

SYNFORM

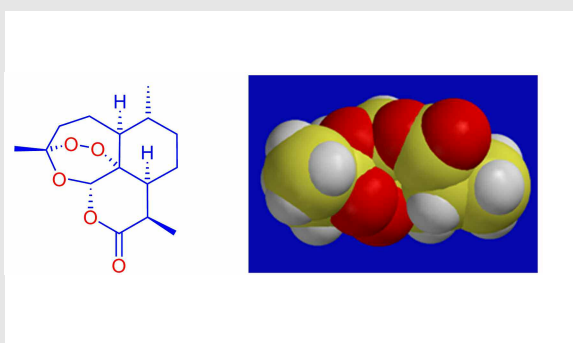
People, Trends and Views in Synthetic Organic Chemistry

2008/03

SYNSTORIES

■ **Functionalization of Unactivated sp^3 C–H Bonds: Not All C–H Bonds Are Equal**

■ **Strategies in the Development and Chemical Modification of the New Artemisinin Antimalarial Artemisone**



■ **New Access to Functionalized Indoles**

■ **DMEAD – A Separation-Friendly Reagent for the Mitsunobu Reaction**

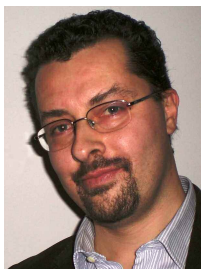
■ **Synthesis of the C1–C13 Fragment of Bistramide D**

CONTACT +++++

Your opinion about SYNFORM is welcome, please correspond if you like: marketing@thieme-chemistry.com



Thieme Chemistry



Dear readers,

Singapore is booming both in basic and applied research. Universities, research organizations and companies in Singapore are attracting talent from around the world. Perhaps other countries, including some on the Old Continent, should be more inspired by the strategy that Singapore is pursuing, and try to follow its example. It was therefore mandatory for this new issue of **SYNFORM** to have a closer look at this nation where so many important things are occurring. One of the next issues will be largely dedicated to "Chemistry in Singapore", whereas this issue features a special section focusing on the *International Symposium on Catalysis and Fine Chemicals – Singapore*, which was held from December 16–21, 2007 at the Nanyang Technological University in a vibrant scientific atmosphere. The Organizing Committee, chaired by Professor Pak Hing Leung, did an excellent job, as the conference was superbly organized and offered a very interesting scientific program under the supervision of the Scientific Committee chaired by Professor Roderick W. Bates. Three communications from the C&FC conference are featured in this issue, which is completed by two **SYNSTORIES**: one about a new and selective aliphatic C–H oxidation reaction that can be exploited for the synthesis of complex molecules, described by Professor Christina White (USA), while the second reports on a new access to functionalized indoles, established by Professors Louis Fensterbank and Max Malacria (France).

Enjoy your reading,

Matteo Zanda

Editor of **SYNFORM**

CONTACT +++++

If you have any questions or wish to send feedback, please write to Matteo Zanda at:
Synform@chem.polimi.it

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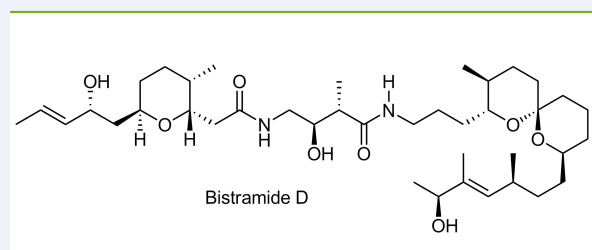
SYNSTORIES ■ ■ ■ ■

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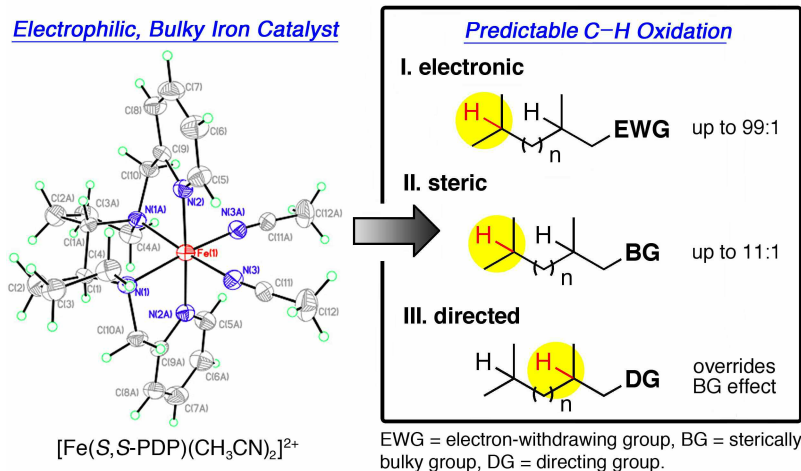


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COMING SOONA37

Functionalization of Unactivated sp^3 C–H Bonds: Not All C–H Bonds Are Equal

Science **2007**, *318*, 783–787

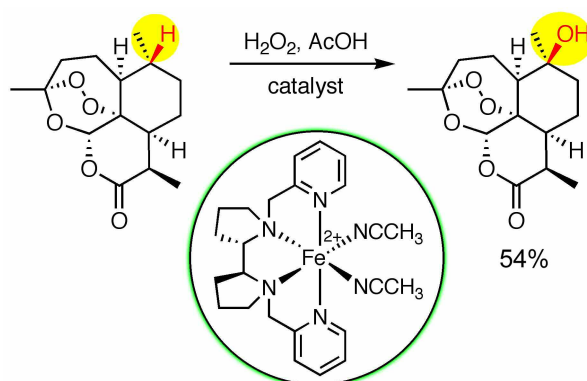


■ If organic chemists were asked “What is your dream reaction?”, many of them would probably answer “a mild and selective functionalization of unactivated sp^3 C–H bonds, having a predictable outcome and with no protection required.” One important step forward in this direction has been recently reported by Professor M. Christina White and graduate student Mark S. Chen from the University of Illinois, Urbana (USA) who described an iron-based catalyst that, in the presence of H_2O_2 , oxidizes selectively and under mild conditions the aliphatic C–H bond of a broad range of substrates, without the need for activating or protecting groups.

“The work described represents the first general and predictably selective aliphatic (sp³) C–H oxidation reaction for complex molecule synthesis,” said Professor White. “Prior to our work, predictable selectivity for C–H oxidations in complex molecule settings had been limited to activated C–H bonds (i.e. next to a heteroatom or π -system) or by using substrate-directing groups. Some very spectacular examples of both of these types of C–H oxidations have appeared in com-

plex molecule settings by Wender (oxidation of an ethereal C–H bond in bryostatin), Du Bois (late-stage directed carbene and nitrene C–H insertion in the synthesis of tetrodotoxin), Breslow (directed C–H oxidations of steroids), Crabtree (directed C–H oxidation of ibuprofen) and our group (allylic C–H amination and oxidations).” The site-selective oxidation of unactivated, isolated aliphatic C–H bonds in the context of complex molecules has long been considered a ‘holy grail’ of catalysis. “In fact, many have argued that this goal is unattainable with a chemical catalyst,” explained Professor White, “and that highly selective reactions of this type are only possible using enzyme catalysis.”

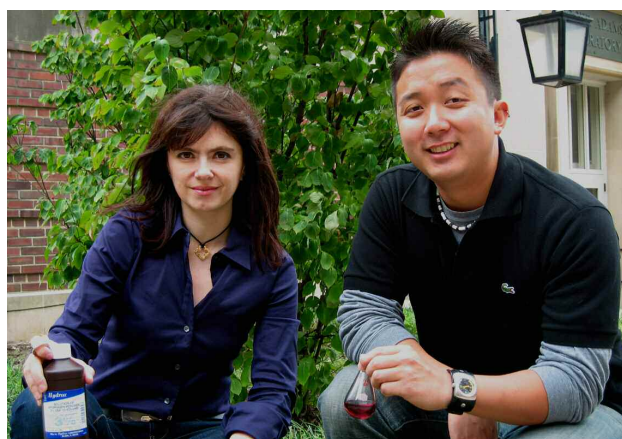
“Inspired by seminal work done by Sharpless on selective olefin oxidations in polyolefin systems, we hypothesized that C–H bonds could be distinguished by the appropriate catalyst,” she continued. “We report that using a highly electrophilic, bulky iron catalyst discrimination between aliphatic C–H bonds is possible based on subtle differences in their electronic properties and steric environments. For example, in



a series of molecules containing two tertiary C–H bonds, we show that electron-withdrawing groups can significantly deactivate the proximal C–H bond towards oxidation (selectivities up to >99:1). Also, in cases where two tertiary C–H bonds are electronically equivalent, we demonstrate that oxidation occurs selectively at the C–H bond that is sterically less hindered. Carboxylic acids can also be used with this catalyst to direct diastereoselective C–H oxidations at secondary C–H bonds.”

White and Chen delineated a series of selectivity rules for this aliphatic C–H oxidation based on electronics, sterics, and directing-group effects. “These rules were tested in several natural products and their derivatives and demonstrated to be predictive!” said Professor White. “For example, the antimalarial natural product artemisinin is predictably oxidized at one out of five tertiary C–H bonds to furnish 10- β hydroxyartemisinin in a yield that surpasses that reported for an enzymatic system.”

“The importance of this discovery is multi-fold. As carbon–oxygen bonds are an essential component of most pharmaceuticals, including those that treat cancer, heart disease



Prof. M. C. White and M. S. Chen (from left) with the two key reagents of their new oxidation system

and diabetes, this new reaction will enable scientists to make and discover important medicines quicker and at lower costs. Furthermore,” she concluded, “since the reaction uses a non-toxic iron catalyst and hydrogen peroxide as oxidant, whose only byproduct is water, this reaction will be dramatically cleaner for the environment.” ■

Matteo Zanda

New Access to Functionalized Indoles

Angew. Chem. Int. Ed. **2007**, *46*, 1881–1884

■ The indole nucleus is present in numerous compounds of biological and/or pharmaceutical interest and new chemical methods for its synthesis have been developed for more than a hundred years. In the last two decades, metal-catalyzed transformations and especially those applying palladium complexes (the topic has been recently reviewed, for example, by S. Cacchi, G. Fabrizi: *Chem. Rev.* **2005**, *105*, 2873) have proven to be among the most versatile methods to synthesize indole substrates. However, most of these strategies rely on the 5-*endo* addition of the nitrogen to an unsaturation in the *ortho* position. On the other hand, the 5-*exo* methodology has been the subject of far less interest. In the meantime, propargylic alcohols have exhibited a vast array of reactivities when submitted to noble metal catalysts.

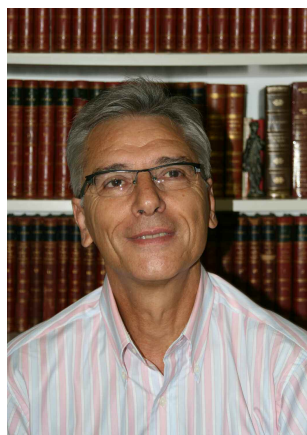


Prof. L. Fensterbank

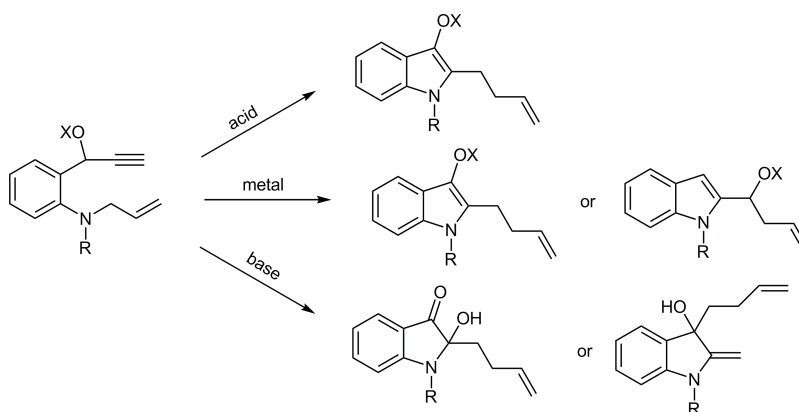
Now, Professor Louis Fensterbank and Professor Max Malacria from the Université Pierre et Marie Curie in Paris (France), in collaboration with Dr. Serge Mignani and Dr. Baptiste Ronan from Sanofi-Aventis at the Vitry-sur-Seine campus (France) and in the context of the PhD thesis of Kevin Cariou that was supported by Sanofi-Aventis, have unified these two concepts (5-*exo* strategy and propargylic alcohol moiety) and focused on 2-hydroxypropargyl anilines. “Amazing results were obtained with *N*-allyl substrates, which are perfectly suitable for an *exo*-dig addition followed by a charge-accelerated 3-*aza*-Cope rearrangement,” explained Professor Fensterbank. “This rearrangement and the subsequent rearomatization provide the driving force of the reaction. We have been able to test the reactivity of these simple, although new, compounds towards acidic, basic and organo-metallic reaction conditions and developed complementary and selective transformations.”



Dr. K. Cariou



Prof. M. Malacria





Dr. B. Ronan



Dr. S. Mignani

Mere silica has proven to be a very efficient reagent to promote the formation of 3-hydroxyindoles, with the transfer of the allylic chain. Noble metals such as platinum(II) can also promote this reaction, but more interestingly they can induce an additional migration if an acetate group is used, thus furnishing indoles with a substituent on the side chain. Finally, another simple reagent, potassium carbonate, can afford hydroxyindolones via the same type of rearrangement followed by the oxidation of the indole nucleus. By adjusting the reaction time, two products can be obtained selectively, with the thermodynamic product resulting from an α -ketol rearrangement of the kinetic product.

“These new transformations provide an easy access to various indolic scaffolds,” concluded Professor Fensterbank, “which can be produced selectively by tuning the substrate and/or the reaction conditions.”

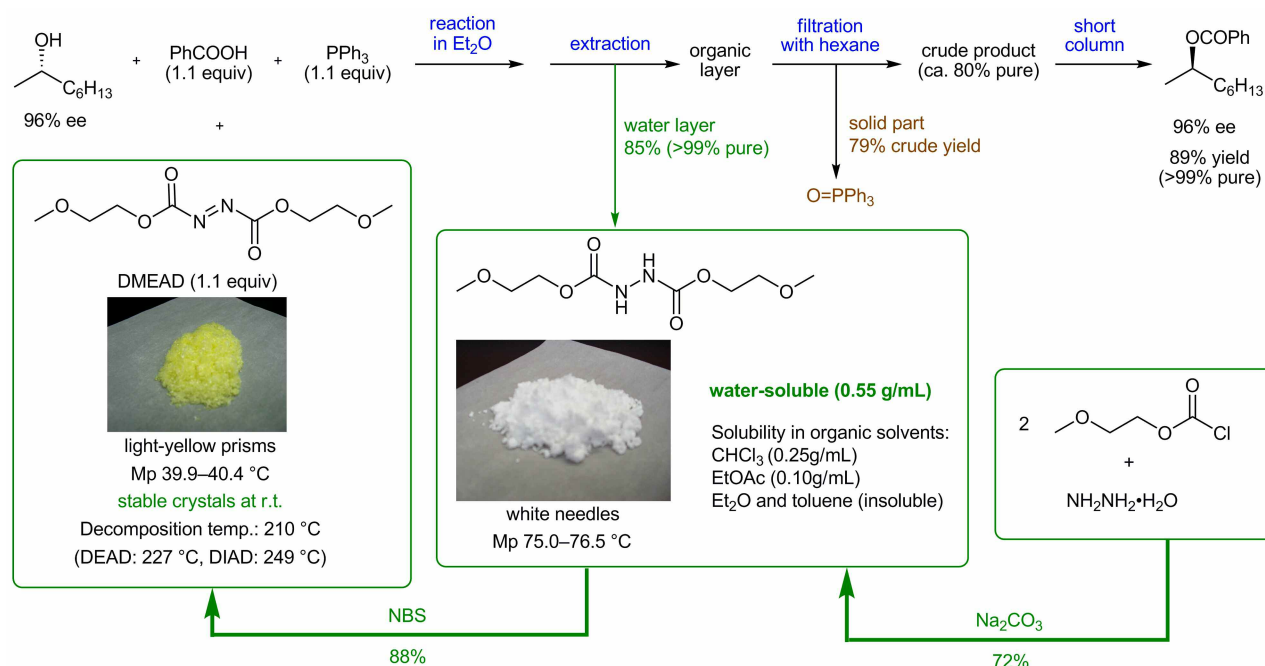
Matteo Zanda

DMEAD – A Separation-Friendly Reagent for the Mitsunobu Reaction

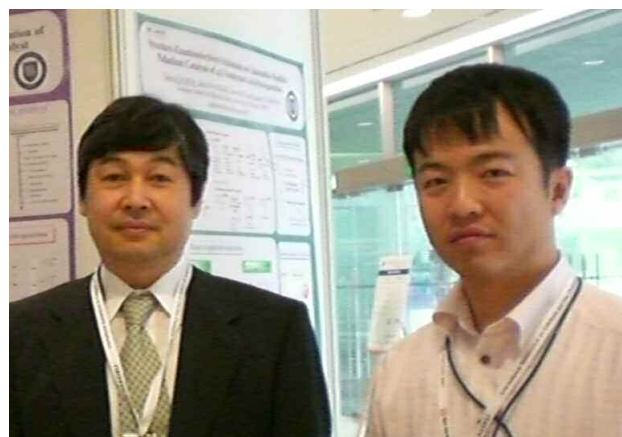
Selected Presentation from the International Symposium on Catalysis and Fine Chemicals, Singapore, December 16–21, 2007

■ The Mitsunobu reaction is a dehydration reaction to introduce an acidic pronucleophile replacing an alcoholic function under complete stereo-inversion. The procedure simply consists of mixing an alcohol and a pronucleophile with diethyl or diisopropyl azodicarboxylate (DEAD or DIAD) and triphenylphosphine at room temperature to give a condensed product. However, both DEAD and DIAD are potentially explosive and shock-sensitive liquids (particularly the former); therefore, their shipment and commercialization have become a major problem, particularly when dry and neat. Another major drawback of the Mitsunobu process is the formation of two co-products, hydrazinedicarboxylate and triphenylphosphine oxide. Formation of $\text{Ph}_3\text{P}=\text{O}$ is certainly not a problem in the separation process, due to its facile crystallization in non-polar solvents, but separation of diethyl or diisopropyl hydrazinedicarboxylate requires highly capable column chromatography to isolate the target Mitsunobu-reaction product. Many efforts have been undertaken to solve this issue: for example, the reagent is supported by polymer or solid to per-

form the separation by filtration, or is attached to an acidic, basic, or fluorous function to allow the separation by extraction into a basic or acidic aqueous layer or into fluorous solvent. However, none of these reagents has hitherto found a place as a real alternative to DEAD or DIAD due to the high production costs. Recently, Professor Takashi Sugimura and Kazutake Hagiya from the University of Hyogo (Japan) have disclosed a new interesting solution to the ‘DEAD/DIAD problem’. “Here, we have made another approach to address the separation problem by molecular design to enable the separation of a hydrazinedicarboxylate by extraction with neutral water,” explained Professor Sugimura. “The preparation cost, handling, and reuse were also considered to compete with DEAD and DIAD. Di-2-methoxyethyl azodicarboxylate (DMEAD) is a newly developed reagent (*Chem. Lett.* **2007**, *36*, 566–567) and now commercially available from Toyo Kasei Kogyo Co., Ltd. (<http://www.toyokaseikogyo.co.jp/global/index.html>).”



DMEAD was prepared in two steps from hydrazine hydrate and 2-methoxyethyl chloroformate, and could be purified by recrystallization, avoiding a distillation process of the potentially explosive compound. “Thus, DMEAD has a big advantage over DEAD and DIAD in their production processes,” said Professor Sugimura. “By using DMEAD, the Mitsunobu reaction with a variety of alcohols and pronucleophiles (carboxylic acid, phenol, imide, thiol, etc.) resulted in good yields of the products under sufficient stereospecificity of the inversion, almost identical to the performance of DIAD. Isolation of the product is, however, much easier with DMEAD than that with DIAD (DEAD), because the hydrazine produced from DMEAD is highly hydrophilic and is completely separable by a simple extraction into neutral water. Purification of the organic layer, after separation of the other co-product, triphenylphosphine oxide, by filtration, easily results in high purity of the product in a good yield. Concentration of the water layer yields the hydrazine, which can be reused for the preparation of DMEAD. So far,” concluded Professor Sugimura, “we have not found any reason not to switch to DMEAD to carry out the Mitsunobu reaction.”



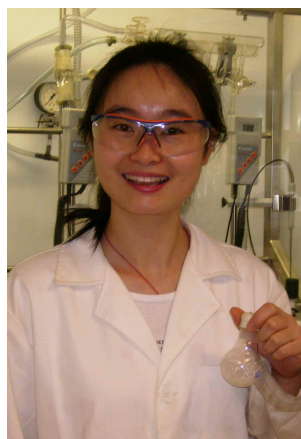
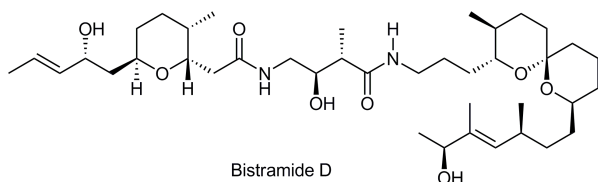
Prof. T. Sugimura (left), Mr. K. Hagiya (right)

Matteo Zanda

Synthesis of the C1–C13 Fragment of Bistramide D

Selected Presentation from the International Symposium on Catalysis and Fine Chemicals, Singapore, December 16–21, 2007

■ Bistramides are macrolide metabolites, produced by the marine organism *Lissoclinum bistratum*, which exhibit cytotoxic properties against a variety of human cancer cells. Bistramide D is particularly interesting, as it seems to be less toxic than bistramides A, B, and C. Interestingly, no total synthesis of bistramide D has appeared except for a hemisynthesis,¹ although elegant syntheses of bistramides A and C have been reported.²



S. Ping holding diospongins A

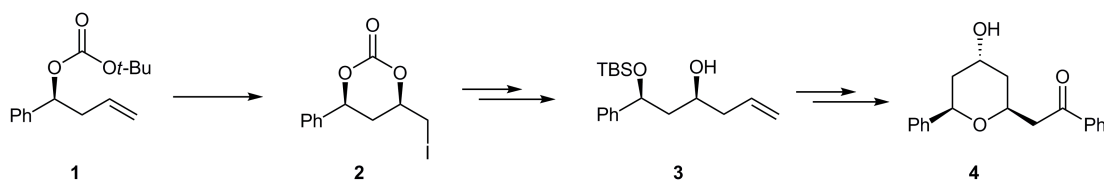
Recently, Professor Roderick W. Bates and graduate student Song Ping from the Nanyang Technological University of Singapore reported a synthesis of diospongins A (**4**)³ using a combination of cross-metathesis and intramolecular Michael addition to generate the tetrahydropyran (THP) ring, and an iodocyclization to establish the *syn*-1,3-diol motif in precursor **3**.

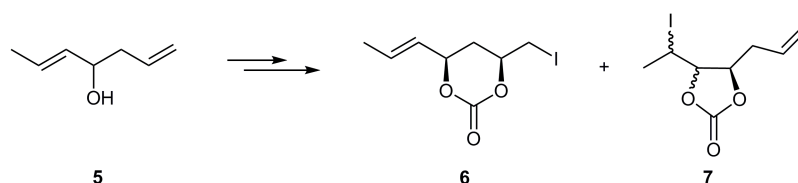
As this appeared to be a quite straightforward and robust method for constructing THP, Professor Bates and coworkers, in particular graduate student Kalpana Palani, sought an additional target. “We were interested in something that would present both us and the methodology with a greater challenge,” Kalpana explained. “We settled on bistramide D. Not only are the bistramides a topical group of molecules,⁴ but the structure of the THP moiety includes the *syn*-1,3-diol motif. And, it would be a greater challenge, as a kinetic Michael

reaction would be needed, to put in an axial, not equatorial, substituent. Thus, we set about adapting our diospongins method to the new target.”

“Initially and optimistically,” she continued, “we opted to apply the Bartlett–Cardillo iodocyclization⁵ method in a ‘left-to-right’ fashion starting from the readily available allylic alcohol **5**. Not surprisingly, this gave a mixture of the five- and six-membered-ring products.”

“We therefore turned to the ‘right-to-left’ option, constructing the required homoallylic alcohol **8** from resolved epichlorohydrin. After encountering difficulties in generating appropriate butene organometallics, we chose lithio-butyne, and luckily, a smaller cylinder of butyne was available in Singapore. Availability of chemicals at short notice is a major obstacle for chemists in ‘far away’ places,” Kalpana admitted. “With the last obstacle cleared, we were able to get through to our cross-metathesis Michael precursor, a model of the real thing, with one methyl group missing. The model system was selected as it allowed us to use commercially available

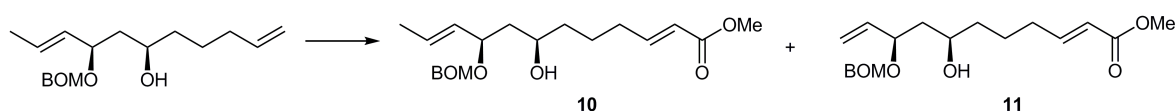
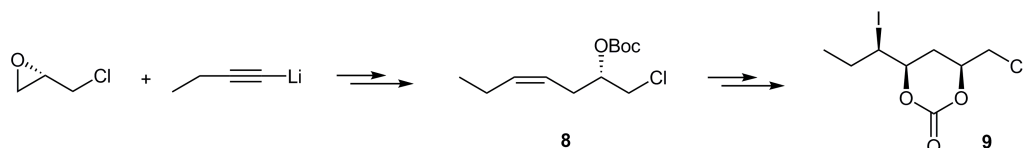




1-bromo-3-butene, although we are now able to make the ‘real’ bromide via both a long and a short way.”

“The cross-metathesis proved instructive, giving an inseparable mixture of two very similar compounds,” Kalpana said. “Fortunately, alkene protons display distinctive patterns in ^1H NMR spectra and, backed up by PENDANT and COSY data, we convinced ourselves that we had a mixture of the desired compound **10** and its demethylated lower homologue **11**.”

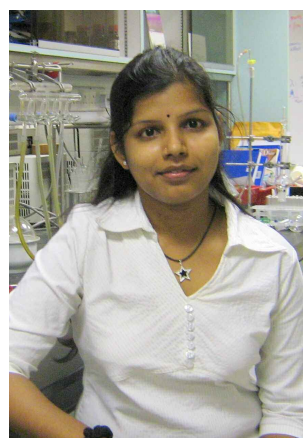
place and find out how it will affect both the metathesis and the cyclization, then to make the other moieties: the amino acid, for which we have a method, and the big challenge of the spiroketal. I would like to express my sincere thanks to Professor Rod Bates for his valuable guidance,” she concluded. ■



The latter compound clearly arose from the desired cross-metathesis with methyl acrylate at the terminal alkene, followed by cross-metathesis with the ethylene by-product at the internal alkene. This little problem was solved by passing N_2 over the reaction mixture to sweep out the ethylene.

“Finally, we turned to the intramolecular Michael addition. It was a genuine pleasure to find that Martin Banwell’s conditions⁶ yielded a mixture of isomers in favor of the desired one, with the same ratio reported by Banwell for a simpler substrate,” Kalpana said. “The same coincidence of values was found when we compared our ^1H NMR data, particularly the chemical shifts of the ring protons α to the oxygen, with data reported by Banwell for his simple THPs and the data for the natural product.”

“Where are we now?” Kalpana asked herself. “We need to go back and repeat the procedure with the methyl group in



K. Palani



Prof. R. Bates

REFERENCES

- (1) C. Bauder, J.-F. Biard, G. Solladié *Org. Biomol. Chem.* **2006**, *4*, 1860.
- (2) (a) J. S. Yadav, L. Chetia *Org. Lett.* **2007**, *9*, 4587. (b) J. T. Lowe, I. E. Wrona, J. S. Panek *Org. Lett.* **2007**, *9*, 327. (c) M. T. Crimmins, A. C. DeBaillie *J. Am. Chem. Soc.* **2006**, *128*, 4936. (d) P. Wipf, T. D. Hopkins *Chem. Commun.* **2005**, 3421. (e) A. V. Statsuk, D. Liu, S. A. Kozmin *J. Am. Chem. Soc.* **2004**, *126*, 9546.
- (3) R. W. Bates, S. Ping *Tetrahedron* **2007**, *63*, 4497.
- (4) J.-F. Biard, C. Roussakis, J.-M. Kornprobst, D. Gouffes-Barbin, J.-F. Verbist, P. Cotellet, M. P. Foster, C. M. Ireland, C. Debitus *J. Nat. Prod.* **1994**, *57*, 1336.
- (5) (a) P. A. Bartlett, J. D. Meadows, E. G. Brown, A. Morimoto, K. K. Jernstedt *J. Org. Chem.* **1982**, *47*, 13. (b) G. Cardillo, M. Orena, G. Porzi, S. Sandri *J. Chem. Soc., Chem. Commun.* **1981**, 465. (c) A. Bongini, G. Cardillo, M. Orena, G. Porzi, S. Sandri *J. Org. Chem.* **1982**, *47*, 4626.
- (6) M. G. Banwell, C. T. Bui, H. T. T. Pham, G. W. Simpson *J. Chem. Soc., Perkin Trans. 1*, **1996**, 967.

Matteo Zanda

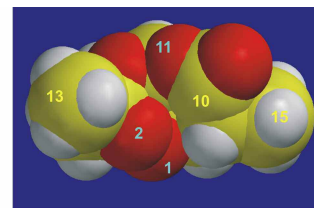
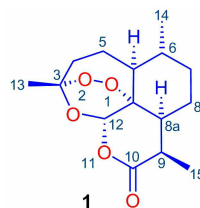
Strategies in the Development and Chemical Modification of the New Artemisinin Antimalarial Artemisone

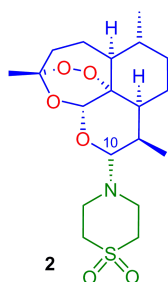
Selected Presentation from the International Symposium on Catalysis and Fine Chemicals, Singapore, December 16–21, 2007

■ Qinghaosu (artemisinin; **1**) was isolated from the traditional herb qing hao (*Artemisia annua*) by Chinese groups working together in the remarkable collaborative effort known as ‘Project 523’.¹ This compound and derivatives such as artesunate are now used for the treatment of malaria.² However, chemical and metabolic instabilities and neurotoxicity in laboratory studies bestow difficulties both in formulation and compliance with drug regulatory guidelines.³ Therefore, under a contract agreement with Bayer AG, the group of Professor Richard K. Haynes from the Institute of Molecular Technology for Drug Discovery and Synthesis, The Hong Kong University of Science and Technology, Hong Kong (P. R. of China) embarked on a medicinal-chemistry-guided program to develop new artemisinin derivatives. “Thereby emerged a new artemisinin class,” explained Professor Haynes, “10-amino-artemisinins,⁴ of which artemisone **2**, in possessing good physicochemical properties, non-neurotoxicity in laboratory screens, and greatly enhanced efficacy against the malaria parasite, was carried forward by Bayer under the combined support from Bayer, the Medicines for Malaria Venture in Geneva, the HKUST Research Infrastructure Grants Scheme, and the Hong Kong Research Grants Council

as a development candidate. It successfully completed all pre-clinical studies, and Phase IIa trials in Thailand with non-severe malaria patients. It is curative at one-third of the dose of artesunate, previously the most active artemisinin derivative.”

“We may stand in awe of the ‘synthetic mastery’ evident in some syntheses of complex natural products,” said Professor Haynes. “However, it is true that too many of such efforts, whilst being admired in the same way as a work of art, are not very useful – one hears that the synthesis of this or that complex or biologically active structure will be used for ‘structure–activity’ studies, but this rarely occurs; the work is





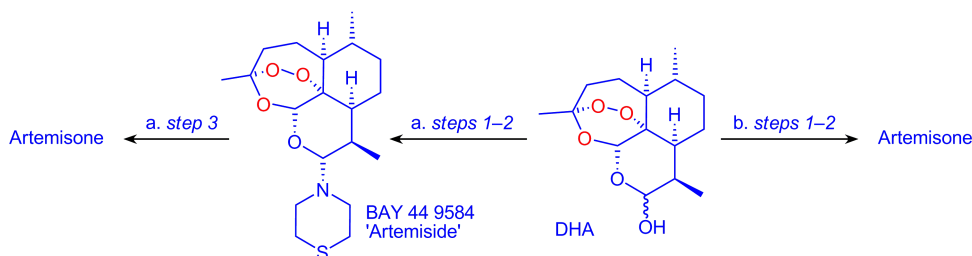
published, and the grandmaster moves on to the next exotic, suddenly rather more ‘interesting’ structure. In our case,” he continued, “a drug for malaria must be *economic* – about US\$1 per treatment course – and this *does* pose a challenge! Our ‘research’ synthesis required three process steps and the use of an expensive reagent, bromotrimethylsilane.”⁴ A much more economical route, eventually carried out at Bayer on a multi-kilogram scale, also involved three process steps wherein DHA was converted into the 10- β chloride, and thence into artemisone via reaction with thiomorpholine and oxidation of the intermediate artemiside (Scheme; **a**). “The best potential route, involving one process step, was to use oxalyl chloride activated by catalytic DMSO to generate the chloride in situ in the preferred solvent toluene, then to treat it with thiomorpholine *S,S*-dioxide to give artemisone directly,” said Professor Haynes.

“Artemisone is a structurally distinct artemisinin. It has a different metabolic profile to current artemisinins, and has the potential to be used for a one-day treatment of malaria, together with a longer half-life quinoline antimalarial, in accordance with the recommendations of the World Health Organization. Further, we have shown that artemisone effects complete cure in a cerebral malaria mouse model, in contrast to

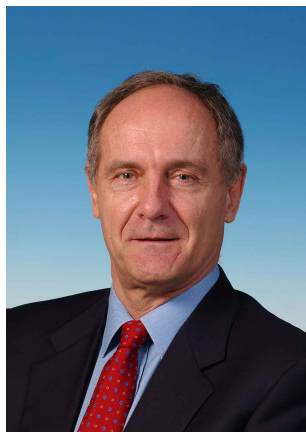
the current artemisinins artesunate and DHA.⁵ Therefore, it seems promising for the treatment of severe/cerebral malaria for which the only current drug is intravenous formulation of quinine, although a special formulation of artesunate is in the pipeline,” he said.

“I express my gratitude to the insight, perseverance, and fortitude of the members of my group at HKUST in conducting the process optimization studies,” concluded Professor Haynes, “in particular to Dr. Dennis Ho-Wai Chan, my post-doctoral research associate, and to Gigi Wing-Chi Chan, the M.Phil. graduate research associate, who have worked so precisely and carefully at what on many occasions was a frustrating task.”

About the corresponding author. **Richard K. Haynes** obtained his PhD from the University of Western Australia, then spent two years as Gillette International Fellow at the University of Karlsruhe (Germany) with Hans Musso, before moving to Imperial College London (UK) to work with Sir Derek Barton. It was in these early years that he was exposed to naturally occurring peroxides. After a short period at Monash University (Australia), he moved to the University of Sydney (Australia) where he conducted ‘methods-oriented’ organic synthesis of biologically active natural products. Sabbatical years were spent at the ETH Zürich and the University of Geneva (Switzerland). Interest in artemisinin was stimulated through visits to China as a participant of the Australian Academy of Science–Chinese Academy of Science Exchange Programs in 1988 and 1991, and later in antimalarial drugs, in general through participation as external co-opted member to the Chemotherapy of Malaria Committee and then the Drug Discovery Research Committee, within Tropical Diseases Research, World Health Organization, Geneva. He moved to the Hong Kong University of Science and Technology in



*Scheme: Reagents and conditions: a) step 1: HCl, LiCl, CH₂Cl₂, 0 °C, N₂; step 2: thiomorpholine, Et₃N, 0 °C, N₂ (55% from DHA); step 3: 30% H₂O₂–MeCN, MeOH, K₂CO₃ (91–98% from BAY 44 9584); b) step 1: (COCl)₂, DMSO (catalytic), toluene, r.t., 0.5 h; step 2: thiomorpholine *S,S*-dioxide, Et₃N, r.t. (55–73% from DHA)*



Prof. R. K. Haynes

1993. His research interests are in organophosphorus chemistry and P-chiral ligands for asymmetric catalysis, reagent- and mechanism-based synthesis of bioactive natural products, peroxidic antimalarials, mode of action and application to other targets, drug design in synthesis of quinoline antimalarials, peptidomimetics and peptide conjugates, and the development of selectively cytotoxic agents for targeting cancer cells. ■

REFERENCES

- (1) *A Detailed Chronological Record of Project 523 and the Discovery and Development of Qinghaosu (Artemisinin)*; J. Zhang, Editor; Beijing, December **2005**.
- (2) Co-operative research group on qinghaosu 'A Novel Type of Sesquiterpene Lactone – Qinghaosu' *Ke Xue Tong Bao* **1977**, 22, 142.
- (3) (a) R. K. Haynes *Curr. Top. Med. Chem.* **2006**, 6, 509. (b) R. K. Haynes, H.-W. Chan, C.-M. Lung, N.-C. Ng, H.-N. Wong, L. Y. Shek, I. D. Williams, A. Cartwright, M. F. Gomes *ChemMedChem* **2007**, 2, 1448.
- (4) R. K. Haynes, B. Fugmann, J. Stetter, K. Rieckmann, H.-D. Heilmann, H.-W. Chan, M.-K. Cheung, W.-L. Lam, H.-N. Wong, S. L. Croft, L. Vivas, L. Rattray, L. Stewart, W. Peters, B. L. Robinson, M. D. Edstein, B. Kotecka, D. E. Kyle, B. Beckermann, M. Gerisch, M. Radtke, G. Schmuck, W. Steinke, U. Wollborn, K. Schmeer, A. Römer *Angew. Chem. Int. Ed.* **2006**, 45, 2082.
- (5) J. Waknine, J. Golenser, R. K. Haynes *unpublished results*.

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