Hetero Diels–Alder Reactions with Nitroso Dienophiles: Application to the Synthesis of Natural Product Derivatives

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Dedicated to Professor Christoph Rüchardt on the occasion of his 65th birthday

Hetero Diels–Alder (HDA) reactions with nitroso dienophiles R–N=O are reviewed within the scope of natural product synthesis. These cycladditions often represent the pivotal reaction step of a total synthesis, because of their high stereo- and regioselective outcome; also because of the introduction of multifunctionality as a direct consequence of the HDA cycladdition. Asymmetric total syntheses are particularly emphasised using chiral dienes or chiral nitroso dienophiles.

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1. Introduction

During the last fifteen years Hetero Diels–Alder (HDA) cycladdition reactions with nitroso dienophiles R–N=O have become an integral part of the modern armamentarium for the total synthesis of some natural products.1,2,3 Quite often HDA with R–N=O represents a key step in a total synthesis, and for very good reasons (Scheme 1):

- in most instances HDA are concerted [4π supra + 2π] cycladditions, which consequently occur with complete stereoselection;
- if the diene component is disymmetric enough in terms of π-electron density, the HDA with R–N=O usually occurs with high regioselectivity;
- the N–O bond of the primary cycladduct is easily cleaved via reduction leading thereby to an alcohol and to an amine in syn orientation;
- all four carbon atoms of the primary cycladduct bear a potential functionality; furthermore they can all be made asymmetric (chiral) in a stereoselective (enantioselective or diastereoselective) manner, given a proper choice of reagents;
- the perhydro-1,2-oxazine, after cleavage of the N–O bond can easily be transformed into a pyrrolidine ring, via stereospecific reactions.

Inducing a well defined chirality at four contiguous carbon atoms each containing a functional group, in only 3 to 4 high yielding reaction steps, represents a powerful synthesis methodology indeed. A few research groups have been able to use creatively this pivotal methodology in the total synthesis of natural products.

2. Nitroso Dienophiles

The most reactive dienophiles are those where the nitroso group is directly linked to an electron-withdrawing group as in nitrosyl cyanide A, in C-nitrosocarbonyl compounds RCON=O B, and in C-nitrosoformate esters RCON=O C (Figure 1). The latter are used quite often because of easy removal of the formate moiety after the cycladdition step. Nitrosocarbonyl dienophiles are prepared in situ as transient intermediates by oxidation of the corresponding hydroxamic acids RCONH=O and RCONH=O with periodate.5 Generated in the presence of the appropriate 1,3-dienes they lead at once to 3,6-dihydro-1,2-oxazines in good yields (Scheme 1).3 Nitrosyl cyanide A, which is seldom used, is prepared by reaction of nitrosyl chloride with silver cyanide.6

Nitrosyl cyanide A and the C-nitrosocarbonyl dienophiles B and C are conveniently stored in the form of their cycladducts with 9,10-dimethylanthracene or with cyclopentadiene, from which they are readily regenerated by warming in benzene or toluene solution (some typical examples are cited below).5

Should periodate be too strong a reagent during the formation of C-nitrosoformate dienophiles C, the Swern–Moffatt protocol may be applied, i.e., treatment of hydroxamic acids with oxalyl dichloride and dimethyl sulfoxide (DMSO) in dichloromethane at −78°C, followed by decomposition of the resulting complex with triethylamine in the presence of the appropriate diene.7 To cite but one example, the chiral alcohol 1 was transformed into its hydroxamic acid 2 whose oxidation (Swern–Mof-
Bicyclic Oxazine 4:
To a stirred solution of oxalyl chloride (190 mg, 1.5 mmol) in CH₂Cl₂ (2 mL) at –78°C was slowly added DMSO (234 mg, 3.0 mmol) in CH₂Cl₂ (1 mL) and then 2 (299 mg, 1 mmol); after 15 min, cyclohexadiene (120 mg, 1.5 mmol) was introduced. Triethylamine (604 mg, 6.0 mmol) in CH₂Cl₂ (3 mL) was then added using a syringe pump (1 h). After 3 h at –78°C, the mixture was allowed to warm slowly to r.t. and stirred overnight. Addition of sat. NH₄Cl (5 mL), and extractive workup (Et₂O, 3 × 15 mL) gave a mixture of 4 (major isomer) and its diastereoisomer, which were separated by HPLC (hexane/EtOAc 8:1).

As to α-chloronitrosoalkanes E (Figure 1), which were among the very first nitroso dienophiles to be used in HDA cycloadditions, their reactions with dienes are usually sluggish. Nevertheless in aliphatic solvents they may be of preparative value, since the initial adducts are solvolysed to give the corresponding 3,6-dihydro-1,2-oxazines.1,2,3 Quite often though the instability of many α-chloronitrosoalkanes E requires low reaction temperatures and therefore long reaction times, thus limiting the scope of cycloadditions. Vasella and Kresze were able to circumvent these difficulties: chiral α-chloronitroso ether derivative 6, which is easily available from the mannolactone oxime 5 and tert-butyl hypochlorite, proved to be a stable (in the dark) and reactive dienophile; furthermore it led to excellent asymmetric inductions.8a,8b For example reaction of 6 with cyclohexa-1,3-diene gave cycloadduct (+)-9 (1R,4S) in 87% yield and better than 96% ee, as well as chiral lactone 10.8c The primary cycloadduct 7 and the ensuing iminium salt 8 are postulated intermediates; 8 breaks down to 9 and 10 by alcoholysis (Scheme 3).9 As a bonus lactone 10 can be recycled to 6 via oxime 5.

Biographical Sketches

Jacques Streith received his B.Sc. and D.Sc. degrees from the University of Strasbourg working with Prof. Guy Ourisson on sesquiterpenes. After a postdoctoral fellowship with Prof. E.J. Corey (Harvard University) he joined the Faculty of Strasbourg. In 1972 he became a professor at the Université de Haute-Alsace in Mulhouse, France. His research interests include preparative photochemistry as a tool in organic synthesis, and more recently asymmetric synthesis and the total syntheses of glycosidase inhibitors.

Albert Defoin received his B.Sc., "ingénieur chimiste", and D.Sc. degrees from the Ecole Supérieure de Physique et de Chimie Industrielles and from the Université Pierre et Marie Curie in Paris, working with Prof. J. Rigaudy. After a postdoctoral fellowship with Prof. K. Schaffner at Mülheim-Ruhr (Max Plank Institut für Strahlenchemie) Germany, he joined the group of Prof. Streith in Mulhouse as a Research Associate of the C.N.R.S.
in cooperation with the Zurich based Vasella team, the latter one having developed for that purpose the chiral and quite reactive nitroso dienophiles 6 and 11. The C$_2$-symmetric diene (±)-12, when reacted with chiral 6 in a 5:1 ratio, led to excellent kinetic resolution whereby (−)-13 was formed in good yield (ca. 80%) and excellent ee (≥ 96%). Likewise when applying the same reaction conditions, but replacing 6 with nitrosoribose dienophile 11, (+)-13 was obtained in good yield (82%) and excellent ee (≥ 96%). Reductive cleavage of the N–O bond of (−)-13 followed by acetylation gave chiral conduramine derivative (−)-14 as a crystalline compound in 76% yield. cis-Hydroxylation of this latter compound (KMnO$_4$) followed by acetylation led to crystalline (−)-15 (82%) whose saponification followed by acidification with HCl gave inosamine derivative 16 as an oily compound (95%) (Scheme 5).

(±)-12

(−)-13

(a) Zn/AcOH; (b) Ac$_2$O, pyridine; (c) KMnO$_4$; (d) HCl

Scheme 5

(1S,4R,7S,8R)-7,8-Dimethoxy-2-oxa-3-azabicyclo[2.2.2]oct-5-ene Hydrochloride [(−)-13]:

To a stirred solution of 6 (20 mmol) in CH$_2$Cl$_2$ (60 mL) kept at −20°C was added dropwise diene (±)-12 (100 mmol) in EtOH (20 mL). After disappearance of the blue colour the solution was extracted with H$_2$O (3 × 50 mL) and 0.05 N HCl (20 mL). The organic layer was dried (MgSO$_4$) and its volume reduced in vacuo whereby lactone 10 crystallized out in ca. 80% yield. The combined aqueous solutions were adjusted to pH = 8 with KHCO$_3$ and extracted with CH$_2$Cl$_2$ (5 × 50 mL). The combined organic layers were dried (MgSO$_4$) and evaporated to dryness. Treatment of the residue with 1% HCl in MeOH gave (−)-13 as a crystalline compound (yield: ca. 80%); mp 165°C dec.

The meso diene–diacetate 17 reacted slowly at −40°C with dienophile 6 and led in high yield (89%) and excellent ee (94%) to bicyclic compound 18. Clearly in this case a very pronounced face selectivity is obtained. Reduction of the N–O single bond followed by acetylation gave a conduramine tetraacetate derivative whose absolute configuration 19 was demonstrated to be as indicated in Scheme 6. The high diastereoselectivity of this HDA reaction seems to indicate that the most reactive conformation of dienophile 6 corresponds to a synperiplanar orientation of the N–O group to the C(1)–O(4) bond, the absolute configuration of 18 being the result of an exo attack of the diene.

3. Conduramines and Inosamines

In recent years asymmetric synthesis of aminocyclitols represented a major goal of the Kresze group in Munich,
(1S,4R,7S,8S)-(+)-7,8-Diacetoxy-2-oxa-3-azabicyclo[2.2.2]oct-5-ene Hydrochloride (18):\(^{1}\)

3.07 g (10 mmol) of 1-C-nitroso-2,3,5,6-di-O-isopropylidenemanofuranosyl chloride 6 was dissolved in CHCl\(_3\) (10 mL) and the solution added dropwise at \(-70^\circ\text{C}\) to a solution of 17 (2.35 g, 12 mmol) in EtOH (10 mL). After 4 d at \(-40^\circ\text{C}\) the blue colour had disappeared, and Et\(_2\)O (10 mL) was added. The product crystallized upon cooling. Recrystallization from EtOH/Et\(_2\)O gave colourless crystalline 18 (2.34 g, 89%), mp 177°C (dec.), \([\alpha]\)\(_D\)\(^{20}\) = +26° (c = 5.0, MeOH), (ee > 99%).

(3R,4S,5R,6S)-(±)-3-Acetamido-4,5,6-triacyclexoyclobex-1-ene (Conduramine A1 Tetraacetate) (19):\(^{1}\)

To a solution of 18 (930 mg, 3.52 mmol) in H\(_2\)O (20 mL), cooled to 5°C, zinc dust (4.6 g) and conc. HCl (5 mL) were slowly added over a period of 7 h. Unreacted zinc was filtered off, and the solution brought to pH = 9 by addition of conc. NaOH. The zinc hydroxide was removed by filtration, the solution was evaporated to dryness, and acetylated with Ac\(_2\)O and pyridine. Recrystallization from Et\(_2\)O/hexane gave 19 (902 mg, 82%), mp 121°C, \([\alpha]\)\(_D\)\(^{20}\) = 35.6° (c = 5.0, CHCl\(_3\)).

It would be of interest to undertake the HDA cyclization of the C\(_2\)-symmetrical diacetate (±)-12 with the chiral nitroso dienophile 11, to check the expected kinetic resolution, and the absolute configuration of the major enantiomer which is expected to be (±)-13. Likewise HDA cyclization of meso diacetate 17 with chiral dienophile 11 would be expected to give the enantiomer of 18 as the major product.

4. Pyrrolidine, and Piperidine Alkaloids

Naturally occurring N-containing 1-deoxy sugars, which have been discovered in several plants in recent years,\(^{1,2}\) can be considered as polyhydroxylated pyrrolidines, piperidines, octahydroindolizines and hexahydropyrrolizines. All these polyhydroxylated alkaloids are sugar mimics which act as glycosidase inhibitors.\(^{13}\) Of particular interest is the observation that some of these deoxyamino sugars, which inhibit glycoprotein processing, have potential anti-human immunodeficiency virus (HIV) activity.\(^{14,15}\) Syntheses of mono- and bicyclic glycosidase inhibitors with modified structure and configuration are, therefore, of potential relevance.\(^{16,17}\)

Many such syntheses have been described starting from chiral carbohydrate precursors taken out of the "chiral pool".\(^{18}\) In a few instances though de novo syntheses have been described which make use of HDA methodology with R–N=O dienophiles.

In a model reaction in situ generated BnOCON=O reacted with complete regioselectivity with butadiene derivative 20 to give adduct (±)-21 in 47% yield. A sequence of straightforward reaction steps led to hemiaminal (±)-22 whose treatment with Ba(OH)\(_2\), then with SO\(_2\) gave the crystalline deoxyminoerythrose bisulfitic derivative (±)-23. Base-induced hydrolysis of 23 led to an oily mixture of dihydroxy pyrrolidine (±)-24 and its pyrrolidine hemiaminal (±)-25.\(^{19}\) (Scheme 7). When N-butadienyl tert-buty1 1-pyrrol glutamate (R = t-Bu) 26 was reacted with BnOCON=O in MeOH solution at \(-20^\circ\text{C}\), chiral 27 was formed as the major diastereoisomer with a de of 76%. It was easily separated from the minor isomer 28. The absolute configuration of a similar compound 27 (R = Me) had already been ascertained by X-ray diffraction of a cis-glycol derivative.\(^{20}\)

Chiral aminoerythritol derivative 33 was synthesized as follows: the dimethylpyrrolidine N-acrylimino dienophile 29 reacted with silyloxy butadiene 30 to give 31 as the only detected and isolated cycloadduct (50%). cis-Hydroxylation of 31 was achieved with Os\(_4\)O\(_4\) (catalytic amount) in the presence of N-methylmorpholine N-oxide (NMO) as the cooxidant. It led to 32 in which the cis-diol functionality is anti with respect to the silyloxy group, as shown by X-ray diffraction which also allowed the determination of the (S)-configuration of C(6).\(^{22}\) The stereostructure of 32 having been ascertained, the geometry of the HDA transition state was formulated as indicated in Scheme 8, the formation of the acyltiroso dienophile being s-cis.\(^{22,23}\) Raney nickel catalyzed hydrogenolysis of 32, followed by two consecutive steps (i: elimination of the silyloxy group; ii: catalytic reduction of the ensuing aldehyde) gave ultimately the expected L-1- amino-1-deoxyerythritol derivative 33.\(^{22}\)
(6S,6‘-(C-Benzyl-1-Oxy-2,6-dimethyl-4-pyrroolidinyl-3,6-dihydro-1H,2H-dioxazine 31): 
To a stirred solution of diene 30 (490 mg, 2.7 mmol) in CH₂Cl₂ 
(5 mL) at 0 °C, containing ca. 50 beads of 4 Å molecular sieves, was added 
Pr₃NIO₂ (1/3 mol/mol of acid) and then portionwise the 
hydroxyacid (0.42 g, 2.7 mmol; 1 equiv). After ca. 4 h the red 
solution was diluted with Et₂O, treated with 1 N Na₂CO₃, 
containing some Na₂SO₃, and finally with brine (3 ×). The 
organic phases were 
extracted again with Et₂O and the combined organic layers dried (MgSO₄) 
and evaporated. The ratio of minor isomer to adduct was 
determined by ¹H and ¹³C NMR on the crude residue: no minor 
aduct could be detected. The crude product was purified by flash 
chromatography (EtOAc/cyclohexane 2:8) to give 31 (0.455 g, 
50%) as colourless crystals, mp 55 °C (pentane at −20 °C).

(2S,3R)-4[(2R,5R)-2,5-Dimethylpyrrolidin-1-yl-carbonyl]amino-butane-1,2,3-triol 33:
A solution of 32 (139 mg, 0.37 mmol) in EtOH (5 mL) was hažo-
genously with H₂ (1 atm.) 1 d at 40 °C over Raney nickel (previously 
ashed under H₂ in EtOH). After filtration on Celite, the solvent was 
evaporated, the solid recrystallized; 33 (66 mg, 72%); colourless 
crystals. mp 110 °C (EtOAc, i-Pr₂O). [(b) 29 = −36.4 °C (c = 1.0, 
MeOH).

Scheme 8
N-Benzylcarbonylnitroso BnONCON = O dienophile, 
which was obtained by in situ oxidation of the corre-
sponding hydroxamic acid with periodate (see above), 
reacted with 34 to give a major HDA cycloaduct in 
excellent yield. Catalytic osmylation (in the presence of 
NMO) of the latter led to the cis-diol 35 which on 
hydrogenolysis (H₂/ 
Pd/C) gave the acyclic aminooligosaccharide 
dimethyl acetal 36. 
When a solution of 36 in water was 
reacted with SO₂ for 3 days at 40 °C the bisulfite 37 
(β-anomer) was formed in 90% yield as colourless 
crystals (mp 146−147 °C). Saponification of 37 in water using 
a small excess of Ba(OH)₂, at room temperature gave a 
mixture of 5-amino-5,6-dideoxyoligosaccharide (2 anomers) and 
the corresponding imine. Catalytic hydrogenation (5% 
Pd/C; r.t.; 20 h) of this mixture led quantitatively to the 
sole aminotriol (±)-38, i.e., 1.6-dideoxyallobiurinimycin 
which was characterized as its tetraacetyl derivative (±)- 
39 (mp 120−121 °C) (Scheme 9).

Wyatt performed a similar reaction sequence using 
optically active diene 40, (1S,2S)-pseudophedrine being the 
chiral auxiliary. Reaction of 40 at low temperature 
with BnONCON = O led to a mixture of four compounds 
from which the major cycloaduct 41 could be isolated 
(32%) after several flash chromatographies. Catalytic 
osmylation of 41 in the presence of Ba(ClO₃)₂ as a re-

Scheme 9

(a) BnONCON = O; (b) OsO₄, NMO; (c) H₂, Pd–C; 
(d) SO₂; 
(b) OsO₄ cat., Ba(ClO₃)₂; (c) H₂, Pd–C; 
(d) Ac₂O, pyridine

Scheme 10

The key step of Kibayashi’s total synthesis of the pipe-
idine alkaloid (−)-nupharimine (47) is based on the 
intramolecular HDA cycloaddition of chiral acylnitro-
so-diene 44. The corresponding hydroxamic acid 43 was obtained from (R)-citronellol according to some known 
procedures. The two primary cycloaducts 45 and 46 were 
formed in a 1.8:1.0 mixture (88% overall yield) 
from which 45 was separated by chromatography and 
recrystallization. This stereoisomer was then converted 
into the alkaloid 47 in seven steps. 

5. Indolizidine, and Pyrrolizidine Alkaloids

Starting once again from (R)-citronellol and applying 
the same intramolecular HDA cycloaddition Kibayashi 
and Shishido achieved the total synthesis of several chiral 
indolizidine alkaloids. Let us have a closer look at the 
synthetic scheme of (−)-indolizidine 205-A 53. 

Hydro-
xamic acid 43 was oxidised to 44 which cyclized at once to the Diels–Alder adducts 45 and 46 as above. Reductive alkylation of the hydrogenated derivative 48 gave stereospecifically 49 whose N–O bond was reduced by zinc in aqueous acetic acid (90%). Upon exposure to PPH3/ CBr4 and then to triethylamine 50 smoothly underwent intramolecular cyclodehydration to 52 via the alkoxophosphonium salt 51. Eventually removal of the trimethylsilyl group with alkali provided 53, i.e. (−)-indolizidine 205-A (Scheme 12).29

(4aR)-5-Methyl-4a,5,6,7-tetrahydro-2H-pyrido[1,2-b][1,2]oxazin-8-one (45):

To a cold (0°C) stirred solution of tetrapropylammonium periodate (7.18 g, 19.0 mmol) in CHCl3 (380 mL) was slowly added a solution of 43 (2.83 g, 16.7 mmol) in CHCl3 (220 mL). The mixture was stirred for 1 h at 0°C, and then it was washed, successively, with 5%aq Na2S2O3, 5% KOH, and brine. The CHCl3 solution was dried (MgSO4) and concentrated. The residue was purified by column chromatography on silica gel (CHCl3) to give a 1:1.5 mixture of 45 and 46 (2.47 g, 88%) as a colourless semisolid. Compound 45 was separated from the oily cis-adduct 46 by column chromatography on silica gel (CHCl3). Recrystallization (i-Pr2O) gave pure 45 (1.40 g, 50%); mp 93–94°C; [α]D20 = +25° (c = 0.93, CHCl3).

Synthetically Scheme 12 is of particular interest in spite of the poor stereoelectivity of the HDA cycloaddition step: (i) during the intramolecular [4r + 2r] process the piperidine ring was formed having the optical handle with the required absolute configuration and in the right position; (ii) reductive cleavage of the N–O bond followed by intramolecular cyclodehydration led to the oxazolidine-pyrrolidine ring contraction.29

Keck and Romer applied a similar methodology – i.e. piperidine ring formation via intramolecular HDA, and ring contraction of the 1,2-oxazolidine 59 into a pyrroloidine 60 – to the total synthesis of chiral stereoisomers of the alkaloid swainsonine.30 Starting from L-glutamic acid they obtained chiral diene 54 in 6 steps and better than 60% overall yield. The following steps are rather straightforward as depicted in Scheme 13. The only weak point is, once again, the rather poor stereoelectivity of the intramolecular HDA cycloaddition: at −78°C cycloadducts 57 and 58 were obtained as optically pure products in a 2:4:1:0 ratio.

(55S)-5-[(tert-Butylidiphenylsilyl)oxy]tetrahydro 4a,5,6,7-tetrahydropyrido[1,2-b][1,2]oxazin-8 ones 57 and 58:

To a solution of tetrapropylammonium periodate (188 mg, 0.499 mmol) in CH2Cl2 (10 mL) at −78°C was added dropwise, a solution of the hydroxamic acid 55 (186 mg, 0.454 mmol) in CH2Cl2 (5 mL). After stirring at −78°C for 4 h, the reaction mixture was allowed to warm to 0°C over a 30 min period. The solution was taken up in EtOAc (50 mL) and washed with sat. aq Na2SO4 (2×10 mL) and then dried (Na2SO4). Concentration followed by flash chromatography of the residue eluting with 75% EtOAc/hexanes gave 180 mg (96%) of 57 and 58 as a mixture of diastereomers. The isomers were separated by preparative HPLC (10 μm silica, 25 cm × 21.4 mm column) eluting with 30% THF/hexanes, to give a 2.4:1 ratio of the two diastereomeric cycloadducts. Analysis of the major 88,8aR (swainsonine numbering) isomer 57 Rf, 0.20 (50% EtOAc/hexanes); [α]D20 = −79.5° (c = 3.9, CHCl3). Analysis of the minor 85, 8aS (swainsonine numbering) isomer 58 Rf, 0.20 (50% EtOAc/hexanes); [α]D20 = −57.3° (c = 2.7, CHCl3).

The total synthesis of (+)-heliotridine (74) and (±)-retronecine (76) by Keck and Nickell illustrates the elegance and efficiency of a well designed HDA cycloaddition with RCON = O.31 The route these authors chose relies heavily on the intramolecular dienophile transfer technique they had developed32 to simultaneously form the key N–C(8) carbon nitrogen bond, establish the A1,2 double bond, and functionalize C(3) appropriately for eventual formation of the N–C(3) bond (Scheme 14). The readily available acetylenic ester 63 led quantitatively to butadiene 64 and thence to its reduced form 66. Condensation with 67 followed by protection of the secondary alcohol gave 69 (diastereoisomeric mixture) in 64% overall yield from 65. The key intermediate 69 now contains all carbon and nitrogen atoms destined to appear in the final alkaloids, as well as differentially protected hydroxyl moieties destined to appear at C(7) and C(9). Intramolecular transfer of the acylnitroso dienophile proceeded readily by thermolysis32 to afford 1,2-oxazine derivative 70 (mixture of two (±)-diastereoisomers) whose N–O bond was cleaved reductively to afford 71. LDA treatment of the two mesylates 72 gave the bicyclic lactams 73 and 75.
(50% overall yield from 70) which could easily be separated. The conversion of 73 into (+)-heliotridine (74), and of 75 into (+)-retronecine (76) was achieved readily (Scheme 14).31

6. Tropane Alkaloids

Kibayashi applied a synthetic methodology for tropane alkaloids which is based, (i) on the HDA cycloaddition of cyclohepta-1,3,5-dienes with nitroso dienophiles, and (ii) on the ring contraction of the perhydroxazine to the corresponding pyrrolidines.33 Let us look at one example: the synthesis of pseudotropine 85. HDA of cyclohepta-3,5-dienyl benzate 77 with 1-chloro-1-nitrocyclohexane 78 gave cycloadducts 79 (exo)/80 (endo) as a 4:1 mixture of the hydrochlorides which were separated. The major exo form 79 was submitted to catalytic hydrogenation and the resulting amino alcohol 81 to selective N-acetylation with ethyl chloroformate, affording thereby carba-
7. Tabtoxin and Tabtoxinidine-β-Lactam

The first total synthesis of the exotoxin tabtoxin (±)-91 was accomplished by Baldwin and co-workers. It represents a brilliant application of HDA with a nitroso dienophile, albeit a rather large number of functional group interconversions proved to be indispensable, particularly in view of the oxidative double bond cleavage (K,MnO₄) of 88 to the diacid 89. As a consequence the overall yield of this total synthesis is only moderate (Scheme 16). The crucial stereochemical relationship between C(2) and C(5) was achieved by simultaneous formation of C(2)-N and C(5)-O bonds via regioselective HDA reaction of BrOCON=O with ethyl cyclohexa-1,3-diene carboxylate (86). Lastly the sensitive β-lactam ring was closed in the final steps of the synthesis. A similar methodology led to the total synthesis of (±) tabtoxinidine-β-lactam 92, as performed also by the Baldwin group.

Ethyl 3-Benzoyloxy carbonyl-2-oxa-3-azabicyclo[2.2.2]oct-5-ene-1-carboxylate (87):

To a stirred solution of ethyl cyclohexa-1,3-diene carboxylate (86) (31.63 g, 0.21 mol) and benzyl N-hydroxy carbamate (38.2 g, 0.23 mol) in CH₂Cl₂ (350 mL), a solution of Et₃NIO₄ (73.5 g, 0.23 mol) in CH₂Cl₂, was added over 1 h whilst maintaining the temperature at −5 ± 2 °C. After stirring for a further 20 min the solution was washed with aqueous sodium bisulphite (15%, 3 x 200 mL), saturated aqueous NaHCO₃ (2 x 150 mL) and brine (150 mL), dried (MgSO₄) and concentrated in vacuo. The resulting brown oil was purified by flash chromatography (stepwise elution with CH₂Cl₂, 5% EtOAc-CH₂Cl₂) to give 87 as a viscous yellow oil (61.29 g, 93%).
(ca. 5 mg, 4 μmol) in MeCN (2.4 mL) was heated at 80°C in a sealed tube under an Ar atmosphere for 10 h. The reaction mixture turned dark orange after ca. 10 min, and the catalyst platted out on the walls of the tube as a shiny layer of palladium metal upon completion of the reaction. The reaction mixture was cooled to r.t.; the reaction was quenched with aq NaHCO₃, and the mixture was extracted with EtOAc (4 ×). The organic extracts were washed with aq Na₂SO₄ (1 ×), water (1 ×), and brine (1 ×) and dried (MgSO₄). Filtration, concentration, and purification of the orange residue by flash chromatography (45:55 Et₂O/hexanes) gave 66 mg (90%) of 97 as a colourless solid: mp 193–194°C; Rf = 0.29 (8:2 Et₂O/hexanes).

(a) NaHCO₃, benzene, 80°C; (b) Pd(PPh₃)₄, Et₂N, MeCN

Scheme 17

(±)-Mitomycin K (104).[38] – The key step for the total synthesis of mitomycin K (104) is an intramolecular regioselective HDA of an arylnitroso moiety with an ortho-attached ketodiene. This particular polyfunctionalized arylnitroso–ketodiene was generated via a photoinduced (UV) intramolecular Redox process from the corresponding isomeric arylnitro–dienol 101. The arylnitroso–ketodiene (not shown in Scheme 18) underwent at once a regioselective HDA to adduct 102, a photolabile compound which rearranged to the hemiaminal 103. Tricyclic compound 103 led to mitomycin K (104) in no less than ten steps and in low overall yield.[38]

Photochemical Generation of (±)-2,4a-Dihydro-4a,6,7,9-tetramethoxy-5H-1,2,3-oxazino[2,3-α]indol-5-one (102) and (±)-3,9a-Dihydro-3-hydroxy-5,7,8,9a-tetramethoxy-6-methyl-9H-pyrrolo[1,2-α]indol-9-one (103):

A solution of the nitro diene 101 (0.260 g, 380 mmol) in THF (76 mL) was degassed for 30 min with a stream of argon. The stirred solution was irradiated in a Rayonet system with four 350-nm lamps for 15 h. The resulting orange solution was concentrated, and the residue was purified by flash chromatography (25 g SiO₂: 50% EtOAc/hexanes) to provide 0.037 g (15%) of 102 (Rf = 0.47) and 0.111 g (45%) of 103 (Rf = 0.47).

9. Lycoricidine

The narcissus alkaloids, of which (+)-lycoricidine (112) is a prominent member, possess considerable medicinal potential because of their wide range of biological activities. Extremely low abundance warrants synthetic efforts towards these substances. The following total synthesis of (+)-lycoricidine (112) by Hudlicky is elegant and efficient; it was performed in only nine steps in good overall yield (Scheme 19).[39] Enzymatic hydroxylation of bromobenzene being performed on an industrial scale, chiral cis-diol 105 and its acetone 106 were easily available in large amounts. In situ oxidation of hydroxamic acid 107 led to the corresponding acyl nitroso dienophile which underwent regioselective HDA reaction with 106 to the expected bicyclic adduct 108. Reduction of the

(a) THF, –78°C; (b) hv, MeOH (350 nm)

Scheme 18

(a) DMP, acetone, p-TsOH; (b) 107. Bu₄N⁺NO₂, CH₂Cl₂; (c) Al(Hg), THF; (d) i-PrMe₂SiCl, imidazole, CH₂Cl₂; (e) Pd(OAc)₂, Ti(OAc)₅, DIPHOS, anisole; (f) H₂, Pd-C; (g) CF₃COH

Scheme 19
N–O and of the C–Br bonds led stereospecifically to 109. Cyclization of its derivative 110 followed by catalytic hydrogenolysis gave 111, the immediate precursor of (+)-lyricidine (112) (Scheme 19).

10. Chiral Amino Acids

Ghosez has worked out a novel approach toward the asymmetric synthesis of amino acids which uses the HDA reaction of 2-azadienes 113 with chiral acyltrinitro compounds for the stereocontrolled formation of the new C–N bond.\textsuperscript{40,41} In order to improve asymmetric induction C\textsubscript{2}-symmetric chiral pyrroolidine 114 was used (Scheme 20). Cycloaddition proved to be facial- and regioselective so that the isolated adducts 115 were optically pure. During the last step amino acids 117 were obtained as enantiopure entities in fair yield.\textsuperscript{40,41} Ghosez developed also a new and efficient method for the in situ generation of the acyltrinitro dienophile 114: hydroxamic acid 118 was treated with the sulfoxide reagent 119 developed by Corey\textsuperscript{42} to give intermediate 120 which upon treatment with triethylamine yielded the desired nitroso compound 114 (Scheme 20).

\[
\begin{align*}
\text{113} & \quad \text{114} \\
\text{115} & \quad \text{optically pure} \\
\text{116} & \quad \text{117} \\
\text{117} & \quad \text{enantiomerically pure} \\
\text{118} & \quad \text{119} \\
\text{120} & \quad \text{114}
\end{align*}
\]

(a) Mo(CO)\textsubscript{6} in refluxing H\textsubscript{2}O–MeCN; (b) 6 N HCl, 4

Scheme 20

11. Conclusion and Outlook

With a few exceptions nitroso dienophiles which were employed in the total synthesis of natural products are in situ generated acyltrinitro reagents, RCON = O. Because of their extraordinarily high reactivity these synths appeared to be attractive species for a number of synthetic operations. As a consequence, some of the leading contemporary organic chemists based the key process of their retrosynthetic analyses (of complex natural products) on HDA cycloreversion disconnections toward acyltrinitro dienophiles. The emerging total syntheses were accomplished with great success, as shown in this review article. This notwithstanding, we believe that the chemistry of acyltrinitro compounds, RCON = O, bears more potential and should be explored further, particularly in the field of HDA cycloadditions. To the best of our knowledge Lewis acid (LA) catalysis has not been described so far for such HDA cycloaddition reactions. Since type A, B, and C (Figure 1) nitroso dienophiles undergo cycloaddition instantaneously with conjugated dienes as soon as they are formed, rate enhancement via LA catalysis can hardly be expected. By the same token asymmetric catalysis with chiral LA is not expected to operate with nitrosoyl cyanoide and with acyltrinitro dienophiles. However, acyltrinitro dienophiles which undergo HDA at a much slower rate, may be amenable to LA catalysis, particularly if they bear a carbonyl or a cyano group in the para position. Actually, the N=O functional group itself may undergo a bonding interaction with a Lewis acid. If so, would it still react as a dienophile? Some exploratory experiments along these lines should be undertaken.

As to inter- or intramolecular Alder–ene reactions of an acyltrinitro moiety with simple olefins, they would afford a method for effecting carbon–nitrogen bond formation as indicated in Scheme 21 for inter- and intramolecular reactions.\textsuperscript{43} Unfortunately this methodology, which can be considered as an extension of the HDA cycloaddition, remains largely unexplored. The elegant total synthesis of \((\pm\)-erinane (128)\textsuperscript{44} reported by Keck represents one of the rare applications of the Alder–ene reaction. It is based on the thermal cycloreversion of the anthracene adduct 125 which led quantitatively to the N-hydroxy \(\beta\)-lactam 126. A four-step sequence led to pyrrolidine 127 whose Pictet–Spengler reaction with the Eschenmoser salt gave \((\pm\)-erinane (128) in good yield (Scheme 22).\textsuperscript{44}

9.10-Dihydro-12-\{[1-3,4-(methylene dioxy)phenyl]cyclohex-2-enyl acetyl\}-9,10-dimethyl-10,9-(oepxino) anthracene (125): A solution of hydroxamic acid 124 (1.29 g, 4.7 mmol) in CH\textsubscript{3}Cl, (5 mL) and DMF (1 mL) was added slowly and dropwise (syringe drive) to a suspension of 9,10-dimethylanthracene (0.967 g, 4.7 mmol) and tetrapropylammonium periodiate (1.94 g, 5.17 mmol) in CH\textsubscript{3}Cl, (10 mL) and DMF (2 mL). The syringe drive was adjusted to deliver 1 drop every 8–10 s, and the addition was completed after 5 h. The dark yellow solution was then poured into CH\textsubscript{3}Cl, overlaid with sat. aq sodium thiosulfate solution, and the phases were separated. The aqueous phase was back-extracted with CH\textsubscript{3}Cl, (3 × 10 mL), and the combined organic layers were washed with brine, dried (Na\textsubscript{2}SO\textsubscript{4}), and concentrated in vacuo to give a brown solid. The crude product was dissolved in CH\textsubscript{3}Cl,–THF and chromatographed on a 1 × 100 cm silica gel column slurry packed in 35% THF–hexanes (elution with the same fractions): fractions 19–33 were combined and concentrated in vacuo to give 1.90 g (85%) of white solid, homogeneous by NMR and TLC analysis: mp 67–70°C dec.

\(\text{N-Hydroxy-3a-[3,4-(methylene dioxy)phenyl]-2-oxo-2,3,3a,4,5,7a-}
\text{hexahydroindole (126): Diels–Alder adduct 125 (0.9 g, 1.87 mmol) was decomposed in re-}
\text{fluxing toluene (250 mL). After 15 min, TLC detailed the consump-}
\text{tion of starting material with formation of 9,10-dimethylanthracene and a polar UV spot which stained purple on exposure to FeCl\textsubscript{3} (2% in EtOH, 1% HCl). The crude yellow solid that remained after removal of the toluene was chromatographed on a 1 × 50 cm silica gel column slurry packed in CH\textsubscript{3}Cl, and eluted with 2% MeOH in CH\textsubscript{3}Cl, fractions 21–25 were combined and concentrated in vacuo to yield 508 mg (100%) of light pink solid. One crystallization}
from CH₂Cl₂-pentane yielded analytically pure material as colourless rosettes: mp 160–163°C.

Finally a novel fragmentation of some 3,6-dihydro-1,2-oxazine HDA cycloadducts 129 from their 3-lithio form 130 should be mentioned (R = CBZ or Boc) since it leads to 131 and hence to 2,5-dihydro-2-furanylamines 132 via ring contraction, as indicated in Scheme 23.55 This ring contraction should be potentially useful in the total synthesis of some natural products.

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