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Review

Natural and synthetic cage compounds incorporating the 2,9,10-trioxatricyclo[$4.3.1.0^{3,8}$]decane type moiety

Elena Stanoeva,[†] Weidong He and Norbert De Kimpe[*]

Department of Organic Chemistry, Faculty of Agricultural and Applied Biological Sciences, Ghent University, Coupure Links 653, B-9000 Ghent, Belgium

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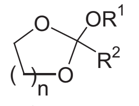
Abstract—The 2,9,10-trioxatricyclo[$4.3.1.0^{3,8}$]decane moiety is a tetracyclic cage-like orthoester incorporated in the structure of a series of daphnane derivatives such as resiniferatoxin (RTX), kirkinine, synaptolepis factors, huratoxin etc., exhibiting various biological activities. The approaches to the preparation of cage-like orthoesters starting from partially acylated or unmodified 1,2,4-trihydroxycyclohexane moieties built onto natural as well as synthetic compounds are discussed. Orthoester derivatives of RTX analogs, Ceverathrum alkaloids, myoinositol and pyranoses are included. Stereochemical requirements to the formation of the orthoester unit are discussed. The biological activity of different compounds containing the cage-like orthoester structural fragment is given. The literature is reviewed till 2004.

Contents

1. Introduction

Orthoesters constitute a group of compounds used mostly as carboxylic acid protective groups.[1–5] Some orthoesters include one or more of the oxygen atoms in a cyclic system and therefore can be regarded as heterocyclic compounds such as 2-alkoxy-1,3-dioxolanes (**1**) ($n = 1$), 2-alkoxy-1,3-dioxanes (**1**) ($n = 2$), lactone acetals (**2**), 2,6,7-trioxabicyclo[2.2.2]octanes (**3**) and 2,4,10-trioxaadamantanes (**4**).[2]



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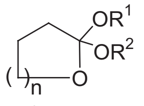

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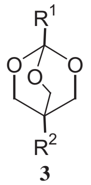

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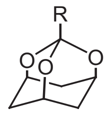

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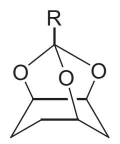

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[*] Corresponding author. Tel.: +32 9 264 5951; fax: +32 9 264 6243; e-mail: norbert.dekimpe@ugent.be

[†] On leave from the University of Sofia, Faculty of Chemistry, Sofia, Bulgaria.

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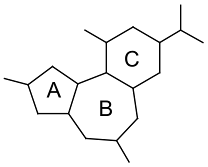
The latter compounds are symmetrically substituted 1,3,5-trioxygenated cyclohexanes in which the oxygen atoms make part of a roof-like orthoester moiety. Such symmetric cage-like orthoesters have been studied in detail.[2] On the contrary, the asymmetrically substituted tetracyclic cage-like orthoesters (**5**) received less focus until they were discovered as an important structural unit in physiologically active natural products. It is the purpose of this review to highlight these tetracyclic orthoesters (**5**) with a 1,2,4-trioxygenated pattern of cyclohexane in view of their occurrence in natural products, their physiological activities and synthetic approaches.

2. Natural products containing the 2,9,10-trioxatricyclo[4.3.1.0^{3,8}]decane unit-chemical classification and biological activity

Recently, 2,9,10-trioxatricyclo[4.3.1.0^{3,8}]decanes of type **5** attracted a lot of attention, since it has been shown that this structural unit is incorporated in a number of diterpenes with a daphnane-type skeleton (**6**). Plants from the Thymelaeaceae and the Euphorbiaceae families provide rich sources of daphnane derivatives, which generally occur as ring C-orthoesters.[6–12] Most of the daphnanes possessing an orthoester function exhibit various physiological activities.[6–12]



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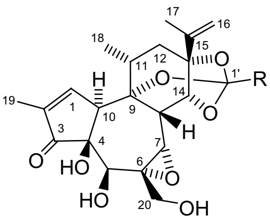
There are several reviews concerning the structural and phytochemical investigations on daphnane derivatives.[6–10] Recently some of us published a review providing a detailed list of about 80 naturally occurring daphnane compounds, the plant sources and the overview of their biological activities.[12] Furthermore, classification has been proposed based on the presence of oxygen containing functions at the B and C rings, as well as on the substitution pattern of A ring.[12] Having in mind this exhaustive description, here the most representative examples in view of chemical structures and biological activities will be given.

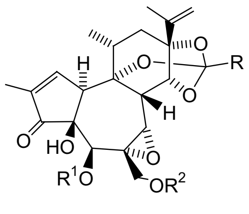
Four major structural classes, for example, classes 1, 2, 3 and 4 of daphnane derivatives have been outlayed as daphnetoxins, 12-hydroxydaphnetoxins, alkyldaphnanes and resiniferonoids, respectively.[12] Biological activities of structurally similar compounds vary even with small changes such as the length of a carbon chain or the position of an ester group. There are in fact few data available about structure–activity relationship (SAR) of those compounds. The main reason is that of difficulties in obtaining sizable amounts of the isolated products, which is an obstacle for the chemical modifications.

Classes 1–3 possess a 5β-OH and 6α,7α-epoxy groups in the seven-membered B ring. The compounds of class 1 are based on the absence of C-12 hydroxylation represented by daphnetoxin (**7**), an orthobenzoate.[13] It is isolated from plants of the Thymelaeaceae, though its analog with an aliphatic orthoester chain, huratoxin (**8**)[14,15] is also found in plants of the Euphorbiaceae. The structure and the absolute stereochemistry of daphnetoxin (**7**) were resolved by means of the X-ray analysis of its 5,20-bisbromoacetate derivative, therefore, a boat geometry of ring C caused by the orthoester moiety was demonstrated.[13] Huratoxin (**8**) exhibits an extraordinary piscicidal activity, which is much higher than that of rotenone.[14] Other important compounds of this class are simplexin (**9**) and Pimelea factor P_4 (**10**).[16] They are the toxic principles of plants of *Pimelea* species, which were known for a long time to cause the St. George disease in cattle in Australia and New Zealand.[16–18]



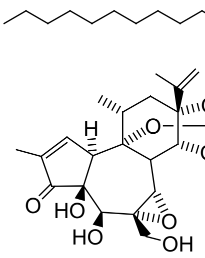
7 R= C_6H_5
8 R = $(CH=CH)_2(CH_2)_8CH_3$
9 R = C_9H_{19}
10 R = $C_{13}H_{27}$

A mixture of huratoxin analogs, so-called factors M_x (**11**), esterified at the C-20 OH with a long chain saturated aliphatic acids (from C-16 to C-26) were isolated from the toxic latex of the poisonous manchineel tree (Euphorbiaceae) in tropical America.[19] The latex as well as the barks and leaves of the tree exhibit a strong skin irritating and carcinogenic activity, while they do not exhibit strong odour or taste.[19] Chemical modification of these factors M_x (**11**) was carried out and demonstrated that both orthoester moiety and C-1 double bond on A ring were very important for the biological activity, while the presence of double bonds in the ester moieties as well as the α-epoxide ring were less important.[19] After a hydrolytic removal of the ester at C-20 to a free 20-OH group, derivatives with much higher activities were obtained.[19]



11 R = $(CH=CH)_{2-3}(CH_2)_8CH_3$;
R^1 = $COCH=CH(CH_2)_{14-24}CH_3$; R^2 = H or $COCH_3$

A series of daphnane orthoesters were isolated recently from the non-polar extracts of the roots of the Kenyan plant *Synaptolepis kirkii* (Thymelaeaceae).[20–22] Synaptolepis factor K_7 (**12**) was shown to possess a very strong neurotrophic activity.[21]



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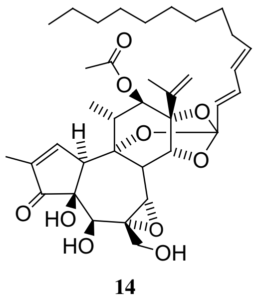
The daphnane-type orthoesters of class 2 contain a 12β-OH group, which is either free as in 12β-hydroxydaphnetoxin (**13**)[23] or esterified as in 12β-acetoxyhuratoxin (**14**),[21,24] kirkinine (**15**)[20] and kirkinine D (**16**).[21] 12β-Acetoxyhuratoxin (**14**) exhibits termite killing activity.[23] Kirkinine (**15**), kirkinine D (**16**) and yuanhuadine (**17**) exhibit a strong neurotrophic activity similarly to synaptolepis factor K_7 (**12**).[20,21] When assayed in primary cultures of chick embryo dorsal root ganglion (DRG) neurons, compounds **12**, **14**–**17** promoted neuronal survival at an EC_{50} at nM level.[20,21] This potency observed for compounds **12**, **14**–**17** was shown to depend on the length and the unsaturation of the aliphatic chain. In this respect, kirkinine (**15**) exhibited a much higher activity than its analogs **14**, **16** and **17**.[20,21] It should be noted that 12β-hydroxydaphnetoxin (**13**) is devoid of cytotoxic or tumor promoting activity thus showing the significance of the acylation of the 12β-OH group for the biological activity.[23,25] Similarly, the irritating activity of **14** is higher than that of simplexin (**9**), which evidences again the significance of the 12-acyloxy substituent, as well as the presence of double bonds in the orthoester side chain.[21] The esterification at position 20 leads to a decrease of the biological activity, which is recovered after the hydrolysis.[21] This gave a reason why the esters were referred to as cryptic poisons.[11,22]



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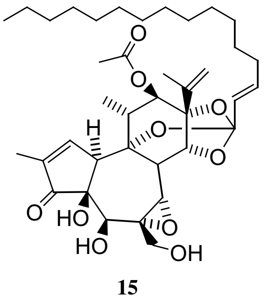

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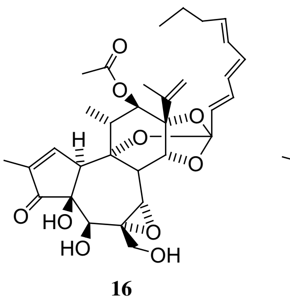

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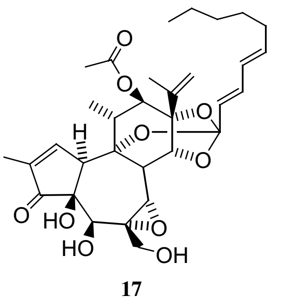

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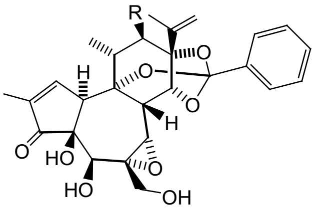
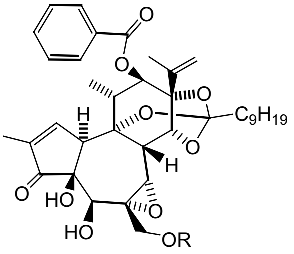
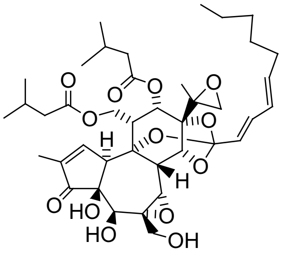
Other analogs with 12β-acyloxy group are the series of compounds isolated from *Gnidia* species (Thymelaeaceae), such as mezerein (**18**), gnididin (**19**), gniditrin (**20**), gnidilatin (**21**) and its 20-palmitate (**22**).[25–28] Compounds **18**–**20** contain an orthobenzoate moiety and they possess significant in vivo activity against P-388 leukemia in mice.[25,26] Plants containing mezerein (**18**) were shown to be highly toxic for the livestock in South Africa.[23] The absolute stereochemistry of mezerein (**18**) has been established.[29] The strong cytotoxicity of 12β-acetoxydaphnanes makes them attractive for cancer research.[12]



13 R = OH
18 R = $OCO(CH{=}CH)_2C_6H_5$
19 R = $OCO(CH{=}CH)_2(CH_2)_4CH_3$
20 R = $OCO(CH{=}CH)_3(CH_2)_2CH_3$



21 R = H
22 R = $CO(CH_2)_{14}CH_3$



23

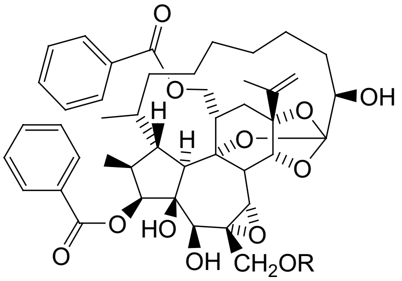
Maprouneacin **23** is remarkable for its 12α,18-diisobutyroyloxy groups.[30] Its in vivo antidiabetic activity deserves special attention because of the social significance of diabetes.

It is a fact that most of the naturally occurring daphnane-type orthoesters, more than 50 compounds up to date, are found to belong to classes 1 and 2.[12]

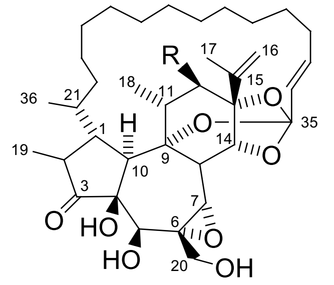
Class 3 is those of the so-called 1α-alkyldaphnanes containing an orthoester group incorporating to a macrocyclic bridge from C-1′ to C-1 of the daphnane skeleton. Correspondingly, there is no C-1 double bond at the A ring.[31–37] Most of the compounds in this class are isolated from the Thymelaeaceae. Gnidimacrin (**24**) and its 20-palmitate (**25**) make part of a subclass possessing 3β-benzoyloxy group instead of the 3-C carbonyl function.[31,33] The structures and stereochemistry of **24** and **25** were established by means of X-ray analysis.[31] Bioassays have shown the absence of antileukemia activity,[31] unlike the other *Gnidia* components with an open chain at the orthoester carbon cited above.[25–28]

The other subclass includes compounds like kirkinine B (**26**) and kirkinine C (**27**), which possess an unchanged

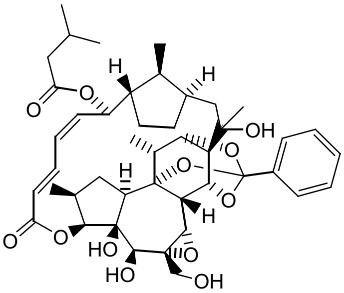
3-carbonyl group at ring A.[21] Similarly to the mentioned synaptolepis factor K_7 (**12**), kirkinine B (**26**) exhibits neurotrophic activity at nanomolar level.[21] The powerful antileukemia activity of kirkinine B (**26**) and C (**27**) has also been described.[21]



24 R = H
25 R = $COC_{15}H_{31}$



26 R = H
27 R = $OCOCH_3$



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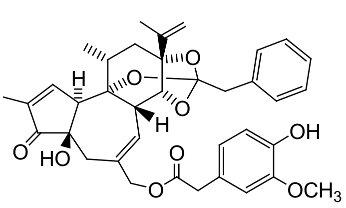

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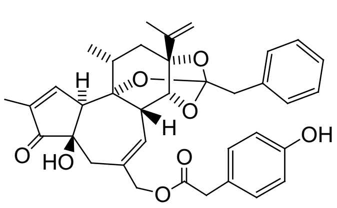

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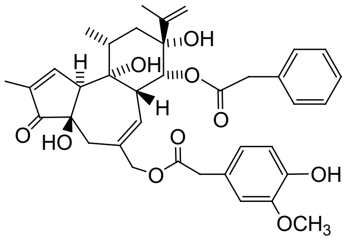
Rediocide A (**28**) from *Trigonostemon reidioides* (Euphorbiaceae) is an exceptional example of a daphnane having the unusual 9,12,14-orthoester moiety instead of 9,13,14-pattern.[38] The macrocyclic fragment incorporates also a lactone group. The NMR data of **28** are in agreement with the six-membered C ring in a chair type of conformation.[38] Rediocide A (**28**) displays exceedingly high insecticidal properties at a subnanomolar level against flea larvae.[38]

Class 4 is that of the resiniferonoids, which are devoid of a 5-OH group as well as of a 6,7-epoxide moiety, but having a 6,7-double bond instead on ring B. Resiniferonoids have a very narrow distribution in plants of the Euphorbiaceae family. The best-known compound of this group is resiniferatoxin (RTX, **29**), which was isolated from Euphorbium, the dried latex of *Euphorbia resinifera*.[9,39] Structurally related compounds, tinyatoxin (**30**) and proresiniferatoxin (**31**) were co-extracted with RTX.[39,40] Adolf et al. investigated chemical modifications of **29** and showed that the correct structure of it corresponds to resiniferonol-9α,13α,14α-orthophenylacetate-20-(4-hydroxy-3-methoxy)phenylacetate.[41] Recently, Wender et al. have published an enantioselective total synthesis of RTX.[42,43] Their brilliant work was recently reviewed.[44]

The recent interest in RTX (**29**) arises from its biological activity to relieve pain especially in connection with diabetic neuropathy and bladder hyperreflexia.[9,10,45,46] A similar biological activity is exhibited by capsaicin (**32**), the pungent principle of hot pepper.[9] Both compounds are also pronounced skin and mucous membrane irritants.[9,10,39,47,48] The comparison of the irritant activity of RTX with that of other daphnane compounds, such as factors M_x (**11**), has shown that RTX exhibited the maximal irritant activity within 2–5 h after application, when M_x took 24 h.[19] It was reported that the extremely high irritating properties of RTX gave severe problems during its isolation from plant materials.[48]

RTX (**29**) and capsaicin (**32**) possess a homovanillyl residue as a common structural unit.[9,10] Due to this common structural feature as well as the similarity of the physiological activity, **29** and **32** are united in the group of vanilloids.[10] RTX seems to be more promising than capsaicin from a pharmaceutical point of view, because it is more potent and at the same time better tolerated by the patients in clinical trials.[10] Recently it has been shown that both RTX and capsaicin exert a protective effect on rat gastric epithelial cells,[49] which demonstrates their great potential in medicinal chemistry.

While there are numerous investigations on SAR of capsaicin,[50,51] still less is known for that of RTX. It was supposed that both of compounds **29** and **32** bind with the same receptor named vanilloid receptor (VR1). The receptor has been cloned from rat dorsal root ganglia (DRG) and recognized as a common molecular target for protons, noxious heat as well as vanilloid compounds.[52] As an agonist to VR1, the vanilloid is required to own in its structure three pharmacophoric regions designated as A, B and C.[50–60] The binding of RTX to VR1 was demonstrated by use of ^{3}H-labelled



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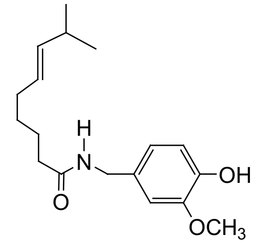

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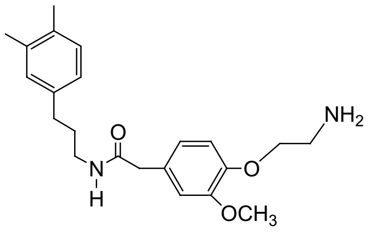


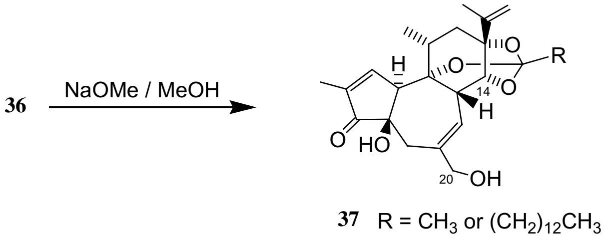
33

RTX,[50,54] where RTX presents typically the A and B regions with the homovanilloyl residue at C-20 and the diterpene tricyclic skeleton as the C region (the hydrophobic side chain).[46,51,57] Its C-3 carbonyl and the phenyl of the orthoester moiety (as lipophylic group) are considered as crucial structural elements for the extremely high analgesic potency,[46,50,51,53,54] which may also be important for RTX's multi-bioactivities other than that of capsaicin. Therefore, RTX is much more potent at the receptor, but moderately pungent as compared to capsaicin. Meanwhile, the analgesic effect of RTX is characterized with a very long duration, for example, the desensitization period is prolonged obviously after a single treatment with RTX.[46,57] Nevertheless, this VR1 model created possibilities for the design of structurally simple and easily accessible analogs as analgesics, of which DA 5018 (**33**) is under clinical trial.[55,57,58]

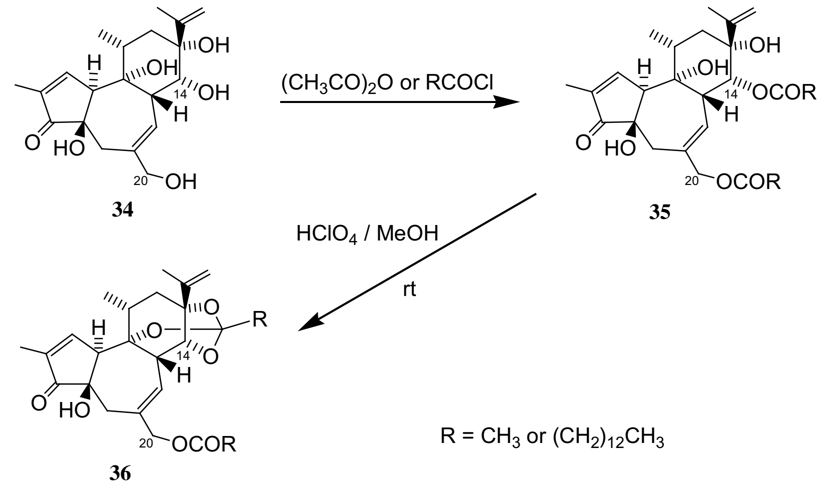
3. Synthesis and stereochemistry of RTX derivatives and more simple analogs incorporating the 2,9,10-trioxatricyclo[4.3.1.0^{3,8}]decane moiety

Most often, 2,9,10-trioxatricyclo[4.3.1.0^{3,8}]decanes are prepared from trihydroxycyclohexanes in which one or two hydroxy groups are acylated. As it will be shown below, it is not necessary that all three oxygenated groups are in a *cis* relationship. Thus, Adolf et al. acylated resiniferonol (**34**) to obtain two derivatives, namely 14,20-diacylresiniferonols **35** ($R = CH_3$ or $(CH_2)_{12}CH_3$), which upon treatment with a solution of perchloric acid in methanol at room temperature afforded orthoacetic and orthotetradecanoic analogs **36** ($R = CH_3$ or $(CH_2)_{12}CH_3$) of RTX in good yields (Scheme 1).[41] By this mild acid treatment, proresiniferatoxin (**31**) can be readily converted into RTX (**29**).[39] It has been suggested that RTX in plants is biosynthesized from proresiniferatoxin with a scheme similar to the chemical pathway discussed above.[41,61] On methanolysis with sodium methoxide in methanol, compounds **36** afforded orthoesters **37** derived from resiniferonol (**34**) (Scheme 2).[41]

The irritant activity of compounds **36** and **37** ($R = CH_3$ or $(CH_2)_{12}CH_3$) was shown to be similar to that of RTX (**29**).[41] The results were regarded as a confirmation of the suggestion about the importance of the orthoester moiety for the physiological activity of this group of compounds. Later, this synthetic approach was extended to other aliphatic homologues of RTX, containing an alkyl chain from C_2 to C_{18} of the orthoester



Scheme 2.



Scheme 1.

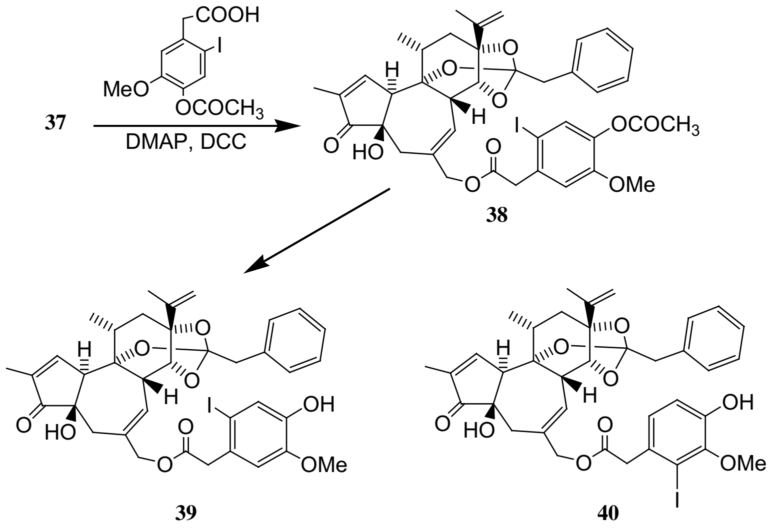
group.[61] In this case, however, the specific irritant activity was found to be lower as compared to the results obtained with the orthoacetate and orthotetradecanoate **36** (R = CH_3, resp. $(CH_2)_{12}CH_3$) discussed above.[41] The same happens to resiniferonol orthophenylacetate (ROPA, **37**: R = $CH_2C_6H_5$) exhibiting no vanilloid (free 20-OH) and very weak irritant activity.[41,48]

The orthobenzoate analog of RTX was also synthesized in several steps starting from resiniferonol 14,20-dibenzoate (**35**, R = C_6H_5).[51] The formation of orthobenzoate moiety was carried out in the presence of *p*-toluenesulfonic acid and boiling dichloromethane. In the further two steps the vanilloyl residue at C-20 was introduced. The orthobenzoate analog of RTX showed similar high activity in several bioassays.[51]

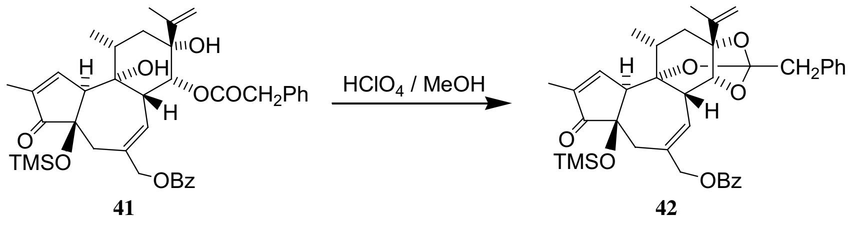
A smooth hydrolysis of RTX derivatives (**36**) into resiniferonol orthoesters (**37**) was performed when isolating RTX from plant materials that alleviate the hazards connected with the manipulation of the diterpene fraction from the plant.[48] The mixture of diterpenes was mildly hydrolyzed by means of a short treatment with NaOMe in methanol at room temperature.[48] By this way, RTX (**29**) was converted into ROPA (**37**, R = $CH_2C_6H_5$), which is less toxic and more easily separated by means of column chromatography from the accompanying noxious diterpenes, mostly ingenol and 12-deoxyphorbol esters. Thereafter, ROPA was reconverted into RTX in 67% yield by treatment with a mixture of homovanilloic acid, di-*t*-butyl azodicarboxylate and triphenylphosphine (Mitsunobu esterification procedure).[48]

ROPA (**37**, R = $CH_2C_6H_5$) was reacted with 2-iodo-4-acetoxy-5-methoxyphenylacetic acid in the presence of 4-(dimethylamino)pyridine (DMAP) and dicyclohexylcarbodiimide (DCC) to give the protected 2-iodo-RTX analog (**38**), which was further deprotected to the 2-iodo-substituted derivative at the vanilloyl moiety of RTX (**39**) (Scheme 3).[62] This procedure allowed the preparation of labelled RTX derivatives, mostly with ^{125}I. Direct iodination of RTX gave rise to the isomeric 2-iodo-4-hydroxy-3-methoxyphenylacetate (**40**).[62] Interestingly, the two iodinated RTX derivatives, **39** and **40**, showed different biological activities in receptor binding studies. More specifically, compound **39** was an agonist to VR1, while compound **40** was an antagonist.[62]

The formation of the orthoester moiety via mild acid treatment of the monoacylated 1,2,4-cyclohexanetriol moiety, introduced by Adolf co-workers,[41,61] was used by Wender et al. in their multi-step enantioselective total synthesis of (+)-RTX (**29**).[42,43] Thus, in the key step, the protected derivative **41** was converted into orthoester **42** in 46% yield (Scheme 4). Further, compound **42** furnished resiniferatoxin (**29**) after several more steps.[42] The orthoester moiety was introduced at the last steps



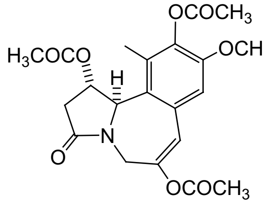
Scheme 3.



Scheme 4.

of this long synthetic sequence in order to minimize handling of potentially active intermediates.[42,43] This elaborated synthesis allowed introduction of a great diversity of orthoester moieties into the daphnane skeleton for different biochemical studies.[42] Therefore, the procedure of Adolf affords resiniferonol orthoesters as suitable precursors for the preparation of various resiniferatoxin analogs.

The brilliant work of Wender and co-workers was recently reviewed.[44] Moreover, Wender's total synthesis of RTX provoked other scientists to elaborate the daphnane skeleton using different synthetic approaches.[63] A synthesis of an aza analog (**43**) of daphnane was also proposed.[64]



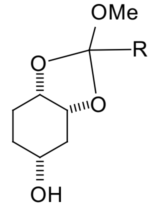
43

Utilizing 1-O-phenylacetyl-2-O-(*p*-tolylsulfonyl)-*c*-3-[3-(*tert*-butyldiphenylsilyloxy)prop-1-ynyl]-cyclohexane-*r*-1,*t*-2,*c*-4-triol (**44**) as a starting compound, Bloomfield et al. performed the synthesis of orthoester **46**, structurally analogous to RTX at ring C.[65,66] It was shown that compound **44** underwent an intramolecular nucleophilic substitution to orthophenylacetate **45** at a temperature of 170 °C, which is accompanied by a configurational change from 1,2-*trans* in **44** to 1,2-*cis* in **45** (Scheme 5). The orthoacetate **45** was obtained in 73% yield after isolation by silica gel column chromatography. The harsh reaction conditions necessary to convert **44** into **45** are explained with the energetically unfavourable change of the conformation of the cyclohexane ring from chair in cyclohexanol **44** to boat in orthoester **45**.[65,66]

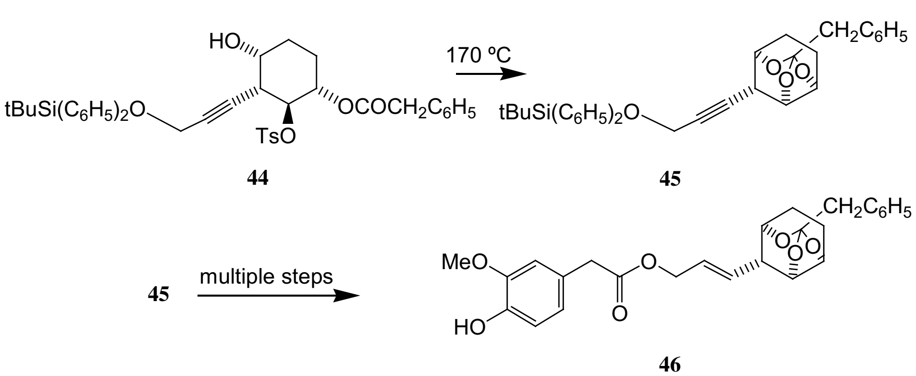
As pointed out above, the formation of the orthoester moiety in the synthetic studies related to RTX is strongly dependent on the conformation of ring C of RTX. Up to now there is little knowledge about the stereochemistry of RTX and other daphnane compounds with orthoester functionality probably because of the complexity of the molecules, low isolation yields from the plant material and non-crystallizability of the compounds. NMR investigations in combination with molecular modeling studies were carried out in order to shed more light at the stereochemistry of RTX.[67] It was suggested that the orthophenylacetate group can act as a conformational lock for the six-membered C ring, forcing it to adopt a boat conformation.[67]

All-*cis*-1,2,4-trihydroxycyclohexane (**47**) is a suitable starting material for the preparation of 2,9,10-trioxatricyclo[4.3.1.0^{3,8}]decanes (**48**) with a structure analogous to that of ring C in RTX. Gero and co-workers used (−)-quinic acid as a starting material via acetalization, reduction and a hydrolysis protocol for the synthesis of (+)-**47** (Scheme 6).[68,69] Unfortunately, this very low overall yield (0.5–1.5%) indicated that this was not a convenient method for the preparation of (+)-**47** on a larger scale. Instead, a high pressure hydrogenation of 1,2,4-trihydroxybenzene over Rh/Al$_2$O$_3$ catalyst in tetrahydrofuran at 100 °C presented a good yield of the racemic **47** (50%) (Scheme 7).[70] This product was finally used for the synthesis of a series of orthoesters **48**.[71]

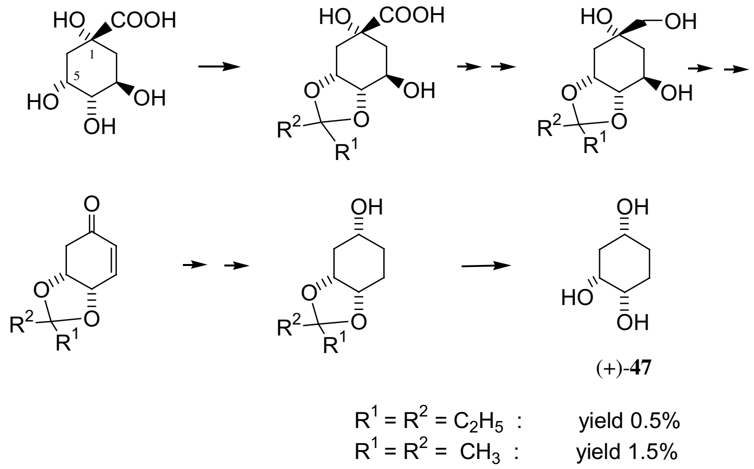
A transetherification reaction was carried out by reacting trimethyl orthoesters of carboxylic acids with (±)-all-*cis*-cyclohexane-1,2,4-triol (**47**) in DMF containing Amberlite IR-120 plus as acid catalyst and 4 Å molecular sieves (Scheme 8).[71] The orthoesters **48** were isolated from the reaction mixture by means of flash silica gel column chromatography or medium pressure liquid chromatography (MPLC) with reversed phase in yields ranging from 20% to 80%. In some cases, side products (**49**) were isolated as a result of a partial transetherification. The reaction required prolonged heating from 24



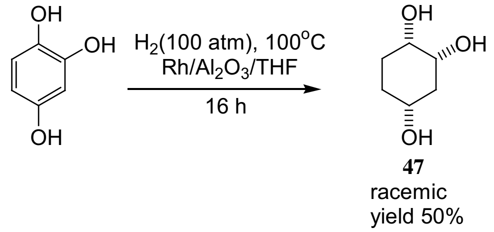
49



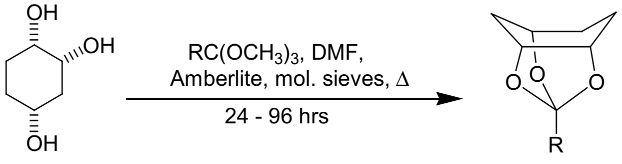
Scheme 5.



Scheme 6.



Scheme 7.



47 48

Scheme 8. R = H (yield 28%); C_6H_5 (80%); C_4H_9 (36%); C_9H_{19} (50%); $C_{15}H_{31}$ (66%); (*E*)-$CH_2CH{=}CHCH_3$ (65%); (*E*)-$CH{=}CHC_2H_5$ (20%); (*E*)-$CH{=}CHC_3H_7$ (10%); (*E*)-$CH{=}CHC_4H_9$ (10%).

to 96h at 80–100°C. Such vigorous reaction conditions could be attributed to the conformational change of the cyclohexane ring, which is forced to occupy the less favoured boat form fixed by the orthoester cage.[66]

4. Cage orthoesters of Ceverathrum alkaloids

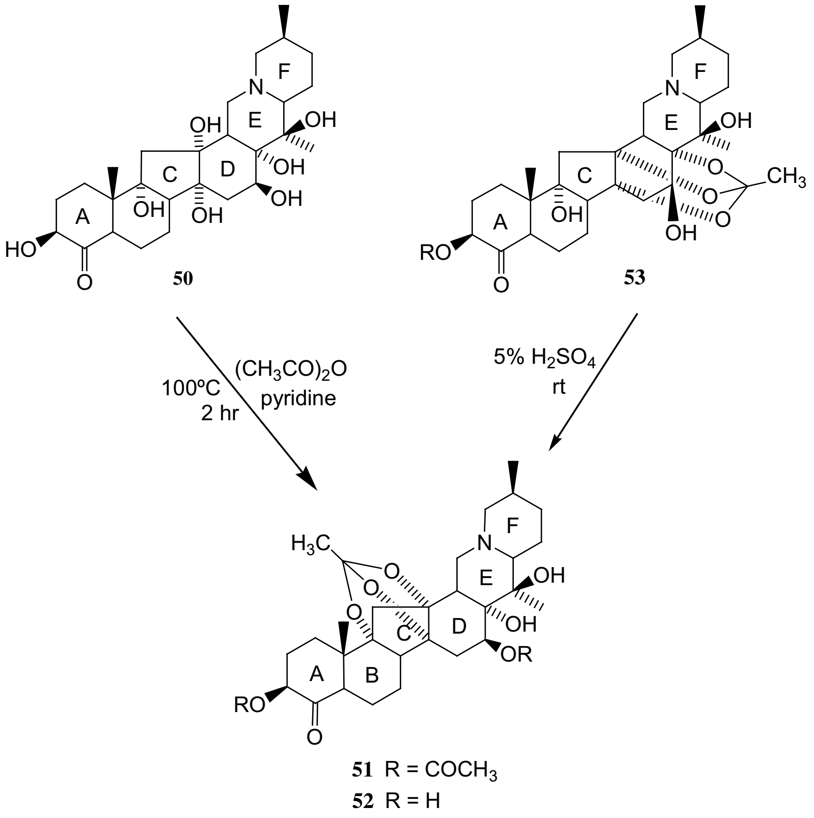
The formation of cage orthoesters was investigated with several polyhydroxylated Ceverathrum alkaloids.[72–76] The type of the orthoester formed depended on the structure of the starting alkaloid, but in all cases studied, the *cis* orientation of the hydroxyl groups of the alkaloids favoured the formation of the orthoester moiety. Thus, upon heating with a mixture of acetic anhydride and pyridine, cevagenine (**50**) gave rise to an orthoacetate (**51**) at the five-membered ring C (Scheme 9).[73] The orthoester moiety of **51** was very stable to hot alcoholic potassium hydroxide, though acetoxy groups at 3 and 16 position were converted into the alcoholic functions of compound **52** by means of methanolysis.[73]

Cevagenine D-orthoacetate (**53**) was also prepared from cevadine (**54**).[72] Thus, cevadine (**54**) and its diacetate **55** were converted into the orthoacetate **56** at the six-membered D ring by the use of acetic anhydride and perchloric acid (Scheme 10).[72] When compound **56** was treated with 5% methanolic potassium hydroxide, cevagenine D-orthoacetate (**53**) was obtained (Scheme 10).[73] Both kinds of orthoesters **51** and **53** differ in their stability, **51** being more stable, while **53** is easily isomerized in acidic medium to **52**.[72] Additionally, **53** was converted to **52** by heating with a mixture of acetic anhydride and pyridine (Scheme 9).[72] The lower stability of **53** as compared to **51** and **52** is attributed to the more strained structure of **53**, which incorporates a seven-membered ring.[73]

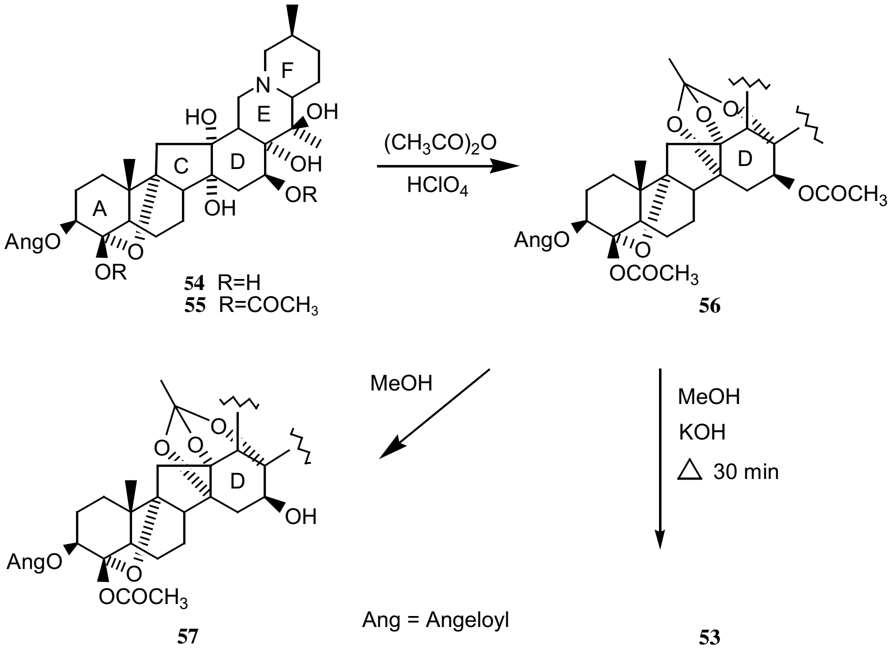
The methanolysis of the acetoxy group at C-16 of ring D of compounds **55** and **56** was studied.[74] It was found that the rate of solvolysis of the orthoacetate diacetate **56** to give monoacetate **57** was lower as compared to the one of cevadine diacetate **55**. The difference of the reactivity of the two compounds **55** and **56** was attributed to the twist boat conformation of the cyclohexane D ring of the orthoacetate **56** in which the targeted acetoxy group at C-16 of on ring D is axial, and hence, more hindered.[74]

5. Orthoester derivatives of sugars and polyhydroxylated cyclohexanes

Other cyclic polyhydroxylated compounds, suitable to be investigated in orthoester formation reactions within the scope of this review from *cis*-1,2,4-trihydroxycyclohexanes are the ones present in sugars and 1,2,3,4,5,6-hexahydroxycyclohexanes. Orthoesters derived from sugars represent relatively rigid systems and are

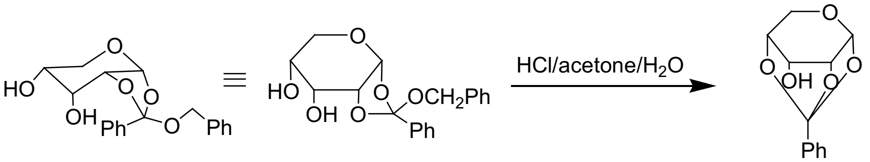


Scheme 9.



Scheme 10.

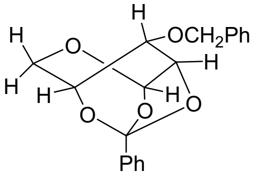
interesting not only as protective groups, but also from the point of view of their stereochemistry. The formation of orthoesters has been investigated in α-D-ribopyranose and α-D-xylopyranose.[77–79] For instance, the protected ribopyranoside **58**, incorporating a bicyclic orthoester moiety, was rearranged into the cage structure of the tricyclic orthobenzoate **59** by reaction with hydrogen chloride in aqueous acetone (Scheme 11).[77]



58 **59**

Scheme 11.

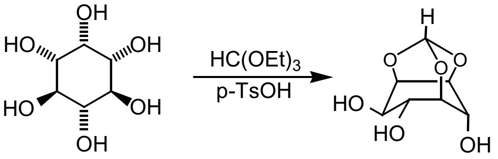
From general stereochemical considerations, it is assumed that the six-membered ring of orthoesters, such as in **59** is in a skew boat conformation. Thus, compound **60** was prepared and its ^{1}H NMR spectrum was investigated for the purposes of detailed conformational analysis.[78]



60

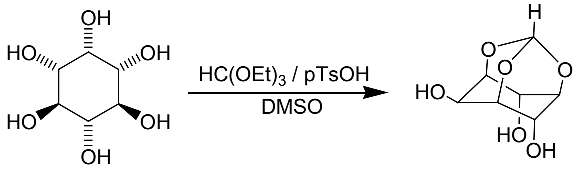
The observed values of the geminal, vicinal and long range coupling constants were compared with the ones calculated on the basis of the assumed skew boat conformation of **60**.[78] A satisfactory good agreement between the observed and the calculated values was found.[78] Similarly, the skew boat conformation was adopted for α-D-xylopyranose tricyclic orthoesters,[79] which are C-3 epimers of **60**, again on the basis of an analogy of the ^{1}H NMR spectra within both epimeric series of compounds. In this way, the orthoesters of the sugars discussed above proved to be interesting stereochemical models for the investigation of their preferred conformation by means of ^{1}H NMR spectroscopy.

Lukyanov and Tolkachev described a reaction of myoinositol (**61**) and triethyl orthoformate in the presence of a catalytic amount of *p*-toluenesulfonic acid in toluene and assumed the structure of myoinositol-1,2,5-orthoformate (**62**) for the compound obtained (Scheme 12).[80] In this respect it was also suggested that myoinositol reacted in its boat type of conformation.[80] Later, the interest in the derivatives of myoinositol (**61**) and its stereoisomers revived because it was shown that inositol-1,4,5-triphosphate plays an important role as a cellular second messenger.[81]



61 **62** (20%)

Scheme 12.



61 **63** (76%)

Scheme 13.

Lee and Kishi have performed a similar work as above in 1985 and produced cage compound **63** in 76% yield from myoinositol utilizing triethyl orthoformate and *p*-toluenesulfonic acid in DMSO (Scheme 13).[82] With ^{1}H NMR spectral data, it was found out that **63** corroborated with the structure of 2,4,10-trioxaadamantane of type **4**,[83,84] but not with myoinositol-1,2,5-orthoformate.

Although the discussion of 2,4,10-trioxaadamantane type of orthoester **63** lays beyond the scope of this review, it should be noted that it is extensively exploited as protective group in connection of multi-step syntheses of inositol-1,4,5-triphosphate and its stereoisomers.[82,85–93] From one side, the investigation of them supplies an additional support for the structure of orthoesters of type **63**, and from the other side, it demonstrates the usefulness of this kind of protective group for the synthesis of interesting biologically active compounds.[85]

Acknowledgements

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Biographical sketch

Elena Stanoeva was born in Montana, Bulgaria, in 1946. She received her M.Sc. in chemistry from 'St. Kliment Ohridski' University of Sofia in 1969 and her Ph.D. (1981) from the University of Sofia working with Professor M. Haimova on diastereomeric isoquinoline and indole compounds. Since 1983 she was an Assistant Professor in the Department of Organic Chemistry of the Faculty of Chemistry at the University of Sofia. In 1994 she was promoted to Associate Professor in Organic Chemistry at the University of Sofia. She carried out postdoctoral work with Professor De Kimpe at Ghent University, Belgium. Her research is concerned with the synthesis and stereochemistry of biologically active nitrogen containing heterocyclic compounds.

Weidong He was born in Beijing, China. He graduated with a Bachelor degree of Medicine from the Second Military Medical University, Shanghai, in 1983. After five years teaching at the School of Pharmacy, he began his career at Ghent University of Belgium where he carried out research in the field of Toxicology and Clinical Chemistry, and received a postgraduate diploma of Pharmaceutical Technology in 1989. In 1995, he joined the research program at the Department of Organic Chemistry, focusing on drug discovery of plant origin and natural product chemistry. Under the guidance of Professor Norbert De Kimpe and Dr. Luc Van Puyvelde, he worked on daphnane-type natural products from plant sources for which he obtained the Ph.D. degree in chemistry. In 2001, he joined Fytolab Company as a research scientist and a technical manager specialized in pesticide analysis of foodstuffs with hyphenated chromatographic techniques. He received also a Master degree in Knowledge Management in 2002. He is a regular badminton player, and enjoys photography, reading, traveling and gardening in his spare time.

Norbert De Kimpe obtained the diploma of chemical agricultural engineer in 1971, the Ph.D. degree in 1975, and the habilitation degree in 1985, all from Ghent University. He performed postdoctoral research work at the University of Massachusetts, Harbor Campus, at Boston (USA) (1979) and at the Centre National de Recherche Scientifique in Thiais, Paris (France) (1983), where he worked on unstable nitrogen-substituted sulfenyl derivatives and electron-deficient carbenium ions, respectively. He made his scientific career at the Belgian National Fund for Scientific Research where he went through all stages up to the position of Research Director. During this career, he was affiliated with the Department of Organic Chemistry, Faculty of Agricultural and Applied Biological Sciences at the University of Ghent, where he took up teaching positions since 1987. He is now Professor in organic chemistry at the latter institution. He was a guest-professor at the Centre Universitaire de Recherche sur la Pharmacopée et la médecine Traditionelle in Butare (Rwanda, Central Africa), and at the Universities of Perpignan (France), Helsinki (Finland), Leuven (Belgium), Siena (Italy), Barcelona (Spain), Sofia (Bulgaria), Buenos Aires (Argentina) and Pretoria (South Africa). He was awarded the degree of Doctor honoris causa from the Russian Academy of Sciences in Novosibirsk (Russia) in 1998. He is the author of 330 articles in international peer-reviewed journals. His research interests include (1) the synthesis of heterocyclic compounds, with focus on agrochemicals, pharmaceuticals, and natural products, (2) flavour chemistry, and (3) the bioassay-guided isolation of physiologically active natural products from medicinal plants.