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The Barton ester free-radical reaction: a brief review of applications

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In memory of Sir Derek H. R. Barton (1918–1998)

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Abbreviations: Ac, acetyl; AIBN, 2,2′-azobisisobutyronitrile; DCC, dicyclohexylcarbodiimide; DIPEA, diisopropylethylamine; DMAP, *N*,*N*-4-dimethylaminopyridine; DME, ethylene glycol dimethyl ether; DMF, *N*,*N*-dimethylformamide; DMTHF, tetrahydro-2,5-dimethoxyfuran; EDC, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; Fmoc, 9-fluorenylmethyloxycarbonyl; HBTU, 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; KDO, 3-deoxy-D-*manno*-2-octulosonic acid; L-CCGs, L-(carboxycyclopropyl)glycines; MOM, methoxymethyl; NMM, 4-methylmorpholine; PTOC, pyridine-2-thione-*N*-oxycarbonyl; PyS, 2-pyridylthiyl; TBAF, tetra-*n*-butylammonium fluoride; TBDPS, *tert*-butyldiphenylsilyl; TBS, *tert*-butyldimethylsilyl; TBTH, tri-*n*-butyltin hydride; THF, tetrahydrofuran; TMS, trimethylsilyl; TTMSS, tris(trimethylsilyl)silane; (UDP-Gal*f*), uridine diphosphate-α-D-galactofuranose; (UDP-Gal*p*), uridine diphosphate-α-D-galactopyranose; WSC, water-soluble carbodiimide.

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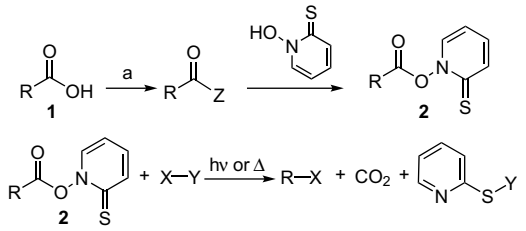
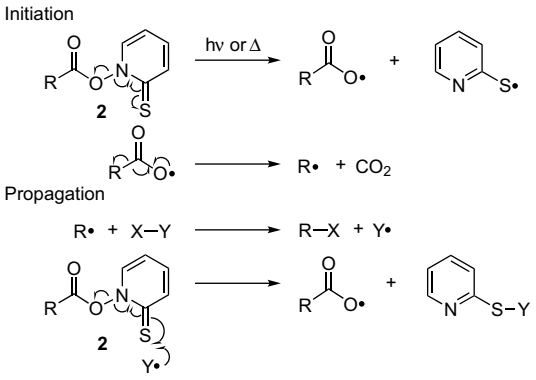
1. Introduction

Free-radical reactions offer a powerful tool in organic synthesis and much attention has been given to this class of reactions. Among these, the conversion of a carboxylic acid **1** into a thiohydroxamate ester **2**, followed by homolytic cleavage, has furnished an important source of radicals. This sequence of reactions has been used to remove a carboxylic acid group and to replace it by another functional group, thereby generating new bonds such as carbon–carbon, carbon–oxygen, carbon–sulfur, carbon–selenium and carbon–halogen bonds. The preparation of thiohydroxamate esters **2**, known as Barton esters (Scheme 1), was achieved in 1983 by the Barton group[1,2] and several improvements in the preparation have since been reported.[3–5] The tremendous flexibility in the controlled generation of radical species from these thiohydroxamate esters is one of the most attractive features for organic synthesis. For example, Barton esters have been largely used for the synthesis of biologically active compounds such as carbohydrates,[6–10] amino acids,[11–15] vitamins[16] and terpenoids.[17–22]



Scheme 1. (a) $SOCl_2$; $(COCl)_2$ or DCC.

Many examples in the literature describe the cleavage of the nitrogen–oxygen bond of thiohydroxamate esters **2**.[23] The reaction mechanism was proposed to involve homolytic cleavage, generally initiated by light or heat, leading to a 2-pyridylthiyl radical (PyS•) and an acyloxy radical (RCOO•). The alkyl radical (R•), generated by radical decarboxylation, reacts with a radical-trapping species X–Y, resulting in the formation of R–X, the trapped product bearing a new functional group. The radical Y• attacks the sulfur atom of the thiohydroxamate ester, forming an S–Y bond (Scheme 2).



Scheme 2. General mechanism for generation and trapping of radicals from thiohydroxamic ester derivative.

2. New bond formation by radical reactions via thiohydroxamate esters

2.1. Reductive decarboxylation

The Barton reductive radical decarboxylation is a sequence of reactions in which a carboxylic acid is first converted into a thiohydroxamate ester and then heated in the presence of a suitable hydrogen donor such as TBTH, TTMSS or *t*-BuSH.

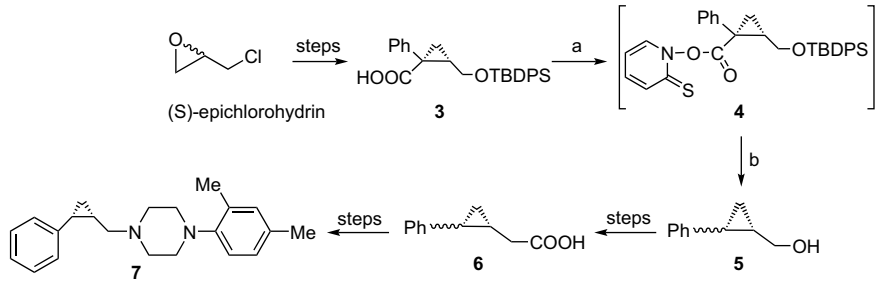
Shuto and co-workers[24a] have used Barton reductive radical decarboxylation as the key step in the enantioselective synthesis of haloperidol analogues, an effective antipsychotic agent and a representative compound of the butyrophenone class. The key point in the synthesis of these analogues is the construction of the chiral *cis*- and *trans*-cyclopropane structures that can be stereoselectively prepared by the Barton reductive decarboxylation of the chiral phenylcyclopropanecarboxylic acid **3** under radical conditions.[24b] The synthetic plan for the *cis*-cyclopropane **7** with a (1*S*,2*R*) configuration is described in Scheme 3. The key intermediate **5** was obtained by treatment of cyclopropanecarboxylic acid **3** with 2,2′-dithiobis-(pyridine *N*-oxide), tributylphosphine and a hydrogen donor, leading to *O*-acyl thiohydroxamate ester **4**, followed by in situ radical decarboxylation by addition of an initiator or irradiation with a high-pressure mercury lamp (Scheme 3). The yield and cis/trans ratio of the products were determined after removal of the silyl protecting group and the results are summarized in Table 1.

After the preparation of the intermediate compound **5**, two subsequent steps furnished the carboxylic acid **6**. When **6** was

Table 1
Radical decarboxylation[a] of Barton ester **4** to produce compound **5**

Entry	Reductant	Initiator	Solvent	Temp (°C)	Yield (%)[b]	cis/trans[c]
1	Bu_3SnH	Et_3B	THF	rt	70	2.8/1
2	Bu_3SnH	Me_2Zn	THF	rt	48	2.8/1
3	Bu_3SnH	*hν*	THF	rt	36	2.6/1
4	Bu_3SnH	AIBN	PhH	80	80	2.7/1
5	Bu_3SnH	AIBN	PhCl	130	69	2.6/1
6	*t*-BuSH	Et_3B	THF	rt	80	3.0/1
7	PhSH	Et_3B	THF	rt	70	3.1/1
8	Ph_2SiH_2	AIBN	PhH	80	27	2.5/1
9	TMS_3SiH	Et_3B	THF	rt	74	10/1
10	TMS_3SiH	Et_3B	THF	0	47	14/1
11	TMS_3SiH	Et_3B	THF	−20	22	14/1
12	TMS_3SiH	AIBN	PhH	80	75	11/1

[a] Radical reaction carried out using 5 equiv of reductant in the presence of initiator (Et_3B, 0.3 equiv; Me_2Zn, 0.3 equiv; *hν* high-pressure mercury lamp, 300 W; AIBN, 0.2 equiv).
[b] Isolated yield after deprotection.
[c] Determined by ^1H NMR.



Scheme 3. (a) Bu_3P, 2,2′-dithiobis-(pyridine *N*-oxide), hydrogen donor (THF, benzene or chlorobenzene); (b) (i) radical reaction; (ii) TBAF, THF.

condensed with *N*-(2,4-dimethylphenyl)piperazine using 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC), the cis isomer was obtained in a pure form after column chromatography. AlH_3 reduction of the carboxamide furnished compound **7** with a *cis*-cyclopropane structure.

Similarly, starting from (*R*)-epichlorohydrin, the *cis*-cyclopropane analogue with a (1*R*,2*S*) configuration was synthesized.

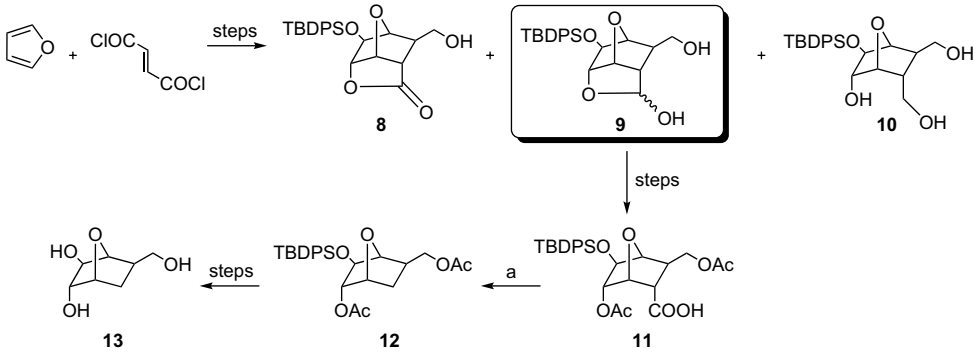
Another important result in the stereocontrolled synthesis of cyclopropane rings via a Barton ester was described by Oba and co-workers,[11] who achieved the preparation of pharmacologically important cyclopropane amino acids, such as L-CCGs and 3,4-methano-L-prolines, constrained analogues of L-glutamic acid and L-proline, respectively.

Thomas and co-workers[7] described the synthesis of a carbasugar, the 1,4-anhydro-β-D-galactopyranose derivative **13** (Scheme 4), diendioate employing efficient Barton decarboxylation generating the methyl group without loss of stereochemical integrity.[25]

2.2. Carbon–carbon bond formation

A wide variety of compounds can be prepared using the Barton ester reaction and trapping of the decarboxylated radical with a variety of compounds, allowing the formation of new bonds.

A carbon–carbon bond can be formed when the homolytic cleavage of an *O*-acyl thiohydroxamate is performed in situ in the presence of allylic or vinylic compounds. This method has been used by Barton's group[8] in the synthesis of 3-deoxy-D-*manno*-2-octulosonic acid (KDO) derivatives from D-glucono-1,5-lactone (Scheme 5). A similar procedure was previously described[26] using penta-*O*-acetyl-D-gluconic acid, but with lower diastereoselectivity.



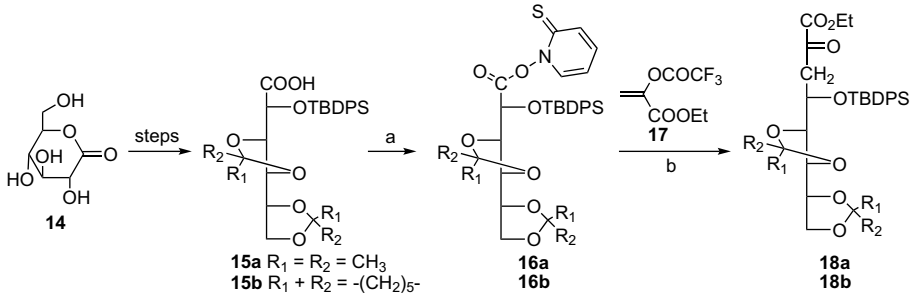
Scheme 4. (a) (i) $(COCl)_2$, CH_2Cl_2, 15 min; (ii) 2-mercaptopyridine *N*-oxide, DMAP, *t*-BuSH, benzene, 1 h, reflux, *hν* (300 W tungsten lamp).

and evaluated its capacity to inhibit (UDP-Gal*p*) mutase, a flavoenzyme that catalyzes the interconversion of (UDP-Gal*p*) and (UDP-Gal*f*). Compound **13** was synthesized from furan and methyl acrylate via a Diels–Alder reaction for the construction of the key 7-oxabicyclo[2.2.1]heptane skeleton. Six subsequent steps led to a mixture of three products: lactone **8**, lactol **9** and triol **10** in 97% overall yield. Lactol **9** was separated from the lactone and triol byproducts by flash chromatography. After three steps, the lactol was converted into the carboxylic acid **11**, which was first activated by oxalyl chloride in dichloromethane and then treated with 2-mercaptopyridine *N*-oxide, DMAP and *t*-BuSH in anhydrous benzene, resulting in the reductive decarboxylation product **12** in 84% yield. The oxanorbornane **13** was obtained from **12** in two steps.

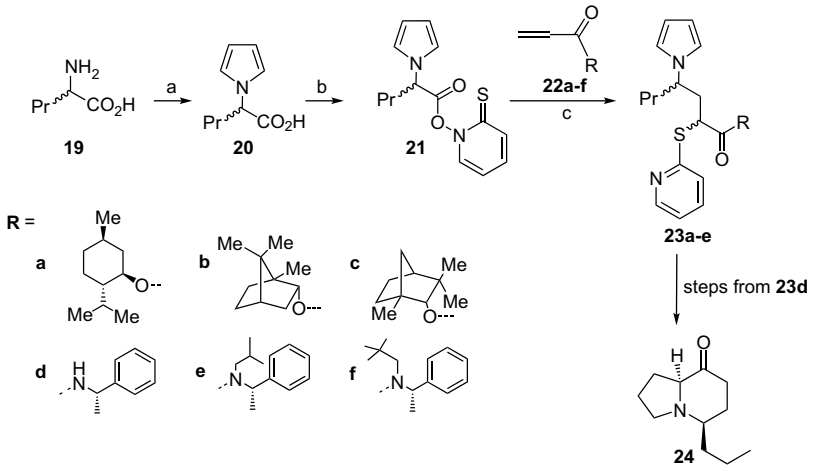
Reductive decarboxylation has been successfully applied to a very wide range of complex substrates.[25] An expeditious asymmetric synthesis of pent-3-yl (*R*)-6-methyl-cyclohex-1-ene-carboxylate has been achieved, by Garrido and co-workers,[25] in four steps in 42% overall yield from dipent-3-yl (*E*,*E*)-nona-2,7-

Carboxylic acids **15a** and **15b**, obtained in three steps from D-glucono-1,5-lactone **14**, were treated with *N*-hydroxy-2-thiopyridone in the presence of dicyclohexylcarbodiimide (DCC) in anhydrous dichloromethane to furnish the corresponding Barton esters **16a** and **16b**. Decarboxylation under irradiation in the presence of ethyl α-(trifluoro-acetoxy)acrylate **17**, furnished the protected *gluco*-KDO derivatives **18a** and **18b** in 53% yield as single isomers.

Corvo and Pereira[27] used acrylates and acrylamides as trapping compounds in their synthesis of (−)-indolizidine 167B **24** from racemic norvaline **19** (Scheme 6). Indolizidine is a biologically active alkaloid isolated in trace amounts from the skin of neotropical frogs and the literature shows several asymmetric syntheses of these alkaloids.[28] The reaction stereocontrol is achieved by the stereoselective addition of a carbon radical to an optically pure acrylamide. This strategy involves the use of a Barton ester as the carbon radical precursor. The authors investigated the relationship between the substituents and the diastereoselectivity. The



Scheme 5. (a) *N*-hydroxy-2-thiopyridone, DCC, CH_2Cl_2, 0 °C, 1 h; (b) (i) $H_2C{=}C(OCOCF_3)(COOEt)$, *hν*, −30 °C, 1 h; (ii) satd aq K_2CO_3/acetone 1:1, −20 °C to rt, 12 h.



Scheme 6. (a) (i) $SOCl_2$, MeOH; (ii) DMTHF, NaOAc, AcOH; (iii) KOH, MeOH; (b) *N*-hydroxy-2-thiopyridone, DCC, CH_2Cl_2, 0 °C to rt; (c) H_2C=CHCOR, *hν*, CH_2Cl_2, −40 °C.

carboxylic acid **20**, obtained by the reaction of **19** with tetrahydro-2,5-dimethoxyfuran, was transformed into the corresponding thiohydroxamate ester **21** using DCC and *N*-hydroxy-2-thiopyridone. The Barton ester **21** was then irradiated in the presence of chiral acrylates or acrylamides **22a–e**, furnishing the addition products **23a–e** in 12–58% yield as a mixture of diastereomers. Using the hindered acrylamide **22f**, no addition product was formed under similar conditions. Cyclization of **23d** in the presence of BBr_3, treatment with nickel boride and hydrogenation over palladium/carbon yielded 74% of the desired (−)-indolizidine 167B **24** (Scheme 6).

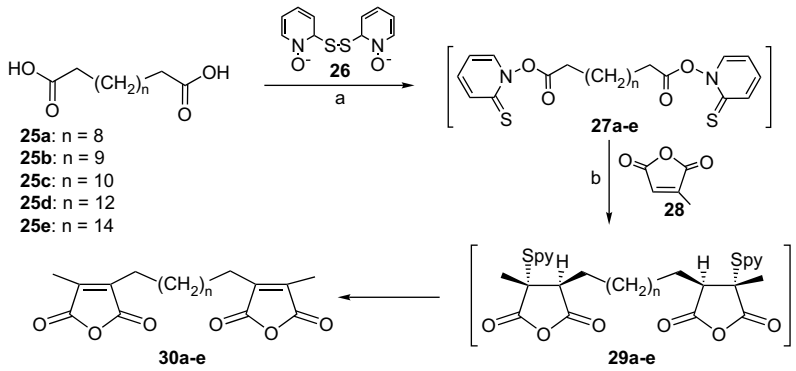
A number of syntheses of substituted anhydride derivatives have been reported in the literature, based on Barton decarboxylation.[29–32] For example, Samadi and co-workers[30] described the one-step synthesis of tyromycin A **30e** and derivatives **30a–d** (Scheme 7), natural inhibitors of leucine and cysteine aminopeptidases, containing two citraconic anhydride units. In this methodology, the diacids **25a–e** were treated with triphenylphosphine and 2,2′-dithiobis-(pyridine *N*-oxide) **26**, furnishing the thio hydroxamic diesters **27a–e**. Irradiation in situ of **27a–e** in the presence of citraconic anhydride **28** generated the intermediates **29a–e**, which, after purification on silica gel, led to the elimination products **30a–e** in 65–78% yields. The *syn* elimination of the 2-pyridylthio group of the intermediate **29** established the trans stereochemical relationship of the pyridylthio group and the alkyl substituents, which is the result of a trans addition of the radical to citraconic anhydride.[33]

Zard and co-workers[33] described an unexpected ring expansion using Barton's radical reaction in an attempt to synthesize the tricyclic skeleton of pleuromutilin, an antimicrobial agent frequently used in veterinary medicine (Scheme 8). These authors hoped that the visible light irradiation of the Barton ester **31** would generate a primary radical **32**, which would then be trapped by phenyl vinyl sulfone, followed by a 5-*exo*-*trig* ring closure, furnishing the *cis*-hydrindanyl radical **33**. The expected adduct was not however isolated and, instead, the reaction furnished compound **34**, containing a cycloheptene ring, in 20% yield. This yield was increased to 80% when the reaction was performed in the absence of phenyl vinyl sulfone. Although the alternative pathway adopted by Zard and co-workers to hydrindanone structure construction was frustrated, it represents, nevertheless, an interesting route to cycloheptenes, since it combines alkylative Birch reduction with the mildness and flexibility of the Barton decarboxylation.

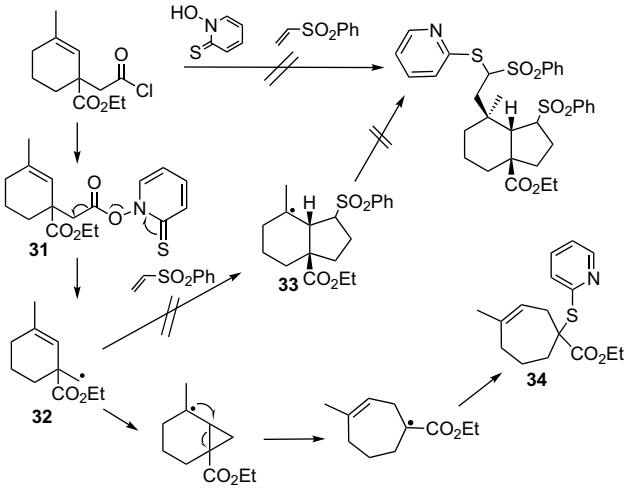
2.3. Decarboxylative oxygenation

Decarboxylative oxygenation by homolytic cleavage of *O*-acyl thiohydroxamates in the presence of oxygen has been widely applied in the synthesis of terpenoids and was reported for the first time by Barton and co-workers in 1984.[34]

(−)-Verrucarol **39** (Scheme 9) is a compound belonging to the family of structurally related sesquiterpenoids, isolated by Tamm and co-workers[35] as an alkaline hydrolysis product of the macrocyclic trichothecene, verrucarin A. This terpenoid has a trichotecane skeleton, which generally shows an *exo*-*epoxy* ring at the methylene bridge constituting the B and C rings. Tadano and co-workers[36] have described the total synthesis of (−)-verrucarol **39** using Barton's decarboxylative oxygenation (Scheme 9). The oxatricyclic acid **36**



Scheme 7. Reagents and conditions: (a) Ph_3P/2,2′-dithiobis-(pyridine *N*-oxide), CH_2Cl_2; (b) **28**, *hν*, CH_2Cl_2, 10–15 °C, 30 min.



Scheme 8. Initial synthetic plan and unexpected ring expansion.

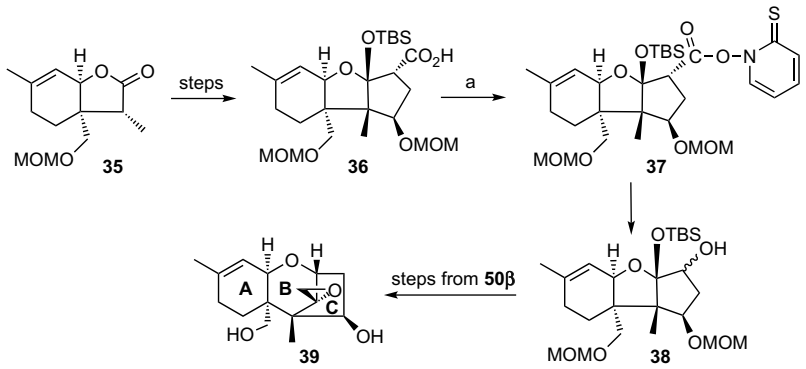
cyclopentyl ring was shown to be essential for ring enlargement, furnishing (−)-verrucarol **39** after nine steps from **38β**.

Paeoniflorin **44** is a natural monoterpenic glycoside, appearing as the major physiologically active principle from *Paeoniae radix*.[22] This natural product has been extensively used in oriental medicine as a sedative, analgesic and antispasmodic. Hatakeyama and co-workers[22] described a total synthesis of **44** using Barton's decarboxylative oxygenation (Scheme 10). The synthetic route presented by these authors starts from the aldehyde **40**, furnishing, after nineteen steps, the nitrile **41**. The latter compound was hydrolyzed and first converted into an acid chloride, and then to the Barton ester **42**. Decarboxylation of compound **42** in the presence of molecular oxygen generated the hydroxy compound **43** in 54% yield from **41**, which after five steps furnished (−)-paeoniflorin **44**.

For more work regarding Barton's decarboxylative oxygenation, see Refs. [18,37–40]

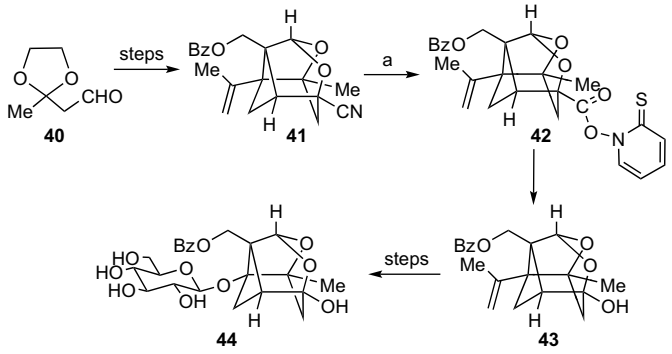
2.4. Carbon–sulfur bond formation

The use of disulfides as radical-trapping species results in the formation of thioethers. Originally, these conversions were



Scheme 9. (a) *N*-Hydroxy-2-thiopyridone, CH_2Cl_2, WSC, DMAP, *t*-BuSH, O_2.

was first prepared from α-methylated bicyclic γ-lactone **35** in ten steps. The conversion of the carboxylic acid group of **36** into a thiohydroxamic ester **37**, followed by radical decarboxylation, led to a methylene radical on the cyclopentyl ring, which was then trapped by molecular oxygen. Reductive workup in the presence of *t*-BuSH finally provided the hydroxylated product **38** as a diastereomeric mixture. These diastereomers were separated as their acetates giving **38α** and **38β** in 58 and 40% yield, respectively. The key skeletal rearrangement for the construction of the trichothecene framework was provided from **38β**. The oxygenated carbon of the

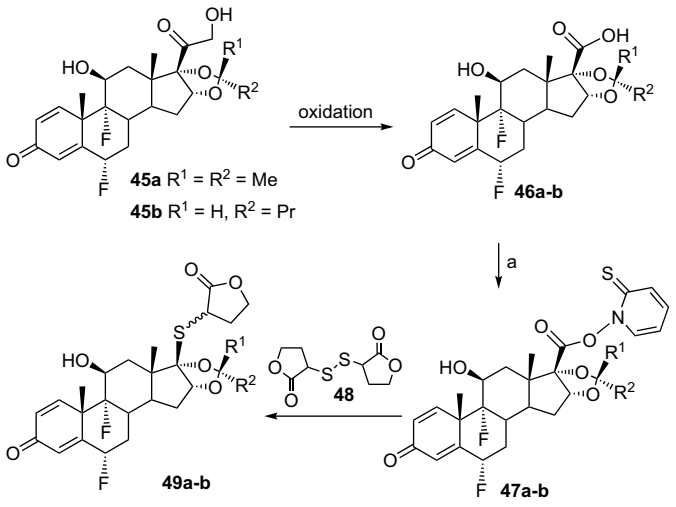


Scheme 10. (a) (i) Concd HCl–dioxane (1:4), 40 °C; (ii) $(COCl)_2$, DMF (cat.), benzene; (iii) *N*-hydroxythiopyridone, pyridine-DMAP (cat.), toluene, introduce O_2 at 80 °C, then $(MeO)_3P$.

carried out by heating the reaction mixture under refluxing toluene and required a large amount of dichalcogenide to minimize competitive basic decarboxylative rearrangement to alkyl pyridyl sulfides.[41] Barton and co-workers, however, found that, by operating under photolytic conditions at low temperatures, clean reactions occurred using only a slight excess of reagents.[42]

An important result concerning carbon–sulfur bond formation via a Barton ester was described by Beckwith and co-workers,[43] who reported the kinetics of intramolecular alkyl radical attack on sulfur in disulfides and thioesters.

Procopiou and co-workers[44] synthesized butylidene and its 1,2-dihydro analogues from fluocinolone acetonide **45a**, a commercially available glucocorticoid (Scheme 11). Barton radical decarboxylation, followed by trapping with butyrolactone disulfides, was used to link the sulfur atom of the γ-lactone group to the 17β-position of the androstane nucleus, furnishing analogues of the highly potent anti-inflammatory, 17β-thioalkylandrostane. Compound **45a** and its derivative **45b** were converted into the carboxylic acids **46a** and **46b** by K_2CO_3-catalyzed air oxidation. After activation by diethyl chlorophosphate, the mixed anhydrides were generated and transformed into their corresponding thiohydroxamate esters **47a** and **47b** by treatment with 2-mercaptopyridine *N*-oxide sodium salt in DMF. The Barton esters **47a** and **47b** were irradiated in the presence of the disulfide **48**, furnishing a mixture of diastereoisomers of the androstane-17β-(γ-lactone) sulfides **49a** and **49b**. The diastereoisomers, separated by HPLC, were obtained in 26–30% yield.

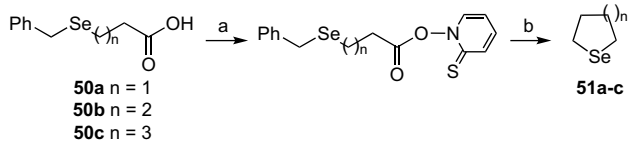


Scheme 11. (a) (i) $ClPO(OEt)_2$, Et_3N, THF; (ii) 2-mercaptopyridine *N*-oxide sodium salt, DMF; (b) **48**, DMF, light.

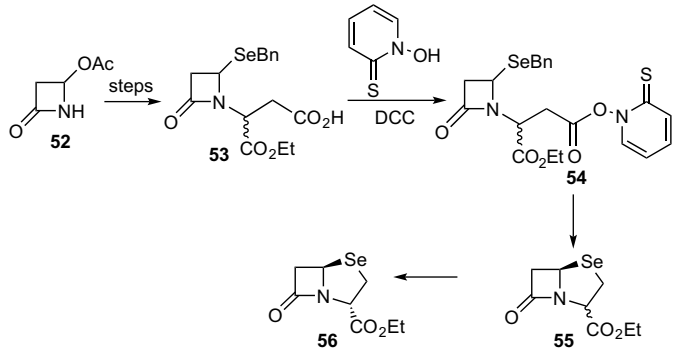
A similar synthesis was described by Ashton and co-workers[45] using dimethyl disulfide as the trapping compound.

2.5. Carbon–selenium bond formation

An important result in carbon–selenium bond formation via intramolecular attack of a carbon-centred free radical at a selenium atom was described by Schiesser and Sutej,[46] pioneers in the synthesis of five-, six- and seven-membered selenium-containing rings. This class of compounds was synthesized from 5-(benzylseleno)-pentanoic acid (**50a**), 6-(benzylseleno)-hexanoic acid (**50b**) and 7-(benzylseleno)-heptanoic acid (**50c**) using Barton's procedure,[39] furnishing the respective heterocycles **51a–c** in good yields (50–79%) (Scheme 12). This strategy was chosen by the same authors to avoid the use of chain carriers such as tri-*n*-butyltin or tris(trimethylsilyl)silyl radicals, species known to attack alkyl selenides.[46]



Scheme 12. Reagents and conditions: (a) *N*-hydroxy-2-thiopyridone, DCC, CH_2Cl_2; (b) *hν*, benzene.



Scheme 13. Synthesis of general core structure of β-lactamase inhibitor.

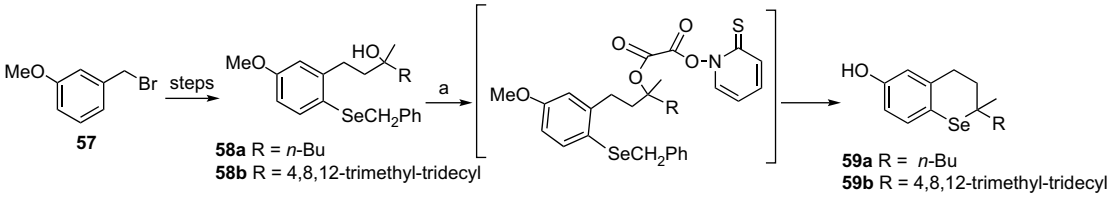
This synthetic strategy has been extensively used for the preparation of different biocompounds containing selenium heterocycles. For example, Carland and Schiesser[47] synthesized selenium analogues of a β-lactam antibiotic **56** (Scheme 13). Their synthetic route began with 4-acetoxy-2-azetidinone **52**, which, after three steps, afforded the mixed monoacid **53** in quantitative yield. Reaction of **53** with *N*-hydroxypyridine-2-thione in the presence of DCC afforded the pyridinethione-oxycarbonyl ester free-radical precursor **54** (Scheme 13). A concentrated solution of **54** was irradiated with a tungsten lamp and the required selenapenam **55** was isolated as an inseparable mixture of diastereoisomers. The diastereomeric ratios ranged from 1:1 to 8:1, depending upon the conditions.[47] Epimerization to a single diastereoisomer **56** was, however, observed within 72 h (Scheme 13).

Barton and Crich[48] reported the preparation of *O*-acyl thiohydroxamate esters from alcohols by treatment with oxalyl chloride, followed by reaction with *N*-hydroxy-2-thiopyridone, furnishing a hemi-oxalate ester, which generates an alkyl radical by consecutive loss of two molecules of carbon dioxide. Schiesser and co-workers[49] adapted this procedure for the synthesis of novel selenium-containing vitamin E analogues using the deoxygenation of alcohols (Scheme 14). The tertiary alcohols **58a** and **58b** were obtained from 3-methoxybenzyl bromide **57** in ten steps. Treatment of **58a** or **58b** with oxalyl chloride in benzene, followed by the reaction with 2-mercaptopyridine *N*-oxide sodium salt in the presence of DMAP, furnished the desired cyclized selenide. The crude product was subjected to treatment with boron tribromide to afford the selenochromane **59a** in 48% yield from **58a**. The selenide analogue **59b** was prepared similarly in 62% yield from compound **58b**.

2.6. Carbon–halogen bond formation

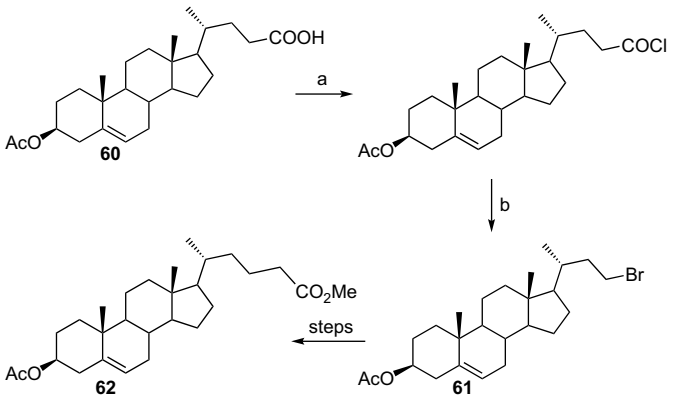
Decarboxylative chlorination of *O*-acyl thiohydroxamates is achieved using carbon tetrachloride as the trapping species, resulting in the formation of the norchloride. Carbon tetrachloride is used as a solvent and the reaction is initiated by photolysis or by heating under reflux. Analogous decarboxylative bromination is achieved using bromotrichloromethane as the solvent, and iodination can be performed with iodoform in benzene or cyclohexene.[41]

Kutner and co-workers[16] developed a method for the homologation of a cholanic acid derivative into its one-carbon homologue using the Barton bromodecarboxylation reaction as a practical approach to prepare 25-hydroxy vitamin D and its



Scheme 14. (a) (i) $(COCl)_2$, benzene; (ii) 2-mercaptopyridine *N*-oxide sodium salt, DMAP, benzene; (iii) BBr_3, CH_2Cl_2.

congeners. This method involves the transformation of a cholanic acid derivative **60** into a bromide **61** using 2-mercaptopyridine *N*-oxide sodium salt and bromotrichloromethane as a radical quencher (Scheme 15). Alkylation of the bromide with dimethyl malonate, followed by dealkoxycarbonylation, allowed the isolation of the one-carbon homologue product **62** in 80% yield.



Scheme 15. (a) $SOCl_2$; (b) DMAP, $CBrCl_3$, 2-mercaptopyridine *N*-oxide sodium salt, *hν* (73%).

Attardi and Taddei[12] reported the use of photochemical bromo decarboxylation of a Barton ester intermediate on a solid support to generate peptides containing modified amino acids. For example, tripeptides **65a–c** were obtained from the allyl ester **63** (Scheme 16). Compound **63** was deprotected with $Pd(PPh_3)_4$ to afford the corresponding carboxylic acid, which was transformed into the Barton ester following the standard procedure.[12] Irradiation in the presence of $CBrCl_3$ in DMF gave compound **64**, which was then deprotected and reacted with different nucleophiles to furnish tripeptides **65a–c**.

2.7. Carbon–nitrogen bond formation

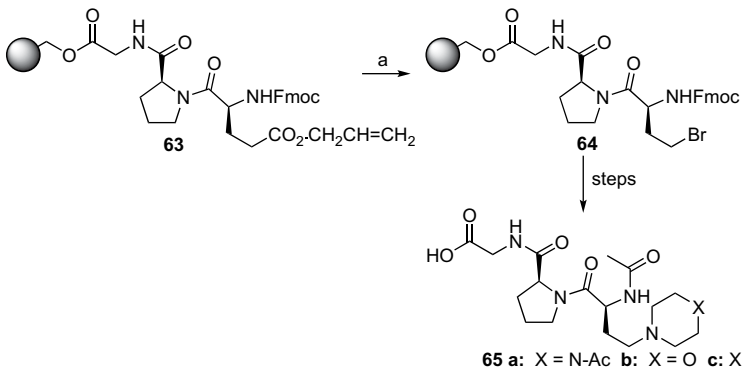
Carbon–nitrogen bond formation and functionalization using radical reactions is an important tool in the synthesis of peptides. Barton and Ferreira[15] have shown that acyl derivatives of thiohydroxamic acid could be applicable to the synthesis of unhindered and sterically congested carboxamides, which are compounds of importance in the synthesis of selected dipeptides containing sterically hindered α-amino acid residues.

The method reported by Barton and Ferreira for the construction of the peptide bond utilizes the formal activation of the carboxyl terminus of one amino acid residue and the indirect N-activation of the other required residue.[15] The carboxylic component is activated by transformation into the corresponding Barton PTOC ester **66**, which is readily accessible through a variety of methods. Barton demonstrated the usefulness of this approach by synthesizing dipeptides containing sterically congested residues. For example, sarcosine (i.e., *N*-methylglycine) derivative **68** was obtained by stoichiometric reaction of the Barton ester **66** with the 4-chloro benzenesulfenamide **67** (Scheme 17).

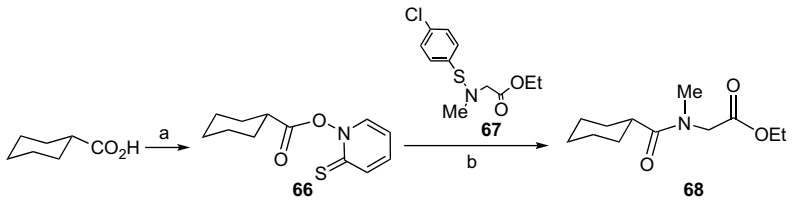
In further applications of decarboxylation reactions to obtain other functional groups, Masterson and Porter reported the preparation of substituted β-silyl Barton esters and their use in free-radical halogenation, azidation and thiopyridyl rearrangement reactions.[50] In this review, the azidation reaction is presented as an example of this procedure (Scheme 18). The thiohydroxamate esters were prepared by the reaction of substituted β-silyl carboxylic acids with the sodium salt of 2-mercaptopyridine-*N*-oxide in the dark. Free-radical azidation was performed by irradiation of the thiohydroxamate esters in a methylene chloride solution in the presence of ethanesulfonyl azide. Mixtures of alkyl azides were observed and the course of the azidation appeared to be highly substrate dependent. When the R substituent in compound **69** was a simple alkyl group (**69b** and **69c**, entries 2 and 3, Table 2) or a cycloalkyl group (**69a**, entry 1), the diastereomeric ratio (dr) of the alkyl azide products was of the order of 60–76:40–24. When R was a phenyl group (**69d** and **69e**, entries 4 and 5), the dr observed for **70** was greater than that observed when R was alkyl or cycloalkyl. The highest level of diastereoselectivity was achieved with **69d**, which gave a dr of 92:8 in 56% yield at −10 °C, as determined by ^1H NMR.[50]

The results obtained for azidation and thiopyridyl formation from α-silyl radicals showed that considerable levels of diastereocontrol can be achieved for a variety of substrates. The transformations described may prove to be useful for a variety of synthetic transformations.

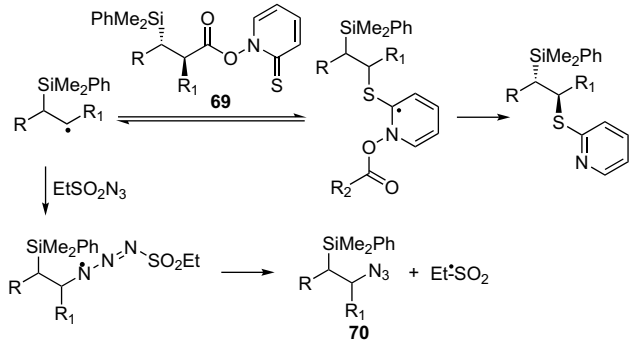
An important result in carbon–nitrogen bond formation is the decarboxylative nitrosation described by Motherwell and co-workers (Scheme 19).[51] The reaction of *O*-acyl thiohydroxamate derivative **71** with thionitrite **72** proceeds via the addition of a thiyl radical to the radicophilic thiocarbonyl group. A decarboxylative sequence gives an alkyl radical, which then undergoes reaction with the thionitrite to produce, in the first instance, a monomeric nitroso compound. Close examination of the Barton nitrite photolysis, however, reveals that an unusually facile dimerization to give nitrosodimers is predominant, and is even the preferred pathway over tautomerisation to an oxime when this is a possible alternative.[34,51] The trans nitroso dimer **73** was obtained from **71** in 54% yield as the dominant product.[51]



Scheme 16. (a) (i) $Pd(PPh_3)_4$, $CHCl_3$/AcOH/NMM (37/2/1) rt, 2 h; (ii) 1-hydroxy-2-pyridinethione, HBTU, DIPEA, DMF, rt, 4 h; (iii) *hν* (200 W lamp), $CBrCl_3$, DMF, rt, 40 min.



Scheme 17. (a) DCC, CH_2Cl_2, dark; (b) **67**, CH_2Cl_2, dark, 0 °C to rt, 3 h.



Scheme 18. Formation of azides from α-silyl radicals.

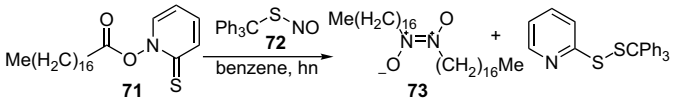
Table 2
Formation of azides from Barton esters **69**

Entry	Substrate	R	R_1	**70** dr
1	**69a**	C_6H_{11}	Me	60:40
2	**69b**	C_8H_{17}	Me	76:24
3	**69c**	Me	Me	67:33
4	**69d**	Ph	Me	92:8
5	**69e**	Ph	Bn	91:9

Although the reaction is limited to primary and secondary carboxylic acids, the nitroso dimers can be transformed into a variety of functional groups.[34,51]

2.8. Decarboxylative introduction of cyanide

The replacement of a carboxylic acid group by a nitrile function is a useful method, which does not require the preparation and dehydration of an amide.[34] The reaction of methanesulfonyl cyanide **75a** or *p*-toluenesulfonyl cyanide **75b** with the carbon radical generated from **74** led to the nitrile **76** in 81% yield (Scheme 20).



Scheme 19. Decarboxylative nitrosation of *O*-acyl thiohydroxamate.

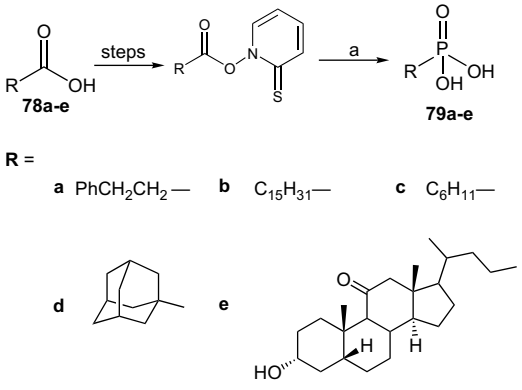
Hydrolysis of compound **76** afforded linoleic acid **77** in 81% yield. Such reactions can be used to introduce labelled carboxylic groups.[52]

2.9. Carbon–phosphorus bond formation

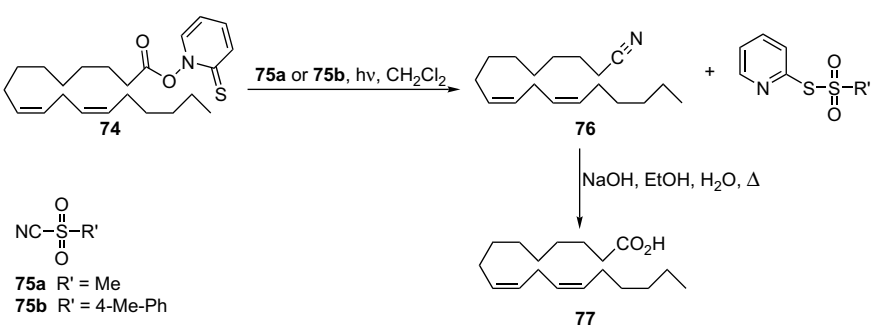
White phosphorus is an efficient trap for carbon radicals, providing a convenient route for the conversion of carboxylic acids into the corresponding phosphonic acids.

Barton and Zhu[53] have demonstrated that, on irradiation with white light, a rapid radical reaction takes place between elemental white phosphorus (P_4) and carbon-centred radicals generated via photolysis of the corresponding Barton PTOC esters. Oxidation of the resulting products afforded phosphonic acids **79a–e** in good yields (71–86%) (Scheme 21).

Barton and Embse[54] described a modification of the initial experimental procedure, providing a more efficient and higher-yielding synthesis of the phosphonic acids **79**. Using THF as the solvent, evolution of carbon dioxide was spontaneous upon addition of the Barton ester to the P_4 solution accompanied by a colour change. The reactions were found to be complete within a few minutes, even in complete darkness. The isolated yields of the phosphonic acids after oxidation with aqueous H_2O_2 were consistently higher than those found previously by Barton and Zhu[53] (Table 3).



Scheme 21. (a) (i) P_4, *hν*, CH_2Cl_2/CS_2; H_2O_2, H_2O, DME, reflux.



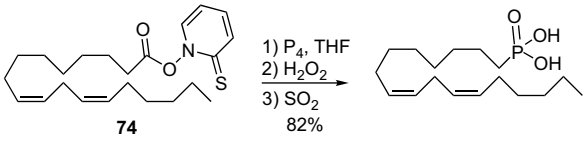
Scheme 20. Decarboxylative introduction of cyanide.

Table 3
Comparison of improved procedure to previous method of phosphonic acid synthesis

Entry	Starting material	Product	Yield[a] (%)	Yield[b] (%)
1	**78a**	**79a**	91	74
2	**78c**	**79c**	90	73
3	**78d**	**79d**	96	86

[a] Isolated yields of the phosphonic acids reported by Barton and Embse.[54]
[b] Previously reported yields by Barton and Zhu.[53]

In order to further probe the scope of this procedure, Barton and Embse incorporated the phosphonic acid moiety into several natural compounds, such as linoleic acid (Scheme 22).[54] The conversion of this compound occurred with no attack at the diene unit.[34,54]



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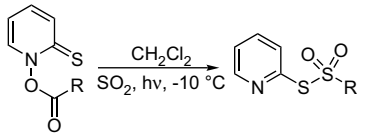
Scheme 22. Preparation of phosphonic acids using white phosphorous.

2.10. Decarboxylative sulfonation

Sulfur dioxide, when used in a sufficiently large excess, can act as favourable trap to afford thiosulphonates.[34,55] Zard and co-workers[55] have described the conversion of Barton esters into sulfonates using high concentrations of liquid sulfur dioxide in dichloromethane at −10 °C under irradiation (Scheme 23).



a) R = *n*-$C_{15}H_{31}$– (91%)
b) R = $PhCH_2CH_2$– (65%)
c) R = C_6H_{11}– (90%)
d) R = 1-adamantyl (85%)

Scheme 23. Decarboxylative sulfonation.

3. Conclusions

We have described in this review some applications of *N*-hydroxy-2-thiopyridone for the generation of *O*-acyl thiohydroxamate esters (Barton esters) and its reactions with several substrates to provide new bonds on a broad range of compound classes, for the most part in good yields. The versatile generation of disciplined carbon radicals via the Barton esters has been, since its discovery, an important tool in the chemistry of radical reactions and has been widely applied for the synthesis of biocompounds.

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Biographical sketch

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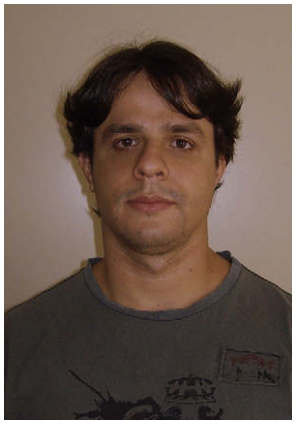
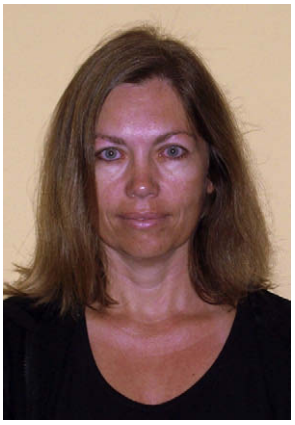
Mara R. Couri was born in Santos Dumont, Minas Gerais, Brazil. After receiving an MD degree in chemistry at Universidade Federal de Juiz de Fora, she carried out her Ph.D. under the supervision of Dr. Rosemeire B. Alves at Universidade Federal de Minas Gerais. She is now a professor of organic chemistry at UFJF.



Maurício F. Saraiva was born in Januária, Minas Gerais, Brazil. He graduated from Universidade Federal de Juiz de Fora in 2005, where he is currently carrying out his Ph.D. studies under the supervision of Dr. Mauro V. de Almeida. Part of his research is being developed at the Institut de Chimie des Substances Naturelles (CNRS, Gif/Yvette) under the supervision of Dr. Robert H. Dodd.



Mireille Le Hyaric was born in Arpajon, France. After receiving a graduation degree of biochemistry (Maitrise) at the University Paris-XI Orsay, she carried out her DEA and Ph.D. (1994) in chemistry under the supervision of Dr. Robert H. Dodd at the Institut de Chimie des Substances Naturelles (CNRS, Gif/Yvette). Since 2005, she has been a professor of organic chemistry at Universidade Federal de Juiz de Fora (Brazil). Her main research interest is the synthesis of biologically active amphiphilic compounds derived from carbohydrates.