34. Synthesis of (+)-Multifidene

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(+)-Multifidene ((+)-**1**) has been synthesized starting from (*R*)-(cyclopent-2-enyl)methanol ((+)-**2**) *via* its chloroformate **4**, Co-mediated radical cyclization reaction to the lactone (+)-**6**, and introduction of the olefinic side chains.

Introduction. – Free radical cyclizations have been used extensively in organic synthesis [1]. A vast majority of free radical reactions are performed under reductive conditions and are usually terminated with hydrogen transfer, thus resulting in the loss of a functionality after the cyclization. Transition-metal-mediated radical reactions provide a useful alternative [2]. The versatility of the free radical cyclization in the latter case is enhanced by the introduction of a new functionality in the product *via* group transfer. In the past few years, Co-mediated free radical reactions have received considerable attention in organic synthesis [3], and a variety of organocobalt complexes have been employed as precursors for carbon centered radicals, in C–C bond forming reactions. Vitamin-B_{12}-catalyzed nucleophilic acylation of activated olefins has been reported earlier form our laboratory [4].

(+)-Multifidene (= (+)-(3*S*,4*S*)-*cis*-3-[(Z)-but-1-enyl]-4-vinylcyclopent-1-ene; (+)-**1**) is a main constituent of the pheromone released by the brown algae *Cutleria multifida* [5]. Several syntheses have been reported [6] of which only one pertains to the naturally occurring enantiomerically pure compound [6d]. The key step in our synthesis involves a Co-mediated 5-*exo*-*trig*-cyclization of an alkoxycarbonyl radical.

Results and Discussion. – The starting material, (*R*)-(cyclopent-2-enyl)methanol ((+)-**2**)[3]) was prepared by $LiAlH_4$ reduction [8] of the acid (+)-**3** (ee 99%), which was prepared from cyclopentadiene as described in [9] (*Scheme*). Treatment of the alcohol (+)-**2** with trichloromethyl chloroformate [10] and pyridine afforded the chloroformate (+)-**4** in 81% yield.

The requisite radical precursor, (oxycarbonyl)cobalt complex **5** was prepared by treating the chloroformate **4** with sodium(salen)cobalt(I), which in turn was obtained by the reduction of Co^{II}(salen) with 1% Na/Hg in THF [11]. Irradiation of a solution of **5** in CH_2Cl_2 generated the alkoxycarbonyl radical, by the homolysis of the C–Co bond [12],

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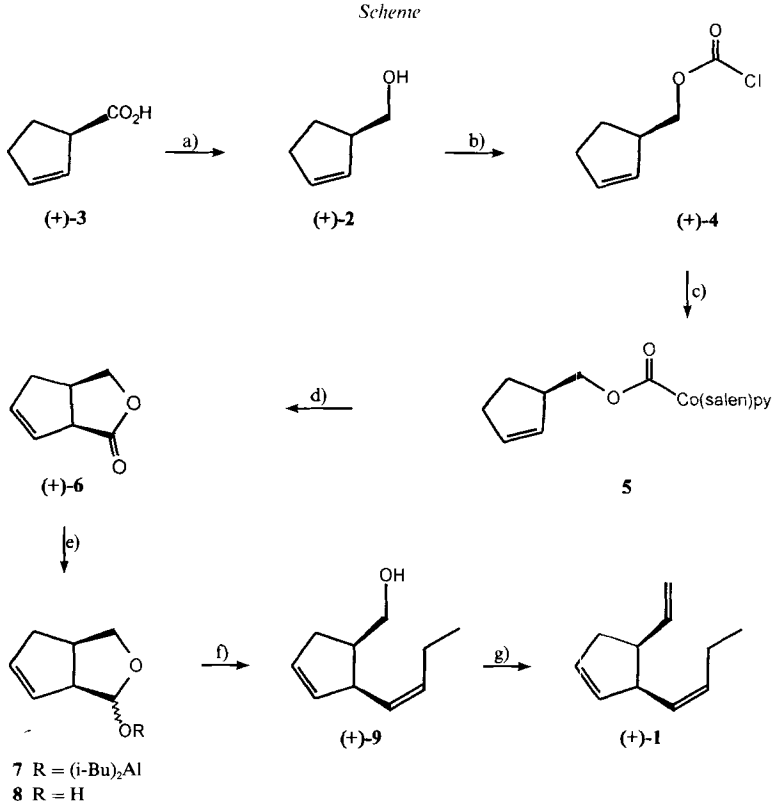
[3]) The enantiomer (–)-(*S*)-**2** has been used for the synthesis of (–)-carbovir [7].

Scheme



a) $LiAlH_4$, Et_2O, 0°. b) CCl_3OCOCl, CH_2Cl_2, pyridine, 0°–r.t. c) *i*) $NaCo^I$(salen), THF, –78°–r.t.; *ii*) CH_2Cl_2/pyridine 19:1. d) *hv*, CH_2Cl_2, reflux. e) DIBAL, toluene, –78°. f) *t*-BuOK, $Ph_3PCH_2CH_2CH_3Br$, THF, –80°–r.t. g) *i*) PCC, CH_2Cl_2, r.t.; *ii*) BuLi, Ph_3PCH_3Br, THF, –15°–r.t.

which underwent intramolecular 5-*exo*-*trig*-addition onto the olefin followed by dehydrocobaltation to yield the bicyclic lactone (+)-**6** in 65% yield. Decarbonylation of the intermediate radical with the formation of (+)-**2** was observed only to an extent of *ca.* 10%.

The *cis*-butenyl side chain was introduced by reductive olefination [13]. Thus, treatment of the lactone **6** with diisobutylaluminium hydride (DIBAL) and subsequent reaction of the resulting organoaluminium complexed hemiacetal **7** (88:12 mixture of the diastereoisomeric hemiacetals **8**) with 5 equiv. of propylidene(triphenyl)phosphorane furnished the olefinic alcohol (+)-**9** with very high side-chain (*Z*)-stereoselectivity (> 99%, GC) and in 70% overall yield. Under these reaction conditions, epimerization to the *trans*-disubstituted cyclopentene was always observed to the extent of *ca.* 15% (GC)[4]). Finally, it has been found that olefination, without isolation of **8**, with 2.5 equiv. of the phosphorane resulted in very low epimerization (1–1.4%) and high side-chain (*Z*)-stereoselectivity (> 99%).

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[4]) In the ^{1}H-NMR spectrum, the tertiary proton at C(2) in the *cis*-disubstituted product **9** appeared at 3.7 ppm, whereas the corresponding H–C(2) in the *trans*-disubstituted product appeared at 3.4 ppm.

Oxidation of the alcohol **9** (> 98% *cis*) with pyridinium chlorochromate (PCC) followed by *Wittig* olefination of the intermediate aldehyde with methylidene(triphenyl)-phosphorane [6d] furnished (+)-(3*S*,4*S*)-multifidene ((+)-**1**) in > 98% *cis*-disubstitution, 99% (*Z*)-stereoselectivity, and 98% ee (enantioselective GC). The spectral data (IR, ^{1}H- and ^{13}C-NMR, and MS) of (+)-**1** were found to be identical with those given in [6b] [6e].

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Experimental Part

General. All reactions were carried out under inert atmosphere. THF and Et_2O were distilled over K and Na benzophenone ketyl, respectively, under N_2. Toluene was distilled over NaH and stored over molecular sieves. Pyridine was distilled over KOH pellets and stored over molecular sieves. CH_2Cl_2 (*Super purity solvent*) was purchased from *Romil Chemicals.* All the other solvents were distilled prior to use. Co^{II}(salen) was prepared according to the procedure described in [14]. DIBAL (1M soln. in toluene) and *t*-BuOK (1M soln. in THF from *Aldrich.* BuLi (1.6M soln. in hexane), trichloromethyl chloroformate, propyl(triphenyl)phosphonium bromide, methyl(triphenyl)phosphonium bromide, and PCC from *Fluka.* Flash chromatography (FC): silica gel (30–60 μm), *Baker Analysed reagent.* Anal. GC: *Hewlett-Packard-5890* gas chromatography; 10-m fused silica capillary column coated with 5% phenyl-methyl-siloxan (df 0.11 μm), temp. program from 40° to 220°, 3°/min; flame ionization detector (FID). Enantioselective GC: *Hewlett-Packard-5890* with heptakis{2,3-di-*O*-methyl-6-*O*-[(*tert*-butyl)dimethylsilyl]}-β-cyclodextrin (0.09394M) in *OV-1701* as chiral stationary phase; 25 m. M.p. (uncorrected): *Büchi 510.* $[\alpha]_{578}$: *Perkin-Elmer-241* polarimeter. IR: *Perkin-Elmer-782* spectrometer; only characteristic absorptions are given. ^{1}H-NMR: *Bruker-AC-300* (300 MHz) spectrometer; δ in ppm and TMS (= 0 ppm) as internal standard. ^{13}C-NMR: *Bruker-AC-300* (75 MHz) spectrometer; δ in ppm and TMS (= 0 ppm) as internal standard; Multiplicities are derived from DEPT measurements. MS (*m*/*z* (%)): *Varian-MAT-CH-7A* mass spectrometer, ionization energy 70 eV.

(+)-(1R)-(Cyclopent-2-enyl)methyl Chloroformate (**4**). To a magnetically stirred soln. of trichloromethyl chloroformate (2.42 ml, 20 mmol) in CH_2Cl_2 (18 ml) was added dry pyridine (0.82 ml, 10 mmol) at 0°, and the resulting suspension was stirred at r.t. for 30 min. Then, a soln. of *(R)-(cyclopent-2-enyl)methanol* ((+)-**2**; 980 mg, 10 mmol) in CH_2Cl_2 (8 ml) was added dropwise at 0°, and the mixture was stirred at r.t. for 5 h, diluted with Et_2O (30 ml), filtered through *Celite*, and the solvent was evaporated. Bulb-to-bulb distillation (20–30°/25 Torr) of the resulting dark brown liquid furnished **4** (1.30 g, 81%). Colorless liquid. $[\alpha]_{578}^{20} = +131$ ($c = 3.56$, $CHCl_3$). IR (neat): 3060*w*, 2960*m*, 1780*s*, 1150*s*, 810*w*, 690*w*. ^{1}H-NMR ($CDCl_3$): 1.56–1.67 (*m*, 1H); 2.02–2.15 (*m*, 1H); 2.3–2.5 (*m*, 2H); 3.05–3.16 (*m*, H–C(1)); 4.23, 4.26 (*AB*, $J_{AB} = 7$, CH_2OCO); 5.62–5.66 (*m*, 1H); 5.89–5.93 (*m*, 1H). ^{13}C-NMR ($CDCl_3$): 26.3 (*t*); 31.8 (*t*); 44.8 (*d*); 75.1 (*t*); 129.5 (*d*); 134.1 (*d*); 150.8 (*s*, OCO). MS: 161 (3, M^+), 82 (34), 81 (84), 80 (97), 79 (66), 78 (34), 77 (18), 69 (15), 68 (74), 67 (100), 66 (41), 65 (52), 64 (21), 63 (43), 57 (15), 55 (23), 54 (22), 53 (32), 52 (28), 51 (28), 50 (20), 44 (26), 42 (12), 41 (46), 40 (39), 39 (37), 38 (24), 36 (19).

[(1R)-(Cyclopent-2-enyl)methoxycarbonyl](pyridinato)(salen)cobalt(III) (**5**). To a magnetically stirred soln. of sodium(salen)cobalt(I) (2.5 mmol) in dry, deoxygenated THF (100 ml), was added **4** (neat, 400 mg, 2.5 mmol) at −78°. The greenish blue color of cobalt^I(salen) was discharged. The resulting red-brown suspension was stirred in the dark and warmed to r.t. over a period of 30 min. The solvent was evaporated under reduced pressure at 30°, in the dark. The solid residue was dissolved in CH_2Cl_2/pyridine 19:1 (30 ml) and purified by FC (neutral alumina, CH_2Cl_2/pyridine 19:1). The product was eluted as an orange-red soln., which was diluted with hexane and evaporated under reduced pressure in the dark at 30°. Excess of pyridine was removed by azeotropic distillation by adding further amounts of CH_2Cl_2 (30 ml) and hexane (100 ml) to yield **5** (980 mg, 75%). Orange-red solid. M.p. > 350°. IR (KBr): 3050*w*, 2940*w*, 2860*w*, 1675*s*, 1630*s*, 1600*s*, 1040*s*, 900*m*, 740*m*. ^{1}H-NMR ($CDCl_3$): 1.13–1.27 (*m*, 1H); 1.57–1.69 (*m*, 1H); 2.11–2.28 (*m*, 2H); 2.56–2.61 (*m*, H–C(1)); 3.34–3.62 (*m*, $N(CH_2)_2N$); 4.05, 4.14 (*AB* of *ABX*, $J_{AB} = 17$, $J_{AX} = 6.3$, $J_{BX} = 6.9$, CH_2OCO); 5.24–5.28 (*m*, 1H); 5.59–5.63 (*m*, 1H); 6.50 (*t*, $J = 7$, 2H); 7.07–7.24 (*m*, 6H); 7.25–7.29 (*m*, 2H); 7.69 (*tt*, $J = 7.7$, 1.5, 1H); 7.81 (br. *s*, 2H); 8.48 (*dt*, $J = 5$, 1.5, 2H). ^{13}C-NMR ($CDCl_3$): 25.9 (*t*); 31.8 (*t*); 45.7 (*d*); 58.25 (*t*); 58.25 (*t*); 70.4 (*t*); 113.8 (*d*); 113.9 (*d*); 119.9 (*s*); 123.8 (*d* and *s*, 2C); 124.6 (*d*); 131.5 (*d*); 131.8 (*d*); 133.3 (*d*); 133.7 (*d*); 136.7 (*d*); 149.7 (*d*); 164.0 (*d*); 167.1 (*s*). FAB-MS: 451 ($[M - py]^+$), 326 ($[Co(salen)H]^+$).

(+)-(1S,5R)-3-Oxabicyclo[3.3.0]oct-7-en-2-one ((+)-**6**). A magnetically stirred soln. of **5** (350 mg, 0.66 mmol) in dry, deoxygenated CH_2Cl_2 (180 ml) was irradiated with a 300-W halogen lamp under reflux for 7 h. The solvent was evaporated under reduced pressure, and the residue was mixed with silica gel and then purified by FC (silica gel, Et_2O/pentane 1:1) furnished **2** (6.5 mg, 10%) followed by **6** (56 mg, 68%, 99% ee). Colorless oil. $[\alpha]_{578}^{20} = +359.5$ ($c = 1.075$, $CHCl_3$; [15]: $[\alpha]_{578}^{20} = +352.3$ ($c = 12.71$, $CHCl_3$)). IR (neat): 3075*w*, 2920*m*, 2860*m*, 1770 (br.), 1190*m*, 1020*m*, 930*w*, 680*m*. ^{1}H-NMR ($CDCl_3$): 2.28–2.38 (*m*, 1H); 2.69–2.79 (*m*, 1H); 3.21–3.33 (*m*, H–C(5)); 3.63–3.69 (*m*, H–C(1)); 3.88 (*dd*, $J = 9$, 7.3 H–C(4)); 4.58 (*t*, $J = 9$, H–C(4)); 5.74–5.77 (*m*, 1H); 5.78–5.92 (*m*, 1H). ^{13}C-NMR ($CDCl_3$): 37.1 (*d*); 39.1 (*t*); 52.5 (*d*); 74.3 (*t*); 126.3 (*d*); 132.7 (*d*); 177.1 (*s*, OCO). MS: 124 (14, M^+), 80 (81), 79 (100), 77 (32), 66 (17), 65 (15), 39 (27).

(+)-{(1R,2S)-cis-2-[(Z)-But-1-enyl]cyclopent-3-enyl}methanol ((+)-**9**). To a magnetically stirred soln. of **6** (124 mg, 1 mmol) in dry toluene (6 ml) was added a 1M soln. of DIBAL in toluene (1.5 ml, 1.5 mmol) dropwise at −78°. The mixture was stirred at −78° for 1 h. Excess DIBAL was destroyed by the addition of dry MeOH (25 µl, 0.5 mmol), and the soln. was stirred at the same temp. for 10 min. Subsequently, the cold reaction mixture was rapidly transferred into a soln. of propylidene(triphenyl)phosphorane (2.5 mmol, prepared from propyl(triphenyl)phosphonium bromide (1.01 g, 2.62 mmol) and 1M soln. of *t*-BuOK in THF (2.5 ml, 2.5 mmol)) in dry THF (6 ml) at −80°. The soln. was rapidly warmed to r.t. and stirred for 24 h. Then, the mixture was hydrolyzed with 5% HCl (10 ml), and the aq. phase was extracted with pentane (2 × 20 ml). The combined org. extracts were successively washed with 5% HCl (10 ml), sat. $NaHCO_3$ soln. (10 ml), water (10 ml), and then cooled (−20°, 6 H) to precipitate the triphenylphosphine oxide. The clear filtrate was dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by FC (silica gel, Et_2O/pentane 3:7) to furnish **9** (76 mg, 50%, > 99% side-chain (*Z*)-stereoselectivity and 98.6% *cis*-disubstitution, 97.5% ee). Colorless liquid. $[\alpha]_{578}^{20} = +249$ ($c = 0.51$, CCl_4; [6d]: $[\alpha]_{578}^{20} = +223$ ($c = 1.53$, CCl_4)). IR (neat): 3500–3200 (br., OH), 2960*m*, 2860*m*, 1460*w*, 1020*m*, 710*w*, ^{1}H-NMR ($CDCl_3$): 1.00 (*t*, $J = 7.6$, Me); 1.65 (br. *s*, OH); 2.07–2.19 (*m*, 3H); 2.38–2.51 (*m*, 1H); 2.53–2.67 (*m*, 1H); 3.57, 3.69 (*AB* of *ABX*, $J_{AB} = 11$, $J_{AX} = 6.4$, $J_{BX} = 8.1$, CH_2OH); 3.63–3.75 (*m*, H–C(2)); 5.26 (*tt*, $J = 11$, 1.5, H–C(1′)); 5.51 (*dt* = 11, 7.3, H–C(2′)); 5.53–5.58 (*m*, 1H); 5.76–5.81 (*m*, 1H). ^{13}C-NMR ($CDCl_3$): 14.4 (*q*); 20.7 (*t*); 34.9 (*t*); 44.1 (*d*); 44.2 (*d*); 64.2 (*t*); 128.1 (*d*); 130.1 (*d*); 133.4 (*d*); 133.8 (*d*). MS: 152 (22, M^+), 134 (31), 123 (41), 121 (53), 119 (68), 110 (47), 106 (24), 105 (100), 96 (13), 95 (77), 94 (14), 93 (84), 92 (68), 91 (95), 81 (28), 80 (25), 79 (99), 78 (28), 77 (63), 73 (20), 70 (17), 67 (39), 66 (12), 65 (16), 61 (15), 55 (34), 45 (31), 43 (72), 41 (26).

(1R,5R)-3-Oxabicyclo[3.3.0]oct-7-en-2-ol (**8**). To a magnetically stirred soln. of **6** (53 mg, 0.43 mmol) in dry toluene (3 ml) was added a 1M soln. of DIBAL (0.65 ml, 0.65 mmol) dropwise at −78°. The mixture was stirred at −78° for 1 h. Excess DIBAL was destroyed by the addition of dry MeOH (30 µl, 0.73 mmol) and the soln. was warmed to 0°. After stirring for 10 min, H_2O (1 ml), Et_2O (10 ml), and a mixture of silica gel and Na_2SO_4 (300 mg) were added successively [16]. The soln. was stirred for 10 min between each addition. After filtration, the solid was washed with Et_2O (2 × 10 ml). The filtrate was dried (Na_2SO_4), and the solvent was evaporated to furnish **8** (38% mg, 70%) as a mixture of diastereoisomers (88:12). Colorless liquid. IR (neat): 3600–3100 (br., OH), 2960*m*, 2920*m*, 1090*m*, 1050*m*, 960*m*, 700*w*. ^{1}H-NMR ($CDCl_3$): major isomer: 2.25–2.34 (*m*, 1H); 2.68–2.79 (*m*, 1H); 3.03–3.13 (*m*, H–C(5)); 3.36–3.40 (*m*, H–C(1), OH); 3.74 (*dd*, $J = 8.5$, 2.9, H–C(4)); 4.33 (*t*, $J = 8.5$, H–C(4)); 5.33 (*s*, OCHO); 5.64–5.67 (*m*, 1H); 5.77–5.82 (*m*, 1H); minor isomer: 2.22–2.29 (*m*, 1H); 2.51–2.60 (*m*, 1H); 2.95–3.02 (*m*, H–C(5)); 3.52–3.58 (*m*, H–C(1)); 3.55 (*t*, $J = 8.5$, H–C(4)); 4.08 (*t*, $J = 8.5$, H–C(4)); 5.52 (*m*, OCHO); 5.64–5.67 (*m*, 1H); 5.87–5.89 (*m*, 1H).

Wittig *Reaction of* **8**. To a magnetically stirred suspension of propyl(triphenyl)phosphonium bromide (608 mg, 1.58 mmol) in dry THF (3 ml) was added a 1M soln. of *t*-BuOK in THF (1.5 ml, 1.5 mmol) and the resulting orange red suspension was stirred at r.t. After 1 h, it was cooled to −80°, and a soln. of **8** (38 mg, 0.30 mmol) in dry THF (1 ml) was added dropwise. The mixture was rapidly warmed to r.t. and stirred for 15 h. Workup of the mixture and purification of the residue as described for the reductive olefination of **6** yielded **9** (28 mg, 62%) with > 99% side-chain (*Z*)-stereoselectivity and 78% *cis*-disubstitution.

(+)-(3S,4S)-cis-3-[(Z)-But-1-enyl]-4-vinyl-1-cyclopentene ((+)-**1**). To a soln. of **9** (52 mg, 0.34 mmol) in dry CH_2Cl_2 (6 ml) was added PCC (225 mg, 1.05 mmol), and the resulting dark brown soln. was stirred at r.t. After 2 h, the chromium salts were precipitated by the addition of pentane (2 × 15 ml), and the clear filtrate was concentrated to half its volume. The crude aldehyde was immediately transferred into a soln. of methylidene(triphenyl)phosphorane (1.31 mmol, prepared from methyl(triphenyl)phosphonium bromide (485 mg, 1.36 mmol) and 1.6M soln. of BuLi in hexane (0.82 ml, 1.31 mmol)) in dry THF (7 ml) at −15°, and the reaction mixture was stirred at r.t. for 30 min. The mixture was hydrolyzed with H_2O (15 ml) and extracted with pentane (3 × 20 ml). The combined org. extracts were dried (Na_2SO_4) and evaporated. Purification of the residue by FC (silica gel, pentane) furnished (+)-**1** (27 mg, 52%, 98% ee, and > 98% *cis*-disubstitution). Colorless liquid. $[\alpha]_{578}^{20} = +255$ ($c = 0.955$, CCl_4; [6d]: $[\alpha]_{578}^{20} = +261$ ($c = 0.830$, CCl_4)). IR (neat): 3050*m*, 3000*m*, 2960*m*, 2960*m*, 1640*m*, 1610*w*, 990*m*, 910*m*,

710*m*. ^{1}H-NMR ($CDCl_3$): 0.94 (*t*, *J* = 7.6, Me); 2.01–2.12 (*m*, 2 H–C(3′)); 2.23–2.34 (*m*, 1 H); 2.42–2.49 (*m*, 1 H); 2.98 (*quint.*, *J* = 8.2, H–C(4)); 3.63 (*m*, (*t*-like), H–C(3)); 4.91–5.02 (*m*, 2H–C(2″)); 5.13 (*tt*, *J* = 11, 1.5, H–C(1′)); 5.39 (*dt*, *J* = 11, 7.3, H–C(2′)); 5.58–5.62 (*m*, 1 H); 5.75–5.81 (*m*, 1 H); 5.87 (*ddd*, *J* = 17.3, 10.3, 8.1, H–C(1″)). ^{13}C-NMR ($CDCl_3$): 14.4 (*q*); 20.7 (*t*); 37.1 (*t*); 46.7 (*d*); 46.8 (*d*); 114.0 (*t*); 128.3 (*d*); 129.9 (*d*); 131.9 (*d*); 134.3 (*d*); 140.2 (*d*). MS: 148 (16, M^+), 133 (14), 119 (68), 117 (16), 107 (18), 106 (17), 105 (60), 93 (13), 92 (32), 91 (100), 86 (19), 84 (30), 82 (45), 80 (21), 79 (93), 78 (26), 77 (42), 67 (34), 66 (41), 65 (16), 43 (17), 41 (24).

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