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TRIOXACARCINS AS A PROMISING CLASS OF ANTICANCER DRUGS

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ABSTRACT

Trioxacarcins are intricate and polyoxygenated natural products with exceptional anti-malarial and antineoplastic flair. Trioxacarcins are extracted disclosing six of their types, namely, trioxacarcin A, B, C, D, E and F. Much valuable work has been executed in the line of synthesis of trioxacarcins and their derivatives keeping brevity of steps and efficiency of reactions in focus. Additional efforts are still requisite in formulation and biological studies of trioxacarcin D, E and F as literature proves efforts made on exploration of A, B and C types mainly. This class has an outstanding feature of covalently binding with DNA duplex, therefore, underlining its prospectives to manipulate genes for impeding serious diseases. Nature encloses remedy for every affliction and trioxacarcins class of drugs is a medicinal treasure for modern world facing agitating health complications like cancer.

KEYWORDS: Trioxacarcins, polyoxygenated, DNA, cancer, antineoplastic, anti-malarial.

1. INTRODUCTION

In 1981, trioxacarcins were primarily isolated from the culture broth of actinomycetes strain DO-45 by Tomita. The producing organism was a new strain and named *Streptomyces bottropensis.*[1,2] They are complex natural antitumor antibiotics exhibiting cytotoxicity against profuse cancerous cells and active against Gram-positive and Gram-negative bacteria along with significant anti-malarial activity.[3] Structural elucidation of the said class of drugs was conducted by Sirahata who explained their novelty as having polycyclic chromophores

and the origin of the name trioxacarcin was elaborated to be due to aglycones with three cyclized ether components.[4]

In 2004, trioxacarcins A, B and C were isolated from the ethyl acetate extract of *Streptomyces* sp. isolate B8652 with additional three new derivatives trioxacarcins D, E and F. All the mentioned types have marked anti-bacterial efficacy with some demonstrating antitumor effect.[3] Five structurally related compounds were isolated from the crude extract of a marine *Streptomyces* strain acquired from deep sea sediments having antifouling properties.[5]

Trioxacarcins (Fig. 1) are eminently connected, overly oxygenated molecules which are encoded within the genes of various Streptomycetes and function as growth inhibitors of cultured human cancer cell lines.[6] Structural characterization of, on average, twenty trioxacarcins has been done all resembling the natural product DC-45-A2.[7] Trioxacarcin A comprises of a complex ring system adjoint to sugars at the 4th and 13th positions, thereby, imparting intense green fluorescence in solution and yellow in powdered state.[8]

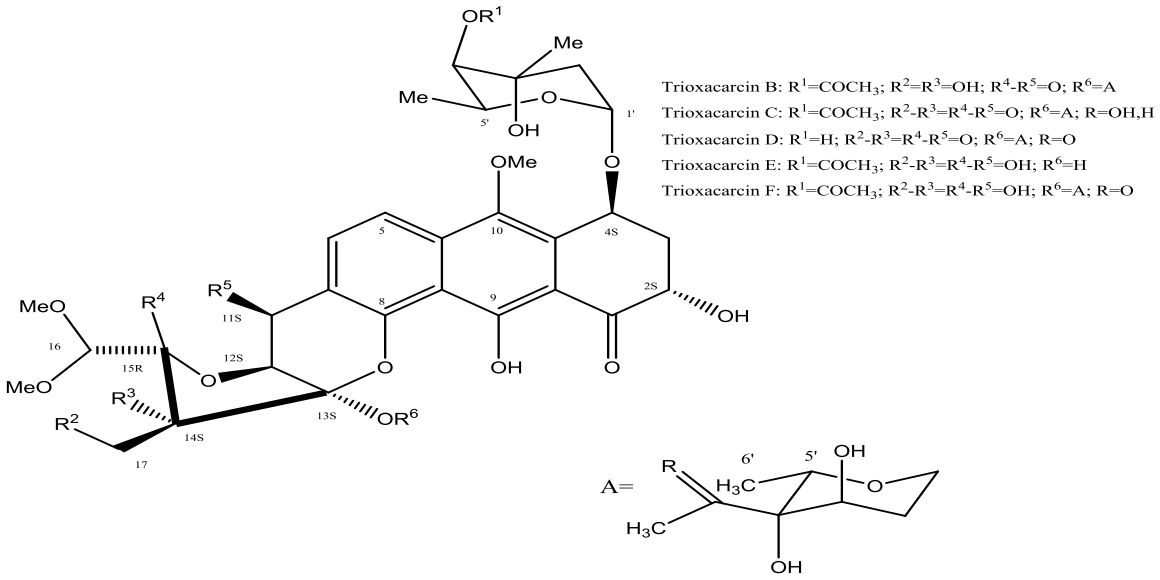


Fig 1: Structure of trioxacarcins.[5]

Study of physical characteristics of trioxacarcins reveals molecular formula and molecular mass of trioxacarcin A, B, C, D, E and F to be $C_{42}H_{52}O_{20}$ (877), $C_{42}H_{54}O_{21}$ (895), $C_{42}H_{54}O_{20}$ (879), $C_{40}H_{50}O_{19}$ (834), $C_{34}H_{44}O_{18}$ (740), $C_{42}H_{58}O_{22}$ (914), respectively. All the forms have yellow colour and trioxacarcin A, B and C have powdery appearance, whereas, D, E and F have solid physical state.[2-3]

The present review aims to give highlights of the investigations undergone so far on trioxacarcins for grasping attention of synthetic organic chemists towards this enchanting scaffold. The drug class has many active centers which is a point of interest, thereby, thrilling the innate desire of scientists to work on this magical molecule gifted by nature.

2. Structural Analysis of Trioxacarcins

A crystal structure was reported showing an antibiotic extracting a nucleobase from a DNA molecule. A covalent bond was formed before leaving with the base. Using MAD phasing and utilizing brominated oligonucleotides the structure of trioxacarcin A covalently bonded to double-stranded d (AACCGGTT) was determined to be 1.78A°. At the N7 position of a guanine, the DNA–drug complex was observed to combine *via* alkylation and on the 3'-side of the alkylated guanine intercalation was observed accompanying base flip-out. For the first time, an antibiotic-induced flipping-out of a single, non-terminal nucleobase from a DNA duplex was noticed in a crystal structure.[8] Temperature-dependent UV and CD spectroscopy, HPLC analysis and ESI mass spectrometry were employed for the making and fragmentation of complexes between trioxacarcin A and varied DNA sequences. Natural product, gutingimycin, was obscured by path of cleavage of the complexes formed through guanine removal. The DNA, thus produced, had an abasic site which was further fragmented into a DNA fragment with a furanyl unit and oligonucleotide at the 3′ and a phosphorylated 5′end, respectively.[9] X-ray crystallography of Trioxacarcins, derived from natural and synthetic sources, was conducted to highlight reactivity and mode of action of the drug class. Retention of the antiproliferative activity was vivid in the incubated synthetic derivative of trioxacarcin in which a carbohydrate residue was missing and it was oxygenated at C2 and C4 positions. Its self-complimentary duplex oligonucleotide generated crystalline adducts of guanine. The adduct, so produced, had resemblance with gutingimycin which was an addition product formed through incubation of natural trioxacarcin A and duplex DNA. This also proposed the similarity of cytotoxicity of trioxacarcin A and the analogue. A new, dark-red crystal of guanine adduct was also isolated from incubation of trioxacarcin A having a self-complimentary duplex oligonucleotide. Crystallographic studies revealed one adduct to be an anthraquinone derivative. This derivative was generated by guanosine alkylation within DNA duplex, depurination, subtraction of the trioxacarcinose A carbohydrate residue through base catalysis following oxidative rearrangement. Trioxacarcin derivatives with C4 oxygenated sites were scrutinized to be chemically unfaltering.[10] Incubation of the completely synthetic analogue of trioxacarcin with missing carbohydrate residue as compared to trioxacarcin A

and oxygenation at C2 and C4 was probed to retain antiproliferative potential. It had characteristic of self-complimentary duplex oligonucleotide d (AACCGGTT) generating crystalline covalent guanine adduct (Fig 2 and Scheme 1).[11]

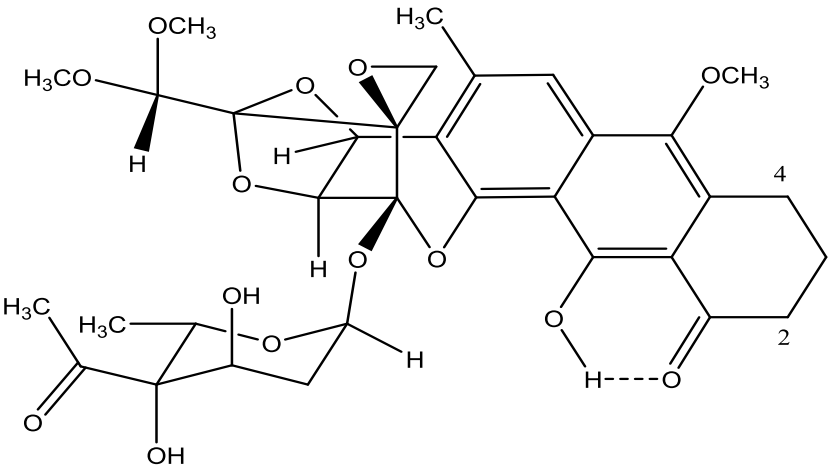
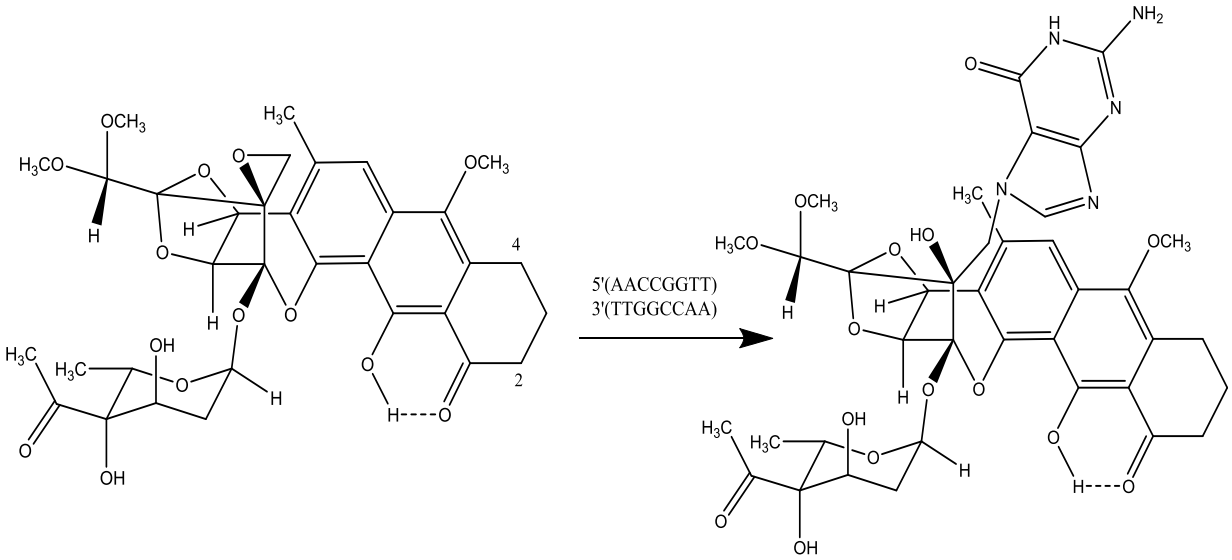


Fig 2: Fully synthetic trioxacarcin analogue.[11]



Scheme 1: Formation of guanine adduct from the fully synthetic trioxacarcin analogue.[11]

3. Biosynthesis of Trioxacarcins

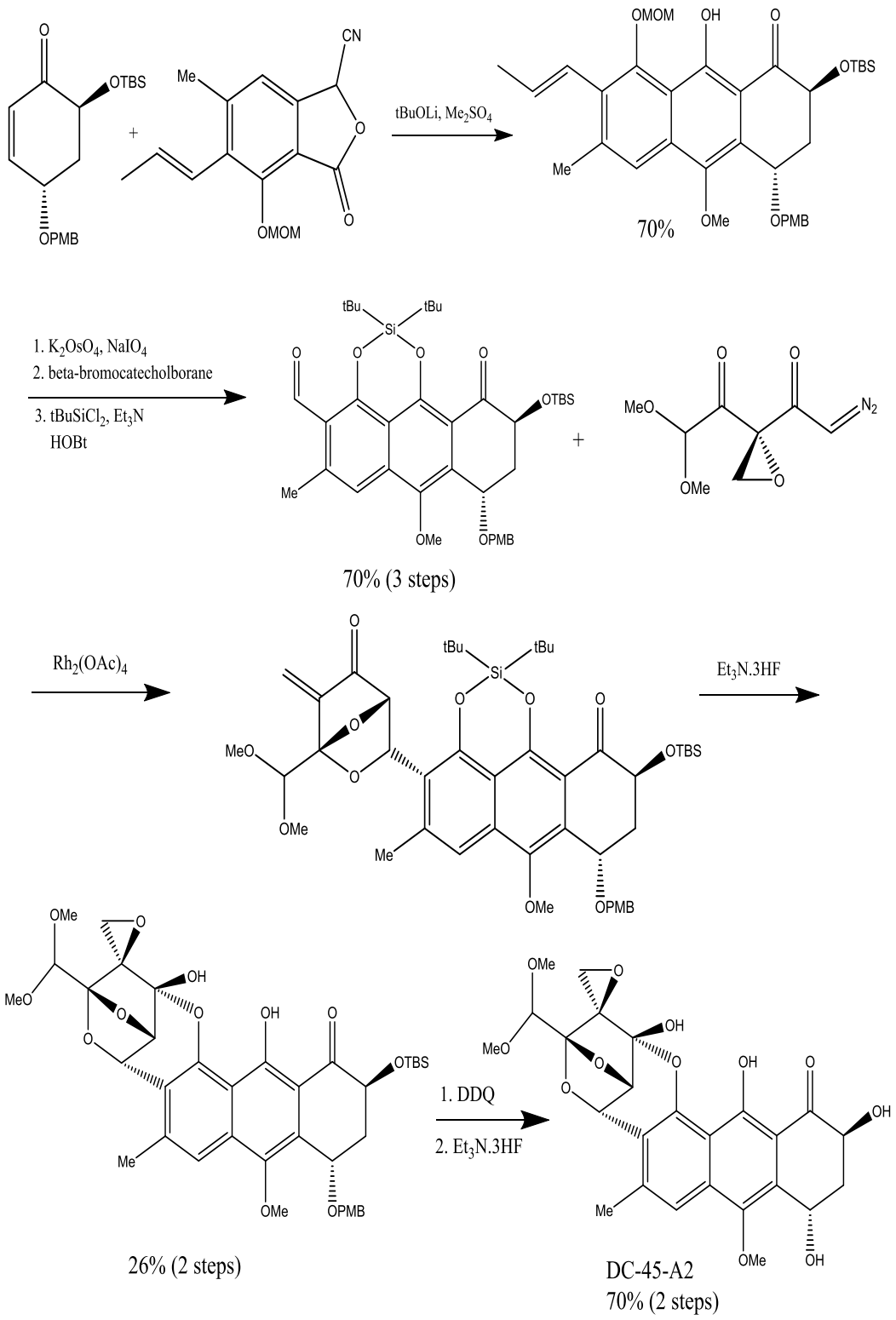
The biosynthetic pathway of trioxacarcin incorporate type II polyketide synthases (PKSs) and L-isoleucine as a starter unit along with multiple complex post-PKS tailoring enzymes. Diverse resistance and regulatory proteins are also explored to be part of the biosynthesis route. The SARP family regulator Txn9 and two-component response regulator Txn11 were identified to be key activators for trioxacarcin biosynthesis in *Streptomyces bottropensis* by inactivating all the six annotated regulatory genes one by one in the gene cluster. No

regulatory cascade relationship was visible through complementation assay. Moreover, fifteen of the twenty eight trioxacarcin operons were noticed to be the prime factor for trioxacarcin generation.[12] Another following study demonstrated involvement of one unit of L-isoleucine and nine units of malonyl-CoA in biosynthesis of the said moiety.[13] The biosynthetic pathway of trioxacarcins was also undergone modification by means of deactivation of an acyltransferase (Trx49) gene. The cytotoxicity of the genetically mutated counterpart was mildly lower than trioxacarcin A, but, anti-tumor activity was remarkable with IC_{50} value of 4.86 nmol.L^{-1}.[14]

4. Historical Background of Trioxacarcins Synthesis

Stereoselectively synthesizing biologically active natural products by dint of total synthesis renders prospects to gain reasonable yield of the natural products and their structural equivalents. Additionally, it serves as a parameter to check validity and efficiency of existing synthetic strategies to lead to superior synthetic routes. By adopting total synthesis, corroboration of the complex structures of natural origin, emendation leading to accurate structure ascertainment is made possible.[15]

The first total synthesis of trioxacarcin DC-45-A2 was proposed by Andrew Meyers (Scheme 2).[16] Routes to monosaccharides trioxacarcinoside A and B were devised by Myers which paved path for the synthesis of trioxacarcin A.[17,18]The scheme leading to the desired product commenced with Hauser-Kraus annulations.[19-21]

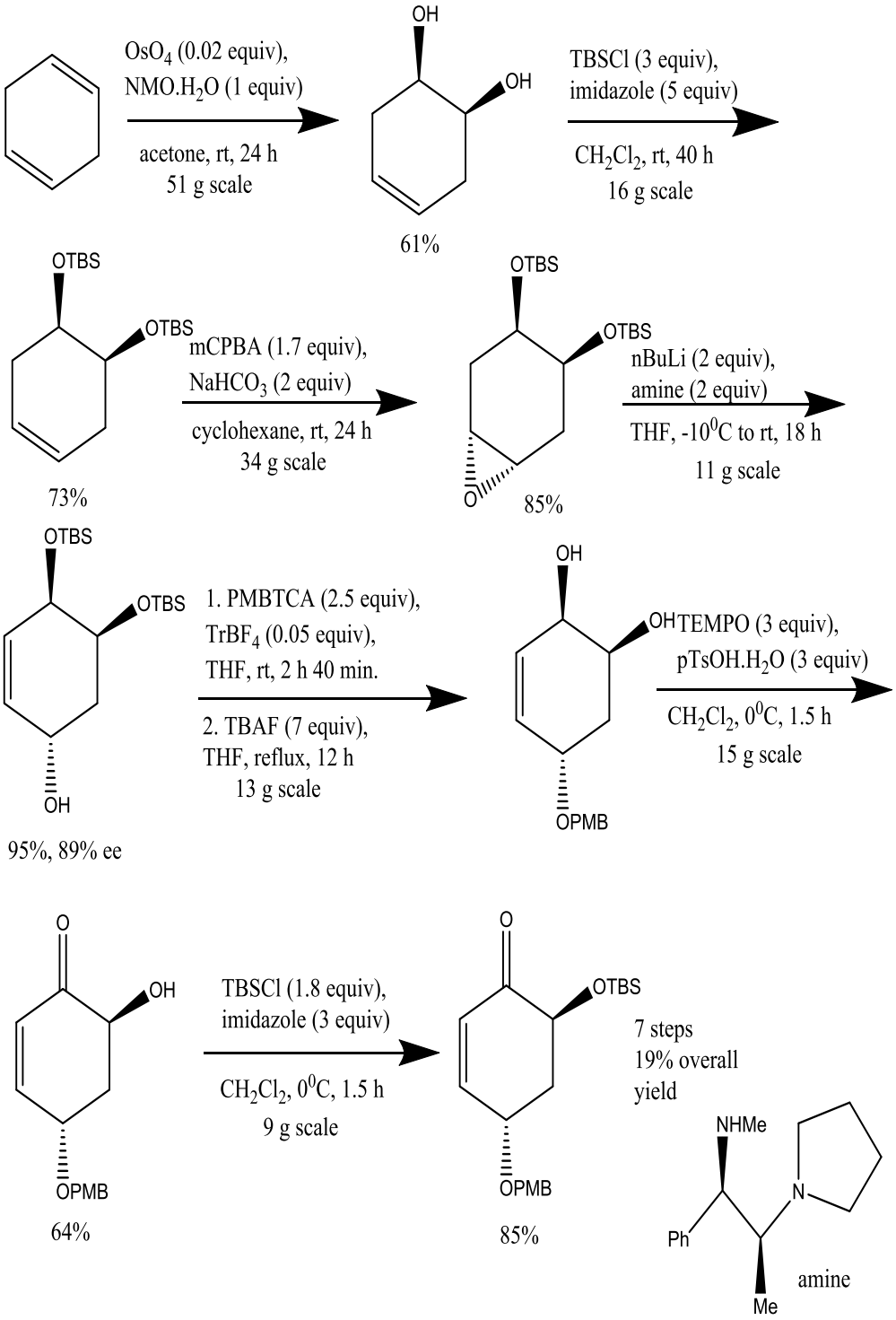


Scheme 2: Myers' total synthesis of trioxacarcin DC-45-A2.[16]

Primarily, Myers' group had successfully designed and investigated three synthetic pathways for cyclohexenone as part of their trioxacarcin total synthesis program and one proposal from

Ueda was also presented during their development of new fluorescence-labelled probes.[22,23] The Nicolaou group had four routes for cyclohexenone as a foundation stone of their work.

Myers' first synthetic route comprising of four steps initiated with L-malic acid and led to lactone. The lactone so produced was converted to Weinreb amide by way of oxidation, chemoselective vinyl addition and PMB-protection. Through ten step synthetic scheme, including vinyl group addition and RCM, procurement of cyclohexenone up to 19% was accomplished.[24,25] The second three step proposed route started off with TBS-protected resorcinol which was modified to trans-diol. In further seven steps, inclusive of DMP oxidation, shuffling of protection group with PMB protection along side, production of 12% cyclohexenone was achieved.[26] The last seven step synthetic pathway by Myers initiated with transformation of quinic acid to PMB-protected cyclohexenone.[27,28] With silyl enol ether origination accompanied Rubottom oxidation which resulted in hydroxyketone. The scheme prolongation to further ten steps, including TBS-protection, formulated cyclohexenone having 6% yield.[29] The Minuro Ueda group published their work for cyclohexenone production as part of their investigations on fluorescence-labelled probes.[22,23] The course for synthesis instigated with d-glucose being modified to iodide by an eight step mechanism. Alkene was afforded *via* TBS-protection besides Ferrier carbocyclization, methoxy demethylation and consequently elimination to give cyclohexenone up to 14% adding overall twelve steps to the mechanistic path.[30] The Nicolaou group aimed for scalable synthesis methodology as the previous inquiries lacked encouraging outcomes in this respect(Scheme 3).[31]



Scheme 3: Optimized conditions for the new route developed in the K. C. Nicolaou lab for the synthesis of cyclohexenone.[31]

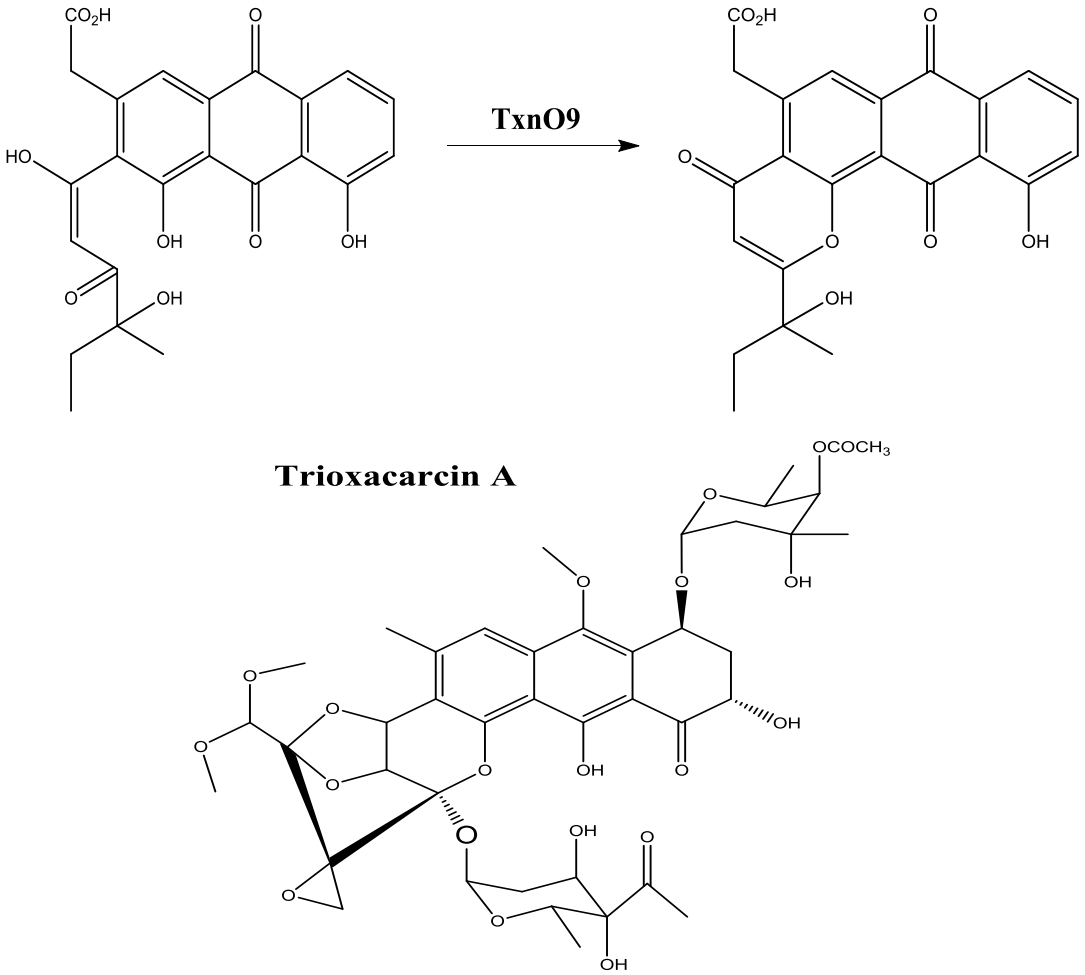
The new synthetic scheme evolved through endeavours of Nicolaou group counted on the accessibility to allylic alcohol as communicated by the O'Brien group.[32,33] The mechanism had 1,4-cyclohexadiene as the starting material which underwent conversion to meso-diol through Upjohn method.[34,35] Modification was introduced in Woodward conditions by the

O'Brien group (KIO_3, I_2, KOAc),[36] but, Nicolaou group didn't have access to the Amberlite resin for acetate hydrolysis so alternative procedure was adopted. By way of double TBS-protection bis-TBS ether was generated, which, in turn was diastereoselectively epoxidized with mCPBA. One-pot PMB protection, allylic oxidation and ultimately TBS-protection processed cyclohexenone as the major product.[37]

5. Synthesis of Trioxacarcins and Analogues

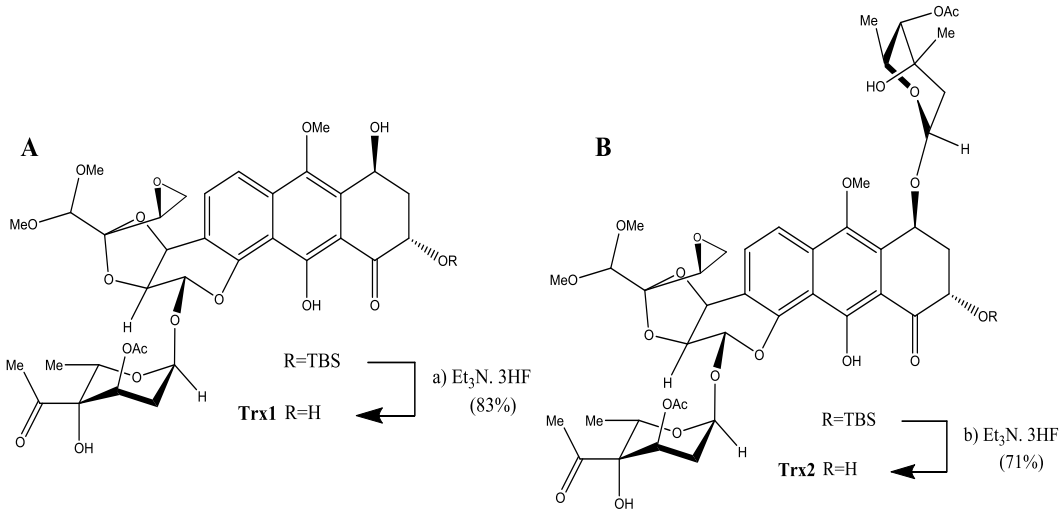
We herein describe different strategies adopted so far to gain access to these potent anti-tumor drugs which will present recommendations for the synthesis of other members of the class, both, natural or designed.

A CalC-like protein belonging to a START family, was established to function as an anthraquinone-γ-pyrone synthase in the biosynthesis of anti-tumor antibiotic trioxacarcin A (TXN-A)(Scheme 4).[38]



Scheme 4: Biosynthesis and enzyme mechanism.[38]

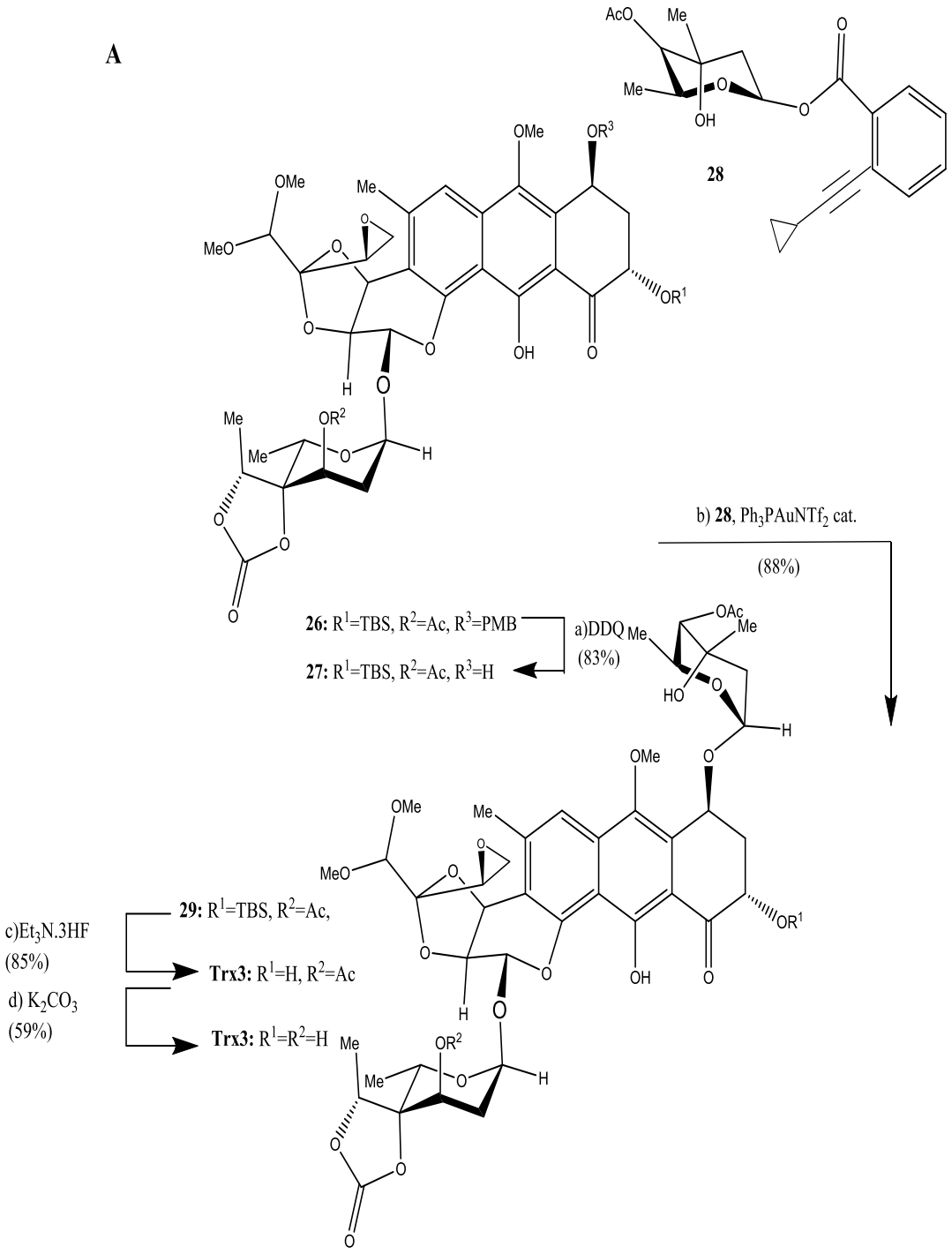
Six naturally occurring trioxacarcins were synthesized through streamlined total synthesis and they were applied to formulate a series of analogues of these complex natural products (Scheme 5 and 6).[39]



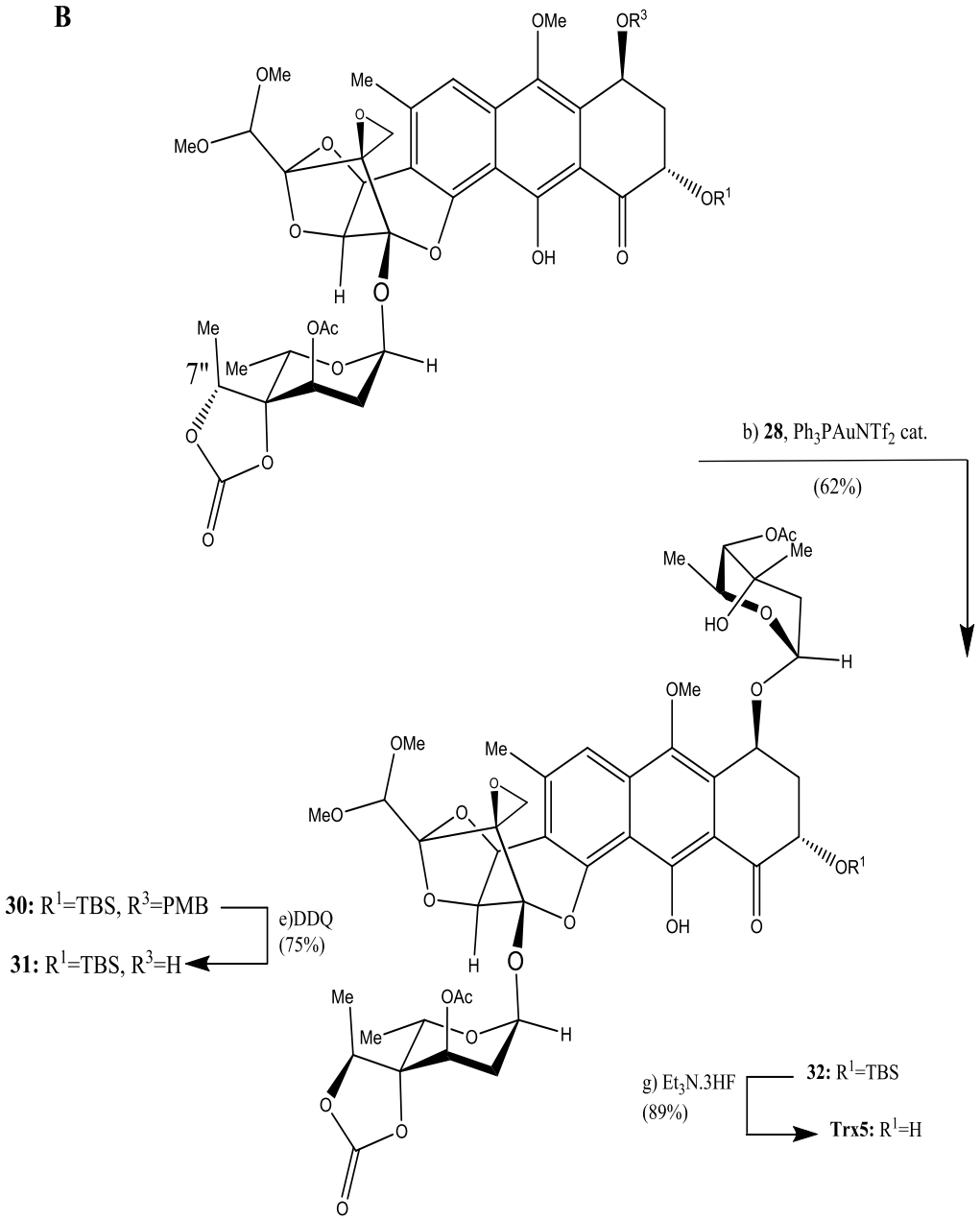
Reagents and conditions: (a) $Et_3N{\cdot}3HF$ (36 equiv), CH_3CN, 23 °C, 12 h, 83%; (b) $Et_3N{\cdot}3HF$ (57 equiv), CH_3CN, 23 °C, 12 h, 71%.

Scheme 5: Synthesis of trioxacarcin analogues Trx1 and Trx2.[39]

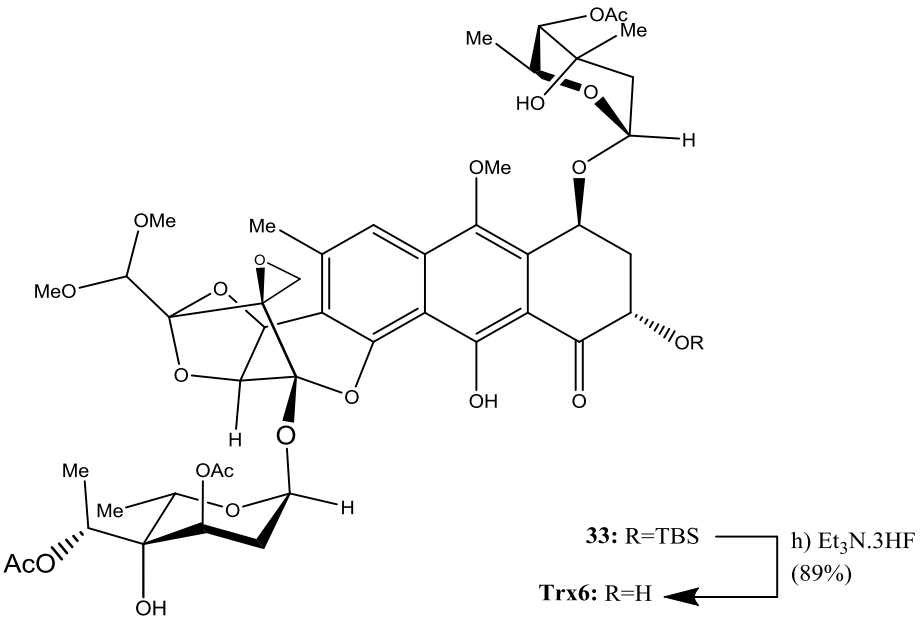
A


28
b) 28, Ph3PAuNTf2 cat.
(88%)
26: R1=TBS, R2=Ac, R3=PMB
27: R1=TBS, R2=Ac, R3=H
a)DDQ
(83%)
29: R1=TBS, R2=Ac,
c)Et3N.3HF
(85%)
Trx3: R1=H, R2=Ac
d) K2CO3
(59%)
Trx3: R1=R2=H

B


b) 28, Ph3PAuNTf2 cat.
(62%)
30: R1=TBS, R3=PMB
31: R1=TBS, R3=H
e)DDQ
(75%)
g) Et3N.3HF
(89%)
32: R1=TBS
Trx5: R1=H

C



Scheme 6: Synthesis of C4, C14-bisglycosylated analogues Trx3-Trx6.[39]

Reagents and conditions: (a) DDQ (2.9 equiv), CH_2Cl_2/H_2O (4:1, v/v, pH 7.0 buffer), 23°C, 3 h, 83%; (b) $Ph_3PAuNTf_2$ (0.3 equiv), 28 (2.0 equiv), 4 Å MS, CH_2Cl_2, 0°C, 5 min, 88%; (c) $Et_3N{\cdot}3HF$ (65 equiv), CH_3CN, 23°C, 12 h, 85%; (d) K_2CO_3 (7.7 equiv), MeOH, 0°C, 45 min; 59%; (e) DDQ (3.0 equiv), CH_2Cl_2/H_2O (4:1, v/v, Ph 7.0 buffer), 23°C, 3 h, 75%; (f) $Ph_3PAuNTf_2$ (0.3 equiv), 28 (2.0 equiv), 4 Å MS, CH_2Cl_2, 0°C, 15 min, 62%; (g) $Et_3N{\cdot}3HF$ (41 equiv), CH_3CN, 23°C, 12 h, 89%; (h) $Et_3N{\cdot}3HF$ (20 equiv), CH_3CN, 23°C, 12 h, 89%.

Another invention encompassed synthesis of novel derivatives of trioxacarcin analogues (Fig 3).[40]

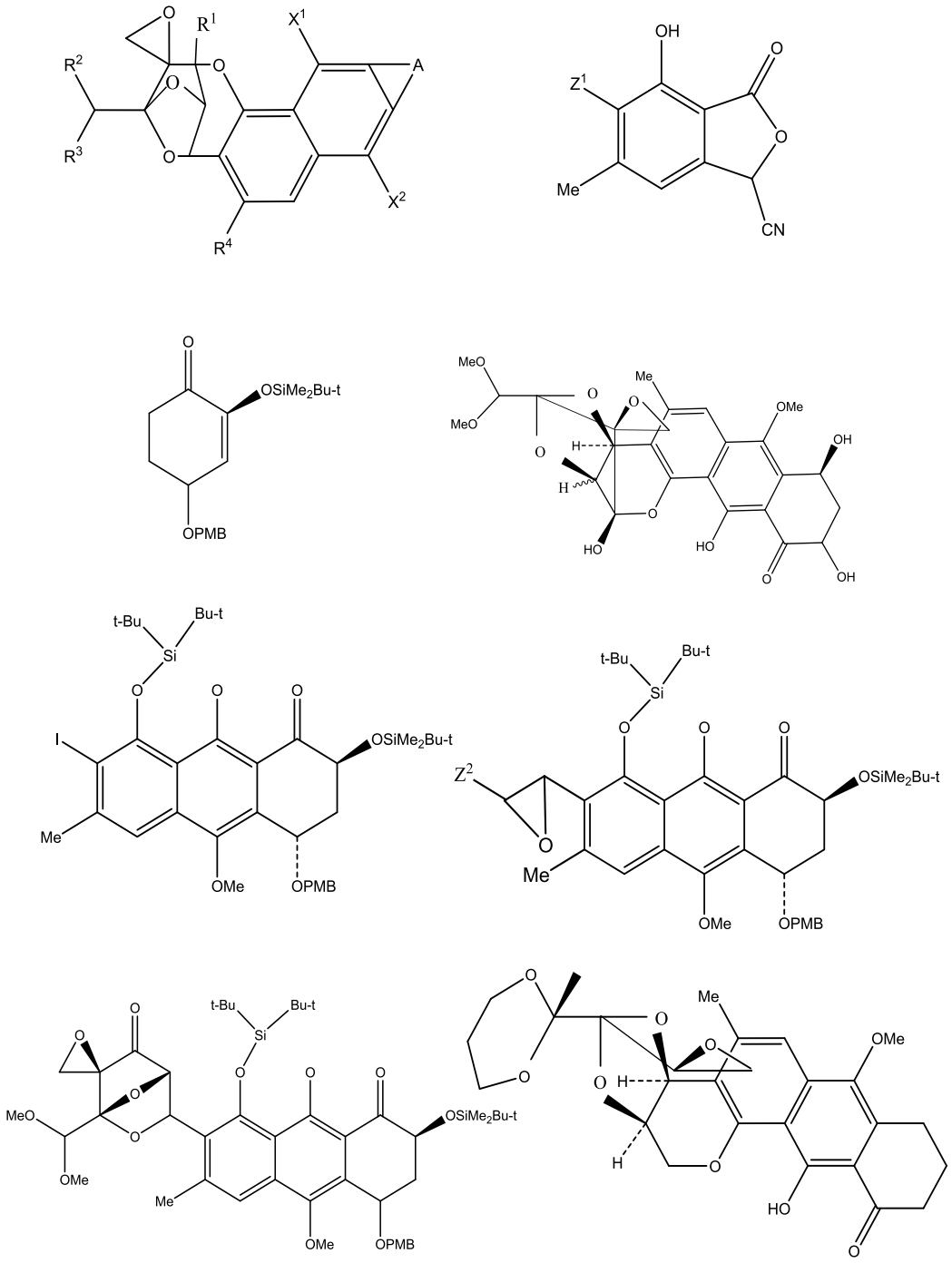
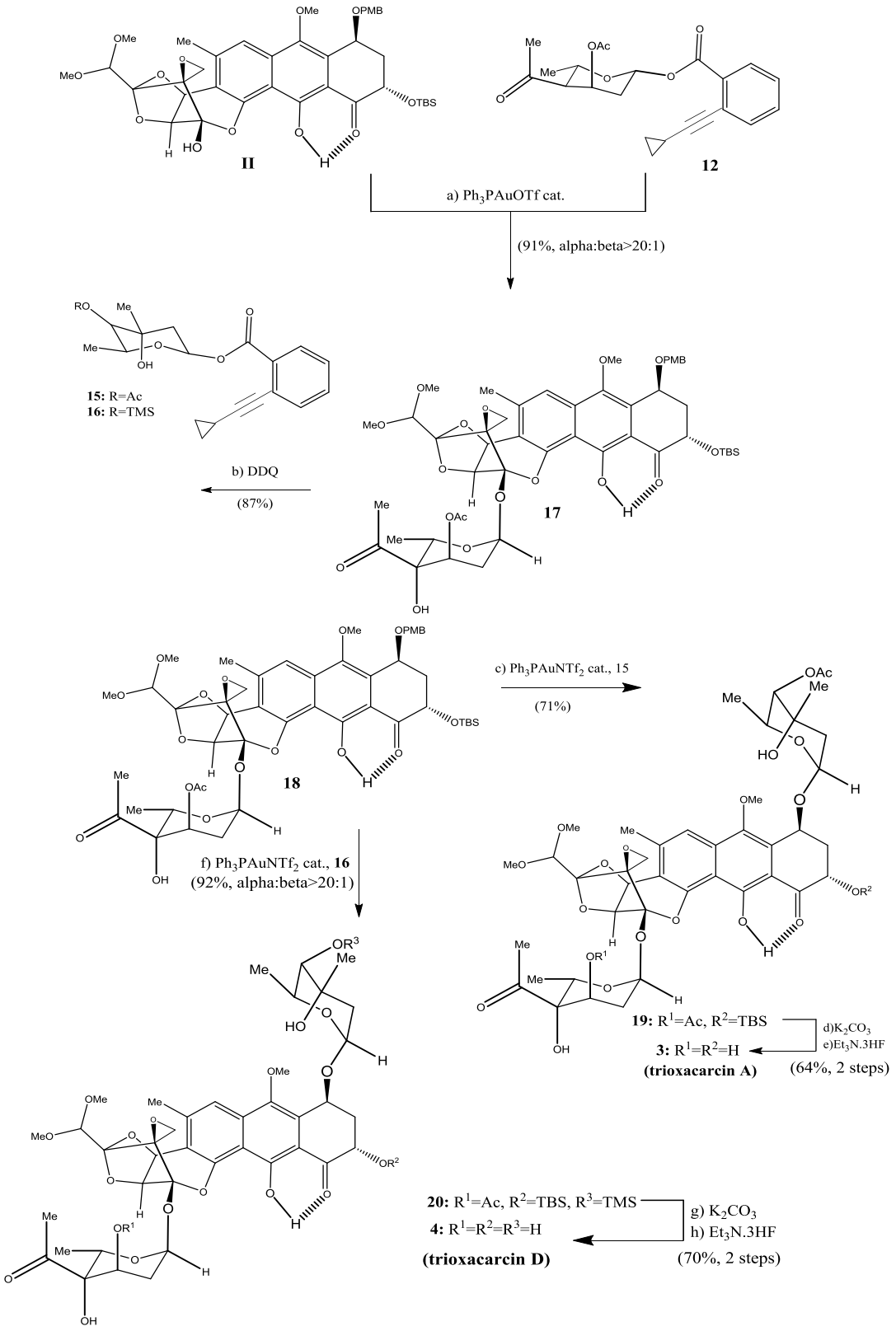


Fig 3: Trioxacarcin analogues.[40]

[A = is a fused cycloalkanediyl; R^1=NH_2, OH, SH; R^2 and R^3= H, NH_2, OH, SH; R^4=H, NH_2, halogen, OH, SH; Z^1 = H; PMB = $CH_2C_6H_4OMe$-4; $HOCH_2CH{:}CHSnBu_3$; Z^2 = CHO with $(MeO)_2CHC(:O)CH{:}CH_2$; Z^2 = $CH(OSiMe_3)C(:CH_2)C(:O)CH(OMe)_2$]

Total synthesis of four analogous structural representatives of trioxacarcin DC-45-A2, DC-45-A1, A, D, C7"-epi-C and C were reportedly synthesized by stereoselectivity employing $BF_3.Et_2O$ catalysis (Scheme7 and Figure 4). The mechanism followed ketone-epoxide

opening and glycosylation reactions under gold catalysis. Structural studies of trioxacarcin C were accomplished through synthesis of its C7" epimers.[41]



Scheme 7: Total synthesis of trioxacarcins A and D.[41]

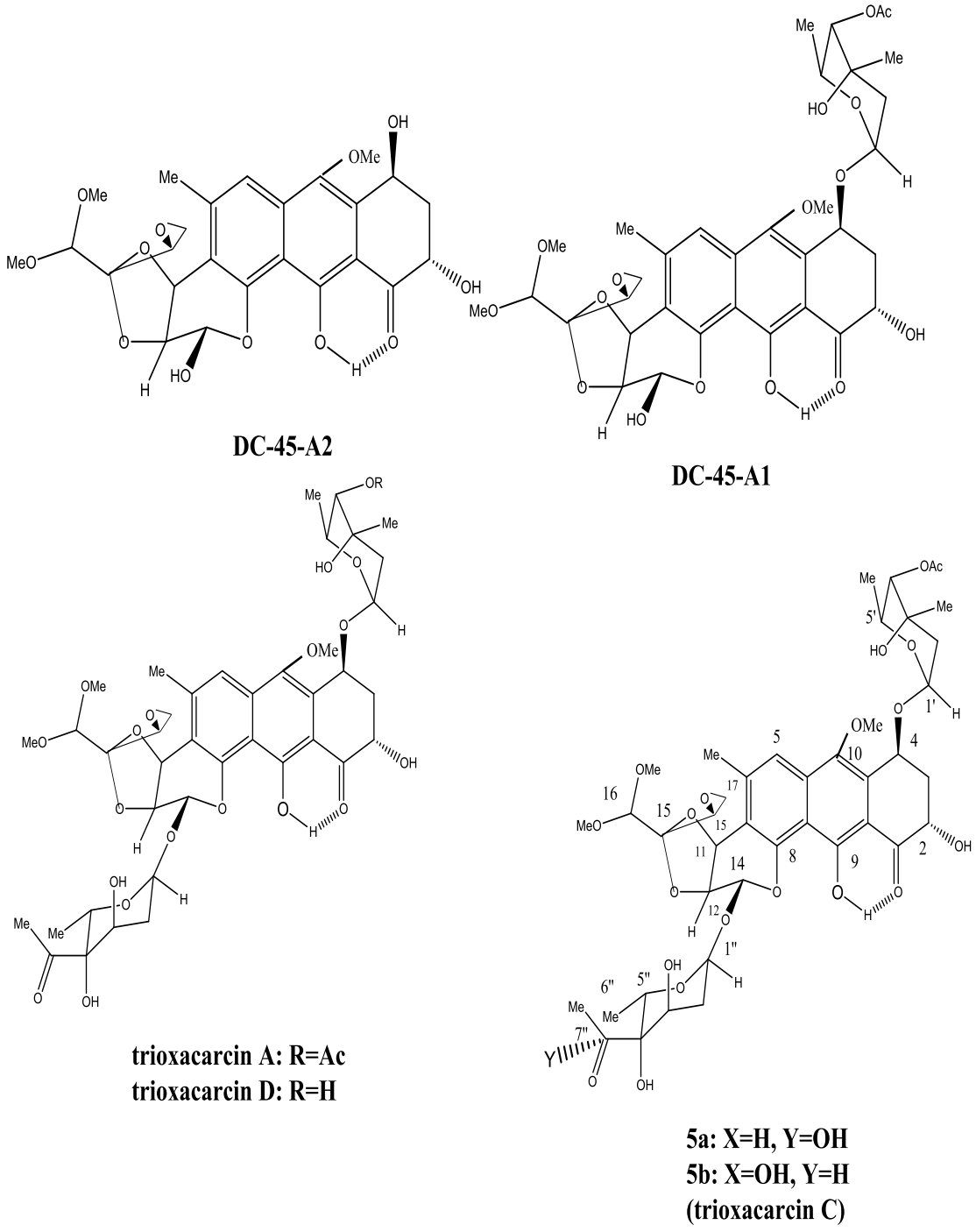
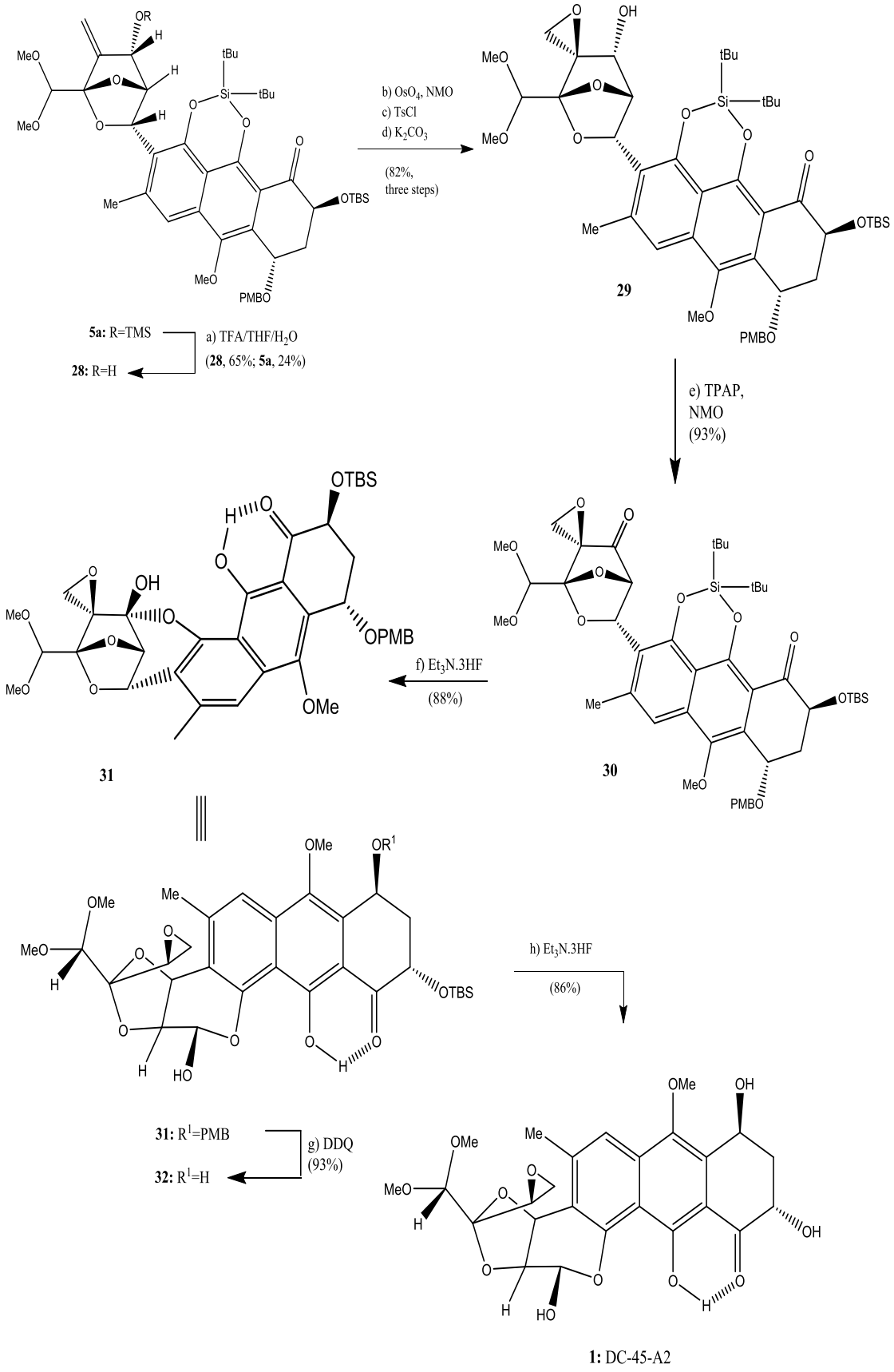


Figure 4: Structures of trioxacarcin DC-45-A2, DC-45-A1, A, D, C.[41]

An enantioselective total synthesis of trioxacarcin DC-45-A2 attributing a novel Lewis acid-induced cascade rearrangement of epoxyketone to forge the polyoxygenated 2,7-dioxabicyclo[2.2.1]heptane core of the molecule has been proposed (Scheme 8 and Figure 5).[42]



Scheme 8: Total synthesis of DC-45-A2.[42]

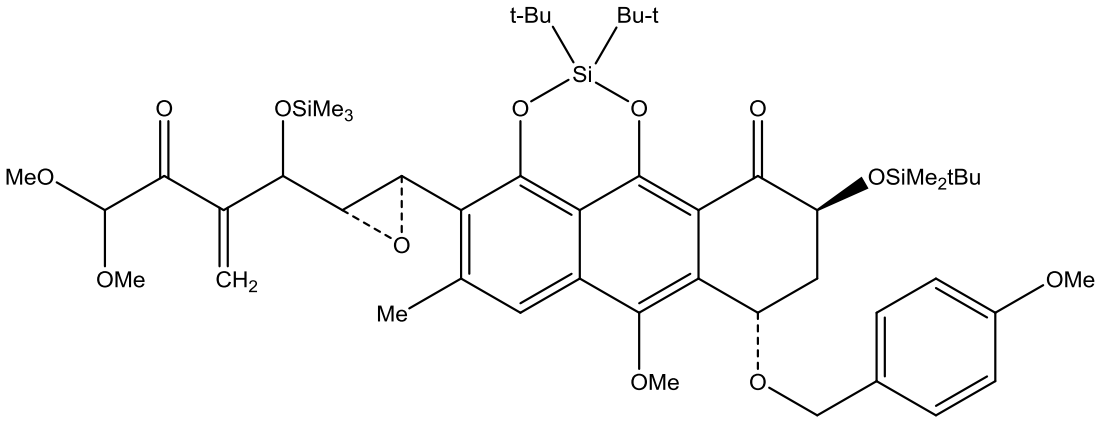
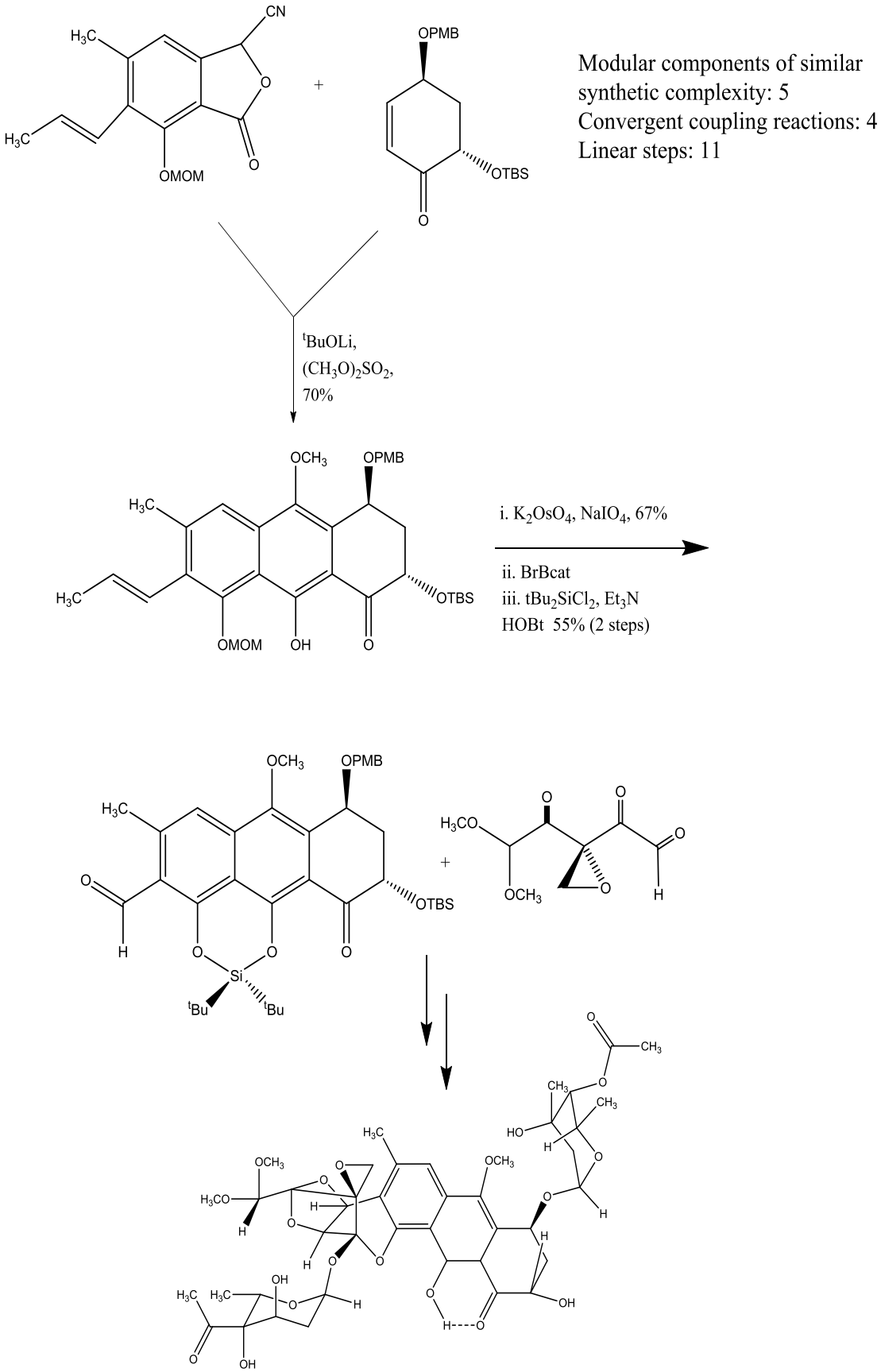


Figure 5: Epoxyketone for the polyoxygenated 2,7-dioxabicyclo[2.2.1] heptane core synthesis.[42]

Fully functionalized and differentially protected aglycon substrates were subjected to glycosylation reactions stereoselectively for the generation of DC-45-A1 and related structural motifs (Scheme 9 and Fig 6). The prominent feature of the investigation is activation and protection of trioxacarcinose A and trioxacarcinose B with an exceptional aspect of operable sequencing of the glycosidic couplings. This sequencing paved way for sprouting of biologically active and diverse series of drug counterparts. In just eleven steps or less, variety of structural equivalents were designed proving efficacious against human cancer cell lines.[43]



Scheme 9: Modular synthesis of trioxacarcin A.[43]

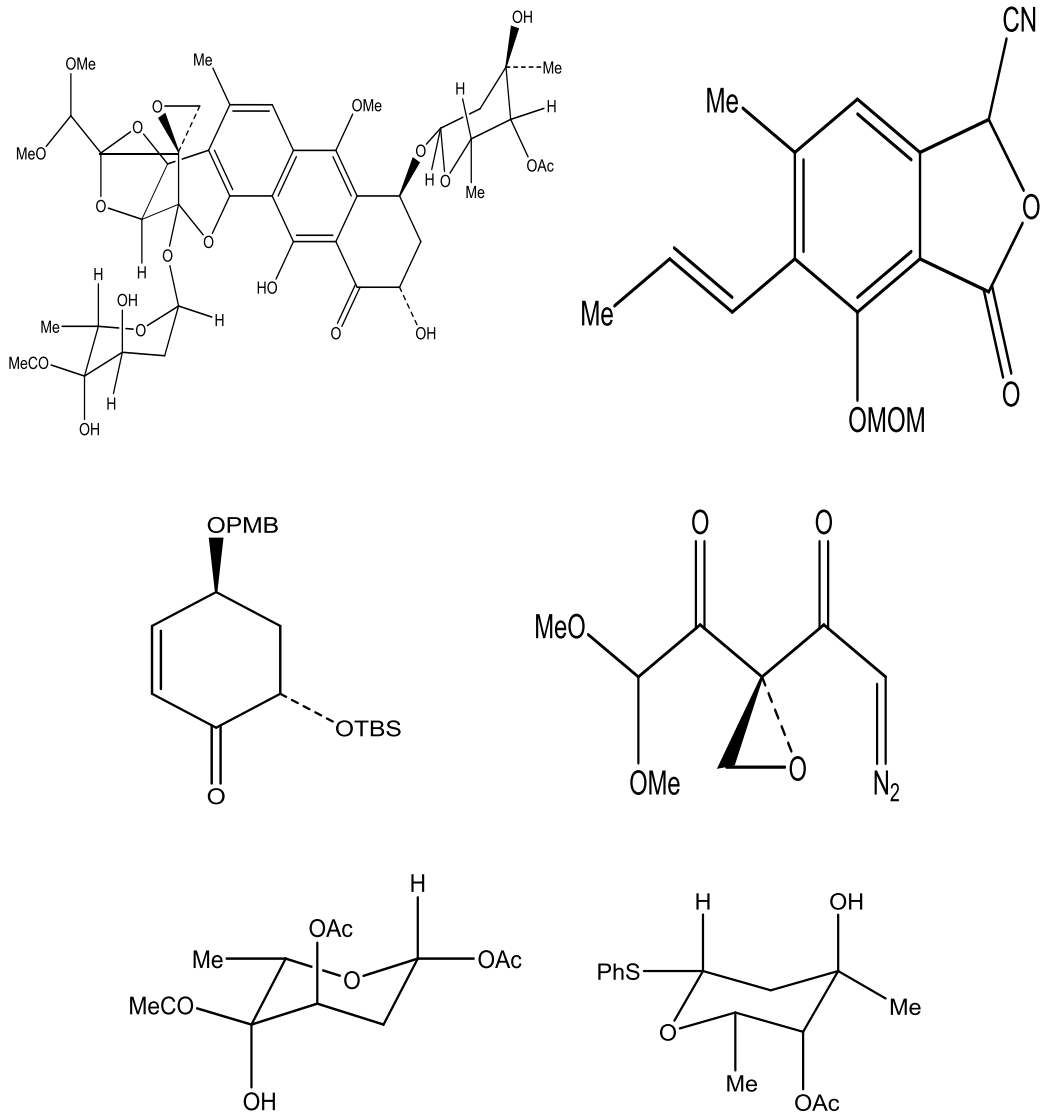
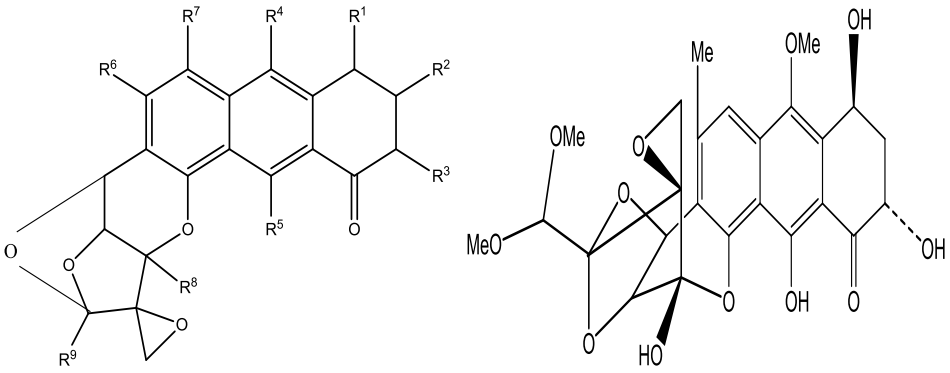


Figure 6: Structures of DC-45-A1 and analogues.[43]

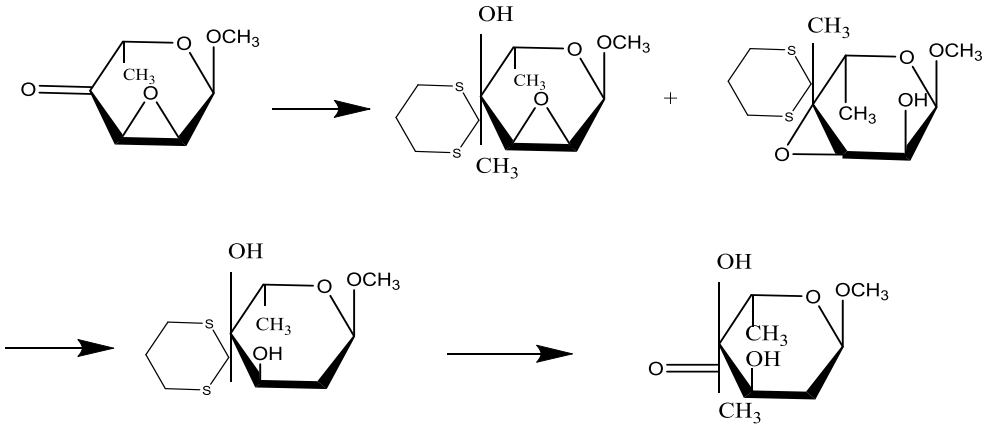
Anti-tumor glycoside trioxacarcins I and II were formulated (R^1-R^7 and R^9=H, halogen, cyclic, acyclic, aryl, heteroaryl; R^8=OR, R=H, sugar residue, protecting group, cyclic or acyclic heteroaliphatic, aryl, heteroaryl; halogen, cyclic, acyclic) (Fig 7). Optional selection of R^1, R^2, R^4, R^6 and R^7 with the intervening carbon atoms yielded optionally substituted cyclic structures. Synthesis of trioxacarcin aglycon II was done *via* cyclization and coupling reaction catalyzed with $Rh_2(OAc)_4$. For structural scrutiny, DNA-alkylation was conducted by analyzing the activity of trioxacarcin II towards 12-mer d (AATTACGTAATT) self-complementary DNA code. The procured compounds exhibited effectiveness against cancer, diabetes, inflammatory complications, autoimmune maladies, bacterial, fungal and malarial infections.[44]



Trioxacarcin I **Trioxacarcin II**

Figure 7: Structures of trioxacarcin I and II.[44]

Both natural and synthetic structural derivatives of trioxacarcins, like DC-45-A2, were procured from a differentially protected precursor which was foregathered using three components in six compendious steps.[45] Seven step reaction scheme led to the designing of methyl α-trioxacarcinoside B from Me 2,3-anhydro-6-deoxy-α-L-ribo-hexopyranosid-4-ulose (Scheme 10). This scaffold is a fascinating carbohydrate part of trioxacarcin A. The yield obtained was around 4.3%.[46]



Scheme 10: Synthesis of methyl α-trioxacarcinoside B.[46]

Methyl glycoside of trioxacarcinose B was contrived from hexopyranoside following seven step synthetic pathway (Fig 8).[47]

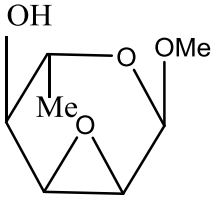


Figure 8: Structure of hexopyranoside.[47]

6. Biological Effectiveness of Trioxacarcins

Trioxacarcins have marked their role as agents for treating infections caused by fungi, parasites, viruses or bacteria. Both natural and synthetic precursors have given favourable results in the treatment of multifarious tumors and inflammatory ailments.[48,49] They have potent antitumor,[50] antimalarial,[51] and antibiotic activity.[52] Extremely high antiplasmodial activity was documented of trioxacarcins A and D comparable to artemisinin, being most active against malarial pathogen.[53,54] Trioxacarcins have manifested their antibacterial activity against a range of bacteria and trioxacarcin D has consequential antitumor activity resembling that of cultured Nereus™ strain of *S. aureoverticillatus*.[55] Producers of trioxacarcins are also known to furnish gutingimycin.[3] This drug family will sprout fruitful results with continuous efforts to dig the hidden bioactivities.

CONCLUSION

Many of the anti-cancer drugs, known to date, are natural by origin. They are either obtained as such from natural sources or are extracted by chemical modification. The trioxacarcins are polyoxygenated, structurally complex DNA alkylating agents which make a rising class of antiproliferative compounds having microbial origin. Though composite, the structure is highly modifiable giving diversified structural equivalents with comparable and remarkable biological potencies like that of parent molecule. Trioxacarcin DC-45-A2 has already exhibited proficiency and can be further undergone evaluation as a biosynthetic precursor to other potential candidates of the same class. Their synergy with other cancer drugs can yield highly functional pharmacologically proficient drug members. Extensive drug modification can reveal hidden medicinal effectiveness of the class, like, hypo and hyperlipidemic, cardioprotective, antiasthmatic etc. potentials. The exploration of brief yet efficient synthetic schemes can lead to healthy yields of members of this supreme class. In present era, trioxacarcins can be rightly considered as master drugs for combating dilemma of cancer and other havoc causing diseases.

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