[18] Three-dimensional linked patterns do not require an oxo ligand hapticity > 3, as stated in ref. [1].
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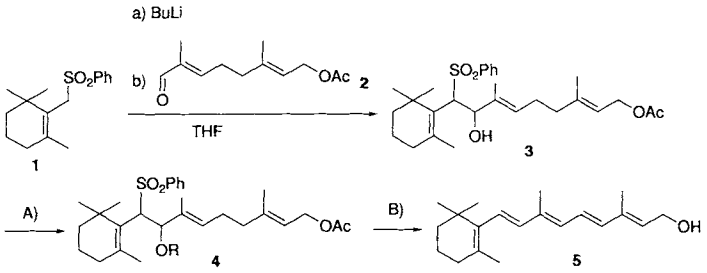

Scheme 1. Stepwise synthesis of vitamin A (**5**). A) Dihydropyran (R = tetrahydropyranyl), ethylvinyl ether/*p*-toluenesulfonic acid (R = 1-ethoxyethyl) or $(MeO)_2CH_2/P_2O_5$ (R = MOM) in CH_2Cl_2 or neat. B) *t*BuOK or MeOK in cyclohexane.

Integrated Chemical Process: An Extremely Concise Synthesis of Vitamin A

Akihiro Orita, Yasuo Yamashita, Akiji Toh, and Junzo Otera*

Compaction of multistep chemical syntheses is strongly desired from both economical and ecological points of view. The ultimate goal is the one-pot process that has received extensive attention under names such as tandem, cascade, or domino reactions.[1] Although these reactions, once realized, are very elegant, much elaboration is necessary for preparing the precursors to the consecutive reactions. Hence, the overall process does not always gain in brevity when all steps from real starting materials are taken into account. In these reactions, the focus has been primarily on the carbon–carbon bond formation. This is quite reasonable in terms of the central role this manipulation plays in organic synthesis. In actual chemical processes, however, other steps such as functional group transformation and protection or deprotection of functional groups are equally important. Thus, it is more practical to devise one-pot processes that can accommodate chemical transformations of wider scope.

In conventional synthesis, a route to a target molecule is appropriately designed by, for example, retrosynthesis and fractioned into unit reactions. Each reaction then is optimized independently; in most cases, each step is conducted under different conditions. One-pot consecutive reactions are therefore only feasible when the reaction conditions of the successive steps are the same or similar *by chance*. Our basic idea has the opposite approach. First, reaction conditions that can be shared by all steps are chosen. Second, every step is optimized under these conditions. Consequently, all the steps can then be integrated to give a one-pot procedure.[2] Here, we exemplify the effectiveness of this "integrated chemical process" for a synthesis of vitamin A based on the double-elimination method previously disclosed.[3]

The stepwise procedure is illustrated in Scheme 1. The lithium salt of cyclogeranylsulfone **1** was treated with aldehyde **2** to give the addition product **3** (step 1). Alcohol **3** was converted to acetal **4** (step 2), and finally, exposure of **4** to *t*BuOK or MeOK furnished vitamin A (**5**) (step 3). Steps 1 and 3 were conducted under basic conditions, and step 2 under acidic conditions. We anticipated that a one-pot process would be feasible if the conditions for step 2 were made compatible with the others. This was indeed the case.

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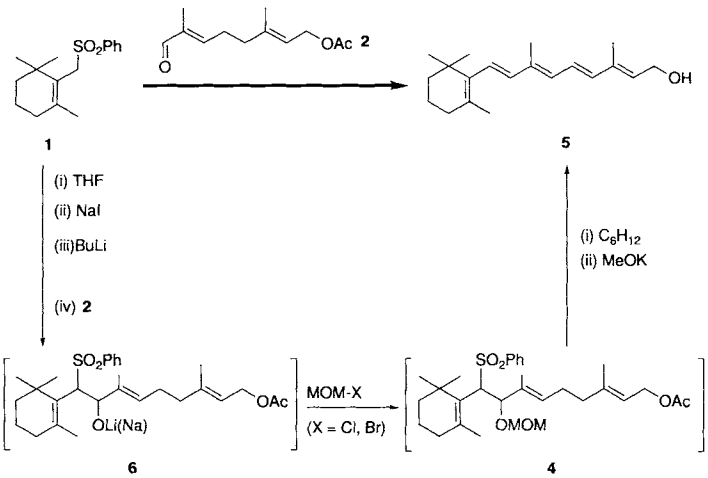
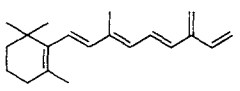
A typical one-pot procedure is depicted in Scheme 2; all steps were conducted under basic conditions. The lithium salt of **1** was treated with **2**, and the resulting addition product **6** was trapped with $MeOCH_2Br$ (MOMBr). The MOM ether **4** then underwent double elimination upon exposure to MeOK (10 equiv) to



Scheme 2. One-pot synthesis of vitamin A (**5**).

afford vitamin A. The yield of the acetate form was determined by HPLC to be about 50%. This is not too bad considering it is the total yield of the four sequential reactions (step 3 consists of elimination of first MOMOH and then $PhSO_2H$).[3c] However, polymeric materials derived from diene **7** formed as by-products. Fortunately, elimination of the terminal allylic alkoxide was suppressed by addition of NaI, which was given to the reaction mixture from the beginning since it did not influence the reaction in step 1. Moreover, addition of NaI allowed use of the more readily available MOMCl, which otherwise had failed to acetalize **6** in situ, probably by conversion of MOMCl to MOMI. Finally, addition of cyclohexane as a co-solvent in the elimination step increased the yield slightly (by ca. 3%). These modifications improved the yield to 76%, which is higher than 67% obtained by the corresponding stepwise process (step 1: 93, step 2: 92, step 3: 78%)[3c] Provided that the yield of step 3 was the same as that in the stepwise process (78%),[4] the total yield of 76% should have resulted from nearly quantitative reactions for steps 1 and 2. Apparently, material loss due to isolation and purification of the intermediates in the stepwise process is circumvented. Of further note is the isomeric purity of **1**: the high



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all-*E* content characteristic of the double elimination process holds for the present case as well: all-*E*:9*Z*:[(11*Z*) + (13*Z*)] = 91:4:5.

We compared this new process with those used commercially.[5] The Hoffmann–La-Roche process involves a $C_{14} + C_6$ route, and BASF makes use of the Wittig reaction between C_{15} and C_5 building blocks. Rhône–Poulenc also employs the $C_{15} + C_5$ combination based on the Julia sulfone coupling. Our strategy is novel in that two C_{10} components are coupled. The C_{10} skeletons are one of the most common units in terpenoid derivatives and, accordingly, readily available. As a whole, our process has the twofold benefit of ready availability of the starting materials and simple operation.[6]

We have shown that the following reactions can be integrated: a) addition of carbanion to carbonyl, b) O-alkylation of the addition product, and c) successive elimination of the alkoxy and sulfinyl groups. The only modification of the stepwise process is made for the O-alkylation. This results in not only compaction of the process but increase in the total yield. Although we took up a rather simple case in this study, it has proved that even a slight modification can bring about critical improvements of the chemical process. This suggests the importance and potential of the integrated chemical process for designing a synthesis.

Experimental Section

NaI (225 mg, 1.5 mmol), cyclogeranyl sulfone **1** [3c] (362 mg, 1.3 mmol), and THF (2 mL, dried over sodium benzophenoneketyl) were placed in a flame-dried, two-necked flask. A solution of BuLi in hexane (1.6 M, 0.75 mL, 1.2 mmol) was added, and the mixture stirred at −78 °C (dry ice/MeOH) under argon for 1 h. After the addition of aldehyde **2** [3c] (211 mg, 1.0 mmol) in THF (1 mL) followed by MOMCl (0.09 mL, 1.2 mmol), the solution was stirred for 4 h at −78 °C and 1 h at room temperature. Cyclohexane (3 mL) and KOMe (701 mg, 10 mmol) were added, and the mixture stirred for 1 h at room temperature and 1 h at 40 °C. The reaction was quenched with aqueous $NaHCO_3$ solution (10 mL) and ethyl acetate (15 mL). After separation of the organic layer and extraction of the aqueous phase with ethyl acetate (2 × 15 mL), the combined organic fractions were washed with brine (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure (crude, 452 mg). Hexane (5 mL), pyridine (0.5 mL), acetic anhydride (2 mL), and DMAP (48 mg, 0.4 mmol) were added to the crude product under argon, and the mixture stirred for 1 h at room temperature. Aqueous $NaHCO_3$ solution (20 mL) and ethyl acetate (15 mL) were added at 0 °C, and the organic layer separated. The aqueous phase was extracted with ethyl acetate (2 × 15 mL), and the combined organic fractions washed with brine (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure (crude, 504 mg). The crude oil was analyzed by HPLC; 76% yield, 248 mg, all-*E*:9*Z*:[(11*Z*) + (13*Z*)] = 91:4:5 (column: ZORBAX SIL 4.6 mm × 25 cm; eluent: *tert*-butylmethyl ether/hexane 5/100; internal standard: 2,6-xylenol).

Received: November 12, 1996 [Z9760IE]
German version: *Angew. Chem.* **1997**, *109*, 804–805

Key words: eliminations · one-pot reactions · vitamins

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[2] Hudlicky pointed out that "a multistep synthesis must therefore be considered as a dynamic continuum in which every event depends on all others": T. Hudlicky, *Chem. Rev.* **1996**, *96*, 3.

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[4] Note that the yield of step 3 (78%) should come from the successive high-yielding elimination reactions (2 × 88%).

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[6] Of course, accessibility of the key building blocks is an important factor for assessing the overall brevity of the process. A more detailed discussion will be given in a full paper.

Combinatorial Chemistry with Laser Optical Encoding

Xiao-yi Xiao,* Chanfeng Zhao, Hanan Potash, and Michael P. Nova

In the rapid development of synthetic and combinatorial chemistry,[1] solid-phase combinatorial synthesis[2] continues to be one of the most effective techniques for building diverse libraries. Advantages of solid-phase synthesis over solution chemistry include ease of intermediate isolation, use of excess reagents to drive reactions to completion, and potential use of the highly efficient pool and split[3] synthesis technique. Two elements are essential for successful solid-phase combinatorial library generation and evaluation: an efficient solid-support chemical reaction sequence and a reliable means for structural elucidation and confirmation[4] of library members. Although considerable efforts have been devoted to the development of solid-support chemistry,[2] the choice of methods for structural elucidation (spatial addressing,[5] mixture deconvolution,[6] direct microanalysis,[7] or chemical tagging[8]) is rather limited. Tagging—especially nonchemical, noninvasive tagging—is potentially the most efficient and reliable encoding method. We have recently developed a new, nonchemical, noninvasive radiofrequency encoding technology.[9] Here we report another strategy for noninvasive synthetic chemistry encoding, namely, laser optical tagging, with LOSCs (*L*aser *O*ptical *S*ynthesis *C*hips). This technology is applicable to library synthesis of all types of compounds including small molecules, peptides, and oligonucleotides in multimilligram quantities.

The LOSC technology combines the most advanced developments in laser bar code etching and identification as well as organic synthesis on novel solid supports. The initial LOSC is shown in Figure 1. It is fabricated by combining a two-dimensional 16-digit bar code for encoding and a polymeric support for chemical synthesis. The 2-D bar codes are laser-etched with a CO_2 laser on 6 × 6 segments of a chemically inert alumina ceramic plate (the actual size of each bar code is 3 × 3 mm). The surrounding synthesis support is a stable polypropylene or fluoropolymer square (10 × 10 × 2 mm), which is radiolytically

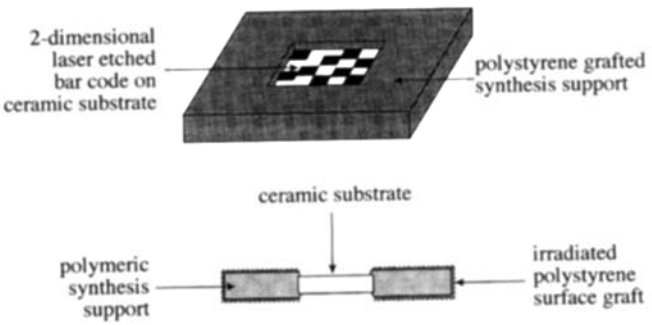

Figure 1. Illustration of the laser optical synthesis chip (LOSC), viewed from the top (top) and in cross-section (bottom). The size of the LOSC is 10 × 10 × 2 mm.

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[**] We thank Prof. K. C. Nicolaou, who is an advisor to IRORI Quantum Microchemistry, and Dr. A. W. Czarnik for valuable discussions, and Mr. Bill Ewing for software development.