

Classics in Total Synthesis

K. C. Nicolaou and
E. J. Sorensen

Targets, Strategies, Methods

With a Foreword by
E. J. Corey



Weinheim
New York
Basel
Cambridge
Tokyo

Table of Contents

Chapter 1

Introduction: Constructing the Molecules of Nature

1.1	Synthetic Chemistry and Total Synthesis	2
1.2	The Scope of Organic Synthesis	3
1.3	A Brief History of Organic Synthesis	5
1.4	The Practice of Total Synthesis	7
1.5	Target Molecules	8
1.6	Natural Products as Synthetic Targets	9
1.7	Designed Molecules as Synthetic Targets	12
1.8	Synthetic Strategy	13
1.9	Retrosynthetic Analysis	14
1.10	Classics in Total Synthesis	17

Chapter 2

Strychnine

R. B. Woodward (1954)

2.1	Introduction	21
2.2	Retrosynthetic Analysis and Strategy	22
2.3	Total Synthesis	27
2.4	Conclusion	40

Chapter 3

Penicillin V

J. C. Sheehan (1957)

3.1	Introduction	41
3.2	Retrosynthetic Analysis and Strategy	44
3.3	Total Synthesis	45
3.4	Conclusion	50

Chapter 4

*Reserpine**R. B. Woodward (1958)*

4.1	Introduction	55
4.2	Retrosynthetic Analysis and Strategy	56
4.3	Total Synthesis	57
4.4	Conclusion	63

Chapter 5

*Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$)
and Prostaglandin E_2 (PGE_2)**E. J. Corey (1969)*

5.1	Introduction	65
5.2	Retrosynthetic Analysis and Strategy	67
5.3	Total Synthesis	71
5.4	Conclusion	81

Chapter 6

*Progesterone**W. S. Johnson (1971)*

6.1	Introduction	83
6.2	Retrosynthetic Analysis and Strategy	85
6.3	Total Synthesis	88
6.4	Conclusion	92

Chapter 7

*Carpanone**O. L. Chapman (1971)*

7.1	Introduction	95
7.2	Retrosynthetic Analysis and Strategy	95
7.3	Total Synthesis	96
7.4	Conclusion	97

Chapter 8

*Vitamin B₁₂**R. B. Woodward and A. Eschenmoser (1973)*

8.1	Introduction	99
8.2	Retrosynthetic Analysis and Strategy	100
8.3	Total Synthesis	105
8.3.1	The Woodward Synthesis of Cyanobromide 6	105
8.3.2	The Eschenmoser Synthesis of B-Ring Intermediate 8	113
8.3.3	The Woodward Synthesis of C-Ring Intermediate 9	115
8.3.4	The Eschenmoser Synthesis of C-Ring Intermediate 9	115
8.3.5	The Eschenmoser Synthesis of Thiodextrolin (7)	117
8.3.6	The Woodward-Eschenmoser Macrocyclization Strategy	121
8.3.7	The Eschenmoser Synthesis of A-Ring Intermediate 24 and D-Ring Intermediate 25	123
8.3.8	The Eschenmoser Cyclization Strategy	126
8.3.9	Completion of the Woodward-Eschenmoser Total Synthesis of Cobyric Acid and Vitamin B ₁₂	130
8.4	Conclusion	134

Chapter 9

*Prostaglandin A₂ (PGA₂)
and Prostaglandin F_{2α} (PGF_{2α})**G. Stork (1976, 1978)*

9.1	Introduction	137
9.2	Retrosynthetic Analysis and Strategy for PGA ₂	138
9.3	Total Synthesis of PGA ₂	140
9.4	Retrosynthetic Analysis and Strategy for PGF _{2α}	144
9.5	Total Synthesis of PGF _{2α}	146
9.6	Conclusion	151

Chapter 10

*Estrone**K. P. C. Vollhardt (1977)*

10.1	Introduction	153
10.2	Retrosynthetic Analysis and Strategy	160
10.3	Total Synthesis	162
10.4	Conclusion	165

Chapter 11

*Erythronolide B**E. J. Corey (1978)*

11.1	Introduction	167
11.2	Retrosynthetic Analysis and Strategy	169
11.3	Total Synthesis	172
11.4	Conclusion	183

Chapter 12

*Monensin**Y. Kishi (1979)*

12.1	Introduction	185
12.2	Retrosynthetic Analysis and Strategy	187
12.3	Total Synthesis	194
12.4	Conclusion	207

Chapter 13

*Periplanone B**W. C. Still (1979)*

13.1	Introduction	211
13.2	Retrosynthetic Analysis and Strategy	212
13.3	Total Synthesis	215
13.4	Conclusion	219

Chapter 14

*Isocomene**M. C. Pirrung (1979)*

14.1	Introduction	221
14.2	Retrosynthetic Analysis and Strategy	221
14.3	Total Synthesis	223
14.4	Conclusion	225

Chapter 15

*Monensin**W. C. Still (1980)*

15.1	Introduction	227
15.2	Retrosynthetic Analysis and Strategy	230
15.3	Total Synthesis	235
15.4	Conclusion	246

Chapter 16

*Thienamycin**Merck (1980)*

16.1	Introduction	249
16.2	Retrosynthetic Analysis and Strategy	250
16.3	Total Synthesis	251
16.4	Conclusion	262

Chapter 17

*Endiandric Acids A–D**K. C. Nicolaou (1982)*

17.1	Introduction	265
17.2	Retrosynthetic Analysis and Strategy	267
17.3	Total Synthesis	270
17.3.1	Stepwise, Stereocontrolled Total Synthesis of Endiandric Acids A–D (and E–G)	270
17.3.2	“Biomimetic”, One-Step Total Synthesis of Endiandric Acids A–D (and E–G)	275
17.4	Conclusion	283

Chapter 18

*Biotin**Hoffmann-La Roche (1982)*

18.1	Introduction	285
18.2	Retrosynthetic Analysis and Strategy	286
18.3	Total Synthesis	288
18.4	Conclusion	291

Chapter 19

*L-Hexoses**S. Masamune and K. B. Sharpless (1983)*

19.1	Introduction	293
19.2	Retrosynthetic Analysis and Strategy	298
19.3	Total Synthesis	310
19.4	Conclusion	313

Chapter 20

*Asteltoxin**S. L. Schreiber (1983)*

20.1	Introduction	317
20.2	Retrosynthetic Analysis and Strategy	322
20.3	Total Synthesis	324
20.4	Conclusion	331

Chapter 21

*Periplanone B**S. L. Schreiber (1984)*

21.1	Introduction	333
21.2	Retrosynthetic Analysis and Strategy	336
21.3	Total Synthesis	337
21.4	Conclusion	340

Chapter 22

*Menthol**Takasago (1984)*

22.1	Introduction	343
22.2	Retrosynthetic Analysis and Strategy	354
22.3	Total Synthesis	355
22.4	Conclusion	357
22.5	Appendix: Catalytic Asymmetric Reactions, an Overview	358

Chapter 23

*Hirsutene and
 $\Delta^{9(12)}$ -Capnellene**D. P. Curran (1986)*

23.1	Introduction	381
23.2	Retrosynthetic Analysis and Strategy	409
23.3	Total Synthesis	410
23.4	Conclusion	416

Chapter 24

*Amphoterionolide B and
Amphotericin B**K. C. Nicolaou (1987)*

24.1	Introduction	421
24.1.1	Degradation Studies	421
24.2	Retrosynthetic Analysis and Strategy	425
24.3	Total Synthesis	429
24.3.1	Construction of Building Blocks 16 and 19	429
24.3.2	Construction of Building Blocks 17 and 18 : The Carbohydrate Approach	432
24.3.3	Construction of Building Blocks 17 and 18 : The Sharpless Asymmetric Epoxidation Approach . . .	434
24.3.4	Completion of the Synthesis of Amphoterionolide B	438
24.3.5	Completion of the Synthesis of Amphotericin B	444
24.4	Conclusion	448

Chapter 25

*Ginkgolide B**E. J. Corey (1988)*

25.1	Introduction	451
25.2	Retrosynthetic Analysis and Strategy	452
25.3	Total Synthesis	456
25.4	Conclusion	463

Chapter 26

*Methyl
Homosecodaphniphyllate**C. H. Heathcock (1988)*

26.1	Introduction	465
26.2	Retrosynthetic Analysis and Strategy	465
26.3	Total Synthesis	467
26.4	Conclusion	469

Chapter 27

*Indolizomycin**S. J. Danishefsky (1990)*

27.1	Introduction	471
27.2	Retrosynthetic Analysis and Strategy	472
27.3	Total Synthesis	475
27.4	Conclusion	483

Chapter 28

*Cytovaricin**D. A. Evans (1990)*

28.1	Introduction	485
28.2	Retrosynthetic Analysis and Strategy	487
28.3	Total Synthesis	491
28.3.1	Synthesis of Spiroketal Subunit 6	491
28.3.2	Synthesis of Polyol Glycoside Subunit 7	497
28.3.3	Synthesis of Seco Acid 4 and Completion of the Total Synthesis of Cytovaricin	503
28.4	Conclusion	506

Chapter 29

*Gilvocarcin M and
Gilvocarcin V**K. Suzuki (1992, 1994)*

29.1	Introduction	509
29.2	Retrosynthetic Analysis and Strategy	510
29.3	Total Synthesis	512
29.4	Conclusion	519

Chapter 30

Calicheamicin γ_1^I *K. C. Nicolaou (1992)*

30.1	Introduction	523
30.2	Retrosynthetic Analysis and Strategy	525
30.3	Total Synthesis	535
30.3.1	Synthesis of Oligosaccharide 8	535
30.3.2	Synthesis of Aglycon 5	548
30.3.3	Coupling of Intermediates 8 and 9 and Completion of the Total Synthesis of Calicheamicin γ_1^I	556
30.4	Conclusion	562

Chapter 31

*Rapamycin**K. C. Nicolaou (1993)*

31.1	Introduction	565
31.1.1	The Heck Reaction	566
31.1.2	Palladium-Catalyzed Cycloisomerizations	578
31.1.3	The Stephens-Castro and the Sonogashira Couplings	582
31.1.4	The Suzuki Coupling	586
31.1.5	The Stille Coupling	591
31.2	Retrosynthetic Analysis and Strategy	599
31.3	Total Synthesis	607
31.3.1	Synthesis of Intermediates 147 and 158–160	607
31.3.2	Coupling of Key Intermediates 147 and 158–160	620
31.3.3	Final Stages and Cyclization to Rapamycin	624
31.4	Conclusion	626

Chapter 32

*Paeoniflorigenin and
Paeoniflorin**E. J. Corey (1993)*

32.1	Introduction	633
32.3	Retrosynthetic Analysis and Strategy	633
32.3	Total Synthesis	636
32.4	Conclusion	640

Chapter 33

*Strychnine**L. E. Overman (1993)*

33.1	Introduction	641
33.2	Retrosynthetic Analysis and Strategy	643
33.3	Total Synthesis	646
33.4	Conclusion	652

Chapter 34

*Taxol**K. C. Nicolaou (1994)*

34.1	Introduction	655
34.2	Retrosynthetic Analysis and Strategy	656
34.3	Total Synthesis	660
34.4	Conclusion	671

Chapter 35

*Zaragozic Acid A/
Squalestatin S1**K. C. Nicolaou (1994)*

35.1	Introduction	673
35.1.1	The Asymmetric Dihydroxylation	675
35.2	Retrosynthetic Analysis and Strategy	691
35.3	Total Synthesis	694
35.3.1	Degradation and Reconstitution Chemistry	694
35.3.2	Synthesis of Key Intermediate Aldehyde 68	695
35.3.3	Model Studies	699

35.3.4	Synthesis of the Side Chains	702
35.3.5	Coupling of Key Intermediates and Completion of the Total Synthesis of Zaragozic Acid A/Squalestatin S1	704
35.4	Conclusion	707

Chapter 36

Palytoxin

Y. Kishi (1994)

36.1	Introduction	711
36.1.1	The NiCl ₂ /CrCl ₂ Coupling Reaction	712
36.2	Retrosynthetic Analysis and Strategy	717
36.3	Total Synthesis	719
36.4	Conclusion	729

Chapter 37

Brevetoxin B

K. C. Nicolaou (1995)

37.1	Introduction	731
37.1.1	The Invention and Development of New Synthetic Methods	733
	a. Tetrahydropyran Systems	733
	b. Didehydrooxocane	735
	c. Oxepane Systems	737
37.2	Retrosynthetic Analysis and Strategy	748
37.2.1	The Triply Convergent Approach: The First-Generation Strategy	750
37.2.2	Stepwise Bis(oxepane) Synthesis Approach: The Second-Generation Strategy	752
37.2.3	The Doubly Convergent Approach with Stepwise Formation of the Bis(oxepane) System: The Third-Generation Strategy	755
37.3	Total Synthesis	762
37.3.1	Synthesis of IJK Framework 86	762
37.3.2	Synthesis of ABCDEFG Framework 87	768
37.3.3	Final Stages and Completion of the Total Synthesis of Brevetoxin B	781
37.4	Conclusion	784

<i>Author Index</i>	787
---------------------	-----

<i>Subject Index</i>	789
----------------------	-----