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Research Topics

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Abstract. Quantum-mechanical calculations have been applied to predict thermodynamic and reactivity properties of unknown organic molecules, being stable compounds or reactive intermediates. Through synthesis some of the theoretical systems become real compounds that can be synthons (synthetic intermediates) or chirons (optically pure synthetic intermediates) useful in the preparation of natural products and analogues of biological interest (anti-cancer, anti-virus, antibiotic, anti-diabetes agents). Our interests concentrate on remote substituent effects as we want to play with them together with polyfunctional systems and reactions that constitute new synthetic approaches. These have to be convergent, highly stereoselective, and versatile (applicable to a large variety of derivatives: molecular diversity). We often rely on tandem reactions or/and reaction cascades. Sometimes the new compounds and their new reactions send us back to the theory and to mechanistic studies.

The Electron-Releasing Carbonyl Group and the 'Naked Sugars of the First Generation'

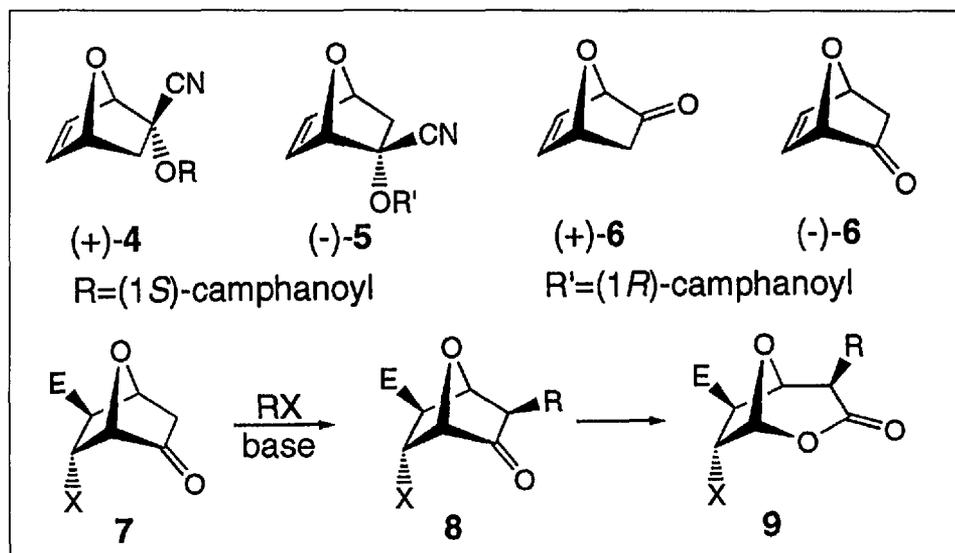
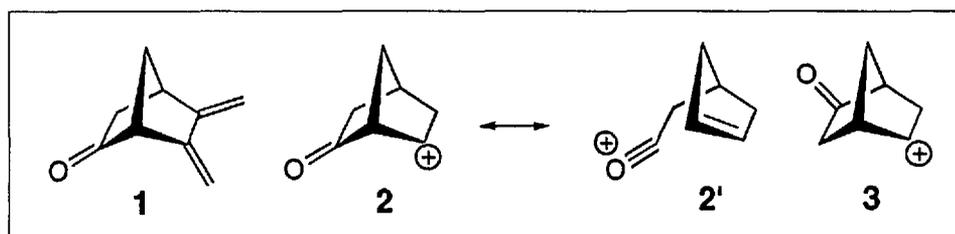
In 1978, we reported that 5,6-dimethylidenebicyclo[2.2.1]heptan-2-one (**1**) adds to methyl propynoate and methyl vinyl ketone with 'para'-regioselectivity in agreement with predictions based on frontier molecular orbital (FMO) theory [1]. A closer look at the HOMO of dienone **1** suggested that this system is capable to exchange electrons from the n orbitals of the carbonyl group with those of the homoconjugated π system through a relay σ -bond [2]. Quantum calculations confirmed this hypothesis particularly by predicting that 6-oxobicyclo[2.2.1]hept-2-yl cation (**2**) is *ca.* 7 kcal/mol more stable than 5-oxobicyclo[2.2.1]hept-2-yl cation (**3**) [3]. Further theoretical studies [4] suggested that the carbonyl group in **1** and **2** can be electron-releasing because of hyperconjugative $n(\text{CO}) \leftrightarrow \sigma \leftrightarrow \pi$ interaction that is reminiscent of the frangomeric effect discussed by *Grob* [5].

Although cations of type **2** and **3** may not be intermediates in electrophilic addi-

tions of bicyclo[2.2.1]hept-5-en-2-one, we predicted that these reactions would have the opposite regioselectivity than the electrophilic additions of 2-cyanobicyclo[2.2.1]hept-5-en-2-yl acetate, the synthetic precursor of bicyclo[2.2.1]hept-5-en-2-one. These predictions were verified for a large variety of electrophiles and for other bicyclic olefins [6]. The concept

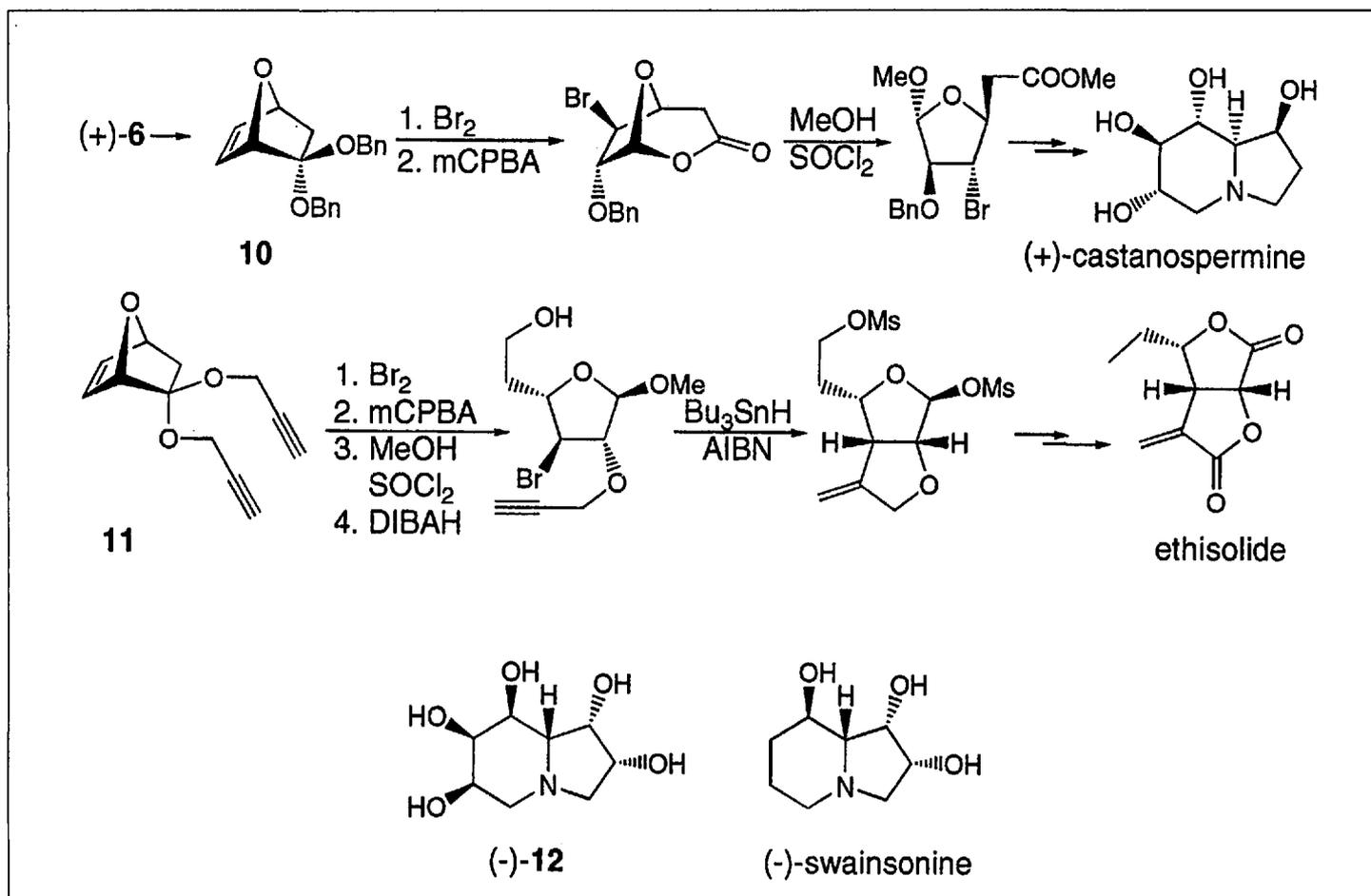
became a useful synthetic tool when applied to optically pure 7-oxabicyclo[2.2.1]hept-5-en-2-yl derivatives such as (+)-**4**, (-)-**5**, (+)-**6**, and (-)-**6**. Indeed, in one step, electrophilic additions introduce two substituents at C(5) and C(6) of the bicyclic alkenes with high facial selectivity and high regioselectivity (*e.g.* **7**). Reactions of the corresponding enolate with electrophilic agents introduce a third substituent at C(3) with high *exo* face selectivity, giving polysubstituted 7-oxanorbornanones (*e.g.* **8**) that possess the same density of stereochemical information than a sugar such as D-glucose. A *Baeyer-Villiger* oxidation transforms the 7-oxanorbornanones into the corresponding uronolactones (*e.g.* **9**) with high regioselectivity. This led us to call the optically pure systems (+)-**4**, (-)-**5**, (+)-**6**, and (-)-**6** 'naked sugars'; they are unexpensive compounds obtained from furan and 1-cyanovinyl esters [7] and represent templates that can be converted into a wide variety of enantiomerically pure compounds [8], such as rare D- or L-sugars and analogues, C-nucleosides [9], conduritols [10], conduramines [11], polyfunctional cyclopentanes (carbapentoses) [12], and natural products of biological interest [13][14].

Electrophilic additions of alkenes can also be controlled by the participation of remote substituents as illustrated with the bromine additions of acetals **10** and **11**.



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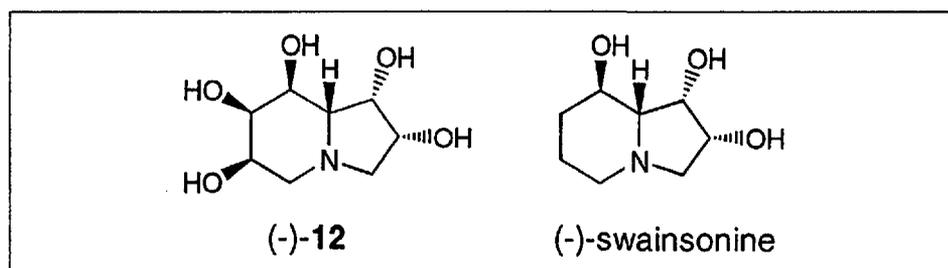
Scheme 1



This feature has been exploited by us in a total, asymmetric synthesis of (+)-castanosperime, a natural glycosidase inhibitor [15]. On their side, *Cossy* and coworkers [16] have realized a short and elegant total synthesis of ethisolide based on the same principle (Scheme 1).

The 'naked sugar' methodology is powerful in generating long-chain carbohydrates and analogues with predictable configurations. In 1992, we reported the first syntheses of 1,5-dideoxy-1,5-iminoctols and their one-step conversion into the corresponding 1,2,6,7,8-pentahydroxyindolizidines [17]. Among them, derivative (-)-12 which has the same configuration as that of (-)-swainsonine is a potent inhibitor of α -mannosidases but unlike the natural alkaloid, it does not inhibit β -galactosidases [18].

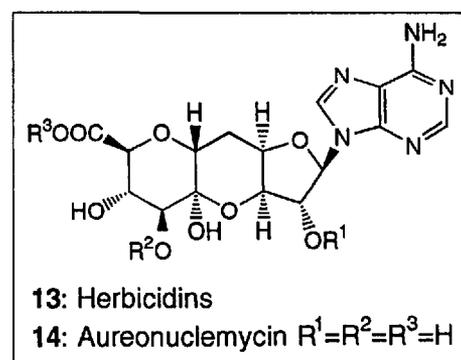
The search for new antibiotics by fermentation technologies has produced unusual nucleosides such as mildiomycin containing a branched decose derivative, the tunicamycines, the streptoviridins, the corynetoxins, hikizimycin, the herbicidins (1), and aureonuclemycin (2) that incorporate undecose moieties within their structure. The herbicidins exhibit herbicidal and antifungal activity. Aureonuclemycin (2) is an efficient inhibitor of *Xanthomonas*



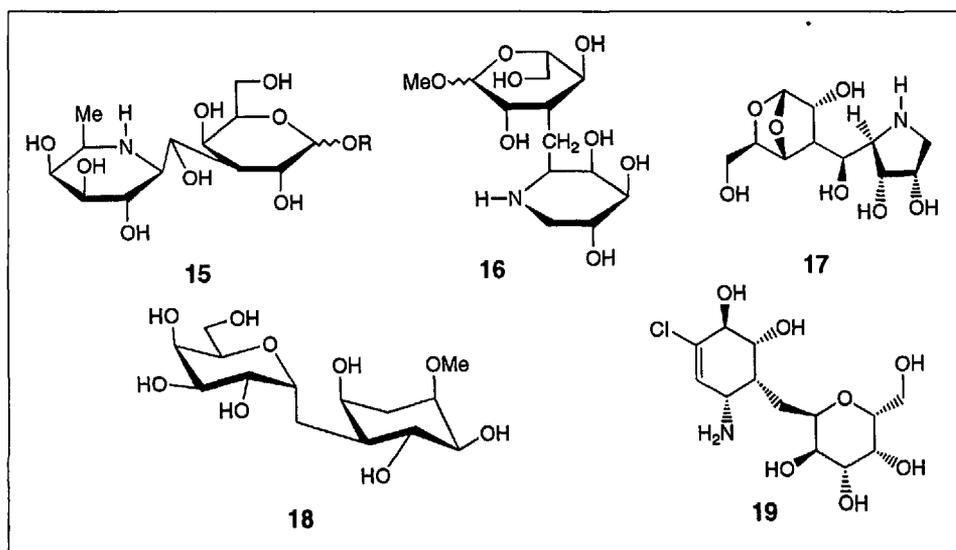
oryzae, a bacterium which causes rice infection. Their carbohydrate moiety is composed of 6,10-anhydro-5-deoxy- β -D-arabino-L-ido-7-undeculo-(7,3-pyranose)-furanosiduronic acid, a rare long-chain carbohydrate that has an unusual furano-pyrano-pyran skeleton which can be viewed as 5-C-(α -D-arabino-2-hexulopyranosyl)-5-deoxy-D-xylo-furanose. This rare sugar has been obtained *via* a cross-aldolization between a derivative of D-glucose and a derivative of the 'naked sugar' (+)-6 [19].

Asymmetric Synthesis of Sugar Mimics

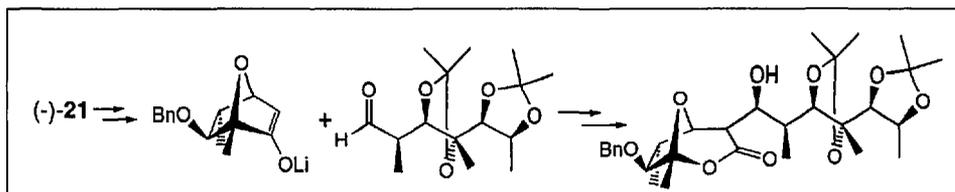
Glycosidases are key enzymes in the biosynthesis and processing of glycoproteins, which are macromolecules involved in recognition (cell-cell, host-pathogene



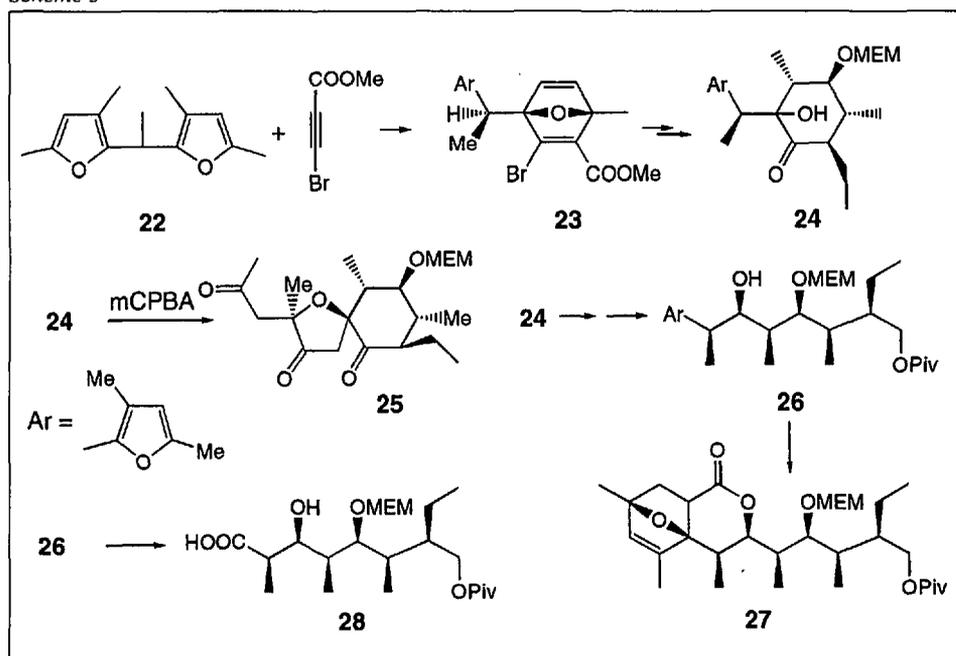
interactions) and control of biological mechanisms and structures. Inhibition of glycosidases may be useful for the treatment of diseases such as diabetes, cancer, viral and bacterial infections, and inflammation. The hydroxylated indolizidines such as (+)-castanospermine and (-)-



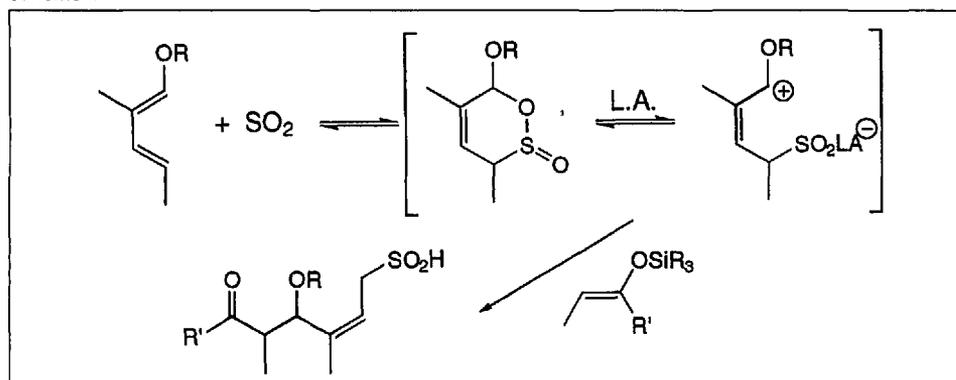
Scheme 2



Scheme 3



Scheme 4



swainsonine and simpler piperidines and pyrrolidines (azasugars, one kind of sugar mimics) are promising inhibitors; unfortunately, they often inhibit more than one enzyme *in vivo*. It is believed that selectivity would be increased if the azasugar would include not only the steric and charge information of the glycosyl moiety which is liberated during the glycosidase-catalyzed hydrolysis, but also that of the aglycone which it is attached to. Such inhibitors could be dideoxy-iminoalditols attached to other sugars through non-hydrolyzable links such as the aza-C-disaccharides. Systems such as **15** [20], **16** [21], and **17** [22] have been prepared from the 'naked sugars'. The same methodology has allowed one to generate the first examples of C-glycosides carbapyranoses such as **18** [23] and of C-glycosides of aminoconduritols such as **19** [24].

'Naked Sugars of the Second Generation': Asymmetric Synthesis of Polypropionate Antibiotics

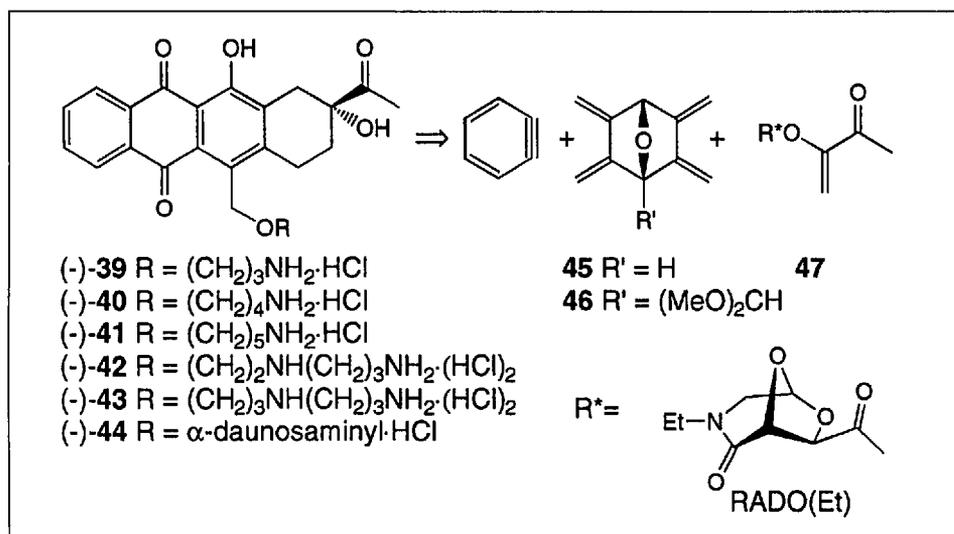
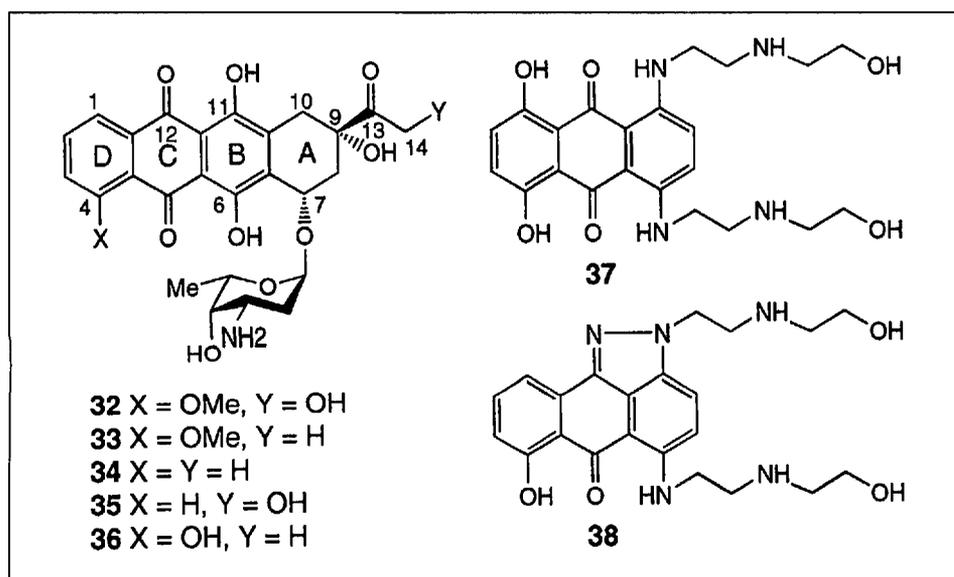
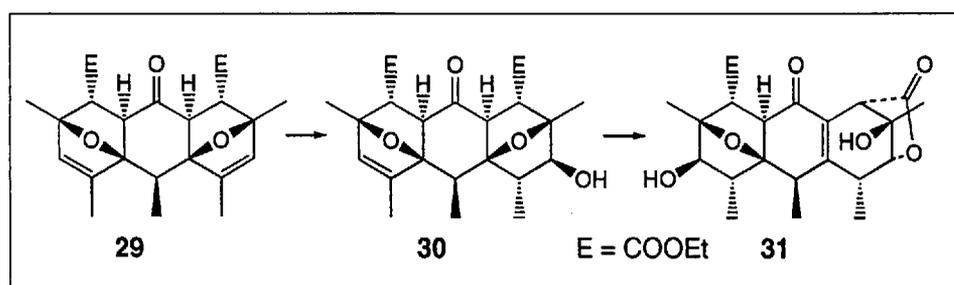
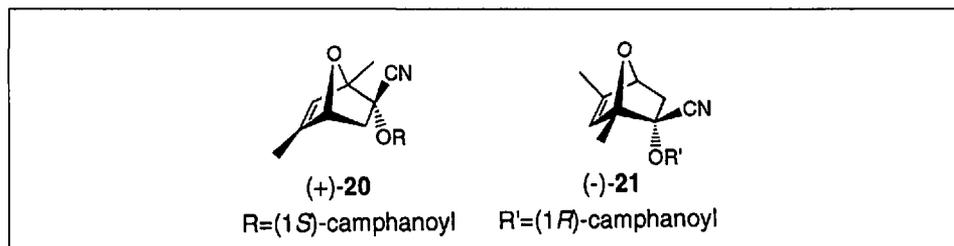
Nature provides us with a number of products of biological interest containing long-chain polypropionate fragments (chain with alternating OH and Me substituents) [25]. Because of their rarity, total synthesis can, in principle, supply sufficient quantities for their pharmaceutical testing, and very importantly, for obtaining non-natural analogues. Although very efficient methods are now available to construct these systems that possess a high density of stereochemical information, we are trying to propose new and alternative approaches which exploit the high stereoselectivities of the reactions of bicyclic templates such as 7-oxabicyclo[2.2.1]hept-2-yl derivatives. We have found [26] that the ZnI_2 -catalyzed *Diels-Alder* additions of 2,4-dimethylfuran (a inexpensive compound obtained in two steps from mesityl oxide) to 1-cyanovinyl (*1R*)- or (*1S*)-camphanate leads to high yield of optically pure adducts (+)-**20** and (-)-**21** ('naked sugars of the second generation'). These compounds have allowed the development of a convergent and highly stereoselective method for the preparation of long-chain polypropionate fragments containing up to eleven contiguous stereogenic centres and tertiary-alcohol moieties [27] as illustrated in *Scheme 2*. In this approach, the chiral auxiliaries ((*1R*)- or (*1S*)-camphanic acid) are recovered at an early stage of the synthesis, and both enantiomeric forms of the polypropionate fragments are available with the same ease.

In parallel with our studies of the chemistry of templates (+)-**20** and (-)-**21**, we have explored the possibility to use the *Diels-Alder* adducts **23** of 2,2'-ethylidenebis[3,5-dimethylfuran] (**22**), a compound obtained in one step by condensation of

2,4-dimethylfuran with acetaldehyde. Experiments have allowed us to transform **23** into the polypropionate fragments **25-28** (Scheme 3) as racemic mixtures [28].

More recently [29] we have discovered that **22** can undergo two simultaneous

Diels-Alder additions with a bis-dienophile such as diethyl (*E,E*)-4-oxohepta-2,5-diene-1,7-dioate. The single adduct **29** so obtained can be desymmetrized through chirality, using monoisopinocampheylborane ((+)-IpcBH₂) as hydroborating agent. After oxidation of the alcohol **30**, treatment with BH₃ (Me₂S and then with NaBO₃) led to the formation of **31** selectively. We are, therefore, able to desymmetrize **29** and to carry out different chemistries with its two 7-oxabicyclo[2.2.1]heptyl systems. Future work will tell us whether these discoveries will lead us or not to a new approach to the synthesis of complicated, long-chain polypropionate fragments.



New DNA Intercalators and Topoisomerase Inhibitors

The clinical utility of the anthracycline antitumor antibiotics such as adriamycin (**32**) and daunomycin (**33**) is well demonstrated [30]. Their effectiveness, however, is restricted due to acute bone marrow toxicity, cardiotoxicity, and drug resistance development [31]. More than 2000 analogues have been synthesized and tested during the last 30 years. Among them, idarubicin (**34**) 4-demethoxyadriamycin (**35**) [32], and carminomycin (**36**) [33] have comparable or better *in vivo* activity than **32** and **33** at lower dose.

Simple 1,4-bis[(aminoalkyl)amino]-9,10-anthraquinones [34] such as mitoxantrone (**37**) [35] and isoxantrone (**38**) [36] have also useful anticancer properties. These observations together with the fact that polyamines are able to inhibit cancer cell growth [37] led us to conceive a new series of anthracycline analogues (-)-**39**-(-)-**43** bearing aminoalkyl chains through a benzyl ether link at C(6). We have also prepared the α-L-daunosaminyl derivative (-)-**44** and have evaluated the ability of these new analogues to bind calf thymus DNA through interaction, and, for some of them, their ability to inhibit topoisomerase-I-induced relaxation of circular plasmids and topoisomerase-II-induced DNA strand religation. The newly developed synthetic approach in this work has led us to propose a new synthesis of (-)-(*R*)-4-demethoxy-7-deoxydaunomycinone, a known precursor of idarubicin (**34**). While (-)-**42**-(-)-**44** do not intercalate calf thymus DNA, (-)-**39**-(-)-**41** do bind with DNA. Compound (-)-**39** inhibits the topoisomerase-I-induced relaxation and the topoisomerase-II-induced DNA strand religation [38].

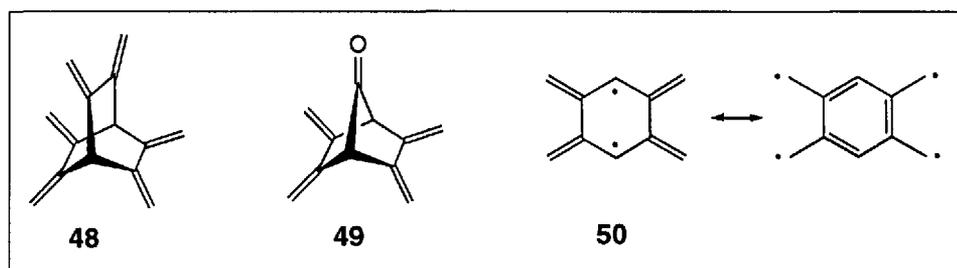
In 1979, our group [39] demonstrated that the readily available tetraene **45** can be converted through two successive *Diels-Alder* additions with two different dienophiles into a variety of linearly condensed polycyclic systems including racemic anthracyclinone derivatives. This concept, which is referred nowadays to combinatorial chemistry (synthesis of libraries of compounds), was patented in 1979 already [40]. The method has been applied to the synthesis of 4-demethoxydaunomycinone [41], daunomycinone [42], and 11-deoxydaunomycinone [43]. 1-(Dimethoxymethyl)-2,3,5,6-tetramethylidene-7-oxabicyclo[2.2.1]heptane (**46**), a tetraene obtained readily from furfural, has now been used as a precursor of anthracyclinone analogues bearing a carbon substituent at C(6), as required for (–)-**39**–(–)-**44** [38]. This method involves desymmetrization through *Diels-Alder* additions to 1-acetylvinyll esters of type **47** derived from diacetyl and our RADO(Et)-Cl chiral auxiliary, derived itself from (*R,R*)-tartaric acid (SADO(Et)-Cl is derived from (*S,S*)-tartaric acid) [45].

New Avenues for Synthesis and Theoretical Chemistry

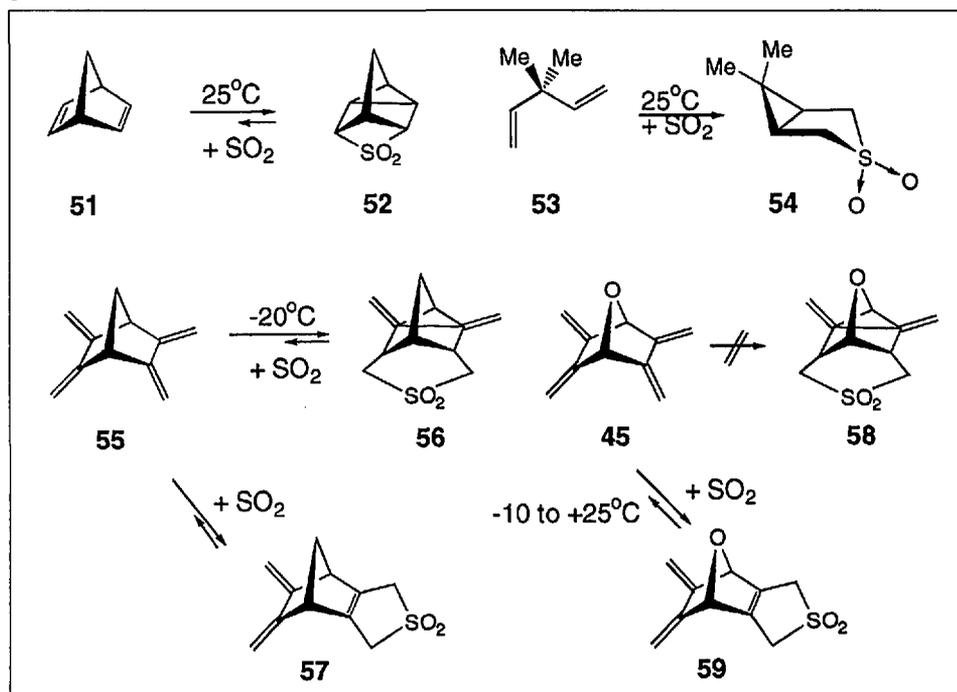
For more than 20 years, our group has been interested in designing new polyfunctional systems such as tetraenes **45**, **46**, and other polyenes such as the [2.2.2]hericene (**48**) and the 7-oxa[2.2.1]hericene (**49**). These compounds have been crucial in the development of theories that explain the decreasing tandem *Diels-Alder* reactivity [46] exploited in our syntheses of anthracyclinones and analogues. They are also ligands for transition-metal complexes [47]. Concurrent groups have used our polyenes to construct all kind of molecular devices [48]. In collaboration with Prof. J.A. Berson at Yale University, we have found that **49** can be used to generate the singlet diradical **50** (tetramethylidenebenzene), a compound of considerable theoretical interest [49].

New Reactions of Sulfur Dioxide

The cheletropic reaction [$\omega^2_s + \pi^4_s$] of SO_2 with 1,3-dienes to give 2,5-dihydrothiophene 1,1-dioxides (sulfolenes) is known since 1914 [50]. Before our work the hetero-*Diels-Alder* addition [$\pi^4_s + \pi^2_s$] of SO_2 to 1,3-dienes had been reported for two cases only (*ortho*-xylylene [51], and the highly reactive 1,4,5,6-tetramethyl-2,3-dimethylidenebicyclo[2.1.1]heptane-



Scheme 5



hexane [52]). In the presence of a suitable catalyst (CF_3COOH , $\text{BF}_3(\text{Et}_2\text{O})$) and below -70° , simple 1,3-dienes such as isoprene and (*E*)-piperilene undergo hetero-*Diels-Alder* additions giving the corresponding 3,6-dihydro-1,3-oxathian 2-oxides (sultines) with high regio- and stereoselectivity [53]. We are trying to develop a new method for the creation of C–C bonds through the oxyallylation of enoxysilanes, the oxyallylating agents arising from the Lewis-acid (LA)-promoted heterolysis of sultines formed by the cycloaddition of 1-oxy-1,3-dienes and SO_2 (Scheme 4) [54].

Homoconjugated dienes can be rearranged into conjugated 1,3-dienes in the presence of SO_2 via ene reactions (Scheme 5). In the cases of norbornadiene (**51**) [55] and 3,3-dimethylpenta-1,4-diene (**53**) that cannot undergo ene reactions, their reactions with SO_2 give the corresponding sulfolanes **52** and **54**, respectively, resulting from homocheletropic additions in a [$\omega^2_s + \pi^2_s + \pi^2_s$] fashion [56]. When 2,3,5,6-tetramethylidenebicyclo[2.2.1]heptane (**55**) is allowed to react at -20° with SO_2 , the sulfolane **56** is formed as single product. At 0° , **56** undergoes slow cyclorever-

sion into **55** + SO_2 and then formation of the more stable sulfolene **57** resulting from the cheletropic addition of an exocyclic 1,3-diene unit. At 25° , an equilibrium constant $K = [\mathbf{57}]/[\mathbf{56}] = 5:1$ is observed. In this case, the homocheletropic addition $\mathbf{55} + \text{SO}_2 \rightarrow \mathbf{56}$ is kinetically favored but thermodynamically disfavored compared with the cheletropic addition $\mathbf{55} + \text{SO}_2 \rightarrow \mathbf{57}$. In contrast, 2,3,5,6-tetramethylidene-7-oxabicyclo[2.2.1]heptane (**45**) does not undergo the homocheletropic addition of SO_2 between -30 and $+30^\circ$. Above -10° , slow formation of sulfolene **59** is observed [55]. Work is underway in our laboratory to understand the effect described above and to find synthetic applications to the homocheletropic additions of sulfur dioxide.

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