EXTENDED ABSTRACT

Journal of Medicinal and Organic Chemistry

New organic chemistry of sulfur dioxide: new reactions, new reagents, total asymmetric synthesis of polypropionate antibiotics

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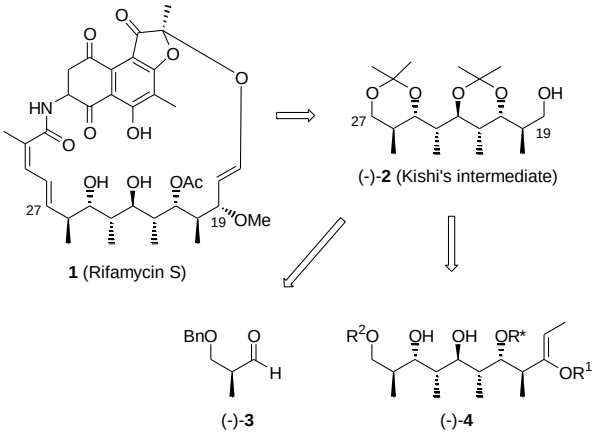
Introduction

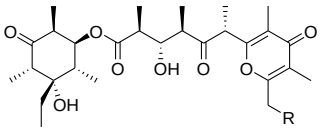
Although sulfur dioxide (SO_2) is one of the major natural and man-made air pollutant and that burning of sulfur, which generates SO_2, has been used for more than 8000 years to sanitize containers of food and beverages, the organic chemistry of SO_2 is today quite limited in scope. Applying high level quantum calculations, we intend to understand newly discovered reactions and reaction cascades involving SO_2. These studies have led us to invent new synthetic procedures of high potential for material sciences and medicinal chemistry. Our studies are also pertinent to acid rain and smog formation. They help in the interpretation of experimental data (thermodynamics, kinetics, isotope effects) in connection with the ene-reaction, the cheletropic and the hetero-Diels-Alder additions of SO_2. We are studying also the catalysis of these reactions and of others involving polysulfone polymers. The project establishes a fruitful synergy between experience (EPFL) and theory (Oviedo). In this presentation well shall illustrate the power of our recently discovered reaction cascades based on pericyclic reactions of SO_2 to the efficient asymmetric synthesis of complicated antibiotics such as Rifamycin S, Apoptolidin and Baconipyrones. We shall present although new sulfur dioxide mediated one-pot, three and four-component synthesis of polyfunctional sulfonamides, sulfonic esters and sulfones (combinatorial chemistry) and the invention of new strategies for polyols semi-protection and protection using silyl methallylsulfinates for the neutral silylation of alcohols.

Synthetic targets.

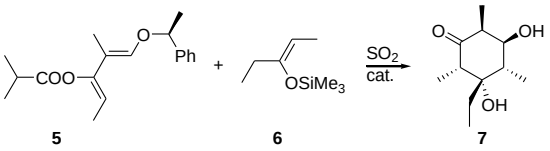
Rifamycins[1] are antibiotics belonging to the group of naphthalenic ansamycins[2] characterized by an aliphatic bridge (polypropionate chain) linking two non-adjacent centers of an aromatic moiety. They are produced from *Streptomyces mediterranei*[3] and are active against a large variety of organisms; including bacteria, eukaryotes, and viruses.[4] Rifamycins have shown also antitumour[5] and anti-inflammatory activity,[6] but at present are mainly used for the treatment of tuberculosis. Their antimicrobial activity is due to the inhibition of bacterial DNA-dependent RNA polymerase.[7] Several derivatives of Ryfamicin S (**1**) have been prepared and many of them have shown promising activities.[8]



The first total synthesis of Rifamycin S was reported by Kishi and co-workers in 1980.[9] The stereoheptad (-)-**2** was a key-intermediate for the construction of the ansa chain. It was obtained in 26 steps and 5.2% overall yield from (2*S*)-3-benzyloxy-2-methylpropanal ((+)-**3**[10] We present a very short synthesis of (-)-**4** and (-)-**2** starting with simple, inexpensive starting materials and (+)-**3**.[11] Baconipyrones A-B were isolated in 1989 by Faulkner and co-workers from *Siphonaria baconi*.[12] They constitute an exception to the normal polypropionic skeleton with their noncontiguous, ester-type backbone.[13] The first total synthesis of (-)-baconipyrone C was presented by Paterson and co-workers[14] in 2000.

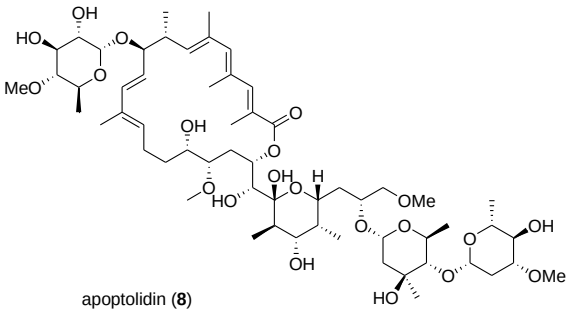


In two steps only, we have prepared the cyclohexanone units[7] of these antibiotics, condensing diene **5** and enoxysilane **6** in the presence of SO_2.[15]



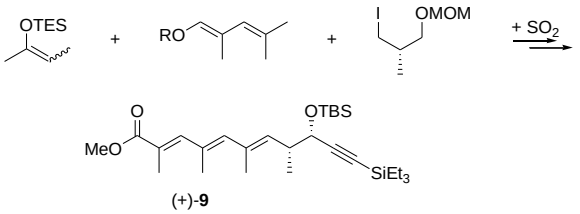
Apoptosis,[16] or programmed cell death, is an important mechanism in the treatment of cancer. Apoptolidin (**8**) isolated from the cultivation broth of an actinomycete identified as *Nocardiopsis sp*., was found[17] to have considerable potency with regard to selectively induced cell death by apoptosis in rat glia cells transformed with adenovirus E1A and

E1A/E1B19 K oncogenes.[18] Apoptolidin was found to be among the top 0.1% of most selective cytotoxic agents.[19,20]



apoptolidin (**8**)

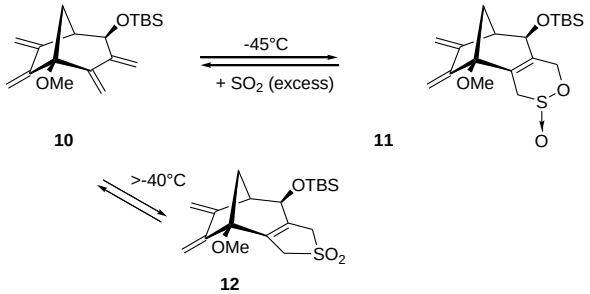
The Nicolaou's intermediate (+)-**9**[21] of the C(1)-C(11) fragment of **8** have been obtained in four steps[22] only applying our new method for the asymmetric synthesis of dienones.[23] Effort toward the synthesis of the aglycone of **8** will also be presented.



(+)-**9**

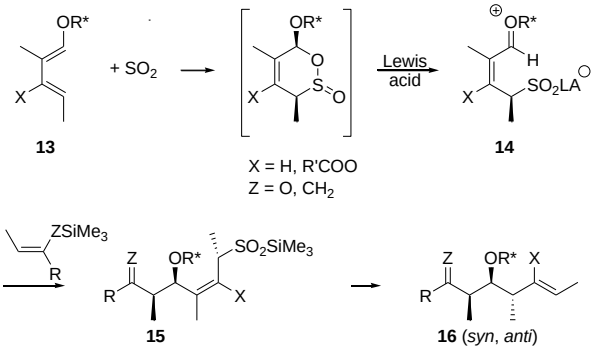
Scientific curiosity and unplanned research: source for discoveries.

As we had found that tetraene **10** reacted toward dienophiles (Diels-Alder reaction) faster with its diene moiety at C(2,3) than with the other diene unit at C(6,7), we were curious whether the cheletropic addition of SO_2 would also show the same chemoselectivity. At -45°C SO_2 adds to **10** equilibrating with ca. 5% of sulfine **11**, and with sulfolene **12** above -40°C.[24]



10 **11** **12**

We had thus discovered that the hetero-Diels-Alder addition of SO_2 leads to instable sulfines which are formed faster than the stable isomeric sulfolenes. This is the case for all 1,3-dienes that can exist in their *s-cis*-conformation.[25] Using 1-alkoxy or 1-silyloxy-1,3-dienes **13**, the sultines are not seen at low temperature, but are formed as intermediates that are ionized into the corresponding zwitterions **14**. The latter react with electron-rich alkenes such as enoxysilanes and allylsilanes, giving the corresponding silyl sulfinates **15**. After desilylation, retro-ene elimination, the β,□-unsaturated sulfinic acids generate polypropionate fragments **16** that contain up to 3 contiguous stereogenic centers, this in one-pot procedures (Vogel's cascade).[26] Depending upon the configuration of the enoxysilanes, stereotriads *syn,anti* (e.g. **16**, Z=O) or *anti,anti* are obtained. Enantiomerically pure compounds are prepared using the inexpensive (1*R*)-1-phenylethanol as chiral auxiliaries (R*OH).

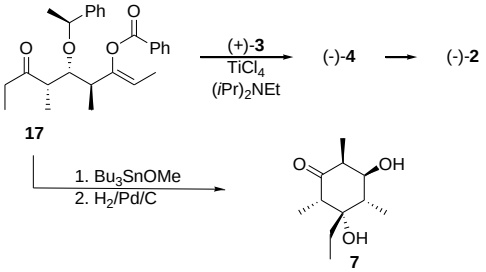


13 **14** **15** **16** (*syn*, *anti*)

Synthetic applications of the Vogel's cascade.

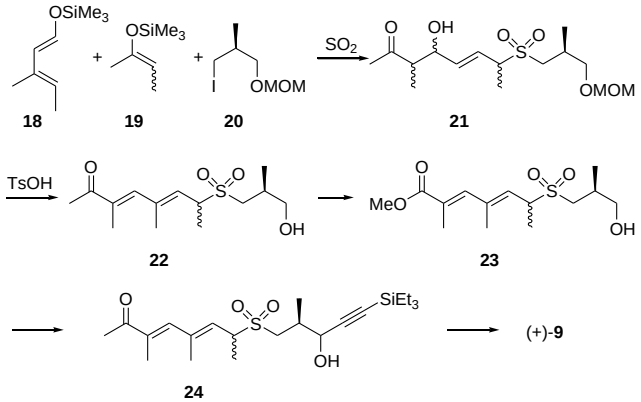
Stereotriad **17** obtained in one step following the Vogel's cascade undergoes Mukaiyama's cross aldol reaction with aldehydes (+)-**3** producing an aldol that was reduced with $Me_4NBH(OAc)_3$ into the stereoheptad (-)-**4**, corresponding to fragment C_{19}-C_{27} of Ryfamycin S. It was converted in two steps into Kishi's intermediate (-)-**2**.[11]

Compound **17** reacted with Bu_3SnOMe and produced **7** in an one-pot operation.[15]



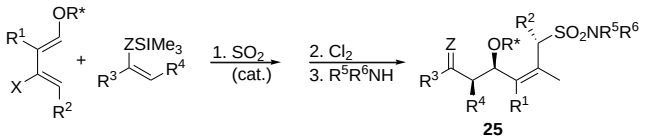
17 **7**

Reaction of diene **18**, enoxysilane **19** with SO_2, $(CF_3SO_2)_2NH$, followed by treatment with Bu_4NF (desilylation) and iodide **20** gave methyl ketones **21** that were not isolated, but treated with paratoluensesulfonic acid to give dienones **22**.[23] Conversion of the methyl ketone into methyl ester **23** (one-pot) followed by oxidation of the primary alcohol into the corresponding aldehydes and reaction with Li-C≡C-$SiEt_3$ furnished **24**. Ramberg-Bäcklund olefination converted **24** into (+)-**9**,[22] the C-C, fragment of apoptolidin prepared by Nicolaou in 11 steps!



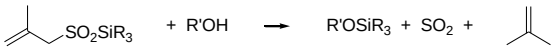
18 **19** **20** **21** **22** **23** **24**

The silyl sulfinates (e.g. **15**) obtained as intermediates in the Vogel's cascade can be reacted with all kinds of electrophiles, this realizing an one-pot, four-component synthesis of polyfunctional sulfones.[27] Upon treatment of these silylsulfinates by N-chlorosucinimide, or Cl_2, the corresponding sulfonyl chlorides are obtained that can be reacted *in situ* with amines and alcohols, thus realizing one-pot, four component syntheses of polyfunctional sulfonamides (e.g. **25**) and sulfonic esters.[25]



25

We have also found that sulfonyl chlorides are excellent electrophilic partners in C-C bond forming cross-coupling reactions under desulfitation conditions (Stille,[29] Suzuki,[30] Sonogashira,[31] Heck[32]). We have discovered also that allylsilanes undergo ene-reactions with SO_2 giving silyl alkenylsulfinates (**26**). The latter are excellent reagents for the selective silylation of polyols, phenols and carboxylic acids under neutral conditions. No purification of the silylated products is necessary as the co-products are volatile.[33]



26

At 20°C, SO_2 forms with alkenes 1:1 copolymers: the polysulfones. We have discovered that some polysulfones are solid, organic catalysts for chemoselective alkene isomerization.[34] This has led us to propose a new strategy for the polyol semi-protection.[35]

Conclusion.

If the organic chemistry of sulfur dioxide was born at the beginning of the 21st century, it means to us that many other simple inorganic and organic compounds might offer new palettes of reactions. For us organic chemistry is an immature science. Although many tools are now available for the construction of almost any complicated target compounds, there is a huge space for the discovery of new strategies, new reagents, new catalysts, and new reaction cascades that will be most profitable to mankind. Cheaper reagents will be combined in fewer steps into useful drugs and materials, producing less garbage and using less energy. To reach this goal, chemists should not follow fashion but their scientific curiosity.

Acknowledgement

We are most grateful to the Swiss National Science Foundation for generous financial support and for the freedom given to the grant-applicants in their planning of research. We thank also the Roche Research Foundation, the "Secretariat d'Etat à l'Education et la Recherche" SER, Bern), the SOCRATES program (EPF/Oviedo; EPFL/Seville), the "Centro Svizzero di Calcolo Scientifico" (Manno, Ticino) and the Spanish Government (grants MECD, BQU-3660-CO2-01, BQU-07405-C02-02) for support.

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