Biotin: A Timeless Challenge for Total Synthesis

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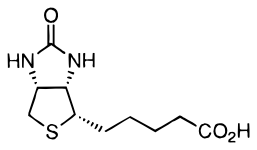
Contents

I. Introduction

Biotin is one of the water-soluble B vitamins.[1] It plays an essential role as a coenzyme in carboxylation reactions related to biochemical processes such as gluconeogenesis and fatty acid biosynthesis. The main sources of biotin are liver, kidney, pancreas, yeast, milk, and egg yolk. Biotin deficiency in poultry and swine causes a series of severe symptoms. These deficiencies are corrected by using biotin as a feed additive. Hence, its commercial importance.

In 1936, biotin was isolated from egg yolk.[2] Later du Vigneaud and co-workers isolated it from beef liver and milk concentrates.[3,4] The same group determined its empirical formula in 1941 and its structure in 1942.[5,6] This structure was confirmed by the first total synthesis of racemic biotin in the Merck Research Laboratories.[7] Finally, in 1966, X-ray crystallographic analysis established the absolute configuration of natural (+)-biotin as **1**.[8]



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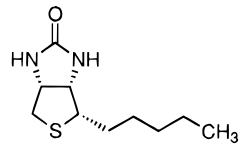
In comparison with most present-day synthetic targets biotin possesses a deceptively simple-looking structure. Its skeleton consists of a bi-heterocyclic core, to which is attached a carboxybutyl side chain. The heterocyclic system comprises a cyclic urea and a tetrahydrothiophene ring (which will subsequently be called thiophane). It further possesses three contiguous stereocenters on the thiophane ring in the *all-cis* configuration. Because of the fundamental and commercial importance, biotin has, ever since it was discovered, attracted the attention of both academic and industrial synthetic chemists.



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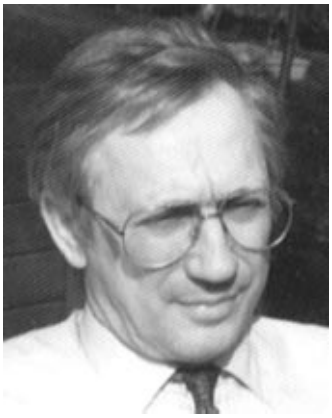
A continuous endeavor over a period of more than 50 years has now resulted in more than 40 original contributions in the field. The writing of an in depth review on the total synthesis of biotin is appropriate for two reasons. First, to the best of my knowledge, no comprehensive review on the topic has appeared so far. Second, biotin is unique in that it allows for a timely analysis of the merits and shortcomings of synthetic strategies that have been conceived over a long period of time. It may also serve as a test case



Pierre De Clercq is a Full Professor at the University of Ghent since 1994. He was born in Ghent in 1948 and earned his doctorate degree in organic synthesis at the University of Ghent in 1973. He held postdoctoral appointments at the University of California (Santa Cruz) and at the University Chemical Laboratories in Cambridge. For 20 years he has conducted his scientific career as a research fellow of the National Fund for Scientific Research. During that period he has been a visiting Professor at the Free University of Brussels (1984–86) and at the Catholic University of Leuven (1987–88). In 1989 he joined the faculty at the University of Ghent as Professor. His research interests have focused on the total synthesis of natural products and derivatives thereof with potential biological activity. More recently his research has centered on the design and synthesis of model derivatives for the study of biogenetic processes.

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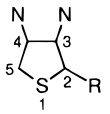
to determine how total synthesis in this particular field has benefitted from advances in synthetic methodology. For the above reasons this review article consists of two distinct parts. In the first part, all synthetic work that constitutes a real contribution in the field is discussed in a comprehensive way. This part is directed to the synthetic chemist who is interested in biotin. In the second part, an attempt has been made to evaluate the different strategies used and to put those in perspective. That part is directed to the organic chemist who has an interest in synthesis.

Section II consists of a series of 63 schemes. Each scheme describes either a total synthesis or a sequence of synthetic steps that may be related to an already existing approach when providing some new potential. Original approaches that have led to deoxybiotin (**2**) have also been included. The latter may be considered as formal total syntheses since the microbial oxidative conversion of (+)-deoxybiotin (**2**) into (+)-biotin (**1**) is known.[9] The literature covered involves the period from 1943 to September 1996 and includes the patent literature. However, only those patents are considered for discussion and taken in the list of references whose contents are not reported in the current journal literature.

Schemes constitute the vehicle of the synthetic chemist. They are conceived so that the chemist can grasp the important stages in each shown sequence. Relevant experimental conditions are listed, including yields when they have been clearly reported in the original literature. The following stereochemical designations are used in the schemes: an unprefixed Arabic numeral is used for achiral molecules and for chiral molecules which possess the correct enantiomeric configuration for eventual conversion into (+)-biotin; the opposite enantiomeric configuration is indicated by the prefix *ent* and racemic mixtures by the prefix *rac*. Throughout the paper, the atom numbering along the thiophane nucleus shown below will be used:



The schemes in section II are not listed in chronological order. Rather they have been gathered into three groups. Section II.A comprises the syntheses that are enantioselective as well as those that have the potential of leading to the chiral target compound by using a reaction step that induces asymmetry. In this part, several approaches are also discussed that involve a resolution process but with the possibility of recycling of the undesired enantiomer. Enantiospecific syntheses are discussed in section II.B. A further distinction is made between the two different type of chiral pool members that have been employed: L-cystine or L-cysteine and carbohydrates. In the last section (III.C), the syntheses are grouped that are not considered enantioselective for they either led to *rac*-biotin or produced (+)-biotin via a sequence in which a resolution process without recycling was involved.

As stated earlier, section III aims at offering a timely evaluation of the different strategies used in biotin synthesis. An attempt has been made to compare synthetic efficiencies by the inclusion of the length of the longest linear sequence for each synthesis in a table. All known total syntheses are listed in this table in chronological order. The table also contains information concerning the origin of the scientific group, the starting materials used, and the enantioselectivity issue. In a second part within this section, the merits and shortcomings of the different strategies are discussed. For that purpose, all syntheses have been grouped in six charts with the intent of, whenever possible, stressing relationships that exist among different synthetic approaches. Section III is written in a way that allows the chemist to read it independently from the previous section. Since the charts contain references to the previous 63 schemes, the reader can immediately gather more precise information about the actual sequence if desired. Finally, this chartered approach also allows, at least in my opinion, to discover which general approaches still offer a potential for the development of efficient biotin syntheses in the future.

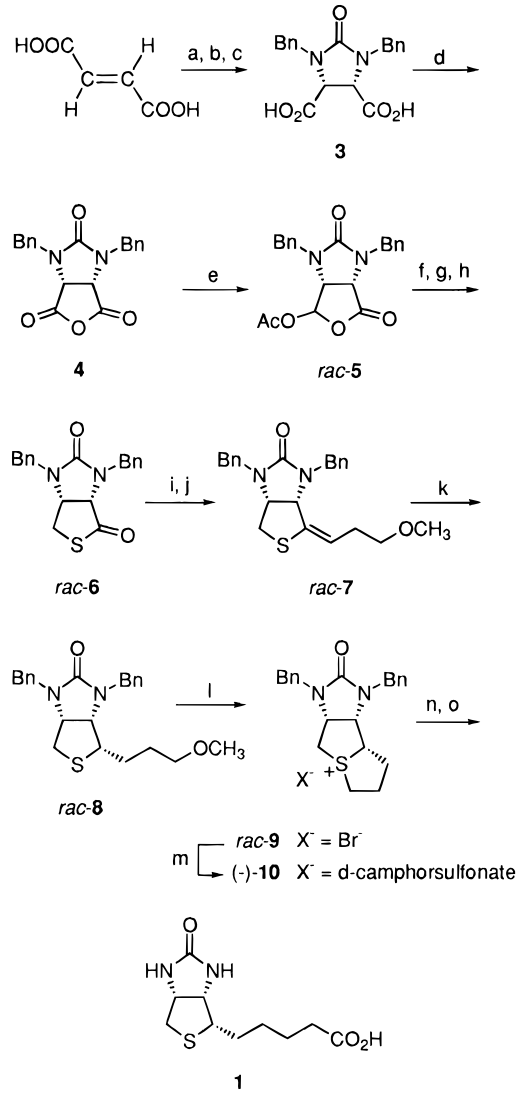
II. Syntheses

A. Enantioselective (Asymmetric) Syntheses

1. Hoffmann-La Roche's Lactone–Thiolactone Approach[10]

On May 31, 1946, Goldberg and Sternbach, assignors to Hoffmann-La Roche Inc., applied for the first in a series of three patents that describe the synthesis of (+)-biotin shown in Scheme 1.[11−13] One may distinguish five stages in the synthesis. First, fumaric acid is converted into the cyclic anhydride **4** via a four-step sequence involving bromination of fumaric acid to yield *meso*-dibromosuccinic acid, double substitution of the latter with benzylamine, formation of the cyclic ureide **3** upon reaction of the acid in alkaline solution with phosgene, and formation of anhydride **4** upon treatment of **3** with acetic anhydride. In this first stage, the imidazolidone part of biotin is constructed in such a way as to obtain the *cis* relation of the vicinal amino groups at centers C-3 and C-4. In the second stage, the thiophane nucleus is formed by conversion of *meso*-**4** into thiolactone **6**. This involves reduction of anhydride **4** with zinc in acetic acid, treatment of the obtained acetoxy lactone **5** with hydrogen sulfide, and further reduction with zinc to yield thiolactone **6** in racemic form. In the third stage, part of the carboxybutyl chain of biotin is introduced via Grignard reaction with subsequent dehydration to form the exocyclic olefin **7** with undefined double-bond stereochemistry. Catalytic hydrogenation of the latter yields **8** with the desired *all-cis* relative configuration at centers C-2, C-3, and C-4. In the fourth stage, ether **8** is converted into the thiophanium salt **9** by treatment with hydrobromic acid. At this point, resolution is effected by conversion of bromide **9** into the diastereomeric camphorsulfonate salts (**10**) which are readily separated in excellent yield by a simple fractional crystallization. In the final stage of the synthesis, the side chain is first completed by reaction of diastereomer (−)-**10** with sodium diethylmalonate. In this important step selective attack is observed at the least-hindered primary center of the trimethylene

Scheme 1[a]

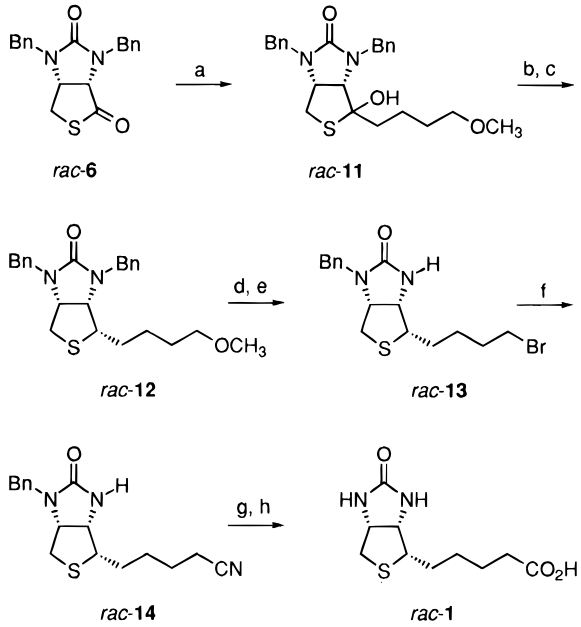


[a] Conditions: (a) Br_2; (b) $PhCH_2NH_2$, EtOH; (c) $COCl_2$, KOH; (d) Ac_2O; (e) Zn, Ac_2O, HOAc; (f) H_2S, HCl; (g) KSH, EtOH; (h) Zn, HOAc; (i) $ClMg(CH_2)_3OCH_3$; (j) HOAc; (k) H_2, cat.; (l) HBr; (m) silver *d*-camphorsulfonate, followed by fractional crystallization; (n) $NaCH(COOEt)_2$; (o) 48% HBr.

thiophanium moiety. Finally, the authors found that heating with concentrated hydrobromic acid effected saponification of the obtained diester, subsequent decarboxylation, and debenzylation all in one operation with direct formation of biotin.

Although the efficiency of this synthesis cannot be evaluated correctly due to lack of precise information regarding obtained yields and selectivities, the above process constitutes a landmark accomplishment in the context of biotin synthesis. Several intermediates described in Scheme 1, and in particular, thiolactone **6** has been obtained later in racemic or homochiral form by other groups, thus constituting new formal syntheses of *rac*-biotin or (+)-biotin, respectively. The establishment of stereocenter 2 via catalytic hydrogenation of an exocyclic olefin was also used subsequently by several other groups. The use of benzyl groups as protective groups in the imidazolidothiophane and related intermediates with the possibility of deprotection using concentrated hydrogen bromide is repeated in almost all later syntheses. It is interesting to note that the sulfonium intermediate **9** has been used later in the synthesis of α-dehydro-

Scheme 2[a]



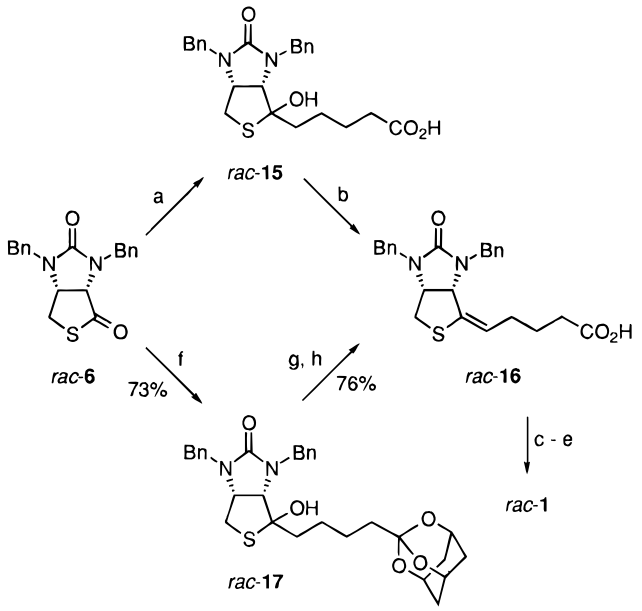
[a] Conditions: (a) $CH_3O(CH_2)_4Br$, Mg, ether, PhH; (b) HOAc, reflux; (c) H_2, Pd/C, MeOH; (d) Na, liq NH_3; (e) HBr, HOAc, 90 °C; (f) KCN, H_2O; (g) NaOH, H_2O/MeOH; (h) Na, liq NH_3.

biotin, an efficient antagonist of biotin, and that, for that purpose, orthophosphoric acid containing phenol was used for benzyl group removal (53% yield).[14] Despite the fact that the obtainment of the required enantiomer proceeded via a classical resolution of diastereomeric salts at a late stage of the synthesis, the followed strategy, in particular the involvement of *meso*-derivatives such as **3** and **4** early in the synthetic scheme, allows for the further development of efficient asymmetric modifications. Finally, it is generally accepted that this process is at the origin of a commercial production of biotin via total synthesis even if the actual detailed sequence is unknown.

Not surprisingly, a few later contributions have focussed on developing alternative ways of transforming thiolactone **6** into compounds possessing an exocyclic double bond as in **7**. In fact, the first Goldberg and Sternbach patent described a route in which the thiophanium salts were not involved.[11] The conversion of thiolactone **6** into *rac*-biotin involved a sequence of eight steps (Scheme 2): Grignard reaction with 4-methoxybutyl bromide to form alcohol **11**, dehydration followed by catalytic hydrogenation to form **12**, removal of one benzyl group with sodium in liquid ammonia and conversion of the terminal methoxyalkyl group into the corresponding bromide **13** (hydrobromic acid, acetic acid), substitution of the primary bromide with potassium cyanide to form **14**, basic hydrolysis of the latter to the corresponding carboxylic acid, and final benzyl deprotection with sodium in liquid ammonia. It is interesting to note that the correct structure of the mono-debenzylated derivatives shown in Scheme 2 was assigned subsequently and allowed for the selective synthesis of 3′-*N*-methylbiotin.[15] The possibility of direct conversion of the Grignard adducts to the reduced *all-cis* derivatives (i.e., **11** to **12**) using a nickel catalyst in the presence of acid has been claimed.[16]

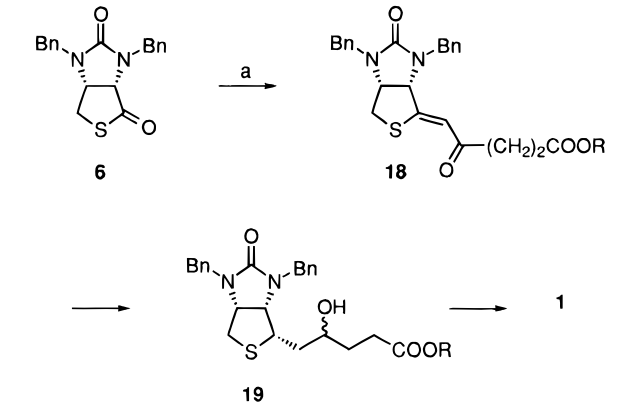
In 1968 Isaka and co-workers introduced the complete carboxybutyl chain by treatment of **6** with

Scheme 3[a]



[a] Conditions: (a) $ClMg(CH_2)_4MgCl$, $PhCH_3$, −35 °C, CO_2; (b) HOAc, reflux; (c) H_2, MeOH, Ni cat.; (d) 48% HBr; (e) $COCl_2$, NaOH; (f) $BrMg(CH_2)_4C(OC_2H_3)_3$, THF; (g) *p*-TsOH, $PhCH_3$, reflux; (h) dioxane, dilute H_2SO_4, reflux.

Scheme 4[a]



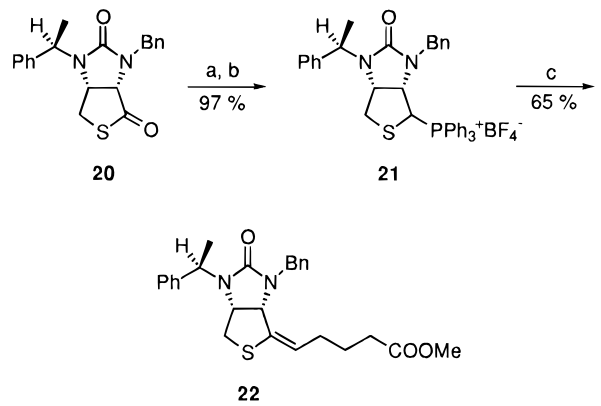
[a] Conditions: (a) $Ph_3P{=}CHC(O)CH_2CH_2COOR$, 120 °C.

butylenedimagnesium chloride followed by in situ reaction with carbon dioxide to yield **15** (Scheme 3).[17] After dehydration of the obtained alcohol to unsaturated acid **16**, the latter is converted to *rac*-biotin by quantitative catalytic reduction using a nickel−diatomaceous earth catalyst in methanol, followed by deprotection and treatment with phosgene. More recently chemists at Hoffmann-La Roche (Basel) claimed the use of 4-(2,4,10-trioxaadamantyl)butylmagnesium bromide with subsequent acid treatment in the context of a more direct introduction of the carboxybutyl chain (Scheme 3).[18]

Wittig condensations have also been reported for the conversion of thiolactone **6** into the required ylidene derivatives. Japanese chemists at Sumitomo treated **6** with the phosphor ylide derived from 5-bromo-4-oxopentanoate and obtained **18** in good yield (Scheme 4).[19] Further conversion to biotin involved reduction to **19** and reductive removal of the secondary alcohol via the corresponding chloride.

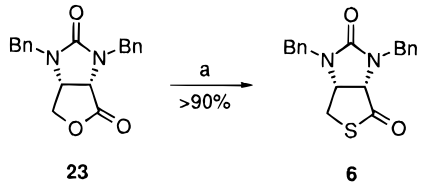
More recently Eyer at Lonza A.-G. developed an alternative Wittig sequence starting from thiolactone **20** (Scheme 5).[20] The sequence involves reduction

Scheme 5[a]



[a] Conditions: (a) $(Me_2CHCH_2)_2AlH$, $PhCH_3$, −70 °C; (b) Ph_3PH-BF_4, CH_3CN, reflux; (c) KOtBu, THF; $OHC(CH_2)_3CO_2Me$, THF.

Scheme 6[a]



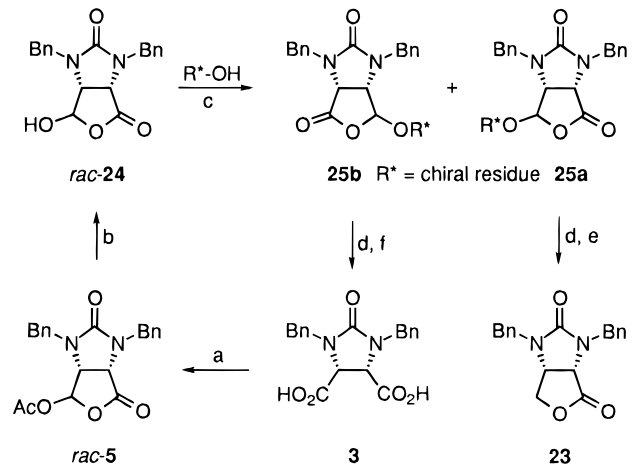
[a] Conditions: (a) CH_3COSK, DMF, 150 °C.

with diisobutylaluminum hydride (DIBALH) to the corresponding hydroxy derivative which is directly converted to phosphonium salt **21** with triphenylphosphine hydrogen tetrafluoroborate. Condensation of the corresponding ylide with methyl 5-oxopentanoate gave **22** in fair yield.

In 1970 Gerecke, Zimmerman, and Aschwanden from Hoffmann-La Roche (Basel and Paris) reported on a further important development of the original Goldberg−Sternbach scheme that allows for the efficient production of the key thiolactone **6** in the required enantiomeric form starting from *meso*-acid **3** or *meso*-anhydride **4**.[21] Crucial to this new development was the finding that lactone **23** could be converted in very high yield into the corresponding thiolactone **6** by treatment with potassium thioacetate in dimethylformamide at 150 °C (Scheme 6). Hence, any synthesis of *rac*- or (+)-**23** would constitute a new formal synthesis of *rac*- or (+)-biotin, respectively. The sequences that were originally used to convert the *meso*-compounds **3** and **4** into (+)-**23** are shown in Schemes 7, 9 and 10.[21]

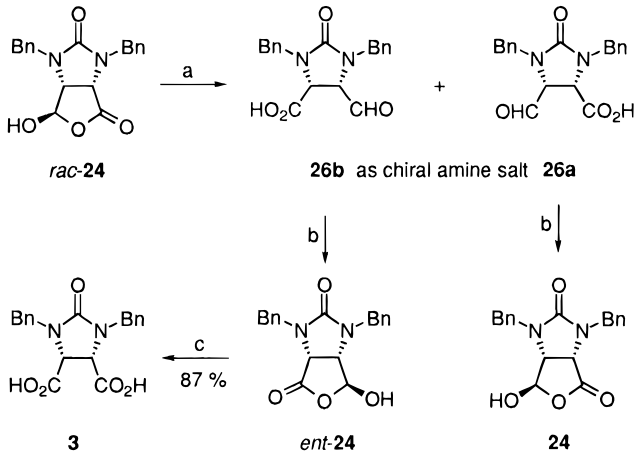
The first method involves conversion of **3** into hydroxylactone **24** (undefined stereo-chemistry) via acetoxylactone **5** (Scheme 7). Treatment of **24** with an optically active alcohol leads to a diastereomeric mixture composed of **25a** and of **25b** (both as epimeric mixtures). Selectivity in obtaining *cis*- or *trans*-epimers could not be realized. Depending on the optically active alcohol used, i.e. (−)-menthol, (−)-borneol, or (−)-4,4-dimethyl-3-hydroxydihydro-2(3*H*)-furanone, the obtained diastereomers **25** crystallize in a different order and only two of the four possible diastereomers could be obtained in pure form. The required lactone (+)-**23** is further obtained from the **a**-series via acid hydrolysis followed by sodium borohydride reduction, while the unwanted stereoisomers of the **b**-series were recycled through acid hydrolysis followed by chromic oxidation to *meso*-**3**.

Scheme 7[a]



[a] Conditions: (a) Ac_2O, Zn/HOAc; (b) NaOH, dioxane; (c) R*-OH = (−)-menthol; (−)-borneol; (−)-4,4-dimethyl-3-hydroxydihydro-2(3*H*)-furanone, *p*-TsOH, $PhCH_3$; (d) H_2SO_4, dioxane; (e) $NaBH_4$, EtOH; (f) CrO_3/H_2SO_4, dioxane.

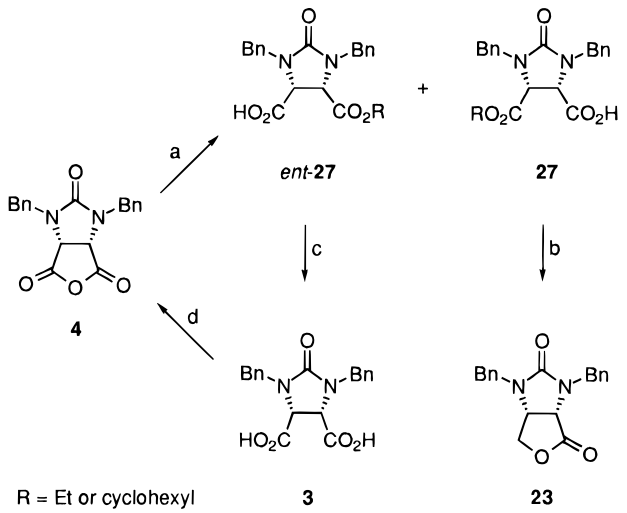
Scheme 8[a]



[a] Conditions: (a) cinchonidine:45% of precipitated salt or *N*-*n*-butyl-D-glucosamine derivative:46% of precipitated salt; (b) HCl; (c) $NaClO_2$.

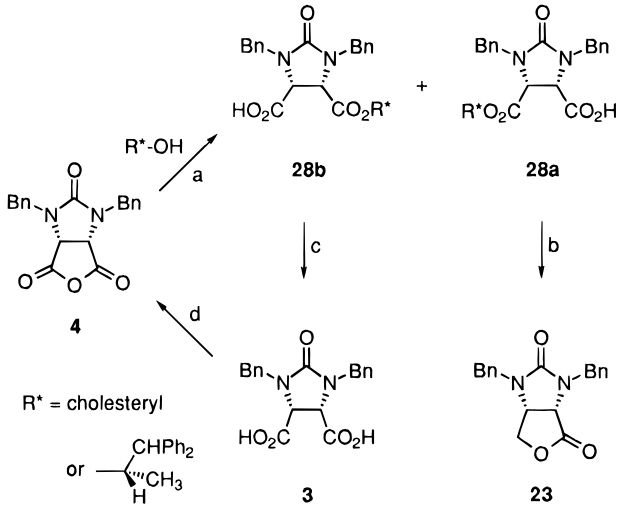
An alternative method for the industrial resolution of hydroxylactone **24** was reported by Senuma and co-workers in 1990 (Scheme 8).[22] It involves the direct resolution of the hydroxylactone *rac*-**24** (*trans*-epimer) with optically active amines. Reaction of *rac*-**24** with cinchonidine readily gave the cinchonidine salt of **26a** in 45% yield with an optical purity evaluated at more than 98%. Upon acidification, the salt readily underwent cyclization to give a 42% overall yield of **24**. Evaporation of the mother liquor of the salt gave, after acidification, *ent*-**24** in 36% yield. The undesired enantiomer is readily converted to *meso*-diacid **3** by facile oxidation with sodium chlorite. To find a more practical and inexpensive resolving agent applicable for industrial use, the authors also examined the optical resolution of *rac*-**24** with various *N*-alkyl-D-glucamines. In particular the N-*n*-butyl derivative, obtained from D-glucose with *n*-butylamine followed by reduction over Raney nickel (RaNi), proved suitable for industrial use. Upon reaction with *rac*-**24**, the crystalline salt of **26a** precipitated in 46% yield. Upon acidification, this salt regenerated the desired **24** enantiomer in nearly quantitative yield. The precise structure of the salt remains uncertain. It could not be simply identified as the D-glucamine salt of the aldehyde carboxylic acid; spectral data suggest the hemiacetal formation of the aldehyde group with one of the hydroxyl groups of a glucamine moiety.

Scheme 9[a]



[a] Conditions: (a) R-OH = cyclohexanol, followed by resolution with (−)-ephedrine (39% of **27**) or R-OH = ethanol, followed by resolution with (+)-dehydroabietylamine; (b) $LiBH_4$, THF, H_3O^+; (c) H_3O^+, DMF; (d) Ac_2O.

Scheme 10[a]

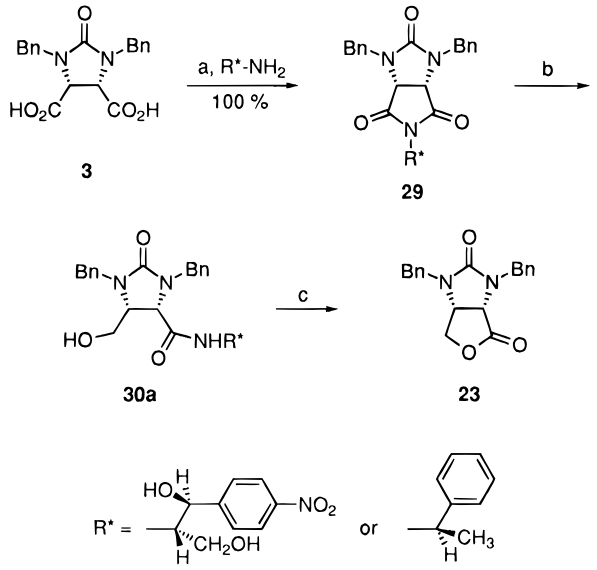


[a] Conditions: (a) R*-OH = cholesterol, followed by resolution of triethylamine salts (27% of **28a**) or R*-OH = (e.g.) (*S*)-$CH_3CH(OH)CHPh_2$, diazabicyclooctane, $PhCH_3$, −10 °C; (b) $LiBH_4$ or KBH_4, THF, LiCl; (c) H_3O^+, DMF; (d) Ac_2O.

Two different approaches involving the formation of hemiesters from *meso*-anhydride **4** have been developed (Schemes 9 and 10). In a first approach, **4** is converted to a racemic mixture of hemiesters **27** after treatment with cyclohexanol and resolution is realized via fractional crystallization of the diastereomeric (−)-ephedrine salts.[21] An analogous procedure involving ethanol instead of cyclohexanol and (+)-dehydroabietylamine as resolving agent has been reported in 1986.[23] The salt of the hemiester **27** is further reduced with lithium borohydride to (+)-**23**, while the undesired stereoisomer is reconverted to *meso*-diacid **3** via acid hydrolysis.

In a different approach, shown in Scheme 10, anhydride **4** is treated with cholesterol leading to a diastereomeric mixture of **28a** and **28b**. Separation

Scheme 11[a]



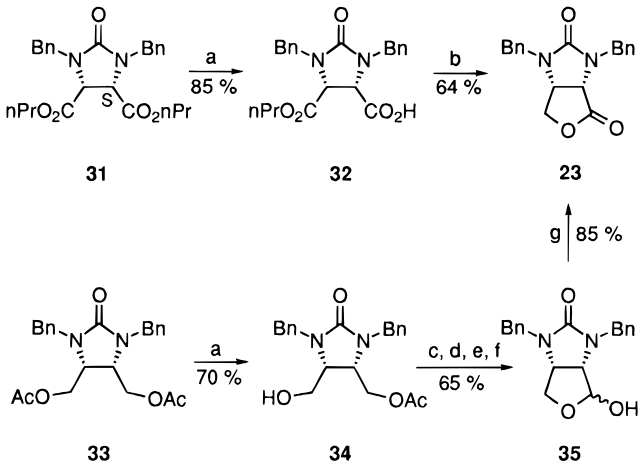
[a] Conditions: (a) R*-NH_2 = (*S*,*S*)-*p*-$NO_2C_6H_4CH(OH)CH(NH_2)$-CH_2OH; (b) $NaBH_4$, EtOH (60−65% after recrystallization) or (a) R*-NH_2 = (*R*)-$C_6H_5CH(NH_2)CH_3$; (b) $NaBH_4$, EtOH (50−55% after recrystallization); (c) HCl.

was effected by fractional crystallization of the corresponding triethylammonium salts.[21] In the same context, a major improvement was claimed in 1986.[24] Treatment of anhydride **4** with (*S*)-1,1-diphenyl-2-propanol and diazabicyclooctane, followed by reduction with lithium borohydride, gave the desired **23** in 80% yield and 96% enantiomeric excess (ee). After one recrystallization from 2-propanol, a 99% ee was obtained.

Previously, chemists from Sumitomo had described the asymmetric conversion shown in Scheme 11.[25] The *meso*-diacid **3** is first converted in quantitative yield to the homochiral imide **29** via reaction with (*S*,*S*)-2-amino-1-(4-nitrophenyl)-1,-3-propanediol (an intermediate in the production of the antibiotic chloramphenicol). Reductive opening of the cyclic imide **29** with sodium borohydride led with surprising stereoselectivity to the hydroxyamide **30a** in 65% yield after recrystallization. Acid treatment of the latter gives the desired lactone (+)-**23**.

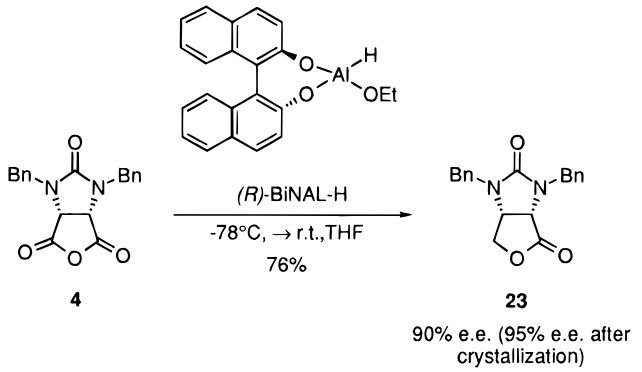
The application of enzymatic resolution procedures to obtain the chiral lactone (+)-**23** has been reported by two groups (Scheme 12). In 1982, Iriuchijima and co-workers described the asymmetric hydrolysis of the prochiral diester **31** with pig liver esterase (PLE).[26] The *meso*-diester **31** has an interesting structure since it combines both a natural (*S*)-amino acid part and a unnatural (*R*)-amino acid part: enzymes are expected to preferentially hydrolyze the (*S*)-ester rather than the (*R*)-ester in **31**. Hydrolysis of the di-*n*-propyl ester with PLE gave **32** in 85% yield. Further reduction with lithium borohydride yielded (+)-**23** in 64% yield (75% ee). The need to improve the enantioselectivity of the enzymic hydrolytic reaction prompted Sih in 1984 to use a different approach.[27] When the diacetate **33** was incubated with PLE, alcohol **34** was obtained (70% yield; 92% ee) indicating that the *pro-R* acetoxy group had been preferentially cleaved. Indeed, when **34** was subjected to a sequence involving Jones oxidation, basic hydrolysis, and lactonization, *ent*-**23** was obtained.

Scheme 12[a]



[a] Conditions: (a) PLE, phosphate buffer; (b) $LiBH_4$ (75% ee; 87% ee after recrystallization); (c) CH_3OCH_2Cl, *N*,*N*-diisopropylethylamine, CH_2Cl_2; (d) $LiAlH_4$, ether/THF; (e) Collins; (f) HCl, THF/H_2O; (g) Collins (93% ee).

Scheme 13



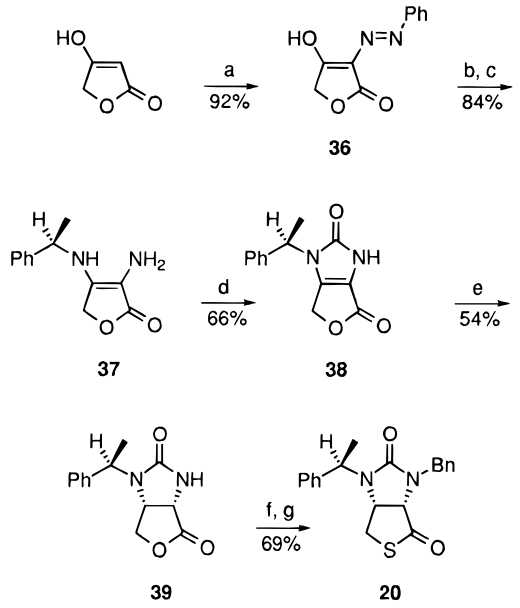
Eventually **34** was converted into the desired enantiomer **23** via the uneventful sequence shown in Scheme 12.

The further development of efficient asymmetric strategies in the context of the original Hoffmann-La Roche scheme culminated in 1993 when Matsuki and co-workers reported on the highly enantioselective reduction of *meso*-1,2-dicarboxylic anhydrides to yield optically active lactones using Noyori's lithium aluminium hydride−ethanol−1,1′-bi-2-naphtol complex (BINAL-H).[28] When applied to *meso*-**4**, the desired lactone (+)-**23** was directly obtained in 76% yield with 90% ee, which was enriched to 95% ee by recrystallization from benzene/cyclohexane (Scheme 13). Although the chiral recognition mechanism is not clear, the general mechanism proposed by Noyori can be applied.[29]

With this final accomplishment, the original Goldberg and Sternbach 1949 route evolved after 44 years into a scheme that can be regarded as, at present, one of the most efficient ones for the production of natural biotin. The sequence involves the 10-step conversion of fumaric acid (**2**) into biotin via **3** and **4** (Scheme 1), **23** (Scheme 13), and **6** (Scheme 6) and one of the sequences described in Schemes 1−5.

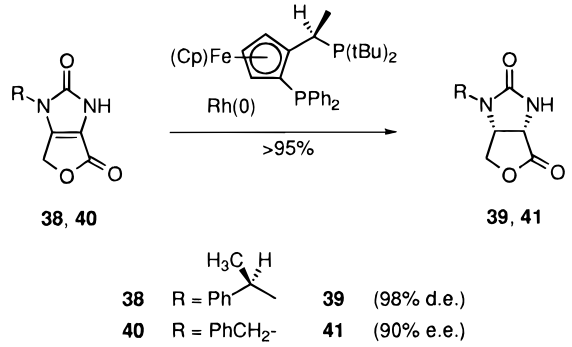
An interesting asymmetric approach has been developed by chemists at Lonza that centers about the hydrogenation of furoimidazole derivatives as **38** (Schemes 14 and 15).[30−33] The synthesis of these involves a straightforward four-step sequence start-

Scheme 14[a]



[a] Conditions: (a) $PhNH_2$, $NaNO_2$, HCl; (b) (*R*)-$PhCH(NH_2)CH_3$, $B(OEt)_3$, $PhCH_3$, 80 °C; (c) H_2, Pt/C, EtOAc, 40 bar; (d) $ClCO_2Et$, Et_3N, THF; Et_3N, CH_3CN, reflux; (e) H_2, Rh/Al_2O_3, DMF, 40 bar; (f) NaH, DME, $PhCH_2Br$; (g) CH_3COSK, $CH_3CON(CH_3)_2$, 150 °C.

Scheme 15[a]



[a] Conditions: (a) Rh(0) = [Rh(norbornadiene)Cl]$_2$, chiral ligand, $PhCH_3$, 70 °C, 50 bar.

ing from tetronic acid. Treatment of the latter with the diazonium salt derived from aniline leads to diazo compound **36** which is converted into **38** via reaction with a primary amine such as (*S*)-1-phenylethylamine followed by reduction to **37** and subsequent imidazolone ring formation with ethyl chloroformate.[30] It is interesting to note that both **38** and *ent*-**38** can lead to the diastereomer with the desired (3*S*,4*R*)-configuration, depending on the hydrogenation conditions: rhodium on aluminum oxide in DMF for **38** (54% yield of crystalline **39**) and palladium on carbon in acetic acid for *ent*-**38** (54% yield).[31] A further dramatic improvement has been claimed very recently when the hydrogenation is performed in the presence of a rhodium complex and a chiral ferrocenylphosphine ligand (Scheme 15).[32,33] The reduction of achiral **40** into **41** (95% yield; 90% ee) constitutes a second example in which the chirality is introduced in a catalytic way.

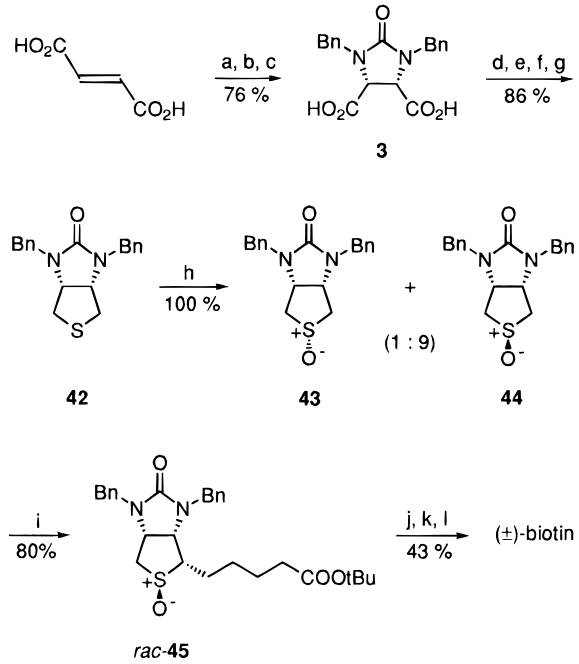
Upon closing this chapter, it has to be mentioned that very recently (1994) a third asymmetric approach has been claimed which will, however, be discussed in another context (see Scheme 56).

2. The Thiophane Approach

In 1975, the Marquet group reported a conceptually simple total synthesis of *rac*-biotin that is based on the stereoselective alkylation of cyclic sulfoxides.[34] The essential steps are shown in Scheme 16.

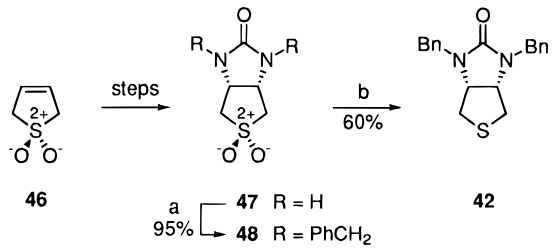
The known *meso*-diacid **3** is first converted via a straightforward four-step sequence into the bicyclic sulfide **42** in high yield. This sulfide is next oxidized with sodium periodate to yield quantitatively a mixture of diastereomeric sulfoxides in which the *trans*-isomer **44** predominates (ratio 9:1). This is the required isomer for the stereoselective α-introduction of the carboxybutyl chain since the alkylation of cyclic sulfoxides was known, at least in the six-membered ring case, to occur exclusively *trans* to the sulfoxide bond. When **44** was deprotonated with methyllithium at −30 °C in a mixture of tetrahydrofuran or diglyme containing hexamethylphosphoramide (HMPA) and treated with *tert*-butyl ω-iodovalerate, the desired stereoisomer **45** was obtained as a single isomer in 80% yield. The choice of the base and solvent was crucial for the alkylation yield. Indeed, with *n*-butyllithium, reaction at sulfur is taking place, whereas without HMPA, the reprotonation of the intermediate carbanion competes with the alkylation. Following reduction of the sulfoxide and hydrolysis of the *tert*-butyl ester in acid, debenzylation was effected by refluxing the acid for 3 h in 48% aqueous hydrobromic acid. Next to *rac*-biotin, monobenzylbiotin, which can be recycled, and the diamino acid originating from the hydrolysis of the urea ring, which can be recycled with phosgene, were obtained. The yield is about 50%. The synthetic scheme was also used for the preparation of analogues of biotin. In this context it was desirable to develop an alternative protective group for the imidazolidone nitrogens.

Scheme 16[a]



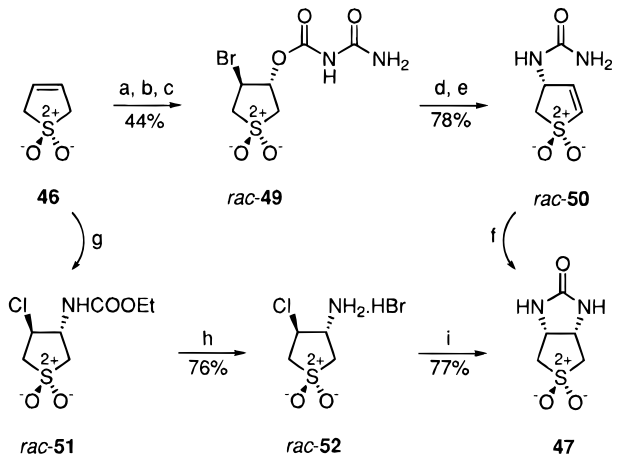
[a] Conditions: (a) Br_2; (b) $PhCH_2NH_2$, EtOH; (c) $COCl_2$, NaOH, $PhCH_3$; (d) MeOH, H_2SO_4, $Cl(CH_2)_2Cl$, reflux or MeOH, $BF_3 \cdot Et_2O$; (e) $LiAlH_4$, THF/ether; (f) MsCl, CH_2Cl_2, Et_3N; (g) Na_2S, EtOH; (h) $NaIO_4$, H_2O; (i) CH_3Li, −30 °C, HMPA (THF or diglyme); (j) Ph_3P, CCl_4 or $TiCl_3$, MeOH/$CHCl_3$; (k) HOAc, HCl; (l) HBr (48%). MsCl = methanesulfonyl chloride.

Scheme 17[a]



[a] Conditions: (a) $PhCH_2Br$, NaOH, H_2O; (b) $LiAlH_4$ (activated), ether, <0 °C.

Scheme 18[a]

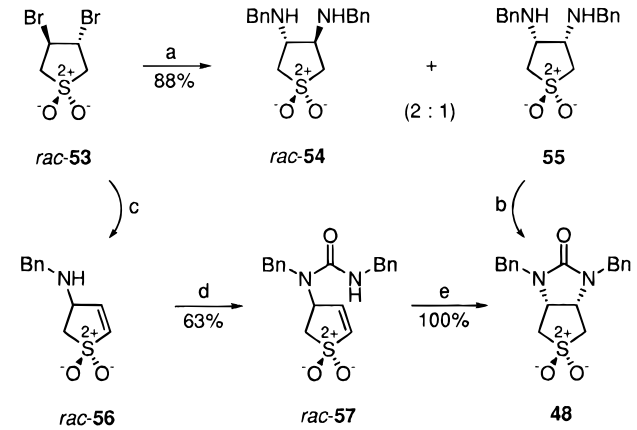


[a] Conditions: (a) Br_2, H_2O, 5 °C, 3 d; (b) quinoline, $COCl_2$, PhH; (c) NH_2CONH_2, 100 °C, 24 h; (d) quinoline, H_2O; (e) $NaHCO_3$, H_2O; (f) Na_2CO_3, H_2O, reflux; (g) $Cl_2NCOOEt$, $NaHSO_3$; (h) 47% HBr; (i) KNCO, H_2O, reflux.

The allyl group was found useful in that deprotection could be effected in a two-step sequence involving allylic isomerization using Wilkinson's catalyst in benzene/water (50% yield next to starting material) followed by hydrolysis.[35]

In line with the Marquet approach, a synthesis of a sulfone such as **47** or **48** would constitute a novel formal synthesis of *rac*-biotin, provided that the sulfone can be converted into thiophane **42** (Scheme 17). Several groups have concentrated on this approach with the readily available 3-sulfolene (2,5-dihydrothiophene 1,1-dioxide, **46**) as starting material. Two approaches which led to the unsubstituted sulfone **47** are further outlined in Scheme 18.[36,37] At the time, however, they were not considered as biotin syntheses since the Marquet synthesis was not yet known. Also, the reduction of the sulfone had not been described. Eventually, the successful reduction of **48** to **42** with lithium aluminum hydride (LAH) in ether at low temperature was reported by Kinoshita in 1983.[38] Subsequently, Bates and co-workers reported that the best yields are obtained by highly active LAH in ether between −15 and 0 °C.[39] Attempted reduction in THF afforded a complex mixture. Interestingly, DIBALH, a reagent recommended for sulfone reduction, reduced the urea moiety rather than the sulfone. The same group also observed that the corresponding unbenzylated derivate **47** was remarkably insoluble in organic solvents compatible with sulfone reduction. In order to gain increased organic solubility, **47**, which had been obtained before starting from sulfolene, was N-benzylated to **48** with a large excess of benzyl bromide in aqueous sodium hydroxide.

Scheme 19[a]

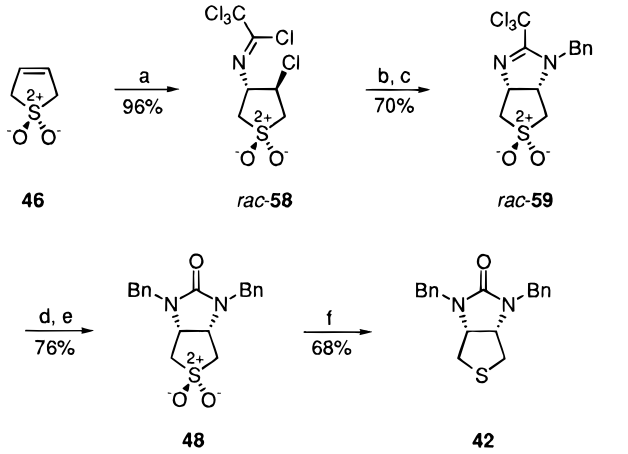


[a] Conditions: (a) $PhCH_2NH_2$; CH_3OH; (b) $COCl_2$, Et_3N, CH_2Cl_2, rt; (c) Et_3N; $PhCH_2NH_2$ (1 equiv); (d) $PhCH_2NCO$; (e) alkaline, $MeOH/H_2O$.

In the first approach (1972) shown in Scheme 18, sulfolene **46** is converted into **47** via a six-step sequence.[36] The known bromohydrin derived from **46** is converted into the corresponding chloroformate, and after reaction with urea, the allophanate **49** is obtained. Treatment of the latter under basic conditions led to dehydrobromination, and further treatment of the allyl allophanate with aqueous sodium hydrogen carbonate to the allylic urea derivative **50**. Further base treatment of **50** gave cyclization to **47**. The approach is based on the susceptibility of the double bond of 2,3-dihydrothiophene dioxide to addition reactions. The second approach shown in Scheme 18 constitutes a shorter sequence to unprotected **47**.[37] The chlorourethane **51** was first prepared by addition of *N*,*N*-dichlorourethane to 3-sulfolene. Subsequent treatment with concentrated hydrobromic acid afforded the chloroaminothiophane hydrobromide **52** in good yield. Treatment of the latter with potassium cyanate proceeded smoothly to yield the cyclic urea **47**.

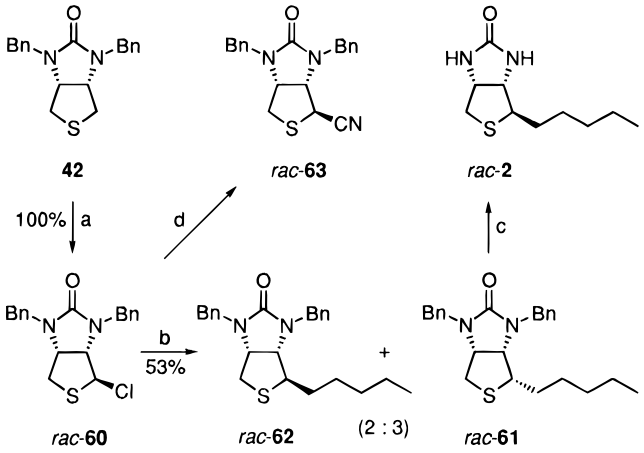
In 1976, the first full synthetic sequence to *rac*-biotin starting from 3-sulfolene was reported (Scheme 19).[40] The approach was based on the substitution of vicinal *trans*-dibromide **53** by amines.[41] When **53** was treated with benzylamine in methanol a mixture of the *trans*- and *cis*-substituted derivatives **54** and **55** was obtained in 88% yield (ratio 2:1, respectively). Reaction of the *cis*-derivative **55** with phosgene led to **48**. Albeit short, this route is unsatisfactory since the necessary *cis*-diamino derivative was obtained as the minor compound. It is interesting to note that when the crude mixture of **54** and **55** is treated with phosgene, simple crystallization will yield the pure *cis*-derivative **48** in 36% yield.[39] It is also interesting to note that when the *trans*-dibromide **53** was treated with dimethylamine, the *trans*-substituted diamino compound was formed exclusively.[40,41] Presumably, the mixture of **54** and **55** originates from reaction of benzylamine on the first formed 4-amino-2-sulfolene derivative **56**. The latter is an isolable intermediate in the sequence described by Bates and co-workers in 1985 (Scheme 19).[42] It is formed in good yield when **53** was treated with triethylamine followed by 1 equiv of benzylamine. Reaction of the amine **56** with benzyl isocyanate led to acyclic urea **57**, which spontaneously cyclized in slightly alkaline aqueous

Scheme 20[a]



[a] Conditions: (a) SO_2Cl_2 (4 equiv), CH_3CN, rt; (b) $PhCH_2NH_2$, Et_3N, THF, rt; (c) basic alumina (excess), CH_3CN, rt; (d) NaOH, EtOH, reflux; (e) nBuLi, $PhCH_2Br$, THF/HMPA (2:1), −40 °C; (f) $LiAlH_4$, ether, −10 °C.

Scheme 21[a]



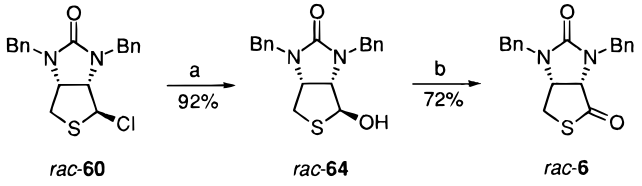
[a] Conditions: (a) NCS, PhH; (b) *n*-pentyl(Me)CuLI (mol of LiCl/mol of R_2CuLi = 1), −60 °C, ether; (c) Na, liq NH_3 or HBr (48%); (d) NaCN.

methanol to afford essentially quantitatively the desired **48**. Cyclic *trans*-fused urea derivatives have also been described.[43,44]

In the same context, the Kinoshita group described in 1983 a six-step synthesis of **42** in which sulfolene **46** is first converted to the imidoyl chloride **58** in high yield by reaction with sulfuryl chloride in acetonitrile (Scheme 20).[38] After vinylic chloride displacement by benzylamine, cyclization is effected with a large excess of basic alumina to afford **59** in good yield. Basic hydrolysis of the latter generated the amido group, which was further benzylated to yield **48**. Final reduction to **42** was performed with LAH in ether at low temperature.

Prior to 1985, the further transformation of cyclic sulfide **42** to *rac*-biotin was based on the Marquet scheme. In 1986, Bates and Rosenblum described alternative uses of **42**.[45] Scheme 21 displays how chlorination of **42** with *N*-chlorosuccinimide stereoselectively leads to **60** without interference of benzylic halogenation in essentially quantitative yield. Formation of the chloride occurs via initial sulfur chlorination, followed by migration analogous to the Pummerer rearrangement. The direct introduction of the biotin side chain with the correct stereochemistry must occur via displacement of **60** with inversion of configuration. In accord with the observation that organocuprates generally displace secondary halides with inversion of configuration, Bates and Rosenblum could achieve, after considerable experimentation, a moderate stereoselectivity in favor of the required *endo*-isomer by using methyl pentylcuprate in ether at −60 °C (53% yield). A slightly more favorable 65:35 ratio was obtained with halide-free reagent but the yield dropped to 42%. It should be stressed that the process must be performed using rigorously anaerobic conditions, since adventitious oxygen readily oxidizes pentyllithium to lithium pentyl oxide which rapidly substitutes chlorine in **60**. In order to complete the synthesis, **61** was debenzylated to afford *rac*-deoxybiotin (**2**). The conversion of deoxybiotin into biotin by microbial oxidation has been accomplished.[9] This interesting approach suffers from lack of stereoselectivity. In fact other substitutions on **60** proceed exclusively via S_N1 displacement with nucleophilic attack from the less-hindered *exo*-face of the bicyclic molecule (e.g., **60** to **63**).

Scheme 22[a]



[a] Conditions: (a) NaOH, DME; (b) DMSO, $(CF_3CO)_2O$, $CHCl_3$.

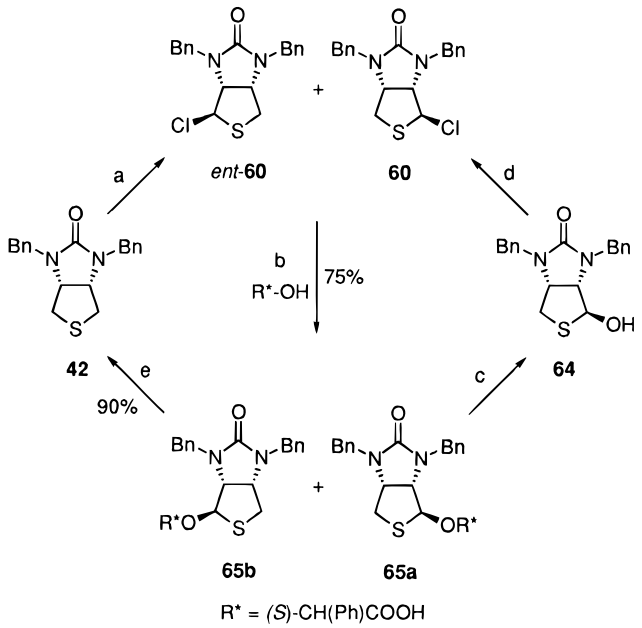
Alternatively, the stable chlorothioether **60** is hydrolyzed to thiolactol **64** with sodium hydroxide in dimethoxyethane (DME) and water (Scheme 22). Oxidation with dimethyl sulfoxide (DMSO) and trifluoroacetic anhydride leads to the known thiolactone **6**, the key component in the approach of Hoffmann-La Roche. Overall this constitutes an eight-step conversion of 3-sulfolene to *rac*-**6**.[45]

As for the Hoffmann-La Roche synthesis, a *meso*-derivative, i.e., bicyclic sulfide **42**, has a central position in the above described synthetic work. Not surprisingly, work has been accomplished in order to develop asymmetric modifications.

Bihovsky and Bodepudi form Stony Brook succeeded in resolving alcohol **64** as shown in Scheme 23.[46] The resolution was accomplished by separation of the diastereomeric alkoxy derivatives **65a** and **65b** that were obtained by reaction of *rac*-**60** with optically active secondary alcohols. The most favorable alcohol for preparative purposes was (*S*)-(+)-mandelic acid, since the diastereomers could be readily separated by crystallization. Acid hydrolysis of **65a** led to (+)-**64**, and hence to (+)-**6**, via oxidation or to **60** via treatment with hydrochloric acid. On the other hand, the undesired enantiomer *ent*-**64** was easily recycled by reduction with boron trifluoride/triethylsilane to **42**. Under the same conditions, unwanted **65b** is also converted to **42**.

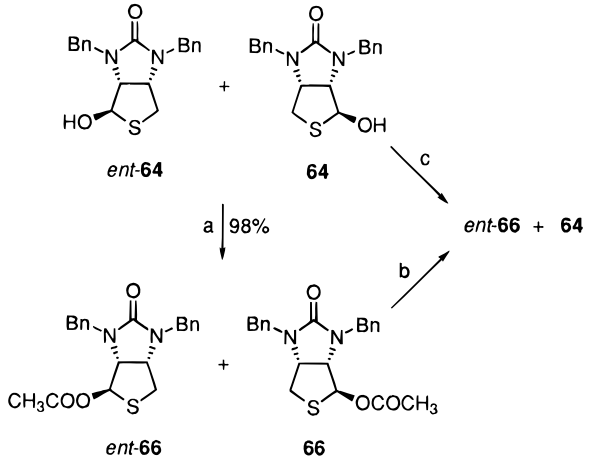
Successful enzyme-catalyzed kinetic resolutions were reported by Yamano and co-workers of Takeda Chemical Industries (Scheme 24).[47] A variety of commercially available enzymes and microorganisms were investigated in order to effect the enantioselective hydrolysis of the ester **66**, which was obtained

Scheme 23[a]



[a] Conditions: (a) NCS; (b) R*-OH = (*S*)-(+)-mandelic acid; diastereomer separation by crystallization; CCl_4, reflux; 33% isolated with R* = -CH(Ph)COOH; (c) H_2SO_4/dioxane; (d) HCl, $CHCl_3$; (e) Et_3SiH, CF_3COOH.

Scheme 24[a]



[a] Conditions: (a) Ac_2O, pyridine, (b) *Streptomyces rochei* var. *volubilis*; 27% conversion; 92 and 94% ee after crystallization; (c) LIP (*P. aeruginosa* TE3285; TOYOBO immobilized lipase), 0.3% H_2O, 4 Å molecular sieves (MS), $PhCH_3$, vinyl acetate; 56% conversion; 99 and 99.8% ee after crystallization of alcohol.

by conventional acylation of *rac*-**64**. In most cases, the preferred hydrolysis of *ent*-**66** is observed. Although the desired enantiomer **64** was obtained by the hydrolysis of the remaining ester **66**, a more efficient process in the context of biotin synthesis requires (*S*)-preferred hydrolysis. Eventually it was found that the hydrolysis using *Streptomyces rochei* var. *volubilis* proceeded with 27% conversion and 92% ee. The separation of alcohol **64** was readily accomplished by crystallization from the reaction mixture.

In a second approach, the same group found that direct resolution of alcohol **64** was accomplished via acylation with the lipoprotein lipase from *Pseudomonas aeruginosa* TE3285 in toluene.[48] The lipase acylated the (*R*)-alcohol *ent*-**64** enantioselectively. Unreacted **64** was isolated in excellent chemical and optical yields (>99% ee). Among the acylating agents tested, vinyl acetate and vinyl hexanoate exhibited the highest reactivities. Curiously, addition of molecular sieves (MS) 4A to the reaction mixture improved the reactivity, while at the same time a small amount of water was beneficial for the reaction.

B. Enantiospecific (Chiral Pool) Syntheses

In this section, the numerous enantiospecific syntheses that have taken advantage of some chiral information stored in either L-cystine and L-cysteine or in carbohydrates are grouped.

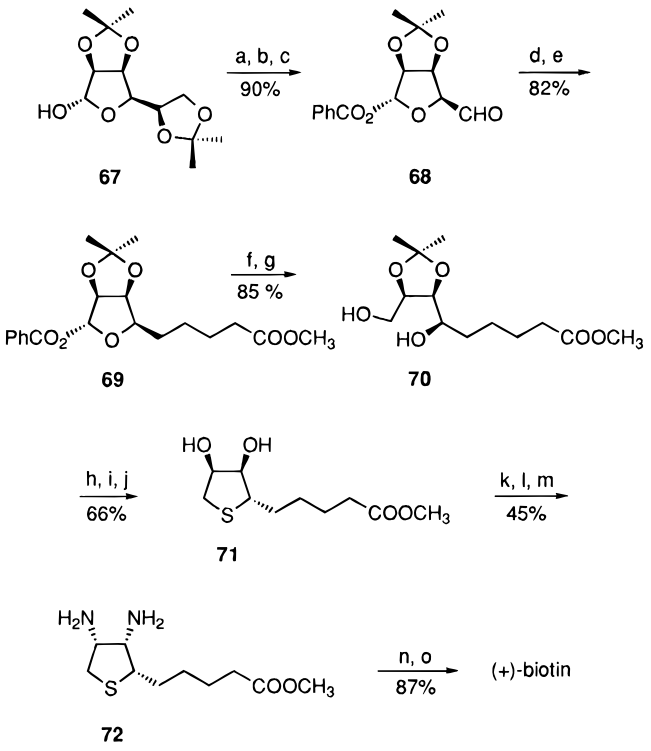
1. From Carbohydrates[49]

The monosaccharides that have been used as chiral starting materials for further multistep conversion to (+)-biotin are further shown in a way that immediately allows analysis of the sequences that will be necessary for their conversion to biotin (see Chart 3). Four different hexoses and one pentose, D-arabinose, have ben used as starting materials. Crucial in the design of all syntheses in this area is the obtention of the thiophane nucleus via double S_N2 displacement of a dimesylate obtained from a diol. In view of the configuration at C-2 in biotin and the inversion that occurs at this center during the final thiophane closure step, the absolute configuration at this specific center is crucial. It corresponds to the (*R*)-configuration at C-4 in the hexoses that have been used and to the (*S*)-configuration at C-2 in the pentose D-arabinose. All syntheses additionally have in common that the biotin carboxyalkyl side chain is introduced via Wittig condensation using 3-(methoxycarbonyl)-2-propenylidene triphenylphosphorane followed by catalytic hydrogenation. In all cases, the amino groups will also be introduced via sequences involving S_N2 substitution of a leaving group by azide followed by reduction of the azide.

Ohrui and Emoto began the series in 1975 (Scheme 25).[50] In their approach the di-*O*-isopropylidene-protected α-D-mannofuranose **67** is converted to diol **70**. The sequence involves formation of the benzoate of the anomeric alcohol, selective hydrolysis of the 5,6-isopropylidene group, and oxidative cleavage of the vicinal diol to yield aldehyde **68**. Subsequent Wittig treatment and catalytic hydrogenation afforded **69**. Base treatment of the latter generated the hemiacetal that was reduced to diol **70**. After thiophane formation and hydrolysis the obtained diol **71** is converted to the diamine **72** via inversion. Final obtention of (+)-biotin occurs after saponification and phosgene treatment. Alternative sequences for converting diol **71** into (+)-biotin have been claimed.[51]

Ogawa and co-workers have used D-glucose as starting material (Scheme 26).[52] Its conversion to diol **80**, which upon thiophane formation leads to biotin, requires no less than 18 steps when starting from **73**. It is of interest to note that within the scheme the introduction of the second amine required the displacement of a mesylate in the bridged intermediate **76**. Since this would demand a sterically very hindered displacement, it was decided to convert the congested cyclic acetal **76** into the linear mesylate **78** which was found to be an adequate substrate for substitution.

Scheme 25[a]



[a] Conditions: (a) PhCOCl, C_5H_5N; (b) HOAc, H_2O; (c) $NaIO_4$, CH_3COCH_3/H_2O; (d) $Ph_3P{=}CHCH{=}CHCOOCH_3$, CH_2Cl_2; (e) H_2, Pd/C, CH_3OH; (f) $NaOCH_3$, CH_3OH; (g) $NaBH_4$; (h) CH_3SO_2Cl; (i) Na_2S, HMPA, 100 °C; (j) 90% HCOOH, 20 °C; (k) CH_3SO_2Cl; (l) NaN_3, HMPA, 80 °C; (m) PtO_2, MeOH/Ac_2O; (n) $Ba(OH)_2$, H_2O, 140 °C; (o) $COCl_2$.

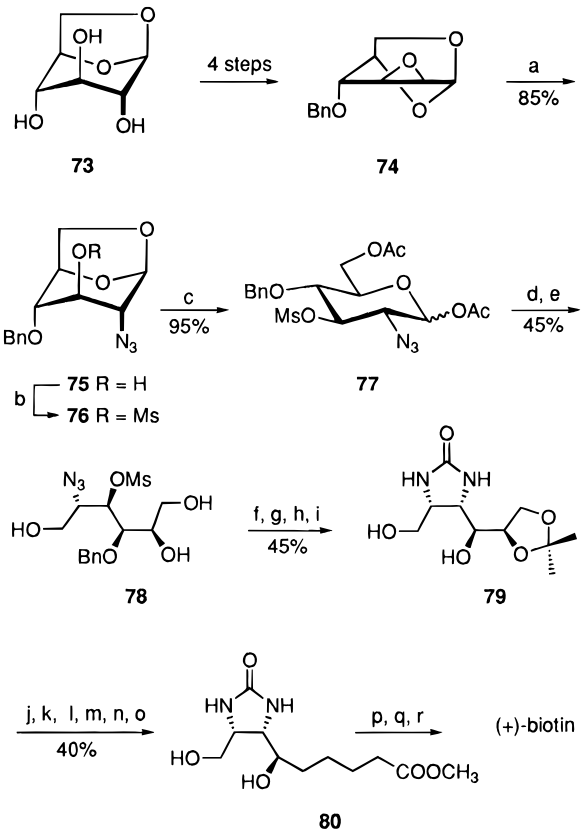
Subsequent to this work, the Ohrui group developed a shorter sequence to the same diol **80** that took advantage of the correct absolute configuration of the amino group in D-glucosamine that will eventually appear at C-4 in (+)-biotin (Scheme 27).[53] Worthy of note here is the use of a benzyloxycarbonyl group as reactive amine protecting group to form the imidazolidinone ring upon treatment of **83** with sodium hydride.

A modified synthesis of (+)-biotin from D-glucose was reported by Ravindranathan and co-workers in 1984.[54] The synthesis which is outlined in Scheme 28 leads to the Ohrui intermediate **69**. The starting substance is D-glucurono-6,3-lactone (**84**) which is first reduced to L-gulono-1,4-lactone (**85**). The remaining steps are essentially similar to the Ohrui sequence (Scheme 25).

In the context of the use of carbohydrates as starting material for (+)-biotin, D-arabinose is the most logical choice. Vogel and co-workers of BASF reported on this approach in 1980 (Scheme 29).[55] Starting from **88** the corresponding hemiacetal was subjected to Wittig treatment, reduction, and benzoate removal to yield the known diol **70**. This sequence suffered, however, from a low yield in the Wittig reaction. This was partly due to the formation of the tetrahydropyran **90** intermediate through intramolecular Michael addition of the free hydroxy group to the unsaturated system of **89**.

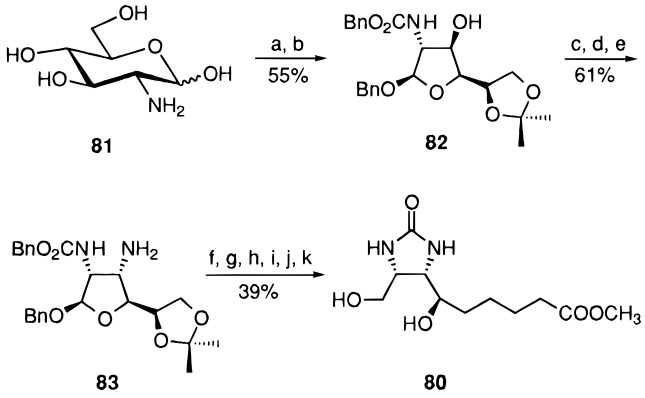
This major shortcoming was solved by Schmidt and Maier in 1982 (Scheme 30).[56] D-Arabinose is first converted to the 3,4-*O*-isopropylidene derivative **91**. The latter reacted under the dihydroxy aldehyde form

Scheme 26[a]



[a] Conditions: (a) NaN_3, NH_4Cl, $CH_3OCH_2CH_2OH/H_2O$, 120 °C; (b) MsCl; (c) $BF_3{\cdot}Et_2O$, Ac_2O; (d) HCl, CH_3OH; (e) $NaBH_4$, $B(OH)_3$, EtOH; (f) $(CH_3)_2C(OCH_3)_2$, DMF, *p*-TsOH; (g) LiN_3, DMF, 80 °C; (h) H_2, Lindlar, EtOH; (i) $COCl_2$; (j) Ac_2O, C_5H_5N; (k) AcOH/H_2O, 70 °C; (l) $NaIO_4$, EtOH/H_2O; (m) $Ph_3P{=}CHCH{=}CHCOOCH_3$, CH_2Cl_2; (n) H_2, Pd/C, CH_3OH; (o) CH_3ONa, CH_3OH; (p) CH_3SO_2Cl, C_5H_5N, −10 °C; (q) Na_2S, DMF, 100 °C; (r) NaOH.

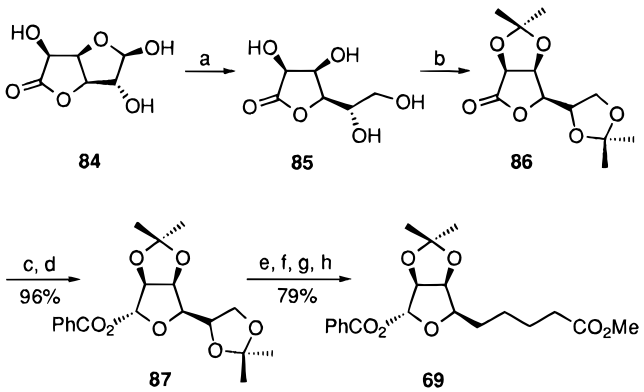
Scheme 27[a]



[a] Conditions: (a) $PhCH_2OC(O)Cl$, $NaHCO_3$; (b) $(CH_3)_2C(OCH_2Ph)_2$, *p*-TsOH, DMF, 120 °C; (c) *p*-TsCl, C_5H_5N; (d) NaN_3, DMF; (e) H_2, RaNi; (f) NaH, DMF; (g) HOAc/H_2O; (h) $NaIO_4$; (i) $Ph_3P{=}CHCH{=}CHCOOCH_3$; (j) H_2, Pd/C; (k) $NaBH_4$, CH_3OH.

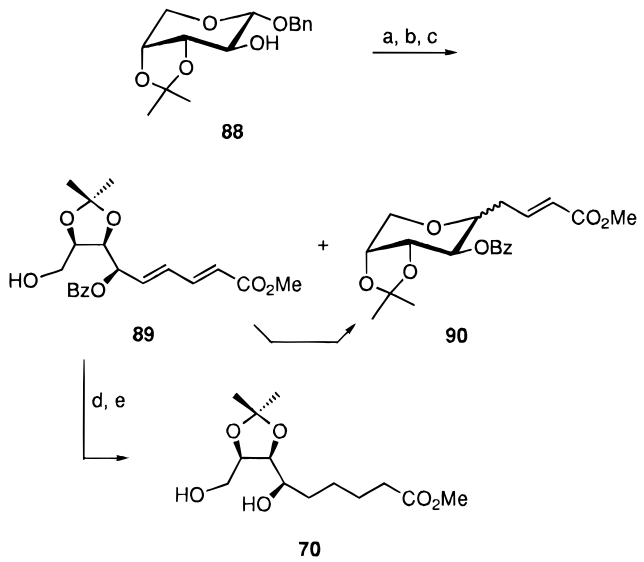
with the usual Wittig reagent, in the presence of benzoic acid, to yield after subsequent catalytic hydrogenation diol **70** in 39% yield. The same Wittig transformation in the presence of an acid ion exchange resin has been claimed to proceed in 53% yield.[57] In 1988, Schmidt and Maier claimed an 82% yield of Wittig product upon simple heating in toluene.[58] The same sequence as shown in Scheme 30 has also been reported but starting from 3,4-cyclohexylidene-D-arabinose.[59]

Scheme 28[a]



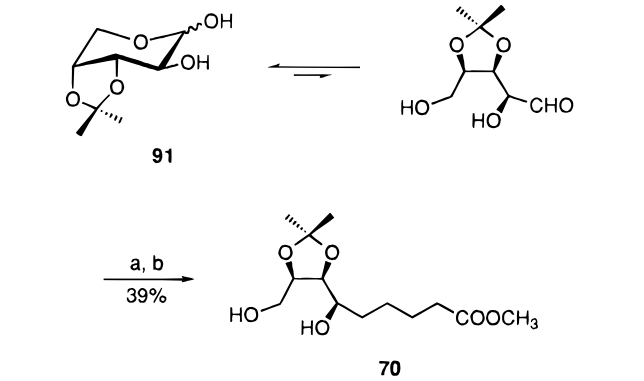
[a] Conditions: (a) H_2, RaNi; (b) $(CH_3)_2C(OCH_3)_2$, DMF, *p*-TsOH; (c) $NaBH_4$, CH_3OH, 0 °C; (d) PhCOCl, C_5H_5N; (e) CH_3OH, HCl; (f) $NaIO_4$, acetone/H_2O, 0 °C; (g) $Ph_3P{=}CHCH{=}CHCOOCH_3$, CH_2Cl_2; (h) H_2, $Pd(NaBH_4)$.

Scheme 29[a]



[a] Conditions: (a) PhCOCl, C_5H_5N; (b) H_2, Pd/C, dioxane; (c) $Ph_3P{=}CHCH{=}CHCOOCH_3$, CH_2Cl_2; (d) H_2, Pd/C; (e) $NaOCH_3$, CH_3OH (65% yield).

Scheme 30[a]



[a] Conditions: (a) $Ph_3P{=}CHCH{=}CHCOOCH_3$, PhCOOH; (b) H_2, Pd.

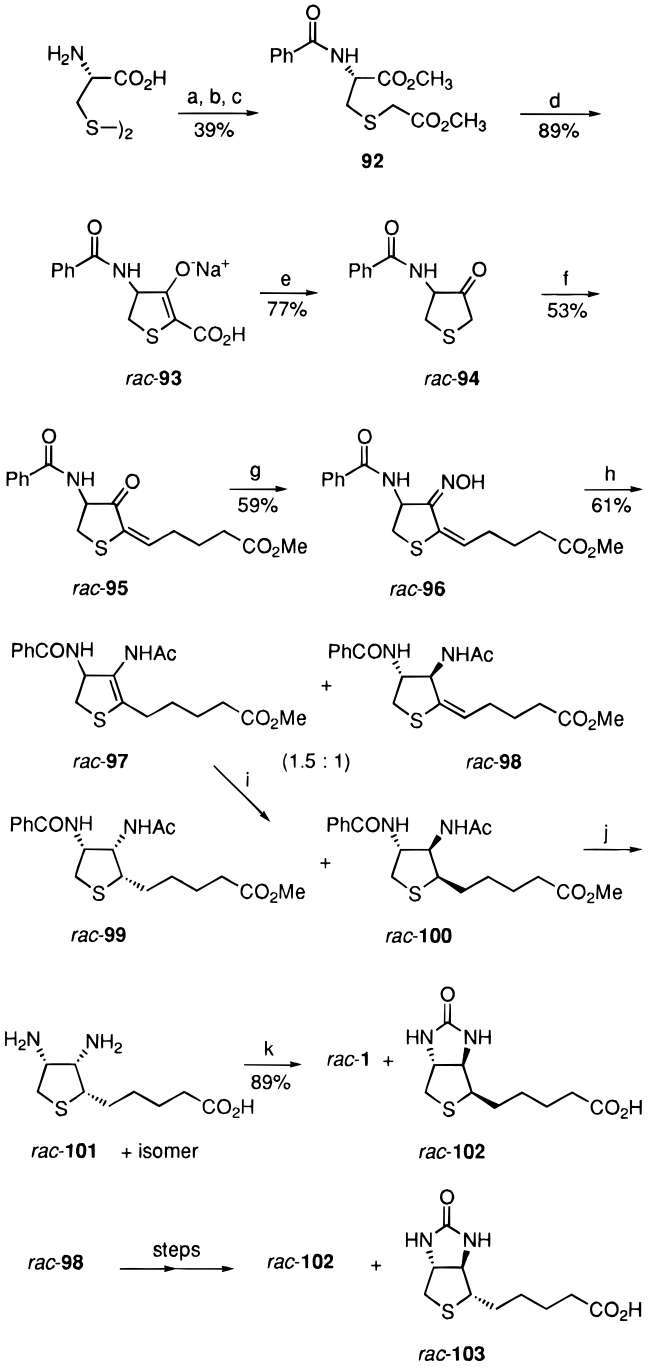
2. From L-Cystine and L-Cysteine

No less than 10 enantiospecific syntheses of (+)-biotin starting from either L-cystine or L-cysteine have been reported. Within the context of this review they are divided in two series. In the first series, formation of the bond between C-2 and C-3 is central in the strategy. In the second series, bond formation between S and C-2 terminates the thiophane construction. The individual syntheses within each series are not dicussed in chronological order. We will start this section, however, with an account of the first published synthesis of biotin, since the starting material was L-cystine and since in principle the sequence could have been enantiospecific.

In 1943, Harris and co-workers of the Merck Research Laboratory, Rahway, NJ, reported that they had synthesized biotin and recorded a comparison of their synthetic material with natural biotin, in particular melting point and optical rotation.[7] The synthetic optically active (+)-biotin was obtained by resolution and hydrolysis of the (−)-mandelic acid esters of *rac*-biotin. Full details about their work were published subsequently in a series of six papers (1943−1945).[60−65] The synthesis is shown in Scheme 31 and proceeds in three stages. In the first stage starting from L-cystine, the protected 4-amino-3-oxothiophane derivative **94** is obtained as a racemic mixture. This sequence involves five steps. After reductive cleavage of L-cystine, the obtained thiolate is treated with chloroacetic acid, and the resulting diacid converted to the N-protected diester **92**. During the subsequent Dieckmann condensation, racemization occurred, however, and the condensation product was isolated as the sodium salt *rac*-**93**. The salt was further hydrolyzed and decarboxylated in acid to yield **94**. In the second stage, the side chain was introduced via condensation of **94** with the known methyl 5-oxopentanoate using piperidine acetate as catalyst, and the resulting enone **95** was converted to the unsaturated oxime **96**. In the last stage of the synthesis, *rac*-biotin was obtained in a non-stereoselective manner that involved two reduction steps. First, the unsaturated oxime was reduced with zinc in acetic acid/acetic anhydride leading to a mixture of **97** and the *trans*-diamine derivative **98**. Further catalytic hydrogenation of **97** led to two stereoisomeric diamine derivatives **99** and **100**. The former was further converted to biotin via deprotection to diamino acid **101** and treatment with phosgene. The required enantiomer was obtained through resolution of *rac*-biotin. A more satisfactory resolution procedure was found using (+)-arginine that gave a crystalline salt of biotin as the less-soluble salt which separated in 92% yield.[64]

The stereoisomer that was obtained together with **99** was converted to *rac*-**102** or (±)-allobiotin, epimeric at C-2 and C-3. Catalytic hydrogenation of the *trans*-derivative **98** led via a similar sequence to *rac*-**102** and *rac*-**103** or *epi*-allobiotin, the C-3 epimer of biotin. For the sake of clarity, the correct configurational assignments are included in the figure. At the time however the relative configuration at stereocenter 2 could not be assigned: "Since different conditions effect different modes of hydrogen addition (i.e., *cis* versus *trans*), the configuration of the side chain in respect to the adjacent nitrogen atom is not known".[65] It is interesting to observe that the first reported scheme would have led directly to the biologically active enantiomer of biotin, if racemization had not occurred.

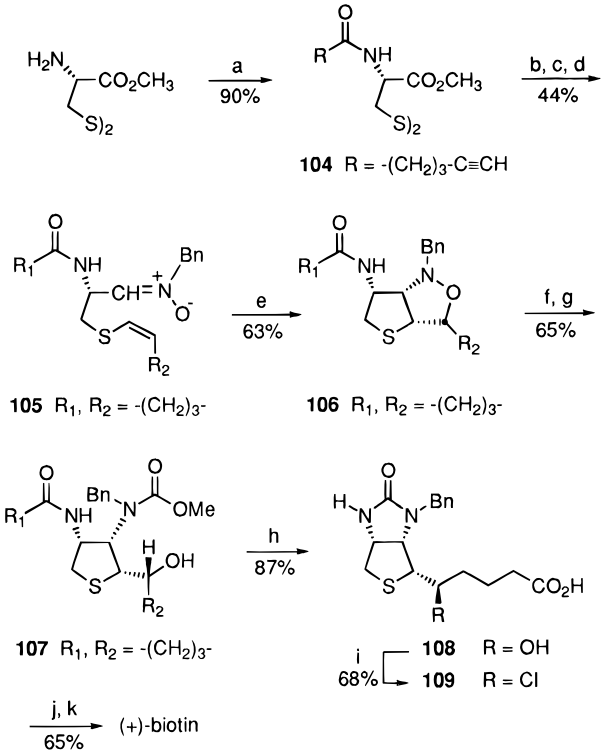
Scheme 31[a]



[a] Conditions: (a) Na, liq NH_3; $ClCH_2COOH$; (b) PhCOCl; (c) CH_3OH, HCl; (d) $NaOCH_3$; (e) HOAc, HCl; (f) $OHC(CH_2)_3CO_2Me$, $C_5H_{11}N$, HOAc; (g) NH_2OH, C_5H_5N; (h) Zn, HOAc, Ac_2O; (i) H_2, Pd; (j) $Ba(OH)_2$, 140 °C; (k) $COCl_2$, Na_2CO_3.

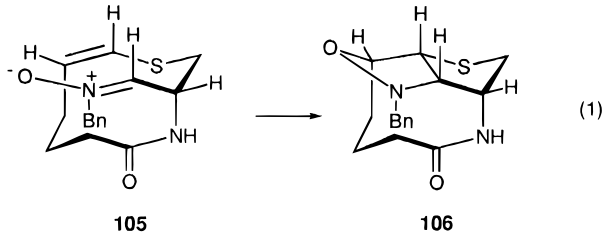
Baggiolini and co-workers at Hoffmann-La Roche have reported two syntheses (1982 and 1987) in which the same bond formation between C-2 and C-3 was realized via an intramolecular [3 + 2] dipolar cycloaddition.[66,67] The first of these provides a nice example of the use of a cyclic template to enforce the stereochemical outcome of a reaction into the desired sense (Scheme 32).[66] The crucial step in the synthesis involves the intramolecular cycloaddition of the nitrone (*Z*)-alkene **105** whereby the tricyclic oxazolidine **106** is formed. Substrate **105** is constrained into a ten-membered lactam ring to enforce the cyclization to produce stereoselectively the isomer

Scheme 32[a]

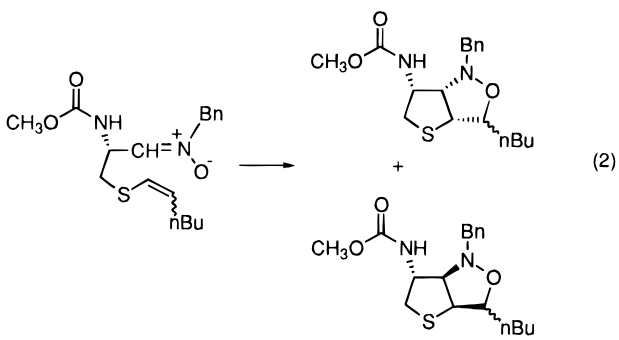


[a] Conditions: (a) $HC{\equiv}C(CH_2)_3C(O)Cl$, C_5H_5N, CH_2Cl_2; (b) Zn dust, CH_3COOH, air; (c) DIBALH, $PhCH_3$, −78 °C; (d) $PhCH_2$-NHOH·HCl, CH_2Cl_2; (e) $PhCH_3$, reflux, BaO; (f) Zn dust, AcOH/H_2O, 70 °C; (g) $ClCO_2Me$, Na_2CO_3, THF, 0 °C; (h) $Ba(OH)_2$, dioxane/H_2O, reflux; (i) $SOCl_2$, ether, MeOH; (j) $NaBH_4$, DMF, 80 °C; (k) 48% HBr.

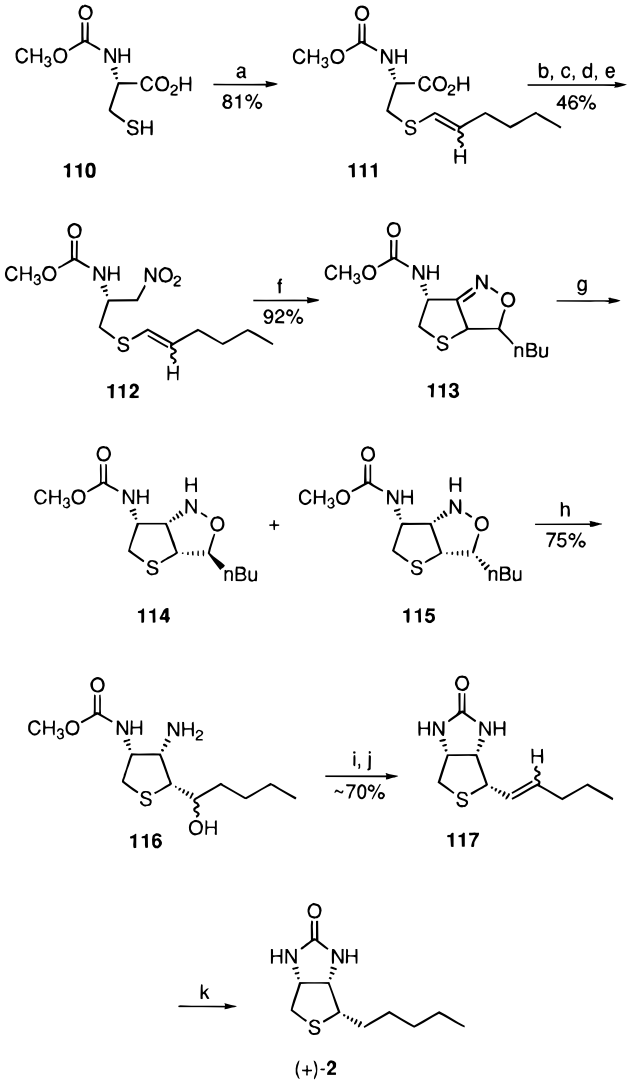
with the required *all-cis* configuration about the thiophane ring (eq 1).



Model studies had shown indeed that the acyclic derivative **105** (R_1 = methoxy; R_2 = *n*-butyl), as a mixture of (*E*)-and (*Z*)-thioenol ethers, cyclized spontaneously at room temperature to give in high yield the desired cycloadduct **106** (R_1 = methoxy; R_2 = *n*-butyl), as a mixture of epimers at the center bearing the *n*-butyl chain, together with the diastereomer with epimeric configuration at C-2 and C-3 (eq 2).



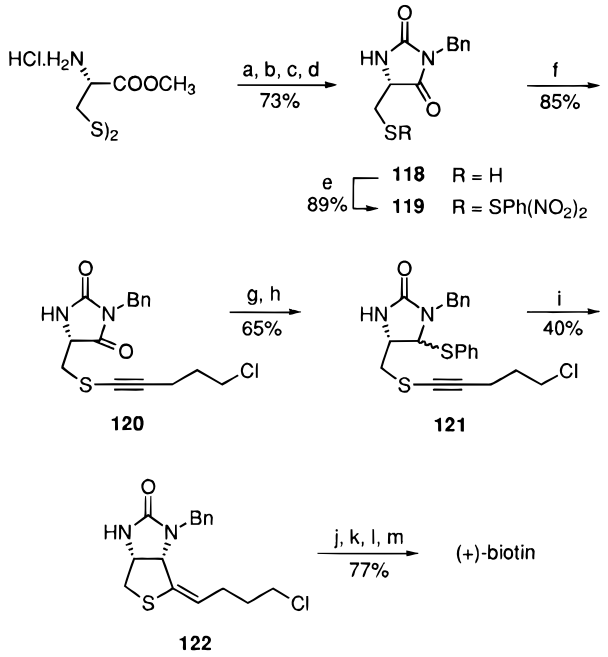
Scheme 33[a]



[a] Conditions: (a) $CH_3(CH_2)_3C{\equiv}CH$, AIBN, dioxane; (b) ClCOOCH$_3$; NaBH$_4$; (c) MsCl, C_5H_5N; (d) NaI, acetone; (e) $NaNO_2$, DMF, urea phloroglucinol; (f) PhH, reflux, PnNCO; (g) DIBALH, PhCH$_3$, −78 °C, followed by easy separation by column chromatography; (h) Pd/C, HOAc/H_2O; (i) $Ba(OH)_2$, dioxane/H_2O; (j) *p*-TsOH, PhCH$_3$, reflux; (k) H_2, Pd/C, HOAc/H_2O.

The synthesis of the ten-membered lactam **105** from L-cystine proceeded via a four-step sequence. First, L-cystine is acylated at nitrogen with 5-hexynoyl chloride, followed by reduction with zinc in acetic acid. Under these conditions, the disulfide bond is cleaved, and if the reaction is carried out in the presence of air, further cyclization takes place simultaneously to produce a 9:1 mixture of the *Z*-olefinic product (65% yield) and the corresponding *E*-isomer. After separation, the desired *Z*-isomer was reduced with DIBALH and the reduction product treated with benzylhydroxylamine to give nitrone **105**. When refluxed in toluene, the latter underwent cycloaddition with the exclusive formation of the required adduct **106** in 63% yield. The presence of small amounts of barium or calcium oxide prevented partial racemization in the cycloaddition step which was due to the formation of traces of acid in the reaction medium. Cleavage of the isoxazolidine ring and urethane formation led to **107** which underwent hydrolysis of the lactam moiety and concomitant cyclization to the imidazolidinone **108** upon treatment with barium hydroxide in refluxing aqueous dioxane. Finally, the superfluous hydroxy group was removed via the corresponding chloro ester **109**; the latter was obtained with retention of configuration by treatment with thionyl chloride followed by quenching with methanol. Dechlorination was effected with sodium borohydride in dimethylformamide. Debenzylation eventually led to biotin.

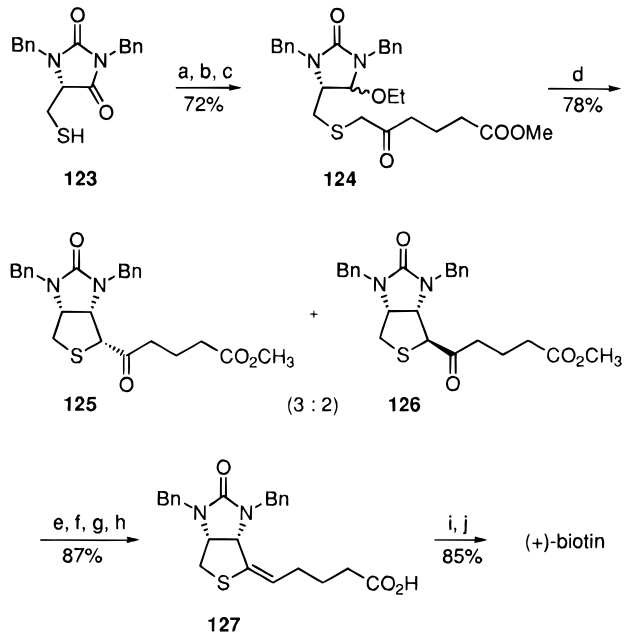
Scheme 34[a]



[a] Conditions: (a) $COCl_2$, PhCH$_3$, reflux; (b) $PhCH_2NH_2$, CH_2Cl_2; CH$_3$OH; (c) Ph_3P, $CH_3OCH_2CH_2OCH_3$; CH$_3$OH/H_2O, 90 °C; (d) 6 N HCl, 100 °C; (e) 2,4-dinitrobenzenesulfenyl chloride, CH_2Cl_2; (f) $Cl(CH_2)_3C{\equiv}CLi$, $CeCl_3$, −78 °C; (g) iBu_2AlH, PhCH$_3$, −78 °C; (h) $(PhS)_2$, nBu_3P, CH_2Cl_2; (i) $(C_6H_{11})_3SnH$, AIBN, PhH; (j) NaCN, EtOH/H_2O, reflux; (k) H_2, Pd/C, EtOAc; (l) NaOH/H_2O, reflux; (m) 48% HBr, reflux, 2 h.

The synthesis of deoxybiotin (+)-**2** via an analogous [2 + 3] cycloaddition step, but now involving an intermediate nitrile oxide as 1,3-dipole was reported in 1987 by the same group.[67] The synthesis of nitro thioenol ether **112** proceeded from *N*-(methoxycarbonyl)-L-cysteine in five steps involving first thioether formation via reaction with *n*-hexyne in the presence of 2,2′-bisisobutyronitrile (AIBN) to yield **111** as a 1:1 mixture of geometrical isomers (Scheme 33). The required nitro function was further introduced via sodium borohydride reduction of the mixed anhydride, conversion of the resulting primary alcohol to the corresponding mesylate, and substitution with sodium nitrite in the presence of urea and phloroglucinol in order to minimize the formation of nitrite ester. Refluxing **112** in the presence of an excess of phenylisocyanate generated a mixture of isomeric isoxazolines **113**. Further reduction with DIBALH led to four isoxazolidines which were readily separated by column chromatography. Of these four isomers, only **114** and **115** are of further use in the context of biotin synthesis. The two other stereoisomers possess the epimeric configurations at C-2 and C-3. Hydrogenation of the mixture of **114** and **115** gave alcohol **116** as an epimeric mixture. Removal of the superfluous hydroxy group was effected through elimination to the disubstituted olefin **117** and catalytic hydrogenation. Final deprotection led

Scheme 35[a]

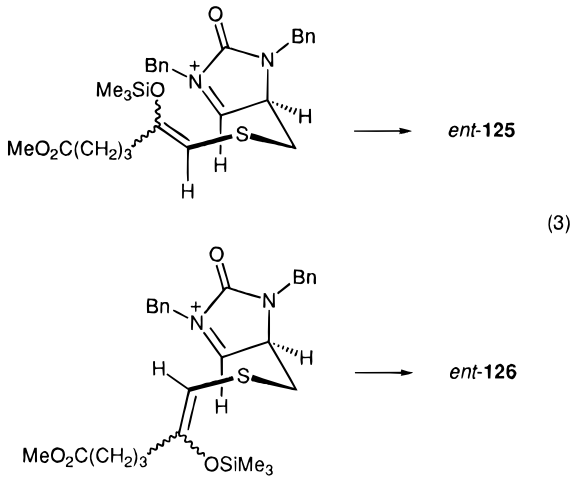


[a] Conditions: (a) DIBALH, THF, −70 °C, 1 h; (b) $MeO_2C(CH_2)_3C(O)CH_2Cl$, Et_3N, 4 h; (c) H_2SO_4/EtOH, methyl orange, pH = 3.1, 0 °C, 2 h; (d) 2.1 equiv of $(TMS)CH_2CO_2Et$, 0.03 equiv of TBAF, THF, −78 °C → 25 °C, 18 h, then 1.5 equiv of TMSOTf, CH_2Cl_2, −78 °C, 1 h; (e) $NaBH_4$, MeOH, 25 °C; (f) $MeSO_2Cl$, Et_3N, CH_2Cl_2; (g) DBU, 60 °C, 2 h; (h) KOH/MeOH, 2 h; (i) H_2 (10 bar), 10% Pd/C, 2-propanol, 50 °C, 18 h; (j) 48% HBr, 100 °C, 2 h. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene. TBAF = tetrabutylammonium fluoride.

to (+)-deoxybiotin, which can be converted to (+)-biotin via the known microbiological oxidation process.[9]

In 1988, Corey and Mehrotra reported a synthesis of (+)-biotin in which the radical cyclization step of **121** to **122** is central (Scheme 34).[68] L-Cystine dimethyl ester dihydrochloride was first converted to the mercapto hydantoin **118** via consecutive formation of a diisocyanate and a bisurea; reduction of the disulfide linkage and acid treatment produced **118**, which was further converted to the corresponding mixed sulfide **119**. The latter was next reacted with the lithio derivative of 5-chloro-1-pentyne in the presence of cerium trichloride to give the acetylenic hydantoin **120** in 85% yield. After selective reduction of **120** with DIBALH and treatment of the resulting hydroxy ureide with diphenyl disulfide and tri-*n*-butylphosphine, the phenylthio-substituted ureide **121** was obtained as a mixture of diastereomers (ratio 5.5:1). Treatment of this mixture with tricyclohexyltin hydride and AIBN afforded 50% of the desired five-membered cyclization product **122** as a single stereoisomer and 8% of an isomeric six-membered ring cyclization product. Final conversion of **122** into biotin is straightforward and involves substitution to the corresponding cyano derivative and hydrogenation using the Pearlman catalyst, followed by base hydrolysis of the nitrile and debenzylation with hydrobromic acid.

Two groups have elaborated ionic variants of this ring closure.[69,70] In a joined effort, Speckamp and coworkers, and Poetsch and Casutt from E. Merck (Darmstadt) have used the intramolecular version of the condensation of a silyl enol ether with *N*-acyliminium intermediates to effect the ring closure of thioether **124** to the thiophane nucleus (Scheme 35).[69] From the known **123**, readily available from L-cysteine, reduction with DIBALH led to the corresponding hydroxyimidazolidinone (10:1 ratio of *cis*:*trans* diastereomers); after coupling with the appropriate α-chloro ketone, the obtained thioether was converted into the ethoxy derivative **124**. The crucial cyclization step involved the use of ethyl trimethylsilylacetate/tetra-*n*-butylammonium fluoride for the in situ enol ether formation and addition of trimethylsilyl triflate (TMSOTf) to induce the cyclization. This led to a 78% yield of the two diastereomers **125** and **126** (3:2 ratio). Together with the expected cyclization via a chairlike transition state to yield **125** possessing the required *all-cis* configuration, cyclization also proceeds partly through a boatlike conformation to give diastereomer **126** (eq 3).



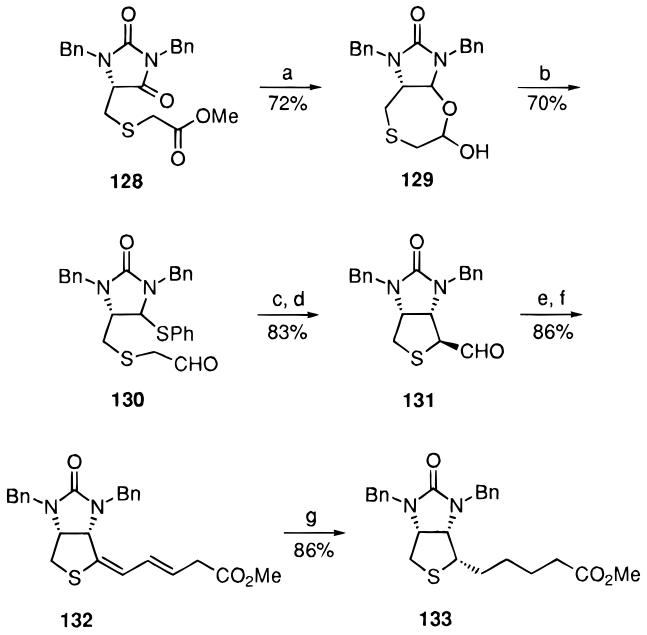
(3)

The loss of stereochemical control does not influence, however, the further conversion into biotin. Indeed, the mixture is converted to the same exocyclic olefin **127** via sodium borohydride reduction, mesylation, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) elimination, and saponification. Final conversion of **127** to biotin proceeds in the usual way.

Ravindranathan and co-workers of the council of Scientific and Industrial Research have reported the biotin synthesis shown in Scheme 36 that centers around a similar cyclization step as in the previous synthesis.[70] Conversion of thioaldehyde **130** to the corresponding silyl enol ether followed by trialkyl triflate leads to the thermodynamically more stable thiophane aldehyde **131**. The synthesis of aldehyde **130** involves reduction of hydantoin ester **128** to yield the cyclic hemiacetal **109** which is further converted to **130** by treatment with thiophenol. The transformation of **131** into biotin involved first Wittig reaction with the propylidene ylide, followed by deconjugation in base to yield the exocyclic olefin **132**. Further catalytic hydrogenation led to protected biotin methyl ester **133**.

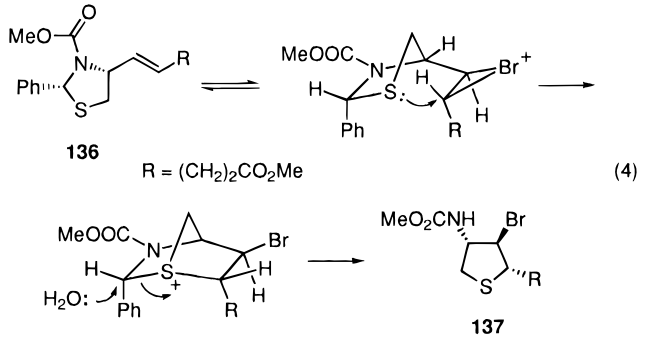
In 1975, Confalone and co-workers reported an interesting approach in which bromination of olefin **136** resulted in a spectacular and stereospecific rearrangement (Scheme 37).[71] As shown in eq 4, anchimeric participation by sulfur in order to stabilize the incipient bromonium ion presumably yields a bridged sulfonium cation which then expels ben-

Scheme 36[a]



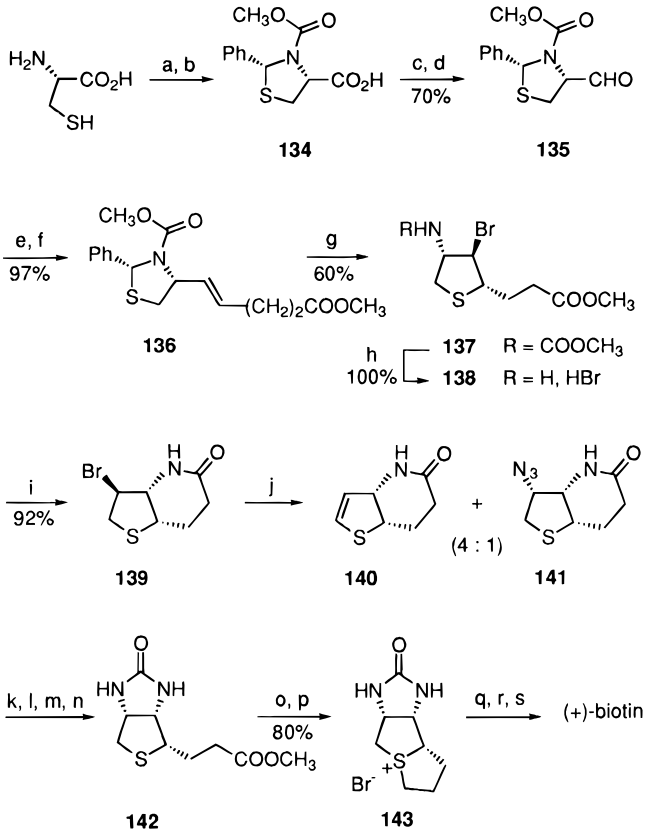
[a] Conditions: (a) DIBALH, $PhCH_3$; (b) *p*-TsOH, PhSH; (c) $tBuMe_2SiCl$, DBU, CH_2Cl_2; (d) $tBuMe_2SiOTf$ (cat.), *p*-NO_2PhCHO, CH_2Cl_2; (e) $Ph_3P{=}CHCH{=}CHCO_2Me$, CH_2Cl_2; (f) DBU, CH_2Cl_2; (g) H_2 (3 bar), Pd/C, MeOH.

zaldehyde to afford the tetrahydrothiophene **137** in 60% yield.



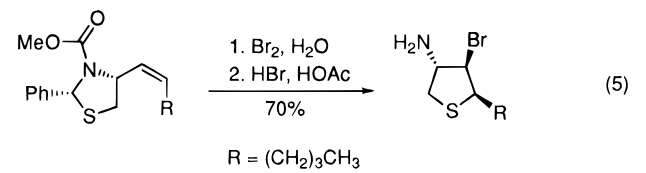
No other diastereomers were detected in the reaction mixture. After cleavage of the urethane grouping, the amino bromide **138** was obtained quantitatively. From **138**, the further conversion to biotin formally only necessitates the introduction of an amine at C-3 with inversion of configuration and completion of the side chain. Attempts to displace the bromide with excess of sodium azide produced, however, a *trans*-azide that resulted from the opening of an intermediate aziridine. However, when the amino bromide **138** was refluxed in acetic acid, an equilibrium was established between the two isomeric amino bromides that resulted from the bromide-induced aziridine opening. Owing to the length of the side chain at C-2, one of the amino bromides was removed from the equilibrium as it formed the crystalline *trans*-bromo lactam **139** in quantitative yield. When **139** was first reacted with sodium azide in dioxane/water, the corresponding azido lactam was produced but the displacement occurred with full retention at C-4. This presumably results from anchimeric assistance by sulfur in the bromide via an intermediate sulfonium cation. The desired S_N2 displacement became favored when the reaction was

Scheme 37[a]

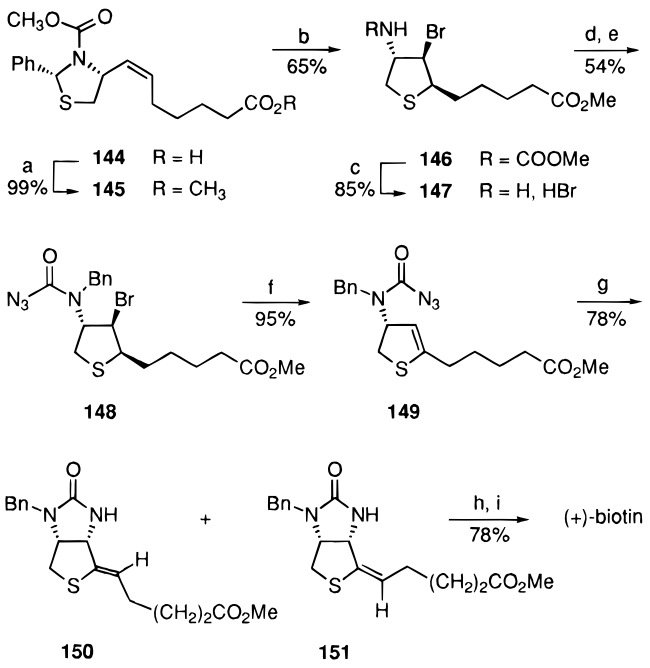


[a] Conditions: (a) PhCHO; (b) $ClCOOCH_3$; (c) BH_3, THF, 25 °C; (d) CrO_3·pyridine; (e) $ClMgCH{=}CH_2$, CH_2Cl_2, −70 °C; (f) $HC(OMe)_3$, CH_3CH_2COOH, PhH, 85 °C; (g) $C_5H_5NHBr{\cdot}Br_2$, CH_3OH; (h) HBr, HOAc, 25 °C, 20 h; (i) HOAc, reflux, 3 h; (j) LiN_3, DMF, 140 °C, 3.5 h; (k) catalytic hydrogenation; (l) $Ba(OH)_2$, reflux, 20 h; (m) $COCl_2$, $NaHCO_3$, H_2O; (n) CH_3OH, acid; (o) $LiBH_4$, THF, reflux; (p) HBr, HOAc, reflux; (q) $NaCH(COOEt)_2$, (r) $Ba(OH)_2$; (s) H_2O, reflux.

performed with lithium azide in a polar aprotic solvent. Under these conditions, however, in addition to to the desired **141**, the E2 elimination product **140** was formed as major reaction product. Eventual conversion of **141** into biotin necessitated an additional nine steps with a thiophanium bromide as an intermediate (see Scheme 1). The synthesis of the (*E*)-olefin **136** proceeded in six steps starting from L-cysteine. After condensation with benzaldehyde to the corresponding thiazolidine, the nitrogen was protected as methylurethane **134** and the carboxyl function converted to the corresponding aldehyde **135** via a reduction−oxidation sequence. Since this aldehyde is easily epimerized the subsequent transformations are performed on crude **135**. Reaction with a vinyl Grignard reagent and Claisen rearrangement of the resulting alcohol afforded the desired (*E*)-olefin in excellent yield. It is interesting to note here that the rearrangement occurring upon bromination of **136** is stereospecific. Indeed, when a (*Z*)-olefin was subjected to bromination followed by urethane cleavage, the corresponding *trans*-amino bromide was obtained (eq 5).

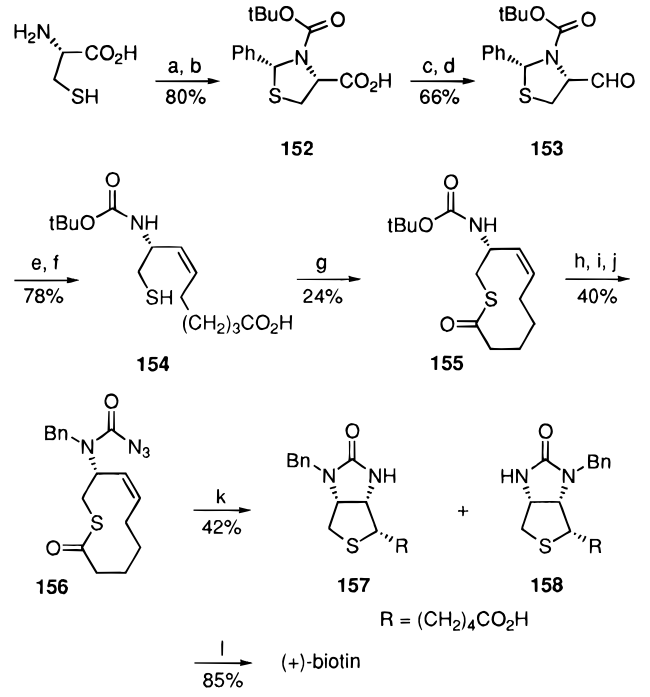


Scheme 38[a]



[a] Conditions: (a) CH_2N_2, Et_2O, 0 °C; (b) Br_2, $CHCl_3$, H_2O, rt; (c) HBr, HOAc; (d) PhCHO, $NaCNBH_3$, THF, H_2O, rt; (e) $COCl_2$, DBU, CH_2Cl_2, 0 °C; NaN_3, acetone/H_2O, rt; (f) DBU, THF, reflux; (g) autoclave, CH_2Cl_2, 150 °C, 3 h; (h) H_2 (4 bar), $Pd(OH)_2/C$, EtOAc, rt; (i) HBr (48%), reflux.

Scheme 39[a]

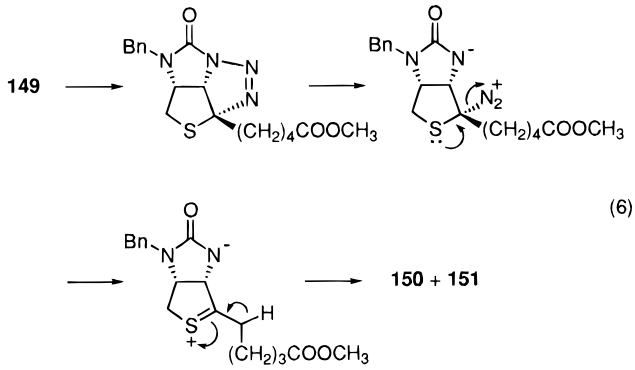


[a] Conditions: (a) PhCHO, KOAc, H_2O, EtOH, rt; (b) $(Boc)_2O$, NaOH, H_2O, dioxane; (c) Me_2S/BH_3, THF; (d) $(COCl)_2$, DMSO, −60 °C, Et_3N; (e) $[Ph_3P(CH_2)_5COOH]Br$, 2 equiv of LDA, THF, rt, 1 h; (f) Na, liq NH_3; H_3O^+; (g) $PhOP(O)Cl_2$/DMF, CH_2Cl_2, rt; (h) HCl, Et_2O, 0 °C; (i) PhCHO, $NaCNBH_3$, THF/H_2O (pH = 4), 0 °C; (j) $COCl_2$, DBU; NaN_3, acetone/H_2, rt; (k) H_2O, autoclave, 145 °C, 2 h; (l) HBr (48%), reflux, 2 h.

In the context of the Hoffmann-La Roche strategy, such a thiophane intermediate with inverted configuration at C-2 was useless. The finding, however, provided an important clue in the context of the next synthesis of biotin to be discussed.

In 1993 and 1994, De Clercq and Deroose described two different approaches of biotin that both rested on a thermal intramolecular 1,3-dipolar cycloaddition of a carbamoyl azide to an alkene.[72−74] The approach described in Scheme 38 fully takes advantage of the stereochemical outcome of the above discussed rearrangement.[72] Indeed, when the methyl ester **145** was brominated in the presence of water, bromide **146** was obtained as the sole isomer. The amino group in **146** was further converted into the benzylated carbamoyl azide **148** via cleavage of the urethane to yield **147**, followed by N-benzylation via reductive amination, and introduction of the acylazide group. When bromide **148** was treated with DBU, the expected E2 elimination product **149** was obtained in excellent yield. The projected intramolecular 1,3-dipolar cycloaddition was effected by treatment of **149** at high temperature in an autoclave. This led to a mixture of (*E*)-and (*Z*)-exocyclic olefins **150** and **151** that was further converted into biotin in the usual way.

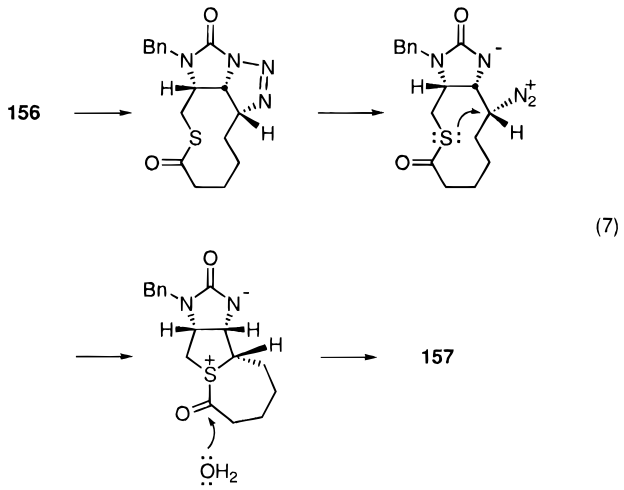
This rather unconventional reaction of **149** presumably involves formation of a triazoline and fragmentation to a betaine intermediate where sulfur-assisted nitrogen expulsion is followed by proton elimination to yield the mixture of olefins (eq 6).



(6)

The second approach involved the intramolecular cycloaddition of the benzylated carbamoyl azide **156** (Scheme 39).[73] When this reaction was effected in water as solvent at 145 °C (autoclave), a mixture of the two monobenzylated forms of biotin, **157** and **158**, was directly obtained. The mechanism of this transformation would involve formation of a triazoline, subsequent fragmentation to yield a betaine, nitrogen expulsion with assistance of the proximal sulfur with the concomitant formation of a tricyclic sulfonium intermediate, and final nucleophilic attack of water to form the carboxylic side chain of biotin (eq 7).

The occurrence of the benzyl shift during the cyclization was fully unexpected and proved to involve an intramolecular process that did not occur when dichloromethane was used as the solvent. The obtention of the desired *all-cis* configuration as the sole isomer is dictated by the cyclic template. Indeed, a model study showed the unclosed derivative to lead to a useless imidazolidone instead.[74] The use of a ten-membered thiolactone ring is reminiscent of a previous Hoffmann-La Roche approach when a ten-membered lactam ring served the same purpose in yet another intramolecular 1,3-dipolar cycloaddition process (Scheme 32). The synthesis of the required ten-membered thiolactone, which combines a ther-

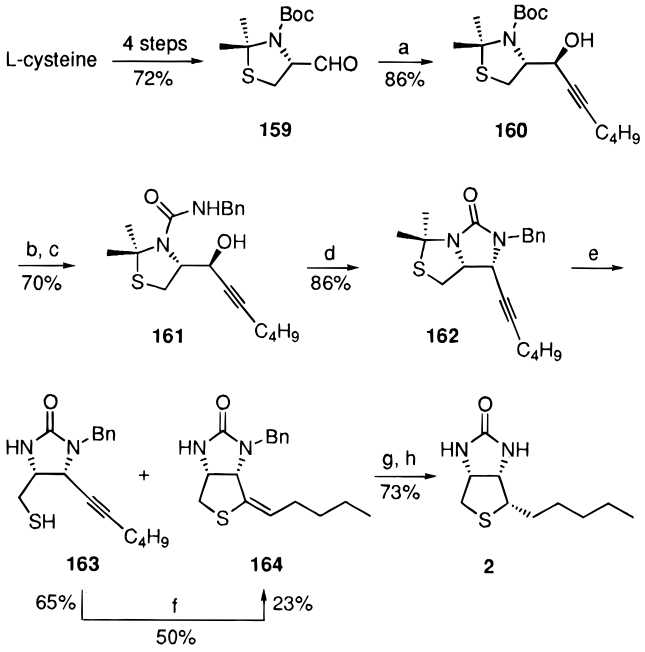


(7)

modynamically unstable ring size, and a kinetically unstable thioester function is the weak step in the synthesis. After considerable experimentation, it was found that when a solution of **154** and of pyridine in dichloromethane was added over a period of 6 h (syringe pump) to the in situ prepared phenyldichlorophosphate/DMF complex, a 24% yield of ring closed **155** was obtained. Further transformation of **155** into the cycloaddition precursor **156** involved hydrolysis of the *tert*-butylurethane to the amine and subsequent introduction of the carbamoyl azide grouping as before. The synthesis of the required (*Z*)-alkene proceeded via a sequence very similar to the one that Hoffmann-La Roche developed previously (see Scheme 37). Starting from L-cysteine, the thiazolidine is formed and the nitrogen protected as the *tert*-butylurethane. The choice of a *tert*-butyl rather than a methylurethane was dictated by its ease of removal. The (*Z*)-olefinic geometry was obtained exclusively when aldehyde **153**, obtained from **152** following a conventional reduction−oxidation sequence, was treated with the appropriate Wittig reagent. Generation of the required thiol acid for eventual cyclization was effected by reductive cleavage of the thiazolidine with sodium in liquid ammonia, which unfortunately also led to debenzylation.

Recently (1994), an interesting approach to (+)-deoxybiotin (**2**) was reported by Fujisawa and coworkers (see Scheme 40).[75] Central in the synthesis stands the diastereoface discrimination in the addition of an acetylide to chiral aldehyde **159**. The latter is obtained from L-cysteine via a known four-step sequence involving thiazolidine formation, *N*-urethane protection, esterification, and reduction with DIBALH.[76] When the chlorozinc acetylide derived from 1-hexyne was condensed with aldehyde **159**, the propargylic alcohol **160** was obtained as sole isomer in very good yield. The high selectivity is rationalized in terms of a chelation-control model in which the metal is chelated by the aldehyde and carbamate oxygens. This result constituted the reward of extensive experimentation where the influence of metal, solvent, additives, and substrate on yield and diastereoselectivity were thoroughly investigated. Introduction of the amino group at C-3 in the required configuration resulted from an internal S_N2 displacement via potassium hydride treatment of the tosylated alcohol **161**. The latter was obtained from

Scheme 40[a]

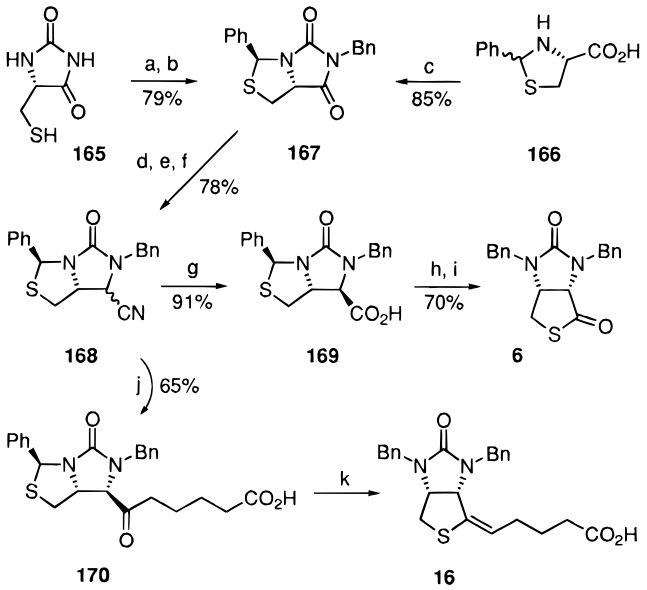


[a] Conditions: (a) $C_4H_9C{\equiv}CZnCl$, Et_2O, 10 h; (b) *p*-TsOH, MeOH, 35 °C, 11 h; (c) $PhCH_2NCO$, C_5H_5N, 0 °C; (d) KH (5 equiv), *p*-TsCl, HMPA (30 equiv), THF; (e) *p*-TsOH, MeOH/H_2O, 40 °C, 15 h (O_2-free!); (f) CsOH, H_2O/THF (10:1), 40 °C; (g) H_2 (10 bar), Pd/C, 2-propanol/H_2O (6:1), 40 °C; (h) HBr (47%), reflux.

160 after hydrolysis and formation of the mixed urea. Deprotection of the acetonide in **162** with 1 equiv of *p*-toluenesulfonic acid (*p*-TsOH) led to the cyclized thiophane **164** (23% yield) along with thiol **163** in 65% yield. The use of oxygen-free methanol and water as solvent system proved to be essential for reproducible results. Further cyclization of thiol **163** presented a regiochemical problem, since a six-membered isomer was formed in addition to desired **164**. Eventually, the best result was obtained when cyclization was effected with 2 equiv of cesium hydroxide in water/THF at 40 °C for 10 h. Even then, however, the six-membered isomer was produced in 46% yield. The final conversion of **164** into (+)-deoxybiotin further involved catalytic hydrogenation and debenzylation.

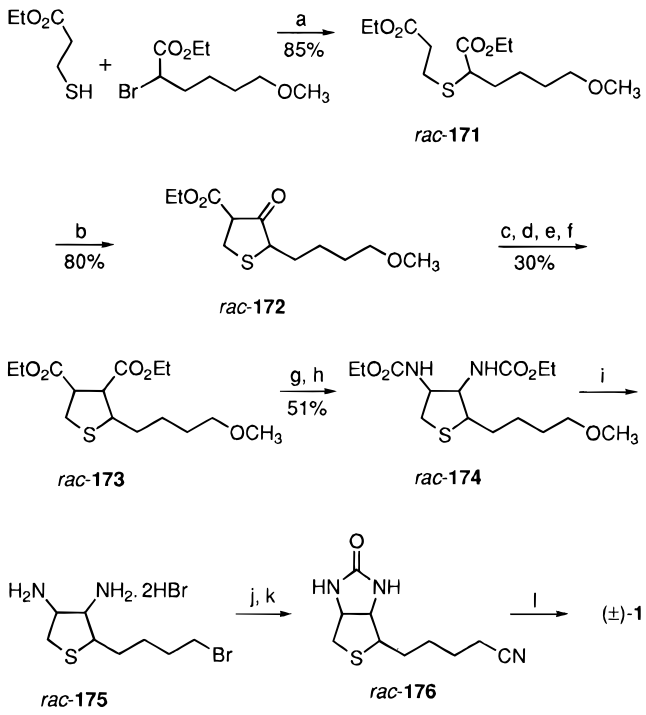
We will close this section with a biotin synthesis that was reported in 1987 by Poetsch and Casutt of the Merck Laboratories (Scheme 41).[77] Part of the work described in this scheme constitutes the shortest enantiospecific sequence to (+)-biotin that has been reported so far. The crucial intermediate in the synthesis is nitrile **168**. This is obtained from the bicyclic thiazolidine hydantoin **167** via selective reduction and cyanide introduction on the activated 1-(alkoxycarbonyl)imidazole derivative. The starting material **167** is obtained either from the readily available hydantoin **165**[78] or from the known thiazolidine **166**.[79] Two different routes were developed that allow the conversion of **168** into biotin. The direct Grignard reaction to **170** followed by reductive opening of the thiazolidine leads to an intermediate thiol that is cyclized using piperidine acetate/acetic acid to yield the known biotin precursor **16**. This nine-step sequence starting from L-cysteine is the shortest route that has been described in the nonpatent literature. Alternatively, nitrile **168** is converted to the thermodynamically more stable acid

Scheme 41[a]



[a] Conditions: (a) PhCHO, $POCl_3$, $PhCH_3$; (b) $PhCH_2Cl$, K_2CO_3, DMF; (c) $PhCH_2NCO$, acetone; HCl, CH_2Cl_2; (d) $NaBH_4$, THF/H_2O; (e) 1,1′-carbonyldiimidazole, THF; (f) Ch_3I, DMF; KCN, DMF; (g) KOH, EtOH, H_2O; (h) Zn, HOAc; (i) *N*,*N*′-dicyclohexylcarbodiimide, C_5H_5N, *p*-TsOH; (j) $Br(CH_2)_4Br$, Mg, THF; CO_2; HCl; (k) Zn, HOAc; piperidine, HOAc.

Scheme 42[a]



[a] Conditions: (a) NaOEt, EtOH, −20 °C; (b) NaOEt, EtOH; (c) KCN, ether, HCl; (d) HCl, H_2O, EtOH; (e) $CHCl_3$, C_5H_5N, $SOCl_2$, (f) HOAc, KI, Zn; (g) MeOH, NH_2NH_2/H_2O; (h) HCl, ether, $NaNO_2$; (i) HBr (48%), <123 °C; (j) NaOH, $COCl_2$; (k) EtOH, KCN; (l) NaOH, 70 °C.

that, after reductive cleavage to the corresponding thiol acid, is cyclized to thiolactone **6**.

C. Nonenantioselective Syntheses

1. The First Keto Thiophane Approaches

Shortly after the first reported synthesis of biotin (Scheme 31), a non-stereoselective approach toward *rac*-biotin was reported by Schnider, Bourquin, and Grüssner of the Hoffmann-La Roche Co. in Basel (Scheme 42).[80−82]

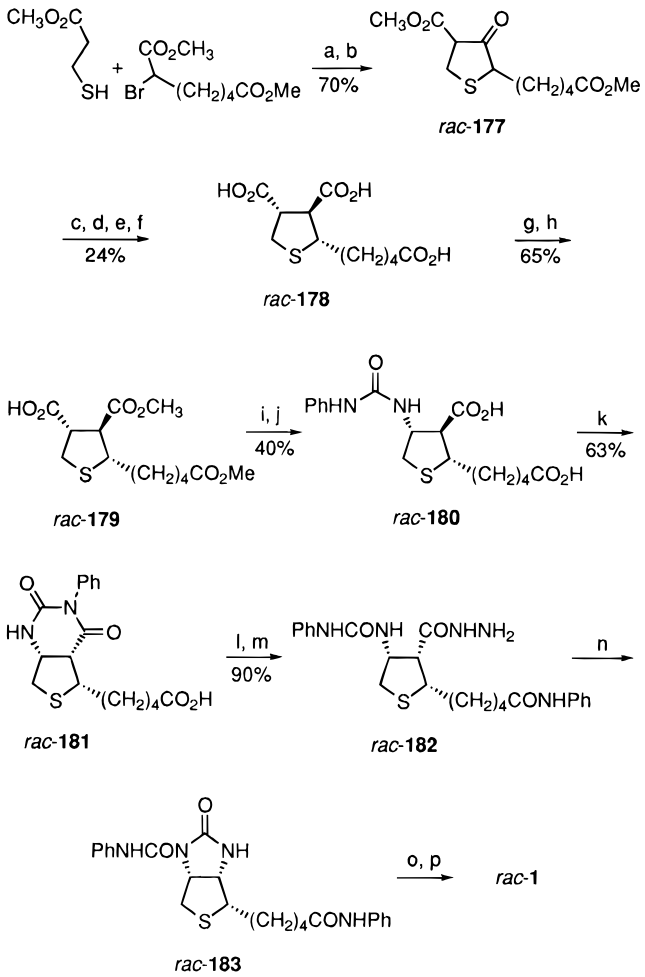
Central in the scheme stands the synthesis of diester **173** which is transformed into the diamino derivative **174** through a Curtius rearrangement sequence. After treatment of the solution with concentrated hydrobromic acid, the obtained diamino bromide **175** is converted into biotin via a sequence involving cyclic urea formation, sodium cyanide substitution, and basic hydrolysis. The synthesis is, however, not stereoselective. Three diastereomers were present at the stage of **173**. The separation into three separate series further occurred at the stage of the intermediate hydrazides and that of **174**. The diester **173** was obtained starting from the thiophanone **172**. The latter was obtained via the previously studied Dieckmann condensation of diester **171**.[83]

The same basic strategy was applied in 1947 by Baker and co-workers from the Lederle Laboratories (Pearl River, NY), but adapted in such a way as to lead stereoselectively to *rac*-biotin (Scheme 43).[84−89] Starting from pimelic acid, the average yield of *rac*-biotin was on the order of 1.7%. In the first stage, the 2-substituted-4-(methoxycarbonyl)-3-oxothiophane **177**, which is obtained via a two-step sequence involving substitution of 2-bromopimelate followed by Dieckmann condensation, is converted to the *all-trans* triacid **178**. This four-step sequence involves formation of an intermediate cyanohydrin with liquid hydrogen cyanide, dehydration with phosphorous oxychloride to double bond isomers, acid hydrolysis to the unsaturated triacid, and smooth reduction with sodium amalgam. In the second and crucial stage of the synthesis, the *trans*-dicarboxythiophane **178** is converted stereoselectively into the *cis*-diamino compound **183** through stepwise fragmentation. After triester formation and partial saponification to acid **179**, the latter was degraded by treating its acid chloride with sodium azide, and the intermediate acyl azide was rearranged to the isocyanate and condensed with aniline to form **180**. When a solution of **180** was refluxed with acetic anhydride and sodium acetate, followed by hydrolysis of the acetyl group with dilute hydrochloric acid, the *cis*-uracil **181** was obtained. When the latter was treated with hydrazine, the expected ring cleavage occurred with partial inversion to a mixture of *cis*- and *trans*-hydrazides. When the carboxyl group of **181** was blocked by conversion to its anilide, then hydrazine smoothly opened the ring in 95% yield to the insoluble *cis*-hydrazide **182**. When the diazotization of the latter was run at 100 °C with butyl nitrite in dry butanol containing hydrogen chloride, a 55% yield of the imidazolone **183** was obtained. Final hydrolysis and treatment of the resulting diamine with phosgene gave *rac*-biotin.

2. Involving Catalytic Hydrogenation at C-3 and C-4

Within the same context and in the same period, Cheney and Piening at Parke, Davis, and Co. described in 1945 the approach shown in Scheme 44.[90,91] Central in the synthesis stands the aromatization of a 2-substituted-4-(alkoxycarbonyl)-3-oxothiophane such as **184** upon treatment with hydroxylamine, followed by acid hydrolysis. A sequence involving a rearrangement further converts **185** into the protected

Scheme 43[a]



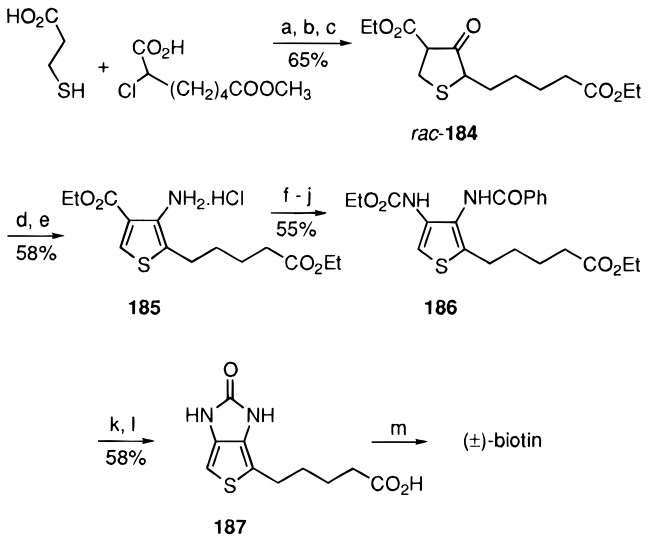
[a] Conditions: (a) CH_3OH, $NaOCH_3$, −20 °C; (b) $NaOCH_3$, PhH, 25 °C; (c) HCN, KOH; (d) $POCl_3$, PhH; (e) HOAc, HCl, reflux; (f) Na(Hg); (g) CH_3OH, $CHCl_3$, H_2SO_4; (h) CH_3OH, NaOH; (i) $SOCl_2$, PhH; NaN_3, $PhNH_2$; (j) NaOH, reflux; (k) NaOAc, Ac_2O; HCl, reflux; (l) $SOCl_2$, $C_5H_5N/PhNH_2$, ether; (m) $NH_2NH_2{\cdot}H_2O$; (n) nBuOH, HCl, BuONO; (o) MeOH, $Ba(OH)_2$; (p) K_2CO_3, $COCl_2$.

diamino thiophene derivative **186**. After the solution was subjected to deprotection and phosgene treatment, 2,3,4,5-tetradehydrobiotin **187** is obtained.

In view of the known resistance of thiophenes toward catalytic hydrogenation, quite drastic conditions had to be developed. The use of metal sulfides as catalyst for performing the hydrogenation of **187** to *rac*-biotin (high temperatures and under high pressure) was claimed by Cheney already in 1945.[92]

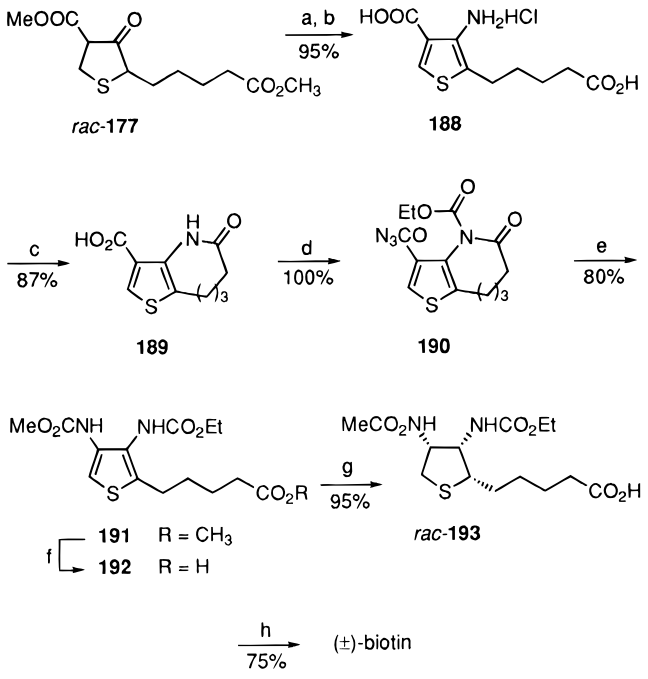
The same basic approach has been revisited in 1976 by Confalone and co-workers at Hoffmann-La Roche (Scheme 45).[93] They made the important discovery that thiophane diurethane **192** could be converted in excellent yield (>95%) to the corresponding *all-cis* acid **193**. Final treatment of this bisurethane with barium hydroxide at 100 °C led directly to biotin, obviating the need for a subsequent phosgene step. No previous approaches had explored the use of a 3,4-diurethane to fulfill the dual role of a protecting group for nitrogen and of a precusor for the imidazolidone moiety. The synthesis starts from the known keto diester **177** that is aromatized by acid treatment of the derived oxime. Differentiation of the two acid functions in **188** was achieved by smooth ring closure to the eight-membered lactone **189**. The latter was next converted to acyl azide **190** via mixed

Scheme 44[a]



[a] Conditions: (a) NaOH, H_2O; (b) EtOH, H_2SO_4, reflux; (c) NaOEt, PhH; (d) $NH_2OH{\cdot}HCl$, EtOH; (e) HCl, ether; (f) KOH, EtOH; (g) $PhCOCl$, $PhNMe_2$, $CHCl_3$; (h) NH_2NH_2, KOEt, EtOH, PhH; (i) $NaNO_2$, HOAc, HCl; (j) EtOH, reflux; (k) KOH, MeOH, reflux; (l) $COCl_2$, (m) H_2, MoS_3/alumina gel, dioxane, 200 °C, P > 50 atm.

Scheme 45[a]

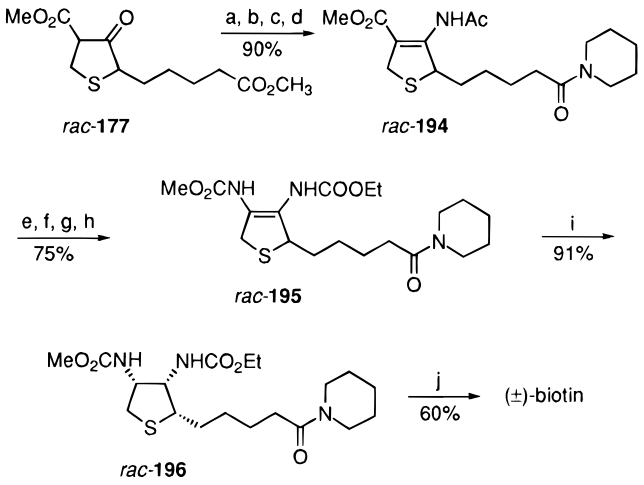


[a] Conditions: (a) NH_2OH, C_5H_5N, rt; (b) HCl, ether; (c) xylene, reflux; (d) ClCOOEt (2 equiv); NaN_3; (e) CH_3OH, reflux; (f) NaOH/H_2O; (g) H_2 (1800 psi), Pd/C (10%), HOAc, 50 °C, 10 h; (h) $Ba(OH)_2$, H_2O, reflux

anhydride formation. In this step, the cyclic lactam nitrogen was converted to a urethane. When derivative **190** was heated in methanol under reflux, diurethane **191** was obtained, a result of the expected Curtius rearrangement of the acyl azide and of selective methanolysis of the imide function at the more strained lactam carbonyl. After mild basic treatment, the methyl ester was converted to acid **192**, the substrate for catalytic hydrogenation.

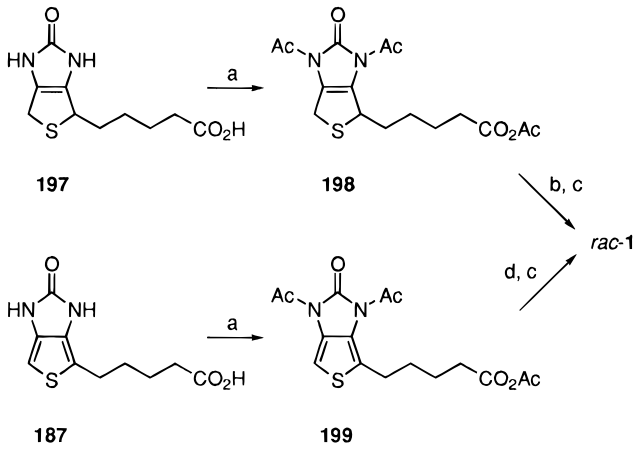
In a similar vein, Confalone and co-workers reported the approach shown in Scheme 46.[94] Here, the desired *all-cis* configuration results from the catalytic hydrogenation of the protected 3,4-diamino-

Scheme 46[a]



[a] Conditions: (a) $HCOONH_4$, EtOH, reflux; (b) NaOH, AcOH, reflux; (c) ClCOOEt, THF, Et_3N; piperidine; (d) Ac_2O, $HClO_4$; (e) MeOH, NaOH; (f) ClCOOEt, acetone/H_2O, Et_3N; NaN_3; (g) MeOH, reflux; (h) NaOH, THF; (i) H_2 (1800 psi), Pd/C (10%), HOAc, 50 °C; (j) NaOH.

Scheme 47[a]

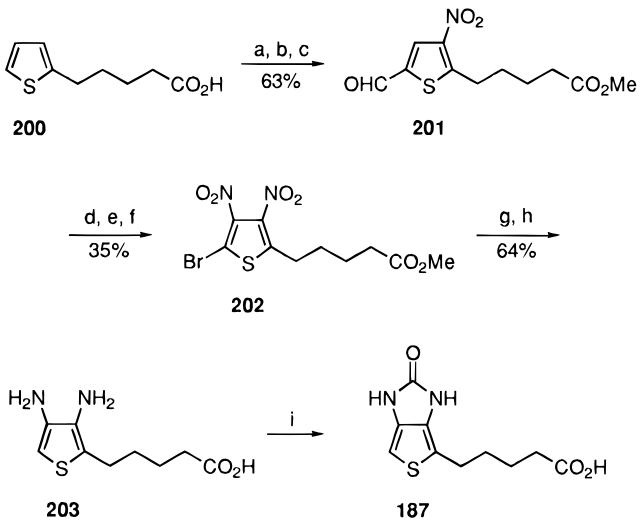


[a] Conditions: (a) $(CH_3CO)_2O$, 115 °C; (b) H_2 (>60 psi), Pd/C, HOAc, 85 °C; or Et_3SiH, acid; (c) NaOH; (d) H_2 (>550 psi), Pd/C, $(CH_3CO)_2O$, 85 °C.

2,5-dihydrothiophene derivative **195**. First, the same keto diester **177** is converted into the corresponding dihydrothiophene derivative **194**. This sequence involves formation of an enamine diester, selective conversion of the side chain methyl ester into a piperidide and acylation of the amino group. The further transformation of **194** involves a Curtius rearrangement sequence to yield after deacylation the stable diurethane **195**. Catalytic hydrogenation of the latter occurred smoothly under conditions which had no effect upon similarly substituted thiophenes, and the desired *all-cis* tetrahydrothiophene **196** was obtained in high yield. Finally, basic hydrolysis of **196** led directly to *rac*-biotin.

In the context of the discovery that the catalytic hydrogenation of imidazolone derivatives occurs much more readily when both nitrogens are derivatized, Vasilevskis of Hoffmann-La Roche claimed that both 2,3,4,5-tetradehydrobiotin (**187**) and 2,5-didehydrobiotin (**197**) can be reduced under classical hydrogenation conditions with the substantial absence of sulfur poisoning if they are diacylated prior to hydrogenation (Scheme 47).[95] It is interesting to mention that this "dearomatization" effect enabling

Scheme 48[a]



[a] Conditions: (a) MeOH, HCl, reflux; (b) $POCl_3$, DMF, 100 °C; (c) HNO_3, H_2SO_4; (d) $KMnO_4$; (e) KOH, $AgNO_3$; Br_2, CCl_4, reflux; (f) HNO_3, H_2SO_4; (g) HCl, HOAc, reflux; (h) Sn, HCl; (i) $COCl_2$, NaOH.

smooth catalytic reduction caused by the presence of acetyl groups had been reported before (1948) in the context of biotin synthesis.[96] Finally, it should be mentioned that the low-yield (10%) ionic hydrogenation (triethylsilane/trifluoroacetic acid) of **187** to *rac*-biotin was reported in the same period (1975) by Russian chemists.[97]

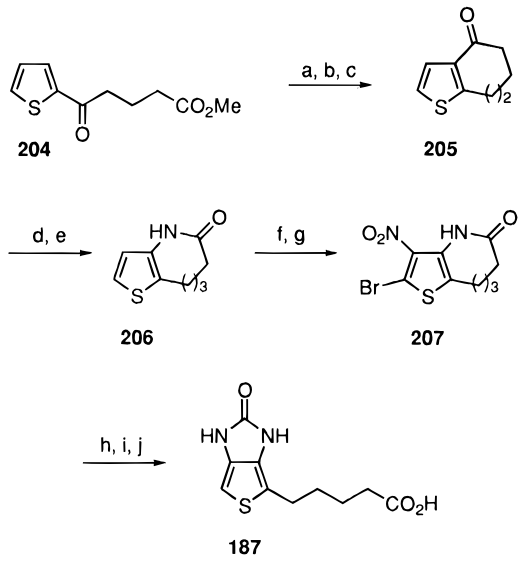
In the following, more approaches are discussed that have led to tetradehydrobiotin and, which in view of the findings mentioned above, constitute formal total syntheses of *rac*-biotin.

The approach followed by Nishimura and Imoto (1962) requires the introduction of two amino groups in the 3- and 4-positions of a 2-alkyl-substituted thiophene nucleus, i.e., **200** to **203** (Scheme 48).[98] An eight-step sequence was developed whereby the formyl group in **201**, necessary for the introduction of the first nitro group at C-3, was subsequently transformed, via Hunsdiecker reaction of the corresponding acid, into a bromo substituent necessary for the introduction of the second nitro group in **202**. Treatment of the acid, obtained from **202**, with tin and hydrochloric acid led to unstable **203** that was further converted to **187**. The alkylated thiophene **200** is obtained from the corresponding acylated derivative **204**, the starting material of the next synthesis.

In the approach of Fabrichnyi and co-workers (1965), the lactam **206** is transformed into **187** via a sequence similar to the one previously discussed (Scheme 49).[99] The lactam originates from a Beckmann rearrangement sequence performed on ketone **205**.

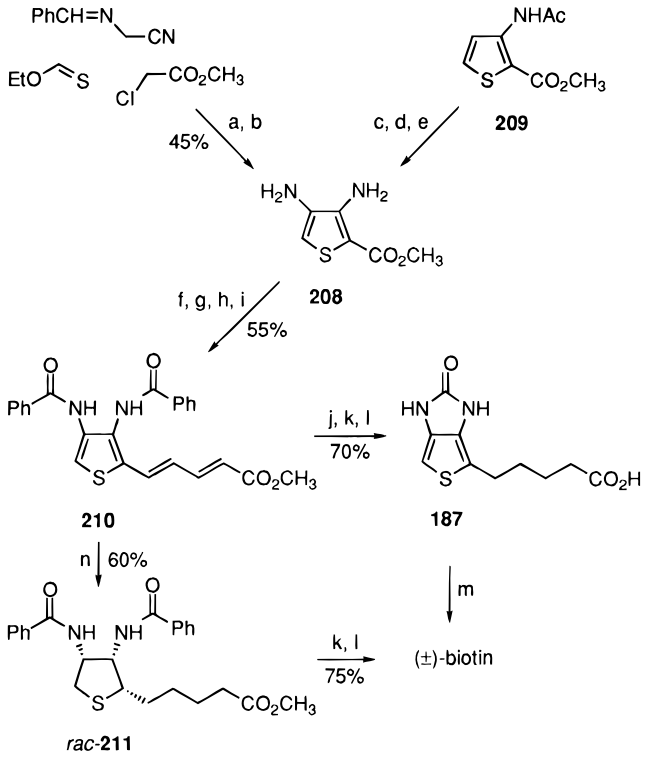
In the thiophene approach of Rossy, Vogel, and coworkers (BASF AG), the N-acylated 3,4-diamino thiophane **210** stands central (Scheme 50).[100] Similar to the above methods the acylated derivative is reduced directly to the *all-cis* derivative **211** in 60% yield using palladium on carbon at 90 bar (100 °C) in acetic acid. Final saponification of **211** followed by phosgene treatment led to *rac*-biotin. Alternatively, **210** can be converted to **187**, the reduction of which has been described before. The important

Scheme 49[a]



[a] Conditions: (a) N_2H_4, KOH; (b) $SOCl_2$; (c) $SnCl_4$; (d) NH_2OH; (e) $PhSO_2Cl$, C_5H_5N; KOAc, H_2O/EtOH, reflux; (f) Br_2; (g) HNO_3; (h) HCl, (i) Sn, HCl; (j) $COCl_2$.

Scheme 50[a]

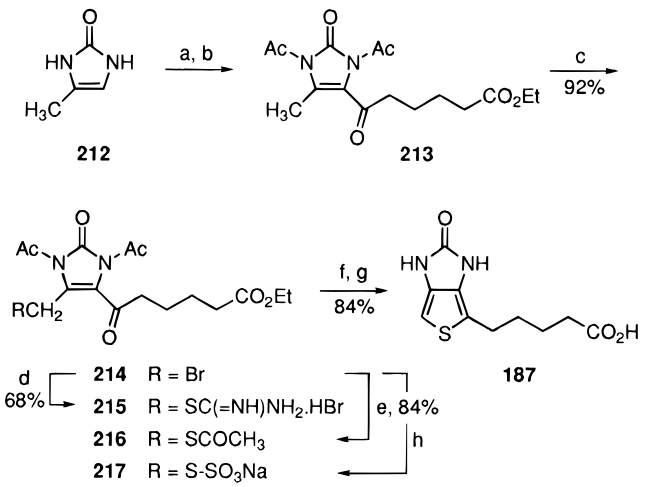


[a] Conditions: (a) NaH, THF; $ClCH_2COOMe$; (b) HCl, H_2O/ether; (c) HNO_3/H_2SO_4, −30 °C; (d) NaOMe, MeOH; (e) H_2; (f) PhCOCl, C_5H_5N, $CHCl_3$; (g) $LiAlH_4$, THF, 0 °C; (h) PCC, CH_2Cl_2; (i) $Ph_3P{=}CHCH{=}CHCOOCH_3$, $PhCH_3$; (j) H_2, Pd/C; (k) $Ba(OH)_2$, H_2O; (l) $COCl_2$; (m) for the hydrogenation of the N-acylated derivative; see Scheme 47; (n) H_2 (90 bar), Pd/C, 100 °C, HOAc. PCC = pyridinium chlorochromate.

intermediate **210** is obtained from the 3,4-diamino thiophene ester **208** via a classical four-step sequence. The latter can be obtained either via a condensation involving benzylidineaminoacetonitrile, ethyl thioformate, and methyl chloroacetate or via a more conventional approach starting from thiophene ester **209**.

4-Methyl-2-imidazolone (**212**) has also served as starting material in a sequence that leads to **187**

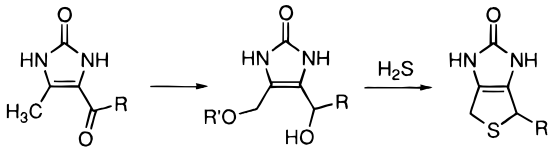
Scheme 51[a]



[a] Conditions: (a) Ac_2O; (b) $ClCO(CH_2)_4COOEt$, $AlCl_3$, sulfolane, $CHCl_3$; (c) NBS, CCl_4, reflux; (d) $(H_2N)_2C{=}S$; (e) CH_3COSH, Et_3N, CH_3CN; (f) NaOH, H_2O; (g) HCl, H_2O; (h) $Na_2SSO_3{\cdot}(H_2O)_5$, CH_3CN, rt.

(Scheme 51). Interestingly, it originates from early work by Duchinsky and Dolan at Hoffmann-La Roche in 1948 who developed a synthesis of imidazolones structurally related to biotin.[96] Bromination of **213** according to Ziegler led to bromide **214** in high yield. The acylated imidazolone derivative **213** was obtained from **212** via consecutive acetylation and acylation steps. Substitution of the bromide by various nucleophiles was extensively studied, and the conversion of **214** to **215** by treatment with thiourea was described. However, the use of these results in the context of a biotin synthesis was eventually described by other groups.

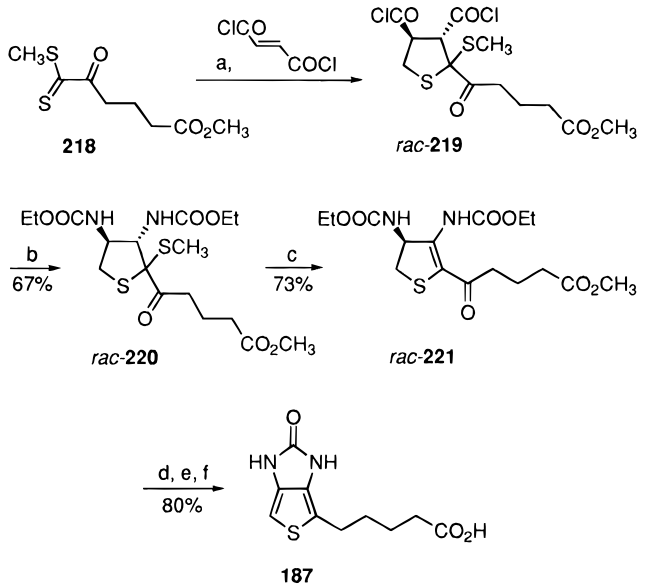
Isaka and co-workers first reported in 1968 the formation of a cyclization product from **215** but misassigned the structure.[101] In 1973, Zav'yalov and co-workers correctly identified **187** as the product resulting from successive base and acid treatment of **215** or **216**.[102] At about the same time, a Japanese group reported the same sequence wherein the thioester **216** was cyclized.[103] It is interesting to note that more recently the use of the Bunte salt **217** in the same sequence has been claimed.[104] The formation of the didehydro derivative along similar lines has also been claimed (eq 8).[105]



(8)

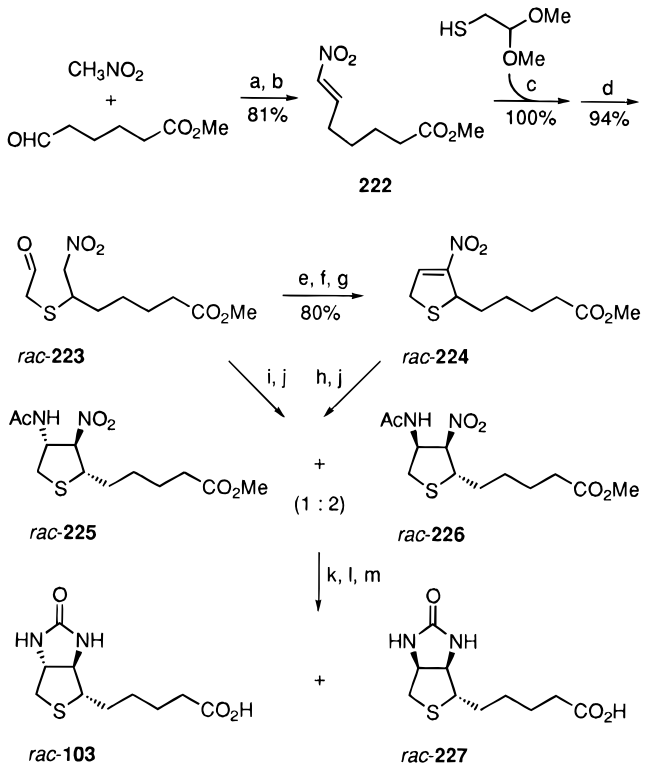
More recently Morán and co-workers described a quite elaborate scheme for the synthesis of thiophene **187** (Scheme 52).[106] First, the thiophane nucleus is assembled through a [3 + 2] cycloaddition between a thiocarbonyl ylide and fumaroyl dichloride as dipolarophile. The ylide dipole is generated upon loss of nitrogen from the intermediate thiadiazoline that is obtained from the reaction of diazomethane with the α-keto dithioester **218**.[107] Treatment of **219** with hydrazoic acid and ethanol leads to the *trans*-3,4-diurethane **220**. In a further four-step sequence, the latter is converted to **187**.

Scheme 52[a]



[a] Conditions: (a) CH_2N_2, hexane/CH_2Cl_2, −90 °C; (b) HN_3, $CHCl_3$, C_5H_5N; EtOH; (c) H_2SO_4/P_2O_5, CH_2Cl_2; (d) $NaBH_4$, THF; (e) CH_3SO_2Cl, C_5H_5N; (f) KOH, MeOH.

Scheme 53[a]

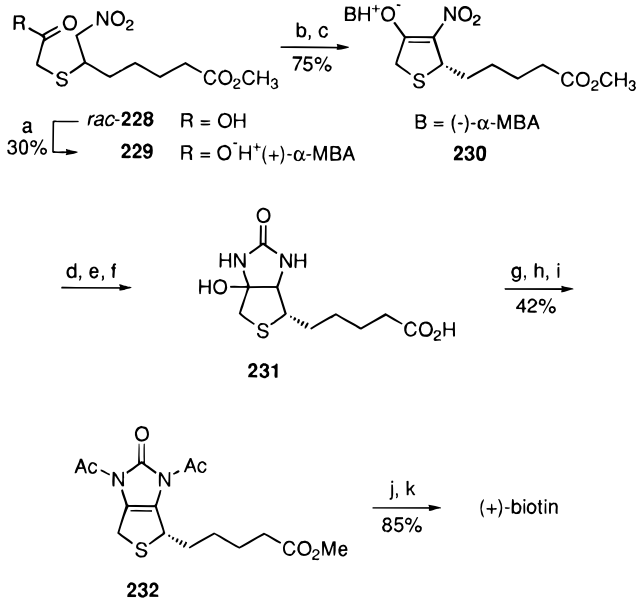


[a] Conditions: (a) NaOH, MeOH, 20 °C, 14 h; (b) CH_3COCl; (c) NaOMe, RSH; (d) HCl, dioxane/H_2O; (e) NaOMe; (f) CH_3COCl; (g) $KHCO_3$, ether; (h) dioxane, NH_3; (i) NH_3, autoclave, 30 °C, 20 h; (j) HOAc, Ac_2O, 75 °C; (k) Al, Hg; (l) $Ba(OH)_2$; (m) $COCl_2$.

In the following, a few syntheses are grouped that have in common the formation of the bond between C-3 and C-4 via a condensation reaction involving a nitro derivative.

The early approach of Grob and von Sprecher (1952) is rather straightforward in concept but did not lead to the correct biotin stereoisomer (Scheme 53).[108] Central in the approach stands the conjugate addition of ammonia to the unsaturated nitro derivative **224**. After acetylation, the two diastereoisomers

Scheme 54[a]



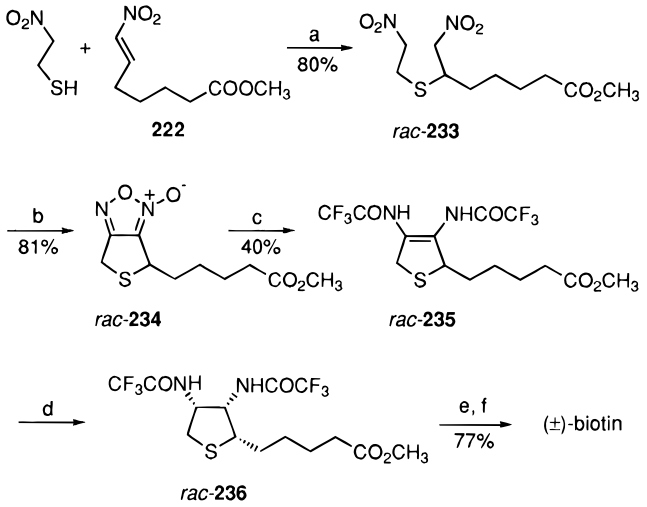
[a] Conditions: (a) (+)-α-methylbenzylamine ((+)-α-MBA), EtOAc; 30% yield, >97% ee after recrystallization; (b) dicyclohexylamine; (c) PhOH, $SOCl_2$, pyridine (cat.); (−)-α-methylbenzylamine, EtOAc; (d) Pd/C (10%), HOAc/HCl; (e) KNCO, H_2O; (f) NaOH; (g) HOAc, stripping at 55 °C; (h) MeOH, H^+, (i) Ac_2O, 110 °C; (j) H_2 (550 psi), 5% Pd/C (10% loading), Ac_2O, 85 °C; (k) NaOH, CH_3OH.

225 and **226** are obtained in high yield (ratio 1:2, respectively). Further reduction, base treatment, and reaction with phosgene led to the two biotin diastereomers **103** and **227**. The unsaturated nitro derivative **224** results from the condensation reaction of nitro aldehyde **223**. The latter is the result of a thiolate addition reaction to the unsaturated nitro ester **222**.

The approach of Field and co-workers at Hoffmann-La Roche (1978) presents several interesting aspects (Scheme 54).[109] It involves the synthesis of the bicyclic dihydrothiophene derivative **232** in homochiral form, followed by catalytic hydrogenation at moderate hydrogen pressure (see Scheme 47). The enantioselectivity in the sequence is the result of an early resolution of the α-nitro ketone (cf. **230**) or even earlier in the sequence of the acid **228**. As in the previous synthesis the first step involves a conjugate thiol addition, here thioglycolic acid, to the unsaturated nitro ester **222**. A salt of the (*S*)-enantiomer of **228** is obtained by treatment with (+)-α-methylbenzylamine (MBA). This salt is converted into the more stable dicyclohexylamine salt, which is converted to the phenol ester in 95% yield. When this ester is treated with (−)-α-methylbenzylamine in ethyl acetate **230** as (−)-α-MBA salt is obtained. The construction of the imidazolone ring of **232** further involves a six-step sequence. After low-pressure hydrogenation of the nitro group, the resulting amino ketone is treated with aqueous potassium cyanate and after acidification alcohol **231** is obtained. Dehydration is effected in acetic acid. Finally, esterification and acetylation yields **232**.

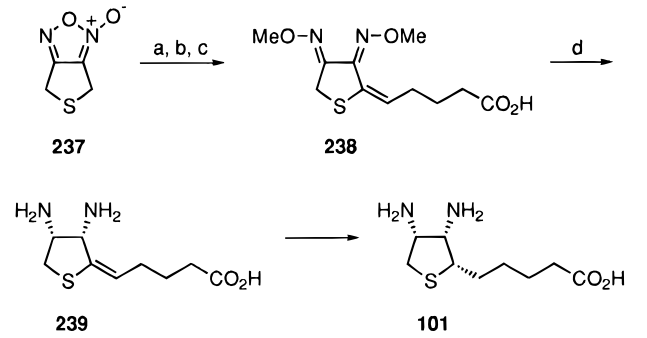
In 1977, Marx and co-workers at Synthex Research, Palo Alto, CA, reported a very short approach to *rac*-biotin in which dihydrothiophene **235** was hydrogenated using Pearlman's catalyst (Scheme 55).[110] With conventional palladium catalysts, no

Scheme 55[a]



[a] Conditions: (a) MeOH, 20 °C; (b) $POCl_3$, Et_3N, $CHCl_3$; (c) Zn/Ag, DME, $(CF_3CO)_2O$; (d) H_2 (60 psi), $Pd(OH)_2/C$ (20%), MeOH; (e) K_2CO_3, MeOH, H_2O; (f) $COCl_2$, PhH.

Scheme 56[a]



[a] Conditions: (a) LDA, $OHC(CH_2)_3CO_2H$; (b) PhNHNHPh; (c) methylation; (d) BH_3/THF, norephedrine. LDA = lithium diisopropylamide.

reduction of **235** was observed at moderate hydrogen pressures. The obtained *all-cis* derivative **236** was readily converted into *rac*-biotin (77% overall yield from **235**). The synthesis of the important intermediate **235** involved the formation of the novel thienofuroxan ring system **234** via intramolecular dimerization of a bis-nitrile oxide obtained from the dinitro ester **233**. Treatment of furoxan **234** with a zinc/silver couple in dimethoxyethane/trifluoroacetic anhydride led to the acylated enediamine **235** as unusual reduction product. The starting ester **233** resulted from the conjugate addition of 2-nitroethanethiol to nitro olefin **222**. The latter was obtained via a sequence involving condensation of methyl 6-oxohexanoate with nitromethane to the nitro alcohol followed by elimination via the acetate.

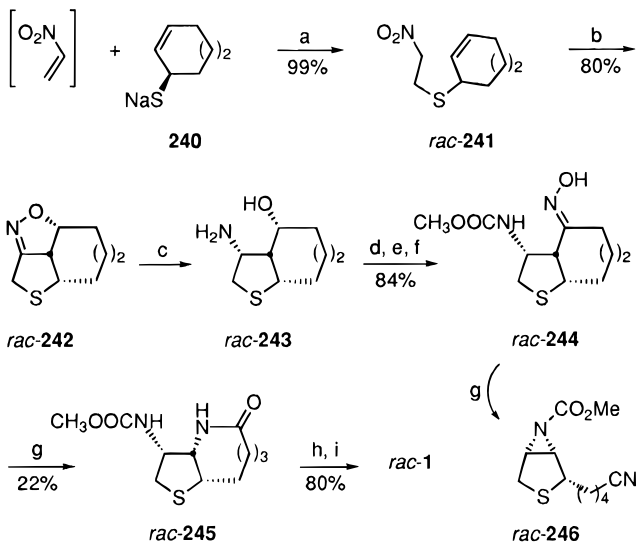
In the same context, quite recently an interesting enantioselective synthesis of (+)-biotin has been claimed by Kurimoto and co-workers of the Sumitomo Chemical Co.[111] Starting from **237**, the carboxybutyl chain is introduced via condensation with 5-oxopentanoic acid. After reduction of the furoxan ring with hydrazobenzene and methylation, acid **238** is obtained. When the latter is reduced with borane·tetrahydrofuran in the presence of norephedrine the *cis*-3,4-diamino derivative **239** is formed, which is, via **101**, a known precursor of (+)-biotin.

3. Involving a Pericyclic Key Step

In this last section, those remaining syntheses that lead to *rac*-biotin and use a pericyclic process as a key step are grouped.

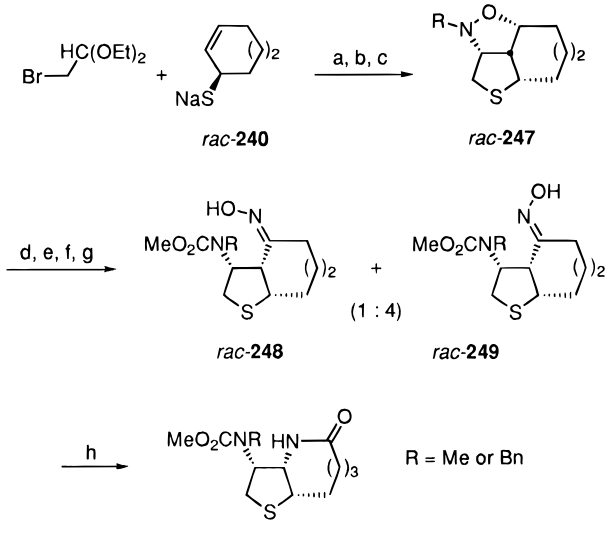
The scientists from Hoffmann-La Roche also contributed to the area in this section. Confalone and co-workers described two approaches that are based on the construction of the thiophane nucleus with obtention of the required *all-cis* configuration using an intramolecular [3 + 2] cycloaddition strategy (Schemes 57 and 58).[112,113] The starting material for both syntheses is **240**, the sodium salt of cycloheptenethiol. This reactive mercaptide is obtained via a sequence involving allylic bromination of cycloheptene with *N*-bromosuccinimide (NBS), subsequent reaction with thiolacetic acid, and final treatment

Scheme 57[a]



[a] Conditions: (a) $NO_2CH_2CH_2OAc$, EtOH, 0 °C, 3 h; (b) PhNCO, PhH, Et_3N (cat.), 25 °C, 24 h; (c) $LiAlH_4$, Et_2O, reflux, 4 h; (d) CH_3OH, CH_3OCOCl, 10% $NaHCO_3$, 25 °C, 0.5 h; (e) Me_2SO/Ac_2O (3:2), 25 °C, 18 h; (f) $EtOH/C_5H_5N$ (25:1), NH_2OH/HCl, reflux, 0.5 h; (g) PPA, 100 °C, 15′; (h) $Ba(OH)_2$, H_2O, reflux, 20 h; (i) $COCl_2$, 0 °C. PPA = poly(phosphoric acid).

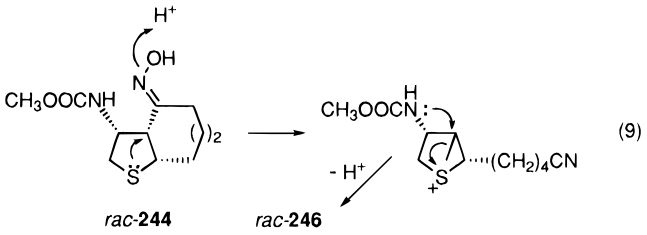
Scheme 58[a]



[a] Conditions: (a) $BrCH_2CH(OEt)_2$; (b) H_3O^+; (c) MeNHOH; (d) Zn/HOAc/H_2O; (e) ClCOOMe; (f) DMSO/Ac_2O; (g) NH_2OH; (h) PPA, 100 °C.

with sodium ethoxide. Treatment of **240** with 1-nitro-2-acetoxyethane generates presumably nitroethylene and the mercaptan, which undergoes a Michael reaction to yield nitro olefin **241**.[112] Treatment of this nitro compound with phenyl isocyanate led directly and stereoselectively to the tricyclic adduct **242**. This process involves a key intramolecular [3 + 2] cycloaddition reaction of an intermediate nitrile oxide. Two of the three ultimate stereocenters of biotin are created in this step. The third is generated in the desired *cis* configuration via lithium aluminum hydride reduction which occurs from the less-hindered convex side of the cup-shaped molecule. Concomitantly, the N−O bond is cleaved. The molecule is next set up for a Beckmann rearrangement that will eventually produce the 3-amino group in the required configuration. After protection of the amine in **243**, the alcohol is oxidized and converted to oxime **244** which possesses the required *anti* configuration for the subsequent rearrangement. The latter is effected in acid medium but leads to the expected **245** in a low 22% yield.

A competing and facile fragmentation was found to yield aziridine **246**, a process in which formation of a transient episulfonium cation is very probable (eq 9).

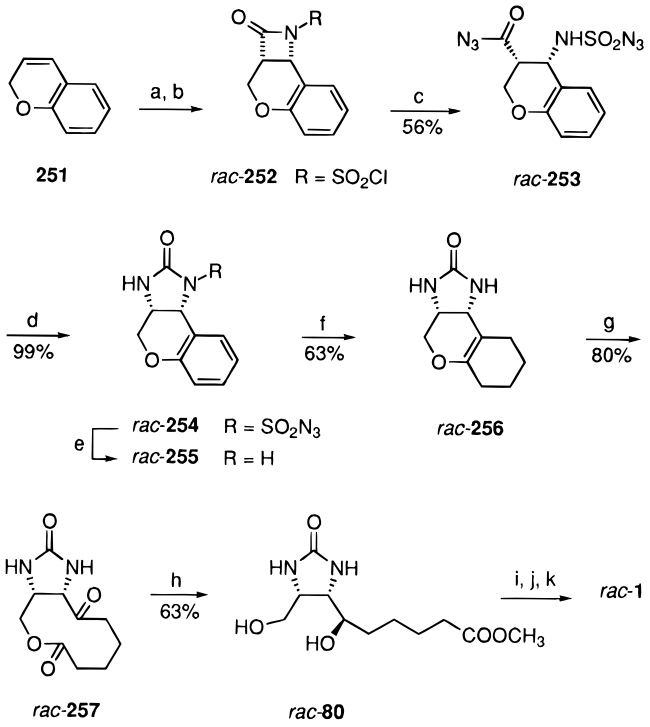


rac-**244** *rac*-**246** (9)

The synthesis elaborated in Scheme 57 was initiated following a similar, more direct but eventually less-successful approach that is shown in Scheme 58.[113] Here, the intramolecular cycloaddition would involve a nitrone and, hence, an isoxazolidine as cyclization product with the correct oxidation level at C-4, rather than a nitrile oxide and an isoxazoline as cyclization product that needs to be reduced further. The main stream synthesis proceeds as the previous one, until the Beckmann rearrangement step. The success of this step was found to be highly dependent on the nature of the R group of the urethane protected **249**. Whereas the *N*-benzyl-protected **249** could not be induced to undergo the rearrangement under any circumstances, the *N*-methyl analogue did convert to the desired *all-cis* lactam **250** (R = Me) in polyphosphoric acid at 100 °C. Therefore, the *anti*-oxime **244**, the *N*-desmethyl derivative of **249**, became the obvious target intermediate that was eventually obtained via the sequence shown in Scheme 57.

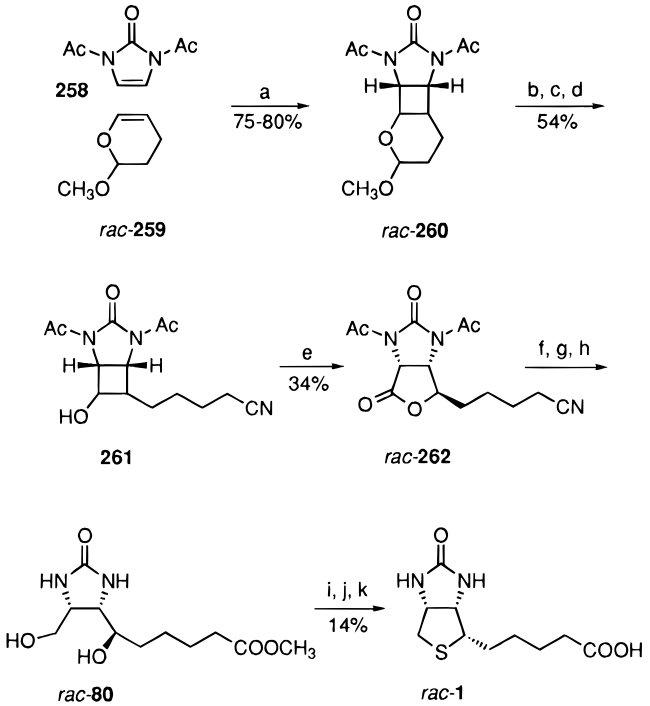
The syntheses discussed in Schemes 59 and 60 eventually form the thiophane nucleus of biotin through a classical substitution−cyclization process centering around diol **80**. After dimesylation, the obtained dimesylate is treated with sodium sulfide whereby, through S_N2 inversion at C-2 the bicyclic biotin skeleton is obtained with the required *all-cis* configuration about the thiophane nucleus. The obtention of the shown configuration of the secondary alcohol in **80** is, of course, mandatory.

Scheme 59[a]



[a] Conditions: (a) $ClSO_2NCS$, ether, −35 °C; (b) NaI, $NaHCO_3$; (c) $Et_3NH^+N_3^-/HN_3$ buffer, CH_2Cl_2, −18 °C; (d) toluene, 85 °C; (e) Na_2SO_3, H_2O; (f) $LiNH_2$; Li, $EtNH_2$; (g) *m*-$ClC_6H_4CO_3H$, ether; $NaIO_4$; (h) $NaBH_4$, MeOH, molecular sieves 3 Å; (i) MsCl, C_5H_5N, −10 °C; (j) Na_2S, HMPT, 100 °C; (k) NaOH; H_3O^+. HMPT = hexamethylphosphorous triamide.

Scheme 60[a]

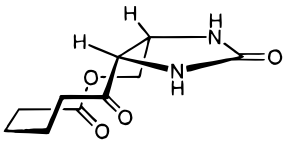


[a] Conditions: (a) *hν*, CH_3COCH_3; (b) CH_3COOH, H_2O; (c) $Ph_3P{=}CHCN$, CH_2Cl_2; (d) H_2, Pd/C, EtOAc; (e) $RuCl_3{\cdot}NaOCl$, H_2O, CH_2Cl_2; (f) $NaBH_4$, EtOH, H_2O; (g) NaOH, H_2O; H_3O^+; (h) CH_2N_2, Et_2O, CH_3OH; (i) MsCl, C_5H_5N; (j) Na_2S, DMF; (k) NaOH, H_2O; H_3O^+.

In the 1980 synthesis of Fliri and Hohenlohe-Oehringen, the starting material 2*H*-chromene (**251**) contains all the carbon atoms of biotin except the urea carbonyl (Scheme 59).[114] This carbon is introduced via *syn*-addition of chlorosulfonyl isocyanate,

a process whereby the *cis* relation of the 3,4-diamino groups of biotin is secured. Treatment of the obtained *N*-chlorosulfonyl-β-lactam (**252**) with azide leads to bisazide **253**, and after Curtius rearrangement to sulfonazide **254**. Reduction with sodium sulfite further removes the azidosulfonyl group. The obtained **255** is treated under Benkeser conditions resulting in the tricyclic enolether **256**. The *N*-benzyl fission is inhibited by prior formation of the lithium salt of **255**. Oxidative fission of the enol ether leads to the ten-membered keto lactone **257**. Subsequent treatment with sodium borohydride in methanol leads to diol **80** via stereoselective carbonyl reduction and transesterification.

The stereoselectivity of the reduction is determined by the peripheral attack of hydride on the preferred conformation of the strained bicyclic ring system as shown in eq 10.



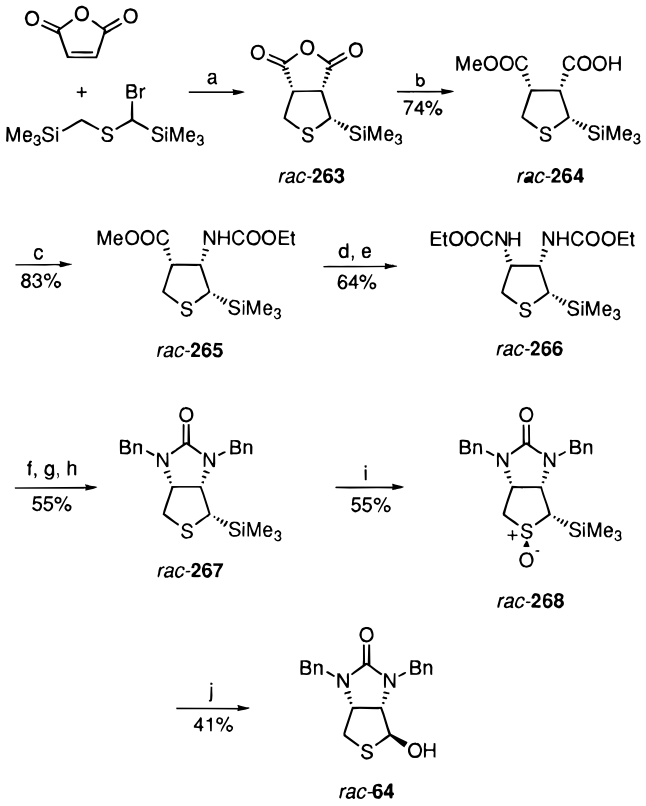
(10)

rac-**257**

The 1983 approach of Whitney is shown in Scheme 60 and starts with the photochemical [2 + 2] cycloaddition between 1,3-diacetylimidazolin-2-one (**258**) and commercially available 3,4-dihydro-2-methoxy-2*H*-pyran (**259**) as the alkene component.[115] Acetone is used as solvent and sensitizer. Photoadduct **260** was obtained as a mixture of four stereoisomers, presumably the two anomers of each of the *syn* and *anti* photoadducts. Liberation of the cyclobutanol portion of the photoadduct and completion of the biotin carboxybutyl chain involved acid hydrolysis, direct treatment of the resulting hemiacetal with (cyanomethylene)triphenylphoshorane, and catalytic hydrogenation of the intermediate α,β-unsaturated nitrile that was obtained as mixture of (*E*)- and (*Z*)-alkene isomers to **261**. In a crucial subsequent stage of the synthesis, cyclobutanol derivative **261** is transformed into the corresponding five-membered ring lactone **262**. This oxidative rearrangement was effected, as in a previous analogous synthetic experience that led to (+)-deoxybiotin,[116] in a two-phase mixed system comprised of ruthenium tetroxide in the organic phase and sodium hypochlorite in the aqueous phase. In this manner, a mixture of rearrangement products was obtained from which the desired lactone **262** was recrystallized in 34% yield. Eventually, conversion of this lactone into **80** involved complete reduction using sodium borohydride in aqueous ethanol at reflux and conversion of the nitrile into the corresponding methyl ester.

Subsequent to the development of an effective optical resolution of alcohol *rac*-**64** by Yamano and co-workers (Scheme 24), the same group developed an interesting route to the racemic alcohol, which is described in Scheme 61.[117] The synthesis basically involves three stages. In the first stage, the thiophane nucleus of biotin is constructed via a 1,3-cycloaddition process between maleic anhydride and a thiocarbonyl ylide that is generated from a sulfide according to Achiwa *et al.*[118] Subsequent methanolysis of **263** that was obtained with excellent stereoselectivity, led to

Scheme 61[a]

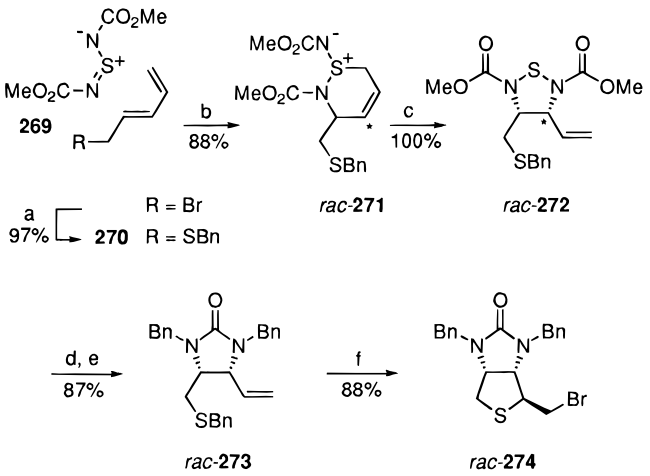


[a] Conditions: (a) DMF, 130 °C; (b) CH_3OH, *p*-TsOH, reflux; (c) $Ph_2P(O)N_3$; EtOH; (d) NH_2NH_2; (e) $NaNO_2$; EtOH; (f) 48% HBr; (g) $COCl_2$; (h) $PhCH_2Cl$, NaH; (i) $NaIO_4$; (j) *p*-TsOH.

acid **264**, at which point the shown *all-cis* configuration was determined. In the following stage of the synthesis, acid **264** is transformed into **267** through two stepwise Curtius rearrangement sequences, to yield **265** and **266**, followed by the construction of the urea ring in the usual way. In the last stage, the crucial transformation of the (trimethylsilyl)-thiophane derivative **267** into **64** is realized via a sila-Pummerer rearrangement. Therefore, the thiophane was oxidized with sodium metaperiodate to give the *trans*-sulfoxide **268** as sole reaction product. This is shown to be the incorrect configuration for the classical rearrangement to occur. In the presence of *p*-toluenesulfonic acid, however, presumably through acid-catalyzed epimerization of the sulfoxide, migration of the trimethylsilyl group to oxygen leads to a siloxysulfonium ylide which itself rearranges by the Pummerer pathway to give an α-siloxy sulfide and then **64** in the acidic medium.

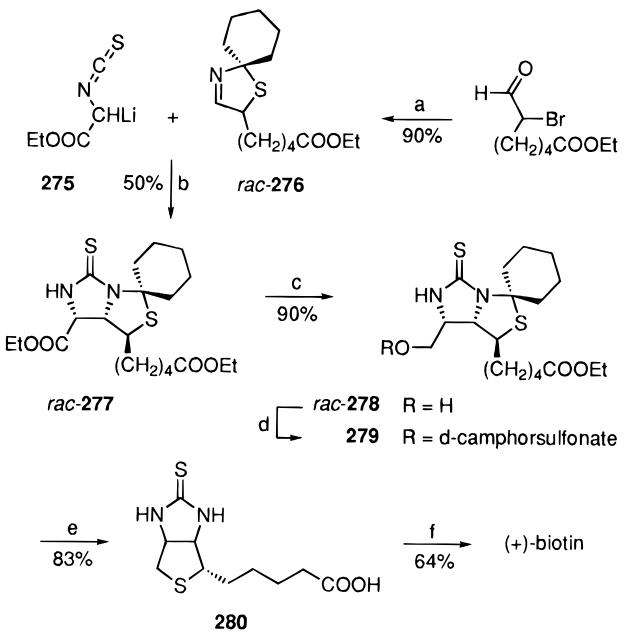
In 1988, Weinreb and co-workers described synthetic work that aimed at the synthesis of biotin (Scheme 62).[119] Although the goal was not reached, the route will be discussed here because it yielded the biotin bicyclic core in a short and unclassical way in which two consecutive pericyclic processes are determining. First, a Diels−Alder cycloaddition between diene **270** and sulfur diimide **269** occurred in high yield at room temperature to produce **271** and the corresponding *trans*-derivative with good selectivity (7.7:1 in favor of desired **271**). Heating the mixture in refluxing toluene induced a [2,3] sigmatropic rearrangement leading to thiadiazolidine **272** and its epimer (ratio 7.7:1, respectively) in quantitative yield. This rearrangement was shown to be stereospecific. Urea **273** was readily obtained via

Scheme 62[a]



[a] Conditions: (a) $NaSCH_2Ph$; (b) $PhCH_3$; rt; (c) $PhCH_3$, reflux, separation of diastereomers; (d) $NaBH_4$; (e) NaH, $PhCH_2Br$; (f) Br_2/dioxane, CH_3CN.

Scheme 63[a]



[a] Conditions: (a) NaSH, cyclohexanone, NH_3; (b) $SCNCH_2COOEt$, LDA, THF; $BF_3{\cdot}OEt_2$, THF, −78 °C; (c) $NaBH_4$, CH_3OH, THF, 0 °C; (d) Et_3N, *d*-camphorsulfonyl chloride, CH_2Cl_2; (e) CF_3COOH, H_2O, 45 to 100 °C; (f) $BrCH_2CH_2OH$, *N*-methylpyrrolidinone, 110 °C; Na_2CO_3.

reduction with sodium borohydride and cyclization using sodium hydride. Treatment of olefinic sulfide **273** with bromine/dioxane complex in acetonitrile led to a single cyclization product with, unfortunately, a stereochemistry at C-2 that was not compatible with further work toward biotin.

We close this chapter with a very short approach by Volkmann and co-workers of Pfizer Central Research (Scheme 63).[120] This approach is enantioselective for (+)-biotin through a resolution step at a late stage of the sequence. Central in the synthesis is the obtainment of thiazolidine **277** via a process which involves an ester enolate imine addition followed by an intramolecular amine/isothiocyanate condensation. The imine substrate **276** is obtained as the 3-thiazoline through reaction of brominated ethyl 7-oxoheptanoate with sodium hydrogen sulfide, cyclohexanone, and ammonia. Crucial to the success of the addition of the lithium enolate of the isothiocyanato acetate ester (**275**) to thiazoline **276** is the prior activation of the imine through addition of an equivalent of boron trifluoride. In practice the diester **277** was obtained in ca. 50% yield as the major product. Treatment of **277** with sodium borohydride resulted in the selective reduction of the α-substituted ester to give alcohol **278**. This was converted to a mixture of *d*-camphorsulfonates, which were separated by silica gel chromatography. Isomer **279** was converted upon acid treatment to 2-thiobiotin (**280**) in 83% yield. The reaction conditions affected thiazolidine ring hydrolysis, thiophane ring formation, and ester hydrolysis. The eventual thiourea/urea transformation was realized by basic treatment with bromoethanol. In this procedure, the nucleophilic character of the thiourea sulfur atom was exploited in order to deliver, intramolecularly, the required oxygen atom via a labile alkoxyimidazoline.

III. Strategy Evaluation

A. The Objective Way

As mentioned in the Introduction, biotin is an ideal target for total synthesis. Indeed, the $C_{10}H_{16}O_3N_2S$ molecule possesses a structure that is characterized by an attractive combination of constitution and stereochemistry. It possesses a bicyclic heterocyclic skeleton to which is appended a functionalized side chain. The heterocyclic nature of the skeleton, a combination of a cyclic urea and a thiophane ring, is not one of a kind that would normally be reserved exclusively to the heterocyclic chemist. The biologically active enantiomer further possesses an array of three contiguous stereocenters in the *all-cis* configuration relative to the thiophane ring. Thus, there is a stereochemical issue to be solved both in the enantio- and diastereoselective sense. More importantly, the "human" dimension of the molecule and of the synthetic problems that need to be solved makes biotin a target within the reach of every laboratory that has an interest in synthetic organic chemistry. This stands in contrast with numerous target structures that, because of structural dimension and complexity, eventually only yield to a chemical army. A total synthesis of biotin is well within the reach of a single doctoral student proposal. As a matter of fact, in my research group, one gifted student was able to achieve two original approaches during his doctoral term.

Biotin also provides an ideal case in the context of evaluation of synthetic strategies. Indeed, it has attracted the continuous attention of two scientific communities that are committed to total synthesis for different reasons. The academic community can use the fundamental nature of biotin as a pretext to engage in a synthetic approach that primarily will serve to exemplify a novel concept or a new reaction method. On the other hand, the chemical industry has shown, ever since the discovery of biotin, a sustained interest in the development of commercially applicable routes. The result of this dual endeavor is a plethora of successful syntheses that have been completed in a time span of more than 50 years.

A synthesis evaluation requires in principle the identification of one or more criteria that can be used

Table 1. Chronological List of the Full Contributions to the Total Synthesis of Biotin and Deoxybiotin

	author (company)[a]	starting material	sequence length	Product	Scheme	ref
1943−45	Harris (Merck)[b]	L-cystine	11	*rac*-**1**	31	60−65
1945	Grüssner (HLR)	5-methoxyhexanoic acid	13	*rac*-**1**	42	80−82
1945−50	Cheney (Parke, Davis)	pimelic acid	14	*rac*-**1**	44	90−92
1947	Baker (Lederle)	pimelic acid	17	*rac*-**1**	43	84−89
1949	Sternbach (HLR)	fumaric acid	15	(+)-**1**[c]	1	11−13
1962	Nishimura	thiophene	12	*rac*-**1**	48	98
1965	Fabrichnyi	thiophene	12	*rac*-**1**	49	99
1968−73	Isaka/Zav'yalov	methylimidazolone	7	*rac*-**1**	51	101/102
1970	Gerecke (HLR)	fumaric acid	11	(+)-**1**[d]	1, 6, 10	21
1975	Marquet	fumaric acid	12	*rac*-**1**	16	34
1975	Ohrui	D-mannose	16	(+)-**1**	25	50
1975	Confalone (HLR)	L-cystine	19	(+)-**1**	37	71
1976	Confalone (HLR)	pimelic acid	11	*rac*-**1**	45	93
1977	Ogawa	D-glucose	23	(+)-**1**	26	52
1977	Confalone (HLR)	pimelic acid	13	*rac*-**1**	46	94
1977	Marx (Syntex)	methyl 6-hexanoate	8	*rac*-**1**	55	110
1978	Sueda	D-glucosamine	14	(+)-**1**	27	53
1978	Field (HLR)	methyl 6-hexanoate	12	(+)-**1**[e]	54	109
1980	Vogel	D-arabinose	15	(+)-**1**	29	55
1980	Confalone (HLR)	cycloheptene	11	*rac*-**1**	57	113
1980	Hohenlohe-Oehringen	2*H*-chromene	11	*rac*-**1**	59	114
1981	Rossy (BASF)	methyl chloroacetate	10	*rac*-**1**	50	100
1982	Schmidt	D-arabinose	11	(+)-**1**	30	56, 58
1982	Baggiolini (HLR)	L-cystine	11	(+)-**1**	32	66
1983	Whitney	*N*,*N* -diacetylimidozalinone	11	*rac*-**1**	60	115
1983	Volkmann (Pfizer)	ethyl 7-oxoheptanoate	7	(+)-**1**[c]	63	120
1984	Ravindranathan	D-glucose	19	(+)-**1**	28	54
1986	Bates	sulfolene	8	*rac*-**2**	19, 21	45
1987	Poetsch (Merck)	L-cysteine	9	(+)-**1**	41	77
1987	Lee (HLR)	L-cysteine	12	(+)-**2**	33	67
1988	McGarrity (Lonza)	tetronic acid	12	(+)-**1**	5, 14	30, 31
1988	Corey	L-cystine	13	(+)-**1**	34	68
1990	Moran	*N*-phenylglutarimide	11	*rac*-**1**	52	106
1991	Speckamp, Poetsch (Merck)	L-cystine	13	(+)-**1**	35	69
1993	Ravindranathan	L-cysteine	12	(+)-**1**	36	70
1993	De Clercq	L-cysteine	12	(+)-**1**	39	73
1994	De Clercq	L-cysteine	14	(+)-**1**	38	72
1994	Fusijawa	L-cysteine	12	(+)-**2**	40	75
1994	Sumimoto		8	(+)-**1**	56	111

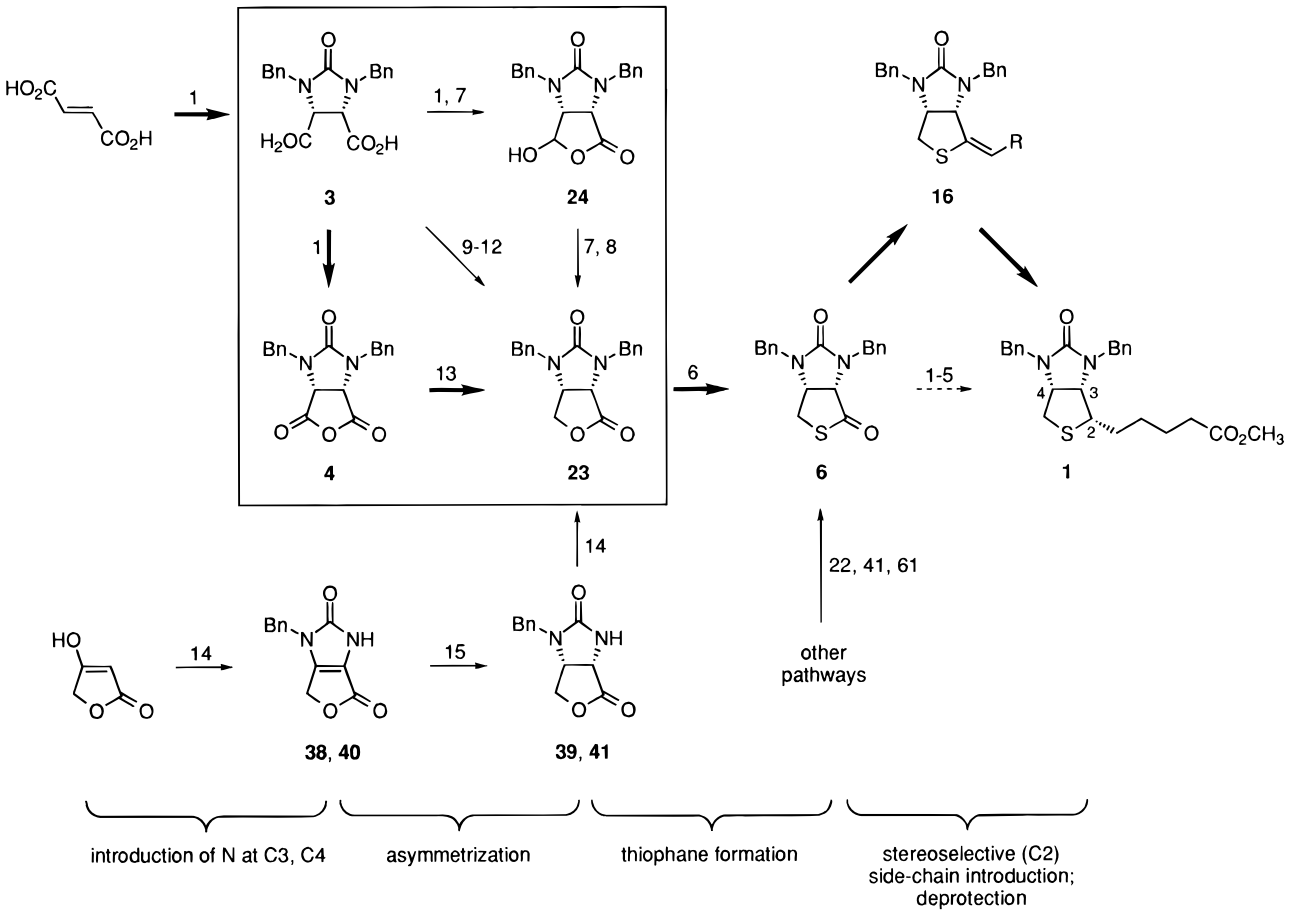
[a] HLR = Hoffman-La Roche. [b] Research Laboratory, Merck & Co., Inc., Rahway, NJ. [c] Late resolution. [d] Resolution with recycling of the undesired enantiomer. [e] early resolution.

to compare the merits and shortcomings of the different approaches. In an industrial context, the preferred biotin synthesis is likely to be the most economical one. However, not only may the price of a synthesis vary with time but the relevant information for a cost calculation will not be made available especially if the sequence has a commercial potential. Furthermore, the author of this review does not have the correct background for that purpose. In an academic context the preferred biotin synthesis is likely to be the one that is conceptually the most innovative. The choice here may also vary in time and is very much a matter of taste.

In the light of this duality, the only criterion that can probably serve our purpose is one that takes into account the number of steps that are involved in a synthesis. This obviously has a direct impact on the economy of the process but will also be a reflection of conceptual simplicity, which is, in the author's view, the single most valuable feature of a synthetic scheme. A synthetic scheme that aims at an efficient molecular construction will feature maximal convergency with a minimal number of steps. In the context of biotin, a molecule containing 16 heavy atoms (10C, 3O, 2N, 1S), the ideal convergent synthesis as far as the skeletal construction is concerned would involve the direct connection of two molecules that are readily available as commercial starting materials and that each contain eight heavy atoms. The next most efficient construction scheme, in which maximal convergency is pursued, would involve one in which the two above eight-atom pieces are each prepared by connecting two four-atom starting materials. The latter scheme is characterized by a total number of three steps and a maximal sequence length from any starting material to final product of two. The latter number is the one that best reflects the efficiency of the construct.[121] In defining the longest sequence length from a starting material, a few conventions will be adopted. In the context of biotin, it is reasonable to define a starting material as a reasonable priced commercially available molecule that contains four or more heavy atoms that are eventually found in the molecular constitution. The length of the sequence is defined by the number of synthetic steps that are involved in the longest sequence. When comparing sequence lengths, the reader should be aware that this criterion does not necessarily reflect correctly the actual cost of a synthesis, since the latter is determined by many more factors. It may therefore be that a more lengthy sequence still is cheaper than the shorter equivalent.

In Table 1 are listed the characteristic features of all reported contributions that can be considered as constituting original full total syntheses of biotin and deoxybiotin. The listing follows the order of chronol-

Chart 1. The Lactone−Thiolactone Asymmetric Avenue (Schemes 1−15)



ogy. It includes the name of the principal author and the name of the company when the synthesis was developed in an industrial laboratory. The single most important starting material is also mentioned in the table. The latter is determining in establishing the actual sequence length of a synthesis. A note concerning the stereochemical issue is also included. Finally, for each synthesis, referencing to the scheme(s) and to the literature is provided.

B. Perspectives

Does biotin still have a future as target for total synthesis? This question is justified in that after more than 50 years of constant attention one could possibly have exhausted the synthetic possibilities. An attempt at answering this question requires a somewhat different evaluation than the one provided by a mere comparison of sequence lengths. What is needed is an appreciation of the merits and shortcomings of broader strategies, rather than of individual approaches. Often strategies are conceived on the basis of the choice of starting materials, or of a key transformation, i.e., the driving force behind a strategy can be quite different. For that reason I have, in this last section, regrouped the different reported approaches in six charts. The different approaches within a chart obviously have one or more conceptual features in common. In this way, it becomes possible to compare "optimized" strategies. In the context of sequence length, is there a realistic minimal length that one can put forward? Considering the structure of biotin a set of three basic starting materials is a logical one that will require two construction steps. It is not unreasonable to assume that during these connection steps the stereochemical issues can be simultaneously solved. If two extra steps per construction step are involved for refunctionalization purposes this scenario would yield a six-step synthesis. We will further consider this as the ultimate goal.

In Chart 1 are shown the syntheses that fit in what I like to describe as the lactone/thiolactone asymmetric avenue. At the origin of this approach stands the exceptional synthetic work developed at Hoffmann-La Roche. It is also generally believed that this work constitutes the essence of the sequence followed in their commercial production of biotin, although I have not been able to get a personal confirmation on that issue. The development of what can be considered as the final approach that is summarized in the chart occurred in three phases. In a first phase (1949), Goldberg and Sternbach described the following route: fumaric acid is transformed into the cyclic anhydride **4**, and then via a reductive sequence into thiolactone **6**; the latter is converted into biotin via a sequence that involves the introduction of an exocyclic double bond (as in **16**), and the establishment of the *all-cis* stereochemistry via catalytic hydrogenation. At this point a classical resolution was involved at a late stage of the sequence with the involvement of a rather nonclassical tricyclic thiophanium intermediate. This shortcoming was solved in a remarkable way by the same company 20 years later. Indeed, the discovery that

lactone **23** could be directly converted into **6** in very high yield paved the way for an asymmetric version of the approach. First, a scheme was developed in which diacid **3** was converted to optically active hemiesters with possibility of recycling of the undesired configuration. Other resolution schemes with incorporation of possible recycling involved hydroxy lactone **24**. Enzymatic kinetic resolutions have also been applied. The conversion of anhydride **4** into a homochiral cyclic imide followed by subsequent reductive differentiation of the diastereotopic carbonyl groups is worthy of note. In the last phase, the search for asymmetric efficiency culminated with the discovery by Matsuki that Noyori's BINAL reagent effects the asymmetric reduction of **4** into **23** in very high chemical and optical yields. Within the box are shown those intermediates that play an important role in this essential part of the synthesis. It provides excellent illustrations of the various possible ways of realizing enantioselectivity within a sequence. This approach has also initiated considerable work in other laboratories where alternative routes to lactone **23** or to thiolactone **6** were developed. Also, alternative and shorter pathways for converting thiolactone **6** into biotin were investigated. In essence only three steps are required for the latter purpose: introduction of the carboxybutyl chain with concomitant formation of an exocyclic bond, catalytic hydrogenation, and deprotection. As for the first part of the synthesis, the enantioselective obtention of lactone **23** by reductive differentiation of the enantiotopic acid groups in **3** (e.g., using a chiral borane reagent) would further shorten the sequence by one step. Hence, the basic approach is one that has the potential of an eight-step asymmetric sequence.

Another approach that fits into Chart 1 has been developed by scientists at Lonza and centers about the catalytic hydrogenation of unsaturated lactones such as **38** and **40** to yield direct precursors of lactone **23**. In this context the enantioselective reduction of achiral **40** to yield **41** in excellent chemical and optical yields using a rhodium catalyst with a chiral ferrocenyl-based diphosphine ligand has been claimed very recently. A third asymmetric approach that has been claimed lately (1994) will be discussed in another context.

The Hoffmann-La Roche synthesis of biotin constitutes without any doubt a major achievement in organic synthesis. The driving force behind the conceptual strategy is not one that can be identified with a particular choice of starting material as in chiral pool syntheses or of a key reaction type. It rather constitutes an almost perfect illustration of what total synthesis should aim to achieve: the gradual construction of the functionalized skeleton with the simultaneous solution of the stereochemical issues in a minimal number of steps. One should note how the skeletal construction and obtention of the required *all-cis* stereochemical relation are intimately interrelated. First, the nitrogens are introduced in the correct relative configuration via bromination of (*E*)-fumaric acid, followed by benzylamine substitution. The heterocyclic core is next completed by formation of the cyclic urea, followed by thiophane ring closure. In the final stage, the side chain is introduced in a way that allows for the stereoselective introduction of the third stereocenter. Finally, the enantioselectivity in the approach is realized in a most efficient way, i.e., via asymmetrization of a *meso* derivative.

In Chart 2 are summarized two different approaches that center around the *meso*-thiophane **42**. In the Marquet route (1975), fumaric acid (again!) is the starting material that is converted into **42** via a straightforward seven-step sequence. Subsequently other groups discovered that the cheap sulfolene **46** offered the potential for a shorter four-step conversion into **42**. The power of the Marquet strategy lies in the possibility of introducing the full side chain with the correct stereochemistry by alkylation of the *trans*-sulfoxide **44**. So far, however, this essential step has not been adapted in the light of an enantioselective application. Bates has reported alternative uses of thiophane **42** that rest on the interesting chloride **60**. Possible asymmetric applications shown in the box are based on resolution schemes involving hydroxythiophane **64** as intermediate with possibility of recycling. Unfortunately, the usefulness of the latter approach is severely limited by the problems encountered when **60** is used for the stereoselective introduction of the side chain. As a closing remark, it is fair to state that the thiophane approach involving sulfolene **46** as the starting material also has the potential of an eight-step asymmetric sequence, provided that an efficient solution is found for the enantioselective conversion of **44** into **45**.

Not surprisingly, a quite large number of syntheses of (+)-biotin have taken advantage of chiral and structural information available within the chiral pool. Carbohydrates have been used as starting material by several groups. The characteristic features of these syntheses are shown in Chart 3. They all have in common the following three sequences: (1) the introduction of the nitrogens with the correct stereochemistry is realized via S_N2 substitution processes in which the hydroxy stereocenters at C-3 and C-4 are inverted; (2) the thiophane ring is formed by direct substitution of a dimesylate with sodium sulfide and (again) the inversion mode of the process determines the stereogenicity at the C-2 hydroxy center; (3) the construction of the side chain involves a Wittig condensation followed by catalytic hydrogenation. We note that in this sugar approach the introduction of the N and S heteroatoms and the creation of the correct stereogenic centers occur in the same substitution processes. The identification of D-arabinose as the preferred carbohydrate candidate is the next logical step. Several publications have appeared in this context where the crucial issue is related to how effectively the Wittig condensation can be performed. The most evolved sequence, with little room for further shortening, still comprises eleven steps. This is quite symptomatic for carbohydrate-based approaches. Often a series of unavoidable steps that are related to protection and deprotection events renders conceptually straightforward approaches unattractive and inefficient. This very last aspect is also nicely illustrated in the biotin field. Indeed, a less judicious choice of the starting carbohydrate, such as a hexose in which a superfluous carbon needs to be removed, is invariably punished by the generation of lengthy sequences. Although it

Chart 2. The Thiophane Highway (Schemes 16−24)

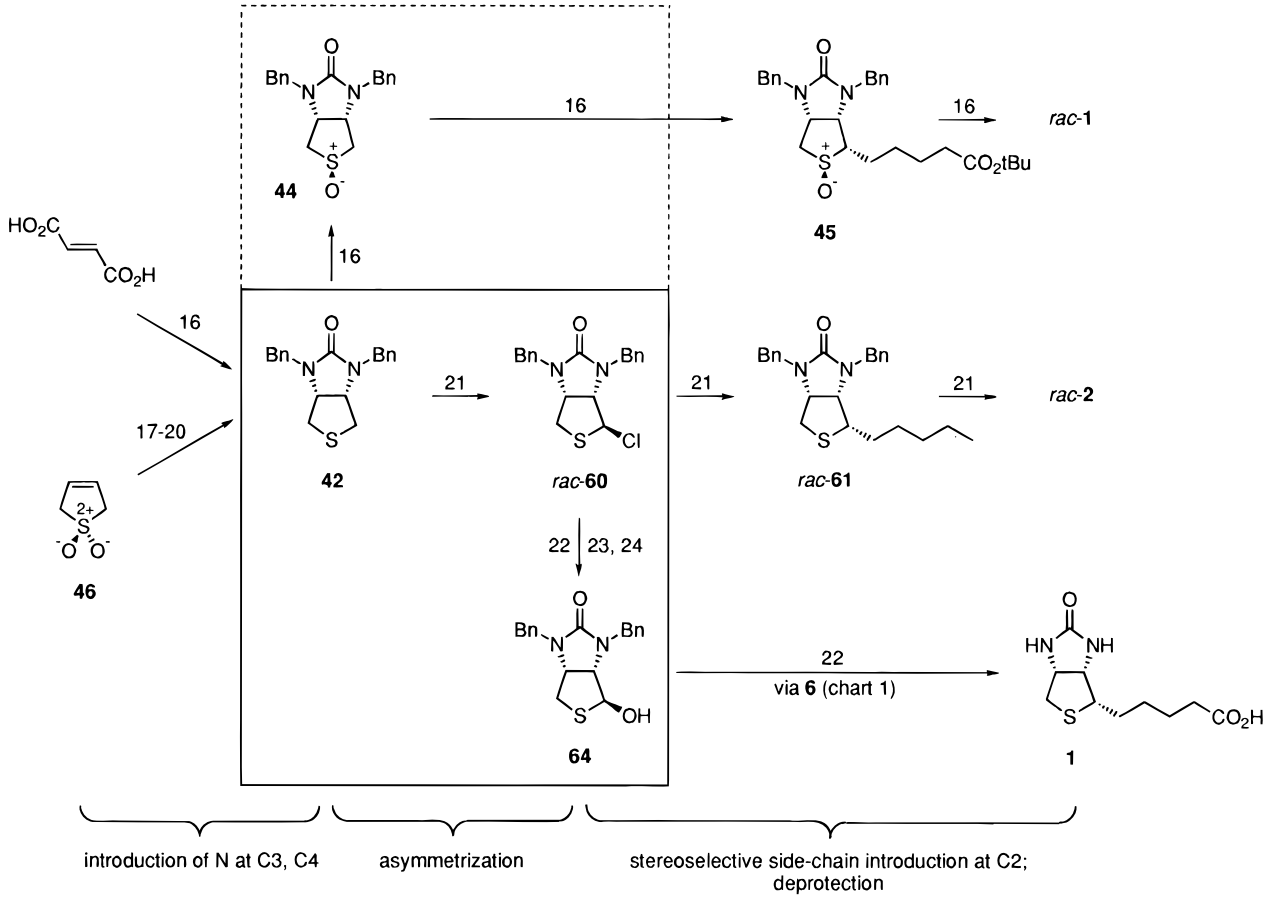
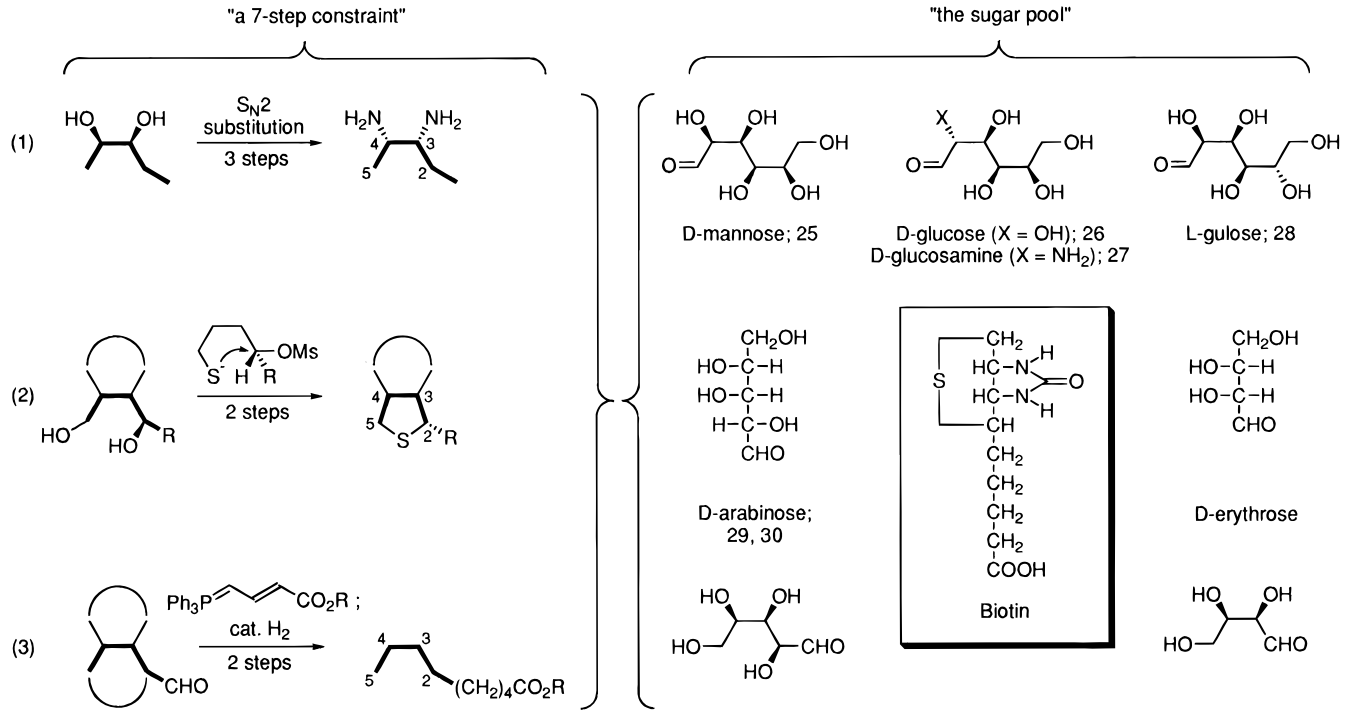


Chart 3. The Sweet Promenade (Schemes 25−30)



is highly improbable that a sugar-based strategy will ever lead to a short synthesis of biotin, D-erythrose may offer some interesting and thus far unexploited potentials as starting material.

Ten different approaches have used L-cystine or L-cysteine as starting material (Chart 4). This choice is a very logical one in the first place, since those amino acids combine two heteroatoms and three carbon atoms that are part of the heterocyclic core, together with one of the three stereogenic centers in the correct absolute configuration. Although this choice suggests a biomimetic one, it is not. It has been shown, indeed, that in the biosynthesis the sulfur atom is introduced at a very late stage.[122] It

Chart 4. The L-Cyst(e)ine Trail (Schemes 31−41)

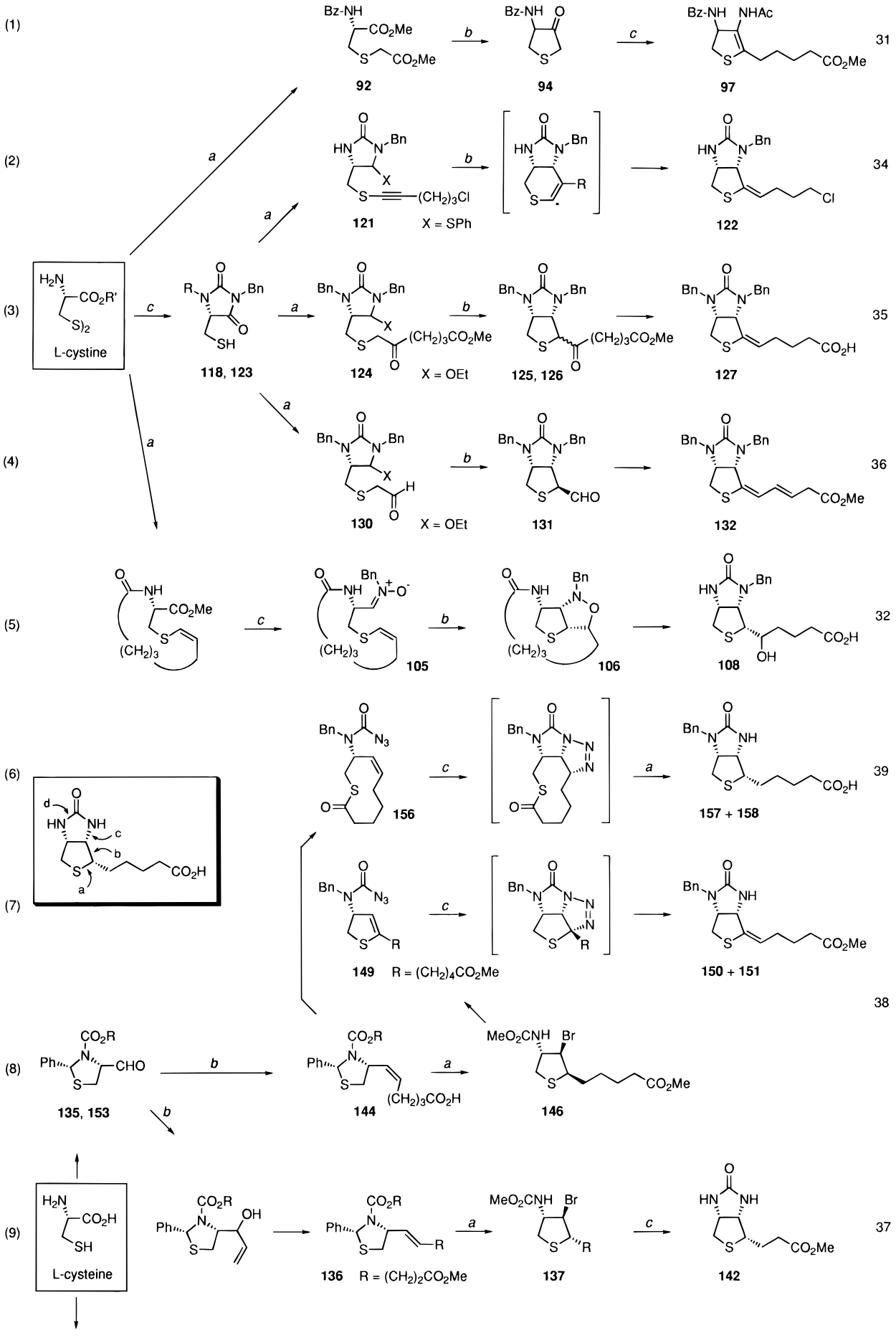
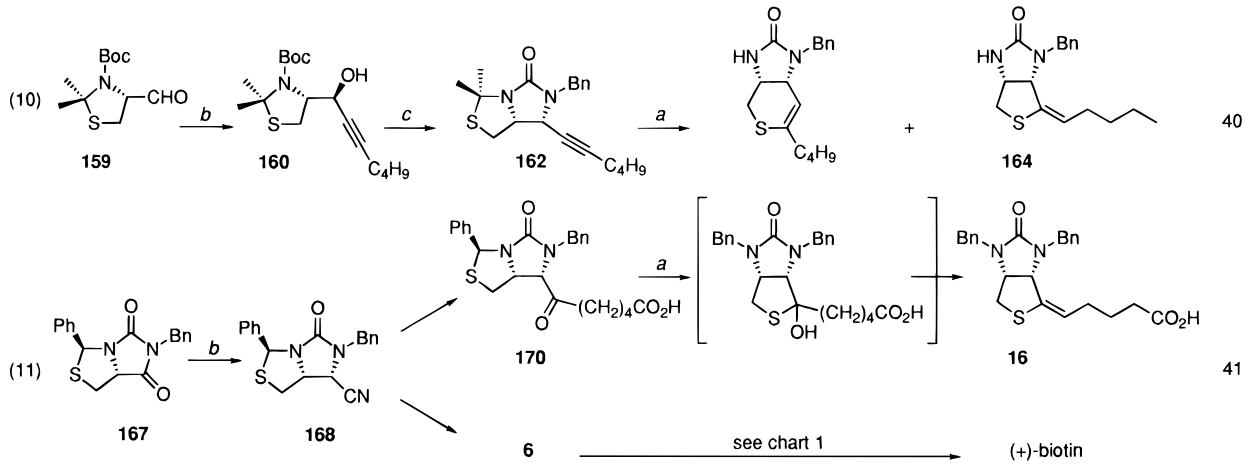


Chart 4. Continued



is further obvious that by choosing L-cyst(e)ine as a starting material one commits oneself to the construction of the minimal bond set shown in the box, i.e., bonds *a*−*d*. Within this set, bond *d* is less important. For this reason, Chart 4 has been conceived in a way that the steps in which bonds *a*−*c* are formed are explicitely shown and, at the same time, relationships existing between intermediates of the different approaches are highlighted. As will be seen shortly, the driving force behind almost each synthesis in this series is dictated by the use of a particular key construction step. In the first five syntheses listed in the chart, this step involves formation of bond *b*; in the remaining syntheses, it rather involves bond *a* and/or bond *c*. It is also worthy of note that as far as the three bonds *a*−*c* are concerned each possible scenario in relative order of bond formation has been applied in practice. An almost trivial calculation indicates that the mere choice of L-cyst(e)ine as starting material will imply somewhat lengthy sequences. Indeed, if one assumes that each necessary bond formation will necessitate on the average two extra steps, one may reasonably expect sequence lengths of 12 steps. A glance at Table 1 indicates that this is indeed the case.

The approaches 1−5 are conceived around the late formation of thiophane bond *b*. In cases 2−4, L-cystine is first converted into a protected hydantoin derivative (**118** and **123**). The thiol function in the latter is employed in forming bond *a*, and the molecule is further prepared for the crucial ring closure process via appropriate functionalization of the C-3 carbonyl. This closure step involves the radical cyclization of **121** and *N*-acyliminium-promoted cyclizations of **124** and **130**. In the three cases, the ring closure step leads to a selectivity problem. The radical cyclization proposed by Corey affords substantial amounts of the six-membered cyclized product next to desired **122**. The Speckamp *N*-acyliminium pathway leads to a diastereomeric mixture at C-2 (**125** and **126**), and the analogous cyclization of **130** affords the thermodynamically more stable C-2 epimer **131** exclusively. The latter problem will be solved through generation of an exocyclic double bond (**127** and **132**) that will allow creation of the correct stereochemistry at C-2 in the usual catalytic hydrogenation way. The fifth approach has been conceived by Confalone at Hoffmann-La Roche and rests on the formation of thiophane bond *b*, with concomitant generation of the required *all-cis* stereochemistry, through the single−step intramolecular [2 + 3] nitrone cycloaddition of **105**. It is important to stress here that the desired stereoselectivity was obtained through the concept of conformational bridging where the correct geometry for closure is enforced by the ten-membered lactam ring in **105**. This conceptually very attractive synthesis, which involves eleven steps for converting L-cystine into (+)-biotin, was recently selected as a "classic" in organic synthesis.[123] Quite characteristic for the approach is that the key step creates an intermediate **106**, which is structurally far more complex than the target product. In the first four steps, all but one heavy atoms of the target are assembled and the molecule prepared for its crucial cyclization step. The further unraveling of the polycyclic **106** into biotin requires six steps. Although fundamentally different, the approach of De Clercq has a few features that are similar to the above strategy. First, the key step also centers about an intramolecular [2 + 3] dipolar cycloaddition step, however, involving the rather unfamiliar carbonyl azide **156**. Second, the same concept of conformational enforcement via bridging is used to solve the stereochemical issue, here through formation of a ten-membered thiolactone ring. The two approaches have also in common that in the key cycloaddition step next to the *all-cis* stereochemical pattern also a key thiophane bond is formed. Interestingly, in the De Clercq approach the key step is the penultimate step and the success-determining step is the formation of the thermodynamic and kinetic unstable thiolactone **156**.

All syntheses which involve the late formation of bond *a* use a thiazolidine (**135**, **153**, and **159**) as an early intermediate. In this cyclic derivative N and S are protected simultaneously, so that full attention can be paid to the formation of bond *b*. This invariably involves a nucleophilic addition process on a aldehyde. At this point it is appropriate to discuss yet another highlight in the biotin field, which again originates from the Hoffmann-La Roche laboratories. The story is exceptional in that what was conceived to become a very short fully stereoselective synthesis, eventually resulted in a non-stereoselective inefficient 19-step sequence. The key step in the approach is the bromination of the *E* double bond of derivative **136**, which is accompanied by the in-

tramolecular sulfur displacement of the intermediate bromonium ion and in situ deprotection to yield thiophane bromide **137** in high yield. All that remains to be achieved is the introduction of the last nitrogen via a classical S_N2 substitution process. The lengthy sequence that eventually resulted originates from (1) the stepwise and somewhat laborious way that was followed to introduce the side chain whereby the obtention of the *E* stereochemistry in alkene **136** is of prime importance and (2) the reluctance of the bromide in **137** to yield to substitution by nucleophilic attack from the more-hindered concave side of the molecule. The combination of both shortcomings eventually resulted in a 12-step sequence for the conversion of **137** into biotin. In yet another approach where the intramolecular cycloaddition of a carbamoyl azide is the key step, De Clercq took advantage of the stereospecificity of the above bromonium-induced oxidative cyclization. When the (*Z*)-alkene **144**, readily available through Wittig reaction of **153**, was brominated, the bromothiophane **146** resulted. The latter possesses the correct stereochemistry for further high yield E2 elimination to form the endocyclic double bond as in **149**, which is the required position for the further cycloaddition−rearrangement process. The tenth synthesis in the chart provides another interesting example of late formation of thiophane bond *a* which eventually led to deoxybiotin (**2**). The sequence involves the diastereoselective formation of acetylenic alcohol **160**, introduction of N in the required configuration via an intramolecular S_N2 displacement, and base-promoted ring closure of the acetylenic thiol, formed upon deprotection of **162**. Unfortunately, as in the radical cyclization of **121**, the cyclization step to **164** also led to the formation of substantial amounts of a six-membered side-product.

The last synthesis is one developed at Merck, where in the early intermediate **167** the features of an hydantoin and of a thiazolidine are combined. Thiophane formation involves the conversion of **170** into **16** which possesses the classical exocyclic double bond pattern. Here we note, as in the Hoffmann-La Roche approach of Chart 1, the gradual construction of the functionalized skeleton with eventual obtention of the *all-cis* stereochemistry via catalytic hydrogenation of the exocyclic double bond in **16**. Interestingly, the approach also offers a possible link to the pathway of Chart 1 via the hydrolysis of nitrile **168** to the well-known thiolactone **6**.

The reader will probably regard the syntheses of Chart 4 as the conceptually most attractive among all biotin syntheses. Yet it is important to stress that, except for the Merck synthesis, they are not among the most efficient. This must be due to the drastic restrictions in bond construction that are imposed by the very choice of L-cyst(e)ine as the starting material. In spite of this, I believe that at least two among the shown approaches in Chart 4 still may hide some further potential. First there is the stereospecific bromothiophane pathway of Hoffmann-La Roche that certainly deserves further attention. A second approach that merits renewed attention is the first reported synthesis of biotin in 1944. This route has been neglected since probably because one of the benefits of using L-cysteine as the starting material was lost due to racemization. Revisiting the 11-step sequence that is characterized by a sound gradual buildup of skeleton and stereochemistry may well prove to be rewarding.

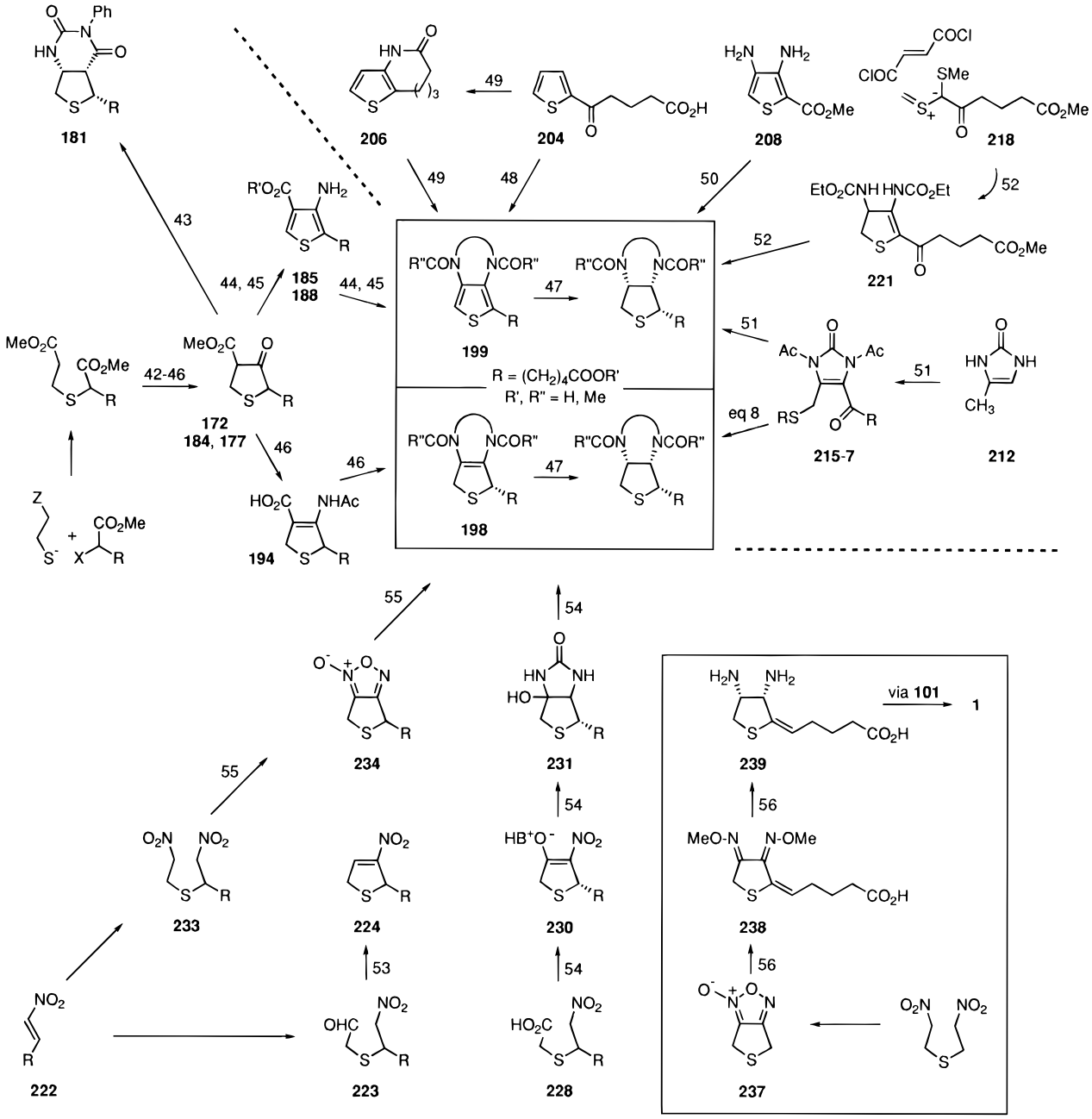
Chart 5 constitutes a potpourri of syntheses in which the *all-cis* stereochemistry is obtained via catalytic hydrogenation of a side chain substituted thiophene or 2,5-dihydrothiophene derivative. However, the applicability of the approach has been deferred for some time because of the known resistance of a thiophene ring, and also of a fully vicinal diamino-substituted double bond, toward catalytic hydrogenation. This issue was solved when it was discovered that upon acylation of both nitrogens (**198** and **199**) catalytic hydrogenation could be effected under normal conditions. The major shortcoming of the thiophene approach is the absence of an enantioselective version of the reduction.

In this context, a large number of approaches have concentrated on the synthesis of 2-alkyl-3,4-diaminothiophene derivatives. Thiophene itself turns out to be a poor starting material. The controlled introduction of both nitrogen substituents on the aromatic ring via **204** requires quite some work. A more direct route was developed at BASF. Despite the early obtainment of a 2-alkyl-3,4-diaminothiophene derivative (**208**), the overall sequence leading to *rac*-biotin still requires 10 steps. The chemistry involved in Morán's approach is interesting in that an unusual [2 + 3] cycloaddition step between sulfur ylide **218** and fumaroyl chloride leads to the formation of the thiophane ring. In this context it is a bit unfortunate that the interesting derivative **221** was aromatized. The most efficient pathway to a bis-acylated 3,4-diaminothiophene derivative is the approach that was originally conceived by Duchinsky and Dolan (again at Hoffmann-La Roche!) and subsequently materialized by Russian and Japanese groups. Starting from **212** an eight-step sequence to *rac*-biotin is potentially available provided that the thiophene reduction is now effected prior to the N-deacetylation.

The remaining syntheses within the chart are characterized in that the formation of bond C-3, C-4 is part of the skeletal construction and is performed early in the sequence. One option is the formation of substituted keto thiophane derivatives (**172**, **177**, and **184**) via Dieckmann condensation of the corresponding diester. The conversion of this type of intermediate into the thiophene derivative **185** was first conceived by Cheney and Piening of Parke-Davis and subsequently optimized by the Confalone group at Hoffmann-La Roche. A conceptually similar approach led to **198** via the dihydro derivative **194**. It is interesting to note that the aforementioned keto thiophane **177** was an intermediate in one of the early syntheses of *rac*-biotin, which had the special merit of featuring full stereochemical control (Scheme 43).

A second option for the skeletal C-3, C-4 bond formation is the intramolecular condensation of nitro derivatives (**223** and **228**). The Field group at Hoffmann-La Roche developed a synthesis that leads to (+)-biotin via an unusual resolution process very early in the sequence. The overall sequence comprises more than 10 steps. It is interesting to mention that the intramolecular Henry reaction (**223**

Chart 5. The C3,C4-Connection (Schemes 42−56)[a]



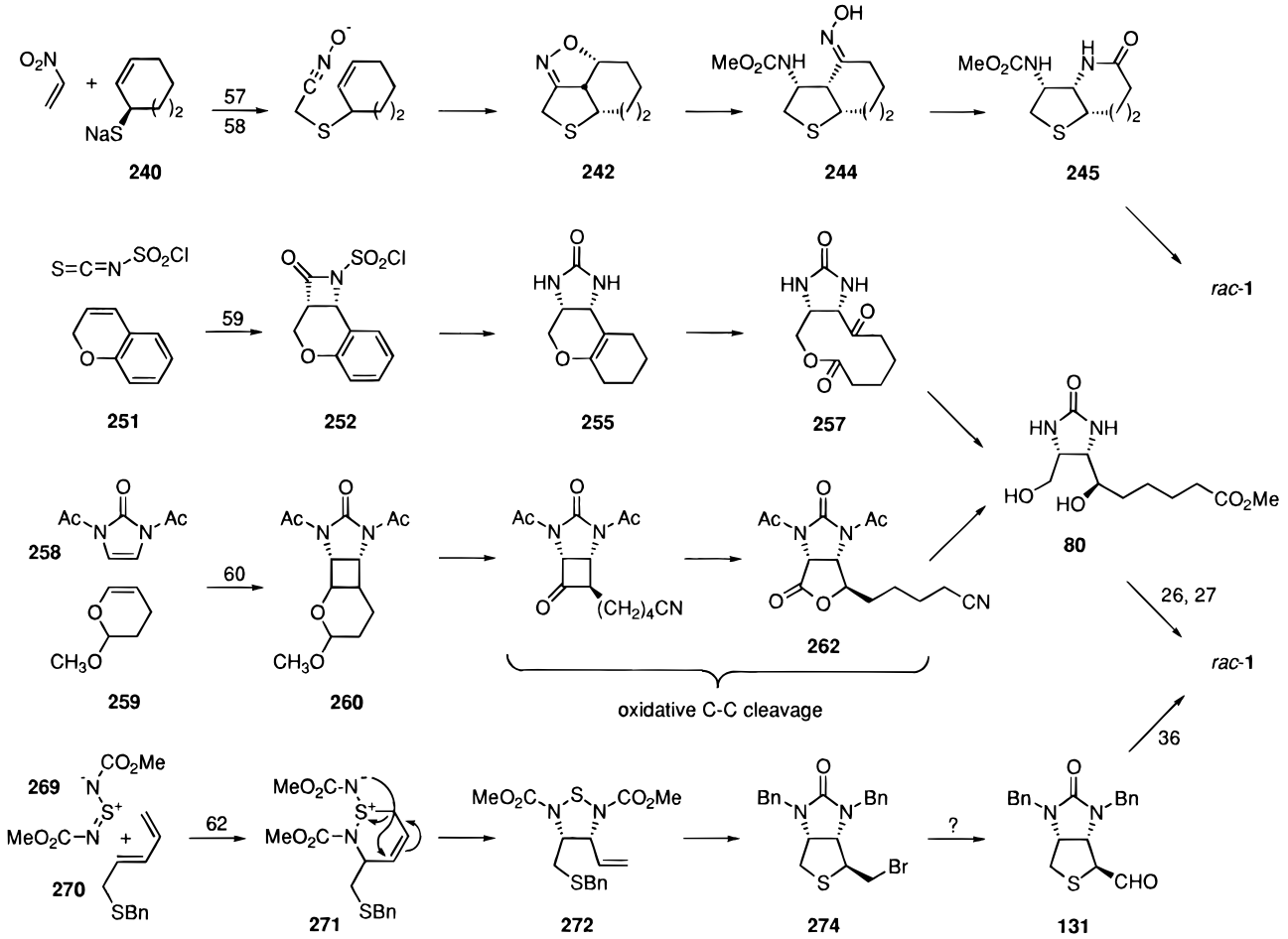
[a] All shown chiral structures are racemic except **230**, **231**, and **239**.

to **224**) was used very early in the biotin field; unfortunately, the subsequent route led to diastereomers of biotin.

A last option is the unusual and interesting formation of a furoxan ring (**234**) upon dehydration of a bis-nitro compound (**233**), which presumably involves the intermediacy of nitrile oxides. The required sulfide **233** is obtained via conjugate addition of 2-nitroethanethiol on conjugated nitroalkene **222**, an intermediate also used in the preparation of **228**. The route provides *rac*-biotin in eight steps. Very recently an eight-step synthesis of (+)-biotin has been claimed by chemists at Sumitomo that involves the same furoxan strategy (see box). After construction of the bicyclic heterocyclic core (**237**), the side chain is introduced via a condensation reaction that also generates an exocyclic double bond (**238**). Subsequently, the stereochemical issue is solved via two consecutive hydrogenation steps. In the first one, the required enantioselectivity is obtained; the second hydrogenation generates the *all-cis* stereochemistry in the usual way. This approach is a remarkably short asymmetric synthesis that could have also fitted in Chart 1 or 2.

In Chart 6 are gathered four very different approaches that show, however, conceptual similarities worth to be stressed. First, a key construction step involves a pericyclic reaction in all cases. Second, the approaches are also characterized by the occurrence of one or more somewhat surprising skeletal changes. In three of the listed syntheses, this change consists in the oxidative cleavage of a carbon−carbon bond. Retrosynthetically, this involves a bond reconnective step instead of the usual bond disconnection. This is an intellectually more demanding process, which often evokes elegancy as a feature in describing the synthesis. In the first one within this series, an intramolecular [2 + 3] cycloaddition is the

Chart 6. The Retropathway (Schemes 57−62)[a]



[a] All chiral structures shown are racemic.

key construction step. At this point the reader will not be surprised to learn that (again!) this approach was conceived by the Hoffmann-La Roche scientists. The 1,3-dipole involves a nitrile oxide that upon cycloaddition on the cycloheptene double bond leads to the tricyclic derivative **242** and, after refunctionalization, to **244**. The Beckmann rearrangement of the latter constitutes the oxidative step whereby the amidated C-3 in **245** is formed. The two subsequent approaches in the series are very different, yet they follow a similar basic scenario: (1) skeletal assembly via a [2 + 2] cycloaddition to **252** and **260**; (2) unraveling of key functional groups via oxidative fragmentation to **257** and **262**; (3) thiophane formation via direct substitution by sulfide of a dimesylate that is obtained from diol **80** which in both syntheses is obtained via reduction. In the latter process the configuration at stereocenter 2, which bears the secondary hydroxy group that will be inverted upon thiophane ring formation, is crucial. For **257**, this is obtained via the diastereoselective reduction of a ketone comprised within a ten-membered ring (a kinetic event); for **262**, it is the consequence of the preferred orientation of the side chain on the convex side of the cyclobutanone derivative (a thermodynamic event). The last synthesis of Weinreb in the chart is a conceptually surprising one. Two consecutive pericyclic processes, involving an unusual [4 + 2] cycloaddition to **271**, followed by a likewise unusual [2 + 3] sigmatropic process, to yield **272**. The thiophane formation via oxidative bromination of **272** led to bromide **274** with, however, the epimeric configuration at C-2. Although the authors of this approach did not pursue this work, a further oxidation to the aldehyde **131** is certainly conceivable which in the light of work that was subsequently performed (cf. Scheme 36) would have constituted a new synthesis of (±)-biotin in its own right. The syntheses within this chart all involve sequences of 11 steps and count among the most ingenious ones. The synthesis described in Scheme 61 features both an unusual pericyclic construction step and a crucial oxidative fragmentation sequence. Whereas the chemistry involved is quite interesting, the eventual achievement in the context of biotin synthesis is less obvious, since 11 steps are required for the production of the familiar thiolactone *rac*-**6**.

I close this series with the Volkmann (1983) approach outlined in Scheme 63. Indeed, although the synthesis may not really fit in any of the previous charts, it does constitute a remarkable piece of work. It provides the shortest route to biotin, i.e., six steps from ethyl 7-oxoheptanoate to *rac*-biotin. The possibility of obtaining the required (+)-enantiomer has also been worked out but it involves a late resolution step in the sequence. The synthesis involves the early formation of the C-3, C-4 bond which concomitant obtention of the required relative configuration at the three vicinal stereocenters in a single intermolecular step. The intermediate that is thereby formed (**277**) possesses all functional features for further conversion into biotin. The thiophane con-

struction will involve the rather unusual C-5, S closure. The final conversion of thiobiotin into biotin is also worth noting. Apart from the enantioselectivity issue, this work probably best reflects what can be achieved via optimization of synthetic methodology. The shortest synthesis turns out to be one of the most elaborate ones.

IV. Conclusion

The most salient feature in biotin synthesis is the enormous diversity in synthetic approaches that have been pursued toward the same goal. As a result, biotin provides an ideal pretext for the teacher of organic synthesis. It is somewhat frustrating to have to close this review without the certainty of knowledge of the sequences that are used in the actual commercial production of biotin. Moreover, a breakthrough in the microbiological production could signify the end of synthetic manufacturing. In any event, a special tribute should be paid to the scientists of Hoffmann-La Roche who have dominated the biotin total synthesis scene for almost 50 years. The mere fact that the original 1949 approach, albeit in somewhat modified form, can still be considered as the conceptually most attractive one through its simplicity and proven efficiency justifies, at least in my opinion, its identification as one of the best total syntheses ever.

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VI. References

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