Application of butane-2,3-diaceptals in the synthesis of optically active natural products

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Introduction
Small and large optically active compounds of natural origin have number of important biological properties, among others they are insecticides, herbicides, antibiotics, and they exhibit antifungal and anticancerous properties. (-)-Pentenomycin I and (-)-epipentenomycin I exhibit activity against various Gram-positive and Gram-negative bacteria. Rapamycin is immunosuppressant. (-)-epipentenomycin I exhibit activity against various Gram-positive antifungal and anticancerous properties. (-)-Pentenomycin I and they are insecticides, herbicides, antibiotics, and they exhibit number of important biological properties, among others.

Synthesis of butane diacetals
Initially for the synthesis of BDAs 2,2,3,3-tetramethoxybutane (TMB) was used, that as a result of transacetalization reaction gives desired BDA derivatives. It has been replaced by 3,3-dimethoxybutan-2-on and then by butanediol. Both reagents with 1,2-diol in reaction catalysed by boron trifluoride (BF₃•Et₂O) or by camphorsulfonic acid (CSA) give BDA.

Steven Ley and coworkers have introduced optically active butane diacetals of glyceraldehyde (R)-1 and (S)-1 as alternative for isomers of glyceraldehyde acetone, which is an useful building block in asymmetric synthesis, but is unstable, which is its serious disadvantage (Fig. 2) [5, 6].

Fig. 2. Butane di acetals (R)-1 and (S)-1 and corresponding enantiomers of glyceraldehyde acetone

In most of syntheses, due to the rapid polymerization, glyceraldehyde acetone must be prepared immediately before reaction. While BDA analogues (R)-1 and (S)-1 are stable compounds and might be stored for up to one year in -20°C. These authors have also presented syntheses of butanediol protected methyl esters of glyceric acid (R)-4 and (2S,5R,6R)-5,6-Dimethoxy-5,6-dimethyl-1,4-dioxanyl-2-carboxylic acid methyl ester (R)-4 is obtained by this method from D-mannitol 2 (Fig. 3). In the first step, it is double-protected by use of butanedione and trimethyl orthoformate in methanol. The product of this reaction undergoes then oxidative cleavage with sodium metaperiodate in a water-methanol solution to hemiacetal, followed by bromine oxidation. Alternatively, oxidative cleavage with sodium metaperiodate in dichloromethane gives aldehyde derivative (R)-1. The opposite enantiomer of aldehyde (S)-1 and ester (S)-4 is obtained from L-ascorbic acid 5 (Fig. 4) blocked in the first step by butanediol and orthoformate to diacetal 6. Its oxidative cleavage with hydrogen peroxide and subsequent esterification by dimethyl sulphate gives methyl ester 7, which is reduced by sodium borohydride to diol 8. The subsequent reactions to obtain aldehyde (S)-1 and ester (S)-4 are the same as for enantiomers described above.
derivatives (\(R\))—purified by vacuum distillation. Likewise, the synthesis of glycolate (\(\text{R}\))—step synthesis of monoesters (\(\text{R}\)) by means of vacuum distillation or crystallization. In the case of multi-
give high yield (70–71%).

Butanedione in the presence of camphorsulfonic acid. These reactions (Fig. 6) from optically active dimethyl tartrates (\(\text{R}\)) and (\(\text{R}\)) obtained
ring of butane diacetal are derivatives (\(\text{R}\)). The second enantiomer is obtained in similar manner as (\(\text{S}\))—11 using aldehyde (\(\text{S}\))—1 as starting compound.

The important building blocks in asymmetric synthesis with rigid
ring of butane diacetal are derivatives (\(\text{R}\))—13 and (\(\text{S}\))—13 obtained
from optically active dimethyl tartrates (\(\text{R}\))—12 and (\(\text{S}\))—12 (Fig. 6) [9, 10]. These compounds are produced in one-step reaction with butanedione in the presence of camphorsulfonic acid. These reactions give high yield (70–71%).

It is such type of reaction that was used in synthesis of (\(\text{R}\))—pentenomycin I isolated from Streptomyces eurythermus and its
diastereoisomer (\(\text{S}\))—epipentenomycin I found in Peziza fungi collected from horse manure (Fig. 8) [12].

The equatorial position of ester group in BDA derivative might be
to change to axial one by acting on enolate ion with alcohol, e.g. tert-
butanol, used as source of protons [5]. The isomer 14 obtained in this
way and transformed into Weinreb amide has been used for synthesis
of C7–C20 fragment of amphidinolides C and F, compounds belonging
to the group of antibiotics (Fig. 8) [13].

The great advantage of BDAs is the ease of their purification
by means of vacuum distillation or crystallization. In the case of multi-
step synthesis of monoesters (\(\text{R}\))—4 and (\(\text{S}\))—4, only final products are
purified by vacuum distillation. Likewise, the synthesis of glycolate
derivatives (\(\text{R}\))—11 and (\(\text{S}\))—11, despite that it is the longest one,
is carried out with crude intermediates. Only final products are
purified using column chromatography. The crystallization is used
for purification of tartrate derivatives (\(\text{R}\))—13 and (\(\text{S}\))—13. These
derivatives are stable and can be stored for a long time. Currently,
they are also the only commercially available products.

Use of butane diacets in natural product synthesis

Due to the rigid structure, BDA molecules might be used in
creating new asymmetric centres or in isomerization of existing ones.
They might be used also as protection of asymmetric functional
groups. Recent years have brought the development of number of
such reactions with use of BDAs, i.e. diastereoselective alkylation,

diastereoselective aldol reaction or addition to aldehyde derivative
of BDA. The creation of new methods based on the application of
BDAs has brought the possibility to use them as optically active
building blocks in asymmetric synthesis of small and large molecular
natural products.

The reaction of monoesters (\(\text{R}\))—4 and (\(\text{S}\))—4 with lithium
disopropylamide (LDA) give enolate ions that react stereoselectively
with various electrophiles (Fig. 7) [11]. The obtained products have
electrophilic fragment located in equatorial position, while the
position of ester group changes to axial one. The direction of this
reaction might be determined by spatial arrangement of substituents
and interactions stabilizing formed lithium enolate with oxygen atom
drom dioxane and methoxy substituent.

Fig. 4. Synthesis of methyl ester (\(\text{R}\))—4 and (\(\text{S}\))—4, 5,6-dimethoxy-5,6-
dimethyl-1,4-dioxanyl-2-carboxylic acid (\(\text{R}\))—4 and (\(\text{S}\))—4, 5,6-
dimethoxy-5,6-dimethyl-1,4-dioxanyl-2-carbaldehyde (\(\text{S}\))—1

Fig. 5. Synthesis of (\(\text{S}\))—5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-
one (\(\text{R}\))—11

Fig. 6. Synthesis of derivatives of tartrate (\(\text{R}\))—13 and (\(\text{S}\))—13

Fig. 7. The general scheme of reaction of butane diacetal monoester
(\(\text{R}\))—4 with various electrophiles

Fig. 8. Examples of natural products obtained from derivatives
of butane diacetal (\(\text{R}\))—1 and (\(\text{S}\))—1 as well as (\(\text{R}\))—4 and (\(\text{S}\))—4
occurs (Fig. 9A) [5]. In these reactions, directing nucleophile is explained by $\beta$-chelation effect, where metal atom is chelated by oxygen atom adjacent to $\beta$ carbon atom of dioxane ring (Fig. 9B). While syn-selectivity occurs for addition of organozinc derivatives to BDAs with aldehyde group in equatorial position (Fig. 9C) [14]. The model proposed by authors to explain the stereochemistry of resulting product, shows $\alpha$-chelation, where oxygen atom adjacent to $\alpha$ carbon atom in relation to carbonyl group chelates metal atom. These reactions have been used for synthesis of polyoxamic acid derivatives (Fig. 8).

Another building block used in the synthesis of natural products are glycolate derivatives ($R$)-11 and ($S$)-11. From these ketones, enolate anions are generated using lithium hexamethyldisilazane (LiHMDS). The reaction of enolate anions with halogen derivatives leads to formation of ketone derivatives with substituent at $\alpha$ carbon atom in equatorial position (Fig. 10A) [15]. The direction of electrophile approach in this reaction is explained by steric hindrance (Fig. 11B). The steric hindrance explains also stereochemistry of aldol reaction with enolate anion formed from ketone (Fig. 10A and 10C) [16]. Both reactions have been used in the synthesis of herbarum II that is produced by fungi Phoma herbarium (Fig. 11) [17]. The analogous synthetic strategy has been applied for synthesis of rapamycin and ceramide (Fig. 11) [18,19].

The biggest importance in the field of natural compound synthesis among BDAs is attributed to tartaric acid derivatives ($R$, $R$)-13 and ($S$, $S$)-13. These diesters have been used for synthesis of 10-hydroxyasimicin and antascomicin B (Fig. 12) [20,21].

Fig. 9. A) anti-selectivity of addition reaction to aldehyde 15; B) proposed chelating models of derivative of butane diacetal with aldehyde group in equatorial or axial position; C) syn-selectivity of addition reaction to aldehyde ($R$)-1

Fig. 10. A) Alkylation reaction and aldol reaction ($R$)-11; B) electrophile approach in stereoreactive reaction of glycolate alkylation ($R$)-11; C) model of aldol reaction with ketone ($R$)-11

Fig. 11. Examples of natural products obtained from butane diacetal derivatives ($R$)-11 and ($S$)-11

Fig. 12. Examples of natural products obtained from butane diacetals ($R$, $R$)-13 and ($S$, $S$)-13

The desymmetrization of placed equatorially ester groups of these BDA derivatives is a very important reaction [10]. The reduction of obtained ester, where one ester group is in equatorial position and the other in axial one, gives diol 17 (Fig. 13). Both hydroxyl groups have different vicinity, therefore they are chemically distinguishable and one of them might be blocked selectively [22]. The reaction of diol 17 with one equivalent of tert-butylidimethylsilyl chloride in the presence of imidazole in tetrahydrofuran leads to monosilyl products 18 and 19 with high preference toward silyl ether 18. Whereas, if the hydroxyl group is deprotonated previously by sodium hydride, axial hydroxyl group is silylated selectively (Fig. 13). The selective blocking of hydroxyl groups makes it possible to use these derivatives as building blocks in the synthesis of (+)-aspicilin, muricatetrocin C and (+)-didemniserinolipid B (Fig. 14) [10, 23, 24].

Fig. 13. Reaction of diester isomerisation ($R,R$)-13 to ($R,S$)-13 and methods for selective blocking of hydroxyl groups in diol 17
It is worth noting that there are several methods for unblocking butane diacetal. The most important reaction in this group of compounds is the use of mixture of trifluoroacetic acid and water with 9:1 ratio [25]. This deprotection might be also carried out catalytically using complex of boron trifluoride-diethyl ether with 1,2-ethanedithiol or with 9:1 ratio [25]. The deprotection might also be carried out by using 1:1 mixture of trifluoroacetic acid and water.

**Literature**