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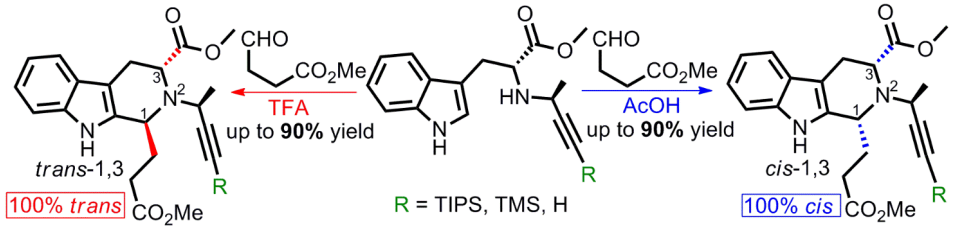
Unprecedented Stereocontrol in the Synthesis of 1,2,3-Trisubstituted Tetrahydro-β-carbolines Through an Asymmetric Pictet—Spengler Reaction Towards Sarpagine-Type Indole Alkaloids

M. Toufiqur Rahman and James M. Cook

Eur. J. Org. Chem. **2018**, 3224–3229. **DOI:** 10.1002/ejoc.201800600

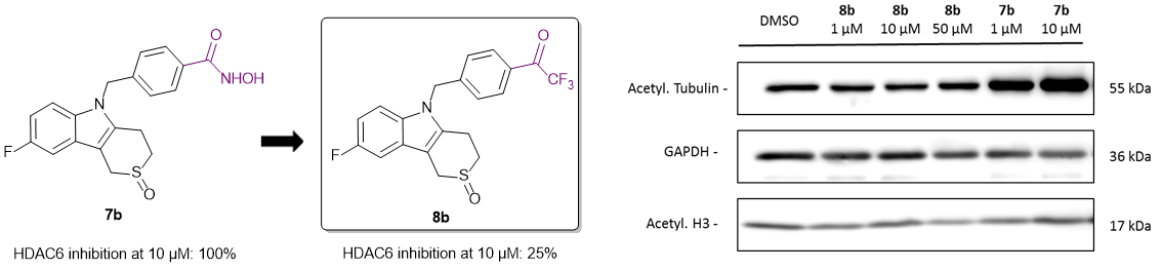


Abstract: The asymmetric Pictet-Spengler (P-S) reaction of chiral N_b-ethynyl substituted tryptophan methyl ester derivatives (from both D- and L-tryptophan) with a simple aliphatic aldehyde, exhibited unprecedented selectivity towards either of the diastereomeric products. A simple variation of conditions could alter the outcome of the cyclization from either 100% *trans*-selective to 100% *cis*-selective originating entirely from internal asymmetric induction under mild conditions. This resulted in a highly efficient access to both 1,3-*cis*-(1,2,3-trisubstituted tetrahydro-β-carbolines, THβCs) and 1,3-*trans*-(1,2,3-trisubstituted THβCs). To the best of our knowledge, this type of stereocontrol has never been observed from tryptophan methyl ester derivatives (either D or L) in accessing either 1,3-disubstituted or 1,2,3-trisubstituted THβCs. By exploiting this very useful ambidextrous-diastereoselectivity, we have set the crucial C-3 and C-5 stereocenters of C-19 methyl substituted sarpagine/macroline-ajmaline alkaloids beginning with the DNA-encoded and cheaper L-(–)-tryptophan, as well as optionally from commercially available D-(+)-tryptophan.

Assessment of the Trifluoromethyl Ketone Functionality as an Alternative Zinc-Binding Group for Selective HDAC6 Inhibition

Yves Depetter, Silke Geurs, Flore Vanden Bussche, Rob De Vreese, Jorick Franceus, Tom Desmet, Olivier De Wever, Matthias D'hooghe

Med. Chem. Commun. **2018**, *9*, 1011–1016. **DOI:** 10.1039/c8md00107c

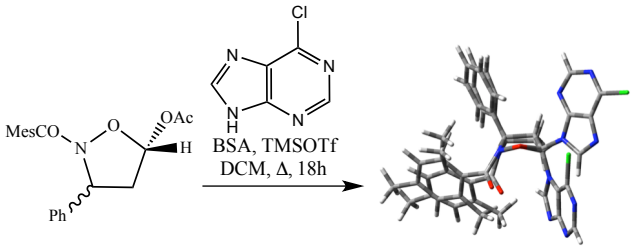


Abstract: Recent studies point towards the possible disadvantages of using hydroxamic acid-based zinc-binding groups in HDAC inhibitors due to e.g. mutagenicity issues. In this work, we elaborated on our previously developed Tubathian series, a class of highly selective thiaheterocyclic HDAC6 inhibitors, by replacing the benzohydroxamic acid function by an alternative zinc chelator, i.e., an aromatic trifluoromethyl ketone. Unfortunately, these compounds showed a reduced potency to inhibit HDAC6 as compared to their hydroxamic acid counterparts. In agreement, the most active trifluoromethyl ketone was unable to influence the growth of SK-OV-3 ovarian cancer cells nor to alter the acetylation status of tubulin and histone H3. These data suggest that replacement of the zinc-binding hydroxamic acid function with a trifluoromethyl ketone zinc-binding moiety within reported benzohydroxamic HDAC6 inhibitors should not be considered as a standard strategy in HDAC inhibitor development.

Ene Reaction of Nitrosocarbonyl Mesitylene with the Cinnamyl Alcohol: Metabolic Activity and Apoptosis of the Synthetized 6-Chloropurine *N,O*-Nucleoside Analogues

Misal Giuseppe Memeo, Elena Valletta, Beatice Macchi, Alessio Porta, Bruna Bovio, Mattia Moiola, Paolo Quadrelli

ACS Omega, **2018**, *3*, 7621–7629. **DOI:** 10.1021/acsomega.8b00970

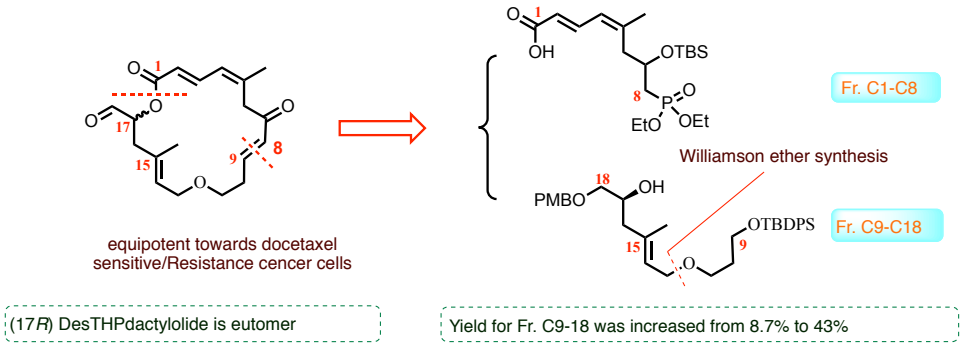


Abstract: Nitrosocarbonyl mesitylene intermediate undergoes an ene reaction with cinnamyl alcohol affording the corresponding 5-hydroxy-isoxazolidine in fair yields. The synthesized 5-acetoxy-isoxazolidine serves as synthon for the preparation of 6-chloropurine *N,O*-nucleoside analogues, according to the Vorbrüggen reaction. The compounds were evaluated for their metabolic and apototic activity and their structure-activity relationship is discussed.

Optimized Synthesis and Antiproliferative Activity of DesTHPdactylolides

Guanglin Chen, Rubing Wang, Bao Vue, Manee Patanapongpibul, Qiang Zhang, Shilong Zheng, Guangdi Wang, James D. White, Qiao-Hong Chen

Bioorg. Med. Chem. **2018**, *26*, 3514–3520. **DOI:** 10.1016/j.bmc.2018.05.026

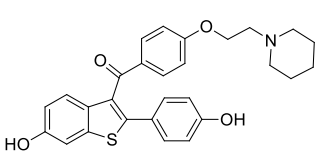


Abstract: Dactylolide and certain analogues are attractive targets for study due to their structural resemblance to zampanolide, a very promising anticancer lead compound and a unique covalent-binding microtubule stabilizing agent. The primary goal of this project is identification and synthesis of simplified analogues of dactylolide that would be easier to prepare and could be investigated for antiproliferative activity in comparison with zampanolide. Extension of Almann's concept of a simplified zampanolide analogue to dactylolide in the form of desTHPdactylolide was attractive not only for reasons of synthetic simplification but also for the prospect that analogues of dactylolide could be prepared in both (17*S*) and (17*R*) configurations. Since Altmann's overall yield for the six-step procedure leading to the C9–C18 fragment of desTHPdactylolide was only 8.7%, a study focused on optimized synthesis and antiproliferative evaluation of each enantiomer of desTHPdactylolide was initiated using Altmann's route as a framework. To this end, two optimized approaches to this fragment C9–C18 were successfully developed by us using allyl iodide or allyl tosylate as the starting material for a critical Williamson ether synthesis. Both (17*S*) and (17*R*) desTHPdactylolides were readily synthesized in our laboratory using optimized methods in yields of 37–43%. Antiproliferative activity of the pair of enantiomeric desTHPdactylolides, together with their analogues, was evaluated in three docetaxel-sensitive and two docetaxel-resistant prostate cancer cell models using a WST-1 cell proliferation assay. Surprisingly, (17*R*) desTHPdactylolide was identified as the eutomer in the prostate cancer cell models. It was found that (17*S*) and (17*R*) desTHPdactylolide exhibit equivalent antiproliferative potency towards both docetaxel-sensitive (PC-3 and DU145) and docetaxel-resistant prostate cancer cell lines (PC-3/DTX and DU145/DTX).

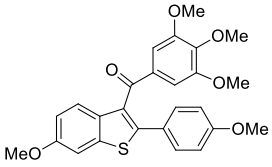
Efficient Synthesis of 3-Benzoyl Benzo[*b*]thiophenes and Raloxifene *via* Mercury(II)-Catalyzed Cyclization of 2-Alkynylphenyl Alkyl Sulfoxides

Shi-Ming Wen, Cheng-Han Lin, Chin-Chau Chen, Ming-Jung Wu

Tetrahedron **2018**, *74*, 2493–2499. **DOI:** 10.1016/j.tet.2018.03.067



Raloxifene (1)



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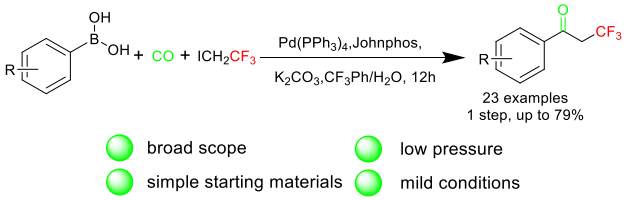
Abstract: The unique selective estrogen receptor modulator, Raloxifene (**1**), and antitubulin agent **2** were synthesized through the key intermediate, 4-methoxybenzyl 2-bromo-4-methoxyphenyl sulfoxide (**6**), respectively. It was found that compared with the o-sulfanyl aryl bromides, the sulfinyl group at ortho position accelerated the Sonogashira coupling reaction of aryl bromides. Thus, compound **6** was coupled with 3,4,5-trimethoxyphenyl acetylene, followed by mercury-catalyzed cyclization reaction to afford compound **2** in 79% overall yield. Raloxifene (**1**) was prepared from compound **6** in four steps and 33% overall yield via coupling reaction with 1-trimethylsily-2-(4-tert-butyldimethylsiloxy)phenylethyne, mercury-catalyzed cyclization reaction, alkylation and demethylation.

Palladium-catalyzed Direct Approach to α-CF_3 Aryl Ketones from Arylboronic Acids

Bo Jiang, Xiaofei Zhang, Chunhao Yang

Org. Chem. Front. **2018**, *5*, 1724–1727. **DOI:** 10.1039/C8QO00289D

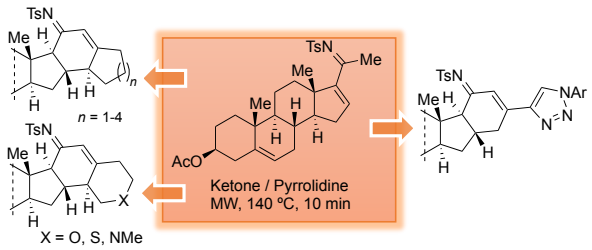


Abstract: A concise and practical method for synthesis of α-CF_3 aryl ketones with stable and commercial available arylboronic acids, ICH_2CF_3 was reported. α-CF_3 aryl ketones could be easily obtained with a CO balloon (1 atm) in the presence of palladium catalyst. This protocol provided a direct approach to α-CF_3 aryl ketones from carbonylative cross-coupling reactions from easily accessible starting materials and the one-step reaction was conducted under a very practical CO pressure.

Reactivity of Steroidal 1-Azadienes toward Carbonyl Compounds under Enamine Catalysis: Chiral Penta- and Hexacyclic Steroids

Susana M. M. Lopes, Clara S. B. Gomes, Teresa M. V. D. Pinho e Melo

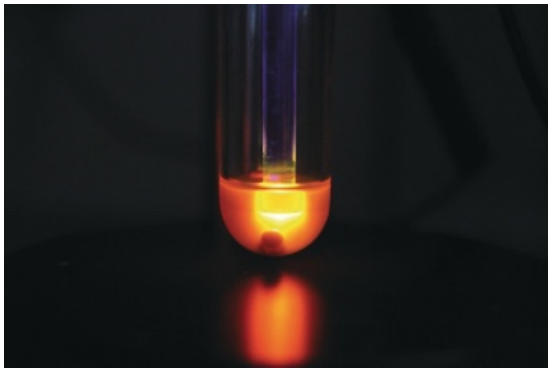
Org. Lett. **2018**, *20*, 4332–4336. **DOI:** 10.1021/acs.orglett.8b01783



Abstract: The synthesis and reactivity of a steroidal *N*-sulfonyl-1-azadiene, derived from 16-dehydropregnenolone acetate, towards carbonyl compounds under enamine catalysis was disclosed. An unexpected annulation reaction was observed involving an initial stereoselective conjugate addition of the *in situ* generated enamine to the steroidal 1-azadiene. The developed diastereoselective synthetic methodology is a novel approach to a new class of chiral pentacyclic and hexacyclic steroids.

Visible-Light Photocatalysis: Does It Make a Difference in Organic Synthesis?

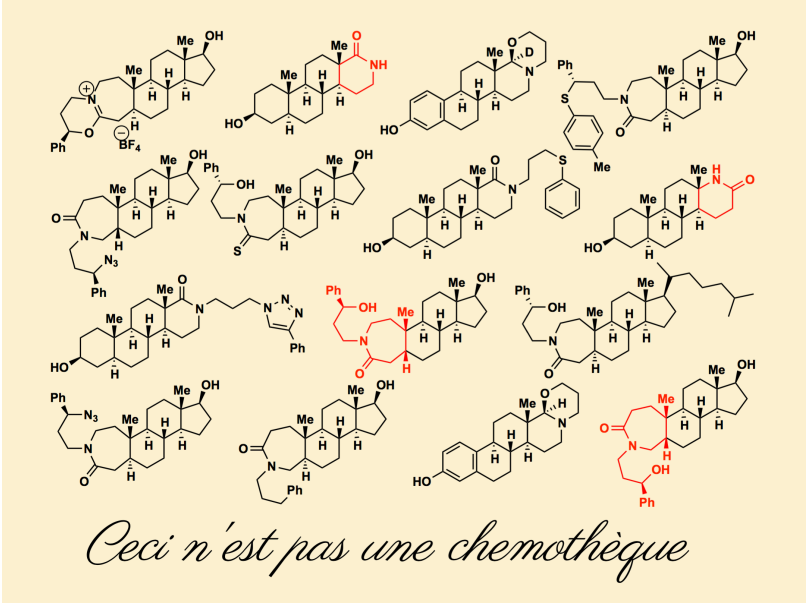
Leyre Marzo, Santosh K. Pagire, Oliver Reiser, Burkhard König
Angew. Chem. Int. Ed. **2018**, *57*, 10034–10072. **DOI:** 10.1002/anie.201709766



Abstract: *Seeing the light of day:* Visible light has evolved into a widely used "reagent" for many types of transformations in organic synthesis. Are photocatalytic reactions better, different, or even unique? This Review discusses selected classes of reactions for which classical and photocatalytic variants have been reported and tries to highlight differences and advantages of using visible-light irradiation.

Reagent-controlled Regiodivergent Ring Expansions of Steroids

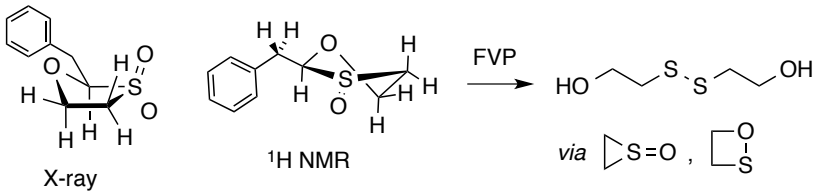
Manwika Charaschanya and Jeffrey Aubé
Nature Commun. **2018**, *9*, Article number 934, 1–8. **DOI:** 10.1038/s41467-018-03248-2



Abstract: Ring expansion provides a powerful way of introducing a heteroatom substituent into a carbocyclic framework. However, such reactions are often limited by the tendency of a given substrate to afford only one of the two rearrangement products or fail to achieve high selectivity at all. These limitations are particularly acute when seeking to carry out late-stage functionalization of natural products as starting points in drug discovery. In this work, we present a stereoelectronically controlled ring expansion sequence towards selective and flexible access to complementary ring systems derived from common steroidal substrates. Chemical diversification of the reaction intermediate affords over 100 isomerically pure analogs with spatial and functional diversity. This regiodivergent rearrangement, and the concept of using chiral reagents to affect regiocontrol in chiral natural products, should be broadly applicable to late-stage natural product diversification programs.

Structure and Thermal Reactivity of Some 2-Substituted 1,3-Oxathiolane *S*-Oxides

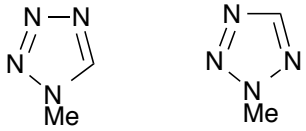
R. Alan Aitken, Sarah Henderson, Alexandra M. Z. Slawin
J. Sulfur Chem. **2018**, *39*, 422–434. **DOI:** 10.1080/17415993.2018.1449844



Abstract: Isomerisation of 2-benzylidene-1,3-dioxolane to 3-phenylbutyrolactone occurs readily under flash vacuum pyrolysis (FVP) conditions. 2-Diphenylmethyl-1,3-oxathiolane and 2-benzyl-1,3-oxathiolane have been prepared and the latter compound has been oxidised to the corresponding sulfoxide, whose structure and conformation is examined by ^{1}H NMR, and to the sulfone whose X-ray structure is determined. 2-Benzylidene-1,3-oxathiolane is also prepared and the behaviour of the three *S*-oxidised oxathiolane derivatives upon FVP is examined. While extrusion of SO_n to give ethene and a carbonyl compound predominates in all three cases, the sulfoxide also gives bis(2-hydroxyethyl) disulfide, most likely formed via thiirane *S*-oxide and 1,2-oxathietane.

The Photoelectron Spectra of the Isomeric 1- and 2-Methyltetrazoles; Their Equilibrium Structures and Vibrational Analysis by *ab initio* Calculations

Michael H. Palmer, Marcello Coreno, Monica de Simone, Cesare Grazioli, Søren Vrønning Hoffmann, Nykola C. Jones, Kirk A. Peterson, R. Alan Aitken, Cécile Rouxel
J. Chem. Phys. **2018**, *149*, 034305-1–034305-9. **DOI:** 10.1063/1.5041249



Abstract: New synchrotron based studies of the photoelectron ionization spectra (PES) for the isomeric 1- and 2-methyltetrazoles (1- and 2-MeTet) show markedly higher resolution than previous reports. The unusual spectral profiles suggest that a considerable overlay of the ionic states occurs for both molecules. Under these circumstances of near degeneracy of two or more ionic states, mutual annihilation of vibrational fine structure occurs for all except the strongest vibrational states; the PES just reflects the resultants rather than full spectra. Theoretical determination of the adiabatic ionization energies (AIEs) proved a challenge; the most successful method was second order Møller-Plesset perturbation theory (MP2). These calculations suggest that the lowest PES bands for both isomers contain ionization both from lone pair □-orbitals (^{2}A') on the N-atoms (LP_N) and π-orbitals (^{2}A"). The lowest experimental AIEs are as follows: 1-MeTet is 10.315 eV assigned to 1^2A', while 2-MeTet is 10.543 eV assigned to 1^2A". Franck-Condon analysis shows that the lowest ionization energy regions of both spectra are dominated by IE from the LP_N ^{2}A' manifold, even though the ^{2}A" states have a higher absolute intensity. In this example, we have utilized a VUV Rydberg state to assist simplification of the PES; more frequently, the PES assignment is simpler and assists the location of Rydberg states in the VUV. The very slow spectral onset for 2-MeTet demonstrates the importance of vertical ionization energy calculations since maxima are more readily measured than slow onsets. These were performed at the equilibrium structure of the X^1A' state, using both multi-reference multiroot configuration interaction and the ionization potential variant of the equations-of-motion coupled cluster method, with single and double excitations (EOMIP-CCSD). This enabled the principal ionization bands to be identified over a wider range of energy. Attempts to study the higher ionic states by EOMIP-CCSD showed that several states of each symmetry are close to degenerate for 1-MeTet, in particular. A multi-configuration self-consistent field study confirmed the small separation of ionic states, but state switching during the optimization process largely disabled this method.