TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl) an Important Reagent in Alcohol Oxidation and its Application in Synthesis of Natural Products

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Abstract: The oxidation of alcohols is a fundamental transformation in organic synthesis and a large number of reagents have been developed for this purpose. In spite of the different methodologies, the modern organic synthesis still requires more efficient oxidant reagents. In this context, TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl) has emerged as the chosen reagent. The aim of this review is to highlight the TEMPO oxidation as a very important procedure in the synthesis of natural products accomplished between 2000 and 2004.

Keywords: Oxidation, alcohol, TEMPO.

INTRODUCTION

Oxidation is a fundamental transformation in organic synthesis and a large number of reagents have been developed for this purpose. In the case of the alcohol oxidations, many reagents are known to obtain aldehydes, ketones and carboxylic acids in mild conditions and high yields, such as Swern reaction [1], Dess-Martin periodinane [2], manganese dioxide [3] and tetrapropylammonium perruthenate [4]. Although these and other reagents have been successfully employed, the chemo and regioselective oxidation of one alcohol group in the presence of others is generally difficult to achieve. Due to this and other problems, the modern organic synthesis still demands more efficient, fast, selectivity new oxidant reagents of alcohols, made in mild and catalytic conditions and it can tolerate sensitive functional groups such as neighboring chiral centers and electron-rich aromatic rings. In this context, the TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl) (Fig. **1**) has emerged as the chosen reagent and due to its the efficacy, different methodologies using TEMPO-catalyzed oxidation of alcohols have been reported. The aim of this review is to highlight the TEMPO as an important oxidant reagent in the synthesis of natural products accomplished between 2000 and 2004.

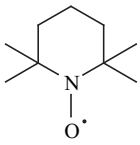

Fig. (1).

A BRIEF HISTORY OF THE TEMPO AS AN OXIDANT REAGENT

The nitroxyl radical is a class of compounds that possesses the *N, N*-disubstituted NO-group with one unpaired electron [5] with different applications, such as biological field [5], polymer stabilizers [6] and trapping agents [7]. In the case of the nitroxyl TEMPO, their radical could be considered stable, which means the radical is unreactive to air and moisture resulting in easily handled and stored compounds without precautions that represent an advantage over other oxidants. The TEMPO was first prepared by Ledebev and Kazarnovskii in 1960 [8] and was the first non-conjugate nitroxyl radical to be synthesized, although, the application of nitroxyl radical as oxidant was described for the first time by Goulev and co-workers in 1965 [9]. Despite the fact that different studies with stoichiometric amounts of nitroxyl radical have been achieved by Endo and co-workers [10], nowadays, several methodologies have been described mainly with focus on nitroxyl radicals-catalyzed oxidation. The TEMPO-catalyzed oxidation of alcohols was reported for the first time by Cella [11] and co-workers and Ganem [12] in 1975, when both used 3-chloroperbenzoic acid as the regenerating oxidant. After that, many procedures have been elaborated by several groups with different oxidants that are well described in Bekkum and co-workers review [13] and other articles [14]. The selective oxidation of primary alcohols in the presence of secondary ones using nitroxyl radicals have been described by Semmelhack and co-workers in 1983 [15]. In the case of the application of nitroxyl radicals as oxidant in total synthesis, it was first described by Wovkulich and co-workers in 1993 in the synthesis of the natural product 1233A [16].

The mechanism of the nitroxyl radical as an oxidant of alcohols has been intensively studied by different groups, such as Goulev [9], Cella [11], Ganem [12], Bobbit [17], Semmelhack [15,18] and Bekkum group [19]. Basically, the nitroxyl radicals can be oxidized to furnish the respective oxoammonium salt **1** or reduced to form a hydroxylamine **2** (Fig. **2**) [20,17a]. The catalytic cycle of TEMPO oxidation is based on the generation *in situ* of oxoammonium salt **1** by an oxidant, followed by the reaction with the respective alcohol that produced the alcohol oxidation and the hydroxylamine **2** that is regenerated in oxoammonium salt **1** by an oxidant that continues the catalytic cycle (Fig. **3**) [13]. The mechanism of the adduct formed between oxoammonium salt **1** and the alcohol in question can be proposed by a cyclic or acyclic concerted elimination (Fig.

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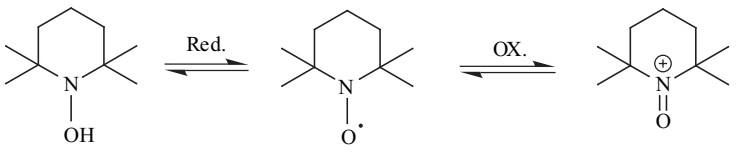


Fig. (2).

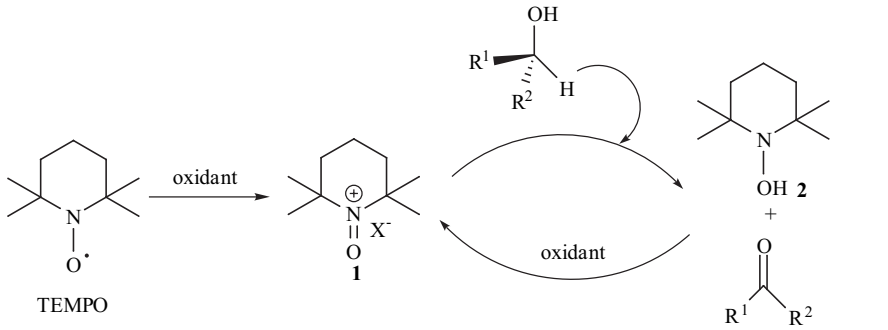


Fig. (3).

4) [17b,18]. In the case of the oxidant used to produce oxoammonium salt **1**, there is a large number of the reagents used such as *m*-chloroperbenzoic acid [11], sodium hypochlorite (NaClO) [21], sodium chlorite ($NaClO_2$) [22], *ter*-butyl hypochlorite (tBuOCl) [23], sodium bromite ($NaBrO_2$) [24], oxone (potassium monopersulfate $2KHSO_5.KHSO_4.K_2SO_4$) [25], *N*-chlorosuccinimide [26], [bis-(acetoxy)-iodo]benzene [27], various peroxides in the presence of a silver cocatalyst [28], oxygen in combination with high-valent metal salts [29] and electrooxidation [15,17d,30].

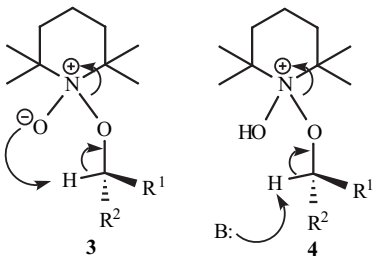
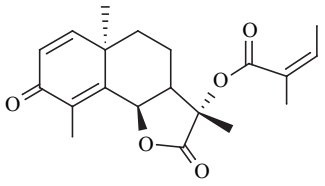


Fig. (4).

APPLICATION OF TEMPO IN THE SYNTHESIS OF NATURAL PRODUCTS

Decipienin A

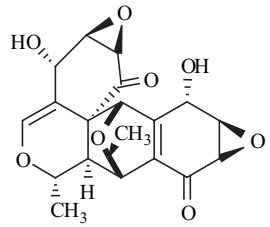


Decipienin A

Fig. (5).

An important problem solved by using TEMPO as an oxidant was in the enantioselective synthesis of Decipienin A (Fig. **5**), performed by Massanet and co-workers (Scheme **1**) [31]. This sesquiterpene lactone was isolated from *Melanoselinum decipiens* on the archipelago of Madeira, Portugal [32] and belongs to the class of eudesmanolides [33]. This class is largely found in nature in diverse groups, with a wide range of biological activity, such as antiulcer, cardiotonic, antitumor and neurotoxic activities [34]. The oxidation of the glycol **6** was the key step of Massanet synthesis, which under oxidative process, provided the ketone **7** and not the desired α-hydroxy-γ-lactone **8** due to the easily cleaved 1,2-diol group that required extremely mild conditions. In order to solve this problem, the oxidation was carried out by using TEMPO in the presence of a catalytic amount of NaClO and stoichiometric amount of $NaClO_2$, which provided the desired intermediate **8** in 57% yield in mild conditions.

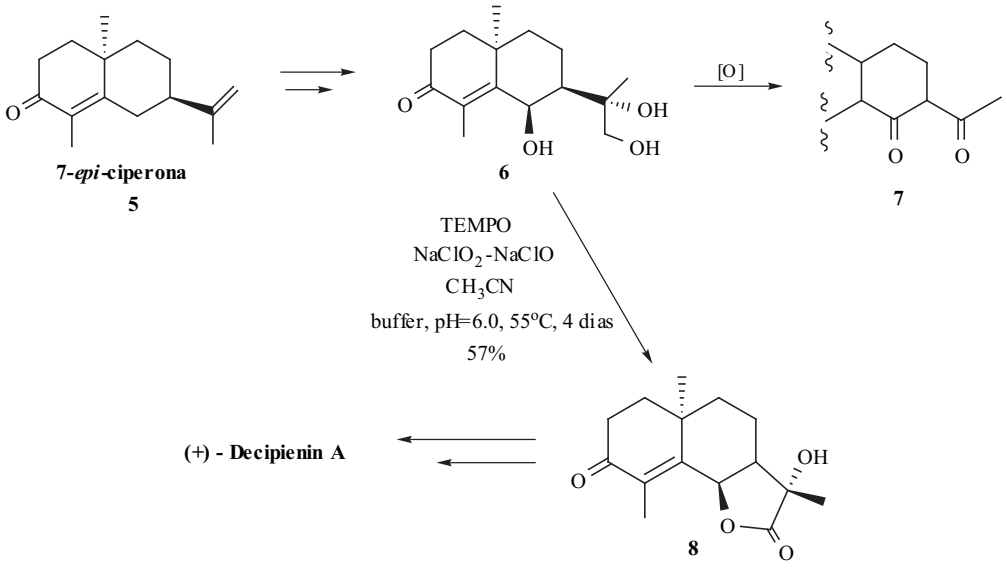
Epoxyquinol A



(+) - Epoxyquinol A

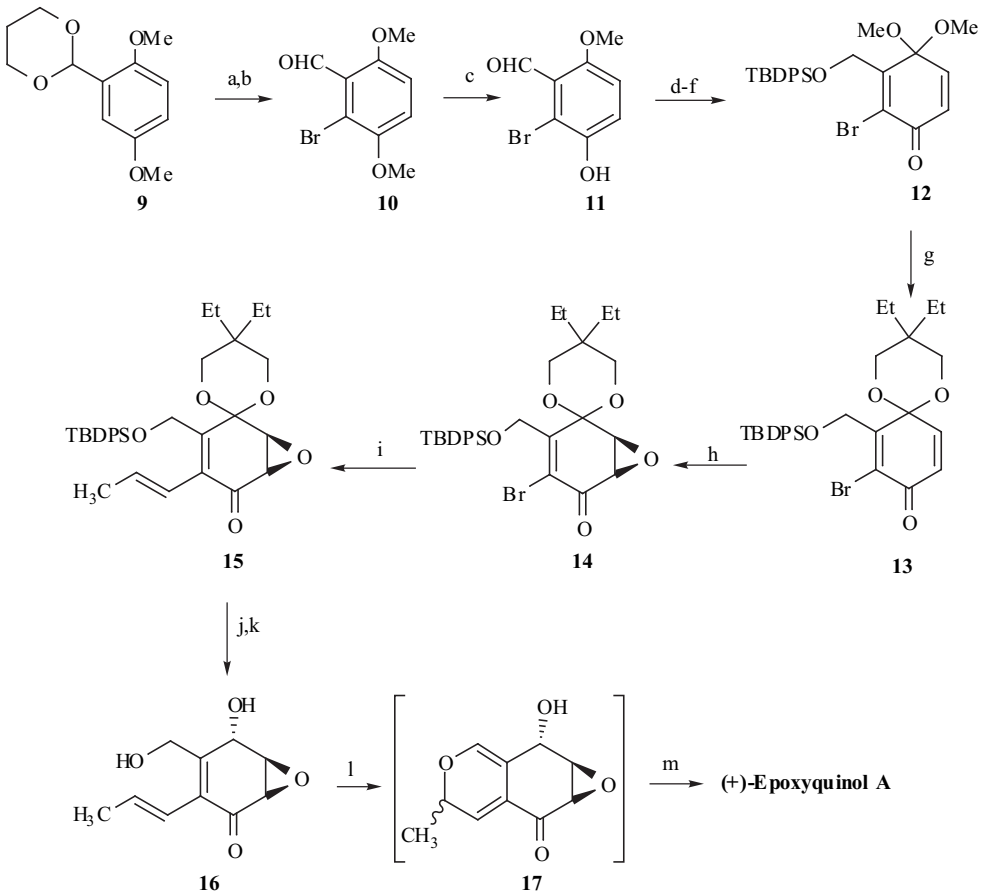
Fig. (6).

Porco Jr. and co-workers have achieved the asymmetric synthesis of the natural product (+)-epoxyquinoid (Fig. **6** and Scheme **2**), as well as others polyketide natural products [35]. This pentaketide dimmer was isolated from an uncharacterized fungus by Osada and co-workers and demonstrated potent antiangiogenic activity [36].



Scheme 1.

Angiogenesis is a new blood vessel formation and is supposed to be a very important requisite for tumor growth and metastasis. In their synthesis (Scheme **2**), the 1,3-dioxane derivative **9** was lithiated, followed by bromination and acidic hydrolysis to produce the aldehyde **10**. After that, the regioselective demethylation furnished the phenol **11** in



Scheme 2.

a) (i) BuLi 3:1, hexane/benzene, -25 ^{0}C, 10h (ii) $BrCF_2CF_2Br$, THF, 0.5 h, 74%; b) 13 M HCl, THF, 10 min 100%; c) H_2SO_4, 70^{0}C, 14h, 52%; d) $NaBH_4$, EtOH, 0.5h; e) TBDSPCl, imidazole, DMF, 2.5h 97% (two steps); f) $PhI(OAc)_2$, MeOH, rt, 30 min, 84%; g) 2,2-diethyl-1,3-propanediol, PPTS, benzene 70^{0}C, 80 min, 89%; h) NaHMDS, L-DIPT, Ph_3CO_2H, $PhCH_3$ (20% THF), -50^{0}C, 30h, 97%, 96% ee; i) (*E*)-tributyl-1-propenyl-stannane, Pd_2dba_3, $AsPh_3$, $PhCH_3$, 100^{0}C, 2h, 98%; j) 48% HF, CH_3CN, rt, 1h, 84%; k) DIBAL-H, THF, -78^{0}C, 10 min., 72%; l) O_2 (1 atm), TEMPO, CuCl, DMF, 3h; m) 40% MeOH-H_2O, 10h, (+)-Epoxyquinol A (55%).

52% yield followed by oxidation, borohydride reduction and silyl protection, which afforded the intermediate **12**. The monoacetal **13** was furnished by transketalization of **12** with 2,2-diethyl-1,3-propanediol in 89% yield, which after Sharples epoxidation produced the compound **14** in 97% with 96%ee. The intermediate **14** was accomplished by Stille coupling in quantitative yield, followed by the cyclic acetal, silyl group and the regio and stereoselective reduction using the Kiyooka´s conditions (2 equiv. of DIBAL-H, THF, -78ºC) to furnished the compound **16** in 72% yield as the major diastereomer. Finally, the synthesis of the (+)-epoxyquinol A was accomplished by using TEMPO that was the best oxidation method evaluated. The Semmelhack conditions (CuCl (cat.), O_2, TEMPO, DMF) furnished the intermediate **17** and did not produce oxidation of the secondary allylic alcohol or overoxidation to the carboxylic acid. After oxidation, the crude product was carried out in 40% aqueous methanol to furnish the *endo* dimmer ((+)-epoxyquinol A) in 55% yield.

Eupenoxide, Phomoxide and Cycloepoxydon

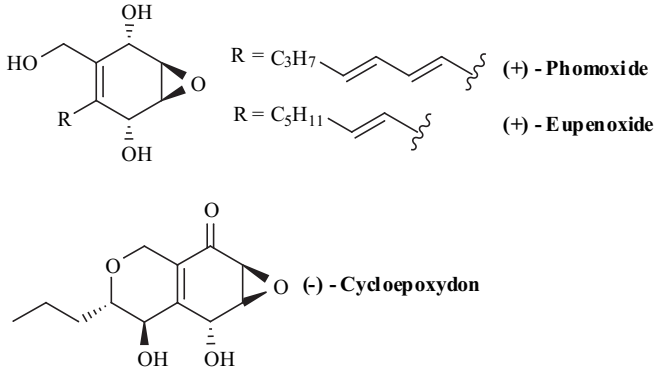
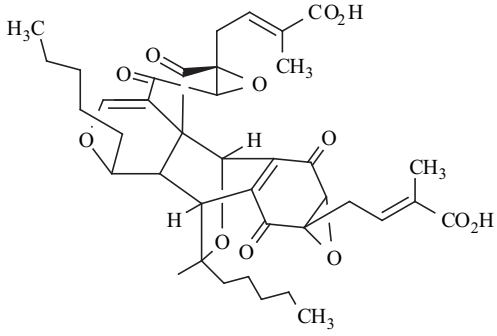


Fig. (7).

Base on other strategies, Metha and his group have employed similar intermediates as described above to synthesize other polyketide natural products, such as (+)-eupenoxide [37], (+)-phomoxide [37], (-)-cycloepoxydon [38] (Fig. **7**) and torreyanic acid [39] (Fig. **8**). In all these syntheses, TEMPO was chosen as an oxidant in some steps due to the best yields, chemoselectivity and mild conditions. For example, Mehta and Roy had made the enantioselective total synthesis of the natural polyketide antibiotic (+)-eupenoxide and (+)-phomoxide (Scheme **3**), as well as the revision of structures and assignment of absolute configuration [37]. The eupenoxide was isolated and synthesized for the first time by Duke and Richards [40]. Twenty years later, in 2003, Liu, Jensen and Fenical published the isolation and characterization of eupenoxide and phomoxide from the fermentation broth of a marine derived fungus of the genus *Phoma* (strain CNC-651) [41]. The Meth and Roy synthesis of these polyoxygenated cyclohexenoid natural products was based on the intermediate **20** that was prepared by enzymatic desymmetrization of **19** in 99% ee and 84% yield which, in turn, had been prepared from the Diels-Alder adduct **18** of cyclopentadiene and benzoquinone. The regio and stereoselectivity reduction was achieved by using DIBAL-H that furnished the enone (-) **22** in 74% yield. The influence of the epoxide group can also be seen in the Luche reduction of (-) **22** that produced the *cis*-1,4-cyclohexenediol (-) **23** in 85% yield. The chemoselective oxidation of (-) **23** was achieved in mild conditions by using the TEMPO that furnished the aldehyde **24** in 55% yield. This intermediate was also used to synthesize the natural product (-) cycloepoxydon [38] (Fig. **8**) extracted from a *deuteromycete* strain that has been shown to inhibit activation of NF-*k*B, a transcription factor responsible for the regulation of the expression of different cellular genes involved in the immune and inflammatory response and apoptosis [42].

Torreyanic Acid

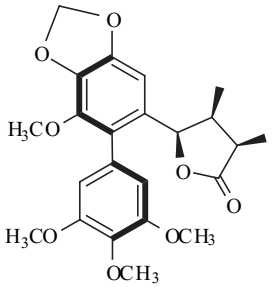


(±)**Torreyanic acid**

Fig. (8).

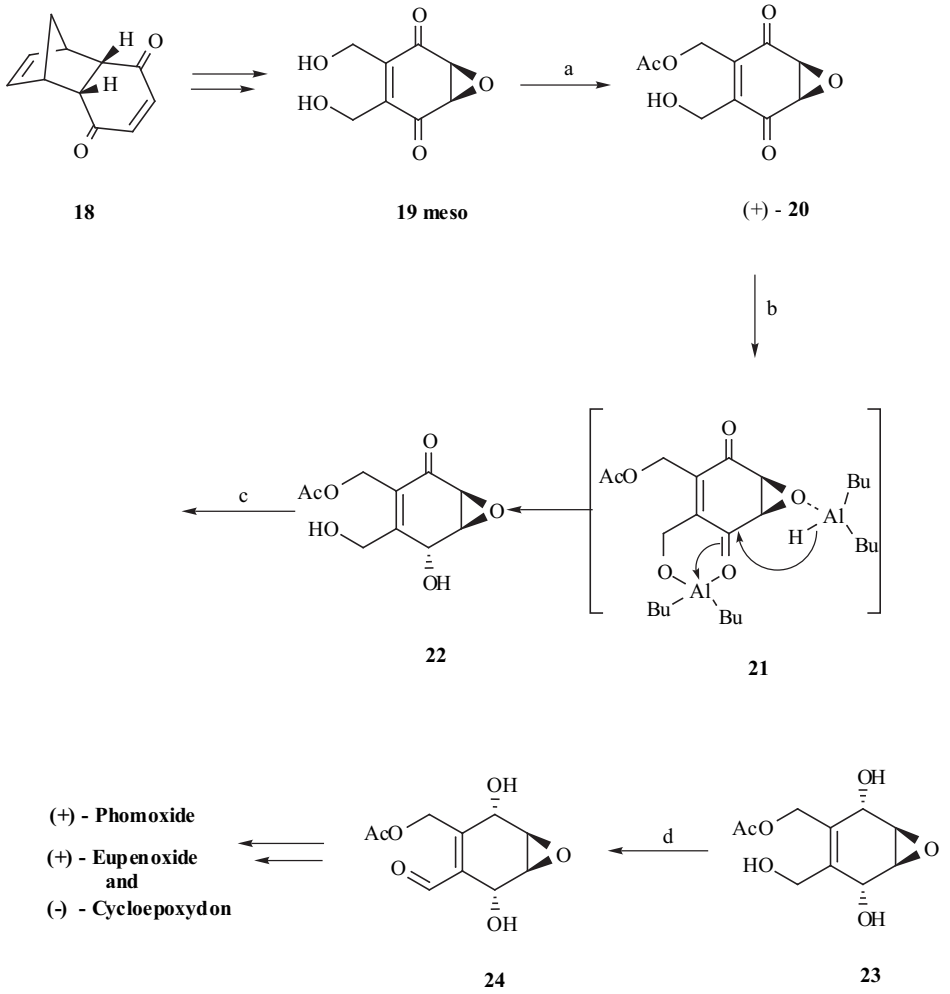
Another example of the TEMPO application in total synthesis made by Metha and his group was in the synthesis of the dimeric natural product torreyanic acid (Fig. **8**) [39,43]. This natural product was isolated and elucidated in 1996 by Lee and co-workers, who extracted it from an endophytic fungus *Pestalotiopsis microspora* with selective cytotoxicity against cancer cell lines [44]. This synthesis (Scheme **4**) is based on the 2-ally-*p*-benzoquinone **25** as a starting material which, after Diels-Alder reaction with cyclopentadiene in quantitative yield, led to the tricyclic endo-adduct **26**, followed by stereo and chemoselective epoxidation that afforded only the epoxide **27** in 92% yield. The stereo and regioselective hydroxymethylation, protection of hydroxy group, *exo*-stereoselective hydroxymethylation and finally, regio and stereoselective $NaBH_4$ reduction led to the *endo*-alcohol **31** as the only product. The key intermediate **33** was obtained after retro-Diels-Alder and chemoselective oxidation of the primary hydroxyl group with the TEMPO and, after thirteen steps, the racemic torreyanic acid was successfully obtained (Scheme **4**).

Eupomatilones 4



Eupomatilone 4

Fig. (9).



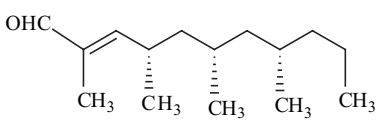
Scheme 3.

a) Lípase (Amano) vinyl acetate, THF, 0ºC, 84%, 99ee; b) DIBAL-H (1M), THF, 78ºC, 74%; c) $NBH_4.CeCl_3.7H_2O$, MeOH, 0ºC, 85%; d) TEMPO, O_2, CuCl, DMF, 55%.

Coleman and Gurrala [45] made a convergent and diastereocontrolled total synthesis of the eupomatilones 4 (Fig. **9**). This natural product was isolated in 1991 by Carroll and Taylor from the indigenous Australian shrub *Eupomatia bennetii* [46]. The synthesis (Scheme **5**) was based on the aldehyde **34** and, after regioselective bromination, methylation, coupling and alcohol protection, led to the fragment **36**. This fragment was coupled with the aryllithium **38**, previously prepared from aryl bromide **37**, which provided the intermediate **39** in 51% yield. The hydroboration to produce the primary alcohol **40** was furnished in quantitative yield, with complete control of diastereoselectivity. Finally, the eupomatilone 4 was obtained after deprotection of the silyl group and chemoselective oxidation of the primary alcohol in mild condition with TEMPO followed by lactonization, which furnished the desired eupomatilone 4 in 92% yield (two steps).

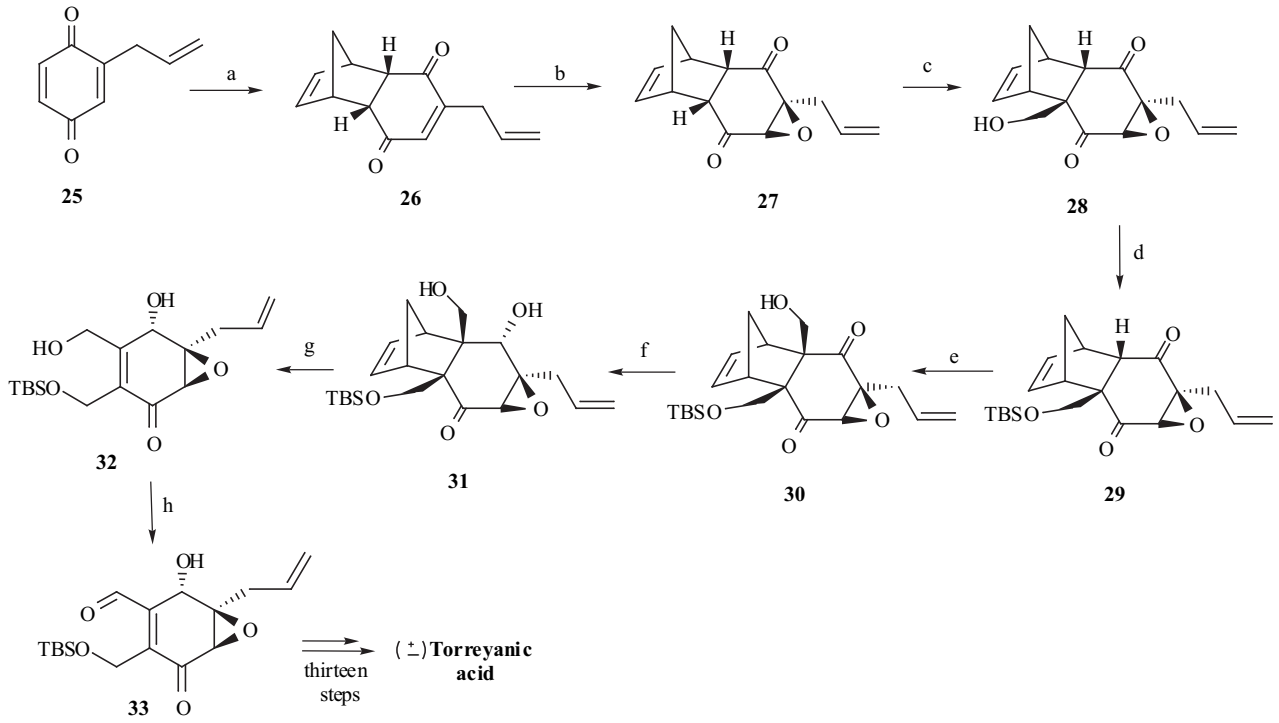
Siphonarienal

The natural product siphonarienal (Fig. **10**) [47] is a member of a class produced by mollusks of the genus *Siphonaria* and the large majority of these compounds are active against Gram-positive bacteria, yeast and different human cancer cell lines [48]. The asymmetric synthesis of siphonarienal made by Calter and co-workers (Scheme **6**) have used the anhydride **40** as starting material to furnish the fragment **44** after three steps. After protection and reduction reactions, this fragment led to the intermediate **45** followed by iodobenzene diacetate/TEMPO system that allowed the aldehyde **46** in high yield. Finally, the siphonarienal synthesis was accomplished in there steps: Wittig homologation, reduction and oxidation (Scheme **6**).



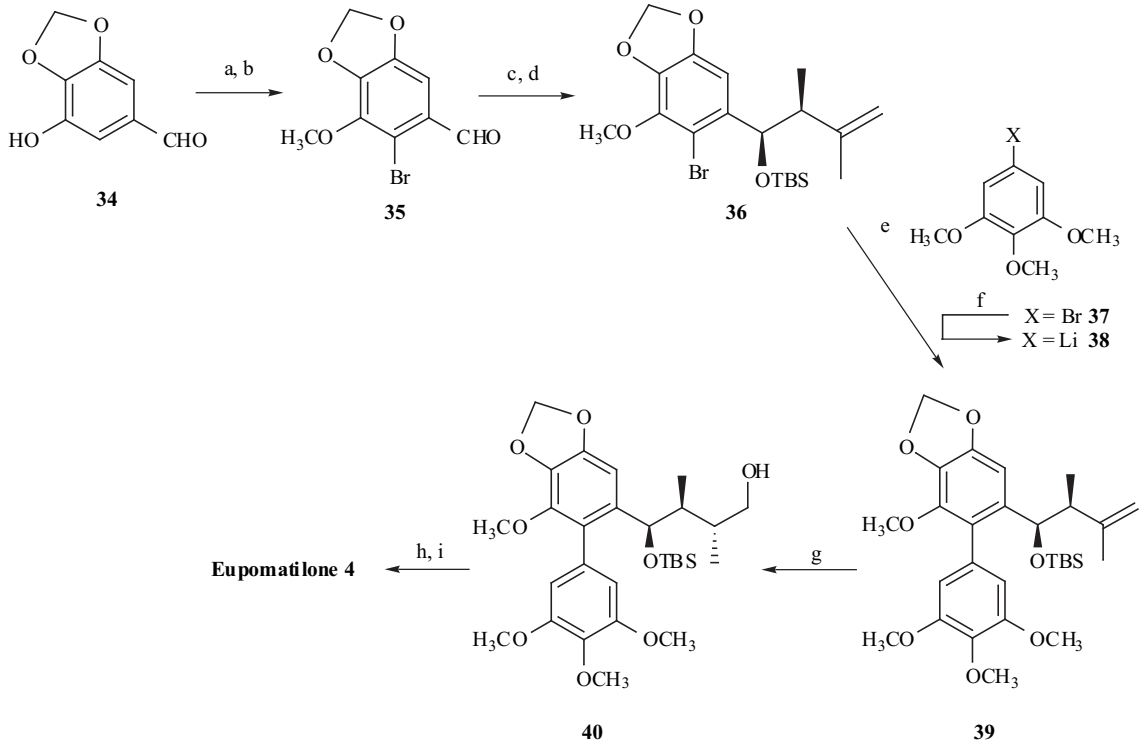
Siphonarienal

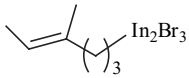
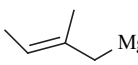
Fig. (10).

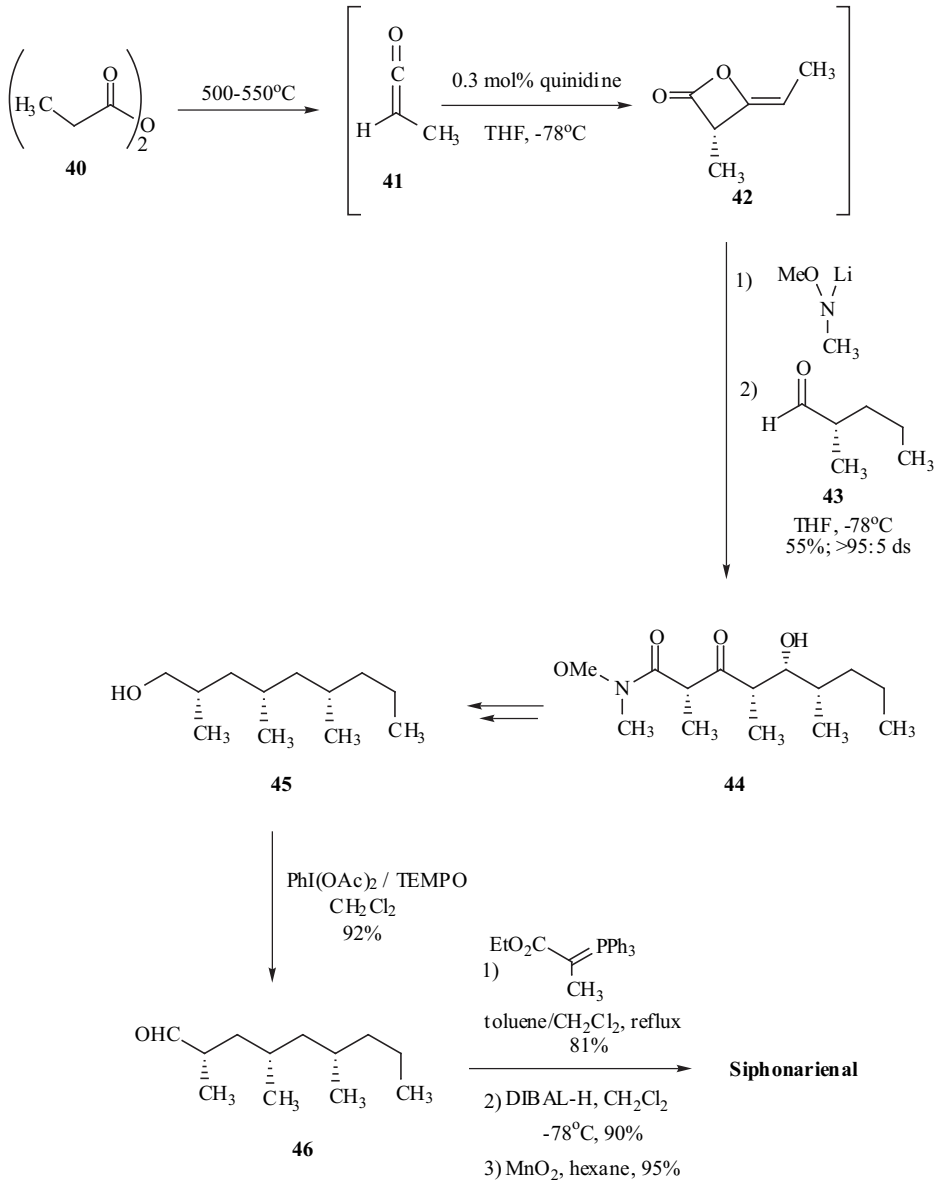


Scheme 4.

a) cyclopentadiene, methanol, 0^0C, 98%; b) 10% Na_2CO_3, 30% H_2O_2, acetone, 0^0C, 92%; c) 35%, formalin, DBU, THF, 0^0C, 30 min. 95%; d) TBDSCl, imidazole, DMAP, DMF, 0^0C, 90%; e) 35%, formalin, DBU, THF, rt, 36 h. 95%; f) $NaBH_4$, MeOH, -5^0C, 84%; g) diphenyl ether, 220^0C, 96%; h) TEMPO, O_2, CuCl, DMF, 90%.



Scheme 5. a) NBS, dioxane, 15°C, 97%; b) $(CH_3)_2SO_4$, K_2CO_3, 85%; c)  In_2Br_3 92%; (95:5); in the case of  MgBr 91%; (1:1); d) *t*-BuMe$_2$SiOTf, 2,6-lutidine, CH_2Cl_2, -78°C, 20´, 98% e) *t*-BuLi , MeTHF , - 78°C, then CuCN, MeTH , - 40°C and after **38** (-125°C , 3 h.) 51%; f) *t*-BuLi MeTHF , - 78°C ; g) 9-BBN , THF , 0 - 25°C, 12 h then H_2O_2 , NaOH , 98% ; h) n-Bu_4NF , 94%; i) TEMPO, 98%



Scheme 6.

Hyaluron (Hyaluronic Acid)

Hyaluron (hyaluronic acid) [-β-Sodium glucuronic-(1→ 3)-β-N-acetyl glucosamine-(1→ 4)-]$_n$ (Fig. **11**) is a polysaccharide of the class glycosaminoglycans made up of repeating disaccharide units, which can exist in molecular weights above 1x10^7 Da [49]. This natural product is found in all tissues and body fluids in every mammalian species as well as in microorganisms. In the last years, much attention has been paid to the hyaluronan and its derivatives as an important new material for a diverse range of medical and biomaterial applications. For example, studies have focused on hyaluronan in ophthalmology, tissue repair and reconstruction, drug delivery systems, anti-cancer treatments, joint recovery and engineering [50].

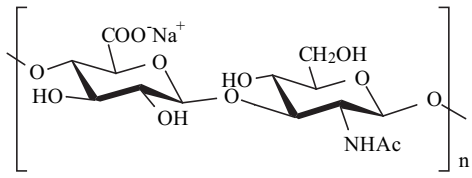
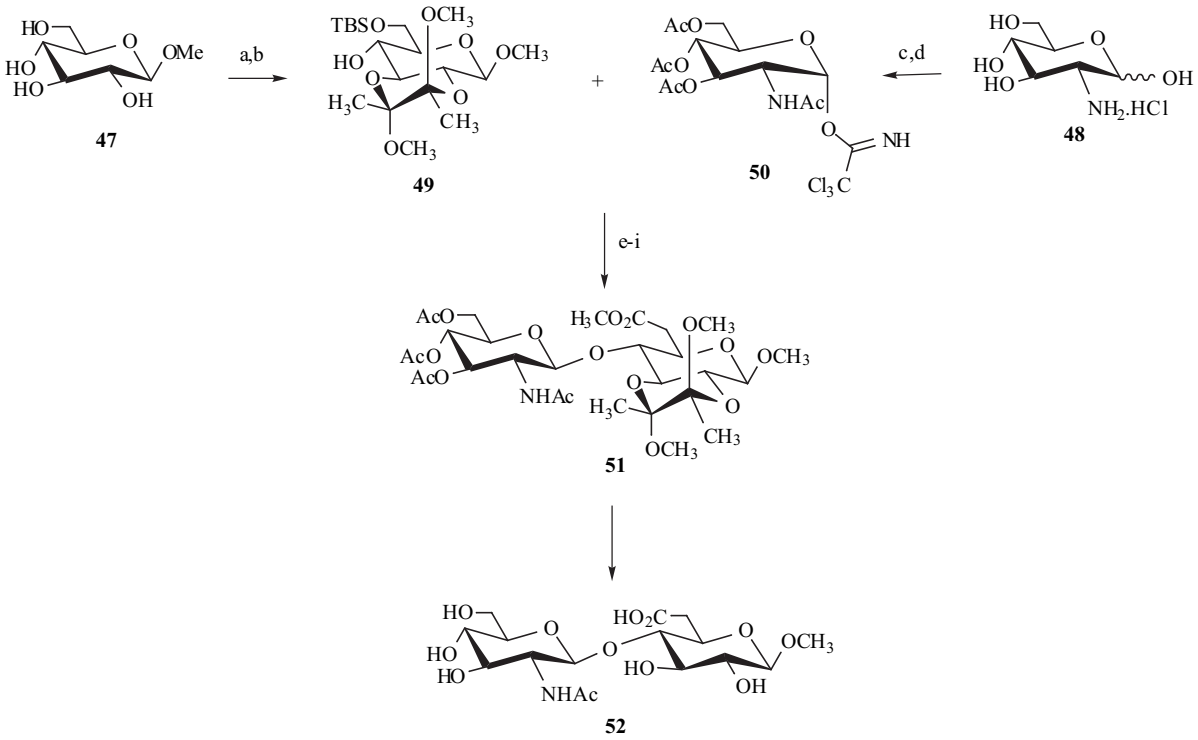


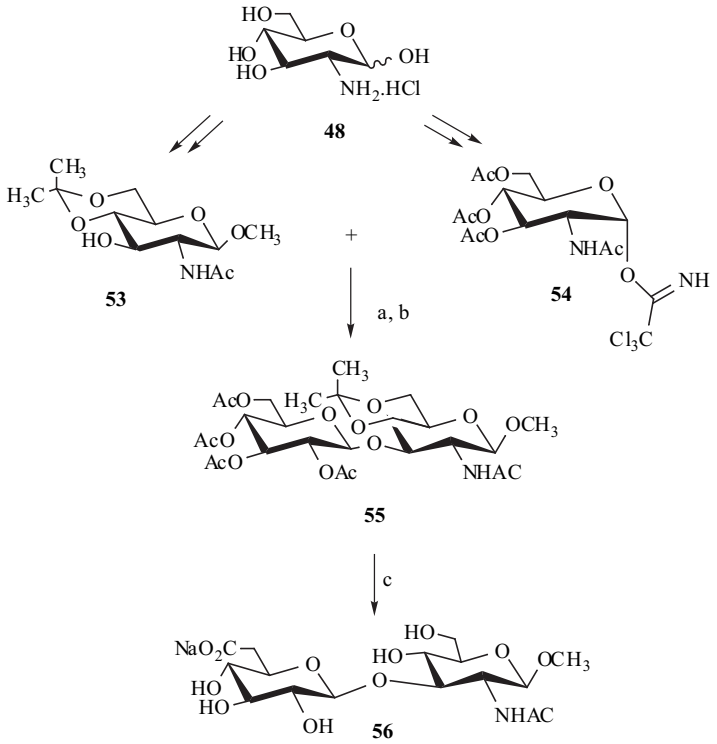
Fig. (11).

Petillo and co-workers described the gram-scale synthesis of (1→ 3) and (1→ 4) linked hyaluronan disaccharides (Scheme **7**). For the construction of the (1→ 4) linked hyaluronan disaccharide, the methyl β-D-glucopyranoside **47** and glucosamine hydrochloride **48** furnished the intermediates **49** and **50** in two and four steps respectively. The glycosidation reaction of these intermediates furnished the protected disaccharide, which after deprotection of the silyl group, the desired primary alcohol was transformed in carboxylic acid by using the TEMPO with NaOCl, which after methylation produced the intermediate **51**. Finally, the (1→ 4) linked hyaluronan disaccharide **52** was prepared after five steps.



Scheme 7.

a) 2,2,3,3-tetramethoxybutane, trimethylorthoformate, 10-camphorsulfonic acid, MeOH, 60ºC, 19h, 56%; b) TBSCl, py, 25ºC, 24h, 67%; c) (i) $ClCO_2CH_3$, $NaHCO_3$, 1:1 $CHCl_3$-H_2O, 25ºC, 1h; (ii) Ac_2O, py, 25ºC, 12h, 92%; d) (i) $NH_2NH_2.HOAc$, DMF, 25ºC, 4h; (ii) CCl_3CN, DBU, CH_2Cl_2, 25ºC, 12h, 61%; e) (i) TMSOTf, 4A molecular sieves, CH_2Cl_2, -30ºC, 10h; (ii) TBAF, THF, 0ºC, 12h, 81%; f) (i) TEMPO, NaBr, TBABr, 5%, $NaHCO_3$, 6:1 CH_2Cl_2-H_2O, 0ºC, 30 min. (ii) CH_2N_2, Et_2O, 25ºC, 71%; g) (i) $MeSiCl_3$, Et_3N, THF, 70ºC, 22h; (ii) Ac_2O, py, 25ºC, 2h, 98%; h) (i) 19:1 TFA-H_2O, 25ºC, 17h, 58%; i) (i) 1N NaOH, MeOH, pH 12, 0ºC, 14h; (ii) AcOH, pH 6, 25ºC, 100%.



Scheme 8.

a) BF_3OEt_3, CH_2Cl_2, -30ºC, 24h, 84%; b) (i) $MeSiCl_3$, Et_3N, THF, 70ºC, 72h; (ii) Ac_2O, py, 25ºC, 4h, 23% (two steps); c) (i) Na^o, MeOH, 25ºC, 3h (ii) TEMPO, NaBr, TBABr, 5% NaOCl, $NaHCO_3$, 1:6 CH_2Cl_2-H_2O, 0ºC, 30 min., 92% (two steps).

For the construction of the (1→ 3) linked hyaluronan disaccharide (Scheme **8**) [51], the glucosamine hydrochloride **48** was used as a starting material that furnished the intermediates **53** and **54** after several steps. After glycosidation reaction between the intermediates **53** and **54**, deprotection of the methyl carbamate group and acetamide formation, the intermediate **55** was obtained. Finally, the (1→ 3) linked hyaluronan disaccharide **56** was obtained after deprotection of the acetyl groups and chemoselective TEMPO oxidation that furnished the carboxylic acid at C-6 position in mild conditions and high yield.

Isoquercetin

Quercetin (Fig. **12**) is a flavonol present in different fruits, vegetables and plants in different glycosidic forms, although the highest concentrations are found in onions. This natural product is a very efficient antioxidant [52] and seems to be active in many diseases related to aging, such as cancer [53], cardiovascular [54] and neurodegenerative diseases [55]. The regio and stereoselective synthesis of quercetin-3-*O*-β-D-glucuronide (isoquercetin) (Scheme **9**) performed by Rolando and co-workers was based on quercetin as a starting material [56]. After coupling, the glucoside was selectively oxidized to the corresponding glucuronide by using the TEMPO in catalytic amount, NaClO and NaBr under phase transfer conditions, which after deprotection of the ketal group by hydrogenolysis, furnished the desired isoquercetin in 27% isolated yield from quercetin.

CONCLUSION

Nowadays, the modern organic synthesis of natural products derived from living organisms, plants, animals and

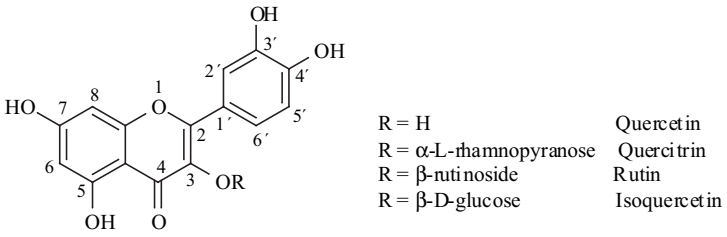
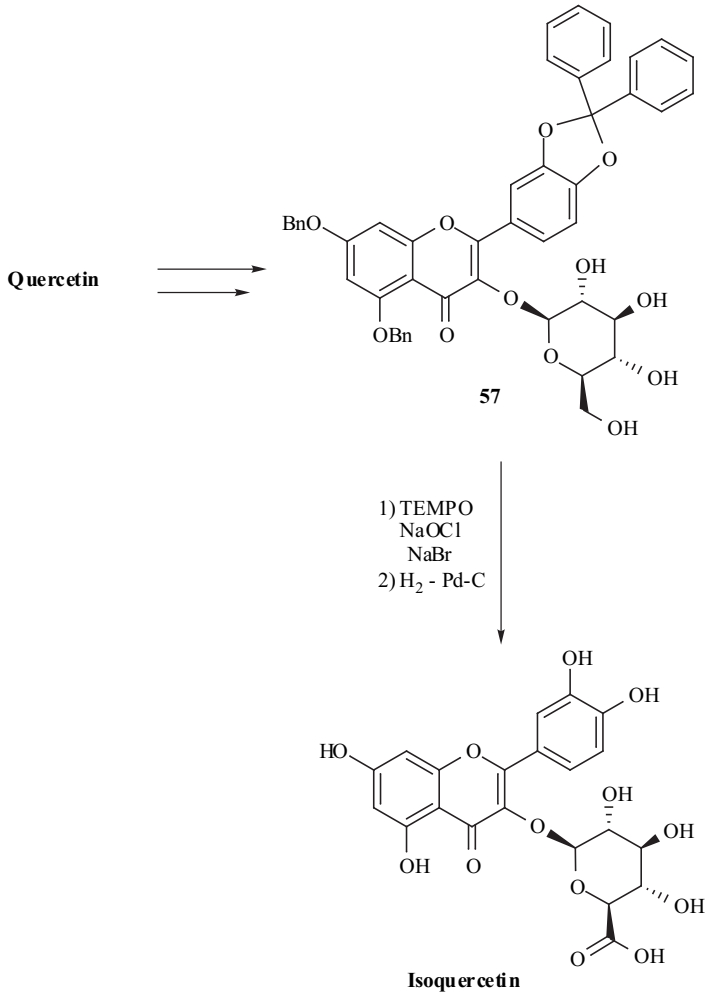


Fig. (12).



insects are very important in the drug discovery. In this context, oxidation carried out by the TEMPO is an important synthetic methodology to obtain ketones, aldehydes and carboxylic acids from alcohols in high yield, mild conditions and easy purification.

ABBREVIATIONS

Ac	=	Acetyl
AIBN	=	2,2'-Azobisisobutyronitrile
9-BBN	=	9-Borabicyclo[3.3.1]nonane
Bu	=	Butyl
Bn	=	Benzyl
dba	=	Dibenzylideneacetone
DBU	=	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	=	1,3-Dicyclohexylcarbodiimide
DIAD	=	Diisopropyl azodicarboxylate
DIBAL-H	=	Diisobutylaluminum hydride
DIPT DMAP	=	4-Dimethylaminopyridine
DMF	=	*N,N*-Dimethylformamide
DMSO	=	Methyl sulfoxide
Et	=	Ethyl
HMPA	=	Hexametylphosphoramide
Ms	=	Mesyl
NBS	=	*N* - Bromosuccinimide
NMP	=	1-Methyl-2-pyrrolidinone
Oxone	=	[Potassium monopersulfate $2KHSO_5$. $KHSO_4$. K_2SO_4]
Ph	=	Phenyl
PPTS	=	Pyridinium *p*-toluenesulfonate
pyr	=	Pyridine
TBA	=	*n*-Tetrabutylammonium
TBS	=	*Tert*-butyldimethylsilyl
TBDPS	=	*Tert*-butyldiphenylsilyl
TEMPO	=	2,2,6,6-Tetramethylpiperidine-*N*-oxyl
TFA	=	Trifluoroacetic acid
TIPS	=	Triisopropylsilyl
TC	=	Thiophene-2-carboxylate
Tf	=	Triflate
THF	=	Tetrahydropyran
TMSE	=	Trimethylsilylethyl
t-Bu	=	*Tert*-butyl

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Received: March 6, 2005 **Revised: March 25, 2005** **Accepted: March 26, 2005**