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Review Article

The preparation of isotopically labelled macrocyclic compounds by organic synthesis

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Summary

The preparation of isotopically labelled macrocyclic compounds is reviewed with pertinent literature references through the end of 2000. Copyright © 2001 John Wiley & Sons, Ltd.

Key Words: macrocyclic compounds; isotopic labelling; organic synthesis

Introduction

Macrocyclic compounds, both naturally occurring and rationally synthesized, are among the most valuable and challenging substances for organic chemists to prepare. Equally useful and no less daunting has been the labelling of such substances with stable or radioisotopes and the purpose of this paper will be to review the topic. This discussion is meant to be an illustrative survey of the isotopic labelling of various macrocyclic compound families and not necessarily an exhaustive compilation of all known literature references. In fact, many articles were located that provided no indication at all of the synthetic method. Although it was difficult to find an exact textbook definition of the term macrocycle, for the purpose of this review it will include ring systems of ten or more covalently attached atoms (carbon or hetero) and most examples here are of far larger ring size. The literature surveyed includes

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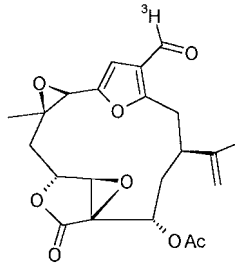
those references up to the end of the year 2000 found both in a meticulous examination of certain key journals and also specific computer searches. One such computer search was an inquiry into all macrocycles listed in the Merck Index 12th Edition that might be isotopically labelled. This review does not include references to isotopic labelling by fermentation or enzymatic syntheses, nor does it contain examples of isotopic elements co-ordinated or chelated with nonlabelled macrocycles since such topics would deserve separate treatment.

The discussion is organized as follows: Highly functionalized macrocycles (often with significant biological activity); Nitrogen containing macrocycles; Macrocyclic peptides; and Miscellaneous macrocycles. Clearly, some overlap has occurred, and on occasion the placement of certain compounds is somewhat arbitrary. Within each section, the order of discussion typically proceeds through isotopes of increasing atomic weight (^{2}H, ^{3}H, ^{13}C, ^{14}C, etc.) and references are usually arranged from earliest to latest unless the juxtaposition of certain related citations was more appropriate.

Highly functionalized macrocycles

Perhaps the most arresting images provoked by the term macrocycle are those highly functionalized molecules with significant (often antibiotic) biological activity. The predominant functionality (among others) decorating these compounds are alcohols, epoxides and esters, presenting both challenges and opportunities for isotopic labelling. Cytochalasin B is a macrocycle and is a useful tool, especially in the study of cellular sugar transport. Lin and co-workers were the first to devise the preparation of [4-^{3}H] cytochalasin B by the reduction of a ketone precursor, cytochalasin A, with sodium borotritide achieving a specific activity of 6 Ci/mmol.[1] Shortly afterward, our laboratories using sodium borotritide of higher specific activity were able to increase the compound's specific activity and since then, the widespread commercial availability of this product has resulted in scores of publications in cytological research. Bristling with functionality that may have interfered with a selective tritiation, the rifamycin analogue rifaximin was labelled by Italian investigators in a stepwise process.[2] It was found expedient to first prepare [^{3}H] 2-amino-4-methylpyridine and then react it with 3-bromorifamycin S. The labelled compound was required to study the antibiotic's absorption and localization in organs and fluids.

The anthelminthic macrocycles avermectin B_1a and B_2a were labelled in the 5-position by a reasonably stereoselective reduction of a 5-ketoavermectin precursor with sodium borotritide.[3] Molecular models of the respective ketone precursors suggested that tritide reduction of the less hindered alpha face would afford mostly the desired isomers and this proved to be the case. These labelled products were needed to clarify the mode of avermectin biological action thought to be the selective blockade of gamma-aminobutyric acid mediated neurotransmission. In a related report and motivated by the need to achieve higher specific activity, Toth and co-workers prepared [22, 23-^{3}H] ivermectin by the homogeneous catalytic tritiation of avermectin B_1a.[4] Most likely the steric bulk of the Wilkinson's catalyst facilitated the selective reduction of one olefin in the presence of four others and the compound was prepared at a specific activity of 57.7 Ci/mmol, allowing its nematotoxic activity to be studied. Lophotoxin and related macrocyclic diterpene analogues are obtained from gorgonian corals and a tritiated product was required to study its interaction with the nicotinic acetylcholine receptor. The aldehyde moeity of lophotoxin was labelled first by reduction with sodium borotritide followed by gentle oxidation to afford product **1** below. It is very rare to see an aldehyde group directly labelled with tritium, but the purified product although low in specific activity was successfully employed to demonstrate a selective and covalent binding of the toxin to the alpha subunit of the receptor.[5]



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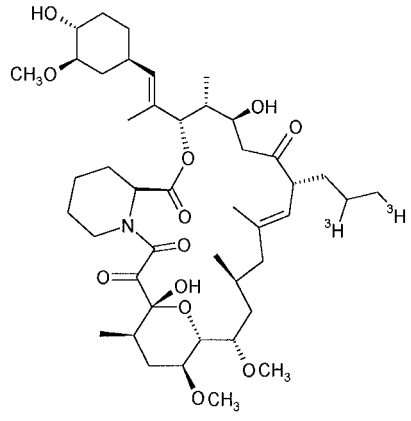
Verrucarin A, a trichothecene fungal metabolite, was radiolabelled by a sodium borotritide reduction of a mesyloxy precursor.[6] A key to the successful labelling procedure was the modification of the reaction conditions to ensure that the rate of mesyloxy precursor reduction would exceed sodium borotritide decomposition by the phase transfer catalyst. The labelling position was chosen for the sake of stability to

provide a product for metabolic studies. The protein kinase C activator bryostatin 4 and related compounds in its family are of marine origin from the sea moss *Bugula neritina* and are interesting in that they induce only a portion of the biological responses elicited by the structurally distinct phorbol esters. [26-^{3}H] Bryostatin 4 (the natural isomer with the R configuration at C26) and [26-^{3}H] epi-bryostatin 4 (the unnatural isomer with the S configuration at C26) were both synthesized by the sodium borotritide reduction of 26 oxo-bryostatin 4. The creation of this tritiated diastereomeric pair allowed separation by normal phase HPLC.[7] It was discovered that [26-^{3}H] epi-bryostatin 4 had a dramatically decreased binding affinity for protein kinase C. Furthermore, using [26-^{3}H] bryostatin 4, the competitive binding of a dozen bryostatin analogues at protein kinase C was evaluated, resulting in a refined modelling of the pharmacophoric requirements of the receptor compared to the phorbol family.[8,9] The ansamycin antibiotic herbimycin A was selectively labelled with tritium in a two-step procedure.[10] Zinc–copper couple mediated tritiated water reduction of 19-bromoherbimycin A afforded an intermediate hydroquinone which was oxidized to [19-^{3}H] herbimycin A when treated with manganese dioxide. This successful approach followed the author's initial unsuccessful strategy to reduce the same precursor with tri-*n*-butyltin tritide despite encouraging positive results on an analogous compound with an unlabelled reagent.

The immunosuppressant tacrolimus (FK-506) was reportedly labelled with tritium but neither synthetic details nor specific activity data were described.[11] In this study, the labelled product was employed to characterize its binding with human plasma protein. At about this same time, we were able to prepare [propyl-^{3}H] dihydrotacrolimus **2** below by the relatively selective heterogeneous catalytic tritiation of tacrolimus.[12] The crude reduction was rich in **2**, but also contaminated with small amounts ($\sim$4% each) of two (likely over-reduced) side products eluting earlier on reverse phase HPLC. [Propyl-^{3}H] Dihydrotacrolimus could be HPLC purified to homogeneity by this method and characterized by mass spectral analysis as well as ^{3}H NMR. With a specific activity in excess of 80 Ci/mmol, its ^{3}H NMR afforded a pattern characteristic of a tritiated propyl side chain[13] and the product was used to further elucidate the tacrolimus binding site.[14] French workers accomplished the tritiation of brefeldin A using tritium and a palladium catalyst. A ^{3}H NMR study clearly revealed that the label was present in four specific positions and several mechanisms were proposed to account for the interesting pattern of tritium incorporation.[15] Abbott chemists prepared



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[11-^{3}H] ABT-229, an erythromycin analogue and gastroprokinetic motilin agonist, by a ketone reduction with sodium borotritide.[16] The synthesis appears to be the first one in which the macrolide ring of an erythromycin analogue was labelled with tritium. Perhaps the most ingenious example of macrolide tritiation was recently reported by Moenius and Andres of the Novartis (Basel) group. Citing an earlier strategy by Curran to prepare [^{2}H] rapamycin *via* a radical intramolecular hydrogen transfer,[17] the Swiss chemists applied and optimized the technique to prepare [^{3}H] RAD001 using tri-*n*-butyltin tritide (TBTT).[18] Crucial to the success of the labelling was the quality of the TBTT[19] and the generation of radicals at low temperature perfected by a novel procedure. It appears that they will disclose the successful labelling of other macrocycles by this methodology in due course.

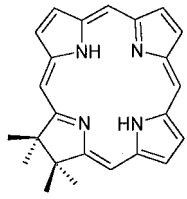
Merck chemists discovered a hydroxide mediated benzilic acid rearrangement of tacrolimus at its tricarbonyl system.[20] To elucidate the mechanism involved, the compound was labelled with ^{13}C in the 9-position carbonyl group. When subjected to basic conditions it afforded a product consistent with an acyl shift mechanism in accord with expectations.[21] For an entirely different reason the Schreiber group at Harvard synthesized [8,9-^{13}C] tacrolimus.[22] The lengthy asymmetric synthesis was designed to provide a product needed to clarify the interaction between tacrolimus and its receptor, the immunophilin FKBP. Lilly chemists appear to be the first to have published the labelling of erythromycin with ^{14}C.[23] The antibiotic was first demethylated and the resulting precursor was converted to [*N*-methyl-^{14}C] erythromycin by a reductive methylation with [^{14}C]

formaldehyde. Later, Lilly workers also reported the labelling of tilmicosin with ^{14}C.[24] In a six-step procedure [ring-^{14}C] 3,5-dimethylpiperidine was prepared as a mixture of *cis*, *trans* isomers and reacted with an aldehyde precursor *via* a reductive amination reaction. The synthesis was intriguing for its creative solution to a labelling challenge. A ratio of 85:15 for the *cis*, *trans* isomers of 3,5-dimethylpiperidine was ideally required to mimic the commercial process outcome of the hydrogenation of 3,5-lutidine. However, it was anticipated that the synthesis of [^{14}C] 3,5-lutidine would be daunting and therefore a clever alternative was designed. [^{14}C] 3,5-Dimethyl-2,6-piperidinedione was efficiently prepared in five steps from [2-^{14}C] diethyl malonate. Its reduction with lithium aluminum hydride accomplished the satisfactory *cis*, *trans* product ratio of 83:17. Fontana and colleagues described the efficient synthesis of the antibacterial [^{14}C] rifabutin.[25] The labelled starting material, [methylene-^{14}C] *N*-isobutyl-4-piperidone, was synthesized and reacted with an available diamine precursor. The authors reported that attempts to obtain a tritiated product of useful specific activity were largely unsuccessful. The synthesis of [^{14}C] A-62514, related to erythromycin A, has been described. [2-^{14}C] *N*,*N*-Dimethylethylenediamine was synthesized and reaction of this with a suitable macrocyclic precursor followed by hydrogenation provided the needed product.[26]

The preparation of [*N*-methyl-^{11}C] erythromycin A has been published, first in preliminary form[27] and then later in more detail.[28] The labelled component, [^{11}C] formaldehyde, was rapidly prepared from [^{11}C] carbon dioxide and reductively reacted with desmethylerythromycin A to obtain the product. In somewhat analogous fashion, the antibiotic [*N*-methyl-^{11}C] roxithromycine was also synthesized using an *N*-desmethyl precursor, but in this case, [^{11}C] methyl iodide was efficiently used as the labelling reagent.[29] Finally, with regard to ^{125}I labelling, an azido ansamycin analogue was labelled in a two-step procedure and used as a photoaffinity probe.[30] Correspondingly, the preparation of several [^{125}I] rapamycin photoaffinity analogues using a destannylation strategy have been described.[31]

Nitrogen containing macrocycles

Among the earliest and most active areas of alkaloid isotopic labelling was the porphyrin class of compounds. Indeed it has also attracted some of the most notable luminaries of 20th century organic chemistry.



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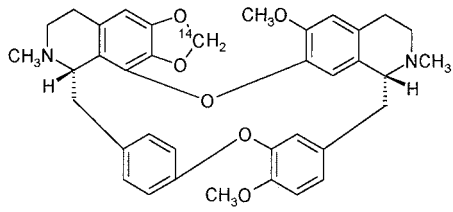
R. B. Woodward was the first to observe and report in 1961 that certain bridge positions of chlorins (general structure **3** above) were exchangeable after heating with CH_3CO_2D.[32] This ground-breaking observation provided not only an entry into the isotopic labelling of this important compound class but also insight into their general electrophilic chemistry and biological mechanisms of action. Soon afterward, this approach was also applied to the deuteration of chlorophyll *a* itself[33] and from that point forward a number of papers appeared that explored and expanded these findings for both acid and base catalyzed isotopic labelling.[34–53] Several of the more interesting papers related regiospecific labelling success. Gurd and co-workers were able to selectivity deuterate the acetyl groups of 2,4-diacetylhemin at room temperature by means of CH_3OD in 7% D_2SO_4 overnight.[45] LaMar and colleagues reported the first base catalyzed deuteration of the ring 1,3 methyl groups of protoporphyrin IX.[46] Using CH_3ONa/CH_3OD in DMF for five days afforded the product that was characterized by both mass spectrometry and NMR. The explanation suggested for this selectively was the activating effect of the vinyl substituents on the A and B ring systems. From the very beginning, NMR was an absolutely indispensable tool for these studies. In fact the availability of deuterated porphyrins and metalloporphyrins served to clarify NMR peak assignments for this compound class as well as provide *in situ* deuterium NMR spectroscopy of reactive species. To achieve other positions of deuterium labelling, there have been several reports[54,55] of total syntheses of deuterated porphyrins from deuterated precursors such as pyrroles. The preparation of [alpha, gamma-^{14}C] uroporphyrin III using [^{14}C] dimethylformamide has been described.[56] Finally, [$^{15}N_4$] octamethylporphyrin was synthesized from the corresponding [^{15}N] pyrrole components.[57]

Sodium borotritide reduction of a bis imine intermediate afforded [^{3}H] cyclam, a tetraaza macrocycle.[58] An analogous compound was also labelled with ^{14}C by a reductive formylation using [^{14}C] formaldehyde.[59] The structurally similar tetraaza macrocycle gadoteridol was labelled with ^{14}C using [^{14}C] propylene oxide[60] and related macrocycle DOTA



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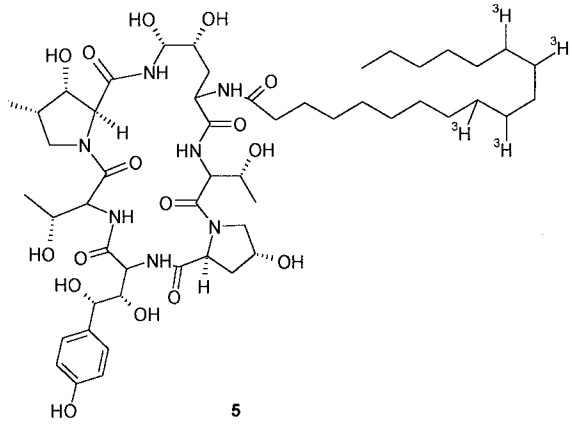
was labelled with [^{14}C] bromoacetic acid.[61] In the mid-1970s, we were able to prepare [13-^{3}H] tubocurarine chloride by the catalytic tritiation of the corresponding iodo precursor.[62] By employing a catalytic tritium exchange, the structurally similar alkaloid berbamine was labelled with tritium at 8.8 Ci/mmol[63] and the bisbenzyl tetrahydroisoquinoline alkaloid tetrandrine was tritiated by tritium gas exposure.[64] The related alkaloid cepharanthine was labelled with ^{14}C in the methylenedioxy group (**4** above) by the treatment of a catechol intermediate with [^{14}C] methylene iodide.[65] The macrocyclic alkaloid retrorsine was used as a precursor for the preparation of [^{14}C] senecionine and [^{14}C] isosenecionine *via* [^{14}C] methylmagnesium iodide.[66]

Macrocyclic peptides

With regard to the isotopic labelling of macrocyclic peptides, it was somewhat surprising to find fewer published articles than expected. No doubt, given the importance of this compound class, far more examples reside in confidential industrial notebooks. However, the examples located and noted here are illustrative. Echinocandin B was catalytically reduced with both deuterium and tritium to afford the isotopically labelled tetrahydroechinocandin B.[67] Interestingly, the tritiated version (**5** below) of this macrocyclic peptide manifested isotopic fractionation[68] on reverse phase HPLC; that is, the chromatographic separation of the unlabelled and labelled compounds with the order of elution being first **5**, then [^{2}H] tetrahydroechinocandin B and finally the unlabelled compound. Apparently, the high specific activity of 129 Ci/mmol was a key factor in the chromatographic separation. To prepare [*N*-methyl-^{3}H] SKF 107260, an appropriate amino acid precursor was alkylated with [^{3}H] methyl iodide and then employed to prepare the cyclic peptide by means of standard solution phase peptide synthesis.[69] Pleiss and co-workers at Bayer radiolabelled the anthelminthic peptide



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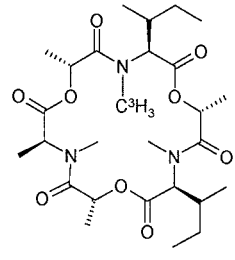

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PF 1022A by the methylation of a bis desmethyl precursor with [^{3}H] methyl iodide.[70] In an analogous fashion, the related cyclic peptide [*N*-methyl-^{3}H] JES 1798 (**6** above) was prepared soon afterward by the same group.[71] These labelled compounds were used for receptor binding studies to characterize their mode of action. The synthesis of [^{3}H] cyclosporin A was accomplished by the catalytic tritium dehalogenation of a bromo precursor.[72]

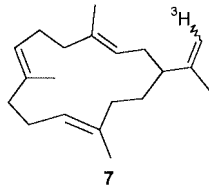
The complex depsipeptide R 106-1 was isotopically labelled in a rather unique way. The authors were initially encouraged by the acid catalyzed hydrogenolysis of R 106-4, a hydroxybenzyl precursor, with hydrogen or deuterium to obtain R 106-1 or [^{2}H] R 106-1. However, for reasons not yet clear, the method failed for tritium and another approach was explored for ^{14}C labelling. Trimethylamine N-oxide was found to be a useful reagent to accomplish the retro aldol cleavage of acetone from the compound.[73] The authors then found suitable conditions to add [2-^{14}C] acetone to the precursor, affording the labelled compound.[74] The synthesis of photoactivatable cyclic tetrapeptide [carbonyl-^{14}C] 4-benzoylbenzoyl MeSer^1-tentoxin from [^{14}C]

4-benzoylbenzoic acid has been described.[75] The ^{14}C and ^{125}I labelled versions of insulin derivative NN 304 have also been reported.[76]

Miscellaneous macrocycles

This final section addresses the isotopic labelling strategies for macrocyclic compounds not yet covered. First, there are those macrocycles which are in large part hydrocarbon in nature with little or no functionality. The Turro group, requiring perdeutero 2-phenylcyclododecanone to probe the magnetic isotope effect at radical centers of flexible biradicals, prepared the compound by a general exchange procedure.[77] Japanese investigators have described the preparation of deuterated [2.2] metacyclophanes. One group prepared [8,16-^{2}H] [2.2] metacyclophane by a Wurtz dimerization process[78] and another laboratory reported the synthesis of [4,5,6,8-^{2}H] [2.2] metacyclophane by a multi-step approach starting from [^{2}H] isophthalic acid.[79] Prestwich has detailed the preparation of [16-^{3}H] cembrene A (**7** below) in an efficient four-step synthesis culminating in a selenoxide elimination to regenerate the non-ring olefin with a specific activity of 1.5 Ci/mmol.[80] The terpene humulene, an isomer of caryophyllene, was labelled in the 2-methyl group with tritium by the preparation and reduction of a bromo precursor with lithium aluminum tritide.[81] With regard to carbon isotopes, the 2-phenylcyclododecanones mentioned earlier were labelled with ^{13}C *via* a multi-step path using the ring closure of a bis carboxylic ester.[77] Susan and Duncan successfully prepared [$^{14}C_6$] 1,5,9-cyclododecatriene by the Ziegler catalyst trimerization of [^{14}C] 1,3-butadiene. Exacting attention to experimental details and timing followed by a careful distillation purification afforded pure product in good yield.[82]

In the area of host–guest chemistry, the macrocyclic cyclodextrins are some of the most versatile compounds. Deuteration of cyclodextrins would therefore be useful to study the steric features and isotope effects



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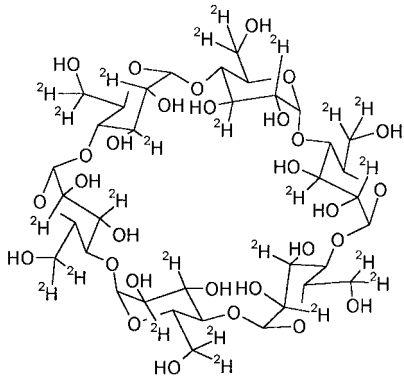

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of binding by NMR and several papers concerning this have appeared. Canadian investigators appear to have been the first to publish,[83] the deuteration of alpha-cyclodextrin (cyclohexaamylose) to [2,3,6,6′-^{2}H] alpha-cyclodextrin **8** (above). Using D_2O at reflux with Raney nickel catalyst, they prepared the compound and characterized it with proton coupled ^{13}C NMR, clarifying an earlier discrepancy in the literature concerning signal assignments. Curiously, a decade later, Japanese chemists reported[84] essentially the same alpha-cyclodextrin deuteration methodology, but not citing and apparently unaware of the earlier publication just mentioned. These later authors did however, extend the technique to produce both [^{2}H] beta-cyclodextrin and [^{2}H] gamma-cyclodextrin. Their NMR analysis of reaction mixtures taken at various time intervals provided a rough estimate for the rate of exchange at the 2,3,6 and 6′ positions. These results were elegantly extended by French chemists using a more detailed NMR analysis, to find that regio- and some stereoselective deuteration could be achieved by the control of reaction temperature and time.[85] They discovered that at low temperature, Raney nickel catalyzed D_2O exchange occurred almost exclusively at the 2-position without affecting other sites. The synthesis of the polyether [1,2-^{14}C] 18-crown-6 from [^{14}C] oxalic acid has also been reported.[86]

Conclusion

For nearly five decades, resourceful chemists have skillfully labelled macrocyclic compounds with both stable and radioisotopes. Success has

been cleverly achieved by many methods including isotopic exchange reactions on the parent compound or closely related intermediates. When these methods could not be used, elegant total synthesis from labelled precursors were employed. On occasion, work in this area prompted the creation of new reagents or optimization of reaction conditions to realize success. This review has summarized the remarkable progress to date and looks forward to future achievements in this challenging area.

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