2H), 4.06 (m, 2H), 3.63 (dd, $J=9.2$, 6.2 Hz, 1H), 2.42 (s, 3H), 2.22–1.86 (4H). ^{13}C NMR ($CDCl_3$) δ: 171.7 (s), 145.0 (s), 139.5 (s), 136.4 (s), 129.6 (d), 129.1 (d), 128.9 (d), 128.4 (d), 127.4 (d), 50.8 (d), 47.3 (t), 29.7 (t), 22.2 (t), 22.0 (q). CI^+ (CH_4) MS *m*/*z* (relative intensity): 330 ($M+H^+$, 100), 204 (12), 176 (67), 175 (14), 174 (48), 157 (18), 154 (15), 133 (14), 125 (23). HRMS (CI^+, CH_4): calcd for $C_{18}H_{20}NO_3S$ ($M+H^+$): 330.1164. Found: 330.1171.

4.2.2. *N*-Benzyl-3-phenyl-2-piperidinone (4).[16] Following the procedure outlined above, bromobenzene (78.5 mg, 0.5 mmol) and *N*-benzyl-2-piperidinone **3** (210 mg, 1.1 mmol) gave **4** (130 mg, 98%) after chromatography. IR (neat): 2940, 1640, 1488, 1450, 1349, 1250, 1190 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.29–7.22 (7H), 7.19–7.14 (3H), 4.65 (d, $J=14.5$ Hz, 1H), 4.57 (d, $J=14.5$ Hz, 1H), 3.68 (dd, $J=8.1$, 5.9 Hz, 1H), 3.26 (m, 2H), 2.10 (m, 1H), 1.97–1.62 (3H). ^{13}C NMR ($CDCl_3$) δ: 170.5 (s), 141.7 (s), 137.4 (s), 128.6 (d), 128.5 (d), 128.4 (d), 128.3 (d), 127.4 (d), 126.6 (d), 50.4 (t), 48.7 (d), 47.4 (t), 30.4 (t), 20.9 (t). EI MS *m*/*z* (relative intensity) 265 ($M^{+\cdot}$, 100), 174 (27), 148 (6), 132 (11), 131 (78), 117 (6), 116 (6), 115 (6), 104 (11), 92 (6), 91 (71), 77 (5), 65 (7), 51 (2). HRMS (EI) calcd for $C_{18}H_{19}NO$: 265.1467. Found: 265.1462.

4.2.3. *N*-Benzyl-3-(2,4-dimethoxyphenyl)-2-piperidinone (12).[6] Following the procedure outlined above, 2,4-dimethoxy-bromobenzene (108.5 mg, 0.5 mmol) and *N*-benzyl-2-piperidinone **3** (210 mg, 1.1 mmol) gave **12** (137 mg, 84%) after chromatography (30% ethyl acetate in cyclohexane). IR (neat): 2936, 1638, 1508, 1450, 1295, 1212, 1155, 1030 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.36–7.28 (5H), 7.03 (d, $J=8.1$ Hz, 1H), 6.47 (d, $J=2.6$ Hz, 1H), 6.44 (dd, $J=8.1$, 2.6 Hz, 1H), 4.94 (d, $J=14.3$ Hz, 1H), 4.41 (d, $J=14.3$ Hz, 1H), 3.79 (s, 3H), 3.78 (m, 1H), 3.73 (s, 3H), 3.36 (m, 1H), 3.27 (m, 1H), 2.05–1.95 (2H), 1.90–1.74 (2H). ^{13}C NMR ($CDCl_3$) δ: 171.6 (s), 160.0 (s), 157.9 (s), 138.1 (s), 130.6 (d), 128.7 (d), 127.5 (d), 123.5 (s), 104.4 (d), 99.3 (d), 55.6 (q), 55.5 (q), 51.0 (t), 48.0 (t), 45.0 (d), 29.4 (t), 22.5 (t). EI MS *m*/*z* (relative intensity) 325 ($M^{+\cdot}$, 98), 191 (19), 190 (17), 189 (15), 187 (37), 177 (19), 160 (19), 159 (100), 158 (20), 151 (21), 149 (13), 121 (19), 91 (57). HRMS (EI) calcd for $C_{20}H_{23}NO_3$: 325.1678. Found: 325.1683.

4.2.4. *N*-Benzyl-3-(2-chlorophenyl)-2-piperidinone (14). Following the procedure outlined above, 2-chloro-bromobenzene (95.7 mg, 0.5 mmol) and *N*-benzyl-2-piperidinone **3** (210 mg, 1.1 mmol) gave **14** (115 mg, 77%) after chromatography. Mp: 85 °C. IR (KBr): 2916, 1634, 1493, 1433, 1351, 1263, 1166, 1032 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.39–7.30 (6H), 7.23–7.17 (3H), 4.72 (d, $J=14.7$ Hz, 1H), 4.67 (d, $J=14.7$ Hz, 1H), 4.08 (dd, $J=9.4$, 6.4 Hz, 1H), 3.40 (ddd, $J=12.1$, 8.8, 5.1 Hz, 1H), 3.32 (m, 1H), 2.13 (m, 1H), 2.01 (m, 1H), 1.87 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 170.1 (s), 139.9 (s), 137.6 (s), 133.8 (s), 130.6 (d), 130.1 (d), 128.8 (d), 128.7 (d), 128.3 (d), 127.7 (d), 127.2 (d), 50.9 (t), 47.8 (t), 47.4 (d), 29.0 (t), 22.0 (t). EI MS *m*/*z* (relative intensity) 299 ($M^{+\cdot}$, 2), 265 (22), 264 (100), 165 (10), 130 (7), 125 (7), 91 (30). HRMS (IC^+, CH_4) calcd for $C_{18}H_{19}^{35}ClNO$: 300.1155. Found: 300.1151. Calcd for $C_{18}H_{19}^{37}ClNO$: 302.1132. Found: 302.1134.

4.2.5. *N*-Tosyl-3-(2-methylphenyl)-2-piperidinone (17).[6] Following the procedure outlined above, 2-methyl-bromobenzene (85.5 mg, 0.5 mmol) and *N*-tosyl-2-piperidinone **1** (280 mg, 1.1 mmol) gave **17** (70 mg, 41%) after chromatography. IR (neat): 2952, 1690, 1456, 1350, 1281, 1168, 1089, 1006, 814 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.94 (d, $J=8.2$ Hz, 2H), 7.31 (d, $J=8.2$ Hz, 2H), 7.13–7.04 (3H), 6.89 (d, $J=7.0$ Hz, 1H), 4.21 (m, 1H), 3.95 (m, 1H), 3.77 (m, 1H), 2.43 (s, 3H), 2.16–2.10 (2H), 2.12 (s, 3H), 2.01–1.81 (2H). ^{13}C NMR ($CDCl_3$) δ: 171.5 (s), 144.8 (s), 138.4 (s), 136.2 (s), 135.6 (s), 130.9 (d), 129.3 (d), 128.9 (d), 128.6 (d), 127.3 (d), 126.3 (d), 48.5 (d), 47.3 (t), 28.9 (t), 22.6 (t), 21,7 (q), 19.6 (q). EI MS *m*/*z* (relative intensity) 344 ($M^{+\cdot}$, 1), 343 ($M^{+\cdot}$, 5), 280 (21), 279 (100), 188 (13), 172 (8), 146 (10), 145 (75), 131 (8), 130 (16), 129 (8), 120 (16), 119 (30), 117 (21), 115 (13), 105 (25), 91 (33), 65 (8). HRMS (IC^+, CH_4): calcd for $C_{19}H_{22}NO_3S$ ($M+H^+$): 344.1320. Found: 344.1322.

4.2.6. *N*-Tosyl-3-(4-methoxyphenyl)-2-piperidinone (18). Following the procedure outlined above, 4-methoxy-bromobenzene (93.5 mg, 0.5 mmol) and *N*-tosyl-2-piperidinone **1** (280 mg, 1.1 mmol) gave **18** (108 mg, 60%) after chromatography. Mp: 121 °C. IR (KBr): 2962, 1691, 1612, 1518, 1463, 1352, 1278, 1232, 1161, 1022, 832 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.92 (d, $J=8.1$ Hz, 2H), 7.29 (d, $J=8.1$ Hz, 2H), 6.97 (d, $J=8.7$ Hz, 2H), 6.79 (d, $J=8.7$ Hz, 2H), 4.10–3.94 (2H), 3.75 (s, 3H), 3.57 (dd, $J=9.4$, 6.0 Hz, 1H), 2.42 (s, 3H), 2.18–2.02 (2H), 2.00–1.88 (2H). ^{13}C NMR ($CDCl_3$) δ: 171.8 (s), 158.8 (s), 144.7 (s), 136.3 (s), 131.3 (s), 129.4 (d), 129.2 (d), 128.9 (d), 114.2 (d), 55.3 (q), 49.8 (d), 47.0 (t), 29.3 (t), 22.1 (t), 21.7 (q). EI MS *m*/*z* (relative intensity) 359 ($M^{+\cdot}$, 4), 296 (17), 295 (81), 205 (9), 204 (64), 176 (11), 162 (12), 161 (100), 160 (12), 159 (8), 147 (8), 146 (15), 135 (25), 134 (23), 133 (17), 129 (8), 121 (31), 119 (14), 115 (7), 91 (60), 77 (9), 65 (18).

4.2.7. *N*-Tosyl-3-(3,4-dichlorophenyl)-2-piperidinone (19). Following the procedure outlined above, 3,4-dichloro-bromobenzene (113.0 mg, 0.5 mmol) and *N*-tosyl-2-piperidinone **1** (280 mg, 1.1 mmol) gave **18** (84 mg, 50%) after chromatography. Mp: 68 °C. IR (KBr): 2930, 1680, 1488, 1450, 1352, 1241, 1193 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.40 (d, $J=9.0$ Hz, 1H), 7.37–7.30 (5H), 7.34 (d, $J=3.0$ Hz, 1H), 7.08

(dd, J=9.0, 3.0 Hz, 1H), 4.66 (s, 2H), 3.68 (dd, J=8.65, 6.02 Hz, 1H), 3.35 (m, 2H), 2.17 (m, 1H), 2.00–1.74 (3H). ^{13}C NMR ($CDCl_3$) δ: 169.5 (s), 141.7 (s), 137.1 (s), 132.2 (s), 130.6 (s), 130.3 (d), 130.2 (d), 128.6 (d), 128.2 (d), 127.8 (d), 127.4 (d), 50.5 (t), 47.9 (d), 47.4 (t), 30.0 (t), 21.1 (t). EI MS m/z (relative intensity) 337 ($M^{+\cdot}$, 8), 335 ($M^{+\cdot}$, 47), 333 ($M^{+\cdot}$, 78), 244 (20), 242 (35), 201 (35), 199 (59), 164 (19), 91 (100). Anal. calcd for $C_{18}H_{17}Cl_2NO$: C: 64.67, H: 5.09, N: 4.19. Found: C: 64.70, H: 5.32, N: 4.01.

4.2.8. *N*-Benzoyl-3-phenyl-2-piperidinone (21). Following the procedure outlined above, bromobenzene (78.5 mg, 0.5 mmol) and *N*-benzoyl-2-piperidinone **20** (224 mg, 1.1 mmol) gave **21** (112 mg, 80%) after chromatography. Mp: 139 °C. IR (KBr): 2943, 1672, 1447, 1384, 1289, 1148, 806, 701 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.55–7.52 (2H), 7.42 (m, 1H), 7.37–7.31 (4H), 7.29–7.23 (3H), 4.01 (m, 1H), 3.93–3.80 (2H), 2.32 (m, 1H), 2.23–2.04 (3H). ^{13}C NMR ($CDCl_3$) δ: 174.8 (s), 174.6 (s), 139.0 (s), 136.2 (s), 131.4 (d), 128.6 (d), 128.5 (d), 128.2 (d), 127.8 (d), 127.2 (d), 51.1 (d), 46.4 (t), 30.3 (t), 22.2 (t). EI MS m/z (relative intensity) 279 ($M^{+\cdot}$, 18), 174 (1), 132 (2), 115 (2), 105 (100), 91 (4), 77 (23), 51 (3). HRMS (EI) calcd for $C_{18}H_{17}NO_2$: 279.1259. Found: 279.1253.

4.2.9. *N*-Benzoyl-3-(2-methylphenyl)-2-piperidinone (22). Following the procedure outlined above, 2-methylbromobenzene (85.5 mg, 0.5 mmol) and *N*-benzoyl-2-piperidinone **20** (224 mg, 1.1 mmol) gave **22** (54 mg, 43%) after chromatography. IR (neat): 2933, 1678, 1448, 1288, 1148 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.57–7.54 (2H), 7.45–7.32 (3H), 7.16 (m, 4H), 4.12–4.00 (2H), 3.90 (m, 1H), 2.32 (s, 3H), 2.32–2.08 (4H). ^{13}C NMR ($CDCl_3$) δ: 174.9 (s), 174.4 (s), 137.8 (s), 136.4 (s), 136.2 (s), 131.5 (d), 130.9 (d), 128.2 (d), 128.1 (d), 127.8 (d), 127.3 (d), 126.3 (d), 48.1 (d), 46.6 (t), 29.8 (t), 22.9 (t), 19.9 (q). EI MS m/z (relative intensity) 294 ($M^{+\cdot}$, 4), 293 ($M^{+\cdot}$, 19), 276 (16), 275 (32), 171 (6), 145 (5), 117 (5), 115 (4), 106 (8), 105 (100), 77 (25). HRMS (EI) calcd for $C_{19}H_{19}NO_2$: 293.1416. Found: 293.1410.

4.2.10. *N*-Benzoyl-3-(4-methoxyphenyl)-2-piperidinone (23). Following the procedure outlined above, 4-methoxybromobenzene (93.5 mg, 0.5 mmol) and *N*-benzoyl-2-piperidinone **20** (224 mg, 1.1 mmol) gave **23** (78 mg, 50%) after chromatography. Mp: 136 °C. IR (KBr): 2958, 1675, 1517, 1292, 1233, 1152, 1032, 831, 739, 699 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.43–7.39 (2H), 7.34–7.20 (3H), 7.06 (d, J=8.7 Hz, 2H), 6.77 (d, J=8.7 Hz, 2H), 3.88 (m, 1H), 3.82–3.73 (2H), 3.67 (s, 3H), 2.19 (m, 1H), 2.11–1.92 (3H). ^{13}C NMR ($CDCl_3$) δ: 174.9 (s), 174.8 (s), 158.8 (s), 136.2 (s), 131.4 (d), 131.0 (s), 129.5 (d), 128.2 (d), 127.8 (d), 114.1 (d), 55.3 (q), 50.3 (d), 46.3 (t), 30.3 (t), 22.3 (t). EI MS m/z (relative intensity) 310 ($M^{+\cdot}$, 21), 309 ($M^{+\cdot}$, 97), 205 (11), 204 (79), 162 (5), 161 (40), 146 (5), 135 (13), 134 (10), 121 (13), 119 (7), 106 (8), 105 (100), 91 (12), 78 (6), 77 (50), 51 (9).

4.2.11. *N*-Benzoyl-3-(3,4-dichlorophenyl)-2-piperidinone (24). Following the procedure outlined above, 3,4-dichlorobromobenzene (113.0 mg, 0.5 mmol) and *N*-benzoyl-2-piperidinone **20** (224 mg, 1.1 mmol) gave **24** (105 mg, 60%) after chromatography. Mp: 137 °C. IR (KBr): 2944, 1693, 1670, 1470, 1388, 1289, 1148, 1028, 828 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.55–7.30 (7H), 7.05 (dd, J=8.5, 2.2 Hz, 1H), 3.92 (m, 2H), 3.78 (m, 1H), 2.31 (m, 1H), 2.23–2.02 (3H). ^{13}C NMR ($CDCl_3$) δ: 174.8 (s), 173.9 (s), 139.2 (s), 136.2 (s), 132.8 (s), 131.9 (d), 131.6 (s), 130.9 (d), 130.7 (d), 128.5 (d), 128.3 (d), 128.0 (d), 50.5 (d), 46.6 (t), 30.5 (t), 22.6 (t). EI MS m/z (relative intensity) 351 ($M^{+\cdot}$, 1), 349 ($M^{+\cdot}$, 4), 347 ($M^{+\cdot}$, 5), 172 (2), 159 (1), 149 (1), 137 (1), 128 (1), 115 (1), 105 (100), 77 (19), 51 (2). HRMS (EI) calcd for $C_{18}H_{15}^{35}Cl_2NO_2$: 347.0480. Found: 347.0472. HRMS (EI) calcd for $C_{18}H_{15}^{35}Cl^{37}ClNO_2$: 349.0454. Found: 349.0443.

4.3. Reaction procedure for α-arylation of *N*-benzyl-2-piperidinone 3 with *sec*-BuLi

To a stirred solution of *N*-benzyl-2-piperidone **3** (1.1 mmol, 2.2 equiv.) in THF (2 mL) at 0 °C was added a solution of *s*-BuLi (0.7 mL, 2.0 equiv.). After 20 min, a solution of $ZnCl_2$ (0.150 g, 1.1 mmol, 2.2 equiv.) in THF (1 mL) was added, and after 20 min, a solution of zinc enolate was cannulated to a solution of 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino) biphenyl **L** (0.015 g, 37.5 μmol, 7.5 mol%), $Pd(dba)_2$ (0.014 g, 25.0 μmol, 5.0 mol%) and aryl bromide (0.5 mmol, 1.0 equiv.) in THF (1 mL). The solution was then heated in an oil bath at 65 °C for 8 h, cooled to rt, quenched with aqueous NH_4Cl and extracted with Et_2O. The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was then purified by chromatography on silica gel using 80:20 cyclohexane/ethyl acetate, unless otherwise stated.

4.3.1. *N*-Benzyl-3-(4-methylphenyl)-2-piperidinone (5).[6] Following the procedure outlined above, 4-methyl-bromobenzene (85.5 mg, 0.5 mmol) gave **5** (137 mg, 98%) after chromatography. IR (neat): 2940, 1680, 1490, 1450, 1350, 1192 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.37–7.29 (5H), 7.17–7.11 (4H), 4.73 (d, J=14.5 Hz, 1H), 4.63 (d, J=14.5 Hz, 1H), 3.71 (dd, J=8.1, 6.3 Hz, 1H), 3.32 (m, 2H), 2.34 (s, 3H), 2.15 (m, 1H), 2.03–1.70 (3H). ^{13}C NMR ($CDCl_3$) δ: 171.1 (s), 139.0 (s), 137.8 (s), 136.3 (s), 129.4 (d), 128. 8 (d), 128.6 (d), 128.4 (d), 127.6 (d), 50.8 (t), 48.6 (d), 47.8 (t), 30.7 (t), 27.2 (t), 21.3 (q). EI MS m/z (relative intensity) 279 ($M^{+\cdot}$, 100), 188 (21), 145 (67), 130 (10), 119 (17), 118 (12), 117 (17), 105 (19), 91 (48). HRMS (EI) calcd for $C_{19}H_{21}NO$: 279.1623. Found: 279.1626.

4.3.2. *N*-Benzyl-3-(3-methylphenyl)-2-piperidinone (6). Following the procedure outlined above, 3-methyl-bromobenzene (85.5 mg, 0.5 mmol) gave **6** (135 mg, 97%) after chromatography. IR (neat): 2940, 1640, 1490, 1450, 1352, 1255, 1193 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.38–7.20 (6H), 7.07–7.01 (3H), 4.74 (d, J=14.3 Hz, 1H), 4.63 (d, J=14.3 Hz, 1H), 3.71 (dd, J=8.1, 6.2 Hz, 1H), 3.34 (m, 2H), 2.34 (s, 3H), 2.17 (m, 1H), 2.03–1.69 (3H). ^{13}C NMR ($CDCl_3$) δ: 171.1 (s), 142. 0 (s), 138. 3 (s), 137. 9 (s), 129.4 (d), 129.0 (d), 128.7 (d), 127.9 (d), 127.7 (d), 127.6 (d), 125.7 (d), 50.8 (t), 49.0 (d), 47.8 (t), 30.8 (t), 21.8 (t), 21.3 (q). EI MS m/z (relative intensity) 279 ($M^{+\cdot}$, 100), 188 (21), 145 (59), 130 (9), 119 (18), 117 (14), 105 (16), 91 (43). HRMS (IE) calcd for $C_{19}H_{21}NO$: 279.1623. Found: 279.1622.

4.3.3. *N*-Benzyl-3-(2-methylphenyl)-2-piperidinone (7).[6] Following the procedure outlined above, 2-methyl-bromobenzene (85.5 mg, 0.5 mmol) gave **7** (116 mg, 83%) after chromatography. IR (neat): 2940, 1635, 1490, 1452, 1350, 1198 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.39–7.29 (5H), 7.19–7.14 (3H), 7.09 (m, 1H), 4.75 (d, J=14.5 Hz, 1H), 4.66 (d, J=14.5 Hz, 1H), 3.93 (dd, J=7.7, 6.6 Hz, 1H), 3.36 (m, 2H), 2.36 (s, 3H), 2.12 (m, 1H), 1.96–1.75 (3H). ^{13}C NMR ($CDCl_3$) δ: 171.2 (s), 140.7 (s), 137.7 (s), 136.1 (s), 130.9 (d), 128.9 (d), 128.7 (d), 128.4 (d), 127.7 (d), 126.9 (d), 126.3 (d), 50.9 (t), 47.9 (t), 46.3 (d), 29.6 (t), 21.6 (t), 19.8 (q). EI MS *m/z* (relative intensity) 279 ($M^{+\cdot}$, 100), 264 (7), 188 (14), 174 (36), 145 (37), 130 (9), 119 (12), 117 (17), 115 (9), 105 (18), 91 (51). HRMS (EI) calcd for $C_{19}H_{21}NO$: 279.1623. Found: 279.1626.

4.3.4. *N*-Benzyl-3-(2-naphtyl)-2-piperidone (9). Following the procedure outlined above, 2-bromonaphthalene (103.5 mg, 0.5 mmol) gave **9** (128 mg, 81%) after chromatography. IR (neat): 2938, 1638, 1490, 1450, 1351, 1245, 1190 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.86–7.78 (3H), 7.69 (d, J=0.1 Hz, 1H), 7.49–7.45 (2H), 7.42–7.34 (6H), 4.81 (d, J=14.3 Hz, 1H), 4.66 (d, J=14.3 Hz, 1H), 3.94 (dd, J=8.1, 6.3 Hz, 1H), 3.37 (m, 2H), 2.23 (m, 1H), 2.08 (m, 1H), 1.84 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 170.9 (s), 139.5 (s), 137.8 (s), 133.7 (s), 132.6 (s), 128.9 (d), 128.7 (d), 128.4 (d), 128.0 (d), 127.8 (d), 127.7 (d), 127.2 (d), 126.8 (d), 126.2 (d), 125.8 (d), 50.8 (t), 49.1 (d), 47.8 (t), 30.6 (t), 21.2 (t). EI MS *m/z* (relative intensity) 315 ($M^{+\cdot}$, 100), 224 (22), 181 (54), 166 (27), 155 (45), 154 (23), 153 (22), 141 (20), 91 (39). HRMS (IE) calcd for $C_{22}H_{21}NO$: 315.1623. Found: 315.1618.

4.3.5. *N*-Benzyl-3-(4-methoxyphenyl)-2-piperidinone (10).[6] Following the procedure outlined above, 4-methoxy-bromobenzene (93.5 mg, 0.5 mmol) gave **10** (146 mg, 99%) after chromatography (30% ethyl acetate in cyclohexane). IR (neat): 2938, 1638, 1510, 1451, 1245, 1180, 1035 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.37–7.29 (5H), 7.16 (d, J=8.6 Hz, 2H), 6.88 (d, J=8.6 Hz, 2H), 4.72 (d, J=14.5 Hz, 1H), 4.63 (d, J=14.5 Hz, 1H), 3.79 (s, 3H), 3.70 (dd, J=8.4, 6.0 Hz, 1H), 3.32 (m, 2H), 2.15 (m, 1H), 2.03–1.70 (3H). ^{13}C NMR ($CDCl_3$) δ: 171.1 (s), 158.5 (s), 137.7 (s), 134.1 (s), 129.4 (d), 128.8 (d), 128.5 (d), 127.6 (d), 55.5 (q), 50.7 (t), 48.1 (d), 47.7 (t), 30.7 (t), 21.3 (t). EI MS *m/z* (relative intensity) 295 ($M^{+\cdot}$, 100), 204 (19), 187 (12), 161 (52), 160 (29), 159 (59), 147 (11), 135 (14), 134 (22), 121 (20), 91 (69). HRMS (EI) calcd for $C_{19}H_{21}NO_2$: 295.1572. Found: 295.1570.

4.3.6. *N*-Benzyl-3-(3-methoxyphenyl)-2-piperidinone (11).[6] Following the procedure outlined above, 3-methoxy-bromobenzene (85.5 mg, 0.5 mmol) gave **11** (140 mg, 95%) after chromatography (30% ethyl acetate in cyclohexane). IR (neat): 2940, 1638, 1490, 1452, 1260 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.36–7.22 (6H), 6.84–6.77 (3H), 4.76 (d, J=14.5 Hz, 1H), 4.59 (d, J=14.5 Hz, 1H), 3.78 (s, 3H), 3.73 (dd, J=7.5, 6.0 Hz, 1H), 3.33 (m, 2H), 2.16 (m, 1H), 2.03–1.70 (3H). ^{13}C NMR ($CDCl_3$) δ: 170.8 (s), 159.9 (s), 143.6 (s), 137.8 (s), 129.7 (d), 128.9 (d), 128.6 (d), 127.7 (d), 120.9 (d), 114.5 (d), 112.3 (d), 55.4 (q), 50.8 (t), 49.0 (d), 47.8 (t), 30.7 (t), 21.2 (t). EI MS *m/z* (relative intensity) 295 ($M^{+\cdot}$, 100), 204 (25), 176 (7), 161 (57), 148 (7), 134 (13), 135 (15), 121 (13), 91 (64), 65 (8). HRMS (EI) calcd for $C_{19}H_{21}NO_2$: 295.1572. Found: 295.1575.

4.3.7. *N*-Benzyl-3-(4-chlorophenyl)-2-piperidone (13). Following the procedure outlined above, 4-chloro-bromobenzene (95.7 mg, 0.5 mmol) gave **13** (126 mg, 84%) after chromatography. Mp: 127 °C. IR (KBr): 2924, 1618, 1491, 1431, 1349, 1244, 1195, 1085, 818 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.38–7.27 (5H), 7.30 (d, J=8.5 Hz, 2H), 7.16 (d, J=8.5 Hz, 2H), 4.69 (d, J=14.7 Hz, 1H), 4.63 (d, J=14.7 Hz, 1H), 3.70 (dd, J=8.6, 6.0 Hz, 1H), 3.33 (m, 2H), 2.16 (m, 1H), 1.99–1.74 (3H). ^{13}C NMR ($CDCl_3$) δ: 170.4 (s), 140.5 (s), 137.6 (s), 132.6 (s), 130.0 (d), 128.9 (d), 128.8 (d), 128.6 (d), 127.7 (d), 50.8 (t), 48.5 (d), 47.8 (t), 30.6 (t), 21.4 (t). EI MS *m/z* (relative intensity) 299 ($M^{+\cdot}$, 100), 208 (40), 167 (27), 165 (84), 130 (25), 129 (17), 125 (20), 115 (11), 91 (90), 65 (11). Anal. calcd for $C_{18}H_{18}NOCl$: C: 72.12, H: 6.05, N: 4.67. Found: C: 71.79, H: 6.20, N: 4.47.

4.3.8. *N*-Benzyl-3-(3,4-dichlorophenyl)-2-piperidone (15). Following the procedure outlined above, 3,4-dichloro-bromobenzene (113 mg, 0.5 mmol) gave **15** (117 mg, 70%) after chromatography. Mp: 68 °C. IR (KBr): 2930, 1680, 1488, 1450, 1352, 1241, 1193 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.40 (d, J=9.0 Hz, 1H), 7.37–7.30 (5H), 7.34 (d, J=3.0 Hz, 1H), 7.08 (dd, J=9.0, 3.0 Hz, 1H), 4.66 (s, 2H), 3.68 (dd, J=8.65, 6.02 Hz, 1H), 3.35 (m, 2H), 2.17 (m, 1H), 2.00–1.74 (3H). ^{13}C NMR ($CDCl_3$) δ: 169.5 (s), 141.7 (s), 137.1 (s), 132.2 (s), 130.6 (s), 130.3 (d), 130.2 (d), 128.6 (d), 128.2 (d), 127.8 (d), 127.4 (d), 50.5 (t), 47.9 (d), 47.4 (t), 30.0 (t), 21.1 (t). EI MS *m/z* (relative intensity) 337 ($M^{+\cdot}$, 8), 335 ($M^{+\cdot}$, 47), 333 ($M^{+\cdot}$, 78), 244 (20), 242 (35), 201 (35), 199 (59), 164 (19), 91 (100). Anal. calcd for $C_{18}H_{17}Cl_2NO$: C: 64.67, H: 5.09, N: 4.19. Found: C: 64.70, H: 5.32, N: 4.01.

4.3.9. *N*-Benzyl-3-(3,4-difluorophenyl)-2-piperidone (16). Following the procedure outlined above, 3,4-difluoro-bromobenzene (96.5 mg, 0.5 mmol) gave **16** (124 mg, 82%) after chromatography. Mp: 106 °C. IR (KBr): 2934, 1620, 1521, 1432, 1289, 1195, 1117 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.39–7.27 (5H), 7.15–7.01 (2H), 6.95 (m, 1H), 4.65 (s, 2H), 3.68 (dd, J=8.6, 6.0 Hz, 1H), 3.33 (m, 2H), 2.16 (m, 1H), 1.99–1.72 (3H). ^{13}C NMR ($CDCl_3$) δ: 170.2 (s), 150.4 (sdd, J=247.0, 12.5 Hz), 149.5 (sdd, J=247.0, 12.5 Hz), 138.8 (sdd, J=5.5, 3.7 Hz), 137.5 (s), 129.0 (d), 128.6 (d), 127.8 (d), 124.7 (ddd, J=6.1, 3.7 Hz), 117.6 (dd, J=17.1 Hz), 117.4 (ddd, J=17.1, 1.2 Hz), 50.9 (t), 48.3 (d), 47.8 (t), 30.5 (t), 21.5 (t). EI MS *m/z* (relative intensity) 301 ($M^{+\cdot}$, 100), 210 (29), 168 (11), 167 (94), 140 (9), 127 (29), 91 (85), 65 (8). HRMS (IE) calcd for $C_{18}H_{17}F_2NO$: 301.1278. Found: 301.1284.

Acknowledgements

We gratefully acknowledge Sanofi-Synthelabo for a grant (A. de F.) and financial support.

References and notes

1. (a) Bunnett, J. F.; Zahler, R. E. *Chem. Rev.* **1952**, *49*, 273–412. (b) Bunnett, J. F. *Acc. Chem. Res.* **1972**, *5*, 139–147. (c) Paradisi, C. *Comprehensive Organic Synthesis*, Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon: New York, 1991; Vol. 4, Chapter 2.1 and references cited therein. (d) Norris, R. K. *Comprehensive Organic Synthesis*, Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon: New York, 1991; Vol. 4, Chapter 2.2 and references cited therein. (e) Kessar, S. V. *Comprehensive Organic Synthesis*, Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon: New York, 1991; Vol. 4, Chapter 2.3 and references cited therein.
2. (a) Scolastico, C.; Poli, G. *Chemtracts* **1999**, *12*, 498–507. (b) Bolm, C.; Hildebrand, J. P.; Muniz, K.; Hermanns, N. *Angew. Chem., Int. Ed.* **2001**, *40*, 3284–3308. (c) Prim, D.; Campagne, J.-M.; Joseph, D.; Andrioletti, B. *Tetrahedron* **2002**, *58*, 2041–2075. (d) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176–4211. (e) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 211–241. (f) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234–245.
3. (a) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108–11109. (b) Blake, C. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382–12383. (c) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360–1370 and references cited therein. (d) Solé, D.; Vallverdu, L.; Bonjoch, J. *Adv. Synth. Catal.* **2001**, *343*, 439–442. (e) Solé, D.; Vallverdu, L.; Peidro, E.; Bonjoch, J. *Chem. Commun.* **2001**, 1888–1889. (f) Mutter, R.; Campbell, I. B.; Martin de la Nava, E. M.; Merritt, A. T.; Wills, M. *J. Org. Chem.* **2001**, *56*, 3284–3290. (g) Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 5816–5817. (h) Ehrentraut, A.; Zapf, A.; Beller, M. *Adv. Synth. Catal.* **2002**, *344*, 209–217. (i) Ahman, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1261–1268. (j) Viciu, M. S.; Kelly, R. A.; Stevens, E. D.; Naud, F.; Studer, M.; Nolan, S. P. *Org. Lett.* **2003**, *5*, 1479–1482 and references cited therein.
4. (a) Moradi, W. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7996–8002. (b) Lee, S.; Beare, N. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 8410–8411. (c) Jorgensen, M.; Lee, S.; Liu, X.; Wolkowski, J. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 12557–12565 and references cited therein.
5. (a) Shaughnessy, K. H.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1998**, *63*, 6546–6553. (b) Freund, R.; Mederski, W. W. K. R. *Helv. Chim. Acta* **2000**, *83*, 1247–1255. (c) Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402–3415. (d) Honda, T.; Namiki, H.; Satoh, H. *Org. Lett.* **2001**, *3*, 631–633. (e) Zhang, T. Y.; Zhang, H. *Tetrahedron Lett.* **2002**, *43*, 193–195.
6. Cossy, J.; de Filippis, A.; Gomez Pardo, D. *Org. Lett.* **2003**, *5*, 3037–3039.
7. For cross-coupling reactions of zinc enolates of esters, see: (a) Fauvarque, J. F.; Jutand, A. *J. Organomet. Chem.* **1977**, *132*, C17–C19. (b) Negishi, E.-I.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821–1823. (c) Fauvarque, J. F.; Jutand, A. *J. Organomet. Chem.* **1979**, *177*, 273–281. (d) Kosugi, M.; Negishi, Y.; Kameyana, M.; Migita, T. *Bull. Chem. Soc. Jpn* **1985**, *58*, 3383–3384. (e) Orsini, F.; Pelizzoni, F. *Synth. Commun.* **1987**, *17*, 1389–1402. (f) Orsini, F.; Pelizzoni, F.; Vallarino, L. M. *J. Organomet. Chem.* **1989**, *367*, 375–382.
8. For cross-coupling reactions of zinc enolates of amides, see: Hama, T.; Liu, X.; Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 11176–11177.
9. Catalysts tested: (a) $Pd(OAc)_2$ and PPh_3. (b) $Pd(dba)_2$ and $P(^tBu)_3$. (c) $Pd(dba)_2$ and PCy_3. (d) $Pd(dba)_2$ and BINAP. (e) $Pd(acac)_2$ and ligand L. (f) $PdCl_2$.dppf. (g) Nolan's catalyst: (SIPr)Pd(allyl)Cl.[3j]
10. (a) Bordwell, F. G.; Drucker, G. E.; Fried, H. E. *J. Org. Chem.* **1981**, *46*, 632–635. (b) Bordwell, F. G.; Fried, H. E. *J. Org. Chem.* **1981**, *46*, 4327–4331. (c) http://www.chem.wisc.edu/areas/reich/pkatable/http://daecr1.harvard.edu/pKa/pka.html.
11. van der Steen, F. H.; Boersma, J.; Spek, A. L.; van Koten, G. *Organomettalics* **1991**, *10*, 2467–2480.
12. Cossy, J.; de Filippis, A.; Gomez Pardo, D. *Synlett* **2003**, 2171–2174.
13. Padwa, A.; Eidell, C. K.; Ginn, J. D.; McClure, M. S. *J. Org. Chem.* **2002**, *67*, 1595–1606.
14. Nakagawa, M.; Torisawa, Y.; Hosaka, T.; Tanaba, K.; Tavet, F.; Aikawa, M.; Hino, T. *Heterocycles* **1993**, *35*, 1157–1170.
15. Foti, C. L.; Comins, D. L. *J. Org. Chem.* **1995**, *60*, 2656–2657.
16. Grunewald, G. L.; Brouillette, W. J. *J. Org. Chem.* **1978**, *43*, 1839–1841.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 60 (2004) 9769–9784
Tetrahedron

Highly diastereo- and enantioselective reactions of enecarbamates with an aldehyde

Ryosuke Matsubara, Paulo Vital, Yoshitaka Nakamura, Hiroshi Kiyohara and Shū Kobayashi*

Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

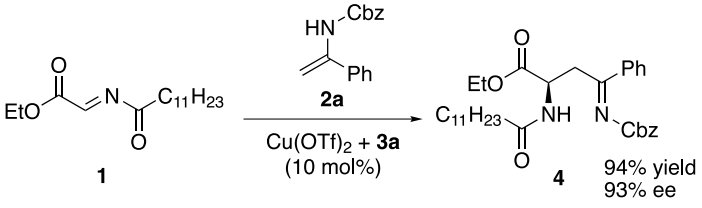
Received 30 June 2004; revised 3 July 2004; accepted 7 July 2004

Available online 24 August 2004

Abstract—Catalytic asymmetric addition reactions of enecarbamates with ethyl glyoxylate have been developed using $CuClO_4 \cdot 4CH_3CN$ and a diimine ligand as the catalyst. Highly diastereo- and enantioselective addition reactions of α-mono-substituted enecarbamates have been also achieved. These reactions afforded the corresponding adducts with high selectivity; that is, *syn* adducts from *Z*-enecarbamates and *anti* adducts from *E*-enecarbamates. The proposed reaction mechanism is an aza-ene type pathway, where the proton of an enecarbamate's N–H group plays an important role, not only for accelerating the reaction but also for providing a transition state suitable for the highly selective chiral induction.

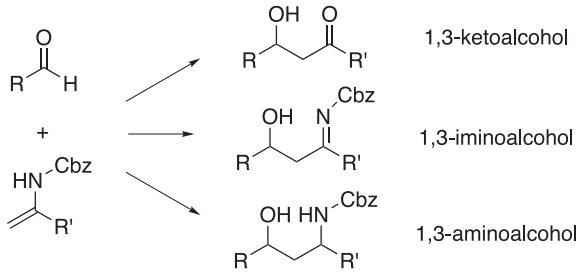
1. Introduction

Enamides and enecarbamates are potentially useful nucleophiles, which bear amide and carbamate moieties after undergoing nucleophilic additions. While enamides are readily prepared,[1] are easy to handle, and can be stored at room temperature, their use in organic synthesis is limited.[2] Recently, we have reported the first catalytic enantioselective addition of enamides and enecarbamates to imines, which afforded imine **4** in high yield with high selectivity (Scheme 1).[3] A C_2-symmetric copper catalyst prepared from $Cu(OTf)_2$ and diamine ligand **3a**, derived from 1,2-diphenyl ethylenediamine, catalyzed the reaction efficiently.[4] Imine **4** is a versatile compound, which can be converted into 1,3-diamides, 5-membered lactams, 3-keto 1-amides, etc. The use of aldehydes instead of imines as substrates for this reaction might lead to 1,3-ketoalcohols, 1,3-iminoalcohols, and 1,3-aminoalcohols, etc.



Scheme 1.

The objective of this research effort is to investigate the reactions of enamides with aldehydes.[5] The reaction of ethyl glyoxylate with enecarbamates would lead to products which have α-hydroxy γ-imino ester functionalities (Scheme 2). In the absence of a Lewis-acid catalyst, the reaction of ethyl glyoxylate (1.2 equiv.) with enecarbamate **2a** (1.0 equiv.) proceeded at 0 °C for 1.5 h to give **6a**, which was hydrolized to **7a** by treatment with HBr aq. (13% yield,

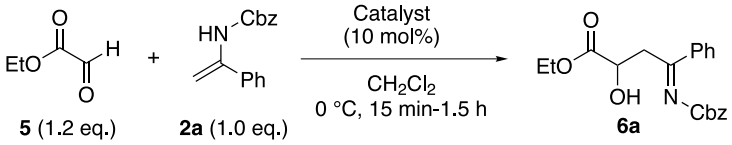


Scheme 2.

Keywords: Enamide; Enecarbamate; Asymmetric catalysis; Aza-ene reaction; Copper; N ligands.
* Corresponding author. Tel.: +81-3-5841-4790; fax: +81-3-5684-0634; e-mail: skobayas@mol.f.u-tokyo.ac.jp

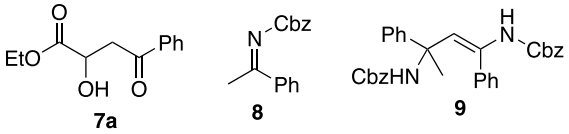
0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.07.045

Table 1. Reaction of enecarbamate **2a** with ethyl glyoxylate (**5**). Initial results



5 (1.2 eq.) **2a** (1.0 eq.) **6a**

Entry	Catalyst	Yield (%)[a]	ee (%)
1	None	13	—
2	$Cu(OTf)_2$	18	—
3	$CuClO_4 \cdot 4CH_3CN$	67	—
4	$Sc(OTf)_3$	40	—
5	$Yb(OTf)_3$	59	—
6[b]	$Cu(OTf)_2$ + **3a**	93	55



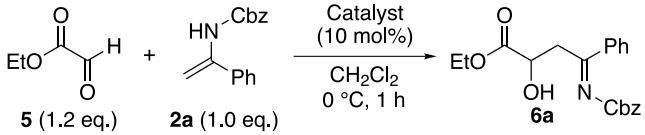
7a **8** **9**

[a] Yield of **7a** following an acidic work-up.
[b] 15 min.

entry 1 in Table 1). Use of copper (II) triflate as a catalyst (10 mol%) resulted in the formation of **8** and **9**, which indicated that an equilibrium between **2a** and **8** existed under Lewis acidic conditions and caused a self-coupling reaction between **2a** and **8** to form **9** (ca. 30% yield, entry 2 in Table 1). A similar phenomenon was observed when other Lewis acids such as $CuClO_4 \cdot 4CH_3CN$, $Sc(OTf)_3$, and $Yb(OTf)_3$ were employed as catalysts (entries 2–5 in Table 1). It is noted that a complex derived from $Cu(OTf)_2$ and diamine ligand **3a** did not accelerate the formation of **8** from **2a** at all, and that **7a** was isolated in high yield with modest enantioselectivity (93% yield, 55% ee, entry 6 in Table 1). This result would be attributed to lower Lewis acidity of the copper coordinated to diamine ligand **3a**.

These results prompted us to screen various metals in the presence of a range of diamine ligands, and the results are summarized in Table 2. The use of $Sc(OTf)_3$, $CoCl_2$, or $Zn(OTf)_2$ was found to accelerate the reaction of enecarbamates with ethyl glyoxylate selectively (58–86% yields), and in these cases the enecarbamate self-coupling

Table 2. Reaction of enecarbamate **2a** with **5** using various catalysts



5 (1.2 eq.) **2a** (1.0 eq.) **6a**

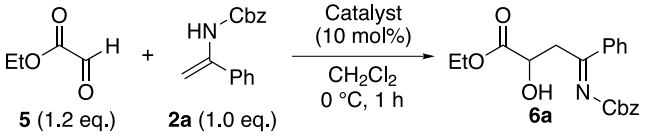
Entry	Metal	Ligand	Yield (%)	ee (%)
1	$Cu(OTf)_2$	**3a**	93	55
2	$CuClO_4 \cdot 4CH_3CN$	**3a**	90	35
3	$LiClO_4$	**3d**	21	0
4	NaOTf	**3d**	Trace	—
5	$Mg(OTf)_2$	**3b**	5	38
6	$Sc(OTf)_3$	**3d**	58	28
7	$Sc(OTf)_3$	**3h**	60	1
8	$FeCl_2$	**3d**	38	2
9	$CoCl_2$	**3d**	77	2
10	$CoCl_2$	**3h**	73	1
11	$Zn(OTf)_2$	**3a**	86	39
12	$Zn(OTf)_2$	**3i**	62	16
13	$AgSbF_6$	**3i**	14	18
14	AgOTf	**3i**	31	35
15	$Sn(OTf)_2$	**3d**	44	8
16	$La(OTf)_3$	**3d**	70	0
17	$Ce(OTf)_3$	**3d**	68	0
18	$Pr(OTf)_3$	**3d**	61	0
19	$Nd(OTf)_3$	**3d**	74	2
20	$Sm(OTf)_3$	**3d**	72	0
21	$Sm(OTf)_3$	**3i**	65	2
22	$Sm(OTf)_3$	**3h**	88	0
23	$Ho(OTf)_3$	**3d**	66	0
24	$Yb(OTf)_3$	**3b**	40	2
25	$Lu(OTf)_3$	**3d**	53	6

compound **9** was not observed. Ag (I) and Sn (II) salts were less active catalysts for this reaction. When various lanthanide salts were employed as catalysts (entries 16–25 in Table 2) in the presence of diamine ligand (commonly **3d**), the desired adducts were formed in moderate to high yields (40–88% yields), albeit enantioselectivities were negligible (<6% ee).

The copper complexes showed the best catalytic activity in this reaction, which led to the selection of Cu (I) and (II) in the parallel screening of ligand types. Diamine ligands **3a–f** derived from diphenyl ethylenediamine, box-type ligands **3g** and **3h**, diimine ligands **3i–3t** derived from cyclohexyl diamine, and diamine ligands **3v–3x** derived from cyclohexyl diamine were all used in conjunction with the Cu (I) and Cu (II). Among Cu (II) complexes (Table 3), a complex prepared from $Cu(OTf)_2$ and box ligand **3h** gave the highest enantioselectivity (73% ee).[6]

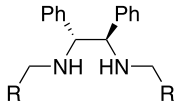
Preliminary tests using $CuClO_4 \cdot 4CH_3CN$ as a Lewis acid revealed that a catalyst derived from Cu (I) and diimine ligand **3i** exhibited good facial discrimination (entry 2 in Table 4, 93% ee).[7] Alternate counter anions $^{-}PF_6$ and ^{-}OTf gave adducts with lower selectivities (82% ee and 78% ee, respectively, entries 3 and 4 in Table 4). When 1-naphthyl and 2-naphthyl-substituted ligands **3j** and **3k** were examined (entries 5 and 6 in Table 4), moderate enantioselectivities were observed (73% ee and 68% ee,

Table 3. Reactions of enecarbamate **2a** with **5** using various copper(II) catalysts

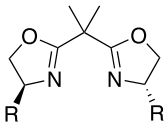


5 (1.2 eq.) **2a** (1.0 eq.) **6a**

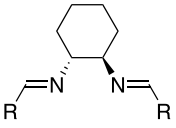
Entry	Metal	Ligand	Yield (%)	ee (%)[a]
1	$Cu(OTf)_2$	**3a**	93	55
2[b]	$Cu(OTf)_2$	**3a**	91	54
3[c]	$Cu(OTf)_2$	**3a**	89	58
4	$Cu(OTf)_2$	**3b**	74	59
5[d]	$Cu(OTf)_2$	**3b**	44	47
6	$Cu(OTf)_2$	**3c**	58	57
7	$Cu(OTf)_2$	**3d**	96	46
8	$Cu(OTf)_2$	**3e**	97	37
9	$Cu(OTf)_2$	**3f**	94	31
10	$Cu(OTf)_2$	**3g**	85	31[a]
11[c]	$Cu(OTf)_2$	**3g**	91	31[a]
12	$Cu(OTf)_2$	**3h**	70	73[a]
13	$Cu(OTf)_2$	**3i**	65	70
14	$Cu(OTf)_2$	**3j**	66	28
15	$Cu(OTf)_2$	**3k**	71	52
16	$Cu(OTf)_2$	**3l**	68	17
17	$Cu(OTf)_2$	**3v**	89	51
18	$Cu(OTf)_2$	**3w**	91	50
19	$Cu(OTf)_2$	**3x**	Quant	62
20	$CuCl_2$	**3a**	47	17
21	$CuCl_2$	**3b**	55	26
22	$CuCl_2$	**3i**	50	19[a]
23	$Cu(SbF_6)_2$	**3b**	77	44



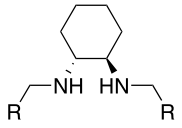
3a: R = 1-nap
3b: R = (3,5-(^{t}Bu)$_2$)-Ph
3c: R = ^{t}Bu
3d: R = Ph
3e: R = (*o*-F)-Ph
3f: R = (*o*-OMe)-Ph



3g: R = Ph
3h: R = ^{t}Bu



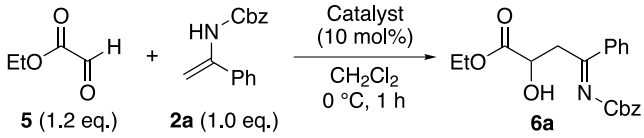
3i: R = Ph
3j: R = 1-nap
3k: R = 2-nap
3l: R = (3,5-di^{t}Bu)-C_6H_3
3m: R = *o*-Tol
3n: R = *m*-Tol
3o: R = *p*-Tol
3p: R = *p*-Et-C_6H_4
3q: R = *p*-^{i}Pr-C_6H_4
3r: R = *p*-F-C_6H_4
3s: R = *p*-Cl-C_6H_4
3t: R = *p*-Br-C_6H_4



3v: R = Ph
3w: R = 2-nap
3x: R = (3,5-(^{t}Bu)$_2$)-Ph

[a] The absolute configuration is *R* except in entries 10–12 and 22 (*S*).
[b] Catalyst (30 mol%) was used.
[c] −20 °C.
[d] −78 °C.

Table 4. Reactions of enecarbamate **2a** with **5** using various copper(I) catalysts



5 (1.2 eq.) **2a** (1.0 eq.) **6a**

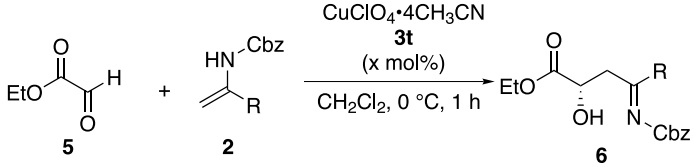
Entry	Metal	Ligand	Yield (%)	ee (%)[a]
1	$CuClO_4 \cdot 4CH_3CN$	**3a**	90	35[a]
2	$CuClO_4 \cdot 4CH_3CN$	**3i**	94	93
3	$CuPF_6 \cdot 4CH_3CN$	**3i**	94	82
4	$CuOTf \cdot 0.5C_6H_5CH_3$	**3i**	66	78
5	$CuClO_4 \cdot 4CH_3CN$	**3j**	92	73
6	$CuClO_4 \cdot 4CH_3CN$	**3k**	52	68
7[b]	$CuClO_4 \cdot 4CH_3CN$	**3i**	48	91
8[c]	$CuClO_4 \cdot 4CH_3CN$	**3i**	97	93
9[d]	$CuClO_4 \cdot 4CH_3CN$	**3i**	Quant	94
10[d]	$CuClO_4 \cdot 4CH_3CN$	**3m**	97	81
11[d]	$CuClO_4 \cdot 4CH_3CN$	**3n**	Quant	86
12[d]	$CuClO_4 \cdot 4CH_3CN$	**3o**	98	95
13[d,e]	$CuClO_4 \cdot 4CH_3CN$	**3o**	20	17
14[d,f]	$CuClO_4 \cdot 4CH_3CN$	**3o**	Trace	—
15[d]	$CuClO_4 \cdot 4CH_3CN$	**3p**	87	94
16[d]	$CuClO_4 \cdot 4CH_3CN$	**3q**	93	94
17[d]	$CuClO_4 \cdot 4CH_3CN$	**3r**	97	96
18[d]	$CuClO_4 \cdot 4CH_3CN$	**3s**	93	96.5
19[d]	$CuClO_4 \cdot 4CH_3CN$	**3t**	93	97.0

[a] The absolute configuration is *S* except in entry 1 (*R*).
[b] −78 °C.
[c] Ethyl glyoxylate (1.5 equiv.) was used.
[d] Ethyl glyoxylate (2.0 equiv.) was used.
[e] Toluene was used as a solvent.
[f] Acetonitrile was used as a solvent.

respectively). The reaction catalyzed by a copper complex derived from $CuClO_4 \cdot 4CH_3CN$ and ligand **3i** proceeded at −78 °C to give a lower yield (48% yield, entry 7 in Table 4). Use of excess amounts of ethyl glyoxylate (1.5 and 2.0 equiv.) gave higher yields, 91% and quantitative yields, respectively (entries 8 and 9 in Table 4). Ligands bearing *para*-substituents on the phenyl arms led to higher enantiomeric excesses in the Cu (I)-catalyzed reaction (compare entry 12 with entries 2, 10 and 11 in Table 4). Finally, the Cu (I) complex of *para*-bromo ligand **3t** was found to give the highest stereoselectivity (97% ee, entry 19 in Table 4). The ligand **3t** gave rise to the best stereoselectivity in catalysis, presumably due to a strong steric contribution from the *para* substituent of the ancilary phenyl groups about the C_2 environment of the catalysts. Solvents other than dichloromethane were tested (toluene and acetonitrile, entries 13 and 14 in Table 4, respectively), but the catalytic activity of the resultant Cu (I) complexes was decreased significantly.

The optimal ligand, metal source, and solvent (**3t**, $CuClO_4 \cdot 4CH_3CN$ and CH_2Cl_2, respectively) were, therefore, employed in experiments where the loadings of both metal and ligand were reduced (entries 1–4 in Table 5). Only 1 mol% of the catalyst ($CuClO_4 \cdot 4CH_3CN$ 1 mol%, ligand **3t** 1.1 mol%) afforded **7a** in good yield with a slightly reduced enantiomeric excess (90% yield, 94% ee, entry 4 in Table 5). Other enecarbamates (**2b–e**) derived from

Table 5. Catalytic asymmetric reactions of various enecarbamates **2** with **5**



5 **2** **6**

Entry	**2**	*x* (mol%)	Yield (%)	ee (%)
1	**2a** (R=Ph)	10	93	97
2	**2a**	5	94	96
3	**2a**	2	96	95
4	**2a**	1	90	94
5	**2b** (R=PMP)	10	94	93
6	**2c** (R=PCP)	10	97	97
7	**2d** (R=PMeP)	10	Quant	96
8	**2e** (R=2-Nap)	10	91	96

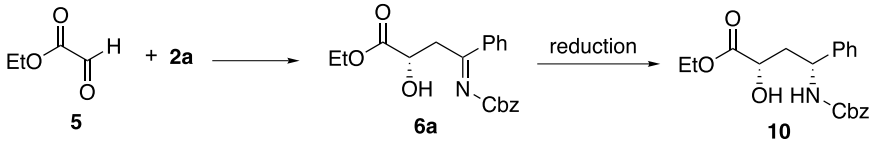
Cbz, benzyloxycarbonyl; PMP, *p*-methoxyphenyl; PCP, *p*-chlorophenyl; PMeP, *p*-methylphenyl; 2-Nap, 2-naphthyl.

aromatic ketones also reacted with ethyl glyoxylate to provide the corresponding adducts **7b–e** in high yields (91% to quant.) with high enantioselectivities (93–97% ee). It is noteworthy that all reactions were complete within only 1 h at 0 °C.

The Cu (I)-catalyzed protocol was able to furnish the potentially useful β-iminoalcohols in high ee, and subsequent reduction was then performed in order to demonstrate the utility of this enecarbamate process. Whilst the diastereoselective reduction of 1,3-ketoalcohols is well known,[8] there are relatively few reports concerning the diastereoselective reduction of 1,3-iminoalcohols.[9] Attempts for the selective reduction of **6a** are summarized in Table 6 (**6a** was prepared freshly as per entry 1 in Table 5). It has been previously reported that chelation of 1,3-ketoalcohols is often crucial for stereoselective reduction. Considering that β-iminoalcohols might coordinate in an analogous fashion, similar protocols were adopted. The use of $Zn(BH_4)_2$[8b] as a reducing agent resulted in around 60% yield with modest *syn*-selectivities. Reduction of **6a** did not proceed at −78 °C when $LiAlH(O^tBu)_3$[8g] was employed as a reductant, (**6a** was completely recovered). Sodium borohydride in the presence of $ZnCl_2$[10] at −78 °C gave benzylalcohol mainly, and only a trace amount of the desired product was observed (entry 5 in Table 6). Although benzylalcohol is assumed to be derived from the Cbz group attached to the nitrogen, the precise mechanism for the formation of benzylalcohol remains unclear. Additionally, K-selectride also formed a considerable amount of benzylalcohol even at −78 °C (entries 8–10 in Table 6), while L-selectride afforded the desired product in moderate yield (ca. 59% yield) with modest *anti*-selectivity (*syn*/*anti*=22/78, entry 11 in Table 6). Satisfactory selectivity was observed (*syn*/*anti*=94/6) when $NaBH_4$ was used in the presence of $Et_2B(OMe)$ which is known to aid chelation of 1,3-ketoalcohols in a THF/MeOH mixtures,[8d] and a slightly modified procedure was used (entry 13 in Table 6). Optimization studies showed that a threefold excess of reductants at −78 °C over 2 h afforded **10** in 65% yield with high *anti*-selectivity (94/6, entry 18 in Table 6). The relative configuration of **10** was assigned on the basis of NMR NOE experiments performed in the cyclic derivative **12** (Scheme 3).

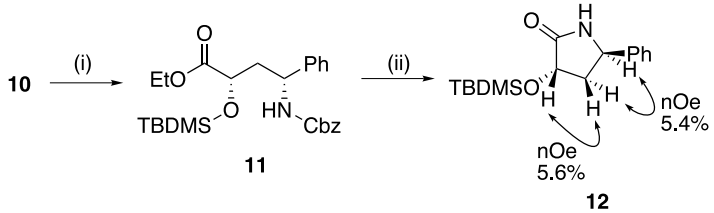
Diastereoselection in addition reactions of α-mono-substituted

Table 6. Selective reduction of **6a** into **10**

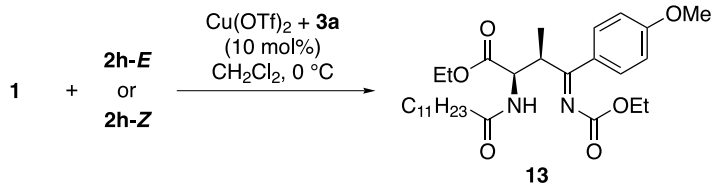


Entry	Reagent (equiv.)	Additive (equiv.)	Solvent	Temperature	Time (h)	Yield (%)[a]	*syn*/*anti*
1	$Zn(BH_4)_2$ (1.0)	—	Et_2O	−78	1	<65	71/29
2	$Zn(BH_4)_2$ (1.0)	—	Et_2O	−78	3	<66	78/22
3	$Zn(BH_4)_2$ (1.0)	MS4A[b]	Et_2O	−78	3	<75	78/22
4	$Zn(BH_4)_2$ (1.0)	—	Toluene–Et_2O[c]	−78	1	<75	75/25
5	$NaBH_4$ (2.0)	$ZnCl_2$ (1.5)	MeOH	−78	5.5	Trace	—
6	$LiAlH(O^tBu)_3$ (5.0)	—	Et_2O	−78	20	Trace	—
7	$LiAlH(O^tBu)_3$ (5.0)	LiL (5.0)	Et_2O	−78	20	Trace	—
8	K-Selectride (2.2)	—	THF	−20	1.2	0	—
9	K-Selectride (2.2)	—	THF	−45	4	0	—
10	K-Selectride (2.2)	—	THF	−78	4	0	—
11	L-Selectride (2.2)	—	THF	−20	16.5	<59	22/78
12	9-BBN (3.0)	—	THF	−20	16.5	Trace	—
13	$NaBH_4$ (2.2)	$Et_2B(OMe)$ (1.1)	THF–MeOH[d]	−78	3	<60	94/6
14	$NaBH_4$ (2.2)	$Et_2B(OMe)$ (1.1)	THF–MeOH[d]	−45	3	<68	91/9
15	$NaBH_4$ (2.2)	$Et_2B(OMe)$ (2.2)	THF–MeOH[d]	−78	5.5	55	91/9
16	$NaBH_4$ (2.2)	$Et_2B(OMe)$ (2.2)	THF–MeOH[d]	−45	5.5	69	88/12
17	$NaBH_4$ (2.2)	$Et_2B(OMe)$ (2.2)	THF–MeOH[e]	−78	2	<37	ND[f]
18	$NaBH_4$ (3.0)	$Et_2B(OMe)$ (3.0)	THF–MeOH[d]	−78	2	65	94/6

[a] The yields from **2**. A small amount of unknown compounds was contained except in entries 15, 16, and 18.
[b] 10 mg/0.1 mmol.
[c] Toluene/Et_2O=1/1.
[d] THF/MeOH=4/1.
[e] THF/MeOH=3/2.
[f] Not determined.



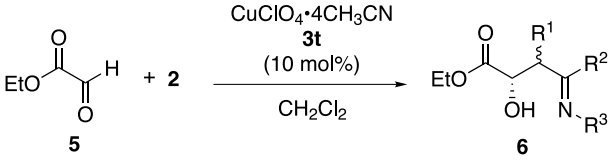
Scheme 3. (i) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 92% (ii) Pd/C, H_2, AcOH, AcOEt, quant



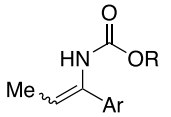
Scheme 4. **2h**–***E***: 77% y, *syn*/*anti*=86/14, 94% ee (*syn*) **2h**–**Z**: 63% y, *syn*/*anti*=68/32, 32% ee (*syn*)

enecarbamates with carbonyls is of great interest not only from a synthetic point of view but also from a mechanistic aspect. In our recent report *syn*-adducts were obtained from both (*E*)- and (*Z*)-enecarbamates **2h** and imine **1** catalyzed by a complex derived from Cu (II) and diamine ligand **3a** (Scheme 4).[3] Unlike their silicon enolate analogues, both geometric isomers of **2h** are stable on silica gel and separable by a standard chromatography technique. The α-substituted enecarbamate **2f** reacted with ethyl glyoxylate smoothly in the presence of $CuClO_4 \cdot 4CH_3CN$ and diimine ligand **3t** to afford **6f** in good yield (entries 1 and 4 in Table 7). It is noted that *anti*- and *syn*-adducts were obtained from the *E*- and *Z*-enecarbamates, respectively. The diastereoselectivities were excellent (*syn*/*anti*=1/99 and 98/2, respectively) and the enantiomeric excess of the major diastereomer was 98% ee in both cases. The same tendency on selectivity was observed for enecarbamates derived from *para*-substituted propiophenone (entries 7–12 in Table 7). The enecarbamates having an ethyl group at the α-position also gave similar diastereo- and enantioselectivities (entries 13 and 14 in Table 7). This reaction could be applied to aliphatic ketone-derived enecarbamates (entries 15–17 in Table 7). The reaction of enecarbamate **2l** derived from cyclohexanone afforded the desired product **6l** in good yield (85% yield) with slightly lower diastereoselectivity (*syn*/*anti*=16/84). Although prolonged reaction time (6–46 h) and lower temperature (−20 °C) were sometimes necessary, decrease of the catalyst loading

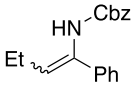
Table 7. Reactions of enecarbamates derived from α-substituted ketones



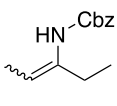
Entry	2	Product	Yield (%)[a]	*syn*/*anti*[b]	Ee (%)[c]
1	**2f***E*	**7f**	83	1/99	98
2[d]	**2f***E*[e]	**7f**	93	1/99	97
3[d]	**2f***E*[f]	**7f**	95	1/99	98
4	**2f***Z*	**7f**	82	98/2	98
5	**2f***Z*[e]	**7f**	93	98/2	98
6	**2f***Z*[f]	**7f**	96	98/2	98
7	**2g***E*	**7g**	96	2/98	98
8	**2g***Z*	**7g**	97	98/2	98
9	**2h***E*	**7g**	82	3/97	96
10	**2h***Z*	**7g**	96	99/1	98
11	**2i***E*	**7i**	85	2/98	98
12	**2i***Z*	**7i**	79	99/1	98
13	**2j***E*[g]	**7j**	58	1/99	98
14	**2j***Z*	**7j**	92	99/1	98
15[d]	**2k***E*	**7k**	83	3/97[h]	97
16[d]	**2k***Z*	**7k**	89	92/8[h]	98
17	**2l**	**7l**	85	16/84[h]	94



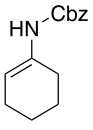
2f: Ar = Ph, R = Bn
2g: Ar = PMP, R = Bn
2h: Ar = PMP, R = Et
2i: Ar = PCP, R = Bn



2j

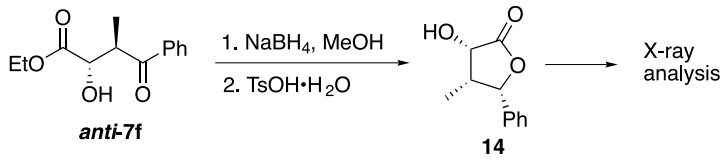


2k



2l

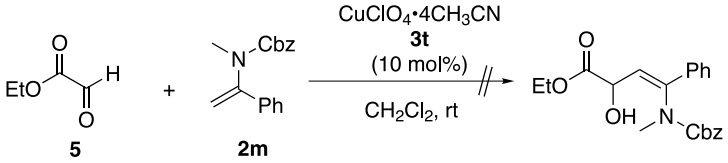
[a] Isolated yield of ketone product.
[b] Determined by HPLC.
[c] Ee of the major diastereomer, determined by HPLC.
[d] −20 °C.
[e] 1 mol% of catalyst was used.
[f] 0.1 mol% of catalyst was used.
[g] **5** (1.0 equiv.) and **2** (2.0 equiv.) were used.
[h] Determined by NMR analysis.



Scheme 5.

gave slightly better yields as shown in entries 1–6 of Table 7. Thus, the (*E*)- and (*Z*)-enecarbamates **2f** reacted with ethyl glyoxylate in the presence of only 0.1 mol% of the catalyst to afford the corresponding adducts in excellent yield (95 and 96%, respectively) with high diastereoselectivity (*syn*/*anti*=1/99 and 98/2, respectively) and enantioselelctivity (98% ee in both cases). The relative configuration of adduct **7f** was determined by the X-ray crystal structure analysis of **14**, which was synthesized from **7f** by reduction and subsequent cyclization in one pot (Scheme 5). The relative configuration of other adducts, general formula **7**, was determined by an analogy of the ^{1}H NMR spectrum of **7f**.

In a bid to elucidate the reaction mechanism, enecarbamate **2m**, which has a tertiary amide moiety, was used to assess the role of the proton attached to the nitrogen. It was interesting to find that no reaction occurred in the presence of 10 mol% of the catalyst even at room temperature (Scheme 6). That the reaction proceeded stereospecifically when α-substituted enecarbamates bear N–H functionalities suggests a concerted aza-ene type reaction mechanism;[11] that is, a hydrogen atom attached to the nitrogen of enecarbamates would accelerate the reaction rate considerably through an intramolecular hydrogen transfer pathway. Two possible modes of a nucleophilic attack exist; an open transition state model or a concerted 6-membered ring fashion. Possible open transition states are shown in Figure 1; *E*-enecarbamates are used in TS-1 and TS-2, while *Z*-enecarbamates are used in TS-3 and TS-4. The steric interaction between the methyl group at the α-position of an enecarbamate and the copper complex is believed to be large, TS-2 would be favorable over TS-1. Similarly, since TS-3 would predominate over TS-4, *syn*-adducts are obtained in both cases. This contradicts the experimental results (*syn*-products from *Z*-enecarbamates, *anti*-products from *E*-enecarbamates). Possible concerted cyclic transition states are shown in Figure 2; TS-5 and TS-7 are derived from *Z*-enecarbamates, TS-6 and TS-8 are derived from *E*-enecarmates. In TS-7 and TS-8, since the steric interaction between the R group of enecarbamates and ethyl glyoxylate would be large, TS-5 and TS-6 are believed to predominate over TS-7 and TS-8, respectively. This explains the observed stereoselectivity and the role of the



Scheme 6.

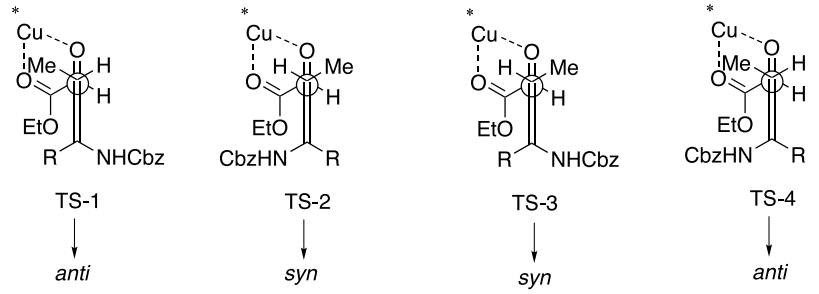


Figure 1. Possible acyclic transition state models.

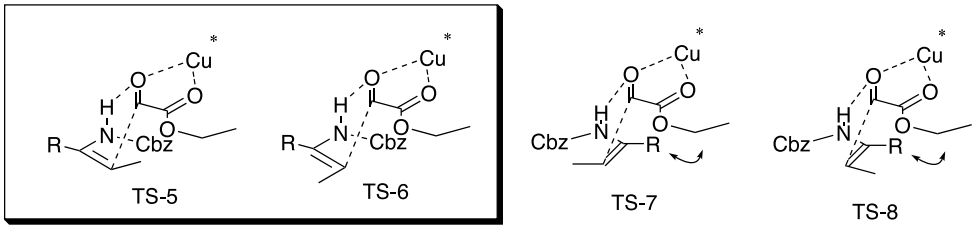


Figure 2. Possible cyclic transition state models.

N–H proton of enecarbamates. Attempts to crystallize model systems for X-ray diffraction are now under way.

In conclusion, catalytic asymmetric addition reactions of enecarbamates with ethyl glyoxylate have been developed using $CuClO_4 \cdot 4CH_3CN$ and diimine ligand **3t** as a catalyst. The products were 1,3-iminoalcohols, which were converted to the corresponding 1,3-amidealcohols diastereoselectively, employing $NaBH_4$ and $Et_2B(OMe)$ in the reduction. We have also developed highly diastereo- and enantioselective addition reactions of α-mono-substituted enecarbamates. These reactions afforded the corresponding adducts with high selectivity; that is, *syn* adducts from *Z*-enecarbamates and *anti* adducts from *E*-enecarbamates. The reaction proceeded smoothly in the presence of only 0.1 mol% of the catalyst to afford 1,3-iminoalcohols in high yields with high diastereo- and enantioselectivities. Aromatic ketone-derived enecarbamates as well as those derived from aliphatic and cyclic ketones were also found to be good substrates. The proposed reaction mechanism is an aza-ene type pathway, where the proton of an enecarbamate's N–H group plays an important role, not only accelerating the reaction but also providing a transition state suitable for the highly selective chiral induction.

2. Experimental

2.1. General

Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-LA300, JNM-LA400, or JNM-LA500 spectrometer in $CDCl_3$ unless otherwise noted. Tetramethylsilane (TMS) served as internal standard ($\delta=0$) for ^1H NMR, and $CDCl_3$ was used as internal standard ($\delta=77.0$) for ^{13}C NMR. IR spectra were measured with a JASCO FT/IR-610. Optical rotations were measured with a JASCO P-1010 polarimeter. High-performance liquid chromatography was carried out using following apparatuses; SHIMADZU LC-10AT (liquid chromatograph), SHIMADZU SPD-10A (UV detector), and SHIMADZU C-R6A Chromatopac. Gas chromatography and mass spectrometry analysis were carried out using the following apparatuses; SHIMADZU GC-17A, SHIMADZU GCMS-QP5050A. Column chromatography was conducted on Silica gel 60 (Merck), and preparative thin-layer chromatography was carried out using Wakogel B-5F. All reactions were carried out under argon atmosphere in dried glassware. All solvents were dried and distilled by standard procedures. Enecarbamates **2a–j** were prepared according to the method reported by Kagan et al.[1a] Enecarbamates **2k** and **2l** were prepared by using a modified procedure reported by Machida et al.[1b,12] Enecarbamate **2m** was prepared from **2a**. Diamine ligands **3a–f** were prepared according to the reported method.[4b] Diimine ligands **3i–t** were prepared from commercially available (1*R*,2*R*)-(+)-1,2-diaminocyclohexane L-tartrate according to the reported method.[13] Diamine ligands **3v–x** were prepared by reduction of **3i**, **3k**, and **3l**, respectively using $NaBH_4$ in MeOH.

3. Enecarbamates

3.1. Analytical data for enecarbamates 2a–j

3.1.1. (1-Phenyl-vinyl)-carbamic acid benzyl ester (2a). Mp 69.4–69.5 °C; ^1H NMR ($CDCl_3$) $\delta=4.96$ (s, 1H), 5.16 (s, 2H), 5.63 (s, 1H), 6.33 (s, 1H), 7.25–7.45 (m, 10H); ^{13}C NMR ($CDCl_3$) $\delta=67.0$, 99.6, 126.0, 128.3, 128.5, 128.6, 128.7, 136.0, 138.1, 140.5, 153.7; IR (neat) 3310, 3060, 3033, 1739, 1701, 1634, 1523, 1452, 1227, 1125, 1063, 857, 772, 740, 696, 596 cm^{-1}; HRMS (EI). Exact mass calcd for $C_{16}H_{15}NO_2$ $[M]^+$, 253.1103. Found 253.1093. Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.77; H, 6.16; N, 5.52.

3.1.2. [1-(4-Methoxy-phenyl)-vinyl]-carbamic acid benzyl ester (2b). Mp 54.7–54.8 °C; ^1H NMR ($CDCl_3$) $\delta=3.81$ (s, 3H), 4.89 (d, 1H, $J=1.0$ Hz), 5.18 (s, 2H), 5.54 (s, 1H), 6.26 (s, 1H), 6.85–6.90 (m, 2H), 7.30–7.40 (m, 7H); ^{13}C NMR ($CDCl_3$) $\delta=55.3$, 66.9, 98.4, 113.9, 127.2, 128.3, 128.5, 130.6, 136.0, 140.1, 153.7, 160.0; IR (neat) 3330, 1736, 1632, 1608, 1509, 1456, 1219, 1179, 1126, 1063, 1030, 834, 742, 698 cm^{-1}; HRMS (EI). Exact mass calcd for $C_{17}H_{17}NO_3$ $[M]^+$, 283.1208. Found 283.1208. Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 71.84; H, 6.09; N, 4.91.

3.1.3. [1-(4-Chloro-phenyl)-vinyl]-carbamic acid benzyl ester (2c). Mp 79.0–79.1 °C; ^1H NMR ($CDCl_3$) $\delta=4.96$ (s, 1H), 5.17 (s, 2H), 5.59 (s, 1H), 6.25 (s, 1H), 7.28–7.43 (m, 9H); ^{13}C NMR ($CDCl_3$) $\delta=67.1$, 100.6, 127.3, 128.3, 128.4, 128.6, 128.8, 134.6, 135.8, 136.5, 139.7, 153.6; IR (neat) 3299, 1699, 1532, 1239, 1059, 838, 741, 696 cm^{-1}; HRMS (EI). Exact mass calcd for $C_{16}H_{14}ClNO_2$ $[M]^+$, 287.0713. Found 287.0708. Anal. Calcd for $C_{16}H_{14}ClNO_2$: C, 66.79; H, 4.90; N, 4.87. Found: C, 66.53; H, 5.02; N, 4.91.

3.1.4. (1-*p*-Tolyl-vinyl)-carbamic acid benzyl ester (2d). Mp 52.3–53 °C; ^1H NMR ($CDCl_3$) $\delta=2.34$ (s, 3H), 4.93 (s, 1H), 5.16 (s, 2H), 5.58 (s, 1H), 6.30 (s, 1H), 7.14 (apparent d, 2H, $J=7.8$ Hz), 7.25–7.40 (m, 7H); ^{13}C NMR ($CDCl_3$) $\delta=21.1$, 66.9, 98.8, 125.8, 128.3, 128.5, 129.3, 135.3, 136.0, 138.7, 140.4, 153.7; IR (neat) 3398, 3327, 3032, 1736, 1361, 1508, 1454, 1383, 1321, 1219, 1124, 1063, 955, 852, 825, 735 cm^{-1}; LRMS (FAB) $m/z=268$ ($M+H^+$); Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.20; H, 6.48; N, 5.21.

3.1.5. (1-Naphthalen-2-yl-vinyl)-carbamic acid benzyl ester (2e). Mp 100.3–101.5 °C; ^1H NMR ($CDCl_3$) $\delta=5.11$ (s, 1H), 5.19 (s, 2H), 5.72 (s, 1H), 6.45 (s, 1H), 7.30–7.60 (m, 8H), 7.76–7.86 (m, 4H); ^{13}C NMR ($CDCl_3$) $\delta=67.1$, 100.4, 124.0, 124.7, 126.5, 127.6, 128.2, 128.3, 128.4, 128.6, 133.1, 133.3, 135.3, 135.9, 140.5, 153.8; IR (neat) 3282, 3046, 1701, 1622, 1527, 1226, 1106, 1064, 968, 884, 827, 694, 583 cm^{-1}; HRMS (EI). Exact mass calcd for $C_{20}H_{17}NO_2$ $[M]^+$, 303.1259. Found 303.1251. Anal. Calcd for $C_{20}H_{17}NO_2$: C, 79.19; H, 5.65; N, 4.62. Found: C, 79.49; H, 5.82; N, 4.64.

3.1.6. (*Z*)-(1-Phenyl-propenyl)-carbamic acid benzyl ester (2f*Z*). Mp 73.5–74.0 °C; ^1H NMR ($CDCl_3$) $\delta=1.79$

(d, 3H, $J=6.8$ Hz), 5.13 (s, 2H), 5.79 (q, 1H, $J=6.8$ Hz), (6.00 (brs, 1 H), 7.00–7.62 (m, 10 H); ^{13}C NMR (C_6D_6) $\delta=$ 13.5, 67.0, 119.5, 126.0, 127.7, 128.5, 128.5, 135.0, 137.1, 139.2; IR (neat) 3385, 3296, 3032, 2941, 1701, 1498, 1452, 1399, 1329, 1225, 1089, 1018, 916, 824, 760, 695 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{17}H_{18}NO_2$ $[M+H]^+$, 268.1338. Found 268.1339.

3.1.7. (*E*)-(1-Phenyl-propenyl)-carbamic acid benzyl ester (2f*E*). Mp 63.9–64.0 °C; ^{1}H NMR ($CDCl_3$) $\delta=1.70$ (d, 3H, $J=7.3$ Hz), 5.11 (s, 2H), 5.90–6.25 (br, 2H), 7.20–7.50 (m, 10H); ^{13}C NMR (C_6D_6) $\delta=13.7$, 66.7, 112.0, 128.0, 128.1, 128.5, 128.5, 128.6, 129.1, 134.6, 137.0, 137.2, 153.9; IR (neat) 3398, 3316, 3032, 2938, 1713, 1516, 1449, 1393, 1328, 1213, 1137, 1033, 922, 835, 771, 739, 699, 587 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{17}H_{18}NO_2$ $[M+H]^+$, 268.1338. Found 268.1347.

3.1.8. (*Z*)-[1-(4-Methoxy-phenyl)-propenyl]-carbamic acid benzyl ester (2g*Z*). Mp 110–110.5 °C; ^{1}H NMR ($CDCl_3$) $\delta=1.77$ (d, 3H, $J=6.9$ Hz), 3.80 (s, 3H), 5.14 (s, 2H), 5.68 (q, 1H, $J=6.9$ Hz), 5.96 (brs, 1H), 6.84 (apparent d, 2H, $J=8.8$ Hz), 7.32 (m, 7H); ^{13}C NMR (C_6D_6) $\delta=13.5$, 54.8, 66.9, 114.0, 117.6, 127.2, 128.5, 131.8, 134.6, 137.2, 154.1, 159.8; IR (neat) 3305, 3039, 2945, 2843, 1709, 1611, 1509, 1452, 1400, 1334, 1294, 1247, 1176, 1089, 1029, 820, 742, 699, 590 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{18}H_{20}NO_3$ $[M+H]^+$, 298.1443. Found 298.1435.

3.1.9. (*E*)-[1-(4-Methoxy-phenyl)-propenyl]-carbamic acid benzyl ester (2g*E*). Mp 66.0–66.5 °C; ^{1}H NMR ($CDCl_3$) $\delta=1.69$ (d, 3H, $J=7.1$ Hz), 3.82 (s, 3H), 5.11 (s, 2H), 5.80–6.15 (m, 2H), 6.85–6.95 (m, 2H), 7.20–7.50 (m, 7H); ^{13}C NMR (C_6D_6) $\delta=13.8$, 54.7, 66.6, 111.1, 114.0, 128.1, 128.5, 128.6, 129.5, 130.3, 134.4, 137.1, 153.9, 159.7; IR (neat) 3323, 3033, 2941, 2843, 1719, 1609, 1509, 1296, 1247, 1177, 1135, 1027, 840, 739, 697 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{18}H_{20}NO_3$ $[M+H]^+$, 298.1443. Found 298.1452.

3.1.10. (*Z*)-[1-(4-Methoxy-phenyl)-propenyl]-carbamic acid ethyl ester (2h*Z*). Mp 57.1–57.2 °C; ^{1}H NMR ($CDCl_3$) $\delta=1.25$ (brs, 3H), 1.75 (d, 3H, $J=7.1$ Hz), 3.78 (s, 3H), 4.13 (q, 2H, $J=7.1$ Hz), 5.66 (q, 1H, $J=7.1$ Hz), 5.88 (brs, 1H), 6.80–6.85 (m, 2H), 7.28–7.36 (m, 2H); ^{13}C NMR ($CDCl_3$) $\delta=13.4$, 14.5, 55.2, 61.2, 113.6, 117.4, 126.7, 131.1, 133.9, 159.2; IR (neat) 3301, 2979, 1703, 1609, 1510, 1376, 1329, 1245, 1178, 1099, 1037, 824, 774, 594, 448 cm^{-1}; HRMS (EI). Exact mass calcd for $C_{13}H_{17}NO_3$ $[M]^+$, 235.1208. Found 235.1204. Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.21; H, 7.32; N, 5.95.

3.1.11. (*E*)-[1-(4-Methoxy-phenyl)-propenyl]-carbamic acid ethyl ester (2h*E*). ^{1}H NMR ($CDCl_3$) $\delta=1.11$ (t, 3H, $J=7.1$ Hz), 1.57 (d, 3H, $J=7.3$ Hz), 3.70 (s, 3H), 4.01 (q, 2H, $J=7.1$ Hz), 5.70–5.95 (m, 2H), 6.73–6.80 (m, 2H), 7.10–7.16 (m, 2H); ^{13}C NMR ($CDCl_3$) $\delta=13.7$, 14.5, 55.2, 60.8, 111.6, 113.6, 129.1, 129.9, 133.7, 154.3, 159.1; IR (neat) 3319, 2980, 1715, 1608, 1511, 1382, 1293, 1247, 1175, 1138, 1037, 836, 614, 499 cm^{-1}; HRMS (EI). Exact mass calcd for $C_{13}H_{17}NO_3$ $[M]^+$, 235.1208. Found 235.1201.

3.1.12. (*Z*)-[1-(4-Chloro-phenyl)-propenyl]-carbamic acid benzyl ester (2i*Z*). Mp 95.2–95.3 °C; ^{1}H NMR (C_6D_6) $\delta=1.48$ (br, 3H), 5.02 (brs, 2H), 5.20–5.90 (br, 2H), 6.60–7.40 (m, 9H); ^{13}C NMR (C_6D_6) $\delta=13.4$, 67.1, 119.8, 127.2, 128.3, 128.6, 133.4, 134.0, 136.9, 137.7, 153.8; IR (neat) 3292, 3033, 2947, 1706, 1589, 1494k 1398, 1327, 1299, 1094, 1016, 819, 741, 697 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{17}H_{17}ClNO_2$ $[M+H]^+$, 302.0948. Found 302.0936.

3.1.13. (*E*)-[1-(4-Chloro-phenyl)-propenyl]-carbamic acid benzyl ester (2i*E*). Mp 71.2–71.3 °C; ^{1}H NMR (C_6D_6) $\delta=1.44$ (d, 3H, $J=7.4$ Hz), 5.02 (s, 2H), 5.47 (brs, 1H), 6.12 (brs, 1H), 6.70–6.80 (m, 2H), 6.95–7.25 (m, 7H); ^{13}C NMR (C_6D_6) $\delta=13.5$, 66.8, 128.6, 128.6, 128.7, 130.4, 133.5, 133.8, 135.4, 136.9, 153.7; IR (neat) 3398, 3309, 3033, 2941, 1708, 1595, 1517, 1497, 1458, 1393, 1327, 1219, 1138, 1093, 1034, 836, 740, 701 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{17}H_{17}ClNO_2$ $[M+H]^+$, 302.0948. Found 302.0943.

3.1.14. (*Z*)-(1-Phenyl-but-1-enyl)-carbamic acid benzyl ester (2j*Z*). Mp 60.3–60.8 °C; ^{1}H NMR (C_6D_6) $\delta=0.89$ (t, 3H, $J=7.1$ Hz), 2.03 (br, 2H), 5.04 (s, 2H), 5.30–5.55 (m, 2H), 7.00–7.25 (m, 8H), 7.28–7.36 (m, 2H); ^{13}C NMR (C_6D_6) $\delta=13.6$, 21.6, 67.0, 126.1, 126.8, 127.4, 128.1, 128.5, 128.6, 133.5, 137.1, 139.2; IR (neat) 3294, 3033, 2961, 2876, 1705, 1498, 1458, 1400, 1334, 1223, 1092, 1026, 753, 691 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{18}H_{20}NO_2$ $[M+H]^+$, 282.1494. Found 282.1495.

3.1.15. (*E*)-(1-Phenyl-but-1-enyl)-carbamic acid benzyl ester (2j*E*). ^{1}H NMR (C_6D_6) $\delta=0.87$ (t, 3H, $J=7.4$ Hz), 1.99 (quint, 3H, $J=7.4$ Hz), 5.01 (s, 2H), 5.56 (brs, 1H), 6.26 (brs, 1H), 6.95–7.25 (m, 10H); ^{13}C NMR (C_6D_6) $\delta=$ 15.1, 21.0, 66.6, 118.8, 126.4, 126.9, 128.2, 128.5, 128.6, 128.6, 129.0, 133.6, 137.1, 137.5, 153.6; IR (neat) 3398, 3319, 3032, 2962, 2876, 1723, 1514, 1454, 1367, 1327, 1219, 1134, 1039, 984, 922, 857, 743, 698 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{18}H_{20}NO_2$ $[M+H]^+$, 282.1494. Found 282.1481.

3.2. Preparation and analytical data for enecarbamates 2k and 2l

3.2.1. Enecarbamate 2k*E* and 2k*Z*. To a solution of NaN_3 (1.675 g, 25.8 mmol) in H_2O (12 mL) was added a solution of **15**[14] (2.85 g, 21.47 mmol) in THF (7 mL) dropwise at 0 °C. The mixture was vigorously stirred overnight and Et_2O was added. After separation of the phases, the organic layer was washed with a saturated Na_2CO_3 aqueous solution and brine sequentially. Et_2O was evaporated under reduced pressure of 300 mm Hg (Caution!) to give the crude adduct **16** in THF. This solution was added to boiling THF (10 mL) at 80 °C very slowly for over 1.5 h. After completion of the addition, the mixture was stirred at 80 °C until evolution of N_2 gas stopped (for about 2 h). The mixture was allowed to cool to room temperature (rt), and THF was evaporated at 100 mm Hg. The residue was distilled 2 times (65 °C, 100 mm Hg) to give pure **17** (1.113 g, 47% yield). Benzyl alcohol was added to **17** (1.113 g, 10.0 mmol) at −78 °C. The freezed reaction mixture was allowed to warm to rt for over 6 h, and was stirred until **17** was not detected in NMR

analysis (about over 3 days). The mixture was chromatogaphed on silica gel to afford geometric isomer **2k***Z* as a white solid (1.86 g, 85% yield). To a solution of **2k***Z* (237 mg, 1.079 mmol) in THF (12 mL) was added KO^{t}Bu (145.5 mg, 1.29 mmol) at rt. The reaction mixture was kept stirred for 14 h. The reaction was quenched by addition of a saturated NH_4Cl aqueous solution at rt, and the product was extracted with Et_2O. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under vacuum. The crude mixture was purified by chromatography on silica gel to afford almost 1:1 geometric mixture **2k** (184 mg, 78% yield). The mixture was separated by careful thin layer chromatography on silica gel (eluent: toluene/Et_2O=10/1) to afford geometric isomer **2k***E* (Scheme 7).

3.2.2. Enecarbamate 2l. According to the procedure mentioned above, **2l** was obtained. The boiling point of the corresponding isocyanate was 78 °C/40 mm Hg.

3.2.3. (*Z*)-(1-Ethyl-propenyl)-carbamic acid benzyl ester (2k*Z*). Mp 33.0–33.5 °C; ^{1}H NMR (C_6D_6) δ=0.79 (t, 3H, J=7.5 Hz), 1.45 (d, 3H, J=7.0 Hz), 1.95 (q, 2H, J=7.5 Hz), 5.04 (s, 2H), 5.38 (brs, 1H), 5.72 (q, 1H, J=7.0 Hz), 7.00–7.30 (m, 5H); ^{13}C NMR (C_6D_6) δ=11.9, 12.4, 22.7, 66.5, 128.2, 128.6, 128.6, 136.2, 137.3; IR (neat) 3322, 3064, 3033, 2969, 2935, 2877, 1706, 1523, 1455, 1380, 1351, 1307, 1234, 1097, 1029, 998, 831, 738 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{13}H_{18}NO_2$ $[M+H]^+$, 220.1338. Found 220.1347.

3.2.4. (*E*)-(1-Ethyl-propenyl)-carbamic acid benzyl ester (2k*E*). Mp 53.0–54.0 °C; ^{1}H NMR (C_6D_6) δ=0.95 (t, 3H, J=7.5 Hz), 1.28 (d, 3H, J=6.8 Hz), 2.34 (brq, 2H, J=7.5 Hz), 4.70 (q, 1H, J=6.8 Hz), 5.05 (s, 2H), 5.50 (brs, 1H), 7.00–7.26 (m, 5H); ^{13}C NMR (C_6D_6) δ=11.7, 12.6, 27.9, 66.7, 110.5, 128.2, 128.5, 128.6, 137.2, 137.3; IR (neat) 3305, 2967, 2751, 1693, 1515, 1450, 1321, 1257, 1108, 966, 848, 738, 698 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{13}H_{18}NO_2$ $[M+H]^+$, 220.1338. Found 220.1348.

3.2.5. Cyclohex-1-enyl-carbamic acid benzyl ester (2l). Mp 49.0–50.0 °C; ^{1}H NMR (C_6D_6) δ=1.26–1.45 (m, 4H), 1.70–1.80 (m, 2H), 1.86–1.98 (m, 2H), 5.03 (s, 2H), 5.31 (brs, 1H), 6.01 (brs, 1H), 7.00–7.25 (m, 5H); ^{13}C NMR (C_6D_6) δ=22.4, 22.8, 24.1, 27.7, 66.4, 109.3, 128.2, 128.6, 128.6, 132.3, 137.3, 153.2; IR (neat) 3322, 3058, 3033, 2931, 2838, 1706, 1538, 1452, 1380, 1348, 1305, 1232, 1062, 1037, 917, 840, 804, 736, 696 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{14}H_{18}NO_2$ $[M+H]^+$, 232.1338. Found 232.1342.

3.3. Preparation and analytical data for enecarbamte 2m

NaH (60%, 94.7 mg, 2.37 mmol) freshly washed with pentane was added to a flask, followed by addition of DMF (2.0 mL). The suspension was cooled to 0 °C, and **2a** (300 mg, 1.18 mmol) in DMF (3.0 mL) was added. The mixture was stirred for 30 min at rt, and then cooled to 0 °C. MeI (0.30 mL, 4.74 mmol) was added and the reaction mixture was stirred overnight at rt until the starting material disappeared. The reaction was quenched by addition of saturated aqueous NH_4Cl, and the aqueous layer was extracted with AcOEt. The organic layer was washed with water twice and brine, and then dried over $MgSO_4$. The solvents were evaporated and the residue was purified by chromatography on silica gel to afford **2m** (307.8 mg, 97% yield).

3.3.1. Methyl-(1-phenyl-vinyl)-carbamic acid benzyl ester (2m). Mp 34.0–35.0 °C; ^{1}H NMR ($CDCl_3$) δ=3.21 (s, 3H), 5.04 (s, 2H), 5.16 (s, 1H), 5.46 (s, 1H), 6.80–7.40 (m, 10H); ^{13}C NMR ($CDCl_3$) δ=37.6, 67.2, 110.0, 125.5, 127.5, 127.6, 128.2, 128.3, 128.5, 136.3, 137.2, 148.1, 155.5; IR (neat) 3032, 2954, 2888, 1703, 1626, 1446, 1389, 1337, 1203, 1146, 1027, 955, 902, 777, 696 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{17}H_{18}NO_2$ $[M+H]^+$, 268.1338. Found 268.1349.

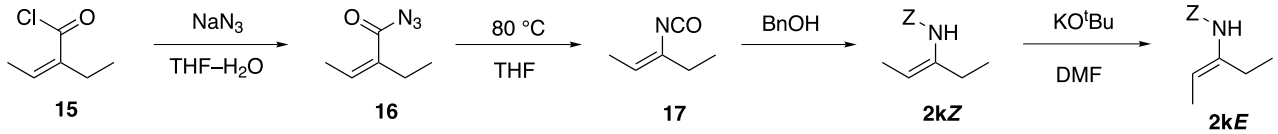
4. Typical procedure for distillation of ethyl glyoxylate

Ethyl glyoxylate was purchased from Tokyo Kasei Kogyo (TCI) as a polymer form in toluene. The ethyl glyoxylate toluene solution (30 g) was added to the flame dried flask. Toluene was evaporated completely under vacuum (<1 mm Hg) at rt, and P_2O_5 (ca. 300 mg) was added to the polymeric ethyl glyoxylate. The mixture was distilled to give almost-toluene-free monomeric ethyl glyoxylate as a slightly yellow liquid (150 mm Hg, 80 °C). Monomeric ethyl glyoxylate easily polymerizes within 30 min to give viscous liquid. Therefore, distilled ethyl glyoxylate should be used immediately after purification.

5. Addition reactions of enecarbamates to ethyl glyoxylate

5.1. Typical procedure for addition reactions of enecarbamates to ethyl glyoxylate using a chiral copper catalyst prepared from $CuClO_4\cdot 4CH_3CN$ and chiral diimine ligand 3t

Ligand **3t** (9.9 mg, 0.022 mmol) in CH_2Cl_2 (1.5 mL) was added to the $CuClO_4\cdot 4CH_3CN$ (6.5 mg, 0.020 mmol) flask under argon The yellow solution was stirred for over 12 h, and cooled to 0 °C. Freshly distilled ethyl glyoxylate (100 μL, 0.40 mmol) in CH_2Cl_2 (0.8 mL) was added to the mixture, and then enecarbamate **2** (0.20 mmol) in CH_2Cl_2 (0.8 mL) was added in one portion. The reaction mixture was stirred at 0 °C, and was quenched by addition of saturated aqueous $NaHCO_3$. The reaction mixture was allowed to warm to rt, and was extracted with CH_2Cl_2. The



Scheme 7.

organic layer was washed with brine and dried over anhydrous $MgSO_4$. After the solvent was evaporated, the residue was dissolved in EtOH (3.0 mL), and a 48% HBr aqueous solution (0.3 mL) was added to the solution. The mixture was stirred at rt for 1.5 min, and then the reaction was quenched by addition of saturated aqueous $NaHCO_3$ at 0 °C. The reaction mixture was allowed to warm to rt. The mixture was extracted with CH_2Cl_2, and the organic layer was washed with brine and dried over anhydrous $MgSO_4$. After the solvents were evaporated, the crude product was purified by chromatography on silica gel to afford the desired compound **7**.

5.2. Analytical data for 7

5.2.1. (2*S*)-2-Hydroxy-4-oxo-4-phenyl-butyric acid ethyl ester (7a). ^{1}H NMR ($CDCl_3$) δ=1.27 (t, 3H, J=7.1 Hz), 3.29 (brs, 1H), 3.44 (dd, 1H, J=6.1, 17.6 Hz), 3.52 (dd, 1H, J=3.9, 17.6 Hz), 4.25 (q, 2H, J=7.1 Hz), 4.61–4.67 (m, 1H), 7.44–7.50 (m, 2H), 7.54–7.60 (m, 1H), 7.92–7.98 (m, 2H); ^{13}C NMR ($CDCl_3$) δ=14.0, 42.1, 61.8, 67.1, 128.1, 128.6, 133.5, 136.4, 173.7, 197.5. IR (neat) 3475, 3063, 2983, 1737, 1687, 1597, 1580, 1449, 1368, 1213, 1098, 1045, 860, 759, 690, 582, 499 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{12}H_{15}O_4$ $[M+H]^+$, 223.0970. Found 223.0972; HPLC, Daicel Chiralcel ADH, hexane/^{i}PrOH=4/1, flow rate=0.5 mL/min: t_R=19.9 min (*S*), t_R=22.2 min (*R*).

5.2.2. (2*S*)-2-Hydroxy-4-(4-methoxy-phenyl)-4-oxo-butyric acid ethyl ester (7b). ^{1}H NMR ($CDCl_3$) δ=1.28 (t, 3H, J=7.1 Hz), 3.41 (dd, 1H, J=5.9, 17.4 Hz), 3.48 (dd, 1H, J=4.0, 17.4 Hz), 3.48 (brd, 1H, J=6.8 Hz), 3.87 (s, 3H), 4.26 (q, 2H, J=7.1 Hz), 4.60–4.70 (m, 1H), 6.91–6.97 (m, 2H), 7.90–7.97 (m, 2H); ^{13}C NMR ($CDCl_3$) δ=14.0, 41.7, 55.4, 61.7, 67.3, 113.8, 129.5, 130.4, 163.8, 173.8, 196.1. IR (neat) 3483, 2979, 2841, 1739, 1677, 1600, 1575, 1512, 1465, 1421, 1368, 1265, 1172, 1099, 1027, 988, 895, 834, 737, 579 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{13}H_{17}O_5$ $[M+H]^+$, 253.1076. Found 253.1097; HPLC, Daicel Chiralcel ADH, hexane/^{i}PrOH=4/1, flow rate=0.4 mL/min: t_R=43.1 min (*S*), t_R=45.7 min (*R*).

5.2.3. (2*S*)-4-(4-Chloro-phenyl)-2-hydroxy-4-oxo-butyric acid ethyl ester (7c). ^{1}H NMR ($CDCl_3$) δ=1.28 (t, 3H, J=7.1 Hz), 3.42 (dd, 1H, J=6.1, 17.3 Hz), 3.49 (dd, 1H, J=3.9, 17.3 Hz), 3.41–3.47 (brd, 1H), 4.26 (q, 2H, J=7.1 Hz), 4.62–4.70 (m, 1H), 7.42–7.48 (m, 2H), 7.86–7.93 (m, 2H); ^{13}C NMR ($CDCl_3$) δ=14.1, 42.2, 62.0, 67.1, 129.0, 129.6, 134.8, 140.1, 173.7, 196.3. IR (neat) 3480, 2982, 1739, 1684, 1590, 1573, 1402, 1213, 1093, 1045, 820, 531 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{12}H_{14}ClO_4$ $[M+H]^+$, 257.0580. Found 257.0584; HPLC, Daicel Chiralcel ADH, hexane/^{i}PrOH=4/1, flow rate=0.5 mL/min: t_R=24.2 min (*S*), t_R=26.5 min (*R*).

5.2.4. (2*S*)-2-Hydroxy-4-oxo-4-*p*-tolyl-butyric acid ethyl ester (7d). ^{1}H NMR ($CDCl_3$) δ=1.28 (t, 3H, J=7.1 Hz), 2.41 (s, 3H), 3.44 (dd, 1H, J=5.9, 17.4 Hz), 3.51 (dd, 1H, J=4.0, 17.4 Hz), 3.45–3.55 (brs, 1H), 4.26 (q, 2H, J=7.1 Hz), 4.66 (dt, 1H, J=4.2, 5.5 Hz), 7.26 (apparent d, 2H, J=8.0 Hz), 7.85 (apparent d, 2H, J=8.2 Hz); ^{13}C NMR ($CDCl_3$) δ=14.0, 21.6, 42.0, 61.7, 67.2, 128.2, 129.3, 133.9, 144.4, 173.7, 197.1. IR (neat) 3483, 2981, 1742, 1682, 1606, 1405, 1365, 1212, 1098, 1044, 813, 578 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{13}H_{17}O_4$ $[M+H]^+$, 237.1127. Found 237.1120; HPLC, Daicel Chiralcel ADH, hexane/^{i}PrOH=4/1, flow rate=0.3 mL/min: t_R=36.1 min (*S*), t_R=38.2 min (*R*).

5.2.5. (2*S*)-2-Hydroxy-4-naphthalen-2-yl-4-oxo-butyric acid ethyl ester (7e). ^{1}H NMR ($CDCl_3$) δ=1.28 (t, 3H, J=7.1 Hz), 3.52 (d, 1H, J=5.9 Hz), 3.59 (dd, 1H, J=6.1, 17.3 Hz), 3.66 (dd, 1H, J=3.9, 17.3 Hz), 4.28 (q, 2H, J=7.1 Hz), 4.73 (dt, 1H, J=4.2, 5.4 Hz), 7.50–7.65 (m, 2H), 7.82–8.20 (m, 4H), 8.45 (s, 1H); ^{13}C NMR ($CDCl_3$) δ=14.1, 42.3, 61.9, 67.3, 123.6, 126.9, 127.8, 128.6, 128.8, 129.6, 130.2, 132.4, 133.8, 135.8, 173.9, 197.5. IR (neat) 3481, 3058, 2982, 1741, 1681, 1627, 1469, 1369, 1209, 1097, 1045, 859, 824, 749, 477 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{16}H_{17}O_4$ $[M+H]^+$, 273.1127. Found 273.1125; HPLC, Daicel Chiralcel ADH, hexane/^{i}PrOH=4/1, flow rate=0.5 mL/min: t_R=27.0 min (*S*), t_R=30.4 min (*R*).

5.2.6. (2*S*)-2-Hydroxy-3-methyl-4-oxo-4-phenyl-butyric acid ethyl ester (7f, *syn/anti* mixture). ^{1}H NMR *syn* ($CDCl_3$) δ=1.26 (t, 3H, J=7.0 Hz), 1.29 (d, 3H, J=7.0 Hz), 3.28 (br, 1H), 3.93 (dq, 1H, J=4.2, 7.0 Hz), 4.25 (q, 2H, J=7.0 Hz), 4.58 (d, 1H, J=4.2 Hz), 7.40–7.65 (m, 3H), 7.90–8.05 (m, 2H); *anti* ($CDCl_3$) δ=1.20 (t, 3H, J=7.1 Hz), 1.36 (d, 3H, J=7.3 Hz), 3.61 (d, 1H, J=8.3 Hz), 3.98 (dq, 1H, J=4.6, 7.1 Hz), 4.10–4.25 (m, 2H), 4.39 (dd, 1H, J=4.6, 8.3 Hz), 7.40–7.65 (m, 3H); ^{13}C NMR *syn* ($CDCl_3$) δ=12.1, 14.0, 44.3, 61.9, 71.6, 128.4, 128.7, 133.3, 135.7, 173.1, 201.6; *anti* ($CDCl_3$) δ=14.0, 14.1, 44.0, 61.5, 73.1, 128.3, 128.7, 133.4, 135.9, 173.1; IR (neat) *syn* 3480, 3063, 2978, 2936, 1734, 1678, 1596, 1579, 1449, 1369, 1217, 1133, 1062, 1023, 1001, 975, 952, 862, 794, 708; *anti* 3481, 3059, 2981, 2941, 1738, 1685, 1588, 1454, 1372, 1255, 1209, 1144, 1092, 1024, 973, 701 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{13}H_{17}O_4$ $[M+H]^+$, 237.1127. Found 237.1118; HPLC, Daicel Chiralcel AS+ADH+AD, hexane/^{i}PrOH=4/1, flow rate=0.5 mL/min: t_R=46.7 min (2*S*,3*S*), t_R=50.6 min (2*R*,3*R*), t_R=54.3 min (2*S*,3*R*), t_R=61.9 min (2*R*,3*S*).

5.2.7. (2*S*)-2-Hydroxy-4-(4-methoxy-phenyl)-3-methyl-4-oxo-butyric acid ethyl ester (7g, *syn/anti* mixture). ^{1}H NMR *syn* ($CDCl_3$) δ=1.28 (t, 3H, J=7.1 Hz), 1.29 (d, 3H, J=7.1 Hz), 3.35 (br, 1H), 3.84–3.96 (m, 4H), 4.27 (q, 2H, J=7.1 Hz), 4.58 (t, 1H, J=4.2 Hz), 6.96 (apparent d, 2H, J=9.0 Hz), 7.30–7.45 (m, 5H), 7.95 (apparent d, 2H, J=8.8 Hz); *anti* ($CDCl_3$) δ=1.19 (t, 3H, J=7.1 Hz), 1.36 (d, 3H, J=7.3 Hz), 3.75 (d, 1H, J=9.3 Hz), 3.88 (s, 3H), 3.94 (dq, 1H, J=4.6, 7.3 Hz), 4.15 (apparent dq, 2H, J=3.2, 7.1 Hz), 4.36 (dd, 1H, J=4.6, 9.3 Hz), 6.92–6.99 (m, 2H), 7.90–7.97 (m, 2H); ^{13}C NMR *syn* ($CDCl_3$) δ=12.3, 14.0, 43.7, 55.4, 61.8, 71.7, 113.9, 128.5, 130.7, 163.7, 173.1, 200.4; *anti* ($CDCl_3$) δ=14.0, 14.6, 43.2, 55.5, 61.4, 73.4, 113.9, 128.7, 130.8, 163.8, 173.2, 201.9; IR (neat) *syn* 3477, 2979, 2935, 2850, 1730, 1670, 1600, 1573, 1510, 1463, 1420, 1308, 1261, 1173, 1125, 1027, 976, 843, 770, 604; *anti* 3478, 2979, 2941, 2843, 1738, 1671, 1599, 1580, 1510, 1457, 1419, 1370, 1308, 1257, 1216, 1172, 1092, 1026, 974, 841 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{14}H_{19}O_5$ $[M+H]^+$, 267.1232. Found 267.1232; HPLC, Daicel

Chiralcel ADH, hexane/^{i}PrOH=4/1, flow rate=0.2 mL/min: t_R=60.5 min (2*R*,3*R*), t_R=65.4 min (2*S*,2*S*), t_R=75.2 min (2*R*,3*S*), t_R=78.9 min (2*S*,3*R*).

5.2.8. (2*S*)-4-(4-Chloro-phenyl)-2-hydroxy-3-methyl-4-oxo-butyric acid ethyl ester (7i, *syn/anti* mixture). ^{1}H NMR *syn* ($CDCl_3$) δ=1.26 (t, 3H, *J*=7.0 Hz), 1.28 (d, 3H, *J*=7.0 Hz), 3.27 (brs, 1H), 3.87 (dq, 1H, *J*=4.4, 7.0 Hz), 4.25 (q, 2H, *J*=7.0 Hz), 4.55 (d, 1H, *J*=4.4 Hz), 7.40–7.55 (m, 2H), 7.84–7.97 (m, 2H); *anti* ($CDCl_3$) δ=1.21 (t, 3H, *J*=7.1 Hz), 1.34 (d, 3H, *J*=7.1 Hz), 3.53 (d, 1H, *J*=8.2 Hz), 3.91 (dq, 1H, *J*=5.0, 7.1 Hz), 4.08–4.24 (m, 2H), 4.38 (dd, 1H, *J*=5.0, 8.2 Hz), 7.42–7.52 (m, 2H), 7.80–7.95 (m, 2H); ^{13}C NMR *syn* ($CDCl_3$) δ=12.1, 14.0, 44.4, 62.0, 71.5, 129.0, 129.8, 134.1, 139.7, 173.1, 200.3; *anti* ($CDCl_3$) δ=13.9, 14.0, 44.1, 61.6, 73.0, 129.0, 129.8, 134.3, 139.9, 173.0, 201.8; IR (neat) *syn* 3485, 2982, 2938, 1730, 1682, 1589, 1571, 1488, 1455, 1401, 1217, 1132, 1092, 1013, 977, 843, 758, 692, 533, 478; *anti* 3478, 3092, 2982, 2935, 1738, 1686, 1589, 1455, 1402, 1255, 1208, 1144, 1092, 1022, 976, 842, 751, 527 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{13}H_{16}ClO_4$ $[M+H]^+$, 271.0737. Found 271.0745; HPLC, Daicel Chiralcel AS, hexane/^{i}PrOH=4/1, flow rate=0.5 mL/min: t_R=15.1 min (2*S*,3*S*), t_R=16.6 min (2*S*,3*R*), t_R=21.4 min (2*R*,3*S*), t_R=23.9 min (2*R*,3*R*).

5.2.9. (2*S*)-3-Benzoyl-2-hydroxy-pentanoic acid ethyl ester (7j, *syn/anti* mixture). ^{1}H NMR *syn* ($CDCl_3$) δ=0.93 (t, 3H, *J*=7.5 Hz), 1.19 (t, 3H, *J*=7.1 Hz), 1.70–2.05 (m, 2H), 3.18 (brs, 1H), 3.83 (dt, 1H, *J*=5.3, 8.3 Hz), 4.19 (q, 2H, *J*=7.1 Hz), 4.51 (d, 1H, *J*=5.3 Hz), 7.42–7.54 (m, 2H), 7.54–7.62 (m, 1H), 7.90–8.02 (m, 2H); *anti* ($CDCl_3$) δ=1.04 (t, 3H, *J*=7.6 Hz), 1.15 (t, 3H, *J*=7.1 Hz), 1.80–1.95 (m, 2H), 3.70 (d, 1H, *J*=9.5 Hz), 3.83 (dt, 1H, *J*=4.2, 7.1 Hz), 4.09 (q, 2H, *J*=7.1 Hz), 4.43 (dd, 1H, *J*=4.2, 9.5 Hz), 7.46–7.52 (m, 2H), 7.56–7.63 (m, 1H), 7.88–7.95 (m, 2H); ^{13}C NMR *syn* ($CDCl_3$) δ=12.0, 13.9, 21.3, 51.2, 61.9, 71.1, 128.3, 128.6, 133.2, 137.0, 173.6, 201.5; *anti* ($CDCl_3$) δ=12.0, 13.9, 22.3, 50.1, 61.4, 71.3, 128.3, 128.7, 133.5, 136.6, 173.4, 203.9; IR (neat) *syn* 3477, 2972, 2876, 1738, 1675, 1596, 1447, 1372, 1255, 1220, 1118, 1023, 931, 849, 779, 701; *anti* 3485, 3062, 2966, 2941, 2875, 1738, 1682, 1596, 1579, 1448, 1368, 1268, 1208, 1134, 1100, 1028, 914, 849, 785, 699 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{14}H_{19}O_4$ $[M+H]^+$, 251.1283. Found 251.1277; HPLC, Daicel Chiralcel AS, hexane/^{i}PrOH=4/1, flow rate=0.5 mL/min: t_R=13.7 min (2*S*,3*S*), t_R=15.3 min (2*S*,3*R*), t_R=17.6 min (2*R*,3*R*), t_R=23.1 min (2*R*,3*S*).

5.2.10. (2*S*)-2-Hydroxy-3-methyl-4-oxo-hexanoic acid ethyl ester (7k, *syn/anti* mixture). ^{1}H NMR *syn* (C_6D_6) δ=0.89 (t, 3H, *J*=7.1 Hz), 0.99 (d, 3H, *J*=7.2 Hz), 1.97–2.08 (m, 2H), 2.70 (dq, 1H, *J*=4.9, 7.2 Hz), 3.39 (d, 1H, *J*=6.7 Hz), 3.80–4.00 (m, 2H), 4.11 (dd, 1H, *J*=4.9, 6.7 Hz); *anti* (C_6D_6) δ=0.87 (t, 3H, *J*=7.1 Hz), 0.93 (t, 3H, *J*=7.3 Hz), 1.02 (d, 3H, *J*=7.2 Hz), 1.95–2.22 (m, 2H), 2.65 (dq, 1H, *J*=4.4, 7.2 Hz), 3.05–3.23 (m, 1H), 3.80–4.00 (m, 2H), 4.38–4.47 (m, 1H); ^{13}C NMR *syn* ($CDCl_3$) δ=7.58, 12.8, 14.0, 34.6, 49.4, 61.3, 73.0, 173.5, 211.3; *anti* (C_6D_6) δ=7.7, 11.0, 14.0, 34.0, 49.5, 61.6, 71.7, 173.7, 209.9; IR (neat) *syn* 3484, 2981, 2940, 1739, 1716, 1459, 1409, 1375, 1268, 1209, 1108, 1066, 1025, 975, 862, 808, 748; *anti* 3488, 2981, 2940, 1733, 1716, 1459, 1373, 1218, 1145, 1025, 977, 862, 800, 752 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_9H_{17}O_4$ $[M+H]^+$, 189.1127. Found 189.1120.

5.2.11. (1*S*)-Hydroxy-(2-oxo-cyclohexyl)-acetic acid ethyl ester (7l, *syn/anti* mixture). ^{1}H NMR *anti* ((1*S*,1′*R*), tentatively assignment) (C_6D_6) δ=0.95 (t, 3H, *J*=7.1 Hz), 0.94–1.20 (m, 2H), 1.30–1.42 (m, 2H), 1.56–1.84 (m, 3H), 2.02–2.12 (m, 1H), 2.60–2.70 (m, 1H), 3.35 (d, 1H, *J*=7.2 Hz), 3.84 (dd, 1H, *J*=3.2, 7.2 Hz), 4.02 (dq, 2H, *J*=1.9, 7.1 Hz); distingishable *syn* peaks δ=0.88 (t, 3H, *J*=7.1 Hz), 2.12–2.21 (m, 1H), 2.48–2.57 (m,1H), 2.94 (d, 1H, *J*=5.0 Hz), 4.60 (dd, 1H, *J*=3.2, 5.0 Hz); ^{13}C NMR *anti* ($CDCl_3$) δ=14.1, 24.8, 26.9, 30.1, 42.0, 53.7, 61.6, 71.1, 173.4, 211.2; distinguishable *syn* peaks δ=14.2, 24.6, 27.1, 41.9, 53.8, 61.7, 69.2, 173.6, 210.4; HRMS (FAB). Exact mass calcd for $C_{10}H_{17}O_4$ $[M+H]^+$, 201.1127. Found 201.1127.

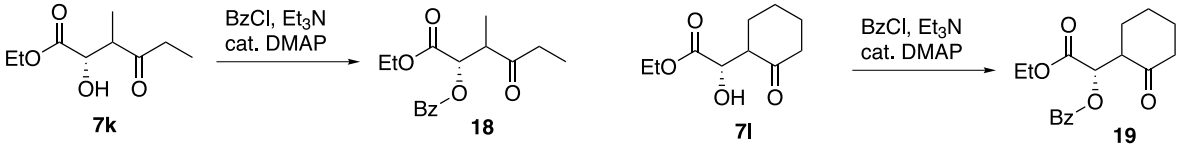
6. Determination of the ee's of 7k and 7l

In order to determine the ee's of **7k** and **7l** whose ee's could not be determined by HPLC analysis as their UV absorbance were very weak, they were converted to **18** and **19**, respectively (Scheme 8).

6.1. Synthesis of 18

To a solution of **7k** (17.9 mg, 0.095 mmol) in CH_2Cl_2 (0.4 mL) was added a solution of Et_3N (19.9 μL, 0.143 mmol) in CH_2Cl_2 (0.3 mL) followed by a solution of BzCl (16.6 μL, 0.143 mmol) in CH_2Cl_2 (0.3 mL) and DMAP (catalytic amount) at 0 °C. The reaction mixture was stirred for 5 h at 0 °C, and water was added, followed by addition of a 1N HCl aqueous solution. The reaction mixture was extracted with Et_2O, and the organic phase was washed with a saturated $NaHCO_3$ aqueous solution and brine, and dried over anhydrous $MgSO_4$. After evaporation of solvents, the crude adduct was purified by chromatography on silica gel to afford **18** (22.2 mg, 80% yield). **19** was also synthesized by using the same method mentioned above (74% yield).

6.1.1. (1*S*)-Benzoic acid 1-ethoxycarbonyl-2-methyl-3-oxo-pentyl ester (18, *syn/anti* mixture). ^{1}H NMR *syn* ($CDCl_3$) δ=1.09 (t, 3H, *J*=7.1 Hz), 1.23 (t, 3H, *J*=7.1 Hz),



Scheme 8.

1.25 (t, 3H, J=7.1 Hz), 2.59 (q, 2H, J=7.1 Hz), 3.23 (quint, 1H, J=7.1 Hz), 4.22 (q, 1H, J=7.1 Hz), 4.22 (q, 1H, J=7.1 Hz), 5.39 (d, 1H, J=7.1 Hz), 7.35–7.50 (m, 2H), 7.50–7.60 (m, 1H), 7.92–8.04 (m, 2H); *anti* δ=1.05 (t, 3H, J=7.3 Hz), 1.24 (t, 3H, J=7.1 Hz), 1.26 (t, 3H, J=7.1 Hz), 2.57 (q, 2H, J=7.3 Hz), 3.21 (dq, 1H, J=5.1, 7.1 Hz), 4.21 (q, 2H, J=7.1 Hz), 5.69 (d, 1H, J=5.1 Hz), 7.42 (apparent t, 2H, J=7.5 Hz), 7.50–7.60 (m, 1H), 7.95–8.05 (m, 2H); ^{13}C NMR *anti* ($CDCl_3$) δ=7.7, 11.6, 14.1, 34.1, 47.1, 61.8, 72.6, 128.4, 129.2, 129.8, 133.4, 165.6, 168.9, 209.6; distinguishable *syn* peaks δ=12.6, 35.0, 61.6, 73.9, 129.1, 129.9, 130.2, 133.7, 209.7; IR (neat) 2981, 2940, 1725, 1602, 1454, 1375, 1348, 1280, 1211, 1103, 1070, 1027, 977, 713 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{16}H_{21}O_5$ $[M+H]^+$, 293.1389. Found 293.1380; HPLC, Daicel Chiralcel ADH+ADH, hexane/^{i}PrOH=19/1, flow rate=0.5 mL/min: t_R=42.7 min (1*R*,2*R*), t_R=51.3 min (1*S*,2*S*), t_R=54.7 min (1*S*,2*R*), t_R=56.8 min (1*R*,2*S*).

6.1.2. (1*S*)-Benzoic acid ethoxycarbonyl-(2-oxo-cyclohexyl)-methyl ester (19, *syn/anti* mixture). ^{1}H NMR *anti* ((1*S*,1′*R*) tentatively assignment) ($CDCl_3$) δ=1.26 (t, 3H, J=7.1 Hz), 1.60–1.85 (m, 3H), 1.85–2.20 (m, 3H), 2.25–2.60 (m, 2H), 3.14–3.30 (m, 1H), 4.23 (q, 2H, J=7.1 Hz), 5.51 (d, 1H, J=4.8 Hz), 7.40–7.50 (m, 2H), 7.52–7.61 (m, 1H), 7.98–8.14 (m, 2H); distinguishable *syn* peaks δ=1.27 (t, 3H, J=7.0 Hz), 2.96–3.10 (m, 1H), 4.23 (q, 2H, J=7.0 Hz), 5.86 (d, 1H, J=3.3 Hz); ^{13}C NMR *anti* ($CDCl_3$) δ=14.0, 24.6, 26.8, 29.5, 41.8, 51.7, 61.5, 70.9, 128.4, 129.4, 129.9, 133.3, 165.9, 169.2, 207.5; *syn* δ=14.1, 26.7, 27.8, 41.7, 51.6, 61.6, 70.1, 128.3, 129.6, 129.8, 133.2, 165.5, 169.6, 207.3; HRMS (FAB). Exact mass calcd for $C_{17}H_{21}O_5$ $[M+H]^+$, 305.1389. Found 305.1382; HPLC, Daicel Chiralcel ADH+AS, hexane/^{i}PrOH=9/1, flow rate=0.9 mL/min: t_R=25.2 min (1*S*,1′*R*), t_R=27.4 min (*syn*, the absolute configuration was not determined.), t_R=29.9 min (1*R*,1′*S*), t_R=36.6 min (*syn*).

7. Reduction of 6a

7.1. Procedure for the synthesis of 10

Ligand **3t** (9.9 mg, 0.022 mmol) in CH_2Cl_2 (1.5 mL) was added to the $CuClO_4 \cdot 4CH_3CN$ (6.5 mg, 0.020 mmol) flask under argon The yellow solution was stirred for over 8 h, and cooled to 0 °C. Freshly distilled ethyl glyoxylate (100 μL, 0.40 mmol) in CH_2Cl_2 (0.8 mL) was added to the mixture, and then enecarbamate **2a** (50.7 mg, 0.20 mmol) in CH_2Cl_2 (0.8 mL) was added in one portion. The reaction mixture was stirred at 0 °C for 1 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$. The reaction mixture was allowed to warm to rt, and was extracted with CH_2Cl_2. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated, and then the residue was dried with benzene azeotropy three times and then under vacuum. THF (2.0 mL) and MeOH (0.5 mL) were added to the residue, and then the solution was cooled to −78 °C. Diethyl methoxyborane (79 μL, 0.6 mmol) was added, and the mixture was stirred for 15 min. To the mixture was added $NaBH_4$ (22.7 mg, 0.6 mmol) in one portion. The mixture was stirred for 2 h at −78 °C. The reaction was quenched by addition of AcOH (0.3 mL) and was allowed to warm to rt. The mixture was alkalized at 0 °C by addition of saturated aqueous $NaHCO_3$. The mixture was extracted with Et_2O twice. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. After the solvents were evaporated, the crude product was purified by chromatography on silica gel to afford the desired compound **10** (46.5 mg, 65% yield in two steps, *syn/anti*=94/6).

7.1.1. 4-Benzyloxycarbonylamino-2-hydroxy-4-phenyl-butyric acid ethyl ester: (10, *syn/anti*=94/6). ^{1}H NMR ($CDCl_3$) δ=1.23 (t, 3H x 19/20, J=7.1 Hz), 1.25 (t, 3H x 1/20, J=7.0 Hz), 1.95–2.40 (m, 2H), 3.33 (brs, 1H x 19/20), 3.51 (brs, 1H x 1/20), 4.00–4.40 (m, 3H), 4.85–5.20 (m, 3H), 5.52 (d, 1H x 19/20, J=7.3 Hz), 5.96 (d, 1H x 1/20, J=8.2 Hz), 7.00–7.60 (m, 10H); ^{13}C NMR ($CDCl_3$) *syn*: δ=14.1, 40.3, 52.6, 61.8, 66.8, 68.4, 126.4, 127.6, 128.1, 128.4, 128.7, 136.3, 141.4, 155.7, 174.4; *anti*: (distinguishable peak) 40.2, 52.4, 67.8, 126.2, 127.4, 141.1, 156.0, 174.3; LRMS (FAB) m/z=358 $[M+H]^+$

7.2. Determination of relative configuration of compound 10

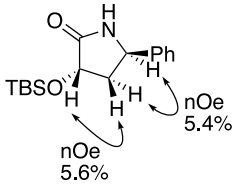
7.2.1. Synthesis of 11. To a solution of **10** (31.3 mg, 0.088 mmol) in CH_2Cl_2 (0.6 mL) was added 2,6-lutidine (12.0 mg, 0.114 mmol) in CH_2Cl_2 (0.2 mL) and TBDMSOTf (27.8 mg, 0.105 mmol) in CH_2Cl_2 (0.2 mL) successively at 0 °C. The reaction mixture was allowed to warm to rt, and was stirred for 10 h. H_2O was added and the mixture was extracted with CH_2Cl_2. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. After the solvent was evaporated, the crude product was purified on silica gel column chromatography to give **11** (37.9 mg, 92% yield).

7.2.2. 4-Benzyloxycarbonylamino-2-(*tert*-butyl-dimethyl-silanyloxy)-4-phenyl-butyric acid ethyl ester (11, diastereomer mixture). ^{1}H NMR ($CDCl_3$) δ=*syn*: −0.03 (s, 3H), 0.02 (s, 3H), 0.90 (s, 9H), 1.15–1.27 (m, 3H), 2.00–2.35 (m, 2H), 3.90–4.30 (m, 3H), 4.80–5.15 (m, 3H), 5.50 (brs, 1H), 7.15–7.40 (m, 10 H); *anti*: (distinguishable peak) δ=−0.02 (s, 3H), 0.03 (s, 3H), 5.62 (brd, 1H, J=7.7 Hz); ^{13}C NMR ($CDCl_3$) *syn*: δ=−5.4, −5.0, 14.0, 18.1, 25.7, 41.0, 52.9, 61.0, 66.6, 70.3, 126.4, 127.4, 128.0, 128.1, 128.4, 128.6, 136.4, 141.8, 155.3, 173.2; *anti*: (distinguishable peak) −5.0, 14.1, 41.8, 52.3, 69.8, 126.0, 127.3, 128.6, 142.2, 155.6, 173.1; IR (neat) 3343, 2940, 1720, 1518, 1254, 1131, 1038, 839, 781, 699 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{26}H_{38}NO_5Si$ $[M+H]^+$, 472.2519. Found 472.2508.

7.2.3. Synthesis of 12. To a solution of **11** (21.4 mg, 0.0454 mmol) in AcOEt (2.0 mL) was added AcOH (16.8 mg, 0.0.272 mmol) and 5% wet Pd/C (9.7 mg, 10 mol%) at rt. After replacement of argon by hydrogen, the mixture was stirred at rt until the starting material completely disappeared (11 h). Pd/C was filtered off and saturated aqueous $NaHCO_3$ was added to the filtrate. The mixture was extracted with AcOEt, and then the organic layer was washed with brine and dried over anhydrous $MgSO_4$. After the solvent was evaporated, the crude product was purified on silica gel column chromatography to give **12**

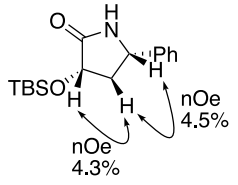
(13.4 mg, quantitative yield). Diastereomers **12** were separated by silica gel column chromatography.

7.2.4. (3*S*,5*R*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-5-phenyl-pyrrolidin-2-one (12-major). ^{1}H NMR ($CDCl_3$) δ= 0.14 (s, 3H), 0.16 (s, 3H), 0.91 (s, 9H), 2.21 (ddd, 1H, J=5.1, 7.1, 13.2 Hz), 2.46 (ddd, 1H, J=5.1, 7.5, 13.2 Hz), 4.38 (dd, 1H, J=5.1, 7.1 Hz), 4.83 (dd, 1H, J=5.0, 7.5 Hz), 6.02 (brs, 1H), 7.20–7.43 (m, 5H); ^{13}C NMR ($CDCl_3$) δ=−5.1, −4.5, 18.3, 25.8, 41.5, 55.1, 69.9, 125.5, 127.9, 129.0, 142.1, 176.3; IR (neat) 3226, 2927, 2892, 2855, 1715, 1496, 1471, 1331, 1253, 1151, 1091, 1028, 963, 880, 839, 780, 699 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{16}H_{26}NO_2Si$ $[M+H]^+$, 292.1733. Found 292.1733 (Scheme 9).



Scheme 9.

7.2.5. (3*S*,5*S*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-5-phenyl-pyrrolidin-2-one (12-minor). ^{1}H NMR ($CDCl_3$) δ= 0.15 (s, 3H), 0.20 (s, 3H), 0.91 (s, 9H), 1.94 (dt, 1H, J=9.2, 12.6 Hz), 2.75–2.87 (m, 1H), 4.42 (dd, 1H, J=7.9, 9.2 Hz), 4.53 (dd, 1H, J=6.2, 8.6 Hz), 5.76 (brs, 1H), 7.30–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ=−5.1, −4.5, 18.3, 25.8, 42.0, 53.9, 70.8, 126.1, 128.1, 128.9, 176.0; IR (neat) 3220, 2936, 2858, 2359, 1717, 1463, 1330, 1247, 1151, 882, 838, 781, 698 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{16}H_{26}NO_2Si$ $[M+H]^+$, 292.1733. Found 292.1736 (Scheme 10).



Scheme 10.

8. Determination of the absolute and relative configuration of 7f

8.1. Determination of the relative configuration of 7f

To a solution of *anti*-**7f** (45.6 mg, 0.193 mmol) in MeOH (1.0 mL) was added $NaBH_4$ (14.6 mg, 0.39 mmol) at 0 °C. The reaction mixture was stirred for 10 min, and the reaction was quenched by addition of acetone. The mixture was kept stirred for 5 min, and then saturated NH_4Cl aqueous solution was added. The mixture was extracted with CH_2Cl_2 three times, and the extract was dried over anhydrous $MgSO_4$. The solvents were evaporated to give a crude keto alcohol. To a solution of the crude product in CH_2Cl_2 (1 mL) was added $TsOH\cdot H_2O$, and the reaction mixture was stirred for 13.5 h at rt. The reaction was quenched by addition of a saturated $NaHCO_3$ aqueous solution, and was extracted with CH_2Cl_2 three times. The extract was dried over anhydrous $MgSO_4$. The solvents were evaporated to give a residue, followed by purification on silica gel chromatography to afford **14** as a diastereomer mixture (19.8 mg, 53% yield, **14**/*epi*-**14**=55/45). **14** was recrystallized from CH_2Cl_2/hexane to give single crystals which were suitable for X-ray structure analysis. From *syn*-**7f**, **20** was obtained as a diastereomer mixture (84% yield, **20**/*epi*-**20**=86/14) according to the same procedure as mentioned above. The relative stereochemisty of **20** was determined by NOE analysis. Lactones **14** and **20** were used for determination of the absolute configuration as follows.

8.1.1. (3*S*,4*R*,5*S*)-3-Hydroxy-4-methyl-5-phenyl-dihydro-furan-2-one (14). Mp 150–151 °C; ^{1}H NMR ($CDCl_3$) δ=0.65 (d, 3H, J=7.3 Hz), 2.75 (brs, 1H), 2.98–3.08 (m, 1H), 4.79 (d, 1H, J=6.8 Hz), 5.57 (d, 1H, J= 4.6 Hz), 7.25–7.30 (m, 2H), 7.30–7.38 (m, 1H), 7.38–7.45 (m, 2H); ^{13}C NMR ($CDCl_3$) δ=7.4, 41.1, 72.1, 80.2, 125.2, 128.2, 128.6, 135.1, 177.0; IR (neat) 3443, 2963, 1758, 1452, 1414, 1294, 1194, 1148, 1051, 956, 754, 701, 622, 478 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{11}H_{13}O_3$ $[M+H]^+$, 193.0865. Found 193.0872.

8.1.2. (3*S*,4*R*,5*R*)-3-Hydroxy-4-methyl-5-phenyl-dihydro-furan-2-one (*epi*-14). ^{1}H NMR ($CDCl_3$) δ=1.22 (d, 3H, J=7.1 Hz), 2.62 (tq, 1H, J=5.1, 6.8 Hz), 2.86 (brs, 1H), 4.47 (d, 1H, J=6.8 Hz), 5.26 (d, 1H, J=5.1 Hz), 7.20–7.45 (m, 5H); ^{13}C NMR ($CDCl_3$) δ=10.8, 43.2, 69.7, 85.8, 125.3, 128.6, 128.8, 137.7, 176.9; IR (neat) 3430, 3039, 2924, 2857, 1772, 1455, 1275, 1202, 1143, 1093, 986, 889, 805, 742, 702 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{11}H_{13}O_3$ $[M+H]^+$, 193.0865. Found 193.0864.

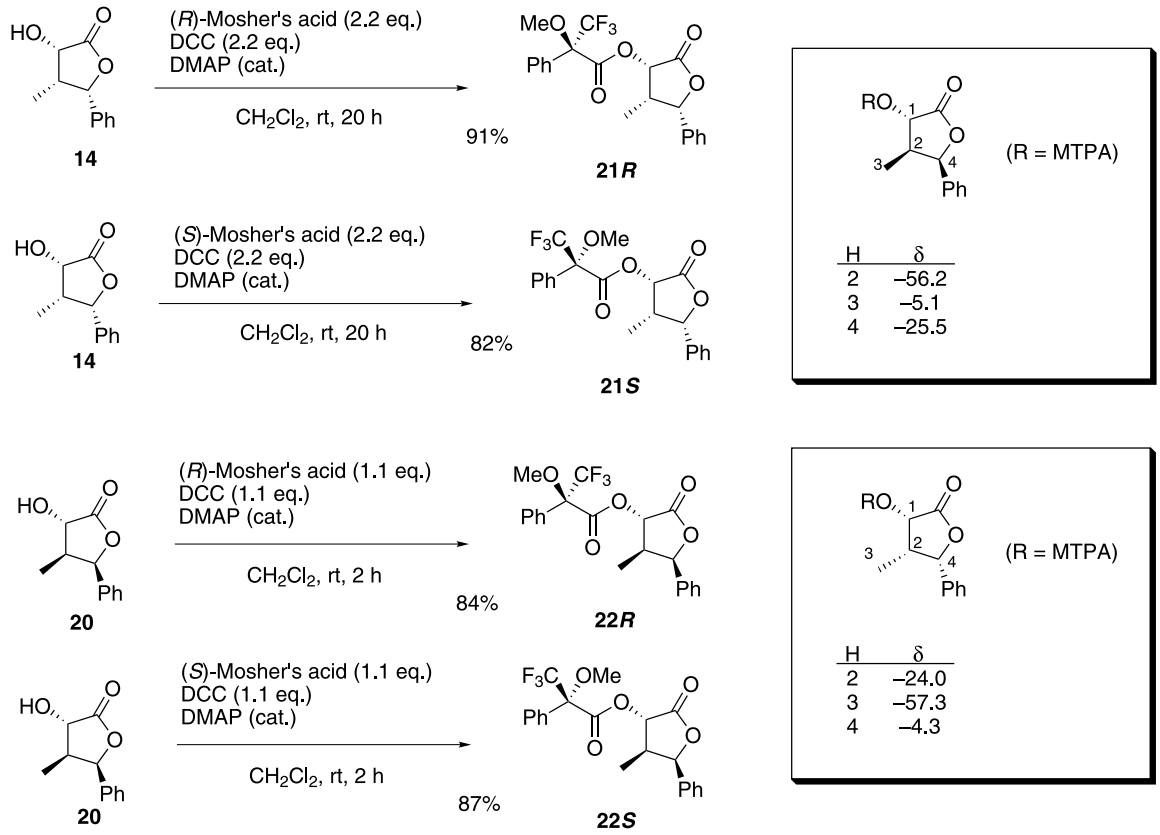
8.1.3. (3*S*,4*S*,5*R*)-3-Hydroxy-4-methyl-5-phenyl-dihydro-furan-2-one (20). ^{1}H NMR ($CDCl_3$) δ=0.87 (d, 3H, J=7.0 Hz), 2.70–2.92 (m, 1H), 3.18 (brs, 1H), 4.24 (d, 1H, J=9.9 Hz), 5.63 (d, 1H, J=8.1 Hz), 7.05–7.18 (m, 2H), 7.30–7.45 (m, 3H); ^{13}C NMR ($CDCl_3$) δ=13.3, 42.1, 72.2, 82.4, 125.7, 128.5, 128.6, 135.5, 177.5; IR (neat) 3362, 2970, 1776, 1455, 1334, 1184, 1145, 1096, 991, 897, 755, 701, 464 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{11}H_{13}O_3$ $[M+H]^+$, 193.0865. Found 193.0872.

8.1.4. (3*S*,4*S*,5*S*)-3-Hydroxy-4-methyl-5-phenyl-dihydro-furan-2-one (*epi*-20). ^{1}H NMR ($CDCl_3$) δ=1.24 (d, 3H, J=6.4 Hz), 2.41 (tq, 1H, J=6.4, 10.6 Hz), 3.24 (brs, 1H), 4.25 (d, 1H, J=11.0 Hz), 4.87 (d, 1H, J=10.1 Hz), 7.30–7.50 (m, 5H); ^{13}C NMR ($CDCl_3$) δ=13.3, 47.5, 74.7, 84.1, 126.5, 128.8, 129.2, 136.2, 176.8; IR (neat) 3319, 2967, 2921, 1776, 1459, 1318, 1237, 1152, 1110, 981, 765, 700, 540 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{11}H_{13}O_3$ $[M+H]^+$, 193.0865. Found 193.0857.

8.2. Determination of the absolute configuration of 7f

Lactones **14** and **20** were converted into **21** and **22** respectively, by using a standard method as shown below (Scheme 11).

$\Delta\delta$ ($\delta_S-\delta_R$) in the ^{1}H NMR analysis showed minus values for all H2, H3, and H4. As expected from an analogy of **7a**, the absolute configuration of C3 was determined to be *S*.[15]



Scheme 11.

From the knowledge of the absolute stereochemistry of **14** and **20**, the absolute configurations of both *anti*-**7f** and *syn*-**7f** were determined.

8.2.1. (3*S*,4*S*,5*S*,2′*R*)-3,3,3-Trifluoro-2-methoxy-2-phenyl-propionic acid 4-methyl-2-oxo-5-phenyl-tetrahydro-furan-3-yl ester (21*R*). ^{1}H NMR ($CDCl_3$) δ=0.66 (d, 3H, J=7.1 Hz), 3.10–3.26 (m, 1H), 3.54 (d, 3H, J=0.9 Hz), 5.67 (d, 1H, J=4.8 Hz), 6.04 (d, 1H, J=7.1 Hz), 7.20–7.30 (m, 2H), 7.30–7.50 (m, 6H), 7.55–7.68 (m, 2H); ^{13}C NMR ($CDCl_3$) δ=8.4, 39.3, 55.5, 73.3, 80.1, 125.2, 127.8, 128.5, 128.5, 128.7, 129.9, 131.0, 134.4, 165.7, 170.4; IR (neat) 3063, 3033, 2987, 2947, 2850, 1802, 1754, 1504, 1455, 1364, 1245, 1179, 1111, 1089, 1057, 975, 698 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{21}H_{20}F_3O_5$ $[M+H]^+$, 409.1263. Found 409.1277.

8.2.2. (3*S*,4*S*,5*S*,2′*S*)-3,3,3-Trifluoro-2-methoxy-2-phenyl-propionic acid 4-methyl-2-oxo-5-phenyl-tetrahydro-furan-3-yl ester (21*S*). ^{1}H NMR ($CDCl_3$) δ=0.47 (d, 3H, J=7.1 Hz), 3.00–3.20 (m, 1H), 3.66 (d, 3H, J=0.9 Hz), 5.66 (d, 1H, J=5.0 Hz), 6.07 (d, 1H, J=7.1 Hz), 7.20–7.30 (m, 2H), 7.30–7.50 (m, 6H), 7.60–7.70 (m, 2H); ^{13}C NMR ($CDCl_3$) δ=8.1, 39.4, 55.8, 73.0, 80.2, 125.2, 127.3, 128.5, 128.5, 128.7, 129.9, 131.6, 134.4, 165.7, 170.8; IR (neat) 3065, 2941, 2857, 1802, 1755, 1497, 1455, 1393, 1367, 1243, 1178, 1125, 1058, 977, 705 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{21}H_{20}F_3O_5$ $[M+H]^+$, 409.1263. Found 409.1277.

8.2.3. (3*S*,4*R*,5*R*,2′*R*)-3,3,3-Trifluoro-2-methoxy-2-phenyl-propionic acid 4-methyl-2-oxo-5-phenyl-tetrahydro-furan-3-yl ester (22*R*). ^{1}H NMR (C_6D_6) δ=0.30 (d, 3H, J=7.0 Hz), 2.38–2.50 (m, 1H), 3.46 (d, 3H, J=0.9 Hz), 4.91 (d, 1H, J=8.6 Hz), 5.37 (d, 1H, J=11 Hz), 6.65–6.73 (m, 2H), 6.96–7.05 (m, 3H), 7.08–7.12 (m, 1H), 7.18–7.24 (m, 2H), 7.91 (apparent d, 2H, J=7.9 Hz); ^{13}C NMR (C_6D_6) δ=12.7, 39.0, 55.4, 74.2, 81.6, 125.9, 128.6, 128.7, 128.8, 130.0, 132.1, 135.3, 166.0, 170.6; IR (neat) 3033, 2974, 2945, 2850, 1800, 1757, 1497, 1453, 1340, 1243, 1170, 1116, 1056, 998, 909, 757, 699 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{21}H_{20}F_3O_5$ $[M+H]^+$, 409.1263. Found 409.1245.

8.2.4. (3*S*,4*R*,5*R*,2′*S*)-3,3,3-Trifluoro-2-methoxy-2-phenyl-propionic acid 4-methyl-2-oxo-5-phenyl-tetrahydro-furan-3-yl ester (22*S*). ^{1}H NMR (C_6D_6) δ=0.28 (d, 3H, J=6.9 Hz), 2.15–2.35 (m, 1H), 3.65 (d, 3H, J=0.7 Hz), 4.83 (d, 1H, J=8.2 Hz), 5.61 (d, 1H, J=10.6 Hz), 6.64–6.72 (m, 2H), 6.90–7.05 (m, 3H), 7.05–7.25 (m, 3H), 7.80–7.90 (m, 2H); ^{13}C NMR (C_6D_6) δ=12.5, 39.4, 55.7, 73.6, 81.8, 122.2, 125.9, 127.9, 128.6, 128.8, 128.8, 130.0, 132.6, 135.2, 166.3, 171.2; IR (neat) 3065, 3033, 2945, 2851, 1800, 1759, 1496, 1454, 1342, 1273, 1247, 1172, 1123, 1081, 1057, 994, 903, 795, 763, 723 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{21}H_{20}F_3O_5$ $[M+H]^+$, 409.1263. Found 409.1282.

Acknowledgements

This work was partially supported by CREST, SORT, and ERATO, Japan Science and Technology Corporation (JST), and a Grant-in-Aid for Scientific Research from Japan

Society for the Promotion of Science (JSPS). R.M. is grateful for a JSPS fellowship for Japanese Junior Scientists.

References and notes

1. For example, (a) Suen, Y. H.; Horeau, A.; Kagan, H. B. *Bull. Soc. Chim. Fr.* **1965**, *5*, 1454. (b) Machida, S.; Tanaka, I. *Kyoto Kogei Sen'i Daigaku Sen'igakubu Gakujutsu Hokoku* **1975**, *7*, 423; CA *84*, 122382. (c) Burk, M. J.; Casy, G.; Johnson, N. B. *J. Org. Chem.* **1998**, *63*, 6084.
2. (a) Shono, T.; Matsumura, Y.; Tsubata, K.; Sugihara, Y.; Yamane, S.; Kanazawa, T.; Aoki, T. *J. Am. Chem. Soc.* **1982**, *104*, 6697. (b) Eberson, L.; Malmberg, M.; Nyberg, K. *Acta Chem. Scand.* **1984**, *38*, 391. (c) For the use of a diene in Diels–Alder reactions, see: Jessup, P. J.; Petty, C. B.; Roos, J.; Overman, L. E. *Org. Synth.* **1980**, *59*, 1. (d) Meth-Cohn, O.; Westwood, K. T. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1173. (e) Chigr, M.; Fillion, H.; Rougny, A. *Tetrahedron Lett.* **1987**, *28*, 4529. (f) Wipf, P.; Wang, X. *Tetrahedron Lett.* **2000**, *41*, 8747.
3. Matsubara, R.; Nakamura, Y.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 1679.
4. (a) Kobayashi, S.; Matsubara, R.; Kitagawa, H. *Org. Lett.* **2002**, *4*, 143. (b) Kobayashi, S.; Matsubara, R.; Nakamura, Y.; Kitagawa, H.; Sugiura, M. *J. Am. Chem. Soc.* **2003**, *125*, 2507. (c) Nakamura, Y.; Matsubara, R.; Kiyohara, H.; Kobayashi, S. *Org. Lett.* **2003**, *5*, 2481. (d) Kobayashi, S.; Kiyohara, H.; Nakamura, Y.; Matsubara, R. *J. Am. Chem. Soc.* **2004**, *126*, 6558.
5. Matsubara, R.; Nakamura, Y.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3258.
6. This complex was already shown to be an excellent catalyst for Diels–Alder reaction by D. A. Evans, et al. Review: Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325.
7. Li, Z.; Conser, K. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1993**, *115*, 5326.
8. (a) Saksena, A. K.; Mangiaracina, P. *Tetrahedron Lett.* **1983**, *24*, 273. (b) Nakata, T.; Tani, Y.; Hatozaki, M.; Oishi, T. *Chem. Pharm. Bull.* **1984**, *32*, 1411. (c) Narasaka, K.; Pai, F.-C. *Tetrahedron* **1984**, *40*, 2233. (d) Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155. (e) Mori, Y.; Kuhara, M.; Takeuchi, A.; Suzuki, M. *Tetrahedron Lett.* **1988**, *29*, 5419. (f) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560. (g) Mori, Y.; Suzuki, M. *Tetrahedron Lett.* **1989**, *30*, 4383.
9. Kochi, T.; Tang, T. P.; Ellman, J. A. *J. Am. Chem. Soc.* **2003**, *125*, 11276.
10. Yun, J. M.; Sim, T. B.; Hahm, H. S.; Lee, W. K.; Ha, H.-J. *J. Org. Chem.* **2003**, *68*, 7675.
11. A concerted aza-ene-type reaction was proposed for the Michael reaction with a chiral enamine: (a) Ambroise, L.; Desmaële, D.; Mahuteau, J.; d'Angelo, J. *Tetrahedron Lett.* **1994**, *35*, 9705. (b) Lucero, M. J.; Houk, K. N. *J. Am. Chem. Soc.* **1997**, *119*, 826. (c) Bahmanyar, S.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 11273.
12. Masao, S. *J. Org. Chem.* **1961**, *26*, 770.
13. Mimoun, H.; Laumer, J. Y. S.; Giannini, L.; Scopelliti, R.; Floriani, C. *J. Am. Chem. Soc.* **1999**, *121*, 6158.
14. (a) Brittelli, D. R. *J. Org. Chem.* **1981**, *46*, 2514. (b) Jackson, D. A.; Rey, M.; Dreiding, A. S. *Helv. Chim. Acta* **1983**, *66*, 2330.
15. Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.