Oxazoline-N-oxide mediated asymmetric cycloadditions. Recent progress in the stereo-selective syntheses of β-lactones and β-lactams

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Abstract: Camphor-derived oxazoline-N-oxides are versatile dipoles in a new kind of asymmetric [2+3] cycloadditions. Recent applications of this methodology allowed the stereo-selective syntheses of several β-lactones natural products such as 1233A and tetrahydrolipstatine. Two formal syntheses of β-lactams antibiotics, β-methyl thienamycin and carpetimycin A, have also been achieved using this type of cycloaddition.

Cycloaddition reactions are one of the most important tools for the straightforward construction of complex molecules. Some years ago we described a new type of asymmetric [2+3] cycloaddition using camphor-derived oxazoline-N-oxides as dipoles. It was anticipated according to Scheme 1 that cycloadditions between dipole 1 and an appropriate dipolarophile should give to adduct 2 in which latent carbonyl and alcohol functional groups are inherently protected. This particular feature should allow functional group transformation on substituents R2 and R3. Final hydrolysis and hydrogenolysis should give rise to anti aldol 3 and the whole process could be considered as an asymmetric hydroxyacylation of alkenes. This type of cycloaddition can also be compared with [2+3] cycloadditions with nitrile oxides, but the control of the asymmetric induction should be much easier in the case of rigid tricyclic dipoles, such as 1, than with a linear functional group as nitrile oxide.

Camphor-derived oxazoline-N-oxides 1 are easily prepared from camphorquinone 4 according to Scheme 2. Oximation of the less hindered ketone in 4 gave rise to oximino camphor 5 which was sequentially reduced into hydroxylamino iso borneol 6 [1,2]. According to a process described by Coates [3] in achiral series, condensation of 6 with trimethoxy orthoesters in the presence of 4 Å molecular sieves as methanol scavenger afforded the anticipated dipole 1. These compounds proved to be rather unstable, and purification induced loss of material. However, direct cycloaddition with a reactive dipo-

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larophile such as phenyl isocyanate afforded in very good yield the anticipated adduct 7. This experiment is an indirect proof of the efficiency of condensation reaction between 6 and orthoesters [1].

Dipoles 1 reacted smoothly with various β-substituted α,β-unsaturated esters in dichloromethane or toluene as solvents. These cycloadditions are highly regio, endo, and diastereoselective, and single cycloadducts 8 were isolated in good yields. However, selectivities are not so good with acrylic esters, a small amount of regio and exo isomers being also obtained in these cases (Scheme 3) [1]. These cycloadditions are the result of highest occupied molecular orbital (HOMO) dipole and lowest unoccupied molecular orbital (LUMO) dipolarophile interaction. Semi-empirical calculations revealed that the presence of an endocyclic oxygen atom in oxazoline-N-oxides reduces the frontier orbital separation compared to the corresponding nitrones: it shifts the HOMO to higher energy and LUMO to a lower energy. This allows for a stronger interaction between the dipole HOMO and dipolarophile LUMO [4]. The presence of syn methyl group in the camphor bicyclic framework precludes any approach by the β face of the dipole as indicated in the proposed transition state.

Scheme 2

Scheme 3
An example of functional group transformation followed by an oxidative acidic hydrolysis is depicted in Scheme 4. Accordingly, adduct 9 was transformed in compound 10 by a three-step sequence: reduction with LiAlH₄, tosylation of the resulting primary alcohol, and hydrogenolysis of the tosylate with the same reagent. Compound 10 was then treated with mCPBA and the resulting N-oxide intermediate 11 gave rise spontaneously to nitrone 12 which was in turn hydrolyzed in acidic medium affording oximino alcohol 13, a precursor of the chiral auxiliary hydroxylamino iso borneol 6, and an anti aldol 14 in 64% overall yield for five steps. Obviously, one can remark that this is a rather lengthy sequence of reaction to obtain aldol 14, which can result from a one step aldolization. However, aldol 14 is formed by a different disconnection, the cycloaddition is performed under neutral condition which is compatible with other functional groups which would be deprotonated under strongly basic condition, and the intermediate tosylate could be also submitted to other transformation such as nucleophilic alkylation. It is also noteworthy that adduct 9 is stable in the presence of a strongly reactive reducing agent such as LiAlH₄ [1].

Finally, the whole process can be summarized by the cyclic Scheme 5.
Camphor-derived oxazoline-N-oxides 1 proved to be a valuable tool for various applications in synthesis as depicted in Scheme 6. The syntheses of tetrahydrolipstatin and of frontaline as an application of cycloadditions with \(\alpha,\beta\)-unsaturated esters will be first presented. Two formal syntheses of carabapenems \(\beta\)-methyl thienamycin and of carpetimycin A which begin by cycloadditions with \(\alpha,\beta\)-unsaturated nitriles or derivatives, will then be described. Finally, a new type of preparation of various \(\beta\)-hydroxy \(\alpha\)-aminoacids as an application of cycloadditions with nitroalkenes actually under development will be discussed.

Scheme 6

Tetrahydrolipstatin 15 is a potent pancreatic lipase inhibitor and is used for the treatment of obesity. A number of syntheses of this \(\beta\)-lactone has already been described [5]. After the achievement of the synthesis of 1233A 16 [6], an HMG CoA inhibitor, we began to be interested by the synthesis of tetrahydrolipstatin 15. Several remarks can be made before planning the synthesis of this \(\beta\)-lactone. Obviously, (+)-camphor-derived oxazoline-N-oxide has to be used as chiral auxiliary, due to the reverse absolute configuration at carbons C3 and C4 when compared with 1233A 16. The second difference between these two compounds lies in the position of the second asymmetric center on the side chain, in 1233A 16 the asymmetric centre on C7′ is far from C3 and C4, so it had to be introduced independently. The situation is quite different in tetrahydrolipstatin 15 in which the secondary alcohol at C2′ is in \(\beta\)-position and could be introduced either before or after cycloaddition. Moreover, as we will see, a nice kinetic resolution during cycloaddition let us control the three asymmetric centers in a single operation (Scheme 7).
From a retrosynthetic point of view, the synthesis of tetrahydrolipstatin 15 can be quite versatile. Thus, asymmetric centers at C4 and C2′ can be controlled either by retention or by inversion of configuration depending if the β-lactone formation and the introduction of the N-formyl leucine unit are performed under Mitsunobu conditions or by simple acylation. In the previous syntheses, the Mitsunobu process gave generally better results for the introduction of N-formyl leucine. For the control of the asymmetric center at C4, it turns out that it is possible to use E or Z α,β-unsaturated esters as dipolarophiles. Ester 17a and lactone 18 seemed a priori good candidates as dipolarophiles in this type of [2+3] cycloaddition (Scheme 8).

Ester 17b was prepared by a classical sequence of reactions as described in Scheme 9. Asymmetric allylation of the commercially available dodecanaldehyde afforded the corresponding homoallylic alcohol 19 in 90% ee. Protection of the alcohol as its benzyl ether and oxidative cleavage of the double bond followed by a Wittig–Horner olefination gave rise to the anticipated $\alpha,\beta$-unsaturated ester 17b in 44% overall yield. Cycloaddition with oxazoline-N-oxide 20 under standard conditions afforded the endo cycloadduct 21 in 58% yield in 95% de with small amount of the exo adduct.

Scheme 9

Reduction of the ester group in compound 21 followed by oxidation of the resulting alcohol afforded the aldehyde 22 in good yield. The Wittig olefination to introduce the aliphatic chain proved to be problematic. Deprotonation of the phosphonium salt 23 with BuLi, lithium diisopropylamide (LDA) or lithium hexamethyl disilyamide (LiHMDS) gave poor yields of the expected compound 24. It was found that working under salt-free conditions overcame this poor reactivity which was probably due to lithium chelation. Thus the phosphorane was prepared by deprotonation of the phosphonium salt with sodium amide in toluene, the sodium bromide was filtered off, and the resulting solution of phosphorane was introduced into the solution of aldehyde 22 in THF. Under these conditions the reaction is nearly instantaneous. However, the resulting compound 24 was unexpectedly unstable and was engaged directly in the following sequence of reactions. Accordingly, acid alcohol 25 was isolated in 65% overall yield for the four steps after oxidative acidic hydrolysis and oxidation of the resulting aldehyde intermediate. $\beta$-Lactone formation was performed with retention of configuration at C4 and was followed by reduction of the double bond and concomitant hydrogenolysis of the benzyl ether. $\beta$-Lactone 26 was thus isolated in 72% yield from compound 25. Compound 26 was finally coupled with (S)-N-formyleucine under Mitsunobu conditions and afforded tetrahydrolipstatin 15 in 93% yield (Scheme 10) [7].

Cycloaddition with $\alpha,\beta$-unsaturated $\delta$-lactone 18 was also of interest from both reactivity and selectivity points of view. This lactone was easily prepared from the homoallylic alcohol 19 previously obtained. Acylation was performed with crotonic acid in the presence of DCC. The same reaction with acrylic acid gave poor yield and was contaminated by several by-products. Metathesis was performed in the presence of the Grubbs classical catalyst in the presence of Ti(OiPr)$_4$ in order to preclude any chelation of the catalyst with the carbonyl group [8]. Cycloaddition between the (R)-lactone 18a and (-) and (+)-oxazoline-N-oxides 27 and 20 showed that dipolarophile (R)-18a and the two enantiomeric dipoles constituted respectively a matched and a mismatched pair. In the first case exo adduct 28 was obtained in good yield, and in the second experiment, cycloaddition was very slow and gave poor yield of the endo cycloadduct 29 (Scheme 11). The exo selectivity observed in the first case was not completely unexpected, because such selectivity was observed previously with other cyclic dipolarophiles, such as cyclopentadiene during the synthesis of carbovir [9].
Scheme 10

Scheme 11

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This result suggested that a kinetic resolution could occur during cycloaddition between dipoles 20 or 27 and racemic lactone 18. Results are summarized in Scheme 12. As indicated, best results were obtained when 2 equivalents of dipole 27 were used. Under this condition, the exo adduct 28 was isolated in 41% yield (de > 95%) and the starting lactone 18b was recovered as the (S) enantiomer in 58% yield and 69% ee. This value fits well with the calculated value 71% ee.

\[
\begin{align*}
\text{Dipole} & \quad \text{Dipolarophile} & \quad \text{Cycloadduct} & \quad \text{Starting Lactone (S)} \\
2 \text{ equiv} & \quad 1 \text{ equiv} & \quad \text{exo} \quad \text{end} & \quad 41\% \quad 31\% \quad 1.4\% & \quad 58\% \quad 63\% \quad 45\% & \quad \text{observed} \quad \text{calculated}^* \\
1 \text{ equiv} & \quad 1 \text{ equiv} & & & & \\
\end{align*}
\]

\[
^*\text{ee} = \frac{(1 - \text{Y minor}) - (1 - \text{Y major})}{(1 - \text{Y major}) + (1 - \text{Y minor})}
\]

Scheme 12

The use of Courtieu’s method [10] allowed an easy measurement of the enantiomeric purity of the recovered lactone 18 by $^{13}$C proton decoupled $^1$H NMR spectroscopy in a solution of poly-$\gamma$-benzyl-l-glutamate (Scheme 13). It is worthy of note that the ee measurement can be performed on a solution of the crude mixture containing both adduct 28 and lactone 18b [11].

\[
^1C \text{ proton decoupled } ^1H \text{ NMR spectra of lactone in a solution of poly-}\gamma\text{-benzyl-L-glutamate (PBLG) / CHCl}_3
\]

\[
\text{ee : d : 69 } \pm \text{ 5% R : c : 21 } \pm \text{ 5% S, h : 36 } \pm \text{ 5% R, a : racemic}
\]


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The cycloaddition between a β-substituted ester and oxazoline-N-oxide gave rise as described above to 4-substituted isoxazolidine, whereas the same cycloaddition with α-substituted ester affords a 5-substituted isoxazolidine. The reverse regioselectivity observed in this case is due to dipole LUMO/dipolarophile HOMO interaction, which becomes more important in this case [4]. This particular regioselectivity was used in a short synthesis of pheromone frontaline as described in Scheme 14. Accordingly, cycloaddition between oxazoline-N-oxide 20 and methyl metacrylate gave rise to adduct 30. Reduction of the ester group in 30 and benzylation of the resulting alcohol was followed by the classical oxidation and careful acidic hydrolysis, which afforded the acid-sensitive aldehyde 31. Wittig olefination with the stabilized phosphorane 32 led to the α,β-unsaturated ketone 33. Simultaneous hydrogenation and hydrogenolysis followed by intramolecular ketalization afforded the anticipated pheromone 34 in 56% overall yield from adduct 30 [4].

\[
\begin{align*}
\text{4-substituted isoxazolidine} & \quad \text{5-substituted isoxazolidine} \\
\text{30} & \quad \text{65\% (deo\textgreater95\%)} \quad \text{31} \\
\text{H}_2, \text{Pd-C, MeOH} & \quad \text{Frontaline 34}
\end{align*}
\]

Scheme 14

Since the discovery of thienamycin 35a more than 20 years ago, the carbapenem family remains of first importance in antibiotherapy. β-Methyl thienamycin 35b, which showed a better resistance to various inactivating enzymes, is the prototype of several powerful antibiotics exemplified in Scheme 15. Some of these derivatives, such as compound 37, are even active against vancomycin-resistant strains. These carbapenem derivatives, which are structurally characterized by a trans relationship between the two substituents at C4 and C3, are generally prepared by hemisynthesis from β-lactam 39 available in large quantities [12].

Olivanic acid 40 and carpetimycin A 41—two natural products related to thienamycin 35a—showed a particular cis relationship between the two substituents at C4 and C3.

Both β-methyl thienamycin 35b and carpetimycin A 41 showed a β-hydroxy carbonyl moiety which can be the result of a [2+3] oxazoline-N-oxide mediated cycloaddition. In β-methyl thienamycin 35b two asymmetric centers could be controlled by cycloaddition, and the two remaining asymmetric centers could be introduced by diastereoselective reactions. The difficulty in this synthesis is to control four contiguous asymmetric centers (Scheme 15).

The case of carpetimycin A 41 is quite different, and the structure of this carbapenem is obviously simpler. However, a problem of reactivity could occur during the cycloaddition as far as a tertiary alcohol has to be introduced on the side chain, which implied the use of trisubstituted alkene as dipolarophile. Comparison between the two structures also showed that if an endo selective cycloaddition could reasonably be predicted in both cases, (+)-camphor-derived oxazoline-N-oxide should be used as chiral auxiliary in β-methyl thienamycin 35b synthesis, whereas the enantiomeric dipole should be used in carpetimycin A 41 synthesis (Scheme 16).
A simple retrosynthetic analysis of carpetimycin A 41 is described in Scheme 17. Carbapenem 42 is a known precursor of the antibiotic [13]. This β-lactam is the result of an intramolecular acylation of β-amino acid 43. This compound could in turn be obtained by a known sequence of reactions, the crucial step being the diasteroselective reduction of enamino ester unit in compound 44. This particular functional group could finally be introduced by a Blaise condensation between organozincic intermediate 45 and adduct 46. Adduct 46 itself should be obtained by a cycloaddition between dipole 28 and 3-methyl-2-butenitrile.

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It rapidly appeared that such cycloaddition was not interesting from a synthetic point of view. The reaction is slow due to the steric hindrance on dipolarophile and gave a 50:50 mixture of endo and exo adducts in 16% yield. So two alternative ways were studied to overcome this particular lack of reactivity. In the first one, following a known concept, cyclopropyl derivative was used as surrogate of the gem dimethyl unit. The second possibility resulted from an unexpected observation concerning the reactivity of γ,δ-unsaturated enamino esters.

The use of cyclopropyl derivative is a well-known means of improving the reactivity of one of the partners in cycloadditions. These types of compounds have been used in both [2+4] and [2+3] cycloadditions [14]. However, we have been surprised to observe that cyanomethylene cyclopropane 47, which could be used instead of 3-methyl-2-butenitrile, was virtually unknown [15]. This compound has been prepared following a sequence of reactions already used for the corresponding cyclopropyl esters. The known phosphorane 48 was obtained by deprotonation of the corresponding phosphonium salt 49 in absence of oxygen, in order to preclude decomposition and extensive formation of triphenylphosphine oxide. Condensation of phosphorane 48 with 1-ethoxy-1-hydroxycyclopropane, which resulted itself from the hydrolysis of 1-ethoxy-1-trimethylsilyloxycyclopropane 50, afforded the volatile cyanomethylene cyclopropane 47. 1H NMR of a solution of the crude compound showed that it was the only product of the reaction. However, the volatility of this compound precluded its isolation in high yield, whatever was the solvent used (Scheme 18).

Scheme 17

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Scheme 18

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An endo selective cycloaddition between dipole 27 and cyanomethylene cyclopropane 47 occurred under mild conditions and afforded cycloadduct 51 in high yield [15]. A preliminary experiment in order to hydrogenolise the cyclopropyl ring was not fruitful, and more interesting results obtained with γ,δ-unsaturated enamino esters led us to leave this way unexplored for the moment.

The poor reactivity of 3-methyl-2-butenitrile precluded the use of this compound in cycloaddition. However, it seemed of interest to change our tactic and to perform the Blaise condensation before and not after cycloaddition as initially planned. Accordingly, 3-methyl-2-butenitrile was treated with the Reformatsky reagent 53 and after hydrolysis in basic medium the γ,δ-unsaturated enamino ester 54 was isolated in 62% yield [16,17].

Compound 54 proved to be unexpectedly reactive in cycloaddition with dipole 27 and the exo adduct 55 was isolated in 54% yield after 1.5 h at 40 °C (Scheme 19). Longer reaction time induced hydrolysis of the enamino group in 55 affording the corresponding β-keto ester. This particular reactivity could be the result of the protonation of the enamino group with one equivalent of hydrochloric acid, as hydroxylamino isoborneol was used as its hydrochloride, affording an imminium intermediate which would be much more reactive than compound 54. Thus, if triethylamine is added to the reaction medium, the rate of cycloaddition decreased dramatically, and only a small amount of cycloadduct 55 was isolated. The exo selectivity of this cycloaddition is unusual with noncyclic dipolarophile. It could result either from steric interaction between dipole 27 and the gem-dimethyl group or from a stepwise reaction. Thus, the imminium intermediate should well be partially under a tertiary carbocation mesomeric form and, in this case, a stepwise process giving rise to the observed exo adduct 55 could also be likely. To test this hypothesis, the same cycloaddition was performed with a dipolarophile bearing a benzyl group instead of the gem-dimethyl. However, in that case, despite the possible formation of a benzylic carbocation, only the endo adduct was isolated. It turns out that the exo selectivity is probably the result of purely steric factors. The structure of adduct 55 was not secured at this stage, but by an X-ray analysis of a derived compound (vide infra).

Scheme 19

The stereoselective reduction of the enamino moiety in compound 55 was next addressed. This reaction was classically performed with sodium cyanoborohydride as reducing agent in acidic medium. Low temperature was necessary in order to get a good 10:1 diastereoselectivity. The resulting diastereoisomeric amino derivatives were acylated with a carbobenzyloxy group, and purification was performed at this stage. The major carbamate 57a was thus isolated in 78% yield.

The direction of the asymmetric induction was established after deprotection of benzyloxy carbonyl group in 57a and sulfonlation of the resulting amine. The crystalline sulfonamide 57b was subjected to an X-ray analysis which allowed the determination of the absolute configurations of the two asymmetric centers resulting from the unexpected exo cycloaddition and from sodium cyanoborohydride reduction (Scheme 20).

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On the other hand, compound 57a was submitted to the classical sequence of reactions already used in β-lactone syntheses, namely oxidation, acidic hydrolysis, and oxidation of the aldehyde intermediate. Nitrogen in the resulting acid was then deprotected by hydrogenolysis, and the resulting β-amino acid afforded the expected β-lactam 58 in 31% overall yield from compound 57a.

![Scheme 20](image)

A chemical correlation with a carpetimycin A 41 precursor described previously [13] confirmed the synthesis. Accordingly, β-lactam 58 was transformed into the known β-lactam 59 (Scheme 21). The absolute value of the rotatory power is in accord with literature data. Obviously, β-lactams enantiomeric to 58 or 59, precursors of natural (+)-carpetimycin A 41, can be obtained using (+)-camphor-derived dipole 20 [18].

![Scheme 21](image)

The same strategy was used for β-methyl thienamycin 35b synthesis. Blaise condensation between butenenitrile and methyl 2-bromo propionate 60 afforded the enamino ester 61. Cycloaddition between compound 61 and dipole 20 afforded under mild reaction condition the anticipated adduct 63. For comparison, cycloaddition with butenenitrile was also studied. Here again the superior reactivity of γ,δ-unsaturated enamino ester 61 is worthy of note. Adduct 62 resulting from cycloaddition between butenenitrile and camphor-derived oxazoline-N-oxide 20 was submitted to a Blaise condensation and afforded as expected compound 63 (Scheme 22).
As previously, enamino unit reduction was performed in acidic medium with sodium cyanoborohydride as reducing agent. Here again, low temperature was crucial to ensure selectivity. However, protonation of enamine, which created the first asymmetric center, was poorly selective (3:1). As in the case of carpetimycin A synthesis, the reductive step was much more stereoselective (10:1). The mixture of diastereoisomers 64 was directly transformed into the corresponding carbamate 65, and purification was performed at this stage. The major compound 65 was thus isolated in 44% yield from adduct 63 (Scheme 23).

Compound 65 was then submitted to the same sequence of reaction used in carpetimycin A synthesis. \(\beta\)-Lactam 66 was isolated in 32% overall yield for five steps. Mitsunobu reaction allowed the inversion of configuration of the side-chain secondary alcohol, and saponification of the benzoate ester in the resulting compound 67a afforded the known \(\beta\)-lactam 67b [19]. Comparison of the rotatory power and of NMR spectra showed a good concordance with literature [20].

Scheme 23
Cycloadditions between nitroalkenes and camphor-derived oxazoline-N-oxides were also studied. Thus, the resulting adducts 68 are quite promising compounds for the preparation of β-substituted tertiary or quaternary-substituted α-amino acids 69.

Cycloadditions were performed under mild conditions. The same regioselectivity (4-substituted isoxazolidines were obtained) was observed whatever was the substitution pattern of the double bond. This particular regioselectivity contrasts with the behaviour of α,β-unsaturated esters (vide supra). Results are summarized in Scheme 24 and the large variety of nitroalkenes used in cycloaddition is worthy of note [4].

Scheme 24

Preliminary studies were developed to transform these adducts into amino acid derivatives. Accordingly, the nitro group in adduct 78 was reduced by hydride transfer hydrogenation, and the resulting amino derivative was protected as Fmoc carbamate 79. Then, the classical sequence, oxidation hydrolysis, was studied with compound 79 or other carbamate-protected derivatives. However, this type of transformation proved to be more difficult than in the previous cases. This could be due to side retro aldol reaction during acidic hydrolysis. Clearly, this reaction has to be optimized (Scheme 25).

Scheme 25

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Another possible application of nitroalkenes adducts has been also studied. Adduct 78, submitted to radical denitration reaction condition, afforded stereoselectively compound 82. This reaction opened the way to further synthetic applications. Using this type of transformation, nitroalkenes could be considered as equivalents of dipolarophiles unconjugated with an electron-withdrawing group. We have shown [1] that cycloaddition between such dipolarophiles and oxazoline-\(\text{N}\)-oxides are possible as in the synthesis of pheromone 86 (Scheme 26), but the low reactivity of such unactivated dipolarophile precluded a number of synthetic applications.

Another reaction which could be of interest takes advantage of the formation of a radical as an intermediate 87 to perform stereoselectively a new carbon–carbon bond formation.

![Scheme 26](image)

**CONCLUSION**

The various applications of camphor-derived oxazoline-\(\text{N}\)-oxide cycloadditions in natural or unnatural products syntheses have been exemplified by the above examples. Further developments, particularly with nitroalkenes adducts as starting material, should in the future bring other examples of the versatility of this particular case of [2+3] asymmetric cycloadditions.

**REFERENCES**


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