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

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Introduction

Although sulfur dioxide (SO₂) is one of the major natural and man-made air pollutants and that burning of sulfur, which generates SO₂, has been used for more than 8000 years to sanitize containers of food and beverages, the organic chemistry of SO₂ is today quite limited in scope. Applying high level quantum calculations, we intend to understand newly discovered reactions and reaction cascades involving SO₂. 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 SO₂. 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 SO₂ to the efficient asymmetric synthesis of complicated antibiotics such as Rifamycin S, Apoptolodin 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 methallylsulfinate for the neutral silylation of alcohols.

Synthetic targets.

Rifamycins¹ are antibiotics belonging to the group of naphthalenic ansamycins² characterized by an aliphatic bridge (polypropionate chain) linking two non-adjacent centers of an aromatic moiety. They are produced from Streptomyces mediterranei³ and are active against a large variety of organisms; including bacteria, eukaryotes, and viruses.⁴ Rifamycins have shown also antitumour⁵ 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 (2S)-3-benzoxoy-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-workers¹⁴ in 2000.

In two steps only, we have prepared the cyclohexanone units⁷ of these antibiotics, condensing diene 5 and enoxysilane 6 in the presence of SO₂.¹⁵

Apoptosis,¹⁶ or programmed cell death, is an important mechanism in the treatment of cancer. Apoptolodin (8) isolated from the cultivation broth of an actinomycete identified as Novocardiosps sp., was found¹⁷ 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.\textsuperscript{18} Apoptolidin was found to be among the top 0.1% of most selective cytotoxic agents.\textsuperscript{19,20}

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

\textbf{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 \textit{Alder reaction) faster with its diene moiety at C(2,3). After desilylation, retrogrouped this realizing an aldol that was reduced with MeNBH(OAc)\textsubscript{3} into the stereohedal (-)-4, corresponding to fragment C(10)-C(27) of Ryfamycin S. It was converted in two steps into Kishi’s intermediate (-)-2.\textsuperscript{11}

Compound 17 reacted with Bu\textsubscript{4}SnOMe and produced 7 in an one-pot operation.\textsuperscript{15}

Reaction of diene 18, enoxysilane 19 with SO\textsubscript{2}, (CF\textsubscript{3}SO\textsubscript{2})\textsubscript{3}NOH, followed by treatment with Bu\textsubscript{4}NF (desilylation) and iodide 20 gave methyl ketones 21 that were not isolated, but treated with paratoluensulfonic acid to give dienes 22.\textsuperscript{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\textsubscript{6}C=SiEt\textsubscript{3} furnished 24. Ramberg-Bäcklund olefination converted 24 into (+)-9,\textsuperscript{22} the C-C, fragment of apoptolidin prepared by Nicolaou in 11 steps!

We had thus discovered that the hetero-Diels-Alder addition of SO\textsubscript{2} leads to instable sulfines which are formed faster than the stable isomeric sulfones. This is the case for all 1,3-diienes that can exist in their \textit{s-cis-conformation.}\textsuperscript{25} Using 1-alkoxy or 1-silyloxy-1,3-diienes 13, the sulfines are not seen at low temperature, but are formed as intermediates that are ionized into the corresponding zwitarians 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 \textit{β,γ-unsaturated sulfinic acids generate polypropionate fragments 16 that contain up to 3 contiguous stereogenic centers, this in one-pot procedures (Vogel’s cascade).}\textsuperscript{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 (1R)-1-phenylethanol as chiral auxiliaries (R*OH).

\textbf{Synthetic applications of the Vogel’s cascade.}

To evaluate the synthetic potential of the Vogel’s cascade, compounds 13 and 14 were treated with dienophiles. Compound 13 was 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 \textit{Alder reaction) faster with its diene moiety at C(2,3)\textsuperscript{21} of apoptolidin (8). After desilylation, retro-

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.\textsuperscript{27} Upon treatment of these silylsulfinates by N-chlorosucinimide, or Cl\textsubscript{2}, the corresponding sulfonyl chlorides are obtained that can be reacted \textit{in situ} with amines and alcohols, thus realizing one-pot, four component syntheses of polyfunctional sulfonamides (e.g. \textbf{25}) and sulfonic esters.\textsuperscript{25
We have also found that sulfonyl chlorides are excellent electrophilic partners in C-C bond forming cross-coupling reactions under defusification conditions (Stille, Suzuki, Sonogashira, Heck). We have discovered also that allylsilanes undergo ene-reactions with SO2 giving silyl alkylsulfonilates (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.

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SO_2SiR_3 + ROH \rightarrow ROSiR_3 + SO_2 + \ \ \ \ (26)
\]

At 20°C, SO2 forms with alkenes 1:1 copolymers: the polysulfones. We have discovered that some polysulfones are solid, organic catalysts for chemoselective alkane isomerization. This has led us to propose a new strategy for the poloyl semi-protection.

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.

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